SIGN

Scottish Intercollegiate Guidelines Network

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Risk estimation and the prevention of cardiovascular disease

A national clinical guideline

February 2007

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1++   High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+   Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1 -   Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

2++   High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+   Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2 -   Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3   Non-analytic studies, eg case reports, case series

4   Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A   At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B   A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C   A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D   Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

GOOD PRACTICE POINTS

☑   Recommended best practice based on the clinical experience of the guideline development group

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Coronary heart disease (CHD) will directly affect the majority of the Scottish population at some point in their life. In 2003 around one per 300 were newly diagnosed with some form of CHD in Scotland.[1] The incidence of CHD is higher amongst men, the elderly and in deprived areas of Scotland. The annual prevalence rates in 2005 were 4.2% in men and 3.0% in women, although this underestimates the true scale of the disease as it only records patients treated in hospital.[2]

Recent estimates of disease incidence show that rates are falling and, although the reasons for this decline are complex, improvements in diet and a reduction in smoking rates are significant factors.

There has been an increasing recognition that it is no longer sufficient to predict the risk of vascular disease only in terms of CHD as this underestimates the risk of stroke. All cardiovascular disease (CVD) should be considered as a spectrum of disorder including coronary artery disease, cerebrovascular disease and peripheral arterial disease and the guideline has been extended to include the prevention of other forms of cardiovascular disease. A recent meta-analysis of randomised controlled trials (RCTs) shows that statins are effective in the primary and secondary prevention not only of CHD events and coronary revascularisation, but also of strokes and combined major vascular events.[3]

Cardiovascular disease has a multifactorial aetiology with a number of potentially modifiable risk factors. The classical Framingham risk factors, age, sex, cigarette smoking, blood pressure, total cholesterol and high density lipoprotein (HDL) cholesterol have proved consistent risk factors in every population studied. Various ethnic groups may display differences in population baseline risk.[4] Scotland's minority ethnic population is small, but growing. At the 2001 census around 2% of the country's five million people were from minority ethnic backgrounds.[5]

Of particular relevance to the Scottish context, are the effects of socioeconomic status on the risk of developing cardiovascular disease. The incidence and mortality rates from acute myocardial infarction in those aged under 65 are higher in deprived areas than in more affluent areas.[6-9]

Recognising cardiovascular disease as a continuum challenges the traditional concepts of primary and secondary prevention, with healthcare professionals adopting a "high-risk" approach to prevention.[10] In fact, most CVD cases occur in the large number of individuals at lower levels of absolute risk.[11] High risk approaches have been facilitated both by the availability of scoring systems to estimate absolute risk (rather than the traditional use of single risk factors) and by the advent of several treatments, principally statins and blood pressure reducing drugs, which produce marked and apparently independent reductions in CVD risk in high risk subjects.[12]

The guideline has attempted to devise effective strategies for the reduction of CVD that take a combined approach using both "high risk" and a population approach.

1.2 REMIT OF THE GUIDELINE

This guideline deals with both primary prevention, defined as the potential for intervention prior to the disease presenting through a specified event, and secondary prevention, defined as the potential for intervention after an event has occurred. The guideline group have tried to consider cardiovascular disease as a continuum from the pre-clinical to the end stage disease, potentially offering different opportunities to intervene, both prior to, and after an event, so creating the potential to alter the outcome of the disease process. The group believes that it is more relevant to consider an individual in terms of whether they have a high or low risk of CVD rather than in terms of primary or secondary prevention.

1.3 RISK ESTIMATION

For many health professionals the calculation of absolute cardiovascular risk is the starting point for the development of CHD prevention strategies.

1.3.1 DEFINITIONS

"Absolute risk" is also known as "total risk" or "global risk". This risk is defined as the percentage chance of an individual developing a CVD event over a given period of time, eg a ten year risk of 15%. "Relative risk" refers to the risk of someone developing a CVD event who has risk factors compared to an individual of the same age and sex who does not.

1.3.2 RISK SCORES

Risk scores cannot predict absolute risk. They are extremely useful in assessing or estimating risk and in prioritising treatment on an equitable basis.

In Scotland absolute CVD risk is usually calculated from electronic decision support tools based on the US Framingham heart study.[13] Framingham risk equations have been validated in different populations.[14]

A large systematic review of cardiovascular risk assessment in primary prevention has shown that the performance of Framingham risk scores vary considerably between populations and that accuracy relates to the background risk of the population to which it has been applied.[15] There is general agreement that Framingham overpredicts absolute risk in populations with low observed CHD mortality and underpredicts in populations, such as the socially deprived, with high CHD mortality.[15]

The accuracy of Framingham cardiovascular risk assessments is limited by the exclusion of certain risk factors including obesity, physical inactivity, family history of cardiovascular disease and social status. Work done using the Scottish MIDSPAN data suggests that the exclusion of social deprivation in the estimation of cardiovascular risk results in a serious underestimation of absolute risk.[16]

Based on these findings SIGN has commissioned work to incorporate risk coefficients, accounting for both family history and social deprivation in a new risk scoring system (*see section 2.3.4*).[17,18]

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.4.1 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, **www.sign.ac.uk**

1.4.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in the section on implementation.

1.5 REVIEW AND UPDATING

This guideline was issued in 2007 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

2 Cardiovascular risk

2.1 RISK FACTORS

The INTERHEART study assessed the importance of risk factors for coronary artery disease worldwide.[19] Nine measured and potentially modifiable risk factors, accounted for more than 90% of the proportion of the risk for acute myocardial infarction. Smoking, history of hypertension or diabetes, waist hip ratio, dietary pattern, physical activity, alcohol consumption, blood apolipoproteins and psychosocial factors were identified as the key risk factors. The effect of these risk factors was consistent in men and women across different geographic regions and by ethnic group. The British Regional Heart Study also found that smoking, blood pressure and cholesterol accounted for 90% of attributable risk of CHD.[20]

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Worldwide, the two most important modifiable cardiovascular risk factors are smoking and abnormal lipids. Hypertension, diabetes, psychosocial factors and abdominal obesity are the next most important but their relative effects vary in different regions of the world.

2.2 THE CONCEPT OF RISK AND WHY IT MATTERS

Most cardiovascular deaths will occur in individuals at moderate risk as they constitute the largest group. High risk individuals will have the most to gain from risk factor modification and historically are given the highest priority in clinical practice.[21]

When estimating risk, total CVD mortality, rather than CHD endpoints should be used to encompass stroke prevention as well as CHD prevention. Stroke deaths are underestimated using traditional CHD endpoints.[4] Current risk prediction systems do not predict accurately the different risk profiles that exist in different ethnic groupings and cultures. A risk score derived from Caucasian cohorts may substantially overpredict the risk in a Chinese population.[22] CVD risk prediction based on absolute risk is now advocated for treatment decisions for aspirin, statins, antihypertensives and in people with atrial fibrillation, for warfarin.

2.2.1 PREDICTING RISK

Intervention studies have shown that while relative risk reduction may remain broadly constant, absolute risk reduction varies considerably because it is a function of the initial level of baseline risk. Consider the example in Table 1 of a man with a baseline risk of a cardiovascular event of 10% over ten years who takes effective preventative treatment and lifestyle measures. His relative risk falls by a third, while his absolute risk is reduced to 6.7%, an absolute risk reduction of 3.3%. If another man with a higher baseline risk of 30% takes the same effective treatments his relative risk also falls by about a third to 20%. However, his absolute risk reduction is 10%. Relative risk reductions in CHD events in the statin trials appear similar regardless of baseline risk and baseline cholesterol (except where baseline cholesterol is < 5 mmol/l when relative risk reduction is less.[3,23] This would support the concept that the best way to target patients is to calculate absolute risk.

Table 1: Example illustrating absolute and relative risk reductions

Baseline ten year CVD risk	Relative risk reduction	Post-treatment ten year CVD risk	Absolute risk reduction
10%	33%	6.7%	3.3%
30%	33%	20%	10%

Overprediction of CVD risk means that people with little to gain potentially become patients and are exposed to the questionable benefits and risks of lifelong treatment. Underprediction means that people with much to gain may not be offered preventative treatment. The best way to target patients for risk reducing interventions is to calculate absolute risk.

2.3 RISK SCORING SYSTEMS

2.3.1 FRAMINGHAM BASED SCORING SYSTEMS

A large number of risk scoring systems for CHD and CVD have been devised for use in clinical practice, the majority of which are based on the American Framingham study.[24,25] The Framingham equations are the most widely accepted method for projecting cardiovascular disease/coronary disease risks, and are used in the British, European and New Zealand guidelines.

These risk scoring systems are reliable in ranking individual CHD and CVD risks within populations, based on conventional risk factors, but have been shown to give a variable performance when predicting actual events within populations.[15] Framingham risk equations are based on event rates which occurred in a predominately white, United States population during the 1970s. CHD rates have been declining in the US and many other countries, resulting in a tendency for the event rates predicted by Framingham–based scores to be higher than actual event rates in populations.

Framingham-based scoring systems tend to overestimate risk in low and medium risk groups and underestimate risk for certain subgroups including British Asians; people with Type 1 diabetes; people with Type 2 diabetes with nephropathy; those with familial hypercholesterolaemia; those with a strong family history of premature CHD; those with left ventricular hypertrophy on electrocardiography; and those with chronic renal disease.[26] Framingham significantly underpredicted CHD risk in a Scottish male general population cohort (Renfrew and Paisley) which is explained partly by the high CHD mortality rates in this population. A Framingham-based risk score also underestimated the true level of CVD and CHD risk in men with lower socioeconomic status whether this was assessed using social class or a postcode-based deprivation score.[16]

These results were tested in an analysis commissioned by SIGN based on the Scottish Heart Health Extended Cohort (SHHEC), involving 6,419 men and 6,618 women aged 30-74 years from 25 local government districts in Scotland, for whom baseline data were collected between 1984 and 1995.[17] While the Framingham score overestimated the actual observed CHD risk in the cohort as a whole, it seriously underestimated the large gradient in risk by socioeconomic status, particularly in women. Application of the score as a basis for preventive treatment would result in relative undertreatment of the most socially deprived, compared with the least deprived, potentially exacerbating social disparities in disease rates.

While risk scores are superior to clinical assessment alone, they can be misleading when used to guide treatment decisions among people at different levels of social deprivation or of different ethnic backgrounds. Without correction, such scores may foster the relative undertreatment of the socially deprived.[18]

In order to reduce the deprivation-related difference in the numbers eligible for preventive treatment, risk scoring systems need to adjust for deprivation, as the ASSIGN (ASsessing cardiovascular risk using SIGN guidelines to ASSIGN preventive treatment) score has been developed to do *(see section 2.3.4).*

2.3.2   USING SCORING SYSTEMS IN PRACTICE

Basing treatment decisions on predetermined levels of a risk score replaces potentially arbitrary decisions with transparency, consistency and potential for audit. It may maximise efficient use of limited resources and implies fairness in ensuring equitable distribution. Determining by score those whose condition warrants treatment eliminates many possible sources of bias.

No clear information is available on how GPs are using risk scoring systems in Scotland. This makes it difficult to predict the effect of introducing a new system. The proposed introduction of ASSIGN offers the prospect of an improved understanding of how general practice manages risk and allows an opportunity to evaluate resource usage and the effectiveness of preventative interventions.

A central aim of this guideline is to ensure that the scoring system recommended to identify high risk, is as accurate as possible and that the treatments suggested are appropriate and in line with scientific evidence. Risk scoring systems are important tools but are limited by changes in disease and population patterns.

2.3.3   THE JOINT BRITISH CARDIAC HYPERTENSION AND HYPERLIPIDAEMIA SOCIETIES

The British Cardiac, Hypertension, and Hyperlipidaemia Societies (JBS) have jointly provided modified charts of graded risk which are valid for use in primary care as their diagnostic accuracy is unaffected by approximations in age and blood pressure.[27] The JBS guidelines were updated in December 2005 with the publication of JBS2.[28] The revised guidelines include all atherosclerotic CVD (acute coronary syndromes, exertional angina, cerebrovascular disease and peripheral arterial disease), rather than CHD alone. In JBS2 the definition of high risk has been lowered from a 30% or greater ten year risk of CHD (equivalent to over 40% ten year CVD risk) to a ≥20% CVD risk over ten years. JBS2 emphasises that individuals with any symptomatic manifestation of CVD, including diabetes, are assumed to be at high risk of cardiovascular events and do not require formal risk estimation.

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This assumption of high risk means that many more individuals (around 635,000 in Scotland) will fall into the high risk category. If implemented widely, this definition of high risk will have a significant impact on health professional workload and resource expenditure (*see NHSQIS CVD Clinical and Resource Impact Assessment Report*).[29] It may also result in unnecessary treatment for many individuals.

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The evidence supporting the decision of JBS2 to reduce the intervention threshold for high CVD risk over ten years is not clear. Where evidence is lacking, thresholds are often determined by balancing workload against projected medium to long term costs. Existing guidelines which specify treatment thresholds for statin prescribing have been influenced by the costs of these drugs and have tended to set intervention levels relatively high with respect to the actual risks observed in those with coronary heart disease.[27] Any risk assessment method that demonstrates a low specificity and high false positive rate will necessarily cause an inevitable increase in total prescribing costs.[30]

2.3.4   ASSIGN

The ASSIGN score (ASsessing cardiovascular risk using SIGN guidelines to ASSIGN preventive treatment) has been developed to include social deprivation as a risk factor. The inclusion of family history provides an indirect approach to ethnic susceptibility.

ASSIGN is based on the Scottish Heart Health Extended Cohort, a series of population studies from the 1980s and 1990s followed up until the end of 2005. The Scottish Heart Health study recruited men and women across 25 districts of Scotland in 1984-87 and the Scottish MONICA Project recruited in Edinburgh and Glasgow in 1986 and in Glasgow alone in 1989, 1992 and 1995.[31]

ASSIGN uses similar classic risk factors to Framingham, entered as continuous variables rather than categories. It includes the SIMD (Scottish Index of Multiple Deprivation) score for residential postcode. It also includes family history of cardiovascular disease, defined as coronary disease or stroke in parents or siblings below age 60 or in several close relatives. Like Framingham it does not include obesity as a risk factor; unlike Framingham it excludes left ventricular hypertrophy as a risk factor.

Results from ASSIGN are similar to those from the Framingham cardiovascular score in many respects but the overall estimation of ten year cardiovascular risk is rather lower, consistent with some overestimation in the Framingham score.[18]

ASSIGN tends to classify more people with a positive family history and who are socially deprived as being at high risk. When used in its own host population it abolished a large social gradient in future CVD victims not identified for preventive treatment by the Framingham cardiovascular score. It therefore improved social equity, although overall discrimination of future events was not greatly improved.[18]

A demonstration of the ASSIGN tool is available at http://assign-score.com

2.4   WHAT IS MEANT BY HIGH RISK?

There are considerable variations in the definitions of the categories of risk. Both JBS2[28] and the current European guidelines in CVD prevention[32] include patients with established coronary heart disease, peripheral arterial disease or cerebrovascular arterial sclerotic disease or diabetes in their definitions of high risk. The European guidelines are based on assessments of asymptomatic patients. In the European guidelines high risk is calculated as a ten year risk of 5% or greater for developing a fatal CVD event. The JBS2 guideline defines high risk as at least 20% risk of developing a first cardiovascular event over ten years.

In the great majority of cases, an individual's risk is the product of multiple risk factors and there is a need for an absolute risk estimation to be made for individuals believed to be at risk who have not presented as high risk by the presence of established disease.

The main debate around what constitutes high risk relates to the vast majority of the asymptomatic population who have no history of CVD or diabetes. The onset of statins has raised fundamental questions about the risk and prevention of CVD. The cardiovascular benefit of treatment with a statin is observed among people with annual levels of risk as low as 1%[33] and the annual CHD risk may be nearing 1% in the US and in Northern European countries. In this scenario, most middle aged men and women could benefit from a statin and CVD risk reduction.[34] The long term safety profile of statin therapy in relatively healthy adults has not yet been established.

3 Estimating cardiovascular risk

3.1 ASSESSING RISK

Treatment decisions are based on the likelihood that an individual will have a cardiovascular event over a given period of time. Assessment of absolute cardiovascular risk is the starting point for discussions between clinicians and patients who are potentially at significant risk of a cardiovascular event. The prevention of cardiovascular events is the goal of treatment.

This guideline uses many of the risk assessment strategies outlined in JBS2.[28]　　　　| 4

The following individuals should have an assessment of cardiovascular risk at least every five years:

- all adults aged 40 years or above, and
- individuals at any age with a first-degree relative who has premature atherosclerotic CVD or familial dyslipidaemia.

The following groups of people should be assumed to be at high risk (a ten year CVD risk $\geq 20\%$ based on clinical history alone) and do not require risk assessment with a scoring system: [28]

- people who have had a previous cardiovascular event (angina, myocardial infarction, stroke, transient ischaemic attack or peripheral arterial disease)
- people with diabetes (type 1 or 2) over the age of 40 years
- people with familial hypercholesterolaemia.

3.2 RECORDING RISK FACTOR INFORMATION

Cardiovascular risk is the product of the effect of several risk factors. Individual risk factors can cluster together in significant patterns and tend to have a multiplicative effect on an individual's total cardiovascular risk.[35] Measuring any single risk factor will usually not adequately estimate total cardiovascular risk.

3.2.1 TAKING A CLINICAL HISTORY

The following items of information should be collected routinely when assessing cardiovascular risk.[28]

Table 2: Items to include in a clinical history for cardiovascular risk assessment

Risk factor	Rationale for measurement
age	Cardiovascular risk increases with age.
sex	Other factors being equal, men are at higher risk of a cardiovascular event.
lifetime smoking habit (and number of cigarettes smoked per day)	Categorising an individual's smoking status as current smoker or non-smoker is insufficient for the calculation of accurate CVD risk. A current smoker may have less lifetime exposure to tobacco and less associated cardiovascular damage than an ex-smoker. The CVD risk of an ex-smoker is likely to be intermediate between a current smoker and a lifelong non-smoker.
family history of cardiovascular disease	In people with a family history of clinically proven cardiovascular disease (angina, myocardial infarction, transient ischaemic attack, or ischaemic stroke) in a first-degree relative (parent, sibling) before the age of 60 years, the risk of a coronary event is approximately doubled.[36] The risk of ischaemic stroke in men with a family history of stroke is slightly less than double that risk for those without a family history, relative risk, RR,1.89 (95% confidence interval, CI,1.23 to 2.91).[37]
socioeconomic status	For given levels of other risk factors, populations which are more deprived have a higher CVD risk.

3.2.2   CLINICAL MEASUREMENTS

The following should be measured when assessing cardiovascular risk:[28]

Table 3: Factors that should be measured for cardiovascular risk assessment

Risk factor	Rationale for measurement
blood pressure	Systolic blood pressure should be measured according to the British Hypertension Society (BHS) guidelines.[38] The mean systolic pressure measured over two separate occasions should be used to calculate risk. In individuals taking antihypertensive medication, the most recently recorded pre-treatment value should be adopted.
weight and waist circumference	Individuals with a body mass index (BMI) > 30 kg/m² have a 40-fold increased risk of developing diabetes and a two to three-fold increased risk of CHD[39,40] and stroke compared to individuals with a normal BMI (≤ 25 kg/m²).[41] Central obesity, as measured by waist circumference, is a better predictor of cardiovascular risk than BMI.[40,42] Central obesity is present if the waist circumference is ≥ 102 cm in men (≥ 90 cm in Asian men) and ≥ 88 cm in women (≥ 80 cm in Asian women).
total cholesterol and high density lipoprotein cholesterol	Total cholesterol (TC) and HDL cholesterol should be measured in a laboratory from a random (non-fasting) sample of blood. In individuals taking lipid lowering medication, the most recently recorded pre-treatment value should be adopted.
glucose	In order to screen for diabetes, impaired glucose tolerance or insulin resistance should be measured from the same random (non-fasting) blood sample that is drawn to measure cholesterol levels. A value of ≤ 6.0 mmol/l indicates a normal level. A value of ≥ 6.1 mmol/l but ≤ 7.0 mmol/l requires a repeat measurement on a fasting blood sample. If the value is ≥ 7.0 mmol/l an oral glucose tolerance test should be performed.
renal function	Individuals with chronic kidney disease (CKD) are at significantly increased risk of cardiovascular events.[43] To aid the differential diagnosis of CKD, renal function should be estimated from glomerular filtration rate (GFR). A GFR < 60 ml/min/1.73m² is indicative of stage 3 CKD and such individuals should have aggressive risk reduction interventions to reduce their risk of cardiovascular events.

3.3   USING RISK ASSESSMENT TOOLS

The ASSIGN cardiovascular risk assessment tool allows clinicians to estimate ten year risk of CVD events in asymptomatic individuals with no clinical evidence of cardiovascular disease. The calculation of risk will be via a computer based desktop tool. Computer programs give a more precise estimate of risk than charts, presenting risk as a continuous variable rather than a threshold, such as ≥ 20%.[44]

Unless recent pre-treatment risk factor values are available it is generally safest to assume that CVD risk is higher than that predicted by current levels of blood pressure or lipids on treatment.

True CVD risk will be higher than the results indicated by estimation tools in:[28]

- those with raised triglyceride values (>1.7 mmol/l)
- women with premature menopause
- those who are not yet diabetic, but have impaired fasting glycaemia (>6.1 but <7.0 mmol/l) or impaired glucose tolerance (two hour glucose in an oral glucose tolerance test >7.8 mmol/l but <11.1 mmol/l)

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In some ethnic minorities risk tools underestimate CVD risk, because they have not been validated in these populations. For example, in people originating from the south Asian subcontinent it is safest to assume that the CVD risk is higher than predicted from most scoring tools (*see section 1.1*). The ASSIGN risk tool incorporates family history as a risk factor which may account for some or all of the excess CVD risk of individuals from some ethnic minorities.

