National Clinical Guideline Centre

MI - secondary prevention

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

Partial update of NICE CG48

Methods, evidence and recommendations

November 2013

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Royal College of Nursing

The Royal College of Surgeons of England

RCGP Royal College of General Practitioners

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Appendices A – Q are in separate files.

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Acknowledgements 2007

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1 Introduction

Myocardial infarction (MI) remains one of the most dramatic presentations of coronary artery disease (CAD). Complete occlusion of the artery often produces myocardial necrosis and the classical picture of a heart attack with severe chest pain, electrocardiographic (ECG) changes of ST-segment elevation, and an elevated concentration of myocardial specific proteins in the circulation. Such people are described as having a ST-segment elevation myocardial infarction (STEMI). Intermittent or partial occlusion produces similar, but often less severe clinical features, although no or transient and undetected ST elevation. Such cases are described as a non-ST segment elevation myocardial infarction (NSTEMI). People who have suffered from either of these conditions are amenable to treatment to reduce the risk of further MI or other manifestations of vascular disease, secondary prevention.

1.1.1 Epidemiology

The acute treatment of both STEMI and NSTEMI has changed considerably over the last decade. In England and Wales, the Myocardial Ischaemia National Audit Project (originally Myocardial Infarction National Audit Project) has documented the application of these changes in treatment and of the extent of application of secondary prevention measures, the MINAP reports clearly describes the accompanying reductions in mortality since the late 1990s. The 2012 report describes more than 79,000 hospital admissions due to MI in the previous year, 41% STEMI and 59% NSTEMI.[304] Twice as many men had MIs as women, their average age for a first MI being 65 years, while women had their first MI at 73 years. Thirty-day mortality was almost 13% for STEMI in 2003-4, falling to 8% in 2011-12 with similar falls for NSTEMI.

Despite dramatic advances in treatment and prevention, particularly secondary prevention, MI remains a common and important cause of death and morbidity. There are currently around 1 million men and nearly 500,000 women who have had an MI in the UK, a large number of people in whom secondary prevention is important.

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1.1.2 Secondary prevention of myocardial infarction

People who had an MI have a considerably increased risk of a further attack. Since seminal studies in the 1980s, clinical trials have demonstrated that various secondary prevention treatments improve outcomes in such people, drug therapy such as aspirin, clopidogrel, beta-blockers, ACE inhibitors and statins, changes in lifestyle, for example stopping smoking, and cardiac rehabilitation. Such interventions need to be applied in a systematic fashion to be successful in the whole population; clinical guidelines are an important tool to support this application.

The previous guideline, CG48, was published in 2007, offering comprehensive advice to prevent further myocardial infarction and progression of vascular disease in those who had already suffered an MI, either recently or in the past, considered to be those with an MI more than 12 months ago. Since 2007, there has been a major change in the management of MI, both STEMI and NSTEMI, although more dramatically the former. Primary percutaneous coronary intervention (PPCI) has replaced thrombolysis in most cases of STEMI. In 2007 15% cases underwent PPCI, 60% receiving lytic therapy. The MINAP report for 2011-12 demonstrates that only 5% of people with STEMI underwent thrombolysis, 30% had no reperfusion therapy (due to contraindications or late presentation) the remaining 65% undergoing PPCI. This improvement in acute treatment may impact on the efficacy of secondary prevention, hence one reason to update the guideline. New findings on enhancing people's uptake of cardiac rehabilitation, on antithrombotic therapy, omega-3 fatty acid supplementation, ACE inhibitors and beta-blockers have all contributed to a need for this guideline to be updated.

Drug therapy for secondary prevention is already effectively applied, nationally. For England, the 2012 MINAP report shows prescription of aspirin at hospital discharge was 99%, beta-blockers 96%, statins 97%, ACE inhibitors 95% and clopidogrel or other thienopyridine inhibitors 96%. These figures take into account contraindications, but do not include the tendency for a reduction in use of these agents over the months following an MI. However uptake of cardiac rehabilitation is still low, only 44% started outpatient cardiac rehabilitation programmes in England, Northern Ireland and Wales, following an MI. This figure is taken from the 2012 National Audit of Cardiac Rehabilitation Report, which also describes a mean 53 day wait for the beginning of an outpatient rehabilitation programme. Interventions which may enhance uptake and adherence to cardiac rehabilitation programmes, given the established benefit described in CG48, should be part of the guideline for secondary prevention.

Update 2013

1.1.3 Changes in the universal definition of myocardial infarction

A further consideration in this update was the change in the definition of MI that took place after 2007. In 2007 the European Society of Cardiology jointly with the American Heart Association, the American College of Cardiology and the World Heart Federation published recommendations re-defining myocardial infarction. This was necessary due to the increasing use of more sensitive circulating markers of myocardial damage. It had become clear that people who had not been diagnosed with myocardial infarction before the use of these markers, had indeed had MIs, and were at the increased risk associated with this condition.

1.2 Introduction (2007)

1.2.1 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).

1.2.2 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 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help people to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- guideline topic is referred to NICE from the Department of Health
- stakeholders register an interest in the guideline and are consulted throughout the development process
- the scope is prepared by the National Clinical Guideline Centre (NCGC)
- the NCGC establishes a guideline development group
- a draft guideline is produced after the group assesses the available evidence and makes recommendations
- there is a consultation on the draft guideline
- the final guideline is produced

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- information for the public is written using suitable language for people without specialist medical knowledge
- the NICE pathway brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

This is a partial update of 'MI: secondary prevention', NICE clinical guideline 48 (2007). See Section 2.4 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

Update 2013

This update is being undertaken as part of the guideline review cycle.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Care Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Dr Philip Adams in accordance with guidance from the National Institute for Health and Care Excellence (NICE).

The group met every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

Update 2013

2.4 What this guideline covers

The guideline covers the following populations:

- Adults aged 18 and older who had a myocardial infarction (type 1 according to the universal definition). This will include people who have not yet been discharged from hospital, where relevant and those who have had an MI in the past (more than 12 months ago).
- Specific consideration will be given to the needs of populations thought to have reduced uptake and adherence to cardiac rehabilitation programmes, including people from South Asian communities, black and minority ethnic groups, low socioeconomic groups or rural communities, people with physical and learning disabilities, women and people with anxiety and/or depression.

The guideline updates the following clinical areas from CG48:

- fish diet and omega-3 fatty acids
- interventions to increase uptake of and adherence to cardiac rehabilitation programmes
- barriers to the uptake of and adherence to cardiac rehabilitation programmes
- initiation, duration and dose titration of ACE inhibitors
- initiation of antiplatelet agents after the acute phase
- duration of antiplatelet therapy (including after stenting)
- antiplatelet therapy in those with an additional indication for anticoagulation
- beta-blockers
- angiotensin II receptor blockers .

For further details please refer to the scope in Appendix A and review questions in section 3.2.

2.5 What this guideline does not cover

The guideline does not cover:

- children and young people under 18 years
- people being diagnosed as having a type 2, 3, 4a, 4b or 5 according to the universal definition of myocardial infarction.

The guideline does not cover the acute management of MI. Recommendations on the acute management of MI can be found in:

- Myocardial infarction with ST-segment elevation. NICE clinical guideline TBC (due for publication July 2013).
- Unstable and angina and NSTEMI. NICE clinical guideline 94 (2010).

2.6 Relationships between the guideline and other NICE guidance

Health Technology Appraisals to be updated by this guidance:

Recommendation 1.3 from Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. NICE technology appraisal 80 (2010).

Related NICE Health Technology Appraisals:

Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisal 236 (2011).

Clopidogrel and modified-release dipyridamole from the prevention of occlusive vascular events. NICE technology appraisal 210 (2010).

Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal 182 (2009).

Drug eluting stents for the treatment of coronary artery disease. NICE technology appraisal 152 (2008).

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal 132 (2007).Implantable cardioverter defibrillators for arrhythmias. NICE technology appraisal 95 (2006).

Statins for the prevention of cardiovascular disease. NICE technology appraisal 94 (2006).

Guidance on the use of coronary artery stents. NICE technology appraisal 71 (2003).

Related NICE Clinical Guidelines:

General

Patient experience in adult NHS services. NICE clinical guideline 138 (2012).

Medicines adherence. NICE clinical guideline 76 (2011).

Condition specific

Dyspepsia. NICE clinical guideline 17 (2004).

Familial hypercholesterolemia. NICE clinical guideline 71 (2008).

Depression in adults. NICE clinical guideline 90 (2009).

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Depression in adults with a chronic physical health problem. NICE clinical guideline 91 (2009).

Lipid modification. NICE clinical guideline 67 (2010).

Chest pain of recent onset. NICE clinical guideline 95 (2010).

Obesity. NICE clinical guideline 43 (2010).

Unstable angina and NSTEMI. NICE clinical guideline 94 (2010)

Chronic heart failure. NICE clinical guideline 108 (2011).

Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. NICE clinical guideline 113 (2011).

Management of stable angina. NICE clinical guideline 126 (2011).

Hypertension. NICE clinical guideline 127 (2012).

Myocardial infarction with ST-segment elevation. NICE clinical guideline 167 (2013).

Related NICE Public Health Guidance:

Brief interventions and referral for smoking cessation. NICE public health guidance 1 (2006).

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

Prevention of cardiovascular disease. NICE public health guidance 25 (2010).

NICE Related Guidance currently in development:

Dyspepsia/GORD. NICE clinical guideline. Publication TBC.

Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention (update). NICE technology appraisal guidance. Publication TBC.

Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome. NICE technology appraisal. Publication expected March 2015.

Lipid modification (update). NICE clinical guideline. Publication expected July 2014.

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2.6.1 Aim of the guideline (2007)

Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'.[98]

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.

2.6.2 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 Q.

2.6.3 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

2.6.4 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 retrospectively. 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.

Update 2013

3 Methods

3.1 Methods (2013)

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2012.[318]

3.1.1 Amendments to 2007 text

All text and recommendations from the previous guideline, CG48, that has not been updated (therefore review questions have not been generated and evidence has not been searched for) has been left unchanged. Amendments to recommendations are detailed in Appendix O.

3.2 Developing the review questions and outcomes

Review questions were developed in a PICO framework (population, intervention, comparison and outcome) for intervention reviews. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A). Further information on the outcome measures examined follows this section.

Chapter	Review questions	Outcomes
Lifestyle	What is the clinical and cost effectiveness of omega-3 fatty acids in all people with myocardial infarction?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
	What is the clinical and cost effectiveness of an oily fish diet in all people with myocardial infarction?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
Cardiac rehabilitation	Which factors are associated with a person's uptake and adherence to a cardiac rehabilitation programme after an MI?	• Factors associated with a person's uptake and adherence to cardiac rehabilitation programme. • Factors associated with healthcare professionals in promoting a person's uptake and adherence to cardiac rehabilitation programme.
	Which interventions designed to increase engagement in and/or adherence to cardiac rehabilitation programmes are effective and cost effective in people who have had an MI?	• Adherence • Uptake • Completion • Reasons for withdrawal

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Chapter	Review questions	Outcomes
		• Quality of life • Adverse effects.
Drug therapy	What is the clinical and cost effectiveness of adding ACE inhibitors versus placebo to improve outcome in people after an MI and is there an optimal duration?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
	Is there an optimal time for ACE inhibitors to be initiated in people who have had a MI?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
	Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had a MI?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
	What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
	What optimal duration clopidogrel should be continued in people after MI?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
	In people with an MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation

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Chapter	Review questions	Outcomes
		• Stroke • Readmission/hospitalisation • Side effects/adverse events.
	What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an MI and an indication for anticoagulation?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
	Is there an optimal time for a beta-blocker to be initiated in people who have had a MI?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.
	What is the clinical and cost effectiveness of adding a beta-blocker versus placebo to improve outcome in people after an MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?	• Mortality (all cause, cardiac or sudden) • Quality of life • Reinfarction • Revascularisation • Stroke • Readmission/hospitalisation • Side effects/adverse events.

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3.3 Searching for evidence

3.3.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual 2012.[318] Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in the English language. All searches were conducted on core databases: MEDLINE, Embase and The Cochrane Library. Additional subject specific databases were used for some questions: AMED for the search on omega-3 fatty acids and oily fish consumption, Psycinfo for the search on barriers to the uptake of and adherence to cardiac rehabilitation and Cinahl for the search on barriers to the uptake of and adherence to cardiac rehabilitation and interventions to increase uptake and adherence to cardiac rehabilitation. All searches were updated on 25th March 2013. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

3.3.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to people who had an MI in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2011, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in the English language.

The search strategies for health economics are included in Appendix F. All searches were updated on 25th March 2013. No papers published after this date were considered.

3.4 Evidence of effectiveness

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The research fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C).
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual.[318]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G).
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
  - Observational studies: data presented as a range of values in GRADE profiles
  - Qualitative studies: each study is summarised in a table and presented in a narrative. The quality of reporting for each study was summarised in the Evidence Table and in the Linking of Evidence to Recommendations.

3.4.1 Inclusion/exclusion of studies

See the review protocols in Appendix C for full details.

The inclusion or exclusion of studies was based on the review protocols. The GDG were consulted about any uncertainty regarding inclusion/exclusion of selected studies.

The proportion of people who had an MI was among the criteria used for the inclusion of studies in the evidence reviews. A direct study population was defined as adults who had a myocardial infarction (type 1 universal definition) and made up more than 75% of the study numbers. This threshold was chosen by the GDG as a minimum number of people who had an MI that would provide relevant data, taking into account uncertainty in diagnosis of MI, the need to include relevant populations and changes in medical practice. In older studies of acute coronary syndrome, a large proportion of subjects were classified as having unstable angina based on changes in ECG and enzyme levels. If these subjects were recruited to studies of MI using current practice, they would be diagnosed as having an NSTEMI based on troponin concentrations. This is because of changes in the definition of MI reflecting the use of the more sensitive marker of myocardial damage, troponin. This change came about in 2007, with the publication of the Universal definition of myocardial infarction [440,441].

If insufficient high quality data were available, all people with a history of coronary heart disease (stable angina, unstable angina, or revascularisation) and less than 75% people who had an MI were included but the quality of the evidence was downgraded for indirectness. For indirect populations, a maximum of 30% people with heart failure was accepted. If people had Killip Class II or NHYA Class II or above, they were considered to have heart failure. Those with Killip Class I were not considered to have heart failure, whereas those with NYHA Class I were classified as unclear.

The 30% threshold was chosen by the GDG as a maximum number of people with heart failure that would be acceptable to include as part of the post MI population and yet still provide relevant data. Those with heart failure compromise a subset of readily identifiable people after MI. They have a different prognosis, and suffer major adverse events of a different nature and at a higher rate than uncomplicated people after an MI. Thus the inclusion of a large number of people with heart failure in a post MI population will be potentially misleading. The percentage chosen was therefore selected by the GDG as a compromise taking into account uncertainty in diagnosis of MI and of heart failure, the need to include relevant populations and changes in medical practice.

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For outcomes such as adverse events, direct and indirect study populations were often combined in the meta-analysis since the type of coronary heart disease is unlikely to influence results such as major and minor bleeding.

If large clinical trials with a mixed population provided a subgroup analysis on people who had an MI we included this data in the review. However, it is important to note that this carries a risk of bias if the subgroups were not predetermined by the authors. In such instances, randomisation will no longer be maintained and there is a chance the groups will not be matched at baseline. Furthermore, there is a risk of reporting bias if the authors only provide one outcome for the subgroups and a risk of publication bias if the subgroup is not predetermined.

Composite outcomes were only included if no single outcomes were available from the study. The GDG decided to only include single outcomes since they are more meaningful and better defined. The outcomes included in the composite can vary across studies thus making it difficult to meta-analyse. Composite outcomes carry a risk of reporting bias since it is unknown if the authors combined certain outcomes in order to report a positive result. Also, it is not known if one outcome occurs more often than another and is driving any overall effect.

The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality as critical outcomes. However, quality of life was also considered of critical importance given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation.

Rehospitalisation was considered an important outcome by the GDG. It is clearly undesirable and has significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered important outcomes. The number and/or the type of adverse events recorded in the study were reported in the guideline, not the number of people who had 1 or more adverse events.

For the qualitative review, the GDG decided that only studies from the UK should be used since the participants' experience with cardiac rehabilitation programs are likely vary from country to country, as do costs, population demographics and access to care.

Only studies that used prescribed drugs licensed within the UK were included in the reviews.

Cohort studies were only included in the review if randomised controlled trials were not available. RCTs are less susceptible to selection bias because background factors (confounders) are mostly similar in the two treatment arms since participants are randomised to the groups. Also, unlike observational studies, RCTs rely less on people's recollection that can be misreported. There is also a chance in cohort studies that something fundamentally different between the groups may explain why they are receiving different treatments (i.e. different health status) or have different lifestyles (i.e. consume large quantities of fish).

Abstracts were only included if randomised controlled trials, cohort studies or relevant qualitative papers were unavailable.

3.4.2 Methods of combining studies

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Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: all-cause mortality, cardiac death, sudden death, reinfarction, stroke, revascularisation, rehospitalisation and adverse events. If there was heterogeneity random effects techniques were used. The continuous outcome of mean attendance to a cardiac rehabilitation programme was analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales or if only one study was available, standardised mean differences were used. The continuous outcome, quality of life, was not available for any of the reviews. Where reported, time-to-event data were presented as a hazard ratio.

Hazard ratios were presented in preference to relative risk for outcomes that were influenced by trial duration i.e. all-cause mortality, reinfarction, regardless of the number of papers available for each calculation. The exceptions to this were: 1) when the quality of the hazard ratio data were low or; 2) key papers that influence current medical practice were excluded from the analysis because they only provide relative risk data. In such instances relative risk was also presented.

The hazard ratio equals a weighted relative risk over the entire duration of a study and is derived from a time-to-event curve or Kaplan-Meier curve. This curve describes the status of both population groups at different time points after a defined starting point. Because some participants are often followed for a longer period of time than others (because they remained in the study while others dropped out), the time-to-event curve usually extends beyond the mean follow-up duration.

Hazard ratios were calculated wherever possible. To calculate hazard ratios, the log rank p value of the survival curves and the control and intervention event rates were needed. An Excel spread sheet with macros was used to calculate the log of the hazard ratio and its standard error. The generic inverse variance (GIV) method in Review Manager was then used to analyse the HR data. Alternatively, O-E and V data could be extracted from the spreadsheet and the O-E method could be

used in RevMan. The O-E and V data refer to the observed minus the expected number of events and is variance (calculated from individual patient data). The number of events and total number of participants in the experimental and control groups can also be entered in RevMan which are needed for the calculation of absolute risk in GRADEpro.

Hazard ratios differ from relative risk ratios in that the latter are cumulative over an entire study, using a defined endpoint, while the former represent an instantaneous risk over the study time period. In contrast to relative risk, hazard ratios take into account the timing of events which may not be evenly distributed throughout the study period.

As the trial progresses, at some point prediction of treatment effect becomes very imprecise because there are few participants available to estimate the probability of the outcome of interest. Confidence intervals around the survival curves capture the precision of the estimate. We can estimate relative risk by applying an average, weighted for the number of participants available, over the entire study duration. Such an estimate is the hazard ratio.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. The p value is taken as <0.1 instead of the standard <0.05 since the test for heterogeneity has low power. The number of studies is usually low and may fail to detect heterogeneity as statistically significant when it exists. To compensate for the low power of the test a higher significance level is taken, $P < 0.1$, for statistical significance. Heterogeneity was also investigated if the forest plot showed inconsistency in the results but it was not detected by the chi-squared test. Where significant heterogeneity was present, we carried out predefined subgroup analyses on a selection of the following variables: timing of onset of the treatment, type of intervention, directness of the population, type of myocardial infarction, type of acute treatment, country the study was conducted in, comorbidity, age, ethnicity, type of stent, left ventricular systolic dysfunction, duration of treatment, indication for treatment. Details of these subgroups can be found in the review protocols. Sensitivity analysis based on the quality of studies was also carried out if there were differences, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 20% missing data or differential missing data of 10% or higher than the event rate, this was examined in a sensitivity analysis. For the latter, the duration of follow-up was also taken into consideration prior to including in a sensitivity analysis.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

For binary outcomes, absolute event rates were calculated using the GRADEpro software using event rate in the control arm of the pooled results. These results are presented in the GRADE tables and in a summary of findings table for GDG discussion only.

Relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers, and standard errors were calculated from the 95% confidence intervals. The log of the effect size with its standard error was entered into the generic inverse variance technique in the Cochrane Review Manager (RevMan5) software. Observational Studies were not combined in a meta-analysis. Sensitivity analyses were carried out on the basis of study quality and results were presented from each individual paper. The means and standard deviations of continuous outcomes were required for meta-analysis.

1.1.2.1 Strata

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For a number of reviews, the results were presented separately for pre-stratified groups or strata. Strata included:

- left ventricular (LV) function
- type of omega-3 fatty acid supplementation)
- timing of the onset of treatment after the myocardial infarction
- duration of treatment
- population (that is, STEMI versus NSTEMI and patient versus healthcare professional)

For more details on these strata refer to the protocols (see Appendix C).

Where the LV function was considered as a stratum, papers were divided into the following categories:

- Left ventricular systolic dysfunction (LVSD) – those specified as having left ventricular dysfunction, left ventricular failure or an ejection fraction of less than 40%.
- No left ventricular systolic dysfunction (N).
- Unselected patients (Us) – including papers with a mixture of LV function, studies reporting a mean ejection fraction of 40% and where LV status was not reported however, it is likely that they included people with a range of LV function.
- Unclear (Uc) – not reported.

The LVSD status of the participants in each study was highlighted in the forest plots by the preceding letters: LV for those with LVSD; N for people without LVSD; Us unselected patients and Uc for those that were unclear (that is, not reported).

Where the timing of the onset of treatment after the myocardial infarction was considered as a stratum, papers were divided in the following categories:

- people who had an MI, in whom treatment was initiated between 0 and 72 hours of the MI (acute MI).
- people who had an MI in whom treatment was initiated between 72 hours and 1 year of the MI (sub-acute MI).
- people who have had an MI and who were treated was more than a year after the MI (MI in the past).

For the review on beta-blockers, the presence of chronic obstructive pulmonary disease was considered as a stratum, papers were divided into the following categories wherever possible:

- COPD – where participants had bronchial asthma, bronchospasm, “bronchospastic lung disease”, bronchitis or require bronchodialators.
- Unselected (Us) – including people with mixed COPD status.
- Unclear (Uc) – where people were described as being smokers, having pulmonary oedema, pulmonary venous congestion, severe disease of the respiratory system, dyspnoea, pulmonary rales, pulmonary congestion or chronic bronchopneumopathy and papers where no information was provided.

Data synthesis for qualitative studies

Factors associated with the uptake and adherence to cardiac rehabilitation programmes were extracted from qualitative papers (for example interviews, questionnaires) and summarised under the strata that were identified by the GDG as populations with low levels of participation. The results were presented in a table and reported in a narrative in the guideline text. Data from qualitative studies were extracted until the point of saturation, that is, when no more additional findings were

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found. Studies using Interviews and questionnaires were included because they are considered higher quality qualitative studies compared with case studies or observational studies because they provide more insight and provide data rich information.

Appraising the quality of evidence by outcomes for qualitative studies

The criteria used to assess the studies' quality included the clarity of the aims; the rigor of the methodology; the clarity of the description of the role of the researcher; the clarity of the description of the context; the adequacy of the data analysis; the reliability of the analysis; the clarity of the findings; the relevance of the findings to the study aims and the appropriateness of the conclusions. The limitations of the studies were summarised in the extraction tables and comments were made in the "Linking Evidence to Recommendations" (LETRs).

Appraising the quality of evidence by outcomes for RCTs and observational studies

The evidence for each outcome from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as two separate tables in this guideline. The "Clinical/Economic Study Characteristics" table includes details of the quality assessment while the "Clinical /Economic Summary of Findings" table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and a summary statement grading the quality of evidence for that outcome. In this table, for continuous outcomes, the columns for intervention and control indicate the sample size, summed across the included studies. For binary outcomes such as number of participants with an adverse event, the event rates (n/N: sum of number of participants with events divided by sum of number of participants) are shown with percentages. Publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent.

Each binary outcome was examined separately for the quality elements listed and defined in Table 1 and each graded using the quality levels listed in Table 2. The main criteria considered in the rating of these elements are discussed below (see section 3.4.3). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

The GRADE toolbox is currently designed only for randomised trials and observational studies.

Table 1: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few participants and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

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Table 2: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level.
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels.

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

3.4.3 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias were rated down 1 or 2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 3.4.5, 3.4.6 and 3.4.7.

Grading the quality of qualitative studies
A customised quality assessment was carried out on the qualitative studies. A narrative summary of the quality is provided in the Linking Evidence to Recommendation (LETR) tables and in the Evidence Tables. The assessment included how well the methods and population were reported, the richness of the data extracted from the participants (interviews are preferred to questionnaires), interpretation of the results by the authors and relevance of the findings to the guideline.

3.4.4 Study limitations

The main limitations considered for randomised controlled trials are listed in Table 4.

The GDG accepted that investigator and participant blinding in warfarin intervention studies is difficult to achieve in most situations. Nevertheless, open-label studies for warfarin were downgraded to maintain a consistent approach in quality rating across the guideline.

Outcomes provided by a subgroup analysis conducted retrospectively by the authors and not first described in the methodology (and hence participants were not first stratified and then randomised) were downgraded for risk of bias.

Numerous studies were published during a time when study details were not well described, so information on methods of randomisation and allocation concealment were often omitted but these procedures may have been carried out appropriately. However, the studies were downgraded to maintain a consistent approach in quality rating across the guideline.

Table 4 lists the limitations considered for randomised controlled trials.

Table 4: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling participants are aware of the group to which the next enrolled patient will be allocated (for example major problems in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number).
Lack of blinding	Participant, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which participants are allocated.
Incomplete accounting of participants and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Recruitment bias in cluster randomised trials • Small participant number/insufficient power Subgroup analysis not pre-specified.

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3.4.5 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of greater than 50%), but no plausible explanation can be found, the quality of evidence was downgraded by 1 or 2 levels. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

3.4.6 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is

important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

In this guideline, papers that included people who had an MI that made up less than 75% of the entire pool of participants were classed as indirect. These papers were only included if no direct studies were available (75 to 100% people who had an MI) and were subsequently downgraded for indirectness in GRADE pro. A 75% minimum was also used as threshold for indirectness for other populations, for example, people who had a STEMI.

3.4.7 Imprecision

Imprecision refers to the certainty in the effect of the outcome. When results are imprecise we are uncertain if there is an important difference between intervention or not.

The sample size, event rates and the resulting width of confidence intervals were the main criteria considered for imprecision. For all dichotomous outcomes the width of the confidence intervals were compared against the default minimal important differences (MID), 0.75 and 1.25. If the confidence interval crossed either one of these MIDs the precision of the result was downgraded in GRADE software. However, the MIDs were not considered a single rigid boundary because they are an estimate and have some variability. For this reason discretion was used when a confidence interval just crossed an MID (i.e. 1.26), in such cases the results were not necessarily downgraded.

The GDG were asked at the outset of the guideline if they were aware of any established values for MIDs for the outcomes included in the review. No published or established MIDs were identified. Therefore, the GDG agreed that the default values stated in GRADEpro were appropriate for our outcomes. The default thresholds suggested by GRADE are a relative risk reduction of 25% (relative risk of 0.75 for negative outcomes) or a relative risk increase of 25% (risk ratio 1.25 for positive outcomes) for dichotomous outcomes. For continuous outcomes, if only one trial was included as the evidence base for an outcome, the mean difference was converted to the standardised mean difference (SMD) and checked to see if the confidence interval crossed 0.5. However, the mean difference (95% confidence interval) was still presented in the GRADE tables. If 2 or more included trials reported a continuous outcome then the default approach of multiplying 0.5 by the standard deviation (taken as the median of the standard deviations across the meta-analysed studies) was employed.

When one of the interventions had zero events, the Peto fixed effects method for odds ratios was used instead of relative risk.

The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect as outlined in Table 5.

Table 5: Criteria applied to determine precision

Dichotomous and continuous outcomes **The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect:**	
No serious imprecision	Does not cross either of the 2 minimal important difference (MID) thresholds (the threshold lines for appreciable benefit or harm); defined as precise.
Serious	Crosses one of the 2 MID thresholds (appreciable benefit or appreciable harm); defined as imprecise.
Very serious	Crosses both of the 2 MID thresholds (appreciable benefit and appreciable harm); defined as imprecise.

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3.4.8 Evidence statements

Evidence statements were produced for each outcome indicating the quantity and quality of evidence available, and the outcome and population to which they relate.

3.5 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas

3.5.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual.[318]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

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3.5.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per individual), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, [318] Appendix C and the health economics research protocol in Appendix D.

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

3.5.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual.[318] It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. See Table 6 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[340]

Table 6: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual, Appendix G.[318]

3.5.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for

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new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis were identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendix L for details of the health economic analysis undertaken for the guideline.

3.5.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[314]

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all 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.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.[314]

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If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

3.6 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix G and Appendix H.
- Summary of clinical and economic evidence and quality (as presented in chapters 5-7).
- Forest plots (Appendix I).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline. (Appendix L)

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. The GDG decided whether the intervention was either beneficial, harmful or had no effect based on the number of people who would benefit (or not) from the treatment compared with the number who had an event in the control group (adjusted for 1000 people). For all-cause mortality, cardiac mortality and sudden

death, 5 more or less people per 1000 influenced by the treatment compared with the controls was considered effective. For reinfarction, stroke, revascularisation, rehospitalisation, 8 more or less participants influenced by the intervention compared with the controls was considered effective. For adverse events, a difference of at least 10 people compared with the control rate was considered effective. In addition to the number of people the intervention affected, the degree of imprecision was also taken into account when deciding if the intervention was clinically effective or not.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic costs or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were made through discussions in the GDG. The GDG also considered whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Appendix N).

The main considerations specific to each recommendation are outlined in the Linking Evidence to Recommendation Section.

3.6.1 Research recommendations

When areas were identified for which good evidence was lacking, the Guideline Development Group (GDG) considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

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3.6.2 Validation process

The guidance is subject to a 6 week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn individually and posted on the NICE website.

3.6.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.6.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

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3.6.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

3.7 Methods (2007)

3.7.1 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).

3.7.2 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 Q. 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 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.

3.7.3 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 Q.

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 were 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).

3.7.4 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.

3.7.5 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 Q. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

3.7.6 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 up to £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.[130] 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 synthesise 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 Q. 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.

3.7.7 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++	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-	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+

Recommendation grade	Evidence
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

3.7.8 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.

3.7.9 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.

3.7.10 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.

3.7.11 The relationship between the guideline and other national guidance

3.7.11.1 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.

3.7.11.2 National Service Frameworks

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

3.7.11.3 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.

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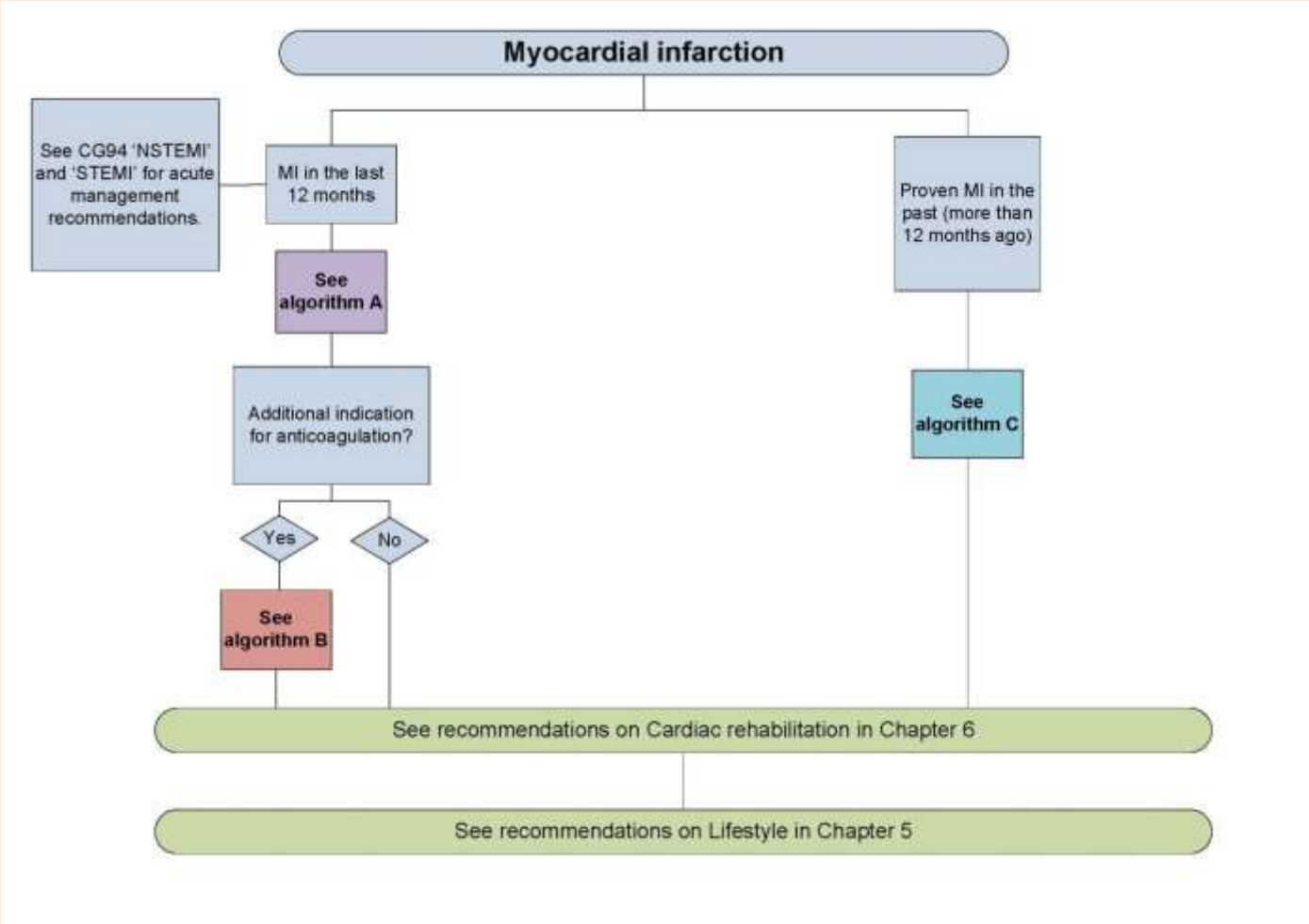
4 Guideline summary

4.1 Algorithms (2013)



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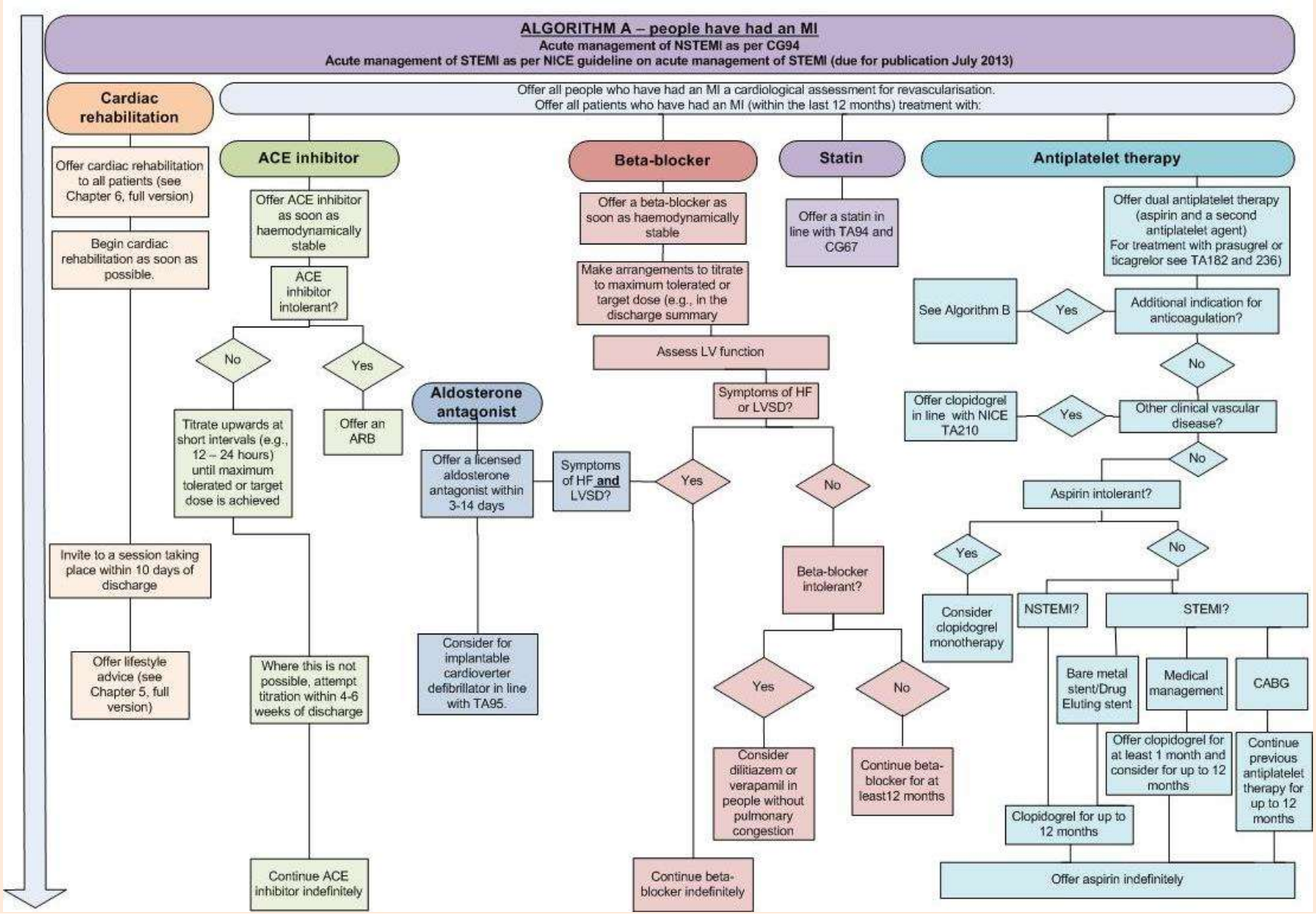
ALGORITHM A – people have had an MI
Acute management of NSTEMI as per CG94
Acute management of STEMI as per NICE guideline on acute management of STEMI (due for publication July 2013)
Cardiac rehabilitation
Offer all people who have had an MI a cardiological assessment for revascularisation.
Offer all patients who have had an MI (within the last 12 months) treatment with:
ACE inhibitor
Beta-blocker
Statin
Antiplatelet therapy
Offer cardiac rehabilitation to all patients (see Chapter 6, full version)
Begin cardiac rehabilitation as soon as possible.
Invite to a session taking place within 10 days of discharge
Offer lifestyle advice (see Chapter 5, full version)
Offer ACE inhibitor as soon as haemodynamically stable
ACE inhibitor intolerant?
No
Yes
Titrate upwards at short intervals (e.g., 12 – 24 hours) until maximum tolerated or target dose is achieved
Offer an ARB
Where this is not possible, attempt titration within 4-6 weeks of discharge
Continue ACE inhibitor indefinitely
Aldosterone antagonist
Offer a licensed aldosterone antagonist within 3-14 days
Consider for implantable cardioverter defibrillator in line with TA95.
Offer a beta-blocker as soon as haemodynamically stable
Make arrangements to titrate to maximum tolerated or target dose (e.g., in the discharge summary
Assess LV function
Symptoms of HF or LVSD?
Symptoms of HF and LVSD?
Yes
No
Beta-blocker intolerant?
Yes
No
Consider dilitiazem or verapamil in people without pulmonary congestion
Continue beta-blocker for at least12 months
Continue beta-blocker indefinitely
Offer a statin in line with TA94 and CG67
Offer dual antiplatelet therapy (aspirin and a second antiplatelet agent)
For treatment with prasugrel or ticagrelor see TA182 and 236)
Additional indication for anticoagulation?
Yes
See Algorithm B
No
Other clinical vascular disease?
Yes
Offer clopidogrel in line with NICE TA210
No
Aspirin intolerant?
Yes
No
Consider clopidogrel monotherapy
NSTEMI?
STEMI?
Bare metal stent/Drug Eluting stent
Medical management
CABG
Offer clopidogrel for at least 1 month and consider for up to 12 months
Continue previous antiplatelet therapy for up to 12 months
Clopidogrel for up to 12 months
Offer aspirin indefinitely

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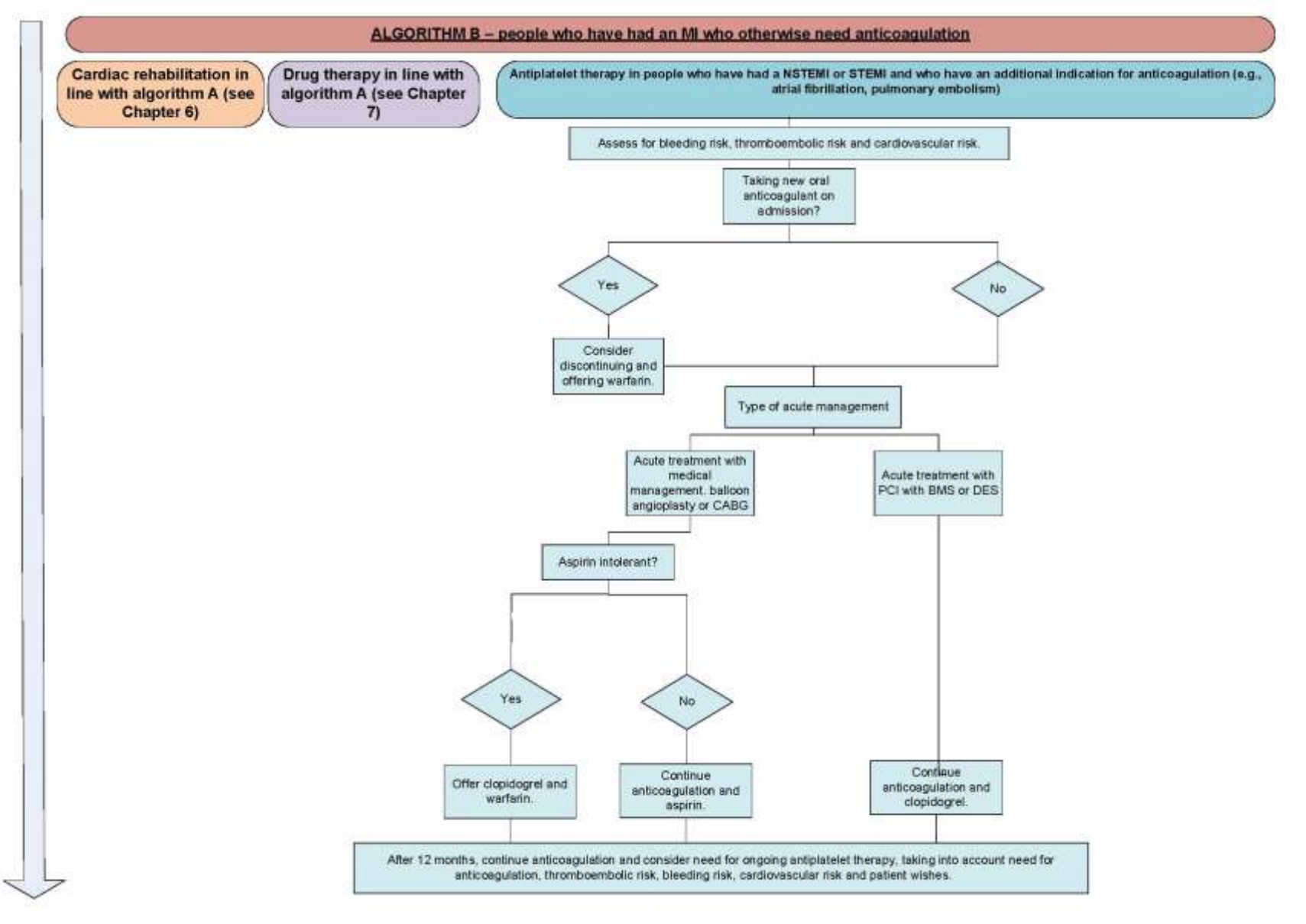
ALGORITHM B – people who have had an MI who otherwise need anticoagulation
Cardiac rehabilitation in line with algorithm A (see Chapter 6)
Drug therapy in line with algorithm A (see Chapter 7)
Antiplatelet therapy in people who have had a NSTEMI or STEMI and who have an additional indication for anticoagulation (e.g., atrial fibrillation, pulmonary embolism)
Assess for bleeding risk, thromboembolic risk and cardiovascular risk.
Taking new oral anticoagulant on admission?
Yes
No
Consider discontinuing and offering warfarin.
Type of acute management
Acute treatment with medical management, balloon angioplasty or CABG
Acute treatment with PCI with BMS or DES
Aspirin intolerant?
Yes
No
Offer clopidogrel and warfarin.
Continue anticoagulation and aspirin.
Continue anticoagulation and clopidogrel.
After 12 months, continue anticoagulation and consider need for ongoing antiplatelet therapy, taking into account need for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and patient wishes.

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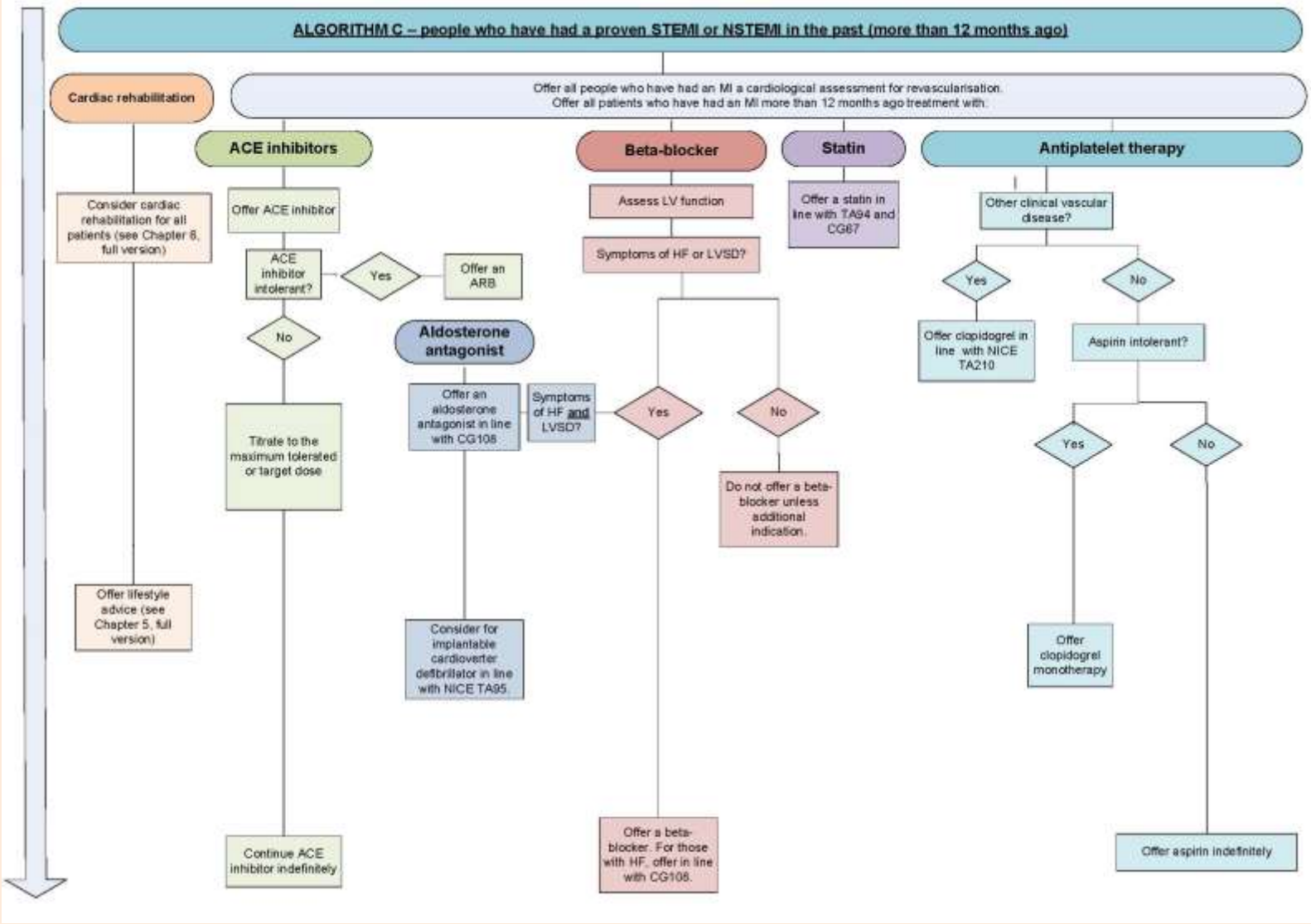
ALGORITHM C – people who have had a proven STEMI or NSTEMI in the past (more than 12 months ago)
Cardiac rehabilitation
Offer all people who have had an MI a cardiological assessment for revascularisation.
Offer all patients who have had an MI more than 12 months ago treatment with:
ACE inhibitors
Beta-blocker
Statin
Antiplatelet therapy
Consider cardiac rehabilitation for all patients (see Chapter 6, full version)
Offer lifestyle advice (see Chapter 5, full version)
Offer ACE inhibitor
ACE inhibitor intolerant?
Yes
Offer an ARB
No
Titrate to the maximum tolerated or target dose
Continue ACE inhibitor indefinitely
Aldosterone antagonist
Offer an aldosterone antagonist in line with CG108
Symptoms of HF and LVSD?
Consider for implantable cardioverter defibrillator in line with NICE TA95
Assess LV function
Symptoms of HF or LVSD?
Yes
No
Offer a beta-blocker. For those with HF, offer in line with CG108.
Do not offer a beta-blocker unless additional indication.
Offer a statin in line with TA94 and CG67
Other clinical vascular disease?
Yes
No
Offer clopidogrel in line with NICE TA210
Aspirin intolerant?
Yes
No
Offer clopidogrel monotherapy
Offer aspirin indefinitely

4.2 Key priorities for implementation

From the full set of recommendations, the GDG selected 10 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual.[316] The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

- Advise people to eat a Mediterranean-style diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on plant oils).[2007] [1.2.1]
- Advise people to be physically active for 20–30 minutes a day to the point of slight breathlessness. Advise people who are not active to this level 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.[2007] [1.2.10]
- Advise all people who smoke to stop and offer assistance from a smoking cessation service in line with 'Brief interventions and referral for smoking cessation' (NICE public health guidance 1).[2007] [1.2.12]
- Offer cardiac rehabilitation programmes designed to motivate people to attend and complete the programme. Explain the benefits of attending.[new 2013] [1.1.7]
- Begin cardiac rehabilitation as soon as possible after admission and before discharge from hospital. Invite the person to a cardiac rehabilitation session which should start within 10 days of their discharge from hospital.[new 2013] [1.1.13]
- Offer all people who have had an acute MI treatment with the following drugs:
  - ACE (angiotensin-converting enzyme) inhibitor
  - dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
  - beta-blocker
  - statin.[2007, amended 2013] [1.3.1]
- Offer an assessment of left ventricular function to all people who have had an MI.[2013] [1.3.4]
- Titrate the ACE inhibitor dose upwards at short intervals (for example, every 12–24 hours) before the person leaves hospital until the maximum tolerated or target dose is reached. If it is not possible to complete the titration during this time, it should be completed within 4–6 weeks of hospital discharge.[new 2013] [1.3.6]
- Communicate plans for titrating beta-blockers up to the maximum tolerated or target dose, for example, in the discharge summary.[new 2013] [1.3.32]
- After an acute MI, ensure that the following are part of every discharge summary:
  - confirmation of the diagnosis of acute MI
  - results of investigations
  - incomplete drug titrations
  - future management plans
  - advice on secondary prevention[2007, amended 2013] [1.6.1]

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4.3 Key priorities for implementation (2007)

- 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.
- Patients should be advised to undertake regular physical activity sufficient to increase exercise capacity.

- 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.
- 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).
- 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.
- 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:
    - 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.
- 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.
- 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.
- All patients should be offered a cardiological assessment to consider whether coronary revascularisation is appropriate. This should take into account comorbidity.
- 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

4.4 Full list of recommendations

Lifestyle

Update 2013

1. Do not routinely recommend eating oily fish for the sole purpose of preventing another MI. If people after an MI choose to consume oily fish, be aware that there is no evidence of harm, and fish may form part of a Mediterranean-style diet. [new 2013]

2. Do not offer or advise people to use the following to prevent another MI:

- omega-3 fatty acid capsules
- omega-3 fatty acid supplemented foods.

If people choose to take omega-3 fatty acid capsules or eat omega-3 fatty acid supplemented foods, be aware that there is no evidence of harm.[new 2013]

3. Advise people to eat a Mediterranean-style diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on plant oils). [2007]

4. Advise people not to take supplements containing beta-carotene. Do not recommend antioxidant supplements (vitamin E and/or C) or folic acid to reduce cardiovascular risk. [2007]

5. Offer people an individual consultation to discuss diet, including their current eating habits, and advice on improving their diet. [2007]

6. Give people consistent dietary advice tailored to their needs. [2007]

7. Give people healthy eating advice that can be extended to the whole family. [2007]

8. Advise people who drink alcohol 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). [2007]

9. Advise people to undertake regular physical activity sufficient to increase exercise capacity.[2007]

10. Advise people to be physically active for 20-30 minutes a day to the point of slight breathlessness. Advise people who are not active to this level 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. [2007]

11. 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. [2007]

12. Advise all people who smoke to stop and offer assistance from a smoking cessation service in line with 'Brief interventions and referral for smoking cessation' (NICE public health guidance 1). [2007]

13. 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' (NICE public health guidance 1). If a patient is unable or unwilling to accept a referral they should be offered pharmacotherapy in line with the recommendations in 'Smoking cessation services' (NICE public health guidance 10). [2007]

14. After an MI, offer all patients who are overweight or obese advice and support to achieve and maintain a healthy weight in line with 'Obesity' (NICE clinical guideline 43). [2007]

Cardiac rehabilitation

15. All patients (regardless of their age) should be given advice about and offered a cardiac rehabilitation programme with an exercise component. [2007]

Update 2013

16. 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. [2007]

17. 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. [2007]

18. Patients with left ventricular dysfunction who are stable can safely be offered the exercise component of cardiac rehabilitation. [2007]

19. Deliver cardiac rehabilitation in a non-judgemental, respectful and culturally sensitive manner. Consider employing bilingual peer educators or cardiac rehabilitation assistants who reflect the diversity of the local population.[new 2013]

20. Offer cardiac rehabilitation programmes designed to motivate people to attend and complete the programme. Explain the benefits of attending. [new 2013]

21. Discuss with the person any factors that might stop them attending a cardiac rehabilitation programme, such as transport difficulties. [new 2013]

22. Offer cardiac rehabilitation programmes in a choice of venues (including at the person's home, in hospital and in the community) and at a choice of times of day, for example, sessions outside of working hours. Explain the options available. [new 2013]

23. Provide a range of different types of exercise, as part of the cardiac rehabilitation programme, to meet the needs of people of all ages, or those with significant comorbidity. Do not exclude people from the whole programme if they choose not to attend specific components. [new 2013]

Update 2013

24. Offer single-sex cardiac rehabilitation classes if there is sufficient demand. [new 2013]

25. Seek feedback from cardiac rehabilitation programme users and aim to use this feedback to increase the number of people starting and attending the programme. [new 2013]

26. Establish people's health beliefs and their specific illness perceptions before offering appropriate lifestyle advice and to encourage attendance to a cardiac rehabilitation programme. [new 2013]

27. Be aware of the wider health and social needs of a person who has had an MI. Offer information and sources of help on:

- economic issues
- welfare rights
- housing and social support issues. [new 2013]

28. Enrol people who have had an MI in a system of structured care, ensuring that there are clear lines of responsibility for arranging the early initiation of cardiac rehabilitation. [new 2013]

29. Begin cardiac rehabilitation as soon as possible after admission and before discharge from hospital. Invite the person to a cardiac rehabilitation session which should start within 10 days of their discharge from hospital.[new 2013]

30. Contact people who do not start or do not continue to attend the cardiac rehabilitation programme with a further reminder, such as:

- a motivational letter
- a prearranged visit from a member of the cardiac rehabilitation team
- a telephone call
- a combination of the above. [new 2013]

31. Make cardiac rehabilitation equally accessible and relevant to all people 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, people with a learning disability and people with mental and physical health conditions. [2007, amended 2013]

32. Encourage all staff, including senior medical staff, involved in providing care for people after an MI, to actively promote cardiac rehabilitation. [2013]

33. Comprehensive cardiac rehabilitation programmes should include health education and stress management components. [2007]

34. A home-based programme validated for patients who have had an MI (such as 'The heart manual'; see www.theheartmanual.com) that incorporates education, exercise and stress management components with follow-ups by a trained facilitator may be used to provide comprehensive cardiac rehabilitation. [2007]

35. Take into account the physical and psychological status of the patient, the nature of their work and their work environment when giving advice on returning to work. [2007]

36. Be up to date with the latest Driver and Vehicle Licensing Agency guidelines. Regular updates are published on the DVLA website (www.dvla.gov.uk). [2007]

37. After an MI without complications, people who wish to travel by air should seek advice from the Civil Aviation Authority (www.caa.co.uk). People who have had a complicated MI need expert individual advice. [2007, amended 2013]

38. People who have had an MI who hold a pilot's licence should seek advice from the Civil Aviation Authority. [2007]

39. Take into account the patient's physical and psychological status, as well as the type of activity planned when offering advice about the timing of returning to normal activities. [2007]

40. 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). Advise patients how to use a perceived exertion scale to help monitor physiological demand. Patients who have had a complicated MI may need expert advice. [2007]

41. 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.[2007]

42. Offer stress management in the context of comprehensive cardiac rehabilitation. [2007]

43. Do not routinely offer complex psychological interventions such as cognitive behavioural therapy. [2007]

44. Involve partners or carers in the cardiac rehabilitation programme if the patient wishes. [2007]

Update 2013

45. For recommendations on the management of patients with clinical anxiety or depression, refer to 'Anxiety' (NICE clinical guideline 113), 'Depression in adults' (NICE clinical guideline 90) and 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91). [2007]

46. Reassure patients 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. [2007]

47. Advise patients who have made an uncomplicated recovery after their MI that they can resume sexual activity when they feel comfortable to do so, usually after about 4 weeks. [2007]

48. Raise the subject of sexual activity with patients within the context of cardiac rehabilitation and aftercare. [2007]

49. When treating erectile dysfunction, treatment with a PDE5 (phosphodiesterase type 5) inhibitor may be considered in men who have had an MI more than 6 months earlier and who are now stable. [2007]

50. PDE5 inhibitors must be avoided in patients treated with nitrates or nicorandil because this can lead to dangerously low blood pressure. [2007]

Drug therapy

51. Offer all people who have had an acute MI treatment with the following drugs:

- ACE (angiotensin-converting enzyme) inhibitor
- dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
- beta-blocker
- statin.[2007, amended 2013]

Update 2013

ACE inhibitors

52. Offer people who present acutely with an MI an ACE inhibitor as soon as they are haemodynamically stable. Continue the ACE inhibitor indefinitely. [new 2013]

53. Titrate the ACE inhibitor dose upwards at short intervals (for example, every 12–24 hours) before the person leaves hospital until the maximum tolerated or target dose is reached. If it is not possible to complete titration during this time, it should be completed within 4–6 weeks of hospital discharge. [new 2013]

54. Offer people after an MI who are intolerant to ACE inhibitors an ARB instead of an ACE inhibitor. [new 2013]

55. Do not offer combined treatment with an ACE inhibitor and an angiotensin II receptor blocker (ARB) to people after an MI, unless there are other reasons to use this combination. [new 2013]

56. Offer an ACE inhibitor to people who have had an MI more than 12 months ago. Titrate to the maximum tolerated or target dose (over a 4–6 week period) and continue indefinitely. [new 2013]

57. Offer people who have had an MI more than 12 months ago and who are intolerant to ACE inhibitors an ARB instead of an ACE inhibitor. [new 2013]

58. Ensure that a clear management plan is available to the person who has had an MI and is also sent to the GP, including:

- details and timing of any further drug titration
- monitoring of blood pressure
- monitoring of renal function. [new 2013]

59. Offer an assessment of left ventricular function to all people who have had an MI.[2013]

60. 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 reach, 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 108).[2007]

Antiplatelet therapy

61. Offer aspirin to all people after an MI and continue it indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. [2007, amended 2013]

62. Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely [new 2013].

63. For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment. [2007, amended 2013]

64. People with a history of dyspepsia should be considered for treatment in line with 'Dyspepsia' (NICE clinical guideline 17). [2007, amended 2013]

65. After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for *Helicobacter pylori* should be considered for treatment in line with 'Dyspepsia' (NICE clinical guideline 17). [2007, amended 2013]

Update 2013

This guidance incorporates NICE technology appraisal guidance 236 on ticagrelor for the treatment of acute coronary syndromes. Guidance on prasugrel for the treatment of acute coronary syndromes has not been incorporated in this guidance because this technology appraisal is currently scheduled for update. For further information about this appraisal, see the NICE website.

66. Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes (ACS) that is, people:

- with ST-segment-elevation myocardial infarction (STEMI) – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary percutaneous coronary intervention (PCI) or
- with non-ST-segment-elevation myocardial infarction (NSTEMI).

This recommendation is from 'Ticagrelor for the treatment of acute coronary syndromes' (NICE technology appraisal guidance 236). [new 2013]

67. Offer clopidogrel as a treatment option for up to 12 months to:

- people who have had an NSTEMI, regardless of treatment.
- people who have had a STEMI and received a bare metal or drug-eluting stent. [new 2013]

68. Offer clopidogrel as a treatment option for at least 1 month and consider continuing for up to 12 months to:

- people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent. [new 2013]

69. Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received coronary artery bypass graft (CABG) surgery. [new 2013]

70. Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease, in line with 'Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events' (NICE technology appraisal guidance 210) and who have:

- had an MI and stopped dual antiplatelet therapy or
- had an MI more than 12 months ago. [new 2013]

71. Offer all people who have had an MI an assessment of bleeding risk at their follow-up appointment. [new 2013]

72. Take into account all of the following when thinking about treatment for people who have had an MI and who have an indication for anticoagulation:

- bleeding risk
- thromboembolic risk
- cardiovascular risk. [new 2013]

73. Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who:

- have had their condition managed medically or
- have undergone balloon angioplasty or
- have undergone CABG surgery. [new 2013]

74. Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone percutaneous coronary intervention (PCI) with bare-metal or drug-eluting stents and who otherwise need anticoagulation. [new 2013]

75. Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. [new 2013]

76. Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. [new 2013]

77. Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it. [new 2013]

78. Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. [new 2013]

79. After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following:

Update 2013

- the indication for anticoagulation
- thromboembolic risk
- bleeding risk
- cardiovascular risk
- the person's wishes. [new 2013]

Beta-blockers

80. Offer people a beta-blocker as soon as possible after an MI, when the person is haemodynamically stable. [new 2013]

81. Communicate plans for titrating beta-blockers up to the maximum tolerated or target dose – for example, in the discharge summary. [new 2013]

82. Continue a beta-blocker for at least 12 months after an MI in people without left ventricular systolic dysfunction or heart failure. [new 2013]

83. Continue a beta-blocker indefinitely in people with left ventricular systolic dysfunction. [new 2013]

84. Offer all people who have had an MI more than 12 months ago, who have left ventricular systolic dysfunction, a beta-blocker whether or not they have symptoms. For people with heart failure plus left ventricular dysfunction, manage the condition in line with 'Chronic heart failure' (NICE clinical guideline 108). [new 2013]

85. Do not offer people without left ventricular systolic dysfunction or heart failure, who have had an MI more than 12 months ago, treatment with a beta-blocker unless there is an additional clinical indication for a beta-blocker. [new 2013]

Calcium channel blockers

86. Do not routinely offer calcium channel blockers to reduce cardiovascular risk after an MI. [2007]

87. 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. [2007]

88. 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, use amlodipine, and avoid verapamil, diltiazem and short-acting dihydropyridine agents in line with 'Chronic heart failure' (NICE clinical guideline 108). [2007]

Potassium channel activators

89. Do not offer nicorandil to reduce cardiovascular risk in patients after an MI. [2007]

Update 2013

Aldosterone antagonists

90. For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, initiate treatment with an aldosterone antagonist licensed for post-MI treatment within 3–14 days of the MI, preferably after ACE inhibitor therapy. [2007]

91. 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. [2007]

92. 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 108). [2007]

93. Monitor renal function and serum potassium before and during treatment with an aldosterone antagonist. If hyperkalaemia is a problem, halve the dose of the aldosterone antagonist or stop the drug. [2007]

Statins and other lipid lowering agents

94. 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) and 'Lipid modification' (NICE clinical guideline 67). [2007]

Coronary revascularisation

95. Offer everyone who has had an MI a cardiological assessment to consider whether coronary revascularisation is appropriate. This should take into account comorbidity. [2007]

Update 2013

Selected patient subgroups

96. Treat hypertension in line with 'Hypertension' (NICE clinical guideline 127). [2007, amended 2013]

97. 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).[2007]

Communication of diagnosis and advice

98. After an acute MI, ensure that the following are part of every discharge summary:

- confirmation of the diagnosis of acute MI
- results of investigations
- incomplete drug titrations
- future management plans
- advice on secondary prevention. [2007, amended 2013]

99. Offer a copy of the discharge summary to the patient. [2007]

Key research recommendations

Further details on the key research recommendations are provided in Appendix N.

1. In people who have not undergone revascularisation after an MI, does clopidogrel and placebo have a better outcome than clopidogrel and aspirin?

2. Does continuing beta-blocker treatment beyond 1 year after an MI improve outcomes in people with normal LV function?

3. Is treatment with an oral anticoagulant, aspirin and clopidogrel preferable to treatment with an oral anticoagulant and clopidogrel in people who have had an MI, have an indication for oral anticoagulation and are treated either medically, by primary percutaneous coronary intervention or by coronary artery bypass grafting surgery?

4. What characteristics are associated with uptake and adherence to cardiac rehabilitation after an acute MI when rehabilitation is started early?

5. In people who have had a STEMI who undergo PPCI with a bare metal stent, and 4 weeks of aspirin and clopidogrel, is there an additional benefit to continuing clopidogrel for a further 11 months?

Update 2013

4.5 Research recommendations (2007)

- 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.

- 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 randomised 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.

- 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.

- 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 minority ethnic groups, 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 minority ethnic groups, women, the elderly and those on low incomes or with physical or mental comorbidities who have had an MI?

- 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.

- 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.

- 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?

5 Lifestyle

The updated review questions in this chapter are:

- What is the clinical and cost effectiveness of omega-3 fatty acids supplementation in all people who have had a myocardial infarction?
- What is the clinical and cost effectiveness of an oily fish diet in all people who have had amyocardial infarction?

The evidence and text from the previous guideline, CG48, that has been superseded by this update is included in Appendices G and P.

No new review questions have been included in this chapter.

Sections not updated in this chapter are:

- Supplementation with antioxidants vitamin C, vitamin E, beta-carotene and coenzyme Q10.
- Folic acid supplementation.
- Mediterranean diet.
- Low saturated fat.
- Plant sterols esters.
- Low glycaemic diet.
- Fruit and vegetables.
- High fibre diet.
- Delivery of dietary advice.
- Alcohol consumption.
- Regular physical activity.
- Smoking cessation.
- Weight management.

Update 2013

5.1 Changing diet

Dietary interventions play an important role and have long been recognised as key in the management of secondary prevention of cardiovascular disease. Assessing a person's diet following a myocardial infarction (MI) aims to advise and provide information to assist an individual to make healthy eating choices to reduce the risk of a further event.

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

5.1.1.1 Clinical evidence

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.[411] 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).[411] 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.[167] 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.[376] While there were dosage differences between the trials), [376] the baseline risk of both fatal and non-fatal MIs was approximately equivalent in the two studies.[411]

The systematic review identified five randomised controlled studies of coenzyme Q supplementation compared to placebo.[411] 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.[239]

The systematic review identified four randomised controlled studies of vitamin C supplementation compared to placebo.[411] 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.[411]

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.[294] No meta-analysis was undertaken. For vitamin C and E, the studies identified were included in the previous systematic review.[411] For beta-carotene, one study was identified which found that beta-carotene significantly increased the incidence of fatal coronary heart disease compared with placebo.[376] 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.

5.1.2 Folic acid supplementation

5.1.2.1 Clinical evidence

A randomised controlled trial investigated folic acid supplementation in patients with stable coronary artery disease.[252] 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).[253]

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.[63] 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.[63]

5.1.3 Omega-3 fatty acids

Omega-3 fatty acids are polyunsaturated essential fatty acids not manufactured by the human body, but found in some fish and plant oils. Three are important in human physiology – α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is a shorter chain omega-3 fatty acid contained in some plant oils and is poorly converted to longer chain EPA and DHA in the body. EPA and DHA are contained in oily fish (for example herring, salmon, sardines, mackerel, tuna).

Omega-3 fatty acids supplementation can be delivered via fortified foods (for example margarine) or in capsule form, available as prescription medicine or over-the-counter. Capsules are available on NHS prescription in order to reduce triglycerides, licensed as an alternative to a fibrate and in addition to a statin, in people with combined (mixed) hyperlipidaemia not adequately controlled with a statin alone. These are also licensed as an adjunct in secondary prevention in those who had a myocardial infarction in the preceding 3 months.

Proposed mechanisms for the protective role of omega-3 fatty acids against cardiovascular diseases include: lowering of blood pressure; altered lipid profile; especially reduced serum triglyceride concentration; reduced thrombotic tendency; anti-inflammatory effects; anti-arrhythmic effects including reduction in heart rate; improved vascular endothelial function; increased plaque stability; increased paraoxonase levels and improved insulin sensitivity.

The previous guideline, CG48, recommended consideration of omega-3-acid ethyl ester supplements for the secondary prevention of MI for those people not achieving sufficient consumption in their diet. Since publication of the guideline, a number of new studies of omega-3 fatty acids have been published. In this section we review these studies and the exsiting recommendation.

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5.1.3.1 What is the clinical and cost effectiveness of omega-3 fatty acids supplementation in all people who have had a myocardial infarction?

For full details see review protocol in Appendix C.

5.1.3.2 Clinical evidence

A search was carried out for randomised clinical trials from June 2006 which studied the effectiveness of omega-3 fatty acids on the secondary prevention of myocardial infarction.

Four studies were identified that met the inclusion criteria.[157,238,274,377] Two of the 3 papers reviewed in the original guideline were included.[167,324] A third study was excluded as it used an indirect population (less than 75% of people who had an MI) and data from direct MI populations were available.[76,77] Indirect studies were used where there were no data available for an outcome.[157,274] Where there was significant heterogeneity, the type of supplement (food or capsule) was investigated by subgroup analysis.

It is acknowledged that observational epidemiological studies are useful for finding associations between disease and lifestyle factors, since they can include large numbers and it can be impractical or unethical to conduct RCTs for factors such as smoking. However, RCTs were identified for this review and were therefore used in preference to cohort studies, as they can control for the effects of confounders such as background medication, are less reliant on the self-reporting of omega-3 fatty acid intake and measured and non-measured confounders should be randomly distributed.

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Table 7: Summary of included studies

	Study	Included in CG48 or new to update	Study design	Intervention/ comparisons	Dose	Outcomes reported	Follow up period	% people with MI / Time since MI
1.	Galan 2011[156,157] SU.FOL.OM3	New	RCT	EPA plus DHA with or without vitamin B capsules versus placebo with or without vitamin B capsules (Pierre Fabre)	600mg/day	• All-cause mortality(HR, RR) • Cardiac death(RR) • MI (non-fatal)(HR, RR) • Stroke(HR, RR) • All revascularisation(HR, RR)	Median 4.7 years	46% MI No acute details Less than 12 months (median 101 days)
2.	GISSI-P 1999[167] GISSI-P	CG48	RCT (participants not blinded)	EPA plus DHA with or without vitamin E capsules versus placebo with or without vitamin E capsules (Pharmacia UpJohn + Societa Prodotti Antibiotici)	850-882mg/day	• All-cause mortality(HR) • Cardiac death(RR) • Sudden death(RR) • MI (non-fatal)(RR) • Stroke(fatal and non-fatal) (RR) • Revascularisation(RR) • Adverse events(RR)	Median 3.5 years	100% MI CABG or PTCA = 5% Median 25 days
3.	Kromhout 2010[238,238] Alpha Omega	New	RCT	Margarine with EPA plus DHA with or without ALA versus placebo with or without ALA margarine (Uniliver)	400mg/day of EPA plus DHA 2g of ALA or combination	• All-cause mortality (HR) • Cardiac death (HR) • Averse events	Median 3.4 years	100% MI No details of acute treatment Up to 10 years. Median 3.7 years
4.	Matsuzaki 2009A [274,274]	New	RCT (participants not blinded)	EPA capsules plus statin versus statin (no brand provided)	1800mg/day	• Coronary death (HR, RR) • MI (fatal or non-fatal)	5 years Median 4.7 years	Approx. 28% MI Historically PTCA or CABG = 24%

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	Study	Included in	Study design	Intervention/	Dose	Outcomes reported	Follow up	% people with MI
	JELIS					(HR, RR) • Revascularisation (HR, RR) • Hospitalisation (HR, RR)		Over 6 months
5.	Nilsen 2001[324]	CG48	RCT	EPA plus DHA capsules versus placebo (corn oil) capsules (Omacor-R)	1700mg/day	• All-cause mortality (HR, RR) • Cardiac mortality (HR,RR) • MI (HR, RR) • Revascularisation (HR, RR)	2 years Median 1.5 years	100% MI Thrombolysis = 38% Unclear remainder 4-8 days after MI
6.	Rauch 2010[377,378] OMEGA	New	RCT	EPA plus DHA capsules versus placebo (olive oil) capsules (Pronova Biocare)	1000mg/day	• All-cause mortality (RR) • Sudden death (RR) • Revascularisation (RR) • Stroke (RR) • Adverse events (frequency of reported event rather than number of participants)	1 year	100% MI PCI =78% Thrombolysis = 8% No revascularisation = 19% 3-14 days

Table 8: Subgroups based on direct (75-100% people who had an MI) and indirect populations (less than 75% people who had an MI)

Study	Intervention/ Comparisons	Dose	Follow up period (years)	% people with MI	Time since MI	No. participants	Control
75-100% people who had an MI							
Kromhout 2010[238,238]	Margarine with EPA plus DHA with or without ALA	400mg/day	Median 3.4years	100%	Up to 10 years. Median 3.7 years	4837	Margarine with ALA
GISSI-P 1999[167]	EPA plus DHA capsule with or without vitamin E	850-882 mg/day	3.5years	100%	Median 16 days	11324	Vitamin E with or without placebo

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Study	Intervention/ Comparisons	Dose	Follow up period (years)	% people with MI	Time since MI	No. participants	Control
Nilsen 2001[324]	EPA plus DHA capsule	1700mg/day	2 years Median 1.5 years	100%	4-8 days after MI	300	Corn oil
Rauch 2010[377,378]	EPA plus DHA capsule	1000mg/day	1 year	100%	3-14 days	3851	Olive oil
Less than 75% people who had an MI							
Galan 2011[156,157]	EPA plus DHA capsules with or without vitamin B	600mg/day	Median 4.7 years	Approx 46%	Less than 12 months. Median 101 days	2501	Vitamin B plus placebo
Matsuzaki 2009A[274,274]	EPA capsules plus statin	1800 mg/day	5 years Median 4.7 years	Approx 28%	Over 6 months	3664	Statin

Table 9: Subgroups based on onset of omega-3 fatty acids intervention after MI; less than 3 months versus more than 3 months

Study	Intervention/ Comparisons	Dose	Follow up period (years)	% people with MI	Time since MI	No. participants	Control
Less than 3 months after an MI							
GISSI-P1999[167]	EPA plus DHA capsule with or without vitamin E	850-882mg/day	3.5 years	100%	Median 16 days	11324	Vitamin E with or without placebo
Nilsen 2001[324]	EPA plus DHA capsule	1700mg/day	2 years Median 1.5years	100%	4-8 days after MI	300	Corn oil
Rauch 2010[377,378]	EPA plus DHA capsule	1000mg/day	1 year	100%	3-14 days	3851	Olive oil
More than 3 months following an MI							
Galan 2011[156,157]	EPA plus DHA capsules with or without vitamin B	600mg/day	Median 4.7 years	46%	Less than 12 months. Median 101 days	2501	Vitamin B plus placebo
Kromhout 2010[238,238]	Margarine with EPA plus DHA with or	400mg/day	Median 3.4 years	100%	Up to 10 yrs. Median 3.7 years	4837	Margarine with ALA

Study	Intervention/ Comparisons	Dose	Follow up period (years)	% people with MI	Time since MI	No. participants	Control
	without ALA						
Matsuzaki 2009A [274,274]	EPA capsules plus statin	1800 mg/day	5 years Median 4.7 years	28%	Over 6 months	3664	Statin

Table 10: Subgroups based on food versus capsule form of omega-3 fatty acids

Study	Intervention/ Comparisons	Dose	Follow up period (years)	% people who had an MI	Time since MI	No. participants	Control
Food source							
Kromhout 2010[238,238]	Margarine with EPA plus DHA with or without ALA	400mg/day	Median 3.4 years	100%	Up to 10 years. Median 3.7 years	4837	Margarine with ALA
Capsule							
Galan 2011[156,157]	EPA plus DHA capsules with or without vitamin B	600mg/day	Median 4.7 years	46%	Less than 12 months. Median 101 days	2501	Vitamin B plus placebo
GISSI-P 1999[167]	EPA plus DHA capsule with or without vitamin E	850-882mg/day	3.5 years	100%	Median 16 days	11324	Vitamin E with or without placebo
Nilsen 2001[324]	EPA plus DHA capsule	1700mg/day	2 years Median 1.5 years	100%	4-8 days after MI	300	Corn oil
Matsuzaki 2009A[274,274]	EPA capsules plus statin	1800 mg/day	5 years Median 4.7 years	28%	Over 6 months	3664	Statin
Rauch 2010[377,378]	EPA plus DHA capsule	1000mg/day	1 year	100%	3-14 days	3851	Olive oil

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Table 11: GRADE profile: omega-3 fatty acids versus placebo (all-cause mortality)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Omega-3-fatty acids	Control	Relative (95% CI)	Absolute		
All-cause mortality (hazard ratio) - all cause mortality[167,238,324,377]												
4	Randomised trials	Serious[a]	Serious[b]	No serious indirectness[c,d]	No serious imprecision	None[e]	518/7310 (7.1%)	558/7296 (7.6%)	HR 0.93 (0.82 to 1.05)	5 fewer per 1000 (from 13 fewer to 4 more)	LOW	CRITICAL
All-cause mortality and timing - treatment within 3 months of MI[167,324,377]												
3	Randomised trials	Serious[f]	Serious[g]	No serious indirectness[d]	No serious imprecision	None[h]	355/4905 (7.2%)	374/4863 (7.7%)	HR 0.89 (0.77 to 1.03)	8 fewer per 1000 (from 17 fewer to 2 more)	LOW	CRITICAL
All-cause mortality and timing - treatment initiated more 3 months after MI[238,238]												
1	Randomised trial	Serious[i]	No serious inconsistency[j]	No serious indirectness[k]	No serious imprecision	None[l]	183/2405 (7.6%)	184/2433 (7.6%)	HR 1.02 (0.82 to 1.27)	1 more per 1000 (from 13 fewer to 19 more)	MODERATE	CRITICAL
All-cause mortality, food source of omega-3 fatty acids (spreads/margarines)[238,238]												
1	Randomised trial	Serious[i]	No serious inconsistency	No serious indirectness	No serious imprecision	None	183/2405 (7.6%)	184/2433 (7.6%)	HR 1.02 (0.82 to 1.27)	1 more per 1000 (from 13 fewer to 19 more)	MODERATE	CRITICAL
All-cause mortality, capsule source [167,324,377]												
3	Randomised trials	Serious[m]	Serious[n]	No serious indirectness[k,d]	No serious imprecision	None[o]	335/4905 (6.8%)	374/4863 (7.7%)	HR 0.89 (0.77 to 1.03)	8 fewer per 1000 (from 17 fewer to 2 more)	LOW	CRITICAL

(a) Two of the 4 studies had unclear methods of randomisation and allocation concealment. Two of the 4 provided hazard ratio data and it was calculated in remaining 2 studies. In 1 study participants were not blinded. In the study by GISSI, that contributed the most to the overall result, participants had not undergone acute management strategies in-line with current practice.

(b) I2 = 58%, p=0.07. This is resolved when separating data by onset of treatment (less than 3 vs.more than 3 months) and by method of supplementation (capsule versus food supplement).

(c) All studies included a 100% population of people who had an MI.

(d) Nilsen[324] participants were recruited from a coastal area in Norway and according to the authors received a diet rich in fish product, however no dietary analysis was provided.
(e) In 5 of the 7 studies the study was funded by the same company that provided the intervention (either a pharmaceutical company or Unilever).
(f) In 2 of the 3 studies it was unclear if the groups were followed up for equal durations, although it was possible to calculate hazard ratios. In 2 of the 3 studies it was unclear if the authors performed allocation concealment. In 1 study participants were not blinded. In the study by GISSI, that contributed the most to the overall result, participants had not undergone acute management strategies in-line with current practice.
(g) I2=70%.
(h) In 2 of the 3 studies the study was funded by the same company that provided the intervention (either a pharmaceutical company or Unilever).
(i) There were unclear methods reported on randomisation. The authors provided hazard ratio calculations to account for any differences in follow-up periods. The study was underpowered to detect differences in fatal coronary heart disease.
(j) Heterogeneity could not be calculated.
(k) The study included a 100% population of people who had an MI.
(l) The study was funded by the same company that provided the intervention (Unilever).
(m) For 2 of the 3 studies it was unclear whether the authors performed allocation concealment and in one study it was unclear how the authors randomised participants. Hazard ratios were calculated for 2 of the 3 studies. In the study by GISSI, that contributed the most to the overall result, participants had not undergone acute management strategies in-line with current practice.
(n) I2 = 67% (p=0.05).
(o) Two of the 3 studies were funded by the pharmaceutical company that provided the supplement. It was unclear if this was the same for 1 of the 3 studies.

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Table 12: GRADE profile: omega-3 fatty acids versus placebo (cardiac mortality)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Omega-3 fatty acids	Control	Relative (95% CI)	Absolute		
Cardiac mortality (hazard ratio)[238,324]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness[b,c]	Serious[d]	None[e]	88/2555 (3.4%)	90/2583 (3.5%)	HR 0.98 (0.73 to 1.32)	1 fewer per 1000 (from 9 fewer to 11 more)	VERY LOW	CRITICAL
Cardiac mortality and food source of omega-3 fatty acids (spreads/margarine) (hazard ratio)[238,238]												
1	Randomised trial	Serious[f]	No serious inconsistency[g]	No serious indirectness	Very serious[h]	None	80/2405 (3.3%)	82/2433 (3.4%)	HR 0.98 (0.72 to 1.34)	1 fewer per 1000 (from 9 fewer to 11 more)	VERY LOW	CRITICAL
Cardiac mortality and capsule omega-3 fatty acids (hazard ratio)[324]												
1	Randomised	Serious[i]	No serious	No serious	Very	None	8/150	8/150	HR 1.02	1 more per	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
	trial		inconsistency[g]	indirectness[c]	serious[h]		(5.3%)	(5.3%)	(0.38 to 2.73)	1000 (from 33 fewer to 86 more)		
Cardiac mortality, and treatment initiated within 3 months of MI(hazard ratio)[324]												
1	Randomised trial	Serious[i]	No serious inconsistency[g]	No serious indirectness[c]	Very serious[h]	None	8/150 (5.3%)	8/150 (5.3%)	HR 1.02 (0.38 to 2.73)	1 more per 1000 (from 33 fewer to 86 more)	VERY LOW	CRITICAL
Cardiac mortality, and treatment initiated more than 3 months after MI (hazard ratio)[238,238]												
1	Randomised trials	Serious[f]	No serious inconsistency[g]	No serious indirectness	Very serious[h]	None	80/2405 (3.3%)	82/2433 (3.4%)	HR 0.98 (0.72 to 1.34)	1 fewer per 1000 (from 9 fewer to 11 more)	VERY LOW	CRITICAL
Cardiac mortality (relative risk)[167,238,324]												
3	Randomised trials	Serious[j]	No serious inconsistency	No serious indirectness[c]	No serious imprecision	None	379/8221 (4.6%)	438/8251 (5.3%)	RR 0.87 (0.76 to 0.99)	7 fewer per 1000 (from 1 fewer to 13 fewer)	MODERATE	CRITICAL
Cardiac mortality plus food source of omega-3 fatty acids (spreads/margarines)[238,238]												
1	Randomised trial	Serious[f]	No serious inconsistency[g]	No serious indirectness	Serious[d]	None	80/2405 (3.3%)	82/2433 (3.4%)	RR 0.99 (0.73 to 1.34)	0 fewer per 1000 (from 9 fewer to 11 more)	LOW	CRITICAL
Cardiac mortality plus capsule[167,324]												
2	Randomised trials	Serious[j]	No serious inconsistency	No serious indirectness[c]	Serious[k]	None	299/5816 (5.1%)	356/5818 (6.1%)	RR 0.84 (0.72 to 0.98)	10 fewer per 1000 (from 1 fewer to 17 fewer)	MODERATE	CRITICAL

(a) In 2 of the 2 studies, it was unclear how the authors randomised participants, and 1 of the 2 studies it was unclear whether the authors performed allocation concealment.
(b) The study used a 100% population of people who had an MI.
(c) Nilsen[324] participants were recruited from a coastal area in Norway and according to the authors received a diet rich in fish product, however no dietary analysis was provided.
(d) 95% confidence intervals crossed 1 MID (1.25).
(e) 2 of 2 studies were sponsored by the same companies that provided the intervention.
(f) It was unclear how the authors randomised participants. The study was underpowered to detect differences in fatal coronary heart disease.
(g) Heterogeneity not applicable.
(h) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25.).

(i) It was unclear whether the authors performed allocation concealment or randomisation. Nor did the authors provide power calculations, thus there is a risk of a Type II error.
(j) In the study that contributed to the majority of the outcome, it is unclear how the authors randomised or whether they performed allocation concealment. In the study by GISSI, that contributed the most to the overall result, participants had not undergone acute management strategies in-line with current practice.
(k) 95% confidence interval crossed 1 MID (0.75)

Table 13: GRADE profile: omega-3 fatty acids versus placebo (sudden death)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Omega-3 fatty acids	Control	Relative (95% CI)	Absolute		
Sudden death (hazard ratio)[377,378]												
1	Randomised trial	Serious [a]	No serious inconsistency	No serious indirectness	Very serious[b]	None[c]	28/1919 (1.5%)	29/1885 (1.5%)	HR 0.95 (0.57 to 1.60)	1 fewer per 1000 (from 7 fewer to 9 more)	VERY LOW	CRITICAL
Sudden death (relative risk)[167,377]												
2	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	150/7585 (2%)	193/7553 (2.6%)	RR 0.78 (0.63 to 0.96)	6 fewer per 1000 (from 1 fewer to 9 fewer)	LOW	CRITICAL

(a) One study with 100% population of people who had an MI had large confidence intervals. It was unclear whether the authors performed allocation concealment. The study was underpowered to detect differences in sudden cardiac death.
(b) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(c) The paper was sponsored by the same company that provided the intervention.
(d) Participants in the GISSI-P[167] study were not blinded. Nor had the participants undergone acute management strategies in-line with current practice.
(e) 95% confidence intervals crossed 1 MID (0.75).

Table 14: GRADE profile: omega-3 fatty acids versus placebo (reinfarction)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Omega-3 fatty	Control	Relative (95% CI)	Absolute		

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Quality assessment							No of patients		Effect		Quality	Importance
							acids					
Reinfarction (hazard ratio)[324]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	21/150 (14%)	15/150 (10%)	HR 1.43 (0.74 to 2.78)	40 more per 1000 (from 25 fewer to 154 more)	LOW	IMPORTANT
Reinfarction (relative risk)[167,324]												
2	Randomised trials	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision[d]	None	154/5816 (2.6%)	152/5818 (2.6%)	RR 1.01 (0.81 to 1.26)	0 more per 1000 (from 5 fewer to 7 more)	MODERATE	IMPORTANT

(a) It was unclear how the authors performed randomisation or whether allocation concealment was performed. However, the authors did calculate hazard ratios to take into account any differences in follow-up. No power calculations were provided, so there is risk of a Type II error.
(b) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(c) Participants in the GISSI-P[167] study were not blinded and contributed to 90.1% of overall outcome. Nor had the participants undergone acute management strategies in-line with current practice.
(d) The confidence intervals just crossed 1 MID (1.25) but were within range of being acceptable.

Table 15: GRADE profile: omega-3 fatty acids versus placebo (revascularisation)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Omega-3 fatty acids	Control	Relative (95% CI)	Absolute		
Revascularisation (hazard ratio)[324]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness[b]	No serious imprecision[c]	None	43/150 (28.7%)	49/150 (32.7%)	HR 0.92 (0.61 to 1.39)	22 fewer per 1000 (from 112 fewer to 96 more)	MODERATE	IMPORTANT
Revascularisation (relative risk)[167,324,377]												
3	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness[b]	No serious imprecision	None	1878/7735 (24.3%)	1852/7703 (24%)	RR 1.01 (0.95 to 1.07)	2 more per 1000 (from 12 fewer to 17 more)	MODERATE	IMPORTANT

(a) It was unclear whether allocation concealment was performed or how the authors randomised participants. No power calculations were provided, so there is risk of a Type II error.

(b) 100% of the population had an MI. Nilsen[324] participants were recruited from a coastal area in Norway and according to the authors received a diet rich in fish product, however no dietary analysis was provided.
(c) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(d) Participants in the GISSI-P[167] study were not blinded and made the greatest contribution to the overall result. Nor had the participants undergone acute management strategies in-line with current practice.

Table 16: GRADE profile: omega-3 fatty acids versus placebo (stroke)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Omega-3 fatty acids	Control	Relative (95% CI)	Absolute		
Stroke (hazard ratio)[156,157]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness[a]	Very serious[b]	None[c]	29/1253 (2.3%)	28/1248 (2.2%)	HR 1.04 (0.63 to 1.71)	1 more per 1000 (from 8 fewer to 16 more)	LOW	IMPORTANT
Stroke (relative risk)[167]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	424/5666 (7.5%)	585/5668 (10.3%)	RR 0.3 (0.64 to 0.82)	72 fewer per 1000 (from 19 fewer to 37 fewer)	LOW	IMPORTANT

(a) Less than 50% of the population used in the study had an MI.
(b) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(c) The study was sponsored by the same company that provided the intervention.
(d) Participants were not blinded. Nor had the participants undergone acute management strategies in-line with current practice.
(e) 95% confidence intervals crossed 1 MID (0.75).

Table 17: GRADE profile: omega-3 fatty acids versus placebo (adverse events)

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Omega-3	Control	Relative	Absolute		

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Quality assessment							No of patients		Effect		Quality	Importance
studies		bias					fatty acids		(95% CI)			
Adverse events: gastrointestinal disturbances, nausea, prostate cancer, cancer mortality [167,238]												
2	Randomised trials	Serious[a]	Very serious[b]	No serious indirectness[c]	No serious imprecision	None[d]	338/8071 (4.2%)	242/8101 (3%)	RR 1.40 (1.19 to 1.65)	12 more per 1000 (from 6 more to 19 more)	VERY LOW	IMPORTANT
Adverse events and timing less than 3months[167]												
1	Randomised trial	Serious[e]	No serious inconsistency[f]	No serious indirectness	No serious imprecision	None	215/5666 (3.8%)	119/56668 (0.21%)	RR 1.81 (1.45 to 2.25)	2 more per 1000 (from 1 more to 3 more)	MODERATE	IMPORTANT
Adverse events and timing over 3months[238,238]												
1	Randomised trial	Serious[g]	No serious inconsistency	No serious indirectness	Serious[h]	None	123/2405 (5.1%)	123/2433 (5.1%)	RR 1.01 (0.79 to 1.29)	0 more per 1000 (from 10 fewer to 14 more)	LOW	IMPORTANT
Adverse events and food source of omega-3 fatty acids(spreads/margarines)[238,238]												
1	Randomised trial	Serious[g]	No serious inconsistency	No serious indirectness	Serious[h]	None	123/2405 (5.1%)	123/2433 (5.1%)	RR 1.01 (0.79 to 1.29)	1 more per 1000 (from 11 fewer to 15 more)	LOW	IMPORTANT
Adverse events and capsule source of omega-3 fatty acids[167]												
1	Randomised trial	Serious[e]	No serious inconsistency[f]	No serious indirectness	No serious imprecision	None[i]	215/5666 (3.8%)	119/5668 (2.1%)	RR 1.81 (1.45 to 2.25)	17 more per 1000 (from 9 more to 26 more)	MODERATE	IMPORTANT

(a) In 1 of the 2 studies the participants were not blinded, which may influence the outcome. In the study by GISSI, that contributed the most to the overall result, participants had not undergone acute management strategies in-line with current practice.
(b) I2 =92%, p< 0.0001
(c) 100% of the population had an MI.
(d) Both studies were sponsored by the same companies that provided the intervention.
(e) The study was not blinded. Nor had the participants undergone acute management strategies in-line with current practice
(f) Heterogeneity could not be calculated.

Update 2013

(g) It was unclear how the authors randomised. The study was underpowered to detect differences in fatal coronary heart disease. Unclear if underpowered to detect differences in adverse events.
(h) 95% confidence intervals crossed 1 MID (1.25).
(i) The paper was funded by the pharmaceutical company that provided the intervention.

Update 2013

Table 18: GRADE profile: omega-3 fatty acids versus placebo (hospitalisation)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Omega -3 fatty acids	Control	Relative (95% CI)	Absolute		
Hospitalisation (hazard ratio)[274,274]												
1	Randomised trial	No serious risk of bias	No serious inconsistency[a]	Serious[b]	Serious[c]	None	145/1808 (8%)	178/1826 (9.7%)	HR 0.79 (0.63 to 0.99)	20 fewer per 1000 (from 1 fewer to 35 fewer)	LOW	IMPORTANT

(a) No heterogeneity was detected.
(b) The paper had a mixed population consisting of people who had an MI and people who have hypercholesterolaemia.
(c) 95% confidence intervals crossed line of no effect and 1 MID (0.75).

Table 19: GRADE profile: omega-3 fatty acids versus placebo (quality of life)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Omega -3 fatty acids	Control	Relative (95% CI)	Absolute		
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

5.1.3.3 Economic evidence

Published literature

Three studies with the relevant comparison were included in CG48: 2 published non-UK analyses, [150, 242] and 1 unpublished UK analysis submitted by Solvay as part of a call for evidence.[202] Two additional studies were identified from the update searches published since the cut-off date for searches in CG48: Quilici 2006[372,372] which appears to be the publication of the unpublished UK analysis submitted for CG48, and Schmier 2006.[401,401] All analyses were based on effectiveness data from the GISSI-P clinical trial.[167]

None of the studies from CG48 were included in the update review because of their potentially serious limitations; in fact they are based on effectiveness evidence from the GISSI-P study which does not reflect the overall current evidence base. [167]

Although the GISSI-P study was included in our clinical review (see Table 7), its results favour treatment with omega-3 fatty acids which is in disagreement with more recent studies. If the review were only to consider the results of the GISSI-P trial this would be ignoring evidence more applicable to the current setting (Kromhout et al (2010)[238,238] and Rauch et al (2010)).[377,378] In these studies, people who had an MI were treated with current strategies such as percutaneous coronary intervention and modern medical treatments including statins. These newer studies reach conclusions at odds with the GISSI-P study. As these newer studies are more applicable to current clinical practice, the conclusions of an economic evaluation based on the GISSI-P study would be unreliable.

Update 2013

CG48 cost effectiveness modelling

A model was developed for the previous guideline, CG48, to estimate the cost effectiveness of omega-3-fatty acids supplements for people after a recent MI who cannot comply with recommendations for the dietary intake of fatty fish. This model was based on the GISSI-P [167] and DART1 trial.[321] In this guideline update, DART1 has been included in the review on oily fish consumption (see Section 5.1.4) and excluded from this review on omega-3 fatty acids as the intervention was consumption of fish. Although a sensitivity analysis was carried out where results from GISSI-P were analysed separately, as explained above, any economic evaluation based solely on the GISSI-P study would be considered not reflective of the current evidence base. For these reasons, the original model developed for CG48 was excluded from the evidence review.

A new cost-effectiveness analysis was not developed for this question. In fact, the clinical evidence update shows that omega-3 fatty acids are not clinically effective in the context of current care. Given they are associated with some costs, no formal economic evaluation is required to show that they are not cost-effective.

Intervention costs

Capsules available over-the-counter and margarine-supplemented with omega-3 fatty acids will both be purchased by people who had an MI and so will not have a cost to the NHS. See Table 20 for costs of capsules available on prescription.

Table 20: Unit cost of capsules available on prescription

Drug	Units/pack	Cost/pack	Units/day	Cost/day	Cost/year
Omacor (EHA 460mg, DHA 380 mg)	28	£14.24	1	£0.51	£185.63
Maxepa (EHA 170mg, DHA 115mg)	200	£29.28	3	£0.44	£160.31

EHA = eicosapentaenoic acid; DHA = docosahexaenoic acid
Costs are from the Drug Tariff August 2012; Omacor® dose for secondary prevention of MI from the British National Formulary 63[208]; Maxepa® dose calculated to achieve similar EHA and DHA levels as for Omacor® as MI secondary not licensed indication.

5.1.3.4 Evidence statements

5.1.3.4.1 Clinical

All-cause mortality

Hazard ratio

- Four studies with 14,606 people found omega-3 fatty acids treatment (food source and capsule) may reduce the risk of all-cause mortality compared with placebo (HR 0.93 [0.82 to 1.05]) [Low quality evidence].
- One study with 4837 people showed a food source of omega-3 fatty acids has a similar effect on the risk of all-cause mortality compared with placebo, but there was some uncertainty (HR 1.02 [0.82 to 1.27]) [Moderate quality evidence].
- Three studies with 9768 people showed a capsule form of omega-3 fatty acids may reduce the risk of all-cause mortality compared with placebo treatment (HR 0.89 [0.77 to 1.03]) [Low quality evidence].
- One study with 4837 people showed that omega-3 fatty acids treatment initiated within 3 months after an MI may reduce the risk of all-cause mortality compared with placebo treatment (HR 0.89 [0.77 to 1.03]) [Low quality evidence].
- Three studies with 9768 people showed that omega-3 fatty acids treatment starting more than 3 months after an MI has no effect on the risk of all-cause mortality compared with placebo treatment, but there was some uncertainty (HR 1.02 [0.82 to 1.27]) [Moderate quality evidence].

