LIPID MODIFICATION:

Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Full Guideline

May 2008

Revised March 2010 following decision by NICE Guidance Executive to modify the recommendations regarding choice of equation for assessment of cardiovascular risk – see chapter 3.

Citation

Cooper A, Nherera L, Calvert N, O'Flynn N, Turnbull N, Robson J, Camosso-Stefinovic J, Rule C, Browne N, Ritchie G, Stokes T, Mannan R, Brindle P, Gill P, Gujral R, Hogg M, Marshall T, Minhas R, Pavitt L, Reckless J, Rutherford A, Thorogood M, Wood D(2008) *Clinical Guidelines and Evidence Review for Lipid Modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease* London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.

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Preface

As a practising GP, I know just how important it is to prevent cardiovascular disease. Seeing a young patient in the prime of their life suddenly struck by a vascular event is devastating. Sadly this is something that still occurs all too frequently. From talking to many GPs and nurses it has become clear that there is considerable uncertainty about which patients to target for preventative treatment, how to respond to a request for lipid measurement and the thresholds at which to initiate treatment. As a result there is considerable variation in practice and in outcomes. So I really welcome this guideline which brings much needed clarity for clinicians who have to manage patients with risk factors for heart disease every day.

It is particularly timely as there considerably interest from the public in staying healthy. Indeed the NHS is being reshaped to focus much more on health rather than disease and is introducing initiatives in vascular disease screening. This is right because cardiovascular disease is a major cause of disability and death in the United Kingdom. In particular it is the most common cause of premature death. We now know much about the epidemiology of cardiovascular disease, risk factors for its development and have available interventions that reduce morbidity and mortality. The risk of a future CVD event can be calculated from these risk factors and people at highest risk can be identified.

Although this guideline is relevant to all settings, it emphasizes the important role of primary care. The guideline promotes the adoption of a systematic strategy in primary care to identify those at risk and to offer to them the benefit of lifestyle advice and preventative care. The emphasis is on treating patients according to their overall level of risk rather than treating cholesterol levels in isolation. The use of the general practice electronic patient record and the routine data collected there allows practitioners to search for and offer treatment to those patients in their community who are at highest risk.

The guideline rightly emphasises the requirement for a partnership with patients and the importance of patient understanding of concepts of risk and preventative care. Communication with patients remains important in relation to drug treatment. As well

as recommendations in regard to identifying patients at risk, there is guidance on the use of lipid lowering drugs in primary prevention and for those patients who have already had a cardiovascular event. Happily this is not considered in isolation but in the context of appropriate lifestyle advice.

I commend this guideline to clinicians and healthcare organisations and urge them to implement it as widely as possible: I know that I will use on a daily basis in clinical practice.

Professor Mayur Lakhani CBE FRCP FRCPE FRCGP

GP and Immediate Past Chairman of the Royal College of General Practitioners

Medical Director, NHS East Midlands

Key priorities for implementation

Primary prevention of CVD

- For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people aged between 40 and 74 who are likely to be at high risk.

- People should be prioritised on the basis of an estimate of their CVD risk before a full formal risk assessment. Their CVD risk should be estimated using CVD risk factors already recorded in primary care electronic medical records.

- Risk equations[*] should be used to assess CVD risk.

- People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. This information should be in a form that:

  - presents individualised risk and benefit scenarios

  - presents the absolute risk of events numerically

  - uses appropriate diagrams and text.

  (See www.npci.org.uk)

- Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimised if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

  - smoking status

  - alcohol consumption

  - blood pressure (see 'Hypertension', NICE clinical guideline 34)

  - body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)

  - fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)

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[*]This recommendation has been modified in line with decision taken by NICE Guidance Executive in February 2010 that the Framingham risk equation should no longer be considered the equation of choice for assessment of CVD risk, but should be considered as one of the possible equations to use.

- fasting blood glucose

- renal function

- liver function (transaminases)

- thyroid-stimulating hormone (TSH) if dyslipidaemia is present.

- Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available or appropriate (for example, older people, people with diabetes or people in high-risk ethnic groups).[†]

- Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

Secondary prevention of CVD

- For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors. Blood tests and clinical assessment should be performed, and comordbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

  - smoking status

  - alcohol consumption

  - blood pressure (see 'Hypertension', NICE clinical guideline 34)

  - body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)

  - fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)

  - fasting blood glucose

  - renal function

  - liver function (transaminases)

[†] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094

- thyroid-stimulating hormone (TSH) if dyslipidaemia is present.

- Statin therapy is recommended for adults with clinical evidence of CVD.[‡]

- People with acute coronary syndrome should be treated with a higher intensity statin[§]. Any decision to offer a higher intensity statin should take into account the patient's informed preference, comorbidities, multiple drug therapy, and the benefits and risks of treatment.

- Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

- In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity statin[8] should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.

[‡] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094

[§] 'Higher intensity statins' are statins used in doses that produce greater cholesterol lowering than simvastatin 40 mg, for example simvastatin 80 mg.

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1 Introduction

1.1 Background

Cardiovascular disease (CVD), which comprises coronary heart disease (CHD) and stroke, is the main cause of death in England and Wales. There are more than 3 million people living with CVD. In 2005, CVD was the cause of one in three deaths, accounting for 124 000 deaths; 39 000 of those who died were younger than 75 years of age. For every one fatality, there are at least two people who have a major non-fatal cardiovascular event. There are over 3 million people living with coronary heart disease or stroke.

This epidemic has been socially generated by smoking, diets high in saturated fats and salt and a sedentary lifestyle. The epidemic peaked in the 1970s and 1980s and death rates have halved since then. Despite this reduction CVD remains a leading cause of death, in particular of premature death, an increasing cause of morbidity and a major cause of disability and ill-health. The UK CVD death rates continue to exceed those of its European neighbours. It is estimated that 60% of the CVD mortality decline in the UK during the 1980s and 1990s was attributable to reductions in major risk factors, principally smoking. Treatment of individuals, including secondary prevention, accounts for the remaining 40% of the decline in mortality (Unal, B., Critchley, J. A., and Capewell, S., 2004).

In spite of evidence that mortality from CVD is falling, morbidity appears to be rising. CVD has significant cost implications and was estimated to cost the NHS almost £14750 million in 2003 and the economy around £30 billion a year.

Age is the main determinant of CVD which predominantly affects people over 50 years. Men under 75 years are three times more likely than women to die from CVD. Apart from age and sex, three modifiable risk factors, smoking, raised blood pressure and cholesterol make the major contribution to CVD incidence, particularly in combination. They account for 80% of all premature coronary heart disease (Emberson, J. R., Whincup, P. H., Morris, R. W. et al , 2003). There are in addition identifiable population groups who may be at particular risk and could be targeted for treatment. CVD is strongly associated with low income and social deprivation and

shows a North-South divide in both the UK and Europe as a whole. Despite the male propensity to CVD, the lifetime burden is greater in women because of their longevity and their increased risk of stroke over the age of 75 years (Seshadri, S., Beiser, A., Kelly-Hayes, M. et al , 2006). Women have a higher case-fatality rate, are more likely to be under-diagnosed and less likely to be optimally treated. Women in low income groups are the exception to the trend of reducing mortality from CVD over the past 20 years. South Asian men are more likely to develop CVD at a younger age. Family history of premature coronary heart disease identifies an important group which contains those people with a genetic pre-disposition.

1.2   Management

Strategies for the prevention of CVD are threefold. First are interventions to reduce the prevalence of CVD risk factors in the general population. The largest number of CVD events will occur in those at low risk. Smoking cessation combined with changes in mean blood pressure and cholesterol through national reductions in salt intake, saturated fat consumption and increases in physical activity are fundamental to the national strategy for improvement.

The second strategy is interventions in individual people at high risk of developing CVD and focusing health service resources on those at greatest risk with most to gain. This strategy, largely based in primary care, includes smoking cessation and the identification and assessment of those at high risk with appropriate advice on diet, physical activity and treatment for high blood pressure and lipid modification. The NSF for CHD in England and Wales advocates both approaches. For primary prevention, the NICE technology appraisal, 'Statins for the prevention of cardiovascular events' (TA 94, 2007) recommends that the current National Service Framework threshold for statin treatment (30% CHD ten-year risk, equivalent to a 40% CVD risk) be reduced by half, to a 20% CVD ten-year risk.. In addition to those people who are already known to have diabetes or CVD, the adoption of this new threshold will identify 5 million more people as potential candidates for treatment depending on which risk score is used (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007).

The third strategy is for secondary prevention in people with established cardiovascular disease which includes modification of lipids. Serum cholesterol often remains at unacceptably high levels (Capewell, S., Unal, B., Critchley, J. A. et al , 2006) and can be further improved with advice, support and treatment. Treatment for high blood pressure and other preventive treatment may also be sub-optimal (EUROASPIRE I and II Group., 2001).

Trials of statin therapy have demonstrated that lowering LDL cholesterol by 1 mmol/l reduces CVD events by 21% and total mortality by 12%, irrespective of baseline risk. Although there have been major improvements in the use of statins for secondary prevention there is still substantial variation in their use by clinicians. Wider and improved use of statins would have a major public health impact.

Adherence to treatment is poor even among those who have experienced a CVD event and non-adherence is associated with worse outcomes (Howell, N., Trotter, R., Mottram, D. R. et al , 2004) (Rasmussen, J. N., Chong, A., and Alter, D. A., 2007) (Wei, L., Ebrahim, S., Bartlett, C. et al , 2005).

For primary prevention, adherence to treatment is an even greater challenge than for those who have had a major event. Convincing people who feel well, that they need lifestyle change or lifelong drug treatment requires high quality information and communication.

The scope for this guideline was limited to the identification and assessment of CVD risk and to the assessment and modification of lipids in people at risk of CVD or people with known cardiovascular disease. The guideline development group wishes to make it clear that lipid modification should take place as part of a programme of risk reduction and also include attention to the management of all other known risk factors.

1.3   Aim of the guideline

Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances' (Committee to Advise the Public Health Service on Clinical Practice Guidelines and Institute of Medicine., 1990).

This guideline gives recommendations to clinicians and other groups listed in 2.5.1, about lifestyle modification, drug therapy, patient information and the communication of patient risk assessment and information surrounding lipid modification for primary and secondary prevention of CVD.

1.4 How the guideline is set out

The recommendations for all the topics in each clinical chapter are listed at the start of the chapter. Both the evidence statements and narratives of the research studies on which our recommendations are based are found within each topic section. The evidence statements precede the narrative for each topic. The evidence extraction reports that describe the studies reviewed are found in Appendices D and E.

1.5 Scope

The guideline was developed in accordance with a scope given by NICE. The scope set the remit of the guideline and specified those aspects of lipid modification to be included and excluded. The scope was published in August 2005 and is reproduced in Appendix B.

1.5.1 Who the guideline is intended for

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales. This includes:

- healthcare professionals who work within the primary, community, community pharmacy and hospital secondary care settings.

- those with responsibilities for commissioning and planning health services such as primary care trust commissioners, Welsh Assembly government officers

- public health and trust managers

- people (aged 18 years and older) with CVD or without established CVD but who are at high risk of developing CVD due to a combination of cardiovascular risk factors including raised blood pressure and hypertension, and/or who are overweight or obese.

1.5.2 Areas outside the remit of the guideline

The guideline does not cover people:

a) with familial hypercholesterolaemia and familial hypertriglyceridaemia (familial lipoprotein lipase deficiency; familial apolipoprotein C-II deficiency)

b) with type 1 and type 2 diabetes

c) with familial clotting disorders and/or other defined genetic disorders that increase cardiovascular risk

d) who are at high risk of CVD or abnormalities of lipid metabolism as a result of endocrine or other secondary disease processes or as a result of drug treatment

e) The scope was altered in December 2006 to encompass use of statins post MI.

The statement of explanation from the NICE website is 'The Institute is currently preparing clinical guidelines on 'MI: Secondary Prevention' (scheduled publication March 2007), and on 'Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' (scheduled publication December 2007). The guidelines have been developed alongside the technology appraisal advice on Statins for the prevention of cardiovascular events (published January 2006), and also Ezetimibe for the treatment of hypercholesterolemia (scheduled publication August 2007). The scope for the MI Secondary Prevention states that it will provide advice on "lipid modifying drugs with specific reference to the additional advice for patients post MI and incorporating the statins technology appraisal and cross referencing to the hyperlipidaemia guideline". In the light of the more detailed recommendations being developed in the Lipids Modification guideline, the Institute has agreed the most appropriate way forward is for the MI guideline to confine its recommendations to those in

the technology appraisal on Statins, and does not include recommendations on dosage or cholesterol monitoring etc. The Lipids guideline will then take on responsibility for making recommendations regarding statin doses and targets, and include recommendations for patients following an MI.'

This guideline also does not cover:

a) the identification, assessment and management of people with pre-diabetes/metabolic syndrome.

b) the clinical management of conditions considered to be risk factors for CVD, including raised blood pressure/hypertension, smoking, obesity, and blood clotting abnormalities.

c) self-medication of individuals with lipid-regulating drugs, specifically use of over-the-counter drugs, including statins.

d) the clinical management of people with lipid disorders considered to merit referral to secondary care for specialist assessment and follow-up.

e) the clinical management of people with CHD (angina), stroke and peripheral arterial disease except as it relates to lipid modification in the context of secondary prevention.

1.6   *Responsibility and support for guideline development*

1.6.1   The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC is a partnership of primary care professional associations and academic units, formed as collaborating centre to develop guidelines under contract to NICE, and is entirely funded by NICE. The NCC-PC is contracted to develop five guidelines at any one time, although there is some overlap at start and finish. Unlike many of the other centres that focus on a particular clinical area, the NCC-PC has a broad range of topics relevant to primary care. However, it does not develop guidelines exclusively for primary care. Each guideline may, depending on the scope, provide guidance to other health sectors in addition to primary care.

The Royal College of General Practitioners (RCGP) acts as the NCC-PC's host organisation. The Royal Pharmaceutical Society and the Community Practitioners' and Health Visitors' Association are partner members with representation of other professional and lay bodies on the Board. The RCGP holds the contract with NICE for the NCC-PC. The work has been carried out on two sites in London, where the work on this particular guideline was based, and in Leicester under contract to the University of Leicester.

1.6.2 The Development Team

The Development Team had the responsibility for this guideline throughout its development. It is responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The development team working on this guideline consisted of the:

Guideline Lead, who is a senior member of the NCC-PC team and has overall responsibility for the guideline.

Information Scientist, who searched the bibliographic databases for evidence to answer the questions posed by the GDG.

Reviewer (Senior Health Services Research Fellow), with knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG.

Health Economist, who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost effectiveness.

Project Manager, who was responsible for organising and planning the development, for meetings and minutes and for liaising between NICE and external bodies.

Clinical Adviser, with an academic understanding of the research in the area and its practical implications for the healthcare service, who advised the Development Team on searches and interpretation of the literature.

With the exception of the Clinical Adviser, all of the Development Team was based at the NCC-PC. Applications were invited for the post of Clinical Adviser, who was recruited to work on average one half-day per week on the guideline. The members of the Development Team attended the GDG meetings and participated in them.

For this guideline, the Clinical Adviser also took the role of Chair for the GDG meetings.

1.6.3   The Guideline Development Group (GDG)

The Chair was selected for the group based on his understanding of the field. The primary role of the Chair was to facilitate the work at GDG meetings.

GDGs are working groups whose members are chosen with the aim of encompassing the range of experience and expertise needed to address the scope of the guideline. Nominations for GDG members were invited from the relevant stakeholder organisations, who were sent the draft scope of the guideline and some guidance on the expertise needed. From the nominations, two patient representatives and the healthcare professionals joined the GDG.

Nominees who were not selected for the GDG were invited to act as Expert Peer Reviewers. They were sent drafts of the guideline during the consultation periods and invited to submit comments by the same process as stakeholders.

Each member of the GDG served as an individual expert in his or her own right and not as a representative of the nominating organisation.

In accordance with guidance from NICE, all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, shareholdings, fellowship, and support from the healthcare industry.

Full GDG members included:
Dr John Robson (Chair and Clinical Adviser)
Senior Clinical Lecturer in General Practice, Institute of Community Health Sciences, Queen Mary University London

Dr Peter Brindle

General Practitioner Wellspring Surgery, Bristol and R&D Lead, Bristol, North Somerset and South Gloucestershire Primary Care Trusts

Dr Paramjit Gill

General Practitioner and Reader in Primary Care Research, Department of Primary Care and General Practice, University of Birmingham

Mrs Renu Gujral

Patient representative

Mrs Maureen Hogg

Coronary Heart Disease Lead Nurse, Cleland Hospital, North Lanarkshire

Dr Tom Marshall

Senior Lecturer in Public Health, University of Birmingham

Dr Rubin Minhas

General Practitioner, Primary Care Coronary Heart Disease Lead, Medway Primary Care Trust, Gillingham, Kent

Ms Lesley Pavitt

Patient representative

Dr John Reckless

Consultant Physician and Endocrinologist, Royal United Hospital, Bath

Mr Alaster Rutherford (until June 2007)

Head of Medicines Management, Bristol Primary Care Trust

Professor Margaret Thorogood

Professor of Epidemiology, University of Warwick

Professor David Wood

Garfield Weston Chair of Cardiovascular Medicine, Imperial College London

Co-opted Experts

Experts were co-opted onto the GDG to attend meetings at which their expertise was required.

Professor Phillip Bath (Co-optee for secondary prevention and attended the meetings for secondary prevention)

Stroke Association Professor of Stroke Medicine, University of Nottingham

Dr Jane Skinner (representing the Secondary Prevention of MI guideline)

Consultant Community Cardiologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust

Ms Alison Mead

Cardiac Prevention and Rehabilitation Dietitian, Hammersmith NHS Trust and Imperial College

Dr Dermot Neely

Consultant Chemical Pathologist and Lipidologist, Newcastle upon Tyne Hospitals NHS Trust, Royal Victoria Infirmary

Members of the Guideline Development Group from the National Collaborating Centre for Primary Care

Dr Tim Stokes (until December 2006**)**

Clinical Director and Guideline Lead

Dr Norma O'Flynn (from February 2007)

Clinical Director and Guideline Lead

Dr Angela Cooper

Senior Health Services Research Fellow

Mr Leo Nherera

Health Economist

Dr. Neill Calvert

Health Economist

Ms Rifna Mannan (until August 2006)
Health Services Research Fellow

Ms Nicola Browne (from August 2006)
Health Services Research Associate

Ms Gabrielle Shaw (until December 2005)
Project Manager

Ms Charmaine Larment (until July 2006)
Project Manager

Mr Christopher Rule (from August 2006 until September 2007)
Project Manager

Mrs Janette Camosso-Stefinovic
Information Scientist

1.6.4　Guideline Development Group Meetings

The GDG met at 4- to 5- week intervals for 18 months to review the evidence identified by the Development Team, to comment on its quality and relevance and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the full GDG, which met following the consultation to review and agree any changes to the guideline resulting from stakeholder comments

1.7　Care pathways

Two clinical care pathways have been designed to indicate the essential components of lipid modification for the primary and secondary prevention of CVD.

1.7.1 Primary prevention care pathway

A. Population: People aged 40 years or more

B. Exclude people with:
Atherosclerosis: acute coronary syndrome, angina, stroke, transient ischaemic attack, peripheral arterial disease
Type 1 and 2 diabetes
Familial lipid disorders
Clotting disorders or other conditions and treatments known to be associated with increased CVD risk (e.g. HIC patients on treatment)
People in whom preventive treatment for CVD may be inappropriate

C. Prioritise those at greater than 20% CVD risk for formal risk assessment
Estimate prior CVD risk in people 40 years or more using the persons pre-existing record of risk factors or estimates if they are not recorded.
In practice populations rank CVD risk from highest to lowest and prioritise those at 20% risk or more for a formal risk assessment starting with people at highest risk

D. Discuss the consequences and benefits of cardiovascular risk assessment with the patient Discuss the process of formal risk assessment, the management options including treatment and likely benefits or adverse effects. In those wishing to process formally assess CVD risk

E. Self presenting

F. Perform full formal CVD risk assessment
Smoking status
Blood pressure (average 2 readings)
Measure total and HDL cholesterol (non-fasting sample adequate)

Calculate 10 yr CVD risk
Modify risk where appropriate

G. Risk modifiers (Depending on choice of risk equation)
South Asian Men
Positive family history of heart disease
Social deprivation
Obesity
Patient already on treatment for BP, recently stopped smoking, connective tissue diseases

H. Advise all patients where appropriate
Smoking cessation
Anti-hypertensive treatment control BP <140/90mmHg
Diet and weight control, Physical activity
Alcohol reduction

K. CVD risk < 20%
Reinforce lifestyle advice

I. CVD risk 20% or more
Present individualised risk and benefit scenarios for statin treatment using both graphical and written formats

Before starting drug treatment : fasting total cholesterol, HDL cholesterol and triglycerides (if not already available)
Fasting blood glucose, Liver function tests, Renal function
Secondary causes of dyslipidaemia should be considered and excluded before starting lipid therapy. This should include measurement of TSH.

J. Simvastatin 40mg
A lower dose or alternative preparation such as pravastatin may be indicated as a result of clinical contraindications.
Repeat LFT within 3 months and at 1 year but not again unless clinically indicated

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1.7.2 Secondary prevention care pathway

Patients with established cardiovascular disease

Advise all patients where appropriate
Smoking cessation, Diet and weight control, Physical activity, Alcohol reduction

Discuss cardiovascular risks and management options including....
Statin treatment, Blood pressure control, Anti-platelet agents, Post MI: Beta-blockers; ACE inhibitors

A. People with the following:

Angina, stroke, transient ischaemic episode, peripheral arterial disease or other symptomatic atherosclerotic disease

D: Patients with Acute Coronary Syndrome should be treated with high intensity statin

B. Assessment should include

Smoking
Alcohol
Blood pressure
BMI
Fasting total cholesterol, HDL cholesterol and triglycerides (if not already available)
Fasting blood glucose.
Liver function tests
Renal Function
Secondary causes of dyslipidaemia should be considered and treated. This should include measurement of TSH.

C. Initiate treatment with simvastatin 40mg

A lower dose or alternative preparation may be indicated as a result of clinical contraindications

If a level of total cholesterol of < 4mmol/l OR LDL cholesterol of < 2mmol/l is not achieved on the initial dose, increase to simvastatin 80mg or statin of similar potency and acquisition cost.

E.Review   *Repeat LFT within 3 months and at 1 year but not again unless clinically indicated*

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1.8   Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1.8.1   Risk estimation methods

How can CVD risk be best estimated in the population of England and Wales to identify people at high risk of developing CVD for lipid modification therapy?

Why this is important

Current risk estimation is based upon the American Framingham equations which are limited for use in the UK by their development in a historic American population. The Framingham equations overestimate risk by up to 50% in contemporary northern European populations, particularly people living in more affluent areas. They underestimate risk in higher risk populations, such as those that are most socially deprived. Framingham makes no allowance for family history of premature CHD and does not take account of ethnicity, but does have a full dataset. Two new risk scores have recently been developed in the UK. ASSIGN was developed using a Scottish cohort and QRISK using data from UK general practice databases. These scores have the advantage of including other variables such as measures of social deprivation and family history. There is an urgent need to establish which score is most acceptable for use in the population of England and Wales. NICE should review the relevant recommendations relating to risk assessment as soon as sufficient new data are available to address this.

Research is required:

- to adjust Framingham for use in the UK population, to assess the use of ASSIGN in UK populations outside Scotland, to validate QRISK in independent and clinical datasets and to assess the performance of the scores against each other
- to assess the feasibility of using scores with an increased number of variables, such as social deprivation, in routine

clinical practice, particularly in community and secondary care settings where access to patient electronic records and computers is less likely to be available

- to assess the added value of including variables such as ethnicity, alcohol intake and chronic kidney disease to risk assessment scores.

1.8.2 Plant sterols and stanols

What is the effectiveness of plant sterols and stanols in people who are at high risk of a first CVD event?

Why this is important

Some people at increased risk of CVD might avoid the need to use drugs to modify their cholesterol levels if they make sufficient changes to their diet. Plant sterols and stanols have been shown to reduce cholesterol levels, but it is not known whether the consumption of plant sterols as part of a low-fat diet will provide worthwhile additional benefit and whether they reduce CVD events.

There is a need for trials to test both efficacy and effectiveness of plant sterols and stanols in people who are at high risk of a first CVD event. These trials should test whether plant sterols or stanols change lipid profiles and reduce CVD events under best possible conditions. Randomised controlled trials are needed to test the effectiveness of advising people who are at high risk of experiencing a first CVD event to include food items containing plant sterols or stanols in a low fat diet. The trial should last for at least 2 years and should consider appropriate outcomes.

1.8.3 Communication of CVD risk

How is CVD risk most effectively communicated to patients? What methods are best and how do these differ for particular groups, such as older people or members of minority ethnic groups?

Why this is important

The methods of risk communication (both the content and means of delivery) should be guided by current evidence. Controlled trials should be conducted comparing the impact of different methods of risk communication and decision aids on patient comprehension, the patient experience of decision-making and actual treatment decisions taken by patients. The aim should be to generate evidence to support the improvement of risk communication and patient decision-making. The content should include absolute rather than relative risks. Numerical data should be presented in both words and numbers, and visual and graphical aids should be used. Such studies might consider a number of delivery mechanisms, including advice from a clinician, a trained 'coach', self-accessed educational presentations via computer or DVDs, peer or lay advisers, and other appropriate means. Trials should also investigate the preferences and views of people from different ethnic groups and of different ages and sex.

1.8.4 Impact of decision aids

What is the impact of using clinical decision aids that include an assessment of absolute risk to prioritise the prescription of risk-reducing treatment for the primary prevention of CVD?

Why this is important

Risk scoring methods are recommended to help target preventive treatment at people who are asymptomatic but at high risk of CVD. As with any health technology, risk scoring methods should be shown to favourably influence individual people's health outcomes or risk factors, if they are to be used in primary prevention strategies.

There are no studies involving risk scoring methods in general community populations. Importantly, there is no evidence to support the use of computer-based clinical decision support systems in the primary prevention of CVD.

Being offered long-term primary prevention treatment, or not, is highly significant for individuals, and because of the large numbers of people involved, the medical, financial and social implications for society are

considerable. Although the use of clinical decision aids incorporating CVD risk assessment has intuitive appeal and is encouraged in guidelines, the components of an effective decision aid and its impact on individuals remain almost completely unknown.

Outcomes should include morbidity, individual absolute risk, adverse effects, changes in risk behaviours such as smoking, changes in treatment, and a qualitative assessment of the views of both the clinicians using the decision aids and the people being prioritised to either receive preventive treatment or not.

1.8.5 Treating to target

What is the clinical and cost effectiveness of incremental lipid lowering with HMG CoA reductase inhibitors (statins) and/or ezetimibe to reduce CVD events: (i) in people without established CVD disease who have a 20% or greater risk of CVD events over 10 years; (ii) in people with established CVD?

Why this is important

Several studies with CVD outcomes were identified during the development of this guideline that randomised participants to specific doses of statins to assess the additional effect of higher intensity statins versus lower intensity statins. The incremental cost effectiveness (including adverse events) of these drugs (either alone or in combination with other classes of drug) to reduce CVD events by treating to target levels of total cholesterol of either 5 mmol/litre or 4 mmol/litre (or comparable LDL cholesterol levels) is unknown.

1.8.6 Vascular dementia

Does lowering cholesterol with statins reduce cognitive decline and dementia in patients with prior stroke and other vascular events?

Why is this important?

People who have had a stroke are at a very increased risk of losing the ability to think and remember things ('cognitive decline') and of developing dementia. Approximately half of dementia is related to poor circulation in the brain

('vascular dementia'). Statins reduce blood cholesterol levels and the development of narrow blood vessels, and vascular events including stroke and myocardial infarction. However, it is not known whether statins reduce cognitive decline and vascular dementia. There is a need for trials to test the efficacy of statins on cognitive function in people who have had a previous stroke. Since most people with a recent stroke are taking a statin, trials might compare the intensity of statin treatment in preventing cognitive decline and dementia.

1.9   Acknowledgements

The staff at NICE who have helped us with this guideline in particular Dr. Phil Alderson, Sarah Willet and Colette Marshall.

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Prof Alistair Gray for his contribution to the economic models.

1.10 Glossary

Acute coronary syndrome (ACS)	Acute coronary syndrome refers to a spectrum of acute myocardial ischaemic states from unstable angina to transmural myocardial infarction
Absolute risk reduction	Absolute risk reduction refers to the difference in new events between the treatment under investigation and the placebo or comparator drug. If treatment A results in 5/1000 CVD events per year and treatment B results in 10/1000 CVD events per year, the absolute risk reduction is 10/1000 minus 5/1000 =5/1000 per year.
Atherosclerosis	A general term describing hardening, narrowing and loss of elasticity of arteries. It results from a deposition of rigid collagen in the arterial wall and also from the development of fatty plaques or atheroma on the inside of the artery wall. This increases the stiffness, decreases the elasticity of the artery wall and narrows the artery. The deposition of dietary fat as atheroma is the major factor in atherosclerosis which may be made worse by high blood pressure, smoking or other factors particularly when several factors are present at the same time. Atheromatous plaques may then be the site of blood clots that further narrow or even close the artery with resulting loss of oxygen and damage to the affected organ.
Cardiovascular event	Fatal or non-fatal myocardial infarct; acute coronary syndrome; fatal or non-fatal stroke; transient ischaemic attack
Cardiovascular risk (CVD)	The risk of a cardiovascular event occurring
Cardiovascular risk assessment	Involves the use of predictive equations and the adjustment of cardiovascular risk estimates based on clinical assessment or social factors such as ethnicity, family history or social deprivation or other relevant factors.
Cardiovascular outcomes	One or more of the following: death from stroke or myocardial infarction; non-fatal myocardial infarction or stroke; transient ischaemic episodes; acute coronary syndrome; angina; clinical interventions such as revascularisation are also considered as outcomes in some studies.
CVD: cardiovascular disease	In this document CVD refers to the combined outcome fatal and non-fatal myocardial infarction, fatal and non fatal stroke, transient ischaemic attack, angina and acute coronary syndrome.
Clinical care pathway	A series of clinical processes that a patient might experience. For example CVD risk assessment – consideration of management options – treatment – follow-up.
Clinical risk stratification	A method of allocating patients to different levels of risk of them suffering an adverse event, based on their clinical characteristics

Cost-benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-minimisation analysis	An economic evaluation that finds the least costly alternative therapy after the proposed interventions has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and toxicity.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Incremental Cost effectiveness ratio	Is the difference in costs between two interventions being compared divided by the difference in effect of the two interventions. For instance if A and B are being compared Cost of A – costs of B divided by effects of A- effects of B.
Decision analysis	A systematic way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.
Discounting	Costs and benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominant if there is an alternative intervention that is both less costly and more effective.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature
Evidence-based questions (EBQs)	Questions that are based on a conscientious, explicit and judicious use of current best evidence
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of healthcare resources.
Health-related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.

High intensity statin	High intensity statin is the term used in the guideline to indicate statins whose effect on cholesterol lowering is greater than that of simvastatin 40mg. This includes simvastatin 80mg. The statin lowering effect of drugs at different doses are listed in table 7 in chapter 7.
ICER	Incremental cost effectiveness ratio – this is the difference between the mean costs in the population of interest divided by the difference in the mean outcomes in the population of interest
Life-year	A measure of health outcome that shows the number of years of remaining life expectancy.
Life-years gained	Average years of life gained per person as a result o fan intervention.
Median	The value at the halfway mark when data are ranked in order.
Meta-regression analysis	An approach for aggregating data from different clinical trials that examine the same question and report the same outcomes, and relating sources of variation in treatment effects to specific study characteristics.
Myocardial infarction (MI)	Event that results in necrosis of heart muscle.
Multiple logistic regression analysis	In a clinical study, an approach to examine which variables independently explain an outcome
Number needed to harm (NNH)	The number of people who need to be treated with a drug in order to harm one person in a set period of time.
Open-labelled randomised trial	A study in which patients are randomised to one treatment or another, and in which the clinician or investigator is aware of which treatment arm the patient is in.
Opportunity cost	.The opportunity cost of investing in a healthcare intervention is the other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Primary prevention	In the context of this document, primary prevention refers to interventions to modify lifestyle or drug treatments, in people who have not already got established cardiovascular disease. This particular guidance excludes people with diabetes.
Probabilistic sensitivity analysis	Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Quality adjusted life-years (QALYS)	An index of survival that is adjusted to account for the person's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis, QALYS are calculated by estimating the number of years of life gained from a treatment and weighting each year with a quality-of-life score between zero and one.
Relative risk reduction	The relative risk reduction is the proportionate reduction in risk between the drug under investigation and a placebo or comparator drug. If treatment A results in 5/1000 CVD events per year and treatment B results in 10/1000 CVD events per year, the relative risk reduction is 5/10 =50%.
Secondary prevention	In the context of this document secondary prevention refers to interventions to modify lifestyle or drug treatments in people who already have established cardiovascular disease.
Time horizon	The time span used in the NICE appraisal that reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.

2   Methods

2.1   Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the NICE in 'Clinical guideline development methods' (2006) (available at: http://www.nice.org.uk/).

2.2   Developing key clinical questions

The first step in the development of the guideline was to refine the guideline scope into a series of key clinical questions (KCQs). These KCQs formed the starting point for the subsequent review and as a guide to facilitate the development of recommendations by the GDG.

The KCQs were developed by the GDG with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs), specifying the interventions and outcomes to be searched for by the methodology team. These EBQs formed the basis for literature searching, appraisal and synthesis.

The total list of KCQs identified is shown in Appendix F. The methodology team and the GDG agreed that a full literature search and critical appraisal should not be undertaken for all of these KCQs in view of the time and resource limitations within the guideline development process. The methodology team, in liaison with the GDG, identified those KCQs where literature searches and critical appraisal were essential. Literature searches were not undertaken where there was already national guidance on the topic to which the guideline could cross refer. This is detailed in section 2.10 (The relationship between the guideline and other national guidance).

2.3   Literature search strategy

The purpose of searching the literature is to identify published evidence that can be used to answer the clinical questions identified by the methodology

team and the GDG. The Information Scientist developed search strategies for each searchable question, with guidance from the GDG, using relevant MeSH (medical subject headings) or indexing terms, and relevant free text terms. Searches were conducted between September 2005 and August 2006. The Information Specialist agreed in advance with the Reviewer and Health Economist the sources to be searched for a given question. The parameters of literature searches, including any population limits and exclusions, were detailed on pro formas developed for each question. Updated searches for each question, to identify recent evidence, were carried out in April 2007. Full details of the sources and databases searched and the search strategies are contained in Appendix F.

An initial search for published guidelines or systematic reviews was carried out on the following databases or websites: National Electronic Library for Health (NeLH) Guidelines Finder, National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, BMJ Clinical Evidence, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA).

If a recent, high quality, systematic review or guideline was identified to answer a clinical question, then in some instances no further searching was carried out.

Depending on the question, some or all of the following bibliographic databases were also searched to the latest date available: MEDLINE, EMBASE, CINAHL, CENTRAL (Cochrane Controlled Trials Register), PsycINFO, Allied & Complementary Medicine (AMED).

2.4   Identifying the evidence

After the search of titles and abstracts was undertaken, full papers were obtained if – based on abstract and title – they appeared relevant to the topic addressed in the GDG's question. The highest level of evidence was sought first. Wherever appropriate, the searches for evidence for both primary and secondary cardiovascular disease prevention were conducted simultaneously, and the results of these were then scanned to address separate questions. Where randomised controlled trials were not available, observational studies, surveys and expert formal consensus results were used. Only papers published in English were reviewed. Following a critical review of the full version of the study, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded. Submitted evidence from stakeholders was included where the evidence was relevant to the GDG's clinical question and when it was either better or equivalent in quality to the research identified in the literature searches. Specialist advice was obtained from a dietitian, Alison Mead, to aid in the identification of useful terms for inclusion in searches for questions relating to lifestyle interventions.

The reasons for rejecting any paper ordered were recorded.

2.5   Critical appraisal of the evidence

The Systematic Reviewer synthesised the evidence from the papers retrieved for each question or questions into a narrative summary. These formed the basis of this guideline. Each study was critically appraised using NICE criteria for quality assessment. The information extracted from the included studies is given in Appendices D and E. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

2.6   Economic analysis

The essence of economic evaluation is that it provides a balance sheet of the benefits and harms as well as the costs of each option. A well conducted

economic evaluation will help to identify, measure, value and compare costs and consequences of alternative policy options. Thus, the starting point of an economic appraisal is to ensure that health services are clinically effective and cost-effective. Although NICE does not have a threshold for cost-effectiveness, interventions with a cost per quality adjusted life-year of up to £20 000 are deemed cost-effective, those between £20 000 and £30 000 may be cost-effective and those above £30 000 are unlikely to be judged cost-effective. If a particular treatment strategy was found to yield little health gain relative to the resources used, then it could be advantageous to redeploy resources to other activities that yield greater health gain.

To assess the cost-effectiveness of the different policy questions for this guideline, a comprehensive systematic review of the economic literature relating to primary and secondary prevention of cardiovascular disease was conducted. For selected components of the guideline original cost-effectiveness analyses were performed.

Literature review for health economics
The following information sources were searched: Medline (Ovid) (1966- April 2007), Embase (1980-April 2007), NHS Economic Evaluations Database (NHS EED), PsycINFO and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

The electronic search strategies were developed in Medline and adapted for use with the other information databases. The clinical search strategy was supplemented with economic search terms. The Information Scientist carried out the searches for health economics evidence. Identified titles and abstracts from the economic searches were reviewed by a single health economist and full papers obtained as appropriate. No criteria for study design were imposed a priori. In this way the searches were not constrained to randomised controlled trials (RCTs) containing formal economic evaluations.

Papers were included if they were full/partial economic evaluations, considered patients at risk of or those who have had a cardiovascular event. Thus, patients who have had stroke, angina, peripheral artery disease,

transient ischaemic stroke or myocardial infarction were considered for the secondary prevention section. Only papers written in English were considered.