3.4 HOW TO DETERMINE CARDIOVASCULAR RISK

D **Individuals with symptoms of cardiovascular disease or who are over the age of 40 years and have diabetes** *(type 1 or 2)* **or familial hypercholesterolaemia should be considered at high risk (≥20% risk over ten years) of cardiovascular events.**

D **Cardiovascular risk should be estimated at least once every five years in adults over the age of 40 years with no history of cardiovascular disease, familial hypercholesterolaemia or diabetes and who are not being treated for blood pressure or lipid reduction.**

D **Asymptomatic individuals should be considered at high risk if they are assessed as having ≥20% risk of a first cardiovascular event over ten years.**

D **Individuals at high cardiovascular risk warrant intervention with lifestyle changes and consideration for drug therapy, to reduce their absolute risk.**

☑ Risk factors should be monitored at least annually in people who are on antihypertensive or lipid lowering therapy.

☑ Individuals from deprived socioeconomic groups must be regarded as being at higher total cardiovascular risk than indicated by risk estimation tools that do not use social deprivation to calculate total risk.

☑ Other risk factors not included in the CVD risk prediction should be taken into account in assessing and managing a person's overall CVD risk. These include: ethnicity, abdominal obesity, impaired glucose tolerance, raised fasting triglyceride and a family history of premature CVD.

Asymptomatic people without established atherosclerotic CVD who have a combination of risk factors which puts them at an estimated multifactorial risk of ≥20% over ten years should be considered for treatment. Other risk factors which should be taken into account in the overall assessment include: ethnicity, social deprivation, renal disease, abdominal obesity, impaired glucose tolerance, raised fasting triglyceride and a family history of premature CVD. The ASSIGN risk estimation tool takes account of social deprivation and family history.

Some individuals will have extreme values of single risk factors. Although absolute risk takes several risk factors into account, possession of such a 'lighthouse' risk may mandate intervention.[38] Single risk factors in this range include total cholesterol ≥8 mmol/l (*see section 9.9.2*) or elevated blood pressure (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg, or lesser degrees of hypertension with associated target organ damage (*see section 10*).[28,45] In these cases, whilst treatment is aimed at the lighthouse risk, the reduction of global risk is the ultimate goal. Management of other risk factors is also important, especially where the key risk factor proves refractory.

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4   Diet

Environmental factors, including diet, play an important role in the development of CHD. The diet of any individual is related to other lifestyle factors (smoking, exercise, etc). Randomised controlled trials of diet are able to eliminate such bias but are more difficult to conduct than those of drugs or supplements.

4.1   ALTERING DIETARY FAT INTAKE

There is more evidence about the role of fat in risk modification than of other dietary factors. Reduction of fat, in particular of saturated fat is one of the pillars of dietary advice to prevent CHD.[46] Modifying the composition rather than the amount of fat in the diet may be a more effective strategy.

4.1.1   SATURATED FAT

A Cochrane review of 27 trials (18,196 participants) examined the effect of reduction or modification of dietary fats for at least six months on reducing serum cholesterol levels and on total and cardiovascular mortality and morbidity. The review included trials of high (seven), moderate (six) and low risk (14) participants. Trials involving high risk participants included men only. There was no significant effect on total mortality (rate ratio 0.98, 95% CI 0.86 to 1.12), a trend towards protection from cardiovascular mortality (rate ratio 0.91, 95% CI 0.77 to 1.07), and significant protection from cardiovascular events (rate ratio 0.84, 95% CI 0.72 to 0.99). This effect was non-significant if studies at high risk of bias were removed. Trials with at least two years' of follow up provided stronger evidence of protection against cardiovascular events (rate ratio 0.76, 95% CI 0.65 to 0.90). The reviewers concluded that there is a small but potentially important reduction in cardiovascular risk with a reduction or modification of dietary fat intake, seen particularly in trials of longer duration.[47]

> **A**   **Diets low in total and saturated fats should be recommended to all for the reduction of cardiovascular risk.**

4.1.2   OMEGA 3 FATS

There is conflicting evidence on the benefits associated with increased consumption of omega 3 fats. Some studies had suggested that omega 3 fatty acids were beneficial in preventing and treating CHD.[48] A meta-analysis of 48 RCTs and 26 cohort studies does not support this.[49] Analysis of the cohort studies alone did suggest that omega 3 fats would reduce total mortality, although insufficient adjustment for confounding lifestyle was a common feature in many of the studies. The pooled results from the RCTs in patients with CHD showed omega 3 fats had no benefits on mortality or cardiovascular events. There was considerable heterogeneity among the RCTs which disappeared when studies at high risk of bias were removed from the analysis.

Relative risk for total mortality was 0.98 (95% CI 0.86 to 1.12). There were similar findings for cardiovascular events. There was no evidence of benefit from plant oil omega 3 (mainly α-linolenic acid) either. Nor did the results differ when considering whether the increased intake of omega 3 was from dietary advice or supplements. There is no current evidence of benefit from omega 3 fats, although confidence intervals do not exclude either a moderate benefit or harm.

In view of this uncertain effect and in order to avoid conflicting dietary advice, no change is recommended from the advice given in the current dietary guideline (two 140 g portions of fish, one of which should be a fatty fish, per week).[50]

Fish consumption may help to reduce intake of (saturated) fat from meat.

> ☑   All individuals should eat at least two portions of fish per week, one of which should be a fatty fish.

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4.2 REDUCING DIETARY SALT

A meta-analysis of 28 trials on the effect of moderate salt reduction on blood pressure demonstrated that a modest reduction in salt intake for four or more weeks has a significant effect on blood pressure in both hypertensive and normotensive individuals. The pooled estimates of blood pressure fall were 4.96/2.73 $\pm$ 0.40/0.24 mm Hg in hypertensive patients (p < 0.001 for both systolic and diastolic) and 2.03/0.97 $\pm$ 0.27/0.21 mm Hg in normotensive individuals (p < 0.001 for both systolic and diastolic). A reduction of salt intake of 6 g per day (100 mmol or 2.3 g sodium per day) predicted a fall in blood pressure of 7.11/3.88 mm Hg (p < 0.001 for both systolic and diastolic) in hypertensive patients and 3.57/1.66 mm Hg in normotensive individuals (systolic: p < 0.001; diastolic: p < 0.05).[51]

A Cochrane review of salt restriction for the prevention of CHD cited too few cardiovascular events in the trials of at least six months duration to make a clear conclusion. It did report a small but significant reduction in systolic blood pressure in participants who had followed a salt-restricted diet and, reductions were greater in subgroups with hypertension.[52] Another Cochrane review of advice to reduce salt intake lasting at least six months, also reported small but significant benefits to blood pressure. Long term maintenance of low sodium diets was difficult for individuals, even with considerable advice, support and encouragement (*see section 10*).[53]

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The Food Standards Agency has recommended that adults should consume no more than 6 g of salt per day (approximately equivalent to one teaspoonful).[54]

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> **A** **People with hypertension should be advised to reduce their salt intake as much as possible to lower blood pressure.**

> ☑ All individuals should aim to consume less than 6 g of salt per day.

4.3 FRUIT AND VEGETABLE INTAKE

Diets with at least 400 g of fruit and vegetables per day are recommended in Scotland.[47] Diets rich in fruit and vegetables tend also to be low in fat. Two systematic reviews of cohort studies examined the benefits of fruit and vegetable consumption for the reduction of CHD risk. There is evidence from cohort studies to support reduced CHD event rates from increased vegetable (risk ratio 0.77) and fruit (risk ratio 0.86) intake in one review,[55] and 15% reduced relative risk of CHD in those consuming high levels of fruit and vegetables compared to those consuming low levels (equivalent to a four-fold increase in fruit and doubling of vegetables) in another.[56]

2[++]
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> **C** **Increased fruit and vegetable consumption is recommended to reduce cardiovascular risk for the entire population.**

4.4 EFFECT OF SPECIFIC MINOR DIETARY COMPONENTS

4.4.1 ANTIOXIDANT VITAMIN SUPPLEMENTATION

Several systematic reviews of RCTs were identified that investigated the association between vitamin supplementation and prevention of CHD. One systematic review of 84 RCTs found that neither supplements of vitamin E alone nor given with other agents yielded a statistically significant beneficial or adverse pooled relative risk for all-cause mortality, cardiovascular mortality, fatal or non-fatal myocardial infarction or reduction in blood lipids.[57] Another meta-analysis of RCTs of vitamin supplementation identified a lack of any statistically significant or clinically important effects of vitamin E on cardiovascular disease.[58]

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A meta-analysis examining the effect of vitamin E dose on all cause mortality identified that high dose ($\geq$ 400 IU per day) vitamin E increased all cause mortality by 39 per 10,000 persons treated (95% CI: 3 to 74 per 10,000; p < 0.035). Low dose trials did not significantly reduce all cause mortality.[59]

1[++]

The US Preventive Services Task Force guideline investigated the evidence on the role of antioxidant supplementation in reducing the incidence of or progression to CHD. The guideline found little evidence that any single vitamin supplementation (vitamin A, vitamin C, vitamin E, β-carotene), combined antioxidants or multivitamins had a benefit on primary or secondary prevention.[60]

4

> **A**   **Antioxidant vitamin supplementation is not recommended for the prevention or treatment of coronary heart disease.**

4.4.2 FOLATE SUPPLEMENTATION

A general overview examined the association between vitamin deficiency and chronic disease. It suggested that folate and vitamins B_6 and B_{12} are required for homocysteine metabolism and their deficiency may be associated with coronary heart disease risk.[61] In contrast, two systematic reviews suggest that the link between hyperhomocysteinaemia and CHD may be overstated.[62,63] In one review the summary odds ratios for a 5 micromol/l increase in homocysteine concentration ranged from 1.06 (95% CI 0.99 to 1.13) to 1.70 (95% CI: 1.50 to 1.93).[62] Prospective cohort studies appear to offer weaker support than case control studies for an association between homocysteine concentration and cardiovascular disease. Further research using robust methodologies should be carried out in this area.

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4.4.3 STANOL ESTERS AND PLANT STEROLS

Stanol esters and plant sterols are present in small amounts in normal diets, and can be supplemented using dietary products such as certain margarines and yoghurt drinks. Two systematic reviews provide evidence that they can reduce LDL cholesterol.[64,65] In the larger review of 41 RCTs of the effect on serum lipids, 2 g per day supplements of stanol esters and plant sterols led to 10% reductions in LDL cholesterol.[64] There was no benefit from further dosage increases. The cost to the individual of this supplement has been estimated at £70 per year.[65]

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1[-]

As yet, there is no evidence on whether these reductions in cholesterol translate in the longer term into reduction in CVD, nor is there long term data (more than five years) on their safety.

4.4.4 NUTS

There is limited evidence from two RCTs that consuming certain nuts may improve lipid profiles, reducing serum cholesterol by up to 0.4 mmol/l.[66,67] The trials were small with short term follow up only, and involved consuming large amounts of unsalted nuts, which may be unrealistic for the general population in Scotland – 20% of calorie intake was derived from nuts (averaging about 75 g/day).

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More evidence is needed before recommendations can be made.

4.4.5 SOYA INTAKE

Soya based foods are an important constituent in many vegetarian diets and have been investigated for possible beneficial effects on lipid profiles. Two small randomised trials, have suggested that substitution of moderate to large amounts of soya based foods in the diet may have a small impact in lipid profiles.[68,69] Consuming 50 g soya protein a day (in the form of burgers) was reported to reduce total cholesterol by 0.4 mmol/l.

1[-]

More evidence is needed before recommendations can be made.

4.5 GIVING DIETARY ADVICE

Randomised trials have shown that dietary advice can have effects on self reported dietary intake and objective risk factors. Most evidence on beneficial effects is for patients with cardiovascular disease. These effects reduce with time,[70] although, in one study a measurable effect persisted for six to nine years.[71]

4.5.1 WHO SHOULD GIVE DIETARY ADVICE?

In one systematic review dietitians were better than doctors at lowering cholesterol through dietary advice alone, but there were no significant differences between dietitians and nurses or self help resources.[72]

<div align="right">1++</div>

4.5.2 HOW SHOULD DIETARY ADVICE BE GIVEN?

A variety of methods have been attempted varying from brief advice to comprehensive multifactorial lifestyle interventions. In one RCT, up to two hours of counselling achieved greater effects than 10 minutes counselling, but the differences were small.[73] In another RCT, 14 group sessions (90 minutes each) during one year increased self reported fruit and vegetable intake and reduced self reported fat intake, but without significant changes to lipid profiles.[74] One RCT found that telephone "coaching" led to a 10% reduction in total and LDL cholesterol.[75] The intervention involved five telephone calls over 24 weeks and included assessment to establish knowledge, explanation, assertiveness training, goal setting, and reassessment. Length of telephone calls varied, but median times were 20 minutes for the first call and 10 minutes for subsequent calls.

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The SIGN guideline on cardiac rehabilitation reported that interventions to improve lifestyle were more successful if founded on the established education principles of relevance, individualisation, feedback, reinforcement, and facilitation.[76]

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☑   Interventions to improve diet should be based on educational competencies (improved knowledge, relevance, individualisation, feedback, reinforcement and facilitation).

4.6 WEIGHT REDUCTION AND CARDIOVASCULAR RISK

One systematic review of RCTs of diet to reduce weight which evaluated the effect on blood pressure was identified. Only small numbers of patients were included in the trials (six trials including 361 participants).[77] Dietary interventions to reduce weight were moderately effective at reducing blood pressure. Diets producing weight loss in the range 3% to 9% body weight were partially associated with blood pressure reductions of about 3 mm Hg systolic and diastolic. The review had insufficient power to detect differences in morbidity or mortality outcomes.

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Other studies have shown that improvements in blood pressure,[78] lipid profile[79] and glucose handling[80,81] are produced by maintained weight loss, and it is possible to extrapolate these to the reduction of the cardiac events that would be predicted by risk analysis.

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B   **Patients, and individuals at risk of cardiovascular disease, who are overweight, should be targeted with interventions designed to reduce weight, and to maintain this reduction.**

4.7 MANAGING METABOLIC SYNDROME

The metabolic syndrome is characterised by insulin resistance and visceral obesity and is associated with hypertension, impaired glucose handling, lipid abnormalities and a variety of more subtle metabolic and thrombotic anomalies. The lipid profile mirrors that of diabetes, with small, dense LDL, low HDL, and raised triglycerides, and is highly atherogenic.

Individuals with the metabolic syndrome have a cardiovascular risk approaching that of full diabetes and should be treated accordingly.[82-84] The natural progression of untreated metabolic syndrome is to develop overt type 2 diabetes.

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The diagnostic criteria for metabolic syndrome vary, with different definitions available from the World Health Organisation (WHO), International Diabetes Federation[85] (IDF), and the US National Cholesterol Education Program Adult Treatment Panel[86] (ATP). The ATP definitions were updated in 2005 by the American Heart Association/National Heart, Lung, and Blood Institute[87] (AHA/NHLBI). The AHA/NHLBI and IDF definitions are most recent and are very similar, identifying many of the same individuals.

The AHA/NHLBI and IDF define metabolic syndrome as any three of the following:

- increased waist circumference (≥102 cm in men and ≥88 cm in women; ≥90 cm for Asian men and ≥ 80 cm in Asian women), indicating central obesity
- elevated triglycerides (≥1.7 mmol/l)
- decreased HDL cholesterol (<1.03 mmol/l for men, <1.29 mmol/l for women)
- blood pressure above 130/85 mm Hg or active treatment for hypertension
- fasting plasma glucose level above 5.6 mmol/l or active treatment for hyperglycemia.

Asians have a genetic predisposition to the syndrome. Action to prevent or reverse excess weight gain will prevent or sometimes even reverse the metabolic abnormalities and hypertension.[88] Weight reduction often requires an exercise programme as well as dietary intervention, since these individuals commonly have a low basal metabolic rate. Insulin sensitising drugs (eg, metformin, glitazones) are known to be effective in centrally obese patients with overt diabetes, and may also be useful in patients with metabolic syndrome and at high risk.

4

☑ All patients with the metabolic syndrome should be identified and offered professional advice in relation to a cardioprotective diet, exercise and weight monitoring. They should be followed up regularly according to the progress they are making in reducing their total cardiovascular risk.

5 Physical activity

Physical activity has been defined as any bodily movement that results in energy expenditure.[89] Physical activity can be categorised as occupational (physical activity at work), leisure time (non-occupational physical activity), exercise (physical activity that is structured and done for a specific reason) and active living (eg non-recreational walking, housework and gardening). Physical activity is commonly described as having three dimensions: duration (eg minutes, hours), frequency (eg times per week or month) and intensity (eg rate of energy expenditure).[90]

Regular activity has both preventive and therapeutic effects on many chronic conditions such as CHD, stroke, cancer, musculoskeletal disorders, obesity, diabetes and mental illness.[91]

| 4 |

5.1 PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK

5.1.1 PHYSICAL ACTIVITY AS AN INDEPENDENT RISK FACTOR

Ten observational studies that examined the effects of physical activity on CVD, after controlling for other key risk factors, were identified. All studies (or specific elements of the studies) confirmed an inverse relationship between physical activity and the risk of a coronary event.[19, 92-100]

Effect sizes ranged from non-significant relationships for specific types of activity (eg active commuting; hazard ratio = 1.08, 95% CI 0.95 to 1.23)[93] to highly significant associations (eg men who ran for an hour or more per week had a 42% risk reduction, RR 0.58, 95% CI 0.44 to 0.77) compared with men who did not run (p < .001).[100] One well conducted case control study reported a multivariate odds ratio of 0.51 (95% CI 0.29 to 0.90) when comparing low levels of occupational physical activity against higher levels.[92] Similar results were reported for leisure time activity. This suggests that physical activity can reduce the risk of a coronary event, when all other major risk factors are controlled for, by as much as a half.

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5.1.2 LEVELS OF PHYSICAL ACTIVITY

The types of activity, durations, frequencies and intensities utilised in the ten studies varied greatly. This lack of consistency makes it difficult to draw detailed conclusions in relation to the exact type, quantity and quality of activity required for a benefit.

The evidence indicates that activities of moderate intensity are protective. For example, INTERHEART, one of the largest case control studies of its kind, reported an odds ratio of 0.86 (95% CI 0.76 to 0.97) for reduction in incidence of myocardial infarction for activities that included walking, cycling or gardening.[19] In another study that compared distance walked per day, those who walked less than 0.25 miles per day had double the risk of CHD mortality or morbidity of those who walked more than 1.5 miles per day (RR 2.3, 95% CI,1.3 to 4.1) which represented an increase in absolute risk of 2.6%.[94]

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The evidence also suggests a dose response relationship for both intensity and duration. For example, a study of postmenopausal women showed that women in increasing quintiles of energy expenditure measured in metabolic equivalents (METS) had adjusted relative risks of coronary events of 1.00, 0.89, 0.81, 0.78 and 0.72 respectively (p for trend <0.001).[96] Similar trends exist for duration of exercise.[95]

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The type of activity appears to be relatively unimportant. For example, one good quality study reported comparable effects for both occupational and leisure time activity.[92]

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Activity may not need to be continuous to be of benefit. One study reported that after accounting for total energy expended on physical activity and potential confounders, duration of activity did not have an independent effect on CHD risk (p trend = 0.25); that is, longer sessions of exercise did not have a different effect on risk compared with shorter sessions, as long as the total energy expended was similar.[97]

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Although no major adverse events were reported in the studies reviewed and it is generally accepted that the benefits of activity greatly outweigh the risks,[91] there is some evidence of increased risk with activity, particularly in those who are currently sedentary. It has been suggested that those with low levels of habitual vigorous activity are twice as likely to suffer sudden cardiac death during or after exercise compared to those with high levels of habitual activity.[101]

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| **B** | **Physical activity of at least moderate intensity** *(eg makes person slightly out of breath)* **is recommended for the whole population** *(unless contraindicated by condition).* |

| **B** | **Physical activity should include occupational and/or leisure time activity and incorporate accumulated bouts of moderate intensity activities such as brisk walking.** |

| **B** | **Those who are moderately active and are able to increase their activity should be encouraged to do so. Activity can be increased through a combination of changes to intensity, duration or frequency.** |

| ☑ | All patients, irrespective of health, fitness or activity level, should be encouraged to increase activity levels gradually. |

The evidence reviewed and corresponding recommendations are in general agreement with nationally recognised recommendations that state all adults should accumulate 30 minutes, and children 60 minutes, of moderate intensity activity on most days of the week.[102]

4

National guidance is available on the most effective way to promote physical activity.[46,103]

5.1.3 EFFECTS OF PHYSICAL ACTIVITY ON OTHER KEY RISK FACTORS

Several meta-analyses provide evidence for a significant effect of exercise on CHD risk factors. One meta-analysis combined results of 28 RCTs of mainly healthy white adults.[104] Diets which reduce saturated fats aiming to lower LDL cholesterol levels also tend to reduce the level of protective HDL cholesterol; however, exercise can attenuate this effect. Despite a large degree of variability, endurance exercise training had a favourable influence overall on the blood lipid profile relative to future risk of CHD. The most commonly observed lipid change in all weight categories in relation to endurance training was a significant ($p < 0.05$) increase in HDL cholesterol. Reductions in LDL cholesterol (-5.0%, $p < 0.05$), triglycerides (-3.7%, $p < 0.05\%$), and total cholesterol (-1%, not significant) were observed less frequently (independent of dietary interventions). There was a marked inconsistency in response of blood lipids. Twenty-four of 51 studies showed an increase in HDL cholesterol but the range over all studies was from -5.8% to $+25\%$. It was not possible to establish a dose-response relationship between duration, intensity or frequency of exercise and blood lipid response.

