Post Myocardial Infarction

Secondary prevention in primary and secondary care for patients following a myocardial infarction

Full guideline – Final Version

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National Collaborating Centre for

Primary Care

Royal College of General Practitioners

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The guideline updates the previous NICE guideline entitled 'Prophylaxis for patients who have experienced a myocardial infarction' 2001. The guideline has updated the previous guideline's information on drug therapy. The guideline has enlarged the information on cardiac rehabilitation and lifestyle chages provided in the previous guideline, to reflect the the remit of the scope of the guideline.

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Preface

The immediate care of heart attack in England and Wales has improved substantially over the last few years. These improvements have resulted from a number of major drivers coming together including modernisation and redesign of services, clinical enthusiasm, a national audit with publication of data and the implementation of the National Service Framework for Coronary Heart Disease.

Every extra life saved because of better care is welcome while at the same time presenting an additional challenge to the National Health Service. This challenge is to ensure that every individual surviving a heart attack is offered the best chance of a long and healthy life free, as far as possible, of further events.

One of the mantras of the National Service Framework was to make sure that simple things were done right all the time. In many ways the clinical community has responded to this need so that record numbers of patients leaving hospital are now being prescribed the drugs that are effective in reducing risk after heart attack. Drugs such as aspirin, beta-blockers and statins are being provided for almost all eligible patients as they leave hospital.

Some of the actions that improve outcomes after heart attack are less simple to provide and are clearly outlined in this guideline. These measures include ensuring that the best guidance is given to every individual on the lifestyle that will improve life expectancy and help to ensure freedom from further events. Patients not only need to understand these benefits but also need to help to attain these goals. Here, exercise programmes in the form of cardiac rehabilitation schemes and other programmes have a vital role in helping the 1.2 million people who suffer a heart attack per year in the United Kingdom each of whom warrants the very best of care as they recover.

This guideline is very welcome as it clearly emphasises the importance of exercise, smoking habit, diet and cardiac rehabilitation as the pillars that support full recovery. It also clarifies the role of the various treatments available including the best drugs and defines which patients might benefit from interventions such as angioplasty and coronary bypass surgery.

Professor Roger Boyle CBE FRCP FRCPE

National Director for Heart Disease and Stroke

Department of Health, London

1 Key priorities for implementation

A number of key priority recommendations have been identified for implementation listed below. These recommendations are considered by the GDG to have the most significant impact on patients' care and patients' outcomes.

- After an acute myocardial infarction (MI), confirmation of the diagnosis of acute MI and results of investigations, future management plans and advice on secondary prevention should be part of every discharge summary (GPP).
- Patients should be advised to undertake regular physical activity sufficient to increase exercise capacity (Grade B).
- Patients should be advised to be physically active for 20-30 mins a day to the point of slight breathlessness. Those who are not achieving this should be advised to increase their activity in a gradual step by step fashion, aiming to increase exercise capacity. They should start at a level that is comfortable and increase the duration and intensity of activity as they gain fitness (GPP).
- All patients who smoke should be advised to quit and be offered assistance from a smoking cessation service in line with 'Brief interventions and referral for smoking cessation in primary care and other settings' (NICE public health intervention guidance 1) (Grade A).
- Patients should be advised to eat a Mediterranean-style diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils) (Grade A).
- Cardiac rehabilitation should be equally accessible and relevant to all patients after an MI; particularly people from groups that are less likely to access this service. These include people from black and minority ethnic groups, older people, people from lower socioeconomic groups, women, people from rural communities and people with mental and physical health comorbidities.
- All patients who have had an acute MI should be offered treatment with a combination of the following drugs (Grade A):
  - ACE (angiotensin-converting enzyme) inhibitor

  - aspirin
  - beta blocker
  - statin.

- For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment should be initiated within 3–14 days of the MI, preferably after ACE inhibitor therapy (Grade B).
- Treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of non-ST-segment-elevation acute coronary syndrome. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended unless there are other indications to continue dual antiplatelet therapy (Grade A).
- After an ST-segment-elevation MI, patients treated with a combination of aspirin and clopidogrel during the first 24 hours after the MI should continue this treatment for at least 4 weeks. Thereafter, standard treatment including low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy (Grade A).
- All patients should be offered a cardiological assessment to consider whether coronary revascularisation is appropriate. This should take into account comorbidity (Grade A).

The criteria the GDG used to select these key priorities for implementation included whether a recommendation is likely to:

- have a high **impact** on patients' outcomes in particular mortality and morbidity
- have a **high impact** on reducing variation in the treatment offered to patients
- lead to a **more efficient** use of NHS resources
- enable patients to **reach important points in the care pathway more rapidly**

2 Introduction

2.1 Background (Epidemiology)

The annual incidence of myocardial infarction (MI) for men aged between 30-69 is about 600 per 100 000 and for women about 200 per 100 000. The British Heart Foundation (2004) has estimated that there are about 147 000 MIs per year in men of all ages in the UK and 121,000 in women, giving a total of 268 000 cases. In the UK, about 838 000 men and 394 000 women have had an MI (British Heart Foundation, 2004).

MI is a complication of coronary heart disease (CHD) which is preventable. The death rate from CHD has been falling since the early 1970s; for people aged below 75, rates have fallen by almost 25% since 1996 (Department of Health, 2004). In spite of these improvements, when compared internationally, the UK death rate from CHD is relatively high with more than 103 000 deaths per year (Department of Health, 2003). Comparing Western European countries, only Ireland and Finland have a higher death rate from coronary artery disease than the UK (British Heart Foundation, 2004).

CHD death rates vary with age, gender, socio-economic status, ethnicity and UK geographic location. Death rates in men aged less than 75 years are three times as high as those in women, and death rates in affluent areas in the UK are half of those in deprived areas (Department of Health, 2003). People of South Asian origin have almost a 50% higher death rate compared with the general population (Wild and McKeigue, 1997).

2.2 Management

Cardiac rehabilitation programmes have been consistently shown to reduce mortality rates in CHD patients (Canadian Coordinating Office for Health Technology Assessment, 2003). Cardiac rehabilitation is the coordinated sum of interventions required to ensure the best possible physical, psychological and social conditions to enable the CHD patient to preserve or resume optimal functioning in society. It also aims to slow or reverse progression of the disease. Cardiac rehabilitation cannot be

regarded as an isolated form or stage of therapy, but must be integrated within secondary prevention services, of which it forms only one facet (WHO definition, 1993).

Lifestyle factors also have an impact on the prognosis of CHD patients. Healthy eating, regular exercise and smoking cessation are important elements in the prevention of further cardiovascular events.

A number of drugs have been shown to improve outcome after MI; beta blockers, ACE inhibitors, anti-platelet agents and statins.

2.3 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 others about lifestyle modification, cardiac rehabilitation, drug therapy and advice about which patients to refer for further assessment for possible coronary revascularisation.

2.4 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 preceede the narrative for each topic. The evidence tables with details of the research studies that describe the studies reviewed are found in the Appendices D and E.

2.5 Scope

The guideline was developed in accordance with a scope given by National Institute for Health and Clinical Excellence (NICE). The scope set the remit of the guideline

and specified those aspects of post MI management to be included and excluded. The scope was published in 2004 and is reproduced here in Appendix B

2.5.1 Whom 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:

- healthcare professionals who work within the acute and primary healthcare sectors and who have direct contact with patients following a heart attack
- those with responsibilities for commissioning and planning health services such as Primary Care Trust commissioners, Welsh Assembly Government officers
- public health and trust managers
- patients who have had a heart attack, their partners, families and other carers

2.5.2 Areas outside the remit of the guideline

The guideline does not cover patients who have had a non-spontaneous MI (for example, a peri-procedural, which may occur after percutaneous coronary intervention) nor patients who have had a non-atherosclerotic-induced MI (which is an MI in patients without underlying coronary artery disease (CAD)). The guideline does not cover the diagnosis of an MI either acutely or restrospectively. Interventions specific to the early phase of the acute MI are not considered, such as thrombolysis. The guideline does not address different methods of assessment of cardiac status before possible coronary revascularisation. The guideline does not cover the additional management of diabetes and glycaemic control in patients who have had an MI, as this is more appropriately placed in the revisions of the diabetes guidelines. Similarly, the additional management of chronic heart failure which would be more appropriately placed in revisions of the chronic heart failure guideline is not included. The guideline does not cover symptom control such as the management of angina.

2.6 Responsibility and support for guideline development

2.6.1 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 the NICE. It 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 which 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 a 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 the Institute for the NCC-PC. The work is 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.

2.6.2 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 who 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 the Institute and external bodies

- **Clinical Advisor**, with an academic understanding of the research in the area and its practical implications to the service, who advised the Development Team on searches and the interpretation of the literature.

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

The Development Team met regularly with the Chairman of the GDG during the development of the guideline to review progress and plan work.

2.6.3 The Guideline Development Group (GDG)

A Chairman was chosen for the group for his understanding of the field. His primary role was to facilitate the work at GDG meetings.

Guideline Development Groups (GDGs) are working groups with the aim to get 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 which 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 and were sent drafts of the guideline by the Institute 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 their own right and not as a representative of their nominating organisation, although they were encouraged to keep the nominating organisation informed of progress.

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

The names of GDG members appear list below.

Professor Gene Feder (Chairman)

Professor of Primary Care Research and Development, Barts and the London Queen Mary's School of Medicine and Dentistry, London

Dr Jane Skinner (Clinical Advisor)

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

Dr Keith MacDermott

General Practitioner, York

Dr Rubin Minhas

General Practitioner, Primary Care CHD Lead, Kent

Dr Chris Packham

Director of Public Health, Nottingham City Primary Care Trust, Nottingham

Mrs Helen Squires (until April 2006)

Superintendent Physiotherapist, Luton & Dunstable Hospital NHS Trust, Bedfordshire

Mr David Thomson

Patient, Buckinghamshire

Professor Adam Timmis

Professor of Clinical Cardiology, Barts, London and the London Queen Mary's School of Medicine and Dentistry

Mr John Walsh

Patient, Swindon

Ms Helen Williams

Pharmacy Team Leader for Cardiac Services & London Region CHD Advisor for Clinical Pharmacy. King's College Hospital, London

Ms Anne White

British Heart Foundation Cardiac Specialist Nurse, Cambridgeshire PCT and Addenbrooke's NHS Trust

Members of the GDG from the NCC-PC were:

Ms Nancy Turnbull

Guideline Lead and Chief Executive, National Collaborating Centre for Primary Care

Dr Angela Cooper

Senior Health Services Research Fellow, National Collaborating Centre for Primary Care

Ms Gabrielle Shaw (until Dec 2005) and Dr Meeta Kathoria (from May 2006)

Project Manager, National Collaborating Centre for Primary Care

Mr Leo Nherera

Health Economist, National Collaborating Centre for Primary Care

Observers

Ms Colette Marshall

Commissioning Manager, National Institute for Health and Clinical Excellence

2.6.4 Guideline Development Group Meetings

The GDG met at 4 to 5 weekly 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

2.7 Care pathway

Two clinical care pathways have been designed to indicate the essential components in the secondary prevention of patients after an MI, one for patients with a recent MI, and one for patients with a proven MI in past. Each pathway has three main sections. These are; secondary prevention drug treatment, specialist cardiological assessment, and lifestyle and cardiac rehabilitation. Recommendations for key secondary prevention measures in each section are indicated.

Patient with MI in the past year

RECENT MI IN THE PAST YEAR

Assess secondary prevention management and manage as described below

LIFE STYLE CHANGES AND CARDIAC REHABILITATION

Offer lifestyle advice

- Mediterranean style diet
- Sources of omega 3 fatty acids (for example from oily fish, or from treatment with omega-3-acid ethyl esters if necessary within 3 months of acute MI)
- Alcohol consumption
- Physical activity
- Weight management
- Smoking (offer help to stop at every opportunity, combine pharmacotherapy with an appropriate support programme)

Offer cardiac rehabilitation with the following components;

- Exercise (if a patient has cardiac or other clinical conditions that may worsen during exercise, these should be treated if possible before the patient is offered the exercise component of cardiac rehabilitation. In others the exercise component may be adapted by a suitably qualified health professional)
- Health education and information
- Stress management

Involve partners or carers in accordance with the patient's wishes
Give support and advice to help patients achieve and maintain lifestyle changes
Interventions should take into account patients' wider health and social needs

Refer to the NICE guidelines on anxiety and depression (NICE clinical guidelines 22 and 23), for the management of patients with clinical anxiety and depression.

SECONDARY PREVENTION DRUG TREATMENT

Optimise long term secondary prevention drug therapy in all patients, if no contra-indications:

- Aspirin
- Beta blockers
- ACE inhibitors
- Statin

Review planned duration of combined treatment with clopidogrel and aspirin. Providing there are no other indications to continue for longer (eg coronary stenting), continue clopidogrel for;

- At least 4 weeks after STEMI
- For 12 months after NSTEMI

Treat with an aldosterone antagonist (licensed for this indication) if within 14 days of MI with symptoms and or signs of heart failure, and LV systolic dysfunction (LVSD) if no contra-indications

Treat hypertension to the target given in the NICE guideline for Hypertension, currently 140/90 mmHg or lower. Treatment should in particular be to a lower target blood pressure in patients with relevant comorbidities, for example diabetes or renal disease.

Make arrangements for appropriate monitoring. Refer to the NICE guidelines for the diagnosis and management of chronic heart failure in primary and secondary care for the long term management of patients with LV systolic dysfunction who develop chronic heart failure.

For other management in patients with diabetes, refer to the appropriate NICE guidelines for the management of diabetes

CARDIOLOGICAL ASSESSMENT

Arrange cardiological assessment taking into account co-morbidity

- Assess LV function
- Consider the need for coronary revascularisation
- Consider the need for ICD implantation (refer to NICE TA95; Arrhythmia - implantable cardioverter defibrillators (ICD))

PROVEN MI IN THE PAST

Patient with proven MI in the past (> 1 year ago)

Assess secondary prevention management and manage as described below

LIFESTYLE CHANGES AND CARDIAC REHABILITATION

Offer lifestyle advice

- Mediterranean style diet
- Sources of omega 3 fatty acids (for example from oily fish, or from treatment with omega-3-acid ethyl esters if necessary within 3 months of acute MI)
- Alcohol consumption
- Physical activity
- Weight management
- Smoking (offer help to stop at every opportunity, combine pharmacotherapy with an appropriate support programme)

Offer cardiac rehabilitation with the following components if patients have specific needs to be addressed;

- Exercise (if a patient has cardiac or other clinical conditions that may worsen during exercise, these should be treated if possible before the patient is offered the exercise component of cardiac rehabilitation. In others the exercise component may be adapted by a suitably qualified health professional)
- Health education and information
- Stress management

Involve partners or carers in accordance with the patient's wishes
Give support and advice to help patients achieve and maintain lifestyle changes
Interventions should take into account patients' wider health and social needs

Refer to the NICE guidelines on anxiety and depression (NICE clinical guidelines 22 and 23), for the management of patients with clinical anxiety and depression.

SECONDARY PREVENTION DRUG TREATMENT

Optimise long term secondary prevention drug therapy in all patients, if no contra-indications:

- Aspirin
- ACE inhibitors
- Statin

Beta blockers in patients with LVSD and in patients with preserved LV function if they are identified to be at increased risk of further cardiovascular events or there are other compelling indications for beta blocker treatment
Make arrangements for appropriate monitoring

Treat hypertension to the target given in the NICE guideline for Hypertension, currently 140/90 mmHg or lower. Treatment should in particular be to a lower target blood pressure in patients with relevant comorbidities, for example diabetes or renal disease.

Refer to the NICE guidelines for the diagnosis and management of chronic heart failure in primary and secondary care for the long term management of patients with LV systolic dysfunction and chronic heart failure.

For other management in patients with diabetes, refer to the appropriate NICE guidelines for the management of diabetes.

CARDIOLOGICAL ASSESSMENT

Consider the need for cardiological assessment taking into account of co-morbidity;

- LV function
- Coronary revascularisation
- ICD implantation (refer to NICE TA95; Arrhythmia - implantable cardioverter defibrillators (ICD))

2.8 Research recommendations

2.8.1 What is the optimal duration of treatment with the combination of aspirin and clopidogrel, compared with aspirin alone, in patients with ST elevation MI treated with thrombolysis?

The addition of clopidogrel to other standard treatment, including aspirin and thrombolysis, in patients presenting with ST elevation MI has been shown to improve coronary patency and clinical outcome. This effect appears to be mediated by preventing re-occlusion of the open infarct related artery rather than by facilitating early reperfusion. The trials examining the effects of the addition of clopidogrel in patients with ST elevation MI were of short duration (about 4 weeks or less). The trial which reported a clinical benefit of treating patients with non ST elevation MI with the combination of aspirin and clopidogrel, compared to aspirin alone, was for duration up to 12 months, mean 9 months. The optimal duration of treatment with the combination of aspirin and clopidogrel in patients with ST elevation MI is unknown.

2.8.2 Could a discontinuation trial of ACE inhibitors in patients without LV dysfunction determine the clinical and cost effectiveness of long-term secondary prevention treatment in patients after an MI?

Most trials of secondary prevention drugs after a myocardial infarction follow up patients for a limited period of time, rarely more than 5 years after the event.

In current guidance there is an assumption that the benefit demonstrated in these trials persists indefinitely and therefore, provided they are tolerated, secondary prevention drugs such as beta blockers, statins, aspirin and ACE inhibitors should be continued long-term. Further research is needed to test this assumption. Specific patient groups may not benefit from extended treatment, for example groups based on baseline left ventricular function, the extent of coronary disease and the presence of coronary risk factors. It would be ethically and logistically difficult to study

withdrawal of drug therapy using the traditional randomized controlled trial design. Alternative designs, such as large cohort studies, based on routinely collected (or enhanced) data would allow comparison of people stopping one or more secondary prevention drugs with a cohort continuing their secondary prevention therapy. Close attention would need to be paid to confounders. This question is particularly pertinent for ACE inhibitors and beta blockers, as it is not clear to what extent patients without significant LV dysfunction benefit from long-term use of these agents after a myocardial infarction.

2.8.3 What is the clinical and cost effectiveness of treatment with spironolactone compared with eplerenone in patients with heart failure early after myocardial infarction?

Heart failure is the major cause of death after the acute phase of myocardial infarction. We know that eplerenone, in addition to conventional treatments, can reduce mortality from heart failure early after myocardial infarction (EPHESUS). Spironolactone, another aldosterone antagonist, is less expensive but is not always well tolerated, particularly in men. We need to know whether spironolactone is as effective as eplerenone in reducing mortality in all grades of heart failure after acute myocardial infarction.

2.8.4 Uptake and adherence to comprehensive cardiac rehabilitation

Participation of patients after an MI in cardiac rehabilitation has been shown to reduce all-cause mortality and cardiac mortality when compared to usual care. The National Service Framework for Coronary Heart Disease states that more than 85% of people discharged from hospital with a primary diagnosis of acute MI or after coronary revascularisation should be offered cardiac rehabilitation. However, less than a third of all patients with a prior MI and those who have undergone coronary revascularisation attend comprehensive cardiac rehabilitation, and uptake is particularly poor among certain groups including ethnic minorities, women, the elderly and those on low incomes or with physical or mental comorbidities. Studies investigating methods to improve uptake and adherence of comprehensive cardiac rehabilitation have been small and limited to individual programmes or geographical

locations and have not evaluated interventions specifically for underrepresented patient groups. Consequently, the ability of NICE to provide specific recommendations in this area is limited, as the most clinically and cost effective strategies are unknown. The following research questions arise from the limited information in evidence based medicine;

- What strategies are effective in improving the uptake and adherence to comprehensive cardiac rehabilitation in patients who have had an MI?
- What strategies are effective in improving the uptake and adherence to comprehensive cardiac rehabilitation in patients who have had an MI and are from under represented groups such as ethnic minorities, women, the elderly and those on low incomes or with physical or mental comorbidities who have had an MI?

2.8.5 Added value of the non-exercise components of the cardiac rehabilitation programmes

Both exercise-only cardiac rehabilitation and comprehensive cardiac rehabilitation have been shown to reduce cardiac mortality when compared to usual care. Exercise-only programmes have been shown to reduce all-cause mortality when compared to usual care. Studies investigating non-exercise elements of comprehensive cardiac rehabilitation have been small, of short duration and have employed outcome measures that have made meta analysis of these studies impractical. Considerable professional time is dedicated to providing a variety of non-exercise components of comprehensive cardiac rehabilitation and qualitative studies have demonstrated benefits of educational elements and psychological support provided as part of CR both for patients and their families. However, the benefits in terms of reduced mortality and morbidity of the non-exercise elements of comprehensive cardiac rehabilitation are unknown.

2.8.6 What is the clinical and cost effectiveness of omega-3-acid ethyl esters treatment in all patients after MI

One trial has shown a benefit of treatment with omega-3-acid ethyl esters in patients within 3 months of an MI. However, other secondary prevention treatment had not been optimised in this trial and the majority of patients had preserved left ventricular function. There is some uncertainty about how much additional benefit patients after acute MI optimally managed for secondary prevention, including those with left ventricular systolic dysfunction, will obtain from the addition of omega-3-acid ethyl esters treatment. There is also a paucity of evidence for the effectiveness of treating patients who have had an MI in the past, at least 3 months earlier. The efficacy of omega-3-acid ethyl esters treatment in patients both early and later after MI deserves further research.

2.8.7 Maintaining exercise and dietary changes after comprehensive cardiac rehabilitation

Long term regular exercise and following a Mediterranean style diet have been shown to reduce all-cause and cardiac mortality in patients after an MI. A Mediterranean diet has also been shown to reduce recurrent MI. Maintenance of these lifestyle changes in patients after an MI has been shown to decline following the end of the patient's participation in coordinated comprehensive cardiac rehabilitation. The strategies that are effective in maintaining these lifestyle activities are unknown. The research question is as follows;

- What encourages the maintenance of regular exercise and a Mediterranean style diet beyond the period of comprehensive cardiac rehabilitation?

2.9 Acknowledgements

We gratefully acknowledge the contributions of Dr John Robson (Chairman of the Lipids Modification guideline) for his contribution to the Statins section of the guideline and of Anne Spencer (Queen Mary's University of London), Emanuela

Castelnuovo (former member of the NCC-PC team) and Joanne Lord (NICE) for the advice on the health economics. Our thanks also goes to Rifna Mannan, Dr. Kathleen De Mott, both of the NCC-PC, for their contributions to reviewing the guideline and to Dr Tim Stokes (Clinical Director of the NCC-PC) for his advice. We are also very appreciative of the editorial support that both NCC-PC health research associates Gary Britton and Christopher Tack provided during the validation phase. Finally we are also very grateful to these people and others who advised the Technical Team and GDG and so contributed to the guideline process, in particular the Dietician Lynda Evans.

2.10 Glossary

ACE inhibitor	Angiotensin converting enzyme inhibitor, a drug which inhibits the angiotensin converting enzyme
Annual risk Reduction	The difference between the percentage annual incidence of an adverse outcome in a treatment group compared with that in a control group
Cardiac rehabilitation	A programme for patients with heart disease aimed at ensuring patients preserve or resume best possible health and functional capacity. Usually includes an exercise training component.
Cardiovascular event	An acute coronary, cerebrovascular or peripheral vascular event
Cardiovascular risk	The risk of a cardiovascular event occurring
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).
Cost effectiveness Ratio	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.
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 dominated 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.
Extended dominance	The principle of extended dominance is applied in incremental cost effectiveness analysis to eliminate from consideration strategies whose costs and benefits are improved by a mixed strategy of two other alternatives, thus compared with the next best alternative, an option will be less effective and has a higher ICER
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature
Evidence-based questions (EBQs)	Questions which are based on a conscientious, explicit and judicious use of current best evidence
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 health.
Health related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
High fibre diet	A diet which is high in dietary fibre
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.
Life year	A measure of health outcome which shows the number of years of remaining life expectancy.
Life-years gained	Average years of life gained per person as a result of the intervention.
Lifestyle changes	The behavioural changes that can be made to an individual pattern of living
Median	The value which comes half way when the data are ranked in order
Meta regression Analysis	An approach for aggregating data from different clinical trials which examine the same question and report the same outcomes, and relating sources of variation in treatment effects to specific study characteristics
Multiple logistic regression analysis	In a clinical study, an approach to examine which variables independently explain an outcome
Open Labelled Randomised Trial	A study in which patients are randomised to one treatment or another, and in which the clinician or investigator are 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.
Physical work	An activity which involves increased energy expenditure
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).
Psycho educational Programmes	Programmes which include one or more of health education, behavioural modification, counselling and stress management
Psychological Intervention	Non drug interventions which aim to address the emotional impact of an event or illness, and reduce distress

Quality adjusted life years (QALYS)	An index of survival that is adjusted to account for the patient'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.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.
Specialist	A healthcare professional who has expert knowledge of and skills in a particular clinical area
Structured exercise	A planned exercise programme which aims to meet the needs of an individual patient
Time horizon	The time span used in the NICE appraisal which 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.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Willingness to pay	Is a technique that is used to measure preference for health benefits of health services or interventions in monetary terms. In health economics this will refer to the amount individuals or policy makers are willing to pay to acquire additional health benefits.

3 Methods

3.1 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 National Institute for Health and Clinical Excellence (the Institute) in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (2005) (available at: http://www.nice.org.uk).

3.2 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 Guideline Development Group (GDG).

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

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

3.3 Literature search strategy

The purpose of searching the literature is to identify all the available published evidence to answer the clinical questions identified by the methodology team and the GDG. The Information Scientist developed search strategies for each question, with guidance from the GDG, using relevant MeSH (medical subject headings) or indexing terms, and free text terms. Searches were conducted between October 2004 and February 2006. Update searches for each question, to identify recent evidence, were carried out in June 2006. Full details of the sources and databases searched and the strategies are available 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 found that answered the clinical question posed, then in some instances no further searching was carried out.

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

Databases of the results of the searches for each question or topic area were created using the bibliographic management software Reference Manager.

Systematic reviews and randomised controlled trials were searched for using methodological search filters designed to limit searches to these study designs. Where studies with a long follow-up was required a cohort filter was used. In some instances depending on the nature of the question or the small size of the literature

any study design was looked for. The filters used were devised by the Centre of Reviews and Dissemination, The Cochrane Collaboration or the Scottish Intercollegiate Guidelines Network (SIGN).

3.4 Identifying the Evidence

After the search of titles and abstracts was undertaken, full papers were obtained if they appeared to address the GDG's question relevant to the topic. The highest level of evidence was sought. However observational studies, surveys and expert formal consensus results were used when randomised control trials were not available. Only English language papers 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 clinical question and when it was either better or equivalent in quality to the research identified in the literature searches.

The reasons for rejecting any paper ordered were recorded.

3.5 Critical appraisal of the evidence

From the papers retrieved the Senior Health Service Research Fellow (SHSRF) synthesised the evidence for each question or questions into a narrative summary. These form the basis of this guideline. Each study was critically appraised using the Institute's criteria for quality assessment and the information extracted about included studies is given in Appendix C. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

3.6 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 then also cost

effective. Although NICE does not have a threshold for cost effectiveness, interventions with a cost per quality adjusted life year of upto £20,000 are deemed cost effective, those between £20-30,000 may be cost effective and those above £30,000 are unlikely to be judged cost effective. If a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy resources to other activities that yield greater health gain.

To assess the cost effectiveness of the proposed secondary prevention strategies a comprehensive systematic review of the economic literature relating to post MI patients was conducted. For selected components of the guideline original cost effectiveness analyses were performed. The primary criteria applied for an intervention to be considered cost effective were either:

a) The intervention dominated other relevant strategies (that is it is both less costly in terms of resource use and more clinically effective compared with the other relevant alternative strategies); or

b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (or usual care)

Literature review for Health Economics

The following information sources were searched:

Medline (Ovid) (1966-June 2006), Embase (1980-June 2006), 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 post MI (secondary prevention), were written in English, and reported health economic information that could be generalised to UK.

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.

Each study was categorized as one of the following: cost effectiveness analysis or cost utility analysis (i.e. cost effectiveness analysis with effectiveness measured in terms of QALYs or life year gained). Some studies were categorized as 'cost consequences analyses' or 'cost minimisation analyses'. These studies did not provide an overall measure of health gain or attempt to sythesise costs and benefits together. Such studies were considered as partial economic evaluations.

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.

The following three areas were chosen for further analysis

- The cost effectiveness of cardiac rehabilitation and the methods used to increase uptake of cardiac rehabilitation.
- The cost effectiveness of ACE inhibitors in patients with preserved left ventricular function.
- The cost effectiveness of beta blockers in post MI patients with left ventricular dysfunction.

Full reports for each topic are in the Appendix 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 done in accordance to the NICE reference case outlined in the Guideline Technical Manual 2004.

3.7 Assigning levels to the evidence

The evidence levels and recommendation are based on the Institute's technical manual. (http://www.nice.org.uk/page.aspx?o=guidelinestechnicalmanual). Evidence levels for included studies were assigned based upon the table below.

Level of evidence	Type of evidence
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2^{+}	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^{-}	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

The grading of recommendations was carried out in accordance with the NICE Technical Manual in use at the outset of the guideline development process. However, grading of recommendations is no longer included in the NICE version. They have been retained, as a matter of record, in the full guideline per the table below.

Classification of recommendations on interventions

Recommendation grade	**Evidence**
A	At least one meta analysis, systematic review, or randomised controlled trial (RCT) that is rated as 1^{++}, and is directly applicable to the target population, or A systematic review of RCTs or a body of evidence that consists principally of studies rated as 1+, is directly applicable to the target population and demonstrates overall consistency of results, or Evidence drawn from a NICE technology appraisal
B	A body of evidence that includes studies rated as 2^{++}, is directly

	applicable to the target population and demonstrates overall consistency of results, or Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence that includes studies rated as 2^{+}, is directly applicable to the target population and demonstrates overall consistency of results, or Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2^{+}, or Formal consensus
D(GPP)	A good practice point D(GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

3.8 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 these.

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.

3.9 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, the GDG derived the recommendations via informal consensus methods for example in access to cardiac rehabilitation.

3.10 Consultation

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

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.

3.11 The Relationship between the guideline and other national guidance

3.11.1 NICE Guideline - Prophylaxis for patients who have experienced a myocardial infarction (2001)

Prophylaxis for patients who have experienced a myocardial infarction (2001) developed by North of England Evidence-based Guidelines Development Project, Centre for Health Services Research,University of Newcastle upon Tyne which was published as an inherited guideline by NICE in 2001. The current guideline updates and expands upon this work.

3.11.2 National Service Frameworks

In formulating recommendations consideration was given to the National Service Framework for Coronary Heart Disease (2000).

3.11.3 Related NICE Guidance

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

Guidelines

Hypertension – management of hypertension in adult patients in primary care, August 2004 – Partial update June 2006

Chronic heart failure – management of chronic heart failure in adults in primary and secondary care - October 2003.

Type 1 diabetes - diagnosis and management of diabetes in children, young people and adults - July 2004

Type 2 diabetes - management of blood pressure and blood lipids (guideline H) - October 2002

Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease - January 2008

Obesity – the prevention, identification, evaluation, treatment and weight maintenance of overweight and obesity in adults - November 2006

Familial hypercholesterolaemia - identification and management - (ongoing)

Technology Appraisals:

The clinical effectiveness and cost effectiveness of bupropion (Zyban) and Nicotine Replacement Therapy for smoking cessation **TA039** (March 2002).

Clopidogrel and dipyridamole for the prevention of artherosclerotic events **TA090** (May 2005).

Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome **TA080 (**July 2004).

Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease **TA094** (January 2006).

Angina and myocardial infarction - myocardial perfusion scintigraphy, **TA073 (**November 2003).

Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias - review of guidance **TA095** (January 2006).

Public health intervention guidance

Brief interventions and referral for smoking cessation in primary care and other settings (March 2006).

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.

4 Lifestyle

4.1 Recommendations for lifestyle

4.1.1 Changing dietary regimen recommendations

Hyperlink to the related evidence statements

4.1.1.1	Patients should be advised not to take supplements containing beta-carotene (Garde B), and should not be advised to take antioxidant supplements (vitamin E and/or C) or folic acid to reduce cardiovascular risk (Grade A).
4.1.1.2	Patients should be advised to consume at least 7 g of omega 3 fatty acids per week from two to four portions of oily fish per week (see appendix H for the equivalent quantity of oily fish consumption required to provide 7 g of omega 3 fatty acids per week) (Grade B).
4.1.1.3	For patients who have had an MI within 3 months and who are not achieving this, consider providing at least 1g daily of omega-3-acid ethyl esters treatment licensed for secondary prevention post MI for up to 4 years (Grade B).
4.1.1.4	Initiation of omega-3-acid ethyl esters supplement treatment is not routinely recommended in patients that have had an MI more than 3 months earlier (GPP).
4.1.1.5	Patients should be advised to eat a Mediterranean-style diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils) (Grade A).

4.1.2 Delivery of dietary advice recommendations

Hyperlink to the related evidence statements

4.1.2.1	Patients should be given consistent dietary advice, tailored to their needs (GPP).
4.1.2.2	Patients should be offered an individual consultation to discuss diet, including their current eating habits, and advice on improving their diet (Grade B).
4.1.2.3	Patients should be given healthy eating advice that can be extended to the whole family (GPP).

4.1.3 Alcohol consumption recommendations

Hyperlink to the related evidence statements

4.1.3.1	Patients who drink alcohol should be advised to keep weekly consumption within safe limits (no more than 21 units of alcohol per week for men, or 14 units per week for women) and to avoid binge drinking (more than 3 alcoholic drinks in 1–2 hours) (GPP).

4.1.4 Regular physical activity recommendations

Hyperlink to the related evidence statements

4.1.4.1	Patients should be advised to undertake regular physical activity sufficient to increase exercise capacity (Grade B).
4.1.4.2	Patients should be advised to be physically active for 20–30 minutes a day to the point of slight breathlessness. Patients who are not achieving this should be advised to increase their activity in a gradual, step by step way, aiming to increase their exercise capacity. They should start at a level that is comfortable, and increase the duration and intensity of activity as they gain fitness (GPP).
4.1.4.3	Advice on physical activity should involve a discussion about current and

	past activity levels and preferences. The benefit of exercise may be enhanced by tailored advice from a suitably qualified professional (GPP).

4.1.5 Smoking cessation recommendations

Hyperlink to the related narrative

4.1.5.1	All patients who smoke should be advised to quit and be offered assistance from a smoking cessation service in line with 'Brief interventions and referral for smoking cessation in primary care and other settings' (NICE public health intervention guidance 1) (Grade A).
4.1.5.2	All patients who smoke and who have expressed a desire to quit should be offered support and advice, and referral to an intensive support service (for example the NHS Stop Smoking Services) in line with 'Brief interventions and referral for smoking cessation in primary care and other settings' (NICE public health intervention guidance 1) (Grade A). If a patient is unable or unwilling to accept a referral they should be offered pharmacotherapy in line with the recommendations in 'Nicotine replacement therapy (NRT) and bupropion for smoking cessation' (NICE technology appraisal guidance 39) (Grade A).

4.1.6 Weight management recommendations

Hyperlink to the related narrative

4.1.6.1	After an MI, all patients who are overweight or obese should be offered advice and support to achieve and maintain a healthy weight in line with 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43' (Grade A).

4.2 Effectiveness of changing dietary regimen

4.2.1 Evidence statements for changing dietary regimen

Antioxidants	
4.2.1.1	In patients after an MI there is conflicting evidence for an effect of vitamin E supplementation (alone or in combination with other anti-oxidants) on the risk of fatal and non-fatal MI with no consistent evidence of a benefit or harm (1++).
4.2.1.2	In patients after an MI, vitamin C supplementation does not appear to have any benefit (1++).
4.2.1.3	In patients after an MI, beta-carotene may increase cardiovascular deaths (1+).
Fish oils	
4.2.1.4	In patients after an MI, advice to increase consumption of oily fish reduced all-cause mortality (1+).
4.2.1.5	The only large trial of supplementation with 1g of omega 3 polyunsaturated fatty acids has shown a reduction in mortality and cardiovascular morbidity, although there was a low uptake to statins and other secondary prevention drugs at baseline in this trial (1++).
Folic acid supplementation	
4.2.1.6	In unselected patients after an MI, folic acid plus vitamin B12 and B6 supplementation does not reduce all-cause mortality or cardiovascular events (1++).
4.2.1.7	In patients with hypercholesterolemia after an MI, the addition of folic acid to statin therapy did not confer any additional benefit in reducing cardiovascular events or mortality compared with statin therapy alone (1+).

Mediterranean diet	
4.2.1.8	In patients after an MI, a 'Mediterranean' diet (more bread, fruit, vegetables, fish, and less meat, and replacing butter with margarine) comparable to the fat content of rapeseed oil and olive oil reduces all-cause mortality, cardiovascular mortality, and recurrent MI (1+).
Plant sterol esters	
4.2.1.9	No studies were found of interventions with plant sterol esters for secondary prevention in patients after an MI.
Low glycaemic diets	
4.2.1.10	No studies were found of interventions with low glycaemic diets for secondary prevention in patients after an MI.
Fruit and vegetables	
4.2.1.11	No studies were found of interventions that only examined an increase in fruit and vegetable intake for secondary prevention in patients after an MI.
Low saturated fat	
4.2.1.12	In a single trial of patients after an MI, advice to reduce dietary saturated fat did not reduce mortality (1-).
Dietary fibre	
4.2.1.13	In a single trial of patients after an MI, an increase in dietary fibre did not reduce all-cause mortality (1-).

Back to recommendations

4.2.2 Supplementation with antioxidants vitamin C, vitamin E, beta-carotene and coenzyme Q10

Two systematic reviews were identified on antioxidant vitamin supplementation for the prevention and treatment of cardiovascular disease.

The first included 10 secondary prevention trials on patients with multiple risks of cardiovascular disease in various pooled analysis (Shekelle, P., Morton, S., and Hardy, M. 2003). The four outcomes of clinical importance for analysis were all-cause mortality, cardiovascular mortality, fatal MI, and non-fatal MI. Only vitamin E supplementation alone had a sufficient number of clinically similar studies to undertake meta analysis; vitamin C and coenzyme Q10 trials were reported descriptively.