The full papers were critically appraised by the health economist using a standard validated checklist (Drummond, M. F. and Jefferson, T. O., 1996). A general descriptive overview of the studies, their quality, and conclusions was presented and summarised in the form of a narrative review.

Cost-effectiveness modelling

Some areas were selected for further economic analysis if there was likelihood that the recommendation made would substantially change clinical practice in the NHS and have important consequences for resource use. For this guideline three areas were chosen for further economic analysis:

- Cost-effectiveness of strategies for identification of patients at high risk of CVD in primary care

- Cost-effectiveness of high intensity statins compared with lower intensity statins in patients with coronary heart disease

- Cost-effectiveness of a strategy of 'titration threshold' (treating to target of 5mmol/l and 4mmol/l) compared with a strategy of using a standard dose of statin in people with CVD including a full incremental analysis.

Full reports for each topic are in Appendix C of the guideline. The GDG was consulted during the construction and interpretation of each model to ensure that appropriate assumptions, model structure and data sources were used. All models were constructed in accordance with the NICE reference case outlined in the 'Guideline technical manual' (2007).

2.7   Forming recommendations

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any changes were made to the electronic version of the text on a laptop and projected onto a screen until the GDG were satisfied with them.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

The recommendations and evidence statements were posted on an electronic forum. The discussion was reviewed at the next meeting and the recommendations finalised.

2.8   Areas without evidence and consensus methodology

The table of clinical questions in Appendix F indicates which questions were searched.

In cases where evidence was sparse, or where the question was not deemed searchable, the GDG derived the recommendations via informal consensus methods, for example in the case of Question 23: 'How necessary is it to monitor liver function tests?'

In a few cases where there was a lack of consensus a formal vote was taken. Cooptees and GDG members with a declared interest did not vote.

2.9   Consultation

The guideline has been developed in accordance with the NICE guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the drafts of the full and short versions of the guideline. In addition, the draft was reviewed by an independent Guideline Review Panel (GRP) established by NICE.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were

considered systematically by the GDG and the project team recorded the agreed responses.

2.10 The relationship between the guideline and other national guidance

2.10.1 Related NICE guidance

It was identified that this guideline intersected with the following NICE guidelines published or in development. Cross reference was made to the following guidelines when appropriate.

Published

Clinical guidelines:

- MI: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from www.nice.org/CG048
- Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43 (2006). Available from www.nice.org/CG043
- Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). Available from www.nice.org/CG033
- Type 2 diabetes: the management of type 2 diabetes (update). NICE clinical guideline 66 (2008). Available from www.nice.org.uk/CG066

Public health intervention guidelines:

- Brief interventions and referral for smoking cessation in primary care and other settings. NICE Public health intervention guidance 1 (2006). Available from www.nice.org/PHI001
- Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling. NICE

public health intervention guidance 2 (2006). Available from www.nice.org.uk/PHI002

- Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities. NICE public health guidance 10 (2008). Available from www.nice.org.uk/PH010

Technology appraisal guidance:

- Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007). Available from www.nice.org.uk/TA132
- Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from www.nice.org/TA094
- Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation. NICE technology appraisal guidance 39 (2002). Available from www.nice.org/TA039

- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from www.nice.org.uk/TA123

Under development
- Familial hypercholesterolemia: identification and management. NICE clinical guideline. Publication expected August 2008.

Amended March 2010 Identification and management of familial hypercholesterolaemia' (NICE clinical guideline 71). Available from www.nice.org.uk/guidance/CG71

2.10.2 Other national guidance

In formulating recommendations consideration was given to:

- National Service Framework (NSF) for Coronary Heart Disease (2000).

- JBS 2: Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice (2005)

Lipid modification: Full Guideline May 2008 (revised March 2010)

Reference was made to the Food Standards Agency website (www.eatwell.gov.uk/healthydiet/) for advice on cardioprotective dietary changes.

Reference was made to the Chief Medical Officer's report 2004 a: www.dh.gov.uk for advice on physical activity.

Through review of published guidance, personal contact and commenting on guideline scope, endeavours were made to ensure that boundaries between guidance were clear and advice was consistent.

3 Identification and assessment of people at high risk of cardiovascular disease (CVD)

3.1 Recommendations

Identifying people requiring full formal risk assessment

[Hyperlink to Evidence Statements & Narratives]

3.1.1 For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people aged between 40 and 74 who are likely to be at high risk.

3.1.2 People should be prioritised on the basis of an estimate of their CVD risk before a full formal risk assessment. Their CVD risk should be estimated using CVD risk factors already recorded in primary care electronic medical records.

3.1.3 People older than 40 should have their estimate of CVD risk reviewed on an ongoing basis.

3.1.4 People should be prioritised for a full formal risk assessment if their estimated 10-year risk of CVD is 20% or more.

3.1.5 Healthcare professionals should discuss the process of risk assessment with the person identified as being at risk, including the option of declining any formal risk assessment.

3.1.6 Opportunistic assessment should not be the main strategy used in primary care to identify CVD risk in unselected people.

Full formal risk assessment

[Hyperlink to Evidence Statements & Narratives]

NICE Guidance Executive agreed in February 2010 that the Framingham risk equation should no longer be considered the equation of choice for the assessment of CVD risk but should be considered one of the possible equations to use. The recommendations that relate specifically to the use and modification of the Framingham risk equation are indicated and listed in a separate section below.

3.1.7   Healthcare professionals should always be aware that all CVD risk estimation tools can provide only an approximation of CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement.

3.1.8   Risk equations should be used to assess CVD risk[5].

3.1.9   This recommendation relates specifically to the use or modification of the Framingham risk equation – see below

3.1.10   Risk equations should not be used for people with pre-existing:

- **CHD or angina**
- **stroke or transient ischaemic attack**
- **peripheral vascular disease. [8]**

3.1.11   Risk equations should not be used for people who are already considered at high risk of CVD because of:

- **familial hypercholesterolaemia[6] or other monogenic disorders of lipid metabolism**
- **diabetes, see 'Type 2 diabetes: the management of type 2 diabetes (update)' (NICE clinical guideline 66). [8]**

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[5] This recommendation has been modified in line with decision taken by NICE Guidance Executive in February 2010 that the Framingham risk equation should no longer be considered the equation of choice for assessment of CVD risk, but should be considered as one of the possible equations to use.

[6] See 'Identification and management of familial hypercholesterolaemia' (NICE clinical guideline 71). Available from www.nice.org.uk/guidance/CG71

Lipid modification: Full Guideline May 2008 (revised March 2010)

3.1.12 This recommendation relates specifically to the use or modification of the Framingham risk equation – see below.

3.1.13 **When using the risk score to inform drug treatment decisions, particularly if it is near to the threshold of 20%[7], healthcare professionals should consider other factors that:**

- **may predispose the person to premature CVD, and**
- **may not be included in calculated risk scores.**

3.1.14 **Ethnicity, body mass index and family history of premature heart disease should be routinely recorded in medical records.**

3.1.15 This recommendation relates specifically to the use or modification of the Framingham risk equation – see below.

3.1.16 This recommendation relates specifically to the use or modification of the Framingham risk equation – see below.

3.1.17 This recommendation relates specifically to the use or modification of the Framingham risk equation – see below.

3.1.18 **Socioeconomic status should be considered when using CVD risk scores to inform treatment decisions.**

3.1.19 **Severe obesity (body mass index greater than 40 kg/m^2) affects CVD risk and should be considered when using risk scores to inform treatment decisions (see 'Obesity', NICE clinical guideline 43).**

3.1.20 **CVD risk may be underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Clinical judgement should be**

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used to decide on further treatment of risk factors in people who are below the 20% CVD risk threshold.

3.1.21 CVD risk scores may not be appropriate as a way of assessing risk in people who are at increased CVD risk because of underlying medical conditions or treatments. These include people treated for HIV or with antipsychotic medication, people with chronic kidney disease[8] and people with autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.

3.1.22 People aged 75 or older should be considered at increased risk of CVD, particularly people who smoke or have raised blood pressure. They are likely to benefit from statin treatment. Assessment and treatment should be guided by the benefits and risks of treatment, informed preference and comorbidities that may make treatment inappropriate.

Recommendations relating specifically to the use and modification of the Framingham risk equation for the assessment of CVD risk. These recommendations should be considered when using Framingham risk equation.

3.1.9   The following variables should be used for formal estimation of CVD risk with the Framingham 1991 equations:

- age
- sex
- systolic blood pressure (mean of previous two systolic readings)
- total cholesterol
- HDL cholesterol
- smoking status
- presence of left ventricular hypertrophy.

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[8] See 'Chronic kidney disease' NICE clinical guideline 73). Available from www.nice.org.uk/uidance/CG73

Lipid modification: Full Guideline May 2008 (revised March 2010)

3.1.12   Healthcare professionals should be aware that Framingham 1991 risk equations may overestimate risk in UK populations.

3.1.15   The estimated CVD risk should be increased by a factor of 1.5 in people with a first-degree relative with a history of premature CHD (age at onset younger than 55 in fathers, sons or brothers or younger than 65 in mothers, daughters or sisters).

3.1.16   The estimated CVD risk should be increased by a factor of between 1.5 and 2.0 if more than one first-degree relative has a history of premature CHD.

3.1.17   The estimated CVD risk for men with a South Asian background should be increased by a factor of 1.4.

Lipid measurement

[Hyperlink to Evidence Statements & Narratives]

3.1.23 **Both total and HDL cholesterol should be measured to achieve the best estimate of CVD risk equations.**

3.1.24 **Before starting lipid modification therapy for primary prevention, people should have at least one fasting lipid sample taken to measure total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.**

3.1.25 **People in whom familial hypercholesterolaemia or other monogenic disorders are suspected because of a combination of clinical findings, lipid profiles and family history of premature CHD should be considered for further investigation and specialist review[9].**

3.1.26 **People with severe hyperlipidaemia should be considered for further investigation and/or specialist review.**

3.2 Identification of people requiring assessment of CVD risk

3.2.1 **Evidence statements for the identification of people at high risk of developing CVD**

> *3.2.1.1 Economic modelling in an English primary care population showed that the most efficient strategy for identifying people at high risk of developing CVD is one which initially prioritises individuals based upon a prior estimate of their CVD risk using data already held in general practitioners' electronic medical records compared to using age or random assessment.*

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[9] See www.nice.org/uk for more details.

Lipid modification: Full Guideline May 2008 (revised March 2010)

3.2.2 Clinical effectiveness of identification of people requiring assessment of CVD risk

In current clinical practice formal assessment of cardiovascular risk is done opportunistically. Entry into formal cardiovascular risk assessment is dependent on whether a person consults their general practitioner/general practice and or whether a risk factor such as high total cholesterol or high blood pressure is identified. This is also dependent on whether the clinician has the opportunity or makes the clinical decision to consider other issues in the consultation. This is therefore a two-stage process in which some initial choice is made over who receives a formal risk assessment. This has resulted in relatively low levels of both risk estimation and treatment of people at high risk of CVD and may also lead to treatment of people who are not at high risk by current criteria (Primatesta, P. and Poulter, N. R., 2004), (Primatesta, P. and Poulter, N. R., 2006), (McElduff, P., Lyratzopoulos, G., Edwards, R. et al , 2004).

To improve primary prevention people at high risk must be identified and managed in the most efficient and coherent way. Half of men over 50 years and 20% of women over 65 years have a CVD risk of 20% or more. Within this group are people who have risks in excess of 30% or even 40%. A systematic approach to selection requires prior stratification of risk so that those at highest risk are reviewed first. This will result in a more effective choice of people for inclusion and a more efficient use of staff time and health service resources than an opportunistic approach.

This is not to say that people should never be assessed opportunistically outside of their rank order. Primary care will always involve random assessment initiated by either the patient or the clinician.

General practice records are now universally computerised and a high proportion of people have recording of smoking, blood pressure and, to a lesser extent, serum lipids. These records contain most of the information necessary to generate a prior estimate of cardiovascular risk based on existing data. Where data are missing they can be imputed on the basis of

age- and sex-specific values drawn from population surveys (Marshall, T., 2006).

Using the recommended CVD risk equations, a prior estimate of CVD risk based on pre-existing information can be obtained and the practice population can be ranked from highest to lowest risk. Starting with those at highest risk, people can then be invited for a formal clinical assessment and risk factor estimation based on the measurement of blood pressure, lipids and current smoking status and taking account of other relevant factors such as family history, ethnicity and social or clinical circumstance.

3.2.3 Cost-effectiveness identification of people requiring assessment of CVD risk

There were no full economic evaluation studies found discussing the identification strategies of patients eligible for CVD prevention in a primary care population. Marshall and Rouse modeled the costs and outcomes of a series of strategies for identification of patients eligible for CVD prevention in a primary care population (Marshall, T. and Rouse, A., 2002). The GDG requested Marshall's work be updated. The update included a markov model estimating QALY gain from lifetime treatment with statins and the costs in different age bands and CVD risk bands. We used data derived from the Health Survey for England 2003 which consisted of 4264 individuals aged 30 to 74, free from CVD and without diabetes.

Various strategies were considered for identification of patients, the main comparisons being made between:

- Random assessment whereby patients are assessed in random order.

- Prioritisation by age whereby older individuals are assessed first

- Prioritisation by age those aged over 50 then over 40 years

- Prioritisation by a prior estimate of CVD risk whereby ten-year CVD risk is calculated for every individual based on risk factor data held in their electronic medical records

The cost effectiveness outcome was cost per QALY by decile for the different strategies. The most efficient strategy will allocate people to treatment earlier, thus they will benefit from the statins. It will also misclassify fewer people as needing treatment when they don't need it.

If all 4264 patients were assessed, the model estimates that 652 individuals will be diagnosed as clinically eligible for treatment. Untreated, we would expect these individuals to suffer from 81 CVD events over the next ten years. We would expect the 652 individuals diagnosed as clinically eligible for treatment to include 14 (2% of the total) individuals at low risk of CVD (less than 10% ten-year CVD risk) who had been misclassified as eligible for treatment. The screening process will identify 1% of the population aged between 35-44 years as eligible while the majority 87% of the patients will be aged over 65.

The cost-effectiveness results showed that using prior CVD information is the most cost-effective method of identifying those at risk of developing heart disease. When all the relevant 12 strategies are compared, the analysis suggests that it's cost-effective to screen 20% of the relevant population. The ICER is about £7,604/QALY when prior CVD is compared with the next best non-dominated option (10% prior CVD). The ICER for 30% prior CVD compared with the next best non-dominated option (20% prior CVD) is about £37,644 per QALY.

Conclusions

Primary prevention of CVD should make use of strategies to prioritise patients likely to be at highest risk and to invite patients in descending order of CVD risk estimated from available data in the GP database. UK general practices have enough data to use this systematic way. .

3.3   Assessment of cardiovascular risk

3.3.1   Introduction

Estimates of CVD risk derived from equations are not an exact science but are better than clinical judgment alone for the estimation of CVD risk.

A number of risk assessment equations are available that estimate cardiovascular risk in individuals. They have been derived from studies of individuals who have been followed up often for substantial lengths of time. Risk assessment equations predict risk best in the type of population from which they were derived. Equations derived from North American populations from the 1960s to the 1980s when coronary heart disease (CHD) was at its peak overestimate risk in contemporary European populations by around 100% in Southern European populations and by 50% or more in Northern European populations including the UK. Conversely, such equations may underestimate risk in populations such as people with diabetes, South Asian men or the most socially deprived who are at higher than average risk.

3.3.2 Evidence statements for assessment of cardiovascular risk

[Return to Recommendations]

3.3.2.1	*Different risk assessment methods exist. The most widely used and researched are derived from the Framingham cohort.*
3.3.2.2	*In representative populations, recognised Framingham-based methods offer reasonable discrimination between high- and low-risk individuals but tend to overestimate the absolute risk of CVD in lower risk populations and underestimate risk in high-risk populations. There has been concern that estimates derived from North American populations dating back 30 years may not accurately estimate risk in contemporary European populations when CHD mortality has fallen by more than half during this period. Overall the Framingham risk equation is likely to overestimate risk in the current UK population, more so in Southern England than Northern England or Scotland.*
3.3.2.3	*Framingham-based methods may underestimate risk in people at high risk such as people with a strong family history of premature CVD, certain ethnic groups and those from relatively socio-economically deprived backgrounds. They may also underestimate risk in people with extreme risk factors or other clinical risks not included in the model.*
3.3.2.4	*There are no consistent differences in the generalisability of one Framingham model over another.*
3.3.2.5	*The following endpoints have been used by the statin technology appraisal report to establish treatment thresholds: fatal and non-fatal myocardial infarction, acute coronary syndrome, stable angina, stroke, and transient ischaemic attacks. (NICE technology*

	appraisal 94, 'Statins for the prevention of cardiovascular events').
3.3.2.6	*When used in conjunction with the Framingham estimates, those defined by the NICE Technology Appraisal are the most appropriate. When considering management strategies based on other risk equations, endpoints such as revascularisation, peripheral arterial disease and other disease processes associated with atherosclerosis may also be relevant.*
3.3.2.7	*Framingham based risk scoring methods do not accurately estimate risks in some groups of people.*
3.3.2.8	*Several risk factors have not been included in the Framingham risk equations and some adjustment of this risk estimate may be required to more accurately represent an individual's absolute risk:* • *Family history of a premature event from CVD: first-degree male relatives under the age of 55 years and first-degree female relatives under the age of 65 years* • *Ethnic group* • *Socio-economic status* • *People already on treatment that modifies CV risk* • *Extremes of risk factors, for example people who have a body mass index over 40 kg/m^2.*
3.3.2.9	*There are differences in cardiovascular risk between black and minority ethnic groups and the white population in England and Wales.*
3.3.2.10	*For men, the risk of CVD was higher in South Asian ethnic groups (with some subgroup heterogeneity) than for men in the white population.*
3.3.2.11	*For men there is no robust evidence for a difference in the risks of CVD other than that between men from South Asian ethnic groups*

	and the general population.
3.3.2.12	*For women there is no robust evidence for a difference in the risks of CVD between South Asian ethnic groups (with considerable subgroup heterogeneity) and the general population.*
3.3.2.13	*There is increased risk of CVD in people with a family history of premature CVD.*
3.3.2.14	*Cohort studies have shown a consistent association between having a positive family history of CVD and an increased risk of developing CVD. This risk remains even when adjusted for age, socioeconomic status, body mass index, systolic blood pressure, blood lipids (cholesterol, triglycerides), fasting glucose and smoking status. The exact relative risk varies according to sex and nature of relationship between the individual with premature CVD and the index case.*
3.3.2.15	*The younger the age at which the family event occurred and the greater the number of family members involved, the greater the relative risk.*
3.3.2.16	*Cardiovascular risk is closely associated with socio-economic status. Framingham equations do not include socio-economic status and underestimate risk in people who are relatively socially deprived. The use of equations that do not include a measure of socio-economic status may exacerbate inequalities in CVD.*
3.3.2.17	*ASSIGN is a CV risk score developed in a Scottish cohort that includes similar variables to Framingham in addition to an index of social status based on postcode of residence at recruitment, and family history of CVD.*
3.3.2.18	*The ASSIGN score improved discrimination of estimated 10 year*

	CVD risk in a Scottish cohort compared with Framingham.
3.3.2.19	*Observed CVD risk in the Scottish cohort varied significantly according to socioeconomic status. Framingham risk score estimates did not reflect this significant variation, while estimates using the ASSIGN score correlated with socioeconomic status*
3.3.2.20	*QRISK is a new risk score that has been developed using routine data from UK electronic primary care patient records.*
3.3.2.21	*QRISK includes social deprivation, family history, body mass index and antihypertensive treatment that are not included in the Framingham equation.*
3.3.2.22	*Initial validation of the QRISK score in a UK electronic primary care patient cohort found that QRISK was a better discriminator of CVD risk compared with the Framingham risk score.*
3.3.2.23	*The performance of the QRISK score for predicting CVD risk was assessed in a second UK medical records database. A revised equation for QRISK was used that improved the method for multiple imputation of missing data by including the following; binary variables for diagnosis of hypertension and incident diabetes, and continuous variables for the number of prescriptions for aspirin, statins and antihypertensive treatments for each patient during the study period. A correction was also made regarding the total cholesterol to HDL cholesterol ratio. The revised QRISK score was more predictive of CVD risk in the second UK cohort compared with the Framingham risk score.*
3.3.2.24	*Little evidence was found supporting or refuting the assumption that CVD assessment by clinicians improves health outcomes. The interventions showed no improvement in predicted absolute CVD risk or in declared primary outcomes.*

3.3.2.25	*A study in hypertensive patients has shown a small reduction in systolic blood pressure associated with the use of a risk chart but not when used in conjunction with a computer based clinical decision support system.*
3.3.2.26	*Another study has shown very low uptake of risk-scoring methods by clinicians that would have obscured any beneficial effect on blood pressure by the intervention.*
3.3.2.27	*The accuracy of use of chart based systems has been questioned. Current evidence is an insufficient basis on which to judge the effectiveness of CVD risk estimation as a method of improving health outcomes.*

3.3.3 Methods for multiple risk factor assessment to estimate absolute cardiovascular risk in people who are at risk of CVD

A recent systematic review (Beswick, A. D., Brindle, P., Fahey, T. et al , 2008) (Appendix J) was used as the evidence source. Literature searching beyond the search date of the systematic review identified two further risk scores developed in UK populations (QRISK discussed in section 3.3.5, and ASSIGN discussed in section 3.3.5). The Beswick *et al* systematic review compared the accuracy of risk scoring methods such as charts and tables compared with full prediction models, namely, the Framingham-Anderson model of 1991(Anderson, K. M., 1991). A complete reference to the materials and evidence reviewed is given in Appendix J.

Eleven derived risk charts, tables and nomograms were identified comparing risk calculations with the original Framingham-Anderson prediction model (1991).

The tools identified were as follows:

- Sheffield tables (2 versions) (Haq, I. U., Jackson, P. R., Yeo, W. W. et al , 1995) (Ramsay, L. E., Haq, I. U., Jackson, P. R. et al , 1996) (Wallis, E. J., Ramsay, L. E., Ul, Haqi et al , 2000)

- Joint British Societies (JBS) charts (2 versions) (Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, British Diabetic Association, 2000) (Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association, 1998)

- Joint European Societies (JBS) charts (2 versions) (Wood, D., De, BackerG, Faergeman, O. et al , 1998) (Conroy, R. M., Pyorala, K., Fitzgerald, A. P. et al , 2003)

- Canadian nomograms (McCormack, J. P., Levine, M., and Rangno, R. E., 1997)

- New Zealand charts (3 versions) (1996 National Heart Foundation clinical guidelines for the assessment and management of dyslipidaemia. Dyslipidaemia Advisory Group on behalf of the scientific committee of the National Heart Foundation of New Zealand., 1996) (McLeod, A. J. and Armitage, M., 1998) (Jackson, R., 2000)

- World Health Organization and the International Society for Hypertension (WHO-ISH) chart http://www.ish-world.com/default.aspx?Guidelines.

It was found that the early versions of the Sheffield Tables (Haq, I. U., Jackson, P. R., Yeo, W. W. et al , 1995) (Ramsay, L. E., Haq, I. U., Jackson, P. R. et al , 1996) and the Joint European Societies charts (Wood, D., De, BackerG, Faergeman, O. et al , 1998) (Conroy, R. M., Pyorala, K., Fitzgerald, A. P. et al , 2003) had poor sensitivity as they did not include individual values for HDL cholesterol in the risk calculation. More recent Sheffield tables

(Wallis, E. J., Ramsay, L. E., Ul, Haql et al , 2000) and Joint British Society charts (Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, British Diabetic Association, 2000) (Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association, 1998) show reasonable sensitivity and specificity compared with the full Framingham Anderson model. The 1997 Canadian nomograms (McCormack, J. P., Levine, M., and Rangno, R. E., 1997) included HDL cholesterol in their risk calculation however they were very poor at identifying patients at high levels of risk. The WHO-ISH 1999 table suffers from generalisation of the Framingham-Anderson model with risk factor counting substituting for continuous clinical variables. The New Zealand charts have only moderate sensitivity and specificity and provide assessment of CVD risk (1996 National Heart Foundation clinical guidelines for the assessment and management of dyslipidaemia. Dyslipidaemia Advisory Group on behalf of the scientific committee of the National Heart Foundation of New Zealand., 1996) (McLeod, A. J. and Armitage, M., 1998) (Jackson, R., 2000). The most recent Joint British Society charts estimate CVD risk but were not available at the time of this review.

In conclusion, the systematic review by Beswick *et al* (Beswick, A. D., Brindle, P., Fahey, T. et al , 2008) (Appendix J of the full guideline) showed that comprehensive information is required in risk tables and charts. The inclusion of HDL cholesterol gives the most accurate estimate of cardiovascular risk.

3.3.4 Endpoints used for assessment when estimating cardiovascular risk

The choice of CVD endpoint is important as it affects the numbers of people reaching treatment thresholds and the numbers targeted for risk reduction treatments.

The endpoints recommended in this guideline are the same as those used in the NICE Technology Appraisal 94: Statins for the prevention of cardiovascular events (2006). The scope for this guideline includes risk factor modification for symptomatic atherosclerotic vascular disease including revascularisation and peripheral arterial disease and these endpoints should be included where appropriate in other recommended risk equations.

3.3.5 Adjustments to Framingham cardiovascular risk estimates

Adjusting the calculated Framingham cardiovascular risk estimate by other risk factors

A systematic review by Brindle *et al* (Brindle, P. M., Beswick, A. D., Fahey, T. et al , 2006) (Appendix J) reviewed the accuracy of Framingham-based methods to estimate risk in populations other than those in which the models were derived (external validation).

Data were extracted on the ratio of the predicted to the observed 10-year risk of CVD and CHD from 27 studies with data from 71,727 participants. These studies used either the Framingham-Anderson (1991) (Anderson, K. M., 1991) or Wilson (Wilson, P. W. F., D'Agostino, R. B., Levy, D. et al , 1998) risk scores (methods using the outcomes of combined fatal and non-fatal CHD or CVD) and covered a wide range of different population groups: Populations varied in nationality, age range and sex, date of recruitment and outcomes studied. The groups studied were representative samples of men and women, people with diabetes, people with raised cholesterol, people on treatment for hypertension, people with no CHD determined by angiography and people with a family history of CVD.

For CHD, the predicted to observed ratios ranged from 0.43 in a study of people with a family history of CHD (that is, predicting a lower risk than was observed) to 2.87 in a study of women from Germany (PROCAM) (that is, predicting a much higher risk than was observed) (Hense, H. W., Schulte, H., Lowel, H. et al , 2003). Under-prediction was observed in studies of higher risk patients such as those with diabetes, a strong family history of premature

CVD, people from geographical areas with a high incidence of disease and people in socio-economically deprived groups.

For CVD, there was similar trend of increasing under-prediction with increasing risk of the population.

Over-prediction of risk occurs when Framingham equations are applied to populations with a lower baseline risk than that experienced by the Framingham cohort. Over-prediction was seen in lower and medium risk primary care and occupational populations in Germany (Hense, H. W., Schulte, H., Lowel, H. et al , 2003), France and Northern Ireland (Empana, J. P., Ducimetiere, P., Arveiler, D. et al , 2003) and a US screening cohort with a medium level of observed risk (Greenland, P., La Bree, L., Azen, S. P. et al , 2004). In the multicentre clinical trial of Bastuji-Garin *et al*, CHD risk was over-estimated and this was seen across eight Western European countries and Israel (Bastuji-Garin, S., Deverly, A., Moyse, D. et al , 2002). Within England, Wales and Scotland, over-prediction by the Framingham equations occurred in all regions but was greater in the South and the Midlands/Wales where there was relatively lower mortality and morbidity than in Scotland and the North of England (Brindle, P., Emberson, J., Lampe, F. et al , 2003).

This systematic review shows that the accuracy of the Framingham risk estimates cannot be assumed, and that it relates to the background risk of CVD in the population to which it is being applied. Over-estimation of risk tends to occur in populations with low observed risk and underestimation in high-risk groups.

Adjustment of the Framingham cardiovascular risk score to take account of ethnicity
The rates of CVD vary between ethnic groups; however, the Framingham risk score does not take ethnicity into account as a risk factor.

Studies were identified which provide evidence for differences in risk by ethnic group in the UK and the need to adjust risk estimates to take into account ethnic origin when estimating an individual's risk of CVD (Cappuccio, F. P.,

Oakeshott, P., Strazzullo, P. et al , 2002) (Quirke, T. P., Gill, P. S., Mant, J. W. et al , 2003) .

The method of adjustment was considered in three papers. Bhopal et al's (Bhopal, R., Fischbacher, C., Vartiainen, E. et al , 2005) paper included 6448 men and women aged 25 to 74 years from the Newcastle Health and Lifestyle Survey. The hazard ratio adjusted for age and sex for CHD death in South Asians combined compared with Europeans was 2.23 (95% CI 1.13 to 4.38), the corresponding ratio for stroke mortality was 1.35 (95% CI 0.32 to 5.7).

A study by Aarabi and Jackson (Aarabi, M. and Jackson, P. R., 2005) used risk factor data from 4497 individuals identified from the Health Surveys for England 1998 and 1999, who were eligible to have their risk of a first CHD event calculated by the Framingham equation. Arabi and Jackson considered adding 10 years to the age of South Asian people as the simplest way of calculating CHD risk using paper based methods. The validity of this method, which assumes an excess risk of 1.79, is uncertain.

The study by Brindle et al (Brindle, P., May, M., Gill, P. et al , 2006) included 3,778 men and 4544 women aged 35 to 54 years from the Health Surveys for England 1998 and 1999 and the Wandsworth Heart and Stroke Study, both of which are community-based surveys. The authors estimated the incidence rate from prevalence data for 7 minority ethnic groups: Indians, Pakistanis, Bangladeshis, black Caribbean, Chinese (from the Health Surveys for England 1998/99) and black Africans (from the Wandsworth Heart and Stroke Study). The incidence rate was estimated because of the lack of prospective data on British black and minority ethnic groups.

The sex-specific and age-standardised prevalence ratio for CHD and for CVD for each ethnic group compared with the general British population was obtained from the Health Surveys for England 1998/99. Separate risk estimates were developed for CHD and CVD for both men and women for each ethnic group.

Calculated age-adjusted CVD prevalence ratios for seven ethnic groups showed considerable variation. In men, the highest ratio was observed in Bangladeshis (HR1.39, CI 0.82 to1.96) and the lowest among Chinese (HR0.49, CI 0.16 to 0.82); in women, the highest ratio (HR1.33, CI 0.70 to 1.96) was in Pakistanis and the lowest (HR 0.22, CI 0 to 0.53) among Chinese.

This model has not been validated.

In summary, there is consistent evidence to support the need for adjustment of Framingham risk estimates to take account of ethnicity in UK populations but the best method for achieving this remains uncertain. Current guidance by the Joint British Societies (JBS2) (Wood, D., Wray, R., Poulter, N. et al , 2005) recommends multiplying the Framingham score by a correction factor of 1.4 for South Asian people; however, this does not acknowledge the difference between the sexes. There are particular problems in estimating risk for people of Afro-Caribbean origin who have a higher risk of stroke but a lower risk of ischemic heart disease.

It was noted that the determination of ethnicity itself is problematic despite much debate (Gill, P. S., Kai, J., Bhopal, R. S. et al , 2007). It is a multidimensional concept and embodies one or more of the following: 'shared origins or social background; shared culture and traditions that are distinctive, maintained between generations, and lead to a sense of identity and group; and a common language or religious tradition'. For pragmatic reasons the self-determined Census question on ethnic group is acceptable. South Asian is a broad category and is generally defined as people assigning themselves as Indian, Pakistani, Bangladeshi and Sri Lankans.

The GDG agreed with the data compiled by Brindle *et al* (Brindle, P., May, M., Gill, P. et al , 2006) that indicated that a risk estimate 1.4 times that of the white population was the most appropriate weighting to use for adjustment of the Framingham equation in men of South Asian origin. There was no significant increase in risk among South Asian women. Although some other

ethnic groups had low levels of risk in comparison to white people, this was not sufficiently robust on which to base a recommendation.

Adjustment of the Framingham cardiovascular risk score to take into account family history

Three studies were found addressing the extent to which family history predicts risk. These studies are the Framingham Offspring Study by Lloyd-Jones et al (Lloyd-Jones, D. M., Nam, B. H., D'Agostino, R. B., Sr. et al , 2004) the Malmo Preventive Project (MPP) by Nilsson et al (Nilsson, P. M., Nilsson, J. A., and Berglund, G., 2004) (follow up study) and the Physicians' Health Study (PHS) and the Women's Health Study (WHS) (Sesso, H. D., Lee, I. M., Gaziano, J. M. et al , 2001).

The Framingham Offspring Study

Lloyd-Jones *et al* (Lloyd-Jones, D. M., Nam, B. H., D'Agostino, R. B., Sr. et al , 2004) determined whether parental CVD predicts offspring events independent of traditional risk factors. The population consisted of 2302 men and women with a mean age of 44 years in the Framingham Offspring Study, who were free of CVD and whose parents were both in the original Framingham cohort. The authors examined the association of parental CVD with an 8-year risk of offspring CVD using pooled logistic regression.

Compared with the participants with no parental CVD, those with at least 1 parent with premature CVD (onset age < 55 years in father, < 65 years in mother) had a greater risk for events, with age-adjusted odds ratios of 2.6 (95% CI 1.7 to 4.1) for men and 2.3 (95% CI 1.3 to 4.3) for women. Multivariate adjustment resulted in odds ratios of 2.0 (95% CI 1.2 to 3.1) for men and 1.7 (95% CI 0.9 to 3.1) for women. Non-premature parental CVD and parental coronary disease were weaker predictors.

The Malmo Preventive Project (MPP)

Nilsson et al (Nilsson, P. M., Nilsson, J. A., and Berglund, G., 2004) studied the adjusted relative risk of CVD events in offspring of parents with cardiovascular mortality before 75 years. A total of 22 444 men and 10 902

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women attended a screening programme between 1974 and 1992 and were followed up through national record linkage.

There was an increased risk of CVD events (mortality and morbidity) in offspring in relation to a positive family history of parental CVD mortality before 75 years. The multivariate adjusted relative risk (RR) for father-son heritage was 1.22 (95% CI 1.02 to 1.47; P < 0.05), for mother-son heritage, RR = 1.51 (95% CI 1.23 to 1.84, P < 0.001), for father-daughter heritage, RR = 1.20 (95% CI 0.83 to 1.73) and for mother-daughter heritage, RR = 0.87 (95% CI 0.54 to 1.41).

Subdividing parental age of early death into age groups 50-68, 69-72 and 73-75 years showed a graded association for maternal influence: RR = 1.82 (95% CI 1.35 to 1.46), 1.55 (95% CI 1.14 to 2.10) and 1.50 (95% CI 1.13 to 1.98) respectively but not for paternal influence, RR 1.29 (95% CI 0.99 to 1.69), 1.08 (95% CI 0.81 to 1.44) and 1.40 (95% CI 1.12 to 1.76) respectively using surviving parents or mortality after 75 years as the reference group.

The Physicians' Health Study (PHS) and the Women's Health Study (WHS)

Sesso et al (Sesso, H. D., Lee, I. M., Gaziano, J. M. et al , 2001) prospectively studied 22 071 men from the Physicians' Health Study (PHS) and 39 876 women from the Women's Health Study (WHS) with data on parental history and age at MI.

Compared with men with no parental history, those with a maternal, paternal and both maternal and paternal history of MI had a RR of CVD of 1.71, 1.40 and 1.85 respectively; among women, the corresponding RRs were 1.46, 1.15 and 2.05 respectively.

Sesso *et al* (Sesso, H. D., Lee, I. M., Gaziano, J. M. et al , 2001) also looked at the effect of parental age: For men, maternal age at MI of < 50, 50 to 59, 60 to 69, 70 to 79 and ≥ 80 years had RRs of 1.00, 1.88, 1.88, 1.67 and 1.17. For women, the RRs for maternal age at MI of < 50, 50 to 59 and ≥ 60 years were 2.57, 1.33 and 1.52. Paternal age at MI of < 50, 50 to 59, 60 to 69, 70 to 79

and ≥ 80 years in men had RRs of 2.19, 1.64, 1.42 1.16 and 0.92; in women, for paternal age at MI of < 50, 50 to 59 and ≥ 60 years, the RRs were 1.63, 1.33 and 1.13.

The GDG noted that there was a continuous distribution of risk, which tended to increase the younger the age at which the family member had an event. Increased risk was noted to be present even up to age 75 years. The number of family members was also related to risk, and risk was greater where female relatives were affected. For simplicity the GDG considered that risk should be adjusted by 1.5 where there was a history of female first-degree relative under 65 years with CHD or a history of first-degree male relative under 55 years. Additional family members in this category would further increase risk. If more than one first-degree relative is affected, the risk estimate should be increased by a factor of up to 2.0.

Adjustment of the Framingham cardiovascular risk score to take into account socio-economic status

There is a widening relative gap in mortality and morbidity associated with socio-economic status. There has been a substantial reduction in CVD in the past two decades but the poorer sections of society have not improved as fast as the more affluent. In 1986 to 1992 mortality from circulatory disease was 69% greater in people from social classes IV and V than that in people in social classes I and II and by 1997 to 1999 this had increased to 86% (White, C., von Galen, F., and Chow, Y. H., 2003). This represents a decrease between socio-economic groups in absolute mortality difference but a widening of the relative difference. This relative inequality has been a cause for governmental concern and tackling health inequalities in CVD is a major component of current governmental strategy (Department of Health, 2003). Mortality from circulatory diseases in the most deprived category is currently threefold higher in women and 2.7 times higher in men than in the least deprived category.

General cardiovascular risk score developed for use in primary care

At the end of the development of this guideline a study was published on the use of a new cardiovascular risk score for use in primary care. This study was not reviewed by the GDG because its publication occurred after formal discussion of the evidence for cardiovascular risk assessment. The study identified participants from the original Framingham Heart study and the Framingham Offspring study. A sex specific multivariable risk factor algorithm was developed that included the following; age, total and HDL cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status. This general algorithm was used to evaluate the risk of developing a first CVD, and it showed good calibration and discrimination for combined CVD events over 12 years of follow-up. It also showed good calibration for the following individual outcomes; coronary artery disease, stroke, peripheral artery disease or heart disease. A simpler CVD risk equation that was developed for use using non-laboratory predictors (body mass index substituted for total and HDL cholesterol) showed reasonable discrimination for the estimation of risk compared with the general CVD algorithm (D'Agostino et al, Circulation, 2008; 117: 743-753).