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A further meta-analysis of 54 trials showed that previously sedentary adults could decrease systolic blood pressure by 3.8 mm Hg (95% CI 2.7 to 5.0 mm Hg, $p < 0.001$) and diastolic blood pressure by 2.6 mm Hg (95% CI 1.8 to 3.4 mm Hg, $p < 0.001$) with regular aerobic exercise.[105] Exercise lowered blood pressure in people who were normotensive or hypertensive; overweight or of normal weight; and black, white, or Asian. The blood pressure reductions tended to be less marked in trials with longer follow up periods, most likely because adherence to the intervention programme decreased over time. All forms of exercise studied appeared to be effective in reducing blood pressure, and again, there was no relation between the frequency or intensity of the exercise and the clinical result.

1+

6 Smoking

6.1 TOBACCO EXPOSURE AND CARDIOVASCULAR RISK

This section summarises the evidence describing the relationship between tobacco exposure and cardiovascular health and focuses on cessation interventions for two vulnerable population subgroups: those with a history of depression or schizophrenia. No relevant evidence was identified for interventions in ethnic subgroups.

6.1.1 ACTIVE SMOKING

Tobacco smoking is strongly and dose-dependently associated with all cardiovascular events, including CHD, stroke, peripheral arterial disease (PAD) and cardiovascular death.[106,107] Smoking cessation reduces these risks substantially, although the decrease is dependent on the duration of cessation.[108,109] Men who smoke are three times more likely to die aged 45-64 years, and twice as likely to die aged 65-84 years than non-smokers.[106] Studies done among women during the 1950s and 1960s reported relative risks for total mortality ranging from 1.3 to 1.4. Smokers in the Nurses' Health Study were at nearly 1.9 times the risk compared with people who have never smoked.[110]

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The additional risk of cardiovascular disease conferred by smoking is mediated by the number of cigarettes smoked. A large case control study noted the strong relation between risk of myocardial infarction (MI) and number of cigarettes smoked, with individuals who smoked over 40 cigarettes per day having almost ten times the relative risk of MI as non-smokers (odds ratio 9.16, 99% CI 6.18 to 13.58).[19]

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The prevalence of regular (at least weekly) smoking among 13 year olds has decreased since 1998 from 9% to 5% among boys and from 11% to 7% among girls. Among 15 year old boys, the prevalence of regular smoking has decreased from 30% in 1996 to 15% in 2000 and has since remained around that level. The drop among 15 year old girls over the same period (from 30% in 1996 to 24% in 2000) was smaller and not statistically significant; prevalence has remained at 24% since 2000.[111] There is evidence that young people can become addicted to tobacco very quickly[112] and many want to stop smoking.[113]

<div style="text-align:right">4</div>

☑ Priority should be given to identifying and supporting young people to help them stop smoking.

The prevalence of smoking is highest amongst those on low incomes. Amongst some groups smoking rates as high as 75% have been reported.[114]

<div style="text-align:right">4</div>

☑ Priority should be given to developing programmes and targeting smokers on low incomes to stop smoking, recognising the particular difficulties experienced by this group of smokers.

A prospective cohort study of over 120,000 males suggested that smoking cigars increases risk of early death from CHD.[115] The association between cigar smoking and death from CHD was stronger among younger men and current rather than former smokers, as is observed with cigarette smoking. No increased risk was observed among current cigar smokers aged 75 years or older, or for former cigar smokers of any age. For men younger than 75 years who were current cigar smokers at baseline, the adjusted rate ratio for CHD mortality was 1.30 (95% CI 1.05 to 1.62).

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A case control study involving 587 case subjects and 2,685 controls who smoked cigarettes with known tar yields indicated that smoking higher-yield cigarettes is associated with an increased risk of MI. The study revealed a dose-response relationship between total tar consumption per day and MI.[116] The odds ratios for subjects smoking medium- and high compared with low-tar-yield cigarettes were 1.86 (95% CI 1.21 to 2.87) and 2.21 (95% CI 1.47 to 3.34), respectively.

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B **All people who smoke should be advised to stop and offered support to help facilitate this in order to minimise cardiovascular and general health risks.**

6.1.2 PASSIVE SMOKE EXPOSURE

Several systematic reviews and observational studies provide evidence that exposure to environmental tobacco smoke (ETS) is associated with CVD events.

One systematic review calculated that environmental exposure to tobacco smoke causes an increase in relative risk of CHD of around 25%. It is of similar magnitude to the effects of exposure to environmental tobacco smoke on lung cancer, but the number of excess death from heart disease compared with lung cancer will be far greater in non-smokers due to the higher prevalence of CHD.

Individuals who have never smoked have an estimated 30% increased relative risk of CHD if they live with a smoker (p < 0.001). The excess risk from smoking one cigarette per day is 39%, similar to the risk in a non-smoker living with a smoker. Reversal of the effect would reduce the risk of CHD by about as much as taking aspirin or by what many people could achieve through dietary change.[107] Other systematic reviews highlight the increased risk of CHD events through exposure to ETS in the workplace[117] and at home. [118]

2++
2+

Two observational studies indicated that non-smokers exposed to cigarette smoke had an increased risk of acute coronary syndromes of 51% (OR = 1.51, 95% CI 1.21 to 2.99) compared with non-smokers not exposed to smoke.[119,120]

2++
2+

Another case control study examined the relationship between ETS and MI, in the workplace and at home.[121] The odds ratio for MI was 1.58 (95% CI 0.97 to 2.56) for an average daily passive exposure to the smoke from 20 cigarettes per day or more at home. Combined exposure at home and work showed an increasing odds ratio for MI, up to 1.55 (95% CI 1.02 to 2.34) in the highest category of weighted duration, that is, more than 90 "hour-years" of exposure (1 "hour-year" = 365 hours, or one hour per day for one year). In addition, more recent exposure appeared to convey a higher risk. This study confirms an increased risk of MI from exposure to ETS and suggests that intensity of spousal exposure, combined exposure from home and work, and time since last exposure are important.

2++

> **B** **Exposure to passive smoking increases cardiovascular risk and should be minimised.**

6.2 SMOKING CESSATION INTERVENTIONS

6.2.1 THE GENERAL POPULATION

There are many guidelines and policy documents covering mainstream NHS smoking cessation services and wider primary prevention.[122-124]

4

One systematic review and two RCTs comparing smoking cessation interventions were identified.

A systematic review of 20 studies concluded that quitting smoking is associated with a 36% reduction in crude relative risk of mortality for patients with CHD who quit compared with those who continued smoking (RR 0.64; 95% CI 0.58 to 0.71).[125]

2++

Two RCTs addressed lifestyle advice/training and reported a reduction in smoking in those who went through an educational programme.[126,127] Both studies only included male patients and lacked sufficient power to allow a firm conclusion to be derived.

In the Oslo Diet and Antismoking Trial, advice to change diet and smoking habits reduced the relative risk of CHD mortality after 23 years in men with high triacylglycerol concentrations. Men with normal triacylglycerol concentrations did not appear to achieve this long term benefit of lifestyle intervention.[126]

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The Vestfold Heartcare Study Group trial investigated whether a comprehensive programme of lifestyle modification could favourably influence dietary and exercise habits in addition to smoking cessation.[127] After following a low-fat diet, regular exercise, smoking cessation and psychological support and education sessions, patients in the lifestyle intervention group reduced the intake of saturated fat, sugar and cholesterol ($p < 0.001$), increased their exercise level ($p < 0.01$) and stopped smoking ($p < 0.05$) when compared with the usual care group. Results indicated a relative risk reduction of 22% in five-year risk of CHD in males (95% CI 9 to 35), however, the study lacked statistical power and should be interpreted with caution.

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One systematic review which compared different forms of nicotine replacement therapy (NRT) concluded that all forms of NRT can help people to stop smoking, almost doubling long term success rates. The odds ratio (OR) for abstinence with NRT compared to control was 1.77 (95% CI 1.66 to 1.88).[128]

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A systematic review of the effect of antidepressants on smoking cessation showed that buproprion and nortryptiline approximately doubled the odds of a motivated individual stopping smoking.[129] Based on 19 trials of bupropion monotherapy with over 4,000 participants the pooled odds ratio for smoking cessation was 2.06 (95% CI 1.77 to 2.40). Serious adverse effects using bupropion at the doses indicated for smoking cessation are rare (less than one per 1,000 treated).[130]

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Nortryptiline is not licensed for use in smoking cessation and is contraindicated in patients with recent myocardial infarction or arrhythmias (particularly heart block).[131]

| | 4 |

> **A**   **Nicotine replacement therapies or bupropion should be used as part of a smoking cessation programme to augment professional advice and increase long term abstinence rates.**

6.2.2   SPECIAL POPULATIONS

Patients with depression

One meta-analysis[132] and three RCTs[133-135] were identified which considered smoking cessation in individuals with clinical depression.

The meta-analysis considered whether a history of major depression is associated with failure to quit smoking. No differences in either short term ($\leq$ three months) or long term abstinence rates ($\geq$ six months) were observed between smokers who were positive versus negative for history of depression. The authors conclude that a lifetime history of major depression does not appear to be an independent risk factor for cessation failure in smoking cessation treatment.

| | 2++ |

The three RCTs considered different smoking cessation strategies for patients with depression. One trial investigated the effect of nortriptyline hydrochloride and cognitive behaviour therapy (CBT) on smoking treatment outcome in smokers with a history of major depressive disorders.[133] Nortriptyline produced higher abstinence rates than placebo, independent of depression history and alleviated a negative affect occurring after smoking cessation. Cognitive behaviour therapy was more effective for participants with a history of depression.

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A smaller trial investigated the effect of sertraline as a cessation aid to patients with clinical depression. The trial showed that sertraline did not add to the efficacy of an intensive individual counselling. However, given that the end-of-treatment abstinence rate for the placebo group was much higher than expected, it is unclear whether a ceiling effect of the high level of psychological intervention received by all subjects prevented an adequate test of the drug.[134]

| | 1+ |

One small trial examined the efficacy of a mood management intervention for smoking cessation in abstinent alcoholics with a history of major depression.[135] Patients were randomised to either behavioural counselling (BC) alone or counselling with a CBT component. Significantly more smokers in the CBT group had quit smoking by the end of the intervention period (69.2%; 9 of 13) than in BC (31.3%; 5 of 16) ($p = 0.04$). The abstinence rates remained unchanged at one month follow up. At three months follow up, differences in smoking abstinence rates were not significant between CBT (46.2%; 6 of 13) and BC (25.0%; 4 of 16) conditions. At 12 months follow up, significantly more participants in CBT were abstinent from smoking (46.2%; 6 of 13) than in BC (12.5%; 2 of 16) ($p = 0.04$).

| | 1- |

Antidepressants have an effect on smoking cessation rates in this group (but are not licensed specifically for this indication). It is not clear whether this effect is mechanistic or related directly to the treatment of depression. There are no significant trials of other pharmacological interventions (eg NRT, buproprion) in this group of patients.

B	**Smokers with coronary heart disease and comorbid clinical depression should have their depression treated both for alleviation of depressive symptoms and to increase the likelihood of stopping smoking.**

Patients with schizophrenia

Two poor quality RCTs[136,137] and a follow up study[138] were identified which considered smoking cessation in individuals with schizophrenia.

One trial of the effect of adding sustained-release bupropion to CBT on smoking behaviour and stability of psychiatric symptoms was identified in patients with schizophrenia. The study was flawed by omission of method of randomisation and concealment, and also involved only nine patients in experimental and control arms. Bupropion treatment was associated with an apparently greater reduction in smoking, as measured by self-report and carbon monoxide expiration, which may not have been sufficiently sensitive to detect changes in smoking status. Bupropion was only used at half the dose recommended because of seizure risk.[136]

1-

A study which followed up the same patients suggested that most individuals who achieved ≥ 50% reduction in smoking at the end of the trial maintained at least that level of reduction after two years. Smoking reduction during the treatment intervention was correlated with smoking reduction at follow up (r = 0.60, p = 0.01).[138]

2-

Another small RCT compared sustained-release bupropion with placebo for smoking cessation in patients with schizophrenic disorders. Results indicated an increase in self-reported smoking abstinence with bupropion compared with placebo at 10 weeks but no significant difference at six months. Patients who consented and were proven to be highly motivated using a Likert scale were not likely to be typical of people with schizophrenia. The method of randomisation was not described.[137]

1-

Independent studies of bupropion for smoking cessation in people with schizophrenia are needed.

Patients from ethnic minorities

There have been no statistically reliable nationwide surveys of the prevalence of smoking or effectiveness of cessation interventions among ethnic minorities in Scotland. Research from England done in the late 1990s provides some information on tobacco use and cessation rates in ethnic subgroups (*see Table 4*).[139]

Table 4: Cigarette smoking by sex and minority ethnic group in England (as a percentage of the population)

	General population	Black Caribbean	Black African	Indian	Pakistani	Bangladeshi	Chinese
Men	24	25	21	20	29	40	21
Women	23	24	10	5	5	2	8

In general, smoking rates among ethnic minorities were the same, or lower, than those found in the wider population of England. While smoking rates for men and women in the UK on the whole are converging, amongst minority ethnic groups there are still marked gender differences in smoking behaviour. Rates are low in particular among South Asian women, however research conducted by Action on Smoking and Health (ASH) Scotland has indicated that smoking is escalating among South Asian girls in Scotland, particularly in young Pakistani women.[140]

ASH Scotland has conducted a mapping exercise to identify smoking cessation projects, services, resources and training courses available to individuals from ethnic subgroups. Although some material was identified which had been specifically targeted to ethnic subgroups (mostly leaflets), generally, mainstream tobacco services were not attracting representative proportions of individuals from ethnic subgroups.[141]

7 Alcohol

7.1 ALCOHOL AND CARDIOVASCULAR RISK

Alcohol is known to have both beneficial and harmful effects on the biochemical basis for CHD and the psychological consequences of the disease.[142]

In Scotland, 32% of men and 14% of women drink above weekly recommended limits. Patterns of drinking vary and 44% of men who had drunk in the last week consumed eight units or more on their heaviest drinking day (where one unit is defined as approximately 8 g /10 ml of alcohol), indicating that binge drinking may be a particular problem.[143] | 3

The adverse effects of alcohol on other clinical conditions (eg mental health, liver disease, cancer risk and societal effects) have not been reviewed in this guideline and should be taken into account when advice is provided in the clinical setting. Long term alcohol related health consequences are now giving rise to serious concerns in Scotland.

Consuming over 40 g/day alcohol increases a man's risk for liver disease, raised blood pressure, some cancers (for which smoking is a confounding factor) and violent death. For women, consuming over 24 g/day average alcohol increases their risk for developing liver disease and breast cancer.[144] | 4

7.1.1 HOW DO ALCOHOL CONSUMPTION LEVELS ALTER CARDIOVASCULAR DISEASE MORTALITY AND MORBIDITY?

Systematic reviews of cohort and case control studies, show a 'J' shaped relationship between alcohol consumption and either vascular[145] or CHD risk[146-148] of mortality and morbidity. Most studies report data for middle-aged men. Where data is reported for subgroups of men and women, the maximum benefit for men is at 25 g alcohol per day (equivalent to three units/day), with some protection up to 87 g/day (equivalent to just under 9 units/day), and the maximum benefit for women is at 10 g/day (equivalent to approximately one unit/day), with some protection at up to 31 g/day (equivalent to approximately 4 units/day). The degree of reduction in risk of coronary events following light or moderate drinking is small but significant (RR = 0.80, 95% CI 0.78 to 0.83).[146] This is supported by some evidence of improved lipid profiles with regular drinking in moderation.[146,149] Conversely, binge drinking is harmful and associated with a poorer lipid profile, and adverse effect on systolic blood pressure and increased risk of thrombosis.[149,150] There does not appear to be any differential effect associated with type of alcohol consumed.[145,151] | 2++ 2+ 4

It has been suggested that the apparent cardioprotective effect of alcohol may be accounted for by methodological flaws in the evidence. There may be a bias towards the publication of studies which identify a benefit, suggesting that intakes lower than the maximum reported may be optimal.[146] Abstainers may have higher rates of pre-existing ill health, which would result in a relatively poorer outcome in comparative studies with alcohol drinkers.[152] However, there is broad consistency of findings across systematic reviews, and with other guidelines. [29,153,154] | 2++ 4

> **B** **Patients with no evidence of coronary heart disease may be advised that light to moderate alcohol consumption may be protective against the development of coronary heart disease.**

Two cohort studies, which were nested within high quality RCTs, of the effects of alcohol consumption in secondary prevention subgroups confirmed the protective effective of moderate drinking.[155,156] | 2+

> **C** **Patients with established coronary heart disease may be advised that light to moderate alcohol consumption may be protective against further coronary events.**

☑ When giving advice to patients with coronary heart disease, the current general advice of no more than two to three units of alcohol per day for women and no more than three to four units of alcohol per day for men, with at least two drink-free days per week for both men and women, should be recommended.[157,158]

There is considerable confusion over the definition of a standard "unit" of alcohol. One unit of alcohol in the UK means a beverage containing 8 g or 10 ml of ethanol. The amount of alcohol in units is calculated as: volume of drink (litres) x percentage by volume alcohol.[144] There is a commonly held belief that half a pint of beer, or one glass of wine equate to a unit, but exact strength and volume are critical, as the examples in Table 5 illustrate. Standard pub measures are often smaller than drinks poured at home.

Table 5: Volumes of drinks equivalent to one unit of alcohol

Drink	Percentage alcohol	Volume equivalent to one unit
Beer/lager	3.5 %	0.5 pint
Beer/lager	5.0 %	0.35 pint
Wine	10 %	100 ml (one 750 ml bottle = 7.5 units)
Wine	13 %	77 ml (one 750 ml bottle = 9.75 units)
Fortified wine/sherry	17.5 %	57.1 ml
Spirits	40 %	25 ml

☑ Examples of what constitutes a 'drink' or unit of alcohol should be given to the patient.

7.1.2 WHAT IS THE BEST WAY TO MODIFY ALCOHOL CONSUMPTION?

Three systematic reviews consider methods of reducing alcohol intake in those whose drinking is considered to be harmful or risky.[159-161] All conclude that brief interventions are the most effective method with increased benefit from multi-contact interventions. One review concluded that for benefit an intervention had to include two of the three key elements: feedback, advice and goal setting.[160] Many of the individual studies included in the reviews were not UK-based and some reviews included interventions which may not be deliverable in primary care in the UK (eg electric aversion therapy).

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Brief interventions may include some of the following: information, feedback and advice on prevalence of drinking, adverse effects of alcohol, drinking cues, drinking diaries, drinking agreement/contract, retrospective self report of drinking alcohol or current alcohol qualities and types of alcohol consumed, injuries, healthcare utilisation, recommended levels of alcohol consumption, education on risks involved in consumption of alcohol, strategies for changing drinking habits, feedback of personal health data.[162,163]

There are a range of suggested time scales for brief interventions from five minutes to 20 minutes, from a single occasion up to five sessions, and vary from face to face to via the telephone.

A single RCT in subjects with type 2 diabetes and/or hypertension confirmed the benefit of multi-contact, brief counselling to reduce alcohol consumption in high risk patients (11% absolute reduction in numbers of heavy drinkers in intervention group).[162]

1[++]

One review specifically looked at the effectiveness of untargeted screening prior to delivering a brief intervention to modify alcohol consumption.[163] It found that of 1,000 patients 90 screened positive, 25 of whom qualified for a brief intervention. At one year, two or three of these would have reduced their drinking to within the recommended alcohol intake levels.

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A **Brief multi-contact interventions should be used to encourage patients to reduce their levels of drinking if their current intake is hazardous to their health.**

☑ Universal screening as a case-finding exercise in primary care is not recommended.

SIGN guideline 74 provides detailed guidance on managing harmful drinking and alcohol dependence alcohol consumption in primary care.[144]

4

8 Antiplatelet therapy

8.1 USE OF ANTIPLATELET AGENTS IN PEOPLE WITH ESTABLISHED CARDIOVASCULAR DISEASE

The favourable benefit to risk profile of aspirin for patients with established cardiovascular disease is well recognised. In meta-analyses, the Antithrombotic Trialist's Collaboration showed clear evidence of a reduction in all cause mortality, vascular mortality, non-fatal reinfarction of the myocardium, and non-fatal stroke in people with acute coronary syndromes, stroke, transient ischaemic attacks (TIAs), or other vascular disease.[164,165] The trials used aspirin doses between 50–325 mg/day. The meta-analysis provided no evidence of any greater benefit from high dose aspirin, while adverse effects from aspirin are minimised at lower dosages.

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A meta-analysis compared the benefit and gastrointestinal risk of low dose (< 325 mg) aspirin use for the secondary prevention of thromboembolic events. It showed that aspirin reduced all-cause mortality by 18%, the number of strokes by 20%, myocardial infarctions by 30%, and other vascular events by 30%. Patients who took aspirin were 2.5 times more likely than those in the placebo group to have gastrointestinal tract bleeding. The number needed to treat for aspirin to prevent one death from any cause of mortality was 67, while 100 needed to be treated to detect one nonfatal gastrointestinal tract bleeding.[166]

> 1++

The evidence supports daily doses of aspirin in the range of 75–325 mg for the long term prevention of serious vascular events in high risk people, and it is usual practice to prescribe 75 mg daily. Although there is no clinical trial evidence of treatment beyond a few years, there is likely to be ongoing benefit, so it is usual to continue aspirin therapy for life.