Meta analysis using a random effects model found that vitamin E supplementation alone did not reduce all-cause mortality (RR 0.96, 95% CI 0.84 to 1.10) or cardiovascular death (RR 0.97, 95% CI 0.80 to 1.19) compared with placebo. For vitamin E supplementation in combination with other agents (such as beta-carotene, vitamin C, omega-3 fatty acids) there was insufficient data for meta analysis. Meta analysis was performed for cardiovascular death and there was no treatment effect compared with placebo (RR 1.03, 95% CI 0.81 to 1.32) (Shekelle, P., Morton, S., and Hardy, M. 2003). The evidence on vitamin E supplementation and the risk of fatal and non-fatal MI is mixed. No pooled analysis showed a beneficial or adverse effect, either alone or in combination. Two individual studies did report significant findings. One study found a benefit on fatal MI and a non significant adverse effect on non-fatal MI (GISSI Prevenzione Investigators. 1999). In contrast, another trial reported a significant adverse effect of vitamin E on fatal MI, but a nearly significant beneficial effect of vitamin E on non-fatal MI (Rapola, J. M. et al 1997). While there were dosage differences between the trials (Rapola, J. M., Virtamo, J., Ripatti, S. et al 1997)), the baseline risk of both fatal and non-fatal MIs was approximately equivalent in the two studies (Shekelle, P., Morton, S., and Hardy, M. 2003).

The systematic review identified five randomised controlled studies of coenzyme Q supplementation compared to placebo (Shekelle, P., Morton, S., and Hardy, M. 2003). Four studies recruited heart failure patients and the fifth study recruited post MI patients. The heart failure patient studies did not report on relevant outcomes.

The study on the post MI patients reported that at one year follow up, six patients had died in the placebo group, while one patient in the antioxidant group had died following a pulmonary embolism (Kuklinski, B., Weissenbacher, E., and Fahnrich, A. 1994).

The systematic review identified four randomised controlled studies of vitamin C supplementation compared to placebo (Shekelle, P., Morton, S., and Hardy, M. 2003). Vitamin C supplementation (mostly in combination with vitamin E) was found to have no benefit in cardiovascular health.

In conclusion, the authors of this systematic review stated that the available scientific studies offer little evidence that supplementation with vitamin C, vitamin E, or coenzyme Q10 has any benefit on secondary prevention in cardiovascular disease (Shekelle, P., Morton, S., and Hardy, M. 2003).

A second systematic review examined the effectiveness of vitamin supplementation in preventing cardiovascular disease, specifically vitamin A, C, and E, beta-carotene, folic acid, antioxidant combinations and multivitamin supplementation (Morris, C. D. and Carson, S. 2001). No meta analysis was undertaken. For vitamin C and E, the studies identified were included in the previous systematic review (Shekelle, P., Morton, S., and Hardy, M. 2003). For beta-carotene, one study was identified which found that beta-carotene significantly increased the incidence of fatal coronary heart disease compared with placebo (Rapola, J. M., Virtamo, J., Ripatti, S. et al 1997). Although the overall risk for all myocardial infarction was not affected, the incidence of fatal myocardial infarction increased significantly with beta-carotene supplementation. No studies were identified in the systematic review on vitamin A or folic acid alone for secondary prevention and no studies were found on multivitamin supplementation for post MI patients. The authors concluded that randomised controlled trials of specific supplements had failed to demonstrate a consistent or significant effect on incidence of, or death from, cardiovascular disease.

4.2.3 Folic acid supplementation

A randomised controlled trial investigated folic acid supplementation in patients with stable coronary artery disease (Liem, A. et al 2003). Approximately half the patients

had a history of MI and approximately half had received coronary artery bypass surgery. The participants were randomised to receive folic acid (0.5 mg/day) or no supplementation and the mean follow up time was 24 months. Folic acid supplementation did not reduce the primary outcome which was the combination of all-cause mortality and a composite of vascular events compared with the control group (RR 1.05, 95% CI 0.63 to 1.75).

A second 12 month randomised control trial in patients with a prior MI and a total cholesterol > 6.65 mmol/dl found that folic acid supplementation (0.5 mg/day) did not reduce any of the outcomes (fatal MI, fatal stroke, sudden death, other cardiovascular death, recurrent death, stroke, recurrent ischaemia compared with no supplementation) (Liem, A. H. et al 2004).

A third more recent randomised controlled trial recruited patients within 7 days of an acute MI and randomised them in a two-by-two factorial design to receive one of the following four treatments; 0.8 mg of folic acid, 0.4 mg of vitamin B12, and 40 mg of vitamin B6 per day (referred to as combination therapy); 0.8 mg of folic acid plus 0.4 mg of vitamin B12 per day; 40 mg of vitamin B6 per day; or placebo (Bonaa, K. H. et al 2006). The median follow up was 40 months, and the primary endpoint was the combination of new non-fatal myocardial infarction and fatal myocardial infarction, fatal and non-fatal stroke or sudden death attributed to coronary heart disease. There was no significant reduction in the primary endpoint from treatment with folic acid and vitamin B12, with or without vitamin B6 compared to placebo. However, treatment with combination therapy compared to placebo was associated with a non-significant increase in risk in the primary endpoint (RR 1.22, 95% CI 1.00 to 1.50). There was no effect of treatment with folic acid plus vitamin B12 on the secondary endpoints of myocardial infarction, stroke, death from any cause, unstable angina pectoris requiring hospitalisation and revascularisation. The combination of folic acid plus vitamin B12 plus vitamin B6 was associated with a non-significant increase in risk of non-fatal MI compared to placebo (RR 1.30, 95% CI 1.00 to 1.68). However, it was noted that these analyses were not adjusted for multiple comparisons, and the apparent associations could be explained by chance (Bonaa, K. H., Njolstad, I., Ueland, P. M et al 2006).

4.2.4 Fish diet

Advice to eat oily fish has been examined in a randomised trial in men under the age of 70 years following a recent MI (DART1) (Burr, M. L. et al 1989). There were 1015 patients recruited to the oily fish advice group and 1018 patients recruited to the no diet advice group. The mean age at recruitment was 57 years, and the recruitment mean interval after the incident MI was 41 days. Patients were advised to eat at least two weekly portions (220 to 400 g) of oily fish (mackerel, herring, kipper, pilchard, sardine, salmon or trout). Advice to eat oily fish was compared with no dietary advice and two further dietary advice regimes; fat advice (to reduce fat intake to 30% of total energy and to increase the polyunsaturated fat / saturated fat ratio to 1.0) and fibre advice (to eat more cereal fibre). Patients in the oily fish advice group who could not tolerate oily fish were given omega-3- acid ethyl esters capsules; 3 x 0.5 g per day supplying 2.5 g of eicosapentaenoic acid per week as well as docosahexaenoic acid. Study duration was 2 years and at 6 months 14% of patients were taking omega-3-acid ethyl esters capsules, while at 2 years 22% of patients were taking omega-3-acid ethyl esters capsules as a partial or total substitute for oily fish. Percentages of plasma eicosapentaenoic acid in total plasma fatty acid were measured in a subset of the dietary advice group and the no diet advice group. The differences were consistent with the reported dietary changes, in that oily fish intake was approximately 35 g per day in the oily fish advice group and 9 g per day in those receiving no diet advice.

Advice to eat oily fish was associated with a reduction in all-cause mortality compared with no dietary advice after adjustment for confounders (RR 0.71, 95%CI 0.54 to 0.92). There was no reduction in ischaemic heart disease events (ischaemic heart disease death and non-fatal MI) in the oily fish advice group compared with the group given no advice (RR 0.84, 95% CI 0.67 to 1.07). Patients given oily fish advice had a lower mortality than patients within other dietary groups (percentage difference in all-cause mortality for oily fish advice minus no fish advice in the following groups; fat advice, fibre advice, fat and fibre advice, and no dietary advice was -4.3%, -2.1%, -5.5% and -2.1%, respectively) (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989).

A follow up study of DART was conducted ten years after the end of the original trial (Ness, A. R. et al 2002). In the oily fish group, 447 of 1015 patients had survived

and in the diet advice group 432 of 1018 survived. Oily fish intake (g/day) in the fish advice group was 21 g compared with 13 g in the no fish advice group ($P < 0.01$). Prescription fish oil supplementation was higher in the fish advice group (10%) compared with the no fish advice group (2%) ($P = 0.02$). Fish oil supplementation of unknown source (not reported) was also higher in the fish advice group (26.9%) compared with the no fish advice group (19.3%) ($P < 0.01$). At 10 year follow up, oily fish advice was not associated with a reduction in all-cause mortality (HR 0.95, 95% CI 0.85 to 1.07), coronary heart disease mortality (HR 0.92, 95% CI 0.80 to 1.07) or stroke (HR 1.23, 95% CI 0.71 to 2.14). This study may suggest that advice to eat oily fish does not have a sustained effect on mortality, or that the original findings were a chance effect. There are a number of limitations to the follow up study. Data was only available for oily fish intake at the end of the study, and it is possible that the diets of those who survived were different from those who did not. The results may also be confounded by the fact that compliance in the oily fish advice group was 56% at the end of the 10 year trial follow up period (patients reported a much lower intake of oily fish compared with intake during the trial, 21 g/day versus 35 g/day), while in the no diet advice group compliance was 37% (patients reported an increase oily fish consumption from 9 g/day during the trial to 13 g/day, and increased their supplement intake) (Ness, A. R., Hughes, J., Elwood, P. C. et al 2002).

4.2.5 Omega-3- acid ethyl esters treatment

A randomised trial of 11 324 patients with a prior MI within 3 months of recruitment compared the effectiveness of omega-3- acid ethyl esters with no supplementation (GISSI Prevenzione Investigators. 1999). There was no upper age limit and the mean age ± standard deviation was 59±10 years. Fourteen percent had impaired LV function (ejection fraction < 40%) and more than 70% of patients reported eating fish at least once a week at the start of the randomised controlled trial in both the treatment and control groups, with no difference between the groups. At 42 months, this had risen to 82% in both groups. The type of fish was not stipulated. At the start of the trial, the percentage of patients prescribed cholesterol lowering drug therapy in the treatment and control groups was 4.4% and 5.1%, respectively. At 42 months the percentage rose in the treatment and the control groups to 46.0% and 44.4%, respectively. Patients in the treatment group were given a 1 g capsule to be taken

daily containing 850 to 882 mg of eicosapenteanoic acid and docosahexaenic acid in a ratio of 1.2:1. This supplied approximately 3.3 g of eicosapentaenoic acid per week.

Compared with control, omega-3- acid ethyl esters treatment was associated with a lower risk of the two primary endpoints; the combination of death, non-fatal MI, or non-fatal stroke (RR 0.85, 95% CI 0.74 to 0.98) and the combination of cardiovascular death, non-fatal MI, or non-fatal stroke (RR 0.80, 95% CI 0.68 to 0.95). There was also a lower risk of the following secondary endpoints: all fatal events (RR 0.80, 95% CI 0.67 to 0.95), cardiovascular deaths (RR 0.70, 95% CI 0.56 to 0.87), cardiac deaths (RR 0.65, 95% CI 0.51 to 0.82), coronary death (RR 0.65, 95% CI 0.51 to 0.84) and sudden death (RR 0.55, 95% CI 0.40 to 0.76) (GISSI Prevenzione Investigators. 1999).

In contrast, a much smaller randomised controlled trial (Nilsen, D. W. et al 2001) of 300 patients found that compared to corn oil, treatment with omega-3- acid ethyl esters was not associated with a reduced risk of; cardiac death, resuscitation, recurrent MI, unstable angina pectoris, revascularisation, total mortality. The median follow up was 1.5 years. The study was powered to measure the effects of omega-3-acids ethyl esters only on serum lipids. Total cholesterol concentrations decreased in both the omega-3- acid ethyl esters and corn oil groups. HDL-cholesterol levels increased in the omega-3- acids ethyl esters group compared with corn oil group. Triacylglycerol concentrations decreased in the omega-3- acid ethyl esters group, whereas they increased in the corn oil group.

The guideline development group recognised that there was only one major trial of omega-3- acid ethyl esters supplementation in patients within 3 months of an MI which reported a favourable impact on clinical outcome. It was noted that a high proportion of participants in this trial reported eating fish at least once per week throughout the trial in both the treatment and control groups. The low cholesterol lowering drug therapy at the start of the trial and its subsequent increase in both groups was also recognised. The consensus of the guideline development group was that the results of the trial should not be dismissed and that treatment with omega-3-acid ethyl esters should be considered in patients within 3 months of an MI, although the results could not be extrapolated to recommending initiation of

supplementation beyond 3 months after the acute event. A study in angina patients of which 50% had a prior MI found that advice to each oily fish or take omega-3- acid ethyl esters supplements was not associated with clinical benefits compared with no advice or no supplementation (Burr, M. L. et al 2003). This may suggest that the clinical benefit of omega-3- acid ethyl esters treatment is resistricted to commencing therapy within 3 months of an MI.

4.2.6 Health economics of omega-3- acid ethyl esters treatment

Three studies were identified which examined the economic consequences of omega-3- acid ethyl esters supplements compared to no supplements in improving outcomes in patients after MI from the National Health Service (NHS) perspective. All three analyses used effectiveness data from a single trial (GISSI Prevenzione Investigators. 1999) of post MI patients with no age restriction.

An Italian study (Franzosi, M. G. et al 2004), (Lamotte, M. et al 2006) reported omega-3- acid ethyl esters supplements compared to no supplements resulted in 0.0332 life years gained. The incremental cost effectiveness was 24 603 Euros/LYG in the base case model. It is unclear whether this estimate would lie below the NICE threshold of £20-30 000 per QALY. Results were sensitive to the cost of omega-3-acid ethyl esters supplements and a worst case scenario.

A report by Innovus Research on behalf of Solvay Pharmaceutical submitted to NICE was a cost utility analysis (Innovus Research (UK) Ltd. 2004), extrapolating data for lifetime treatment from the NHS perspective. The authors considered a short term model (until the end of the trial) and a longer term model (lifetime). Omega-3-acid ethyl esters supplements were found to be cost effective as long as the NHS was willing to pay £15 189/QALY over 4 years or £3717/QALY over a lifetime. Although the authors did some sensitivity analysis on some parameters which was robust. The authors stated that the parametric form assumed for fitting the survival curves to the trial data, and their method for extrapolating survival benefits beyond the trial period. However they didnot provide any evidence for the fit of this curve, or do any sensitivity analysis over the assumptions. They also did not do any sensitivity analysis around their estimates of effectiveness which weakened their study.

A third study (Lamotte, M., Annemans, L., Kawalec, P. et al 2006) assessed the cost effectiveness of adding omega-3- acid ethyl esters supplements to the current secondary prevention treatment versus standard prevention alone after acute MI in five countries: Australia, Belgium, Canada, Germany and Poland from the healthcare payers perspective using a decision model. Treatment with highly concentrated omega-3- acid ethyl esters supplements yielded between 0.261 (Poland) and 0.284 (Australia) LYG, at an additional cost of 787 Euros (Canada) to 1439 Euros (Belgium). The ICER varied between 2788 Euros (Canada) and 5097 Euros (Belgium) per LYG. Sensitivity analyses on effectiveness, cost of complications and discounting suggested the robustness of the results. A second-order Monte Carlo simulation based on the 95% confidence intervals obtained from GISSI-P trial (GISSI Prevenzione Investigators. 1999) suggests that highly concentrated omega-3- acid ethyl esters supplements are cost effective in 93% of simulations in Poland and in > 98% of simulations in the other countries, using the country-specific societal willingness-to-pay threshold. The authors rightly acknowledge that a markov model could have been more appropriate than the decision model as it can take account of more than one event over time.

We developed a model to estimate the cost effectiveness of omega-3- acid ethyl esters supplements for patients after a recent MI who cannot comply with recommendations for the dietary intake of fatty fish (see appendix B). The model was subjected to extensive sensitivity analysis to test the robustness of the results to changes in the input data and assumptions. The findings were broadly consistent with those of the submitted company model and two published cost effectiveness analyses (Lamotte M et al, 2006 5301). (Franzosi, M. G., Brunetti, M., Marchioli, R. et al 2004) (Company submission to NICE from Innovus Research on behalf of Solvay Pharmaceutical).

The guideline model found omega-3- acid ethyl esters supplements to be cost effective when compared with no supplements in patients after a recent MI, with estimated ICERs of about £12 500. This result is sensitive to uncertainty over the size of treatment effects and supplements do not appear to be cost effective at the upper confidence limit for the relative risk of mortality. These results depend on the assumption that treatment effects do not persist beyond the longest trial period, 3.5

years for the GISSI-P trial (GISSI Prevenzione Investigators. 1999), and that supplements are not continued after this time. DART1 was of shorter duration (2 years), and clinical benefits may not be sustained beyond this period (Ness et al 2002). If treatment effects do not persist beyond two years, supplements are of borderline cost effectiveness (£23 400 per QALY). From an NHS perspective, it will clearly be more cost effective for patients to obtain omega 3 fatty acids from dietary sources. But if a patient is unable to do this, provision of supplements does appear to be a cost effective use of NHS resources. The model assumed use of the cheapest available supplement with the correct quantities of eicosapentaenoic acid and docosahexaenoic acid (Maxepa). The use of a second supplement (Omacor) also appears to be cost effective compared with no supplementation; however, it will not be cost effective when compared with the cheaper alternative (assuming clinical equivalence between these products). Other supplements are available for patients to purchase over-the-counter. However, the clinical efficacy and safety of these alternatives has not been considered in randomised controlled trials in a post MI population. It is important to note that the validity of the cost effectiveness analysis depends on the premise that the benefits of omega 3 fatty acids are confined to people with a recent MI, as clinical effectiveness data was used from two randomised controlled trials recruiting patients within 3 months of an MI. Omega-3-acid ethyl esters supplements would not be clinically or cost effective if the evidence base was broadened to include a randomised controlled trial in patients with angina (DART2).

In conclusion omega-3- acid ethyl esters treatment compared to no treatment in patients after MI appears to be cost effective not withstanding the caveats mentioned above.

4.2.7 Mediterranean diet

A randomised controlled trial (de Lorgeril, M. et al 1999) recruited patients with a prior MI into either an experimental group (who were advised to eat more bread, fruit and vegetables, fish, and less meat, and to replace butter and cheese with rapeseed margarine or a control group (who received no dietary advice). After 27 months, the trial was stopped prematurely due to better outcomes in the intervention group (mortality: intervention 2.6% compared with controls 6.6%). The results of an

extended follow up were published three years later (de Lorgeril, M., Salen, P., Martin, J. L. et al 1999). Mean follow up for survival in the control group was 44.9 month and 46.7 months in the experimental group. All-cause mortality (RR 0.44, 95% CI 0.21 to 0.94, *P* = 0.03), cardiovascular mortality (RR 0.35, 95% CI 0.15 to 0.83, *P* = 0.01) and the combination of recurrent MI and cardiac death (RR 0.28, 95% CI 0.15 to 0.53, *P* = 0.03, *P* = 0.0001) all were reduced in the treatment group compared to the control group.

4.2.8 Low saturated fat

One large randomised controlled trial in patients with a prior MI compared three dietary regimens: fat advice (to reduce fat intake to 30% of total energy and to increase the polyunsaturated fat to saturated fat ratio to 1.0), fibre advice (to eat more cereal fibre) and fish advice (to eat at least two portions of oily fish a week) (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989). A description of this study has been described in section 4.2.2. Each intervention was compared to a no advice control group and trial follow up was for 2 years. Fat intake only reduced slightly in the fat advice group, although fruit and vegetable intake increased. After adjustment for confounders, the fat advice group had the same risk of death as those given no advice (RR 1.00, 95% CI 0.77 to 1.30) (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989).

4.2.9 Plant sterols esters

No studies were found of interventions with plant sterol esters for secondary prevention in patients after an MI.

4.2.10 Low glycaemic diets

No studies were found of interventions with low glycaemic diets for secondary prevention in patients after an MI.

4.2.11 Fruit and vegetables

No studies were found of interventions that only increase fruit and vegetable intake for secondary prevention in patients after an MI. A trial of the Mediterranean diet

described in Section 4.2.5 had an increase in fruit and vegetable component in the diet (GISSI Prevenzione Investigators. 1999).

4.2.12 High fibre diets

Advice to eat more fibre was examined in a large randomised controlled trial in patients with a prior MI (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989). Three dietary regimens were compared with no change in diet: fat advice, fibre advice (to eat more cereal fibre to 18g daily) and fish advice (to eat at least two portions of oily fish a week). A description of this study has been described in section 4.2.2. Cereal fibre intake in the fibre advice group was double that in the group that was not given fibre advice. After adjustment for confounders, the fibre advice group did not have a reduced risk of death compared with the group given no advice (RR 1.27, 95% CI 0.99 to 1.67).

4.3 Delivery of dietary advice

4.3.1 Evidence statements for delivery of dietary advice

4.3.1.1	Individualised dietary advice (including education about eating habits) for patients after an MI improves eating habits, as assessed by questionnaire (2+).

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4.3.2 Delivery of dietary advice

A survey of dietetic departments in the UK published in 2001, found that dietetic advice for people following an MI was out of line with current best evidence (Hooper, L. 2001). Dietary fat advice was prioritised by 84% of departments, fruit and vegetables by 45%, oily fish by 45% and fibre by 28%. Most dieticians (81%) felt that this advice would protect from further cardiovascular disease (Hooper, L. 2001).

Three cohort studies on post MI patients were identified for methods of delivering dietary advice.

The first study examined behaviour change outcomes in patients undergoing a 6 week cardiac rehabilitation programme (Timlin, M. T., Shores, K. V., and Reicks, M. 2002). Patients were referred following an MI, revascularisation, or those suffering from angina. Fifty six percent of patients in the intervention group and 60% of patients in the control group had had a prior MI. Participants in the treatment group attended two group nutrition education classes and one individual diet counselling session, all led by the same dietician. Participants in the control group received usual non-individualised care. The outcome measures were changes in fat, saturated fat, cholesterol, and carbohydrate intake, and restaurant eating habits as assessed by the Diet Habit Survey, changes in diet self efficacy, and changes in health-related quality of life. At the end of the 6 week programme, there was a significant reduction in cholesterol-saturated fat index in both groups. However, there was no difference between the two groups. The percentage of energy obtained from carbohydrate increased significantly in both groups, although there was no difference between the treatment and control groups. Using the Cardiac Diet Self-Efficacy Instrument, there

was a positive correlation for the mean change in the Restaurant and Recipe Scores from programme entry to discharge for the treatment group alone ($P < 0.05$). The authors concluded that nutrition education within an outpatient cardiac rehabilitation programme can improve dietary choices at restaurants and boost self confidence in the ability to adhere to a lipid-lowering (Timlin, M. T., Shores, K. V., and Reicks, M. 2002).

The second study recruited patients four weeks after discharge from hospital following an MI either to an education intervention program or to usual care (Carlsson, R. 1997). The education program included visits to a secondary prevention unit. Total dietary education time was approximately 5.5 hours. This included time with the individual patient and the spouse, and time in group sessions with other patients. A nurse rehabilitator extended the education during the follow-up year. Written and oral advice was given. Food habits were assessed at admission to hospital and at the one year follow-up. Patients referred to the intervention group significantly improved their eating habits (89%) compared with patients who received usual care (62%, $P = 0.008$) (Carlsson, R. 1997).

The third study randomly assigned patients with a prior MI into an intervention or control group at discharge from hospital (Karvetti, R. L. 1981). A dietary history of the participant's previous year was obtained for each patient in the treatment group. The intervention was a nutrition education program directed to correcting the main fault in each patient's diet. This included information on lowering excess caloric intakes, reducing fat, sugar, salt and cholesterol in the diet and introducing polyunsaturated fats and low fat foods and vegetables. The nutrition education programme consisted of 3 individual counselling sessions (1 at the beginning of and 2 in the latter part of the intervention year), in addition to six nutrition classes in groups. Compared to the control group, patients in the intervention group at both 1 and 2 year follow up, significantly reduced their intake of cakes ($P < 0.001$, $P < 0.01$ respectively), high fat cheese ($P < 0.01$, $P < 0.05$ respectively), medium fat milk ($P < 0.001$, $P < 0.05$ respectively), low fat milk ($P < 0.01$, $P < 0.05$ respectively) and increased their vegetable oil intake ($P < 0.05$, $P < 0.01$ respectively), fruit intake and vegetable intake ($P < 0.001$, $P < 0.01$ respectively) (Karvetti, R. L. 1981).

4.4 Alcohol consumption

4.4.1 Evidence statements on alcohol consumption

4.4.1.1	There is no evidence of an adverse effect from low to moderate alcohol consumption by men after an MI and there may be some benefit in cardiovascular outcomes (2+).
4.4.1.2	There is insufficient evidence about the effect of alcohol consumption by women after an MI.

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4.4.2 Alcohol consumption

A number of case-control and cohort studies have shown evidence supporting a potential protective effect of moderate alcohol consumption on coronary heart disease risk among healthy drinkers as compared with abstainers. In contrast, data on the impact of alcohol drinking in patients with established coronary artery disease is limited. A recent prospective inception cohort study interviewed 1935 patients hospitalised between 1989 and 1994 to determine the frequency of binge drinking in the year prior to their incident MI (Mukamal, K. J. et al 2005). Binge drinking was defined as an intake of more than 3 drinks in 1 to 2 hours. Binge drinkers were found to have a 2 fold increase risk of death compared with those who were not binge drinkers (HR 2.0, 95% CI 1.3 to 3.0) (Mukamal, K. J., Jensen, M. K., Gronbaek, M. et al 2005).

Five studies were identified on alcohol consumption in patients with coronary artery disease.

The first study examined the association between ethanol (alcohol) intake and the risk of recurrence of coronary heart disease events in patients with a prior MI from the Lyon Diet Heart Study (GISSI Prevenzione Investigators. 1999). The Lyon Diet heart study was a randomised secondary prevention trial examining whether a Mediterranean type diet reduced the rate of recurrence following a first MI (GISSI

Prevenzione Investigators. 1999). Using the calculated mean consumption of ethanol intake, patients were categorized into quartiles of ethanol consumption, with quartiles 1, 2, 3 and 4 as follows; zero percent of energy intake per day derived from ethanol (non-drinkers) (44 patients), <5.4% of total energy intake per day (37 patients), >5.41% but <9.84% of total energy intake per day (44 patients), and >9.84% of energy (38 patients) respectively. In terms of dietary habits, smoking, weight, age, and systolic blood pressure, there was no significant difference across the quartile categories. Women were excluded from the analysis because they were not evenly distributed between the 4 quartiles. Binge drinkers and irregular drinkers were also excluded. Most of the alcohol consumed by patients in the analysis came from wine (92%).

During a mean follow up of 4 years, there were 104 complications. All but 9 were coronary heart disease recurrences. There were 4 deaths, 14 recurrent acute MIs, 15 episodes of unstable angina, 24 episodes of recurrent angina requiring hospitalisation, 17 cases of post-angioplasty restenosis and 24 patients needed myocardial revascularisation. There were 36, 34, 18 and 16 complications in the quartiles 1, 2, 3, and 4, respectively. In comparison with the abstainer group, and controlling for potential confounders using multivariate analysis, the risk of recurrence of cardiovascular complications was lower among quartile 3 (about 2 drinks per day) (RR 0.41, 95% CI 0.23 to 0.88) and quartile 4 (an average of 4 to 5 drinks per day) (RR 0.48, 95% CI 0.24 to 0.86) (P= 0.07) (GISSI Prevenzione Investigators. 1999).

A second study (Muntwyler, J. et al 1998) examined subjects recruited into the Physicians' Health Study (Steering Committee of the Physicians; Health Research Group, 1989, (Steering Committee of the Physicians' Health Study Research Group. 1989). This was a randomised, double-blind placebo-controlled trial testing two primary prevention hypotheses. Namely, whether 325 mg of aspirin taken on alternate days decreases cardiovascular disease, and whether 50 mg of beta-carotene taken on alternate days decreases risk of cancer. From this study, 5358 men were identified who had reported a history of MI and had provided information on alcohol intake. Patients drinking habits were classified as follows: rarely / never, 1

to 4 drinks per month, 2 to 6 drinks per week, 1 drink per day and > 2 drinks per day (Muntwyler, J., Hennekens, C. H., Buring, J. E. et al 1998).

During a mean follow up period of 5 years, 920 (17.2%) of the 5358 men died. After multivariate adjustment, the total mortality risk in men who drank 2 to 6 drinks per week was lower compared to men who never or rarely drank (RR 0.72, 95% CI 0.58 to 0.89). Patients who reported drinking one alcoholic drink per day also had a decreased mortality risk compared with men who never or rarely drank (RR 0.79, 95% CI 0.64 to 0.96) (Muntwyler, J., Hennekens, C. H., Buring, J. E. et al 1998).

For death due to cardiovascular diseases, the risk was reduced in patients who drank between 2 to 6 drinks per week compared with those who never or rarely drank alcohol. Alcohol association and total mortality did not significantly differ between people above and below 65 years of age (Muntwyler, J., Hennekens, C. H., Buring, J. E. et al 1998).

The third study (Aguilar, D. et al 2002) used the database from the SAVE trial (Moye, L. A., Pfeffer, M. A., and Braunwald, E. 1991) (Pfeffer, M. A. et al 1992) to assess the influence of alcohol intake on the development of symptomatic heart failure in patients with left ventricular dysfunction after MI (Aguilar, D., Skali, H., Moye, L. A. et al 2002). The SAVE trial was a randomised double-blind placebo-controlled study designed to test the hypothesis that long-term administration of an angiotensin-converting enzyme inhibitor to MI survivors would lessen mortality and improve clinical outcomes (Moye, L. A., Pfeffer, M. A., and Braunwald, E. 1991) (Pfeffer, M. A., Braunwald, E., Moye, L. A. et al 1992). Alcohol intake was classified as follows: non drinkers (0 drinks/week) (1276 patients), light-to-moderate drinkers (1 to 10 drinks/week) (717 patients), and heavy drinkers (>10 drinks/week) (235 patients). Alcohol consumption was assessed at 3 months post MI. The primary endpoints were: need for hospitalisation for heart failure, or need for an open label angiotensin-converting inhibitor (Aguilar, D., Skali, H., Moye, L. A. et al 2002).

Three months after MI, 71% were non-drinkers, 26% were light-to-moderate drinkers and 3% were heavy drinkers. Alcohol consumption was similar at 6, 12 and 24 months. Using endpoints that only occurred 90 days after enrolment, 316 patients developed heart failure. Compared with non drinkers, the unadjusted hazard ratio for

the development of heart failure was lower in the light-to-moderate drinkers (HR 0.70, 95% CI 0.53 to 0.91). After adjustment for baseline characteristics, the difference was no longer statistically different (HR 0.93, 95% CI 0.71 to 1.23). In the heavy drinkers, no significant hazard was found, although the number of participants in this category was small. For the secondary endpoints of total mortality, recurrent MI, and cardiovascular death, there was no significant difference in the unadjusted and adjusted hazard ratios between the three drinking categories (Aguilar, D., Skali, H., Moye, L. A. et al 2002).

The fourth study examined the effects of alcohol on risk of death from coronary heart disease, cardiovascular disease, and all-causes in men with established coronary heart disease (Shaper, A. G. and Wannamethee, S. G. 2000). The study was based on the British Regional Heart Study (Shaper, A. G. et al 1981). This was a population based prospective study of patients with cardiovascular disease aged 40-59 years, selected from the age-sex registers of a single group general practice in each of 24 towns in England, Wales and Scotland. From the original 7735 men, 455 post MI patients and 200 angina patients were analyzed. Alcohol consumption was classified as follows: lifelong teetotallers (n= 43), ex-drinkers (n= 59), occasional drinkers (< 1 drink per month, n= 199) light drinkers (1-15 units per week, n= 230) moderate drinkers (16-42 units per week, n= 104), heavy drinkers (> 42 units per week, n= 20). The occasional drinkers group was defined as the reference group. Men in the heavy drinking group were combined with the moderate drinking group because of the small numbers. During the mean follow-up period of 12.8 years, there were 294 deaths from all-causes, of which 208 were attributable to cardiovascular causes, mainly caused by coronary heart disease (175 deaths). There was little difference in risk of coronary heart disease events, cardiovascular, non-cardiovascular, and all-cause mortality between lifelong teetotalers and light drinkers compared with occasional drinkers. Moderate/heavy drinkers showed an increased risk of coronary heart disease events, cardiovascular disease mortality (RR 1.50, 95% CI 0.96 to 2.53), and all-cause mortality (RR 1.50, 95% CI 1.01 to 2.23) compared to occasional drinkers, but these differences were only of marginal significance (Shaper, A. G. and Wannamethee, S. G. 2000).

The fifth study was a retrospective case-control study in unselected patients who had suffered sudden cardiac arrest and had a clinical history of coronary artery disease (de Vreede Swagemakers, J. J. et al 1999). These patients were compared with a group of unselected age- and gender-matched coronary artery disease control patients (de Vreede Swagemakers, J. J., Gorgels, A. P., Weijenberg, M. P. et al 1999).

Multiple logistic regression, with sudden cardiac arrest as the dependent variable, and the following independent variables: hypertension, hypercholesterolemia, diabetes mellitus, smoking, previous MI, coffee and alcohol consumption (and matching factors age and gender) found that alcohol consumption of 1-21 glasses per week was negatively associated with sudden cardiac arrest (OR 0.50, 95% CI 0.20 to 0.90). When left ventricular ejection fraction was also included as an independent variable alcohol, consumption of 1-21 glasses per week was also negatively associated with sudden cardiac arrest (OR 0.50, 95% CI 0.20 to 0.98). The authors suggested that alcohol consumption of 1-21 glasses per week appears to protect patients with coronary heart disease from sudden cardiac arrest (de Vreede Swagemakers, J. J., Gorgels, A. P., Weijenberg, M. P. et al 1999).

Based upon the available evidence, the guideline development group decided to recommend a weekly alcohol consumption limit, and to recommend the avoidance of binge drinking. The quantity of alcohol per week that is recommended is below the Department of Health recommendation that advises ‘men should not regularly drink more than 3 - 4 units of alcohol per day, and women should not regularly drink more than 2 - 3 units of alcohol per day’. The GDG considered that a lower quantity of alcohol was appropriate in the post MI population.

4.5 Regular physical activity

4.5.1 Evidence statements for regular physical activity

4.5.1.1	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 (1+).
4.5.1.2	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 (1+).
4.5.1.3	Patients after MI who choose to exercise regularly have improved survival rates and a reduced incidence of non-fatal reinfarction (2+).

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4.5.2 Regular physical activity

Four 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 35-64 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. 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.

At the 3 year follow up, the cumulative mortality in the exercise group was 15/323 (4.6%) compared with 24/328 (7.3%) in the control group, observed effectiveness = 37% (95% CI -15% to 68%, *P* = 0.22). There were 14 (4.3%) cardiovascular deaths in the exercise group compared with 20 (6.1%) in control group, observed effectiveness = 29% (95% CI -33% to 66%, *P* < 0.40). There was 1 (0.3%) MI death in the exercise group, compared with 8 (2.4%) in control group, observed effectiveness = 87% (95% CI 22% to 98%, *P* < 0.047). 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).

The second study (Dorn, J. et al 1999) was a secondary analysis of the first study (Naughton, J., Dorn, J., and Imamura, D. 2000) and examined the relationship between changes in physical work capacity and both all-cause mortality and cardiovascular disease mortality. The authors found that each single stage (1 metabolic equivalent (MET)) increase in PWC of the MSET was associated with reduction in all-cause mortality in the range of 8% to 14% depending on the time period examined. The relative risk of all-cause mortality and cardiovascular mortality were determined according to the change in physical work capacity, which was defined at the maximal attained stage final MSET minus the maximal attained stage baseline MSET. For long term follow up at 3, 5, 10, 15 and 19 years the age adjusted relative risk reductions for all-cause mortality were 0.86 (95% CI 0.76 to 0.98), 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 long term follow up at 3, 5, 10, 15 and 19 years, the age adjusted relative risk reductions for cardiovascular disease mortality were 0.87 (95% CI 0.74 to 1.02), 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.

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 (Dorn, J., Naughton, J., Imamura, D. et al 1999).

The third study (Blumenthal, J. A. et al 2004) prospectively examined the association between self reported exercise and all-cause mortality and cardiovascular morbidity among patients participating in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study (Barefoot, J. C. et al 2003). The participants were selected on the basis of their perceived lack of social support and/or symptoms of depression. There were 2078 men and 903 women in the study. Six months after experiencing an acute MI, patients were surveyed about their exercise habits and were then followed up for 4 years. Of these, 982 (47.2%) reported that they had exercised regularly since their acute MI. During up to 4 years follow-up, 187 patients had died, 5.7% of those taking regular exercise compared with 12.0% of those not exercising. After statistical adjustment for clinical and demographic characteristics, regular exercise was found to be significantly associated with increased probability of survival (HR 0.62, 95% CI 0.44 to 0.86, $P < 0.004$). After adjustment for modification of diet, counselling sessions, smoking and participation in cardiac rehabilitation, regular exercise remained statistically associated with survival (HR 0.69, 95% CI 0.49 to 0.98, $P = 0.037$). The rate of non-fatal MI amongst those taking regular exercise was 6.5% compared with 10.5% of those not exercising. Exercise was significantly associated with a reduced likelihood of non-fatal MI (HR 0.72, 95% CI 0.52 to 0.99, $P = 0.044$) (Blumenthal, J. A., Babyak, M. A., Carney, R. M. et al 2004).

The fourth study was a cohort study comparing 62 patients with a prior MI taking part in an aerobic training programme for 12 months with 62 control patients with a prior MI who did not receive any formal exercise training (Dugmore, L. D. et al 1999). Patients were followed up for up to 5 years by questionnaire and interview. Although this was a small study, the compliance rate was 95.6% (119 patients).There were 5 attributed deaths in the follow up period: 2 in the treatment group and 3 in the controls. There were fewer non-fatal reinfarctions (8%) in the exercise group compared with control group (22%) ($P < 0.05$). Compared with controls, those patients exercising visited their general practitioners less frequently ($P < 0.01$), returned to work earlier, and reported less angina ($P < 0.001$) (Dugmore, L. D.,

Tipson, R. J., Phillips, M. H. et al 1999). The non-randomised design means these results may be confounded by selection bias.

