

**An economic evaluation of cardiovascular disease
prevention in primary care**

by

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Abstract

This study is an analysis using economic modelling of cardiovascular disease prevention in primary care. The costs of cardiovascular disease prevention are considered from the perspective of the health service. The benefits of cardiovascular disease prevention are measured as the number of major cardiovascular events prevented over a five-year time horizon. The study population consists of adults in the Health Survey for England 1998 who are free from cardiovascular disease.

The analysis estimates the cost-effectiveness of strategies for identification of patients for prevention of cardiovascular disease and identifies the most efficient identification strategy. The analysis estimates the cost-effectiveness of a number of preventive interventions, then ranks these interventions by their cost-effectiveness and calculates the incremental cost-effectiveness of adding additional interventions. Finally the analysis estimates the efficiency characteristics of different strategies for identification and treatment in the study population. An extensive sensitivity analysis of the findings is carried out.

There are three main findings. First there are more efficient selection strategies than those currently recommended. Second, cost-effectiveness rankings of preventive interventions are robust. Third, prevention strategies are more cost-effective when treatment eligibility criteria are informed by cost-effectiveness analysis.

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Abbreviations

ACE 2 = Angiotensin II Receptor Blocker

ACE inhibitor = Angiotensin Converting Enzyme inhibitor

CHD = Coronary Heart Disease

CVA = Cerebrovascular disease

CVD = Cardiovascular Disease

NHS = National Health Service

1. Aim of PhD

The aim of this study is to design a comprehensive, cost-effective strategy for primary prevention of cardiovascular disease in primary care. The method is through the development of a model of the economic consequences of CVD prevention in a population. This model is used to analyse strategies for cardiovascular disease prevention in primary care.

CVD prevention process in primary care

There are three basic steps in the process of cardiovascular disease prevention in primary care. First identify patients likely to benefit from a preventive intervention, second offer the preventive intervention or treatment to these identified patients, third follow-up patients on treatment.

Cost-effectiveness of CVD prevention is therefore influenced by three key elements: the cost-effectiveness of identifying new patients in a population; the cost-effectiveness of risk-lowering interventions; and the cost-effectiveness of follow-up. Each of these elements can be implemented in different ways. There are numerous potential identification strategies, innumerable potential treatment strategies and many potential follow-up strategies. Even when optimum strategies are identified for each element, there remain potential trade-offs, for example: more resources can be devoted to identification and fewer to treatment; or more resources can be devoted to follow-up and fewer to identification.

Weaknesses of current analyses

Traditional cost-effectiveness analyses fail to consider cost-effectiveness in a completely satisfactory manner. Most traditional analyses treat some of the elements of a prevention strategy as a given and explore the costs and effects of varying the remaining elements. For example, some analyses ignore the resource implications of identifying patients. Such analyses focus on the cost-effectiveness of alternative treatment strategies for identified patients. Many analyses compare the cost-effectiveness of preventive interventions that affect only one risk factor. Interventions that affect other risk factors are not seen as alternatives to the primary intervention. Only a handful of analyses consider cost-effectiveness within the context of a complete strategy. Even these analyses tend to assume that there are only a limited number of ways of identifying patients for treatment. Few analyses consider the

incremental cost-effectiveness of adding additional treatments to a strategy or of identifying additional patients to treat.

In effect there are few complete accounts of the costs and effects of preventive strategies, making it difficult to take account of the interactions between changing the selection strategy, changing treatment eligibility criteria or offering alternative preventive interventions. Traditional cost-effectiveness analyses provide only a series of snapshots of the cost-effectiveness, which may be insufficient to inform a complete prevention strategy.

Analytic approach in this study

The approach taken in this study remedies a number of deficiencies in traditional analyses.

- It considers the economic consequences of CVD prevention in a natural population, rather than in individual patients or in pre-defined populations with particular risk factor characteristics (e.g. persons with hypertension or hyperlipidaemia).
- It considers the economic consequences of all three steps in CVD prevention: identification, intervention or treatment, and follow-up.
- It considers all preventive interventions within the same analytic framework.

This approach makes it possible to compare the economic consequences of treatment strategies within the same population. It also makes it possible to compare the economic consequences of altering identification strategies with the economic consequences of altering treatment or follow-up strategies. This makes it possible to devise a comprehensive prevention strategy for CVD in primary care.

Factors not considered in this study

To make the analysis manageable, some issues are not considered within this study. The study is primarily concerned with efficiency and does not address the question of distributional equity. If there is a societal judgement that health gain in some types of individuals should be given more weight than others, it must be taken into account outside of the framework of this analysis.

Nor is this study concerned with distributional efficiency within healthcare: resource allocation to CVD prevention in comparison to other aspects of healthcare. In most cases the incremental benefits of additional resource allocation to most healthcare

programmes is unknown, making direct comparison of resource allocation between programmes very difficult.

The study also is not concerned with patient preference for CVD prevention. Since interventions to prevent CVD may have an impact on quality of life, the optimum decision for any given individual depends on the relative weight they attach to reducing their risk of CVD in relation to their quality of life. Since individuals' preferences for CVD prevention are not known, it is not possible to take them into account in a model. However some of the implications of patient preferences can be explored in the sensitivity analysis.

2. Policy background – the evolution of guidelines for CVD prevention

History of cardiovascular risk prediction

Early epidemiology of CHD and risk prediction

Coronary heart disease and stroke have long been recognised to be more frequent in the elderly than the young. A link between cholesterol levels and heart disease was first proposed in 1950.¹ Strong evidence linking high blood pressure to coronary heart disease dates back to the 1950s.^{2,3} Evidence for the importance of smoking as a risk factor for CHD was first published in the 1960s.^{4,5,6} During this period observations were also made on the link between diabetes and heart disease.^{7,8,9,10}

An early awareness that several risk factors were associated with CHD was followed by attempts to predict probability of CHD in individuals. The first attempt to do so and to validate the results in a separate cohort dates from the 1950s.^{11,12} A predictive function derived from the Framingham dataset, using blood pressure and cholesterol alone was published in 1962.¹³ A prediction equation was derived from a cohort of 700 London busmen, followed up for five years.¹⁴ This identified age, systolic blood pressure, cholesterol level, smoking and exercise (conductors versus drivers) as important risk factors. The study did not derive a multivariate risk equation but instead produced scores based on systolic blood pressure and cholesterol level. Analysis at this time was constrained by the ability to fit curves to the data. However, the authors presciently observed: “better mathematical models will surely come”. Another early attempt to predict CHD risk men used lipid levels, blood pressure and personality type to identify middle-aged men at low risk.¹⁵ However mathematical equations were not developed in this study. Confidence in the power of predictive equations was high at this time, with one commentator noting, “Predictive tests of similar power are not available for any other chronic disease.”¹⁶

1970s risk equations

An early example of the use of risk tables was an attempt to use age, total cholesterol and triglyceride levels to calculate probability of CHD in men with cardiac symptoms.¹⁷ During the 1970s a number of multivariate coronary risk equations were derived from large cohort studies of men. Prediction of CHD was even the subject of an enthusiastic editorial in the *New England Journal of Medicine* as early as 1974.¹⁸

Keys derived risk equation for men aged 40 to 59 in the seven-countries study using age, systolic blood pressure and cholesterol level and smoking status.¹⁹ The Italian part of the same study used age, systolic blood pressure, cholesterol level, smoking status and physical activity to predict risk of CHD.²⁰ A US study used age, cholesterol, behaviour (exercise), smoking status and systolic blood pressure to predict risk of CHD in older and in men aged 39 to 59.²¹ A French study used cholesterol level, blood pressure, smoking status, diabetic status and ECG findings to predict risk of CHD in middle-aged men.²² Most significantly, a prediction equation for both men and women aged 35 to 70 was derived from the Framingham cohort using cholesterol, blood pressure, smoking history, an electrocardiogram and diabetic status.²³ Close agreement was observed between the predictions of the Framingham and Western Collaborative Group Study equations, suggesting that both are valid outside of their original study populations.²⁴

1980s risk equations

In the early 1980s a tool was developed to assess an individual's probability of coronary heart disease in clinical practice: albeit in the field of aviation medicine.²⁵ In the same year, it was suggested that risk tables derived from these equations might be used to determine prognosis and hence potential benefit from antihypertensive treatment.²⁶ Throughout the 1980s further studies confirmed the validity of the Framingham risk equation in US populations.²⁷

1990s risk equations

The most widely used versions of the Framingham risk equations were derived in the early 1990s, with separate equations derived to predict all cardiovascular events, coronary events and strokes. The Framingham CVD risk equation predicts risk of any vascular event. It uses as predictors age, sex, blood pressure, smoking status, total and HDL cholesterol level, diabetic status whether there is electrocardiographic evidence of left ventricular hypertrophy.²⁸ The Framingham CHD risk equation predicts risk of coronary events using the same predictors.²⁹ The Framingham cerebrovascular disease risk equation predicts risk of stroke (cerebrovascular accident or transient ischaemic attack).³⁰ Its predictors are an individual's age, sex, blood pressure, smoking status, diabetes status and whether they take antihypertensive drugs, have CVD or atrial fibrillation.

2000 to the present

More recent work has suggested that addition of lipoprotein (a), coagulation factors (such as fibrinogen), or C-reactive protein levels will improve the predictive value of risk equations.^{31,32,33} Two risk prediction systems based on European cohorts have been published in recent years. The first uses similar risk factors to those in the Framingham equations but adds triglyceride levels and family history as independent predictors.³⁴ The second adds body mass index and family history as independent predictors.³⁵ There is some evidence that European risk predictors may be better predictors of CHD risk in European populations.^{36,37,38}

History of evidence of effectiveness and guidelines for preventive interventions

Antihypertensive treatment

Early evidence and guidelines

Antihypertensive treatment was first used to treat malignant hypertension (now referred to as accelerated hypertension).³⁹ This is a distinct condition characterised by a number of clinical signs (evidence of renal damage) and a very high blood pressure. Clinical trials showing the benefits of antihypertensive treatment for what was then termed essential hypertension were first published in the 1960s.⁴⁰ This early trial showed a reduction in heart failure and coronary events in patients aged 21 to 70. The first large trial of drug treatment of severe hypertension was published in 1967.⁴¹ It showed a reduction in major cardiovascular events in patients aged 35 to 70 with diastolic blood pressures over 115 mm Hg. A subsequent trial confirmed a similar reduction in cardiovascular events (principally heart failure and stroke) in patients aged 35 to 70 with diastolic blood pressure in the range 90 to 114 mm Hg.⁴² In the same year a trial confirmed that antihypertensive treatment in persons aged 40 to 80 reduced the incidence of stroke.⁴³ In the 1970s a number of further trials were published. The Hypertension-Stroke Cooperative study showed a non-significant reduction in stroke.⁴⁴ The Treatment of Mild Hypertension Study showed no effect on coronary heart disease but a reduction in incidence of stroke and heart failure.⁴⁵ Early results of the VA-NHLBI showed no significant effect.⁴⁶

Early hypertension guidelines

US blood pressure guidelines from the early 1970s categorise patients as hypertensive on the basis of a blood pressure threshold alone.⁴⁷ At this time it was believed that “the prognosis of hypertension in the age group 15-30 is particularly poor”.⁴⁷ The guideline therefore sets lower blood pressure thresholds for referral (for diagnosis and possible treatment) in those under 40 than those over 40: 140/90 mm Hg and 159/94 mm Hg respectively.

Conceptually similar recommendations are found in UK guidelines from the same era, although the actual thresholds and ages differ.⁴⁸ These recommend treatment of diastolic blood pressure over 100 mm Hg in men under 65. In men over 65 (and women of any age) they recommend treatment at higher thresholds. The UK

guidelines recommend treatment because of its effectiveness in reducing stroke and left ventricular failure and are cautious about its potential effects on reducing CHD.

Falling treatment thresholds, evidence and guidelines in the early 1980s

The 1980s saw the publication of large North American, Australian and British clinical trials. The Hypertension Detection and Follow-up Programme found that a stepped-care programme for treatment of hypertension resulted in a lower incidence of CVA and lower cardiovascular mortality rates than usual care.^{49,50} The Oslo study found no significant effect overall, but noted a marked reduction in CVA and a non-significant increase in CHD.⁵¹ *Post hoc* analysis of this study suggested that treatment might be effective in patients whose diastolic blood pressure exceeded 100 mm Hg. Both the Australian Therapeutic trial in mild hypertension and the Medical Research Council study found a reduced incidence of stroke and a non-significant reduction in CHD.^{52,53} The European Working Party on high blood pressure in the elderly found a significant reduction in CHD mortality and overall cardiovascular mortality and a non-significant reduction in CVA mortality.⁵⁴

Around this time, epidemiologists began to conduct systematic reviews of the effectiveness of interventions.⁵⁵ Applying this analytic technique to studies of blood pressure lowering confirmed that it reversed most of the epidemiological risk of CVA, but that there was uncertainty about the effects of blood pressure lowering on CHD.⁵⁶ It was also beginning to be recognised that the benefits of treatment were dependent on the patient's pre-treatment risk factor profile and changes to these risk factors, rather than effects on blood pressure alone.⁵⁷

Guidelines in the early 1980s

Guidelines in the early 1980s continue to define hypertension (or recommend treatment) on the basis of blood pressure alone: usually concentrating on diastolic blood pressures. Age and co-morbidities are used to adjust the threshold at which treatment should be initiated: generally thresholds are higher in older patients and lower in patients with co-morbidities.

WHO/ISH guidelines for the treatment of mild hypertension were published in 1983 with updated versions published in 1986 and 1989. The 1983 guidelines recommend treatment if blood pressure is persistently over 95 mm Hg.⁵⁸ However they are more conservative about treating elderly patients, stating that: "There is as yet no evidence that antihypertensive treatment is of benefit in persons over the age of 70." The

guidelines specifically recommend a higher threshold for treatment (diastolic blood pressure over 109 mm Hg) of patients over 70 “who are frail or who have evidence of advanced cardiovascular disease, dementia or other debilitating illnesses...” Confusingly, the guidelines regard cardiac signs, kidney disease or a family history of CVD as additional reasons to treat patients under 70, while regarding “advanced cardiovascular disease” as a reason not to treat patients over 70. The goal of treatment is stated to be to lower diastolic blood pressure to below 90 mm Hg. The 1986 guidelines make the same recommendations.⁵⁹ However the statement in relation to age changes: “There is as yet no evidence that antihypertensive treatment is of benefit in persons aged 80 and over.”

US hypertension guidelines from 1980 recommend treatment of blood pressure over 115 mm Hg diastolic or persistently over 160/95 mm Hg.⁶⁰ Additional guidelines refer to hypertension as a “diagnosis” and refer to normotension as a goal of treatment.⁶¹

UK guidelines at this time recommend routinely measuring blood pressure in all adults aged 30 to 65 “because above 65 years the treatment of asymptomatic hypertension has not yet been shown to confer benefit”.⁶² They are conservative about recommending treatment for mild hypertension because “the value of drug therapy in mild hypertension is not yet proven” but recommend treatment if diastolic blood pressure is persistently over 105 mm Hg.

Cardiovascular risk factors: guidelines in the late 1980s

Towards the end of the 1980s views of hypertension changed. Guidelines explicitly talk of risk of cardiovascular disease when recommending treatment. Some guidelines suggest that the goal of treatment is primarily to prevent cardiovascular disease – not simply to restore normotension. Treatment of the elderly is also assigned greater importance.

The 1989 WHO/ISH guidelines include a number of important changes to previous WHO/ISH guidelines that begin to undermine the concept of hypertension as a clear-cut diagnostic category. They introduce the concept of cardiovascular risk, explicitly stating that “There is a continuum of cardiovascular risk associated with blood pressure level: the higher the pressure the higher the risk.”⁶³ They go on to state that the level at which “hypertension” is diagnosed is therefore a matter of judgement. In practice, the diastolic blood pressure treatment thresholds are the same as the previous two guidelines, with the addition of a systolic blood pressure treatment threshold (160

mm Hg). Attitude to age changes radically: “The benefits of antihypertensive therapy are more conspicuous in older subjects.” The goal of treatment remains the same: “to lower the blood pressure to normotensive levels”.

US guidelines in this era differ considerably from their predecessors.⁶⁴ They are much more comprehensive, longer and more extensively referenced to clinical trials. They also introduce the concept of cardiovascular risk and emphasise the continuous relationship of both systolic and diastolic blood pressure to risk of cardiovascular disease and they state that: “the goal of treating patients with hypertension is to prevent morbidity and mortality”. Achieving target blood pressures (under 140/90 mm Hg) are seen as a means to this end. Drug treatment is recommended for patients whose diastolic blood pressure exceeds 94 mm Hg and for those whose blood pressure exceeds 90 mm Hg who are “otherwise at high risk”. The US guidelines also introduce a treatment threshold for systolic blood pressure (160 mm Hg).

During this era, UK guidelines also began to change. As with the US guidelines, numerous clinical trials are cited to support the views of the authors. The main recommendation is that patients under 80 with blood pressures over 100 mm Hg should be treated. The same review also states “there is no justification for withholding antihypertensive drugs from the elderly (at least those under 80) on the grounds of age alone.”⁶⁵ These recommendations echo those of the British Cardiac Society guidelines a few years earlier, all patients with diastolic blood pressure over 100 mm Hg should be treated.⁶⁶

Systolic hypertension and cardiovascular risk: evidence and guidelines since 1990

Early studies of blood pressure treatment tended to define high blood pressure in terms of diastolic blood pressure. Since isolated systolic hypertension is often found in older persons, this raised doubts about the effectiveness of treating systolic hypertension. As early as the 1970s, epidemiological evidence suggested that systolic blood pressure might be a better predictor of CHD than diastolic.⁶⁷ Some early clinical trials included patients with isolated systolic hypertension.⁶⁸ However this was insufficient to persuade guideline authors of the importance of systolic blood pressure. Trials demonstrating the effectiveness of treating isolated systolic hypertension were published in the early 1990s.^{69,70}

By the 1990s there was both substantial epidemiological evidence of the relationship between blood pressure and cardiovascular disease and large numbers of clinical trials

of the effectiveness of antihypertensive treatment. Systematic review of the effectiveness of antihypertensive treatment in relation to epidemiological evidence concluded that treatment approximately reversed epidemiological risk of CVA and largely reversed epidemiological risk of CHD.^{71,72} The finding that treatment largely reverses epidemiological risk has remained largely unchallenged since this date, with subsequent clinical trials largely confirming the view.

In the late 1990s the HOT and UKPDS clinical trials specifically demonstrated that further blood pressure lowering is associated with further reductions in cardiovascular events.^{73,74} Subsequent trials also demonstrated benefits to blood pressure lowering when blood pressure is not necessarily high.^{75,76} Meta-analysis has confirmed that antihypertensive treatment reverses epidemiological risk of strokes and heart disease in the very elderly (over 80), although it remains unclear whether this translates into a mortality benefit.⁷⁷

Recent clinical trials and meta-analyses have moved away from the effectiveness of blood pressure lowering and have tended to address more specific questions. Trials have compared the blood pressure effects and adverse effects of a number of different drugs.⁷⁸ Trials have addressed the effectiveness of different drugs in relation to one another.^{79,80,81,82} Trials have specifically investigated the effectiveness of calcium channel blockers in comparison to thiazide diuretics.^{83,84,85,86,87} Trials have investigated the effectiveness of calcium channel blockers compared to drugs acting on the angiotensin converting-enzyme system.^{88,89} Meta-analyses from this era have tended to show that evidence of effectiveness is strongest for thiazide diuretics.^{90,91} However more recent meta-analyses suggest that drugs acting on the angiotensin converting-enzyme system may offer advantages over diuretics.⁹²

Emerging concepts of cardiovascular risk: guidelines in the 1990s

Throughout most of the 1990s hypertension guidelines move gradually towards the concept of treating cardiovascular risk. The rationale for this is that risk predicts benefit. This represents a fundamental shift away from treating physiological deviancy and towards an outcome-focused view of hypertension and its treatment. It is worth remembering that this view was far from new, having been first suggested a decade earlier.²⁶ However, guidelines proved slow to adopt the new paradigm.

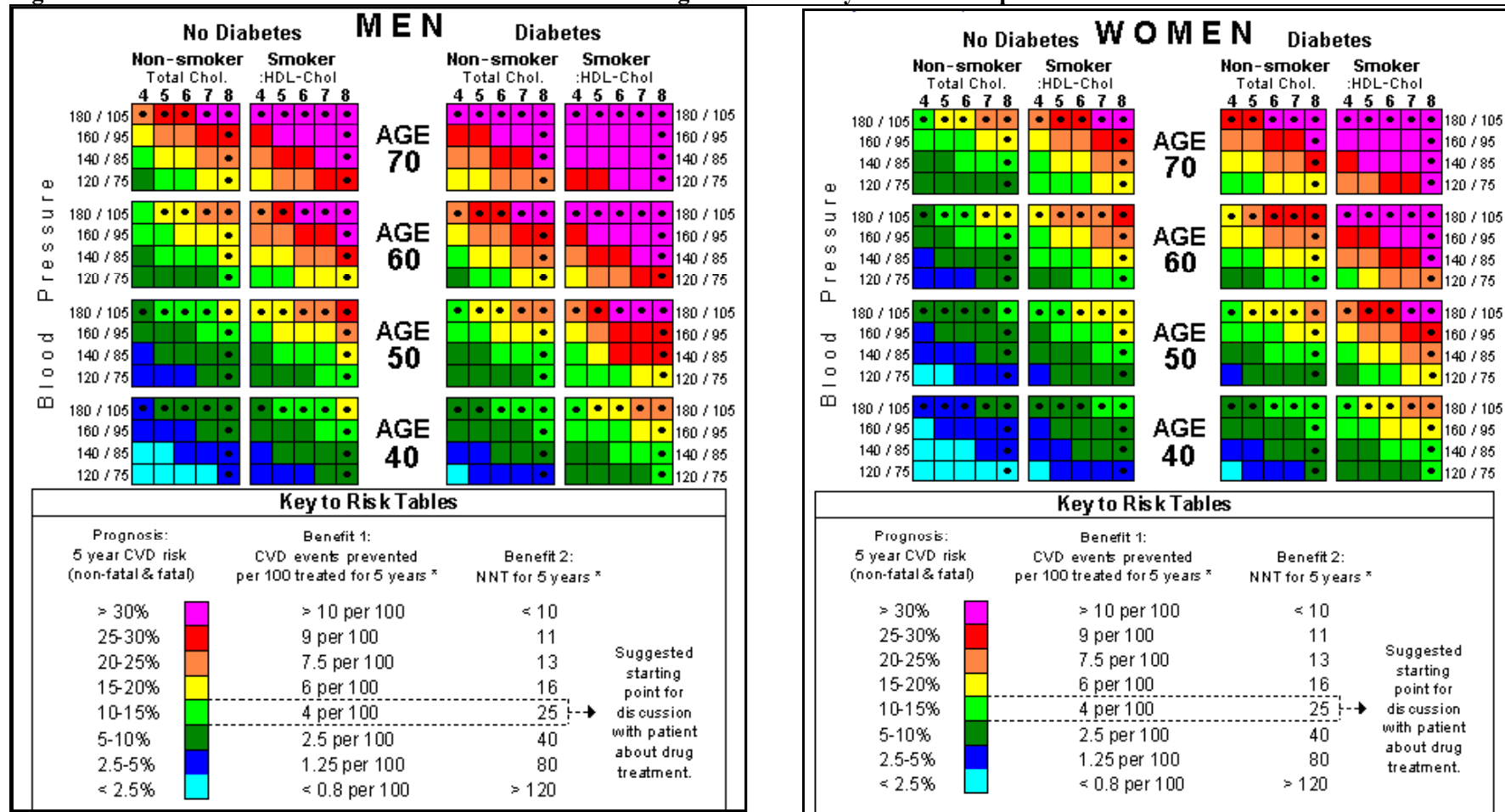
The rate of at which cardiovascular risk has been adopted as a determinant of treatment differs from one country to another. Most national guidelines incorporate

consideration of risk by allocating patients to high-risk or low-risk categories on the basis of the presence or absence of categorical risk factors: age over 55, diabetes, smoking status, target organ damage. However one guideline formally estimates cardiovascular risk using risk tables. By the end of the 1990s many national guidelines incorporate explicit consideration of cardiovascular risk in the form of risk tables.

The most rapid adoption of cardiovascular risk as a determinant of treatment has undoubtedly been in New Zealand. In 1993 the New Zealand Guidelines Group published a discussion document on the management of raised blood pressure.⁹³ These were followed by publication of national guidelines.⁹⁴ The guidelines incorporated risk tables - based on the Framingham risk equation⁹⁵ - to calculate risk cardiovascular disease. (Figure 1) They made explicit use of these risk tables to calculate probability of benefit from treatment and recommended that the decision to offer treatment should be largely guided by estimated cardiovascular risk (and hence probable benefit).

The observation that blood pressure alone is a poor predictor of benefit was made more than a decade before publication of the New Zealand discussion paper.²⁶ However the New Zealand guidelines prompted considerable debate among authors of hypertension guidelines. It was observed that the recommendations of guidelines in the USA and the UK had been influenced by different clinical trials.⁹⁶ The MRC Mild Hypertension Trial showed small absolute benefits of treatment.⁵³ British guidelines were therefore conservative about recommending treatment. However the Hypertension Detection and Follow-up Program showed larger absolute benefits of treatment, particularly in patients with target organ damage.⁴⁹ The US guidelines were therefore more enthusiastic about treating lower blood pressures. However, differences in absolute mortality benefit reported in these trials could be explained by differences in the absolute cardiovascular risk of patients included in the clinical trials.⁹⁶ In other words, risk predicts benefit. In the same paper, the authors called for all treatment decisions to be based on a formal estimate of absolute cardiovascular risk.

Figure 1: Risk tables for New Zealand Guidelines for the management of mildly raised blood pressure



Source: http://www.nzgg.org.nz/library/gl_complete/bloodpressure/table1.cfm

Figure 2: Risk charts recommended for use in the report of the third working party of the British Hypertension Society, 1999

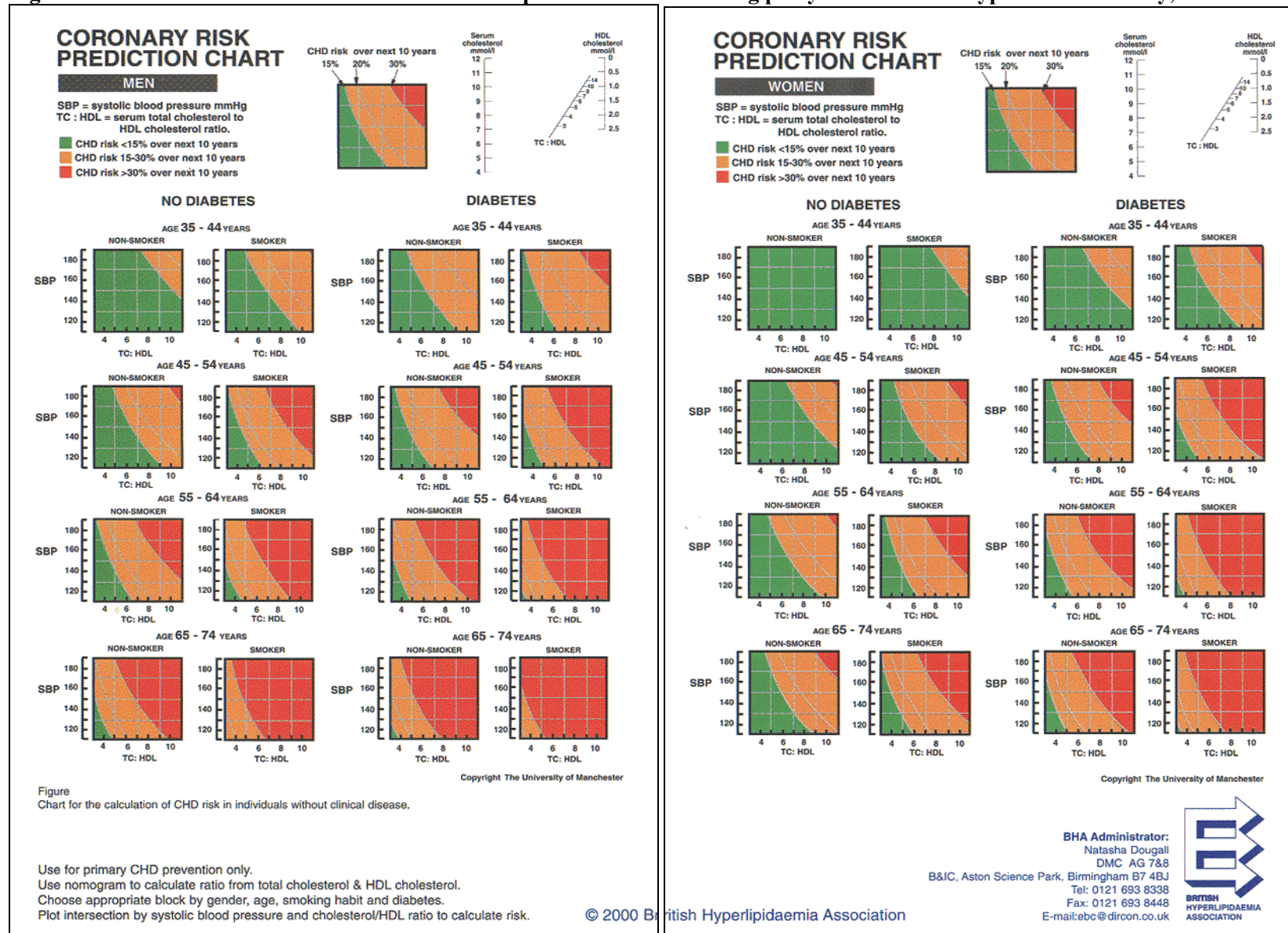


Figure
Chart for the calculation of CHD risk in individuals without clinical disease.

Use for primary CHD prevention only.
Use nomogram to calculate ratio from total cholesterol & HDL cholesterol.
Choose appropriate block by gender, age, smoking habit and diabetes.
Plot intersection by systolic blood pressure and cholesterol/HDL ratio to calculate risk.

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BRITISH
HYPERLIPIDAEMIA
ASSOCIATION

Source: Joint British recommendations on prevention of coronary heart disease in clinical practice

UK guidelines in the early 1990s build on the concept of cardiovascular risk introduced in previous guidelines. They do this by using the presence of dichotomous risk factors to systematically stratify patients into those with additional risk factors and those without.⁹⁷ Treatment is recommended at a lower threshold for patients over 60, patients with co-existing risk factors (male sex, hypercholesterolaemia or smoking) and patients with target organ damage. In the late 1990s the British Hypertension Society produced its own guidelines incorporating risk tables.⁹⁸ (Figure 2) Unlike the New Zealand risk tables (which used the Framingham cardiovascular risk equation) these tables are derived from the Framingham coronary risk equation.²⁹ Treatment is recommended for all patients whose blood pressure exceeds 160/100 mm Hg and for those whose blood pressure exceeds 140/90 mm Hg if they suffer from diabetes, target organ damage or have a ten-year CHD risk greater than 15%.

Figure 3: Classification of high blood pressure in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

BP CLASSIFICATION	SBP* mmHg	DBP* mmHg	LIFESTYLE MODIFICATION	INITIAL DRUG THERAPY	
				WITHOUT COMPELLING INDICATION	WITH COMPELLING INDICATIONS (SEE TABLE 8)
NORMAL	<120	and <80	Encourage		
PREHYPERTENSION	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
STAGE 1 HYPERTENSION	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
STAGE 2 HYPERTENSION	≥160	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

DBP, diastolic blood pressure; SBP, systolic blood pressure.
Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

* Treatment determined by highest BP category.
† Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.
‡ Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

US guidelines from the 1990s and until the present follow the general pattern towards consideration of risk factors, but do not advocate the use of risk tables. The fifth report of the Joint National Committee (1993) recommends treatment of all patients whose blood pressure exceeds 140/90 mm Hg.⁹⁹ It is not until the sixth report of the Joint National Committee (1997) that greater emphasis is placed on risk stratification

using a number of dichotomous risk factors.¹⁰⁰ In the sixth report high-risk patients, such as those with target organ damage, may be treated if their blood pressure is persistently over 130/85 mm Hg, whereas blood pressure of over 140/90 mm Hg without additional risk factors could be tolerated for up to a year before starting treatment. The seventh report of the Joint National Committee adopts a similar approach.¹⁰¹ Blood pressure reduction is recommended for all patients whose blood pressure exceeds 140/90 mm Hg and even for those with lower blood pressures in the presence of “compelling indications”. (Figure 3)

Figure 4: WHO-ISH Hypertension Guidelines classification of high blood pressure

	BLOOD PRESSURE (mm Hg)		
	SBP 140-159 or DBP 90-99	SBP 160-179 or DBP 100-109	SBP ≥ 180 or DBP ≥ 110
no other risk factors	LOW RISK	MEDIUM RISK	HIGH RISK
1-2 risk factors	MEDIUM RISK	MEDIUM RISK	V HIGH RISK
3 or more risk factors or TOD or diabetes	HIGH RISK	HIGH RISK	V HIGH RISK
ACC	V HIGH RISK	V HIGH RISK	V HIGH RISK

WHO/ISH guidelines in 1993 take a similar approach to US guidelines, however they use a different treatment threshold. They recommend treatment if blood pressure exceeds 160/95 mm Hg, without formal consideration of cardiovascular risk.¹⁰² More recent WHO/ISH guidelines adopt the philosophy of risk prediction wholeheartedly, stating “The best predictor of absolute treatment effects for any individual patient will be provided by application of the estimate of the relative risk reduction from trials to an estimate of the absolute disease risk for the individual in question.”¹⁰³ However their practical advice remains less sophisticated, with patients stratified on the basis of dichotomous risk factors, the presence or absence of target organ damage (TOD) and associated clinical conditions (ACC). (Figure 4) Treatment is recommended for all those at high or very high-risk; for those at medium-risk if blood pressure exceeds 140/90 mm Hg; for those at low-risk if blood pressure exceeds 150/95 mm Hg. This advice means that a low-risk patient whose blood pressure is 151/96 mm Hg will be treated, whereas a medium-risk patient whose blood pressure is 139/89 mm Hg will not be treated.

Cholesterol lowering

Early evidence and guidelines

A large study showing a beneficial effect on coronary heart disease of dietary intervention to lower cholesterol was published in 1969.¹⁰⁴ However a subsequent trial using drug intervention reported no benefit.¹⁰⁵ Drug trials throughout the 1970s and 1980s consistently showed reductions in coronary heart disease with treatment.^{106,107,108,109,110,111} However these findings were complicated by the fact that these trials included few women and that some trials recorded increases in non-cardiac deaths.¹⁰⁷ Nevertheless, the consensus view was that cholesterol lowering was beneficial.¹¹² This meant that by the early 1990s, there was substantial evidence that cholesterol lowering could reduce coronary heart disease.¹¹³ At the same time there was still genuine uncertainty about whether cholesterol-lowering drugs could lower overall mortality.¹¹⁴ One influential view of the evidence on cholesterol lowering at this stage was that it was consistent with a beneficial effect in high-risk patients and harm in low-risk patients.¹¹⁵

Early cholesterol guidelines

The general pattern to early cholesterol guidelines is to recommend treatment of raised cholesterol with diet and with drugs. Treatment thresholds are set largely on the basis of total cholesterol levels. Treatment thresholds are set lower in patients with additional risk factors and higher in older patients. This mirrors the recommendations of hypertension guidelines from the same era. Guidelines recognise that additional factors are important determinants of risk, but ignore the role of age. In some cases this appears to be partly the result of confusion between relative risks and absolute risks associated with higher cholesterol levels. Relative risks are larger in the young, but absolute risks greater in the elderly.

European guidelines categorise patients as suffering from mild (>5.2 mmol/l) or severe hypercholesterolaemia (>6.5 mmol/l).¹¹⁶ They recommend taking account of categorical risk factors in assessing patients in either category and drug treatment for those with severe hypercholesterolaemia. Younger age is considered an additional risk factor.¹¹⁷

UK hyperlipidaemia guidelines in 1987 recommend that all adults have their cholesterol checked, preferably before the age of 30.¹¹⁸ They recommend general dietary advice for those whose cholesterol levels are over 5.2 mmol/l; clinical care for

those over 6.5 mmol/l; and drug treatment for those over 7.8 mmol/l. The aim of treatment is said to be to reduce cholesterol to 5.2 mmol/l – described as “the optimal value for subjects in the general population”. The guidelines state that the relative risk associated with higher cholesterol levels is greater in younger patients and therefore emphasise the importance of treating those under 30. They also emphasise the importance of treating those with coronary heart disease or with additional risk factors.

Canadian guidelines from 1990 recommend treatment mainly on the basis of total cholesterol level, with higher thresholds for those over 40 (>7 mmol/l), than those over 30 (>6.5 mmol/l), over 20 (>6 mmol/l) or under 20 (>5 mmol/l).¹¹⁹

USA guidelines in 1988 categorise cholesterol levels as desirable (<5.2 mmol/l), borderline-high (5.2 to 6.2 mmol/l) and high (>6.2 mmol/l). Dietary intervention is recommended for patients in the borderline-high category and drug treatment if they have any of a series of additional categorical risk factors (male sex, history of smoking, hypertension, diabetes). For those in the high category, further investigation of LDL levels and drug treatment is recommended.¹²⁰ USA guidelines from 1994 are similar but place a greater emphasis on treating patients with CHD and introduce a target LDL cholesterol level.¹²¹

Later evidence and guidelines

Further evidence on the effectiveness of cholesterol lowering was published in the 1990s.¹²² However the picture changed dramatically with the development of the statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors). In the early 1990s trials showed these to be effective at lowering serum cholesterol and well tolerated.¹²³ However the real breakthrough came when a large clinical trial in Scandinavia demonstrated that these prevented coronary disease in secondary prevention.¹²⁴ Within a few years large studies had demonstrated similar effects in primary prevention¹²⁵ and in patients with average cholesterol levels.^{126,127} The most recent large study confirmed a similar effectiveness across all pre-treatment cholesterol levels.¹²⁸

Recent cholesterol guidelines

The first modern UK guidelines are those developed by the Sheffield group. These adapt the Framingham risk equations to derive a risk table for use by clinicians. Statin treatment is recommended for patients at over 30% five-year CHD risk – provided

their total cholesterol exceeds 5.0 mmol/l.¹²⁹ Since this date, formal calculation of CHD risk has been adopted widely in cholesterol guidelines. It is seen in 1998 Canadian guidelines.¹³⁰

The most recent US guidelines recommend that treatment be guided by a formal estimate of CHD risk.¹³¹ However the US guidelines are not entirely consistent. It acknowledges that “those at higher risk are likely to get greater benefit”, but continues to advocate treatment of persons at low risk with very high LDL levels “to reduce long-term risk”. It also continues to use categorical risk factors to identify those in whom formal risk estimation should be carried out.

Figure 5: Treatment recommendations from the Third Report of the National Cholesterol Education Program (NCEP)

Table 5: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify tri-glycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

Different countries have incorporated formal CHD risk calculation into their guidelines in different ways. Guidelines from the Netherlands categorise patients on the basis of CHD risk and age, with risk higher thresholds for older patients. For example drug treatment is recommended for a total cholesterol >5.0 mmol/l and ten-year CHD risk >25% at the age of 40 years, increasing to >35-40% at the age of 70 years.¹³²

Aspirin

Since 1980 clinical trials have shown aspirin to be effective at preventing recurrence after myocardial infarction.^{133,134} However evidence for the effectiveness of aspirin in

primary prevention emerged later.^{135,136} By 1994 it was clear that aspirin was effective in preventing vascular events in high-risk patients, but it remained unclear whether its effects in primary prevention were balanced by the hazards of treatment.¹³⁷ Later studies of primary prevention confirmed that the benefits of treatment with aspirin could indeed outweigh the hazards.^{138,139,140}

Combined prevention guidelines

The observation that there is a strong relationship between epidemiological risk and the benefits of treatment has led recent commentators to question the utility of categorising patients as hypertensive or hypercholesterolaemic.¹⁴¹ If risk is a predictor of benefit, treatment should be targeted at those at highest risk. If risk is multifactorial then those at highest risk with a high blood pressure might also benefit from other interventions to reduce risk: such as cholesterol lowering. This is particularly true if the benefits of antihypertensive or cholesterol-lowering treatments are not confined to those with raised blood pressure or raised cholesterol. This would mean that all risk-lowering treatments should be considered in any individual at high risk for any reason. The logical conclusion of this approach is to offer multiple risk-lowering treatments to all those at high-risk of cardiovascular disease.¹⁴²

Combined CHD guidelines

Combined European guidelines were published in 1998.¹⁴³ These recommend estimation of CHD risk using tables derived from the Framingham CHD risk equation. For primary prevention in high-risk patients they recommend aspirin, antihypertensive treatment if blood pressure exceeds 140/90 mm Hg and statins if cholesterol exceeds 5 mmol/l. High-risk is defined as greater than 20% ten-year CHD risk. Combined British guidelines were published in the same year.¹⁴⁴ They make very similar recommendations. However they define high-risk more loosely: greater than 30% ten-year CHD risk but reducing to 15% ten-year CHD risk as resources permit. Because of their relevance to a UK setting the joint British recommendations are explored in some detail.

Joint British Recommendations on the prevention of CHD in primary care

The Joint British recommendations are specific in their advice on preventing coronary heart disease. They advocate secondary prevention in patients with existing CVD and primary prevention in patients at asymptomatic high-risk patients. The

recommendations' advice on identification of asymptomatic high-risk patients is to assess all adult patients at least five-yearly.

Selection of patients for assessment

It is difficult to be clear what is intended by the recommendations with regard to identification of patients. However some of the recommendations are clarified in a summary written by one of the authors.¹⁴⁵ All patients' CHD risk should be assessed opportunistically, when they attend for other reasons. The guidelines do not indicate the age at which patients become eligible for five-yearly assessment nor do they indicate the age (if any) at which it should finish.

Patient assessment and treatment

Blood pressure and cholesterol level measured on the first occasion should be used to estimate CHD risk. On the basis of their blood pressure, cholesterol level and CHD risk, patients should either be treated, or reassessed annually, or reassessed five-yearly. Patients should be treated if their blood pressure exceeds 140/90 mm Hg or whose total cholesterol exceeds 5.0 mmol/l and are at greater than 30% ten-year risk (equivalent to 15% five-year risk). Patients whose blood pressure exceeds 140/90 mm Hg or whose total cholesterol exceeds 5.0 mmol/l but who are at less than 30% ten-year CHD risk (equivalent to 15% five-year risk) should be assessed annually. Other patients should be reassessed five-yearly. (Table 1)

Table 1: Joint British recommendations on assessment of patients

Assessment	Five-yearly	Annually
Estimation of blood pressure	Blood pressure <140/90 mm Hg Five-year CHD risk <15%	Blood pressure ≥140/90 mm Hg Five-year CHD risk <15%
Estimation of serum cholesterol	Total cholesterol <5.0 mmol Five-year CHD risk <15%	Total cholesterol ≥5.0 mmol Five-year CHD risk <15%

Source: Joint British Recommendations on prevention of CHD in primary care

The recommendations refer to four main interventions: lifestyle advice, drugs to lower blood pressure, drugs to lower cholesterol levels and aspirin. Lifestyle advice includes advice on smoking cessation, dietary advice (on obesity, a cholesterol lowering diet, and salt) and advice on alcohol consumption. (Table 2)

Table 2: Joint British recommendations criteria for treatment

Intervention	Treatment criteria
Lifestyle advice	All patients
Aspirin	Age >50 and five-year CHD risk >15%
Drugs to lower blood pressure	Blood pressure ≥160/100 mm Hg and any risk level Five-year CHD risk >15% and blood pressure ≥140/90 mm Hg
Drugs to lower serum cholesterol	Total cholesterol ≥9 mmol/l (any risk level) Five-year CHD risk >15% and total cholesterol ≥5.0 mmol/l

Source: Joint British Recommendations on prevention of CHD in primary care

Follow-up of patients on treatment

Patients on treatment should be followed up at least twice yearly.

Weaknesses of the joint British recommendations

Despite the fact that they combine guidelines on a number of treatments, the authors of the recommendations perpetuate a number of failings of previous guidelines. Their very title indicates that they consider the effects of treatment on CHD but not on CVA. As a result, treatment decisions are based on CHD risk rather than CVD risk. This is an incomplete assessment of the benefits of intervention. However the practical effect of using CHD risk rather than CVD risk is not great as the two measures of risk correlate closely.

Although in large part the decision to treat is guided by CHD risk, the guidelines only adopt this approach to a limited extent. They continue to recommend treatment of persons with blood pressure over 160/100 mm Hg even if they are at low risk of CHD. They also continue to recommend treatment of persons with cholesterol levels over 9.0 mmol/l even if they are at low risk of CHD.

The guidelines also take no account of resources and make no attempt to target intervention on the basis of resources. As a result they recommend primary care teams to screen all adult patients at least five-yearly. This may be unrealistic. They also recommend treating virtually all patients at greater than 15% five-year CHD risk, advising that this should be extended to all those at 7.5% five-year CHD risk as resources permit. This may also be unrealistic. However as the fact that this may be unachievable is not acknowledged, the guidelines give no advice on which preventive activities to prioritise.

Government policy: the National Service Framework for prevention of CHD

Until recently, bodies representing health professionals produced recommendations for CVD prevention. Unsurprisingly, their recommendations paid little attention to implementation strategies or resource implications, as these were not the concern of professional bodies. This changed with the publication of the National Service Framework for Coronary Heart Disease (NSF-CHD) by the UK government in 2000.¹⁴⁶

Chapter 2 of the NSF-CHD aims “to set out how primary care can best help people with clinical evidence of coronary heart disease (CHD) and others at high-risk of developing heart disease to reduce their risk of death, heart attack, heart failure or

other manifestations of CHD.”¹⁴⁶ The NSF-CHD is the first attempt to devise a comprehensive strategy for CHD prevention in the UK. It adopts a coherent approach to CHD prevention; it discusses identification strategies, interventions and follow-up of patients on treatment. Its recommendations for primary prevention of CHD in primary care are summarised below.

The approach of the NSF-CHD

The NSF-CHD adopts a utilitarian perspective. It endorses the concept of targeting those most likely to benefit from prevention – because this is more cost-effective – and clearly identifies those at highest risk as most likely to benefit. (Box 1) Consistent with this approach, the NSF-CHD recommends first identifying and treating persons with clinical evidence of ischaemic vascular disease and then identifying and treating persons at greater than 30% ten-year risk of CHD without clinical evidence of ischaemic vascular disease. These recommendations are encapsulated in two standards (Box 2).

Box 1: Rationale of the NSF-CHD.

The people likely to benefit most from these treatments are those at greatest risk of a cardiovascular event. These are also the people in whom treatment is most cost-effective. People, who have already had a heart attack, have angina or who have undergone coronary revascularisation are at particularly high-risk. **Identifying and treating those at greatest risk is one of the highest priorities of this NSF.**

Source: Chapter Two - Preventing coronary heart disease in high-risk patients. National Service Framework for Coronary Heart Disease.

Box 2: Objectives of chapter 2 of the NSF-CHD.

Standard three

General practitioners and primary care teams should identify all people with established cardiovascular disease and offer them comprehensive advice and appropriate treatment to reduce their risks.

Standard four

General practitioners and primary health care teams should identify all people at significant risk of cardiovascular disease but who have not yet developed symptoms and offer them appropriate advice and treatment to reduce their risks.

Source: Chapter Two - Preventing coronary heart disease in high-risk patients. National Service Framework for Coronary Heart Disease.

Identification strategy

The NSF-CHD recommends a systematic (rather than an opportunistic) approach to patient identification. It suggests that high-risk patients should initially be sought among patients with diagnoses of diabetes and hypertension. (Box 3) However in a somewhat contradictory recommendation it is suggested that new patients are offered lifestyle checks and blood pressure estimation. Furthermore the example of a protocol

in the appendix requires all adults over 16 to be interviewed (to find out family history of CHD, smoking and level of physical activity) and have their blood pressure measured.

Box 3: Recommended strategy for identifying and treating patients.

Use a systematic approach for:

- Identifying people at high-risk of CHD
- Identifying and recording modifiable risk factors of people at high-risk of CHD
- Providing and documenting the delivery of appropriate advice and treatment and offering regular review to people at high-risk of CHD.

Source: Chapter Two - Preventing coronary heart disease in high-risk patients. National Service Framework for Coronary Heart Disease.

The decision to treat and the treatment strategy

The decision to treat is based primarily on an assessment of each individual patient's CHD risk and whether they meet specific criteria for treatment. Four interventions are recommended for patients at high-risk of CHD. (Box 4) However these interventions are not prioritised in terms of their cost-effectiveness. It is advised that most patients on antihypertensives should be treated with thiazides or beta-blockers.

Box 4: Interventions recommended in the NSF-CHD for patients without ischaemic vascular disease.

People without ischaemic vascular disease

- Smoking cessation advice & Nicotine Replacement Therapy
- Lifestyle advice (exercise, diet, alcohol)
- Antihypertensive treatment to maintain BP <140/85 mm Hg
- Statins and dietary advice to lower cholesterol by 30% or to below 5 mmol/l
- Meticulous blood pressure and glucose control in patients with diabetes

Source: Chapter Two - Preventing coronary heart disease in high-risk patients. National Service Framework for Coronary Heart Disease.

Follow-up of patients on treatment

It is recommended that care be provided systematically rather than opportunistically - for example in structured, nurse-led clinics.

Problems with the NSF-CHD

While the NSF attempts to map out a comprehensive and cost-effective prevention strategy, it fails in a number of respects.

- It fails to explicitly consider the resource implications and health benefits of following its recommendations in a typical practice population.

- It fails to consider the interaction between the three steps in CVD prevention. It is therefore not clear whether the recommended strategy approach to identification, treatment and follow-up is indeed the most cost-effective.

History of the health economics of cardiovascular disease prevention

The first economic analyses of cardiovascular disease prevention are simple cost-effectiveness analyses of clinical trials. These generally compare a preventive intervention with a placebo.

Modelling studies – early

Antihypertensive treatment

One of the earliest economic analyses of CVD prevention was published in 1978.¹⁴⁷ This used data from the Framingham study to estimate benefits and made assumptions about costs. Results were reported as costs per life year gained. It concluded that the cost-effectiveness of antihypertensive treatment was sensitive to age, sex, initial blood pressure and achieved blood pressure. Overall, antihypertensive treatment was found to be more cost-effective in men and in those with higher blood pressures. In women antihypertensive treatment became more cost-effective with age and in men it became less cost-effective with age. The authors used this finding to recommend levels of blood pressure at which treatment should be started in men and women of different ages: with lower thresholds in older women and in younger men. The finding of declining benefit (and increasing cost per life year gained) in older men is a reflection of the method used to estimate benefit. The blood pressure coefficients used to estimate benefits decline with age. However subsequent studies have shown that the relative risk reduction with treatment does not. Nevertheless the paper is remarkable for using economic analysis to derive criteria for clinical treatment, although it is apparent from the discussion that some of the audience were not ready for such a radical approach.¹⁴⁸

A decade later an economic analysis of stroke prevention through antihypertensive treatment was published.¹⁴⁹ This estimated benefits using the relative risk reductions for CVA cited in a systematic review. At the time it was unclear whether antihypertensive treatment reduced risk of CHD. It was observed that the cost per life-year gained would be lower in men and in older patients.

Analysis of the effects of CVD prevention policies in the USA was given a considerable boost with the development of the Coronary Heart Disease Policy Model.¹⁵⁰ This simulation model combines a number of sub models. A demographic-

epidemiologic model describes the US population, with an appropriate distribution of CVD risk factors and incidence of CHD. A bridge model describes the immediate outcome of CHD events in the first 30 days. A disease history model describes the long-term outcome of CHD events (increased risk of subsequent CHD events). This model could be used to predict the effects of population interventions or treatments. This model was used to analyse the cost-effectiveness of alternative antihypertensive treatments.¹⁵¹ The analysis concluded that thiazides and beta-blockers were the most cost-effective first-line drugs, largely reflecting their lower cost. It also found that even small changes in quality of life as a result of treatment would eliminate the benefits of antihypertensive treatment.

Cholesterol lowering treatment

Early cost-effectiveness analysis of the lipid-lowering therapy in men concluded that it was more cost-effective (cost per life year gained) in younger men and in men with additional risk factors.¹⁵² However this analysis used the Framingham cholesterol coefficients – which decline with age – to estimate benefit.

An early modelling study of the effects of simvastatin predicted it would be more cost effective than cholestyramine.¹⁵³ It also suggested that the cost per life year gained was sensitive to age, sex and initial cholesterol level: with costs lowest in men aged 40 with the highest cholesterol levels and higher in women, older persons and those with lower cholesterol levels.

Modelling studies – 1990s

Antihypertensive treatment

Further studies investigated the cost-effectiveness of antihypertensive treatments in the 1990s. Jonsson's analysis in 1994 confirmed the findings that the cost per life year gained varied by sex, age, pre-treatment blood pressure and choice of drug. Older drugs (thiazides and beta-blockers) were more cost-effective than newer drugs (Ca blockers and angiotensin converting enzyme inhibitors).¹⁵⁴ Treatment of older men with higher blood pressures was more cost-effective than treatment of younger women with lower blood pressures. This author also carried out an incremental cost-effectiveness analysis. This found the incremental cost per event prevented by prescribing low-cost drugs to a patient without previous treatment was lower than that

of switching a patient on low-cost drugs to high-cost drugs. This finding has been confirmed in subsequent analyses.¹⁵⁵

A Swedish simulation model was developed in 1991.¹⁵⁶ This was used to analyse the cost-effectiveness of antihypertensive treatment using thiazides and beta-blockers.¹⁵⁷ It used the Framingham equations to estimate risk and the relative risk with treatment to calculate benefit. The analysis found that the cost per life-year gained fell with age. In related publications the same author reported that while the treatment of moderate hypertension (diastolic blood pressure >90 mm Hg) is cost-effective in persons aged 45 and over, treatment of mild hypertension (diastolic blood pressure 90 to 94 mm Hg) in younger women was not cost-effective.¹⁵⁸ This analysis also concluded that newer (high-cost) antihypertensives might be cost-effective in patients in whom low-cost antihypertensives were contraindicated.

The incremental cost-effectiveness of a lower blood pressure target in diabetic hypertensives was evaluated using a Markov model.¹⁵⁹ This used the Framingham equation to predict absolute risks of treatment but used relative risks associated with antihypertensive treatment to calculate benefits. It concluded that the lower blood pressure target was cost-effective. A similar analysis based on the findings of the UK Prospective Diabetes Study reached similar conclusions.¹⁶⁰

A cost-effectiveness analysis in Catalonia concluded that age, sex, choice of drug and blood pressure were independent predictors of cost-effectiveness.¹⁶¹ Antihypertensive treatment was more cost-effective with older (low-cost) than newer drugs, in men than women, with higher blood pressures and in patients aged 50 to 59 (rather than younger patients).

Cholesterol lowering treatment

The Coronary Heart Disease Policy Model was used to calculate cost-effectiveness of lovastatin.¹⁶² This demonstrated that cost-effectiveness was sensitive to age, sex, cholesterol level and smoking status. In primary prevention lovastatin was most cost-effective in men aged 55 to 64 with adverse risk profiles. It was least cost effective in young women. This study incorporates two interesting features. Firstly it makes use of incremental cost-effectiveness analysis to demonstrate that increasing doses of lovastatin in secondary prevention are much less cost-effective. Secondly it examines the cost-effectiveness of cholesterol lowering in secondary prevention patients whose

cholesterol lies below the usual treatment threshold (at the time). This is sometimes more cost-effective than treating those with higher cholesterol levels.

A study based on a different model analysed the cost-effectiveness of lovastatin in men and women aged 35 to 55.¹⁶³ This study also used the cholesterol coefficients in the Framingham equations to predict benefits. It found that cost-effectiveness is strongly related to overall CVD risk, with treatment most cost effective in higher risk men aged 55 and least cost-effective in lower risk women aged 35.

The practice of using the Framingham risk equations to predict benefit was challenged by an analysis of the results of the Lipid Research Clinics Coronary Primary Prevention Trial.^{110,164} This found that the Framingham equations underpredicted absolute risk and absolute benefits of treatment in this clinical trial. Nevertheless, in the absence of clinical trial data on statins, further Framingham based models of the potential cost-effectiveness of a number of statin therapies were published.¹⁶⁵

Cost per life-year gained with statins was estimated for a Canadian cohort aged 30 to 70 using a CHD prevention model.¹⁶⁶ This found that the cost per life-year gained was lower for men than women and for younger than older patients. However the cost-effectiveness was sensitive to inclusion of additional non-CHD costs of treatment.

Cost-effectiveness analyses of two studies of primary prevention strategies in the UK were published in the mid 1990s. One of these concluded that prevention through multiple risk factor intervention in primary care could be cost-effective.¹⁶⁷ Another, similar study observed that prevention was more cost-effective in older than younger persons and in men than women. Statins accounted for 70% of the cost of the strategy and the cost-effectiveness of the prevention strategy is therefore improved by restricting statin use to patients with cholesterol levels over 9.5 mmol/l.¹⁶⁸ However the overall effectiveness of this approach to primary prevention was sensitive to assumptions about the duration of observed lifestyle changes.¹⁶⁹

Studies throughout the 1990s and early 2000s have consistently found that the presence of pre-treatment CVD risk factors (higher CVD risk) increases the cost-effectiveness of statins.^{170,171,172} Not all of these analyses include the costs of identifying patients in their analysis. One analysis that did compared the cost-effectiveness of cholesterol screening and treatment in individuals stratified by levels

of CHD risk.¹⁷³ This concluded that screening and treatment was most cost-effective in patients at highest risk.

One incremental cost-effectiveness analysis concluded that the additional risk reduction resulting from further cholesterol lowering with higher doses of a statin was insufficient to justify the additional cost.¹⁷⁴ Comparisons between statins suggested that those with the greatest effects on lipids were the most cost-effective.^{175,176,177}

A review of cost-effectiveness analyses of statins made comparisons of the cost-effectiveness of statins with a number of other interventions.¹⁷⁸ Overall it concluded that the relationship between CHD risk and cost-effectiveness was well established and that in the US it would be cost-effective to use statins in anyone at 5% five-year CHD risk. A similar analysis in the UK came to the same general conclusions about the relationship between CHD risk and cost-effectiveness but set the CHD threshold for intervention at 15% five-year CHD risk.¹⁷⁹

Other interventions

Recent studies have also investigated the potential cost-effectiveness of folic acid supplementation.^{180,181} These have concluded that it is potentially cost-effective, justifying trials to investigate its effectiveness.

Multiple risk lowering interventions

Later analyses have attempted to compare cost-effectiveness of a range of treatments. A review of a range of preventive interventions pointed out that many cost-effectiveness analyses of statins ignored the costs of patient identification.¹⁸² It also confirmed the importance of pre-treatment risk as an indicator of cost-effectiveness. In hypertension it confirmed the importance of choice of medication as an indicator of cost-effectiveness. The review concluded that aspirin is cost-effective in secondary prevention. The authors caution against the use of cost-effectiveness league tables for comparing interventions, as ranking are sensitive to changes in the population studied and the underlying assumptions. Analyses of a number of different approaches to CHD prevention in Spain concluded that of four prevention programmes considered - smoking cessation, dietary intervention to lower cholesterol, antihypertensive treatment and statins – statins were the least cost-effective and smoking cessation the most cost-effective.¹⁸³ This analysis may have been over optimistic in its assumptions

about the effectiveness of dietary intervention to lower cholesterol levels. It also did not analyse the incremental cost-effectiveness of one programme over another.

A modelling study was carried out in 1996 to estimate the number of persons who would still be sufficiently high risk of CHD to justify use of a statin if non-lipid lowering treatments were first used to reduce their risk.¹⁸⁴ This study is interesting in one key aspect. It is the first study that acknowledges that just because a patient's lipid levels are high it does not follow that lipid lowering is the only (or most efficient) way to reduce their CHD risk. This point was taken up in the Effective Health Care bulletin's review of the evidence for the effectiveness of statins.¹⁸⁵ The bulletin compares the effectiveness of statins to advice on smoking cessation, dietary interventions (a Mediterranean diet or oily fish), aspirin and antihypertensive treatment. It concludes that all these interventions are more cost-effective than statins. It also confirms the importance of pre-treatment CHD risk and includes the cost of patient identification in its analysis. Very similar conclusions were reached in a later analysis of the cost-effectiveness of statins compared to a number of alternative interventions.¹⁸⁶ However neither analysis considered the incremental cost-effectiveness of statins in patients in whom other preventive treatment have already been used.

Further models have been developed to analyse the cost-effectiveness of CHD prevention policies.^{187,188} These simulate the development of CHD risk factors and of CHD in modelled populations. However neither has as yet been used to investigate the cost-effectiveness of preventive treatments or guidelines.

Modelling studies – overview

Modelling studies have provided considerable insights into the cost-effectiveness of interventions to prevent CHD. They have generally concluded that intervention is sensitive to pre-treatment risk and is more cost-effective in higher-risk patients. This means that it is necessary to analyse the cost-effectiveness of competing interventions in similar populations.

Analyses have been marred by a number of weaknesses. Many ignore the costs of identifying patients for treatment. Most consider treatments that affect only one risk factor. This means that they sometimes ignore more efficient means of reducing risk. Recent analyses have attempted to address this problem but these considered each

preventive intervention or programme in comparison to no intervention.^{183,185,186} This is an inappropriate analysis given that one intervention can be used to lower risk before another is considered.¹⁸⁴ A more appropriate approach is to consider the incremental costs of one programme over another.

Despite early attempts to use cost-effectiveness criteria to derive intervention criteria, modelling analyses generally take clinical criteria for intervention as a given. This means that criteria for antihypertensive treatment or lipid-lowering therapy – for example that they should always be offered to patients whose blood pressure exceeds a certain limit – are not questioned: even when they may be a poor indicator of cost-effectiveness.

Summary: evolution of cardiovascular disease prevention guidelines

The traditional approach to hypertension draws on a medical model of illness. The medical model categorises patients as either ill or not ill: the decision to treat follows the categorisation. Illness is determined by deviancy from the population norm. The goal of treatment is to restore individuals to that population norm.

This approach is reflected in early hypertension guidelines. Hypertension is seen as a quasi-illness, defined by deviation of the blood pressure from the population norm. The decision to treat follows directly from this diagnostic categorisation. Physicians have a duty to treat the ill but no such duty towards those who are not ill. The underlying basis for the treatment decision is therefore deontological or rule-based: if illness is present the physician has a duty to treat.

This approach has a number of implications. Since mean blood pressures are higher in older persons, the threshold for diagnosing (and hence treating) hypertension should logically be higher. Indeed, some guidelines from this era record reluctance to diagnose or treat hypertension in older persons. Because the reason for treating hypertension is to restore physiological normality, there is no need to quantify benefits of treatment. The fact that it is beneficial is considered sufficient.

Early hyperlipidaemia guidelines adopt a similar approach. Hyperlipidaemia is regarded as a quasi-illness and treatment is recommended on this basis. Paradoxically, this means that hyperlipidaemia is treated less frequently in older than younger patients.

Evolution of concepts of cardiovascular risk

The simple categorisation of patients by measurement of a single risk factor is refined in the 1980s to incorporate additional CVD risk factors. This small change in the guidelines represents a fundamental change in thinking. Identifying patients on the basis of their risk of CVD is an attempt to categorise patients according to their probability of benefiting from treatment. This means that the treatment decision is based on likelihood of benefit - the outcomes of treatment. The underlying basis for the treatment decision is therefore consequentialist (utilitarian). Consideration of patients' CVD risk therefore marks a shift away from a simple duty to provide treatment that is effective. At first this is a simple categorisation of patients as high-

risk or low-risk by the presence or absence of categorical risk factors (age over 55, diabetes, target organ damage). However the stage is set for a more sophisticated approach to estimating likelihood of benefit from treatment.

It is striking at this stage that so little attempt was made to incorporate epidemiological knowledge into guidelines. The science of CHD risk prediction was already decades old in the 1980s, nevertheless it took over a decade before formal estimation of CHD risk became a routine part of hypertension or hypercholesterolaemia guidelines.

Continuous risk and formal quantified estimates of benefit

There is an intrinsic contradiction in the use of categories to define risk. It is a fact that diabetics, men, persons with higher blood pressure and persons with higher cholesterol levels are at higher risk of CVD. But each factor alone is a poor predictor of risk. The adoption of risk tables and risk equations are more logical methods of predicting likelihood of benefiting from treatment. However this approach has an unexpected consequence. Once it is acknowledged that treatment should be targeted at persons who benefit most, it appears illogical to consider treatments that affect one risk factor separately from those that affect another. The emergence of guidelines that advocate formal risk assessment therefore is accompanied by moves to produce combined guidelines.

Present combined guidelines: half-way to utilitarianism

In addition to their increasingly utilitarian outlook present combined guidelines for prevention of CVD retain traces of their origins. The guidelines recommend treatment on the basis of likelihood of benefit – albeit indirectly through their focus on coronary risk. However they do not formally estimate likelihood of benefit from treatment.

The guidelines recommend treatment in the absence of formal consideration of health service resources. This means that they consider it appropriate to use a great deal more resources to prevent one CVD event with some treatments (statins) than with others (aspirin). This is clearly illogical from a utilitarian perspective.

The guidelines continue to recommend treatment on the basis of single risk factor thresholds. In effect this is because they still regard normalisation of a deviant risk factor as an important goal. This vestigial remnant of a disease or deviancy model of preventive treatment appears increasingly at odds with the evidence.

How the study develops these ideas

This study adopts a broadly utilitarian perspective with respect to CVD prevention. Within a utilitarian framework there are a number of weaknesses to the current approach to making recommendations about CVD prevention.

Weaknesses of current approaches to CVD prevention

Effectiveness: separation of different kinds of prevention

Firstly recommendations divide CVD prevention into arbitrary clinically defined categories, such as hypertensive or normotensive, high-risk or low risk. These categories are intended to reflect likely benefit from treatment. However risk is continuous not dichotomous and likely benefit from preventive interventions is also continuous. It is incorrect to regard only some individuals as likely to benefit from preventive interventions. The evidence suggests that most individuals could potentially benefit. The difference between high-risk and low-risk individuals is simply one of degree.

Secondly preventive interventions are sub-categorised according to the risk factor that they affect. Thus treatment of patients categorised as hypertensive is considered separately to treatment of patients categorised as hyperlipidaemic. This sub-categorisation leads to some odd conclusions. Hypertensive patients are only offered treatments that affect their blood pressure. Hyperlipidaemic patients are only offered treatments that affect their lipid levels. Because the preventive interventions belong to different categories, the cost-effectiveness of lipid lowering is not considered in a patient whose blood pressure is high, nor is the cost-effectiveness of blood pressure lowering considered in a patient whose lipid levels are high. As a result the cost-effectiveness of lipid lowering has not been compared to the cost-effectiveness of antihypertensive treatment in the same patients. From a utilitarian perspective this is not rational. Both interventions produce the same outcome (a reduction in the number of CVD events) and are therefore directly comparable. A rational CVD prevention policy would take account of such direct comparisons.

Thirdly prevention of CHD is often considered separately from the prevention of CVA. Again, from a utilitarian perspective this is irrational. Treatments that prevent CHD also prevent CVA. When determining cost-effectiveness, all of the health consequences of treatment should be considered.

Costs: failure to consider patient identification and assessment

Current recommendations do not consider the whole process of CVD prevention: identification, assessment, treatment and follow-up. Instead they either assume that patients' risk factor status is already known or that assessing their risk factors has no resource implications. This is patently untrue. Patients' CVD risk factor status must be assessed before their eligibility for treatment is known and this has resource implications. Conventional economic evaluations assess cost-effectiveness of treatment in isolation from arrangements for identification of patients and fail to consider different follow-up arrangements. This focuses attention on the cost-effectiveness of treatment, when there may be important improvements to prevention programmes by making changes to the process of patient identification and follow-up.

Costs: failure to consider resources

Current recommendations assume no limit to the number of patients who can be identified and followed up. This leads to the assumption that all patients who might benefit will be identified and treated. This is unlikely to be true. There are many patients eligible for treatment and many potential treatments. But CVD prevention is only one of many tasks for which primary care teams have responsibility. Staff time is not infinite and time spent identifying patients competes with time spent on patient follow-up.

3. Overview of methods

In this study I design a comprehensive prevention strategy in a series of steps. I construct a model of CVD prevention and use this to analyse current prevention policies. The selection and treatment strategies underlying current policies are then changed to obtain a prevention policy closer to the optimum. The model is then used to analyse the impact of these changes on costs and effects of the policy.

The focus of this model is on achieving cost-effective CVD prevention from the perspective of the primary care sector. The model does not consider patient preferences for CVD prevention. Patient preferences are clearly important. It is entirely possible for utility losses resulting from a preventive intervention to outweigh any utility gains from a reduced risk of CVD. However this is a separate question to that facing the primary care sector. The model does not consider equity, unless inequity is also inefficient. Again this is a separate question. Indeed it is difficult to address inequity before determining an efficient prevention strategy.

Constructing a model of cost-effectiveness in a population

The first step is to construct a model of the cost-effectiveness of CVD prevention in a population. The model is based on a population of individuals. Each individual has a series of characteristics (age, sex and CVD risk factors). Each individual can potentially be assessed and if they are found to be eligible, they can receive any of a number of preventive interventions. There are costs associated with assessing each individual. There are also costs associated with each preventive intervention that an individual receives. There are quantifiable benefits (reduced risk of CVD) associated with each preventive intervention that an individual receives.

The model calculates the health service costs of assessing each individual in the population selected for assessment. It also calculates the health service costs of treating each individual identified as eligible for a preventive intervention. Finally it calculates the health effects (reduced risk of CVD) in each individual receiving a preventive intervention. The total health service cost of a preventive strategy in the population is the sum of the cost in each individual. The total health effect of a preventive strategy is the sum of the health effects (reduced risk of CVD) in each individual receiving a preventive intervention. The cost-effectiveness of a prevention

strategy in a population is therefore the sum total of the costs of the strategy divided by the sum total of the benefits.

To provide this information the study:

- Estimates the costs of assessing each individual patient;
- Estimates the costs of preventive interventions in each individual patient eligible for treatment;
- Estimates the benefits of prevention in each individual patient eligible for treatment.

Sub-models

The model is built up from two principal sub-models. The first sub-model determines the optimum order in which to offer preventive interventions to individuals already known to be eligible for treatment. The second sub-model determines the optimum order in which to assess individuals in a population with the aim of finding those who are eligible for treatment.

Cost-effectiveness of preventive interventions

In the first sub-model I estimate the cost-effectiveness of preventive interventions in individual patients. The estimate of cost-effectiveness is built up from an estimate of the cost of each preventive intervention (costs of treatment and follow-up) and an estimate of the benefits of each preventive intervention. From this is derived a cost-effectiveness ratio for each preventive intervention in an individual patient. If there were resource scarcity, only the most cost-effective preventive intervention would be offered. If more resources became available, the next most cost-effective preventive intervention would be offered and so on. The preventive interventions are therefore ranked in order of their cost-effectiveness ratios. This is the order in which they will be considered within a preventive strategy.

Cost-effectiveness of selection strategies

In the second sub-model I determine the cost-effectiveness of strategies for patient identification in a model population. The starting point for this is a population of individuals eligible for inclusion in a primary prevention programme. Each individual patient has an age, sex and risk factor characteristics: it is therefore possible to determine whether or not they are eligible for each preventive intervention. I then determine the costs associated with assessing each individual's risk factor status. I can

then calculate the costs of assessing 50, 100 or 200 selected individuals within the population and calculate the number of individuals that would be identified as eligible for treatment from that 50, 100 or 200. Knowing those individual's individual CVD risks, it is also possible to calculate the total number of CVD events expected in patients identified as eligible for treatment: this is the sum of their individual CVD risks. From this I can calculate the total cost per eligible patient identified and the total cost per CVD event identified (in a treatable patient). These two cost-effectiveness ratios are measures of the efficiency of selection strategies. They can be used to assess the cost-effectiveness of a number of different patient selection strategies.

There are many different ways of selecting patients to assess within our population. Any given selection strategy means that patients within the model population are selected for assessment in a particular order. For a number of selection strategies the order in which patients are selected is modelled. This allows us to investigate the efficiency of these selection strategies. We do this by calculating the costs and number of CVD events (in treatable patients) in the first 50, 100 or 200 individuals within the target population. We can therefore construct a graph of the costs and total burden of CVD in patients identified as eligible for treatment when 50, 100 or 200 patients are assessed. This allows strategies to be directly compared and an optimum selection strategy to be identified.

Combining selection strategies with treatment strategies

I then combine the two sub-models. This means combining an optimum selection strategy with an optimum treatment strategy. I combine the total health service costs of assessing the first 50, 100 or 200 individuals within the target population with the total cost of interventions (treatment and follow-up) in those of the first 50, 100 or 200 eligible for a preventive intervention. This is the total cost of a prevention strategy in the first 50, 100 or 200.

The total benefit of a preventive strategy is the total reduction in CVD risk in each individual receiving a preventive intervention. The benefit in the first 50, 100 or 200 patients is therefore the sum of the individual reductions in CVD risk in each individual patient. From this I calculate the cost-effectiveness of a prevention strategy as it is used to assess and treat an increasing number of patients. Moreover the model

can be used to construct a number of graphs illustrating the costs and effects of assessing increasing numbers of patients under a number of alternative strategies.

Eliminating less cost-effective interventions and changing the treatment eligibility criteria

Once a model has been constructed it is possible to conduct further analysis of the prevention strategies. I first investigate the cost-effectiveness of prevention strategies that eliminate the less cost-effective interventions. In other words, I calculate the incremental costs and incremental benefits resulting from the addition of each further intervention to the overall policy.

I also investigate the factors that predict cost-effectiveness of interventions in individual patients. An understanding of these factors allows then informs changes in the treatment eligibility criteria so that they more closely reflect cost-effectiveness.

Sensitivity analysis

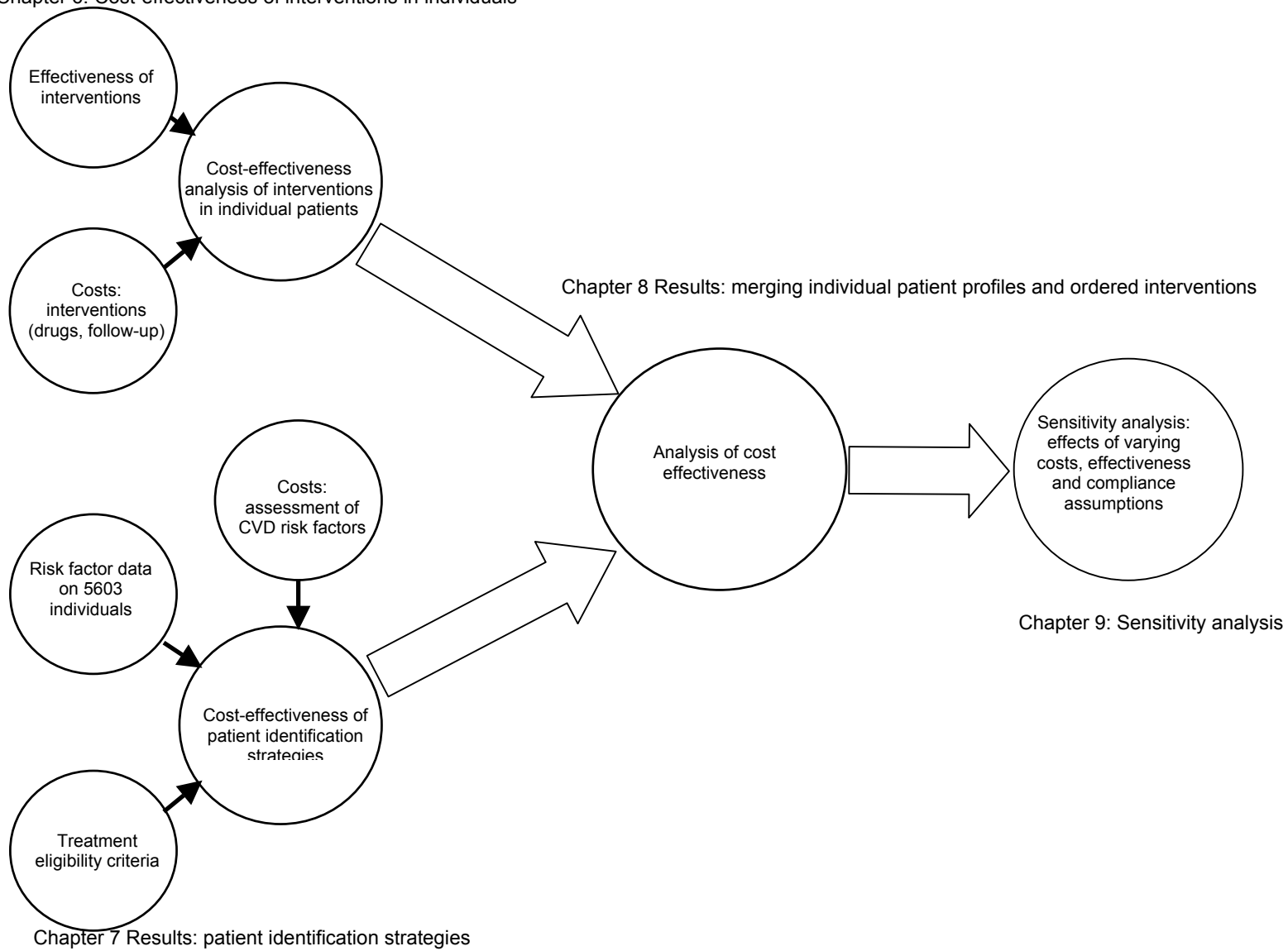
The final stage of the analysis is a sensitivity analysis. This investigates the overall accuracy of the model population in predicting CVD risk. It also investigates the implications of eliminating various interventions from the prevention strategy.

Overall structure of the method

Because the results of one analysis become the basic assumptions of further analysis, the method of constructing the model is somewhat complex. An overall map of the method is shown in Figure 6.

Figure 6: Relationship between different parts of the study

Chapter 6: Cost-effectiveness of interventions in individuals



4. Methods

A comprehensive strategy for CVD prevention requires an explicit model of the resource implications and health benefits of CVD prevention strategies. This has two basic components: analysis of the costs and effects of preventive interventions in individuals and investigation of different selection strategies in a population.

The most rational strategy for CVD prevention would assess individuals in a population in order of their capacity to benefit from intervention and to offer interventions in order of their cost-effectiveness. This means that when resources are scarce, the patients least likely to benefit from intervention are not assessed and the least cost-effective interventions are not offered.

Analysis of the cost-effectiveness of interventions provides information on the order in which treatments should be offered to individuals. Investigation of different selection strategies provides information on the order in which to assess individuals within a population. To create an efficient prevention strategy we combine information from both analyses. The third step of the process is therefore analysis of the cost-effectiveness of a complete prevention strategy. The final stage is an investigation of the cost-effectiveness implications of changing the treatment eligibility criteria underlying the prevention strategy.

Choice of a five-year time horizon

Throughout this analysis costs and benefits are considered over a five-year time horizon. One disadvantage of this is that a five-year time horizon may underestimate some of the costs avoided by prevention: these include reduced health service utilisation from reduced CVD. It may also underestimate some benefits of prevention: since persons who suffer CVD events are at high subsequent risk and prevention reduces the numbers of such persons.

On the other hand, a five-year time horizon reduces the number of assumptions required for the analysis. Since follow up in clinical trials is rarely for longer than five years, treatment discontinuation rates after five years are not known, adding to the uncertainty in estimating long-term costs or effectiveness.

As will be seen, costs and benefits of CVD prevention generally accrue at the same time therefore a five-year analysis is unlikely to be misleading. The most important question is therefore whether analysis over a five-year time horizon is sufficient to

improve prevention policy. As becomes clear throughout this study, such analysis is clearly sufficient for this purpose. More complex analysis may be justified, if it can result in further improvements in prevention policy.

Cost-effectiveness analysis of prevention in individuals (chapter 6)

In this part of the study I identify a number of preventive interventions. I then review the evidence for their effectiveness. For interventions with sufficient evidence of effectiveness I obtain an estimate of the relative risk on treatment and an estimate of the costs of the intervention. I then calculate a cost-effectiveness ratio for each intervention in an individual patient. The cost-effectiveness ratios are used to determine the cost-effectiveness rankings of each preventive intervention. This in turn informs the optimum order in which interventions should be offered to patients. The last part of this section, analyses the incremental cost-effectiveness of interventions offered in the optimum order.

At this stage in the analysis, interventions for which there is insufficient evidence of effectiveness and interventions that are dominated by other interventions (more costly and less effective) are eliminated.

Throughout the analysis I adopt an inclusive rather than a sceptical approach to possible preventive interventions. Any intervention with reasonable evidence of effectiveness is included. This is contrary to usual practice in the development of guidelines. However including interventions with relatively weak evidence allows us to assess their potential cost-effectiveness and hence their potential importance. This is important in determining research priorities. The effect of excluding interventions for which evidence is weakest is considered in the sensitivity analysis.

Evidence of effectiveness

Sources of evidence of effectiveness

In order to construct a model of effectiveness I need an estimate of the relative risks of CHD and CVA attributable to the intervention. In order to have a high degree of internal validity the estimate should be derived from high quality evidence. This means it should be derived from a systematic review of randomised controlled trials with the outcome measured in CHD and CVA events prevented. If no systematic review is available, evidence from a single randomised controlled trial with the outcome measured in CHD and CVA events prevented will suffice. If no randomised controlled trial with outcome events measured is available, evidence of effectiveness may be imputed from the likely effects on clinical outcomes of changes in proxy measures (cholesterol levels or blood pressure).

In order to have a high degree of external validity (generalisability) estimates of effectiveness should be based on studies in a patient group comparable to the population of interest in this study. This means that studies should be of primary prevention. However if evidence of effectiveness in primary prevention is not available I have substituted evidence of effectiveness in secondary prevention or specific sub-groups of patients. For some interventions – in particular dietary interventions – direct evidence of effectiveness in preventing clinical outcomes is not available. However there may be substantial evidence of changes in proxy outcomes that are important predictors of clinical outcomes (cholesterol levels). In these cases I have indirectly derived an estimate of effectiveness, using the effects of the intervention on proxy outcomes to estimate its likely effects on clinical outcomes. Table 3 shows the hierarchy of evidence used in estimating benefits of treatment. Where possible I have used evidence fulfilling the criteria shown in the top left box.

Table 3: Hierarchy of evidence of effectiveness used in this study

Type of study Patients & outcomes	Outcome data in similar patient group	Outcome data in different patient group	Proxy outcome measures – imputed effectiveness
Systematic review of randomised controlled trials	Very high internal validity Very high external validity	Very high internal validity Moderate external validity	Very high internal validity Fair external validity
Single randomised controlled trial	High internal validity Very high external validity	High internal validity Moderate external validity	High internal validity Fair external validity

Search protocol

In the first instance I sought systematic reviews and randomised controlled trials in the following databases in the stated order. I first searched the Cochrane Library,

including Cochrane Reviews; I then searched the Database of Abstracts of Effectiveness, the Controlled Trials Register and the Health Technology Assessment Database.¹ The NHS Centre for Reviews and Disseminations database was searched next.² If these two search engines did not yield sufficient controlled trials or systematic reviews I carried out a Medline search. If necessary, I obtained clinical trials used in systematic reviews or meta-analyses.

Relative risk on treatment

In most cases there is no evidence that the relative risk associated with a preventive intervention differs in patients with different characteristics. The absolute reduction in CVD risk is therefore the product of the pre-treatment risk and the proportional risk reduction (Proportional Risk Reduction = 1 – Relative Risk) with treatment.

Estimated relative risk on treatment

The relative risk associated with a preventive intervention is informed by evidence from clinical trials. However, there is not direct evidence of the effectiveness of every possible intervention in every possible type of patient in every conceivable combination of treatment. Therefore some questions cannot be answered directly by reference to clinical trials. For example is more intensive treatment more effective than less intensive treatment? Are all drugs of a particular class equally effective? Are the effects of treatment B independent of those of treatment A? If not, there will be no additional benefit to combining treatments. Evidence of effectiveness therefore also needs to be informed by a theory about effectiveness. For each of the interventions considered I will outline an explicit theory of its effectiveness from which can be derived estimates of the relative risk associated with that intervention. This can then be used to derive an estimate of the effectiveness under a wide range of possible circumstances.

Confidence intervals of relative risk on treatment

Each relative risk has an associated 95% confidence interval. Where possible this is derived directly from published data. However in some cases the effects of treatment have been calculated indirectly and a 95% confidence interval has been estimated or a notional 95% confidence interval cited. Treatments that might cause net harm – if the 95% confidence interval includes a relative risk of 1.0 – are eliminated at this stage.

¹ The Cochrane Library, Issue 1, 2003. Oxford: Update Software.

² <http://144.32.228.3/scripts/WEBC.EXE/NHSCRD/start>

Costs of preventive interventions

Since the purpose of the model is to design a strategy for the optimum use of health service resources, I consider resource implications from a health service perspective. Since I am concerned with prevention of CVD, I measured benefits as CVD events prevented. Costs and benefits are considered over a five-year time horizon. Costs are discounted at 6%.

Each intervention is associated with a set of costs. These include the costs of drugs, staff costs associated with follow-up clinic visits or ongoing dietary advice, and the costs of laboratory tests. These costs of follow-up are assumed to be similar from one patient to another, irrespective of other patient characteristics. For example the follow-up costs for a patient whose blood pressure is 160/100 mm Hg are the same as those for a patient whose blood pressure is 150/90 mm Hg.

Incremental costs of additional treatments

Patients are often eligible for more than one intervention. Since patients receiving one drug treatment do not need to be followed up more frequently than patients receiving two drug treatments, this means that in some cases there are economies associated with multiple interventions. For example, the incremental costs of adding further antihypertensive treatment to initial antihypertensive treatment are therefore only the costs of the drug itself, because the patient is already being followed up and having appropriate laboratory investigations. Incremental costs of treatment calculated for each patient must therefore take account of whether the patient is already being followed up or having laboratory investigations.

Cost-effectiveness of preventive interventions

I estimate the cost-effectiveness of preventive interventions by dividing the cost of a preventive intervention in a patient by the absolute risk reduction with that preventive intervention. There are two reasons for this step in the analysis: to eliminate interventions that are not cost-effective and by determining cost-effectiveness rankings to determine the optimum order in which to offer preventive interventions.

Average cost-effectiveness of individual interventions

At this stage I considered each intervention in a single patient, as if it were the only intervention the patient received. The cost per CVD event prevented as the total five-year cost of the intervention and divided by the absolute reduction in five-year CVD

risk. The total cost of the intervention includes drug costs, staff costs and any investigations all discounted over five-years. The absolute reduction in CVD risk is the sum of the reduction in CVA risk and CHD risk.

In fact, in most cases the sum of CVA and CHD risk is slightly less than total CVD risk. The reason for that is that CVD risk includes risk of two important outcomes, heart failure and peripheral vascular disease, that are not included in either the CVA or CHD risk equations. In addition, there are no published estimates of the effects of preventive interventions on CVD events that are not CVA or CHD, although the preventive effect is likely to be similar to that for CHD. However, in practice heart failure and peripheral vascular disease are uncommon in the absence of CVA or CHD and the omission makes little difference to the calculation of benefits.

Elimination of some preventive interventions from the model

At this stage I eliminated any interventions where the confidence intervals include the possibility of net harm. I directly compared interventions that are direct substitutes – for example treatments that act through the same mechanism of action and therefore cannot be combined – and eliminated any dominated (more costly and less effective) interventions.

Ordering interventions by their cost-effectiveness

Having calculated the cost per CVD event prevented, it is possible to rank the interventions in order of their cost-effectiveness. The cost-effectiveness rankings are used to derive the order in which treatments should be offered in the context of a comprehensive CVD prevention policy.

Sensitivity analysis of cost-effectiveness

It is beyond the scope of this study to model every conceivable range of effectiveness and every conceivable range of costs in every possible intervention.³

Instead, for each preventive intervention I carried out a sensitivity analysis using the upper and lower confidence limits of the relative risk. I also varied the cost of each intervention to determine the threshold at which the cost-effectiveness ranking of one

³ Twelve interventions each have a mean and two confidence limits of estimates of relative risk: 36 estimates of effectiveness. Altering assumptions about effectiveness could therefore lead to dozens of different cost-effectiveness rankings, each ranking requiring a separate analysis.

intervention might change in relation to another. I also investigated the effects on cost-effectiveness of changing the patient's pre-treatment CVD risk level.

Incremental cost-effectiveness of preventive interventions

Up to this point I have investigated the cost-effectiveness of each preventive intervention as if it were the only intervention the patient received. The next step is to investigate incremental cost-effectiveness of the preventive interventions. Both the incremental cost and the incremental effect of an intervention are different when it is an additional intervention than when it is the only intervention the patient receives. Incremental and average cost-effectiveness therefore differ significantly.

Incremental costs

Because there are economies associated with multiple interventions, the incremental costs of an intervention may be affected by the fact that a patient is already receiving a preventive intervention. This means that the incremental cost of an intervention added to previous treatments may be lower than its cost given alone. For example the cost of clopidogrel treatment in a patient who is offered it as a first treatment includes the cost of the drug and the cost of follow-up visits. However as a patient on antihypertensive treatment is already being followed up, the cost of clopidogrel treatment in a patient who is already receiving antihypertensive treatment is just the cost of the drug.

Incremental benefits

Because the absolute risk reduction with an intervention is determined by pre-treatment risk, absolute risk reduction with an intervention is to an extent determined by previous interventions. Absolute reduction in CVD risk with additional treatment is smaller in a patient whose risk of CVD has already been lowered by previous treatments. For example, a statin has a slightly smaller effect on CVD risk in a patient already receiving antihypertensive treatment than a similar patient who is not.