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Cardiac mortality

Hazard ratio

- Two studies with 5138 people showed omega-3 fatty acids(food source and capsule) has no effect on the risk of cardiac mortality compared with placebo, but there was considerable uncertainty (HR 0.98 [0.73 to 1.32]) [Very low quality evidence].
- One study with 4837 people reported a food source of omega-3 fatty acids has no effect on the risk of cardiac mortality compared with placebo, but there was considerable uncertainty (HR 0.98 [0.72 to 1.34]) [Very low quality evidence].
- One study with 300 people reported a capsule form of omega-3 fatty acids has no effect on the risk of cardiac mortality compared with placebo, but there was considerable uncertainty (HR 1.02 [0.38 to 2.73]) [Very low quality evidence].

- One study with 300 people reported starting omega-3 fatty acids treatment within the first 3 months after an MI has no effect on the risk of cardiac mortality compared with placebo, but there was considerable uncertainty (HR 1.02 [0.38 to 2.73]) [Very low quality evidence].
- One study with 4837 people reported omega-3 fatty acids treatment starting more than 3 months after an MI has a similar effect on the risk of cardiac mortality compared with placebo, but there was considerable uncertainty (HR 0.98 [0.72 to 1.34]) [Very low quality evidence].

Relative risk

- Three studies with 16,472 people reported omega-3 fatty acids(food source and capsule) may reduce the risk of cardiac mortality compared with placebo in people who had an MI (RR 0.87 [0.76 to 0.99]) [Moderate quality evidence].
- One study with 4837 people reported a food source of omega-3 fatty acids has no effect on the risk of cardiac mortality compared with placebo in people who had an MI, but there was considerable uncertainty (RR 0.99 [0.73 to 1.34]) [Low quality evidence].
- Two studies with 11,634 people reported a capsule form of omega-3 fatty acids may reduce the risk cardiac mortality compared with placebo in people who had an MI, but there was some uncertainty (RR 0.84 [0.72 to 0.98]) [Moderate quality evidence].

Sudden death

Hazard ratio

- One study with 3804 people reported omega-3 fatty acids treatment has no effect on the risk of sudden death compared with placebo in people who had an MI, but there was considerable uncertainty (HR 0.95 [0.56 to 1.59]) [Very low quality evidence].

Relative risk

- Two studies with 15,138 people reported omega-3 fatty acids may reduce the risk of sudden death compared with placebo in people who had an MI, but there was some uncertainty (RR 0.78 [0.63 to 0.96]) [Low quality evidence].

Myocardial infarction

Hazard ratio

- One study with 300 people reported capsule form of omega-3 fatty acids increases the risk of reinfarction compared with placebo in people who had an MI but there was considerable uncertainty (HR 1.43 [0.74 to 2.78]) [Low quality evidence].

Relative risk

- Two studies with 11,634 people reported capsule form of omega-3 fatty acids has no effect on the risk of reinfarction in people who had an MI compared with placebo, but there was some uncertainty (RR 1.01 [0.81 to 1.26]) [Moderate quality evidence].

Revascularisation

Hazard ratio

- One study with 300 people reported capsule form of omega-3 fatty acids may reduce the risk of revascularisation compared with placebo but there was considerable uncertainty (HR 0.92 [0.61 to 1.39]) [Moderate quality evidence].

Update 2013

Relative risk

- Three studies with 15,438 people reported capsule form of omega-3 fatty acids has no effect on the risk of revascularisation compared with placebo in people who had an MI (RR 1.01 [0.95 to 1.07]) [Moderate quality evidence].

Stroke

Hazard ratio

- One study with 2501 people reported capsule form of omega-3 fatty acids has no effect on the risk of stroke as compared with placebo in people who had an MI, but there was considerable uncertainty (HR 1.04 [0.63 to 1.71]) [Low quality evidence].
- One study with 11,334 people reported omega-3 fatty acids may reduce the risk of stroke compared with placebo in people who had an MI, but there was some uncertainty (RR 0.73 [0.64 to 0.82]) [Low quality evidence].

Adverse events

Relative risk

- Two studies with 16,172 people reported omega-3 fatty acids (food source and capsule) increased the number of adverse events compared with placebo, but there was some uncertainty (RR 1.40 [1.19 to 1.65]) [Very low quality evidence].
- One study with 11,334 people reported initiating omega-3 fatty acids within 3 months of MI increased the number of adverse events compared with placebo people who had an MI (RR 1.81 [1.45 to 2.25]) [Moderate quality evidence].
- One study with 4838 people reported initiating omega-3 fatty acids treatment more than 3 months following an MI has a similar effect on the number of adverse events compared with placebo but there was some uncertainty(RR 1.01 [0.79 to 1.29]) [Low quality evidence].
- One study with 4838 people reported a food source of omega-3 fatty acids has a similar effect on the number of adverse events compared with placebo but there was some uncertainty (RR 1.01 [0.79 to 1.47]) [Low quality evidence].
- One study with people 11,334 reported capsule form of omega-3 fatty acids increased the risk of adverse events compared with controls placebo (RR 1.81 [1.45 to 2.25]) [Moderate quality evidence].
- Gastrointestinal disturbances and nausea were the most commonly reported events (4.9% and 1.4% respectively).

Rehospitalisation

Hazard ratio

- One study with 3634 people reported omega-3 fatty acids decreased the risk of rehospitalisation compared with placebo but there was some uncertainty (HR 0.79[0.63 to 0.99]) [Low quality evidence].

Quality of life

- No evidence was found on quality of life.

Update 2013

5.1.3.4.2 Economic

- No economic evidence was included for this question.

5.1.4 Oily fish

A diet rich in oily fish has been included in the recommendation given to people after an MI. The previous guideline, CG48, recommended the consumption of 2-4 portions of oily fish per week. There is considerable epidemiological evidence that high intake of n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) commonly found in oily fish such as salmon, herring and mackerel, may be associated with low coronary heart disease mortality in the primary prevention of cardiovascular disease.

A meta-analysis of cohort studies suggests fish consumption may reduce the risk of coronary heart disease.[188,235,462] However, there are limitations with these reviews because they often include primary prevention of coronary heart disease studies (not secondary prevention) and it is difficult to control for unknown confounders that may influence the outcomes (such as background medication and baseline characteristics). It is acknowledged that observational epidemiological studies are useful for finding associations between disease and lifestyle factors, since they can include large numbers and it can be impractical or unethical to do RCTs for factors such as smoking. However, RCTs are available for this review and therefore they were used in preference to cohort studies. RCTs are less susceptible to selection bias because background factors (confounders) are mostly similar in the 2 treatment arms since participants are randomised to the groups. Also, unlike observational studies, RCTs rely less on people's recollection of fish intake which can lead to misreporting of outcomes. There is also a chance in cohort studies that something fundamentally different between the groups may explain why one group consumes more fish than the other.

Update 2013

The GDG were interested in finding out what is the clinical evidence for a diet rich in oily fish in the secondary prevention of myocardial infarction and the impact this intervention has on all-cause mortality, cardiac mortality and reinfarction, in light of new evidence available on the use of omega-3 fatty acids and to identify any new evidence on oily fish consumption.

5.1.4.1 What is the clinical and cost effectiveness of consumption of oily fish in all people who have had a myocardial infarction?

For full details see review protocol in Appendix C.

5.1.4.2 Clinical evidence

A literature search identified one new RCT relevant to the review.[76,77] The 2 studies reviewed in the original guideline were also included in this review.[75,321] Published evidence from these studies are summarised in the clinical GRADE evidence profile below (see Table 11 to Table 19). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

The previous guideline, CG48, recommended that people who had an MI should be advised to consume at least 7g of omega 3 fatty acids per week from 2 to 4 portions of oily fish per week. This recommendation is based on the DART 1 study by Burr et al and the 10 year follow-up data on this trial by Ness et al.[75,321]

Update 2013

Table 21: Summary of included studies

	Study	Included in CG48 or new to update?	Study design	Intervention/ comparisons	Dose	Outcomes reported	Follow up period	% people with MI Time since MI
1.	Burr 1989[75,77] DART1	CG48	RCT	Fatty fish/no fish advice	At least 2 portions/week	• All-cause mortality (RR) • Myocardial infarction (non-fatal) (RR) • Cardiac mortality (RR)	2 years	100% post MI After discharge
2.	Burr 2003[76,77] DART2	New	RCT	Oily fish or EPA+DHA capsules versus fruit plus sensible eating	420mg/day	• All-cause mortality (HR) • Cardiac mortality (HR) • Sudden death (HR)	3-9 years	50% History
3.	Ness 2002[321] FOLLOW-UP TO DART1	CG48	RCT (follow-up DART1)	Fatty fish/no fish advice	At least 2 portions/week	• All-cause mortality (HR) • Cardiac mortality (HR) • Stroke (fatal) (HR)	10 or more years	100% post MI

Update 2013

Table 22: GRADE profile: consumption of oily fish versus control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oily fish	Control	Relative (95% CI)	Absolute		
All-cause mortality (hazard ratio)[321]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	530/1015 (52.2%)	553/1018 (54.3%)	HR 0.95 (0.85 to 1.07)	18 fewer per 1000 (from 57 fewer to 24 more)	MODERATE	CRITICAL
Cardiac mortality (hazard ratio)[321]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	354/1015 (34.9%)	384/1018 (37.7%)	HR 0.92 (0.8 to 1.06)	24 fewer per 1000 (from 62 fewer to 17 more)	MODERATE	CRITICAL
Sudden death (hazard ratio)[76,77]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Serious[b]	None	49/1109 (4.4%)	47/1543 (3%)	HR 1.43 (0.95 to 2.15)	13 more per 1000 (from 2 fewer to 34 more)	VERY LOW	CRITICAL
Reinfarction[75,77]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	49/1015 (4.8%)	33/1018 (3.2%)	RR 1.49 (0.97 to 2.30)	16 more per 1000 (from 1 fewer to 42 more)	LOW	IMPORTANT
Stroke (hazard ratio)[321]												
1	Randomised trial	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	29/1015 (2.9%)	23/1018 (2.3%)	HR 1.23 (0.71 to 2.14)	5 more per 1000 (from 6 fewer to 25 more)	LOW	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Rehospitalisation												

Update 2013

Quality assessment							No of patients		Effect		Quality	Importance
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) It was unclear whether the authors performed allocation concealment or randomisation.
(b) The population consisted of less than 50% people who had an MI.
(c) 95% confidence intervals crossed the line of no effect and 2 MIDs.

5.1.4.3 Economic evidence

Published literature

No economic evaluations comparing consumption of oily fish with control were identified.

5.1.4.4 Evidence statements

5.1.4.4.1 Clinical evidence

All-cause mortality

- One RCT with 2033 people showed that consumption of oily fish decreases the risk of all-cause mortality calculated with time-to-event data compared with a control diet (HR 0.95 [0.85 to 1.07]) [Moderate quality evidence].

Cardiac mortality

- One RCT with 2033 people showed that consumption of oily fish decreases the risk of cardiac mortality calculated with time-to-event data compared with a control diet (HR 0.92 [0.80 to 1.06]) [Moderate quality evidence].

Update 2013

Sudden death

- One RCT with 2652 people reported some uncertainty whether consumption of oily fish increases the risk of sudden death calculated as time to event data compared with a control diet (HR 1.43 [0.95 to 2.15]) [Very low quality evidence].

Reinfarction

- One RCT with 2037 people reported some uncertainty whether consumption of oily fish increases the risk of reinfarction compared with a control diet (RR 1.48 [0.96 to 2.24] [Low quality evidence].

Stroke

- One RCT with 2033 people reported considerable uncertainty whether consumption of oily fish increases the risk of stroke calculated as time to event data compared with a control diet (HR 1.23 [0.71 to 2.14]) [Low quality evidence].

5.1.4.4.2 Economic

- No relevant economic evaluations were identified.

5.1.5 Mediterranean diet

5.1.5.1 Clinical evidence

A randomised controlled trial [113] 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.[113] 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.

5.1.6 Low saturated fat

5.1.6.1 Clinical evidence

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).[75,77] 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).[75,77]

5.1.7 Plant sterols esters

5.1.7.1 Clinical evidence

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

5.1.8 Low glycaemic diets

5.1.8.1 Clinical evidence

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

5.1.9 Fruit and vegetables

5.1.9.1 Clinical evidence

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.[167]

5.1.10 High fibre diets

5.1.10.1 Clinical evidence

Advice to eat more fibre was examined in a large randomised controlled trial in patients with a prior MI.[75,77] 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).

5.1.10.2 Evidence statement(s)

5.1.10.2.1 Clinical

Antioxidants

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++).

In patients after an MI, vitamin C supplementation does not appear to have any benefit (1++).

In patients after an MI, beta-carotene may increase cardiovascular deaths (1+).

Folic acid supplementation

In unselected patients after an MI, folic acid plus vitamin B12 and B6 supplementation does not reduce all-cause mortality or cardiovascular events (1++).

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

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

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

Low glycaemic diet

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

Fruit and vegetables

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

In a single trial of patients after an MI, advice to reduce dietary saturated fat did not reduce mortality (1-).

Dietary fibre

In a single trial of patients after an MI, an increase in dietary fibre did not reduce all-cause mortality (1-).

5.1.11 Recommendations and links to evidence

Recommendation	1. **Do not routinely recommend eating oily fish for the sole purpose of preventing another MI. If people after an MI choose to consume oily fish, be aware that there is no evidence of harm, and fish may form part of a Mediterranean-style diet. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It is clearly undesirable and in addition has significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	Two large randomised controlled trials that compared people who consumed oily fish with those who consumed a usual or healthy diet were included in this review. No clear evidence was found to show either a net benefit or harm. The risk of all-cause mortality and cardiac mortality appeared to be reduced in the long-term follow-up of people who had an MI who consumed oily fish. In contrast, the risk of sudden death and reinfarction appeared to be increased in the same people but after a short term follow-up. The results on stroke in the long-term follow up are unclear. Possible reasons for the conflicting results in mortality are described below in 'Quality of evidence'. No clinical evidence on health-related quality of life or adverse events was identified. The GDG considered the impact of the results in light of people not being treated using current therapies, such as dual antiplatelet medicines, statins and PCI. Thus, the GDG felt the population and their risk of subsequent cardiovascular events is very different today and any impact an oily fish diet may have on clinical outcomes could be minimal. Thus, overall the GDG felt there was a lack of high quality evidence to support the consumption of oily fish for the secondary prevention of myocardial infarction or mortality, particularly in the context of negative studies of omega-3 fatty acids supplementation using capsules.
Economic considerations	No relevant published economic studies were identified. The resource use implications to the NHS of advising people to consume oily fish, compared to not doing so, will mostly be the time spent giving this information to people. Although this would likely take place as part of a wider consultation on dietary and lifestyle changes and it is unlikely to have significant time or cost implications, the clinical evidence did not support the use of oily fish and therefore any time spent to discuss this diet would increase costs without necessarily improving outcomes.

Update 2013

Quality of evidence	Overall there was no clear evidence to support a recommendation to consume oily fish. Moderate quality evidence suggested that consumption of oily fish had no effect on all-cause mortality and cardiac mortality. In contrast, very low to low quality evidence showed a negative effect of consumption of oily fish on sudden death and reinfarction. The results were downgraded because of imprecision and/or indirectness. There are a number of differences between the studies that reported a negative effect of the consumption of oily fish on sudden death versus a positive effect on all-cause and cardiac mortality. For instance the study that reported a negative effect used an indirect population (50% versus 100% people who had an MI) and more people chose to take fish oil capsules than consume fish (42% versus 22%). However, other variables such as study design, geographical area, EPA intake per week, participant blinding, study duration and matching baseline characteristics were similar between the 2 studies. The GDG highlighted that the numerous people who stopped consuming fish reflects the tolerability and possibly the adverse events associated with eating oily fish. No adverse events possibly linked to a fish diet, such as neurological problems, diagnosis of cancers or birth defects were reported in either study.
Other considerations	The previous guideline, CG48, recommended the consumption of at least 7g per week of omega-3 fatty acids from 2 to 4 portions of oily fish. This was based on the results of DART 1 where people consumed much lower levels of fish, averaging 2.5g of omega-3 fatty acids per week. The GDG did not feel that the current evidence supported this and therefore this would be a change in practice which may have implementation considerations. The GDG felt that compliance to sustaining a diet rich in oily fish may also be difficult. This is reflected by the findings of the RCTs of people switching to the capsule form of omega-3 fatty acids instead of eating oily fish (22 to 42%). The lack of compliance to the consumption of oily fish may have also reduced the likelihood of finding an association between oily fish intake and coronary heart disease. Although a diet rich in oily fish may not decrease the risk of mortality, stroke or reinfarction, promoting a healthy diet is important and healthcare professionals could discuss with people who had an MI that although there is no clear evidence to support the benefits of oily fish on secondary prevention of MI, there is no evidence of harm. The GDG noted that people who had an MI may choose to consume oily fish as part of a Mediterranean diet, low in saturated fat. The consumption of fish is recommended as part of a Mediterranean style diet (see Mediterranean diet). It is worth noting that a meta-analysis of prospective cohort studies suggests fish consumption may reduce the risk of coronary heart disease. However, there are limitations with these reviews because they often include studies of the primary prevention of coronary heart disease (rather than secondary prevention) and it is difficult to control for other variables that may influence the outcomes (i.e. background medication and baseline characteristics). Although it is acknowledged that observational epidemiological studies are useful for finding associations between disease and lifestyle factors, since they can include large numbers and it can be impractical or unethical to do RCTs for factors such as smoking, RCTs are available for this review. These were therefore used in preference to cohort studies. RCTs can control for the effects of background medication and rely less on people's recollection of fish intake that can be misreported.

Update 2013

Recommendation	2. **Do not offer or advise people to use the following to prevent another MI:** • **omega-3 fatty acid capsules** • **omega-3 fatty acid supplemented foods.** **If people choose to take omega-3 fatty acid capsules or eat omega-3 fatty acid supplemented foods, be aware that there is no evidence of harm.[new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It is clearly undesirable and in addition has significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	**Omega-3 fatty acid capsules** There was mostly low quality evidence for a reduction in all-cause mortality, cardiac mortality and sudden death for omega-3 fatty acid capsules alone. There was inconclusive evidence for a reduction in revascularisation and stroke. There was an increase in the risk of reinfarction and adverse events (although they were considered minor, that is gastrointestinal disturbances or nausea). No data were identified on health related quality of life. The GDG did not consider the evidence for a decrease in rehospitalisation to be in line with other related outcomes, for example, reinfarction. The GDG decided that the evidence was not strong enough to recommend the use of omega-3 fatty acids capsules. They felt that the benefit of current treatments on a cardiac event is likely to over-ride any small gains that omega 3 fatty capsules may provide. This is supported by new evidence that has been published since publication of the previous guideline, CG48. This well-designed RCT, in a population receiving treatments in line with current practice (for example 78% of participants had PCI, 82% statins, 88% clopidogrel and 94% aspirin), found no benefit of omega-3 fatty acid capsules. This is in contrast to what was concluded in the previous guideline, CG48, in the absence of this evidence. Therefore, the GDG decided to change the recommendation from CG48, which recommended omega-3-acid ethyl esters for the secondary prevention of MI. **Foods supplemented with omega-3 fatty acids** There was low to very low quality evidence that foods supplemented with omega-3 fatty acids have no effect on all-cause mortality or cardiac mortality. No data were identified on quality of life, sudden death, reinfarction, stroke, revascularisation or rehospitalisation, specifically. However, a composite endpoint reported in the paper, including major cardiovascular events, PCI and CABG, but not presented in the review (since composite outcomes are only reported if no other data were identified) suggested that a benefit was unlikely. There was no effect of the

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	supplemented foods on the number of reported adverse events. In conclusion, it appears foods supplemented with omega-3 fatty acids do not provide any health benefits in the secondary prevention of MI and therefore the GDG did not wish to recommend their use. The GDG therefore agreed that foods supplemented with omega-3 fatty acids should not be recommended for the secondary prevention of myocardial infarction.
Economic considerations	Margarine (and other foods) supplemented with omega-3 fatty acids and capsules available over the counter will be purchased by people who had an MI and so will not have a cost to the NHS in terms of intervention costs. However, prescribed capsules cost around £160-£185 per year. Given that omega-3 fatty acids supplementation was judged not to be of clinical benefit to people who had an MI on the basis of current effectiveness evidence and prescribed capsules have a considerable cost to the NHS, their use was considered no longer to be cost effective. None of the studies from the old guideline (CG48) were included in the update review because of their potentially serious limitations; in fact they are based on effectiveness evidence from the GISSI-P study which does not reflect the overall current evidence base. Studies that conducted a cost-effective analysis of omega-3 fatty acids based on the data by GISSI-P were also excluded from the review.
Quality of evidence	**Omega-3 fatty acid capsules** The quality of the evidence for the clinical outcomes identified ranged from being graded as very low to moderate quality however the majority was graded as low or very low quality. There are differences in the conclusions that can be drawn from the hazard ratio versus the relative risk data. Hazard ratios have a reduced risk of reporting bias compared with relative risk (as there is less chance of choosing a desired follow-up time period), therefore hazard ratio data were used in preference to relative risk (see Chapter 3). In this review hazard ratio data were available for the following outcomes: all-cause mortality, cardiac mortality, sudden death, reinfarction, stroke, revascularisation and rehospitalisation. The data were mostly low quality evidence because of some imprecision and indirectness in the population. A number of outcomes, such as sudden death and revascularisation, were downgraded because the study was underpowered to detect a difference. There was some evidence graded as a moderate quality for a clinical benefit of omega-3 fatty acids on cardiac mortality however the GDG weighed this up against inconclusive results for all-cause mortality and sudden death and an increased risk for reinfarction. In the previous guideline, CG48, the study that reported the positive effects of omega 3 fatty acids on all-cause mortality, sudden death, cardiac mortality was on people who were not blinded to the study design, nor did they receive concomitant therapies or acute care that is in line with current practice. Because of this the quality of this data was downgraded for indirectness. All of the evidence identified was from a direct population of people who had an MI, with the exception of an indirect population that provided hazard ratio data on the risk of stroke and rehospitalisation. The majority of evidence identified did not include people who had undergone acute management strategies that are in line with current practice, for example, people received treatment with thrombolysis as opposed to primary PCI. Therefore any reductions in all-cause mortality, cardiac

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	mortality and sudden death may not be transferrable to people receiving the improved acute treatment of primary PCI and long-term medications of statins and dual-antiplatelet therapy. Another limitation is that the background intake of omega-3 fatty acids may have varied between the different populations and the doses varied between studies which may explain the varied results. However, the effect of dose could not be explored because not enough studies were available. The effect of initiating treatment early versus later after the MI (less than or over 3 months) could not be thoroughly investigated as only a few outcomes were available for this comparison. However, the results that were available showed that initiating treatment within 3 months of an MI reduced the risk of all-cause mortality but also increased the risk of adverse events (the GDG considered gastrointestinal disturbances and nausea as minor events). No benefit or harm on either outcome was found after 3 months however the findings may also be explained by the source of omega-3 fatty acids provided, as the study that initiated treatment within 3 months gave capsules, while the study that started treatment more than 3 months after an MI provided a food source of omega-3 fatty acids (margarine). Thus, it was difficult to come to any conclusion on the effect of timing or dose of omega-3 fatty acids. In conclusion, the older evidence in people not receiving current therapies was used to make the recommendation to consume omega-3 fatty acids capsules in the previous guideline, CG48. Newer evidence is now available in people receiving up-to-date treatments. As this showed no benefit of omega-3 fatty acids, the recommendation has been changed. **Foods supplemented with omega-3 fatty acids** Overall there was no clear evidence to support a recommendation of omega-3 fatty acids in a form of supplemented foods (spreads and margarines). No evidence was found on other supplemented foods, or foods which are rich in omega-3 fatty acids (for example, rape seed oil). One study has been published on the effects of omega-3 fatty acids supplemented margarine on people who had an MI. However, the data were graded as low quality and no difference was detected between the treatment arms for all-cause mortality, cardiac mortality, and the risk of adverse events. The data is only relevant for people who had an MI at some point the in the past, as the people included had an MI a median of 3.7 years prior to the onset of treatment. The data is also indirect since it is likely that the people included were treated acutely with thrombolysis and not with modern therapy. The GDG highlighted that the dose of omega-3 fatty acids provided in supplemented foods was low compared with that provided in capsule form: 400mg/d of EPA plus DHA versus 850 to 1800 mg per day respectively, although such doses were associated with improved cardiovascular outcomes in cohort studies.
Other considerations	**Omega-3 fatty acid capsules** The GDG identified that the change in recommendation from the previous guideline, CG48, may represent a change in practice and therefore, there may be implementation issues. However, the GDG felt that the previous recommendation was not widely adopted due to the newly available evidence, and therefore the impact of changing the recommendation may be small. The GDG noted that clinicians may discuss issues raised by people who had an MI about continuing treatment, taking into account potential benefits and lack of

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	evidence regarding harm. **A**lthough omega-3 fatty acid capsules can be prescribed and considered a medicinal product the GDG felt that their use is related to diet and lifestyle factors (for example, eating oily fish) and therefore felt that this should sit within the chapter on 'Lifestyle'. **Foods supplemented with omega-3 fatty acids** This is a new recommendation as data on the effectiveness of omega-3 fatty acids supplemented foods was not available when the previous guideline, CG48, was published. This recommendation relates to the secondary prevention of myocardial infarction only. Recommendations on the use of omega-3 fatty acids for prevention of cardiovascular events can be found in the updated NICE guideline on Lipid modification, which is due for publication in 2014.

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3. **Advise people to eat a Mediterranean-style diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on plant oils). [2007]**

4. **Advise people not to take supplements containing beta-carotene. Do not recommend antioxidant supplements (vitamin E and/or C) or folic acid to reduce cardiovascular risk. [2007]**

5.2 Delivery of dietary advice

5.2.1 Clinical evidence

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.[196] Dietary fat advice was prioritised by 84% of departments, fruit and vegetables by 45%, oily fish by 45% and fibre by 28%. Most dietitians (81%) felt that this advice would protect from further cardiovascular disease.[196]

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.[442] 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 dietitian. 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.[442]

The second study recruited patients four weeks after discharge from hospital following an MI either to an education intervention program or to usual care.[80] 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).[80]

The third study randomly assigned patients with a prior MI into an intervention or control group at discharge from hospital.[225] 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).[225]

5.2.2 Evidence statements

5.2.2.1 Clinical

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

5.2.3 Summary of recommendations

5. **Offer people an individual consultation to discuss diet, including their current eating habits, and advice on improving their diet. [2007]**

6. **Give people consistent dietary advice tailored to their needs. [2007]**

7. **Give people healthy eating advice that can be extended to the whole family. [2007]**

5.3 Alcohol consumption

5.3.1 Clinical evidence

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.[300] 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).[300]

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.[167] 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.[167] 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).[167]

A second study [303] examined subjects recruited into the Physicians' Health Study (Steering Committee of the Physicians; Health Research Group, 1989).[420] 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 more than 2 drinks per day.[303]

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).[303]

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.[303]

The third study [18] used the database from the SAVE trial [297 357,359] to assess the influence of alcohol intake on the development of symptomatic heart failure in patients with left ventricular dysfunction after MI.[18] 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.[297 357,359] 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.[18]

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.[18]

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.[408] The study was based on the British Regional Heart Study.[407] 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 analysed. Alcohol consumption was classified as follows: lifelong teetotallers (n= 43), ex-drinkers (n= 59), occasional drinkers (less than 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 (more than 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.[408]

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.[114] These patients were compared with a group of unselected age- and gender-matched coronary artery disease control patients.[114]

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.[114]

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.

5.3.2 Evidence statements

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+).

There is insufficient evidence about the effect of alcohol consumption by women after an MI.

5.3.3 Summary of recommendations

8. **Advise people who drink alcohol 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). [2007]**

5.4 Regular physical activity

5.4.1 Clinical evidence

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.[319] 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.[319]

The second study [127] was a secondary analysis of the first study [319] 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.[127]

The third study [55,56] 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.[36] 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).[55,56]

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.[132] 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).[132] The non-randomised design means these results may be confounded by selection bias.

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 5.4.1.[319] 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, [127] also described in Section 5.4.1, conducted a secondary analysis of the first study [319] 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.[127] 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).[127]

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[195] recruited 79 patients and randomised them to 12 weeks of supervised exercise of at least 45 minutes duration for 2 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 [16] randomised 29 patients (25 male, mean SD age 52 X 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 [16].

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 6.1[269] 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.[269]

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 years, 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.[269]

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.[465] 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 1 year follow up, compared to the control group (P < 0.001). However, at 4 year follow up, there were no significant differences found in all-cause mortality or cardiovascular deaths between the two groups.

5.4.2 Evidence statements

5.4.2.1 Clinical

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+).

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+).

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

5.4.3 Summary of recommendations

9. **Advise people to undertake regular physical activity sufficient to increase exercise capacity.[2007]**

10. **Advise people to be physically active for 20-30 minutes a day to the point of slight breathlessness. Advise people who are not active to this level 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. [2007]**

11. **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. [2007]**

5.5 Smoking cessation

For guidance on smoking cessation refer to the NICE Public Health guidance 10 'Smoking cessation services'. [313]

5.5.1 Summary of recommendations

12. **Advise all people who smoke to stop and offer assistance from a smoking cessation service in line with 'Brief interventions and referral for smoking cessation' (NICE public health guidance 1). [2007]**

13. **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' (NICE public health guidance 1). If a patient is unable or unwilling to accept a referral they should be offered pharmacotherapy in line with the recommendations in 'Smoking cessation services' (NICE public health guidance 10). [2007]**

5.6 Weight management

For guidance in weight management in patients with a prior MI refer to NICE guideline 48 'Obesity'.[309]

5.6.1 Summary of recommendations

14. **After an MI, offer all patients who are overweight or obese advice and support to achieve and maintain a healthy weight in line with 'Obesity' (NICE clinical guideline 43). [2007]**

6 Cardiac rehabilitation

6.1 Comprehensive cardiac rehabilitation

The updated review questions in this chapter are:

- Which interventions designed to increase engagement in and/or adherence to cardiac rehabilitation programmes are effective and cost effective in people who have had an MI?
- Which factors are associated with a person's uptake and adherence to cardiac rehabilitation programmes after an MI?

The evidence and text from the previous guideline, CG48, that has been superseded by this update is included in Appendix K.

Sections not updated in this chapter are:

- Comprehensive cardiac rehabilitation.
- Education and information provision.
- Psychological support.
- Sexual activity.

Update 2013

Cardiac rehabilitation is a coordinated and structured programme of care designed to influence favourably the underlying causes of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that people may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of the disease. Cardiac rehabilitation should consist of a multidisciplinary, integrated approach delivering care in lifestyle risk factor management, psychosocial health, medical risk factor management and the optimal use of cardioprotective therapies, underpinned by psychologically informed methods of health behaviour change and education.

However, despite these benefits there is considerable variation in service provision and many people do not participate in cardiac rehabilitation. The National Audit for Cardiac Rehabilitation (NACR) tells us that participation rates range from 18% to 90% across the United Kingdom.[305] The GDG were interested in critically evaluating the evidence for models of care and interventions that reduce this variation in care whilst effectively increasing both service uptake and programme completion.

The previous guideline, CG48, provided recommendations on the effectiveness of cardiac rehabilitation, patient engagement, education and information provision, psychological support and sexual activity. This 2013 update focuses on updating and expanding upon the review looking at which interventions help to improve uptake and adherence to cardiac rehabilitation. The update also examines barriers to the engagement in and adherence to cardiac rehabilitation. This provides recommendations to help understand why people fail to take up and adhere to these programmes.

6.2 Clinical effectiveness of cardiac rehabilitation

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/).

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

6.2.1.1 Clinical evidence

Three recent systematic reviews were identified that assessed exercise-only cardiac rehabilitation versus usual care, and comprehensive cardiac rehabilitation versus usual care.[69,70 210 92,94]

The first systematic review was published by the Canadian Coordinating Office for Health Technology Assessment.[69,70] 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.[69,70]

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).[69,70]

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.[69,70]

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.[210] 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.[210]

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).[210]

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).[210]

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.[210]

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).[210]

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.[251] Another study showed substantial and significant improvement in both the rehabilitation and control groups over 12 months.[334,335] 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.[210]

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.[92,94] 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).[92,94]

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).[92,94]

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).[92,94]

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.[92,94]

6.2.2 Individualised comprehensive cardiac rehabilitation

6.2.2.1 Clinical evidence

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.[276] 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.[115,116] 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.[115,116] 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.[41] 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.[41]

6.2.2.2 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, [406] 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 [418] 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 [52] 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

6.2.2.3 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.[218] 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.[341] 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.[341]

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.[341]

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.[163,164] 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 ischaemia (<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.[163,164]

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.[163,164]

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.[131] 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.[131]

6.2.2.4 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 [269] 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.[131]

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).[131]

The second study [419] 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).[419]

6.2.2.5 Economic evidence

Five studies were found which addressed the health economics of cardiac rehabilitation.[430,433] [333,334] [182] [250] [17] One study [430,433] 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 [430,433] 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 [17] 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 [182] 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 [333,334] 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 fifth study [250] 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 [431,433 210 92,94] and follow up data from RITA 2.[192]

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.

6.2.2.6 Evidence statements

Cardiac rehabilitation in patients after MI reduces all-cause and cardiovascular mortality rates provided it includes an exercise component (1++).

The majority of studies showed there was no significant effect of comprehensive cardiac rehabilitation on quality of life outcomes in patients after MI (1++).

Cardiac rehabilitation in patients after MI compared no cardiac rehabilitation is cost effective.

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

There is no evidence that stable patients are harmed by the exercise component of cardiac rehabilitation.

Exercise training does not appear to endanger stable patients with left ventricular dysfunction (1+).

There is limited evidence on the safety of the exercise component of cardiac rehabilitation in older people (1+).

6.2.3 Summary of recommendations

15. All patients (regardless of their age) should be given advice about and offered a cardiac rehabilitation programme with an exercise component. [2007]

16. 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. [2007]

17. 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. [2007]

18. Patients with left ventricular dysfunction who are stable can safely be offered the exercise component of cardiac rehabilitation. [2007]

6.3 Barriers to the uptake of and adherence to cardiac rehabilitation

6.3.1 Which factors are associated with a person's uptake and adherence to cardiac rehabilitation programmes after an MI?

For full details see review protocol in Appendix C.

6.3.1.1 Clinical evidence

The aim of this review was to explore factors that could increase the uptake of and adherence to cardiac rehabilitation programmes. The recommendations and the link between evidence and recommendations can be found in Section 6.4.2.

During the scoping process, stakeholders identified groups that require special attention because of low reported attendance to cardiac rehabilitation programmes that were not considered in CG48. These included: people suffering from anxiety or depression, people with physical or learning disabilities, older or younger age groups, non-English speakers and people who are unemployed.[46,105,285,382]

The quality of qualitative evidence was assessed using methods described in Chapter 3. Appendix G contains details of the limitations of each study included in the review.

Two approaches were used to extract the evidence:

Part 1

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Information on why people withdrew from a cardiac rehabilitation programme was extracted from 6 RCTs and 1 prospective cohort study reviewed as part of Section 6.4.[46,175,184,211,212,288,468] Information from the RCT by West 2001 was presented in the Health Technology Appraisal by Beswick et al. 2004.[46,47] These studies provided a list of reasons why people withdrew from the cardiac rehabilitation programme and what the most commonly reported reasons were. It is not clear if they were pre-specified reasons generated by the authors and people selected from this list, or if the reasons were raised independently by the people who withdrew. If it is the former this could be a source of bias as the studies may not fully explore the reasons for failure to take up or adhere to the programme.

Studies conducted outside the UK were included where these were identified as part of the review from Section 6.4, as for the purposes of the review on interventions to increase uptake and adherence to a cardiac rehabilitation programme, the GDG considered that, it would be likely that the effectiveness of an intervention would not be dependent upon the country in which the study was conducted.

Part 2

Qualitative studies exploring peoples' experiences in a cardiac rehabilitation programme were analysed. Existing systematic reviews or syntheses of qualitative studies were included where available. Two systematic reviews were found that met the inclusion criteria focusing on people from South Asian populations and people from low socioeconomic backgrounds.[38,159]Additional information was not extracted on these populations from individual papers given that these reviews were available.

In addition to the 2 systematic reviews, 18 individual qualitative studies were included in Part 2 of the review.[54,91,93,181,205,216,217,260,262,271,278,329,350,370,371,373,386,445] These studies provided insight into the variety of reasons that either inhibit or encourage people to participate in a cardiac rehabilitation programme following an MI. All relevant UK studies were reviewed and non-UK papers were

excluded. Only UK data were considered relevant by the GDG as cardiac rehabilitation programmes vary from country to country, as do population demographics and access to care. Only 1 of the 11 qualitative studies included in CG48 was used in this update.[350] The remaining papers were excluded because they were either superseded by a recent review or they were not from the UK.

The review stopped when there was data saturation. Data saturation is usually considered the point at which no more studies need to be included in the review because the information has become repetitive and the studies are no longer offering anything new. However, if papers captured other reasons for not participating they were included in this review.

The GDG made a judgement that issues relating to South Asian women were more likely related to the person being of South Asian descent than being female. For this reason the comments made by South Asian women were recorded under the category 'minority ethnic groups'. It is acknowledged that other minority ethnic groups may also need separate consideration. However people from a South Asian population were identified by stakeholders as being less likely to uptake and adhere to a cardiac rehabilitation programme. This was supported by a retrospective UK hospital audit which found a low attendance among people of South Asian origin.[443]

Other subgroups identified by stakeholders as less likely to start and continue cardiac rehabilitation programmes were those with anxiety or depression, those who had physical or learning disabilities, those who were unemployed and those from rural communities. No specific information was identified about these groups. However, it is likely that some of the people included in the qualitative studies could be from these populations.

Common themes that explained why people did not participate, or conversely what helped them start or adhere to a cardiac rehabilitation programme were extracted from the papers in Part 1 and Part 2 of the review and summarised under headings that covered:

- Barriers and facilitators that influence a person's participation in a cardiac rehabilitation programme.
- Barriers and facilitators that influence healthcare professionals in promoting cardiac rehabilitation programmes.

Healthcare professionals play a crucial role in referring people to a cardiac rehabilitation programme. Thus, the GDG considered it important to identify factors that influence healthcare professionals when inviting and supporting people to start and continue a cardiac rehabilitation programme.

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Table 23: Summary of quantitative studies included in Part 1 of the review

For details of the limitations of each study, please see Appendix G.

	Study Country	New to update or included in CG48	Study type	Intervention	Comparison	Population Duration	Outcomes reported
1.	Grace et al 2007[173,175] CANADA	New	Prospective	Referral strategy: automatic - hospital electronic patient records to prompt the standard order for a cardiac rehabilitation referral for all eligible people with cardiac diseases. An information package, including a personalised letter stating the name of the referring physician, a programme brochure, a schedule of classes, and a request that the person telephones to book an appointment, is mailed to the person's home.	Control group consisted of referral to cardiac rehabilitation at the discretion of the cardiologist, cardiovascular surgeon, general practitioner or other healthcare provider, through paper-based means.	Acute coronary syndrome (MI, UA, CHF or PCI or ACB) PCI =38-61% NYHF Class I=86% n=661 9 months	• Reasons for withdrawing.
2.	Hansen et al 2009[183,184] BELGIUM	New	RCT	Short duration (40 minute exercise session).	Long duration (60 minute exercise session).	40% MI 60% stable coronary artery disease n=417 7 weeks	• Reasons for withdrawing. (Medical reasons were defined as cardiovascular events, orthopaedic injuries and/or hospitalisation or surgery.)
3.	Jolly et al 1999 [211,213]	CG48	RCT	Nurse follow-up support. The transfer of responsibility for care between hospital and general	Usual care.	MI = 100% n=389	• Reasons for withdrawing.

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	Study Country	New to update or included in CG48	Study type	Intervention	Comparison	Population Duration	Outcomes reported
	SHIP UK			practice at the time of discharge and the support of practice nurses.		(people with angina as well, but only reported MI) 1+4 m, 1yr	
4.	Jolly et al 2009 Heart BRUM [212,213] UK	New	RCT	Home care cardiac rehabilitation programme (exercise, relaxation, education and lifestyle counselling). Home-based programme consisted of a manual, 3 home visits (at 10 days, 6 weeks and 12 weeks) and telephone contact at 3 weeks. People who had an MI or revascularisation were discharged with the Heart manual or an adapted version (manual encourages gradual exercise to achieve minimum 15 minutes of moderately intense exercise). Additional visits were made as deemed necessary by the rehabilitation nurse (nurses delivering home programme were trained for 2 days).	Centre based. Centre-based programmes varied in length including 9 sessions at weekly intervals, 12 sessions over 8 weeks and 24 individualised sessions over 12 weeks. Programmes commenced between 4 and 8 weeks following the cardiac event. People exercised to 65-75% of their predicted maximal heart rate and the exercise element of the programme lasted from 25-40 minutes plus warm-up and cool-down times.	Post MI=50% PCI =40% CABG=10% n=525 6, 12 weeks data used.	• Reasons for withdrawing.
5.	Miller et al 1988[287,288]	CG48	RCT	Nurse intervention and goal setting.	Usual care.	MI=100% n=115	• Reasons for withdrawing

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	Study Country	New to update or included in CG48	Study type	Intervention	Comparison	Population Duration	Outcomes reported
	USA			Each participant completed a 10-15 day cardiac rehabilitation programme in hospital. The aim of the study was to measure the influence of a post hospitalisation nursing intervention on medical regimen compliance and personal adjustments 30 and 60 days and 1 year after discharge.	Completed the same measurement scales as experimental group just prior to dismissal from hospital, and at 30 and 60 day visits to home. Received no nurse intervention and no discussion of medical regimen or problems experienced.	30 days, 60 days.	•
6.	West2001[46,47] UK	New	RCT	Rehabilitation.	No rehabilitation.	MI=100% n=2144 1 year	• Reasons for withdrawing.
7.	Wyer et al 2001 [468] UK	CG48	RCT	Two letters given to people 3 weeks following MI. The letters intended to influence the person's attitude towards attending cardiac rehabilitation, highlight how they are following medical recommendations, that they will be supported and there is a point of contact.	Nominal letters including course dates.	MI=100% n=87	• Reasons for withdrawing.

UA= unstable angina, CHF= chronic heart failure, ACB= aortocoronary bypass

Table 24: Summary of qualitative studies included in Part 2 of the review

	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
1.	Beauchamp 2010[38,38]	New	Systematic review.	Four studies of effectiveness of cardiac rehabilitation after an MI by socioeconomic groups.	• Too costly. • Transport. • Comorbidities. • Attitude of professionals.	• Programme appropriate including language, timing, location, transport.
2.	Blake 2009[54,54]	New	Semi-structured interviews; content analysis.	Five people who had attended a phase III hospital programme; 4 people who had attended a community programme; 4 hospital and community staff members.	• Uncomfortable exercising in a public gym/in a group.	-
3.	Clark 2004[91,94]	New	Eight focus groups; audio taped; themes identified.	Purposive sample of people eligible for a cardiac rehabilitation programme (following MI or CABG; unclear how many people had MI) from a mixed urban-rural region: high-attendance (over 60%, n=27), high attrition (less than 60% attendance, n=9) and non-attendance (0%; n=8); range of ages.	• Lack of understanding that lifestyle factors contributed to MI. • Belief that MI due to factors outside person's control rather than lifestyle factors; fatalistic. • Ambience at cardiac rehabilitation programme. • Lack of appropriately trained staff. • Not seen as beneficial.	• Health in the participant's own hands; self-efficacy. • MI seen as a warning/ motivator for change. • Peer support. • Felt the benefit from cardiac rehabilitation programme. • Positive attitude of healthcare professionals. • Desire to reduce risk of secondary MI.
4.	Clark 2005[93,94]	New	Focus groups; realist approach focusing on explaining why programmes do and do not work for people by exploring	Forty seven people with coronary heart disease who had attended cardiac rehabilitation programme 3 years previously.	• Lack of understanding of the importance of cardiac rehabilitation programme on recovery or what the programme entails. • Uncomfortable exercising in a	-

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	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
			choices and capacities (mechanisms) they offer in different circumstances (contexts); audiotaped; transcribed; analysed separately by two researchers; theme compared.		public gym/in a group.	
5.	Galdas 2012[159,160]	New	Systematic review.	People of South Asian origin (originating from India, Pakistan, Bangladesh or Sri Lanka) in 11 primary studies.	• Lack of understanding of cardiac rehabilitation programme. • Location/ transport/ mobility/ distance difficulties. • Referral issues. • Time constraints. • Reluctant to exercise. • Unsure about safety (location). • Unmotivated. • Religious reasons. • Uncomfortable exercising in a public gym/in a group. • Lack of support at home. • Clothing. • Belief that exercise is harmful. • Exercise not helpful/ inappropriate/ excessive/ unnecessary. • Programme culturally	• Programme appropriate including language, timing and location. • Timing. • Religious reasons. • Positive attitude of healthcare professionals. • Peer support. • Preference for hospital-based cardiac rehabilitation programme.

Update 2013

	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
					insensitive. • Language/interpreters.	
6.	Halcox 2011[181,181]	New	Questionnaire survey.	GPs (n=250) and cardiologists (n=53).	• Problems of tailoring cardiac rehabilitation programme to the individual. • Primary/secondary care interface.	• Support from other health care professionals to aid uptake and adherence on cardiac rehabilitation programme. • Tailoring advice to individuals.
7.	Jackson2012[205,205]	New	In depth interviews.	Twenty seven people who had not participated in either hospital based cardiac rehabilitation or coronary heart disease group, 6-14 months post MI and 17 significant others in Lothian, Scotland.	• Referral issues. • Uncomfortable asking for support. • Uncomfortable exercising in a public gym/in a group. • Location/ transport/ mobility/ distance difficulties. • Comorbidities. • Time constraints. • Lack of appropriately trained staff. • Lack of understanding on the importance of cardiac rehabilitation programme on recovery or what the programme entails. • Lack of support.	-
8.	Jones 2009[216,217]	New	3 hospital focus groups and 2 home focus groups; tape	Sixteen people from 4 hospital programmes and 10 from a home programme.	• Programme appropriate including language, timing, location, transport.	• Positive attitude of healthcare professionals.

Update 2013

	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
			recorded and transcribed; analysed for themes.		• Reluctant to exercise.	• Peer support. • Preference for hospital-based cardiac rehabilitation programme. • Aspects and components of cardiac rehabilitation programme. • Availability of specialist staff. • Part of routine. • Sense of purpose and identity. • Health in the participant's own hands; self-efficacy. • Felt the benefit from cardiac rehabilitation programme. • Preference for home-based programme.
9.	Jones 2007[217,217]	New	Semi-structured interview; tapes transcribed; themes identified.	Forty nine people in an RCT of home versus hospital based cardiac rehabilitation programme who did not complete the programme (purposive sampling; people invited until at least 10 interviewed from each category: female; elderly (aged 70 or over); minority ethnic groups; and middle-	• Lack of understanding on the importance of cardiac rehabilitation programme on recovery or what the programme entails. • Location/ transport/ mobility/ distance difficulties. • Lack of information on where and when the cardiac rehabilitation programme is	• Desire to achieve goals. • Support at home. • Peer support. • Preference for hospital-based cardiac rehabilitation programme. • Aspects and components of cardiac rehabilitation programme.

Update 2013

	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
				aged males).	available/ referral issues. • Time constraints. • Reluctant to exercise. • Unmotivated. • Not seen as beneficial. • Comorbidities. • Exercise not helpful/ inappropriate/ excessive/ unnecessary. • Ambience at cardiac rehabilitation programme.	
10.	MacInnes 2005[260,260]	New	Semi-structured interviews; field notes; tapes transcribed and returned to participants for checking; framework method of analysis.	Purposive sample of 10 women from a range of age groups (30-59; 60-79; 80 and over); clinically stable; English as first language.	• Not seen as beneficial.	• Desire to achieve goals. • Health in the participant's own hands; self-efficacy.
11.	Madden 2011[262,262]	New	Semi-structured interviews.	Thirty five participants and 12 staff members delivering a pilot programme in 5 rehabilitation services.	• Lack of understanding on the importance of cardiac rehabilitation programme on recovery or what cardiac rehabilitation programme entails • Location/ transport/ mobility/ distance difficulties • Lack of information on where and when cardiac rehabilitation is available/ referral issues.	• Programme appropriate including language, timing, location. • Preference for hospital-based cardiac rehabilitation programme.

Update 2013

	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
					• Time constraints. • Lack of appropriately trained staff. • Unmotivated.	
12.	Martin 2012[270,271]	New	Focus group discussions (three for men, 2 for women; 4-7 participants in each); notes from focus groups recorded; participant verification; constant comparative analysis; theme identification.	Individuals with established coronary heart disease (single to multiple cardiac events; unclear if all had MI); 24 long-term adherers to cardiac rehabilitation programme (at least 6 months attendance with lapse no more 1 month).	• Desire to reduce risk of secondary MI. • Support at home. • Positive attitude of healthcare professionals. • Peer support. • Aspects and components of cardiac rehabilitation programme. • Availability of specialist staff. • Part of routine. • Sense of purpose and identity. • Health in the participant's own hands; self-efficacy. • Method of recruitment.	-
13.	McCorry 2009[278,278]	New	Semi-structured interviews; taped and transcribed verbatim; units of meaning funnelled into themes; themes organised and inter-related; later themes tested against earlier transcripts; recruitment until data	Eight men and 6 women who had an MI who did not attend a formal cardiac rehabilitation programme; age range 34-82 years	• Lack of understanding on the importance of cardiac rehabilitation programme on recovery or what cardiac rehabilitation entails. • Time constraints. • Not seen as beneficial. • Comorbidities. • Belief that exercise is harmful.	-

Update 2013

	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
			saturation.		• Exercise not helpful/ inappropriate/ excessive/ unnecessary. • Perceived as only to get people back to normal, not long-term behaviour change. • Attitude/ remarks of healthcare professionals. • Lack of understanding that lifestyle factors contributed to MI. • Belief that MI due to factors outside person's control rather than lifestyle factors; fatalistic.	
14.	O'Driscoll 2007[329]	New	Individual case studies; participant observation; in-depth semi-structured interviews.	Three people who had an MI and 11 healthcare professionals.	• Location/ transport/ mobility/ distance difficulties. • Time constraints. • Lack of appropriately trained staff. • Lack of support at home • Comorbidities. • Poor communication between departments. • Problems of tailoring cardiac rehabilitation to the individual. • Lack of resources. • Need to follow up people who do not attend.	-

Update 2013

	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
					• Staff morale.	
15.	Pell 1998[350]	CG48	Questionnaires.	Two hundred and eight people who had been invited to cardiac rehabilitation programme after MI.	• Location/ transport/ mobility/ distance difficulties. • Time constraints. • Reluctant to exercise. • Uncomfortable exercising in a public gym/in a group. • Not seen as beneficial. • Comorbidities. • Belief that exercise is harmful. • Exercise not helpful/ inappropriate/ excessive/ unnecessary.	-
16.	Proudfoot 2007[370,370]	New	Questionnaire to 247 cardiac rehabilitation centres.	People with acute coronary syndromes.	• Lack of resources.	-
17.	Pullen 2009[371,371]	New	Semi-structured face-to-face interviews; interpretative phenomenological analysis.	Females with a cardiac condition who had accepted (n=5) or declined (n=3) a cardiac rehabilitation programme (all except 1 had an MI).	• Lack of understanding on the importance of cardiac rehabilitation programme on recovery or what cardiac rehabilitation entails. • Transport. • Comorbidities.	• Desire to reduce risk of secondary MI. • Desire to achieve goals. • Support at home. • Peer support. • Availability of specialist staff. • Health in the participant's own hands; self-efficacy.
18.	Radley 1998[373]	CG48	Interviews.	Sixty women and 60 men 6 months after an MI.	• Location/ transport/ mobility/ distance difficulties	• Peer support.

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	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
					• Lack of information on where and when cardiac rehabilitation programme is available/ referral issues. • Uncomfortable exercising in a public gym/in a group. • Unhelpful comments from healthcare professionals.	
19.	Rivett 2009[386,386]	New	Telephone interviews (10 minutes each).	One hundred and one people who withdrew from a community based cardiac rehabilitation programme (Heart Watch).	• Lack of support at home. • Ambience at cardiac rehabilitation programme. • Too costly. • Time constraints. • Location/ transport/ mobility/ distance difficulties. • Unmotivated. • Time constraints. • Comorbidities. • Exercise not helpful/ inappropriate/ excessive/ unnecessary.	-
20.	Tolmie 2009[445,445]	New	Mixed-methods: structured questionnaire; brief clinical assessment; in-depth interviews.	Thirty one older men and women (over 65 years) who had an MI in last 6 months with full, partial or non-attendance at cardiac rehabilitation programme.	• Time constraints. • Unmotivated. • Lack of support at home. • Not seen as beneficial. • Comorbidities. • Exercise not helpful/ inappropriate/ excessive/	• Desire to achieve goals.

	Study	New to update or included in CG48	Study type	Population	Themes: Barriers reported	Themes: Facilitators reported
					unnecessary. • Discontinued when participant felt no further benefit. • Unhelpful comments from healthcare professionals. • No desire to extend lifespan.	

6.3.1.1.1 *Results of Part 1*

Update 2013

The findings are extracted from RCTs that aimed to improve uptake and adherence to a cardiac rehabilitation programme, the results are presented in Section 6.4. In the Table 25, the number of people who withdrew from the cardiac rehabilitation programme is shown as a fraction of the total number who withdrew from the study (n), the percentage of people this equated to shown.

Table 25: Results for Part 1- reasons why participants withdrew from cardiac rehabilitation programmes.

Reason for not participating or withdrawing	Grace2007 [173,175] n=103 (+)	Hansen2009 [183,184] n=83	Jolly1999 [211,213] n=74	Jolly2009 [212,213] n=79	Miller1988 [287,288] n=10	Pack2013 [343,343] n=148	West2001 [46,47] n=300	Wyer2001 [468] n=9
Not interested, lack of motivation	Listed as a reason, but no were numbers provided.	39.7%, n=32/83	-	-	-	3%, n = 2/69	23.6%, n=71/300	-
Health or mobility issues	13%, n=13/103	18.2%, n=15/83	-	-	-	-	20.6%, n=62/300	-
Conflicts with employment	6.7%, n=7/103	15.7%, n=13/83	-	-	-	5%, n = 4/69	6%, n=18/300	-
Too distant or inconvenient	13% n=13/103	14.4% n=12/83	-	-	-	7%, n = 5/69	14.3%, n=43/300	-

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Reason for not participating or withdrawing	Grace2007 [173,175] n=103 (+)	Hansen2009 [183,184] n=83	Jolly1999 [211,213] n=74	Jolly2009 [212,213] n=79	Miller1988 [287,288] n=10	Pack2013 [343,343] n=148	West2001 [46,47] n=300	Wyer2001 [468] n=9
Holidays or other appointments	-	-	-	-	-	4%, n= 3/69	6%, n=15/300	-
Lack of referral from physician or administrative failure	57%, n=59/103	-	-	-	-	-	3%, n=9/300	-
Dissatisfaction with the course (age group, male/female/content)	-	-	-	-	-	-	2%, n=6/300	-
Taken ill at rehabilitation class	-	-	-	-	-	-	2%, n=6/300	-
Did not attend follow-up (no reason provided)	-	-	55.4% n=41/74	80%, n=63/79	50%, n=5/10	43%, n= 30/69	15.3%, n=46/300	-
No longer wished to participate (no reason provided)	-	4.8% n=4/83	-	13%, n=10/79	40%, n=4/10	23%, n= 16/69	-	100%, n=9/9
Continued at home	-	4.8%, n=4/83	-	-	-	-	-	-
Died	-	-	44.5%, n=33/74	7%, n=6/79	20%, n=2/10	-	-	-
Physician said they do not need cardiac rehabilitation	Listed as a reason, but no numbers provided	1.2%, n=1/83	-	-	-	-	4.3%, n=13/300	-
Rehabilitation staff thought unnecessary (fit enough)	-	-	-	-	-	-	3%, n=1/300	-
Attending another rehabilitation course	-	-	-	-	-	-	0.7%, n=2/300	-
Too demanding/looking after dependent relative	-	1.2%, n=1/83	-	-	-	-	2%, n=6/300	-

Update 2013

Reason for not participating or withdrawing	Grace2007 [173,175] n=103 (+)	Hansen2009 [183,184] n=83	Jolly1999 [211,213] n=74	Jolly2009 [212,213] n=79	Miller1988 [287,288] n=10	Pack2013 [343,343] n=148	West2001 [46,47] n=300	Wyer2001 [468] n=9
Did not know about the cardiac rehabilitation programme	11%, n=11/103	-	-	-	-	-	-	-
Not understanding why they need to attend cardiac rehabilitation	Listed as a reason, but no were numbers provided	-	-	-	-	-	-	-
Indirect costs	Listed as a reason, but no were numbers provided	-	-	-	-	13%, n = 9/69	-	-
No capacity for new participants	Listed as a reason, but no were numbers provided	-	-	-	-	-	-	-

6.3.1.1.2 *Results of Part 2*

Common themes for participants

Forty themes or reasons (25 barriers and 15 facilitators) were identified that influenced uptake of or adherence to a cardiac rehabilitation programme. These were identified from Part 1 of this review and expanded upon by Part 2 from qualitative studies that questioned people who had an MI on their experiences with cardiac rehabilitation programmes. Please note that some of these themes overlap.

The findings are separated into different groups, the first is on a general MI population and then on groups that need special consideration because they are considered at high risk of not participating. Many of the reasons captured in these subgroups were the same as those recorded for a general MI population. Therefore, only themes that appear to be unique to these populations are presented in an attempt to highlight areas that require special attention. Details of these outcomes are presented below and in Appendix G.

General MI population

People's barriers to cardiac rehabilitation

- *Not understanding the benefits of cardiac rehabilitation programmes and what the cardiac rehabilitation programme entails*: people did not feel a cardiac rehabilitation programme would benefit them because they felt the MI was not the result of lifestyle factors. People who were offered a cardiac rehabilitation programme did not know what it entailed.[91,93,205,217,217,262,278,350]

- *Location/transport difficulties*: the location of the cardiac rehabilitation centre posed a problem for some individuals because it was located in a city, had insufficient parking, there was heavy traffic or there was a lack of public transport. It was unclear if the hospital would provide transport and people preferred a community based venue.[205,216,217,262,329,350,386]

- *Referral issues or insufficient information*: insufficient information on whether to choose a home-based or centre-based cardiac rehabilitation programme was provided. Some people were not referred to a cardiac rehabilitation programme or were left to find their own programme.[205,217,262]

- *Time constraints:* barriers identified included restricted time to attend the programme and the programme being held at inconvenient times for both work and family reasons. Other barriers included that people perceived cardiac rehabilitation as being a large time commitment and that there were demands on their partners to accommodate them.[205,217,262,278,329,386] People still working found little time to join a cardiac rehabilitation programme and often felt unmotivated to exercise on their own. For this reason, people felt that a home-based programme would be more suitable.[262,262]

- *Needs not being met by cardiac rehabilitation staff*: barriers identified included that staff running home-based clinics were unable to answer questions, there was no consistency in the care (high staff turnover), methods of communicating were poor and that the information given was at times contradictory. There was also a lack of advice, staff were perceived as overly negative or too intense, there was minimal support and no psychological advice provided. The knowledge that family members could attend sessions was often not shared.[91,205,262,329,386]

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- *Reluctant to exercise and unmotivated*: people were worried about exercising at home and felt unmotivated, whereas people who had never exercised before did not know what to expect or how to perform exercises.[54,205,217,262,350,386]

- *Cost*: people felt that cardiac rehabilitation may be too expensive [386,386] including people from low socioeconomic backgrounds.[38,38]

- *Lack of family support:* the knowledge that family could attend sessions was often not shared and there was a lack of support available.[329,386]

- *Comorbidities:* people who were invited to cardiac rehabilitation programmes had comorbidities which affected their ability to participate, for example, limited concentration, worsening cardiac symptoms and various health problems affecting their ability to exercise (i.e. arthritis pain, back pain, angina).[205,217,278,329,350,386]

- *Feeling that exercise is inappropriate*: people felt that exercise intensity was inappropriate (either too high or low), that everyday activities were sufficient, or they used other exercise facilities. It was perceived that attendance would increase the risk of having another cardiac event.[217,278,350,386]

- *Attitude remarks of healthcare professionals:* if the heart attack was described as mild, people felt there was no need to attend a cardiac rehabilitation programme.[278,278]

- *Ambience at cardiac rehabilitation centre:* people felt that classes were overcrowded, they did not enjoy the programme, there was insufficient intensity, the classes did not attend to their individual needs, they felt other members were too old, the classes were too focused on their illness, they had never been in a gym before or they did not like group or mixed sex classes.[54,93,205,217,350,386]

- *Uncomfortable seeking help or had lack of support from staff:* people felt there was a lack of support from healthcare professionals or they felt too uncomfortable to ask for support. When support did become available it was deemed too late or too brief. Others felt there was no support regarding mental, emotional or cognitive issues.[205,205]

People's facilitators to cardiac rehabilitation

- *Desire to reduce risk of reinfarction:* people felt that reinforcement by healthcare professionals on the benefits of exercise was likely to enhance adherence. Some people felt attendance was a rational decision and that the CHD event was a motivator to change their behaviour.[91,270]

- *Desire to achieve goals:* people felt motivated to return to work.[217,217]

- *Support from family and friends:* family and friends provided emotional support and transport to the cardiac rehabilitation centre. Friends joining in some of the exercises also helped.[216,270]

- *Programme well suited, including language, timing, location, transport*: some people felt that the home based programme was convenient; whereas other felt the centre based programme was more convenient. Exercises were well planned and people found an education programme on medication particularly useful [216,217,262]

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- *Support of healthcare professionals:* support from healthcare professionals was instrumental for motivating people and keeping them informed about schedules. Their knowledge and positive support was helpful. Availability of staff to assist with learning the exercises was helpful and gave them reassurance that what they were doing was safe. It also gave people the security of knowing healthcare professionals were close by if something happened.[91,93,270]

- *Peer support:* support from fellow participants was important, created a fun friendly environment, provided motivation, confidence and decreased embarrassment.[91,217,270]

- *Opportunity to attend either a home based or hospital based cardiac rehabilitation programme:* some people felt hospital based healthcare professionals could give more support and that the centre was larger and better equipped. Hospital staff could also provide motivation and feedback. Regular appointments also provided motivation, unlike a home based programme.[216,262] A home based programme gave some people the opportunity to participate in the cardiac rehabilitation programme, whereas they would not have been able to do so if only a hospital based programme was available, due to transport issues and carer responsibilities.[216,217]

- *Design of the cardiac rehabilitation programme:* exercises were novel, stimulating and increasingly challenging. Fitness tests and feedback also provided motivation. People learned a lot about diet, their condition, how to decrease stress, medication management and found the Heart Manual a useful reference.[93,216,217]

- *Able to incorporate components of cardiac rehabilitation programme into daily routine:* developing a routine helped people to create targets and ensured that they developed long-term lifestyle changes. Home-based cardiac rehabilitation programmes also allowed people to fit the exercise routines around their own schedule, unlike a hospital-based programme. It also helped people to see it as a normal part of their lives.[93,216,262]

- *Developed a sense of purpose and identity:* the cardiac rehabilitation programme gave people a sense of purpose, a goal for the day, and being part of a group gave them a sense of community and provided support.[93,216,262]

- *Provided feeling of control, that their health was in their hands, self-efficacy:* performing the exercises successfully gave people the confidence to know they could do it and that they were safe. The home programme gave them more control over their rehabilitation and the feeling that they were in control over their health.[93,216,262]

- *Ideas to improve recruitment*: people felt existing participants could be used to aid uptake to cardiac rehabilitation programme. It was also felt that information for healthcare professionals on the importance of cardiac rehabilitation programme would raise awareness of availability of classes and a quick transfer between different phases of rehabilitation would help.[271,271]

- *Felt the benefit of cardiac rehabilitation programme:* feeling the benefit from the cardiac rehabilitation programme motivated people to continue the programme. Seeing other people's progress and proof that exercise is safe were motivators and increased confidence.[91,93,216]

Update 2013

Ethnicity

Barriers specific to South Asians

- *Religious reasons:* some South Asian Muslims, Gujarati and Hindu participants felt that their recovery was tied to fate or to God's will. Some South Asian Muslim women preferred not to participate in a mixed-sex exercise class, and because of their clothing felt uncomfortable exercising in front of others. It was reported that some sessions conflicted with call to prayer.[159,160]

- *Lack of support at home:* it was reported that some people from South Asian communities were less likely to encourage family members to participate in cardiac rehabilitation and that support was sometimes more evident for men. Some women reported that they needed their husband's permission to attend the cardiac rehabilitation programme.[159,160]

- *Clothing*: some people reported that clothing preferences for people from South Asian communities made it difficult to exercise.[159,160]

- *Culturally insensitive:* some people felt that dietary advice was inappropriate to their communities. In addition, some women felt uncomfortable discussing sexual activity.[159,160]

Facilitators specific to South Asians

- *Religious reasons (MI seen as a warning from God):* some South Asian people felt the MI was an indication from God that they had not looked after their health, so they were willing to make changes to their lifestyle.[159,160]

Update 2013

Age

Barriers specific to certain age groups

- *Not believing that the MI was due to health-related reasons*: young people did not feel that lifestyle-related issues contributed to the reason they had an MI.[278,278]

- *Exercise not appropriate to their age group:* younger and middle aged people felt that the exercise was not appropriate to their age group.[217,278,445]

- *No desire to expand lifespan:* some older adults felt they would become a burden to people.[445,445]

Sex

Barriers specific to women

- *Believed they could recover independently:* some women felt they could make lifestyle changes independently of the cardiac rehabilitation programme.[371,371] Other women felt that an MI was not linked to lifestyle-related factors.[278,278]

Facilitators specific to women

- *Increased their confidence and independence:* some women felt the cardiac rehabilitation programme could increase their confidence and offered reassurance. Some single women felt that it was their responsibility to look after themselves.[260,371]

Socioeconomic

Barriers specific to low socioeconomic groups

- *Mental health*: some people from low socioeconomic background had depression.[38,38]

- *Prejudices of healthcare professionals:* it was reported that some people from a low socioeconomic background felt they detected scepticism from healthcare professionals that they would make changes to their lifestyle.[38,38]

Language

Barriers specific to non-English speaking populations

- *Culturally insensitive*: Some South Asian people were unable to speak English and there was a lack of resource materials available in other languages. Interpreters were not always available.[159,160]

Common themes for healthcare professionals

Ten themes (7 barriers and 3 facilitators) were identified that influenced healthcare professionals in encouraging people who had an MI to take up and adhere to a cardiac rehabilitation programme. These were identified from qualitative studies and details of these studies are presented in Appendix G.

Barriers to healthcare professionals' promoting cardiac rehabilitation programmes

Update 2013

- *Unsure whose role it is to arrange a cardiac rehabilitation programme, referral issues*: there were often gaps in individual patient pathways, especially for people who moved between hospitals for treatment.[262,262]

- *Problems of tailoring cardiac rehabilitation programme to the individual*: there was a lack of understanding on the importance of tailoring the cardiac rehabilitation programme to a person's individual needs, including their socioeconomic background.[181,329]

- *Primary/secondary care interface:* better integration was needed between primary and secondary care to improve provision of consistent service.[181,181]

- *Lack of resources*: barriers identified included insufficiently trained staff, a lack of interpreters, limited funding, limited staff time for each person, limited personal resources and few physiotherapists, dietitians, clinical psychologists available.[262,329,370]

- *Restricted choice of location:* home based programmes were not always promoted unless the person refused to exercise or could not participate in hospital or community settings.[262,262]

- *Need to follow-up people who do not attend*: it was considered important that cardiac staff contacted people to explore possible barriers and if possible provide assistance to facilitate attendance.[329]

- *Lack of staff morale due to budget cuts in NHS:* some people reported that the modernisation of NHS had increased their workload and pressure and decreased inspiration and enthusiasm.[329]

Facilitators to healthcare professional's promoting cardiac rehabilitation programmes

- *Support from healthcare professionals to aid uptake and adherence to cardiac rehabilitation programme*: GPs and cardiologists used regular consultations or involved other healthcare professionals to motivate people to pursue a healthy lifestyle.[181,181]

- *Tailoring advice to individuals*: it was considered important to take ethnicity into account when delivering dietary advice; address health and social needs and tailor advice to health beliefs or culture.[181,181]

- *Choice of location:* offering a choice between hospital and community location was considered important.[262,262]

6.3.1.2 Economic evidence

Published literature

No relevant economic evaluations addressing factors associated with uptake of and adherence to cardiac rehabilitation programmes after an MI that met the inclusion criteria were identified.

6.3.1.3 Evidence statements

6.3.1.3.1 Clinical

PART 1

- Six RCTs and 1 cohort study that aimed to increase uptake and adherence of people who had an MI to a cardiac rehabilitation programme showed that the most common reasons for people withdrawing are that they were not interested or motivated, they have health or mobility issues, that it conflicted with employment, the centre was too distant or inconveniently located or that they were not referred by a physician.

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PART 2

- Twenty qualitative studies, including 2 reviews, identified 39 themes (24 barriers and 15 facilitators) that explained why people who had an MI do not participate in a cardiac rehabilitation programme or conversely, what factors enhance uptake to a cardiac rehabilitation programme. These reasons ranged from patient-related factors, to service-related factors and included factors that pertained to the healthcare professionals themselves.

- One review on people who had an MI from South Asian communities identified 4 reasons unique to this community to explain why people may not participate in a cardiac rehabilitation programme. These were: religious reasons, lack of support at home for the women to attend a cardiac rehabilitation programme, clothing requirements (for women) and that healthcare professionals were culturally insensitive. Conversely, religious reasons were invoked as a reason to promote uptake to a cardiac rehabilitation programme, since people saw the MI as a health warning from God.

- Two qualitative papers identified 2 unique reasons why younger people who had an MI may not participate in a cardiac rehabilitation programme. They felt lifestyle related reasons did not explain why they had an MI and that the cardiac rehabilitation programme was aimed at older people. In contrast, older people felt that they were becoming a burden to others and some did not wish to increase their lifespan.

- Two qualitative studies on women discovered that some felt they did not need a cardiac rehabilitation programme and that they could recover on their own. These feelings of independence were particularly important to women because it was for the same reason they felt the need to recover.

- One review on people from low socioeconomic backgrounds who had an MI revealed they sometimes had depression and this could inhibit their participation in a cardiac rehabilitation programme. Also, some people felt healthcare professionals were prejudiced against them, feeling that the healthcare professionals felt they were incapable of making changes to their lifestyle.

- One review on South Asian communities discovered people felt there was a lack of provision within the health care service to accommodate people who could not speak English.

- Five qualitative papers identified 10 themes (7 barriers and 3 facilitators) that explained why healthcare professionals either promoted cardiac rehabilitation or felt that it was difficult to refer people who had an MI to a cardiac rehabilitation programme.

- No direct evidence was found on people who had an MI who suffered from anxiety or depression, had physical or learning disabilities, were unemployed or were from rural communities.

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6.3.1.3.2 Economic

No relevant economic evaluations were identified.

6.3.2 Recommendations and link to evidence

Recommendations relating to 'Barriers to the uptake of and adherence to cardiac rehabilitation' can be found in Section 6.4.2.

6.4 Interventions to increase uptake of and adherence to cardiac rehabilitation programmes

6.4.1 Which interventions designed to increase engagement in and/or adherence to cardiac rehabilitation programmes are effective and cost effective in people who have had an MI?

For full details see review protocol in Appendix C.

6.4.1.1 Clinical evidence

The review searched for randomised controlled trials investigating whether an intervention can increase the uptake of and/or adherence to a cardiac rehabilitation programme (CRP) after a myocardial infarction. Where RCTs were not identified cohort studies were considered.

A Cochrane review on home-based versus centre-based cardiac rehabilitation was identified but the outcomes included in this review, adherence and update to a cardiac rehabilitation programme, were not included in the review; only the number of people who completed the cardiac rehabilitation program. [432,433] For this reason the Cochrane review by Taylor et al. was not included.

Twenty-three studies were identified which met the inclusion criteria.[39,81,104,107,107,108,174,175,184,211,212,288,293,298,336,343-345,355,363,404,414,415,468] These are summarised in Table 26. See also the full study evidence tables in Appendix G and forest plots in Appendix I.

Papers with similar interventions were grouped where appropriate but most of the interventions were unique so only one paper was available for each outcome.

The definition of adherence was not consistent across the studies. The authors used their own criteria for what they considered adherence. These varied from engaging in a minimum amount of exercise in the last week (for example 150 minutes per week), attending a minimum number of sessions (i.e. 80%), the number of people who remained in the study, to the number of people who received support throughout the cardiac rehabilitation programme. Three papers provided the average number of cardiac rehabilitation sessions attended by the study group.[108,174,211] This is not consistent with definitions of adherence used in other studies, as it reflects the success of the programme as opposed to the number of people who adhered. Studies that provided average attendance were included as they provided an indication of adherence. However, results from Jolly were excluded as standard deviations were not provided.[211,213]

Three papers were in indirect populations (that is less than 75% people who had an MI) which were included and downgraded where this was the only paper providing that outcome.[103,174,175] In 4 papers it was unclear whether indirect populations were included as insufficient information was provided.[39,184,363,415]

Table 27 summarises the populations included in each study, and from these, information on relevant strata were extrapolated. For instance, Beckie et al[39,40] investigated whether a tailored programme for women was more effective in improving adherence than a traditional cardiac rehabilitation programme and Parker et al and Miller et al introduced an intervention in people who were younger than 75 years of age.[288,344]

A health technology assessment (HTA) on "provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups" was published in October 2004.[46,47] Outcomes from this HTA on interventions aimed at improving uptake and adherence to a cardiac rehabilitation programme were referred to in CG48. All 22 papers from the HTA were ordered, of these 5 met our inclusion criteria.[108,211,288,336,404,468] Sixteen were excluded for reasons such as they were abstracts only, there were less than 100 people in the study, the study was not published in English, the study was a PhD thesis, the study was not readily available, the study measured activity levels post discharge not necessarily adherence to a cardiac rehabilitation programme or the study did not use a rehabilitation programme that included an exercise component.

Reasons for withdrawing from the cardiac rehabilitation programme were extracted from 8 RCTs and are presented in Part 1 of the review on barriers to uptake and adherence to a the cardiac rehabilitation programme.[46,175,184,211,212,288,343,468]

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Table 26: Summary of included studies

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
1.	Beckie et al 2010 [39,40]	New	RCT	Gender-tailored intervention. The gender-tailored exercise protocol was identical to that of the traditional cardiac rehabilitation programme except that participants exercised exclusively with women in their cohort and the time of the intervention was restricted to 1 time slot when the traditional cardiac rehabilitation facility was closed. The intervention, guided by the Transtheoretical Model (TTM) of behaviour change and delivered with a motivational interviewing (MI) counselling style was administered by female research nurses and exercise physiologists.	Traditional intervention. Same exercise protocol as the cardiac rehabilitation programme but these were mixed exercise classes and did not have the gender-focused educational sessions.	MI, angina or CABG or PCI within the last year. 12 weeks n=252	• Adherence: number of people who attended more than 80% of exercise cardiac rehabilitation programme from week 1-12. • Subgroup analysis of the participation rates amongst different populations.
2.	Carroll et al. 2007 [81,81]	New	RCT	Home visit within 72 hours and telephone calls at 2, 6 and 10 weeks from an advanced practice nurse and 12 weekly telephone calls from a peer advisor.	Pamphlet with information on the benefits and drawbacks of exercise.	Post MI or coronary artery bypass surgery. n=247	• Uptake: collected from both groups over the telephone via interview by trained assistants. • Reported cardiac rehabilitation at 3, 6 and 12 months after hospital admission.

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	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
3.	Cossette et al 2012[102,104]	New	RCT	1. Face-to-face meeting before discharge; 2. telephone call 3 days post-discharge; 3. final contact of telephone call or a hospital meeting 10 days post-discharge. A family member was invited to participate at any time (but involvement was not mandatory). The goal of step 1 was to address management of symptoms and physical activity after discharge, their understanding of the illness episode, and their concerns and worries. The focus of step 2 was the clinical condition and ability to manage the disease after discharge, and any other worries or concerns including risk factor modification. The focus of step 3 was also clinical and treatment issues, as well as addressing risk factor and	The regular nurse continued to provide their care until hospital discharge. Both groups: after hospital discharge, all participants in both groups were referred to rehab centre with a programme including multifactorial and multidisciplinary interventions. Staff (blinded to group assignment) phoned all study people to invite them to enrol and people who accepted were scheduled for first appointment within 6 weeks after discharge. People in both groups were encouraged to call the rehabilitation centre themselves at any time to schedule an appointment.	MI 57% Angina 42% n=242	• Uptake: enrolment in the free-access rehabilitation programme near the hospital. Enrolment was defined as having attended at least 1 rehabilitation session within 6 weeks of discharge.

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population Duration	Outcomes reported
				lifestyle modification, including rehabilitation enrolment. This meeting occurred mean of 10 days after discharge. Nurse also discussed participants anticipated difficulties with risk factor modification to improve the perceived benefits and lower the barriers to entering rehabilitation.			
4.	Daltroy et al 1985[108]	CG48	RCT	Communication to enhance adherence via telephone and letters to participant and spouse.	Received a mailed pamphlet.	Mixed CHD, 81% MI n=174	• Adherence: mean percentage of sessions attended.
5.	**Dalal et al 2007 [107,107]**	**New**	**RCT**	**Home based programme versus**	**Hospital based rehabilitation**	**Post MI** **N=104**	• **Adherence – author reported satisfactory adherence**
6.	Grace et al 2011[173,174]	New	Prospective cohort	Referral strategy: Liaison. Automatic. Liaison and automatic. Liaison = the referral is facilitated through a personal discussion	Usual referral at the discretion of health care providers.	Stable cardiac inpatients Cardiac condition: 30% PCI: 15-90% CABG:3-73%	• Uptake: self-reported by people whether they attended a cardiac rehabilitation intake assessment (enrolment). • Adherence/attendance: self-reported estimate of percentage of prescribed

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population Duration	Outcomes reported
				with a health care professional (i.e. nurse or physiotherapist) and or/peer graduate (at the bedside or in some cases by telephone shortly after discharge); Automatic only referral using electronic patient records or standard discharge orders as a systematic prompt before hospital discharge.		Heart failure:5-15% Arrhythmia:5-17% Valve repair/ replacement: 2-12% n=1809 1 year	sessions they attended (this is considered an incorrect definition.)
7.	Grace et al 2007[173,175]	New	Prospective cohort	Referral strategy: Automatic -hospital electronic patient records to prompt the standard order for a cardiac rehabilitation referral for all eligible people with cardiac diseases. An information package, including a personalised letter stating the name of the referring physician, a programme brochure, a schedule of classes, and a request that the person telephones to book an appointment, is mailed to the home.	Control group received a referral to cardiac rehabilitation programme at the discretion of the cardiologist, cardiovascular surgeon, general practitioner, or other healthcare provider through paper-based means.	Acute coronary syndrome (MI, UA, CHF or PCI or ACB) PCI =38-61% NYHF Class I=86%. n=661 9 months	• Uptake: participant survey and cardiac rehabilitation centre contacted to verify attendance to a cardiac rehabilitation intake assessment. • Adherence: results only report participation • Completion: yes/no. • Reasons for withdrawing.
8.	Grace et al. 2012[172,173]	New	Prospective cohort	Pre-approved, pre-booked, and early education.	Each strategy was tested individually in comparison to	MI 28% PCI 33.5%	• Uptake • Mean attendance

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				Pre-approved: given that clinical practice guidelines promote cardiac rehabilitation referral as the standard of care, some cardiac wards have standing orders in place so that nurses, allied healthcare professionals, and ward clerks can facilitate referral form completion and submission for indicated people as pre-approved by the cardiac program leadership. The forms would be specific to the cardiac rehabilitation programme to which people are referred. There is no requirement for this process to occur, however it is assumed that verbal consent is secured. This process is perceived to overcome referral failure because there is no time demand for physicians. Pre-booked: inpatients are provided with a cardiac rehabilitation intake appointment prior to discharge. This would be done routinely for all people providing verbal consent. Early education: third outpatient strategy, here cardiac rehabilitation programs arranged	people who were not exposed to that specific strategy, because they were not mutually exclusive.	CABG 41.3% HF 10.8% Valve replacement/ repair 8.5%	

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				interprofessional education sessions for outpatients shortly after referral, but before commencing the cardiac rehabilitation programme. These patient education sessions generally conveyed information regarding cardiac risk factors and their reduction, cardiac medications, the nature of the cardiac rehabilitation programme, and answering any questions participants may have. While this is not a referral strategy per se, more people may ultimately enroll in cardiac rehabilitation if they learned about the cardiac rehabilitation programme at a time when they are more motivated from their recent cardiac episode and discharge.			
9.	Hansen et al 2009[183,184]	New	RCT	Short duration (40minute exercise session).	Long duration (60min exercise session).	40% MI 60% stable CAD n=417 7 weeks	• Adherence: percentage attending each week. Participants were assessed every week but included result was evaluated at end of the 6th week of exercise training (at least 18 sessions). • Reasons for withdrawing:

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
							medical reasons were defined as cardiovascular events, orthopaedic injuries and/or hospitalisation or surgery.
10.	Jolly et al 1999 [211,213]	CG48	RCT	Nurse follow-up support The transfer of responsibility for care between hospital and general practice at the time of discharge and the support of practice nurses. A liaison nurse telephoned the practice (speaking to the practice nurse if possible) shortly before participants were to be discharged to discuss the care of each person and to book the first follow up visit to the practice. Practice nurses were encouraged to telephone back to discuss problems or to seek advice on clinical or organisational issues. Evidence based guidance on clinical management was attached to each discharge communication, which was given to each person	Usual care.	MI = 100% n=389 (people who had angina as well, but only reported MI) 1 and 4 months, 1 year	• Uptake: attending at least one session of rehabilitation session. • Adherence: mean number of sessions attended by participants in 12 months. Not included. • Reasons for withdrawal.

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				(or relative) to give to the general practitioner. Each participant was also given a patient held record, which prompted and guided follow up at standard intervals. The liaison nurses provided support to practice staff both by telephone and by visiting each practice every 3–6 months. The liaison nurses also encouraged practice nurses to attend both initial training on behavioural change and an on-going support group to tackle their information needs as they arose.			
11.	Jolly et al 2009 [212,213]	New	RCT	Home care cardiac rehabilitation programme (exercise, relaxation, education and lifestyle counselling). Home-based programme consisted of a manual, 3 home visits (at 10 days, 6 weeks and 12 weeks) and telephone contact at 3	Centre based. Centre-based programmes varied in length including 9 sessions at weekly intervals, 12 sessions over 8 weeks and 24 individualised sessions over 12 weeks. Programmes commenced between 4 and	MI=50% PCI =40% CABG=10% n=525 6,12 weeks	• Adherence: confined to physical activity component. Questionnaires sent out at 6, 8, 12 weeks to assess the number of people who engaged in at least 3x 15min of physical activity in the last 7 days.

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				weeks. People who had MI or revascularisation were discharged with the Heart manual or an adapted version (manual encourages gradual exercise to achieve minimum 15 minutes of moderately intense exercise). Additional visits were made as deemed necessary by the rehab nurse (nurses delivering home programme were trained for 2 days).	8 weeks following the cardiac event. People exercised to 65-75% of their predicted maximal heart rate and the exercise element of the programme lasted from 25-40 minutes plus warm-up and cool-down times.	data used.	
12.	Miller et al 1988[287,288]	CG48	RCT	Nurse intervention plus goal setting. Each participant completed a 10-15 day cardiac rehabilitation programme in hospital. The aim of the study was to measure the influence of a post hospitalisation nursing intervention on medical regimen compliance and personal adjustments 30 and 60 days and 1 year after discharge. The nursing intervention	Usual care. Completed the same measurement scales as experimental group just prior to dismissal from hospital, and at 30 and 60 day visits to home. Received no nurse intervention and no discussion of medical regimen or problems experienced.	MI=100% n=115 30 days, 60 days.	• Adherence: measured using a health behavioural scale, a 5 point Likert scale which measures adherence to medical regimen. Added up results from all components – diet, smoking, activity, stress, medications. • Adherence: used the number of participants who remained in the study at 60 days. • Reasons for withdrawal.

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	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				administered to the experimental group at the 30 day visit consisted of 3 steps: Assessment: data were obtained by self-assessment of attitudes and perceived beliefs of others toward regimen compliance, personal psychological and social adjustments, and reported regimen compliance by participant and spouse. This information was combined with baseline data collected during hospitalisation. Problem identification: all data from step 1 were evaluated by participant, spouse and nurse. Problem areas were defined and factors contributing to noncompliance or difficulties in personal adjustments were discussed. Goal setting: on the basis of problems identified in step 2, alternative actions were discussed, and a health plan with specific goals was developed. Subjects were revisited 60 days and 1 year after hospitalisation (see Miller 1989).			

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				Specific societal adjustments and coping methods were examined for their effectiveness. Unclear or missing info from the rehab programme was also discussed. Problems identified and people's perceptions were used to develop alternative actions that met the criteria of a desired lifestyle, within the limitation of the disease, were explored with the participant and spouse. Health plan developed that included specific goals to address problems of adherence, attitudes, coping methods and societal adjustments in different life situations.			
13.	Miller et al 1989[287,289]	CG48	RCT– 1 year data of above.	As above.	Usual care. Received no nurse intervention, but completed the same scales as the experimental group.	MI=100% n=115 1 year	• Adherence: measured using a health behavioural scale, a 5 point Likert scale which measures adherence to medical regimen. Twenty point

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
							scale. Added up results from all components – diet, smoking, activity, stress, medications. • Adherence: used the number of people who remained in the study at 60 days.
14.	Moore et al 2006[293,293]	CG48	RCT	Cardiac nurse implementing CHANGE programme (self-assessment, goal setting, problem solving). Three 1.5 hour sessions once a week during the last 3 weeks of the CRP and 2 sessions held at 1 and 2 month post cardiac rehabilitation programme. At end of cardiac rehabilitation programme participants were counselled to exercise at least 5 times per week for 30 minutes. The CHANGE programme was 5 small-group (6-8 people) counselling and behaviour modification sessions for participants attending a cardiac rehabilitation programme in which they are taught self-efficacy	Usual care: routine care provided at the cardiac rehabilitation programme.	Recent cardiac event: MI=50% CABG=50% Angioplasty =50% n=250 1 month and 12 months post CRP. Reported 1 month	• Adherence: met the minimum guideline for exercise amount of 10 hours of moderate intensity exercise a month (150minutes per week). • Reasons for withdrawal.

Update 2013

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				enhancement, problem solving skills, and relapse prevention strategies to address their identified exercise maintenance problems. The CHANGE programme was based on cognitive-behavioural theoretical frameworks.			
15.	Oldridge et al 1983[334,336]	CG48	RCT	Self-management techniques plus diary. Asked to sign an agreement to comply for 6 months and to record in diaries the following: 1) self-monitored heart rate response to submax exercise test and 2) daily physical activity levels and 3) weight changes and smoking.	Control group, same as experimental group in that the length of participation, periodic reassessment, supervision, exercise prescription and education lectures were all the same but did not receive self-management techniques plus diary.	MI = 73% CABG = 16% Angina =12% n=120 6 months	• Adherence/Compliance: had to attend more than 60% of the 48 scheduled exercise sessions. • Reasons for withdrawal.
16.	Pack et al 2013[343,343]	New	RCT	Early appointment to cardiac rehabilitation (within 10 days).	Standard care appointment to cardiac rehabilitation (35 days).	STEMI = 9-24% NTEMI = 47% PCI without MI = 24-36% Angina with stress test =6% n=148	• Uptake: attended cardiac rehabilitation orientation. • Adherence: completed cardiac rehabilitation programme.

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	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
						More than 12 sessions.	
17.	Parker et al 2011[344]	New	Prospective cohort	Early access to cardiac rehabilitation: a pre-scheduled early cardiac access clinic (ECAC) visit booked within 4-14 days of the expected hospital discharge date, and emergency telephone contact support between the time of discharge and the ECAC visit. Where possible, people were given expedited access to cardiac rehabilitation programme and support services, such as social workers, psychologists and dietitians.	Traditional models (access to cardiac rehabilitation service weeks to months of discharge).	STEMI=100% n=469 12 weeks	• Adherence: completed an initial graded exercise test, enrolled into cardiac rehabilitation programme and received support to engage in cardiac rehabilitation exercise • Uptake: orientation attendance • Completion: actively received regular support from affiliated cardiac rehabilitation staff over the course of a 12 week programme.
18.	Parry et al 2009[345,345]	New	RCT	In addition to usual care, participants received peer-generated telephone calls for eight weeks following hospital discharge. Peer volunteers used usual care material to focus their telephone conversations on pain management, exercise and encouragement to attend cardiac	Received preoperative and postoperative education, and visits from in-hospital peer volunteers.	Emergency CABG n=95	• Uptake: cardiac rehabilitation enrolment was used to determine the number of people who had been referred for outpatient cardiac rehabilitation and who had attended at least 1 session.

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				rehabilitation programme. The intervention was standard in that peer volunteers participated in a 4 hour training session. Peer volunteers included men and women who had undergone CABG surgery in the previous 5 years.		8 weeks	
19.	Pinto et al 2011[363,363]	New	RCT	Maintenance counselling after completion of Phase II cardiac rehabilitation programme. 6-month programme of exercise counselling delivered via telephone, as well as print materials and feedback report.	This group received tip-sheet on cardiovascular health. After the 12-month assessment, they received the exercise tip-sheet.	Completed Phase II cardiac rehabilitation n=130 6 month data	• Adherence: measured as attrition at 6 months. Included people who died, had been lost to follow-up and who had medical issues.
20.	Peterson et al 2011[355,355]	New	Medical record review. Pre and post intervention	Quality improvement approach to optimise prescription of medications, education regarding lifestyle modifications including cardiac rehabilitation; and communication between hospital staff, participants and GPs. Educational meetings (aimed at changing practice and enhancing patient outcomes), academic detailing (involves training staff in	Baseline measurements of referrals to cardiac rehabilitation programme.	Acute coronary syndrome: STEMI 22% NSTEMI: 38% Unstable angina: 20% Unspecified ACS = 20%	• Uptake: referral to cardiac rehabilitation.

Update 2013

Update 2013

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				techniques to behaviour change designed to influence how clinical staff use evidence-based information in their practice) and point of care reminders and feedback of baseline audit results.			
21.	Scott et al 2000[404,405]	CG48	Cohort	Dissemination of locally developed clinical practice guidelines and regular feedback of clinical indicators to providers coupled with quality thresholds.	No pre-intervention data was available.	MI =100% n=245 1 year	• Uptake: utilisation rates.
22.	Sniehotta et al 2006[414,414]	New	RCT	Action planning: participants formed up to 3 action plans about when, where, and how they intended to exercise and/or intended to implement extra everyday physical activities after discharge. Combined planning group: participants additionally formed up to 3 coping plans about strategies to overcome anticipated barriers. All treatments were conducted by trained consultants in a one-to-one session. Participants wrote	Received no additional intervention (planning sessions).	CHD MI=45-60% Bypass =8-14% Angioplasty =32-40% n=246 Time 1 was in the second week of rehab programme. Time 2 was 2 months after	• Adherence: measured at time 2 as adherence to the recommendation to exercise at least 90 minutes per week. • Reasons for withdrawal.

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	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				down all plans.		discharge. 10 weeks.	
23.	Sniehotta et al 2005[414,415]	New	RCT	Planning, planning plus diary. Planning: participants formed up to 3 action plans about when, where, and how they intended to exercise and/or intended to implement extra everyday physical activities after discharge, as well as how to cope. Planning plus diary: participants additionally received in the mail 6 weekly diaries after discharge, which contained their plan and was to record how often they adhered to their plan and how they felt. Plans could also be modified.	Received no additional intervention (planning sessions).	CHD Unclear% MI n=240 4 months	• Adherence: attended a cardiac rehab training group within the 4 months of discharge.
24.	Wyer et al 2001[468]	CG48	RCT	Two letters given to participants 3 weeks after an MI. The letters intended to influence the person's: attitude towards attending cardiac rehabilitation highlight how they are following medical recommendations, emphasise the offer of support;	Nominal letters including course dates.	MI=100% n=87	• Uptake: classed as those who attended the first week of programme. • Adherence: compliance rates of all those who attended cardiac rehabilitation programme were collected from cardiac rehabilitation

	Study	Included in CG48 or new to update	Study type	Intervention	Comparison	Population / Duration	Outcomes reported
				offer a point of contact.			programme weekly adherence records held by the cardiac rehabilitation team. Unclear in text. • Reasons for non-adherence.

Table 27: Summary of studies based on pre-selected strata

Study	Sex (% women)	% White / % Minority ethnic group	Socioeconomic background / % Middle class	Rural communities	Anxiety and depression	Physical and learning disabilities / % High school educated or greater	Age (less than 75 years, over 75 years)	% English speaking	Working / % blue collared workers	Timing of recruitment	Programmes targeting particular groups
Beckie[39,40]	100%	82% 17%	-	-	-	0% 92%	31-87 years	100%	-	Referred to outpatient cardiac rehabilitation programme.	Women
Carroll[81,81]	66%	92% 8%	- 20% earned over $40,000 US dollars	-	-	- 81%	76.3 ± 6.3	100%	18% -	Inpatients.	-
Cossette[10] 2,104	10-20%	- -	-	- 90% drives a car.	0%	- 50%	Less than65 years =	100% (Canada –all	62% -	6 weeks of discharge.	-

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Study	Sex (% women)	% White / % Minority ethnic group	Socioeconomic background / % Middle class	Rural communities	Anxiety and depression	Physical and learning disabilities / % High school educated or greater	Age (less than 75 years, over 75 years)	% English speaking	Working / % blue collared workers	Timing of recruitment	Programmes targeting particular groups
							70% Over 65 years = 30%	spoke English or French)			
Dalal[107,107]	21%	-	-	-	2-4%	1%	Mean 62	-	26-51% employed	Inpatients	-
Daltroy[108]	5-8%	92-98% 3-8%	-	-	-	- 57-61%	53±8.7	-	71% 43%	People who had a history of CHD.	-
Grace[173,174]	27%	82% -	- 48% earned over 50,000 Canadian dollars	19%	0% psychiatric condition.	0% 73%	65 ± 11	100% (Canada –all spoke English or French)	50% -	Inpatients.	-
Grace[173,175]	23%	84% -	- 58% earned over 50,000 Canadian dollars	-	0% psychiatric condition.	- 52%	62 ± 10	100%	-	Inpatients.	-

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Study	Sex (% women)	% White / % Minority ethnic group	Socioeconomic background / % Middle class	Rural communities	Anxiety and depression	Physical and learning disabilities / % High school educated or greater	Age (less than 75 years, over 75 years)	% English speaking	Working / % blue collared workers	Timing of recruitment	Programmes targeting particular groups
Grace[172,173]	25%	83.4%		17.3%	-	-	65 ± 10	100%	48%	In and out patients.	-
		-	50% earned over 50,000 Canadian dollars			74.8%			-		
Hansen[183,184]	22%	-	-	-	-	-	63 ± 10	-	-	Inpatients.	-
Jolly[211,213]	30%	-	-	-	Anxiety: 23% Depression : 8%.	-	64 ± 10	-	-	Inpatients considered well enough by staff to participate.	-
Jolly[212,213]	24%	80%	-	Predominately inner city.	Unclear provided means.	-	60 ± 10	-	42%	Within 12 weeks.	-
		20%							-		
Miller[287,289]	18%	98%	-	-	-	6-20 years	30-65yrs	-	88%	Inpatients.	-
		2%							65%		
Moore[293,293]	40%	78-85%	<30K 23%	-	-	10-24years	-	100%	-	Near end of cardiac rehabilitation programme.	-
		15-22%	30-60K 37% 37-41K 34%								

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Study	Sex (% women)	% White / % Minority ethnic group	Socioeconomic background / % Middle class	Rural communities	Anxiety and depression	Physical and learning disabilities / % High school educated or greater	Age (less than 75 years, over 75 years)	% English speaking	Working / % blue collared workers	Timing of recruitment	Programmes targeting particular groups
Oldridge[33] 4,336	-	-	-	-	-	49%	51 ± 9	58%	62% 42%	Referred to cardiac rehabilitation programme.	-
Pack [343,343]	55%	43%	-	Distance to cardiac rehabilitation miles = 8.6.	-	-	Age 61 ± 12	-	-	Within 10 days versus 35 days	-
Parker[344]	20%	-	-	Resides within 1 hour 100Km of city limits	0% mental illness.	-	56 (55-57)	100%	-	In hospital, referred by physician to cardiac rehabilitation programme.	-
Peterson[35] 5,355	29%	-	-	-	-	-	66	-	-	-	-
Pinto[363,363]	20%	95% 3%	<40K 30% 40-80K 30% >80K 40%	-	-	High school diploma or less 20%.	63 ± 10	100%	50% -	Participating in Phase II cardiac rehabilitation programme.	-
Scott[404,405]	27%	-	-	-	-	-	66 ± 14	-	-	Inpatients.	-
Sniehotta[4] 14,414	-	-	-	-	-	Grade 9 or less 33%.	-	-	96% -	Cardiac rehabilitation centre.	-

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Study	Sex (% women)	% White / % Minority ethnic group	Socioeconomic background / % Middle class	Rural communities	Anxiety and depression	Physical and learning disabilities / % High school educated or greater	Age (less than 75 years, over 75 years)	% English speaking	Working / % blue collared workers	Timing of recruitment	Programmes targeting particular groups
Sniehotta[4] 14,415	18%	-	-	-	-	9 years or less 28%	57 ± 10 (31-80)	-	48%	Cardiac rehabilitation centre.	-
Wyer[468]	14%	-	-	Mean distance from programme 7 miles.	-	-	63 years.	-	-	Admitted to hospital and referred to cardiac rehabilitation programme.	-

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Table 28: GRADE profile: early versus late onset of cardiac rehabilitation programme to increase adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early onset	Late onset	Relative (95% CI)	Absolute		
Adherence[344]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association	215/245 (87.8%)	75/224 (33.5%)	RR 2.62 (2.17 to 3.17)	542 more per 1000 (from 392 more to 727 more)	LOW	CRITICAL
Uptake[343,343]												
1	Randomised trial	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	No serious inconsistency	57/77 (74%)	44/74(59.5%)	RR 1.30 (1.03 to 1.62)	178 more per 1000 (from 18 more to 369 more)	HIGH	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Completion												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) In Parker[344], the study groups were not randomly assigned. The authors retrospectively collected data on a control group meaning that allocation concealment was not performed. However, the groups were matched at baseline.
(b) Participants in Pack[343,343] were blinded and randomly allocated to group. Allocation concealment was performed.

Table 29: GRADE profile: gendered tailored programme versus traditional cardiac rehabilitation programme to increase adherence to cardiac rehabilitation programme.