4.5.3 Physical work capacity requirements (recommended levels of physical activity)

Two studies were found which examined the effect of increasing work capacity on clinical outcome in patients with a history of a previous MI.

The first study was a three year randomised controlled trial in patients with a prior MI (≥ 8 weeks but < 3 years) and is described in Section 4.5.2 (Naughton, J., Dorn, J., and Imamura, D. 2000). After 3 years of the trial, the patients were followed up for 5, 10, 15 and 19 years. Failure to reach 85% of age predicted heart rate was associated with an increased risk of all-cause mortality after adjusting for smoking habit, resting systolic blood pressure, and study medications at all follow up stages (5 years RR 2.00, 95% CI 1.07 to 3.74, 10 years RR 1.76, 95% CI 1.27 to 2.44, 15 years RR 1.55, 95% CI 1.18 to 2.04, 19 years RR 1.65, 95% CI 1.31 to 2.09).

A second study (Dorn, J., Naughton, J., Imamura, D. et al 1999), also described in Section 4.5.2, conducted a secondary analysis of the first study (Naughton, J., Dorn, J., and Imamura, D. 2000) and reported that a 1 MET increase in the physical work capacity was associated with a reduction in all-cause mortality risk in the range of 8% to 14% in the follow up period of 5 to 19 years (Dorn, J., Naughton, J., Imamura, D. et al 1999). Analysis after adjustment for age and baseline physical work capacity showed that the intervention reduced the risk of all-cause mortality at 10 and 15 years after the incident infarction (10 years RR 0.92, 95% CI 0.86 to 0.98, 15 years RR 0.92, 95% CI 0.86 to 0.99). The authors also noted that patients with a baseline low initial physical work capacity (< 7 METs) derived more benefit than those with a higher baseline work capacity (≥ 7 METs) (Dorn, J., Naughton, J., Imamura, D. et al 1999).

Five further studies were found which examined the effectiveness of exercise training in improving exercise capacity in patients with a prior MI.

Two small studies also examined the effectiveness of exercise training in improving exercise capacity in patients with a prior MI. One study (Holmback, A. M., Sawe, U.,

and Fagher, B. 1994) recruited 79 patients and randomised them to 12 weeks of supervised exercise of at least 45 minutes duration for two sessions per week or no supervised exercise. Heart rate target during the initial sessions was 70-85% of target and workload was adjusted thereafter to achieve desired heart rate. However, after one year, the maximal exercise capacity (10% compared with 2%, $P = 0.10$) and mean exercise capacity (172 Watts compared with 144 Watts) did not differ between the two groups. The second study (Adachi, H. et al 1996) randomised 29 patients (25 male, mean ± SD age 52 ± 11 years) to one of three arms, a control group with no exercise training (n= 8), a low intensity training group (n= 11) which was defined when the heart rate reached 80% of the gas exchange threshold heart rate in each patient, and a high intensity training group (n= 10) for which the difference in heart rate between that at the gas exchange threshold and that at peak exercise was measured for each patient. Patients in the low and high intensity group performed 15 minutes of rapid walking at home, twice a day, 5 days a week for 2 months to maintain their heart rate. In both the low intensity and high intensity groups, the maximal work rate (Watts) increased, 93.1 ± 16.0 compared with 105.3 ± 22.9 ($P < 0.05$), and 109.5 ± 21.6 compared with 125.0 ± 29.8 ($P < 0.05$) respectively. This parameter did not significantly change in the control group, 98.4 ± 19.9; compared with 106.4 ± 22.5 (Adachi, H., Koike, A., Obayashi, T. et al 1996).

A third study which examined the effectiveness of exercise training in improving exercise capacity in patients of different ages is also referred to in the cardiac rehabilitation section 5.2.3.5 (Marchionni, N. et al 2003). This was a randomised controlled trial in patients with a prior MI (4 to 6 weeks earlier) over the age of 45 years that were referred to a cardiac rehabilitation unit over a 48 month period (Marchionni, N., Fattirolli, F., Fumagalli, S. et al 2003).

The trial included 3 groups: hospital based cardiac rehabilitation, home based cardiac rehabilitation and a control group. The hospital based cardiac rehabilitation programme consisted of 40 exercise sessions; 24 sessions (3 times per week) of endurance training on a cycle ergometer (5 minutes warm up, 20 minutes training at constant workload, 5 minutes cool down and 5 minutes post exercise monitoring) plus 16 (twice a week) 1 hour sessions of stretching and flexibility exercises. Home based cardiac rehabilitation patients participated in 4 to 8 supervised instruction

sessions in the cardiac rehabilitation unit, where they were taught necessary precautions and how to perform their training at home. The control group attended a single structured education session on cardiovascular risk factor management without any exercise prescription. For the outcome of total work capacity, the home based cardiac rehabilitation intervention group had significant improvements at 14 months post enrolment for all age groups examined compared with baseline (45-65 years, $P < 0.001$, 66 to 75 yrs, $P < 0.05$, >75yrs, $P < 0.05$). For hospital based cardiac rehabilitation at 14 months follow up, total work capacity was improved in the 45 to 45 year age group ($P < 0.001$) alone. No improvements were found in the control group (Marchionni, N., Fattirolli, F., Fumagalli, S. et al 2003).

The fifth cohort study randomised patients with a prior MI into a training group (n= 158) and a control group (n= 157), 3 months after discharge from hospital (Wilhelmsen, L. et al 1975). Patients in the treatment group were advised about the benefit of regular exercise and were encouraged to attend an exercise programme. This consisted of 3 half hour supervised training sessions a week. The training group had a higher physical work capacity at one year follow up, compared to the control group ($P < 0.001$). However, at four year follow up, there were no significant differences found in all-cause mortality or cardiovascular deaths between the two groups.

4.6 Smoking cessation

For guidance on smoking cessation refer to the NICE Technology appraisal:

Smoking cessation - Bupropion and nicotine replacement therapy (Number 39) The clinical effectiveness and cost effectiveness of bupropion (Zyban) and Nicotine Replacement Therapy for smoking cessation, March 2002.

And also the NICE Public health intervention guidance:

Smoking cessation- Brief interventions and referral for smoking cessation in primary care and other settings: March 2006

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4.7 Weight management

For guidance in weight management in patients with a prior MI refer to the NICE guideline:

Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children: December 2006

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5 Cardiac rehabilitation

5.1 Recommendations for cardiac rehabilitation

5.1.1 Comprehensive cardiac rehabilitation recommendations

Hyperlink to the related evidence statements

5.1.1.1	All patients (regardless of their age) should be given advice about and offered a cardiac rehabilitation programme with an exercise component (Grade A).
5.1.1.2	Cardiac rehabilitation programmes should provide a range of options, and patients should be encouraged to attend all those appropriate to their clinical needs. Patients should not be excluded from the entire programme if they choose not to attend certain components (GPP).
5.1.1.3	If a patient has cardiac or other clinical conditions that may worsen during exercise, these should be treated if possible before the patient is offered the exercise component of cardiac rehabilitation. For some patients, the exercise component may be adapted by an appropriately qualified healthcare professional (GPP).
5.1.1.4	Patients with left ventricular dysfunction who are stable can safely be offered the exercise component of cardiac rehabilitation (Grade B).

5.1.2 Patient engagement recommendations

Hyperlink to the related evidence statements

5.1.2.1	Cardiac rehabilitation should be equally accessible and relevant to all patients after an MI, particularly people from groups that are less likely to access this service. These include people from black and minority ethnic groups, older people, people from lower socioeconomic groups, women, people from rural communities and people with mental and

	physical health comorbidities (GPP).
5.1.2.2	Healthcare professionals should take into account patients' wider health and social needs, which may involve identifying and addressing economic, welfare rights, housing or social support issues. This may be a particular issue for patients in more deprived circumstances, and rehabilitation services should assess the likely scale of these needs when planning how their services meet the needs of the local population (GPP).
5.1.2.3	Cardiac rehabilitation programmes should be culturally sensitive. Employing bilingual peer educators or cardiac rehabilitation assistants who reflect the diversity of the local population should be considered (GPP).
5.1.2.4	Cardiac rehabilitation programmes should include an exercise component designed to meet the needs of older patients or patients with significant comorbidity. Any transport problems should be addressed (GPP).
5.1.2.5	Healthcare professionals should ask patients whether they would prefer single-sex classes or mixed classes (GPP).
5.1.2.6	Healthcare professionals should establish patients' health beliefs and level of health literacy before offering appropriate lifestyle advice (GPP).
5.1.2.7	Healthcare professionals, including senior medical staff involved in providing care for patients after an MI, should actively promote cardiac rehabilitation (GPP).
5.1.2.8	Reminders such as: • telephone calls • telephone calls in combination with direct contact from a healthcare professional

- motivational letters

should be used to improve uptake of cardiac rehabilitation (Grade A).

5.1.3 Health education and information needs recommendations

Hyperlink to the related evidence statements

5.1.3.1	Comprehensive cardiac rehabilitation programmes should include health education and stress management components (Grade A).
5.1.3.2	A home based programme validated for patients who have had an MI (such as 'The Edinburgh heart manual'; see http://www.cardiacrehabilitation.org.uk/heart_manual/heartmanual.htm) that incorporates education, exercise and stress management components with follow-ups by a trained facilitator may be used to provide comprehensive cardiac rehabilitation (Grade A).
5.1.3.3	Most patients who have had an MI can return to work. Any advice should take into account the physical and psychological status of the patient, the nature of the work and the work environment (GPP).
5.1.3.4	Healthcare professionals should be up to date with the latest Driver and Vehicle Licensing Agency guidelines. Regular updates are published on the website (www.dvla.gov.uk) (GPP).
5.1.3.5	After an MI without complications, patients can usually travel by air within 2 –3 weeks. Patients who have had a complicated MI need expert individual advice (GPP).
5.1.3.6	Patients who hold a pilot's licence should seek advice from the Civil Aviation Authority (GPP).
5.1.3.7	Most patients can return to normal activities of daily living. Any advice about the timing of this should take into account the patient's physical

	and psychological status, as well as the type of activity planned (GPP).
5.1.3.8	An estimate of the physical demand of a particular activity, and a comparison between activities, can be made using tables of metabolic equivalents (METS) of different activities (for further information please refer to http://www.cdc.gov/nccdphp/dnpa/physical/measuring/met.htm). Patients should also be advised how to use a perceived exertion scale to help monitor physiological demand. Patients who have had a complicated MI may need expert advice (GPP).
5.1.3.9	Advice on competitive sport may need expert assessment of function and risk, and is dependent on what sport is being discussed and the level of competitiveness (GPP).

5.1.4 Psychological and social support recommendations

Hyperlink to the related evidence statements

5.1.4.1	Stress management should be offered in the context of comprehensive cardiac rehabilitation (Grade A).
5.1.4.2	Complex psychological interventions such as cognitive behavioural therapy should not be offered routinely (GPP).
5.1.4.3	There should be provision to involve partners or carers in the cardiac rehabilitation programme if the patient wishes (GPP).
5.1.4.4	For recommendations on the management of patients with clinical anxiety and/or depression, refer to ‘Anxiety. NICE clinical guideline 22’ and ‘Depression. NICE clinical guideline 23’ (Grade A).

5.1.5 Sexual activity recommendations

Hyperlink to the related evidence statements

5.1.5.1	Patients should be reassured that after recovery from an MI, sexual activity presents no greater risk of triggering a subsequent MI than if they had never had an MI (Grade C).
5.1.5.2	Patients who have made an uncomplicated recovery after their MI can resume sexual activity when they feel comfortable to do so, usually after about 4 weeks (GPP).
5.1.5.3	The subject of sexual activity should be raised with patients within the context of cardiac rehabilitation and aftercare (GPP).
5.1.5.4	When treating erectile dysfunction, treatment with a PDE5 (phosphodiesterase type 5) inhibitor may be considered in patients who had an MI more than 6 months earlier and who are now stable (Grade A).
5.1.5.5	PDE5 inhibitors must be avoided in patients treated with nitrates and/or nicorandil because this can lead to dangerously low blood pressure (GPP).

5.2 Comprehensive cardiac rehabilitation

5.2.1 Evidence statements for comprehensive cardiac rehabilitation

5.2.1.1	Cardiac rehabilitation in patients after MI reduces all-cause and cardiovascular mortality rates provided it includes an exercise component (1++).
5.2.1.2	The majority of studies showed there was no significant effect of comprehensive cardiac rehabilitation on quality of life outcomes in patients after MI (1++).
5.2.1.3	Cardiac rehabilitation in patients after MI compared no cardiac rehabilitation is cost effective.
5.2.1.4	There were no studies found which compared individualised (menu-based) and non-individualised programmes in patients after MI.
Safety in the exercise component of comprehensive cardiac rehabilitation	
5.2.1.5	There is no evidence that stable patients are harmed by the exercise component of cardiac rehabilitation.
5.2.1.6	Exercise training does not appear to endanger stable patients with left ventricular dysfunction (1+).
5.2.1.7	There is limited evidence on the safety of the exercise component of cardiac rehabilitation in older people (1+).

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5.2.2 Introduction

Cardiac rehabilitation focused originally on exercise training, but more recently programmes have evolved to emphasise overall risk factor and behavioural modification. The World Health Organisation has defined cardiac rehabilitation as 'the sum of activity and interventions required to ensure the best physical, mental,

and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume their proper place in society and lead an active life' (http://www.who.int/en/).

The National Service Framework for Coronary Heart Disease (Department of Health 2000) details four phases of cardiac rehabilitation detailed in Appendix G.

5.2.3 Clinical effectiveness of comprehensive cardiac rehabilitation

5.2.3.1 Comprehensive cardiac rehabilitation and exercise only cardiac rehabilitation effectiveness versus standard care

Three recent systematic reviews were identified that assessed exercise-only cardiac rehabilitation versus usual care, and comprehensive cardiac rehabilitation versus usual care (Brown, A. et al 2003) (Joliffe, J. A. et al 2003) (Clark, A. M. et al 2005).

The first systematic review was published by the Canadian Coordinating Office for Health Technology Assessment (Brown, A., Taylor, R., Noorani, H. et al 2003). Its aim was to assess the evidence base for the clinical effectiveness of exercise-based cardiac rehabilitation for secondary prevention of coronary artery disease (CAD) through meta analysis of randomised controlled trials. The review was divided into two comparisons: firstly exercise training interventions versus usual care, and secondly exercise training combined with psychosocial and/or educational interventions (comprehensive cardiac rehabilitation) versus usual care. The main outcome measures were: all-cause mortality, cardiac mortality non-fatal MI, revascularisation and health related quality of life (HRQoL). A total of 19 randomised controlled trials of exercise-only cardiac rehabilitation were identified, of which 16 exclusively recruited patients with a prior MI. The mean follow up was 24 months with a range of 6 months to 5 years. A total of 27 randomised controlled trials of comprehensive cardiac rehabilitation were identified, of which 16 trials exclusively recruited patients with a prior MI. The mean follow up was 26 months with a range of 6 months to 72 months (Brown, A., Taylor, R., Noorani, H. et al 2003).

In the meta analysis, the exercise-only intervention compared with usual care reduced both all-cause mortality and total cardiac mortality (RR 0.76, 95% CI 0.59 to 0.98 and 0.73, 95% CI 0.56 to 0.96, respectively). Comprehensive cardiac rehabilitation, compared with usual care, reduced cardiac mortality (RR 0.80, 95% CI 0.65 to 0.99) but the trend in the reduction in all-cause mortality did not reach statistical significance (RR 0.87, 95% CI 0.71 to 1.05). Neither intervention had a significant effect on the subsequent occurrence of non-fatal MI or the need for coronary revascularisation (coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) (Brown, A., Taylor, R., Noorani, H. et al 2003).

A total of 9 trials assessed HRQoL; there were variations in both methodology and the HRQoL outcome measures. As the outcome measures were so varied, it was considered inappropriate to pool data for analysis. Most studies reporting either exercise-only or comprehensive cardiac rehabilitation interventions reported improvements in HRQoL domain scores. However, there was only one study where the improvement exceeded that of usual care (Brown, A., Taylor, R., Noorani, H. et al 2003).

A second Cochrane systematic review compared exercise-only cardiac rehabilitation versus usual care, and comprehensive cardiac rehabilitation versus usual care in patients who have had a prior MI, CABG or PCI, or who have angina pectoris or CAD defined by angiography (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003). Comprehensive cardiac rehabilitation was defined as exercise training in addition to psychosocial and/or educational interventions. The principal outcome measures were; all-cause mortality, cardiac mortality subdivided into deaths from MI, sudden cardiac deaths, death from cerebrovascular disease, non-fatal MI, revascularisation (CABG, PCI), non-fatal cerebrovascular disease and HRQoL. A total of 51 trials were identified (32 trials of exercise-based cardiac rehabilitation). For exercise-only studies, 2845 patients were included in the meta analysis while 5595 patients were included in the comprehensive cardiac rehabilitation group (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003).

For the exercise-only intervention, the pooled effect estimate for total mortality showed a 27% reduction in all-cause mortality compared with usual care (random effects model OR 0.73, 95% CI 0.54 to 0.98). Similarly, comprehensive cardiac

rehabilitation reduced all-cause mortality compared with usual care, but to a lesser, and non-significant extent (13% reduction, OR 0.87, 95% CI 0.71 to 1.05) (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003).

Total cardiac mortality was reduced by 31% in the exercise-only intervention (OR 0.69, 95% CI 0.51 to 0.94) and by 26% in the comprehensive cardiac rehabilitation intervention (OR 0.74, 95% CI 0.57 to 0.96) compared with usual care. Cerebrovascular disease mortality was reported in only 1 exercise-only trial, and compared with usual care there was a trend in reduction of cardiovascular mortality (OR 0.45, 95% CI 0.18 to 1.08). In a meta analysis of 12 trials comparing comprehensive cardiac rehabilitation with usual care there was a non-significant reduction in cerebrovascular disease mortality with comprehensive cardiac rehabilitation (OR 0.83, 95% CI 0.61 to 1.13) (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003).

Neither exercise-only rehabilitation nor comprehensive cardiac rehabilitation had an effect on recurrence of non-fatal MI, with OR of 0.96 (95% CI 0.69 to 1.35) and 0.88 (95% CI 0.7 to 1.12) respectively. There was no overall difference in the rate of CABG in the 5 trials of exercise-only rehabilitation which reported this as an outcome measure, and the results from individual trials showed heterogeneity between studies. Similarly there was no significant effect of comprehensive cardiac rehabilitation on the rate of CABG (OR for 10 trials was 0.83, 95% CI 0.6 to 1.13). Very few trials reported PCI as an outcome measure. In a single trial of exercise-only rehabilitation compared with usual care there was no difference between the two groups in the rates of PCI. For comprehensive cardiac rehabilitation compared with usual care there was considerable heterogeneity between studies reporting this outcome (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003).

Analysis of the combined outcomes of all-cause mortality, non-fatal MI and revascularisations (CABG and PCI), found that both exercise-only rehabilitation and comprehensive cardiac rehabilitation resulted in a reduction in these combined outcomes compared with usual care (OR 0.81, 95% CI 0.65 to 1.01, OR 0.81, 95% CI 0.69 to 0.96 respectively) (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003).

A total of 11 trials reported HRQoL outcomes using eighteen different assessment instruments and therefore the data were not reported in a combined quantitative way. Overall in the 4 trials of exercise-only intervention, there were small changes or no change in HRQoL measures. In the 7 RCTs examining comprehensive cardiac rehabilitation intervention, most showed small and variable effects in HRQoL measures. One trial did find significant improvements with the intervention compared with usual care, reporting reductions in anxiety and depression (Lewin, B. et al 1992). Another study showed substantial and significant improvement in both the rehabilitation and control groups over 12 months (Oldridge, N. et al 1991). However, there was no significant difference between the two groups. The authors of the review noted that the significant improvement in both the intervention and control groups highlights the importance of recognising that there is a natural course of recovery after MI (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003).

The third systematic review examined three types of intervention compared with usual care: first, exercise-only cardiac rehabilitation versus usual care, second, comprehensive cardiac rehabilitation versus usual care, and third, programmes that included risk factor education or counselling and without an exercise component versus usual care in patients with CAD (Clark, A. M., Hartling, L., Vandermeer, B. et al 2005). A total of forty trials (16 142 patients) were identified that reported all-cause mortality, and for the combination of all interventions there was a reduction in all-cause mortality compared with usual care was 0.85 (95% CI 0.77 to 0.94). Meta analysis found that two of the interventions evaluated reduced all-cause mortality compared with usual care, namely, the programme without exercise (RR 0.87, 95% CI 0.76 to 0.99) and exercise only cardiac rehabilitation (RR 0.72, 95% CI 0.54 to 0.95). Meta analysis of the comprehensive programmes showed a trend in the reduction of all-cause mortality compared with usual care (RR 0.88, 95% CI 0.74 to 1.04) (Clark, A. M., Hartling, L., Vandermeer, B. et al 2005).

The effects of rehabilitation programmes differed over time. In a meta analysis of 20 trials (9462 patients) there was no significant difference in all-cause mortality at 12 months (RR 0.97, 95% CI 0.82 to 1.14), in those with and without rehabilitation, while in an analysis of 6 trials (1780 patients) all-cause mortality was significantly reduced at 24 months in the rehabilitation group (RR 0.53, 95% CI 0.35 to 0.81). At 5 years, 7

trials reported follow up data with a reduction in all-cause mortality (RR 0.77, 95% CI 0.63 to 0.93) (Clark, A. M., Hartling, L., Vandermeer, B. et al 2005).

A total of 27 trials (11 723 patients) were identified that reported recurrent MI rate, and the overall summary risk ratio for the combination of all interventions compared with usual care was 0.83 (95% CI 0.74 to 0.94). Meta analysis found that the comprehensive programme reduced recurrent MI compared with usual care (RR 0.62, 95% CI 0.44 to 0.87), while the two other interventions did not reach statistical significance compared with usual care (exercise-only cardiac rehabilitation: RR 0.76, 95% CI 0.57 to 1.01 and programme without exercise: RR 0.86, 95% CI 0.72 to 1.03). However, among all programmes that incorporated exercise (comprehensive cardiac rehabilitation plus exercise-only cardiac rehabilitation combined, a total of 22 trials and 6194 patients) meta analysis showed that the intervention reduced the risk of recurrent MI compared with usual care (RR 0.86, 95% CI 0.60 to 0.89) (Clark, A. M., Hartling, L., Vandermeer, B. et al 2005).

Twenty four trials out of 42 evaluated HRQoL measures or functional status and reported significantly better scores in patients exposed to the intervention programmes. The authors noted that the effect sizes were generally small (Clark, A. M., Hartling, L., Vandermeer, B. et al 2005).

5.2.3.2 Individualised comprehensive cardiac rehabilitation

Patients may be assessed for their individual needs and risks for cardiac rehabilitation and an individual plan made to meet those needs, or alternatively patients may be offered a pre-planned programme which is not individualised.

No randomised controlled studies or cohort studies were found comparing an individualised cardiac rehabilitation programme with a non-individualised cardiac programme to improve outcome in patients after MI.

However a randomised controlled study that examined the effectiveness of an individualised education intervention in patients after MI aged less than 70 years compared with usual care was identified (Mayou, R. A. et al 2002). Fifty six hospitalised patients who were given information sheets on return to activities of daily living and secondary preventions, and a relaxation tape. Following discharge,

patients were telephoned to review goals and to discuss any problems. There were 56 patients who received usual care. The outcome measures were the Hospital Anxiety and Depression Scale and the Dartmouth COOP scale for health-related quality of life. The primary outcome based on the Dartmouth COOP scale at 3 months showed that the intervention group significantly improved compared with the control group (59% versus 33% respectively: OR 0.34, 95% CI 0.16 to 0.73). There was also significant improvement in the Hospital Anxiety and Depression Scale in intervention group compared with the control group: median score 5 (2.75 to 8.25) versus 8 (5 to 12), respectively, (*P* = 0.002). At 12 months there was little further improvement in the intervention group. However, the control group scores in the Dartmouth COOP and Hospital Anxiety and Depression Scale had improved at 12 months, such that there was no significant difference between the control and intervention groups.

Two other narrative reviews have emphasised the importance of providing a programme based on individual patient requirements. In the first it was noted that determining functional capacity early after MI helped inform the level of physical activity recommended for individual patients (DeBusk, R. F. 1977). The author concluded that an individualised approach to evaluation of prognosis and enhancement of functional capacity appeared to have substantial psychological, as well as medical benefits in patients after MI (DeBusk, R. F. 1977). In the second review it was noted that cardiac rehabilitation should not be considered to be exercise training, but rather as a programme based on the individual's requirements (Benzer, W. and Oldridge, N. B. 2001). The aims of the programmes that were recommended were; improvement in quality of life and cardiac outcomes by reduction (or abolition) of classical risk factors (such as smoking, cholesterol levels, coupled with modification of dietary habits) increase and maintenance of endurance training, psychological support, and guidance on returning to work (Benzer, W. and Oldridge, N. B. 2001).

5.2.3.3 Safety in the exercise component of comprehensive cardiac rehabilitation

Three publications were found which make recommendations describing which patients the exercise component of cardiac rehabilitation is contra-indicated for safety reasons.

The SIGN Guideline on Cardiac Rehabilitation, 2002 (Scottish Intercollegiate Guidelines Network (SIGN). 2002), states that for most patients clinical risk stratification for assessment of suitability for exercise can be based on history, examination, and resting ECG combined with a functional capacity test such as the shuttle walk. SIGN defines high-risk patients as those who have:

- experienced an MI complicated by heart failure, cardiogenic shock and/or complex ventricular arrhythmias
- angina or breathlessness occurring at a low level of exercise, for example, inability to complete the first 4 minutes of the shuttle walking test
- ST segment depression ≥ 1 mm on resting ECG
- undergone exercise testing with marked ST depression ≥ 2 mm or angina at < 5 METS (for example, 3 minutes of a Bruce protocol)

SIGN made a consensus recommendation that high-risk patients (or those patients engaging in high-intensity exercise training) should undergo exercise testing and echocardiography.

A narrative review (Squires, R. W. et al 1987) that was not evidence based, stated that the following conditions are absolute contraindications to exercise training:

- Unstable angina pectoris
- Dangerous arrhythmias
- Overt cardiac failure
- Severe obstruction of the left ventricular outflow tract
- Dissecting aneurysm
- Myocarditis or pericarditis (acute)
- Recent systemic or pulmonary embolism
- Thrombophlebitis

- Serious systemic disease
- Severe hypertension
- Overt psychoneurotic disorders
- Uncontrolled diabetes mellitus
- Severe orthopaedic limitations

The American Heart Association (Bjarnason-Wehrens, B. et al 2004) has the following recommendation that is not evidence-based:

Exercise training is contraindicated in patients with the following clinical indications:

- unstable angina
- severe and symptomatic valvular stenosis or regurgitation
- symptoms of heart failure, especially NYHA Class IV
- arrhythmias refractory to therapy
- other clinical entities that worsen during exercise

5.2.3.4 Exercise-based cardiac rehabilitation in patients with severe left ventricular dysfunction after acute MI

Patients with left ventricular (LV) dysfunction have traditionally been excluded from formal cardiac rehabilitation programme on the basis that they are at much higher risk of sudden death during exercise. It has been suggested that exercise training may induce LV remodelling in patients with large anterior MI (Jugdutt, B. I. 1993). LV remodelling is a complex process, characterized by progressive ventricular dilatation, hypertrophy and wall thinning. This may lead to further LV dysfunction and congestive heart failure after MI.

Three studies were identified on reduced ventricular function, exercise training and LV remodelling.

The first was a cohort study that studied post MI patients with moderate to severe LV dysfunction to assess whether patients would benefit from exercise training starting early after MI, without a deterioration in LV remodelling (Otsuka, Y. et al 2003). Patients were divided into 3 groups according to LV ejection fraction (EF) at the start of exercise training: 74 patients with left ventricular ejection fraction (LVEF) ≥ 45% (Group H), 35 patients with 35% ≤ LVEF < 45% (Group M), and 17 patients with LVEF < 35% (Group L). Patients with no angina or ischaemic changes in electrocardiogram at low level exercise training were enrolled approximately 10-14 days post MI. The exercise programme consisted of walking, cycling on an ergometer and aerobic dance (50-90 min/session), 3-5 sessions/week for 3 months (Otsuka, Y., Takaki, H., Okano, Y. et al 2003).

After 3 months of exercise training, exercise capacity and peak work rate increased and resting heart rate reduced in all 3 groups. At 35±8 months follow up there were no significant differences in the incidence of cardiac events among the 3 groups. For reinfarction, the percentage of events for groups H, M and L were 5%, 3% and 6%, respectively. For angina or myocardial ischaemia requiring angioplasty, the percentage of events for groups H, M and L were 9%, 26% and 12%, respectively. For CABG, the percentage of events for groups H, M and L were 1%, 11% and 0%, respectively. There was no incidence of heart failure or cardiac death in any of the groups. There was also no significant change in LV end-diastolic dimension in each group. The authors concluded that patients with moderate to severe LV dysfunction would benefit from exercise training, commencing soon after acute MI without leading to deterioration in LV remodelling (Otsuka, Y., Takaki, H., Okano, Y. et al 2003).

The second study was a randomised controlled trial recruiting patients with an EF of < 40% after a first Q-wave myocardial infarction into a 6 month exercise training programme or control group (Giannuzzi, P. et al 1997). There were 39 patients in the exercise training programme and 38 patients in the control group. Inclusion criteria included: (1) history of a recent (3 to 5 weeks previously) first Q-wave acute myocardial infarction, (2) sinus rhythm and no atrioventricular or intraventricular

conduction disturbances, (3) echocardiographic LVEF of <40%, (4) no contraindications to exercise training. Exclusion criteria were (1) systemic disease, (2) clinical instability (angina at rest and signs or symptoms of heart failure) at the time of the initial evaluation, (3) low-threshold ischemia (<50 W) or exertional angina uncontrolled by medical therapy, (4) low work capacity (<50 W), and (5) inability to participate in a prospective study for any logistic reason.

Patients randomised to physical training participated in a supervised, continuous session of 30 minute bicycle ergometry at least three times per week for 2 months. Thereafter for 4 months, they continued the exercise programme (30 minute bicycle ergometry, 3 times per week) at home, reporting to the laboratory every 2 weeks when a new level of exercise could be tested and prescribed to maintain the target heart rate (80% of the previously determined maximum) for physical training (Giannuzzi, P., Temporelli, P. L., Corra, U. et al 1997).

After 6 months, a significant increase in work capacity was observed only in the training group but not in the control group, whereas left ventricular volumes had increased in the control group but not in the training group. Conversely, EF had improved in the training group (from 34±5% to 38±8%, *P* = < 0.01) but not in the control group (from 34±5% to 33±7%, *P* = not significant). The authors concluded that in post MI patients with left ventricular systolic dysfunction, long-term exercise training may attenuate the unfavourable remodelling response and even improve ventricular function over time (Giannuzzi, P., Temporelli, P. L., Corra, U. et al 1997).

The third study was a very small randomised controlled trial recruiting 25 patients with reduced left ventricular function (mean EF, 32.3±6%) after an MI into an exercise group or a control group (Dubach, P. et al 1997). All patients had sustained a recent MI, and their hospital course included the diagnosis of heart failure. All patients had stable symptoms after their myocardial infarction before randomisation.

Patients in the exercise group resided in a rehabilitation centre for 2 months and underwent a training programme consisting of two 1-hour sessions of walking daily, along with 4 monitored 45-minute sessions of stationary cycling weekly. Before and after the study period, maximal exercise testing and cardiac magnetic resonance imaging (MRI) were performed. Oxygen uptake increased 26% at maximal exercise

in the exercise group, whereas for control patients the values did not change. No differences were observed within or between groups in MRI measures of end-diastolic volumes, end-systolic volumes, EFs or myocardial wall thickness (Dubach, P., Myers, J., Dziekan, G. et al 1997).

5.2.3.5 Exercise-based cardiac rehabilitation in elderly patients after acute MI

Most randomised control studies assessing exercise-based cardiac rehabilitation programmes have recruited patients below 65 years of age. There have been few randomised controlled studies of post MI patients over 75 years of age. Literature searching identified two studies examining exercise-based cardiac rehabilitation in older patients post MI.

In the first study (Marchionni, N., Fattirolli, F., Fumagalli, S. et al 2003) post MI patients were split into 3 age groups: middle aged (45-65 years), old (66-75 years) and very old (> 75 years). Patients with severe cognitive impairment, LVEF < 35%, or contraindications to vigorous exercise were excluded. Within each age group, participants were randomised into hospital-based cardiac rehabilitation, home-based cardiac rehabilitation or no cardiac rehabilitation. The hospital-based cardiac rehabilitation intervention programme consisted of 40 exercise sessions, 24 sessions (3 times per week) of endurance training on a cycle ergometer (35 minutes) plus 16 sessions (2 times per week) of stretching and flexibility exercises (60 minutes). The home-based cardiac rehabilitation group participated in 4 to 8 supervised exercise training sessions in the cardiac rehabilitation unit where they were taught how to perform training at home (and the necessary precautions). Patients were provided with a cycle ergometer and physical therapist made home visits every other week to adjust the exercise prescription if necessary. Patients in the control group attended a single structured education session on cardiovascular risk factor management with no exercise prescription, and then they were referred back to their family physician. Total work capacity was assessed at baseline, at the end of the 2 month programme and 6 and 14 months thereafter. At each assessment, HRQoL was assessed using the Sickness Impact Profile (Dubach, P., Myers, J., Dziekan, G. et al 1997).

Over the 14 month duration of the trial, total work capacity improved in the hospital-based cardiac rehabilitation and home-based cardiac rehabilitation groups but not in

the controls. In terms of the age groupings, treatment-time interactions showed a greater effect of both interventions compared with controls in middle aged patients ($P = 0.002$) and old patients ($P < 0.001$) but not in very old patients ($P = 0.143$). In middle aged and old patients, HRQoL improved significantly over the study period regardless of treatment assignment, whereas in very old patients, HRQoL improved with both hospital-based cardiac rehabilitation and home-based cardiac rehabilitation ($P = 0.013$ and $P < 0.035$, respectively), but not in the control group ($P = 0.079$) (Dubach, P., Myers, J., Dziekan, G. et al 1997).

The second study (Stahle, A., Lindquist, I., and Mattsson, E. 2000) randomised 43 post MI patients ≥ 65 years old into either a supervised outpatient training programme (50 min, 3 times per week for 3 months), or to a control group. Patients with overt heart failure, neurological sequelae, orthopaedic disability, memory dysfunction or planned coronary intervention were excluded. The outcome measures were self motivation, outcome expectation, efficacy and physical activity at 3 and 12 months follow up. There was no significant difference between the intervention and control group at baseline. Reported physical activity at 12 months was significantly higher in the intervention group compared with controls ($P < 0.0001$). A multiple regression analysis between level of activity at 12 months and age, gender, BMI, support, self motivation, activity level before admission, and group (intervention and controls) found that group and reported activity at 12 months were correlated ($R = 0.74$, $P < 0.001$) (Stahle, A., Lindquist, I., and Mattsson, E. 2000).

5.2.4 Health economics of cardiac rehabilitation

Five studies were found which addressed the health economics of cardiac rehabilitation (Taylor, R. and Kirby, B. 1999) (Oldridge, N. et al 1993) (Hall, J. P. et al 2002) (Levin, L. A., Perk, J., and Hedback, B. 1991) (Ades, P. A., Pashkow, F. J., and Nestor, J. R. 1997). One study (Taylor, R. and Kirby, B. 1999) was a costing study which synthesised cost effectiveness information using UK cost data, while the rest of the economic evaluations were done outside UK. An additional analysis from the UK perspective was also undertaken and is reported in Appendix C.

The UK Study (Taylor, R. and Kirby, B. 1999) was a review of economic evaluations including costs of a UK cardiac rehabilitation programme. The authors reported the

costs of a comprehensive cardiac rehabilitation programme to be £140 per patient excluding the indirect costs and £207 including indirect costs. The study found that the cost effectiveness from the NHS perspective was £6400/life year gained and £2700/QALY gained. It was acknowledged that this study was never designed as an economic evaluation. However the results seem to agree with the findings of properly designed economic evaluations.

A second study (Ades, P. A., Pashkow, F. J., and Nestor, J. R. 1997) compared the costs and benefits of comprehensive cardiac rehabilitation with no cardiac rehabilitation, in unselected patients from a US third payer's perspective. The authors acknowledge that their data were derived from a heterogeneous population of mainly younger men. Cardiac rehabilitation was found to be cost effective with the estimated incremental cost effectiveness ratio of $2130/LYS in 1985 and projected cost was $4950/LYS in 1995 (at a 5% discount rate).

A third study (Hall, J. P., Wiseman, V. L., King, M. T. et al 2002) assessed the cost and consequences of comprehensive cardiac rehabilitation compared to no rehabilitation in low-risk patients after MI from an Australian perspective. The authors considered quality of life outcomes and four measures of early return to normal activities (paid and unpaid return to pre-MI level of work/activities). There were no statistically significant differences between the two groups in most of the outcomes measured. Return to any paid work was statistically different, with the no rehabilitation group returning to work earlier. There was no difference in health service resource use. The cost of rehabilitation was estimated to be about $400/patient. The authors concluded that this represented the net cost that could be saved by the health service by targeting rehabilitation to high-risk patients. However this conclusion assumed that there would be improved outcomes in high-risk patients. The evidence seems to be that there is a cost saving from targeting cardiac rehabilitation away from low-risk patients. Their findings have not been confirmed by any other studies.

A fourth study (Oldridge, N., Furlong, W., Feeny, D. et al 1993) assessed the cost utility of comprehensive cardiac rehabilitation compared to usual care in patients with anxiety or mild to moderate depression or both, from a US perspective. Quality of life

scores were obtained using time trade off at the end of the study period. The estimated ICER was $9200/QALY gained during the year of follow up.