Incremental cost-effectiveness rankings

Because both the incremental costs and the incremental benefits of any treatment are affected by whether it is being added to previous treatments or is being offered alone, it follows that the incremental cost-effectiveness of an intervention may differ from its average cost-effectiveness. It is therefore important to test whether the cost-effectiveness rankings derived in chapter 6 are robust when incremental cost-effectiveness is considered. The cost-effectiveness rankings determine the order in which treatment should be offered to individual patients.

Incremental cost-effectiveness in a natural population

One of the aims of the cost-effectiveness analysis is to rank the interventions in order of their cost-effectiveness. However the incremental cost-effectiveness analysis is carried out only for a hypothetical patient eligible for a wide range of interventions.

As will be seen, the incremental cost-effectiveness of a preventive intervention in a real patient is influenced by a number of characteristics. Firstly it is a function both of their pre-treatment CHD risk and CVA risk. Secondly it is a function of the extent to which he (or she) is eligible for other interventions. This makes prediction of cost-effectiveness in individuals somewhat more complex than in a theoretical individual eligible for all interventions. Within a natural population such as a GP list there are individuals at a wide range of pre-treatment CHD and CVA risks. Some of these individuals are eligible for many preventive interventions and some are eligible for only a few.

To test the cost-effectiveness rankings of interventions in real patients, it is important to determine cost-effectiveness in real individuals within a natural population. To do this I identify a natural population of individuals whose age, sex and risk factor status is known. I then determine from each individual's risk factor status whether they are eligible for the range of preventive interventions. Finally, assuming that treatments are offered in the order suggested by the previous analysis, I calculate incremental cost-effectiveness ratios for each intervention in each individual in the population.

Identifying a study population: the Health Survey for England 1998

The population to be analysed consists of adults aged 35 to 74 in the Health Survey for England.¹⁸⁹ The Health Survey for England 1998 was designed to provide an estimate of the prevalence and distribution of cardiovascular risk factors living in private households in the English population. It provides the best estimate of the prevalence and distribution of cardiovascular risk factors in the English population. As part of the original survey, all persons in sampled addresses were asked questions about demographic, social and personal health information. Anthropometric measurements, blood pressure and serum cholesterol measurements were requested.¹⁹⁰ In total the Health Survey for England includes 5603 persons aged 35 to 74, with complete risk factor profiles who are eligible for primary prevention.

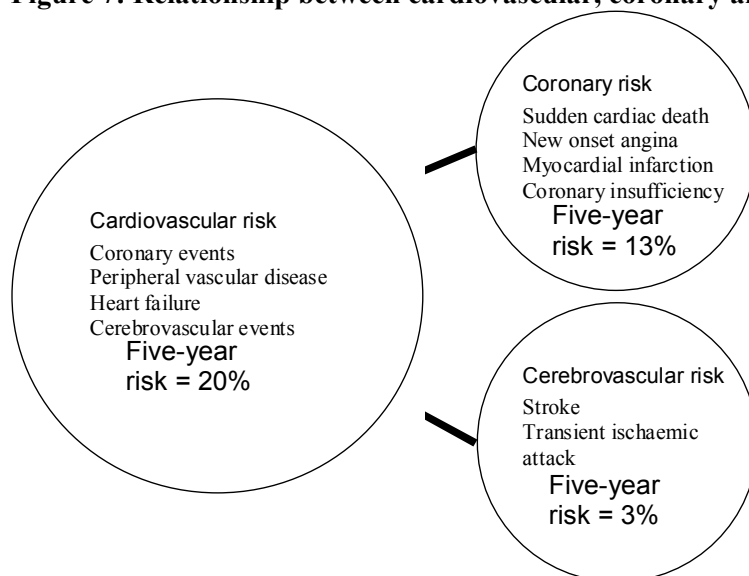
Framingham risk equations

Cardiovascular risk can be calculated for each individual in the Health Survey for England 1998 using the Framingham risk equations. There are three risk equations, each predicting the occurrence of different kinds of CVD events.

CHD risk equation

The Framingham coronary (CHD) risk equation predicts the occurrence of coronary events (myocardial infarction, new onset angina or cardiac death).²⁹ It requires information on age, sex, either systolic or diastolic blood pressure, total cholesterol to high-density lipoprotein cholesterol ratio, smoking status, diabetes status and whether there is electrocardiographic evidence of left ventricular hypertrophy. It has been validated in a range of populations.¹⁹¹

Figure 7: Relationship between cardiovascular, coronary and cerebrovascular risk



Five-year risk values are those of a 55-year-old male smoker with high blood pressure.

CVA risk equation

The Framingham CVA risk equation predicts risk of stroke (cerebrovascular accident or transient ischaemic attack).³⁰ It requires information on age, sex, either systolic or diastolic blood pressure, smoking status, diabetic status, whether the person is taking antihypertensive drugs, history of atrial fibrillation and whether there is electrocardiographic evidence of left ventricular hypertrophy.

CVD risk equation

The combined Framingham CVD risk equation predicts risk of any cardiovascular event (stroke, coronary event, peripheral vascular disease or heart failure).²⁸ Figure 7 shows the relationship between the three risk equations in a man aged 55, who

smokes, is not diabetic and has a total to HDL cholesterol ratio of 5.2 and a blood pressure 160/100 mmHg. His total five-year CVD risk is 20%, his five-year CHD risk is 13% and his five-year CVA risk is 3%.

Distribution of cardiovascular risk in the English population

I entered risk factor data from the Health Survey for England into an Excel spreadsheet. Using the three Framingham risk equations I calculated five-year CHD risk, CVA risk and CVD risk for each person included in the survey. Risks were calculated with systolic rather than diastolic blood pressures because systolic blood pressure is generally a better predictor of coronary risk than diastolic blood pressure.^{192,193}

Eligibility of patients for treatment

I determined the eligibility of patients for treatment using criteria derived from the joint British recommendations for prevention of CHD in primary care.¹⁴⁴ The eligibility criteria are summarised in Table 4. Because the joint British recommendations do not suggest treatment criteria for all possible interventions, it was necessary for me to adapt some of the recommendations.

Table 4: Treatment eligibility criteria derived from the joint British recommendations

Intervention	Treatment criteria	
	Non risk criteria	Five-year CHD risk threshold
Aspirin	Age ≥50	>7.5%
Antihypertensive treatment	Blood pressure ≥160/100 mm Hg	Any risk level
	Blood pressure ≥140/90 mm Hg	>7.5%
Simvastatin	Total cholesterol ≥9 mmol/l	Any risk level
	Total cholesterol ≥5.0 mmol/l	>7.5%

Source: Adapted from Joint British Recommendations on prevention of CHD in primary care

Determining treatment eligibility in individual patients

I created a list in an Excel spreadsheet of all individuals in the Health Survey for England 1998 for whom I had complete risk factor information. Each individual patient's record includes a number of personal characteristics: age, sex, blood pressure, cholesterol level, smoking history, diabetic history and whether or not they are on antihypertensive treatment. In addition each patient's record includes a number of derived characteristics: five-year CVD risk, five-year CHD risk and five-year CVA risk. (Appendix A Illustration 1)

I used a series of logical functions in Excel to categorise every patient's eligibility for each preventive intervention. For example, eligibility criteria for antihypertensive treatment are summarised in Box 5. This logical function summarises the statements

in Box 6. Using these logical functions, all patients are classified as either eligible or ineligible for treatment with aspirin, antihypertensives, advice on a Mediterranean diet or a statin.

Box 5: Logical function determining eligibility for initial antihypertensive treatment

=IF(\$AB5=1,0,IF(AND(OR(\$M5≥140,\$N5≥90),\$AO5>0.075),1,IF(OR(\$M5≥160,100),1,0)))

- \$AB5 refers to the whether the patient is already receiving treatment for high blood pressure (1 = yes, 0 = no)
- \$M5 refers to a cell containing the patient's systolic blood pressure
- \$N5 refers to a cell containing the patient's diastolic blood pressure
- \$AO5 refers to a cell containing the patient's five-year CHD risk

Box 6: Eligibility criteria in Box 5 stated in words

- If the patient is already on antihypertensive treatment, they are not eligible for treatment. Enter 0 (not eligible).
- If the patient is not already on antihypertensive treatment and either their systolic blood pressure exceeds 140 mm Hg or their diastolic blood pressure exceeds 90 mm Hg and their five-year CHD risk exceeds 7.5% they are eligible for treatment. Enter 1 (eligible).
- If the patient is not already on antihypertensive treatment and either their systolic blood pressure exceeds 160 mm Hg or their diastolic blood pressure exceeds 100 mm Hg they are eligible for treatment. Enter 1 (eligible).
- In all other cases. Enter 0 (not eligible).

Calculation of incremental cost-effectiveness

Incremental cost-effectiveness is calculated for each intervention in each individual using the method described earlier.

Testing the robustness of incremental cost-effectiveness rankings

This analysis means that it is possible to compare the cost-effectiveness of the first ranked (most cost-effective) intervention with the second ranked (next most cost-effective) intervention in every individual in a natural population who is eligible for both interventions. This tests the assumption that the first ranked intervention is consistently more cost-effective than the second ranked intervention in every individual. Similarly it is possible to compare the cost-effectiveness of the second ranked intervention with that of the third-ranked intervention, the third ranked intervention with the fourth and so on. Overall this tests the extent to which the cost-effectiveness rankings derived in the previous analysis.

Predictors of cost-effectiveness

Analysis of incremental cost-effectiveness in a natural population also makes it possible to investigate the factors that predict cost-effectiveness in individual patients. The aim is to determine whether CHD risk or CVD risk is a better predictor of benefit for each intervention.

CHD risk, CVD risk and cost-effectiveness

I plot the relationship between CHD risk and cost-effectiveness for each individual intervention. This is compared to the relationship between CVD risk and cost-effectiveness for each individual intervention. Either visual inspection or more formal analysis should indicate whether CHD risk or CVD risk is a better predictor of benefit for each intervention.

Patient identification strategies (chapter 7)

There are a number of steps in the investigation of the efficiency of patient identification strategies in a population. I identify a population of persons whose CVD risk is known or can be easily calculated. I then categorise individuals within that population as either eligible or ineligible for treatment with each of the potential interventions. I can then investigate the characteristics of a number of selection strategies for identifying patients.

Individual risk of cardiovascular disease in members of a study population

Identification of a study population

The study population consists of individuals aged 35 to 74, in the Health Survey for England 1998, for whom full risk factor information is available. This is the same study population as is used for the incremental cost-effectiveness analysis in a natural population.

Calculation of CVA, CHD and CVD risks

Risk of CVA, CHD and CVD are calculated for each individual in the study population, in the same way as is described in the previous section.

Determining treatment eligibility

Treatment eligibility criteria are those described in Table 4. Treatment eligibility is determined using logical functions in Excel in the same way as described in the previous section.

Calculation of default risk factor values

Some of the selection strategies will use prior estimates of an individual's CVD risk. These prior estimates are derived from some known characteristics (age and sex) and some risk factors that may be unknown at the time of making the prior estimate of CVD risk. A number of potentially unknown factors are categorical: diabetic status, smoking status, whether the individual is taking antihypertensive medication and whether or not they have a history of CVD. Other potentially unknown risk factors are continuous variables: blood pressure and cholesterol level. When a person's risk factor status is unknown, I substitute a prior estimate of their most likely risk factor status. I generated prior estimates of each risk factor from the Health Survey for England 1998.

Prior estimates of categorical risk factors

At all ages, non-diabetics outnumber diabetics. At all ages, non-smokers outnumber smokers. At all ages, men and women who do not have CVD outnumber those who do have CVD. At all ages, persons who are not receiving antihypertensive treatment outnumber those who do. In the absence of complete information, our prior estimate should therefore be that our patient is a non-smoker, non-diabetic, has no history of CVD and is not receiving antihypertensive treatment.

Prior estimates of continuous risk factors

The best prior estimate of a patient's blood pressure is that it is average for an individual of their age, sex and risk factor status. Similarly for cholesterol levels, a best prior estimate is that a patient's total cholesterol to HDL cholesterol ratio is average for an individual of their age, sex and risk factor status. In other words, I use the patient's other characteristics to predict their most likely blood pressure and cholesterol levels.

To determine these average values, I assigned each individual to a category defined by their age (in ten year bands), sex, smoking status, diabetic status, whether they had a history of CVD and whether they were already receiving antihypertensive treatment. There are eight age categories (16 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84 and 85 or over) and five binary categories: sex, smoking status, diabetic status, history of CVD and antihypertensive treatment. In total this means patients are assigned to 256 ($8 \times 2^5 = 256$) different categories. Using data from the Health Survey for England I calculated the mean blood pressure and total cholesterol to HDL cholesterol ratio for each of these 256 categories.

Strategies for the identification of eligible patients

Strategies for the identification of patients select a number of patients to undergo full clinical assessment. Strategies either select patients for assessment at random; select them because they have are diabetic or on antihypertensive drugs; or select patients on the basis of a prior estimate of their CVD risk.

Patient assessment involves making three clinical measurements of blood pressure and cholesterol level. Any patient who is eligible for at least one treatment on the basis of these three measurements is classified as “test positive”. If they are eligible for treatment on the basis of their true blood pressure and cholesterol level they are designated a “true positive”. It is straightforward using a Pivot Table analysis in Excel to identify how many true positives would be identified using each strategy and to determine the total CVD risk in those identified as true positives.

Traditional strategies for prioritising individuals in a population for assessment

Two traditional approaches to CVD risk assessment are recommended by two distinct UK guidelines. The National Service Framework suggests that primary care teams prioritise those with diabetes and those already receiving antihypertensive treatment before assessing all remaining adults. The joint British recommendations suggest that all patients undergo an initial assessment of CVD risk factors including a single measurement of blood pressure and a single measurement of cholesterol levels. Their CHD risk is estimated from this initial assessment and decisions about further assessment or treatment follow their CHD risk. Both these traditional approaches rely on obtaining a clinical estimate of risk.

Novel strategies for prioritising individuals in a population for assessment

An ideal strategy would prioritise patients for assessment in order of their capacity to benefit from preventive interventions. As will be seen from discussion of the effectiveness of preventive interventions, CVD risk is a strong predictor of the benefits of treatment. Although we do not know an individual’s CVD risk before they have undergone assessment, knowledge of an individual’s age, sex and medical history is sufficient to calculate a prior estimate of CVD risk, based on incomplete risk factor information. Therefore knowledge of an individual’s age, sex and diabetic status gives us some information with which to prioritise patients for CVD risk assessment. Knowledge of additional risk factors, for example smoking status, blood pressure or cholesterol levels, can be used to refine the prior estimate of CVD risk and

hence refine the prioritisation. Depending on how much information is available, it is therefore possible to calculate a number of different prior estimates of CVD risk, based on increasing CVD risk factor information. These are explained in Table 5.

Table 5: Cardiovascular risk estimates used in the model.

Cardiovascular risk estimate	Age	Sex	History of CVD	Diabetes	Smoking status	Blood pressure	Total to HDL cholesterol
Age sex CVD	Known	Known	Known	Default	Default	Default	Default
Age sex CVD DM	Known	Known	Known	Known	Default	Default	Default
Age sex CVD DM cigs	Known	Known	Known	Known	Known	Default	Default
Age sex CVD DM cigs BP	Known	Known	Known	Known	Known	Known	Default
Age sex CVD DM BP	Known	Known	Known	Known	Default	Known	Default
True CVD risk	Known	Known	Known	Known	Known	Known	Known

In chapter 7 I investigate how knowledge of age, sex and diabetic status can be used to obtain a prior estimate of CVD risk. I then rank patients by their prior estimate of CVD risk and compare the rankings obtained using prior estimates of CVD risk with those obtained an estimate of CVD risk based on complete risk factor data.

Clinical assessment of cardiovascular risk

In clinical practice an estimate of CVD risk requires the estimation of age, sex, blood pressure, total cholesterol to HDL cholesterol ratio, smoking history, diabetic status and history of cardiovascular disease. Estimation of each of these factors is subject to error. Errors in the estimation of age and sex are likely to be negligible. Errors in the estimation of smoking history may be significant if patients underreport smoking. Errors in the estimation of diabetic status and history of CVD are also likely to be small. However errors in the estimation of blood pressure and total cholesterol to HDL cholesterol ratio are both finite and calculable. It should therefore be possible to estimate the effects of these errors on the estimation of CVD risk in clinical practice.

Blood pressure measurement error

A blood pressure reading is an estimate of the true mean blood pressure. The accuracy of the estimate depends on a number of factors, for example measurement technique, accuracy of equipment and patient anxiety. However, even if these factors are controlled, blood pressure is subject to biological variation from beat-to-beat, minute-to-minute and day-to-day. To minimise the effects of biological variation, it is recommended that an estimate of blood pressure should be based on the mean of at least three measurements.¹⁴⁴ Mathematically, the standard deviation of an estimate is inversely proportional to the square root of the number of blood pressure measurements on which it is based. The standard error of an estimate of blood

pressure based on the average of three measurements is 0.58 times that of an estimate based on a single measurement ($1/\sqrt{3} = 0.58$).

An estimate of between visit intra-individual variation in measured blood pressure was obtained from a meta-analysis of individual patient data from large randomised controlled trials of blood pressure treatment. A recent estimate of variation in intra-individual measurements of blood pressure concluded that systolic blood pressure has a coefficient of variation of 9% and diastolic blood pressure 8%.¹⁹⁴ This is somewhat smaller than the coefficient of variation derived from data on 159,000 individuals in the Hypertension Detection Program.¹⁹⁵ The coefficient of variation for diastolic blood pressure was cited as 11.4% to 16.6%.¹⁹⁶ I have used the former estimate because it is more recent and because it includes an estimate of coefficient of variation for both systolic and diastolic blood pressure. This degree of variability means that in a patient whose true mean systolic blood pressure is 120/80 mm Hg, an estimate of blood pressure based on a single measurement has a standard error of 10.8 mm Hg systolic (9% x 120 mm Hg) and 6.4 mm Hg diastolic (8% x 80 mm Hg). An estimate of blood pressure based on the mean of three measurements therefore has a coefficient of variation of 5.2% / 4.6% (systolic/diastolic) and a standard error of 6.2/3.7 mm Hg.

Estimating the effects of blood pressure measurement error

I assumed that blood pressure measurement errors were normally distributed. For each individual patient in the Health Survey for England 1998 I calculated a blood pressure error term. The error term has a mean of 0% and a standard deviation based on the coefficient of variation: 9% for systolic blood pressure and 8% for diastolic blood pressure. For each patient I then calculated three separate blood pressures with an error term. These are equivalent to the first, second and third clinic measurements. The clinic measurements are the sum of the true blood pressure and product of the error term and the true blood pressure. The relationship is illustrated for diastolic blood pressure in Box 7. Finally a mean of all three blood pressures is calculated, representing the mean of three blood pressure measurements.

Box 7: Relationship between measured blood pressure and true blood pressure

DBP_m	=	$DBP + E_{DBP} \times (DBP)$
E_{DBP}	=	within individual coefficient of variation for diastolic blood pressure (error term)
DBP	=	diastolic blood pressure
DBP_m	=	clinic measured blood pressure

Total cholesterol to HDL cholesterol ratio measurement error

A measurement of the total cholesterol to HDL cholesterol ratio is an estimate of the true total cholesterol to HDL cholesterol ratio. There are a number of estimates of biological variation in cholesterol levels. A review of 30 studies of biological variation concluded that coefficients of variation for total cholesterol and HDL cholesterol are 6.1% and 7.4% respectively.¹⁹⁷ A more recent estimate found coefficients of variation for total cholesterol and HDL cholesterol of 7.2% and 7.5% respectively.¹⁹⁸ As total to HDL cholesterol ratio is a more important predictor of risk, I used a direct estimate of variation in the ratio. This is based on a study that found a coefficient of variation of 6.8%.¹⁹⁹ In order to minimise the effects of biological variation, it is recommended that an estimate of the total cholesterol to HDL cholesterol ratio should be based on the mean of at least two measurements.¹⁴⁴ The coefficient of variation of an estimate based on three measurements is therefore 3.9% ($3.9\% = 6.8\% \times 1/\sqrt{3}$).

Estimating the effects of cholesterol measurement error

I assumed that cholesterol measurement errors were normally distributed. For each individual patient in the Health Survey for England 1998 I calculated a cholesterol error term with a mean of 0% and a standard deviation based of 6.8%. For each patient I then calculated three clinic measurements of cholesterol level and a mean cholesterol level based on these three clinic measurements.

Clinically estimated cardiovascular risk

Using the clinically estimated systolic blood pressures and total cholesterol to HDL cholesterol ratios I calculated a clinically estimated cardiovascular risk for each patient. This incorporates the degree of measurement error we would expect to find in a cardiovascular risk estimated on the basis of three blood pressure measurements and two cholesterol measurements.

Analysis of identification strategies

The aim of assessing members of a population is to identify those who can benefit most from preventive interventions. Those who can benefit most are those who are eligible for preventive interventions and at highest risk of CVD. There are therefore two measures of the effectiveness of an identifications strategy. The simplest is the total number of individuals identified as eligible for at least one treatment. However a more complete picture of effectiveness is the sum of individual CVD risks in patients

eligible for treatment. This is their total burden of CVD risk, an indication of the total number of potentially preventable CVD events.

Resource costs and cost-effectiveness of patient identification

The aim of an efficient patient identification strategy is to identify as much preventable CVD as possible within the available resources. It is therefore important to describe the relationship between resource costs and the total burden of CVD identified in patients eligible for treatment. The previous section explained how to calculate CVD identified in patients eligible for treatment. It is also necessary to identify the total costs of identifying CVD in patients eligible for treatment: the cost of implementing each patient identification strategy. The costs of implementing a patient identification strategy can be broken down into a number of elements. These are:

- The costs of selecting (or prioritising) patients for assessment.
- The costs of assessing the first selected patient's risk factor status.
- The costs of assessing the next selected patient's risk factor status – and so on until all patients have been assessed.

There are two elements to assessing a patient's risk factor status, clinical staff time and laboratory investigations.

Cost-effectiveness of identification strategies

The outputs of this analysis are the total cost of implementing a patient identification strategy; the total number of patients identified who are eligible for treatment; and the total burden of CVD identified in patients eligible for treatment. This can best be illustrated in graphical form. The X-axis illustrates the cost of selecting and assessing increasing numbers of patients under a particular patient identification strategy. The Y-axis illustrates the total burden of CVD identified in patients eligible for treatment under that strategy. This allows direct comparisons of the yield of different identification strategies implemented with equivalent resources.

Costs and effects of prevention in a model population (chapter 8)

Having analysed the incremental cost-effectiveness of different interventions and the incremental cost-effectiveness of different selection strategies, I can analyse the cost-effectiveness of a complete CVD prevention strategy. An optimum complete CVD prevention strategy combines the most cost-effective selection strategy and the most cost-effective interventions. In effect this means using the results of the previous analyses to determine the most cost-effective order in which to assess patients and combine this with the most cost effective order in which to offer interventions. To analyse the costs, health benefits and other characteristics of this strategy, we must investigate its effects in a model population.

The model population

The model population that will be used as a unit of analysis for a prevention strategy should be demographically similar to a typical English population. This means that it can be taken to be representative of the country as a whole. It should also be sufficiently large to produce stable results.

The original population of 5603 individuals aged 35 to 74 cannot be used at this stage of the analysis for two reasons. Firstly its demographic differs from that of the English population (Figure 9). Secondly, because calculating individual cost-effectiveness ratios on hundreds or thousands of patients requires considerable computing power, a population of 5603 is too large.

It is therefore assumed that CVD prevention will be carried out in eligible patients in a medium-sized group practice. This means modelling the cost and effects of prevention in 2000 to 2250 persons. This is because about 40% to 45% of the population are eligible for CVD prevention and a medium-sized group practice includes about 5000 persons (between two and three GP lists - 2000 registered patients per whole time equivalent GP).²⁰⁰

Number of persons eligible for CVD prevention in a population of 5000

The age-sex structure of the English population in 1998 is shown in Figure 8. A population of 5000 therefore includes 2288 persons aged between 35 and 74. Applying the prevalence of CVD from the Health Survey for England 1998 to this population indicates that 130 of these 2288 have CVD and 2158 are free from CVD. (Table 6) For the age-sex structure of the population to be equivalent to that of the

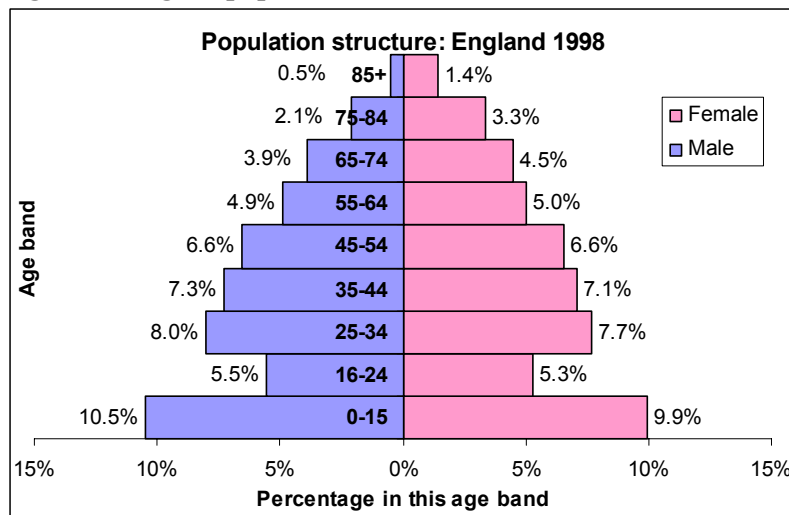
English population, numbers equal to those shown in Table 6 need to be sampled from each age-sex group. This can easily be carried out using an Excel spreadsheet to sample from our population of 5603 persons aged 35 to 74 free from CVD.

Table 6: Persons aged 35 to 74, with and without CVD in a population of 5000 in England

Age band	Male		Female	
	No CVD	CVD	No CVD	CVD
35-44	361	3	351	4
45-54	318	11	325	4
55-64	218	26	237	13
65-74	155	38	193	31
Total	1052	78	1106	52

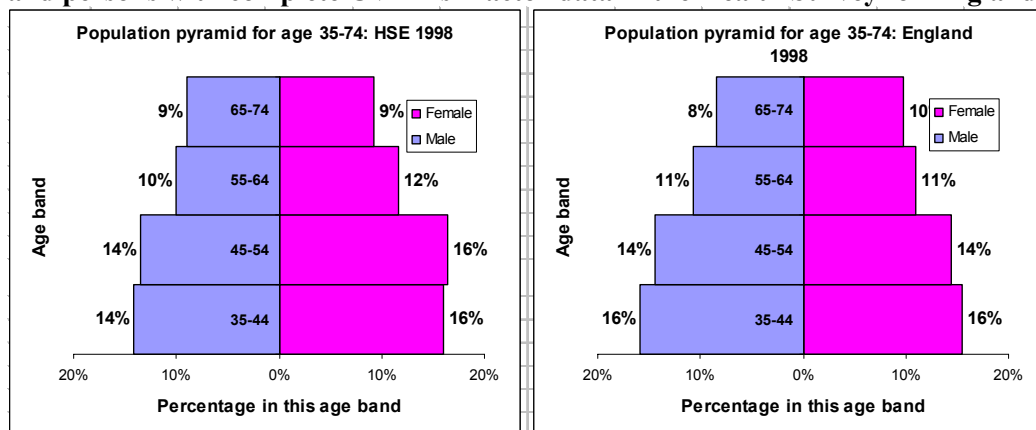
Source: Office of National Statistics 1998 and Health Survey for England 1998

Figure 8: English population structure 1998



Source: Office of National Statistics 1998

Figure 9: The population structure of persons aged 35 to 74 in the English population and persons with complete CVD risk factor data in the Health Survey for England 1998.



Source: Health Survey for England 1998.

Source of the model population

The model population will be drawn from the Health Survey for England 1998 because it is based on a representative sample of householders. However patients in

the Health Survey for England for whom complete risk factor data is available are not necessarily a representative part of the total sample. The population structure of the Health Survey for England therefore differs from that of the English population. A simple random sample of the individuals in the survey will not reflect a typical English population. (Figure 9) To take account of this, individuals are sampled proportionately from the appropriate age-sex strata.

Base-case cost-effectiveness analysis in the model population

In the base-case the cost-effectiveness of three distinct prevention strategies is analysed. Under these prevention strategies patients are identified in three different ways but eligibility for treatment is determined using traditional treatment criteria. The first identification strategy is that recommended by the joint British recommendations. This is essentially that all patients undergo at least a minimum risk factor assessment. The second identification strategy follows the NSF-CHD recommendations. These are that all patients undergo risk factor assessment but that those with diabetes and those on antihypertensive treatment are prioritised. The third identification strategy will be informed by the analysis of identification strategies in chapter 7.

Analysis of prevention strategies in the model population

Each individual in the model population has a series of characteristics. These are age, sex and cardiovascular risk factors. Each row in Excel represents a separate individual and each column lists one of that individual's characteristics. (Table 7)

Table 7: Illustration of characteristics of individuals in the model population

ID number	Sex	Age	Systolic BP	Diastolic BP	Smoking status	Total cholesterol	HDL cholesterol	Diabetes	ECG LVH	On BP drugs	IHDIS	CVD	Irregular pulse (AF)
146	Male	73	169	85	0	4.9	1.2	Yes	No	No	No	No	No
321	Male	68	143	81	0	7.8	1.2	Yes	No	No	No	No	No
2,181	Male	67	135	68	0	4.2	1.2	Yes	No	No	No	No	No
42	Male	66	152	70	1	6.4	1.2	Yes	No	No	No	No	No

Source: Health Survey for England 1998

True five-year CVD, CHD and CVA risk

For each individual patient I calculate a true five-year CVD risk, a true five-year CHD risk and a true five-year CVA risk. (Table 8) I use the true five-year CHD and CVA risks to calculate benefits of treatment.

Table 8: True five-year risks calculated for individuals in the model population

ID number	Five year CVD risk - TRUE	Five year CHD risk – TRUE	Five year CVA risk - TRUE
146	30.3%	16.2%	7.1%
321	27.0%	18.0%	3.9%
2,181	15.4%	8.2%	3.3%
42	36.7%	21.6%	6.6%

Source: Derived from Health Survey for England 1998

Clinically estimated risk factors

For each individual I calculate a series of clinically estimated blood pressures, each incorporating a degree of measurement error. These clinically estimated blood pressures clinically measured blood pressure on the first, second and third visits. In the same way I calculate a series of cholesterol estimations, incorporating a degree of measurement error and reflecting clinically measured cholesterol levels on the first, second and third visits. I use these clinically estimated blood pressures and cholesterol levels to calculate a clinically estimated CHD and CVA risk.

In clinical practice a patient’s true blood pressure, cholesterol level and risk are not known. The decision to offer a preventive intervention is made on the basis of clinically estimated risk factors and clinically estimated risk. To reflect this, I determine each patient’s eligibility for preventive interventions from their clinically estimated blood pressure, cholesterol level and CHD risk. An illustration of clinical estimates of blood pressure and cholesterol levels is shown in Table 9.

Table 9: Illustration of clinical estimates of blood pressure and cholesterol level for individuals in the model population

ID number	Clinical estimates of blood pressure								Clinical estimates of cholesterol levels							
	First visit		Second visit		Third visit		Mean of three visits		First visit		Second visit		Third visit		Mean of three visits	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Total	HDL	Total	HDL	Total	HDL	Total	HDL
146	171	86	183	90	169	78	174	85	4.8	1.2	4.6	1.2	5.1	1.2	4.8	1.2
321	146	80	142	80	142	83	144	81	8.1	1.2	7.3	1.2	8.1	1.2	7.8	1.2
2,181	142	75	123	65	131	65	132	69	4.2	1.2	4.2	1.2	4.1	1.2	4.2	1.2
42	153	74	156	66	155	66	155	68	6.6	1.2	6.7	1.2	6.5	1.2	6.6	1.2

Source: Derived from Health Survey for England 1998

Prior estimates of five-year CVD risk

In addition to clinical estimates of CHD and CVA risk, I calculate a number of prior estimates of CVD risk. These are estimates of CVD risk calculated from a combination of known risk factors and estimated (default) risk factors. The known risk factors are age, sex, diabetic status and antihypertensive treatment status. The estimated risk factors are smoking status, blood pressure and cholesterol levels. In total there are five prior estimates of CVD risk. These are illustrated in Table 10.

- First estimate: smoking status is known, blood pressure obtained from a single measurement taken at the first clinic visit and a default cholesterol level.
- Second estimate: smoking status is known, blood pressure and cholesterol level are both obtained from a single measurement of each taken at the first clinic visit.
- Third estimate: smoking status is known, blood pressure and cholesterol level are both obtained from the mean of three measurements of each taken at the first three clinic visits. This is a *clinical estimate* of CVD risk: an estimate derived from full clinical assessment.
- Fourth estimate: smoking status is known, default blood pressure and cholesterol level.
- Fifth estimate: default smoking status, blood pressure and cholesterol level.

These prior estimates of CVD are necessary to model the selection strategies that use a prior estimate of CVD risk to prioritise patients for cardiovascular risk assessment.

Table 10: Estimates of CVD risk derived from age, sex, diabetic and antihypertensive treatment status and following risk factor information

Patient ID number	Estimates of CVD risk derived from age, sex, diabetic and antihypertensive treatment status and the following risk factor information				
	Smoking history and clinical estimates of blood pressure or cholesterol			Smoking history*†	No additional information*†
	Mean of blood pressure and cholesterol level at three visits	Blood pressure and cholesterol level at first visit	Blood pressure at first visit*		
146	31.5%	30.5%	31.8%	25.4%	25.4%
321	27.3%	28.7%	21.7%	21.8%	21.8%
2,181	14.8%	17.2%	19.9%	21.1%	21.1%
42	38.1%	37.5%	33.2%	31.5%	20.4%

Source: Derived from Health Survey for England 1998

* Cholesterol level is derived from a prior estimate. † Blood pressure is derived from a prior estimate.

Prior estimates of five-year CHD risk

Finally I calculate a series of prior estimates of CHD risk using a combination of known risk factors and estimated risk factors in the same way as the prior estimates of CVD risk described above. In total there are two prior estimates of CHD risk. (Table 11)

- First estimate: smoking status is known, blood pressure and cholesterol level are both obtained from a single measurement of each taken at the first clinic visit.
- Second estimate: smoking status is known, blood pressure and cholesterol level are both obtained from the mean of three measurements of each taken at three separate clinic visits. This is a *clinical estimate* of CVD risk: an estimate derived from full clinical assessment.

These prior estimates of CHD are necessary to model eligibility for further assessment or for treatment. In some selection strategies, clinicians determine whether patients should undergo further assessment from a measurement of blood pressure and cholesterol (and an estimate of CHD risk) taken at the first clinic visit. In all strategies, clinicians determine treatment eligibility from a clinical estimate of CHD risk in combination with clinical estimates of blood pressure and cholesterol level (i.e. estimates based on the mean of three clinical measurements of blood pressure).

Table 11: Estimates of CHD risk derived from age, sex, diabetic and antihypertensive treatment status and following risk factor information

ID number	Blood pressure and cholesterol level at first visit	Mean of blood pressure and cholesterol level at three visits
146	16.1%	16.7%
321	19.3%	18.2%
2,181	8.9%	7.9%
42	22.2%	22.6%

Cost effectiveness in the first patient assessed

To model the costs of a prevention strategy I first determine the patient selection strategy. I then calculate the cost of clinically assessing the first selected individual within that population.

Treatment eligibility

From the clinical estimate of their blood pressure, cholesterol level and CHD risk, I then determine whether that individual is eligible for any preventive interventions. Eligibility is therefore based on the results of clinical assessment: clinically estimated level of CHD risk, the mean of three clinical measurements of blood pressure and cholesterol level. Eligibility therefore incorporates a degree of measurement error.

Costs of treatment and follow-up

I then calculate the costs of any preventive interventions for which the patient is eligible. These include drug costs, costs of consultations and laboratory costs associated with follow-up.

Benefits of treatment

Finally I calculate the benefits of each preventive intervention in this first patient and the total benefit resulting from all interventions in this first patient. Benefit is calculated as follows.

Pre-treatment risk of CHD before the first intervention is the patient's five-year CHD risk as calculated from their true risk factor status. This true five-year CHD risk does not incorporate any measurement error or estimates of risk factor status. Risk of CHD

after the first intervention is product of the patient's pre-treatment risk and the relative risk with the intervention. The benefit of the first intervention is the difference between pre and post treatment risk: the absolute risk reduction.

Pre-treatment risk of CHD before the second intervention is the patient's post-treatment risk of CHD after the first intervention. Risk of CHD after the second intervention is product of the patient's risk before the second intervention and the relative risk with the intervention. The benefit of the second intervention is the difference between pre and post treatment risk: the absolute risk reduction.

The incremental reduction in risk of CHD is calculated in the same way for each intervention. The incremental reduction in risk of CVA is calculated in a similar way: using the patient's true five-year CVA risk as their risk before the first treatment and the appropriate relative risks for CVA.

The total benefit for this individual is the sum total reduction in absolute risk of CHD and the sum total reduction in absolute risk of CVA minus the increased risk of major extra-cranial bleeding attributable to aspirin.

Cost-effectiveness in the first patient

The cost-effectiveness of the strategy in the first patient is the total cost of assessment, treatment and follow-up divided by the total reduction in CVD risk. This gives an actuarial cost per CVD event prevented.

Cost effectiveness in the second and subsequent patients assessed

Cost effectiveness is calculated in exactly the same way for the second patient. The costs of assessment are calculated. The patient's treatment eligibility is determined from clinical estimates of their risk factor status and risk. The costs of treatment and follow-up are calculated. The benefits of treatment are calculated. The cost-effectiveness of the strategy in the first two patients is the total cost of assessing, treating and following-up both patients divided by the total reduction in CVD risk in both patients. This process is repeated for every patient in the model population.

Measures of cost-effectiveness obtained from the model

Cumulative total cost and cumulative total benefit

The two main outputs of the model are the cumulative total cost and the cumulative total benefits of the strategy. These are presented in graphical form, with the cumulative cost of implementing the strategy in increasing numbers of patients on the

x-axis and the cumulative benefit of implementing the strategy on the y-axis. This allows visual comparison of the cost-effectiveness of implementing strategies.

Costs and benefits of implementing the strategy in successive groups of 100 patients

A number of further outputs of the model are presented. The total cost and total benefits of implementing the strategy in each successive group of 100 patients is presented in tabular form. The total number of patients eligible for each intervention in each successive group of 100 is also presented and a breakdown of the costs: drug costs and workload implications.

Incremental cost-effectiveness of specific interventions in successive groups of 100 patients

Since the model can identify the incremental costs and the incremental benefits of each intervention separately in each patient, it is possible to calculate the incremental cost-effectiveness of each individual intervention in each individual patient. For the first intervention offered to a patient, the incremental costs are the costs of assessment, treatment and follow-up. For the second intervention the incremental costs are only the costs of additional treatment (because the patient has already been assessed) and costs of additional follow-up (because the patient is already being followed-up).

In some cases several patients are assessed without one being eligible for any intervention. This means that the cost per event prevented is infinite for a number of patients. A more reliable estimate of incremental cost-effectiveness is therefore provided by identifying the incremental costs and the incremental benefits of each intervention in successive groups of 100 patients. This is a very useful output, since it allows us to compare the incremental cost-effectiveness of adding further interventions to patients already on treatment with the incremental cost-effectiveness of assessing and treating additional patients. This gives an indication of how the strategy might be made more efficient. Eligibility criteria for less cost-effective treatments can be made more restrictive. Eligibility criteria for more cost-effective treatments can be made less restrictive.

Further cost-effectiveness analysis in the model population

With an understanding of the factors that affect cost-effectiveness in a real population, it is possible to make changes to the CVD prevention strategy in order to improve its cost-effectiveness. Treatment eligibility criteria are informed by the incremental cost-effectiveness analysis of preventive interventions in chapter 6. For example if analysis

suggests that an intervention is very cost-effective, it may be worth considering altering the treatment eligibility criteria to increase the numbers of patients receiving the intervention. Similarly if analysis suggests that in the model population a treatment is not cost-effective, it may be appropriate to consider altering the treatment eligibility criteria to restrict its use to those in whom it is most likely to be cost-effective.

The cost-effectiveness characteristics of this optimal prevention strategy can then be compared to the current strategy by analysing the costs and effects of the strategy using the full model of CVD prevention in a population of 2158. This allows graphs to be constructed comparing the cost-effectiveness of implementing a number of different strategies in increasing numbers of patients.

Sensitivity analysis (chapter 9)

Because there are many assumptions in the model, it is possible that altering some of these assumptions may affect the optimal prevention strategy. In this chapter I explore the robustness of some of aspects of the model and how this is likely to affect the results of the analysis and of the optimal prevention strategy.

Changed assumptions about effectiveness

Evidence of effectiveness for some interventions is more robust than for others. In other cases there are alternative estimates of the effectiveness of interventions. The impact of changing assumptions about the effectiveness of interventions is explored. For some interventions the changed assumptions mean recognising that they may not be effective. For other interventions the changed assumptions about effectiveness are derived from alternative (and in some cases more recent) reviews of the evidence.

Changed assumptions about risk estimation

The risk equations used throughout this analysis are derived from the Framingham cohort. However these may not be representative of the English population. In addition they may not accurately estimate CVD risk in some sub groups of patients. The generalisability of the Framingham risk equations to an English population is investigated by comparing observed CHD mortality in England and Wales with estimated mortality using the Framingham risk equations. The impact of changing the way in which CHD risk is calculated for patients with familial hypercholesterolaemia is also investigated. Finally the effect of using a different risk equation is explored.

Changed assumptions about cost

Prices of drugs can change rapidly, particularly with the expiry of patents. I therefore investigate the effects on the analysis of a large change in the price of those drugs for which the patent has recently expired.

Changed measures of benefits

It is beyond the scope of this work to undertake an analysis of cost per Quality Adjusted Life Year. However it is possible to approximately estimate the number of life years gained through the interventions described and to investigate whether benefit measured by this unit is very different to benefit measured as CVD events prevented.

5. Assumptions

This chapter outlines some of the assumptions underlying the model. These concern estimates of the effectiveness of interventions, cost estimates and the uptake of the strategy.

General model of effectiveness of preventive interventions

Five-year time horizon and effectiveness

It is likely that the effectiveness of some interventions is less in the first year of treatment. To model this perfectly we should attenuate the effects of some interventions in the first year. However it is difficult to know the extent this attenuation of effect should be applied to different interventions. Estimates of the effectiveness of interventions are derived from randomised controlled trials and systematic reviews following-up patients for two to five years. The time horizon of the study is five years. An estimate of effectiveness over two to five years is a fairly close approximation of benefit over five years and this is therefore used as an estimate of benefit over five years.

Measures of effectiveness

The measure of effectiveness used in this analysis is the number of CVD events prevented. This is a less complete measure of outcome than life-years or quality adjusted life-years. However, calculating the number of life-years gained requires additional assumptions. These concern compliance with treatment in the long-term and long-term prognosis with and without treatment. Such assumptions add to the uncertainty around the model. The purpose of this analysis is to provide sufficient information to improve decision-making without rendering the analysis too complex. As will be seen, analysis using CVD events prevented is sufficient for this purpose.

Box 8: Estimating the absolute benefits of antihypertensive treatment.

The best predictor of absolute treatment effects for any individual patient will be provided by application of the estimate of the relative risk reduction from trials to an estimate of the absolute disease risk for the individual in question.

Source: WHO-ISH 1999

Effectiveness of interventions

The general assumption common to each model is that the absolute reduction in CVD with treatment is equal to the relative risk on treatment multiplied by prior risk of

CVD. This model of effectiveness has gained increasing currency since publication of the New Zealand guidelines and has now gained widespread acceptance.¹⁰³ (Box 8)

Effectiveness of multiple interventions

This assumption is extended to treatment combinations. For treatments believed to act through different mechanisms, the treatment effects are assumed to be independent. This means that the relative risk of CVD for patients on treatment A is the same whether or not patients are receiving treatment B. It also means that compared to no treatment the relative risk of CVD for patients on both treatment A and treatment B is the product of the two relative risks [$RR_{AB} = RR_A \times RR_B$].

It has to be acknowledged that this assumption is to a large extent untestable, as it is impossible to conduct clinical trials of every possible treatment combination. However it is an assumption that underlies all polypharmacy in prevention and therefore is widely accepted.^{201,142}

Cost estimates

Cost estimates are treated as deterministic rather than stochastic. That is they are fixed values without any variation. Clearly stochastic estimations would more closely reflect experience in clinical practice. However dealing with stochastic cost estimations is considerably more complex from a modelling perspective and may not add greatly to our understanding. The primary aim of the model is not to provide a model of current costs and benefits, but to inform development of guidelines. Were we to use stochastic cost estimates our decisions would be guided by the most likely cost (i.e. would be guided by the mean or modal costs). Seen in this context the use of deterministic cost estimates is less significant.

Costs of interventions

It is assumed that the costs of follow-up are independent of individual patient characteristics and risk factor status. This means that the cost of follow-up in patients on treatment at very high risk, with very high blood pressure or very high cholesterol levels are the same as the cost of follow-up in individuals on treatment at moderate risk, with moderately raised blood pressure or moderately high cholesterol levels. This is likely to be a reasonable assumption as persons with raised blood pressure and raised cholesterol levels are generally asymptomatic. There is therefore no reason for

patients with higher blood pressures or cholesterol levels to seek more frequent appointments than those with lower blood pressures or cholesterol levels.

Predicted risk of CVD in the modelled population

The Framingham risk equations

It is assumed that the Framingham risk equations accurately predict CVD. It is not strictly necessary that our model exactly predicts risk of CVD in individual patients – indeed this is probably not possible. However it is important that the Framingham risk equation provides the best available description of which patients are likely to develop CVD and therefore which patients are likely to benefit. Even if it is imperfect it will therefore offer the best approach to predicting benefits and cost-effectiveness in the population under study.

The modelled population

It is assumed that the distribution of CVD risk and of treatment eligibility in the modelled population accurately reflects the distribution of CVD risk and of treatment eligibility in the English population. If there are systematic distortions in our modelled population they could lead us to recommend a selection strategy that was optimum for the modelled population but not optimum for the population of England.

6. Cost-effectiveness of interventions in individuals

In this chapter I outline the potential preventive interventions identified by the search strategy. I then review the evidence for the effectiveness of these preventive interventions and derive quantitative estimates of their effectiveness. Some interventions can be eliminated because there is insufficient evidence that they are effective. I then derive estimates of the costs of the remaining interventions and calculate cost-effectiveness ratios for each intervention. Further interventions can be eliminated when cost-effectiveness ratios are calculated because they are less effective and more costly than alternative interventions. This allows a short list of interventions to be identified that can be used in a prevention programme. The last part of the chapter uses the cost-effectiveness ratios derived for each preventive intervention to determine the optimum order in which to offer treatments and calculates incremental cost-effectiveness ratios for each intervention.

Identification of interventions

The interventions considered in this review include the most widely advocated interventions for prevention of CHD and CVA. For simplicity these have been categorised into a number of groups. These are:

- Antiplatelet drugs, including aspirin and clopidogrel.
- Cholesterol lowering through a number of approaches:
 - Statins
 - Dietary supplementation with sitostanol
 - Advice on a cholesterol-lowering diet
- Dietary advice not aimed at reducing cholesterol levels:
 - Dietary supplementation with fish oil or oily fish
 - Advice to follow a Mediterranean diet.
- Blood pressure lowering through any of a number of approaches:
 - Dietary interventions
 - Antihypertensive drugs (including initial antihypertensive treatment and more intensive antihypertensive treatment)
- Advice or interventions to help smoking cessation
- Multiple risk-factor interventions.

Effectiveness of interventions

Antiplatelet drugs

Aspirin

Evidence for the effectiveness of aspirin in primary prevention is derived from a systematic review carried out for the US Preventive Services Task Force. This is the most recent systematic review of aspirin in primary prevention. It concluded that evidence from clinical trials supports the hypothesis that the relative risk of CHD for patients on aspirin is 0.72 (95% confidence interval: 0.60 to 0.87) and the relative risk of CVA is 1.02 (95% confidence interval: 0.85 to 1.23).²⁰²

This hypothesis becomes my mathematical model of effectiveness. Unless there is specific evidence to the contrary, I assume that any patient, of any age or sex, on any combination of treatments who takes aspirin has a relative risk of CHD of 0.72 (95% confidence interval: 0.60 to 0.87) and a relative risk of CVA of 1.02 (95% confidence interval: 0.60 to 0.87).

Adverse effects of aspirin

Aspirin also increases major bleeding events. Estimates of the frequency of major bleeding events are fairly consistent. An early large systematic review of aspirin use estimated the increased risk in major bleeding events to be 0.02% to 0.1% annually (0.1 to 0.5% per five years).²⁰³ The US Preventive Services Task Force review also estimated the incidence of major bleeding in trials of primary prevention of CVD. It is therefore both the most recent and the most relevant estimate of the adverse effects of aspirin. It concluded that the relative risk of major bleeding was 1.7 in patients on aspirin. This is an absolute increase in incidence of major bleeding of 0.7 (95% CI, 0.4 to 0.9) per 1000 patient years: 0.3% (95% CI, 0.2% to 0.4%) per five years of treatment.²⁰²

Overall effectiveness of aspirin including adverse effects

For the purposes of this analysis, one major bleeding event is considered equivalent to one CVD event. To take account of this I offset the absolute reduction in cardiovascular risk by 0.3% to take account of the increased risk of bleeding. This means that I can estimate the overall effectiveness (including adverse effects) of aspirin using the equation shown in Box 10.

Dose of aspirin

There are insufficient data to compare the effects of different doses of aspirin in primary prevention of CHD or CVA. However the Antithrombotic Trialists' Collaboration meta-analysis review of antiplatelet therapy in high-risk patients (generally patients with ischaemic vascular disease) did address this question.²⁰⁴ It found that the proportional reduction in vascular events was greatest with a daily dose of 75 to 150mg aspirin. Since it is likely that lower doses of aspirin also result in fewer major bleeding events, this argues for a low daily dose of aspirin. In this study I assume that aspirin is given in a dose of 75mg a day.

Clopidogrel

One meta-analysis has assessed the effectiveness of thienopyridines (clopidogrel or its analogue ticlopidine) in comparison to aspirin. This concluded that compared to aspirin, relative risk of a CVA was 0.88 (95% confidence interval: 0.79 to 0.98). The meta-analysis does not provide an estimate of the relative risk of a CHD event therefore the relative risk of MI is used as a near approximation: the relative risk of myocardial infarction 0.88 (95% confidence interval: 0.76 to 1.01).²⁰⁵ Empirical studies suggest that an indirect estimate of the effects of clopidogrel compared to placebo should be accurate provided the population groups in studies are similar.²⁰⁶ An indirect estimate of the relative risk of a CVA on clopidogrel compared to placebo is the product of the relative risk of CVA on aspirin and that on clopidogrel. The 95% confidence intervals of the indirect estimates of relative risk are calculated in the following way. The variance of the indirect estimate is the sum of the variances of the direct estimates. The standard deviation of the indirect estimate is therefore the square root of the sum of the variances of the indirect estimates. The 95% confidence interval of the indirect estimate is therefore the indirectly estimated relative risk plus two standard deviations and the indirectly estimated relative risk minus two standard deviations. This is illustrated in Box 9.

Box 9: Calculation of confidence intervals for indirect estimates of effectiveness

$$\begin{aligned} \text{Upper 95\% Confidence Limit of } RR_{12} &= RR_{12} + 2 \times \sqrt{[(\text{Standard dev. } RR_1)^2 + (\text{Standard dev. } RR_2)^2]} \\ \text{Lower 95\% Confidence Limit of } RR_{12} &= RR_{12} - 2 \times \sqrt{[(\text{Standard dev. } RR_1)^2 + (\text{Standard dev. } RR_2)^2]} \end{aligned}$$

The relative risk of CVA on clopidogrel compared to placebo is therefore 0.90 (95% confidence interval: 0.70 to 1.13) [0.90 = 1.02 x 0.88] and an indirect estimate of the relative risk of a CHD event is 0.63 (95% confidence interval: 0.46 to 0.83) [0.63 = 0.72 x 0.88]. Major bleeding is rare on clopidogrel.^{207,208}

Box 10: Modelled effectiveness of aspirin and clopidogrel

Relative risk of a major outcome event on aspirin

$$= [0.72 \times \text{five-year risk of CHD}] + [1.02 \times \text{five-year risk of CVA}] + 0.003^*$$

Relative risk of a major outcome event on clopidogrel

$$= [0.63 \times \text{five-year risk of CHD}] + [0.90 \times \text{five-year risk of CVA}]$$

* One major bleeding event is considered equivalent to one CVD event.

Cholesterol lowering

Statins

There are two recent meta-analyses of the effects of statins on risk of CHD.^{209,210} Both report very similar results, but only one reports the relative risk of major coronary events (CHD). It concludes that patients on statins have a relative risk of CHD of 0.69 (95% confidence interval: 0.64 to 0.74).²⁰⁹ Two recent meta-analyses report the effects of statins on risk of CVA.^{210,211} Both report similar results, however only one calculates the relative risk of all CVA. It concludes that patients on statins have a relative risk of CVA of 0.70 (95% confidence interval 0.57 to 0.86).²¹¹ For the purposes of this model, we assume that the effectiveness of statins is given using the equation shown in Box 11.

Box 11: Modelled effectiveness of statins

Relative risk of a major outcome event on statin

$$= [0.69 \times \text{five-year risk of CHD}] + [0.70 \times \text{five-year risk of CVA}]$$

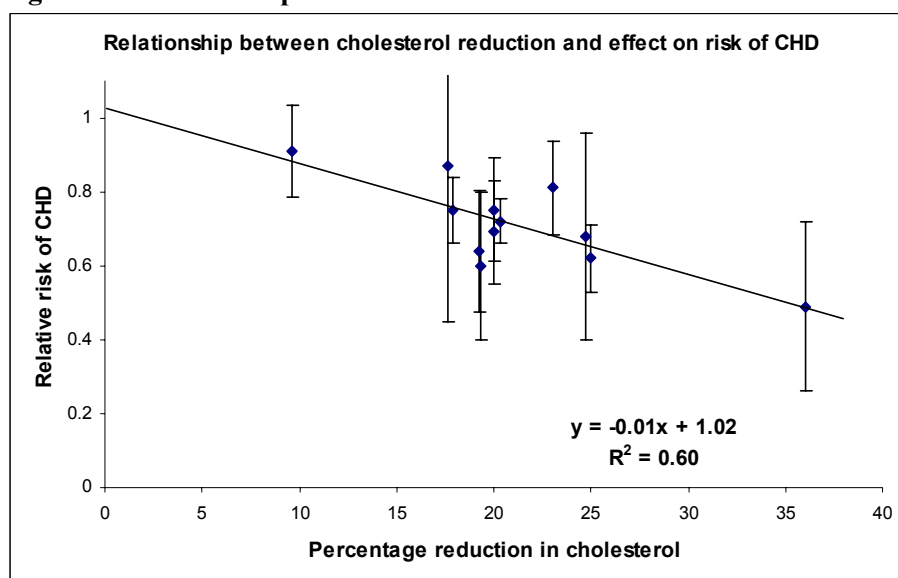
The dose-response effect of cholesterol lowering

There is strong epidemiological evidence for a continuous association between cholesterol level and CVD risk.²¹² It is consistent with the epidemiological evidence that cholesterol lowering is effective at any initial cholesterol level and that the effectiveness of cholesterol lowering in reducing CVD risk is proportional to the reduction in cholesterol.

Since publication of the meta-analyses of statins there have been several large randomised controlled trials of statins. One confirms that statins are effective irrespective of initial cholesterol levels, across a wide range of risks.¹²⁸ The other shows that a modest (9.6%) reduction in total cholesterol levels results in a modest reduction in risk of CHD.²¹³ Recent clinical trials are consistent with the observation that the reduction in CHD events is proportionate to the reduction in cholesterol levels.^{214,215,216} A summary of the results of twelve clinical trials of statins confirms

that there is a strong relationship between the percentage reduction in total cholesterol and relative risk of CHD. (Figure 10)

Figure 10: Relationship between reduction in total cholesterol and relative risk of CHD



Source: Graph adapted from data reported in ALLHAT-LLT with additional data from ASCOT, PROSPER and GREACE studies.

There is also evidence from clinical trials that more aggressive cholesterol lowering reduces (and may reverse) atheroma progression in patients with familial hypercholesterolaemia²¹⁷ and reduces the need for revascularisation following angioplasty.²¹⁸ Clinical trials are under way to confirm whether these improved surrogate endpoints translate into reduced risk of CVD events.^{219,220,221}

Taken together all this supports the hypothesis that cholesterol lowering is effective at any initial cholesterol level and that the effectiveness of cholesterol lowering in reducing CVD risk is proportional to the reduction in cholesterol. This is important when we come to estimate the likely effects of other cholesterol-lowering interventions.

Evidence for the need to reduce cholesterol by at least 30%

Guidelines emphasise the need to reduce cholesterol levels by 30% (or to below 5.0 mmol/l) in order to achieve optimum effect.¹⁴⁴ This advice implies the existence of a threshold reduction in cholesterol: reducing serum cholesterol by less than 30% is ineffective and further reduction in serum cholesterol is no more effective. This model is not supported by epidemiological evidence – which demonstrates a continuous relationship between cholesterol and risk of CVD. Nor is it supported by evidence from clinical trials. There is evidence that further cholesterol lowering leads to

regression of atherosclerosis, suggesting that more aggressive treatment leads to additional benefits.^{217,222} I therefore assume that the risk reduction with cholesterol lowering is proportional to the reduction in LDL cholesterol levels. I use this assumption to estimate the effects of other cholesterol-lowering interventions either alone or in combination with a statin.

Evidence that cholesterol lowering is effective only in patients whose total cholesterol exceeds 5 mmol/l. Guidelines indicate that patients are eligible for cholesterol lowering only if their total cholesterol level exceeds 5.0 mmol/l.¹³⁹ However epidemiological evidence does not support the existence of a threshold.²¹² Recent evidence from clinical trials also indicates that pre-treatment cholesterol levels do not determine the effectiveness of cholesterol lowering.¹²⁸

Cholesterol lowering through dietary intervention

Direct evidence of benefit

A meta-analysis of 27 randomised controlled trials of trials modifying dietary fat intake concluded that this seemed to lead to a significant reduction in significant protection from cardiovascular events (rate ratio 0.84, 95% confidence interval: 0.72 to 0.99).²²³ However there was no significant effect on cardiovascular mortality. The meta-analysis was further complicated by the fact that one trial included an increase in marine omega-3 fatty acids as part of the intervention. When this trial was excluded the effect on cardiovascular events was no longer significant (rate ratio 0.86, 95% confidence interval: 0.72 to 1.03). The magnitude of benefit is therefore not clear from the direct evidence.

Modelled evidence of benefit

A systematic review of the effects of dietary interventions on cholesterol levels indicates that they lead to a reduction in serum cholesterol of about 6%.²²⁴ However these studies did not report clinical outcomes. In addition it is difficult to know whether these effects are generalisable to clinical practice. The dietary intervention had its greatest impact on cholesterol levels in the first three months (8.5% reduction) and the impact on cholesterol levels had declined to 4.4% at 24 months. It was also clear that participants received more intensive dietary intervention than is likely to be possible in clinical practice. In almost all the trials, there was more than one session or contact between adviser and patient per month and in some there were contacts more than twice a month.

I assume that monthly contact with a dietician leads to a reduction in total cholesterol of 6%. I have already established that there is evidence to support to the hypothesis that reduction in risk of CVD is proportional to reduction in cholesterol levels. Simvastatin 40mg typically reduces serum total cholesterol by 30%.²²⁵ The effect of dietetic advice on risk of CHD and CVA is therefore 0.20 times effect of a statin ($0.20 = 6\% / 30\%$). In patients receiving dietary intervention the relative risk of CHD is therefore 0.94 [$0.94 = 1 - ((1-0.69) \times 0.20)$] and the relative risk of CVA is therefore 0.94 [$0.94 = 1 - ((1-0.70) \times 0.20)$]. It is not possible to calculate confidence intervals for the effect of dietary cholesterol lowering from published data. Instead notional confidence intervals have been estimated using the confidence intervals for statins. Relative risk of CHD with a dietary intervention is therefore 0.94 (notional confidence interval: 0.95 to 0.93) and relative risk of CVA is 0.94 (notional confidence interval: 0.97 to 0.91). (Box 12)

Dietary supplementation with sitostanol

One systematic review estimates the effect of consumption of margarine containing stanol esters (in particular sitostanol) on serum cholesterol levels. This concludes that dietary supplementation with margarine containing stanol esters reduces serum LDL cholesterol levels by 14% in persons aged 50 to 59 and by slightly less in younger persons.²²⁶ There is also evidence that they are effective in combination with statins.²²⁷ There is no direct evidence that this influences risk of CHD or CVA. However simvastatin 40mg reduces LDL cholesterol by 41% and reduces CHD risk by 31%.²²⁵ However under the assumptions of this model a 14% reduction in LDL cholesterol is expected to have 34% of the effect of simvastatin 40mg ($0.34 = 14\% / 41\%$). The relative risk of CHD with sitostanol is therefore 0.89 [$0.89 = 1 - ((1-0.69) \times 0.34)$] and the relative risk of CVA is therefore 0.90 [$0.90 = 1 - ((1-0.70) \times 0.34)$]. (Box 12) It is not possible to calculate confidence intervals for the effect of dietary supplementation with sitostanol. Instead I estimated notional confidence intervals using the confidence intervals for statins. Relative risk of CHD with sitostanol is therefore 0.89 (notional confidence interval: 0.88 to 0.91) and relative risk of CVA is 0.90 (notional confidence interval: 0.85 to 0.95). (Box 12)

Box 12: Modelled effectiveness of dietary advice to lower cholesterol levels

Relative risk of a major outcome event in patients taking sitostanol

= [0.89 x five-year risk of CHD] + [0.90 x five-year risk of CVA]

Relative risk of a major outcome event in patients receiving dietary advice

= [0.94 x five-year risk of CHD] + [0.94 x five-year risk of CVA]

Dietary interventions not aimed at reducing cholesterol levels

Dietary supplementation with fish oil

Since the observation that Inuit peoples suffer little heart disease there has been epidemiological evidence that a diet rich in fish-oil (long chain polyunsaturated fatty acids) protects against CHD mortality. A systematic review of epidemiological evidence before 1999 confirms that consumption of fish is inversely associated with CHD mortality in high-risk populations.²²⁸ Recent large epidemiological studies confirm this effect.^{229,230} There is also some epidemiological evidence that diets rich in fish oil are associated with a lower risk of stroke.^{231,232}

Clinical trials

There is substantial evidence from clinical trials that dietary supplementation with fish oil (omega-3 polyunsaturated fatty acids) - either as capsules or as oily fish - reduces mortality from CHD in patients with existing CHD. Preliminary results of a Cochrane review of the effects of fish oil on mortality indicate that the relative risk of death was 0.83 (95% confidence interval: 0.73 to 0.94) in patients given advice to increase intake of oily fish or fish-oil supplementation.²³³ This result is based on three randomised controlled trials.^{234,235,236} A recent meta-analysis of randomised controlled trials of fish-oil supplementation concluded fish-oil supplementation was associated with a reduced risk of fatal myocardial infarction (relative risk 0.70, 95% confidence interval: 0.6 to 0.8).²³⁷ However there was significant heterogeneity between the results of different clinical trials.

Given that there is evidence that fish oil supplementation is effective in patients with CHD it is very plausible that it is also effective in primary prevention of CHD. In this model I assume that patients receiving dietary supplementation with fish oil have a relative risk of CHD of 0.75 (95% confidence interval: 0.62 to 0.90) – the figure indicated in the largest trial of fish oil supplementation.²³⁶ The same trial reported an increased risk of CVA (non-significant) in patients taking fish-oil: relative risk 1.3 (95% confidence interval: 0.87 to 1.96).

Box 13: Modelled effectiveness of dietary supplementation with fish oil

Relative risk of a major outcome event in patients supplementing their diet with oily fish or fish oil

$$= [0.75 \times \text{five-year risk of CHD}] + [1.30 \times \text{five-year risk of CVA}]$$

Mediterranean diet

There is evidence from one clinical trial that patients with CHD substantially reduce their risk of CHD by adhering to a Mediterranean diet. This clinical trial has a number of weaknesses. All participants had suffered a myocardial infarction and may have been well motivated to make dietary changes. It was conducted in France, where a Mediterranean diet is not entirely foreign: reducing barriers to dietary change. It included only men. Nevertheless, evidence of effectiveness is sufficient to include the Mediterranean diet as an intervention. The effects of assuming it is ineffective are explored in the sensitivity analysis. The relative risk of MI or cardiac death for those advised to follow the diet was 0.28 (95% confidence interval: 0.15 to 0.53).²³⁸ In this clinical trial no patients in the intervention group and four in the control group suffered from a stroke: a relative risk of 0.00. However because it is based on such a small number of events this estimate of effectiveness has a wide confidence interval. If strokes are Poisson events the upper 95% confidence interval for a frequency of 0 is 3.7 events. This means that the upper 95% confidence interval for the relative risk of stroke is almost 1.00. It is therefore difficult to provide an accurate estimate of the effect of a Mediterranean diet on risk of CVA. Nevertheless, it is very unlikely that it increases the risk. I therefore assume that a Mediterranean diet has no effect on risk of CVA. (Box 14)

Box 14: Modelled effectiveness of a Mediterranean diet

Relative risk of a major outcome event in patients following a Mediterranean diet

$$= [0.28 \times \text{five-year risk of CHD}] + [1.00 \times \text{five-year risk of CVA}]$$

Combining dietary interventions

The Mediterranean diet involved a complex series of dietary changes: increasing intake of fruit, vegetables and cereals; decreasing intake of total and saturated fats and increasing intake of omega-3 polyunsaturated fatty acids (from either marine or vegetable sources). Elements of the Mediterranean diet include increases in dietary intake of fish oil. A Mediterranean diet and dietary supplementation with oily fish cannot be regarded as entirely independent interventions. The Mediterranean diet should rather be regarded as a more intensive dietary change.

Blood pressure lowering

Evidence for the effectiveness of blood pressure lowering through reduction in dietary salt
A meta-analysis of eleven clinical trials of interventions to reduce dietary salt concluded that intensive interventions resulted in only minimal changes in blood pressure in the long-term.²³⁹ It also concluded that these intensive interventions were probably unsuited to a clinical setting. This suggests that less intensive dietary interventions to reduce salt intake are likely to be of little practical benefit. I therefore do not consider dietary interventions to lower blood pressure any further.

Evidence for the effectiveness of blood pressure lowering with antihypertensive drugs
There is strong evidence that blood pressure lowering with antihypertensive drugs reduces risk of CVA and of CHD. The effects on risk of CHD and CVA are similar in persons older and younger than 60²⁴⁰ and in both men and women.²⁴¹ A Cochrane review of the effects of antihypertensive treatment in the persons aged 60 to 80 indicates that on treatment the relative risk of CHD is 0.80 and of CVA is 0.63.²⁴² However, because this study is concerned with effects in persons aged both over and under 60, the estimate of effectiveness used in the model is derived from the overall effectiveness of antihypertensives in the most recent meta-analysis.²⁴¹ The relative risk of CHD is 0.83 (95% confidence interval 0.72 to 0.91) and the relative risk of CVA is 0.64 (95% confidence interval 0.57 to 0.75) (Box 15)

Box 15: Modelled effectiveness of initial antihypertensive treatment

Relative risk of a major outcome event on initial antihypertensive treatment compared to placebo

= [0.83 x five-year risk of CHD] + [0.64 x five-year risk of CVA]

Epidemiology of blood pressure and risk of CVD

In addition to the evidence for the effectiveness of antihypertensive treatment, there is strong epidemiological evidence for a continuous relationship between blood pressure, CVA risk and CHD risk. A diastolic blood pressure 5 mm Hg lower is associated with a relative risk of 0.66 for CVA and of 0.79 for CHD.⁷¹ A recent meta-analysis of data on one million patients investigated the effects of blood pressure on mortality from CVA and CHD.²⁴³ It demonstrated three things. The relative effect of blood pressure on mortality is greater at younger ages. A 20 mm Hg difference in systolic blood pressure is equivalent in effect to a 10 mm Hg difference in diastolic blood pressure. The relationship between blood pressure and CVA or CHD mortality

is the same at all usual blood pressures down to 115/75 mm Hg. Early estimates of the effects on risk of CVA and CHD showed that the 5 mm Hg reduction in diastolic blood pressure with antihypertensive treatment produced an effect consistent with a reversal of the epidemiological risk.⁷² This has been confirmed in subsequent studies.^{240,241,242}

Table 12: Relative risk of CVD mortality associated with diastolic blood pressure 5 mm Hg lower

Age band	Relative risk of a cardiovascular event with diastolic blood pressure 10 mm Hg lower	
	CVA	CHD
40-49	0.59	0.69
50-59	0.58	0.72
60-69	0.63	0.75
70-79	0.69	0.79
80-89	0.79	0.84

Source: Derived from Prospective Studies Collaboration *Lancet* 2002

Choice of antihypertensive and effects of treatment

When they are directly compared, thiazide diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, alpha-blockers and centrally acting drugs have similar effects on blood pressure.^{244,245} Systematic review of drug-drug comparisons suggests that thiazides may lower systolic blood pressure by 2 mm Hg more than calcium-channel blockers or beta-blockers, but no significant differences in CVD event rates were found.²⁴⁶ A subsequent systematic review of drug-drug comparisons between calcium-channel blockers and other antihypertensives as first-line antihypertensive agents concluded that patients on calcium-channel blockers were significantly more likely to suffer from CVD.²⁴⁷ Systematic review of drug-placebo comparisons shows that evidence of effectiveness is strongest for treatment regimes using low dose thiazide diuretics as a first line treatment.²⁴⁶ This impression is confirmed in a recent large randomised controlled trial comparing regimes with a thiazide diuretic, a calcium channel blocker or an ACE inhibitor as a first step treatment. This concluded that a chlorthalidone-based regime prevented more CVD events than regimes based on either amlodipine or lisinopril.²⁴⁸

Initial antihypertensive treatment with losartan

There is evidence from one randomised controlled trial that an initial antihypertensive regime including losartan (an angiotensin-II receptor antagonist – ACE-II receptor blocker) and a thiazide diuretic may be more effective than one based on atenolol and a thiazide diuretic.²⁴⁹ This is despite only trivial differences in achieved blood

pressure. The evidence is unclear as to whether this effect is specific to ACE-II receptor blockers, as a randomised controlled trial comparing the ACE inhibitor captopril with losartan in post- myocardial infarction patients, found no significant differences between the two drugs.²⁵⁰

Compared to an atenolol based, regime, the relative risk of a major cardiovascular event on a regime including losartan is 0.87 (95% confidence interval: 0.77 to 0.98).²⁴⁹ The relative risk of a fatal or non-fatal myocardial infarction on losartan is 1.07 (95% confidence interval: 0.88 to 1.31). This is a close approximation of the relative risk of any CHD event.

In comparison to placebo, the indirectly estimated relative risk of CVA on a losartan-based initial antihypertensive regime is 0.89 (estimated 95% confidence interval: 0.68 to 1.14) and relative risk of CHD 0.48 (estimated 95% confidence interval: 0.34 to 0.64). (Box 16)

Box 16: Modelled effectiveness of initial antihypertensive treatment with losartan

Relative risk of a major outcome event on initial antihypertensive treatment with losartan compared to placebo

= [0.89 x five-year risk of CHD] + [0.48 x five-year risk of CVA]

Effectiveness of further blood pressure lowering

Epidemiological evidence supports the view that further reductions in blood pressure will be associated with further reductions in risk. There is some further evidence to support this view. In two case-control studies of treated hypertensives, cases that had suffered from a CVA and cases that had suffered from myocardial infarction had higher blood pressures than controls that had not.^{251,252} The differences in achieved blood pressure - and hence risk of CVD - were not explained by known confounders such as other risk factors or pre-treatment blood pressure.

Prospective studies also support the view that lower achieved blood pressure is associated with a reduced risk of CVD,^{253,254} and that treated blood pressure is a better predictor of subsequent CVD risk than pre-treatment blood pressure.²⁵⁵

Meta-analysis of randomised controlled trials of more intensive versus less intensive antihypertensive therapy suggests that on more intensive antihypertensive treatment, relative risk of CVA is 0.80 (95% confidence interval: 0.65 to 0.98) and of CHD is 0.81 (95% confidence interval: 0.67 to 0.98).²⁵⁶ This conclusion is based on the results

of three randomised controlled trials. There are a number of uncertainties about this finding. Firstly, it is not clear that treatment of the control group was equivalent to standard antihypertensive therapy or was somewhat less intensive than standard antihypertensive therapy. Secondly, it is not clear whether the effect only applies to intensive treatment regimes including an angiotensin enzyme inhibitor. In two of the clinical trials, the intensive treatment group included an angiotensin enzyme inhibitor whereas the control group did not.^{257,258,259} In the third, treatment regimes in both the less intensive and the more intensive groups included an angiotensin converting enzyme inhibitor, but a higher proportion of patients in the more intensive (intervention) group received it.²⁶⁰

Relative risk on intensive antihypertensive treatment compared to initial antihypertensive treatment
 Overall this suggests that more intensive treatment leads to further reduction in risk of CVD. It is possible that this effect may be specific to drugs affecting the renin-angiotensin system. In this model, I assume that patients on more intensive antihypertensive treatment have a relative risk of CVA of 0.80 (95% confidence interval: 0.65 to 0.98) and relative risk of CHD of 0.81 (95% confidence interval: 0.67 to 0.98). (Box 17)

Box 17: Modelled effectiveness of further versus initial antihypertensive treatment

Relative risk of a major outcome event on intensive antihypertensive treatment compared to initial antihypertensive treatment

Standard treatment regimen = [0.81 x five-year risk of CHD] + [0.80 x five-year risk of CVA]

Indirectly estimated relative risk of intensive antihypertensive treatment compared to placebo
 I indirectly estimate the effectiveness of intensive antihypertensive treatment in comparison to placebo. The indirectly estimated relative risk of CHD with intensive antihypertensive treatment is 0.67 (estimated 95% confidence interval: 0.51 to 0.86) and the relative risk of CVA is 0.51 (estimated 95% confidence interval: 0.34 to 0.71).

For a losartan-based intensive antihypertensive treatment in comparison to placebo the indirectly estimated relative risk of CHD is 0.72 (estimated 95% confidence interval: 0.48 to 1.01) and the relative risk of CVA is 0.38 (estimated 95% confidence interval: 0.19 to 0.61). (Box 18)

Box 18: Modelled effectiveness of further versus initial antihypertensive treatment

Relative risk of a major outcome event on intensive antihypertensive treatment compared to placebo

Standard treatment regimen = [0.67 x five-year risk of CHD] + [0.51 x five-year risk of CVA]

Losartan-based regimen = [0.72 x five-year risk of CHD] + [0.38 x five-year risk of CVA]

Smoking cessation

The relationship between smoking and risk of CHD is well established.^{261,262,263} Taking account of confounding factors, epidemiological evidence suggests that compared to smokers, non-smokers have a relative risk of CHD of 0.65 and a relative risk of CVA of 0.60.^{29,30} There is substantial evidence that quitting smoking reduces risk of CHD and CVA. Following myocardial infarction, the relative risk of CHD in those who quit compared to those who continue to smoke is 0.64.²⁶⁴ Stopping smoking roughly halves the risk of CVA within a few years.²⁶⁵ In this model I assume that stopping smoking reverses the epidemiological risk associated with smoking. (Box 19)

Box 19: Modelled effects of quitting smoking on risk of CVD

Relative risk of a major outcome event in patients quitting smoking
 = [0.65 x five-year risk of CHD] + [0.60 x five-year risk of CVA]

Interventions to increase smoking cessation

There is evidence that a number of interventions increase the number of smokers successfully quitting.^{266,267,268,269} Bupropion in combination with nicotine replacement and intensive support appears to be one of the most effective interventions, increasing the quit rate at one year by up to 20%.²⁶⁹ The effectiveness of these interventions at promoting abstinence at six months has been summarised in a recent review.²⁷⁰ However approximately 46% of persons who quit smoking at one year will relapse within three and a half years.²⁷¹ The overall effectiveness of these interventions are summarised in Table 13.

Table 13: Effectiveness of smoking cessation interventions

Intervention	Effect size - (increase in quit rate)		Total patient contact (minutes)
	At 6 months	Long-term	
Brief advice from a physician	2%	1%	5
Nicotine replacement patch and limited behavioural support	5%	2%	10
Nicotine replacement patch and intensive behavioural support	6%	3%	30
Nicotine nasal spray and intensive behavioural support	12%	6%	30
Bupropion 300mg a day and intensive behavioural support	9%	4%	30
Bupropion 300mg a day and nicotine replacement patch intensive behavioural support	20%	9%	30

Multiple risk factor interventions

The evidence for the effectiveness of lifestyle interventions is weak. Those multifactorial interventions that reduce risk of CVD appear to be effective are those that involve the use of antihypertensive and cholesterol lowering drugs.²⁷² Since the effects of antihypertensive and cholesterol lowering drugs are considered separately in this study, multifactorial interventions have been excluded from this analysis.

Resource costs of interventions

From the perspective of the health service there are three cost elements for patients receiving interventions to prevent CVD: cost of drugs, cost of consultations (clinic visits) and cost of investigations.

Drug costs

Drug costs are obtained from the British National Formulary.²⁷³ Where possible the lowest cost drug with a once daily dosage is chosen from the relevant drug class. Dispensing costs are calculated at 87.4p per prescribed item on the assumption that four prescriptions are issued per year for long-term medication.²⁷⁴ (Table 16)

Antiplatelet drugs

Aspirin

The effects of aspirin on risk of CVD do not seem to be dose dependent. The lowest practical dose of aspirin is 75mg per day ($\frac{1}{4}$ of a 300mg aspirin tablet).²⁰² There also appear to be no advantages to using enteric-coated aspirin (which is more costly).²⁷⁵ The annual cost including dispensing costs is therefore £4.36. (Table 16)

Clopidogrel

The standard dose of clopidogrel is 75mg per day.²⁰⁵ The annual cost including dispensing costs is therefore £463.79. (Table 16)

Cholesterol lowering

Statins

Evidence is strongest for the effectiveness of simvastatin in the prevention of CHD.²⁷⁶ It is one of the more effective drugs at lowering serum cholesterol levels.²²⁵ In this model I assume that treatment with a statin means simvastatin 40mg once a day: the dose used in the Heart Protection Study.¹²⁸ The annual cost including dispensing costs is therefore £390.53. (Table 16)

Dietary advice to reduce serum cholesterol

This does not have any associated drug costs.

Dietary supplementation with sitostanol

Margarine containing sitostanol costs approximately £2.50 per 250g (Benecol Spread 250g: £2.49).⁴ However this must be offset against the cost of other margarines (50p

⁴ Source: <http://www.tesco.com/superstore/> last accessed 24th April 2003 -

per 250g). The excess cost is therefore £2.00 per 250g. Since 12g of margarine contain 1g of sitostanol, to consume 2g of sitostanol per day requires an intake of 25g of margarine per day: a cost of £73 per year. (Table 16) I assume that this excess cost is provided by the health service, in the form of redeemable vouchers.

Dietary interventions not aimed at reducing cholesterol levels

Dietary supplementation with fish oil

The active components of fish-oil are believed to be omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In clinical trials, daily doses of EPA and DPA varied from 0.3g to 6.0 g and 0.6g to 3.7g respectively.²³⁷ The lowest cost method of achieving this intake is to follow the DART recommendations: to consume at least two weekly portions (200g to 400g) of oily fish.²³⁵ Three tins of sardines per week will achieve this intake at a cost of under £1.20 per week (Tesco Sardines In Brine 120g: 0.33p).⁴ This is an annual cost of £62.57 per year. I assume that this is provided by the health service.

An alternative approach would be to take fish-oil supplements. Each 1g capsule of Maxepa ® contains 0.18g of EPA and 0.12g of DHA. To achieve a total intake of 0.9g of omega-3 fatty acids would require 3 capsules a day. The total annual cost including dispensing would therefore be £152.85. (Table 16)

Mediterranean diet

In addition to advice to follow a Mediterranean diet subjects were provided with a rapeseed oil-based margarine for the whole family.²⁷⁷ On the assumption that an average family consumes 500g margarine per week this could be expected to cost £0.50 per week: £26 per year. (Table 16) I assume that this is provided by the health service.

Blood pressure lowering

Cost of antihypertensive treatment

The average cost of initial antihypertensive treatment is accounted for by a combination of drugs. This combination varies from men to women and is explained below.

Initial antihypertensive treatment with a thiazide and a beta-blocker

In this study initial antihypertensive treatment is with a low-dose thiazide diuretic. In clinical trials patients are typically prescribed one to three antihypertensive drugs.²⁴¹ In clinical practice, patients are prescribed on average 1.7 antihypertensive drugs.²⁷⁸

In the model it is therefore assumed that patients on standard antihypertensive treatment require two drugs. The first drug is bendrofluazide 2.5mg; the second drug is atenolol 50mg. These respectively are the lowest-cost thiazide and beta-blocker that can be taken once daily. There is evidence that the combination of a low-dose thiazide and beta-blocker such as this is more effective than either drug alone.²⁷⁹

Some patients have specific contraindications to thiazide diuretics and to beta-blockers. Gout is the principal contraindication to thiazide diuretics, affecting 4.4% of men and 0.9% of women aged 55 and over.²⁸⁰ In the model, I assume that patients in whom thiazide diuretics are contraindicated are prescribed a calcium channel blocker. Felodipine 5mg is the calcium channel blocker because it has a once-daily dosage. Obstructive airways disease is the principle contraindication to beta-blockers. We can regard a history of having wheezed in the past year as evidence of obstructive airways disease, this affects 26% per cent of men and 23% of women 55 and over.²⁸¹ In the model I assume that patients in whom beta-blockers are contraindicated are prescribed a centrally acting drug: methyldopa 500mg twice a day.

The percentages prescribed each of the drugs combinations are calculated as follows: men prescribed atenolol and bendrofluazide, 70.7% [70.7% = (1-4.4%) x (1-26%)]; men prescribed methyldopa and bendrofluazide, 24.9% [24.9% = (1-4.4%) x 26%]. From this the average annual cost per year of antihypertensive treatment (including dispensing costs of £6.99 – two prescription drugs four times a year) is calculated to be £40.77 for men and £37.40 for women. (Table 14)

Table 14: Average annual costs of antihypertensive drugs in men and women

Men						
Proportion offered these treatments			Annual cost of treatment with this combination			
Second drug First drug	Atenolol 50mg	Methyldopa 500mg bd	Second drug First drug	Atenolol 50mg	Methyldopa 500mg bd	Average cost per patient
Bendrofluazide 2.5mg	70.7%	24.9%	Bendrofluazide 2.5mg	£20.75	£54.57	£33.78
Felodipine 5mg	3.3%	1.1%	Felodipine 5mg	£116.93	£150.75	
Women						
Proportion offered this treatment			Annual cost of treatment with this combination			
Second drug First drug	Atenolol 50mg	Methyldopa 500mg bd	Second drug First drug	Atenolol 50mg	Methyldopa 500mg bd	Average cost per patient
Bendrofluazide 2.5mg	73.3%	25.8%	Bendrofluazide 2.5mg	£20.75	£54.57	£30.41
Felodipine 5mg	0.7%	0.2%	Felodipine 5mg	£116.93	£150.75	

Initial antihypertensive treatment with a thiazide and an ACE-II receptor blocker

Initial antihypertensive treatment with a thiazide and an ACE-II inhibitor is based on bendrofluazide 2.5mg and losartan 50mg. This closely approximates to the regime used in the LIFE study.²⁴⁹

As in the atenolol-based regime, patients in whom thiazide diuretics are contraindicated are prescribed the calcium channel blocker Felodipine. Obstructive airways disease is not a contraindication to losartan; indeed there are few contraindications to losartan. The percentages prescribed each of the drugs combinations are calculated as follows: men prescribed losartan and bendrofluazide, 95.6% [95.6% = (1-4.4%)]; men prescribed Felodipine and bendrofluazide, 4.4%. From this the average annual cost per year of antihypertensive treatment (including dispensing costs) is £245.50 for men and £242.14 for women. (Table 15)

Table 15: Average annual costs of antihypertensive drugs in men and women

Men						
Proportion offered these treatments			Annual cost of treatment with this combination			
Second drug First drug	Losartan 50mg	Methyldopa 500mg bd	Second drug First drug	Losartan 50mg	Methyldopa 500mg bd	Average cost per patient
Bendrofluazide 2.5mg	95.6%	0.0%	Bendrofluazide 2.5mg	£234.28	£54.57	£238.51
Felodipine 5mg	4.4%	0.0%	Felodipine 5mg	£330.46	£150.75	
Women						
Proportion offered this treatment			Annual cost of treatment with this combination			
Second drug First drug	Losartan 50mg	Methyldopa 500mg bd	Second drug First drug	Losartan 50mg	Methyldopa 500mg bd	Average cost per patient
Bendrofluazide 2.5mg	99.1%	0.0%	Bendrofluazide 2.5mg	£234.28	£54.57	£235.14
Felodipine 5mg	0.9%	0.0%	Felodipine 5mg	£330.46	£150.75	

Further blood pressure lowering adding enalapril to a thiazide and a beta-blocker

I assume that further blood pressure lowering is achieved by adding an angiotensin converting enzyme inhibitor to initial antihypertensive treatment. Because it combines the advantages of low cost and a once-daily dosage, in the model, the cost of further blood pressure lowering is the cost of prescribing enalapril 20mg. The annual cost of further blood pressure lowering is therefore £124.04 in men and £120.68 in women. (Table 16)

Further blood pressure lowering adding Felodipine or methyldopa to a thiazide and an ACE-II receptor blocker

In patients prescribed losartan it is unlikely that further blood pressure lowering will be achieved by adding a drug such as enalapril that has a similar mechanism of action. It is therefore assumed that further blood pressure lowering is achieved by adding Felodipine 5mg to initial antihypertensive treatment. For 4.4% of men and 0.9% of

women who are already taking Felodipine methyldopa 500mg twice a day is an alternative third line treatment. The annual cost of further blood pressure lowering is therefore £352.17 in men and £350.93 in women. (Table 16)

Table 16: Drug and dispensing costs of interventions

Intervention	Annual drug and dispensing costs
Aspirin 75mg	£4.36
Clopidrogel 75mg	£463.79
Initial BP Rx (men)	£40.77
Initial BP Rx (women)	£37.40
Initial BP Rx with ACE 2 (men)	£245.50
Initial BP Rx with ACE 2 (women)	£242.14
Intensive BP Rx (men)	£124.04
Intensive BP Rx (women)	£120.68
Intensive BP Rx ACE 2 (men)	£352.17
Intensive BP Rx ACE 2 (women)	£350.93
Simvastatin 40mg	£390.53
Margarine containing sitostanol	£73.00
Cholesterol lowering diet	£0.00
Oily fish 3 days a week	£62.57
Maxepa 3 a day	£152.85
Mediterranean diet	£26.00

* Assumed to be provided by NHS.

Smoking cessation

Nicotine replacement patches are worn for a total of 12 weeks. Seven days' supply costs £9.07.²⁷³ Allowing for dispensing costs (one prescription) the cost of nicotine replacement is therefore £109.71.

Nicotine replacement nasal spray is taken for eight weeks at a standard dose and for four weeks at reducing doses. A person smoking 20 cigarettes a day might therefore require two sprays 20 times a day for eight weeks and an average of half this dose for the next four weeks. A spray-dispenser (enough for 200 sprays) costs £10.99.²⁷³ A smoker requires on average 14 spray-dispensers for each attempt. Allowing for dispensing costs (one prescription) this means a cost of £154.73.

Bupropion is taken at a dose of 150mg a day for 6 days, followed by 150mg twice daily for 7 to 9 weeks. This is a total of 104 to 132 tablets: approximately two packs of 60: a total cost of £86.57 including dispensing costs.

Table 17: Drug and dispensing costs of smoking cessation interventions

Intervention	Annual drug and dispensing costs	
	Year 1 of intervention	Years 2 to 5 of intervention
Nicotine replacement patches	£109.71	None
Nicotine replacement spray	£154.73	None
Bupropion	£86.57	None
Nicotine replacement patches and bupropion	£196.28	None

Costs of consultations and laboratory investigations

Patients on drug treatment require follow-up and in some cases laboratory investigations. The cost of laboratory investigations has been derived from a report by Grün R. carried out for London School of Hygiene & Tropical Medicine in 1996. Costs have been adjusted for inflation (3% per year). (Table 18)

Table 18: Costs of pathology tests.

Test	1996	2002
Serum urea and electrolytes (U&E)	£2.96	£3.53
Serum lipids	£2.92	£3.49
Lipid profile (total and HDL cholesterol)	£3.56	£4.25
Liver function tests (LFT)	£2.65	£3.16
Full blood count (FBC)	£2.61	£3.12
Erythrocyte sedimentation rate (ESR)	£1.76	£2.10

Source: Reinhold Grün – LSHTM 1996

Routine follow-up appointments take ten minutes of staff time and I assume that these appointments are with a practice nurse. Patients receiving dietary advice require follow-up consultations with a dietician. Routine follow-up appointments with a dietician take fifteen minutes of staff time. The cost of staff time is dependent on the health professionals used. The costs are given in Table 19.

Table 19: Costs per hour of client contact with different health care professionals

Type of staff	Cost per hour of client contact
Dietician	£33
Physician	£119
Practice Nurse	£32
General Practitioner	£118

Source: Netten A., Curtin L. Unit costs of health and social care 2002. Personal Social Services Research Unit. University of Kent. (Last accessed 25th April 2003)

Antiplatelet drugs

Patients on either aspirin, or clopidogrel will be followed up twice a year in all years. These patients do not require pathology tests. (Table 20)

Cholesterol lowering

Statins

Because the doses of statins may need adjustment during the first year, I assume that patients on statins will require review four times during the first year of follow-up and will subsequently be followed up twice a year. These patients require annual estimation of liver function and annual serum cholesterol levels.