Quality assessment	No of patients	Effect	Quality	Importance

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Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Gender tailored programme	Control	Relative (95% CI)	Absolute		
Adherence[39,40]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very Serious[b]	Serious[c]	None	123/141 (87.2%)	74/111 (66.7%)	RR 1.31 (1.13 to 1.51)	207 more per 1000 (from 87 more to 340 more)	VERY LOW	CRITICAL
Uptake												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) The authors state that a biased randomisation procedure was used to accommodate a maximum of 8-ECG monitoring units per group.
(b) It was unclear what percentage of the population had an MI. The study design limits the ability to isolate the effect of any one of the multifaceted intervention components on attendance. It is therefore unknown which component led to the effect on attendance. The intervention used motivational interviewing, stage matching, gender tailoring and social support, and they may have a synergising effect.
(c) 95% confidence intervals crossed 1 MID (1.25).

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Table 30: GRADE profile: planning and goal setting to increase uptake of and adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Planning (goal-setting)	Control	Relative (95% CI)	Absolute		
Uptake[102,104]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious	None	55/121 (45.5%)	29/121 (24%)	RR 1.90 (1.31 to 2.75)	216 more per 1000 (from 74 more to 419 more)	LOW	CRITICAL
Adherence[288,293,414,415]												
4	Randomised trials	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	None	168/301 (55.8%)	149/348 (42.8%)	RR 1.26 (1.09 to 1.45)	111 more per 1000 (from 39 more to 193 more)	LOW	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) In Cossette [102,104] participants were not blinded to the procedure but it is difficult to do so. It is unclear how the authors randomised in the study by Cossette and participants were not all matched at baseline.

(b) The study was an indirect population, 57% had an MI, 43% had angina.

(c) In 1 paper the consultant assigned participants to treatment groups. In 1 paper, it is unclear how the authors randomised participants. However, in both of these studies participants were matched at baseline. Adherence was measured by the number of people who did not drop out. The authors used a Likert 5 point scale to measure adherence to 5 different outcomes, but the scale was difficult to interpret. In Moore[293,293] investigators were blind. Moore also provided data from 1 and 12 months, however data reported here is 1 month data since it was closer to timing of CRP, the other measure was reflecting more long-term lifestyle changes.

(d) 95% confidence intervals crossed 1 MID (1.25).

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Table 31: GRADE profile: planning, goal setting and diary versus goal setting, signed commitment and diary to increase adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Planning (commitment)+ diary	Control	Relative (95% CI)	Absolute		
Adherence -planning, goal setting and diary[414,415]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness [b]	Serious[c]	None	28/65 (43.1%)	23/79 (29.1%)	RR 1.48 (0.95 to 2.30)	140 more per 1000 (from 15 fewer to 378 more)	LOW	CRITICAL
Adherence- planning, signed commitment and diary[334,336]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[c]	None	31/48 (64.6%)	24/57 (42.1%)	RR 1.53 (1.06 to 2.22)	223 more per 1000 (from 25 more to 514 more)	LOW	CRITICAL
Uptake												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) It was unclear if participants were blinded to the intervention.
(b) The study was a cohort study.
(c) Grace 2007[173,175] included a population of 86-90% people classified as NYHA Class I
(d) 95% confidence intervals crossed 1 MID (1.25).

Table 32: GRADE profile: automatic versus usual referral to increase uptake of and adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Automatic	Usual referral	Relative (95% CI)	Absolute		
Uptake[174,175]												
2	Observational studies	Serious[a]	Serious[b]	Serious[c]	No serious imprecision	Increased effect for RR ~1 [d]	439/792 (55.4%)	179/562 (31.9%)	RR 1.75 (1.52 to 2.02)	239 more per 1000 (from 166 more to 325 more)	VERY LOW	CRITICAL
Adherence[173,175]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[c]	No serious imprecision	Increased effect for RR ~1 [d]	109/241(55.3%)	90/265 (34.1%)	RR 1.33 (1.07 to 1.66)	113 more per 1000 (from 24 more to 341 more)	VERY LOW	CRITICAL
Attendance[173,174]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	83/100 (83%)	83/100 (83%)	-	830 fewer per 1000 (from 830 fewer to 830 fewer)	VERY LOW	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) In 1 paper, participants were not matched at baseline for the type of MI. Participants and investigators were not blinded.
(b) Heterogeneity was detected but direction of the effect was the same so it was unlikely to have a significant impact.
(c) Grace 2007[173,175] included a population of 86-90% NYHA Class I; whereas Grace 2011[173,174] included a population of 5-15% heart failure.
(d) No evidence that confounding effects reduced the effects or suggest a spurious effect, RR>1.

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Table 33: GRADE profile: automatic and liaison versus usual referral to increase uptake of and adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Automatic +Liaison	Usual referral	Relative (95% CI)	Absolute		
Uptake[173,174]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness[d]	No serious imprecision	Strong association[b] Increased effect for RR ~1[c]	335/471 (71.1%)	83/297 (27.9%)	RR 2.55 (2.1 to 3.08)	433 more per 1000 (from 307 more to 581 more)	LOW	CRITICAL
Attendance[173,174]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision	None	81/100 (81%)	83/100 (83%)	-	-	VERY LOW	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) The study was a prospective study. Participants were not matched at baseline. It was unclear whether participants or investigators were blinded.
(b) The effect size is large. RR>2.
(c) There is no evidence that confounding effects reduced the effects or suggest a spurious effect.
(d) Grace 2011[173,174] included 5-15% people with heart failure.

Table 34: GRADE profile: short versus long sessions to increase adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Short	Long	Relative (95% CI)	Absolute		
Adherence[183,184]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	160/198 (80.8%)	185/219 (84.5%)	RR 0.96 (0.88 to 1.05)	34 fewer per 1000 (from 101 fewer to 42 more)	LOW	CRITICAL
Uptake												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) It was unclear whether participants were blinded to the outcome. It was also unclear how the authors randomised or performed allocation concealment. The authors did not measure baseline activity levels.

(b) The study used a mixed population with around 40% of people who had an MI and 60%who had stable CAD (no further details are reported).

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Table 35: GRADE profile: home based versus centre based to increase adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Home based	Centre	Relative (95% CI)	Absolute		
Adherence[107,107,212,213]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	274/314 (87.3%)	274/302 (90.7%)	RR 0.97 (0.92 to 1.02)	27 fewer per 1000 (from 73 fewer to 18 more)	MODERATE	CRITICAL
Uptake												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) Home and centre based cardiac rehabilitation programmes were different. Participants were randomised but it was unclear what methods were used or if the authors performed allocation concealment. It was also unclear whether participants were blinded to the outcome or the aim of study. Given the study design, it was unlikely that participants or investigators were blinded.

Table 36: GRADE profile: letters or telephone call to influence attitude versus usual communication to increase uptake of and adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Letters or call influence attitude	Usual	Relative (95% CI)	Absolute	Quality	Importance
Uptake[468]												
1	Randomised trial	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[b]	None[c]	37/43 (86%)	26/44 (59.1%)	RR 1.46 (1.11 to 1.91)	272 more per 1000 (from 65 more to 538 more)	MODERATE	CRITICAL
Adherence[363,468]												
2	Randomised trials	Serious[d]	Serious[e]	No serious indirectness	No serious imprecision	None	84/101 (83.2%)	77/92 (83.7%)	RR 0.99 (0.87 to 1.73)	8 fewer per 1000 (from 109 fewer to 611 more)	LOW	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) Participants were randomly assigned and allocation concealment was performed. Participants did not appear blinded but the cardiac rehabilitation nurse was unaware of group assignment. However there was no procedure in place to stop people from telling the nurse which letter they received. Adherence in the study by Pinto et a[363,363]l was measured by the number of people who withdrew. The definition of adherence in the study by Wyer et al[468]. was unclear.
(b) 95% confidence intervals crossed 1 MID (1.25).
(c) There was no evidence that confounding effects reduced the effects or suggested a spurious effect.
(d) It is unclear whether participants and investigators were blinded to aim of the study.
(e) Heterogeneity present I^2 = 88%.

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Table 37: GRADE profile: telephone calls versus usual care to increase uptake to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Home visit + phone call	Control	Relative (95% CI)	Absolute		
Uptake[81,81]												
1	Randomised trial	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	92/121 (76%)	46/126 (36.5%)	RR 2.08 (1.62 to 2.68)	394 more per 1000 (from 226 more to 613 more)	LOW	CRITICAL
Adherence												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) It was unclear how the authors randomised, or whether allocation concealment was performed. It was also unclear which groups the participants withdrew from and whether investigators or participants were blinded to aim of the study.

Table 38: GRADE profile: staff training to increase referrals to cardiac rehabilitation programme.

Quality assessment	No of patients	Effect	Quality	Importance

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Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Baseline	Educational training	Relative (95% CI)	Absolute		
Referral[355,355]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	878/1545 (56.8%)	1078/1589 (67.8%)	RR 1.19 (1.13 to 1.26)	129 more per 1000 (88 more to 176 more)	VERY LOW	IMPORTANT
Adherence												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITCAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) The study was not an RCT and the staff were not blinded.
(b) The study measured referral to cardiac rehabilitation rather than uptake of the programme. The authors also measured referral in 3 different ways, 1) medical records, 2) GP survey and 3) patient survey.

Table 39: GRADE profile: telephone calls aimed at increasing uptake to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Telephone calls	Control	Relative (95% CI)	Absolute		
Uptake[345,345]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	11/45 (24.4%)	6/50(12 %)	RR 2.04 (0.82 to 5.06)	125 more per 1000 (from 22	LOW	CRITICAL

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Quality assessment							No of patients		Effect		Quality	Importance
										fewer to 487 more)		
Adherence												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) There were no details provided on allocation concealment and it was unclear whether people were blinded to aim of the study.
(b) In the study by Parry[345,345] people had undergone CABG however, it was unclear what their diagnosis was.

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Table 40: GRADE profile: telephone calls and letters versus letters alone at increasing attendance to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Letters and phone calls	Control	Relative (95% CI)	Absolute		
Mean adherence(better indicated by higher values)[108]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	90	84	-	Mean 1.6 higher (6.63 lower to 9.83 higher)	LOW	CRITICAL
Uptake												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) It was unclear whether the author performed randomisation or allocation concealment. It was also unclear whether people were blinded to the intervention.
(b) The authors measured mean attendance by the 2 groups, however there could be a large variation within the group that may be undetected in measuring mean attendance.

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Table 41: GRADE profile: pre-approved versus usual referral to increase uptake of and attendance to a cardiac rehabilitation programme.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Letters and phone calls	Control	Relative (95% CI)	Absolute		
Uptake[172,173]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	735/1172 (62.7%)	242/637 (38%)	RR 1.64 (1.48 to 1.83)	243 more per 1000 (from 182 more to 315 more)	VERY LOW	CRITICAL
Mean attendance[172,173]												
1	Observational studies	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	82/100 (82%)	84/100 (84%)	-	-	VERY LOW	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) The study was a cohort study. In addition, it was the same pool of subjects re-analysed in 3 different ways.
(b) The study used an indirect population of 28% people who have MI but included 34% people who had PCI and 41.3% people who had undergone CABG.

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Table 42: GRADE profile: gendered tailored programme versus traditional cardiac rehabilitation programme to increase adherence to cardiac rehabilitation programme.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Pre-booked	Usual referral	Relative (95% CI)	Absolute	Quality	Importance
Uptake[172,173]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	324/478 (67.8%)	654/1331 (49.1%)	RR 1.38 (1.27 to 1.50)	187 more per 1000 (from 133 more to 246 more)	VERY LOW	CRITICAL
Mean attendance[172,173]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	80/100 (80%)	84/100 (84%)	-	-	VERY LOW	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) The study was a cohort study. In addition, the same pool of subjects was re-analysed 3 different ways.
(b) The study used an indirect population of 28% people who had an MI, but included 34% people who had undergone PCI and 41.3% people who have undergone CABG.

Table 43: GRADE profile: early education versus usual referral to increase uptake of and attendance to a cardiac rehabilitation programme.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early education	Usual referral	Relative (95% CI)	Absolute	Quality	Importance
Uptake[172,173]												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early education	Usual referral	Relative (95% CI)	Absolute	Quality	Importance
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	324/478 (67.8%)	654/1661 (39.4%)	RR 1.58 (1.45 to 1.72)	228 more per 1000 (from 177 more to 283 more)	VERY LOW	CRITICAL
Mean attendance[172,173]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	80/100 (80%)	83/100 (83%)	-	-	VERY LOW	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) The study was a cohort study. In addition, the same pool of subjects was re-analysed in 3 different ways.
(b) The study used an indirect population of 28% people who had an MI, but included 34% people who had PCI and 41.3% who had undergone CABG.

6.4.1.2 Economic evidence

Published literature

No relevant studies were included in CG48.

One study was included from the update search with a relevant comparison.[212,213] This compared home versus centre cardiac rehabilitation. It is summarised in the economic evidence profile below (Table 44). See also the evidence table in Appendix H.

CG48 cost effectiveness modelling

A model was developed as part of CG48 to look at the cost effectiveness of certain interventions to increase uptake to cardiac rehabilitation. It compared usual care, the use of motivational letters and the use of telephone calls plus a visit from a healthcare professional (HCP).

Effectiveness, in terms of increase of uptake to cardiac rehabilitation, of letters versus usual care was based on the study reported by Wyer and colleagues.[468] Effectiveness of telephone calls plus an HCP visit was based on the study reported by Hillebrand and colleagues.[193] These were reported as part of an HTA report included in the clinical evidence review for the previous guideline, CG48.[46,47]

The impact of interventions to increase uptake on QALYs was modelled indirectly via the difference in rates of participations (uptake) in cardiac rehabilitation. Interventions were modelled as mutually exclusive alternatives. Differences in uptake were converted to a difference in clinical events by modelling the participation in cardiac rehabilitation as having improved outcomes over non-participation (reviewed in the previous guideline, CG48, and not being updated). Events modelled as differing with participation were reinfarction, revascularisation and death. These in conjunction with relevant quality of life weights were then used to estimate QALYs.

The strategy of using phone calls plus home visits by an HCP was the optimal strategy, being the intervention that produced a higher number of QALYs with an incremental cost effectiveness ratio of £8,425 per QALY.

This analysis is also summarised in the economic evidence profile below (Table 44). The full methods and results from CG48 are included in Appendix Q.

New cost effectiveness analysis

This area was prioritised for new cost-effectiveness analysis. The results of this analysis can be found in Section 6.4.1.3. There is also a full description of the methods and results in Appendix L.

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Table 44: Economic evidence profile: interventions to increase uptake and adherence to cardiac rehabilitation

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects	Cost effectiveness	Uncertainty
Jolly 2009[212, 213] (UK)	Partially applicable	Potentially serious limitations (a), (b)	Comparators: • Centre-based cardiac rehabilitation • Home-based cardiac rehabilitation • One year follow-up within-RCT [212,213]	41[(c)]	EQ5D: No significant difference [(b)]	NR	The mean cost per person was sensitive to how the service was organised. If telephone consultations were assumed to replace all the nurse visits in the home arm, the cost per person would have fallen below that for the centre-based arm and vice versa if hospital staff required extra time to prepare for rehabilitation sessions.
CG48 model	Directly applicable[(e)]	Minor limitations	• Interventions to increase uptake Comparators: • Int 1: Usual care • Int 2: Letters • Int 3: Phone calls + healthcare professional visit • Lifetime horizon.	2 vs. 1:849 3 vs. 2:1052 [(f)]	2 vs. 1: 0.106 QALYs 3 vs. 2: 0.125 QALYs	2 vs. 1: £7,999 per QALY gained 3 vs. 2: £8,425 per QALY gained	Probability most cost effective option at a £20,000/QALY threshold: Int 1: 15% Int 2: 1% Int 3: 84% Model not sensitive to changes in efficacy of letters, the type of healthcare professional who made the home visits. When the increase in uptake with phone calls was reduced to less than 55%, letters became the most cost effective option.
NCGC model - update	Directly applicable	Potentially serious limitations [(g)]	• See Appendix I for details.				

(a) Analysis only includes one of a number of interventions to increase adherence identified by clinical review. Cost year unclear .While change in EQ5D utility was described, full cost effectiveness results are not reported in terms of ICERs and the joint distribution of costs and effects.EQ5D described narratively only. Limited sensitivity analysis.
(b) EQ5D described narratively only. Limited sensitivity analysis.
(c) GBP, Cost year unclear.
(d) Other outcomes were reported as well – see full evidence table in Appendix H
(e) Analysis only includes 2 of a number of interventions to increase uptake identified by clinical review.

(f) GBP, year 2005.
(g) The model relies on some assumptions, for example for the probabilities of uptake or adherence under some of the interventions, for the costs and QALYs associated with the uptake but no adhere outcome of the model which were assumed to be the average of the uptake and adhere outcome and the no uptake outcome.
(h) Abbreviations: ARD CC = cost comparison; CEAC = cost-effectiveness acceptability curve; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HCP = healthcare professional; NR = not reported; QALYs = quality-adjusted life years.

6.4.1.3 Health economic modelling

Model overview

A decision tree was built in TreeAge® to calculate cost (£) and effectiveness, measured in quality adjusted life years (QALYs), of interventions aimed at increasing uptake of and adherence to cardiac rehabilitation programmes.

The time horizon is defined as a lifetime using lifetime costs and outcomes from the previous guideline, CG48, which were discounted using 3.5% discount rates on both costs and outcomes, as per the NICE reference case.[312] Intervention costs were updated and, because they occur only once and are assumed to happen during the first year, they do not need to be discounted for subsequent years. The analysis is conducted from the National Health Service and Personal Social Service perspective.

The interventions compared are:

- Usual care (UC)
- Automatic referral (AR)
- Cardiac rehabilitation (CR) liaison (CRL)
- Automatic referral with a CR liaison (ARCRL)
- Personalised goal setting (PGS)
- Calls,-letters and-home visits (CLHV)
- Letters (L)
- Phone calls (PC)
- Early initiation of CR (EI)
- EI followed by automatic referral (EI + AR)
- EI followed by CR liaison (EI + CRL)
- EI followed by automatic referral with a CR liaison (EI + ARCRL)
- EI followed by personalised goal setting (EI + PGS)
- EI followed by Calls-Letters-Home visits (EI + CLHV)
- EI followed by letters (EI + L)
- EI followed by phone calls (EI + PC).

Within each of the single interventions, a person who has had an MI would either take up or not take up cardiac rehabilitation. People that take up cardiac rehabilitation in the first place can either adhere to it or not. The probability of taking up cardiac rehabilitation and the following probability of adherence to cardiac rehabilitation are determined by the strategy. In strategies where an additional intervention is added to early initiation when this fails to achieve uptake or adherence, the second intervention would be implemented determining the second probability of either taking up or adhering to the programme.

The possible outcomes of each strategy are:

- Cardiac rehabilitation uptake and adherence (CR U & A)
- No uptake of cardiac rehabilitation (no CR)
- Cardiac rehabilitation uptake cardiac rehabilitation but not adherence (CR U).

Costs and QALYs are assigned to each one of these outcomes.

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Lifetime QALYs were taken from CG48 for the 'CR U & A' and 'no CR' outcomes, these were essentially the overall QALYs calculated respectively for the CR strategy and for the no CR strategy in the CG48 model evaluating the cost-effectiveness of CR versus no CR. QALYs for the outcome 'CR U' could not be obtained from the CG48 model, so an assumption was made that the QALYs associated with this outcome are an average between the QALYs of CRU & A and no CR. The rationale behind this assumption was that QALYs are highly dependent on the recurrence of cardiovascular events, and that these are driven by the attendance or not of cardiac rehabilitation.

Costs in the model were the cost of the intervention to increase uptake and adherence of cardiac rehabilitation, and the cost associated with each of the possible outcomes (CR U & A, no CR, and CR U). Similarly to the approach used for QALYs, costs for the CR U & A and no CR outcomes were respectively the total cost of the cardiac rehabilitation arm and the total cost of no cardiac rehabilitation arm in the CG48 model. We used the lifetime costs of cardiac rehabilitation and no cardiac rehabilitation respectively for the outcomes 'CR U & A' and for the outcome 'no CR'. As with the QALYs parameter, for people who uptake cardiac rehabilitation but do not adhere to it, we assumed that the costs associated with this outcome 'CR U' are an average between the costs of CRU & A and no CR.

We assumed that the effectiveness of interventions to increase uptake and adherence to cardiac rehabilitation observed in independent studies could be combined in sequences of interventions without affecting the effectiveness of the second intervention (for example. in the sequence EI + L, the effectiveness of letters at increasing uptake and/or adherence to cardiac rehabilitation in people that did not attend in the same place, is assumed to be the same as in letters alone). This assumption could be an overestimation of the effectiveness of the strategies that are a sequence of 2 interventions to increase uptake and adherence to cardiac rehabilitation.

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Results

In the base case, EI+L is likely to be the most cost effective strategy to increase uptake and adherence to CR; however other strategies involving EI could possibly be cost-effective as well. In the base case incremental analysis, other interventions were either dominated or extendedly dominated by combinations of EI+L and letters. However, when looking at the ranking by NMB, dominated strategies such as EI+CLHV or EI+ARCRL could be cost-effective if EI+L is not an option. Generally, strategies involving EI ranked higher than strategies where EI is not contemplated. The results of the probabilistic analysis are reported in Table 45.

In this model, interventions to increase uptake and adherence to cardiac rehabilitation are more costly the more effective they are. The reason is that, by increasing uptake and adherence to cardiac rehabilitation, the additional cost of cardiac rehabilitation is added to the total costs of the strategy.

Table 45: Base case results – probabilistic analysis

Strategy	Costs (£)	QALYs	Net Monetary Benefit (£)	Incremental Net Monetary Benefit (INMB) vs usual care (£)	Ranking (by NMB)
Usual Care (UC)	£6,842	5.915	£111,458	-	16
CR Liaison (CRL)	£7,337	5.983	£112,323	£865	15
Automatic referral (AR)	£7,404	6.001	£112,616	£1,158	14
Phone calls (PC)	£7,602	6.032	£113,038	£1,580	13
Personalised goal setting (PGS)	£7,857	6.062	£113,383	£1,925	12

Strategy	Costs (£)	QALYs	Net Monetary Benefit (£)	Incremental Net Monetary Benefit (INMB) vs usual care (£)	Ranking (by NMB)
Early initiation of CR (EI)	£7,994	6.071	£113,426	£1,968	11
Calls-Letters-Home visits (CLHV)	£8,126	6.088	£113,634	£2,176	10
Automatic referral with a CR liaison (ARCRL)	£8,288	6.134	£114,393	£2,935	8
Letters (L)	£8,315	6.142	£114,525	£3,067	7
EI + Phone calls (EI+PC)	£8,370	6.129	£114,210	£2,752	9
EI + CR liaison (EI+CRL)	£8,787	6.192	£115,053	£3,595	6
EI + Automatic referral (EI+AR)	£8,792	6.195	£115,108	£3,650	5
EI + Personalised goal setting (EI+PGS)	£8,992	6.223	£115,468	£4,010	4
EI + Calls-Letters-Home visits (EI+CLHV)	£9,092	6.232	£115,548	£4,090	3
EI + Automatic referral with a CR liaison (EI+ARCRL)	£9,157	6.251	£115,863	£4,406	2
EI + Letters (EI+L)	£9,172	6.255	£115,928	£4,470	1

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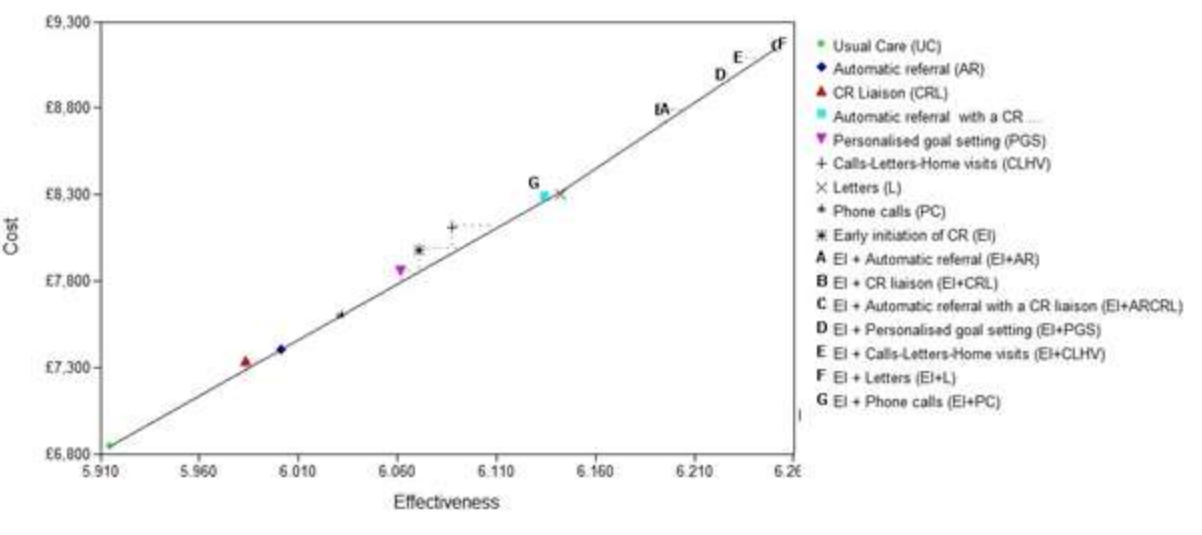
The strategies in Table 45 are sorted from lowest to highest cost. Usual care generates the lowest number of QALYs and the least costs. EI +L is the strategy that generates the highest costs and the highest number of QALYs. Some interventions (EI+PC) are dominated as another intervention (letters) is less costly and yields more QALYs.

To establish which of the treatments with positive incremental net monetary benefit (INMB) is the most cost-effective, we can look at the graph in Figure 1. Here some interventions are above the line connecting all the interventions that are cost-effective. Although some interventions were not subject to simple dominance (more costly and less effective), the line representing their ICER is steeper than the line representing the ICER of the other interventions lying on the line. This shows that most of them are extendedly dominated with the exception of UC (the baseline), Letters, and EI + Letters (see Table 46).

Table 46: Results table without dominated options (simple or extended)

Strategy	Costs (£)	QALYs	ICER in full incremental analysis (£/QALY)
Usual Care (UC)	6,842	5.915	
Letters (L)	8,315	6.142	6,479
EI + Letters (EI+L)	9,172	6.255	7,624

Figure 1: Cost-effectiveness graph



The results of the model need to be treated with caution due to some limitations and assumptions. QALYs for the outcome 'Cardiac Rehabilitation Uptake' could not be obtained from the CG48 model, so an assumption was made that the QALYs associated with this outcome are an average between the QALYs of 'Uptake & Adherence' and 'no Cardiac Rehabilitation'. As with the QALYs parameter, for people who take up cardiac rehabilitation but do not adhere to it, we assumed that the costs associated with this outcome are an average between the costs of 'Uptake and Adherence' and 'no Cardiac Rehabilitation'.

We also assumed that the effectiveness of interventions to increase uptake and adherence to cardiac rehabilitation observed in independent studies could be combined in sequences of interventions without affecting the effectiveness of the second intervention. This assumption could be an overestimation of the effectiveness of the strategies that are a sequence of 2 interventions to increase uptake and adherence to cardiac rehabilitation.

Another limitation of our model is that interventions are compared in a non-randomised setting and therefore the populations on which the clinical data are based on are likely to have some differences.

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6.4.1.4 Evidence statements

6.4.1.4.1 Clinical

Early versus late initiation of cardiac rehabilitation programme

- One cohort study with 469 people showed that an early initiation of a cardiac rehabilitation programme increases the adherence to a cardiac rehabilitation programme compared with a late onset (Low quality evidence).
- One RCT with 148 people showed that an early initiation of a cardiac rehabilitation programme increases the uptake to a cardiac rehabilitation programme compared with a late onset (High quality evidence).
- No evidence was identified on the impact of early initiation of a cardiac rehabilitation programme on quality of life.
- No evidence was identified on the impact of early initiation of a cardiac rehabilitation programme on adverse events.
- No evidence was identified on the impact of early initiation on completion of a cardiac rehabilitation programme.

Tailored cardiac rehabilitation programme for women

- One RCT with 252 people showed that a tailored program for women increased the adherence to a cardiac rehabilitation programme compared with a traditional cardiac rehabilitation programme (Very low quality evidence).
- No evidence was identified on the provision of a tailored cardiac rehabilitation programme for women on uptake to a cardiac rehabilitation programme.
- No evidence was identified on the impact of a tailored cardiac rehabilitation programme for women on quality of life.
- No evidence was identified on the impact of a tailored cardiac rehabilitation programme for women on adverse events.

Planning and goal setting

- One RCT with 242 people showed that planning and goal setting increases uptake to a cardiac rehabilitation programme compared with no additional support (Low quality evidence).
- Four RCTs with 649 people showed that planning and goal setting increases adherence to a cardiac rehabilitation programme compared with no additional support (Low quality evidence).
- No evidence was identified on the impact of planning and goal setting on quality of life.
- No evidence was identified on the impact of planning and goal setting on adverse events.

Planning, goal setting and diary or signed commitment or diary

- One RCT with 144 people showed that planning, goal setting and keeping a diary increased adherence to a cardiac rehabilitation programme compared with not additional support (Low quality evidence).
- One RCT with 105 people showed that planning, signing a commitment and keeping a diary increased adherence to a cardiac rehabilitation programme compared with not additional support (Low quality evidence).
- No evidence was identified on the impact of planning, goal setting and diary or signed commitment or diary on uptake to a cardiac rehabilitation programme
- No evidence was identified on the impact of planning, goal setting and diary or signed commitment or diary on quality of life.
- No evidence was identified on the impact of planning, goal setting and diary or signed commitment or diary on adverse events.

Liaison referral versus usual referral

- One RCT with 389 people showed that liaison referral increased uptake to a cardiac rehabilitation programme compared with usual referral by hospital staff (Low quality evidence).
- One cohort with 378 people showed that liaison referral had a similar effect to usual referral by hospital staff on mean attendance to a cardiac rehabilitation programme (Low quality evidence).
- No evidence was identified on the impact of liaison referral on quality of life.
- No evidence was identified on the impact of liaison referral on adverse events.

Automatic referral versus usual referral

- Two cohort studies with 1354 people showed that automatic referral increased uptake to a cardiac rehabilitation programme compared with usual referral by hospital staff (Very low quality evidence).

- One cohort study with 506 people showed that automatic referral increased adherence to a cardiac rehabilitation programme compared with usual referral by hospital (Very low quality evidence).
- One cohort study with 476 people showed that automatic referral had a similar effect as usual referral by hospital staff on mean attendance to a cardiac rehabilitation programme (Very low quality evidence).
- No evidence was identified on the impact of automatic referral on quality of life.
- No evidence was identified on the impact of automatic referral on adverse events.

Automatic and liaison referral versus usual referral

- One cohort study with 778 people showed that automatic and liaison referral increased uptake to a cardiac rehabilitation programme compared with usual referral by hospital staff (Low quality evidence).
- One cohort study with 490 people showed that automatic referral had a similar effect as usual referral by hospital staff on mean attendance to a cardiac rehabilitation programme (Very low quality evidence).
- No evidence was identified on the impact of automatic and liaison referral on quality of life.
- No evidence was identified on the impact of automatic and liaison referral on adverse events.

Short versus long sessions in a cardiac rehabilitation programme

- One RCT with 417 people showed that short sessions had a similar effect to long sessions on adherence to a cardiac rehabilitation programme (Low quality evidence).
- No evidence was identified on the impact of length of session on uptake to a cardiac rehabilitation programme.
- No evidence was identified on the impact of length of session on quality of life.
- No evidence was identified on the impact of length of session on adverse events.

Home based versus centre based cardiac rehabilitation programme

- Two RCTs with 616 people showed that a home based cardiac rehabilitation programme had a similar effect on adherence to a centre based cardiac rehabilitation programme (Moderate quality evidence).
- No evidence was identified on the impact of home based cardiac rehabilitation programme on uptake to a cardiac rehabilitation programme
- No evidence was identified on the impact of home based cardiac rehabilitation programme on quality of life.
- No evidence was identified on the impact of home based cardiac rehabilitation programme on adverse events.

Letters and calling to influence attitude and behaviour

- One RCT with 87 people showed that letters and calling increase uptake to a cardiac rehabilitation programme compared with usual communication (Moderate quality evidence).
- Two RCTs with 193 people showed that letters and calling had a similar effect to usual communication on adherence to a cardiac rehabilitation programme (Low quality evidence).
- No evidence was identified on the impact of letters and calling on quality of life.
- No evidence was identified on the impact of letters and calling on adverse events.

Home visit and calling

- One RCT with 247 people showed that home visits and calling increased uptake to a cardiac rehabilitation programme compared with usual communication (Low quality evidence).
- No evidence was identified on the impact of home visit and calling on adherence to a cardiac rehabilitation programme.
- No evidence was identified on the impact of home visit and calling on quality of life.
- No evidence was identified on the impact of home visit and calling adverse events.

Staff educational training

- One observational study with 45 hospitals showed that educational training for clinical staff can increase the referral of people to cardiac rehabilitation programme compared with baseline numbers calculated from inpatient medical records (Very low quality evidence).
- No evidence was identified on the impact of staff education on adherence to a cardiac rehabilitation programme.
- No evidence was identified on the impact of staff education on quality of life.
- No evidence was identified on the impact of staff education on adverse events.

Telephone calls

- One RCT with 95 people showed that phone calls over an 8 week period post discharge increased uptake to cardiac rehabilitation programmes compared with usual care, which consisted of education pre-operative and post-operative and visits in-hospital from peer volunteers (Low quality evidence).
- No evidence was identified on the impact of telephone calls on adherence to a cardiac rehabilitation programme.
- No evidence was identified on the impact of telephone calls on quality of life.
- No evidence was identified on the impact of telephone calls on adverse events.

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Telephone calls and letters versus letters

- One RCT with 174 people showed that letters and telephone calls compared with letters alone had a similar effect on the mean attendance to a cardiac rehabilitation programme following an MI (Low quality evidence).
- No evidence was identified on the impact of telephone calls and letters on uptake to a cardiac rehabilitation programme.
- No evidence was identified on the impact of telephone calls and letters on quality of life.
- No evidence was identified on the impact of telephone calls and letters on adverse events.

Pre-approved versus usual referral

- One cohort study with 1809 people showed that pre-approved referral increased uptake to a cardiac rehabilitation programme compared with usual referral methods (Very low quality evidence).
- One cohort study with 1809 people showed that pre-approved referral had no effect on the mean attendance to a cardiac rehabilitation programme compared with usual referral methods (Very low quality evidence).
- No evidence was identified on the impact of pre-approved referral on quality of life.
- No evidence was identified on the impact of pre-approved referral on adverse events.

Pre-booked versus usual referral

- One cohort study with 1809 people showed that pre-booked referral increased uptake to a cardiac rehabilitation programme compared with usual referral methods (Very low quality evidence).
- One cohort study with 1809 people showed that pre-booked referral had no effect on the mean attendance to a cardiac rehabilitation programme compared with usual referral methods (Very low quality evidence).
- No evidence was identified on the impact of pre-booked referral on quality of life.
- No evidence was identified on the impact of pre-booked referral on adverse events.

Early education versus usual referral

- One cohort study with 1809 people showed that early education referral increased uptake to a cardiac rehabilitation programme compared with usual referral methods (Very low quality evidence).
- One cohort study with 1809 people showed that early education referral had no effect on the mean attendance to a cardiac rehabilitation programme compared with usual referral methods (Very low quality evidence).
- No evidence was identified on the impact of early education on quality of life.
- No evidence was identified on the impact of early education on adverse events.

6.4.1.4.2 Economic

- One original cost-effectiveness analysis suggested that 'early initiation followed by letters' may be the most cost-effective intervention for increasing uptake and adherence of cardiac rehabilitation following MI. 'Early initiation' increases both costs and QALYs compared to 'non-early initiation' strategies; however this is within the £20,000/QALY threshold. This evidence is directly applicable with potentially serious limitations.

Update 2013

6.4.2 Recommendations and link to evidence

Recommendation	**19. Deliver cardiac rehabilitation in a non-judgemental, respectful and culturally sensitive manner. Consider employing bilingual peer educators or cardiac rehabilitation assistants who reflect the diversity of the local population.[new 2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend or adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	A systematic review identified a number of reasons why people from South Asian communities (originating from India, Pakistan, Bangladesh, or Sri Lanka) do not uptake or adhere to a cardiac rehabilitation programme. Some South Asian people felt that dietary advice was sometimes culturally inappropriate and women were often uncomfortable discussing sexual activity. In

	addition, the clothing worn meant that it was sometimes difficult for people from South Asian communities to partake in the exercises. Women from these communities also cited the lack of family support to participate and some reported that they needed their husband's permission to attend. Furthermore, some women were not able to participate in mixed-sex classes. South Asian people were also often unable to speak English and there was a lack of resource material available in other languages, or interpreters available to aid participation. The GDG therefore felt that cardiac rehabilitation programmes should be delivered in a manner that allowed for differences between cultures, to facilitate uptake of and adherence to cardiac rehabilitation programmes in these populations. This would allow for these communities to benefit from the improvements in health outcomes associated with uptake and adherence to cardiac rehabilitation programmes. No potential negative effects of designing a cardiac rehabilitation service in this way were identified by the GDG. The GDG felt that it was important that there were healthcare professionals involved who were reflective of the local population and that staff were available to help with any potential language barriers if possible.
Economic considerations	No economic studies were identified on factors associated with uptake and adherence to cardiac rehabilitation programme. There are costs associated with employing bilingual peer educators or cardiac rehabilitation assistants who reflect the diversity of the local population. The GDG has also considered the evidence from CG48 which shows that cardiac rehabilitation is cost-effective and concluded that the costs associated with the employment of additional staff could be offset by the health gain from the increased uptake and adherence in some settings.
Quality of evidence	The systematic review that provided insight into the barriers of South Asian communities included 11 qualitative papers, 8 of which were conducted within the UK, so the results are moderately indirect. However, the evidence was considered high quality because the data were very rich since a lot of information was available from the 11 original papers, the majority of which included interviews. The authors were very clear what the aims of the study were, performed sufficient data analysis and made appropriate conclusions based on the results. No evidence on other specific cultures with lower uptake and adherence rates to cardiac rehabilitation was identified; however the GDG noted that there were likely to be specific barriers for other communities. No economic evidence was found on this question.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006).

Update 2013

Recommendation	**20. Offer cardiac rehabilitation programmes designed to motivate people to attend and complete the programme. Explain the benefits of attending. [new 2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review

	therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend or adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	The review used both quantitative and qualitative evidence to support the recommendations. Some people highlighted that they felt exercise intensity was inappropriate (either too high or too low) or other exercise facilities were used by the person who had an MI instead. This was identified as a barrier to participation. People who had an MI also identified that the perception that attendance would increase the risk of having another cardiac event was a barrier to uptake and adherence, as was the belief that everyday activities would provide sufficient exercise. Additionally, people were worried about exercising at home and felt unmotivated to do so. Numerous people who had never exercised before did not know what to expect or how to perform exercises. One RCT found that some people who withdrew from the cardiac rehabilitation programme did so because of dissatisfaction with the course (including the course content). In addition, 3 RCTs found that people who had an MI who withdrew from the cardiac rehabilitation programme did so because they were not interested or motivated to attend. Additionally, people highlighted in 1 qualitative study that a desire to achieve goals and return to work was a facilitator to the uptake of and adherence to cardiac rehabilitation. As such, the GDG felt that it was important that cardiac rehabilitation programmes were designed to motivate people to attend. Given the additional health benefits associated with completion of a cardiac rehabilitation programme, the GDG expanded the recommendation to highlight the importance of motivating people to also complete the programme. The GDG also noted that some people who had an MI were not aware of the benefits of attending cardiac rehabilitation, including the exercise component of the programme. The GDG therefore amended the recommendation further to highlight the importance of explaining the benefits of cardiac rehabilitation programme to those who had an MI, in the hope that this would promote the benefits of participation and completion.
Economic considerations	No economic studies were identified on factors associated with uptake and adherence to cardiac rehabilitation programme. The GDG has also considered the evidence from CG48 which shows that cardiac rehabilitation is cost-effective and concluded that offering cardiac rehabilitation programmes which motivate people would lead to health gain from the increased uptake and adherence.
Quality of evidence	Overall, the results from the qualitative studies were considered high quality qualitative evidence since they mostly provided an in depth analysis of the barriers relating to uptake and adherence to a cardiac rehabilitation programme. The aims of the studies were clearly defined, the results were clear, the findings were relevant and adequate conclusions were made. Of the 9 qualitative papers used for this recommendation, 8 interviewed between 26 and 101 people. These papers carried some risk of bias as 1 paper interviewed people a long time after they had completed the cardiac rehabilitation programme,

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	thus the responses are at risk of retrospective bias. Another paper only used a selected population who made themselves available to interview. One paper used a questionnaire to extract information from 208 people who had an MI, but the results were not considered rich because they lacked context and further explanation from the participants. The data from the RCTs was graded as low to moderate quality since it was not the aim of the study to investigate why people withdrew from the RCTs. Therefore, how the authors extracted these reasons was unclear and if they used a pre-defined list of reasons for withdrawal it could cause bias. No economic evidence was found to inform this recommendation.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006). The GDG identified this recommendation as a key priority for implementation. The GDG felt that the benefits of attending a cardiac rehabilitation programme were significant and that attendance and completion of the programme were key to obtaining these benefits. Designing the programme to motivate people to attend and explaining the benefits of attending were considered fundamental in encouraging the uptake of and adherence to cardiac rehabilitation. The GDG considered that identifying characteristics of cardiac rehabilitation programmes associated with uptake and adherence after an MI was an important area for further research. A research recommendation was therefore made for a survey based research study, to identify the characteristics of cardiac rehabilitation programmes which are associated with high rates of uptake and adherence (see Appendix N).

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Recommendation	**21. Discuss with the person any factors that might stop them attending a cardiac rehabilitation programme, such as transport difficulties. [new 2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend or adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	The review used both quantitative and qualitative evidence to develop the recommendations. Throughout both reviews, numerous barriers were identified which may have hindered attendance at a cardiac rehabilitation programme. Location was identified as a significant barrier to the uptake of and adherence to a cardiac rehabilitation programme. Four RCTs found that 7-14% of people who withdrew from the cardiac rehabilitation programme did so because of the location;

	with the programme being held in a location that was either too distant or inconvenient. Similarly, qualitative evidence supported this, with studies suggesting that the location of the cardiac rehabilitation centre posed a problem for people because it was located in a city, it had insufficient parking, there was heavy traffic or there was a lack of public transport. People felt that it was unclear if the hospital would provide transport and people often preferred a community based venue. The GDG noted that it was important for healthcare professionals to consider any specific barriers that may prevent someone who has had an MI taking up and adhering to the cardiac rehabilitation programme and an example of one such issue was difficulties with transportation to the programme. The GDG felt that it was important for the healthcare professional to discuss these issues with an individual so that any ways to address these issues are explored. The GDG therefore developed a recommendation highlighting the importance of discussing any potential barriers with people who had an MI, highlighting difficulties with transport as an example.
Economic considerations	No economic studies were identified on factors associated with uptake and adherence to cardiac rehabilitation programme. There may be small costs associated with the staff time to discuss with the person any specific barriers and facilitators to their uptake and adherence to cardiac rehabilitation. The GDG has also considered the evidence from CG48 which shows that cardiac rehabilitation is cost-effective and concluded that the small cost associated with the discussion with the participant is likely to be offset by the health gain from the increased uptake and adherence.
Quality of evidence	The 7 qualitative studies that assessed barriers to the uptake of and adherence to the cardiac rehabilitation programme were of moderate quality for qualitative evidence since all bar one (n=208 participants) were interview-based studies. This meant that the data were rich, allowing the researcher to probe and clarify, something that cannot be achieved from a questionnaire. One study was at risk of bias since people were interviewed a long time after the cardiac rehabilitation programme. The number of participants interviewed ranged from 14 to 101. The aims of the studies were clearly defined, the results were clear and adequate conclusions were made. The 6 qualitative studies that cited reasons that aided or facilitated uptake of and adherence to a cardiac rehabilitation programme were of moderate quality since all were interview based studies on 26 up to 204 people who had an MI. The data was considered moderate to high quality for qualitative evidence with a risk of bias because in 2 studies the participants were interviewed a long time after the cardiac rehabilitation programme. One study may have been in an indirect population because it was unclear if all the participants had an MI. The data from the RCTs is graded as low quality since it was not the aim of the study to investigate why people withdrew from the RCTs. Therefore, how the authors extracted these reasons was unclear and if they used a pre-defined list of reasons for withdrawal, this could cause bias. No economic evidence was found on this question.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006).

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Recommendation	22. Offer cardiac rehabilitation programmes in a choice of venues (including at the person's home, in hospital and in the community) and at a choice of times of day, for example, sessions outside of working hours. Explain the options available. [new 2013]
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend or adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	The review used both quantitative and qualitative evidence to develop the recommendations. There was no evidence identified specifically relating to the timing of access to cardiac rehabilitation services for those populations considered to be at high risk of low uptake and adherence. However, a quantitative review, carried out for the review question on 'interventions to increase the uptake and adherence to cardiac rehabilitation', identified that conflict with employment was a common reason found for people not participating in or withdrawing from cardiac rehabilitation programmes. Additionally, evidence identified via the qualitative review, suggested that time constraints were often highlighted as a personal barrier for people in taking up and adhering to cardiac rehabilitation. Finally, the qualitative review also identified that providing a choice of venues in which cardiac rehabilitation could be provided was a facilitator for healthcare professionals in encouraging people who had an MI to attend the programme. The GDG therefore considered that offering cardiac rehabilitation programmes at a range of times, including outside working hours, would be likely to increase both uptake of and adherence to the programme. Services should recognise the need for flexibility in the times that rehabilitation is provided and the format of the programme. It was noted that many programmes are designed for older people and therefore, sessions were often offered during working hours. The GDG felt that it was important to ensure that sessions were available outside working hours so that cardiac rehabilitation programmes were accessible to those in employment and those with other commitments. The GDG felt that these sessions should be offered throughout the working day, outside of working hours and at weekends to ensure that there are sessions available which can be attended by all. The GDG also considered where cardiac rehabilitation programmes should be available. Location was identified as a significant barrier to the uptake of and adherence to a cardiac rehabilitation programme. Four RCTs found that 7-14% of people who withdrew from the cardiac rehabilitation programme did so because of the location, with the programme being held in a location that was either too distant or inconvenient. Similarly, qualitative evidence supported this, with studies suggesting that the location of the cardiac rehabilitation centre posed a problem because it was mostly

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	located in a city, it had insufficient parking, there was heavy traffic or there was a lack of public transport. People felt that it was unclear if the hospital would provide transport and often preferred a community based venue. The GDG therefore felt that cardiac rehabilitation programmes should be made available in a variety of settings, to help to ensure that people could attend sessions in their preferred venue. It was acknowledged that different people would prefer to attend in different locations and some individuals would prefer home or community based programmes to hospital based ones. Based upon the evidence identified, the GDG recommended that programmes should be provided in the home, in the hospital and in the community. Further qualitative evidence suggested that a lack of available information as to whether to choose home or hospital based cardiac rehabilitation programmes was a barrier to the uptake and adherence of cardiac rehabilitation. The GDG therefore also acknowledged that it was important that different options for timing and venue of settings were thoroughly explaining to the individual to ensure that people who had an MI are able to make an informed choice about which session to attend.
Economic considerations	No economic studies were identified on factors associated with uptake and adherence to cardiac rehabilitation programme. There are costs associated with offering cardiac rehabilitation at different times and in different venues for example delivering the programme at the person's home and other settings. The GDG has also considered the evidence from CG48 which shows that cardiac rehabilitation is cost-effective and concluded that the costs associated with the provision of cardiac rehabilitation in different venues and at different times are likely to be offset by the health gain from the increased uptake and adherence.
Quality of evidence	Overall the evidence was high quality qualitative evidence. All of the qualitative data identified were collected from interviews thus the findings were considered rich in content since interviews allow further probing and clarification. The selection of the participants was mostly broad, so the findings are likely to be applicable to the wider population. The data were considered to be rigorous since the number of people interviewed ranged from 14 to 101, the role of the researcher was generally well defined and adequate conclusions were made since quotes matched up with those of the author. There are limitations in the use of quantitative evidence to answer this review question. The body of evidence identified did not aim to investigate factors associated with uptake of and adherence to cardiac rehabilitation and the studies may be insufficiently powered to detect differences between outcomes. Therefore, the studies did not consistently report all the reasons why people withdrew from cardiac rehabilitation and it was unclear how these reasons were captured. Many of the studies were not carried out in the UK and the GDG acknowledged that there are likely to be innate differences in cardiac rehabilitation programmes in other countries. Many of the participants included in the literature will have been provided with cardiac rehabilitation programmes that take a different format to those which are provided in the current clinical context, therefore there may be differences in the factors that are associated with their uptake and adherence to the programme. However, all studies were conducted within the UK and the GDG acknowledged that timing of and venue for cardiac rehabilitation programmes was likely to be similar between the studies. Some of the studies were also downgraded because the researchers interviewed

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	people many months after the cardiac rehabilitation programme so accounts may be prone to retrospective re-interpretation. No economic evidence was found on this question.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006).

Recommendation	**23. Provide a range of different types of exercise, as part of the cardiac rehabilitation programme, to meet the needs of people of all ages, or those with significant comorbidity. Do not exclude people from the whole programme if they choose not to attend specific components. [new 2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend or adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	The review used both quantitative and qualitative evidence to develop the recommendations. One RCT identified that dissatisfaction with the course content was a reason for no longer participating in a cardiac rehabilitation programme. Further evidence identified from qualitative studies showed that people felt the exercise intensity was inappropriate (either too high or low), they felt everyday activities would be sufficient or they used other exercise facilities. A number of participants had never exercised before and did not know what to expect or how to perform the exercises. Data from qualitative studies highlighted that many people felt that their comorbidities affected their ability to participate in the exercise component of cardiac rehabilitation. Evidence also highlighted that many younger and middle aged people felt that exercise was not appropriate to their age range. The GDG did acknowledge that there were likely to be some implications to providing a range of types of exercise and that this may have some effect on resources. However, the GDG felt that the benefits of providing a range of types of exercise to ensure that as many people as possible felt comfortable participating outweighed any possible harms. The GDG noted that it was particularly important to ensure that younger people who had an MI were able to access exercise programmes appropriate to their age. The GDG noted that there may be some individuals who did not feel comfortable attending parts of the cardiac rehabilitation programme. The GDG felt that it was important to highlight to individuals who did not attend a specific component of the programme (for example, the exercise module) that they were not subsequently excluded from the other elements of cardiac rehabilitation. The recommendation was therefore amended to emphasise that people should not be excluded if they

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	choose not to attend specific components of the programme.
Economic considerations	No economic studies were identified on factors associated with uptake and adherence to cardiac rehabilitation programme. There may be costs associated with offering different modalities of exercise in a cardiac rehabilitation programme as for example, rehabilitation centres might need to be better equipped. The GDG has also considered the evidence from CG48 which shows that cardiac rehabilitation is cost-effective and concluded that the costs associated with the provision of different modalities of exercise are likely to be offset by the health gain from the increased uptake and adherence.
Quality of evidence	Overall the quality of the evidence was of low to high quality. Evidence from quantitative studies were graded as low quality as it was not the aim of the studies to investigate factors associated with the adherence to and uptake of cardiac rehabilitation. Therefore, the studies did not consistently report all the reasons why people withdrew from cardiac rehabilitation and it was unclear how these reasons were captured. Many of the studies were not carried out in the UK and the GDG acknowledged that there are likely to be differences in cardiac rehabilitation programmes in other countries, particularly in the exercise provided. Many of the participants included in the qualitative literature will have been provided with cardiac rehabilitation programmes that take a different format to those which are provided in the current clinical context. Therefore, there may be differences in the factors from many years ago compared with today associated with uptake and adherence to a cardiac rehabilitation programme. All of the data, except from 1 study, were collected from interviews thus the findings were considered rich in content since interviews allow further probing and clarification. The selection of the participants was mostly broad, so the findings apply to the wider population. The data were rigorous since the number of people interviewed ranged from 14 to 101, the role of the researcher was mostly defined and adequate conclusions were made since quotes matched up with those of the author. The study that used a questionnaire was considered less rich in content since the questions can be misleading and do not allow the participant to explain their answers. Often participants will leave open ended questions blank. Some of the studies were downgraded because people were interviewed many months after cardiac rehabilitation programmes so accounts may be prone to retrospective re-interpretation. In some cases the participants were a selected group that would be unlikely to translate to a wider population. No economic evidence was found on this question.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006).

Recommendation	**24. Offer single-sex cardiac rehabilitation classes if there is sufficient demand. [new 2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the

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	likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend or adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	The review used both quantitative and qualitative evidence to develop the recommendations. No quantitative studies identified mixed sex classes as the reason why people withdrew from the cardiac rehabilitation programmes. However, 2 qualitative studies found that some women from South Asian communities did not feel able to participate in mixed sex classes and that this presented a barrier to the uptake of and adherence to the cardiac rehabilitation programme. The GDG agreed that there may be situations in which single sex classes would be preferable to promote uptake and adherence for people who had an MI. However, it was acknowledged that provision of such services would have resource implications and it was agreed that it was only necessary to provide this option where there is sufficient demand. As a result, this recommendation was developed to highlight that single sex classes should be offered where there is sufficient demand.
Economic considerations	No economic studies were identified on factors associated with participants' uptake and adherence to cardiac rehabilitation programme. This recommendation is not expected to have any significant associated costs as the same number of classes would need to be delivered and the expected change is simply the distribution of men and women within the classes.
Quality of evidence	The qualitative study that identified large mixed-sex classes as a reason for not participating in a cardiac rehabilitation programme was low quality qualitative evidence since it was a questionnaire based study not an interview. In addition, the role of the researcher was not clearly defined. However, the authors did question a large number of people who had an MI who had failed to attend a cardiac rehabilitation programme (n=208). The aims of the study were clear and the findings were relevant to the study aims. The study that found some South Asian women may not start or continue to attend mixed-sex classes due to religions and cultural reasons was a large systematic review published by a research group within the UK. This study was graded as high quality since it reviewed 11 primary papers that met the inclusion criteria, 8 of which were from the UK. The conclusion made by the author matched up with the quotes provided in the study and the aims were clearly defined and the findings were relevant to our review question. The same systematic review found that clothing was a reason why some Muslim women do not participate in a cardiac rehabilitation programme. Because of their cultural expectations and religious beliefs many women felt that they needed to wear appropriate clothing in mixed groups, sometimes making it difficult for them to exercise. No economic evidence was found on this question.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006).

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Recommendation	25. Seek feedback from cardiac rehabilitation programme users and aim to use this feedback to increase the number of people starting and attending the programme. [new 2013]
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend, that is adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	The review used both quantitative and qualitative evidence to develop the recommendations. A qualitative study on health care professionals found there was a need to follow-up people who do not attend cardiac rehabilitation programmes. By contacting them healthcare professionals can explore individual barriers to uptake and adherence and if possible find ways to facilitate their attendance. A second qualitative study found that people who took up and attended the cardiac rehabilitation programme could be used to aid uptake to the programme. Furthermore, gathering feedback can provide information on specific factors, from the participants point of view, that could be limiting uptake and adherence to individual cardiac rehabilitation programmes and may provide insight into local barriers (see Recommendation 24). The GDG felt that feedback from this contact could also be used to improve services in the future and help to improve rates of uptake and adherence. However, the group acknowledged that it was often difficult and time consuming to contact people who did not start and adhere to programmes and therefore, the recommendation focused on seeking feedback from those who did attend and adhere to the programme.
Economic considerations	An original economic model was developed for this guideline update comparing strategies to increase uptake and adherence to cardiac rehabilitations versus usual care (no strategies). The model showed that adopting strategies that increased the uptake and adherence were in general cost-effective. Seeking feedback on improving uptake and adherence to the programme would be associated with small costs and is likely to generate health benefits. The GDG believe that these benefits are likely to outweigh the small costs.
Quality of evidence	The evidence for this recommendation was derived from 2 studies. One study was moderate quality qualitative evidence. The information was derived from the interviews with 14 healthcare professionals. The answers were considered rich because the responses could be explored, the conclusions matched up with the aims of the study and what the result showed but the number of people interviewed was relatively low and they came from only one study. A second study was also used to inform the recommendation which used focus group discussions with men and women with coronary heart disease. This evidence was considered high quality since the conclusions of the author matched up with the quotes provided in the paper, the aims of the study were clearly defined and the findings and population were relevant to this review question.

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	No economic evidence was found on this question.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006).

Recommendation	**26. Establish people's health beliefs and their specific illness perceptions before offering appropriate lifestyle advice and to encourage attendance to a cardiac rehabilitation programme. [new 2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend, that is adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	The review used both quantitative and qualitative evidence to develop the recommendations. Barriers relating to health beliefs and illness perceptions were identified in a number of qualitative studies and related to both the person who had an MI and the healthcare professional. Four qualitative studies found that some people believed that exercise is inappropriate. People felt that everyday activities were sufficient, or that attendance would increase their risk of having another cardiac event. One of these studies also identified health care professionals may discourage people to participate in a cardiac rehabilitation programme if they described their heart attack as mild. Eight qualitative studies also discovered people did not participate in a cardiac rehabilitation programme because they failed to understand the benefit of the programme and what the programme entailed. People did not believe it would benefit them because they felt the MI was not the result of lifestyle factors. Finally, there was evidence from qualitative studies to suggest that young people did not always identify that their MI was a result of lifestyle factors. This finding from the qualitative studies was further supported by the finding from an RCT where people listed the reasons for failing to attend or withdrawing from a rehabilitation programme. One reason listed was that they did not understand why they needed to attend the cardiac rehabilitation programme. One qualitative study also identified that it was a facilitator for healthcare professionals in promoting cardiac rehabilitation programmes if lifestyle advice provided was tailored to the individual. The GDG noted that these barriers all related to an individual's beliefs and perceptions of their illness and health. The recommendation was therefore developed to highlight the importance of considering the health beliefs and illness perceptions of those who had an MI and noted that it was likely that this would encourage attendance. Additionally, the GDG noted that specific advice should be tailored to account for any differences in beliefs and perceptions between individuals.

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Economic considerations	No economic studies were identified on factors associated with participants' uptake and adherence to cardiac rehabilitation programmes. There may be small costs associated with the staff time to establish the person's health beliefs and level of health literacy. The GDG has also considered the evidence from CG48 which shows that cardiac rehabilitation is cost-effective and concluded that the small cost associated with this assessment is likely to be offset by the health gain from the increased uptake and adherence.
Quality of evidence	The evidence found was of moderate quality qualitative evidence. The studies were mostly interviews therefore the results are considered rich because it allows researchers to delve into the response and clarify any answers. The number of people interviewed ranged from 13 to 101. The quality was downgraded because some of the information was obtained retrospectively, a long time after the cardiac rehabilitation programme. However generally the information was reliable and sufficiently supported by the answers of the participants. In 1 study the data were derived from a questionnaire of 208 people, so it was considered to be low quality qualitative evidence since it was a questionnaire but it did include a large number of participants. One RCT provided evidence that people withdrew from a cardiac rehabilitation programme because they did not understand why they needed to attend. The quality was graded as low as it was not clear how many people withdrew for this reason and it was unclear how the authors derived the response. If it was from a predefined list of reasons this could have biased the answers, nor was investigating reasons for not participating in a cardiac rehabilitation programme one of the goals of the study. No economic evidence was found on this question.
Other considerations	A meta-analysis of 8 studies[152,153] reported a correlation between attendance at cardiac rehabilitation programmes and people's illness perceptions. The findings support the results of the qualitative review.

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Recommendation	**27. Be aware of the wider health and social needs of a person who has had an MI. Offer information and sources of help on:** • **economic issues** • **welfare rights** • **housing and social support issues. [new 2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend or adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and	The review used both quantitative and qualitative evidence to develop the recommendations.

harms	Two qualitative studies found that cost was a reason for people not participating in cardiac rehabilitation. One of these studies was a systematic review of people from low socioeconomic background. Although the evidence was taken from a study in the US, the GDG considered it likely that these issues would be applicable to the UK. Two RCTs also found that cost was a reason for people withdrawing from a cardiac rehabilitation programme. One study found 13% of people withdrew for this reason. Qualitative evidence also suggested that the availability of both social and family support was a facilitator to the uptake of and adherence to a cardiac rehabilitation programme. The GDG highlighted that there may be specific health and social needs which may affect an individual's ability to take up and attend a cardiac rehabilitation programme. It was acknowledged that potential issues are likely to include economic factors, welfare rights and housing and social support factors. The GDG recognised that the cardiac rehabilitation programme represented a contact point with people who had an MI which offered an opportunity for staff to be aware of these factors. The GDG agreed that it was important for healthcare professionals to point people who had an MI to relevant information and sources of help relating to these factors and therefore developed a recommendation to reflect this.
Economic considerations	No economic studies were identified on factors associated with uptake of and adherence to cardiac rehabilitation programmes. There may be small costs associated with the staff time required to establish the person's wider health and social needs and with the staff time spent to provide information. However the GDG considered these small costs to be justified.
Quality of evidence	Overall, the evidence identified was taken from randomised controlled trials graded as low quality and high quality qualitative evidence. One study interviewed 101 people and provided high quality qualitative evidence from an in-depth analysis of the reasons why they did not participate in the cardiac rehabilitation programme. The other was a systematic review of people who had an MI from a low socioeconomic background. The data were considered low quality because there was little exploration of the socioeconomic barriers to their uptake. Only some broad themes and key messages were identified. Furthermore, the majority of the original papers used in the systematic review were from the US so the findings are somewhat indirect, given the differences in healthcare systems. The quality of the evidence from the RCTs was graded as low since these RCTs did not aim to investigate factors associated with adherence and uptake to cardiac rehabilitation and it was unclear how these reasons were captured. Many of the studies were not carried out in the UK and the GDG acknowledged that there are likely to be differences in cardiac rehabilitation programmes in other countries. No economic evidence was found on this question.
Other considerations	There were no other considerations.

Recommendation	**28. Enrol people who have had an MI in a system of structured care, ensuring that there are clear lines of responsibility for arranging the early initiation of cardiac rehabilitation. [new 2013]**
Relative values of different outcomes	The GDG considered that uptake and adherence to cardiac rehabilitation was the most critical outcomes to the current review. It was noted that uptake and

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	adherence were necessary to gain subsequent health benefits of cardiac rehabilitation. Important outcomes were completion, reasons for withdrawal, quality of life and adverse effects.
Trade-off between clinical benefits and harms	The GDG considered that in order to allow people to have contact with a member of the cardiac rehabilitation team early in their care, people who had an MI should be enrolled into a structured system of care, before discharge from hospital. This would help to ensure that it was clear whose responsibility it would be to initiate early cardiac rehabilitation and ensure swift referral between teams was made. The GDG felt that this was potentially a particular problem where PCI centres were situated in a different area to the relevant cardiac rehabilitation services or in situations where a person who had undergone primary PCI was discharged shortly before a weekend, meaning that contact may not be made until the following week. These were situations identified by the GDG as being likely to result in the person failing to uptake cardiac rehabilitation as a result of service difficulties. Whilst enrolling a person in such a structured system may have resource implications it was considered that the potential improvement in uptake of and adherence to cardiac rehabilitation programmes and associated health gains would offset this.
Economic considerations	An original economic analysis showed that early initiation of cardiac rehabilitation is likely to be cost-effective compared to usual care or non-early initiation interventions. Therefore the GDG considered as cost-effective those strategies that favour the early initiation of cardiac rehabilitation.
Quality of evidence	No evidence was identified in relation to this recommendation. The GDG therefore used informal consensus to develop the recommendation. The economic evidence relating to the early initiation of cardiac rehabilitation is directly applicable with potentially serious limitations.
Other considerations	The GDG highlighted that healthcare professionals in England should refer to the NICE commissioning guide for cardiac rehabilitation.

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Recommendation	**29. Begin cardiac rehabilitation as soon as possible after admission and before discharge from hospital. Invite the person to a cardiac rehabilitation session which should start within 10 days of their discharge from hospital.[new 2013]**
Relative values of different outcomes	The GDG considered that uptake and adherence to cardiac rehabilitation was the most critical outcomes to the current review. It was noted that uptake and adherence were necessary to gain subsequent health benefits of cardiac rehabilitation. Important outcomes were completion, reasons for withdrawal, quality of life and adverse effects.
Trade-off between clinical benefits and harms	The evidence identified suggested a benefit to the uptake of, adherence to and completion of a cardiac rehabilitation programme, where the orientation class for cardiac rehabilitation was initiated early after discharge from hospital (within 4-14 days) compared with standard care. The GDG noted that although the evidence supported contact between 4-14 days, for practical reasons the GDG recommended that cardiac rehabilitation should be

	started as soon as possible following an MI, to ensure that people who had an MI receive contact with a cardiac rehabilitation team member before discharge from hospital. The GDG highlighted that this was particularly important for people who have been discharged from hospital within a short time frame, for example people who had a STEMI and who have undergone primary PCI. Additionally, the GDG noted that it was important to clarify when attendance to the first cardiac rehabilitation session should occur following hospital discharge. Additional evidence supported the idea of early uptake since the authors showed in a cohort study that people who are automatically pre-approved for a cardiac rehabilitation programme or those who are pre-booked before discharge show a higher rate of uptake and adherence compared with those who are referred using standard methods. Given the evidence available on uptake and completion, highlighting the importance of early initiation of rehabilitation (within 10 days), the GDG felt that the recommendation should specify that the first attendance at cardiac rehabilitation should be made within 10 days. The GDG highlighted that ensuring contact with the cardiac rehabilitation team prior to discharge from hospital would also help those people who may not be able to undergo early initiation of cardiac rehabilitation, for example, because they are admitted and discharged over the course of a weekend. No specific harms of initiating cardiac rehabilitation early were identified and the potential health benefits from increased uptake and adherence led the GDG to make this recommendation.
Economic considerations	An original economic analysis showed that early initiation of cardiac rehabilitation is likely to be cost-effective compared to usual care or non-early initiation interventions. Therefore the GDG considered as cost-effective those strategies that favour the early initiation of cardiac rehabilitation.
Quality of evidence	The evidence identified ranged from being graded as low to high quality. The evidence on the effect of an early appointment on the uptake and completion of a cardiac rehabilitation programme was mostly on people who had an MI and undergone PCI. Thus, this data is relevant given the current shorter hospital stays in these people (around 75% of people who had an MI and who have undergone PCI leave within 3 days). One study was an RCT which was graded as high quality data since people were randomised and blinded regarding the purpose of the study. Allocation concealment was performed and results were mostly precise. The low quality evidence on adherence was from a non-RCT that used a retrospective control group however they were matched with the intervention group for most of the baseline characteristics. The data were downgraded since it was not an RCT, and the people selected to be part of the study may have been more motivated to engage in a cardiac rehabilitation programme. The additional data supporting the idea of an early uptake was very low quality evidence since it was a cohort study and the population was indirect, although most of the participants needed revascularisation.

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	No evidence was identified on quality of life or adverse events. The economic evidence is directly applicable with potentially serious limitations.
Other considerations	The GDG highlighted that it was important to take into account people's wishes when establishing contact regarding cardiac rehabilitation and noted that some people may not wish to have contact with a healthcare professional so soon after an MI. The GDG identified this recommendation as a key priority for implementation, as early initiation of cardiac rehabilitation was considered to be the most important factor in encouraging people who had an MI to take up and adhere to a cardiac rehabilitation programme.

Recommendation	**30. Contact people who do not start or do not continue to attend the cardiac rehabilitation programme with a further reminder, such as:** • **a motivational letter** • **a prearranged visit from a member of the cardiac rehabilitation team** • **a telephone call** • **a combination of the above. [new 2013]**
Relative values of different outcomes	The GDG considered that uptake and adherence to cardiac rehabilitation was the most critical outcomes to the current review. It was noted that uptake and adherence were necessary to gain subsequent health benefits of cardiac rehabilitation. Important outcomes were completion, reasons for withdrawal, quality of life and adverse effects.
Trade-off between clinical benefits and harms	The GDG felt where people who had an MI do not take up or adhere to cardiac rehabilitation, interventions to encourage them to do so should be considered. This was particularly relevant for people who had received an early invite to participate in a cardiac rehabilitation programme. The following interventions appeared to increase uptake to a cardiac rehabilitation programme compared with usual care: letters and telephone calls, home visits and telephone calls, telephone calls alone, pre-booked referral (with or without a person's consent) and taking part in a pre-educational session. However, letters and telephone calls compared with usual care or letters alone had no effect on adherence to a cardiac rehabilitation programme. Nor did the pre-booked referral (with or without a person's consent) or taking part in pre-educational sessions. It was felt that there was little difference in the benefits of the interventions identified and therefore, given the range of potential barriers to uptake of and adherence to cardiac rehabilitation, the GDG chose to recommend a number of possible interventions. The GDG suggested that healthcare professionals consider service and patient factors in selecting an intervention to follow up people who do not take up or attend cardiac rehabilitation. Further information on barriers to uptake of and adherence to cardiac rehabilitation can be found in the Linking Evidence to Recommendations tables for Recommendations 19 to 27.

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Economic considerations	An original economic analysis showed that early initiation of cardiac rehabilitation is likely to be cost-effective compared to usual care or non-early initiation interventions. After early initiation has failed to ensure uptake or adherence to cardiac rehabilitation, adding another intervention such as letters, phone calls, home visits etc. can be cost-effective as the model showed that they increase effectiveness with some little extra cost. Given the uncertainty in the results, the GDG did not select specific interventions to recommend and believed that if a centre already has a particular system in place to increase uptake and adherence it may be more cost-effective to retain that system rather than change it for a specific intervention. The economic evidence is directly applicable with potentially serious limitations.
Quality of evidence	Evidence relating to interventions to increase uptake to a cardiac rehabilitation programme ranged from being graded as very low to moderate quality. One of the studies was an observational or prospective cohort study; the others were randomised controlled trials. No evidence was identified on quality of life or adverse events. Results from the qualitative review on factors and barriers influencing people's participation to a cardiac rehabilitation programme were used to develop this recommendation. The information was derived from the interviews of 14 healthcare professionals. The answers were considered rich because they could be explored but the number of people interviewed was relatively low and they came from only one study. No economic evidence was found on this question.
Other considerations	The GDG highlighted that there may be confidentiality issues with telephoning people who had an MI, particularly when leaving telephone messages. Healthcare professionals may wish to consider other methods of contact with individuals in these situations, for example, sending text messages or emails.

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Recommendation	**31. Make cardiac rehabilitation equally accessible and relevant to all people 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, people with a learning disability and people with mental and physical health conditions. [2007, amended 2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend or adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	No quantitative or qualitative studies specifically identified ethnicity, age, socioeconomic background, sex, living in a rural community or mental health as reasons for not participating in a cardiac rehabilitation programme.

	These groups were identified by stakeholders during the scoping process and by the GDG as populations who may be at risk of low participation levels in cardiac rehabilitation programmes. However, this review looked at evidence on these groups in particular to see what their specific barriers to uptake and adherence were. Some specific barriers were therefore identified as being relevant to certain populations. For example, qualitative evidence identified that certain age groups felt that exercise was not appropriate to their age range, a disbelief that the MI was due to health reasons and a desire to not expand their lifespan. Evidence suggested that women may not take up and attend rehabilitation because they believed they could recover independently but conversely found that uptake and adherence increased their confidence and independence. Specific recommendations have been made by the GDG where appropriate for these groups. The GDG however felt that it was important to highlight to healthcare professionals that there were specific groups which may be more at risk of low participation. As such, an overarching recommendation was developed using GDG consensus to ensure that healthcare professionals are aware of the groups that were identified during the scoping period as being at risk of failing to take up or adhere to a cardiac rehabilitation programme. Additionally, the recommendation highlights the importance of ensuring that programmes are accessible and relevant to all.
Economic considerations	No economic studies were identified on factors associated with uptake and adherence to cardiac rehabilitation programmes. Making cardiac rehabilitation programmes more accessible helps with the provision of a cost-effective intervention.
Quality of evidence	No economic, quantitative or qualitative evidence was found on this question. The recommendation was developed through informal consensus of the GDG.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006).

Update 2013

Recommendation	**32. Encourage all staff, including senior medical staff, involved in providing care for people after an MI, to actively promote cardiac rehabilitation. [2013]**
Relative values of different outcomes	The GDG accepted the benefits of cardiac rehabilitation established in CG48 and other sources. Clearly these benefits are critically dependent on the person starting cardiac rehabilitation and continuing to engage with the programme. This review therefore was concerned with assessing the impact of various interventions on the likelihood that people would take up, or begin, their cardiac rehabilitation programme, and also whether they would continue to attend ie adhere to the programme. Measures of uptake and adherence were clearly the critical outcomes for this analysis. Less critical but still important outcomes were completion, reasons for withdrawal, quality of life and adverse effects of the programme.
Trade-off between clinical benefits and harms	The review used both quantitative and qualitative evidence to develop the recommendations. Five qualitative studies revealed that peoples' needs were not being consistently met by cardiac rehabilitation staff. People reported that staff running home-based clinics were sometimes unable to answer questions, there was some inconsistency in the care provided (high staff turnover), methods of communicating were poor and the

	information given was at times contradictory, lacking advice, overly negative or too intense. Additionally, no psychological advice was provided. Knowledge that family members could attend sessions was not always shared. Three qualitative studies identified referral issues or insufficient information as reasons for people not participating in a cardiac rehabilitation programme. People felt there was insufficient information on whether to choose a home-based or centre-based cardiac rehabilitation programme. Numerous people were not referred to a cardiac rehabilitation programme or were left to find their own programme. One study found that attitudes or remarks of healthcare professionals were reasons for not attending a cardiac rehabilitation programme. Some people were told that the heart attack was mild, so they felt that there was no need to attend rehabilitation. Two qualitative studies investigated barriers and facilitators for health care professionals to promote cardiac rehabilitation programmes and the authors found better integration between primary and secondary care is needed to improve the provision of a consistent service. In addition, gaps in individual patient pathways, especially for people who moved between hospitals for treatment were barriers for people who had an MI. No quantitative studies identified data relating to this recommendation. The GDG felt that the evidence highlighted the need for healthcare professionals to be actively involved in the promotion and provision of cardiac rehabilitation programmes. Issues relating to staff, including problems with referral, provision of information, negative attitudes and a lack of support were all identified as being barriers to uptake of and adherence to a cardiac rehabilitation programme. The GDG were aware that there were often difficulties in ensuring that healthcare professionals promoted the availability of cardiac rehabilitation programmes and referred people who had an MI appropriately. As such, the GDG developed a recommendation to encourage all staff to actively promote cardiac rehabilitation. The GDG amended the recommendation to highlight that this responsibility fell on all staff, including those at a senior level.
Economic considerations	No economic studies were identified on factors associated with uptake and adherence to cardiac rehabilitation programmes. Promoting cardiac rehabilitation helps with the provision of a cost-effective intervention
Quality of evidence	The evidence on people who had an MI was moderate quality qualitative evidence. The answers were provided from interviews so the responses could be explored sufficiently by the researchers. The number of people interviewed ranged from 14 to 101. The quality was downgraded because some of the data were obtained retrospectively from people a long time after the MI. The evidence on healthcare professionals was low to high quality qualitative evidence since 1 study was based on a questionnaire of 303 people and the other was an interview based study on 42 people. Neither study showed any major risks of bias. No economic evidence was found on this question.
Other considerations	Recommendations on planning, delivering and evaluating public health activities aimed at changing health related behaviours can be found in the NICE Public Health Guidance 6 'Behaviour change' (2006).

Update 2013

6.5 Education and information provision

6.5.1 Clinical effectiveness of education and information provision

6.5.1.1 Clinical evidence

A systematic review examined the effects of psycho-educational (health education and / or stress management) programs on CAD patients.[133] 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.[133]

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.[133]

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.[133]

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.[133]

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.[133]

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.[356] 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.[356]

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.[276] 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.[276]

6.5.2 The Heart Manual

The Heart Manual (previously 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.[251] 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 were 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).[251]

A second randomised controlled trial compared the relative efficacy of two different rehabilitation programmes, one with and one without the Edinburgh Heart Manual.[330] 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.[330]

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.[330]

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.[330]

6.5.3 Return to work

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

6.5.4 Activities of daily living

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

6.5.5 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.

6.5.6 Travel/flying

The Civil Aviation Authority makes recommendations on when people are able to fly, following an MI. Healthcare professionals should refer to the CAA website (http://www.caa.co.uk).

6.5.7 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.[351] 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:[351]

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.

6.5.7.1 Evidence statements

6.5.7.1.1 Clinical

Education and stress management programmes reduce cardiac mortality and MI recurrence in post MI patients (1++).

Education/stress management programmes may aid in return to work (1+), and reduce anxiety after a 3 month recovery period following an MI (1+).

Use of the Edinburgh Heart Manual reduces anxiety and depression and increases perception of control over illness (1+).

6.5.8 Summary of recommendations

33. Comprehensive cardiac rehabilitation programmes should include health education and stress management components. [2007]

34. A home-based programme validated for patients who have had an MI (such as 'The heart manual'; see www.theheartmanual.com) that incorporates education, exercise and stress management components with follow-ups by a trained facilitator may be used to provide comprehensive cardiac rehabilitation. [2007]

35. Take into account the physical and psychological status of the patient, the nature of their work and their work environment when giving advice on returning to work. [2007]

36. Be up to date with the latest Driver and Vehicle Licensing Agency guidelines. Regular updates are published on the DVLA website (www.dvla.gov.uk). [2007]

37. After an MI without complications, people who wish to travel by air should seek advice from the Civil Aviation Authority (www.caa.co.uk)[a]. People who have had a complicated MI need expert individual advice. [2007, amended 2013]

38. People who have had an MI who hold a pilot's licence should seek advice from the Civil Aviation Authority. [2007]

39. Take into account the patient's physical and psychological status, as well as the type of activity planned when offering advice about the timing of returning to normal activities. [2007]

40. 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

[a] Recommendation amended to reflect updated information available on air travel after an MI from the Civil Aviation Authority (CAA).

http://www.cdc.gov/nccdphp/dnpa/physical/measuring/met.htm). Advise patients how to use a perceived exertion scale to help monitor physiological demand. Patients who have had a complicated MI may need expert advice. [2007]

41. 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.[2007]

6.6 Psychological support

6.6.1 Clinical effectiveness of psychological support

6.6.1.1 Clinical evidence

A systematic review on psychological intervention for coronary heart disease (CHD) identified randomised controlled trials of non-pharmacological psychological interventions.[381,382] 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.[381,382]

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.[381,382]

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.[381,382]

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, [44 214,217] both of which produced null findings for all clinical outcomes.[381,382]

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).[381,382]

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.[424] Only one of these 8 trials examined the effects of a stress management intervention without the influence of other rehabilitation interventions.[214,217]

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 [214,217] 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)).[381,382]

The randomised controlled trials identified in the systematic review [381,382] were extremely heterogeneous 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.

6.6.2 Clinical effectiveness of social support

A systematic overview examined social support and its relationship to morbidity and mortality after acute MI.[292] 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.[292]

A systematic review identified interventions designed to promote family function during the recovery phase of a cardiac event.[454] 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 [129 74] found that family intervention decreased anxiety in the spouse. One study found that anxiety was also decreased in the patient.[74] 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.[428,433] Two studies found no positive effect of family intervention on the Adaptation, Partnership, Growth, Affection, and Resolve Family Scale.[169 166] A study measuring the effect of family intervention with a social network and social support scale showed no effect of family intervention.[154]

A study training spouses on cardio-pulmonary resuscitation found that perceived control on the Family Control Attitudes Scale increased significantly.[166]

6.6.2.1 Evidence statements

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++).

There is limited evidence (based on three studies of married couples) that involving spouses may have beneficial effects on family anxiety (1++).

6.6.3 Summary of recommendations

42. Offer stress management in the context of comprehensive cardiac rehabilitation. [2007]

43. Do not routinely offer complex psychological interventions such as cognitive behavioural therapy. [2007]

44. Involve partners or carers in the cardiac rehabilitation programme if the patient wishes. [2007]

45. For recommendations on the management of patients with clinical anxiety or depression, refer to 'Anxiety' (NICE clinical guideline 113), 'Depression in adults' (NICE clinical guideline 90) and 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91). [2007]

6.7 Sexual activity

6.7.1 Clinical effectiveness and sexual function

6.7.1.1 Clinical evidence

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. [283,284] 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.[139] The survey was conducted 5-7 months after MI, on men aged below 59 years (mean age 52 years).

6.7.1.2 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 O2/kg per minute). Sexual activity is relatively low on this scale as outlined in the Table 2.[60]

Table 47: Metabolic equivalent of energy expenditure for varying levels of activity

Activity	Metabolic equivalent of energy expenditure (MET) (1 MET ≈ 3.5 mL O2/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 [301] 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.[301]

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.[301]

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).[85] 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.[296] 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.[421,422]

6.7.1.3 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.[99] 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%)).[99]

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.[337,339] 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.[116,117] 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.[116,117]

6.7.1.4 Counselling

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

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

Table 48: 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	The proportion of records recording Age Gender Postcode Ethnic origin	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.

Recommendation	Criterion	Exception	Definitions
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.	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. Patients from diverse minority groups receive advice and interventions that are culturally and linguistically appropriate.		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 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.	

6.7.1.6 Evidence statements

6.7.1.6.1 Clinical

Sexual function

The MET (metabolic equivalent of energy expenditure) of sexual activity is between 2 and 6 METs.

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).

There was no evidence found on the risk of sexual activity resulting in sudden death.

Sexual education

In male patients after MI with erectile dysfunction, treatment with sildenafil inhibitors improves erectile dysfunction (1+).

There is no added risk in using PDE5 inhibitors for post MI patients compared with the general population (1+).

Sildenafil, used correctly, does not increase overall cardiovascular risk in patients after an MI (1+).

The trials of PDE5 inhibitors to treat erectile dysfunction which included patients after MI excluded those treated with nitrates (1+).

6.7.2 Summary of recommendations

46. Reassure patients 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. [2007]

47. Advise patients who have made an uncomplicated recovery after their MI that they can resume sexual activity when they feel comfortable to do so, usually after about 4 weeks. [2007]

48. Raise the subject of sexual activity with patients within the context of cardiac rehabilitation and aftercare. [2007]

49. When treating erectile dysfunction, treatment with a PDE5 (phosphodiesterase type 5) inhibitor may be considered in men who have had an MI more than 6 months earlier and who are now stable. [2007]

50. PDE5 inhibitors must be avoided in patients treated with nitrates or nicorandil because this can lead to dangerously low blood pressure. [2007]

7 Drug therapy

The following chapter covers drug therapy following an MI. The following are considered:

1. Overall drug therapy recommendations
2. ACE inhibitors [updated 2013]
3. ARBs [updated 2013]
4. Antiplatelet therapy [updated 2013]
5. Beta-blockers [updated 2013]
6. Calcium channel blockers
7. Potassium channel activators
8. Aldosterone antagonists

The updated review questions in this chapter are:

- What is the clinical and cost effectiveness of adding ACE inhibitors versus placebo to improve outcome in people after an MI and is there an optimal duration?
- Is there an optimal time for ACE inhibitors to be initiated in people who have had a MI?
- What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?
- What is the optimal duration that clopidogrel should be continued in people after MI?
- In people with an MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?
- What is the clinical and cost effectiveness of adding a beta-blocker versus placebo to improve outcome in people after an MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?
- Is there an optimal time for beta-blockers to be initiated in people who have had a MI?

Update 2013

The evidence and text from the previous guideline, CG48, that has been superseded by this update is included in Appendices P and W.

The new review questions are included in this chapter are:

- Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had a MI?
- What is the most effective and cost effective combination of antiplatelet and anticoagulant therapies for people with MI and an indication for anticoagulation?

Sections not updated in this chapter are:

- Antiplatelet agents (excluding those questions outlined above relating to the duration of clopidogrel therapy, the late initiation of antiplatelet therapy and antiplatelet therapy in those with another clinical indication for oral anticoagulation.)
- Calcium channel blockers
- Potassium channel activators
- Aldosterone antagonists

The following sections have been removed:

- Vitamin K antagonists (please note that relevant recommendations have been included in Section 7.4 on Antiplatelet therapy)
- Lipid lowering agents

7.1 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) and summary of product characteristics (SPC) as appropriate;

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

7.2 Overall drug therapy recommendations

Update 2013

The use of specific drugs is examined in the following sections however, the GDG felt that the following recommendation was useful to summarise drug therapy for people following an MI. It was amended from CG48 to ensure consistency across the recommendations.

The GDG identified this recommendation as a key priority for implementation, as the recommendation covered the key components of drug therapy for secondary prevention of MI.

Summary recommendation

51. Offer all people who have had an acute MI treatment with the following drugs:

- **ACE (angiotensin-converting enzyme) inhibitor**
- **dual antiplatelet therapy (aspirin plus a second antiplatelet agent)**
- **beta-blocker**
- **statin.[b] [2007, amended 2013]**

Update 2013

The GDG also made 3 further overall drug therapy recommendations relating to:

- Management plans (see Recommendation 98)
- Assessment of LV function (see Recommendation 59)
- Assessment of bleeding risk (see Recommendation 71).

b Recommendation amended from CG48 to reflect updated recommendations. Previous recommendation from CG48 recommended aspirin alone for all people who had an MI, therefore the recommendation has been amended to reflect that all people who had an MI should receive dual antiplatelet therapy, unless contraindicated.

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

Blood pressure, fluid and electrolyte homeostasis are regulated by the Renin-Angiotensin-Aldosterone-System (RAAS). Renin, an enzyme released from the kidney, converts the inactive plasma protein, angiotensinogen, to angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin converting enzyme, and it is the angiotensin II which binds to AT-receptors, principally AT1. The activation of AT1 receptors has a number of physiological actions including: renal tubular sodium re-absorption and water retention; aldosterone and ADH secretion; arteriolar vasoconstriction and enhanced sympathetic activity. Angiotensin converting enzyme (ACE) inhibitors reduce the activity of RAAS by blocking the conversion of angiotensin I to angiotensin II and have a variety of clinical indications including the treatment of hypertension, congestive cardiac failure and attenuation of diabetic nephropathy. In addition, certain ACE inhibitors have been shown to improve survival in people who have sustained a myocardial infarction (MI).

ACE inhibitors are currently routinely initiated following an MI, based upon previous evidence that ACE inhibitor therapy can improve clinical outcomes, including mortality and the development of heart failure.

CG48 recommended that all people who had an MI should be offered an ACE inhibitor indefinitely, following an MI. The results of MINAP have clearly demonstrated that many clinicians use ACE inhibitors according to this recommendation, with 94% of people in England receiving ACE inhibitors at discharge following admission with an MI. [304] CG48 recommended ACE inhibitor therapy for those with preserved left ventricular (LV) function, as well as those with left ventricular systolic dysfunction (LVSD), although it was acknowledged that benefits of treatment were greater in the latter population.

However changes in the acute management of an MI since publication of CG48 have meant that it is now important to identify whether there needs to be a change in when ACE inhibitors should be initiated, how long they are given for and the speed at which they should be titrated. Additionally, since publication of CG48, it has become apparent that inconsistencies in the speed of ACE inhibitor titration are commonplace and that the clinically effective dose is often not reached at the time of hospital discharge and in the community. This issue has become particularly important given changes in the length of inpatient admission associated with newer acute management strategies. The guideline update therefore aims to update recommendations on the initiation of ACE inhibitor therapy, the duration of treatment and the optimum titration regimen and whether there are differences in these recommendations for those who had an MI in the past, those with left ventricular dysfunction and those with preserved ventricular function.

Update 2013

7.3.1 Clinical effectiveness of ACE inhibitors and optimal duration of therapy

7.3.2 What is the clinical and cost effectiveness of adding ACE inhibitors versus placebo to improve outcome in people after an MI and is there an optimal duration?

For full details see review protocol in Appendix C.

7.3.2.1 Clinical evidence

Thirty-three studies were included in the review. Evidence from these are summarised in the clinical GRADE evidence profile below (Table 51 to Table 56). See also the study selection flow chart in Appendix B, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

In the previous guideline, CG48, there are recommendations on the use of ACE inhibitors in people who had an MI with LV dysfunction (LVSD) or normal (preserved) LV function. The recommendations stated that early after an MI all people should be offered an ACE inhibitor. Also after an MI, it is recommended that all people 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.

The recommendations in the previous guideline, CG48, on the clinical effectiveness of ACE inhibitors were derived from a meta-analysis from NICE clinical guideline A (2001) "Prophylaxis for patients who have experienced a myocardial infarction"[310] which looked at the effectiveness of ACE inhibitors in people with unselected LV function and people with LVSD. Papers from this meta-analysis were included in this review if they met the inclusion criteria. Other studies were excluded because they were not published in English, used an ACE inhibitor not currently licensed in the UK or because they treated people acutely with ACE inhibitors intravenously.[8,22,206,389,402,456] All other 18 papers were included in this review.

Recommendations in CG48 on the long-term effectiveness of ACE inhibitors in people who had an MI with preserved left ventricular function were derived from a systematic review.[19] Of the 6 studies included, 2 were included in the current review.[146,476,476] Four were excluded as they used an indirect population with no subgroup analysis, an unlicensed ACE inhibitor or it was not possible to extract data.[65,261,325,365] For the purposes of the current review, people with preserved ventricular function are referred to as people without left ventricular dysfunction.

For people who had an MI with LVSD, all papers from CG48 were included in this review, except for 1 that was not published in English and 1 which was a long-term follow-up of people who were no longer on ACE inhibitors.[72,456]Three new papers on people with LVSD were included in this review.[359,409,416]

Update 2013

Unlike CG48, this review isolates the long-term effects of ACE inhibitors by presenting the results in distinct time periods. For instance, isolating mortality rates between 0 to 6 months, 6 months to 12 months after the MI and not just over the entire 12 month period, with the aim of identifying whether the benefit of ACE inhibitors varied over time. This data were only available for people who had an MI who have unselected LV function (that is, where the population includes a range of left ventricular ejection fractions, or those with and without LVSD). As a result, the long-term effectiveness of ACE inhibitors was mostly addressed by comparing the outcomes from short-term follow-up papers (6 months of treatment), with long term follow-up papers (more than 2 years of treatment). An important limitation of this approach is that the populations in the different subgroups may not be directly comparable.

For the remainder of the data, if papers provided data at different time points, only 1 set of data was presented and always the longest follow-up time period was presented to avoid double-counting.

Heterogeneity was detected in 4 outcomes; however none of the subgroups could explain this heterogeneity. In these cases, the results are shown as random effects instead of fixed effects.

Data on people who had undergone revascularisation was extracted from a sub-group analysis of people who had an MI with normal LV function who were a subgroup of a larger trial (EUROPA).[147,148] Only 1 other paper included people who had undergone PCI, 26%, but the study population was too small to extract any reliable data.[230]

7.3.2.2 People who have had an MI in the past

Four trials matching the inclusion criteria (see Table 49).[146,148,417,478] were identified on the clinical effectiveness of ACE inhibitor therapy in people who have had an MI in the past.

No studies were found using a direct study design (that is, trials comparing the effectiveness of the same ACE inhibitor given for different durations (6 months versus 12 months)) to identify the optimal duration of ACE inhibitor therapy in people who have had an MI in the past. Therefore, the review used the 4 trials found earlier comparing ACE inhibitors versus placebo and observed their long-term effectiveness. Evidence from these are summarised in the clinical GRADE evidence profile below (Table 51 to Table 56). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

For this review, the outcomes are separated as to whether or not the people had LV dysfunction and/or heart failure. Only 1 study considered separately people with heart failure and those with asymptomatic LVSD[417] while the other 3 included people without heart failure.[146,148,478]

Two papers are from the same trial, EUROPA, and the data presented in this review are from a subgroup analysis of people who had an MI at some point in the past (n=7910).[146,148] The exception to this was adverse events, where the numbers from the larger trial (that included people with a range of cardiovascular disease) were used since it was felt that adverse events are unlikely to vary with the precise clinical presentation within the trial population.[146,147] From the HOPE trial, only data on people who had an MI at some point in the past was included in this review.[12]

Update 2013

The previous guideline, CG48, included recommendations on ACE inhibitors for people who had an MI in the past which vary depending on whether the person has heart failure or LV dysfunction. It states that "in people with an MI in the past (more than 1 year ago) and with heart failure and 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 people with heart failure and left ventricular systolic dysfunction". Also,"in people with an MI in the past with heart failure and with preserved LV function, ACE inhibitor treatment should be offered and the dose titrated upwards, as tolerated, to the effective clinical dose".

A study by Pfeffer et al. was used in the previous guideline, CG48, for this review question. However it was excluded from this analysis because it enrolled people at a mean of 20 days from the onset of MI who for the purposes of this review were considered a sub-acute MI population (that is, who were initiated with treatment between 72 hours and 12 months after the onset of symptoms).[358,359]

Update 2013

Table 49: Summary of included studies

- MI (less than 72 hours after the onset of symptoms) and LVSD
- MI (less than 72 hours after the onset of symptoms) and unselected LV function
- MI (72 hours – less than 12 months after the onset of symptoms) and LVSD
- MI (72 hours – less than 12 months after the onset of symptoms) and without LVSD
- MI (72 hours – less than 12 months after the onset of symptoms) and unselected LV function
- MI in the past (more than 12 months) and LVSD
- MI in the past (more than 12 months) and without LVSD

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
MI (less than 72 hours after the onset of symptoms) and LVSD					
1.	Galcera-Tomas 1993 [158]	Captopril 3x25mg/day versus placebo	MI (less than 24 hours since the onset of symptoms) LVSD n=43	• All-cause mortality	One group had no LV dysfunction.
	CG48	14 days	Thrombolytic therapy = 77%		
2.	Pfeffer 1992[357,359] SAVE	Captopril 3x25mg/day versus placebo	MI (less than 3 days since the onset of symptoms) LVSD (EF less than 40%) n=2,231	• Death • CV death • Sudden death • Reinfarction (fatal and non-fatal) • Hospitalisation(due to heart failure)	-
	CG48	Mean 42 months	Thrombolytic= 33% Catheterization= 55% Percutaneous transluminal coronary		

Update 2013

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
			angioplasty (PTCA) = 17%		
3.	Sharpe 1991[409,410]	Captopril 2x50mg/day versus placebo	MI (24-48 hours since the onset of symptoms) LVSD (p<0.001 versus normal EF) n=100	• Sudden death • Reinfarction • Hypotension	The review by Abdulla[14,14] categorised LVSD as LVEF less than 45%.
	CG48	3 months	Thrombolytic = 72%		
MI (less than 72 hours after the onset of symptoms) and unselected LV function					
1.	Kinga 1994 [229] CATS	Captopril 25mg/day versus placebo	MI (less than 6 hours since the onset of symptoms) Unselected LV function n=298	• Hypotension • All-cause mortality • Revascularisation • Reinfarction	The review by Abdulla[14,14] categorised LVSD as LVEF over 45%.
	CG48	3 months	Thrombolysis 100%		
2.	CCS 1995 [11] CCS	Captopril 3x12mg/day versus placebo	MI (less than 72 hours since the onset of symptoms) Unselected LV function n=13,634	• All-cause mortality • Hypotension • Hypokalaemia	-
	CG48	4 weeks	Unclear		
3.	Dipasquale 1994[123]	Captopril 3x25mg/day versus placebo	STEMI (less than 4 hours since the onset of symptoms) n=87	• All-cause mortality • Revascularisation	-
	New	30 months	Thrombolysis= 100%		
4.	Dipasquale 1997[125]	Captopril 3x25mg/day	MI (less than 72 hours since the onset of	• All-cause mortality	-

Update 2013

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
		versus placebo	symptoms) Unselected LV function		
	New	10 days	n=30		
5.	Kleber 1997 [230] ECCE	Captopril 69mg/day versus placebo	MI (24 to 72 hours since the onset of symptoms) Unselected LV function n=208	• All-cause mortality • Sudden death • Reinfarction (fatal) • Hypotension • Adverse event	-
	CG48	4 weeks	Thrombolysis: 63% PTCA = 30% CABG = 10%		
6.	FAMIS[64,64] FAMIS	Fosinopril 20mg/day versus placebo	MI (less than 9 hours since the onset of symptoms) Unselected LV function n=285	• All-cause mortality (3months, 2 years) • Reinfarction • Revascularisation (PTCA, CABG) • Adverse events • Hyperkalaemia	The review by Abdulla[14,14] categorised LVSD as LVEF over 45%.
	New	3 months, 2 years	Thrombolysis Reperfused: 72% Not reperfused: 28%		
7.	French 1999[153,153]	Captopril 3x50mg/day versus placebo	MI (less than 72 hours since the onset of symptoms) Unselected LV function	• All-cause mortality (30 days) • Sudden death (30 days) • Reinfarction (30	-

Update 2013

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
			n=493	days)	
	New	30 days	Thrombolysis, streptokinase 100%		
8.	GISSI-3-1994[178] GISSI-3	Lisinopril 10mg/day versus placebo	MI (less than 24 hours since the onset of symptoms) Unselected LV function n=19,394	• All-cause mortality • Reinfarction • Renal dysfunction • Stroke • Hypotension • Revascularisation (CABG + PTCA)	-
	CG48	6 weeks	Thrombolysis (fibrinolytic) = 72%		
9.	Hargreaves 1992[186]	Captopril 3x12.5mg/day versus isorbide monontrate3x20mg/day versus placebo	MI (less than 24 hours since the onset of symptoms) Unselected LV function n=72	• All-cause mortality • Reinfarction • Hypotension	-
	New	28 days	Thrombolysis = 85%		
10.	Hussain 2010 [199,199]	Captopril 3x 12.5-25mg/day versus conventional therapy	MI (less than 72 hours since the onset of symptoms) Unselected LV function n=100	• All-cause mortality	-
	New	1 month (in hospital)	Thrombolysis = 100%		
11.	Flather[141,141] ISIS-4 PILOT	Captopril 37.5 – 100mg/day versus placebo	MI (less than 36 hours since the onset of symptoms) Unclear LV function	• All-cause mortality • Reinfarction • Adverse events	The study was a three-way and 2x2 study.