The fith study (Levin, L. A., Perk, J., and Hedback, B. 1991) assessed the cost effectiveness of a comprehensive cardiac rehabilitation programme in 147 unselected post MI patients aged less than 65 years (124 men and 23 women), compared with standard care from the Swedish perspective. This was a cost consequence analysis, which did not aggregate costs and benefits, but rather reported them separately. The estimated total costs in the cardiac rehabilitation group were SEK 484 260 compared with SEK 557 770 in the usual care group. The cost difference was SEK 73 500 in favour of the rehabilitation group. Total and cardiac mortality did not differ between the groups. Compared to the usual care group, readmission was less frequent in the rehabilitation group (13.7 days versus 19.3 days $P < 0.05$), and there was also a reduction in non-fatal reinfarction (17.3 versus 33.3%, $P = < 0.05$) and total cardiac events (39.5 versus 53.2% $P = 0.001$).

An additional analysis requested by the GDG was undertaken to examine the cost effectiveness of cardiac rehabilitation compared to no cardiac rehabilitation in unselected patients after MI. The model used clinical effectiveness data from three recent meta-analyses (Taylor, R. S. et al 2004) (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003) (Clark, A. M., Hartling, L., Vandermeer, B. et al 2005) and follow up data from RITA 2 (Henderson, R. A. et al 2003).

The results suggested that cardiac rehabilitation was cost effective when compared with no cardiac rehabilitation. The estimated ICER is about £7860 and £8360 per QALY gained for men and women respectively, which is well below the level usually considered to be affordable in the NHS (about £20 000 to £30 000 per QALY). The results were robust in sensitivity analysis.

In conclusion, in patients after MI cardiac rehabilitation compared no cardiac rehabilitation is cost effective. The results of the additional analysis are consistent with the findings from other healthcare systems.

5.3 Patient engagement

5.3.1 Evidence statements for patient engagement

5.3.1.1	In unselected patients after MI, uptake of cardiac rehabilitation programmes can be improved by motivational communication such as written letters, or pamphlets, or conversation with a healthcare professional (1++).
5.3.1.2	Regular support and practical help from lay volunteers may improve uptake in unselected patients after MI (1++).
5.3.1.3	Effective co-ordination between hospital and primary care to encourage patients to see the practice nurse after discharge improves uptake of cardiac rehabilitation programmes in unselected patients after MI (1++).
5.3.1.4	There was little evidence found on interventions to improve adherence to cardiac rehabilitation and it was of poor quality.
5.3.1.5	The use of letters or telephone calls plus a visit from a healthcare professional to improve uptake of cardiac rehabilitation was found to be cost effective, but the result was sensitive to efficacy of the interventions.
5.3.1.6	There was no evidence found of interventions to improve either uptake or adherence to cardiac rehabilitation in ethnic minority groups, patients living in socially deprived areas, deprived areas, elderly patients, women, or patients in rural areas.

Back to recommendations

5.3.2 Clinical effectiveness of patient engagement

5.3.2.1 Introduction

A Health Technology Assessment entitled 'Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups' (Beswick, A. D. et al 2004) examined hospital discharge statistics for 2000. In England, Wales and Northern Ireland there were nearly 146 000 patients discharged from hospital with primary diagnosis of acute MI, unstable angina or following revascularisation that were potentially eligible for cardiac rehabilitation. In England, 45 to 67% of these patients were referred, with 27 to 41% attendance rates, of those eligible for cardiac rehabilitation. Surveys in the UK of patients after MI attendance at cardiac rehabilitation centres have cited participation rates ranging from 14 to 43%. The review (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) found that response rates in patients referred to, joining and completing programmes from under-represented groups was much poorer. The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) conducted an audit of cardiac rehabilitation in the south-west of England and areas of high ethnic minority populations in London and the Midlands. From January to July 2002, audit data was obtained from 24 centres (42% of centres contacted). The proportion of discharged patients attending rehabilitation was 35%, and of those referred attendance was 55%. Of those attending a programme, 77% subsequently completed it. In five centres providing a service to a high proportion of ethnic minorities, the percentage of discharged patients referred was significantly lower than in three centres from other areas (29% compared with 45%).

The National Service Framework on Coronary Heart Disease (Department of Health 2000) states that every hospital should ensure that 85% of people discharged from hospital with a primary diagnosis of acute MI, or after coronary revascularisation, are offered cardiac rehabilitation.

The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) presented information from an NHS-funded, multicentre randomised controlled trial that was deemed to represent a more optimal protocol-led level of care than that given in cardiac rehabilitation centres (West, R. 2003). Healthcare professionals

identified 73-81% of patients with acute MI as eligible for cardiac rehabilitation. Excluded patients tended to have a previous MI, pre-existing angina, MI with left ventricular failure, or MI with cardiac shock. They also tended to be older. The experiences of the recruited patients identified a number of areas which could be addressed to improve uptake;

- motivation and relevance of rehabilitation to future well-being
- comorbidities
- site and time of programme
- transport
- care for dependents

The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) also summarised the literature on barriers to uptake and adherence to cardiac rehabilitation as follows:

Patient factors

- lack of interest
- reluctance to change lifestyle
- depression
- dislike of classes / hospitals
- work or domestic commitments
- lack of family support
- rural residence / distance and transport problems
- misconceptions about cardiac problems

Service Factors

- cost and reimbursement
- ECG monitoring requirement
- location and accessibility
- car parking
- lack of flexibility

Professional factors

- knowledge and attitudes
- referral
- prejudice (age, race and gender)

5.3.2.2 Patient engagement to improve uptake to comprehensive cardiac rehabilitation

The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) conducted a systematic review of studies to improve uptake to comprehensive cardiac rehabilitation. Eight studies were identified that reported an evaluation of an intervention relating to uptake by an appropriate patient group, and with a relevant outcome (Wyer, S. J. et al 2001) (Jolly, K. et al 1999) (Osika, J. S. 2001) (Mosca, L. et al 1998) (Imich, J. 1997) (Scott, I. A. et al 2000) (Hillebrand, T. et al 1995) (Krasemann, E. O. and Busch, T. 2006).

Six of these studies reported interventions designed to increase uptake of outpatient cardiac rehabilitation (Wyer, S. J., Earll, L., Joseph, S. et al 2001) (Jolly, K., Bradley, F., Sharp, S. et al 1999) (Osika, J. S. 2001) (Mosca, L., Han, R., McGillen, C. et al 1998) (Imich, J. 1997) (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000). The other 2 studies described interventions designed to improve uptake of community or voluntary services (cardiac or heart clubs) following discharge from inpatient cardiac rehabilitation (Hillebrand, T., Frodermann, H., Lehr, D. et al 1995)

(Krasemann, E. O. and Busch, T. 2006). All studies recruited post MI patients. One study also included patients with angina (Jolly, K., Bradley, F., Sharp, S. et al 1999) and another included post cardiac surgery patients (Imich, J. 1997).

Three of the eight studies were randomised controlled trials (Wyer, S. J., Earll, L., Joseph, S. et al 2001) (Hillebrand, T., Frodermann, H., Lehr, D. et al 1995) (Jolly, K., Bradley, F., Sharp, S. et al 1999). Five studies reported non-randomised studies. One study compared a district providing the intervention with another not giving any intervention (Osika, J. S. 2001). The two districts had patient populations with comparable demographics, and they were served by the same general hospital. The other four studies compared uptake of cardiac rehabilitation before and after implementation of an intervention (Mosca, L., Han, R., McGillen, C. et al 1998) (Imich, J. 1997) (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000) (Krasemann, E. O. and Busch, T. 2006). All studies evaluated generic interventions that were applicable to general patients after MI, rather than interventions specifically for underrepresented patient groups. The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) grouped the interventions into four themes:

1. healthcare led professional interventions at the patient level

2. trained lay volunteers

3. coordination of referral post-discharge care at the service level

4. written or aural motivational communications

The authors stated that the evidence for benefits from motivational communications was reasonably good. There were improvements in uptake of outpatient cardiac rehabilitation and heart groups demonstrated in two randomised controlled trials (Wyer, S. J., Earll, L., Joseph, S. et al 2001) (Hillebrand, T., Frodermann, H., Lehr, D. et al 1995) and in one before and after study (Krasemann, E. O. and Busch, T. 2006). Methods of communication used were written letters (Wyer, S. J., Earll, L., Joseph, S. et al 2001), or pamphlets (Krasemann, E. O. and Busch, T. 2006) or conversation with a healthcare professional (Hillebrand, T., Frodermann, H., Lehr, D. et al 1995).

There was limited information reported in the one study assessing the effectiveness of an intensive home-based nurse-led approach (Imich, J. 1997). The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) stated that no conclusions could be drawn.

A multifaceted approach to the coordination of transfer of care from hospital to general practice was effective in improving cardiac rehabilitation in a randomised control trial (Jolly, K., Bradley, F., Sharp, S. et al 1999). It was noted that the two non-randomised studies on the multifaceted approach had problems in study design and therefore were of limited value (Mosca, L., Han, R., McGillen, C. et al 1998) (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000). Regular support and practical help from lay volunteers were effective in improving uptake in a non-randomised study conducted in two separate districts (Osika, J. S. 2001).

All studies reported that there was benefit from intervention to improve uptake. The authors of the Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) noted that there might be publication bias.

5.3.2.3 Patient engagement to improve adherence to comprehensive cardiac rehabilitation

The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) conducted a systematic review of studies to improve adherence to comprehensive cardiac rehabilitation. A broad definition of adherence was applied, and studies were included on interventions reporting attempts to improve overall adherence and also studies on compliance with aspects of cardiac rehabilitation. Fourteen studies were identified that reported an evaluation of an intervention relating to adherence in an appropriate patient group, and with a relevant outcome (Oldridge, N. B. and Jones, N. L. 1983) (Daltroy, L. H. 1985) (Marshall, J., Penckofer, S., and Llewellyn, J. 1986) (Aish, A. E. and Isenberg, M. 1996) (Ashe, E. D. 1993) (Duncan, K., Pozehl, B., and Rosado, K. 2001) (Hooper, D. L. 1995) (Leslie, M. and Schuster, P. A. 1991) (Miller, P. et al 1988) (Miller, P. et al 1989) (Lack, E. R. 1985) (Marshall, J., Penckofer, S., and Llewellyn, J. 1986) (Huerin, M. 1998) (McKenna, M. 1988) (Erling, J. and Oldridge, N. B. 1985).

Seven of the fourteen studies identified were randomised controlled trials (Oldridge, N. B. and Jones, N. L. 1983) (Daltroy, L. H. 1985) (Marshall, J., Penckofer, S., and Llewellyn, J. 1986) (Aish, A. E. and Isenberg, M. 1996) (Ashe, E. D. 1993) (Hooper, D. L. 1995) (Duncan, K., Pozehl, B., and Rosado, K. 2001). The other seven studies were non-randomised studies (Leslie, M. and Schuster, P. A. 1991) (Miller, P., Wikoff, R., McMahon, M. et al 1988) (Miller, P., Wikoff, R., McMahon, M. et al 1989), (Lack, E. R. 1985) (Huerin, M. 1998) (McKenna, M. 1988) (Erling, J. and Oldridge, N. B. 1985). One randomised (Marshall, J., Penckofer, S., and Llewellyn, J. 1986) and one non-randomised study (McKenna, M. 1988) reported two distinct interventions. In two studies the group allocation was not clearly described (Huerin, M. 1998) (McKenna, M. 1988).

Three studies were of post MI patients (Aish, A. E. and Isenberg, M. 1996) (Miller, P., Wikoff, R., McMahon, M. et al 1988) (Miller, P., Wikoff, R., McMahon, M. et al 1989) (McKenna, M. 1988). Eight studies included post MI patients in the recruitment group, and three studies had no post MI patients in their recruits (Marshall, J., Penckofer, S., and Llewellyn, J. 1986) (Duncan, K., Pozehl, B., and Rosado, K. 2001) (Marshall, J., Penckofer, S., and Llewellyn, J. 1986).

The outcome of eight studies was attendance at exercise sessions (Oldridge, N. B. and Jones, N. L. 1983) (Oldridge, N. B. and Jones, N. L. 1983) (Marshall, J., Penckofer, S., and Llewellyn, J. 1986) (Ashe, E. D. 1993) (Leslie, M. and Schuster, P. A. 1991) (Lack, E. R. 1985) (Huerin, M. 1998) (McKenna, M. 1988) (Erling, J. and Oldridge, N. B. 1985). The outcome of the other six studies was questionnaire assessment of diet or exercise behaviours to ascertain compliance with lifestyle changes (Miller, P., Wikoff, R., McMahon, M. et al 1988) (Miller, P., Wikoff, R., McMahon, M. et al 1989) (Marshall, J., Penckofer, S., and Llewellyn, J. 1986) (Aish, A. E. and Isenberg, M. 1996) (Hooper, D. L. 1995) (Duncan, K., Pozehl, B., and Rosado, K. 2001).

All studies found were generic interventions that were applicable to general patients, rather than interventions for under-represented patient groups. The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) grouped the interventions into five themes:

1. formal patients, commitment
2. spouse or family involvement
3. strategies to aid self-management
4. education
5. psychological interventions

There were four studies that utilised a formal agreement strategy between patient and healthcare professionals (Oldridge, N. B. and Jones, N. L. 1983) (Daltroy, L. H. 1985) (Leslie, M. and Schuster, P. A. 1991) (Huerin, M. 1998).The findings of these studies do not support the use of formal commitment in promoting adherence to cardiac rehabilitation. One study used a written contract, but this showed no effect using a non-randomised study design (Leslie, M. and Schuster, P. A. 1991). A randomised controlled trial of a self-management programme incorporating a signed agreement to participate as an adjunct to an exercise program showed no effect (Oldridge, N. B. and Jones, N. L. 1983). Similarly, a package of persuasive telephone conversations, with spouse counselling, and oral commitment, did not improve attendance (Daltroy, L. H. 1985).

The evidence for the benefits of spouse or family member involvement enhancing adherence is limited by the design of the studies. A spouse support study did not provide information on baseline characteristics or group allocation (Erling, J. and Oldridge, N. B. 1985). A randomised study utilising telephone counselling for spouses and intensive patient counselling had no effect on adherence (Daltroy, L. H. 1985). The study on family involvement in adherence-promoting behaviour provided little information on design or methodology (Huerin, M. 1998).

There is some evidence for the benefits of self-management to improve adherence to cardiac rehabilitation. One randomised controlled study showed improvement in dietary habits (Aish, A. E. and Isenberg, M. 1996), and a small randomised controlled study showed benefit in reduced sodium intake (Duncan, K., Pozehl, B., and Rosado, K. 2001). Another randomised control study of self-evaluation and information feedback on exercise and risk factors demonstrated a non-significant

improvement in attendance at rehabilitation (Oldridge, N. B. and Jones, N. L. 1983). However, one randomised controlled study (Ashe, E. D. 1993) and a study with non-random assignment to groups (Miller, P., Wikoff, R., McMahon, M. et al 1988) (Miller, P., Wikoff, R., McMahon, M. et al 1989) showed no benefit for assessment and goal setting for improving health behaviours or exercise adherence. In the discussions of these studies, it was noted that control patients received regular self-evaluation questionnaires and nurse visits, which may have affected outcomes.

There was little evidence that educational interventions improve adherence. Two randomised controlled studies showed no benefit of education and counselling (telephone intervention) on attendance at an exercise programme (Daltroy, L. H. 1985) (Hooper, D. L. 1995). A videotaped educational intervention given pre-discharge was effective in increasing diet and exercise compliance (Marshall, J., Penckofer, S., and Llewellyn, J. 1986). It was noted that this approach might help initially, but may be of limited value in the promotion of adherence to a cardiac rehabilitation programme. A non-randomised study using a before-and-after structured teaching approach was effective in increasing diet and exercise (Marshall, J., Penckofer, S., and Llewellyn, J. 1986).

Only one partially randomised study used a psychological approach to improve adherence (Lack, E. R. 1985). No significant improvement was found in self-reported exercise, but the patients in the psychological intervention group did attend more cardiac rehabilitation classes.

Two other studies described alternative approaches to adherence: the inclusion of recreational sports in cardiac rehabilitation (Huerin, M. 1998) and the use of outpatient rehabilitation designed specifically for women (McKenna, M. 1988). Insufficient information on the patients and methodology of these studies prevented any analysis of the studies.

In summary, the authors of the Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) stated that they found few studies of sufficient quality to make specific recommendations on methods to improve adherence to cardiac rehabilitation. Their opinion was that the most promising approach was the

use of self-management techniques based around individualised assessment, problem-solving, goal-setting and follow up.

5.3.2.4 Professional compliance with cardiac rehabilitation

The Health Technology Assessment systematic review (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) searched the literature up to the end of 2001, with the aim to identify interventions that encourage healthcare professionals to comply with guidelines or good practice regarding invitation and support of patients' cardiac rehabilitation. Six studies were identified that reported an evaluation of an intervention to improve professional compliance with cardiac rehabilitation (Suskin, N. et al 2000) (Jolly, K., Bradley, F., Sharp, S. et al 1999) (Mosca, L., Han, R., McGillen, C. et al 1998) (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000) (Kalayi, C., Rimmer, F., and Maxwell, M. 1999) (Caulin-Glaser, T. and Schmeizel, R. 2000).

Two of the studies identified were randomised controlled trials. One randomised on an individual basis (Suskin, N., Wisenberg, G., Barnett, P. et al 2000) and the second randomised patients by general practice (Jolly, K., Bradley, F., Sharp, S. et al 1999). This study described methods of randomisation, blind outcome assessment and baseline characteristics of the group, and the loss to follow up in this study was small. None of the other studies reported loss to follow up. Four of the studies described outcomes in periods before and after implementation (Mosca, L., Han, R., McGillen, C. et al 1998) (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000) (Kalayi, C., Rimmer, F., and Maxwell, M. 1999) (Caulin-Glaser, T. and Schmeizel, R. 2000).

The outcome for three studies was attendance (Mosca, L., Han, R., McGillen, C. et al 1998) (Jolly, K., Bradley, F., Sharp, S. et al 1999) (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000). Referral was the outcome in two studies (Kalayi, C., Rimmer, F., and Maxwell, M. 1999) and another study had an outcome of patient commitment to attend cardiac rehabilitation (Suskin, N., Wisenberg, G., Barnett, P. et al 2000). There were four studies that recruited post MI patients (Mosca, L., Han, R., McGillen, C. et al 1998) (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000) (Kalayi, C., Rimmer, F., and Maxwell, M. 1999) (Suskin, N., Wisenberg, G., Barnett,

P. et al 2000). One study included both post MI and angina patients (Jolly, K., Bradley, F., Sharp, S. et al 1999) and another study recruited only post-revascularisation patients (Caulin-Glaser, T. and Schmeizel, R. 2000).

Three themes were identified from the systematic review:

1. improvement of the referral process

2. coordination of transfer of care

3. physician endorsement

There were four studies that evaluated methods to improve the referral process (Mosca, L., Han, R., McGillen, C. et al 1998) (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000) (Kalayi, C., Rimmer, F., and Maxwell, M. 1999) (Caulin-Glaser, T. and Schmeizel, R. 2000). One study compared patient referral before and after the introduction of an electronic referral pathway (Kalayi, C., Rimmer, F., and Maxwell, M. 1999). The intervention was initiated with a referral section on the patient record of patients discharged with a diagnosis of MI. There was a significant increase in patient referral to rehabilitation. Another study compared participation before and after the introduction of a prompt for cardiac rehabilitation in a discharge critical care pathway (Mosca, L., Han, R., McGillen, C. et al 1998). The improvement in participation was not statistically significant. Two studies reported an educational intervention for healthcare providers, which included information on the comprehensive nature and benefits of cardiac rehabilitation (Caulin-Glaser, T. and Schmeizel, R. 2000). Information on health outcomes and cost effectiveness was given to members of the clinical cardiology council. After the intervention, there was significantly increased referral from both the hospital and the physician office (Scott, I. A., Eyeson-Annan, M. L., Huxley, S. L. et al 2000). These were before, during and after dissemination of clinical guidelines and feedback of clinical indicators to healthcare professionals. During the implementation period, the cardiac rehabilitation programme was operational and this served as a baseline period for evaluation. There was a steady increase in participation in the rehabilitation program and this was attributed to the intervention. However, no comparisons of the patients' characteristics were made in the three time periods.

A cluster randomised controlled study of coordination of care of MI and angina patients between hospital and general practice by specialist cardiac liaison nurses found there was a significant increase in attendance at one or more cardiac rehabilitation sessions for the intervention patients (Jolly, K., Bradley, F., Sharp, S. et al 1999). The intervention involved three components: liaison nurse support for practice nurses, liaison nurse encouragement for patients to see the practice nurse, and prompts and guidance for patients by means of a personal record card.

A randomised controlled trial comparing attending physician cardiac rehabilitation endorsement with a generic endorsement found that the intervention was associated with a non-significant increase in patient-reported intention to participate in a cardiac rehabilitation program (Suskin, N., Wisenberg, G., Barnett, P. et al 2000).

In summary, the authors of the Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) stated that none of the four studies reporting interventions to improve the referral process included adequate methodological information. A randomised controlled study utilising a multifaceted approach to the coordination of transfer of care from hospital to general practice was effective in improving cardiac rehabilitation uptake (Jolly, K., Bradley, F., Sharp, S. et al 1999). In contrast, the value of physician endorsement in encouraging patient participation in cardiac rehabilitation is not confirmed. It was noted that uptake of cardiac rehabilitation is influenced by the knowledge and enthusiasm of the healthcare providers in the referral process. Therefore, education of healthcare providers on the benefits of cardiac rehabilitation may help to improve uptake and referral.

5.3.2.5 Further interventions that may improve compliance of cardiac rehabilitation

The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) identified a number of suggested interventions for improving professional compliance with cardiac rehabilitation. The interventions were not evaluated and were as follows:

- appointment of a cardiac rehabilitation programme director to lead, audit and commission appropriate resources

- programme run in accordance with national guidelines
- physicians and insurers educated on benefits for patient groups
- education for cardiac rehabilitation coordinators and staff
- explicit criteria for cardiac rehabilitation eligibility
- streamlining of referral
- centralised cardiac rehabilitation attendance and contact records
- clinical pathway and clinical quality improvement tool
- early social services involvement to improve social support and hence uptake of cardiac rehabilitation
- cardiac rehabilitation commenced earlier
- removal of time restriction for start of programme

One further small intervention study was found that examined adherence in a total of 31 cardiac patients (20 with a prior MI and 11 post CABG) following successful completion of a phase III exercise programme at a district hospital in Scotland (Hughes, A. R. et al 2002). Participants were randomised to an intervention group receiving an exercise consultation plus a standard exercise leaflet or to a control group receiving the exercise leaflet alone. The exercise consultation was a 30-minute individualised counselling session between a trained researcher and the patient. The following were discussed: patient's past and present perceived physical activity behaviour, a discussion of the patterns of unsatisfactory activity and ways to overcome these, encouraging social support, setting realistic short-term goals, and relapse prevention. The participants were informed of current activity guidelines to perform 30 minutes of accumulated moderate intensity activity on most days of the week. At four week follow up, leisure physical activity of the intervention group increased by 29.5%,, while there was a non-significant decline in the physical activity of the control groups by 12% (Hughes, A. R., Gillies, F., Kirk, A. F. et al 2002).

5.3.2.6 Groups requiring specific consideration

Ethnic minority groups

No studies were found of randomised controlled trials to improve uptake or adherence to cardiac rehabilitation in this under-represented group. The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) identified one abstract with potential suggestions to improve compliance in South Asian patients (Eftekhari, H. et al 2005). The authors describe the following strategies to improve the cardiac rehabilitation programme based at Coventry that have been implemented: translating current material into Asian languages, utilising Asian language videos, providing post-cardiac surgery tapes, increasing the numbers of home visits for Asian patients, and trialling the Heart Manual audio cassette tapes which have recently been translated.

An audit was conducted of cardiac patients of south Asian origin who were admitted to a large teaching hospital in Sheffield (Tod, A. M. et al 2001). From the audit, the patient's suggested improvements for information giving are shown in the Table 1.

Table 1
Suggested improvements for information giving (n=76)

Tasks	Number of patients
The availability of interpreters should be increased	26 (34%)
An interpreter should be available during ward rounds	7 (9%)
The proportion of staff of all grades who speak South Asian languages should be increased	7 (9%)
Medication instructions should be available in a range of South Asian languages	7 (9%)
Link-workers or interpreters should actively pursue South Asian patients on a regular, daily basis	1 (1%)
Female patients should be able to choose to be seen by a female doctor	1 (1%)
More leaflets should be available in South Asian languages	1 (1%)
More verbal communication should be provided for patients who cannot read any language	1 (1%)

Adapted from (Tod, A. M., Wadsworth, E., Asif, S. et al 2001)

The authors raised the following problems that were identified from the audit to improve access for this patient group (Tod, A. M., Wadsworth, E., Asif, S. et al 2001);

- poor access and use of interpreting services by patients and staff

- untrained interpreters and whether friends, family or staff have been shown to alter or omit information putting the patient at a disadvantage
- there was negligible access to interpreting services after discharge
- written information may have a limited impact because of the number of patients who could not read
- the low uptake of the cardiac rehabilitation

The authors recommended the following to improve access to cardiac rehabilitation programs for South Asian cardiac patients (Tod, A. M., Wadsworth, E., Asif, S. et al 2001);

- at all points in the care pathway patients should be offered the use of a trained interpreter
- there is a need for more responsive and ward-based interpreters
- reliance on written literature should be avoided when large numbers of the patient population cannot read
- information on health, treatments and services can be recorded on tape for patients and their families

A qualitative research approach to explore the needs and experiences of Gujarati-speaking Hindu patients and their partners in the first month after an MI has been conducted (Webster, R. A., Thompson, D. R., and Mayou, R. A. 2002). There were 35 patients in total, 25 men and 10 women. The average age was 65 years. The quantitative analysis of the data revealed eight major categories

1. lack of information and advice about their diagnosis and its implications
2. poor performance of activity
3. little lifestyle adjustment
4. poor expectations of recovery

5. lack of future plans

6. strong family support

7. dissatisfaction with the family doctor

8. significant belief in fate

The authors concluded that the patient's lack of knowledge is likely to lead to poor adherence to conventional cardiac rehabilitation programmes and secondary prevention strategies (Webster, R. A., Thompson, D. R., and Mayou, R. A. 2002).

Patients living in socially deprived areas

No studies were found of randomised controlled trials to improve uptake or adherence to cardiac rehabilitation in this under-represented group. The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) identified one study that conducted a survey with the aim to determine factors associated with patients failing to attend cardiac rehabilitation (Pell, J. P. and Morrison, C. E. 1998). The study reported measuring social deprivation using the Carstairs deprivation score, but this information was not utilised in the analysis for reasons of non-attendance. The authors suggested in the discussion that socially deprived patients with a prior MI may prefer a community-based cardiac rehabilitation program. The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) identified a second study that used a retrospective analysis to identify factors associated with the uptake of cardiac rehabilitation following an MI (Melville, M. R. et al 1999). A multivariate logistic regression model approach was used to identify these factors from cohorts of patients admitted with MI in 1992 and 1996. Social deprivation was the only factor independently and significantly associated with poor uptake of cardiac rehabilitation in both years using the Townsend score. In 1992, being admitted to hospital and older age were also independently associated with a reduced likelihood of attendance Receiving thrombolysis increased the likelihood of attendance In 1996, a previous MI or revascularisation and not receiving an outpatient appointment were associated with reduced likelihood of attendance (Melville, M. R., Packham, C., Brown, N. et al 1999).

Patients living in rural areas

No studies were found on improving uptake or adherence to cardiac rehabilitation in patients in rural areas.

Women

We found no randomised controlled trials of interventions to improve uptake or adherence to cardiac rehabilitation in women following an MI.

The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) cited four studies which gave suggestions to improve women's access to cardiac rehabilitation. A survey of 60 men and 40 women 6 months after MI found that in men, 15% did not attend cardiac rehabilitation (Radley, A. et al 1998). Reasons given by men were almost exclusively related to their medical condition. Of the women that did not attend (42%) the majority that stated that they were not given the opportunity. The authors recommended in their discussion that cardiac rehabilitation for women should encompass a one-off education session. This may help to address gender-sensitive issues such as returning to sexual relations and housework. Focus-group interviews conducted on 10 women having completed phase II of cardiac rehabilitation (4 with a prior MI) found that women wanted more women-specific support (Moore, S. M. 1996). This was defined as improvements in social support, better exercise variety and choice, and social opportunities during the programme. A comparative semi-structured interview and questionnaire study to identify gender differences in psychosocial profile at entry into cardiac rehabilitation found that women had higher scores of social inhibition compared with men (Brezinka, V., Dusseldorp, E., and Maes, S. 1998). The authors concluded that women may benefit from women-specific counselling and women-only smaller exercise classes (Brezinka, V., Dusseldorp, E., and Maes, S. 1998). A small randomised controlled trial compared a 7-day retreat designed to begin lifestyle changes for postmenopausal women with coronary heart disease (including exercise training, yoga, diet, and smoking cessation) with usual care (defined as no intervention beyond the usual care of their physician) (Toobert, D. J. et al 1998). There were 10 women in the intervention (9 post MI or CABG, 1 primary PCI) and 9 (8 post MI or CABG, 1 primary PCI) in the control group. At 4 and 12 months follow

up, there were significant behavioural improvements in adherence to diet, physical activity and stress management for the intervention group. The authors concluded that a women's retreat may be effective in improving emotional social support and relationships with cardiac rehabilitation staff (Toobert, D. J., Glasgow, R. E., Nettekoven, L. A. et al 1998).

In summary, suggested interventions to improve uptake in women patients include women-only education sessions, appropriate exercise choices, specific counselling, strategies to improve social support, and a women's retreat.

Older patients

We found no controlled trials of interventions to improve uptake or adherence to cardiac rehabilitation in elderly patients following an MI. The Health Technology Assessment (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) noted that older patients may not receive the same amount of advice from physicians on cardiac risk reduction as younger patients. Invitation to cardiac rehabilitation is often lower in older patients (Filip, J., McGillen, C., and Mosca, L. 1999). A US survey has found that older patients prefer home-based programmes while younger patients have a preference for comprehensive clinic-based rehabilitation (Young, R. F. and Kahana, E. 1989).

Overall, the literature on access to cardiac rehabilitation programmes for specific patients groups (elderly, women, socially deprived, ethnic minority groups, patients from rural areas) is scarce. The majority of interventions that have been suggested have not been evaluated. An important aspect in enhancing participation is the need to create 'user friendly' rehabilitation that minimises barriers and is adaptable to individual patient needs. There is a need for trials of interventions applicable to all patients, particularly targeting under-represented groups.

A set of audit criteria developed by GDG members for under-represented groups is at the end of this chapter.

Health economics for methods of inceasing uptake of cardiac rehabilitation

There were no studies found examining the cost effectiveness of methods used to increase uptake of cardiac rehabilitation. The GDG asked for an economic analysis to be done. Using effectiveness data from (Beswick, A. D., Rees, K., Griebsch, I. et al 2004) and output data from the cardiac rehabilitation versus no cardiac rehabilitation economic model described in the appendix, a simple model was constructed comparing three different strategies used to increase the uptake of cardiac rehabilitation, usual care, the use of motivational letters and the use of telephone calls plus a visit from a healthcare professional.

The base case model showed that the cost effectiveness of the strategy of sending letters compared to usual care to increase uptake of cardiac rehabilitation is about £ 8000/QALY gained. The strategy of using a telephone call and a home visit by a healthcare professional compared to sending letters is about £ 8400/QALY gained, both of which are below the level usually considered to be affordable in the NHS. These results are sensitivive to assumptions about efficacy of letters and the use of phones plus healthcare professionals

In conclusion, the use of letters or telephone calls plus a visit from a healthcare professional to improve uptake of cardiac rehabilitation is cost effective, but the result is sensitive to efficacy of the interventions.

5.4 Education and information provision

5.4.1 Evidence statements for education and information provision

5.4.1.1	Education and stress management programmes reduce cardiac mortality and MI recurrence in post MI patients (1++).
5.4.1.2	Education/stress management programmes may aid in return to work (1+), and reduce anxiety after a 3 month recovery period following an MI (1+).
5.4.1.3	Use of the Edinburgh Heart Manual reduces anxiety and depression and increases perception of control over illness (1+).

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5.4.2 Clinical effectiveness of education and information provision

A systematic review examined the effects of psycho-educational (health education and / or stress management) programs on CAD patients (Dusseldorp, E. et al 1999). Health education was defined as institutional activities organised in a systematic way. The patients had personal contact with a healthcare professional to facilitate positive changes in risk factors for coronary heart disease. Stress management was defined as either psychotherapeutic interventions, or relaxation training, or supportive interventions. Included studies were limited to those recruiting patients within 6 months of a cardiac event and a cardiac event was defined as MI, CABG, PCI, or some combination of these. Studies were only included if they had a controlled or comparison condition. The authors noted that most of the primary studies inadequately described the effective mechanisms or components of the cardiac rehabilitation programmes. For example, some programmes were so vaguely described that the boundary between health education and information provision was not clear (Dusseldorp, E., Van, Elderen T., Maes, S. et al 1999).

Thirty-seven studies in patients with coronary heart disease were included. The proximal outcomes (such as systolic blood pressure, cholesterol, body weight,

smoking behaviour, physical exercise and emotional distress) were coded on whether they were a targeted outcome of the intervention. The distal outcomes (such as cardiac mortality and recurrence of MI) were coded on whether the study had achieved the proximal intervention target(s). If a health education study did not explicitly formulate the proximal targets, risk factors were considered proximal targets. For a stress management study, measures of emotional distress (anxiety and depression) were considered proximal target interventions (Dusseldorp, E., Van, Elderen T., Maes, S. et al 1999).

For cardiac mortality, the follow up time of studies ranged from 6 months to 10 years. Studies were analysed using a population size effect model dependent upon the length of the trial. A short-term study was defined as less than 1 year, medium term as from 1 year to 2 years and long term as longer than 2 years. The estimate of the population size effect was significant for the long-term studies (6 studies in total) and the odds of surviving were 1.52 times higher for the treatment group (34% reduction in cardiac mortality) than for the control group. Short (3 studies) and medium-term studies (8 studies) did not show a benefit of the psychoeducational interventions compared with no intervention (Dusseldorp, E., Van, Elderen T., Maes, S. et al 1999).

For reinfarction, the follow up time of included studies ranged from 1 year to 10 years. The population size effect was significant in the medium (15 studies) and long-term studies (7 studies), but not in the short term (3 studies) for the intervention groups compared to the control groups. There was a 20% (total term), 26% (medium term) and 29% (long term) reduction in recurrence of MI. Psycho-education intervention did not have a benefit in the rate of CABG in any duration of studies (Dusseldorp, E., Van, Elderen T., Maes, S. et al 1999).

For depression and anxiety, no significant favourable results were found. The authors noted that the majority of patients may cope with their recovery in a functional way, and do not require intense or extended stress management. They suggested that for the minority of patients that do not cope in a functional way, more intense clinical management may be necessary. It was also possible that study recruitment had selected less vulnerable groups of patients (Dusseldorp, E., Van, Elderen T., Maes, S. et al 1999).

A randomised controlled trial recruited 56 patients with a prior MI to either an intervention designed to alter their perceptions about their MI, or to usual care from rehabilitation nurses (Petrie, K. J. et al 2002). There were 3 intervention sessions aimed at addressing the following: the pathophysiology of MI, patient's beliefs, misconceptions, developing a plan to minimise future events, advice on exercise, diet and return to work, writing and reviewing a plan for self-management, symptom management, side effects of drugs, reinforcing the need to take medication regularly. The outcome measures were illness perception and return to work. Each session lasted 30-40 minutes and was conducted by a psychologist during the hospital stay. At 3 months, there was a significant success in changing patient's belief to a more positive and controllable view of MI compared to control patients. Controlling for confounding factors, and applying a binary logistic regression, the intervention group had a shorter delay in return to work compared with the control and the estimated rate of returning to work for the control group was 0.45 times the rate of returning to work for the intervention group (Petrie, K. J., Cameron, L. D., Ellis, C. J. et al 2002).

A second randomised controlled trial that has previously been described in the section on individualised comprehensive rehabilitation (Section 5.2.3.2) compared an individualised education intervention (information sheets on return to activities of daily living and secondary prevention and a relaxation tape) with usual care (Mayou, R. A., Thompson, D. R., Clements, A. et al 2002). The study recruited patients with a prior MI aged less than 70 years of age. Fifty six-hospitalised patients were given information sheets on return to activities of daily living, secondary prevention and a relaxation tape. Following discharge, patients were telephoned to review goals and to discuss any problems. Another fifty six patients received usual care. The outcome measures were the Hospital Anxiety and Depression Scale and on the Dartmouth COOP scale for health-related quality of life. For the primary outcome (Dartmouth COOP scale) for health related quality of life, after 3 months the intervention group significantly improved compared with the control group (59% versus 33% respectively: OR 0.34, 95% CI 0.16 to 0.73). There was also significant improvement in the Hospital Anxiety and Depression Scale score in the intervention group compared with the control group; median score 5 (2.75 to 8.25) versus 8 (5 to 12), respectively (P = 0.002). At 12 months there was little further improvement in the intervention group, but the Dartmouth COOP and Hospital Anxiety and Depression

Scale scores improved in the control group, such that there was no significant difference between the control and intervention groups (Mayou, R. A., Thompson, D. R., Clements, A. et al 2002).

5.4.2.1 Edinburgh Heart Manual

The Edinburgh Heart Manual is a self-help rehabilitation programme incorporating education, exercise and stress management components, with follow ups at 1, 3 and 6 weeks post MI by a trained facilitator. A randomised controlled trial in 176 patients with a prior MI compared a home-based care programme using the Edinburgh Heart Manual with standard care (Lewin, B., Robertson, I. H., Cay, E. L. et al 1992). Outcomes were measured at 6 weeks, 6 months and 1 year using both the General Health Questionnaire and the Hospital Anxiety and Depression Scale. Analysis showed a significant effect of treatment between groups across time for anxiety ($P < 0.04$) and caseness ($P < 0.01$) but not for depression ($P = 0.11$). Further analysis was done on a subset of 'distressed' post MI patients (in both study groups) who where identified before discharge using the Hospital Anxiety and Depression Scale. The controls were significantly more anxious and depressed at all follow up periods compared with the intervention group. Analysis of variance showed a significant effect of treatment between groups across time for anxiety ($P < 0.001$), caseness ($P < 0.002$) and for depression ($P < 0.03$). In addition, the intervention group made fewer visits to their GP at both 6 months ($P < 0.0001$) and at 12 months ($P < 0.05$) (Lewin, B., Robertson, I. H., Cay, E. L. et al 1992).