3.3.6 ASSIGN

During the course of the development of this guideline, the Scottish ASSIGN score has been published and adopted as part of SIGN guidance. ASSIGN was developed from the Scottish Heart Health Extended Cohort (SHEC), which was a series of population studies from the 1980s to 1990s which were followed up until the end of 2005 (Woodward, M., Brindle, P., Tunstall-Pedoe, H. et al , 2007). Participants qualified for inclusion in the analysis if they met the following criteria; risk factor data available, permitted follow up, aged 30 to 74 years at recruitment, reported neither coronary artery disease or stroke, no preceding hospital diagnosis of coronary heart disease, stoke or transient ischaemic stroke. The endpoints for the ASSIGN score were; deaths from cardiovascular disease or any hospital discharge of diagnosis of coronary heart disease or cerebrovascular disease post recruitment, or first coronary intervention.

There were 6540 men and 6757 women in the study and the mean age at recruitment was 48.8 years. Follow up at 30th December 2005 ranged from 10 to 21 years. Of 6540 men, 4936 remained disease free and 1604 developed disease, 743 within 10 years. Of 6757 women, 5742 remained disease free and 1015 developed cardiovascular disease, 422 within 10 years. The ASSIGN score incorporated similar risk factors to Framingham which were entered as continuous variables rather than categories, in addition to, an index of social status based on postcode of residence at recruitment (Scottish Index of Multiple Deprivation, SMID) and family history of cardiovascular disease. The ASSIGN score was compared with Framingham score (working model comparing the scores at www.assign.com). The rank correlations between Framingham and ASSIGN were 0.92 for men and 0.90 for women. ASSIGN scores while lower on average, correlated closely with Framingham, and the discrimination of risk in the SHHEC was significantly, but marginally improved by ASSIGN. The predicted 10 year cardiovascular risk overall for men using ASSIGN was 14.4% and using Framingham was 16.0%. The observed incidence was 11.7%...The distribution of the risk scoring was highly skewed. The median ASSIGN value in the SHHEC population was the same as the observed incidence at 11.6%, while for Framingham it was 13.6%. The predicted 10 year cardiovascular risk overall for women using ASSIGN was 9.3% and using Framingham was 9.6%. The observed incidence was 6.4%. The median ASSIGN value in the SHHEC population was the similar to the observed incidence (6.2% versus 6.4%) while for Framingham it higher at 7.1%. A previous report by the authors found that the SIMID correlates highly with coronary risk when compared across population fifths in the SHHEC population (Tunstall-Pedoe, H. and Woodward, M., 2005). Observed risk had a steep gradient according to social status, varying two fold in men at the top (least) and the bottom (most deprived) fifth of the population (from 4.9% to 10.0%), and fivefold, although at lower levels in women (from 1.1% to 5.5%). Hence the relative risk of observed 10-year CVD risk (sexes combined) analysed across population fifths from least to most deprived was 1.00, 1.81, 1.98, 2.22, and 2.57. Expected risk based on Framingham had one quarter of the gradient, and gave relative risks of 1.00, 1.17, 1.19, 1.28, and 1.36)

(Tunstall-Pedoe, H. and Woodward, M., 2005). Comparison of the performance of ASSIGN versus Framingham by fifths of the SIMD score found that ASSIGN abolished this gradient, while it remained significant for the expected risk from the Framingham score versus the observed event rate. Hence ASSIGN classifies more people with social deprivation and anticipates more of their events compared with Framingham (Woodward, M., Brindle, P., Tunstall-Pedoe, H. et al , 2007).

3.3.7   QRISK

During the last phase of the development of the guideline a new CVD risk score, QRISK, has been derived and validated using data from a UK primary care population (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007). Data were retrieved from the QRESEARCH database (www.qresearch.org), a large electronic database representative of primary care, and containing the health records of 10 million patients over a 17 year period from 529 general practices using the EMIS computer system. QRESEARCH contains area measures of ethnicity and also deprivation (Townsend score) based on the 2001 UK census, and linked to every patient's record. Information from two thirds of the QRESEARCH database was used for modelling dataset and the remaining third was used for validation dataset. An open cohort of patients aged 35 to 74 years at the date of study entry was identified that was drawn from patients registered from 1 January 1995 to 1 April 2007. The following patient groups were excluded; those with diabetes or CVD before their entry date into the database, temporary residents or those with interrupted periods of registration at the practices and 4% of patients that did not have a valid postcode ethnicity score (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007).

The primary outcome was the first recorded diagnosis of CVD (including MI, CHD, stroke and transient ischaemic attack) on the general practitioners clinical computer system, either before or at death occurring between 1 January 1995 and 1 April 2007. The following risk factors were included in the

analysis using the closest to the entry date to the cohort for each patient and imputing missing values when necessary; age (in single years), sex, smoking status (current smoker, non smoker-including former smoker), systolic blood pressure (continuous), ratio of total serum cholesterol to high density lipoprotein levels (continuous), left ventricular hypertrophy recorded on clinical records (yes or no), body mass index (continuous), family history of CVD in first degree relative aged less than 60 years (yes or no), body mass index (continuous), Townsend deprivation score, percentage of South Asian residents at output areas, current prescription of at least one antihypertensive (yes or no). A Cox proportional hazard model was used to estimate the coefficients associated with each potential risk factor for the first ever recorded diagnosis of CVD for men and women separately. The variables to be included in the model were specified a priori. Models were compared using the Bayes information criterion (a likelihood measure which in lower values indicate better fit, and in which a penalty is paid for increasing variables). The strength of the association between one unit increases in each continuous risk factor was examined, and categories for other variables such as smoking compared with non-smoking were compared. The proportional hazards model's assumptions were tested for any non-linear relation between continuous independent variables and the outcome. Interactions between systolic blood pressure and antihypertensive treatment and also between smoking and deprivation were examined. The log of the hazard ratios for each of the risk factors (the coefficients from the Cox regression) from the model were used as weights for the new CVD risk equation. An estimate of each patient's probability of experiencing a CV event was made by combining these weights, the characteristics of the patient, and also using the baseline survivor function for all participants. The baseline survivor function was estimated from the Cox regression model centred on the means of continuous risk factors, and the value for 10 year follow-up was extracted (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007).

The performance of the risk equation in the derivation dataset (QRISK score) was tested in the validation dataset by calculating the 10 year estimated CVD

risk for each patient in the dataset. Missing values for continuous variables were replaced with mean values obtained from the derivation dataset by five-year age-sex bands, and assuming patients were non smokers if status was not recorded. Calibration (the degree of accuracy) was assessed by calculating the mean predicted risk of CVD at 10 years and the observed risk at 10 years obtained using the 10 year Kaplan-Meier estimate. The ratio of the predicted to the observed CVD risk for patients was then compared in patients in the validation cohort in each tenth of predicted risk. The predicted and observed risks were also compared for men and women by age band and fifth of the Townsend score. Discrimination was assessed by receiver operated curve, and also by the R^2 and D^2 statistics (measures of discrimination and explained variation for survival models). The performance of QRISK was compared to the Framingham and ASSIGN equation (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007).

There were 478 UK practices that met the study inclusion criteria, 318 practices were randomly assigned to the derivation dataset (total patient number aged 35 to 74 years = 1 283 174, 50.4% women) and 160 practices to the validation dataset (total patient number aged 35 to 74 years = 614 553, 50.3% women). In the derivation dataset there were 65 671 incident cases of CVD and these were higher in men than women. The median follow up was 6.5 years and 306 259 patients were followed up for at least 10 years. The 10 year observed risk of a CV event in women was 6.69% (95%CI 6.61% to 6.78%), and in men was 9.46% (95%CI 9.36% to 9.56%). In the validation dataset, the 10 year observed risk of a CV event in women was 6.60% (95%CI 6.48% to 6.72%), and in men was 9.46% (95%CI 9.14% to 9.43%). The final Cox regression model used in the study included the logarithm of age, ratio of serum cholesterol to HDL cholesterol, systolic blood pressure, body mass index, family history of premature CHD, smoking status, Townsend deprivation score, and the use of at least one blood pressure treatment. The final model also included an interaction term between systolic pressure and blood pressure treatment. Left ventricular hypertrophy and the area measure of ethnicity were omitted. Hazard ratios for the final Cox

regression analysis showed in the risk of CVD was increased with increasing age, body mass index and Townsend deprivation score. The risk was higher in patients who smoked, had a family history of CVD, and were receiving antihypertensive therapy. The hazard ratio for the ratio of total cholesterol to HDL cholesterol was just above and close to one, but it had been decided to include this factor a priori (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007).

From the calibration and discrimination modelling, the Framingham equation over-predicted risk at 10 years by 35%, ASSIGN by 36% and QRISK by 0.4%. All three equations tend to over predict risk in the lowest three tenths of risk at 10 years, the greatest over prediction occurred with ASSIGN, followed by Framingham and then QRISK. The receiver operator curve (ROC) statistic indicated that the final QRISK score had at least as good as, if not slightly better discrimination than the Framingham and ASSIGN equations. The R^2 statistics (standard error) for QRISK, Framingham and ASSIGN for women were; 36.4% (0.43), 31.7% (0.44) and 34.1% (0.43), respectively. The D^2 statistics (standard error) for QRISK, Framingham and ASIGN for men were; 33.3% (0.39), 29.1% (0.38) and 30.5% (0.38), respectively. Comparison of the proportion of patients with a CVD risk score ≥ 20% by Townsend fifths and sex for the three risk prediction scores found that the biggest difference was observed in women. QRISK predicted 9.8% of women aged 35 to 74 years from the most deprived fifth to be at high risk compared with 3.0% of women from the most affluent fifth. The corresponding values for the Framingham equation were 6.3% (most deprived) and 4.6% (most affluent). QRISK predicted 12.6% of men from the most deprived areas to be at high risk compared with 9.6% of those from the most affluent areas. The values for the Framingham equation were 19.5% (most deprived) and 20.5% (most affluent). Overall, QRISK predicted 8.5% of patients aged 35 to 74 years to be at high risk compared with 12.8% for the Framingham equation and 14.0% for ASSIGN. Using QRISK, 34.5% of women and 72.9% of men would be at high risk compared with 24.1% and 86.0% using the Framingham equation (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007).

The performance of the QRISK score for predicting CVD risk was assessed in a second medical records database; The Health Improvement Network (THIN). This new electronic database contains records from general practices, some of which have or continue to participate in the General Practice Research Database (GPRD) and others that have never participated in the in GPRD. Hippisley-Cox *et al* identified the second cohort of patients from the THIN database, with the same inclusion and exclusion criteria as that for the original study (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2008), registered between 1 January 1995 and 31 March 2006. A Framingham score and QRISK score was generated for each individual patient in the THIN cohort and also the validation QRISK cohort. Hippisley-Cox *et al* used a revised equation for QRISK that had taken account of improvements in the method for multiple imputation of missing data. In addition to the original variables, the following were included in the imputation model; binary variables for diagnosis of hypertension and incident diabetes, and continuous variables for the number of prescriptions for aspirin, statins and antihypertensive treatments for each patient during the study period. The revised equation excluded patients taking statins at baseline. The revised QRISK equation also corrected for an analytical error in the first published QRISK equation, which had found that the total cholesterol to HDL cholesterol ratio was of borderline significance. Following this correction, the current published QRISK equation shows that the total cholesterol to HDL cholesterol ratio is highly predictive of CV risk. The adjusted hazard ratios for the ratio of cholesterol to HDL ratio was 1.20 (95% CI 1.17 to 1.22) in females and 1.25 (95% CI 1.23 to 1.27) in males (see QRISK authors' response http://www.bmj.com/cgi/eletters/335/7611/136#174181). (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2008).

There were 1 072 800 patients in the THIN cohort that were analysed (529 813 men (49.39%)). The corresponding cohort on QRESEARCH had 607 733 patients. The baseline characteristics were similar for THIN and QRESEARCH for age, sex, risk factors and medication, however, the family history of premature CHD was substantially lower in THIN than QRESEARCH

(3.5% in males in THIN versus 9.2% in males in QRESEARCH). The Framingham equation over predicted risk by 28% in the THIN cohort while, QRISK under predicted by 10%. QRISK performed better than Framingham for the discrimination and calibration statistics (receiver operator curve statistic, R^2 statistic, D^2 statistic). The validation statistics for both QRISK and Framingham were similar in the THIN cohort and the QRESEARCH cohort (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2008).

3.3.8   Cost- effectiveness of assessment of cardiovascular risk

There is no cost effectiveness evidence regarding the choice of tool. Refer to Section 4.2.3 of the full guideline.

3.3.9   Evidence to Recommendations

One of the most difficult decisions that the GDG faced during development was that of recommending a risk assessment equation. First, the evidence base in this area is rapidly developing with two new risk scores being published in the UK during the development of the guideline. Second, after reviewing the research evidence, in the view of the GDG, all available equations had significant limitations.

Conduct of meetings and discussion

In the initial development of the guideline the evidence presented to the GDG involved the choice of which Framingham risk equation to use and how that equation could be adapted. All members of the GDG took part in the discussions and decisions.

Towards the end of the development of the guideline two members of the GDG, one of whom was the chairman, declared an interest as researchers involved in the development of the new QRISK score and related publications. This was a conflict and they were treated as experts for these discussions. They were invited to present the case for QRISK but not to participate in the discussion unless asked a direct question. They left the room prior to voting and the GDG conducted their final deliberations in their absence and voted.

Discussions related to risk scores was chaired by the NCC-PC lead /Clinical Director.

The other members of the GDG were asked to declare interests in other existing risk scores. Several declared previous or ongoing work in relation to risk scores (refer to the Declatation of Interests in Appendix L) such as supervising PhD students investigating the use of risk scores, research on validation and adaptation of risk scores, and co-authors of reports that recommended adaptations to Framingham for the UK population. All GDG members declared these interests and all members were aware of them during discussions, but they were not regarded as significant conflicts which required exclusion from the discussion or voting.

The expert co-opted onto the GDG for secondary prevention, took part in the discussions but did not vote.

Background

The Framingham equation, as detailed above, is based on a U.S. population and has been the dominant method of calculating risk, despite its limitations, and is familiar to clinicians.

Early in the development the GDG discussed the limitations of Framingham equation including:

- The tendency of Framingham equation to over estimate risk in contemporary European populations
- The tendency of Framingham equation to under-estimate risk in people from deprived backgrounds
- The difficulties in adjusting Framingham in clinical practice when patients may already be on BP treatment
- Difficulties in adjusting Framingham for additional known risk factors such as a family history of CHD,
- Framingham equation being based on a fixed population with baseline data collected in the late 1960s and 1970s.

The GDG recognized the potential value of a risk score developed in the UK population and in the later stages of development of the guideline the GDG became aware of the development of the QRISK equation and invited the principal investigator to attend a GDG meeting and present the preliminary findings.

Discussion

At the time of the first consultation of this guideline, there was no published research on QRISK equation and the GDG only had preliminary data available to them. Based on the published evidence, the GDG recommended the Framingham equation. They examined the existing literature on adjustments to Framingham and recommended how the Framingham equation should be adjusted to the UK population.

The GDG met again in September 2007 to consider stakeholder comments on the draft guideline. The first paper describing QRISK (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007) and the rapid responses to that paper including authors reply (http://www.bmj.com/cgi/content/short/bmj.39261.471806.55v1) had been published. The GDG also had access at this time to a second unpublished paper validating QRISK and addressing many of the criticisms in the original paper. The second paper is now published (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2008)

The performance of QRISK in this primary care population was better than the Framingham equation across each statistical measure. It reclassified a greater proportion of people from deprived backgrounds as being at high risk, relative to Framingham, as it took into account the increased risk associated with social deprivation. It appeared to address many of the limitations of Framingham because;

- in addition to standard risk factors QRISK includes variables relating to

    - Social deprivation (Townsend score)

- Being on BP treatment
- Having a family history of CHD
- Body Mass Index

- QRISK can be regularly updated and so keep up with secular changes in CVD incidence

- QRISK uses current primary care data to derive a risk score in the population in which it is to be used. i.e. UK primary care.

At the time of this meeting (September 2007) the GDG had two main concerns about recommending QRISK:

1   The GDG did not have the technical skills to assess the appropriateness and accuracy of the advanced statistical techniques (i.e. multiple imputation) employed.

2   Only one paper (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2007).had been published and subject to scientific review. This process had revealed some problems with the first equation. The subsequent paper detailing the corrections and adjustments (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2008) had not been published and subject to peer review and comment.

Because of these concerns, the GDG (excluding the two researchers who left the room) felt unanimously that they were not able to recommend QRISK on the basis of the evidence available to them. They recommended to the Institute however that as the evidence in this area was rapidly changing the recommendation on risk score might need early review.

As the Institute did not wish to update a guideline so soon after publication, it was agreed with the GDG that publication be delayed while independent expert opinion was sought in regard to technical issues of concern to the GDG. With the agreement of the GDG, the Institute sought advice from experts independent of the groups that had derived either QRISK or modified the Framingham equations or guidelines that advocate them. Advice was sought from a:

- Biostatistician:- Professor Doug Altman

- Epidemiologist: - Professor Sir Richard Peto FRS

- Expert in Cardiovascular Risk Estimation: Professor Rod Jackson

Their reviews are attached as an appendix.

The GDG reconvened in January 2008 to discuss the now published QRISK paper (Hippisley-Cox, J., Coupland, C., Vinogradova, Y. et al , 2008) and the independent reviews. The GDG discussed the independent reviews and sought clarification of some points from the two QRISK researchers who were GDG members. The GDG addressed methods for dealing with missing data, calibration and discrimination statistics for QRISK and the applicability and use of QRISK in different clinical settings.

The GDG had some outstanding concerns:

1)   The calculation of the additional risk of some ethnic groups, in particular those of south Asian background.

The QRISK equation does not include a variable for ethnicity, but does include a variable for deprivation and family history. The previous recommended increase of a factor of 1.4 in risk for South Asian males when using the Framingham equation would overestimate the risk using the QRISK equation. As there is no information currently available on what, if any, increase would be appropriate for ethnicity, if ethnicity were accounted for, the GDG decided not to include any adjustment.

2)   The management of patients who had previously been assessed with the Framingham equation and were currently on treatment. The GDG regarded it as inappropriate for a patient currently on treatment to be reassessed with the possibility of the treatment being stopped. The GDG agreed that patients already on treatment should not be reassessed using QRISK.

3)   Accessibility of QRISK

The view of the GDG was that QRISK must be freely available for incorporation into primary care management software and to secondary care clinicians for use in hospital. The GDG agreed to ask for a guarantee from the developers of QRISK that the algorithms will be freely available from their website prior to publication.

4) Updating the algorithms

A major advantage of QRISK is that it can be updated to, for example, reflect changes in the UK population, or to include more variables such as ethnicity and chronic kidney disease. However there must be strict version control, therefore the GDG recommends that NICE work with developers to co-ordinate updates in QRISK with the publication of updates of the guideline.

The GDG (excluding the two researchers who left the room) unanimously agreed that QRISK should be recommended noting that this decision would go to wider consultation. The GDG agreed that the recommendation of QRISK will also allow the score to be improved with the potential to include other variables and outcomes of interest.

This section of the guideline went out for a four week stakeholder consultation and **the GDG met for the final time in March 2008** to review stakeholder comments. The GDG recognised that the three independent experts consulted had recommended QRISK but stakeholders had taken a broader view and identified areas of concern. The areas of concern discussed by the GDG are not listed in any particular order.

1) Ascertainment

Concern was expressed by stakeholders and discussed by the GDG that the validation of QRISK against Framingham and ASSIGN had used outcomes as measured in general practice databases and in ONS statistics. Ascertainment is likely to be less certain than in cohort studies.

2) Accuracy of data recorded in datasets

Some stakeholders had expressed concern about quality of data in GP datasets. The GDG were not concerned about recording of risk factors as these are the readings practitioners will use in clinical practice. They agreed with concerns regarding accuracy of outcome data as above.

3) Independent validation of QRISK

The details of the QRISK equation have not yet been made available. The GDG understood that the QRISK research group had valid reasons for this but were concerned that the current lack of availability means that independent validation and comparison with other scores has not yet been possible. This had made it difficult for stakeholders to examine validation. One group submitted an unpublished paper, where they had tried to derive the QRISK equation and replicate the QRISK validation papers. There were some major differences between their results and the QRISK validation papers. The GDG recognised the limitations of the paper in that it was not peer reviewed or published and they did not have the correct equation. However the paper highlighted the difficulties in comparing scores at this time.

4) Validation of QRISK other than in general practice records

The GDG agreed that ideally QRISK should be validated in clinical datasets as well as in databases for the reasons already discussed.

5) Use in practice

The GDG continued to have concerns about the practical use of QRISK in all health care settings. The GDG were not aware of any use of QRISK in clinical settings while clinicians have experience of use of Framingham.

6) Comparisons of ASSIGN and QRISK in the UK populations

A cogent case was made by the ASSIGN research group suggesting that overall the differences between Framingham, ASSIGN and QRISK were extremely similar in terms of discrimination. Neither the GDG nor the independent experts had compared QRISK to ASSIGN. Both ASSIGN and

QRISK are relatively new scores. ASSIGN could not currently be used in the UK population other than Scotland but a version of ASSIGN using a different, England and Wales appropriate, index of deprivation could be developed. The GDG did not think that they had enough evidence to decide that QRISK was the definitively better score for the UK over ASSIGN.

7) Overestimation of risk versus underestimation of risk

The available evidence indicates that Framingham overestimates risk in a UK population and QRISK underestimates risk. The GDG were less concerned about overestimating risk as interventions are known to have benefit below the thresholds currently used.

Final Decision

The GDG could not on the basis of the evidence or expertise before them make a decision that one risk assessment equation was clearly superior in the UK population.

The GDG debated the following in reaching their decision.

- *Should no equation be recommended as no one was definitively superior?* The GDG considered that if they did not give definitive guidance there may be a perception that risk assessment was not important. The evidence is clear that any structured assessment is superior to clinical judgement in assessing risk and enabling high risk people to access treatment. It would also not be in the interest of patients to potentially be assessed by different scores. This confusion could well lead to poorer uptake of treatment. All risk equations are blunt instruments which should be used in clinical practice as the starting point for a discussion between clinicians and patients and excessive emphasis on which risk score better estimates CVD risk for the individual patient obscures the primary importance of undertaking a structured risk assessment.

- *Was the uncertainty associated with adopting a new CVD risk score estimation equation acceptable?*

The GDG recognised that there is a strong case for the use of a risk equation developed and validated on a UK population and takes account of deprivation. There were however concerns about QRISK within the GDG and the wider community as evidenced by stakeholder comments. The Framingham equations are currently the most widely used and understood. Recommending a different score required a higher level of certainty than the GDG had with regard to QRISK.

The GDG then voted (the secondary prevention expert left the room for part of the discussion and for the vote). Seven members were in favour of recommending risk assessment based on the Framingham equation with adaptations. One member voted in favour of recommending an equation based on UK data. One member abstained.

Conclusion

The GDG's decision was that Framingham despite its known limitations is currently in use and its limitations understood. Therefore there needs to be great confidence that the introduction of a new model will bring greater benefits. As QRISK is still a model in evolution, they were not certain that this was currently the case. The large confidence intervals with both models mean that either model will largely identify the same proportion of patients. The limitations of Framingham (e.g. over prediction, equity, other risk factors) are addressed in the recommendations.

GDG members had the opportunity to read and comment on the narrative, describing how the GDG came to its decision regarding choice of risk score, after the final meeting and the majority regarded this as an accurate representation of the decision. The QRISK researchers who had not been present for all of the discussion pointed out that the current underestimation of risk by QRISK in the THIN database was related to poor recording of family history and that the implementation of QRISK would increase the recording of this.

An issue of importance remains the implication of choice of risk score for vulnerable groups. The recommendation to use Framingham does not address issues of equity and people from an under deprived background remain less likely to be considered >20% risk. The recommendations include advice to adjust the Framingham score for ethnicity, family history and socioeconomic status. There is some evidence on how the Framingham score should be adjusted for ethnicity and family history but further validation of these adjustments is required. There is no direct evidence as to how it should be adjusted for socioeconomic status. QRISK does include socioeconomic status and family history but it is not known whether additional adjustment is required for ethnicity.

A research recommendation has been added to this guideline on further validation of all available risk scores in the UK population, on feasibility of using scores in different settings and the added value of including additional variables in risk scores.

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Following the publication of the guideline two further papers addressing QRISK validation were published. A paper comparing QRISK 2 and adjusted Framingham equations was published in 2008 (Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008; 336: p332) and in 2009 an independent evaluation of QRISK1 was published (Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. *BMJ* 2009;339:p2584).

Members of the guideline development group were consulted as to whether an update was appropriate but there was no consensus. NICE's Guidance Executive considered this feedback and came to the view that, although the evidence has moved on, an update was not appropriate as it did not seem that a clear conclusion would be reached favouring one method over another. In these circumstances the decision was taken by Guidance Executive in February 2010 to withdraw the guidance relating to a particular method of estimation so that the decision could be left to the healthcare practitioners to use the method best suited to their requirements.

3.4 Methods of delivering tools for risk estimation to clinicians

3.4.1 Clinical effectiveness narrative

A systematic review has examined methods to aid the healthcare professional in reporting cardiovascular risk score (Beswick, A. D., Brindle, P., Fahey, T. et al , 2008) (Appendix K). Only two studies were identified; one in people with a diagnosis of diabetes and the second in people diagnosed with hypertension.

The first study compared the documentation of the cardiovascular risk score at the front of the patient's notes with no documentation at the front of the notes in the control group (Hall, L. M., Jung, R. T., and Leese, G. P., 2003). For both the intervention and the control group the physicians were given standard information on weight, haemoglobin, microalbuninaria and cholesterol. At 6-month follow-up, treatment with antihypertensives and lipid lowering drugs was increased in the group with clearly identified risk scoring. However, this was only significant in patients at greater cardiovascular risk (> 20% 5-year risk) compared with those at lower risk (≤ 20% 5-year risk).

The second study, in people with hypertension, compared the use of the Framingham-Anderson 1991 risk calculation with an estimation of cardiovascular risk by a physician (Hanon, O., Franconi, G., Mourad, J. J. et al , 2000). The physician in the intervention group was told the estimated risk calculation, while the control group had their risk estimated by a physician using clinical judgment. At eight-week follow-up, there was no benefit for inclusion of Framingham-Alderson 1991 10-year CVD risk in the therapeutic strategy. There was no difference between the groups in change in systolic and diastolic pressure or in change in prescription of antihypertensives. Concordance between the Framingham-Alderson 1991 calculated risk and the estimated risk by the physician was 35%.

A limitation to the methodological quality of the two studies is that they did not describe the method of randomisation, blinding or power calculation. As such

the results of these studies should be interpreted with caution (Hall, L. M., Jung, R. T., and Leese, G. P., 2003) (Hanon, O., Franconi, G., Mourad, J. J. et al , 2000).

3.4.2   Cost-effectiveness narrative

There were no cost-effectiveness studies found surrounding the most effective method of providing tools for risk estimation to people at high risk of developing CVD.

3.5   Lipid measurement

3.5.1   Introduction

HDL cholesterol is an independent predictor of cardiovascular risk, high levels being 'protective' and lower levels of HDL cholesterol are associated with increased risk. The inclusion of the total/ HDL cholesterol ratio as a component of risk estimation has a substantial impact compared with the use of total cholesterol alone. A person with a total cholesterol of 5.2mmol/l and an HDL cholesterol of 0.7mmol/l has a ratio of 7.4 which confers a greater CVD risk than someone with a total cholesterol of 8mmol/l and an HDL cholesterol of 1.6mmol/l who has a ratio of 5.0. The ratio of total cholesterol/HDL cholesterol has been shown to be the optimal predictor of CVD risk when incorporated in multiple risk factor equations (Grover, S. A., Coupal, L., and Hu, X. P., 1995).

The GDG also considered the number of pre-treatment readings, the utility of a fasting lipid profile prior to treatment and the time in which treatment should usually be initiated. Concern has been expressed about the lack of laboratory standardisation for lipid measurement.

3.5.2 Evidence statements for lipid measurement

> *3.5.2.1*   *Both HDL cholesterol and total cholesterol form integral aspects of the Framingham, QRISK and ASSIGN equations. Management decisions should use both parameters as they are known to make independent contributions to CVD risk. Total and HDL cholesterol can be measured in non-fasting specimens.*
>
> *3.5.2.2*   *Estimation of LDL cholesterol requires a fasting specimen which gives total cholesterol, HDL cholesterol and triglycerides. The LDLcholesterol is then calculated using the Friedewald equation. Currently available direct methods are inadequately standardised and validated and cannot be recommended)*
>
> *3.5.2.3*   *Once an individual has had their risk factors measured and is found to be in a high- risk group for which active management is recommended, it may require several consultations and some time may be necessary for this information to be conveyed and assimilated and other clinical issues addressed. It would normally be expected that these issues would be dealt with and appropriate treatment started within 6 months of full risk factor assessment.*
>
> *3.5.2.4*   *Individuals who are identified from their history or clinical findings to be at high increased risk of premature cardiovascular disease due to familial or other genetic factors require full investigation and/or specialist review. These people will include those with familial hypercholesterolaemia or monogenic lipid disorders.*

3.5.3 Measurement of lipid parameters for risk assessment

Framingham takes account of the ratio of total to HDL cholesterol in estimating risk. The ratio of the total cholesterol to HDL cholesterol is a better predictor of risk than either measure alone (Grover, S. A., Dorais, M., and Coupal, L., 2003; Nam, B. H., Kannel, W. B., and D'Agostino, R. B., 2006).

The Heath Survey for England found that the mean HDL cholesterol level in men in England is 1.4 mmol/l, and in women it is 1.6 mmol/l. HDL cholesterol for women across all age ranges was higher than that for men. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4098712

HDL cholesterol estimation is now widely available in laboratories. For clinical estimation of cardiovascular risk both total and HDL cholesterol should be measured. A non-fasting specimen is sufficient.

Where prior estimation of total or HDL cholesterol is not available, then values based on the average in Health Survey for England (2003), as above are appropriate.

3.5.3.1   *Accuracy of taking one reading of lipid levels versus taking repeated readings of lipid levels*

Framingham risk estimates were based on a single measurement of total and HDL cholesterol and for risk estimation a single reading is sufficient.

Variability of measurement due to physiological variation, laboratory variation and statistical variation are discussed below.

3.5.3.2   *Accuracy of cholesterol measurement*

Measured cholesterol levels incorporate an error term based on the coefficient of variation which, from published studies, is 7.2% for total cholesterol and 7.5% for HDL cholesterol (Nazir, D. J., Roberts, R. S., Hill, S. A. et al , 1999). This error term results from day-to-day physiological variation, from laboratory variation or sample processing and from random variation. Laboratory variation has been a subject of concern and in the USA, and a national quality standard has been established for lipid assay (Warnick, G. R., 2000). The GDG notes that there are concerns, particularly for HDL cholesterol, that no such standardisation exists in the UK.

Because of this individual variation in a single lipid measurement, repeated measurement will give greater precision. Precision is proportional to the

square root of the sample size (Thompson, S. G. and Pocock, S. J., 1990). Typically, someone who has a (true) long-term average total cholesterol level of 4.00 mmol/l will, on any given day, tend to have a measured level that differs by anywhere up to about 0.56 mmol/l (i.e., the within-person standard deviation is about 0.28 mmol/l). Thus, measured total cholesterol for such a person would be expected to lie somewhere between about 3.44 and 4.56 mmol/l based on a single measurement. In order to ensure that an individual had a 90% chance of having a genuine total cholesterol level below 4.00 mmol/l, this would require cholesterol to be lowered to 3.67 mmol/l based on one reading, to a mean of 3.76 mmol/l based on two readings and 3.80 mmol/l based on an average of 3 readings.

In routine practice clinicians find that performing serial replicate reading is not feasible and often base monitoring on one measurement and treatment decisions on two lipid measurements, accepting the imprecision. Where cholesterol levels are used to monitor or guide treatment, the selection of people for optimal treatment on the basis of a single reading is therefore somewhat arbitrary (Westgard, J. O. and Darcy, T., 2004). Some people below the treatment threshold on a particular day may be denied treatment following a single measurement below their 'true' level and in others treatment may be inappropriately given following a single reading above their 'true' level.

3.5.3.3   *The need for a fasting lipid measurement before starting treatment*

There was no substantive evidence to support the view that a fasting specimen is advantageous before starting treatment. It was considered by the GDG that many clinicians view LDL cholesterol and triglycerides as an important adjunct to clinical management because they may inform diagnosis and are a baseline against which the progress and effectiveness of treatment can be judged. The GDG agreed that patients should have at least one fasting lipid measurement performed.

After an acute coronary event, there is an acute phase fall in LDL cholesterol and in HDL cholesterol and potential underestimate of pre-treatment levels. Measurement at this time is not advised. The GDG agreed that in people who

have recently experienced an acute coronary event treatment should not be delayed but measurement can be delayed to 3 months after the event. (Carlsson, R., Lindberg, G., Westin, L. et al , 1995; Ryder, R. E., Hayes, T. M., Mulligan, I. P. et al , 1984).

3.5.3.4 Waiting time between initial assessment and further measurement of risk factors

The practicalities of several clinic attendances to assess and discuss risk and deal with other risk factors or clinical issues may take some time. However, the GDG felt that further delay in commencing treatment should be avoided and that most people wishing to have appropriate treatment should be started within 6 months of assessment.

3.5.3.5 Patients with lipid disorders needing specialist assessment and management

People in whom familial hypercholesterolaemia or other monogenic familial disorders are suspected should be considered for further investigationand/or specialist review.

People with severe hyperlipidaemias should be considered for further investigation and/or specialist review.

The management of familial lipid disorders will be the subject to the forthcoming NICE guideline: Familial hypercholaesterolemia: identification and management (2008).

Amended March 2010 Identification and management of familial hypercholesterolaemia' (NICE clinical guideline 71). Available from www.nice.org.uk/guidance/CG71

3.5.4 Cost-effectiveness narrative

There were no cost effectiveness studies found surrounding the measurement of lipid parameters for risk assessment.

4 Communication of patient risk assessment and information

[Hyperlink to Introduction]

4.1 Recommendations

[Hyperlink to Evidence Statements & Narratives]

4.1.1 **Healthcare professionals should use everyday, jargon-free language to communicate information on risk. If technical terms are used, these should be clearly explained.**

4.1.2 **Adequate time should be set aside during the consultation to provide information on risk assessment and to allow any questions to be answered. Further consultation may be required.**

4.1.3 **The discussion relating to the consultation on risk assessment and the person's decision should be documented.**

4.1.4 **People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. This information should be in a form that:**

- **presents individualised risk and benefit scenarios**
- **presents the absolute risk of events numerically**
- **uses appropriate diagrams and text.**

  (See www.npci.org.uk)

4.1.5 **In order to encourage the person to participate in reducing their CVD risk, the healthcare professional should:**

- **find out what, if anything, the person has already been told about their CVD risk and how they feel about it**
- **explore the person's beliefs about what determines future health (this may affect their attitude to changing risk)**

- **assess their readiness to make changes to their lifestyle (diet, physical activity, smoking and alcohol consumption), to undergo investigations and to take medication**
- **assess their confidence in making changes to their lifestyle, undergoing investigations and taking medication**
- **inform them of potential future management based on current evidence and best practice**
- **involve them in developing a shared management plan**
- **check with them that they have understood what has been discussed.**

4.1.6 People should be informed that CVD risk equations can only provide an estimate of risk. However, the likelihood of misclassification is reduced as the estimated CVD risk increases above the threshold of 20% risk over 10 years.

4.1.7 If the person's CVD risk is considered to be at a level that merits intervention but they decline the offer of treatment, they should be advised that their CVD risk should be considered again in the future.

4.2   Introduction

Risk communication is defined as 'the open, two-way exchange of information and opinion about risk, leading to better decisions about clinical management' (Edwards, A., Elwyn, G., and Mulley, A., 2002). Discussing risk with patients in the clinical consultation has become increasingly important. Patients who are better informed and involved in decisions about their own care are more knowledgeable and also more likely to adhere to their chosen treatment plan (Gigerenzer, G. and Edwards, A., 2003) (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003). Patients' values and preferences vary widely, as do their attitudes to risk. A two-way exchange of information is therefore important to explore the patient's personal beliefs to facilitate treatment decisions.

Communication of risk is not straightforward. Clinicians need to support patients in making choices by turning raw data into information that can be used to aid discussion of risk. Decisions aids are one way of facilitating this process. Decision aids are systematically developed tools to aid patients to understand and participate in medical decisions. Decision aids often include visual representations of risk information and relate this information to more familiar risks. They can be in the form of booklets, DVDs, interactive computer programmes, tapes or web-based products. There is, however, very little evidence of the effectiveness of these aids in communicating risk in patients at high cardiovascular risk.

4.3 Evidence statements – communication of risk assessment and information

[Return to Recommendations]

4.3.1.1 There is limited evidence of the effectiveness of different methods of communicating risk of CVD to patients.
4.3.1.2 One small randomised controlled trial piloting a computerised decision aid has suggested that an individually tailored decision aid about coronary heart disease prevention may facilitate an individual's discussion of risks with their healthcare professional, and also may facilitate risk reduction management plans.
4.3.1.3 A systematic review of the use of decision aids in people facing health treatment or screening decisions has shown that compared with usual care, the use of decision aids: – increase knowledge – increase the perceived probabilities of outcome (a measure of realistic expectation) – lower decisional conflict relating to feeling informed – increase the proportion of people active in decision making – reduce the proportion of people who remain undecided concerning their treatment options.
4.3.1.4 Descriptive studies suggest that: – Numerical presentation of risk should present absolute risk of events rather than relative risk of events. Where absolute risks of events are unavailable, relative risk of events may be presented. – Graphical presentation of risk may aid in the communication of risk.