Update 2013

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
			n=741	• Hypotension	Combined results were given for ACE inhibitors versus placebo.
	CG48	In hospital (unclear)	-		
12.	ISIS-4 1995[204] ISIS-4	Captopril 2x 50mg/day versus placebo	MI (less than 24 hours since the onset of symptoms) Unselected LV function n=58,050	• All-cause mortality (5 weeks, 6 months, 12 months) • Stroke • Reinfarction • Dizziness • Hypotension	-
	CG48	5 weeks, 6 months, 12 months	Fibrinolytic therapy = 79%		
13.	Latini 1994 [245,245] GISSI-3PILOT	Lisinopril 1x10mg/day versus placebo	MI (less than 24 hours since the onset of symptoms) Unselected LV function n=871	• All-cause mortality • Hypotension	-
	CG48	6 weeks	Recommended thrombolysis to all.		
14.	Kongstad Rasmussen 1988 [234]	Ramipril 2x2.5mg/day or 2x1.25mg/day versus placebo	MI (less than 72 hours since the onset of symptoms) and clinical evidence of HF Unselected LV function n=48	• All-cause mortality • Reinfarction • Percutaneous transluminal coronary angioplasty	-
	New	6 months	Thrombolytic = 48%		
15.	Li Cai-Yi 2001[258]	Ramipril (dose NA) versus placebo	MI (less than 72 hours since the onset of symptoms)	• All-cause mortality	-

Update 2013

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
			Unselected LV function n=98		
	CG48		Unclear		
16.	Pfeffer 1997[358,359] HEART	Ramipril 10mg/day (full dose) versus placebo (group I)	MI (less than 24 hours since the onset of symptoms) Unselected LV function n=236	• All-cause mortality • Myocardial infarction • Stroke • Revascularisation • Hypotension	The trial was stopped early because results from GISSI-3 and ISIS-4 showed substantial portion of lives are saved within the first several days of an MI.
	CG48	14 days	Thrombolytic = 73% PTCA = 22%		
17.	PRACTICAL 1994[149] PRACTICAL	Captopril 3x25 mg/day or r enalapril 3x5mg/day versus placebo	MI (less than 24 hours since the onset of symptoms) Unselected LV function n=225	• All-cause mortality • CV death • Sudden death • Adverse events	-
	CG48	12 months	Thrombolytic therapy = 72%		
18.	Ray 1993[379,379]	Captopril 3x25 mg/day versus placebo	MI (less than 24 hours since the onset of symptoms) Unselected LV function n=99	• Reinfarction • Revascularisation (CABG) • Hypotension • Cough	-
	CG48	12 months	No thrombolytic therapy = 0%		
19.	Wagner 2002[459,459]	Ramipril 2.5mg versus	MI (less than 72 hours since the onset of	• All-cause mortality	-

Update 2013

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
		placebo	symptoms) Unclear n=99	• Hypotension	
	New	12 hours	Thrombolysis 100%		
MI (72 hours – 12 months since the onset of symptoms) and LVSD					
1.	Aire 1993 [15] AIRE	Ramipril 2x2.5mg/day or 2x1.25mg/day versus placebo	MI (mean 5 days since onset of symptoms) LVSD + clinical evidence of HF (excluded people with severe HF) n=1,986	• Death in hospital • Reinfarction • Stroke • Serious adverse events • Hypotension	-
	CG48	15 months	Unclear		
2.	Kober 1995 [231] TRACE	Trandolapril 4mg/day versus placebo	MI (mean 4.5 days, range 2-6 days since onset of symptoms) LVSD n=1,749	• All-cause mortality • CV death • Sudden death • Reinfarction (fatal plus non-fatal) (not used, used 10 year data) • Cough • Hypotension • Renal dysfunction • Stroke	-
	CG48	24-50 months	Thrombolysis =45%		
3.	Gotzsche 1992 [170,170]	Captopril 2x25mg/day	MI (7 days since onset of symptoms)	• All-cause mortality	-

Update 2013

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
		versus placebo	LVSD (EF less than or equal to 45%) n=58	• Reinfarction • Revascularisation	
	CG48	6 months	Unclear		
4.	Pfeffer 1988[359,359]	Captopril 3x50mg/day versus placebo	MI (mean 20 days, range 12 to 31 days since onset of symptoms) LVSD (EF less than or equal to 45%) n=59	• All-cause mortality	-
	New	1 year	PTCA or thrombolytic= 17%		
5.	Sharpe 1988 [409,409]	Captopril 3x25mg/day versus placebo	MI (72 hours – 12 months since onset of symptoms; stable in hospital) LVSD (EF less than or equal to 45%) n=40	• All-cause mortality • Reinfarction	It was unclear how many participants were in each group (n=60 in total with 3 groups). Data was only used from 2 groups.
	New	12 months	Unclear - medical		
6.	Sogaard 1993 [416]	Captopril 2x 12.5mg/day versus placebo	MI (7 days since onset of symptoms) LVSD n=64	• All-cause mortality • Revascularisation	75% of participants were on beta-blockers as background medication (metoprolol).
	New	180 days	Medical treatment (excluded CABG)		
MI (72 hours – 12 months since the onset of symptoms) and without LVSD					
1.	Ferrari 2006[138,138]	Perindopril 8mg/day versus placebo	MI (11 days since the onset of symptoms) Without LVSD	• All-cause mortality	-

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	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
	PREAMI		n=1,252	• Hospitalisation • Cough	
	New	12 months	Medical therapy (excluded PCI, CABG)		
MI (72 hours – 12 months since the onset of symptoms) and unselected LV function					
1.	Wu 1997 [466,467] BEIJING	Enalapril 10mg/tab versus placebo	MI (2-4 weeks since the onset of symptoms) Unselected LV function n=721	• Sudden death • Cardiac (HF) deaths	-
	CG48	19 months	Unclear - medical		
MI in the past (over 12 months ago) with LVSD and/or heart failure					
1.	Yusuf 1992[417] SOLVD	Enalapril 20mg/day versus placebo	History of MI (80%) People with HF LVSD (CG48) n=4,228 All-cause mortality data on people without CHF n=3150	• All-cause mortality • CV mortality • Stroke • Reinfarction (fatal) • Hospitalisations • Adverse events • Dizziness	-
	CG48	37.4 months	Unclear – only history of MI		
MI in the past (over 12 months ago) and without LVSD and/or heart failure					
1.	Fox 2003[146,147] EUROPA	Perindopril 1x 8mg/day versus placebo	History of MI (64%) (over 3months ago) Evidence of CAD (61%), coronary revascularisation (55%). Without evidence of HF. n=12,218	• All-cause mortality • Cardiac mortality • Reinfarction (fatal and non-fatal) • Stroke	-

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	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
			Subgroup analysis of previous MI n=7,910	• Revascularisation • Adverse events • Hypotension • Renal dysfunction • Composite outcome: CV death, non-fatal MI, cardiac arrest with successful resuscitation.	
	CG48	4.2 years	Mixed population so no standard therapy		
2.	Fox 2007A(SUBGROUP EUROPA)[147,148]	Perindopril 1x 8mg/day versus placebo	Subgroup analysis of people who had undergone revascularisation and had an MI (more than 3months ago). Without HF n=3,657	• Reinfarction (fatal and non-fatal)	-
	New data	4.2 years	100% revascularisation PCI = 53% CABG = 53%		
3.	YUSUF 2000[472,476] HOPE	Ramipril (10mg/day) versus placebo	History of MI (52%) Evidence of vascular disease or diabetes Without HF or low EF <40% n=9,297 Subgroup analysis of people who had a previous MI (100%) but no data could be extracted. Approximately RR 0.78 (0.69 to	• All-cause mortality • Cardiovascular mortality • Reinfarction • Stroke • Hospitalisation for	-

	Study Included in CG48 or new to update	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
			0.88) for CV death, MI, stroke n=4,892	HF • Revascularisation • Hypotension • Adverse events • No raw data for composite outcome: CV death, MI, stroke. Estimated from figure.	
	CG48	5 years	Unclear – only history of MI History of PCTA = 18% History of CABG = 26%		

Table 50: Summary of included studies – people who have been revascularised and treated with ACE inhibitors or placebo

	Study CG48 or new	Intervention/comparison Duration	Population Acute management	Outcomes reported	Comments
1.	Fox 2007A(SUBGROUP EUROPA)[147,148]	Perindopril 1x 8mg/day versus placebo	Subgroup analysis of people who had undergone revascularisation and had an MI (more than 3months ago) Without HF n=3,657	• Reinfarction (fatal and non-fatal)	Some participants had an MI at some point the past, so were not treated acutely.
	New data	4.2 years	100% Revascularisation PCI = 53% CABG = 53%		

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Table 51: GRADE profile: ACE inhibitor versus placebo(people who had an MI with LVSD)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality[15,158,170,231,357,359,409,416,417]												
9	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1018/5239 (19.4%)	1205/5219 (23.1%)	RR 0.84 (0.78 to 0.90)	37 fewer per 1000 (from 23 fewer to 51 fewer)	MODERATE	CRITICAL
All-cause mortality - 0 to 6 months[158,170,416]												
3	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	None	3/83 (3.6%)	3/82 (3.7%)	RR 1 (0.23 to 4.31)	0 fewer per 1000 (from 28 fewer to 121 more)	VERY LOW	CRITICAL
All-cause mortality - 0 to 12months[359,409]												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	None	0/50 (0%)	2/49 (4.1%)	RR 0.33 (0.04 to 3.05)	27 fewer per 1000 (from 39 fewer to 84 more)	VERY LOW	CRITICAL
All-cause mortality - 0 to 12 months[15,231,357,417]												
4	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1015/5106 (19.9%)	1200/5088 (23.6%)	RR 0.84 (0.78 to 0.91)	38 fewer per 1000 (from 24 fewer to 52 fewer)	MODERATE	CRITICAL
Cardiac mortality - 0 to 12months[231,357,417]												
3	Randomised trials	Serious[a]	Very serious[d]	No serious indirectness	Serious[e]	None	609/4102 (14.8%)	820/4106 (20%)	RR 0.74 (0.68 to 0.82)	52 fewer per 1000 (from 36 fewer to 64 fewer)	VERY LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Sudden death[231,357,410]												
3	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[e]	None	213/2041 (10.4%)	260/2039 (12.8%)	RR 0.82 (0.69 to 0.97)	23 fewer per 1000 (from 4 fewer to 40 fewer)	LOW	CRITICAL
Sudden death - 0 to 6 months[409,410]												
1	Randomised trial	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	None	3/50 (6%)	2/50 (4%)	RR 1.5 (0.26 to 8.6)	20 more per 1000 (from 30 fewer to 304 more)	VERY LOW	CRITICAL
Sudden death - 0 to 12 months[231,357]												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[e]	None	210/1991 (10.5%)	258/1989 (13%)	RR 0.81 (0.69 to 0.96)	25 fewer per 1000 (from 5 fewer to 40 fewer)	LOW	CRITICAL
Revascularisation - 0 to 6 months[170,416]												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	None	3/62 (4.8%)	2/60 (3.3%)	RR 1.46 (0.25 to 8.38)	15 more per 1000 (from 25 fewer to 246 more)	VERY LOW	IMPORTANT
Reinfarction[15,170,231,357,409,410,417]												
7	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	362/5206 (7%)	431/5186 (8.3%)	RR 0.84 (0.73 to 0.95)	13 fewer per 1000 (from 4 fewer to 22 fewer)	MODERATE	IMPORTANT
Reinfarction - 0 to 6 months [170,410]												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	None	2/80 (2.5%)	6/78 (7.7%)	RR 0.32 (0.07 to 1.56)	52 fewer per 1000 (from 72 fewer to 43 more)	VERY LOW	IMPORTANT
Reinfarction - 0 to 12months[409,409]												
1	Randomised trial	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	None	2/20 (10%)	2/20 (10%)	RR 1 (0.16 to 6.42)	0 fewer per 1000 (from 84 fewer to 542 more)	VERY LOW	IMPORTANT
Reinfarction - 0 to 12 months[15,231,357,417]												
4	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	358/5106 (7%)	431/5186 (8.3%)	RR 0.84 (0.73 to 0.95)	13 fewer per 1000 (from 4 fewer to 22 fewer)	MODERATE	IMPORTANT
Rehospitalisation – 0 to 12 months[357,417]												
2	Randomised trials	Serious[b]	Serious[f]	No serious indirectness	No serious imprecision	None	396/3226 (12.3%)	567/3233 (17.5%)	RR 0.70 (0.62 to 0.79)	53 fewer per 1000 (from 37 fewer to 67 fewer)	LOW	IMPORTANT
Stroke - 0 to 12 months[15,231,417]												
3	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	86/3991 (2.2%)	80/3972 (2%)	RR 1.07 (0.79 to 1.44)	1 more per 1000 (from 4 fewer to 9 more)	MODERATE	IMPORTANT
Adverse events [15,417]												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1866/3115 (59.9%)	1747/3099(56.4%)	RR 1.07 (1.03 to 1.11)	39 more per 1000 (from 17	MODERATE	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										more to 62 more)		
Renal dysfunction[15,231]												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[g]	None	135/1880 (7.2%)	106/1855 (5.7%)	RR 1.27 (1 to 1.61)	15 more per 1000 (from 0 more to 35 more)	LOW	IMPORTANT
Hypotension[15,231,410]												
3	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	315/1930 (16.3%)	216/1905 (11.3%)	RR 1.45 (1.24 to 1.69)	51 more per 1000 (from 27 more to 78 more)	MODERATE	IMPORTANT
Dizziness/fainting[357,417]												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	999/3226 (31%)	855/3233 (26.4%)	RR 1.17 (1.09 to 1.26)	45 more per 1000 (from 24 more to 69 more)	MODERATE	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) The majority of studies did not provide clear methods of randomisation or information on whether allocation concealment was performed. They are mostly published prior to 1995 so allocation concealment is less likely to be reported even if it was performed.
(b) There were unclear methods of randomisation or whether the authors performed allocation concealment. The studies are mostly published prior to 1995 and so allocation concealment is less likely to be reported even if it was performed.
(c) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(d) Heterogeneity detected at I^2=90%, p<0.0001.
(e) 95% confidence intervals crossed 1 MID (0.75).
(f) Heterogeneity was detected at I2=66%, p<0.09. However, it is not clear why since all studies fell on the side of favouring ACE inhibitors.

(g) 95% confidence intervals crossed 1 MID (1.25).

Table 52: GRADE profile: ACE inhibitor versus placebo (people who had an MI without LVSD or heart failure)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality – 0 to 12 months[138,138]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	40/631 (6.3%)	37/621 (6%)	RR 1.06 (0.69 to 1.64)	4 more per 1000 (from 18 fewer to 38 more)	VERY LOW	CRITICAL
Reinfarction(fatal+non-fatal) - 0 to 12 months [147,148]												
1	Randomised trial	Serious[c]	No serious inconsistency	Serious indirectness[g]	Serious[d]	None	177/3340 (5.3%)	212/3369 (6.3%)	RR 0.84 (0.69 to 1.02)	10 fewer per 1000 (from 20 fewer to 1 more)	VERY LOW	IMPORTANT
Rehospitalisation[138,138]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	22/631 (3.5%)	30/621 (4.8%)	RR 0.72 (0.42 to 1.24)	14 fewer per 1000 (from 28 fewer to 12 more)	LOW	IMPORTANT
Adverse events[146,147]												
1	Randomised trial	Serious[c]	No serious inconsistency	Serious indirectness[g]	No serious imprecision	None	144/6100 (2.4%)	80/6108 (1.3%)	RR 1.8 (1.37 to 2.36)	10 more per 1000 (from 5 more to 18 more)	LOW	IMPORTANT
Cardiovascular death, non-fatal MI, cardiac arrest - over 12 months[146,147]												
1	Randomised trial	Serious[f]	No serious inconsistency	Serious[d]	Serious[e]	None	353/3962 (8.9%)	446/3948 (11.3%)	RR 0.79 (0.69 to 0.9)	24 fewer per 1000 (from 11 fewer to 35 fewer)	VERY LOW	IMPORTANT
Cardiovascular death, MI, stroke (estimate) - over 12 months[472,476]												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trial	Serious[e, f]	No serious inconsistency	Serious indirectness[g]	Serious[d]	None	393/2410 (16.3%)	519/2482 (20.9%)	RR 0.78 (0.69 to 0.88)	46 fewer per 1000 (from 25 fewer to 65 fewer)	VERY LOW	IMPORTANT
Cardiac mortality[146,476]												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[h]	No serious imprecision	None	497/10755 (4.6%)	626/10760 (5.8%)	RR 0.79 (0.71 to 0.89)	12 fewer per 1000 (from 6 fewer to 17 fewer)	MODERATE	CRITICAL
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Stroke[472,476]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	Serious[h]	Serious[d]	None	156/4645 (3.4%)	226/4652 (4.9%)	RR 0.69 (0.57 to 0.84)	15 fewer per 1000 (from 8 fewer to 21 fewer)	LOW	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) There were unclear methods of allocation concealment.
(b) 95% confidence interval crossed 2 MIDs (0.75 and 1.25).
(c) There were unclear methods of randomisation or allocation concealment. The study was a subgroup analysis from a larger sample, therefore this was not a pre-determined subgroup so there may be a risk of reporting bias.
(d) 95% confidence interval crossed 1 MID (0.75).
(e) There were unclear methods of randomisation or allocation concealment. The study was a subgroup analysis from a larger sample therefore this was not a pre-determined subgroup so there may be a risk of reporting bias. Furthermore, it is a composite outcome which also carries a risk of reporting bia,s that is authors may look for a combination of outcomes that produce a positive effect.

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(f) There were unclear methods of randomisation or allocation concealment. The study was a subgroup analysis from a larger sample, therefore this was not a pre-determined subgroup so there may be a risk of reporting bias. Furthermore, it is a composite outcome which also carries a risk of reporting bias that is authors may look for a combination of outcomes that produce a positive effect. The numbers also had to be estimated from a figure.
(g) People were not treated acutely and participants had an MI at some point in the past.
(h) The study used an indirect population, with less than 75% people who have had an MI.

Table 53: GRADE profile: ACE inhibitor versus placebo (people who have had an MI with unselected LV function)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality(unselected LV function)[11,64,122,141,149,153,178,186,199,204,229,230,234,245,258,358,379,459]												
18	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	3457/47254 (7.3%)	3775/47213 (8%)	RR 0.91 (0.87 to 0.96)	7 fewer per 1000 (from 3 fewer to 10 fewer)	MODERATE	CRITICAL
All-cause mortality(unselected LV function)- 0 to 6 months)[11,122,141,153,178,186,199,204,229,230,234,245,258,358,459]												
15	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	3418/46924 (7.3%)	3734/46954 (8%)	RR 0.92 (0.88 to 0.96)	6 fewer per 1000 (from 3 fewer to 10 fewer)	MODERATE	CRITICAL
All-cause mortality(unselected LV function) - 0 to 12 months[149,379]												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	20/199 (10.1%)	22/125 (17.6%)	RR 0.62 (0.36 to 1.08)	67 fewer per 1000 (from 113 fewer to 14 more)	LOW	CRITICAL
All-cause mortality(unselected LV function) - 0 to 12 months[64,64]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	None	19/131 (14.5%)	19/134 (14.2%)	RR 1.02 (0.57 to 1.84)	3 more per 1000 (from 61 fewer to 119 more)	VERY LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Sudden death(unselected LV function)[149,153,230,379,466]												
5	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[e]	None	19/1045 (1.8%)	18/926 (1.9%)	RR 0.84 (0.45 to 1.58)	3 fewer per 1000 (from 11 fewer to 11 more)	VERY LOW	CRITICAL
Sudden death(unselected LV function) - 0 to 6 months[153,230]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[e]	None	1/347 (0.29%)	1/354 (0.28%)	RR 1.01 (0.14 to 7.21)	0 more per 1000 (from 2 fewer to 18 more)	VERY LOW	CRITICAL
Sudden death(unselected LV function) - 0 to 12 months[149,379,466]												
3	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[e]	None	14/548 (2.6%)	16/497 (3.2%)	RR 0.73 (0.36 to 1.48)	9 fewer per 1000 (from 21 fewer to 15 more)	VERY LOW	CRITICAL
Cardiovascular mortality(unselected LV function) - 0 to 12months[149,466]												
2	Randomised trials	Serious[f]	No serious inconsistency	No serious indirectness	Serious[c]	None	14/499 (2.8%)	20/447 (4.5%)	RR 0.47 (0.24 to 0.9)	24 fewer per 1000 (from 4 fewer to 34 fewer)	LOW	CRITICAL
Reinfarction (unselected LV function)[64,141,153,178,186,204,204,229,230,234,358,379]												
11	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1527/39689 (3.8%)	1447/39 718 (3.6%)	RR 1.06 (0.98 to 1.13)	2 more per 1000 (from 1 fewer to 5 more)	MODERATE	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reinfarction(unselected LV function) - 0 to 6 months[141,153,178,186,204,229,230,234,358]												
9	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1514/39509 (3.8%)	1437/39534 (3.6%)	RR 1.05 (0.98 to 1.13)	2 more per 1000 (from 1 fewer to 5 more)	MODERATE	IMPORTANT
Reinfarction(unselected LV function) - 0 to 12 months[379,379]												
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[e]	None	3/49 (6.1%)	1/50 (2%)	RR 3.06 (0.33 to 28.43)	41 more per 1000 (from 13 fewer to 549 more)	VERY LOW	IMPORTANT
Reinfarction (unselected LV function) - 0 to over 12 months[64,64]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	None	10/131 (7.6%)	9/134 (6.7%)	RR 1.14 (0.48 to 2.71)	9 more per 1000 (from 35 fewer to 115 more)	VERY LOW	IMPORTANT
Stroke(unselected LV function) - 0 to 6 months[142,178,358]												
3	Randomised trials	Serious[g]	No serious inconsistency	No serious indirectness	No serious imprecision[h]	None	367/38582 (0.95%)	336/38599 (0.87%)	RR 1.09 (0.94 to 1.27)	1 more per 1000 (from 1 fewer to 2 more)	MODERATE	IMPORTANT
Revacularisation(unselected LV function)[64,178,229,234,358,379]												
6	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[h]	None	379/9908 (3.8%)	345/9935 (3.5%)	RR 1.1 (0.96 to 1.27)	3 more per 1000 (from 1 fewer to 9 more)	MODERATE	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Revacularisation(unselected LV function) - 0 to 6 months[178,229,234,358]												
4	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[h]	None	363/9728 (3.7%)	333/9751 (3.4%)	RR 1.09 (0.94 to 1.26)	3 more per 1000 (from 2 fewer to 9 more)	MODERATE	IMPORTANT
Revacularisation(unselected LV function) - 0 to 12 months[379,379]												
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[e]	None	1/49 (2%)	1/50 (2%)	RR 1.02 (0.07 to 15.86)	0 more per 1000 (from 19 fewer to 297 more)	VERY LOW	IMPORTANT
Revacularisation(unselected LV function) - 0 to over 12 months[64,64]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	None	15/131 (11.5%)	11/134 (8.2%)	RR 1.39 (0.67 to 2.92)	32 more per 1000 (from 27 fewer to 158 more)	VERY LOW	IMPORTANT
Adverse events(unselected LV function)[64,141,149,230]												
4	Randomised trials	Serious[i]	No serious inconsistency	No serious indirectness	Serious[j]	None	254/755 (33.6%)	198/684 (28.9%)	RR 1.22 (1.05 to 1.42)	64 more per 1000 (from 14 more to 122 more)	LOW	IMPORTANT
Renal dysfunction(unselected LV function)[141,178,186,204]												
4	Randomised trials	Serious[j]	No serious inconsistency	No serious indirectness	No serious imprecision	None	546/37869 (1.4%)	283/38889 (0.73%)	RR 1.97 (1.71 to 2.27)	7 more per 1000 (from 5 more to 9 more)	MODERATE	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Hyperkalaemia(unselected LV function)[11,64]												
2	Randomised trials	Serious[g]	No serious inconsistency	No serious indirectness	Serious[c]	None	60/6945 (0.86%)	70/6954 (1%)	RR 0.86 (0.61 to 1.21)	1 fewer per 1000 (from 4 fewer to 2 more)	LOW	IMPORTANT
Hypotension(unselected LV function)[141,149,178,186,204,229,230,245,379,459]												
10	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	7047/39803 (17.7%)	3915/39745 (9.9%)	RR 1.80 (1.73 to 1.87)	79 more per 1000 (from 72 more to 86 more)	MODERATE	IMPORTANT
Dizziness(unselected LV function)[149,204]												
2	Randomised trials	Serious[i]	No serious inconsistency	No serious indirectness	Serious[j]	None	184/29178 (0.63%)	116/29097 (0.4%)	RR 1.48 (1.17 to 1.87)	2 more per 1000 (from 1 more to 3 more)	LOW	IMPORTANT
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) The majority of studies provided unclear methods of randomisation or it was unclear whether the authors performed allocation concealment. The studies were mostly published prior to 1995 so allocation concealment was less likely to be reported even if it was performed.
(b) The majority of studies provided unclear methods of randomisation and it was not clear whether the authors performed allocation concealment. The studies were mostly published prior to 1995 so allocation concealment is less likely to be reported even if it was performed. There were considerable dropout rates in 2 of the 3 studies (approximately 20%).
(c) 95% confidence intervals crossed 1 MID (0.75).
(d) There were unclear methods of randomisation or allocation concealment. Since it is published prior to 1995, allocation concealment is less likely to be reported even if it was performed.

(e) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(f) There were unclear methods of randomisation or if they performed allocation concealment. The studies are mostly published prior to 1995 therefore it is unlikely that allocation concealment was reported even if it was performed. There are considerable dropout rates in PRACTICAL study[149] (approximately 20%).
(g) There were unclear methods of randomisation and allocation concealment. The studies are mostly published prior to 1995 therefore it is unlikely that allocation concealment was reported even if it was performed.
(h) The confidence intervals just crossed 1 MID (1.25) but within an acceptable range.
(i) It was unclear whether the authors performed allocation concealment. The larger studies that contributed more to the overall meta-analysis performed adequate randomisation methods.
(j) 95% confidence interval crossed 1 MID (1.25).

Table 54: GRADE profile: ACE inhibitor versus placebo (people who have had an MI with unselected LV function)(distinct follow-up time periods)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - 0 to 5 weeks[11,122,141,153,186,199,204,230,358,459]												
10	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2741/36848 (7.4%)	2934/38630 (7.6%)	RR 0.94 (0.89 to 0.98)	5 fewer per 1000 (from 2 fewer to 8 fewer)	MODERATE	CRITICAL
All-cause mortality - 0 to 6 months[64,122,141,149,178,229,234,245,258]												
9	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	718/10750 (6.7%)	835/10726 (7.8%)	RR 0.86 (0.78 to 0.95)	11 fewer per 1000 (from 4 fewer to 17 fewer)	MODERATE	CRITICAL
All-cause mortality -6 to 12 months[149]												
1	Randomised trial	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	2/150 (1.3%)	2/75 (2.7%)	RR 0.2 (0.04 to 1.01)	21 fewer per 1000 (from 26 fewer to 0 more)	LOW	CRITICAL
Sudden death - 0 to 6 months[149,153,230]												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	5/497 (1%)	2/429 (0.47%	RR 1.41 (0.33 to	2 more per 1000 (from	VERY LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
									5.95)	3 fewer to 23 more)		
Sudden death - over 6 to 12 months [149]												
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[d]	None	1/150 (0.67%)	3/75 (4%)	RR 0.17 (0.02 to 1.58)	33 fewer per 1000 (from 39 fewer to 23 more)	VERY LOW	CRITICAL
Cardiac mortality – 0 to 6 months[149]												
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[d]	None	8/150 (5.3%)	7/76 (9.3%)	RR 0.57 (0.22 to 1.52)	40 fewer per 1000 (from 73 fewer to 49more)	VERY LOW	CRITICAL
Cardiac mortality - 6 to 12 months[149]												
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Serious[c]	None	1/150 (0.67%)	5/75 (6.7%)	RR 0.1 (0.01 to 0.84)	60 fewer per 1000 (from 11 fewer to 66 fewer)	LOW	CRITICAL
Reinfarction – 0 to 3 months [64,64]												
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[d]	None	7/131 (5.3%)	3/134 (2.2%)	RR 2.39 (0.63 to 9.03)	31 more per 1000 (from 8 fewer to 180 more)	VERY LOW	IMPORTANT
Reinfarction –3 months to 2 years[64,64]												
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[d]	None	3/131 (2.3%)	5/134 (3.7%)	RR 0.61 (0.15 to 2.52)	15 fewer per 1000 (from 32 fewer to 57 more)	VERY LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Stroke												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) The majority of studies provided unclear methods of randomisation or allocation concealment. The studies are most published prior to 1995 and so allocation concealment is less likely to be reported even if it was performed.
(b) It was unclear whether the authors performed allocation concealment. The larger studies that contributed more to the overall meta-analysis performed adequate randomisation methods.
(c) 95% confidence intervals crossed 1 MID (0.75).
(d) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(e) There were unclear methods of randomisation and allocation concealment.
(f) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).

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Table 55: GRADE profile: ACE inhibitor versus placebo (people who have had MI in the past who have undergone revascularisation and without heart failure)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reinfarction (fatal plus non-fatal) - 0 to 12 months [147,148]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious indirectness[b]	Serious[c]	None	177/3340 (5.3%)	212/3369 (6.3%)	RR 0.84 (0.69 to 1.02)	10 fewer per 1000 (from 20 fewer to 1 more)	VERY LOW	IMPORTANT
All-cause mortality												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Cardiac mortality												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Stroke												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence	-	-	-	-	None	-	-	-	-	-	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
	available											
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) There were unclear methods of randomisation or allocation concealment. The study was a subgroup analysis from a larger sample and not a pre-determined subgroup so there may be a risk of reporting bias and of participants not being matched at baseline. In addition, the authors only reported on the outcome of reinfarction in people who had an MI and who had undergone PCI+CABG and treated with ACE inhibitors, thus there is another risk of reporting bias.
(b) People were not treated acutely. Had an MI at some point in the past. People either had PCI or CABG.
(c) 95% confidence interval crossed 1 MID (0.75).

Table 56: GRADE profile: ACE inhibitor versus placebo (people who have had an MI in the past, with or without LVSD or heart failure)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - with heart failure and LVSD[417]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	313/2111 (14.8%)	334/2117 (15.8%)	RR 0.94 (0.82 to 1.08)	9 fewer per 1000 (from 28 fewer to 13 more)	LOW	CRITICAL
Cardiac mortality -with heart failure and LVSD[417]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	265/2111 (12.6%)	298/2117 (14.1%)	RR 0.89 (0.76 to 1.04)	15 fewer per 1000 (from 34 fewer to 6 more)	LOW	CRITICAL
Rehospitalisation - with heart failure and LVSD[417]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	242/2111 (11.5%)	375/2117 (17.7%)	RR 0.65 (0.56 to 0.75)	62 fewer per 1000 (from 44 fewer to 78	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										fewer)		
Stroke- with heart failure and LVSD[417]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	10/2111 (0.47%)	13/2117 (0.61%)	RR 0.77 (0.34 to 1.76)	1 fewer per 1000 (from 4 fewer to 5 more)	VERY LOW	IMPORTANT
Reinfarction – with heart failure and LVSD[417]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	46/2111 (2.2%)	52/2117 (2.5%)	RR 0.89 (0.6 to 1.31)	3 fewer per 1000 (from 10 fewer to 8 more)	VERY LOW	IMPORTANT
Reinfarction - without heart failure[147,148]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[b]	Serious[e]	None	177/3340 (5.3%)	212/3369 (6.3%)	RR 0.84 (0.69 to 1.02)	10 fewer per 1000 (from 20 fewer to 1 more)	VERY LOW	IMPORTANT
Adverse events – with and without heart failure and LVSD[146,417]												
2	Randomised trials	Serious[a,d]	Serious[f]	Serious[b]	No serious imprecision	None	1748/8211 (21.3%)	1604/8225 (19.5%)	RR 1.09 (1.05 to 1.13)	18 more per 1000 (from 10 more to 25 more)	VERY LOW	IMPORTANT
Adverse events – with heart failure and LVSD[417]												
1	Randomised trial	Serious[g]	No serious inconsistency	Serious[b]	No serious imprecision	None	1604/2111 (76%)	1524/2117 (72%)	RR 1.06 (1.02 to 1.09)	43 more per 1000 (from 14 more to 65 more)	LOW	IMPORTANT
Adverse events - without heart failure or LVSD[146,147]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[a,g]	No serious imprecision	None	144/6100 (2.4%)	80/6108 (1.3%)	RR 1.8 (1.37 to 2.36)	10 more per 1000 (from 5 more to 18	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										more)		
Cardiac death, reinfarction, cardiac arrest – without heart failure or LVSD[146,147]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[b]	Serious[e]	None	353/3962 (8.9%)	446/3948 (11.3%)	RR 0.79 (0.69 to 0.9)	24 fewer per 1000 (from 11 fewer to 35 fewer)	VERY LOW	IMPORTANT
Cardiac death death, reinfarction, stroke - without heart failure or LVSD[472,476]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[b]	Serious[e]	None	393/2410 (16.3%)	519/2482 (20.9%)	RR 0.78 (0.69 to 0.88)	46 fewer per 1000 (from 25 fewer to 65 fewer)	VERY LOW	IMPORTANT
Dizziness or fainting-with heart failure and LVSD[417]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	967/2111 (45.8%)	830/2117 (39.2%)	RR 1.17 (1.09 to 1.25)	67 more per 1000 (from 35 more to 98 more)	LOW	IMPORTANT
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) In the SOLVD study[417], the placebo group had a high dropout rate of 45% compared with 8% in ACE inhibitor group because of adverse events. There were unclear methods of allocation concealment.
(b) It was unclear exactly how much time had passed since the MI.
(c) 95% confidence interval crossed 2 MIDs (0.75 and 1.25).

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(d) The results are a subgroup analysis, so it is unclear whether the participants were matched at baseline. There were also unclear methods of allocation concealment and it was not clear how much time had passed since the MI.
(e) 95% confidence interval crossed 1 MID (0.75).
(f) Heterogeneity detected, I^2 = 94%however this is eliminated when the data is separated into those with LVSD or without HF.
(g) This study included all participants from EUROPA study since adverse events are unlikely to be specific to MI.

7.3.2.3 Economic evidence

Published literature

No relevant economic evaluations comparing an ACE inhibitor with different durations of the same ACE inhibitor in people with or without an MI in the past were identified.

The previous guideline, CG48, included 10 studies comparing ACE inhibitors versus placebo in people after MI with LV systolic dysfunction or with heart failure.[23,100,136,187,249,268,272,286,398,447]

Two studies that compared ACE inhibitor versus placebo were identified in the new search.[67,380] These studies included people with coronary artery disease, with or without an MI.

Among the studies identified in the new search, one economic analysis was conducted in Poland and met the inclusion criteria but was selectively excluded (Redekop2008[380,380]) due to the inclusion of another paper (Briggs2007[67,67]) based on the same clinical study and of similar characteristics but from a UK perspective. The included paper is summarised in the economic evidence profile below (Table 57). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H. Among the studies identified in CG48, one of them was excluded because it is a study based on a non OECD country [23], and the rest were selectively excluded [100,136,187,249,268,286,398,447] due to the inclusion of another paper (Briggs2007[67,67]) that was more applicable. The study by Martinez et al [272,273]was a UK cost-effectiveness analysis but it reported the cost per life years gained instead of QALYs and the cost year used was 1993. Based on these limitations it was selectively excluded; however its results were in agreement with the conclusions of the study by Briggs et al (2007).[67,67]

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CG48 also included 5 studies comparing ACE inhibitors versus placebo in people after MI with preserved LV function.[27,30,53,264,413] They were all selectively excluded in this update as the original model developed for CG48 on this population was considered more applicable and with fewer limitations.

The selectively excluded papers are summarised in Appendix K, with reasons for exclusion given.

CG48 cost-effectiveness modelling

A model was developed as part of CG48 to examine the cost effectiveness of treatment with ACE inhibitors compared to placebo in people with normal left ventricular function.

This analysis is summarised in the economic evidence profile below (Table 57). The full methods and results from CG48 are presented in Appendix Q.

Table 57: Economic evidence profile: ACE inhibitors versus placebo

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects (QALYs)	Cost effectiveness (£/QALY)	Uncertainty
Briggs2007 [67,67] (UK) SUBGROUP A: people with a 29% risk of events over 5 years SUBGROUP B: people with a 14% risk of events over 5 years SUBGROUP C: people with an 8% risk of events over 5 years SUBGROUP D: people with a 7% risk of events over 5 years SUBGROUP E: people with a 3% risk of events over 5 years	Partially applicable (a)	Potentially serious limitations (b)	Markov state transition model. Time horizon = 50 years divided in cycles of 1 year. Probabilities of secondary cardiovascular events and relative treatment effects were estimated from risk equations based on the EUROPA study.[146,147]	SUBGROUP A: 390 SUBGROUP B: 346 SUBGROUP C: 478 SUBGROUP D: 443 SUBGROUP E: 499	SUBGROUP A: 0.104 SUBGROUP B: 0.054 SUBGROUP C: 0.049 SUBGROUP D: 0.031 SUBGROUP E: 0.016	SUBGROUP A: 3,729 SUBGROUP B: 6,408 SUBGROUP C: 9,700 SUBGROUP D: 14,163 SUBGROUP E: 31,195	The following assumptions were tested: length of treatment, protective effect of perindopril on those events subsequent to a first event, costs and quality of life. The model was robust to variations in all those areas. Probabilistic analysis: the probability that perindopril is cost effective at a willingness to pay of £20,000 per QALY gained: SUBGROUP A: 100% SUBGROUP B: 99% SUBGROUP C: 94% SUBGROUP D: 75% SUBGROUP E: 8%

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Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects (QALYs)	Cost effectiveness (£/QALY)	Uncertainty
CG48 Model on ACE inhibitors	Partially applicable (c)	Potentially serious limitation (d)	Markov model. Lifetime horizon.	65 year old male: 1,786 65 year old female: 1,911	65 year old male: 0.52 65 year old female: 0.52	65 year old male: 3,424 65 year old female: 3,707	One way sensitivity analyses were performed to assess the impact of key parameters in the results of the model including: quality of life loss due to side effects, health state utilities, cost of CVD events/health state costs, efficacy of ACE inhibitors treatment, relative risk of non-CVD death, age and sex. The model is sensitive to assumptions about loss of quality of life due to assumed treatment side effects.

(a) Changes in HRQoL not reported from patients and/or carers. Changes in HRQoL were not obtained from EQ-5D but from SF-36 converted into SF-6D.

(b) Estimates of resource use and relative treatment effects were extracted from one out of 40 trials included in the clinical review. Transition probabilities were estimated using risk equations that were based on a composite primary end point from the EUROPA trial. The same limitation in the EUROPA trial was identified in the clinical review. . The study was funded by Servier Laboratories, manufacturers of perindopril.

(c) It is unclear if changes in HRQoL (utilities) were obtained from a representative sample of the public.

(d) Assumptions based on expert opinion were needed about risk of non-CVD death in post MI population and the percentage of people that would have PCI or CABG. Unit costs were presented in 2005 prices.

7.3.2.4 Evidence statements

7.3.2.4.1 Clinical

People who have had an MI with LVSD

All-cause mortality

- Nine RCTs with 10,458 people who have had an MI, with LVSD, showed that ACE inhibitors reduce the risk of all-cause mortality compared with placebo [Moderate quality evidence].
- Three RCTs with 165 people who have had an MI, with LVSD, showed that up to 6 months of ACE inhibitors are equally effective as placebo on the risk of all-cause mortality but there was considerable uncertainty [Very low quality evidence].
- Two RCTs with 99 people who have had an MI, with LVSD, showed that up to 12 months of ACE inhibitors reduce the risk of all-cause mortality compared with placebo but there was considerable uncertainty [Very low quality evidence].
- Four RCTs with 10,194 people who have had an MI, with LVSD, showed that more than 12 months of ACE inhibitors reduce the risk of all-cause mortality compared with placebo [Moderate quality evidence].

Cardiac mortality

- Three RCTs with 8208 people who have had an MI, with LVSD, showed that ACE inhibitors reduce the risk of cardiac mortality compared with placebo but there was some uncertainty [Very low quality evidence].

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Sudden death

- Three RCTs with 4080 people who have had an MI, with LVSD, showed that ACE inhibitors reduce the risk of sudden death compared with placebo but there was some uncertainty [Low quality evidence].
- One RCT with 100 people who have had an MI, with LVSD, showed that up to 6 months of ACE inhibitors increase the risk of sudden death compared with placebo but there was considerable uncertainty [Very low quality evidence].
- Two RCTs with 3980 people who have had an MI, with LVSD, showed that up to 12 months of ACE inhibitors increase the risk of sudden death compared with placebo but there was some uncertainty [Low quality].

Revascularisation

- Two RCTs with 122 people who have had an MI,with LVSD, showed that up to 6 months of ACE inhibitors increase the risk of revascularisation compared with placebo but there was considerable uncertainty [Very low quality evidence].

Reinfarction

- Seven RCTs with 10,392 people who have had an MI, with LVSD, showed that ACE inhibitors reduce the risk of reinfarction compared with placebo [Moderate quality evidence].
- Two RCTs with 158 people who have had an MI, with LVSD, showed that up to 6 months of ACE inhibitors reduce the risk of reinfarction compared with placebo but there was considerable uncertainty [Very low quality evidence].

- One RCT with 50 people who have had an MI, with LVSD, showed that up to 12 months of ACE inhibitors are equally as effective as placebo on the risk of reinfarction but there was considerable uncertainty [Very low quality evidence].
- Four RCTS with 10,194 people who have had an MI, with LVSD, showed that up to 12 months of ACE inhibitors may reduce the risk of reinfarction compared with placebo [Moderate quality evidence].

Rehospitalisation

- Two RCTs with 6459 people who have had an MI with LVSD showed that up to 12 months of ACE inhibitors may reduce the risk of hospitalisation compared with placebo [Low quality evidence].

Stroke

- Three RCTs with 7963 people who have had an MI, with LVSD, showed that up to 12 months of ACE inhibitors are equally effective as placebo on the risk of stroke but there was some uncertainty [Moderate quality evidence].

Adverse events

- Two RCTs with 6214 people who have had an MI, with LVSD, showed that ACE inhibitors increase the risk of adverse events compared with placebo [Moderate quality evidence].
- Two RCTs with 3735 people who have had an MI, with LVSD, showed that ACE inhibitors increase the risk of renal dysfunction compared with placebo [Low quality evidence].
- Three RCTs with 3835 people who have had an MI, with LVSD, showed that ACE inhibitors increase the risk of hypotension compared with placebo [Moderate quality evidence].
- Two RCTs with 6459 people who have had an MI, with LVSD, showed that ACE inhibitors increase the risk of dizziness/fainting compared with placebo [Moderate quality evidence].

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Quality of life

- No evidence was identified on quality of life

<u>People who have had an MI without LVSD or heart failure</u>

- One RCT with 1252 people who have had an MI, without LVSD or heart failure, showed that ACE inhibitors are equally effective on the risk of all-cause mortality as placebo but there was considerable uncertainty [Very low quality evidence].
- One RCT with a subgroup analysis of 6709 people who have had an MI, without LVSD or heart failure, showed that 4.2 years of ACE inhibitors may reduce the risk of reinfarction compared with placebo but there was some uncertainty [Very low quality evidence].
- One RCT with 1252 people who have had an MI, without LVSD or heart failure, showed that up to 12 months of ACE inhibitors may reduce the risk of rehospitalisation compared with placebo but there was considerable uncertainty [Low quality evidence].
- One RCT with a subgroup analysis of 6948 people who have had an MI, without LVSD or heart failire, showed that up to 4.2 years of ACE inhibitors may reduce the risk of a composite outcome of cardiac mortality, cardiac arrest and MI compared with placebo but there was some uncertainty [Very low quality evidence].
- One RCT with a subgroup analysis of 4892 people who have had an MI, without LVSD or heart failure, showed that up to 5 years of ACE inhibitors may reduce the risk of a composite outcome of cardiac mortality, stroke and MI compared with placebo but there was some uncertainty [Very low quality evidence].

- One RCT with 12,208 people with coronary heart disease and no apparent heart failure showed ACE inhibitors increase the risk of adverse events compared with placebo [Low quality evidence].
- Two RCTs with 21,515 people who have had an MI, without LVSD or heart failure, showed that up to 5 years of ACE inhibitors may reduce the risk of cardiac mortality compared with placebo but there was some uncertainty [Moderate quality evidence].
- One RCT with 9297 people who have had an MI, without LVSD or heart failure, showed that up to 5 years of ACE inhibitors may reduce the risk of stroke compared with placebo but there was some uncertainty [Low quality evidence].
- No evidence was identified on revascularisation.
- No evidence was identified on quality of life

People who have had an MI with unselected LV function

All-cause mortality

- Eighteen RCTs with 94,467 people who have had an MI, with unselected LV function, showed that ACE inhibitors may reduce the risk of all-cause mortality compared with placebo [Moderate quality evidence].
- Fifteen RCTs with 93,878 people who have had an MI, with unselected LV function, showed that up to 6 months of ACE inhibitors may reduce the risk of all-cause mortality compared with placebo [Moderate quality evidence].
- Two RCTs with 324 people who have had an MI, with unselected LV function, showed that up to 12 months of ACE inhibitors may reduce the risk of all-cause mortality compared with placebo but there was some uncertainty [Low quality evidence].
- One RCT with 265 people who have had an MI, with unselected LV function, showed that more than 12 months of ACE inhibitors have a similar effect as placebo on the risk of all-cause mortality but there was considerable uncertainty [Very low quality evidence].

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Sudden death

- Five RCTs with 8061 people who have had an MI, with unselected LV function, showed that ACE inhibitors have a similar effect on the risk of sudden death as placebo but there was considerable uncertainty [Very low quality evidence].
- Two RCTs with 701 people who have had an MI, with unselected LV function, showed that up to 6 months of ACE inhibitors have a similar effect on the risk of sudden death as placebo but there was considerable uncertainty [Very low quality evidence].
- Three RCTs with 1045 people who have had an MI, with unselected LV function, showed that up to 12 months of ACE inhibitors may reduce the risk of sudden death compared with placebo but there was considerable uncertainty [Very low quality evidence].

Cardiac mortality

- Two RCTs with 946 people who have had an MI, with unselected LV function, showed that ACE inhibitors may reduce the risk of cardiac mortality compared with placebo but there was some uncertainty [Low quality evidence].

Reinfarction

- Eleven RCTs with 79,407 people who have had an MI, with unselected LV function, showed that ACE inhibitors have a similar effect as placebo on the risk of reinfarction compared with placebo [Moderate quality evidence].

- Nine RCTs with 79,043 people who have had an MI, with unselected LV function, showed that ACE inhibitors have a similar effect as placebo on the risk of reinfarction compared with placebo [Moderate quality evidence].
- One RCT with 99 people who have had an MI, with unselected LV function, showed that up to 12 months of ACE inhibitors increase the risk of reinfarction compared with placebo but there was considerable uncertainty [Very low quality evidence].
- One RCT with 265 people who have had an MI, with unselected LV function, showed that more than 12 months of ACE inhibitors may increase the risk of reinfarction compared with placebo but there was considerable uncertainty [Very low quality evidence].

Stroke

- Three RCTs with 77,184 people who have had an MI, with unselected LV function, showed that ACE inhibitors have a similar effect as placebo on the risk of stroke compared with placebo [Moderate quality evidence].

Revascularisation

- Six RCTs with 19,843 people who have had an MI, with unselected LV function, showed that ACE inhibitors have a similar effect as placebo on the risk of revascularisation compared with placebo [Moderate quality evidence].
- Four RCTs with 19,479 people who have had an MI, with unselected LV function, showed that up to 6 months of ACE inhibitors have a similar effect as placebo on the risk of revascularisation compared with placebo [Moderate quality evidence].
- One RCT with 99 people who have had an MI, with unselected LV function, showed that up to 12 months of ACE inhibitors have a similar effect as placebo on the risk of revascularisation compared with placebo [Very low quality evidence].
- One RCT with 265 people who have had an MI,with unselected LV function, showed that more than 12 months of ACE inhibitors may increase the risk of revascularisation compared with placebo but there was considerable uncertainty [Very low quality evidence].

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Adverse events

- Four RCTs with 1439 people who have had an MI, with unselected LV function, showed that ACE inhibitors may increase the risk of adverse events compared with placebo but there was some uncertainty [Low quality evidence].
- Four RCTs with 76,758 people who have had an MI, with unselected LV function, showed that ACE inhibitors increase the risk of renal dysfunction compared with placebo [Moderate quality evidence].
- Two RCTs with 19,989 people who have had an MI, with unselected LV function, showed that ACE inhibitors have a similar effect as placebo on the risk of hyperkalaemia compared with placebo but there was some uncertainty [Low quality evidence].
- Ten RCTs with 79,548 people who have had an MI, with unselected LV function, showed that ACE inhibitors increase the risk of hypotension compared with placebo [Moderate quality evidence].
- Two RCTs with 58,275 people who have had an MI, with unselected LV function, showed that ACE inhibitors have a similar effect on the risk of dizziness but there was some uncertainty [Moderate quality evidence].

Rehospitalisation

- No evidence was identified on rehospitalisation.

Quality of life

- No evidence was identified on quality of life.

People who have had an MI with unselected LV function and distinct time periods

All-cause mortality

- Ten RCTs with 79,811 people who have had an MI, with unselected LV function, showed that 0 to 5 weeks of ACE inhibitors may reduce the risk of all-cause mortality compared with placebo [Moderate quality evidence].
- Nine RCTs with 21,476 people who have had an MI, with unselected LV function, showed that up to 6 months of ACE inhibitors may reduce the risk of all-cause mortality compared with placebo [Moderate quality evidence].
- Two RCTs with 225 people who have had an MI, with unselected LV function, showed that 6 to 12 months of ACE inhibitors may reduce the risk of all-cause mortality compared with placebo [Low quality evidence].

Sudden death

- Three RCTs with 926 people who have had an MI, with unselected LV function, showed that up to 6 months of ACE inhibitors may increase the risk of sudden death but there was considerable uncertainty [Very low quality evidence].
- One RCT with 225 people who have had an MI, with unselected LV function, showed that 6 to 12 months of ACE inhibitors may reduce the risk of sudden death but there was considerable uncertainty [Very Low quality evidence].

Update 2013

Cardiovascular mortality

- One RCT with 225 people who have had an MI, with unselected LV function, showed that up to 6 months of ACE inhibitors may decrease the risk of cardiac mortality but there was considerable uncertainty [Very low quality evidence].
- One RCT with 225 people who have had an MI, with unselected LV function, showed that 6 to 12 months of ACE inhibitors may reduce the risk of cardiac mortality but there was some uncertainty [Low quality evidence].

Reinfarction

- One RCT with 265 people who have had an MI, with unselected LV function, showed that up to 3 months of ACE inhibitors may increase the risk of reinfarction but there was considerable uncertainty [Very low quality evidence].
- One RCT with 265 people who have had an MI, with unselected LV function, showed that 3 to 12 months of ACE inhibitors may increase the risk of reinfarction but there was considerable uncertainty [Very low quality evidence].

Stroke

- No evidence was identified on stroke.

Revascularisation

- No evidence was identified on revascularisation.

Rehospitalisation

- No evidence was identified on rehospitalisation.

Adverse events

- No evidence was identified on adverse events.

Quality of life

- No evidence was identified on quality of life.

People who have had an MI in the past without heart failure who had undergone revascularisation

- One RCT with people who had an MI in the past without heart failure and had undergone revascularisation showed that ACE inhibitors reduced the risk of reinfarction compared with placebo, but there was some uncertainty (Low quality evidence).
- No evidence was identified on all-cause mortality.
- No evidence was identified on cardiac mortality.
- No evidence was identified on sudden death.
- No evidence was identified on stroke.
- No evidence was identified on revascularisation.
- No evidence was identified on rehospitalisation.
- No evidence was identified on adverse events.
- No evidence was identified on quality of life.

People who have had an MI in the past with or without LVSD or heart failure

Update 2013

- One RCT with 4228 people who had an MI in the past with LVSD or heart failure showed that ACE inhibitors reduce the risk of all-cause mortality compared with placebo [Low quality evidence].
- One RCT with 4228 people who had an MI in the past with LVSD or heart failure showed that ACE inhibitors reduce the risk of cardiac mortality compared with placebo [Low quality evidence].
- One RCT with 4228 people who had an MI in the past with LVSD or heart failure showed that ACE inhibitors reduce the risk of rehospitalisation compared with placebo [Low quality evidence].
- One RCT with 4228 people who had an MI in the past with LVSD or heart failure showed that ACE inhibitors reduce the risk of stroke compared with placebo, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 4228 people who had an MI in the past with LVSD or heart failure showed that ACE inhibitors reduce the risk of reinfarction compared with placebo, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 6709 people who had an MI in the past without heart failure or LVSD showed that ACE inhibitors reduce the risk of reinfarction compared with placebo, but there was some uncertainty [Very low quality evidence].
- Two RCTs with 16,336 people who had an MI in the past with and without LVSD or heart failure showed that ACE inhibitors increase the risk of adverse events compared with placebo [Very low quality evidence].
- One RCT with 4228 people who had an MI in the past with LVSD or heart failure showed that ACE inhibitors increase the risk of adverse events compared with placebo [Low quality evidence].
- One RCT with 12,208 people who had an MI in the pat without heart failure or LVSD showed that ACE inhibitors increase the risk of adverse events compared with placebo [Low quality evidence].

- One RCT with 6709 people who had an MI in the past without heart failure or LVSD showed that ACE inhibitors reduce the risk of cardiac mortality, reinfarction or cardiac arrest compared with placebo but there was some uncertainty [Very low quality evidence].
- One RCT with 4892 people who had an MI in the past without heart failure or LVSD showed that ACE inhibitors reduce the risk of cardiac mortality, reinfarction or stroke compared with placebo but there was some uncertainty [Very low quality evidence].
- One RCT with 4228 people who had an MI in the past with heart failure and LVSD showed that ACE inhibitors increase the risk of dizziness or fainting compared with placebo [Low quality evidence].
- No evidence was identified on sudden death.
- No evidence was identified on revascularisation.
- No evidence was identified on quality of life.

7.3.2.4.2 Economic

- A model developed for CG48 shows that ACE inhibitors are cost effective in people after MI with preserved LV function when compared to placebo and the ICER is in the range of £3,500 per QALY gained. This evidence is partially applicable and it has potentially serious limitations.
- A new cost-effectiveness study shows that ACE inhibitors are cost-effective in the subgroups of people with at least a 7% risk of events over 5 years. This evidence is partially applicable and it has potentially serious limitations.

7.3.3 Is there an optimal time for ACE inhibitors to be initiated in people who have had an MI?

Update 2013

For full details see review protocol in Appendix C.

7.3.3.1 Clinical evidence

Two studies were included in the review.[124,358] Evidence from these are summarised in the clinical GRADE evidence profile below (Table 59). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Di Pasquale (1994A)[124] included people with anterior and inferior acute myocardial infarction and gave people 6.25mg captopril 15 minutes before intravenous administration of urokinase (and then every 8 hours for first 2 days and 12.5mg every 8 hours from third to sixth days). The other group of people had captopril 6.25mg 3 days after thrombolytic treatment (and increased as the earlier initiation group). Pfeffer (1997)[358,359] included people with anterior acute myocardial infarction who received either 10mg ramipril either at the start of the trial (titrated up from 1.25mg and 2.5mg at 24 hour intervals) and continued for up to 90 days or the people received a placebo and then received ramipril 10mg (titrated as before) 14-90 days after the trial. Therefore these studies could not be meta-analysed.

Table 58: Summary of included studies

	Study	Intervention/comparison	Population	Outcomes reported	Comments
1.	Di Pasquale1994A[124]	Early initiation (15 minutes before urokinase) of captopril (6.25mg) versus late initiation (3 days after thrombolytic treatment) of captopril	Anterior or inferior acute myocardial infarction - STEMI (less than 4 hours); unselected LV	• Revascularisation; • All-cause mortality; • Adverse events.	-

	Study	Intervention/comparison	Population	Outcomes reported	Comments
			function		
2.	Pfeffer1997 (HEART trial)[358,359]	Early initiation (1-14 days) of ramipril (10mg) versus late initiation (14 to 90 days) of ramipril (0mg/day for first 14 days and 10mg for 14 to 90 days)	Anterior acute myocardial infarction less than 24 hours; unselected LV function	• Revascularisation; • All-cause mortality; • Myocardial infarction; • Stroke.	Trial stopped early because results from GISSI-3 and ISIS-4 showed substantial portion of lives are saved within the first several days of an MI.

Update 2013

Update 2013

Table 59: GRADE profile: ACE inhibitors (early initiation) versus ACE inhibitors (late initiation)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early initiation	Late initiation	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality – captopril 6.25 mg, 15 minutes before and 3 days after thrombolysis[124]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	7/131 (5.3%)	16/128 (12.5%)	RR 0.43 (0.18 to 1)	71 fewer per 1000 (from 102 fewer to 0 more)	LOW	CRITICAL
All-cause mortality – ramipril 10mg, 1-14 days versus 14-90 days [358,359]												
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	4/117 (3.4%)	6/119 (5%)	RR 0.68 (0.2 to 2.34)	16 fewer per 1000 (from 40 fewer to 68 more)	VERY LOW	CRITICAL
Revascularisation – captopril 6.25mg, 15 minutes before and 3 days after thrombolysis[124]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	44/131 (33.6%)	43/128 (33.6%)	RR 1 (0.71 to 1.41)	0 fewer per 1000 (from 97 fewer to 138 more)	VERY LOW	IMPORTANT
Revascularisation - ramipril 10mg, 1-14 days versus 14-90 days[358,359]												
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Serious[b]	None	19/117 (16.2%)	10/119 (8.4%)	RR 1.93 (0.94 to 3.98)	78 more per 1000 (from 5 fewer to 250 more)	LOW	IMPORTANT
Stroke- ramipril 10mg, 1-14 days versus 14-90 days[358,359]												

Update 2013

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early initiation	Late initiation	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	1/117 (0.9%)	1/119 (0.8%)	RR 1.02 (0.06 to 16.07)	0 more per 1000 (from 8 fewer to 127 more)	VERY LOW	IMPORTANT
Reinfarction- ramipril 10mg, 1-14 days versus 14-90 days[358,359]												
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	6/117 (5.1%)	8/119 (6.7%)	RR 0.76 (0.27 to 2.13)	16 fewer per 1000 (from 49 fewer to 76 more)	VERY LOW	IMPORTANT
Adverse events – hypotension and bradycardia - captopril 6.25mg 15 minutes before and 3 days after thrombolysis[124]												
1	Randomised trial	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	10/47 (21.3%)	8/46 (17.4%)	RR 1.22 (0.53 to 2.82)	38 more per 1000 (from 82 fewer to 317 more)	VERY LOW	RELEVANT
Cardiac morality												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Sudden death												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Rehospitalisation												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

(a) There was unclear randomisation and allocation concealment. The study was a single-blinded study.
(b) 95% confidence interval crossed one MID point.
(c) There were unclear randomisation methods and the number of drop-outs was not reported.
(d) 95% confidence interval crossed both MID points.

7.3.3.2 Economic evidence

No studies were found in CG48 comparing different time points of initiation for ACE inhibitors.

No relevant economic evaluations comparing ACE inhibitor with the same ACE inhibitor initiated at different time points, or comparing ACE inhibitor with placebo that allowed for an indirect comparison of optimal time of initiation of ACE inhibitors were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix M to aid consideration of cost effectiveness.

7.3.3.3 Evidence statements

7.3.3.3.1 Clinical

- One study with 258 people showed that early initiation of ACE inhibitors may reduce the risk of all-cause mortality compared with late initiation, but there was some uncertainty [Low quality evidence].
- One study with 236 people showed that early initiation of ACE inhibitors may reduce the risk of all-cause mortality compared with late initiation, but there was considerable uncertainty [Very low quality evidence].
- One study with 258 people showed that early initiation of ACE inhibitors has no effect on the risk of revascularisation compared with late initiation, but there was considerable uncertainty [Very low quality evidence].
- One study with 236 people showed that early initiation of ACE inhibitors may increase the risk of revascularisation compared with late initiation, but there was some uncertainty [Low quality evidence].
- One study with 236 people showed that early initiation of ACE inhibitors has no effect on the risk of stroke compared with late initiation, but there was considerable uncertainty [Very low quality evidence].
- One study with 236 people showed that early initiation of ACE inhibitors may reduce the risk of reinfarction compared with late initiation, but there was considerable uncertainty [Very low quality evidence].
- One study with 93 people showed that early initiation of ACE inhibitors may increase the risk of adverse events compared with late initiation, but there was considerable uncertainty [Very low quality evidence].
- No evidence was identified on cardiac mortality.
- No evidence was identified on sudden death.
- No evidence was identified on rehospitalisation.
- No evidence was identified on quality of life.

7.3.3.3.2 Economic

- No economic evidence was found on early versus late initiation of ACE inhibitors.

7.3.4 Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had an MI?

For full details see review protocol in Appendix C.

Update 2013

7.3.4.1 Clinical evidence

Two studies were included in the review.[141,358] Evidence from these are summarised in the clinical GRADE evidence profile below (Table 61). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

In the previous guideline, CG48, no evidence was identified to show what the optimal titration of ACE inhibitors should be. The existing recommendation is based on consensus of the Guideline Development Group. The recommendation states "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".

In this review, 2 randomised controlled trials were identified that provided data for this question. The study by Flather et al. was a pilot study for a larger trial called ISIS 4.[141,141] Captopril was titrated over a 12 hour period in both groups, one group (low) was titrated from 6.25 mg per day to 37.5 mg per day, the other group (high) was titrated from 6.25mg per day to 100mg per day. The study by Pfeffer et al (HEART trial) allowed a comparison of 2 different regimens of prescribing ramipril.[358,359] In 1 group, ramipril was titrated from 1.25mg/day up to 10mg/day over a 3 day period and continued for 14 days (fast titration). The other group was given the same low dose, 0.625mg/day, for the entire 14 day study period (low constant).

To answer the question "is early dose titration of ACE inhibitors in hospital more clinically effective than titration over an extended period of time?" the HEART study design best addresses this question out of all 3 RCTs. It compares an in-hospital titration with a group not on a clinically effective dose. Since each study was unique in its study design, a meta-analysis could not be performed on the outcomes.

Section 7.3.4.1.1 summarises the methods used to titrate the ACE inhibitors in the 2 RCTs included in this review and the methods recommended on the Electronic Medicines Compendium (EMC).

Update 2013

Table 60: Summary of included studies

	Study	Intervention/comparison Duration	Population	Outcomes reported
1	ISIS-4 1994 FLATHER[141,141] ISIS - PILOT	Captopril 6.25mg/d to 37.5 mg/d (LOW) versus Captopril 6.25mg/d to 100mg/d (HIGH) In hospital	MI (less than 36hours snice onset of symptoms) Unclear LV function n=741	• All-cause mortality • Reinfarction • Adverse events • Hypotension
2	HEART [358,359] HEART	Ramipril: 1.25 to 10mg/d (HIGH) over 3 days Low dose 0.625 mg/d same (LOW CONSTANT) 14 days	MI (less than 24 hours since onset of symptoms) Unselected LV function n=235	• All-cause mortality • Reinfarction • Hypotension • Stroke • Revascularisation • Reached target dose %

7.3.4.1.1 Titration regimens

7.3.4.1.2 Ramipril

RAMIPRIL (HEART)	Initial	12 hours	+1 day	+2 days	+3 days
Low dose constant	0.625 mg/day	0.625 mg/day	0.625 mg/day	0.625 mg/day	0.625 mg/day

RAMIPRIL (HEART)	Initial	12 hours	+1 day	+2 days	+3 days
High dose titration	1.25 mg/day	2.5 mg/day	5 mg/day	7.5 mg/day	10 mg/day

RAMIPRIL EMC	Initial after 48 hours	Day 4
EMC	5.0 mg/day (2 x 2.5mg)	10 mg/day (2 x 5mg)

After 48 hours, following myocardial infarction, in a person who is clinically and haemodynamically stable, the starting dose is 2.5 mg twice daily for 3 days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for 2 days before increasing to 2.5 mg and 5 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day the treatment should be withdrawn.
Titration and maintenance dose: the daily dose is subsequently increased by doubling the dose at intervals of 1 to 3 days up to the target maintenance dose of 5 mg twice daily

Captopril

CAPTOPRIL (FLATHER)	Initial	2 hours	8-12 hours	12 hours – 28 days
Low dose titration	6.25 mg/day	12.5 mg/day	37.5 mg/day	37.5 mg/day
High dose titration	6.25 mg/day	12.5 mg/day	25 mg/day	100 mg/day

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CAPTOPRIL EMC	Initial	2 hours	12 hours	+1 day post MI	4 weeks
EMC - acute	6.25 mg/day	12.5 mg/day	25mg/day	200 mg/d (100 mg/day x 2)	200 mg/day (100 mg/d x 2

http://www.medicines.org.uk/EMC/medicine/25985/SPC/Captopril+12.5+mg+Tablets/
Myocardial Infarction:-short-term (4 weeks) treatment: Captopril is indicated in a person who is clinically stable within the first 24 hours of an infarction.
Myocardial infarction:short-term treatment: Captopril treatment should begin in hospital as soon as possible following the appearance of the signs and/or symptoms in people with stable haemodynamics. A 6.25 mg test dose should be administered, with a 12.5 mg dose being administered 2 hours afterwards and a 25 mg dose 12 hours later. From the following day, captopril should be administered in a 100 mg/day dose, in 2 daily administrations, for 4 weeks (that is, 50mg twice daily), if warranted by the absence of adverse haemodynamic reactions. At the end of the 4 weeks of treatment, the person's state should be reassessed before a decision is taken concerning treatment for the post-myocardial infarction stage.
- chronic treatment: if captopril treatment has not begun during the first 24 hours of the acute myocardial infarction stage, it is suggested that treatment be instigated between the 3rd and 16th day post-infarction once the necessary treatment conditions have been attained (stable haemodynamics and management of any residual ischaemia). Treatment should be started in hospital under strict surveillance (particularly of blood pressure) until the 75 mg dose is reached. The initial dose must be low (see section 4.4), particularly if the personexhibits normal or low blood pressure at the initiation of therapy. Treatment should be initiated with a dose of 6.25 mg followed by 12.5 mg 3 times daily for 2 days and then 25 mg 3 times daily if warranted by the absence of adverse haemodynamic reactions. The recommended dose for effective cardioprotection during long-term treatment is 75 to 150 mg daily in 2 or 3 doses. In cases of symptomatic hypotension, as in heart failure, the dosage of diuretics and/or other concomitant vasodilators may be reduced in order to attain the steady state dose of captopril. Where necessary, the dose of captopril should be adjusted in accordance with the person's clinical reactions. Captopril may be used in combination with other treatments for myocardial infarction such as thrombolytic agents, beta-blockers and acetylsalicylic acid.

Update 2013

Table 61: GRADE profile: ramipril (fast titration) versus ramipril (constant dose) (people who have had an MI)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Fast titration	Constant dose	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality[358,359]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	3/119 (2.5%)	2/116 (1.7%)	RR 1.46 (0.25 to 8.59)	8 more per 1000 (from 13 fewer to 131 more)	VERY LOW	CRITICAL
Reinfarction[358,359]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	3/119 (2.5%)	1/116 (0.86%)	RR 2.92 (0.31 to 27.71)	17 more per 1000 (from 6 fewer to 230 more)	VERY LOW	IMPORTANT
Stroke[358,359]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	0/119 (0%)	1/116 (0.86%)	RR 0.32 (0.01 to 7.9)	6 fewer per 1000 (from 9 fewer to 59 more)	VERY LOW	IMPORTANT
Hypotension[358,359]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	37/119 (31.1%)	26/116 (22.4%)	RR 1.39 (0.9 to 2.14)	87 more per 1000 (from 22 fewer to 256 more)	VERY LOW	IMPORTANT
Revascularisation[358,359]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	15/119 (12.6%)	10/116 (8.6%)	RR 1.46 (0.69 to 3.12)	40 more per 1000 (from 27 fewer to 183 more)	VERY LOW	IMPORTANT
Reached target dose[358,359]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	105/119 (88.2%)	103/116 (88.8%)	RR 0.99 (0.91 to	9 fewer per 1000 (from 80	LOW	IMPORTANT

Update 2013

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Fast titration	Constant dose	Relative (95% CI)	Absolute	Quality	Importance
									1.09)	fewer to 80 more)		
Cardiac mortality												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Adverse reactions												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) There were unclear methods of randomisation and the number of dropouts was not reported. The study design was not ideal since the 2 of the groups were titrated to a different final dose of ACE inhibitor.
(b) The control arm was prescribed a non-clinical dose of ACE inhibitors thus providing an irrelevant comparison.
(c) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).

Update 2013

Table 62: GRADE profile: captopril (low dose titration) versus captopril (high dose titration)(people who have had an MI)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low dose titration	High dose titration	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality[141,141]												
1	Randomised trial	Very serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	21/237 (8.9%)	3/133 (2.3%)	RR 3.93 (1.19 to 12.92)	66 more per 1000 (from 4 more to 269 more)	VERY LOW	CRITICAL
Reinfarction[141,141]												
1	Randomised trial	Very serious[a]	No serious inconsistency	Serious [b]	Very serious[d]	None	9/237 (3.8%)	5/133 (3.8%)	RR 1.01 (0.35 to 2.95)	0 more per 1000 (from 24 fewer to 73 more)	VERY LOW	IMPORTANT
Hypotension[141,141]												
1	Randomised trial	Very serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	57/237 (24.1%)	20/133 (15%)	RR 1.6 (1.01 to 2.54)	90 more per 1000 (from 2 more to 232 more)	VERY LOW	IMPORTANT
Renal impairment[141,141]												
1	Randomised trial	Very serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	4/237 (1.7%)	0/133 (0%)	RR 5.07 (0.27 to 93.4)	-	VERY LOW	IMPORTANT
Adverse events [141,141]												
1	Randomised trial	Very serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	85/237 (35.9%)	29/133 (21.8%)	RR 1.64 (1.14 to 2.37)	140 more per 1000 (from 31 more to 299 more)	VERY LOW	IMPORTANT
Systolic blood pressure at day 7(better indicated by lower values)[141,141]												
1	Randomised trial	Very serious[a]	No serious inconsistency	Serious[b]	No serious imprecision[e]	None	237	133	-	MD 2 higher (1.79 to 2.21 higher)	MODERATE	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low dose titration	High dose titration	Relative (95% CI)	Absolute	Quality	Importance
Diastolic blood pressure at day 7 (better indicated by lower values)[141,141]												
1	Randomised trial	Very serious[a]	No serious inconsistency	Serious[b]	No serious imprecision[e]	None	237	133	-	MD 2 higher (1.79 to 2.21 higher)	MODERATE	IMPORTANT
Cardiac mortality												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Stroke												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) Participants were not randomised to the 2 captopril groups from the same pool of people. In 1 study people were recruited from 4 UK hospitals and in the other from 6 Polish hospitals. Variation in the pool of people was reflected in the placebo groups not being matched for incidence of heart failure (37% versus 18%). This suggests 1 pool of participants may have been more ill than the other. Other outcomes appeared to be matched amongst the placebo group but no statistical comparison was performed.

(b) The study mostly measures the tolerability of a high versus low dose of ACE inhibitors since the final maximum dose is different between the groups. Some insight can be gained by comparing the 2 groups because it could also be interpreted as a slow versus fast titration of ACE inhibitors.

(c) 95% confidence intervals crossed 1 MID (1.25).

(d) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).

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(e) MID for continuous variables is 0.5 x SD. For this paper it was 0.5.

7.3.4.2 Economic evidence

Published literature

No relevant economic evaluations comparing early titration of an ACE inhibitor with a different titration period of the same ACE inhibitor were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix M to aid consideration of cost effectiveness.

7.3.4.3 Evidence statements

7.3.4.3.1 Ramipril titration in people who have had an MI

- One RCT with 235 people showed that fast titration of ACE inhibitors may increase the risk of all-cause mortality compared with a low constant dose, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 235 people showed that fast titration of ACE inhibitors may increase the risk of reinfarction compared with a low constant dose, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 235 people showed that fast titration of ACE inhibitors may decrease the risk of stroke compared with a low constant dose, but there was considerable uncertainty [VERY Low quality evidence].
- One RCT with 235 people showed that fast titration of ACE inhibitors may increase the risk of hypotension compared with a low constant dose, but there was some uncertainty [VERY Low quality evidence].
- One RCT with 235 people showed that fast titration of ACE inhibitors may increase the risk of revascularisation compared with a low constant dose, but there was some uncertainty [Very low quality evidence].
- One RCT with 235 people showed that fast titration of ACE inhibitors may have no effect on the likelihood of reaching the target dose compared with a low constant dose [Low quality evidence].
- No evidence was identified on cardiac mortality.
- No evidence was identified on sudden death.
- No evidence was identified on rehospitalisation.
- No evidence was identified on quality of life.
- No evidence was identified on adverse reactions.

7.3.4.3.2 Captopril titration in people who have had an MI

- One study with 370 people showed that high and fast dose titration of ACE inhibitors may increase the risk of all-cause mortality compared with a low-dose titration but there was some uncertainty [Very low quality evidence].
- One study with 370 people showed that high and fast dose titration of ACE inhibitors has no effect on the risk of reinfarction compared with a low-dose titration but there was considerable uncertainty [Very low quality evidence].
- One study with 370 people showed that high and fast dose titration of ACE inhibitors may increase the risk of hypotension compared with a low-dose titration but there was some uncertainty [Very low quality evidence].

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- One study with 370 people showed that high and fast dose titration of ACE inhibitors may increase the risk of renal impairment compared with a low-dose titration but there was considerable uncertainty [Very low quality evidence].
- One study with 370 people showed that high and fast dose titration of ACE inhibitors may increase the risk of adverse events compared with a low-dose titration but there was some uncertainty [Very low quality evidence].
- No evidence was identified on cardiac mortality.
- No evidence was identified on sudden death.
- No evidence was identified on stroke.
- No evidence was identified on revascularisation.
- No evidence was identified on rehospitalisation.
- No evidence was identified on quality of life.

7.3.5 Angiotensin receptor blockers (ARBs)

ACE inhibitors have been widely available for over 30 years since the initial Food and Drug Administration (FDA) approval of captopril in 1981, however, significant numbers of people are unable to tolerate this particular class of drugs due to range of side-effects including angioedema (rare, approximately. 0.2%) and dry cough (more common, approximately 2-25%).

Angiotensin receptor blockers (ARBs) also reduce the activity of the RAAS but rather than affect enzymatic pathways, they bind directly and antagonistically at the level of the AT1 receptor. Losartan was the first of this class of drugs to be developed (in 1986) and successfully marketed (in 1995) and a number of licensed products are currently available. ARBs have a broad range of approved clinical indications including hypertension, congestive cardiac failure and renal disease and appear to be better tolerated than ACE inhibitors. One proposed and widely accepted theory for this is that ACE inhibitors lead to the accumulation of bradykinin (since angiotensin converting enzyme is responsible for bradykinin degradation) and it these elevated bradykinin levels that result in symptoms of dry cough and rarely angioedema in certain, susceptible individuals. ARBs do not affect bradykinin degradation and, in general, are not associated with these side-effects. Therefore, the use of ARBs has been very much directed towards those people who have been unable to tolerate ACE inhibitors rather than the use of these agents as first-line therapies. In general, the financial cost of ARBs has been extremely high compared to ACE inhibitors but with most now being available in generic form, the difference in cost is likely to lessen.

Update 2013

7.3.5.1 What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs, or in combination versus ACE inhibitors to improve outcomes in people after an MI?

For full details see review protocol in Appendix C.

Eleven studies were included in this review on "What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?" [176,226,233,280,291,360,375,427,436,469,477] Evidence from these are summarised in the clinical GRADE evidence tables (Table 63 to Table 68). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Since publication of the previous guideline, CG48, 2 large trials have been published which have been used to inform the effectiveness of ACE inhibitors versus ARBs and ACE inhibitors plus ARB versus ACE inhibitors in people with and without left ventricular systolic dysfunction (LVSD)[436] and ARBs versus placebo in people without LVSD.[472,477]

The comparisons for this review are: ACE inhibitors versus ARBs, ACE inhibitors plus ARBs versus ACE inhibitors, and ARB versus placebo. Randomised controlled trials that compared any of these interventions were grouped according to whether the people were treated within 0-72 hours of having an MI (acutely), between 72 hoursand12months (sub-acutely) or over 1 year after having an MI (in the past). One study appeared to initiate treatment at some point in the past, but did not provide any details of when.[176,177] Studies were categorised based on whether the participants had "left ventricular systolic dysfunction"(LVSD), those without "heart failure" or those who had "unselected LV function" (a range of LV function). People described as having left ventricular failure and those with an ejection fraction of less than 40% were categorised as having LVSD. Where a mean of less than 40% was reported, this was categorised as having unselected LV function.

Studies with populations that included less than 75% people who have had an MI were considered "indirect" and studies that included people with heart failure and only a history of coronary heart disease were only included if no other study was available for that category. For a summary of the studies used in this review and whether they used a direct or indirect study population refer to Table 64.

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The previous guideline, CG48, included a paper that was not included in this review as a paper with a direct study population, had since become available.[126] All 3 other papers used in CG48 were included in this review.[176,233,360]

Heterogeneity was investigated in a number of outcomes and was mostly due to few events being reported in a paper, resulting in large 95% confidence intervals. It was not possible to investigate the effects of age on any of the outcomes showing heterogeneity since most of the studies used a similar age range. Treatment type was also difficult to investigate since most studies reported a range of treatment types, only in the study by Suzuki were most people treated by percutaneous coronary intervention (PCI), (90%).[426,427] Other papers either reported a small percentage of people treated with PCI 15-40%, or CABG 20%, or they were treated medically.

Update 2013

Table 63: Summary of included studies

	Study	New or CG48	Intervention/ comparison	MI (onset of symptoms) / Strata	Population	Duration / Numbers	Outcomes reported
ACE inhibitors versus ARB							
1.	Montalescot et al 2009 [290,291] ARCHIPELAGO	New	Irbesartan (300mg/day) versus enalapril (20mg/day)	MI (less than 48 hours since the onset of symptoms) Direct population Without heart failure	MI Excluded people with HF Treatment: Medical Direct population: STEMI (Q-wave less than14%) or NSTEMI LVSD or HF: excluded Age: 62.2 ± 11.5	60 days n=429	• Cardiac mortality • Myocardial infarction • Stroke • Rehospitalisation for angina and revascularisation • Revascularisation
2.	Suzuki et al 2009 [426,427]	New	Valsartan (max dose) versus ACE inhibitor (max dose)	MI (less than 10 days since the onset of symptoms, mean 2 days post MI) Direct population Unselected LVSD	MI plus reperfusion Unselected LVSD Treatment: PCI 90% Direct population: MI 100% LVSD: LV EF mean 54% (mild LV dysfunction) HF: Unclear Age: 63±10	6 months n=256	• All-cause mortality • Non-fatal MI • Revascularisation • Rehospitalisation • Adverse events • Adverse events – renal dysfunction • Adverse events – hyperkalaemia • Adverse events - hypotension
3.	McMurray et al 2006[279,280] VALIANT	New Additional outcomes	Valsartan (160mg twice a day) versus captopril (up to 50mg 3 times a day)	MI (12 hours to 10 days since onset of symptoms)	MI plus HF or LVSD or both LVSD Treatment: PCI = 20 - 40%; Medical	24.7 months	• MI (fatal) • Revascularisation • Rehospitalisation (for angina)

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	Study	New or CG48	Intervention/ comparison	MI (onset of symptoms) / Strata	Population	Duration / Numbers	Outcomes reported
		not reported in 2003.		Direct population LVSD and/or heart failure	35% Direct population: 100% MI HF: included clinical evidence of HF Age = 65±11.8	n=9,818	• Stroke
4.	ONTARGET 2008[436] ONTARGET	New	Telmisartan (80mg/day) versusramipril (10mg/day)	MI (at least 2 days since onset of symptoms, PCI more than 30 days ago, CABG more than 4 years ago) Indirect population Without heart failure	People with coronary, peripheral or cerebrovascular disease CAD=74% History MI = 48% Without heart failure Treatment: no acute treatment Indirect population: history of MI (48%); CAD (74%) HF: 0% excluded congestive HF Age = 66 ± 7	56 months n=17,118	• All-cause mortality • Cardiac mortality • MI • Stroke • Rehospitalisation • AE – renal dysfunction
5.	Pfeffer et al 2003 [359,360] VALIANT	CG48	Valsartan (160mg twice a day) versus captopril (50mg three times a day)	MI (mean 4.8 days, range 0.5-10 days since onset of symptoms) Direct	MI plus LVSD or HF or both LVSD Treatment: PCI 15%; Medical 35%; Direct population: MI 100%; STEMI 66%; NSTEMI 32% LVSD: EF mean less than 35%	24.7 months	• All-cause mortality • Cardiovascular death • Adverse event (any) • Adverse event - renal causes • Hyperkalaemia

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	Study	New or CG48	Intervention/ comparison	MI (onset of symptoms) Strata	Population	Duration Numbers	Outcomes reported
				population	Heart failure: 100% Killip Class: I 28% II 48% III 17% IV 6% Age: 65±11	n=9,818	
ARB versus placebo							
1.	Granger et al 2003 [176,177] CHARM-Alternative trial	CG48	Candesartan (32mg/day) versus placebo	MI in the past Indirect population LVSD and heart failure	Hospital admission for CHF (66-70%) + low left ventricular ejection fraction (LVEF) + intolerant of an ACE inhibitor LVSD Treatment: previous PCI 16%, CABG 26% Indirect population: 62% previous MI LVSD and/or HF = 100% LVEF = less than 40% (mean 30%) HF = NYHA II – IV = 100% Age = 66.3 ± 11.0	33.7 months n=2028	• All-cause mortality • Cardiac mortality • MI • Stroke • Revascularisation • Rehospitalisation • Adverse events • Hypotension • Hyperkalaemia
2.	Kasanuki et al 2009[226,226] HIJ-CREATE	New	Candesartan (4-12mg/day) versus placebo	MI (more than 3 weeks since onset of symptoms) Indirect	CAD and hypertension Excluded: MI within last week Unselected LVSD Treatment: PCI = 52.9%; CABG = 3.2% (previous PCI 83%; CABG 12%)	4.2 years	• All-cause mortality (RR and HR) • Cardiac mortality (RR and HR) • Stroke (RR and HR) • Revascularisation (RR and

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	Study	New or CG48	Intervention/ comparison	MI (onset of symptoms) Strata	Population	Duration Numbers	Outcomes reported
				population	Indirect population: 36% previous MI; 100% CAD; Acute coronary syndrome: 36% LVSD: EF mean 54% HF: NYHA I = 80% NYHA II + III + IV = 20% Age = 65.0 ± 8.9	n=2049	HR) • MI (non-fatal) (RR and HR) • Adverse events - all • Adverse events- hyperkalaemia • Adverse events – renal dysfunction
3.	Kondo et al 2003[233]	CG48	Low-dose candesartan versus placebo	MI (more than 6 months since onset of symptoms) Indirect population Without heart failure or LVSD	History of coronary intervention (no signs of stenosis 6 months after intervention) Excluded HF (EF less than 0.4) Without LVSD Treatment: Medical Indirect population: 67% previous MI LVSD less than 40%: Excluded HF: 0% Age= 65.0 ± 9	Mean 24 months n=406	• All-cause mortality • Cardiac mortality • MI (non-fatal) • Revascularisation • Rehospitalisation
4.	Yusuf et al 2008[472,477] TRANSCEND	New Subgroup analysis of ONTARGET participant s who are	Telmisartan 80mg/day versus placebo	MI (more than 2 days since onset of symptoms, PCI more than30 days ago, CABG more than 4 years	Intolerant to ACE inhibitors and had either coronary artery disease (75%) peripheral vascular (11%) or cerebrovascular disease (22%) or diabetes Without heart failure	Mean 56 months	• All-cause mortality • Cardiovascular death • MI • Stroke • Hospitalisation • Revascularisation

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	Study	New or CG48	Intervention/ comparison	MI (onset of symptoms) Strata	Population	Duration Numbers	Outcomes reported
		intolerant to ACE inhibitors		ago) Indirect population	Treatment: Unclear Indirect population: 47% previous MI; CAD 75% HF: excluded Age= 67 ± 7	n=5926	• Adverse events – renal dysfunction • Adverse events - hyperkalaemia • Adverse events - hyoptension
ACE inhibitors plus ARB versus ACE inhibitors							
1.	McMurray et al 2006[279,280] VALIANT	New Additional outcomes not reported in 2003.	Captopril (up to 50mg three times daily)+ valsartan (160mg twicedaily) versus captopril (up to 50mg three times per day)	MI (12 hours to 10days since onset of symptoms) Direct population	MI plus LVSD or plus HF or both LVSD Treatment: PCI = 20 - 40%; Medical 35% Direct population: 100% MI LVSD and or HF = 100% Age = 65±11.8	24.7 months n=9,794	• MI (fatal) • Revascularisation • Hospitalisation (for angina) • Stroke
2.	ONTARGET[436]	New	Ramipril (10mg/day)and telmisartan (80mg/day) Versus ramipril (10mg/day)	MI (more than 2 days since onset of symptoms, PCI more than30 days ago, CABG more than 4 years ago) Indirect population	Vascular disease or diabetes: MI (more than 2days) or angina or PAD or stroke or diabetes. Treatment: no acute treatment Indirect population: history of MI (48%); CAD = 74% HF: 0% excluded congestive HF Age = 66 ± 7	56 months n=17,078	• All-cause mortality • Cardiac mortality • MI • Stroke • Rehospitalisation • Adverse events – renal dysfunction

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	Study	New or CG48	Intervention/ comparison	MI (onset of symptoms) / Strata	Population	Duration / Numbers	Outcomes reported
3.	Rangoonwala et al 2010 [375,375] ONTARGET	New	Telmisartan (80mg/day) + ramipril (10mg/day) versus ramipril (10mg/day)	MI (more than 2 days since onset of symptoms, PCI more than 30 days ago, CABG more than 4 years ago) Indirect population	Vascular disease or diabetes: MI (more than 2 days ago) or angina or PAD or stroke or diabetes. Without HF Treatment: no acute treatment Indirect population: history of MI (48%); CAD = 74% LVSD = unclear HF = excluded Age = 66 ± 7	Average 56 months n=17,078	• All-cause mortality • Adverse events- renal dysfunction • Hyperkalaemia (serum potassium >5.5mmol/l)
4.	Pfeffer et al 2003 [359,360] VALIANT	CG48	Captopril (50mg three times a day) + valsartan (160mg twice a day) versus captopril (50mg three times a day)	MI (12 hours to 10 days since onset of symptoms) Direct population	MI LVSD Treatment: PCI 15%; Medical 35%; Direct population: MI 100%; STEMI 66%; NSTEMI 32% LVSD: Ejection fraction mean 35% Heart failure 75% (Killip Class II – IV)	24.7 months n=9,741	• All-cause mortality • Cardiovascular death • Rehospitalisation (for MI and HF) • Adverse events (any) • Renal causes • Hyperkalaemia
5.	Yano et al 2012 [469,469]	New	Valsartan (40mg twice a day)+ captopril (25mg three times a day) versus captopril (25mg three times a day)	MI (less than 72 hours since onset of symptoms)	PCI MI EF = not provided	7 months n=160	• Cardiovascular death • Reinfarction • Revascularisation • Adverse events (any)

(a) CHARM-Alternative: people with low left ventricular ejection fraction (LVEF) intolerant to ACE inhibitors, CHARM - Added: people with low LVEF taking an ACE inhibitor; CHARM-Preserved: people with preserved LVEF taking/not taking an ACE inhibitor.

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Table 64: Category of each study

Study	LVSD	Unselected LV function	Without heart failure
ACE inhibitors versus ARB, MI (less than 72 hours since onset of symptoms)			
Montalescot[290,291]	-	-	Direct study population
Suzuki[426,427]	-	Direct study population	-
ACE inhibitors. versus ARB, MI (72 hours – 12 months since onset of symptoms)			
Rangoonwala (ONTARGET)[375,375]	-	-	Indirect study population
ONTARGET [436]	-	-	Indirect study population
McMurray[279,280]	Direct study population	-	-
Pfiffer[359,360]	Direct study population	-	-
ARB versus placebo, MI (more than 12 months ago)			
Granger [176,177]	Indirect study population	-	-
ARB versus placebo, MI (72 hours – 12 months since onset of symptoms)			
Kondo[233]	-	-	Indirect study population
Yusuf [472,477]	-	-	Indirect study population
ACE inhibitors + ARB versus ACE inhibitors, MI (72 hours – 12 months since onset of symptoms)			
Rangoonwala (ONTARGET)[375,375]	-	-	Indirect study population
ONTARGET [436]	-	-	Indirect study population
McMurray[279,280]	Direct study population	-	-
[Pfeffer[359,360]	Direct study population	-	-

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Table 65: GRADE profile: ARB versus ACE inhibitor (people who had an MI, without heart failure or a mixture of LV function (unselected) and who were initiated within 72 hours of the MI).

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
Cardiac mortality - without heart failure[290,291]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	2/212 (0.94%)	3/217 (1.4%)	RR 0.68 (0.12 to 4.04)	4 fewer per 1000 (from 12 fewer to 42 more)	VERY LOW	CRITICAL
Reinfarction (fatal or non-fatal) - without heart failure[290,291]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	9/212 (4.2%)	5/217 (2.3%)	RR 1.84 (0.63 to 5.41)	19 more per 1000 (from 9 fewer to 102 more)	VERY LOW	IMPORTANT
Stroke -without heart failure[290,291]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	0/217 (0%)	0/212 (0%)	Not pooled	Not pooled	MODERATE	IMPORTANT
Revascularisation - without heart failure[290,291]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	4/212 (1.9%)	2/217 (0.92%)	RR 2.05 (0.38 to 11.06)	10 more per 1000 (from 6 fewer to 93 more)	VERY LOW	IMPORTANT
Rehospitalisation - without heart failure[290,291]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	8/212 (3.8%)	7/217 (3.2%)	RR 1.17 (0.43 to 3.17)	5 more per 1000 (from 18 fewer to 70 more)	VERY LOW	IMPORTANT
All-cause mortality – unselected LVSD[426,427]												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trial	Serious [c]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/120 (0%)	1/120 (0.83%)	OR 0.33 (0.01 to 8.26)	50 fewer per 1000 (from 76 fewer to 331 more)	VERY LOW	CRITICAL
Reinfarction (fatal or non-fatal) - unselected[426,427]												
1	Randomised trial	Serious [c]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/120 (0.83%)	1/121 (0.83%)	RR 1.01 (0.06 to 15.94)	0 more per 1000 (from 8 fewer to 123 more)	VERY LOW	IMPORTANT
Revascularisation - unselected[426,427]												
1	Randomised trial	Serious [c]	No serious inconsistency	No serious indirectness	Very serious[b]	None	9/120 (7.5%)	11/121 (9.1%)	RR 0.82 (0.35 to 2.82)	16 fewer per 1000 (from 59 fewer to 165 more)	VERY LOW	IMPORTANT
Rehospitalisation – unselected[426,427]												
1	Randomised trial	Serious [c]	No serious inconsistency	No serious indirectness	Very serious[b]	None	3/120 (2.5%)	4/121 (3.3%)	RR 0.76 (0.17 to 3.31)	8 fewer per 1000 (from 27 fewer to 76 more)	VERY LOW	IMPORTANT
Adverse events - renal dysfunction -all peoples[426,427]												
1	Randomised trial	Serious [d]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/2954 (0.03%)	1/2972 (0.03%)	RR 1.01 (0.06 to 16.08)	0 more per 1000 (from 0 fewer to 5 more)	VERY LOW	IMPORTANT
Adverse events – all people[426,427]												
1	Randomised	Serious	No serious	No serious	Serious[e]	None	4/120	15/121	RR 0.27	90 fewer	LOW	IMPORTANT

Update 2013

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
	trial	[d]	inconsistency	indirectness			(3.3%)	(12.4%)	(0.09 to 0.79)	per 1000 (from 26 fewer to 113 fewer)		
Adverse events - hypotension -all people[426,427]												
1	Randomised trial	Serious [c]	No serious inconsistency	No serious indirectness	Very serious[b]	None	2/120 (1.7%)	1/121 (0.83%)	RR 2.02 (0.19 to 21.95)	8 more per 1000 (from 7 fewer to 173 more)	VERY LOW	CRITICAL
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) There were unclear methods of randomisation.
(b) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(c) It was unclear whether the authors performed allocation concealment and what the methods of randomisation were. Only a small number of events were detected at follow-up. It is also unclear whether participants were blinded.
(d) It was unclear whether the authors performed allocation concealment and what the methods of randomisation were. Participants and investigators were blinded.
(e) 95% confidence intervals crossed 1 MID (0.75).

Update 2013

Table 66: GRADE profile: ARB versus ACE inhibitor (people who had an MI, with LVSD or without heart failure, and who were initiated on treatment between 72 hours and 12 months of the MI)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - LVSD[359,360]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	979/4909 (19.9%)	958/4909 (19.5%)	RR 1.02 (0.94 to 1.11)	4 more per 1000 (from 12 fewer to 21 more)	MODERATE	CRITICAL
All-cause mortality -without heart failure[436]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	989/8542 (11.6%)	1014/8576 (11.8%)	RR 0.98 (0.9 to 1.06)	2 fewer per 1000 (from 12 fewer to 7 more)	LOW	CRITICAL
Cardiac mortality - LVSD[359,360]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	827/4909 (16.8%)	830/4909 (16.9%)	RR 1.0 (0.91 to 1.09)	0 fewer per 1000 (from 15 fewer to 15 more)	MODERATE	CRITICAL
Cardiac mortality - without heart failure[436]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	598/8542 (7%)	603/8576 (7%)	RR 1 (0.89 to 1.11)	0 fewer per 1000 (from 8 fewer to 8 more)	LOW	CRITICAL
Stroke (fatal or non-fatal) - LVSD[279,280]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	180/4909 (3.7%)	211/4909 (4.3%)	RR 0.85 (0.7 to 1.04)	6 fewer per 1000 (from 13 fewer to 2 more)	MODERATE	IMPORTANT
Revascularisation - LVSD[279,280]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1122/4909 (22.9%)	1173/4909 (23.9%)	RR 0.96 (0.89 to 1.03)	10 fewer per 1000 (from 26 fewer to 7 more)	MODERATE	IMPORTANT
Revascularisation -without HF[436]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	1290/8542	1269/8576	RR 1.02 (0.95 to	3 more per 1000 (from 7 fewer to 15	LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
							(15.1%)	(14.8%)	1.1)	more)		
Hospitalisation - LVSD [279,280]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	989/4909 (20.1%)	1021/4909 (20.8%)	RR 0.97 (0.9 to 1.06)	6 fewer per 1000 (from 21 fewer to 12 more)	MODERATE	IMPORTANT
Hospitalisation - without HF[436]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	394/8542 (4.6%)	354/8576 (4.1%)	RR 1.12 (0.97 to 1.29)	5 more per 1000 (from 1 fewer to 12 more)	LOW	IMPORTANT
Reinfarction (fatal or non-fatal) - selected LVSD[279,280]												
1	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	796/4909 (16.2%)	798/4909 (16.3%)	RR 1 (0.91 to 1.09)	0 fewer per 1000 (from 15 fewer to 15 more)	MODERATE	IMPORTANT
Reinfarction (fatal or non-fatal) - without HF[436]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	440/8542 (5.2%)	413/8576 (4.8%)	RR 1.07 (0.94 to 1.22)	3 more per 1000 (from 3 fewer to 11 more)	LOW	IMPORTANT
Adverse events - all[359,360]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	282/4885 (5.8%)	375/4879 (7.7%)	RR 0.75 (0.65 to 0.87)	19 fewer per 1000 (from 10 fewer to 27 fewer)	LOW	IMPORTANT
Adverse events - renal dysfunction -all people[360,375]												
2	Randomised trials	Serious[d]	No serious inconsistency	Serious[b]	No serious imprecision	None	959/13547 (7.1%)	912/13576 (6.7%)	RR 1.06 (0.97 to 1.16)	4 more per 1000 (from 2 fewer to 11 more)	LOW	IMPORTANT
Adverse events - hyperkalaemia -all people[360,375]												
2	Randomised trials	Serious[d]	No serious inconsistency	Serious[b]	No serious imprecision	None	294/13427 (2.2%)	287/13455 (2.1%)	RR 1.03 (0.88 to 1.21)	1 more per 1000 (from 3 fewer to 4 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) It was unclear how the authors randomised participants however allocation concealment was performed and the participants were blinded.
(b) The ONTARGET [436] study included an indirect MI population and included 48%of people who had a history of MI.
(c) 95% confidence intervals crossed 1 MID (1.25).
(d) The authors performed allocation concealment but it was unclear how people were randomised.

Table 67: GRADE profile: ARB versus placebo (people who have been initiated treatment within 72 hours and 12 months of the MI, or who have had an MI over 12 months ago)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	Placebo	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - without HF + had a MI (72 hours – 12 months since onset of symptoms)[233,477]												
2	Randomised trials	Serious[a]	Serious[b]	Serious[c]	No serious imprecision	None	368/3148 (11.7%)	360/3175 (11.3%)	RR 1.03 (0.9 to 1.18)	3 more per 1000 (from 11 fewer to 20 more)	VERY LOW	CRITICAL
All-cause mortality - LVSD + had an MI over 12 months ago [176,177]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	265/1013 (26.2%)	296/1015 (29.2%)	RR 0.90 (0.78 to 1.03)	29 fewer per 1000 (from 64 fewer to 9 more)	LOW	CRITICAL
Cardiac mortality - without HF+ had a MI (72 hours – 12 months since onset of symptoms)[233,477]												
2	Randomised trials	Serious[a]	Serious[f]	Serious[c]	No serious imprecision	None	229/3148	232/3175 (7.3%)	RR 0.99 (0.83 to	1 fewer per 1000 (from 12 fewer to	VERY LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	Placebo	Relative (95% CI)	Absolute	Quality	Importance
							(7.3%)		1.18)	13 more)		
Cardiac mortality - LVSD + had an MI over 12 months ago [176,177]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[e]	No serious imprecision	None	219/1013 (21.6%)	252/1015 (24.8%)	RR 0.87 (0.74 to 1.02)	32 fewer per 1000 (from 65 fewer to 5 more)	LOW	CRITICAL
Reinfarction (fatal + non-fatal) - without HF+ had a MI (72 hours – 12 months since onset of symptoms)[233,477]												
2	Randomised trials	Serious[g]	No serious inconsistency	Serious[c]	Serious[h]	None	118/3148 (3.7%)	148/3175 (4.7%)	RR 0.8 (0.63 to 1.02)	9 fewer per 1000 (from 17 fewer to 1 more)	VERY LOW	IMPORTANT
Reinfarction (fatal + non-fatal) - LVSD + had an MI over 12 months ago [176,177]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[e]	Very serious[i]	None	75/1013 (7.4%)	48/1015 (4.7%)	RR 1.57 (1.1 to 2.23)	27 more per 1000 (from 5 more to 58 more)	VERY LOW	IMPORTANT
Stroke - without HF + had a MI (72 hours – 12 months since onset of symptoms) [472,477]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[j]	Serious[h]	None	112/2954 (3.8%)	136/2972 (4.6%)	RR 0.83 (0.65 to 1.06)	8 fewer per 1000 (from 16 fewer to 3 more)	VERY LOW	IMPORTANT
Stroke – LVSD + had an MI over 12 months ago [176,177]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[e]	Very serious[k]	None	36/1013 (3.6%)	42/1015 (4.1%)	RR 0.86 (0.56 to 1.33)	6 fewer per 1000 (from 18 fewer to 14 more)	VERY LOW	IMPORTANT
Adverse events - hypotension - all patients[176,477]												
2	Randomised trials	Serious[d]	No serious inconsistency	Serious[l]	No serious imprecision	None	39/3937 (0.99%)	10/3987 (0.25%)	RR 3.91 (1.96 to 7.79)	7 more per 1000 (from 2 more to 17 more)	LOW	IMPORTANT
Adverse events - hyperkalaemia- all people [176 472,477]												
2	Randomised trials	Serious[g]	Serious[m]	Serious[l]	No serious imprecision	None	131/3967 (3.3%)	50/3987 (1.3%)	RR 2.63 (1.191 to 3.64)	20 more per 1000 (from 2 more to 33 more)	VERY LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Revascularisation - without HF + had a MI (72 hours – 12 months since onset of symptoms)[233,477]												
2	Randomised trials	Serious[a]	No serious inconsistency	Serious[c]	No serious imprecision	None	357/3148 (11.3%)	405/3175 (12.8%)	RR 0.89 (0.78 to 1.01)	14 fewer per 1000 (from 28 fewer to 1 more)	LOW	IMPORTANT
Revascularisation - LVSD + had an MI over 12 months ago[176,177]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[e]	Very serious[k]	None	49/1013 (4.8%)	50/1015 (4.9%)	RR 0.98 (0.67 to 1.44)	1 fewer per 1000 (from 16 fewer to 22 more)	VERY LOW	IMPORTANT
Hospitalisation - without HF+ had a MI (72 hours – 12 months since onset of symptoms)[233,477]												
2	Randomised trials	Serious[a]	No serious inconsistency	Serious[c]	No serious imprecision	None	1486/3148 (47.2%)	1542/3175 (48.6%)	RR 0.97 (0.92 to 1.02)	15 fewer per 1000 (from 39 fewer to 10 more)	LOW	IMPORTANT
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) It was unclear how the authors randomised participants however allocation concealment was performed. In the study that contributed the most to the overall outcome, participants were blinded.
(b) Heterogeneity was detected, I^2=67% p =0.08.
(c) One study had 47% people who had an MI. One study included people with a history of coronary intervention, with 67% having had a previous MI and 3% who had heart failure.
(d) It was unclear how the authors randomised participants however allocation concealment was performed. Participants and investigators were blinded.
(e) All participants had symptomatic heart failure.67% of participants have had an MI in the past.
(f) Heterogeneity was detected, I^2=72% p =0.06.
(g) It was unclear how the authors randomised participants however allocation concealment was performed. Participants and investigators were blinded.
(h) 95% confidence intervals crossed 1 MID (0.75).
(i) 95% confidence intervals crossed 1 MID (1.25).
(j) People had coronary artery disease (75%), peripheral vascular disease (11%), or cerebrovascular disease (22%) or diabetes.
(k) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).