Margarine containing sitostanol

Patients receiving advice to supplement their diet with margarine containing sitostanol will need ongoing reinforcement of the message. It is assumed that this will need three monthly clinic visits in the first year of follow-up and six monthly clinic visits in subsequent years. These patients do not require pathology tests. (Table 20)

Cholesterol-lowering diet

In clinical trials of advice on a cholesterol-lowering diet, patients typically had monthly consultations a dietician. This model assumes that dietetic advice requires 15 minutes of contact with a practice nurse or dietician for the first appointment, followed by monthly contacts lasting 15 minutes each during the first year. Clinical trials did not generally investigate effectiveness after one year, but it is assumed that to maintain dietary change requires three monthly contacts during subsequent years. These patients do not require pathology tests. (Table 20)

Dietary interventions not aimed at reducing cholesterol levels

Dietary supplementation with fish oil or oily fish

Patients receiving advice to increase intake of oily fish or to supplement their diet with fish oil or margarine containing sitostanol will need ongoing reinforcement of the message. It is assumed that this will need three monthly clinic visits in the first year of follow-up and six monthly clinic visits in subsequent years. These patients do not require pathology tests. (Table 20)

Mediterranean diet

In the clinical trial of advice on a Mediterranean diet, patients had one hour-long consultation with a physician and a dietician. This was followed by a further consultation during the first year and annual follow-up appointments subsequently.²⁷⁷ This model assumes that advice on a Mediterranean diet requires 60 minutes of contact with a physician and a dietician for the first appointment, followed by 30 minutes of contact with a dietician during the first year. It is assumed that to maintain the dietary change requires 60 minutes of contact with a dietician per year in subsequent years. These patients do not require pathology tests. (Table 20)

Blood pressure lowering

Because the doses of antihypertensive drugs or statins may need adjustment I assume that patients on these drugs will require review four times during the first year of follow-up and will subsequently be followed up twice a year. Patients on

antihypertensive drugs also require annual estimation of renal function and electrolytes. (Table 20)

The non-drug resource costs of each intervention are shown in Table 21.

Table 20: Resource use: staff and laboratory investigations of interventions to prevent CVD

Intervention	Costs in year 1			Costs in years 2 to 5		
	Consultations	Which staff?	Laboratory investigations	Consultations	Which staff?	Laboratory investigations
Aspirin 75mg	2 x 10 minute clinic visits	PN		2 x 10 minute clinic visits	PN	
Clopidogrel 75mg	2 x 10 minute clinic visits	PN		2 x 10 minute clinic visits	PN	
Initial BP Rx (men)	4 x 10 minute clinic visits	PN	1 x electrolytes	2 x 10 minute clinic visits	PN	1 x electrolytes
Initial BP Rx (women)	4 x 10 minute clinic visits	PN	1 x electrolytes	2 x 10 minute clinic visits	PN	1 x electrolytes
Initial BP Rx with ACE 2 (men)	4 x 10 minute clinic visits	PN	1 x electrolytes	2 x 10 minute clinic visits	PN	1 x electrolytes
Initial BP Rx with ACE 2 (women)	4 x 10 minute clinic visits	PN	1 x electrolytes	2 x 10 minute clinic visits	PN	1 x electrolytes
Intensive BP Rx (men)	4 x 10 minute clinic visits	PN	1 x electrolytes	2 x 10 minute clinic visits	PN	1 x electrolytes
Intensive BP Rx (women)	4 x 10 minute clinic visits	PN	1 x electrolytes	2 x 10 minute clinic visits	PN	1 x electrolytes
Intensive BP Rx ACE 2 (men)	4 x 10 minute clinic visits	PN	1 x electrolytes	2 x 10 minute clinic visits	PN	1 x electrolytes
Intensive BP Rx ACE 2 (women)	4 x 10 minute clinic visits	PN	1 x electrolytes	2 x 10 minute clinic visits	PN	1 x electrolytes
Simvastatin 40mg daily	4 x 10 minute clinic visits	PN	1 x lipid profile 1 x liver function tests	2 x 10 minute clinic visits	PN	1 x lipid profile 1 x liver function tests
Margarine containing sitostanol	4 x 10 minute clinic visits	PN		2 x 10 minute clinic visits	PN	
Cholesterol lowering diet	12 x 15 minute clinic visits	D		4 x 15 minute clinic visits	D	
Oily fish 3 days a week	4 x 15 minute clinic visits	D		2 x 15 minute clinic visits	D	
Maxepa 3 a day	4 x 10 minute clinic visits	PN		2 x 10minute clinic visits	PN	
Mediterranean diet	60 minute clinic visit 30 minute clinic visit	D & Ph		1 x 60 minute clinic visit	D	

Table 21: Non-drug resource costs: costs per five years of interventions to prevent CVD

Intervention	Costs in year 1 (undiscounted)	Costs in years 2 to 5 (undiscounted)	Discounted 5 year costs*
Aspirin 75mg	£10.67	£10.67	£47.63
Clopidrogel 75mg	£10.67	£10.67	£47.63
Initial BP Rx (men)	£24.86	£14.20	£74.06
Initial BP Rx (women)	£24.86	£14.20	£74.06
Initial BP Rx with ACE 2 (men)	£24.86	£14.20	£74.06
Initial BP Rx with ACE 2 (women)	£24.86	£14.20	£74.06
Intensive BP Rx (men)	£24.86	£14.20	£74.06
Intensive BP Rx (women)	£24.86	£14.20	£74.06
Intensive BP Rx ACE 2 (men)	£24.86	£14.20	£74.06
Intensive BP Rx ACE 2 (women)	£24.86	£14.20	£74.06
Simvastatin 40mg daily	£28.74	£18.08	£91.38
Margarine containing sitostanol	£21.33	£10.67	£58.29
Cholesterol lowering diet	£99.00	£33.00	£213.35
Oily fish 3 days a week	£33.00	£16.50	£90.17
Maxepa 3 a day	£21.33	£10.67	£58.29
Mediterranean diet	£168.50	£33.00	£282.85

* Discount rate is 6%.

Smoking cessation

Patients receiving smoking cessation interventions require staff input during the first year of the intervention. Brief advice from a physician requires 5 minutes of GP time. Patients receiving limited and receiving intensive behavioural support are estimated to require 10 minutes of staff time and 30 minutes of staff time respectively. In both cases practice nurses will be used for behavioural support. (Table 22)

Table 22: Costs of drugs of smoking cessation interventions

Intervention	Total patient contact (minutes)	Cost of staff time (per hour)	Total staff cost
Brief advice from a physician	5	£118	£9.83
Nicotine replacement patch and limited behavioural support	10	£31	£5.17
Nicotine replacement patch and intensive behavioural support	30	£31	£15.50
Nicotine nasal spray and intensive behavioural support	30	£31	£15.50
Bupropion 300mg a day and intensive behavioural support	30	£31	£15.50
Bupropion 300mg a day and nicotine replacement patch intensive behavioural support	30	£31	£15.50

Cost-effectiveness of individual interventions

The cost-effectiveness of interventions is affected by a number of patient characteristics. Because the benefits of interventions are proportional to pre-treatment CVD risk, whereas the costs are unaffected by pre-treatment CVD risk, treatment is more cost-effective in patients at higher risk. However some interventions have different effects on risk of CHD and risk of CVA, therefore the relationship between overall CVD risk and cost-effectiveness may not always be straightforward. Aspirin is a special case because it is associated with a risk of adverse events that is not proportional to pre-treatment CVD risk. This means that if pre-treatment risk is low the probability of an adverse event may be greater than the reduction in risk of CVD. Because there is a threshold CVD risk level at which adverse events are likely to outweigh benefits of aspirin, we need to investigate cost-effectiveness in patients at a range of levels of CHD and CVA risk to determine how this affects the cost-effectiveness rankings.

The cost-effectiveness of antihypertensive treatments is slightly different for men and women. This is because the costs of treatment differ from men to women, whereas the benefits of treatment are similar. Cost-effectiveness must therefore be explored separately in men and women.

Assumptions about effectiveness

Antihypertensive treatment may not be fully effective within the first year of treatment.⁷² Statins also seem to take a year to have their full effect on CVD risk.¹²⁸ I assume that the intervention is fully effective - in other words patients have been on treatment for at least two to three years. The effect of this assumption is to favour those treatments that take one to three years to be fully effective over those that are immediately effective.

Cost-effectiveness in patients at 15% five-year CVD risk

Typically CHD risk is about 0.6 times CVD risk and CVA risk is about times 0.2 CVD risk (see Figure 24 on page 153). The cost-effectiveness of CVD prevention is explored in patients whose five-year CVD risk is 15%. This level of CVD risk is that of a non-smoking, diabetic woman aged 56, whose blood pressure is 170/100 mm Hg and total to HDL-cholesterol ratio is 4.2. She is eligible for the full range of preventive interventions. It is also the level of risk in a non-diabetic, non-smoking

man aged 66, whose blood pressure is 164/106 mm Hg and total to HDL cholesterol ratio is 3.9. He is also eligible for the full range of preventive interventions. Both these patients' five-year CHD risk is 9% and five-year risk of CVA is 3%.

Effectiveness is the discounted sum of the reduction in five-year risk of CHD and five-year risk of CVA with the intervention. Cost is the discounted five-year cost of the intervention. A sensitivity analysis has been carried out using the upper and lower confidence intervals of effectiveness to estimate the upper and lower limits of cost-effectiveness.

Baseline results

Table 23 shows the cost-effectiveness of each of the drug and dietary interventions in men and woman. Figure 11 shows the cost effectiveness of these interventions with error bars representing the sensitivity analysis.

Interventions that may cause net harm

Because of uncertainty about the effectiveness of ACE-II receptor blockers, it is possible that they may cause net harm. This is because an increase in risk of CHD is within the 95% confidence interval of their effectiveness. We can therefore exclude ACE-II receptor blockers from further analysis.

There is also uncertainty about the effects of dietary supplementation with fish oil or oily fish. It is possible that oily fish also causes net harm because of the wide confidence interval around its effect on CVA. We can therefore exclude dietary supplementation with oily fish from further analysis.

Dominated interventions

Antihypertensive regimes including ACE-II receptor blockers prevented fewer CVD events at greater cost than those excluding ACE-II receptor blockers. The lower effectiveness is at odds with the results of the LIFE trial from which the estimates of effectiveness are derived.²⁴⁹ The reason for the finding is that losartan decreased CVA events by 25% but increased CHD events by 7%. As more patients in the LIFE trial suffered from CVA than CHD events: the beneficial effect of losartan on CVA considerably outweighed the increase in CHD events. However, in the general population twice as many persons suffer CHD as CVA events: considerably reducing the overall benefit.

Interventions that are direct substitutes

Dietary supplementation with fish oil capsules is a direct substitute for dietary oily fish. The former is considerably more costly for no additional benefit. This provides an additional reason to exclude fish oil from further analysis.

Adoption of a Mediterranean diet is intended to increase intake of omega-3 fatty acids and is therefore a substitute for dietary supplementation with oily fish. It is not possible to adopt two complete changes in diet at the same time. A Mediterranean diet therefore precludes a cholesterol-lowering diet. However, even at the cost per CVD event prevented of a Mediterranean diet is £5,707 (95% confidence interval: £4,834 to £8,743). The cost per event prevented with dietary supplementation with oily fish is £20,034 (lower 95% confidence interval £9,376; upper 95% confidence interval includes an increase in CVD) and with a cholesterol-lowering diet is £29,696 (95% confidence interval: £24,635 to £38,151). A Mediterranean diet is therefore less costly and more effective than both alternative dietary interventions.

Cost-effectiveness rankings

Excluding interventions that may cause net harm, preventive interventions can be grouped into three categories with respect to cost-effectiveness. Interventions with a low cost per CVD event prevented: aspirin, initial antihypertensive treatment (in men or women) and a Mediterranean diet. Interventions with an intermediate cost per CVD event prevented: intensive antihypertensive treatment (in men or women). Interventions with a high cost per CVD event prevented: simvastatin, clopidogrel.

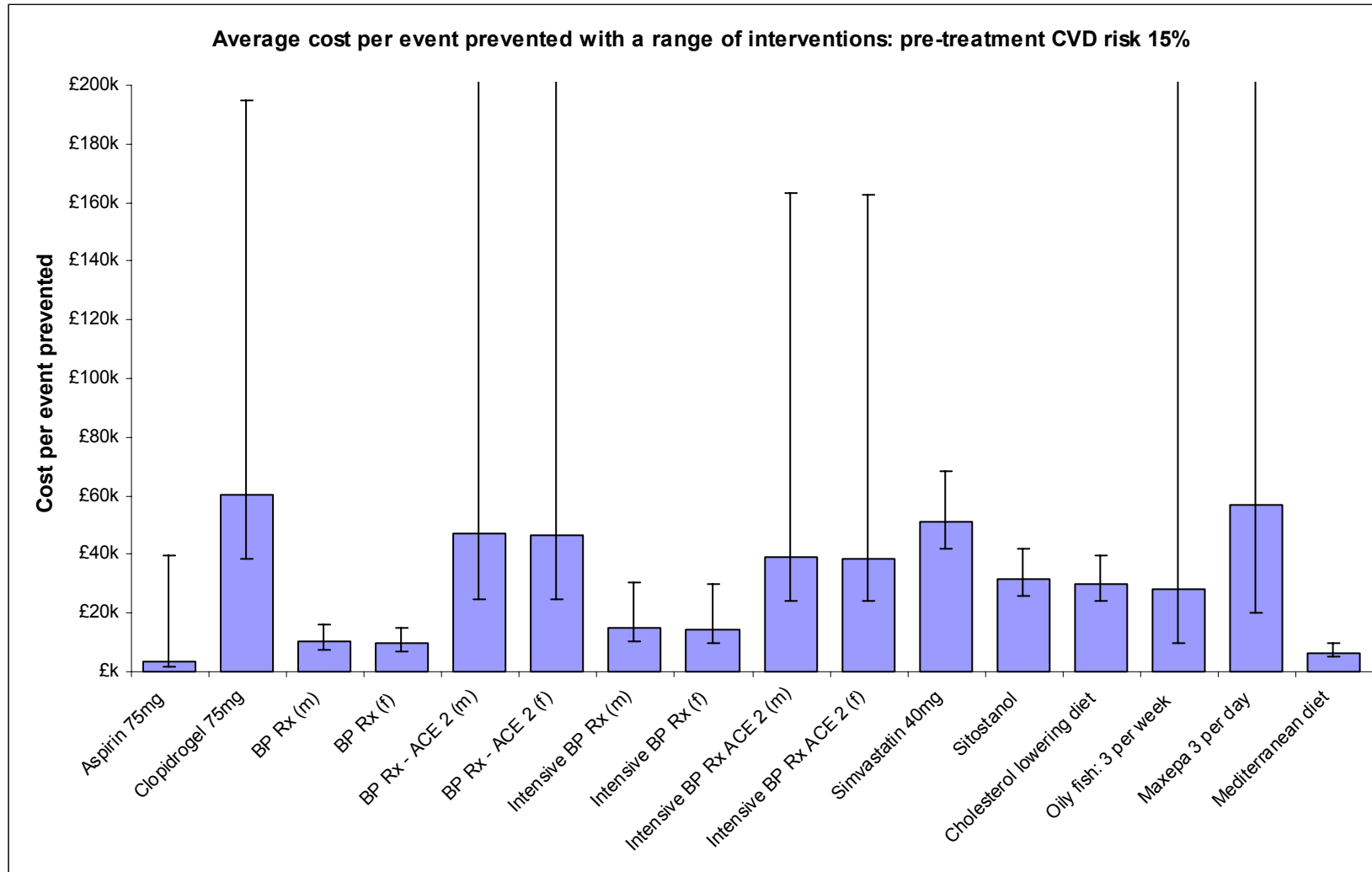
A further finding is that the cost-effectiveness of antihypertensive treatments are similar in men and women at 15% five-year CVD. (Table 23 and Figure 11)

Table 23: Cost-effectiveness of preventive interventions men and women at 15% five-year CVD risk.

Treatment	Reduction in CHD risk	Reduction in CVA risk	Adverse event rate per 5 years	Effect per 5 years	Discounted effect per 5 years	Discounted cost per five years	Cost per event prevented		
							Base case estimate	Sensitivity analysis (lower limit)	Sensitivity analysis (upper limit)
Aspirin 75mg	0.72	1.02	0.3%	2.2%	2.1%	£69	£3,289	£1,895	£39,471
Clopidrogel 75mg	0.63	0.90	0.0%	3.6%	3.5%	£2,120	£60,585	£38,253	£194,897
Initial BP Rx (men)	0.83	0.64	0.0%	2.6%	2.5%	£260	£10,254	£7,540	£16,107
Initial BP Rx (women)	0.83	0.64	0.0%	2.6%	2.5%	£245	£9,661	£7,104	£15,175
Initial BP Rx with ACE 2 (men)	0.89	0.48	0.0%	2.6%	2.5%	£1,174	£47,104	£24,959	Net harm
Initial BP Rx with ACE 2 (women)	0.89	0.48	0.0%	2.6%	2.5%	£1,159	£46,501	£24,640	Net harm
Intensive BP Rx (men)	0.67	0.51	0.0%	4.4%	4.3%	£634	£14,786	£10,252	£30,547
Intensive BP Rx (women)	0.67	0.51	0.0%	4.4%	4.3%	£619	£14,435	£10,009	£29,822
Intensive BP Rx ACE 2 (men)	0.72	0.38	0.0%	4.4%	4.2%	£1,652	£38,907	£24,055	£163,205
Intensive BP Rx ACE 2 (women)	0.72	0.38	0.0%	4.4%	4.2%	£1,647	£38,777	£23,975	£162,661
Simvastatin 40mg	0.69	0.70	0.0%	3.7%	3.6%	£1,837	£51,276	£41,768	£68,554
Margarine containing sitostanol	0.89	0.90	0.0%	1.3%	1.2%	£384	£31,546	£25,696	£42,175
Cholesterol lowering diet	0.94	0.94	0.0%	0.7%	0.7%	£213	£29,776	£24,255	£39,809
Oily fish 3 days a week	0.75	1.30	0.0%	1.4%	1.3%	£370	£28,196	£9,991	Net harm
Maxepa 3 a day	0.75	1.30	0.0%	1.4%	1.3%	£743	£56,663	£20,077	Net harm
Mediterranean diet	0.28	1.00	0.0%	6.5%	6.3%	£399	£6,341	£5,371	£9,714

* Total benefit figure for aspirin takes account of a 0.3% increase in risk of major bleeding.

Figure 11: Cost-effectiveness of interventions in a men and woman at 15% five-year CVD risk



Average cost-effectiveness in patients at 5% five-year CVD risk

The cost-effectiveness of CVD prevention is explored in a man and a woman whose five-year CVD risk is 5%, whose five-year CHD risk is 3% and five-year risk of CVA is 1%. Such levels of CVD risk might be found in a woman who is non-diabetic, aged 44, a non-smoker, with blood pressure is 170/106 mm Hg and total to HDL cholesterol ratio of 5.5. They might also be found in a non-diabetic man, aged 35, who smokes, whose blood pressure is 162/108 mm Hg and total to HDL cholesterol ratio is 4.9. Both patients are eligible for the full range of preventive interventions.

Baseline results

Cost per event prevented is three times higher in patients at 5% CVD risk than those at 15% CVD risk. However the cost per event prevented on aspirin is four times higher because the hazards of aspirin do not decrease proportionately with CVD risk.

Interventions that may cause net harm

In persons at 5% CVD risk, aspirin may cause net harm. This is because at the lower confidence limit of effectiveness the benefits of aspirin (0.87 relative risk of CHD and of 3%) are outweighed by the harms (1.23 relative risk of CVA and a 0.3% increase in major bleeding). The CVD risk threshold at which the benefits of aspirin just outweigh the harm is 10% (i.e. 6% CHD risk and 2% CVA risk). Treatment of persons at less than 6% CHD risk with aspirin might therefore be regarded as imprudent.

Cost-effectiveness rankings

The rankings of preventive interventions by cost-effectiveness are not sensitive to the pre-treatment level of CVD risk. Aspirin, initial antihypertensive treatment (in men or women) and a Mediterranean diet have the lowest cost per CVD event prevented. Intensive antihypertensive treatment (in men or women) has an intermediate cost per CVD event prevented. Simvastatin and clopidogrel have the highest costs per CVD event prevented. (Figure 12 and Table 25)

In men and women at 5% five-year CVD risk differences in the cost-effectiveness of antihypertensive treatments between are small.

Cost-effectiveness rankings of included treatments

When we exclude initial and further antihypertensive treatment with ACE-II receptor blockers, a cholesterol-lowering diet and dietary supplementation with oily fish we

are left with eight potential interventions. The cost-effectiveness rankings of these interventions in patients at 5% and 15% five-year CVD risk are identical. The rankings will only change if there are important differences in the ratio of CVA to CHD events. Antihypertensive treatments are more cost effective in patients with a higher risk of CVA than is typical for their overall CVD risk.

Table 24: Cost-effectiveness rankings in patients at 5% and 15% CVD risk

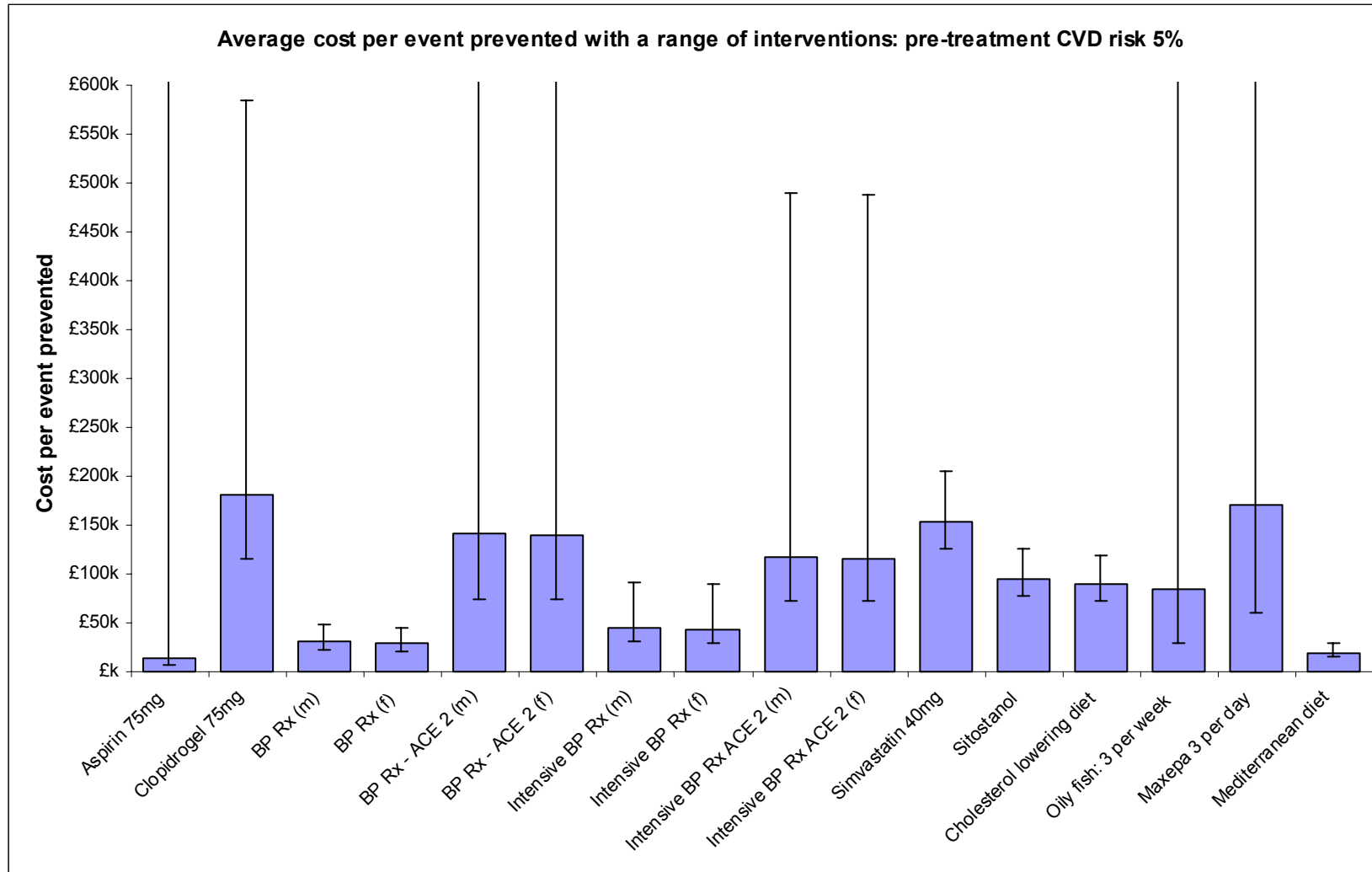
Treatment	Rank in patients at 15% five-year CVD risk	Rank in patients at 5% five-year CVD risk
Aspirin 75mg	1	1
Clopidrogel 75mg	7	7
Initial BP Rx (men & women)	3	3
Intensive BP Rx (men & women)	4	4
Simvastatin 40mg	6	6
Margarine containing sitostanol	5	5
Mediterranean diet	2	2

Table 25: Cost-effectiveness of preventive interventions men and women at 5% five-year CVD risk.

Treatment	Reduction in CHD risk	Reduction in CVA risk	Adverse event rate per 5 years	Effect per 5 years	Discounted effect per 5 years	Discounted cost per five years	Cost per event prevented		
							Base case estimate	Sensitivity analysis (lower limit)	Sensitivity analysis (upper limit)
Aspirin 75mg	0.72	1.02	0.3%	0.5%	0.5%	£69	£13,663	£6,766	Net harm
Clopidrogel 75mg	0.63	0.90	0.0%	1.2%	1.2%	£2,120	£181,754	£114,760	£584,692
Initial BP Rx (men)	0.83	0.64	0.0%	0.9%	0.8%	£260	£30,762	£22,620	£48,321
Initial BP Rx (women)	0.83	0.64	0.0%	0.9%	0.8%	£245	£28,982	£21,312	£45,525
Initial BP Rx with ACE 2 (men)	0.89	0.48	0.0%	0.9%	0.8%	£1,174	£141,312	£74,878	Net harm
Initial BP Rx with ACE 2 (women)	0.89	0.48	0.0%	0.9%	0.8%	£1,159	£139,502	£73,919	Net harm
Intensive BP Rx (men)	0.67	0.51	0.0%	1.5%	1.4%	£634	£44,357	£30,756	£91,642
Intensive BP Rx (women)	0.67	0.51	0.0%	1.5%	1.4%	£619	£43,305	£30,027	£89,467
Intensive BP Rx ACE 2 (men)	0.72	0.38	0.0%	1.5%	1.4%	£1,652	£116,720	£72,165	£489,614
Intensive BP Rx ACE 2 (women)	0.72	0.38	0.0%	1.5%	1.4%	£1,647	£116,331	£71,925	£487,983
Simvastatin 40mg	0.69	0.70	0.0%	1.2%	1.2%	£1,837	£153,829	£125,304	£205,663
Margarine containing sitostanol	0.89	0.90	0.0%	0.4%	0.4%	£384	£94,637	£77,089	£126,526
Cholesterol lowering diet	0.94	0.94	0.0%	0.2%	0.2%	£213	£89,329	£72,764	£119,428
Oily fish 3 days a week	0.75	1.30	0.0%	0.5%	0.4%	£370	£84,588	£29,972	Net harm
Maxepa 3 a day	0.75	1.30	0.0%	0.5%	0.4%	£743	£169,989	£60,232	Net harm
Mediterranean diet	0.28	1.00	0.0%	2.2%	2.1%	£399	£19,024	£16,114	£29,142

* Total benefit figure for aspirin takes account of a 0.3% increase in risk of major bleeding.

Figure 12: Cost-effectiveness of interventions in a men and woman at 5% five-year CVD risk



Sensitivity analysis: the effects of changes in costs

Aspirin

Aspirin is the most cost-effective intervention and in men and women. However, aspirin's cost-effectiveness is due to its lower cost than antihypertensive treatment rather than greater effectiveness. This means that it is very sensitive to assumptions about the costs of treatment and follow-up. If patients on aspirin are not followed up at all, the cost per event prevented of aspirin falls by two thirds; if they are followed-up by a GP the cost trebles, rendering it less cost-effective than a Mediterranean diet.

The cost-effectiveness of aspirin is sensitive to assumptions about its effectiveness. However it is not sensitive to assumptions about the incidence of major bleeding attributable: if the five-year incidence of major bleeding attributable to aspirin is 0.4% (the upper 95% confidence limit)²⁰³ it is still the most cost-effective intervention in patients at 5% CVD risk.

Mediterranean diet

The next most cost-effective intervention is a Mediterranean diet. It costs twice as much per event prevented as aspirin. The cost-effectiveness of a Mediterranean diet is to a limited extent sensitive to assumptions about its effectiveness. It may be no more cost-effective than initial antihypertensive treatment, but it is almost certainly more cost-effective than intensive antihypertensive treatment, margarine containing sitostanol, simvastatin or clopidogrel. The cost-effectiveness of a Mediterranean diet is robust to assumptions about the amount of dietician time needed for long-term follow-up. Even if patients require three hours of dietician contact per year it remains more cost-effective than initial antihypertensive treatment.

Initial antihypertensive treatment

Initial antihypertensive treatment is the next most cost-effective intervention in both men and women. It costs three times as much per event prevented as aspirin. If patients on aspirin or antihypertensive treatment are followed up by a GP it is more cost-effective than aspirin. However reducing the annual cost of drugs to £10 (the cost of treatment with bendrofluazide alone) does not influence the cost-effectiveness rankings.

Initial antihypertensive treatment is not sensitive to assumptions about the cost of treatment. If drugs used for initial antihypertensive treatment cost £100 per annum it

becomes less cost-effective than intensive antihypertensive treatment but remains more cost-effective than sitostanol, simvastatin or clopidogrel.

Intensive antihypertensive treatment

Intensive antihypertensive treatment costs four to five times as much per event prevented as aspirin. If initial antihypertensive treatment costs £100 per annum and the additional drugs needed for intensive antihypertensive treatment cost a further £200 per annum, intensive antihypertensive treatment becomes less cost effective than sitostanol. However it remains more cost-effective than simvastatin or clopidogrel.

Sitostanol

Dietary supplementation with margarine containing sitostanol costs ten times as much per event prevented as aspirin. Its cost-effectiveness is sensitive to assumptions about its effectiveness. Even if patients have no long-term follow-up costs the cost per event prevented is more than eight times that of treatment with aspirin.

Simvastatin

Drug treatment with simvastatin is one of the least cost-effective interventions considered. Its cost-effectiveness is not sensitive to changes in the cost of follow-up and is only likely to be affected by large changes in the cost of treatment. To be of similar cost-effectiveness to initial antihypertensive treatment, the cost of the drug must fall by 85% and to be of similar cost-effectiveness to further antihypertensive treatment with enalapril, the cost must fall by 75%. The price of a drug typically falls by less than 50% when it comes off patent, making such a price fall very unlikely.

Clopidogrel

Drug treatment with clopidogrel is the least cost-effective intervention considered. Its cost-effectiveness is not sensitive to changes in the cost of follow-up and is only likely to be affected by very large changes in the cost of treatment. To be of similar cost-effectiveness to initial antihypertensive treatment, the cost must fall by 85%. This is very unlikely.

Order in which to offer preventive interventions

The order in which interventions are offered is determined by their cost-effectiveness rankings.

The use of aspirin in a patient at less than 6% five-year CHD risk (10% five-year CVD risk) is imprudent. At any level of risk higher than this, aspirin will be offered

first, followed by advice on a Mediterranean diet, initial antihypertensive treatment, intensive antihypertensive treatment, sitostanol, simvastatin and clopidogrel.

In a patient at less than 6% five-year CHD risk (10% five-year CVD risk), advice on a Mediterranean diet will be offered first, then initial antihypertensive treatment, intensive antihypertensive treatment, sitostanol, simvastatin and clopidogrel.

Smoking cessation interventions

Smoking cessation interventions are characterised by high costs in the first year of the intervention, followed by no costs in subsequent years. Because the costs are immediate but the benefits accrue over many years, a model with a five-year time horizon is not well suited to assessing the cost-effectiveness of smoking cessation interventions in relation to other interventions. However observations can still be made about the relative cost-effectiveness of different smoking cessation strategies.

Dominated strategies

Smoking cessation strategies using nicotine replacement patches leads to a long-term quit rate of 2% with limited support and 3% with intensive support. These strategies are dominated by strategies using bupropion with intensive support as achieves a 4% quit rate at lower cost. (Table 26)

Sensitivity analysis

The cost-effectiveness of smoking cessation is sensitive to assumptions about the effectiveness of interventions on the quit rate. If the quit rate attributable to an intervention continues to decline over a number of years (i.e. if quitters tend to restart smoking), smoking cessation becomes much less cost effective.

Cost-effectiveness ranking

Costs per event prevented are illustrated visually in Figure 13. Brief advice from a physician is the most cost-effective intervention over a five-year time horizon, followed by a combination of bupropion, nicotine replacement patches and intensive support. Cost per event prevented is inversely proportional to overall risk of CVD. Because the effects on CHD risk and CVA risk are very similar, cost-effectiveness rankings are not likely to be different in patients whose CVD risk is largely risk of CVA compared to patients whose CVD risk is largely risk of CHD.

Overview of cost-effectiveness of smoking cessation interventions

Compared to drug and dietary interventions, smoking cessation interventions are not cost-effective over a five-year time horizon. This is due to their low effectiveness at

reducing CVD risk rather than a high cost. However, if smoking cessation is maintained, the cost per event prevented over a ten-year time horizon halves compared to a five-year horizon and halves again over a twenty-year time horizon.

Smoking cessation also differs from other CVD prevention interventions in that it confers significant other health benefits. Because of the wide benefits associated with quitting smoking, pharmacological interventions to assist smoking cessation have been found to be highly cost-effective in the long-term.²⁸²

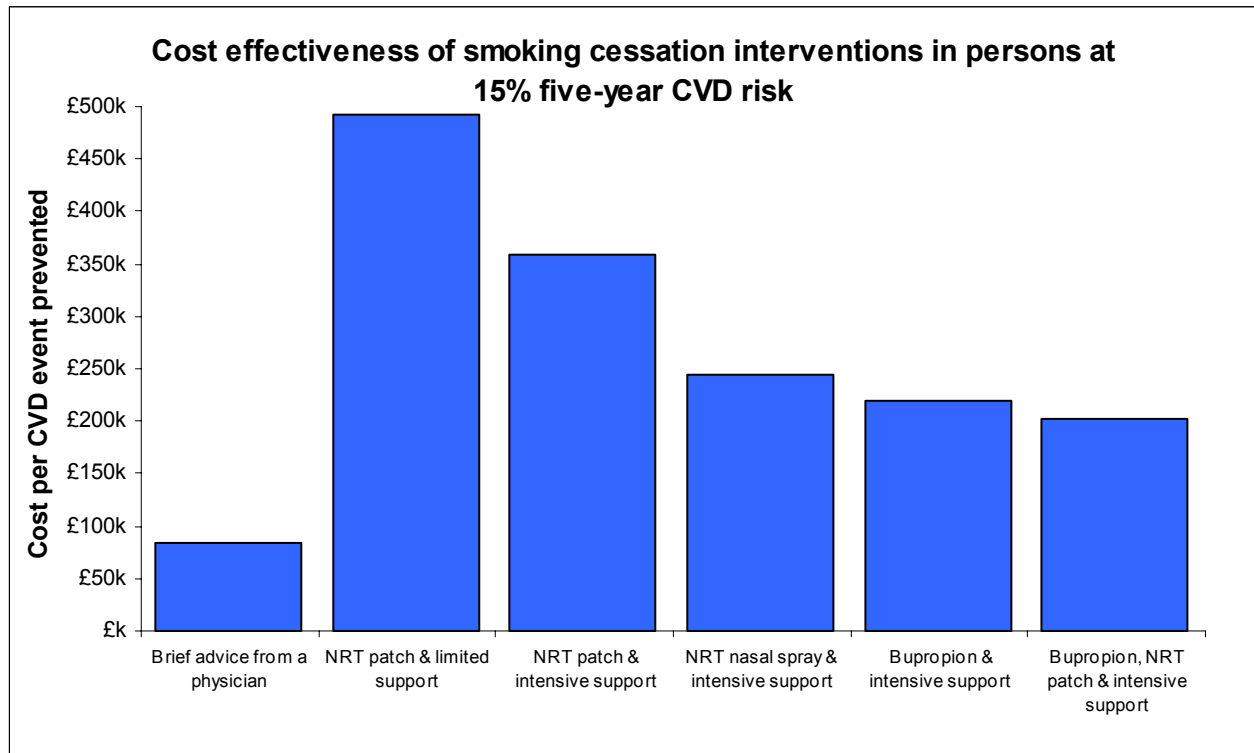
If it is believed that quitters remain non-smokers in the long-term, smoking cessation interventions are likely to be highly cost-effective and should be offered to all smokers. Logically, smokers at highest risk of CVD would benefit most from smoking cessation. If it is believed that quitters tend to take up smoking again, smoking cessation interventions are unlikely to be cost-effective and should not be offered.

Interventions to increase smoking cessation will not be considered further in this analysis. This is because the case for offering smoking cessation interventions does not rely solely on the effect of smoking cessation on CVD. Nevertheless some general principles can be drawn from this analysis. Benefits of smoking cessation interventions are proportional to CVD risk and costs are independent of CVD risk: cost per CVD event is therefore inversely proportional to CVD risk. Since the cost per event prevented with Bupropion, NRT patch and intensive support is about two and a half times greater than with brief advice from a physician, Bupropion, NRT patch and intensive support in a person at 25% CVD risk is equally cost-effective to brief advice in a person at 10% five-year CVD. It follows that the most efficient use of intensive smoking cessation interventions is to prioritise individuals at highest CVD risk.

Table 26: Cost-effectiveness of smoking cessation interventions over five years in men and women at 15% five-year CVD risk.

Smoking cessation strategy	Relative risk on quitting: CHD	Relative risk on quitting: CVA	Quit rate	Reduction in CHD risk	Reduction in CVA risk	Five-year discounted benefit	Five-year discounted cost	Cost per event prevented
Brief advice from a physician	0.65	0.60	1.0%	0.03%	0.01%	0.01%	£10	£84,374
NRT patch & limited support	0.65	0.60	2.0%	0.06%	0.02%	0.02%	£115	£493,025
NRT patch & intensive support	0.65	0.60	3.0%	0.09%	0.04%	0.03%	£125	£358,239
NRT nasal spray & intensive support	0.65	0.60	6.0%	0.19%	0.07%	0.07%	£170	£243,523
Bupropion & intensive support	0.65	0.60	4.0%	0.13%	0.05%	0.05%	£102	£219,024
Bupropion, NRT patch & intensive support	0.65	0.60	9.0%	0.28%	0.11%	0.10%	£212	£201,975

Figure 13: Cost effectiveness of smoking cessation interventions in men and women



Incremental cost-effectiveness of preventive interventions

Because incremental cost-effectiveness differs from average cost-effectiveness it is important to determine incremental rather than average cost-effectiveness. Not all patients are eligible for antihypertensive treatment or eligible for statins. Eligibility for antihypertensive treatment or statins may affect the incremental cost per event prevented of other interventions. It is therefore important to investigate variation in incremental cost-effectiveness in patients eligible and in eligible for these treatments.

In the first case we will consider two patients (male and female) whose five-year CVD risk is 15% (five-year CHD risk 9% and five-year CVA risk 3%).

Patients eligible for all preventive interventions

The results of incremental cost-effectiveness analysis are shown in Table 27. Apart from initial antihypertensive treatment, the results are identical for men and women. (Figure 15) Because it is the first intervention, the incremental cost per event prevented of aspirin is the same as the cost per event prevented with aspirin as a solo treatment. Because each previous intervention attenuates the benefits of each additional intervention, the incremental cost per event prevented rises exponentially the more interventions are given. If the cost per event prevented with aspirin is used as a unit of measurement, the incremental costs per event prevented are three times greater for a Mediterranean diet, five times greater for initial antihypertensive treatment (four times for men), 17 times greater for intensive antihypertensive treatment, 35 times greater for sitostanol, 73 times greater for simvastatin and 172 times greater for clopidogrel. (Figure 14) The incremental cost-effectiveness analysis therefore reinforces the cost-effectiveness rankings and hence the order in which treatment should be offered.

Patients not eligible for all preventive interventions

Patients not eligible for antihypertensives

Table 28 shows the incremental cost-effectiveness in patients not eligible for antihypertensive treatments. In patients not eligible for antihypertensives the costs per event prevented with sitostanol, simvastatin and clopidogrel are half the costs per event prevented in patients eligible for antihypertensives. Nevertheless the cost-effectiveness rankings are the same.

Table 27: Incremental cost-effectiveness in male and female patients at 15% five-year CVD risk

	Relative risk of CHD on Rx	Relative risk of CVA on Rx	Absolute risk reduction CHD	Absolute risk reduction CVA	Adverse event rate per 5 years	Incremental effect per 5 years	Discounted effect per 5 years	Discounted incremental cost per 5 years	Incremental cost per event prevented
Male patient									
Aspirin 75mg	0.72	1.02	2.5%	-0.1%	0.3%	2.2%	2.1%	£69	£3,289
Mediterranean diet	0.28	1.00	4.7%	0.0%	0.0%	4.7%	4.5%	£399	£8,807
Initial BP Rx (men)	0.83	0.64	0.3%	1.1%	0.0%	1.4%	1.4%	£212	£15,501
Intensive BP Rx (men)	0.81	0.80	0.3%	0.4%	0.0%	0.7%	0.7%	£369	£56,123
Margarine containing sitostanol	0.89	0.90	0.1%	0.2%	0.0%	0.3%	0.3%	£326	£116,422
Simvastatin 40mg	0.69	0.70	0.3%	0.4%	0.0%	0.8%	0.7%	£1,779	£240,945
Clopidrogel 75mg	0.63	0.90	0.3%	0.1%	0.0%	0.4%	0.4%	£2,073	£566,688
Female patient									
Aspirin 75mg	0.72	1.02	2.5%	-0.1%	0.3%	2.2%	2.1%	£69	£3,289
Mediterranean diet	0.28	1.00	4.7%	0.0%	0.0%	4.7%	4.5%	£399	£8,807
Initial BP Rx (women)	0.83	0.64	0.3%	1.1%	0.0%	1.4%	1.4%	£197	£14,403
Intensive BP Rx (women)	0.81	0.80	0.3%	0.4%	0.0%	0.7%	0.7%	£369	£56,123
Margarine containing sitostanol	0.89	0.90	0.1%	0.2%	0.0%	0.3%	0.3%	£326	£116,422
Simvastatin 40mg	0.69	0.70	0.3%	0.4%	0.0%	0.8%	0.7%	£1,779	£240,945
Clopidrogel 75mg	0.63	0.90	0.3%	0.1%	0.0%	0.4%	0.4%	£2,073	£566,688

Table 28: Incremental cost-effectiveness in patients at 15% five-year CVD risk who are not eligible for antihypertensives

	Relative risk of CHD on Rx	Relative risk of CVA on Rx	Absolute risk reduction CHD	Absolute risk reduction CVA	Adverse event rate per 5 years	Incremental effect per 5 years	Discounted effect per 5 years	Discounted incremental cost per 5 years	Incremental cost per event prevented
Male and female patients									
Aspirin 75mg	0.72	1.02	2.5%	-0.1%	0.3%	2.2%	2.1%	£69	£3,289
Mediterranean diet	0.28	1.00	4.7%	0.0%	0.0%	4.7%	4.5%	£399	£8,807
Margarine containing sitostanol	0.89	0.90	0.2%	0.3%	0.0%	0.5%	0.5%	£326	£66,698
Simvastatin 40mg	0.69	0.70	0.5%	0.8%	0.0%	1.3%	1.3%	£1,779	£138,003
Clopidrogel 75mg	0.63	0.90	0.4%	0.2%	0.0%	0.6%	0.6%	£2,073	£351,523

Figure 14: Incremental cost-effectiveness of CVD prevention in men and women at 15% five-year CVD risk eligible for all treatments

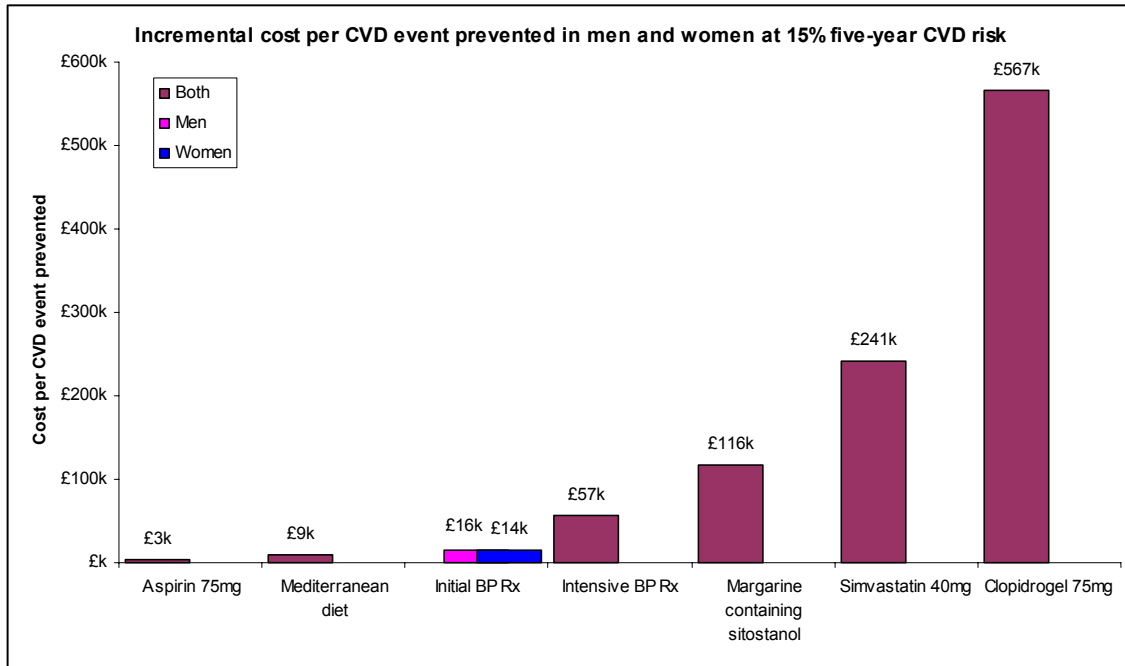
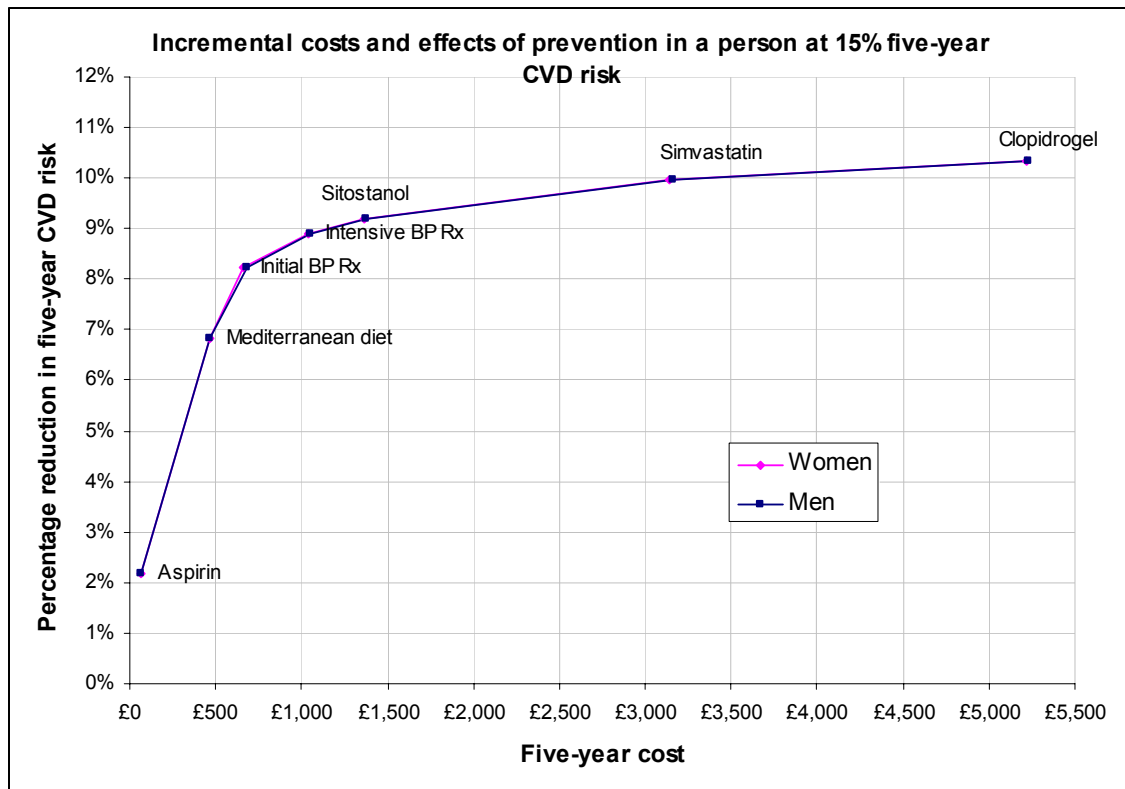


Figure 15: Cost and effectiveness of CVD prevention in men and women at 15% five-year CVD risk eligible for all treatments



Patients not eligible for statins

Table 29 shows incremental cost-effectiveness in patients not eligible for statins. In patients not eligible for statins the cost per event prevented with clopidogrel is slightly lower than in patients eligible for statins. However clopidogrel remains by far the least cost-effective intervention.

Patients not eligible for statins or antihypertensives

Table 30 shows incremental cost-effectiveness in patients not eligible for antihypertensives or statins. In patients not eligible for antihypertensives or statins the cost per event prevented with clopidogrel is considerably lower than in patients who are eligible for these interventions. However clopidogrel remains by far the least cost-effective intervention.

A range of treatment eligibility assumptions

Table 31 shows the cost per event prevented of each intervention under a range of different eligibility assumptions. Even if simvastatin is given as the sole treatment the cost per event prevented is £51,300. This is three times greater than the incremental cost per event prevented of adding initial antihypertensive treatment to a patient already treated with aspirin and following a Mediterranean diet.

Similarly, even if clopidogrel is given as the sole treatment, the cost per event prevented is £60,600: more than the cost per event prevented of adding further antihypertensive treatment to a patient already taking aspirin and initial antihypertensive treatment and already following a Mediterranean diet.

Table 29: Incremental cost-effectiveness in male and female patients at 15% five-year CVD risk who are not eligible for statins

Male patient	Relative risk of CHD on treatment	Relative risk of CVA on treatment	Absolute risk reduction CHD	Absolute risk reduction CVA	Adverse event rate per 5 years	Incremental effect per 5 years	Discounted effect per 5 years	Discounted incremental cost per 5 years	Incremental cost per event prevented
Aspirin 75mg	0.72	1.02	2.5%	-0.1%	0.3%	2.2%	2.1%	£69	£3,289
Mediterranean diet	0.28	1.00	4.7%	0.0%	0.0%	4.7%	4.5%	£399	£8,807
Initial BP Rx (men)	0.83	0.64	0.3%	1.1%	0.0%	1.4%	1.4%	£212	£15,501
Intensive BP Rx (men)	0.81	0.80	0.3%	0.4%	0.0%	0.7%	0.7%	£369	£56,123
Margarine containing sitostanol	0.89	0.90	0.1%	0.2%	0.0%	0.3%	0.3%	£326	£116,422
Clopidogrel 75mg	0.63	0.90	0.4%	0.1%	0.0%	0.5%	0.5%	£2,073	£392,516
Female patient	Relative risk of CHD on treatment	Relative risk of CVA on treatment	Absolute risk reduction CHD	Absolute risk reduction CVA	Adverse event rate per 5 years	Incremental effect per 5 years	Discounted effect per 5 years	Discounted incremental cost per 5 years	Incremental cost per event prevented
Aspirin 75mg	0.72	1.02	2.5%	-0.1%	0.3%	2.2%	2.1%	£69	£3,289
Mediterranean diet	0.28	1.00	4.7%	0.0%	0.0%	4.7%	4.5%	£399	£8,807
Initial BP Rx (women)	0.83	0.64	0.3%	1.1%	0.0%	1.4%	1.4%	£197	£14,403
Intensive BP Rx (women)	0.81	0.80	0.3%	0.4%	0.0%	0.7%	0.7%	£369	£56,123
Margarine containing sitostanol	0.89	0.90	0.1%	0.2%	0.0%	0.3%	0.3%	£326	£116,422
Clopidogrel 75mg	0.63	0.90	0.4%	0.1%	0.0%	0.5%	0.5%	£2,073	£392,516

Table 30: Incremental cost-effectiveness in a patients at 15% five-year CVD risk who are not eligible for statins or antihypertensives

Male and female patients	Relative risk of CHD on treatment	Relative risk of CVA on treatment	Absolute risk reduction CHD	Absolute risk reduction CVA	Adverse event rate per 5 years	Incremental effect per 5 years	Discounted effect per 5 years	Discounted incremental cost per 5 years	Incremental cost per event prevented
Aspirin 75mg	0.72	1.02	2.5%	-0.1%	0.3%	2.2%	2.1%	£69	£3,289
Mediterranean diet	0.28	1.00	4.7%	0.0%	0.0%	4.7%	4.5%	£399	£8,807
Margarine containing sitostanol	0.89	0.90	0.2%	0.3%	0.0%	0.5%	0.5%	£326	£66,698
Clopidogrel 75mg	0.63	0.90	0.6%	0.3%	0.0%	0.9%	0.9%	£2,073	£243,680

Table 31: Incremental cost-effectiveness in male and female patients at 15% five-year CVD risk under a range of assumptions about treatment eligibility

Male patient	Incremental cost per event prevented all treatments	Incremental cost per event prevented no BP treatment	Incremental cost per event prevented no BP treatment or statin	Incremental cost per event prevented no statin	Incremental cost per event prevented no Mediterranean diet	Cost per event prevented as sole treatment
Aspirin 75mg	£3,289	£3,289	£3,289	£3,289	£3,289	£3,289
Mediterranean diet	£8,807	£8,807	£8,807	£8,807		£6,341
Initial BP Rx (men)	£15,501			£15,501	£9,921	£10,254
Intensive BP Rx (men)	£56,123			£56,123	£26,911	£14,786
Margarine containing sitostanol	£116,422	£66,698	£66,698	£116,422	£54,239	£31,546
Simvastatin 40mg	£240,945	£138,003			£112,379	£51,276
Clopidrogel 75mg	£566,688	£351,523	£243,680	£392,516	£196,556	£60,585
Female patient	Incremental cost per event prevented all treatments	Incremental cost per event prevented no BP treatment	Incremental cost per event prevented no BP treatment or statin	Incremental cost per event prevented no statin	Incremental cost per event prevented no Mediterranean diet	Cost per event prevented as sole treatment
Aspirin 75mg	£3,289	£3,289	£3,289	£3,289	£3,289	£3,289
Mediterranean diet	£8,807	£8,807	£8,807	£8,807		£6,341
Initial BP Rx (women)	£14,403			£14,403	£9,218	£9,661
Intensive BP Rx (women)	£56,123			£56,123	£26,911	£14,435
Margarine containing sitostanol	£116,422	£66,698	£66,698	£116,422	£54,239	£31,546
Simvastatin 40mg	£240,945	£138,003			£112,379	£51,276
Clopidrogel 75mg	£566,688	£351,523	£243,680	£392,516	£196,556	£60,585

Conclusions from incremental cost-effectiveness analysis

It is quite clear that the order in which treatments are offered makes a great difference to their cost effectiveness. It is clear that aspirin, advice to follow a Mediterranean diet and initial antihypertensive treatment are the most cost effective preventive interventions and should be offered first. Subsequent preventive interventions cost at least three times more per CVD event prevented. It is also clear that whether or not patients are eligible for other interventions, simvastatin and clopidogrel are the least cost-effective preventive interventions and should therefore be considered last.

Incremental cost-effectiveness in a natural population

Real individuals in a natural population vary in their risk factor characteristics. They therefore vary in their CVD, CHD and CVA risks and in their eligibility for different treatments. Since these characteristics influence the incremental cost-effectiveness of interventions, it follows that cost-effectiveness in real individuals in a natural population will show substantial variation. This section reports the result of incremental cost-effectiveness analysis in 5603 patients from the Health Survey for England, aged between 35 and 74.

Treatment eligibility criteria

Treatment eligibility criteria are based on the Joint British recommendations for the prevention of CHD in primary care.¹⁴⁴ The treatment eligibility criteria used are those summarised in Table 32.

Aspirin

The recommendations state that all persons over 50 whose ten-year CHD risk exceeds 15% are eligible for aspirin. They also state that those with high blood pressure be given aspirin only when their blood pressure is controlled. No operational definition of “controlled” blood pressure is provided. Since it is intended to treat all those with high blood pressure, in this study I assume that all persons whose ten-year CHD risk exceeds 15% are eligible for aspirin. A five-year CHD risk of 7.5% is equivalent to a ten-year CHD risk of 15%.

Mediterranean diet

No specific recommendations are given about advising patients to follow a Mediterranean diet. In this study it is therefore assumed that all persons at high risk of CHD will be given advice to follow a Mediterranean diet. This means all those whose five-year CHD risk exceeds 7.5%.

Antihypertensive treatment

Very clear guidance is given on when to treat patients for high blood pressure. Any person whose systolic blood pressure exceeds 160 mm Hg or whose diastolic blood pressure exceeds 100 mm Hg should be offered treatment, irrespective of their risk of CHD. In addition, any person whose systolic blood pressure exceeds 140 mm Hg or

whose diastolic blood pressure exceeds 90 mm Hg should be offered treatment if their ten-year CHD risk exceeds 15%.

Initial antihypertensive treatment

In this study any patient whose systolic blood pressure exceeds 160 mm Hg or whose diastolic blood pressure exceeds 100 mm Hg is considered eligible for treatment. In addition, any person whose systolic blood pressure exceeds 140 mm Hg or whose diastolic blood pressure exceeds 90 mm Hg is considered eligible for initial antihypertensive treatment if their five-year CHD risk exceeds 7.5%.

Patients who are already receiving antihypertensive treatment are not eligible for initial antihypertensive treatment, but are eligible for intensive antihypertensive treatment.

Intensive antihypertensive treatment

There are no specific recommendations about which patients should be offered intensive antihypertensive treatment. It is likely that all patients eligible for initial antihypertensive treatment could benefit from further blood pressure lowering. In this study, therefore, all patients eligible for initial antihypertensive treatment are considered to be eligible for further antihypertensive treatment. In addition any patients who are already receiving antihypertensive treatment (and are therefore not eligible for initial antihypertensive treatment) are considered to be eligible for intensive antihypertensive treatment if they meet the criteria for initial antihypertensive treatment.

Sitostanol

No specific recommendations are given about advising patients supplement their diet with margarine containing sitostanol. In this study it is therefore assumed that all persons at high risk of CHD will be given advice to consume margarine containing sitostanol. This means all those whose five-year CHD risk exceeds 7.5%.

Statin

Any person who is thought to have familial hypercholesterolaemia should be offered cholesterol-lowering treatment. The guidelines state that persons with familial hypercholesterolaemia typically have total cholesterol levels of 9.0 mmol/l or greater together with clinical signs. In the Policy Statement of the European Atherosclerosis Society total cholesterol greater than 7.8 mmol/l was defined as compatible with adult familial hypercholesterolaemia.²⁸³ However, it has been noted that adult familial

hypercholesterolaemia patients usually have total cholesterol >9.0 mmol/l.²⁸⁴ For the purposes of this analysis, anyone with total cholesterol of 9.0 mmol/l is considered to have familial hypercholesterolaemia and is therefore eligible for treatment.

In addition, anyone whose total cholesterol is over 5.0 mmol/l and whose ten-year CHD risk exceeds 15% (equivalent to a five-year CHD risk of 7.5%) is also eligible for treatment.

Clopidogrel

No specific recommendations are given about clopidogrel. In this study it is therefore assumed that all persons whose five-year CHD risk exceeds 7.5% are eligible for clopidogrel.

Table 32: Treatment eligibility criteria used for incremental cost-effectiveness analysis in a natural population

Intervention	Treatment criteria	
	Non risk criteria	Five-year risk threshold
Aspirin	Age >50	$>7.5\%$ CHD risk
Mediterranean diet		$>7.5\%$ CHD risk
Initial antihypertensive treatment	Blood pressure $\geq 160/100$ mm Hg	Any risk level
	Blood pressure $\geq 140/90$ mm Hg	$>7.5\%$ CHD risk
Intensive antihypertensive treatment	Blood pressure $\geq 160/100$ mm Hg	Any risk level
	Blood pressure $\geq 140/90$ mm Hg	$>7.5\%$ CHD risk
Sitostanol		$>7.5\%$ CHD risk
Simvastatin	Total cholesterol ≥ 9.0 mmol/l	Any risk level
	Total cholesterol ≥ 5.0 mmol/l	$>7.5\%$ CHD risk
Clopidogrel		$>7.5\%$ CHD risk

Source: Adapted from Joint British Recommendations on prevention of CHD in primary care

Incremental cost-effectiveness analysis in 5603 individual patients

Figure 16 shows the cost per CVD event prevented plotted against pre-treatment CVD risk in all 5603 patients in the Health Survey for England. Figure 17 shows the same data plotted against pre-treatment CHD risk. Because the vertical axes are truncated at £200,000 per event prevented, not all the data points for simvastatin and clopidogrel appear on the graphs. Nevertheless, a number of features are clear.

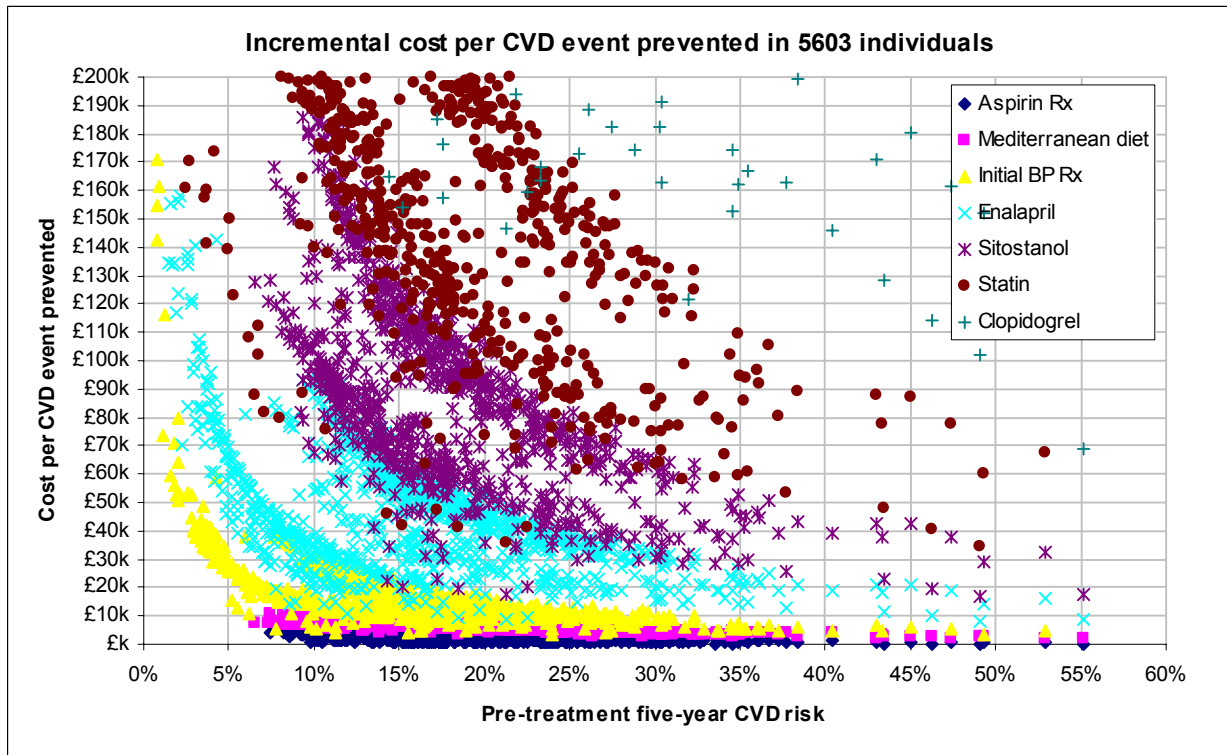
Relationship between pre-treatment risk and cost-effectiveness

For all interventions, cost-effectiveness shows a strong relationship to pre-treatment CVD risk. For all interventions, cost-effectiveness also shows a strong relationship to pre-treatment CHD risk.

Relationship between the preventive intervention and cost-effectiveness

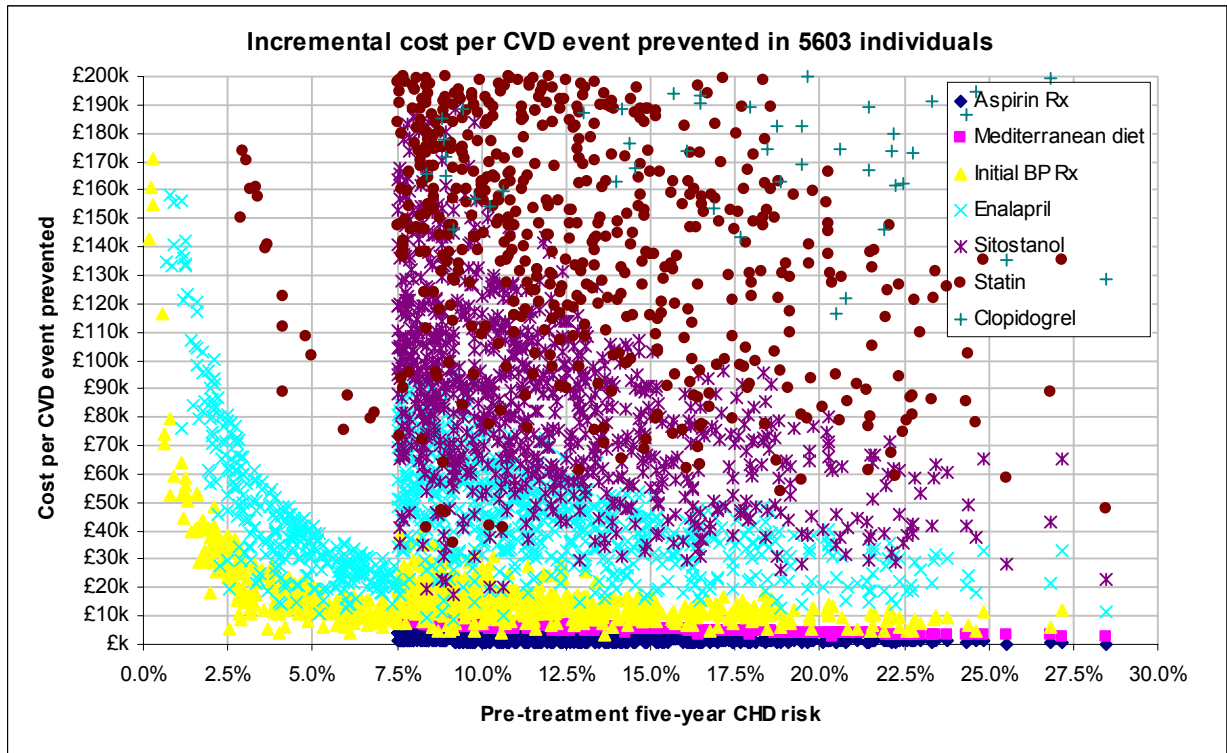
The preventive intervention itself is a strong determinant of cost-effectiveness. In general the cost-effectiveness ranking of each intervention tends to be the same stable across all CVD risks. For example, the majority of data points representing cost per event prevented with aspirin lie below those representing all the other interventions: indicating that it is nearly always more cost-effective than any other intervention. There is some overlap in the cost per event prevented with a Mediterranean diet and initial antihypertensive treatment. Further antihypertensive treatment with enalapril is almost always more cost-effective than sitostanol, which is in turn more cost effective than simvastatin. There is some overlap in the cost per event prevented with simvastatin and clopidogrel.

Figure 16: Cost effectiveness in relation to CVD risk in 5603 individuals aged 35 to 74



Note: vertical axis has been truncated at £200,000 per CVD event prevented

Figure 17: Cost effectiveness in relation to CHD risk in 3775 patients aged 35 to 74



Note: vertical axis has been truncated at £200,000 per CVD event prevented

Figure 17 shows that enalapril and initial antihypertensive treatment are more cost-effective in patients at just 7.5% five-year CHD risk than in those at just over this risk level. This paradoxical finding is because patients at less than 7.5% five-year CHD risk are not eligible for any additional treatments, such as aspirin or advice on a Mediterranean diet whereas patients at more than 7.5% five-year CHD risk are eligible for additional treatment. The incremental benefits of treatment are attenuated by the use of previous preventive interventions and antihypertensive treatment in patients at just over 7.5% five-year CHD risk is therefore less cost-effective.

Cost-effectiveness rankings in 5603 individual patients

The key question from the perspective of cost-effectiveness rankings is whether they hold true in any individual patient with any likely combination of risk factors and any likely combination of treatment eligibilities. In other words, the key question is whether it is always true aspirin is more cost-effective than a Mediterranean diet, that whether a Mediterranean diet always more cost effective than initial antihypertensive treatment and so on. This can be explored by looking at the cost-effectiveness rankings in each individual patient of each treatment for which they are eligible.

Cost-effectiveness ranking of aspirin in a natural population

In total 887 patients are eligible for treatment with aspirin. In all of these individuals aspirin is the most cost-effective treatment for which they are eligible.

Cost-effectiveness ranking of a Mediterranean diet in a natural population

In total 939 persons are eligible for advice to follow a Mediterranean diet. In 916 (97.6%) of these persons, the Mediterranean diet is more cost-effective than all other interventions except aspirin. It is therefore almost always correct to rank a Mediterranean diet as more cost-effective than initial antihypertensive treatment.

In 22 persons, the Mediterranean diet is less cost-effective than aspirin and than initial antihypertensive treatment. In one person it is less cost-effective than aspirin and intensive antihypertensive treatment with enalapril. This latter patient is already on antihypertensive treatment and therefore not eligible for initial antihypertensive treatment. All of these 23 persons share a number of characteristics. They tend to be at high risk of CVA in comparison to their risk of CHD (mean five-year CVA risk 10% and

CHD risk 10%). They also are all at high risk of CVD (mean five-year CVD risk 21%). Because they are at such high CVD risk, in practice such patients are likely to be offered both antihypertensive treatment and a Mediterranean diet. The ranking of a Mediterranean diet in relation to initial antihypertensive treatment or aspirin in these patients is therefore not of great practical significance.

Cost-effectiveness ranking of initial antihypertensive treatment in a natural population

In total 773 persons are eligible for initial antihypertensive treatment. In not one of these is the cost per event prevented with initial antihypertensive treatment greater than the cost per event prevented with more highly ranked interventions (intensive antihypertensive treatment, sitostanol, simvastatin and clopidogrel).

Cost-effectiveness ranking of intensive antihypertensive treatment in a natural population

In total 995 persons are eligible for intensive antihypertensive treatment (enalapril). In not one of these is the cost per event prevented with intensive antihypertensive treatment greater than the cost per event prevented with more highly ranked interventions (sitostanol, simvastatin and clopidogrel).

Cost-effectiveness ranking of sitostanol in a natural population

In total 939 persons are eligible for dietary supplementation with sitostanol. In not one of these is the cost per event prevented with sitostanol greater than the cost per event prevented with more highly ranked interventions (simvastatin and clopidogrel).

Cost-effectiveness ranking of simvastatin in a natural population

In total 853 persons are eligible for simvastatin. In none of these patients is the cost per event prevented greater than the cost per event prevented with the cost per event prevented with clopidogrel.

Cost-effectiveness ranking of simvastatin in a natural population

In total 939 persons are eligible for clopidogrel. In these patients the cost per event prevented is always greater than the cost per event prevented with any other intervention for which they are eligible.

Treatment order and cost-effectiveness rankings

The treatment order derived earlier in this chapter is very robust. A policy of offering treatments in this order would, in almost every case, result in patients being offered treatments in order of their cost-effectiveness. In a tiny minority of patients cost-effectiveness ordering differs from the order derived earlier in this chapter, but this is of no practical significance.

CVD risk as a predictor of cost per event prevented

Having established that the treatment order is robust in individual patients, it is necessary to derive a general model of how cost-effectiveness varies across two dimensions: by five-year CVD risk and by choice of treatment. Table 33 shows the numbers of persons in each CVD risk band who are eligible for each intervention. These are the numbers of observations on which the analysis is based.

Table 33: Numbers of persons eligible for preventive interventions in each CVD risk band

Cardiovascular risk band	Aspirin	Mediterranean diet	Initial BP treatment	Intensive BP treatment	Sitostanol	Simvastatin	Clopidogrel
<2.5%			14	17		1	
2.5-5%			48	56		6	
5-7.5%	1	3	51	64	3	10	3
7.5-10%	24	45	64	82	45	46	45
10-15%	282	315	212	266	315	284	315
15-20%	292	296	196	257	296	255	296
20-25%	151	151	105	136	151	136	151
25-30%	72	74	49	64	74	66	74
30-35%	34	34	19	32	34	30	34
35-40%	10	10	8	10	10	10	10
>40%	11	11	7	11	11	9	11
Total	877	939	773	995	939	853	939

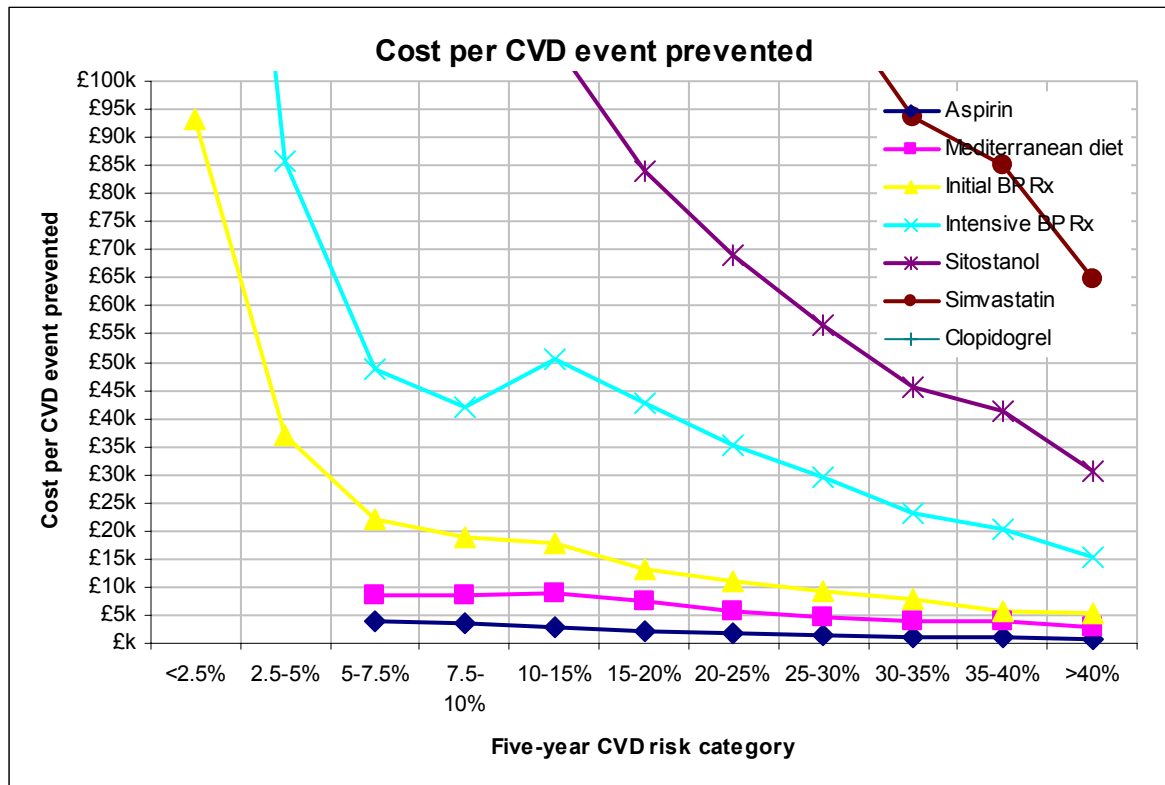
Source: Derived from Health Survey for England 1998

Table 34 and Figure 18 show the average cost per CVD event prevented for each CVD risk band. This allows direct comparison of cost-effectiveness across two dimensions: preventive intervention and individual patient CVD risk. A strategy that was prepared to spend £10,000 per CVD event prevented would offer aspirin and advice on a Mediterranean diet to all eligible patients and initial antihypertensive treatment to those at over 25% five-year CVD risk. No other treatments would be offered. A strategy prepared to spend £25,000 per CVD event prevented would in addition offer initial antihypertensive treatment to those at over 5% five-year CVD risk and intensive antihypertensive treatment to those at over 30% five-year CVD risk.

Table 34: Average cost per CVD event prevented for each preventive intervention in persons in each CVD risk band

Cardiovascular risk band	Aspirin	Mediterranean diet	Initial BP treatment	Intensive BP treatment	Sitostanol	Simvastatin	Clopidogrel
<2.5%			£93,273	£236,447		£160,965	
2.5-5%			£37,112	£85,677		£157,112	
5-7.5%	£3,825	£8,545	£21,940	£48,768	£125,756	£148,458	£434,651
7.5-10%	£3,509	£8,673	£18,926	£42,124	£122,222	£239,330	£474,097
10-15%	£2,958	£8,758	£17,709	£50,590	£106,912	£222,369	£465,687
15-20%	£2,238	£7,400	£13,258	£42,707	£83,966	£176,136	£388,920
20-25%	£1,739	£5,855	£10,964	£35,223	£68,988	£143,285	£320,739
25-30%	£1,373	£4,781	£9,340	£29,510	£56,714	£116,542	£260,095
30-35%	£928	£3,884	£7,750	£23,141	£45,651	£93,608	£209,858
35-40%	£1,109	£3,833	£5,755	£20,217	£41,130	£85,105	£213,752
>40%	£678	£2,691	£5,216	£15,220	£30,723	£64,639	£142,928
All risk bands	£2,266	£7,245	£17,605	£47,854	£86,607	£179,466	£386,553

Figure 18: Cost per CVD event prevented across two dimensions: CVD risk category and choice of intervention



CHD risk as a predictor of cost per event prevented

Because CHD risk is a better predictor of benefit than CVD risk for some interventions it is also important to explore the relationship between cost-effectiveness and five-year CHD risk. Table 35 shows the number of observations on which the analysis is based.

Table 36 shows the average cost per CVD event prevented for each CHD risk band. This allows direct comparison of cost-effectiveness across two dimensions: preventive intervention and individual patient CHD risk.

Table 35: Numbers of persons eligible for each preventive intervention in each CHD risk band

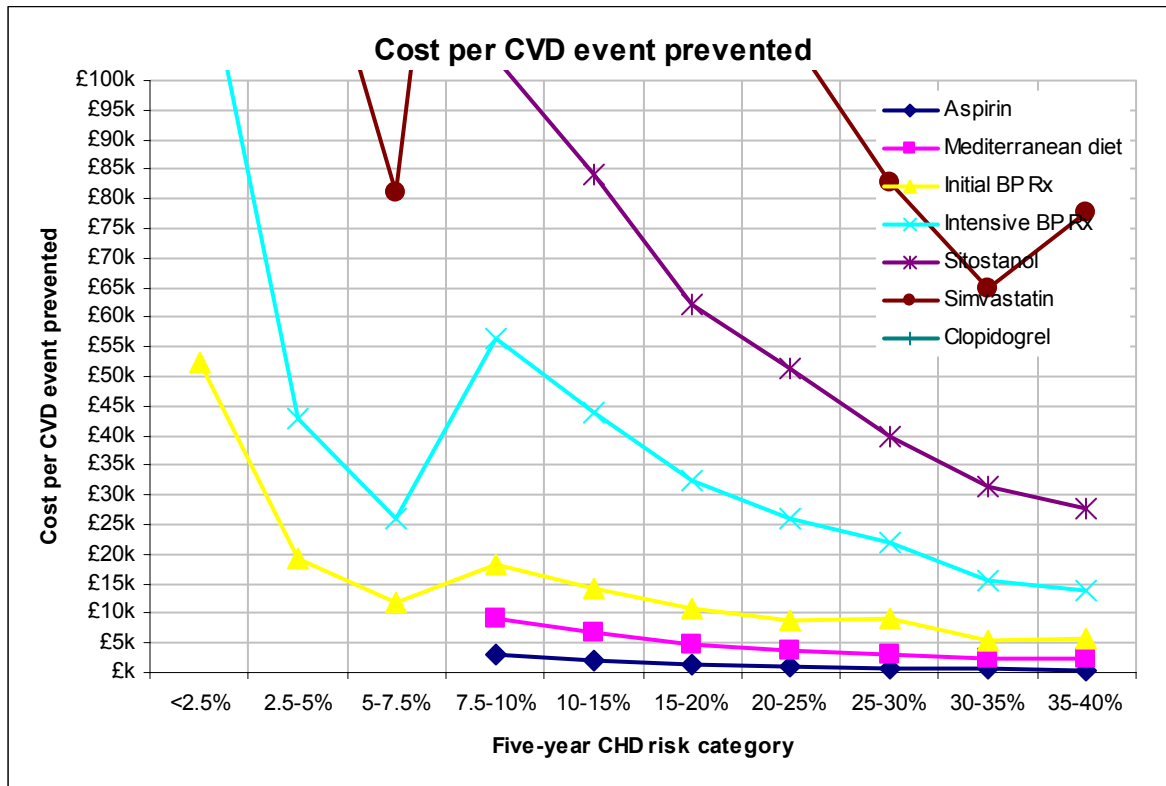
Coronary risk band	Aspirin	Mediterranean diet	Initial BP treatment	Intensive BP treatment	Sitostanol	Simvastatin	Clopidogrel
<2.5%			53	66			
2.5-5%			112	139		13	
5-7.5%			81	109		4	
7.5-10%	336	375	185	237	375	328	375
10-15%	354	374	227	284	374	333	374
15-20%	128	130	76	106	130	120	130
20-25%	46	47	32	42	47	43	47
25-30%	4	4	2	3	4	4	4
30-35%	7	7	4	7	7	7	7
35-40%	2	2	1	2	2	1	2
Total	877	939	773	995	939	853	939

Source: Derived from Health Survey for England 1998

Table 36: Average cost per CVD event prevented for each preventive intervention in persons in each CHD risk band

Coronary risk band	Aspirin	Mediterranean diet	Initial BP treatment	Intensive BP treatment	Sitostanol	Simvastatin	Clopidogrel
<2.5%			£52,351	£124,757			
2.5-5%			£19,144	£42,805		£137,509	
5-7.5%			£11,962	£25,981		£81,137	
7.5-10%	£3,037	£9,249	£18,149	£56,286	£103,825	£218,902	£469,528
10-15%	£2,082	£6,700	£14,169	£44,085	£84,123	£174,787	£371,450
15-20%	£1,362	£4,771	£10,870	£32,465	£62,201	£128,892	£273,718
20-25%	£1,036	£3,704	£8,630	£26,050	£51,210	£107,861	£222,181
25-30%	£652	£3,018	£9,063	£21,973	£39,873	£82,647	£174,233
30-35%	£580	£2,533	£5,317	£15,679	£31,398	£64,995	£146,479
35-40%	£494	£2,280	£5,601	£13,771	£27,628	£77,856	£115,206
Total	£2,266	£7,245	£17,605	£47,854	£86,607	£179,466	£386,553

Figure 19: Cost per CVD event prevented across two dimensions: CHD risk category and choice of intervention



If treatment eligibility is determined by CHD risk, a strategy that was prepared to spend £10,000 per CVD event prevented would offer aspirin and advice on a Mediterranean diet to all eligible patients and initial antihypertensive treatment to those at over 20% five-year CHD risk. No other treatments would be offered.

CHD risk versus CVD risk as predictors of cost per event prevented

Appendix B shows a series of graphs of the relationship between risk and cost-effectiveness. Graphs of the relationship between CHD risk and cost-effectiveness are juxtaposed with graphs of the relationship between CVD risk and cost-effectiveness. It is clear that for aspirin and a Mediterranean diet, CHD risk is a more precise predictor of cost-effectiveness than CVD risk. The two separate lines of data points reflect patients who are already receiving antihypertensive treatment (for whom incremental follow up costs are low) and those who are not already receiving antihypertensive treatment.

Non risk criteria as predictors of cost per event prevented

Eligibility criteria for treatment with aspirin, antihypertensive treatment and statins are based on CHD risk. However each is also based on at least one additional characteristic. For aspirin it is age: patients under 50 are not eligible for aspirin. For antihypertensive treatment it is blood pressure: patients whose blood pressure exceeds 160/100 mm Hg are offered treatment and patients whose blood pressure is less than 140/90 mm Hg are not offered treatment, irrespective of CHD risk. For cholesterol lowering treatment it is cholesterol level: patients whose total cholesterol exceeds 9.0 mol/l are offered treatment and those whose total cholesterol is less than 5.0 mmol/l are not offered treatment, irrespective of CHD risk. However, we need to know the extent to which these criteria accurately identify those in whom treatment is likely to be cost-effective.

Aspirin - the relationship between cost-effectiveness and age

Table 37 shows the number individuals in the population of 5603 who are eligible for aspirin. Because CHD risk is a better predictor of cost-effectiveness of aspirin than CVD risk, these individuals are grouped into five-year CHD risk bands and age-bands. Table 38 shows the mean cost per event prevented in each of the categories.

Table 37: Aspirin: numbers of persons eligible in a range of age and CHD risk bands

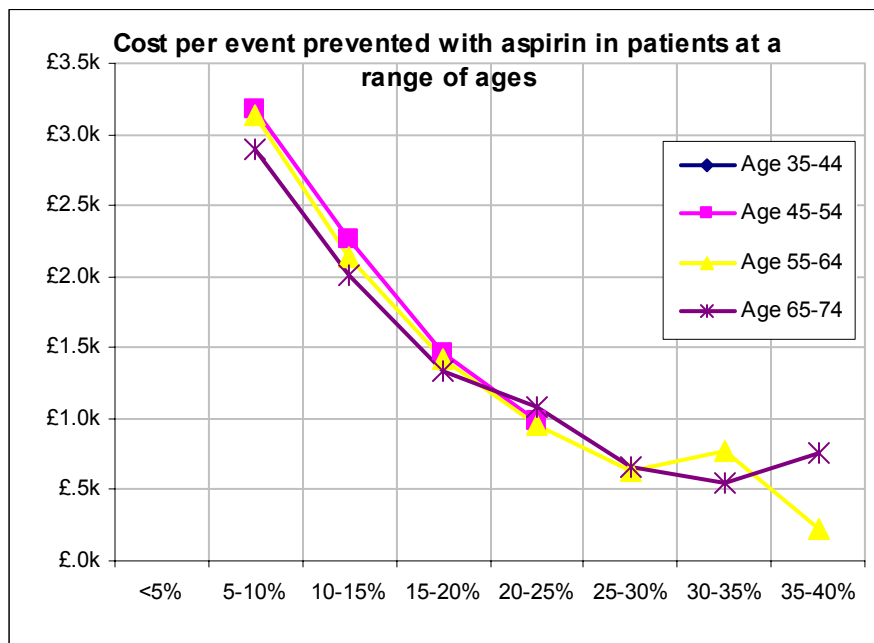
Coronary risk band	Age 35-44	Age 45-54	Age 55-64	Age 65-74
<5%				
5-10%		61	127	148
10-15%		34	134	186
15-20%		7	36	85
20-25%		3	15	28
25-30%			2	2
30-35%			1	6
35-40%			1	1
Grand Total		105	316	456

Our population of 5603 includes 877 persons eligible for aspirin a majority of whom are aged over 65. The mean cost per event prevented is £2,702 in patients aged 45 to 54, £2,379 in those aged 55 to 64 and £2,807 in those aged 65 to 74. When patients are stratified into age and risk bands, it is clear that age is a poor predictor of cost-effectiveness, whereas CHD risk band is a strong predictor of cost-effectiveness. Figure 20.

Table 38: Aspirin: cost per event prevented in a range of age and CHD risk bands

Coronary risk band	Age 35-44	Age 45-54	Age 55-64	Age 65-74
<5%				
5-10%		£3,175	£3,137	£2,895
10-15%		£2,261	£2,133	£2,013
15-20%		£1,463	£1,414	£1,332
20-25%		£982	£958	£1,084
25-30%			£637	£667
30-35%			£768	£548
35-40%			£230	£758
Grand Total		£2,702	£2,379	£2,087

Figure 20: Aspirin: cost per event prevented in a range of age and CHD risk bands



Initial antihypertensive treatment - the relationship between cost-effectiveness and blood pressure

Unlike aspirin, which (used for primary prevention) does not reduce risk of CVA, initial antihypertensive treatment has effects both on CHD and CVA. Because of this effectiveness of antihypertensive treatment is proportional to both CHD and CVA risk. Total CVD risk is therefore be a better indicator of cost-effectiveness than CHD risk.

Table 39 shows the number individuals in the population of 5603 who are eligible for initial antihypertensive treatment grouped into categories reflecting their five-year CVD risk and blood pressure. Our population of 5603 includes 773 persons eligible for initial

antihypertensive treatment. The great majority of these have blood pressures between 140/90 mm Hg and 180/110 mm Hg.