4.4 Clinical effectiveness of methods of communicating risk assessment to individuals at high risk of cardiovascular disease (CVD)

The use of decision aids in people facing health treatment or screening decisions has been examined in a systematic review (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003). The review had two aims: firstly to document an inventory of decision aids focused on healthcare options and secondly to review randomised controlled trials of decisions aids for people contemplating healthcare decisions. The systematic review also examined studies that compared simpler decision aids with more detailed decision aids.

The systematic review identified over 200 decision aids, of which 131 were available for review. Most of these were intended to be used as a preparation for counselling about an important decision. Ninety-four were web-based, 14 were paper based, 12 were videos, 8 were audio-guided print resources, 2 were CD-ROMS and 1 was web-based with a workbook. Analysis of the quality of these aids found that the majority included potential harms and benefits, update policy, description of the development process, credentials of the developers, reference to relevant literature and were free of perceived conflict of interest. However, few decision aids contained a description of the level of uncertainty regarding the evidence, and few had been validated (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

Thirty of the decision aids that were identified in the inventory were assessed in 34 randomised controlled trials. The majority of these studies evaluated decision aids for people considering cancer screening, cancer therapy, and genetic testing or hormone replacement therapy. Examples of the type of decision aid that were compared with usual care are as follows: an audiotape and a booklet, a pamphlet alone, a pamphlet plus a discussion with a healthcare professional, a series of 8 pamphlet decision aids, an interactive video, and a video plus a booklet (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003). No randomised controlled trials were identified that examined

decision aids in the communication of cardiovascular risk in people at high risk of developing CVD.

To determine whether the decision aids achieved their objectives a range of positive and negative effects on the process of decision making, and on the outcomes of decisions were evaluated. Although the decision aids focused on diverse clinical decisions, many had similar objectives. The outcomes were specified in advance of the review and included; knowledge, realistic expectations, decisional conflict relating to feeling informed, the proportion of people active in decision making, the proportion of people who remain undecided concerning their treatment options and choice, satisfaction with the decision aids, anxiety, and health outcomes following use of the decision aids (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

The studies' knowledge tests were based on information contained in the decision aid, thereby establishing content validity. The authors of the systematic review transformed the proportion of accurate responses to a percentage scale ranging from 0% (no correct responses) to 100% (perfectly accurate responses). Perceived outcome probabilities (a measure of a measure of realistic expectation) were classified according to the percentage of individuals whose judgments corresponded to the scientific evidence about the chances of an outcome for similar people. Decisional conflict was assessed using the previously validated Decisional Conflict Scale (O'Connor, A. M., 1995). The scale measures the constructs of uncertainty and factors contributing to uncertainty (such as feeling uninformed, unclear about values, and unsupported in decision making). The scores were standardised to range from zero (no decisional conflict) to 100 points (extreme decisional conflict). Scores of 25 or lower are associated with follow-through with decisions, whereas scores that exceed 38 are associated with delay in decision making. When decision aids are compared to usual care, a negative score indicates a reduction in decisional conflict, which is in favour of the decision aid (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

Compared with usual care, the use of decision aids was found to increase knowledge in all of the included studies. The gains ranged from 9 to 30 percentage points and the weighted mean difference (WMD) was 19 out of 100 (95% CI 13 to 24), Decision aids increased the perceived probabilities of outcome which was a measure of realistic expectation (RR 1.4, 95% CI 1.1 to 1.9). Decisional aids decreased decisional conflict in all of the included studies, and ranged from -2 to -10 out of 100 with a WMD of -9.1 out of 100 (95% CI -12 to -6). Compared with usual care, decisional aids increased the proportion of people active in decision making (RR 1.4, 95% CI 1.0 to 2.3), and reduced the proportion of people who remain undecided concerning their treatment options (RR 0.43, 95% CI 0.3 to 0.7). The authors commented that the findings were important for two reasons. Firstly, people's level of knowledge and perception of health outcomes in the usual care groups appeared insufficient for informed decision making. Secondly, people's healthcare treatment choice often changed once their knowledge and realistic expectation scores improved. Overall, these findings indicate that 'usual care' may be inadequate when people are facing complex value-laden decisions. These findings also suggest that people need to comprehend the options and probable outcomes to aid in their own decision making. Decision aids also may help people to communicate to their clinicians the personal value they place on the benefits versus the harms (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

Compared with usual care, the use of decision aids did not generally increase satisfaction with decision making, nor did their use reduce anxiety. Decision aids also did not have a consistent effect on general health outcomes. The authors noted that measurement of satisfaction is liable to insensitivity because it is more likely to be linked to the relationship of an individual with the clinician than with the decision aid. Also, satisfaction with usual care may already be high. Anxiety as an outcome measure was deemed inappropriate by the author because more effective decision strategies are associated with a moderate increase in anxiety. The predominately null effect of decision aids for health outcomes suggest that rates of actual choices can vary without

affecting quality of life. However, the author suggested that in future studies it may be more appropriate to link the measurement of health outcomes to prior patient choices to provide a more accurate determination of the effect of decision aids because this was not done in the trials identified (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

In summary, compared with usual care strategies, the systematic review found that decision aids consistently improved an individual's involvement in decision making. The review had a number of limitations in that there was variability in the decision contexts, variability in the design of the decision aids (content, format, and use), and in the type of comparison. The choice of the decision aid will depend upon the needs of the individual (for example literacy, motivation), the nature of the intervention to be explained and considered, and also upon the expectations of clinicians (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

For the comparison of simpler decision aids and more detailed decision aids the majority of the included studies had defined the simpler decision aid as pamphlets. Examples of the more detailed decision aids included an audiotape booklet, an audiotape booklet with values clarification, an interactive DVD, a pamphlet plus a video plus a decision tree, and a lecture plus a personal decision exercise (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

Compared with simpler decision aids, the use of more detailed decision aids were found to marginally improve knowledge (4 out of 100 (WMD), 95% CI 3 to 6) and more realistic expectations (RR 1.5, 95% CI 1.3 to 1.7). Detailed decision aids appeared to do no better than comparisons in affecting satisfaction with decision making, anxiety, and health outcomes. There was a variable effect of detailed decision aids on whether a healthcare option under study was selected. Some studies found that detailed decision aids increased the uptake of a healthcare option compared with simpler decision aids, while others did not (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

The authors stated that the small differences in knowledge scores between detailed and simpler versions of decision aids are likely due to the overlapping information presented in the two interventions. In contrast, the effects remained large for expectation measures and for agreement between values and choice. These observations may occur because the detailed interventions, in contrast to the simpler versions, generally contained probabilistic information about outcomes as well as explicit values clarification exercises. The authors also noted that the effect of providing different components of decision support within decision aids was not examined due to lack of available data. The issue of what to include in a decision aid remains unresolved. There is a need to establish the 'essential ingredients' in decision aids and to identify the people who are most likely to benefit from detailed versions (O'Connor, A. M., Stacey, D., Entwistle, V. et al , 2003).

A second systematic review (Beswick, A. D., Brindle, P., Fahey, T. et al , 2008) (Appendix K) identified two randomised controlled trials that assessed the impact of different risk scoring methods on clinical outcomes in populations mainly without a history of CVD (Montgomery, A. A., Fahey, T., Peters, T. J. et al , 2000) (Hetlevik, I., Holmen, J., and Kruger, O., 1999) (Hetlevik, I., Holmen, J., Kruger, O. et al , 1998). Both studies used patients with a pre-defined diagnosis of hypertension.

The first used a cluster randomised controlled trial design with 614 patients from 27 practices in Avon. Three different methods of delivering risk factor scoring systems to clinicians were assessed: a computerised clinical decision support system (CDSS) plus cardiovascular risk chart; cardiovascular risk chart alone; or usual care (Montgomery, A. A., Fahey, T., Peters, T. J. et al , 2000).

No differences were found between the CDSS plus chart group and the usual care group in terms of change in 5 year risk, change in systolic and diastolic blood pressure and odds ratios for taking 2 or 3 or more classes of drugs compared with 0 or 1. The chart-only group did have significantly lower systolic blood pressure (at 6 months) and were more likely to be prescribed

cardiovascular drugs (at 12 months) compared with the usual care group. People with 5-year CVD risk > 20% were more likely to reduce their risk in the chart or computer group than in usual care. The extent to which each group adopted the use of CDSS or charts is not clear. The authors of the study suggested that the CDSS may confuse or distract the healthcare professional in their use of the chart (Montgomery, A. A., Fahey, T., Peters, T. J. et al , 2000).

The second study used a cluster randomised controlled trial design with GPs from 17 Norwegian health centres either being offered CDSS or practising usual care. They found no clinically significant difference in blood pressure or total cholesterol between the two groups at the end of the follow-up period of 21 months (Hetlevik, I., Holmen, J., and Kruger, O., 1999) (Hetlevik, I., Holmen, J., Kruger, O. et al , 1998).

Regarding the quality of the studies, both used cluster randomisation and participants were not blinded to their group. In addition, the first reported losses of 14% at 12 months (Montgomery, A. A., Fahey, T., Peters, T. J. et al , 2000). The second study did not conduct a power calculation or report confidence intervals (Hetlevik, I., Holmen, J., and Kruger, O., 1999) (Hetlevik, I., Holmen, J., Kruger, O. et al , 1998).

Regarding the effectiveness of CDSS, one study showed no clinically significant differences versus usual care but did note that despite an average of 1.5 hours of training, uptake of CDSS in the intervention group was only 12% (Hetlevik, I., Holmen, J., and Kruger, O., 1999) (Hetlevik, I., Holmen, J., Kruger, O. et al , 1998). The other study showed a negative effect on systolic blood pressure when CDSS was added to a risk-chart and a greater reduction in risk in people at high risk. No data were available on the uptake rate (Montgomery, A. A., Fahey, T., Peters, T. J. et al , 2000). It has been suggested that the inclusion of clinicians in the design of decision aids may improve their use (Brindle, P. M., Beswick, A. D., Fahey, T. et al , 2006) and also that paper-based cardiovascular risk tables are inaccurately used (Peters, T. J., Montgomery, A. A., and Fahey, T., 1999).

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In summary, these two studies showed limited or no difference between groups advised to use CDSS and those providing usual care except in people at highest risk. One study indicated uptake of CDSS was very low (Hetlevik, I., Holmen, J., and Kruger, O., 1999) (Hetlevik, I., Holmen, J., Kruger, O. et al , 1998).

A pilot randomised trial has assessed the impact of a decision aid about heart disease prevention in adults with no previous history of heart disease (Sheridan, S., Pignone, M., and Mulrow, C., 2003). This was a small study; 75 people were enrolled and of these, 43% had a 10-year CVD risk of 0-5%, 25% a risk of 6-10%, 24% a risk of 11-20% and 5% a risk of > 20%. The intervention group was given the computerised decision aid 'Heart to Heart' (version 1). This calculates an individual's global risk of CVD events in the next 10 years by combining information on an individual's age, sex, blood pressure, total and HDL-cholesterol, smoking status, diabetes, and left ventricular hypertrophy status using a continuous Framingham equation. 'Heart to Heart' provides individualised information about an individual's global CVD risk, personal risk factors, the benefits and risks of CVD risk reducing therapies (e.g. hypertension therapy, lipid lowering treatment, aspirin), and the risk reductions achievable after one or more therapeutic interventions. 'Heart to Heart 'also encourages the individual to choose therapies that are feasible for long-term CVD risk reduction. In addition, the tool encourages the adoption of a good diet and exercise. The control group received only a list of their CVD risk factors that they could present at the clinical consultation. Forty-one people received the decision aid, and 34 people received the usual care.

Self-reported data were collected at four points in a single study consultation: during initial eligibility assessment, at baseline, after navigation of the study aid (intervention group only), and after the regularly scheduled provider visit. The main effect of the decision aid on decision making was assessed by the proportion of participants who reported discussing their CVD risk with their clinician, and by the proportion of participants who had a specific plan for CVD risk reduction at the post-visit survey. Within-group effects of the decision aid were assessed using pre-post comparisons of an individual's perception that

CVD prevention requires a decision, and the individual's desired participation in decision making. In unadjusted analysis, the decision aid increased the proportion of participants who discussed CVD risk reduction with their clinician (absolute difference 16%, 95% CI -4% to 37%) and increased the proportion who had a specific plan to reduce their risk from 24% to 37% (absolute difference 13%, 95% CI -7% to +34%).The authors stated that there were too few participants in the trial to perform adjusted analysis. In pre-post testing analysis, the decision aid appeared to increase the proportion of people with plans to intervene on their CVD risk (absolute increase ranging from 21% to 47% for planned medication use, and 5% to 16% for planned behavioural interventions) (Sheridan, S., Pignone, M., and Mulrow, C., 2003).

The authors concluded that the trial provides preliminary evidence that an individually tailored decision aid about CVD prevention may facilitate an individual's discussion of CVD risks with their healthcare professional, and also may facilitate in CVD risk reduction management plans (Sheridan, S., Pignone, M., and Mulrow, C., 2003).

A narrative review has discussed the presentation of medical statistics to convey risks to people contemplating a healthcare decision (Gigerenzer, G. and Edwards, A., 2003). Three specific numerical representations were identified that engender confusion, namely single event probabilities, conditional probabilities, and the use of relative risks.

Single event probabilities describe the chance of an event occurring in percentage form, for example 'there is a 5% chance that drug A will cause harmful side effect B'. Confusion can arise as some individuals may interpret this to mean that '5% of the time taking drug A will cause harmful side effect B'. The authors stated that an individual's perception of risk will be clearer if frequency statements are used that specify a reference class. For example, conveying the risk of harmful side effect B can be expressed as '5 out of every 100 people will have side effect B from taking drug A' (Gigerenzer, G. and Edwards, A., 2003). Conditional probabilities, for example the sensitivity, specificity and a positive predictive value of a screening test, are often

misunderstood. Sensitivity refers to the class of people with the illness, while specificity refers to those without the illness. Again, converting the percentage probability of a positive test and the percentage probability of an individual actually having an illness is better represented in the form of frequency statements (Gigerenzer, G. and Edwards, A., 2003).

The use of relative risks can also be misleading. The numerical risk reduction value may be incorrectly linked to the intervention population, rather than the event rate in the population that does not receive the intervention. Misinterpretation of relative risks can result in perceived gross over-estimation of the effectiveness of an intervention. This confusion can be avoided by communicating absolute risk reductions either in the form of percentages or conversion into integers (such as a 1 in 10 chance) (Gigerenzer, G. and Edwards, A., 2003).

In summary the author concluded that single event probabilities, conditional probabilities and relative risks are confusing because they make it difficult to understand what class of events a probability or percentage refers to. The use of transparent representations (such as natural frequencies and absolute risks) clarifies the reference class and should aid in perception of risk (Gigerenzer, G. and Edwards, A., 2003). It is also important to note that presentation of risk should be given with a specified time frame (Thomson, R., Edwards, A., and Grey, J., 2005).

The visual communication of risk has been extensively described by Lipkus and Hollands (Lipkus, I. M. and Hollands, J. G., 1999). Visual displays such as graphs reveal data patterns that may be undetected in numerical information, and graphs can attract and hold people's attention because they display information in concrete, visual terms. To be useful, graphs must convey different risk characteristics such as risk magnitude, the comparison of the magnitude of two risks, cumulative risk (i.e. observing trends over time), uncertainty, and interactions into among different risk factors. A number of different graphical representations of risk have developed, but is important to note that there is little clinical trial evidence available of the effectiveness of

graphs compared with numerical representation of risk. Graphs can be in the form of risk ladders (that displays a range of risk magnitudes such that increased risk is portrayed higher up in the ladder), stick and facial figures, line graphs, dots and related formats, pie charts and histograms. There is a suggestion that simpler bar charts are preferable to more complex representations of data (i.e. pie charts, crowd figures, survival curves) (Thomson, R., Edwards, A., and Grey, J., 2005). It has been suggested that the combination of graphical and numerical risk may provide the best approach. However the visual and numerical communication of risk should be tailored to fit an individual's need (Thomson, R., Edwards, A., and Grey, J., 2005).

4.5 *Evidence to Recommendations*

A self selected group from GDG (including patient representatives) convened to discuss and formulate draft recommendations on the communication of risk assessment. The evidence and the draft recommendations from this subgroup were presented to the GDG. Recommendations were then made collectively. The GDG recognised that there was limited evidence in this important area The GDG made a research recommendation that there is a need for trial evidence on methods of improving risk communication and patient decision making.

5 Lifestyle modifications for the primary and secondary prevention of CVD

[Hyperlink to Introduction]

5.1 Recommendations for lifestyle

Cardioprotective diet

[Hyperlink to Evidence Statements & Narratives]

5.1.1 **People at high risk of or with CVD should be advised to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 10% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and where possible saturated fats are replaced by monounsaturated and polyunsaturated fats. It may be helpful to suggest they look at www.eatwell.gov.uk/healthydiet for further practical advice.**

5.1.2 **People at high risk of or with CVD should be advised to eat at least five portions of fruit and vegetables per day, in line with national guidance for the general population. Examples of what constitutes a portion can be found at www.eatwell.gov.uk/healthydiet and www.5aday.nhs.uk**

5.1.3 **People at high risk of or with CVD should be advised to consume at least two portions of fish per week, including a portion of oily fish. Further information and advice on healthy cooking methods can be found at www.eatwell.gov.uk/healthydiet**

5.1.4 **Pregnant women should be advised to limit their oily fish to no more than two portions per week. Further information and advice on oily fish consumption can be found at www.eatwell.gov.uk/healthydiet**

5.1.5 **People should not routinely be recommended to take omega-3 fatty acid supplements for the primary prevention of CVD.**

Plant stanols and sterols recommendations

[Hyperlink to Evidence Statements & Narratives]

5.1.6 People should not routinely be recommended to take plant sterols and stanols for the primary prevention of CVD.

Physical activity

[Hyperlink to Evidence Statements & Narratives]

5.1.7 People at high risk of or with CVD should be advised to take 30 minutes of physical activity a day, of at least moderate intensity, at least 5 days a week, in line with national guidance for the general population[10].

5.1.8 People who are unable to perform moderate-intensity physical activity at least 5 days a week because of comorbidity, medical conditions or personal circumstances should be encouraged to exercise at their maximum safe capacity.

5.1.9 Recommended types of physical activity include those that can be incorporated into everyday life, such as brisk walking, using stairs and cycling (see 'At least five a week')[16].

5.1.10 People should be advised that bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions (see 'At least five a week')[16].

5.1.11 Advice about physical activity should take into account the person's needs, preferences and circumstances. Goals should be agreed and the person should be provided with written information about the benefits of activity and local opportunities to be active, in line with 'Physical activity' (NICE public health intervention guidance 2).

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[10] Department of Health (2004) *At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer.* London: Department of Health. Available from www.dh.gov.uk

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Combined interventions (diet and physical activity)

[Hyperlink to Evidence Statements & Narratives]

5.1.12 Advice on diet[11] and physical activity[12] should be given in line with national recommendations.

Weight management

[Hyperlink to Evidence Statements & Narratives]

5.1.13 People at high risk of or with CVD who are overweight or obese should be offered appropriate advice and support to work towards achieving and maintaining a healthy weight in line with 'Obesity' (NICE clinical guideline 43).

Alcohol consumption

[Hyperlink to Evidence Statements & Narratives]

5.1.14 Alcohol consumption for men should be limited to up to 3–4 units a day. For women, alcohol consumption should be limited to up to 2–3 units a day. People should avoid binge drinking. Further information can be found at www.eatwell.gov.uk/healthydiet.

Smoking cessation

[Hyperlink to Evidence Statements & Narratives]

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[11] See www. eatwell.gov.uk/healthydiet

[12] Department of Health (2004) *At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer*. London: Department of Health. Available from www.dh.gov.uk

5.1.15 All people who smoke should be advised to stop, in line with 'Smoking cessation services' (NICE public health guidance 10).

5.1.16 People who want to stop smoking should be offered support and advice, and referral to an intensive support service (for example, the NHS Stop Smoking Services).

5.1.17 If a person is unable or unwilling to accept a referral to an intensive support service they should be offered pharmacotherapy in line with ' Smoking cessation services' (NICE public health guidance 10) and 'Varenicline for smoking cessation' (NICE technology appraisal guidance 123).

5.2 Introduction – lifestyle modification for the primary and secondary prevention of CVD

There is a substantive and consistent body of epidemiological, physiological and observational evidence demonstrating that changes in diet modify blood lipids and other risk factors and that these changes are associated with reductions in morbidity and mortality from CVD. Similarly epidemiological, physiological and observational evidence supports the association between cardiovascular health and levels of moderate or greater physical activity and associates a sedentary lifestyle with increased cardiovascular risk.

It is difficult to design, fund or organise randomised trials sufficiently large and rigorous that can yield evidence for the effect of diet, physical activity, smoking cessation or multifactorial lifestyle interventions on cardiovascular events. The observational literature on diet, dietary modification and physical activity provides a large body of evidence that has been periodically reviewed for major national initiatives. It is beyond the resources of this guideline to attempt such a review and we have referenced national reports and systematic reviews and cross referred to appropriate national advice.

To maintain consistency of reporting across both pharmacological and lifestyle interventions, we have limited formal searches for evidence to randomised

trials with outcomes that include cardiovascular events. Such studies are few and we are acutely aware that this limited trial evidence does not adequately reflect either the strength or breadth of evidence that can be derived from epidemiology and other observational work.

The 1976 Doll and Peto study based on 20 years observation of smoking among British doctors (Doll, R. and Peto, R., 1976) remains a seminal descriptor of a clearly defined and modifiable risk factor. The 50 year prospective follow up study (1951 to 2001) showed that men born between 1900 and 1930 who continued to smoke cigarettes died on average about 10 years younger than those who were lifelong non smokers, while those who stopped at around 60, 50, 40 or 30 gained, respectively, on average 3, 6, 9, or 10 years of life expectancy compared with those who continued (Doll, R. and Peto, R., 1976). For men born between 1900 and 1930, the absolute difference between cigarette smokers and non smokers in the probability of death in middle age increased from 18% (42% versus 24%, a twofold death rate ratio) for those born in the first decade of the century, and for those born in the second decade the probability of death increased to 28% (43% versus 15%, a threefold death rate ratio) (Doll, R. and Peto, R., 1976). The authors concluded that among men born around 1920 prolonged cigarette smoking from an early adult age tripled age specific mortality rates, but at age 50 halved the hazard and at age 30 avoided almost all of it (Doll, R. and Peto, R., 1976).

There is extensive and robust trial evidence that smoking cessation programmes are effective in reducing smoking (Wu, P., Wilson, K., Dimoulas, P. et al , 2006). However, no randomised controlled trials with cardiovascular outcomes resulting from smoking cessation have ever been conducted, though there is clear evidence from observational studies that smoking cessation is associated with 40% lower morbidity and mortality (Aberg, A., Bergstrand, R., Johansson, S. et al , 1983). Differences in the prevalence of smoking between the higher and lower social classes has been estimated to account for over half the difference in the risk of premature death faced by these groups (Jha, P., Peto, R., Zatonski, W. et al , 2006). Consumption of

tobacco in forms other than smoking should also be noted. High consumption of alcohol is also associated with substantially increased rates of coronary heart disease and all cause mortality (Emberson, J. R., Shaper, A. G., Wannamethee, S. G. et al , 2005).

For secondary prevention most trial evidence relates to patients following myocardial infarction and that evidence is covered in the NICE guideline: 'Myocardial infarction: Secondary prevention in primary and secondary care for patients following a myocardial infarction', CG48 (2007) http://guidance.nice.org.uk/CG48. Trial literature is almost completely absent for lifestyle interventions in secondary prevention of stroke and peripheral arterial disease.

5.3   Cardioprotective dietary advice

5.3.1 Evidence statements for cardioprotective dietary advice

Low fat diet
5.3.1.1   *No randomised controlled trials were identified in people at high risk of CVD that compared low fat diet with usual diet for the outcomes mortality or morbidity.*
5.3.1.2   *One small randomised controlled trial in people at high risk of CVD with elevated cholesterol and triglycerides found that advice to reduce consumption of fat, sugar and alcohol was associated with reduction in total cholesterol and fasting triglycerides compared with control.*
5.3.1.3   *In patients with suspected CHD, one small randomised controlled trial found that adopting a lipid–lowering diet reduced total cardiac events compared to usual care but did not confer any benefit for the outcomes of cardiovascular mortality, MI, stroke, coronary surgery or angioplasty. Lipid–lowering diet was associated with decreased total and LDL cholesterol compared to baseline levels.*
5.3.1.4   *No randomised controlled trials were identified that compared low fat diet with usual diet in patients with peripheral arterial disease or following stroke.*
Increased fruit and vegetable diet
5.3.1.5   *No randomised controlled trials were identified that compared increased fruit and vegetables diet with usual diet in people at high risk of CVD.*
5.3.1.6   *One randomised controlled trial in patients with angina found that advice to increase consumption of fruit and vegetables was not associated with a reduction in all cause mortality, cardiac death or sudden death compared with advice to eat sensibly.*

5.3.1.7   No randomised controlled trials were identified that compared increased fruit and vegetables diet with usual diet in patients with peripheral arterial disease or following stroke.

5.3.1.8   One randomised controlled trial in patients with angina found that advice to eat oily fish or take omega 3 fatty acid supplements was not associated with a reduction all cause mortality or cardiac death.

5.3.1.9   One randomised controlled trial in hypercholesterolemic people without and with coronary artery disease found that omega 3 fatty acid supplements was associated with a reduction in the primary outcome of any major cardiovascular event, and the secondary outcomes of unstable angina and non fatal coronary events (HR 0.81, 95%CI 0.68 to 0.96)

5.3.2   Clinical effectiveness of low fat diets for the primary prevention of CVD

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of low fat diet versus no change in diet for the outcomes of all cause mortality, cardiovascular mortality or cardiovascular morbidity.

One small randomised controlled trial was identified on the effectiveness of low fat diet versus no change in diet to modify lipid profiles in people at high risk of CVD (Hjerkinn, E. M., Sandvik, L., Hjermann, I. et al , 2004).

The participants in this trial were a sub-sample from a population of 1232 men aged 40-49 years selected for a previous study (Hjermann, I., Velve, Byre K., Holme, I. et al , 1981) according to the following criteria: mean serum cholesterol = 7.5 to 9.8 mmol/l, coronary risk scores (based on cholesterol, smoking and BP) in the upper quartile of the distribution and systolic BP < 150 mmHg. The sub-sample of 104 men were further selected for this trial (Hjerkinn, E. M., Sandvik, L., Hjermann, I. et al , 2004) if fasting triglycerides > 2.5 mmol/l.

A total of 104 men were randomised to either the intervention group which received dietary advice over a five year period or to the control who received no advice.

Participants in the dietary intervention group were given advice to reduce total energy intake (mainly by reducing sugar, alcohol and fat), reduce saturated fat consumption and slightly increase polyunsaturated fat consumption. Participants in the intervention group also received anti-smoking advice.

After five years, the dietary intervention was found to be associated with a reduction in total cholesterol (-10.5%, 95% CI -1.5% to -11.7%) and fasting triglycerides (- 27.2, 95% CI -0.1% to -27.4%) compared with control (Hjerkinn, E. M., Sandvik, L., Hjermann, I. et al , 2004).

5.3.3 Evidence into recommendations

Due to the lack of clinical outcome data in this trial, its small size and problems with generalisibility, it was decided by the GDG that it should be excluded and that recommendations made in the Joint British Societies' guidelines on prevention of CVD in clinical practice (Wood, D., Wray, R., Poulter, N. et al , 2005) would be adopted (total fat intake should be ≤ 30% of total energy intake and saturated fats should comprise ≤ 10% of total energy intake). These targets are slightly lower for total fat than those set by the Department of Heath for the general population (total fat ≤ 35% of total energy intake and saturated fats ≤ 10% of total energy intake) (Department of Health, 2005).

5.3.4 Clinical effectiveness of low fat diets for the secondary prevention of CVD

One randomised controlled trial was identified in patients with a history of CVD that compared advice to adopt a low fat diet with no dietary advice (Watts, G. F., Lewis, B., Brunt, J. N. et al , 1992). This trial recruited men referred for coronary angioplasty to investigate angina pectoris, or other findings suggestive of coronary heart disease (CHD) (70% with angina, 45% with a history of MI). A total of 90 participants were randomised to one of three

groups; usual care, lipid-lowering diet, or lipid-lowering diet plus cholestyramine therapy. Patients in the lipid–lowering diet and lipid–lowering diet plus cholestyramine therapy groups were given the following advice by a dietician: to reduce total fat intake to 27% of dietary energy, to reduce saturated fat intake to 8-10% of dietary energy, to reduce dietary cholesterol to 100 mg / 1000 kcal, to increase omega 3 and 6 fatty acid intake to 8% of dietary energy, and to increase fibre intake. Participants were followed up for a mean duration of 39 months.

Lipid–lowering diet did not confer any benefit over usual care for the outcomes of cardiovascular death, MI, coronary surgery, angioplasty or stroke. Lipid–lowering diet did, however, reduce total cardiac events compared with usual care 10/28 (36%) lipid-lowering diet versus 3/27 (11%) usual care) ($P < 0.05$)) and improve the severity of angina symptoms ($P < 0.01$ lipid-lowering diet versus usual care). Participants in the lipid-lowering diet group had lower total and LDL cholesterol levels at the end of the trial (39 months) compared with their baseline levels ($P < 0.01$), while there was no change in HDL cholesterol (Watts, G. F., Lewis, B., Brunt, J. N. et al , 1992).

5.3.5   Evidence into recommendations

This randomised controlled trial recruited small numbers and was the only trial identified in patients with angina, stroke or peripheral arterial disease. The GDG decided to adopt recommendations made in the Joint British Societies' guidelines on prevention of CVD in clinical practice (Wood, D., Wray, R., Poulter, N. et al , 2005) which recommends that total fat intake should be 30% or less of total energy intake and saturated fats should comprise 10% or less of total energy intake. These targets are slightly lower for total fat than those set by the Department of Heath for the general population (total fat ≤ 35% of total energy intake and saturated fats ≤ 10% of total energy intake) (Department of Health, 2005)

5.3.6 Clinical effectiveness of increased fruit and vegetables diet for the primary prevention of CVD

No randomised controlled trials were identified that compared increased fruit and vegetables diet with usual diet in people at high risk of CVD.

5.3.7 Evidence into recommendations

The GDG decided to recommend five portions of fruit and vegetables per day in line with advice given to the general population. For further information, please refer to the Department of Health's website: 5aday.nhs.uk ,and the Food Standards Agency website: www.eatwell.gov.uk/healthydiet/.

5.3.8 Clinical effectiveness of increased fruit and vegetables diet for the secondary prevention of CVD

One randomised controlled trial was identified in patients with a history of CVD that compared advice to increase fruit and vegetables versus non specific dietary advice (Burr, M. L., shfield-Watt, P. A., Dunstan, F. D. et al , 2003). This trial recruited men under the age of 70 who were being treated for angina (50% also had a prior MI). Recruitment occurred in two phases: Phase I was between 1990 and 1992 and phase II between 1993 and 1996, follow up was in 1999. A total of 3114 participants were randomised to one of four groups:

1. Advice to eat at least 2 portions of oily fish per week or take up to 3 'MaxEPA' fish oil capsules daily (each capsule contains 170 mg EPA and 115 mg DHA) as a partial or total substitute. In the first phase of the study, participants chose diet or capsules or a mixture, in the second phase, participants were sub randomised to receive dietary advice or fish oil capsules.

2. Advice to eat 4-5 portions of fruit and vegetables, to drink one glass of orange juice daily and to increase intake of soluble fibre in the form of oats.

3. A combination of 1. and 2.

4. 'Sensible eating' – non-specific advice that did not include either of the above interventions.

Advice to increase consumption of fruit and vegetables was found to be poorly complied with and the advice did not confer any benefit on mortality (all deaths, cardiac deaths and sudden deaths) compared with 'sensible eating'.

5.3.9   Evidence into recommendations

Only one randomised controlled trial found on the effectiveness of an increased fruit and vegetables diet in patients with angina (Burr, M. L., shfield-Watt, P. A., Dunstan, F. D. et al , 2003) and no randomised controlled trials were identified in patients with peripheral arterial disease or following stroke. The GDG decided to recommend five portions of fruit and vegetables per day in line with advice given to the general population. For further information, please refer to the Department of Health paper 'Choosing a Better Diet: a food and health action plan' (Department of Health, 2005), the Department of Health's website: 5aday.nhs.uk, the COMA report 'Nutritional Aspects of Cardiovascular Disease' (de la Hunty, A., 1995) and the Food Standards Agency website (www.eatwell.gov.uk/healthydiet/) (Food Standards Agency, 2007).

5.3.10   Clinical effectiveness of increased omega 3 fatty acids (dietary or supplementation) for the primary prevention of CVD

One randomised controlled trial was identified that examined the effect of omega 3 fatty acid supplements in Japanese hypercholesterolaemia patients (18 645) without and with coronary artery disease (26% of the total number of recruits in the study, of which 21% had a prior history of MI, 61% had angina and 18% were recruited following revascularisation) (Yokoyama, M., Origasa, H., Matsuzaki, M. et al , 2007). Patients in the intervention group were given omega 3 fatty acid supplements (1800 mg / day) plus a statin, either pravastatin (average dose 10 mg /day) or simvastatin (5.6 mg / day). Patients in the control group received a statin alone, either pravastatin (average dose 10 mg / day) or simvastatin (5.6 mg / day). At a mean follow up of 4.6 years and for patients with and without coronary artery disease, omega 3 fatty acid

supplementation was associated with a reduction in the primary outcome of any major coronary event (including sudden death, fatal and non fatal MI, unstable angina, angioplasty, stenting and CABG) (HR 0.81, 95%CI 0.69 to 0.95). Omega 3 fatty acid supplementation was associated with a reduction in the secondary outcomes of unstable angina (HR 0.76, 95%CI 0.62 to 0.95) and non fatal coronary events (HR 0.81, 95%CI 0.68 to 0.96) Omega 3 fatty acid supplementation did not confer any benefit compared with no supplementation for the following secondary outcomes; sudden death, fatal MI, non fatal MI, CABG or PTCA, coronary death or MI, fatal MI or non fatal MI, and coronary death (Yokoyama, M., Origasa, H., Matsuzaki, M. et al , 2007).

Analysis of the results for patients without coronary artery disease found that omega 3 fatty acid supplementation had no effect on the primary outcome, or any of the secondary outcomes compared with no supplementation. Analysis of the results of omega 3 fatty acid supplementation in the patients with coronary artery disease for the primary outcome of any major coronary event gave a hazard ratio of 0.82 (95%CI 0.657 to 0.998) compared with no supplementation. Unstable angina was reduced in the coronary artery disease population allocated to omega 3 supplementation unstable angina (HR 0.72, 95%CI 0.55 to 0.95) (Yokoyama, M., Origasa, H., Matsuzaki, M. et al , 2007).

5.3.11 Evidence into recommendations

The GDG considered that for dietary fish, the recommendations made by the Joint British Societies' guidelines on prevention of CVD in clinical practice (Wood, D., Wray, R., Poulter, N. et al , 2005) should be adopted, which recommends at least two servings of omega-3 fatty acid containing fish per week. The GDG decided that there was insufficient evidence to recommend omega 3 fatty acid supplementation for people at high risk of CVD.

5.3.12 Clinical effectiveness of increased omega 3 fatty acids (dietary or supplementation) for the secondary prevention of CVD

One randomised controlled trial was identified in patients with a history of CVD which compared increased consumption of oily fish or taking omega 3

fatty acid supplements versus no change in diet (Burr, M. L., shfield-Watt, P. A., Dunstan, F. D. et al , 2003). This trial has previously been described in the section on clinical effectiveness of increased fruit and vegetables diet for the secondary prevention of CVD. Trial participants were men under the age of 70 who were being treated for angina (50% also had a prior MI). A total of 3114 participants were randomised to one of four groups:

1. Advice to eat at least 2 portions of oily fish per week or take up to 3 'MaxEPA' fish oil capsules daily (each capsule contains 170 mg EPA and 115 mg DHA) as a partial or total substitute. In the first phase of the study, participants chose diet or capsules or a mixture, in the second phase, participants were sub randomised to receive dietary advice or fish oil capsules.

2. Advice to eat 4-5 portions of fruit and vegetables, to drink one glass of orange juice daily and to increase intake of soluble fibre in the form of oats.

3. A combination of 1. and 2.

4. 'Sensible eating' – non-specific advice that did not include either of the above interventions.

Four way analysis found that advice to eat oily fish or take supplements was not associated with a significant change in total number of deaths, number of cardiac deaths or number of sudden deaths compared with the control group who were told to 'eat sensibly'.

Two way analysis comparing 'all fish advice' (intervention groups 1 and 3) with 'no fish advice' (intervention group 2 and control group 4) found that advice to eat oily fish or take supplements was not associated with a change in the total number of deaths but was associated with an increase in the number of cardiac deaths (11.5% 'all fish advice' versus 9.0% 'no fish advice', P = 0.02) and number of sudden deaths (4.6% 'all fish advice' versus 3% 'no fish advice', P = 0.02).

Adjusted hazard ratios were calculated for 'all fish advice' (intervention groups 1 and 3) compared to 'no fish advice' (intervention group 2 and control group 4). 'All fish advice' was found to be associated with an increase in the risk of sudden death (HR 1.54, 95% CI 1.06 to 2.23) compared with 'no fish advice' but no change was observed for total or cardiac mortality.

A subgroup analysis was performed and adjusted hazard ratios were calculated separately for those given fish advice (intervention groups 1 and 3) who were sub-randomised to receive omega 3 fatty acid supplements (a subset of 462 patients were sub-randomised to this treatment during the second phase of recruitment) and all others given 'fish advice' who were not sub randomised (n = 1109) compared with 'no fish advice' (intervention group 2 and control group 4). It was found that those sub randomised to receive omega 3 fatty acid supplements during the second phase of the trial had an increased risk of cardiac death (HR 1.45, 95% CI 1.05 to 1.99) and sudden death (HR 1.84, 95% CI 1.11 to 3.05) compared with those randomised to receive 'no fish advice' throughout the trial. All other participants who received 'fish advice' (intervention groups 1 and 3) but were not sub randomised to receive supplements were not found to have an increased risk of total mortality, cardiac mortality or sudden death compared with 'no fish advice'. It should be noted that this was a post hoc subgroup analysis, and the results should be interpreted with caution because the patient numbers in the analysis indicate that the analysis is statistically underpowered.