(l) The population was indirect, all had less than 75% people who had an MI.
(m) Heterogeneity was detected, I^2=57%, p=0.13.

Table 68: GRADE profile: ARB and ACE inhibitors versus ACE inhibitors in people who have had an MI and who have been initiated with treatment between 72 hours and 12 months of the MI

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor + ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - LVSD[359,360]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	941/4885 (19.3%)	958/4909 (19.5%)	RR 0.99 (0.91 to 1.07)	2 fewer per 1000 (from 18 fewer to 14 more)	MODERATE	CRITICAL
All-cause mortality -without heart failure[436]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	1065/8502 (12.5%)	1014/8576 (11.8%)	RR 1.06 (0.98 to 1.15)	7 more per 1000 (from 2 fewer to 18 more)	LOW	CRITICAL
Cardiac mortality – LVSD[359,360]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	827/4885 (16.9%)	830/4909 (16.9%)	RR 1 (0.92 to 1.09)	0 fewer per 1000 (from 14 fewer to 15 more)	MODERATE	CRITICAL
Cardiac mortality - without heart failure[436,469]												
2	Randomised trials	Serious[a,e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	620/8502 (7.3%)	603/8576 (7%)	RR 1.04 (0.93 to 1.16)	3 more per 1000 (from 5 fewer to 11 more)	MODERATE	CRITICAL
Reinfarction (fatal + non-fatal) - LVSD[279,280]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	756/4885 (15.5%)	798/4909 (16.3%)	RR 0.95 (0.87 to 1.04)	8 fewer per 1000 (from 21 fewer to	MODERATE	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor + ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
										7 more)		
Reinfarction (fatal + non-fatal) - without heart failure[436,469]												
2	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	373/8502 (4.4%)	405/8576 (4.7%)	RR 0.93 (0.81 to 1.07)	3 fewer per 1000 (from 9 fewer to 3 more)	LOW	IMPORTANT
Stroke (fatal+non-fatal) – LVSD[436,469]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	183/4885 (3.7%)	211/4909 (4.3%)	RR 0.87 (0.72 to 1.06)	6 fewer per 1000 (from 12 fewer to 3 more)	LOW	IMPORTANT
Revascularisation – LVSD[279,280]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1128/4885 (23.1%)	1173/4909 (23.9%)	RR 0.97 (0.9 to 1.04)	7 fewer per 1000 (from 24 fewer to 10 more)	MODERATE	IMPORTANT
Revascularisation -without heart failure[436,469]												
2	Randomised trials	Serious[a, e]	No serious inconsistency	Serious[b]	No serious imprecision	None	1311/8581 (15.3%)	1281/8657 (14.8%)	RR 1.03 (0.96 to 1.11)	4 more per 1000 (from 6 fewer to 16 more)	LOW	IMPORTANT
Hospitalisation – LVSD[279,280]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1039/4885 (21.3%)	1021/4909 (20.8%)	RR 1.02 (0.95 to 1.1)	4 more per 1000 (from 10 fewer to 21 more)	MODERATE	CRITICAL
Hospitalisation - without heart failure[436]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	332/8502 (3.9%)	354/8576 (4.1%)	RR 0.95 (0.82 to	2 fewer per 1000 (from 7	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor + ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
									1.1)	fewer to 4 more)		
All adverse events - all people[360,469]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	454/4941 (9.2%)	387/4960 (7.8%)	RR 1.18 (1.03 to 1.34)	14 more per 1000 (from 2 more to 27 more)	LOW	CRITICAL
Adverse events- renal causes -all people[360,375]												
2	Randomised trials	Serious[a, e]	No serious inconsistency	Serious[b]	No serious imprecision	None	1209/13364 (9%)	911/13455 (6.8%)	RR 1.34 (1.23 to 1.45)	23 more per 1000 (from 16 more to 30 more)	LOW	CRITICAL
Adverse events - hyperkalaemia -all people[360,375]												
2	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	492/13364 (3.7%)	287/13455 (2.1%)	RR 1.73 (1.5 to 1.99)	16 more per 1000 (from 11 more to 21 more)	LOW	CRITICAL
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) It is unclear how the authors randomised the participants. However, allocation concealment was performed and participants were blinded.
(b) The ONTARGET study[436] included an indirect population of 48% people who had an MI.
(c) 95% confidence intervals crossed 1 MID (0.75).
(d) 95%confidence intervals crossed 1 MID (1.25).
(e) Yano et al[469,469] was an open label study.

7.3.6 Economic evidence

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Published literature

No studies were identified in CG48 comparing ACE inhibitor versus ARB, ACE inhibitors plus ARB versus ACE inhibitors, or ARBs versus placebo.

From the update searches, one study was included in this review with the relevant comparison comparing ARB versus placebo.[429,433] One study[59,59] that met the inclusion criteria was selectively excluded because it reported non-UK costs only. This is summarised in Appendix H, with reasons for exclusion given.

Another study was included which compared ACE inhibitor versus ARB.[243,244] These are summarised in the economic evidence profiles below (Table 69 and Table 70). See also the study selection flow chart in Appendix D and study economic evidence tables in Appendix H.

No relevant economic evaluations comparing ACE inhibitors plus ARB versus ACE inhibitors were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis of ACE inhibitors plus ARB versus ACE inhibitors, relevant unit costs are provided in Appendix M to aid consideration of cost effectiveness.

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Table 69: Economic evidence profile: ARB versus placebo

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects (QALYs)	Cost effectiveness (£/QALY)	Uncertainty
Taylor 2009 [429,433] (UK)	Partially applicable[(a)]	Very serious limitations[(b)]	Patient population: People who had an MI with left ventricular systolic dysfunction, heart failure, or both, who are not suitable for treatment with ACE inhibitors. Comparators: Valsartan (ARB). Placebo. Markov model based on separate studies for the 2 interventions: the VALIANT study [359,360] for the ARB arm and another study for the placebo arm: a meta-analysis [141,143] of the AIRE [15], SAVE [357,359] and TRACE [231] trials. Time horizon = 10 years. Incorporated differences in: cardiovascular death, nonfatal MI, stroke, heart failure, death for other reasons, GP visits, cardiologist visits, nurse visits, exercise tolerance test, angiography, revascularisation and study drug costs.	2860[(c)]	0.502	5338	In the sensitivity analysis the model showed that it was robust to a variety of factors. The probability of valsartan (ARB) being cost-effective at a willingness to pay threshold of £7,500/QALY is 100%.

(a) Utilities were estimated from a study using a time-trade off instrument and from a review of 20 studies.
(b) The estimates of rates of events in the placebo and intervention arms were obtained from different sources and there is therefore a break of randomisation. Some estimates of resource use were based on assumptions and expert clinical opinion. There is a potential conflict of interest.
(c) Costs are presented in 2008 prices and inflated where necessary. Inflation indices used were not stated.

Table 70: Economic evidence profile: ARB versus ACE inhibitor

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects	Cost effectiveness	Uncertainty
Lamy 2011 [243,244] (Multinational)	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Patient population: people with coronary artery, peripheral vascular or cerebrovascular disease or high risk diabetes mellitus with end-organ damage. • Comparators: 1) Ramipril (ACE inhibitor) 2) Telmisartan (ARB) • Cost study based on the ONTARGET study [436]. Follow up: 56 months • Incorporated differences in: hospitalisation events, procedures, and study and non-study drugs.	458 [(c)]	NR [(d)]	NR	Unit costs for new diagnosis of TIA, stroke, and renal failure with or without dialysis were selected for the sensitivity analysis as variations were potentially more significant than other variables. Varying those unit costs by ±25% had limited impact on total costs measured per person either individually or grouped.

Abbreviations: NR = not reported; TIA = Transient Ischaemic attack.

(a) Study from the USA. Discount rate was 3% instead of the 3.5% recommended by NICE. Health effects were not expressed in terms of QALYs.

(b) Resources were estimated from the ONTARGET study. Unit prices are not those of the NHS. There is a potential conflict of interest: this study was supported by an unrestricted grant from Boehringer Ingelheim as part of the ONTARGET study.

(c) Converted from 2008 US dollars using purchasing power parities[340]

(d) Based on the results of the ONTARGET study, there was no significant difference between the 2 groups for: primary outcome (CV death, MI, stroke or hospitalisation for heart failure), death from CV causes, MI, or stroke, cardiovascular death, MI, stroke, hospitalisation for heart failure, death from any cause.

7.3.7 Evidence statements

7.3.7.1 Clinical

7.3.7.1.1 Adverse events (ARBs versus ACE inhibitors)

In people who have had an MI who were initiated with treatment within 72 hours of the MI

- One study with 241 people who have had an MI and who were initiated with treatment within 72 hours showed that ARBs may reduce the risk of adverse events compared with ACE inhibitors [Low quality evidence].
- One study with 5926 people who have had an MI and who were initiated with treatment acutely within 72 hours showed that ARBs and ACE inhibitors have a similar effect on the risk of renal dysfunction, but there was considerable uncertainty [Very low quality evidence].
- One study with 241 people who have had an MI and who were initiated with treatment within 72 hours showed that ARBs may increase the risk of hypotension compared with ACE inhibitors [Very low quality evidence].

In people who have had an MI and who were initiated with treatment between 72 hours and 12 months of the MI

- Two studies with 9764 people who have had an MI and who were initiated with treatment between 72 hours and 12 months showed that ARBs reduce the risk of adverse events compared with ACE inhibitors [Low quality evidence].
- Two studies with 27,123 people who have had an MI and who were initiated with treatment between 72 hours and 12 months showed no difference between ARBs and ACE inhibitors on the risk of renal dysfunction [Low quality evidence].
- Two studies with 26,882 people who have had an MI and who were initiated with treatment between 72 hours and 12 months showed no difference between ARBs and ACE inhibitors on the risk of hyperkalaemia [Low evidence].

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7.3.7.1.2 Adverse events (ARBs versus placebo)

- Two studies with 7924 in people who have had an MI showed that ARBs increase the risk of hypotension compared with placebo [Low quality evidence].
- Two studies with 7954 in people who have had an MI showed that ARBs increase the risk of hyperkalaemia compared with placebo [Very low quality evidence].

7.3.7.1.3 Adverse events (ACE inhibitors plus ARBs versus ACE inhibitors)

- Two studies with 9901 people who have had an MI and were initiated before 72 hours or between 72 hours and 12 months showed that ACE inhibitors + ARBs increased the risk of adverse events compared with ACE inhibitors alone [Low quality evidence].
- Two studies with 26819 people who have had an MI and were initiated between 72 hours and 12 months, showed that ACE inhibitors + ARBs increased the risk of renal dysfunction compared with ACE inhibitors alone [Low quality evidence].
- Two studies with 26819 people who have had an MI and were initiated between 72 hours and 12 months showed that ACE inhibitors + ARBs increased the risk of hyperkalaemia compared with ACE inhibitors alone [Low quality evidence].

People who had an MI with LVSD

7.3.7.1.4 ARBs versus ACE inhibitors in people who have had an MI and who have been initiated with treatment between 72 hours and 12 months after an MI

- One study with 9818 people with LVSD who have had an MI and were initiated with treatment between 72 hours and 12 months showed no difference between ARBs and ACE inhibitors on the risk of all-cause mortality [Moderate quality evidence].
- One study with 9818 people with LVSD who have had an MI and were initiated with treatment between 72 hours and 12 months showed no difference between ARB and ACE inhibitors on the risk of cardiac mortality [Moderate quality evidence].
- One study with 9818 people with LVSD who have had an MI and were initiated with treatment between 72 hours and 12 months showed that ARBs may decrease the risk of stroke compared with ACE inhibitors [Moderate quality evidence].
- One study with 9818 people with LVSD who have had an MI and were initiated with treatment between 72 hours and 12 months showed no difference between ARBs and ACE inhibitors on the risk of revascularisation [Moderate quality evidence].
- One study with 9818 people with LVSD who have had an MI and were initiated with treatment between 72 hours and 12 months showed no difference between ARBs and ACE inhibitors on the risk of reinfarction [Moderate quality evidence].
- One study with 9818 people with LVSD who have had an MI and were initiated with treatment between 72 hours and 12 months showed no difference between ARBs and ACE inhibitors on the risk of rehospitalisation [Moderate quality evidence].
- No evidence on sudden death was identified
- No evidence on quality of life was identified

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7.3.7.1.5 ARBs versus placebo in people who have had an MI at some time in the past

- One study with 2028 people who had an MI at some point in the past with LVSD showed that ARBs may reduce the risk of all-cause mortality compared with placebo [Low quality evidence].
- One study with 2028 people who had an MI at some point in the past with LVSD showed that ARBs may increase the risk of reinfarction compared with placebo [Very low quality evidence].
- One study with 2028 people who had an MI at some point in the past with LVSD showed that ARBs may decrease the risk of stroke compared with placebo, but there was considerable uncertainty [Very low quality evidence].
- One study with 2028 pwoplw who had an MI at some point in the past with LVSD showed no difference between ARBs and placebo on the risk of revascularisation but there was considerable uncertainty [Very low quality evidence].
- No evidence on cardiac mortality was identified.
- No evidence on sudden deat h was identified.
- No evidence on rehospitalisation was identified.
- No evidence on quality of life was identified.

7.3.7.1.6 ACE inhibitors plus ARB versus ACE inhibitor in people who have had an MI and who have been initiated with treatment between 72 hours and 12 months of the MI

- One study with 9794 people with LVSD who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed no difference between ACE inhibitors + ARBs compared with ACE inhibitors alone on the risk of all-cause mortality [Moderate quality evidence].
- One study with 9794 people with LVSD who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed no difference between ACE inhibitors + ARBs compared with ACE inhibitors alone on the risk of cardiac mortality [Moderate quality evidence].

- One study with 9794 people with LVSD who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed ACE inhibitors + ARBs may reduce the risk of reinfarction compared with ACE inhibitors alone [Moderate quality evidence].
- One study with 9794 people with LVSD who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed that ACE inhibitors + ARBs decreased the risk of stroke compared with ACE inhibitors alone [Low quality evidence].
- One study with 9794 people with LVSD who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed no difference between ACE inhibitors + ARBs compared with ACE inhibitors alone on the risk of rehospitalisation [Moderate quality evidence].
- One study with 9794 people with LVSD who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed no difference between ACE inhibitors + ARBs compared with ACE inhibitors alone on the risk of revascularisation [Low quality evidence].
- No evidence on sudden death was identified.
- No evidence on quality of life was identified.

People who had an MI without heart failure

7.3.7.1.7 ARBs versus ACE inhibitors in people who have had an MI and who have been initiated within 72 hours of the MI

- One study with 429 people who have had an MI and initiated with treatment within 72 hours of the MI showed that ARBs and ACE inhibitors have a similar effect on the risk of cardiac mortality, but there was considerable uncertainty [Very low quality evidence].
- One study with 429 people who have had an MI and initiated with treatment within 72 hours of the MI showed that ARBs may increase the risk of reinfarction compared with ACE inhibitors but there was considerable uncertainty [Very low quality evidence].
- One study with 429 people who have had an MI and initiated with treatment within 72 hours of the MI showed that ARBs and ACE inhibitors have a similar effect on the risk of stroke, but there was considerable uncertainty [Moderate quality evidence].
- One study with 429 people who have had an MI and initiated with treatment within 72 hours of the MI showed that ARBs may increase the risk of revascularisation compared with ACE inhibitors, but there was considerable uncertainty [Very low quality evidence].
- One study with 429 people who have had an MI and initiated with treatment within 72 hours of the MI showed that ARBs and ACE inhibitors have a similar effect on the risk of rehospitalisation, but there was considerable uncertainty [Very low quality evidence].
- No evidence on all-cause mortality was identified.
- No evidence on sudden death was identified.
- No evidence on quality of life was identified.

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7.3.7.1.8 ARBs versus ACE inhibitors in people who have had an MI and who have been initiated with treatment between 72 hours and 12 month of the MI

- One study with 17,118 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 month of the MI showed no difference between ARB and ACE inhibitors on the risk of all-cause mortality [Moderate quality evidence].
- One study with 17,118 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 month of the MI showed no difference between ARB and ACE inhibitors on the risk of cardiac mortality [Low quality evidence].

- One study with 17,118 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 month of the MI showed no difference between ARBs and ACE inhibitors on the risk of revascularisation [Low quality evidence].
- One study with 17,118 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 month of the MI showed ARBs may increase the risk of rehospitalisation compared with those treated with ACE inhibitors [Low quality evidence].
- One study with 17,118 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 month of MI showed no difference between ARBs and ACE inhibitors on the risk of reinfarction [Low quality evidence].
- No evidence on sudden death was identified.
- No evidence on quality of life was identified.

7.3.7.1.9 *ARBs versus placebo in people who have had an MI and who have been initiated with treatment between 72 hours and 12 month of the MI*

- Two studies with 6323 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed no difference between ARBs and placebo on the risk of all-cause mortality [Very low quality evidence].
- Two studies with 6323 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed no difference between ARBs and placebo on the risk of cardiac mortality [Very low quality evidence].
- Two studies with 6323 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed ARBs may reduce the risk of reinfarction compared with placebo but there was some uncertainty [Very low quality evidence].
- One study with 5926 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed that ARBS may reduce the risk of stroke compared with placebo, but there was some uncertainty [Very low quality evidence].
- Two studies with 6323 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed that ARBs may reduce the risk of revascularisation compared with placebo [Low quality evidence].
- Two studies with 6323 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed no difference between ARBs and placebo on the risk of rehospitalisation [Low quality evidence].
- No evidence on sudden death was identified.
- No evidence on quality of life was identified.

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7.3.7.1.10 *ACE inhibitors and ARB versus ACE inhibitor in people who have had an MI (with treatment initiated within 72 hours or within 72 hours and 12 months of MI)*

- One study with 17,078 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed that ACE inhibitors + ARBs may increase the risk of all-cause mortality compared with ACE inhibitors alone [Low quality evidence].
- Two studies with 17,238 acute or people without heart failure who have had an MI and initiated with treatment within 72 hours or between 72 hours and 12 months of the MI showed no difference between ACE inhibitors and ARBs compared with ACE inhibitors alone on the risk of cardiac mortality [Moderate quality evidence].
- Two studies with 17,238 people without heart failure who have had an MI and initiated with treatment within 72 hours or between 72 hours and 12 months of the MI without heart failure showed no difference between ACE inhibitors and ARBs compared with ACE inhibitors alone on the risk of reinfarction [Low quality evidence].

- Two studies with 17,238 people without heart failure who have had an MI and initiated with treatment within 72 hours or between 72 hours and 12 months of the MI without heart failure showed no difference between ACE inhibitors and ARBs compared with ACE inhibitors alone on the risk of revascularisation [Low quality evidence].
- One study with 17,078 people without heart failure who have had an MI and initiated with treatment between 72 hours and 12 months of the MI showed no difference between ACE inhibitors and ARBs compared with ACE inhibitors alone on the risk of rehospitalisation [Low quality evidence].
- No evidence on sudden death was identified.
- No evidence on stroke was identified.
- No evidence on quality of life was identified.

People who had an MI with unselected LV function

7.3.7.1.11 ARB versus ACE inhibitors in people who have had an MI (within treatment initiated within 72 hours of MI)

- One study with 241 people with unselected LV function who have been initiated with treatment within 72 hours of the MI showed that ARBs may decrease the risk of all-cause mortality compared with ACE inhibitors, but there was considerable uncertainty [Very low quality evidence].
- One study with 241 people with unselected LV function who have been initiated with treatment within 72 hours of the MI showed that ARBs and ACE inhibitors may have a similar effect on the risk of reinfarction, but there was considerable uncertainty [Very low quality evidence].
- One study with 439 people with unselected LV function who have been initiated with treatment within 72 hours of the MI showed that ARBs may decrease the risk of revascularisation compared with ACE inhibitors, but there was considerable uncertainty [Very low quality evidence].
- One study with 439 people with unselected LV function who have been initiated with treatment within 72 hours of the MI showed that ARBs may decrease the risk of rehospitalisation compared with ACE inhibitors, but there was considerable uncertainty [Very low quality evidence].
- No evidence on sudden death was identified.
- No evidence on cardiac mortality was identified.
- No evidence on stroke was identified.
- No evidence on quality of life was identified.

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7.3.7.2 Economic

- One cost-utility analysis found that treatment with ARB is cost-effective compared to placebo in people who have had an MI with left ventricular systolic dysfunction, heart failure, or both, who are not suitable for treatment with ACE inhibitors (ICER: £5338 per QALY gained). This analysis was assessed as partially applicable with very serious limitations.
- One comparative cost analysis found that that treatment with ARB costs more than treatment with ACE inhibitors in people with coronary artery, peripheral vascular, or cerebrovascular disease or high risk diabetes mellitus with end-organ damage (cost difference: £458 per person). This analysis was assessed as partially applicable with potentially serious limitations.
- No relevant economic evaluations were identified that compared a combination of ACE inhibitors and ARB with single treatment in people who have had an MI.

7.3.7.3 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.[266,267] 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.[444]

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.[308]

Evidence statements

No trials were found comparing frequent with less frequent monitoring of renal function.

Patients after MI with renal dysfunction are at higher risk of adverse cardiovascular outcomes than those with normal renal function (2+).

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.

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+).

Treatment with an ACE inhibitor and ARB combined in patients after MI was associated with an increased risk of renal dysfunction (1++).

7.3.8 Recommendations and link to evidence

Recommendation	**52. Offer people who present acutely with an MI an ACE inhibitor as soon as they are haemodynamically stable. Continue the ACE inhibitor indefinitely. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant.

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	Composite outcomes, such as cardiovascular death, myocardial infarction and stroke were included because of the paucity of evidence in this area.
Trade-off between clinical benefits and harms	**ACE inhibitor versus placebo** In people who have had an MI with left ventricular dysfunction, evidence graded as weak to moderate showed ACE inhibitors reduced the risk of all-cause mortality, cardiovascular mortality, sudden death, reinfarction and rehospitalisation compared with placebo. Conversely, evidence graded as weak to moderate showed ACE inhibitors increased the risk of revascularisation and adverse events, including renal dysfunction, hypotension and dizziness/fainting compared with placebo In people who have had an MI without overt symptoms of left ventricular systolic dysfunction or heart failure, evidence graded as weak showed ACE inhibitors reduced the risk of having the composite outcome of cardiovascular death, reinfarction and stroke or cardiac arrest compared with placebo. The risk of having an independent outcome of cardiac mortality, stroke, reinfarction and rehospitalisation was also reduced. However, ACE inhibitors were also associated with an increased risk of having an adverse event including cough, hypotension, kidney failure or intolerance. In people who have had an MI with unselected LV function, evidence graded as weak to moderate showed compared with placebo ACE inhibitors reduced the risk of all-cause mortality, sudden death and cardiovascular death. In contrast, evidence graded as weak to moderate showed ACE inhibitors increase the risk of reinfarction, revascularisation and adverse events (including renal dysfunction and hypotension) in this group. No effect was detected on the risk of stroke. The GDG considered that the evidence suggesting a benefit of offering ACE inhibitors outweighs any potential harm (for example, adverse events) and therefore, it was agreed that ACE inhibitors should be given following an MI. **Initiation of treatment** There was evidence graded as weak to suggest a reduction in all-cause mortality and reinfarction with early initiation of ACE inhibitors, compared with late initiation of therapy. However, there was evidence graded as weak for an increase in long-term revascularisation and adverse events (including hypotension) with early initiation of ACE inhibitors. There was evidence of no effect of early initiation on stroke and short term revascularisation. The GDG agreed that the benefits of early initiation of ACE inhibitors outweighed any increase in adverse events or revascularisation and therefore it was recommended that ACE inhibitor therapy should be initiated early, after a person has been identified as haemodynamically stable. **Duration of treatment** The GDG felt that the evidence for the long-term use of ACE inhibitors was less robust, particularly in people without overt symptoms of left ventricular dysfunction or unselected LV function. Nevertheless there was no evidence to suggest that there is a particular duration of treatment after which no benefit is derived. Additionally, the GDG noted that there were potential harms associated with withdrawal of an ACE inhibitor.

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	For people who have had an MI with LV dysfunction, there is a reduction in the risk of mortality (all-cause, cardiac and sudden death), reinfarction and rehospitalisation from 15 months, up to 4 years of treatment. No long-term benefit was found on the risk of stroke and there were unclear effects on revascularisation. Adverse events, however, were more frequent in people who had received long-term ACE inhibitor treatment. For people without symptoms of left ventricular dysfunction or heart failure who have had an MI, 4.2 or 5 years of ACE inhibitor treatment appears to reduce the risk of reinfarction and of having a composite outcome (cardiovascular death, reinfarction and stroke or cardiac arrest). No study reported the effects on all-cause mortality beyond 12 months of treatment. Long-term ACE inhibitor treatment is also associated with an increased risk of adverse events. Similarly in unselected people with varying left ventricular function, 6 to 12 months of treatment may reduce the risk of mortality (all cause, cardiac and sudden) and rehospitalisation (no longer time points were captured). Potential harms may be found with long-term treatment on the risk of revascularisation and reinfarction although the evidence was very low quality (see discussion below in quality of evidence). In addition, an increased risk of adverse events is associated with ACE inhibitor treatment in this population. For people who have had an MI without heart failure, who underwent revascularisation (CABG or PCI), low quality data showed 4.2 years of ACE inhibitor treatment may reduce the risk of reinfarction. No other outcomes were reported on this revascularised population. No data on the effects of ACE inhibitors on only people who have been treated with PCI was found. In conclusion, the GDG felt that treatment with ACE inhibitors should be recommended indefinitely in people with and without left ventricular dysfunction (or without heart failure) as the benefits of long term treatment were likely to outweigh any potential adverse events including cough, hypotension, kidney failure or intolerance.
Economic considerations	No economic studies comparing different durations of the same ACE inhibitor were identified. An economic model developed for the previous guideline CG48 showed that life-time treatment with ACE inhibitors is cost-effective compared to placebo, both in people with normal LV function and left ventricular dysfunction. An additional UK cost-utility analysis evaluated the cost effectiveness of ACE inhibitors compared to placebo. In this study the median treatment duration was 3.7 years. Results were stratified by risk group and they showed that ACE inhibitors are cost effective up to a 5 year risk of cardiovascular events of 7%; they are no longer cost effective in people with a 5 year risk of events of 3%. The GDG believe that the 5 year risk of events post MI is usually higher than 3%; furthermore, ACE inhibitors are cheaper now compared to when the study was conducted. For these reasons they concluded that indefinite treatment with ACE inhibitors is likely to be cost-effective.
Quality of evidence	**ACE inhibitor versus placebo** The overall quality of the evidence for the clinical outcomes was graded as very low to moderate quality, however, the majority was graded as very low to low quality. All the evidence was identified from a direct population. The reason for downgrading the quality of the evidence was mostly because of lack of detail provided in the methods. The majority of papers were published prior to the year 2000 and little information was provided on the methods of randomisation or whether allocation concealment was performed. Outcomes were also

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downgraded because of imprecision, i.e. wide 95% confidence interval or the range in which the results fall within. When this was detected it was mostly due to few events recorded or small participant numbers. Two large trials also provided data on stroke and cardiac mortality in those without LVSD but the population was indirect since less than 75% of the people had an MI (at some point in the past).

The quality of the evidence for the composite outcome (cardiovascular death, reinfarction and stroke or cardiac arrest) was downgraded.

No evidence was identified on people who had undergone primary PCI following an MI. Only 1 study provided data on people who had an MI who underwent either PCI or CABG. The data was graded as low quality because it was a subgroup analysis of people from a larger trial. Therefore, it is not known if they were matched at baseline and there is a risk of reporting bias since no other outcome, besides reinfarction, was reported on this subgroup.

The economic evidence was based on a model which was built for the previous guideline, CG48, and on a UK cost-utility analysis. They both were partially applicable to the UK NHS setting but had potentially serious limitations.

Initiation of ACE inhibitors

The quality of the evidence for the clinical outcomes was graded as very low to low quality. All the evidence was identified from a direct population.

No evidence was identified that looked at people who have undergone primary PCI following a myocardial infarction. One study was identified that considered whether ACE inhibitors should be initiated prior to thrombolysis but the GDG did not feel that this evidence was strong enough to make a recommendation relating to this population.

No economic evidence was identified on the initiation of ACE inhibitors.

Duration of ACE inhibitor treatment

To determine the optimal duration of ACE inhibitor treatment, the ideal approach would be to compare the results in people randomised to different durations of treatment that is 6 months versus 2 years. No studies were found that used this approach. As a result alternative approaches were used in studies where people were randomised to either an ACE inhibitor or placebo. We either: 1) captured the number of events occurring in distinct time periods i.e. 0-3 months, 3 months-12months or 2) compared the results in different papers that used varying durations of follow-up up to a maximum of 5 years. For the first approach we only had data on unselected people with unselected LV function, and it was low quality because of few events and low participant numbers. Thus, the GDG had little confidence in making recommendations based on this type of analysis.

The second approach provided the majority of the data for this review. However, this method is not ideal because it is unclear when the events occurred. For example, if a study reported mortality at 12 months it is unknown whether the majority of deaths occurred in the first 3 months. Therefore, it is difficult to distinguish between short and long-term benefits. Despite this limitation, we compared the outcomes at different follow-up time periods up to a maximum of 5 years to see if the benefits or harms were consistent. This appeared to be the case, so the GDG felt confident in recommending ACE inhibitors indefinitely.

No economic evidence was identified on the duration of ACE inhibitors.

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Other considerations	There were no other considerations.

Recommendation	**53. Titrate the ACE inhibitor dose upwards at short intervals (for example, every 12–24 hours) before the person leaves hospital until the maximum tolerated or target dose is reached. If it is not possible to complete titration during this time, it should be completed within 4–6 weeks of hospital discharge. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment (including renal dysfunction, hypotension and dizziness/fainting), which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	No direct evidence was identified on the optimum time period for ACE inhibitors to be titrated to the maximum clinically tolerated dose. This is because no evidence identified, titrated an ACE inhibitor to the same maximum clinically tolerated dose. The indirect evidence identified was of low quality and showed an increased risk of harmful outcomes associated with a high/fast titration method compared with a low/slow titration. However, the GDG felt that the evidence was weak and that the titration regimens used were not representative of those used in clinical practice. In the absence of direct evidence, the GDG felt that guidance should be derived from large clinical trials that showed early titration of ACE inhibitors is clinically effective in people who have had an MI and who have been initiated with treatment within 72 hours (for the 3 largest trials: in ISIS-4, captopril was prescribed at a maximum dose 12 hours after the MI, in GISSI, lisinopril was prescribed at a maximum dose 48 hours after the MI and in CCS-1 captopril was prescribed at a maximum dose when blood pressure was normal after 2 hours). Additionally, the GDG felt that it was practical for titration to occur early, within an inpatient setting. However, the shorter inpatient stay associated with primary PCI in people who have had a STEMI means that this is not consistently achieved. The GDG clarified the recommendation to highlight that where titration in an inpatient setting was not possible, titration to the maximum tolerated dose should continue in the community and be guided by the discharge management plan (see Recommendation 98). In CG48, the previous version of the guideline,, a recommendation on the titration of ACE inhibitors was a good practice point based on the experience of the GDG. They recommended that ACE inhibitor therapy be titrated upwards at short intervals (for example every 1 to 2 weeks) until the maximum tolerated dose is achieved. The

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	current GDG felt that the titration period should be shorter to replicate the titration methods used in large clinical trials and to ensure people reach the maximum tolerated dose before discharge since it is reported that a high proportion of people who have had an MI are on a sub-optimal dose. It is also important to note that the recommendation is to titrate to the maximum tolerated dose, therefore the patient's response to ACE inhibitors will also dictate how quickly the drug is titrated. It is also dependent on the type of ACE inhibitor prescribed. Therefore, the GDG recommended that ACE inhibitors should be titrated to the maximum tolerated or target dose in an inpatient setting. The GDG felt that where this is not achieved, it should occur within 4-6 weeks of hospital discharge.
Economic considerations	No evidence was identified comparing the cost effectiveness of rapid or slow titration regimens. It is likely that the difference in cost between titration strategies is minimal given the low unit cost of ACE inhibitors.
Quality of evidence	No direct evidence was found comparing 1 titration regimen with another that is slow versus fast dose titrations, up to the same maximum dose. Of the limited data available, the evidence was graded as very low to moderate quality. All the data used a direct population. Studies were downgraded for indirectness as the study design did not titrate the ACE inhibitor over different durations to the same maximum dose and instead titrated up to different final doses or used non-clinical doses. A further study was downgraded as both study arms were not selected from the same pool of participants. Furthermore, people were not matched for health status. Numerous outcomes were also downgraded for imprecision mostly because of few events and low participant numbers. Unfortunately because the interventions were different, the data from the 2 studies could not be meta-analysed. No data were identified on people who have undergone primary PCI or on quality of life. The GDG therefore used informal consensus to develop the recommendation. Titration protocols from large clinical trials were used to aid discussion, identified in the review on the optimal duration of ACE inhibitor therapy (GISSI, ISIS-4 and CCS). The 3 studies were of reasonable quality since they showed a low risk of bias for randomisation of participants, used a direct population, and were large, and had low drop-out rates, but it is unclear if they performed allocation concealment and in 1 study participants were not blinded.
Other considerations	The previous guideline, CG48, recommended that 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 achieved'. This recommendation was based upon informal consensus of the GDG. No recommendation is included in the guideline update on the setting in which titration should take place. The GDG highlighted that where titration to the maximum tolerated dose was not achieved within an inpatient setting, titration should continue in the community. In order to achieve this, a discharge summary which includes a clear management plan should be available to both patient and care provider. It was felt appropriate to set a limit to the time by which this should be achieved, taking account of the individual's situation. The GDG also highlighted that when considering titration speed in people who have had an MI, the healthcare provider should consider individual differences which may impact upon the

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	management strategy. For example, people who are hypotensive may require a slower titration regimen. It is acknowledged that the recommendation assumes a class effect and that the data is consistent across ages/sex. The GDG identified this recommendation as a key priority for implementation, as it was felt that titration of ACE inhibitors to the maximum tolerated target dose was often not achieved. Additionally, the GDG felt that this was less likely to be achieved with current acute management methods, given that inpatient stays are shorter.

Recommendation	**54.Offer people after an MI who are intolerant to ACE inhibitors an ARB instead of an ACE inhibitor. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment (including renal dysfunction, hypotension and dizziness/fainting), which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	**ARB versus placebo** Two papers were identified on the use of ARB versus placebo in people who have had an MI, who have had treatment initiated between 72 hours and 12 months of an MI and people without heart failure. The results showed ARBs reduced the risk of reinfarction, stroke, and revascularisation, with no effect on the risk of all-cause or cardiac mortality. Effects on rehospitalisation were unclear. There appeared to be a decreased risk of adverse events, including hypotension and hyperkalaemia compared to placebo. **ACE inhibitor versus ARB** There was a reduced risk of reinfarction and revascularisation for ACE inhibitors in comparison with ARBs, in a population who have had an MI, who have had treatment initiated within 72 hours and did not have heart failure. However, there was no difference in cardiac mortality, stroke or rehospitalisation. In those who had an MI (less than 72 hours since onset of symptoms) and unselected LV function, the results showed ACE inhibitors reduced the risk of mortality compared with ARBs, but were associated with an increased risk for revascularisation and rehospitalisation. There was no effect on reinfarction. All adverse events were increased in those taking ACE inhibitors; however there was an apparent reduction in hypotension. In those who had an MI, who have had treatment initiated between 72 hours and 12 months of the MI, there was no difference between ACE inhibitors and ARBs on all-

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	cause mortality, cardiac mortality, reinfarction, revascularisation or rehospitalisation. However there was an increased risk of stroke in those who took ACE inhibitors and had LVSD, and a decreased risk of rehospitalisation in those who took ACE inhibitors and did not have heart failure. Adverse events were higher in those taking ACE inhibitors compared with ARBs, but there was no difference in the risk of renal dysfunction or hyperkalaemia. In summary, ACE inhibitors generally produced more favourable outcomes than ARBs, although there were inconsistent effects for each outcome, the delay from onset of MI to the introduction of therapy and whether the population had preserved left ventricular function. However, the GDG felt there were sufficient benefits of ARBs, compared to placebo,to recommend treatment for those who were intolerant to ACE inhibitors.
Economic considerations	No economic evidence was found on people who had an MI in the past without LVSD. In the absence of clinical and economic evidence, the GDG considered the unit cost of ARB. As some ARBs are now available as generic, the GDG believe they are likely to be cost-effective.
Quality of evidence	The overall quality of the evidence was generally graded as low. This was because there was some imprecision in the results (that is the 95% CI crossed 1 or 2 minimal important differences) and unclear methods of allocation concealment and randomisation. Evidence in an indirect population (less than 75% MI) was also used. No evidence was identified that specifically considered the use of ACE inhibitors and ARBs in people who have undergone primary PCI and therefore, it was not possible to develop a specific recommendation for this population. The economic evidence was assessed as partially applicable with very serious limitations.
Other considerations	There were no other considerations.

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Recommendation	**55. Do not offer combined treatment with an ACE inhibitor and an angiotensin II receptor blocker (ARB) to people after an MI, unless there are other reasons to use this combination. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment (including renal dysfunction, hypotension and dizziness/fainting), which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	Studies comparing the effectiveness of ACE inhibitors plus ARBs versus ACE inhibitors showed that, in people who have had an MI without heart failure, combination treatment may increase the risk of all-cause mortality and potentially

	revascularisation. There was no effect on the risk of cardiac mortality, reinfarction and rehospitalisation. In those who have had an MI with LVSD, combination treatment compared with ACE inhibitors had no effect on the risk of all-cause or cardiac mortality, revascularisation or rehospitalisation. It did, however, appear to decrease the risk of reinfarction and stroke. For stroke, there was some uncertainty. Any gains should be weighed against the increased risk of hypotension and hyperkalaemia. These adverse events can be managed by reducing treatment dose or withdrawing treatment, where significant effects are observed. However, there appeared to be a decreased risk of adverse events compared with placebo. No data were available on quality of life. The GDG felt there was no clear benefit of combination therapy (ACE inhibitor plus ARB). For this reason, the recommendation on those with heart failure or LVSD was not amended from the previous guideline, CG48.
Economic considerations	No economic evidence was found on the combination of ARB and ACE inhibitors. The GDG considered the unit costs together with the clinical evidence and concluded that there is no evidence that the combination is more effective than single therapy, and therefore the combination of ACE inhibitors and ARB is not a cost-effective strategy.
Quality of evidence	For this comparison, only data on those who have had an MI and been initiated with treatment between 72 hours and 1 year after the MI was available and only 1 study per stratum for those with LVSD and without heart failure. The participant numbers were large. For people who have had an MI, with LVSD, the data was mostly graded as moderate quality. There was good precision and a direct population was studied. However, there was insufficient detail on the methods of randomisation. For those without heart failure, the outcomes were mostly graded as low quality. The data was downgraded because an indirect population was used (less than 75% people who have had an MI) and insufficient information was provided on the methods of randomisation. No economic evidence was found on this question.
Other considerations	No evidence was identified that specifically considered the combined use of ACE inhibitors and ARBs in people who have had an MI and been initiated with treatment within 24 hours, or in those who have undergone primary PCI and therefore, no specific recommendation was developed for this population.

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7.3.8.1 People who have had an MI in the past (more than 12 months ago)

Recommendation	**56. Offer an ACE inhibitor to people who have had an MI more than 12 months ago. Titrate to the maximum tolerated or target dose (over a 4–6 week period) and continue indefinitely. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was

	considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment (including renal dysfunction, hypotension and dizziness/fainting), which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	**ACE inhibitors versus placebo** The GDG discussed the evidence on ACE inhibitors versus placebo relating to a population of people who had an MI in the past. There were apparent benefits of ACE inhibitors compared to placebo on reinfarction, stroke and revascularisation for those people who have had an MI in the past. The GDG felt that the benefits of initiating ACE inhibitors in those who have had an MI in the past outweighed any likely adverse events. Therefore, the GDG made the decision to continue to recommend treatment with ACE inhibitors to people who have had an MI in the past, regardless of LV function or presence of heart failure. **Optimum titration** No direct evidence was identified on what the optimum time period is for ACE inhibitors to be titrated to a maximum clinically tolerated dose in those who had an MI in the past. Of the limited evidence available, that was graded as low quality the results showed an increased risk of harmful outcomes associated with a high/fast titration method compared with a low/slow titration.(see Recommendation 53) However, the GDG felt that the evidence was weak and that the titration regimens were not representative of those used in clinical practice. Additionally, it was noted that the time period for titration would be dependent upon the ACE inhibitor used. Therefore the GDG amended the recommendation to highlight the importance of ensuring that titration to the maximum tolerated or target dose was achieved. The recommended maximum time period over which this should occur was based on the experience of the GDG.
Economic considerations	The economic evidence included both people who had an MI with left ventricular systolic dysfunction and people who had an MI without heart failure with preserved left ventricular systolic dysfunction. The GDG felt that the conclusions of the evidence were applicable to both subgroups. An economic model developed for the previous guideline, CG48, showed that life-time treatment with ACE inhibitors is cost-effective compared to placebo. An additional UK cost-utility analysis evaluated the cost effectiveness of ACE inhibitors compared to placebo. Results were stratified by risk group and they showed that ACE inhibitors are cost effective at a 5 year risk of cardio-vascular events of 7% or higher; they are not cost effective in people with a 5 year risk of events of 3%. The GDG believe that the 5 year risk of events post MI is usually higher than 3%; plus, ACE inhibitors are cheaper now compared to when the study was conducted. For these reasons they concluded that treatment with ACE inhibitors is likely to be cost-effective.
Quality of evidence	Overall, the quality of evidence was graded as moderate. The GDG highlighted that the majority of studies relating to this population did not specify how long ago the people had a myocardial infarction, although it was agreed that this was likely to be reflective of the real life clinical scenario. Furthermore, the evidence identified did

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	not include people who have had a myocardial infarction and had received primary PCI. There were some limitations to the evidence identified as the data were taken from a subgroup analysis of a larger trial, meaning that it was difficult to match participants at baseline for the purposes of the subgroup analysis. No direct evidence was identified on the optimum duration of ACE inhibitor therapy in those who have had an MI in the past. However, 1 trial established benefit in this group for up to 4-5 years. There was also evidence from trials containing lower risk people, without a history of myocardial infarction, to suggest benefits of long term therapy. Therefore the GDG agreed that in people who have had an MI in the past, ACE inhibitor treatment should be continued indefinitely irrespective of left ventricular function or heart failure. **Optimum titration** Data on the optimal method of titration was limited and varied from being graded as very low to moderate quality. However, the data were not specific to those who had an MI in the past and was focused on those who were treated acutely, in a hospital setting. In the absence of data, the GDG agreed that ACE inhibitors should be titrated to a maximum tolerated dose over a 4-6 week period. This is consistent with the recommendation for those who begin treatment acutely. The economic evidence was based on the model which was built for the previous guideline,CG48, and on a UK cost-utility analysis. They both were partially applicable to the UK NHS setting and had potentially serious limitations.
Other considerations	The GDG highlighted the importance of ensuring that ACE inhibitors are titrated to their maximum tolerated clinically effective dose in line with the recommendation in this chapter. People with heart failure should be treated in line with NICE clinical guideline 108 'Chronic Heart Failure'.

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Recommendation	**57.Offer people who have had an MI more than 12 months ago and who are intolerant to ACE inhibitors an ARB instead of an ACE inhibitor. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment (including renal dysfunction, hypotension and dizziness/fainting), which

	impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	One paper was identified on the use of ARB versus placebo on people who had an MI sometime in the past and had LVSD. No data on this population for any other comparison was found. The findings showed that ARBs reduce the risk of all-cause mortality, cardiac mortality and stroke. However, there was an increase in the risk of reinfarction. There was no effect on revascularisation. There was decreased risk of adverse events (including hypotension and hyperkalaemia) compared with placebo. Further evidence was identified on the comparison of ACE inhibitor versus ARBs in people who had an MI who had treatment initiated between 72 hours and 12 months of the MI. In people who have had an MI who have had treatment initiated between 72 hours and 12 months without LVSD or heart failure, ACE inhibitors showed a better outcome than ARBs on the risk of rehospitalisation. No difference was found on the risk of all-cause mortality, cardiac mortality, revascularisation or reinfarction. In people who have had an MI and who have had treatment initiated between 72 hours and 12 months of the MI with LVSD, ACE inhibitors had no effect on the risk of mortality, reinfarction, revascularisation or rehospitalisation compared with ARBs but there was an increased risk of reinfarction. ACE inhibitors also appeared to reduce the risk of stroke. In people who have had an MI and who have had treatment initiated between 72 hours and 12 months of the MI with unselected LV function, ACE inhibitors reduced the risk of all-cause mortality compared with ARBs, but were associated with an increased risk of revascularisation and rehospitalisation, with no effect on the risk of reinfarction. Ninety per cent of people were treated with PCI, therefore the population closely reflects those seen in current practice. The benefits of ACE inhibitors versus ARBs need to be weighed up against the increased risk of adverse events. There appear to be more adverse events in the ACE inhibitor treatment group compared with ARBs, regardless of LV status, for all events, in some studies. However, in other studies there was no difference in the incidence of adverse events between ACE inhibitor and ARBs (renal dysfunction, hyperkalaemia). Furthermore, some studies showed ARBs were either better (all events) or worse than placebo (hypotension, hyperkalaemia). The GDG agreed that the benefits of ACE inhibitor treatment following an MI in the past outweighed any potential harms. However, in people who are intolerant to ACE inhibitors, there were still benefits in providing treatment with an ARB, compared to placebo. Therefore, the GDG agreed that the recommendation from the previous guideline, CG48, should be retained and that, for people who have had an MI in the past, who are intolerant to ACE inhibitors, an ARB should be offered.
Economic considerations	One economic study was found which compared ARB versus placebo in people who have had an MI with left ventricular systolic dysfunction, heart failure, or both.[429,433] This was a cost-utility analysis based on clinical data obtained from separate studies for the 2 interventions: the VALIANT study [359,360] for the ARB arm and for the placebo arm a meta-analysis [141,143] of the AIRE [15] and SAVE [357,359] and TRACE [231] trials. The health and cost parameters incorporated were cardiovascular death, nonfatal MI, stroke, heart failure, death for other reasons, GP visits, cardiologist visits, nurse visits, exercise tolerance test, angiography, revascularisation and drug costs. Over a ten-year time-horizon, treatment with ARB was cost-effective compared to placebo and the ICER was £5,338/QALY. Although the study had various limitations, the sensitivity analysis showed that the model was robust to a variety of factors. The probability of ARB being cost-effective at a willingness to pay threshold of

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	£7,500/QALY was 100%. Therefore the GDG concluded that in those people who cannot take ACE inhibitors, ARBs are a cost-effectiveness option.
Quality of evidence	Evidence relating directly to those who had an MI in the past was graded as low quality. This was because there was imprecision in the results (that is the 95% CI crossed 1 or 2 minimum important differences) and there were unclear methods of allocation concealment and randomisation. Additionally, it was unclear how long ago the participants had their MI. Overall, the quality of the evidence on those who had an MI and who have been initiated with treatment between 72 hours and 12 months of the MI, and compared ARBs versus ACE inhibitors was graded low. In those without heart failure, an indirect population was used (67% post MI) but it did include large participant numbers so the results were precise. In those with LVSD there were a large number of participants and the results were mostly precise. The findings from these studies were downgraded because it was unclear either how they performed allocation concealment or randomisation. One study considered the use of ACE inhibitors and ARBs in people who had undergone primary PCI. The participant numbers were very small and the results showed serious imprecision, therefore, the GDG did not make a specific recommendation for this population. The data on adverse events was from people who have had an MI who have had treatment initiated between 72 hours and 12 months of the MI, rather than those who had an MI more than 12 months ago. Therefore, it was only possible to extrapolate from these findings to this population (regardless of LV status). These data were generally precise but showed mixed results (that is which drug increased risk of adverse events). No economic evidence was found on this population.
Other considerations	There were no other considerations.

Recommendation	**58. Ensure that a clear management plan is available to the person who has had an MI and is also sent to the GP, including:** • **details and timing of any further drug titration** • **monitoring of blood pressure** • **monitoring of renal function. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly

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	undesirable and in addition had significant economic impact. The adverse effects of treatment (including renal dysfunction, hypotension and dizziness/fainting), which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	During the review on titration of ACE inhibitors, the GDG discussed whether titration of ACE inhibitors to the maximum tolerated or target dose was being achieved in an inpatient setting, it was often not achieved in the community post-discharge. The GDG discussed that although people who had an MI are prescribed ACE inhibitors in hospital, many are not titrated to a maximum clinically tolerated dose and some outpatients are on a sub-optimal dose. Furthermore, opportunities in hospital to titrate ACE inhibitors to the correct dose were often not being taken. These findings were considered particularly relevant given the short inpatient stay associated with primary PCI and as such, the importance of ensuring a smooth transfer of care and information between primary, secondary and tertiary care. The GDG therefore agreed that a recommendation should be developed to highlight the importance of ensuring clear communication and that a discharge summary should be made available to both the patient and GP without delay. The group felt that this recommendation should outline a clear management plan for the titration of ACE inhibitors and other drug therapy prescribed following an MI and that this was particularly important given the changes in acute management since the previous guideline, CG48.
Economic considerations	No economic evidence was identified, although there are some costs associated with the management plan (for example, staff time cost). The GDG considered the economic implications and concluded that this intervention will improve the quality of life of the person after an MI. This is because a clear plan for the titration of ACE inhibitors therapy would reduce unnecessary adverse events and increase the effectiveness of the therapy; the improvement in quality of life was considered likely to outweigh the costs.
Quality of evidence	This recommendation and it was based upon informal consensus of the GDG.
Other considerations	Further recommendations on medicines adherence can be found in NICE clinical guideline 76 'Medicines Adherence'. Further recommendations on communication can be found in NICE clinical guideline 138 'Patient experience'.

Recommendation	**59. Offer an assessment of left ventricular function to all people who have had an MI. [2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the patient and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment (including renal dysfunction, hypotension and dizziness/fainting), which impact on quality of life (which was not always measured) were also considered

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	relevant.
Trade-off between clinical benefits and harms	The GDG considered that it was important for people who have had an MI to undergo assessment of their left ventricular function. It was agreed that this was important for those on drug therapy following an MI, given that the effectiveness of treatment with ACE inhibitors, ARBs and beta-blockers was dependent upon left ventricular function. It was noted that the outcome of assessment could impact upon the type, titration and duration of therapy given to a person who has had an MI. No evidence was identified to support this recommendation and it was based on informal consensus of the GDG.
Economic considerations	No economic review was conducted on the assessment of left ventricular function as this recommendation was based on the conclusion from clinical studies that the effectiveness of ACE inhibitors, ARBs and beta-blockers depend on the left ventricular function. This assessment has some costs but it would ensure that treatments are given to the right population, which would ultimately mean that resources are used correctly and efficiency is achieved.
Quality of evidence	This recommendation was based upon informal consensus of the GDG.
Other considerations	The GDG identified this recommendation as a key priority for implementation, as the result of assessment can affect subsequent drug therapy.

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60. 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 reach, 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 108).[2007]

7.4 Antiplatelet therapy

7.4.1 Clinical effectiveness of antiplatelet agents

A meta-analysis of randomised controlled trials of antiplatelet therapy in high risk patients [32] 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.[134 135 26, 101 66] Of these, one randomised controlled trial found a reduction in non-fatal MI (7.1% versus 10.9%, P < 0.05) [135] and another a reduction in mortality (5.8% versus 8.3%, Z value - 1.9).[101]

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).[31] and reinfarction (P < 0.03) [455]

7.4.2 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 [472,478] 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).[353,354]

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.[84]

7.4.3 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.[162]

7.4.4 Clinical effectiveness of aspirin versus aspirin plus clopidogrel

7.4.4.1 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.[311] One randomised control trial was identified. [472,478] 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).

7.4.4.2 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.[394,395] 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).[86,89] 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.[49,50] 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.[49,50]

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.[49,50]

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.[49,50]

In summary, only two trials were identified that examined the effectiveness of clopidogrel plus aspirin treatment versus aspirin alone in patients immediately after ST elevation MI.[394,395 86,89] The combination treatment was not studied beyond 4 weeks and hence it is not clear if there is any further benefit of continuing combination treatment in the longer term for patients after an ST elevation MI.

7.4.4.3 Economic evidence

7.4.4.3.1 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.[215,217 400 223,224 24,25] One of these studies [215,217] was a Health Technology Assessment (HTA). In this section, only the results of the HTA are summarised. And the other paper's evidence tables are in the appendix.

The HTA [215,217] 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.

7.4.4.4 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.[263 140 246 399 161 254,255 222,224] In this section, only the results of the HTA are summarised, and the other paper's evidence tables are in the appendix.

The HTA [263] 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; 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 cannot be recommended beyond 12 months.

7.4.4.5 Evidence statements

After an MI, treatment with aspirin reduces the risk of death and cardiovascular events (1++).

In a subgroup of patients with recent MI, aspirin and clopidogrel have similar cardiovascular benefits (1++).

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

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.

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

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+).

In a study of a mean duration of 28 months that recruited patients with either clinically evident cardiovascular disease or multiple vascular risk factors, 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

"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 Information for patients on the TA for 'Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events'.

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++).

7.4.5 Duration of clopidogrel therapy

Dual antiplatelet therapy with aspirin plus an adenosine diphosphate (ADP) antagonist (clopidogrel, prasugrel or ticagrelor) is standard practice for most people following an acute coronary syndrome event (unstable angina, NSTEMI or STEMI). In England 2010/11, 99% of people eligible received aspirin and 95% clopidogrel or another thienopyridine inhibitor on discharge after an MI; in Wales, 98% received aspirin and 92% clopidogrel or another thienopyridine inhibitor.[304] This is in line with current NICE guidelines' focus on acute management and in line with NICE technology appraisals.[306,307,311,315,317]

Although it is clear that early dual antiplatelet therapy is important, there is less clarity about the question of how long dual therapy should be continued after myocardial infarction. The previous guideline, CG48, recommended that aspirin is continued indefinitely and that the duration of clopidogrel treatment should depend on the type of MI. The guideline recommended treatment for 4 weeks in people who have had a STEMI and 12 months for those who have had an NSTEMI, as per NICE technology appraisal guidance 80 (TA 80). More recently NICE technology appraisal guidance 210 (TA210) published recommendations about long term clopidogrel treatment in people who have multivascular disease.

Since the publication of the previous guideline, CG48, the acute management of MI has changed considerably and many more people now undergo revascularisation as part of their acute management strategy. Revascularisation in this situation is usually by percutaneous coronary intervention, usually with either bare metal or drug eluting stents. Early treatment with dual

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antiplatelet therapy clearly reduces the risk of stent thrombosis. However concerns had arisen about late stent thrombosis after withdrawal of clopidogrel therapy, adding an extra dimension to the issue of duration of therapy in these people.

Furthermore, the cost of clopidogrel has reduced as it is now available generically. Thus any small gains of longer duration therapy that were not cost effective previously may now be worthwhile.

It was therefore important to review the optimal duration of clopidogrel for all peopleas part of this update. This includes updating the recommendation on duration of treatment for people who have had unstable angina and NSTEMI from 'Clopidogrel for the treatment of non-ST-segment-elevation acute coronary syndrome', NICE technology appraisal guidance 80 (TA 80), a recommendation which was also included in CG94 'Unstable angina and NSTEMI'.

This chapter considers evidence relating to clopidogrel only as recommendations on treatment with prasugrel and ticagrelor can be found in TA182 'Acute coronary syndromes – prasugrel' and TA236, 'Acute coronary syndromes – ticagrelor'.

7.4.5.1 What is the optimal duration that clopidogrel should be continued in people after an MI?

For full details see review protocol in Appendix C.

7.4.5.2 Clinical evidence

This review searched for randomised controlled trials comparing the effectiveness of clopidogrel in post-myocardial infarction populations over different durations. Where no RCTs were identified, cohort studies were included.

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Twelve studies were identified.[45,51,89,147,240,284,349,384,394,423,450,473,478] These are summarised in Table 71. See also the full study evidence tables in Appendix G and forest plots in Appendix I. NICE Technology Appraisal 80 "Clopidogrel in the treatment of non-ST-segment-elevation in acute coronary syndrome" (TA80) was also used as a reference.[311]

The data is presented in 3 sections:

1) A comparison of the effects of different durations of clopidogrel and aspirin (Table 72), with people randomised to 1, 6, 12 or 24 months of treatment. This is considered the ideal study design. There were 4 papers with this study design [45,284,423,450] included.
2) A review of the results of TA80[311] (including the CURE study).[284,284] These results are presented as the number of events (that is the combined outcome of cardiovascular death/MI/stroke) recorded within distinct time periods, that is 0-1 months, 1-3months, 3-6months, 6-9months and 9-12months (the events are not cumulative). It is possible to see when the events occurred and how the frequency of these events changes over time within the same population. TA80 used a composite outcome to assess the effectiveness of clopidogrel treatment over time, rather than individual outcomes, limiting the ability to know which outcome (that is MI or stroke) is being impacted most. TA80 is not critiqued in GRADE although the study from which the results were extracted, the CURE trial, is included in the analysis of different durations of follow up.
3) The results from papers that compared clopidogrel and aspirin versus aspirin alone with different follow-up time periods (Table 75). It is possible to observe the number of events occurring at different time points that is 0-30 days, 0-1 year, 0 to 1 year. Rarely were data available from 30 days to 1 year, so for studies that had a 12 month follow-up time period, it is difficult to know when the events occurred.

The results were further analysed to see if they varied by STEMI, NSTEMI or an indirect population (including mixed populations) (Table 76). They were also stratified according to the type of acute

treatment that is PCI, CABG or medical treatment. A subgroup analysis of people who have multivascular disease from the CHARISMA trial was included because it was a large trial with a follow up of 28 months. This study was therefore categorised as a mixed population but it was also considered relevant to people who have had an NSTEMI as treatment patterns were similar to a current NSTEMI population, and was therefore included in the NSTEMI stratum.

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Table 71: Summary of included studies

	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Outcomes reported
1.	Bhatt2007[49,51] CHARISMA	CG48 (new subgroup analysis of larger RCT)	Clopidogrel 75mg/day plusaspirin (75 to 162mg/day) versus aspirin (75 to 162mg/day)	40.5% had prior MI. 23.6months prior to randomisation (median time from diagnosis). 34% had prior stroke. 3.5months prior to randomisation (median time from diagnosis). 30% had symptomatic PAD. 23.6 months (median time from diagnosis). Note: 4.7% fell into multiple categories. Not admitted to hospital and then randomised.	28 months	• All-cause mortality • Cardiovascular mortality • Reinfarction (non-fatal) • Stroke (fatal) • Rehospitalisation for unstable angina, transient ischaemic attack, revascularisation • Bleeding
2.	Bernardi 2007[45,45] RACS	New	Both groups treated with clopidogrel (300mg loading dose then 75mg/day)plus aspirin (75 to 325mg) 300mg clopidogrel was given before angioplasty or immediately afterward. Unclear if it was continued at this	PCI People had • STEMI • ACS • Stable angina	30 days versus 6 months	• All-cause mortality • Cardiovascular death • Reinfarction • Stroke • PCI • CABG • Revascularisation • Adverse events

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Outcomes reported
			dose.			
3.	Chen 2005[86,89] COMMIT	CG48	Clopidogrel 75mg/day plus aspirin 162mg/day versus aspirin 162mg/day	STEMI Timing: suspected MI (within 72 hours of onset of symptoms)	28 days	• All-cause mortality • Cardiovascular death • Reinfarction (fatal and non-fatal) • Ischaemic stroke (nonfatal and fatal) • Stroke (fatal) • Bleeding
4.	Fox 2004[147,147] CURE-CABG	New (Subgroup analysis of people who had CABG from larger RCT-CURE)	Clopidogrel 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to 325mg/day)	People treated with CABG Clopidogrel n=1011 Placebo=n=1061	12 months	• People undergoing CABG • Major bleeding
5.	Kulik 2010[240] CASCADE	New	Clopidogrel 75 mg/day plusaspirin (162 mg/day) versus aspirin (162mg/day)	CABG treated ACS n=12-22%, Heart failure NYHA 3-4 n=17 to 23%	12 months	• All-cause mortality • Cardiovascular death • Reinfarction • Stroke • Revascularisation • Major bleeding • Minor bleeding • Adverse events
6.	Pekdemir 2003 [349,349]	New	Both groups treated with clopidogrel (75 mg/day) plus aspirin 100mg/day	Stents Unstable angina: 30% stable angina: 34-44% silent ischaemia: 4-8% MI: 11-15% heart failure:10-12%	1 month versus 6 months	• Death • Reinfarction (acute) • Pre-percutaneous transluminal coronary angioplasty • Revascularisation

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Outcomes reported
7.	Sabatine 2005[394,395] CLARITY-TIMI 28	CG48	Clopidogrel (300mg loading dose then 75mg/day) plus aspirin (150-325mg 1st day to 75-162mg) versusaspirin	STEMI	30 days	• Cardiovascular death • MI • Reinfarction (recurrent) • Major bleeding • Minor bleeding • Stroke • Recurrent ischaemia leading to urgent revascularisation
8.	Steinhubl et al. 2002[423] CREDO	New	Both groups treated with clopidogrel 75mg/day plus aspirin (81-325mg/day) versus aspirin (81-325mg/day) All participants were on clopidogrel plus aspirin for 1 month, then either clopidogrel plus aspirin or aspirin until 12 months.	PCI (89% had stents) Unstable angina (53%), stable angina (33%), recent MI (14%) Excluded if persistent STEMI less than 24 hours prior to PCI Timing: about to undergo elective PCI	28 days versus 12 months	• All-cause mortality (12months) • Reinfarction (12months) • Stroke (12months) • Revascularisation (12months) • Major bleeding (28 days and 1year) • Minor bleeding (28 days and 1year) • Stent versus no stent (combined end point of death, MI and Stroke) (12 months) • Bleeding result appears cumulative.
9.	Yusuf 2001[472,478] CURE	CG48	Clopidogrel 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to 325mg/day)	ACS (and not an ST-segment elevation of more than 1mm on ECG) Unstable angina (75%) Suspected MI (25%) Medical therapy	12 months	• All-cause mortality • Cardiovascular death • Reinfarction (Q wave and non-Q wave) • Stroke • Recurrent ischaemia (during hospitalisation and after discharge)

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Outcomes reported
				n=8192 (65%) PCI (21%) Clopidogrel n=1313 Placebo n=1345 CABG (14%)		
10.	Yusuf 2003[472,473] CURE	New	Clopidogrel 75mg/day plus aspirin (75 to 162mg/day) ersus aspirin (75 to 625mg/day)	ACS (and not an ST-segment elevation of more than 1mm on ECG) Unstable angina (75%) Suspected MI (25%) Medical therapy n=8192 (65%) PCI (21%) Clopidogrel n=1313 Placebo n=1345 CABG (14%)	24 hours 0-7 days 8-30 days 0-30 days Over 30 days-1year	• Bleeding (24 hours) • Refractory ischaemia (0-30 days, over 30 days-1year) • Severe ischaemia (0-30days, over30 days-1year) • Major Bleeding (0-7 days, 8-30 days, 0-30 days, over 30 days-1 year) • Minor bleeding • Distinct time points (not cumulative)
11.	Mehta 2001[284,284] CURE-PCI	New (subgroup	Clopidogrel 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to	People with NSTEMI who had PCI (82% had stents) ST depression (43%)	PCI to 30 days PCI to 12 months	• People who had PCI • Cardiac mortality • Reinfarction

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Outcomes reported
		analysis of people who have undergone PCI from a larger RCT)	625mg/day). All participants were on clopidogrel plus aspirin for 1 month, then either clopidogrel plus aspirin or aspirin for 11 months.	ST elevation (5%) PCI was done after randomisation at the discretion of the local investigator and clopidogrel and placebo were continued up until this point.		• Revascularisation • Major bleeding • Minor bleeding • Cumulative (but calculated distinct)
12.	Valgimigli 2012 [449,450]	New	Both groups treated with clopidogrel (75 mg/day) plus aspirin (80-160mg/day)	Stable angina 25% ACS 75% Unstable angina 19% NSTEMI 22% STEMI 33%	6 months versus 24 months	• All-cause mortality • Cardiovascular mortality • Reinfarction • Stroke • Major bleeding • Minor bleeding

Table 72: Studies comparing different durations of clopidogrel plus aspirin versus aspirin (short-term versus long-term clopidogrel)

	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Treatment	Outcomes reported
Indirect population							
1.	Bernardi 2007 [45,45] RACS	New	Both groups treated with clopidogrel (300mg loading dose then 75mg/day)plus aspirin (75 to 325mg) for 1 month then either aspirin or clopidogrel plus aspirin for 5 months.	Undergone PCI with stent; people had symptomatic CAD with evidence of ischaemia; target lesion with over 50% stenosis	30 days versus 6 months First 30 days groups were given the same treatment.	PCI	• All-cause mortality • Cardiac mortality • Reinfarction • Stroke • PCI • CABG

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Treatment	Outcomes reported
				72% presented with ACS and 15% had an MI as the indication for PCI. It was unclear whether those who had an MI as an indication for PCI were included in the percentage of people who had ACS.	The results are from 30days to 180 days. Same follow-up time point at 6months.		• Revascularisation • Adverse events
2.	Mehta 2001[284,284] CURE-PCI	New (subgroup analysis of people who have PCI from a larger RCT)	All participants were on clopidogrel (300mg loading dose then 75mg/day) plus aspirin (75-325 mg/day) for 2-4 weeks then aspirin or clopidogrel for 11months.	Direct: People with NSTEMI who had PCI plus 82% stents implanted: • ST depression (43%) • ST elevation (5%) Excluded people who had HF. PCI was done after randomisation at the discretion of the local investigator and clopidogrel and placebo was continued up until	PCI to 30 days PCI up to 12 months	PCI	• Cardiac mortality • Reinfarction • Revascularisation • Major bleeding • Minor bleeding • Cumulative (but calculated distinct)

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Treatment	Outcomes reported
				this point. Note: In older ACS studies, a large proportion of people who had unstable angina would now be classified in the direct population as NSTEMI (based on changes in diagnostic criteria and the use of troponin as a marker of myocardial damage)			
3.	Valgimigli 2012 [449,450]	New	All participants were on clopidogrel (75 mg/day) plus aspirin (80-160mg/day) for 6 months, then either aspirin or clopdiogrel plus asprin for 18 months (24 months total)	Stable angina 25% ACS 75% Unstable angina 19% NSTEMI 22% STEMI 33%	6 months versus 24months	DES (75%) or BMS (25%)	• All-cause mortality • Cardiovascular mortality • Reinfarction • Stroke • Major bleeding • Minor bleeding
4.	Steinhubl 2002[423] CREDO	New	All participants were on clopidogrel 75mg/day plus aspirin (81-325mg/day) for 1 month then either aspirin or clopidogrel plus aspirin for 11 months	PCI (89% had stents) Unstable angina (53%), stable angina (33%), recent MI (14%) Excluded if persistent	28 days versus 12 months		• All-cause mortality (12months) • Reinfarction (12months) • Stroke (12months) • Revascularisation (12months) • Major bleeding (28 days and 1year)

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Treatment	Outcomes reported
				STEMI less than 24 hours prior to PCI Timing: about to undergo elective PCI			• Minor bleeding (28 days and 1year) • Stent versus no stent (combined end point of death, MI and Stroke) (12 months) • Bleeding result appears cumulative.

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Table 73: GRADE profile: clopidogrel (long term) versus clopidogrel (short term)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Long term	Short term	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality direct – 6 months versus 1 month[45,45]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	16/502 (3.2%)	22/502 (4.4%)	RR 0.73 (0.39 to 1.37)	12 fewer per 1000 (from 27 fewer to 16 more)	LOW	CRITICAL
All-cause mortality -direct – 24 months versus 6 months[449,450]												
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Serious[b]	None	65/987 (6.6%)	65/983 (6.6%)	RR 1 (0.71 to 1.39)	0 fewer per 1000 (from 19 fewer to 26 more)	LOW	CRITICAL
Cardiovascular death – 6 months versus 1 month[45,45]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	32/1313 (2.4%)	31/1345 (2.3%)	RR 1.06 (0.65 to 1.72)	1 more per 1000 (from 8 fewer to 17 more)	VERY LOW	CRITICAL
Cardiovascular death – 24 months versus 6 months[449,450]												
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Very serious	None	36/987 (3.6%)	37/983 (3.8%)	RR 0.97 (0.62 to 1.52)	1 fewer per 1000 (from 14 fewer to 20 more)	VERY LOW	CRITICAL
Reinfarction- 6-12 months versus 1 month[45,284]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness[f]	Serious[b]	None	76/1815 (4.2%)	108/1847 (5.8%)	RR 0.72 (0.54 to 0.95)	16 fewer per 1000 (from 3 fewer to 27 fewer)	LOW	IMPORTANT
Reinfarction- 24 months versus 6 months[449,450]												
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	39/987 (4%)	41/983 (4.2%)	RR 0.95 (0.62 to 1.46)	2 fewer per 1000 (from 16 fewer to 19	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Long term	Short term	Relative (95% CI)	Absolute	Quality	Importance
										more)		
Stroke- 6 months versus 1 month[45,45]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	2/502 (0.4%)	3/502 (0.6%)	RR 0.67 (0.11 to 3.97)	2 fewer per 1000 (from 5 fewer to 18 more)	VERY LOW	IMPORTANT
Stroke-direct – 24 months versus 6 months[449,450]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[e]	None	21/987 (2.1%)	14/983 (1.4%)	RR 1.49 (0.76 to 2.92)	7 more per 1000 (from 3 fewer to 27 more)	LOW	IMPORTANT
Revascularisation 6-12 months versus 1 month [45,284]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	204/1773 (11.3%)	256/1806 (14.1%)	RR 0.81(0.69 to 0.97)	27 fewer per 1000 (from 4 fewer to 44 fewer)	LOW	IMPORTANT
Major bleeding – 12 months versus 1 month [284,284]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[e]	None	36/1313 (2.7%)	33/1345 (2.5%)	RR 1.12 (0.7 to 1.78)	3 more per 1000 (from 7 fewer to 19 more)	LOW	IMPORTANT
Major bleeding – 24 months versus 6 months [449,450]												
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Serious[e]	None	16/987 (1.6%)	6/983 (0.61%)	RR 2.66 (1.04 to 6.76)	10 more per 1000 (from 0 more to 35 more)	LOW	IMPORTANT
Minor bleeding – 12 months versus 1 month [284,284]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[e]	None	46/1313 (3.5%)	28/1345 (2.1%)	RR 1.68 (1.06 to 2.68)	14 more per 1000 (from 1 more to 35	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Long term	Short term	Relative (95% CI)	Absolute	Quality	Importance
										more)		
Minor bleeding – 24 months versus 6 months[449,450]												
1	Randomised trial	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	11/987 (1.1%)	9/983 (0.92%)	RR 1.22 (0.51 to 2.92)	2 more per 1000 (from 4 fewer to 18 more)	VERY LOW	IMPORTANT
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) It was unclear whether the authors performed allocation concealment.
(b) 95% confidence intervals crossed 1 MID (0.75).
(c) The authors did not perform allocation concealment.
(d) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(e) 95% confidence intervals crossed 1 MID (1.25).
(f) It was unclear whether the population was direct. 15% of people had PCI due to an MI,however 1 study states that 72% had ACS.

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Table 74: GRADE profile: clopidogrel (6-12months) versus clopidogrel (1 month)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	6-12 months	1 month	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality[45,45]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness[b]	Very serious[c]	None	16/502 (3.2%)	22/502 (4.4%)	RR 0.73 (0.39 to 1.37)	12 fewer per 1000 (from 27 fewer to 16 more)	VERY LOW	CRITICAL
Cardiac mortality[284,284]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[c]	None	32/1313 (2.4%)	31/1345 (2.3%)	RR 1.06 (0.65 to 1.72)	1 more per 1000 (from 8 fewer to 17 more)	VERY LOW	CRITICAL
Reinfarction[45,284]												
2	Randomised trials	Serious[a,d]	No serious inconsistency	Serious[b]	Serious[e]	None	76/1815 (4.2%)	108/1847 (5.8%)	RR 0.72 (0.54 to 0.95)	16 fewer per 1000 (from 3 fewer to 27 fewer)	VERY LOW	IMPORTANT
Stroke[45,45]												
1	Randomised trial	No serious risk of bias[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	2/502 (0.4%)	3/502 (0.5%)	RR 0.67 (0.11 to 9.97)	2 fewer per 1000 (from 5 fewer to 54 more)	VERY LOW	IMPORTANT
Revascularisation[284,284]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	186/1313 (14.2%)	230/1345 (17.1%)	RR 0.83 (0.69 to 0.99)	29 fewer per 1000 (from 2 fewer to 53 more)	LOW	IMPORTANT
Major bleeding[284,423]												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	6-12 months	1 month	Relative (95% CI)	Absolute	Quality	Importance
2	Randomised trials	Serious[a,d]	No serious inconsistency	No serious indirectness	Serious[f]	None	129/2366 (5.5%)	104/2408 (4.3%)	RR 1.26 (0.98 to 1.62)	11 more per 1000 (from 1 fewer to 27 more)	LOW	IMPORTANT
Minor bleeding[284,423]												
2	Randomised trials	Serious[a,d]	No serious inconsistency	No serious indirectness	Serious[f]	None	102/2366 (4.3%)	87/2408 (3.6%)	RR 1.19 (0.90 to 1.57)	7 more per 1000 (from 4 fewer to 21 more)	LOW	IMPORTANT
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) It was unclear whether the authors performed allocation concealment.
(b) In RACS study[45,45] people had CAD with ischaemia. It was unclear whether they had MI or not.
(c) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(d) Mehta[284,284] was a subgroup analysis of PCI CUREstudy.
(e) 95% confidence intervals crossed 1 MID (0.75).
(f) 95% confidence intervals crossed 1 MID (1.25).

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Table 75: Subgrouping by duration

	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Treatment	Outcomes reported
0 to 30 days							
1.	Yusuf 2003[472,473] CURE	New	Clopidogrel 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day)	NSTEMI	24 hours 0-7days 8-30days 0-30days Over 30 days-1 year	Medical treatment; PCI; CABG	• Bleeding (24 hours) • Refractory ischaemia (0-30days, over 30d-1year) • Severe ischaemia (0-30days, more than 30 days – 1 year) • Major Bleeding (0-7 days, 8-30 days, 0-30 days, 30 days-1 year)
2.	Mehta 2001[284,284] CURE-PCI	New	Clopidogrel 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day)	NSTEMI	30 days	PCI	• Cardiovascular death • MI • Revascularization • Major bleeding • Minor bleeding
3.	Sabatine 2005[394,395] CLARITY-TIMI 28	CG48	Clopidogrel (300mg-75mg) plus aspirin (150-325mg 1st day to 75-162mg) versus aspirin	STEMI	30 days	Clopidogrel PCI 57.2% CABG: 2.9% Placebo PCI 56.6% CABG: 6%	• Cardiovascular death • Recurrent MI • Major bleeding • Minor bleeding • Stroke • Recurrent ischaemia leading to urgent revascularisation
4.	Chen 2005[86,89] COMMIT	CG48	Clopidogrel 75mg/day plusaspirin 162mg/day versus aspirin 162mg/day	STEMI	Death 0-6 days 7-13 days 14-20 days	Medical therapy	• All cause death • Cardiovascular death • MI (fatal and non-fatal) • Ischaemic stroke (nonfatal and

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Treatment	Outcomes reported
					21-28 days All others 28 days		fatal) • Stroke (fatal) • Bleeding
5.	Steinhubl. 2002[423] CREDO	New	Clopidogrel 75mg/day plus aspirin (81-325mg/day) versus aspirin (81-325mg/day)	Indirect	28 days 12 months	PCI	• Major bleeding • Minor bleeding
0-12 months							
1.	Yusuf 2001[472,478] CURE	CG48	Clopidogrel (300mg loading dose and 75mg/day plusaspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day)) plus placebo	NSTEMI	12 months	Medical therapy (65%) PCI (21%) CABG (14%)	• Cardiovascular death • MI (Q wave and nonQ wave) • Stroke • Recurrent ischaemia (during hospitalisation and after discharge) • Major bleeding • Minor bleeding
2.	Fox 2004[147,147] CURE-CABG	New	Clopidogrel (300mg loading dose 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day) plus placebo	NSTEMI	12 months	CABG	• Major bleeding
3.	Kulik 2010[240]	New	Clopidogrel 75 mg/day plusaspirin (162 mg/day) versus aspirin (162mg/day)	CABG. ACS n=12-22%,	12 months	CABG	• Death all-cause • Cardiovascular death

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Treatment	Outcomes reported
	CASCADE			Heart failure NYHA 3-4 n=17 to 23%			• MI • Stroke • Revascularization • Major bleeding • Minor bleeding • Adverse events
4.	Mehta 2001[284,284] CURE-PCI	New	Clopidogrel (300mg loading dose 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day) plus placebo	NSTEMI	12 months	PCI	• Cardiovascular deatj • MI • Revascularization • Major bleeding • Minor bleeding
5.	Steinhubl et al. 2002[423] CREDO	New	Clopidogrel 75mg/day plus aspirin (81-325mg/day) versus aspirin (81-325mg/day)	PCI Unstable angina (53%), stable angina (33%), recent MI (14%) Excluded if persistent STEMI less than 24 hours prior to PCI Timing: About to undergo elective PCI	12 months	PCI	• Death • MI • Stroke • Revascularization • Major bleeding • Minor bleeding • Stent versus no stent (combined end point of death, MI andStroke)
6.	Bhatt2007[49,51]	Updated	Clopidogrel 75mg/day	40.5% had prior MI.	28 months	Medical	• All-cause mortality

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	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Treatment	Outcomes reported
	CHARISMA	– subgroup analysis of larger RCT	plusaspirin (75 to 162mg/day) versus aspirin (75 to 162mg/day)	23.6 months prior to randomisation. 34% had prior stroke. 3.5 months prior to randomisation. 30% had symptomatic PAD. 23.6 months median time from diagnosis. Note: 4.7% fell into multiple categories. Not admitted to hospital and then randomised.		therapy	• Cardiovascular death • MI (non-fatal) • Stroke (fatal) • Hospitalisation for unstable angina, transient ischaemic attack, revascularization • Bleeding

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Table 76: Subgrouping of NSTEMI/STEMI and indirect population papers

	Study	Included in CG48 or new to update	Intervention/comparison	% post MI	Duration	Treatment	Outcomes reported
NSTEMI							
1.	Yusuf 2001[472,478] CURE	CG48	Clopidogrel 75mg/day plusaspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day)	ACS (and not an ST-segment elevation of more than 1mm on ECG) Unstable angina (NSTEMI) (75%) Suspected MI (25%) Associated MI (26%) – MI associated with the episode of pain that occurred before randomisation. Note: In older ACS studies, a large proportion of people who had unstable angina would now be classified in the direct population	12months	Medical therapy (65%) PCI (21%) CABG (14%)	• Cardiovascular death • MI (Q wave and nonQ wave) • Stroke • Recurrent ischaemia (during hospitalisation and after discharge) • Major bleeding • Minor bleeding

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	Study	Included in CG48 or new to update	Intervention/comparison	% post MI	Duration	Treatment	Outcomes reported
				as NSTEMI (based on changes in diagnostic criteria and the use of troponin as a marker of myocardial damage)			
2.	Yusuf 2003[472,473] CURE	New	Clopidogrel 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day) Clopidogrel plus aspirin for 1month, then aspirin for 11 months Clopidogrel plus aspirin for 12 months	ACS (and not an ST-segment elevation of more than 1mm on ECG) Unstable angina (NSTEMI) (75%) Suspected MI (25%) Associated MI (26%) – MI associated with the episode of pain that occurred before randomisation. Note: In older ACS studies, a large proportion of people who had unstable angina	24 hours 0-7days 8-30days 0-30days Over 30days-1 year	Medical therapy PCI CABG	• Bleeding (24 hours) • Refractory ischaemia (0-30 days, over 30 days-1year) • Severe ischaemia (0-30days, over 30 days-1year) • Major bleeding (0-7 days, 8-30 days, 0-30days, over 30 days-1year)

Update 2013

	Study	Included in CG48 or new to update	Intervention/comparison	% post MI	Duration	Treatment	Outcomes reported
				would now be classified in the direct population as NSTEMI (based on changes in diagnostic criteria and the use of troponin as a marker of myocardial damage)			
3.	Mehta 2001[284,284] CURE-PCI	New	Clopidogrel 75mg/day plusaspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day) Clopidogrel plus aspirin for 1month, then aspirin for 11 months Clopidogrel plus aspirin for 12 months	People who had PCI ST depression (43%) ST elevation (5%)	30 days 12 months	PCI	• Cardiovascular death • Reinfarction • Revascularisation • Major bleeding • Minor bleeding
STEMI							
1.	Sabatine 2005[394,395] CLARITY-TIMI 28	CG48	Clopidogrel (300mg loading dose then-75mg/day) plus aspirin (150-325mg 1st day to 75-162mg) versus aspirin	STEMI	30 days	PCI 57% CABG: 3-6%	• Cardiovascular death • Reinfarction (recurrent) • Major bleeding • Minor bleeding

Update 2013

	Study	Included in CG48 or new to update	Intervention/comparison	% post MI	Duration	Treatment	Outcomes reported
							• Stroke • Recurrent ischaemia leading to urgent revascularisation
2.	Chen 2005[86,89] COMMIT	CG48	Clopidogrel 75mg/day plusaspirin 162mg/day versus aspirin 162mg/day	STEMI Timing: suspected MI (within 72 hours of onset of symptoms)	Death 0-6 days 7-13days 14-20days 21-28days All others 28 days	Medical therapy	• All-cause mortality • Cardiovascular death • Reinfarction (fatal and non-fatal) • Ischaemic stroke (nonfatal and fatal) • Stroke (fatal) • Bleeding
INDIRECT POPULATION							
1.	Bhatt2007[49,51] CHARISMA	CG48	Clopidogrel 75mg/day plusaspirin (75 to 162mg/day) versus aspirin (75 to 162mg/day)	Mixed population 40.5% had prior MI. 23.6months prior to randomisation 34% had prior stroke. 3.5months prior to randomisation. 30% had symptomatic PAD. 23.6 months median time from	28 months	Medical therapy	• All-cause mortality • Cardiovascular death • Reinfarction (non-fatal) • Stroke (fatal) • Hospitalisation for unstable angina, transient ischaemic attack, revascularisation • Bleeding

Update 2013

	Study	Included in CG48 or new to update	Intervention/comparison	% post MI	Duration	Treatment	Outcomes reported
				diagnosis. Note: 4.7% fell into multiple categories. Not admitted to hospital and then randomised.			
2.	Fox 2004[147,147] CURE-CABG	New	Clopidogrel 75mg/day plus aspirin (75 to 162mg/day) versus aspirin (75 to 625mg/day) Clopidogrel plus aspirin for 1month, then aspirin for 11 months Clopidogrel plus aspirin for 12 months	ACS (and not an ST-segment elevation of more than 1mm on ECG) who had CABG. Note: In older ACS studies, a large proportion of people who had unstable angina would now be classified in the direct population as NSTEMI (based on changes in diagnostic criteria and the use of troponin as a marker of	12months	CABG	• Major bleeding

Update 2013

	Study	Included in CG48 or new to update	Intervention/comparison	% post MI	Duration	Treatment	Outcomes reported
				myocardial damage)			
3.	Kulik 2010[240] CASCADE	New	Clopidogrel 75 mg/day plusaspirin (162 mg/day) versus aspirin (162mg/day)	CABG. ACS n=12-22%, Heart failure NYHA 3-4 n=17 to 23%	12months	CABG n=113	• All-cause mortality • Cardiovascular death • Reinfarction • Stroke • Revascularisation • Major bleeding • Minor bleeding • Adverse events
4.	Steinhubl et al. 2002[423] CREDO	New	Clopidogrel 75mg/day plusaspirin (81-325mg/day) versus aspirin (81-325mg/day) Clopidogrel plus aspirin for 1month Clopidogrel versus aspirin for 11months	PCI Unstable angina (53%), stable angina (33%), recent MI (14%) Excluded if persistent STEMI less than 24 hours prior to PCI Timing: about to undergo elective PCI	28 days and 12 months	PCI CABG	• All-cause mortality • Reinfarction • Stroke • Revascularisation • Major bleeding (28 days and 1year) • Minor bleeding (28 days and 1year) • Stent versus no stent (combined end point of death, MIand stroke)

Update 2013

Table 77: GRADE profile: clopidogrel plus aspirin versus aspirin (all-cause mortality)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel +aspirin	Aspirin	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality(duration)[51,89,240,423]												
4	Randomised trials	Serious[a]	No serious inconsistency	Serious[b,c]	No serious imprecision	None	1979/28805 (6.9%)	2127/28754 (7.7%)	RR 0.93 (0.88 to 0.98)	5 fewer per 1000 (from 2 fewer to 9 fewer)	MODERATE	CRITICAL
All-cause mortality(duration) 0 to 30 days[86,89]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1726/22961 (7.5%)	1845/22891 (8.1%)	RR 0.93 (0.88 to 0.99)	6 fewer per 1000 (from 1 fewer to 10 fewer)	HIGH	CRITICAL
All-cause mortality(duration) 0 to 1 year[240,423]												
2	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	None	18/1109 (1.6%)	25/1120 (2.2%)	RR 0.73 (0.4 to 1.33)	6 fewer per 1000 (from 13 fewer to 7 more)	VERY LOW	CRITICAL
All-cause mortality(duration) 0 to more than 1 year[49,51]												
1	Randomised trial	Serious[f]	No serious inconsistency	Very serious[c]	No serious imprecision	None	253/4735 (5%)	257/4743 (4.5%)	RR 0.92 (0.77 to 1.09)	4 fewer per 1000 (from 12 fewer to 5more)	VERY LOW	CRITICAL
All-cause mortality - STEMI 30 days[86,89]												
1	Randomised trial	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	1726/22961 (7.5%)	1845/22891	RR 0.93 (0.88 to	6 fewer per 1000	HIGH	CRITICAL

Update 2013

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel +aspirin	Aspirin	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias						(8.1%)	0.99)	(from 1 fewer to 10 fewer)		
All-cause mortality - NSTEMI[51,240,284,478]												
4	Randomised trials	Serious[g,h]	No serious inconsistency	Serious[i,c]	No serious imprecision	None	612/12103 (5.1%)	672/12166 (5.5%)	RR 0.92 (0.82 to 1.02)	4 fewer per 1000 (from 10 fewer to 1 more)	LOW	CRITICAL
All-cause mortality - NSTEMI- 0 to 1 year[240,423,478]												
3	Randomised trials	Serious[h,j]	No serious inconsistency	Serious[i]	No serious imprecision	None	377/7368 (5.1%)	415/7423 (5.6%)	RR 0.92 (0.8 to 1.05)	4 fewer per 1000 (from 11 fewer to 3 more)	LOW	CRITICAL
All-cause mortality - mixed population- 0 to over 1 year[49,51]												
1	Randomised trial	Serious[f]	No serious inconsistency	Very serious[c]	No serious imprecision	None	253/4735 (5%)	257/4743 (4.5%)	RR 0.92 (0.77 to 1.09)	4 fewer per 1000 (from 12 fewer to 5 more)	VERY LOW	CRITICAL
All-cause mortality – PCI[423]												
1	Randomised trials	No serious risk of bias	Serious[k]	No serious indirectness	Very serious[c]	None	18/1053 (1.7%)	24/1063 (2.3%)	RR 0.76 (0.41 to 1.39)	5 fewer per 1000 (from 13 fewer to 9 more)	VERY LOW	CRITICAL
All-cause mortality - CABG[240]												
1	Randomised trial	Serious[l]	No serious inconsistency	Serious[e]	Very serious[e]	None	0/56 (0%)	1/57 (1.8%)	RR 0.34 (0.01 to 8.15)	12 fewer per 1000 (from 17	VERY LOW	CRITICAL

Update 2013

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel +aspirin	Aspirin	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 125 more)		
All-cause mortality - Medical treatment[86,89]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1726/22961 (7.5%)	1845/22 891 (8.1%)	RR 0.93 (0.88 to 0.99)	6 fewer per 1000 (from 1 fewer to 10 fewer)	HIGH	CRITICAL

(a) In 1 of the 4 studies, the authors used unclear methods of randomisation.Two of the 4 studies used an indirect population.
(b) One of the 4 studies was a subgroup analysis of a mixed population, with only 40% of participants having had an MI.
(c) Bhatt[49,51] was a subgroup analysis with only 40% of participants having had an MI.
(d) One of the two studies[240] did not match participants at baseline.
(e) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(f) Data is from a post-hoc analysis on a subgroup population and therefore carries a risk of bias.
(g) Steinhubl[423] had a high dropout rate (38%) and few events. Its weighting was only 5.3%.
(h) Two studies[51,240] used an indirect population.
(i) Kulik[240] matched participants at baseline.
(j) Steinhubl[423] had a high dropout rate (38%) and few events.
(k) 95% confidence intervals crossed 1 MID (0.75)
(l) Participants were not matched at baseline.

Update 2013

Table 78: GRADE profile: clopidogrel plus aspirin versus aspirin (cardiac mortality)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Aspirin	Relative (95% CI)	Absolute		
Cardiac mortality - 0 to 30 days[89,394]												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	None	None	1313/24713 (5.3%)	1405/24630 (5.7%)	RR 0.93 (0.87 to 1.00)	4 fewer per 1000 (from 7 fewer to 0 more)	HIGH	CRITICAL
Cardiac mortality - 0 to 1year[472,478]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	318/6259 (5.1%)	345/6303 (5.5%)	RR 0.93 (0.8 to 1.08)	4 fewer per 1000 (from 11 fewer to 4 more)	HIGH	CRITICAL
Cardiac mortality - 0 to over 1 year(mixed population)[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	147/4735 (3.1%)	163/4743 (3.4%)	RR 0.87 (0.7 to 1.09)	4 fewer per 1000 (from 10 fewer to 3 more)	VERY LOW	CRITICAL
Cardiac mortality total duration[51,89,394,478]												
4	Randomised trials	No serious risk of bias	Serious[c]	Serious[d]	No serious imprecision	None	1773/35707 (5%)	1913/35676 (5.4%)	RR 0.93 (0.87 to 0.99)	4 fewer per 1000 (from 1 fewer to 7 fewer)	LOW	CRITICAL
Cardiac mortality STEMI – 0 to 30 days[89,394]												
2	Randomised trials	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[f]	None	210/24713 (0.85%)	179/24630 (0.73%)	RR 1.17 (0.96 to 1.42)	1 more per 1000 (from 0 fewer to 3 more)	MODERATE	CRITICAL
Cardiac mortality NSTEMI - 0 to 30 days[284,284]												
1	Randomised trial	No serious risk of	No serious inconsistency	No serious indirectness	Very serious[h]	None	14/1313 (1.1%)	13/1345 (0.97%)	RR 1.1 (0.52 to 2.34)	1 more per 1000 (from 5 fewer to 13	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
		bias[g]								more)		
Cardiac mortality NSTEMI - 0 to 1 year[472,478]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	318/6259 (5.1%)	345/6303 (5.5%)	RR 0.93 (0.8 to 1.08)	4 fewer per 1000 (from 11 fewer to 4 more)	HIGH	CRITICAL
Cardiac mortality mixed population - 0 to over 1 year[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	142/4735 (3%)	163/4743 (3.4%)	RR 0.87 (0.7 to 1.09)	4 fewer per 1000 (from 10 fewer to 3 more)	VERY LOW	CRITICAL
Cardiac mortality and treatment - PCI[284,284]												
1	Randomised trial	Serious[g,i]	No serious inconsistency	No serious indirectness	Very serious[h]	None	32/1313 (2.4%)	31/1345 (2.3%)	RR 1.06 (0.65 to 1.72)	1 more per 1000 (from 8 fewer to 17 more)	VERY LOW	CRITICAL
Cardiac mortality and treatment - Medical treatment[86,89]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[f]	None	113/22961 (0.4%)	101/22891 (0.44%)	RR 1.12 (0.85 to 1.7)	1 more per 1000 (from 0 more to 3 more)	MODERATE	CRITICAL

(a) Data is from a post-hoc analysis on a subgroup population and therefore carries a risk of bias.
(b) Bhatt[49,51] is a subgroup analysis of a mixed population, with only 40% of participants having had an MI.
(c) Heterogeneity detected I^2=54%, p=0.09.
(d) One of the 4 studies was a subgroup analysis of a mixed population, with only 40% of participants having had an MI.
(e) In 1 study it was unclear if participants were blinded however this is unlikely to influence the outcome.
(f) 95% confidence intervals crossed the line of no effect and 1 MID (1.25).
(g) The study was an unplanned post-hoc analysis of a subgroup, so participants would not have been randomised to these sub-groups. However, the participants were matched at baseline.
(h) 95% confidence intervals crossed the line of no effect and 2 MIDs (0.75 and 1.25).
(i) Participants received the same treatment for the 1st month and thereafter received either clopidogrel or placebo until 12 month follow-up.

Update 2013

Update 2013

Table 79: GRADE profile: clopidogrel plus aspirin versus aspirin (sudden death)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Control	Relative (95% CI)	Absolute		
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

Table 80: GRADE profile: clopidogrel plus aspirin versus aspirin (quality of life)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Control	Relative (95% CI)	Absolute		
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

Table 81: GRADE profile: clopidogrel plus aspirin versus aspirin (myocardial infarction)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Aspirin	Relative (95% CI)	Absolute		
Reinfarction (fatal and non-fatal) - 0 to 30 days[89,394]												
2	Randomised trials	No serious risk of bias	Very serious[a]	No serious indirectness	Very serious[b]	None	185/24713 (0.75%)	204/24630 (0.83%)	RR 0.88 (0.55 to 1.41)	1 fewer per 1000 (from 4 fewer to 3 more)	VERY LOW	IMPORTANT
Reinfarction (fatal and non-fatal) - 0 to 1 year[472,478]												
1	Randomised	No	No serious	No serious	Serious[c]	None	324/6259	419/6303	RR 0.78	15 fewer	MODERATE	IMPORTANT

Update 2013

Quality assessment							No of patients		Effect		Quality	Importance
	trial	serious risk of bias	inconsistency	indirectness			(5.2%)	(6.6%)	(0.68 to 0.9)	per 1000 (from 7 fewer to 21 fewer)		
Reinfarction (fatal and non-fatal) - 0 to over 1 year[49,51]												
1	Randomised trial	Serious risk of bias[d]	No serious inconsistency	Very Serious[e]	Serious[c]	None	117/4735 (2.5%)	145/4743 (3.1%)	RR 0.81 (0.64 to 1.03)	6 fewer per 1000 (from 11 fewer to 1 more)	VERY LOW	IMPORTANT
Reinfarction and STEMI population[89,394]												
2	Randomised trials	No serious risk of bias	Very serious[f]	No serious indirectness	Very serious[b]	None	185/24713 (0.75%)	204/24630 (0.83%)	RR 0.88 (0.55 to 1.4)	1 fewer per 1000 (from 4 fewer to 3 more)	VERY LOW	IMPORTANT
Reinfarction and NSTEMI + mixed population[51,478]												
2	Randomised trials	Serious risk of bias[d]	No serious inconsistency	Serious[g]	No serious imprecision	None	441/10994 (4%)	564/11046 (5.1%)	RR 0.79 (0.7 to 0.89)	11 fewer per 1000 (from 6 fewer to 15 fewer)	LOW	IMPORTANT
Reinfarction and NSTEMI population - 0 to 1 year[472,478]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	324/6259 (5.2%)	419/6303 (6.6%)	RR 0.78 (0.68 to 0.9)	15 fewer per 1000 (from 7 fewer to 21 fewer)	MODERATE	IMPORTANT
Reinfarction and mixed population - 0 to 1 year[49,51]												
1	Randomised trial	Serious risk of bias[d]	No serious inconsistency	Serious[e]	Serious[c]	None	117/4735 (2.5%)	145/4743 (3.1%)	RR 0.81 (0.64 to 1.03)	6 fewer per 1000 (from 11 fewer to 1 more)	VERY LOW	IMPORTANT
Reinfarction and treatment – PCI [284,423]												

Quality assessment							No of patients		Effect		Quality	Importance
2	Randomised trials	Serious[h]	No serious inconsistency	No serious indirectness	Serious[i]	None	129/2366 (5.5%)	175/2408 (7.3%)	RR 0.75 (0.60 to 0.93)	18 fewer per 1000 (from 5 fewer to 29 fewer)	LOW	IMPORTANT
Reinfarction and treatment - medical treatment[86,89]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	479/22961 (2.1%)	533/22891 (2.3%)	RR 0.9 (0.79 to 1.01)	2 fewer per 1000 (from 5 fewer to 0 more)	HIGH	IMPORTANT

(a) Heterogeneity present, I^2=82% (p=0.02).
(b) 95% confidence intervals crossed 2 MID and the line of no effect.
(c) 95% confidence intervals crossed the line of no effect and 1 MID (0.75).
(d) Bhatt[49,51] is a post-hoc analysis on a subgroup population and therefore it carries a risk of bias.
(e) The study used an indirect population with 40% of participants having had an MI.
(f) Heterogeneity present, I^2 =90%, p=0.0001.
(g) The studies were an indirect population.
(h) In both studies all participants received clopidogrel plus aspirin for 1 month, thereafter receiving either clopidogrel or aspirin.
(i) 95% confidence intervals crossed 1 MID.

