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

British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association

1. Introduction

In recent years evidence from randomised controlled trials and meta analyses has strengthened our understanding of the effectiveness of lifestyle and therapeutic interventions in reducing coronary and other atherosclerotic risk. The European Societies of Cardiology, Atherosclerosis, and Hypertension joined forces to publish recommendations on the prevention of coronary heart disease (CHD) in clinical practice in 1994, and these were updated in 1998.[1] This valuable collaboration between professional societies with a common interest in reducing the burden of cardiovascular disease in Europe encouraged the British Cardiac Society to cooperate with the British Hyperlipidaemia Association and the British Hypertension Society in preparing national recommendations, which have also been endorsed by the British Diabetic Association. Until now each society has worked independently, publishing separate guidelines on coronary prevention,[2] and the management of hyperlipidaemia,[3 4] and hypertension.[5] This professional isolation is mirrored in clinical practice where a patient with angina can be under the care of specialists in cardiology, hypertension, lipids, and diabetes all in the same hospital. Too often the cardiologist restricts his view to coronary anatomy and ventricular function, and other specialists to management of single risk factors, and by so doing can overlook the other major determinants of a patient's prognosis.

In putting forward joint recommendations on coronary prevention it is hoped that collaboration between professional societies will result in a more unified, and hence effective, approach to prevention of CHD in clinical practice. It is also appropriate to offer British recommendations in view of the substantially higher levels of CHD, and other atherosclerotic diseases, and their associated risk factors currently prevalent in Britain compared with many other European countries. To achieve a common approach it is necessary to include all cardiovascular risk factors, rather than focusing on a single risk factor and treating it in isolation. Hospital specialists and general practitioners need to coordinate their efforts and, with the support of other health professionals, create an integrated hospital and community based clinical strategy for prevention of CHD and other atherosclerotic diseases.

The recommendations proposed in this document are based on the best current scientific evidence. However, the approach employed is not always strictly evidence based. The volume of evidence in support of various interventions to prevent CHD, and other atherosclerotic disease, and the pressure on available resources that would follow their widespread uncritical adoption necessitates careful appraisal of the scientific evidence and its implications in a clinical context. Thus, the recommendations of our professional societies incorporate value judgments reflecting the practice of medicine based on evidence rather than just "evidence based" medicine.

2. Objectives and priorities for coronary heart disease prevention in clinical practice

While recognising the importance of the public health strategy embodied in the government's Health of the Nation document, which outlines a policy seeking to reduce morbidity and mortality from CHD and other atherosclerotic disease in the population,[6] it is essential that specialists and general practitioners also recognise their responsibilities for preventive medicine in routine clinical practice. The objectives for physicians are different, but complementary, to those of public health medicine. Clinicians regularly see patients who have either presented with CHD or other atherosclerotic disease, or are found to be at high risk of developing atherosclerotic disease because of hypertension, dyslipidaemia, diabetes, or a combination of these risk factors. In defining the objectives for CHD prevention in clinical practice it is implicit that priority is given to those patients who are at highest risk of developing CHD, rather than attempting to reach every adult in the population.

Patients seen by hospital specialists or general practitioners vary enormously in their risk of developing CHD. Individuals with predictors of CHD, such as hypertension or dyslipidaemia are at high risk relative to the general population, particularly if these and other factors coexist. Diabetes mellitus is associated with a particularly high CHD risk. In general, however, those with clinically overt atherosclerotic disease are at highest risk and stand to gain the greatest benefit from intervention. Therefore, such patients should be given the highest priority in prevention strategies.

Despite overwhelming evidence that management of cardiovascular risk factors in patients with established CHD is beneficial, in a national survey of secondary prevention practice (ASPIRE) undertaken by the British Cardiac Society, risk factor recording and management was less than optimal and there is considerable potential to improve secondary prevention practice.[7] These findings provide a

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strong case for the development of practical recommendations which can be widely adopted by physicians in hospitals and general practice throughout Britain.

The following order of priority is proposed for CHD prevention in clinical practice:

(1) (a) Patients with established CHD
(b) Patients with other major atherosclerotic disease
(2) Individuals with hypertension, dyslipidaemia, diabetes mellitus, family history of premature CHD, or a combination of these risk factors, which puts them at high risk of developing CHD or other atherosclerotic disease. Patients with diabetes mellitus are at particularly high risk of CHD.

The aim of these joint recommendations is to encourage a unified approach to the management of patients in these categories. The specific objectives of CHD prevention, and the prevention of other major atherosclerotic disease, are:

In patients with established CHD and/or other atherosclerotic disease
To reduce the risk of a further major cardiac event—that is, unstable angina or myocardial infarction (MI), or reinfarction, the need for coronary revascularisation procedures—and to reduce overall mortality.

In high risk individuals in the general population
To reduce substantially the risk of such individuals developing coronary disease, or other major atherosclerotic disease.

3. Concept of coronary heart disease risk

Patients with angina or a history of MI, or other major atherosclerotic disease, are at high risk of death from CHD. These patients have the highest priority for coronary prevention because the quality of the evidence that their lives can be extended and their morbidity decreased is among the best available for any aspect of medical practice. Such patients identify themselves to medical services and it is not necessary to measure absolute coronary risk before deciding on intervention.

Although patients with CHD are at high absolute risk of a further (or new) event compared to the healthy population, some individuals without any clinical manifestation of CHD, such as those with diabetes mellitus, may be at greater risk because of the coexistence of multiple predisposing factors. Thus, the division of prevention into primary or secondary is to an extent arbitrary, in relation to the biology of atherosclerotic disease and its complications. In medicine, however, this distinction reflects the reality of clinical practice because patients with symptomatic disease present to medical services and thus are already receiving care which should include secondary prevention, whereas high risk individuals in the general population have to be sought through screening, whether opportunistic or systematic, in order to deliver primary prevention.

For those individuals without symptomatic disease, an attendance at hospital or general practice should be seen as an opportunity to assess the absolute risk of CHD—that is, the probability of developing non-fatal MI or fatal CHD over a defined time period given a particular combination of risk factors—and to intervene appropriately depending on the degree to which they are at risk. Taking account of all major cardiovascular risk factors avoids undue emphasis being placed on an individual risk factor at the expense of overall or absolute risk. Risk factors often exert a cumulative effect on absolute CHD risk. Therefore, an individual with a number of mildly abnormal risk factors may be at a level of absolute CHD risk greater than that of someone with just one high risk factor.

For example, by using the Framingham risk equation[8] one can calculate that a man of 50 years, a non-smoker, with a systolic BP of 125 mm Hg, a serum cholesterol reading of 8.2 mmol/l, and a high density lipoprotein (HDL) cholesterol of 1.0 mmol/l, has an absolute risk of developing a CHD event of about 15% over the next 10 years. A man of the same age who has diabetes mellitus, smokes cigarettes, a systolic BP of 140 mm Hg, a cholesterol of 6.2 mmol/l, and an HDL cholesterol of 0.8 mmol/l has an absolute risk of about 30% over the same period. In other words his risk of developing a CHD event compared with the first man (relative risk) is increased twofold, despite the fact that none of his risk factors (apart from smoking) when considered individually, would be deemed sufficiently high to merit intervention. Taking a unifactorial approach the first man's cholesterol level may be thought sufficiently high to require treatment by diet, and possibly even drug therapy, although his absolute CHD risk is lower than that of the second man's.

Because of the increased risk of CHD events with increasing age, older individuals are more likely than younger ones to qualify for intervention on the basis of risk in the next 10 years. It is often stated that an event prevented in the elderly may not be equivalent to one in a younger individual. While it may be easier to demonstrate the economic contribution of the younger individual to society, the elderly may be contributing indirectly to the economic well being of society; certainly in a social context both contribute, although clearly in different ways. Younger individuals, however, certainly stand to accumulate more benefit over their lifetime. Therefore, there is a need to consider the benefit of intervention in the context of life expectancy.

In individuals without symptomatic disease an estimate of absolute risk of developing CHD, or other atherosclerotic disease, should always be made before the decision to introduce medication—for example, to decrease BP or serum cholesterol. There is now evidence from randomised controlled trials that for some risk factors intervention with drugs significantly reduces the risk of CHD events, and all cause mortality, in individuals with a risk as low as 6% of such events over the next 10 years.

However, the identification, investigation, and management of everyone at this level of

risk, particularly with some drug therapies, would be hugely demanding on National Health Service resources and therefore a staged approach to coronary and other atherosclerotic disease prevention is required. Patients with established CHD, or other atherosclerotic disease, are the top priority for prevention because they are at high risk of recurrent disease and are already known to hospital and general practice. To identify other high risk individuals in the population requires screening, which for the most part is undertaken in general practice either as new patient checks or opportunistically at other consultations. Those at highest risk should be targeted first and as a minimum healthy individuals with a 30% or higher CHD risk over 10 years should all be identified, and treated appropriately and effectively now. This is consistent with existing advice—for example, from the Standing Medical Advisory Committee on use of statins,[9] and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines on lipids and primary CHD prevention to be published in 1999. As the scientific evidence clearly justifies risk factor intervention in healthy individuals with a CHD risk lower than 30%, it is entirely appropriate, as the next step, for physicians to progressively expand opportunistic screening and risk factor intervention down to individuals with a 15% CHD risk over 10 years, as long as those at higher levels of risk have already received effective preventive care. Taking a progressive staged approach to coronary prevention in this way ensures that those at highest risk are targeted first and the delivery of care is commensurate with the ability of medical services to identify, investigate, and manage patients properly over the long term. Therefore, to begin with, it is appropriate to concentrate on those at higher levels of risk and demonstrate for patients with CHD or other atherosclerotic disease, and high risk individuals with 30% or higher CHD risk, that they have been identified and treated appropriately and effectively, and then move progressively on to those with a ⩾15% CHD risk.

The computer program "Cardiac Risk Assessor" developed for these recommendations is the preferred method of calculating absolute 10 year CHD risk for an individual based on the Framingham function; it can also be used to calculate cardiovascular risk (including stroke) over the same period.[8] However, this computer method may not be convenient in all clinical settings. Therefore, the coronary risk chart (fig 1) can also be used to identify those healthy individuals at highest CHD risk (30% or higher, red band), those at the next level of CHD risk (15% or higher, orange band) and finally those whose CHD risk is less than 15% (green band). Other risk charts based on the same principle are available and include the European[1] (CHD risk) and New Zealand[10] (cardiovascular risk) charts. All of these approaches use the Framingham function and require a knowledge of all risk factors including total cholesterol, HDL cholesterol, and the total cholesterol:HDL cholesterol ratio. The Sheffield risk and treatment table[11] is used to determine whether total cholesterol and HDL cholesterol need to be measured and, if so, whether the ratio confers an absolute 10 year CHD risk of 30% or more in the context of other risk factors. A table will be published to identify individuals at ⩾ 15% CHD risk.

a. How to calculate coronary heart disease risk

Measuring risk requires an interview and physical measurements, some of which need to be recorded on several occasions (appendix 1). Estimating CHD or cardiovascular risk using clinical judgment is imprecise, and while this imprecision is reduced with the use of epidemiological data based on groups, it still remains to some extent at an individual level. Traditionally, guidelines have not addressed CHD risk estimation and leave this to clinical judgment. Such judgment may well have contributed to inadequate efforts at CHD prevention.

In order to maximise the accuracy of any model designed to estimate CHD or cardiovascular risk, the model should be derived from epidemiologically based prospective data from the population to which the model is to be applied. Furthermore the model should include all the important risk factors which are easily and routinely measured in clinical practice. The following variables are considered important: smoking, BP, total cholesterol, HDL cholesterol, diabetes, family history of premature CHD, and ECG evidence of left ventricular hypertrophy. As yet no such prospective data are available on both men and women from UK based studies. However, the Framingham study from Massachusetts, USA[8] has a reasonably comprehensive set of risk factors which can be used for risk prediction in both women and men, including left ventricular hypertrophy (LVH) on the ECG. Later European prospective studies have included triglycerides and family history but these can only be applied to men.[12] They do, however, give broadly similar results to the Framingham equation.[13–15] Hence, the US guidelines from the National Cholesterol Education Program (NCEP)[16] and the new joint European recommendations of the European Society of Cardiology/European Atherosclerosis Society/European Society of Hypertension[1] are based on data from Framingham.

The Framingham study results were used in the US NCEP guidelines as an algorithm. This approach has the disadvantage that variables which are continuous and quantitatively related to CHD are treated as categorical variables.

The joint European recommendations,[1] based on the same data, use a two dimensional risk chart to allow BP and cholesterol to be treated as continuous variables. In order to use more than two risk factors in this way a computer, or programmable calculator, is required to calculate absolute CHD or cardiovascular risk from the multiple logistic regression equation from Framingham.[8] (See the instructions for using the Cardiac Risk Assessor program, appendix 1.) This approach is likely to become increasingly popular in