Table 39: Initial antihypertensive treatment: numbers of persons eligible grouped by CVD risk and blood pressure

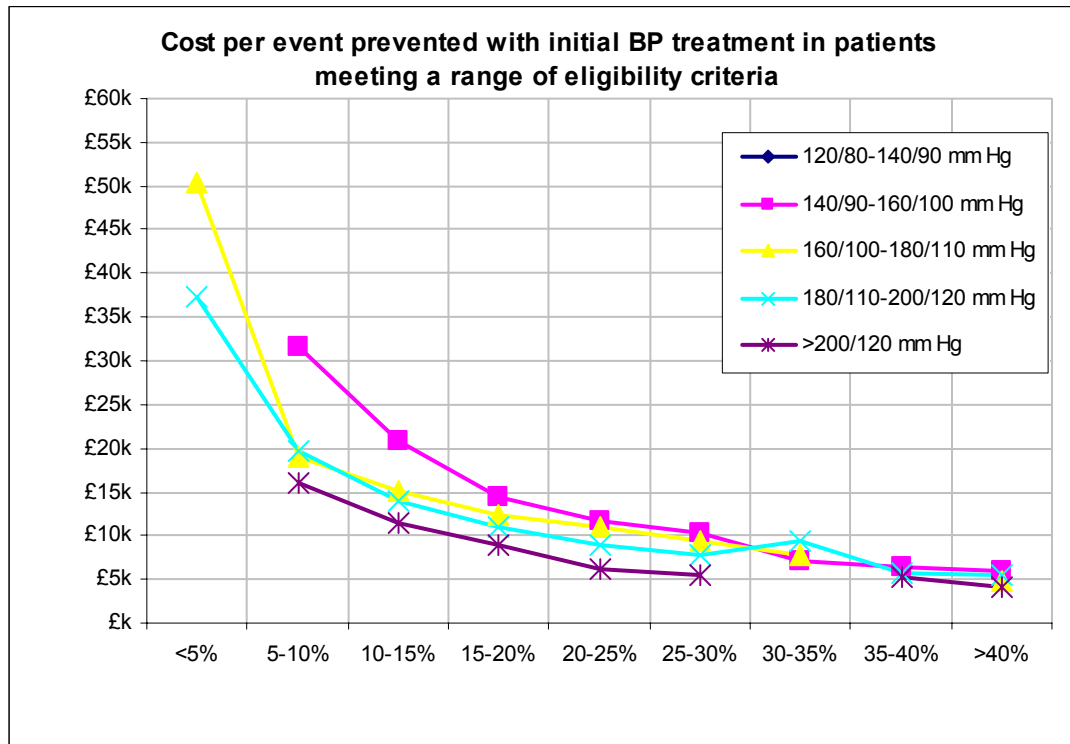
Five year CVD risk	<120/80 mm Hg	120/80 mm Hg to 140/90 mm Hg	140/90 mm Hg to 160/100 mm Hg	160/100 mm Hg to 180/110 mm Hg	180/110 mm Hg to 200/120 mm Hg	>200/120 mm Hg
<5%		3	1	59	3	
5-10%		201	155	85	13	5
10-15%		162	181	84	19	4
15-20%		44	110	70	15	5
20-25%		12	49	42	12	2
25-30%		7	23	16	7	3
30-35%		1	5	12	2	
35-40%			2		3	3
>40%			3	1	1	2
Total		430	529	369	75	24

Table 40 shows the cost per event prevented grouped by CVD risk band and blood pressure. The cost per event prevented is £16,263 in persons whose blood pressure is 140/90 mm Hg to 160/100 mm Hg but only £9,308 in persons whose blood pressure exceeds 200/120 mm Hg. However when patients are stratified by CVD risk the differences in cost-effectiveness between blood pressure categories are small. (Figure 21)

Table 40: Initial antihypertensive treatment: cost per event prevented grouped by CVD risk and blood pressure

Five year CVD risk	<120/80 mm Hg	120/80 mm Hg to 140/90 mm Hg	140/90 mm Hg to 160/100 mm Hg	160/100 mm Hg to 180/110 mm Hg	180/110 mm Hg to 200/120 mm Hg	>200/120 mm Hg
<5%				£50,424	£37,382	
5-10%			£31,693	£19,003	£19,604	£15,951
10-15%			£20,798	£15,003	£13,923	£11,440
15-20%			£14,339	£12,424	£10,958	£8,919
20-25%			£11,714	£10,933	£8,817	£6,126
25-30%			£10,280	£9,363	£7,802	£5,597
30-35%			£7,054	£7,765	£9,403	
35-40%			£6,355		£5,770	£5,341
>40%			£5,978	£4,777	£5,601	£4,100
Total			£16,263	£20,128	£13,307	£9,308

Figure 21: Cost-effectiveness of initial antihypertensive treatment grouped by of blood pressure and by CVD risk band



Cost-effectiveness and eligibility for further antihypertensive treatment

Because further antihypertensive treatment is equally effective at reducing risk of CHD and CVA, total CVD risk is a better indicator of cost-effectiveness than CHD risk. Table 41 shows the number individuals in the population of 5603 grouped into categories reflecting their five-year CVD risk and blood pressure. Of the 995 who are eligible for further antihypertensive treatment the great majority of these have blood pressures between 140/90 mm Hg and 180/110 mm Hg.

Table 42 shows the mean cost per event prevented for patients in each category. These data are displayed visually in Figure 22. Cost per event prevented is £24,425 in persons with blood pressure over 200/120 mm Hg and £50,066 in those with blood pressure between 140/90 mm Hg and 160/100 mm Hg. However these differences disappear when patients are stratified by CVD risk.

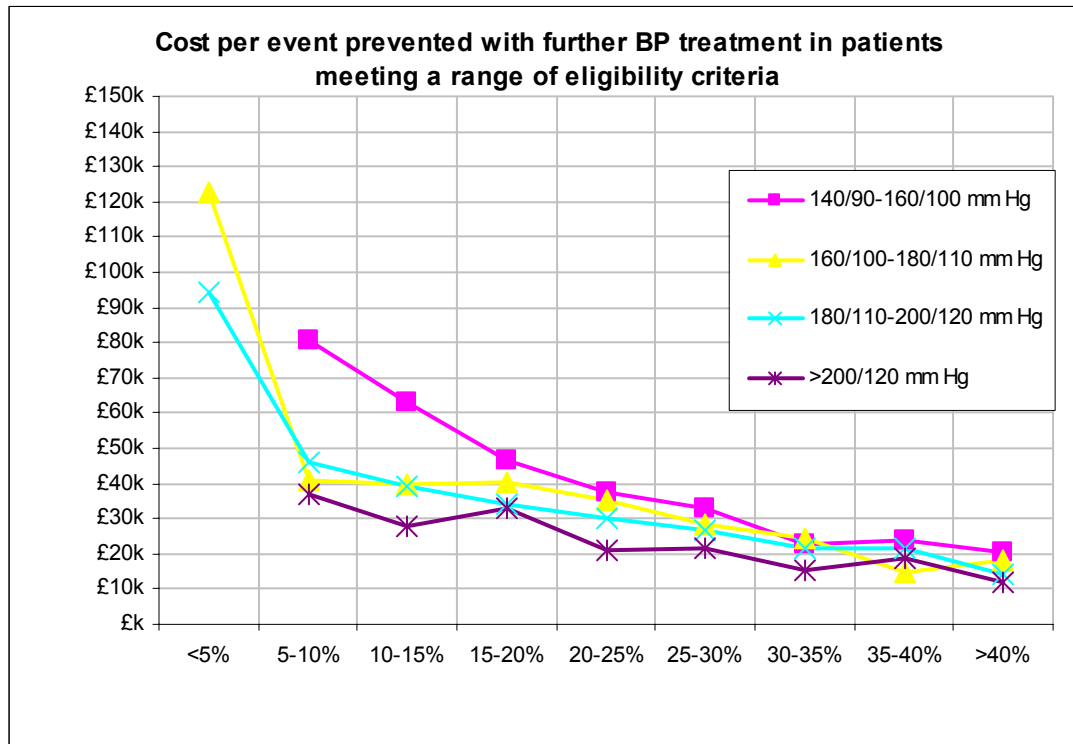
Table 41: Further antihypertensive treatment: numbers of persons eligible criteria grouped by CVD risk and blood pressure

Five year CVD risk	<120/80 mm Hg	120/80 mm Hg to 140/90 mm Hg	140/90 mm Hg to 160/100 mm Hg	160/100 mm Hg to 180/110 mm Hg	180/110 mm Hg to 200/120 mm Hg	>200/120 mm Hg
<5%				68	5	
5-10%			13	109	19	5
10-15%			129	109	23	5
15-20%			131	97	24	5
20-25%			59	55	18	4
25-30%			26	23	10	5
30-35%			9	17	5	1
35-40%			2	1	3	4
>40%			3	1	2	5
Total			372	480	109	34

Table 42: Further antihypertensive treatment: cost per event prevented grouped by CVD risk and blood pressure

Five year CVD risk	<120/80 mm Hg	120/80 mm Hg to 140/90 mm Hg	140/90 mm Hg to 160/100 mm Hg	160/100 mm Hg to 180/110 mm Hg	180/110 mm Hg to 200/120 mm Hg	>200/120 mm Hg
<5%				68	5	
5-10%			13	109	19	5
10-15%			129	109	23	5
15-20%			131	97	24	5
20-25%			59	55	18	4
25-30%			26	23	10	5
30-35%			9	17	5	1
35-40%			2	1	3	4
>40%			3	1	2	5
Total			372	480	109	34

Figure 22: Cost-effectiveness of further antihypertensive treatment in patients meeting a range of potential eligibility criteria



Cost-effectiveness and eligibility for statins

Because statins are equally effective at preventing CVA and CHD, five-year CVD risk is a better predictor of the cost-effectiveness of statins than five-year CHD risk. Eligibility for statins is therefore investigated in relation to CVD risk.

Table 43: Numbers of persons meeting eligibility criteria for statins grouped by risk and total cholesterol

Five year CVD risk	<5 mmol/l	5-6 mmol/l	6-7 mmol/l	7-8 mmol/l	8-9 mmol/l	>9 mmol/l
<5%						7
5-10%		10	21	12	2	11
10-15%		84	120	57	20	3
15-20%		69	108	48	24	6
20-25%		35	61	30	5	5
25-30%		20	25	12	4	5
30-35%		13	12	2	3	
35-40%		3	4	3		
>40%		3	3	2	1	
Total		237	354	166	59	37

Table 43 shows the number of individuals in the population of 5603 who are eligible for statins, grouped into categories reflecting their CVD risk and cholesterol level. In total,

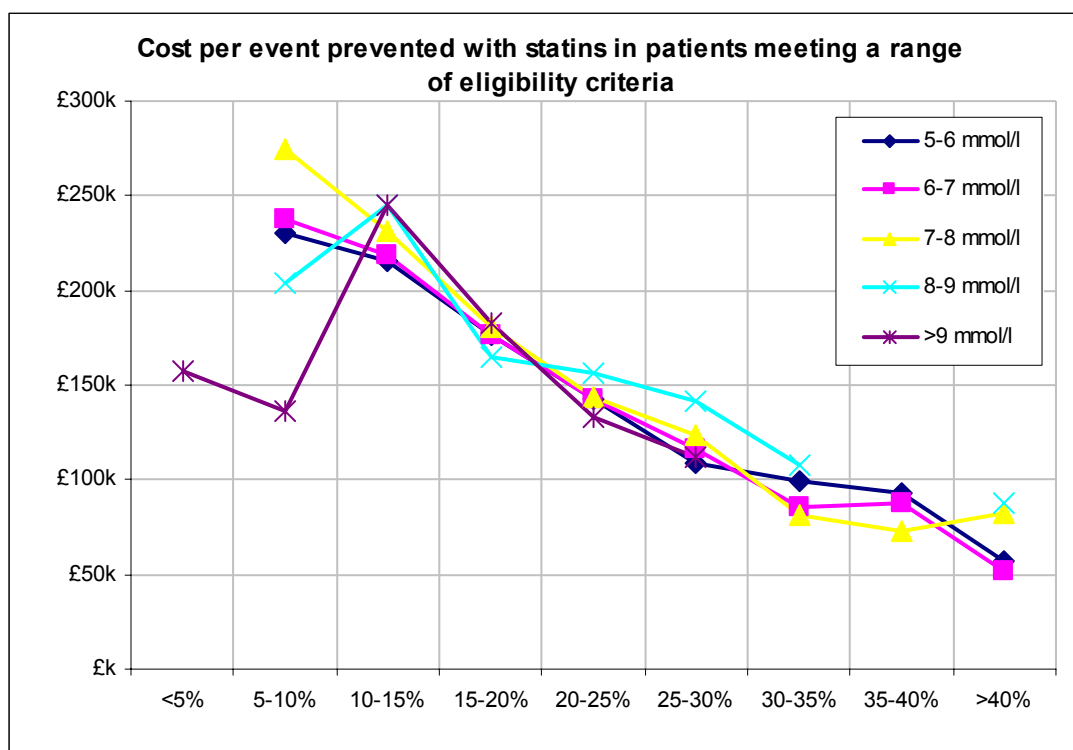
853 persons are eligible for statins. The majority of these have total cholesterol levels over between 5 mmol/l and 7 mmol/l.

Table 44: Cost per event prevented in persons eligible for statins grouped by risk and total cholesterol

Five year CVD risk	<5 mmol/l	5-6 mmol/l	6-7 mmol/l	7-8 mmol/l	8-9 mmol/l	>9 mmol/l
<5%						£157,663
5-10%		£229,763	£237,534	£274,881	£204,328	£136,424
10-15%		£215,707	£218,583	£230,830	£245,511	£245,339
15-20%		£176,379	£175,916	£181,090	£164,897	£182,653
20-25%		£142,873	£142,956	£144,004	£156,450	£132,702
25-30%		£108,392	£116,561	£123,793	£141,787	£111,449
30-35%		£99,567	£85,652	£81,774	£107,507	
35-40%		£93,223	£87,869	£73,303		
>40%		£57,508	£52,030	£82,650	£87,834	
Total		£175,114	£179,059	£189,775	£187,054	£152,892

Table 44 shows the mean cost per event prevented for patients in each category. These data are displayed visually in Figure 23. Cost per event prevented is similar across all cholesterol levels but varies considerably across risk levels. CVD risk is therefore a stronger determinant of cost-effectiveness than total cholesterol level.

Figure 23: Cost-effectiveness of statins in patients meeting a range of potential eligibility criteria



Conclusions from this analysis

A number of things are clear from this analysis.

- Cost-effectiveness rankings are stable for almost all individuals with almost any risk combination of risk factors.
- CHD risk is a better predictor of the cost-effectiveness of aspirin and a Mediterranean diet.
- CVD risk is a better predictor of cost-effectiveness of all other interventions.
- Age, blood pressure and total cholesterol level are poor predictors of cost-effectiveness.
- It is possible to use a threshold cost per event prevented to determine clinical criteria for treatment eligibility.

7. Results: patient identification strategies

This part of the study develops and analyses a number of strategies for identification of patients eligible for preventive interventions. The analysis is carried out in a study population. Two main types of identification strategies are investigated: the first type follows a traditional approach to patient selection (either opportunistic or prioritisation of patients on antihypertensive treatment and those with diabetes); the second type selectively assesses patients on the basis of a prior estimate of their cardiovascular risk. The first part of this chapter therefore explains how prior estimates of CVD risk are derived and how they are used in patient identification strategies.

The second part of this chapter analyses the characteristics of a number of identification strategies. Analysis of the patient identification strategies takes a number of forms. The first analysis assumes that a fixed number of persons are assessed under each strategy. It then identifies the number of persons correctly identified as eligible for at least one intervention (true positives) and the number incorrectly identified as not eligible for at least one intervention (false negatives). The second analysis also assumes that a fixed number of persons are assessed under each strategy but identifies the total burden of CVD disease (sum of individual risks) in persons identified as eligible for treatment under each strategy. The third analysis explores the relationship between the resources allocated to each assessment strategy and the total burden of CVD disease (sum of individual risks) in persons identified as eligible for treatment under each strategy.

Individual risk and prior estimates of cardiovascular risk

To assess the efficiency of strategies for patient identification we must first identify a study population. The study population must include patients whose risk factors are known. We can then calculate CVD risk, CHD risk and CVA risk for each individual in the study population. From their risk factors and CHD risk status, we can determine the treatment eligibility of every individual in the study population.

Study population

The study population is the same as that used for the incremental cost effectiveness analysis in a natural population. It is derived from the Health Survey for England 1998.

The Health Survey for England 1998 includes 15,908 persons aged 16 and over. Age, sex, diabetic status and history of cardiovascular disease are available on all of these persons. Smoking status is available on almost all. Blood pressures and cholesterol levels are available on the majority of these patients. (Table 45)

Table 45: Completeness of recording of cardiovascular risk factors in the Health Survey for England

Data item	Number of records with this data item	Percentage of total records with this data item
Gender	15908	100.0%
Age	15908	100.0%
Systolic blood pressure	11884	74.7%
Diastolic blood pressure	11884	74.7%
HDL Cholesterol Result	10304	64.8%
Cholesterol Result	10332	64.9%
Smoking status (yes or no)	15850	99.6%
Had CVD (Angina, Heart Attack or Stroke)	15903	100.0%
Any medicines for high BP	3101	19.5%
Doctor diagnosed diabetes (excluding pregnant)	15906	100.0%

Source: Health Survey for England 1998

The survey includes 8,850 persons aged 35 to 74 who do not have cardiovascular disease. (Table 46) In 62% of participants aged 35 to 74 (5603), sufficient information is available to calculate CVD risk. (Table 46) The population for analysis therefore consists of 5603 individuals aged 35 to 74 who are eligible for prevention of cardiovascular disease.

Table 46: Completeness of recording of cardiovascular risk factors in persons aged 35 to 74 without cardiovascular disease

Data item	Number of records with this data item	Percentage of total records with this data item
Gender	8,850	100%
Age	8,850	100%
Systolic blood pressure	6,801	77%
Diastolic blood pressure	6,801	77%
Total cholesterol	6,281	71%
HDL cholesterol	6,261	71%
Enough risk factor information to calculate CVD risk	5,603	63%

Source: Health Survey for England 1998

A CHD risk and CVD risk is calculated for each individual in this population. The study population is also used to generate default risk factor values for patients with each possible combination of age, sex and cardiovascular risk factors.

Default risk factor values

Some identification strategies require us make a prior estimate of patients' CVD risk and assess patients in that order. This prior estimate will be derived from their age, sex, diabetic and antihypertensive drug treatment status and estimates of their smoking status, blood pressure and cholesterol level. Calculating a prior estimate of CVD risk therefore requires default estimates of smoking status, blood pressure and cholesterol level.

Non-smokers outnumber smokers at all ages therefore the most likely smoking status is non-smoker. The default smoking status is non-smoking. The most likely blood pressure or cholesterol level is the average for a person of that age, sex, cardiovascular disease risk status, diabetic status, antihypertensive drug treatment status and smoking status. In other words the patient's other characteristics are used to predict their most likely blood pressure or cholesterol level. The first step in the process of estimating a default risk factor status is to estimate average blood pressures and cholesterol levels for persons of every possible age, sex, diabetic, antihypertensive drug treatment status and smoking status.

Frequency of each possible combination of risk factors

Some combinations of age, sex and risk factors are uncommon. As a result some combinations of age, sex and risk factors are not represented by a single valid blood pressure or cholesterol level in the Health Survey for England 1998. For example the Health Survey for England contains no blood pressures for male diabetic smokers aged 25 to 34, who were not on antihypertensives and had no history of CVD. The effect of this is to make it impossible to calculate a mean value for this category.

Other categories contain only small numbers of individuals with valid measurements. A mean derived from a small sample size has a large sampling error. Analysis of the Health Survey for England data indicates that when the mean systolic blood pressure is derived from 10 measurements the standard error of the mean systolic blood pressure is between 4 and 8 mm Hg. This is not sufficiently accurate to be a valid measurement. Similarly, when the mean total to HDL cholesterol ratio is derived from 10 measurements the standard error of the mean ratio is between 0.3 and 0.6. This is also not sufficiently accurate to be a valid measurement. It was therefore decided that if a risk category

contained fewer than 10 individual measurements (of blood pressure or cholesterol levels) the risk category should be combined with another.

Combining risk factor categories

In the first place, smokers and non-smokers were combined and common mean blood pressures and cholesterol ratios calculated for both. If this did not produce 10 measurements on which to base a mean, diabetics and non-diabetics were also combined. If this did not produce 10 measurements, those with and without CVD were combined. In this way a list of default blood pressures was calculated for every possible age, sex and risk factor category. Table 47 and Table 49 show the default systolic blood pressure values for each risk factor category. Table 48 and Table 50 show the number of valid systolic blood pressures in each risk factor category. Table 51 and Table 53 show the default cholesterol ratios for each risk factor category. Table 52 and Table 54 show the number of valid cholesterol ratios in each risk factor category.

Table 47: Default values for systolic blood pressure (mm Hg) in males.

On antihypertensive treatment History of cardiovascular disease Diabetes Smoker	Male															
	No								Yes							
	No				Yes				No				Yes			
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Age 16-24	128.7	128.0	128.5	128.5	128.5	128.5	128.5	128.5	128.5	128.5	128.5	128.5	128.5	128.5	128.5	128.5
Age 25-34	130.8	129.3	130.4	130.4	130.4	130.4	130.4	130.4	130.4	130.4	130.4	130.4	130.4	130.4	130.4	130.4
Age 35-44	131.3	130.6	131.2	131.2	131.2	131.2	131.2	131.2	131.2	138.5	131.2	131.2	131.2	131.2	131.2	131.2
Age 45-54	135.9	135.5	132.8	136.2	131.2	134.0	136.2	136.2	142.5	134.3	136.2	136.2	146.2	136.2	136.2	136.2
Age 55-64	140.5	141.2	138.7	142.1	138.3	135.0	142.1	142.1	148.0	156.8	142.1	142.1	149.9	142.1	142.1	142.1
Age 65-74	147.9	149.4	136.3	147.8	144.8	147.8	145.1	147.8	152.5	147.8	147.8	147.8	143.2	147.8	147.8	147.8
Age 75-84	151.4	145.1	150.1	150.1	142.1	150.1	150.1	150.1	157.4	150.1	150.1	150.1	148.6	150.1	150.1	150.1
Age 85+	150.0	151.1	151.1	151.1	153.9	151.1	151.1	151.1	161.2	151.1	151.1	151.1	151.1	151.1	151.1	151.1

Table 48: Numbers of valid systolic blood pressures in the Health Survey for England 1998 for each risk category of males.

On antihypertensive treatment History of cardiovascular disease Diabetes Smoker	Male															
	No								Yes							
	No				Yes				No				Yes			
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Age 16-24	369	212	1		2											
Age 25-34	652	315	6	2	2	2			2	1						
Age 35-44	700	242	4	4	8		0	0	12	6	1		3		1	
Age 45-54	653	198	13	3	25	14	4		40	11	4	1	8	3	1	
Age 55-64	414	116	13	5	60	16	7	2	68	17	6	2	24	5	9	1
Age 65-74	334	50	17	6	98	9	10	3	76	10	6	2	28	7	8	
Age 75-84	169	19	8	1	64	7	6	0	42	1	9		23	3	4	
Age 85+	33	1	5		19	1			9		2		4			

Table 49: Default values for systolic blood pressure (mm Hg) in females.

On antihypertensive treatment History of cardiovascular disease Diabetes Smoker	Male															
	No								Yes							
	No				Yes				No				Yes			
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Age 16-24	120.7	119.5	120.2	120.2	120.2	120.2	120.2	120.2	120.2	120.2	120.2	120.2	120.2	120.2	120.2	120.2
Age 25-34	120.7	119.8	122.0	120.4	120.4	120.4	120.4	120.4	120.4	120.4	120.4	120.4	120.4	120.4	120.4	120.4
Age 35-44	123.4	122.4	123.5	123.5	118.5	123.5	123.5	123.5	139.7	123.5	123.5	123.5	123.5	123.5	123.5	123.5
Age 45-54	130.3	131.9	131.7	131.7	133.8	131.7	131.7	131.7	145.3	131.7	131.7	131.7	131.7	131.7	131.7	131.7
Age 55-64	137.9	139.3	141.4	140.1	138.9	143.5	140.1	140.1	148.7	146.3	140.1	140.1	148.3	140.1	140.1	140.1
Age 65-74	147.0	146.8	153.8	149.1	146.4	149.1	132.8	149.1	152.9	161.5	166.5	149.1	152.1	149.1	149.1	149.1
Age 75-84	155.1	156.2	156.3	156.3	145.7	149.3	156.3	156.3	164.6	156.3	162.3	156.3	155.7	156.3	156.3	156.3
Age 85+	148.1	150.9	150.9	150.9	141.2	150.9	150.9	150.9	163.4	150.9	150.9	150.9	161.1	150.9	150.9	150.9

Table 50: Numbers of valid systolic blood pressures in the Health Survey for England 1998 for each risk category of females.

On antihypertensive treatment History of cardiovascular disease Diabetes Smoker	Male															
	No								Yes							
	No				Yes				No				Yes			
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Age 16-24	433	241	2	2	2	0	0		1							
Age 25-34	769	350	8	3	3	3			6							
Age 35-44	818	320	4	3	10	5	1		23	5						
Age 45-54	808	255	4	3	13	9		0	52	7	4	2	2	2	1	1
Age 55-64	538	156	15	1	30	14	2	1	88	24	5	2	15	2	3	
Age 65-74	355	75	18	1	58	8	10	1	145	16	14		37	7	5	
Age 75-84	241	32	8	2	62	11	2	1	108	5	11		42	3	4	
Age 85+	49	2	2		24		6		19	1	2		9		2	

Table 51: Default values for total cholesterol to high-density lipoprotein cholesterol in males.

On antihypertensive treatment History of cardiovascular disease Diabetes Smoker	Male																
	No								Yes								
	No				Yes				No				Yes				
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	
Age 16-24	3.50	3.60	3.54	3.54	3.54	3.54	3.54	3.54	3.54	3.54	3.54	3.54	3.54	3.54	3.54	3.54	3.54
Age 25-34	4.20	4.50	4.32	4.32	4.32	4.32	4.32	4.32	4.32	4.32	4.32	4.32	4.32	4.32	4.32	4.32	4.32
Age 35-44	4.50	4.70	4.58	4.58	4.58	4.58	4.58	4.58	5.77	4.58	4.58	4.58	4.58	4.58	4.58	4.58	4.58
Age 45-54	4.80	5.00	4.90	4.91	5.30	4.91	4.91	4.91	5.30	4.91	4.91	4.91	4.91	4.91	4.91	4.91	4.91
Age 55-64	4.90	4.90	5.60	4.94	4.70	4.30	4.94	4.94	5.10	5.60	4.94	4.94	4.50	4.94	4.94	4.94	4.94
Age 65-74	4.90	4.80	4.50	4.97	5.30	5.70	4.97	4.97	4.80	4.97	4.97	4.97	5.20	4.97	4.97	4.97	4.97
Age 75-84	4.40	4.20	4.53	4.53	4.80	4.53	4.53	4.53	4.60	4.53	4.53	4.53	4.70	4.53	4.53	4.53	4.53
Age 85+	4.50	4.34	4.34	4.34	4.00	4.34	4.34	4.34	4.56	4.34	4.34	4.34	4.34	4.34	4.34	4.34	4.34

Table 52: Numbers of valid total cholesterol to high density lipoprotein cholesterol ratios in the Health Survey for England 1998 for each risk category of males.

On antihypertensive treatment History of cardiovascular disease Diabetes Smoker	Male																
	No								Yes								
	No				Yes				No				Yes				
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	
Age 16-24	246	170	1		1												
Age 25-34	578	314	5	2	2	2			2	1							
Age 35-44	653	271	3	6	6		0	1	10	5	1		2		0		
Age 45-54	621	222	15	3	17	7	2		25	9	3	1	3	3	0		
Age 55-64	388	114	13	3	30	17	2	1	60	12	4	2	12	3	6	1	
Age 65-74	306	60	11	7	68	12	6	3	64	9	5	2	21	3	5		
Age 75-84	152	22	5	2	62	6	4	0	38	1	7		15	3	2		
Age 85+	32	2	3		17	0			9		2		3				

Table 53: Default values for total cholesterol to high-density lipoprotein cholesterol in females.

On antihypertensive treatment History of cardiovascular disease Diabetes Smoker	Male																
	No								Yes								
	No				Yes				No				Yes				
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	
Age 16-24	3.00	3.40	3.16	3.16	3.16	3.16	3.16	3.16	3.16	3.16	3.16	3.16	3.16	3.16	3.16	3.16	3.16
Age 25-34	3.40	3.50	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45
Age 35-44	3.40	3.80	3.55	3.55	3.45	3.55	3.55	3.55	4.80	3.55	3.55	3.55	3.55	3.55	3.55	3.55	3.55
Age 45-54	3.70	4.30	3.91	3.91	5.04	3.91	3.91	3.91	4.20	3.91	3.91	3.91	3.91	3.91	3.91	3.91	3.91
Age 55-64	4.00	4.50	4.80	4.20	4.60	4.20	4.20	4.20	4.60	4.60	4.20	4.20	4.20	4.20	4.20	4.20	4.20
Age 65-74	4.30	4.30	4.50	4.56	5.00	4.56	4.56	4.56	5.00	5.30	4.56	4.56	4.40	4.56	4.56	4.56	4.56
Age 75-84	4.00	4.10	4.18	4.18	4.50	4.60	4.18	4.18	4.20	4.18	4.18	4.18	4.50	4.18	4.18	4.18	4.18
Age 85+	4.00	4.31	4.31	4.31	4.60	4.31	4.31	4.31	4.70	4.31	4.31	4.31	4.31	4.31	4.31	4.31	4.31

Table 54: Numbers of valid total cholesterol to high density lipoprotein cholesterol ratios in the Health Survey for England 1998 for each risk category of females.

On antihypertensive treatment History of cardiovascular disease Diabetes Smoker	Male																
	No								Yes								
	No				Yes				No				Yes				
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	
Age 16-24	269	171	2	2	0	0	0	0	1								
Age 25-34	632	316	6	3	1	2			3								
Age 35-44	704	314	5	5	8	3	0		18	5							
Age 45-54	737	261	5	4	5	6		0	44	7	4	0	0	2	0	1	
Age 55-64	473	155	13	0	19	9	3	1	64	14	3	0	7	0	1		
Age 65-74	296	80	12	3	41	7	5	0	96	11	10		22	5	2		
Age 75-84	214	33	6	3	42	13	1	1	81	4	7		31	2	3		
Age 85+	44	1	2		24		2		11	0	1		8		2		

Prior estimates of CVD risk

We can now calculate a prior estimate of CVD risk using the Framingham risk equation. This uses information about patients' age, sex and known cardiovascular risk factors and default values for unknown cardiovascular risk factors. For example, consider a man about whom we only know that he is aged 53 and is not taking antihypertensives. Since non-smokers outnumber smokers, non-diabetics outnumber diabetics and those without CVD outnumber those with CVD, our prior estimate of his categorical risk factors is that he is a non-smoker without diabetes or CVD. The average systolic blood pressure for a man with these characteristics is 135.9 mm Hg (Table 47) and the average total to HDL cholesterol ratio is 4.8 (Table 51). We therefore use these as our prior estimates of his continuous risk factors. We now have sufficient data to calculate a CVD risk.

Population eligible for primary prevention

In chapter 7 it was observed that the Health Survey for England 1998 included 5603 individuals aged 35 to 74 who are eligible for primary prevention of CVD and for whom full risk factor information is available. For each of these 5603 individuals a series of estimates of CVD risk, CHD risk and CVD risk are calculated.

Estimates of risk

We calculate six estimates of risk based on varying amounts of information about patients' risk factors. These are illustrated in Table 55.

The first risks are the true CVD risk, true CHD risk and true CVA risk. These are each calculated from the complete set of risk factor data.

Estimates of cardiovascular risk

Six further estimated CVD risks are then calculated. A minimum amount of information on every patient is available to any primary care team with electronic records. All primary care teams in the UK data on every patients' age and sex, whether or not they are on antihypertensives and (since 2002) registers of patients with cardiovascular disease and diabetes. Search facilities in electronic practice databases make it easy for practices to identify these risk factors.

The least accurate CVD risk is therefore that calculated from every patient's age, sex, diabetic status and information on whether or not the individual is on antihypertensives. These data are used to determine default smoking status (non

smoking), default blood pressure and default total to HDL cholesterol ratios. The CVD risk is calculated from the combined categorical risk factors and default risk factors.

The next CVD risk is calculated from the minimum range of risk factor data and whether or not the individual smokes. A CVD risk is then calculated from the minimum range of risk factors plus smoking status plus a single clinic measurement of blood pressure (including a degree of measurement error). A CVD risk is then calculated from the minimum range of risk factors, plus smoking status, plus the mean of three clinic measurements of blood pressure (including a smaller degree of measurement error). A CVD risk is then calculated from the full range of risk factor data with blood pressure and cholesterol ratio both based on single clinic measurements (both therefore including a degree of measurement error). Finally a full clinical estimate of CVD risk is calculated. This is based on the full range of risk factor data with blood pressure and cholesterol ratio both based on the mean of three clinic measurements (both therefore including a small degree of measurement error).

Estimates of coronary risk

Two estimates of CHD risks are also calculated. The first estimate of CHD risk is calculated from the full range of risk factor data with blood pressure and cholesterol ratio both based on single clinic measurements (both therefore including a degree of measurement error). The second estimate of CVD risk is calculated from the full range of risk factor data with blood pressure and cholesterol ratio both based on the mean of three clinic measurements (both therefore including a small degree of measurement error).

Table 55: Cardiovascular risk estimates used in the model.

Label	Definition	How derived
Cardiovascular risk		
CVD5y TRUE	True five year CVD risk	All risk factor data
CVD no TC, BP, cig	Estimate of five year CVD risk	Derived from data on age, sex, diabetic status and whether patient takes antihypertensives
CVD no TC, BP	Estimate of five year CVD risk	Derived from data on age, sex, diabetic status, whether patient takes antihypertensives and smoking status
CVD BP1 no TC	Estimate of five year CVD risk	Derived from data on age, sex, diabetic status, whether patient takes antihypertensives, smoking status and a single measurement of blood pressure
CVD BP3 no TC	Estimate of five year CVD risk	Derived from data on age, sex, diabetic status, whether patient takes antihypertensives, smoking status and the mean of three measurements of blood pressure
CVD TC1 BP1	Estimate of five year CVD risk	Derived from data on age, sex, diabetic status, whether patient takes antihypertensives, smoking status, a single measurement of blood pressure and a single cholesterol measurement
CVD TC3 BP3	Estimate of five year CVD risk	Derived from data on age, sex, diabetic status, whether patient takes antihypertensives, smoking status, the mean of three measurements of blood pressure and the mean of three measurements of cholesterol
Coronary risk		
CHD5y TRUE	True five year CHD risk	All risk factor data
CHD TC1 BP1	Estimate of five year CHD risk	Derived from data on age, sex, diabetic status, whether patient takes antihypertensives, smoking status, a single measurement of blood pressure and a single cholesterol measurement
CHD TC3 BP3	Estimate of five year CHD risk	Derived from data on age, sex, diabetic status, whether patient takes antihypertensives, smoking status, the mean of three measurements of blood pressure and the mean of three measurements of cholesterol
Cerebrovascular risk		
CVA5y TRUE	True five year CVA risk	All risk factor data

The relationship between risks: cardiovascular, coronary and cerebrovascular risk
 Figure 24 shows the relationship between true cardiovascular (CVD) risk (x axis) and true coronary (CHD) risk (on the y axis) and true cerebrovascular (CVA) risk (on the y axis). Coronary (CHD) risk is typically about three fifths of total cardiovascular (CVD) risk and the two correlate closely. Cerebrovascular (CVA) risk is typically one fifth of cardiovascular (CVD) risk and these also show significant correlation.

Figure 25 shows the relationship between cardiovascular risk (on the x axis) and the sum of coronary risk and cerebrovascular risk (on the y axis). The sum of CHD and CVA risk is slightly lower than cardiovascular risk, but it correlates very closely with CVD risk.

Figure 24: Cardiovascular risk (CVD risk) as a predictor of coronary risk (CHD risk) and cerebrovascular risk (CVA risk).

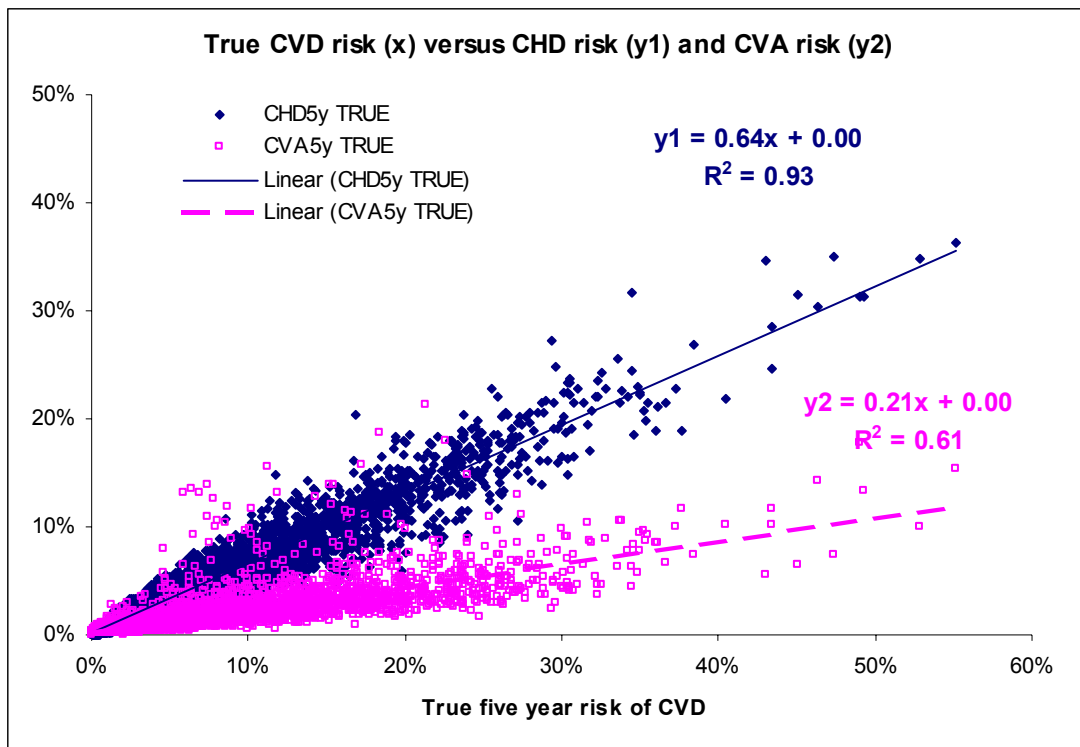
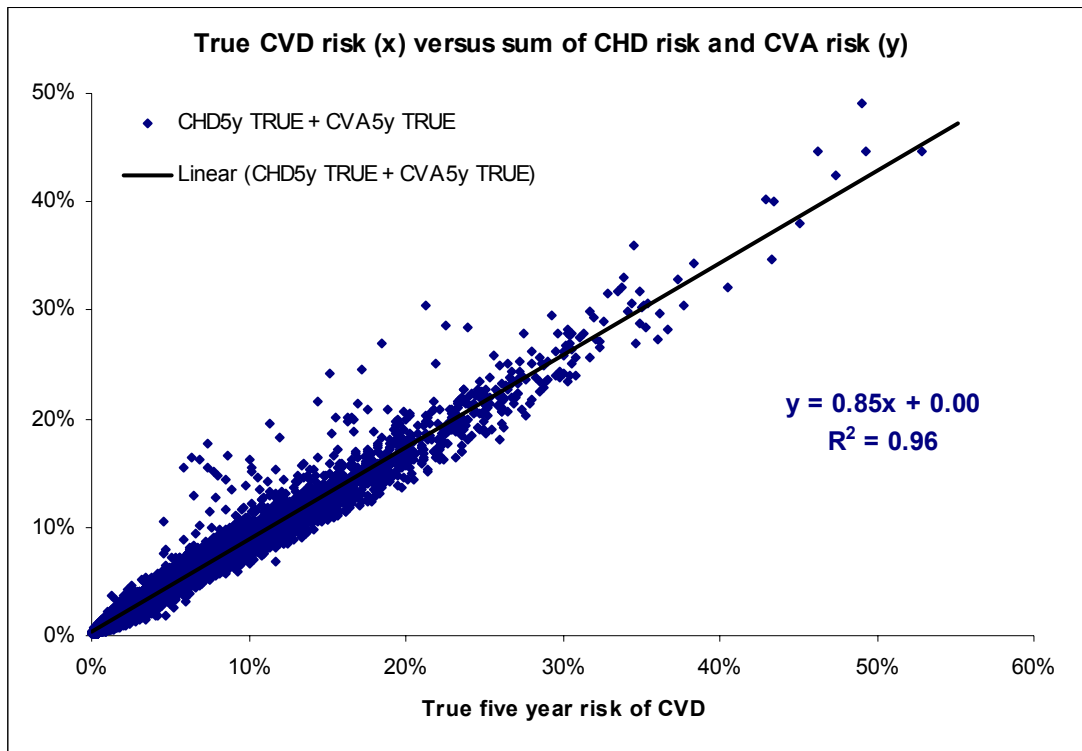


Figure 25: Cardiovascular risk (CVD risk) as a predictor of the sum of coronary risk (CHD risk) and cerebrovascular risk (CVA risk).

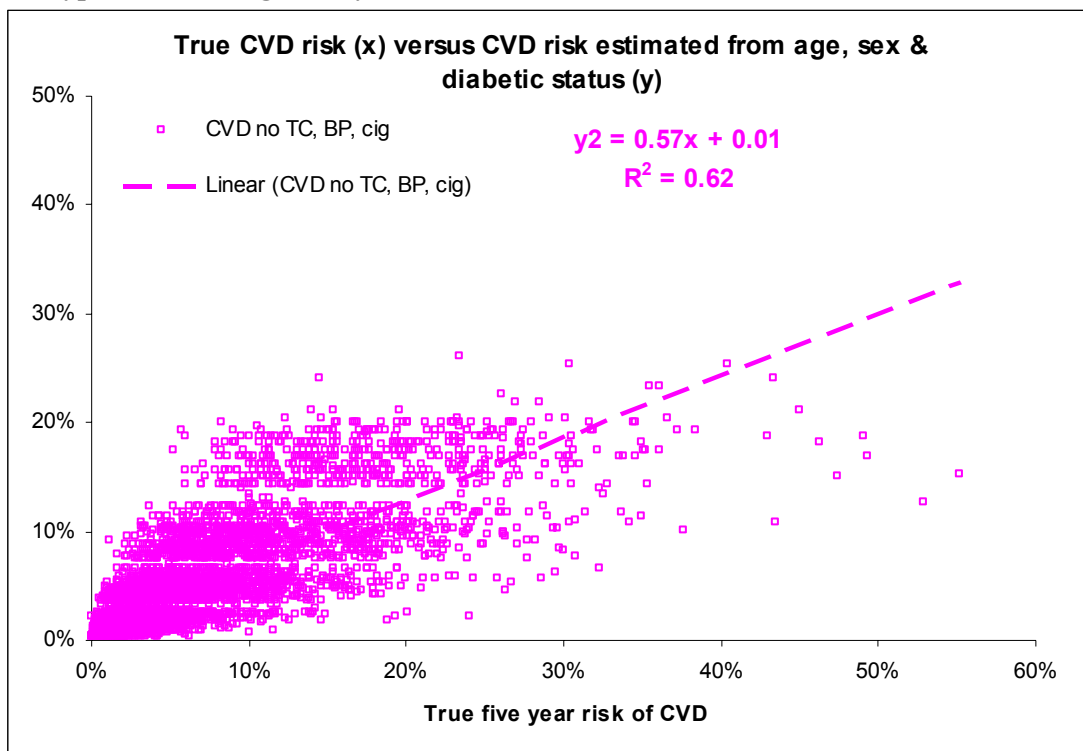


The relationship between risks: estimated and true cardiovascular risks

Risks estimated from minimal data

Figure 26 shows the relationship between true cardiovascular (CVD) risk and a prior estimate of cardiovascular (CVD) risk based on the minimum available data (age, sex, antihypertensive treatment status and diabetic status). The prior estimate of cardiovascular risk shows a moderate degree of correlation with true cardiovascular risk.

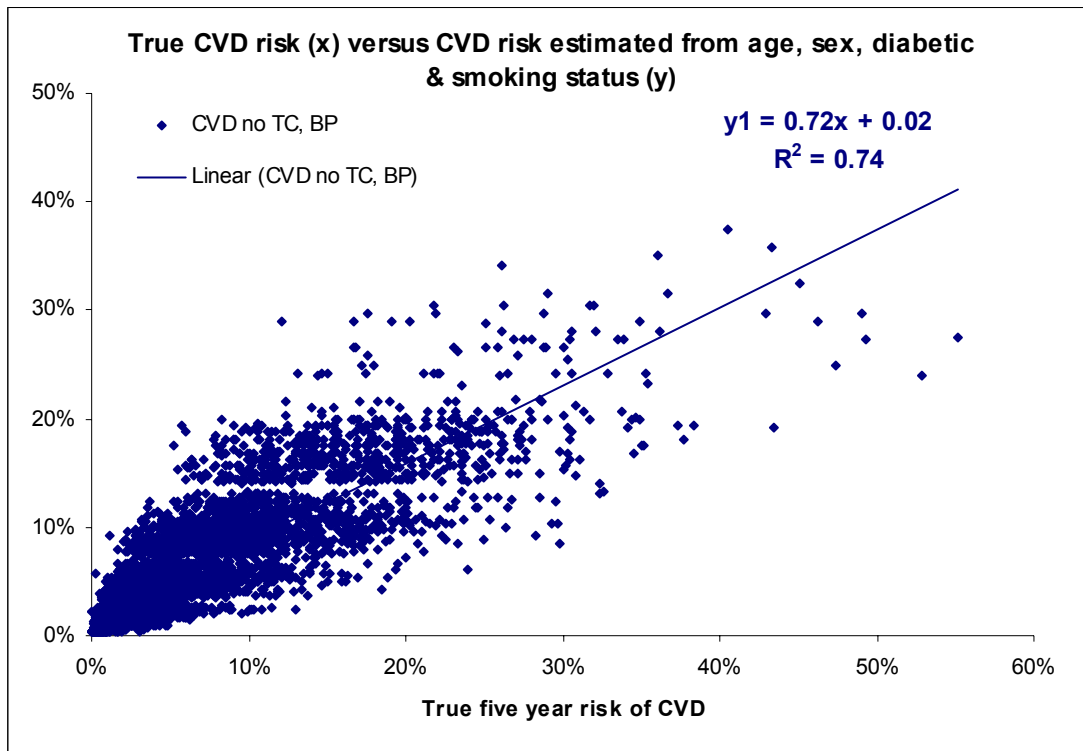
Figure 26: True cardiovascular risk and cardiovascular risk estimated from age, sex, antihypertensive drug history and diabetic status



Risks estimated from minimal data plus smoking status

Figure 27 shows the relationship between true cardiovascular (CVD) risk and a prior estimate of cardiovascular (CVD) risk based on smoking status plus the minimum available data. The prior estimate of cardiovascular risk shows a good degree of correlation with true cardiovascular risk. Addition of smoking information therefore improves the accuracy of the risk estimation.

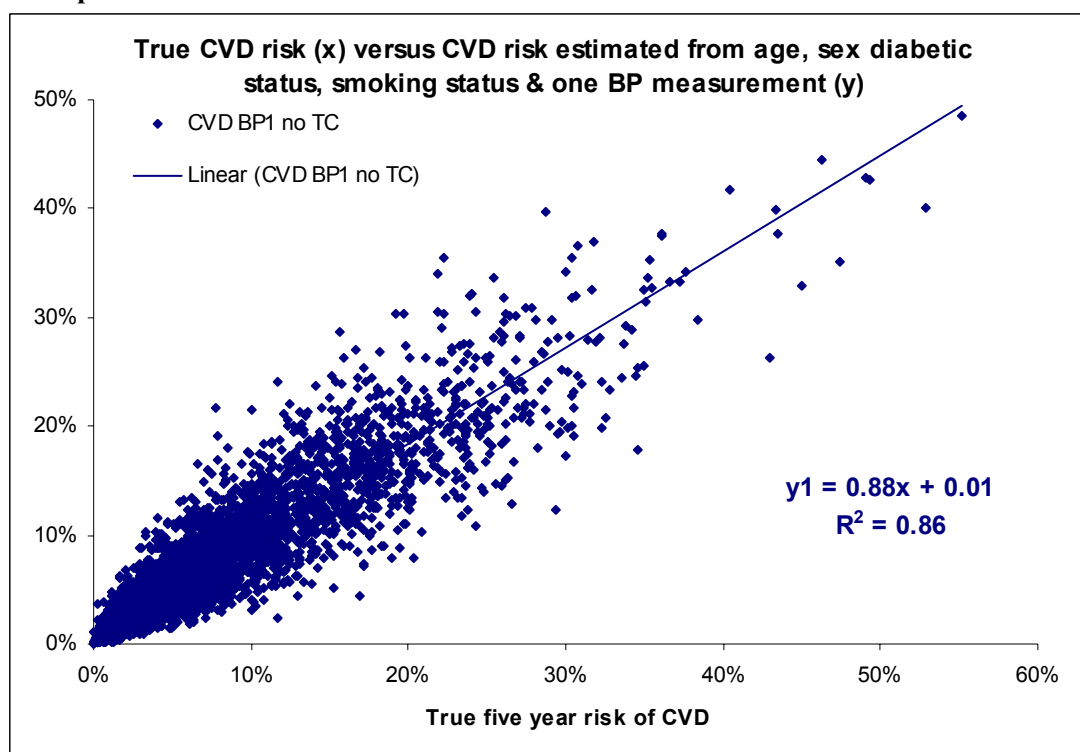
Figure 27: True cardiovascular risk and cardiovascular risk estimated from age, sex, antihypertensive drug history, diabetic and smoking status



Risks estimated from minimal data, smoking status plus a single blood pressure measurement

Figure 28 shows the relationship between true CVD risk and a prior estimate of CVD risk based on age, sex, diabetic status, smoking history and single clinically measured blood pressure. The prior estimate of CVD risk shows a strong correlation with true CVD risk. Inclusion of a single clinical measurement of blood pressure significantly improves the accuracy of the risk estimate.

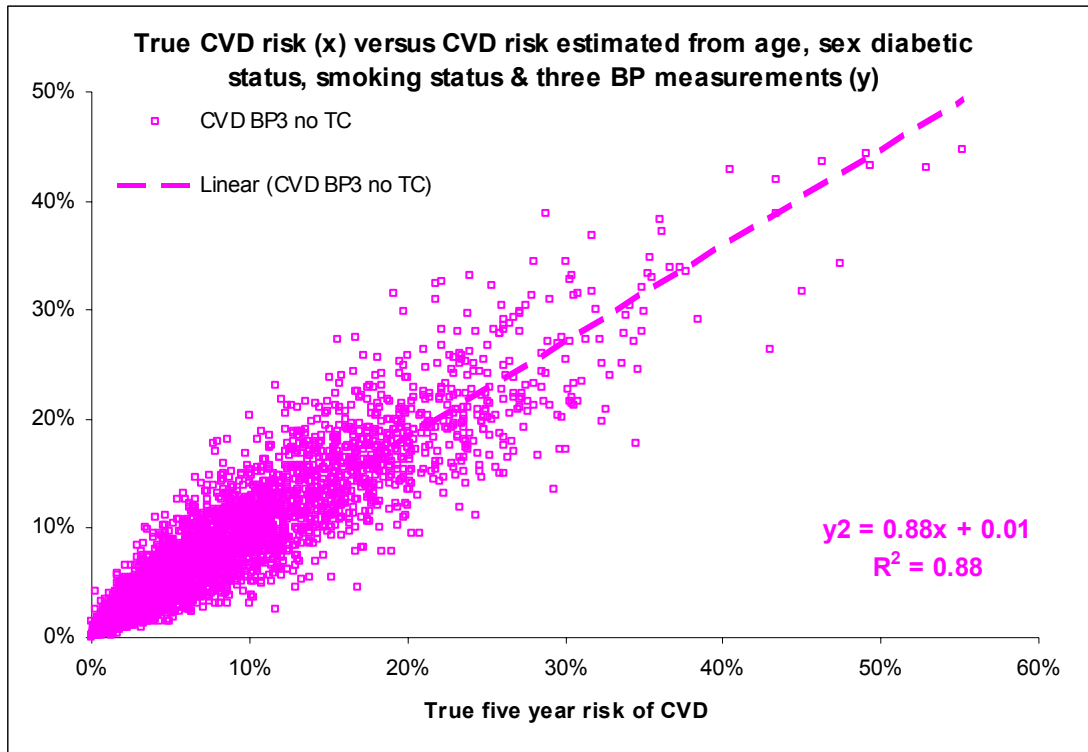
Figure 28: True cardiovascular risk and cardiovascular risk estimated from age, sex, antihypertensive drug history, diabetic and smoking status and one clinical estimate of blood pressure



Risks estimated from minimal data, smoking status plus three blood pressure measurements

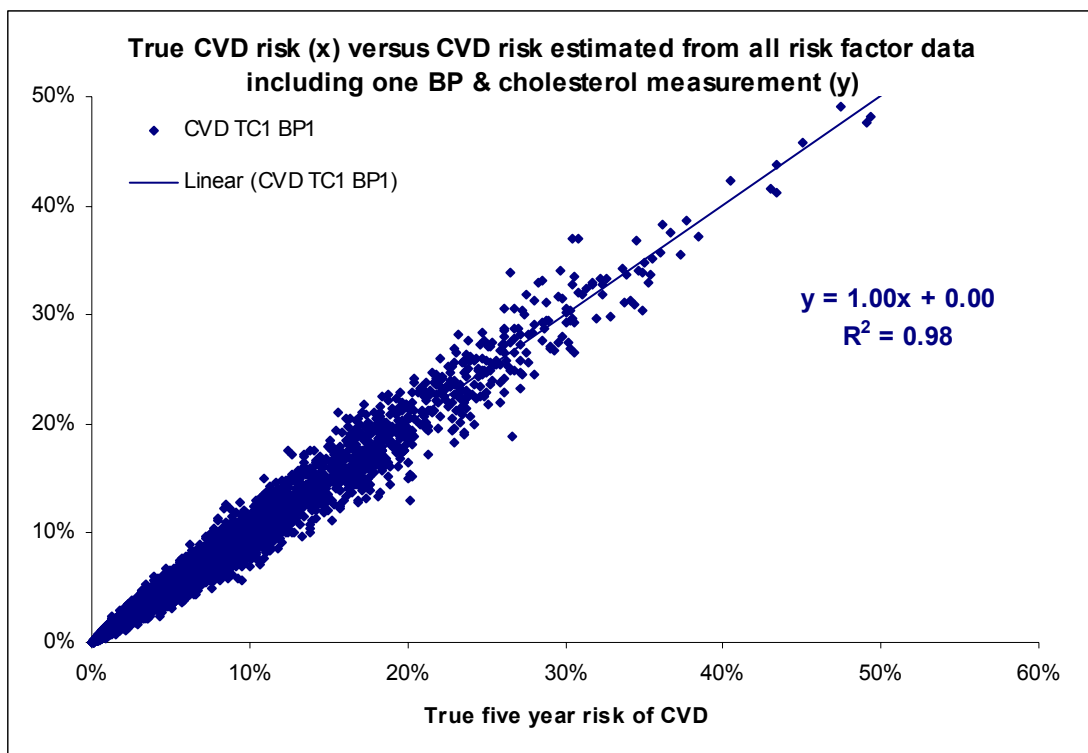
Figure 29 shows the relationship between true cardiovascular risk and a prior estimate of CVD risk based on age, sex, diabetic status, smoking history and the mean of three clinically measured blood pressures. The prior estimate of CVD risk shows a strong correlation with true CVD risk, but correlation is not significantly greater than that with a prior estimate based on a single clinically measured blood pressure. Two further clinical measurements of blood pressure only marginally improve the accuracy of the risk estimate.

Figure 29: True cardiovascular risk and cardiovascular risk estimated from age, sex, antihypertensive drug history, diabetic and smoking status and three clinical estimates of blood pressure



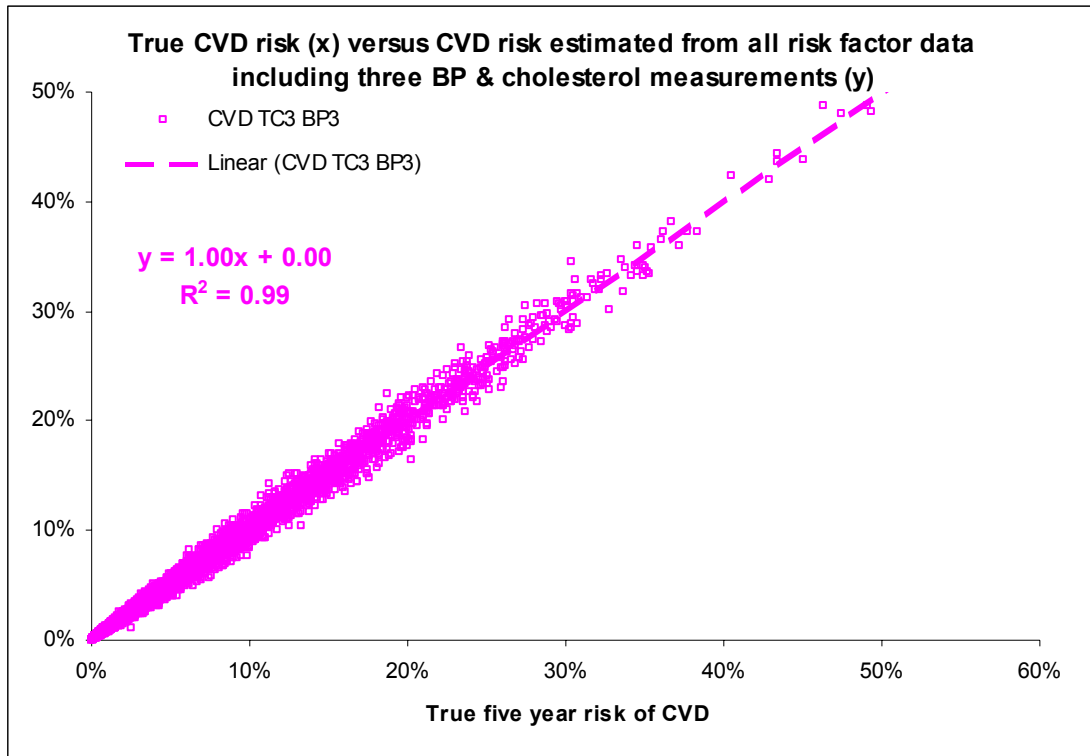
Risks estimated from minimal data, smoking status, plus a single blood pressure and cholesterol level
Figure 30 shows the relationship between true CVD risk and clinically estimated CVD risk where blood pressure and cholesterol have been estimated from a single clinical measurement. There is a very close correlation between the two measures, indicating that a clinical estimate of CVD risk provides a very good estimate of true CVD risk.

Figure 30: True cardiovascular risk and clinically estimated cardiovascular risk based on all risk factor data: blood pressure and cholesterol based on a single clinical measurement



Risks estimated from minimal data, smoking status, plus three blood pressure and cholesterol levels
Figure 31 shows the relationship between true CVD risk and clinically estimated CVD risk where blood pressure and cholesterol have been estimated from three clinical measurements. There is a near perfect correlation between the two measures, indicating that a clinical estimate of CVD risk provides a very good estimate of true CVD risk. It is apparent that the addition of two further measures of blood pressure and cholesterol level contribute only tiny improvements in the precision of CVD risk estimation.

Figure 31: True cardiovascular risk and clinically estimated cardiovascular risk based on all risk factor data: blood pressure and cholesterol based on the mean of three clinical measurements



Treatment eligibility criteria

Baseline treatment recommendations

Treatment eligibility criteria are based on the Joint British recommendations for the prevention of CHD in primary care.¹⁴⁴ At a later stage in the study the effects of changing some of these recommendations are tested. The treatment eligibility criteria used are those summarised in Table 56. In effect they mean that anyone whose five-year CHD risk exceeds 7.5% is eligible for at least one treatment as is anyone whose blood pressure exceeds 160/100 mm Hg or whose total cholesterol exceeds 9.0 mmol/l.

Table 56: Treatment eligibility criteria used for analysis of selection strategies

Intervention	Treatment criteria	
	Non risk criteria	Five-year risk threshold
Aspirin	Age >50	>7.5% CHD risk
Mediterranean diet		>7.5% CHD risk
Initial antihypertensive treatment	Blood pressure \geq 160/100 mm Hg	Any risk level
	Blood pressure \geq 140/90 mm Hg	>7.5% CHD risk
Intensive antihypertensive treatment	Blood pressure \geq 160/100 mm Hg	Any risk level
	Blood pressure \geq 140/90 mm Hg	>7.5% CHD risk
Sitostanol		>7.5% CHD risk
Simvastatin	Total cholesterol \geq 9.0 mmol/l	Any risk level
	Total cholesterol \geq 5.0 mmol/l	>7.5% CHD risk
Clopidogrel		>7.5% CHD risk

Source: Adapted from Joint British Recommendations on prevention of CHD in primary care

Identification strategies

Traditional identification strategies

A series of identification strategies are modelled. In assessing the test characteristics of the strategies, I assume that 574 individuals in our population of 5603 are assessed because this is the number of patients with diabetes and on antihypertensive treatment.

Opportunistic strategy

The simplest traditional strategy is to assess patients opportunistically. To model this, all 5603 patients are sorted into random order and the first 574 individuals are assessed.

National Service Framework for CHD strategy

The next strategy follows the advice of the NSF-CHD to assess all patients with diabetes and those who are already receiving antihypertensive treatment. This means that 574 individuals with diabetes and on antihypertensive treatment are assessed.

Novel identification strategies

The novel identification strategies prioritise patients for assessment on the basis of a prior estimate of their CVD risk.

A prior risk estimated from basic data: age, sex, diabetic and antihypertensive treatment status

The simplest strategy uses information on age, sex, diabetic and antihypertensive treatment status to calculate prior estimates of CVD risk on all patients. Patients are ranked by their prior estimate of CVD risk. The highest ranked 574 are assessed.

A prior risk estimated from basic information plus smoking status

The next simplest strategy uses information on age, sex, diabetic, antihypertensive treatment and smoking status to calculate prior estimates of CVD risk on all patients. Patients are ranked by their prior estimate of CVD risk and the highest ranked 574 are assessed.

A prior risk estimated from basic information, smoking status and a single blood pressure measurement

The next strategy uses information on age, sex, diabetic, antihypertensive treatment, smoking status and one clinically measured blood pressure to calculate prior CVD risk estimates. Patients are ranked by their prior estimate of CVD risk and the highest ranked 574 are assessed.

A prior risk estimated from basic information, smoking status and three blood pressure measurements
The next strategy uses information on age, sex, diabetic, antihypertensive treatment, smoking status and three clinical measurements of blood pressure to calculate prior estimates of CVD risk. Patients are ranked by their prior estimate of CVD risk and the highest ranked 574 are assessed.

A prior risk estimated from basic information, smoking status and one measurement of blood pressure and cholesterol level

The next strategy uses information on age, sex, diabetic, antihypertensive treatment, smoking status and clinically measured blood pressure and cholesterol level to calculate prior estimates of CVD risk. Patients are ranked by their prior estimate of CVD risk and the highest ranked 574 are assessed.

Full clinical assessment of all patients

The most accurate ranking of patients by CVD risk can be obtained by undertaking clinical assessment in the whole population and ranking them on this basis. This is not really a selection strategy as it involves undertaking full clinical assessment on all patients.

Test characteristics of different selection strategies

Assessment of CVD risk factors is used as a diagnostic test to identify patients eligible for treatment. Any patient who is – on the basis of their true CHD risk, CVD risk, blood pressure and cholesterol level eligible for at least one treatment – is a true positive. A series of identification strategies are modelled. Under these strategies, a number of pre-selected patients undergo clinical assessment. This means making three clinical measurements of blood pressure and cholesterol level. Any patient who is eligible for treatment on the basis of these three measurements is classified as test positive. Eligibility for treatment is determined under the criteria defined in Table 56.

The total burden of CVD risk in treatable patients is an indication of the total number of CVD events expected in treatable patients. It is therefore an indication of the total quantity of preventable CVD under each strategy. In addition to the number of true positives and test positives, the total burden of preventable CVD is calculated for each prevention strategy.

Opportunistic strategy

Under this strategy, 27% (156) of those screened will be identified as eligible for at least one treatment. (Table 57) Five (0.9%) are incorrectly classified as eligible for treatment. The sum of the cardiovascular risks in the 156 patients identified as eligible for treatment is 20.2 CVD events (Table 58). This is a mean five-year CVD risk of 13% per identified patient.

Table 57: Test characteristics of assessing 574 from a population of 5603: individuals selected at random (opportunistically)

Clinically determined treatment eligibility	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	151	5	156
Test –ve		418	418
Grand Total	151	423	574

Table 58: Sum of cardiovascular risk in 574 individuals selected at random (opportunistically)

Sum of cardiovascular risk in 574 assessed patients*	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	20.0	0.2	20.2
Test –ve		11.6	11.6
Grand Total	20.0	11.8	31.7

* Sum of CVD risks = number of CVD events predicted in this population

National Service Framework for CHD strategy

Under this strategy, 65% (371) of those screened are classified as eligible for at least one treatment. (Table 59) Two patients (0.3%) are incorrectly classified as eligible for treatment. The sum of the cardiovascular risks in the 369 correctly identified patients is 60.5 CVD events (Table 60). This is a mean five-year CVD risk of 16% per identified patient.

Table 59: Test characteristics of assessing 574 from a population of 5603: individuals selected using the National Service Framework recommendations

Clinically determined treatment eligibility	True treatment eligibility		Grand Total
	True +ve	True -ve	
Test +ve	369	2	371
Test -ve		203	203
Grand Total	369	205	574

Table 60: Sum of cardiovascular risk in 574 individuals selected using the National Service Framework recommendations

Sum of cardiovascular risk in 574 assessed patients	True treatment eligibility		Grand Total
	True +ve	True -ve	
Test +ve	60.5	0.3	60.8
Test -ve		10.0	10.0
Grand Total	60.5	10.3	70.8

Novel strategies

A prior risk estimated from basic data: age, sex, diabetic and antihypertensive treatment status

When 574 patients are identified using a prior risk estimate based on minimal data (age, sex, diabetic and antihypertensive treatment status) and then assessed, 90% (516) are categorised as eligible for at least one treatment. Four (0.7%) are incorrectly classified as eligible for treatment. (Table 61) The total burden of CVD risk in the 512 correctly identified patients is 98.4 – a mean five-year CVD risk of 19% per eligible patient. (Table 62)

Table 61: Test characteristics of assessing 574 from a population of 5603: individuals selected using a prior risk estimated derived from basic risk factor information

Clinically determined treatment eligibility	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	512	4	516
Test –ve		58	58
Grand Total	512	62	574

Table 62: Sum of cardiovascular risk in 574 individuals identified using basic risk factor information

Sum of cardiovascular risk in 574 assessed patients	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	98.4	0.5	98.8
Test –ve		5.1	5.1
Grand Total	98.4	5.6	104.0

A prior risk estimated from basic information plus smoking status

When the prior risk estimate includes smoking data, 92% (526) are categorised as eligible for at least one treatment, 0.5% are incorrectly categorised as needing treatment. (Table 63) The total burden of CVD risk in the 523 correctly identified patients is 104.7 – a mean five-year CVD risk of 20% per patient. (Table 64)

Table 63: Test characteristics of assessing 574 from a population of 5603: individuals selected using a prior risk estimated derived from basic information and smoking status

Clinically determined treatment eligibility	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	523	3	526
Test –ve		48	48
Grand Total	523	51	574

Table 64: Sum of cardiovascular risk in 574 individuals identified using the strategy in Table 63

Sum of cardiovascular risk in 574 assessed patients	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	104.7	0.4	105.1
Test –ve		4.5	4.5
Grand Total	104.7	4.8	109.6

A prior risk estimated from basic information, smoking status and blood pressure measurement
 When a single blood pressure measurement is included in addition to smoking data, 96% (552) are categorised as eligible for at least one treatment, rising to 97% (558) when three measurements are taken. (Table 65 and Table 67) In both cases only one is incorrectly identified as needing treatment. The total burden of CVD risk in the treatable patients is 114.5 and 116.2 respectively – a mean five-year CVD risk of 21% per eligible patient (Table 66 and Table 68).

Table 65: Test characteristics of assessing 574 from a population of 5603: individuals selected using a prior risk estimated derived from basic information, smoking status and a single clinical measurement of blood pressure

Clinically determined treatment eligibility	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	550	2	552
Test –ve		22	22
Grand Total	550	24	574

Table 66: Sum of cardiovascular risk in 574 individuals identified using the strategy in Table 65

Sum of cardiovascular risk in 574 assessed patients	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	114.5	0.3	114.7
Test –ve		2.4	2.4
Grand Total	114.5	2.7	117.1

Table 67: Test characteristics of assessing 574 from a population of 5603: individuals selected using a prior risk estimated derived from basic information, smoking status and three clinical measurements of blood pressure

Clinically determined treatment eligibility	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	556	2	558
Test –ve		16	16
Grand Total	556	18	574

Table 68: Sum of cardiovascular risk in 574 individuals identified using the strategy in Table 67

Sum of cardiovascular risk in 574 assessed patients	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	116.2	0.3	116.5
Test –ve		1.9	1.9
Grand Total	116.2	2.1	118.3

A prior risk estimated from basic information, smoking status and one measurement of blood pressure and cholesterol level

When patients are identified on the basis of a full risk factor assessment with blood pressure and cholesterol measured on a single occasion, 100% (573) patients are identified as eligible for at least one treatment. One (0.2%) is incorrectly identified as eligible for treatment. (Table 69) The total burden of CVD risk in identified patients is 123.1 – a mean five-year CVD risk per patient of 22% per eligible patient (Table 70).

Table 69: Test characteristics of assessing 574 from a population of 5603: individuals selected using a prior risk estimated derived from basic information, smoking status and one clinical measurement of blood pressure and cholesterol level

Clinically determined treatment eligibility	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	572	1	573
Test –ve		1	1
Grand Total	572	2	574

Table 70: Sum of cardiovascular risk in 574 individuals identified using the strategy in Table 69

Sum of cardiovascular risk in 574 assessed patients	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	123.0	0.1	123.1
Test –ve		0.2	0.2
Grand Total	123.0	0.3	123.3

Full clinical assessment of all patients

When patients are identified on the basis of full risk factor assessment derived from three clinical measurements of blood pressure and cholesterol level, 100% (573) are identified as eligible for at least one treatment (Table 71). One (0.2%) is incorrectly identified as eligible for treatment. The total burden of CVD risk in those correctly identified as eligible for treatment is 123.8 – a mean five-year CVD risk of 22% per eligible patient. (Table 72)

Table 71: Test characteristics of assessing 574 from a population of 5603: individuals selected using clinically estimated CVD risk derived from full risk factor information, derived from three clinical measurements of blood pressure and cholesterol level

Clinically determined treatment eligibility	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	572	1	573
Test –ve		1	1
Grand Total	572	2	574

Table 72: Sum of cardiovascular risk in 574 individuals identified using the strategy in Table 71

Sum of cardiovascular risk in 574 assessed patients	True treatment eligibility		Grand Total
	True +ve	True –ve	
Test +ve	123.8	0.1	124.0
Test –ve		0.2	0.2
Grand Total	123.8	0.3	124.2

Comparison of selection strategies

Table 73 summarises the results of assessing 574 different patients selected using a variety of different strategies. Both the number of patients identified as eligible for treatment and the total burden of CVD risk in identified patients increases as more information is used to select patients for assessment. The most we can achieve from a selection strategy is to identify 573 patients with a total burden of 124 CVD events in identified patients.

Table 73: Summary of results of different selection strategies

Patient identification strategy	Number (%) of patients identified as eligible for treatment		Total burden of CVD risk in patients identified as eligible for treatment
Random (opportunistic)	156	(27%)	20
NSF-CHD	371	(65%)	61
Basic data ranking	516	(90%)	99
Basic data ranking + smoking	526	(92%)	105
Basic data ranking + smoking + BP1	552	(96%)	115
Basic data ranking + smoking + BP3	558	(97%)	116
Basic data ranking + smoking + BP1 + C1	573	(100%)	123
Basic data ranking + smoking + BP3 + C3	573	(100%)	124

Traditional strategies

Opportunistically assessing 574 individuals in an eligible population is the least effective strategy. Opportunistic (random) assessment identifies only 27% of the number of patients and 16% of the burden of CVD that would be identified under the optimum strategy. Selectively assessing those with diabetes or on antihypertensive treatment identifies 64% of the identifiable patients and optimum and the burden of CVD in those patients to 49%.

Novel strategies

A novel strategy that ranks patients by a prior estimate of CVD risk derived from age, sex, diabetic status and antihypertensive treatment status identifies 90% of patients eligible and 80% of the burden of CVD. Each incremental addition of further risk factor information –smoking status, blood pressure, cholesterol level – improves this slightly.

Costs and cost-effectiveness of patient identification strategies

Eligibility for treatment is determined by key risk factors (blood pressure, cholesterol level or smoking status) and by CHD risk. Identification of patients eligible for treatment therefore requires assessment of CVD risk factors: age, sex, blood pressure, total cholesterol to HDL cholesterol ratio, smoking history, history of diabetes, history of ischaemic vascular disease and the presence of left ventricular hypertrophy on ECG.

Resource costs of patient selection

Traditional selection strategies

Selection of patients at random (opportunistically) for assessment has no resource costs. Similarly, selection of patients with diabetes and those on antihypertensive treatment has little or no cost, since this information is already recorded on the practice database.

Novel selection strategies

Selection of patients on the basis of a prior estimate of their CVD risk has a resource cost. To calculate a prior estimate of CVD risk from age, sex, diabetic and antihypertensive treatment status, risk factor information must be extracted from the practice database and exported into an Excel template that calculates prior risk estimates. Patients are then sorted in descending order of estimated CVD risk.

In a practice of 6500 patients it took under two hours of staff time to search the practice database and extract risk factor information on 2800 patients eligible for primary prevention of CVD. Practice Nurse time costs £32 per hour and GP time costs £118.²⁸⁵ The time to obtain information from a practice database is constant, irrespective of the size of the practice. The cost of this exercise is therefore £64 to £236 for a practice.

Resource costs of patient assessment

Even if they have never consulted, a patient's age and sex are recorded on the practice database from the date they register with the practice. Diabetic status, history of cardiovascular disease and prescribing of antihypertensive drugs are recorded in virtually all practices. Obtaining this information therefore has no cost.

Smoking status

To ascertain smoking history requires the patient to be interviewed. This can take place face to face or as a telephone consultation. A typical telephone consultation takes 11 minutes of clinical staff time.²⁸⁵ The cost of obtaining smoking history is therefore the cost of 11 minutes of clinical contact by either a PN or a GP: £5.87 or £21.63. (Table 74)

If the patient visits for blood pressure or cholesterol measurement, the clinician can inquire about smoking history at the same time. There is therefore no additional cost to ascertaining smoking history in addition to blood pressure or cholesterol measurement.

Estimating blood pressure

To measure blood pressure once requires the patient to visit the practice. Blood pressure should be measured with the patient seated and at rest for five minutes.¹⁴⁴ Failure to allow sufficient rest period leads to systematic overestimation of blood pressure.²⁸⁶ A single blood pressure measurement therefore takes a minimum of ten minutes of clinical staff time. Full clinical estimation of blood pressure requires three clinic appointments of ten minutes each: a total of 30 minutes of clinical staff time.

The cost of blood pressure measurement is dependent on the type of staff used. The cost of a single blood pressure measurement is therefore £5.33 to £19.67 and the total cost of estimating blood pressure £16.00 to £59.00. (Table 74)

Estimating serum cholesterol levels

To measure total cholesterol to HDL cholesterol ratio once requires the patient to have a blood test.¹⁴⁴ Each visit takes a minimum of 10 minutes. The cost of measuring total cholesterol to HDL cholesterol ratio is therefore 10 minutes of clinical contact and the laboratory cost of a lipid profile. However if serum cholesterol estimation is combined with blood pressure measurement, the total consultation time is 15 minutes. This means that the cost of measuring blood pressure and total cholesterol to HDL cholesterol ratio at the same consultation is 15 minutes of clinical contact and the laboratory cost of a lipid profile. (Table 74)

Full clinical estimation of total cholesterol to HDL cholesterol ratio requires three separate measurements. The costs of laboratory investigations are shown in Table 18. The cost of a single cholesterol measurement is therefore £9.58 to £23.92 and the total cost is of cholesterol estimation from £28.25 to £71.75. (Table 74)

Resource costs identification strategies

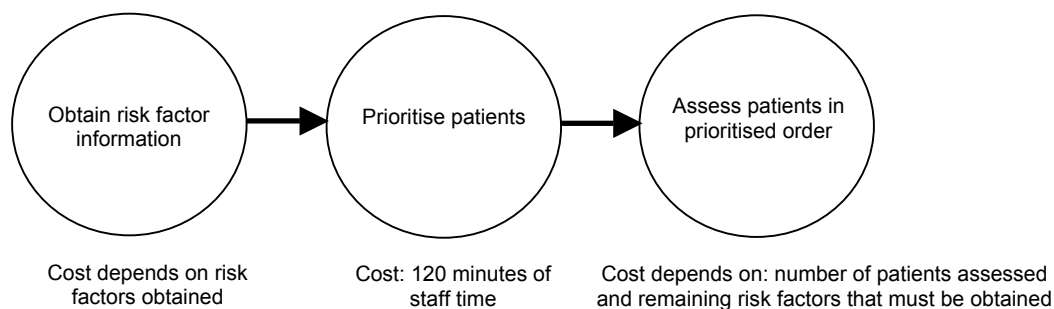
Traditional identification strategies

Because traditional strategies do not require pre-selection the only costs are those of assessing individual patients. The cost per patient assessed of the opportunistic strategy and the National Service Framework for CHD strategy is the number of patients multiplied by the costs of a full assessment. (Table 75)

Novel identification strategies

The novel identification strategies prioritise patients for assessment on the basis of a prior estimate of their CVD risk. The costs of these strategies have a fixed element – the cost of obtaining risk factor information and prioritising patients using this information – and a variable element: the cost of completing the risk factor assessment on each patient.

Figure 32: Novel identification strategies



A prior risk estimated from basic data: age, sex, diabetic and antihypertensive treatment status

Under this strategy, the costs of obtaining risk information are zero. The costs of prioritising patients are the cost of 120 minutes of staff time. The cost of assessing patients is the number of patients multiplied by the costs of a full assessment.

A prior risk estimated from basic information plus smoking status

Under this strategy, the costs of obtaining risk information are the costs of 11 minutes of staff time (a telephone consultation) per patient for every patient in the population. The costs of prioritising patients are the cost of 120 minutes of staff time. A smoking history has already been obtained on every patient, but this does not reduce the time needed to measure blood pressure and cholesterol levels. The cost of assessing patients is therefore the number of patients multiplied by the costs of a full assessment. (Table 75)

A prior risk estimated from basic information, smoking status and a single blood pressure measurement
The costs of obtaining risk information the costs of 10 minutes of staff time per patient for every patient in the population. The costs of prioritising patients are the cost of 120 minutes of staff time. A single measurement of blood pressure has already been obtained on each patient. This means that each patient needs only two further blood pressures and three cholesterol measurements to complete a full assessment (one 10 and two 15 minute consultations). The cost of assessing patients is therefore the number of patients multiplied by the costs this shorter assessment. (Table 75)

A prior risk estimated from basic information, smoking status and three blood pressure measurements
The costs of obtaining risk information are the costs of 30 minutes of staff time per patient for every patient in the population. The costs of prioritising patients are the cost of 120 minutes of staff time. Three measurement of blood pressure have already been obtained on each patient. This means that each patient needs only three cholesterol measurements to complete a full assessment (three 10 minute consultations). The cost of assessing patients is therefore the number of patients multiplied by the costs this shorter assessment. (Table 75)

A prior risk estimated from basic information, smoking status and one measurement of blood pressure and cholesterol level
The costs of obtaining risk information the costs of 15 minutes of staff time per patient for every patient in the population. The costs of prioritising patients are the cost of 120 minutes of staff time. A single blood pressure and cholesterol measurement have already been obtained on each patient. This means that each patient needs only two further cholesterol measurements and two further blood pressure measurements to complete a full assessment (two 15 minute consultations). The cost of assessing patients is therefore the number of patients multiplied by the costs this shorter assessment. (Table 75)

Table 74: Resource implications of obtaining risk factor information for an individual patient.

Activity	Laboratory costs	Staff activity	Total staff time (minutes)	Total cost for whole population	
				Practice Nurse	General Practitioner
Basic data: age, sex, diabetic and antihypertensive treatment status	-	Computer search	120	£64.00	£236.00
Activity	Laboratory costs	Staff activity	Total staff time (minutes)	Total cost per patient assessed	
Practice Nurse	General Practitioner				
Basic data, smoking status and blood pressure x1	-	Clinic visit x1	10	£5.33	£19.67
Basic data, smoking status and blood pressure x3	-	Clinic visits x3	30	£16.00	£59.00
Basic data, smoking status, blood pressure x1 and cholesterol level x1	£4.25	Clinic visits x3	45	£9.58	£23.92
Basic data, smoking status, blood pressure x3 and cholesterol level x3	£12.75	Clinic visits x3	45	£12.25	£33.75

Minimum based on £32 per hour of patient contact (Practice Nurse). Maximum based on £118 per hour of patient contact (GP).

Table 75: Costs of patient identification strategies

Patient selection method	Cost of patient selection	Cost per patient of full patient assessment
Traditional strategies		
Opportunistic	No cost	N x (45 minutes of staff time + 3 x cholesterol measurements)
NSF-CHD strategy	No cost	N x (45 minutes of staff time + 3 x cholesterol measurements)
Novel strategies: prioritise by a prior estimate of CVD risk derived from:		
Basic data	120 minutes staff time	N x (45 minutes of staff time + 3 x cholesterol measurements)
Basic data + smoking status	N x (120 minutes staff time + 11 minutes of staff time per patient)	N x (45 minutes of staff time + 3 x cholesterol measurements)
Basic data, smoking status + single BP measurement	N x (120 minutes staff time + 10 minutes of staff time per patient)	N x (40 minutes of staff time + 3 x cholesterol measurements)
Basic data, smoking status + three BP measurements	N x (120 minutes staff time + 30 minutes of staff time per patient)	N x (30 minutes of staff time + 3 x cholesterol measurements)
Basic data, smoking status + single BP and cholesterol measurements	N x (120 minutes staff time + 15 minutes of staff time per patient)	N x (30 minutes of staff time + 2 x cholesterol measurements)

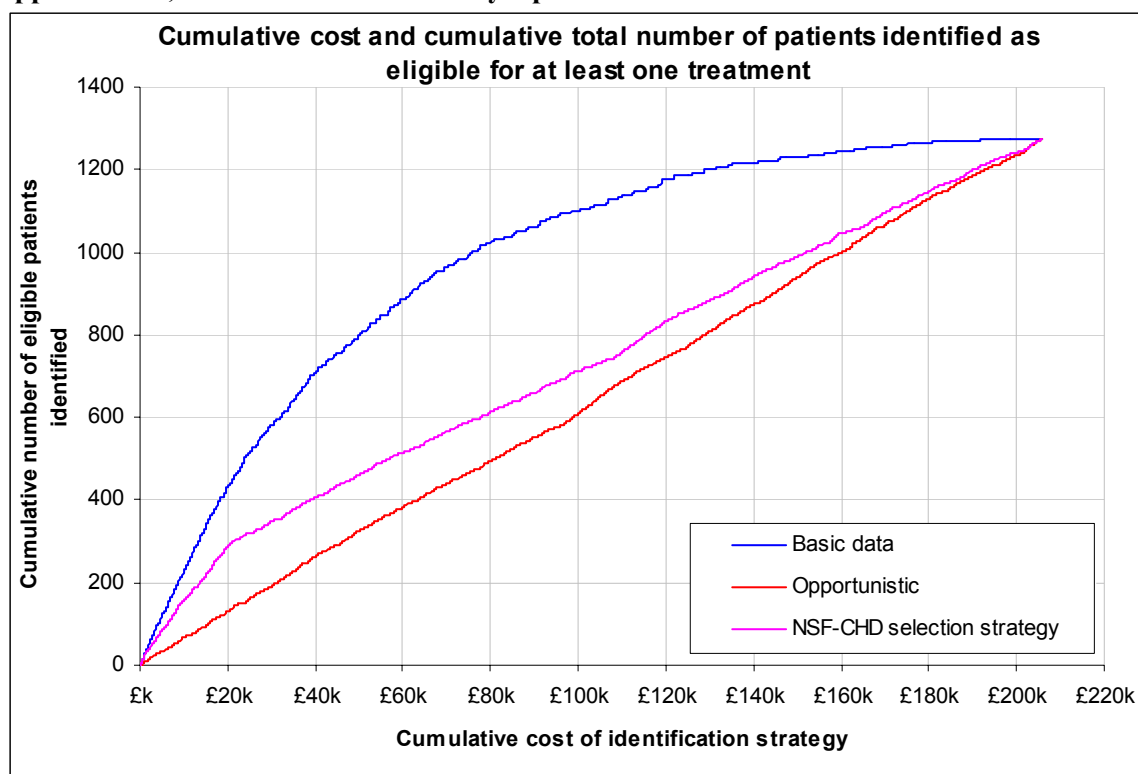
Cost-effectiveness of identification strategies

The cost-effectiveness of identification strategies can be expressed in two ways. The first is to describe the relationship between the total cost of a strategy and the total numbers of eligible patients identified under the strategy. The second is to describe the relationship between the total cost of a strategy and the total number of CVD events predicted to occur in patients identified as eligible for treatment.

Opportunistic, NSF-CHD and prior risk estimation strategies

The relationship between the total cost of a strategy and the total number of eligible patients identified is shown for three strategies in Figure 33.

Figure 33: Costs and numbers of eligible patients identified under three strategies: opportunistic, NSF-CHD and ranked by a prior estimate of CVD risk

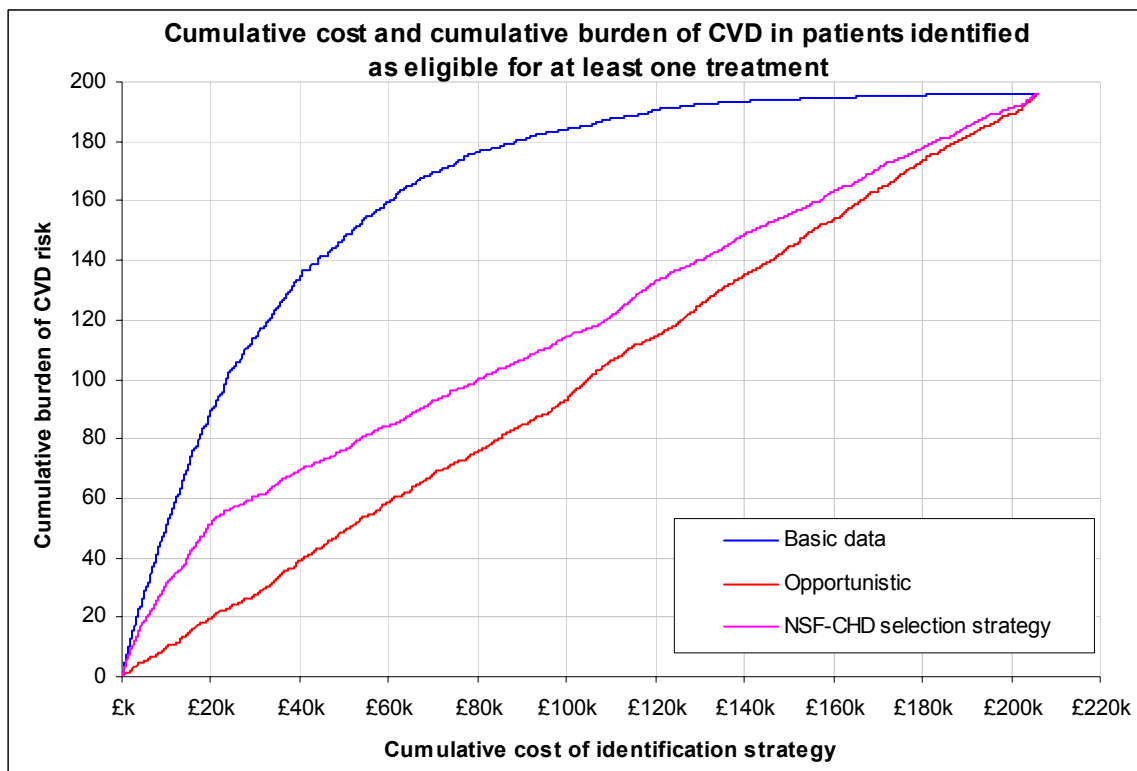


A maximum of 1274 patients eligible for treatment can be identified under the identification strategies. It is evident that for any given level of resources, the least efficient of these three strategies is to assess patients opportunistically (in random order). A strategy that prioritises patients on the basis of NSF recommendations (diabetics and those on antihypertensive treatment first) is more efficient. However the most efficient strategy is to prioritise patients on the basis of a prior estimate of their CVD risk derived from a minimum amount of data. The differences in efficiency are large: £30,000 will identify 191 patients assessed opportunistically, 348 patients

assessed using NSF criteria and 579 patients assessed in order of a prior estimate of their CVD risk (derived from a minimum of data).

Figure 34 shows the relationship between the total cost of a strategy and the total number of CVD events predicted to occur in patients identified as eligible for treatment. In total there will be 189 CVD events over the next five years in patients eligible for treatment. The same three strategies are shown as in Figure 33. When the total burden of CVD in eligible patients is considered, differences between the three strategies appears even more striking. £30,000 of resources under an opportunistic strategy will identify treatment-eligible patients with a total five-year CVD risk of 27; under a NSF strategy it will identify treatment-eligible patients with a total five-year CVD risk of 61; and under a strategy prioritising by estimated CVD risk it will identify treatment-eligible patients with a total CVD risk of 114.