A second randomised controlled trial compared the relative efficacy of two different rehabilitation programmes, one with and one without the Edinburgh Heart Manual (O'Rourke, A and Hampson, S. E. 1999). They examined psychosocial outcomes following a first MI. Patients at hospital 1 received the Edinburgh Heart Manual within 48 hours of the acute event. A trained facilitator monitored progress and provided encouragement and reassurance (where appropriate) at 1, 3 and 6 weeks post MI. Patients at hospital 2 did not receive the Edinburgh Heart Manual, nor the follow up. Two months after the MI, all the patients (in both groups) were offered a place in a hospital-based exercise and education programme. They met twice weekly for eight weeks. The content of the outpatient programmes were similar for both patient groups (O'Rourke, A and Hampson, S. E. 1999).

The effects of group (hospital 1 versus hospital 2) and time (baseline versus 6 month follow up) were evaluated for each of the psychosocial variables. There was a significant interaction between group and time for perceptions of control over the illness ($F(1,45) = 4.14$, $P < 0.05$, effect size 0.08) and depression ($F(1,53) = 6.55$, $P < 0.01$, effect size 0.11). Thus, controlling for baseline differences, patients in hospital 1 had significantly higher perceptions of control over their illness and lower levels of depression compared with patients in hospital 2 (O'Rourke, A and Hampson, S. E. 1999).

Analysis restricted to patients with clinically significant levels of both anxiety and depression at baseline showed that there were significant reductions for patients in hospital 1 over 6 months (anxiety: $P < 0.002$, depression $P < 0.006$). For patients in hospital 2, there were too few cases of depression or anxiety at baseline to warrant further analysis. No significant differences were found between groups for either hospital admissions or GP contact (O'Rourke, A and Hampson, S. E. 1999).

5.4.2.2 Return to work

No studies were identified which examined the impact of specific advice on return to work in patients after MI.

5.4.2.3 Activities of daily living

No studies were identified from searching the literature on advice and return to activities of daily living.

5.4.2.4 Driving

The Driver and Vehicle Licensing Authority makes recommendations about driving by patients after MI. Healthcare professionals should be up to date with these recommendations, referring to the website as necessary (www.dvla.gov.uk/) and providing patients with accurate information and advice.

5.4.2.5 Travel/flying

The Aerospace Medical Association, Medical Guidelines Task Force (2003, Alexandria, Virginia) recommends that patients with recent uncomplicated MI should

not fly until at least 2 to 3 weeks have passed, and they are back to usual daily activities. It is noted that some airlines allow travel earlier. The Taskforce on Practice Guidelines of the American College of Cardiology / American Heart Association recommend that post MI patients should undergo a symptom-limited treadmill test at 10-14 days for prognosis and functional capacity. The data obtained by stress testing prior to flight is invaluable in estimating the patient's ability to tolerate air travel. The absence of residual ischaemia or symptoms on maximal testing is reassuring and probably more helpful than arbitrary time restrictions (Aerospace Medical Association Medical Guidelines Taskforce 2005). Patients with complicated MIs or with limited ambulation should wait longer, or at least until they are medically stable on their treatment regimen. Patients with an MI in the past should not have a problem with air travel, unless there is significant angina or left ventricular dysfunction when individual assessment may be required (Aerospace Medical Association Medical Guidelines Taskforce 2005).

5.4.2.6 Sports (competitive)

The only paper found on competitive sports and CAD was a consensus document from the 36th Bethesda Conference on Eligibility for Competitive Athletes with Cardiovascular Abnormalities (Pelliccia, A. et al 2005). It recommends classifying athletes with CAD based on two levels of risk defined on the basis of testing (LV function and maximal treadmill exercise test). Two levels of risk were identified; mildly increased risk (preserved LV systolic function at rest, EF > 50%), normal exercise tolerance for age, absence of exercise-induced ischaemia and exercise-induced or post-exercise complex ventricular arrhythmias, absence of stenosis), and substantially increased risk (any of the following: impaired LV systolic function at rest, EF < 50%, exercise-induced myocardial ischaemia, complex ventricular arrhythmias, haemodynamically significant stenosis of a major coronary artery.

The following recommendations were made (Pelliccia, A., Fagard, R., Bjornstad, H. H. et al 2005):

1. Athletes in the mildly increased risk group can participate in low dynamic and low/moderate static competitive sports, but should avoid intensely competitive situations.

2. Athletes in the substantially increased risk category should generally be restricted to low-intensity competitive sports.

3. Athletes should be informed of the nature of prodromal symptoms (such as chest, arm, jaw and shoulder discomfort, unusual dyspnoea) and should be instructed to cease their sports activity promptly and to contact their physician if symptoms appear.

4. Those with a recent MI should cease their athletic training and competition until recovery is deemed complete. This interval depends on the severity of the cardiovascular event. After the recuperation period, the risk and activity level should be defined as in recommendations 1 and 2.

5.5 Psychological and social support

5.5.1 Evidence statements for psychological and social support

5.5.1.1	Psychological intervention in patients with coronary heart disease, including patients after MI, reduces the risk of depression, anxiety and non-fatal MI. Psychological intervention does not affect total mortality or cardiac mortality (1++).
5.5.1.2	There is limited evidence (based on three studies of married couples) that involving spouses may have beneficial effects on family anxiety (1++).

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5.5.2 Clinical effectiveness of psychological support

A systematic review on psychological intervention for coronary heart disease (CHD) identified randomised controlled trials of non-pharmacological psychological interventions (Rees, K. et al 2004). The interventions were administered by trained staff, either as a single modality intervention or as part of comprehensive cardiac rehabilitation programme. Randomised controlled trials had to have a minimum follow up of 6 months. Patients were adults of all ages with CHD (prior MI, CABG or PCI, angina pectoris or CAD defined by angiography). Trials were only considered where the comparison group was usual care (Rees, K., Bennett, P., West, R. et al 2004).

Stress management trials were identified and reported in combination with other psychological interventions and separately. Stress management was defined as the use of specific cognitive techniques, such as self-instruction training, and cognitive challenge, and/or consideration of specific coping strategies to be used at times of stress. Less specific therapeutic approaches including counselling, psychodynamic and educational interventions were excluded from this definition, as were self-management techniques used to change risk factors such as smoking and low levels

of exercise and that were not specifically targeted at stress reduction. The cognitive behavioural treatment of other aversive mood states including anger and depression were also excluded (Rees, K., Bennett, P., West, R. et al 2004).

Thirty six trials with 12 841 patients were included. Of these, 18 studies (5242 patients) were stress management trials. The authors noted that the quality of many trials was poor with the majority not reporting adequate concealment of allocation, and only 6 blinded outcome assessors (Rees, K., Bennett, P., West, R. et al 2004).

For the combined studies of psychological interventions and stress management, meta analysis of 22 trials (10 634 patients) showed no effect on total mortality (OR 0.93, 95% CI 0.81 to 1.06). Cardiac mortality was reported in 11 trials (7544 patients) where similarly there was no strong evidence of a reduction in the intervention group compared with the control group (OR 0.86, 95% CI 0.72 to 1.03). There was a statistically significant 22% reduction in non-fatal myocardial infarction in the intervention group in the 18 trials (10 200 patients) reporting this outcome (OR 0.78, 95% CI 0.67 to 0.90). The authors noted that there was significant heterogeneity of effects for some of these clinical outcomes, and there was evidence of publication bias for the non-fatal myocardial infarction findings. In addition, the evidence was dominated by two large trials (Berkman, L. F. and Blumenthal, J. 2003) (Jones, D. A. and West, R. R. 1996), both of which produced null findings for all clinical outcomes (Rees, K., Bennett, P., West, R. et al 2004).

Psychological outcomes were anxiety and depression. Anxiety was measured in only 9 trials (2756 patients) overall, using a number of different measures. Pooled results are presented as standardised mean differences to take account of the number of different scales used. A small but statistically significant reduction in anxiety with the intervention was seen, where the SMD was -0.08 (-0.16, -0.01). Depression was measured in 11 trials overall (4535 patients), again using a number of different measures. There was significant heterogeneity between trials. Across all trials there was a significant reduction in depression (SMD -0.3 (-0.48, -0.13)). Several studies reported composite measures for anxiety, depression and mental health, and these were analysed separately. For these 5 trials (347 patients) there was a beneficial reduction (SMD -0.22 (-0.44, -0.01) (Rees, K., Bennett, P., West, R. et al 2004).

Eighteen trials were identified that included some form of stress management. Results were presented on 18 trials with a stress management component versus usual care or other rehabilitation. There was no strong evidence of effect of stress management on total mortality in the 10 trials (3425 patients) reporting this as an outcome (OR 0.88, 95% CI 0.67 to 1.15). Cardiac mortality was reported in 4 trials where weak evidence of a reduction in the number of deaths was seen in the intervention group (OR 0.62, 95% CI 0.38 to 0.99), and of a 31% reduction in non-fatal myocardial infarction in the intervention group in the 8 trials (3990 patients) reporting this outcome (OR 0.69, 95% CI 0.52 to 0.92). One of these 8 trials recruited patients with identified levels of psychopathology prior to randomisation (Stern, M. J., Gorman, P. A., and Kaslow, L. 1983). Only one of these 8 trials examined the effects of a stress management intervention without the influence of other rehabilitation interventions (Jones, D. A. and West, R. R. 1996).

For anxiety, there was only weak evidence of a small decrease in anxiety with the intervention (SMD -0.07 (-0.15, 0.01)). For depression, there was evidence of a reduction in depression scores in the intervention group (SMD -0.32 (-0.56, -0.08)). Results are dominated by one large trial (Jones, D. A. and West, R. R. 1996) which showed a null effect, and hence there was significant heterogeneity between studies. Several studies reported composite measures for anxiety, depression and mental health. For the 5 trials overall (347 patients), there was evidence of a reduction (SMD -0.22 (-0.44, -0.01)) (Rees, K., Bennett, P., West, R. et al 2004).

The randomised controlled trials identified in the systematic review (Rees, K., Bennett, P., West, R. et al 2004) were extremely heterogenous both in terms of the interventions offered (type and intensity), and also in the effect size of some of the outcomes. The guideline development group recognised that stress management should be included in comprehensive cardiac rehabilitation programmes. The benefit of complex psychological interventions is uncertain.

5.5.3 Clinical effectiveness of social support

A systematic overview examined social support and its relationship to morbidity and mortality after acute MI (Mookadam, F. and Arthur, H. M. 2004). Social isolation or lack of a social support network was found to be associated with increased mortality

and morbidity (OR 2.0 and 3.0, respectively). This excess morbidity and mortality was independent of known predictors of cardiac mortality in the short term (≤ 6 months) and long term (≤ 6 years) post MI periods (Mookadam, F. and Arthur, H. M. 2004).

A systematic review identified interventions designed to promote family function during the recovery phase of a cardiac event (Van Horn, E., Fleury, J., and Moore, S. 2002). A total of 7 family intervention studies were found. The majority of studies were conducted with family members of patients in the coronary care unit. Subjects were primarily wives or female family members of patients. Types of intervention included educationally oriented discussion, physical conditioning and home visits or telephone calls made by registered nurses. Two studies (Dracup, K. et al 1984) (Buls, P. 1995) found that family intervention decreased anxiety in the spouse. One study found that anxiety was also decreased in the patient (Buls, P. 1995). One study showed that wives perception of the husbands' cardiac efficacy improved when the wives' observed the husbands' treadmill test and also utilised it themselves (Taylor, C. B. et al 1985). Two studies found no positive effect of family intervention on the Adaptation, Partnership, Growth, Affection, and Resolve Family Scale (Gortner, S. R. et al 1988), (Gilliss, C. L., Neuhaus, J. M., and Hauck, W. W. 1990). A study measuring the effect of family intervention with a social network and social support scale showed no effect of family intervention (Fridlund, B. et al 1991).

A study training spouses on cardio-pulmonary resuscitation found that perceived control on the Family Control Attitudes Scale increased significantly (Gilliss, C. L., Neuhaus, J. M., and Hauck, W. W. 1990).

5.6 Sexual Activity

5.6.1 Evidence statements for sexual function

5.6.1.1	The MET (metabolic equivalent of energy expenditure) of sexual activity is between 2 and 6 METs.
5.6.1.2	A study of myocardial infarction survivors found that the risk of sexual activity triggering the onset of a further MI is not significantly greater in stable patients with a history of prior MI compared to those without a history of MI (3).
5.6.1.3	There was no evidence found on the risk of sexual activity resulting in sudden death.

5.6.2 Evidence statements for sexual education

5.6.2.1	In male patients after MI with erectile dysfunction, treatment with sildenafil inhibitors improves erectile dysfunction (1+).
5.6.2.2	There is no added risk in using PDE5 inhibitors for post MI patients compared with the general population (1+).
5.6.2.3	Sildenafil, used correctly, does not increase overall cardiovascular risk in patients after an MI (1+).
5.6.2.4	The trials of PDE5 inhibitors to treat erectile dysfunction which included patients after MI excluded those treated with nitrates (1+).

Back to recommendations

5.6.3 Clinical effectiveness and sexual function

Erectile dysfunction is the persistent inability to obtain and/or maintain an erection satisfactory for sexual activity. After an MI this may occur for a number of reasons.

The primary organic cause is an impairment of the haemodynamic mechanisms in the penile and ischaemic vasculature, but there may also be a psychogenic component due to fear of precipitating an MI and certain drugs (for example beta blockers, thiazide diuretics and centrally acting anti-hypertensive agents) used to treat cardiac disease have been linked to erectile dysfunction. Depression and anxiety may also occur in patients after MI and cause or contribute to erectile dysfunction.

Two studies were identified specifically on the incidence of erectile dysfunction in men after MI. The first found that 30% of patients cited erectile difficulties for their changes in sexual activity following an MI (Mehta, Jawahar 1979). The mean age of the patients was 59 years (range 42-69 years), and the patients were surveyed six months after hospital discharge. The second found that erectile dysfunction occurred in 32% of men who had previously did not experience erectile dysfunction (Filipiak, K. J. et al 2002). The survey was conducted 5-7 months after MI, on men aged below 59 years (mean age 52 years).

5.6.4 Clinical effectiveness and sexual activity

When comparing sexual activity with other forms of activity, the most commonly used clinical measure is the metabolic equivalent of energy expenditure (MET) (1 MET = ≈ 3.5 mL O_2/kg per minute). Sexual activity is relatively low on this scale as outlined in the Table 2 (Bohlen, J. G. et al 1984).

Table 2

Metabolic equivalent of energy expenditure for varying levels of activity

Activity	Metabolic equivalent of energy expenditure (MET) (1 MET ≈ 3.5 mL O_2/kg per minute)
Sitting quietly in chair	1
Walking at ground level	2

Walking at 3 mph	3
Sexual activity pre-orgasm	2-3
Sexual activity during orgasm	3-4
Vigorous sexual activity	5-6
Cycling at 10 mph	6-7
Walking to stage 4 of a Bruce protocol on the treadmill	13

The Onset study (Muller, J. E. et al 1996) examined the relative risks of non-fatal MI triggered by sexual activity among the general population and in patients with prior coronary heart disease. A total of 1774 hospitalised MI patients were interviewed. Of these, 858 reported that they were sexually active in the year preceding the MI (48%). There were 643 MI patients with a prior history of MI or angina. Of these, 273 were sexually active (42%). For patients with no prior history of coronary heart disease (angina or previous MI), there was a 2.5 fold relative risk (95% CI 1.7 to 3.7) of an MI occurring in the 2 hours after sexual activity compared to 3 and 4 hours after sexual activity. The relative risk of triggering onset of MI among patients with a history of previous angina (2.1, 95% CI 0.8 to 5.8) or those with a history of previous MI (2.9, 95% CI 1.3 to 6.5) was not greater than that observed in those without prior coronary heart disease (Muller, J. E., Mittleman, A., Maclure, M. et al 1996).

There were too few women who reported sexual activity in the hazard period preceding MI to determine if the relative risk varied by sex. It should be noted that the data may be biased in that there are a lack of data for the possibility that sexual activity might be more likely to cause sudden death than non-fatal MI. However, the authors noted that the baseline risk of sudden death is much lower than the baseline risk of non-fatal MI (Muller, J. E., Mittleman, A., Maclure, M. et al 1996).

A narrative review stated that the risk of MI occurring in a healthy 50-year-old man is estimated at 1% per year, or about 1 chance in a million per hour (based on

Framingham data) (Cheitlin, M. D. 2006). Sexual activity multiplies the relative risk of an MI by 2 to 3, increasing the hourly risk to 2 to 3 chances in a million, and only for a 2 hour period. For a man with a previous MI, the annual risk of reinfarction or death is estimated to be 10%, or as low as 3% if he has good exercise tolerance (Moss, A. J. and Benhorin, J. 1990). Sexual activity in patients with a 10% annual risk transiently increases the risk from 10 chances in a million per hour to 20 to 30 chances in a million per hour (Stein, R. A. 1977).

5.6.5 Clinical effectiveness of PDE5 inhibitors

PDE5 inhibitors such as sildenafil prolong smooth muscle and arterial, arteriolar and venous relaxation, and cause a decrease in peripheral vascular resistance. Hence they work as mild vasodilators. The major danger recognised with use of sildenafil is the marked decrease in arterial blood pressure that can result from its interaction with organic nitrates. In patients with severely obstructed vessels, myocardial blood flow is dependent on perfusion pressure, and a steep decrease in blood pressure could result in severe ischaemia and an MI.

Three studies were identified on the use of sildenafil and the treatment of erectile dysfunction in men with cardiovascular disease where the patient population included at least > 10% post MI patients.

A retrospective sub-group analysis of data from randomised controlled trials assessed the efficacy (9 studies) and safety (11 studies) of sildenafil in patients with erectile dysfunction and ischaemic heart disease who were not taking nitrates (Conti, C. R., Pepine, C. J., and Sweeney, M. 1999). Efficacy was assessed by using end of treatment responses on questions concerning ability to achieve an erection, ability to sustain an erection and scoring on the 5 domains of sexual function of the International Index of Erectile function questionnaire. Patients enrolled were randomised to sildenafil (5-200 mg) or placebo for 4 weeks to 6 months. Ischaemic heart disease was defined as acute MI**,** another acute or sub-acute form of ischaemic heart disease, old (> 8 weeks) MI or angina pectoris. The mean end of treatment scores for achieving an erection and maintaining an erection were

significantly higher in the sildenafil group than for the placebo group ($P < 0.0001$). On the 5 sexual function domains, scoring was significantly higher in the treatment group than the placebo group ($P < 0.0001$). At the end of treatment, improved erections were reported by 70% of patients with ischaemic heart disease who received sildenafil and by 20% of those in the placebo group (OR 10.3, 95% CI 5.6 to 19.1, $P < 0.0001$ for treatment effect). In the 11 randomised controlled trials that examined safety, the incidences of the common adverse events of all-causes (such as headache, flushing and dyspepsia) for the sildenafil group were comparable for those with and without ischaemic heart disease. For the treatment group, the overall incidence of cardiovascular adverse events other than flushing in those with ischaemic heart disease was 5% (13 of 237 patients), compared with 3% (66 of 2103 patients) for those without ischaemic heart disease. The corresponding incidences for the placebo groups were 8% and 4%, respectively. Serious cardiovascular adverse events occurred in 17 patients (7%) with ischaemic heart disease who received sildenafil. For the placebo group, there were 12 patients (10%) who had a serious cardiovascular adverse event. The incidences of the serious cardiovascular events were MI (sildenafil: 8 patients (3%), placebo: 3 patients (3%)) and unstable angina (sildenafil: 5 patients (2%), placebo: 2 patients (2%)) (Conti, C. R., Pepine, C. J., and Sweeney, M. 1999).

In a second study, a randomised controlled trial was conducted in 21 urology departments in Sweden, recruiting patients with a clinical diagnosis of stable cardiovascular disease who were treated with beta blockers and / or ACE inhibitors, and / or calcium channel blockers (Olsson, A. M., Persson, C. A., and Swedish, SildenafilInvestigatorsGroup 2001). After a 4 week run-in period, patients received sildenafil (50 mg) or placebo. Treatment continued for 12 weeks, during which time the dose of sildenafil or placebo could be increased to 100 mg for those patients with insufficient efficacy or decreased (25 mg) for those patients with significant side effects. Twenty percent of the placebo group and 18% of the sildenafil group respectively had had a prior MI. Patients had to have had an MI within the previous 6 months. The outcome was the ability to achieve and maintain an erection. At the end of the 12-week treatment period, the mean scores for achieving an erection and maintaining an erection were significantly higher in the sildenafil group compared

with the placebo group ($P < 0.0001$). Similarly, the end of treatment responses to a global efficacy question found that the intervention group reported improved erections compared with the placebo group ($P < 0.0001$). The rates of cessation of treatment were similar for the two groups (sildenafil: 7%, placebo: 9%). Four percent and 3% of the sildenafil and placebo groups, respectively, stopped treatment because of insufficient clinical response. Only one patient was withdrawn for an adverse event, and this patient was in the placebo group. The most frequent adverse events were flushing, headache and dyspepsia (sildenafil: 17%, 5%, and 2%, respectively, placebo: 2%, 1%, 0%, respectively). Besides flushing, no treatment-related cardiovascular event was reported, and sildenafil did not produce any changes in blood pressure compared with either placebo or baseline values.

A third study was a randomised controlled trial of the efficacy and safety of sildenafil in patients with clinically stable CAD and erectile dysfunction (DeBusk, R. F. et al 2004). Of these, 65% of the patients in the placebo group were over 8 weeks post MI as were 50% of the patients in the sildenafil group. The study follow up was for 12 weeks. Patients taking nitrates, with uncontrolled hypertension, with unstable angina, with hypotension or at high cardiac risk were excluded. After 12 weeks of treatment, the mean end of treatment scores for achieving an erection and maintaining an erection were significantly higher in the sildenafil group than for the placebo group ($P < 0.01$). Larger percentages of sildenafil-treated patients reported improved erections (64%) and improved intercourse (65%) compared with placebo-treated patients (21% and 19%, respectively). During treatment, 47% of sildenafil- and 32% of placebo-treated patients experienced adverse events. Headache was reported in 8% in the sildenafil group, and 1% in the placebo group. In the sildenafil group chest pain, flushing, nasal congestion and abnormal vision occurred in 1%, 7%, 2% and 1% respectively. None of these adverse events were deemed to be treatment related in the placebo group (DeBusk, R. F., Pepine, C. J., Glasser, D. B. et al 2004).

5.6.6 Counselling

No studies were identified that specifically evaluated sexual counselling in patients with a prior MI.

Audit table for cardiac rehabilitation: patient engagement and equity of uptake

Recommendation	Criterion	Exception	Definitions
Social support, patient engagement and equity of access			
1. All patients after an acute MI, should be offered cardiac rehabilitation. .	The existence of a database able to identify those individuals eligible for cardiac rehabilitation over an agreed time period and from an agreed population base. Record of the reasons why patients are deemed to be ineligible for cardiac rehabilitation. The proportion of eligible patients offered Cardiac rehabilitation. The proportion of eligible patients who initiate attendance at a formal cardiac rehabilitation programme. The proportion of eligible patients who complete their formal programme. Record of eligible patients not completing rehabilitation programmes, including reasons why and patient satisfaction measurement: evidence of attempts to contact defaulters.	Patients who specifically and actively decline any subsequent involvement in formal cardiac rehabilitation. Patients who, for medical reasons are thought not appropriate for components of formal cardiac rehabilitation programmes (such as exercise components) should not be denied other beneficial aspects of the programme.	Formal cardiac rehabilitation to include agreed hospital and/or community programmes accessible to the patient. This includes phases 1-4 and programmes which are menu-driven where only individual aspects are accessed (by patient choice in consultation with a health professional). Completion of a programme based on agreed achievement of individual goals.
2. Cardiac rehabilitation should be equally accessible and relevant to all patients following an MI, explicitly including those groups less likely to access cardiac rehabilitation. These include black and diverse minorities, older people, those from lower socio-economic groups, women, those from rural communities, and those with mental and physical health comorbidities.	The proportion of records recording Age Gender Postcode Ethnic origin Language. The proportion of patients taking up cardiac rehabilitation from each of the group listed in column 1. All patients whose first language is not English are offered language support where they feel it is needed.	Uptake (initiation) target should be 85% (overall and for any sub-group) (National Service Framework for coronary heart disease target)	UK census definitions of ethnic origin. Full seven digit postcodes. Availability of translators or use of bilingual support workers. Provision of specific health education materials or advice which may be either written, audio or oral which provides

	Patients from diverse minority groups receive advice and interventions that are culturally and linguistically appropriate.		appropriate language support and is culturally specific.
3. All healthcare professionals involved in providing care for patients following an MI should actively promote cardiac rehabilitation	All patients discharged from hospital eligible for cardiac rehabilitation have received written information encouraging and informing them of local cardiac rehabilitation provision. Patients from diverse minority groups should receive advice on local cardiac rehabilitation services that is linguistically appropriate.	None	All patients whose first language is not English are offered language support. Promotion of cardiac rehabilitation services may be either written, audio or where language support is required.
4. There should be provision to involve partners/carers in the aftercare of patients, where this is in accordance with the patient's wishes.	Database to identify partners/carers. Proportion of partners/carers involved in rehabilitation process.	Patients with no direct carer or partner. Patients who decline such involvement.	

6 Drug Therapy

6.1 Recommendations for Drug Therapy

6.1.1 Overall drug therapy recommendation

6.1.1.1	All patients who have had an acute MI should be offered treatment with a combination of the following drugs (Grade A): • ACE (angiotensin-converting enzyme) inhibitor • aspirin • beta-blocker • statin.

6.1.2 ACE inhibitors recommendations

Hyperlink to the related evidence statements

6.1.2.1	Early after presenting with an acute MI, all patients should be offered an ACE inhibitor (Grade A).
6.1.2.2	ACE inhibitor therapy should be initiated at the appropriate dose, and titrated upwards at short intervals (for example every 1 to 2 weeks) until the maximum tolerated or target dose is reached (GPP).
6.1.2.3	Assessment of left ventricular function is recommended in all patients who have had an MI (GPP).
6.1.2.4	After an MI, all patients with preserved left ventricular function or with left ventricular systolic dysfunction should continue treatment with an ACE inhibitor indefinitely, whether or not they have symptoms of heart failure (Grade A).
6.1.2.5	Routine prescription of angiotensin receptor blockers (ARBs) after an acute MI is not recommended (GPP).
6.1.2.6	For patients after an acute MI who have had to discontinue an ACE

	inhibitor because of intolerance (for example because of cough) or allergy, an ARB should be substituted (Grade A).
6.1.2.7	Combined treatment with an ACE inhibitor and an ARB is not recommended for routine use in patients early after an acute MI with heart failure and/or left ventricular systolic dysfunction (Grade A).
6.1.2.8	In patients with a proven MI in the past (more than 1 year ago) and with heart failure and left ventricular systolic dysfunction, ACE inhibitor and ARB treatment should be in line with 'Chronic heart failure. NICE clinical guideline 5' (Grade A).
6.1.2.9	In patients with a proven MI in the past and with left ventricular systolic dysfunction, who are asymptomatic, ACE inhibitor treatment should be offered and the dose titrated upwards, as tolerated, to the effective clinical dose for patients with heart failure and left ventricular systolic dysfunction (Grade A).
6.1.2.10	In patients with a proven MI in the past without heart failure and with preserved left ventricular function, ACE inhibitor treatment should be offered and the dose titrated upwards, as tolerated, to the effective clinical dose (Grade A).
6.1.2.11	In patients with a proven MI in the past with left ventricular systolic dysfunction, who are asymptomatic and who have had to discontinue an ACE inhibitor because of intolerance (for example because of cough) or allergy, an ARB should be substituted (Grade A).
6.1.2.12	Renal function, serum electrolytes and blood pressure should be measured before starting an ACE inhibitor or ARB and again within 1 or 2 weeks of starting treatment. Patients should be monitored as appropriate as the dose is titrated upwards, until the maximum tolerated or target dose is reached, and then at least annually. More frequent monitoring may be needed in patients who are at increased risk of deterioration in renal function. Patients with chronic heart failure should be monitored in line with 'Chronic heart failure. NICE clinical

	guideline 5' (GPP).

6.1.3 Anti-platelet recommendations

Hyperlink to the related evidence statements

6.1.3.1	Aspirin should be offered to all patients after an MI, and should be continued indefinitely (Grade A).
6.1.3.2	Clopidogrel should not be offered as first-line monotherapy after an MI (Grade A).
6.1.3.3	Clopidogrel, in combination with low-dose aspirin, is recommended for use in the management of non-ST-segment-elevation acute coronary syndrome in people who are at moderate to high risk of MI or death (Grade A).[1]
6.1.3.4	People at moderate to high risk of MI or death, presenting with non-ST-segment-elevation acute coronary syndrome can be determined by clinical signs and symptoms, accompanied by one or both of the following: • the results of clinical investigations, such as new ECG changes (other than persistent ST segment elevation) indicating ongoing myocardial ischaemia, particularly dynamic or unstable patterns • the presence of raised blood levels of markers of cardiac cell damage such as troponin (Grade A).[1]
6.1.3.5	Treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of non-ST-

[1] This recommendation is from NICE technology appraisal 80 (see section 6 for details), and has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

	segment-elevation acute coronary syndrome. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended unless there are other indications to continue dual antiplatelet therapy (Grade A).[1]
6.1.3.6	After an ST-segment-elevation MI, patients treated with a combination of aspirin and clopidogrel during the first 24 hours after the MI should continue this treatment for at least 4 weeks. Thereafter, standard treatment including low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy (Grade A).
6.1.3.7	If the patient has not been treated with a combination of aspirin and clopidogrel during the acute phase of an MI, this combination should not routinely be initiated (GPP).
6.1.3.8	The combination of aspirin and clopidogrel is not recommended for routine use for any longer than 12 months after the acute phase of MI, unless there are other indications to continue dual anti-platelet therapy, and the combination is usually recommended for a shorter duration after an ST-elevation MI (Grade A).
6.1.3.9	For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment (Grade B).
6.1.3.10	In patients with a history of dyspepsia, treatment with a proton pump inhibitor and low-dose aspirin should be considered in line with 'Dyspepsia. NICE clinical guideline 17' (Grade A).
6.1.3.11	After appropriate treatment, patients with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for *Helicobacter pylori* should be considered for treatment with a full-dose proton pump inhibitor and low-dose aspirin. Refer to 'Dyspepsia. NICE clinical guideline 17' (Grade A).

6.1.4 Beta blockers recommendations

Hyperlink to the related evidence statements

6.1.4.1	Early after an acute MI, all patients without left ventricular systolic dysfunction or with left ventricular systolic dysfunction (symptomatic or asymptomatic) should be offered treatment with a beta-blocker (Grade A).
6.1.4.2	For patients after an MI with left ventricular systolic dysfunction, who are being offered treatment with a beta-blocker, clinicians may prefer to consider treatment with a beta-blocker licensed for use in heart failure (Grade B).
6.1.4.3	Beta-blockers should be continued indefinitely after an acute MI (GPP).
6.1.4.4	After a proven MI in the past, all patients with left ventricular systolic dysfunction should be offered treatment with a beta-blocker whether or not they have symptoms, and those with heart failure plus left ventricular systolic dysfunction should be managed in line with 'Chronic heart failure. NICE clinical guideline 5' (Grade A).
6.1.4.5	After a proven MI in the past, patients with preserved left ventricular function who are asymptomatic should not be routinely offered treatment with a beta-blocker, unless they are identified to be at increased risk of further CVD events, or there are other compelling indications for beta-blocker treatment (GPP).
6.1.4.6	Beta-blockers should be initiated as soon as possible when the patient is clinically stable and titrated upwards to the maximum tolerated dose (GPP).

6.1.5 Vitamin K antagonists recommendations

Hyperlink to the related evidence statements

6.1.5.1	For patients who have had an MI, high-intensity warfarin (INR >3) should

	not be considered as an alternative to aspirin in first-line treatment (Grade A).
6.1.5.2	For patients who have had an MI and are unable to tolerate either aspirin or clopidogrel, treatment with moderate-intensity warfarin (INR 2–3) should be considered for up to 4 years, and possibly longer (Grade A).
6.1.5.3	For patients who have had an acute MI, are intolerant to clopidogrel and have a low risk of bleeding, treatment with aspirin and moderate-intensity warfarin (INR 2–3) combined should be considered (GPP).
6.1.5.4	For patients already being treated for another indication (mechanical valve, recurrent deep vein thrombosis, atrial fibrillation, left ventricular thrombus), warfarin should be continued. For patients treated with moderate-intensity warfarin (INR 2–3) and who are at low risk of bleeding, the addition of aspirin should be considered (Grade B).
6.1.5.5	The combination of warfarin and clopidogrel is not routinely recommended (GPP).

6.1.6 Calcium channel blockers recommendations

Hyperlink to related evidence statements

6.1.6.1	Calcium channel blockers should not routinely be used to reduce cardiovascular risk after an MI (Grade A).
6.1.6.2	If beta-blockers are contraindicated or need to be discontinued, diltiazem

	or verapamil may be considered for secondary prevention in patients without pulmonary congestion or left ventricular systolic dysfunction. (Grade B).
6.1.6.3	For patients who are stable after an MI, calcium channel blockers may be used to treat hypertension and/or angina. For patients with heart failure, amlodipine should be used, and verapamil, diltiazem and short-acting dihydropyridine agents should be avoided in line with 'Chronic heart failure. NICE clinical guideline 5' (Grade A).

6.1.7 Potassium channel activators recommendations

Hyperlink to the related evidence statements

6.1.7.1	Nicorandil is not recommended to reduce cardiovascular risk in patients after an MI (Grade A).

6.1.8 Aldosterone antagonists in patients with heart failure and LV dysfunction recommendations

Hyperlink to related evidence statements

6.1.8.1	For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment should be initiated within 3–14 days of the MI, preferably after ACE inhibitor therapy

[2] These drugs do not have UK marketing authorisation for this indication at the time of publication (March 2007) and specialist advice should be sought. Prescribers should check each drug's Summary of product characteristics for current licensed indications

	(Grade B).
6.1.8.2	Patients who have recently had an acute MI and have clinical heart failure and left ventricular systolic dysfunction, but who are already being treated with an aldosterone antagonist for a concomitant condition (for example, chronic heart failure), should continue with the aldosterone antagonist or an alternative, licensed for early post-MI treatment (GPP).
6.1.8.3	For patients who have had a proven MI in the past and heart failure due to left ventricular systolic dysfunction, treatment with an aldosterone antagonist should be in line with 'Chronic heart failure. NICE clinical guideline 5' (GPP).
6.1.8.4	Renal function and serum potassium should be monitored before and during treatment with an aldosterone antagonist. If hyperkalaemia is a problem, the dose of the aldosterone antagonist should be halved or the drug stopped (GPP).

6.1.9 Statins and other lipid lowering agents recommendations

Hyperlink to related evidence statements

6.1.9.1	Statin therapy is recommended for adults with clinical evidence of cardiovascular disease in line with 'Statins for the prevention of cardiovascular events' (NICE technology appraisal guidance 94).[3]
6.1.9.2	After an MI, all patients should be offered treatment with a statin as soon as possible (GPP).
6.1.9.3	The decision whether to initiate statin therapy should be made after an

3 The NICE clinical guideline 'Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' is in development and is expected to be published in January 2008. 3 The NICE clinical guideline 'Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' is in development and is expected to be published in December 2008.

	informed discussion between the healthcare professional and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidities and life expectancy (GPP).
6.1.9.4	Baseline liver enzymes should be measured before initiation of a statin (GPP).
6.1.9.5	Patients who have raised liver enzymes should not routinely be excluded from statin therapy (GPP).
6.1.9.6	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) (Grade A).
6.1.9.7	Patients who are intolerant of statins should be considered for other lipid lowering agents (GPP).
6.1.9.8	Routine monitoring of creatine kinase in asymptomatic patients who are being treated with a statin after an MI is not recommended (Grade A).
6.1.9.9	Patients who are being treated with a statin and who develop muscle symptoms (pain, tenderness or weakness) should be advised to seek medical advice so that creatine kinase can be measured (Grade A).
6.1.9.10	The dose of any statin may need to be reduced or stopped if there are issues surrounding the metabolic pathway, food and/or drug interactions and/or concomitant illness (GPP).
6.1.9.11	Statins should be discontinued in patients who develop peripheral neuropathy that may be attributable to the statin treatment, and further advice from a specialist should be sought (Grade A).

Introduction

Pharmacotherapy is an important part of the treatment which should be offered for secondary prevention after MI. This chapter reviews the evidence for each of the different agents, and makes specific recommendations on which drugs should be offered. The recommendations generally refer to drug classes, and fall within licensed indications. However, other drugs have been included if there is evidence of clinical effectiveness. Where appropriate drugs should be prescribed in doses and at a frequency shown to be effective in the clinical trials. If this is not possible, this should be to the maximum tolerated.

The majority of drugs are intended as long term therapy, and it is clearly stated if any drugs should be routinely discontinued after an interval. However, some patients may wish to review the benefits of long term treatment. This requires a careful assessment and discussion of individual tolerance and preference, balanced against the magnitude of benefit in risk reduction. The risk reducing benefit is influenced by the level of individual patient risk and in some cases referral for specialist advice may be appropriate.

It is the responsibility of the individual prescriber to review each patient for the following, referring to the British National Formulary (www.bnf.org.uk) as appropriate;

- indications
- drug doses
- contra-indications
- supervision and monitoring
- product characteristics

6.2 Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)

6.2.1 Evidence statements for ACE inhibitors and ARBs

6.2.1.1	Short term treatment with an ACE inhibitor in unselected patients immediately after an MI was associated with a small reduction in mortality (1++).
6.2.1.2	Long term treatment with an ACE inhibitor in patients with signs of heart failure and or left ventricular systolic dysfunction who have recently experienced an MI was associated with substantial reduction in all-cause mortality, recurrent MI and readmission for heart failure (1++).
6.2.1.3	In patients with chronic heart failure and left ventricular systolic dysfunction, including patients who had had an MI in the past, treatment with ACE inhibitors improved life expectancy and reduced the risk of hospitalisation for heart failure (1++).
6.2.1.4	In stable patients with coronary artery disease without heart failure or known left ventricular systolic dysfunction, long term treatment with an ACE inhibitor was associated with a modest reduction in total and cardiovascular mortality, non-fatal MI and coronary revascularisation (1++).
6.2.1.5	Long term treatment with an ACE inhibitor in patients after MI with heart failure or left ventricular systolic dysfunction, with or without heart failure is cost effective when compared to placebo.
6.2.1.6	In stable patients with coronary artery disease without heart failure or known left ventricular systolic dysfunction, long term treatment with an ACE inhibitor was cost effective.