A second randomised controlled trial was identified that examined the effect of omega 3 fatty acid supplements in Japanese hypercholesterolaemia patients (18 645) without and with coronary artery disease. Patients with coronary artery disease accounted for 26% of the total number of participants in the study, and 21% had a prior history of MI, 61% had angina and 18% were recruited following revascularisation) (Yokoyama, M., Origasa, H., Matsuzaki, M. et al , 2007). This study has been described in the section on clinical effectiveness of increased omega 3 fatty acids (dietary or supplementation) for the <u>primary prevention of CVD.</u> Patients in the intervention group were given omega 3 fatty acid supplements (1800 mg / day) plus a statin either

pravastatin (average dose 10 mg /day) or simvastatin (5.6 mg / day). Patients in the control group received a statin alone, either pravastatin (average dose 10 mg / day) or simvastatin (5.6 mg / day). Analysis of the results of omega 3 fatty acid supplementation in the patients with coronary artery disease for the primary outcome of any major coronary event gave a hazard ratio of 0.82 (95%CI 0.657 to 0.998) compared with no supplementation. Unstable angina was reduced in the coronary artery disease population allocated to omega 3 supplementation unstable angina (HR 0.72, 95%CI 0.55 to 0.95).

5.3.13 Evidence into recommendations

Due to the conflicting results of the two studies described for oily fish consumption / omega 3 fatty acid supplementation (Burr, M. L., shfield-Watt, P. A., Dunstan, F. D. et al , 2003) (Yokoyama, M., Origasa, H., Matsuzaki, M. et al , 2007), and the lack of evidence for patients with peripheral arterial disease or following stroke, the GDG considered that for dietary fish, the recommendations made by the Joint British Societies' guidelines on prevention of CVD in clinical practice (2005) (Wood, D., Wray, R., Poulter, N. et al , 2005) should be adopted, which recommends at least two servings of omega-3 fatty acid containing fish per week. The GDG decided that there was insufficient evidence to recommend omega 3 fatty acid supplementation in patients with angina, peripheral arterial disease or stroke.

5.4   Plant stanols and sterols

[Return to Recommendations]

5.4.1 Evidence statements for plants stanols and sterols

5.4.1.1 No randomised controlled trials were identified in people at high risk of CVD that compared giving plant stanols and sterols with usual diet for the outcomes of mortality or morbidity.

5.4.1.2 No randomised controlled trials with cardiovascular endpoints were identified that compared giving plant stanols or sterols with usual diet in patients with CVD

5.4.2 Evidence into recommendations

No randomised controlled trials were identified which examined the effectiveness of plant stanols and sterols in primary and secondary prevention with respect to cardiovascular outcomes. The GDG therefore decided that there was insufficient evidence to recommend their use.

5.5   Regular physical activity

[Return to Recommendations]

5.5.1   Evidence Statements for physical activity

5.5.1.1	*No randomised controlled trials were identified in people at high risk of CVD that compared regular physical activity with sedentary lifestyle for the outcomes mortality or morbidity.*
5.5.1.2	*Two studies found that programmes to increase physical activities were cost effective compared to no exercise programmes in improving outcomes for people at risk of CVD.*
5.5.1.3	*No randomised controlled trials were identified in patients with angina, peripheral arterial disease or following stroke that compared regular physical activity with sedentary lifestyle for the outcomes of mortality or morbidity.*
5.5.1.4	*In selected patients after an MI, randomisation to an exercise prescription programme reduced the risk of death from MI after 3 years, but not all cause or cardiovascular mortality.*
5.5.1.5	*In selected patients after an MI, exercise performed at a level sufficient to increase physical work reduced all cause mortality and cardiovascular mortality in long term follow up.*
5.5.1.6	*One small randomised controlled trial in patients with stable intermittent claudication showed that physical training classes were not associated with a reduction in total cholesterol or triglyceride levels compared with usual care.*
5.5.1.7	*Two cost effectiveness studies concluded that exercise programmes are cost effective compared to no exercise programme in patients with CHD.*

5.5.2 Clinical effectiveness of regular physical activity for the primary prevention of CVD

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of regular physical activity versus sedentary lifestyle for the outcomes of all cause mortality, cardiovascular mortality or cardiovascular morbidity.

5.5.3 Cost effectiveness of regular physical activity for the primary prevention of CVD

Two studies were found which addressed this question, one Canadian (Lowensteyn, I., Coupal, L., Zowall, H. et al , 2000) and one American (Marshall, T., Bryan, S., Gill, P. et al , 2005). None of the studies were done in the UK.

Study (Marshall, T., Bryan, S., Gill, P. et al , 2005) was a cost utility analysis which used effectiveness data from the Framingham study. It was not clear as to the sources of the utility data they used in their decision model however it did use appropriate methodology. The authors did not provide resource use and quantities separately which makes it difficult to reproduce their work.

The authors reported that exercise resulted in 529.8 discounted QALYs over the 30 year follow up. Cost/QALY gained was $1395/QALY. A range of univariate sensitivity analyses were done, and the model was robust to all changes in assumptions that were tested.

The second study (Lowensteyn, I., Coupal, L., Zowall, H. et al , 2000) was a cost effectiveness which used effectiveness data from a number of different studies published between 1980 and 1999. The authors were very detailed in their reporting and references were provided. Resource use and quantities were provided separately.

The authors reported results separately for men and women and stratified results into three age groups. The results showed that exercise, especially unsupervised exercise was a cost effective intervention compared to no exercise. The benefits were more for younger men and less in the elderly man

and women. The cost per life year gained ranged between $645/LYG for the 35-54year age group in unsupervised men to $30704 in the 65-74 year age group attending supervised sessions. For women the incremental cost effectiveness ratios for women ranged between $4915 to $ 87166 respectively.

In conclusion, a programme to increase physical activity compared to no programme is cost effective in improving outcomes for people at risk of CVD. The results from the two studies showed that younger men benefit more from such programmes than older men and women. Results also showed that unsupervised activity is more cost effective than supervised classes. This however depended on the assumption that there is almost 100% adherence to the exercise programme.

5.5.4 Evidence into recommendations

Due to the lack of clinical outcome data, it was decided by the GDG that recommendations would be made based on those of the following documents:

- The Chief Medical Officer's report 'At least five a week: Evidence on the impact of physical activity and its relationship to health' (Department of Health., 2004)

- The NICE public health intervention guidance no. 2 'Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling' (National Institute for Health and Clinical Excellence, 2006)

- The Joint British Societies' guidelines on prevention of CVD in clinical practice (Wood, D., Wray, R., Poulter, N. et al , 2005).

These guidelines recommend that thirty minutes of at least moderate intensity activity should be taken per day, at least five days a week. The chief medical officer's report (ref) describes what is meant by moderate intensity activity: A person who is doing moderate intensity activity will usually experience:

- An increase in breathing rate

- An increase in heart rate, to the level where the pulse can be felt, and

- A feeling of increased warmth, possibly accompanied by sweating on hot or humid days.

Also, a bout of moderate intensity activity can be continued for many minutes without a feeling of exhaustion.

The typical activity pattern of a moderately active person would include doing one or more of the following:

- Regular active commuting on foot or by bicycle

- Regular work related physical tasks

- Regular household and garden activities

- Regular active recreation or social sport at moderate intensity.

Examples of the intensities and energy expenditures for common types of physical activity are given in Table 1.

Table 1

Intensities and energy expenditures for common types of physical activity

Activity	Intensity	Intensity (METS)	Energy expenditure (Kcal equivalent, for a person of 60kg doing the activity for 30minutes)
Ironing	Light	2.3	69
Cleaning and dusting	Light	2.5	75
Walking – strolling, 2mph	Light	2.5	75
Painting/decorating	Moderate	3.0	90
Walking – 3mph	Moderate	3.3	99
Hoovering	Moderate	3.5	105
Golf – walking, pulling clubs	Moderate	4.3	129
Badminton – social	Moderate	4.5	135
Tennis – doubles	Moderate	5.0	150
Walking – brisk, 4mph	Moderate	5.0	150
Mowing lawn – walking, using power-mower	Moderate	5.5	165
Cycling – 10-12mph	Moderate	6.0	180
Aerobic dancing	Vigorous	6.5	195
Cycling – 12 -14mph	Vigorous	8.0	240
Swimming – slow crawl, 50 yards per-minute	Vigorous	8.0	240
Tennis – singles	Vigorous	8.0	240
Running – 6mph (10minutes/mile)	Vigorous	10.0	300
Running – 7mph (8.5minutes/mile)	Vigorous	11.5	345
Running – 8mph (7.5 minutes/mile)	Vigorous	13.5	405

MET = Metabolic equivalent
1 MET = A persons metabolic rate (rate of energy expenditure) when at rest
2 METs = A doubling of the resting metabolic rate

Adapted from the Chief Medical Officers (2004). Found at: www.dh.gov.uk

The Chief Medical Officer's report also provides useful information on the potential risks associated with physical activity. It stresses that the risks associated with taking part in physical activity at levels that promote health are

low and that the health benefits far outweigh the risks. The report states that the greatest risks in terms of sustaining sports injuries are faced by:

- People who take part in vigorous sports and exercise

- People to do 'excessive' amounts of exercise, and

- People with existing musculoskeletal disease or at high risk of disease.

In relation to cardiovascular risk, the report states that 'extremely rarely, inactive and unfit individuals who start doing vigorous physical activity may face increased cardiovascular risks'. In addition, it states that vigorous levels of activity may increase the risk of heart attack, although this increased risk appears to only apply to men with high blood pressure and is largely limited to people who do not exercise regularly.

5.5.5 Clinical effectiveness of regular physical activity for primary and secondary prevention of CVD

No randomised controlled trials were identified in patients with a history of angina alone, stroke, or peripheral arterial disease that examined the effect of regular physical activity versus a sedentary lifestyle for the outcomes of all cause mortality, cardiovascular mortality or cardiovascular morbidity.

One randomised controlled trial was identified on the effectiveness of regular physical activity versus sedentary lifestyle to modify lipid profiles in patients with a history of stable intermittent claudication for at least six months (Gelin, J., Jivegard, L., Taft, C. et al , 2001). The trial recruited men and women from a regional cohort of 400 to 500 people. A total of 264 participants were randomised to one of three groups:

1. Usual care

2. Physical training classes (a program of 3 X 30 minute sessions of specific walking training per week for the first six months, supervised by a physiotherapist. From 6 months to 1 year, 2 sessions per week were offered)

3. Invasive treatment (endovascular or open surgical procedure).

Participants were then followed up for 1 year. Physical training classes did not confer any benefit over usual care for the primary outcome of maximum exercise power in Watts or for the secondary physiological endpoints. Total cholesterol and triglycerides were measured at randomisation and at 1 year and there were no differences between the physical training class and usual care groups. In addition, no difference in the number of deaths was seen between groups however, this was not a pre-specified outcome measure.

Due to the lack of clinical outcome data in this trial, it was decided by the GDG to consider evidence used in the NICE guidance: 'Myocardial infarction: Secondary prevention in primary and secondary care for patients following a myocardial infarction', CG48 (2007)

Two studies were identified which examined the impact of regular physical activity to improve outcome in patients with a prior MI. The first study was a randomised controlled trial in 651 men, aged 35 to 64 years with a documented MI greater than or equal to 8 weeks but less than 3 years before recruitment conducted between 1976 and 1979 (Naughton, J., Dorn, J., and Imamura, D., 2000).

The exercise intervention was an individualised exercise prescription based on the patient's ECG-monitored treadmill multistage graded test (MSET). An exercise target heart rate guided the prescription and was determined as 85% of the peak rate achieved on the MSET. This group performed brisk physical activity in the laboratory for 8 weeks (1 hour per day, 3 times per week). After 8 weeks, participants exercised in a gymnasium or swimming pool (15 minutes cardiac exercise followed by 25 minutes of recreational games). Participants were encouraged to attend 3 sessions per week. Patients in the control group were told to maintain their normal routine but not to participate in any regular exercise.

At the 3 year follow up, randomisation to the exercise prescription programme was found to be associated with a reduction in death from MI (RR 0.13, 95%

CI 0.02 to 0.78) compared with control. The exercise intervention was not associated with a reduction in all cause mortality (RR 0.63, 95% CI 0.32 to 1.15) or cardiovascular mortality (RR 0.71, 95% CI 0.34 to 1.33) compared with control. The authors noted that by the end of the trial 23% of the treatment group had stopped attending exercise sessions, whereas 31% of the control group reported that they were exercising regularly (Naughton, J., Dorn, J., and Imamura, D., 2000). A secondary analysis of this data (Dorn, J., Naughton, J., Imamura, D. et al , 1999) presented age- adjusted risk ratios and it was found that at the 3 year follow up point, the exercise intervention was associated with a reduction in all cause mortality (0.86, 95% CI 0.76 to 0.98) but not CVD mortality (0.87, 95% CI 0.74 to 1.02) compared with control.

After 3 years of the trial, the patients were followed up for 5, 10, 15 and 19 years examining all cause mortality and cardiovascular mortality. The results of this follow - up were published in the second study (Dorn, J., Naughton, J., Imamura, D. et al , 1999) which was a secondary analysis of the first study. For long term follow up at 5, 10, 15 and 19 years, the age adjusted relative risk reductions for all cause mortality were 0.91 (95% CI 0.82 to1.00), 0.88 (95% CI 0.83 to 0.95), 0.89 (95% CI 0.84 to 0.95) and 0.92 (95% CI 0.87 to 0.97), respectively for the exercise prescription programme compared with control. For long term follow up at 5, 10, 15 and 19 years, the age adjusted relative risk reductions for CVD mortality were 0.91 (95% CI 0.81 to 1.03), 0.89 (95% CI 0.82 to 0.96), 0.89 (95% CI 0.82 to 0.96) and 0.93 (95% CI 0.87 to 0.99), respectively for the exercise prescription programme compared with control.

Thus, improvement in physical work capacity resulted in consistent survival benefits throughout the full 19 years. The authors concluded that exercise performed at a level sufficient to increase physical work capacity may have long-term survival benefits in MI survivors.

5.5.6   Evidence into recommendations

It was decided by the GDG that recommendations would be made based on those of the Chief Medical Officer's report 'At least five a week: Evidence on the impact of physical activity and its relationship to health' (Department of Health., 2004) and the NICE public health intervention guidance no. 2 'Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling' (National Institute for Health and Clinical Excellence, 2006) and the Joint British societies' guidelines on prevention of CVD in clinical practice (Wood, D., Wray, R., Poulter, N. et al , 2005).

Please refer to chapter 5 (lifestyle for the primary prevention of CVD) for further details of the Chief Medical Officer's report and see the full report at www.dh.gov.uk.

5.6 Combined cardioprotective dietary advice and regular physical activity (primary prevention of CVD)

5.6.1 Evidence statements for combined cardioprotective dietary advice and regular physical activity

5.6.1.1 *No randomised controlled trials were identified in people at high risk of CVD that compared combined cardioprotective dietary advice and regular physical activity with usual lifestyle for the outcomes mortality or morbidity.*

5.6.1.2 *One randomised controlled trial in people at high risk of CVD found that a combination of low fat diet and aerobic exercise was associated with a reduction in total cholesterol and triglycerides and an increase in HDL cholesterol levels compared with control.*

5.6.1.3 *A second randomised controlled trial found that a combination of low fat diet and aerobic exercise was associated with a reduction in total cholesterol and LDL cholesterol compared with usual diet.*

5.6.1.4 *A third randomised controlled trial found that a combination of diet and aerobic exercise was not associated with a change in lipid levels compared with control.*

5.6.2 Clinical effectiveness of combined cardioprotective dietary advice and regular physical activity for the primary prevention of CVD

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of dietary advice versus usual diet and / or regular physical activity versus sedentary lifestyle for the outcomes of all cause mortality, cardiovascular mortality or cardiovascular morbidity.

Three randomised controlled trials were identified which examined the effectiveness of diet, regular physical activity and the combination of both

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interventions to improve serum lipid level profiles in people with elevated CVD risk factors (Anderssen, S. A., Haaland, A., Hjerman, I. et al , 1995; Hellenius ML, de Faire U, Berglund B et al , 1993; Stefanick, M. L., Mackey, S., Sheehan, M. et al , 1998).

The first study was a randomised controlled trial of six months duration in 158 healthy men aged 35 to 60 years with moderately elevated CVD risk factors (Hellenius ML, de Faire U, Berglund B et al , 1993). Participants were randomised to one of three intervention groups or to the control group (usual lifestyle). The first intervention was diet whereby participants were given verbal and written dietary advice that total fat consumption should comprise no more than 30% of energy intake, saturated fat no more than 10% of energy, cholesterol consumption should be less than 300 mg/day, polyunsaturated fat up to 10% of energy, monounsaturated fat 10-15% energy, carbohydrates (mainly complex) 50-60% energy and protein 10-20% energy.

The second intervention was physical activity; participants were given verbal and written advice to take regular physical activity of an aerobic type 2-3 times per week for 30-45 minutes at 60-80% maximum heart rate.

The third intervention was a combination of diet and physical activity. The control group was told to continue with the diet and lifestyle as prior to joining the study.

After six months, lipid levels were measured and no significant differences were found in total cholesterol, LDL cholesterol or HDL cholesterol for any of the intervention groups compared to control.

The second study was a randomised controlled trial (Anderssen, S. A., Haaland, A., Hjerman, I. et al , 1995) of one year duration in 198 men and 21 women aged 41-50. Participants who each had several coronary risk factors were recruited in Oslo and were then randomised to one of three intervention groups or to the control group. The dietary intervention consisted of

counseling to reduce intake of saturated fat and cholesterol and to consume more fish. Energy restriction advice was given to those overweight.

For the physical activity intervention, participants attended aerobic exercise sessions 3 times per week for one hour where they exercised at 60-80% of their peak heart rate in supervised classes of 14 to 20 people.

The third intervention group was a combination of diet and physical activity as already described. The control group was told not to change their lifestyle during the trial but as all the other participants they were advised against smoking.

After one year, no significant differences in total, LDL or HDL cholesterol were observed for the diet only or physical activity only interventions compared to control. For the combined diet and physical activity intervention, a significant decrease in total cholesterol and a significant increase in HDL cholesterol were observed compared to control. In addition, triglycerides were found to be significantly reduced in all three intervention groups compared to control.

The final randomised controlled trial (Stefanick, M. L., Mackey, S., Sheehan, M. et al , 1998) was of one year duration and included 197 men and 180 postmenopausal women. Women were 45 to 64 years of age, had HDL cholesterol levels < 1.55 mmol/l, and LDL cholesterol levels between 3.23 and 5.42 mmol/l. Men were 30 to 64 years of age, had HDL cholesterol levels < 1.14 mmol/l, and LDL cholesterol levels between 3.23 and 4.90 mmol/l.

Participants were randomised to one of three intervention groups or to the control group. The first intervention was diet where participants were advised to follow the National Cholesterol Education Program (NCEP) Step 2 diet: total fat less than 30% of energy intake, saturated fat less than 7% of energy and cholesterol less than 200 mg per day.

The second intervention was aerobic exercise: participants attended 6 weeks of supervised 1 hour sessions, 3 times per week (held separately for groups 2 and 3). For the remaining 7 to 8 months of the trial, they could attend supervised classes and / or undertake home-based activities with the goal of

engaging in aerobic activity equivalent to at least 16km of brisk walking or jogging each week.

The control group was asked to maintain their usual diet and exercise habits.

After one year, for both men and postmenopausal women, significant decreases in total and LDL cholesterol levels were observed in the diet plus physical activity intervention group compared to control.

In addition, one systematic review was identified that assessed the effectiveness of multiple risk factor interventions which included smoking cessation, physical activity and dietary advice with or without pharmacological intervention on a number of outcomes including all cause and CHD mortality (Ebrahim, S., Beswick, A., Burke, M. et al , 2006). A total of 39 randomised controlled trials were identified in adults of ≥ 40 years of age from general populations, workforce populations and high risk groups. Ten of these trials reported clinical event data and a meta-analysis of these ten trials found that multiple risk factor interventions were not associated with a reduction in total or coronary heart disease (CHD) mortality.

The conclusion of the review was that 'The pooled effects suggest multiple risk factor intervention has no effect on mortality. However, a small but potentially important benefit of treatment (about a 10% reduction in CHD mortality) may have been missed. Risk factor changes were relatively modest, were related to the amount of pharmacological treatment used, and in some cases may have been over-estimated because of regression to the mean effects, lack of intention to treat analysis, habituation to blood pressure measurement, and use of self-reports on smoking.'

5.6.3   Evidence into recommendations

Due to the lack of evidence on the effectiveness of combined approaches, it was decided by the GDG that cardioprotective dietary advice and regular physical activity interventions would be considered separately.

5.6.4 Cost effectiveness of combined cardioprotective dietary advice and regular physical activity for the primary prevention of CVD

There were no cost effectiveness studies found surrounding the use of combined dietary advice and regular physical activity in the prevention of CVD.

5.7 Alcohol

[Return to Recommendations]

Alcohol consumption for men should be limited to up 3 to 4 units a day, and for women alcohol should be limited to up to 2 to 3 units of alcohol a day. People should avoid binge drinking. Further information can be found on the Foods Standards Agency website www.eatwell.gov/healthdiet/.

5.8 Weight management

[Return to Recommendations]

For guidance in weight management in people at high risk of CVD refer to the NICE guideline:

- Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children CG43 (2006) http://guidance.nice.org.uk/CG43.

5.9 Smoking cessation

[Return to Recommendations]

For guidance on smoking cessation refer to the NICE Technology appraisals and guidance on public health interventions:

- Smoking cessation - bupropion and nicotine replacement therapy. The clinical effectiveness and cost effectiveness of bupropion (Zyban) and Nicotine Replacement Therapy for smoking cessation TA039 (2002).

- Brief interventions and referral for smoking cessation in primary care and other settings PHI001, (2006)

- .Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007).

- Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities. NICE public health guidance 10 (2008).

6 Drug therapy for the primary prevention of cardiovascular disease (CVD)

[Hyperlink to Introduction]

6.1 Recommendations for drug therapy

6.1.1 When considering lipid modification therapy in primary and secondary prevention, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality.

Drug therapy for primary prevention

6.1.2 Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimised if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

- **smoking status**
- **alcohol consumption**
- **blood pressure (see 'Hypertension', NICE clinical guideline 34)**
- **body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)**

- **fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)**
- **fasting blood glucose**
- **renal function**
- **liver function (transaminases)**
- **thyroid-stimulating hormone (TSH) if dyslipidaemia is present.**

Statins for primary prevention

6.1.3 **Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available or appropriate (for example, older people, people with diabetes or people in high-risk ethnic groups).[13]**

6.1.4 **The decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as comorbidities and life expectancy.[17]**

6.1.5 **If statin treatment is appropriate, it should be offered as soon as practicable after a full risk factor assessment.**

6.1.6 **When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).[17]**

6.1.7 **Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.**

6.1.8 **Higher intensity statins[14] should not routinely be offered to people for the primary prevention of CVD.**

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[13] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094

[14] 'Higher intensity statins' are statins used in doses that produce greater cholesterol lowering than simvastatin 40 mg, for example simvastatin 80 mg.

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6.1.9 A target for total or LDL cholesterol is not recommended for people who are treated with a statin for primary prevention of CVD.

6.1.10 Once a person has been started on a statin for primary prevention, repeat lipid measurement is unnecessary. Clinical judgement and patient preference should guide the review of drug therapy and whether to review the lipid profile.

Fibrates for primary prevention

6.1.11 Fibrates should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, fibrates may be considered.

Nicotinic acid for primary prevention

6.1.12 Nicotinic acid should not be offered for the primary prevention of CVD.

Anion exchange resins for primary prevention

6.1.13 Anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, an anion exchange resin may be considered.

Ezetimibe for primary prevention

6.1.14 People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' (NICE technology appraisal guidance 132).

Combination therapy for primary prevention

6.1.15 The combination of an anion exchange resin, fibrate or nicotinic acid with a statin should not be offered for the primary prevention of CVD.

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6.1.16 The combination of a fish oil supplement with a statin should not be offered for the primary prevention of CVD.

Monitoring of statin treatment for primary and secondary prevention

6.1.17 If a person taking a statin starts taking additional drugs, or needs treatment for a concomitant illness that interferes with metabolic pathways or increases the propensity for drug and food interactions, consider reducing the dose of the statin, or temporarily or permanently stopping it.

6.1.18 People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, creatine kinase should be measured.

6.1.19 Creatine kinase should not be routinely monitored in asymptomatic people who are being treated with a statin.

6.1.20 Baseline liver enzymes should be measured before starting a statin. Liver function (transaminases) should be measured within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.

6.1.21 People who have liver enzymes (transaminases) that are raised but are less than 3 times the upper limit of normal should not be routinely excluded from statin therapy.

6.1.22 If a person develops an unexplained peripheral neuropathy, statins should be discontinued and specialist advice sought.

6.2 Introduction to drug therapy for the primary prevention of CVD

This chapter considers pharmacological treatments for people whose 10 year risk of developing CVD is greater than 20% but who have not yet experienced an event. People with diabetes or familial lipid disorders are excluded from these recommendations and are considered in alternative NICE guidance.

Statins are the drug of first choice for the primary prevention of CVD as they are more effective at lowering LDL cholesterol than other drugs currently licensed for primary prevention and have been shown to have a greater impact on clinical outcome.

The NICE Technology Appraisal (NICE technology appraisal guidance 94, 'Statins for the prevention of cardiovascular events' 2006) has thoroughly and comprehensively reviewed the evidence on the effectiveness and cost effectiveness of statins and our recommendations on the initiation of statin therapy are based upon this report (National Institute for Health and Clinical Excellence, 2006).

The NICE Technology Appraisal recommends statin therapy as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This may result in more than half of the men aged over 50 years and 20% of the women over 65 years being considered for lipid lowering therapy.

The routine use of higher intensity statins has not been recommended for primary prevention. Neither has this guideline recommended the use of cholesterol targets for primary prevention. Treatment targets are considered further in the secondary prevention drug therapy chapter.

This guideline has not made a detailed study of the safety of statins which is the proper concern of other regulatory agencies but has considered evidence from one systematic review and two meta-analyses of statin safety. Statins are generally well tolerated and the occurrences of serious adverse events are rare especially at the doses used for primary prevention.

Before the licensing of statins, fibrates were one of the mainstays of lipid modification, usually for people with established CVD. Their use for primary prevention was controversial and the failure to demonstrate reductions in total mortality in the 1978 cooperative World Health Organisation primary prevention trial (World Health Organization., 1978) and the 1987 Helsinki Heart Study (Frick, M. H., Elo, O., Haapa, K. et al , 1987) led to concerns about the effectiveness of fibrates.

Anion exchange resins were also used as first line agents for the management of dyslipidaemia and in secondary prevention before the advent of statins. The 1984 Lipid Research Clinics coronary primary prevention trial (Insull, W., Gotto, A. M., Probstfield, J. et al , 1984) was an early trial of effectiveness with significant reductions in cardiovascular endpoints but no significant difference in total mortality.

In the last 20 years little further progress has been made on randomised trials with cardiovascular outcomes testing the effectiveness of fibrates or anion exchange resins for primary prevention.

6.3 Statins

6.3.1   Evidence statements for statins

Statin therapy
6.3.1.1   *For people without clinical evidence of CVD at study entry, a meta-analysis found that statin therapy was associated with a reduction in the risk of fatal MI and nonfatal MI and the composite outcomes of CHD death and nonfatal MI, and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization compared with placebo.* 6.3.1.2   *For people without clinical evidence of CHD at study entry, a meta-analysis found that statin therapy was associated with a reduction in the risk of all cause mortality, fatal MI, nonfatal MI and stable angina and the composite outcomes of CHD death and nonfatal MI, and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization compared with placebo.*
6.3.1.3   *No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity therapy in people at high risk of CVD.*
6.3.1.4   *The NICE Statin TA94, concluded that statin treatment in patients with CVD is cost effective compared with no statin treatment (NICE Technology Appraisal guidance, 'Statins for the prevention of cardiovascular events' TA 94, 2006).*
Adverse events

6.3.1.5   In a systematic review of cohort studies, randomised trials, voluntary notifications to regulatory authorities and published case reports, the incidence of major adverse events associated with skeletal muscle and the liver was low.

6.3.1.6   Incidence of rhabdomyolysis was estimated at 3.4 per 100,000 person years (this rose to 4.2 per 100,000 person years in patients treated with statins which are metabolised by cytochrome P450 3A4 and was ten fold higher when a statin was combined with gemfibrozil).

6.3.1.7   Statin therapy was not found to be associated with a significant increase in the incidence of raised creatine kinase. Incidence of myopathy was estimated at 11 per 100,000 person years and incidence of peripheral neuropathy was estimated at 12 per 100,000 person years.

6.3.1.8   Elevations of the liver enzymes alanine aminotransferase and / or aspartate aminotransferase were reported more frequently in those treated with statins compared with placebo, especially at higher doses. Trials showed no excess of liver disease or chronic kidneyl disease in statin allocated participants.

6.3.1.9   A meta-analysis of data from 18 randomised controlled trials found statin therapy to be associated with a greater odds of any adverse event compared with placebo. A number needed to harm (NNH) analysis was performed and compared to placebo the number of people that would need to be treated with a statin to observe any statin-related adverse event was197 people, to observe a statin-related rhabdomyolysis was 7,428 people and to observe statin-related rhabdomyolysis or creatine kinase > 10 x upper limit of normal was 3,400 people.

> *6.3.1.10* *A meta-analysis of 26 randomised controlled trials showed cancer incidence and cancer death to be unaffected by statin therapy. A subgroup analysis by cancer type also found no effect of statin therapy.*

6.3.2 Clinical effectiveness of statins

Throughout the guideline, we have reported 95% confidence intervals for relative risks (RR) and odds ratios (OR). Where the 95% confidence interval crosses the 'line of no effect' i.e., when the confidence intervals included 1, we have interpreted this as being non-significant. This interpretation holds even when the upper or lower limit of the confidence interval is 1.00.

The NICE Technology Appraisal (National Institute for Health and Clinical Excellence, 2006) entitled '*Statins for the prevention of cardiovascular events*' 2006 states that:

- Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.

The recommendation was based upon assessment of the effectiveness of statin therapy in people without clinical evidence of CVD at study entry and in people without clinical evidence of coronary heart disease (CHD) at study entry (some or all of whom had other CVD at study entry).

Two randomised controlled trials were identified that compared statin therapy with placebo in people without clinical evidence of CVD at study entry; CAIUS (Mercuri, M., Bond, M. G., Sirtori, C. R. et al , 1996) and CARDS (Colhoun, H. M., Betteridge, D. J., Durrington, P. N. et al , 2004), and a further three randomised controlled trials were identified that presented subgroup analyses for people without CVD; ASCOT-LLA (Sever, P. S., Dahlof, B., Poulter, N. R. et al , 2003), PROSPER (Shepherd, J., Blauw, G. J., Murphy, M. B. et al , 2002) and WOSCOPS (Shepherd, J., Cobbe, S. M., Ford, I. et al , 1995).

A meta-analysis was conducted that included data from three of these trials, two of which used pravastatin 40 mg; CAIUS (Mercuri, M., Bond, M. G., Sirtori, C. R. et al , 1996) and PROSPER (Shepherd, J., Blauw, G. J., Murphy, M. B. et al , 2002), and one used atorvastatin 10 mg; CARDS (Colhoun, H. M., Betteridge, D. J., Durrington, P. N. et al , 2004). Subgroup data from the ASCOT-LLA (Sever, P. S., Dahlof, B., Poulter, N. R. et al , 2003) and WOSCOPS (Shepherd, J., Cobbe, S. M., Ford, I. et al , 1995) trials was presented in a form that meant it could not be included in the meta-analysis. The meta-analysis found that statin therapy was associated with a reduction in the risk of fatal MI (RR 0.41, 95% CI 0.19 to 0.88), nonfatal MI (RR 0.60, 95% CI 0.37 to 0.97) and the composite outcomes of CHD death and nonfatal MI (RR 0.66, 95% CI 0.46 to 0.96) and of CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization (RR 0.64, 95% CI 0.48 to 0.84). Statin therapy was not found to be associated with a reduction in the risk of the following outcomes; all cause mortality, cardiovascular mortality, CHD mortality, stroke mortality, nonfatal stroke, unstable angina and revascularisation (National Institute for Health and Clinical Excellence, 2006).

Four randomised controlled trials were identified that compared statin therapy with placebo in people without clinical evidence of CHD at study entry; CAIUS (Mercuri, M., Bond, M. G., Sirtori, C. R. et al , 1996), CARDS (Colhoun, H. M., Betteridge, D. J., Durrington, P. N. et al , 2004), DALI (Diabetes Atorvastin Lipid Intervention (DALI) Study Group., 2001) and ASCOT-LLA (Sever, P. S., Dahlof, B., Poulter, N. R. et al , 2003). A further three randomised controlled trials were identified that presented subgroup analyses for people without CHD; PROSPER (Shepherd, J., Blauw, G. J., Murphy, M. B. et al , 2002), WOSCOPS (Shepherd, J., Cobbe, S. M., Ford, I. et al , 1995) and HPS (Heart Protection Study Collaborative Group., 2002).

A meta-analysis was conducted that included data from six of these trials, two of which used pravastatin 40 mg; CAIUS (Mercuri, M., Bond, M. G., Sirtori, C. R. et al , 1996) and PROSPER (Shepherd, J., Blauw, G. J., Murphy, M. B. et al , 2002). One used simvastatin 40 mg; HPS (Heart Protection Study Collaborative Group., 2002), and three used atorvastatin 10 mg; ASCOT-LLA

(Sever, P. S., Dahlof, B., Poulter, N. R. et al , 2003), CARDS (Colhoun, H. M., Betteridge, D. J., Durrington, P. N. et al , 2004), and DALI (Diabetes Atorvastin Lipid Intervention (DALI) Study Group., 2001). Subgroup data from the WOSCOPS trial was presented in a form that meant it could not be included in the meta-analysis. The meta-analysis found that statin therapy was associated with a reduction in the risk of all cause mortality (RR 0.83, 95% CI 0.70 to 0.98), fatal MI (RR 0.41, 95% CI 0.19 to 0.88), nonfatal MI (RR 0.58, 95% CI 0.36 to 0.94) and stable angina (RR 0.59, 95% CI 0.38 to 0.90) and the composite outcomes of CHD death and nonfatal MI (RR 0.64, 95% CI 0.50 to 0.82) and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization (RR 0.73, 95% CI 0.63 to 0.86). Statin therapy was not found to be associated with a reduction in the risk of the following outcomes: cardiovascular mortality, CHD mortality, stroke mortality, nonfatal stroke, PAD, unstable angina and revascularization (National Institute for Health and Clinical Excellence, 2006).

Results from the largest primary prevention study (n = 10,305) (ASCOT-LLA (Sever, P. S., Dahlof, B., Poulter, N. R. et al , 2003), which compared atorvastatin with placebo over approximately 3 years, suggested that the number needed to treat (NNT) to avoid either a death from CHD or a nonfatal MI, in people without existing CHD, was 95 (95% CI 60 to 216).

The NICE Technology Appraisal also considered whether statins differ in their relative effectiveness in the following population subgroups: In women compared with men at a similar level of cardiovascular risk; in people with diabetes compared to people without diabetes; or in people aged over 65 years compared with people aged under 65 years. Evidence from placebo-controlled trials showed that statins do not differ in their relative effectiveness in these subgroups. No placebo-controlled trials were identified that provided information relating to people from different ethnic groups.

The NICE Technology Appraisal (National Institute for Health and Clinical Excellence, 2006) states further that:

- When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug of low acquisition cost (taking into account required daily dose and product price per dose).

Cost effectiveness analysis indicates that simvastatin 40 mg and pravastatin 40 mg are both cost effective options for the primary prevention of CVD and the GDG considered that they were the most effective preparations at the lowest acquisition cost.

6.3.2.1 High intensity versus standard intensity statin therapy

No randomised controlled trials were identified that included cardiovascular events and compared higher intensity statin therapy with lower intensity therapy in people at high risk of CVD. Higher intensity statin therapy is understood as statins, including simvastatin 80mg, whose effect on cholesterol lowering is greater than that of simvastatin 40mg. The GDG thus considered it was inappropriate to routinely recommend their use for the primary prevention of CVD.

6.3.2.2 Cholesterol 'targets'

There are no clinical trials in primary prevention that have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL cholesterol targets in relation to clinical events. In addition, the clinical effectiveness of higher intensity statins and of combining statins with other lipid lowering drugs has yet to be demonstrated for primary prevention. It was decided that due to the lack of evidence, this guideline would not recommend the use of target levels of cholesterol for people at high risk of CVD. This is discussed further under the drug therapy secondary prevention.

6.3.2.3 Adverse events associated with lower intensity statin therapy

Three papers were identified on the adverse events associated with lower intensity statin therapy. Two papers reviewed and meta-analysed all adverse

events (especially those connected with skeletal muscle and the liver) (Law, M. and Rudnicka, A. R., 2006) (Silva, M. A., Swanson, A. C., Gandhi, P. J. et al , 2006) and one examined statin usage and the risk of cancer (Dale, K. M., Coleman, C. I., Henyan, N. N. et al , 2006).

It was noted by the GDG that there are limitations associated with these studies which may result in underestimation of adverse events. Firstly, all randomised controlled trials which have examined the effectiveness of statin therapy excluded some potential participants and a number of randomised controlled trials have also included a pre-randomisation run-in phase during which participants were treated with an open label statin. At the end of this time, some chose not to enter the trial or had some other reason not to do so. Thus, tolerability may be better and the incidences of adverse events lower in the trials than in unselected patients. Secondly, trials may not necessarily report all side effects that are experienced, although it is likely that serious side effects are reported. Thirdly, the duration of randomised controlled trials may be shorter than the lag time expected for cancer manifestation.