A | **Individuals with established atherosclerotic disease should be treated with 75 mg aspirin daily.**

The platelet receptor blocker clopidogrel was equivalent to aspirin in prevention of further events in patients with CHD or ischaemic stroke.[167] In subgroup analysis, clopidogrel appeared to be more effective than aspirin among patients with peripheral vascular disease, although the study was not powered to detect a significant effect in any subgroup (*see SIGN guideline 89 on diagnosis and management of peripheral arterial disease*).[168] It is indicated in combination with aspirin in patients with proven troponin-positive acute coronary syndromes for up to three months following the acute event (*see SIGN guideline on acute coronary syndromes*).[169] It is more expensive than aspirin and should be used if aspirin causes side effects.[167]

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☑ | Clopidogrel should be considered in patients with symptomatic cardiovascular disease who have aspirin hypersensitivity or intolerance or in whom aspirin causes unacceptable side effects.

Meta-analysis of two large RCTs with 20,000 patients in each showed that starting daily aspirin (160 - 300 mg) promptly in patients with suspected acute ischaemic stroke reduced the immediate risk of further stroke or death in hospital and the overall risk of death or dependency.[170] Relative risk for recurrent ischaemic stroke was reduced by 30% in the group taking aspirin (odds ratio 0.70, $p < 0.000001$; ARR 0.7%). Death without further stroke was reduced by 8% (odds ratio 0.92, $p = 0.05$; ARR 0.4%). In total there was a net decrease of 11% in the overall risk of further stroke or death in hospital (odds ratio 0.89, $p = 0.001$; ARR 0.9%).

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One RCT assigned patients to aspirin (30 - 325 mg daily, median 75 mg) with (n = 1,363) or without (n = 1,376) dipyridamole (200 mg twice daily) within six months of a transient ischaemic attack or minor stroke of presumed arterial origin.[171] Combination therapy with aspirin and dipyridamole reduced the composite outcome of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication by 20% (hazard ratio 0.80, 95% CI 0.66 to 0.98; ARR 1.0% per year, 95% CI 0.1 to 1.8).

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> **A** **Individuals with a history of stroke or transient ischaemic attack and who are in sinus rhythm should be considered for low dose aspirin** *(75–300 mg daily)* **and dipyridamole** *(200 mg twice daily)* **to prevent stroke recurrence and other vascular events. If aspirin is contraindicated, or there are side effects, clopidogrel 75 mg daily is an alternative.**

8.2   USE OF ANTIPLATELET AGENTS IN PEOPLE WITHOUT CARDIOVASCULAR DISEASE

Aspirin reduces the risk of MI by approximately 30%, but increases the risk for haemorrhagic strokes by about 40% and of major gastrointestinal bleeding by 70%.[172] All-cause mortality has not been shown to be affected. For 1,000 patients with a 10% risk for CHD events over ten years, aspirin would prevent 12 to 40 myocardial infarctions but would cause zero to four haemorrhagic strokes and four to eight major gastrointestinal bleeding events. For patients with a CHD risk of 2% over ten years, aspirin would prevent two to eight myocardial infarctions but would cause zero to four haemorrhagic strokes and four to eight major gastrointestinal bleeding events. In another analysis, a CHD risk of ≥15% over ten years was defined as the point of benefit over harm for aspirin use in patients with no evidence of atherosclerotic disease.[173]

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Enteric coated products do not prevent the major gastrointestinal complications of aspirin therapy and are significantly more expensive than the standard dispersible formulation.[174-176]

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8.2.1   SEX DIFFERENCES IN RESPONSE TO ASPIRIN THERAPY

A meta-analysis of six trials of aspirin in individuals with no evidence of cardiovascular disease included 51,342 women and 44,114 men. It showed that overall low dose aspirin (50-500mg daily) was associated with a reduction in the relative risk of cardiovascular events in both men and women (*see Table* 6).[177] For women, there is a significant reduction in the likelihood of stroke (mainly ischaemic stroke) whereas in men, no significant effect was observed on all strokes, however a significant 32% reduction in the relative risk of MI was seen. There was no evidence that higher doses of aspirin were more effective in reducing the primary clinical endpoints in the doses used in this meta-analysis. In both men and women aspirin was associated with a significantly increased risk of major bleeding.

1[++]

> **A** **Asymptomatic individuals without established atherosclerotic disease but with a calculated cardiovascular risk of ≥20% over ten years should be considered for treatment with aspirin 75 mg daily.**

Table 6: Cardiovascular risk reduction in asymptomatic individuals treated with aspirin

Cardiovascular endpoint	MEN		WOMEN	
	OR (95% CI, p-value)	ARR (%)	OR (95% CI, p-value)	ARR (%)
Cardiovascular event (cardiovascular mortality, non-fatal MI or non-fatal stroke)	0.86 (0.78-0.94, p = 0.01)	0.35	0.88 (0.79-0.99, p = 0.03)	0.3
MI	0.68 (0.54-0.86, p = 0.001)	0.85	1.01 (0.84-1.21, p = 0.95)	
Any stroke	1.13 (0.96-1.33, p = 0.14)		0.83 (0.70-0.97, p = 0.02)	0.23
Haemorrhagic stroke	1.69 (1.04-2.73, p = 0.03)	0.12	1.07 (0.42-2.69, p = 0.89)	
Ischaemic stroke	1.00 (0.72-1.41, p = 0.98)		0.76 (0.63-0.93, p = 0.008)	0.25
Cardiovascular mortality	0.99 (0.86-1.14, p = 0.87)		0.90 (0.64-1.28, p = 0.56)	
All cause mortality	0.93 (0.85-1.03, p = 0.15		0.94 (0.74-1.19, p = 0.62)	
Major bleeding	1.72 (1.35-2.20, p < 0.001)	-0.32	1.68 (1.13-2.52, p = 0.01)	-0.25
OR – odds ratio, CI – confidence interval, ARR – absolute risk reduction				
Shaded boxes show significant results				

8.3   INDIVIDUALS WITH DIABETES

There are few data on aspirin for primary prevention among diabetic individuals. The Primary Prevention Project (PPP) trial compared aspirin 100 mg/day with a placebo, vitamin E 300 mg/day, in type 2 diabetes mellitus (DM) patients without established cardiovascular disease.[178] Aspirin failed to achieve a significant difference in the composite primary endpoint of cardiovascular death, stroke, or MI in patients with diabetes (relative risk 0.9, 95% CI 0.5 to 1.62, p = 0.71). There was no significant reduction in total cardiovascular events in patients with diabetes taking aspirin (RR 0.89, 95% CI 0.62 to 1.26).

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In the HOT trial there was a reduction by 15% in major cardiovascular events among the 9,399 patients randomised to receive 75 mg aspirin per day (p = 0.03). This cohort was defined by existing hypertension and a diastolic blood pressure between 100 mm Hg and 115 mm Hg and included patients with DM.[179] No significant effect on overall mortality was reported. Fatal bleeds were equally common in the treatment and control groups, but non-fatal major bleeds were significantly more frequent among patients receiving aspirin than in those receiving placebo (risk ratio 1.8, p < 0.001). The trial reported that 2.5 myocardial infarctions could be prevented per 1,000 patient-years in patients with diabetes mellitus.

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There is conflicting evidence on the benefit of aspirin on stroke outcomes on patients with DM.[180]

4

The revised Joint British Societies guideline advises that aspirin 75 mg daily is recommended for all people with type 2 diabetes who are over 50 years of age, and selectively in younger people with one of the following criteria:[28]

- have had the disease for more than ten years; or
- are already receiving treatment for hypertension; or
- have evidence of target organ damage in the form of retinopathy or nephropathy, and whose blood pressure is controlled to at least 150/90 mm Hg, and preferably to the optimal target of 130/80 mm Hg.

☑ Aspirin 75 mg daily is recommended for all people with type 2 diabetes who are over 50 years of age and for selected younger individuals with diabetes who are considered to be at increased cardiovascular risk.

8.4   INDIVIDUALS WITH HYPERTENSION

For every individual the risk of bleeding must be considered against the benefits of cardiovascular protection. Low dose aspirin has been shown in one major randomised trial of hypertensive individuals to be of benefit only in those patients at higher baseline risk.[179] In patients at lower risk there was neither benefit nor harm. Hypertensive patients with a ten year risk ≥20% of cardiovascular disease would be considered to have a high baseline risk, where benefits of antiplatelet treatment would outweigh harms. Patients with uncontrolled blood pressure are at greater risk of cerebral haemorrhage and should not receive antiplatelet therapy until their blood pressure is treated to <150/90 mm Hg.

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☑ Patients with hypertension should be treated with aspirin if their ten year cardiovascular disease risk exceeds 20%, and only once their blood pressure is treated to <150/90 mm Hg.

9 Lipid Lowering

9.1 THE ROLE OF TOTAL AND LOW DENSITY LIPOPROTEIN CHOLESTEROL IN CARDIOVASCULAR DISEASE

The link between cardiovascular risk and variation in blood lipid concentration was shown in a study of over 356,000 men aged 35-57 years who were followed up for six years. The study demonstrated a continuous, graded, strong relationship between serum cholesterol and six year age adjusted CHD mortality.[181] This relationship persisted in smokers and non-smokers, people with and without hypertension and was evident irrespective of the presence or absence of vascular disease.[182-184]

<div style="float:right">2⁺⁺</div>

Low density lipoprotein (LDL) cholesterol usually makes up 60-70% of total serum cholesterol and the strong relationship between total cholesterol level and CHD suggests that LDL cholesterol is a powerful risk factor.[185] The role of LDL cholesterol in atherosclerosis is confirmed by studies carried out in individuals with genetic disorders that result in extreme elevations of cholesterol levels, such as familial hypercholesterolaemia.[186] These individuals tend to develop premature CHD with evidence of advanced atherosclerosis even in the absence of any other risk factor for coronary disease.

Epidemiological evidence has shown that populations with higher cholesterol levels experience more atherosclerosis and CHD than populations with lower levels[187] and the higher the level of cholesterol, the greater the risk of a coronary event.[181]

<div style="float:right">2⁺⁺</div>

9.2 MEASURING LIPID LEVELS

LDL cholesterol can be calculated indirectly by measuring total cholesterol, HDL cholesterol and triglycerides from a fasting venous blood sample and applying the Friedewald equation: $LDL = TC - HDL - (TG/2.2)$.[188] This method is not suitable for individuals with TG levels > 5 mmol/l.

For greatest accuracy 12 hour fasting samples are required as HDL cholesterol and TG levels vary between fasting and non-fasting states. HDL cholesterol is lower by 5% to 10% in the non-fasting state than in the fasting state and TG levels are 20-30% higher.

Given the practical problems of routinely collecting 12 hour fasting samples, non-fasting blood samples are generally collected for estimation of TC and HDL cholesterol.[189] Accurate estimation of LDL cholesterol requires a full lipid profile to be carried out on a fasting venous blood sample.

9.3 THE BENEFITS OF LOWERING CHOLESTEROL FOR CARDIOVASCULAR RISK

Statins (HMG-CoA reductase inhibitors) are central to lipid lowering therapy in the prevention of first and recurrent vascular events. Statins inhibit cholesterol synthesis in the liver, activating hepatocyte LDL receptors and increasing hepatic uptake of LDL from the circulation.

A meta-analysis of lipid lowering in five randomised, placebo-controlled, double-blind trials included two trials in patients without evidence of cardiovascular disease (n = 13,200) and three trials carried out in symptomatic patients (n = 17,617). Active treatment with statins was associated with a 34% relative risk reduction (95% CI 23% to 43%; p < 0.001) in major coronary events in the primary prevention trials and a 30% relative risk reduction (95% CI 24% to 35%; p < 0.001) in the secondary prevention trials. The mean reduction (weighted by sample size) in TC, LDL cholesterol, and triglyceride levels was 20%, 28%, and 13%, respectively, and HDL cholesterol was increased by an average of 5% among the five trials.[190]

<div style="float:right">1⁺⁺</div>

Total cholesterol and CHD mortality reduction was consistent in trials of individuals with and without evidence of cardiovascular disease (*see Table 7*).

Table 7: CHD mortality and total cholesterol reduction in RCTs of statin therapy

Number of trials (type of population)	n	Mean total cholesterol reduction	Mean relative reduction in CHD mortality	95% CI
5 (pooled results)	30,817	20%	29%	20 to 36%
2 (primary prevention)	13,200	19%	27%	-0.5 to 49%
3 (secondary prevention)	17,617	22%	29%	20 to 37%

Two major primary prevention trials included in this meta-analysis were the West of Scotland Coronary Prevention Study (WOSCOPS)[191] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[33] In both trials, statin therapy significantly reduced relative risk for major coronary events (WOSCOPS relative risk reduction 29%, 95% CI 15 to 40, ARR 2.5%; AFCAPS/TexCAPS relative risk reduction 37%, 95% CI 21 to 50, ARR 4.1%). WOSCOPS also showed a significant reduction in coronary mortality (relative risk reduction 33%, 95% CI 1 to 55, ARR 0.6%). In AFCAPS/TexCAPS, the numbers of deaths in both placebo and treatment groups were so small that no conclusions could be drawn about effects of lipid lowering therapy on total mortality, however, no significant adverse effects of statin therapy were detected.

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Regression analyses of RCTs of statin therapy indicate that for every 10% reduction in total cholesterol there will be a 15% reduction in coronary mortality.[192] The absolute reduction in total cholesterol in major statin trials averages around 1 mmol/l. This corresponds to a 20% lowering and would be expected to yield an approximate 30% CHD mortality benefit.[190,193]

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In more recent RCTs of lipid lowering, LDL cholesterol has been identified as a target for therapy. Large trials of statin therapy in patients with and without CVD have indicated the degree of relative risk reduction for major coronary events which can be achieved from a given lowering of LDL cholesterol. They indicate that for every 1% reduction in LDL cholesterol levels, relative risk for major CHD events is reduced by approximately 1%.[194-197]

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A meta-analysis of data from 90,056 participants in 14 randomised trials of statin therapy showed that a 1.0 mmol/l reduction in LDL cholesterol lowered the five year relative risk of a major vascular event by 21%, irrespective of sex, age, blood pressure, pre-existing diabetes or history of a previous vascular event (RR 0.79, CI 0.77 to 0.81; p<0.0001; ARR 3.7%).[3] Individuals at higher levels of vascular risk gained more in absolute terms from statin intervention. The relative risk reduction of around one fifth per mmol/l LDL translates to 48 (95% CI 39 to 57) fewer individuals having a major vascular event per 1,000 among those with established CHD, compared with 25 (19 to 31) fewer per 1,000 among individuals without established CHD.

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This meta-analysis indicates an approximately linear relationship between the LDL cholesterol reductions achieved and the reduction in incidence of coronary and vascular events. The proportional reduction in event rate per mmol/l reduction in LDL cholesterol was independent of the presenting level, (ie lowering LDL cholesterol from 4 mmol/l to 3 mmol/l or from 3 mmol/l to 2 mmol/l) both reduce the risk of vascular events by about 21%, thus a reduction of LDL cholesterol from 4 mmol/l to 2 mmol/l might be expected to reduce risk by around 40% (relative risk 0.79 x 0.79 = 0.62).

9.4 HOW TO REDUCE LDL CHOLESTEROL

An extensive systematic review and meta-analysis quantifying the effect of cholesterol lowering on the risk of vascular events in patients with and without CVD emphasised the importance of cholesterol reduction per se rather than treatment modality.[198] Evidence for lipid lowering drugs other than statins is presented in section 9.10.

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The primary action of statins is to lower LDL cholesterol with only small effects on HDL cholesterol or triglyceride levels (*see sections 9.10 and 9.11*). Meta-analysis of 164 short term RCTs of lipid lowering by different statins showed the absolute LDL cholesterol reduction associated with different doses of different statins (*see Table 8*).[198] The reductions in LDL cholesterol are dose-dependent and log-linear, so that with each doubling of the dose of statin, LDL levels fall by approximately 6%.

Table 8: Reductions in LDL cholesterol estimated from dose response curves by daily statin dose

statin	standard comparator dose	absolute LDL reduction (95% CI)	% LDL reduction	maximum dose	absolute LDL reduction (95% CI)	% LDL reduction
atorvastatin	10 mg	1.79 mmol/l (1.62 to 1.97)	37%	80 mg	2.64 mmol/l (2.31 to 2.96)	55%
fluvastatin	20 mg	1.02 mmol/l (0.90 to 1.13)	21%	80 mg	1.58 mmol/l (1.40 to 1.76)	33%
lovastatin	20 mg	1.40 mmol/l (1.21 to 1.59)	29%	80 mg	2.15 mmol/l (1.86 to 2.43)	45%
pravastatin	20 mg	1.17 mmol/l (1.10 to 1.23)	24%	40 mg	1.38 mmol/l (1.31 to 1.46)	29%
rosuvastatin	20 mg	2.32 mmol/l (2.20 to 2.44)	48%	40 mg	2.56 mmol/l (2.42 to 2.70)	53%
simvastatin	20 mg	1.54 mmol/l (1.46 to 1.63)	32%	80 mg	2.01 mmol/l (1.83 to 2.19)	42%

Percentage reductions are independent of pretreatment LDL cholesterol concentration and are based on an average baseline LDL level of 4.8 mmol/l.

Note: lovastatin is not licensed in the UK

This meta-analysis showed that a reduction in LDL cholesterol of 1.6 mmol/l halves the risk of CHD events after two years and that this reduction can be achieved with standard doses of some statins.[198]

9.5 STATIN THERAPY IN HIGH RISK INDIVIDUALS WITHOUT CARDIOVASCULAR DISEASE

Evidence from WOSCOPS and AFCAPS/TexCAPS indicates that the risk of major coronary events may be significantly reduced by standard doses of statin therapy (*see section 9.3*).[33,191]

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A systematic review of economic evidence reported that it is cost effective to give statins to individuals without evidence of CVD but with a ten-year 20% risk of CVD with statins compared to providing standard diet and lifestyle measures.[199] The model made several simplifying assumptions to conclude that such individuals could be identified with complete accuracy. It used an annual cost for statins of about £320 per person (a weighted average of the drugs used in the pooled trials). The advent of lower priced generic drugs has reduced the annual cost to under £50. The cost effectiveness of statin therapy is discussed in Annex 2.

> **A** All adults over the age of 40 years who are assessed as having a ten year risk of having a first cardiovascular event ≥20% should be considered for treatment with simvastatin 40 mg/day following an informed discussion of risks and benefits between the individual and responsible clinician.

☑ ▪ Patients started on a statin should be advised to report unexplained muscle pains or other adverse effects promptly, especially if associated with fever or malaise.

▪ If such effects are mild, a different statin may be tried and/or the statin dose reduced after discussing the risks involved with the patient.

▪ If severe side effects are experienced statin therapy should be discontinued.

☑ In individuals without established cardiovascular disease, lifestyle measures to reduce cholesterol levels should be encouraged, irrespective of the need for pharmacological treatment.

☑ Secondary causes of dyslipidaemia should be considered and excluded before commencing lipid drug therapy.

Simvastatin undergoes metabolic inactivation by cytochrome P-450 (*see section 9.8*).

9.6   STATIN THERAPY IN INDIVIDUALS WITH SYMPTOMATIC CARDIOVASCULAR DISEASE

Table 8 indicates that treatment with a statin at a standard dose of 10-20 mg is likely to be associated with a 20-50% reduction in LDL level and therefore an approximately similar reduction in the risk of CHD events. Although the reduction in relative risk of CVD events with statin therapy is approximately constant across all baseline levels of total or LDL cholesterol and cardiovascular risk (*see Table 7*), the absolute risk reduction is affected by global cardiovascular risk, with individuals who are at the highest global risk achieving the greatest absolute risk reduction from statins (*see Table 1*). Individuals who are at high cardiovascular risk, such as those with established symptomatic CVD or those with familial hypercholesterolaemia, will gain more benefit from more aggressive lipid lowering than individuals at lower absolute levels of risk.

A meta-analysis of trials, including 27,548 patients with established CVD, compared the lipid lowering power of aggressive versus standard doses of statins.[200] LDL cholesterol was lowered from an average of 3.33 mmol/l at baseline to 2.59 mmol/l (22% reduction) in the group receiving standard statin doses and to 1.92 mmol/l (42% reduction) in the intensively treated group. The high dose statin therapy was associated with a highly significant 16% relative risk reduction in the composite endpoint of CHD death or any cardiovascular event compared with less intensive statin therapy (event rate 32.3% versus 28.8%, OR 0.84, 95% CI 0.80 to 0.89; $p < 0.0000001$; ARR 3.5%). Cardiovascular death tended to be lower in the high-dose groups in three trials, and neutral in the IDEAL trial.[201] Pooling the data yielded a trend to reduction in cardiovascular mortality by 12% (3.8% vs. 3.3%, OR 0.88, 95% CI 0.78 to 1.00, $p = 0.054$).

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The higher doses of statins were associated with an increase in side effects. It is possible that careful patient selection and removal of those presenting with early indications of statin intolerance or adverse effects within the trials included in the meta-analyses could underestimate the actual risk of harm (*see section 9.8*).

Trials in this meta-analysis used fixed doses of statins (at low dose vs high dose) and cannot directly justify whether statins should be prescribed at the doses used in trials or titrated to achieve LDL targets. The benefits shown by this meta-analysis are in addition to those achieved by standard statin therapy, which has been shown to be highly effective in reducing cardiovascular mortality and events.[3]

One systematic review reported that it is cost effective to treat with a statin all individuals with cardiovascular disease compared to providing standard diet and lifestyle measures.[199] This was confirmed in a large trial of treatment with 40 mg/day simvastatin in people with different levels of coronary vascular risk.[202] The cost effectiveness of statin therapy is discussed in Annex 2.