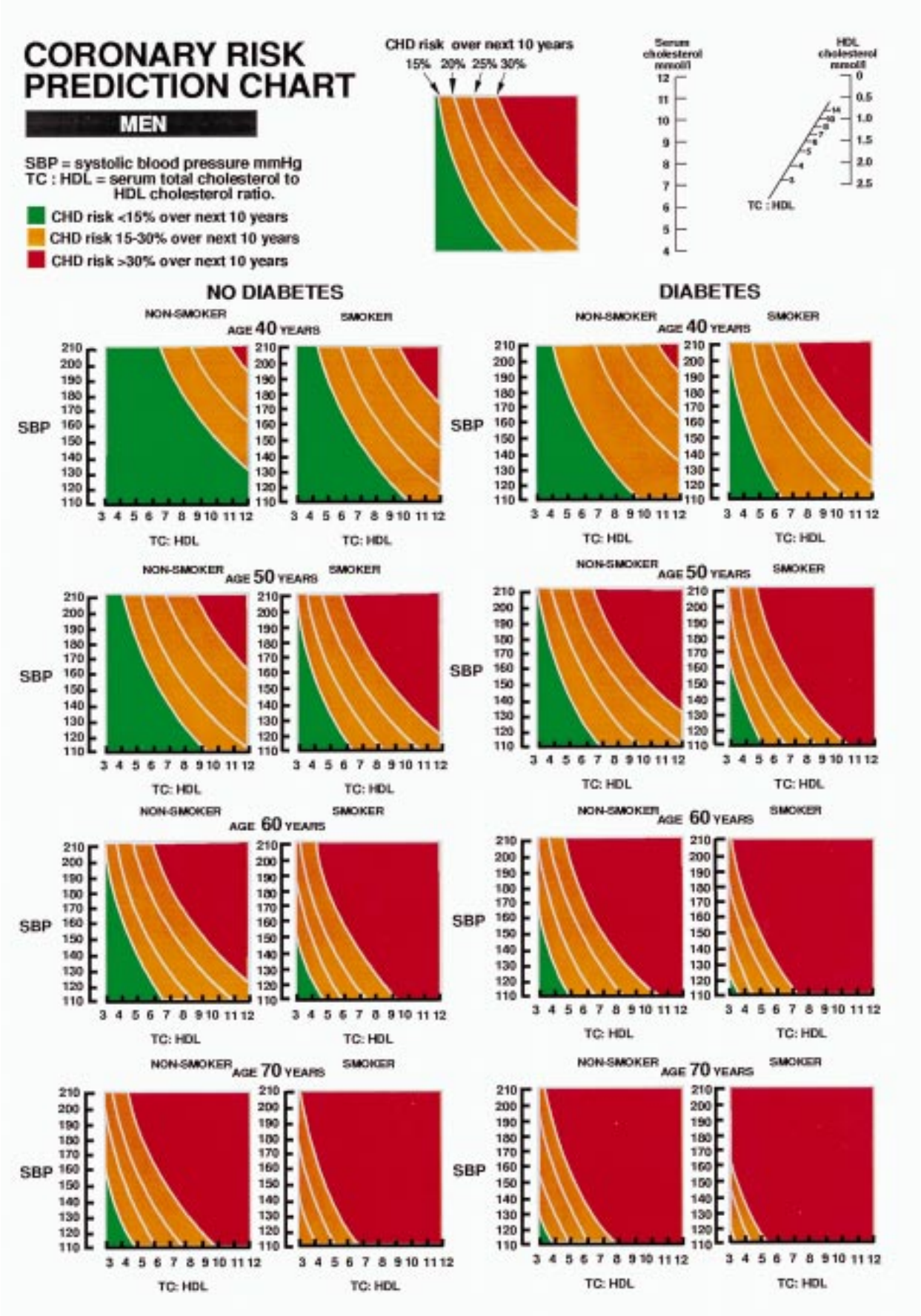
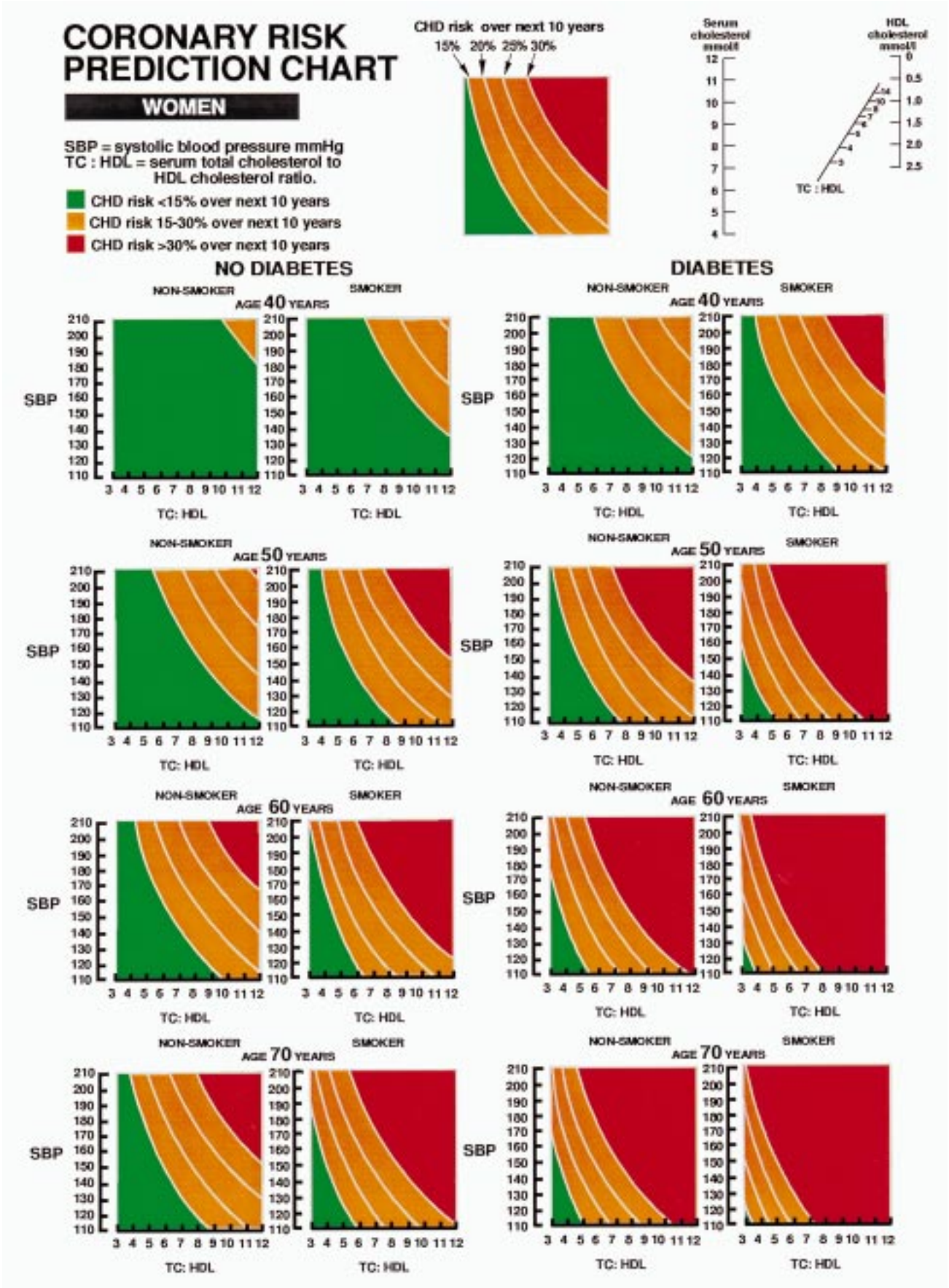


Figure 1 Joint British Societies coronary risk prediction charts for men and women. The chart should not be used for predicting risk in patients with coronary or other major atherosclerotic disease, familial hypercholesterolaemia or those with renal dysfunction. (Copyright The University of Manchester)



clinical practice where a computer is used in consultations. For the present there is also a continuing need for charts for risk prediction in which more than two continuous variables (BP, total cholesterol, and HDL cholesterol) can be included as quantitative variables without resort to three dimensional representation. This can be achieved by using total cholesterol and HDL cholesterol as a ratio[17] (fig 1), which can preferably be reported by the laboratory, or read quickly from a nomogram (inset).

Information required to assess CHD or cardiovascular risk is obtained by asking a few simple questions and measuring BP, total cholesterol, and HDL cholesterol. From the coronary risk chart (fig 1) it is then possible to calculate an individual's absolute risk of developing CHD—that is, the risk of a non-fatal MI or coronary death over 10 years. As risk increases exponentially with age the risk will be closer to the lower decennium for the first six years of each decade—for example, at age 45 the risk will be closer to that at age 40 but at age 47 it will be closer to that at age 50. Family history of premature CHD (for example, in men under 55 years or women under 65 years) increases risk by a factor of approximately 1.5 and should also be taken into account in assessing an individual's risk.

It is important to appreciate that if the level of a risk factor such as BP or cholesterol is based on a series of recordings, this will give a more precise estimate of the true biological mean than a single measurement. Furthermore the slope of the relation between the true mean measurement of a risk factor and risk of developing disease is steeper than that of a single measurement and risk (regression dilution bias). In clinical practice a series of BP readings or cholesterol measurements is usually made before deciding on whether to treat a patient. If these "average" values are used to calculate risk it should be remembered the patient's actual CHD risk will be somewhat higher because the Framingham risk equation is based on measurements made on a single occasion; the slope of the regression line relating CHD risk to risk factor measurements based on a series of recordings is steeper because the effects of biological variation are largely abolished.[18 19] Absolute CHD risk will also be underestimated by using values of BP on treatment, or cholesterol recorded after dietary intervention, because the true risk is likely to be closer to the life long habitual levels of these risk factors. It would by the same token be inappropriate to classify a cigarette smoker, who has recently stopped, as a "non-smoker" because risk will reflect lifetime exposure to tobacco.

4. Secondary prevention: management of risk factors

The evidence for lifestyle and drug interventions in secondary prevention comes from epidemiology and randomised controlled trials which, for the most part, were undertaken after MI. Patients with angina and those following revascularisation, particularly percutaneous transluminal coronary angioplasty, have not been as intensively studied, but where there is evidence—for example, aspirin in angina or lipid lowering therapy following coronary artery bypass surgery—the results are generally consistent with results of trials after MI. The present recommendations on lifestyle and therapeutic management of BP, dyslipidaemia, and diabetes mellitus, and the use of prophylactic drug therapy are thus intended for all patients with any clinical manifestation of CHD. In 1994 the Health Survey for England reported that 7.1% of men and 5.2% of women aged 16–74 years gave a history of angina, myocardial infarction or stroke. In Scotland the reported prevalence of CHD or stroke in 1995 in the age range 16–64 years was 4.6% of men and 3.2% of women.

a. LIFESTYLE

Stopping smoking, modifying diet, and increasing aerobic exercise are all effective in reducing the risk of further CHD. For married couples, there is concordance for lifestyle and risk factors such as obesity, BP, lipids, and glucose.[20 21] In addition, concordance for change within marriages has also been shown and this reinforces the value of offering lifestyle intervention to the whole family.[22] Encouraging the family rather than individuals to make behavioural changes is more likely to be effective.

Although lifestyle change is the starting point for risk reduction, it is only *one component* of the management of coronary patients. It is also essential to measure BP, lipids, and glucose and to manage them rigorously with the use of drug therapy as required.

i. Stopping smoking

Although there is no trial evidence in favour of smoking cessation following the development of coronary disease, observational data show that the risk of recurrent disease is reduced by as much as 50% within one year of stopping, and a favourable effect on mortality is sustained for more then a decade.[23] In a trial of survivors of myocardial infarction in which physicians encouraged patients to stop smoking, reinforced at several visits, the stopping rate was doubled from 28% to 63%, emphasising the importance of such sustained clinical advice in practice.[24] In ASPIRE (action on secondary prevention through intervention to reduce events) one in five patients had resumed smoking cigarettes at follow up, so there is still potential through stopping smoking to reduce the risk of recurrent disease.[7] Uncertainty exists about the use of nicotine replacement therapy in patients with CHD, or other atherosclerotic disease, because some of the cardiotoxic effects of smoking are attributable to nicotine.[25] However, in a recent short term trial of transdermal nicotine in patients with cardiovascular disease, there was no significant increase in the risk of cardiovascular events.[26] Caution, however, is still required and it is imperative that patients know they should not smoke while using these nicotine delivery preparations.

ii. Dietary changes

Early randomised control trials of diet in patients with cardiovascular disease in the 1960s, using a reduced fat (specifically saturated fat) intake, did not convincingly show overall benefit in reducing cardiac events or total mortality. However, more recent trials using diets low in saturated fat and supplemented with polyunsaturated fatty acids, principally from omega 3 fatty acids (fish or fish oil capsules and α linolenic acid margarine), have shown significant reductions in coronary mortality and improvement in survival.[27 28] These dietary interventions probably operate through mechanisms other than simply altering blood lipids, perhaps by reducing the propensity to thrombosis. Fat modified diets have been effective in reducing the prevalence of angiographic progression of coronary disease.[29] The combination of advice on a fat modified diet and smoking cessation in high risk men has also been associated with a reduction in CHD risk.[30] Antioxidant supplement trials have given conflicting results and at the present time there is no justification for prescribing vitamin supplements when the diet is already rich in naturally occurring antioxidants.[31] There have been no studies of reducing obesity following the development of coronary disease, although it is a common problem; 23% of men and 33% of women with CHD in the UK remain significantly obese (body mass index 30 kg/m^2 or greater).[7] Given the association between obesity and hypertension, hyperlipidaemia, and diabetes it is appropriate for dietary advice to include weight reduction.

Dietary goals have been developed for the healthy population.[32] Total dietary intake of fats should be reduced to 35% or less of the total energy intake, the intake of saturated fats to no more than one third of fat intake, and the intake of cholesterol should be less than 300 mg a day. An increase in the use of monounsaturated and polyunsaturated fats (particularly from omega 3 sources) as well as fresh fruit and vegetables is also recommended. It should be emphasised that the dietary recommendations made by the Committee on Medical Aspects of Food (COMA) panel on diet and cardiovascular diseases were intended for the population as a whole, and a more rigorous approach is required by many patients with established CHD or those who are at high CHD risk. Dietary advice is best given on an individual basis, having regard to the presence of obesity, high BP, and plasma lipid and glucose levels.

In patients with hypertension, lifestyle modification should be directed specifically at weight loss, moderation of alcohol consumption (less than 21 units per week in males and less than 14 units per week in females), and reduction in salt intake.[33–38] Vegetarian diets[39 40] and diets high in potassium[41] may also reduce BP.

Reducing saturated fat is the primary objective for all patients with hyperlipidaemia. To encourage weight loss in the obese, the reduced dietary energy intake from decreasing saturated fat should not be replaced. Weight loss improves insulin sensitivity. For those who are normal weight, or have achieved their target weight, the deficit in dietary energy from restricting saturated fat should be replaced with other sources of energy such as unrefined carbohydrate, and mono- and polyunsaturated fats. Although usually recommended only in patients with a normal weight, it may be more realistic for obese patients, who are unable to lose weight by eating less, to substitute mono- and polyunsaturated fats for foods rich in saturated fat. Increasing fish consumption may also help moderate hypertriglyceridaemia, although in severe hypertriglyceridaemia a decrease in the consumption of any type of fat may be required. In the presence of hypertriglyceridaemia restriction of alcohol may be necessary.

An intake of up to 3 units of alcohol per day is associated with a lower risk of CHD compared with both teetotallers and those who consume higher quantities of alcohol,[42] but as consumption rises there is a higher risk of hypertension and other cardiac and non-cardiac diseases, with associated morbidity and premature mortality.[43 44]

iii. Increasing physical activity

Aerobic exercise in patients with coronary disease has been the subject of a large number of clinical trials. Overviews of these trials have shown that, although there is no reduction in non-fatal reinfarction, an exercise programme is associated with a significant reduction in coronary mortality and total mortality.[45 46] Importantly, when these trials were analysed by those using exercise alone compared to others which also incorporated lifestyle interventions to reduce smoking and improve diet, the evidence of benefit for coronary disease and overall survival was only seen in the lifestyle multifactorial intervention programmes.[46]

Exercise recommendations which define the intensity, duration, and frequency of exercise for cardiac patients have been formulated by the British Association for Cardiac Rehabilitation and other expert groups in this field.[47–49]

b. BLOOD PRESSURE

Raised BP continues to be a risk factor for subsequent cardiovascular events in patients after MI.[50 51] Approximately 25% of hypertensive patients in the UK have a history of angina pectoris, MI, or both.[52] However, there are no clinical trials of antihypertensive treatment in patients with established CHD. In the absence of good trial based evidence for BP management in such patients, it seems reasonable to extrapolate from primary prevention trials. Patients with CHD and sustained systolic BP $\geq$ 140 mm Hg and/or diastolic BP $\geq$ 85 mm Hg should have antihypertensive drug therapy.