Table 82: GRADE profile: clopidogrel plus aspirin versus aspirin (stroke)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Aspirin	Relative (95% CI)	Absolute		
Stroke[51,89,284,394,478]												
4	Randomised trials	serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	448/35707 (1.3%)	546/35676 (1.5%)	RR 0.8 (0.67 to 0.96)	3 fewer per 1000 (from 1 fewer to 5 fewer)	VERY LOW	IMPORTANT
Stroke - 0 to 30 days [89,394]												
2	Randomised	No	Serious[d]	No serious	Very	None	229/24713	280/24630	RR 0.63	4 fewer per	VERY LOW	IMPORTANT

Update 2013

Quality assessment							No of patients		Effect		Quality	Importance
	trials	serious risk of bias		indirectness	serious[e]		(0.93%)	(1.1%)	(0.3 to 1.33)	1000 (from 8 fewer to 4 more)		
Stroke - 0 to 1 year[472,478]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[f]	None	75/6259 (1.2%)	87/6303 (1.4%)	RR 0.87 (0.64 to 1.18)	2 fewer per 1000 (from 5 fewer to 2 more)	MODERATE	IMPORTANT
Stroke - 0 to over 1 year[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	Serious[f]	None	144/4735 (3%)	179/4743 (3.8%)	RR 0.81 (0.65 to 1)	7 fewer per 1000 (from 13 fewer to 0 more)	VERY LOW	IMPORTANT
Stroke and STEMI population– less than 30 days[89,394]												
2	Randomised trials	No serious risk of bias	Serious[d]	No serious indirectness	Very serious[e]	None	229/24713 (0.93%)	280/24630 (1.1%)	RR 0.63 (0.3 to 1.33)	4 fewer per 1000 (from 8 fewer to 4 more)	VERY LOW	IMPORTANT
Stroke and NSTEMI population[51,478]												
2	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	224/14061 (1.6%)	272/14104 (1.9%)	RR 0.83 (0.69 to 0.99)	3 fewer per 1000 (from 0 fewer to 6 fewer)	LOW	IMPORTANT
Stroke and NSTEMI population - 0 to 1 year[472,478]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[f]	None	75/6259 (1.2%)	87/6303 (1.4%)	RR 0.87 (0.64 to 1.18)	2 fewer per 1000 (from 5 fewer to 2 more)	MODERATE	IMPORTANT
Stroke and mixed population - 0 to over 1 year[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	Serious[f]	None	144/4735 (3%)	179/4743 (3.8%)	RR 0.81 (0.65 to 1)	7 fewer per 1000 (from 13 fewer to 0 more)	VERY LOW	IMPORTANT
Stroke and treatment – PCI[423]												

Quality assessment							No of patients		Effect		Quality	Importance
1	Randomised trial	serious[g]	No serious inconsistency	No serious indirectness	Very serious[e]	None	9/1053 (0.85%)	12/1063 (1.1%)	RR 0.76 (0.32 to 1.79)	3 fewer per 1000 (from 8 fewer to 9 more)	VERY LOW	IMPORTANT
Stroke and treatment - medical treatment[86,89]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[f]	None	217/22961 (0.95%)	250/22891 (1.1%)	RR 0.87 (0.72 to 1.04)	1 fewer per 1000 (from 3 fewer to 0 more)	MODERATE	IMPORTANT

(a) It was unclear how the authors of 1 study randomised participants. Both Bhatt and Mehta[51,284] are a subgroup analyses and therefore carry a risk of bias.
(b) In 1 study[49,51] some people had an MI 2 years prior to randomisation and overall the population was indirect (a mixed population of MI,stroke and PAD).
(c) 95% confidence intervals crossed 1 MID (0.75).
(d) Heterogeneity present. I^2=80% p=0.03.
(e) 95% CI crossed line of no effect and 2 MIDs.
(f) 95% CI crossed line of no effect and 1 MID (0.75).
(g) All participants received the same clopidogrel plus aspirin for 1 month, thereafter either clopidogrel or aspirin until 12 months follow-up.

Table 83: Clinical evidence profile: clopidogrel plus aspirin versus aspirin (revascularisation)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Aspirin	Relative (95% CI)	Absolute		
Revascularisation and duration - 0 to 30 days[394,395]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	61/1752 (3.5%)	78/1739 (4.5%)	RR 0.78 (0.56 to 1.08)	10 fewer per 1000 (from 20 fewer to 4 more)	MODERATE	IMPORTANT
Revascularisation and duration – 30 days to 1 year[284,284]												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	161/1313 (12.3%)	192/1345 (14.3%)	RR 0.86 (0.71 to 1.04)	20 fewer per 1000 (from 41 fewer to 6 more)	LOW	IMPORTANT

Update 2013

Update 2010

Quality assessment							No of patients		Effect		Quality	Importance
Revascularisation and STEMI population – less than 30 days[394,395]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	61/1752 (3.5%)	78/1739 (4.5%)	RR 0.78 (0.56 to 1.08)	10 fewer per 1000 (from 20 fewer to 4 more)	MODERATE	IMPORTANT
Revascularisation and NSTEMI population – 0 to 1 year[240,284,423]												
3	Randomised trials	Serious[c,d]	No serious inconsistency	Serious[e]	No serious imprecision	None	456/2454 (18.6%)	411/2433 (16.9%)	RR 1.10 (0.98 to 1.24)	17 more per 1000 (from 3 fewer to 41 more)	VERY LOW	IMPORTANT
Revascularisation and PCI[284,423]												
2	Randomised trials	Serious[c,d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	411/2366 (17.4%)	453/2405 (18.8%)	RR 0.92 (0.82 to 1.04)	15 fewer per 1000 (from 34 fewer to 8 more)	MODERATE	IMPORTANT
Revascularisation - CABG [240]												
1	Randomised trial	Serious[c]	No serious inconsistency	Serious[e]	Very serious[f]	None	1/56 (1.8%)	2/57 (3.5%)	RR 0.51 (0.05 to 5.45)	17 fewer per 1000 (from 33 fewer to 156 more)	VERY LOW	IMPORTANT

(a) 95% confidence intervals crossed 1 MID (0.75)
(b) The study is a post-hoc analysis on a subgroup population and therefore it carries a risk of bias
(c) It was unclear whether the studies performed allocation concealment.
(d) Steinhubl[423]. had a high drop-out rate (38%) and few events. Mehta[284,284] was a subgroup analysis and therefore carried a risk of bias.
(e) The study was an indirect population.
(f) 95% confidence intervals crossed line of no effect and 2 MIDs (0.75 and 1.25).

Update 2013

Table 84: GRADE profile: clopidogrel plus aspirin versus clopidogrel (composite outcome CV death/MI/stroke)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Control	Relative (95% CI)	Absolute	Quality	Importance
Cardiovascular death/MI/stroke - NSTEMI and CABG[147,147]												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	147/1011 (14.5%)	172/1061 (16.2%)	RR 0.89 (0.71 to 1.11)	18 fewer per 1000 (from 47 fewer to 18 more)	LOW	IMPORTANT
Cardiovascular death/MI/stroke - NSTEMI and medical treatment[147,147]												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	324/4006 (8.1%)	397/3979 (10%)	RR 0.81 (0.70 to 0.93)	19 fewer per 1000 (from 7 fewer to 30 fewer)	LOW	IMPORTANT
Cardiovascular death/MI/stroke - NSTEMI and PCI[147,147]												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	126/1313 (9.6%)	177/1345 (13.2%)	RR 0.73(0.59 to 0.9)	36 fewer per 1000 (from 13 fewer to 54 fewer)	LOW	IMPORTANT

(a) Subgroup analysis. Participants were not randomised to these groups.
(b) 95% confidence intervals crossed 1 MID (0.75).

Update 2013

Table 85: GRADE profile: clopidogrel plus aspirin versus aspirin (major bleeding)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Aspirin	Relative (95% CI)	Absolute		
Major bleeding and duration - 0 to 7 days[472,473]												
1	Randomised trial	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	54/6259 (0.86%)	46/6303 (0.73%)	RR 1.18 (0.8 to 1.75)	1 more per 1000 (from 1 fewer to 5 more)	MODERATE	IMPORTANT
Major bleeding and duration - 0 to 30 days[89,394,473]												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[b]	None	232/30953 (0.75%)	201/30913 (0.65%)	RR 1.16 (0.96 to 1.39)	1 more per 1000 (from 0 fewer to 3 more)	MODERATE	IMPORTANT
Major bleeding and duration – 30 days to 1 year[423,478]												
2	Randomised trials	Serious[c]	No serious inconsistency	Serious[d]	No serious imprecision	None	153/7312 (2.1%)	107/7366 (1.5%)	RR 1.44 (1.13 to 1.84)	6 more per 1000 (from 2 more to 12 more)	LOW	IMPORTANT
Major bleeding and duration - 0 to over 1 year[49,51]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	Very serious[d]	Serious[b]	None	79/4735 (1.7%)	71/4743 (1.5%)	RR 1.11 (0.81 to 1.53)	2 more per 1000 (from 3 fewer to 8 more)	VERY LOW	IMPORTANT
Major bleeding and treatment - PCI[284,423]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	129/2366 (5.5%)	104/2408 (4.3%)	RR 1.26 (0.98 to 1.62)	11 more per 1000 (from 1 ferwer to 27 more)	LOW	IMPORTANT
Major bleeding and treatment - CABG[147,240]												
2	Randomised	Serious[a]	No serious	No serious	Serious[b]	None	98/1067(9.2%	80/1118	RR 1.28(0.97	20 more per 1000	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
	trials		inconsistency	indirectness			)	(7.2%)	9 to 1.70)	(from 2 fewer to 50 more)		
Major bleeding and treatment - medical treatment[51,89]												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious indirectness[d]	Serious[b]	None	152/27696 (0.55%)	145/27 634 (0.52%)	RR 1.05 (0.84 to 1.31)	0 more per 1000 (from 1 fewer to 2 more)	LOW	IMPORTANT

(a) One study was a subgroup analysis from a larger trial, therefore carrying a risk of bias. However, participants were matched at baseline.
(b) 95% confidence intervals crossed line of no effect and 1 MID (1.25).
(c) It was unclear if 1 of the 2 studies performed allocation concealment.
(d) The studies by Bhatt and Steinhubl[51,423] used an Indirect population.

Table 86: GRADE profile: clopidogrel plus aspirin versus aspirin (minor bleeding)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Aspirin	Relative (95% CI)	Absolute		
Minor bleeding and duration - 0 to 30 days[394,395]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	27/1733 (1.6%)	16/171 9 (0.93%)	RR 1.67 (0.91 to 3.10)	6 more per 1000 (from 1 fewer to 20 more)	MODERATE	IMPORTANT
Minor bleeding and duration – 30 days to 1 year[423]												
1	Randomised trial	Serious[b]	Serious[c]	No serious indirectness	Serious[d]	None	23/1053 (2.2%)	35/106 3 (3.3%)	RR 0.66 (0.39 to 1.11)	11 fewer per 1000 (from 20 fewer to 4 more)	VERY LOW	IMPORTANT
Minor bleeding and duration - 0 to over 1 year[49,51]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	Serious[e]	No serious imprecision	None	97/4735 (2%)	61/474 3 (1.3%)	RR 1.59 (1.16 to 2.19)	8 more per 1000 (from 2 more to 15 more)	MODERATE	IMPORTANT
Minor bleed and treatment – PCI[283,423]												

Update 2013

Update 2013

Quality assessment							No of patients		Effect		Quality	Importance
2	Randomised trials	No serious risk of bias	Serious[f]	No serious indirectness	Serious[g]	None	46/2366 (1.9%)	33/2488 (1.3%)	RR 1.41 (0.91 to 2.2)	5 more per 1000 (from 1 fewer to 16 more)	LOW	IMPORTANT
Minor bleed and treatment - CABG[240]												
1	Randomised trial	Serious[h]	No serious inconsistency	No serious indirectness	Very serious[i]	None	3/56 (5.4%)	3/57 (5.3%)	RR 1.02 (0.21 to 2.43)	1 more per 1000 (from 42 fewer to 75 more)	VERY LOW	IMPORTANT
Minor bleed and treatment - Medical treatment[49,51]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	Very serious indirectness	No serious imprecision	None	97/4735 (2%)	61/4743 (1.3%)	RR 1.59 (1.16 to 2.19)	8 more per 1000 (from 2 more to 15 more)	LOW	IMPORTANT

(a) 95% confidence intervals crossed the line of no effect and 1 MID (1.25).
(b) It was unclear whether the authors performed allocation concealment.
(c) There was a high dropout rate of 38%.
(d) 95% confidence intervals crossed line of no effect and 1 MID 0.75.
(e) Participants had MI more than 2 years prior to randomisation.
(f) One study had a high dropout rate 38%.
(g) 95% confidence intervals crossed 1 MID.
(h) In 1 study, participants were not matched at baseline.
(i) 95% confidence intervals crossed the line of no effect and 2 MIDs (0.75 and 1.25).
(j) Participants were from an indirect population and were randomised more than 2 years after their MI.

Update 2010

Table 87: GRADE profile: clopidogrel plus aspirin versus aspirin (rehospitalisation)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Aspirin	Relative (95% CI)	Absolute		
Readmission - over 1 year and medical treatment[49,51]												
1	Randomised trial	Serious risk of bias[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	542/4735 (11.4%)	626/4743 (13.2%)	RR 0.87 (0.78 to 0.97)	17 fewer per 1000 (from 4 fewer to 29 fewer)	VERY LOW	IMPORTANT

(a) Participants were a subgroup analysis and this therefore carries a risk of bias.
(b) Participants were an indirect population and randomised more than 2 years after their MI.

7.4.5.3 Economic evidence

Published literature

As per the review protocol (see Appendix D), searches were carried out for studies that compared different durations of clopidogrel plus aspirin, or compared clopidogrel plus aspirin versus aspirin alone. As for the clinical effectiveness studies, cost effectiveness analyses that compare different durations of clopidogrel are the most useful to answer the question. However, because such a study may not be available in all relevant populations, studies comparing clopidogrel plus aspirin versus aspirin alone with consideration to the duration of clopidogrel therapy in the study, were also included.

The previous guideline, CG48, included 1 study comparing clopidogrel plus aspirin with aspirin alone that also compared different durations of clopidogrel treatment; this was the assessment group HTA report that informed NICE technology appraisal 80.[263] This looked at treatment for people with non-ST elevation ACS and was based on the CURE trial. Six additional studies were noted in CG48 as meeting the inclusion criteria for the review but these were not included in the evidence summary, presumably as the included study was considered the most relevant to inform the question.[140,161,161,222,246,255,399] From the update searches, 17 relevant studies were identified which had been published since the cut-off date for searches in CG48.[33,34,42,43,71,86-88,165,190,191,224,232,237,390,439,480] Of these, ten included analyses comparing different durations of clopidogrel treatment.[34,42,43,88,190,191,224,232,390,480]

Update 2013

In total 4 published studies were included although some studies reported separate analyses in more than 1 population.[87,190,224,390] These included 3 UK analyses with clopidogrel duration comparisons:1 in people with STEMI,[224,224] 1 in people with NSTEMI[390,390] and 1 in people who had a PCI.[190,190] In addition 3 analyses in different populations were included where there was not a duration comparison but clopidogrel use was longer than the other included studies (28 months – based on the CHARISMA trial and its subgroups).[87,190] Two of these analyses were in indirect populations, however these were included in the economic review as they had also been included in the clinical review based on the fact that data on the direct population was of low quality. The included economic analyses are summarised in the economic evidence profiles below (Table 88 and Table 89). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

The remaining 13 studies that met the inclusion criteria were selectively excluded on the basis of relative applicability and/or quality.[33,34,42,43,71,86,88,165,191,232,237,263,439,480] Note that the analysis used to inform TA80 that was included in CG48[263] is now excluded due to the availability of an updated version of the analysis which has been included.[390,390] Differences between the old and recent analysis are explained below the economic profile tables. The selectively excluded studies are listed in Appendix K, with reasons for exclusion given.

Update 2013

Table 88: Economic evidence profile: duration of clopidogrel review – studies with duration comparisons

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
STEMI							
Karnon 2010[224,224] (UK)	Partially applicable (a)	Potentially serious limitations (b)	Interventions: **1.** Lifetime aspirin **2.** Plus 1 month clopidogrel **3.** Plus 1 year clopidogrel • Lifetime cost–utility model (cost per QALYs gained) • Incorporated differences in further non-fatal MI, non-fatal stroke and death. • Effectiveness: Up to 1 month = COMMIT or CLARITY trial. 2-12 months: CURE trial	COMMIT 2-1: £120 3–2: £610	COMMIT 2-1: 0.053 3–2: 0.133	COMMIT 2 vs. 1: £2284 3 vs. 2: £4586	Sensitivity analyses generally showed low uncertainty about clopidogrel being cost effective. However, analyses were not done for full incremental analysis (all 3 comparators together) and so uncertainty about different durations is not quantified.
Rogowski 2009[390,390] (UK)	Partially applicable (c)	Potentially serious limitations (d)	Interventions: **1.** Lifetime aspirin **2.** Plus 1 month clopidogrel **3.** Plus 3 months clopidogrel **4.** Plus 6 months clopidogrel **5.** Plus 1 year clopidogrel • Lifetime cost–utility model (cost per QALYs gained) • QALYs estimated incorporating differences in further non-fatal MI, non-fatal stroke and death. Stroke and major bleeding incorporated on cost side only. • Effectiveness: CURE trial	Constant RR All patients 2-1: £92 3-2: £114 4-3: £146 5-4: £265 High-risk† 2-1: £117 3-2: £140 4-3: £156 5-4: £287 Low-risk‡ 2-1: £55	Constant RR All patients 2-1: 0.0193 3-2: 0.0119 4-3: 0.0140 5-4: 0.0142 High-risk† 2-1: 0.0241 3-2: 0.0177 4-3: 0.0196 5-4: 0.0214 Low-risk‡ 2-1: 0.0113	Constant RR All patients 2 vs. 1: £4,790 3 vs. 2: £9,489 4 vs. 3: £10,482 5 vs. 4: £18,712 High-risk† 2 vs. 1: £4846 3 vs. 2: £7930 4 vs. 3: £7971 5 vs. 4: £13,380 Low-risk‡ 2 vs. 1: £4891	Probability of intervention being the most cost effective at the £20K per QALY threshold: Constant RR All patients Intervention 1: 15.7% Intervention 2: 7.5% Intervention 3: 2.0% Intervention 4: 18.9% Intervention 5: 51.7% High-risk† Intervention 1: 16.5% Intervention 2: 4.8% Intervention 3: 0.7%

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Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
				3-2: £100 4-3: £119 5-4: £239	3-2: 0.0056 4-3: 0.0033 5-4: 0.0048	3 vs. 2: £17,826 4 vs. 3: £36,226 5 vs. 4: £49,436	Intervention 4: 9.3% Intervention 5: 65.8% Low-risk‡ Intervention 1: 11.1% Intervention 2: 31.6% Intervention 3: 31.3% Intervention 4: 14.8% Intervention 5: 4.9%
-	-	-	-	Varying RR All patients 2-1: £199 3-2: £212 4-3: £159 5-4: £274 High-risk† 2-1: £270 3-2: £284 4-3: £171 5-4: £296 Low-risk ‡ 2-1: £93 3-2: £131 4-3: £126 5-4: £244	Varying RR All patients 2-1: 0.0550 3-2: 0.0517 4-3: 0.0134 5-4: 0.0132 High-risk† 2-1: 0.0747 3-2: 0.0747 4-3: 0.0186 5-4: 0.0186 Low-risk‡ 2-1: 0.0236 3-2: 0.0193 4-3: 0.0019 5-4: 0.0042	Varying RR All patients 2 vs. 1: £3,632 3 vs. 2: £4,095 4 vs. 3: £11,917 5 vs. 4: £20,661 High-risk† 2 vs. 1: £3615 3 vs. 2: £3809 4 vs. 3: £9144 5 vs. 4: £15,063 Low-risk‡ 2 vs. 1: £3936 3 vs. 2: £6780 4: ED 5 vs. 3: £58,691	Varying RR All patients Intervention 1: 0.0% Intervention 2: 0.1% Intervention 3: 24.6% Intervention 4: 32.5% Intervention 5: 42.9% High-risk† Intervention 1: 0.0% Intervention 2: 0.1% Intervention 3: 28.7% Intervention 4: 11.9% Intervention 5: 59.3% Low-risk patients‡ Intervention 1: 0.2% Intervention 2: 6.1% Intervention 3: 81.9% Intervention 4: 6.0% Intervention 5: 4.6%
PCI							
Heeg	Partially	Potentially	Interventions:	PCI-CURE	PCI-CURE	PCI-CURE	Probability that the

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
2007[190,190] (UK)	applicable (e)	serious limitations (f)	**1.** 1 month clopidogrel **2.** 1 year clopidogrel • Lifetime cost-effectiveness model (cost per LYG) • Life years estimated based on reported differences between treatments in terms of MI, stroke, death; differences in bleedingincorporated on cost side only • Effectiveness: PCI-CURE (direct NSTEMI population) or CREDO trial (indirect population)	-£268	0.0293 life years (~0.0197 QALYs*)	1yr clopidogrel dominant	intervention is the most cost effective at the£20K per QALY threshold:: Intervention 1: 27% Intervention 2: 73%
				CREDO -£192	CREDO 0.1068 life years (~0.0717 QALYs*)	CREDO 1yr clopidogrel dominant	Probability that the intervention is the most cost effective at the£20K per QALY threshold: Intervention1: 0% Intervention 2: 100%

DSA = deterministic sensitivity analysis; MI = myocardial infarction; NA = Not applicable; pa = probabilistic analysis; QALYs = quality-adjusted life years
†High-risk patients are defined as by age over 70 years, ST depression or diabetes (58% of all patients belonged to this group).
‡Low-risk patients are defined as the absence of all the previous conditions that define the high risk patients.
** To aid interpretation, where life years were the health outcome used in the analysis QALYs are estimated by multiplying by a quality of life weight (utility) for MI of 0.671 (UK EQ-5D mean for people with old MI)[425,425].*

(a) Some uncertainty about applicability of health state costs based on resource use from over 10 years ago. Cost of clopidogrel higher than current UK context (~£460 per year). Base case discount rate not reported. Some uncertainty about applicability of utility data as methods unclear.

(b) Patients can only remain in stroke health state for 1 year - this may not capture full health outcome or cost impact. Bleeding not incorporated. Only hospital resource use incorporated into "no new event" and "new MI" health states. Baseline event probabilities based on studies published 2005/6, data therefore likely to be from some years before – may relate to old acute MI management strategies. Relative risks with clopidogrel plus aspirin treatment months 2-12 based on NSTEMI trial as no STEMI data available. Funded by BMS/Sanofi-Aventis (manufacture clopidogrel).

(c) Some uncertainty about applicability of health state costs based on resource use from over 10 years ago. Cost of clopidogrel higher than current UK context (~£460 per year). Some uncertainty about applicability of utility data as source methods unclear.

(d) Stroke and major bleeding differences not incorporated into health outcomes only costs. Baseline event probabilities based on UK cohort from 1998-99 (PRAIS-UK) - may therefore relate to old acute management strategies.

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(e) CREDO analysis only - indirect population (less than <75% MI). Some uncertainty about applicability of multinational resource use. Cost of clopidogrel higher than current UK context (£460 per year). QALYs not used therefore interpretation limited.

(f) CREDO analysis only - baseline event probabilities may be an underestimate as based on indirect population (<75% MI). Some methodological limitations with probabilistic methods. No other sensitivity analysis reported.

Table 89: Economic evidence profile: duration of clopidogrel review – studies based on CHARISMA (28 months clopidogrel plus aspirin versus aspirin alone)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Prior MI							
Chen 2011[86,87] (Canada)	Partially applicable (a)	Potentially serious limitations (b,c,d)	• Within-trial analysis of a CHARISMA prior MI subgroup (b) • Lifetime analysis; treatment and effect period 28 months • Life years estimated based on observed differences in CV death, MI and stroke	£684 (e)	0.106 life years (~0.0711 QALYs*)	£6467 per life year gained (~£9,620 per QALY gained*) (e)	Not reported
CVD (indirect populations – less than 75% people who had an MI)							
Chen 2011[86,87] (Canada) CVD	Partially applicable (a,f)	Potentially serious limitations (g,c)	• Within-RCT analysis of CHARISMA CVD subgroup (g) • Analysis as above except QALYs estimated by applying QoL weights to MI and stroke outcomes; short term quality of life loss also applied for major bleeding events.	£785 (e)	0.07 QALYs gained	£11,362 per QALY gained (e)	DSA: • Cost effectiveness ranged from £5,891 to £29,557 per QALY gained • Clopidogrel remained cost effective in most scenarios Reducing clopidogrel cost 50% reduced ICER to £5,891
Heeg 2007[190,190] (UK) CVD and high CV risk	Partially applicable (h)	Potentially serious limitations (i,j)	• Markov model with 6 month cycles • Effectiveness: CHARISMA trial[49,50] (i) • Lifetime analysis; treatment and effect period 28 months • Life years estimated based on	£772	0.0054 life years gained (~0.0036 QALYs*)	£143,071 per life year gained (~£214,444per QALY gained*)	PA: • Probability cost effective (£20K/£30K threshold) = 15%/27% DSA: • None

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			reported differences between treatments in terms of MI, stroke, death; differences in bleeding incorporated on cost side only				

** To aid interpretation, where life years were the health outcome used in the analysis QALYs are estimated by multiplying by a quality of life weight (utility) for MI of 0.671 (UK EQ-5D mean for people with old MI)[425,425].*

CV = cardiovascular; CVD = cardiovascular disease; DSA = deterministic sensitivity analysis; MI = myocardial infarction; pa = probabilistic analysis; QALYs = quality-adjusted life years

(a) Some uncertainty about applicability of Canadian costs and multinational resource use. Cost of clopidogrel higher than current UK context (£485 per year). Discount rate not in line with NICE reference case. Some uncertainty about applicability of utility data as methods unclear.

(b) Effectiveness based on analysis of MI subgroup of CHARISMA established CVD subgroup (defined below).

(c) Study funded by Sanofi-Aventis Canada Inc. and Bristol-Myers Squibb Canada (manufacture clopidogrel).

(d) No sensitivity analysis.

(e) Converted from 2008 Canadian dollars using purchasing power parities[340]

(f) Indirect population: CVD (~40% MI).

(g) Effectiveness based on analysis of CHARISMA established CVD subgroup (defined as pre-existing coronary artery disease [angina, MI, PCI, or coronary artery bypass surgery], cerebrovascular disease [ischaemic stroke, transient ischaemic attack], or symptomatic peripheral arterial disease [PAD]) – clinical review excluded this subgroup analysis in favour of CHARISMA high risk CVD (defined as MI, stroke or symptomatic PAD) subgroup analysis considered more relevant.

(h) Indirect population (~35% MI). Some uncertainty about applicability of multinational resource use. Cost of clopidogrel higher than current UK context (£460 per year). QALYs not used therefore interpretation limited.

(i) Event probabilities based on analysis of CHARISMA full study population (established CVD and multiple CVD risk factors) – clinical review excluded this analysis in favour of CHARISMA high risk CVD (defined as MI, stroke or symptomatic PAD) subgroup analysis considered more relevant.

(j) Some methodological limitations with probabilistic methods. No other sensitivity analysis reported.

7.4.5.3.1 *Update of TA80 model*

As mentioned above, the old model informing TA80 has been updated in the study by Rogowski et al (2009). [390,390]

The updated model reinforced the conclusions from the earlier analysis regarding the cost-effectiveness of alternative durations of clopidogrel.

In the base case analysis, the ICERs associated with the clopidogrel strategies are higher in the updated model in comparison with the earlier model. The reasons for this are: (1) the increase in costs due to applying current prices, and (2) the changes to the discount rates, employing 3.5% for both costs and outcomes (as opposed to 1.5% for outcomes and 6% for costs in the previous model). However, despite the less favourable ICERs, the conclusions arising from the updated model are consistent with those reported previously. That is, a policy of 12 months of clopidogrel for people with NSTE-ACS appears cost-effective both in 'average' people (that is based on the average across all patient risks considered) and in the subgroup of higher-risk people (the presence of any of the following: age over 70 years, ST depression or diabetes) compared with shorter-term durations. However, for lower-risk people, treatment with clopidogrel beyond 3 months does not appear to be cost-effective. These conclusions appeared robust to alternative assumptions related to whether the relative effect of clopidogrel was assumed to remain constant over time or whether the treatment effect in the first 3 months was assumed to be greater than in later periods.

However, the GDG considered the price change in clopidogrel since the drug has become generic after the study publication.[390,390] Table 90 reports the current cost of the generic clopidogrel compared with the cost of the branded drug, which might have been similar to the cost used in the model developed by Rogowski et al (2009).[390,390] Based on the recent introduction of the much cheaper generic drug, the GDG concluded that treatment for 12 months with clopidogrel is likely to be cost-effective also for the low-risk group.

Update 2013

Table 90: Unit costs: clopidogrel

Drug	Units/pack	Cost/pack	Units/day	Cost/day	Cost/year
Clopidogrel (75mg)	30	£2.50	1	£0.08	£30.42
Clopidogrel branded (Plavix) (75 mg)	30	£35.64	1	£1.19	£433.6

Source: Costs and doses from the BNF 2013.[209]

7.4.5.4 Evidence statements

7.4.5.4.1 *Clinical*

All outcomes

Long versus short term treatment

- One study with 1004 people suggested that 6 months of clopidogrel and aspirin treatment may be more effective than 1 month of treatment at reducing the risk of all-cause mortality, but there was considerable uncertainty [Low quality evidence].
- One study with 1970 people suggested that 24 months of clopidogrel and aspirin treatment may be equally effective as 6 month of treatment on the risk of all-cause mortality, but there was considerable uncertainty [Low quality evidence].

- One study with 2658 people suggested that 12 months of clopidogrel and aspirin treatment is equally effective as 1 month of treatment on the risk of cardiac mortality, but there was considerable uncertainty [Very low quality evidence].
- Two studies with 1970 people suggested that 24 months of clopidogrel and aspirin treatment is equally effective as 6 months of treatment on the risk of cardiac mortality, but there was considerable uncertainty [Very low quality evidence].
- Two studies with 3662 people suggested that 6 to 12 months of clopidogrel and aspirin treatment may be more effective than 1 month of treatment at reducing the risk of reinfarction, but there was some uncertainty [Low quality evidence].
- One study with 1970 people suggested that 24 months of clopidogrel and aspirin treatment may reduce the risk of reinfarction compared 6 months of treatment, but there was some uncertainty [Low quality evidence].
- One study with 1004 people suggested that 6 months of clopidogrel and aspirin treatment has a similar effect on the risk of stroke as 1 month of treatment, but there was considerable uncertainty [Very low quality evidence].
- One study with 1970 people suggested that 24 months of clopidogrel and aspirin treatment may increase the risk of stroke compared with 6 months of treatment, but there was some uncertainty [Low quality evidence].
- Two studies with 3579 people suggested that 6 to 12 months of clopidogrel and aspirin treatment may be more effective than 1 month of treatment on the risk of revascularisation but there was some uncertainty [Low quality evidence].
- One study with 2658 people suggested that 12 months of clopidogrel and aspirin treatment may have no effect on the risk of major bleeding compared with 1 month of treatment, but there was some uncertainty [Low quality evidence].
- One study with 1970 people suggested that 24 months of clopidogrel and aspirin treatment may increase the risk of major bleeding compared with 6 months of treatment, but there was some uncertainty [Low quality evidence].
- One study with 2658 people suggested that 12 months of clopidogrel and aspirin treatment may increase the risk of minor bleeding compared with 1 month of treatment, but there was some uncertainty [Low quality evidence].
- One study with 1970 people suggested that 24 months of clopidogrel and aspirin treatment may increase the risk of minor bleeding compared with 6 months of treatment, but there was some uncertainty [Low quality evidence].

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All-cause mortality

Duration (different durations)

- Four studies with 57,559 people showed that clopidogrel and aspirin are more effective than aspirin alone on reducing all-cause mortality, irrespective of follow-up [Moderate quality evidence].
- One study with 45,852 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing all-cause mortality within 28 days of treatment [High quality evidence].
- Two studies with 2229 people suggested that clopidogrel and aspirin may be more effective than aspirin alone at reducing all-cause mortality within 1 year of treatment, but there was considerable uncertainty [Very low quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin are equally effective as aspirin alone at reducing all-cause mortality more than 1 year after treatment [Very low quality

evidence].

People who had a STEMI

- One study with 45,852 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing all-cause mortality within 28 days of treatment in a STEMI population [High quality evidence].

People who had an NSTEMI

- Four studies with 11,707 people showed that clopidogrel and aspirin are equally effective as aspirin alone at reducing all-cause mortality in an NSTEMI population [Very low quality evidence].
- Two studies with 2229 people suggested that clopidogrel and aspirin may be more effective than aspirin alone at reducing all-cause mortality within 1 year of treatment in an NSTEMI population, but there was considerable uncertainty [Very low quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin are equally effective as aspirin alone at reducing all-cause mortality after more than 1 year of treatment in a mixed population [Very low quality evidence].

Type of treatment (PCI, CABG, medical treatment)

- One study with 2116 people suggested that clopidogrel and aspirin may be more effective than aspirin alone in reducing all-cause mortality in people who were treated with PCI, but there was considerable uncertainty [Very low quality evidence].
- One study with 113 people suggested that clopidogrel and aspirin may be more effective than aspirin alone in reducing all-cause mortality in people who were treated with CABG, but there was considerable uncertainty [Very low quality evidence].
- One study with 45,852 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing all-cause mortality in people treated medically post MI [High quality evidence].

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Cardiac mortality

Duration (different durations)

- Two studies with 49,343 people suggested that clopidogrel and aspirin may decrease the risk of cardiac mortality compared with aspirin alone within 28 days of treatment [High quality evidence].
- One study with 12,562 people showed that clopidogrel and aspirin are equally effective as aspirin alone at reducing cardiac mortality in people within 1 year of treatment [High quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin may be more effective than aspirin alone at reducing cardiac mortality in people after more than 1 year of treatment, but there was considerable uncertainty [Very low quality evidence].

People who had a STEMI

- Two studies with 49,343 people suggested that clopidogrel and aspirin may increase the risk of cardiac mortality compared with aspirin alone in people who had a STEMI, but there was considerable uncertainty [Moderate quality evidence].

People who had an NSTEMI

- In 1 study with 2658 people there was too much uncertainty to determine whether there is a difference between clopidogrel and aspirin versus aspirin alone in reducing cardiac mortality within 30 days of treatment in an NSTEMI population [Very low quality evidence].
- One study with 12,562 people showed that clopidogrel and aspirin are equally effective as aspirin alone at reducing cardiac mortality in people within 1 year of treatment [High quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin are equally effective as aspirin alone at reducing cardiac mortality in people after more than 1 year of treatment in a mixedpopulation [Very low quality evidence].

Types of treatment

- One study with 2658 people showed too much uncertainty to determine whether there is a difference between clopidogrel and aspirin and aspirin alone on the risk of cardiac mortality in people treated with PCI, but there was considerable uncertainty [Very low quality evidence].
- One study with 45,852 people showed that clopidogrel and aspirin are equally effective as aspirin alone on the risk of cardiac mortality in people treated medically after an MI. [Moderate quality evidence].

Reinfarction

Duration (different durations)

- Two studies with 49,343 people showed too much uncertainty to determine whether there is a difference between clopidogrel and aspirin versus aspirin alone on the risk of reinfarction within 30 days of treatment [Very low quality evidence].
- One study with 12,562 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of reinfarction within 1 year of treatment [Moderate quality evidence].
- One study with 9478 people suggested that clopidogrel and aspirin may decrease the risk of reinfarction compared with aspirin alone after more than 1 year of treatment, but there was considerable uncertainty [Very low quality evidence].

Update 2013

People who had a STEMI

- Two studies with 49,334 people suggested that clopidogrel and aspirin may decrease the risk of reinfarction compared with aspirin alone in a STEMI population, but there was considerable uncertainty [Very low quality evidence].

People who had an NSTEMI

- Two studies with 22,040 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of reinfarction in an NSTEMI population [Low quality evidence].
- One study with 12,562 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of reinfarction within 1 year of treatment in an NSTEMI population [Moderate quality evidence].
- One study with 9478 people suggested that clopidogrel and aspirin is more effective than aspirin alone at reducing the risk of reinfarction after more than 1 year of treatment in a mixed population, but there was considerable uncertainty [Very low quality evidence].

Types of treatment

- Two studies with 4774 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of reinfarction in people treated with PCI after an MII [Low quality evidence].

- One study with 45,882 people suggests that clopidogrel and aspirin may be more effective than aspirin alone in reducing the risk of reinfarction in people treated medically after an MI, but there was some uncertainty [High quality evidence].

Stroke

Duration (different durations)

- Two studies with 71,383 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of stroke in people after an MI [Low quality evidence].
- Two studies with 49,343 people suggested that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of stroke within 30 days of treatment, but there was considerable uncertainty [Very low quality evidence].
- One study with 12,562 people suggests that clopidogrel and aspirin may be more effective than aspirin alone at reducing the risk of stroke within 1 year of treatment, but there was considerable uncertainty [Moderate quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of stroke after more than 1 year of treatment [Very low quality evidence].

People who had a STEMI

- Two studies with 49,343 people suggested that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of stroke in a STEMI population, but there was considerable uncertainty [Moderate quality evidence].

People who had an NSTEMI

- Two studies with 28,165 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of stroke in an NSTEMI population [Very low quality evidence].
- One study with 12,562 people suggests that clopidogrel and aspirin may be more effective than aspirin alone at reducing the risk of stroke within 1 year of treatment in an NSTEMI population, but there was considerable uncertainty [Moderate quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of stroke after more than 1 year of treatment in a mixed population population [Very low quality evidence].

Types of treatment

- In 1study with 2116 people there was too much uncertainty to determine whether there is a difference between clopidogrel and aspirin versus aspirin alone in reducing the risk of stroke in people treated with PCI after an MI [Low quality evidence].
- One study with 45,582 people suggests that clopidogrel and aspirin may be more effective than aspirin alone at reducing the risk of stroke in people treated medically after an MI, but there was considerable uncertainty [Moderate quality evidence].

Revascularisation

Duration (different duration)

- One study with 3491 people suggested that clopidogrel and aspirin may be more effective than aspirin alone at reducing the risk of revascularisation within 30 days of treatment, but there was some uncertainty [Moderate quality evidence].

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- One study with 2558 peoples suggested that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of revascularisation within 30 days to 1 year of treatment, but there was some uncertainty [Low quality evidence].

People who had a STEMI

- One study with 3491 people suggested that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of revascularisation in a STEMI population, but there was some uncertainty [Moderate quality evidence].

People who had an STEMI

- Three studies with 4887 people showed that clopidogrel and aspirin and aspirin alone are similarly effective on the risk of revascularisation within 1 year of treatment [Very low quality evidence].

Types of treatment

- In 2 studies with 4769 people clopidogrel and aspirin appears to have a similar effect as aspirin alone on the risk of revascularisation in people treated with PCI [Moderate quality evidence].
- In 1 study with 113 people suggested that clopidogrel and aspirin are more effective than aspirin alone at reducing the risk of revascularisation in people treated with CABG, but there was considerable uncertainty [Very low quality evidence].

Cardiovascular death/MI/Stroke

Update 2013

NSTEMI and type of treatment

- One study with 2072 people who had an NSTEMI and who had undergone CABG showed clopidogrel and aspirin may decrease the risk of a having one of the composite outcomes: CV death/MI/stroke compared with placebo but there was some uncertainty [Low quality evidence].
- One study with 7985 people from a mixed population and who had undergone medical treatment showed clopidogrel and aspirin may decrease the risk of having one of the composite outcomes: CV death/MI/stroke compare with placebo but there was some uncertainty [Very low quality evidence].
- One study with 2658 people who had an NSTEMI and who had undergone PCI showed clopidogrel and aspirin may decrease the risk of having one of the composite outcomes: CV death/MI/stroke compare with placebo but there was some uncertainty [Low quality evidence].

Major bleeding

Duration (different durations)

- One study with 12,562 people suggested that clopidogrel and aspirin may increase the risk of major bleeding within 7 days of treatment compared with aspirin alone, but there was considerable uncertainty [Moderate quality evidence].Three studies with 61860 people showed that clopidogrel and aspirin may increase the risk of major bleeding more than aspirin alone within 30 days of treatment, but there was some uncertainty [Moderate quality evidence].
- Two studies with 14,678 people showed that clopidogrel and aspirin increase the risk of major bleeding more than aspirin alone within 30 days to 1 year of treatment [Low quality evidence].
- One study with 9478 people suggests that clopidogrel and aspirin may increase the risk of major bleeding compared with aspirin alone after more than 1 year of treatment, but there was considerable uncertainty [Very low quality evidence].

Types of treatment

- Two studies with 4744 people showed that clopidogrel and aspirin increase the risk of major bleeding more than aspirin after PCI [Moderate quality evidence].
- Two studies with 2185 people suggests that clopidogrel and aspirin may increase the risk of major bleeding compared with aspirin alone after CABG, but there was some uncertainty [Very low quality evidence].
- Two studies with 55,330 people suggests that clopidogrel and aspirin may increase the risk of major bleeding compared with aspirin after medical treatment of MI, but there was considerable uncertainty [Low quality evidence].

Minor-moderate bleeding

Duration (different durations)

- One study with 3452 people suggested that clopidogrel and aspirin may increase the risk of minor-moderate bleeding more than aspirin alone within 30 days of treatment, but there was some uncertainty [Moderate quality evidence].
- One study with 2116 people suggests that clopidogrel and aspirin may decrease the risk of minor bleeding compared with aspirin alone after 30 days to 1 year of treatment, but there was considerable uncertainty [Very low quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin increase the risk of minor-moderate bleeding compared with aspirin alone after more than 1 year of treatment [Low quality evidence].

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Types of treatment

- Two studies with 4774 people showed that clopidogrel and aspirin may increase the risk of minor-moderate bleeding compared with aspirin alone after PCI, but there was some uncertainty [Low quality evidence].
- One study with 113 people suggested that clopidogrel and aspirin may have a similar effect on the risk of minor bleeding compared with aspirin alone after CABG, but there was considerable uncertainty [Low quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin increase the risk of minor-moderate bleeding more than aspirin alone after medical treatment of MI [Low quality evidence].

Rehospitalisation

- One study with 9447 people showed that clopidogrel and aspirin and aspirin alone are equally effective on the risk of rehospitalisation [Very low quality evidence].

Sudden death

- No evidence on sudden death was identified.

Quality of life

- No evidence on sudden death was identified.

7.4.5.4.2 Economic

- A UK cost-effectiveness analysis in a STEMI population found that 1 year of treatment with clopidogrel (plus lifetime aspirin) was the most cost-effective option compared with 1 month or no clopidogrel treatment, Note that effectiveness was based on the STEMI COMMIT or CLARITY

trial up to 1 month but extrapolated from the CURE (UA/NSTEMI) trial beyond that. If the 1 year treatment option is removed, 1 month clopidogrel (plus lifetime aspirin) was cost effective compared to no clopidogrel treatment.

- A UK cost-effectiveness analysis in a UA/NSTEMI population found that 1 year of treatment with clopidogrel (plus lifetime aspirin) was the most cost-effective option in people at higher risk compared to 9 month, 6 month, 3 month or no clopidogrel treatment, while 3 months of treatment was the most cost-effective option in those at lower risk. However, this analysis was carried out when clopidogrel was still branded and the cheaper generic drug was not available. This study was an update of the previous analysis used to inform TA80.
- A UK cost-effectiveness analysis found that that 1 year of treatment with clopidogrel (plus lifetime aspirin) was cost-effective compared to 1 month of treatment with clopidogrel in people with UA/NSTEMI undergoing PCI (effectiveness and baseline risks based on PCI-CURE) and in an indirect population undergoing PCI where less than 75% had MI (effectiveness and baseline risks based on CREDO).
- A Canadian cost-effectiveness analysis in people who had a prior MI at some point (based on a subgroup of the CHARISMA trial) found that 28 months of clopidogrel treatment plus aspirin was cost effective compared to aspirin alone – different durations of clopidogrel treatment were not compared.
- All evidence was judged partially applicable and with potentially serious limitations. In particular, the cost of clopidogrel has greatly reduced since these analyses were undertaken – from over £400 to under £30 per year. This will improve the cost effectiveness of clopidogrel, for a longer duration, even in low-risk groups.

7.4.6 Non-acute initiation of antiplatelet therapy

Update 2013

Most individuals will receive dual antiplatelet therapy (that is aspirin and clopidogrel) during the acute stage of treatment. In 2010/2011 in England, 99% of people eligible received aspirin and 95% clopidogrel or another thienopyridine inhibitor on discharge after an MI; in Wales, 98% received aspirin and 92% clopidogrel or another thienopyridine inhibitor.[304] However, a minority of people who have had an MI will not have received dual antiplatelet therapy acutely, or will have presented with an MI that has occurred in the past. It is important to ascertain whether dual antiplatelet therapy should be initiated in these individuals and whether this population gain any benefit from doing so.

The previous guideline, CG48, recommended that dual antiplatelet therapy is not initiated in those who did not receive it during the acute phase. However, given the availability of new antiplatelet agents (including prasugrel and ticagrelor) and changes in acute management, it was considered that non-acute initiation of dual antiplatelet therapy should be considered, as part of the 2013 update.

7.4.6.1 In people with an MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?

For more details see review protocol in Appendix C.

7.4.6.2 Clinical evidence

This review searched for randomised controlled trials looking at the effectiveness of dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin) in people who have had an MI and in which therapy was not initiated acutely. Where no RCTs were identified, prospective cohort studies were included. This review covers clopidogrel, as well as prasugrel and ticagrelor, as NICE technology appraisal 182 and technology appraisal 236 do not consider initiation of these antiplatelets in people who have not been initiated acutely.

One study was identified, a subgroup analysis from an RCT.[49,51] This is summarised in Table 91 and is a subgroup analysis of the CHARISMA trial, included in CG48. The data were considered to be an indirect population. See also the evidence tables in Appendix G. No relevant clinical studies were identified comparing ticagrelor or prasugrel, in combination with aspirin, with aspirin as the comparator, in people who were not initiated acutely.

The subgroup analysis [49,51] included an additional composite outcome which was included because of a paucity of data relating to people who have had an MI.

Update 2013

Update 2013

Table 91: Summary of included studies

	Study	Included in CG48 or new to update	Intervention/comparison	Population	Duration	Outcomes reported
1.	Bhatt2007[49,51] (CHARISMA)	CG48 (post hoc analysis of a subgroup from larger trial presented in CG48)	Clopidogrel 75mg/day plus aspirin(75 to 162mg/day) vs. aspirin (75 to 162mg/day)	40.5% had prior MI. 23.6 months (median time from diagnosis) prior to randomisation 34% had prior stroke. 3.5 months (median time from diagnosis) prior to randomisation 30% had symptomatic PAD. 23.6 months (median time from diagnosis). Note: 4.7% fell into multiple categories.	28 months	• Cardiovasular death • MI (non-fatal) • Ischaemic stroke (nonfatal) • Stroke (fatal) • Hospitalisation for unstable angina, transient ischaemic attack, revascularization • Major bleeding • Moderate bleeding People who have had an MI only: • Composite outcome: cardiac death, stroke and reinfarction

Update 2013

Table 92: GRADE profile: clopidogrel plus aspirin versus aspirin in those not treated acutely.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel +aspirin	Aspirin	Relative (95% CI)	Absolute		
MIXED POPULATION												
All-cause mortality[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	235/4735 (5%)	257/4743 (5.4%)	RR 0.92 (0.77 to 1.09)	4 fewer per 1000 (from 12 fewer to 5 more)	VERY LOW	CRITICAL
Cardiovascular mortality[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	142/4735 (3%)	163/4743 (3.4%)	RR 0.87 (0.7 to 1.09)	4 fewer per 1000 (from 10 fewer to 3 more)	VERY LOW	CRITICAL
Reinfarction[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	117/4735 (2.5%)	145/4743 (3.1%)	RR 0.81 (0.64 to 1.03)	6 fewer per 1000 (from 11 fewer to 1 more)	VERY LOW	IMPORTANT
Stroke[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	144/4735 (3%)	179/4743 (3.8%)	RR 0.81 (0.65 to 1)	7 fewer per 1000 (from 13 fewer to 0 more)	VERY LOW	IMPORTANT
Rehospitalisation[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	542/4735 (11.4%)	626/4743 (13.2%)	RR 0.87 (0.78 to 0.97)	17 fewer per 1000 (from 4 fewer to 29 fewer)	VERY LOW	IMPORTANT
Major bleeding[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	79/4735 (1.7%)	71/4743 (1.5%)	RR 1.11 (0.81 to	2 more per 1000 (from 3	VERY LOW	IMPORTANT

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Quality assessment							No of patients		Effect		Quality	Importance
									1.53)	fewer to 8 more)		
Moderate bleeding[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	Very serious[b]	Serious[d]	None	97/4735 (2%)	61/4743 (1.3%)	RR 1.59 (1.16 to 2.19)	8 more per 1000 (from 2 more to 15 more)	VERY LOW	IMPORTANT
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
POST MI POPULATION												
Cardiovascular death/MI/stroke- prior MI (hazard ratio)[49,51]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	125/1903 (6.6%)	161/1943 (8.3%)	HR 0.77 (0.61 to 0.98)	18 fewer per 1000 (from 2 fewer to 31 fewer)	LOW	CRITICAL
All-cause mortality												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Cardiac mortality												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Reinfarction												
0	No evidence	-	-	-	-	None	-	-	-	-	-	IMPORTANT

Update 2013

Quality assessment							No of patients		Effect		Quality	Importance
	available											
Stroke												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) The data is taken from a subgroup analysis from the larger CHARISMA trial. Participants were not randomised to groups based on their CHD history to ensure they were evenly matched. However, there were no differences at baseline between the 2 groups.

(b) The study used a mixed population.40.5% had a prior M at 23.6 months prior to randomisation. 34% had prior stroke, 3.5 months prior to randomisation. 30% had symptomatic PAD, 23.6 months median time from diagnosis.

(c) 95% confidence intervals crossed line of no effect and 1 MID.

(d) 95% confidence intervals crossed 1 MID.

(e) There is a risk of bias from using a composite outcome as the authors may look for a significant result by combining different outcomes. It is not possible to identify which outcome is driving the results.

7.4.6.3 Economic evidence

Published literature

No studies addressing this question were included in the previous guideline, CG48. From the update searches, 4 relevant studies were identified which were published since the cut-off date for searches in CG48.[86,87,190,237] Three of them[86,87,190] were comparisons of clopidogrel plus aspirin versus aspirin alone based on the CHARISMA trial – 1 based on the full study population of people with CVD disease or with multiple risk factors for CVD disease and 2 based on a cardiovascular disease (CVD) subgroup. An additional study was found[236,237] which looked at the cost effectiveness of 1 year of treatment with clopidogrel in addition to aspirin versus aspirin alone in people with NSTEMI or unstable angina. No studies were found looking at post-acute initiation of prasugrel or ticagrelor.

Two studies were included –a Canadian analysis based on the CVD subgroup and a UK analysis based on the full trial population.[87,190] Both studies included people with CVD and less than 75% of these had a previous MI, therefore the population in these studies was considered to be indirect for our review. However, in the study by Chen et al (2011)[86,87], a subgroup analysis on people who had a prior MI was conducted. One USA study that met the inclusion criteria was selectively excluded on the basis that a more applicable study (Chen 2011) based on the same CVD subgroup was available.[86,86] The included studies are summarised in the economic evidence profile below (Table 93). See also the study selection flow chart in Appendix D and study evidence tables in Appendix G. Excluded studies are listed in Appendix J, with reasons for exclusion given.

Update 2013

Table 93: Initiation of antiplatelet agents post-acute treatment – clopidogrel plus aspirin versus aspirin alone

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Chen 2011[86,87] (Canada) MI	Partially applicable (a)	Potentially serious limitations (b, c, d)	• Within-trial analysis of a CHARISMA prior MI subgroup (b) • Lifetime analysis; treatment and effect period 28 months • Life years estimated based on observed differences in CV death, MI and stroke	£684 (e)	0.106 life years gained	£6,467 per life year gained (e)	Not reported
Chen 2011[86,87] (Canada) CVD	Partially applicable (a,f)	Potentially serious limitations (g,c)	• Within-RCT analysis of CHARISMA CVD subgroup (g) • Analysis as above except QALYs estimated by applying QoL weights to MI and stroke outcomes; short term quality of life loss also applied for major bleeding events.	£785 (e)	0.07 QALYs gained	£11,362 per QALY gained (e)	DSA: • Cost effectiveness ranged from £5,891 to £29,557 per QALY gained • Clopidogrel remained cost effective in most scenarios • Reducing clopidogrel cost 50% reduced ICER to £5,891
Heeg 2007[190,190] (UK) CVD and high CV risk	Partially applicable (h)	Potentially serious limitations (i,j)	• Markov model with 6 month cycles • Effectiveness: CHARISMA trial[49,50] (i) • Lifetime analysis; treatment and effect period 28 months • Life years estimated based on reported differences between treatments in terms of MI, stroke, death; differences in bleeding incorporated on cost side only	£772	0.0054 life years gained	£143,071 per life year gained	PA: • Probability cost effective (£20K/£30K threshold) = 15%/27% DSA: • None

CV = cardiovascular; CVD = cardiovascular disease; DSA = deterministic sensitivity analysis; MI = myocardial infarction; PA = probabilistic analysis; QALYs = quality-adjusted life years
(a) Some uncertainty about applicability of Canadian costs and multinational resource use. Cost of clopidogrel higher than current UK context (£485 per year).Discount rate not in line with NICE reference case. Some uncertainty about applicability of utility data as methods unclear.
(b) Effectiveness based on analysis of MI subgroup of CHARISMA established CVD subgroup (defined below).
(c) Study funded by Sanofi-aventis Canada Inc. and Bristol-Myers Squibb Canada (manufacture clopidogrel).

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(d) No sensitivity analysis.
(e) Converted from 2008 Canadian dollars using purchasing power parities[340]
(f) Indirect population: CVD (~40% MI).
(g) Effectiveness based on analysis of CHARISMA established CVD subgroup (defined as pre-existing coronary artery disease [angina, MI, PCI, or coronary artery bypass surgery], cerebrovascular disease [ischaemic stroke, transient ischaemic attack], or symptomatic peripheral arterial disease [PAD]) – clinical review excluded this subgroup analysis in favour of CHARISMA high risk CVD (defined as MI, stroke or symptomatic PAD) subgroup analysis considered more relevant.
(h) Indirect population (~35% MI). Some uncertainty about applicability of multinational resource use. Cost of clopidogrel higher than current UK context (£460 per year). QALYs not used, however if life years were adjusted by quality of life the overall results would not change as the ICER would be even higher than the 1 estimated using life years gained.
(i) Event probabilities based on analysis of CHARISMA full study population (established CVD and multiple CVD risk factors) – clinical review excluded this analysis in favour of CHARISMA high risk CVD (defined as MI, stroke or symptomatic PAD) subgroup analysis considered more relevant.
(j) Some methodological limitations with probabilistic methods. No other sensitivity analysis reported.

7.4.6.4 Evidence statements

7.4.6.4.1 Clinical

- One study with 9478 people suggested that clopidogrel and aspirin has no effect on the risk of all-cause mortality compared with aspirin alone in people who had CHD patients who were not treated acutely, but there was some uncertainty [Very low quality evidence].
- One study with 9478 people suggested that clopidogrel and aspirin has no effect on the risk of cardiac mortality compared with aspirin alone in people who had CHD who were not treated acutely, but there was some uncertainty [Very low quality evidence].
- One study with 9478 people suggested that clopidogrel and aspirin has no effect on the risk of reinfarction compared with aspirin alone in people who had CHD who were not treated acutely, but there was some uncertainty [Very low quality evidence].
- One study with 9478 people showed clopidogrel and aspirin is more effective at reducing the risk of stroke compared with aspirin alone in people who had CHD who were not treated acutely, but there was some uncertainty [Very low quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin is more effective at reducing the risk of rehospitalisation compared with aspirin alone in people who had CHD who were not treated acutely [Very low quality evidence].
- One study with 9478 people showed that clopidogrel and aspirin has no effect on the risk of major bleeding compared with aspirin alone in people who had CHD who were not treated acutely, but there was some uncertainty [Very low quality evidence].
- One study with 9478 people showed clopidogrel and aspirin increases the risk of moderate bleeding compared with aspirin alone in people who had CHD who were not treated acutely [Very low quality evidence].
- No evidence on sudden death was identified.
- No evidence on revascularisation was identified.
- No evidence on quality of life was identified.

Update 2013

7.4.6.4.2 Post MI

- One study with 3846 people showed that clopidogrel and aspirin decreases the risk of having 1 or more of the following events: cardiac death, stroke, reinfarction compared with aspirin alone [Low quality evidence].
- No evidence on all-cause mortality was identified.
- No evidence on cardiac morality was identified.
- No evidence on sudden death was identified.
- No evidence on revascularisation was identified.
- No evidence on rehospitalisation was identified.
- No evidence on adverse events was identified.
- No evidence on quality of life was identified.

7.4.6.5 Economic

- A Canadian cost-effectiveness analysis in people who have had a prior MI at some point (based on a subgroup of the CHARISMA trial) found that clopidogrel treatment plus aspirin was cost effective compared to aspirin alone.

- A UK cost-effectiveness analysis in people with CVD and high CV risk found that treatment with clopidogrel plus aspirin was not cost effective compared to aspirin alone.
- All evidence was judged partially applicable and with potentially serious limitations. In particular, the cost of clopidogrel has greatly reduced since these analyses were undertaken – from over £400 to under £30 for a year's worth of treatment. This will improve the cost effectiveness of clopidogrel.
- No relevant economic analyses were identified relating to initiation of prasugrel or ticagrelor in those not initiated acutely.

7.4.7 Antiplatelet therapy in those with an additional indication for anticoagulation

Significant numbers of people presenting with an acute coronary syndrome (ACS) are already taking oral anticoagulants (OAC), usually warfarin, but increasingly dabigatran and other new- oral anticoagulants (NOAC), for an independent indication such as atrial fibrillation or a mechanical prosthetic valve replacement. For example in the RICO study of STEMI in France, 4% of people were taking OAC on admission.[448,448] In addition some people develop complications of myocardial infarction, for example atrial fibrillation or left ventricular thrombus, which require oral anticoagulation. Oral anticoagulation alone is generally considered inadequate in the prevention of recurrent ischaemic events in people with acute myocardial infarction, particularly those treated with intra-coronary stents.

Dual antiplatelet therapy (DAPT) is recommended in people receiving both medical therapy and interventional therapy, to prevent recurrent thrombotic events and in particular, in people who received stents to prevent stent thrombosis. However dual antiplatelet therapy may be inferior to OAC in the prevention of stroke in atrial fibrillation, and for other conditions needing anticoagulation (for example. mechanical prosthetic valve, pulmonary embolism) has little efficacy. Thus people with both conditions may benefit from simultaneous treatment with OAC and dual antiplatelet therapy.

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Yet it is clinically apparent that people who have both a need for DAPT and a need for OAC, who receive both therapies, have a high bleeding risk. The association between bleeding episodes and mortality in people with acute coronary syndromes suggests triple therapy may even increase mortality as well as causing morbidity.[295,295]

New antiplatelet and oral anticoagulant agents are available, increasing the number of potential combinations of agents, for most of which there is little clinical experience of combined anticoagulant and antiplatelet therapy.

Clinicians and patients are thus faced with difficult decisions about the balance between the risk of recurrent coronary event, the risk of thrombotic event due to the pre-existing or new condition requiring OAC, and the risk of bleeding.

The previous guideline, CG48, recommended continuing warfarin with aspirin being added in people at (undefined) low risk of bleeding, but current practice, particularly after stenting, has been to emphasise the use of clopidogrel in addition. However, the availability of new oral anticoagulants and changes in acute management since CG48 mean that it is appropriate to consider whether there is evidence that suggests a change in the recommendation is appropriate.

7.4.7.1 What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an MI and an indication for anticoagulation?

For full details see review protocol in Appendix C.

7.4.7.2 Clinical evidence

This review searched for randomised controlled trials comparing the effectiveness or comparative safety of adding an oral anticoagulant (OAC) to an antiplatelet agent (single or double) for the secondary prevention of myocardial infarction. Where no RCTs were identified, cohort studies were included.

Twenty-four studies were identified, 16 of these were RCTs [13,20,21,68,97,118,121,197,201,221,228,248,269,275,281,281,323,331,347,392,393,397,434,453]. These are summarised in Table 94. See also the full study evidence tables in Appendix G and forest plots in Appendix I.

Table 94 provides a summary of the different comparisons presented in this review. Three populations were identified as potentially relevant:

1. Direct population: people who had an MI and comorbid condition who need oral anticoagulation.
2. Indirect population I: people with an indication for anticoagulation and who have coronary heart disease (CHD) (however, it is unclear if the population has had an MI or less than 75% of the population has had an MI).
3. Indirect population II: people who have CHD or who had an MI but who did not have an indication for anticoagulation.

One paper by Patel et al. provided information on the direct population and compared rivaroxaban plus aspirin or warfarin plus aspirin. A sub-group analysis was available on the risk of bleeding in people who had an MI at some point in the past.[346,347]

For indirect population I, 1 RCT and 8 observational studies were found comparing the effectiveness of triple therapy versus dual therapy in people who had an indication for anticoagulants. One RCT addressed the review question in people who had undergone revascularisation with bare metal stents or drug eluting stents, and required warfarin and antiplatelet therapy. This study compared combined therapy with warfarin, clopidogrel and aspirin with warfarin and clopidogrel.[120,121]

For indirect population II, 11 RCTs were found that included people who had an MI or been diagnosed with coronary heart disease and were treated with single or dual antiplatelet therapy (aspirin and/or clopidogrel), with or without warfarin. None of the people had an indication for anticoagulation however, were being treated with oral anticoagulation to assess its effectiveness in people with CAD.

Data were analysed by dose of warfarin (moderate dose INR 2-2.9 and high dose INR 3-4.5); dose of dabigatran (100 plus 150 mg/day and 220 plus 300 mg/day) and dose of rivaroxaban (5mg/day and 10mg/day). The GDG highlighted that the doses of rivaroxaban used were not licensed for the treatment of atrial fibrillation. The dose for apixaban and the higher dose for dabigatran were considered appropriate but associated with an increased risk of bleeding. Low dose warfarin was excluded as the GDG did not consider this to be clinically relevant any longer.

Time to follow-up was investigated if heterogeneity was detected however heterogeneity was not found in any of the analyses.

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Table 94: Summary of included studies

	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
DIRECT POPULATION - People who had an MI and who have a comorbid condition needing oral anticoagulation.								
RCT								
1.	Patel et al 2011[346,347] RCT ROCKET-AF	Rivaroxaban (20mg/day) plus aspirin and/or theinopyridine Unclear dose and number on concomitant therapy	Warfarin (INR 2-3) plus aspirin and/or theinopyridine Unclear dose and number on concomitant therapy	• Indication for oral anticoagulation (OAC) was nonvalvular atrial fibrillation (AF) Subgroup who had an MI at some point in the past	High risk for stroke	590 days	n=2468	• Major and non-major clinically relevant bleeding while on treatment
INDIRECT POPULATION I - People with an indication for anticoagulation and need stents or have CHD (unclear if they had an MI or less than 75% of the population had an MI)								
RCT								
1.	Dewilde et al.[120,121] WOEST	Warfarin plus clopidogrel (75mg/day) plus aspirin (80mg/day)	Warfarin plus clopidogrel (75mg/day)	• Indication for oral anticoagulation was atrial fibrillation/atrial flutter; mechanical valve orother (pulmonary embolus, EF less than 30%, apical thrombus)	Admitted for bare metal or drug eluting stents. Less than20% ACS at baseline	12 months	n=563	• All-cause mortality • Stroke • Reinfarction • Target vessel revascularisation • Major bleeding • Minor bleeding
Cohort studies								
1.	DeEugenio2007[118,118]	Warfarin (INR 2-3) plus aspirin plus clopidogrel	Without prior anticoagulation	• People in warfarin group were on long term	PCI with stent	182 days	n=194	• Bleeding

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	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
	(retrospective cohort)	Dose of Aspirin plus clopidogrel not reported	Aspirin plus clopidogrel (without prior anticoagulation)	warfarin use (indication for oral anticoagulation not reported).				
2.	Karjalainen2007[221,221] (retrospective registry)	With prior anticoagulation: Wafarin plus aspirin plus clopidogrel Warfarin plus aspirin Warfarin plus clopidogrel Doses not reported	Without prior anticoagulation Aspirin plus clopidogrel	• People in warfarin group were on long term warfarin use. Reasons for needing anticoagulation included: • Atrial fibrillation • Mechanical heart valve • Cerebrovascular accident • Pulmonary or venous thromboembolism • Unidentified	Coronary stent STEMI: 9-14% NSTEMI: 24%	12months	n=446	• Death • Stroke • MI • Major bleeding • Stent thrombosis
3.	Khurram2006[228,228] (retrospective study)	With prior warfarin Warfarin plus aspirin plus clopidogrel (75mg/day) Dose of aspirin doseand warfarin INR not reported.	Without prior warfarin Aspirin plus clopidogrel (75mg/day)	• People on chronic warfarin therapy in warfarin group. Reasons for needing anticoagulation included: • Atrial fibrillation • Prosthetic heart valve • Prophylactic anticoagulation to prevent LV thrombus after large MI • Pulmonary embolism	Coronary stenting	211 days	n=2014	• Fatal from intracranial haemorrhage • Major bleeding

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	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
4.	Mattichak2005[275,275] (retrospective registry cohort study)	Warfarin plus clopidogrel plus aspirin.	Without prior anticoagulation Aspirin plus clopidogrel	• Only triple therapy group needed oral anticoagulation. Reasons for needing warfarin: • LV thrombosis • Atrial fibrillation • Mechanical prosthetic valve • Deep vein thrombosis	Admitted for acute coronary syndrome plus stent	12 months	n=82	• Death • Stroke • Reinfarction • GI bleeding • Transfusion
5.	Nguyen2007[323,323] (prospective cohort)	Warfarin/dual antiplatelet Doses not reported	Warfarin/single antiplatelet	Prior warfarin = 226/800 New warfarin = 574/800 Reasons for needing oral anticoagulation: • Atrial fibrillation • Prosthetic heart valve • Venous embolism • Unidentified	Admitted for acute coronary syndrome STEMI: 61% NSTEMI:23% (84%) Unstable angina: 16% plus stent	6 months	n=800	• Death • Stroke • Unscheduled PCI • Reinfarction • Major bleeding • Rehospitalisation **Subgroup** Cohort with AF
6.	Rubboli2012[393,393] (cohort)	Warfarin plus clopidogrel plus aspirin Doses not reported.	Clopidogrel plus aspirin Or Warfarin plus aspirin	Reasons for needing oral anticoagulation: • Atrial fibrillation • Deep vein thrombosis/pulmonary embolism • Heart valve	Admitted for PCI 63% MI (46% NSTEMI, 17% STEMI) Other: 37%	12 months	n=622	• CV mortality • Reinfarction • Stroke • Revascularisation • Major bleeding

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	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
			Doses not reported.	• Dilated cardiomyopathy • Ischaemic heart disease • Cardiac thrombus • Previous stroke • LV aneurysm				
7.	Rossini2008[392,392] (cohort)	Warfarin/dual antiplatelet (clopidogrel 75mg/day plus aspirin 100mg/day) INR: 2 to 2.5	Dual antiplatelet (clopidogrel 75mg/day plus aspirin 100mg/day)	Only triple therapy group needed oral anticoagulation. Reasons for needing oral anticoagulation: • Atrial fibrillation • LV mural thrombosis • LV aneurysm • Pulmonary embolism • Other	Admitted for coronary stent STEMI: 34% NSTEMI/Unstable angina: 44% Stable angina: 21%	18 months	n=204	• All-cause mortality • Cardiac mortality • Non-fatal reinfarction • Stroke • Major bleeding • Minor bleeding
8.	Sarafoff2008[397,397] (prospective cohort)	Warfarin plus aspirin plus clopidogrel	Aspirin plus clopidogrel	All patients had an indication for oral anticoagulation.. Reasons for needing oral anticoagulation: • Atrial fibrillation • Deep vein thrombosis • Left ventricular aneurysm • Pulmonary embolism • Left ventricular ejection fraction less than 30% • Prosthetic heart valve	Drug eluting coronary stent	4-52weeks Follow-up 2 years	n=515	• Death • MI • Stroke • Major bleeding • Minor bleeding

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	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
INDIRECT POPULATION II People without an indication for anticoagulation but who have CHD(stable angina, unstable angina or revascularisation) or who had an MI (more than 75% OR less than 75% had an MI but the remainder are a CHD population).								
1.	Brouwer2002[68,68] RCT APRICOT-2	Warfarin (INR2-3)plus aspirin (160mg-80mg)	Aspirin(160mg-80mg)	No indication for anticoagulation.	TIMI 3 flow in infarct-related artery (Unstable angina/NSTE MI)	3months	n=308	• Death • Reinfarction • Revascularisation • Bleeding
2.	Cohen1994A[96,97] RCT ATACS	Warfarin (INR 2-3)plus aspirin (162.5mg/day)	Aspirin (162.5mg/day)	No indication for anticoagulation.Excluded: • people with valvular heart disease • current need for anticoagulation for example. pulmonary embolism	NSTEMI: 22% STEMI: 6-9% Unstable rest angina: 69%	3months	n=214	• All-cause death • Reinfarction • Revascularisation • Major bleeding • Minor bleeding
3.	Hurlen2002[197,198] RCT WARIS	Warfarin (INR 2-2.5) plus aspirin (75mg/day)	Aspirin (160mg/day) Warfarin (INR 2.8-4.2)	No indication for anticoagulation.Excluded: • peoplewho had an indication for anticoagulation	MI (100%) STEMI/Q-wave: 60%	4years	n=3630	• Reinfarction • Thromboembolic stroke • Death • Major bleeding • Minor bleeding
4.	Huynh2001[201,201]	Warfarin (INR 2-2.5) plus aspirin	Aspirin (325mg/day)	No indication for anticoagulation.Excluded:	Unstable angina or	1,3,6,12m onths	n=135	• Death

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	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
	RCT	(325mg/day)	Warfarin (INR 2-2.5)	• people who had conditions mandating treatment with warfarin (such as metallic valve prosthesis)	NSTEMI and prior CABG LVEF <40% : 42-56%			• MI • Rehospitalisation • Revascularisation (PCI/CABG)
5.	Leon1998[248,248] RCT	Warfarin (INR 2-2.5) plus aspirin	Aspirin (325mg/day) Aspirin (325mg/day)plus ticlopidine (250mg/day)	No indication for anticoagulation.	Single or multi-vessel disease of coronary artery, treated with stent. Angina grade III/IV: 60%	30 days	n=1653	• Death • Revascularisation • Reinfarction • Haemorrhagic complications
6.	Machraoui1999[259,259] RCT	Warfarin (INR 3.5-4.5) plus aspirin (100mg)	Aspirin (100mg)	No indication for anticoagulation.Excluded: • people previously on warfarin	MI: 2-6% Stable angina: 60% Unstable angina: 17-21%	3months	n=164	• Death • Reinfarction (Q and non-Q wave) • Revascularisation (PCI/CABG) • Cerebral bleeding
7.	OASIS investigators[13] RCT OASIS	Warfarin (2-2.5) plus aspirin	Aspirin	No indication for anticoagulation.Excluded: • those who had a clear clinical indication for warfarin treatment	Unstable angina: 86% NSTEMI: 14%	5 months	n=3712	• CV death • Stroke • Reinfarction • Major bleeding • Minor bleeding • Revascularisation
8.	Tenberg2000[434,434]	Courmarin	Aspirin	No indication for	Symptomati	1 year	n=1058	• Death

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	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
	RCT	~30d INR =2.7 30 days-1 year INR = 3.0 (INR 2.1 -4.8) plus aspirin (100mg/day)	(100mg/day)	anticoagulation.Excluded: • people on current use of oral anticoagulants	c coronary artery disease planning to undergo percutaenous transluminal coronary angioplasty Angina I-IV: 88% Angina IV plus ST-T changes:12 %			• MI • Revascularisation • Stroke • Minor bleeding • Major bleeding
9.	VanEs2002 [452,453] RCT ASPECT-2	Warfarin (INR 3-4) plus aspirin (100mg/day)	Aspirin (100mg/day) Warfarin (INR 3-4)	No indication for anticoagulation.Excluded: • people with established indications for oral anticoagulants (eg. AF, prosthetic heart valve, ventricular aneurysm)	STEMI:45% NSTEMI: 43% Unstable angina: 13%	26months	n=999	• Mortality (HR, RR) • All-cause mortality • Vascular death • Reinfarction • Revascularisation • All stroke • Major bleeding • Minor bleeding
INDIRECT POPULATION II – apixaban plus aspirin plus clopidogrel versus aspirin plus clopidogrel								
1.	Alexander2011	Apixaban (5mg 2xday) plus aspirin plus	Placebo plus aspirin plus clopidogrel	No indication for anticoagulation.Excluded:	STEMI: 62%	241 days median	n=3705	• Death

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	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
	[20,21] RCT APPRAISE-2	clopidogrel Note: trial finished early because of bleeding risk		• people with an indication for ongoing anticoagulation	NSTEMI: 32% Unstable angina: 7%			• Cardiovascular death • Reinfarction • Stroke • Major bleeding • Any bleeding
2.	Alexander2009 [20,20] RCT APPRAISE	Apixaban (2.5mg 2xday) plus aspirin (162mg/day) plus clopidogrel	Aspirin (162mg/day) plus clopidogrel	No indication for anticoagulation.Excluded: • people required ongoing treatment with a parenteral or oral anticoagulant	STEMI: 40% NSTEMI: 42% Unstable angina: 18%	1,3,9,18 and 26weeks	n=1229	• Major bleeding • Any bleeding
INDIRECT POPULATION II - dabigatran plus aspirin plus clopidogrel versus aspirin plus clopidogrel								
1.	Oldegren2011 [331,332] RCT RE-DEEM	Dabigatran (75mg 2xday , 110mg 2xday or 150mg 2xday) plus aspirin (<100mg/day) plus clopidogrel (loading dose 300-600mg followed by 75mg/day)	Aspirin (less than 100mg/day) plus clopidogrel (loading dose 300-600mg following by 75mg/day)	No indication for anticoagulation.Excluded: • on-going or planned treatment with Vitamin K antagonists	STEMI: 62% NSTEMI: 38%	6months	n=1861	• All-cause death • Cardiovascular death • Myocardial infarction (non-fatal) • Stroke • Major bleeding • Minor bleeding
Rivaroxaban plus aspirin plus theinopyridine versus aspirin plus theinopyridine								
1.	Mega2012[281,281] RCT ATLAS ACS TIMI 46	Rivaroxaban (2.5mg 2xday plus 5mg 2xday) plus aspirin (75-100mg/day) plus theinopyridine	Aspirin (75-100mg/day) plus theinopyridine (clopidogrel, or ticlopidine)	No indication for anticoagulation.	STEMI: 50% NSTEMI: 25% Unstable angina: 25%	13months mean	n=15526	• Bleeding • Composite outcome

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	Study	Intervention	Comparison	Population (including indication for anticoagulant)	Reason for treatment	Duration	Number of patients	Outcomes reported
	Phase II study	(clopidogrel, or ticlopidine)						

Table 95: Summary of comparisons included

	Comparison	Study type	Intervention Indication for anticoagulants	Comparison Indication for anticoagulants	CHD	Group
					MI	
1.	Rivaroxaban versus warfarin	RCT – subgroup analysis	√	√	√ √	Direct population
2.	Warfarin plus dual antiplatelet versus dual antiplatelet	non-RCT	√	X (except Rubboli)	√ Unclear (√ Rubboli = 63%)	Indirect population I
3.	Warfarin plus dual antiplatelet versus warfarin plus clopidogrel	RCT	√	√	√ <30% MI	Indirect population I
4.	Warfarin plus dual antiplatelet versus warfarin plus aspirin	Cohort (non-RCT)	√	√	√ √ (<63%)	Indirect population I
5.	Apixaban/dabigatran/rivaroxaban Plus dual antiplatelet versus dual antiplatelet	RCT	X	X	√ √	Indirect population II
6.	Warfarin plus aspirin versus aspirin	RCT	X	X	√ √	Indirect population II
7.	Warfarin plus aspirin versus warfarin	RCT	X	X	√ √	Indirect population II

Table 96: GRADE profile: warfarin plus dual antiplatelet versus warfarin plus clopidogrel

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ dual therapy	Warfarin+ clopidogrel	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality [120,121]												
1	Randomised trial	Serious [a]	No serious inconsistency	Serious[b]	Serious[c]	None	18/284 (6.3%)	7/279 (2.5%)	RR 2.53 (1.07 to 5.95)	38 more per 1000 (from 2 more to 124 more)	VERY LOW	CRITICAL
Reinfarction [120,121]												
1	Randomised trial	Serious [a]	No serious inconsistency	Serious[b]	Very serious[d]	None	13/284 (4.6%)	9/279 (3.2%)	RR 1.42 (0.62 to 3.27)	14 more per 1000 (from 12 fewer to 73 more)	VERY LOW	IMPORTANT
Stroke-[120,121]												
1	Randomised trial	Serious [a]	No serious inconsistency	Serious[b]	Very serious[d]	None	8/284 (2.8%)	3/279 (1.1%)	RR 2.62 (0.70 to 9.77)	17 more per 1000 (from 3 fewer to 94 more)	VERY LOW	IMPORTANT
Major bleeding [120,121]												
1	Randomised trial	Serious [a]	No serious inconsistency	Serious[b]	Serious[c]	None	16/284 (5.6%)	9/279 (3.2%)	RR 1.75 (0.78 to 3.89)	24 more per 1000 (from 7 fewer to 93 more)	VERY LOW	CRITICAL
Minor bleeding[120,121]												
1	Randomised trial	Serious [a]	No serious inconsistency	Serious[b]	No serious imprecision	None	77/284 (27.1%)	31/279 (11.1%)	RR 2.44 (1.66 to 3.58)	160 more per 1000 (from 73 more to	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ dual therapy	Warfarin+ clopidogrel	Relative (95% CI)	Absolute	Quality	Importance
										287 more)		
All bleeding events[120,121]												
1	Randomised trial	Serious [a]	No serious inconsistency	Serious[b]	No serious imprecision	None	128/284 (45.1%)	55/279 (19.7%)	HR 0.36 (0.26 to 0.50)	121 fewer per 1000 (from 93 fewer to 142 fewer)	LOW	CRITICAL
Stent thrombosis[120,121]												
1	Randomised trial	Serious [a]	No serious inconsistency	Serious[b]	No serious imprecision	None	128/284 (45.1%)	55/279 (19.7%)	HR 0.36 (0.26 to 0.50)	121 fewer per 1000 (from 93 fewer to 142 fewer)	LOW	CRITICAL
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) The study was an RCT, but an open label study. It is difficult to blind when treating people with warfarin.
(b) The study used an indirect MI population (less than 75% people had an MI). However, all participants needed PCI.
(c) 95% confidence intervals crossed 1 MID (1.25).
(d) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).

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Table 97: GRADE profile: warfarin plus dual antiplatelet versus warfarin plus clopidogrel (hazard ratio)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ clopidogrel	Warfarin+ dual therapy	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality (hazard ratio)[120,121]												
1	Randomised trial	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None[d]	7/279 (2.5%)	18/284 (6.3%)	HR 0.39 (0.16 to 0.94)	15 fewer per 1000 (from 1 fewer to 21 fewer)	VERY LOW	CRITICAL
Cardiac mortality (hazard ratio)												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Sudden death(hazard ratio)												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Reinfarction(hazard ratio)												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Stroke(hazard ratio)												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revacuarlisation(hazard ratio)												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Rehospitalisation(hazard ratio)												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life(hazard ratio)												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ clopidogrel	Warfarin+ dual therapy	Relative (95% CI)	Absolute		
Adverse events(hazard ratio)												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) The study was an RCT, but was an open label study.It is dDifficult to blind when treating people with warfarin.
(b) The study used an indirect MI population (less than 75% of participants had an MI). However, all participants needed PCI.
(c) 95% confidence intervals crossed 1 MID (0.75).
(d) Hazard ratios presented separately as the authors reported the data in this format.

Table 98: GRADE profile: rivaroxaban versus warfarin

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Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Rivaroxaban	Warfarin	Relative (95% CI)	Absolute		
Major and clinically relevant minor bleeding[346,347]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	Very serious indirectness[b]	Serious[a]	None	287/1182 (24.3%)	268/1449 (18.5%)	RR 1.17 (1.01 to 1.35)	31 more per 1000 (from 2 more to 65 more)	VERY LOW	IMPORTANT
All-cause mortality												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Cardiac mortality												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Sudden death												
0	No evidence	-	-	-	-	None	-	-	-	-	-	CRITICAL

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Quality assessment							No of patients		Effect		Quality	Importance
	available											
Reinfarction												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Stroke												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Minor bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) 95% confidence intervals crossed 1 MID.

(b) . The study was a subgroup analysis from a larger trial. It was unclear when the participants had their MI. It is unclear what percentage of post MI patients were taking aspirin and/or thienopyridine or what dose they were taking. In the larger trial, 34.9% and 36.2% in the rivaroxaban and warfarin groups respectively took aspirin concurrently.

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Table 99: GRADE profile: warfarin plus dual antiplatelet therapy versus warfarin plus aspirin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ dual therapy	Warfarin + aspirin	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality[322,323]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	23/453 (5.1%)	12/184 (6.5%)	RR 0.78 (0.40 to 1.53)	14 fewer per 1000 (from 39 fewer to 35 more)	VERY LOW	CRITICAL
Cardiac mortality[393,393]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	21/205 (10.2%)	11/111 (9.9%)	RR 1.03 (0.52 to 2.06)	3 more per 1000 (from 48 fewer to 105 more)	VERY LOW	CRITICAL
Reinfarction[322,323]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	36/596 (6%)	7/265 (2.6%)	RR 0.73 (0.30 to 1.80)	7 fewer per 1000 (from 18 fewer to 21 more)	VERY LOW	IMPORTANT
Reinfarction [393,393]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	23/205 (11.2%)	10/111 (9%)	RR 1.25 (0.62 to 2.52)	23 more per 1000 (from 34 fewer to 137 more)	VERY LOW	IMPORTANT
Stroke[322,323]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	3/426 (0.7%)	6/179 (3.4%)	RR 0.21 (0.05 to 0.83)	26 fewer per 1000 (from 6 fewer to 32 fewer)	VERY LOW	IMPORTANT
Stroke [393,393]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/205 (0.49%)	1/111 (0.9%)	RR 0.54 (0.03 to	4 fewer per 1000 (from 9	VERY LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Impreci sion	Other	Warfarin+ dual therapy	Warfarin + aspirin	Relative (95% CI)	Absolute	Quality	Importance
									8.57)	fewer to 68 more)		
Major bleeding[393,393]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	5/205 (2.4%)	3/111 (2.7%)	RR 0.9 (0.22 to 3.71)	3 fewer per 1000 (from 21 fewer to 73 more)	VERY LOW	IMPORTANT
Minor bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) The studies are non-RCTs using registry data.
(b) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).

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Table 100: GRADE profile: triple therapy versus dual therapy

							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Triple therapy**	**Dual therapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
All-cause mortality - warfarin (in hospital)[221,221]												
1	Observational study	Very serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None [d]	3/219 (1.4%)	1/227 (0.44%)	RR 3.11 (0.33 to 29.67)	9 more per 1000 (from 3 fewer to 126 more)	VERY LOW	CRITICAL
All-cause mortality - warfarin[221,221]												
1	Observational study	Very serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None [d]	19/219 (8.7%)	4/227 (1.8%)	RR 4.92 (1.70 to 14.24)	69 more per 1000 (from 12 more to 233 more)	VERY LOW	IMPORTANT
All-cause mortality – warfarin[275,275]												
1	Observational study	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None [d]	1/40 (2.5%)	0/42 (0%)	RR 3.15 (0.13 to 75.05)	-	VERY LOW	IMPORTANT
All-cause mortality – warfarin[397,397]												
1	Observational study	Very serious[e]	No serious inconsistency	Serious[b]	Serious[f]	None	6/306 (2%)	9/209 (4.3%)	RR 0.46 (0.16 to 1.26)	23 fewer per 1000 (from 36 fewer to 11 more)	VERY LOW	CRITICAL
All-cause mortality – warfarin[392,392]												
1	Observational study	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None [d]	3/102 (2.9%)	1/102 (0.98%)	RR 3.00 (0.32 to 28.36)	20 more per 1000 (from 7 fewer to 268 more)	VERY LOW	IMPORTANT
All-cause mortality – apixaban[20,21]												

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							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Triple therapy**	**Dual therapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[g]	Serious[h]	None	160/4023 (4%)	155/4286 (3.6%)	RR 1.06 (0.85 to 1.32)	2 more per 1000 (from 5 fewer to 12 more)	LOW	CRITICAL
All-cause mortality - dabigatran 50,75mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[i]	No serious inconsistency	Serious[j]	Very serious[c]	None	18/737 (2.4%)	14/371 (3.8%)	RR 0.65 (0.33 to 1.29)	13 fewer per 1000 (from 25 fewer to 11 more)	VERY LOW	CRITICAL
All-cause mortality - dabigatran 110,150mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[i]	No serious inconsistency	Serious[g]	Serious[f]	None	14/753 (1.9%)	14/371 (3.8%)	RR 0.49 (0.24 to 1.02)	19 fewer per 1000 (from 29 fewer to 1 more)	LOW	CRITICAL
All-cause mortality - rivaroxaban 5mg/day [281,282]												
1	Randomised trial	Serious[k]	No serious inconsistency	Serious[j]	Serious[h]	None	103/5114 (2%)	153/5113 (3%)	RR 0.67 (0.53 to 0.86)	10 fewer per 1000 (from 4 fewer to 14 fewer)	VERY LOW	CRITICAL
All-cause mortality - rivaroxaban 10mg/day[281,282]												
1	Randomised trial	Serious[k]	No serious inconsistency	Serious[g]	No serious imprecision	None	142/5115 (2.8%)	153/5113 (3%)	RR 0.93 (0.74 to 1.16)	2 fewer per 1000 (from 8 fewer to 5 more)	LOW	CRITICAL
Cardiac mortality -warfarin[221,221]												
1	Observational	Serious[a]	No serious	Serious[b]	No serious	None [d]	12/219	1/227	RR 12.44	50 more	LOW	IMPORTANT

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	No of patients: Triple therapy	No of patients: Dual therapy	Effect: Relative (95% CI)	Effect: Absolute	Quality	Importance
	study		inconsistency		imprecision		(5.5%)	(0.44%)	(1.63 to 94.85)	per 1000 (from 3 more to 413 more)		
Cardiac mortality – warfarin[392,392]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	1/102 (0.98%)	1/102 (0.98%)	RR 1.00 (0.06 to 15.77)	0 fewer per 1000 (from 9 fewer to 145 more)	VERY LOW	IMPORTANT
Cardiac mortality – warfarin[393,393]												
1	Observational study	Serious[l]	No serious inconsistency	Serious[m]	Serious[h]	None	21/205 (10.2%)	26/306 (8.5%)	RR 1.21 (0.70 to 2.08)	18 more per 1000 (from 25 fewer to 92 more)	VERY LOW	CRITICAL
Cardiac mortality – apixaban[20,21]												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[g]	Serious[c]	None	109/4020 (2.7%)	120/4286 (2.8%)	RR 0.94 (0.73 to 1.22)	2 fewer per 1000 (from 8 fewer to 6 more)	LOW	CRITICAL
Cardiac mortality - dabigatran 50,75mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[j]	No serious inconsistency	Serious[j]	Very serious[c]	None	17/737 (2.3%)	9/371 (2.4%)	RR 0.95 (0.43 to 2.11)	1 fewer per 1000 (from 14 fewer to 27 more)	VERY LOW	CRITICAL
Cardiac mortality - dabigatran 110,150mg 2xday [331,332]												
1	Randomised trial	No serious	No serious inconsistency	Serious[i]	Serious[f]	None	9/753 (1.2%)	9/371 (2.4%)	RR 0.49 (0.2 to	12 fewer per 1000	LOW	CRITICAL

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	No of patients: Triple therapy	No of patients: Dual therapy	Effect: Relative (95% CI)	Effect: Absolute	Quality	Importance
		risk of bias[j]							1.23)	(from 19 fewer to 6 more)		
Cardiac mortality - rivaroxaban 5mg/day[281,282]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[g]	Serious[f]	None	94/5114 (1.8%)	143/5113 (2.8%)	RR 0.66 (0.51 to 0.85)	10 fewer per 1000 (from 4 fewer to 14 fewer)	VERY LOW	CRITICAL
Cardiac mortality - rivaroxaban 10mg/day[281,282]												
1	Randomised trial	Serious[m]	No serious inconsistency	Serious[i]	No serious imprecision	None	132/5115 (2.6%)	143/5113 (2.8%)	RR 0.92 (0.73 to 1.17)	2 fewer per 1000 (from 8 fewer to 5 more)	LOW	CRITICAL
Reinfarction – warfarin (in hospital)[221,221]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	4/219 (1.8%)	3/227 (1.3%)	RR 1.38 (0.31 to 6.1)	5 more per 1000 (from 9 fewer to 67 more)	VERY LOW	IMPORTANT
Reinfarction - warfarin[221,221]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	4/219 (1.8%)	3/227 (1.3%)	RR 1.38 (0.31 to 6.1)	5 more per 1000 (from 9 fewer to 67 more)	VERY LOW	IMPORTANT
Reinfarction - warfarin[221,221]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	Serious[f]	None [d]	22/219 (10%)	11/227 (4.8%)	RR 2.07 (1.03 to 4.17)	52 more per 100 (from 1	VERY LOW	IMPORTANT

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							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Triple therapy	Dual therapy	Relative (95% CI)	Absolute	Quality	Importance
										more to 154 more)		
Reinfarction - warfarin[275,275]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None [d]	11/40 (27.5%)	4/42 (9.5%)	RR 2.89 (1.0 to 8.33)	180 more per 1000 (from 0 more to 698 more)	VERY LOW	IMPORTANT
Reinfarction - warfarin[397,397]												
1	Observational study	Serious[e]	No serious inconsistency	Serious[b]	Very serious[c]	None	5/306 (1.6%)	4/209 (1.9%)	RR 0.85 (0.23 to 3.14)	3 fewer per 1000 (from 15 fewer to 41 more)	VERY LOW	IMPORTANT
Reinfarction - warfarin[392,392]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	2/102 (2%)	2/102 (2%)	RR 1.00 (0.14 to 6.96)	0 fewer per 1000 (from 17 fewer to 117 more)	VERY LOW	IMPORTANT
Reinfarction – warfarin[393,393]												
1	Observational study	Serious[l]	No serious inconsistency	Serious[d]	No serious imprecision	None	23/205 (11.2%)	17/306 (5.6%)	RR 2.02 (1.11 to 3.68)	57 more per 1000 (from 6 more to 149 more)	VERY LOW	CRITICAL
Reinfarction – apixaban[20,21]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	Serious[g]	No serious imprecision	None	182/3705 (4.9%)	194/3687 (5.3%)	RR 0.93 (0.77 to 1.14)	4 fewer per 1000 (from 12 fewer to 7	MODERATE	IMPORTANT

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	No of patients: Triple therapy	No of patients: Dual therapy	Effect: Relative (95% CI)	Effect: Absolute	Quality	Importance
										more)		
Reinfarction - dabigatran 50,75mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[j]	No serious inconsistency	Serious[j]	Very serious[c]	None	16/737 (2.2%)	4/371 (1.1%)	RR 2.01 (0.68 to 5.98)	11 more per 1000 (from 3 fewer to 54 more)	VERY LOW	IMPORTANT
Reinfarction - dabigatran 110,150mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[j]	No serious inconsistency	Serious[g]	Very serious[c]	None	15/753 (2%)	4/371 (1.1%)	RR 1.85 (0.62 to 5.53)	9 more per 1000 (from 4 fewer to 49 more)	VERY LOW	IMPORTANT
Reinfarction - rivaroxaban 5mg/day[281,282]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[j]	No serious imprecision	None	205/5114 (4%)	229/5113 (4.5%)	RR 0.89 (0.74 to 1.08)	5 fewer per 1000 (from 12 fewer to 4 more)	LOW	IMPORTANT
Reinfarction - rivaroxaban 10mg/day[281,282]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[g]	Serious[f]	None	179/5115 (3.5%)	229/5113 (4.5%)	RR 0.78 (0.65 to 0.95)	10 fewer per 1000 (from 2 fewer to 16 fewer)	VERY LOW	IMPORTANT
Revascularisation – warfarin[120,121]												
1	Randomised trial	Serious[h]	No serious inconsistency	Serious[d]	Very serious[c]	None	19/284 (6.7%)	20/279 (7.2%)	RR 0.93 (0.51 to 1.71)	5 fewer per 1000 (from 35 fewer to 51 more)	VERY LOW	IMPORTANT

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							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Triple therapy	Dual therapy	Relative (95% CI)	Absolute	Quality	Importance
Revascularisation – warfarin (in hospital)[221,221]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None [d]	3/219 (1.4%)	1/227 (0.44%)	RR 3.11 (0.33 to 29.67)	9 more per 1000 (from 3 fewer to 126 more)	VERY LOW	IMPORTANT
Revascularisation – warfarin[221,221]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	Serious[h]	None	24/219 (11%)	17/227 (7.5%)	RR 1.46 (0.81 to 2.65)	34 more per 1000 (from 14 fewer to 124 more)	VERY LOW	IMPORTANT
Revascularisation – warfarin[393,393]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[h]	None	25/205 (12.2%)	32/306 (10.5%)	RR 1.17 (0.71 to 1.91)	18 more per 1000 (from 30 fewer to 95 more)	VERY LOW	IMPORTANT
Stroke- warfarin (in hospital)[221,221]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[e]	Very serious[c]	None [d]	1/219 (0.46%)	0/227 (0%)	RR 3.11 (0.13 to 75.91)	-	VERY LOW	IMPORTANT
Stroke - warfarin[221,221]												
1	Observational study	Serious[a]	No serious inconsistency	Serious[b]	Very serious[c]	None	7/219 (3.2%)	5/227 (2.2%)	RR 1.45 (0.47 to 4.50)	10 more per 1000 (from 12 fewer to 77 more)	VERY LOW	IMPORTANT
Stroke - warfarin[275,275]												
1	Observational	Serious[a]	No serious	No serious	Very	None	0/40	3/42	RR 0.15	61 fewer	VERY LOW	IMPORTANT

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							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Triple therapy**	**Dual therapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
	study		inconsistency	indirectness	serious[c]		(0%)	(7.1%)	(0.01 to 2.81)	per 1000 (from 71 fewer to 129 more)		
Stroke- warfarin[397,397]												
1	Observational study	Serious[l]	No serious inconsistency	Serious[b]	Very serious[c]	None	3/306 (0.98%)	2/209 (0.96%)	RR 1.02 (0.17 to 6.08)	0 more per 1000 (from 8 fewer to 49 more)	VERY LOW	IMPORTANT
Stroke – warfarin[392,392]												
1	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	1/102 (0.98%)	2/102 (2%)	RR 0.5 (0.05 to 5.43)	10 fewer per 1000 (from 19 fewer to 87 more)	VERY LOW	IMPORTANT
Stroke – apixaban[20,21]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	Serious[j]	Serious[c]	None	23/3705 (0.62%)	34/3687 (0.92%)	RR 0.67 (0.4 to 1.14)	3 fewer per 1000 (from 6 fewer to 1 more)	LOW	IMPORTANT
Stroke - dabigatran 50,75mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[j]	No serious inconsistency	Serious[j]	Very serious[c]	None	1/737 (0.14%)	3/371 (0.81%)	RR 0.17 (0.02 to 1.61)	7 fewer per 1000 (from 8 fewer to 5 more)	VERY LOW	IMPORTANT
Stroke - dabigatran 110,150mg 2xday [331,332]												
1	Randomised trial	No serious	No serious inconsistency	Serious[g]	Very serious[c]	None	0/753 (0%)	3/371 (0.81%)	RR 0.07 (0 to	8 fewer per 1000	VERY LOW	IMPORTANT

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	No of patients: Triple therapy	No of patients: Dual therapy	Effect: Relative (95% CI)	Effect: Absolute	Quality	Importance
		risk of bias[j]							1.36)	(from 8 fewer to 3 more)		
Stroke - rivaroxaban 5mg/day[281,282]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[j]	Serious[h]	None	54/5115 (1.1%)	41/5113 (0.8%)	RR 1.32 (0.88 to 1.97)	3 more per 1000 (from 1 fewer to 8 more)	VERY LOW	IMPORTANT
Stroke - rivaroxaban 10mg/day[281,282]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[g]	Serious[h]	None	46/5114 (0.9%)	41/5113 (0.8%)	RR 1.12 (0.74 to 1.71)	1 more per 1000 (from 2 fewer to 6 more)	VERY LOW	IMPORTANT
Major bleeding - Warfarin (in hospital (less than29 days))[221,241]												
2	Observational studies	Very serious[k]	No serious inconsistency	Serious[o]	Serious[h]	None [d]	6/1714 (0.35%)	1/3371 (0.03%)	RR 6.42 (0.98 to 41.97)	2 more per 1000 (from 0 fewer to 12 more)	VERY LOW	IMPORTANT
Major bleeding – warfarin[118,221,228,241,275,392,397,469]												
8	Observational studies	Very serious[o]	No serious inconsistency	Serious[l]	No serious imprecision	None [d]	66/2571 (2.6%)	24/4234(0.57%)	RR 3.07 (1.94 to 4.85)	12 more per 1000 (from 5 more to 22 more)	VERY LOW	IMPORTANT
Major bleeding – apixaban[20,21]												
2	Randomised trials	No serious risk of	No serious inconsistency	Serious[g]	No serious imprecision	None [d]	49/4020 (1.2%)	20/4286 (0.47%)	RR 2.57 (1.53 to 4.31)	7 more per 1000 (from 2	MODERATE	IMPORTANT

							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Triple therapy	Dual therapy	Relative (95% CI)	Absolute	Quality	Importance
		bias								more to 15 more)		
Major bleeding - dabigatran 50,75mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[j]	No serious inconsistency	Serious[j]	Very serious[c]	None	1/737 (0.14%)	1/371 (0.27%)	RR 0.5 (0.03 to 8.03)	1 fewer per 1000 (from 3 fewer to 19 more)	VERY LOW	IMPORTANT
Major bleeding - dabigatran 110,150mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[j]	No serious inconsistency	Serious[g]	Very serious[c]	None [d]	6/753 (0.8%)	1/371 (0.27%)	RR 2.96 (0.36 to 24.47)	5 more per 1000 (from 2 fewer to 63 more)	VERY LOW	IMPORTANT
Major bleeding - rivaroxaban 5mg/day[281,281,281,282]												
2	Randomised trials	Serious[n]	No serious inconsistency	Serious[g]	No serious imprecision	None [d]	66/5267 (1.3%)	20/6014 (0.33%)	RR 3.46 (2.09 to 5.7)	8 more per 1000 (from 4 more to 16 more)	LOW	IMPORTANT
Major bleeding – rivaroxaban 10mg/day[281,282]												
2	Randomised trials	Serious[n]	No serious inconsistency	Serious[g]	No serious imprecision	None [d]	94/5966 (1.6%)	20/6014 (0.33%)	RR 4.72 (2.92 to 7.64)	12 more per 1000 (from 6 more to 22 more)	LOW	IMPORTANT
Major bleeding – rivaroxaban 15m/day [281,281]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[g]	No serious imprecision	None	6/353 (1.7%)	1/901 (0.11%)	RR 15.31 (1.85 to 126.75)	16 more per 1000 (from 1 more to	LOW	IMPORTANT

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	No of patients: Triple therapy	No of patients: Dual therapy	Effect: Relative (95% CI)	Effect: Absolute	Quality	Importance
										140 more)		
Major bleeding – rivaroxaban 20mg/day [281,281,281,281]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[g]	None	None	8/446 (1.8%)	1/901 (0.11%)	RR 16.16 (2.03 to 128.82)	17 more per 1000 (from 1 more to 142 more)	LOW	IMPORTANT
Minor bleeding – warfarin 0-29 days[241,241]												
1	Observational study	Very serious[k]	No serious inconsistency	No serious indirectness	Serious[h]	None	18/1495 (1.2%)	36/3144 (1.1%)	RR 1.64 (1.00 to 2.67)	7 more per 1000 (from 0 more to 19 more)	VERY LOW	IMPORTANT
Minor bleeding – warfarin[221,241,392]												
3	Observational studies	Very serious[k]	No serious inconsistency	Serious[l]	No serious imprecision	None [d]	88/1903 (4.6%)	60/3455 (1.7%)	RR 2.16 (1.58 to 2.95)	20 more per 1000 (from 10 fewer to 34 more)	VERY LOW	IMPORTANT
Minor bleeding – apixaban[20,21]												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[g]	No serious imprecision	None [d d]	36/4020 (0.9%)	14/4286 (0.33%)	RR 2.79 (1.49 to 5.23)	6 more per 1000 (from 2 more to 14 more)	HIGH	IMPORTANT
Minor bleeding - dabigatran 50,75mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[j]	No serious inconsistency	Serious[j]	Serious[h]	None [d d]	24/737 (3.3%)	6/371 (1.6%)	RR 2.01 (0.83 to 4.88)	16 more per 1000 (from 3 fewer to 63 more)	LOW	IMPORTANT

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							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Triple therapy	Dual therapy	Relative (95% CI)	Absolute	Quality	Importance
Minor bleeding - dabigatran 110,150mg 2xday [331,332]												
1	Randomised trial	No serious risk of bias[j]	No serious inconsistency	Serious[g]	No serious imprecision	None [d]	46/753 (6.1%)	6/371 (1.6%)	RR 3.78 (1.63 to 8.76)	45 more per 1000 (from 10 more to 125 more)	MODERATE	IMPORTANT
Minor bleeding - rivaroxaban 5mg/day [281,281,281,282]												
2	Randomised trials	Serious[n]	No serious inconsistency	Serious[j]	Serious[h]	None	33/5267 (0.63%)	22/6014 (0.37%)	RR 1.64 (0.95 to 2.82)	2 more per 1000 (from 0 fewer to 7 more)	VERY LOW	IMPORTANT
Minor bleeding - rivaroxaban 10mg/day [281,281,281,282]												
2	Randomised trials	Serious[n]	No serious inconsistency	Serious[g]	No serious imprecision	None	55/5966 (0.92%)	22/6014 (0.37%)	RR 2.51 (1.54 to 4.11)	6 more per 1000 (from 2 more to 12 more)	LOW	IMPORTANT
Minor bleeding – rivaroxaban 15mg/day [281,281]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[g]	No serious imprecision	None	4/353 (1.1%)	2/901 (0.22%)	RR 5.10 (0.94 to 27.75)	9 more per 1000 (from 0 fewer to 59 more)	LOW	IMPORTANT
Minor bleeding – rivaroxaban dose 20mg/day [281,281]												
1	Randomised trial	Serious[n]	No serious inconsistency	Serious[g]	Very serious[c]	None	4/446 (0.9%)	2/901 (0.22%)	RR 4.04 (0.74 to 21.98)	7 more per 1000 (from 1 fewer to 47 more)	VERY LOW	IMPORTANT
Stent thrombosis												

							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Triple therapy**	**Dual therapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) The study was an observational study, not an RCT. Participants were not matched at baseline and only those treated with OAC had an indication for anticoagulants.
(b) The study used people needing drug eluting stents and it was unclear how many had an MI.
(c) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(d) RR>2.
(e) The study was an observational study, not RCT. Participants were treated for different durations. Although both groups had an indication for OAC, participants were selected to go on OAC based on their risk for emboli or stent thrombosis.
(f) 95% confidence intervals crossed 1 MID (0.75).
(g) Participants did not have an indication for anticoagulation. They had an MI and were randomised to either anticoagulants and/or antiplatelets.
(h) 95% confidence intervals crossed 1 MID (1.25).
(i) Unclear how the authors randomised participants.
(j) Participants did not have an indication for anticoagulation. They had an MI and were randomised to either anticoagulants and/or antiplatelets. A lower dose was used in the trial than that which is licensed for the therapeutic indication.
(k) Dose not relevant for AF.
(l) It was unclear how the authors randomised or if they performed allocation concealment.
(m) They study used an indirect population(less than 75% of participants had an MI) but all needed PCI
(n) It was unclear how the authors randomised or whether they performed allocation concealment.
(o) In most studies the participants did not have an indication for anticoagulants, so only those in the intervention arm needed OAC, meaning the controls are not a relevant comparison, per se.