The first study was a systematic review of cohort studies, randomised trials, voluntary notifications to voluntary regulatory authorities and published case reports (Law, M. and Rudnicka, A. R., 2006). The incidence of rhabdomyolysis was estimated from the cohort studies: for statins other than cerivastatin was 3.4 (95% CI 1.6 to 6.5) per 100,000 person years, with a case fatality of 10%. The rates were about 10 times higher for cerivastatin and also for statins other than cerivastatin when taken with gemfibrozil. For cerivastatin taken with gemfibrozil, the incidence was 2,000 times higher, an absolute annual incidence of about 10%. Gemfibrozil increases the concentration of cerivastatin about 5-fold, which may be as a result of gemfibrozil-based inhibition of cerivastatin acid glucuronidation. Cerivastatin was withdrawn because of this unacceptable risk of serious side effects. In contrast there were no incidences of rhabdomyolysis with pravastatin or fluvastatin (not oxidised by CYP3A4) and the mean incidence of rhabdomyolysis among those taking lovastatin, simvastatin or atorvastatin (oxidised by cytochrome P450 3A4 (CYP3A4)) was 4.2 (95% CI 1.9 to 8.0)

per 100,000 person years. This difference was not statistically significant because relatively few person-years of follow-up were recorded for fluvastatin and pravastatin.

The mean incidence of myopathy in patients treated with statins was 11 per 100,000 person years (estimated from cohort studies, supported by randomised trials). There was no significant difference in the incidence of a raised creatine kinase to ≥ 10 X ULN on a single measurement during routine monitoring between participants in 13 trials allocated to a statin compared to those allocated placebo (83 per 100,000 person years of statin treatment versus 60 per 100,000 person years with placebo). In two trials none had creatine kinase elevated on 2 consecutive measurements (Law, M. and Rudnicka, A. R., 2006).

The incidence of liver disease attributable to statin therapy is rare. In 3 randomised trials of pravastatin, both gall bladder and hepatobiliary disorders were less common in patients allocated statins than in those allocated placebo. Elevations in alanine aminotransferase and or aspartate aminotransferase were reported more frequently in patients treated with statins than with placebo, and elevations of alanine aminotransferase (defined as ≥ 3 times the ULN, or 120 units/l) were found in 300 statin-allocated and 200 placebo-allocated participants per 100,000 person-years. However, statistical heterogeneity across the trials was noted. An elevated alanine aminotransferase on 2 consecutive measurements was found in 110 participants allocated to a statin and in 40 participants allocated to placebo per 100,000 person-years. Elevations in alanine aminotransferase were reported more frequently with higher doses of statin. The systematic review reported that in 100,000 person-years of statin use, denying 300 persons with elevated alanine aminotransferase the benefit of a statin (or 110 persons if repeat measures were used) would prevent liver disease in less than 1 person (Law, M. and Rudnicka, A. R., 2006).

Randomised trials showed no excess of chronic kidney disease or proteinuria in statin allocated participants. There is evidence that statins cause peripheral

neuropathy but the attributable risk is small (12 per 100,000 person years estimated from cohort studies and case reports). No change in cognitive function was found in trials of statins in elderly patients (Law, M. and Rudnicka, A. R., 2006).

The second study was a meta-analysis (Silva, M. A., Swanson, A. C., Gandhi, P. J. et al , 2006) which analysed data from 18 randomised controlled trials published in the last 11 years. The total number of participants randomised to receive a statin was 36 062 and to receive placebo was 35 046. Trials ranged in duration from 6 weeks to 317 weeks. Simvastatin or pravastatin comprised 85.8% of the cumulative statin exposure. Statin therapy was found to be associated with a greater odds of any adverse event that is not directly associated with cardiovascular disease compared with placebo (OR 1.17, 95% CI 1.06 to 1.28). A number needed to harm (NNH) analysis was also performed. The NNH (over 1 year) was 197 for any adverse event (which included myopathy-related events myalgia, myopathy or asthenia), creatine kinase elevation, elevated liver function tests > 3 x ULN or rhabdomyolysis), absolute risk was calculated at 0.51% (95% CI 0.29% to 0.73%). Thus 197 patients would need to be treated for 1 year for one adverse event. For non-serious adverse events (excludes rhabdomyolysis and creatine kinase > 10 X ULN), the NNH was 209 people (over one year), absolute risk = 0.48% (95% CI 0.25% to 0.70%). Rhabdomyolysis was rare; the NNH was 7428 people (7428 people would have to be treated over 1 year for one event), and the absolute risk was 0.01% (95% CI -0.01% to 0.03%). The incidence of rhabdomyolysis or creatine kinase > 10 X ULN was also rare with a NNH of 3400 people and an absolute risk of 0.03% (95% CI -0.03% to 0.09%).

The third study was a meta-analysis (Dale, K. M., Coleman, C. I., Henyan, N. N. et al , 2006) which examined statin usage and the risk of cancer. Twenty six randomised controlled trials were included (n = 86,936 participants). The number of participants ranged between 151 and 20,536 and the duration of patient follow-up for cancer ranged from 1.9 years to 10.4 years. Cancer incidence was found to be unaffected by statin therapy (OR 1.02, 95% CI 0.97 to 1.07), based on 20 studies, and cancer death was similarly unaffected (OR

1.01, 95% CI 0.93 to 1.09), based on 19 studies. A subgroup analysis by cancer type (breast, prostate, gastrointestinal, colon, respiratory and melanoma) was performed which also showed a neutral effect of statin therapy.

6.3.3 Cost effectiveness of statins

The NICE Technology Appraisal (National Institute for Health and Clinical Excellence, 2006) states further that:

- When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug of low acquisition cost (taking into account required daily dose and product price per dose).

Three further cost effectiveness analysis published after the TA were identified. Two of them compared pravastatin 40mg with placebo, Tonkin (Tonkin, A. M., Eckermann, S., White, H. et al , 2006), Nagata-Kobayashi (Nagata-Kobayashi, S., Shimbo, T., Matsui, K. et al , 2005) and concluded that pravastatin 40 mg is a cost effective option for the primary prevention of CVD especially for the high risk group. Nagata-Kobayashi (Nagata-Kobayashi, S., Shimbo, T., Matsui, K. et al , 2005) found that pravastatin 40 mg was not cost effective in low risk patients compared with placebo. The third study by Lindgren (Lindgren, P., Buxton, M., Kahan, T. et al , 2005) compared atorvastatin 10 mg with placebo in the prevention of coronary and stroke events using data from the Anglo-Scandinavian Cardiac Outcomes Trial-lipid lowering arm (ASCOT-LLA) (Sever, P. S., Dahlof, B., Poulter, N. R. et al , 2003). They found that Atorvastatin 10mg was cost effective with an estimated ICER of about £7349 per event avoided. There was an average of 97 events per 1000 patients in the treatment group at an additional cost of £260 per patient compared to 132 events per 1000 patients in the placebo group. The study was well conducted and used appropriate methodology. The findings were robust in sensitivity analysis. They provided a cost per life year gained in their discussion which is a better measure of cost effectiveness than the cost per event avoided they used in their main analysis.

In conclusion lower intensity statins are cost effective. Following the NICE Technology Appraisal (National Institute for Health and Clinical Excellence, 2006), statins with lowest acquisition cost should be used for treatment in primary prevention. The GDG based its recommendation not to recommend higher intensity statins for primary prevention on the lack of trial evidence of benefit from a reduction of cardiovascular events. A cost effectiveness analysis was therefore not considered appropriate. This decision was made on a majority basis.

6.3.4   Evidence to recommendations – statins

The NICE Technology Appraisal (National Institute for Health and Clinical Excellence, 2006) review confirms that for primary prevention, statins are effective in reducing fatal and nonfatal MI and the composite outcome CHD death or nonfatal MI, fatal and nonfatal stroke and revascularisation. In trials predominantly comprising primary prevention but including a minority of people with established CVD, meta-analysis found that statin therapy was associated with a reduction in the risk of all cause mortality, fatal and nonfatal MI and the composite outcomes of CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization. For primary prevention lower intensity statins are safe and cost-effective and there is trial evidence of cardiovascular benefit and low acquisition cost for simvastatin 40 mg and pravastatin 40 mg.

6.4 Fibrates

[Return to Recommendations]

6.4.1 Evidence Statements for fibrates

6.4.1.1 One randomised controlled trial in men with elevated non-HDL cholesterol found that gemfibrozil therapy was associated with a reduction in the incidence of the combination of fatal and nonfatal MI and cardiac death compared with placebo. Gemfibrozil therapy was not associated with a reduction in total mortality compared with placebo.
6.4.1.2 One randomised controlled trial in men with elevated total cholesterol found that clofibrate therapy was associated with a reduction in the incidence of the combination of fatal ischaemic heart disease and nonfatal MI compared with placebo. Analysis of the individual components of this endpoint found that clofibrate therapy was associated with a reduction in nonfatal MI compared with placebo but not fatal ischaemic heart disease.
6.4.1.3 Clofibrate therapy was found to be associated with an increase in all cause mortality compared with placebo.

6.4.2 Clinical effectiveness of fibrates

Two randomised controlled trials were identified that compared fibrate therapy with placebo in people at high risk of CVD (World Health Organization., 1978).

The first randomised controlled trial (World Health Organization., 1978) recruited healthy men aged 30 to 59 years on the basis of their serum cholesterol levels. A total of 15,745 participants were stratified according to their total cholesterol level and randomised to one of three groups (one intervention group and two control groups):

1. Intervention group: Men with a mean total cholesterol level of 6.45 +/- 0.01 mmol/l chosen at random from the upper third of the total cholesterol distribution were allocated to receive clofibrate 1.6 g daily.

2. High cholesterol control group: Men with a mean total cholesterol level of 6.40 +/- 0.01 mmol/l chosen at random from the upper third of the total cholesterol distribution were allocated to receive placebo (olive oil capsules).

3. Low cholesterol control group: Men with a mean total cholesterol level of 4.69 +/- 0.01 mmol/l chosen at random from the lowest third of the total cholesterol distribution were allocated to receive placebo (olive oil capsules).

The trial was conducted in three European centres: Prague, Budapest and Edinburgh and participants were followed up for 5 years. Clofibrate therapy was associated with a reduction in the incidence of the combination of fatal ischaemic heart disease and nonfatal MI compared with the high cholesterol control group (167/5331 group 1 versus 208/5296 group 2, $P < 0.05$). When the individual components of this endpoint were analysed separately, clofibrate therapy was found to be associated with a reduction in nonfatal MI (131/5331 group 1 versus 174/5296 group 2, $P < 0.05$) whereas no difference was found for the outcome of fatal ischaemic heart disease (World Health Organization., 1978).

Clofibrate therapy was found to be associated with an increase in all cause mortality compared with the high cholesterol control group (162/5331 group 1 versus 127/5296 group 2, $P < 0.05$). The results were also analysed separately by cause of death and clofibrate therapy was found to be associated with an increase in mortality from 'other medical causes' (16/5331 group 1 versus 5/5296 group 2, $P < 0.05$), 'all causes other than IHD' (108/5331 group 1 versus 79/5296 group 2, $P < 0.05$) and 'all causes other than IHD, Vascular and Accidents and Violence' (77/5331 group 1 versus 47/5296 group 2, $P < 0.01$) compared with the high cholesterol control group. There was no difference in the numbers of deaths due to ischaemic heart

disease, 'other vascular causes or accidents' and violence between groups 1 and 2. This initial analysis was not conducted on an intention to treat basis, however, a reanalysis on an intention to treat basis reported by the authors confirmed a significant 30% excess in standardized death rates from all causes in the clofibrate arm; Group 1 236/5331 versus Group 2 181/5296 $P < 0.01$ (Heady, J. A., Morris, J. N., and Oliver, M. F., 1992).

The cholecystectomy rate for gall stones was higher in group 1 (rate 2.1 per 1000 p.a, ($P < 0.001$) compared with groups 2 (rate 0.9 per 1000) and 3 (rate 0.9 per 1000) (World Health Organization., 1978).

This trial was one of the first large randomised controlled trials to be conducted and had some caveats. Olive oil capsules were given which are not considered a true placebo. The initial analysis was not conducted on a conventional intention to treat basis, however subsequent analysis on this basis was provided (Heady, J. A., Morris, J. N., and Oliver, M. F., 1992).

It should be noted that clofibrate has now been withdrawn from the British National Formulary.

The second randomised controlled trial (Frick, M. H., Elo, O., Haapa, K. et al , 1987) recruited asymptomatic men aged 40 to 55 years with dyslipidaemia (non-HDL cholesterol levels of ≥ 5.2 mmol/l on two successive measurements). A total of 4081 participants were randomised to receive either gemfibrozil or placebo and were followed up for five years. In addition, both groups were given advice to adopt a cholesterol-lowering diet, to increase physical activity and to reduce smoking and body weight.

Gemfibrozil therapy was associated with a 34% reduction (95% CI 8.2% to 52.6%) in the incidence of the combination outcome of fatal and nonfatal MI and cardiac death. After five years, the number of definite cardiac events in the gemfibrozil group was 56/2051 (an incidence rate of 27.3 per 1000) compared with 84/2030 in the placebo group (an incidence rate of 41.4 per 1000). There were no differences between groups in the total mortality rate.

Gemfibrozil therapy was associated with an increase in HDL cholesterol compared with baseline during the first year of more than 10%, this was followed by a small decline in HDL cholesterol with time. Gemfibrozil therapy was also associated with initial reductions in the levels of total cholesterol (11%), LDL cholesterol (10%), non-HDL cholesterol (14%) and triglycerides (43%). These changes were followed by a consistent level of total and LDL cholesterol and a small increase in triglyceride levels during the remaining time. Cholesterol levels did not differ significantly from baseline during the study in those allocated placebo (Frick, M. H., Elo, O., Haapa, K. et al , 1987).

During the first year, 11.3% of those randomised to receive gemfibrozil and 7% of those receiving placebo reported moderate to severe upper gastrointestinal symptoms ($P < 0.001$). During subsequent years, these rates decreased to 2.4% for the gemfibrozil group and 1.2% for the placebo group ($P < 0.05$). No significant difference between treatment groups were observed in the occurrence of constipation, diarrhoea, or nausea and vomiting (Frick, M. H., Elo, O., Haapa, K. et al , 1987).

6.4.3 Cost effectiveness of fibrates

There were no cost effectiveness studies found on the use of fibrates compared with placebo in the prevention of CVD.

6.4.4 Evidence to recommendations - fibrates

The GDG considered that there was insufficient evidence to routinely recommend the use of fibrates as a first line treatment for the primary prevention of CVD. It was decided, however, that they may be offered as an alternative for those who are intolerant of statin therapy.

6.5 Nicotinic acids

[Return to Recommendations]

Evidence statements for nicotinic acids

> 6.5.1.1   *No randomised controlled trials in people at high risk of CVD were identified that compared nicotinic acid therapy with placebo and reported cardiovascular event outcomes.*

6.5.2   Clinical effectiveness of nicotinic acids

No randomised controlled trials in people at high risk of CVD were identified that compared nicotinic acid therapy with placebo and reported cardiovascular event outcomes.

6.5.3   Cost effectiveness of nicotinic acids

There were no cost effectiveness studies found on the use of nicotinic acids compared with placebo in the prevention of CVD.

6.6   Anion exchange resins

[Return to Recommendations]

6.6.1   Evidence statements for anion exchange resins

> 6.6.1.1   *One randomised controlled trial in men with elevated total and LDL cholesterol found that cholestyramine therapy was associated with a reduction in the incidence of the combination of CHD death and nonfatal MI but did not confer any benefit for the individual components of this outcome compared with placebo. Cholestyramine therapy was not associated with a reduction in all cause mortality compared with placebo.*

6.6.2   Clinical effectiveness of anion exchange resins

One randomised controlled trial, the Lipid Research Clinics Coronary Primary Prevention Trial was identified that compared anion exchange resin therapy with placebo in people at high risk of CVD (Insull, W., Gotto, A. M., Probstfield, J. et al ,   1984; Lipid Research Clinics Coronary Primary Prevention Trial., 1984).

This trial recruited men aged 35-59 years with a total cholesterol level of ≥ 6.88 mmol/l and an LDL cholesterol level of ≥ 4.92 mmol/l. A total of 3,806 men were randomised to receive either cholestyramine (24 g per day) or placebo. During a pre-randomisation phase, all participants received dietary advice which aimed to decrease total cholesterol levels by 3-5%. Participants were then followed up for a mean duration of 7.4 years (Insull, W., Gotto, A. M., Probstfield, J. et al , 1984; Lipid Research Clinics Coronary Primary Prevention Trial., 1984).

Cholestyramine therapy was associated with a reduction in the primary endpoint of a combination of CHD death and nonfatal MI (reduction in risk 19%, 90% CI 3% to 32%, P < 0.05). Cholestyramine therapy did not confer any benefit compared with placebo for the individual components of this endpoint or for the outcome of all cause mortality.

Cholestyramine therapy was associated with a reduction in the secondary outcomes of development of angina (P < 0.01) and the development of a new positive exercise test result (P < 0.001) but did not confer any benefit compared with placebo for the outcomes of coronary bypass surgery or peripheral arterial disease.

Gastrointestinal side effects occurred more frequently in the group that received cholestyramine compared with those allocated placebo after 1 year (43% reported at least one gastrointestinal side effect in the placebo group versus 68% in the cholestyramine group). After seven years, incidence of side effects was similar between groups. There were no differences in the incidence of non gastrointestinal side effects between the groups (Insull, W., Gotto, A. M., Probstfield, J. et al , 1984; Lipid Research Clinics Coronary Primary Prevention Trial., 1984).

6.6.3 Cost effectiveness of anion exchange resins

There were no cost effectiveness studies found on the use of anion exchange resins compared with placebo in the prevention of CVD.

6.6.4 Evidence to recommendations – anion exchange resins

The GDG considered that there was insufficient evidence to routinely recommend the use of anion exchange resins as a first line treatment for the primary prevention of CVD. It was decided, however, that they may be offered as an alternative for those who are intolerant of statin therapy.

6.7   Ezetimibe

[Return to Recommendations]

6.7.1 Evidence statements for ezetimibe

> *6.7.1.1   Please refer to NICE Technology Appraisal No. 132 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia', (National Institute for Health and Clinical Excellence. 2007)*

6.7.2 Clinical effectiveness of ezetimibe

The NICE Technology Appraisal 132 is entitled 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia', (National Institute for Health and Clinical Excellence., 2007). The guidance recommends ezetimibe as a treatment option for primary (heterozygous familial and non-familial) hypercholesterolaemia and states that its recommendations should be read in the context of the lipid modification clinical guideline (this guidance).

The population groups covered by the ezetimibe Technology Appraisal 132 (National Institute for Health and Clinical Excellence., 2007) are:

- Adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and;

- whose condition is not appropriately controlled with a statin alone or;

- in whom a statin is considered inappropriate or is not tolerated.

The term "not appropriately controlled with a statin alone" is defined as failure to achieve a target lipid level that is appropriate for a particular group or individual. It also assumes that statin therapy is optimised and tolerated.

The NICE Technology Appraisal 132 (National Institute for Health and Clinical Excellence., 2007) 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia' did not identify any randomised controlled trials that reported health-related quality of life or clinical endpoints such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were used as indicators of clinical outcomes.

To represent the population of people with hypercholesterolaemia that is not appropriately controlled with statin therapy, six 12-week fixed-dose randomised controlled trials (n = 3610) were identified that compared ezetimibe plus statin therapy with statin therapy alone.

Seven randomised controlled trials (n = 2577) comparing ezetimibe monotherapy with placebo represented the population where statin therapy is considered inappropriate or is not tolerated. All were 12-week studies and were included in a meta-analysis performed by the Assessment Group.

All trials involved people with primary hypercholesterolaemia with average baseline LDL cholesterol levels ranging from 3.4 mmol/l to 6.5 mmol/l and included mixed populations of people with and without a history of CVD.

6.7.3   Cost effectiveness of ezetimibe

Please refer to the cost effectiveness analysis carried out by the NICE Technology Appraisal 132 (National Institute for Health and Clinical Excellence, 2007).

6.7.4 Evidence to recommendations - ezetimibe

Please refer to recommendations of the NICE Technology Appraisal 132 entitled 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia' .

6.8 Combination drug therapy

[Return to Recommendations]

6.8.1 Evidence statements for combination drug therapy

6.8.1.1 No randomised controlled trials with cardiovascular outcomes were identified that compared adding a fibrate, anion exchange resin, or nicotinic acid to a statin with statin monotherapy in people at high risk of CVD.

6.8.1.2 A systematic review of cohort studies, randomised trials, voluntary notifications to regulatory authorities and published case reports found the incidence of rhabdomyolysis to be ten fold higher when a statin was combined with the fibrate gemfibrozil.

6.8.2 Evidence to recommendations – combination drug therapy

The GDG considered that there was insufficient evidence to recommend combining a statin with a fibrate, anion exchange resin, or nicotinic acid in primary prevention. In addition, it was noted that the combination of a statin with a fibrate may be associated with an increased risk of adverse events, in particular the combination of the fibrate gemfibrozil with a statin.

7 Drug therapy for the secondary prevention of cardiovascular disease (CVD)

7.1 Recommendations

[Hyperlink to Introduction]

7.1.1 When considering lipid modification therapy in primary and secondary prevention, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality.

Drug therapy for secondary prevention

7.1.2 For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors. Blood tests and clinical assessment should be performed, and comordbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

- **smoking status**
- **alcohol consumption**
- **blood pressure (see 'Hypertension', NICE clinical guideline 34)**
- **body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)**
- **fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)**
- **fasting blood glucose**
- **renal function**
- **liver function (transaminases)**
- **thyroid-stimulating hormone (TSH) if dyslipidaemia is present.**

7.1.3 If a person has acute coronary syndrome, statin treatment should not be delayed until lipid levels are available. A fasting

lipid sample should be taken about 3 months after the start of treatment.

Statins for secondary prevention

7.1.4   Statin therapy is recommended for adults with clinical evidence of CVD.[15]

7.1.5   The decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as comorbidities and life expectancy. [16]

7.1.6   When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).[20]

7.1.7   People with acute coronary syndrome should be treated with a higher intensity statin[17]. Any decision to offer a higher intensity statin should take into account the patient's informed preference, comorbidities, multiple drug therapy, and the benefits and risks of treatment.

7.1.8   Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

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[15] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094

[16] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094

[17] 'Higher intensity statins' are statins used in doses that produce greater cholesterol lowering than simvastatin 40 mg, for example simvastatin 80 mg.

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7.1.9 In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity statin[21] should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.

7.1.10 An 'audit' level of total cholesterol of 5 mmol/litre should be used to assess progress in populations or groups of people with CVD, in recognition that more than a half of patients will not achieve a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre.

Fibrates for secondary prevention

7.1.11 Fibrates may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

Nicotinic acid for secondary prevention

7.1.12 Nicotinic acid may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

Anion exchange resins for secondary prevention

7.1.13 Anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

Ezetimibe for secondary prevention

7.1.14 People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' (NICE technology appraisal guidance 132).

Monitoring of statin treatment for primary and secondary prevention

7.1.15 If a person taking a statin starts taking additional drugs, or needs treatment for a concomitant illness that interferes with metabolic

pathways or increases the propensity for drug and food interactions, consider reducing the dose of the statin, or temporarily or permanently stopping it.

7.1.16 People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, creatine kinase should be measured.

7.1.17 Creatine kinase should not be routinely monitored in asymptomatic people who are being treated with a statin.

7.1.18 Baseline liver enzymes should be measured before starting a statin. Liver function (transaminases) should be measured within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.

7.1.19 People who have liver enzymes (transaminases) that are raised but are less than 3 times the upper limit of normal should not be routinely excluded from statin therapy.

7.1.20 If a person develops an unexplained peripheral neuropathy, statins should be discontinued and specialist advice sought.

7.2   Introduction to drug therapy for secondary prevention

7.2.1   The effectiveness of lipid modifying drugs

The GDG based recommendations to use lipid modifying drugs on trial evidence of improvement in cardiovascular outcomes and where available, total mortality. For people with established CVD there is substantive trial evidence that statins reduce total mortality, cardiovascular mortality and morbidity and total mortality, and are cost-effective. This evidence is strongest for people with coronary heart disease (CHD) (Baigent, C., Keech, A., Kearney, P. M. et al , 2005; National Institute for Health and Clinical Excellence, 2006).

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Among people with CHD treated with statins there is a reduction in recurrent CHD events of about 23%, (rate ratio (RR) 95% CI 0.74 to 0.80) and a reduction in stroke events by 17% (0.78 to 0.88) (Baigent, C., Keech, A., Kearney, P. M. et al , 2005). For people with stroke there is a reduction in stroke and cardiovascular events using higher intensity statins (Amarenco, P., Bogousslavsky, J., Callahan, A. S. et al , 2003). No trials have compared the effectiveness of higher intensity statin therapy with standard intensity statin therapy in people following a stroke.

Although there have been no statin trials specifically in people with peripheral arterial disease (PAD), the Heart Protection Study demonstrated the benefits of statin therapy in patients with PAD. Allocation to simvastatin 40 mg daily reduced the rate of first major vascular events by about one-quarter, and that of peripheral arterial events by about one-sixth, with large absolute benefits seen in participants with PAD because of their high vascular risk (Heart Protection Study Collaborative Group., 2007).

Fibrates have been shown to reduce some cardiovascular events in people with CHD though in comparison to statins their lower efficacy and adverse event profile has meant that statins are the drug of first choice for most people. Nicotinic acid and anion-exchange resins have also shown evidence of cardiovascular benefit.

The NICE Statin Technology Appraisal 'Statins for the prevention of cardiovascular events' 2006 has thoroughly and comprehensively reviewed the evidence on the effectiveness and cost-effectiveness of statins, and our recommendations on the initiation of statin therapy are based upon this report which states that:

- Statin therapy is recommended for adults with clinical evidence of CVD

- The decision to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidity and life expectancy

- When the decision has been made to prescribe a statin, it is recommended that therapy should be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).

7.2.2 The association between lipid modification using drugs and cardiovascular events

The epidemiological relationship between cholesterol as a risk factor in populations and groups and cardiovascular events is well established. As cholesterol increases, so does the risk of CVD. This relationship is such that each 1mmol/l rise in total cholesterol is associated with a 72% increase in the risk of a major coronary event (Emberson, J. R., Whincup, P. H., Morris, R. W. et al , 2003).

There is now compelling randomised controlled trial evidence in people with established CVD, that lowering cholesterol with statins reduces total mortality, cardiovascular mortality and morbidity. For the statin class at lower and moderate intensity each 1 mmol/l reduction in LDL cholesterol will produce a proportional reduction in major vascular events of 23% (at least down to an LDL cholesterol of 2 mmol/l) (Baigent, C., Keech, A., Kearney, P. M. et al , 2005).

Statins are highly cost-effective with a good record of safety. There is also good evidence that higher intensity statins are associated with additional cost-effective reductions in cardiovascular events for people after recent myocardial infarction (MI) and acute coronary syndrome (ACS).

However the benefits of cholesterol lowering and safety cannot be assumed for all drug classes or for all drugs within the same class (Psaty, B. M., Weiss, N. S., Furberg, C. D. et al , 1999) and cardiovascular outcome and adverse event data should be available for every drug from clinical trials. The withdrawal of the statin cerivastatin because of adverse events is a salutary reminder that all drugs within a class are not the same and that there may be specific drug effects within a drug class.

The same strength of evidence that exists for statins does not exist for other classes of lipid lowering drugs (fibrates, anion exchange resins, nicotinic acid) where the trials are fewer in number, the total patient population studied can be small, and trials have shown variable benefits on cardiovascular events despite reduction in cholesterol.

Other classes of drug have either failed to improve cardiovascular outcomes or even increased mortality. Torcetrapib, one of a new class of lipid modifying drug therapies (CETP inhibitor) which raises HDL cholesterol, was being evaluated in a clinical trial which was stopped prematurely because of excess mortality (Jensen, G. B. and Hampton, J., 2007; Nissen, S. E., Tardif, J. C., Nicholls, S. J. et al , 2007).

The potential advantages of drug combinations from different classes cannot be assumed as there are no cardiovascular outcome data for any drug combination in lipid management. There is a greater propensity for major adverse events when statins are combined with fibrates or other drugs particularly when statins are used at higher doses.

7.2.3 The use of statins in clinical practice

In the period 1981-2000, CHD mortality under age 84 years in England and Wales fell by 54%; 68 230 fewer deaths. Modelling of the effects of changes in the three major risk factors, smoking, blood pressure and serum cholesterol suggests that these changes are associated with 45 370 fewer deaths. The biggest single contribution to reduction in mortality was estimated to be a decrease in smoking. Approximately 2135 fewer deaths were attributed to statin treatment: 1990 in CHD patients and 145 in people without established disease (Unal, B., Critchley, J. A., and Capewell, S., 2005).

Prescription of statins and other drugs to improve risk factors remains suboptimal despite the fact that half the survivors of hospital admission for acute MI or angina experience a further major coronary event or death within 5 years of discharge (Capewell, S., Unal, B., Critchley, J. A. et al , 2006).

Statin prescription has increased dramatically in the last 10 years particularly for people with established CVD. In 1997 Brady *et al* reported 18% of people with CHD in primary care were on statins (Brady, A. J., Oliver, M. A., and Pittard, J. B., 2001). In 2006, among 150 general practices in East London, statin prescription for people with CHD was 81% (Report: East London Clinical Effectiveness Group Queen Mary University of London 2007).

There is still considerable variation in prescribing and under-dosing by practice and evidence of inequity in prescribing by age and also by sex. Statins are less likely to be prescribed to people over 75 years and women (de Lusignan, S., Belsey, J., Hague, N. et al , 2006; DeWilde, S., Carey, I. M., Bremner, S. A. et al , 2003).

Patient adherence to treatment with statins remains a major challenge and only half the patients at highest risk after MI continue to take their statins at 2 years (Penning-van Beest, F. J., Termorshuizen, F., Goettsch, W. G. et al , 2007; Wei, L., Ebrahim, S., Bartlett, C. et al , 2005).

7.3   Statins

[Return to Recommendations]

7.3.1   Evidence statements for statins

NICE Technology Appraisal evidence statement for statins
7.3.1.1   *In a meta-analysis of 14 randomised controlled trials of secondary prevention in CHD, statin therapy was associated with a reduction in all-cause mortality, CVD mortality, CHD mortality, fatal MI, and coronary revascularisation compared with placebo. (NICE technology appraisal 94, 'Statins for the prevention of cardiovascular events' 2007).*

7.3.2   Evidence statements for higher intensity statin therapy

7.3.2.1   *Meta-analysis of four randomised controlled trials in patients with CHD found that higher intensity statin therapy compared with lower intensity statin therapy was associated with a reduction in the composite outcome of coronary death or MI, and with a reduction in the composite outcome of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina or any revascularisation).*
7.3.2.2   *Higher intensity statin therapy was not associated with a reduction in all cause mortality but there was a trend for significance in cardiovascular mortality compared with lower intensity statin therapy. Higher intensity statins reduced coronary death or any cardiovascular event compared with lower intensity statins.*
7.3.2.3   *No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity statin therapy in patients with peripheral arterial disease or following stroke.*
7.3.2.4   *One randomised controlled trial in patients following stroke or*

	transient ischaemic attack found that higher intensity statin therapy with atorvastatin 80 mg was associated with a reduction in fatal stroke, the composite of fatal and non-fatal stroke and any cardiovascular event compared with placebo. Post-hoc analysis found this beneficial effect to be restricted to patients after ischaemic stroke whereas a harmful effect was found for those patients after hemorrhagic stroke.
7.3.2.5	*Higher intensity statin therapy did not confer any benefit over placebo for the outcome of non-fatal stroke compared with placebo.*
7.3.2.6	*Using a model developed for the guideline, higher intensity statin therapy compared to low intensity statin therapy was found to be cost-effective in the base case in patients following acute coronary syndrome. Treatment is most cost-effective using drugs with lowest acquisition costs*
7.3.2.7	*Using a model developed for the guideline, higher intensity statin therapy is not cost-effective in the base case compared to low intensity statin therapy in patients with stable coronary artery disease (£27,840/QALY). However if generic drug prices are assumed high intensity statins will dominate lower intensity statins (they will result in more QALYs and cost savings) in patients with stable CAD.*
7.3.2.8	*Using a model developed for the guideline, a titration strategy based on a target total cholesterol of 4mmol/l was found to be cost-effective compared to a fixed dose strategy of low intensity statins, but only if titrating using generic drugs.*
Adverse events associated with higher intensity statin therapy	
7.3.2.9	*Four randomised controlled trials in patients with CHD found that higher intensity statin therapy was associated with a greater*

	persistent elevation in alanine aminotransferase and / or aspartate aminotransferase levels compared with lower intensity therapy. This was not found to be associated with a significant increase in clinical liver disease.
7.3.2.10	*Three of the four trials found higher intensity statin therapy was not associated with an increase in myalgia compared with lower intensity therapy and one found an excess of myalgia but no increase in the incidence of myopathy.*
7.3.2.11	*Three of the four trials found that higher intensity statin therapy was not associated with an increase in rhabdomyolysis compared with lower intensity therapy and one found an excess of rhabdomyolysis in the higher intensity group which was found to be associated with identifiable secondary causes.*
7.3.2.12	*A retrospective analysis of pooled data from 49 clinical trials found higher intensity statin therapy with atorvastatin 80 mg to be associated with a greater incidence of persistent elevations in alanine aminotransferase and / or aspartate aminotransferase > 3 x ULN compared to standard intensity therapy with atorvastatin 10 mg or placebo.* *No incidences of myopathy or rhabdomyolysis were reported and serious hepatic adverse events were rare although a small number of patients receiving high intensity statin therapy developed hepatitis which resolved after discontinuation of drug therapy.*

7.3.3 Clinical effectiveness of statins

Throughout the guideline, we have reported 95% confidence intervals for relative risks (RR) and odds ratios (OR). Where the 95% confidence interval crosses the 'line of no effect' i.e., when the confidence intervals included 1, we have interpreted this as being non-significant. This interpretation holds even when the upper or lower limit of the confidence interval is 1.00.

The NICE Technology Appraisal 94 (NICE technology appraisal guidance 94, 'Statins for the prevention of cardiovascular events' 2006) states that:

- Statin therapy is recommended for adults with clinical evidence of CVD.

The recommendation was based on the meta-analysis of 14 randomised controlled trials of secondary prevention in CHD. Of these, four were conducted in MI and / or angina patients (Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group., 1998; Liem, A. H., van Boven, A. J., Veeger, N. J. et al , 2002; Pedersen, T. R., Kjekshus, J., Berg, K. et al , 2004; Sacks, F. M., Tonkin, A. M., Shepherd, J. et al , 2000). Four studies recruited patients with CAD (Crouse, J. R., Byington, R. P., Bond, M. G. et al , 1995; Jukema, J. W., Bruschke, A. V., van Boven, A. J. et al , 1995; Pitt, B., Mancini, G. B., Ellis, S. G. et al , 1995; Teo, K. K., Burton, J. R., Buller, C. E. et al , 2000) two studies recruited patients with CAD and hypercholesterolaemia (Bestehorn, H. P., Rensing, U. F., Roskamm, H. et al , 1997; Riegger, G., Abletshauser, C., Ludwig, M. et al , 1999) one study recruited patients with mild CAD (Oliver, M. F., de Feyter, P. J., Lubsen, J. et al , 1994) two studies enrolled patients after coronary balloon angioplasty (Serruys, P. W., Foley, D. P., Jackson, G. et al , 1999) and (Bertrand, M. E., McFadden, E. P., Fruchart, J. C. et al , 1997), and one study enrolled patients after percutaneous coronary intervention (Serruys, P. W., de Feyter, P., Macaya, C. et al , 2002). Statin therapy was associated with a reduction in the following clinical outcomes compared with placebo: all-cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), CHD mortality (RR 0.72, 95% CI 0.64 to 0.80), fatal MI (RR 0.57, 95% CI 0.45 to 0.72), unstable angina (RR 0.82, 95% CI 0.72 to 0.94), hospitalisation for unstable angina (RR 0.90, 95% CI 0.70 to 0.90), nonfatal stroke (RR 0.75, 95% CI 0.59 to 0.95), new or worse intermittent claudication (RR 0.64, 95% CI 0.46 to 0.91) and coronary revascularisation (RR 0.77, 95% CI 0.69 to 0.85).

The NICE Technology Appraisal 94 (NICE technology appraisal guidance 94, Statins for the prevention of cardiovascular events' 2006) further states that:

- The decision to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidity and life expectancy.

- When the decision has been made to prescribe a statin, it is recommended that therapy should be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).

7.3.4 Clinical effectiveness of higher intensity versus lower intensity statin therapy

No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity therapy in patients with angina alone, stroke or peripheral arterial disease. In addition, no randomised controlled trials were identified on the effectiveness of up-titrating statin dose compared with giving a fixed dose.

Three randomised controlled trials compared higher intensity statin therapy with lower intensity statin therapy in patients with CHD: one in patients after ACS (PROVE-IT-TIMI-22) (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004), one in patients with previous MI (IDEAL) (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005) and one which included previous MI 58% and/or angina/revascularization (TNT) (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005)). None of these trials treated to a pre-specified target total or LDL cholesterol, although the achieved levels were lower in each of the higher intensity statin groups, compared with the respective lower intensity statin groups. A fourth trial in patients after ACS, compared early intensive statin therapy with delayed conservative statin therapy (A to Z) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004).

The first randomised controlled trial (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004) recruited patients within 10 days of an ACS event (29% had unstable angina, 36% non-ST elevation MI and 35% ST elevation MI). A high proportion of trial participants were taking other secondary prevention drugs and over two thirds were revascularised for treatment of the index event. At recruitment patients had to have a total cholesterol of 6.21 mmol/l or less. Patients were randomised to receive either higher intensity statin therapy with atorvastatin (80 mg once daily) or lower intensity statin therapy with pravastatin (40 mg once daily). Lipid values at the start of the study were similar in both groups. At follow up, patients in the atorvastatin group achieved lower levels of LDL cholesterol compared with the pravastatin group (1.60 mmol/l versus 2.46 mmol/l) and patients in the pravastatin group achieved higher HDL cholesterol levels.