6.2.1.7	No trials were found which looked at the effectiveness of an ARB compared with placebo in patients after acute MI.
6.2.1.8	In one small trial of patients with stable coronary artery disease, without heart failure or left ventricular systolic dysfunction, treatment with an ARB compared to placebo was associated with a reduction in the composite end point of revascularisation, non-fatal MI and cardiovascular death (1-).
6.2.1.9	In one study, although not in a second, there were fewer cardiovascular deaths in patients treated with an ACE inhibitor compared to in those treated with an ARB (1++)
6.2.1.10	There were no trials found comparing treatment with an ACE inhibitor and an ARB which included patients early after MI without heart failure or left ventricular systolic dysfunction.
6.2.1.11	There was no difference in total mortality or cardiovascular mortality and morbidity in patients with heart failure and or left ventricular systolic dysfunction treated within 10 days of acute MI with the combination of an ACE inhibitor and ARB compared to those treated with either agent alone (1++).
6.2.1.12	In patients with chronic heart failure and left ventricular systolic dysfunction, including patients who had had an MI in the past, treatment with an ARB did not improve life expectancy compared to treatment with an ACE inhibitor (1++).
6.2.1.13	A post hoc analysis showed a reduction in investigator reported hospitalisation for MI or heart failure in patients with heart failure and or LV systolic dysfunction treated within 10 days of acute MI with the combination of an ACE inhibitor and ARB compared to those treated with either agent alone (1++).
6.2.1.14	No trials were found comparing frequent with less frequent monitoring of renal function.

6.2.1.15	Patients after MI with renal dysfunction are at higher risk of adverse cardiovascular outcomes than those with normal renal function (2+).
6.2.1.16	No randomised controlled trials were found of treatment with ACE inhibitors and or ARBs in patients after acute MI with a serum creatinine > 220mmol/l or in the majority, a serum potassium of 5.6 mmol/l or more.
6.2.1.17	In patients after MI with a serum creatinine of up to 220 mmol/l, ACE Inhibitor treatment was associated with a significant reduction in cardiovascular events regardless of the baseline renal function (2+).
6.2.1.18	Treatment with an ACE inhibitor and ARB combined in patients after MI was associated with an increased risk of renal dysfunction (1++).

Back to recommendations

6.2.2 Clinical effectiveness of ACE inhibitors

6.2.2.1 Unselected patients

A meta analysis of 18 randomised controlled trials in unselected patients immediately following an acute MI found that ACE inhibitor treatment improved survival compared with placebo (OR 7%, 95% CI 2% to 11% by a fixed effects model, OR 7%, 95% CI -1% to 14% by a random effects model), (National Institute for Clinical Excellence 2001). Trial follow up ranged from 3 days to 19 months. However, the majority of patients were randomised in two large trials (ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. 1995) (Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. 1994) in which recruitment was within the first 24 hours of MI and the follow up duration was five and six weeks respectively.

6.2.2.2 Patients with left ventricular systolic dysfunction

A meta analysis of six randomised controlled trials of patients who had experienced an acute MI and who had heart failure and or left ventricular systolic dysfunction found that ACE inhibitor treatment increased survival compared with placebo (OR 26%, 95% CI 17% to 34% by a fixed effects model, OR 26%, 95% CI 14% to 38% by

a random effects model) (National Institute for Clinical Excellence 2001). The duration of follow up in the trials ranged from 2 weeks to 42 months, and all but one had at least six months follow up.

In a study of patients with anterior MI and systolic blood pressure ≥ 100 mmHg early (day 1) initiation of the ACE inhibitor ramipril compared with delayed initiation (day 14) was associated with attenuation of left ventricular remodelling and a more rapid recovery of left ventricular ejection (Pfeffer, M. A. et al 1997).

6.2.3 Clinical Effectiveness of long term ACE inhibitor therapy

Patients with preserved left ventricular function

A meta analysis of six randomised controlled trials in patients with stable coronary artery disease (CAD) and preserved left ventricular function found that treatment with an ACE inhibitor compared to placebo was associated with a reduction in cardiovascular mortality (RR 0.83, 95% CI 0.72 to 0.96), non-fatal MI (RR 0.84, 95% CI 0.75 to 0.94), all-cause mortality (RR 0.87, 95% CI 0.81 to 0.94), and coronary revascularisation rates (RR 0.93, 95% CI 0.85 to 1.00) (Al-Mallah, M. H. et al 2006). Mean duration of follow up was 4.4 years, range 2 to 4.8 years. The majority of patients were recruited to three large trials (Arnold, J. M. O. et al 2003) (Braunwald, E. et al 2004) (Fox, K. M. and EUROPA investigators 2003) in which 53%, 65% and 55% respectively had had a prior MI, at least one month earlier in one trial (Arnold, J. M. O., Yusuf, S., Young, J. et al 2003) and at least three months in the other two trials (Braunwald, E. et al 2004) (Fox, K. M. and EUROPA investigators 2003).

Patients with left ventricular systolic dysfunction

A systematic review of long term trials of patients after MI with left ventricular systolic dysfunction identified 3 large trials which each recruited more than 1000 patients with a minimum follow up of one year. Assignment to treatment with an ACE inhibitor, initiated between 3 and 16 days after an acute MI, was associated with a reduction in mortality (OR 0.74, 95% CI 0.66 to 0.83), readmission for heart failure

(OR 0.73, 95% CI 0.63 to 0.85) and recurrent MI (OR 0.80, 95% CI 0.69 to 0.94) compared with placebo, over a median follow up of 31 months (Flather, M. D. et al 2000). With the inclusion in the meta analysis of two randomised control trials of patients with reduced left ventricular systolic function, with (SOLVD Investigators 1991) or without (SOLVD Investigators 1992) symptoms of heart failure, the findings were similar. Seventy five percent of patients in these other two trials had a previous history of MI.

A 12 year follow up study of the SOLVD trials, in which 75% of participants had a previous MI (SOLVD Investigators 1991) (SOLVD Investigators 1992) found a reduction in all-cause mortality (OR 0.90, 95% CI 0.84 to 0.95) and cardiac deaths in those assigned for the duration of the trial to ACE inhibitor treatment compared to those assigned to placebo (Jong, P. et al 2003). This result was consistent in both the prevention trial which recruited asymptomatic patients, and the treatment trial which recruited patients with symptomatic CHF. A follow up study of a randomised controlled trial which recruited patients with left ventricular systolic dysfunction 3 to 7 days after acute MI (Pfeffer, M. A., Braunwald, E., Moye, L. A. et al 1992) found that at 12 years, patients who had been assigned to ACE inhibitor treatment during the original trial period for 2 to 4 years had a reduced risk of all-cause mortality (RR 0.89, 95% CI 0.80 to 0.99), all-cause hospitalisation (RR 0.92, 95% CI 0.88 to 0.96), and cardiovascular hospitalisations (RR 0.95, 95% CI 0.91 to 1.00) (Buch, P. et al 2005). Randomised controlled trials of the effectiveness of ACE inhibitor treatment in patients with chronic heart failure and left ventricular systolic dysfunction, which included patients with an MI in the past, is examined in The NICE guideline *Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care*, 2003 (National Collaborating Centre for Chronic Conditions. 2003). These guidelines state that systematic reviews of randomised controlled trials comparing ACE inhibitor to placebo have found that ACE inhibitor therapy in patients with heart failure due to left ventricular systolic dysfunction increases life expectancy compared to placebo. The effect is more marked in patients with more severe LV systolic impairment, or more severe symptoms, although there is benefit for all New York Heart Association functional classes (NYHA). Compared with placebo, ACE inhibitor therapy also reduces the risk of hospitalisation for heart failure in such patients, and also for patients with asymptomatic left ventricular systolic dysfunction.

6.2.4 Clinical effectiveness of ARBs

Only one trial comparing an ARB with placebo in patients after MI without chronic heart failure was found. This was a small un-blinded study which randomised 406 patients with CAD, of which 69% had a previous MI, to treatment with candesartan or placebo. Treatment with candesartan was associated with a reduction in the primary endpoint which was the combination of revascularisation, non-fatal MI and cardiovascular mortaliy ($P < 0.03$) (Kondo, J. et al 2003). There were no studies found which specifically examined the efficacy of treatment with an ARB in asymptomatic patients with left ventricular dysfunction.

6.2.5 Clinical Effectiveness of ACE inhibitors versus ARBs

No randomised controlled trials were identified that evaluated treatment with an ARB compared to treatment with an ACE inhibitor in patients with acute MI and preserved left ventricular function.

Two randomised controlled trials compared treatment with an ACE inhibitor to an ARB in patients with acute MI complicated by left ventricular systolic dysfunction and found no significant difference in all-cause mortality between the two groups (Dickstein, K., Kjekshus, J., and OPTIMAAL Steering Committee of the OPTIMAAL Study Group 2002) (Pfeffer, M. A. et al 2003). One randomised controlled trial showed a non significant difference in all-cause mortality (RR 1.13, 95% CI 0.99 to 1.28) and a significant reduction in cardiovascular mortality in favour of the ACE inhibitor captopril compared with the ARB losartan (RR 1.17, 95% CI 1.01 to 1.34) (Dickstein, K., Kjekshus, J., and OPTIMAAL Steering Committee of the OPTIMAAL Study Group 2002), although in the second study there was no significant difference in mortality between treatment with the ACE inhibitor captopril and the ARB valsartan (HR 1.00, 95% CI 0.90 to 1.11) (Pfeffer, M. A., McMurray, J. J., Velazquez, E. J. et al 2003). Treatment with the ARB losartan was better tolerated than with the ACE inhibitor captopril in one trial (Dickstein, K., Kjekshus, J., and OPTIMAAL Steering Committee of the OPTIMAAL Study Group 2002).

Randomised controlled trials of the effectiveness of ARB treatment in patients with chronic heart failure and left ventricular systolic dysfunction, including those with an MI in the past, were reviewed in the NICE guideline *Chronic Heart Failure: national*

clinical guideline for diagnosis and management in primary and secondary care, 2003 (National Collaborating Centre for Chronic Conditions. 2003). This guideline recognised that the evidence for ARB treatment in patients with chronic heart failure was still emerging and at the time of publication none of the ARBs were licensed for use in heart failure in the UK. Several large randomised trials were ongoing, but at the time that the NICE guideline for chronic heart failure were published, ARBs had not been shown to increase life expectancy compared to ACE inhibitor therapy for patients with heart failure due to left ventricular systolic dysfunction in several randomised controlled trials. However, the 2003 NICE guideline for the management of chronic heart failure states; 'ARBs may provide an alternative to ACE inhibitors for patients intolerant of ACE inhibitors (for example, because of cough)'

Adverse effects of ACE inhibitors were reported for three trials included in the systematic review of treatment with an ACE inhibitor in patients with left ventricular systolic dysfunction (Flather, M. D., Yusuf, S., Kober, L. et al 2000). Hypotension and renal dysfunction occurred more frequently in the ACE inhibitor treated group.

A randomised controlled trial conducted in patients with symptomatic heart failure and left ventricular systolic dysfunction, who were not receiving ACE inhibitors due to previous intolerance, found that patients were more likely to stop treatment with the ARB candesartan than placebo due to renal dysfunction (6.1% versus 2.7% in all patients, respectively), hyperkalaemia (1.9% versus 0.3% in all patients, respectively) and hypotension (3.7% versus 0.9% in all patients, respectively) (Granger, C. B. et al 2003). Patients were more likely to stop treatment with candesartan for a particular reason if they had previously been intolerant to treatment with an ACE inhibitor for the same reason.

Based on the available evidence the guideline development group came to the decision that treatment with an ARB should be considered as a second line alternative to an ACE inhibitor for those individuals with a documented history of ACE inhibitor intolerance.

6.2.6 Clinical effectiveness of ACE inhibitors plus ARBs versus ARBs or ACE inhibitors

A randomised controlled trial of patients within 0.5 to 10 days of an acute MI complicated by left ventricular systolic dysfunction compared treatment with the combination of an ARB plus an ACE inhibitor with an ACE inhibitor alone, or an ARB alone. During a median follow up of 24.7 months, treatment with the combination of the ARB valsartan and the ACE inhibitor captopril had no effect on all-cause mortality (HR 0.98, 95% CI 0.90 to 1.09), cardiovascular mortality (RR 1.00, 95% CI 0.89 to 1.11), non-fatal MI or hospitalisation for heart failure compared either with captopril alone or valsartan alone (Pfeffer, M. A., McMurray, J. J., Velazquez, E. J. et al 2003). Combination therapy was associated with an increased rate of adverse events compared with either captopril alone or valsartan alone.

Randomised controlled trials of the effectiveness of ACE inhibitor and ARB treatment combined in patients with chronic heart failure and left ventricular systolic dysfunction, which included patients with an MI in the past, is examined in The NICE guideline *Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care*, 2003 (National Collaborating Centre for Chronic Conditions. 2003). This guideline states that one systematic review of 17 randomised controlled trials demonstrated that the combination of ARBs and ACE inhibitors did not reduce risk of mortality as compared to ACE inhibitors on their own. However, significantly fewer patients required hospitalisation with the dual therapy. A large randomised controlled trial reported similar effects on mortality and hospitalisation with worsening heart failure. It was recognized that at the time of publication other trials were in progress which would further inform the use of the combination of ACE inhibitors and ARBs in patients with chronic heart failure (National Collaborating Centre for Chronic Conditions. 2003).

6.2.7 Clinical effectiveness of renal function and ACE inhibitor / ARB treatment

No studies were identified of post MI patients with poor renal function that specifically addressed at what level of renal function the risks of therapy with ACE inhibitors outweigh the benefits. *Post hoc* analysis of a randomised controlled trial of patients

with, or at high risk of, CAD with mild renal insufficiency found that the cumulative incidence of the primary outcome (cardiovascular death, non-fatal MI or stroke) was higher in patients with renal insufficiency compared to those without, and also increased with serum creatinine concentration. ACE inhibitor treatment with ramipril reduced the subsequent risk of cardiovascular events in patients with and without renal insufficiency, without increasing adverse events (Mann, J. F. E. et al 2001). A second *post hoc* analysis of a randomised controlled trial in post MI patients with left ventricular dysfunction showed that treatment with the ACE inhibitor captopril reduced cardiovascular events irrespective of baseline kidney function (Tokmakova, M. P. et al 2004).

The 2003 NICE Guideline: *Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care* stated that it is very rarely necessary to stop an ACE inhibitor and that clinical deterioration is likely if treatment is withdrawn (National Collaborating Centre for Chronic Conditions. 2003).

6.2.8 Health economics of ACE inhibitors in patients after MI with LV systolic dysfunction, or with heart failure

Ten studies were found which compared the use of ACE inhibitors in selected patients after MI with left ventricular systolic dysfunction with and without heart failure, or with heart failure. Nine studies used effectiveness data from studies of patients early after MI; five from the AIRE study, (Schadlich, P. K., Huppertz, E., and Brecht, J. G. 1998) (Martinez, C. and Ball, S. G. 1995) (Anderson, A. N., Moodley, I., and Kropman, K. 2000) (Erhardt, L. et al 1997) (Hart, W. M. et al 2002) three from the SAVE study (Mantovani, L. G., Belisari, A., and Szucs, T. D. 1998) (Michel, B. C. et al 1996) (Tsevat, J. et al 1995) and one from the TRACE study (LePen, C. et al 1998). The tenth study (Cook, J. R. et al 1998) used effectiveness data from the SOLVD trial in which 66% patients in the treatment study and 80% in the prevention study had a previous history of MI.

The NICE guidelines for the diagnosis and management of chronic heart failure in primary and secondary care also makes recommendation for treatment with ACE

inhibitors in patients with heart failure due to left ventricular systolic dysfunction, including patients with chronic heart failure and a history of an MI in the past. This guideline states that 'Treatment of heart failure with ACE inhibitors is cost effective, largely due to the costs saved from the reduced risk of hospitalisation. Treatment can be cost saving and has very favorable cost effectiveness ratios even when conservative assumptions are employed.'

The AIRE Study (Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. 1993) recruited patients with clinical heart failure early after acute MI, and examined the effectiveness of treatment with ramipril compared with placebo. Five studies examined cost effectiveness based on the AIRE study (Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. 1993) in different healthcare systems.

A Spanish study (Hart, W. M., Rubio-Terres, C., Pajuelo, F. et al 2002) found that compared with placebo, the incremental cost per life year gained with ramipril ranged between Euro 4784 in year 1 to Euro 1550 in the fourth year. The sensitivity analyses showed that the estimated cost per LYG was robust to wide variations in the baseline values.

A South African study (Anderson, A. N., Moodley, I., and Kropman, K. 2000) assessed the cost effectiveness of ramipril compared to placebo. The results were stratified according to age. The use of ramipril results in an incremental cost/life year gained, which ranges between R67 907 (approximately £6200) in the first year to R16 808/LYG (approximately £1500) in the fourth year. When the quality of life of the patients was taken into account, the cost-utility analysis shows an incremental cost/QALY of R21 382 (approximately £1900) for those younger than 65 years of age and R18 029 (approximately £1600) for those older than 65 years of age. The results were robust in sensitivity analyses.

A German study (Schadlich, P. K., Huppertz, E., and Brecht, J. G. 1998) reported an estimated ICER for ramipril compared to placebo of DM 2456/life year gained after 3.8 years (approximately £1100) and DM 8271/LYG (approximately £3650) for the first year. Monte-Carlo simulation results showed that ramipril was cost effective, dominating the alternative in 5% of the cases. In 99% of the cases the ICER ranged between DM 2500 to DM 8500 suggesting that ramipril is highly cost effective.

A Swedish study (Erhardt, L., Ball, S., Andersson, F. et al 1997) reported incremental cost effectiveness ratios of treatment with ramipril compared with placebo over 3 treatment periods: 1, 2, and 3.8 years. The ICERs ranged from SEK 33 033 for the 1-year treatment to (approximately £2800) SEK 14 148 (approximately £1200) for the 3.8-year treatment period. Two way-sensitivity analyses indicated that the study results were robust although hospital costs had an impact on the ICERs.

Finally, a UK based study (Martinez, C. and Ball, S. G. 1995), reported cost/life years gained from treatment with ramipril compared to placebo ranging between £425 for the first year to £286 in the fourth year. These results were not sensitive to the timeframe of the model, but were sensitive to changes in hospitalisation costs.

The SAVE study recruited patients early after acute MI without symptoms of heart failure and a left ventricular ejection fraction of equal to, or less than, 40%, and examined the effectiveness of treatment with captopril compared to placebo. Three studies examined cost effectiveness in different healthcare systems.

An Italian study (Mantovani, L. G., Belisari, A., and Szucs, T. D. 1998) reported an incremental cost per death avoided with captopril treatment of 33, 229 million lira (approximately £13 800). The cost/life year gained was 14, 708 million lira (approximately £6100). The model was sensitive to changes in values of the prices of captopril, cost of revascularisation procedures, the number of cardiovascular deaths prevented, and the number of years of life saved.

A Dutch study (Michel, B. C., Al, M. J., Remme, W. J. et al 1996) estimated the costs and effects of treatment. The cost per life year gained with captopril treatments was DF122 887 (approximately £2350) at 4 years. Costs per life-year gained for 20 years of treatment was estimated at DF115 729 (approximately £1600), with 95% of all estimates between DF10 and DF150 000 for the 20 year treatment. The results were sensitive to the cost of captopril and the occurrence and prevention of clinical heart failure, although the authors did not report by how much the result would change.

An American study (Tsevat, J., Duke, D., Goldman, L. et al 1995) developed a Markov model from a US third payer's perspective to assess the cost effectiveness of captopril compared to placebo. The model used two scenarios based on

assumptions about death rates with captopril versus placebo beyond 4 years. The first scenario included equal mortality rates, whilst the second extrapolated a difference in mortality for the remaining time in the model. In the first scenario, the ICER of captopril ranged from $3600/QALY (approximately £2000) for 80-year old patients to $60 800/QALY (approximately £34 500) for 50-year old patients. In the second scenario, ICERs ranged from $3700 to $10 400/QALY, depending on age. The model was robust to changes in estimates of variables when they were varied individually over wide ranges for patients aged over 60 years, but for those aged 50 years it was only sensitive to the cost of captopril and changes in utilities.

The TRACE study (Kober, L. et al 1995) recruited patients early after acute MI with left ventricular systolic dysfunction (corresponding to a left ventricular ejection fraction ≤ 35%) and examined the effectiveness of treatment with trandolapril compared with placebo.

A French study (LePen, C., Lilliu, H., Keller, T. et al 1998) evaluated the cost effectiveness of trandolapril. The cost/life year saved was 6950 French francs (approximately £900). Probabilistic sensitivity analyses showed that in 7.4% of the cases trandolapril use was cost saving (trandolapril dominated placebo) and in 92.6% of the cases the ICER was positive, and still within the acceptable ranges of cost/LYS, lying between FF 8410 (95%CI 7990 to 8840) according to the bootstrap method (approximately £1050).

The SOLVD trials recruited patients with left ventricular systolic dysfunction (ejection fraction ≤ 35%) with (SOLVD Investigators 1991) and without (SOLVD Investigators 1992) symptoms of heart failure and examined the effectiveness of treatment with enalapril compared to placebo. At baseline, 66% and 80% of patients respectively had a history of MI. One study was found examining cost effectiveness of ACE inhibitors using SOLVD data from the prevention arm.

One study (Cook, J. R., Glick, H. A., Gerth, W. et al 1998) based on US costs modelled the long-term economic and clinical impact of using enalapril versus usual therapy for hypertensive patients with left ventricular dysfunction. Enalapril dominated the alternative (more effective and less costly) in the base-case. These results were robust in sensitivity analysis. The cost effectiveness acceptability curve

showed that there was a less than 10% probability that enalapril treatment would increase the costs in comparison with placebo, and less than 3% probability that the cost per life-year gained would exceed $3,000 (approximately £1800) in the trial observation period analysis. In the lifetime projection analysis, the probability that enalapril dominated placebo was 94%.

In summary treatment with ACE inhibitors compared to placebo is cost effective in patients early after MI with left ventricular systolic dysfunction, with and without heart failure. Treatment with ACE inhibitors in patients with heart failure and left ventricular systolic dysfunction, which includes those with an MI in the past, has previously been reported as cost effective in the NICE guideline for the diagnosis and management of chronic heart failure in primary and secondary care.

6.2.9 Health economics of ACE inhibitors in patients after MI with preserved LV function

Five studies were found which addressed this question, (Malik, I. S., Bhatia, V. K., and Kooner, J. S. 2001) (Aurbach, A. et al 2004) (Smith, M. G., Neville, A. M., and Middleton, J. C. 2003) (Backhouse, M. E., Richter, A., and Gaffney, L. 2000) (Bjorholt, I. et al 2002). The use of ACE inhibitors was compared with placebo in MI patients without left ventricular systolic dysfunction but at high risk of cardiovascular events. All five studies used data from the HOPE study which examined the effectiveness of treatment with ramipril compared to placebo, and in which 53% had a history of a previous MI at least 1 month earlier. Two were UK studies (Backhouse, M. E., Richter, A., and Gaffney, L. 2000) (Malik, I. S., Bhatia, V. K., and Kooner, J. S. 2001).

The first UK study (Backhouse, M. E., Richter, A., and Gaffney, L. 2000) constructed a decision analytical model to estimate long-term benefits and costs of treatment with ramipril compared to placebo from the NHS perspective. The base-case analysis showed a discounted ICER of £5544 per LYG. The ICERs did not vary substantially with age. For example the ICER reduces to £2814 for those aged 52

year while increasing to £10 291 in for those aged 80 years due to differences in life expectancy.

The second UK study (Malik, I. S., Bhatia, V. K., and Kooner, J. S. 2001) assessed treatment with ramipril compared to placebo in patients with different risks of cardiovascular death classified as low, medium and high. The cost effectiveness of ramipril for the base case analysis was £14 700 (5 years) and £2800 (lifetime treatment). These results were sensitive to drug costs as well as pre-treatment risk. The costs of ACE inhibitors have fallen since this study was done.

Three studies have examined the cost effectiveness of treatment with ramipril compared to placebo in three other healthcare systems.

The first study (Smith, M. G., Neville, A. M., and Middleton, J. C. 2003) assessed the clinical and economic impacts of treatment with ramipril in an Australian high-risk population. The incremental cost effectiveness analysis showed the estimated cost per life-year saved to be A$17 214, 95% CI (A$8 338 to 39 536), approximately (£6600/LYG) The results were sensitive to risk of cardiovascular death, cost and risk of revascularisation.

The second study (Aurbach, A., Russ, W., Battegay, E. et al 2004) modelled the cost effectiveness of ramipril in patients with an increased risk of cardiovascular events, including a subgroup of patients with diabetes, in a Swiss context. The incremental cost effectiveness ratio of ramipril versus placebo was CHF 6 005 per life-year gained in the base case analysis (approximately £2500/LYG). The diabetic population had a much more favourable ICER of CHF 3790/LYG (approximately £1600).The results remained robust in sensitivity analysis and showed that ramipril was cost effective in more than 90% of the cases, if society was willing to pay up to CHF10000/LYG (approximately £4100) per additional LYG.

The third study (Bjorholt, I., Andersson, F. L., Kahan, T. et al 2002) evaluated the long-term treatment with ramipril in patients at high risk of cardiovascular events in a Swedish context. The estimated ICERs were SEK 16 600/LYG (approximately £1200) when direct medical costs for cardiovascular reasons only were considered and SEK 45 400/LYG (approximately £3400) when direct medical costs for all diseases were considered. Using quality of life weights from the literature they found

that the cost/QALY to be SEK 26 600 (approximately £2000). The results were sensitive to reduction in life expectancy at the end of the trial period.

An additional analysis was undertaken to examine the cost effectiveness of treatment with ACE inhibitors compared to placebo in patients with preserved left ventricular dysfunction. The analysis used effectiveness data from a meta analysis (Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006) which meta analysed data from six trials (Braunwald, E., Domanski, M. J., Fowler, S. E. et al 2004) (Nissen, S. E. et al 2004) (Fox, K. M. and EUROPA Investigators 2003) (Arnold, J. M. O., Yusuf, S., Young, J. et al 2003) (MacMahon, S. et al 2000) (Pitt, B. et al 2001). A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment with ACE inhibitors from a UK NHS perspective. The results suggested treatment with ACE inhibitors was cost effective with an estimated ICER of about £3400/QALY gained for men and about £3700 for women compared with placebo; well below the level considered affordable in the NHS (about £20 000 to £30 000 per QALY). This was robust in sensitivity analysis.

In conclusion treatment with ACE inhibitors in patients with an MI at least 1 month earlier and preserved left ventricular function is cost effective. See Appendix C for the full model.

6.3 Antiplatelet therapy

6.3.1 Evidence statements for antiplatelet therapy

6.3.1.1	After an MI, treatment with aspirin reduces the risk of death and cardiovascular events (1++).
6.3.1.2	In a subgroup of patients with recent MI, aspirin and clopidogrel have similar cardiovascular benefits (1++).
6.3.1.3	Long term treatment with aspirin is more cost effective compared to clopidogrel in the management of occlusive vascular events.
Patients after non-ST segment elevation MI	
6.3.1.4	Clopidogrel plus aspirin therapy was significantly more effective than placebo plus aspirin in patients with non-ST elevation acute coronary syndrome for the combination endpoint of death from cardiovascular causes, non-fatal MI or stroke (1++). Refer to the NICE Technology Appraisal Clopidogrel in Non-ST segment elevation acute coronary syndromes.
6.3.1.5	In patients with a non ST segment elevation acute coronary syndrome, treatment with aspirin plus clopidogrel compared to aspirin alone for 12 months is cost effective.
Patients after ST segment elevation MI	
6.3.1.6	In one study of patients scheduled for fibrinolytic therapy, presenting within 12 hours of a ST elevation MI or with new left bundle branch block, treatment with clopidogrel in addition to other standard therapy, for a median of 4 doses reduced the composite end point of an occluded infarct-related artery or reinfarction or death if these occurred before angiography was performed. At 30 days in this same study, there was a reduction in the composite end point of cardiovascular death, recurrent MI or recurrent

	ischaemia leading to the need for urgent revascularisation. In a second study of patients presenting within 24 hours of a suspected acute MI, (87% STEMI), treatment with clopidogrel for a mean duration of 14.9 days in addition to standard therapy, reduced the risk of the composite endpoint of death, reinfarction or stroke. There was no significant increased risk of major bleeding (1+).
6.3.1.7	In a study of a mean duration of 28 months that recruited patients with either clinically evident cardiovascular disease or multiple vascular risk factors, the treatment with clopidogrel in addition to other standard therapy was not associated with a reduction in the combination outcome of first occurrence of cardiovascular death, MI, or stroke, compared with standard therapy (1++).
Aspirin	
6.3.1.8	"Aspirin intolerance is defined as either • a proven hypersensitivity to aspirin, or • a history of severe indigestion caused by low-dose aspirin" Definition taken from NICE IFP on the TA for 'Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events'.
6.3.1.9	In patients who have had aspirin-induced ulcer bleeding that has been appropriately treated and are H pylori negative, treatment with aspirin plus high dose proton pump inhibitor has been shown to have a lower risk of recurrent bleeding episodes than treatment with clopidogrel alone (1++).

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6.3.2 Clinical effectiveness of antiplatelet agents

A meta analysis of randomised control trials of antiplatelet therapy in high risk patients (Baigent, C. et al 2002) identified 12 trials on patients with a history of MI. A total of 20 006 patients were allocated to a mean duration of 27 months of therapy.

For patients after MI, treatment resulted in 36 (standard error 5) fewer serious vascular events per 1000 (non-fatal MI: 18 (SE 3) fewer per 1000, $P < 0.001$; vascular death: 14 (SE 4) fewer per 1000 $P < 0.0006$; non-fatal stroke: 5 (SE 1) fewer per 1000, $P < 0.002$). The estimated risk of extra-cranial bleeding due to antiplatelet therapy was calculated as approximately 1 patient per 1000 per year. Six of the 12 trials compared aspirin with placebo, three used a combination of aspirin and dipyridamole, and one used sulphinpyrazone. Five of the six aspirin trials were available for review (Elwood, P. C. et al 1974) (Elwood, P. C. and Sweetnam, P. M. 1979) (Aspirin Myocardial Infarction Study Research Group. 1980), (Coronary Drug Project Research Group. 1980) (Breddin, K. et al 1979). Of these, one randomised controlled trial found a reduction in non-fatal MI (7.1% versus 10.9%, $P < 0.05$) (Elwood, P. C. and Sweetnam, P. M. 1979) and another a reduction in mortality (5.8% versus 8.3%, Z value - 1.9) (Coronary Drug Project Research Group. 1980).

Two short-term randomised control trials that recruited post MI patients within 24 hours of infarction found that aspirin therapy reduced mortality (RR 0.78, 95% CI 0.71 to 0.85) (Baigent, C. et al 1998) and reinfarction ($P < 0.03$) (Verheugt, F. W. et al 1990).

6.3.2.1 Antiplatelet therapy in patients who are aspirin intolerant

Literature searching did not identify any studies of patients after MI with aspirin sensitivity.

Post-hoc analysis of the CURE trial (Yusuf, S. et al 2001) found that bleeding risk increased with aspirin dose, with or without clopidogrel, without any increase in efficacy (HR 1.9, 95% CI 1.29 to 2.72 in the placebo group, HR 1.6, 95% CI 1.19 to 2.23 in the clopidogrel group, HR 1.7, 95% CI 1.36 to 2.20 in the combined group) (Peters, R. J. et al 2003).

A randomised control trial has been conducted on patients at high vascular risk (CAD, cerebrovascular insufficiency and/or peripheral vascular disease) and also with ulcer bleeding which could have been gastric or duodenal. The patients were all Helicobacter pylori negative before randomisation. The study found that treatment with aspirin plus esomeprazole was superior to clopidogrel plus placebo in the prevention of recurrent bleeding (0.7%, 95% CI 0% to 2%, versus 8.6%, 95% CI 4.1

to 13.1%, *P* = 0.001). No patients were treated with the combination of clopidogrel and esomeprazole (Chan, F. K. et al 2005).

6.3.2.2 Clinical effectiveness of aspirin versus clopidogrel

In patients after recent MI, treatment with aspirin was as effective as clopidogrel in reducing the combined risk of ischaemic stroke, MI, or vascular death in a randomised control trial which recruited stroke, peripheral artery disease and post MI patients.(Gent, M. 1996).

6.3.2.3 Clinical effectiveness of aspirin versus aspirin plus clopidogrel

Patients after non-ST segment elevation MI

A Health Technology Appraisal examined clopidogrel use in combination with aspirin compared with aspirin alone in the treatment of non-ST segment elevation acute coronary syndromes (National Institute for Clinical Excellence. 2004). One randomised control trial was identified (Yusuf, S., Zhao, F., Mehta, S. R. et al 2001). Clopidogrel in addition to aspirin was significantly more effective than placebo plus aspirin in patients with non-ST elevation acute coronary syndromes for the composite outcome of death from cardiovascular causes, non-fatal MI or stroke over the mean 9 month treatment period (RR 0.80, 95% CI 0.72 to 0.90). There were significantly more patients with major bleeds in the clopidogrel group (RR 1.38, 95% CI 1.13 to 1.67), but there were not significantly more patients with episodes of life-threatening bleeding or haemorrhagic strokes (RR 1.21, 95% CI 0.95 to 1.56).

Patients after ST elevation MI

A randomised control trial of patients presenting within 12 hours of a ST segment elevation MI or with new left bundle branch block examined the effectiveness of the addition of clopidogrel to aspirin, fibrinolytic therapy, and, where appropriate, heparin (Sabatine, M. S. et al 2005). Participants received a median of 4 doses of study medication and were scheduled to undergo coronary angiography 48 to 192 hours after the start of treatment. Clopidogrel reduced the composite primary end point of occluded infarct-related artery, or reinfaction or death if these occurred before

angiography was performed (OR 20%, *P* < 0.03).The study was not powered to detect a survival benefit, and had a short clinical follow up of 30 days. At 30 days, treatment with clopidogrel was associated with a reduction in the composite end point of cardiovascular death, recurrent MI or recurrent ischaemia leading to the need for urgent revascularisation. The rates of major bleeding and intracranial haemorrhage were similar in the two groups.

A randomised control trial which recruited patients within 24 hours of a suspected acute MI found that the addition of clopidogrel to aspirin and other standard treatment reduced the risk of the primary endpoint of the combination of death, reinfarction or stroke, compared with aspirin treatment alone (OR 0.91, 95% CI 0.86 to 0.97) (Chen, Z. M. et al 2005a). Clopigogrel plus aspirin also reduced the risk of the co-primary endpoint of all-cause mortality (OR 0.93, 95% CI 0.87 to 0.99). Follow up was until hospital discharge or for up to 4 weeks, and mean duration of trial treatment in survivors was 14.9 days, 87% of patients had ST elevation MI and 6% left bundle branch block. The rate of fatal and non-fatal bleeding was low and similar in both treatment groups.

A randomised control trial recruited patients with either clinically evident cardiovascular disease or multiple vascular risk factors (Bhatt, D. L. et al 2006). Patients received clopidogrel plus aspirin or placebo plus aspirin. Thirty five percent of patients had had a prior MI in the previous 5 years. Forty eight percent of patients had documented coronary artery disease in the previous five years. The median follow up time of the study was 28 months. For the primary endpoint (combination of first occurrence of cardiovascular death, MI, or stroke) there was no benefit observed in patients who received clopidogrel plus aspirin compared with those who received placebo plus aspirin. For the principal secondary endpoint (combination of MI, stroke, death from cardiovascular causes, hospitalisation for unstable angina, transient ischaemic attack, or revascularisation), clopidogrel plus aspirin treatment did reduce the event rate compared to aspirin therapy alone. For the other secondary endpoints (death from all-causes, cardiovascular death, non-fatal MI, non-fatal ischaemic stroke, and non-fatal stroke) there was no difference observed between the two treatment groups (Bhatt, D. L., Fox, K. A. A, Hacke, W. et al 2006).

In pre-specified subgroup analysis of participants with 'symptomatic' (previous cardiovascular disease) and 'asymptomatic' patients with no multiple risk factors were designated 'asymptomatic' (of whom some did have a history of reported cardiovascular events) it was found that asymptomatic patients treated with clopidogrel plus aspirin had an increase in the rate of primary events, in all-cause mortality and cardiovascular mortality compared with those treated with aspirin alone. In contrast, the symptomatic patients treated with clopidogrel plus aspirin had a marginally significant reduction in the rate of primary events compared with patients treated with aspirin therapy alone (6.9% versus 7.9% respectively, *P* = 0.046), although there was no significant effect on death from cardiovascular causes (Bhatt, D. L., Fox, K. A. A, Hacke, W. et al 2006).

Clopidogrel plus aspirin treatment was associated with an increase in moderate bleeding (bleeding which led to transfusion, but did not fulfil the criteria for severe bleeding) compared with the placebo plus aspirin treatment (RR 1.62, 95% CI 1.27 to 2.1). Severe bleeding, fatal bleeding and primary intracranial haemorrhage events were similar in the two comparison groups (Bhatt, D. L., Fox, K. A. A, Hacke, W. et al 2006).

In summary, only two trials were identifird that examined the effectiveness of clopidogrel plus aspirin treatment versus aspirin alone in patients immediately after ST elevation MI (Sabatine, M. S., Cannon, C. P., Gibson, C. M. et al 2005) (Chen, Z. M., Jiang, L. X., Chen, Y. P. et al 2005a). The combination treatment was not studied beyond 4 weeks and hence it is not clear if there is any further benefit of contininuing combination treatment in the longer term for patients after an ST elevation MI.