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Table 101: GRADE profile: warfarin plus aspirin versus aspirin.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ aspirin	Aspirin	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality[68,96,197,201,248,269,434,453]												
8	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	424/4624 (9.2%)	441/4595 (9.6%)	RR 0.96 (0.85 to 1.08)	4 fewer per 1000 (from 14 fewer to 8 more)	LOW	CRITICAL
All-cause mortality – moderate dose INR 2-2.9[68,96,197,201,248]												
5	Randomised trials	Serious[c]	No serious inconsistency	Serious[b]	No serious imprecision	None	409/3647 (11.2%)	418/3652 (11.4%)	RR 0.97 (0.86 to 1.1)	3 fewer per 1000 (from 16 fewer to 11 more)	LOW	CRITICAL
All-cause mortality - high dose INR 3-4.5[269,434,453]												
3	Randomised trials	Serious[d]	No serious inconsistency	Serious[b]	Serious[e]	None	15/977 (1.5%)	23/943 (2.4%)	RR 0.65 (0.34 to 1.22)	9 fewer per 1000 (from 16 fewer to 5 more)	VERY LOW	CRITICAL
Cardiovascular mortality[13,453]												
2	Randomised trials	No serious risk of bias[f]	No serious inconsistency	Serious[b]	Serious[g]	None	82/2180 (3.8%)	81/2200 (3.7%)	RR 1.02 (0.76 to 1.38)	1 more per 1000 (from 9 fewer to 14 more)	LOW	IMPORTANT
Cardiovascular mortality - moderate dose INR 2- 2-2.9 [13]												
1	Randomised trial	No serious	No serious inconsistency	Serious[b]	Serious[g]	None	74/1848 (4%)	69/1864 (3.7%)	RR 1.08 (0.78 to	3 more per 1000	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ aspirin	Aspirin	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias							1.49)	(from 8 fewer to 18 more)		
Cardiovascular mortality - High dose INR 3-4.5[452,453]												
1	Randomised trial	Serious	No serious inconsistency	Serious[b]	Very serious[h]	None	8/332 (2.4%)	12/336 (3.6%)	RR 0.67 (0.28 to 1.63)	12 fewer per 1000 (from 26 fewer to 23 more)	VERY LOW	IMPORTANT
Reinfarction[13,68,96,197,201,248]												
9	Randomised trials	Serious[i]	No serious inconsistency	Serious[b]	Serious[j]	None	208/4837 (4.3%)	291/4864 (6%)	RR 0.72 (0.6 to 0.85)	17 fewer per 1000 (from 9 fewer to 24 fewer)	VERY LOW	IMPORTANT
Reinfarction - moderate dose INR 2-2.9[13,68,96,197,201,248,269,434,453]												
6	Randomised trials	Serious[k]	No serious inconsistency	Serious[b]	No serious imprecision	None	180/3890 (4.6%)	248/3921 (6.3%)	RR 0.73 (0.61 to 0.88)	17 fewer per 1000 (from 8 fewer to 25 fewer)	LOW	IMPORTANT
Reinfarction - high dose INR 3-4.5[269,434,453]												
3	Randomised trials	Serious[l]	No serious inconsistency	Serious[b]	Serious[e]	None	28/947 (3%)	43/943 (4.6%)	RR 0.64 (0.4 to 1.03)	16 fewer per 1000 (from 27 fewer to 1 more)	VERY LOW	IMPORTANT
Stroke[13,197,248,269,434,453]												
6	Randomised trials	Serious[m]	No serious inconsistency	Serious[b]	No serious imprecision	None	33/4553 (0.72%)	61/4570 (1.3%)	RR 0.55 (0.36 to 0.83)	6 fewer per 1000 (from 2	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ aspirin	Aspirin	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 9 fewer)		
Stroke - moderate dose INR 2-2.9[13,197,248]												
3	Randomised trials	Serious[n]	No serious inconsistency	Serious[b]	No serious imprecision	None	29/3606 (0.8%)	52/3627 (1.4%)	RR 0.56 (0.36 to 0.88)	6 fewer per 1000 (from 2 fewer to 9 fewer)	LOW	IMPORTANT
Stroke - high dose INR 3-4.5[269,434,453]												
3	Randomised trials	Serious[l]	No serious inconsistency	Serious[b]	Very serious[h]	None	4/947 (0.42%)	9/943 (0.95%)	RR 0.47 (0.15 to 1.44)	5 fewer per 1000 (from 8 fewer to 4 more)	VERY LOW	IMPORTANT
Revascularisation[13,68,96,201,248,269,434,453]												
8	Randomised trials	Serious[o]	Serious[p]	Serious[b]	Very serious[h]	None	601/3629 (16.6%)	683/3658 (18.7%)	RR 0.78 (0.6 to 1.2)	41 fewer per 1000 (from 75 fewer to 37 fewer)	VERY LOW	IMPORTANT
Revascularisation - high dose INR 3-4.5[269,434,453]												
3	Randomised trials	Serious[l]	No serious inconsistency	Serious[b]	Serious[j]	None	104/947 (11%)	146/943 (15.5%)	RR 0.71 (0.56 to 0.9)	45 fewer per 1000 (from 15 fewer to 68 fewer)	VERY LOW	IMPORTANT
Revascularisation - moderate INR 2-2.9[13,68,96,201,248]												
5	Randomised trials	Serious[q]	Serious[r]	Serious[b]	Very serious[h]	None	497/2682 (18.5%)	537/2715 (19.8%)	RR 0.85 (0.55 to 1.31)	30 fewer per 1000 (from 89 fewer to	VERY LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ aspirin	Aspirin	Relative (95% CI)	Absolute	Quality	Importance
										61 more)		
Rehospitalisation[201,201]												
1	Randomised trial	Serious[s]	No serious inconsistency	Serious[b]	Very serious[h]	None	10/44 (22.7%)	13/46 (28.3%)	RR 0.8 (0.39 to 1.64)	57 fewer per 1000 (from 172 fewer to 181 more)	VERY LOW	IMPORTANT
Major bleeding[13,68,96,197,201,434,453]												
7	Randomised trials	Serious[t]	No serious inconsistency	Serious[b]	No serious imprecision	None	96/4202 (2.3%)	38/4228 (0.9%)	RR 2.49 (1.72 to 3.59)	13 more per 1000 (from 6 more to 23 more)	MODERATE	IMPORTANT
Major bleeding - moderate INR 2-2.9[13,68,96,197,201]												
5	Randomised trials	Serious[v]	No serious inconsistency	Serious[b]	No serious imprecision	None	84/3340 (2.5%)	35/3364 (1%)	RR 2.38 (1.62 to 3.5)	14 more per 1000 (from 6 more to 26 more)	MODERATE	IMPORTANT
Major bleeding - high dose INR 3-4.5[434,453]												
2	Randomised trials	Serious[x]	No serious inconsistency	Serious[b]	No serious imprecision	None	12/862 (1.4%)	3/864 (0.35%)	RR 3.6 (1.1 to 11.73)	9 more per 1000 (from 0 more to 37 more)	MODERATE	IMPORTANT
Minor bleeding[13,68,197,201,434,453]												
6	Randomised trials	Serious[y]	Serious[z]	Serious[b]	No serious imprecision	None	303/4097 (7.4%)	111/4119 (2.7%)	RR 2.77 (2.25 to 3.4)	48 more per 1000 (from 34 more to 65 more)	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ aspirin	Aspirin	Relative (95% CI)	Absolute	Quality	Importance
Minor bleeding - moderate INR 2-2.9[13,68,197,201]												
4	Randomised trials	Serious[a a]	Serious[bb]	Serious[b]	No serious imprecision	None	232/3235 (7.2%)	93/3255 (2.9%)	RR 2.51 (2 to 3.14)	43 more per 1000 (from 29 more to 61 more)	LOW	IMPORTANT
Minor bleeding - high dose INR 3-4.5[434,453]												
2	Randomised trials	Serious[w]	Serious[u]	Serious[b]	No serious imprecision	None	71/862 (8.2%)	18/864 (2.1%)	RR 4.16 (2.52 to 6.69)	66 more per 1000 (from 32 more to 119 more)	LOW	IMPORTANT
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) In 3 of the 8 studies it was unclear how the authors randomised participants. In 5 of the 8 studies it was unclear whether the authors performed allocation concealment. In 1 of the 8 studies participants had an uneven dropout rate.
(b) None of the participants had an indication for anticoagulation. All participants had an MI and were treated with anticoagulants and/or antiplatelets.
(c) In 1 of the 5 studies it was unclear how the authors randomised participants. In 4 of the 5 studies it was unclear if the authors performed allocation concealment.
(d) In 1 of the 3 studies it was unclear how the authors randomised participants. In 2 of the 3 studies it was unclear if the authors performed allocation concealment. In 1 of the 3 studies participants had an uneven dropout rate.
(e) 95% confidence intervals crossed the line of no effect and 1 MID (0.75).
(f) In 1 of the 2 studies it was unclear how the authors randomised participants. No details are provided.
(g) 95% confidence intervals crossed the line of no effect and 1 MID (1.25).
(h) 95% confidence intervals crossed the line of no effect and 2 MIDs (0.75 and 1.25).
(i) In 3 of the 9 studies it was unclear how the authors randomised participants. In 5 of the 9 studies it was unclear if the authors performed allocation concealment. In 2 of the 9 studies there was greater than 10% variation in dropout rate.
(j) 95% confidence intervals crossed 1MID.

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(k) In 1 of the 3 studies it was unclear how the authors randomised participants. In 1 of the 3 studies it was unclear if the authors performed allocation concealment. In 1 of the 3 studies there was greater than 10% variation in dropout rate.
(l) In 1 of the 3 studies it was unclear how the authors randomised. In 1 of the 3 studies it was unclear if the authors performed allocation concealment. In 1 of the 3 studies there was greater than 10% variation in dropout rate.
(m) In 2 of the 6 studies it was unclear how the authors randomised participants. In 3 of the 6 studies it was unclear if the authors performed allocation concealment. In 1 of the 6 studiesthere was greater than 10% variation in dropout rate.
(n) In 1 of the 3 studies it was unclear how the authors randomised participants. In 2 of the 3 studies it was unclear if the authors performed allocation concealment.
(o) In 4 of the 8 studies it was unclear how the authors randomised participants. In 4 of the 8 studies it was unclear if the authors performed allocation concealment. In 2 of the 8 there was greater than 10% variation in dropout rate.
(p) Heterogeneity present. I^2=63% p=0.008.
(q) In 3 of the 5 studies it was unclear how the authors randomised participants. In 3 of the 5 studies it was unclear if the authors performed allocation concealment.
(r) Heterogeneity present. I^2=70% p=0.01.
(s) It was unclear how the authors randomised or if the authors performed allocation concealment.
(t) In 4 of the 7 studies it was unclear how the authors randomised participants. In 3 of the 7 studies it was unclear if the authors performed allocation concealment. In 2 of the 7 studies there was greater than 10% variation in dropout rate.
(u) Heterogeneity is present. I^2=58% p=0.12.
(v) In 3 of the 5 studies it was unclear how the authors randomised. In 3 of the 5 studies it was unclear if the authors performed allocation concealment.
(w) In 1 of the 2 studies it was unclear how the authors randomised. In 1 of the 2 studies there was greater than 10% variation in dropout rate between the 2 groups .
(x) In 1 of the 2 studies it was unclear how the authors randomised. In 1 of the 2 studies there was greater than 10% variation in dropout rate.
(y) In 3 of the 6 studies it was unclear how the authors randomised. In 2 of the 6 studies it was unclear if the authors performed allocation concealment. In 1 of the 6 studies there was greater than 10% variation in dropout rate.
(z) Heterogeneity present. I^2 = 614% p = 0.03.
(aa) In 2 of the 4 studies it was unclear how the authors randomised. In 2 of the 4 studies it was unclear if the authors performed allocation concealment.
(bb) Heterogeneity present. I^2=64% p = 0.04.
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Table 102: GRADE profile: warfarin plus aspirin versus warfarin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Warfarin+ aspirin	Warfarin	Relative (95% CI)	Absolute		
All-cause mortality [197,201,453]												
3	Randomised trials	Serious	No serious inconsistency	Serious[a]	Serious[b]	None	106/1584 (6.7%)	101/1586 (6.4%)	RR 1.05 (0.81 to 1.37)	3 more per 1000 (from 12 fewer to 24 more)	VERY LOW	CRITICAL
All-cause mortality - moderate dose INR 2-2.9 [197,201]												
2	Randomised trials	Serious[c]	No serious inconsistency	Serious[a]	Serious[b]	None	97/1252 (7.7%)	97/1261 (7.7%)	RR 1.01 (0.77 to 1.32)	1 more per 1000 (from 18 fewer to 25 more)	VERY LOW	CRITICAL
All-cause mortality - high dose INR 3-4.5 [452,453]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[a]	Very serious[e]	None	9/332 (2.7%)	4/325 (1.2%)	RR 2.2 (0.69 to 7.08)	15 more per 1000 (from 4 fewer to 75 more)	VERY LOW	CRITICAL
Cardiac mortality [452,453]												
1	Randomised trial	Serious[f]	No serious inconsistency	Serious[a]	Very serious[e]	None	8/332 (2.4%)	4/325 (1.2%)	RR 1.96 (0.6 to 6.44)	12 more per 1000 (from 5 fewer to 67 more)	VERY LOW	CRITICAL
Reinfarction [197,201,453]												
3	Randomised trials	Serious[g]	No serious inconsistency	Serious[a]	Serious[h]	None	81/1584 (5.1%)	107/1586 (6.7%)	RR 0.76 (0.57 to 1.01)	16 fewer per 1000 (from 29 fewer to 1 more)	VERY LOW	IMPORTANT
Reinfarction - moderate dose INR 2-2.9[197,201]												
2	Randomised trials	Serious[c]	No serious inconsistency	Serious[a]	Serious[h]	None	71/1252 (5.7%)	94/1261 (7.5%)	RR 0.76 (0.56 to 1.02)	18 fewer per 1000 (from 33 fewer to	VERY LOW	IMPORTANT

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Quality assessment							No of patients		Effect		Quality	Importance
										1 more)		
Reinfarction - high dose INR 3-4.5[452,453]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[a]	Very serious[e]	None	10/332 (3%)	13/325 (4%)	RR 0.75 (0.33 to 1.69)	10 fewer per 1000 (from 27 fewer to 28 more)	VERY LOW	IMPORTANT
Stroke[197,453]												
2	Randomised trials	Serious[i]	No serious inconsistency	Serious[a]	Very serious[e]	None	18/1540 (1.2%)	17/1541 (1.1%)	RR 1.06 (0.56 to 2.03)	1 more per 1000 (from 5 fewer to 11 more)	VERY LOW	IMPORTANT
Stroke - moderate dose INR 2-2.9[197,198]												
1	Randomised trial	Serious[j]	No serious inconsistency	Serious[a]	Very serious[e]	None	17/1208 (1.4%)	17/1216 (1.4%)	RR 1.01 (0.52 to 1.96)	0 more per 1000 (from 7 fewer to 13 more)	VERY LOW	IMPORTANT
Stroke - high dose INR 3-4.5[452,453]												
1	Randomised trial	Serious[k]	No serious inconsistency	Serious[a]	Very serious[e]	None	1/332 (0.3%)	0/325 (0%)	RR 2.94 (0.12 to 71.83)	-	VERY LOW	IMPORTANT
Revascularisation[452,453]												
2	Randomised trials	Serious[c]	No serious inconsistency	Serious[a]	Very serious[e]	None	37/376 (9.8%)	36/371 (9.7%)	RR 1.01 (0.66 to 1.56)	1 more per 1000 (from 33 fewer to 54 more)	VERY LOW	IMPORTANT
Revascularisation - moderate dose INR 2-2.9 [197,198]												
1	Randomised trial	Serious[j]	No serious inconsistency	Serious[a]	Very serious[e]	None	5/44 (11.4%)	2/46 (4.3%)	RR 2.61 (0.53 to 12.78)	70 more per 1000 (from 20 fewer to 512 more)	VERY LOW	IMPORTANT
Revascularisation - high dose INR 3-4.5 [452,453]												
1	Randomised trial	Serious[k]	No serious inconsistency	Serious[a]	Very serious[e]	None	32/332 (9.6%)	34/325 (10.5%)	RR 0.92 (0.58 to 1.46)	8 fewer per 1000 (from 44 fewer to	VERY LOW	IMPORTANT

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Quality assessment							No of patients		Effect		Quality	Importance
										48 more)		
Rehospitalisation[197,198]												
1	Randomised trial	Serious[j]	No serious inconsistency	Serious[a]	Very serious[e]	None	10/44 (22.7%)	16/46 (34.8%)	RR 0.65 (0.33 to 1.28)	122 fewer per 1000 (from 233 fewer to 97 more)	VERY LOW	CRITICAL
Major bleeding[197,201,453]												
3	Randomised trials	Serious[g]	No serious inconsistency	Serious[a]	Very serious[e]	None	37/1584 (2.3%)	37/1587 (2.3%)	RR 1 (0.64 to 1.58)	0 fewer per 1000 (from 8 fewer to 14 more)	VERY LOW	CRITICAL
Major bleeding - moderate dose INR 2-2.9[197,201]												
2	Randomised trials	Serious[c]	No serious inconsistency	Serious[a]	Very serious[e]	None	30/1252 (2.4%)	34/1262 (2.7%)	RR 0.89 (0.55 to 1.44)	3 fewer per 1000 (from 12 fewer to 12 more)	VERY LOW	CRITICAL
Major bleeding - high dose INR 3-4.5[452,453]												
1	Randomised trial	Serious[d]	No serious inconsistency	Serious[a]	Very serious[e]	None	7/332 (2.1%)	3/325 (0.92%)	RR 2.28 (0.6 to 8.76)	12 more per 1000 (from 4 fewer to 72 more)	VERY LOW	CRITICAL
Minor bleeding [197,201,453]												
3	Randomised trials	Serious[g]	No serious inconsistency	Serious[a]	No serious imprecision	None	192/1584 (12.1%)	139/1587 (8.8%)	RR 1.38 (1.13 to 1.7)	33 more per 1000 (from 11 more to 61 more)	LOW	IMPORTANT
Minor bleeding - moderate dose INR 2-2.9[197,201]												
2	Randomised trials	Serious[c]	No serious inconsistency	Serious[a]	Serious[b]	None	142/1252 (11.3%)	113/1262 (9%)	RR 1.27 (1 to 1.6)	24 more per 1000 (from 0 more to 54 more)	VERY LOW	IMPORTANT
Minor bleeding - high dose INR 3-4.5 [452,453]												
1	Randomised	Serious[d]	No serious	Serious[a]	No serious	None	50/332	26/325	RR 1.88	70 more per	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
	trial		inconsistency		imprecision		(15.1%)	(8%)	(1.2 to 2.95)	1000 (from 16 more to 156 more)		
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Qualty of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) None of the participants had an indication for anticoagulation however all had an MI and were treated with anticoagulants and or antiplatelets. However, only treating with antiplatelets is not a relevant treatment for people who need anticoagulation.
(b) 95% confidence intervals crossed the line of no effect and 1 MID (1.25).
(c) In 1 of the 2 studies, it was unclear how the authors randomised and in both studies it was unclear whether the authors performed allocation concealment.
(d) It was unclear how the authors randomised or whether the authors performed allocation concealment. The dropout rate was different in each arm.
(e) 95% confidence intervals crossed the line of no effect and 2 MIDs (0.75 and 1.25).
(f) It was unclear how the authors randomised. There was an uneven dropout rate.
(g) In 2 of the 3 studies it was unclear how the authors randomised and in 2 of the 3 it was unclear how the authors performed allocation concealment. In 1 of the 3 studies participants had an uneven dropout rate.
(h) 95% confidence intervals crossed the line of no effect and 1 MID (0.75).
(i) In 1 of the 2 studies, it was unclear how the authors randomised and in 1 of the 2 studies it was unclear if the authors performed allocation concealment. In 1 of the2 studies therewas an uneven dropout rate.
(j) It was unclear if the authors performed allocation concealment.
(k) It was unclear how randomised was conducted. There was an uneven dropout rate.

7.4.7.3 Economic evidence

Published literature

No relevant economic evaluations were included in CG48 or identified from the update search.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix M to aid consideration of cost effectiveness.

7.4.7.4 Evidence statements

7.4.7.4.1 Clinical

Warfarin plus dual therapy versus warfarin plus clopidogrel (RCT)

Rivaroxaban plus aspirin versus warfarin plus aspirin

Direct population - subgroup analysis on people who had an MI who had an indication for anticoagulation

- One RCT with 2468 people showed that rivaroxaban plus aspirin increase the risk of major and non-major clinically relevant bleeding compared with warfarin plus aspirin in people who had an MI, but there was some uncertainty [Very low quality evidence].
- No evidence on all-cause mortality was identified.
- No evidence on sudden death was identified.
- No evidence on cardiac mortality was identified.
- No evidence on reinfarction was identified.
- No evidence on rehospitalisation was identified.
- No evidence on stroke was identified.
- No evidence on revascularisation was identified.
- No evidence on adverse events was identified.
- No evidence on quality of life was identified.

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Warfarin plus dual antiplatelet versus warfarin plus aspirin

Indirect population I - people who have CHD (less than 75% had an MI) with an indication for anticoagulation

- One non-RCT with 637 people showed that warfarin plus dual antiplatelet therapy decrease the risk of all-cause mortality compared with warfarin plus aspirin, but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 316 people showed that warfarin plus dual antiplatelet therapy have a similar effect on the risk of cardiac mortality compared with warfarin plus aspirin but there was considerable uncertainty [Very low quality evidence].
- One non-RCTs with 545 people showed that warfarin plus dual antiplatelet therapy reduce the risk of reinfarction compared with warfarin plus aspirin but there was considerable uncertainty [Very low quality evidence].

- One non-RCT with 316 people showed that warfarin plus dual antiplatelet therapy increase the risk of reinfarction compared with warfarin plus aspirin but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 605 people showed that warfarin plus dual antiplatelet therapy decrease the risk of stroke compared with warfarin plus aspirin but there was some uncertainty [Very low quality evidence].
- One non-RCTs with 316 people showed that warfarin plus dual antiplatelet therapy decrease the risk of stroke compared with warfarin plus aspirin but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 316 people showed that warfarin plus dual antiplatelet therapy have a similar effect on the risk of major bleeding compared with warfarin plus aspirin but there was considerable uncertainty [Very low quality evidence].
- No evidence on sudden death was identified.
- No evidence on rehospitalisation was identified.
- No evidence on revascularisation was identified.
- No evidence on adverse events was identified.
- No evidence on quality of life.
- No evidence on stent thrombosis was identified.

Triple therapy versus dual therapy (warfarin/apixaban/dabigatran or rivaroxaban plus aspirin plus clopidogrel versus aspirin plus clopidogrel)

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Indirect population I - people who have CHD (less than 75% had an MI) with an indication for anticoagulation

All-cause mortality

- One cohort study with 446 people, showed that warfarin plus dual antiplatelet therapy increase the risk of all-cause mortality in hospital compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One cohort study with 446 people showed that warfarin plus dual antiplatelet therapy increase the risk of all-cause mortality compared with dual antiplatelet therapy [Very low quality evidence].
- One cohort study with 204 people, showed that warfarin plus dual antiplatelet therapy increase the risk of all-cause mortality compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- In cohort study with 82 people, it was unclear whether warfarin plus dual antiplatelet therapy had an effect on the risk of all-cause mortality compared with dual antiplatelet therapy [Very low quality evidence]
- One cohort study with 515 people, showed that warfarin plus dual antiplatelet therapy reduce the risk of all-cause mortality compared with dual antiplatelet therapy, but there was some uncertainty [Very low quality evidence].
- One cohort study with 511 people showed that warfarin plus dual antiplatelet therapy increase the risk of all-cause mortality compared with dual antiplatelet therapy, but there was some uncertainty [Very low quality evidence].
- Two RCTs with 8309 people, showed that apixaban plus dual antiplatelet therapy was equally effective as dual antiplatelet therapy on the risk of all-cause mortality, but there was considerable uncertainty [Low quality evidence].

- One RCT with 1108 people showed that low dose dabigatran plus dual antiplatelet therapy reduce the risk of all-cause mortality more dual therapy alone, but there was some uncertainty [Very low quality evidence].
- One RCT with 1125 people showed that high dose dabigatran plus dual antiplatelet therapy reduce the risk of all-cause mortality more dual therapy alone, but there was some uncertainty [Low quality evidence].
- One RCT with 10,227 people showed that 5mg/day rivaroxaban plus dual antiplatelet therapy reduce the risk of all-cause mortality compared withdual antiplatelet therapy but there was some uncertainty [Very low quality evidence]
- One RCT with 10,228 people showed that 10mg/day dose rivaroxaban plus dual antiplatelet therapy is equally effective as dual antiplatelet therapy alone on the risk of all-cause mortality, but there was some uncertainty [Low quality evidence].

Cardiac mortality

- One non-RCT with 446 people showed that warfarin plus dual antiplatelet therapy increase the risk of cardiac mortality compared with dual antiplatelet therapy [Low quality evidence].
- One non-RCT with 204 people showed that warfarin plus dual antiplatelet therapy has a similar effect the risk of cardiac mortality compared with dual antiplatelet therapy but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 511 people showed that warfarin plus dual antiplatelet therapy increase the risk of all-cause mortality compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- Two RCTs with 8306 people showed that apixaban plus dual antiplatelet therapy has no effect on the risk of cardiac mortality compared with dual antiplatelet therapy [Low quality evidence].
- One RCT with 1108 people showed that low dose dabigatran plus dual antiplatelet therapy has no effect on the risk of cardiac mortality compared with dual antiplatelet therapy but there was some uncertainty [Very low quality evidence].
- One RCT with 1124 people showed that moderate dose dabigatran plus dual antiplatelet therapy reduce the risk of cardiac mortality compared with dual antiplatelet therapy, but there was some uncertainty [Low quality evidence].• One RCT with 10,227 people showed that 5mg/day rivaroxaban plus dual antiplatelet therapy reduce the risk of cardiac mortality compared with dual antiplatelet therapy, but there was some uncertainty [Very low quality evidence].
- One RCT with 10,228 people showed that 10mg/day rivaroxaban plus dual antiplatelet therapy has no effect on the risk of cardiac mortality compared with dual antiplatelet therapy [Low quality evidence].

Reinfarction

- One non-RCT with 446 people showed that warfarin plus dual antiplatelet therapy has no effect on the risk of reinfarction in hospital compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 446 people showed that warfarin plus dual antiplatelet therapy increase the risk of reinfarction compared with dual antiplatelet therapy, but there was some uncertainty [Very low quality evidence].
- One non-RCT with 515 people showed that warfarin plus dual antiplatelet therapy increase the risk of reinfarction compared with dual antiplatelet therapy, but there was some uncertainty [Very low quality evidence].

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- One non-RCT with 511 people showed that warfarin plus dual antiplatelet therapy increase the risk of reinfarction compared with dual antiplatelet therapy, but there was some uncertainty[Very low quality evidence].
- One non-RCT with 961 peoples showed that warfarin plus dual antiplatelet therapy has no effect on the risk reinfarction compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 1861 people showed that apixaban plus dual antiplatelet therapy has no effect on the risk reinfarction compared with dual antiplatelet therapy [Moderate quality evidence].
- One RCT with 1108 people showed that low dose dabigatran plus dual antiplatelet therapy increase the risk of reinfarction compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 1124 people showed that moderate dose dabigatran plus dual antiplatelet therapy may increase the risk of reinfarction compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 10,227 people showed that 5mg/day rivaroxaban plus dual antiplatelet therapy is equally effective as dual antiplatelet therapy on the risk of reinfarction. [Low quality evidence].
- One RCT with 10,228 people showed that 10mg/day rivaroxaban plus dual antiplatelet therapy reduce the risk of reinfarction compared with dual antiplatelet therapy [Very low quality evidence].

Revascularisation

- One RCT with 563 people showed that warfarin plus dual antiplatelet therapy decrease the risk of revascularisation compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 446 people showed that warfarin plus dual antiplatelet therapy increase the risk of revascularisation in hospital compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 446 people showed that warfarin plus dual antiplatelet therapy increase the risk of revascularisation compared with dual therapy alone, but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 511 people showed that warfarin plus dual antiplatelet therapy increase the risk of revascularisation compared with dual antiplatelet therapy, but there was some uncertainty [Very low quality evidence].

Stroke

- One non-RCT with 446 people showed that warfarin plus dual antiplatelet therapy increase the risk of stroke compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 82 people showed that warfarin plus dual antiplatelet therapy reduce the risk of stroke compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 511 people showed that warfarin plus dual antiplatelet therapy decrease the risk of stroke compared with dual antiplatelet therapy [Very low quality evidence].
- One non-RCT with 515 people showed that warfarin plus dual antiplatelet therapy has no effect on the risk of stroke compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One non-RCT with 204 people showed that warfarin plus dual antiplatelet therapy has no effect on the risk of stroke compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].

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- One RCT with 7392 people showed that apixaban plus dual antiplatelet therapy has no effect on the risk of stroke compared with dual therapy alone, but there was some uncertainty [Low quality evidence].
- One RCT with 1108 people suggested that low dose dabigatran plus dual therapy reduce the risk of stroke compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 1125 people suggested that moderate dose dabigatran plus dual therapy reduce the risk of stroke compared with dual antiplatelet therapy, but there was considerable uncertainty [Very low quality evidence].
- One RCT with 10,227 people suggested that 5mg/day rivaroxaban plus dual therapy has no effect on the risk of stroke compared with dual antiplatelet therapy alone, but there was some uncertainty [Very low quality evidence].
- One RCT with 10,228 people suggested that 10mg/day rivaroxaban plus dual therapy has no effect on the risk of stroke compared with dual antiplatelet therapy alone, but there was considerable uncertainty [Very low quality evidence].

Major bleeding

- Two non-RCTs with 5085 people showed that warfarin plus dual antiplatelet therapy have a similar effect as dual antiplatelet therapy alone on the risk of major bleeding, but there was some uncertainty [Very low quality evidence]
- Eight non-RCTs with 6805 people showed that warfarin plus dual antiplatelet therapy increase the risk of major bleeding compared with dual antiplatelet therapy alone [Very low quality evidence].
- Two RCTs with 8306 people showed that apixaban plus dual antiplatelet therapy increase the risk of major bleeding compared with dual antiplatelet therapy [Moderate quality evidence].
- One RCT with 1108 people suggested that low dose dabigatran plus dual therapy has no effect on the risk of major bleeding compared with dual antiplatelet therapy but there was considerable uncertainty [Very low quality evidence].
- One RCT with 1125 people showed that moderate dose dabigatran plus dual antiplatelet therapy has no effect on the risk of major bleeding compared with dual antiplatelet therapy alone but there was considerable uncertainty [Very low quality evidence].
- Two RCTs with 11,281 people showed that 5mg/day rivaroxaban plus dual antiplatelet therapy increase the risk of major bleeding compared with dual therapy alone [Low quality evidence].
- Two RCTs with 11,980 people showed that 10mg/day rivaroxaban plus dual antiplatelet therapy increase the risk of major bleeding compared with dual antiplatelet therapy alone [Low quality evidence].
- One RCT with 1254 people showed that 15mg/day rivaroxaban plus dual antiplatelet therapy increase the risk of major bleeding compared with dual antiplatelet therapy alone [Low quality evidence]
- One RCT with 1347 people showed that 20mg/day dose of rivaroxaban plus dual antiplatelet therapy increase the risk of major bleeding compared with dual antiplatelet therapy alone [Very low quality evidence]

Minor bleeding

- One non-RCT with 4639 showed that warfarin plus dual antiplatelet therapy increase the risk of minor bleeding compared with dual antiplatelet therapy alone but there was some uncertainty [Very low evidence]
- Three non- RCTs with 5358 people showed that warfarin plus dual antiplatelet therapy increase the risk of minor bleeding compared with dual antiplatelet therapy alone [Very low quality evidence].

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- Two RCTs with 8306 people showed that apixaban plus dual antiplatelet therapy increase the risk of minor bleeding compared with dual therapy alone [High quality evidence].
- One RCT with 1108 people suggested that low dose dabigatran plus dual antiplatelet therapy increase the risk of minor bleeding compared with dual antiplatelet therapy alone, but there was some uncertainty [Low quality evidence].
- One RCT with 1125 people showed that moderate dose dabigatran plus dual antiplatelet therapy increase the risk of minor bleeding compared with dual antiplatelet therapy alone [Moderate quality evidence].
- Two RCTs with 11,281 people showed that 5mg/day rivaroxaban plus dual therapy has no effect on the risk of minor bleeding compared with dual antiplatelet therapy alone, but there was some uncertainty [Very low quality evidence].
- Two RCTs with 11,980 people showed that 10mg/day rivaroxaban plus dual therapy increase the risk of minor bleeding compared with dual therapy alone [Low quality evidence].
- One RCT with 1254 people showed that 15mg/day dose of rivaroxaban plus dual antiplatelet therapy increase the risk of major bleeding compared with dual antiplatelet therapy alone [Low quality evidence]
- One RCT with 1347 people showed that 20mg/day dose of rivaroxaban plus dual antiplatelet therapy increase the risk of major bleeding compared with dual antiplatelet therapy alone [Very low quality evidence]

Sudden death

- No evidence on sudden death was identified.

Rehospitalisation

- No evidence on rehospitalisation was identified.

Quality of life

- No evidence on quality of life was identified.

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Warfarin plus aspirin versus aspirin

Indirect population II – people who have CHD and/or who had an MI without an indication for anticoagulation

All-cause mortality

- Eight RCTs with 9218 people showed that warfarin plus aspirin and aspirin alone are similarly effective on the risk of all-cause mortality [Low quality evidence].
- Five RCTs with 7299 people showed that moderate dose warfarin plus aspirin and aspirin alone are equally effective on the risk of all-cause mortality [Low quality evidence].
- Three RCTs with 1290 people showed that high dose warfarin plus aspirin reduce the risk all-cause mortality compared with aspirin alone, but there was some uncertainty [Very low quality evidence].

Cardiac mortality

- Two RCTs with 4380 people showed warfarin plus aspirin are equally effective as aspirin on the risk of cardiac mortality but there was some uncertainty [Low quality evidence].
- One RCT with 3712 people showed that moderate dose warfarin plus aspirin are equally effective as aspirin on the risk of cardiac mortality but there was some uncertainty [Low quality evidence].
- One RCT with 668 people showed that high dose warfarin plus aspirin increase the risk of cardiac mortality compared with aspirin, but there was considerable uncertainty [Very low quality evidence].

Reinfarction

- Nine RCTs with 9701 people showed that warfarin and aspirin reduce the risk of reinfarction compared with aspirin, but there was some uncertainty [Very low quality evidence].
- Six RCTs with 7811 people showed that moderate dose warfarin and aspirin reduce the risk of reinfarction compared with aspirin alone, but there was some uncertainty [Low quality evidence].
- Three RCTs with 1890 people, showed that high dose warfarin and aspirin reduce the risk of reinfarction compared with aspirin alone but there was considerable uncertainty [Very low quality evidence].

Stroke

- Six RCTs with 9123 people showed that warfarin and aspirin reduce the risk of stroke compared with aspirin alone, but there was some uncertainty [Low quality evidence].
- Three RCTs with 7233 people showed that moderate dose warfarin and aspirin reduce the risk of stroke compared with aspirin alone, but there was considerable uncertainty [Low quality evidence].
- Three RCTs with 1890 people showed that high dose warfarin and aspirin are equally effective on the risk of stroke, but there was some uncertainty [Very low quality evidence].

Revascularisation

- Eight RCTs with 7287 people showed that warfarin and aspirin reduce the risk of revascularisation compared with aspirin alone, but there was considerable uncertainty [Very low quality evidence].
- Five RCTs with 5397 people showed that moderate dose warfarin and aspirin reduce the risk of revascularisation compared with aspirin alone, but there was considerable uncertainty [Very low quality evidence].
- Three RCTs with 1890 people showed that high dose warfarin and aspirin reduce the risk of revascularisation more than aspirin alone but there was some uncertainty [Very low quality evidence].

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Rehospitalisation

- One RCT with 90 people, showed that high dose warfarin and aspirin reduce the risk of rehospitalisation compared with aspirin alone, but there was considerable uncertainty [Very low quality evidence].

Major bleeding

- Seven RCT with 8430 people showed that warfarin and aspirin may increase the risk of major bleeding compared with aspirin alone [Moderate quality evidence].
- Five RCTs with 6704 people showed that moderate dose warfarin and aspirin increase the risk of minor bleeding compared with aspirin alone but there was some uncertainty [Moderate quality evidence].
- Two RCTs with 1726 people showed that high dose warfarin and aspirin increase the risk of major bleeding compared with aspirin alone [Moderate quality evidence].

Minor bleeding

- Six RCTs with 8216 people showed that warfarin and aspirin increase the risk of minor bleeding compared with aspirin alone [Low quality evidence].

- Four RCTs with 6490 people showed that moderate dose warfarin and aspirin increase the risk of minor bleeding compared with aspirin alone [Low quality evidence].
- Two RCTs with 1726 people showed that high dose warfarin and aspirin increase the risk of minor bleeding compared with aspirin alone [Low quality evidence].

Sudden death

- No evidence on sudden death was identified.

Quality of life

- No evidence on quality of life was identified.

7.4.7.5 Economic

- No relevant economic evaluations were identified.

7.4.8 Recommendations and link to evidence

61. Offer aspirin to all people after an MI and continue it indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. [2007, amended 2013]

Recommendation	62. Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely [new 2013].
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the patient and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	A sub-group analysis of people who had an MI in the past 5 years and were part of a larger clinical trial, showed that late clopidogrel and aspirin treatment reduced the composite outcome of cardiac death, reinfarction and stroke compared with aspirin treatment alone. However, the size of the effect was small and the benefits need to be counterbalanced by the risk of bleeding. The results from another sub-group analysis (from the same clinical trial) of people with a mix of cardiovascular disease showed that late clopidogrel and aspirin therapy may reduce the risk of reinfarction, stroke and rehospitalisation compared with aspirin alone. No benefit was detected for all-cause or cardiac mortality. However, the small benefits of this dual therapy need to be weighed up against an

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	increased risk of moderate bleeding, but not major bleeding (it should be noted that these outcomes were secondary endpoints of the CHARISMA trial and it was underpowered to show an effect on the risk of bleeding and for subsequent subgroup analyses.) No evidence was found on people who had an MI in the past and subsequently treated with dual antiplatelet therapy using ticagrelor or prasugrel with aspirin. No studies reporting on quality of life were identified. Because of the small gains, the risk of bias in reporting from a subgroup, issues in reporting a composite outcome, and 1 subgroup being indirect the GDG decided to continue recommending that dual treatment should not be initiated for people who had an MI more than 12 months ago. The original recommendation from the previous guideline, CG48, was updated to reflect other antiplatelets now available, using GDG consensus as there was no data on these agents in this setting. NICE technology appraisal 210 provides recommendations for people who had an MI and who have multivascular disease. The recommendation was amended to highlight that people who had an MI who also have multivascular disease should be treated with clopidogrel, rather than aspirin, in line with this guidance.
Economic considerations	Health economic modelling based on MI and CVD subgroups of the trial used to inform the clinical evidence found a net health improvement in terms of life years and QALYs respectively. However, the GDG had a number of concerns about this study and its subgroup analyses. On this basis, the GDG concluded that it would not be appropriate for this data to be used as the basis for recommending initiation of clopidogrel treatment in those not initiated acutely. As discussed above the CHARISMA trial included people who had a prior MI and compared treatment with clopidogrel plus aspirin versus aspirin alone. Analyses based on subgroup analyses from this trial in people with who had an MI or CVD found that clopidogrel plus aspirin was cost effective compared with aspirin alone. However, although the study was included, the GDG did not consider it appropriate to use the CHARISMA study to support initiation of clopidogrel treatment in those not initiated acutely for the reasons outlined above.
Quality of evidence	The quality of the data ranged from being graded as low to very low. One RCT was found for this review and the data was on 2 different subgroups that were part of a larger clinical trial. One subgroup provided data on people who had an MI only, the other comprised people with documented prior MI (46-47%), ischaemic stroke, or symptomatic peripheral arterial disease. The data on people who had an MI was graded as low quality because there was some imprecision and it used a composite outcome rather than individually reported outcomes. However, the authors did report the preferred time-to-event (hazard ratio) calculation on the composite outcome. The data from the larger mixed subgroup was graded as low to very low quality because it was from an indirect population. Additionally, it was unclear why the authors combined a heterogeneous group of people (although the participants were matched at baseline). Most of the participants (99.8%) were taking aspirin prior to onset of clopidogrel treatment, because of an MI in the past. Thus, the GDG felt that the long-term use of aspirin may have minimised any benefit from adding another antiplatelet agent (clopidogrel).

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	No data were identified for the new antiplatelet agents, prasugrel and ticagrelor. The GDG felt that the body of evidence available to answer the review question was generally poor and only small gains were detected in the context of increased adverse reactions. Therefore on balance, the GDG felt that clopidogrel should not be added to aspirin in people who had an MI in the past.
Other considerations	In the previous guideline, CG48, the GDG based their decision on the results from the larger subgroup analysis that was also used in this review. They concluded that there was no perceived benefit of initiating antiplatelet therapy non-acutely in a mixed population with either cardiovascular disease or multiple vascular risk factors not relevant to this guideline. The statistical analysis showed no significant difference between the treatment arms (p>0.05).

63. For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment. [2007, amended 2013]

64. People with a history of dyspepsia should be considered for treatment in line with 'Dyspepsia' (NICE clinical guideline 17). [2007, amended 2013]

65. After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for *Helicobacter pylori* should be considered for treatment in line with 'Dyspepsia' (NICE clinical guideline 17). [2007, amended 2013]

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This guidance incorporates NICE technology appraisal guidance 236 on ticagrelor for the treatment of acute coronary syndromes. Guidance on prasugrel for the treatment of acute coronary syndromes has not been incorporated in this guidance because this technology appraisal is currently scheduled for update. For further information about this appraisal, see the NICE website.

Recommendation	**66. Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes (ACS) that is, people:** • **with ST-segment-elevation myocardial infarction (STEMI) – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary percutaneous coronary intervention (PCI) or** • **with non-ST-segment-elevation myocardial infarction (NSTEMI).** **This recommendation is from 'Ticagrelor for the treatment of acute coronary syndromes' (NICE technology appraisal guidance 236). [new 2013]**
Relative values of different outcomes	The recommendation is based upon NICE technology appraisal 236.
Trade-off between clinical benefits and harms	The GDG wished to highlight that recommendations on the use of ticagrelor for the treatment of acute coronary syndromes can be found in NICE technology appraisal 236 'Ticagrelor for the treatment of acute coronary syndromes'. Further information can be found on the NICE website.

Economic considerations	Economic considerations were discussed during development of the TA.
Quality of evidence	For discussion of the quality of the evidence, please see TA236.
Other considerations	There were no other considerations.

Recommendation	**67.Offer clopidogrel as a treatment option for up to 12 months to:** • **people who have had an NSTEMI, regardless of treatment.** [c] • **people who have had a STEMI and received a bare metal or drug-eluting stent. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the patient and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	The GDG considered the evidence for people who had an NSTEMI and people who had a STEMI and received a bare metal or drug eluting stent. **People who had an NSTEMI and are medically managed** In medically treated people who had an NSTEMI, there was a small benefit of clopidogrel and aspirin (dual antiplatelet therapy) on the risk of all-cause mortality compared with aspirin alone. However, although there was considerable uncertainty, the GDG considered this benefit to be clinically important. Benefits of dual antiplatelet therapy in people who had an NSTEMI, most of who were treated medically, were also detected on the risk of stroke and reinfarction, with considerably large benefits detected in the latter. Conversely, dual antiplatelet therapy increased the risk of revascularisation and major and minor bleeding. There was no effect on cardiac mortality. A subgroup analysis on medically treated people who had an NSTEMI also showed dual antiplatelet therapy decreased the risk of each of CV mortality, MI and stroke. No studies reported on the quality of life. Benefits of reduction in all-cause mortality were detected for up to 1 year. For

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[c] 'This recommendation updates recommendation 1.3 in Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome (NICE technology appraisal guidance 80).

reinfarction and stroke, the length of benefit varied and it was difficult to identify the optimal length of treatment because events may have happened at any point. See discussion on this below in "quality of evidence".

Despite some data suggesting benefits of long term treatment with clopidogrel and aspirin, the GDG felt that recommending treatment with clopidogrel and aspirin for more than 12 months was difficult, as data demonstrating benefits up to 28 months was taken from an indirect population where treatment was not initiated acutely. Additionally, the GDG felt that in further evidence suggesting effectiveness for up to 24 months following an MI, the risk of adverse events outweighed possible benefit. The GDG therefore agreed to recommend treatment with clopidogrel for up to 12 months in people who had an NSTEMI and are medically managed, as the benefits identified outweighed potential harms up to this time point.

People who had an NSTEMI and who had a bare metal or drug eluting stent

There was some evidence on the optimal duration of clopidogrel and aspirin treatment for people who had an NSTEMI who underwent PCI and most of whom received a bare metal stent. Six and 12 months of therapy was associated with a greater reduction on the risk of all-cause mortality, revascularisation and reinfarction compared with 1 month of treatment but this treatment was also carried an increased risk of major and minor bleeding. There was no apparent difference on the effect of duration of treatment on cardiac mortality or stroke.

There was no evidence for people who had NSTEMI who had been treated acutely with drug eluting stents. However, indirect evidence was available in those who have ACS who needed PCI, as well as evidence from a composite outcome of CV mortality, MI and stroke, which support a recommendation for treatment up to 12 months. Composite outcomes are only included if single outcomes are not available, see Chapter 3.

Additionally, the GDG highlighted that different stent manufacturers recommend different durations of clopidogrel following implantation and the recommendation was therefore made to highlight that clopidogrel should be given for 'up to 12 months' to allow for flexibility in prescribing duration. This is particularly relevant in the context of rapid development in stent technology.

People who had an NSTEMI and who had CABG surgery

In people that had an NSTEMI who were treated with CABG (half acutely, half post hospital discharge), there was a reduction in the risk of the composite outcome: cardiac mortality, MI and stroke with 12 months of dual antiplatelet therapy.

Furthermore, data extrapolated from other populations (for example, people who had bare metal or drug eluting stents and those who are medically managed) provided evidence to suggest benefit for up to 12 months. The GDG felt that similar benefits were likely to be derived by people who had CABG surgery.

The GDG felt that there was a risk of major and minor bleeding associated with continuing dual antiplatelet therapy. However, the GDG acknowledged that people who had an NSTEMI treated with CABG should be receiving a bleeding assessment in their follow-up appointment, as per recommendation 72.

No studies reported on the quality of life.

No data were identified on treatment with clopidogrel in people after CABG for

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	longer than 12 months and the GDG were concerned about the potential of an increase in adverse events with longer term treatment, particularly the risk of bleeding. The GDG therefore felt that the potential benefits of reduced cardiac mortality, MI and stroke outweighed the potential for adverse effects and recommended treating people who had an NSTEMI, who had CABG, with clopidogrel and aspirin for up to 12 months. **People who had a STEMI and who had a bare metal or drug eluting stent** One study on people who had a STEMI where 57% of the participants had PCI and stents implanted was identified in this review. This study found a decreased risk of reinfarction, revascularisation and stroke compared with aspirin alone in people treated with clopidogrel for 30 days. There were unclear effects on all-cause or cardiac mortality. The results from studies in people who had an NSTEMI who had PCI and bare metal stents implanted showed that 12 months of dual antiplatelet therapy may result in a greater decrease in revascularisation and reinfarction compared with 1 month of treatment, with no apparent effect on cardiac mortality. However, the risk of major and minor bleeding is increased with the longer the duration of treatment (12 months versus 1 month). For this reason, the GDG recommended that all people should have a bleeding risk assessment at follow-up appointment. The results should subsequently be used by the healthcare professional and patient to consider potential benefits and harms of continuing combined treatment. One study compared the effects of 24 months versus 6 months of clopidogrel treatment after a PCI but in an indirect population for people who had a STEMI. The results showed that 24 months of treatment had a similar effect as 6 months of treatment on the risk of all-cause mortality, cardiac mortality, reinfarction and minor bleeding, but there was an increased risk of stroke and major bleeding with longer term treatment. No studies reported on the quality of life. Given the paucity of longer term data in this group, the GDG considered indirect population data and decided that, on balance the benefits of recommending clopidogrel for up to 12 months for people who have been treated with bare metal or drug eluting stents, outweighed the risk of adverse effects. The manufacturers of the different stents have different recommended times for clopidogrel treatment and the GDG felt that recommending treatment up to 12 months would allow the manufacturers' recommendations to be followed, as appropriate.
Economic considerations	**People who had an NSTEMI and who have been medically managed, or who had a bare metal or drug eluting stent** A cost effectiveness analysis was undertaken in NICE TA80 that compared no clopidogrel treatment with 1 year, 6 months, 3 months, 1 month clopidogrel treatment (all with lifetime aspirin) in people with UA/STEMI based on the CURE trial which included people who are managed medically or who have been revascularised (PCI or CABG). This informed the NICE recommendation for 12 months of treatment that was included in the previous guideline, CG48. Since then, an updated version of this analysis has been published that incorporates further exploration of how relative risk changes over time. This analysis found that 1 year of treatment with clopidogrel

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(plus lifetime aspirin) was the most cost-effective option in people at higher risk, while 3 months of treatment was the most cost-effective option in those at lower risk. The analysis was judged to be partially applicable with potentially serious limitations. Of particular note, the cost of clopidogrel has reduced from around £460 per year at the time of the analysis to around £28 per year currently. This will increase the cost effectiveness of 1-year treatment with clopidogrel also in the low-risk group. Also of note is the fact that baseline risks in the analysis are based on a 1998-99 UK cohort – as acute management has improved over time, baseline risks used in the analysis may be higher than in the current context. This would be likely to decrease the cost effectiveness of clopidogrel. However, overall the GDG concluded that the effect of the cost decrease was likely to outweigh this possible effect. The GDG discussed whether clopidogrel duration should be stratified by risk but decided not to do so as, the cost reduction of clopidogrel means that a longer duration is now likely to be cost effective for every person who has had an MI. This is in line with the recommendation in the TA80 where stratification was also discussed but the final recommendation about duration was not stratified by risk either.

In addition to the UK study which informed the TA, a UK cost-effectiveness analysis in people who were undergoing PCI for ACS based on the PCI-CURE subgroup found that 1 year of treatment with clopidogrel (plus lifetime aspirin) was cost-effective compared to 1 month of treatment with clopidogrel.

Health economic modelling based on the CURE trial found net health gains as measured in QALYs with increasing durations of clopidogrel treatment (it compared 1 year, 6 months, 3 months, 1 month and no clopidogrel treatment). However, non-fatal bleeding events were considered not to impact QALYs.

Health economic modelling based on MI and CVD subgroups of the CHARISMA trial found a net health improvement in terms of life years and QALYs respectively. However, the GDG had a number of concerns about this study.

The CHARISMA trial included a subset of people who had a prior MI and compared treatment with clopidogrel plus aspirin versus aspirin alone – on average clopidogrel duration was 28 months and so while not comparing different durations of clopidogrel provides some evidence for longer term clopidogrel use than other included studies. These analyses found that clopidogrel plus aspirin was cost effective compared to aspirin alone for this duration. However, the GDG did not consider it appropriate to use the CHARISMA study to support longer durations of clopidogrel for the reasons outlined in the 'Trade-off between clinical benefits and harms' section above.

People who had an NSTEMI and who had CABG surgery

No economic analysis was identified specifically for those treated with coronary artery bypass grafts (CABG) although these people were included in the overall CURE analysis. This study was the effectiveness source for some important parameters in the economic studies included for the review on people with non-ST-segment-elevation myocardial infarction and treated with medical therapy alone or PCI and drug eluting stents. Therefore the GDG considered it likely that treatment for up to 1 year with clopidogrel is cost-effective in people who have received CAGB surgery as well.

People who had a STEMI and received a bare metal or drug eluting stent

No economic evidence was identified. For people that had a STEMI who undergo bare metal stent placement as part of PCI procedure it was considered that the manufacturer instructions regarding the duration of clopidogrel should be taken into consideration.

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Quality of evidence	**People who ad an NSTEMI and who have been medically managed or who had a drug eluting or bare metal stent** Overall, the quality of the evidence on people who had an NSTEMI was graded as moderate to very low. Three RCTs with a study design that compared different durations of clopidogrel were identified but provided overall low quality evidence, mostly because of imprecision (wide 95% CI). The power calculations were based on a composite outcome so the studies were not necessarily powered to detect differences in single outcomes. Indirect evidence was used to inform this recommendation since less than 75% of the people had an MI. Studies using different durations of follow up had limitations as it is unclear when an event occurred. Taking into account this limitation, we compared the results at different durations of follow-up to see if the benefits or harms were consistent with the other data. The quality of the evidence for this approach ranged from very low to moderate mostly because of imprecision and some indirectness (less than 75% post MI). Composite outcomes (CV death/MI/stroke) were downgraded because it is not clear which outcome/s may have contributed the most. The economic evidence was judged to be partially applicable and with potentially serious limitations. **People who had an NSTEMI and who had CABG surgery** The quality of the evidence was graded as low to very low. One sub-group analysis from an RCT on people who had an NSTEMI who had CABG either during the initial hospitalisation phase or after discharge provided low quality evidence that dual antiplatelet therapy decreases the risk of 1 or more of the following outcomes: CV death/MI/stroke compared with aspirin alone. Very low quality evidence was available on all-cause mortality, major and minor bleeding, thus it was difficult for the GDG to be confident of the outcomes. The quality of the results was downgraded because of 1 or more of the following reasons: high imprecision, small patient numbers and event rates, composite outcome only and data were from a subgroup analysis of participants from a larger trial. No economic evidence was found specifically on this population. **People who had a STEMI and who have received a bare metal or drug eluting stent** Overall the quality of the evidence was graded as low, ranging from moderate to very low. One RCT published data on the effects of dual antiplatelet therapy on people who had a STEMI who had PCI and stents implanted (30 days). However, the data iwere indirect since only 57% of the entire sample had bare metal stents implanted. The results are also somewhat imprecise, although there is a mostly positive effect. Data is available on people who had an NSTEMI who had PCI and had bare metal stents implanted (85%), but this is an indirect population given that this part of the recommendation focusses on people who had a STEMI. The overall quality is low

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	because of some imprecision, however the study does provide insight into people treated with PCI. Another RCT compared a longer duration of clopidogrel for 24 months versus 6 months. The findings were generally low quality because although all the participants had PCI with drug eluting or bare metal stents, only 33% were people who had a STEMI and therefore, the population was slightly indirect. The results also showed some imprecision, that is the 95% CI crossed were wide. The data on the risk of bleeding in people treated with PCI treated is from a mix of people who had an NSTEMI or a STEMI, however the GDG felt the type of MI is unlikely to influence the risk of bleeding and that the type of acute management is likely to be important. No economic evidence was found specifically on this population.
Other considerations	This recommendation has been updated from NICE technology Appraisal 80 (TA80) 'Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome'. Recommendations on when to continue clopidogrel treatment after 12 months can be found in NICE technology appraisal 210 (TA210) 'Vascular disease – clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events'. The GDG noted that acute management procedures have changed since the trials had been conducted, affecting the baseline risk of patients. The GDG considered how the duration of clopidogrel therapy varied, depending on the type of acute management given. It was agreed that it was helpful to healthcare professionals to align treatment across acute management groups, as this would mean that the people who had an NSTEMI would receive treatment with clopidogrel for up to 12 months, except for those with or who develop contraindications. It is likely that this would simplify treatment following an MI and aid implementation. However, the GDG felt that it was important to highlight that healthcare professionals should weigh up a potential increased risk of bleeding against cardiovascular benefits in people who had CABG, in particular. The GDG discussed changes in the universal definition of myocardial infarction since the trials were conducted. These changes have meant that many people who would have been categorised as unstable angina patients in the past would now be diagnosed as having had an NSTEMI. Therefore, for the purposes of the review, people who had unstable angina in the CURE trial were considered to be people who had an NSTEMI. The GDG highlighted the need for further research in this area, to identify whether the benefits of dual antiplatelet therapy (aspirin and clopidogrel) are actually achieved with clopidogrel alone in people who have undergone revascularisation. A research recommendation for an RCT was therefore developed (see Appendix N). The GDG wished to highlight that it was important for healthcare professionals to ensure that patients' wishes are taken into consideration regarding the trade-off between harms and benefits. The GDG noted that NICE clinical guideline 94 'Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction' (CG94) recommended that treatment with clopidogrel should be suspended 5 days before CABG in people with a low risk of cardiovascular events.

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	The GDG felt that it was important to note that people undergoing CABG should be reinitiated on clopidogrel therapy following surgery. Recommendations on the use of prasugrel and ticagrelor can be found in NICE TA182 and 236. The GDG therefore wished to highlight that the use of clopidogrel is an option for treatment in people who have had an MI. The GDG felt that there was a lack of evidence relating to the optimal duration of clopidogrel therapy in people who had a STEMI and who have undergone primary PCI with a bare metal stent. Therefore, a research recommendation was developed by the GDG to recommend a RCT for dual antiplatelet therapy for 4 weeks versus 12 months (see Appendix N), to identify whether there is any additional benefit to continuing treatment with clopidogrel for an additional 11 months.

Recommendation	**68. Offer clopidogrel as a treatment option for at least 1 month and consider continuing for up to 12 months to:** • **people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the patient and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	**People who had a STEMI and who are medically managed** Data on people who had a STEMI treated medically (that is, with thrombolysis or no reperfusion therapy) and with dual antiplatelet therapy showed a small but clinically important decrease in all-cause mortality, cardiac mortality, reinfarction and stroke compared with aspirin, as well as a large decrease in revascularisation after 28 days of treatment. No studies reported on quality of life. The GDG felt that benefits of dual antiplatelet therapy need to be weighed up against the large increased risk of minor bleeding in peoples treated with dual-antiplatelet therapy. No effect on the risk on major bleeding was detected. Thus, the GDG agreed that it was important to ensure that patients' wishes are taken into consideration with regards to the trade-off between harms and benefits. Given the paucity of longer term data, the GDG felt the recommendation should be clear that treatment should be offered for 1 month and that extending treatment for up to 1 year could be based on an assessment of risk and benefit for individual patients alongside the patient's wishes.

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	No studies reported on the quality of life. Given the paucity of longer term data in this group, the GDG considered indirect population data and decided that, on balance the benefits of recommending clopidogrel for up to 12 months for people who have been treated with bare metal or drug eluting stents, outweighed the risk of adverse effects. The manufacturers of the different stents have different recommended times from clopidogrel treatment and the GDG felt that by recommending treatment up to 12 months would allow the manufacturers' recommendations to be followed.
Economic considerations	**People who had a STEMI and who are medically managed** A UK cost-effectiveness analysis in a STEMI population found that 1 year of treatment with clopidogrel (plus lifetime aspirin) was the most cost-effective option compared with 1 month or no clopidogrel treatment. This analysis was judged to be partially applicable with potentially serious limitations. The key issue was that while relative effectiveness data was based on the STEMI COMMIT or CLARITY trial up to 1 month that are included in the clinical review, from 2 to 12 months the relative effectiveness of clopidogrel was extrapolated from the CURE (UA/NSTEMI) trial as no studies are available for clopidogrel use beyond 1 month specifically in people who had a STEMI. The GDG discussed whether they felt this extrapolation was appropriate but concluded that they were not confident that it was. This was because the time course of events in people who had a STEMI or an NSTEMI is different and the GDG were concerned that this extrapolation may overestimate the benefits in people who had a STEMI, and therefore overestimate cost effectiveness. If the 1 year treatment option is removed, 1 month clopidogrel (plus lifetime aspirin) was cost effective compared to no clopidogrel treatment. In addition, the cost of clopidogrel has reduced from around £460 per year at the time of this analysis to around £28 per year currently. It was also noted that baseline risks used in the analysis are likely to be higher than in the current context due to changes in the acute management of STEMI with a much increased use of primary PCI. The GDG considered it was reasonable to conclude that 1 month of clopidogrel would be cost effective in people who had a STEMI. As discussed above the CHARISMA trial included people who had a prior MI and compared treatment with clopidogrel plus aspirin versus aspirin alone – on average clopidogrel duration was 28 months and so while not comparing different durations of clopidogrel provides more evidence for longer term clopidogrel use than other included studies. These analyses found that clopidogrel plus aspirin was cost effective compared to aspirin alone for this duration. However, the GDG did not consider it appropriate to use the CHARISMA study to support longer durations of clopidogrel for the reasons outlined in the 'Trade-off between clinical benefits and harms' section above
Quality of evidence	**People who had a STEMI and who are medically managed** Overall, the quality of the evidence was graded as moderate, ranging from high to very low. The results were derived from two 28-30 day RCTs. In 1 trial all participants were treated medically and in the other approximately 40% were (the majority underwent PCI). Both sets of data included the end points of cardiac mortality, stroke, and reinfarction. The trial with 100% people who had been medically treated was much larger and contributed more to the overall result, thus our analysis was affected little by the number of people receiving PCI. The results ranged from moderate to very low quality because of imprecision and some heterogeneity.

	In contrast, the results on all-cause mortality were high quality and only from people who were treated medically. The results on major bleeding within the first 30 days of treatment and in people who had been medically treated were extracted from STEMI and NSTEMI trials (However, the same results were found in people who had a STEMI alone). The GDG felt it was acceptable to combine the results from different trial populations since the risk of bleeding is unlikely to be influenced by the type of MI. The evidence was moderate quality because of some imprecision. See Recommendation 72. For the risk of minor bleeding, the 30 day results were of moderate quality because not all of the people who had a STEMI were treated medically and there was some imprecision in the results (that is wide 95% confidence interval). Also, data on people who had been medically treated was moderate quality because the studies included people who had an MI at some point in the past. However, when it comes to bleeding risk, the population was not considered that important. Although there was evidence of an increased risk of minor bleeding (but not major bleeding) the GDG felt the benefits on cardiac outcomes are important and felt the recommendation should include the wording of "consider" continuing clopidogrel for up to 12 months. Because of this increased risk of minor bleeding, the GDG recommended that all people should have a bleeding risk assessment at their follow-up appointment. The results should subsequently be used by the healthcare professional and patient to consider potential benefits and harms of combined treatment. The economic evidence was judged to be partially applicable and with potentially serious limitations.
Other considerations	The GDG noted that acute management procedures have changed since the trials have been conducted, affecting the baseline risk of patients. Currently few people who had a STEMI are treated medically, most are treated with PCI. Thus, the GDG made separate recommendations according to the acute management of the MI. For the purposes of the review, data were stratified by the type of acute management and type of myocardial infarction. The GDG noted that this was particularly important, given the changes in current practice. The GDG noted that the use of stents in people who had been treated with PCI became accepted practice after the publication of the COURAGE trial in 2007, so earlier trials rarely used stents. As a result, limited data is available on people who had a STEMI or an NSTEMI and who received stents. The previous guideline, CG48, recommended continuing clopidogrel and aspirin treatment for those with STEMI for at least 4 weeks, thereafter standard treatment with low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy. Although there is no new evidence to inform this recommendation, the GDG decided to amend the recommendation to suggest consideration of continuing treatment for up to 12 months. It was felt that the indirect evidence was of sufficient weight in the context of standard use of 12 months' treatment in people who had stents to extend the option for prolonged treatment to this group. It is worth noting that the absolute number of people (effect size) who will benefit

	from clopidogrel and aspirin are small. However, this should be compared with the baseline risk in the aspirin group. Because this risk is also small, the absolute number of people who benefit from clopidogrel and aspirin treatment generally translates to more than 10% of people.

Recommendation	**69. Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received coronary artery bypass graft (CABG) surgery. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the patient and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant.
Trade-off between clinical benefits and harms	No studies have specifically considered patients undergoing CABG shortly after myocardial infarction, although this population has been included in some larger studies. It was not possible to extract data specifically about this population. NICE technology appraisals 182 and 236 have currently recommended treatment with prasugrel and ticagrelor in the general population after myocardial infarction. and this guideline has reviewed indirect evidence of the benefit of clopidogrel in the general population after MI. The GDG discussed the appropriate treatment in this subpopulation after MI, and felt that in the absence of direct evidence, the best option was to recommend continuing the second antiplatelet treatment that had been given before the CABG, as this prescription would have taken into account individual patient characteristics in balancing potential benefits and harms. Aspirin would also be offered as part of the the treatment as stated in previous recommendations.
Economic considerations	No economic evidence was identified.
Quality of evidence	Overall the quality of the evidence was graded as low, ranging from moderate to very low. One RCT published data on the effects of dual antiplatelet therapy on people who had a STEMI who had PCI and stents implanted (30 days). However, the data were indirect since only 3-6% had CABG. The results are also somewhat imprecise, although there is a mostly positive effect. Data were also available on people who had an NSTEMI who had PCI and had bare metal stents implanted (85%), but this is an indirect population given that the

	recommendation focusses on people who had a STEMI. The overall quality is low because of some imprecision, however the study may provide some insight into people who had a STEMI. The data on the risk of bleeding in people who have been treated with PCI is from a mix of people who had an NSTEMI or a STEMI, however the GDG felt the type of MI is unlikely to influence the risk of bleeding and that the type of acute management is likely to be important. The recommendation was developed using informal consensus of the GDG.
Other considerations	There were no other considerations.

Recommendation	**70. Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease, in line with 'Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events' (NICE technology appraisal guidance 210) and who have:** • **had an MI and stopped dual antiplatelet therapy or** • **had an MI more than 12 months ago. [new 2013]**
Relative values of different outcomes	The recommendation is based upon NICE technology appraisal 210.
Trade-off between clinical benefits and harms	The GDG wished to highlight that recommendations on the use of clopidogrel for people who have other clinical vascular disease can be found in NICE technology appraisal 210 'Clopidogrel and modified release dipyridamole for the prevention of occlusive vascular events'. Further information can be found on the NICE website.
Economic considerations	Economic considerations were discussed during development of the TA.
Quality of evidence	For discussion of the quality of the evidence, please see TA210.
Other considerations	There were no other considerations.

Recommendation	**71. Offer all people who have had an MI an assessment of bleeding risk at their follow-up appointment. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the patient and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant.

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	Bleeding events were considered are of particular concern in people receiving more potent modern antithrombotic therapy.
Trade-off between clinical benefits and harms	The GDG sought to balance the time and resources required to perform a bleeding risk assessment and the benefits in terms of identifying those patients who might need to discontinue or modify aspects of their therapy in order to reduce the risk of bleeding. Whilst there is evidence of the effectiveness of antiplatelet therapy in reducing undesirable outcomes such as cardiac mortality and stroke compared with aspirin alone, there is an increased risk of major bleeding in those treated with PCI and CABG (up to 12 months) and minor bleeding in those medically managed (over 12 months). The risk of major and minor bleeding is also greater in those treated with clopidogrel for 24 versus 6 months and 12 versus 1 month, respectively. Quality of life was the only outcome not reported in any of the studies in this review. As the GDG decided to recommend the use of clopidogrel in combination with aspirin for up to 12 months, but were concerned about the risk of bleeding, they felt that it was a good use of resources to offer an assessment of bleeding risk to all people who had an MI once they were established on their treatment.
Economic considerations	Given the increased risk of bleeding due to adding clopidogrel to aspirin, the GDG believed the extra cost associated with the assessment of this risk to be outweighed by any bleeding event prevented by the assessment.
Quality of evidence	Overall, the evidence on bleeding risk and all other outcomes ranged was graded as high to very low quality. The evidence on bleeding risk was derived from a mixed MI population (STEMI and NSTEMI) since it was thought that the type of MI is unlikely to significantly impact the risk of bleeding. The patient numbers were high but the number of events was low (less than 10% for number of events/total population), and there was some uncertainty in the results because of imprecision (that is, wide 95% CI). Approximately half of the results showed some imprecision, so the GDG made a decision based on the best estimate of the effect , or the mean, and was confident using this approach since the results were generally consistent. The evidence on the risk of major bleeding in people who underwent PCI was graded as moderate quality and those who had CABG was graded as very low quality. The reasons for downgrading included imprecision, high dropout rates and some of the data being extracted from subgroup analysis from a larger trial. Similarly, for minor bleeding the evidence on people treated with PCI and CABG treated was graded as low and very low respectively because of some imprecision. In addition, 1 study had a high drop-out rate of more than 20%. Despite these shortlcomings, the GDG agreed that all people should be given a bleeding risk assessment at follow up appointment.
Other considerations	There are no recommendations on bleeding risk assessment in the previous guideline, CG48, thus this is a new recommendation.

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7.4.8.1.1.1 Antiplatelet therapy in those with a pre-existing indication for anticoagulation

Recommendation	**72.Take into account all of the following when thinking about treatment for**

	people who have had an MI and who have an indication for anticoagulation: • **bleeding risk** • **thromboembolic risk** • **cardiovascular risk. [new 2013]**
Relative values of different outcomes	The GDG identified mortality and quality of life as critical outcomes. Reinfarction, stroke, and rehospitalisation were considered important outcomes. Major and minor bleeding were considered relevant to the review. The GDG felt that when considering the appropriateness of triple therapy, it was particularly important to consider the type of stent, risk of bleeding, risk of embolism and the risk of cerebral bleeding.
Trade-off between clinical benefits and harms	No evidence was identified relating to this recommendation. However, the GDG felt that any decision on whether warfarin and antiplatelet agents should be continued together should be dependent upon individual patient factors. Given the potential increased risk of bleeding in individuals taking anticoagulants and antiplatelets in combination, the group felt that it was important to assess these individuals for their risk of bleeding, as well as their thromboembolic and cardiovascular risk. The results of these assessments should subsequently be used by the healthcare professional and patient to consider potential benefits and harms of combined treatment. The GDG felt that there were no important harms associated with this recommendation for the patient. They felt that the time taken to undertake the assessment for the staff and patients was worthwhile given the potential to allow the treatment to be tailored to the individual patient. A recommendation to assess all people who had an MI and who have an indication for anticoagulation for bleeding, thromboembolic and cardiovascular risk was therefore developed by consensus of the GDG.
Economic considerations	No economic studies were identified. Assessment of the patient's ongoing indication for anticoagulation, thromboembolic risk, bleeding risk and risk of a further coronary event will take a small amount of staff time but this is offset by the health gains by ensuring people are on the right treatment for their individual circumstances.
Quality of evidence	No evidence was specifically identified regarding the assessment of bleeding, thromboembolic and cardiovascular risk in people who had an MI with a pre-existing indication for anticoagulation. The recommendation was therefore developed by GDG consensus.
Other considerations	There were no other considerations.

Recommendation	**73. Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who:** • **have had their condition managed medically or** • **have undergone balloon angioplasty or** • **have undergone CABG surgery. [new 2013]**
Relative values of different outcomes	The GDG identified mortality and quality of life as critical outcomes. Reinfarction, stroke, and rehospitalisation were considered important outcomes. Major and minor bleeding were considered relevant to the review. The GDG discussed the importance and relevance of various outcomes in assessing

	treatments in the context of secondary prevention of MI in people also needing anticoagulation. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the patient and society, were stroke, reinfarction and revascularization, stroke (embolic or haemorrhagic) or systemic embolism being of particular concern in this population needing anticoagulation. Rehospitalisation was considered a relevant outcome, given its economic impact, and its impact on quality of life. The adverse effects of treatment, particularly bleeding, which impact on both mortality and morbidity, as well as quality of life (which was not always measured) were particularly important in this subpopulation.
Trade-off between clinical benefits and harms	**People who have been medically managed** There was evidence on an indirect population, most of whom are likely to have been medically managed for an MI, but who had no indication for anticoagulation, that showed treatment with warfarin plus aspirin decreased the risk of all-cause mortality, cardiovascular mortality, reinfarction, revascularisation, rehospitalisation and stroke, compared with aspirin alone. However, this combined treatment appeared to increases the risk of both major and minor bleeding. In contrast, there was non-RCT data on a population who had an MI or had stents implanted, of whom only 1 arm had an indication for anticoagulation and compared warfarin plus dual antiplatelet therapy versus dual antiplatelet therapy. The results suggested that dual antiplatelet therapy reduce the risk of all-cause mortality, cardiac mortality, revascularisation, reinfarction and major and minor bleeding compared with warfarin plus dual antiplatelet therapy. There were unclear effects on stroke. There were additional non-RCT data on a population who did have an indication for anticoagulation and the majority of whom had an MI that showed warfarin plus aspirin reduced the risk of all-cause mortality and stroke compared with warfarin plus dual antiplatelet therapy. No difference was detected for reinfarction, cardiac mortality or major bleeding. Although warfarin plus aspirin was associated with better outcomes compared with warfarin plus dual antiplatelet therapy or aspirin alone (except on the risk of bleeding), dual antiplatelet therapy was more effective than warfarin plus dual antiplatelet therapy. However, the GDG discussed that most people who have an indication for anticoagulation would be given an anticoagulant such as warfarin, as opposed to dual antiplatelet therapy alone. Therefore the relevant question in this population is do we just give warfarin or do they need aspirin as well? Therefore, after deciding that this evidence is the most relevant, the GDG agreed that warfarin should be continued and aspirin should be added in people who had an MI. However, the group did highlight that it was important to consider individual risk of bleeding when making a decision as to how treatment should progress. No data were found on warfarin plus clopidogrel versus clopidogrel alone in this population. For this reason aspirin was recommended.

	The GDG felt that, in those with an indication for anticoagulation, it was important to reassess continuing anti-platelet therapy at 12 months, as after 12 months, all people who had an MI who do not have an indication for anticoagulation would have completed treatment with clopidogrel and be recommended indefinite treatment with aspirin. The GDG felt that this assessment should include the indication for anticoagulation, the risks of bleeding, an assessment of cardiovascular and embolic risk and the wishes of the person. The GDG did not feel it was possible to provide a general recommendation regarding the appropriate treatment in this group, and that it would vary according to the assessment outlined. **People who had balloon angioplasty** The GDG felt the recommendation for those who had balloon angioplasty should be based on the same evidence used for those who were medically managed as there were no separate data to inform the decision, and in the absence of stents, the risk of thrombosis was likely to be similar to that after medical management. The GDG therefore agreed that warfarin and aspirin should be continued in this population. However, the group did highlight that it was important to consider individual risk of bleeding when making a decision as to how treatment should progress. **People who had CABG surgery** No direct evidence was identified on a population of people who have undergone CABG surgery. Given the risk of bleeding associated with CABG surgery, the GDG did not feel that recommending treatment with clopidogrel, in combination with anticoagulation was appropriate. As such, the GDG felt that it was appropriate to extrapolate from evidence in a medically managed population and therefore included the population of people who have undergone CABG surgery in this recommendation.
Economic considerations	**People who have been medically managed** No economic studies were identified. The unit costs of drugs were considered by the GDG. Treating people with aspirin, clopidogrel and warfarin would cost a maximum £5 per month and £60 per year when only the cost of drugs are considered. However, the clinical evidence showed that warfarin plus aspirin was more effective than warfarin plus clopidogrel and aspirin. From an economic perspective this lead to the conclusion that triple therapy (warfarin plus clopidogrel and aspirin) is dominated (that is it is more costly and less effective) and therefore adding aspirin alone in people who are already taking warfarin is the optimal choice. **People who had balloon angioplasty and people who had CABG surgery** No economic studies were identified for these specific populations. The GDG felt it was appropriate to extrapolate from evidence in a medically managed population.
Quality of evidence	The RCT evidence on those who had an MI and were likely to have been medically managed, but who had no prior indication for anticoagulation was graded as very low quality. The results were downgraded because of indirectness (no indication for oral anticoagulation) and some imprecision that is wide 95% confidence intervals. The comparisons used in the RCT (warfarin plus aspirin versus aspirin) although relevant do not take into account that common practice is to recommend clopidogrel either alone or in conjuction with aspirin. In contrast to aspirin, clopidogrel is more effective at reducing the risk of vascular events.

	The non-RCT data (warfarin plus dual versus dual antiplatelet therapy) on those who had an MI or who had a stent implanted was indirect because some had a stent and were not medically managed. Additionally, only 1 treatment arm had an indication for anticoagulation. The data was also downgraded because it was non-randomised data and could not be meta-analysed. However, they did include the use of clopidogrel which is a clinically relevant therapy. The non-RCT data on warfarin plus dual antiplatelet therapy versuswarfarin plus aspirin was downgraded because they were non-randomised and 1 of the studies included an indirect population of 63% who had an MI, all of whom needed PCI. This data were considered since these comparisons were not found on a medically managed population. No evidence was identified for prasugrel or ticagrelor. **People who had balloon angioplasty and whom had CABG surgery** No direct evidence was identified for these populations and evidence was extrapolated from people who have been medically managed.
Other considerations	There were no other considerations.

Recommendation	**74. Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone percutaneous coronary intervention (PCI) with bare-metal or drug-eluting stents and who otherwise need anticoagulation. [new 2013]**
Relative values of different outcomes	The GDG identified mortality and quality of life as critical outcomes. Reinfarction, stroke, and rehospitalisation were considered important outcomes. Major and minor bleeding were considered relevant to the review. No evidence on quality of life was identified. The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI in people also needing anticoagulation. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the patient and society, were stroke, reinfarction and revascularization, stroke (embolic or haemorrhagic) or systemic embolism being of particular concern in this population needing anticoagulation. Rehospitalisation was considered a relevant outcome, given its economic impact, and its impact on quality of life. The adverse effects of treatment, particularly bleeding, which impact on both mortality and morbidity, as well as quality of life (which was not always measured) were particularly important in this subpopulation.
Trade-off between clinical benefits and harms	The GDG discussed the potential benefits and risks of triple therapy (dual antiplatelet therapy in combination with warfarin) compared to dual therapy (warfarin plus single antiplatelet) in people with a pre-existing indication for anticoagulation who had undergone PCI with stent implantation following an MI.

	Evidence from an indirect population suggested that warfarin plus single antiplatelet therapy (warfarin plus clopidogrel) was more beneficial than triple therapy. Triple therapy increased the risk of all-cause mortality, reinfarction, stroke, major and minor bleeding, but not revascularisation. This was applicable to people who had received drug eluting and bare metal stents. Stent thrombosis is a side effect associated with stents. We found stent thrombosis was higher in those given the triple versus the dual therapy (3.2% versus 1.4%), although the difference was small. The GDG felt that this observation was likely to represent stent thrombosis in people who had needed to stop antithrombotic therapy because of bleeding complications. Thus, until further evidence is available there was no convincing evidence to recommend triple therapy for a short time in those who have a stent and are at a high risk of stent thrombosis. There was no evidence that triple therapy was beneficial at any time after PCI. The GDG agreed that the benefits associated with continued anticoagulation were likely to be greater than the benefits of giving dual antiplatelet therapy and discontinuing warfarin, so felt that in most people warfarin should continue. Given the risk of bleeding and other adverse outcomes (including the potential of an increase in the risk of stent thrombosis) associated with triple therapy, the GDG felt that triple therapy was undesirable. The data from the WOEST trial with clopidogrel were the only randomised data regarding anticoagulation with a single antiplatelet agent in people with stents after PCI. As the benefit in this study of using clopidogrel with warfarin rather than triple therapy were so large, and the benefit of clopidogrel in the prevention of stent thrombosis appears well established, the GDG felt that clopidogrel should be recommended with warfarin, rather than aspirin in people who have been stented. The GDG therefore recommended the combination of warfarin with clopidogrel in this group, as used in the WOEST study.
Economic considerations	No economic studies were identified. The unit costs of drugs were considered by the GDG. Treating people with aspirin, clopidogrel and warfarin would cost a maximum £5 per month and £60 per year when only the cost of drugs are considered. However, there are additional costs associated with the monitoring required in people treated with warfarin. However, the clinical evidence showed that dual therapy (warfarin plus clopidogrel) was more effective than triple therapy (warfarin plus clopidogrel and aspirin) in this population. From an economic perspective this lead to the conclusion that triple therapy is dominated (that is it is more costly and less effective) by dual therapy and therefore dual therapy is the optimal choice. The GDG considered that the improved outcomes associated with dual therapy meant that the costs are likely to be outweighed by the benefits.
Quality of evidence	Overall the quality of evidence was graded as low to very low. The GDG agreed that because the data is from an RCT, evidence from cohort studies would not be considered for this population. Although the population had less than 75% people who had an MI, all people needed revascularisation and had coronary heart disease. All people had a drug eluting or bare metal stent implanted. The majority of people had atrial fibrillation as their pre-existing indication for anticoagulation. The GDG noted that although the study was not blinded, it is difficult to do so with warfarin treatment. It was also acknowledged that the primary aim of the study was to identify bleeding risk as opposed to mortality, although there was a large

	difference in total mortality. No evidence was identified for prasugrel or ticagrelor in combination with anticoagulation. However, the GDG felt that it was likely that any increase in major bleeding with anticoagulation would be further increased if these new antiplatelet agents were added, given the evidence for increased bleeding associated with their use in combination with aspirin in other studies.
Other considerations	The GDG highlighted that it was important to consider the manufacturer's instructions for stents when considering treatment in people who have received stents following an MI and who have a pre-existing indication for anticoagulation. The GDG felt that this was an area in which further research would be beneficial, to clarify whether triple therapy (warfarin, clopidogrel and aspirin) was more effective than warfarin and clopidogrel alone in this population. Therefore, a research recommendation was developed for an RCT on triple therapy versus warfarin and clopidogrel alone (see Appendix N).

Recommendation	**75. Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. [new 2013]**
Relative values of different outcomes	The GDG identified mortality and quality of life as critical outcomes. Reinfarction, stroke, and rehospitalisation were considered important outcomes. Major and minor bleeding were considered relevant to the review. No evidence on quality of life was identified. The adverse effects of treatment, particularly bleeding, which impact on both mortality and morbidity, as well as quality of life were particularly important in this population. Stroke and other manifestations of embolism were also important.
Trade-off between clinical benefits and harms	No data were identified on people who have a sensitivity to aspirin. However, data was identified from an RCT that showed warfarin and clopidogrel was more effective than warfarin plus clopidogrel plus aspirin in the reduction of all-cause mortality, cardiac mortality, reinfarction, stroke, major and minor bleeding (but not stroke) in a population who have an indication for anticoagulation and who have coronary heart disease. Given that people with a sensitivity to aspirin cannot be offered aspirin, studies treating people with warfarin and aspirin were not considered relevant. The GDG therefore felt more confident recommending the combination of clopidogrel plus warfarin based on the evidence provided by the RCT and recommended that clopidogrel should be offered with warfarin in place of aspirin in those who have sensitivity to the use of aspirin.
Economic considerations	No economic studies were identified.
Quality of evidence	Overall the quality of evidence was graded as low to very low. The GDG agreed that because there is some data from an RCT, evidence from cohort studies will not be prioritised when developing the recommendation for this population. Although the population had less than 75% people who had an MI, all people needed revascularisation and had coronary heart disease. For this reason, other indirect evidence was not considered for this recommendation.

	However, the RCT data were on a clinically relevant population since all people had a drug eluting or bare metal stent implanted. The majority of people had atrial fibrillation as their pre-existing indication for anticoagulation. The GDG noted that although the study was not blinded, it is difficult to do so with warfarin treatment. It was also acknowledged that the primary aim of the study was to identify bleeding risk as opposed to mortality.
Other considerations	There are no other considerations.

Recommendation	**76. Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. [new 2013]**
Relative values of different outcomes	The GDG identified mortality and quality of life as critical outcomes. Reinfarction, stroke, and rehospitalisation were considered important outcomes. Major and minor bleeding were considered relevant to the review. No evidence on quality of life was identified. The GDG felt that when considering the appropriateness of adding new anticoagulants to dual therapy, it was particularly important to consider the type of stent, risk of bleeding, risk of embolism and the risk of cerebral bleeding.
Trade-off between clinical benefits and harms	For people presenting with an acute coronary syndrome who are already on the new oral anticoagulants for a pre-exisiting condition such as atrial fibrillation, the effects of adding dual antiplatelet therapy to treat their MI needed to be investigated. Because anticoagulants and antiplatets was the combination considered, the effect of anticoagulants on their own was not reviewed. The effects of the new oral anticoagulants, dabigatran, rivaroxaban and apixaban varied and were dependent upon the dose and drug in use. All the evidence identified was downgraded, as the studies were performed in a post MI population who did not have an indication for anticoagulation. There was no benefit for apixaban plus dual antiplatelet therapy on all-cause mortality, cardiac mortality, reinfarction, and stroke compared with dual antiplatelet therapy. However, there was an increase in the risk of major bleeding. There was a reduced risk for all-cause mortality (50, 75, 110, 150 mg 2xday dose), cardiac mortality (110, 150 mg 2xday) and stroke (50, 75, 110, 150 mg 2xday dose) in response to dabigatran plus dual antiplatelet therapy compared with dual antiplatelet therapy alone. Conversely, there was an increased risk of reinfarction (50, 75, 110, 150 mg 2xday dose) and minor bleeding (50, 75, 110, 150 mg 2xday dose). There was no effect on the risk of major bleeding (50, 75, 110, 150 mg 2xday dose). Trials comparing different doses of rivaroxaban plus antiplatelet therapy with antiplatelet therapy alone found a reduced risk for all-cause mortality (5mg/d), cardiac mortality (5mg/d) and reinfarction (10mg/d) in response to rivaroxaban plus dual antiplatelet therapy compared with dual antiplatet therapy alone. In contrast, there was an increased risk for major bleeding (5, 10, 15 and 20mg/d) and mild bleeding (10,15 and 20mg/d) in response to rivaroxaban plus dual antiplatelet

	therapy compared with dual antiplatet therapy alone. There was no effect on the risk of stroke. In the ROCKET-AF trial directly comparing two different anticoagulants, rivaroxaban versus warfarin on a background of antiplatelet therapy there was an increased risk for major and minor bleeding in those taking rivaroxaban plus dual antiplatelet compared with those taking warfarin plus antiplatelet. The GDG did not feel that there was sufficient data identified to recommend the use of new oral anticoagulants, given the varied increases in reinfarction, major and minor bleeding for different agents at different doses. Furthermore, the dose used in some studies was lower than would be used for the majority of indications for anticoagulation and therefore, it was not possible to extrapolate the results. Nor were the studies designed to answer the review question, so the population was not direct since the patients did not have an indication for anticoagulation. The GDG felt that the use of new oral anticoagulant agents may be appropriate in those who are intolerant to warfarin, however, no evidence was identified to support this.
Economic considerations	No economic studies were identified. The unit costs of drugs were considered by the GDG to aid economic considerations. Given the high unit costs associated with new oral anticoagulants, the GDG concluded that these drugs are unlikely to be cost effective when used in combination with dual antiplatelet therapy in people who have had an MI as they are associated with an increase in risk of bleeding and no sufficient evidence was found on their additional effectiveness compared to dual antiplatelet therapy alone.
Quality of evidence	Overall, the evidence for the new oral anticoagulants was graded as very low. A major reason for this was the dose used in the studies. The rivaroxaban dose at 5mg/d and 10mg/d were too low for people with atrial fibrillation, and moderate dose dabigatran (but not 50, 75 mg 2xday dose) is relevant but showed a large increase in the risk of bleeding when combined with antiplatelet agents. The apxiaban and 15 and 20mg/d dose of rivaroxaban were appropriate for people with atrial fibrillation. However, the apixaban trial stopped early because of the high risk of bleeding and it was unclear in the rivaroxaban study how many people were taking double the daily dose. The quality of the evidence was also downgraded because the populations were indirect. Although all studies included people who had an MI, none of them had an additional indication for anticoagulation. The results also showed serious imprecision. The ROCKET-AF study that compared rivaroxaban with warfarin was very low quality evidence as it was a subgroup analysis from the larger trial in only those who had an MI. There is therefore a risk that the groups were not matched at baseline. It was unclear when people had an MI and the results showed some imprecision. Additionally, it was unclear in this subgroup what antiplatelet therapy the patients were taking and at what dose. From the larger trial sample 34-36% were taking aspirin but patients could also be on dual-antiplatelet therapy (aspirin and a thienopyridine) if they were undergoing a cardiovascular intervention; with the post MI subgroup included in this review it is very likely. No evidence was identified for prasugrel or ticagrelor.

	No evidence was available on the use of new oral anticoagulants with antiplatelet therapy for people who have a mechanical heart valve prosthesis or recurrent pulmonary embolism. The GDG felt that as no evidence was available suggesting benefit from new oral anticoagulants in these people, it was appropriate to recommend they not be used in combination with dual antiplatelet therapy, given the potential risk of bleeding.
Other considerations	NICE TA532 'Acute coronary syndrome – rivaroxaban' is currently in development and considers the use of rivaroxaban in those with acute coronary syndrome without an additional indication for anticoagulation.

Recommendation	**77. Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it. [new 2013]**
Relative values of different outcomes	The GDG identified mortality and quality of life as critical outcomes. Reinfarction, stroke, and rehospitalisation were considered important outcomes. Major and minor bleeding were considered relevant to the review. No evidence on quality of life was identified. The GDG felt that when considering the appropriateness of adding new acting anticoagulants to dual therapy, it was particularly important to consider the type of stent, risk of bleeding, risk of embolism and the risk of cerebral bleeding.
Trade-off between clinical benefits and harms	The evidence on the new oral anticoagulants has been thoroughly discussed in the discussion on "Do not offer a new oral anticoagulant". In summary, the studies showed that compared with clopidogrel plus aspirin alone, triple therapy (with dabigatran, rivarxoaban, apixaban) is associated with a decreased risk of clinical outcomes such as mortality, but an increased risk of bleeding. In contrast, there was an increased risk for major bleeding (high and lose dose5, 10, 15 and 20mg/d) and mild bleeding (high dose10,15 and 20mg/d) in response to rivaroxaban plus dual antiplatelet therapy compared with dual antiplatelet therapy alone. Given this risk and the limitations with the data, there is currently insufficient evidence to recommend new oral anticoagulants in people who otherwise need anticoagulation and who have an MI. Warfarin was associated with a reduced risk of bleeding compared with rivaroxaban. The evidence on warfarin and antiplatelets has been discussed in the section on "offering an anticoagulant and aspirin for people who have been medically managed". In summary the studies showed that warfarin plus aspirin is more effective than aspirin alone on the risk of all-cause mortality, but it is associated with an increased risk of bleeding. The GDG agreed the data supports the use of warfarin over new oral anticoagulants and recommendations were made to reflect this. The GDG felt that given this, and the possible risks associated with the use of new oral anticoagulants in this population, healthcare professionals should consider discontinuing treatment with these agents and use warfarin for anticoagulation. The GDG highlighted that any discontinuation of treatment should only be conducted following discussion with the patient and that there may be specific indications for

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	which it is appropriate to continue treatment (for example, people who are intolerant to warfarin).
Economic considerations	No economic studies were identified. The unit costs of drugs were considered by the GDG to aid economic considerations. Given the high unit costs associated with new oral anticoagulants, the GDG concluded that these drugs are unlikely to be cost effective when used in combination with dual antiplatelet therapy in people who have had an MI as they are associated with an increase in risk of bleeding and no sufficient evidence was found on their additional effectiveness compared to dual antiplatelet therapy alone..
Quality of evidence	Overall, the quality of evidence was graded as low. The data on new oral anticoagulants was generally low quality (for more detail see previous discussion on the use of new oral anticoagulants). There were concerns about the relevance of the data since the doses were not always appropriate for peope who need anticoagulation and the participants did not have an indication for anticoagulation. The quality of the evidence was also downgraded because the populations were indirect. Although all studies included people who had an MI, none of them had an additional indication for anticoagulation. The data on warfarin was also low quality (for more detail see previous discussion on warfarin and aspirin). The data was either non-randomised or the population was indirect since either 1 group or both treatment groups did not have an indication for anticoagulants. There was often insufficient detail on the methods of randomisation or it was unclear whether allocation concealment was performed. No evidence was available on the use of new oral anticoagulants with antiplatelet therapy for people who have a mechanical heart valve prosthesis or recurrent pulmonary embolism. The GDG felt that as no evidence was available suggesting benefit from new oral anticoagulants in these people, it was appropriate to recommend they not be used in combination with dual antiplatelet therapy, given the potential risk of bleeding.
Other considerations	There were no other considerations.