An overview of β blockade during and after MI has shown a reduction in mortality of 23% compared with placebo among MI survivors.[53] No direct comparisons between antihypertensive agents in hypertensive MI survivors have been made. However, pending further evidence, β blockers are the preferred drug group in this situation.

In MI survivors, rate limiting calcium antagonists (verapamil and diltiazem) have also been demonstrated to reduce all cause mortality and deaths from recurrent MI.[54–57] The benefits are restricted to patients without left ventricular impairment and are significant in retrospective analyses of subsets with prior hypertension.[54 57–59] Therefore, verapamil and diltiazem may be options in patients intolerant of β blockers.

The benefit of ACE inhibitors for patients with heart failure, including those who have sustained a MI, has been clearly established in trials.[60 61] Although β blockers and ACE inhibitors are not a particularly effective combination in terms of BP lowering, it may be the most efficient combination for reducing cardiovascular risk in hypertensives requiring more than one agent to lower BP following a MI. If β blockers are poorly tolerated, the combination of ACE inhibitors with verapamil or diltiazem is an alternative. β blockers should not be combined with diltiazem or verapamil because of the risk of profound bradyarrhythmias and heart failure.

Some studies have suggested that the relation between death and BP is J shaped and concern has been raised that excess lowering of diastolic BP may result in increasing rates of premature death due to CHD, particularly in those hypertensives with pre-existing CHD or LVH.[62 63] Although maximum coronary blood flow occurs during diastole, the hypothesis remains controversial; it has not been supported by recent trials of antihypertensive treatment in elderly patients,[64–66] a proportion of whom were likely to have at least preclinical coronary heart disease, or in trials of treatment of heart failure in which low levels of BP were attained.[60]

Although not supported by direct evidence from clinical trials, it is recommended that the target BP for patients with established CHD is < 140 mm Hg systolic and < 85 mm Hg diastolic. In ASPIRE almost 56% of patients had BP levels greater than this, and of those on antihypertensive therapy up to a third still had diastolic BP of 85 mm Hg or higher.[7]

c. SERUM LIPIDS

Serum cholesterol and HDL cholesterol continue to be risk factors for recurrent CHD events after MI.[67] Evidence that patients with established CHD benefit from cholesterol reduction is exceptionally strong. The most comprehensive meta analysis conducted before the major statins trials, described later in detail, included 21 trials in patients with CHD employing diet, drugs (clofibrate, gemfibrozil, cholestyramine, colestipol, niacin) or partial ileal bypass surgery.[68 69] The mean serum cholesterol in those trials was 6 mmol/l and the average reduction in the actively treated patients was 10%. Total mortality also decreased by 10% (confidence intervals (CI) 3–16%; p = 0.008) in patients who received active intervention. There was no effect of active intervention on non-cardiac mortality. The great majority of trials which have used coronary angiography to assess the effects of lipid lowering intervention have also resulted in significantly slower rates of progression and higher rates of regression of coronary atheroma, regardless of whether the active intervention was with diet, statins, bile acid sequestrants, nicotinic acid, or fibrates.[29 70 71]

The most compelling evidence that cholesterol lowering in patients with CHD is beneficial has, however, come from trials employing statins with clinical events as end points. The Scandinavian simvastatin survival study (4S) was the first of these.[72 73] In this study 4444 patients with serum cholesterol in the range 5.5–8.0 mmol/l after dietary intervention were randomised to receive simvastatin or placebo. The patients had either had a definite MI at least six months previously (79%) or had angina with a positive exercise ECG. They were aged between 35 and 70 years (52% were 60 years or older) and 18% were women. The average serum cholesterol was 6.7 mmol/l at randomisation. The initial dose of simvastatin was 20 mg daily and the aim of therapy was to decrease serum cholesterol to between 3.0 and 5.2 mmol/l. In only two patients the dose was reduced to 10 mg daily and in 37% it was increased to 40 mg daily. The duration of the trial was 5.4 years and the mean cholesterol reduction was 29%. There was a 30% decrease in total mortality in the active treatment group. This was due to a 42% decrease in CHD deaths. CHD incidence (combined morbidity and mortality—the usual primary end point of cholesterol lowering trials) declined by 33% and the need for coronary artery surgery or angioplasty was reduced by 37%. All these decreases were highly significant. The relative decrease in CHD incidence was the same in those who were older than 60 years as in those who were younger. The relative decline in CHD incidence was also the same regardless of the initial cholesterol level.[73] Women showed the same relative decrease in CHD risk as did men (although there were too few women to be confident about effects on overall mortality). Patients with serum triglyceride levels exceeding 2.5 mmol/l were excluded from the trial. However, the trial provides powerful evidence that lowering cholesterol, particularly low density lipoprotein (LDL) cholesterol, in patients with established CHD is beneficial.

A second trial of statin therapy in patients with established CHD was the cholesterol and recurrent events (CARE) trial.[74] In CARE 4159 patients (14% women) were randomised to receive either pravastatin 40 mg daily or placebo. All had serum cholesterol levels of 6.2 mmol/l or less at randomisation, the mean value being 5.4 mmol/l. In each patient acute MI had been diagnosed 3–20 months earlier. The duration of the trial was on average five years. Serum cholesterol was 20% lower on active therapy compared to placebo. CHD mortality and CHD incidence decreased by 20% and 24%, respectively, in the pravastatin treated group, and the need for coronary surgery or angioplasty declined by 27%. These differences were all significant. However, overall mortality decreased by only 9% and this was not significant. The smaller quantitative

outcome in CARE compared to 4S was probably in part caused by a lower rate of CHD deaths (5.7% in five years in CARE compared to 8.5% in 5.4 years in 4S) and the wider use of coronary artery surgery and other medical advances since 4S. Two important differences in entry criteria compared to 4S were the lower serum cholesterol concentrations at randomisation in CARE and the admission of patients with serum triglycerides up to 4 mmol/l. Subgroup analysis revealed no reduction of CHD risk in patients whose serum LDL cholesterol was less than 3.2 mmol/l (a total cholesterol of about 4.8 mmol/l) at randomisation. The results in patients with serum cholesterol greater than 4.8 mmol/l would seem to be similar to those in 4S. As in 4S, the effect of statin therapy in reducing relative CHD risk was unaffected by age and was at least as good in women on active treatment as for men. In patients whose serum triglyceride concentration exceeded the average (1.63 mmol/l), the reduction in CHD risk (15%; not significant) was less than in those with lower serum triglycerides (32%; $p < 0.001$). It should be emphasised that in the west of Scotland coronary prevention study (WOSCOPS), a trial of pravastatin in which the entry criterion for triglycerides was similar to CARE, a similar relative reduction in CHD risk was found in those with triglycerides greater than 1.63 mmol/l as in those with lower concentrations.[75] The long term intervention with pravastatin in ischaemic disease (LIPID) study is a third and larger trial in 9014 patients aged between 31 and 75 years (17% women) with established CHD randomised to receive either pravastatin 40 mg daily or placebo.[76] The median cholesterol was 5.6 mmol/l (interquartile range 5.1–6.2 mmol/l) and triglycerides of 1.6 mmol/l. Patients had had an acute MI or unstable angina between 3 and 36 months earlier. The duration of the trial was 6.1 years and the mean cholesterol reduction was 18%. There was a 22% decrease in total mortality due to a 24% decrease in coronary mortality in the pravastatin group. CHD incidence (non-fatal MI and coronary death) also decreased by 24% and the need for coronary artery surgery or angioplasty was reduced by 20%. A predefined end point of the trial was stroke and all stroke decreased by 19%. All these differences in clinical event reduction were statistically significant. Within prespecified subgroups there was also evidence of benefit in reducing CHD incidence in both those with MI and unstable angina, and in those aged over 65 years. Women had a smaller relative decrease (11%) in incident CHD compared to men (26%) as did patients with a total cholesterol < 5.5 mmol/l (19%) or an LDL cholesterol < 3.5 mmol/l (16%) compared to those with higher values, but there was no evidence of significant heterogeneity of treatment effect in any of these subgroups. Unlike CARE patients, those in LIPID with serum triglyceride concentrations > 2.6 mmol/l had the same degree of benefit (a 25% reduction) compared to those with lower triglyceride levels.

Thus, there is strong evidence that statin therapy should be introduced in MI survivors whose serum cholesterol is 5.0 mmol/l or greater. In ASPIRE 78% of men and 86% of women had a cholesterol reading of 5.0 mmol/l or greater. Of the minority on lipid lowering therapy, over half had not reduced their cholesterol below 5.0 mmol/l.The benefit of statins may not be apparent for coronary patients with lower concentrations of cholesterol and this group requires further research. Although the majority of patients in clinical trials have been men it is reasonable to manage women with CHD in the same way as men. Most patients in these trials had had an MI but for those with angina the evidence of benefit was consistent with that observed for infarct survivors. Therefore, all patients with established coronary artery disease should have their serum cholesterol reduced to at least below 5.0 mmol/l. Cholesterol lowering in the context of secondary CHD prevention also reduces the risk of stroke. Therefore patients with cerebrovascular disease could potentially benefit from such therapy and this is currently the subject of controlled trials. Similarly, patients with atherosclerosis of the aorta and lower limbs, who most commonly die from CHD because of coexistent coronary atherosclerosis, may also benefit from cholesterol lowering therapy.

In patients with acute myocardial ischaemia, and in particular with MI, serum total cholesterol and LDL cholesterol, as well as serum HDL cholesterol, decrease.[77] Other physical stress such as surgery and illnesses will have a similar effect on serum lipids and HDL cholesterol.[78] The depression of serum cholesterol following MI generally lasts no longer than six weeks but can be longer if there is a complicated recovery. A measurement as soon as possible, and not later than 24 hours, from the onset of symptoms may, however, give some reflection of the concentration of total cholesterol and HDL cholesterol before the acute event. The value of estimating cholesterol at the onset of acute myocardial ischaemia or infarction is that a raised total cholesterol can be a motivation for dietary change, including weight loss, following the acute illness. Whatever the total cholesterol is during the acute phase, it is essential to measure the lipid profile (ideally fasting) after six weeks as all patients with CHD should have fasting cholesterol, triglycerides, and HDL cholesterol measured. Fasting plasma glucose can be conveniently measured at the same time.

Dietary advice should be given to all patients. However, it should be recognised that only a small proportion will achieve cholesterol concentrations below 5.0 mmol/l (LDL cholesterol less than 3.0 mmol/l) with diet alone. Therefore, patients admitted with unstable angina or acute MI and who have a random total cholesterol greater than 6.0 mmol/l should, in addition to dietary advice, be prescribed lipid lowering therapy before discharge with a clear statement about the lifelong need for such therapy in the hospital summary. For patients whose cholesterol level at follow up six or more weeks after their acute hospital

admission is still 5.0 mmol/l or greater following dietary advice should also be given lipid lowering therapy.

Those with a cholesterol concentration less than 5.0 mmol/l should be monitored, at least annually, because, despite dietary advice, lipid lowering drug therapy may still be required at a later date. Younger patients (less than 55 years for men and less than 65 years for women) with CHD and cholesterol greater than 5.0 mmol/l, or any patient whose serum cholesterol is particularly high (greater than 8.0 mmol/l) should have their first degree blood relatives screened for serum cholesterol. This is because of the possibility of familial hypercholesterolaemia, or another inherited form of hyperlipidaemia, which has a sufficiently high risk of atherosclerosis to justify primary CHD prevention.

The threshold for initiating treatment with a statin is a total cholesterol $\geq$ 5.0 mmol/l and/or an LDL cholesterol $\geq$ 3.0 mmol/l on diet. The best evidence of benefit from cholesterol lowering in secondary prevention comes from randomised controlled trials using statins; these drugs are thus the preferred class for CHD patients. Most earlier guidelines have defined the therapeutic target of such therapy as an absolute level usually of LDL cholesterol. For example the NCEP recommended a target LDL cholesterol of 2.5 mmol/l or less. Another approach based on trial evidence is, however, to recommend decreasing LDL cholesterol by more than 33% in secondary prevention,[79] and this will usually be achieved if the statin doses used in the trials are prescribed.

The lipid target in patients with established CHD, and in selected patients with other atherosclerotic disease, is at least to an LDL cholesterol less than 3.0 mmol/l (total cholesterol less than 5.0 mmol/l). The dose of statin prescribed should be the same as that used in the trials and should be increased every four to six weeks to achieve this target. Patients who fail to reach this target should be referred to a specialist clinic.

A meta analysis of clinical trials suggests that fibric acid derivatives also decrease CHD incidence.[80] The decrease in CHD incidence is likely to be most pronounced in patients with an increase in both serum cholesterol and triglycerides (type IIB hyperlipoproteinaemia), and such patients are at greater risk than those with similar levels of cholesterol unaccompanied by hypertriglyceridaemia.[81] However, doubts about the effects of fibrates on other causes of death in primary prevention trials still exist,[80] and this class of drug has yet to be shown in secondary prevention trials to be as effective as statins in decreasing all cause mortality. The preliminary results of a secondary prevention trial of a fibric acid derivative, bezafibrate were reported at the ESC congress in August 1998 and there was no significant overall benefit. The active treatment and placebo group in this study had not shown any evidence of differential toxicity.[82] Generally a statin should be the initial choice of therapy in combined hyperlipidaemia, certainly when the triglycerides are less than 5.0 mmol/l. In particularly high risk patients with persisting hypertriglyceridaemia, despite statin therapy, the use of a fibrate drug[83 84] or fish oil as alternatives, or in addition to, a statin may be justified but more clinical trial evidence would be welcome.

d. GLUCOSE

All patients with a diagnosis of CHD should have fasting blood glucose measured. However, because the level may rise acutely during acute myocardial ischaemia or infarction, an elevation of blood glucose in patients who are not clearly diabetic should be confirmed six weeks after the event. Patients with CHD whose fasting blood glucose is < 7.8 mmol/l but whose 2 hour level is $\geq$ 7.8 mmol/l and < 11.1 mmol/l, and particularly in those who have hypertriglyceridaemia (regardless of total cholesterol level), are at higher than expected risk of subsequently developing overt diabetes mellitus and therefore require further fasting blood glucose determinations at annual review.[85] (See Diabetes and impaired glucose tolerance, Section 5e.) Patients with diabetes and CHD should be managed in the same way as those without diabetes in terms of lifestyle advice. A re-evaluation of diet may be required to emphasise the importance of avoiding obesity and decreasing fat intake, particularly saturated fat, rather than simply reducing carbohydrate.