During a mean follow up of 24 months, there was a reduction in the primary outcome (a composite of death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation or stroke) with higher intensity therapy compared with lower intensity (HR 0.84, 95% CI 0.74 to 0.95). Similarly, higher intensity therapy was associated with a risk reduction of 14% (P = 0.029) for the secondary outcome of a composite of death from CHD, nonfatal MI or revascularisation. There was no significant reduction in death from any cause or reinfarction with higher intensity therapy compared with lower intensity (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004).

The second study was an open label randomised trial in patients with prior MI (median time since last MI was 22 months) (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005). Most trial participants were taking aspirin and beta blockers, but almost 2/3 were not taking ACE inhibitors or ARBs. Patients were assigned to higher intensity atorvastatin 80 mg once daily or lower intensity simvastatin (20 mg once daily). Further drug titration could be undertaken at 24 weeks within the study protocol, based on achieved total cholesterol levels. Twenty one percent of patients in the simvastatin group had their dose increased to 40 mg daily, and 6% of patients in the atorvastatin

group had their dose reduced to 40 mg daily. At the end of the study, 23% were treated with simvastatin 40 mg daily and 13% with atorvastatin 40 mg daily. During treatment, patients in the atorvastatin group had lower levels of LDL cholesterol, total cholesterol, triglycerides and apolipoprotein B compared with the simvastatin group. HDL cholesterol and apolipoprotein A1 levels were higher in the simvastatin group compared with the atorvastatin group. Mean LDL cholesterol levels were 2.7 mmol/l in the simvastatin group and 2.1 mmol/l in the atorvastatin group.

For the primary endpoint of major coronary event (defined as coronary death, hospitalisation for nonfatal acute MI, or cardiac arrest with resuscitation) there was no significant difference in event rates between the two treatment groups during a median follow up of 4.8 years. There was a reduction in the nonfatal MI component of this primary endpoint with atorvastatin therapy compared with simvastatin treatment (HR 0.83, 95% CI 0.71 to 0.98). Atorvastatin treatment was associated with a reduction in the secondary endpoint of any CHD event (HR 0.84, 95% CI 0.76 to 0.91) and also a reduction in any major cardiovascular event (HR 0.87, 95% CI 0.78 to 0.98) compared with simvastatin treatment. There were no differences in cardiovascular or all cause mortality (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005).

The third randomised controlled trial recruited patients with clinically evident stable CHD (59% had a prior MI, 82% angina) (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005). To ensure that, at baseline, all patients had LDL cholesterol levels consistent with the then current guidelines for the treatment of stable CHD, patients with LDL cholesterol levels between 3.4 and 6.5 mmol/l entered an eight week run in period of open-label treatment with 10 mg of atorvastatin per day. At the end of the run in phase, those patients with a mean LDL cholesterol of less than 3.4 mmmo/l were randomised. Patients were assigned to either higher intensity atorvastatin (80 mg once daily) or lower intensity atorvastatin (10 mg once daily). The trial follow up was for a median of 4.9 years. No information was given on concomitant medications at baseline or during the trial but it was stated that medication usage was similar

in the two groups at the start of the trial. Mean LDL cholesterol levels during the study were 2.0 mmol/l in the group treated with atorvastatin 80 mg once daily and 2.6 mmol/l in the group treated with atorvastatin 10 mg once daily. There was a 22% reduction (95% CI 11% to 31%) in the primary end point (defined as the combination of death from CHD, nonfatal non-procedural MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) in patients treated with atorvastatin 80 mg daily compared with patients treated with atorvastatin10 mg daily. Patients treated with high dose atorvastatin had a decreased incidence of the following components of this primary endpoint: nonfatal MI (HR 0.78, 95% CI 0.66 to 0.93), and fatal or nonfatal stroke (HR 0.75, 95% CI 0.59 to 0.96). Higher intensity treatment was also associated with a lower incidence of the following secondary outcomes: major coronary event (HR 0.80, 95% CI 0.69 to 0.92), cerebrovascular event (HR 0.77, 95% CI 0.64 to 0.93), hospitalisation for congestive heart failure (HR 0.75, 95% CI 0.59 to 0.93), any cardiovascular event (HR 0.81, 95% CI 0.75 to 0.87) and any coronary event (HR 0.79, 95% CI 0.73 to 0.86). There was no difference in all cause mortality between higher and lower intensity atorvastatin treatment (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005).

A fourth trial compared early intensive statin therapy with delayed lower intensity statin therapy (A to Z) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004). This trial consisted of 2 overlapping phases. The first phase was an open labelled trial comparing enoxaprin with unfractionated heparin in patients with non ST elevation ACS who were treated with tirofiban and aspirin. The second phase recruited patients initially from the first phase who had stabilised (for at least 12 consecutive hours within 5 days after symptom onset). In addition, recruits had at least one of the following characteristics: age older than 70 years, diabetes mellitus, prior history of coronary artery disease, peripheral arterial disease or stroke. Subsequently, the protocol was amended to allow patients with non ST elevation ACS who were not enrolled in the first phase, and also patients with ST elevation MI to enter into the second phase directly (overall non ST-segment elevation ACS: 60%, ST elevation MI: 40%).

At baseline almost all the participants were taking aspirin and beta blockers, three quarters were taking ACE inhibitors and almost half were revascularised for treatment of the index event. Patients were randomised to either simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter (early higher intensive therapy) or placebo for 4 months followed by simvastatin 20 mg once daily thereafter (delayed conservative therapy) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004).

Early high intensity statin therapy decreased LDL cholesterol levels by 39% compared with baseline levels during the first month of therapy with simvastatin 40 mg, and then by a further 6% following an increase in simvastatin dosage to 80 mg. For the delayed conservative statin treatment group, LDL cholesterol levels increased by 11% during the 4 month placebo period, then decreased from baseline by 31% after 4 months of therapy with simvastatin 20 mg (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004).

For the primary endpoint of the combination of cardiovascular death, nonfatal MI, readmission for ACS or stroke, early higher intensity statin therapy did not confer benefit compared with delayed lower intensity therapy. There was also no benefit found in any of the individual components of the primary endpoint. Likewise no benefit was observed in the secondary endpoints of all cause mortality and coronary revascularisation due to documented ischaemia. There was a reduction in the incidence of new onset congestive heart failure in the early intensive statin treatment group compared with the delayed conservative treatment group (HR 0.72, 95% CI 0.53 to 0.98) but not a reduction in cardiovascular related death (HR 0.75, 95% CI 0.51 to 1.00) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004).

A meta-analysis of these four studies has been conducted by Cannon *et al* (Cannon, C. P., Steinberg, B. A., Murphy, S. A. et al , 2006) using a fixed-effects model. Higher intensity statin therapy did not confer any significant benefit over lower intensity statin therapy for the outcomes of all cause mortality (OR 0.94, 95 % CI 0.85 to 1.04), cardiovascular mortality (OR 0.88,

95 % CI 0.78 to 1.00) or non-cardiovascular mortality (OR 1.03, 95 % CI 0.88 to 1.20). Higher intensity statin therapy was associated with a reduction in the combination of coronary death or MI (OR 0.84, 95 % CI 0.77 to 0.91), stroke (OR 0.82, 95 % CI 0.71 to 0.96) and coronary death or any cardiovascular event (OR 0.84, 95 % CI 0.80 to 0.89).

In addition to the four trials comparing higher intensity therapy with lower intensity therapy, two randomised controlled trials were identified that compared higher intensity statin therapy with placebo. The first trial recruited patients with ACS (Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al , 2001) and the second recruited patients with a history of stroke or transient ischaemic attack (Amarenco, P., Bogousslavsky, J., Callahan, A., III et al , 2006).

The trial in patients with ACS (Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al , 2001) randomised a total of 3086 patients with unstable angina or non-Q-wave acute MI to receive either atorvastatin 80 mg daily or placebo. Patients were hospitalised within 24 hours of the index event and randomised after a mean of 63 hours of hospitalisation. During or after hospitalisation for the index event, most were treated with aspirin, three quarters with beta blockers and half with ACE inhibitors or ARBs.

The study period was for 16 weeks and during this period the primary end point (combination of death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalisation) was not significantly reduced in patients randomised to atorvastatin compared with those who received placebo (RR 0.84, 95% CI 0.70 to 1.00). Atorvastatin therapy was not associated with a reduction in the following individual components of the primary outcome: death, non-fatal MI or cardiac arrest with resuscitation but was associated with a lower risk of recurrent myocardial ischaemia requiring rehospitalisation compared with placebo (RR 0.74, 95% CI 0.57 to 0.95). However, it should be noted that the study was only powered to detect differences between groups in the primary outcome. At the end of the study,

compared to baseline, LDL cholesterol had increased by an adjusted mean of 12% in the placebo group and had decreased by an adjusted mean of 40% in the atorvastatin group (Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al , 2001).

Incidences of the following secondary outcomes were not different in the atorvastatin group compared with placebo: coronary revascularisation procedures, worsening congestive heart failure or worsening angina. Non-fatal stroke was reduced in the atorvastatin group compared with placebo (RR 0.41, 95% CI 0.20 to 0.87) as was the composite outcome of fatal and non-fatal stroke (RR 0.50, 95% CI 0.26 to 0.99) (Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al , 2001).

The second randomised controlled trial (Amarenco, P., Bogousslavsky, J., Callahan, A., III et al , 2006) recruited patients without known CHD and with previously documented stroke (69%) (66.5% ischaemic and 2.5% haemorrhagic) or transient ischaemic attack (31%), 1 to 6 months prior to randomisation. A total of 4731 participants were randomised to receive either 80 mg atorvastatin or placebo and were followed up for a mean duration of 4.9 years. Most patients were taking aspirin or other antiplatelets (not heparin) although only 29% were taking ACE inhibitors and 18% beta blockers. For the primary endpoints, high dose atorvastatin decreased the risk of fatal stroke (HR 0.57, 95 % CI 0.35 to 0.95) and the composite of fatal and non-fatal stroke (HR 0.84, 95 % CI 0.71 to 0.99) compared with placebo. High dose atorvastatin also reduced the risk of any cardiovascular event (stroke plus any major coronary event) (HR 0.80, 95 % CI 0.69 to 0.92) compared with placebo. No benefit was found for the outcome of non-fatal stroke. Post hoc analysis indicated significant differences in hazard ratios based on the type of stroke occurring during the trial; the cause specific adjusted hazard ratios compared to placebo showed a beneficial effect in those experiencing ischaemic stroke during the trial (HR 0.78, 95 % CI 0.66 to 0.94), but a harmful effect on those experiencing hemorrhagic stroke (HR 1.66, 95 % CI 1.08 to 2.55). Atorvastatin conferred benefit compared with placebo for the following secondary outcomes: major coronary event (HR 0.65, 95 % CI 0.49

to 0.87), major cardiovascular event (HR 0.80, 95 % CI 0.69 to 0.92), any cardiovascular event (HR 0.74, 95 % CI 0.66 to 0.83), acute coronary event (HR 0.65, 95 % CI 0.50 to 0.84), any coronary event (HR 0.58, 95 % CI 0.46 to 0.73), non-fatal MI (HR 0.51, 95 % CI 0.35 to 0.74), revascularisation (HR 0.55, 95 % CI 0.43 to 0.72), transient ischaemic attack (HR 0.74, 95 % CI 0.60 to 0.91), the composite of stroke or transient ischaemic attack (HR 0.77, 95 % CI 0.67 to 0.88). No benefit was seen for the outcomes of cardiovascular mortality or all cause mortality but the trial was not statistically powered for this endpoint (Amarenco, P., Bogousslavsky, J., Callahan, A., III et al , 2006).

7.3.5 Cost-effectiveness of statins

The NICE Technology Appraisal (NICE technology appraisal guidance 94, Statins for the prevention of cardiovascular events' 2006) states that:

- When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug of low acquisition cost (taking into account required daily dose and product price per dose).

7.3.6 Cost-effectiveness of higher intensity statin therapy compared with lower intensity statin therapy

When initial searches were undertaken, no studies were found which compared cost-effectiveness of higher intensity statins with lower intensity statins in patients with coronary artery disease (CAD). Consequently, the GDG requested the development of an economic model to help inform the guideline.

A Markov model was developed to estimate the incremental cost per quality adjusted life year (QALY) of lifetime treatment with high intensity statins (atorvastatin 80 mg and simvastatin 80 mg) compared with low intensity statins (simvastatin 40 mg) from a UK NHS perspective. The base case assumptions model two cohorts of hypothetical patients aged 65 years of age:

i   Patients with acute ACS, and;

ii   Patients with stable coronary artery disease (CAD).

Intermediate outcomes included in the model include the numbers of MI, stroke, TIA, PAD, heart failure, revascularisation, and angina events, and deaths from CVD and other causes. Effectiveness data for ACS patients were drawn from two studies which were meta-analysed; A to Z (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004), in which patients were randomised to either simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter (early intensive therapy) or placebo for 4 months followed by simvastatin 20 mg once daily thereafter (delayed conservative therapy) and PROVE-IT where patients were randomised to receive either higher intensity statin therapy with atorvastatin (80 mg once daily) or lower intensity statin therapy with pravastatin (40 mg once daily) (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004) For the stable CAD patient model, effectiveness data were drawn from the TNT where patients were assigned to either higher intensity atorvastatin (80 mg once daily) or lower intensity atorvastatin (10 mg once daily) (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005) and IDEAL where patients were assigned to higher intensity atorvastatin 80 mg once daily or lower intensity simvastatin (20 mg once daily) (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005) trials. Again, these were meta-analysed.

The models make the conservative assumption that the all cause mortality rate in the modelled population is twice that of the general population. Health state utility values were taken from published sources (see Appendix C for details). All cause mortality rates were taken from the Government Actuarial Department.(Government Actuaries Department, 2006), The model makes the conservative assumption of no adverse events from treatment using high intensity statins. Cost of drugs were taken from the Prescription Pricing Authority Drug Tariff Feb 27th 2008 (atorvastatin 80 mg £367.74/year, simvastatin 80 mg £64.53/year, simvastatin 40 mg, £18.12/year) (NHS Prescription Pricing Authority, 2008). Costs of cardiovascular events were taken from the statins TA94 (National Institute for Health and Clinical Excellence, 2006). In order to reflect social values for time preference, as is

standard in economic models, costs and QALYs have been discounted at 3.5% as recommended by NICE.(National Institute for Health & Clinical Excellence., 2006) All of these and other model assumptions have been tested in sensitivity analyses.

The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY.

7.3.6.1 Results for patients with ACS

Table 2 indicates the modelled number of events for a hypothetical population of 1,000 ACS patients treated with either high intensity or low intensity statins. The table indicates that fewer cardiovascular events occur in the population treated with high intensity statins. This translates to a gain of 0.32 discounted QALYs when compared with low intensity statins.

Table 2 Lifetime modelled events for a cohort of 1,000 ACS patients treated with either low or high intensity statins

Heath state	Low Intensity	High Intensity
MI	386	400
Stroke	112	102
Heart Failure	317	246
Revascularisations	444	431
Unstable Angina	270	258
Cardiovascular Mortality	389	333
Death from other causes	611	667

a) Cost-effectiveness results for ACS patients

The model estimates the life-time incremental cost per QALY of using high intensity statins (both simvastatin and atorvastatin 80mg) compared with low intensity statins both simvastatin and pravastatin is about £4,700, indicating

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that high intensity statins are cost-effective in ACS patients. The probability that high intensity statins is cost-effective is about 94% when compared with low intensity statins. .

7.3.6.2   Results for patients with stable coronary artery disease (CAD)

Table 2 indicates the modelled number of lifetime events for a hypothetical 1000 patients treated with either high or low intensity statins. The table indicates that fewer cardiovascular events occur in the population treated high intensity statins. This translates to a gain of 0.08 discounted QALYs per patient when compared with low intensity statins.

Table 3: Lifetime modelled events for a cohort of 1000 CAD patients treated with either low or high intensity statins

Heath state	Low Intensity	High Intensity
MI	170	138
Stroke	134	102
Transient Ischemic Attack	60	51
Peripheral Artery Disease	63	59
Heart Failure	109	81
Revascularisations	224	181
Unstable Angina	126	103
Cardiovascular Mortality	424	416
Death from other causes	576	584

a) Cost-effectiveness results

The model estimates the life-time incremental cost per QALY of using high intensity statins (atorvastatin 80mg) compared with low intensity statins (simvastatin 40mg) is about £27,840 indicating that high intensity statins are not cost-effective in patients with stable CAD. The probability that high

intensity statins is cost-effective is about 42% when compared with low intensity statins. .

Updated Economic Publication Searches

Subsequent to this model being built, updated searches retrieved one publication which compared higher intensity statins with lower intensity statins in patients with ACS and stable CAD in North America.(Chan, P. S., Nallamothu, B. K., Gurm, H. S. et al , 2007) The study is a cost-utility analysis conducted from a third payer's perspective, using a Markov model for a hypothetical population of 60 year old patients. Effectiveness data were drawn from the A to Z (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004) and PROVE-IT (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004) trials for the ACS model, and from the TNT (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005) and IDEAL (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005) trials for the stable CAD model. Utility data were derived from published literature. The estimated ICER for the ACS population was below US$30,000/QALY and is stable in sensitivity analysis. The ICER for the stable CAD population was reported as US$33,400/QALY but the ICER is very sensitive to assumptions about statin efficacy (ICER range from $10,300/QALY to dominated) and cost of statins. ICERs range from dominant using the lower price of atorvastatin to $84,000/QALY when the higher price is used. The results of this study are similar to those found as a result of our modelling work.

Summary of cost-effectiveness of higher versus lower intensity statins

In conclusion, compared with low intensity statins, high intensity statins in patients with ACS are cost-effective when compared with low intensity statins.

In patients with stable CAD, atorvastatin 80 mg is not cost-effective using a £20,000/QALY threshold. However, assuming the use of generic simvastatin 80 mg is makes the model highly cost-effective. Thus cheaper generic high intensity statins may be used in patients with stable CAD.

Cost-effectiveness of treating to target (titration threshold) compared with fixed doses of statins

A systematic literature search identified 408 papers. Eighteen papers were assessed in full. None of them met the inclusion criteria. In light of the lack of published evidence, the GDG requested the development of an economic model in order to generate cost-effectiveness estimates.

Model Structure and Assumptions

The population modelled is a hypothetical cohort of 1000 adults with hyperlypidemia and with a history of CHD/CVD, and who are free from diabetes. The population modelled was based on a distribution of patients taken from The Health Improvement Network (THIN) database, having an average untreated total cholesterol level of 6.1 mmol/l and an average age of 61 years.

The model estimates lifetime costs and quality adjusted life years (QALYs) of statin treatment using a target titration treatment strategy versus a fixed dose treatment strategy. The model has been used to estimate the cost-effectiveness of both 4 mmol/l and 5 mmol/l targets using 1 and 2 step titrations.

In the fixed dose strategy, all patients are assumed to be given simvastatin 40 mg daily, with no further consultations, or measurements performed. This treatment strategy was initially compared with a two-stage titration strategy, in which patients are initially given simvastatin 40 mg daily, with those failing to

reach the pre-specified target then being titrated to the next therapy (simvastatin 80 mg). Measurements are again taken for the latter group of patients, and anyone still not achieving the pre-specified target is then assumed to be titrated up to atorvastatin 80 mg. In the one-step titration model, patients not achieving target on simvastatin 40 mg are titrated once only up to simvastatin 80 mg, with no further up-titration.

For both treatment arms, the modelled percentage reductions in cholesterol levels are estimated using the results of the STELLAR trial (Jones, P. H., Hunninghake, D. B., Ferdinand, K. C. et al , 2004). Subsequent reductions in CVD event and mortality outcomes were estimated using equations derived from a meta-analysis by Law *et al* (Law, M. R., Wald, N. J., Rudnicka, A. R. et al , 2003).

Costs of drugs are based on prices quoted by the PPA as at February 27th 2008.

Table 4: Costs of modelled Statins as at Feb 27th 2008

	Price per 28 pack	Annual Cost
Simvastatin 40 mg	£1.39	£18.12
Simvastatin 80 mg	£4.95	£64.53
Atorvastatin 80 mg	£28.21	£367.74

Each titration step is assumed to cost £26 based on the cost of a GP consultation and a blood test.(Netten, A. & Curtis L., 2007) Cost of health states including treatment for MI, stroke, TIA, PAD, HF, and angina were estimated using various published sources (details in Appendix C). Health state utility values were taken from published sources (Appendix C). All cause mortality rates are from the Government Actuarial Department.(Government Actuaries Department, 2006) The model makes the conservative assumption that the all cause mortality rate in the modelled population is twice that of the general population. Also, the model assumes no adverse events from treatment using high dose statins.

As recommended by NICE (National Institute for Health & Clinical Excellence., 2006) and to reflect social values, future costs and QALYs are both discounted at a rate of 3.5% in the model. These and other model assumptions have been tested in sensitivity analyses.

Results

Table 5 indicates that with a target of 5 mmol/l total cholesterol, the majority of patients (69%) are modelled to reach target on simvastatin 40 mg. This is true

of both the fixed and the titration population groups in the model. With a target of 4 mmol/l, only 31% of patients will reach target on simvastatin 40 mg. In the 2 step titration model an additional 15% of patients reach target on simvastatin 80 mg, if the target is 5 mmol/l and an additional 6% reach target using 4 mmol/l.

Table 5: Proportion of patients modelled to be on each of the three included drugs under four treatment strategies

	2-Step Target 5	2-Step Target 4	1-Step Target 5	1-Step Target 4
Simva 40 mg	69%	31%	69%	31%
Simva 80 mg	15%	6%	31%	69%
Atorva 80 mg	16%	63%	-	-

Table 6 indicates the modelled number of events for the hypothetical 1000 patient cohorts having assumed a 2-step titration and a target total cholesterol of 5 mmol/l for illustrative purposes. The table indicates that fewer CVD events occur in the population treated using the titration strategy.

Table 6: Lifetime event outputs modelled for a cohort of 1,000 patients using a 2-stage titration treatment strategy with a target of 5 mmol/l total cholesterol compared with a fixed low dose treatment strategy

| | F&F | Titration to 5 mmol/l | | | |
	sim 40	sim 40	sim80	Atorva80	Titration Total
No of patients	1000.00	690.00	150.00	160.00	1000.00
Total MIs	135	93	18	16	127
Total Strokes	168	116	25	26	167
total TIA	86	59	13	14	86
Total PAD	60	41	8	8	57
Total HF	78	54	11	9	74
Total Stable Angina	184	127	25	22	174
Total Unstable Angina	94	65	13	12	90
CVD deaths	104	72	14	13	99
Other Deaths	896	618	136	147	901
Titration costs	-				£34,060
Tot. Discounted Costs	£9,280,374				£ 10,002,892
Discounted QALYS	8,116				8135

The incremental cost-effectiveness analysis indicates that compared to a fixed dose treatment strategy, a 1-step titration to simvastatin 80mg treatment strategy using a target of 4mmol/l has an ICER of £14,089 per QALY. One step titration to 5mmol/l is ruled out by extended dominance and 2 –step titration to 5 is dominated by I step titration to 4mmol/l. Two step-titration to 4mmol/l is not cost-effective and has an ICER of £66,819/QALY when compared to 1 step-titration to 4mmol/l. Our model indicates that with the 1 step titration to a target of 4 mmol/l (simvastatin 80mg) 63% of patients would not achieve this target, however the analysis indicates that it would not be cost-effective to try to get more patients to target.

Conclusion

In conclusion, the result of modelling suggest that titration using a threshold target of 4 mmol/l total cholesterol is cost-effective so long as titration stops at simvastatin 80 mg. Most patients would not achieve a target of 4mmol/l total cholesterol and modelling suggests that it is not cost-effective to try to take more patients to target using higher cost statins such as atorvastatin. Details of the economic model and the analyses are available in Appendix C.

7.3.7   Adverse events associated with lower intensity statin therapy

Adverse events associated with lower intensity statin therapy are discussed in the primary prevention drug therapy chapter (Section 6.3.2.3).

7.3.8   Adverse events associated with higher intensity statin therapy

Four randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity statin therapy, the details and results of which have been described in section 1.3.3 (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004) (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005) (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004).

The first trial (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004) found elevations in alanine aminotransferase levels to be greater in patients who received atorvastatin 80 mg compared with those receiving pravastatin 40 mg. Discontinuation of study medication due to myalgia, muscle aches or elevations in creatine kinase levels were similar in the two treatment groups. No cases of rhabdomyolysis were reported in either group (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004).

The second trial (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005) found that patients who received atorvastatin 80 mg had higher rates of discontinuation due to non-serious adverse events than those allocated to simvastatin 20 mg. There were no differences in the frequency of serious

adverse events between the two treatment groups. Serious myopathy and rhabdomyolysis were rare in both groups (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005).

The third trial (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005)) found therapy with atorvastatin 80 mg to be associated with an increase in adverse events, with a higher rate of treatment discontinuation compared with the atorvastatin 10 mg group. Treatment related myalgia was similar in the two groups and there were no persistent elevations in creatine kinase. Five cases of rhabdomyolysis were reported (2 in the high dose group, 3 in the low dose group). More patients in the high dose group had persistent elevation in alanine aminotransferase, aspartate aminotransferase or both, compared with the low dose group (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005).

The fourth trial (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004) compared early intensive therapy (simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter) with delayed conservative therapy (placebo for 4 months followed by simvastatin 20 mg once daily thereafter). Incidences of elevated alanine aminotransferase or aspartate transaminase levels (greater than 3 X ULN) were found to be similar in the two treatment groups. Discontinuation of study medication due to muscle-related adverse events was also comparable between the two groups. A total of 10 patients developed myopathy (creatine kinase > 10 X ULN on 2 consecutive measurements). Of the nine patients treated with simvastatin 80 mg, three patients had creatine kinase levels > 10 000 units/l and met the criteria for rhabdomyolosis. Of these 3 patients, 1 had contrast media renal failure and 1 patient was receiving concomitant verapamil (inhibitor of cytochrome P450 3A4 (CYP3A4)). In addition, 1 patient receiving 80 mg simvastatin had a creatine kinase level 10 X ULN without muscle symptoms, which was associated with alcohol abuse (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004).

Two randomised controlled trials were identified that compared higher intensity statin therapy with placebo (Amarenco, P., Bogousslavsky, J.,

Callahan, A., III et al , 2006; Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al , 2001), the details and results of which have also been described in section 9.3.3.

The first trial (Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al , 2001) found that more patients in the atorvastatin 80 mg group developed liver transaminase levels > 3 X ULN compared with those allocated placebo. There were no cases of myositis.

The second trial (Amarenco, P., Bogousslavsky, J., Callahan, A., III et al , 2006) compared treatment with atorvastatin 80 mg to placebo and found no significant difference in the incidence of serious adverse events between groups, although persistent elevation of alanine or aspartate aminotransferase (> 3 ULN on two consecutive occasions) was more frequent in the atorvastatin group (2.2 %) versus placebo (0.5 %), $P < 0.001$.

A retrospective analysis of pooled data from 49 clinical trials of atorvastatin was identified which compared the relative safety of lower intensity atorvastatin 10 mg with higher intensity atorvastatin 80 mg (Newman, C., Tsai, J., Szarek, M. et al , 2006). Data were pooled from 49 clinical trials (n = 14 236 participants) in which patients were randomised to receive active treatment for a period ranging from 2 weeks to 52 months (atorvastatin 10 mg: n = 7258, atorvastatin 80 mg: n = 4798 and placebo: n = 2180). The incidence rate (per 1000 patient-years of exposure) of various safety parameters and adverse events was calculated for each of the three groups. The overall safety profile was comparable between atorvastatin 80 mg, 10 mg and placebo in terms of incidence rate of patients experiencing ≥1 adverse event, withdrawals due to adverse events and serious, nonfatal adverse events. Musculoskeletal safety parameters were also similar across groups and there were no incidences of myopathy or rhabdomyolysis reported. In this analysis, a greater incidence of persistent alanine aminotransferase and / or aspartate aminotransferase > 3 X ULN was observed in the atorvastatin 80 mg group compared with the other two groups. Serious hepatic adverse events were rare although five patients in the atorvastatin 80 mg group developed

hepatitis, which resolved after discontinuation of atorvastatin. The adverse events of haematuria and albuminuria were also examined but the incidence in each atorvastatin group was low compared to placebo. Incidence of death was low in all groups and none were considered to be related to treatment.

A number of cohort studies have examined the safety of rosuvastatin used in clinical practice.

The first was a Dutch study that followed three separate cohorts, namely incident rosuvastatin users, other incident cohort users and non-statin exposed controls for cases of myopathy, rhabdomyolysis, acute renal failure and liver impairment / failure (Goettsch, W. G., Heintjes, E. M., Kastelein, J. J. et al , 2006). Exclusion criteria for the two statin cohorts were as follows; not incident users, statin use < 12 months, age < 20 or > 84 years, missing information in the PHARMO system, serious adverse event in history (e.g. of myopathy, rhabdomyolysis). The control cohort had to be aged between 20 and 84 and have no history of statin usage (≥ 12 months), and individuals were excluded if they had a history of a serious adverse event (e.g. of myopathy, rhabdomyolysis). Data were obtained from the PHARMO medical record linkage system that included drug-dispensing records from community pharmacies and hospital discharge records of more than 2 million residents throughout the Netherlands. Potential cases of hospitalisation for myopathy, rhabdomyolysis, acute renal failure or hepatic impairment for each of the three cohorts were validated through a multi-step process using data obtained from hospital records. Cases of all cause mortality were obtained from notifications in the hospital and pharmacy databases and were not validated (Goettsch, W. G., Heintjes, E. M., Kastelein, J. J. et al , 2006).

In 2002 and 2004, of 119 681 statin users 47 543 incident statin users met the inclusion criteria. More than 20% of those patients started with rosuvastatin (10 147), 15 091 patients with atorvastatin, 14 198 with simvastatin, 7290 with pravastatin and 817 with floatation. There were 99 935 controls selected from the PHARMO system. In total, 102 events (excluding death) were identified in 96 patients, 21 in the category myopathy/rhabdomyolysis, 48 in acute renal

failure, and 33 events as hepatic Impairment. Only 81% of cases could be validated (79.4%) because some hospitals did not cooperate for several not medical reasons. The validation process resulted in 1 case of myopathy, 1 case of rhabdomyolysis, 13 cases of renal impairment and 11 cases of hepatic impairment. The total number of deaths identified was 1388, and after adjustment for age and gender in the three cohorts, all cause mortality was not increased in the statin user groups compared with the control group (Goettsch, W. G., Heintjes, E. M., Kastelein, J. J. et al , 2006).

The total incidence of serious adverse event was very low, in the users of statins only 15 validated events were identified in more than 45 000 years of follow up (> 1 per 3000 person years). Only one case of myopathy could be identified among the users of other statins cohort, and one case of rhabdomyolysis in the non statin control cohort. The number of validated cases of acute renal failure was higher, and the incidence in both statin cohorts was increased compared with controls (rosuvastatin RR 5.91, 95%CI 1.19 to 29.36, other statins RR 3.27 95%CI 0.84 to 12.75). No significant difference was observed in the incidence of acute renal failure between the rosuvastatin and other statin cohorts (RR 1.81, 95%CI 0.47 to 7.02). Hepatic impairment incidences' were comparable in the other statin and control cohorts, while no incidences of hepatic impairment were found in the rosuvastatin cohort (Goettsch, W. G., Heintjes, E. M., Kastelein, J. J. et al , 2006).

The second study was an observational cohort study in which patients were identified from dispensed prescriptions issued by primary care physicians / general practitioners between August and December in the England (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007). At least 6 months after the initial prescription, questionnaires known as Green forms were sent to the general practitioners requesting information regarding any event that occurred since initiation of rosuvastatin. The term event was defined as 'any new diagnosis, any reason for referral to a consultant or hospital admission, any unexpected deterioration (or improvement in concurrent illness, and suspected drug reaction, any alteration of clinical importance in laboratory values, or any other

significant event requiring documentation. All returned forms were reviewed by medically qualified staff, and events that required further assessment were followed up. These included muscular, hepatic and renal events, suspected adverse drug events, and events with unknown aetiology for example jaundice (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

Of 31 228 Green forms sent, 12 543 (40.2%) were returned, and 863 (6.9%) were classified as void and excluded from the study. The study cohort comprised of 11 680 patients, of which 50.3% were male (5880), 49.2% (5745) were female, and for 0.5% (55) the sex was not specified. The median age was 64 years (interquartile range 56 to 72 years), and the age range was 17 to 101 years. The median treatment period was 9.8 months (interquartile range 4.6 to 11.7 months) (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

Data derived from the Green forms were used in an incident density analysis of all events reported during treatment within specified time periods and also provided information on clinical events reported as the reason for discontinuation of rosuvastatin (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

 A total of 2047 (17.5%) patients were reported to have stopped treatment with rosuvastatin. Musculoskeletal events accounted for 20.3% (414 of 2037) of the reasons for discontinuation. Myalgia was the most frequents cause (277 cases, 13.6% of all reasons specified), followed by patient request (144 of 2037), drug information including adverse publicity / reports in the media (123 of 2037), non formulary reasons such as change in general practitioner, prescribing policy (91 of 2037). Abnormal liver function tests and elevated creatine kinase levels accounted for 57 and 33 cases of discontinuation, respectively (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

Incident densities (ID) were calculated for events occurring in the first month (ID_1) of treatment, during months 2-6 (ID_{2-6}) of treatment and for events occurring during the overall treatment period. The ten most common adverse events in order of first month IDs were: Myalgia, malaise, dizziness,

nausea/vomiting, intolerance, headache / migraine, abdominal pain, dyspepsia, abnormal LFTs and joint pain. Myalgia was the adverse event with the highest incident density during month 1 (ID_1 = 7.70 events per 1000 patient-months of treatment) and it also had the highest ID for the whole treatment period. The difference between IDs for the first month and during months 2-6 were calculated to establish which events may have been early-onset events with rosuvastatin. There were six clinical events for which the rate of event in month 1 was significantly greater than the rate of event in months 2-6: Myalgia (ID_1-ID_{2-6} = 4.0 (99% CI 1.67 to 6.33)), malaise (ID_1-ID_{2-6} = 2.28 (99% CI 0.64 to 3.91)), dizziness (ID_1-ID_{2-6} = 1.90 (99% CI 0.49 to 3.30)), nausea / vomiting (ID_1-ID_{2-6} = 1.54 (99% CI 0.17 to 2.91)), intolerance (ID_1-ID_{2-6} = 1.71 (99% CI 0.38 to 3.04)), and headache / migraine (ID_1-ID_{2-6} = 1.43 (99% CI 0.11 to 2.75)) (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007),

IDs were also stratified by starting dose of rosuvastatin: the IDs for the 20 mg/day and 40 mg/day dosages were compared with the 10 mg/day dose. A 2.5 fold increase in the rate of abnormal LFT results was found for patients started on the rosuvastatin 40 mg/day dose compared with those started on the 10 mg/day dose (Incidence density ratio = 2.71 (95% CI 1.53 to 4.53)). Although there was an increase in the incidence density ratio for the 40 mg/day dose compared with the 10 mg/day dose for elevated CK, raised urea / creatinine, haematuria and proteinuria, these differences were not significant. No differences were found between dosage groups in the rates of myalgia, limb pain or cramps (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

Where events described on the Green forms required further assessment, follow-up questionnaires were sent to the GPs. A total of 685 questionnaires were posted to prescribing GPs of which 585 (85%) were returned. Data from these questionnaires were used in a causality assessment for adverse events relating to the muscular, hepatic and renal system-organ classes. Events were assessed as 'probably' or 'possibly' related to rosuvastatin depending upon various factors including whether the adverse events were clinically

and/or pathologically well-defined with reasonable time-sequence in relation to administration of rosuvastatin and whether they were more likely to be attributed to rosuvastatin than to concurrent disease or other drugs and whether dechallenge or rechallenge was positive (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

Regarding musculoskeletal events, there were no cases of rhabdomyolysis reported in this cohort; there were 2 cases of myopathy reported however follow-up data was not available and thus causality assessment was not performed. Of the 229 cases of myalgia that were followed up, 128 were assessed as probably related to rosuvastatin and 69 possibly related to rosuvastatin. Overall, musculoskeletal events were the most frequently reported adverse event. Where causality assessment was conducted, a high proportion of musculoskeletal events were assessed as probably or possibly related to rosuvastatin (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

Regarding hepatic events, follow-up data was available for 101 cases of abnormal LFTs, 19 and 48 of these were assessed as probably or possibly related to rosuvastatin respectively. In addition, one case of autoimmune hepatitis and another case of jaundice, raised alkaline phosphatise and ALT were assessed as possibly related to rosuvastatin (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

Regarding renal events, there were 25 cases of raised urea / creatinine, 5 of which were assessed as possibly related to rosuvastatin; there were 7 cases of haematuria, 3 of which were assessed as possibly related to rosuvastatin; 9 cases of proteinuria, one of which were assessed as possibly related to rosuvastatin and another was assessed as probably related to rosuvastatin. Two cases of renal failure were reported although follow-up data was not available for either of these cases (Kasliwal, R., Wilton, L. V., Cornelius, V. et al , 2007).

The fourth study was a retrospective matched cohort study with a follow-up duration of up to 18 months in patients initiating treatment with rosuvastatin compared with other statins (McAfee, A. T., Ming, E. E., Seeger, J. D. et al ,

2006). All patients receiving a statin were identified from the administrative database of a large health insurer in the U.S. for the period 1st September 2003 to 29th February 2004. Patients were included in the cohort if they had no prescription for a statin (naïve initiators) or if they had been prescribed a different statin than the index prescription (switcher initiators) during the baseline period defined as 183 days prior to the index date. Only patients who were at least 18 years of age with complete demographic and enrolment information and at least 183 days of complete enrolment before the index date were included. Patients were excluded if they had claims-based diagnoses of myopathy, rhabdomyolysis, renal dysfunction or hepatic dysfunction associated with a hospitalization during the baseline period (McAfee, A. T., Ming, E. E., Seeger, J. D. et al , 2006).