Figure 34: Costs and numbers of CVD events in eligible patients identified under five novel strategies: patients ranked by a prior estimate of CVD risk

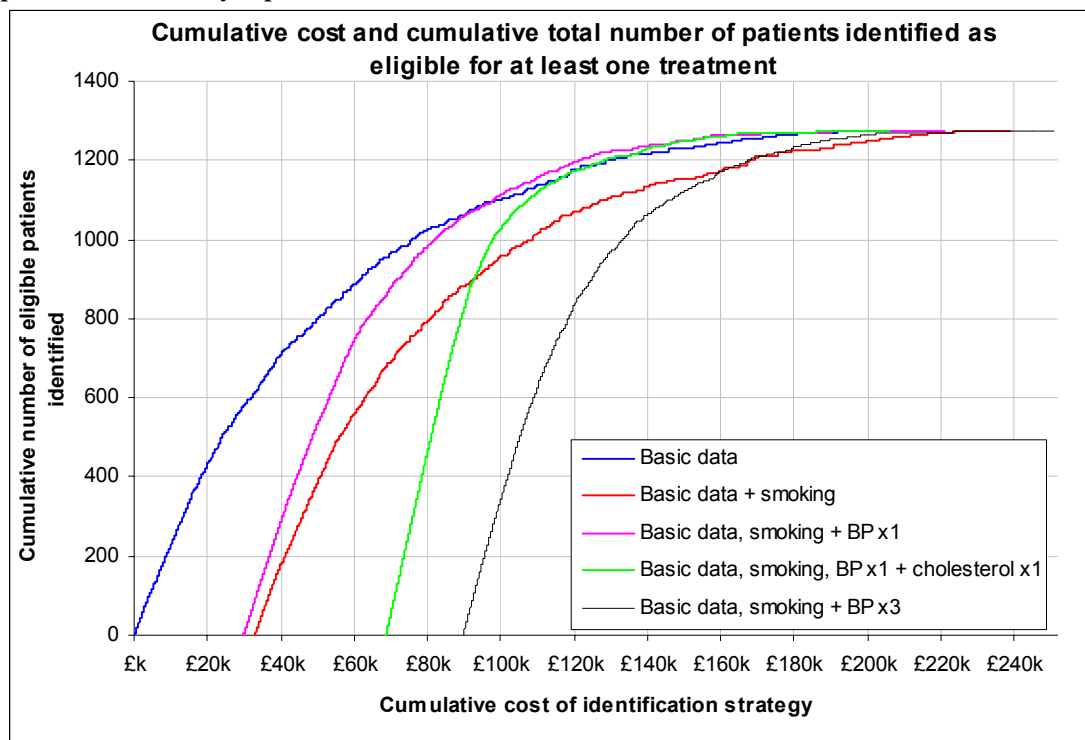


Prior risk estimation strategies using basic data and those collecting additional data

Figure 35 shows the relationship between the total cost of a strategy and the total number of eligible patients identified under five different strategies. These strategies all rank patients by a prior estimate of their CVD risk, however the prior estimates of CVD risk are based on different amounts of data.

The strategy ranking patients by a prior estimate of CVD risk derived from the minimum data has the lowest initial costs, because all the data it requires are held on the practice database. As a result, for almost any given level of resources, it is the most efficient strategy. A selection strategy requiring minimum data plus smoking history and three estimates of blood pressure is dominated by all the other strategies. Similarly, a selection strategy requiring minimum data and a smoking history is dominated by two of the other strategies.

Figure 35: Costs and numbers of eligible patients identified under five novel strategies: patients ranked by a prior estimate of CVD risk

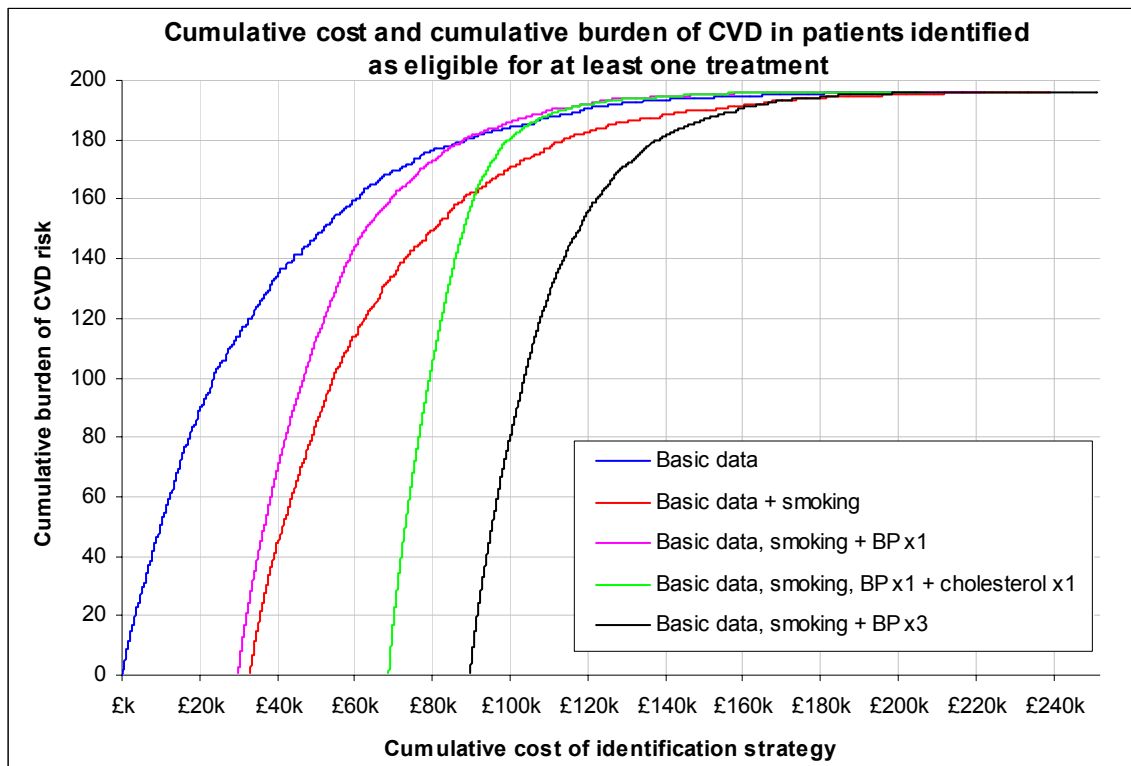


The differences in efficiency between the strategies are important. A number of the strategies require specific risk factor data to be collected on all 5603 patients before ranking can be carried out. Under a strategy prioritising patients on the basis of minimum data, £60,000 would identify 886 patients eligible for at least one treatment. Under a strategy prioritising patients on the basis of minimum data and a smoking history £60,000 would identify 556 patients eligible for at least one treatment. Under a strategy prioritising patients on the basis of minimum data, a smoking history and a single blood pressure measurement, £60,000 would identify 742 patients eligible for treatment. Under two strategies (three blood pressure measurements or a single blood pressure and cholesterol measurement), an allocation of £60,000 to patient

identification is not sufficient even to collect the initial data. As a result, £60,000 of resources on assessment is insufficient to identify any patients under these strategies.

Figure 36 shows the relationship between the total cost of a strategy and the total number of CVD events predicted to occur in patients identified as eligible for treatment. The same five strategies are shown as in Figure 35. Differences between the five strategies are similar when the total burden of CVD in eligible patients is considered as when the number of patients identified is considered. If £60,000 of resources is available for identification of patients, a strategy prioritising patients on the basis of minimum data remains the most efficient. Under a strategy prioritising patients on the basis of minimum data, £60,000 identifies eligible patients the sum of whose CVD risks is 160. Adding smoking history to the minimum data means that £60,000 identifies eligible patients the sum of whose CVD risks is 114. Adding a single blood pressure measurement to smoking history, the sum of the CVD risks in eligible patients becomes 144.

Figure 36: Costs and numbers of CVD events in eligible patients identified under five novel strategies: patients ranked by a prior estimate of CVD risk



Comparing selection strategies

Selection strategies that estimate patients CVD risk and prioritise them for assessment on this basis are clearly superior to those that assess patients in random order or that assess patients on antihypertensive treatment and with diabetes first. This is not surprising, since neither diabetic status nor antihypertensive treatment status are good proxies for CVD risk.

Selection strategy that prioritise patients for assessment on the basis of more risk factor information clearly are more efficient at identifying patients eligible for treatment and identifying patients with a high total risk of CVD. However, when the resource cost of patient identification is taken into account it is clear that the cost of collecting additional risk factor data is high whereas the additional benefits in terms of patients identified or burden of CVD in those patients is not justified by the increased cost.

Next step in the analysis

Clearly the aim of a prevention strategy is not merely to identify patients for treatment or even to identify burden of CVD in treatable patients. The aim of a CVD prevention strategy is to prevent CVD. We have found more efficient ways of identifying patients and burden of CVD. A further question now arises. What are the benefits of our novel selection strategy *in terms of CVD events prevented* in relation to its cost? The next step in this study is therefore to estimate the total resource costs and total benefits of our novel selection strategy in comparison to traditional selection strategies. This means the costs of assessment, treatment and follow-up that result from using a particular strategy and the health benefits (in terms of CVD events prevented) that result from the same strategy.

8. Results: merging individual patient profiles and ordered interventions

In this chapter I combine analysis of the cost-effectiveness of treatment with analysis of the cost-effectiveness of treatments. The result is a complete analysis of the cost-effectiveness of a prevention strategy. The population analysed consists of 2158 persons aged 35 to 74 who are eligible for primary prevention. The analysis describes the effectiveness (number of CVD events prevented) of allocating increasing resources to each strategy. The results of analysis are presented graphically to allow comparison of the marginal returns to expanding each of a number of prevention strategies. The analysis also permits a breakdown of the contributions of different treatments to costs and to effectiveness within the context of a prevention strategy.

In the first part of this chapter I analyse the cost-effectiveness of strategies that use a number of different approaches to patient selection but continue to use current treatment eligibility criteria. In the second part I analyse the cost-effectiveness of strategies that use three novel approaches to patient selection and use revised treatment eligibility criteria.

Base case analysis: current treatment criteria

In the base case analysis I present the results of cost-effectiveness analysis using three different patient identification strategies, but following the treatment criteria outlined in Table 76.

Table 76: Traditional prevention strategy: treatment eligibility criteria

Intervention	Treatment criteria	
	Non risk criteria	Five-year CHD risk threshold
Aspirin	Age \geq 50	>7.5%
Mediterranean diet		>7.5%
Initial antihypertensive treatment	Blood pressure \geq 160/100 mm Hg	Any risk level
	Blood pressure \geq 140/90 mm Hg	>7.5%
Intensive antihypertensive treatment	Blood pressure \geq 160/100 mm Hg	Any risk level
	Blood pressure \geq 140/90 mm Hg	>7.5%
Sitostanol		>7.5%
Simvastatin	Total cholesterol \geq 9 mmol/l	Any risk level
	Total cholesterol \geq 5.0 mmol/l	>7.5%
Clopidogrel		Not used

Source: Adapted from Joint British Recommendations on prevention of CHD in primary care

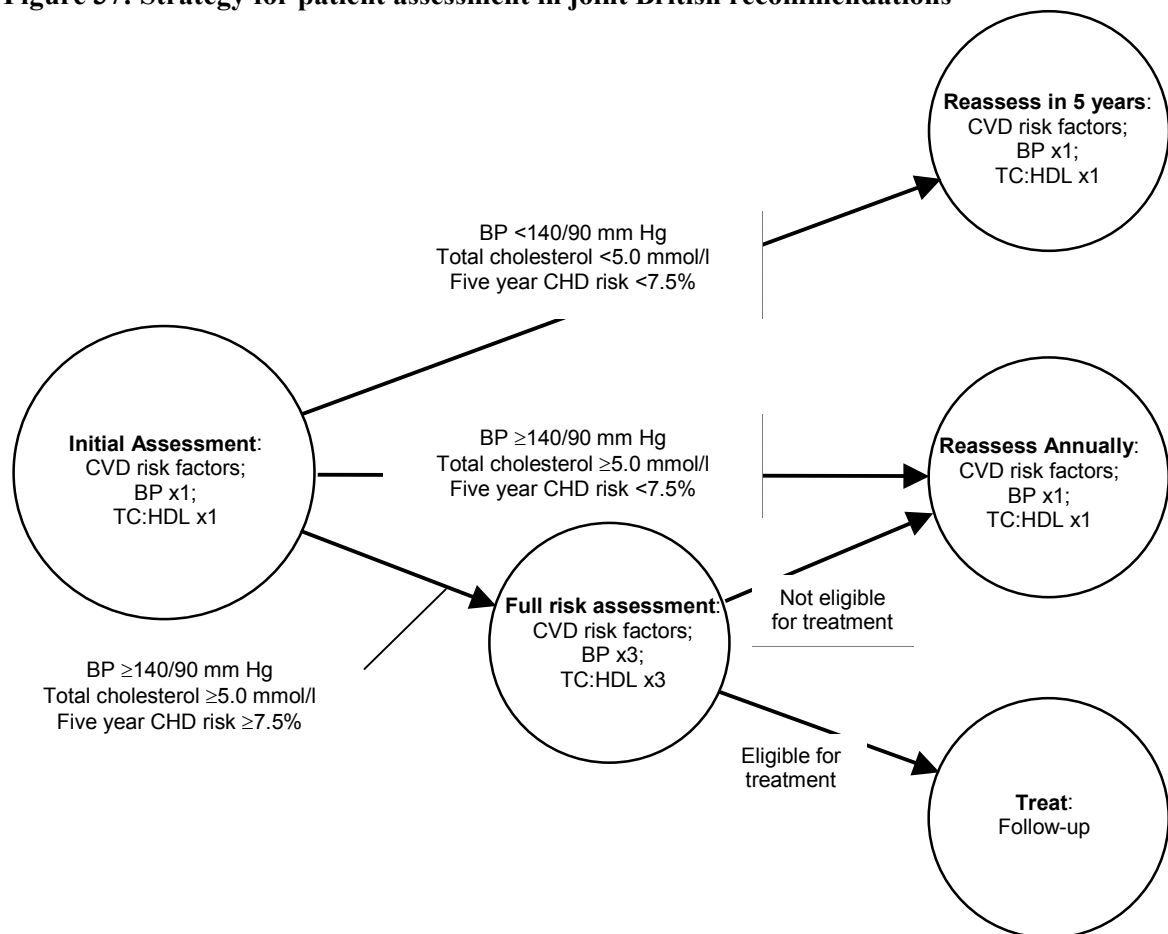
Traditional prevention strategy informed by the joint British recommendations

Identification strategy

The identification strategy modelled follows the approach to patient selection suggested by the joint British recommendations. This means that patients are assessed opportunistically – that is, in random order.

A model of this approach is achieved by allocating all individuals in the population a random number (generated by Excel). Individuals are then ranked in descending order of their random number.

Figure 37: Strategy for patient assessment in joint British recommendations



Assessment strategy

Patient assessment follows the advice of the joint British recommendations. All patients have one clinical measurement of their blood pressure and cholesterol level. Their CHD risk is then estimated using these single clinical measurements. Depending on these initial clinical estimates of blood pressure, cholesterol level and CHD risk, one of three things may happen. They may undergo a complete assessment of their risk factors – three clinical measurements of their blood pressure and

cholesterol level – with a view to and then started on treatment. They may undergo annual reassessment of risk factors. They may be assessed again in five years. (Figure 37)

Full clinical assessment

Patients eligible for treatment on the basis of a single blood pressure and cholesterol measurement go on to have a full cardiovascular risk assessment based on three blood pressure and cholesterol measurements. Those who on the basis of three clinical measurements are eligible for treatment under the criteria in Table 76 are treated. Those who are not eligible for treatment on the basis of three measurements undergo annual blood pressure or cholesterol checks or are reassessed in five years depending on their five-year CHD risk, blood pressure and cholesterol levels.

Annual reassessment

Individuals undergo annual reassessment of blood pressure if their blood pressure exceeds 140/90 mm Hg and their five-year CHD risk is less than 7.5%. Individuals who are on treatment that requires them to be followed up – for example those already on antihypertensive treatment and those eligible for antihypertensive treatment, aspirin, or a statin – are assumed to have their blood pressure checked during routine follow-up. In these individuals, annual blood pressure checks incur no additional cost.

Individuals whose total cholesterol exceeds 5.0 mmol/l but whose five-year CHD risk is less than 7.5% undergo annual reassessment of cholesterol levels. Those who are eligible for a statin are assumed to have their cholesterol checked during routine follow-up.

Five-yearly reassessment

Individuals whose five-year CHD risk is less than 7.5%, whose blood pressure is less than 140/90 mm Hg and whose total cholesterol is less than 5.0 mmol/l are reassessed in five years.

Treatment strategy

In the traditional strategy, eligibility for treatment is based on the joint British recommendations. (Table 76) As the joint British recommendations do not include criteria for advice on a Mediterranean diet or sitostanol patients are considered eligible for these interventions if their five-year CVD risk exceeds 7.5%. The joint British recommendations also do not recommend or include criteria for clopidogrel. In

view of this and because of the very high cost per CVD event prevented with clopidogrel, it is not used in this strategy.

Traditional prevention strategy informed by NSF-CHD

Because neither the joint British recommendations nor the National Service Framework for CHD contain sufficient guidance to form the basis of a complete prevention strategy, the traditional prevention strategy modelled is based on a combination of both.

Identification strategy

The identification strategy modelled follows the approach to patient selection suggested by the NSF-CHD. This means that patients with diabetes and those on antihypertensive treatment are prioritised for assessment. Those on antihypertensive treatment with diabetes are assessed first, then those with diabetes and then those on antihypertensive treatment. Patients with equal priority are assessed in random order.

A model of this approach is achieved by allocating all individuals in the population a score indicating their priority in the NSF-CHD strategy and a random number (generated by Excel). Individuals with diabetes are allocated two points, those on antihypertensives are allocated one point and those with both are allocated three points. Individuals are then ranked in descending order of their risk score and where the risk scores are equal they are ranked in order of their random number.

Assessment strategy

Patient assessment follows the advice of the joint British recommendations described above. All patients have one clinical measurement of their blood pressure and cholesterol level. Those whose blood pressure, cholesterol level or CHD risk exceed a given threshold undergo a complete assessment of their risk factors – three clinical measurements of their blood pressure and cholesterol level – with a view to and then started on treatment. Those with intermediate blood pressure or cholesterol levels undergo annual reassessment. Those at low risk with low blood pressure and cholesterol levels are reassessed in five years. (Figure 37)

Treatment strategy

In the traditional strategy, eligibility for treatment is based on the joint British recommendations. (Table 76)

Novel prevention strategy

Identification strategy

In the novel identification strategy, patients are prioritised for assessment using a prior estimate of their CVD risk. This prior estimate of CVD risk is based on a minimum of risk factor data on each individual patient (age, sex, diabetic status and antihypertensive drug treatment status). These data are available on every primary care practice database. Patients are prioritised in order of their prior estimate of CVD risk and invited for full clinical assessment in that order.

Assessment strategy

A full CVD risk assessment is carried out on all patients included in the strategy.

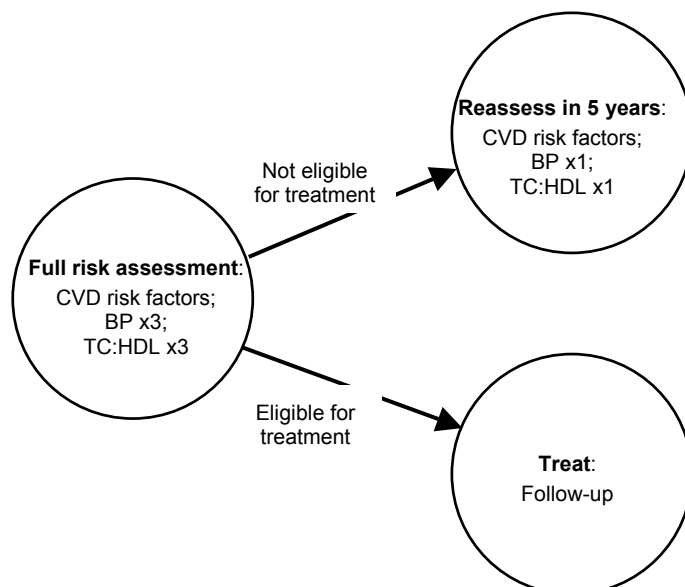
Full clinical assessment

Full clinical assessment means undertaking three clinical measurements of blood pressure and cholesterol and determining treatment eligibility on this basis.

Eligibility for treatment

Eligibility for treatment is based on the joint British recommendations. (Table 76) Patients who are eligible for treatment on the basis of full CVD risk assessment are treated. Those who are not are reassessed in five-years.

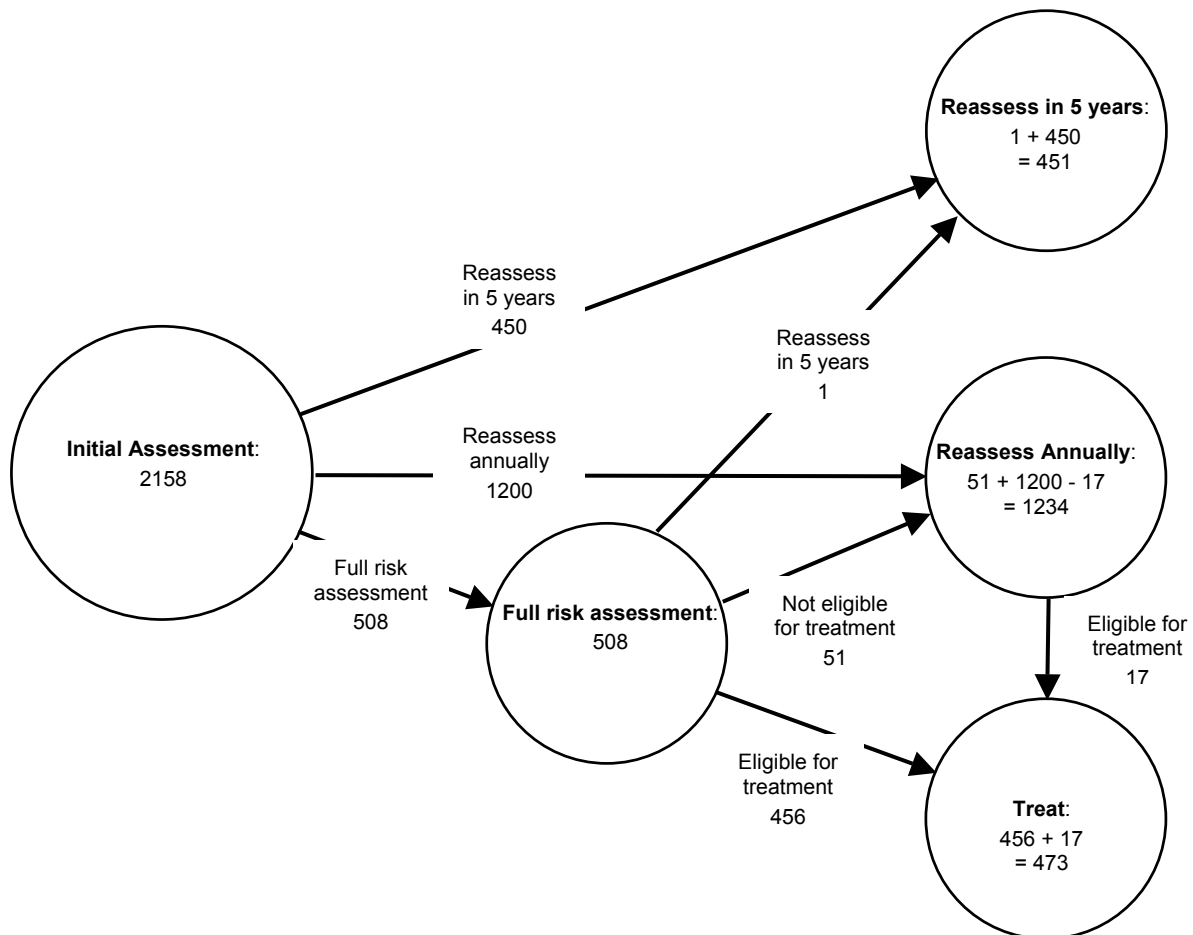
Figure 38: Novel strategy for patient assessment



Results: numbers of patients assessed and treated

Traditional prevention strategy informed by the joint British recommendations
 Figure 39 shows what happens when 2158 patients are assessed under a strategy following the joint British recommendations. When all patients undergo initial assessment, 508 (23.5%) will require full clinical assessment, 1200 (55.6%) will require annual reassessment and 450 (20.9%) can be discharged and reassessed in five years. Of the 508 undergoing full assessment, 456 (89.8%) will be eligible for at least one treatment, 51 (10.0%) will not be eligible but will require annual reassessment and one (0.2%) will be discharged and reassessed in five years. Of the 1200 undergoing annual reassessment, 17 (1.4%) will be found to require treatment.

Figure 39: What happens to 2158 patients assessed under a strategy following the joint British recommendations



This means that following this strategy will result in 473 (21.9%) patients starting treatment, 1234 (57.2%) undergoing annual reassessment and 451 (20.9%) being reassessed in five-years.

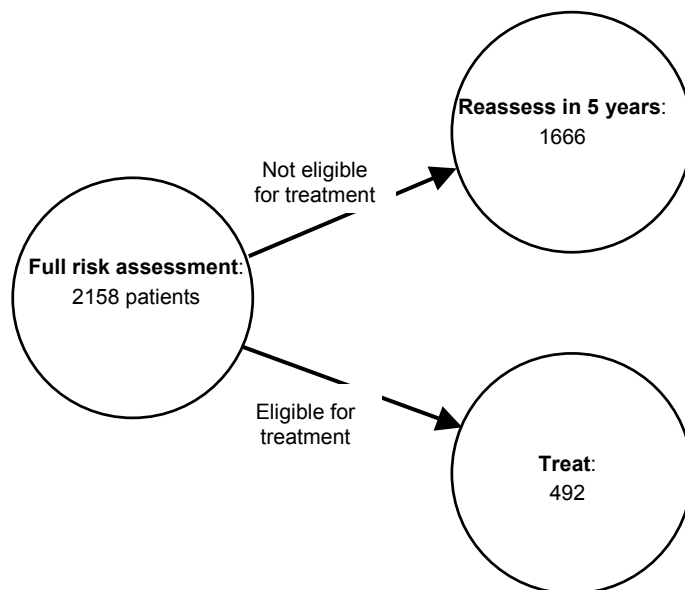
Traditional prevention strategy informed by NSF-CHD

Under a strategy informed by the NSF-CHD patients are prioritised for assessment in a different order, but are assessed according to the same algorithm. The numbers of patients requiring treatment, requiring annual reassessment and reassessed in five years are therefore the same as under a strategy following the joint British recommendations.

Novel prevention strategy

If all 2158 patients are assessed under the novel prevention strategy, 492 are found to be eligible for at least one preventive treatment. The remaining 1666 patients are reassessed in five years. (Figure 40) The numbers found to be eligible for treatment are slightly higher than under a traditional strategy. This is because in traditional strategies, an initial assessment fails to identify a small number of patients as needing full assessment.

Figure 40: What happens to 2158 patients assessed under a novel patient assessment strategy



Results: cost-effectiveness analysis

This section reports the results of cost-effectiveness analysis of a complete strategy in a population. It reports the cost per event prevented of assessing and treating each additional 100 patients in a population. It also reports the cost per event prevented of adding each additional preventive intervention to a group of 100 assessed patients. This latter analysis is important because it allows a direct comparison to be made between the incremental cost-effectiveness of assessing and treating additional patients and the incremental cost-effectiveness of treating known patients with additional (less cost-effective) interventions. The incremental cost-effectiveness analyses are presented graphically.

Traditional prevention strategy informed by the joint British recommendations

Under this strategy patients are selected for initial assessment opportunistically (in random order). Those that meet certain criteria on initial assessment undergo a full assessment.

Under the traditional strategy, 473 individuals from the total population of 2158 are eligible for at least one treatment. Of these 322 are eligible for aspirin, 342 for a Mediterranean diet (and the same number for sitostanol), 306 are eligible for initial antihypertensive treatment, 389 are eligible for further antihypertensive treatment (enalapril) and 306 are eligible for a statin. In total, 46 CVD events can be prevented if all patients are assessed and all those eligible treated.

Incremental cost-effectiveness of assessing increasing numbers of patients

Under this traditional prevention strategy 22 of the first 100 persons assessed are eligible for at least one treatment. The numbers eligible are similar for each successive 100 patients assessed.

The total discounted cost of assessing, treating and following the first 100 patients is £45,687 and the benefits of treatment are a total of 2.2 CVD events prevented per five years. Most of the cost (£36,214 or 79% of the total) is accounted for by the cost of drugs. The cost per event prevented for the first 100 patients is therefore £20,333.

Twenty-two of the next 100 patients assessed are eligible for at least one treatment. The benefits are 3.2 CVD events prevented per five-years and the costs are £64,414. The cost per event prevented for the first 100 patients is therefore £20,021.

For every additional 100 patients assessed about one fifth are eligible for at least one treatment and about two CVD events can be prevented. The cost per event prevented and varies randomly depending on the actual risk levels of the eligible patients in the each 100 assessed patients. (Table 77)

Marginal cost-effectiveness of individual interventions

The incremental cost-effectiveness of an intervention is the additional cost of the intervention in these patients divided by the additional number of CVD events prevented: the same as is calculated in chapter 6. However it is also of interest to know the incremental cost-effectiveness of each individual intervention in the first 100 patients assessed, the second 100 patients assessed and so on. The incremental costs of assessing and treating 100 patients with the aspirin are divided by the total number of CVD events prevented by the use of aspirin. The incremental costs of offering Mediterranean diet to 100 patients (no further assessment is required as this has already been done to determine eligibility for aspirin) are divided by the incremental benefits and so on. The results of this analysis are shown in Table 78.

If all 2158 patients are assessed, under a traditional strategy, the marginal cost per CVD event prevented is lowest with advice to follow a Mediterranean diet (overall mean of £5,742), followed by aspirin (£10,508), and initial antihypertensive treatment (£11,394). Cost per event prevented is significantly higher with further antihypertensive treatment (£32,160), sitostanol (£65,134) and with a statin (£135,795). The cost per event prevented with aspirin is higher than with a Mediterranean diet because all of the costs of patient assessment have been attributed to aspirin. This means that the marginal cost of treating with aspirin is relatively high and the marginal cost of advice on a Mediterranean diet is relatively low.

This analysis suggests that the efficiency of the traditional strategy could be improved considerably by decreasing the numbers of persons treated with a statin (the least cost-effective intervention) and reallocating resources to assessing and treating additional patients with aspirin, advice on a Mediterranean diet and initial antihypertensive treatment.

Table 77: Cost-effectiveness of a traditional strategy for CVD prevention

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	13	15	16	18	15	14	0	23	80	£36,214	£45,687	2.2	£20,333
101-200	23	23	20	25	23	20	0	32	80	£52,090	£64,414	3.2	£20,021
201-300	9	10	6	11	10	11	0	15	76	£25,925	£33,370	1.3	£26,423
301-400	10	10	10	11	10	10	0	14	76	£24,611	£31,978	1.2	£27,477
401-500	18	18	11	17	18	18	0	23	86	£43,003	£53,597	2.6	£20,715
501-600	21	22	18	21	22	17	0	26	78	£45,335	£56,979	3.2	£18,065
601-700	17	18	18	22	18	16	0	25	81	£42,238	£52,836	2.3	£23,421
701-800	9	10	6	9	10	8	0	14	81	£20,383	£27,907	1.3	£21,484
801-900	14	14	17	20	14	12	0	23	82	£33,986	£43,340	1.8	£23,811
901-1000	19	19	11	17	19	16	0	22	77	£40,285	£50,546	2.2	£23,506
1001-2158	169	183	173	218	183	164	0	256	954	£430,890	£544,744	24.9	£21,913

Table 78: Average cost per CVD event prevented with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£9,853	£5,087	£10,993	£33,896	£62,622	£127,751
101-200	£7,193	£5,607	£10,234	£31,468	£63,076	£131,744
201-300	£17,498	£5,746	£12,711	£34,378	£62,899	£131,612
301-400	£15,920	£6,595	£14,783	£39,389	£78,836	£163,868
401-500	£8,466	£5,346	£10,424	£29,376	£54,593	£113,483
501-1000	£10,309	£6,003	£11,005	£32,940	£65,809	£135,700
1001-2158	£10,757	£5,707	£11,631	£31,665	£66,067	£138,950
All 2158	£10,508	£5,742	£11,394	£32,160	£65,134	£135,795

Traditional prevention strategy informed by the NSF-CHD

Under this strategy diabetic patients on antihypertensive treatments are selected for initial assessment first, followed by diabetic patients and patients on antihypertensive treatments. Those that meet certain criteria on initial assessment undergo a full assessment.

Patients are assessed in the same way, albeit in a different order to the traditional opportunistic strategy. This means that the same numbers of patients from the total population of 2158 are eligible for aspirin, a Mediterranean diet (and sitostanol), initial antihypertensive treatment, further antihypertensive treatment (enalapril) and a statin. It also means that the same number of CVD events (46 per five years) can be prevented if all patients are assessed and all eligible patients treated.

Incremental cost-effectiveness of assessing increasing numbers of patients

Under a traditional prevention strategy informed by the NSF-CHD, 60 of the first 100 persons assessed are eligible for at least one treatment. Forty-nine of the next 100 assessed are eligible for at least one treatment, followed by 22 and 29 of the next two groups of 100 patients assessed.

The total discounted cost of assessing, treating and following the first 100 patients is £125,641 and the benefits of treatment are a total of 7.4 CVD events prevented per five years. Most of the cost (84% of the total) is accounted for by the cost of drugs. The cost per event prevented for the first 100 patients is therefore £16,901.

Forty-nine of the next 100 patients assessed are eligible for at least one treatment. The benefits are 4.1 CVD events prevented per five-years and the costs are £79,589. The cost per event prevented for the first 100 patients is therefore £19,406.

Approximately two CVD events are prevented for each additional 100 patients assessed and the cost per CVD event prevented is around £23,000. (Table 79)

Marginal cost-effectiveness of individual interventions

The incremental cost-effectiveness of adding additional interventions to each group of 100 assessed patients is shown in Table 80.

When 2158 all patients are assessed, the incremental cost per event prevented is the same as under the previously described traditional strategy. Because they are all

already on antihypertensive treatment none of the patients ranked 101 to 200 are eligible for initial antihypertensive treatment.

For any given intervention, the cost per event prevented is lower for the first two hundred patients assessed than for the remaining patients. However after the first 200 have been assessed, it is of similar cost effectiveness to add any given treatment to patients ranked 201 to 300 as it is to add the same treatment those ranked 1001 to 2158.

It is clearly more cost-effective to assess all 2158 patients and treat them with aspirin, advice on a Mediterranean diet and initial antihypertensive treatment than to treat the first 100 with enalapril. This suggests that it may be more cost effective to use aspirin, advice on a Mediterranean diet and initial antihypertensive treatment in a wider range of individuals and reduce the number eligible for statins, sitostanol and enalapril.

Table 79: Cost-effectiveness of a traditional strategy for CVD prevention

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	48	50	17	54	50	41	0	60	77	£105,485	£125,641	7.4	£16,901
101-200	30	31	0	44	31	25	0	49	73	£66,154	£79,589	4.1	£19,406
201-300	11	13	15	17	13	12	0	22	81	£31,767	£40,674	2.0	£20,498
301-400	21	21	21	21	21	18	0	29	79	£46,964	£58,685	2.8	£20,732
401-500	4	4	4	4	4	5	0	7	77	£11,214	£16,572	0.5	£35,209
501-600	9	9	9	9	9	9	0	12	74	£22,032	£29,080	0.9	£31,092
601-700	17	17	17	17	17	16	0	22	87	£40,426	£51,052	2.5	£20,351
701-800	12	13	15	15	13	9	0	18	80	£26,443	£35,150	1.6	£22,467
801-900	14	15	13	13	15	15	0	19	80	£35,811	£45,302	1.9	£23,310
901-1000	8	8	17	17	8	7	0	18	87	£22,467	£30,138	1.1	£26,734
1001-2158	148	161	178	178	161	149	0	217	957	£386,199	£493,516	21.1	£23,371

Table 80: Average cost per CVD event prevented with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£3,393	£4,979	£8,322	£24,918	£48,671	£102,198
101-200	£5,268	£6,053	None eligible	£20,477	£44,961	£90,528
201-300	£11,410	£5,044	£11,042	£34,069	£61,917	£125,881
301-400	£8,034	£5,790	£10,978	£35,046	£67,419	£142,693
401-500	£39,928	£6,916	£12,510	£37,844	£72,488	£148,699
501-1000	£13,694	£6,047	£11,840	£37,905	£74,735	£153,397
1001-2158	£12,634	£5,883	£11,673	£38,154	£75,615	£155,832
All 2158	£10,508	£5,742	£11,394	£32,160	£65,134	£135,795

Novel prevention strategies

Under the novel strategies 492 individuals from the total population of 2158 are eligible for at least one treatment: 337 are eligible for aspirin, 361 for a Mediterranean diet (and for sitostanol), 319 for initial antihypertensive treatment, 403 for further antihypertensive treatment (enalapril) and 324 for a statin. If all patients are assessed and all eligible patients treated, slightly more CVD events are prevented. This is because this strategy identifies a greater number of eligible patients and because all eligible patients are identified at the start of the strategy whereas under the traditional strategies some are not identified until the second year.

Incremental cost-effectiveness of assessing increasing numbers of patients

When the order in which individuals are assessed and treated is determined from minimum risk factor data, 81 of the first 100 persons assessed are eligible for at least one intervention. The discounted cost of assessing, treating and following up these patients is £193,244 and the benefits of treatment are a total of 12.3 CVD events prevented per five years. Drugs account for most of the cost (£165,550 or 86% of the total). The cost per event prevented is £15,648.

Seventy-six of the next 100 patients assessed are eligible for at least one treatment and the benefits are 9.4 CVD events prevented per five-years. The cost per event prevented is £19,140.

A diminishing proportion of every further 100 patients assessed are eligible for treatment and a diminishing number of CVD events can be prevented. The cost per event prevented tends to increase as additional patients are assessed. (Table 81)

Marginal cost-effectiveness of individual interventions

The incremental cost-effectiveness of adding additional interventions to each group of 100 assessed patients is shown in Table 82. Overall, the cost per CVD event prevented is lowest with advice on a Mediterranean diet, then aspirin and initial antihypertensive treatment. The costs per event prevented with aspirin, advice on a Mediterranean diet and initial antihypertensive treatment are much lower than with enalapril, sitostanol and a statin. However, because the patients eligible for treatment are concentrated in the first patients assessed, the cost per event prevented also rises as additional patients are assessed. This means that it is much more cost-effective to assess and treat the first 1000 patients with aspirin and initial antihypertensive

treatment than to assess and treat further patients with these interventions. A strategy such as this may be made more efficient by increasing the number of patients eligible for the more cost-effective treatments and reducing the number eligible for the less cost-effective treatments.

Table 81: Cost-effectiveness of a novel strategy for CVD prevention using a prior estimate of CVD risk based on minimum risk factor data

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	81	81	48	63	81	66	0	81	77	£165,550	£196,844	12.3	£15,939
101-200	75	75	42	55	75	63	0	76	75	£154,702	£183,929	9.4	£19,522
201-300	49	49	39	49	49	43	0	56	75	£110,167	£131,081	6.7	£19,493
301-400	37	37	25	36	37	35	0	48	75	£85,897	£102,698	4.5	£22,604
401-500	25	25	22	30	25	22	0	37	75	£58,242	£70,982	3.3	£21,652
501-600	16	16	21	27	16	15	0	28	75	£42,443	£52,229	2.2	£23,745
601-700	21	21	25	26	21	20	0	32	75	£52,620	£64,354	2.5	£25,814
701-800	16	17	16	22	17	17	0	25	75	£43,523	£53,381	1.8	£28,956
801-900	5	10	12	17	10	9	0	18	75	£25,692	£33,112	1.1	£30,553
901-1000	5	7	10	11	7	7	0	16	75	£19,039	£25,601	0.9	£29,979
1001-2158	7	23	59	67	23	27	0	75	869	£83,189	£136,198	2.8	£48,579

Table 82: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£2,780	£5,024	£7,671	£25,787	£51,237	£100,958
101-200	£3,326	£5,803	£10,342	£32,127	£63,495	£138,928
201-300	£4,000	£5,516	£10,429	£31,986	£72,275	£147,731
301-400	£5,899	£6,783	£8,966	£26,435	£60,752	£128,503
401-500	£7,129	£6,328	£10,067	£28,165	£70,793	£143,620
501-1000	£13,940	£6,838	£13,103	£34,651	£90,258	£183,087
1001-2158	£229,651	£5,768	£26,599	£58,965	£100,499	£196,030
All 2158	£9,502	£5,842	£11,717	£32,904	£66,549	£138,890

Traditional versus novel strategies

In terms of cost-effectiveness, the novel strategy offers modest advantages over either a strategy informed by the NSF-CHD guidance or an opportunistic strategy. The relative advantage of one strategy over another is illustrated more clearly in a graph. The X-axis shows the cost of assessing increasing numbers of patients under each of the three strategies. The Y-axis shows the numbers of CVD events prevented per five years by assessing increasing numbers of patients under the three strategies. A strategy ranking patients by a prior estimate of their CVD risk offers significant advantages over the traditional strategies. (Figure 41)

Figure 41: Costs and benefits of assessing and treating increasing numbers of patients under three prevention strategies



Alternative novel prevention strategies

There are a number of potential novel prevention strategies, each using increasing amounts of information on individual patients to derive an estimate of their CVD risk. Novel strategies requiring risk factor information in addition to age, sex and diabetic status require further risk factor data to be gathered in advance and then used to estimate CVD risk. This makes the initial costs of the strategy somewhat higher, but ranking of patients for assessment more closely reflects their true CVD risk. The analysis in chapter 7 suggests that the three most promising novel strategies are to prioritise patients for assessment based on minimal risk factor data (age, sex and diabetic status); based on minimal data, smoking history and a single estimate of blood pressure; and based on minimal data, smoking history, a single estimate of blood pressure and a single estimate of cholesterol levels.

Novel strategy based on minimum data, smoking history and a single blood pressure

Under this strategy 97 of the first 100 persons assessed are eligible for at least one intervention. The discounted cost of assessing, treating and following up these patients is £243,135 and the benefits of treatment are a total of 15.5 CVD events prevented per five years. Drugs account for 81% of the cost. The cost per event prevented is £15,674.

Eighty-four of the next 100 patients assessed are eligible for at least one treatment and the benefits are 9.8 further CVD events prevented per five-years. The cost per event prevented is £19,700.

Eighty-one of the patients ranked 201 to 300 are eligible for at least one treatment and a diminishing proportion of every further 100 patients assessed are eligible for treatment. As a result a diminishing number of CVD events can be prevented as further patients are assessed and the cost per event prevented increases as additional patients are assessed. (Table 83)

Marginal cost-effectiveness of individual interventions

The marginal cost per event prevented is shown in Table 84. The marginal cost per event prevented tends to rise as further treatments are added (although advice on a Mediterranean diet is more cost-effective than aspirin). The cost per event prevented by treating with aspirin, then offering advice on a Mediterranean diet, and initial antihypertensive treatment to the first 1000 patients is much lower than offering even

any of the remaining interventions in subsequent patients. These interventions in these patients are also much more cost effective than enalapril, sitostanol or a statin.

Table 83: Cost-effectiveness of a novel strategy for CVD prevention using a prior estimate of CVD risk based on minimum risk factor data plus smoking history and a single blood pressure measurement

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	92	92	76	92	92	74	0	97	426	£196,846	£243,135	15.5	£15,674
101-200	71	72	54	76	72	64	0	84	67	£163,899	£192,310	9.8	£19,700
201-300	68	69	43	60	69	61	0	81	67	£150,756	£178,160	8.0	£22,240
301-400	41	42	43	50	42	39	0	62	67	£101,841	£120,833	5.2	£23,428
401-500	18	20	22	28	20	19	0	34	67	£50,839	£61,705	2.3	£26,886
501-600	17	18	18	22	18	16	0	32	67	£42,603	£52,677	1.9	£27,757
601-700	16	19	7	11	19	18	0	23	67	£40,703	£50,612	1.9	£27,042
701-800	4	6	8	9	6	6	0	10	67	£16,101	£21,665	0.6	£36,259
801-900	4	10	6	10	10	9	0	15	67	£22,375	£29,200	0.9	£32,504
901-1000	2	3	10	11	3	3	0	13	67	£11,167	£16,031	0.4	£43,903
1001-2158	4	10	32	34	10	15	0	41	772	£43,933	£86,598	1.2	£70,577

Table 84: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£5,535	£4,699	£7,545	£24,803	£49,580	£101,987
101-200	£3,228	£5,770	£9,780	£28,789	£63,895	£130,690
201-300	£3,824	£6,488	£11,051	£33,004	£70,772	£148,291
301-400	£4,962	£6,446	£13,006	£35,536	£80,495	£167,161
401-500	£9,496	£6,922	£16,034	£35,430	£84,556	£172,993
501-1000	£18,442	£6,985	£18,197	£43,138	£89,944	£183,658
1001-2158	£353,852	£5,961	£34,863	£77,533	£111,131	£186,170
All 2158	£9,751	£5,842	£11,717	£32,904	£66,549	£138,890

Novel strategy based on minimum data, smoking history, a single blood pressure and a single cholesterol level

Under this strategy all of the first 100 persons assessed are eligible for at least one intervention. The discounted cost of assessing, treating and following up these patients is £285,228 and the benefits of treatment are a total of 18.2 CVD events prevented per five years. Drugs account for 81% of the cost. The cost per event prevented is £15,710.

Ninety-nine of the next 100 patients assessed are eligible for at least one treatment and the benefits are 11.6 further CVD events prevented per five-years. The cost per event prevented is £20,450.

Ninety-three of the patients ranked 201 to 300 are eligible for at least one treatment and 66 of the patients ranked 301 to 400. This means that when 400 patients have been assessed, three quarters of those eligible for treatment will have been identified. A diminishing proportion of every further 100 patients assessed are eligible for treatment, a diminishing number of CVD events are prevented and the cost per event prevented increases. (Table 85)

Marginal cost-effectiveness of individual interventions

The marginal cost per event prevented is shown in Table 86.

The marginal cost per event prevented tends to rise as further treatments are added (although advice on a Mediterranean diet is more cost-effective than aspirin). The cost per event prevented by treating with aspirin, then offering advice on a Mediterranean diet, and initial antihypertensive treatment to the first 500 patients is much lower than offering even any of the remaining interventions in subsequent patients. These interventions in these patients are much more cost effective than enalapril, sitostanol or a statin.

Table 85: Cost-effectiveness of a novel strategy for CVD prevention using a prior estimate of CVD risk based on minimum risk factor data plus smoking history and a single blood pressure and cholesterol measurement

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	99	100	74	93	100	94	0	100	590	£231,293	£285,228	18.2	£15,710
101-200	94	96	72	87	96	78	0	99	50	£202,258	£237,834	11.6	£20,450
201-300	76	79	52	67	79	71	0	93	50	£174,255	£204,629	8.6	£23,887
301-400	42	47	26	42	47	40	0	66	50	£100,054	£119,051	4.5	£26,334
401-500	20	24	25	30	24	22	0	41	50	£58,196	£69,896	2.4	£28,674
501-600	6	11	14	18	11	11	0	22	50	£29,892	£36,721	1.1	£34,225
601-700	0	4	7	11	4	3	0	12	50	£11,080	£15,186	0.5	£31,380
701-800	0	0	8	10	0	1	0	11	50	£6,172	£9,204	0.2	£49,525
801-900	0	0	8	8	0	1	0	8	50	£5,499	£8,461	0.1	£60,885
901-1000	0	0	10	11	0	0	0	11	50	£5,268	£8,340	0.1	£61,170
1001-2158	0	0	23	26	0	3	0	29	579	£17,097	£46,687	0.3	£174,794

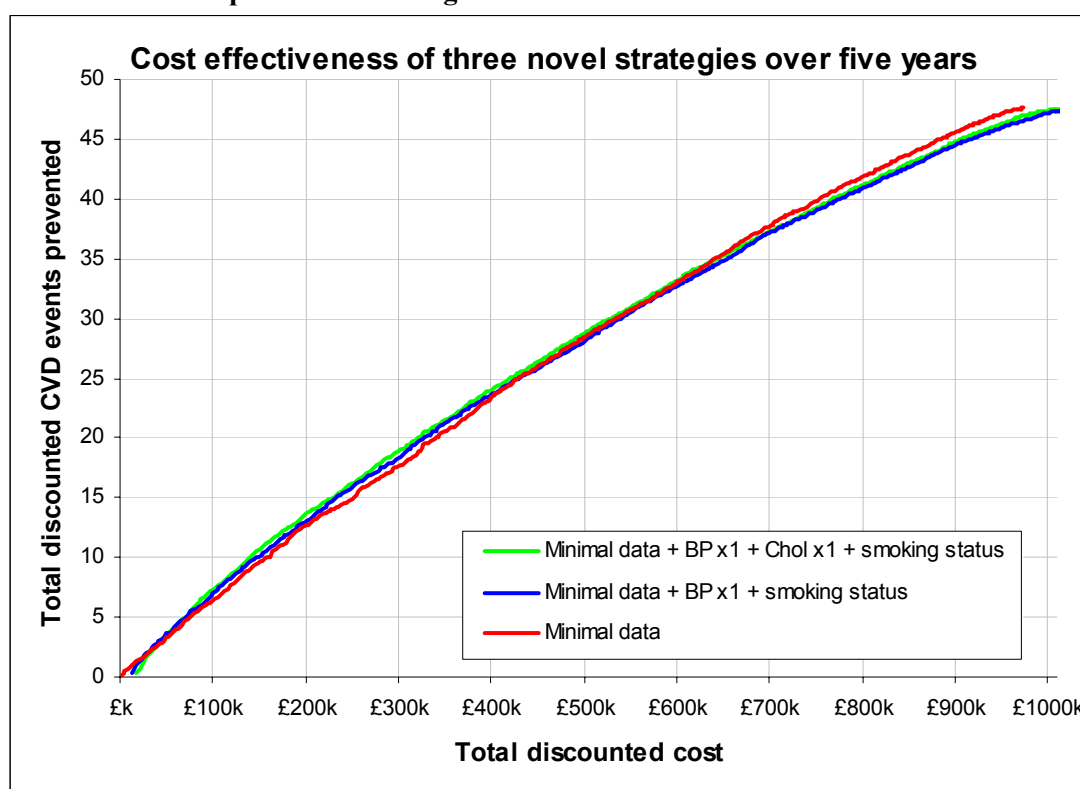
Table 86: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£5,736	£4,174	£7,726	£24,697	£48,714	£102,321
101-200	£2,865	£6,267	£10,499	£34,521	£67,994	£144,415
201-300	£3,599	£7,094	£10,510	£32,390	£75,619	£158,699
301-400	£5,189	£7,583	£14,745	£31,043	£82,912	£171,270
401-500	£8,667	£7,668	£14,544	£34,845	£104,760	£217,579
501-1000	£108,708	£7,303	£19,551	£41,568	£121,305	£223,981
1001-2158	None eligible	None eligible	£38,913	£88,608	None eligible	£142,219
All 2158	£8,594	£5,842	£11,717	£32,904	£66,549	£138,890

Comparing three novel strategies

The relative advantage of one novel strategy over another is illustrated more clearly in a graph. The X-axis shows the cost of assessing increasing numbers of patients under each of the three strategies. The Y-axis shows the numbers of CVD events prevented per five years by assessing increasing numbers of patients under the three strategies. (Figure 42) In terms of cost-effectiveness, there is little to choose between the three novel prevention strategies. This finding differs from that of chapter 7, which found that novel strategies that required more risk factor data were less efficient than those requiring less risk factor data. The apparent anomaly can be easily explained. The greatest costs of any of these prevention strategies are drug costs – the costs of treating patients – small differences in the staff costs associated with identifying patients therefore have little impact on the overall efficiency of any strategy.

Figure 42: Costs and benefits of assessing and treating increasing numbers of patients under three novel prevention strategies



Conclusions from the analysis of strategies using current treatment criteria

Novel selection strategies are significantly more efficient than traditional strategies based on either opportunistic screening or prioritising patients by diabetic and antihypertensive treatment status. However, because drugs account for most of the cost of strategies using current treatment criteria there is little to choose between

different novel strategies. It is clear that treating patients with aspirin, advice on a Mediterranean diet and initial antihypertensive treatment is much more cost-effective than treating patients with enalapril, sitostanol or a statin. This suggests that treatment criteria could be altered to improve the efficiency of the CVD prevention strategy.

Prevention strategies with revised treatment criteria

This section analyses the effects of altering treatment criteria on CVD prevention strategies. We have already demonstrated that CVD prevention strategies using novel selection criteria are more efficient than those using traditional selection criteria. Further analysis will therefore be confined to strategies using novel selection criteria. The next step is to revise the treatment eligibility criteria.

A rational treatment strategy would offer treatments of similar incremental cost-effectiveness. Under current guidelines some potentially cost-effective treatments would not be offered because patients are not considered eligible for treatment. This is particularly true of high-risk individuals with blood pressures less than 140/90 mm Hg and cholesterol levels less than 5.0 mmol/l. In addition some treatments would be offered even though they are not cost-effective. This is true of patients whose CVD risk is not particularly high but whose blood pressure exceeds 160/90 mm Hg or whose cholesterol level exceeds 9.0 mmol/l. There is therefore a case for altering current treatment criteria so that they are more closely follow indicators of cost-effectiveness.

Revised treatment eligibility criteria

Aspirin

Aspirin is a highly cost-effective intervention. It is therefore rational to extend its use to all individuals in whom it is likely to be effective. The first change is to remove the criterion that requires patients to be over 50 to be considered eligible for aspirin. This criterion is not evidence-based because the most recent systematic review of the effects of aspirin includes patients aged under 50.²⁰² The analysis cost-effectiveness indicates that CHD risk is a better predictor of the cost-effectiveness of aspirin than CVD risk. (Chapter 6 and Figure 80, Appendix B)

Previous analysis indicates that the five-year cost of assessing, treating and following up a patient on aspirin is £97.60. The benefits are approximately the product of the five-year CHD risk and 0.28 (relative risk reduction with treatment). This means that, allowing for a 0.3% five-year bleed rate, the cost-effectiveness of aspirin can be calculated as $£97.60 \div (0.28 \times \text{CHD}_{5\text{yr}} - 0.003)$. The cost per CVD event prevented with aspirin is approximately £9,000 at 5% five-year CHD risk and £24,000 at 2.5%

five-year risk. Treatment eligibility criteria for aspirin are therefore altered so that it is offered to all persons at greater than 5% five-year CHD risk. (Table 88)

Advice on a Mediterranean diet

Advice on a Mediterranean diet is also a highly cost-effective intervention. As with aspirin, CHD risk is a better predictor of cost-effectiveness than CVD risk. (Chapter 6 and Figure 81, Appendix B) The five-year cost of advice on a Mediterranean diet is £365.79. The benefit is approximately the product of the five-year CHD risk and 0.72 (relative risk reduction with treatment). The cost-effectiveness of advice on a Mediterranean diet is therefore $£365.79 \div (0.72 \times \text{CHD}_{5\text{yr}})$. This means that the cost per CVD event prevented is approximately £10,000 for a person at 5% five-year CHD risk. The treatment eligibility criteria are therefore altered so that advice on a Mediterranean diet is offered to all persons at greater than 5% five-year CHD risk. (Table 88)

Initial antihypertensive treatment

There is little relationship between blood pressure and cost-effectiveness of treatment for hypertension. The cost-effectiveness of initial antihypertensive treatment is best predicted by CVD risk (Chapter 6 and Figure 82, Appendix B). In order to be consistent with the cost-effectiveness thresholds for aspirin and a Mediterranean diet, the threshold for initial antihypertensive treatment is set at 20% CVD risk; this corresponds to a cost per event prevented of about £10,000. (Table 40)

Epidemiological evidence indicates that for any blood pressure over 115/75 mm Hg there is no threshold at which a lower blood pressure is not associated with a lower risk of CVD.²⁴³ Evidence also suggests that lowering blood pressure that is not higher than average confers similar benefits to lowering blood pressure that is higher than average.⁷⁵ Indeed US guidelines already recommend treatment of blood pressure over 120/80 mm Hg in patients with compelling indications.¹⁰¹ However it is likely that lowering blood pressure that is less than 120/80 mm Hg runs a higher risk of symptomatic hypotension. The guidelines are therefore altered so that all patients whose blood pressure exceeds 120/80 mm Hg are eligible for treatment if their CVD risk exceeds 20%.

Current guidelines recommend treatment for patients whose blood pressure exceeds 160/100 mm Hg irrespective of their CVD risk. The rationale for this is that

excessively high blood pressure may lead to accelerated (also known as malignant) hypertension, with blood pressure causing renal damage and continuing to increase as the result of that renal damage. This means that there is blood pressure threshold above which high blood pressure must be treated, irrespective of calculated CVD risk.

Table 87: Prevalence of blood pressures in each band in persons aged 35 to 74

Age band	<120/80 mm Hg	120/80 - 140/90 mm Hg	140/90 - 160/100 mm Hg	160/100 - 180/110 mm Hg	180/110 - 200/120 mm Hg	>200/120 mm Hg
35-44	29.8%	52.3%	15.1%	2.5%	0.3%	0.0%
45-54	19.6%	47.8%	24.9%	6.1%	1.2%	0.3%
55-64	12.7%	38.3%	33.2%	11.5%	3.3%	0.9%
65-74	6.8%	28.0%	37.1%	21.4%	4.8%	1.9%
Grand Total	19.3%	44.0%	25.5%	8.6%	1.9%	0.6%

Source: Health Survey for England 1998

However accelerated hypertension is rare, with an annual incidence in England reported as 1 to 2 per 100,000.²⁸⁷ Patients with accelerated hypertension who present to hospital have diastolic blood pressures of at least 120 mm Hg.²⁸⁸ By contrast, blood pressure over 160/100 mm Hg (the current “must treat” limit) is common, affecting 11.1% of persons aged 35 to 74 free from CVD. (Table 87) It is not rational to treat 11,100 members of the population because of concern that 1 or 2 per year will develop accelerated hypertension. A more reasonable assumption would be to set the threshold at 180/110 mm Hg – representing respectively 2.6% of persons aged 35 to 74. The eligibility criteria are therefore altered so that patients are eligible for initial antihypertensive treatment if their blood pressure exceeds 180/110 mm Hg. (Table 88)

Further antihypertensive treatment

A similar rationale applies to eligibility for further antihypertensive treatment. Cost-effectiveness is best predicted by CVD risk (Chapter 6 and Figure 83, Appendix B). However as cost per event prevented is never less than £10,000, only patients whose blood pressure exceeds 180/110 mm Hg are eligible for treatment. (Table 88)

Sitostanol

The cost-effectiveness of sitostanol is better predicted by CVD risk than by CHD risk. (Chapter 6 and Figure 84, Appendix B) However the cost per event prevented with sitostanol is never less than £10,000, therefore it is never sufficiently cost-effective to be recommended. (Table 88)

Statins

Current guidelines recommend statins for patients whose total cholesterol exceeds 9.0 mmol/l and at for patients greater than 7.5% five-year CHD risk whose total

cholesterol exceeds 5.0 mmol/l. This recommendation is irrational in several respects. CVD risk is a better predictor of benefit from statins than CHD risk and is therefore a more rational criterion for treatment eligibility. (Chapter 6 and Figure 85, Appendix B) Patients with high cholesterol levels are not necessarily at high risk and treatment of such patients may therefore not be cost-effective.

Evidence suggests that statin treatment is equally effective in persons with cholesterol levels above and below 5.0 mmol/l.¹²⁸ The analysis in chapter 6 indicates that it is equally cost-effective to offer treatment to patients at high risk of CVD with cholesterol levels under and over 5.0 mmol/l. This suggests that there is no clear rationale for a lower cholesterol threshold as a determinant of treatment eligibility. There is however a rationale for treating those with very high cholesterol levels (>9.0 mmol/l), since these may indicate familial hypercholesterolaemia. Untreated patients aged under 40 with familial hypercholesterolaemia have CHD mortality rates 80 times higher than the general population and 5 times the average when aged 40 to 59.²⁸⁹ Mortality from stroke does not appear to be increased in familial hypercholesterolaemia.²⁹⁰ This means that the Framingham CHD risk equation may underestimate risk in these patients. Familial hypercholesterolaemia is believed to affect about one in 500 of the UK population.²⁹¹ About one in 125 of the population of persons without CVD aged 35 to 74 have total cholesterol levels >9.0 mmol/l.

Cost-effectiveness of statins never approaches £10,000 per CVD event prevented, therefore patients are considered eligible for statins only if their total cholesterol exceeds 9.0 mmol/l, irrespective of their calculated CVD risk. (Table 88)

Table 88: Revised treatment eligibility criteria - £10,000 per CVD event prevented

Intervention	Treatment criteria	
	Non risk criteria	Five-year risk threshold
Aspirin		>5% CHD risk
Mediterranean diet		>5% CHD risk
Initial antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
	Blood pressure \geq 120/80 mm Hg	>20% CVD risk
Intensive antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
Simvastatin	Total cholesterol \geq 9.0 mmol/l	Any risk level

Source: See text above

I now can undertake analysis of the cost-effectiveness of three strategies using novel selection criteria, but with the treatment recommendations outlined in Table 88.

Comparing novel preventive strategies with revised treatment criteria

Under the novel strategies with revised prevention criteria 644 individuals from the total population of 2158 are eligible for at least one treatment: 628 are eligible for aspirin, 628 for a Mediterranean diet, 65 for initial antihypertensive treatment, 65 for further antihypertensive treatment (enalapril) and 16 for a statin. If all patients are assessed and all eligible patients treated, 47.1 CVD events are prevented. The total cost of assessing all patients and treating those eligible is £324,184 with a strategy using minimal data, £404,390 with a strategy using minimal data and a single estimate of blood pressure and £392,701 with a strategy using minimal data, a single estimate of blood pressure and cholesterol.

Strategy with revised treatment criteria using minimal data

Incremental cost-effectiveness of assessing increasing numbers of patients

When the order in which individuals are assessed and treated is determined from minimum risk factor data, 94 of the first 100 persons assessed are eligible for at least one intervention. The discounted cost of assessing, treating and following up these patients is £47,083 and the benefits of treatment are a total of 10.0 CVD events prevented per five years. Drugs account for 40% of the cost. The cost per event prevented is £4,697.

Ninety-one of the next 100 patients assessed are eligible for at least one treatment and the benefits are 8.0 CVD events prevented per five-years. The cost per event prevented is £5,180.

A diminishing proportion of every further 100 patients assessed are eligible for treatment and a diminishing number of CVD events can be prevented. The cost per event prevented tends to increase as additional patients are assessed, but remains less than £12,000 throughout the strategy. (Table 89)

Marginal cost-effectiveness of individual interventions

Overall, the cost per CVD event prevented is lowest with advice on a Mediterranean diet, then aspirin and initial antihypertensive treatment. (Table 90) Cost per event prevented is highest with a statin. The cost per event prevented rises as additional patients are assessed.

Table 89: Cost-effectiveness of a novel strategy for CVD prevention with revised treatment eligibility criteria. Patients are ranked for assessment using a prior estimate of CVD risk based on minimum risk factor data

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	94	94	12	11	0	1	0	94	75	£18,790	£47,083	10.0	£4,697
101-200	91	91	7	6	0	0	0	91	75	£14,350	£41,569	8.0	£5,180
201-300	69	69	12	7	0	1	0	69	75	£14,348	£35,132	6.1	£5,775
301-400	55	55	7	9	0	4	0	55	75	£17,083	£33,796	4.1	£8,156
401-500	55	55	4	6	0	2	0	56	75	£12,512	£29,162	3.7	£7,933
501-600	47	47	2	2	0	0	0	48	75	£6,747	£20,772	2.8	£7,468
601-700	43	43	3	3	0	1	0	43	75	£8,317	£21,489	2.7	£7,947
701-800	46	46	3	3	0	0	0	47	75	£7,140	£20,885	2.6	£8,071
801-900	40	40	2	3	0	1	0	40	75	£7,783	£19,603	2.1	£9,400
901-1000	29	29	4	4	0	1	0	30	75	£7,088	£15,976	1.5	£10,353
1001-2158	59	59	9	11	0	5	0	71	869	£20,138	£38,716	3.5	£11,189

Table 90: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£1,678	£5,462	£5,529	£16,814	None eligible	£83,051
101-200	£1,971	£6,359	£7,371	£18,387	None eligible	None eligible
201-300	£2,007	£6,526	£7,893	£33,310	None eligible	£87,569
301-400	£2,523	£7,804	£7,076	£23,340	None eligible	£91,747
401-500	£2,814	£8,533	£7,071	£22,305	None eligible	£87,499
501-1000	£3,193	£9,634	£10,732	£40,263	None eligible	£159,356
1001-2158	£3,320	£9,673	£21,444	£54,897	None eligible	£144,446
All 2158	£2,420	£7,563	£8,284	£26,858	None eligible	£111,805

Strategy with revised treatment criteria using minimal data and a single blood pressure

Incremental cost-effectiveness of assessing increasing numbers of patients

When the order in which individuals are assessed and treated is determined from minimum risk factor data and a single estimate of blood pressure, 97 of the first 100 persons assessed are eligible for at least one intervention. The discounted cost of assessing, treating and following up these patients is £73,015 and the benefits of treatment are a total of 12.3 CVD events prevented per five years. Drugs account for 40% of the cost. The cost per event prevented is £5,939.

Ninety-three of the next 100 patients assessed are eligible for at least one treatment and the benefits are 8.1 CVD events prevented per five-years. The cost per event prevented is £6,347.

A diminishing proportion of every further 100 patients assessed are eligible for treatment and a diminishing number of CVD events can be prevented. The cost per event prevented increases as additional patients are assessed. After 1000 patients have been assessed, the cost per event prevented rises to £28,780. (Table 91)

Marginal cost-effectiveness of individual interventions

Overall, the cost per CVD event prevented is lowest with advice on a Mediterranean diet, then aspirin and initial antihypertensive treatment. (Table 92) Cost per event prevented is highest with a statin. The cost per event prevented rises as additional patients are assessed. This means that it is more cost-effective to assess and treat the first 1000 patients with aspirin, advice on a Mediterranean diet and initial antihypertensive treatment than to assess and treat further patients or to use further interventions. Statins are the least cost-effective intervention under this strategy.

Table 91: Cost-effectiveness of a novel strategy for CVD prevention with revised treatment eligibility criteria. Patients are ranked for assessment using a prior estimate of CVD risk based on minimum risk factor data and a single blood pressure measurement

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	97	97	30	27	0	2	0	97	426	£29,023	£73,015	12.3	£5,939
101-200	92	92	11	13	0	2	0	93	67	£20,517	£51,209	8.1	£6,347
201-300	88	88	4	6	0	2	0	90	67	£16,549	£46,250	6.8	£6,828
301-400	69	69	9	7	0	1	0	71	67	£13,784	£37,909	4.9	£7,715
401-500	61	61	2	2	0	0	0	61	67	£8,479	£29,927	3.4	£8,908
501-600	48	48	2	2	0	1	0	49	67	£8,442	£26,016	2.6	£10,103
601-700	57	57	2	2	0	1	0	57	67	£9,560	£29,876	3.2	£9,351
701-800	32	32	0	0	0	0	0	32	67	£3,928	£16,706	1.5	£10,888
801-900	26	26	2	3	0	0	0	29	67	£4,506	£15,600	1.4	£11,206
901-1000	14	14	1	1	0	1	0	15	67	£3,780	£11,270	0.7	£16,245
1001-2158	44	44	2	2	0	6	0	50	772	£15,732	£66,611	2.3	£28,780

Table 92: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£5,487	£4,870	£6,248	£20,269	None eligible	£77,342
101-200	£3,262	£6,550	£7,527	£22,688	None eligible	£90,405
201-300	£3,825	£7,179	£8,916	£33,856	None eligible	£88,289
301-400	£4,696	£7,862	£12,404	£45,259	None eligible	£87,569
401-500	£6,338	£9,697	£25,632	£98,326	None eligible	None eligible
501-1000	£9,000	£10,171	£18,706	£55,458	None eligible	£131,411
1001-2158	£56,966	£10,446	£46,498	£117,223	None eligible	£155,710
All 2158	£8,069	£7,563	£8,284	£26,858	None eligible	£111,805

Strategy with revised treatment criteria using minimal data and a single blood pressure and a single cholesterol measurement

Incremental cost-effectiveness of assessing increasing numbers of patients

When the order in which individuals are assessed and treated is determined from minimum risk factor data and a single estimate of blood pressure, all of the first 100 persons assessed are eligible for at least one intervention. The discounted cost of assessing, treating and following up these patients is £85,252 and the benefits of treatment are a total of 14.5 CVD events prevented per five years. Drugs account for 40% of the cost of the strategy in the first 100 patients. The cost per event prevented is £5,873.

All of the next 100 patients assessed are also eligible for at least one treatment and the benefits are 8.7 CVD events prevented per five-years. The cost per event prevented is £5,845.

A diminishing proportion of every further 100 patients assessed are eligible for treatment and a diminishing number of CVD events can be prevented. The cost per event prevented increases as additional patients are assessed. After 1000 patients have been assessed there are virtually no further benefits to the strategy and, the cost per event prevented rises to £257,069. (Table 93)

Marginal cost-effectiveness of individual interventions

Overall, the cost per CVD event prevented is lowest with advice on a Mediterranean diet, then aspirin and initial antihypertensive treatment. (Table 94) Cost per event prevented is highest with a statin. It is more cost-effective to assess and treat the first 1000 patients with aspirin, advice on a Mediterranean diet and initial antihypertensive treatment than to assess and treat further patients or to use further interventions. Statins are the least cost-effective intervention under this strategy.

Table 93: Cost-effectiveness of a novel strategy for CVD prevention with revised treatment eligibility criteria. Patients are ranked for assessment using a prior estimate of CVD risk based on minimum risk factor data, a single blood pressure and a single cholesterol measurement

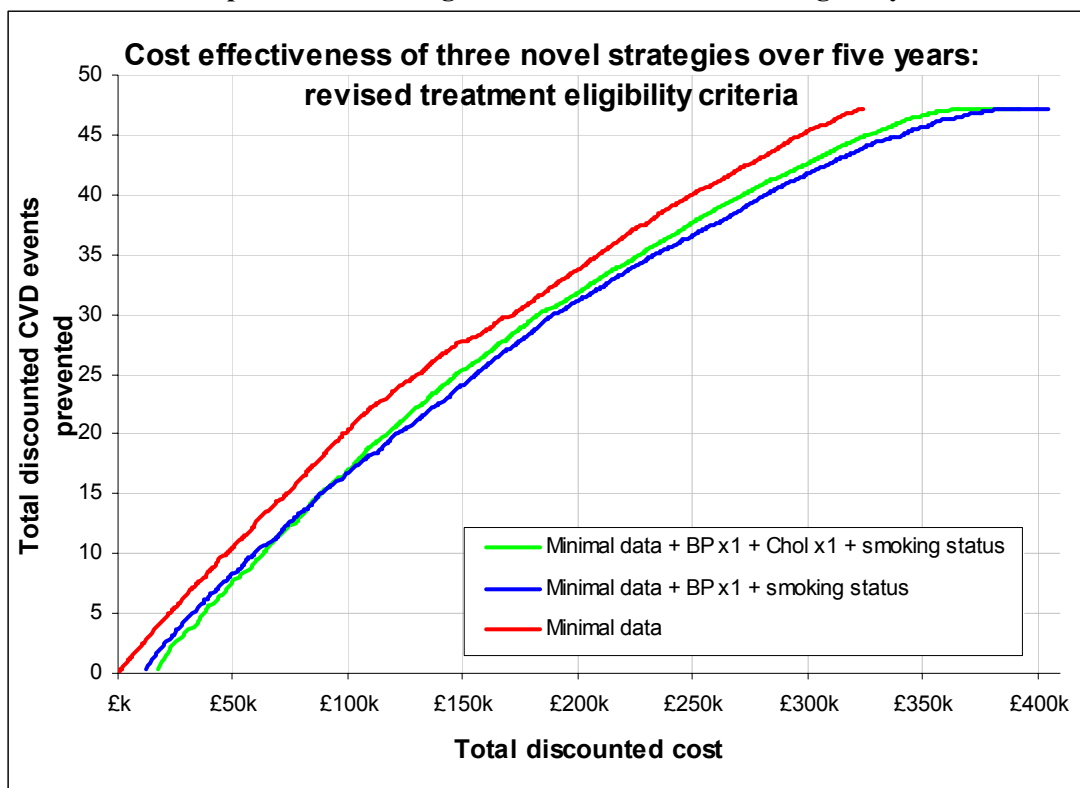
Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	100	100	31	26	0	6	0	100	590	£35,456	£85,272	14.5	£5,873
101-200	100	100	9	10	0	1	0	100	50	£18,612	£51,020	8.7	£5,845
201-300	97	97	9	10	0	1	0	98	50	£18,230	£49,767	7.1	£7,033
301-400	92	92	2	4	0	2	0	93	50	£16,061	£45,879	5.3	£8,643
401-500	79	79	5	5	0	0	0	81	50	£12,169	£38,456	4.2	£9,214
501-600	66	66	3	3	0	1	0	67	50	£11,140	£33,422	3.2	£10,570
601-700	47	47	0	0	0	0	0	47	50	£5,769	£22,232	2.1	£10,814
701-800	28	28	1	1	0	1	0	29	50	£5,498	£16,325	1.2	£13,825
801-900	11	11	2	2	0	1	0	14	50	£3,887	£9,810	0.5	£19,590
901-1000	6	6	1	1	0	0	0	7	50	£1,226	£5,477	0.3	£20,183
1001-2158	2	2	2	3	0	3	0	8	579	£6,250	£35,039	0.1	£257,069

Table 94: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£5,675	£4,216	£6,436	£19,830	None eligible	£83,175
101-200	£2,891	£6,412	£9,081	£28,460	None eligible	£100,730
201-300	£3,592	£7,733	£7,439	£27,884	None eligible	£114,253
301-400	£4,485	£9,365	£13,160	£39,594	None eligible	£123,945
401-500	£5,467	£10,259	£15,586	£49,176	None eligible	None eligible
501-1000	£9,761	£11,824	£18,165	£50,639	None eligible	£195,227
1001-2158	£1,165,433	£13,145	£42,451	£88,922	None eligible	£142,219
All 2158	£7,246	£7,563	£8,284	£26,858	None eligible	£111,805

Comparing three novel selection strategies with revised treatment eligibility criteria
 The relative advantage of one novel selection strategy over another is illustrated more clearly in a graph. (Figure 43) In terms of cost-effectiveness, the strategy using minimal data has a significant advantage over the strategies requiring further risk factor information on patients. This finding differs from that earlier in this chapter. The change in the findings is explained by the fact that staff costs are now a larger part of the total costs than drug costs. The costs of obtaining additional risk factor data therefore have an important impact on overall cost-effectiveness of the strategy.

Figure 43: Costs and benefits of assessing and treating increasing numbers of patients under three novel prevention strategies with revised treatment eligibility criteria



Prevention strategies with further revised treatment criteria

The previous section analyses the effects of altering treatment criteria so that the cost per CVD event prevented is around £10,000. However, the choice of £10,000 per event prevented is arbitrary. In this section I analyse the effect of altering treatment eligibility criteria to reflect a cost per event prevented of around £25,000. The analysis will be confined to strategies using novel selection criteria.

Further revision of treatment eligibility criteria

The simplest way to further revise treatment eligibility criteria is to plot a graph of cost per CVD event prevented (Y-axis) against risk. This is done for the original population of 5603 from the Health Survey for England 1998. Cost-effectiveness ratios are calculated for everyone at over a minimal risk threshold: 2.5% CHD risk. Patients are aggregated into five-year risk bands of and we can read off the risk band at which the cost per CVD event prevented is £25,000. Figure 44 and Figure 45 show the relationship between cost-effectiveness and CHD risk band and the relationship between cost-effectiveness and CVD risk band respectively.

Figure 44: Cost per CVD event prevented across two dimensions: CHD risk category and choice of intervention

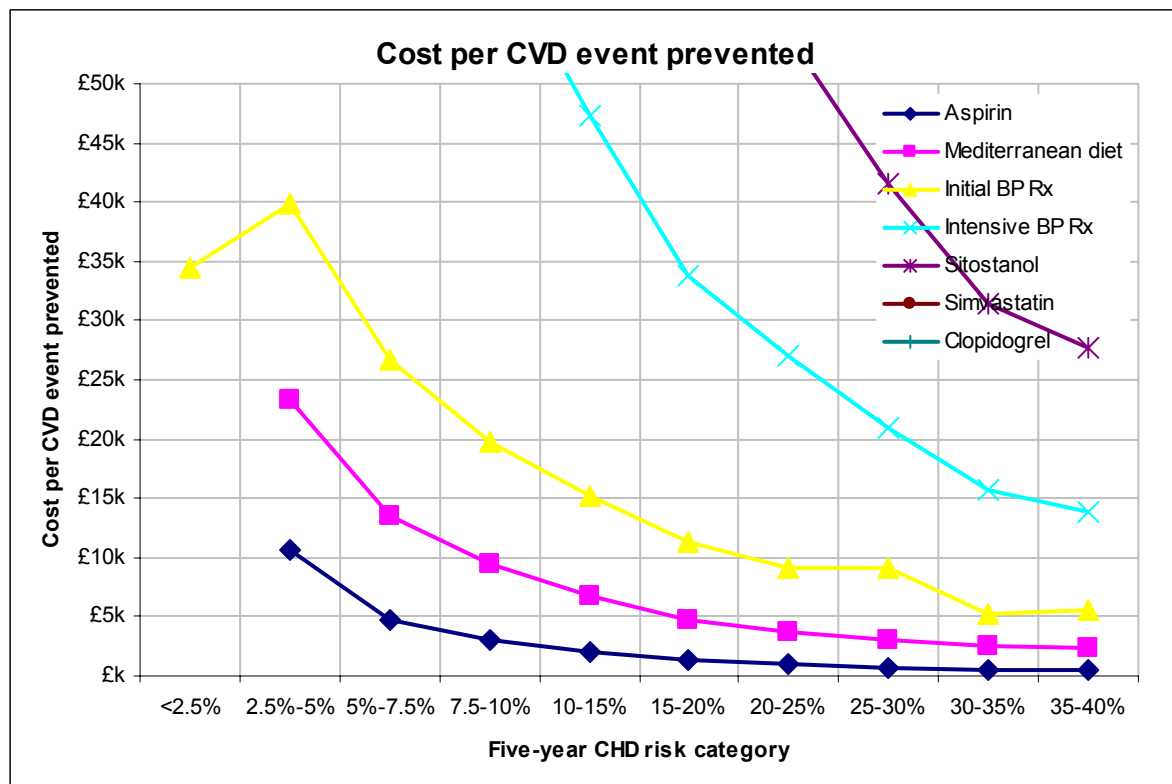
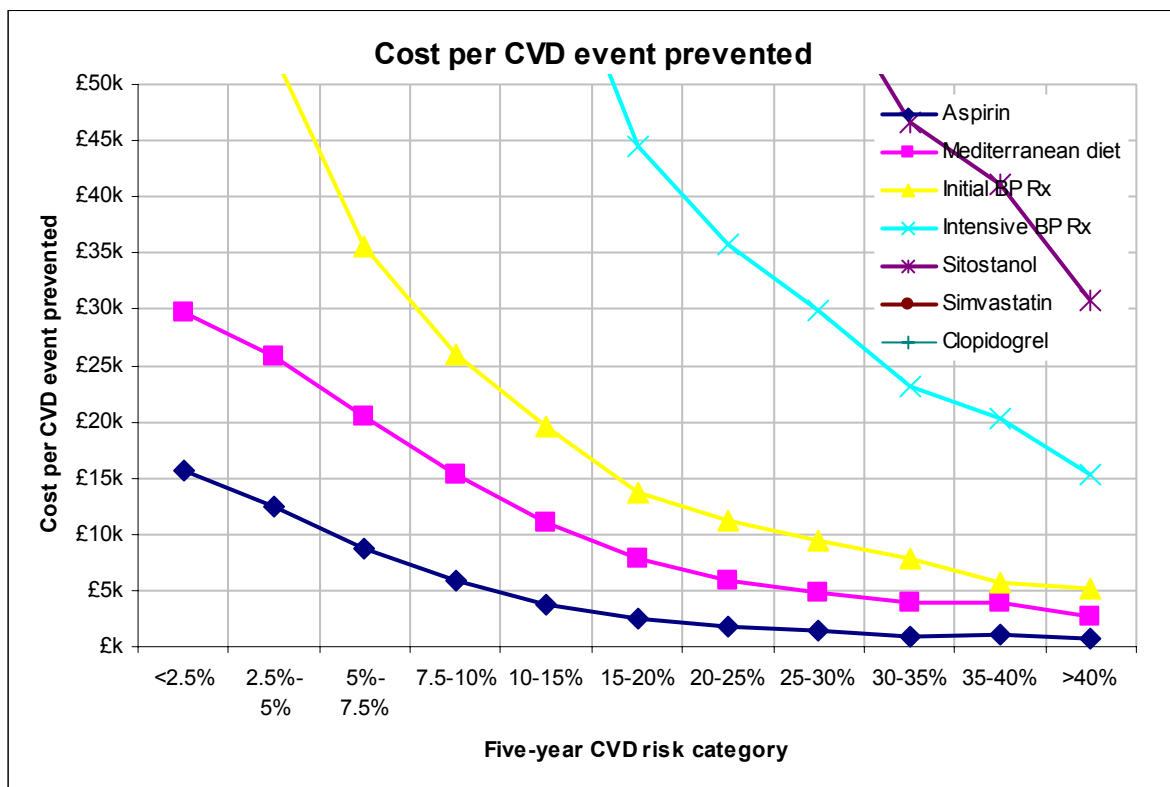


Figure 45: Cost per CVD event prevented across two dimensions: CVD risk category and choice of intervention



Aspirin

The cost per CVD event prevented with aspirin is under £25,000 at 2.5% five-year CHD risk. Treatment eligibility criteria for aspirin are therefore altered so that it is offered to all persons at greater than 2.5% five-year CHD risk. (Table 95)

Advice on a Mediterranean diet

The cost per CVD event prevented with advice on a Mediterranean diet is under £25,000 at 2.5% five-year CHD risk. Treatment eligibility criteria are altered so that advice on a Mediterranean diet is offered to all persons at greater than 2.5% five-year CHD risk. (Table 95)

Initial antihypertensive treatment

Cost per CVD event with initial antihypertensive treatment is about £25,000 at 7.5% five-year CVD risk. Treatment eligibility criteria are altered to this threshold. (Table 95)

Further antihypertensive treatment

Cost per CVD event with initial antihypertensive treatment is under £25,000 at 30% five-year CVD risk. Treatment eligibility criteria are altered to this threshold. (Table 95)

Sitostanol

Sitostanol is never sufficiently cost-effective to be offered.

Statins

Statins are only offered to patients whose total cholesterol exceeds 9.0 mmol/l. (Table 95)

Table 95: Revised treatment eligibility criteria - £25,000 per CVD event prevented

Intervention	Treatment criteria	
	Non risk criteria	Five-year risk threshold
Aspirin		>2.5% CHD risk
Mediterranean diet		>2.5% CHD risk
Initial antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
	Blood pressure \geq 120/80 mm Hg	>7.5% CVD risk
Intensive antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
	Blood pressure \geq 120/80 mm Hg	>30% CVD risk
Simvastatin	Total cholesterol \geq 9.0 mmol/l	Any risk level

Source: See text above

I now can undertake analysis of the cost-effectiveness of further revised treatment recommendations outlined in Table 95.

Comparing novel preventive strategies with further revised treatment criteria

Under the novel strategies with revised prevention criteria 1101 individuals from the total population of 2158 are eligible for at least one treatment: 1096 are eligible for aspirin, 1096 for a Mediterranean diet, 318 for initial antihypertensive treatment, 67 for further antihypertensive treatment (enalapril) and 16 for a statin. If all patients are assessed and all eligible patients treated, 62.6 CVD events are prevented. The total cost of assessing all patients and treating those eligible is £570,154 with a strategy using minimal data, £638,751 with a strategy using minimal data and a single estimate of blood pressure and £650,360 with a strategy using minimal data, a single estimate of blood pressure and cholesterol.

Strategy with further revised treatment criteria using minimal data

Incremental cost-effectiveness of assessing increasing numbers of patients

When the order in which individuals are assessed and treated is determined from minimum risk factor data, all of the first 100 persons assessed are eligible for at least

one intervention. The discounted cost of assessing, treating and following up these patients is £60,196 and the benefits of treatment are a total of 11.3 CVD events prevented per five years. Drugs account for 48% of the cost. The cost per event prevented is £5,335.

All of the next 100 patients assessed are eligible for at least one treatment and the benefits are 9.1 CVD events prevented per five-years. The cost per event prevented is £6,072.

A diminishing proportion of every further 100 patients assessed are eligible for treatment and a diminishing number of CVD events can be prevented. The cost per event increases as additional patients are assessed, rising to over £15,000 after 1000 patients have been assessed. (Table 96)

Marginal cost-effectiveness of individual interventions

Overall, the cost per CVD event prevented is lowest with aspirin, then advice on a Mediterranean diet, and initial antihypertensive treatment. (Table 97) Cost per event prevented is highest with a statin.

Table 96: Cost-effectiveness of a novel strategy for CVD prevention with further revised treatment eligibility criteria. Patients are ranked for assessment using a prior estimate of CVD risk based on minimum risk factor data

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	100	100	65	13	0	1	0	100	75	£28,953	£60,196	11.3	£5,335
101-200	100	100	59	6	0	0	0	100	75	£24,055	£55,115	9.1	£6,072
201-300	94	94	43	7	0	1	0	94	75	£22,506	£51,510	7.2	£7,156
301-400	87	87	31	9	0	4	0	87	75	£24,845	£51,512	5.4	£9,626
401-500	88	88	22	6	0	2	0	88	75	£19,495	£46,411	4.8	£9,618
501-600	84	84	14	2	0	0	0	84	75	£13,226	£38,593	3.9	£9,873
601-700	86	86	19	3	0	1	0	86	75	£16,209	£42,731	4.0	£10,685
701-800	82	82	16	3	0	0	0	82	75	£13,702	£38,593	3.6	£10,625
801-900	68	68	10	3	0	1	0	68	75	£12,494	£32,936	2.9	£11,233
901-1000	56	56	10	4	0	1	0	56	75	£11,344	£28,503	2.3	£12,478
1001-2158	251	251	29	11	0	5	0	256	869	£46,928	£124,054	8.1	£15,290

Table 97: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£1,729	£5,689	£8,500	£16,975	None eligible	£112,874
101-200	£2,085	£6,751	£11,370	£18,387	None eligible	None eligible
201-300	£2,521	£7,858	£11,402	£33,310	None eligible	£87,569
301-400	£3,270	£9,917	£10,566	£23,340	None eligible	£104,824
401-500	£3,728	£10,732	£10,580	£23,464	None eligible	£87,499
501-1000	£4,496	£12,452	£14,939	£45,863	None eligible	£201,192
1001-2158	£6,753	£16,493	£22,455	£70,626	None eligible	£346,234
All 2158	£3,545	£10,262	£11,521	£27,585	None eligible	£144,721

Strategy with further revised treatment criteria using minimal data and a single blood pressure

Incremental cost-effectiveness of assessing increasing numbers of patients

When the order in which individuals are assessed and treated is determined from minimum risk factor data and a single estimate of blood pressure, all of the first 200 persons assessed are eligible for at least one intervention. The discounted cost of assessing, treating and following up the first 100 patients is £94,354 and the benefits of treatment are a total of 13.6 CVD events prevented: a cost per event prevented of £6,936. The discounted cost of assessing, treating and following up the next 100 patients is £63,792 and the benefits of treatment are a total of 9.3 CVD events prevented: a cost per event prevented of £7,974.

A diminishing proportion of every further 100 patients assessed are eligible for treatment and a diminishing number of CVD events can be prevented. The cost per event prevented increases as additional patients are assessed, rising to over £24,000 after 1000 patients have been assessed. (Table 98)

Marginal cost-effectiveness of individual interventions

Overall, the cost per CVD event prevented is lowest with aspirin, advice on a Mediterranean diet and then initial antihypertensive treatment. (Table 99) Cost per event prevented is highest with a statin. It is more cost-effective to assess and treat the first 1000 patients with aspirin and advice on a Mediterranean diet and the first 300 with initial antihypertensive treatment than to assess and treat further patients or to use further interventions. Statins are the least cost-effective intervention under this strategy.

Table 98: Cost-effectiveness of a novel strategy for CVD prevention with revised treatment eligibility criteria. Patients are ranked for assessment using a prior estimate of CVD risk based on minimum risk factor data and a single blood pressure measurement

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	100	100	80	37	0	2	0	100	420	£45,835	£94,354	13.6	£6,936
101-200	200	100	74	15	0	2	0	100	58	£36,367	£74,391	9.3	£7,974
201-300	300	99	80	6	0	2	0	99	58	£33,936	£72,090	8.2	£8,835
301-400	400	97	78	7	0	1	0	97	58	£31,741	£69,438	6.5	£10,670
401-500	500	94	61	2	0	0	0	94	58	£24,660	£60,661	4.8	£12,570
501-600	600	89	54	2	0	1	0	89	58	£24,328	£58,672	4.2	£14,068
601-700	700	88	45	2	0	1	0	88	58	£22,744	£56,642	4.3	£13,035
701-800	800	80	25	0	0	0	0	80	58	£15,399	£46,006	3.0	£15,274
801-900	900	68	15	3	0	0	0	70	58	£13,158	£39,656	2.6	£15,533
901-1000	1000	63	8	1	0	1	0	64	58	£12,193	£36,774	1.9	£18,888
1001-2158	2158	218	13	2	0	6	0	220	676	£43,500	£153,969	6.5	£23,789

Table 99: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£5,497	£4,980	£7,547	£20,219	None eligible	£88,169
101-200	£3,325	£6,911	£10,403	£22,624	None eligible	£90,405
201-300	£3,856	£7,658	£12,199	£41,170	None eligible	£119,800
301-400	£5,082	£9,386	£14,181	£56,447	None eligible	£87,569
401-500	£6,523	£11,655	£16,983	£98,326	None eligible	None eligible
501-1000	£8,796	£13,694	£21,567	£68,746	None eligible	£154,192
1001-2158	£28,025	£17,489	£27,168	£117,223	None eligible	£327,635
All 2158	£8,160	£10,262	£11,521	£27,585	None eligible	£144,721

Strategy with further revised treatment criteria using minimal data and a single blood pressure and a single cholesterol measurement

Incremental cost-effectiveness of assessing increasing numbers of patients

When the order in which individuals are assessed and treated is determined from minimum risk factor data and a single estimate of blood pressure, all of the first 500 persons assessed are eligible for at least one intervention. The cost per event prevented is £6,116 in the first 100 patients, £6,492 in the next 100 and so on. Cost per event rises continuously as additional patients are assessed. (Table 100)

Marginal cost-effectiveness of individual interventions

Overall, the cost per CVD event prevented is lowest with aspirin, advice on a Mediterranean diet, then aspirin and initial antihypertensive treatment. (Table 101) Cost per event prevented is highest with a statin. It is more cost-effective to assess and treat the first 1000 patients with aspirin, then the first 500 with advice on a Mediterranean diet and then the first 200 with initial antihypertensive treatment than to assess and treat further patients or to use further interventions.