Although there have been no trials of blood pressure lowering in patients with diabetes and CHD, a lower target blood pressure < 130 mm Hg systolic and < 80 mm Hg diastolic is appropriate for this patient group because of the trial evidence for reducing macrovascular and microvascular complications in primary prevention. Similarly there have been no trials of lipid lowering therapy in diabetic patients with CHD, but subgroup analyses are available from both the 4S and CARE studies. There were 202 (158 men) diabetic patients in 4S of whom 12% received insulin, 38% oral hypoglycaemic drugs, and 50% were treated with diet alone.[86] There was a 43% decrease in all cause mortality (not significant) and a 55% decrease in CHD incidence ($p = 0.002$) in those who were treated with simvastatin, indicating at least as great a benefit as in the non-diabetic participants. In CARE there were 586 patients with diabetes and their CHD incidence declined by 25% ($p = 0.05$) with pravastatin treatment,[74] and in LIPID there were only 164 patients with diabetes whose CHD incidence fell by 19% but this was not significant.[76] Thus on available evidence there is a consistent reduction in CHD risk for patients with diabetes in these trials and therefore it would be reasonable to adopt a similar protocol to that for non-diabetics with CHD, commencing with a statin if serum cholesterol exceeds 5.0 mmol/l and triglycerides are less than 5.0 mmol/l despite diet.[87] In the absence of a CHD prevention trial of lipid lowering therapy in diabetic patients, in whom hypertriglyceridaemia is more common, the most appropriate lipid lowering drug is less certain when hypertriglyceridaemia is pronounced, or triglycerides are high but cholesterol is relatively low.[88]

Whether such patients with higher triglycerides would benefit from a fibrate drug, or the combination of a statin and a fibrate, is not clear at present and is now the subject of clinical trials.

There are two important additional considerations in CHD prevention in diabetes. Firstly, improving glycaemic control whether by diet, hypoglycaemic drugs, or insulin decreases serum cholesterol and triglycerides. Until recently there has been a lack of clinical trial evidence on whether glycaemic control in diabetes favourably modifies CHD risk. However, interest in this area has now been stimulated by the two studies of intensive insulin treatment, one showing a decrease in mortality in the first year after MI,[89 90] and by a re-evaluation of earlier epidemiological studies.[91] This evidence, while reinforcing the desirability of achieving good glycaemic control, does not, however, obviate the need to treat high BP and hyperlipidaemia appropriately.

Secondly, annual diabetic hospital review is not compatible with the frequent monitoring necessary for introducing lipid lowering or antihypertensive medication. Therefore, agreed management protocols between hospital and general practice, which include hypertension and hyperlipidaemia, are required.

e. CARDIOPROTECTIVE DRUG THERAPY

Six different classes of drugs—aspirin and other platelet anti-aggregatory compounds,[92] β blockers,[53] rate limiting calcium antagonists,[54–59] ACE inhibitors,[60 61 93–99] cholesterol lowering drugs (discussed above), and coumarin anticoagulants[100]—have each been shown in randomised controlled trials (or meta analyses of trials) of MI survivors to reduce the risk of further cardiovascular morbidity and mortality and to improve survival.

Although there are many trials of aspirin use in patients with CHD, no single study provided definitive results. However, a meta analysis of platelet inhibitor therapy has shown a 31% reduction in non-fatal reinfarction, a 42% reduction in non-fatal stroke, and a 13% reduction in cardiovascular mortality. Aspirin alone was as effective as the combination of aspirin and dipyridamole and more effective than sulphinpyrazone. Aspirin in the dose range of 75–325 mg was as effective as higher dose aspirin. Aspirin, unless specifically contraindicated, is therefore recommended for all patients who have established CHD. A dose of 75 mg is appropriate as it is efficacious and associated with the lowest risk of side effects.

β Blockers are also recommended for patients following MI, unless there are contraindications such as obstructive airways disease or significant left ventricular systolic dysfunction. Diltiazem or verapamil are alternatives in patients with obstructive airways disease if systolic function is preserved. ACE inhibitors are indicated for patients following MI, primarily for those with clinical evidence of heart failure in the acute phase,[61] and for those in whom there is left ventricular systolic dysfunction (ejection fraction less than 40%).[60] Oral anticoagulation with the coumarins in MI survivors is also associated with a lower risk of reinfarction, coronary death, and stroke. This class of drug is usually reserved for those patients with large anterior infarctions, left ventricular aneurysm, paroxysmal tachyarrhythmias, chronic heart failure, and systemic embolic disease.

f. CORONARY ARTERY BYPASS SURGERY AND ANGIOPLASTY

Patients treated by coronary artery bypass grafting or angioplasty have native coronary artery disease and therefore require the same lifestyle and therapeutic interventions already described. Evidence that risk factor modification will influence the natural history of venous and arterial conduits is very limited, but trials of lipid lowering therapy have shown a significant reduction in the rate of progression of atherosclerosis in saphenous vein coronary bypass grafts.[101 102] In the longest and most recent of these trials[102] treatment with lovastatin in full dose, and if necessary combined with cholestyramine (with the aim of reducing LDL cholesterol below 2.4 mmol/l), was compared with lovastatin in a fixed dose of 25 mg daily for 4.3 years. The percentage of grafts with substantial progression of disease was 27% in the intensively treated patients and 39% in the moderate treatment group, a difference which was significant ($p < 0.001$). There was no evidence of regression of graft disease. Nor is there any evidence that such treatment will reduce the risk of restenosis following angioplasty. However, lipid lowering therapy after both coronary artery bypass surgery and angioplasty is rational because of the evidence that it will delay the progression of atherosclerosis and clinical events caused by disease in the native coronary circulation.

g. OTHER ATHEROSCLEROTIC DISEASE

Patients with cerebrovascular and peripheral arterial disease should be managed in the same way as those with established CHD. There is virtually no clinical trial evidence to support such a view, but what trial data are available support the treatment of BP, serum cholesterol, and blood glucose as risk factors for atheroma in these other vascular territories. Patients with cerebrovascular disease or peripheral arterial disease are at as high a risk of developing or dying from CHD as many patients surviving their first MI.

Two trials of antihypertensive therapy in patients surviving strokes or transient ischaemic attacks were carried out over 20 years ago. The first, in severe hypertensives, demonstrated a significant reduction in all cause mortality,[103] whereas the other larger study, in milder hypertensives, demonstrated only non-significant reductions in cerebrovascular and cardiovascular morbidity.[104] Further trials evaluating optimal therapy after strokes are in progress. Because acute stroke often induces BP elevation which may last for several days, the timing and threshold for intervention on BP after a stroke remains uncertain. However, if raised BP is maintained once the neurological condition is stable, and severe carotid

stenosis is not present, introduction of antihypertensive medication is appropriate. Precipitous falls in BP should be avoided.

Patients with peripheral arterial disease frequently have concomitant coronary disease, cerebrovascular disease, or renal artery stenosis which may not be clinically evident.[105] Optimal therapy can be achieved either with a β blocker (this drug class will not worsen intermittent claudication but does reduce skinflow and therefore should be avoided in patients with critical ischaemia) or a vasodilating agent, but not with the combination of β blockers and vasodilating drugs. ACE inhibitors and angiotensin II antagonists should be used with caution in these patients, and ideally only after appropriate investigations, because of the risk of reducing glomerular filtration in bilateral renal artery stenosis or unilateral stenosis in a single functioning kidney.[106] Serum creatinine should be measured before commencing ACE inhibitor therapy, when the BP has been stabilised on this medication, and sooner if there is a decrease in BP of unexpected magnitude. A rise in serum creatinine or a very large fall in BP after starting an ACE inhibitor is strongly suggestive of renal artery stenosis.[107]

5. Primary prevention: management of risk factors

For patients without clinical atherosclerotic disease the absolute risk of developing CHD (non-fatal MI or coronary death), or other atherosclerotic disease, during the next 10 years should strongly influence the intensity of lifestyle and therapeutic intervention.[1] As the absolute CHD risk increases so should the intensity of intervention, thus maximising the potential benefit from risk factor reduction. In addition, as the absolute risk increases so the threshold for drug treatment of BP and dyslipidaemia should be lowered. It must be emphasised that a decision not to introduce a particular therapy for a particular individual should be reviewed regularly. With advancing age the absolute risk associated with any one risk factor, or combination of risk factors, may over time become sufficiently great to justify intervention.

a. CHD RISK AT WHICH CLINICAL INTERVENTION WITH PHARMACOTHERAPY IS JUSTIFIED

The concept of intervention based on absolute CHD risk for a particular patient is justified by evidence that a given reduction in blood pressure or serum cholesterol produces a constant proportional reduction in risk independent of absolute risk. For example, the relative risk reduction with statin treatment is constant at 33%. Therefore, the absolute benefit is determined by an individual's absolute risk. Consider two men aged 45 years with a serum cholesterol of 6.0 mmol/l; one has no other risk factors while the other smokes cigarettes, has diabetes mellitus, and hypertension complicated by left ventricular hypertrophy. Absolute risks of CHD in the next 10 years are < 10% and > 30% respectively; both would gain the same relative risk reduction from treatment with a statin but absolute benefit is more than three times greater in the latter individual (> 10% *v* < 3%).

i. Evidence that absolute CHD risk is a sound basis for intervention

If an intervention (A) provides a 50% reduction in risk of an event, the intervention may reasonably be considered very effective. However, if the incidence (equivalent to absolute risk) of that event is only two per million per year, then one million people have to be exposed to the intervention for one year to save one event. Therefore it would probably be considered an inappropriate intervention despite its efficacy. In contrast an intervention (B) which reduces the risk of an event by 10%, where the absolute risk is 5% per year, requires only 200 people to be exposed to the intervention for one year to prevent one event. Consequently depending on the nature and severity of the event and the cost of the intervention, intervention (B) may well be considered appropriate. It becomes clear from this analogy that for an intervention to be soundly based the correct balance between efficacy (for example, 50% reduction in risk) and incidence of the event to be prevented (for example, 5% per annum) have to be considered. The absolute benefits likely to accrue for the intervention can then be anticipated.

BP and serum cholesterol exhibit a log linear relation with risk of CHD in prospective epidemiological studies, with little evidence of a lower threshold. Therefore, a given proportional reduction in a risk factor should produce a constant proportional relative reduction in CHD risk. However, the absolute reduction in risk (benefit to the individual) will depend on baseline absolute risk. Risk factors have at least additive effects on the magnitude of absolute risk but the shape of the relation is unaltered. Thus, epidemiological findings strongly support the use of absolute CHD risk as a sound basis for intervention. Clinical trial evidence for antihypertensive and lipid lowering therapy are consistent with these observations.

In the trials of antihypertensive therapy, established CHD does not complicate the interpretation because these were all primary prevention trials. Meta-analysis of clinical trials of antihypertensive agents has shown a statistically significant (12%) decrease in all cause mortality. Significant reductions were seen in individual trials,[64 108] and in trials of older patients significant decreases in CHD deaths were also observed.[65 66] This reflects the greater absolute CHD risk in the elderly. The British Hypertension Society guidelines for the management of hypertension recognise this by recommending that treatment should generally be started at higher levels of BP in younger patients, without other CHD risk factors, compared with the elderly.[5]

The majority of trials of cholesterol lowering therapy have not selected populations with levels of cholesterol which have been particularly high. Indeed the average serum cholesterol in trial participants is only around the average of the middle aged British population.[69] A major

Table 1 Percentage of men and women in England and Scotland at different levels of CHD risk

	England (aged 30 to 74 years)		*Scotland (aged 30 to 64 years)*	
*Absolute CHD risk (%)**	*Men*	*Women*	*Men*	*Women*
⩾ 30	3	–	2	0.3
25 to 29	5	2	3	1
20 to 24	8	2	6	1
15 to 19	12	5	10	4

*Framingham function: absolute risk of non-fatal myocardial infarction and coronary death over 10 years.

factor determining whether there was a significant decrease in all cause mortality in these trials was the absolute risk and therefore numbers of CHD deaths in the populations studied.[109] The likelihood that there is a similar relative reduction in the risk of CHD events, including death, regardless of the absolute risk of CHD, is supported by a comparison of the results of the 4S study, in which the annual CHD event rate was 4.5%,[72] and the WOSCOPS study, in which the annual CHD event rate was 1.5%.[75] In relative terms the decreases in CHD events and mortality are similar in the two trials, but the number of patients who must receive treatment to prevent one such event is fewer in 4S. The implication is that the difference between primary and secondary prevention trials is largely explicable in terms of absolute risk rather than any therapeutic responsiveness induced by clinically overt CHD.

ii. Level of absolute CHD risk at which clinical intervention is justified

If antihypertensive or cholesterol lowering therapy is associated with a definite risk of major adverse effects, unrelated to BP or cholesterol, then it is possible to balance this risk against the decrease in CHD events which treatment will achieve, and thus establish the threshold of risk above which the overall therapeutic outcome is favourable. In the case of thiazide diuretic and β blocker treatment for hypertension, and statin therapy for cholesterol reduction, during the five year course of most trials major adverse events have been few. There is thus little to offset the benefits of such therapies. In the case of fibrate treatment the same has not yet been demonstrated with confidence and some of the newer antihypertensive drugs remain to be evaluated.

The threshold for drug treatment of blood pressure and blood lipids in terms of absolute CHD risk is a matter of judgment, and for blood pressure it is necessary to consider cardiovascular risk because of the additional benefit seen for stroke. Considerations include the absolute CHD (or cardiovascular) risk of patients in the trials that demonstrated benefit and the number of at risk patients at these levels of risk who must be treated for a defined period of time for one individual to benefit. It is also necessary to consider the cost of preventing that CHD event at these different levels of absolute CHD or cardiovascular risk. One difficulty with basing recommendations entirely on cost benefit analysis is that the costs of drugs change. Cost benefit analysis of antihypertensive therapy with thiazide diuretics is, for example, favourable because these drugs are cheap and highly effective in decreasing stroke risk even though they are less effective in preventing CHD than cholesterol lowering medication. Statin therapy for lowering cholesterol is currently expensive, but is likely to become cheaper with increasing competition and as patents expire. Importantly, the cost of drug therapy is only one part of the cost as there are resource implications for screening, investigation, and follow up of individuals at different levels of CHD risk, principally in general practice but also in specialised hospital clinics. The evidence from clinical trials has unequivocally shown that individuals with an absolute CHD risk as low as 15% (equivalent to a cardiovascular risk of 20%) over 10 years do benefit from blood pressure and lipid lowering therapies that reduce coronary and cardiovascular morbidity and mortality. So the scientific evidence justifies lifestyle and therapeutic interventions in the population, at least down to a 15% absolute CHD risk, but the magnitude of this task and its cost for the medical services would be considerable. The costs would include those of opportunistic screening, follow up, laboratory and other investigations, referral of some patients for a specialist opinion, etc, as well as the cost of drugs. In advocating an order of priorities for coronary prevention, and having started with patients with established atherosclerotic disease, it is appropriate to stage risk factor intervention in the general population, and audit the results achieved at each stage. As a minimum all individuals with an absolute CHD risk of 30% or more over 10 years should be targeted now for comprehensive risk factor management, which will include, as appropriate, blood pressure and lipid lowering therapy. There is already compelling evidence from national audits such as ASPIRE and other local studies that the potential for comprehensive risk factor intervention has not even been achieved in these coronary patients and other high risk individuals. When it has been shown that those at highest risk have been effectively targeted the scientific evidence justifies a progressive expansion of coronary prevention from 30% down to 15% absolute CHD risk, linked to NHS resources needed to deliver effective preventive care. For individuals with an absolute CHD risk less than 15% over the next 10 years, drug therapy is not normally recommended.