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1⁺

The statins tested in major trials produced broadly similar beneficial outcomes indicating that their effect is generic rather than statin specific, with different levels of potency among the different drugs. Statin treatment produces substantial total and LDL cholesterol reductions in all individuals at high risk of any type of major vascular event, irrespective of their pre-treatment total or LDL cholesterol values, although the pleiotropic effects of statins are not fully understood and may play an important part in mediating their overall effect.

> **B** **All patients with established symptomatic atherosclerotic cardiovascular disease should be considered for more intensive statin therapy following an informed discussion of risks and benefits between the individual and responsible clinician.**

☑
- Patients should be advised to report unexplained muscle pains or other adverse effects promptly, especially if associated with fever or malaise.

- If such effects are mild, a different statin may be tried and/or the statin dose reduced after discussing the risks involved with the patient.

- If severe side effects are experienced statin therapy should be discontinued.

9.7 CHOLESTEROL TARGETS FOR THERAPY IN PATIENTS WITH SYMPTOMATIC CARDIOVASCULAR DISEASE

The JBS2 guideline states "there are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL cholesterol targets in relation to clinical events".[28] Establishing a cholesterol target for therapy is therefore an extrapolation from the apparent benefits indicated by major trials of lipid lowering, while maintaining appropriate margins for safety, given that there are still no long term follow up studies of statin therapy.

| 4

Several national guidelines have recommended titration of lipid lowering therapy to achieve LDL cholesterol levels less than 2.5 mmol/l for patients at high cardiovascular risk.[28,185]

Current guidance from the Department of Health in England and Wales recommends that patients with established CHD should receive statins and dietary advice to lower serum cholesterol concentrations either to less than 5 mmol/l (LDL cholesterol to below 3 mmol/l) or by 25% (30% for LDL cholesterol), whichever is greater.[203]

| 4

A systematic review of RCTs, cohort studies, and case control studies that examined the independent relationship between LDL cholesterol and major cardiovascular outcomes in patients with LDL cholesterol levels less than 3.36 mmol/l found no clinical trial subgroup analyses, valid cohort or case control analyses suggesting that the degree to which LDL cholesterol responds to a statin independently predicts the degree of cardiovascular risk reduction.[204]

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Although the review indicated that there was compelling evidence for the effectiveness of statin therapy in lowering cholesterol in patients at high cardiovascular risk (regardless of their natural LDL cholesterol values) it concluded that current clinical evidence does not demonstrate that lipid therapy should be titrated to achieve proposed LDL cholesterol targets.

While patients with established symptomatic cardiovascular disease should be considered for intensive statin therapy, the long term safety and cost effectiveness of such therapy has not been established.[200]

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The current NHSScotland target for individuals at high cardiovascular risk is a TC level of <5 mmol/l. This level is consistent with the Quality and Outcomes Framework.[205]

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Reducing this target to 4.5 or 4.0 mmol/l would have major resource implications for NHSScotland. Pending further studies on mortality, safety and cost-effectiveness, the guideline development group suggests that current NHSScotland targets are maintained, as the minimum standard of care.

☑ The existing total cholesterol target of < 5 mmol/l in individuals with established symptomatic cardiovascular disease should be regarded as the minimum standard of care.

9.8 SAFETY OF STATIN THERAPY

A comprehensive review of all statin trials to date, undertaken by a Task Force of the US National Lipid Association, provides strong support for the safety of statins[206] which is endorsed by a second meta-analysis.[3] Overall, there was no increased risk of cancer or non-cardiovascular mortality. Raised levels of liver enzymes (aspartate and alanine aminotransferase) to more than three times their upper normal limit occur in fewer than 1% of subjects treated across the dose range of the marketed statins, with the exception of atorvastatin administered at maximal (80 mg) dose and combination statin and ezetimibe therapy *(see section 9.10.1)*. This effect is completely reversible upon withdrawal of treatment. Minor muscle discomfort is common, though its incidence varies.[3,207] Myopathy, with raised levels of creatine kinase to more than ten times the upper normal limit, though more serious, is rare, occurring in less than one in 1,000 subjects. Rhabdomyolysis, in which myopathy is associated with end organ (renal) damage is even rarer, with a frequency of less than 1 in 10,000 per year of exposure to statins. Withdrawal of therapy leads to recovery in the majority of cases, although deaths have been reported in some subjects suffering from pathology of several systems and receiving multiple concomitant drug therapies.[206]

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Statins interact with a number of other medications. The risk of myopathy increases when statins are used in combination with fibrates (eg gemfibrozil) or nicotinic acid (niacin) and they should only be used concomitantly under specialist supervision.

Some statins (particularly atorvastatin and simvastatin) are metabolised by cytochrome P450 and concomitant use of other potent inhibitors of this enzyme (eg 'azole' anti-fungal agents and HIV protease inhibitors) may increase plasma levels of these statins and increase the risk of adverse effects, such as rhabdomyolysis. The risk of serious myopathy is also increased when high doses of simvastatin are combined with less potent cytochrome P450 inhibitors, including amiodarone, verapamil, and diltiazem. The consumption of even modest quantities of grapefruit juice can significantly increase exposure to simvastatin, increasing the risk of serious myopathy. Patients taking atorvastatin should also avoid drinking large quantities of grapefruit juice. These concerns do not apply to fluvastatin, which is metabolised by a different cytochrome P450 enzyme, or to pravastatin and rosuvastatin, which are not substantially metabolised by cytochrome P450.[208]

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Statins are contraindicated in patients with active liver disease (or persistently abnormal liver function tests), in pregnancy (adequate contraception is required during treatment and for one month afterwards) and patients who are breast-feeding.[131]

The US National Lipid Association recommends monitoring and testing of patients who are being considered for statin therapy. These are reproduced in annexes 3-6.

Atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin are licensed for use in the UK.

☑ Patients who are using medications that influence cytochrome P450 metabolism should avoid concomitant use of atorvastatin or simvastatin. In such cases, pravastatin is an acceptable alternative lipid lowering therapy.

9.9 SPECIAL CONSIDERATIONS

9.9.1 PEOPLE WITH DIABETES

Statin therapy in people with diabetes appears to be associated with a statistically significant reduction in the relative risk of various clinical endpoints including all-cause mortality and fatal and non-fatal MI.[199]

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Three major trials of statin therapy in individuals with CVD and one trial of individuals with no evidence of CVD involved subgroups of patients with diabetes.[33,209-211] There were 483 subjects in the 4S trial with a clinical diagnosis of diabetes. In this subgroup, simvastatin therapy was associated with a 42% reduction in major CHD (fatal and non-fatal CHD) (p = 0.001) compared with a 32% reduction in major CHD in subjects without diabetes.[210] In the CARE study, 586 subjects with a clinical diagnosis of diabetes were identified. Pravastatin therapy reduced the risk for CHD (fatal plus non-fatal MI, CABG and PTCA) by 25% in the group with diabetes (p = 0.05) as compared to 23% in the group without diabetes (p < 0.001).[210] In the LIPID study, pravastatin reduced the incidence of fatal and non-fatal CHD by 19% in 792 subjects with diabetes (not significant) and 25% in subjects without diabetes (p < 0.001). Although the reduction in CHD events in subjects with diabetes was not significant with pravastatin, the test for heterogeneity in response between subjects with and without diabetes was not statistically significant. In AFCAPS/TexCAPS, a primary prevention study, only 155 subjects had a clinical diagnosis of diabetes. Among this small number of subjects, a 42% reduction in CHD was seen (not significant) which was similar to the 37% reduction in CHD seen in the overall study population.[33]

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Individuals over the age of 40 years with diabetes should be considered for statin therapy (*see section 3.1*).

9.9.2 FAMILIAL HYPERCHOLESTEROLAEMIA

Subjects with familial hypercholesterolaemia based on clinical or genetic evidence should be considered for aggressive statin therapy, irrespective of their calculated cardiovascular risk. Their total cholesterol will usually exceed 8 mmol/l and may be substantially higher than this. In general, this treatment should only be considered in children of 12 years or older although it may be applied to younger patients at high risk because of severe hypercholesterolaemia if proper monitoring facilities are available.[212,213] Under such circumstances, ezetimibe or anion exhange resin therapy may be added to the statin in order to provide adequate cholesterol reduction.

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9.9.3 PREGNANCY

Statins are contraindicated in women who are pregnant or are likely to be pregnant (*see section 9.8*).[131]

9.9.4 ELDERLY PEOPLE

In the elderly, the decision to start statin therapy should be based on individual ten year cardiovascular risk estimation, life expectancy, and quality of life. Age alone is not a contraindication to drug therapy.[195]

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9.10 OTHER LIPID LOWERING AGENTS

Meta-analysis of 58 trials of lipid lowering by means other than statins showed a 36% (95% CI 26 to 45%) reduction in risk of CHD death and non-fatal MI associated with a 1.0 mmol/l reduction in LDL cholesterol after six years.[198]

9.10.1 ANION EXCHANGE RESINS

The effect of statins can be accentuated by combining them with agents which interfere with steroid absorption, eg cholestyramine and colestipol. These drugs lower serum total and LDL cholesterol and cause mild and usually transient elevation of triglyceride levels.[214,215]

Clinical trial evidence from the 1980s demonstrates the benefit of these drugs as monotherapy in primary CHD prevention, but their side effect profile (gastrointestinal irritation, constipation) frequently makes them unacceptable to patients.[216] Nevertheless, they may be indicated for the treatment of hypercholesterolaemia where statins are not tolerated or are contraindicated; or they may be added to statin therapy to enhance cholesterol reduction. Whereas doubling the dose of a statin produces only a six percent further reduction in LDL cholesterol, adding a moderate dose of a resin to a statin can further lower LDL cholesterol by 12–16%.[217,218]

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Ezetimibe is a cholesterol absorption inhibitor without significant side effects.[219] As monotherapy, its cholesterol lowering capability is modest (a reduction of 15-20% in total cholesterol when prescribed as a single dose of 10 mg) but it has a role in statin-intolerant patients.[220,221] Its co-prescription with low dose statin therapy results in a cholesterol reduction equivalent to that seen with maximum dose statin monotherapy. Statin-ezetemibe combination therapy may help in the management of patients in whom there is difficulty in achieving adequate cholesterol reduction despite high dose statin therapy, or who are intolerant of higher doses of statins, or in the treatment of severe genetic hyperlipidaemias.

> ☑ Combination therapy of a standard dose statin and anion exchange resin or ezetimibe is indicated in patients who are intolerant of higher-dose statin therapy.

9.10.2 FIBRATES

Fibrates are primarily used for lowering triglycerides and raising low HDL levels because their LDL cholesterol lowering effects are generally in the range of 10% or less in persons with primary hypercholesterolemia.

Three major trials, the Helsinki Heart Study (HHS)[222], the Bezafibrate Infarction Prevention (BIP) Study[223] and the Veterans Affairs HDL Intervention Trial (VA-HIT)[224] have shown that fibrates can raise HDL cholesterol by approximately 10-15%. They typically reduce triglyceride by 25–50% with greater reductions occurring in individuals with severe hypertriglyceridaemia.[225]

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The HHS employed gemfibrozil (600 mg twice daily) to treat asymptomatic middle aged (40-55 years old) men with primary dyslipidaemia (non-HDL cholesterol >5.13 mmol/l). The drug raised HDL cholesterol by 9%, reduced plasma triglyceride by 34%, and lowered the risk of a first coronary event by 34%. This benefit was more strongly associated with both reductions in LDL cholesterol and increases in HDL cholesterol substantiating the proposed protective benefit of the latter.[226] Despite its magnitude, the fall in plasma triglyceride appeared to play little role in conferring cardioprotection.

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The BIP Study employed bezafibrate, 400 mg/day to treat men with existing coronary artery disease, low levels of HDL cholesterol in their circulation and raised triglyceride. Although overall there was no significant reduction in fatal and non-fatal myocardial infarction or sudden death, the drug raised HDL cholesterol by 18% and lowered triglyceride by 21% and, in a subgroup of patients with baseline triglyceride greater than 2.26 mmol/l, the decrease in coronary morbidity and mortality was significant, suggesting that, as in primary CHD prevention, fibrates may help prevent repeat heart attacks, probably through their action on HDL cholesterol and plasma triglyceride.

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A similar conclusion followed from the outcome of the VA-HIT trial in which 1,200 mg of gemfibrozil was administered to men with CHD, low levels of HDL cholesterol (<1.03 mmol/l) and LDL cholesterol of 3.62 mmol/l. Treatment lowered fatal and non-fatal MI by 22% (p<0.006) and reduced stroke and transient ischaemic attack risk by 31% and 59% respectively. The main lipid changes were a 6% increase in HDL cholesterol and a 31% fall in triglyceride. Levels of LDL cholesterol remained unchanged throughout the study, although the circulating LDL particles may have become larger, more buoyant, and less atherogenic.[227,228] This may help explain why the magnitude of reduction of events with gemfibrozil was greater than appeared likely from HDL cholesterol increases alone.

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The consistency of these major fibrate-based trials supports the view that HDL cholesterol elevation and triglyceride reduction offer cardiovascular benefit which, at least in part, is independent of LDL cholesterol reduction.

9.10.3   NICOTINIC ACID

Nicotinic acid, or niacin, is the most effective HDL-raising agent currently available.[229] Two forms of niacin are available, crystalline immediate-release which is taken three times daily and modified (extended) release taken once daily. Elevations of 15-35% in HDL cholesterol are reported following dosing with 1-3 g of the drug in its crystalline form, and are usually accompanied by a drop of 20-30% in LDL cholesterol and of 35-50% in triglyceride.[230] An RCT that compared the efficacy and safety of treatment with 1.5 g /day immediate release (IR) with modified release (MR) niacin found similar effects on lipids for both preparations.[231] Levels of the liver enzyme aspartate aminotransferase (AST) increased 5.0% versus 4.8% (difference not significant) with MR niacin and IR niacin respectively. Fasting plasma glucose increased 4.8% versus 4.5% (not significant). Skin flushing events were more frequent with IR versus MR niacin (1,905 vs 576, p < 0.001).

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In the Coronary Drug Project niacin was administered in a daily dose of 3 g over 6.5 years to men who had already had a myocardial infarction. Treatment reduced the frequency of subsequent events by 14% (p < 0.005), though there was no effect on overall mortality.[232] After another eight years follow up and despite no attempt being made to maintain those conditions, total mortality showed significant reduction in the niacin treated cohort.[233]

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More recent data were reported in the HATS trial, an angiography based investigation of 160 men and women with low HDL cholesterol (1.0 mmol/l in females and < 0.9 mmol/l in males), normal LDL cholesterol, and triglycerides of < 4.5 mmol/l.[234] When compared to placebo, the combination of simvastatin and niacin lowered LDL cholesterol by 42% and increased HDL cholesterol by 26%. These positive changes in the lipid profile produced 0.4% regression in coronary atherosclerosis over the three year study observation period, while the placebo cohort showed 3.9% stenosis progression, a highly significant difference between the two groups (p < 0.001).

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Although this study was not powered to show major coronary endpoint differences as a result of the treatments, of the 38 subjects in the placebo-treated cohort, nine experienced one of these endpoints compared to one in the simvastatin-niacin group (p = 0.03).

A meta-analysis of 53 trials (n = 16,802) using fibrates and 30 trials (n = 4,749) using niacin showed that each drug significantly lowered TC, LDL cholesterol and triglyceride levels and raised HDL cholesterol (see Table 9).[235] Fibrates reduced the risk for major coronary events by 25% and current available data for niacin indicate a 27% reduction.[233]

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Table 9:   The effect of fibrates and niacin on cholesterol and CHD risk

	Fibrates	**Niacin**
	53 trials (16,802 subjects)	30 trials (4,749 subjects)
net TC lowering	0.66 mmol/l (95% CI 0.75 to 0.55 mmol/l), p < 0.00001), 11%	0.66 mmol/l (95% CI 0.49 to 0.82 mmol/l), p < 0.00001), 10%
net HDL raising	0.11 mmol/l (95% CI 0.09 to 0.13 mmol/l p < 0.00001), 10%.	0.17 mmol/l (95% CI 0.13 to0.22 mmol/l, p < 0.00001), 16%
net LDL lowering	0.30 mmol/l (95% CI 0.14 to 0.46 mmol/l, p < 0.0002), 8%	0.53 mmol/l (95% CI 0.34 to 0.73 mmol/l, p < 0.00001), 12%.
net triglycerides lowering	0.80 mmol/l (95% CI 0.69 to 0.90 mmol/l, p < 0.00001), 36%	0.53 mmol/l (95% CI 0.39 to 0.69 mmol/l, p < 0.00001), 20%.
CHD risk reduction	coronary events: 25% (95% CI 11% to 37%) coronary death: not significant	27% (from Coronary Drug Project)

> **A** Individuals with hypertriglyceridaemia *(>1.7 mmol/l)* **and/or low high density lipoprotein cholesterol level** *(<1 mmol/l in men, or <1.2 mmol/l in women)* **should be considered for treatment with a fibrate or nicotinic acid.**

9.11 MANAGEMENT OF COMBINED DYSLIPIDAEMIA

Combined dyslipidaemia, characterised by abnormalities in all of the major lipoprotein species, is associated with increased risk of vascular disease which goes beyond that produced by raised LDL cholesterol alone. Plasma triglyceride is elevated, HDL cholesterol is low and LDL particles are smaller, denser and more atherogenic than normal.[236,237] This profile clusters in particular disease states and is particularly characteristic of the metabolic syndrome and diabetes mellitus (diabetic dyslipidaemia).

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A number of clinical trials have shown that LDL cholesterol lowering with statins reduces the risk of vascular events (myocardial infarction, stroke and coronary revascularisation) in diabetic subjects with raised LDL cholesterol *(see also section 9.9.1).*[238,239] The greater the LDL cholesterol reduction, the greater the benefit.[240]

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The largest vascular endpoint trial undertaken with fibrates (FIELD) provided limited evidence for their benefit in a similar diabetic cohort.[241] Although treatment with fenofibrate did not significantly reduce the risk of a coronary event, it produced a 24% reduction (p = 0.01) in risk of non-fatal MI. There was a non-significant rise in coronary deaths, but overall cardiovascular disease events (fatal and non-fatal myocardial infarction, stroke and coronary and carotid revascularisation) fell by 11% (p = 0.35). Fenofibrate treatment resulted in less albuminuria progression (p = 0.002) and less retinopathy requiring laser treatment (p = 0.0003). Pancreatitis and pulmonary embolism risk rose in the actively treated group (p = 0.031 and 0.022 respectively).

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In FIELD there was a significantly greater increase in statin use in subjects allocated to the placebo cohort, but a prespecified statistical adjustment made to take account of statin use suggested that attribution of failure to achieve primary endpoint benefit to post-randomisation statin drop-in therapy might not explain the outcomes of this trial.

Combined statin/fibrate therapy improves the entire dyslipidaemic profile over that seen with statin therapy alone. Trials have reported a significant increase in HDL cholesterol levels and significant reductions in triglyceride and LDL cholesterol levels in patients on combined statin/fibrate therapy compared to patients on statins or fibrate monotherapy.[242,243] The effect of combined statin/fibrate therapy has not been tested on cardiovascular endpoints, and it is not possible to recommend this combination as an effective method of reducing CVD risk.

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It has been suggested that the potential for impaired metabolism of statins with gemfibrozil[244] may be greater than with other fibrates, such as fenofibrate.[245] This is supported by evidence from healthy volunteers that the combination of fenofibrate with statins is associated with minimal differences in the concentrations of either fenofibrate or statin.[246] In contrast, the concurrent use of certain statins with gemfibrozil has shown a two- to three-fold increase in statin levels.[247] Analyses of the US Food and Drug Administration Adverse Event Reporting System have suggested that the use of fenofibrate with statins results in fewer reports of rhabdomyolysis per million prescriptions than does the use of gemfibrozil with statins.[248]

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> **A** **Statins are the drugs of choice in the management of diabetic subjects with mixed dyslipidaemia and elevated low density lipoprotein cholesterol.**

> ☑ Combination therapy with a statin and a fibrate may be required for combined dyslipidaemia.

> ☑ Particular care should be taken when coadministering statins with gemfibrozil.

10   Blood pressure lowering

Elevated blood pressure (BP) increases the risk of CHD, heart failure, stroke and renal failure.[249] Systematic reviews of trials of antihypertensive drugs versus placebo have shown that blood pressure lowering is associated with reductions in CHD, stroke, heart failure, and cardiovascular and total mortality.[250]

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A dietary pattern low in total fat, saturated fatty acids, and dietary cholesterol, and rich in fruits, vegetables, and low-fat dairy products can produce blood pressure reductions exceeding 11/5 mm Hg in people at higher cardiovascular risk.[251] Weight loss, the restriction of dietary sodium, and regular intake of oily fish may enhance these effects (*see section 4*).[252,253]

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10.1   BLOOD PRESSURE THRESHOLDS FOR INTERVENTION WITH DRUG THERAPY

The relationship between blood pressure and cardiovascular risk is approximately linear between the values of 115/70 and 170/100 mm Hg. Within this range, treatment results in similar relative benefits regardless of the baseline blood pressure.[254] People at greater cardiovascular risk derive the most absolute benefit from treatment and are subject to lower intervention thresholds.

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Lowering blood pressure has been shown to reduce the risk of both cardiovascular and total mortality, without adverse effect on quality of life. Trials of antihypertensive drugs show a similar relative reduction in coronary heart disease risk of 15-25% and reduction in ischaemic stroke risk of 30-40%.[179,255-259] One Health Technology Assessment shows that the risk from pre-existing vascular disease strongly outweighs any other risk factor calculation, and concludes that all such patients should be offered, and will benefit from, blood pressure lowering. Lowering diastolic blood pressure by 5 mm Hg reduces the risk of stroke by an estimated 34% and ischaemic heart disease by 21% from any pre-treatment level and there is no threshold.[260]

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The British Hypertension Society guideline[38] indicates that the following lifestyle activities are associated with a potential reduction in blood pressure:

- weight reduction
- reduced salt intake
- limitation of alcohol consumption
- increased physical activity
- increased fruit and vegetable consumption
- reduced total fat and saturated fat intake.