A total of 194 320 patients were identified as having at least one prescription claim for a statin during the defined time period who were either naïve or switcher initiators of a particular statin. Of these patients, 106 926 met the inclusion criteria, 12 217 of which were rosuvastatin initiators and 94 709 were initiated on other statins. Rosuvastatin initiators were matched to other statin initiators by a multivariate technique (propensity score analysis and matching) in order to balance covariate patterns and account for any baseline characteristics of rosuvastatin initiators that differed from other statin initiators in that time period. All analyses were also adjusted by the number of matched comparators. Thus, 11 249 rosuvastatin initiators were matched to 37 282 other statin initiators (statin used: 54.2% atorvastatin, 21.2% simvastatin, 11.0% pravastatin, 10.6% lovastatin and 3.1% fluvastatin) (McAfee, A. T., Ming, E. E., Seeger, J. D. et al , 2006).

Potential incident cases associated with hospitalization for myopathy, rhabdomyolysis, renal dysfunction, or hepatic dysfunction and in-hospital death were identified from health insurance claims and data on 403 (81%) of these potential outcomes were successfully abstracted from written medical records with 125 (31%) cases of outcome incidence being confirmed (McAfee, A. T., Ming, E. E., Seeger, J. D. et al , 2006).

Incidences of adverse events were low. Five cases of rhabdomyolysis or myopathy were found among 43 585 person-years for the entire study cohort (Incidence Rate = 1.15 per 10 000 person-years (95% CI 0.37 to 2.68)). Adjusted Hazard Ratios were calculated and it was found that there were no significant differences between those initiated on rosuvastatin compared with those initiated on other statins for any outcome measure (HR = 1.98 (95% CI 0.18 to 21.90) for rhabdomyolysis, HR= 0.90 (95% CI 0.47 to 1.73) for renal dysfunction, HR not calculable for myopathy, HR=0.87 (95% CI 0.18 to 4.14) for hepatic dysfunction and HR=0.51 (95% CI 0.24 to 1.10) for in-hospital death) (McAfee, A. T., Ming, E. E., Seeger, J. D. et al , 2006) .

The fifth study reviewed adverse event reports (AERs) to the Food and Drug Administration USA (FDA) to determine the frequency of rosuvastatin-associated events relative to other commonly used statins, namely; atorvastatin, simvastatin, pravastatin and cerivastatin (for cerivastatin during the time it was available). Two comparative primary analyses were performed. For the first analysis, AERs were determined for the first year during which rosuvastatin was available in the USA (October 2003 to September 2004) and these AERs were compared with the concomitant time period for the other statins (defined as 'concurrent time period analysis'). The mean doses of statins during this time period was as follows; rosuvastatin 16.7±1.2 mg, simvastatin 53±2.8 mg, pravastatin 18.8±2.0 mg and atorvastatin 21.8±1.4 mg. The second analysis was performed to address the potential of preferential reporting of adverse events with newly marketed drugs. Thus rates of rosuvastatin-associated AERs were compared with those during the first year of marketing for atorvastatin (1997), simvastatin (1992), pravastatin (1992) and cerivastatin (1998). This was defined as 'first year of marketing analysis'. The rates of AERs were calculated as AERs per million prescriptions for various AERs associated with each of the statins (Alsheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al , 2005).

For the concurrent time period analysis, the rate of rosuvastatin AERs (a composite of rhabdomyolysis, proteinuria / nephropathy, or renal failure) was higher than AERs for simvastatin (*P* < 0.001), pravastatin (*P* < 0.001) and

atorvastatin ($P < 0.001$). For the first year of marketing analysis the rate of rosuvastatin-associated composite AERs was not significantly different than simvastatin AERs, but was significantly higher compared with pravastatin ($P < 0.001$) and atorvastatin ($P < 0.001$). Compared with AERs for cerivastatin during its first post marketing year, rosuvastatin composite AERs were less frequent ($P < 0.001$). Sixty two percent of rosuvastatin-associated AERs occurred at doses of ≤ 10 mg / day, and occurred earlier after the initiation of therapy (within the first 12 weeks) compared to other statins. There was no gender predominance. While fatalities were rare, most composite AERs listed hospitalisation as an outcome (Alsheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al , 2005).

The increased rate of rosuvastatin-associated AERs relative to the other statins was also observed in secondary analysis.

For the concurrent time period analysis, the rate of rosuvastatin-associated AERs for any adverse event was higher than that observed for simvastatin, pravastatin and atorvastatin ($P < 0.001$ all statins versus rosuvastatin). Likewise for serious AERs (life threatening or requiring hospitalisation), liver AERs, muscle AERs without rhabdomyolysis and also renal failure AERs, rosuvastatin had higher rates of adverse events ($P < 0.001$ all statins versus rosuvastatin). Furthermore, rhabdomyolysis AERs, although rare, were also higher for rosuvastatin (simvastatin; $P < 0.01$, pravastatin and atorvastatin; $P < 0.001$) (Alsheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al , 2005).

For the first year of marketing analysis the rate of rosuvastatin-associated AERs was similarly higher for the following AERs compared with other statins; all AERs (simvastatin, pravastatin atorvastatin, cerivastatin $P < 0.001$ all statins versus rosuvastatin), muscle AERs without rhabdomyolysis (simvastatin, pravastatin atorvastatin, cerivastatin $P < 0.001$ all statins versus rosuvastatin). Liver AERs were higher for rosuvastatin compared with simvastatin, pravastatin and atorvastatin, but were not significantly different with the rate observed with cerivastatin. Serious AERs were higher for rosuvastatin compared with pravastatin and atorvastatin ($P < 0.001$ for both);

however, the rosuvastatin rate was lower than that observed for simvastatin ($P < 0.001$) and cerivastatin ($P < 0.01$). Rosuvastatin was also significantly more likely than simvastatin, pravastatin and atorvastatin to be associated with reports of rhabdomyolysis ($P < 0.001$ all statins versus rosuvastatin), but compared with the first year of cerivastatin, the rate of rosuvastatin rhabdomyolysis events was significantly less ($P < 0.001$). Finally, the rate of rosuvastatin-associated renal failure AERs was higher compared with pravastatin and atorvastatin ($P < 0.001$ for both), but similar to that observed with simvastatin and cerivastatin (Alsheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al , 2005).

There are a number of intrinsic limitations of post marketing adverse event analysis. The analysis is based on reporting rates, not on actual adverse event rates. In clinical practice, adverse events are under reported, and serious adverse events are more likely to be reported than less serious events. The retrospective nature of the analysis does not allow confirmation of causality, or control of potential confounders. For example, providers tend to report preferentially adverse events with newly marketed drugs. In addition, certain adverse events may not be recognised as related to a particular class of drug. Post marketing analysis can also be influenced by publicity, favourably or unfavourably. Another time dependent post marketing variable could be related to the availability of drug dosage. In this context, the relatively low rate of atorvastatin-associated AERs during its first year of marketing may be partially attributable to the fact that only the 10 mg dose was available in the first year (Alsheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al , 2005).

Not with standing these limitations, the review found that rosuvastatin had a higher rate of AERs compared with other commonly prescribed statins based upon adverse event reports to the FDA. The authors of the review stated that the reported occurrence of these AERs early after initiation of therapy (within 12 weeks on average) suggests that vigilant monitoring for adverse events may ameliorate the risk of toxicity when rosuvastatin is used. They also stated that it would seem prudent for healthcare providers to consider other statins as first line therapy, to initiate rosuvastatin therapy in appropriate patients at

lower doses as well as careful monitoring for adverse events (Alsheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al , 2005).

7.3.9 Evidence to recommendations – statins

The NICE technology appraisal on statins (NICE technology appraisal guidance 94, Statins for the prevention of cardiovascular events' 2006) considered twenty-eight randomised controlled trials of statins in adults with or at risk of CVD.

No studies that reported cardiovascular events as outcomes were identified for rosuvastatin. Fourteen placebo-controlled studies in which all participants had CHD at study entry were identified for inclusion in a meta-analysis. There were significant reductions in all cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), CHD mortality (RR 0.72, 95% CI 0.64 to 0.80), fatal MI (RR 0.57, 95% CI 0.45 to 0.72), nonfatal MI (RR 0.69, 95% CI 0.59 to 0.95), new or worsening intermittent claudication (RR 0.64, 95% CI 0.46 to 0.91). There was no significant reduction in stroke mortality (RR 1.07, 95% CI 0.67 to 1.71) or TIA (RR 0.66 95% CI 0.37 to 1.17). The relative effectiveness of statins did not differ by sex, in people with and without diabetes, or in people over 65 years compared with younger people. For secondary CHD prevention the incremental cost per QALY ranged from £10,000 to £16,000 for all age groups with little difference for men and women.

The NICE technology appraisal (NICE technology appraisal guidance 94, 'Statins for the prevention of cardiovascular events' 2006) recommended statin therapy for all adults with clinical evidence of CVD and that when the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose). The GDG considered that for initiation of treatment, simvastatin 40 mg was the most effective drug with a low acquisition cost in secondary prevention.

7.3.10 The use of higher intensity statins and cholesterol targets

International and national guidelines on lipid lowering for CVD prevention have all defined goals or targets of therapy. These target levels have become progressively lower over time and differ between guidelines. The Joint British Societies first recommended in 1998 a total cholesterol target of less than 5.0 mmol/l and an LDL cholesterol target of less than 3.0 mmol/l, or a 25% total cholesterol reduction or a 30% LDL cholesterol reduction, whichever is greater (Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association, 1998). The National Service Framework for CHD in 2000 recommended levels less than total cholesterol 5 mmol/l or LDL cholesterol 3 mmol/l (or a 25% TC reduction or 30% LDL cholesterol reduction whichever is greater) and these remain the current national advice (DoH March 2000 website). In 2003 the Joint European Societies Task Force on CVD Prevention recommended a total cholesterol level less than 4.5 mmol/l and LDL cholesterol levels below 2.5 mmol/l. Since 2004 in the USA high risk CVD patients are advised to achieve LDL cholesterol levels below 1.81 mmol/l (http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm). The most recent Joint British Societies 2005 guideline recommended target levels below total cholesterol 4 mmol/l and LDL cholesterol 2 mmol/l (or a 25% reduction in total cholesterol and a 30% reduction in cholesterol if that yields a lower value) (Wood, D., Wray, R., Poulter, N. et al , 2005). More recently the Scottish Sign Guideline 2007 considered total cholesterol targets of 4 mmol/l or 4.5 mmol/l would have major resource implications for NHS Scotland (Scottish Intercollegiate Guidelines Network., 2007), but this was not based on a formal cost-effectiveness analysis. SIGN recommended that pending further studies on mortality, safety, and cost-effectiveness, a total cholesterol target of less than 5 mmol/l in individuals with CVD should be a minimum standard of care (Scottish Intercollegiate Guidelines Network., 2007).

The Cholesterol Trialists Collaboration (Baigent, C., Keech, A., Kearney, P. M. et al , 2005) reported an approximately linear relationship between the

absolute reductions in LDL cholesterol achieved 14 statin trials and the proportional reductions in the incidence of coronary and other events. The authors of the Cholesterol Trialists Collaboration state that there is a significant trend towards greater proportional reductions in major coronary events being associated with greater mean absolute LDL cholesterol reductions in the different trials (Baigent, C., Keech, A., Kearney, P. M. et al , 2005). There was no significant heterogeneity between the relative effects after weighting for the absolute LDL cholesterol reduction (Baigent, C., Keech, A., Kearney, P. M. et al , 2005). They found that the proportional reduction in the event rate per mmol/l reduction in LDL cholesterol was largely independent of the presenting cholesterol level. So, lowering the LDL cholesterol level from 4 mmol/l to 3 mmol/l reduced the risk of vascular events by about 23% and lowering LDL cholesterol from 3 mmol/l to 2 mmol/l also reduced residual risk by about 23%. There is a near linear relationship between the log of the risk and cholesterol reduction, but it is important to appreciate that although the relative risk reduction remains constant, at lower cholesterol levels there is a smaller *absolute* reduction in cardiovascular events, and it is absolute risk reduction that determines cost-effectiveness.

This log linear relationship describes the effect of cholesterol lowering with statins, at least down to a LDL cholesterol of 2 mmol/l. A meta-analysis of higher intensity statins (Cannon, C. P., Steinberg, B. A., Murphy, S. A. et al , 2006) confirmed that the observed 0.67 mmol/l reduction in LDL cholesterol would be expected to lead to a 14% reduction in cardiovascular events on the basis of the log linear hypothesis and the observed reduction of 16% was consistent with this.

The majority of randomised controlled trials to date have not shown a reduction in LDL cholesterol below 2 mmol/l with statin therapy (Figure 1, JBS2 (Wood, D., Wray, R., Poulter, N. et al , 2005)). LDL cholesterol was reduced below an average value of 2 mmol/l in only three of the twenty trials shown; PROVE-IT 1.6 mmol/l (Cannon, C. P., Braunwald, E., McCabe, C. H. et al , 2004), A-Z 1.7 mmol/l (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al , 2004), MIRACL 1.9 mmol/l (Schwartz, G. G., Olsson, A. G., Ezekowitz, M.

D. et al , 2001). These are all recent randomised controlled trials at maximal licensed statin dosage. These trials had strict recruitment criteria and patients with higher levels of LDL cholesterol tended to be excluded, and are not representative of the general population with CVD. Moreover, the reported LDL cholesterol reductions were median values of the trial participants.

Figure 1 Statin trials showing % reduction in major cardiac events and LDL   cholesterol   (mmol/l)
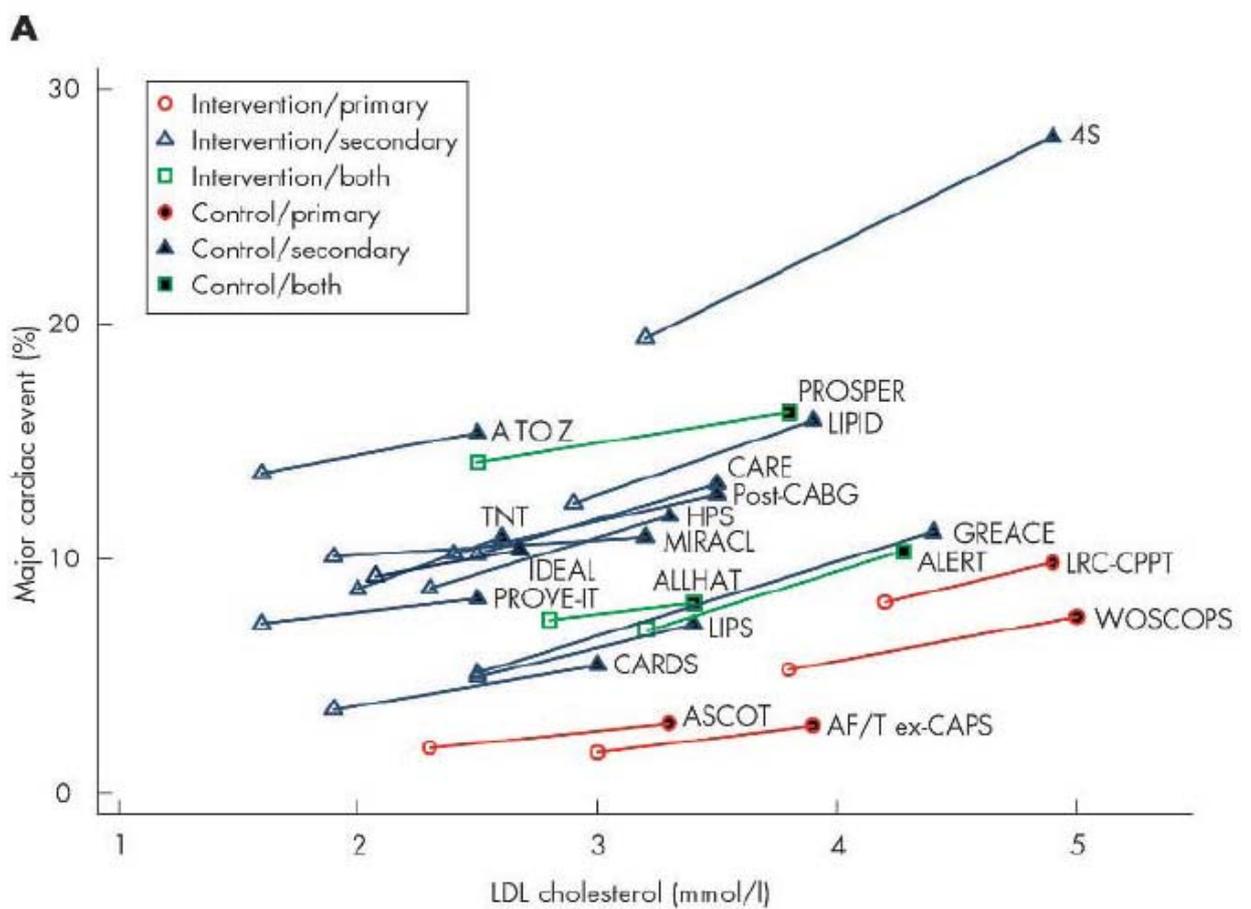
(Figure from JBS2 (Wood, D., Wray, R., Poulter, N. et al , 2005))

GDG discussion on use of targets

Within the GDG, there were differing views on the use of cholesterol "targets" i.e. levels of total and LDL cholesterol that patients on lipid lowering therapy should either aim to be below or should achieve. Proponents of targets considered that the log linear hypothesis from the Cholesterol Trialists Collaboration (Baigent, C., Keech, A., Kearney, P. M. et al , 2005) supported the use of targets because it confirmed that for LDL cholesterol "lower is better". GDG members were concerned that patients could be potentially under treated if no goal or target were specified. As a proportion of patients can reach cholesterol targets of total cholesterol of less than 4 mmol/l or LDL cholesterol of less than 2 mmol/l on standard doses of statins such as simvastatin 40mg the use of a target would reduce the likelihood that patients would be under-treated with suboptimal doses of statins such as simvastatin 10mg.

Opponents of setting targets raised a number of concerns. There was a minority view within the GDG that any targets are essentially misleading as trials have not treated to target but have used specific drugs to treat patients. For other members of the GDG there was concern as to how targets may be interpreted. Firstly, in practice targets can be interpreted to mean that all patients on treatment should attain the recommended level, irrespective of their starting cholesterol level. This takes no account of the distribution of cholesterol levels in the population prior to commencement of treatment, nor of differing responses to treatment and differing adherence to treatment. It is also important to note that the majority of randomised controlled trials which recruited selected populations did not find statin therapy reduced LDL cholesterol below 2 mmol/l (Figure 1). Opponents of setting targets considered it misleading for both professionals and patients, to set a target that is interpreted as 'should be achieved', knowing that many patients will not achieve this.

Secondly, two-thirds of the gain from a statin is realised by the initial dose. Lower cholesterol levels for individual patients may be achieved by using higher intensity statins but for each doubling of dose there is a smaller absolute reduction in cardiovascular events. There was concern that the adoption of targets may encourage the indiscriminate use of either high dose statins or combination lipid therapy.

Finally, there is no trial evidence that drug combinations such as a statin plus a fibrate, will produce additional cost-effective absolute reductions in cardiovascular events.

The GDG concluded by majority that the use of higher intensity statins or drug combinations should be driven by trial evidence of absolute benefit in clinical outcomes and cost effectiveness, and less by targets and relative risk. The GDG accepted again by a majority that the use of a target figure can be helpful in guiding increases of lipid lowering drugs as long as it is clear that this figure is intended to guide treatment rather than be a figure patients are expected to achieve. The wording of the recommendations was agreed to reflect this.

The GDG agreed using the clinical and cost effectiveness evidence that patients with ACS benefit from immediate high intensity statins. Health economic analyses for this guideline and published literature indicate that high intensity statins are less cost effective for patients with CAD. These patients should start on a standard dose of statin and the target figure used to inform increases in treatment.

The GDG recognised from the health economic modelling that over half of patients with stable CAD will not achieve total cholesterol level of 4 mmol/l and LDL cholesterol of 2 mmol/l when given 80 mg simvastatin.. An audit level of total cholesterol 5 mmol/l may help to assess progress in populations and groups.

Table 7 and Table 8 show absolute total and LDL cholesterol reduction and percentage reductions in serum concentrations according to statin and daily dose

Table 7:Absolute LDL cholesterol reduction* and percentage reductions[#] in serum LDL cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised controlled trials)

Statin	Daily dose (mg)	Absolute LDL cholesterol reduction (mmol/l) (95% confidence intervals)	Percentage reduction LDL cholesterol in serum
Atorvastatin	10	1.79 (1.62 to 1.97)	37%
Atorvastatin	20	2.07 (1.90 to 2.25)	43%
Atorvastatin	40	2.36 (2.12 to 2.59)	49%
Atorvastatin	80	2.64 (2.31 to 2.96)	55%
Pravastatin	40	1.38 (1.31 to 1.46)	29%
Rosuvastatin	5	1.84 (1.74 to 1.94)	38%
Rosuvastatin	10	2.08 (1.98 to 2.18)	43%
Rosuvastatin	20	2.32 (2.20 to 2.44)	48%
Simvastatin	40	1.78 (1.66 to 1.90)	37%
Simvastatin	80	2.01 (1.83 to 2.19)	42%

- Absolute reductions are standardised to usual LDL cholesterol concentration of 4.8 mmol/l before treatment (mean concentration in trials). #Percentage reductions are independent of pre-treatment LDL cholesterol concentration; 95% confidence intervals on percentage reductions can be derived by dividing those on absolute reductions by 4.8.
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Table 8: Absolute cholesterol reduction* and percentage reductions[#] in serum total cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised controlled trials)

Statin	Daily dose (mg)	Absolute total cholesterol reduction (mmol/l) (95% confidence intervals)	Percentage reduction total cholesterol in serum
Atorvastatin	10	2.15 (1.94 to 2.33)	32%
Atorvastatin	20	2.45 (2.28 to 2.70)	36%
Atorvastatin	40	2.83 (2.54 to 3.11)	42%
Atorvastatin	80	3.17 (2.77 to 3.55)	47%
Pravastatin	40	1.99 (1.88 to 2.10)	29%
Rosuvastatin	5	2.21 (2.09 to 2.33)	33%
Rosuvastatin	10	2.50 (2.38 to 2.62)	37%
Rosuvastatin	20	2.74 (2.64 to 2.93)	40%
Simvastatin	40	2.14 (1.99 to 2.28)	31%
Simvastatin	80	2.41 (2.20 to 2.63)	35%

*Absolute reductions are standardised to usual total cholesterol concentration of 6.8 mmol/l before treatment (mean concentration in trials). #Percentage reductions are independent of pre-treatment total cholesterol concentration; 95% confidence intervals on percentage reductions can be derived by dividing those on absolute reductions by 6.8.

7.4   Fibrates

[Return to Recommendations]

7.4.1   Evidence statements for fibrates

7.4.1.1   Two randomised controlled trials in patients after an MI and / or with angina found that clofibrate therapy was not associated with a reduction in fatal MI or sudden death in people with angina compared with placebo. One trial found that clofibrate therapy was not associated with a reduction in cardiovascular morbidity compared with placebo while the other found that clofibrate therapy was associated with a reduction in the rate of first non-fatal infarct in women with a history of angina compared with placebo.
7.4.1.2   One randomised controlled in patients after an MI and / or with angina found that bezafibrate therapy was not associated with a reduction in the composite of fatal MI, non-fatal MI and sudden death compared with placebo. In addition, no benefit was seen for cardiovascular morbidity.
7.4.1.3   One randomised controlled trial in men after an MI and / or with angina found that gemfibrozil therapy was associated with a reduction in the composite of fatal MI, sudden death, death due to congestive heart failure and death as a complication of invasive cardiac procedures compared with placebo.
7.4.1.4   Two randomised controlled trials in patients following stroke or TIA found that clofibrate therapy was not associated with a reduction in all cause mortality or cardiovascular morbidity compared with placebo.

7.4.1.5 *One randomised controlled trial in patients with peripheral arterial disease showed that bezafibrate therapy was not associated with a reduction in the combination outcome of fatal and nonfatal CHD events and stroke compared with placebo although bezafibrate therapy was associated with a reduction in the incidence of non-fatal coronary heart disease.*

7.4.2 Clinical effectiveness of fibrates

Seven randomised controlled trials were identified that compared fibrate therapy with placebo in patients with a history of CVD. Four of these were in patients after an MI and / or with angina, two were in patients following a stroke or transient ischaemic attack and one was in patients with peripheral arterial disease.

Four randomised controlled trials were identified in patients after an MI and / or with angina (Behar, S., Brunner, D., Kaplinsky, E. et al , 2000) (Rubins, H. B., Robins, S. J., Collins, D. et al , 1999) (Research Committee of the Scottish Society of Physicians., 1971), (Group of Physicians of the Newcastle Upon Tyne Region., 1971).

The first randomised controlled trial (Research Committee of the Scottish Society of Physicians., 1971) recruited patients aged 40-69 years with a history of angina, MI or both (27% had angina only). A total of 717 patients were randomised to receive either clofibrate or placebo (olive oil) and were followed up for a mean duration of 4 years. In patients with a history of angina only, treatment with clofibrate did not decrease the rates of sudden death, fatal MI or first non-fatal MI compared to placebo.

The second randomised controlled trial (Group of Physicians of the Newcastle Upon Tyne Region., 1971) recruited patients under 65 years with a history of angina, MI or both (40% had angina only). A total of 497 patients were randomised to receive either clofibrate or placebo (corn oil) and were followed up for 5 years. In patients with a history of angina only, treatment with clofibrate did not decrease the rates of sudden death or fatal MI compared to

placebo but was found to decrease the rate of first non-fatal infarct compared to placebo in women with a history of angina ($P < 0.05$) but not men.

Both of these studies used the drug clofibrate which has now been withdrawn from the British National Formulary.

The third randomised controlled trial (Rubins, H. B., Robins, S. J., Collins, D. et al , 1999) recruited men with an HDL cholesterol of 1.0 mmol/l or less, LDL cholesterol 3.6 mmol/l or less and triglycerides less than 3.4 mmol/l with documented coronary artery disease defined as a history of MI, angina, having undergone coronary revascularization, or angiographic evidence of coronary stenosis. Of these, 61% had a prior history of MI. Concomitant drug therapy at the start of the trial was as follows; aspirin 82%, beta blockers 43%, nitrates 46%, ACE inhibitors 21%, calcium channel blockers 53%. Patients were randomised to either gemfibrozil or placebo. Patients were followed for a mean 5.1 years. Gemfibrozil therapy was associated with a reduction in the primary endpoint of a combination of nonfatal MI and death from CHD compared with placebo. The incidence of the secondary outcome of a combination of nonfatal MI, death from CHD and confirmed stroke was also reduced in the gemfibrozil treatment group compared with the placebo. In addition, gemfibrozil therapy was associated with a reduction in the following outcomes compared with placebo: nonfatal MI, investigator-designated stroke, transient ischaemic attack, carotid endarterectomy and hospitalisation for congestive heart failure. Treatment with gemfibrozil was not associated with any benefit for the following outcomes: death due to coronary heart disease, death from any cause, confirmed stroke, revascularisation, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, peripheral vascular surgery and hospitalisation for unstable angina.

Patients assigned to gemfibrozil had lower total cholesterol and triglycerides levels and higher HDL cholesterol levels compared to patients in the placebo group. LDL cholesterol levels were the same in both groups. Gemfibrozil treatment was associated with a greater incidence of dyspepsia (Rubins, H. B., Robins, S. J., Collins, D. et al , 1999).

The fourth randomised controlled trial (Behar, S., Brunner, D., Kaplinsky, E. et al , 2000) recruited patients with a history stable angina pectoris and / or MI. Of these, 57% had prior angina (and 78% had a history of MI). A total of 3090 patients were randomised to receive either bezafibrate (retard) or placebo and were followed up for a mean duration of 6.2 years. Treatment with bezafibrate did not confer any benefit over placebo for the primary endpoint of a composite of fatal MI, nonfatal MI and sudden death. There was also no benefit observed for any of the individual components of this endpoint. Bezafibrate had no benefit over placebo for the following secondary endpoints: combination of hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty or coronary artery bypass graft, hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, mortality, cardiac mortality, noncardiac mortality, stroke or ischemic stroke.

Compared with the placebo group, triglyceride levels were lower in the bezafibrate subgroup that had triglyceride levels ≥ 2.26 mmol/l. The overall incidence of any adverse event was 69% in both groups, and the frequency of each type adverse event was similar in both groups (Behar, S., Brunner, D., Kaplinsky, E. et al , 2000).

Two randomised controlled trials were identified that compared fibrate therapy with placebo in patients with a history of stroke or transient ischaemic attack (Acheson, J. and Hutchinson, E. C., 1972) (Noble, J. D., Feringa, E. R., Greenhouse, A. H. et al , 1973). Both of these trials used clofibrate.

The first randomised controlled trial (Acheson, J. and Hutchinson, E. C., 1972) recruited patients with focal cerebral vascular disease (those with one stroke, multiple strokes or transient cerebral ischaemia) who had a serum cholesterol level of 250 mg /100ml or higher. A total of 95 patients were randomised to receive either clofibrate or placebo and the period of observation was from 4 months to 4 years. Compared with placebo, clofibrate therapy was not associated with a decrease in all cause mortality. Patients assigned to clofibrate had lower levels of serum cholesterol compared to

those who received placebo; mean proportional change in serum cholesterol level was -12.69% for control and -21.41% for clofibrate (*P* < 0.05). It should be noted that this was a small study and is likely to be underpowered for the outcomes described.

The second randomised controlled trial (Noble, J. D., Feringa, E. R., Greenhouse, A. H. et al , 1973) recruited male veterans with one or more cerebral infarctions or transient ischaemic attack within the past 12 months. A total of 532 men were randomised to receive either clofibrate or placebo and were followed up for an average duration of 21 months. Compared with placebo, clofibrate therapy was associated with a non significant decrease in all cause mortality: 30/264 deaths occurred in the placebo group versus 22/268 in the group allocated to receive clofibrate. For the outcome of vascular morbidity, there was no difference between the groups in the incidence of MI, TIA or angina. There was an increase in recurrence of cerebral infarction (23/264 placebo versus 37/268 clofibrate) and an increase in the incidence of congestive heart failure (4/264 placebo versus 15/268 clofibrate) in the clofibrate group compared to those receiving placebo but these differences were not tested for statistical significance. All other side effects were similar between groups. Regarding blood lipids, clofibrate decreased triglycerides compared to the control group (29% decrease clofibrate versus a 4% increase control) but had a negligible effect on cholesterol levels. Again, no statistical analysis was performed so the significance of these results is unknown It should be noted that this was a small study and is likely to be underpowered for the outcomes described.

One randomised controlled trial was identified that compared fibrate therapy with placebo in patients with a history of peripheral arterial disease (Meade, T., Zuhrie, R., Cook, C. et al , 2002). This trial recruited men with lower extremity arterial disease, 24% had stable angina, 21% had a previous MI and 12% had a history of stroke. A total of 1568 men were randomised to receive either bezafibrate (as Bezalip mono) or placebo and were followed up for a mean of 4.6 years. Bezafibrate therapy did not confer any benefit over placebo for the primary endpoint of a composite of CHD events (both fatal and

non-fatal) and all strokes. When the individual endpoints were analysed separately, bezafibrate had no benefit over placebo for the primary outcome of a composite of CHD events and all strokes, but was associated with a reduction in the incidence of non-fatal CHD events (RR 0.60, 95% CI 0.36 to 0.99).

7.4.3   Cost-effectiveness of fibrates

There were no cost-effectiveness studies found on the use of fibrates compared with placebo in secondary prevention of CVD.

7.4.4   Evidence into recommendations

The GDG considered that there was insufficient evidence to routinely recommend the use of fibrates as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.

7.5   *Nicotinic acids*

7.5.1   Evidence statements for nicotinic acids

7.5.1.1   No randomised controlled trials were identified that compared nicotinic acid therapy with placebo in patients with angina, peripheral arterial disease or following stroke.
7.5.1.2   One randomised controlled trial in patients after MI found that nicotinic acid therapy was associated with a reduction in non-fatal MI and the combination of coronary death or non-fatal MI compared with placebo. Nicotinic acid therapy was not associated with a reduction in all cause mortality, cardiovascular mortality or cardiovascular morbidity compared with placebo.

7.5.2   Clinical effectiveness of nicotinic acids

No randomised controlled trials were identified that compared nicotinic acid therapy with placebo in patients with angina, peripheral arterial disease or

following stroke. Due to the lack of trial evidence, it was decided by the GDG to consider evidence used in the NICE Myocardial Infarction guidance (Myocardial infarction - Secondary prevention in primary and secondary care for patients following a myocardial infarction, CG48, 2007)

One paper was identified that compared niacin treatment with placebo in patients after an MI (Wilkins, R. W., Bearman, J. E., Boyle, E. et al , 1975). The Coronary Drug Project Research Group randomly assigned post MI patients to six treatment groups: low and high conjugated oestrogen therapy, clofibrate, dextrothyroxine sodium, niacin and a placebo. The oestrogen and dextrothyroxine arms were stopped early because of an excess of nonfatal cardiovascular events and death, respectively. Patients were followed for 5 years.

Compared with placebo, niacin was not associated with a reduction in the incidence of the following outcomes: all cause mortality, the individual components of all cause mortality, definite pulmonary embolism (fatal or nonfatal), fatal or nonfatal stroke or intermittent cerebral ischaemic attack, definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis and also any definite or suspected fatal or nonfatal cardiovascular event. Niacin therapy reduced the incidence of nonfatal MI and also the combination of coronary death or nonfatal MI, compared with placebo. Cholesterol and triglycerides levels decreased in the niacin group compared with the placebo group.

Patients in the niacin group had a greater incidence of the following side effects compared with the placebo group: the combination of diarrhea, nausea, vomiting, black tarry stools, stomach pain, flushing, itching of skin, urticaria, other type of rash, pain or burning when urinating, decrease in appetite, unexpected weight loss, and excessive sweating (Wilkins, R. W., Bearman, J. E., Boyle, E. et al , 1975).

7.5.3   Cost-effectiveness of nicotinic acids

There were no cost-effectiveness studies found on the use of nicotinic acids compared with placebo in secondary prevention of CVD.

7.5.4   Evidence into recommendations

The GDG considered that there was insufficient evidence to routinely recommend the use of nicotinic acids as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.

7.6   *Anion exchange resins*

[Return to Recommendations]

7.6.1   Evidence statements for anion exchange resins

7.6.1.1   No randomised controlled trials were identified in patients with CVD that compared anion exchange resin therapy with placebo for the outcomes mortality or morbidity.
7.6.1.2   One small randomised controlled trial in patients with a history of CVD found that cholestyramine therapy was associated with a reduction in total cholesterol and LDL cholesterol compared with placebo.

7.6.2   Clinical effectiveness of anion exchange resins

No randomised controlled trials were identified in patients with CVD that compared anion exchange resin therapy with placebo for the outcomes mortality or morbidity.

One small randomised controlled trial was identified on the clinical effectiveness of anion exchange resins compared with placebo to improve lipid level profiles in patients with coronary artery disease (Brensike, JF., 1984). This trial recruited people with elevated LDL cholesterol and angiographic evidence of coronary artery disease (50% of whom had symptomatic angina and / or MI). A total of 143 patients were randomised to receive either cholestyramine 24 g per day or placebo and were followed up for five years. Treatment with cholestyramine resulted in decreases in total

and LDL cholesterol compared with placebo (5 year mean lipid level differences were - 0.1 mmol/l placebo versus - 1.4 mmol/l cholestyramine (*P* < 0.001) for total cholesterol and - 0.26 mmol/l placebo versus - 1.66 mmol/l cholestyramine (*P* < 0.001) for LDL cholesterol). Cholestyramine therapy did not have an effect on triglycerides or HDL cholesterol. There were negligible differences between groups for the ancillary outcomes of mortality and morbidity.

7.6.3   Cost-effectiveness of anion exchange Resins

There were no cost-effectiveness studies found on the use of anion exchange resins compared with placebo in secondary prevention of CVD.

7.6.4   Evidence into recommendations

The GDG considered that there was insufficient evidence to routinely recommend the use of anion exchange resins as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.

7.7   Ezetimibe

[Return to Recommendations]

7.7.1   Evidence statements for ezetimibe

> *7.7.1.1   Please refer to NICE Technology Appraisal No. TA132 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia', (National Institute for Health and Clinical Excellence., 2007)*

7.7.2   Clinical effectiveness of ezetimibe

The NICE Technology Appraisal TA132 is entitled 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia', (National Institute for Health and Clinical Excellence., 2007). The guidance recommends ezetimibe as a treatment option for primary (heterozygous

familial and non-familial) hypercholesterolaemia and states that its recommendations should be read in the context of the lipid modification clinical guideline (this guidance).

The population groups covered by the ezetimibe Technology Appraisal TA132 (National Institute for Health and Clinical Excellence., 2007) are:

- Adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and;

- whose condition is not appropriately controlled with a statin alone or;

- in whom a statin is considered inappropriate or is not tolerated.

The term "not appropriately controlled with a statin alone" is defined as failure to achieve a target lipid level that is appropriate for a particular group or individual. It also assumes that statin therapy is optimised.

The NICE Technology Appraisal TA132 (National Institute for Health and Clinical Excellence., 2007) 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia' did not identify any randomised controlled trials that reported health-related quality of life or clinical endpoints such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were used as indicators of clinical outcomes.

To represent the population of people with hypercholesterolaemia that is not appropriately controlled with statin therapy, six 12-week fixed-dose randomised controlled trials (n = 3610) were identified that compared ezetimibe plus statin therapy with statin therapy alone.

Seven randomised controlled trials (n = 2577) comparing ezetimibe monotherapy with placebo represented the population where statin therapy is

considered inappropriate or is not tolerated. All were 12-week studies and were included in a meta-analysis performed by the Assessment Group.

All trials involved people with primary hypercholesterolaemia with average baseline LDL cholesterol levels ranging from 3.4 mmol/litre to 6.5 mmol/litre and included mixed populations of people with and without a history of CVD.

7.7.3 Cost-effectiveness of ezetimibe

Please refer to results of the cost-effectiveness analysis carried out by the NICE Technology Appraisal 132 (National Institute for Health and Clinical Excellence, 2007).

7.7.4 Evidence into recommendations

Please refer to the NICE Technology Appraisal 132 entitled 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia'.

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