The exceptions to treatment in the context of absolute CHD risk are severe hypertension (systolic > 160 mm Hg and/or diastolic > 100 mm Hg), familial hypercholesterolaemia or other inherited dyslipidaemia, or patients with diabetes mellitus with associated target organ damage.

iii. Proportions of men and women in the UK potentially eligible for treatment

The proportions of men and women (excluding patients with reported CHD or other atherosclerotic disease) who are potentially eligible for treatment at different levels of

absolute CHD risk (table 1) in England and Scotland has been estimated by applying the Framingham risk function to the Health Survey for England (1994) and the Scottish Health Survey. The Health Survey for England did not measure HDL cholesterol and this has been estimated from the Scottish data. The Scottish survey is based on people aged 30–64 whereas in England the population 30–75 years was surveyed. For the age group 64–75 in England the average HDL cholesterol at age 64 years in Scotland was used.

b. LIFESTYLE

Priority should be given to lifestyle. Indeed, for many patients whose absolute CHD risk is not sufficiently high to justify pharmacotherapy at their present age, lifestyle intervention will be the only approach offered for primary prevention. All cigarette smokers should be encouraged to stop smoking. Men and women who do so experience a rapid decline in the risk of CHD, by as much as half after one year, but up to 10 years may be needed to reach the risk level of those people who never smoked.[110–115] Physician advice and encouragement given repeatedly over time to healthy high risk men has been shown in randomised controlled trials to reduce smoking by 21%. All forms of nicotine replacement therapy are effective aids for nicotine dependent smokers, particularly for those who seek help in stopping smoking.[24] Nicotine gum (2 mg) and patch reduced smoking by 11% and 13%, respectively, in trials of self referred smokers compared to placebo. However, in unselected smokers nicotine gum and patch only reduced smoking by 3% and 4%, respectively. Nicotine gum (4 mg) was more useful in the more dependent smokers. Many individuals will require dietary advice, including weight reduction,[32] and would also benefit from increased physical activity.[116] Physical activity, either at work or in leisure time, is associated with a lower risk of CHD in both men and women.[117–121] The largest reduction in risk is seen between sedentary and moderately active individuals and the additional reduction in risk between moderately and vigorously active individuals is more modest. Protection is lost when people stop exercising and, conversely, inactive people who take up exercise acquire a lower risk of CHD. Although any activity appears to be of benefit, those which are more active such as brisk walking or heavy gardening appear to be more protective. However, where the absolute risk of CHD is sufficiently high to justify more intensive intervention, or when the level of any one risk factor is already associated with target organ damage, lifestyle measures alone are not sufficient and drugs should also be used.[122 123]

c. BLOOD PRESSURE

In 17 unconfounded trials of pharmacological treatment involving almost 50,000 individuals with mean follow up of 4.9 years, the average treatment induced fall in diastolic BP of 5–6 mm Hg was associated with highly significant reductions in fatal and non-fatal stroke (38%), and fatal and non-fatal heart attacks (16%); there were no significant differences among the individual trials.[124] Non-vascular deaths were evenly distributed among treatment groups and therefore all cause mortality was also reduced (12%). This overview provides direct and highly significant evidence that just a few years of BP lowering prevents the proportion of stroke events anticipated from prospective epidemiological data, although there may have been a shortfall in prevention of CHD events (16% observed *v* 20–25% expected). Uncertainties about the value of antihypertensive therapy in preventing CHD events may reflect the limited power of individual trials for a statistically reliable assessment of treatment effect. It is likely that the benefits of antihypertensive treatment have been underestimated in most of the randomised controlled trials because, overall, up to 25% of patients randomised to placebo—those with the highest pressures—were switched to active therapy.[64–66 125] In addition, most trials were short term, and relatively low risk patients were included preferentially (those with other major concomitant risk factors or target organ damage were excluded), reducing the likelihood of absolute risk reduction.[126 127]

Although cardiovascular risk increases across the whole BP range,[128] recommendations for the threshold of intervention are based on the level of BP above which treatment has been shown to reduce cardiovascular risk in randomised controlled trials. Evidence from both observational studies and randomised control trials suggest that cardiovascular risk is at least as closely associated with systolic BP as with diastolic BP.[129 130] However, because entry into the randomised controlled trials was based on diastolic BP level,[124] with two exceptions,[66 131] thresholds for intervention have usually been based on diastolic BP. In addition to BP the threshold for therapeutic intervention with antihypertensive drugs should also be influenced by an assessment of all cardiovascular risk factors, and not simply the level of BP.

Diastolic BP measurements of 110 mm Hg or greater should be repeated over one to two weeks to confirm a sustained increase, despite lifestyle intervention, after which drug treatment should be started. Individuals with diastolic BP in the range 100–109 mm Hg, but with no evidence of target organ damage, should be given lifestyle advice and observed, initially weekly and thereafter monthly. If there is a downward trend in BP (diastolic less than 100 mm Hg), observations should be continued together with reinforced lifestyle advice. If diastolic BP is sustained at or above 100 mm Hg during this three to six month period, drug treatment should be started.[5]

Although trial data in individuals aged younger than 60 years are lacking, it seems reasonable to recommend the systolic treatment threshold established in two trials of isolated systolic hypertension in the elderly,[66 131] namely a systolic BP persistently raised above 160 mm Hg.

The management of individuals in whom diastolic BP remains between 90 and

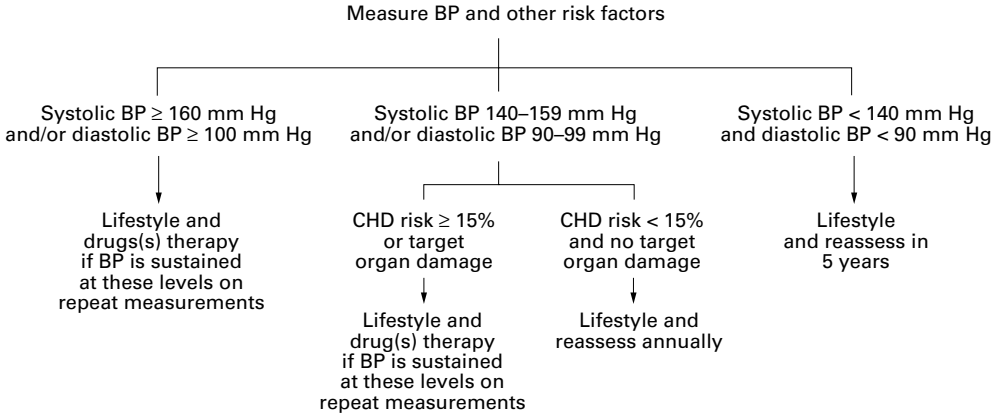


Figure 2 Absolute CHD risk and management of blood pressure in primary prevention of CHD and other atherosclerotic disease. CHD risk, non-fatal myocardial infarction and coronary death over 10 years.

99 mm Hg and/or systolic BP between 140 and 159 mm Hg on repeated measurements should be considered in the context of their absolute risk of CHD and stroke, not CHD alone.[124 132 133] Risk of CHD and stroke increases across this BP range, but the scale of the risk for BP alone and hence potential benefit of drug treatment is relatively small.[128 134] However, the risk of hypertension is greatly increased when complicated by pre-existing target organ damage or the presence of other cardiovascular risk factors. Treatment decreases the risk and the absolute risk reduction is greater than in treating uncomplicated individuals, although the level of risk attained remains increased.[135] Consequently, in patients with target organ damage (LVH, retinopathy—haemorrhages or exudates—renal impairment or proteinuria, for example) or if they have other cardiovascular risk factors antihypertensive treatment is indicated.

On the basis of clinical trial data several national and international guidelines on hypertension management have been produced in recent years.[133 136–138] These guidelines are mainly, although not totally, in agreement over the management of BP. The only national guidelines which deviate from a management policy based primarily on BP levels are those from New Zealand.[133] These were the first to recommend a management policy based on BP levels assessed in the context of absolute cardiovascular risk, including stroke. In New Zealand a risk of 20% or higher of cardiovascular events over 10 years is considered acceptable for drug treatment since benefits are likely to exceed drug related adverse effects.

In the management of hypertension, such an approach is logical for the prevention of CHD. Individuals with a sustained diastolic BP of 100 mm Hg or greater, and/or systolic BP over 160 mm Hg, should be prescribed antihypertensive drugs because of established benefit in reducing total cardiovascular risk, and stroke in particular. In those with lower levels of sustained diastolic or systolic BP, 10 year cardiovascular (CHD and stroke) risk should be calculated (see appendix 1). It is important to calculate cardiovascular, and not just CHD, risk in the management of hypertension because of the additional benefit of BP lowering in relation to stroke. An absolute cardiovascular risk of 20% over 10 years is equivalent to an absolute CHD risk of 15% over the same time and this is the recommended threshold for antihypertensive drug treatment (fig 2). Relative risk reduction with antihypertensive treatment is 16% and this is lower than the 33% attained by statin treatment. So the number of patients requiring treatment with antihypertensive drugs over a defined period at this level of absolute CHD risk, in order to prevent one major coronary event, will be larger than the number requiring cholesterol lowering therapy over the same period for the same benefit, although antihypertensive therapy will have a greater effect in reducing stroke events.

Many hypertensive individuals will have other cardiovascular risk factors such as smoking, dyslipidaemia, a strong family history of CHD or other atherosclerotic disease, or a tendency to glucose intolerance even if they do not yet have frank diabetes. Lipids should be measured in all hypertensive patients and lipid lowering medication considered. Other modifiable risk factors should also be addressed and managed with lifestyle and, when appropriate, drug therapies.

Two classes of drugs—diuretics (particularly thiazides)[64–66 125 133 135 139 140] and β blockers[64 65 132] — have been tested extensively in long term morbidity and mortality trials. While other newer classes of drugs such as ACE inhibitors, calcium antagonists, and α blockers may in some circumstances be equally or even more effective in lowering BP,[141 142] only dihydropyridine calcium antagonists have been evaluated in one long term trial.[131]

For elderly hypertensive patients, evidence from the Medical Research Council trial[65] suggests that a thiazide diuretic combined with a potassium sparing drug may be preferable to a β blocker as first line treatment; broadly similar benefits were, however, seen in the systolic hypertension in the elderly program (SHEP) study when chlorthalidone was used,[66] and in the systolic hypertension-Europe (SYST-EUR) trial where nitrendipine was the active agent.[131] In the Swedish trial in old patients with

hypertension (STOP-hypertension), β blockers were equally efficacious.[64]

The metabolic effects of diuretics and β blockers should be considered in certain groups of patients but are much less pronounced at currently recommended doses—for example, bendrofluazide 2.5 mg daily which has similar antihypertensive efficacy to 5 mg daily.[143] Thiazide diuretics tend to increase serum cholesterol and serum triglycerides.[143] The latter effect is most likely in patients with diabetes, in whom thiazides also exacerbate hyperglycaemia, but it has now been shown that thiazides actually improve the prognosis of hypertensive patients with diabetes. β adrenoreceptor blocking drugs, particularly those which are not cardioselective, increase serum triglycerides and decrease serum HDL cholesterol[144]; these changes are most marked in those with pre-existing hypertriglyceridaemia.

Newer classes of drugs may be considered as "alternative" first line agents when diuretics and β blockers are contraindicated, or ineffective, or when side effects occur. New drugs may be preferred as first line agents in patients with coexistent conditions such as diabetes mellitus, renal impairment, asthma, heart failure, LVH, severe dyslipidaemia, peripheral arterial disease, prostatism, and gout. Unfortunately, patients with these concomitant conditions were excluded from the long term hypertension trials and hence optimal therapy for such patients remains to be established in randomised controlled trials.

It may be difficult to demonstrate any significant benefit of one antihypertensive regimen over another in terms of CHD prevention, because to do so might require the observation of several thousand CHD events in directly randomised comparisons.[145] However, several comparative outcome trials are in progress and others are required among subgroups such as patients with diabetes and those with LVH or evidence of other atherosclerotic disease.[146]

The average BP fall induced by the usual doses of different categories of drugs is similar,[142] but large individual variations in response occur frequently. In addition, significant variation in response to different drug groups has been reported among different ethnic groups[141] and age groups.[147]

If all therapeutic considerations are equal, drug costs become critically important. Thiazide diuretics and β blockers are inexpensive and much cheaper than the newer agents. However, in determining health policy, cost effectiveness rather than the cost of drugs is of pivotal importance. It is clear that treatment of the elderly and those at highest risk is more cost effective.

Drug combinations may be required in up to half of all cases of hypertension. Combinations should be selected rationally and examples of such combinations include: diuretics + β blockers; diuretics + ACE inhibitors; β blockers + long acting dihydropyridine calcium channel blockers; β blockers + α blockers; ACE inhibitors + calcium channel blockers; and ACE inhibitors + α blockers. For reasons of convenience, cost and increased patient compliance, preparations that combine two drugs in a single tablet or capsule may be appropriate once the need for and dose of the constituent drugs have been established.