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☑   All individuals with a persistent blood pressure ≥140/90 mm Hg or a family history of hypertension should receive lifestyle advice to help reduce their blood pressure and CVD risk. Lifestyle advice should continue even when drug therapy is initiated.

10.1.1   BLOOD PRESSURE THRESHOLDS FOR INDIVIDUALS WITH SYMPTOMATIC CARDIOVASCULAR DISEASE

Randomised controlled trials show a benefit in treating people with established cardiovascular disease or diabetes irrespective of baseline blood pressure.[255,257,261]

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A   **Individuals with sustained systolic blood pressures >140 mm Hg systolic and/or diastolic blood pressures >90 mm Hg and clinical evidence of cardiovascular disease should be considered for blood pressure lowering drug therapy.**

People with established cardiovascular disease, who also have chronic renal disease or diabetes with complications, or target organ damage may be considered for treatment at the lower threshold of systolic >130 mm Hg and/or diastolic >80 mm Hg.[28] These individuals are assumed to be at even greater risk of cardiovascular events and are targeted with more aggressive thresholds for treatment. Data regarding the optimal treatment regimen of older individuals are sparse. Treatment decisions should balance potential benefits in the context of other comorbidities. Blood pressure lowering will reduce stroke and CHD, although no benefit on overall mortality has yet been demonstrated.[262]

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The Joint British Societies' guideline on the prevention of cardiovascular disease defines target organ damage as any of the following:[28]

- heart failure
- established coronary heart disease
- stroke or transient ischaemic attack
- peripheral arterial disease
- abnormal renal function (elevated serum creatinine or proteinuria/microalbuminuria)
- hypertensive or diabetic retinopathy
- left ventricular hypertrophy on electrocardiogram or echocardiogram.

> **A**   **Individuals with established cardiovascular disease, who also have chronic renal disease or diabetes with complications, or target organ damage may be considered for treatment at the lower threshold of systolic > 130 mm Hg and/or diastolic > 80 mm Hg.**

10.1.2   BLOOD PRESSURE THRESHOLDS FOR INDIVIDUALS WITHOUT SYMPTOMATIC CARDIOVASCULAR DISEASE

The following good practice points are based on the recommendations from the JBS2 and British Hypertension Society guidelines:[28,38]

| 4

> ☑   - Asymptomatic individuals with sustained systolic blood pressures ≥ 140 mm Hg systolic and/or diastolic blood pressures ≥ 90 mm Hg and whose ten year risk of a first CVD event is calculated to be ≥ 20% should be considered for blood pressure lowering drug therapy.
>
>   - Individuals with such blood pressure levels whose ten year risk of a first CVD event is < 20% should continue with lifestyle strategies and have their blood pressure and total CVD risk reassessed every one to five years, depending on clinical circumstances.

Persistent blood pressure elevation ≥ 160 mm Hg systolic and/or ≥ 100 mm Hg diastolic causes sufficient CVD risk on the basis of blood pressure levels alone to require drug therapy to reduce blood pressure.[28,45]

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> **B**   **Individuals with blood pressure greater than 160/100 mm Hg should have drug treatment and specific lifestyle advice to lower their blood pressure and risk of cardiovascular disease.**

10.2   TARGET VALUES FOR BLOOD PRESSURE LOWERING

The relationship between blood pressure and cardiovascular risk is continuous and there has been a lowering of targets over recent years as evidence of benefit and safety has accumulated. The evidence for diastolic blood pressure targets[179] is more robust than that for systolic BP, although for most patients above 50 years, systolic BP appears to be more important for the prediction of adverse CVD outcomes.[254]

Evidence for an optimal level of diastolic blood pressure, drawn from a large meta-analysis of antihypertension intervention trials, indicates that the further the diastolic blood pressure can be reduced, the greater the reduction in cardiovascular risk without any convincing evidence of a J-curve relationship.[263] The Hypertension Optimal Treatment (HOT) trial reported that the optimal target blood pressure in patients with a diastolic BP of 100-115 mm Hg was 139/83 mm Hg. Reduction of BP below the optimal level caused no harm.[179]

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The cost effectiveness of different targets for the reduction in BP was analysed using clinical data from the HOT trial.[264] The trial randomised patients to three target groups for diastolic BP, with the hypothesis that the lower the target, the better the outcome but the higher the drug costs. The clinical trial showed no statistical difference in the number of events avoided for the three target groups. Significant reductions in event rates were found in a subset analysis of people with diabetes, which limited the cost effectiveness analysis to this group. The study concluded that in patients with diabetes, compared to maintenance doses of calcium channel blockers, intensive treatment to a lower blood pressure target (≤ 80 mm Hg), was cost effective.

☑ Treatment targets defined by the Joint British Societies state optimal blood pressure control for patients at high cardiovascular risk (established cardiovascular disease or asymptomatic patients with a ten year risk of CVD ≥20%) as <140/85 mm Hg.

☑ For individuals with established CVD and diabetes, chronic renal disease or target organ damage a lower blood pressure target of <130/80 mm Hg is recommended.

10.3 SELECTION OF ANTIHYPERTENSIVE THERAPY

There are four major classes of antihypertensive drug (thiazides, angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists (ARB) and calcium channel blockers) which are about as effective as each other and more effective than beta-blockers at reducing cardiovascular morbidity and mortality per unit fall in blood pressure. There are some important cautions and contraindications for all of the antihypertensive drug classes.[263,266,267]

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In a meta-analysis, the five main categories of blood pressure lowering drugs all significantly reduce blood pressure from all pre-treatment levels. The extent of blood pressure reduction increased with pre-treatment blood pressure. The reductions were similar at standard dose for the five categories; average reduction was 9.1 mm Hg systolic and 5 mm Hg diastolic. The effect of combinations of two drugs on blood pressure was additive.[260] The adverse effect profiles of drugs could be minimised by using half-standard or standard doses, rather than titrating any given drug to higher doses. This does not apply to ACE inhibitors or ARBs, where the adverse effects are present or absent, regardless of dose. The meta-analysis presents a rationale for polypharmacy, utilising modest doses of more than one antihypertensive agent in order to maximise control whilst minimising adverse effects.

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The ASCOT-BPLA study recruited 19,257 patients, including many from Scotland, to treatment by two combinations of antihypertensive drugs.[268] The study tested whether a newer antihypertensive combination treatment, comprising the calcium channel blocker (CCB) amlodipine and the ACE inhibitor perindopril, was more effective than an older combination regimen of the beta-blocker atenolol and the diuretic bendroflumethiazide. The trial was terminated early because of a large difference in mortality between the older drugs and the newer ones, favouring the amlodipine+perindopril combination. The trial showed that amlodipine+perindopril were significantly more effective at reducing strokes (327 vs 422; unadjusted hazard ratio (HR) 0.77, 95% CI 0.66 to 0.89, p=0.0003), total cardiovascular events (1362 vs 1602; HR 0.84, 95% CI 0.78 to 0.90, p<0.0001) and all cause mortality (738 vs 820; HR 0.89, 95% CI 0.81 to 0.99, p=0.025) than atenolol with bendroflumethiazide.

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A large RCT of 33,357 patients reported on blood pressure lowering in individuals with high global risk and hypertension. A significant proportion of the subjects had overt vascular disease as manifested by previous cardiovascular events (MI, stroke), or ongoing symptoms (angina, intermittent claudication). All had moderate hypertension, on therapy or untreated. Extensive analysis of this trial and data subsets shows evidence of reduced event rate regardless of starting blood pressure, within the parameters of trial inclusion.[269] Participants were randomised to receive a thiazide-like diuretic (chlorthalidone, 12.5 to 25 mg daily); a calcium channel blocker (amlodipine, 2.5 to 10 mg daily); or an ACE inhibitor (lisinopril, 10 to 40 mg daily). There was no significant difference between groups in combined fatal CHD or non-fatal myocardial infarction. Five year systolic blood pressures were significantly higher in the amlodipine (0.8 mm Hg, p=0.03) and lisinopril (2 mm Hg, p<0.001) groups compared with chlorthalidone, and five year diastolic blood pressure was significantly lower with amlodipine (0.8 mm Hg, p<0.001). For amlodipine vs chlorthalidone, outcomes were similar except for a higher six year rate of heart failure with amlodipine (10.2% vs 7.7%; RR, 1.38; 95% CI 1.25 to 1.52).

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☑ In any individual with hypertension, consideration should be given to using two or more antihypertensive agents, in half to standard doses, to achieve additive blood pressure lowering whilst minimising the adverse effect profile.

10.3.1   THE BRITISH HYPERTENSION SOCIETY ALGORITHM

The British Hypertension Society AB/CD algorithm has been widely adopted for deciding drug therapy for an individual.[38] The algorithm was substantially ratified by the ASCOT trial and AB/CD has now been accepted by JBS2 as the best method of defining combination drug therapy. The AB/CD algorithm was designed to improve blood pressure control based on age-related renin levels and appropriate combinations.

In June 2006 the National Institute for Clinical Health and Excellence (NICE) and the BHS jointly released a revised guideline that updated the clinical evidence base to include recent meta-analyses and RCTs and included a cost effectiveness analysis comparing the various blood pressure lowering drug classes.[270] The results showed that:

- beta blockers were the least clinically and cost effective drug at preventing major cardiovascular events
- calcium channel blockers and thiazide-type diuretics were the most clinically and cost effective choice for the majority of cases
- for people under the age of 55, drugs affecting the renin-angiotensin system are likely to be most effective.

The recommendations based on this evidence are summarised in the A/CD algorithm shown in Figure 1. It incorporates all classes of antihypertensive drugs. Although not specifically validated by a clinical trial, the recommended drug combinations and sequencing are similar to those used in many clinical trials of blood pressure lowering drugs.

Figure 1: The British Hypertension Society A/CD algorithm for blood pressure
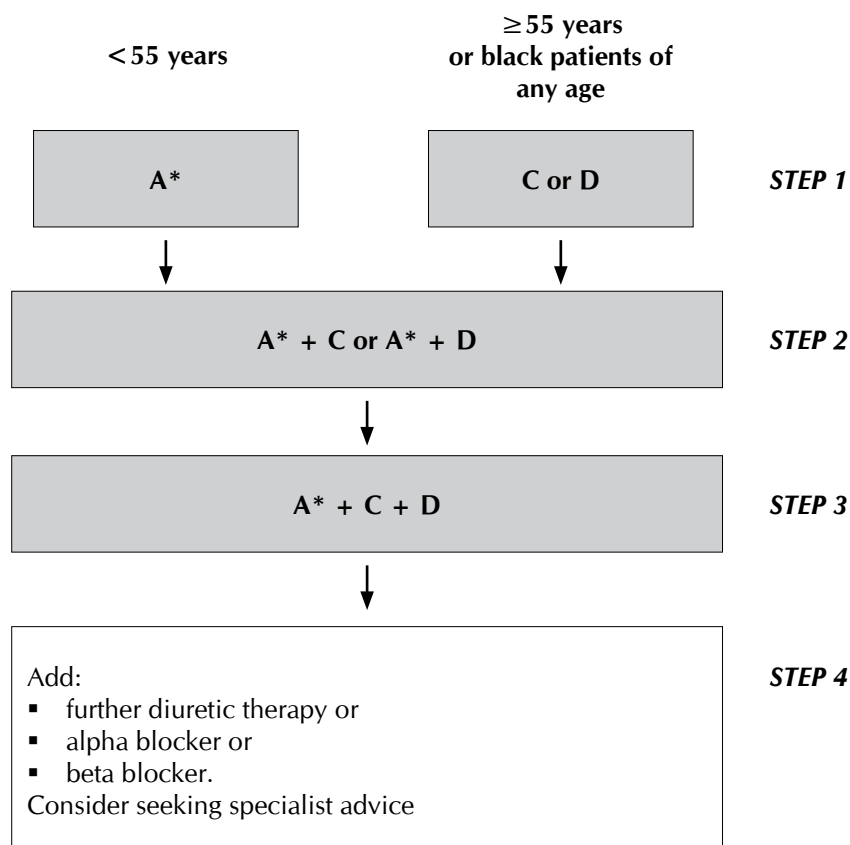
A = ACE inhibitor (or ARB if intolerant to ACE inhibitor), C = calcium channel blocker, D = thiazide-type diuretic.*

Beta blockers are not a preferred initial therapy for hypertension but are an alternative to ACE inhibitors in patients <55 years in whom ACE inhibitors or ARBs are not tolerated, or contraindicated (includes women of childbearing potential). Black patients are only those of African or Caribbean descent. In the absence of evidence, all other patients should be treated according to the algorithm as non-black.

10.4　MULTIPLE RISK INTERVENTIONS

One Cochrane review investigated the effects of multiple risk factor interventions on blood pressure, cholesterol and smoking in primary prevention.[271] Individuals with the highest baseline blood pressure, smoking and cholesterol levels showed the largest reductions in event rates following intervention. Pooled effects suggest that multiple risk factor intervention has no effect on mortality. Multiple interventions appear to be more effective in high risk populations. Treating large numbers of individuals in low risk populations may result in small treatment benefits being outweighed by small treatment risks.[272,273]

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11 Psychological issues

11.1 THE IMPACT OF STRESS, PSYCHOLOGICAL DISTRESS AND PERSONALITY VARIABLES ON CARDIOVASCULAR RISK

11.1.1 STRESS

Stress is perceived by the majority of cardiac patients to have been an important cause of their heart disease. This belief is also common among the general public, and confusion exists among health professionals as to its role in the development of and outcome with CHD. While stress is a commonly used term it has no precise definition and cannot be readily measured. Stress is generally accepted to include a number of components which are measurable, and have been studied, including:

- depression, anxiety, panic attacks
- social isolation or lack of social support
- acute and chronic life events
- psychosocial work characteristics
- type A personality, hostility.

A review of systematic reviews undertaken by an Expert Working Group of the National Heart Foundation of Australia identified 15 reviews showing strong and consistent evidence that depression and social isolation or lack of quality social support are independent risk factors for the development of and prognosis with CHD.[277] The largest of these reviews provides strong and consistent evidence for both these factors but also evidence that aspects of work-related stress may be associated with increased risk.[278]

The review concluded that depression, social isolation and lack of social support are significant risk factors for CHD and are independent of conventional risk factors such as smoking, hypercholesterolaemia and hypertension with a similar strength of association (one to two-fold increased risk of developing CHD with minor depression and three to five-fold increase with major depression). Social isolation/lack of quality social support is also of a clinically significant magnitude (two to three-fold increased risk of developing CHD and three to five-fold increased risk of death in patients with CHD).

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There is no clear evidence to suggest that treating depression is effective in reducing risk. Increased attention to conventional risk factors in patients with depression may be appropriate.[279] Further research is necessary to determine the underlying mechanisms accounting for this increased risk and to determine which interventions are effective in treating this risk.

There is consistent evidence that catastrophic life events of a highly stressful nature such as earthquakes or terrorist attacks and, to a lesser degree, bereavement are associated with increased cardiac risk, but no consistent evidence for chronic life stress including stress in the workplace.[277] The implications of these findings for the individual patient are not clear.

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There is no consistent evidence to suggest that anxiety or panic attacks are risk factors for CHD. Neither is there clear evidence to support the view that stress at work increases the risk of developing or dying from CHD. There is lack of precision in defining 'work stress' and consistency of measurement in studies. There was some evidence that CHD risk in relation to work was related to individual personality factors such as coping styles, availability of support and other psychosocial factors rather than work specific characteristics. While early studies suggested that personality traits such as type A behaviour or hostility might be associated with increased cardiovascular risk, there is now clear evidence that this is not the case.[278]

2++

The INTERHEART study reported on risk factors, including psychosocial factors, for 11,119 MI cases and 13,648 controls across 52 countries.[280] Composite variables of subjective stress (home, work, and financial stress, low self-efficacy and self reported retrospective rating of depression) appeared to be associated with increased risk of developing an acute MI across gender, nationality, ethnic groups, and to be independent of smoking and socioeconomic status. There are some major concerns regarding the methods of measurement of stress in this study, which was undertaken in a non-standardised way and retrospectively relying on patient memory and perception over the previous 12 months. It does indicate that some undefined elements of stress contribute to increased risk of cardiac events across cultures.

1[+]

> **B**   **Depression and social isolation or lack of quality social support are risk factors for the development of and prognosis with coronary heart disease and should be taken into account when assessing individual risk.**

Further research is necessary to determine the underlying mechanisms accounting for this increased risk and to determine the most effective interventions for treatment.

11.2   PSYCHOLOGICAL INTERVENTIONS

11.2.1   STRESS MANAGEMENT

Stress management is defined as "using cognitive behavioural strategies to reduce or manage stress". Relaxation alone or combined with cognitive or problem solving techniques is included in this definition. Venting feelings and/or discussion only or counselling and cognitive behaviour therapy for clinical depression are excluded.

One Cochrane review of psychological interventions for coronary heart disease examined stress management (SM) techniques.[281] Thirty six trials with 12,841 patients were included. Of these, 18 (5,242 patients) were SM trials. The quality of many trials was poor with the majority not reporting adequate concealment of allocation, and only six used blinded outcome assessors.

Patients were not selected for level of stress, anxiety or depression etc. Measures of outcome for mood were by self-report on a continuous scale, rather than using cut-offs to identify those who were clinically depressed.

There was a reduction by 22% in the number of non-fatal reinfarctions in the intervention group (OR 0.78, 95% CI 0.67 to 0.90), but the two largest trials (with 4,809 patients randomised) were null for this outcome, and there was statistical evidence of publication bias. Overall psychological interventions showed no evidence of effect on total or cardiac mortality, but did show small reductions in anxiety and depression in patients with CHD ($p < 0.025$). Similar results were seen for SM interventions when considered separately. The poor quality of trials, considerable heterogeneity observed between trials and evidence of significant publication bias make the pooled finding of a reduction in non-fatal myocardial infarction insecure.

1[++]

> **A**   **Stress management training is not recommended as a technique to reduce coronary heart disease mortality or morbidity or conventional risk factors. It may have a role in improving patients' mood, including depressed mood.**

11.2.2   MOTIVATIONAL INTERVIEWING, HEALTH BEHAVIOUR CHANGE AND STAGES OF CHANGE MODEL

Clinical approaches to helping people change behaviour include use of cognitive behaviour therapy, motivational interviewing, stages of change approach, counselling and education. Research has focussed on identifying models to explain the intention to change and behaviour relationship eg Theory of Planned Behaviour,[282] and also examined attributions and health beliefs *(see SIGN guideline 57 on cardiac rehabilitation and SIGN guideline 96 on management of stable angina)*.[76,283]

Interventions

Cognitive behaviour therapy is a structured therapy addressing individuals' core beliefs, assumptions, thinking patterns and behaviour.

The stages of change model[284] and motivational interviewing[285] are different but related approaches to helping people change behaviour. Stages of change based approaches propose that tailoring interventions to the individual's readiness to change is more effective than using the same approach for all. There is less clarity about the specific nature of the therapeutic strategies to be used at each stage. Motivational interviewing and its adaptations (including health behaviour change) use structured strategies to help minimise resistance and elicit desire to change from within the individual.[286]

Cognitive Behaviour Therapy

Cognitive behaviour therapy (CBT) has been shown to be effective in patients with a wide range of conditions, including anxiety, depression, post-traumatic stress disorder and medical conditions.[287] Use of this approach with cardiac patients and other physical health problems (chronic fatigue and chronic pain) as part of an educational and rehabilitation programme has addressed beliefs and attributions and used goal setting and pacing principles to shape the desired behaviour. Studies note positive outcomes in exercise, activities and mood.[288-291]

1++
4

Stages of Change model

A high quality systematic review of effectiveness of interventions based on a 'stages of change ' approach, reviewed 37 RCTs (12 aimed at smoking cessation, seven on promotion of physical activity, five on dietary change and six on multiple lifestyle changes).[292] There was little evidence to suggest that stage-based interventions are more effective compared to non-stage based interventions, no intervention or usual care. Of 37 trials, 17 showed no significant differences between groups, eight showed mixed effects and ten trials showed effects in favour of a stage based intervention. A further meta-analysis looked specifically at studies using these approaches for smoking cessation, and found interventions based on the stages of change model were no more effective than interventions based on other models or no intervention.[293] Methodological shortcomings of the studies reviewed contribute to the conclusion that current research does not demonstrate effectiveness of stages of change based interventions in reducing risk factors for CHD.

1++

Motivational Interviewing

Two meta-analyses and a systematic review of motivational interviewing have examined the efficacy of this approach. One meta-analysis reviewed 30 trials covering alcohol, drug misuse, exercise and diet problems, smoking cessation and HIV/risk behaviour.[294] Adaptations of motivational interviewing were equivalent to other active treatments and superior to no-treatment or placebo for problems involving alcohol, drugs, diet and exercise, though not for smoking cessation and HIV risk behaviour. There were higher effect sizes for diet and exercise studies. Effect sizes for motivational interviewing were equivalent to other psychotherapeutic treatments (0.50), with motivational interviewing being delivered in fewer sessions. The lack of evidence for smoking may be due to the small number of studies meeting inclusion criteria. Training, supervision and competence of therapist were addressed.