6.3.3 Health economics of clopidogrel versus aspirin in the management of occlusive vascular events

Aspirin is widely available and cheap, whilst clopidogrel is more expensive. A review was undertaken to establish if the additional costs of clopidogrel are worth the extra gains in quality adjusted survival in patients after an acute MI. Four studies were found that met the inclusion criteria examining the cost effectiveness of aspirin

compared to clopidogrel (Jones, L. et al 2004) (Schleinitz, M. D., Weiss, J. P., and Owens, D. K. 2004) (Karnon, J. et al 2005) (Annemans, L. et al 2003). One of these studies (Jones, L., Griffin, S., Palmer, S. et al 2004) was a Health Technology Assessment (HTA). In this section, only the results of the HTA are summarised. And the other papers's evidence tables are in the appendix.

The HTA (Jones, L., Griffin, S., Palmer, S. et al 2004) assessed the clinical and cost effectiveness of clopidogrel in the secondary prevention of occlusive vascular events (OVE) in patients with vascular disease The incremental cost effectiveness ratio (ICERs) for the lifetime model excluding the effect of treatment on vascular death is £31 400/QALY. The short term model had an ICER of about £17 000/QALY. The probability that clopidogrel is cost effective was 48% for the life time treatment and 71% for the short term model at £30 000/QALY threshold. These results are sensitive to the inclusion/exclusion of the relative risk of vascular death in the model. In the lifetime model the ICERs rise to £94 448/QALY and short term model they rise to £21 448/QALY when the effect of treatment on vascular death is included.

In conclusion, the use of clopidogrel compared with aspirin is unlikely to be cost effective especially in the long term at £30 000/QALY threshold. In the short term, clopidogrel has been found to be cost effective in the wider population of patients with occlusive vascular disease, but it is unclear if this is applicable to the whole population of patients after acute MI.

6.3.4 Health economics of clopidogrel plus aspirin versus aspirin in patients with non-ST segment elevation MI

Seven studies were found which met the inclusion criteria (Main, C. et al 2004) (Fiore, L. D. et al 2002) (Latour-Perez, J. et al 2004) (Schleinitz, M. D. and Heidenreich, P. A. 2005) (Gaspoz, J.-M. et al 2002) (Lindgren, P. et al 2005). (J.Karnon , A. Bakhai b A. Brennan A. Pandor M. Flather E. Warren D. Gray R. Akehurst 2006) In this section, only the results of the HTA are summarised, and the other papers's evidence tables are in the appendix.

The HTA (Main, C., Palmer, S., Griffin, S. et al 2004) was undertaken in the UK and assessed the cost effectiveness of clopidogrel plus aspirin compared to placebo plus

aspirin in patients with non-ST segment elevation acute coronary syndrome. The results from the base-case model suggested that treatment with clopidogrel as an adjunct to aspirin for 12 months compared to aspirin alone was cost effective as long as the health service was willing to pay £6078/QALY. These results were robust in sensitivity analysis. When the time horizon was reduced from 40 years to 5 years the ICERs increased to £14 844/QALY with a 71% probability that clopidogrel compared to placebo will be cost effective if the NHS was willing to pay £30 000/QALY. The authors explored the cost effectiveness of using clopidogrel for periods shorter than 1 year. The strategies of using clopidogrel for 3 or 6 months were ruled out by extended dominance, and the ICER for 12 months of treatment with clopidogrel compared with 1 month was £5159 per QALY, with a 83% probability that clopidogrel is cost effective at £30 000/QALY. These results remained robust even in low risk populations.

In conclusion, clopidogrel used as an adjunct to aspirin is cost effective in patients with non-ST segment elevation acute coronary syndrome; including those with non ST segment elevation MI, although the evidence derives largely from a single trial. Duration of clopidogrel treatment affects the cost effectiveness, with more favourable ICERs obtained in the first three months. Current evidence suggests that clopidogrel can not be recommended beyond 12 months.

6.4 Beta blockers

6.4.1 Evidence statements for beta blockers

6.4.1.1	In unselected patients after acute MI, long-term treatment, (greater than 6 months and up to 4 years) with beta blockers resulted in 1.2% annual risk reduction and 23% reduced odds of death compared with placebo (1++).
6.4.1.2	In one randomised controlled trial of patients after acute MI with LV systolic dysfunction, treatment with carvedilol, in addition to ACE inhibitor therapy, reduced all-cause mortality, cardiovascular-cause mortality, non-fatal MI, and the combination of all-cause mortality or non-fatal MI (1++).
6.4.1.3	Carvedilol compared to placebo is cost effective in patients with LV dysfunction.
6.4.1.4	In patients after acute MI with asymptomatic left ventricular systolic dysfunction, beta blocker treatment reduced cardiovascular mortality and the risk of developing CHF (2+).
6.4.1.5	There is inconclusive evidence about the optimum time to initiate beta - blocker treatment in patients after an MI.
6.4.1.6	There is no evidence that unselected patients after acute MI treated with a beta blocker should routinely stop treatment.
6.4.1.7	No trials were found which examined the effectiveness of initiating beta blocker treatment in patients with a proven MI in the past and preserved left ventricular function.
6.4.1.8	In randomised controlled trials, initiation of beta blocker treatment in patients with chronic heart failure, of whom some had had a previous MI, reduced mortality and the need for hospitalisation. (NICE Chronic Heart Failure guideline) (1++).

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6.4.2 Clinical effectiveness of beta blockers

6.4.2.1 In unselected patients

A meta analysis of 51 short term randomised controlled trials (up to 6 weeks) of treatment with beta blockers in patients after acute MI, found a non significant reduction in the odds of death compared with placebo (Freemantle, N. et al 1999). In a more recent short term randomised controlled trial in patients recruited within 24 hours of a suspected acute MI and with a mean follow up of 16 days after MI, intravenous beta blocker treatment followed by oral therapy did not reduce total mortality in hospital (Chen, Z. M. et al 2005b). Beta blocker therapy reduced the risk of reinfarction (OR 0.82, 95% CI 0.72 to 0.89) and ventricular fibrillation (OR 0.83, 95% CI 0.75 to 0.93), although there was an increase in the risk of cardiogenic shock (OR 1.30, 95% CI 1.19 to 1.41). The excess of cardiogenic shock was mainly during days 0 to 1, whereas the reduction in risk of ventricular fibrillation and reinfarction emerged more gradually.

An observational study of post MI patients aged 65 years or older found that the rate of in-hospital mortality was lower in patients treated with beta blockers compared with untreated patients (mortality rate: 5.1% and 8.1% respectively, $P \leq 0.001$), even after adjustment for baseline differences in demographic, clinical, and treatment characteristics between the two groups (OR 0.81, 95% CI 0.75 to 0.87) (Krumholz, H. M. et al 1998).

A meta analysis of 31 long term randomised controlled trials (6 weeks to 48 months) found that treatment with beta blockers in patients after acute MI reduced the odds of death by 23% compared with placeb (pooled random effects, OR 0.77, 95% CI 0.69 to 0.85) (Freemantle, N., Cleland, J., Young, P. et al 1999). The number needed to treat for one year to avoid one death was 84. Individually, four out of nine beta blockers were found to significantly reduce the odds of death, namely propranolol (OR 0.71, 95% CI 0.59 to 0.85), timolol (OR 0.59, 95% CI 0.46 to 0.77), metoprolol (OR 0.80, 95% CI 0.66 to 0.96), and acebutolol (OR 0.49, 95% CI 0.25 to 0.93). The randomised controlled trials that included propranolol, timolol and metoprol made up

63% of the available evidence in the meta analysis. The evidence for acebutolol was supported by a single moderately sized study which is open to considerable measurement error.

No randomised controlled trials were found comparing different times for initiating beta blocker therapy after acute MI. However, a separate analysis of the meta analysis of long term randomised controlled trials showed that an initial intravenous dose of beta blocker had no additional benefit on mortality, although there was no reason to delay treatment (Freemantle, N., Cleland, J., Young, P. et al 1999).

No randomised trials were found which compared the effectiveness of different available beta blockers. However, the Cooperative Cardiovascular Project (Gottlieb, S. S., McCarter, R. J., and Vogel, R. A. 1998) examined the two year survival of patients after MI, and reported outcomes in patients prescribed different beta blockers. This survey was based on the entire population of acute care hospital claims for acute MI to the Health Care Financing Administration for Medicare for an 8 month period, with data staggered so that most discharges fell between February 1994 and July 1995. 69 338 patients after MI were prescribed a beta blocker on discharge (metoprolol 65%, atenolol 25%, propranolol 6%, other 4%). Overall, patients treated with any beta blocker on discharge had a 40% reduction in mortality compared with those not treated with a beta blocker. Those prescribed metoprolol and atenolol had very similar survival rates after 1 and 2 years of follow up, while patients discharged on propranolol had a lower survival rate (Gottlieb, S. S. and McCarter, R. J. 2001).

Literature searching did not identify any randomised controlled trials of initiating beta blocker treatment in unselected patients with a proven MI in the past (greater than 1 years).

No randomised controlled trials were identified which examined the effectiveness of continued beta blocker treatment in patients treated after an acute MI. A follow up study after a 3 year randomised trial examined the effect of the withdrawal of the beta blocker metoprolol during a mean of 51 months. After beta blocker withdrawal the number of deaths, reinfarctions or cerebrovascular events in patients previously assigned to a beta blocker was not significantly different to the number of events in

patients assigned to placebo (Olsson, G. et al 1988). However, patients who had had a further MI within the last year before withdrawal were not included, and a third of patients who stopped beta blocker treatment restarted treatment, for clinical indications. A further follow up study was conducted after a 3 year randomised controlled trial comparing beta blocker therapy with timolol versus placebo in patients after acute MI. In patients who survived the entire period, beta blocker prescription increased gradually to 28.7% in the previously allocated placebo group, and decreased to 59.5% in the previously allocated beta blocker group, whereas in those who died beta blocker therapy was prescribed less frequently 18.6% and 44.3%, respectively (Pedersen, T. R. 1985). During follow up, the mortality curves of the two groups identified by the original randomisation to timolol treatment or placebo continued to rise in parallel, demonstrating a consistent effect on mortality over the period of the observation period. The mortality curves for patients divided by age (less than 65 years, or 65 years and older) showed the same pattern.

A systematic review examined the incidence of fatigue, sexual dysfunction and depression in randomised placebo controlled trials of beta blocker therapy. Fatigue occurred more frequently, and was more likely to lead to withdrawal from treatment in patients assigned to beta blockers compared to in those assigned to placebo. The occurrence of sexual dysfunction was similar in the two groups, although more patients in the beta blocker group withdrew from treatment due to sexual dysfunction. There was no difference in the incidence of depressive symptoms (Ko, D. T. et al 2002).

6.4.2.2 Patients with left ventricular systolic dysfunction and or heart failure

A meta regression analysis assessed the extent to which inclusion of patients with heart failure or evidence of major cardiac dysfunction influenced the outcome of randomised controlled trials of beta blocker therapy in patients with a history of MI. Treatment may have begun at any stage after MI, and may have commenced intravenously (Houghton, T., Freemantle, N., and Cleland, J. G. 2000). There was a non significant interaction between treatment with beta blockers and the presence of heart failure, and the authors concluded that there is a lack of evidence to show that the relative benefits of beta blockers after MI are different in patients with or without

heart failure, but that the absolute benefit may be greater in the former because of a higher baseline risk of heart failure and death.

A more recent randomised placebo controlled trial examined the effectiveness of beta blocker treatment with carvedilol in addition to other standard current therapy in patients after acute MI with reduced left ventricular function (ejection fraction ≤ 40%). Patients were recruited within 3 to 21 days of an acute MI, 46% had had thrombolysis or primary angioplasty and 97% were treated with an ACE inhibitor. Trial follow up was for a mean of 1.3 years and a minimum of 3 months, and all-cause mortality (HR 0.77, 95% CI 0.60 to 0.98), cardiovascular mortality (HR 0.75, 95% CI 0.58 to 0.96), non-fatal MI (HR 0.59, 95% CI 0.39 to 0.90), and the combination of all-cause mortality or non-fatal MI (HR 0.71, 95% CI 0.57 to 0.89) was lower in those treated with carvediolol compared with placebo (Dargie, H. J. 2001).

Randomised controlled trials of the effectiveness of beta blocker treatment in patients with chronic heart failure and left ventricular systolic dysfunction, which included patients with an MI in the past is examined in The NICE guideline *Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care*, 2003 (National Collaborating Centre for Chronic Conditions. 2003). This guideline states that many large clinical trials reviewed in four meta-analyses, and one subsequent randomised controlled trial, have shown that several beta blockers increase life expectancy in patients with heart failure due to LV systolic dysfunction compared with placebo. The best evidence exists for bisoprolol, carvediol and modified-release metoprolol, while there is little evidence for other beta blockers. There are no randomised controlled trials of atenolol, or some other commonly used beta blockers, in patients with heart failure**.**

6.4.2.3 Patients with asymptomatic left ventricular dysfunction

No randomised controlled trials were identified that assessed beta blocker therapy only in patients with asymptomatic LV dysfunction.

A *post hoc* analysis of a randomised controlled trial examining the effectiveness of ACE inhibitor therapy versus placebo in early post MI patients with left ventricular dysfunction without overt heart failure (Pfeffer, M. A., Braunwald, E., Moye, L. A. et al 1992) found that beta blocker usage was associated with a reduction in the risk of cardiovascular death and the development of CHF (Vantrimpont, P. et al 1997).

Two studies examined the impact of beta blocker treatment in patients with a previous MI. A *post hoc* analysis of a randomised controlled trial of ACE inhibitor therapy versus placebo in asymptomatic patients with left ventricular dysfunction, in which 75% had a history of MI (SOLVD Investigators 1992), found that beta blocker usage was associated with a lower mortality rate compared with placebo ($P = 0.01$) (Exner, D. V. et al 1999).

An observational study in elderly patients with prior MI and asymptomatic left ventricular systolic dysfunction examined four patient treatment groups: treatment with beta blockers alone, treatment with ACE inhibitors alone, treatment with the combination of beta blockers and ACE inhibitors, and no treatment. Follow up ranged from a mean of 19 to 34 months. Compared with no treatment, there was a reduction in new coronary events of 25% by treatment with beta blockers alone ($P = 0.001$), of 17% by treatment with ACE inhibitors alone ($P = 0.001$), and of 37% by treatment with the combination of beta blockers and ACE inhibitors ($P = 0.001$). Compared with no treatment, the development of CHF was reduced by 41% with beta blocker treatment alone ($P = 0.001$), by 32% with ACE inhibitors alone ($P = 0.001$), and by 60% with the combination of beta blockers and ACE inhibitors ($P = 0.001$) (Aronow, W. S., Ahn, C., and Kronzon, I. 2001).

6.4.3 Health economics of beta blockers

Two studies from outside the UK comparing beta blockers and placebo were appraised. A Swedish study (Olsson, G., Levin, L.-A., and Rehnqvist, N. 1987) was a cost consequence study which compared metoprolol with placebo enumerating arrays of health outcome measures alongside costs. Effectiveness data were drawn from the Stockholm Metoprolol study which included 66% post MI patients. The use of beta blockers resulted in a reduction of cardiovascular events and the cost per patient for metoprolol treated participants was Kr 118610 (approximately £11 981)

compared to Kr 137220 (approximately £13 861) for participants in the control arm. However there was no difference in mortality.

An American cost effectiveness analysis (Goldman, L. et al 1988) used effectiveness data from a pooled meta analysis of beta blocker trials conducted by the authors. Results were stratified by age and risk groups. Risk was defined as low, medium and high risk of mortality observed in a 15 year prognostic study The age groups were 45, 55 or 65 years. The authors explored two possibilities in their analysis. One was a conservative assumption that observed treatment gains will cease immediately once the treatment is stopped, and another that the gains will gradually disappear. The cost/LYG ranged between $23 457 for a low risk 45 year old man to $3609/LYG for a high risk 65 year old man using a conservative assumption. When a best guess assumption is used the cost/LYG ranged between $12 855 for a low risk 45 year old man to $2427/LYG for a high risk 65 year old man.

Mortality risk was the major cost effectiveness driver and age did not affect the cost effectiveness ratios (ICERs), The ICERs for the low risk groups were over 5 fold the ICERs for the high risk groups for all age groups.

An additional analysis was undertaken to inform the decisions of the guideline group. This examined the cost effectiveness of treatment with the beta blocker, carvedilol, in patients with left ventricular systolic dysfunction who met the inclusion criteria of the CAPRICORN trial (Dargie, H. J. 2001). A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment from a UK NHS perspective, and the base case results were presented for 65-year-old men and women early after MI with left ventricular dysfunction. The results suggested that treatment with carvedilol is highly cost effective for this population with an ICER of about £1100/QALY gained, compared with placebo which is well below the level usually considered to be affordable in the NHS (about £20 000 to £30 000 per QALY).

In conclusion treatment with beta blockers compared to placebo in patients early after MI is cost effective. This conclusion for unselected patients is based on two non-UK studies. However, given the substantial clinical effectiveness of beta blockers and their cost, it is highly unlikely that any new cost effectiveness study will

conclude differently. The findings in patients with left ventricular systolic dysfunction are robust and the use of beta blockers in these patients is cost effective.

6.5 Vitamin K antagonists

6.5.1 Evidence statements for vitamin K antagonists

6.5.1.1	In patients after acute MI high-intensity warfarin compared to placebo is associated with reduction in cardiovascular events and mortality (Grade 1+).
6.5.1.2	There is inconsistent evidence that high-intensity warfarin is more effective than aspirin in reduction of mortality or reinfarction and stroke (Grade 1+).
6.5.1.3	High-intensity warfarin is associated with a higher incidence of major bleeding compared to aspirin (1+).
6.5.1.4	Treatment with aspirin is likely to be more cost effective when compared with with warfarin in patients with CAD.
6.5.1.5	In patients after acute MI, the combination of low intensity warfarin and aspirin did not consistently reduce the incidence of major cardiovascular events compared to aspirin on its own, and was associated with an increased risk of haemorrhagic complications (1+).
6.5.1.6	In patients after an acute MI, the combination of moderate intensity warfarin (target INR 2 to 2.5) and aspirin compared to aspirin on its own resulted in a reduction in the composite end point of death, non-fatal MI or stroke (1+).
6.5.1.7	In patients after an acute MI, the combination of moderate intensity warfarin (target INR 2 to 2.5) and aspirin compared to aspirin on its own was associated with an increased risk of bleeding (Grade 1+).
6.5.1.8	In patients after acute MI, the combination of moderate intensity warfarin (target INR 2 to 2.5) and aspirin did not reduce the incidence of major cardiovascular events compared to high intensity warfarin (target INR 2.8 to 4.2) on its own, and was associated with a similar

risk of bleeding (Grade 1+).

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6.5.2 Clinical effectiveness of vitamin K antagonists

6.5.2.1 Introduction

Oral anticoagulants have been used in patients with vascular disease for over 40 years, but their role is controversial due to a number of reasons. Firstly, initial randomised control trials in patients who have experienced an MI have provided conflicting results. Secondly, anticoagulants are inconvenient to use because they require careful monitoring and dose adjustment, and in clinical trials may be more closely managed than in everyday clinical practice. Thirdly, there is debate over whether the associated risk of bleeding justifies their use. Fourthly, antiplatelet therapies have proven to be effective in reducing vascular complications and to be relatively safe.

Two important findings directed further research on anticoagulants in CAD. Rates of recurrent vascular events in patients with suspected unstable angina or MI without initial ST elevation remained high, despite the use of antiplatelet agents (Yusuf, S. et al 1998). In addition, there was evidence of persistent biochemical stimulus to thrombosis for several months after an acute MI and in unstable angina patients, even in the presence of aspirin (Merlini, P. A. et al 1994).

These observations stimulated a number of large well conducted randomised controlled trials examining anticoagulation therapy at different intensities with and without concomitant aspirin therapy. Initially randomised controlled trials tested high intensity anticoagulation therapy, International normalised ratio (INR) = 2.8 to 4.8, versus placebo (Smith, P. 1992), (Van Bergen, P. F. M. M. et al 1994). The INR is a value derived from a standardized laboratory test that measures the effect of anticoagulant. The laboratory materials used in the test are calibrated against internationally accepted reference preparations, so that variability between laboratories and different reagents is minimized. Normal blood has an INR of 1. Therapeutic anticoagulation often aims to achieve an INR value of 2.0 to 3.5.

More recent randomised controlled trials have evaluated anticoagulants versus aspirin (Hurlen, M. et al 2002) (van Es, R. F. et al 2002) and the combination of anticoagulants and aspirin versus aspirin alone (Hurlen, M., Abdelnoor, M., Smith, P. et al 2002) (van Es, R. F., Jonker, J. J., Verheugt, F. W. et al 2002) (Coumadin Aspirin Reinfarction Study (CARS) Investigators. 1997) (Fiore, L. D., Ezekowitz, M. D., Brophy, M. T. et al 2002) (Herlitz, J. et al 2004) with anti-coagulation treatment in the moderate-intensity (INR = 2 to 3), and the low intensity (INR < 1.5) ranges.

6.5.2.2 Vitamin K antagonists

Two randomised control trials compared high intensity anticoagulant therapy with placebo in patients early after acute MI, both with mean follow up times of 37 months (Smith, P. 1992) (Van Bergen, P. F. M. M., Jonker, J. J. C., Van der Meer, F. J. M. et al 1994). One study found that warfarin treatment resulted in a significant reduction in all-cause mortality (RR 24%, 95% CI 4% to 44%), reinfarction (RR 34%, 95% CI 19% to 54%) and stroke (RR 55%, 95% CI 30% to 30 to 77%) (Smith, P. 1992). The second study showed that nicoumalone or phenprocoumon treatment led to no reduction in all-cause mortality; however anticoagulant therapy did reduce recurrent MI (HR 0.47, 95% CI 0.38 to 0.59), vascular (HR 0.65, 95% CI 0.55 to 0.76) and cerebrovascular events (HR 0.60, 95% CI 0.40 to 0.90) (Van Bergen, P. F. M. M., Jonker, J. J. C., Van der Meer, F. J. M. et al 1994). In both studies, treatment was associated with significantly more major bleeding episodes compared with placebo (Smith, P. 1992) (Van Bergen, P. F. M. M., Jonker, J. J. C., Van der Meer, F. J. M. et al 1994).

A meta analysis of 16 randomised controlled trials of oral anticoagulant therapy in patients with established CAD found that high intensity anticoagulant therapy (INR > 2.8) reduced total mortality (OR 22%, 95% CI 13% to 31%), reinfarction (OR 42%, 95% CI 34% to 48%) and stroke (OR 48%, 95% CI 33% to 60%) compared with control, although it was associated with increased major bleeding (Anand, S. S. and Yusuf, S. 1999). Meta analysis of 4 randomised controlled trials of moderate intensity anticoagulation therapy (INR 2 to 3) found that anticoagulation treatment only reduced reinfarction compared with control (OR 52%, 95% CI 37% to 64%), and was also associated with increased major bleeding (Anand, S. S. and Yusuf, S. 1999).

6.5.2.3 Vitamin K antagonists compared to aspirin alone

Meta analysis of 7 randomised control trials in patients with CAD found that, compared with aspirin, moderate- or high-intensity anticoagulant therapy did not reduce the risk of all-cause mortality, reinfarction or stroke (Anand, S. S. and Yusuf, S. 1999). Major bleeding was increased with anticoagulant therapy. Subsequent to the publication of this meta analysis, two randomised controlled trials showed that high-intensity anticoagulant therapy was more effective than aspirin treatment for reducing the combination endpoint of death, non-fatal MI or stroke (warfarin versus aspirin, RR 0.81, 95% CI 0.69 to 0.95) (Hurlen, M., Abdelnoor, M., Smith, P. et al 2002) (coumadin versus aspirin, HR 0.55, 95% CI 0.3 to 1.00) (van Es, R. F., Jonker, J. J., Verheugt, F. W. et al 2002). In the first study which recruited patients with acute MI, anticoagulation therapy compared to aspirin treatment reduced the risk of reinfarction (warfarin versus aspirin: RR 0.74, 95% CI 0.55 to 0.98) and thromboembolic stroke (warfarin versus aspirin: RR 0.52, 95% CI 0.28 to 0.97) but not mortality during a trial follow up of approximately four years (Hurlen, M., Abdelnoor, M., Smith, P. et al 2002). In contrast, the second study found anticoagulation treatment did reduce risk of mortality compared to aspirin treatment (coumadin versus aspirin: HR 0.28, 95% CI 0.09 to 0.82), with no difference for reinfarction and stroke (van Es, R. F., Jonker, J. J., Verheugt, F. W. et al 2002). This study recruited patients with acute coronary syndrome of which 88% had an MI and the mean follow up was 26 months.

6.5.2.4 Vitamin K antagonists plus aspirin compared to aspirin alone

A randomised controlled trial in patients within 42 days of an acute MI and a mean follow up of 5 years found that low-dose warfarin added to aspirin therapy did not reduce the risk of the combination of cardiovascular death, reinfarction, although it did reduce the risk of stroke (aspirin 7.1% versus aspirin + warfarin 4.7%, $P = 0.004$) when compared to aspirin therapy alone. The combination increased the risk of bleeding (Herlitz, J., Holm, J., Peterson, M. et al 2004). Two further randomised controlled trials in patients with an acute MI up to 3 weeks earlier did not demonstrate any clinical benefit of the combination of aspirin and low intensity anticoagulation therapy over aspirin monotherapy (Coumadin Aspirin Reinfarction Study (CARS) Investigators. 1997) (Fiore, L. D., Ezekowitz, M. D., Brophy, M. T. et

al 2002), although there was a significant increase in major bleeding associated with the combination. Low intensity warfarin therapy was used for these studies: one study achieved an INR of 1.04 with 1 mg warfarin plus aspirin treatment and 1.19 with 3 mg warfarin plus aspirin treatment (Coumadin Aspirin Reinfarction Study (CARS) Investigators. 1997) The second study achieved a mean INR value of 1.8 (Fiore, L. D., Ezekowitz, M. D., Brophy, M. T. et al 2002).

Two randomised controlled trials compared moderate intensity anticoagulant therapy (INR 2.0 to 2.5) plus aspirin with aspirin alone (Hurlen, M., Abdelnoor, M., Smith, P. et al 2002) (van Es, R. F., Jonker, J. J., Verheugt, F. W. et al 2002). One study in patients with acute coronary syndrome of which 88% had an MI found that moderate intensity coumadin therapy was more effective than aspirin alone in reducing coronary events and all-cause mortality (HR 0.28, 95%CI 0.09 to 0.82). A mean INR of 2.4 was achieved and the mean follow up was 26 months. Major bleeding rates were low in both groups. Minor bleeding in the aspirin plus coumadin group was significantly higher compared with the aspirin alone group (van Es, R. F., Jonker, J. J., Verheugt, F. W. et al 2002). The second study in patients hospitalised for acute MI found that aspirin plus warfarin therapy led to a lower risk of the combination outcome of death, non-fatal infarction or thromboembolic stroke compared with aspirin alone (RR 0.71, 95% CI 0.60 to 0.83) (Hurlen, M., Abdelnoor, M., Smith, P. et al 2002). Warfarin plus aspirin therapy was associated with an increased risk of non-fatal bleeding compared to aspirin alone (Hurlen, M., Abdelnoor, M., Smith, P. et al 2002). Trial follow up was for approximately four years and a mean INR of 2.2 was achieved.

6.5.2.5 Vitamin K antagonists plus aspirin compared to warfarin alone

A randomised control trial that compared moderate intensity warfarin treatment plus aspirin with high intensity warfarin treatment alone found the combination treatment did not reduce the risk of the combination endpoint of death, non-fatal reinfarction or thromboembolic stroke compared to warfarin monotherapy. The bleeding risk was similar in the two groups (Hurlen, M., Abdelnoor, M., Smith, P. et al 2002).

6.5.3 Health economics of vitamin K antagonists

6.5.3.1 Warfarin compared to placebo

One non UK study was identified which examined the cost effectiveness of warfarin compared with placebo (Van Bergen, P. F. M. M. et al 1995). This was a cost minimisation analysis and was undertaken in Holland. The authors used effectiveness data from the Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) study and AntiPlatelets Trialists Collaboration study (APT). The total cost was Dfl 17 671 813 (approximately £6800 000) for the warfarin group and Dfl 19 222 590 (approximately £7400 000) for the placebo group. The savings per patient due to the intervention, discounted at 5%, was Dfl 906 (approximately £350). The incremental cost of intervention was negative suggesting that anticoagulation administration results in savings compared to placebo. These results were robust in sensitivity analysis.

6.5.3.2 Warfarin compared to aspirin

One Italian study was identified which compared warfarin with aspirin (Gianetti, J., Gensini, G., and De, Caterina R. 1998).

Gianetti et al assessed the cost effectiveness of warfarin compared to aspirin, for secondary prevention of CAD, within a European context. The authors used effectiveness data from the ASPECT and the APT. This was a cost minimisation analysis since they did not synthesize the costs and benefits.

Costing was done using three different methods, which all yielded comparable results. The total cost per patient per year, using DRG mean total costs, was ECU2, 150 (approximately £1660) for warfarin and ECU2187 (approximately £1680) for aspirin. Results were sensitive to variations in the aspirin-warfarin efficacy ratio. This is a ratio that lies between 0 and 1. If the ratio is 1 or close to 1, it means there is no difference in efficacy between two interventions while the further away from 1 it follows there is a big difference in effectiveness between interventions. Warfarin was no longer the cost effective strategy in Italy once an efficacy ratio of approximately 0.72 is reached. From this analysis, it would appear that the cost effectiveness of warfarin relative to aspirin would be relatively favourable. However if the results of

WARIS II are considered which found the efficacy ratio of 0.81, it appears that aspirin is the cost effective strategy compared to warfarin.

In conclusion the cost effectiveness of warfarin relative to aspirin is unclear, but largely weighs in favour of aspirin especially in light of the new evidence which shows that the efficacy ratio can be as high as 0.81.

6.6 Calcium channel blockers

6.6.1 Evidence statements for calcium channel blockers

6.6.1.1	In a meta analysis of trials with unselected patients after MI diltiazem or verapamil treatment was associated with a reduction in non-fatal infarction, but there was no effect on all-cause mortality (1++).
6.6.1.2	In a randomised controlled trial of unselected patients after MI, verapamil treatment for a mean of 16 months was associated with a reduction in the combined major events of death or first reinfarction and the combined major cardiac events of cardiac death and first reinfaction. Sub-group analysis showed that this benefit was confined to patients without heart failure (1+).
6.6.1.3	In a randomised controlled trial of patients after MI, diltiazem treatment during a mean follow up of 25 months was associated with a reduction in the combined outcome of cardiac death and non-fatal infarction providing there was no evidence of pulmonary congestion. In patients with pulmonary congestion, treatment with diltiazem was associated with an increase in the combined outcome of cardiac death and non-fatal infarction (1+).
6.6.1.4	In a more recent randomised controlled trial of patients after MI without heart failure, treatment with diltiazem during 6 months of follow up, was associated with no significant reduction in the combination of cardiac death, non-fatal reinfarction or refractory ischaemia, although there was a reduction in the outcomes of non-fatal reinfarction and refractory ischaemia which was of borderline significance (1++).
6.6.1.5	In a randomised controlled trial of patients with angiographically confirmed coronary artery disease (45% with previous MI), treatment with amlodipine was not associated with a reduction in progression of coronary atherosclerotic segments, although there was reduction in progression of carotid atherosclerosis. There was no significant effect

	on mortality, infarction or stroke (1+).
6.6.1.6	Three randomised controlled trials with medium to long term follow up suggest that calcium channel blockers do not improve life expectancy compared with placebo in patients with heart failure who are already receiving an ACE inhibitor. Verapamil, diltiazem and short-acting dihydropyridines such as nifedipine can cause clinical deterioration. Amlodipine, a long-acting dihydropyridine, is not harmful in terms of adverse events (NICE Chronic Heart Failure guideline) (1++).
6.6.1.7	Three non-UK studies found that treatment with calcium channel blockers compared to placebo in patients with angiographically documented CHD is cost effective.

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6.6.2 Clinical effectiveness of calcium channel blockers

6.6.2.1 Unselected patients

A meta analysis of 21 randomised controlled trials of unselected patients with a recent MI found that calcium channel blocker therapy was not associated with a reduction in mortality, although there was a reduction in non-fatal MI (OR 0.80, 95% CI 0.70 to 0.92, fixed effects, OR 0.81, 95% CI 0.69 to 0.96, random effects) (National Institute for Clinical Excellence 2001).

Two trials which were included in the meta analysis examined the interaction between diltiazem or verapamil treatment and whether or not patients had heart failure at baseline (Multicenter Diltiazem Postinfarction Trial Research Group. 1988) (Danish Study Group on Verapamil in Myocardial Infarction. 1990). In one trial treatment with diltiazem for an average of 25 months was not associated with a reduction in total mortality, death from cardiac causes, or non-fatal MI compared with placebo (Multicenter Diltiazem Postinfarction Trial Research Group. 1988). However subgroup analysis of the patient population found that in patients without pulmonary congestion, diltiazem was associated with a reduced number of cardiac events (death from cardiac causes, or non-fatal MI) (HR 0.77, 95% CI 0.61 to 0.98). In

patients with pulmonary congestion, diltiazem was associated with an increased number of cardiac events (HR 1.41, 95% CI 1.01 to 1.96) (Multicenter Diltiazem Postinfarction Trial Research Group. 1988).

In a second trial, treatment with verapamil for an average of 16 months was not associated with a reduction in total mortality, cardiac death, or sudden death, compared with placebo, although there was a reduction in first reinfarction (HR 0.77, 95% CI 0.58 to 1.03) and the combination endpoint of first reinfarction or death (HR 0.80, 95% CI 0.66 to 0.99). However, in patients without heart failure immediately before randomisation, treatment with verapamil was associated with a reduction in total mortality, cardiac death, sudden death, first reinfarction or first cardiac event, whereas in patients with heart failure treatment with verapamil did not confer any benefit compared with placebo (Danish Study Group on Verapamil in Myocardial Infarction. 1990).

A more recent randomised controlled trial recruited patients after acute MI and excluded patients with CHF. In this trial, during 6 months of follow up, treatment with diltiazem compared with placebo had no effect on the cumulative first event rate of cardiac death, non-fatal reinfarction or refractory ischaemia (Boden, W. E. et al 2000) although there was a reduction in revascularisation, and the combination endpoint of non-fatal reinfarction or revascularisation (Boden, W. E., van Gilst, W. H., Scheldewaert, R. G. et al 2000).

A randomised controlled trial in patients with CAD, 45% with a prior MI, found that treatment with amlodipine compared with placebo had no effect on all-cause mortality, reinfarction, stroke, CHF or reduction in the progression of early atherosclerotic segments (Pitt, B. et al 2000). The primary objective of the study was to determine if treatment with amlodipine reduced the progression of early atherosclerotic segments detected on coronary angiography and the statistical power to detect a treatment difference in mortality and major morbidity was low. Treatment with amlodipine did reduce the progression of carotid artery atherosclerosis compared with placebo, and there were fewer cases of unstable angina (HR 0.67, 95% CI 0.48 to 0.93) and coronary revascularisation. Trial follow up was for 3 years (Pitt, B., Byington, R. P., Furberg, C. D. et al 2000).

The evidence for the secondary prevention effects of calcium channel blockers is not compelling, but the GDG felt that treatment with a rate limiting calcium channel blocker (diltiazem or verapamil) might be considered in patients not able to tolerate to a beta blocker, providing there were no signs of pulmonary congestion and left ventricular function was not impaired.

6.6.2.2 Patients with left ventricular dysfunction

No randomised controlled trials of the effectiveness of treatment with calcium channel blockers were identified which recruited patients with acute MI and left ventricular systolic dysfunction.

6.6.3 Health economics of calcium channel blockers

Three studies were found which met the inclusion criteria. None of the studies were done in the UK. All the studies used effectiveness data from the PREVENT study which examines the effectiveness of amlodipine compared with placebo in slowing the progression of early atherosclerosis in patients with angiographically documented CHD. The primary end point in the PREVENT was from the angiographic change, although clinical events were also monitored.

The first study (Casciano, R. et al 2002) assessed the cost effectiveness of amlodipine compared to placebo from a US third payer's perspective. The use of amlodipine was effective in reducing hospitalisation and the episodes of revascularisation. The discounted costs/patient over the 3 years were less for amlodipine patients US$14 117 versus US$16 683 for placebo resulting in cost savings of about $2500. The estimated costs were robust in sensitivity analyses. They did a probabilistic simulation and in all cases amlodipine was the strategy of choice.

The second study (Cathomas, G. et al 2002) assessed the cost effectiveness of amlodipine compared to placebo from a Swiss healthcare perspective. There was no statistically significant difference in annual mortality However the adjusted life expectancy calculated using the all-cause mortality of the Swiss population similar to

the PREVENT population resulted in 0.083 years gained due to amlodipine over the three years. The cost per life-year gained was Sfr 14 650 and the result was robust in sensitivity analysis.

The third study (Doyle, J. J. et al 2002) assessed the cost effectiveness of amlodipine compared to placebo from a Swedish healthcare perspective. Amlodipine was associated with fewer hospitalisations. Estimated costs per patient over the 3-year period were SEK 26 600 in the intervention group and SEK 27 400 in the control group. Thus, amlodipine was associated with cost-savings of SEK 800. The authors did not calculate the cost effectiveness ratio because amlodipine was dominant over placebo, that is, it was more effective and less costly. These findings were robust in both univariate and multivariate sensitivity analysis.

In conclusion, the calcium channel blocker, amlodipine compared to placebo in patients with angiographically documented CHD is cost effective. This conclusion is based on three non-UK studies, which were well conducted. However, the generalisability of the studies to post MI patients per se is not very clear since the patients recruited to the PREVENT study which was based on angiographic findings and in which the statistical power to detect a treatment difference in mortality and major morbidity was low.

6.7 Potassium channel activators

6.7.1 Evidence statement for potassium channel activators

6.7.1.1	There is no significant reduction in CHD mortality or non-fatal MI in patients treated with nicorandil (1+).

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6.7.2 Clinical effectiveness of potassium channel activators

A systematic review identified one randomised controlled trial that compared nicorandil therapy versus placebo, although it was too small to provide evidence of benefit because only 70 patients were recruited (National Institute for Clinical Excellence 2001).