The benefits of treatment observed in the trials are related to the BP control achieved, but the risk of both stroke and CHD continue to be related to both the systolic and diastolic BP.[148] Nonetheless, the inadequacy of currently available data is reflected in the variable recommendations made for target levels in several recently published national guidelines.[5 133 136–138] The World Heath Organisation/International Society of Hypertension (WHO/ISH) guidelines consider it appropriate for the goal of treatment to be the maximum BP reduction tolerated.[138] The British Hypertension Society guidelines specified that diastolic BP should be reduced to less than 90 mm Hg.[5] However, because very little definitive information was available to provide guidelines on target systolic BP, a level of less than 160 mm Hg was recommended. Other guidelines recommended more intensive treatment, suggesting a minimum target of less than 140/90 mm Hg and an optimal target of less than 130/80 mm Hg if tolerated (less than 120/80 mm Hg in young adults).[136] From the results of the hypertension optimal treatment (HOT) trial,[149] a target BP of < 140 mm Hg systolic and < 85 mm Hg diastolic is recommended. In patients with hypertension and diabetes the target should be < 130 mm Hg systolic and < 80 mm Hg diastolic. Concerns about possible adverse effects of over enthusiastic treatment should not distract from the real concern that in the UK in 1994 approximately half of treated hypertensive patients had inadequate BP control.[150]

d. LIPIDS

i. Common hyperlipidaemia

With one exception, meta analyses[68 69 80 109 151 152] have unanimously confirmed that cholesterol lowering, whether by diet or diet and drugs, decreases CHD risk. The decrease has been estimated to be around 25% for a 10% decrease in cholesterol (equivalent to 0.6 mmol/l on average in the trials), similar to that found in secondary prevention trials, and to the 27% difference observed in two groups of comparable age to those in the trials whose cholesterol differs spontaneously by 10%.[68] Furthermore the 25% decrease in CHD risk was achieved in the trials after the first two years of treatment. There is, however, no evidence from meta analysis for a statistically significant decrease in all cause mortality in primary prevention trials. There has been much speculation about why this should be, but the fact is that CHD deaths in primary prevention trials comprise a much smaller proportion of all deaths compared to secondary prevention. Thus a decrease of 25% or so in CHD death will only have a clear impact on overall mortality if greater numbers of patients are available for meta analysis than have thus far participated in clinical trials, or trials are conducted in higher risk patients. The major reason for asking whether cholesterol lowering

decreases all cause mortality is to ensure that it does not increase mortality resulting from some cause other than CHD to a greater extent than it reduces CHD mortality. This question cannot be readily answered with certainty for most medical therapies, including antihypertensive treatment, for which all analyses are currently statistically underpowered. When non-CHD deaths in cholesterol lowering trials are analysed they do not appear to be related to the extent of cholesterol lowering.[69 109] The excess of cancer deaths in one diet trial has not been generally encountered in other such trials.[69] There does appear to have been a real increase in deaths due to cholelithiasis (or perhaps more accurately cholecystectomy) in the WHO trial of clofibrate,[153] although now that the intention to treat analysis of this trial is available it is less easy to understand earlier worries about the effect of clofibrate on other causes of death.[154] Nevertheless, the long term follow up of the Helsinki heart study was not entirely reassuring about gemfibrozil and non-CHD deaths. The results of further trials of fibric acid derivatives should, however, help to clarify matters.

Currently, the most reassuring findings about the benefits and safety of lipid lowering treatment in primary prevention come from the WOSCOPS study, the first large primary prevention trial of a statin.[75] In the WOSCOPS study 6595 men aged 45–64 years, with no history of acute MI and whose serum LDL cholesterol was 4.5–6.0 mmol/l despite dietary advice, were randomised to receive pravastatin 40 mg daily. The average serum cholesterol at randomisation was 7.0 mmol/l and the mean serum triglyceride concentration was 1.79 mmol/l. The mean trial observation period was 4.9 years. During this time pravastatin compared with placebo decreased serum cholesterol by 20%, CHD incidence by 31% ($p < 0.001$), and all cause mortality by 22% ($p = 0.051$). As in the 4S study, there was no evidence of an increase in non-cardiovascular deaths and the drug compared favourably with placebo in terms of other side effects.

The results of WOSCOPS have been reinforced by the Air Force/Texas coronary atherosclerosis prevention study (AFCAPS/TEXCAPS),[155] which included 6605 healthy men and women with average total cholesterol (mean 5.7 mmol/l), below average HDL cholesterol (mean for men 0.94 mmol/l and for women 1.03 mmol/l), and whose annual CHD risk averaged 1.3%. After 5.2 years of treatment with lovastatin, in addition to a low saturated fat low cholesterol diet, the incidence of major acute CHD events (fatal or non-fatal myocardial infarction, unstable angina or sudden cardiac death) was reduced by 37% ($p < 0.001$). Total mortality was not changed but the trial was not powered to test for an effect on total mortality. As in 4S, there was no evidence of an increase in non-cardiovascular deaths in WOSCOPS or AFCAPS/TEXCAPS, and the statin drugs compared favourably with placebo in terms of other side affects.

Thus there is strong evidence that decreasing serum cholesterol is effective in the primary prevention of CHD. Cholesterol reduction by diet or by statins appears to be safe (myositis is a comparatively rare event). Although the same may be true of fibric acid derivatives, this is less securely established at present. Although safe and likely to be beneficial in the population as a whole, the achieved effect of diet in decreasing serum cholesterol is often small.[122 123] Although lipid lowering drug treatment is not likely to be associated with harmful effects, the exposure of people with relatively low absolute risk of CHD who would experience only very small benefit from this therapy is to be deprecated. In primary prevention it would be appropriate to treat, as a minimum, those whose CHD risk is 30% or greater over the next 10 years and a policy of treating those whose risk exceeds 15% over 10 years is recommended as the ultimate objective (fig 3). It is logical to employ the same cholesterol target as in secondary prevention, namely cholesterol less than 5.0 mmol/l (LDL cholesterol less 3.0 mmol/l).

There have been few primary prevention trials involving women, but those which have included women generally show a similar relative reduction in CHD risk from cholesterol lowering in women compared to men,[68] as they do in secondary prevention.

It should be emphasised that CHD risk calculation may be less accurate in certain groups of patients. Particular attention is drawn to patients with familial hypercholesterolaemia, patients with diabetes and target organ damage, and patients of Indo-Asian descent. All these groups appear to be at greater risk than that calculated from the Framingham equation.[9] Clinicians should make allowance for this.

For screening purposes, a non-fasting serum cholesterol and non-fasting HDL are adequate. A measurement of HDL cholesterol is essential to assess accurately absolute CHD risk. This is particularly true in women who frequently maintain high serum HDL concentrations long after their menopause, which means that a raised total cholesterol can be misleading. Also, as low HDL tends to cluster with other risk factors such as diabetes and hypertension, reliance on total cholesterol alone in such men or women will often underestimate risk. All patients who have pronounced hyperlipidaemia, or for whom lipid lowering therapy is being considered, should have a fasting lipoprotein profile to include fasting cholesterol, triglycerides, and HDL cholesterol. Fasting serum triglycerides are important to measure before introducing lipid lowering drug therapy because a raised cholesterol may not be caused by increased LDL. If severe hypertriglyceridaemia is present, an increase in serum cholesterol may be caused by cholesterol transported in very low density lipoprotein (VLDL) and chylomicrons (type V hyperlipoproteinaemia).[156]

In all patients whose hyperlipidaemia is severe, or in whom lipid lowering drug therapy is being considered, secondary causes of hyperlipidaemia should be excluded. This includes inquiring about possible excessive

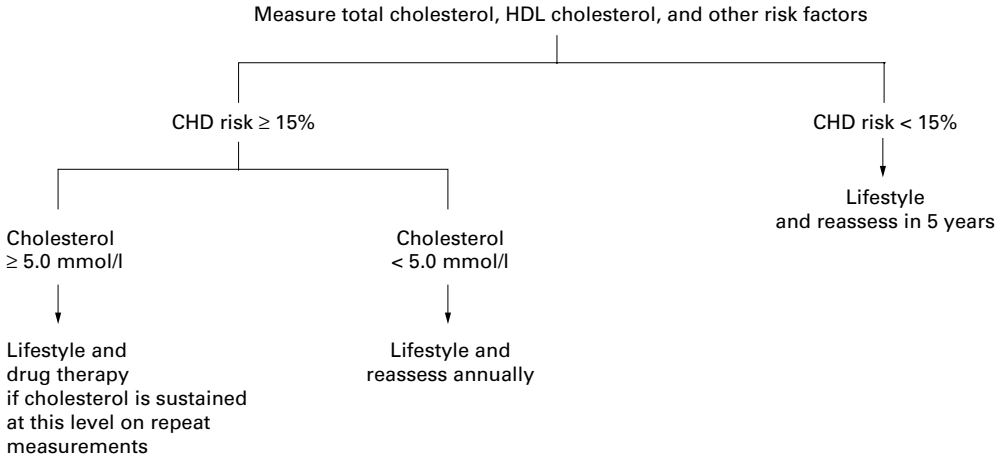


Figure 3 Absolute CHD risk and management of blood lipids in primary prevention of CHD and other atherosclerotic disease. CHD risk, non-fatal myocardial infarction and coronary death over 10 years.

alcohol consumption, and screening for thyroid disorders, renal disease, liver disease, diabetes mellitus, and impaired glucose tolerance.

When monitoring patients to assess therapeutic response, cholesterol can be measured non-fasting in those who do not have hypertriglyceridaemia.

Two other classes of lipid lowering drugs available in the UK have not previously been mentioned: the bile acid sequestrating agents and nicotinic acid (niacin) and its derivatives. Generally bile acid sequestrating agents, such as cholestyramine and colestipol, are poorly tolerated by patients and of all the lipid lowering drugs niacin is associated with the most serious side effects. Fish oils are not generally prescribed in contemporary British clinical practice despite evidence that they improve survival after MI.[27] They are effective in lowering serum triglycerides and may have other beneficial actions—for example, on platelet function. However, fish oil in doses large enough to have these effects are poorly tolerated. The results of trials of refined preparations which concentrate the highly polyunsaturated fatty acid components of fish oil are awaited.

If general practitioners, occupational medical services, or other groups including private health organisations undertake cholesterol screening, it is essential that this is not conducted in isolation from BP measurement and inquiry about other CHD risk factors including family history. A screening pro forma suitable for use in screening examinations, in general practice and elsewhere is included in appendix 2 (table 2).

ii. Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an autosomal dominant condition, affecting 1 in 500 of the UK population. Its pathophysiology is well documented. The primary defect is a mutation of the LDL receptor gene.[157] An enormous number of different mutations have been described. However, the phenotypic expression of the disease is remarkably consistent. Typically, the patient has a cholesterol of around 9 mmol/l or greater together with clinical signs such as tendon xanthomata, early corneal arcus, and the premature development of CHD. Untreated, the majority of male heterozygotes and half of the female heterozygotes will have a clinical CHD event before the age of 60 years. Results from the Simon Broome Register of Genetic Hyperlipidaemia[158] showed that FH patients, who had not already developed CHD, suffered a CHD mortality rate at least 10 times greater than that of patients in WOSCOPS.[75] The relative increase in risk is particularly evident for younger patients. The patients were almost all receiving lipid lowering drug therapy and there was an early indication from the results that CHD mortality may have declined in the years following the advent of statin therapy. Coronary angiographic regression studies also point to the benefit of lipid lowering therapy in FH.[159]

The onset of premature CHD in FH varies between families and between men and women. On average women develop the disease some nine years later than men. In practical terms there is much greater concordance of onset of CHD disease within families, presumably because of a combination of environmental and, more importantly, genetic homogeneity. Once the diagnosis is made, the need to screen the immediate family is implicit in view of its autosomal dominant inheritance.

The management of familial hypercholesterolaemia includes appropriate dietary advice and drug therapy. The drug class of first choice for familial hypercholesterolaemia is a statin. Several members of each family, including children and women in their reproductive years, will commonly require treatment and advice. In addition, combinations of lipid lowering drugs may be necessary and early cardiological investigation is often required. Hence, in general, the diagnosis and management strategy is best coordinated by a specialist. Guidelines for children are to be found in the joint publication of the British Hyperlipidaemia Association and the British Paediatric Association on Paediatric Hyperlipidaemia.[160]

Table 2 Screening pro forma suitable for use in screening examinations

Name	Telephone number		
Gender	Age		
Personal history	Previous myocardial infarction/angina of effort/peripheral arterial disease/cerebral infarction		
Family history	Angina or heart attack in: mother/sister aged < 65 years father/brother aged < 55 years		
Smoking habit			
Current	Cigarettes	/day	
Past	Cigarettes	/day	
	Length of exposure		Years
	Other tobacco		
Diabetes mellitus	Yes/no		
Age at menopause	Years		
Body weight	kg	Height	cm
Blood pressure	Systolic	mm Hg	
(treated hypertension yes/no)	Diastolic	mm Hg	
Xanthelasmata	Yes/no		
Other xanthomata (eg, tendon)	Yes/no		
Corneal arcus in patient aged < 50 years	Yes/no		
Cholesterol	mmol/l		
HDL cholesterol	mmol/l		
Date of last tetanus booster			
Date of last cervical smear			

NB If angina is diagnosed for the first time the screening nurse should refer the patient to the doctor. Referral to a cardiologist for full evaluation may be important because further investigation may be indicated on prognostic grounds even if symptoms are not severe. Of more immediate concern is lifestyle advice, control of blood pressure, blood cholesterol, and diabetes mellitus, and therapy with low dose aspirin.

e. DIABETES AND IMPAIRED GLUCOSE TOLERANCE

For patients with diabetes mellitus CHD risk is greatly increased for both type I (insulin dependent) and type II (non-insulin dependent) diabetes mellitus.[161 162] While there is a clearly recognised chronological sequence of events between the development of impaired glucose tolerance, type II diabetes, and ultimately microvascular disease, the same relation does not pertain for the development of macrovascular disease. In general, over 70% of patients with diabetes die from macrovascular disease (mainly CHD) and this risk is not closely correlated with glycaemic control.[161] Some studies suggest that both established patients with diabetes and patients with impaired glucose tolerance show the same relative increased risk for CHD.[163–165] One interpretation is that macrovascular risk factors are associated with a lower glycaemic level than the one currently employed in the diagnosis of type II diabetes,[166] which is based on risk of microvascular disease.

Thus, implicit in the long term management of diabetic patients is the requirement for multiple risk factor modification for coronary prevention. Patients with type II diabetes often have coexistent hypertension and dyslipidaemia. The American Diabetes Association recently redefined diabetes mellitus as a fasting blood glucose of 7 mmol/1 or greater. The WHO has recently proposed new diagnostic criteria[167] and, if these are adopted, individuals with a fasting plasma glucose $\geq$ 7.0 mmol/1 will be designated as having diabetes, those with fasting glucose < 7.0 mmol/1 but a 2 hour value $\geq$ 7.0 and < 11.1 mmol/1 as having impaired glucose tolerance (IGT), and those with fasting plasma glucose $\geq$ 6.1 mmol/1 but < 7.0 mmol/1 as having impaired fasting glycaemia (IFG). Individuals with IGT and IFG are at increased risk of developing diabetes mellitus, particularly when hypertriglyceridaemia is also present.