Table 100: Cost-effectiveness of a novel strategy for CVD prevention with revised treatment eligibility criteria. Patients are ranked for assessment using a prior estimate of CVD risk based on minimum risk factor data, a single blood pressure and a single cholesterol measurement

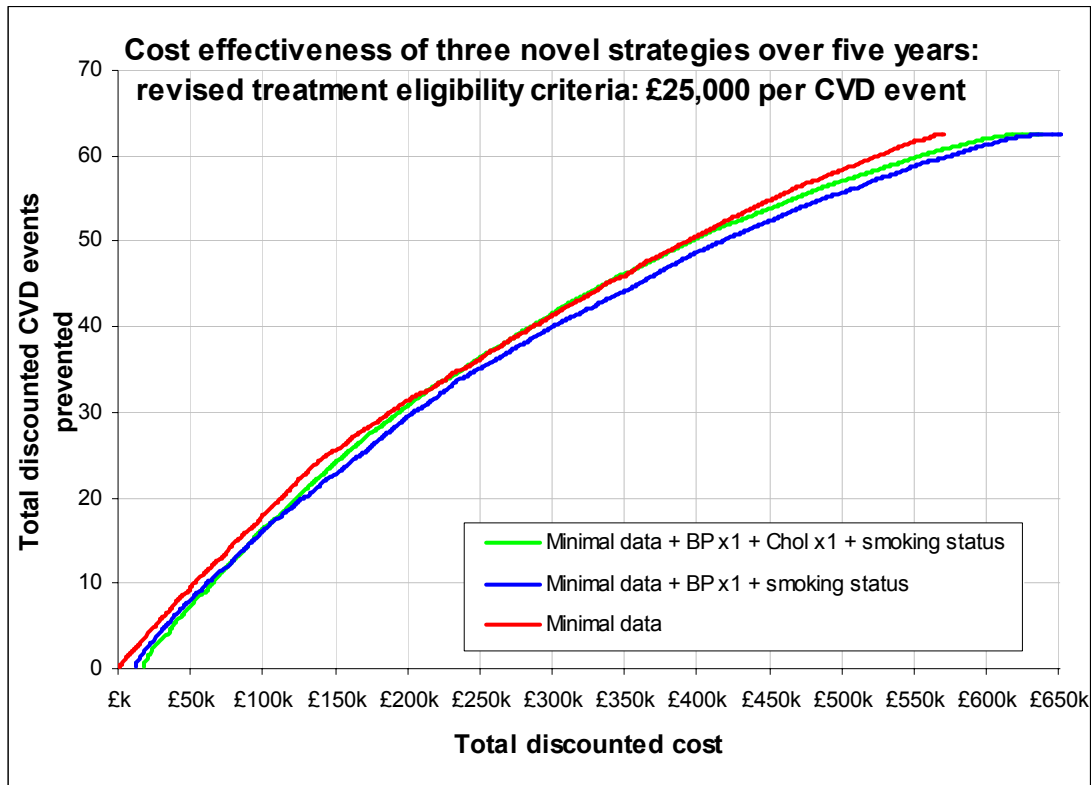
Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	100	100	80	28	0	6	0	100	590	£44,097	£95,059	15.5	£6,116
101-200	100	100	82	10	0	1	0	100	50	£30,535	£64,656	10.0	£6,492
201-300	100	100	72	10	0	1	0	100	50	£28,929	£62,814	8.0	£7,873
301-400	100	100	39	4	0	2	0	100	50	£23,128	£56,033	5.9	£9,456
401-500	100	100	24	5	0	0	0	100	50	£17,818	£50,696	4.9	£10,292
501-600	99	99	12	3	0	1	0	99	50	£16,657	£48,981	4.2	£11,617
601-700	97	97	3	0	0	0	0	97	50	£12,403	£43,745	3.5	£12,623
701-800	97	97	1	1	0	1	0	97	50	£13,967	£45,560	3.0	£15,009
801-900	86	86	2	2	0	1	0	87	50	£13,093	£41,613	2.5	£16,787
901-1000	77	77	1	1	0	0	0	78	50	£9,940	£35,737	2.0	£18,090
1001-2158	140	140	2	3	0	3	0	143	579	£23,188	£93,778	3.1	£30,243

Table 101: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£5,675	£4,216	£7,844	£19,684	None eligible	£91,306
101-200	£2,891	£6,412	£10,801	£28,460	None eligible	£138,745
201-300	£3,647	£7,869	£12,742	£28,964	None eligible	£152,679
301-400	£4,479	£9,705	£17,746	£47,969	None eligible	£137,228
401-500	£5,620	£11,211	£20,689	£70,194	None eligible	None eligible
501-1000	£8,875	£15,613	£24,194	£72,817	None eligible	£302,924
1001-2158	£45,595	£22,539	£42,451	£88,922	None eligible	£444,491
All 2158	£7,487	£10,262	£11,521	£27,585	None eligible	£144,721

Comparing three novel selection strategies with further revised treatment eligibility criteria
 The relative advantage of one novel selection strategy over another is illustrated more clearly in a graph. (Figure 46) In terms of cost-effectiveness, the strategy using minimal data generally has a small significant advantage over the strategies requiring further risk factor information on patients.

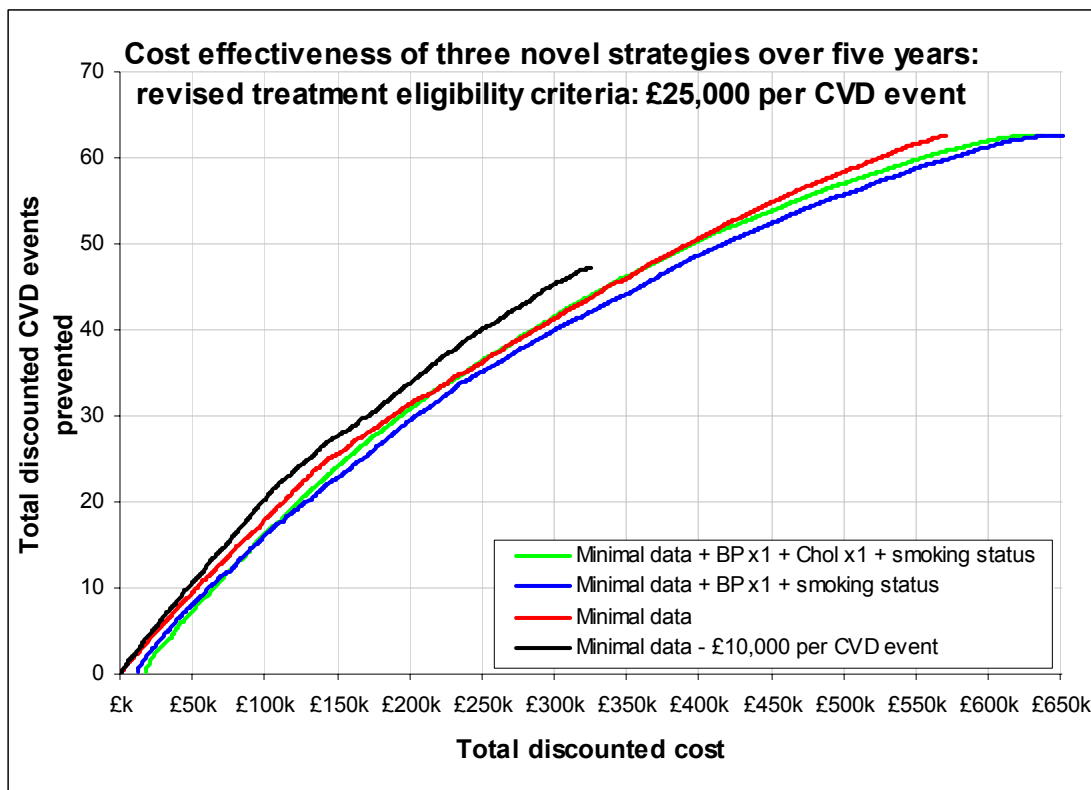
Figure 46: Costs and benefits of assessing and treating increasing numbers of patients under three novel prevention strategies with further revised treatment eligibility criteria



Comparing strategies using treatment eligibility criteria revised to £10,000 and £25,000 per CVD event prevented

A strategy using treatment criteria revised to a threshold of £10,000 per CVD event prevented is more cost-effective than strategies using treatment criteria revised to a threshold of £25,000 per CVD event prevented. The differences are not very great, however, with 17.9 CVD events prevented at a cost of £100,000 under the latter strategy and 20.2 under the former. Because many more patients are eligible for treatment under the latter strategy, it can ultimately prevent more CVD. (Figure 47)

Figure 47: Costs and benefits of assessing and treating increasing numbers of patients under prevention strategies with treatment eligibility criteria offering treatments that cost £25,000 with strategies £10,000 per CVD event prevented



Conclusions from the analysis of strategies using revised treatment criteria
Revising the treatment criteria makes CVD prevention much more efficient. Under these revised criteria, a strategy ranking patients on the basis of minimal data is more efficient than one requiring additional risk factor data.

The next question to ask is how robust these findings are to changes in the underlying assumptions of the model, changes in the estimated effectiveness of treatments and changes in the estimated risk of CVD in eligible patients.

9. Sensitivity analysis

The great strength of the analysis is that it considers the whole prevention process: selection of patients for assessment, patient assessment, treatment and follow-up. The analysis considers the effects of altering a number of characteristics on the cost-effectiveness of prevention strategies. These include, changing the selection strategy, changing eligibility criteria and changing the treatments offered.

The process of designing an efficient CVD preventive strategy has been informed by the results of modelling CVD prevention in a population. The model has in turn been built on a number of assumptions. It is important to explore the limitations of these assumptions and the extent to which they might introduce errors into the analysis and affect the results of the analysis.

Types of error

The purpose of the analysis is to compare the relative cost-effectiveness of strategies and interventions. It is therefore not critical whether the estimated cost-effectiveness of each strategy or intervention reflects the true cost-effectiveness, provided it is not systematically biased in favour of one or another intervention or one or another strategy.

Errors or mistaken assumptions that may affect the analysis can be divided into two types. The first type includes errors or mistaken assumptions that affect all the modelled prevention strategies equally. These errors mean that the results of the analysis will not reflect true estimates of cost-effectiveness for either a particular strategy in a population or a particular intervention in an individual. However, such errors do not introduce systematic bias and do not fundamentally alter the ranking of treatments or the most efficient prevention strategy.

The second type or error includes errors or mistaken assumptions that affect different the modelled prevention strategies equally differently. These systematic errors could potentially change the ranking of treatments and could alter the most efficient prevention strategy.

Uptake and compliance

The model assumes that all eligible patients accept treatment and are that all are fully compliant with medications once treatment has been accepted. This is clearly unlikely to be the case. Long-term compliance with preventive medication is far from complete, but it seems to vary from one intervention to another. Compliance with aspirin in the most recent primary prevention trial (in Italy) was 83% at 3.6 years.²⁹² Compliance with antihypertensive medication also appears to be high, with rates of compliance of 78% reported at one year in Canada.²⁹³ Antihypertensive compliance rates of over 80% have also been reported in the Veterans Administration system in the USA.²⁹⁴ Compliance with statins may be lower. In Canada compliance with statins for primary prevention was 25% at two years.²⁹⁵ A similar study in the USA reported 39% compliance with statin therapy at one year, although it noted that those started in more recent years had improved compliance rates.²⁹⁶

It is difficult to estimate compliance rates in clinical practice in the UK, since it is uncertain how generalisable findings from other health systems are likely to be. Nevertheless it seems that compliance with antihypertensives and aspirin may be expected to be better than with statins. This tends to strengthen the conclusions of the previous analysis. The worst-case scenario is that compliance is universally poor with all medications. The effect of such an assumption is explored below.

How would universal poor compliance affect the analysis? If not all patients accept treatment the costs of assessing patients under remain the same. An assumption of low uptake and compliance maintains the assessment costs while decreasing the costs and benefits of treatment. It is highly implausible that the way in which patients are selected affects their likelihood of accepting or continuing to comply with treatment. Low uptake could systematically favour prevention strategies with lower assessment costs over those with higher assessment costs. This could favour traditional strategies over novel strategies. It is not clear whether it would favour one novel strategy over another.

Method

The effect of altering this assumption is investigated as follows. The most extreme assumption is that only 25% of patients accept treatment. To model this, all patients are allocated a random number between one and four. Only those with a random number of four incur any of the costs and benefits of treatment and follow up.

In the first analysis, traditional approaches are used for patient selection and identification. Patients are treated according to current treatment criteria.

In the second analysis, three novel approaches to patient selection and identification are modelled. Patients according to revised treatment criteria with a threshold of £10,000 per CVD event prevented.

Results of changing assumptions about compliance

The results of applying this assumption to the traditional opportunistic strategy, the traditional NSF-CHD based strategy and the novel strategy based on minimal data is shown in Figure 48. When current treatment criteria are used, the novel strategy based on minimal data maintains its advantage over the remaining strategies.

Figure 48: The effect of reducing uptake of treatment to 25% on the efficiency of preventive strategies

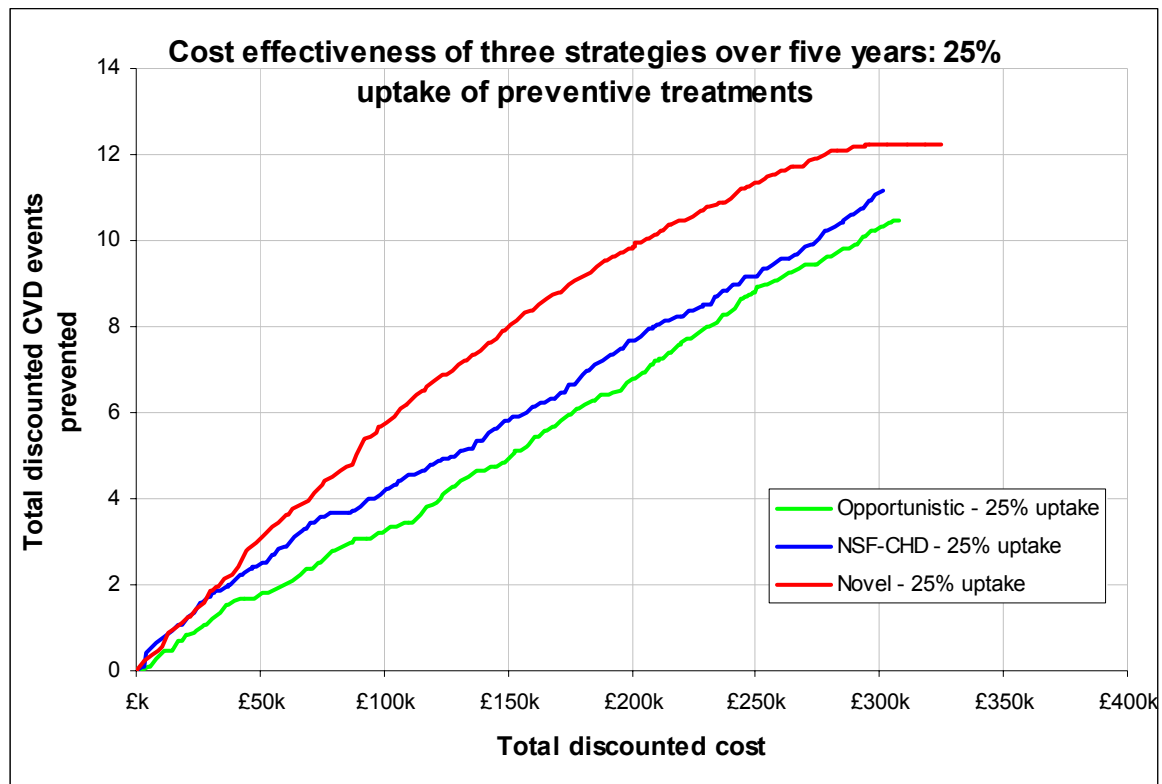


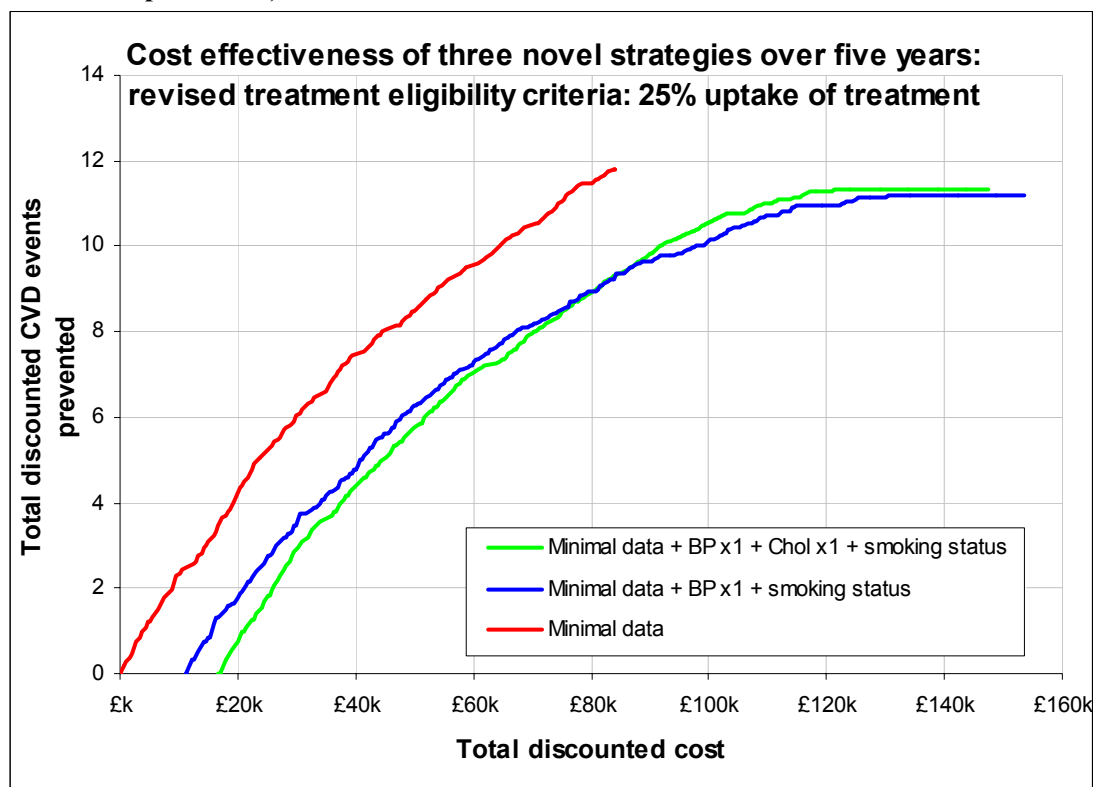
Figure 49 shows the results of applying this assumption to three novel prevention strategies with patients treated according to revised treatment eligibility criteria with a threshold of £10,000 per CVD event prevented.

The revised treatment eligibility criteria maintain their considerable efficiency advantage over current treatment eligibility criteria. For example, £50,000 can prevent at most 3.0 CVD events under current treatment criteria but can prevent up to 8.5

CVD events under revised treatment criteria. Of the three novel selection strategies, the strategy based on minimal data has a distinct advantage over the strategies requiring additional risk factor data.

Table 102 and Table 103 show a more detailed analysis of cost effectiveness of a strategy prioritising patients for assessment based on minimal data. One effect of a 25% compliance rate is to make a Mediterranean diet less cost-effective than initial antihypertensive treatment. However this appears to be a chance effect that arises because the random 25% of patients who are compliant tend to be at higher risk of stroke than average. Generation of a different set of random numbers to select compliant patients results in a lower cost per CVD event with advice on a Mediterranean diet.

Figure 49: The effect of reducing uptake of treatment to 25% on the efficiency of three novel preventive strategies with revised treatment eligibility criteria (to £10,000 per CVD event prevented)



Conclusions: the effects of changing assumptions about compliance
Changing assumptions about compliance in a way consistent with compliance patterns seen in clinical practice makes little difference to the relative efficiency of different CVD prevention strategies.

Table 102: Cost-effectiveness of a novel strategy for CVD prevention with revised treatment eligibility criteria and 25% uptake of treatment. Patients are ranked for assessment using a prior estimate of CVD risk based on minimum risk factor data and a single blood pressure measurement

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	21	21	5	3	0	1	0	21	75	£5,976	£12,480	2.6	£4,838
101-200	25	25	2	1	0	0	0	25	75	£3,737	£11,188	2.5	£4,559
201-300	17	17	1	1	0	0	0	17	75	£2,589	£7,622	1.2	£6,307
301-400	18	18	0	1	0	2	0	18	75	£5,664	£11,160	1.4	£7,780
401-500	9	9	0	0	0	1	0	9	75	£2,664	£5,407	0.6	£9,738
501-600	9	9	0	0	0	0	0	9	75	£1,105	£3,676	0.5	£7,450
601-700	8	8	0	0	0	0	0	8	75	£982	£3,419	0.4	£8,204
701-800	6	6	1	1	0	0	0	6	75	£1,226	£3,077	0.3	£10,604
801-900	12	12	2	2	0	1	0	12	75	£4,010	£7,629	0.7	£10,618
901-1000	12	12	1	1	0	1	0	12	75	£3,534	£7,172	0.6	£11,510
1001-2158	20	20	1	2	0	1	0	22	869	£4,839	£11,006	1.0	£10,870

Table 103: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£1,663	£5,043	£5,180	£15,786	None eligible	£83,051
101-200	£1,727	£5,740	£5,473	£14,431	None eligible	None eligible
201-300	£2,363	£7,796	£6,995	£26,892	None eligible	None eligible
301-400	£2,356	£7,114	None eligible	£8,676	None eligible	£93,119
401-500	£3,051	£8,828	None eligible	None eligible	None eligible	£110,507
501-1000	£3,352	£10,205	£12,382	£51,642	None eligible	£133,736
1001-2158	£3,899	£10,748	£26,384	£81,966	None eligible	£140,849
All 2158	£2,439	£7,546	£7,007	£23,274	None eligible	£108,406

Changed assumptions about effectiveness

Evidence of effectiveness is most robust for aspirin, initial antihypertensive treatment, further antihypertensive treatment and statins. This is because it has been derived from trials that include primary prevention. A recent estimate of the effect of antihypertensive treatment confirms that risk reduction is proportional to reduction in blood pressure and largely independent of the choice of drug.²⁹⁷ This analysis found that compared to less intensive treatment, more intensive blood pressure resulted in a relative risk of 0.77 (95% confidence interval: 0.63 to 0.95) for CVA and 0.95 (95% confidence interval: 0.81 to 1.11) for CHD. This is not greatly different to the estimates used in the analysis.

Evidence for the effectiveness of a Mediterranean diet is derived from one clinical trial of secondary prevention in a population that is culturally different to that found in England. Evidence for the effectiveness of sitostanol is inferred from its effect on serum cholesterol levels. A sceptical view of the evidence might suggest that sitostanol and dietary interventions are ineffective and should not be considered as part of the overall strategy. What impact would this have on the suggested prevention strategy?

Eliminating dietary interventions

Eliminating dietary interventions clearly will alter the incremental cost-effectiveness of interventions offered after dietary interventions. These interventions include initial antihypertensive treatment (offered after advice on a Mediterranean diet); further antihypertensive treatment and simvastatin. This means that the optimum treatment eligibility thresholds for these interventions may be somewhat lower.

Effects of eliminating dietary interventions on incremental cost-effectiveness

The first analysis is to calculate the incremental cost-effectiveness of all interventions given to every patient at over 2.5% five-year CHD risk. This analysis is carried out on the original population of 5603 persons for whom complete risk factor data are available. In effect this means giving just over half of the population at least one intervention.

Because this analysis gives an indication of the cost per CVD event prevented in each risk category, it indicates the appropriate levels at which to set treatment eligibility thresholds under a strategy that uses no dietary interventions.

Results of analysis of incremental cost-effectiveness

If the threshold for prevention of a CVD event is set at £10,000, under a strategy that uses no dietary interventions it is efficient to offer aspirin to all persons at over 5% five year CHD risk, initial antihypertensive treatment to all persons at over 15% five-year CVD risk and further antihypertensive treatment (with enalapril) to all those at over 40% five-year CVD risk.

Figure 50: Cost per CVD event prevented across two dimensions: CHD risk category and choice of intervention (no dietary interventions)

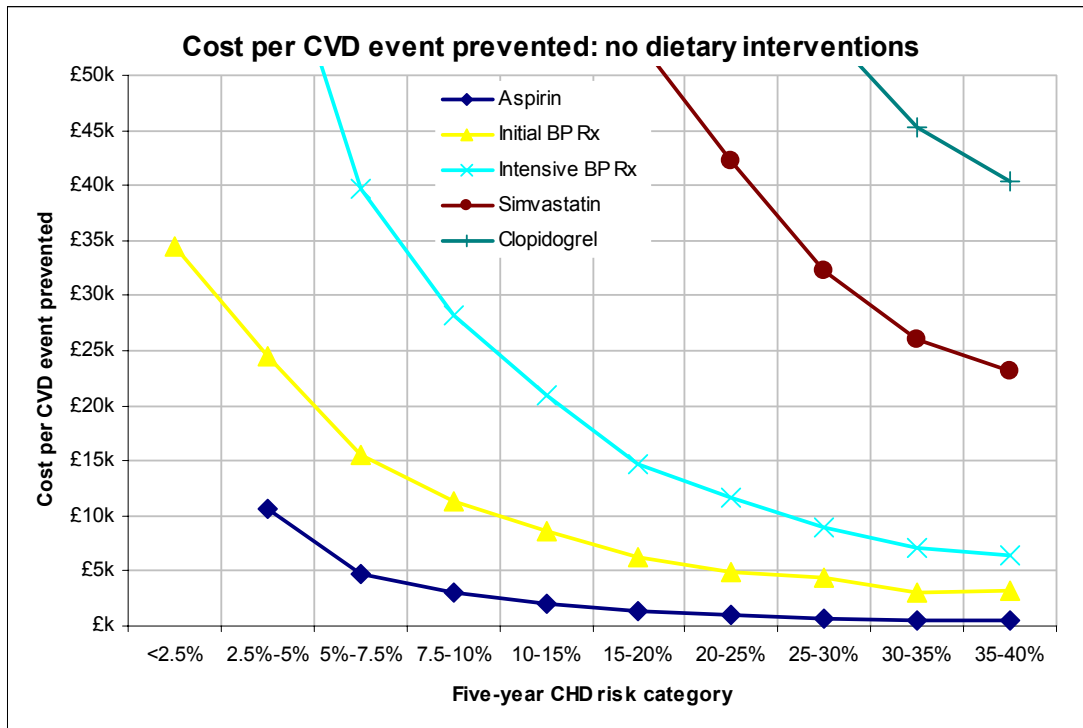
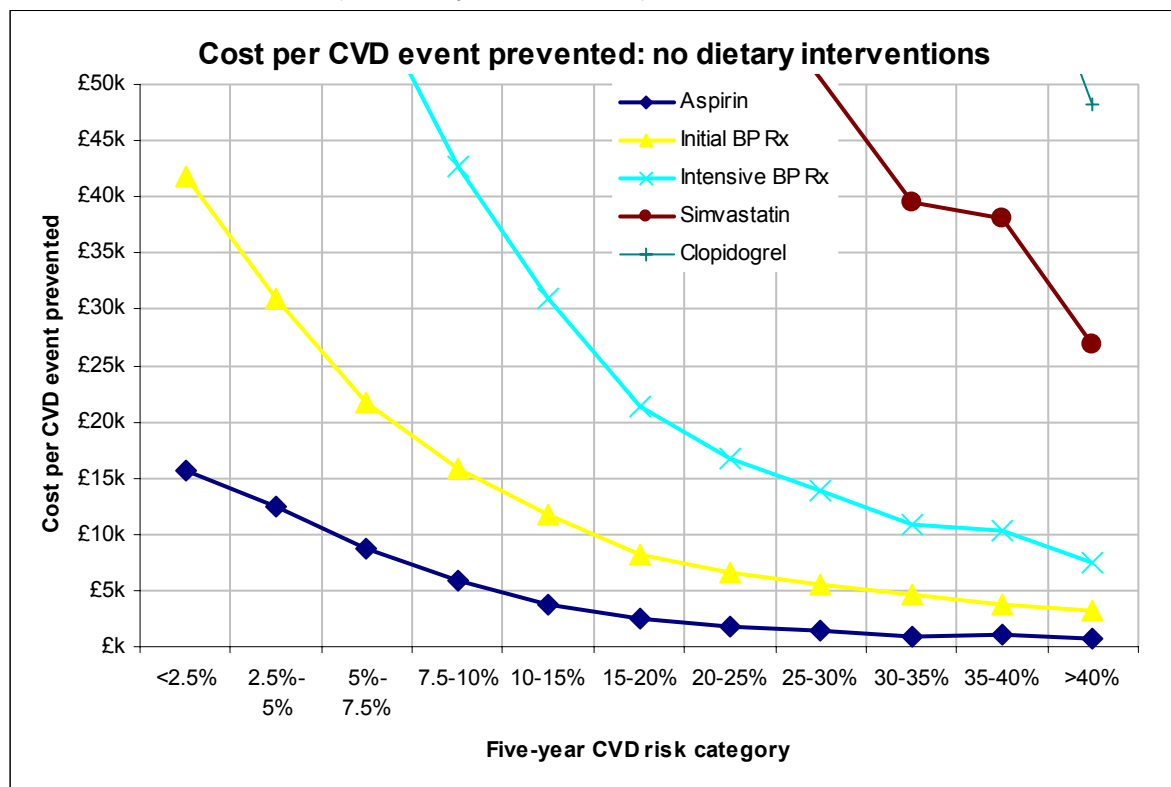


Figure 51: Cost per CVD event prevented across two dimensions: CVD risk category and choice of intervention (no dietary interventions)



If the threshold for prevention of a CVD event is set at £25,000, the thresholds are 2.5% five-year CHD risk for aspirin, 5% five-year CVD risk for initial antihypertensive treatment and 15% five-year CVD risk for further antihypertensive treatment (with enalapril). (Figure 50 and Figure 51) Even under these assumptions, statins are not cost-effective for general use.

Effects of eliminating dietary interventions on prevention policies

The effects of eliminating dietary interventions from the strategy are modelled as follows. The eligibility threshold for advice on a Mediterranean diet is raised to 100% five-year CHD risk and the threshold for dietary supplementation with sitostanol is raised to 100% five-year CVD risk. This means that no patients are now eligible for dietary interventions. The assumption of 100% compliance is maintained and all other eligibility criteria set at the £10,000 per CVD event prevented threshold indicated in the previous paragraph (Table 104). Only the novel selection strategies are modelled, as these are clearly more efficient than the traditional strategies.

Table 104: Revised treatment eligibility criteria with no patients eligible for dietary interventions

Intervention	Treatment criteria	
	Non risk criteria	Five-year risk threshold
Aspirin		>5% CHD risk
Initial antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
	Blood pressure \geq 120/80 mm Hg	>15% CVD risk
Intensive antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
	Blood pressure \geq 120/180 mm Hg	>40% CVD risk
Simvastatin	Total cholesterol \geq 9.0 mmol/l	Any risk level

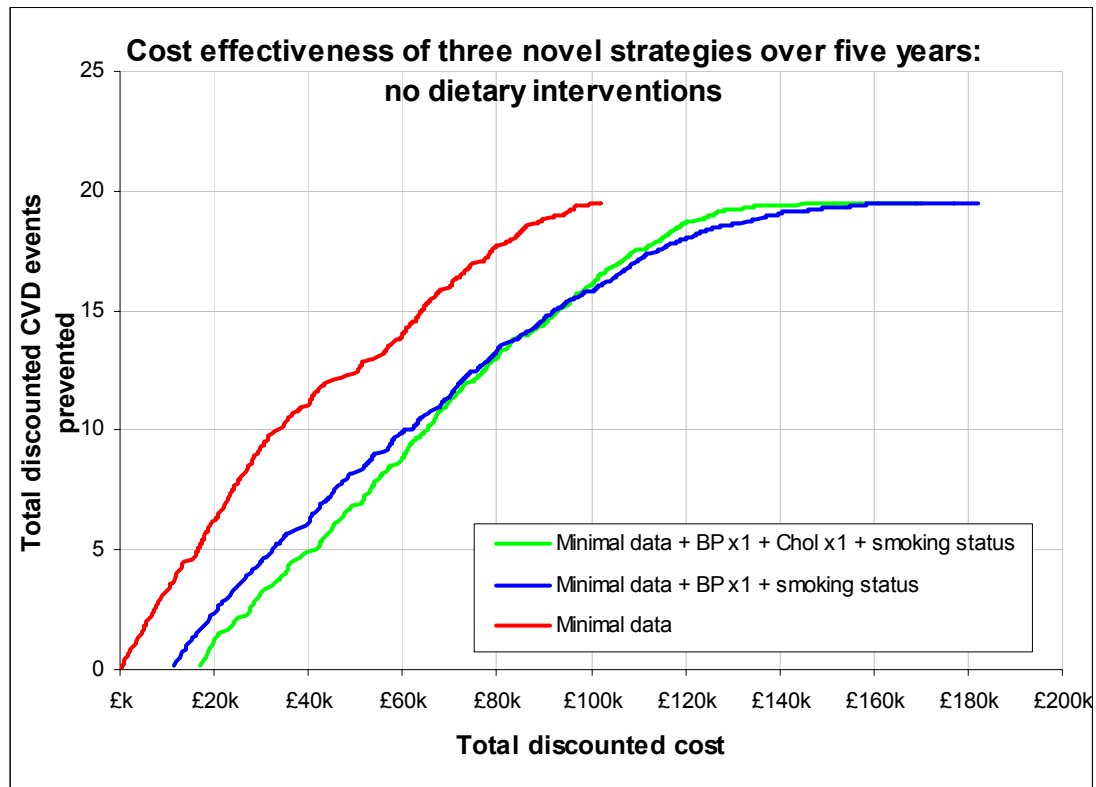
Source: See text above

Results of analysis of prevention policies without dietary interventions

The costs and effects of three prevention policies following three novel selection strategies are shown in Figure 52. The novel selection strategy based on minimum data maintains its advantage over other novel selection strategies.

Compared to a similar strategy that includes dietary intervention (see Table 90) The effect of excluding dietary interventions is to greatly decrease the cost per CVD event prevented with initial antihypertensive treatment (from £8284 to £5722); with enalapril (from £26,858 to £15,914); and with a statin (from £111,805 to £57,281). (Table 106) Nevertheless, aspirin remains much more cost-effective than initial antihypertensive treatment, which remains much more cost-effective than further antihypertensive treatment which in turn remains much more cost-effective than a statin.

Figure 52: Cost-effectiveness of three prevention strategies using novel selection strategies but without any dietary interventions



Conclusions: effects of eliminating dietary interventions

Eliminating dietary interventions makes little difference to the rankings of treatment or to the efficiency of different selection strategies. However optimum eligibility criteria have somewhat lower risk thresholds for initial antihypertensive treatment and for further antihypertensive treatment. Statins remain too expensive for general use under these assumptions.

Table 105: Cost-effectiveness of a CVD prevention strategy: novel selection with minimum risk factor data; revised treatment eligibility criteria and no dietary interventions

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	94	0	27	11	0	1	0	94	75	£11,520	£15,517	4.7	£3,332
101-200	91	0	16	6	0	0	0	91	75	£6,409	£9,988	3.3	£3,009
201-300	69	0	17	7	0	1	0	69	75	£8,024	£10,841	2.6	£4,111
301-400	55	0	9	9	0	4	0	55	75	£11,700	£14,033	1.8	£7,630
401-500	55	0	6	6	0	2	0	56	75	£7,128	£9,409	1.5	£6,410
501-600	47	0	4	2	0	0	0	48	75	£2,206	£3,959	1.0	£4,059
601-700	43	0	5	3	0	1	0	43	75	£4,191	£6,139	1.0	£5,882
701-800	46	0	4	3	0	0	0	47	75	£2,537	£4,248	0.9	£4,750
801-900	40	0	2	3	0	1	0	40	75	£3,636	£4,971	0.8	£6,626
901-1000	29	0	4	4	0	1	0	30	75	£4,082	£5,368	0.6	£9,348
1001-2158	59	0	10	11	0	5	0	71	869	£14,174	£17,311	1.3	£13,180

Table 106: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£1,678	None eligible	£4,379	£9,157	None eligible	£47,093
101-200	£1,971	None eligible	£5,047	£9,244	None eligible	None eligible
201-300	£2,007	None eligible	£5,229	£18,114	None eligible	£29,831
301-400	£2,523	None eligible	£5,358	£14,879	None eligible	£44,016
401-500	£2,814	None eligible	£6,203	£15,497	None eligible	£44,473
501-1000	£3,193	None eligible	£7,895	£25,446	None eligible	£70,357
1001-2158	£3,320	None eligible	£15,779	£41,797	None eligible	£106,129
All 2158	£2,420	None eligible	£5,722	£15,914	None eligible	£57,281

New estimates of the effectiveness of drug treatments

Two recent meta-analyses provide new estimates of the effectiveness of statins and antihypertensive treatment. These estimates follow a more complex model than the fixed relative risk on treatment applied in this model. They also are derived from the efficacy of drugs treatments in reducing LDL cholesterol and systolic blood pressure. This implies full compliance with treatment. They provide a credible alternative estimate of the effectiveness of treatments to prevent CVD.

New estimate the effects of aspirin

Since work began on this analysis, a multiple-therapy strategy for CVD prevention has been outlined. The authors of the strategy undertook a systematic review of trials of aspirin. They calculated the relative risk of CHD on aspirin to be 0.68 and the relative risk of CVA on aspirin to be 0.84.¹⁴²

New estimate the effects of statins

A recent meta-analysis by the same authors has provided a new estimate the effects of statins on CHD and CVA.²⁹⁸ This indicated that with full compliance simvastatin 40mg should result in a fall of LDL cholesterol of 1.8 mmol/l. The authors estimated that the relative risk of CHD on treatment is higher in younger persons and would be 0.23 at age 50, 0.39 and age 60 and 0.41 at age 70.

The same analysis also provided a separate estimate of the effect of statins on CVA in persons with and without known vascular disease. In persons without vascular disease relative risk of CVA is 0.94 (95% CI: 0.78 to 1.14).

Implications for effectiveness of sitostanol

Since the authors' estimate of relative risk on simvastatin is inferred from its effect on LDL cholesterol, it follows that they would expect a commensurate reduction in risk of CHD and CVA with sitostanol. Sitostanol has 34% of the effect of simvastatin on LDL cholesterol. Under this model it would therefore reduce risk of CHD by $34\% \times (1 - 0.23)$ in a person aged 40. This is equivalent to a relative risk of 0.74.

New estimate the effects of antihypertensive drugs

A similar analysis of the effects of antihypertensive medications indicates that two standard-dose drugs (e.g. bendrofluazide 2.5mg and atenolol 50mg) are likely to reduce systolic blood pressure by 18 mm Hg and addition of a third (enalapril 20mg) will reduce blood pressure by a further 8.5 mm Hg.²⁹⁹ This effect is at a mean blood

pressure of 154/97 mm Hg. It also found that each additional 10 mm Hg in pre-treatment systolic blood pressure was associated with a further 1 mm Hg reduction in blood pressure on treatment with each treatment drug. In effect this means that a person with pre-treatment systolic blood pressure could expect to see a 20 mm Hg fall in systolic blood pressure with initial antihypertensive treatment (two drugs at standard dose). [20 mm Hg = 18 mm Hg + 2 × (164-154) ÷ 10]

By this model there is an exponential relationship between achieved blood pressure and CHD (or CVA risk). The authors estimated that two drugs at half standard dose in a person with pre-treatment systolic blood pressure of 150 mm Hg would result in a relative risk of CHD of 0.66 and a relative risk of CVA of 0.51. Three drugs result in a relative risk of CHD of 0.54, therefore the third is responsible for an incremental relative risk of 0.82. (Table 107) Drugs are given at a standard dose and would be expected to result in a greater fall in blood pressure (9.1 mm Hg versus 7.1 mm Hg per drug or 1.28 times greater fall in systolic blood pressure) and produce a commensurately greater fall in CHD and CVD risk (RR^{1.28}). The relative risk of CHD with two drugs at standard dose will therefore be 0.59. [0.59 = 0.66^{1.28}].

The relative risk on treatment also needs to be adjusted by the pre treatment blood pressure. An additional 10 mm Hg level in pre-treatment systolic blood pressure (i.e. 160 mm Hg instead of 150 mm Hg) results in an additional 2 mm Hg fall in the fall in treated systolic blood pressure with two drugs (initial antihypertensive treatment). In addition to the 18 mm Hg fall with two drugs, this will result in a further fall in CHD risk [(2 + 18) ÷ 18 = 1.11]. Hence relative risk in a person with pre-treatment BP of 160 mm Hg is RR^{1.11}. This means that a person with pre-treatment systolic blood pressure of 160 mm Hg would have a relative risk of 0.55 on initial antihypertensive treatment. [0.55 = 0.59^{1.11}]

Table 107: Effectiveness of antihypertensive treatment: recent estimate

Number of drugs	Relative risk on half standard dose		Relative risk on standard dose	
	CHD	CVA	CHD	CVA
One drug	0.81	0.71	0.76	0.65
Two drugs	0.66	0.51	0.59	0.42
Three drugs	0.54	0.37	0.45	0.28
Two drugs compared to one drug	0.81	0.72	0.77	0.65
Three drugs compared to two drugs	0.82	0.73	0.77	0.66

Source: Law M. *et al* BMJ 2003

The impact of new estimates of effectiveness on average cost-effectiveness

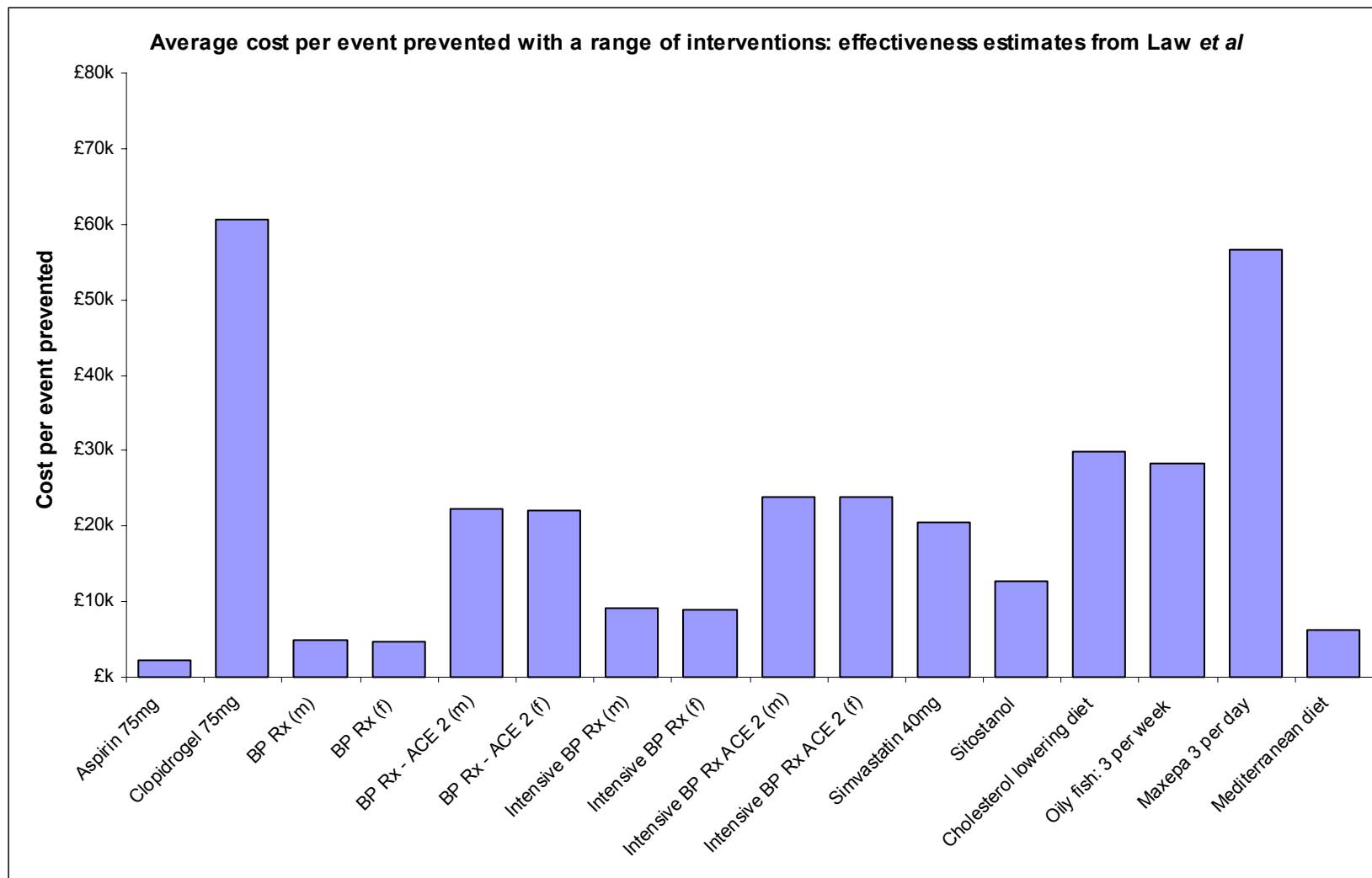
The new estimates of effectiveness could affect the rankings of treatments. To investigate this, average cost-effectiveness of each intervention is recalculated in the way shown in chapter 6. Under the Law *et al* effectiveness assumptions, relative risk on statins is age-dependent. The age at which statins are most effective (age 40 years) is chosen for the patient because this is most likely to change the analysis. The patient is assumed to have a blood pressure of 150/90 mm Hg.

The results of this analysis are shown in Figure 53. The most cost-effective intervention remains aspirin, however initial antihypertensive treatment is now more cost-effective than advice on a Mediterranean diet. This is followed by further antihypertensive treatment, sitostanol and simvastatin.

Conclusions: effects of Law et al's effectiveness estimates on average cost-effectiveness

Using Law *et al*'s estimates of effectiveness complicates the analysis considerably, but makes little difference to the rankings of treatments.

Figure 53: Average cost-effectiveness of interventions with Law *et al* estimates of effectiveness: patient aged 40 with blood pressure of 150/90 mm Hg and at 15% five-year CVD risk

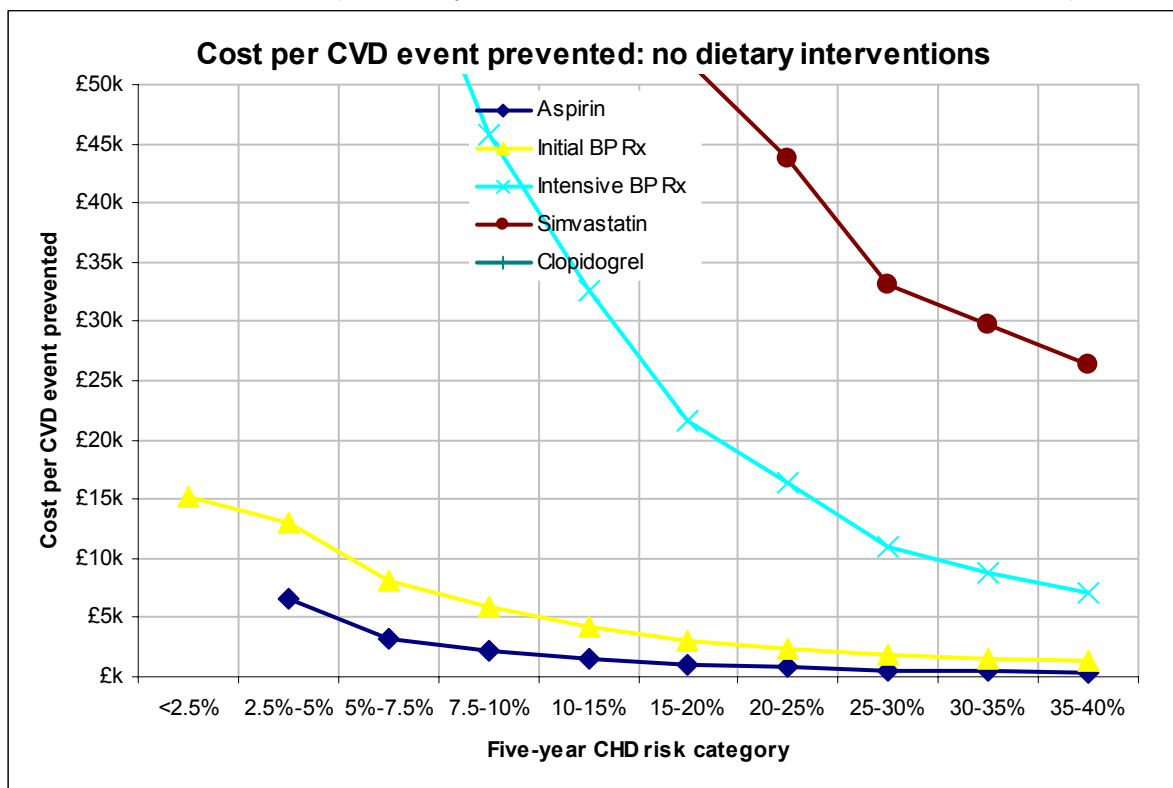


The impact of new estimates of effectiveness on incremental cost-effectiveness and treatment eligibility criteria

CHD and CVD risk as predictors of incremental cost-effectiveness

The incremental cost-effectiveness analysis is repeated with Law *et al*'s estimates of effectiveness. All patients in the population of 5603 whose CHD risk exceeds 2.5% are considered eligible for treatment. No dietary interventions are included, because this assumption tends to favour the use of simvastatin and clopidogrel. The results of the incremental cost-effectiveness analysis are summarised in Figure 54 and Figure 55.

Figure 54: Cost per CVD event prevented across two dimensions: CHD risk category and choice of intervention (no dietary interventions and new estimates of effectiveness)

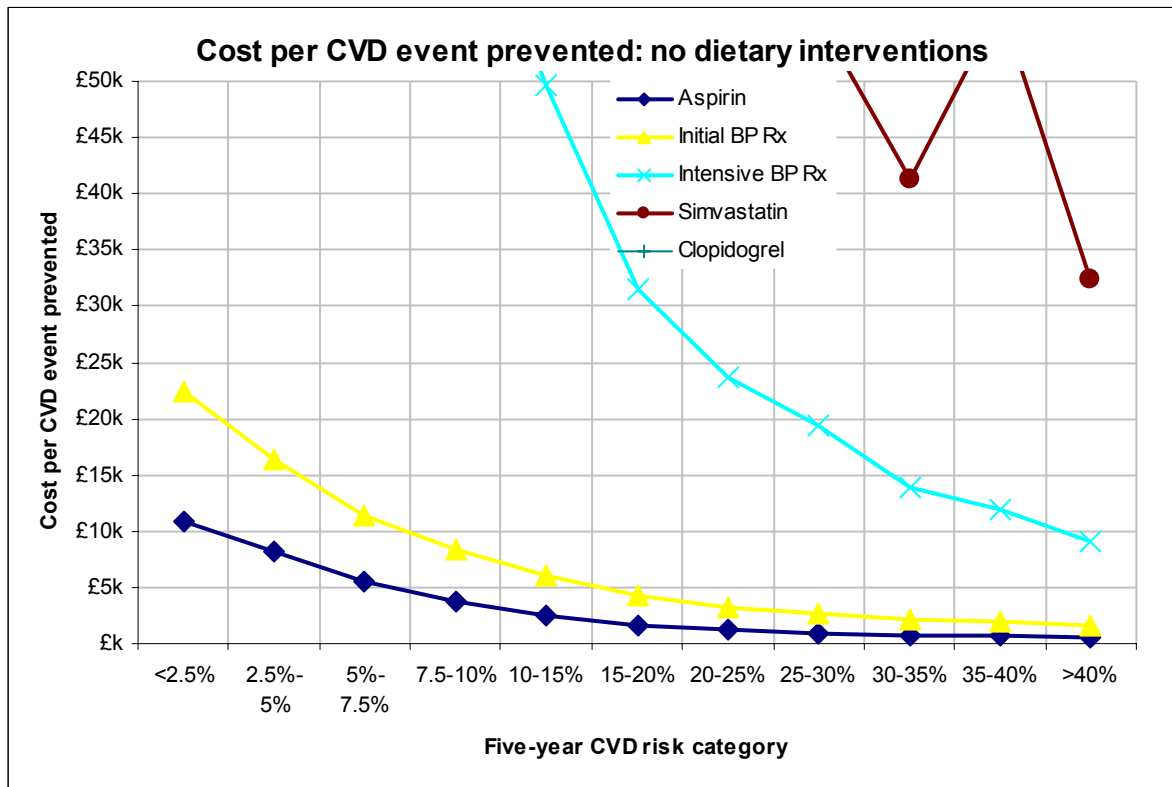


Under the new assumptions, CHD risk is a better predictor of the cost-effectiveness of statins than CVD risk. This is because statins have a greater effect on CHD than CVA.

Cost-effectiveness is strongly related to both CHD and CVD risk. At a threshold of £10,000 per CVD event prevented aspirin would be offered to all patients at over 2.5% CHD risk and initial antihypertensive treatment to all those at over 7.5% CVD risk. No other treatments would be offered.

At a threshold of £25,000 per CVD event prevented, aspirin would be offered to all those at over 2.5% five-year CHD risk and initial antihypertensive treatment to all those at over 2.5% five-year CVD risk. Intensive antihypertensive treatment would be offered to all those at over 20% five-year CVD risk. No other treatments would be offered.

Figure 55: Cost per CVD event prevented across two dimensions: CVD risk category and choice of intervention (no dietary interventions and new estimates of effectiveness)



Blood pressure as a predictor of incremental cost-effectiveness of antihypertensive treatment

The new estimates of the effectiveness of antihypertensive treatment are sensitive to pre-treatment blood pressure. This means that treating persons with higher pre-treatment blood pressures may be more effective than treating those with lower pre-treatment blood pressures.

In chapter 6 an analysis of incremental cost-effectiveness of initial and further antihypertensive treatment was carried out with patients grouped by CVD risk band and by pre-treatment blood pressure. This analysis is repeated with the new estimates of effectiveness. The aim of this is to determine whether there is a strong relationship between cost-effectiveness and pre-treatment blood pressure. The results of this analysis are shown in Figure 56 and Figure 57.

Figure 56: Incremental cost-effectiveness of initial hypertensive treatment with patients grouped by pre-treatment blood pressure and CVD risk

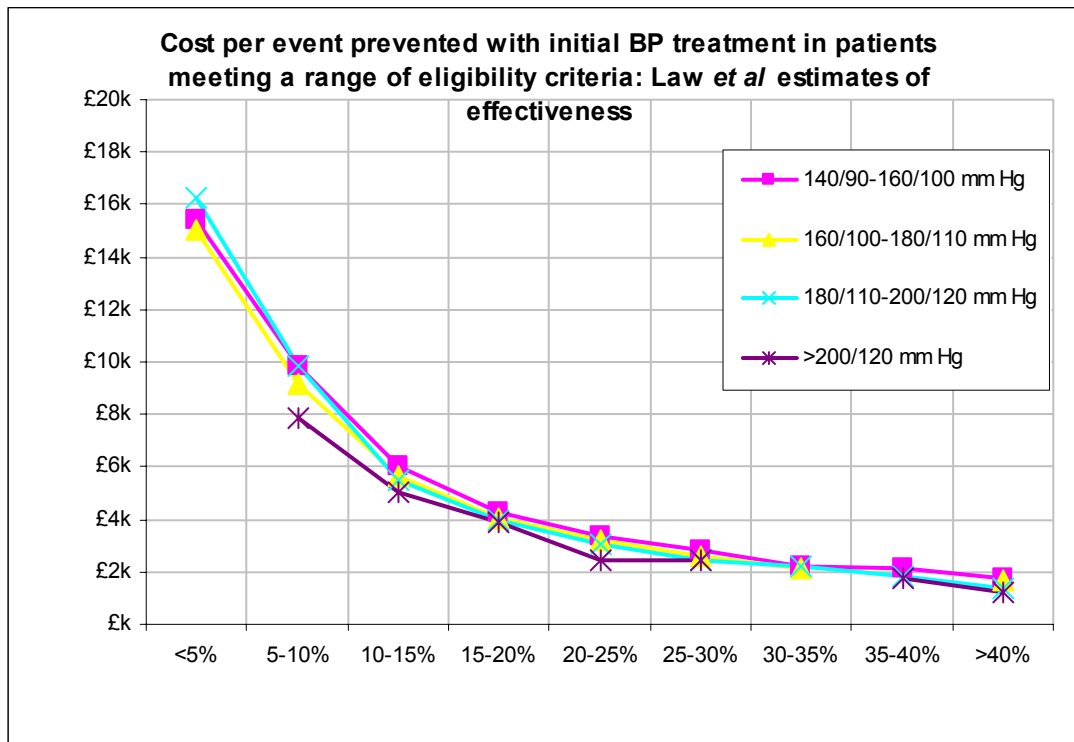
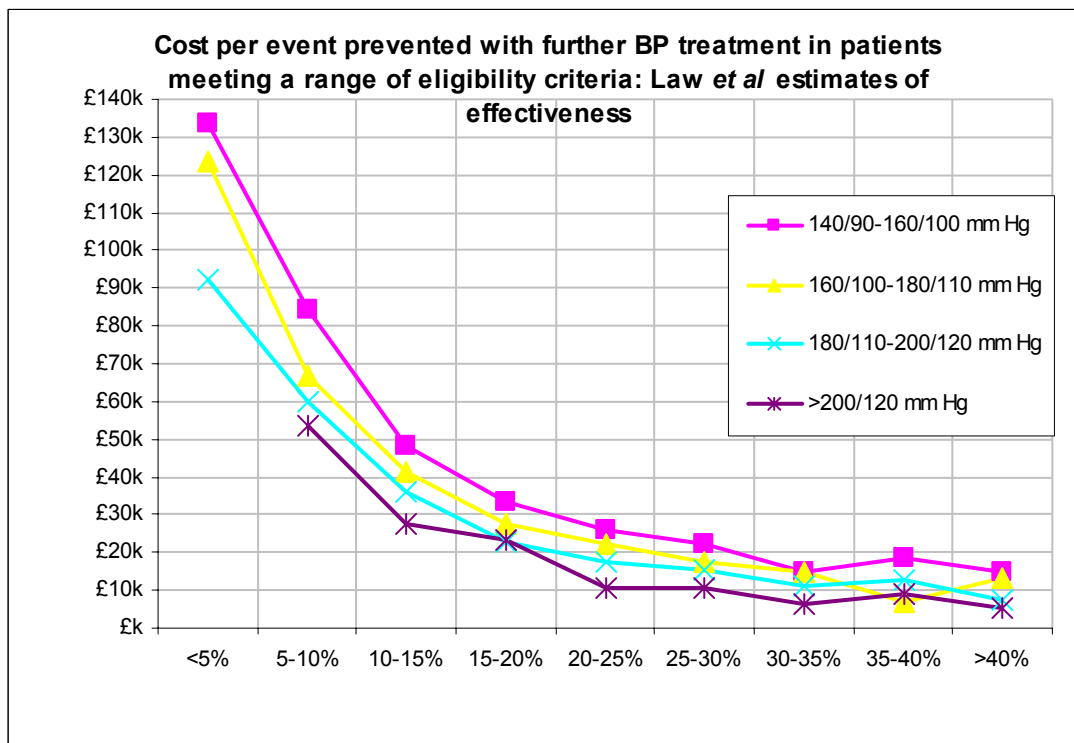


Figure 57: Incremental cost-effectiveness of further hypertensive treatment with patients grouped by pre-treatment blood pressure and CVD risk



Cost per CVD event prevented is much more strongly related to CVD risk than to blood pressure. However, at a threshold of £25,000 per CVD event prevented, there

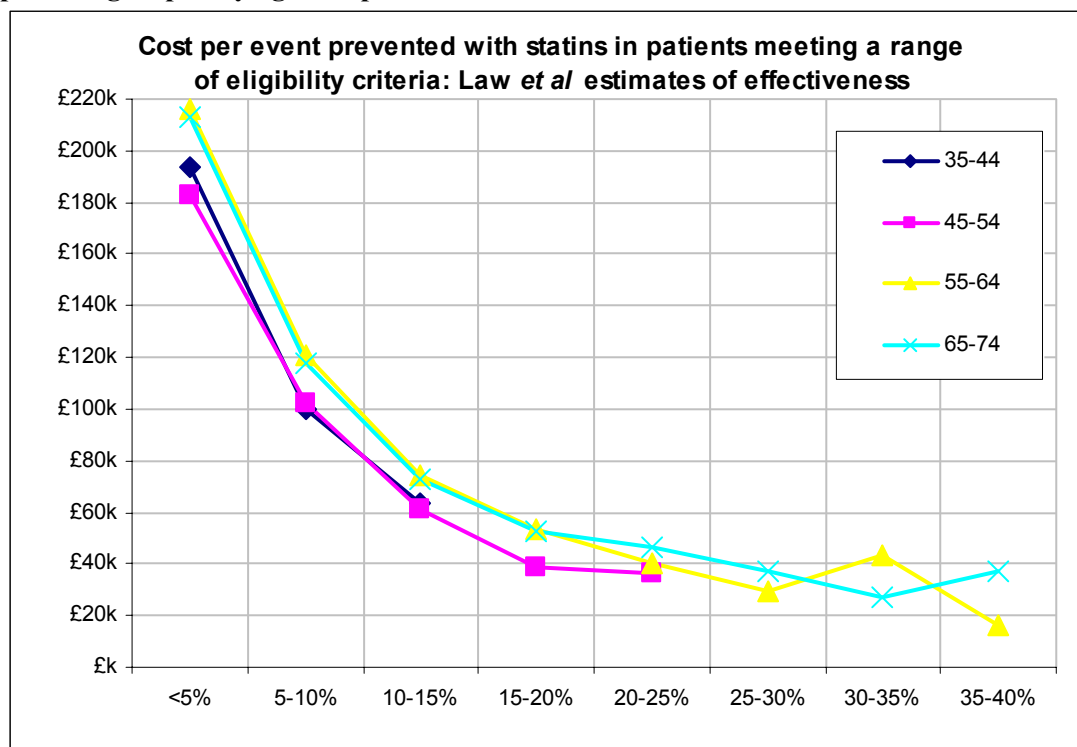
are good grounds for offering further antihypertensive treatment to all persons whose blood pressure exceeds 180/110 mm Hg with a five-year CVD risk of over 15%. At a threshold of £10,000 per CVD event prevented there are good grounds for offering further antihypertensives to all those whose blood pressure exceeds 200/120 mm Hg if their five-year CVD risk is over 20%. This recommendation has no practical implications, as these patients would in any case be treated under the policies recommended following the previous analysis.

Age as a predictor of incremental cost-effectiveness of statin treatment

The new estimates of the effectiveness of statins are sensitive to the patient’s age. This means that treating younger persons may be more effective than treating older persons.

The incremental cost per CVD event for persons at different ages is presented in Figure 57. Patients are grouped by pre-treatment CHD risk, with separate curves for each age band. It is clear that age is a weak predictor of cost per CVD event prevented when compared to pre-treatment CHD risk.

Figure 58: Incremental cost-effectiveness of further hypertensive treatment with patients grouped by age and pre-treatment CHD risk



Conclusions: the effects of new effectiveness estimates

The new assumptions estimate that antihypertensive treatments and statins are considerably more effective than is suggested by current clinical trials. The sensitivity analysis indicates that even under the new effectiveness estimates some of the conclusions of the original analysis remain robust. Despite this, aspirin and initial antihypertensive treatment remain the most cost-effective drug interventions. Statins and clopidogrel remain too costly for general use in a prevention strategy.

A number of features of the analysis also change. Under Law et al's effectiveness estimates, initial antihypertensive treatment is more cost-effective than advice on a Mediterranean diet. Thresholds for treatment also need to be adjusted somewhat under the new assumptions. Individual risk factors (such as blood pressure or age) remain poor predictors of cost-effectiveness and guidelines should still be based on estimates of CHD or CVD risk.

Estimating CVD risk in the general population

The model uses the Framingham risk equations to estimate CVD risk in a population derived from the Health Survey for England. This produces two potential sources of error. Firstly the population of the Health Survey for England for whom complete risk factor data are available may not be representative of the population of England. Secondly the Framingham risk equations may not accurately predict risk in the English population. From the perspective of the model the effect of these two errors can be conflated into one question: is the analysis based on an accurate model of the distribution of CVD risk in the English population? If not, to what extent is it systematically inaccurate?

Recent evidence on accuracy of the Framingham risk equations in England

There is evidence from a prospective study of the incidence of coronary heart disease that the Framingham coronary risk equation is a reasonably accurate predictor of coronary heart disease in an English population.³⁰⁰ However it has also been observed that the Framingham risk equation predicts higher risk than that observed in recent European cohort studies.^{301,302} Evidence also suggests that the Framingham risk equation is reasonably accurate in diabetics.³⁰³

The most recent evidence suggests that the Framingham risk equation may overpredict CHD risk in the English population.³⁰⁴ This study found that compared to a recent English cohort, the Framingham equation overpredicted risk by a constant factor (1.57) for all levels of risk. If this paper is correct, it means that the estimates of cost per event prevented should be increased by a factor of 1.57. However it does not affect the ranking or the overall prevention strategy.

Accuracy of risk predictions in the modelled population

It is possible that the estimated risks in individuals in the modelled population are not an accurate reflection of CVD risk in the English population. This could significantly affect the selection strategy.

I calculated a predicted incidence of CHD for each age-sex group by applying the Framingham equations to the population in the Health Survey for England 1998. I then obtained published estimates of the case fatality of myocardial infarction. From this it is possible to calculate a predicted mortality rate from CHD. Applying this to

the population of England and Wales I calculated a predicted number of deaths from CHD.

I obtained national data on mortality from cardiovascular diseases. I compared predicted mortality rates from CHD by age and sex band to known mortality rates from CHD. This tests accuracy of the Framingham risk equations as applied to the model population against the true CHD mortality rates.

Observed numbers of deaths in England and Wales

Data were obtained from the OPCS on the age-sex, specific mortality from of cardiovascular diseases in England and Wales in 2000. Deaths due to coronary heart disease were defined as deaths recorded under ICD codes 410 to 414. Population figures for England and Wales were obtained from the same OPCS source as mortality figures. From these figures were calculated the annual numbers of deaths due to cardiovascular disease.

Predicted numbers of deaths

The average five year risk of cardiovascular disease in each age-sex band was obtained from the database of the distribution of cardiovascular risks. From this was calculated the annual risk of CVD. $\{1 - \text{annual risk} = [1 - (5 \text{ year risk})]^{(1/5)}\}$ Applying this to the population of England and Wales the annual numbers of CHD events and CVA events expected in each of the age-sex bands were calculated.

Data were obtained from the original Framingham database on the proportion of CHD events that were cardiac deaths, myocardial infarctions, angina or coronary insufficiency.³⁰⁵ (Table 108)

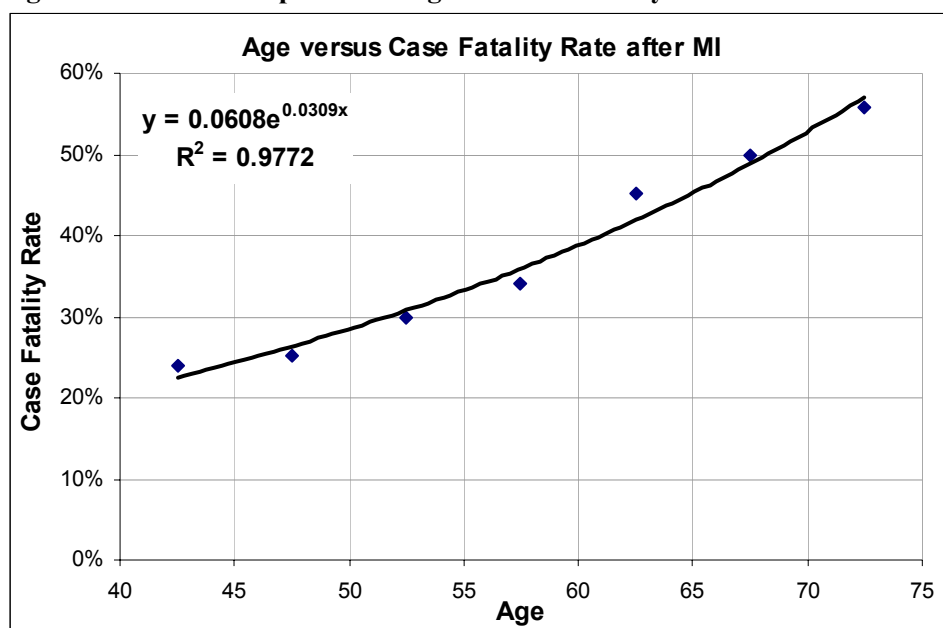
Case fatality rates following new onset angina and coronary insufficiency are assumed to be negligible. The case fatality rates after MI were derived from a published UK estimate.³⁰⁶ These show a strong relationship with age (Figure 59). From this relationship was derived an age-specific case fatality rate for MI. This was combined with data on the proportion of CHD events classified as MI and sudden cardiac death to derive the cases fatality rate per CHD event. (Table 109)

Table 108: Proportion of CHD events classified as MI, angina, coronary insufficiency and CHD death.

	Men	Women
Numbers	4466	5354
Numbers of CHD Event in 10 Years (%)	646 (14%)	406 (8%)
CHD events classified as MI (%)	49%	40%
CHD events classified as Angina (%)	38%	46%
CHD events classified as Coronary Insufficiency (%)	3%	7%
CHD events classified as CHD Death	10%	7%

Source: Personal communication, Lisa Sullivan, Department of Mathematics and Statistics, Boston University.

Figure 59: Relationship between age and case fatality rate after MI



Source: Derived from data reported in Norris RM. *British Medical Journal* 1998.

Table 109: Derived case fatality after MI and after a CHD event

Age band	Case fatality rate after MI	Case fatality rate after CHD event = sudden cardiac deaths + ([% CHD events that are MI] x [% case fatality rate after MI])	
		Men	Women
25-34	15% = $0.0608e^{0.0309(\text{Age})}$	10% + (49% x 15%) = 18%	7% + (40% x 15%) = 13%
35-44	21%	20%	15%
45-54	28%	24%	18%
55-64	39%	29%	23%
65-74	53%	36%	28%
75-84	72%	45%	36%

Source: Derived from Norris RM. *British Medical Journal* 1998.

Dividing the number deaths by the estimated numbers of events in each age-sex band provides an estimate of the case fatality rate of cardiovascular disease in each age-sex band.

Results: observed and predicted numbers of deaths from CHD in England

The predicted annual incidence of CHD and numbers of CHD events calculated from the Health Survey for England and the Framingham equation is shown alongside the observed numbers of deaths in England and Wales in Table 110. The ratios of observed to predicted numbers of deaths due to CHD are shown in Table 111. The results are illustrated in Figure 60.

The observed number of CHD deaths is roughly twice the predicted number in persons 75 to 84. The observed number of CHD deaths is similar to the predicted number in persons aged 65 to 74. The observed number of deaths is approximately half the predicted number in persons 55 to 65; less than half the predicted number in persons aged 45 to 55; and about one quarter the predicted number in persons under 45.

Table 110: Predicted annual incidence and number of CHD events; predicted annual number of CHD deaths; and observed annual numbers of CHD deaths

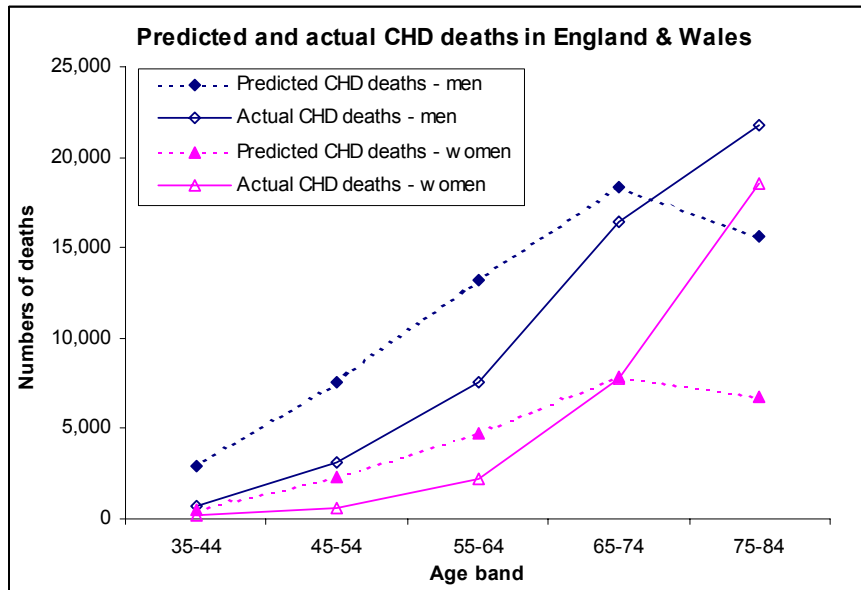
Age band	Predicted annual: incidence, number of CHD events and number of CHD deaths						Observed number of CHD deaths	
	Incidence of CHD events		Number of CHD events		Number of CHD deaths		Men	Women
	Men	Women	Men	Women	Men	Women		
35-44	0.4%	0.1%	15,697	3,506	2,904	489	744	179
45-54	0.9%	0.4%	32,422	12,870	7,556	2,299	3,105	654
55-64	1.7%	0.8%	45,330	20,988	13,227	4,755	7,590	2,192
65-74	2.5%	1.2%	50,821	27,615	18,362	7,824	16,462	7,811
75-84	3.1%	1.1%	35,412	19,315	15,637	6,738	21,772	18,574

Source: Predicted calculated using Framingham equations. Observed obtained from ONS data 2002

Table 111: Ratio between observed and predicted annual number of deaths from cardiovascular disease

Age band	Ratio- observed / predicted		
	Men	Women	Both
35-44	0.26	0.37	0.27
45-54	0.41	0.28	0.38
55-64	0.57	0.46	0.54
65-74	0.90	1.00	0.93
75-84	1.39	2.76	1.80

Figure 60: Predicted and actual CHD deaths in England and Wales



Discussion

A model based on the Framingham risk equation and the Health Survey for England accurately predicts CHD mortality in persons aged 65 to 74. However it may systematically overestimate CHD mortality in persons aged under 65. The overestimation appears to be greater in younger age groups.

There are two possible explanations for this observation. One is that individuals in the Health Survey for England who agreed to have blood pressure estimations and blood tests for cholesterol levels were systematically likely to have worse risk factor profiles. A second reason for this is that the Framingham risk equations systematically overestimate risk in low risk populations such as younger UK birth cohorts. This is consistent with evidence that the equations overpredict risk in low risk populations.

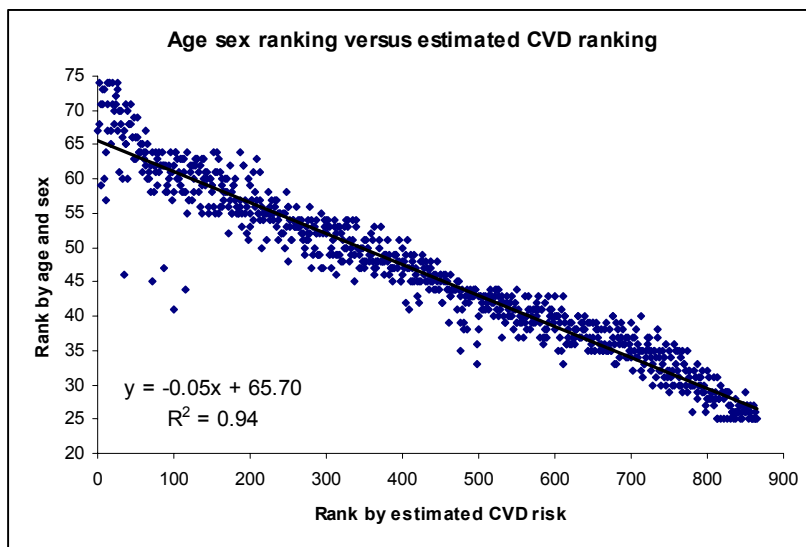
Implications of systematic overestimation of risk for the novel identification strategy
 Systematic overestimation of CHD risk in younger persons does not greatly affect the identification strategy. Indeed if risk is systematically overestimated in the young it strengthens the recommended prevention strategy.

The reason for this is straightforward. The novel patient identification strategy ranks patients by an estimate of their CVD risk that is in effect based on their age and sex. The ranking is therefore very similar to one produced by a simple age-sex algorithm: the patient's age in years for men and age minus 10 for women. Figure 61 shows the relationship between rankings produced by a simple age-sex algorithm and rankings

produced by one using their estimated five-year CVD risk. The rankings are very similar: in effect the novel identification strategy therefore assesses older men first.

Because it overestimates CHD risk in younger persons the analytic model underestimates the strength of association between age and CHD risk. If the true relationship between age and risk of CHD is stronger than that used in the analysis, the strategy of assessing older men first is strengthened rather than weakened.

Figure 61: Ranking by a simple age-sex algorithm versus ranking by a prior estimate of CVD risk.



CHD risk in patients with familial hypercholesterolaemia

Cohort studies suggest that untreated patients with familial hypercholesterolaemia have higher CHD mortality rates than average for their age and sex. Between 1980 and 1991 - a period when statins were not used - CHD mortality was 84.3 times higher than average in the age group 20 to 39; 5.3 times higher in the age group 40 to 59; and 1.2 times higher in the age group 60 to 79.²⁸⁹ Mortality from stroke does not appear to be increased.²⁹⁰

Because of this observation, it is likely that the benefits of treating familial hypercholesterolaemia are greater than that implied by the previous analysis.

Comparing risk predictions with Framingham and those from cohort studies of familial hypercholesterolaemia

Operational definition of familial hypercholesterolaemia

The prevalence of familial hypercholesterolaemia is believed to be around 1 in 500. If we assume that all persons whose total cholesterol ≥ 9.5 mmol/l have familial hypercholesterolaemia, there are 15 such patients in the population of 5603. This is a prevalence of 1 in 374. Total cholesterol ≥ 9.5 mmol/l is therefore used as an operational definition of familial hypercholesterolaemia.

Predicted and true risk of familial hypercholesterolaemia

In persons with total cholesterol ≥ 9.5 mmol/l the Framingham equation predicts five-year CHD risk to be 3.1% in those aged under 40, 5.9% in those aged 40 to 59 and 11.0% in those aged over 60. This is 3.3 times higher than the average CHD risk in persons aged 20 to 39, 1.9 times higher than in the age group 40 to 59; and 1.4 times higher than in the age group 60 to 79. (Table 112)

Table 112: Predicted five-year CHD risk in patients with and without familial hypercholesterolaemia

Age band	Without familial hypercholesterolaemia	With familial hypercholesterolaemia	All patients	Relative risk of CHD with familial hypercholesterolaemia
<40	0.9%	3.1%	0.9%	3.3
40-59	3.2%	5.9%	3.2%	1.9
60-79	8.0%	11.0%	8.0%	1.4

*Familial Hypercholesterolaemia = total cholesterol ≥ 9.5 mmol/l

The cohort study predicts that persons with familial hypercholesterolaemia aged under 40 have a relative risk of CHD death 84.3 times higher than the average; those aged 40 to 59 have a relative risk of CHD death 5.3 times higher than the average; and those aged over 60 have a relative risk of CHD death 1.4 times higher than the average. We would therefore expect the risk of all CHD events to be similarly higher.

The predicted risk of CHD is therefore adjusted to reflect the true risk as suggested by the cohort study. To account for this it is necessary to multiply predicted risk of CHD in patients with familial hypercholesterolaemia by a correction factor. The correction factor is the additional relative risk of CHD that is not accounted for by the Framingham risk equation. For example in persons with familial hypercholesterolaemia aged under 40, the Framingham risk equation predicts their risk will be 3.3 times the average for their age. The cohort study suggests that their risk is 84.3 times greater than the average for their age; therefore the correction factor is 25.6 ($84.3/3.3 = 25.6$). No correction is necessary for those aged 60 and over as the Framingham equation seems to accurately predict their risk. (Table 113)

Table 113: Correction factor for five-year CHD risk in patients with familial hypercholesterolaemia

Age band	Predicted relative risk of CHD with familial hypercholesterolaemia	True relative risk of CHD mortality with familial hypercholesterolaemia	Correction factor for predicted risk of CHD
<40	3.3	84.3	$84.3/3.3 = 25.6$
40-59	1.9	5.3	$5.3/1.9 = 2.9$
60-79	1.4	1.2	No correction

*Familial Hypercholesterolaemia = total cholesterol ≥ 9.5 mmol/l

Effect of adjusting CHD risk in patients with familial hypercholesterolaemia

The main effect of adjusting CHD risk in patients with familial hypercholesterolaemia will be to reduce the cost per CVD event prevented in patients with very high cholesterol levels. Because the prevalence of familial hypercholesterolaemia is low, it has little effect on the selection strategy. However it could have an effect on the cost-effectiveness of treating patients with very high cholesterol levels. This is investigated by analysing cost-effectiveness in the population of 5603 adults. The CHD risk of patients with total cholesterol levels over 9.5 mmol/l is augmented by the age-related factors indicated in Table 113. No dietary interventions are used because this is the assumption most likely to favour simvastatin.

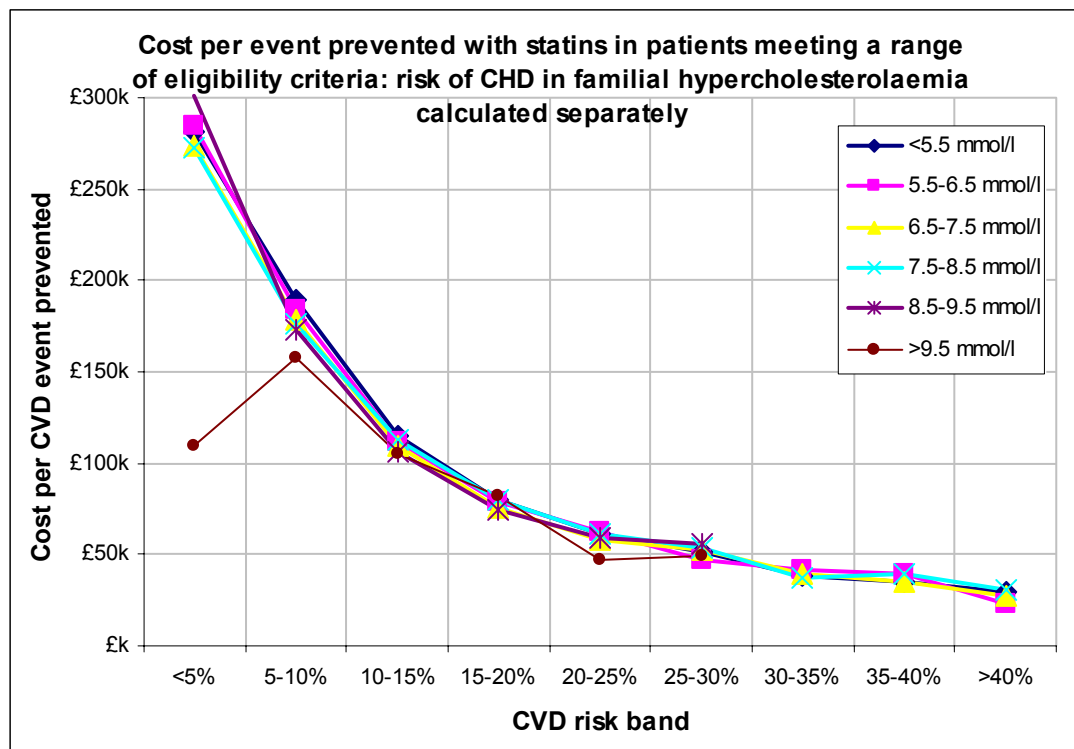
The incremental cost per CVD event prevented in relation to cholesterol levels and CVD risk is shown in Table 114 and presented graphically in Figure 62.

The cost per CVD event prevented is lower in patients with total cholesterol levels greater than 9.5 mmol/l than in those with lower cholesterol levels. However CVD risk remains the strongest predictor of cost per CVD event prevented.

Table 114: Incremental cost per CVD event prevented with simvastatin in patients stratified by age and cholesterol levels – CHD risk has been calculated

CVD risk band	Total cholesterol level						All cholesterol levels
	<5.5 mmol/l	5.5-6.5 mmol/l	6.5-7.5 mmol/l	7.5-8.5 mmol/l	8.5-9.5 mmol/l	>9.5 mmol/l	
<5%	£281,121	£284,242	£274,039	£272,618	£300,828	£109,256	£279,682
5-10%	£189,174	£183,754	£178,527	£176,649	£173,067	£157,316	£183,283
10-15%	£114,809	£111,668	£109,235	£112,285	£105,772	£105,315	£111,783
15-20%	£79,912	£78,616	£75,413	£79,687	£73,934	£82,548	£77,905
20-25%	£61,654	£62,035	£58,555	£61,720	£59,663	£46,691	£60,659
25-30%	£51,104	£47,363	£52,773	£53,296	£56,289	£49,003	£50,462
30-35%	£38,094	£41,093	£39,246	£37,121			£39,486
35-40%	£35,283	£39,834	£35,517	£39,522			£38,052
>40%	£29,984	£23,201	£27,807	£30,202			£26,944
Total	£170,534	£163,687	£153,189	£153,028	£142,900	£101,501	£161,189

Figure 62: Incremental cost-effectiveness of statins with patients grouped by pre-treatment cholesterol level and pre-treatment CVD risk



A new risk estimation equation

Since the main part of this work was carried out a new risk equation for prediction of has been developed. This was derived from combined data from a number of European cohorts.³⁰⁷ Because it is derived from more recent data in a European setting, it has an advantage over the Framingham risk equation. However it also suffers from two disadvantages. First it predicts only fatal CVD events, not all CVD events. Second it fails to include a coefficient to reflect the increased risk associated with diabetes.

Accuracy of the new risk estimation equation

I carried out the same analysis as described earlier in this chapter to estimate the CHD deaths and CVA mortality rates predicted by applying the SCORE equation to the model population. I applied these mortality rates to the population of England and Wales to produce a predicted number of deaths. This is compared to the observed number of deaths in England and Wales in 1998 (Figure 63). (The equivalent graph for the Framingham risk equation is shown in Figure 60)

The combination of the SCORE risk equation and the model population tends to overestimate CHD and CVA mortality in England and Wales. It is therefore not yet clear if the SCORE risk equation provides a better estimate of CHD and CVA risk than the Framingham risk equations.

Relationship between new and old risk equations

The relationship between the new and old risk equations in all 5603 persons aged 35 to 74 is illustrated in Figure 65 (CVA risk), Figure 66 (CHD risk) and Figure 67 (CVD risk).

There is a moderate degree of correlation between the Framingham risk equations and the SCORE mortality risk equations. As we would expect, mortality risk predicted by the SCORE equations is consistently about 35% of the risk of a CVD event predicted by the Framingham equations.