2+

Another meta-analysis reviewed 72 studies (including 31 on alcohol issues, six on smoking cessation, five on treatment compliance and four on diet and exercise).[295] There was wide variability in effect sizes across studies and problem areas (across all studies mean effect size was 0.77, 95% CI 0.35-1.19). Effect size was higher when treatment was not manual based. The effect of motivational interviewing was seen early on and tended to diminish over 12 months follow up. The use of motivational interviewing was effective in areas relevant to the prevention of CHD (diet, exercise effect size 0.78, 95% CI 0.41 to 1.16 across all follow up points, alcohol effect size 0.26 95% CI 0.18 to 0.33 across all follow up points), but not effective in smoking. A study identified that level of 'commitment talk' from the client was a strong predictor of change.[296]

2+

Adding motivational interviewing to other treatment approaches maintained or improved its effect over 12 months (effect size 0.60). As motivational interviewing may be added to a cardiac rehabilitation intervention in CHD patients, this may increase its benefit.

A systematic review looked at eight studies, including four RCTs, in patients with diabetes, asthma, hyperlipidaemia, hypertension and CHD. The majority of RCTs and studies found positive effects of motivational interviewing on psychological, physiological and lifestyle change outcomes, but the quality of studies overall prevented meta-analysis and the drawing of firm conclusions about effectiveness. Problems included sample size, lack of power, disparate outcomes and poorly defined therapy and therapist training.[297]

1[+]

Therapist training, skill and competence

The effectiveness of any intervention depends on the training and competence of the therapist. One study indicated that therapist proficiency was best gained by adding specific feedback and/or coaching to workshop participation.[298] The Department of Health guideline on treatment choice in psychological therapies and counselling, recommends that psychological therapies including CBT, more complex problems, and those where patients are poorly motivated, require the more skilful therapist.[287]

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Summary

The use of CBT in addressing beliefs and structured behaviour change is effective in increasing activities and improving mood in CHD patients and other groups. Motivational interviewing has a strong potential to effect change in physical health behaviour and demonstrates effectiveness in addiction behaviours. Use of these skills can be effective in increasing patient engagement in other active therapy.

| A | **Cognitive behaviour therapy should be considered for increasing physical function and improving mood in patients with coronary heart disease.** |

| A | **Use of the stages of change model alone is not recommended as a method for changing the health behaviour of individuals with coronary heart disease.** |

| B | **Motivational interviewing should be considered in patients with cardiovascular disease who require to change health behaviours including diet, exercise, alcohol and compliance with treatment.** |

☑ Practitioners using techniques which involve cognitive behaviour therapy or motivational interviewing should receive appropriate training.

☑ Patients who are resistant to change or who present with more complex problems should be considered for referral to a clinical psychologist or therapist with a similar level of expertise.

12 Sources of further information and support for patients and carers

Action on Smoking and Health (ASH)
8 Fredrick Street, Edinburgh, EH2 2HB
Tel: 0131 225 4725 • Fax: 0131 225 4759
www.ash.org.uk • E-mail: ashscotland@ashscotland.org.uk

ASH Scotland is a voluntary organisation providing expert information and advice on all aspects of tobacco. It provides a range of written information including advice on passive smoking, smoking and young people, smoking cessation and smoking policies in the workplace.

Blood Pressure Association
60 Cranmer Terrace, London, SW17 0QS
Tel: 020 8772 4994 (Monday - Friday,9.30am - 5.30pm) • Fax: 020 8772 4999
www.bpassoc.org.uk • E-mail Information Service: www.bpassoc.org.uk/mailform.htm

The Blood Pressure Association (BPA) helps people with high blood pressure to become more involved in controlling their condition. Provides a range of information including management of hypertension, medications, lifestyle changes and other risk factors.

British Cardiac Patients Association
BCPA Head Office, 2 Station Road, Swavesey, Cambridge, CB4 5QJ
Tel: 0800 479 2800 • Fax: 01954 202 022
www.bcpa.co.uk • E-mail: enquiries@bcpa.co.uk

The British Cardiac Patients Association is a charitable organisation run by volunteers providing support, advice and information to cardiac patients and their carers.

British Heart Foundation (Scotland)
4 Shore Place, Edinburgh, EH6 6WW
Tel: 0131 555 5891 • Heart Information line: 08450 70 80 70 (Mon-Fri 9am-5pm)
www.bhf.org.uk • E-mail: scotland@bhf.org.uk

The British Heart Foundation provides a telephone information service for those seeking information on heart health issues. Also provides a range of written materials offering advice and information to CHD patients and carers. Topics include physical activity, smoking and diabetes.

Chest Heart and Stroke Scotland
65 North Castle Street, Edinburgh, EH2 3LT
Tel: 0131 225 6963 • Helpline: 0845 0776000
www.chss.org.uk • E-mail: admin@chss.org.uk

Chest Heart and Stroke Scotland provides a 24 hour advice line offering confidential, independent advice on all aspects of chest, heart and stroke illness. A series of information booklets, factsheets and videos is available free of charge to patients and carers. There are over 30 cardiac support groups in Scotland which are affiliated to CHSS, patients can contact CHSS for details of their nearest local support group.

Depression Alliance Scotland
3 Grosvenor Gardens, Edinburgh, EH12 5JU
Tel: 0131 467 3050
www.depressionalliance.org • E-mail: info@dascot.org

Depression Alliance Scotland provides information and support for people in Scotland who have depression.

Diabetes UK
10 Parkway, London, NW1 7AA
Tel: 020 7424 1000 • Careline: 0845 120 2960 (Monday to Friday - 9.00am - 5.00pm)
www.diabetes.org.uk • E-mail: careline@diabetes.org.uk

Diabetes UK is a national organisation providing information and advice on all aspects of diabetes such as diabetic care and diet. Provides a series of information leaflets including Diabetes UK's own magazine *Balance*.

Heart UK
7 North Road, Maidenhead, Berkshire, SL6 1PE
Tel: 01628 628 638 (Monday - Friday, 9.30am - 4pm) • Fax: 01628 628 698
www.heartuk.org.uk • E-mail: ask@heartuk.org.uk

Heart UK is a national charity aiming to offer information and support to anyone at high risk of CHD, particularly families with inherited high cholesterol. It provides a range of information including management of CHD by lifestyle, drugs and diet.

High Blood Pressure Foundation
Department of Medical Sciences, Western General Hospital, Edinburgh, EH4 2XU
Tel: 0131 332 9211 (Monday - Friday, 9.30am – 5pm) • Fax: 0131 332 9211
www.hbpf.org.uk • E-mail: hbpf@hbpf.org.uk

The High Blood Pressure Foundation is a registered charity which aims to improve the assessment, treatment and public awareness of high blood pressure. It provides a range of information leaflets including understanding high blood pressure and cholesterol and cardiovascular risk.

Mental Health Foundation (Scotland)
Merchant's House, 30 George Square, Glasgow, G2 1EG
Tel: 0141 572 0125
www.mentalhealth.org.uk • E-mail: Scotland@mhf.org.uk

The Mental Health Foundation helps people prevent, cope with and recover from mental health problems. It provides a range of factsheets on mental health issues including anxiety and depression.

NHS Health Scotland
Woodburn House, Canaan Lane, Edinburgh, EH10 4SG
Tel: 0131 536 5500 • Textphone: 0131 535 5503 • Fax: 0131 535 5501
www.hebs.com • E-mail: publications@health.scot.org.uk (information on obtaining Health Scotland publications); library.enquiries@health.scot.nhs.uk (help with general health information enquiries)

NHS Health Scotland is a special health board within NHS Scotland. The organisation provides information on projects, publications, support groups and information leaflets relating to CHD.

NHS 24
Tel: 0845 4 24 24 24 • www.nhs24.com

NHS 24 is a nurse led service for members of the public. It is a helpline offering health information, advice and help over the phone.

Scotland's Health on the Web • www.show.scot.nhs.uk

This website provides public access to publications relating to CHD such as the strategy for CHD and stroke in Scotland.

Scottish Nutrition and Diet Resources Initiative
Glasgow Caledonian University, Cowcaddens Road, Glasgow G4 0BA
Tel: 0141 331 8479 • Fax: 0141 331 8795
www.sndri.gcal.ac.uk • E-mail: sndri@gcal.ac.uk

The Scottish Nutrition and Diet Resources Initiative produces a range of easily accessible resources on nutrition and diet, which give consistent health messages to health professionals and the public.

13 Implementation and audit

13.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. It is acknowledged that every Board cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

13.2 SMC AND NICE GUIDANCE

The Scottish Medicines Consortium has issued advice on the use of nicotinic acid (February 2006).[295] Assessments on a number of statins, angiotensin receptor blockers, beta blockers and direct thrombin inhibitors are also published. Further details are available from www.scottishmedicines.org.uk.

The following reports have been approved by NHS Quality Improvement Scotland:

NICE Technology Appraisal Guidance - No. 39 Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation.[300]

NICE Technology Appraisal Guidance No 51 - The use of computerised cognitive behaviour therapy for anxiety and depression.[301]

NICE Technology Appraisal Guidance No 52 - The use of drugs for early thrombolysis in the treatment of acute myocardial infarction.[302]

NICE Technology Appraisal Guidance No 80 - Acute coronary syndromes – clopidogrel.[303]

NICE Technology Appraisal Guidance 90 - Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events.[304]

NICE Technology Appraisal Guidance No. 94 - Statins for the prevention of cardiovascular events.[305]

13.3 KEY POINTS FOR AUDIT

The National Clinical Datasets Development Programme and ISD Scotland are working to develop national standard datasets for implementation in IT systems supporting patient care. The following clinical datasets have been developed and are available at www.datadictionary.scot.nhs.uk

- CHD core
- acute coronary syndromes
- cardiac rehabilitation
- heart failure
- electrophysiology

The CHD and Stroke Programme is setting up working groups to develop methods and coding definitions to support the monitoring of the new SIGN guidelines from new datasets and existing data collections. Where there are gaps in the data ISD Scotland will work to support the necessary information collection.

13.4   **RECOMMENDATIONS FOR RESEARCH**

Risk estimation

- What organisational and resource changes are required within primary care to deliver a comprehensive service for CVD risk assessment, modification and follow up?
- What would be an ideal balance of general practitioner/practice nurse and administration resource? Should these services be provided within structured clinics within primary care or should they be delivered within normal surgeries.

Physical activity and exercise

The dose response of exercise for reducing CVD risk is well recognised. Further questions following from this are:

- Does this dose response apply to individual risk factors, for example, blood pressure?
- Is there a minimum cutoff threshold for frequency, intensity or duration of exercise below which the dose-response effect no longer applies, or below which a minimum effective response is seen?
- What factors motivate long term maintenance of physical activity?
- How is the optimal training programme defined - ie Frequency/Intensity/Time /Type (FITT) - does this apply equally to women/older adults/ethnic groups?

Smoking

- Independent studies of the effectiveness of bupropion for smoking cessation in people with schizophrenia are needed.

Alcohol

- What are the effects of varying doses of alcohol on the symptoms of CHD in those with established CHD?
- How much do the confounding factors identified in previously conducted observational studies of alcohol consumption impact on the reported findings?

Pharmacological intervention

- What is the most effective treatment of resistant hypertension (patients not at target despite triple therapy)?
- Large trials of lipid lowering using multiple agents compared to raising doses of statins are required.
- Well designed RCTs and cohort studies are required to investigate the effect of titrating lipid therapy based on proposed LDL cholesterol targets, controlling for pre-event values of known cardiovascular risk factors, treatment status (placebo vs statin, assessing interactions with deviations from arm of randomisation), and accounting for pill adherence.
- What is the risk/benefit balance for intensive lipid lowering in asymptomatic individuals at high risk of CVD?
- Qualitative evidence on the perceptions of patients currently taking statins on the perceived benefits and harms of adhering to therapy is lacking.
- More evidence is needed to confirm the role of aspirin for patients with diabetes.

Diet

- Does the effect of fish oil fatty acids on CHD risk differ between patients with acute coronary syndromes and patients with stable CHD?
- Does the advice of dietitians or doctors more effectively reduce the risk of CVD?

Other

- What is the value of sustained weight loss in lowering blood pressure?

14   Development of the guideline

14.1   INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practicing clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in "SIGN 50: A Guideline Developer's Handbook", available at **www.sign.ac.uk**

14.2   THE GUIDELINE DEVELOPMENT GROUP

Dr James Grant *(Chair)*	*General Practitioner, Auchterarder*
Mrs Brenda Anderson	*Cardiac Rehabilitation Co-ordinator, Aberdeen Royal Infirmary*
Mrs Mandy Andrew	*Tayside Managed Clinical Network Manager, CHD, Dundee*
Professor Christine Bond	*Consultant in Pharmaceutical Public Health, University of Aberdeen*
Dr Adrian Brady	*Consultant Cardiologist, Glasgow Royal Infirmary*
Dr Neil Campbell	*Reader in General Practice, Department of General Practice and Primary Care, University of Aberdeen*
Ms Joyce Craig	*Senior Health Economist, NHS Quality Improvement Scotland*
Dr John Dick	*Consultant Physician, Ninewells Hospital, Dundee*
Dr Penelope Fraser	*Consultant Clinical Psychologist, Ninewells Hospital, Dundee*
Mr James Grant	*Lay Representative, Balerno*
Ms Marianne Hayward	*Managed Clinical Network Manager for diabetes, Greater Glasgow Health Board*
Dr Matthew Lowther	*Heart Health Network Co-ordinator, NHS Health Scotland*
Dr Jill Murie	*General Practitioner Principal, Forth*
Dr Moray Nairn	*Programme Manager, SIGN Executive*
Professor Rudolph Riemersma	*Consultant Biochemist, University of Edinburgh*
Ms Ann Ross	*Physiotherapist, Western Infirmary, Glasgow*
Mr Duncan Service	*Senior Information Officer, SIGN Executive*
Dr Indrani Sinnak-Aruppan	*Consultant Clinical (Neuro and Health) Psychologist, Ayrshire Central Hospital*
Mr Roger Stableford	*Lay Representative, Falkirk*
Ms Nicola Stuckey	*Consultant Clinical Psychologist, Astley Ainslie Hospital, Edinburgh*
Ms Joan Thain	*Cardiac Rehabilitation Health Visitor, Westburn Centre, Aberdeen*
Dr Deborah Tinson	*Consultant Clinical Psychologist, Astley Ainslie Hospital, Edinburgh*
Dr Iain C Todd	*Consultant in Cardiovascular Rehabilitation, Astley Ainslie Hospital, Edinburgh*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

14.3   THE RISK ESTIMATION SUBGROUP

A small subgroup was established to evaluate methods of estimating cardiovascular risk and to incorporate a measure of social deprivation into a new risk estimation tool.

Dr James Grant (Chair)	*General Practitioner, Auchterader*
Dr Adrian Brady	*Consultant Cardiologist, Glasgow Royal Infirmary*
Dr Peter Brindle	*Welcome Training Fellow in Health Service Research, University of Bristol*
Ms Joyce Craig	*Senior Health Economist, NHS Quality Improvement Scotland*
Mr Alex McConnachie	*Consultant Statistician, University of Glasgow*
Dr Moray Nairn	*Programme Manager, SIGN Executive*
Dr Adam Redpath	*Programme Principal for Coronary Heart Disease and Stroke, Information and Statistics Division, NHSScotland*
Mr Roger Stableford	*Patient Representative, Falkirk*
Professor Hugh Tunstall-Pedoe	*Professor of Cardiovascular Epidemiology, Ninewells Hospital, Dundee*
Professor Graham Watt	*Professor of General Practice, University of Glasgow*

14.4   THE STEERING GROUP

A steering group comprising the chairs of the five SIGN CHD guidelines and other invited experts was established to oversee the progress of the guideline development. This group met regularly throughout the lifetime of the guidelines.

Dr Kevin Jennings	*Co-chair and Consultant Cardiologist, Aberdeen Royal Infirmary*
Professor Lewis Ritchie	*Co-chair and Mackenzie Professor of General Practice, University of Aberdeen*
Dr Alan Begg	*Chair of SIGN stable angina guideline*
Dr Nick Boon	*Consultant Cardiologist, Royal Infirmary of Edinburgh*
Ms Marjory Burns	*Director for Scotland, British Heart Foundation*
Mr David Clark	*Chief Executive, Chest, Heart and Stroke Scotland*
Professor Stuart Cobbe	*Chair of SIGN arrhthymias guideline*
Ms Joyce Craig	*Senior Health Economist, NHS Quality Improvement Scotland*
Dr Iain Findlay	*Chair of SIGN acute coronary syndromes guideline*
Professor Keith Fox	*Professor of Cardiology, University of Edinburgh*
Dr James Grant	*Chair of SIGN prevention guideline*
Mr James Grant	*Lay representative, Balerno*
Dr Grace Lindsay	*Lecturer, Glasgow Caledonian University*
Dr Moray Nairn	*Programme Manager, SIGN Executive*
Professor Allan Struthers	*Chair of SIGN chronic heart failure guideline*
Dr Lorna Thompson	*Programme Manager, SIGN Executive*

14.5   ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Mr Nicol Rainy Brown   *Lay Representative, Nairn*
Dr Hafrun Taylor   *Consultant Clinical Psychologist,*
                                            Astley Ainslie Hospital, Edinburgh
Dr Olivia Wu   *Systematic Reviewer, Glasgow University*
Mr Iain Lowis   *Head of Community Fundraising,*
                                            British Heart Foundation, Edinburgh

14.6   SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Searches were focused on existing guidelines, systematic reviews, randomised controlled trials, and (where appropriate) observational and/or diagnostic studies. Databases searched include Medline, Embase, Cinahl, PsychINFO, and the Cochrane Library. The year range covered was 1999-2005. Internet searches were carried out on various websites including those for the Australian Centre for Clinical Effectiveness, National Institute for Health and Clinical Excellence, the National Library for Health, Swedish Council on Technology Assessment in Healthcare, US Agency for Healthcare Research and Quality, and the US National Guidelines Clearinghouse. The Medline version of the main search strategies can be found on the SIGN website, in the section covering supplementary guideline material. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

14.7   CONSULTATION AND PEER REVIEW

14.7.1   NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group present its draft recommendations for the first time. The national open meeting for the five parallel SIGN guidelines on aspects of cardiovascular disease was held on 16 September 2005 and was attended by over 600 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

14.7.2   SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to the guideline.

Mr James Allison   *Consultant Clinical Scientist, Aberdeen Royal Infirmary*
Professor Iain Broom   *Consultant in Clinical Biochemistry and Metabolic Medicine,*
                                            The Robert Gordon University, Aberdeen
Dr John Byrne   *Consultant Cardiologist,*
                                            Southern General Hospital, Glasgow
Professor Stuart Cobbe   *Consultant Cardiologist, Glasgow Royal Infirmary*
Mrs Margaret Dunbar   *Practice Nurse, The Lanark Doctors*
Professor Paul Durrington   *Professor of Medicine, Machester Royal Infirmary*
Dr Andrew Elder   *Consultant in Acute Elderly Medicine,*
                                            Western General Hospital, Edinburgh

Dr John Gillies	*General Practitioner, The Health Centre, Selkirk*
Ms Patricia Graham	*Physiotherapist, Stobhill Hospital, Glasgow*
Ms Jenny Hally	*Clinical Research Fellow, University of Dundee*
Dr Romana Hunter	*Lecturer in Dental Prosthetics, University of Dundee*
Professor Derek Johnston	*Professor of Psychology, University of Aberdeen*
Mrs Bing Kerr	*Practice Nurse, Rubislaw Medical Group, Aberdeen*
Dr Harpreet Kohli	*Head of Health Services Research and Development, NHS Quality Improvement Scotland*
Dr Dorothy Moir	*Director of Public Health, NHS Lanarkshire*
Professor David Newby	*British Heart Foundation Reader and Consultant Cardiologist, University of Edinburgh*
Professor Chris Packard	*Professor of Vascular Biochemistry, Glasgow Royal Infirmary*
Ms Fiona Reid	*Pharmacist, NHS Lothian*
Dr Leona O'Reilly	*Acting Project Manager, Scottish Nutrition and Diet Resources Initiative, Glasgow*
Mr David Robb	*Lay Reviewer, Aberdeen*
Dr William Simpson	*Consultant Chemical Pathologist and Head of Service, Aberdeen Royal Infirmary*
Dr Falko Sniehotta	*Lecturer in Psychology, University of Aberdeen*
Professor Andrew Tannahill	*Head of Evidence for Action, NHS Health Scotland*

14.7.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewer's comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Dr Keith Brown	*Member of SIGN Council*
Professor Hilary Capell	*Member of SIGN Council*
Mr Robert Carachi	*Member of SIGN Council*
Ms Ann Marie Hawthorne	*Member of SIGN Council*
Dr Bernard Higgins	*Member of SIGN Council*
Professor Gordon Lowe	*Chairman of SIGN; Co-Editor*
Ms Anne Matthew	*Member of SIGN Council*
Dr Safia Qureshi	*SIGN Programme Director; Co-Editor*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

Abbreviations

ACE	angiotensin converting enzyme
AHA	American Heart Association
ARB	angiotensin-II receptor antagonist
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm
ASH	Action on Smoking and Health
ASSIGN	ASsessing cardiovascular risk using SIGN guidelines to ASSIGN preventive treatment
AST	aspartate aminotransferase
ATP	Adult Treatment Panel
BC	behavioural counselling
BHS	British Hypertension Society
BIP	Bezafibrate Infarction Prevention
BMI	body mass index
BP	blood pressure
CAIUS	Carotid Atherosclerosis Italian Ultrasound Study
CARDS	Collaborative Atorvastatin Diabetes Study
CBT	cognitive behavioural therapy
CCB	calcium channel blocker
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
CRP	c-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
DM	diabetes mellitus
ECG	electrocardiogram
ETS	environmental tobacco smoke
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
GFR	glomerular filtration rate
GP	general practitioner
HATS	HDL-Atherosclerosis Treatment Study
HDL	high density lipoprotein
HHS	Helsinki Heart Study
HIV	human immunosuppressive virus
HOT	Hypertension Outcomes Trial
IDF	International Diabetes Federation
IHD	ischaemic heart disease