There is no direct clinical trial evidence that reducing BP or serum lipid concentrations in diabetes decreases CHD incidence. However, reduction of BP and lipids should yield considerable benefit because patients with diabetes have a high absolute CHD risk. Relative benefit of BP lowering in groups with diabetes mellitus was the same as in the non-diabetic population in the hypertension detection and follow up program[135] and SHEP.[168] The threshold for BP intervention in patients with type I and type II diabetes, because of their absolute CHD risk, should be lower than in uncomplicated hypertension particularly in those with evidence of end organ damage such as nephropathy. In type I diabetes in the absence of nephropathy (microalbuminuria or proteinuria), the prevalence of hypertension is similar to that in the non-diabetic population. Thus, in type I diabetes, hypertension usually reflects the presence of diabetic nephropathy.[169] Blood pressure begins to rise as microalbuminuria becomes established (incipient nephropathy) and thereafter rises inexorably year on year as urine albumin excretion increases.[169] Almost all patients with type I diabetes and overt nephropathy (conventional urine stick test positive for protein, urine albumin excretion > 200 mg/24 hours) are hypertensive. The threshold for antihypertensive treatment in type I diabetes is $\geq$ 130 mm Hg systolic and/or $\geq$ 80 mm Hg diastolic. Blood pressure reduction and ACE inhibitor therapy slow the rate of decline of renal function in overt diabetic nephropathy,[170] and delay progression from the microalbuminuric phase to overt nephropathy.[171 172] ACE inhibitors appear to have a specific renoprotective action in patients with incipient or overt nephropathy and are recommended as first line therapy. The ACE inhibitor should be titrated to the maximum dose recommended and tolerated. If ACE inhibitor therapy has to be discontinued due to persistent cough, an angiotensin II receptor antagonist may be considered, although specific renoprotection by this drug class awaits confirmation. For renoprotection, blood pressure control is at least as important as ACE inhibition and additional antihypertensive therapy is invariably required.[173] Diuretics, calcium antagonists, cardioselective β blockers or α blockers are all suitable. The target blood pressure is < 130 mm Hg systolic and < 80 mm Hg diastolic,[149] or lower (< 125 mm Hg systolic and < 75 mm Hg diastolic) when there is proteinuria.[173 174] The same thresholds and targets also apply for type I diabetes with target organ damage, microvascular disease or cardiovascular complications.

Hypertension is very common in type II diabetes and is present at diagnosis in about 40% of patients.[175] It is strongly related to obesity[175] and is highly predictive of cardiovascular complications.[175 176] In type II diabetes, hypertension does not usually indicate nephropathy, does not predict the development of nephropathy[177] but will accelerate the decline of

renal function in patients with established nephropathy. The United Kingdom prospective diabetes study (UKPDS)[178 179] and HOT trial[149] have provided important new evidence on treating hypertension in type II diabetes. In the UKPDS trial patients with type II diabetes with mean blood pressure 160/94 mm Hg were randomised to more or less intensive antihypertensive treatment, with blood pressure on drugs averaging 144/82 mm Hg and 154/87 mm Hg, respectively in the two groups. Intensive blood pressure control reduced the incidence of all macrovascular (non-fatal and fatal) complications by 34% ($p = 0.02$); stroke by 44% ($p = 0.01$), and myocardial infarction by 21% ($p = 0.13$). In addition, there was a 37% ($p = 0.009$) reduction in diabetic microvascular disease complications. Deaths related to diabetes were reduced by 32% ($p = 0.02$) but there was no significant reduction in all cause mortality. In the HOT trial a subgroup analysis of patients with hypertension and diabetes showed that titration of antihypertensive treatment aiming for a diastolic blood pressure $\leqslant$ 80 mm Hg significantly reduced all major (non-fatal and fatal) cardiovascular events by 51% compared to treatment titration aiming for a diastolic blood pressure $\leqslant$ 90 mm Hg.[149] Taken together, these trials support antihypertensive treatment of all patients with type II diabetes and blood pressure $\geqslant$ 160 mm Hg, aiming for a target blood pressure of $<$ 130 mm Hg systolic and $<$ 80 mm Hg diastolic. For patients. with type II diabetes and systolic pressure 140–159 mm Hg but diastolic pressure $<$ 90 mm Hg treatment is recommended if target organ damage, or microvascular or macrovascular complications are present, or if the absolute coronary risk is $\geqslant$ 15% over 10 years. The choice of drug for hypertension in type II diabetes is either an ACE inhibitor or β blocker based regimen as both were equally effective in reducing the macrovascular complications of diabetes in the UKPDS, with no evidence that either drug class has specific benefit or deleterious effects. Subgroup analyses of other outcome trials have shown that other classes of antihypertensive drugs are also beneficial in hypertensive patients with diabetes. Thiazide diuretics, previously contraindicated in diabetes, substantially improved the prognosis of hypertensive patients with diabetes,[168 180] and in the Syst-Eur trial treatment based on the dihydropyridine nitrendipine also had significant clinical benefit in elderly patients with isolated systolic hypertension and diabetes.[131] Thus, there is evidence from outcome trials in hypertensive patients with diabetes for the efficacy and safety of ACE inhibitors, β blockers, dihydropyridines, and low dose thiazides. Blood pressure control will usually require more than one antihypertensive drug, and about 30% of hypertensive patients with diabetes need three or more agents in combination.[131] Many patients with type II diabetes are overweight[175] and have high cardiovascular risk.[175 176] They need intensive and sustained advice on lifestyle and appropriate treatment to achieve other risk factor targets as well as glycaemic control.

For cholesterol lowering therapy in patients with diabetes, 1% of the participants of the recently reported WOSCOPS study were diabetic. Subgroup analysis of this study showed that the reduction in morbidity and mortality observed in the diabetic patients was equivalent to that observed in those without diabetes. Currently outcome trials of antihypertensive and lipid lowering therapy (both statins and fibrates) in type II are in progress. In the interim it is justified to extrapolate data from both primary and secondary prevention studies in the UK to diabetic patients whose 10 year CHD risk is 15% or greater. As is evident from fig 1, this will often mean type II patients aged 40 years and over whose serum cholesterol:HDL cholesterol ratio exceeds 5.5 and who have one additional risk factor. The development of proteinuria is a particularly strong predictor of CHD risk and patients with this complication should be treated as in secondary CHD prevention.[181] In type I patients HDL cholesterol tends to be high for reasons which are not entirely clear but relate in part to insulin therapy. The HDL in type I patients does not confer the same degree of protection against CHD as in those without diabetes. The charts for diabetes (fig 1) could be used in type I patients if the serum cholesterol number in mmol/l was used in place of the serum cholesterol:HDL cholesterol ratio, or the clinician initiated lipid lowering drug therapy at a lower level than that predicted using the ratio, particularly in patients whose CHD risk was close to 15% over 10 years.

A statin is a logical choice of lipid lowering drug in diabetic patients when the dyslipidaemia is associated with an increase in LDL cholesterol. It may be appropriate to use fibrate drugs in patients whose serum triglycerides are also raised because of evidence that they are effective in primary prevention in combined hyperlipidaemia.[81] In the Helsinki heart study, a primary prevention trial comparing gemfibrozil (fibrate derivative) with placebo, there were 135 type II patients at entry. There were eight CHD events during the trial in those receiving placebo ($n = 76$) and only two in those treated with gemfibrozil ($n = 59$), but this was not statistically significant.[182] The risk may be sufficiently high in some diabetic patients with mixed hyperlipidaemia that the combination of a statin and fibrate is justified.

Evidence from ongoing fibrate trials will emerge over the next few years which should help to clarify the medications and benefits of this class of drugs. Fibrates are not suitable for patients with impaired creatinine clearance. Because the risk of CHD in diabetic women approaches that of men it is proposed that these recommendations should be similarly applied to both men and women.

f. ASPIRIN

Aspirin or other platelet modifying drugs have not been recommended in primary prevention of CHD and other atherosclerotic disease until now. However, the results of two recent trials

support the use of prophylactic aspirin in selected high risk individuals. In the HOT trial,[149] low dose (75 mg) aspirin further reduced cardiovascular risk in well controlled hypertensive patients who already had atherosclerotic complications, or who had target organ damage such as left ventricular hypertrophy, proteinuria or renal impairment. So in well controlled hypertensive patients aged 50 years or older with an estimated CHD risk of ⩾ 15% (cardiovascular risk of ⩾ 20%) over 10 years, prophylactic aspirin (75 mg) should be prescribed. Additional evidence comes from the thrombosis prevention trial[183] of aspirin and warfarin in which high risk men, regardless of the presence of hypertension, also benefited from aspirin therapy. So aspirin at a dose of 75 mg is now also recommended in these selected high risk patients over the age of 50 years in primary prevention of CHD and other atherosclerotic disease.

g. CHRONIC RENAL FAILURE

Hypertension and hyperlipidaemia are common in chronic renal disease.[184 185] The coexistence of hypertension and proteinuria is a very powerful marker for CHD.[186] Effective treatment of BP has been shown to slow the decline in renal function in small studies of non-diabetic patients with renal impairment,[187 188] and therefore reduction in CHD events is to be expected, although large scale outcome studies have yet to be published. The threshold for antihypertensive treatment is ⩾ 140 mm Hg systolic and/or ⩾ 90 mm Hg diastolic for patients with proteinuria or renal impairment. Whether ACE inhibitors have a specific renoprotective effect in non-diabetic renal failure, over and above their antihypertensive action, remains uncertain.[189 190] Meta-analysis of all controlled trials showed a 30% reduction in incidence of end stage renal failure with ACE inhibitors[189] but this may be explained by additional blood pressure reduction.[190] ACE inhibitors reduce proteinuria and are probably renoprotective in patients with proteinuria ⩾ 3 g/day who have rapidly progressive renal failure.[188 190] They may not be renoprotective in those with polycystic kidneys or the DD ACE genotype.[190] ACE inhibitors may cause or worsen renal failure in patients with critical renovascular disease or serum creatinine > 250 μmol/l.[136] Blood pressure is particularly salt sensitive in patients with impaired renal function, and dietary salt reduction is important. Thiazide diuretics are ineffective in renal failure, and loop diuretics should be used. The dose of renally excreted antihypertensive drugs may need to be adjusted. Rigorous control of BP is important; a target BP of < 130 mm Hg systolic and < 80 mm Hg diastolic is recommended.

Hypercholesterolaemia occurs in association with proteinuria, its severity often reflecting the degree of proteinuria. Hypertriglyceridaemia is a feature of diminished glomerular filtration, and both proteinuria and chronic renal failure are associated with decreased levels of serum HDL cholesterol. There is increasing concern that with modern management of renal disorders many patients survive their renal disease only to die prematurely of the complications of atherosclerosis. The management of hyperlipidaemia in renal clinics is often complicated by the unsuitability of many lipid lowering drugs and by complex dietary and therapeutic regimens. However, the statin drugs do afford the opportunity of considerably ameliorating hypercholesterolaemia in chronic renal disease. In the case of serum cholesterol, statin therapy appears safe in most patients with renal impairment, unless they are receiving cyclosporin following renal transplantation where such therapy must be carefully monitored. Fibrates should generally be avoided in renal impairment and satisfactory triglyceride reductions may therefore be difficult to achieve other than by dietary restriction. The total and LDL cholesterol targets already recommended for primary CHD prevention in high risk individuals also apply to patients with chronic renal disease.

h. SPECIAL CONSIDERATIONS

i. Gender differences

Few risk factor intervention trials have included women.[191] However, extrapolation of trial results to women may be justified on the grounds that they share the major cardiovascular risk factors with men, and in the few trials which have included women, relative benefits on cardiovascular morbidity and mortality have been similar in both sexes.[192] The absolute risk of CHD is lower in women at all ages up to the very elderly when disease rates almost converge.[124] Over the age of 55 women have more obesity, higher total cholesterol, and more diabetes than men, and over the age of 65 have more hypertension than men.[128] At younger ages, BP and LDL cholesterol are lower among women than men, and throughout life women smoke less and have higher HDL cholesterol levels. One further large difference between men and women is that levels of central obesity, as measured by waist:hip ratios, are very much smaller among women.

While there is some observational evidence to suggest that hormone replacement therapy (HRT) administered to asymptomatic postmenopausal women reduces the risk of CHD,[193] there is as yet no evidence from randomised controlled trials. HRT is therefore not recommended routinely in postmenopausal asymptomatic women solely for the prevention of CHD, or for secondary prevention in women with CHD. It is best avoided when there is a family history of breast cancer.

Premature amenorrhoea, whether caused by spontaneous or surgical menopause, or by polycystic ovary syndrome, is associated with increased risk of premature CHD. Current practice is to prescribe HRT for such women, although as yet there is no evidence from randomised controlled trials to support the observational data that use of unopposed conjugated oestrogens reduces risk of CHD in asymptomatic postmenopausal women.[194 195] Because of the increased risk of endometrial carcinoma associated with the use of HRT containing only oestrogen, HRT usually also

contains a progestogen. The benefits of such HRT in preventing CHD events are less well established than for oestrogen only products. Careful evaluation of the cardiovascular risk profile of women with premature menopause is recommended in view of their increased risk of CHD.

The absolute risk of an adverse cardiovascular event associated with the use of low dose combined oral contraceptives (OCs) among non-smoking women aged below 35 years is vanishingly small.[196–198] For example, the excess or attributable risk of a stroke—the most common serious adverse event—among such women using low dose OCs is approximately 1 per 250 000 women-years.[196 197] Absolute risk of stroke and, to a lesser extent, acute MI associated with OC use are significantly increased among women who smoke or have hypertension, particularly if the user is in the older age range (more than 35 years).[197 198] The use of OCs containing higher doses of oestrogen (equivalent to more than 30 μg ethinyloestradiol) also further increases risk.

ii. The elderly

The absolute risk of CHD, and other atherosclerotic diseases, is higher in the elderly compared with any other age group. The same proportionate risk reduction will therefore potentially have a much more beneficial impact in the elderly compared with younger age groups.

There have been fewer trials in the elderly, compared to those in the middle years of life, to evaluate the efficacy of initiating new treatments (or maintaining existing treatments) in preventing CHD events. However, several trials have consistently confirmed the beneficial effect of lowering BP in patients between 60 and 80 years of age.[66–68 131 133 141] These trials provided evidence that CHD events, in addition to stroke, were reduced by treatment and were safe. In the case of cholesterol lowering, at least as much benefit was reported in a subanalysis from the 4S study in people aged 60–70 years with established CHD as in younger age groups.[72 74 75] It is recommended that in secondary prevention the upper age limit for initiating lipid lowering medication should be 75 years and for primary prevention 69 years. The latter figure was the upper age in WOSCOPS. Neither antihypertensive nor lipid lowering treatment should be stopped at any particular age.

iii. Ethnic minorities

In general, immigrant populations in the immediate period after immigration tend to have disease rates similar to the population from which they have emigrated. However, with more prolonged exposure to the new environment disease rates tend towards those of their host country. Standardised mortality rates for CHD in the UK are notably increased (approximately 40%) among south Asian immigrants, an increase which has been observed among south Asian immigrants in several other countries.[199–201] The determinants of this excess coronary risk appear to be linked to the combination of metabolic variables which constitute the insulin resistance syndrome; increased blood concentrations of triglycerides, glucose, and insulin, increased waist:hip ratio (central obesity), and decreased serum HDL cholesterol.[202–208] While CHD death rates are profoundly reduced among the Afro-Caribbean population (by approximately 50% and 25% among men and women, respectively), stroke rates in the UK are highest among the Afro-Caribbean community. Europeans have the lowest stroke rates[209 210] and the south Asians have rates between those of the Europeans and the Afro-Caribbeans, which is compatible with the prevalence of hypertension among the three ethnic groups.