A more recent randomised controlled trial in 5126 patients with stable angina of which 66% had had a prior MI examined the effectiveness of nicorandil compared with placebo. Treatment with nicorandil resulted in a reduction of the composite primary outcome of CHD death, non-fatal MI, or unplanned hospital admission for cardiac chest pain compared with placebo (HR 0.83, 95% CI 0.72 to 0.97) (IONA Study Group 2002). However, the frequency of the secondary outcome of CHD death or non-fatal MI was similar in the two groups (IONA Study Group 2002) and there was no significant difference in all-cause mortality, CHD mortality and non-fatal MI. The combination of all cardiovascular events (defined as cardiovascular mortality, non-fatal MI, non-fatal stroke, hospital admission for transient ischaemic attack, and unplanned hospital admission for cardiac chest pain) (HR 0.86, 95% CI 0.86 to 0.98) and the combined endpoint of CHD death, non-fatal MI or unstable angina (HR 0.79, 95% CI 0.64 to 0.98) were reduced in the nicorandil group (IONA Study Group 2002).

6.8 Aldosterone antagonists in patients with heart failure and LV dysfunction

6.8.1 Evidence statements for aldosterone antagonists in patients with heart failure and LV dysfunction

6.8.1.1	The only large trial of an aldosterone antagonist in early post MI patients with left ventricular systolic dysfunction (ejection fraction ≤ 40%) and clinical heart failure and or diabetes, showed that early treatment with eplerenone (initiated 3 to 14 days after acute MI), in addition to ACE inhibitors and beta blockers, reduced all-cause mortality, death from cardiovascular causes, sudden cardiac death, and episodes of heart failure. Patients with a serum creatinine concentration greater than 220 micromol/l and/or serum potassium greater than 5.0 mmol/l were excluded from the trial (1++).
6.8.1.2	Treatment with aldosterone antagonist, eplerenone is cost effective, compared with placebo in patients early after MI with left ventricular systolic dysfunction.
6.8.1.3	In one randomised controlled trial, initiation of spironolactone treatment in patients with chronic heart failure (of whom 54% had an ischaemic cause for heart failure) increased life expectancy and reduced the need for hospitalisation for cardiac causes (NICE Chronic Heart Failure guideline) (1++).

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6.8.2 Clinical effectiveness of aldosterone antagonists

A randomised control trial examined the effectiveness of eplerenone in patients with left ventricular dysfunction following an MI. Trial inclusion required a left ventricular ejection fraction of ≤ 40% and also clinical signs of heart failure (90%) and / or diabetes (32%) (Pitt, B. et al 2003a). Eplerenone treatment was associated with reduced risk of the two primary endpoints: death from any cause (RR 0.85, 95% CI

0.75 to 0.96) and the combination of death from cardiovascular causes or hospitalisation for cardiovascular events (RR 0.87, 95% CI 0.79 to 0.95). There was also a lower risk of the following secondary endpoints: death from any cause or any hospitalisation (RR 0.92, 95% CI 0.86 to 0.98), death from cardiovascular causes (RR 0.83, 95% CI 0.72 to 0.94), sudden cardiac death (RR 0.79, 95% CI 0.64 to 0.97), and hospitalisation for heart failure (RR 0.85, 95% CI 0.74 to 0.99). Trial follow up was for a mean of 16 months (Pitt, B., Remme, W., Zannad, F. et al 2003a).

There was an increased risk of serious hyperkalemia in the eplerenone treated patients, while there was an increased risk of serious hypokalemia in the placebo group. Eplerenone treatment was also associated with an increase in the risk of gastrointestinal disorder. Patients in the placebo group reported a higher frequency of respiratory disorders (cough, dyspnea and pneumonia) and hypoglycaemia (Pitt, B., Remme, W., Zannad, F. et al 2003a).

No studies were found that considered how frequently patients with a prior MI treated with eplerenone should undergo testing of renal function and serum potassium.

A randomised controlled trial of the effectiveness of the aldosterone antagonist, spironolactone, in patients with chronic heart failure and left ventricular systolic dysfunction (of whom 54% had an ischaemic cause for heart failure), is examined in the NICE guideline *Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care*, 2003 (National Collaborating Centre for Chronic Conditions. 2003). This guideline states that in patients with moderate to severe heart failure (NYHA Class III and IV) due to LV systolic dysfunction, the addition of low-dose spironolactone to therapy with a loop diuretic and ACE inhibitor (with and without digoxin) has been shown in a large randomised controlled trial to increase life expectancy when compared to placebo. In addition, hospitalisation for cardiac causes is greatly reduced.

The guideline group recognised that there was only one randomised controlled trial of eplerenone in the MI population, and its clinical effectivess has not been compared with a non selective aldosterone antagonist, spironolactone. No trial evidence was found on the clinical effectiveness of spironolactone in patients after an MI. In keeping with the available evidence, the GDG decided to recommend treatment with an aldosterone antagonist licensed for post-MI treatment (which is

currently eplerenone) for patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction.

6.8.3 Health economics of aldosterone antagonists

Two studies were identified which examined the cost effectiveness of the aldosterone antagonist, eplerenone, compared with placebo in patients early after MI with left ventricular systolic dysfunction. Both studies used effectiveness data from the EPHESUS study (Pitt, B., Remme, W., Zannad, F. et al 2003a). From an economic perspective the correct comparison should be between eplerenone with the next best alternative, which in this case is spironolactone. Spironolactone is widely used in post MI patients but the GDG took the position that there was no direct effectiveness evidence of spironolactone in this patient group. This left us with epleronene compared with placebo as the the evidence base. Thus the summary of the two relevant studies that compared eplerenone with placebo in patients early after MI with left ventricular systolic dysfunction is given below.

The first analysis (Pfizer Ltd 2005) was done from the perspective of the Scottish NHS. It was well reported and concluded that eplerenone was cost effective as long as the NHS was willing to pay up to £9048/QALY gained. If the Scottish NHS was willing to pay £20 000 per additional QALY, there was a 92% probability that eplerenone was cost effective. The results were robust in sensitivity analysis.

The second study (Weintraub, W. S. et al 2005) used observational data from the Framingham, Saskatchewan and Worcester databases to extrapolate treatment effect beyond the EPHESUS trial observation period. The incremental cost effectiveness ratios were $21 072/QALY, $30 349 and $17 374/QALY using Framingham, Saskatchewan and Worcester data sources. These results were robust in sensitivity analyses. A probabilistic simulation showed that eplerenone was the optimal strategy in more than 87% for all ages and sexes at a threshold value of $50 000/QALY.

In conclusion eplerenone compared to placebo in patients early after MI with left ventricular systolic dysfunction and heart failure appears to be cost effective.

6.9 Lipid lowering agents

6.9.1 Evidence statements for lipid lowering agents

6.9.1.1	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 (1++).
6.9.1.2	In a systematic review of cohort studies, randomised trials, voluntary notifications to voluntary regulatory authorities and published case reports the incidence of adverse events was low. The estimate for rhabomyolysis was 3.4 per 100 000. However, the incidence of adverse events may be increased in patients treated with high dose statin, compared to low dose, and in patients treated with statins which are oxidised by cytochrome P450 3A4 (1++).
6.9.1.3	There is conflicting evidence that fibrates reduce cardiovascular risk in patients after MI (1++).
6.9.1.4	No studies were found testing the effectiveness of cholesterol absorption inhibitors for secondary prevention in patients after MI.

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6.9.2 Clinical effectiveness of lipid lowering agents

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

Statin therapy is recommended for adults with clinical evidence of cardiovascular disease

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 (Pedersen, T. R. et al 2004) (Sacks, F. M. et al 2000) (Liem, A. H. et al 2002) (Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)

Study Group. 1998). Four studies recruited patients with CAD (Pitt, B. et al 1995) (Crouse, J. R. et al 1995) (Jukema, J. W. et al 1995) (Teo, K. K. et al 2000), two studies recruited patients with CAD and hypercholesterolaemia (Bestehorn, H. P. et al 1997) (Riegger, G. et al 1999) one study recruited patients with mild CAD (Multicentre Anti-Atheroma Study (MAAS). 1994), two studies enrolled patients after coronary balloon angioplasty (Serruys, P. W. et al 1999) and (Bertrand, M. E. et al 1997), and one study enrolled patients after percutaneous coronary intervention (Serruys, P. W. 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), non-fatal 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 (National Institute for Health & Clinical Excellence. 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).

6.9.2.1 Timing of statin therapy

No studies were identified that compared early statin with delayed statin therapy at the same dosage.

A randomised trial examined the effectiveness of early statin initiation in patients with acute coronary syndrome, in which 53% had had an acute non-Q wave MI (Olsson, A. G. et al 2005). This trial randomised patients to either high dose 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, non-fatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalisation) was reduced in patients randomised to atorvastatin, compared to those randomised to placebo, a 16% relative risk reduction. There were no significant differences in the individual outcomes of death, non-fatal MI or cardiac arrest with resuscitation, although there was a lower risk of recurrent symptomatic myocardial ischaemia with objective evidence requiring emergency rehospitalisation in the group assigned to atorvastatin. Stroke was a secondary outcome with a significant lower incidence in the atorvastatin group. The reduction in the primary endpoint did not depend on the baseline level of LDL-cholesterol with similar risk reductions in those with a baseline LDL-cholesterol above or below the median. 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. More patients in the atorvastatin group developed liver transaminase levels more than 3 times the upper limit of normal. There were no cases of myositis (Olsson, A. G., Schwartz, G. G., Szarek, M. et al 2005).

A study has examined early use of statin therapy within the first 24 hours of admission for acute MI using data from the National Registry of Myocardial Infarction 4 (NRMI 4)(Fonarow, G. C. et al 2005). NRMI 4 is a prospective, observational database of consecutive patients admitted with acute MI to 1230 participating hospital throughout the United States. Data was collected on 300 823 patients. A

total of 174 635 patients who had had an acute MI were included in the analysis. Of these, statin therapy was used in the first 24 hours of hopsitalisation in 39 096 patients (22.4%). There were 21 978 patients who were newly started on statin therapy and 17 118 patients who were continued on statin therapy. Statin therapy was discontinued in 9411 patients. There were 126 128 patients who did not receive statins before or within the first 24 hours of hospitalisation. New initiation of statin treatment within the first 24 hours of admission was associated with a decreased risk of in-hospital mortality compared with no statin use (4.0% versus 15.4%, respectively, adjusted OR 0.62, 95% CI 0.57 to 0.67). There was also a decreased risk of in-hospital mortality in patients who continued statin therapy compared with no statin usage (5.3% versus 15.4%, respectively, adjusted OR 0.58, 95% CI 0.54 to 0.63). In contrast, those patients that had been treated with statin therapy before hospitalisation but whose statin therapy had been discontinued had a slightly higher mortality risk compared with patients who did not use statins (16.5% versus 15.4%, respectively, adjusted OR 1.12, 95% CI 1.05 to 1.20). Early stain use, whether newly initiated or continued was also associated with a decreased incidence of cardiac arrest, cardiogenic shock, cardiac rupture, and ventricular tachycardia / ventricular fibrillation. There was no reduced risk of recurrent acute MI in patients treated with early statin therapy compared with no early statin usage (Fonarow, G. C., Wright, R. S., Spencer, F. A. et al 2005).

No randomised controlled trials were identified which examined concordance with statin treatment in patients treated before discharge compared to those treated later. However, the guideline group felt that initiation of statin treatment as soon as possible was likely to have a beneficial effect on concordance.

6.9.2.2 Adverse events

All randomised controlled trials which have examined the effectiveness of statin treatment excluded 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, and were not randomised. Thus, tolerability may be better and the incidences of adverse events lower in the

trials than in unselected patients. However, there are other sources of information which have helped inform the risk of adverse events.

In a systematic review of cohort studies, randomised trials, voluntary notifications to voluntary regulatory authorities and published case reports the incidence of rhabdomyolysis for statins other than cerivastatin was 3.4 (1.6 to 6.5) per 100 000 person years, with a case fatality of 10% (law, M. and Rudnicka, A. R. 2006). The incidence of rhabdomyolysis was higher (4.2 per 100 000 person years) with lovastatin, simvastatin or atorvastatin (which are oxidised by cytochrome P450 3A4 (CYP3A4) than with pravastatin or fluvastatin (which is not oxidised by CYP3A4). The rates were about 10 times higher for cerivastatin and also for statins other than cerivastatin when taken with gemfibrozil. For cervastatin taken with gemfibrozil, the incidence was 2 000 times higher, an absolute annual incidence of about 10%. The mean incidence of myopathy in patients treated with statins was 11 per 100 000 person years. There was no significant difference in the incidence of a raised creatine kinase to ≥ 10 fold the upper limit of normal 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, neither had CK 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. In randomised trials elevations in alanine aminotransferase (ALT) and or aspartate aminotransferase (AST) were reported more frequently in patients treated with statins than with placebo, and elevations of ALT (defined as ≥ 3 times the ULN, or 120 U/L) were found in 300 statin-allocated and 200 placebo-allocated participants per 100 000 person-years. However, statistical heterogeneity across trials was noted. An elevated ALT 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 ALT 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 ALT 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).

The guideline group noted that not treating patients with an elevated ALT prevents clinical liver disease in an extremely small number of patients. There was a consensus to recommend measurement of ALT or AST prior to starting statin treatment, so that in the event of an elevated level being found during statin treatment, it would be known if this had been present before initiation. However, patients with raised liver enzymes should not routinely be excluded from treatment with a statin (law, M. and Rudnicka, A. R. 2006).

Trials showed no excess of renal 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). No change in cognitive function was found in trials of statins in elderly patients (law, M. and Rudnicka, A. R. 2006).

6.9.3 Clinical effectiveness of fibrates, niacin and ezetimibe

A randomised controlled trial in patients with prior MI (≥ 6 months but <5 years before enrolment: 78%), and or stable angina pectoris compared treatment with the fibrate bezafibrate and placebo (Behar, S. et al 2000). Patients were followed up for mean of 6.2 years. Treatment with bezafibrate did not confer any benefit over placebo for the primary endpoint of the combination of fatal MI, non-fatal MI or sudden death. The overall incidence of any adverse event was 69% in both groups, and the frequency of adverse event was similar in both groups (Behar, S., Brunner, D., Kaplinsky, E. et al 2000).

In a further small randomised controlled trial in men aged less than 45 years with a prior MI 3 to 6 months earlier, treatment with bezafibrate, was associated with a reduction in the incidence of coronary events (reinfarction, CABG, PCI, sudden death or cardiovascular death) compared with placebo (de Faire, U. et al 1996). Concomitant drug therapy at the start of the trial was as follows: aspirin 11%, beta blockers 99%, long acting nitrates 27%, ACE inhibitors 0%. At follow up aspirin use had increased to 45% and ACE inhibitor therapy to 5%. Trial follow up was for 5

years. Total cholesterol and very low density lipoprotein cholesterol decreased in both groups, but to a significantly greater extent in the bezafibrate group. Triglyceride levels fell in the bezafibrate group, and increased in the placebo group. LDL-cholesterol did not change substantially in either group (de Faire, U., Ericsson, C. G., Grip, L. et al 1996).

A randomised controlled trial in patients with CAD (61% had a prior MI) recruited men with an HDL-cholesterol of 1.0mmol/l or less, LDL-cholesterol 3.6mmol/l or less and triglycerides less than 3.4 mmol/l (Rubins, H. B. et al 1999). At the start of the trial the majority of participants were taking aspirin, but less than half beta blockers and less than a quarter ACE inhibitors. Patients were randomised to either the fibrate gemfibrozil or placebo. Mean trial follow up was 5.1 years. Compared with placebo, gemfibrozil therapy was associated with a reduction in the primary endpoint (combination of non-fatal MI or death from CHD) (RR 0.78, 95% CI 0.65 to 0.93) and a reduction in the incidence of the secondary combination outcome of non-fatal MI, death from CHD or stroke (RR 0.76, 95% CI 0.64 to 0.89). Compared with placebo, gemfibrozil therapy was also associated with a reduction in non-fatal MI (RR 0.77, 95% CI 0.62 to 0.96) investigator-designated stroke (RR 0.81, 95% CI 0.52 to 0.98), transient ischaemic attack (RR 0.61, 95% CI 0.25 to 0.67), carotid endarterectomy (RR 0.55, 95% CI 0.40 to 0.78) and hospitalisation for CHF (RR 0.78, 95% CI 0.62 to 0.98), but, was not associated with a reduction in death due to CHD, death from any cause, confirmed stroke, CABG or PCI and hospitalisation for unstable angina. One year after randomisation, the mean total cholesterol level was 4% lower, the mean triglyceride level 31% lower and the mean HDL-cholesterol level 6% higher in patients assigned to gemfibrozil. Mean 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 GDG considered that while the trial evidence for fibrate treatment in patients after MI was contradictory, two studies did report evidence of benefit in cardiovascular outcomes (de Faire, U., Ericsson, C. G., Grip, L. et al 1996) (Rubins, H. B., Robins, S. J., Collins, D. et al 1999), and as such fibrates may be offered to those patients after MI who are intolerant of statins.

Treatment with niacin compared with placebo has been examined in a randomised controlled study in patients with a prior MI (Coronary Drug Project Research Group. 1975). This was an early study which randomly assigned patients with prior MI to six treatment groups; low and high conjugated oestrogen therapy, clofibrate, dextrothyroxine sodium, niacin and placebo. Niacin treatment was associated with a 9.9% reduction in total cholesterol from baseline and a 26.1% reduction in triglycerides (after correcting for changes in the placebo group). Compared with placebo, niacin treatment reduced the incidence of non-fatal MI (8.9% Niacin versus 12.2% placebo, $Z = -2.88$, $P < 0.005$) and also the combination of coronary death or non-fatal MI (22.8% Niacin versus 26.2% placebo, $Z = -2.23$, $P < 0.01$), but 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 non-fatal), fatal or non-fatal stroke or intermittent cerebral ischaemic attack, definite or suspected fatal or non-fatal pulmonary embolism or thrombophlebitis and also any definite or suspected fatal or non-fatal cardiovascular event. Patients in the niacin group had a greater incidence of the following side effects compared with the placebo group: the combination of diarrhoea, 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 (Coronary Drug Project Research Group. 1975).

No randomised controlled trials were identified comparing the cholesterol absorption agent, ezetimibe with placebo in patients after MI.

6.9.4 Health economics of lipid lowering agents

6.9.4.1 Economics of statins

The latest HTA on statins was published in 2005 (National Institute for Health & Clinical Excellence. 2006). The HTA covered both primary and secondary prevention and was based on models of cost effectiveness. The guidance recommended statins with the lowest acquisition cost for people with clinical evidence of CVD and its recommendations will be adopted in this guideline. Further cost effectiveness

analyses, including high versus standard dose statin treatment will underpin recommendations in the lipid modification guidelines.

6.9.4.2 Economics of fibrates

Only one study (Nyman, J. A. et al 2002) was found which met the inclusion criteria. This study used data from a single trial the US Department of Veterans Affairs (VA) Cooperative Studies Program HDL-C Intervention Trial (VA-HIT) (Rubins, H. B., Robins, S. J., Collins, D. et al 1999) which compared gemfibrozil with placebo. ICERs were estimated using two sets of prices for gemfibrozil. Using the prices of gemfibrozil that were negotiated by the VA, gemfibrozil was cost saving, while using prices found outside the VA, the ICERs ranged between $6300 and $17 100/QALY.

In conclusion, treatment with gemfibrozil was cost effective in a selected group of men with CHD with low levels of HDL-cholesterol and low levels of LDL-cholesterol. This finding was robust in sensitivity analysis. However the relevance to the general post MI population not selected on the basis of an initial lipid profile or by gender is not clear.

6.10 Monitoring guidance

Monitoring guidance

This section details the guidance for initiation, titration and monitoring of ACE inhibitors and epelenone treatment in patients after MI. The GDG considered that this specific information for these therapies was required in the post MI patient population.

Table 3

Initiation, titration and monitoring of ACE inhibitors in patients after acute MI

Doses

ACE inhibitors should be started at an appropriate dose and titrated upwards until the optimum or target dose* is reached.

Which ACE inhibitor and target dose*

The doses are taken from the BNF for a post MI secondary prevention indication, the notes below indicate the specific licensed indication.

Licensed ACE inhibitor

	Starting dose	Target dose
Captopril**	6.25 mg tds	50 mg tds
Lisinopril	2.5 mg – 5 mg od	10 mg od
Ramipril***	1.25 – 2.5 mg bd	5 mg bd
Trandalopril**	0.5 mg od	4 mg od
Enalapril****	2.5 mg od	20 mg od or 10 mg bd

These are the licensed recommended doses for post MI patients, and may differ

from those for patients with symptomatic heart failure. In patients with asymptomatic LV systolic dysfunction aim for the target dose recommended in those with symptomatic heart failure and LV systolic dysfunction (refer to the NICE guidelines for chronic heart failure).

** licensed for use in patients following MI with left ventricular dysfunction.

*** licensed for use following myocardial infarction in patients with clinical evidence of heart failure and also susceptible patients over 55 years, prevention of MI, stroke, cardiovascular death or need of revascularisation procedures.

**** licensed for use in patients for prevention of symptomatic heart failure in patients with left ventricular dysfunction (this may include patients with MI in the past).

How to use

- Avoid in patients with known severe renal artery stenosis.
- Check renal function (creatinine) and serum electrolytes (particularly potassium), and blood pressure at baseline.
- Seek specialist advice in patients taking a high dose loop diuretic (for example furosemide 80mg od) or if concerned about the risk of renal artery stenosis (for example if severe peripheral vascular disease).
- Initiate a low dose of ACE inhibitor.
- Titrate the dose of ACE inhibitor upwards at short intervals (for example every 1 to 2 weeks).
- Monitor renal function (creatinine) and serum electrolytes, and blood pressure before starting an ACE inhibitor, again within 1 to 2 weeks of starting treatment. Monitor thereafter until treated with a stable dose, and then at least annually. More frequent monitoring should be considered in patients at risk of deterioration in renal function and or of developing hyperkalaemia, or during an intercurrent illness.

- Aim for target dose, or maximum tolerated dose.

What to do if blood pressure is low

- If asymptomatic, low blood pressure does not usually require any change in therapy.
- If low blood pressure is symptomatic (dizziness, lightheadedness and or confusion), stop non-essential hypotensive agents (for example alpha blockers, diuretics if for hypertension and or if no signs of congestion).
- If these measures do not resolve the problem seek specialist advice.

What to do with deteriorating renal function and hyperkalaemia

- If serum creatinine is unchanged, continue to titrate upwards the ACE inhibitor, with monitoring of renal function (creatinine) and serum electrolytes, and blood pressure.
- If serum creatinine increases > 30% from baseline, stop other potentially nephrotoxic drugs (for example NSAIDs), non-essential vasodilators (for example alpha blockers), and potassium retaining drugs (for example amiloride, triamterene), and if no signs of cardiac failure reduce dose of any diuretics. Consider seeking specialist advice.
- Repeat after 1 week and if serum creatinine persistently increased > 30% from baseline, half the dose of ACE inhibitors, and if serum creatinine persistently > 30% above baseline, seek specialist advice.
- If serum creatinine increases ≥ 50% from baseline, stop other potentially nephrotoxic drugs (for example NSAIDs), stop non-essential vasodilators (for example nitrates, alpha blockers), and potassium retaining drugs (for example amiloride, triamterene) and if no signs of congestion, reduce dose of any diuretics. Consider stopping the ACE inhibitor and or seeking specialist advice.
- Repeat after 1 week and if serum creatinine persistently increased > 50%

from baseline, stop the ACE inhibitor if still treated and seek specialist advice

- If serum creatinine increases > 100% from baseline, or serum creatinine is > 350 micromol/l stop the ACE inhibitor and seek specialist advice.
- A rise in serum potassium to ≤ 5.5 mmol/l is acceptable. If serum potassium rises to 5.6-5.9 mmol/l, review concomitant medication, and advice against the use of 'lo-salt' substitutes which may be high in potassium, repeat serum potassium after 1-2 weeks.
- If serum potassium ≥ 6 mmol/l, stop the ACE inhibitor and seek specialist advice.
- The rate of rise as well as the absolute level of serum potassium should be taken into account.

Adapted from the recommendations for monitoring ACE inhibitors in the NICE guidelines for the diagnosis and management of chronic heart failure in primary and secondary care , and part 2 of the renal National Service Framework.

Table 4

Initiation, titration and monitoring of aldosterone antagonists

Only one aldosterone antagonist is licensed for treatment of early post MI patients with heart failure at the time of issue of this guideline.

Eplerenone

Starting dose 25 mg, increasing to a maximum of 50 mg daily after 4 weeks (reduction in dose to 12.5 mg daily may be necessary if hyperkalaemia develops).

How to use

- Check renal function and serum electrolytes.
- Consider seeking specialist advice if concerned about an increased risk of developing serious hyperkalamia, for example in those with reduced renal function and or if baseline serum potassium is greater than 5 mmol/l.
- Initiate eplerenone 25 mg daily.
- Routinely measure blood biochemistry after 48 hours, 1 and 4 weeks, and 3 months, and 3 monthly thereafter, and 1 week after a titration upwards in the dose.
- If serum potassium rises to between 5.5 and 5.9 mmol/l reduce dose of eplerenone by half (to 25 mg on alternate days, or 12.5 mg daily) and monitor closely.
- The rate of rise as well as the absolute level of serum potassium should be taken into account.
- If serum potassium rises to ≥ 6.0 mmol/l, stop eplerenone and seek specialist advice.

Other advice to patients

- Avoid NSAIDs not prescribed by a physician (self-purchased 'over the counter' treatment, for example ibuprofen).
- Temporarily stop eplerenone if diarrhoea and/or vomiting occurs and contact physician.
- Some 'low salt' substitutes have a high potassium content and should be avoided.

Adapted from recommendations for monitoring the aldosterone antagonist, spironolactone, in the NICE guidelines for chronic heart failure and (Pitt, B. et al 2003b).

7 Coronary revascularisation

7.1 Coronary revascularisation recommendations

Hyperlink to the related evidence statements

7.1.1.1	All patients should be offered a cardiological assessment to consider whether coronary revascularisation is appropriate. This should take into account comorbidity (Grade A).

7.2 Clinical effectiveness of coronary revascularisation

7.2.1 Evidence statements for coronary revascularisation

7.2.1.1	Coronary artery bypass graft surgery reduces the incidence of fatal and non-fatal MI and improves survival in selected stable patients with coronary artery disease assessed on the basis of evidence of reversible myocardial ischaemia, the extent of coronary artery disease and left ventricular function (1++).

Back to recommendations

The Coronary Heart Disease National Service Framework (Department of Health 2000) states that for patients who have survived an MI the key investigations and interventions that should be offered to potential candidates for revascularisation are:

A: **Angiography** for those with

- Evidence of continuing extensive ischaemia (e.g. a strongly positive exercise test) and / or
- Angina that persists despite optimal medical therapy and lifestyle advice, followed by

B: **Quantitative assessment of urgency / risk / priority** using a published stratification system for patients accepting an offer of revascularisation to inform the

judgement about the balance of risks and benefits, and to help to determine each patients' relative priority for treatment, followed by

C: **Revascularisation**

Either

- Coronary artery bypass surgery (CABG) for those who meet the criteria for angiography, in whom the benefits are judged to outweigh the risks in terms of either:

o prognosis i.e. the angiogram has shown significant narrowing of:

left main coronary artery, or

three coronary arteries, or

two coronary arteries including the proximal left anterior descending coronary artery

b *symptom relief* i.e. with suitable coronary anatomy where severe angina persists despite optimal medical therapy.

OR

Percutaneous coronary intervention (PCI) with or without stenting for those who have continuous symptoms, in whom the benefits are judged to outweigh the risks and who have operable narrowings of one vessel or two coronary arteries without significant narrowing of the left main stem.

This guideline assessed the evidence for the effectiveness of coronary revascularisation for secondary prevention in patients after MI. It is beyond our scope to make recommendations as to how patients after MI are assessed, although it is recognised that in addition to the example of of exercise testing included in the extract from the Coronary Heart Disease National Service Framework (Department of Health 2000) there are other non-invasive methods to assess the extent of myocardial ischaemia, which include stress imaging.

A systematic review which searched the evidence in November 2002 examined the effectiveness of CABG verses medical treatment alone and PCI versus medical treatment alone in patients with coronary artery disease (CAD) (Pignone, M., Rihal, C., and Bazian Ltd. 2002). This review identified an earlier systematic review which found that after 5 and 10 years, CABG surgery compared with medical treatment reduced the risk of death from CAD (Yusuf, S. et al 1994). Seven randomised controlled trials were included with individual results from 2649 patients with CAD. Most were middle aged men with multi-vessel disease and good LV function who were enrolled between 1972 to 1984 (97% male, mean age 50.8 (standard deviation 6.9) years, (with 7% aged > 60 years), 80% EF > 50%, 60% prior MI, 7% left main stem disease, 83% with 2 to 3 vessel disease). Ninety four percent of patients assigned to CABG underwent surgery, and 37.4% of patients initially assigned to medical treatment alone underwent CABG surgery during the following 10 years.

The relative survival benefits of CABG surgery were similar in patients with normal or abnormal LV function. However, the absolute benefit of CABG surgery was greater in patients with LV dysfunction because the baseline risk of death was higher (Yusuf, S., Zucker, D., Peduzzi, P. et al 1994). The absolute benefit of CABG surgery was also greater in patients with more extensive coronary disease (three vessel disease, left main stem disease or other patients with proximal LAD disease). The authors noted that improvement in survival was greater in patients with left main stem disease, intermediate for those with three vessel disease and least for those with one with one vessel or two vessel disease. There was a trend towards a greater benefit from surgery in those with abnormal exercise tests, compared to those with normal tests. The authors concluded that patients with extensive coronary disease or documented ischaemia and those who have clinical or angiographic features indicating high or moderate risk should be considered for CABG surgery. Patients with one vessel or two vessel disease, and a low risk profile are likely to be better managed initially with medical treatment. CABG surgery may be considered if symptoms are intractable or worsen (Yusuf, S., Zucker, D., Peduzzi, P. et al 1994).

The systematic review (Pignone, M., Rihal, C., and Bazian Ltd. 2002) identified an earlier systematic review which examined the effectiveness of PCI compared to medical treatment in patients with non-acute coronary disease (Bucher, H. C. et al

2000). The review showed that PCI improved angina compared with medical treatment, but PCI was associated with a higher rate of CABG surgery and a statistically non-significant trend towards higher rates of mortality and myocardial infarction Of the 6 randomised controlled trials in the review, 3 included patients with multivessel disease and pre-existing Q wave MI (Folland, E. D., Hartigan, P. M., and Parisi, A. F. 1997) (RITA-2 trial participants. 1997) (Pitt, B. et al 1999). There were 953 patients treated with PCI and 951 patients who received medical treatment. Follow-up varied from 6 to 57 months. There was significant heterogeneity in the studies. The six trials included in this review (Yusuf, S., Zucker, D., Peduzzi, P. et al 1994) were published between 1992 and 1999, and since then there has been further development in the techniques PCI, for example with the use of stents and other adjunctive therapies.

The systematic review (Pignone, M., Rihal, C., and Bazian Ltd. 2002) identified one further randomised controlled trial that compared three different treatment strategies; revascularisation, with either CABG or PCI, versus angina guided drug treatment versus angina plus ischaemia guided drug treatment (Davies, R. F. et al 1997). All patients had angiographically documented CAD, evidence of reversible ischaemia on exercise or pharmacological stress testing and at least one episode of asymptomatic ischaemia during 48 hour ambulatory ECG monitoring (Davies, R. F., Goldberg, A. D., Forman, S. et al 1997) (558 patients, 86% male, average age 61 years, 89% EF ≥ 50%, 40% prior MI, approximately 76% with 2 to 3 vessel disease). Two year mortality was 6.6% for the angina-guided strategy, 4.4% for the ischemia-guided strategy, and 1.1% for the revascularisation strategy ($P < 0.005$ for the angina guided strategy versus revascularisation). At 2 years, the rates for death or myocardial infarction were 12.1% for the angina-guided strategy, 8.8% for the ischemia-guided strategy, and 4.7% for the revascularisation strategy ($P < 0.01$ for the angina guided strategy versus revascularisation) (Davies, R. F., Goldberg, A. D., Forman, S. et al 1997).

The authors of the most recent systematic review (Pignone, M., Rihal, C., and Bazian Ltd. 2002) noted that the included studies may not be easily generalised to current practise because the studies were performed on patients generally 65 years or younger, and the majority of participants were men.

In summary, the GDG concluded that there was evidence of effectiveness of coronary revascularisation for secondary prevention in selected stable patients with non-acute coronary disease, and thus patients after MI who had not been considered for coronary revascularisation during the acute phase of management should be considered for further specialist cardiological assessment.

7.3 Health economics

There were no studies found answering the question which sought to identify stable patients after MI who would or who would not benefit prognostically from revascularisation. Once these patients are identified they are referred for further assessment. The scope of the MI: Secondary Prevention guideline does not include evaluating methods of revascularisation.

8 Selected patient subgroups

8.1 Patients with hypertension

8.1.1 Recommendations for patients with hypertension

8.1.1.1	Hypertension should be treated to the currently recommended target of 140/90 mmHg or lower given in 'Hypertension' (NICE clinical guideline 34). Patients with relevant comorbidities, for example diabetes or renal disease, should be treated to a lower blood pressure target (Grade A).

The National Service framework for coronary heart disease, Department of Health (www.doh.gov.uk) states that for people with diagnosed CHD or other occlusive arterial disease the intervention for blood pressure is:

- Advice and treatment to maintain blood pressure below 140/85 mmHg.

The guideline development group agreed that in uncomplicated patients with a history of MI the optimal target blood pressure should be in accordance with NICE Hypertension Guideline 2006, which is currently ≤ 140/90 mmHg (National Institute for Health and Clinical Excellence. 2006) (National Collaborating Centre for Chronic Conditions 2006).

8.2 Patients with left ventricular dysfunction

8.2.1 Recommendations for patients with left ventricular dysfunction

8.2.1.1	Patients who have left ventricular systolic dysfunction should be considered for an implantable cardioverter defibrillator in line with 'Implantable cardioverter defibrillators for arrhythmias' (NICE technology appraisal guidance 95) (Grade A).

Left ventricular (LV) systolic function is an important predictor of outcome in patients after MI, and patients with LV systolic dysfunction have an adverse prognosis compared to those with preserved LV function. Specific recommendations for secondary prevention in those after MI with LV systolic dysfunction are included in the following chapters, and in addition for those with chronic heart failure reference should be made to the NICE Chronic Heart Failure clinical guideline No. 5.

8.2.2 Cross referenced drug therapy recommendations

Specific evidence statements and recommendations for this patient subgroup have been made for the following drug class groups in the Drug Therapy Chaper 6;

ACE inhibitors and angiotension II receptor blockers Section 6.2

Beta blockers Section 6.4

Aldosterone antagonists Section 6.8

Calcium channel blockers Section 6.6

Other drug treatments are the same for patients with and without LV systolic dysfunction.

8.2.3 Cross referenced cardiac rehabilitation recommendations

Information for cardiac rehabilitation in stable patients with a history of MI and LV systolic dysfunction can be found in Chapter 5.

8.2.4 Cross referenced implantable cardioverter defibrillators

In addition, a Technology Appraisal entitled ‘Evidence summary of Technology Appraisal 95: Implantable cardioverter defibrillators for arrhythmias: NICE 2006’ (Sinclair, A. J. et al 2005) makes recommendations regarding patients with a history of MI and LV systolic dysfunction concerning implantable cardioverter defibrillators, currently as follows:

NICE states that:

Implantable cardioverter defibrillators are recommended for patients in the following categories.

Secondary prevention, that is, for patients who present, in the absence of treatable causes, with one of the following:

- Having survived a cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF)
- Spontaneous sustained VT causing syncope or significant haemodynamic compromise
- Sustained VT without syncope or cardiac arrest, who have an associated reduction in ejection fraction (LVEF of less than 35%) but no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.

Primary prevention, that is, for patients who have:

- A history of previous (more than 4 weeks) myocardial infarction (MI) and:
- Either

LV dysfunction with an LVEF of less than 35% but no worse than class III of the NYHA functional class of heart failure and

Non-sustained VT on Holter (24 hour electrocardiogram [ECD]) monitoring and

Inducible VT on electrophysiological (EP) testing

OR

LV dysfunction with an LVEF of less than 30% (no worse than class III of the New York Heart Association functional classification of heart failure)

and

QRS duration of equal to more than 120 milliseconds.

A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmic right ventricular dysphasia (ARVD), or having undergone surgical repair of congenital heart disease.

8.3 Patients with a proven MI in the past (greater than 1 year)

8.3.1 Cross referenced recommendations for patients with a proven MI in the past (greater than 1 year)

In a number of studies on which this guideline is based, participants with a previous MI were included in the study population, although there were no studies of interventions just recruiting these patients. Below we highlight sections of the guideline addressing this group of patients.

Recommendations about continuing specific drug therapy initiated early after MI, and for initiating treatment in patients with an MI more than 1 year earlier, but not previously treated, are made in Chapter 6. Unless specifically stated, treatment initiated early after MI should be continued long term. While for some patients with a proven MI in the past, referral for specialist cardiological assessment with respect to drug therapy will be appropriate.

Lifestyle changes (dietary modification, physical activity, weight management and advice about smoking) are equally applicable to those with an MI in the past as to those with a more recent MI (Chapter 4).

Comprehensive cardiac rehabilitation (Chapter 5) may be appropriate for some patients with an MI in the past, based upon the patient's individual needs, but it is not recommended that this be routinely offered to all patients with an MI more than 1 year earlier.

9 Communication of diagnosis and advice

9.1 Communication of diagnosis and advice recommendations

9.1.1	After an acute MI, confirmation of the diagnosis of acute MI and results of investigations, future management plans and advice on secondary prevention should be part of every discharge summary (GPP).
9.1.2	A copy of the discharge summary should be offered to the patient (GPP).

The guideline development group considered that explicit communication between specialist and generalist care is a pre-requisite for implemention of the recommendations in this guideline. The discharge summary after an MI has an important role in specifying future management, and as such, will aid the communication between specialist and generalist care.

Appendices A–G are in a separate file

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