Figure 63: Observed numbers of deaths in England and Wales and numbers of deaths predicted by applying the SCORE equation to the to the model population

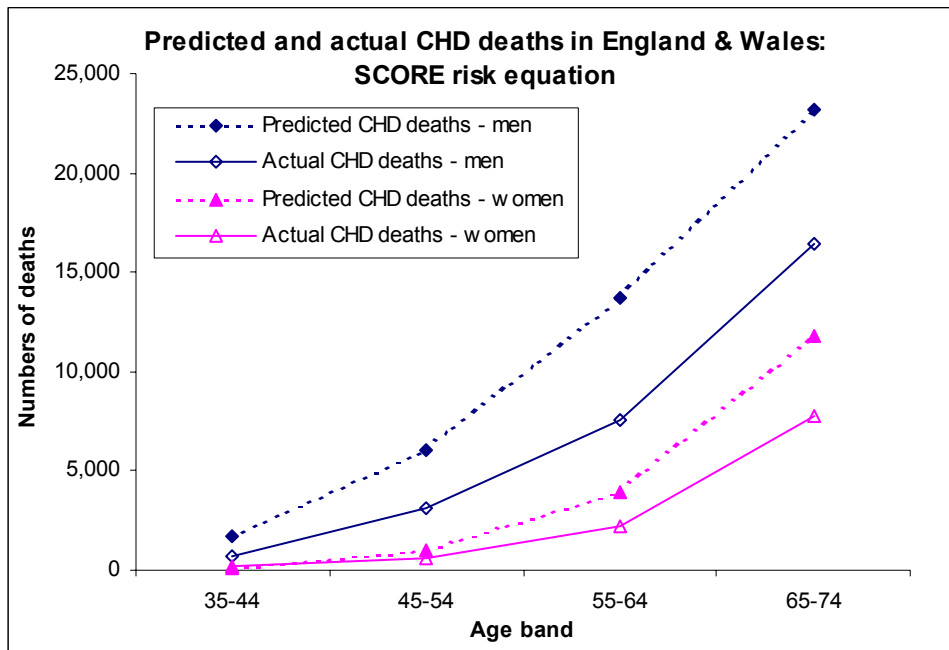


Figure 64: Observed numbers of deaths in England and Wales and numbers of CVA deaths predicted by applying the SCORE equation to the to the model population

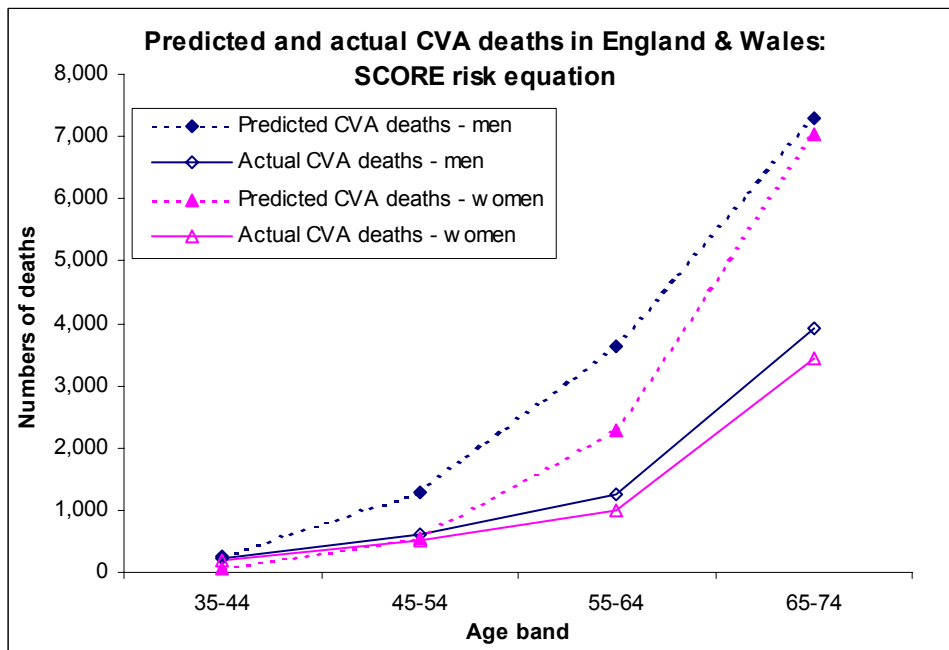


Figure 65: Relationship between five-year CVA risk predicted by Framingham equation and five-year CVA mortality risk predicted by SCORE equation

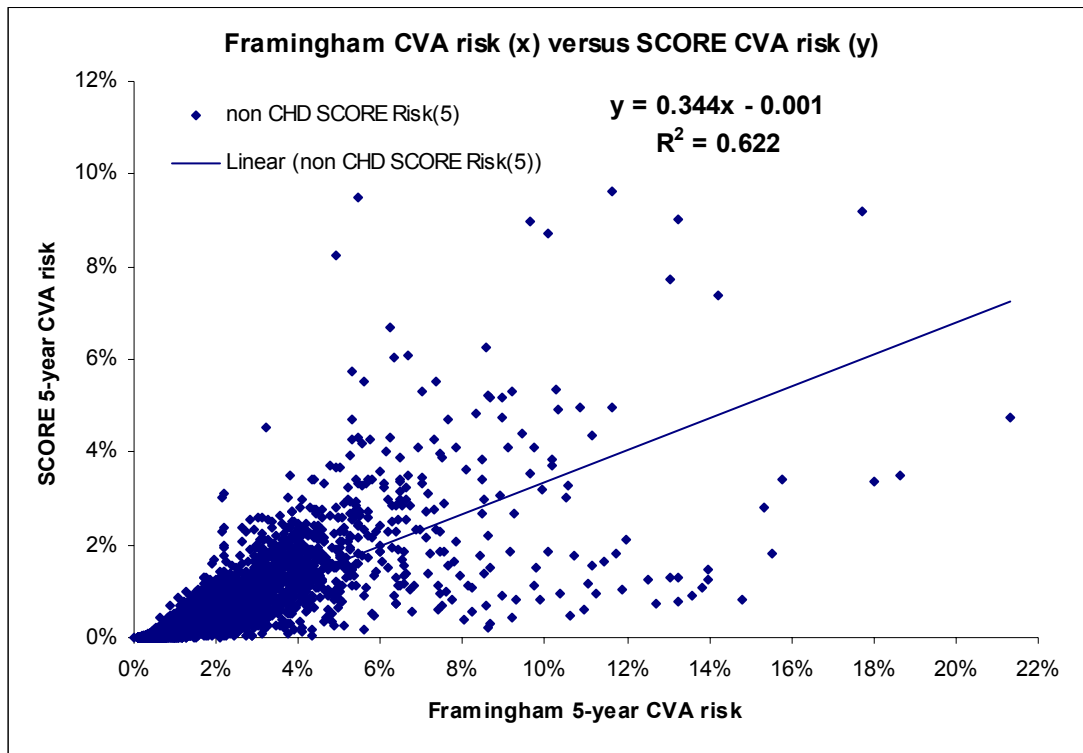


Figure 66: Relationship between five-year CHD risk predicted by Framingham equation and five-year CHD mortality risk predicted by SCORE equation

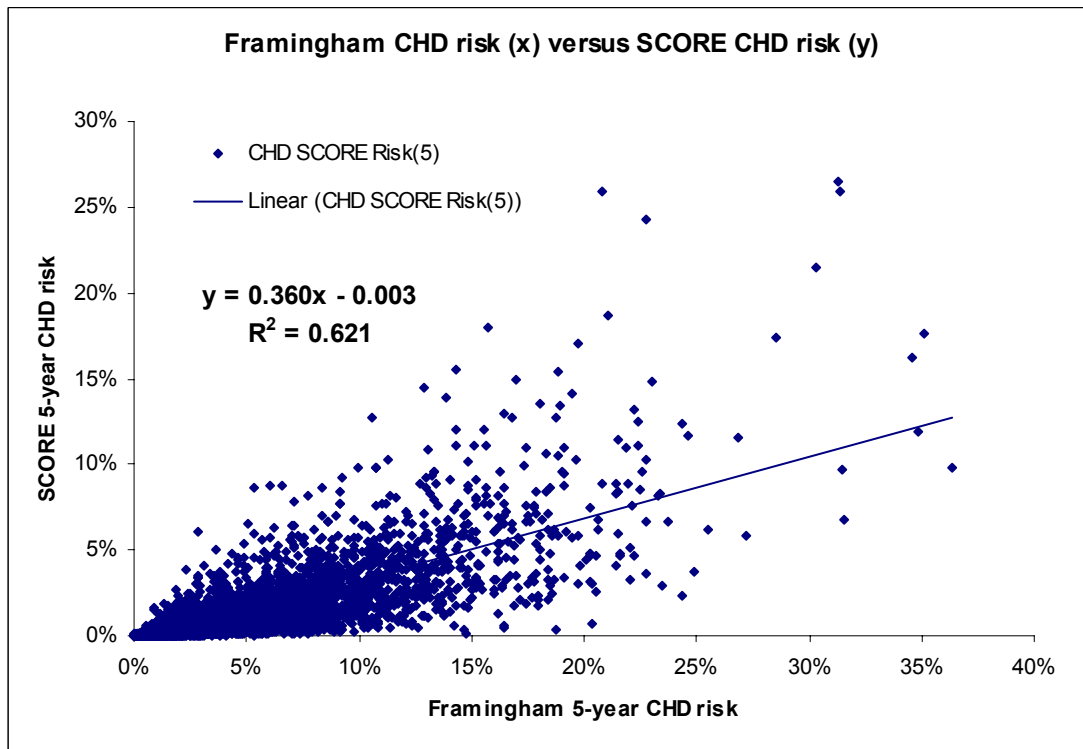
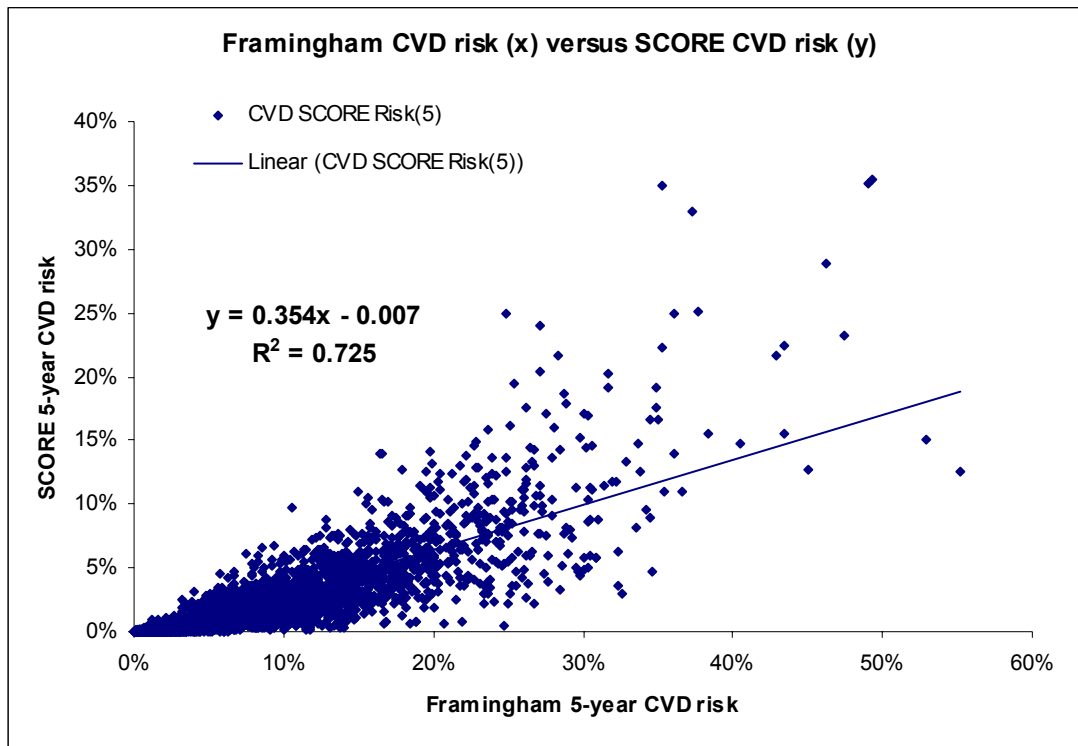


Figure 67: Relationship between five-year CVD risk predicted by Framingham equation and five-year CVD mortality risk predicted by SCORE equation



Relationship between age and CVD risk as predicted by new and old risk equations
Both Framingham CVD risk and SCORE CVD mortality risk are calculated for all persons in the population of 5603 grouped by their age, sex and diabetic status. These are plotted against age in Figure 68 and Figure 69 (non-diabetic men and women), Figure 70 and Figure 71 (diabetic men and women).

Figure 68: Relationship between age and five-year CVD risk in non-diabetic men

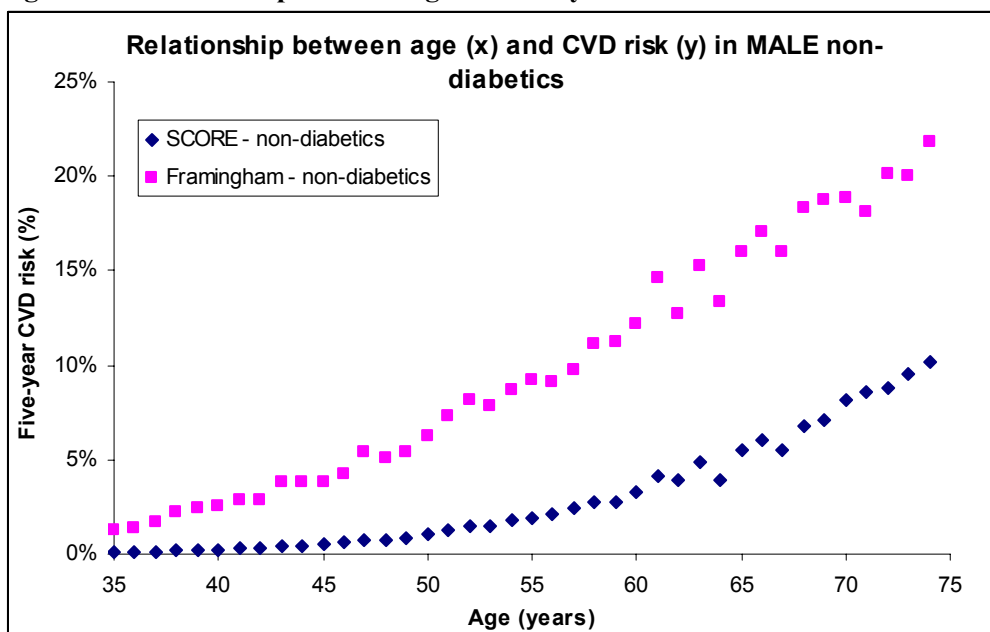


Figure 69: Relationship between age and five-year CVD risk in non-diabetic women

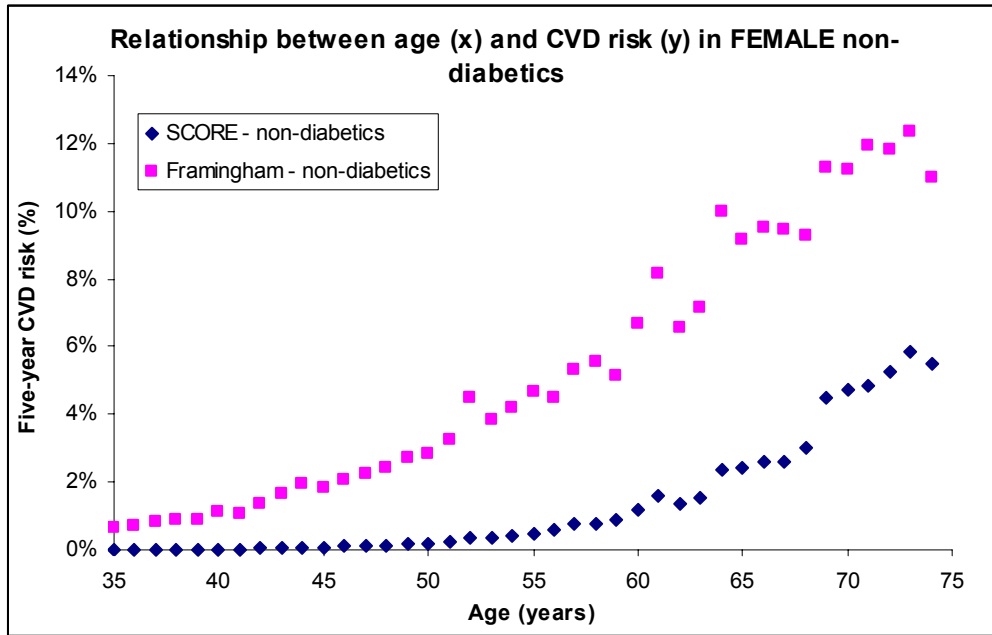
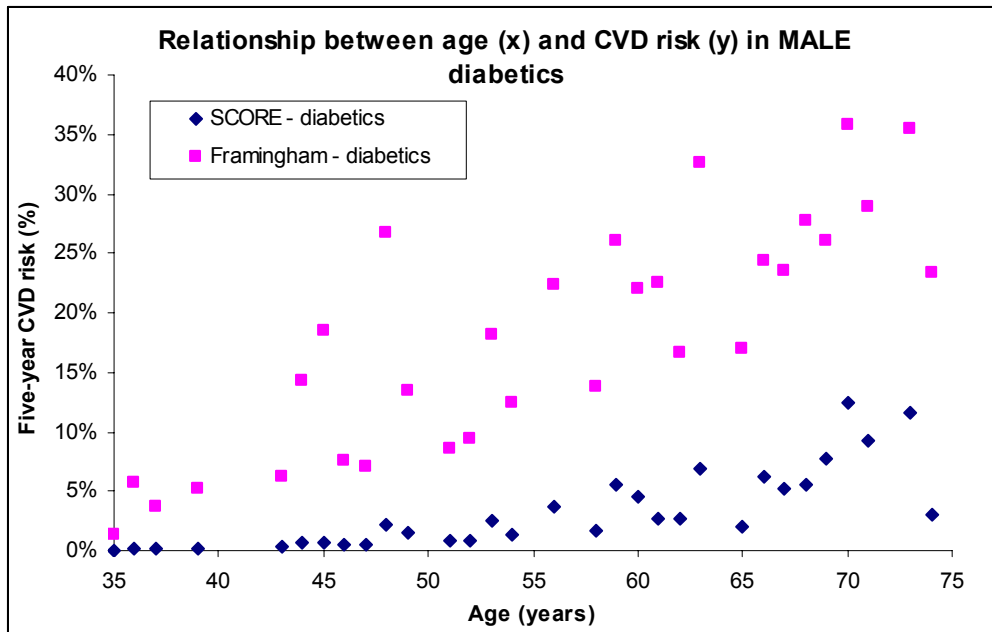


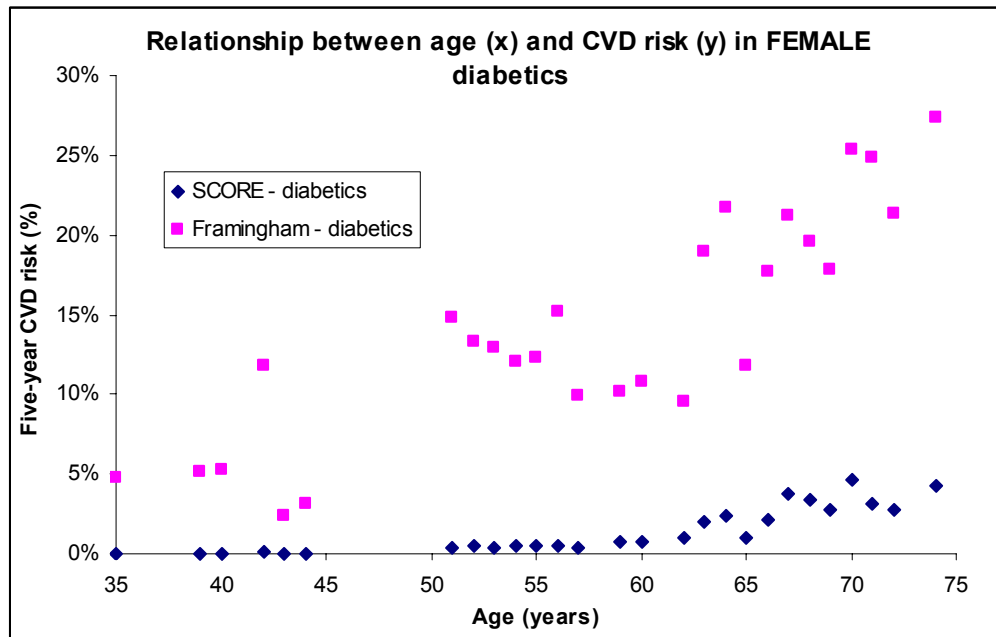
Figure 70: Relationship between age and five-year CVD risk in diabetic men



Results of analysis

In non-diabetic men and non-diabetic women there is a strong relationship between age and CVD risk by the Framingham equation or age and mortality risk by the SCORE equation. In diabetic men and diabetic women there is also a strong relationship between age and CVD risk, although this is less clear because of the smaller numbers of patients on which the analysis is based.

Figure 71: Relationship between age and five-year CVD risk in diabetic women



Effect of using SCORE risk equation on optimum treatment eligibility criteria

Clearly, the cost per CVD event prevented will be three times higher if we estimate individual risk from the SCORE mortality equation. However, because it affects all preventive interventions equally, use of the SCORE equation will not affect the cost-effectiveness rankings of different interventions.

Use of the SCORE equation may affect incremental cost effectiveness in a way that might influence the optimum treatment eligibility thresholds. To investigate this I repeated the analysis in chapter 6 using the SCORE risk equation in place of the Framingham risk equations.

Figure 72: Incremental cost per CVD death prevented in relation to five-year CHD risk category: risk calculated using SCORE risk equation

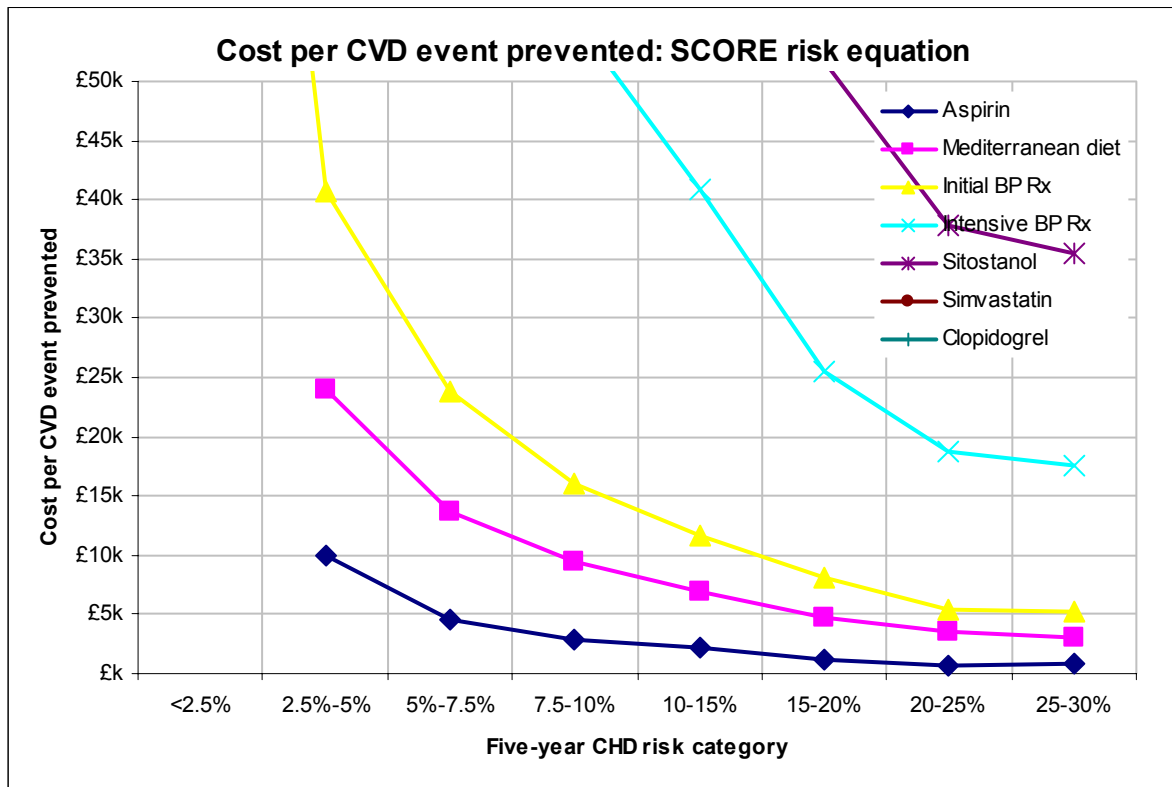
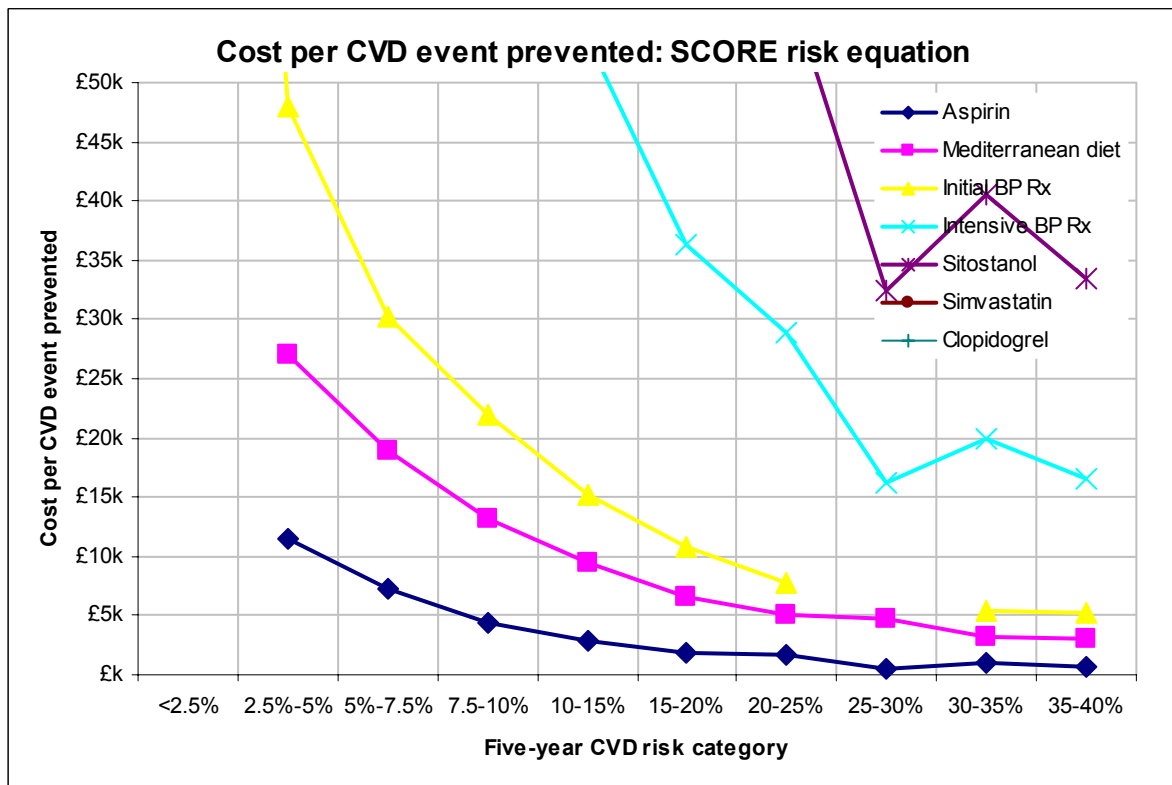


Figure 73: Incremental cost per CVD event prevented in relation to five-year CVD risk category: risk calculated using SCORE risk equation



Effect of the SCORE equation on incremental cost-effectiveness

The results of this analysis are shown in Figure 72 and Figure 73. Using this analysis it is possible to define treatment eligibility criteria appropriate for a cost of £10,000 per CVD event prevented and £25,000 per CVD event prevented. These are shown in Table 115 and Table 116.

Table 115: Treatment eligibility criteria for SCORE analysis - £10,000 per CVD event prevented

Intervention	Treatment criteria	
	Non risk criteria	Five-year risk threshold
Aspirin		>2.5% CHD risk
Mediterranean diet		>7.5% CHD risk
Initial antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
	Blood pressure \geq 120/80 mm Hg	>20% CVD risk
Intensive antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
Simvastatin	Total cholesterol \geq 9.0 mmol/l	Any risk level

Source: See text above

The treatment eligibility criteria are similar to those derived from the previous analysis using the Framingham risk equation.

Table 116: Treatment eligibility criteria for SCORE analysis - £25,000 per CVD event prevented

Intervention	Treatment criteria	
	Non risk criteria	Five-year risk threshold
Aspirin		>2.5% CHD risk
Mediterranean diet		>2.5% CHD risk
Initial antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
	Blood pressure \geq 120/80 mm Hg	>7.5% CVD risk
Intensive antihypertensive treatment	Blood pressure \geq 180/110 mm Hg	Any risk level
	Blood pressure \geq 120/80 mm Hg	>25% CVD risk
Simvastatin	Total cholesterol \geq 9.0 mmol/l	Any risk level

Source: See text above

Effect of using SCORE risk equation on optimum treatment eligibility criteria

Using the treatment eligibility criteria outlined in Table 116 I repeated the analysis carried out in chapter 8. This compares the costs and effects of three novel strategies for CVD prevention.

Effect of the SCORE equation on cost-effectiveness of prevention policies

The results of the analysis are illustrated in Figure 74. A strategy using minimal data to prioritise patients for assessment maintains its advantage over the strategies requiring additional risk factor data. This indicates that the SCORE risk equation does not fundamentally alter the relative efficiency of the selection strategies.

Figure 74: Costs and effects of devoting increasing resources to three novel prevention strategies: treatment eligibility and benefits calculated using SCORE equations

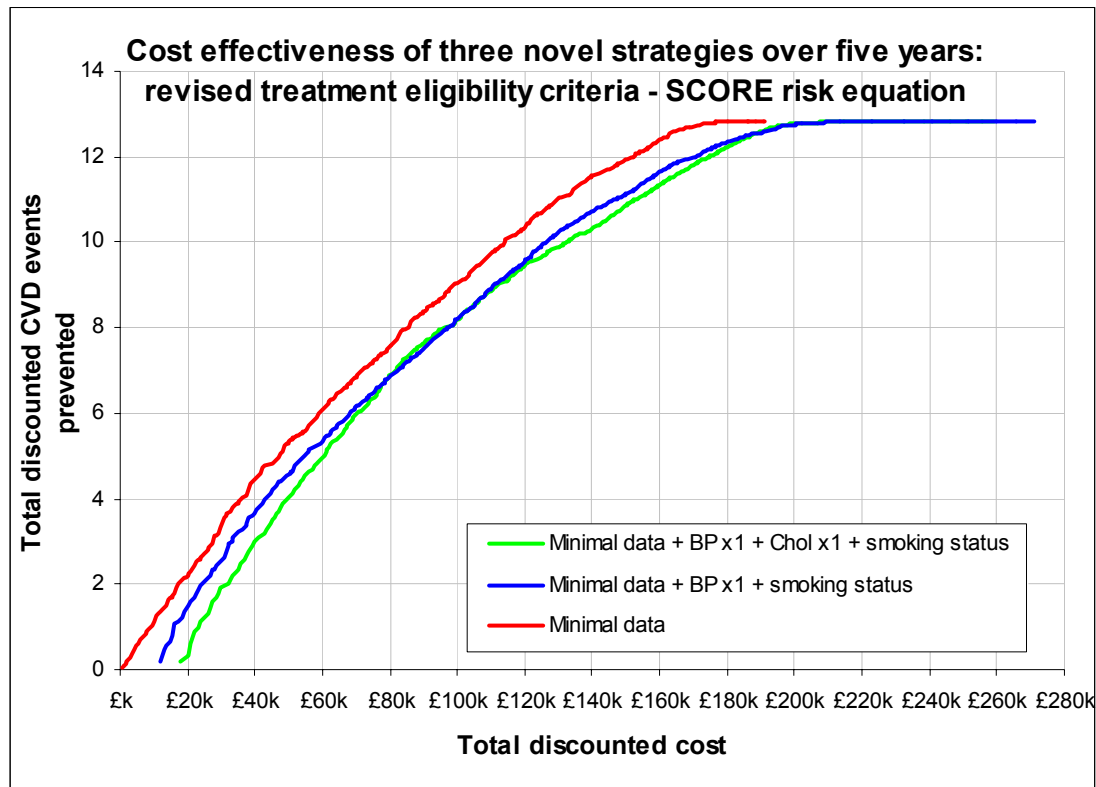


Table 117 shows a detailed breakdown of the costs and effects of the policy based on pre-selection using minimal data. Because only deaths are counted, fewer CVD events are prevented than if the Framingham equation is used. Using the same treatment criteria, only 332 patients are eligible for at least one intervention compared to 1101 in the analysis in Table 96. The selection strategy still correctly identifies those eligible: assessing the first 500 of the 2158 eligible patients identifies 83% of those eligible for at least one treatment.

Table 118 shows the incremental cost-effectiveness of each intervention as it is given to each successive group of 100 patients. The cost per CVD death prevented is higher than the cost per CVD event prevented when the analysis is carried out using the Framingham equations. It is also clear that once the first 1000 patients have been assessed it is not cost-effective to assess further patients.

Table 117: Cost-effectiveness of a novel strategy for CVD prevention using a prior estimate of CVD risk based on minimum risk factor data: risks calculated using SCORE equation

Rank of patients assessed	Number of patients eligible for this intervention								Total hours on assessment	Drug costs	Total costs	Total benefits	Cost per CVD event prevented
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin	Clopidogrel	At least one treatment					
1-100	85	85	24	11	0	1	0	85	75	£19,676	£45,553	4.9	£9,367
101-200	73	73	10	6	0	0	0	73	75	£12,639	£34,529	2.7	£12,681
201-300	50	50	11	7	0	1	0	50	75	£11,837	£26,947	1.9	£14,078
301-400	47	47	10	9	0	4	0	47	75	£16,559	£30,810	1.9	£15,988
401-500	19	19	4	6	0	2	0	20	75	£8,093	£13,904	0.6	£24,911
501-600	15	15	2	2	0	0	0	16	75	£2,819	£7,351	0.4	£20,396
601-700	9	9	3	3	0	1	0	10	75	£4,144	£7,039	0.3	£25,768
701-800	3	3	3	3	0	0	0	6	75	£1,862	£2,975	0.1	£37,439
801-900	2	2	2	3	0	1	0	4	75	£3,119	£3,873	0.1	£49,602
901-1000	0	0	4	4	0	1	0	5	75	£3,529	£3,875	0.0	£116,426
1001-2158	0	0	9	11	0	5	0	16	869	£12,897	£13,921	0.0	£422,876

Table 118: Average cost per CVD event prevented for the strategy with each intervention in each successive group of 100 patients assessed: risks calculated using SCORE equation

Rank of patients assessed	Average cost per CVD event prevented					
	Aspirin	Mediterranean diet	Initial BP treatment	Enalapril	Sitostanol	Statin
1-100	£3,486	£10,494	£10,885	£29,525	None eligible	£197,443
101-200	£5,244	£14,757	£14,417	£53,550	None eligible	None eligible
201-300	£5,283	£14,842	£14,909	£68,924	None eligible	£195,989
301-400	£5,401	£15,224	£9,261	£34,461	None eligible	£91,528
401-500	£7,877	£19,974	£27,254	£61,442	None eligible	£135,069
501-1000	£9,743	£21,827	£31,704	£89,983	None eligible	£239,704
1001-2158	None eligible	None eligible	£147,480	£332,709	None eligible	£999,914
All 2158	£4,886	£13,872	£15,738	£56,728	None eligible	£187,136

Note: Events predicted by the SCORE equation are CVD deaths. This differs from the Framingham equations.

Conclusions: the effect of using SCORE risk equation

It is probably premature to adopt new risk equations in the analysis because of two weaknesses. First, they do not distinguish between CVD risk in diabetics and CVD risk in non-diabetics. Second, it is not clear that they are more accurate predictors of CVD risk than the Framingham risk equations. Preliminary analysis suggests that the Framingham risk equations systematically overestimate CHD mortality, whereas the SCORE risk equations systematically underestimate CHD mortality.

Were new risk equations to be used the model would have to be recalculated. This would affect the analysis in a number of ways.

Because risk levels are substantially lower using the SCORE equation, if the same (or similar) treatment substantially fewer individuals will be eligible for treatment and fewer CVD events will be prevented in those treated. This means that the cost of patient identification in relation to the number of CVD events prevented is greater, whereas the drug costs are similar. This means that

- The rankings of treatments by cost-effectiveness would be unchanged by the use of new risk equations. Aspirin will remain the most cost-effective intervention and statins the least cost-effective.
- Selection strategies for CVD prevention are not significantly affected by the adoption of new risk equations.
- An efficient prevention policy requires modest changes to treatment eligibility criteria.
- The cost per CVD event prevented – particularly with enalapril – is significantly higher.

Changing discount rates

The analysis is robust to wide changes in the discount rates. Because costs and benefits largely accrue in parallel, when discount rates for costs and benefits are the same, the rankings are stable across any likely discount rate. Differential discounting of costs and benefits also does not affect the rankings of treatments within a prevention policy. This is true for when costs are undiscounted and benefits discounted between 0% and 100% or when benefits are undiscounted and costs discounted between 0% and 100%.

Changing assumptions about cost

Staff costs

The analysis is robust to wide changes in staff costs. The most unfavourable assumption is that exclusively physicians carry out assessment and follow-up: at a cost of £118 per hour.²⁸⁵ If this assumption is combined with a 25% compliance rate, the cost per CVD event prevented with aspirin is still less than that with advice on a Mediterranean diet.

Drug costs

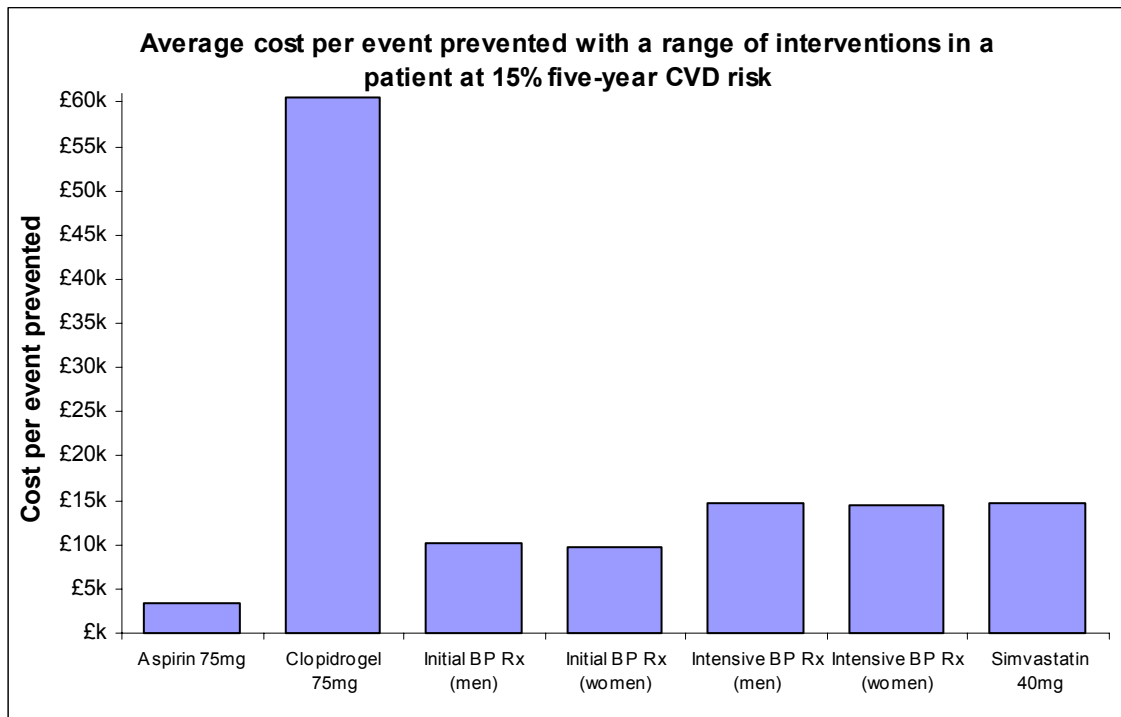
The UK patent on simvastatin expired in May 2003, but that on clopidogrel is valid until February 2013.^{5,6} The price of clopidogrel is therefore unlikely to fall in the near future, however the price of simvastatin is likely to fall.

Following patent expiry, the price of some high-sales drugs in generic form has fallen by as much as half. For example the cost for 30 tablets of generic and branded fluoxetine is £7.61 and £14.21 respectively.³⁰⁸ However in other cases the price has changed little: £17.73 and £18.91 for 28 tablets of generic and branded omeprazole respectively.³⁰⁸

⁵ <http://www.current-patents.com/news/2002/0244/44.asp>

⁶ http://www.bioportfolio.com/news/biotracker_88.htm

Figure 75: Average cost per CVD event prevented in a patient at 15% five-year CVD risk cost of simvastatin has fallen by 75%

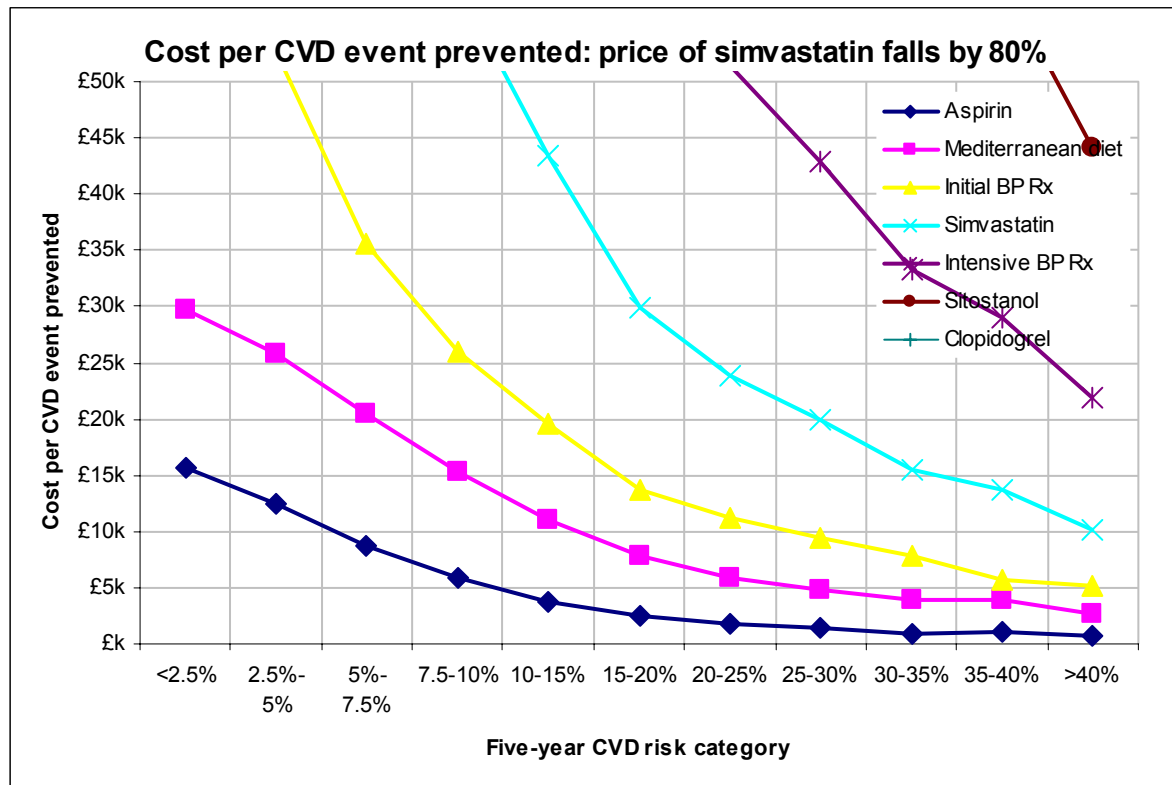


Treatment order and the price of simvastatin

If the price of simvastatin falls by 40% it is more cost effective than dietary supplementation with sitostanol. However, the treatment eligibility criteria informed by this analysis do not recommend simvastatin at either £10,000 or £25,000 per CVD event prevented. This change is therefore of little significance.

For the treatment order to be significantly affected, the price of simvastatin must fall by at least 75% (Figure 75).

Figure 76: Cost per CVD event prevented with price of simvastatin reduced by 80%



Price of simvastatin falls by 80%

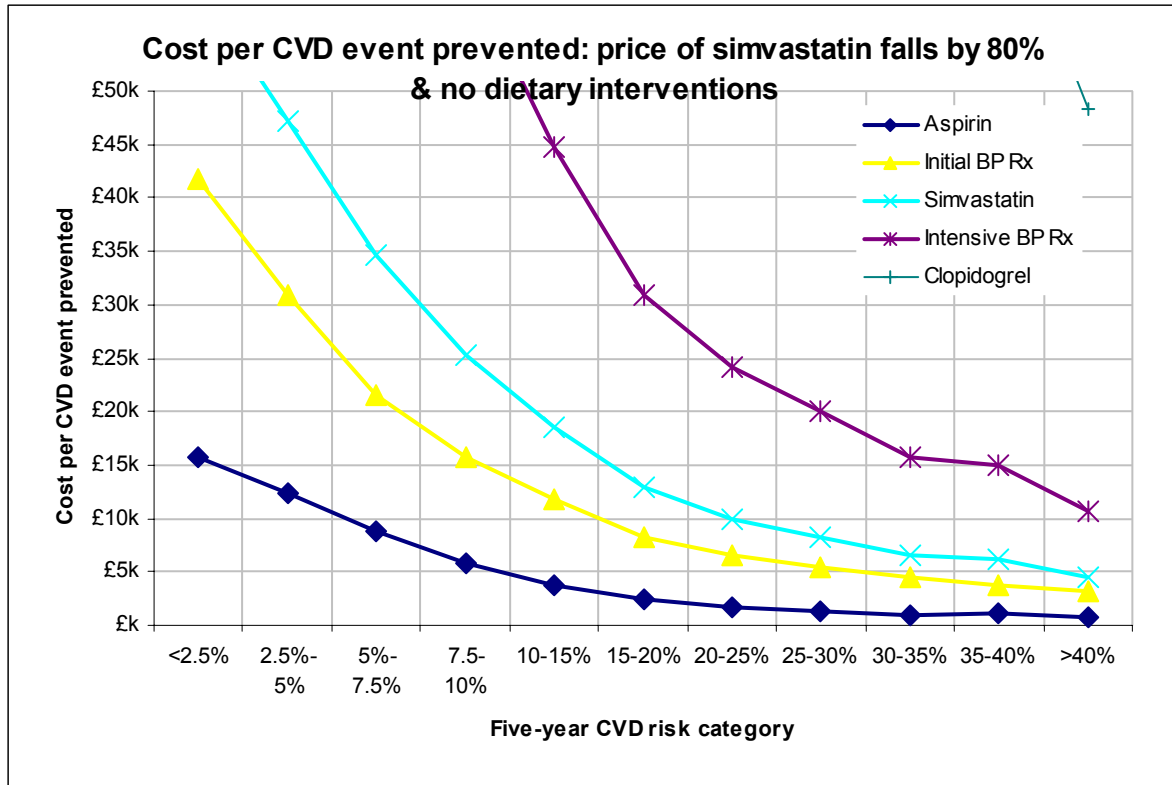
Figure 76 shows the incremental cost-effectiveness of each intervention in relation to five-year CVD risk if the price of simvastatin falls by 80%. Under these circumstances the cost-effectiveness of simvastatin is similar to that of intensive antihypertensive treatment. At a threshold of £10,000 per CVD event prevented it is not cost-effective to offer simvastatin at any risk level. At a threshold of £25,000 per CVD event prevented it is cost-effective to offer simvastatin to patients at 20% five-year CVD risk. At a threshold of £25,000 per CVD event prevented, intensive antihypertensive treatment is only cost effective in the tiny minority (0.2% or 11 of the total population of 5603) of patients at over 40% five-year CVD risk.

No dietary interventions and the price of simvastatin falls by 80%

The most favourable assumptions with regard to simvastatin are that the price falls by 80% and dietary interventions are assumed to be ineffective. This is illustrated in Figure 77. At a threshold of £10,000 per CVD event prevented it is now cost-effective to offer simvastatin at 20% five-year CVD risk.

At a threshold of £25,000 per CVD event prevented it is cost-effective to offer simvastatin to patients at 7.5% five-year CVD risk and intensive antihypertensive treatment to patients over 20% five-year CVD risk.

Figure 77: Cost per CVD event prevented with no dietary interventions and the price of simvastatin reduced by 80%



Changing the measurement of benefits: Life Years Gained

There are a number of problems with using a composite measure of outcome such as CVD events prevented. CHD and CVA events are given equal weight despite having very different health implications. Even the category of CHD (or CVA) event contains a wide range of health outcomes from death to reduced quality of life. Using non-generic units also makes it difficult to compare cost-effectiveness across disease groups. However some of these problems are not soluble with current information. There are insufficient data to indicate whether one preventive intervention or another has different effects on more or less severe outcomes. There is therefore no reason to suppose that such preventive interventions differ.

It is beyond the scope of this study to calculate the numbers of quality adjusted life years gained from prevention of CVD. However it is possible to make a rough estimate of the likely life years gained as a result of the interventions. If benefits expressed as life years gained correlate with benefits expressed as CVD events prevented it follows that an analysis based on life years gained is likely to reach similar conclusions to this one.

Estimating life years gained

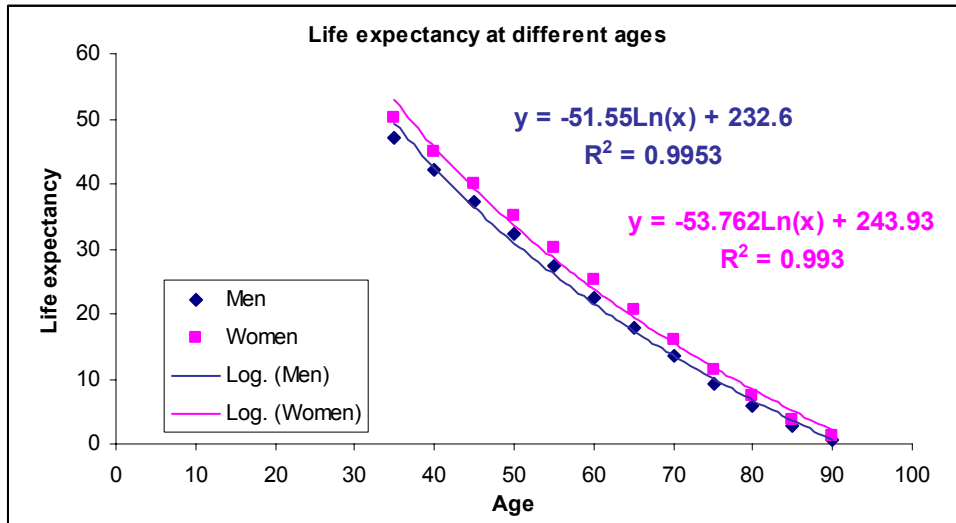
I calculated an annual death rate for each age band from the population and the annual number of deaths in England and Wales in 2000.³⁰⁹

Table 119: Annual death rates and life expectancy in men and women

Age band	Population		Number of deaths		Deaths per 100,000		Survival probability (to end of this age band)		Expected years in this age band		Life expectancy (from start of age band)	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
35-39	2193	2098	2,715	1,590	124	76	0.9938	0.9962	5.0	5.0	47.1	50.0
40-44	1857	1822	3,333	2,284	179	125	0.9911	0.9937	5.0	5.0	42.2	45.0
45-49	1674	1669	4,983	3,333	298	200	0.9852	0.9901	4.9	5.0	37.2	40.1
50-54	1805	1814	8,384	5,757	464	317	0.9770	0.9842	4.9	4.9	32.3	35.1
55-59	1432	1453	11,177	7,248	781	499	0.9616	0.9753	4.8	4.9	27.4	30.2
60-64	1253	1298	16,721	10,387	1,335	800	0.9350	0.9606	4.7	4.8	22.6	25.3
65-69	1095	1189	24,563	16,002	2,243	1,346	0.8928	0.9345	4.5	4.7	17.9	20.5
70-74	941	1131	36,030	26,172	3,830	2,314	0.8226	0.8895	4.1	4.4	13.4	15.9
75-79	739	1043	46,771	41,775	6,327	4,006	0.7212	0.8151	3.6	4.1	9.3	11.4
80-84	406	710	40,355	47,535	9,940	6,692	0.5925	0.7073	3.0	3.5	5.7	7.3
85-89	206	477	32,977	56,192	15,977	11,770	0.4188	0.5347	2.1	2.7	2.8	3.8
90+	80	291	15,216	39,913	23,706	19,674	0.0668	0.1118	0.7	1.1	0.7	1.1

Source: Derived from <http://www.statistics.gov.uk/>

Figure 78: Relationship between age and life expectancy

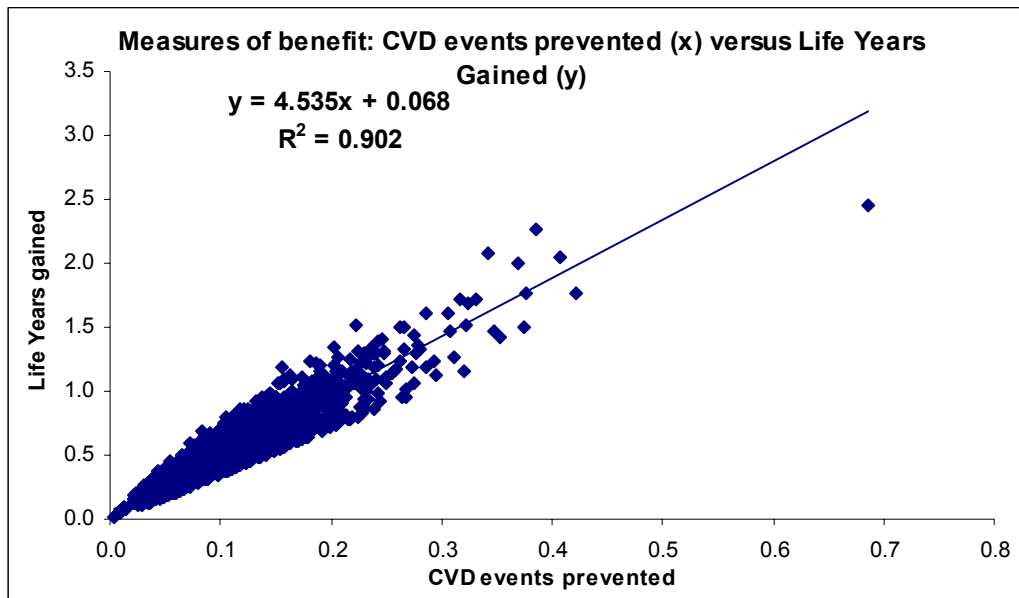


Derived from Table 119.

From the annual death rate it is possible to calculate a survival rate for each age band and from this, a life expectancy at each age. This can in turn be converted into a mathematical equation. (Figure 78) For simplicity I assume that case fatality rates from all CVD events are equal to the case-fatality rates for CHD events given in Table 109. The life years gained from any given intervention is the product of the absolute reduction in mortality rate attributable to the intervention and the life expectancy at that age. The absolute reduction in mortality is the product of the absolute reduction in CVD risk and the case-fatality rate of a CVD event.

In a previous analysis all persons in the total population of 5603 were considered eligible for treatment if their CHD risk exceeded 2.5%. This analysis is revisited and the benefits of treatment converted into life years gained. The relationship between benefits expressed as life years gained and benefits expressed as CVD events prevented is shown in Figure 79. There is a close relationship between benefits expressed as life years gained and benefits expressed as CVD events prevented ($R^2 = 0.902$).

Figure 79: Relationship between benefits expressed as CVD events prevented and life years gained



Conclusions from analysis of estimated life years gained

Benefits as measured by life years gained are closely related to benefits expressed as CVD events prevented. This suggests that the policy recommendations resulting from this analysis are likely to be robust to changes in measures of benefit.

10. Conclusions

A number of conclusions can be drawn from this analysis and a number of critical areas can be identified for further investigation. It is clearly possible to model cost-effectiveness of a number of identification strategies in a population and to derive credible results from the analysis. Some of these have already been published. (Appendix E) The analysis has a number of clear policy implications. These policy implications are robust to changes in the underlying assumptions of the model.

Main lessons from the analysis

It is possible to construct a credible model of CVD prevention in a population incorporating the resource implications of identifying, treating and following up patients on the cost side of the equation and the benefits of treatment over five years on the effectiveness side of the equation. The fact that this is possible empowers – we might argue obliges – policy makers and authors of guidelines quantify the costs and effects of their recommendations.

Identification strategies

The analysis convincingly demonstrates that opportunistic selection strategies and selection strategies that target diabetics and patients on antihypertensive medication are less efficient than strategies that prioritise patients on the basis of a prior estimate of their CVD risk. From a mathematical point of view this is hardly surprising. A policy that uses all available data to identify patients likely to benefit from treatment is likely to be more efficient than one that uses no data or that uses only limited data.

Policies that undertake prior prioritisation on the basis of CVD risk require some data (age, sex, diabetic and antihypertensive drug treatment status) to be recorded in practice databases. The great majority of English general practices record more risk factor data than this minimum, with many patients having a record of their blood pressure (Appendix C). Prior prioritisation will therefore be more efficient in practice than has been modelled in this analysis.

Policy implications of identification strategies

Some policies encourage mass, unselected, screening of all adults. For example, policies that set as a performance target the percentage of persons who have a blood pressure recorded in the past year. (See Box 20) As an alternative, policies should encourage practices to adopt prior prioritisation strategies.

Cost-effectiveness of treatment

Aspirin is undoubtedly the most cost-effective intervention for prevention of CVD in primary care. It is followed by advice on a Mediterranean diet and initial antihypertensive treatment with low cost antihypertensives. At present prices, statins are not cost-effective for general use in primary prevention.

It is much more cost effective to treat large numbers of individuals at medium (>2.5%) five-year CHD risk with aspirin, advice on a Mediterranean diet and initial antihypertensives than it is to treat a small number of individuals at high risk with further antihypertensive drugs, sitostanol or statins. In effect this means that an efficient CVD prevention strategy will target the majority of men over a given age threshold and women over an age threshold about 10 years higher. (Appendix D)

Treatment eligibility criteria

The analysis indicates that current treatment eligibility criteria are irrational from the perspective of evidence and from the perspective of cost-effectiveness. Evidence does not support the existence of risk factor thresholds as determinants of benefit, yet they persist in being used. Clinical guidelines are ultimately resource allocation guidelines. If they are to serve the principle of using public resources to achieve the greatest good for the greatest number they should be informed by a consideration of cost-effectiveness. The simplest way to do this is to set a threshold cost per CVD event prevented and recommend interventions that are more cost effective than this threshold.

Incremental cost-effectiveness and treatment eligibility criteria

Consideration of incremental effectiveness is essential to development of rational treatment eligibility criteria. Most individuals at high risk of CVD could benefit from most preventive interventions. This means that the incremental benefits of the third or fourth intervention are low compared to the incremental benefits of the first or second interventions. In practice this means that the incremental cost per CVD event prevented with the third intervention is likely to be too high for it to be considered.

This finding is important. If some interventions are more cost-effective than others, policy should clearly prioritise the more cost-effective interventions. Similarly if it is not cost-effective to seek additional blood pressure lowering or to achieve further cholesterol lowering it means that the concept of a target blood pressure or target

cholesterol level should be used with caution. It argues against inclusion of rigid performance targets for monitoring of clinical practice in primary care. Unfortunately, exactly such policies form part of the new General Medical Services contract for general practitioners.³¹⁰ (See Box 20)

Box 20: Performance targets linked to payments in the new General Medical Services contract

All patients

Records 11: The blood pressure of patients age 45 and over is recorded in the preceding five years for at least 55 per cent of patients

Records 17: The blood pressure of patients age 45 and over is recorded in the preceding five years for at least 75 per cent of patients

Patients with hypertension

BP 5. The percentage of patients with hypertension in whom the last blood pressure (measured in last 9 months) is 150/90 or less

DM 16. The percentage of patients with diabetes who have a record of total cholesterol in the previous 15 months

DM 17. The percentage of patients with diabetes whose last measured total cholesterol within previous 15 months is 5 or less

Areas of uncertainty

This analysis has a number of limitations, some of which have been mentioned earlier. The main limitations concern the limited scope of the analysis. Because costs and benefits have been considered only over five-years the analysis has not produced an estimate of the cost per life-year gained or cost per QALY. This means that it is difficult to use this analysis to inform distributional efficiency (distribution of resources between health programmes). Because cost savings resulting from deferred need for secondary care have been excluded it is possible that some of the more cost-effective strategies may be cost saving.

The analysis identifies a number of critical areas of uncertainty in prevention policy. These concern evidence of effectiveness, individual patients' preferences for treatment and the appropriate risk equation to use.

Effectiveness of dietary interventions

Because of uncertainty about evidence for the effectiveness of dietary interventions in primary prevention, it is unclear whether these should be part of a primary prevention programme or not. Given the potential cost-effectiveness of advice on a Mediterranean diet, research into its effectiveness and cost-effectiveness in primary

prevention merits a high priority. This is clearly a potentially more cost-effective intervention for primary prevention than either statins or high-cost platelet inhibitors.

Patient preferences

The analysis undertakes a cost-effectiveness analysis from the perspective of the health service. This answers the question: “what should a publicly funded system be prepared to provide?”

However an equally important, but distinct perspective is that of individual patients themselves. This answers the question: “what is it in my best interests to accept?” It is far from clear that patients will prefer the costs, inconveniences and psychological disadvantages of medicalisation in exchange for a small reduction in their absolute risk of CVD. Research in this area to date suggests that individual patients vary greatly in their perspectives. Recent UK studies suggest that only a minority of patients would choose a drug treatment that reduces their five-year CVD risk by less than 5%.^{311,312} An earlier Canadian study suggested that a 1% reduction in five-year risk would be sufficient.³¹³ The absolute benefits of a first intervention are typically much smaller than 5% and sometimes smaller than 1%. Ways need to be found to incorporate patients’ views into individual treatment decisions. Just because a publicly funded system is prepared to provide an intervention, it does not follow that every individual will want to receive it. Combining this observation with the fact that incremental benefits decline with additional treatments, it is clear that from an individual patient’s perspective the incremental benefits of a third or fourth intervention are unlikely to be worth the additional inconvenience of treatment.

Areas of change

Some of the specific findings of the analysis (for example: that statins are not cost-effective for primary prevention) are sensitive to changes in the price of drugs. No economic analysis should be seen as providing a fixed answer to a fixed question. For an economic analysis to be useful it must also be sufficiently flexible for the analysis to be undertaken in a number of ways with a number of different assumptions. Prices change, discount rates change and evidence of effectiveness changes. Perhaps this is the strongest feature of this analysis. The fact that it has been constructed in the form of a model means that any of a number of changes in the underlying assumptions can be investigated and relevant policy guidance produced.

Implications of these findings

Most of the important findings from this analysis are the result of the incremental analysis of both patient identification and treatment. This indicates the importance of incremental cost-effectiveness analysis. The findings indicate that more efficient CVD prevention can be undertaken, but the current primary care system does not lend itself to either the systematic patient identification or treatment according to a strict protocol that this would require. An important research question remains: how can a health care system be designed to best deliver such a prevention programme? As has been noted, the findings cannot inform distributional efficiency questions. To do so requires equivalent analyses to be undertaken for competing programmes. It also requires this kind of analysis to be refined to estimate incremental cost-effectiveness using generic units such as QALYs.

Appendix A. Calculating incremental cost-effectiveness

Illustration 1: Individual patient characteristics in a natural population of 5169

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
2	Patient characteristics																			
3	ID number	Sex (0=male)	Age	Age band	Systolic BP	Diastolic BP	Smoking status	Total chol (HDL)	DM	On BP drugs: 0=no, 1=yes	IHDIS	CVD	Irregular pulse (AF)	Five year CVD risk	Five year CHD risk	Five year CVA risk				
4	2	1	51	5	144	77	0	3.2	0	0	0	0	0	2.5%	1.4%	0.7%				
5	9	1	47	5	116	74	0	4.0	0	0	0	0	0	1.2%	0.9%	0.3%				
6	12	0	79	8	152	67	0	4.3	1	0	1	1	0	31.0%	17.4%	12.5%				
7	13	1	75	8	132	74	0	3.3	0	0	0	0	0	6.4%	2.3%	2.5%				
8	14	0	86	9	162	84	0	4.4	0	1	0	0	0	29.6%	18.0%	12.0%				
9	18	1	51	5	142	88	0	3.9	0	0	0	0	0	3.1%	2.0%	0.6%				
10	25	1	75	8	122	77	0	3.6	0	0	0	0	0	5.7%	2.3%	2.0%				
11	34	1	47	5	119	66	0	5.1	0	0	0	0	0	1.8%	1.6%	0.3%				
12	36	0	64	6	138	92	0	4.3	0	0	0	0	0	10.5%	7.1%	2.1%				
13	37	1	62	6	148	72	0	5.2	0	0	0	0	1	8.1%	5.3%	4.5%				
14	38	0	83	8	155	83	0	3.1	0	0	1	1	0	20.8%	11.1%	11.4%				
15	39	1	81	8	136	70	0	2.9	0	1	0	0	0	7.7%	2.0%	7.9%				
16	49	1	30	3	126	57	1	4.6	0	0	0	0	0	1.0%	0.1%	0.2%				
17	51	0	75	8	112	67	0	3.7	1	1	0	0	1	14.9%	8.6%	9.0%				
18	53	0	50	5	158	97	0	5.1	0	0	0	0	0	7.9%	5.7%	1.4%				
19	54	1	49	5	128	78	0	3.1	0	0	0	0	0	1.4%	0.9%	0.4%				
20	57	1	40	4	145	82	0	5.0	0	0	0	0	0	1.9%	1.1%	0.3%				
21	59	1	77	8	162	90	0	4.3	0	0	0	0	0	14.2%	5.4%	5.0%				
22	61	1	81	8	119	67	0	3.0	0	1	0	0	0	5.4%	1.5%	7.1%				
23	62	0	67	7	148	94	0	4.8	0	1	0	0	0	15.5%	10.3%	4.0%				
24	64	0	32	3	121	71	1	4.3	0	0	0	0	0	1.1%	1.0%	0.6%				

Illustration 2: Estimating individual patient benefit in a natural population

Microsoft Excel - CE in a population

File Edit View Insert Format Tools Data Window Help Acrobat

Arial 10

AM6 =-(\$B*(1-W6)+\$T*(1-AE6)-IF(W6<1,\$AM\$1,0)

Benefits of treatment: relative risk of CHD

Benefits of treatment: relative risk of CVA

	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP	AQ	AR	AS
		Aspirin Rx	Mediterranean diet	Initial BP Rx	Enalapril Rx	Sitostanol Rx	Statin Rx	Clopidogrel Rx	Reduction in risk of CVA	Aspirin Rx	Mediterranean diet	Initial BP Rx	Enalapril Rx	Sitostanol Rx	Clopidogrel Rx	Incremental AFR with treatment	Aspirin Rx	Mediterranean diet	Initial BP Rx	Enalapril Rx	Sitostanol Rx	Statin Rx	Clopidogrel Rx	
3		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
4		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
5		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
6		72%	28%	83%	8%	8%	63%	63%	102%	100%	64%	80%	70%	90%	100%	4.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
7		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
8		72%	28%	100%	8%	8%	63%	63%	102%	100%	100%	80%	90%	70%	90%	4.5%	12%	0.0%	5.8%	3.1%	8.2%	7.8%	0.0%	0.0%
9		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
10		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
11		72%	28%	83%	8%	8%	63%	63%	102%	100%	64%	80%	70%	90%	100%	2.6%	8.0%	6.0%	4.4%	2.3%	0.0%	8.5%	7.7%	0.0%
12		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
13		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
14		72%	28%	83%	8%	8%	63%	63%	102%	100%	64%	80%	70%	90%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
15		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
16		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
17		72%	28%	100%	100%	8%	63%	63%	102%	100%	100%	100%	90%	70%	90%	1.9%	6.2%	0.0%	0.0%	1.8%	0.0%	4.1%	0.0%	0.0%
18		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
19		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
20		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
21		100%	100%	83%	8%	8%	100%	100%	100%	100%	64%	80%	100%	100%	100%	0.0%	0.0%	2.7%	2.0%	0.0%	0.0%	0.0%	0.0%	0.0%
22		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
23		72%	28%	100%	8%	8%	63%	63%	102%	100%	100%	80%	90%	70%	90%	2.5%	7.4%	0.0%	2.8%	1.5%	4.4%	4.2%	0.0%	0.0%
24		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
25		72%	28%	100%	100%	8%	63%	63%	102%	100%	100%	100%	90%	70%	90%	4.0%	11.2%	0.0%	0.0%	1.8%	0.0%	5.3%	5.8%	0.0%
26		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
27		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
28		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
29		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
30		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
31		100%	100%	83%	8%	8%	100%	100%	100%	100%	64%	80%	100%	100%	100%	0.0%	0.0%	4.2%	3.0%	0.0%	0.0%	0.0%	0.0%	0.0%
32		72%	28%	83%	8%	8%	63%	63%	102%	100%	64%	80%	90%	70%	90%	2.4%	7.0%	2.1%	2.1%	1.2%	2.4%	3.7%	0.0%	0.0%
33		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
34		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
35		72%	28%	100%	8%	8%	63%	63%	102%	100%	100%	80%	90%	70%	90%	2.1%	6.2%	0.0%	2.2%	1.2%	2.5%	3.4%	0.0%	0.0%
36		72%	28%	83%	8%	8%	63%	63%	102%	100%	64%	80%	90%	70%	90%	3.0%	8.8%	3.6%	3.2%	1.7%	5.1%	4.9%	0.0%	0.0%
37		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
38		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
39		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
40		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
41		72%	28%	100%	8%	8%	63%	63%	102%	100%	100%	80%	90%	70%	90%	5.3%	15.0%	0.0%	6.1%	3.3%	8.7%	8.7%	0.0%	0.0%
42		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
43		72%	28%	100%	8%	8%	63%	63%	102%	100%	100%	80%	90%	70%	90%	3.4%	10.6%	0.0%	6.8%	3.6%	0.0%	7.4%	0.0%	0.0%
44		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
45		100%	100%	83%	8%	8%	100%	100%	100%	100%	64%	80%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
46		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
47		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Illustration 3: Estimating incremental costs for individuals in a natural population

Microsoft Excel - CE in a population

File Edit View Insert Format Tools Data Window Help Acrobat

Arial 10

BH6 =IF(AZ6=0,IF(SUM(AW6:AX6)>0,BNF 44 - Sept 2002 (2)),\$K\$44,IF(SUM(AU6:AY6,\$N6)=0,AZ6,BNF 44 - Sept 2002 (2)),\$K\$45))

	BB	BC	BD	BE	BF	BG	BH	BI	BJ	BK	BL	BM	BN	BO	BP	BQ
	Incremental follow up costs	Aspirin Rx	Mediterranean diet	Initial BP Rx	Enalapril Rx	Sitostanol Rx	Statin Rx	Clopidogrel Rx	Drug costs	Aspirin Rx	Mediterranean diet	Initial BP Rx	Enalapril Rx	Sitostanol Rx	Statin Rx	Clopidogrel Rx
3		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
4		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
5		£48	£294	£26	£0	£0	£33	£0	£21	£116	£186	£377	£326	£1,746	£2,073	£0
6		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
7		£0	£294	£0	£11	£0	£33	£0	£21	£116	£0	£377	£326	£1,746	£2,073	£0
8		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
9		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
10		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
11		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
12		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
13		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
14		£48	£294	£26	£0	£0	£0	£0	£21	£116	£186	£377	£326	£0	£2,073	£0
15		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
16		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
17		£0	£294	£0	£0	£0	£0	£0	£21	£116	£0	£0	£326	£0	£2,073	£0
18		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
19		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
20		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0
21		£0	£0	£74	£0	£0	£0	£0	£0	£0	£171	£377	£0	£0	£0	£0
22		£0	£0	£												

Illustration 4: Estimating incremental cost-effectiveness

	BR	BS	BT	BU	BV	BW	BX	BY
3	Incremental cost per event prevented	Aspirin Rx	Mediterranean diet	Initial BP Rx	Enalapril	Sitostanol	Statin	Clopidogrel
4								
5								
6		£1,596	£3,270	£2,845	£6,493	£10,485	£19,453	£27,080
7								
8		£476	£3,169		£6,674	£10,466	£19,417	£26,558
9								
10								
11								
12								
13								
14		£2,677	£5,132	£3,550	£8,607	£14,002		£39,666
15								
16								
17		£1,101	£6,586			£17,837		£50,736
18								

Illustration 5: Individual patient CVD risk factor data in modelled GP list

The screenshot shows an Excel spreadsheet with the following columns (A-T):

- 1: RANDOM ISER
- 2: ID number
- 3: Sex (0=male)
- 4: Age
- 5: Systolic BP
- 6: Diastolic BP
- 7: Smoking status
- 8: Total chol (/HDL)
- 9: HDL (nominal)
- 10: DM
- 11: ECG LVH
- 12: On BP drugs: 0=no Rx, 1=Rx
- 13: IHD
- 14: Irregular pulse (AF)
- 15: True 5 year CVD risk
- 16: 6. Clinically estimated CVD risk (with measurement error)
- 17: True 5 year CHD risk
- 18: True 5 year CVA risk
- 19: CHD + CVA risk

The data rows show individual patient records with values for each of these variables.

Each row of data represents a single patient. Patients have an individual age and sex, CVD risk factors and individually calculated CVD, CHD and CVA risks.

Illustration 6: Blood pressure and cholesterol measurements incorporating measurement error in modelled GP list

The screenshot shows an Excel spreadsheet with the following columns (A-S):

- 1: Sex (0=male)
- 2: Age
- 3: Age band
- 4: Systolic BP
- 5: SBP error
- 6: First SBP
- 7: Second SBP
- 8: Third SBP
- 9: Fourth SBP
- 10: Fifth SBP
- 11: Diastolic BP
- 12: Smoking status
- 13: Total chol (/HDL)
- 14: TC:HDL error
- 15: First TC:HDL
- 16: Second TC:HDL
- 17: Third TC:HDL
- 18: Fourth TC:HDL
- 19: Fifth TC:HDL

The data rows show individual patient records with multiple measurements and associated error values.

Each row of data represents a single patient. Individual patients have a series of five blood pressure and cholesterol measurements, incorporating a degree of measurement

error. A CHD risk has been calculated using the first blood pressure and cholesterol measurement. In traditional guidelines this first estimate of CHD risk is used to decide whether further risk factor assessment should be undertaken.

Illustration 7: Modelling the order in which patients are invited for assessment

	A	B	C	D	E	F
	ID number	Diabetes	On BP drugs: 0=no Rx, 1=Rx	Randomiser	2. Estimated CVD risk - age, sex, DM + CVD	Ranking score (based on diabetic status and whether patient takes BP Rx)
1	1932	1	1	93822	20.5%	3
2	3176	1	0	99333	13.9%	2
3	6588	1	0	95732	1.3%	2
4	2256			99698	17.9%	1
5	4999			94191	5.9%	1
6	4525			93428	7.4%	1
7	18197			99946	4.3%	0
8	6373			99867	0.9%	0
9	15729			99635	11.5%	0
10	8302			99613	2.5%	0
11	2326			99336	2.5%	0
12	8543			99092	5.3%	0

Illustration 8: Treatment eligibility and relative risk of CHD on treatment

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
	ID number	Sex (0=male)	Age	Systolic BP	Smoking status	Total chol (HDL)	On BP drugs: 0=no Rx, 1=Rx	True 5 year CHD risk		Relative risk of CHD	Aspirin treatment -RR	Initial BP treatment -RR	Dietary oily fish -RR	Enalapril 20mg -RR
1	3176	0	61	148	0	4.8	0	11.0%			0.74	0.83	1.00	0.81
2	17928	1	67	159	0	6.9	0	9.3%			0.74	0.83	1.00	0.81
3	1655	0	74	156	0	3.2	0	8.7%			0.74	0.83	1.00	0.81
4	1854	0	57	159	1	3.1	0	7.2%			1.00	1.00	1.00	1.00
5	2256	0	67	137	0	3.8	1	6.8%			1.00	1.00	1.00	1.00
6	7631	1	57	223	0	4.0	0	6.7%			1.00	0.83	1.00	0.81
7	15729	1	68	146	0	5.6	0	6.3%			1.00	1.00	1.00	1.00
8	211	1	56	141	1	4.4	0	5.7%			1.00	1.00	1.00	1.00
9	5638	0	48	141	1	3.6	0	4.3%			1.00	1.00	1.00	1.00
10	943	0	49	137	1	3.5	0	4.1%			1.00	1.00	1.00	1.00
11	16481	1	55	152	0	4.7	0	3.9%			1.00	1.00	1.00	1.00
12	8302	0	43	147	1	3.4	0	3.0%			1.00	1.00	1.00	1.00
13	13805	1	40	118	1	7.7	0	2.9%			1.00	1.00	1.00	1.00
14	5899	1	45	122	1	5.2	0	2.8%			1.00	1.00	1.00	1.00
15	6231	0	54	112	0	4.1	0	2.7%			1.00	1.00	1.00	1.00
16	13783	0	37	136	0	6.9	0	2.6%			1.00	1.00	1.00	1.00
17	8279	0	53	147	0	2.9	0	2.5%			1.00	1.00	1.00	1.00
18	11246	1	45	135	0	6.1	0	2.4%			1.00	1.00	1.00	1.00
19	9504	1	58	146	0	3.3	0	2.3%			1.00	1.00	1.00	1.00
20	6588	0	36	145	1	3.3	0	2.3%			1.00	1.00	1.00	1.00
21	18197	1	56	139	0	3.4	0	2.0%			1.00	1.00	1.00	1.00

The relative risk of CHD on all treatments is the product of the relative risks on aspirin, antihypertensive treatment, fish oil etc. The reduction in absolute risk of CHD is the product of the total relative risk and the patient's pre-treatment risk of CHD.

A similar calculation was carried out for CVA risk. The total reduction in risk of CVD events was calculated from the sum of the reduction in CHD risk and the reduction in CVA risk minus 0.015 if the patient was taking aspirin (to account for the increased risk of major bleeding).

Appendix B. Relationship between CVD and CHD risk and cost per event prevented

The following graphs show the relationship between risk and cost per CVD event prevented with each of the interventions modelled. Each data point represents one of the patients in the population aged 35 to 74 from the Health Survey for England 1998. The upper graph in each pair shows the relationship between five-year CVD risk and cost per event prevented, the lower graph shows the relationship between five-year CHD risk and cost per event prevented.

Figure 80 shows CVD and CHD risk as predictors of cost-effectiveness of aspirin. CHD is clearly a better predictor of cost-effectiveness. Data points form two distinct clusters when plotted against CHD risk. The lower line represents patients already on antihypertensives. These patients are already being followed up and therefore incur no additional follow-up costs.

Figure 81 shows CVD and CHD risk as predictors of cost-effectiveness of a Mediterranean diet. CHD is clearly a better predictor of cost-effectiveness because the diet is assumed to have no effect on risk of CVA. Data points form two distinct lines when plotted against CHD risk. The lower line represents patients not eligible for aspirin. The absolute reduction in risk with a Mediterranean diet is greater in these patients. This is because aspirin reduces absolute CHD risk and the incremental effectiveness of a Mediterranean diet is therefore smaller.

Figure 82 shows CVD and CHD risk as predictors of cost-effectiveness of initial antihypertensive treatment. CVD risk is a better predictor of benefit than CHD risk. There are two clusters of data points. The lower one represents patients who are not eligible for a Mediterranean diet. This is because a Mediterranean diet reduces absolute CHD risk and the incremental effectiveness of antihypertensive treatment is therefore smaller.

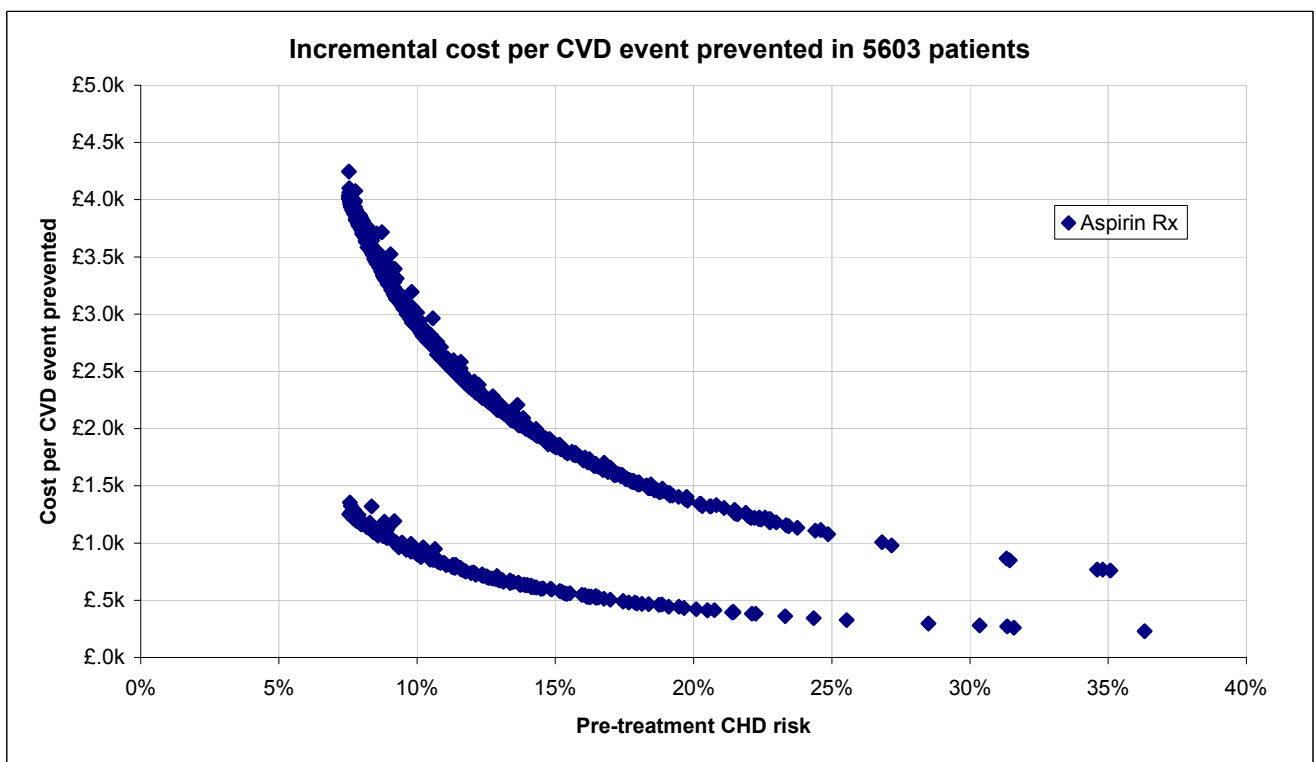
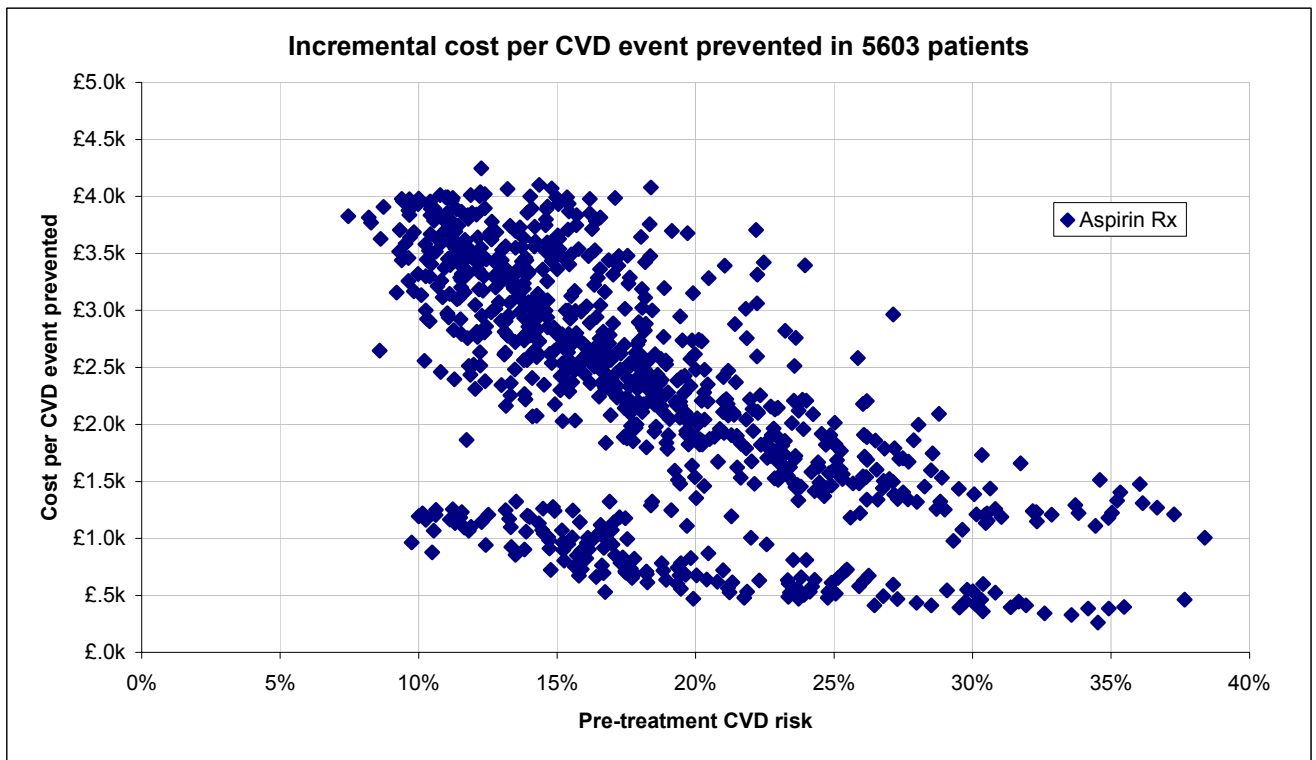
Figure 83 shows CVD and CHD risk as predictors of cost-effectiveness of further antihypertensive treatment. CVD risk is a better predictor of benefit than CHD risk. There are two main clusters of data points, representing patients who are not eligible for a Mediterranean diet and those who are. Other clusters of data points represent patients eligible and ineligible for initial antihypertensive treatment and aspirin.

Figure 84 shows CVD and CHD risk as predictors of cost-effectiveness of sitostanol. CVD risk is a better predictor of benefit than CHD risk. Because patients may be eligible for any of a number of additional treatments, the effectiveness (absolute risk reduction) varies from one individual to another. The effect of this is evident in the wide dispersal of data points. There are two main clusters of data points, representing patients who are not eligible for a Mediterranean diet and those who are.

Figure 85 shows CVD and CHD risk as predictors of cost-effectiveness of statins. CVD risk is a better predictor of benefit than CHD risk. The data are widely dispersed, with two main clusters of data points, representing patients who are and are not eligible for a Mediterranean diet. In a small subgroup of patients with cholesterol over 9.0 mmol/l but five-year CHD risk less than 7.5%, statins are the first treatment they are offered and therefore are more cost effective than the general trend.

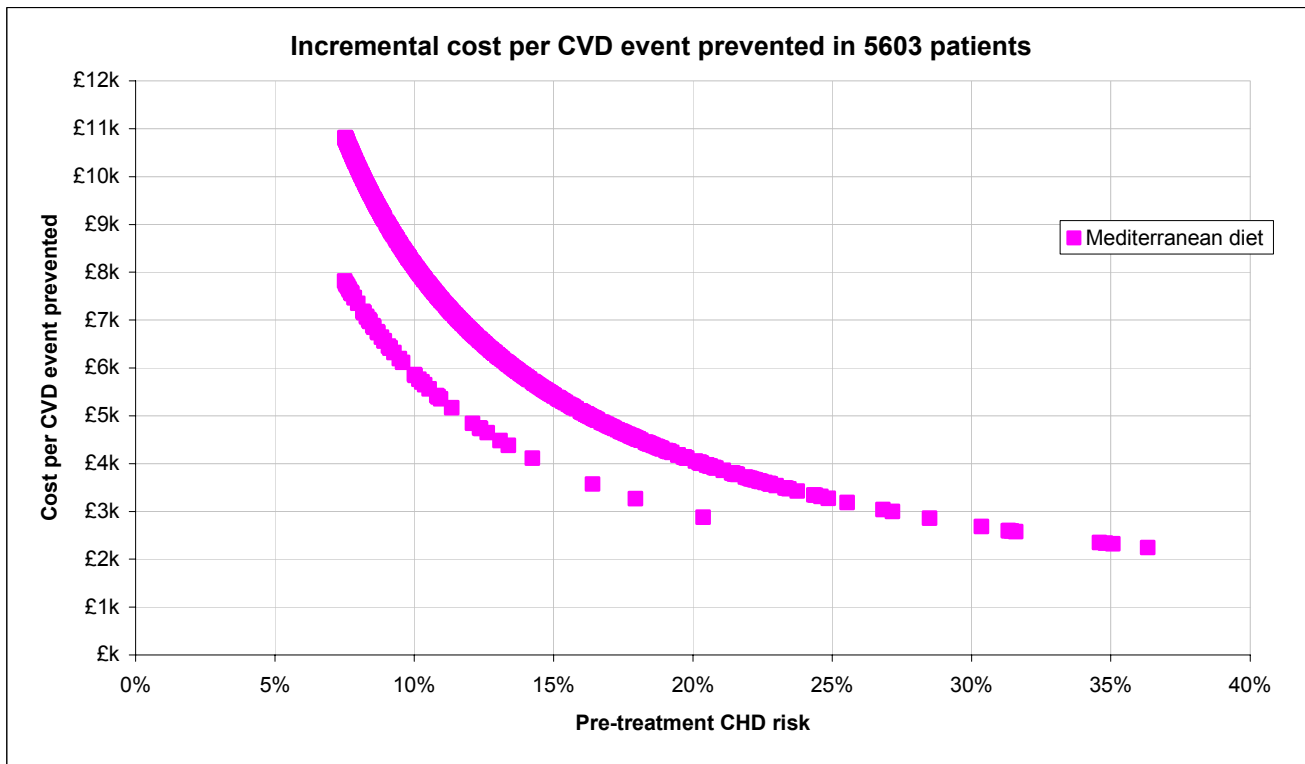
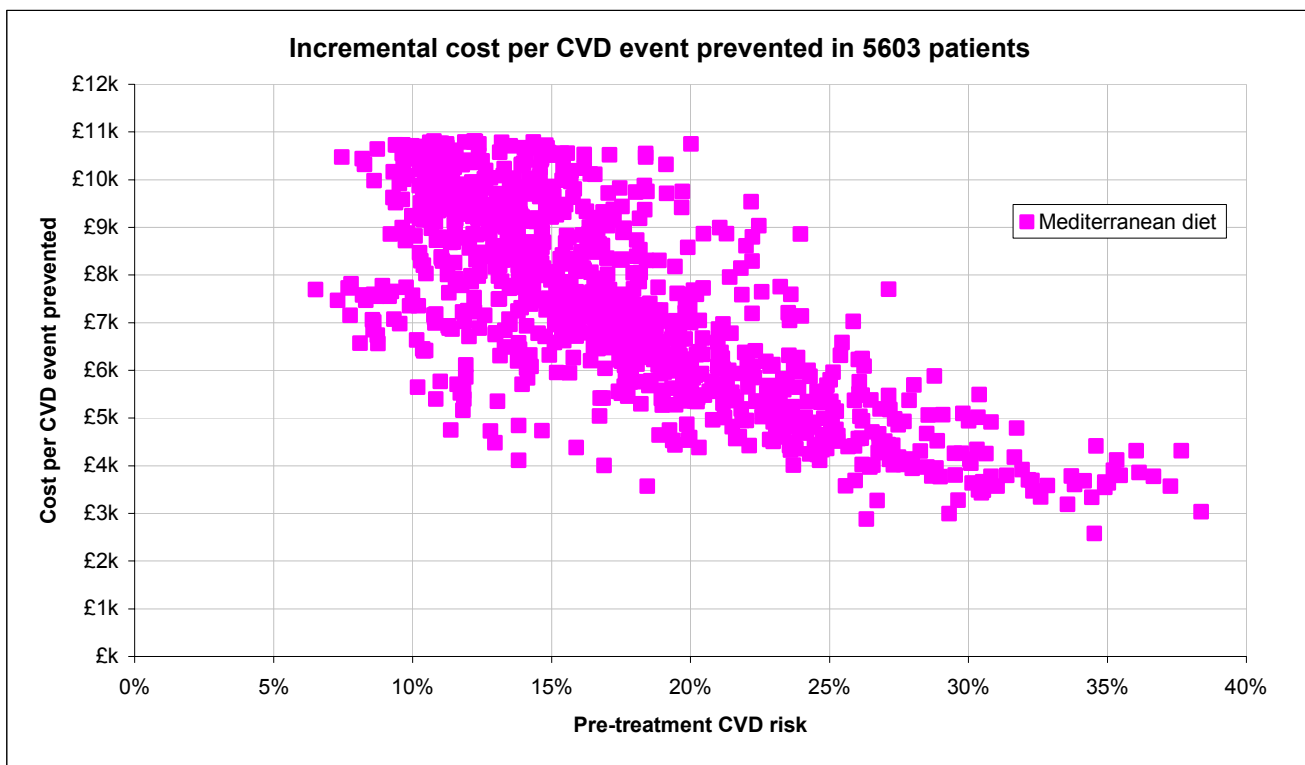
Figure 86 shows CVD and CHD risk as predictors of cost-effectiveness of clopidogrel. CVD risk is a better predictor of benefit than CHD risk. But as patients may be eligible for any of a number of additional treatments, the data points are widely dispersed.