While the Afro-Caribbean population also appear to have high rates of diabetes (and hypertension) compared with whites, they have a lipid profile which is protective against CHD. Consequently the major adverse event found in association with hypertension in Afro-Caribbeans is stroke and not CHD, whereas among the south Asian and white communities, CHD is more common than stroke.

Although few trial data are available to compare the efficacy of interventions on CHD risk factors among the major ethnic minorities, it may be that the different distribution of risk factors among these communities requires a specific approach tailored to the different risk factor profiles.

6. Summary of recommendations

1. PATIENTS WITH CHD OR OTHER MAJOR ATHEROSCLEROTIC DISEASE

- In clinical practice the top priority for prevention should be patients with coronary heart disease, or other major atherosclerotic disease, with the object of reducing the risk of a further major ischaemic event
- Lifestyle intervention to discontinue smoking, make healthier food choices, increase aerobic exercise and moderating alcohol consumption is important in all coronary and other atherosclerotic disease prevention programmes, and involvement of the whole family may be helpful
- In patients with CHD, or other major atherosclerotic disease, rigorous control of BP, lipids, and glucose is recommended with the following treatment targets:
  - BP less than 140 mm Hg systolic and less than 85 mm Hg diastolic
  - total cholesterol less than 5.0 mmol/l (LDL cholesterol less than 3.0 mmol/l)
  - diabetes mellitus should be optimally controlled with insulin during and immediately following acute MI, and BP reduced to < 130 mm Hg systolic and < 80 mm Hg diastolic.
- Cardioprotective drug therapy should be considered and prescribed in selected patients:
  - aspirin for all patients
  - β blockers at the doses prescribed in the clinical trials following MI, particularly in high risk patients, and for at least three years. Verapamil or diltiazem should be considered as alternatives to a β blocker when this drug class is contraindicated
  - cholesterol lowering therapy (statins) at the doses prescribed in the clinical trials
  - ACE inhibitors at the doses prescribed in the clinical trials for patients with symptoms or signs of heart failure at the time of MI, or in those with persistent left ventricular systolic dysfunction (ejection fraction less than 40%)
  - anticoagulants for patients at risk of systemic embolisation with large anterior infarctions, severe heart failure, left ventricular aneurysm, or paroxysmal tachyarrhythmias.
- In hospitals the care of coronary patients, and other patients with atherosclerotic disease, should embrace all aspects of cardiac prevention and rehabilitation, and such an integrated service should be available to all patients: post-MI, treated unstable angina, exertional angina, and all those following revascularisation by angioplasty or coronary artery surgery
- Integration of care of coronary and other patients with atherosclerotic disease between hospital and general practice is essential by using common protocols to ensure optimal long term lifestyle, risk factor, and therapeutic management
- Screening of first degree blood relatives (principally siblings and offspring aged 18 years or older) of patients with premature CHD (men < 55 years and women < 65 years), or other atherosclerotic disease, is encouraged and in the context of familial dyslipidaemias is essential
- Auditing the impact of common clinical protocols for hospital and general practice on the management of patients with CHD and other atherosclerotic disease is strongly recommended.

2. HIGH RISK INDIVIDUALS WITHOUT CLINICALLY OVERT CHD OR OTHER MAJOR ATHEROSCLEROTIC DISEASE

- Other individuals at high risk of developing CHD, or other atherosclerotic disease, because of hypertension, dyslipidaemia, diabetes mellitus, or a combination of these and other risk factors, are the next priority for prevention
- In individuals at high risk of developing CHD, or other atherosclerotic diseases, lifestyle intervention to discontinue smoking, make healthier food choices, and increase physical activity is important. The decision to introduce drug therapy for BP or lipids should be strongly determined by the absolute level of risk of developing disease. As a general guide an absolute risk of 15% or greater of developing CHD (equivalent to a cardiovascular risk of 20%) over the next 10 years is sufficiently high to justify drug treatment, although the physician's final decision about using drug therapy will also be influenced by the patient's age, gender, race, inheritance, coexistent disease, and other factors such as life expectancy
- A staged approach to the management of high risk individuals is advised to ensure that resources for identification, investigation, and management are appropriately and effectively used, starting with those at highest risk. As a minimum those with an absolute CHD risk of 30% or greater over 10 years should be targeted and treated now, as currently recommended. Then as resources allow individuals with a 10 year absolute CHD risk of 15% or greater should be progressively targeted. For individuals with a 10 year absolute CHD risk of less than 15%, appropriate lifestyle advice (for example, stop smoking) should still be given, but drug treatment is usually not justified unless there is severe hypertension (systolic BP greater than 160 mm Hg and/or diastolic BP greater than 100 mm Hg), or associated target organ damage, familial hypercholesterolaemia or other inherited dyslipidaemia, or diabetes mellitus with associated target organ damage
- Treatment targets in patients whose CHD risk is greater than 15% over the next 10 years, and for all patients who are started on drug therapies for primary CHD prevention, should be as follows:
  - BP less than 140 mm Hg systolic and less than 85 mm Hg diastolic
  - total cholesterol less than 5.0 mmol/l (LDL cholesterol less than 3.0 mmol/l)
  - diabetes mellitus should be optimally controlled and blood pressure reduced to

< 130 mm Hg systolic and < 80 mm Hg diastolic
- Aspirin (75 mg) is recommended in individuals who are older than 50 years and are either well controlled hypertensive patients or men at high risk of CHD.

- In the hospital sector the care of high risk patients in hypertension, lipid, and diabetic clinics should be coordinated between specialists based on agreed protocols to ensure a common clinical approach to multifactorial risk assessment, lifestyle, and therapeutic interventions
- The care of such high risk patients treated in specialised hospital clinics should be integrated with general practice to ensure, through the use of agreed clinical protocols, optimal long term management
- Auditing the impact of common clinical protocols for hospital and general practice on the identification and management of high risk individuals is strongly recommended.

APPENDIX 1

How to measure coronary heart disease risk

The computer program provided with these recommendations should be used wherever possible to calculate CHD or cardiovascular risk. If a computer is not available, fig 1 may be used. The computer program or the figures should **not** be used in patients with:

(1) Established CHD or other atherosclerotic disease
(2) Familial hypercholesterolaemia
(3) Malignant hypertension.

See instructions for use of "Cardiac Risk Assessor" computer program on page S25. The following information is needed.

(1) Name
(2) Sex
(3) Age
(4) Systolic BP (mm Hg)
(5) Diastolic BP (mm Hg)
(6) Smoker or non-smoker
(7) Serum cholesterol (any units)
(8) HDL cholesterol (same units as serum cholesterol)
(9) Diabetic or non-diabetic
(10) Presence of LVH on ECG.

The CHD risk is calculated as a probability (%) of developing CHD (non-fatal MI or coronary death) over 10 years—that is, the number of people per 100 expected to have a major CHD event in the next 10 years.

Family history is not included in this risk equation from the Framingham study. Adjusting the computed risk upwards by a factor of 1.5 is appropriate in patients who have a first degree male relative developing CHD, or other atherosclerotic disease, before the age of 55 years, or a female first degree relative with a similar history before the age of 65 years.

In ethnic minorities the Framingham risk equation should be used with caution as it has not been validated in these populations.

Raised serum triglycerides, or evidence of impaired glucose tolerance, or premature menopause may also in the clinician's judgment be used to adjust the calculated risk upwards.

a. AT INTERVIEW

The patient's age, sex, personal history of CHD, or other atherosclerotic disease, and family history of premature atherosclerotic disease are established. In addition, a history of hypertension, hyperlipidaemia, diabetes mellitus, renal, liver, and pancreatic disease, and drug therapy can be recorded. For women it is important to document exposure to the oral contraceptive pill, and hormone replacement therapy, and a gynaecological history including age of menopause (natural or induced) and surgery (hysterectomy/oophorectomy). An accurate assessment of cigarette smoking habit is essential and anyone who has smoked regularly (one cigarette per day) in the last five years is entered into the calculation as a smoker.

b. CLINICAL EXAMINATION

i. Blood pressure

Given the large variability in any individual's BP, the use of a standardised measurement technique is critical in order to measure BP accurately in clinical practice. British Hypertension Society guidelines on measurement of BP are recommended.[211] BP should be measured in the sitting position from the right arm, after the patient has rested for five minutes, using a conventional sphygmomanometer with an appropriate cuff size. The reading of diastolic BP should be taken as the disappearance of the second sound (phase 5) and BP should be read to the nearest 2 mm Hg. At least two measurements are to be made each visit. In elderly people and in patients with diabetes mellitus, standing BP should also be measured because of the potential problem of orthostatic hypotension.

A diagnosis of hypertension should not be made until BP has been shown to be persistently raised. Data from several trials of treatment of mild hypertension have shown that after repeated measurements over a period of up to six months, BP of almost 50% of individuals initially categorised as mildly hypertensive subsequently fall into the normal range.[132 140] On repeated measurement BP levels become stable after 3–4 months of observation. In the long term outcome trials, average diastolic BP over 3–4 years was a much better predictor of events than trial entry BP.[125 132] The period of observation is dependent on severity. In mild uncomplicated hypertension, at least four pairs of measurements should be repeated over a period of 3–6 months. However, in patients with CHD more severe hypertension, or with target organ damage, antihypertensive drugs should be initiated after weeks rather than months of observation.

BP averaged over 24 hours is related more closely to target organ damage than office pressure. However, office BP is the only measurement to be evaluated extensively in large scale morbidity and mortality studies, and the role of 24 hour ambulatory BP monitoring (ABPM) is still undergoing evaluation.[212]

Pending this further evidence, the use of ABPM is mainly restricted to specialist centres where the assessment of labile, refractory, and white coat hypertension is facilitated by its use. When estimating coronary risk the BP (systolic) before treatment, when this is known, should be entered in preference to the current BP on treatment.

ii. Dyslipidaemia

Serum total cholesterol and HDL cholesterol may be measured in a non-fasting state. The analysis should be made in a laboratory participating in the national quality control scheme for cholesterol. When it is required to measure serum triglyceride in addition to total serum cholesterol the analyses should be performed on serum taken after at least a 12 hour fast (usually from 10 pm the previous evening).

Because of biological and laboratory variation in cholesterol measurements, a reliable assessment of plasma total cholesterol level in each individual requires at least three measurements carried out on three separate samples. It is practical to start with a random sample for total and HDL blood cholesterol on the first occasion. This avoids the need for fasting and thus blood can be taken at the time of the first clinical assessment when other risk factors are also being measured.

LDL cholesterol necessary for deciding whether the treatment targets have been attained can be calculated from the Friedewald formula: LDL cholesterol (mmol/l) = total cholesterol − HDL cholesterol − 0.45 × triglyceride

The accuracy of this estimation of LDL cholesterol concentration is a function of the summation of analytical errors in individual lipid measurements. It can also give useful additional information when considering the need for lipid lowering drug therapy. The Friedewald formula cannot be used if plasma triglyceride levels are higher than 4.5 mmol/l.

Plasma triglycerides levels are profoundly influenced by a number of factors, such as changes in nutrition and alcohol intake. Therefore, a finding of raised plasma triglyceride levels (above 2.3 mmol/l) on fasting samples should signal the need for an investigation of secondary causes.

When estimating coronary risk the cholesterol before diet and drug treatment should be entered and not the current cholesterol on treatment.

iii. Plasma glucose

Type II diabetes and impaired glucose tolerance are risk factors for CHD, and other forms of atherosclerotic disease. Fasting blood glucose should be included in the laboratory examinations made during the investigation of all patients with atherosclerotic disease. This is particularly needed for those patients who are overweight and/or have multiple risk factors which tend to be associated with impaired glucose tolerance and type II diabetes, namely low plasma HDL cholesterol and/or hypertriglyceridaemia, and raised BP.

Instructions for using the "Cardiac Risk Assessor" computer program

1) RUNNING THE PROGRAM

This program is designed only for use with Microsoft Excel (version 5 or higher)

(i) Starting from Windows 95
From Run in the Start menu type a:\risk.xls

(ii) Starting from Windows 3.1
From file, run type a:\risk.xls

2) NOTES ON ENTERING DATA

(i) Patient data required is as follows

- gender
- age (years)
- systolic BP (mm Hg)
- diastolic BP (mm Hg)
- smoking status (yes/no)
- total cholesterol (any unit)
- HDL cholesterol (any unit)
- diabetic status (yes/no)
- ECG-LVH status (yes/no) if known

(ii) It is important that all the above data are entered, because missing information would invalidate the results.

Instructions for operating the program are displayed on the screen. Data can be typed into the boxes when the cursor is positioned over them. These data are entered into the calculation when the cursor is moved off the box. To correct data or to enter data for a new patient simply move the cursor back over the box.

(iii) Risk is calculated when the cursor is moved to an area of the screen where it does not occupy a box, or the "enter" key is pressed. the probability (%) of CHD and cardiovascular (CHD and stroke) risk over the next 10 years are each calculated for both systolic and diastolic blood pressure separately.

(iv) The program can be used for a succession of patients by simply entering the next patients's data over the last patient's data.

(v) "Exit" means exit from the whole program.

An MS DOS version of the Cardiac Risk Assessor program is available from Professor Paul Durrington, Department of Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK.

APPENDIX 2

Other useful measurements

i. Obesity

Subjective assessment of obesity, including the presence of central obesity, as it takes account of the patients overall physical build, is useful. A commonly used measurement of obesity is body mass index (BMI), which adjusts weight from height.

BMI is calculated as weight (kg)/height(m^2). Obesity is classified as follows:

- < 25 kg/m^2 — desirable body weight
- 25–< 30 kg/m^2 — overweight
- 30–< 35 kg/m^2 — obese
- ⩾ 35 kg/m^2 — extremely obese.

Obesity of the central type, with accumulation of fat around the abdomen, is associated with a higher prevalence of lipid abnormalities, in particular hypertriglyceridaemia and low HDL cholesterol, hypertension and abnormal glucose tolerance—the cluster of risk factors associated with insulin resistance.

ii. Diet

Information about usual dietary habits (including alcohol) forms the basis for dietary advice. A detailed dietary interview undertaken by a dietician followed by advice is ideal. This assessment should include the person responsible for preparing the food. Dietary change can be more easily accomplished within the family as a whole, rather than one individual trying to change his or her diet while the rest of the family eats the same food as before.

iii. Physical activity and exercise capacity

A brief interview concerning the patient's physical activity at work and at leisure provides the basis for an assessment of his/her general level of physical activity and the need to advise optimal physical exercise.

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