IR	immediate release
JBS	Joint British Societies
JBS2	Joint British Societies' Guideline on Prevention of Cardiovascular Disease in Clinical Practice
LDL	low density lipoprotein
METS	metabolic equivalents
MI	myocardial infarction
MR	modified release
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health Service
NHSQIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NRT	nicotine replacement therapy
OR	odds ratio
PAD	peripheral arterial disease
PPP	Primary Prevention Project
QALY	quality adjusted life year
RCT	randomised controlled trial
RR	relative risk
SHHEC	Scottish Heart Health Extended Cohort
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish index of multiple deprivation
SM	stress management
SMAC	Standing Medical Advisory Committee
SMC	Scottish Medicines Consortium
TC	total cholesterol
TG	triglycerides
TIA	transient ischaemic attack
UK	United Kingdom
VA-HIT	Veterans Affairs HDL Intervention
WHO	World Health Organisation

Annex 1
The recommended interventions, goals and follow up based on cardiovascular risk assessment

Cardiovascular risk	Lifestyle	Drug Therapy	Treatment goals	Follow up
CVD risk clinically determined ≥20%* (Secondary prevention)	Intensive lifestyle advice on a cardioprotective dietary pattern with a dietitian, physical activity and smoking cessation interventions. Lifestyle advice should be given simultaneously with drug treatment	**In all patients:** ▪ aspirin, or other antiplatelet drug if not tolerated/contraindicated ▪ intensive statin therapy **In all patients with CHD:** ▪ an ACE inhibitor *(see SIGN 96)* **Following MI:** ▪ a beta blocker *(see SIGN 93)* **With hypertension** *(≥140/90 mm Hg or >130 mm Hg / >80 mm Hg in patients with diabetes with complications or renal disease and target organ damage)* ▪ antihypertensive drug therapy	Aspirin – lifetime treatment with 75 mg/day Lipids – intensive lipid lowering therapy BP – treat to reduce to <140 mm Hg systolic and/or <90 mm Hg diastolic	Risk factor monitoring every three to six months
CVD risk calculated ≥20% (Primary prevention)	Intensive lifestyle advice on a cardioprotective dietary pattern with a dietitian, physical activity and smoking cessation interventions. Lifestyle advice should be given simultaneously with drug treatment	▪ aspirin ▪ 40 mg simvastatin (or equivalent dose of pravastatin if simvastatin is contraindicated due to concomitant use of medications that influence cytochrome P450 metabolism) ▪ antihypertensive drug therapy (in hypertensive individuals)	Aspirin – lifetime treatment with 75 mg/day Lipids – lifetime treatment with 40 mg simvastatin daily BP – treat to reduce to <140 mm Hg systolic and/or <90 mm Hg diastolic	Risk factor monitoring every six to twelve months
10 to 20% (Primary prevention)	Specific individualised lifestyle advice on a cardioprotective dietary pattern, physical activity and smoking cessation. This lifestyle advice should be given by the primary health care team for three to six months prior to initiating drug treatment	Drug therapy indicated for people with extreme risk factor levels.**		Cardiovascular risk assessments every one to five years, depending on clinical circumstances.
less than 10% (Primary prevention)	General lifestyle advice on a cardioprotective dietary pattern, physical activity and smoking cessation	Non-pharmacological approach to treating multiple risk factors	Lifestyle advice aimed at reducing cardiovascular risk	Further cardiovascular risk assessment in five years.

*People who have had a previous cardiovascular event (angina, MI, angioplasty, coronary artery bypass grafts, TIA, ischaemic stroke or peripheral vascular disease) OR people with certain genetic lipid disorders OR people with diabetes mellitus and who are over 40 years.

**People with isolated high risk-factor levels either TC >8 mmol/l or BP ≥160/100 mm Hg should have these risk factors treated and considered for drug therapy to reduce levels of other modifiable factors and, therefore, global risk.

Annex 2
Cost effectiveness of statin therapy

In Scotland in the year to 31 March 2006 expenditure on statins was £70 million, equivalent to 7.2% of the drugs budget. Five statins, atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin currently have a UK marketing authorisation for a range of licensed indications from primary prevention as an adjunct to dietary control, to secondary prevention in people with manifest cardiovascular disease and for patients with primary or familial hypercholesterolaemia. For a list of licensed indications by individual statin, see the latest edition of the British National Formulary.[131]

No analysis of expenditure by licensed indication is available but the major patient groups currently prescribed statins are those identified as being:

- patients with established cardiovascular disease (CVD) or familial hypercholesterolaemia or
- asymptomatic patients with serum total cholesterol of ≥5.0 mmol/l and a 10 year risk of a major coronary event of ≥30%, who do not respond adequately to diet and other lifestyle advice.

The clinical and cost effectiveness for the use of statins in patients with existing CHD and familial hypercholesterolaemia is well established.[199] There is considerable uncertainty about their cost effectiveness in primary prevention. This is particularly important given other guideline groups have recommended expanding the treatment groups for statins. For example, JBS2[28] proposed widening the patient groups to be prescribed statins (in conjunction with lifestyle interventions and appropriate use of antihypertensive drugs) to:

- asymptomatic individuals with a CVD risk of ≥20% over ten years; or
- those with an elevated systolic blood pressure of ≥160mm Hg or diastolic blood pressure ≥100 mm Hg; or
- individuals with a total cholesterol to HDL ratio of ≥6.0

The JBS2 guidelines also proposed a total cholesterol treatment target of <4.0 mmol/l or a 25% reduction in total cholesterol (LDL cholesterol <2.0 mmol/l or a 50% reduction), whichever gets the person to the lowest absolute value.

Such recommendations raise several important economic issues, particularly around measuring the incremental costs and benefits of population based campaigns. For example, the clinical evidence for a public health campaign to titrate asymptomatic individuals aggressively to low cholesterol targets is not currently available, and is unlikely to be made available from clinical trials. Thus whilst RCTs may show the benefit of using a high dose statin compared to placebo or to a low dose in a defined population, the results may not generalise to a primary prevention population. There may also be other effects associated with giving drugs to individuals at risk of CVD that are difficult to capture as end points in clinical trials, particularly around compliance rates and patient preferences and attitudes.

Cost effectiveness evidence

A literature search was undertaken that identified nine UK studies that were methodologically sound and presented cost effectiveness analyses. Five of these were reported in the Technology Assessment Report from researchers based at Sheffield University, the sixth was that report, itself.[199] The remaining three studies[306-308] were published following the publication of the Technology Assessment Report.

Five of the studies were of the use of statins in primary prevention,[308-312] two were health technology assessments that modelled use in primary and secondary prevention[199,309] and two were secondary prevention only.[306,307] Four of the five primary prevention studies were based on the WOSCOPS trial.[191] The other study modelled the cost effectiveness of the five licensed statins for primary prevention.[308] The secondary prevention studies used data from the Heart Protection Study of 20,536 high risk individuals[194] and the two health technology assessments pooled clinical data from several trials.

All but three of the studies[199,307,308] were completed prior to the introduction of simvastatin as a generic product - at a price (as at November 2006) of £55 a year for simvastatin 40 mg, compared to £367 a year for the proprietary product of atorvastatin 40 mg. Therefore, the results from the earlier studies overstate the cost per life year gained, or cost per quality adjusted life year, for the options that can be delivered using generic simvastatin.

Asymptomatic individuals without established CHD or CVD

The systematic literature review concluded that for asymptomatic individuals, at low levels of risk of CHD, the cost per life year gained from prescribing statins compared to placebo, varied between £20,000 and £30,000.[199] The economic modelling of people with a ≥ 30% ten year risk of CHD (approximating to a ≥ 40% ten year CVD risk) reported a wider range, varying from £9,500 to £36,800 per quality adjusted life year (QALY) in men aged 45 and 85 and £13,700 to £47,400 per QALY for women of the same ages.

Adopting CVD risk levels of 20% over ten years reduced the modelled costs per QALY to £6,800 to £27,600 for men aged 45 and 85 years, with women having similar or slightly lower values.

The CVD analyses have lower incremental cost effectiveness ratios, that is are more cost effective, than the CHD analyses. This is presumably because of the higher costs to manage strokes initially and in subsequent years, compared to CHD diagnoses. This difference is particular notable in the older age groups where the costs per QALY for CVD risks are below £30,000 per QALY in all age groups.

One study looked at treating asymptomatic men with raised baseline cholesterol of 7.5 mmol/l and varying risk factors and found such treatment to be cost effective at all risk levels.[311]

The study comparing the cost effectiveness of the five statins[4] assumed a mean initial baseline total cholesterol of 6.4 mmol/l and applied the efficacy rates observed in trials for each statin to derive a range of treated cholesterol values. These were used, in conjunction with Framingham risk equations, to predict the CHD events saved as a result of the cholesterol reductions. The results from this study may not generalise to Scotland where the baseline total cholesterol for untreated individuals, as observed in the Scottish Heart Survey 2003 was 6.0 mmol/l.

Individuals with established CHD or CVD

The systematic literature review noted the cost per life year gained was lower in secondary prevention of CHD compared to primary prevention because people were at higher risk of events.[199]

This report also modelled the cost effectiveness of adopting a risk measure based on CVD. The resultant costs per QALY were lower than for established CHD, ranging from £9,000 to £13,100 for men between 45 to 85 years of age and slightly lower for women in the same age range being £8,400 to £11,700.

The cost effectiveness of treating those with established CVD was also demonstrated in the economic evaluations that accompanied the Heart Protection Study.[306,307] The first study compared the hospitalisation costs and cost of simvastatin 40 mg for 20,536 individuals with established disease over the five year period of the trial.[306] The second study extrapolated the trial data to evaluate the lifetime benefits for people in different ages and with different risks of CVD.[307]

Prescribing generic simvastatin 40 mg/day was cost saving for most risk and age categories, with the reduced costs from fewer hospital admissions outweighing the drug costs. In people aged from 70 years with a relatively low disease risk, (24% over ten years) the cost per life year gained was under £100.

The economic evaluation also modelled data for younger people and lower risk thresholds than observed in the trial. The results showed that prescribing simvastatin 40 mg/day was cost effective compared to placebo for risk thresholds as low as 10% over ten years and for all age groups.

Weaknesses of the models

All of the economic models assume that identifying patients at the various risk thresholds is costless and that the assessment tool is 100% accurate. None include the cost of adverse events. The absence of such costs could overstate cost effectiveness but such an effect is likely to be much smaller than the savings from using generic statins.

In summary, the published evidence supports prescribing statins to people with established CVD and for individuals with a CVD risk as low as 10% over ten years or with baseline cholesterol levels of over 7.5 mmol/l. No evidence was identified on the cost effectiveness of treating individuals to a total cholesterol target of less than 5 mmol/l or those with the single risk factor of raised blood pressure.

COST EFFECTIVENESS OF CVD PREVENTION PROGRAMMES

The clinical benefits of adopting other treatments that reduce CVD risk have been reviewed in this guideline, particularly interventions to promote physical activity, stop smoking, improve diet, reduce harmful alcohol consumption and lower blood pressure.

No systematic literature reviews were identified which looked at the relative cost effectiveness of such programmes. Two of the studies found in the literature search undertaken for the statins analyses provide some comparative data. One study found that the cost effectiveness of statins was poorer than for other treatments.[313] The gross discounted cost per life gained was: £55 for aspirin post-myocardial infarction, £45 for bendroflumethazide treatment for elderly people with hypertension, £1,510 for low cost mixed drug antihypertensive regimens for middle-aged people, £230 for beta-blockers post-myocardial infarction and £290 for the Mediterranean diet post-myocardial infarction. In comparison, statins had a cost per life year gained of between £5,400 and £13,300 for primary prevention of CHD and £3,800 to £9,300 for secondary prevention.

A similar study of prevention programmes in Spain ranked interventions by cost per life year gained.[314] The ordering, beginning with the most cost effective was: smoking cessation, hypertension, dietary treatment and drug treatment for hypercholesterolaemia. The statins treatment arm had a cost per life year gained of three times that of the dietary programme.

The objective of such comparisons is to improve decision- making on the allocation of scarce resources for competing therapies to prevent and manage CVD. This is not straightforward and best practice[315] suggests such decisions should also consider:

- that the financial costs involved in treating all groups who could potentially benefit from lipid lowering are large. NHS resources are finite and therefore prioritisation is necessary. This should be based on evidence-based estimation of capacity to benefit
- the cost effectiveness of lipid lowering interventions rises as the absolute cardiovascular risk increases. The risk level at which treatment is given needs to be influenced by both cost effectiveness and overall cost, as determined by the price of statins. If more statins were available as generic products, more people who would benefit could be treated for the same resources
- there are interventions in the prevention of CVD (eg lifestyle changes) which are considerably more cost effective than statins and these should already be in place before lipid lowering is initiated. However, for the higher risk groups, cost effectiveness of statins is on a par with many other interventions of proven effectiveness in other disease areas provided by the NHS.

Annex 3
Recommendations to healthcare professionals regarding muscle and statin safety

1. Whenever muscle symptoms or an increased creatine kinase (CK) level is encountered in a patient receiving statin therapy, health professionals should attempt to rule out other aetiologies, because these are most likely to explain the findings. Other common aetiologies include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).

2. Obtaining a pre-treatment, baseline CK level may be considered in patients who are at high risk of experiencing a muscle toxicity (eg, older individuals or when combining a statin with an agent known to increase myotoxicity), but this is not routinely necessary in other patients.

3. It is not necessary to measure CK levels in asymptomatic patients during the course of statin therapy, because marked, clinically important CK elevations are rare and are usually related to physical exertion or other causes.

4. Patients receiving statin therapy should be counselled about the increased risk of muscle complaints, particularly if the initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated; they should be advised to report such muscle symptoms to a health professional.

5. CK measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate a decision of whether to continue therapy or alter doses.

6. In patients who develop intolerable muscle symptoms with or without a CK elevation and in whom other aetiologies have been ruled out, the statin should be discontinued. Once asymptomatic, the same or different statin at the same or lower dose can be restarted to test the reproducibility of symptoms. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy.

7. In patients who develop tolerable muscle complaints or are asymptomatic with a CK < 10 x the upper limit of normal, statin therapy may be continued at the same or reduced doses and symptoms may be used as the clinical guide to stop or continue therapy.

8. In patients who develop rhabdomyolysis (a CK $> 10,000$ IU/L or a CK > 10 times the upper limit of normal with an elevation in serum creatinine or requiring IV hydration therapy), statin therapy should be stopped. IV hydration therapy in a hospital setting should be instituted if indicated for patients experiencing rhabdomyolysis. Once recovered, the risk vs benefit of statin therapy should be carefully reconsidered.

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Source: *McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006;97(8A):89C-94C.*

Annex 4
Recommendations to healthcare professionals regarding the liver and statin safety

1. During the routine general evaluation of patients being considered for statin and other lipid-lowering therapy, it is advisable to obtain liver transaminase levels. If these tests are found to be abnormal, further investigation should be performed to determine the aetiology of the abnormal test results.

2. Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.

3. The clinician should be alert to patient reports of jaundice, malaise, fatigue, lethargy, and related symptoms in patients taking statin therapy as a signal of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased bilirubin level and elevated prothrombin time (rather than simple elevations in liver transaminase levels).

4. The preferred biochemical test to ascertain significant liver injury is bilirubin, which, in the absence of biliary obstruction, is a more accurate prognosticator of liver injury than isolated aminotransferase levels.

5. Should the clinician identify objective evidence of significant liver injury in a patient receiving a statin, the statin should be discontinued. The aetiology should be sought and, if indicated, the patient referred to a gastroenterologist or hepatologist.

6. If an isolated asymptomatic transaminase level is found to be elevated 1–3 times the upper limit of normal, there is no need to discontinue the statin.

7. If an isolated asymptomatic transaminase level is found to be 3 times the upper limit of normal during a routine evaluation of a patient administering a statin, the test should be repeated and, if still elevated, other aetiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment.

8. According to the Expert Liver Panel, patients with chronic liver disease, non-alcoholic fatty liver disease, or non-alcoholic steatohepatitis may safely receive statin therapy.

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Source: *McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006;97(8A):89C-94C.*

Annex 5
Recommendations to healthcare professionals regarding the kidney and statin safety

1. During the management of patients with statin therapy, it is not necessary to carry out serum creatinine and proteinuria monitoring routinely for the purpose of identifying an adverse effect, although an assessment of renal function is advisable before initiating statin therapy.

2. If serum creatinine becomes elevated in a patient without rhabdomyolysis while receiving statin therapy, there is generally no need to withdraw the statin but in some cases, according to prescribing information, an adjustment in the statin dose may be required.

3. If unexpected proteinuria develops in a patient receiving a statin, there is no need to withdraw statin therapy or to alter the dose of the statin. An investigation into the cause of the proteinuria is warranted, as is consideration of a change in the statin dose as guided by the prescribing information for each statin.

4. Chronic kidney disease does not preclude the use of a statin. However, the dose of some statins should be adjusted in cases of moderate or severe renal insufficiency.

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Source: McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006;97(8A):89C-94C.

Annex 6
Recommendations to healthcare professionals regarding neurological disorders and statin safety

1. Routine neurological monitoring of patients administering statin therapy for changes indicative of peripheral neuropathy or impaired cognition is not recommended.

2. Patients experiencing symptoms consistent with peripheral neuropathy while receiving a statin should be evaluated to rule out secondary causes (eg, diabetes mellitus, renal insufficiency, alcohol abuse, vitamin B12 deficiency, cancer, hypothyroidism, acquired immunodeficiency syndrome, Lyme disease, or heavy metal intoxication).

3. If another aetiology of the neurological symptoms is not identified, it is appropriate to withdraw statin therapy for a period of 3–6 months to establish whether an apparent association with statin therapy exists.

4. If the patient's neurological symptoms improve while off statin therapy, a presumptive diagnosis of statin-induced peripheral neuropathy might be made. However, because of the proven benefit of statin therapy, reinitiation of statin therapy should be considered with a different statin and dose.

5. If the patient's neurological symptoms do not improve after statin therapy has been withdrawn for the specified period, statin therapy should be restarted based on a risk–benefit analysis.

6. If the patient experiences impaired cognition while receiving statin therapy it is appropriate to follow a similar course of evaluation as suggested above for peripheral neuropathy, ie, first rule out other aetiologies, and if none are found, then withdraw the statin for 1–3 months. If improvement is not seen, statin therapy should be restarted based on a risk– benefit analysis.

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Source: McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006;97(8A):89C-94C.

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THE RECOMMENDED INTERVENTIONS, GOALS AND FOLLOW UP BASED ON CARDIOVASCULAR RISK ASSESSMENT

Cardiovascular risk	Lifestyle	Drug Therapy	Treatment goals	Follow up
CVD risk clinically determined ≥20%* **(Secondary prevention)**	Intensive lifestyle advice on a cardioprotective dietary pattern with a dietitian, physical activity and smoking cessation interventions. Lifestyle advice should be given simultaneously with drug treatment	**In all patients:** ▪ aspirin, or other antiplatelet drug if not tolerated/contraindicated ▪ intensive statin therapy **In all patients with CHD:** ▪ an ACE inhibitor *(see SIGN 96)* **Following MI:** ▪ a beta blocker *(see SIGN 93)* **With hypertension** *(≥140/90 mm Hg or >130 mm Hg / >80 mm Hg in patients with diabetes with complications or renal disease and target organ damage)* ▪ antihypertensive drug therapy	Aspirin – lifetime treatment with 75 mg/day Lipids – intensive lipid lowering therapy BP – treat to reduce to <140 mm Hg systolic and/or <90 mm Hg diastolic	Risk factor monitoring every three to six months
CVD risk calculated ≥20% **(Primary prevention)**	Intensive lifestyle advice on a cardioprotective dietary pattern with a dietitian, physical activity and smoking cessation interventions. Lifestyle advice should be given simultaneously with drug treatment	▪ aspirin ▪ 40 mg simvastatin (or equivalent dose of pravastatin if simvastatin is contraindicated due to concomitant use of medications that influence cytochrome P450 metabolism) ▪ antihypertensive drug therapy (in hypertensive individuals)	Aspirin – lifetime treatment with 75 mg/day Lipids – lifetime treatment with 40 mg simvastatin daily BP – treat to reduce to <140 mm Hg systolic and/or <90 mm Hg diastolic	Risk factor monitoring every six to twelve months
10 to 20% **(Primary prevention)**	Specific individualised lifestyle advice on a cardioprotective dietary pattern, physical activity and smoking cessation. This lifestyle advice should be given by the primary health care team for three to six months prior to initiating drug treatment	Drug therapy indicated for people with extreme risk factor levels.**		Cardiovascular risk assessments every one to five years, depending on clinical circumstances.
less than 10% **(Primary prevention)**	General lifestyle advice on a cardioprotective dietary pattern, physical activity and smoking cessation	Non-pharmacological approach to treating multiple risk factors	Lifestyle advice aimed at reducing cardiovascular risk	Further cardiovascular risk assessment in five years.

*People who have had a previous cardiovascular event (angina, MI, angioplasty, coronary artery bypass grafts, TIA, ischaemic stroke or peripheral vascular disease) OR people with certain genetic lipid disorders OR people with diabetes mellitus and who are over 40 years.

**People with isolated high risk-factor levels either TC >8 mmol/l or BP ≥160/100 mm Hg should have these risk factors treated and considered for drug therapy to reduce levels of other modifiable factors and, therefore, global risk.