Figure 80: CVD risk and CHD risk and marginal cost-effectiveness of CVD prevention with aspirin in a natural population



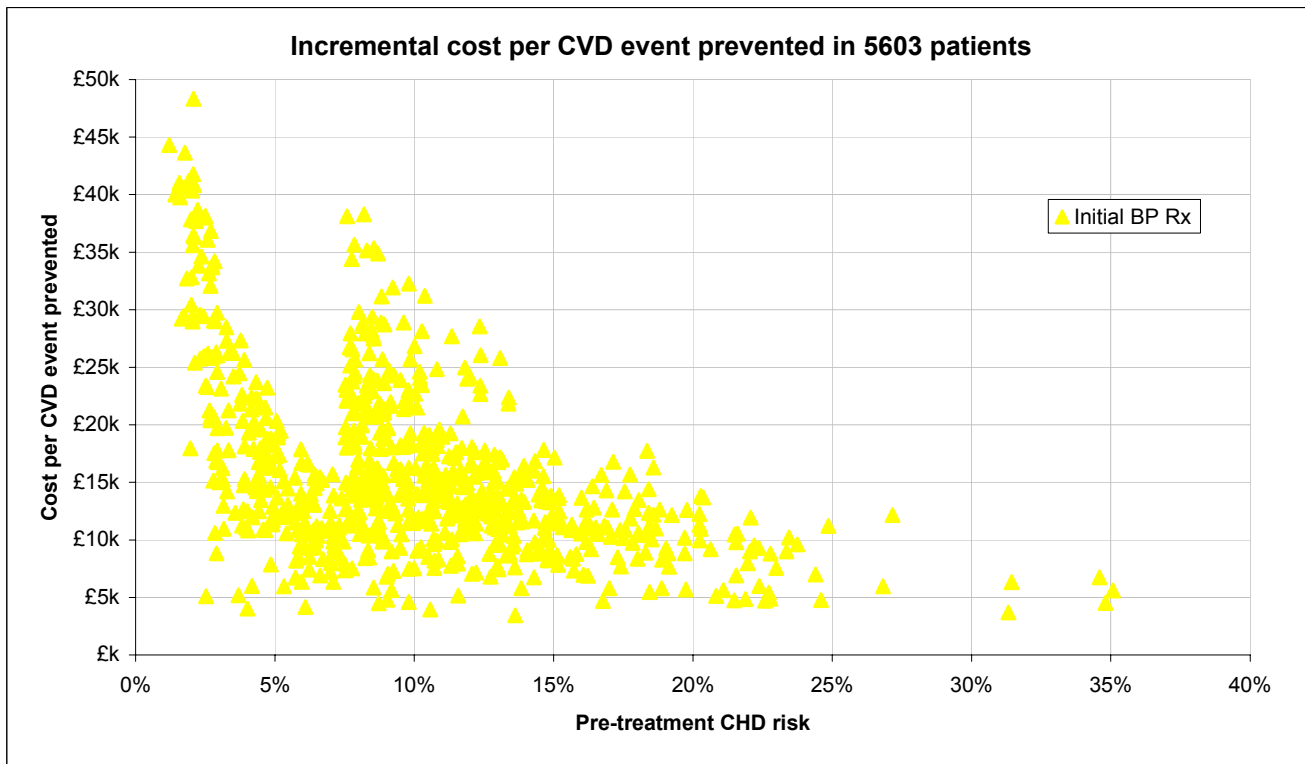
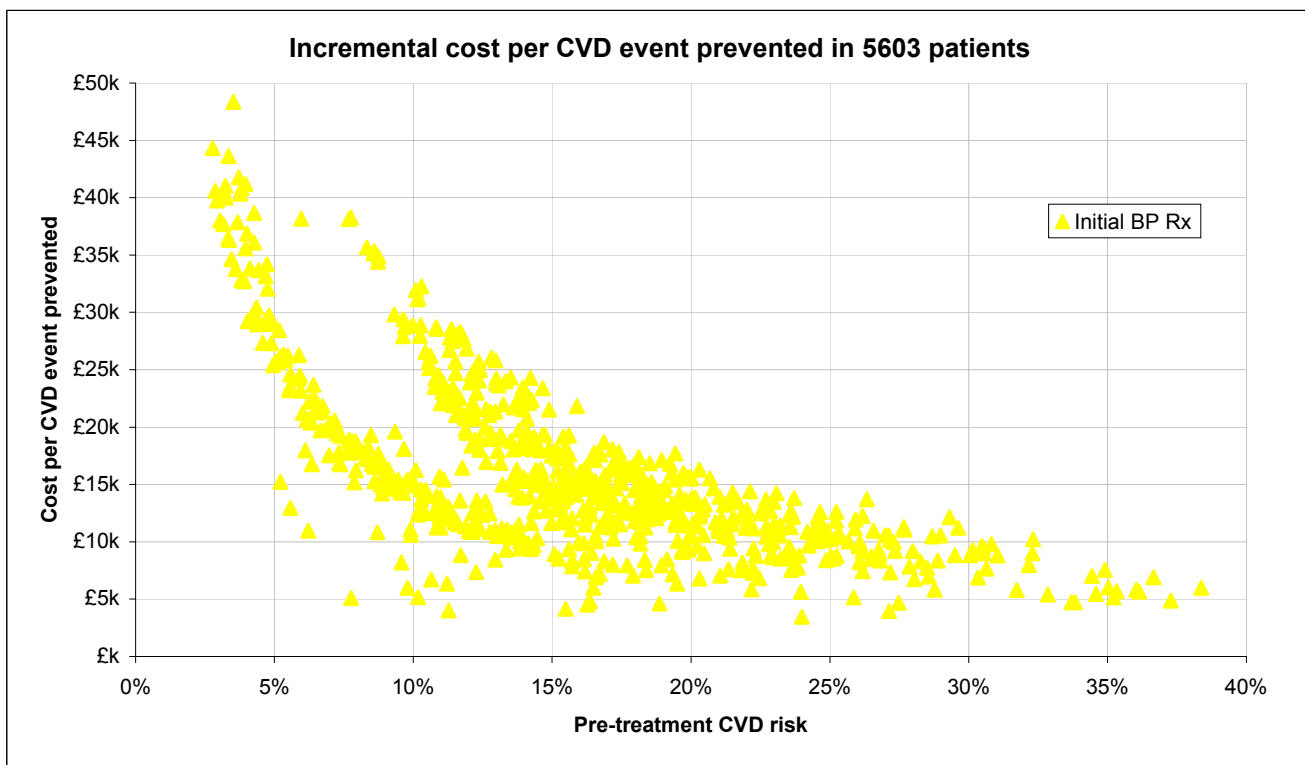
CHD and CVD risk are over five-years.

Figure 81: CVD risk and CHD risk and marginal cost-effectiveness of CVD prevention with a Mediterranean diet in a natural population



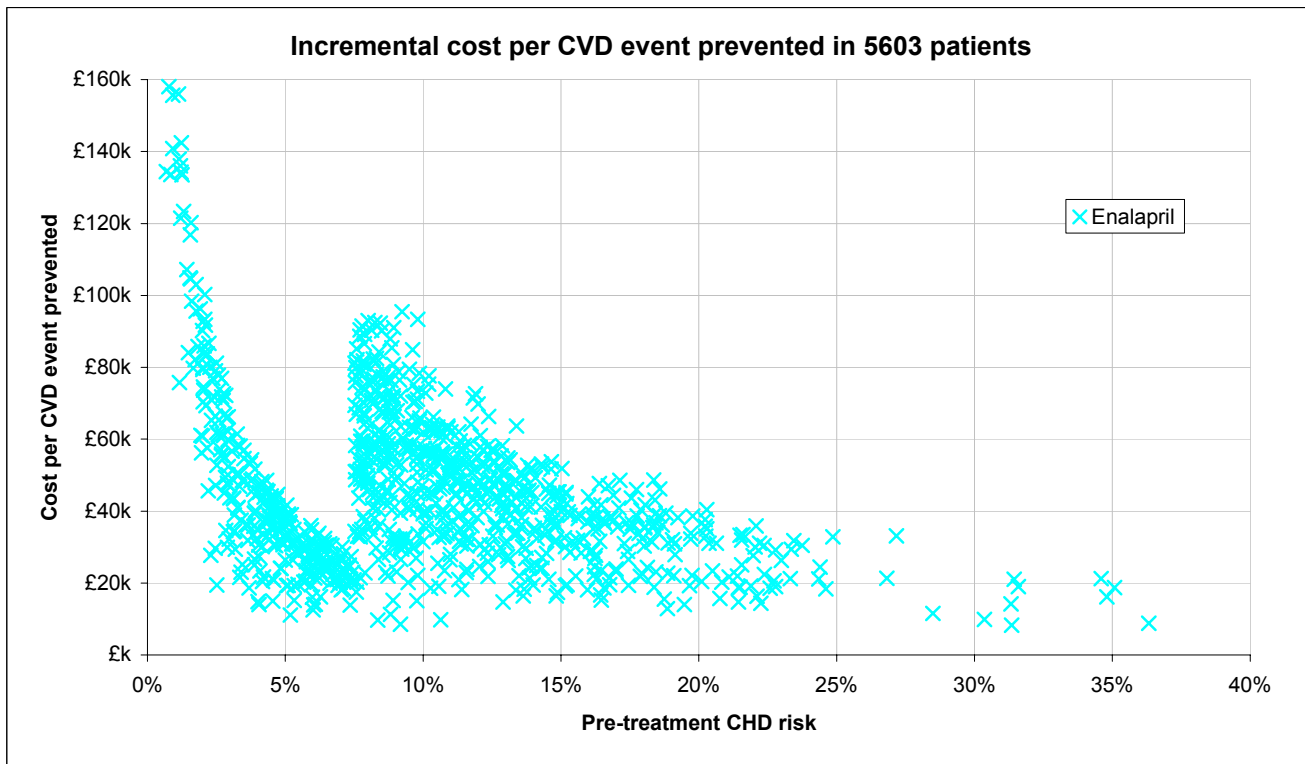
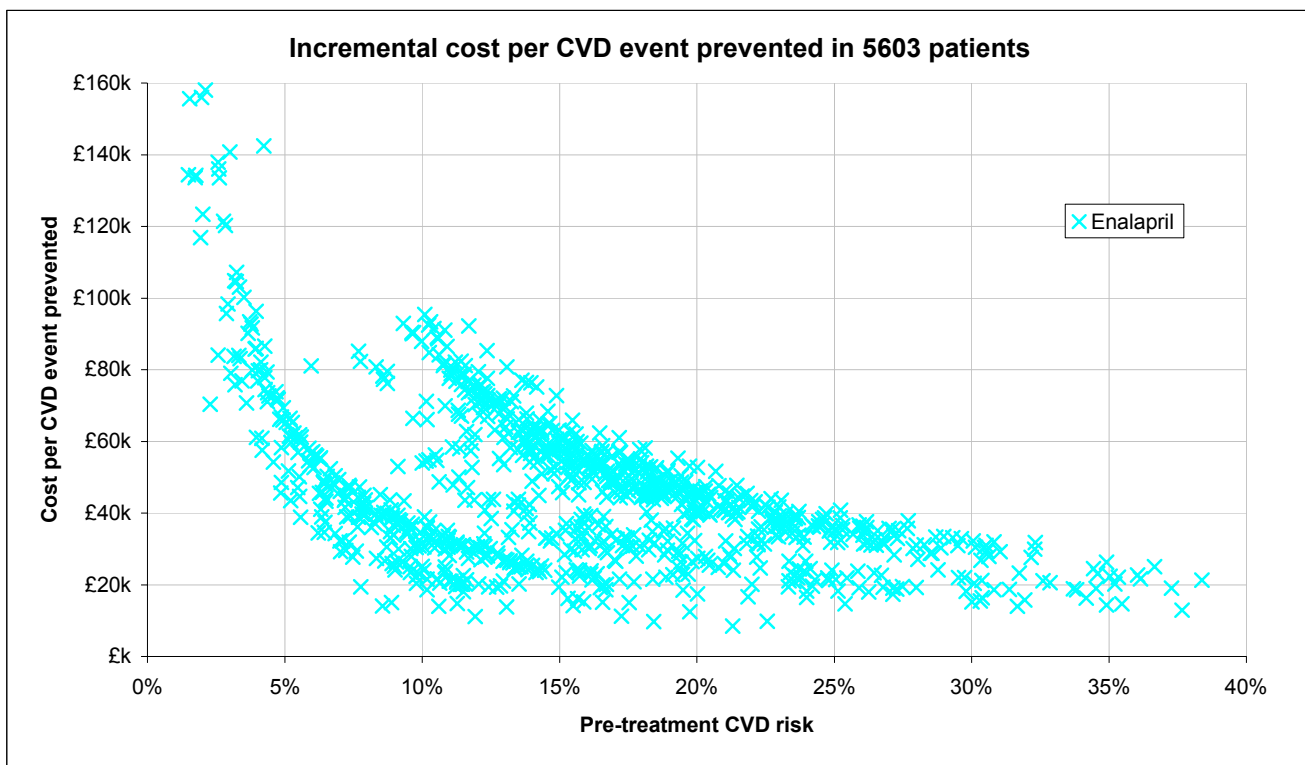
CHD and CVD risk are over five-years.

Figure 82: CVD risk and CHD risk and marginal cost-effectiveness of CVD prevention with initial antihypertensive treatment in a natural population



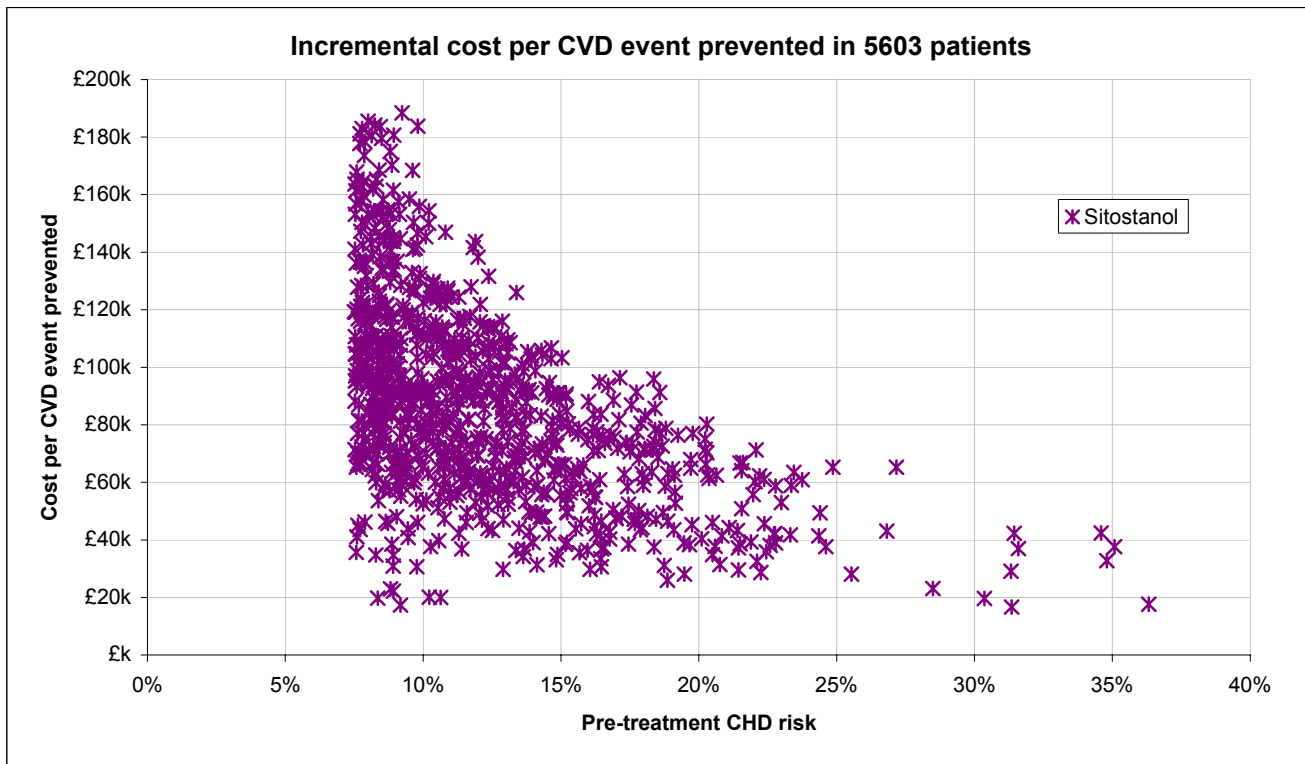
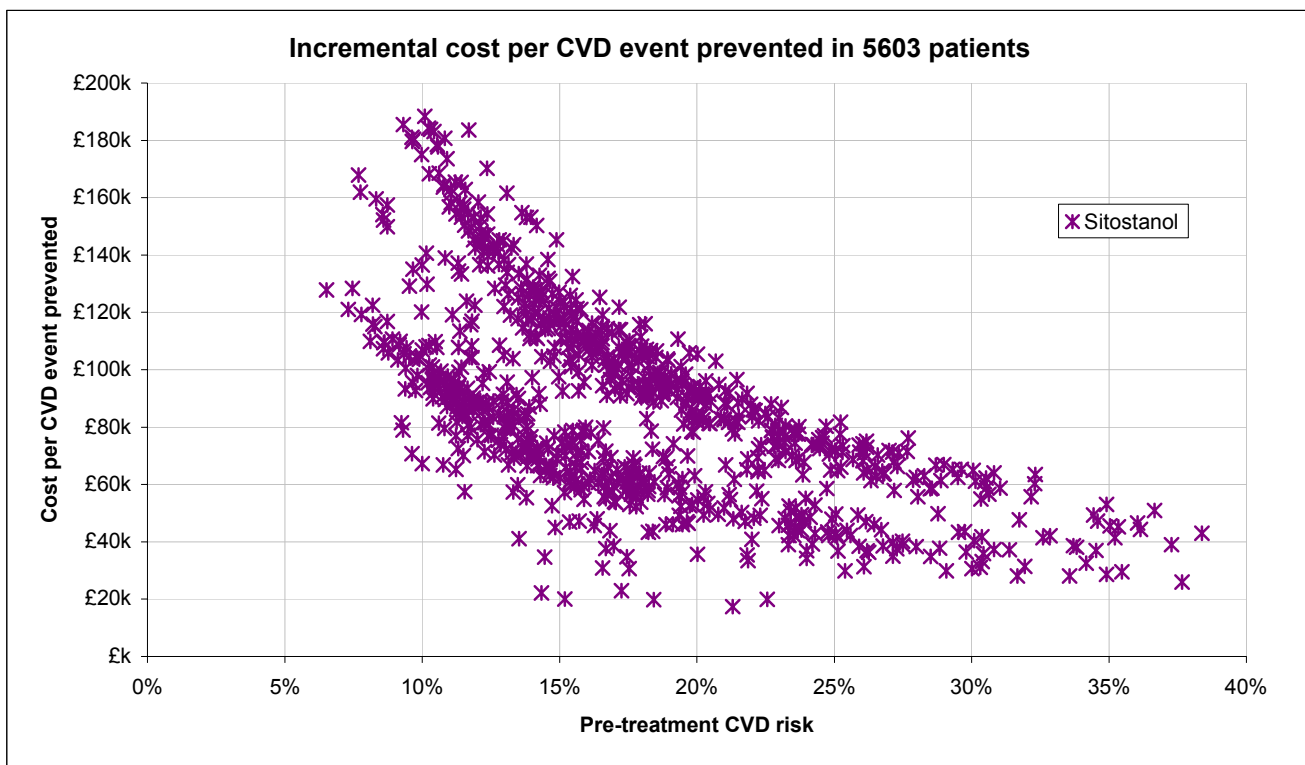
CHD and CVD risk are over five-years.

Figure 83: CVD risk and CHD risk and marginal cost-effectiveness of CVD prevention with intensive antihypertensive treatment (enalapril) in a natural population



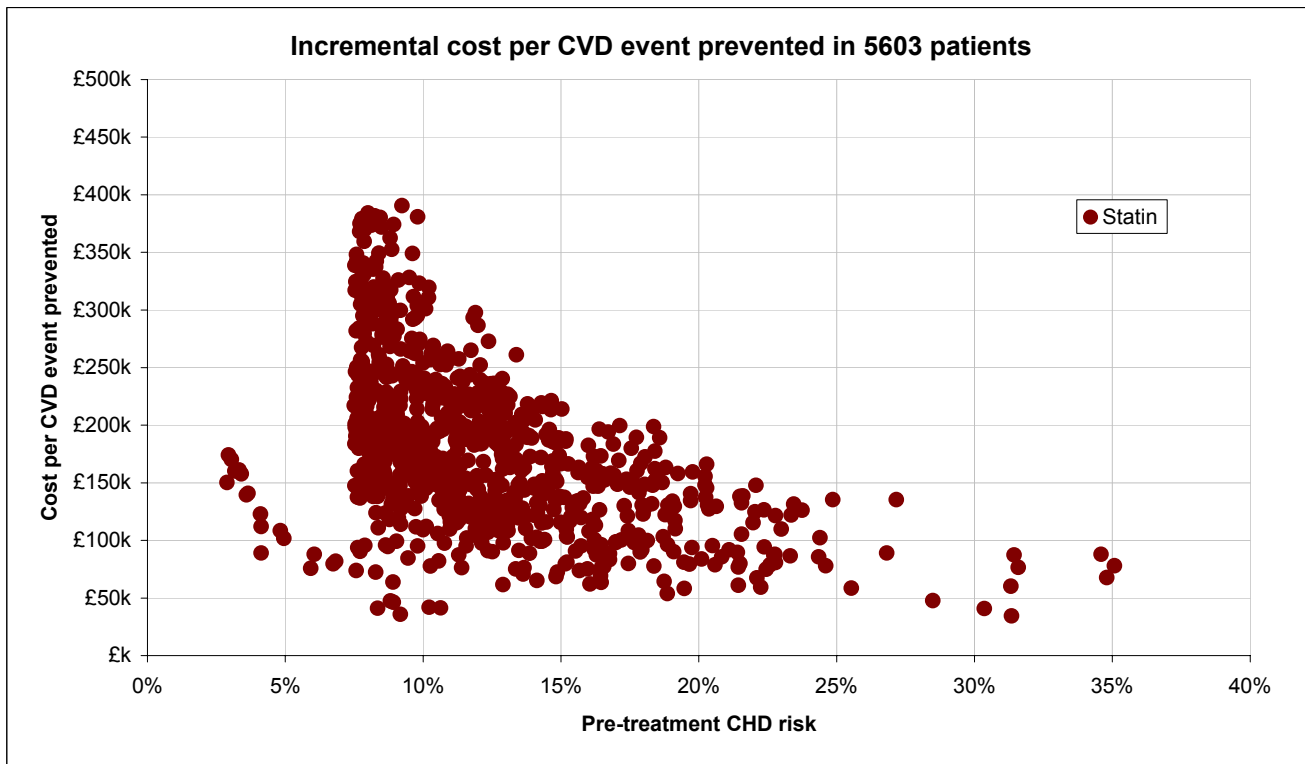
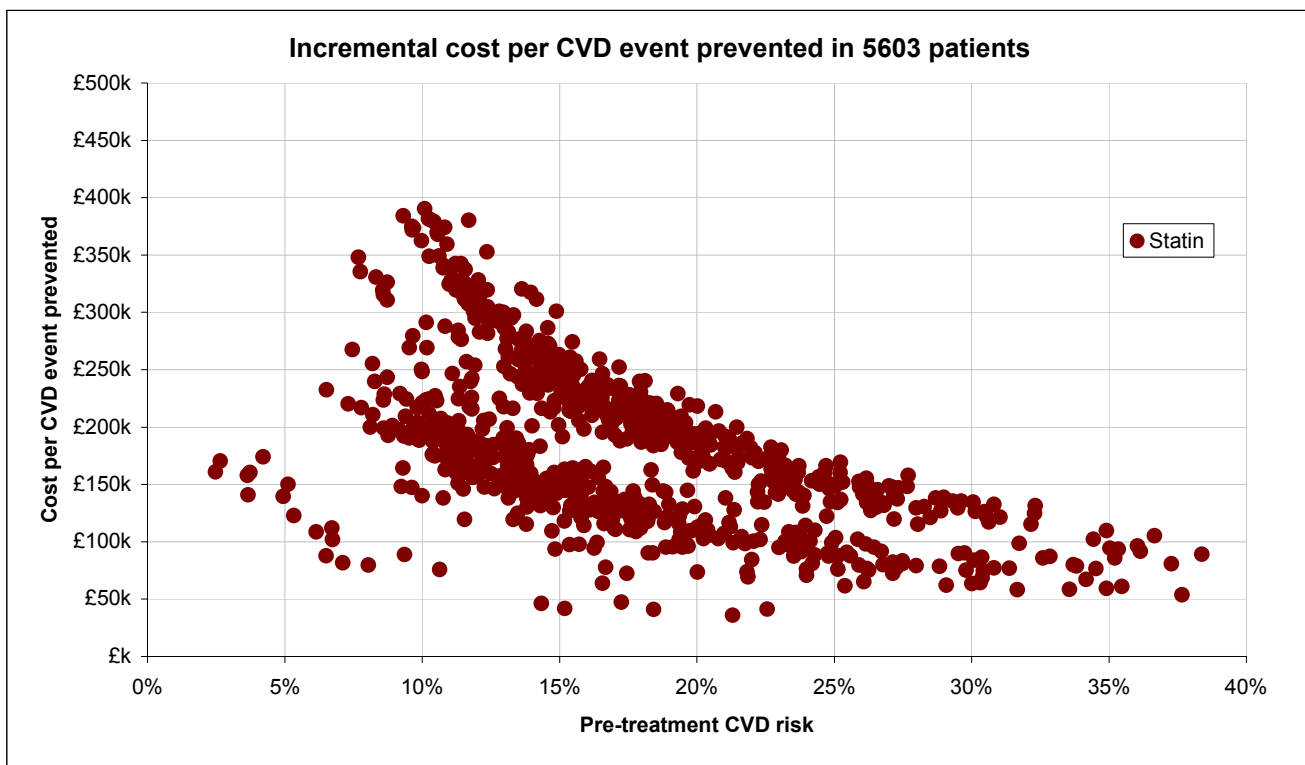
CHD and CVD risk are over five-years.

Figure 84: CVD risk and CHD risk and marginal cost-effectiveness of CVD prevention with sitostanol in a natural population



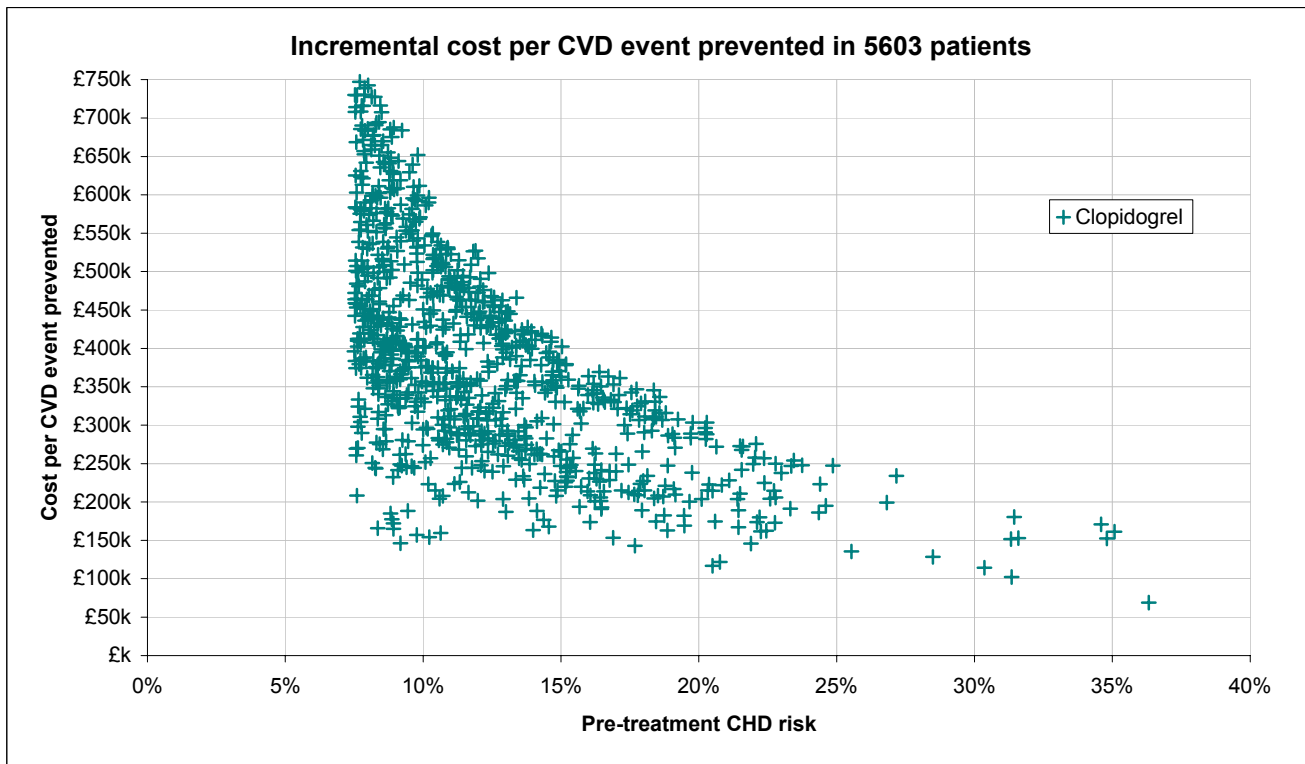
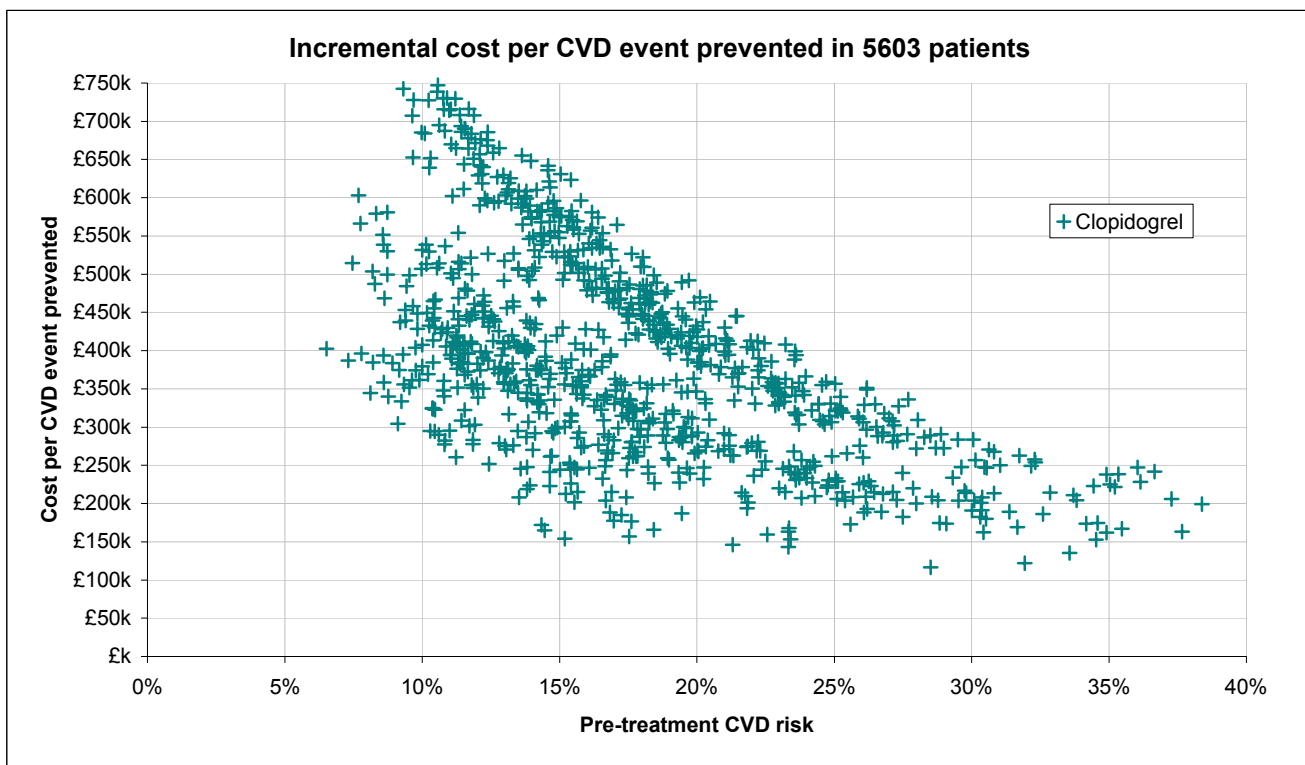
CHD and CVD risk are over five-years.

Figure 85: CVD risk and CHD risk and marginal cost-effectiveness of CVD prevention with simvastatin in a natural population



CHD and CVD risk are over five-years.

Figure 86: CVD risk and CHD risk and marginal cost-effectiveness of CVD prevention with clopidogrel in a natural population



CHD and CVD risk are over five-years.

Appendix C. Are data available for prior selection of patients in clinical practice?

Prioritisation of patients for CVD risk assessment depends on an estimation of individual patients' CVD risk. In this study it has been assumed that practices have access only to a minimum of data on each patient eligible for primary prevention of CVD– their age, sex and diabetic status. Are these data available in practice? A small study was carried out to assess the availability of CVD risk factor data and its ease of access in primary care.

Method

Data were obtained from a practice of 6100 serving a town in the conurbation of the West Midlands. The practice was asked to provide an anonymised list of all patients aged 35 to 74 eligible for primary prevention of CVD. In this practice this was taken to mean patients not included on the CVD register, without diabetes and not known to be receiving antihypertensive treatment.

For each patient the practice provided data from the practice database on age, sex, any blood pressure measurements that had been taken in the previous three years, any cholesterol measurements provided in the previous three years and smoking status. These data were downloaded into an Excel spreadsheet. The number of patients eligible for primary prevention was determined and the proportion of these for whom data were available on each risk factor was calculated.

Results

From the practice list of 6100, 2866 patients were identified as eligible for primary prevention of CVD. Age and gender were available for all of 2866 patients (100%). At least one blood pressure measurement was available for 2226 (78%) patients and 1267 (44%) had two or more blood pressure measurements. The percentages of patients with zero, one and more blood pressure measurements are shown in Figure 87. Either total cholesterol or total to HDL cholesterol ratio was recorded for 474 (17%) patients.

Smoking status was recorded for 1509 (53%) patients. However, it was stated by practice staff that it was usual to record smoking status if patients were smokers and not to record smoking status if they were non-smokers. To test this claim, the prevalence of smoking was calculated with the assumption that all patients without a

record of smoking status are non-smokers. This is compared to the prevalence of smoking in the Health Survey for England. The results are shown in Table 120. The prevalence of smoking recorded in the practice is similar to or higher than that the Health Survey for England. This is consistent with the view that the most smokers have been identified.

Figure 87: Number of BP measurements in the previous three years in a practice population of 2866 eligible for primary prevention of CVD

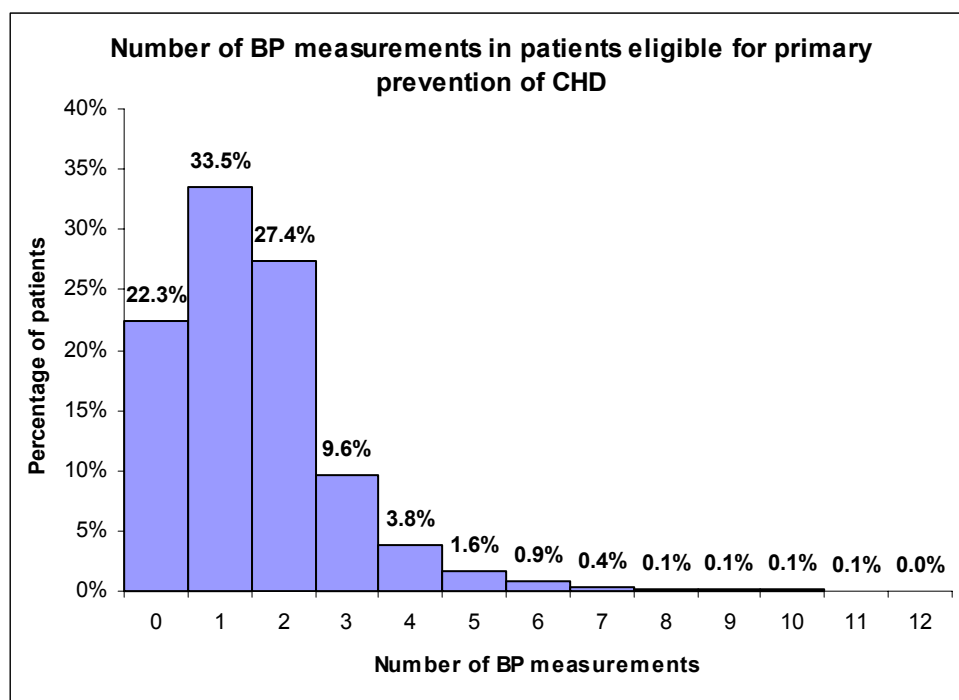


Table 120: Distribution of smokers in the practice

Age band	Smokers			
	Male		Female	
	Study practice	Health Survey for England	Study practice	Health Survey for England
35-44	38%	26%	22%	28%
45-54	35%	23%	19%	24%
55-64	35%	20%	21%	22%
65-74	27%	13%	18%	15%
All ages	35%	22%	20%	23%

Conclusions

This exercise in data extraction from a single practice indicates that age and sex are universally available for patients. In addition the majority of patients have a recorded blood pressure. Many patients have smoking histories and some have recorded cholesterol levels. A practice such as this can easily obtain sufficient data to calculate an estimate of CVD risk and prioritise patients for CVD prevention.

Appendix D. Age, sex and CVD risk

Distribution of CVD risk by age and sex

The proportion of persons in each 5% risk band was calculated from the original dataset of 5939 (5603 persons without CVD and 366 persons with CVD). These are presented by age and sex in Table 121 and Table 122. This analysis gives an indication of which patients are at high risk of CVD. A majority of men over 55 and the half of women over 65 are at over 10% five-year CVD risk. A majority of men over 45 and women over 55 are at over 5% five-year CVD risk. Policies that target persons at over 5% five-year CVD risk are fundamentally policies that target the middle-aged and elderly.

Table 121: Distribution of five-year CVD risk in the eligible population of 5603

Males	Five-year CVD risk band								
	<5%	5-9.9%	10-14.9%	15-19.9%	20-24.9%	25-29.9%	30-34.9%	35-39.9%	40%+
35-44	89.2%	9.2%	1.6%	-	-	-	-	-	-
45-54	46.2%	38.1%	11.7%	3.0%	0.4%	0.5%	0.1%	-	-
55-64	8.1%	37.9%	26.4%	15.8%	6.8%	2.8%	1.7%	-	0.6%
65-74	-	10.1%	27.2%	26.7%	17.8%	9.4%	4.9%	2.1%	1.9%
Females	Five-year CVD risk band								
	<5%	5-9.9%	10-14.9%	15-19.9%	20-24.9%	25-29.9%	30-34.9%	35-39.9%	40%+
35-44	98.0%	1.8%	0.2%	-	-	-	-	-	-
45-54	84.1%	13.2%	2.0%	0.3%	0.4%	-	-	-	-
55-64	45.8%	36.5%	12.5%	3.8%	0.8%	0.6%	-	-	-
65-74	10.4%	42.3%	23.5%	15.0%	5.7%	2.3%	0.6%	0.2%	-

Source: Health Survey for England 1998

Table 122: Distribution of five-year CHD risk in the eligible population of 5603

Males	Five-year CHD risk band								
	<5%	5-9.9%	10-14.9%	15-19.9%	20-24.9%	25-29.9%	30-34.9%	35-39.9%	40%+
35-44	93.2%	6.1%	0.7%	-	-	-	-	-	-
45-54	63.2%	30.0%	5.4%	0.9%	0.5%	-	-	-	-
55-64	26.2%	43.5%	20.3%	6.4%	2.8%	0.4%	0.2%	0.2%	-
65-74	4.4%	35.1%	35.1%	16.6%	6.6%	0.5%	1.4%	0.2%	-
Females	Five-year CHD risk band								
	<5%	5-9.9%	10-14.9%	15-19.9%	20-24.9%	25-29.9%	30-34.9%	35-39.9%	40%+
35-44	99.7%	0.3%	-	-	-	-	-	-	-
45-54	92.8%	6.3%	0.6%	0.2%	-	-	-	-	-
55-64	72.8%	23.0%	4.0%	0.3%	-	-	-	-	-
65-74	55.2%	34.2%	7.6%	3.0%	-	-	-	-	-

Source: Health Survey for England 1998

Average CVD risk by age and sex

The average CVD risk was estimated for patients in ten-year age sex bands, using all 5939 patients for whom complete risk factor information is available in the Health Survey for England. For persons with CVD, five-year risk of CVD is assumed to be

20% or the value given by the Framingham risk equation – whichever is larger. The results are shown in Table 123.

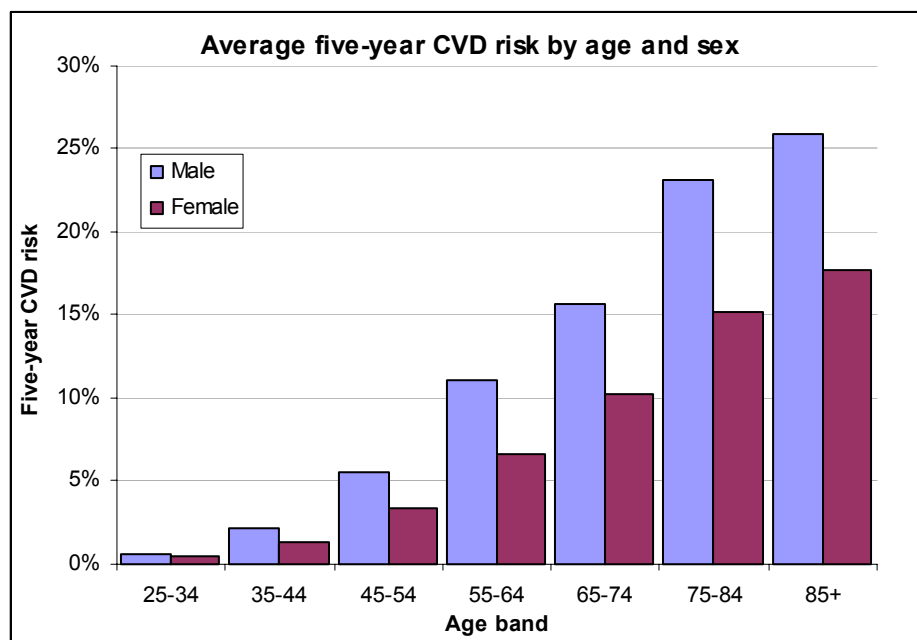
Table 123: Average five-year CVD risk of persons in each age-sex group

Age	Persons without CVD			All persons (with and without CVD)		
	Male	Female	All	Male	Female	All
25-34	0.6%	0.4%	0.5%	0.8%	0.6%	0.6%
35-44	2.1%	1.3%	1.7%	2.3%	1.5%	1.9%
45-54	5.5%	3.3%	4.4%	6.3%	3.7%	5.0%
55-64	11.1%	6.6%	8.6%	12.6%	7.5%	9.9%
65-74	15.6%	10.3%	12.6%	17.2%	12.0%	14.4%
75-84	23.2%	15.1%	18.3%	23.6%	16.6%	19.4%
85+	25.9%	17.7%	21.4%	25.5%	19.6%	21.9%

Source: Health Survey for England 1998

Age is clearly a strong predictor of risk of CVD. In persons without CVD, five-year risk of CVD in men each age band from 35 to 74 is approximately the same as the five-year risk of women ten years older. (Figure 88) It is also apparent that inclusion of persons with CVD makes little difference to the average CVD risk of persons in each age-sex band.

Figure 88: Average five-year CVD risk of persons without CVD in each age-sex group



Source: Health Survey for England 1998

Primary care

Resource implications and health benefits of primary prevention strategies for cardiovascular disease in people aged 30 to 74: mathematical modelling study

Tom Marshall, Andrew Rouse

Abstract

Objective To develop a model to determine resource costs and health benefits of implementing guidelines for the prevention of cardiovascular disease in primary care.

Design Modelling of data from six strategies for prevention of cardiovascular disease. Strategies incorporated two ways of identifying patients for assessment: traditional (assessment of all adults) and novel (preselection of patients for assessment using a prior estimate of their risk of cardiovascular disease). Three treatment strategies were modelled in conjunction with each identification strategy.

Setting England.

Subjects Patients aged 30 to 74 eligible for primary prevention strategies for cardiovascular disease who were selected from a hypothetical population of 2000.

Main outcome measures Resource costs of assessing eligible adults, providing treatment and follow up to those eligible, and number of cardiovascular events this should prevent.

Results Novel strategies prevented more cardiovascular disease, at lower cost, than traditional strategies. Some treatment strategies prevent more cardiovascular disease with fewer resources than others. The findings were robust across a range of different assumptions about workload.

Conclusion Preselecting patients for assessment makes better use of staff time than assessing all adults. Treating many patients with low cost drugs is more efficient than prescribing a few patients intensive antihypertensives and statins. Authors of guidelines should model workload implications and health benefits of following their recommendations.

Introduction

The UK government policy framework for the prevention of coronary heart disease places specific obligations on primary care services.¹ The framework endorses joint British recommendations on preventing coronary heart disease: primary care teams must assess patients' risk of cardiovascular disease every five years and treat eligible patients (box 1).² The recommendations do not consider or evaluate alternative methods of identifying patients for treatment. They require the

commitment of many hours of clinical staff time and considerable cost. Part of this commitment will be devoted to assessing patients who ultimately do not require treatment. The joint British recommendations do not quantify either the resource implications or the health benefits of this policy for the prevention of cardiovascular disease.

We describe a model for estimating the efficiency (total health service resources invested versus cardiovascular events prevented) of strategies for primary care based prevention of cardiovascular disease. The data for our model came from several sources (fig 1). We used our model to evaluate six strategies. Three strategies are based on the joint British recommendations: they assume all patients undergo clinical risk assessment and that those at highest risk are treated.²

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Box 1 Joint British recommendations for prevention of coronary heart disease in primary care

Assessment

- Assess cardiovascular risk of all patients five yearly

Criteria for antihypertensives

- Five year coronary heart disease risk >7.5% (equivalent to 10 year coronary heart disease risk >15%) and blood pressure >140 mm Hg systolic or >90 mm Hg diastolic
- Blood pressure >160 mm Hg systolic or >100 mm Hg diastolic (irrespective of coronary heart disease risk)

Criteria for cholesterol lowering treatment

- Five year coronary heart disease risk >7.5% (equivalent to 10 year coronary heart disease risk >15%) and total cholesterol concentration ≥ 5 mmol/l (equivalent to a total cholesterol to high density lipoprotein cholesterol ratio >3.5)

Criteria for aspirin treatment

- Age over 50 and five year coronary heart disease risk >7.5% (equivalent to 10 year coronary heart disease risk >15%)

Long term management of patients receiving drug treatment

- Review at least twice a year

Three alternative strategies are described. These prioritise patients for clinical risk assessment on the basis of a prior estimate of their risk of cardiovascular disease—only patients most likely to benefit from treatment would be invited for assessment.

Methods

The joint British recommendations require patients to undergo five yearly assessments for risk of cardiovascular disease. Therefore our model analysed resource implications and health benefits over a five year period. Resource implications were considered from the perspective of the health service. Health benefits were limited to an estimate of cardiovascular events prevented.

Hypothetical population

We studied a hypothetical population of 2000 patients: the number registered for each whole time equivalent general practitioner in England.³ Our model assumes patients aged 30 to 74 are eligible for primary prevention services.

We believe few practices consider clinical assessment in patients under 30, as modifiable high risk is uncommon and they are therefore unlikely to benefit.⁴ Patients with ischaemic vascular disease, those taking antihypertensives, and those over 75 are high priority groups. We have excluded them from our model as practices already assess and follow them up.

Cardiovascular risk estimation

The Framingham coronary heart disease risk equation predicts the occurrence of coronary events (myocardial infarction, new onset angina, or sudden cardiac death).⁵ It requires information on age, sex, blood pressure, ratio of total cholesterol to high density lipoprotein cholesterol, smoking history, history of diabetes, and whether there is electrocardiographic evidence of left ventricular hypertrophy. It has been validated in a range of populations.⁶ We used this risk equation to determine eligibility for treatment—reflecting the joint British recommendations—and to estimate the number of coronary events prevented.²

The Framingham cerebrovascular disease risk equation predicts the risk of stroke (cerebrovascular accident or transient ischaemic attack).⁷ We used it to estimate the number of strokes prevented.

The combined Framingham risk equation predicts the risk of all cardiovascular events (stroke, coronary

event, peripheral vascular disease, or heart failure). In some guidelines it is used to determine eligibility for treatment.⁸ A combined Framingham risk of 15% is about equivalent to a 10% risk of coronary heart disease. We used the combined Framingham risk equation to calculate prior risk estimates for the preselection strategies.

Distribution of cardiovascular risk factors and risk in eligible patients

Using data from the 1998 health survey of England, we estimated the distribution (in the English population) of systolic blood pressure and cholesterol concentration by age, sex, history of diabetes, and smoking history in individuals who neither had prior cardiovascular disease nor were receiving antihypertensives.⁹ Using these data and 1998 population estimates for England, we generated a hypothetical population whose distribution for age, sex, and risk factors reflected a typical general practitioner list.

Our typical general practitioner list had 939 patients, aged between 30 and 74, eligible for primary prevention services. We entered data on risk factors for cardiovascular disease in these patients into an Excel spreadsheet. For each we calculated the five year risk of all cardiovascular events, coronary heart disease events, and stroke using the Framingham risk equations. We thus modelled a list of patients eligible for inclusion in a programme for the prevention of cardiovascular disease.

Cardiovascular disease prevention strategies modelled

The joint British recommendations do not indicate how to prioritise assessed patients for treatment. In strategies JBR-1 (joint British recommendations-1), JBR-2, and JBR-3 all patients undergo five yearly assessments for clinical risk. Once assessed the general practitioner treats them in rank order of their risk of coronary heart disease: the total number of patients treated being determined by the total resources available.

In strategies RM-1 (Rouse Marshall-1), RM-2, and RM-3 (see box 2) a two stage assessment is proposed. Firstly, primary care teams make a prior estimate of each patient's total risk of cardiovascular disease, as follows. The teams have an electronic record of every patient's age and sex. They allocate each patient a default blood pressure and cholesterol concentration: the mean value for their age and sex (derived from the health survey of England). The teams determine each patient's diabetic status from electronic prescribing records. As non-smokers outnumber smokers in every age-sex group, they assume a default smoking status of non-smoking. The team then sets up an Excel spreadsheet incorporating the Framingham cardiovascular risk equation. Using the default values, it takes minutes on this spreadsheet to calculate a prior estimate of risk of cardiovascular disease for each patient in the entire practice. This is the best prior indication of their potential to benefit from treatment. It then takes seconds to rank patients by the prior estimate of their risk of cardiovascular disease. Secondly, the team identifies patients for full assessment of clinical risk in rank order. After clinical assessment most patients prioritised for assessment in this way will be found to be eli-

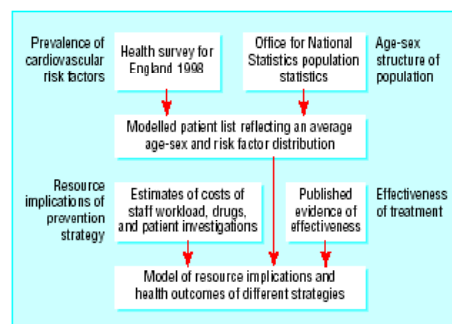


Fig 1 Data sources for model

Box 2 Cardiovascular disease prevention strategies modelled

Identification and prioritisation

Strategies JBR-1, JBR-2, and JBR-3

- Assess cardiovascular risk factors in eligible patients
- Calculate cardiovascular risk in all eligible patients
- Prioritise patients by cardiovascular risk
- Treat highest priority patients who meet criteria in table 1

Strategies RM-1, RM-2, and RM-3

- Calculate a prior estimate of cardiovascular risk using age, sex, diabetes status, and default values for other risk factors
- Prioritise patients by prior cardiovascular risk estimate
- Assess cardiovascular risk factors in highest priority patients
- Treat assessed patients who meet criteria in table 1

Treatment

All strategies:

- Aspirin 150 mg as antiplatelet agent
- Hydrochlorothiazide 25 mg and atenolol 50 mg for initial blood pressure lowering
- In addition JBR-1, JBR-2, RM-1, and RM-2 require enalapril 20 mg for intensive blood pressure lowering and JBR-1 and RM-1 require simvastatin 10 mg

eligible for treatment. Box 2 shows the six identification and treatment strategies.

Resource implications

We assumed that all clinical tasks are carried out by practice nurses. The total health service cost of providing an hour of practice nurse clinic time is £28.¹⁰ Costs of blood tests were derived from the Pathology Services costings.¹¹ Drug costs were obtained from the *British National Formulary*.¹² Dispensing costs were calculated at 87.4p for each prescribed item on the assumption that four prescriptions are issued each year.¹³ Where appropriate, costs have been discounted at 6% a year.

Assessing cardiovascular risk

To estimate the risk of cardiovascular disease with the Framingham risk equation, the clinician must measure each patient's blood pressure and cholesterol concentration and inquire about smoking, diabetes, and atherosclerotic disease. The clinician then calculates the risk of cardiovascular disease (using computer software or risk tables) and discusses the implications of this with the patient. The joint British recommendations give precise directions on measuring blood pressure. The clinician should measure blood pressure with the patient seated on at least three separate occasions, with the patient at rest for five minutes.² Each measurement therefore takes at least five minutes. Accurate cholesterol estimation requires blood specimens to be drawn on at least two separate occasions²; a process requiring at least two and a half minutes. Therefore, even ignoring the time taken to make inquiries, to calculate the risk of cardiovascular disease, and to discuss the implications of this with the patient, each risk

assessment takes a minimum of 20 minutes of clinical staff time.

Treatment and follow up

Ongoing management of patients receiving treatment requires at least two follow up clinic appointments a year, totalling 20 minutes of clinical staff time.² Patients receiving thiazide diuretics require an annual estimation of electrolyte and uric acid, and patients receiving statins require annual liver function tests.

Health benefits

Calculating benefits of treatment

We calculated the benefits of treatment as the number of cardiovascular events prevented. As patients may have two cardiovascular events, this differs from the number of patients having a cardiovascular event. To reflect the joint British recommendations, treatment decisions were determined by the risk of coronary heart disease. However, since treatments prevent both strokes and heart disease—both important health benefits—we included both in our model. Antihypertensives reduce the risk of stroke by more than they reduce the risk of coronary heart disease. In some individuals (patients with high cholesterol concentrations and low blood pressures) the risk of coronary heart disease is high and the risk of stroke low, whereas in others it is the reverse. An average estimate of the effect of treatment would therefore overestimate the number of events prevented in those at relatively high risk of coronary heart disease and underestimate the number of events prevented in those at relatively high risk of stroke. We therefore estimated the joint effects of treatment on reducing the risk of stroke and the risk of coronary heart disease: the sum of two separate effects.

For each patient, the absolute risk reduction is the product of the initial risk and the risk reduction with treatment. Table 1 summarises the assumed risk reductions afforded by treatment.

Eligibility for and benefits of treatment

The criteria for treatment eligibility followed the joint British recommendations as closely as possible and were the same in all six strategies (see box 1).

Aspirin reduces the risk of cardiovascular disease by about 20%, but increases major bleeding events by 0.1% annually (0.5% over five years).¹⁴⁻¹⁷ Our model offsets the absolute reduction in cardiovascular risk by 0.5% to take account of the increased risk of bleeding.

Evidence from randomised controlled trials suggests treatment with one to three antihypertensives (usually including thiazides and β blockers) reduces the risk of coronary heart disease and stroke.¹⁸ Our model assumes patients receive hydrochlorothiazide 25 mg and atenolol 50 mg. Table 1 shows the assumed effectiveness.

Under strategies JBR-1, JBR-2, RM-1, and RM-2, patients eligible for antihypertensives are also given more intensive treatment. Evidence suggests this may further reduce the risk of coronary heart disease and stroke.¹⁹ Our model assumes patients require enalapril 20 mg to achieve the additional effect shown in table 1.

Under strategies JBR-1 and RM-1, eligible patients are treated with statins—we assumed eligible patients receive simvastatin 10 mg. Statins reduce the risk of

Table 1 Treatment criteria for risk of cardiovascular or coronary heart disease and risk reductions with treatment

Treatment and criteria	Absolute reduction in 5 year risk of stroke	Absolute reduction in 5 year risk of coronary heart disease	Other major disease events*
Aspirin*			
Age >50 and 5 year coronary risk >7.5%	20%×initial risk	20%×initial risk	Increase by 0.5%
Thiazide and β blocker†			
Systolic blood pressure ≥160 mm Hg or systolic blood pressure ≥140 mm Hg and 5 year coronary risk >7.5%	36%×initial risk	17%×initial risk	No effect
Angiotensin converting enzyme inhibitor‡			
Systolic blood pressure ≥160 mm Hg or systolic blood pressure ≥140 mm Hg and 5 year coronary risk >7.5%	19%×initial risk	20%×initial risk	No effect
Cholesterol lowering treatment			
Total cholesterol to high density lipoprotein cholesterol ratio ≥3.5 and 5 year cardiovascular risk >7.5%	29%×initial risk	30%×initial risk	No effect

*Absolute benefits allow for increase in five year haemorrhage rate of 0.5%.
 †Initial blood pressure lowering.
 ‡Intensive blood pressure lowering.

cardiovascular disease by 30% and the risk of stroke by 29%.^{20–22}

Results

Cost effectiveness

We illustrate cost effectiveness in two ways. Firstly, we show the number of cardiovascular events that can be prevented under each strategy by using increasing resources. This illustrates technical efficiency: the maximum health benefit achievable with these resources. However, it is more plausible that primary care teams first allocate staff time to devote to this activity and then try to maximise efficiency within the allocated staff time. We illustrate this by assuming the primary care team allocates one, two, or three clinics a month to the prevention of cardiovascular disease and by comparing the costs and health outcomes of the six strategies. This is equivalent to 180 hours of clinical time (180=3 hours×12 months×5 years).

Technical efficiency: maximising health benefits within total resources

For any given allocation of resources to the primary prevention of cardiovascular disease, more cardiovascular events can be prevented under RM strategies than under the equivalent JBR strategies. A primary care team can prevent 13.5 events for £49 960 under strategy RM-2 or 13.5 events for £15 110 under RM-3. The most efficient strategy for a primary care team with this budget is therefore RM-3. A primary care team can prevent 16.7 events for £119 806 under strategy RM-1 or 13.5 events for £73 716 under RM-2. The most efficient strategy for a primary care team with this budget is therefore RM-2. For a primary care team with over £119 806 the most efficient strategy is RM-1. Figure 2 shows the maximum number of events prevented with increasing amounts of resources under each strategy.

Maximising efficiency within available clinical staff time

For practices allocating one, two, or three clinics a month to the primary prevention of cardiovascular disease, RM strategies dominate JBR strategies (fig 3). At one clinic a month there is not sufficient clinical time to assess all eligible adults, JBR strategies therefore cannot be implemented. Strategy RM-3 prevented 9.1 cardiovascular events at a cost of £863 for

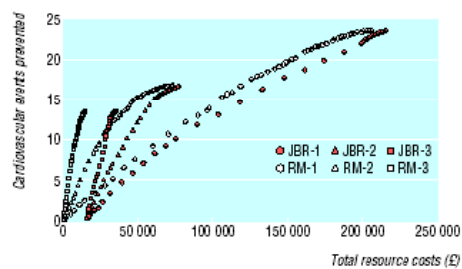


Fig 2 Total resource costs (assessment, follow up, drugs, and investigations) and health benefits of six strategies for primary prevention of cardiovascular disease

each event prevented. RM-2 prevented 1.9 more events at an incremental cost of £10 518 for each event prevented. RM-1 prevented 4.6 more events than RM-2 at an incremental cost of £17 808 for each event prevented.

Compared with one clinic a month, allocating two clinics a month to RM-3 prevented 3.8 more events at a cost of £1445 for each event prevented. Allocating two clinics a month to RM-2 prevented a further 3.0 events at an incremental cost of £14 025 for each event prevented. Two clinics a month following strategy RM-1 prevented a further 6.3 cardiovascular events at an incremental cost of £19 843 for each event prevented (table 2).

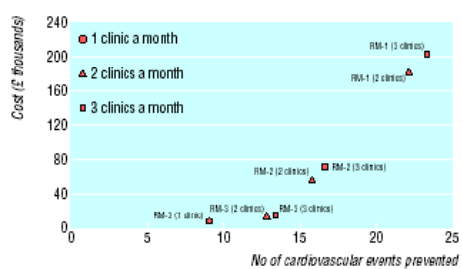


Fig 3 Resource costs and effectiveness of six strategies for prevention of cardiovascular disease in practice allocating one, two, and three clinics a month (only non-dominated strategies shown)

Table 2 Incremental analysis of strategies for prevention of cardiovascular disease in primary care

Strategy	Cost (£)*
One clinic a month:	
RM-3 (1 clinic) v no programme	863
RM-2 (1 clinic) v RM-3 (1 clinic)	10 518
RM-1 (1 clinic) v RM-2 (1 clinic)	17 808
Two clinics a month:	
RM-3 (1 clinic) v no programme	863
RM-3 (2 clinics) v RM-3 (1 clinic)	1 445
RM-2 (2 clinics) v RM-3 (2 clinics)	14 025
RM-1 (2 clinics) v RM-2 (2 clinics)	19 843
Three clinics a month:	
RM-3 (3 clinics) v RM-3 (2 clinics)	3 073
RM-2 (2 clinics) v RM-3 (3 clinics)	16 619
RM-2 (3 clinics) v RM-2 (2 clinics)	19 178
RM-1 (2 clinics) v RM-2 (3 clinics)	19 945

*£1-£1.6; €1.6.

Sensitivity analysis

Prior prioritisation of patients by estimated cardiovascular risk

Our model suggests that more cardiovascular disease could be prevented with the same health service resources by assessing only patients preselected on the basis of a prior estimate of their risk of cardiovascular disease. Even if we assessed only patients over 50, taking only 15 minutes for each patient assessment but requiring one hour a year for follow up of each patient, our model suggests RM strategies prevent more cardiovascular disease than JBR strategies.

Prior knowledge of patients' blood pressures

Primary care teams with an electronic record of their patients' blood pressures could conceivably reduce the time for patient assessment to five minutes, favouring the JBR strategies. However, knowledge of patients' blood pressures also permits a more accurate prior estimate of the risk of cardiovascular disease. Our model shows that strategy RM-3 remains the most efficient for practices with records of their patients' blood pressures.

Effects of not prescribing statins or angiotensin converting enzyme inhibitors

The discounted costs of five years' treatment with simvastatin 10 mg and enalapril 20 mg were £1065 and £385, respectively. The discounted cost of assessing, treating (aspirin, atenolol, and hydrochlorothiazide), and following up the next patient identified according to the RM strategies was £231. The opportunity cost of treating a known patient with simvastatin was not identifying and treating five new patients with aspirin, hydrochlorothiazide, and atenolol. In the case of enalapril, it is two new patients. Only a statin or third line antihypertensive costing under £231 for five years' treatment was likely to alter this finding.

Discussion

Robustness of model

Our model estimated the maximum possible health benefits and minimum resource implications of six strategies for the prevention of cardiovascular and coronary heart disease in primary care. Nevertheless this

did not affect the relative efficiencies of different strategies. We assumed that all eligible patients accepted and complied fully with treatment. In reality some decline assessment; some judge small reductions in absolute risk insufficient to justify treatment, and some do not comply with prescribed treatment. Reducing the rest period before measurement of blood pressure to under four minutes risks significant overestimation.²³ Blood tests take longer than 2.5 minutes and, given the biological variability of cholesterol concentrations, accurate estimation takes more than two measurements.²⁴ Calculating the risks of cardiovascular disease and counselling patients takes time. Patient assessment therefore probably takes longer than 20 minutes. Follow up may also cost more than we estimated. Patients often visit their general practitioner more frequently than twice yearly, and further investigations may be needed. The cost of staff time may be underestimated, since medical time costs more than nursing time.

Our model assumed no patients leave or join the practice over five years. An annual turnover of 10% in the practice population increases the number of five yearly assessments by 41%. In contrast, periodically recalculating prior risk estimates and re-ranking patients takes only minutes, and the primary care team could fill clinic time left by patient departures by inviting the next highest ranked patients for assessment. The turnover of practice populations therefore strongly favours the RM strategies.

Our model assumed that primary care teams following the joint British recommendations do prioritise patients for treatment on the basis of their risk of coronary heart disease. This means that they must first assess all patients' risk and only then select patients at highest risk for treatment. In fact, patients whose risks are above a threshold are likely to be treated as they are identified. A practice list may have 29 eligible patients whose five year risk of coronary heart disease exceeds 15% but only time to follow up 20. The first 20 identified are unlikely to be the 20 patients at highest risk. Our model therefore exaggerates the effectiveness of the joint British recommendations. The RM strategies make no such assumption.

Our model used the lowest cost drug for each category of treatment. Non-generic enalapril costs twice as much as generic enalapril. Simvastatin was costed at 10 mg a day, whereas higher doses are usual.²⁵ Compared with clinical practice, our model therefore exaggerated the cost effectiveness of strategies using simvastatin and enalapril.

Our model assumed treatment effects were multiplicative and that additional benefits accrued from more intensive blood pressure lowering. In general these assumptions are in line with current guidelines for the prevention of cardiovascular disease. However our estimate of the additional benefits of intensive blood pressure lowering comes from studies comparing less intensive treatment with more intensive treatment.¹⁹ Our estimate of the benefits of initial blood pressure lowering comes from studies of all blood pressure lowering.¹⁸ We have probably exaggerated the benefits of intensive blood pressure lowering.

What is already known on this topic

It is possible to estimate patients' risk of cardiovascular disease and their probability of benefiting from treatment

There are data on the distribution of cardiovascular risk factors in the population

What this study adds

A model estimated the efficiency of six strategies for primary prevention of cardiovascular disease: three strategies followed guidelines and three prioritised patients for assessment on the basis of a prior estimate of cardiovascular risk

Strategies that prioritise patients for risk assessment may reduce staff time to the extent that more patients can be treated and more disease prevented within available resources

Statins and angiotensin converting enzyme inhibitors cost more than identifying and treating new patients, so strategies avoiding these may allow more disease to be prevented within available resources

Implications of model for treatment recommendations

Our model raises questions about current treatment recommendations in the context of a population based programme for the prevention of cardiovascular disease. Recent research confirms statins are effective irrespective of initial cholesterol concentrations, across a wide range of risks.²⁰ Our model showed that they are not cost effective even for patients meeting current criteria. More intensive blood pressure lowering may reduce risk but does not justify the additional cost. This casts doubt on the importance of achieving blood pressure targets in a publicly financed, population based programme for the prevention of cardiovascular disease. Aspirin is currently recommended only for patients whose risk of coronary heart disease over five years exceeds 15%.² Our model suggests it may be cost effective for patients at much lower risk levels.

Conclusions

It is possible to calculate both the resource implications and the potential health benefits resulting from implementing guidelines for the prevention of cardiovascular disease. This obliges the authors of guidelines to be explicit about the assumptions they make about resource implications and effectiveness. We recommend that authors of future guidelines should make explicit statements about the resource implications, health benefits, and efficiency of implementation strategies. Our model suggests that the population benefits of following the joint British recommendations for the prevention of cardiovascular disease are modest and that the resource implications are substantial. Furthermore, the efficiency of prevention of cardiovascular disease in primary care could be greatly enhanced by two innovations: prioritising patients for assessment on the basis of a prior estimate of their

cardiovascular risk and avoiding costly drugs such as simvastatin and enalapril.

Contributors: AR and TM constructed the model, carried out the analysis, devised the strategy for preselecting patients by a prior estimate of their cardiovascular risk, and wrote the paper. TM will act as guarantor for the paper.

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Coronary heart disease prevention: insights from modelling incremental cost effectiveness

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Abstract

Objective To determine which treatments for preventing coronary heart disease should be offered to which patients by assessing their incremental cost effectiveness.

Design Modelling study

Data sources Cost estimates (for NHS) and estimates of effectiveness obtained for aspirin, antihypertensive drugs, statins and clopidogrel.

Data synthesis Treatment effects were assumed to be independent, and cost per coronary event prevented was calculated for treatments individually and in combination across patients at a range of coronary risks.

Results The most cost effective preventive treatments are aspirin, initial antihypertensive treatment (bendrofluazide and atenolol), and intensive antihypertensive treatment (bendrofluazide, atenolol and enalapril), whereas simvastatin and clopidogrel are the least cost effective (cost per coronary event prevented in a patient at 10% coronary risk over five years is £3500 for aspirin, £12 500 for initial antihypertensives, £18 300 for intensive antihypertensives, £60 000 for clopidogrel, and £61 400 for simvastatin). Aspirin in a patient at 5% five year coronary risk costs less than a fifth as much per event prevented (£7900) as simvastatin in a patient at 30% five year risk (£40 800).

Discussion A cost effective prevention strategy would offer aspirin and initial antihypertensive treatment to all patients at greater than 7.5% five year coronary risk before offering statins or clopidogrel to patients at greater than 15% five year coronary risk. Incremental cost effectiveness analysis of treatments produces robust, practical cost effectiveness rankings that can be used to inform treatment guidelines.

Introduction

Coronary heart disease is a major cause of morbidity and mortality, and its prevention has assumed increasing importance in UK health policy.¹ Several treatments reduce risk of coronary disease, the absolute benefits of treatment are proportional to pretreatment risk, and individual patients may be eligible for more than one treatment. Moreover, it is argued that treatments for lowering blood pressure and cholesterol are equally effective whether or not blood pressure or cholesterol levels exceed arbitrary thresholds.² This means that virtually all patients might benefit from risk lowering treatments.

A previous analysis explored rational identification strategies for coronary heart disease prevention in primary care, ranking patients by their likelihood of benefiting from treatment.³ Given that health service resources are finite, a

rational approach to treatment would offer patients treatments in order of their expected cost effectiveness. This requires knowledge of the incremental benefits of risk lowering treatments in relation to their incremental costs. Incremental cost effectiveness analysis provides a means of ranking treatments by calculating the incremental changes in both costs and benefits. Although widely advocated, it has seldom been used outside the evaluation of screening programmes. This paper presents an incremental cost effectiveness analysis of risk lowering treatments in patients at varying levels of risk. The treatments analysed are aspirin, initial antihypertensive treatment, intensive antihypertensive treatment, a statin, and clopidogrel.

Methods

Costs

Costs are considered from the perspective of the health service and are discounted at 6% per year.⁴ There are two main components to the costs of long term treatment—follow up costs and prescribing costs.

Follow up costs are based on two clinic appointments (of 15 minutes each) a year with a practice nurse. The total health service cost of a practice nurse clinic is £31 an hour.⁵ Patients taking thiazide diuretics require annual measurement of serum electrolytes and uric acid. Patients taking statins require annual measurement of serum lipid concentrations and liver function tests. I derived costs of blood tests from local standard costs of pathology services compiled by the London School of Hygiene and Tropical Medicine in 1996 (personal communication, Rhemold Gruen) and adjusted for annual price inflation of 6%.

Prescribing costs include drug and dispensing costs. I obtained drug costs from the *British National Formulary*⁶ and calculated dispensing costs at 87.4 pence per prescribed item on the assumption that four prescriptions are issued a year.⁷ Initial antihypertensive treatment is with bendrofluazide (bendroflumethiazide) 2.5 mg and atenolol 50 mg; further antihypertensive treatment adds enalapril 20 mg to these treatments. Cholesterol lowering is with simvastatin 40 mg. Clopidogrel is given at a dose of 75 mg daily.

Effectiveness

I calculated benefits of treatment as major coronary events (myocardial infarctions, new cases of angina, and cardiac deaths) prevented over five years, with the benefits discounted at 1.5% per annum in keeping with current guidelines from the National Institute for Clinical Excellence.⁴

In the base case analysis, I calculated cost effectiveness for a patient whose pretreatment five year coronary risk is 10%.⁸ This

is the coronary risk of a non-diabetic, non-smoking man aged 62 with blood pressure of 160/98 mm Hg, total serum cholesterol concentration of 6.5 mmol/l, and high density lipoprotein cholesterol concentration of 1.3 mmol/l. Under current guidelines he is eligible for antihypertensive treatment, a statin, and aspirin.⁹

For each intervention, I derived relative risk of coronary heart disease from a recent meta-analysis. The relative risk of coronary events for patients taking aspirin is 0.72 (95% confidence interval 0.60 to 0.87).¹⁰ Aspirin also increases in incidence of major bleeding by 0.3% (0.2% to 0.4%) over five years of treatment.¹⁰ To take account of this, I offset the absolute reduction in coronary risk over five years by 0.3%, thus giving major bleeding events equal weight to coronary events. Compared with aspirin, the relative risk of a coronary event while taking clopidogrel is 0.88 (0.76 to 1.01).¹¹ Empirical studies suggest that an indirect estimate of the effects of clopidogrel compared with placebo should be accurate provided that the population groups in studies are similar.¹² Compared with placebo, the relative risk of a coronary event with clopidogrel is therefore 0.63 (0.45 to 0.82) ($0.63 = 0.72 \times 0.88$).

Compared with placebo, the relative risk of a coronary event with antihypertensive treatment is 0.83 (0.72 to 0.91).¹³ Compared with initial antihypertensive treatment, the relative risk of a coronary event with intensive antihypertensive treatment is 0.81 (0.67 to 0.98).¹⁴ The relative risk of intensive antihypertensive treatment in comparison with placebo is therefore 0.67 (estimated 95% confidence interval 0.49 to 0.85). The relative risk of a coronary event with a statin is 0.69 (0.64 to 0.74).¹⁵

In clinical trials the relative risk of coronary events with preventive treatments is similar in patients taking additional treatments and in those who are not.¹⁶ This supports the view that treatment effects are independent.¹⁷ This view is also biologically plausible, since treatments act through different mechanisms. If treatment effects are independent the relative risk with two or more treatments is the product of the relative risk on each treatment. For example, the relative risk of a coronary event with aspirin is 0.72, with a statin is 0.69, and with aspirin and a statin is 0.50 ($0.50 = 0.72 \times 0.69$).

Average cost effectiveness

I calculated the cost of each intervention over a five year time horizon, and calculated the reduction in absolute coronary risk by subtracting post-treatment risk from pretreatment risk. Post-treatment risk is the product of pretreatment risk and the relative risk with treatment. In the case of aspirin, 0.3% is subtracted from the reduction in absolute coronary risk to take account of major adverse effects. The cost effectiveness ratio (cost per event prevented) is the total cost divided by the reduction in absolute coronary risk. I estimated the average cost per

coronary event prevented for each treatment used alone. In a sensitivity analysis I calculated maximum and minimum costs per event prevented for each of the interventions using the upper and lower 95% confidence limits for effectiveness. The average cost effectiveness rankings inform the order in which treatments would be offered in an incremental cost effectiveness analysis. To test the robustness of cost effectiveness rankings, I explored the effects of changes in the costs of interventions and the frequency of adverse effects alongside changed assumptions about effectiveness.

Incremental cost effectiveness

An efficient prevention strategy would offer the most cost effective treatment first, then the next most cost effective treatment, and so on. This enables the largest possible proportion of the benefits of treatment to be achieved at the lowest possible cost. The incremental cost effectiveness ratio is the additional cost associated with adding each treatment divided by the additional benefit of the treatment.

Incremental cost per event prevented is calculated in much the same way as the average cost per event prevented. The incremental cost of treatment includes only additional costs of treatment. The incremental reduction in absolute coronary risk is calculated by subtracting post-treatment risk from pretreatment risk. Post-treatment risk is the product of pretreatment risk and the relative risk on the additional treatment. However, pretreatment risk is the post-treatment risk after any previous treatments. In the case of aspirin, 0.3% is subtracted from the reduction in absolute coronary risk to take account of adverse effects. The cost effectiveness ratio (cost per event prevented) is the total cost divided by the reduction in absolute coronary risk.

A sensitivity analysis tested the robustness of cost effectiveness ratios by changing assumptions about effectiveness and identifying the threshold costs at which cost effectiveness rankings would change. Since the cost per coronary event prevented decreases as patients' coronary risk increases, I also investigated the cost effectiveness of coronary disease prevention in patients at a range of five year coronary risks.

Results

Average cost effectiveness

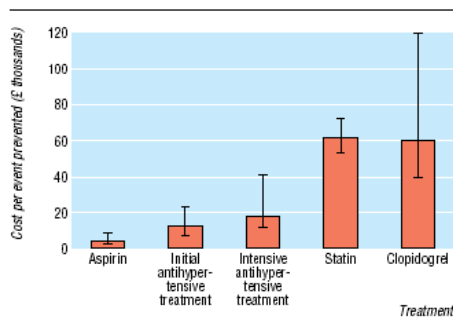
In a patient at 10% coronary risk over five years, aspirin is the most cost effective risk lowering treatment, at £3500 per coronary event prevented. Initial antihypertensive treatment costs £12 500, intensive antihypertensive treatment costs £18 300, clopidogrel costs £60 000, and simvastatin costs £61 400 per coronary event prevented (table 1).

In a sensitivity analysis I calculated the cost per event prevented for each intervention if its effectiveness was given by

Table 1 Average costs, effects, and cost effectiveness of preventive treatments in a patient at 10% risk of a coronary event over five years

Treatment	Relative risk with treatment (A)	Adverse event rate per 5 years (B)	Absolute risk reduction per 5 years		Discounted costs per 5 years*				Cost per event prevented (I=H/D)
			Simple (C=10%×(1-A)-B)	Discounted (D=C×(discount factor))	Prescribing (E)	Laboratory investigations (F)	Follow up (G)	Total (H=E+F+G)	
Aspirin 75 mg	0.72	0.3%	2.5%	2.4%	£19	£0	£65	£85	£3 500
Bendroflumazide 2.5 mg + atenolol 50 mg	0.83	0.0%	1.7%	1.7%	£124	£19	£65	£208	£12 600
Bendroflumazide 2.5 mg, atenolol 50 mg, + enalapril 20 mg*	0.67	0.0%	3.3%	3.2%	£497	£19	£65	£581	£18 300
Clopidogrel 75 mg	0.63	0.0%	3.7%	3.6%	£2071	£0	£65	£2136	£60 100
Simvastatin 40 mg	0.69	0.0%	3.1%	3.0%	£1744	£39	£65	£1848	£61 400

*Costs have been discounted at 6% and benefits at 1.5% in accordance with NICE guidelines.



Average cost effectiveness of preventive treatments in a patient at 10.5% risk of a coronary event over five years. (Error bars represent cost per coronary event prevented if effectiveness is at upper and lower 95% confidence limit)

the upper and lower 95% confidence limits of the estimates (see figure). The cost effectiveness of aspirin, initial antihypertensive treatment, and intensive antihypertensive treatment are sensitive to changes in assumptions about effectiveness. However, for simvastatin to be of similar cost effectiveness to intensive antihypertensive treatment, the relative risk with treatment must be at the lower 95% confidence interval and the cost of the drug 65% lower. This is unlikely, as drug prices typically fall by less than 50% when they come off patent. There is a wide degree of uncertainty about the cost effectiveness of clopidogrel, reflecting uncertainty about the relative risk on treatment.

Varying the discount rates for either costs or benefits from 0% to 10% has no effect on rankings. Using a general practitioner for follow up has no effect on cost effectiveness rankings. Cost effectiveness of initial and intensive antihypertensive treatment is sensitive to increases in the price of drugs. If sufficiently high cost drugs are used (such as for brand name calcium channel blockers) the cost per event prevented with initial antihypertensive drugs is as high as with a statin.

Incremental cost effectiveness of additional treatments

Costs of follow up clinic visits do not increase with extra treatments. The incremental costs of additional treatments therefore include only additional drug costs and additional laboratory investigations. The incremental effectiveness of additional drugs is also smaller than their effectiveness as initial treatments because incremental effects act on progressively smaller pretreatment risks.

If a patient at 10% five year coronary risk is given combination treatments in order of their cost effectiveness, the incremental cost per event prevented rises with each additional treatment. Compared with placebo, clopidogrel is more cost effective than simvastatin. However, clopidogrel as a replacement for aspirin

provides little additional benefit at substantial extra cost. It is therefore the least cost effective in an incremental analysis. Incremental costs per event prevented are £3500 for aspirin, £12 000 for initial antihypertensive treatment, £33 900 for enalapril, £122 400 for simvastatin, and £527 200 for clopidogrel (table 2).

I carried out a sensitivity analysis to investigate the effects of varying the costs and effectiveness of treatments. The most favourable assumption for simvastatin is that relative risks for all other treatments are at the upper 95% confidence limit and for simvastatin is at the lower 95% confidence limit. If this is the case, the incremental costs per event prevented are £8700 for aspirin, £18 800 for initial antihypertensive treatment, £243 000 for intensive antihypertensive treatment, £65 800 for simvastatin, and £177 300 for clopidogrel. Even under these assumptions, the price of simvastatin would have to fall by 70%, and the price of clopidogrel by more than 90%, to be of similar cost effectiveness to initial antihypertensive treatment.

Further analysis

Under the base case analysis, the cost effectiveness rankings of all five treatments are the same for any patient with a five year coronary risk greater than 1.5%. The incremental cost per event prevented in a patient at 5% five year coronary risk is £7900 with aspirin and £24 000 with initial antihypertensive treatment. This is less than the incremental cost per event prevented with simvastatin (£40 800) in a patient at 30% five year coronary risk (see table 3)

The most extreme assumptions we can make are to assume that relative risk on all treatments is at the upper 95% confidence limit (least effective) and assume that the relative risk with simvastatin is at the lower 95% confidence limit (most effective). Under these assumptions, the cost per event prevented with aspirin in a patient at 7.5% five year risk would be £12 900 and the cost per event prevented with simvastatin in a patient at 15% five year risk would be £13 200.

Discussion

This analysis confirms the poor cost effectiveness of statins and clopidogrel compared with aspirin and antihypertensive treatment.^{19 20} By quantifying the treatments' cost effectiveness, the analysis suggests it is likely to be more cost effective to treat patients at 5% five year coronary risk with aspirin than to prescribe further antihypertensive treatment or statins to patients at 30% five year risk.

Limitations of study

A weakness of this analysis is that some of the findings are sensitive to the choice of drug. This is particularly true of the cost effectiveness of initial antihypertensive treatment, where drug prices range from £10 to £290 a year. However, consideration of

Table 2 Incremental costs of preventive treatments in combination per event avoided in a patient at 10% risk of a coronary event over five years

Additional treatment	Incremental relative risk with treatment (A)	Adverse event rate per five years (B)	5 year coronary risk with this treatment (C=10%×(cumulative product of A))*	Incremental risk reduction		Incremental cost	
				Simple (D=C×A-B)	Discounted (E=D×(discount factor))	Discounted (F)	Per event prevented (G=F/E)
Aspirin 75 mg + follow up	0.72	0.3%	7.2%	2.5%	2.4%	£85	£3 500
Bendrofluzide 2.5 mg + atenolol 50 mg	0.83	0.0%	6.0%	1.2%	1.2%	£143	£12 000
Enalapril 20 mg	0.81	0.0%	4.8%	1.1%	1.1%	£374	£33 900
Simvastatin 40 mg	0.69	0.0%	3.3%	1.5%	1.5%	£1783	£122 400
Clopidogrel 75 mg (replaces aspirin)†	0.88	0.0%	2.9%	0.4%	0.4%	£2051	£527 200

*10% (risk with no treatment) multiplied by cumulative product of A (A for each of the rows above (the effects of all previous treatments)).

†Because clopidogrel is not prescribed with aspirin, it replaces aspirin in the incremental analysis; this results in clopidogrel having the highest incremental cost per event prevented even though it had only the second highest individual cost per event prevented.

Table 3 Incremental cost per event prevented of treating patients at a range of pretreatment risks of a coronary event over five years

Treatment	Pretreatment coronary risk over 5 years						
	5%	7.5%	10%	15%	20%	25%	30%
Aspirin 75 mg + follow up	£7 900	£4 900	£3 500	£2 200	£1 600	£1 300	£1 100
Bendrofluzide 2.5 mg + atenolol 50 mg	£24 000	£16 000	£12 000	£8 000	£6 000	£4 800	£4 000
Enalapril 20 mg	£67 800	£45 200	£33 000	£22 600	£16 900	£13 600	£11 300
Simvastatin 40 mg	£244 800	£163 200	£122 400	£81 600	£61 200	£49 000	£40 800
Clopidogrel 75 mg	£1 054 400	£702 900	£527 200	£351 500	£263 600	£210 900	£175 700

every possible antihypertensive regimen is beyond the scope of this paper.

The analysis may overestimate the benefits of some interventions. Estimates of the effects of intensive antihypertensive treatment are derived from studies comparing less intensive with more intensive treatment.¹¹ But the estimate of the benefits of initial antihypertensive treatment include all blood pressure lowering, not just less intensive treatment.¹³ The additional benefits of intensive antihypertensive treatment may therefore be exaggerated.

Apart from major bleeding due to aspirin, the analysis takes no account of adverse effects of treatment. Adverse effects may be considered as minor and reversible on stopping treatment or as major and irreversible. However, major adverse event rates would have to be 0% with a statin and to exceed 2.5% per five years with aspirin and 1.3% with initial antihypertensive treatment for the statin to be more cost effective than the latter two treatments. Minor, reversible adverse effects have little impact on the analysis because patients who stop treatment incur neither further costs nor further benefits. Even if all patients who experience adverse effects discontinue treatment but continue to be followed up, these differences make no differences to the cost effectiveness rankings. Evidence suggests that patients taking a statin report fewer adverse effects than those taking a placebo.²⁰ Among patients taking two low dose antihypertensive drugs, 7.5% reported adverse effects, but few (< 1%) were sufficiently severe to stop treatment and almost all were reversible.²¹ With aspirin, 3.9% of patients report adverse effects,²² but excess risk of major bleeding is under 0.5%.¹⁰

Conclusion

Incremental cost effectiveness analysis of treatments produces robust, practical cost effectiveness rankings. Authors of guidelines should take account of this when making treatment recommendations. If the aim of treatment is to maximise prevention of coronary disease, these results have clear implications for current treatment recommendations. They cast doubt on the wisdom of present policy, which emphasises achievement of target blood pressures and the use of statins for people at 15% five year risk of a coronary event.²³ A more efficient prevention strategy would be to offer aspirin and initial antihypertensive treatment to all people at over 7.5% five year coronary risk before offering statins to patients at 30% five year risk. According to national survey data, 87% of men and 56% of women aged over 65 are at over 7.5% five year risk.²⁴

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What is already known on this topic

Aspirin, antihypertensive treatment, statins, and clopidogrel are all effective in preventing coronary heart disease

These drugs vary in their cost effectiveness, and a rational prevention strategy would offer the most cost effective treatments first

What this study adds

Most of the benefits of prevention can be achieved with aspirin and antihypertensive treatment at a fraction of the cost of simvastatin or clopidogrel

Treating a patient with a five year coronary risk of 7.5% with aspirin and low cost antihypertensives is more cost effective than treating a patient with 30% coronary risk with a statin

Clinical guidelines should be informed by analysis of the incremental costs and incremental benefits resulting from each additional treatment

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