Recommendation	**78. Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. [new 2013]**
Relative values of different outcomes	The GDG identified mortality and quality of life as critical outcomes. Reinfarction, stroke, and rehospitalisation were considered important outcomes. Major and minor bleeding were considered relevant to the review. No evidence on quality of life was identified. The GDG felt that when considering the appropriateness of triple therapy, it was particularly important to consider the type of stent, risk of bleeding, risk of embolism and the risk of cerebral bleeding.
Trade-off between clinical benefits and harms	For people presenting with an acute coronary syndrome who are already on the new oral anticoagulants for a pre-exisiting condition such as atrial fibrillation, the effects of adding dual antiplatelet therapy to treat their MI needed to be investigated. Because anticoagulants and antiplatets was the combination we were interested in, the effect of prasugrel or ticagrelor on their own was not considered.

	No evidence was identified on the combination of prasugrel or ticagrelor with warfarin. The GDG noted that there were specific situations in which the benefits of using prasugrel and ticagrelor would outweigh any potential harms, particularly in people who have developed stent thrombosis while taking clopidogrel. As such, the GDG developed a recommendation to suggest that warfarin should not be used routinely in combination with prasugrel or ticagrelor for people who had an MI with an additional indication for anticoagulation, using informal consensus of the GDG.
Economic considerations	No economic studies were identified. The unit costs of drugs were presented to the GDG to aid economic considerations. Given the high unit costs associated with prasugrel and ticagrelor and the absence of any clinical evidence on these drugs in combination with warfarin in people who have had an MI, the GDG decided not to recommend these drugs.
Quality of evidence	No evidence was identified for prasugrel or ticagrelor. This recommendation was made using informal consensus of the GDG.
Other considerations	Recommendations of the use of prasugrel and ticagrelor for people who had an MI can be found in NICE Technology appraisal 182 and NICE Technology appraisal 236.

Recommendation	**79. After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following:** • **the indication for anticoagulation** • **thromboembolic risk** • **bleeding risk** • **cardiovascular risk** • **the person's wishes. [new 2013]**
Relative values of different outcomes	The GDG identified mortality and quality of life as critical outcomes. Reinfarction, stroke, and rehospitalisation were considered important outcomes. Major and minor bleeding were considered relevant to the review. No evidence on quality of life was identified. The GDG felt that when considering the appropriateness of anticoagulant and antiplatelet therapy it was particularly important to consider the type of stent, risk of bleeding, risk of embolism and the risk of cerebral bleeding.
Trade-off between clinical benefits and harms	The GDG discussed the potential benefits and risks of dual antiplatelet therapy in those with a pre-existing indication for anticoagulation. No evidence was available after 12 months of treatment. After 12 months, all people who had an MI who do not have an indication for anticoagulation would have completed treatment with clopidogrel and be recommended indefinite treatment with aspirin. The GDG felt that, in those with an indication for anticoagulation, it was important to reassess continuing anti-platelet therapy at 12 months. The GDG felt that this assessment should include the indication for anticoagulation, the risks of bleeding, an assessment of cardiovascular and embolic risk and the wishes of the person. The GDG did not feel it was possible to provide a general recommendation regarding the appropriate treatment in this group, and that it would vary according to the assessment outlined.

	The GDG therefore used informal consensus to develop the recommendation.
Economic considerations	No economic studies were identified. The unit costs of drugs were considered by the GDG. Treating people with aspirin, clopidogrel and warfarin would cost a maximum £5 per month and £60 per year when only the cost of drugs are considered. However, there are additional costs associated with the monitoring required in people treated with warfarin. However, the clinical evidence showed that dual therapy (warfarin plus clopidogrel) was more effective than triple therapy (warfarin plus clopidogrel and aspirin). From an economic perspective this lead to the conclusion that triple therapy is dominated (that is it is more costly and less effective) by dual therapy and therefore dual therapy is the optimal choice. Assessment of the patient's ongoing indication for anticoagulation, thromboembolic risk, bleeding risk and risk of a further coronary event will take a small amount of staff time but this is offset by the health gains by ensuring people are on the right treatment for their individual circumstances.
Quality of evidence	No evidence was identified for treatment over 12 months. The GDG therefore used informal consensus to develop the recommendation.
Other considerations	There are no other considerations.

7.5 Beta-blockers

Beta-blocker therapy plays a major role in the treatment of cardiovascular diseases. The benefits of and clinical indications for beta-blockers have been defined in many cardiovascular conditions. Beta-blockers have been used for many years for their anti-ischaemic, anti-arrhythmic and anti-hypertensive properties. More recently, the benefit of beta adreno-receptor blockade was also established in people with heart failure secondary to left ventricular systolic dysfunction.

The use of beta-blockers is well established in the management of MI and in secondary prevention. They are used to reduce heart rate, limit myocardial oxygen demand and reduce the incidence of arrhythmias and cardiac death. Like ACE inhibitors, the exact duration to continue beta-blockers in those with normal left ventricular function after an MI has not been determined. With most beta-blockers being available as generic formulations, best practice is to choose an agent that is licensed following an MI and for the treatment of heart failure, which enables suitable dose titrations to be made at follow-up clinics.

Although relative contraindications once may have been thought to preclude the use of beta-blocker in some people, it is important to emphasise that new evidence may suggest that the benefits of beta-blockers in reducing reinfarction and mortality could outweigh the risk of adverse events, even in people with insulin dependent diabetes mellitus; chronic obstructive pulmonary disease; severe peripheral vascular disease; and with P-R interval up to 0.24 seconds.

However, the optimal timing of initiation of beta-blockers in secondary prevention is unclear. In the clinical setting, the delay to initiation of beta-blockers may vary from 2 hours to up to 28 days. With changes in acute management since publication of the previous guideline, CG48, it has become increasingly important to identify the optimal time for beta-blocker initiation, given reduced inpatient stays associated with primary PCI. Furthermore, the burden of treatment placed upon a person following an MI means that it is important for treatment duration to be carefully considered.

This update of the previous guideline,CG48, therefore aims to identify whether beta-blocker therapy is still clinically effective in a population of people who have undergone modern reperfusion

therapies and if so, what is the optimal time for initiation of therapy. The guideline update also considers the optimal duration of beta-blocker therapy in those who have an MI.

7.5.1 Clinical effectiveness of beta-blockers and optimal duration of therapy

7.5.1.1 What is the clinical and cost effectiveness of adding a beta-blocker versus placebo to improve outcome in people after an MI i) with and ii) without left ventricular dysfunction, and is there an optimal duration?

For full details see review protocol in Appendix C.

7.5.1.2 Clinical evidence

Sixty-five studies were included in this review. Evidence from these are summarised in the clinical GRADE evidence profile below

Table 106 to Table 108.

See also the study selection flow chart in Appendix D, forest plots in Appendix I, evidence tables in Appendix G and exclusion list in Appendix J.

The previous guideline, CG48, provided recommendations on people who had an MI (within 72 hours on onset of symptoms) and those who had an MI in the past (more than 12 months ago). The recommendations also distinguished between those who have left ventricular systolic dysfunction (LVSD) and those without left ventricular systolic dysfunction. Evidence was extracted from a systemic review on beta-blockers versus placebo (Freemantle et al. 1999) and a large RCT by Chen et al 2005 (COMMIT).[90,151] CG48 recommended that early after an MI, all people who had an MI are given treatment with a beta-blocker indefinitely, regardless of whether they have LVSD. For those who had an MI in the past, CG48 recommended treatment with beta-blockers for those with LVSD but not for those who have normal LV function.

This 2013 update has therefore updated these recommendations, as most of the evidence used in CG48 was derived from either old studies that pre-date modern reperfusion or medical therapy, or from heart failure trials where the data has been extrapolated from people with and without coronary heart disease.

In this review, the studies were used to address 2 questions: 1) what is the clinical and cost effectiveness of beta-blockers versus placebo and 2) is there an optimal duration to prescribe beta-blockers? These questions were considered for:

- people who had an MI who had treatment initiated within 72 hours,
- who had an MI who had treatment initiated between 72 hours and 12 months of the MI,
- those who had an MI at some point in the past (over 12 months previously).

For the second question, no direct study designs were found comparing the effects of different durations of the same beta-blocker (that is 2 months versus 12 months), therefore results from indirect study designs that compared beta-blockers with placebo over different durations of follow-up were used.

The results from beta-blocker versus placebo studies were separated into distinct follow-up time periods wherever possible, that is 0 to 6weeks, over 6 weeks to 12 months, over 12 months to 24 months. If the results could not be separated into distinct time periods, the data was presented according to when the follow-up was recorded, that is overlapping time periods of: 0 to 6 weeks, 0 to 6 months,0 to 12 months. The limitation of this is that it is unknown when the event occurred, for instance the number of deaths reported at 12 months could have occurred in the first 6 weeks. Where data at different time periods were presented, only the longest follow-up result was included.

Studies were excluded if they used beta-blockers not licensed in the UK or if they had more than 30% people with heart failure in their study population.

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Table 103: Summary of included studies: beta-blocker treatment in people following an MI (people who were initated within 72 hours of an MI).

A systematic review on this topic was published in the British Medical Journal (BMJ). Where possible, data from relevant papers were directly extracted from this paper (and referred to as BMJ in the second column). For the remaing papers a full extractration was performed.

	Study	Data was extracted from BMJ or full extraction	Intervention/ comparison	Treatment	Population	Strata LVSD, Unselected, Without LVSD With COPD, No COPD, Unselected	Outcomes	Follow-up	Comments
1.	Anon 1986[7] ISI-I	BMJ	Atenolol	Unclear	MI (less than 12 hours since onset of symptoms, mean 5 hours) Age: unclear Ethnicity: Unclear	Unclear	• All-cause mortality • Reinfarction (non-fatal)	1 year	Blinding: No Allocation concealment: Unclear Loss to follow-up: Unclear
2.	Anon 1987A[2] CPRG	BMJ	Oxprenolol	Unclear	MI (less than 72hours since onset of symptoms) Age: 40-69years	Without LVSD (excluded people with left ventricular failure)	• All-cause mortality • Cardiac death • Reinfarction • Adverse events	8 weeks	Blinding: Double Allocation concealment: Unclear Loss to follow-up:0%

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					Ethnicity: unclear				
					HF: excluded	No COPD. Excluded those with obstructive airway disease.			
3.	Anon 1985[6] MIAMI	BMJ	Metoprolol	Unclear	MI (within 72 hours of onset of symptoms) Age: less than 75 years, mean 60 Ethnicity: unclear	Normal LVSD (excluded people with left ventricular failure)	• All-cause mortality • Bradycardia	15 days	Blinding: Double Allocation concealment: Yes Loss to follow-up: 0.4%
					Unclear: BMJ stated 23% but could not detect this number	No COPD. Excluded those with severe COPD. 51% were smokers			
4.	Anon 1966 (Multicentre) (Stephen) [1]	BMJ	Propranolol	Unclear	MI (less than 24 to 48 hours of onset of symptoms)	Unclear	• All-cause mortality • Sudden death • Bradycardia	28 days	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 1%

					Age: 27-83, average 58 years Ethnicity: unclear		• Adverse event		
					HF: 11%	No COPD. Excluded if evidence of bronchospasm or clinical history of bronchial asthma			
5.	Anon 1989[10] TIMI-II	BMJ	Metoprolol	Unclear	MI (timing unclear) Age :unclear Ethnicity: unclear	Unclear Unclear	• All-cause mortality • Reinfarction	5 days	Blinding: No Allocation concealment: Unclear Loss to follow-up: 3.5%
					HF: Unclear				
6.	Azancot 1982[28,28]	BMJ	Acebutolol	Unclear	MI (less than 24 hours since onset of symptoms) Age: 29-63years Ethnicity: unclear	Unselected: Mean EF 44%	• All-cause mortality	1 month	Blinding: No Allocation concealment: Unclear Loss to follow-up: 0%

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					HF=0% 100% Killip Class I	Unclear			
7.	Baber 1980[29,29]	Full extraction	Propranolol 40mg three times daily versus placebo for mean duration around 170 days	Unclear	MI (2-14 days since onset of symptoms, mean 8.5 days) Age: mean 55years Ethnicity: unclear	Without LVSD Excluded those with AV block greater than first degree	• All-cause mortality • Cardiac mortality • Reinfarction • Adverse reaction	9 months	Trial planned to include 2000 participants but terminated prematurely due to no effect
					HF:0% excluded those with HF	No COPD. Excluded those with bronchospasm			
8.	Barber 1967[35,35]	Full extraction	Propranolol 40mg 6-hourly versus placebo for 28 days	Unclear	MI (less than 24 hours since the onset of symptoms) Age: less than and over 60 years Ethnicity: unclear	Without LVSD (no participants with heart rate less than 60BPM, whether due to sinus bradycardia or AV block).	• All-cause mortality	4 weeks	Underpowered; trial terminated due to no effect; unclear if blinded
					Unclear	Unselected			

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						COPD. Asthma or bronchial spasm was regarded as contraindications. They were electrocardiographically monitored in the first 48 hours (suggests that they were included)			
9.	Basu 1997[37,37]	BMJ	Carvedilol 12.5mg bd versus placebo for 6 months	Unclear - thrombolysis	MI (less than 24 hours since the onset of symptoms) Age: mean 62 years Ethnicity: unclear	Unselected (mix of without LVSD and LVSD – 49/146 People had EF less than 42%). LVSD - subgroup analysis of those with LV less than 45%	• All-cause mortality • Reinfarction • Adverse events • Dizziness	6 months	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 0% randomisation/ allocation concealment not stated
					HF:0% excluded.	Unclear COPD.			

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					Excluded people in Killip class IV heart failure	Smokers: 60%			
10.	Campbell 1984[79,79]	BMJ	Timolol	Unclear	Unclear	Unclear Unclear	• All-cause mortality	In hospital	Blinding: Unclear Allocation concealment: Unclear Loss to follow-up: 0%
11.	Chen 2005[86,90] COMMIT	Full extraction (in CG48)	Metoprolol	Medical treatment (excluded those with PCI planned)	MI (less than 16hours since the onset of symptoms) 93% had STEMI or bundle branch block Age: less then 60 to over70, mean 62 Ethnicity: Asian	Unselected LV function (CG48)	• All-cause mortality • Reinfarction (fatal and nonfatal) • Stroke • Adverse events • bradycardia	4 weeks	
					HF: unclear % evidence of moderate heart failure (Killip II or	Unclear			

Update 2013

					III)				
12.	Clausen 1966[95,95]	BMJ	Propranolol	Unclear	MI (less than 24 hours since the onset of symptoms) Age: 39 -82, mean 59 years Ethnicity: unclear	Unclear	• All-cause mortality	22 days	Blinding: Unclear Allocation concealment: Unclear Loss to follow-up: 0% People discharged 28 days after admission Note: All-cause mortality numbers included are from the people with a verified MI. These numbers are therefore slightly different from the BMJ numbers since they reported all verified and non-verified patient deaths.
					HF:0% excluded	No COPD. Only people with bronchial asthma were excluded			
13.	Curtis 1991[106,106]	BMJ	Propranolol	Unclear	MI (less than 30 minutes since onset of symptoms) Age: unclear Ethnicity: unclear	Unclear	• All-cause mortality	3-4 days	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 0%
					HF:0% excluded	Unclear			
14.	Federman	BMJ	Timolol	Unclear	MI (less	Without	• All-cause	28 days	Blinding: Unclear

	1984				than 6hours since onset of symptoms, mean 3.5 hours) Age less than 75 years Ethnicity: unclear	LVSD. Excluded those with left ventricular failure	mortality		Allocation concealment: Unclear Loss to follow-up: 0%
						Unclear			
15.	Fuccella 1968	BMJ	Oxprenolol	Unclear	Unclear	Unclear	• All-cause mortality	21 days	Blinding: Unclear Allocation concealment: Unclear Loss to follow-up: 14%
						Unclear			
16.	Gupta 1984[179,180]	BMJ	Propranolol	Unclear	MI (less than 72 hours since onset of symptoms) Age: unclear Ethnicity: unclear	Unclear	• All-cause mortality	72 hours	Blinding: No Allocation concealment: Unclear Loss to follow-up: Unclear
					HF: unclear	Unclear			
17.	Hansen 1984[183,183]	Full extraction	Alprenolol	Unclear	MI (less than 72 hours since onset of symptoms)	Unselected LV function: some people had left ventricular failure	• All-cause mortality • Bradycardia	28 days plus 12 months	No power calculations. No participants were lost to follow-up.

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					Mean age:63 years Ethnicity: Unclear				
					Unclear	No COPD. Excluded those with pulmonary oedema over2 hours of treatment,			
18.	Heber 1987[189,189]	BMJ	Labetalol	Unclear	MI (unclear how long after initiated treatment) Age: less than 75 years, mean 60 Ethnicity: unclear	Unselected LV function: EF mean: 25 or 50 EF. People were excluded if had severe left ventricular failure.	• All-cause mortality	In hospital and 1 year	Blinding: No Allocation concealment: Unclear Loss to follow-up: Unclear
					HF%: 9%	No COPD: excluded those with a history of bronchiospasm or severe disease of the respiratory			

						system.			
19.	Hjalmarson 1981[194,194]	BMJ	Metoprolol	Medical (excluded those who had planned CABG)	MI (less than 72 hours from onset of symptoms) Age: 40-74 Ethnicity: unclear	Unclear	• Total morality • Bradycardia • Side effects	3 months	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 1.6%
					Excluded HF	No COPD: Excluded those with bronchial asthma			
20.	Hutton 1979[200,200]	BMJ	Propranolol	Unclear	Unclear Age: unclear Ethnicity: unclear	Unclear	• All-cause mortality	2 days	Blinding: Unclear Allocation concealment: Unclear Loss to follow-up: 0%
					HF: unclear	Unclear			
21.	Johansson 1980[207,207]	BMJ	Practolol then atenolol	Unclear	MI (on admission) Age: 47-75 years Ethnicity: unclear	Unselected (P: n=3/45 and BB: 2/40 had left ventricular failure)	• All-cause mortality (total and distinct)	11 days (Hospital) and 6 months	Blinding: Single Allocation concealment: No Loss to follow-up: Unclear
					HF%: unclear	Unclear. Excluded if pulmonary edema			
22.	Kaul	BMJ	Propranolol	Unclear	MI (less	Unselected	• All-cause	6 months	Blinding: Double

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	1988[227,227]				than 24 hours since onset of symptoms) Age: less than 60 to 69 years Ethnicity: unclear	LV function Placebo 53% BB 69% (range 30 to 85)	mortality • Reinfarction (non-fatal) • Side effects	(3-9 months)	Allocation concealment: Unclear Loss to follow-up: 0%
					HF: unclear	No COPD. Excluded if coronary obstructive pulmonary disease			
	Kahler 1968[220,220]	BMJ	Propranolol	Unclear	MI (less than 6hours since onset of symptoms) Age: unclear Ethnicity: Unclear	Unclear	• All-cause mortality • Sudden death • Sinus bradycardia	Up to 35 days	Blinding: Double Allocation concealment: Unclear Loss to follow-up: Unclear
					HF:0% Excluded	No COPD. Excluded those with severe chronic pulmonary disease			
23.	Ledwich	BMJ	Propranolol	Unclear	MI (less	Unclear	• All-cause	7 days	Blinding: Double

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	1968[247,247]				than 48 hours since onset of symptoms) Age:40-80 years Ethnicity: unclear		mortality		Allocation concealment: Unclear Loss to follow-up: Unclear
					HF: unclear	Unclear			
24.	Lloyd 1988[256,256]	BMJ	Sotalol	Unclear	MI (less than 12 hours since onset of symptoms) Age: 34-79, mean 55 years Ethnicity: unclear	Unselected LV Function (Mean 49%, range 21-72)	• All-cause mortality	72 hours	Blinding: No Allocation concealment: Unclear Loss to follow-up: 0%
					HF: unclear	No COPD. Excluded those with severe chronic obstructive airway disease.			
25.	Lombard 1979[257,257]	BMJ	Oxprenolol	Unclear	MI (less than 24 hours since onset of	Unclear	• All-cause mortality • Reinfarction	20 days	Blinding: Double Allocation concealment: Unclear Loss to follow-up: Unclear

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					symptoms) Age:35-79 years Ethnicity: unclear		(fatal) • Bradycardia		
					HF:0% Excluded	No COPD. Excluded those with bronchospasm			
26.	Mueller 1980[299,299]	BMJ	Propranolol	Unclear	MI (less than 13 hours since onset of symptoms) Age:41-75, mean 57 years Ethnicity: unclear	Unclear	• All-cause mortality	To discharge	Blinding: Double Allocation concealment: Unclear Loss to follow-up: Unclear
					HF: unclear.	No COPD Excluded those with spastic lung disease			
27.	Norris 1978[327,328]	BMJ	Propranolol	Unclear	MI (less than 4 hours since onset of symptoms)	Without LVSD	• All-cause mortality	To discharge	Blinding: No Allocation concealment: Unclear Loss to follow-up: 0%

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					Age: 32-65, mean 52 years Ethnicity: unclear				
					HF: Unclear	No COPD. Excluded those with bronchial asthma			
28.	Norris 1968[327,327]	BMJ	Propranolol 20mg 4 times a day versus placebo, started within 3 days of MI, for 3 weeks	Unclear	MI (less than 3days since onset of symptoms) Age: unclear Ethnicity: unclear	Unclear	• All-cause mortality • Bradycardia	3 weeks	short follow up of only 3 weeks
					HF:0% Excluded	Unclear. Six months after the trial participants were excluded if had acute pulmonary oedema.			
29.	Norris 1984[326,327]	BMJ	Propranolol	Unclear	MI (less than 4 hours,	Unclear	• All-cause mortality	To discharge	

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					mean 2.8hours since onset of symptoms) Age: 55± 9 years Ethnicity: unclear		• CV death • Stroke		
					HF: 0%, excluded those who were getting treatment for cardiac failure.	No COPD. Excluded those with a history of asthma or bronchitis requiring bronchodilators, and the presence of dyspnoea or widespread chest rales.			
30.	Olsson 1985[339,339] REHNQVIST	BMJ	Metoprolol	Unclear how many. People were referred to CABG if unresponsive to optimal medical treatment	MI (less than 48 hours since onset of symptoms) Age: 60 ± 7 years Ethnicity: unclear	Unclear	• All-cause mortality • CV death • reinfarction (non-fatal) • Stroke • Adverse events • Bradycardia • Nightmares • Impotence	36 months	Blinding: Unclear Allocation concealment: Unclear Loss to follow-up: 0%

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					HF: 0% excluded	No COPD. Excluded those with obstructive pulmonary disease	• Fatigue		
31.	Owensby 1984	BMJ	Pindolol	Unclear	MI (less than 12 hours since onset of symptoms) Age: unclear Ethnicity: unclear	Unclear	• All-cause mortality	3 days	Blinding: No Allocation concealment: No Loss to follow-up: Unclear
					HF: Unclear	Unclear			
32.	Peter 1978[352,352]	BMJ	Propranolol	Unclear	MI (less than 12 hours since onset of symptoms) Age: 37-68 years Ethnicity: unclear	Unclear	• All-cause mortality • Bradyrrhythmia • Reinfarction	In hospital	Blinding: No Allocation concealment: Unclear Loss to follow-up: 0%
					HF: Unclear	No COPD. Excluded those if X-ray showed interstitial oedema or pulmonary			

Update 2013

						oedema; pulmonary venous congestion but no oedema			
33.	Pitt 1976[368,368]	BMJ	Propranolol	Unclear	MI (less than 24 hours since onset of symptoms) Age: unclear Ethnicity: unclear	Unclear	• All-cause mortality	14 days	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 0%
					HF: Unclear	Unclear			
34.	Ranganathan 1988[374,374]	BMJ	Timolol	Unclear	MI (less than 24 hours since onset of symptoms) Age: 30-79 years Ethnicity: unclear	Unclear	• All-cause mortality • Sinus bradycardia (<40bpm) • Fatigue • Dizziness	28 days	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 2%
					HF: unclear %excluded Killip class III or IV	No COPD. Excluded those with known bronchospasm or clinically			

Update 2013

						significant chronic obstructive pulmonary disease			
	Roberts 1984[387,387]	BMJ	Propranolol	Unclear (excluded if they had undergone major surgery)	MI (8.5hours since onset of symptoms) Age:less than 70 years Ethnicity; unclear HF:unclear % excluded if Killip class III or IV 4.9% had HF in last 3 weeks	Unselected LV function: Mean LVEF: 49% Unclear	• All-cause mortality	36 months	Blinding: Single Allocation concealment: Unclear Loss to follow-up: 0.2%
35.	Rehnquist 1980[383,383]	BMJ	Metropolol	Unclear	HF: Unclear Age: 60 ± 7 years Ethnicity: unclear HF: 0% excluded	Unclear Unclear	• All-cause mortality	12 months	Blinding: Unclear Allocation concealment: Unclear Loss to follow-up: 0%
36.	Roque	BMJ	Timolol,	Medical	MI	Without	• All-cause	1 months,	Study not powered to assess

	1987[391,391]		5.5mg IV, started within 6 hours of onset of pain, then 10mg orally every 12 hours for 1 month.	treatment Excluded patients if needed coronary surgery.	Age: 52 ± 10 years Ethnicity: unclear HF: Unclear	LVSD People were excluded because of left ventricular failure. Unselected. People who had bronchospasm requiring treatment stopped treatment but were included in final analysis.	mortality	24months	mortality. Blinding: Double Allocation concealment: Unclear Loss to follow-up: Unclear
37.	Salathia 1985[396,396]	BMJ	Metoprolol	Unclear	MI (2-6hours since onset of symptoms) Age: Less than 65 years: 69% Over 65 years: 31% E thnicity:	Without LVSD People were excluded because of left ventricular failure	• All-cause mortality (distinct time periods) • Sudden death (distinct time periods) • CV death (distinct Time periods) • Adverse events 3months	Hospital, 3months, 12 months	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 0.5% Also compares early versus late initiation.

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					unclear				
					HF: Excluded those with congestive heart failure.	No COPD. Excluded those with clinical pulmonary oedema			
39.	Sloman 1967[412,412]	BMJ	Propranolol	Unclear	MI (range less than 4months to over 12months since onset of symptoms) Age: 25-69 years Ethnicity: unclear	Unclear	• All-cause mortality	To discharge	Blinding: No Allocation concealment: Unclear Loss to follow-up: Unclear
					HF: Unclear	No COPD Excluded those with a history of asthma			
40.	Tonkin 1981[446,446]	BMJ (abstract)	Timolol	Unclear	MI (less than 10 hours since onset of symptoms) Age: unclear Ethnicity:	Unclear	• Sudden death • Sinus bradycardia	In hospital	Blinding: Double Allocation concealment: Unclear Loss to follow-up: Unclear

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					unclear				
					HF: 0% excluded	No COPD. Excluded those with obstructive airway disease			
41.	UKCSG	BMJ	Timolol	Unclear	MI (less than 6hours since onset of symptoms) Age:less than 70 years Ethnicity: unclear	Without LVSD Excluded those with left ventricular failure.	• All-cause mortality	To discharge	Blinding: Double Allocation concealment: Unclear Loss to follow-up: Unclear Used numbers from review
					HF :Unclear	Unclear			
42.	Vandewerf 1995[451]	BMJ	Atenolol	Unclear	MI (less than 5 hours since onset of symptoms) Age: 39-70 years Ethnicity: unclear	Mean EF = 57% (Unselected)	• All-cause mortality	10-14 days	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 0%
					HF: Unclear	Unclear. 12-16% had basilar			

Update 2013

						pulmonary rales			
43.	Von Essen	BMJ	Metropolol	Unclear	MI (less than 24 hours since onset of symptoms) Age: 38-83 years	Unclear Unclear	• All-cause mortality	14 days	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 0%
44.	Wagstein 1976	BMJ (extracted from BMJ rather than original paper due to differences in data)	Metoprolol	Unclear	MI (3minutes since onset of symptoms) Age: mean 62±1.8 years Ethnicity: unclear	Without LVSD – no sign of left ventricular backward failure such as bilateral lung rales and/or severe dyspnoea	• All-cause mortality	1 week	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 0%
					HF: unclear	Unclear – included those with no sign lung rales and/or severe dyspnoea			
45.	Wilcox 1980[463,463]	BMJ	Propranolol versus placebo	Unclear	MI Age: less than 35 to over 65 years	Unclear	• All-cause mortality (distinct) • Fatigue (muscle)	6week, 1 year	Unclear if adequately powered; high withdrawal rate Blinding: Double Allocation concealment: Done

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					Ethnicity: unclear				Loss to follow-up: 0%
					HF: 0% excluded	No COPD. Excluded those with a history asthma			
46.	Wilcox 1980A[463,464]	BMJ (people who had an MI were extracted from original paper)	Oxprenolol	Unclear	MI Age: 35 – over 66 years Ethnicity: unclear	Unclear	• All-cause mortality • Bradycardia	6 weeks	Blinding: Double Allocation concealment: Yes Loss to follow-up: 0%
					HF:0% excluded	No COPD. Excluded those with a history asthma			
47.	Yoshitomi 2000[470,471]	Full extraction	Bisoprolol 5mg once daily, started within 24 hours of pain and continued for 1 year versus Imidapril 5mg once daily or placebo	PTCR– percutaneous transluminal coronary recanalisation 20-30% PTCA - - percutaneous translumin	MI (direct population) but NB Age: 61 ± 9 Ethnicity: unclear	Without LVSD = appears normal, LVEF greater than 40% .	• All-cause mortality • Reinfarction • CABG	1 year	Small number of participants; underpowered; not designed to assess the effects of early beta-blockers on long-term mortality or morbidity rates after MI.
					17/60 (28%) people with congestive heart failure	Unclear			

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				al coronary angioplasty 35-60% Primary stent implantation – 20-35%					
48.	Yusuf 1979[472,472]	BMJ	Atenolol	Unclear	MI (immediately) Age: 57. 2 years Ethnicity: unclear	Unclear	• All-cause mortality • Side effects • Tiredness	6 months	
					HF: unclear	Unclear			
49.	Yusuf 1980[472,475]	BMJ	Atenolol	Unclear	MI (less than 12 hours since onset of symptoms) Age: mean 56 years Ethnicity: unclear	Unclear	• All-cause mortality • Bradycardia	10 day for reinfarction, 1-4 years for mortality	Blinding: Double Allocation concealment: Unclear Loss to follow-up: 0%

					HF: 6.5% excluded if HF requiring digoxin or more than 80 mg of frusemide.	Unclear			

Table 104: Summary of studies included in the review: beta-blocker treatment in people who had a MI (people initiated with treatment from 72 hours-12 months of the MI).

A systematic review on this topic was published in the British Medical Journal (BMJ). Where possible, data from relevant papers were directly extracted from this paper (and referred to as BMJ in the second column). For the remaing papers a full extractration was performed.

Study	Data was extracted from BMJ or full extraction	Intervention /comparison	Acute treatment	Population Heart failure %	Strata LVSD, Unselected, Normal LVSD. With COPD versus No COPD	Outcomes	Follow-up	Comments
Anon 1982A[3] BHAT	BMJ and full extraction	Propranolol 180-240mg daily versus placebo for mean follow up of 25 months	Medical management	MI (5-21days ago) (direct population) Age: 30-69 years Ethnicity: Unclear	Unclear	• All-cause mortality • CV mortality • Sudden death • Revascularisation • Tiredness • Reduced sexual activity Nightmares • Faintness	25 months	Trial stopped prematurely on grounds of efficacy
				HF: 9.2%	No COPD Excluded people with adult asthma			
ANON	BMJ	Pindolol	Unclear	MI (1-21 days	Unselected LV	• All-cause	2 years	Blinding: Double

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Study	Data was extracted from BMJ or full extraction	Intervention /comparison	Acute treatment	Population Heart failure %	Strata LVSD, Unselected, Normal LVSD. With COPD versus No COPD	Outcomes	Follow-up	Comments
(A+S) 1983[4]				later) Age: 55-69 years Ethnicity: unclear	function (61% LVSD)	mortality • Cardiac death • Sudden death • Reinfarction • Nightmares • Dizziness (subgroup analysis of those who had early versus late entry into trial)		Allocation concealment: Unclear Loss to follow-up: Unclear
				HF: Unclear. 61% had left ventricular failure.	No COPD – excluded people with obstructive airway disease			
ANON[5] EIS	BMJ	Oxprenolol	Unclear	MI (14-36 days later) Age: 35-69 years Ethnicity: unclear	Unselected LV function: Left heart failure: 13%	• All-cause mortality • Sudden death • Cardiac death • Reinfarction (non-fatal) • Revascularisation (CABG) • Bradyarrhythmia • Fatigue/dizziness	1 year	Blinding: Double Allocation concealment: Unclear Loss to follow-up: Unclear
				HF: excluded those with HF 13% HF	No COPD. Excluded those with bronchospasm			
ANON1987	BMJ	Metoprolol	Unclear	MI (6-16 days	Unclear	• All-cause	18	Blinding: Double

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Study	Data was extracted from BMJ or full extraction	Intervention /comparison	Acute treatment	Population	Strata LVSD, Unselected, Normal LVSD.	Outcomes	Follow-up	Comments
				Heart failure %	With COPD versus No COPD			
(LIT Research group)[9]				later) Age: mean 58 years (45-74) Ethnicity: 90% white		mortality (cumulative and distinct) • Cardiac death (cumulative and distinct) • Sudden CV Death(cumulative and distinct) • Reinfarction (cumulative and distinct) • Adverse events	months (0-3months 4-7months 8-12months 13-18months)	Allocation concealment: Unclear Loss to follow-up: 0.2%
				Excluded those with HF	No COPD – excluded people with bronchospastic disease			
Anon 1993 (Navarro)[320] SSSD	BMJ	Metoprolol	Unclear	MI (10-14 days after MI) Age: less than 75 years, mean 59±10 Ethnicity: unclear	LVSD: 20-45%	• All-cause mortality • Reinfarction	3 years	Blinding: No Allocation concealment: Unclear Loss to follow-up: 1.9%
				HF 19%: Killip Class I 79% Killip Class II 19%	Unclear			
Boissel 1990[61,62]	BMJ (2 papers)	Acebutolol	Unclear	MI average 10 days later (2 -21 days later)	Unclear	• All-cause mortality • Sudden death	318 days	Blinding: Double Allocation concealment: yes Loss to follow-up: 0%

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Study	Data was extracted from BMJ or full extraction	Intervention /comparison	Acute treatment	Population Heart failure %	Strata LVSD, Unselected, Normal LVSD. With COPD versus No COPD	Outcomes	Follow-up	Comments
				Age: mean 62 years Ethnicity: Unclear		• Reinfarction (fatal and non-fatal) • Side effects • Sinus bradycardia		
				HF: At acute stage= 27% had congestive HF (if conditions disappeared by 22nd day that could be included)	Unclear COPD: 95% had severe exertional dyspnea. 43% dyspnea on flat ground. Excluded those with asthma or chronic bronchopneumo pathy.			
CAPRICORN 2001[435]	Full extraction	Carvedilol	Thrombolysis (37%) Primary coronary angioplasty (13%)	MI and LVEF less than or equal to 40% (3-21 days after MI) Age: 25-90, mean 63 years Ethnicity: unclear	LVSD	• All-cause mortality • Sudden death • CV death • Reinfarction (fatal and non-fatal) • Hospital admission	1.3 years	Details of methodology published in previous paper so few here
				HF: Killip Class II (30%) and III (4%)	Unclear. 33% current smokers			

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Study	Data was extracted from BMJ or full extraction	Intervention /comparison	Acute treatment	Population Heart failure %	Strata LVSD, Unselected, Normal LVSD. With COPD versus No COPD	Outcomes	Follow-up	Comments
Fonarow2007 [145,145] CAPRICORN	Full extraction	Carvedilol	Thrombolysis (37%) Primary coronary angioplasty (13%)	MI (3-21 days after MI) Age:25-90 years Ethnicity: unclear	LVSD. (LVEF <40%, mean 33%)	• All-cause mortality • Reinfarction (fatal and atal) • Adverse events • Bradycardia	30 days	Short term data for same study as above
				HF: 30% Killip Class II (30%) and III (4%)	Unclear			
Hansteen 1982[185,185]	Full extraction	Propranolol 40mg 4 times daily versus placebo for 12 months	Unclear	MI, high risk group (4-6 days post MI) Age: 35-70 years Ethnicity: unclear	Unselected LV function:.40% had left ventricular failure	• All-cause mortality • Sudden death • CV death • Reinfarction (fatal and non-fatal) • Bradycardia • Nightmares • Dizziness	1 year	Underpowered; premature cessation of recruitment; large number of withdrawals
				HF: 0% excluded	No COPD. Excluded if obstructive airway disease			
Julian 1982[219,219]	BMJ	Sotalol	Unclear	MI (5-14 days post MI, mean 8 days) Age: mean 55 ± 8 Ethnicity: unclear	Unclear	• All-cause mortality • CV mortality • Sudden death • Reinfarction (fatal and	12 months	Blinding: double Allocation concealment: yes Loss to follow-up: 0%

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Study	Data was extracted from BMJ or full extraction	Intervention /comparison	Acute treatment	Population	Strata LVSD, Unselected, Normal LVSD.	Outcomes	Follow-up	Comments
				Heart failure %	With COPD versus No COPD			
						non-fatal) • Adverse reactions • Dizziness • Libido decrease • Change in dreaming		
				HF:0% (excluded)	No COPD. Excluded if history of obstructive airway disease			
Mazur 1984[277,277]	BMJ	Propranolol	Unclear	MI (less than 3months) Age: up to 62 years Ethnicity: unclear	Unclear	• All-cause mortality • CV mortality • Sudden death • Reinfarction (non-fatal)	16.3 months	Blinding: no Allocation concealment: unclear Loss to follow-up: unclear
				HF: Unclear	Unclear			
Mangercats 1983[265]	BMJ	Metoprolol	Unclear	MI (less than 1 week) Age: unclear Ethnicity: unclear	Unclear	• All-cause mortality	1 year	Blinding: double Allocation concealment: unclear Loss to follow-up: 0%
				HF: unclear, all NYHA Class I or II	Unclear			
Pedersen 1983[348,348]	Full extraction	Timolol	Unclear	MI (mean 11 days from MI)	Unselected LV function Group I –	• All-cause mortality	0-33 months	High dropout >20%

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Study	Data was extracted from BMJ or full extraction	Intervention /comparison	Acute treatment	Population Heart failure %	Strata LVSD, Unselected, Normal LVSD. With COPD versus No COPD	Outcomes	Follow-up	Comments
				Age: 61.4 Ethnicity; unclear	recurrent MI Group II – first MI plus transient left ventricular failure Group III – remaining participants	• Cardiac mortality • Sudden death • Reinfarction • Dizziness • Bradycardia		Not matched at baseline for 12 characteristics Reported distinct time points for all-cause mortality
				HF: Unclear %, some had left ventricular failure.	Unselected. 6% had pulmonary congestion.			
Schwartz 1992[403,403]	BMJ	Oxprenolol	n=29 had left cardiac sympathetic denervation	MI (20-40 days post MI) Age: less than 65 years Ethnicity: unclear	Without LVSD	• All-cause mortality • CV death • Sudden death • Reinfarction (fatal and non-fatal) • Dizziness • Libido decrease	22 months	Blinding: Single or Double blind Allocation concealment: unclear Loss to follow-up: 0%
				HF: 2%. Excluded those with Class III/IV heart failure	No COPD. Excluded those with history of chronic pulmonary obstructive disease needing a treatment of IV theophylline or systemic cortisone or beta2stimulants			

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Study	Data was extracted from BMJ or full extraction	Intervention /comparison	Acute treatment	Population	Strata LVSD, Unselected, Normal LVSD.	Outcomes	Follow-up	Comments
				Heart failure %	With COPD versus No COPD			
Taylor 1982[433,433]	BMJ	Oxprenolol 40mg twice a day versus placebo	Unclear	MI mean 13 months (1-90 months previously) Age: mean 51, less than 60 years Ethnicity: unclear	Unclear	• All-cause mortality • CV death • Nonfatal reinfarction • Fatigue	Mean 48 months (6 to 84)	Blinding: Unclear Allocation concealment: Unclear Los to follow-up: 1.9-3.5% Large number of withdrawals in both groups
				HF: 0%, excluded those with evidence of HF	No COPD. Excluded those with symptomatic obstructive airway disease			

Table 105: Summary of studies included in the review: beta-blocker treatment in people who had an MI in the past (over 12 months ago)

	BMJ or full extraction	Intervention /comparison	Acute treatment	Population	Strata LVSD, Unselected, Normal LVSD.	Outcomes	Follow-up	Comments
				Heart failure %	With COPD versus No COPD			
Taylor 1982[433,433]	BMJ	Oxprenolol 40mg twice a day versus	Unclear	MI (less than 12 months),	Unclear	• All-cause mortality • CV death	Mean 48 months (6 to 84)	Blinding: Unclear Allocation concealment: Unclear

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	BMJ or full extraction	Intervention /comparison	Acute treatment	Population	Strata LVSD, Unselected, Normal LVSD.	Outcomes	Follow-up	Comments
				Heart failure %	With COPD versus No COPD			
		placebo		Age: mean 51, less than60 years Ethnicity: unclear		• Non-fatal reinfarction • Fatigue		Los to follow-up: 1.9-3.5% large number of withdrawals in both groups
				HF: 0%, excluded those with evidence of HF	No COPD. Excluded those with symptomatic obstructive airway disease			

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Table 106: GRADE profile: Beta-blocker versus placebo comparison in people who had an acute MI (less than 72 hours after symptom onset)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
Sudden death - distinct - 0 to 3 months[1,220,396,446,464]												
6	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b,]	None	14/587 (2.4%)	20/554 (3.6%)	RR 0.65 (0.34 to 1.27)	13 fewer per 1000 (from 24 fewer to 10more)	LOW	CRITICAL
Sudden death - distinct - 4 to 12 months[396,396]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[b]	None	4/250 (1.6%)	5/224 (2.2%)	RR 0.72 (0.19 to 2.64)	6 fewer per 1000 (from 18 fewer to 37 more)	VERY LOW	CRITICAL
Cardiac death - distinct - 0 to 3 months[328,396]												
2	Randomised trials	Serious[e]	No serious inconsistency	No serious indirectness	Very serious[b]	None	39/614 (6.4%)	35/595 (5.9%)	RR 1.05 (0.68 to 1.63)	3 more per 1000 (from 19 fewer to 37 more)	VERY LOW	CRITICAL
Cardiac death - distinct - 4 to 12 months[396,396]												
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[b]	None	5/250 (2%)	3/224 (1.3%)	RR 1.49 (0.36 to 6.18)	7 more per 1000 (from 9 fewer to 69 more)	VERY LOW	CRITICAL
All-cause mortality - distinct - 0 to 6weeks [1,6,10,28,35,79,90,95,106,137,155,179,183,189,200,207,220,247,256,257,299,326-328,342,352,368,374,391,396,412,451,457,458,464,475]												
39	Randomised trials	Serious[g]	No serious inconsistency	No serious indirectness[h]	No serious imprecision	None	2133/28 031 (7.6%)	2167/28 054 (7.7%)	RR 0.99 (0.93 to 1.04)	1 fewer per 1000 (from 5 fewer to 3 more)	MODERATE	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - distinct – 6 weeks to 12months[183,189,207,396,463]												
5	Randomised trials	Serious[i]	No serious inconsistency	No serious indirectness	Serious[c]	None	45/855 (5.3%)	57/707 (8.1%)	RR 0.67 (0.45 to 0.99)	27 fewer per 1000 (from 1 fewer to 44 fewer)	LOW	CRITICAL
All-cause mortality - distinct – 6 weeks to 24months[391,391]												
1	Randomised trial	Serious[j]	No serious inconsistency	No serious indirectness[k]	Very serious[b]	None	4/102 (3.9%)	5/98 (5.1%)	RR 0.77 (0.21 to 2.78)	12 fewer per 1000 (from 40 fewer to 91 more)	VERY LOW	CRITICAL
Reinfarction (fatal) distinct - 0 to 3months[9]												
1	Randomised trial	Serious[l]	No serious inconsistency	No serious indirectness	Very serious[b]	None	6/1195 (0.5%)	7/1200 (0.58%)	RR 0.86 (0.29 to 2.55)	1 fewer per 1000 (from 4 fewer to 9 more)	VERY LOW	IMPORTANT
Reinfarction (fatal) distinct - 4 to 7months[9]												
1	Randomised trial	Serious[l]	No serious inconsistency	No serious indirectness	Very serious[b]	None	3/1195 (0.25%)	1/1200 (0.08%)	RR 3.01 (0.31 to 28.92)	2 more per 1000 (from 1 fewer to 23 more)	VERY LOW	IMPORTANT
Reinfarction (fatal) distinct - 8 to 12months[9]												
1	Randomised trial	Serious[l]	No serious inconsistency	No serious indirectness	Very serious[b]	None	4/1195 (0.33%)	1/1200 (0.08%)	RR 4.02 (0.45 to 35.88)	3 more per 1000 (from 0 fewer to 29 more)	VERY LOW	IMPORTANT
Reinfarction (fatal) distinct - 13 to 18months[9]												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trial	Serious[l]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/1195 (0%)	1/1200 (0.08%)	RR 0.33 (0.01 to 8.21)	1 fewer per 1000 (from 1 fewer to 6 more)	VERY LOW	IMPORTANT
All-cause mortality[1,6,10,28,35,79,90,95,106,137,155,179,200,220,247,256,257,299,326-328,342,352,368,374,412,451,457,458,464,464,474,475 2,7,10,29,37,183,189,194,207,227,339,383,387,391,396,464,470,472]												
48	Randomised trials	Serious[m]	No serious inconsistency	No serious indirectness	No serious imprecision	None	3244/38 970 (8.3%)	3382/38 749 (8.7%)	RR 0.95 (0.91 to 1)	4 fewer per 1000 (from 8 fewer to 0 more)	MODERATE	CRITICAL
All-cause mortality – 0 to 6 weeks[1,6,10,28,35,79,90,95,106,137,155,179,200,220,247,256,257,299,326-328,342,352,368,374,412,451,457,458,464,464,474,475]												
32	Randomised trials	Serious[g]	No serious inconsistency	Serious[n]	No serious imprecision	None	2059/27 563 (7.5%)	2102/27 610 (7.6%)	RR 0.98 (0.93 to 1.04)	2 fewer per 1000 (from 5 fewer to 3 more)	LOW	CRITICAL
All-cause mortality - 0 to 6 months[2,10,37,194,207,227,472]												
7	Randomised trials	Serious[o]	No serious inconsistency	No serious indirectness	Serious[c]	None	87/1706 (5.1%)	105/166 4 (6.3%)	RR 0.82 (0.62 to 1.08)	11 fewer per 1000 (from 24 fewer to 5 more)	LOW	CRITICAL
All-cause mortality - 0 to 12 months[7,29,183,189,383,396,464,470]												
8	Randomised trials	Serious[p]	No serious inconsistency	No serious indirectness[q]	No serious imprecision	None	1042/93 11 (11.2%)	1112/90 95 (12.2%)	RR 0.91 (0.84 to 0.99)	11 fewer per 1000 (from 1 fewer to 20 fewer)	MODERATE	CRITICAL
All-cause mortality - 0 to over 24 months[339,387,391]												
3	Randomised	Serious[r]	No serious	No serious	Serious[c]	None	56/390	38/380	RR 0.87	13 fewer	LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
	trials		inconsistency	indirectness			(14.4%)	(10%)	(0.67 to 1.2)	per 1000 (from 33 fewer to 20 more)		
Cardiac mortality[2,29,326,339,396]												
5	Randomised trials	Serious[s]	No serious inconsistency	No serious indirectness	Serious[c]	None	91/1300 (7%)	90/1243 (7.2%)	RR 0.96 (0.72 to 1.26)	3 fewer per 1000 (from 20 fewer to 19 more)	LOW	CRITICAL
Cardiac mortality – 0 to 6 weeks[326,327]												
1	Randomised trial	Serious[t]	No serious inconsistency	No serious indirectness	Very serious[b]	None	14/364 (3.8%)	14/371 (3.8%)	RR 1.02 (0.49 to 2.11)	1 more per 1000 (from 19 fewer to 42 more)	VERY LOW	CRITICAL
Cardiac mortality - 0 to 6 months[2]												
1	Randomised trial	Serious[u]	No serious inconsistency	No serious indirectness	Very serious[b]	None	8/177 (4.5%)	5/136 (3.7%)	RR 1.23 (0.41 to 3.67)	8 more per 1000 (from 22 fewer to 98 more)	VERY LOW	CRITICAL
Cardiac mortality - 0 to 12 months[29,396]												
2	Randomised trials	Serious[v]	No serious inconsistency	No serious indirectness	Very serious[b]	None	49/605 (8.1%)	42/589 (7.1%)	RR 1.11 (0.75 to 1.64)	8 more per 1000 (from 18 fewer to 46 more)	VERY LOW	CRITICAL
Cardiac mortality - over 24 months[339,339]												
1	Randomised trial	Serious[w]	No serious inconsistency	No serious indirectness	Serious[c]	None	20/154 (13%)	29/147 (19.7%)	RR 0.66 (0.39 to	67 fewer per 1000	LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
									1.11)	(from 120 fewer to 22 more)		
Sudden death[1,220,339,396,446,464]												
6	Randomised trials	Serious[x]	No serious inconsistency	No serious indirectness	Serious[c]	None	25/740 (3.4%)	46/701 (6.6%)	RR 0.51 (0.32 to 0.82)	32 fewer per 1000 (from 12 fewer to 45 fewer)	LOW	CRITICAL
Sudden cardiac death - less than 6 weeks[1,220,446,464]												
4	Randomised trials	Serious[y]	No serious inconsistency	No serious indirectness	Very serious[b]	None	11/295 (3.7%)	14/284 (4.9%)	RR 0.73 (0.34 to 1.56)	13 fewer per 1000 (from 33 fewer to 28 more)	VERY LOW	CRITICAL
Sudden cardiac death - 0 - 12 months[396,396]												
1	Randomised trial	Serious	No serious inconsistency	No serious indirectness	Serious[c]	None	4/249 (1.6%)	10/224 (4.5%)	RR 0.36 (0.11 to 1.13)	29 fewer per 1000 (from 40 fewer to 6 more)	LOW	IMPORTANT
Sudden cardiac death - 0-25 months[339,339]												
1	Randomised trial	Serious[z]	No serious inconsistency	No serious indirectness	Serious[c]	None	9/154 (5.8%)	21/147 (14.3%)	RR 0.41 (0.19 to 0.86)	84 fewer per 1000 (from 20 fewer to 116 fewer)	LOW	IMPORTANT
Reinfarction[2,7,10,29,37,90,227,257,339,352,446,451,470]												
13	Randomised trials	Serious[z]	Serious[aa]	No serious indirectness[bb]	No serious imprecision[cc]	None	683/33156	832/32690	RR 0.81 (0.73 to	5 fewer per 1000	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
							(2.1%)	(2.5%)	0.89)	(from 3 fewer to 7 fewer)		
Reinfarction (fatal and/or non-fatal)[10,90,352,451]												
4	Randomised trials	Serious	Serious[dd]	No serious indirectness	No serious imprecision[cc]	None	490/24142 (2%)	612/23759 (2.6%)	RR 0.8 (0.71 to 0.89)	5 fewer per 1000 (from 3 fewer to 7 fewer)	LOW	IMPORTANT
Reinfarction(fatal and/or non-fatal) - 0-6months [2,29,37,227,257]												
5	Randomised trials	Serious[e e]	No serious inconsistency	No serious indirectness	Very serious[b]	None	22/761 (2.9%)	27/728 (3.7%)	RR 0.79 (0.45 to 1.37)	8 fewer per 1000 (from 20 fewer to 14 more)	VERY LOW	IMPORTANT
Reinfarction (fatal and/or non-fatal) - 0-12 months[7,446,470]												
3	Randomised trials	Serious[e e]	Serious[ff]	No serious indirectness[gg]	No serious imprecision	None	153/8099 (1.9%)	162/8056 (2%)	RR 0.94 (0.75 to 1.17)	1 fewer per 1000 (from 5 fewer to 3 more)	LOW	IMPORTANT
Reinfarction (fatal and/or non-fatal) - 0-25months[339,339]												
1	Randomised trial	Serious[j]	No serious inconsistency	No serious indirectness	Serious[c]	None	18/154 (11.7%)	31/147 (21.1%)	RR 0.55 (0.32 to 0.95)	95 fewer per 1000 (from 11 fewer to 143 fewer)	LOW	IMPORTANT
Stroke [90,219,326,339,451]												
5	Randomised trials	Serious[h h]	No serious inconsistency	No serious indirectness	Serious[ii]	None	261/24420	230/24118	RR 1.12 (0.94 to	1 more per 1000	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
							(1.1%)	(0.95%)	1.34)	(from 1 fewer to 3 more)		
Stroke – 0 to 6 weeks[90,326,451]												
3	Randomised trials	Serious[jj]	No serious inconsistency	No serious indirectness	Serious[kk]	None	249/23393 (1.1%)	222/23388 (0.95%)	RR 1.12 (0.94 to 1.34)	1 more per 1000 (from 1 fewer to 3 more)	LOW	IMPORTANT
Stroke - 0 to 12 months[219,219]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[b]	None	11/873 (1.3%)	3/583 (0.51%)	RR 2.45 (0.69 to 8.74)	7 more per 1000 (from 2 fewer to 40 more)	LOW	IMPORTANT
Stroke – over 24 months[339,339]												
1	Randomised trial	Serious[ll]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/154 (0.65%)	5/147 (3.4%)	RR 0.19 (0.02 to 1.61)	28 fewer per 1000 (from 33 fewer to 21 more)	VERY LOW	IMPORTANT
Revascularisation[339,470]												
2	Randomised trials	Serious[mm]	No serious inconsistency	No serious indirectness	Serious[c]	None	3/174 (1.7%)	9/167 (5.4%)	RR 0.32 (0.09 to 1.15)	37 fewer per 1000 (from 49 fewer to 8 more)	LOW	IMPORTANT
Revascularisation CABG/PTCA - 0 to 12 months[470,471]												
1	Randomised trial	No serious risk of	No serious inconsistency	Serious[nn]	No serious imprecision	None	0/20 (0%)	0/20 (0%)	Not pooled	Not pooled	MODERATE	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
		bias										
Revascularisation CABG/PTCA - 0 to25 months[339,339]												
2	Randomised trials	Serious[m,m]	No serious inconsistency	No serious indirectness	Serious[c]	None	3/154 (1.9%)	9/147 (6.1%)	RR 0.32 (0.09 to 1.15)	42 fewer per 1000 (from 56 fewer to 9 more)	LOW	IMPORTANT
Nightmares[339,374]												
2	Randomised trials	Serious[ll]	No serious inconsistency	No serious indirectness	Very serious[b]	None	5/199 (2.5%)	1/196 (0.51%)	RR 3.73 (0.63 to 21.97)	14 more per 1000 (from 2 fewer to 107 more)	LOW	IMPORTANT
Adverse events[1,2,29,37,90,194,227,339,396,472]												
10	Randomised trials	Serious[o,o]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1599/24 761 (6.5%)	1474/24 684 (6%)	RR 1.08 (1.01 to 1.15)	5 more per 1000 (from 1 more to 9 more)	MODERATE	CRITICAL
Dizziness[37,185,374]												
3	Randomised trials	Serious[p,p]	Very serious	No serious indirectness	No serious imprecision	None	63/400 (15.8%)	20/337 (5.9%)	RR 1.71 (1.08 to 2.72)	42 more per 1000 (from 5 more to 102 more)	LOW	IMPORTANT
Fatigue/Tiredness[339,374,463,472]												
4	Randomised trials	Serious[q,q]	No serious inconsistency	No serious indirectness	Serious[ii]	None	63/468 (13.5%)	20/337 (5.9%)	RR 1.71 (1.08 to 2.72)	42 more per 1000 (from 5 more to 102 more)	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
Sinus bradycardia[1,6,90,183,185,194,220,257,327,339,352,446,451,464,475]												
15	Randomised trials	Serious[rr]	Serious[ss]	No serious indirectness	No serious imprecision	None	1868/28105 (6.6%)	736/28103 (2.6%)	RR 2.54 (2.33 to 2.75)	40 more per 1000 (from 35 more to 46 more)	MODERATE	CRITICAL
Libido decrease - 0 to 25 months[339,339]												
1	Randomised trial	Serious[j]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2/154 (1.3%)	0/147 (0%)	OR 1.03 (0.96 to 1.11)	-	MODERATE	IMPORTANT
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT

(a) In majority of studies participants were blinded, it was unclear in majority if they performed allocation concealment
(b) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(c) 95% confidence intervals crossed 1 MID (0.75).
(d) Unclear if performed allocation concealment. Only 1 small study.
(e) In 1 study participants were blinded, in the other they were not. It was unclear whether the authors performed allocation concealment in 1 study and did not perform it in the other. Low percentage lost to follow-up.
(f) Only 1 small study and unclear if performed allocation concealment. Only 0.5% lost to follow-up and excluded people who had HF.
(g) It was unclear in the majority of papers if the participants were blinded. One of these papers was by Chen that contributed the largest 85% to overall outcome. It was unclear in <15% if performed allocation concealment, however the Chen paper did perform AC.
(h) Three papers included more than 25% of people who had HF. However, they contributed overall 1% to the meta-analysis.
(i) One of the studies did not blind the participants, although it contributed only 8.5% to overall result. In none of the studies was it clear if they performed allocation concealment.
(j) Unclear if they performed allocation concealment. Only 1 study and small sample size.
(k) Unclear if included people with HF.
(l) Unclear if performed allocation concealment and only 1 paper with reasonable sample size.
(m) Just on half of the studies were double blinded. 12/47 were not blinded, in 7 it was unclear and 2were single blinded. In the majority of papers (41/47) it was unclear if allocation concealment was performed, it was performed in 5, 1 of which contributed to the majority of the overall result.
(n) Two papers included people with more than >25% HF.
(o) Unclear in 6/7 if performed allocation concealment and 1/7 did not. One paper that contributed the second highest percentage to result did not blind the participants to study protocol, however majority of studies did.

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(p) In 5 out of 8 papers, participants were blinded to protocol, 1 it was unclear and in 2 participants were not blinded. Inthe study that contributed most to overall result, the patients were not blinded.
(q) One paper had 28% HF participants, but did not contribute to overall effect because no events were observed.
(r) One of the 3 studies had the participants blinded to the study medication. It was unclear whether the authors performed allocation concealment.
(s) Unclear if any performed allocation concealment. In 3 out of the 5 studies the participants were blinded.
(t) Participants were not blinded. Unclear if performed allocation concealment. Only 1 study with small sample size.
(u) Participants were blinded, but unclear if performed allocation concealment. Only 1 study and small sample size.
(v) Participants were blinded, but unclear if performed allocation concealment. Only 2 studies with small sample size
(w) Unclear if participants were blinded or performed allocation concealment.
(x) It was unclear if any study performed allocation concealment.
(y) All studies participants were blinded. Unclear in any if performed allocation concealment. Only small total number of participants.
(z) Unclear if any performed allocation concealment.
(aa) Heterogeneity was detected, I^2=49%.
(bb) One study had more than 25% peoplewith HF but did not contribute to the overall effect.
(cc) The confidence intervals uust cross 1 MID but can be considered in a buffer zone of 5%.
(dd) Heterogeneity was detected, I^2=68%, p=0.03. The was a large range in the number of participants in the studies from 100 up to 22,929 in 1 arm, and few events in the smaller studies that may have contributed to the inconsistency.
(ee) All studies blinded their participants but it was unclear if any performed allocation concealment.
(ff) The study that contributed 99% to the overall outcome did not blind their participants however they did perform allocation concealment.
(gg) Heterogeneity was detected 65% p=0.09, this is likely to be due to the few events in 1 study that showed a higher number of deaths in the beta-blocker treated group.
(hh) It was unclear if they blinded the participants in these studies.
(ii) 95% confidence interval crossed 1 MID (1.25).
(jj) The study that contributed 98% it was unclear if they blinded the participants, however they did perform allocation concealment.
(kk) The participants were blinded, however unclear if they performed allocation concealment and only 1 study contributed to outcome.
(ll) Unclear if they performed allocation concealment.
(mm) The study that contributed 100% it was unclear if they blinded the participants or if performed allocation concealment.
(nn) Included 33% of people with HF, however an outcome was not calculable given that no events were observed.
(oo) The study that contributed to 90% of the overall outcome - it is unclear if they blnided the participants but they did perform allocation concealment.
(pp) All studies were double-blinded, however unclear if they performed allocation concealment.
(qq) The studies had few participants in each arm and few events recorded. Unclear if performed allocation concealment.
(rr) 11 out of 15 studies were double-blinded and in 11 it was unclear if they performed allocation concealment.
(ss) Heterogeneity was detected, I^2=48%, p=0.02.

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Table 107: GRADE profile: Beta-blocker versus placebo comparison in people who had an MI and who were initiated with treatment from 72 hours – 12months.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
Sudden death - distinct - 0-3months[9]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	6/1196 (0.5%)	12/1200 (1.1%)	RR 0.50 (0.19 to 1.33)	5 fewer per 1000 (from 9 fewer to 4 more)	VERY LOW	CRITICAL
Sudden death - distinct - 4-7months[9]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	6/1196 (0.5%)	6/1200(0.5%)	RR 1 (0.33 to 3.08)	0 fewer per 1000 (from 3 fewer to 10 more)	VERY LOW	CRITICAL
Sudden death - distinct - 8-12months[9]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	2/1196 (0.17%)	1/1200(0.089%)	RR 2.01 (0.18 to 22.01)	1 more per 1000 (from1 fewer to 18more)	LOW	CRITICAL
Sudden death - distinct - 13-18months[9]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	8/1196 (0.67%)	6/1200(0.5%)	RR 1.34 (0.47 to 3.84)	2 more per 1000 (from 3 fewer to 14 more)	VERY LOW	IMPORTANT
Cardiac death - distinct - 0-3months[9]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	none	22/1196 (1.8%)	36/1200 (3%)	RR 0.61 (0.36 to 1.04)	12 fewer per 1000 (from 19 fewer to 1	LOW	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
										more)		
Cardiac death - distinct - 4-7months[9]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	19/1196 (1.6%)	14/1200 (1.2%)	RR 1.36 (0.69 to 2.71)	4 more per 1000 (from 4 fewer to 20 more)	VERY LOW	IMPORTANT
Cardiac death - distinct - 8-12months[9]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	18/1195 (1.5%)	7/1200 (0.58%)	RR 2.58 (1.08 to 6.16)	9 more per 1000 (from 0 more to 30 more)	MODERATE	CRITICAL
Cardiac death - distinct - 13-18months[9]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	19/1195 (1.6%)	23/1200 (1.9%)	RR 0.83 (0.45 to 1.52)	3 fewer per 1000 (from 11 fewer to 10 more)	VERY LOW	CRITICAL
All-cause mortality - distinct - 0-6months[3,9,145,348]												
4	Randomised trials	Serious[e]	No serious inconsistency	No serious indirectness	Serious[c]	None	158/5032 (3.1%)	239/5044 (4.7%)	RR 0.66 (0.54 to 0.81)	16 fewer per 1000 (from 9 fewer to 22 fewer)	LOW	CRITICAL
All-cause mortality - distinct -7-12 months[3,9,348]												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	68/4057 (1.7%)	77/4060 (1.9%)	RR 1.01 (0.45 to 2.29)	2 fewer per 1000 (from 7 fewer to 4 more)	LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - distinct - 13-18 months[3,9,348]												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	92/4057 (2.3%)	115/4060 (2.8%)	RR 0.76 (0.49 to 1.16)	6 fewer per 1000 (from 11 fewer to 1 more)	LOW	CRITICAL
All-cause mortality 25-36 months[3,348]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	22/2861 (0.77%)	34/2860 (1.2%)	RR 0.65 (0.38 to 1.10)	4 fewer per 1000 (from 7 fewer to 1 more)	LOW	CRITICAL
All-cause mortality-distinct – more than 36months[3]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	1/1916 (0.05%)	1/1921 (0.05%)	RR 1.0 (0.06 to 16.02)	0 fewer per 1000 (from 0 fewer to 8 more)	LOW	IMPORTANT
All-cause mortality – 6 weeks-24 months - distinct[435]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	97/975 (9.9%)	118/984 (12%)	RR 0.83(0.64 to 1.07)	20 fewer per 1000 (from 43 fewer to 8 more)	LOW	CRITICAL
Reinfarction - distinct - 0-3 months[9,145]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	19/2171 (0.88%)	30/2184 (1.4%)	RR 0.64 (0.36 to 1.13)	5 fewer per 1000 (from 9 fewer to 2 more)	LOW	IMPORTANT
Reinfarction-distinct 6 weeks to 24 months[435]												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Serious[c]	None	21/975 (2.2%)	34/984 (3.5%)	RR 0.62 (0.36 to 1.07)	13 fewer per 1000 (from 22 fewer to 2 more)	LOW	IMPORTANT
Reinfarction - distinct - 4 to 7 months[3]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	3/1196 (0.25%)	1/1200 (0.08%)	RR 3.01 (0.31 to 28.92)	2 more per 1000 (from 1 fewer to 23 more)	LOW	CRITICAL
Reinfarction - distinct – 8 to 12 months[3]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	4/1196 (0.33%)	1/1200 (0.08%)	RR 4.02 (0.45 to 35.88)	3 more per 1000 (from 0 fewer to 29 more)	LOW	CRITICAL
Reinfarction - distinct - 13 to 18 months[3]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/1196 (0%)	1/1200 (0.08%)	RR 0.33 (0.01 to 8.21)	1 fewer per 1000 (from 1 fewer to 6 more)	VERY LOW	IMPORTANT
All-cause mortality [3-5,62,185,219,265,277,320,348,433]												
14	Randomised trials	Serious[g]	Serious[h,i]	Serious[i]	Serious	None	716/8978 (8%)	911/8664 (10.5%)	RR 0.76 (0.69 to 0.83)	25 fewer per 1000 (from 18 fewer to 33 fewer)	VERY LOW	CRITICAL
All-cause mortality - 0 to 12 months[5,62,185,219,265]												
5	Randomised	Serious[j]	Serious[k]	Serious[l]	Serious[c]	None	172/258	184/233	RR 0.83	13 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
	trials						0 (6.7%)	7 (7.9%)	(0.68 to 1.02)	per 1000 (from 25 fewer to 2 more)		
All-cause mortality - 0 to 24 months[4,9,277,403,435]												
5	Randomised trials	Serious[m]	Serious[n]	Serious[o]	Serious[c]	None	269/3019 (8.9%)	341/3041 (11.2%)	RR 0.8 (0.68 to 0.92)	22 fewer per 1000 (from 9 fewer to 36 fewer)	VERY LOW	CRITICAL
All-cause mortality –over 24 months[3,320,348,433]												
3	Randomised trials	Serious[p]	Serious[q]	No serious indirectness	Serious[c]	None	275/3379 (8.1%)	386/3286 (11.7%)	RR 0.69 (0.60 to 0.80)	36 fewer per 1000 (from 23 fewer to 47 fewer)	VERY LOW	IMPORTANT
Sudden death [3-5,9,62,185,219,277,320,348,403,435]												
12	Randomised trials	Serious[r]	No serious inconsistency	Serious[h]	Serious[c]	None	296/8314(3.6%)	396/8080 (4.9%)	RR 0.73(0.582 to 0.92)	13 fewer per 1000 (from 4 fewer to 21 fewer)	VERY LOW	CRITICAL
Sudden death - 0 to 12 months[5,62,185,219]												
4	Randomised trials	Serious[s]	No serious inconsistency	No serious indirectness[v]	Serious[c]	None	93/2307 (4%)	91/2057 (4.4%)	RR 0.86 (0.65 to 1.14)	6 fewer per 1000 (from 15 fewer to 6 more)	LOW	IMPORTANT
Sudden death - 0 to 24 months[4,9,277,403,435]												
5	Randomised trials	Serious[u]	Serious[v]	Serious[n]	Serious[c]	None	112/3016	167/3040	RR 0.68 (0.54 to	18 fewer per 1000	VERY LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
							(3.7%)	(5.5%)	0.85)	(from 8 fewer to 25 fewer)		
Sudden death - 0 to over 25 months[3,320,348]												
3	Randomised trials	Serious[w]	Serious[x]	No serious indirectness	Serious[c]	None	91/2991 (3%)	138/2983 (4.6%)	RR 0.66 (0.51 to 0.85)	16 fewer per 1000 (from 7 fewer to 23 fewer)	VERY LOW	CRITICAL
Cardiovascular mortality[3-5,9,185,219,277,320,348,403,433,435]												
12	Randomised trials	Serious[y]	Serious[z]	No serious indirectness[aa]	Serious[c]	None	618/8407 (7.4%)	788/8075 (9.8%)	RR 0.77 (0.64 to 0.92)	22 fewer per 1000 (from 8 fewer to 35 fewer)	VERY LOW	CRITICAL
Cardiovascular mortality - 0 to 12 months[5,185,219]												
3	Randomised trials	Serious[bb]	Serious[cc]	No serious indirectness	Serious[e]	None	110/2009 (5.5%)	101/1748 (5.8%)	RR 0.89 (0.68 to 1.15)	6 fewer per 1000 (from 18 fewer to 9 more)	VERY LOW	CRITICAL
Cardiovascular mortality - 0 to 24 months[4,9,277,403,435]												
5	Randomised trials	Serious[dd]	Serious[ee]	Serious[ff]	Serious[c]	None	239/3019 (7.9%)	299/3041 (9.8%)	RR 0.81 (0.69 to 0.95)	19 fewer per 1000 (from 5 fewer to 30 fewer)	VERY LOW	CRITICAL
Cardiovascular mortality - 0 to 25months[3,320,348,433]												
4	Randomised trials	Serious[gg]	Serious[hh]	No serious indirectness	Serious[c]	None	269/3379 (8%)	388/3280 (11.8%)	RR 0.68 (0.51 to 0.90)	39 fewer per 1000 (from 26	VERY LOW	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 51 fewer)		
Reinfarction (fatal and/or non-fatal)[4,5,62,185,219,277,403,435 9,48,320,348,433]												
13	Randomised trials	Serious[ii]	No serious inconsistency	Serious[jj]	Serious[c]	None	362/8708 (4.2%)	435/8381 (5.2%)	RR 0.79 (0.69 to 0.91)	11 fewer per 1000 (from 5 fewer to 16 fewer)	VERY LOW	CRITICAL
Reinfarction (fatal and/or non-fatal) – 0 to 12 months[5,62,185,219]												
4	Randomised trials	Serious[kk]	Serious[ll]	No serious indirectness[t]	Serious[c]	None	112/2307 (4.9%)	116/2057 (5.6%)	RR 0.88 (0.69 to 1.13)	7 fewer per 1000 (from 17 fewer to 7 more)	VERY LOW	IMPORTANT
Reinfarction (fatal and/or non-fatal) - 0 to 24 months[4,277,403,435]												
4	Randomised trials	Serious[mm]	No serious inconsistency	Serious[ff]	Serious[c]	None	95/1827 (5.2%)	146/1838 (7.9%)	RR 0.66 (0.51 to 0.84)	27 fewer per 1000 (from 13 fewer to 39 fewer)	VERY LOW	IMPORTANT
Reinfarction (fatal and/or non-fatal) – 0 to 25 months[9,48,320,348,433]												
5	Randomised trials	Serious[nn]	No serious inconsistency	No serious indirectness	Serious[c]	None	155/4574 (3.4%)	173/4486 (3.9%)	RR 0.85 (0.69 to 1.05)	6 fewer per 1000 (from 12 fewer to 2 more)	LOW	CRITICAL
Rehospitalisation - 0 to 24 months[62,62]												
1	Randomised trial	No serious risk of bias	No serious inconsistency	Serious[oo]	No serious imprecision	None	324/975 (33.2%)	356/984 (36.2%)	RR 0.92 (0.81 to 1.04)	29 fewer per 1000 (from 69 fewer to	MODERATE	CRITICAL

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
										14 more)		
Fatigue [5,48,433]												
2	Randomised trials	No serious risk of bias[pp]	No serious inconsistency	No serious indirectness	Very serious[b]	None	12/1490 (0.81%)	10/1354 (0.74%)	RR 1.13 (0.49 to 2.59)	1 more per 1000 (from 4 fewer to 12 more)	LOW	IMPORTANT
Dizziness [4,48,185,219,348,403]												
6	Randomised trials	Serious[qq]	Very serious[rr]	Serious[ff]	Very serious[d]	None	811/4323 (18.8%)	641/4047 (15.8%)	RR 1.19 (1.08 to 1.30)	30 more per 1000 (from 13 more to 48 more)	VERY LOW	IMPORTANT
Stroke[48]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	29/1916 (1.5%)	30/1921 (1.6%)	RR 0.97 (0.58 to 1.61)	0 fewer per 1000 (from 7 fewer to 10 more)	VERY LOW	IMPORTANT
Bradycardia[5,62,145,185,219,348]												
7	Randomised trials	Serious[ss]	Serious[tt]	Serious[uu]	No serious imprecision	None	111/4269 (2.6%)	19/4026 (0.47%)	RR 5.29 (3.24 to 8.62)	20 more per 1000 (from 11 more to 36 more)	MODERATE	IMPORTANT
Change in dreaming[3,4,185,219]												
4	Randomised trials	Serious[qq]	No serious inconsistency	No serious indirectness	No serious imprecision	None	819/3330 (24.6%)	748/3052 (24.5%)	RR 1.07 (0.99 to 1.16)	17 more per 1000 (from 2 fewer to 39 more)	MODERATE	IMPORTANT

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
Revascularisation (CABG)[5,48,320]												
3	Randomised trials	Serious[vv]	No serious inconsistency	No serious indirectness	No serious imprecision	None	200/2904 (6.9%)	222/2927 (7.6%)	RR 0.90 (0.75 to 1.09)	8 fewer per 1000 (from 19 fewer to 7 more)	MODERATE	IMPORTANT
Revascularisation (CABG) - 0 to 12 months[5]												
1	Randomised trial	Serious[ww]	No serious inconsistency	No serious indirectness	Serious[d]	None	22/858 (2.6%)	16/883 (1.8%)	RR 1.42 (0.75 to 2.68)	8 more per 1000 (from 5 fewer to 30 more)	LOW	IMPORTANT
Revascularisation (CABG) - 0 to 25 months[48,320]												
2	Randomised trials	Serious[ww]	No serious inconsistency	No serious indirectness	No serious imprecision	None	178/2046 (8.7%)	206/2044 (10.1%)	RR 0.87 (0.72 to 1.05)	13 fewer per 1000 (from 28 fewer to 5 more)	MODERATE	IMPORTANT
Adverse events[9,62,145,219,320]												
5	Randomised trials	Serious[xx]	Serious[yy]	Serious[zz]	Serious[d]	None	823/3471 (23.7%)	534/3199 (16.7%)	RR 1.31 (1.19 to 1.43)	52 more per 1000 (from 32 more to 72 more)	VERY LOW	IMPORTANT
Libido decrease[3,219,403]												
3	Randomised trials	Serious[ww]	No serious inconsistency	No serious indirectness	No serious imprecision	None	995/2837 (35.1%)	905/2560 (35.4%)	RR 1.04 (0.97 to 1.12)	14 more per 1000 (from 11 fewer to 42 more)	MODERATE	IMPORTANT
Quality of life												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) Participants were blinded, but it was unclear whether the authors performed allocation concealment.
(b) 95% confidence intervals crossed 2 MIDs (0.75 and 1.25).
(c) 95% confidence intervals crossed 1 MID (0.75).
(d) 95% confidence intervals crossed 1 MID (1.25).
(e) In all studies participants were blinded, however it was unclear whether the authors performed allocation concealment.
(f) Only 1 paper did not blind the participants however, the study only contributed to a small percentage of overall result. In the majority of papers, it was unclear ifthe authors performed allocation concealment.
(g) Heterogeneity was detected, I^2=55%, p=0.006.
(h) One paper had 27% people with HF and 1 had 61% people with left ventricular failure. Together these studies contributed a small percentage to the overall outcome.
(i) In all studies the participants were blinded, however in 3 studies that contributed to 50% of overall outcome, it was unclear if the authors performed allocation concealment.
(j) Heterogeneity detected, I^2=58%, p=0.05. One study showed more deaths in the beta-blocker treated group.
(k) One study had 27% people with HF and contributed to 17% of overall outcome.
(l) All but 1 study blinded the participants, however this paper only contributed to 3.2% of overall outcome. It was unclear in all if the authors performed allocation concealment.
(m) Heterogeneity was detected, I^2=49%, p=0.10.
(n) One study included 61% of people with left ventricular failure. This paper contributed to 14% of overall outcome.
(o) One study did not blind the participants and in 1 study it was unclear if the authors performed allocation concealment.
(p) Heterogeneity was detected, I^2=67%, p=0.03.
(q) All performed blinding of participants, except in 2 that contributed to small percentage of the outcome. It was unclear in 12 studies that contributed to the majority of overall outcome if the authors performed allocation concealment.
(r) Only 1 study with small participant numbers. It was unclear if the authors performed allocation concealment.
(s) All participants were blinded, and in the 2 studies that contributed to 50% of overall outcome, it was unclear if the authors performed allocation concealment.
(t) One study had 27% people with heart failure and contributed to 6% of overall outcome.
(u) All but 1 blinded the participants, however this paper only contributed to 6% of overall outcome. It was unclear in all studies whether the authors performed allocation concealment.
(v) Heterogeneity was detected, I^2=57%, p=0.05.
(w) One study was not blinded. It was unclear for all studies whether the authors performed allocation concealment.
(x) Heterogeneity detected, I^2=69%.
(y) Two studies that only contributed a small % were not double blinded. In 9 studies it was unclear if they performed allocation concealment and contributed to the majority of the outcome.
(z) Heterogeneity was detected I^2=54%, p=0.02.
(aa) One study included 61% ofpeople with left ventricular failure. This paper contributed to 7.5% of overall outcome
(bb) All 3 studies were double-blinded. However, in 2 of the 3 studies it was unclear if allocation concealment was performed.
(cc) Heterogeneity was detected, I^2=66% p=0.05. This is a result of 1 paper showing more deaths in the beta-blocker group, as opposed to the other 2 papers.
(dd) It is unclear in any of the studies if they performed allocation concealment.

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(ee)Heterogeneity was detected I^2=50%, p=0.09.
(ff) One study had 61% of people with left ventricular failure.
(gg) One study did not blind the participants but only contributed to a small percentage of the overall outcome. However, it is unclear whether the authors of the remaining papers performed allocation concealment.
(hh) Heterogeneity was detected, I^2=65%.This is the result of 1 paper that showed higher deaths in the beta-blocker group compared with the other paper.
(ii) Two studies did not blind the participants however they only contributed a small extent to the overall outcome. In 11 studies that contributed to majority of the overall outcome it is unclear if the authors performed allocation concealment.
(jj) One paper had 27% people with heart failure and 1 had 61% people with left ventricular failure. Together these studies contributed 12% to overall outcome
(kk)For all studies the participants were blinded. However, in 2 studies that contributed to 60% it is unclear if the authors performed allocation concealment.
(ll) Heterogeneity was detected, I^2=52% p=0.10.
(mm) It is unclear whether the authors of any paper performed allocation concealment.
(nn) Participants in the majority of studies were blinded. A large contribution to the result is from studies where it is unclear if the authors performed allocation concealment.
(oo) The study included 27% people with HF.
(pp) It is unclear in 1 of the studies that contributed to 66% of the overall outcome whether the authors performed allocation concealment.
(qq) The study that contributed 77% to the overall outcome was double-blinded but it was unclear whether the authors performed allocation concealment.
(rr) Heterogeneity was detected I^2=83%, p<0.00001.
(ss) In all studies participants were double-blinded. However, it was unclear in the studies that contributed majority of the overall outcome whether the authors performed allocation concealment.
(tt) Heterogeneity was detected, I^2=69% p=0.007.
(uu) One study had 27% people with HF and contributed to 41% of overall outcome.
(vv)RR > 5.
(ww) It was unclear if the authors performed allocation concealment.
(xx)It was unclear in studies that contributed more than 50% to overall outcome if the authors performed allocation concealment. However,the studies that contributed 90% of the overall outcome were double-blinded.
(yy)Heterogeneity was detected, I^2=69%.
(zz)One study had 27% people with HF and contributed to 44% of overall outcome.

Table 108: GRADE profile: Beta-blocker versus placebo (people who had an MI in the past (over 12 months ago))

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality[433,433]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	38/244 (15.6%)	11/168 (6.5%)	RR 2.38 (1.25 to 4.52)	90 more per 1000 (from 16 more to 230 more)	MODERATE	CRITICAL
Cardiovascular mortality[433,433]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	32/244 (13.1%)	10/168 (6%)	RR 2.20 (1.11 to 4.36)	71 more per 1000 (from 7 more to 200 more)	HIGH	CRITICAL
Reinfarction[433,433]												
1	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	28/244 (11.5%)	24/168 (14.3%)	RR 0.80 (0.48 to 1.34)	29 fewer per 1000 (from 74 fewer to 49 more)	LOW	IMPORTANT
Sudden death												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Stroke												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Revascularisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Rehospitalisation												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Adverse events												

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Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Beta-blocker	Control	Relative (95% CI)	Absolute	Quality	Importance
0	No evidence available	-	-	-	-	None	-	-	-	-	-	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

(a) There were unclear randomisation and allocation concealment methods. There were a large number of withdrawals in both groups. This is a sub-group analysis of the entire data set meaning that participants were not randomised to different starting dates following an MI.
(b) 95% confidence intervals crossed 1 MID (1.25).

7.5.1.3 Economic evidence

Published literature

The previous guideline, CG48, included 2 studies comparing beta-blocker versus placebo.[168,338]) A model was also developed as part of CG48 comparing carvedilol (beta-blocker) with placebo. Therefore the 2 studies previously included[168,338]) were excluded due to the availability of better evidence, as the CG48 model is more recent and conducted from the UK NHS perspective.

No relevant economic evaluations comparing different durations of treatment with beta-blockers with placebo that met the inclusion criteria were identified in the new search.

CG48 cost effectiveness model

A model was developed as part of CG48 to look at the cost effectiveness of a "new" generation of beta-blocker (carvedilol) in selected people who had an MI.

Only 1 trial [110]) was found which compared carvedilol with placebo and was used as the source of effectiveness data in the model. The treatment effects were measured in terms of prevention of cardiovascular events: non-fatal MI, hospital admission for heart failure, and cardiovascular related deaths. These in conjunction with relevant quality of life weights were then used to estimate QALYs.

The results suggest that third generation beta-blockers are highly cost-effective for this population with an estimated ICER of about £1,100/QALY gained, compared with placebo which is below the NICE threshold of £20,000/QALY.

This analysis is also summarised in the economic evidence profile below (Table 109). The full methods and results from CG48 are included in Appendix L.

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Table 109: Economic evidence profile: beta-blocker versus placebo

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects (QALYs)	Cost effectiveness (£/QALY)	Uncertainty
CG48 model	Partially applicable [(a)]	Minor limitations	• - Intervention to prevent cardiovascular events. • - The beta-blocker analysed was carvedilol • - Lifetime cost-utility model (QALYs) with cycles of 6 months. • - Probabilities and relative treatment effects: i. Probabilities of secondary cardiovascular events and relative treatment effects taken from the CAPRICORN trial [110] ii. Non-cardiovascular mortality by age and sex taken from the life tables for England and Wales prepared by the Government Actuaries Department[171] iii. It was assumed that post MI cohort is at increased risk of non-cardiovascular death (2 fold risk) compared with the general population (expert opinion)	65 year old male: 872 65 year old female: 906	65 year old male: 0.80 65 year old female: 0.82	65 year old male: 1,091 65 year old female: 1,102	Probability that beta-blocker is the most cost effective option when compared to placebo is around 93% at £20,000/QALY willingness to pay threshold. The result is robust to all the parameters tested in sensitivity analysis (efficacy of treatment, relative risk of non CVD death, quality of life loss due to treatment side effects, health state utilities, cost of health states, age and sex, worse case scenarios).

(a)Some uncertainty about the applicability of 2005/2006 prices. Given the change in current care with the introduction of primary PCI, the incidence of major cardiovascular events (with the exception of stroke) may have been reduced since then, affecting the baseline risk of all patient; therefore beta-blockers may be less cost-effective now.

7.5.1.4 Evidence statements

7.5.1.4.1 Clinical

People who had an MI and who have received treatment within 72 hours of the MI

Beta-blocker versus placebo (from overlapping time periods)

- Forty-eight studies with 77,719 people suggested that beta-blockers are equally effective as placebo at reducing the risk of all-cause mortality [Moderate quality evidence].
- Five studies with 2543 people showed there is no difference in the effect between beta-blockers and placebo on the risk of cardiac mortality [Low quality evidence].
- Six studies with 1441 people showed beta-blockers may reduce the risk sudden death compared with placebo, but there was some uncertainty [Low quality evidence].
- Thirteen studies with 65,846 people showed beta-blockers may reduce the risk of reinfarction compared with placebo [Low quality evidence].
- Two studies with 341 people showed beta-blockers may reduce the risk of revascularisation when compared with placebo but there was some uncertainty [Low quality evidence].
- Five studies with 48,538 people showed there is no difference between beta-blockers and placebo on the risk of stroke but there was some uncertainty [Low quality evidence].

Adverse events

- Ten studies with 49,445 people suggested that beta-blockers may increase the risk of adverse events when compared with placebo [Moderate quality evidence].
- Three studies with 737 people showed that beta-blockers increase the risk of dizziness when compared with placebo but there was some uncertainty [Low quality evidence].
- Four studies with 805 people showed that beta-blockers increase the risk of fatigue/tiredness when compared with placebo but there was some uncertainty [Low quality evidence].
- Fifteen studies with 56,208 people showed that beta-blockers increase the risk of sinus bradycardia [Moderate quality evidence].
- Two studies with 405 people showed that beta-blockers increase the risk of nightmares compared with placebo but there was considerable uncertainty [Low quality evidence].
- Unclear effects on libido.
- No evidence on rehospitalisation was identified.
- No evidence on quality of life was identified.

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Optimal duration (distinct time periods)

All-cause mortality

- Thirty-nine studies with 56,085 people showed no difference in the effect between beta-blockers and placebo on the risk of all-cause mortality within 6 weeks of having an MI [Moderate quality evidence].
- Five studies with 1562 people showed beta-blockers may reduce the risk of all-cause mortality compared with placebo from 6 weeks to 12 months after having an MI but there was some uncertainty [Low quality evidence].

- One study with 200 people showed that beta-blockers may reduce the risk of all-cause mortality compared with placebo from 6 weeks to 24 months after having an MI but there was considerable uncertainty [Very low quality evidence].

Cardiac mortality

- Two studies with 1209 people showed that beta-blockers have no effect on the risk of cardiac death compared with placebo from 0-3 months after having an MI [Very low quality evidence].
- One study with 474 people showed that beta-blockers may increase the risk of cardiac mortality compared with placebo from 4-6 months after having an MI, but there was considerable uncertainty [Very low quality evidence].

Sudden death

- Six studies with 1141 people showed that beta-blockers may decrease the risk of sudden death compared with placebo from 0 to 3 months after having an MI, but there was some uncertainty [Low quality evidence].
- One study with 474 people showed that beta-blockers may decrease the risk of sudden death compared with placebo from 4-6 months after having an MI, but there was considerable uncertainty [Very low quality evidence].

Reinfarction

- One study with 1395 people showed no difference between beta-blockers and placebo on the risk of reinfarction from 0 to 3 months after having an MI but there was considerable uncertainty [Very low quality evidence].
- One study with 1395 people showed no difference between beta-blockers and placebo on the risk of reinfarction from 4 to 7 months after having an MI but there was considerable uncertainty [Very low quality evidence].
- One study with 1395 people showed no difference between beta-blockers and placebo on the risk of reinfarction from 8 to 12 months after having an MI but there was considerable uncertainty [Very low quality evidence].
- One study with 1395 people showed no difference between beta-blockers and placebo on the risk of reinfarction from 13 to 18 months after having an MI but there was considerable uncertainty [Very low quality evidence].

Optimal duration (overlapping time points)

All-cause mortality

- Forty-eight studies with 55,173 people showed no difference between beta-blockers and placebo on the risk of all-cause mortality after 6 weeks of treatment [Moderate quality evidence].
- Thirty-two studies with 3370 people showed that up to 6 weeks of beta-blockers may reduce the risk of all-cause mortality compared with placebo but there was some uncertainty [Low quality evidence].
- Eight studies with 19406 people showed that up to 12 months of beta-blockers may reduce the risk of all-cause mortality compared with placebo [Moderate quality evidence].
- Three studies with 770 people showed that up to 24 months of beta-blockers may reduce the risk of all-cause mortality compared with placebo but there was some uncertainty [Low quality evidence].

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Cardiac mortality

- One study with 735 people showed no difference between less than 6 weeks of beta-blockers and placebo on the risk of cardiac mortality but there was some uncertainty [Very low quality evidence].
- One study with 313 people showed that up to 6 months of beta-blockers may increase the risk of cardiac mortality compared with placebo but there was considerable uncertainty [Very low quality evidence].
- Two studies with 1194 people showed that up to 12 months of beta-blockers may increase the risk of cardiac death compared with placebo but there was some uncertainty [Very low quality evidence].
- One study with 301 people showed that up to 24 months of beta-blockers may decrease the risk of cardiac mortality compared with placebo but there was some uncertainty [Low quality evidence].

Sudden death

- Four studies with 667 people showed that less than 6 weeks of beta-blockers may decrease the risk of sudden death compared with placebo but there was considerable uncertainty [Very low quality evidence].
- One study with 473 peoples showed that up to 12 months of beta-blockers may decrease the risk of sudden death compared with placebo but there was considerable uncertainty [Low quality evidence].
- One study with 301 people showed that up to 25 months of beta-blockers may decrease the risk of sudden death compared with placebo but there was some uncertainty [Low quality evidence].

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Reinfarction

- Four studies with 47,901 people showed that less than 6 weeks of beta-blockers may decrease the risk of reinfarction compared with placebo [Low quality evidence].
- Five studies with 1496 people showed that up to 6 months of beta-blockers may decrease the risk of reinfarction compared with placebo but there was considerable uncertainty [Very low quality evidence].
- Three studies with 16,155 people showed that up to 12 months of beta-blockers has no effect on the risk of reinfarction compared with placebo [Low quality evidence].
- One study with 301 people showed that up to 25 months of beta-blockers may decrease the risk of reinfarction compared with placebo but there was some uncertainty [Low quality evidence].

Stroke

- Three studies with 46,781 people showed that up to 6 weeks of beta-blockers has no effect on the risk of stroke compared with placebo [Low quality evidence].
- One study with 1456 people showed that up to 12 months of beta-blockers may increase the risk of stroke compared with placebo but there was considerable uncertainty [Low quality evidence].
- One study with 302 people showed that more than 24 months of beta-blockers may decrease the risk of stroke compared with placebo but there was considerable uncertainty [Very low quality evidence].

Revascularisation

- One study with 40 people showed that more than 25 months of beta-blockers may decrease the risk of revascularisation compared with placebo but there was some uncertainty [Low quality evidence].

People who had an MI and who have been initiated with treatment between 72 hours and 12 months of the MI

Beta-blocker versus placebo (from overlapping time periods)

- Fourteen studies with 17642 people showed that beta-blockers may reduce the risk of all-cause mortality compared with placebo but there was some uncertainty [Very low quality evidence].
- Twelve studies with 16394 people showed that beta-blockers may reduce the risk of cardiac mortality compared with placebo but there was some uncertainty [Low quality evidence].
- Twelve studies with 16482 people showed that beta-blockers may reduce the risk of sudden death compared with placebo, but there was some uncertainty [Very low quality evidence].
- Thirteen studies with 17089 people showed beta-blockers may reduce the risk of reinfarction compared with placebo but there was some uncertainty [Very low quality evidence].
- Two studies with 5831 people showed beta-blockers may reduce the risk of revascularisation compared with placebo [Very low quality evidence.
- One study with 3837 people showed beta-blockers are equally effective as placebo on the risk of stroke, but there was considerable uncertainty [Very low quality evidence].
- Two studies with1959 people showed that beta-blockers may reduce the risk of rehospitalisation compared with placebo [Moderate quality evidence].

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Adverse events

- Five studies with 6670 people suggested that beta-blockers may increase the risk of adverse events compared with placebo but there was some uncertainty [Very low quality evidence].
- Three studies with 6681 people suggested that beta-blockers have no effect on the risk of fatigue compared with placebo but there was considerable uncertainty [High quality evidence].
- Six studies with 8370 people showed that beta-blockers may increase the risk of dizziness compared with placebo but there was some uncertainty [Very low quality evidence].
- Six studies with 8207 people showed that beta-blockers may increase the risk of bradycardia compared with placebo [Very low quality evidence].
- Four studies with 6382 people showed that beta-blockers have no effect on change in dreaming compared with placebo but there was some uncertainty [Low quality evidence].
- Three studies with 5397 people showed that beta-blockers have no effect on libido compared with placebo [Moderate quality evidence].

Optimal duration (distinct time periods)

All-cause mortality

- Four studies with 10076 people showed that beta-blockers may reduce the risk of all-cause mortality compared with placebo within less than 6 months of having an MI but there was some uncertainty [Low quality evidence].

- Three studies with 8117 people showed beta-blockers have no effect on the risk of all-cause mortality compared with placebo from 7 to 12 months after having an MI but there was considerable uncertainty [Low quality evidence].
- Three studies with 8117 people showed that beta-blockers may reduce the risk of all-cause mortality compared with placebo from 13 to 24 months after having an MI but there was some uncertainty [Low quality evidence].
- Two studies with 5721 people showed that beta-blockers have a similar effect on the risk of all-cause mortality compared with placebo from 25 to 36 months after having an MI but there was some uncertainty [Low quality evidence].
- One study with 3837 people showed that beta-blockers have a similar effect on the risk of all-cause mortality compared with placebo after 36 months of having an MI but there was considerable uncertainty [Low quality evidence].
- One studies with 1959 people showed that beta-blockers have a similar effect on the risk of all-cause mortality compared with placebo after 6 week to 24 months of having an MI but there was considerable uncertainty [Low quality evidence].

Cardiac mortality

- One study with 2396 people showed that beta-blockers decrease the risk of cardiac mortality compared with placebo from 0 to 3 months after having an MI but there was some uncertainty [Low quality evidence].
- One study with 2396 people showed that beta-blockers have a similar effect on the risk of cardiac mortality compared with placebo from 4 to 7 months after having an MI, but there was considerable uncertainty [Very low quality evidence].
- One study with 2396 people showed that beta-blockers may increase the risk of cardiac mortality compared with placebo from 8 to 12 months after having an MI, but there was some uncertainty [Moderate quality evidence].
- One study with 2396 people showed that beta-blockers have a similar effect on the risk of cardiac mortality compared with placebo from 13 to 18 months after having an MI, but there was considerable uncertainty [Very low quality evidence].

Sudden death

- One studies with 2396 people showed that beta-blockers may decrease the risk of sudden death compared with placebo within 3 months of having an MI, but there was some uncertainty [Very low quality evidence].
- One study with 2396 people showed that beta-blockers have no effect on the risk of sudden death compared with placebo from 4 to 7 months after having an MI, but there was considerable uncertainty [Very low quality evidence].
- One study with 2396 people showed that beta-blockers have no effect on the risk of sudden death compared with placebo from 8 to 12 months after having an MI, but there was considerable uncertainty [Low quality evidence].
- One study with 2396 people showed that beta-blockers have no effect on the risk of sudden death compared with placebo from 13 to 18 months after having an MI, but there was considerable uncertainty [Very low quality evidence].

Reinfarction

- One study with 4355 people showed that beta-blockers may reduce the risk of reinfarction within 3 months of having an MI but there was some uncertainty [Low quality evidence].

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- One study with 2396 people showed no difference between beta-blockers and placebo on the risk of reinfarction from 4 to 7 months after having an MI but there was considerable uncertainty [Low quality evidence].
- One study with 2396 people showed no difference between beta-blockers and placebo on the risk of reinfarction from 8 to 12 months after having an MI but there was considerable uncertainty [Low quality evidence].
- One study with 2396 people showed no difference between beta-blockers and placebo on the risk of reinfarction from 13 to 18 months after having an MI but there was considerable uncertainty [Very low quality evidence].
- One study with 2396 people showed beta-blockers may reduce the risk of reinfarction compared with placebo from 6 weeks to 24 months after having an MI but there was some uncertainty [Low quality evidence].

Optimal duration (overlapping time points)

All-cause mortality

- Five studies with 4917 people showed beta-blockers reduce the risk of all-cause mortality up until 12 months compared with placebo but there was some uncertainty [Very low quality evidence].
- Five studies with 6060 people showed that beta-blockers may reduce the risk of all-cause mortality compared with placebo up until 24 months but there was some uncertainty [Very low quality evidence].
- Four studies with 6665 people showed that beta-blockers may reduce the risk of all-cause mortality compared with placebo after 24 months but there was some uncertainty [Very low quality evidence].

Sudden death

- Four studies with 4364 people showed beta-blockers reduce the risk of sudden death up until 12 months compared with placebo but there was some uncertainty [Low quality evidence].
- Five studies with 6056 people showed that beta-blockers may reduce the risk of sudden death compared with placebo up until 24 months but there was some uncertainty [Very low quality evidence].
- Three studies with 5974 people showed that beta-blockers may reduce the risk of sudden death compared with placebo after 25 months but there was some uncertainty [Very low quality evidence].

Cardiac mortality

- Three studies with 3757 people showed beta-blockers reduce the risk of cardiac mortality up until 12 months compared with placebo but there was some uncertainty [Very low quality evidence].
- Five studies with 6060 people showed that beta-blockers may reduce the risk of cardiac mortality compared with placebo up until 24 months but there was some uncertainty [Very low quality evidence].
- Four studies with 6665 people showed that beta-blockers may reduce the risk of cardiac mortality compared with placebo after 25 months but there was some uncertainty [Very low quality evidence].

Reinfarction

- Four studies with 4094 people showed that beta-blockers may decrease the risk of reinfarction compared with placebo after 12 months but there was some uncertainty [Very low quality evidence].

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- Four studies with 3665 people showed that beta-blockers may decrease the risk of reinfarction compared with placebo up until 24 months but there was considerable uncertainty [Very low quality evidence].
- Five studies with 9060 people showed that beta-blockers may decrease the risk of reinfarction compared with placebo up after 25 months but there was some uncertainty [Low quality evidence].

Revascularisation

- One study with 1741 people showed that up to 12 months of beta-blockers may increase the risk of revascularisation compared with placebo but there was some uncertainty [Low quality evidence].
- Two studies with 4090 people showed that more than 25 months of beta-blockers may decrease the risk of revascularisation compared with placebo [Moderate quality evidence].

Quality of life

- No evidence on quality of life was identified.

People who had an MI in the past (greater than 12 months ago)

- One study with 412 people showed that beta-blockers may increase the risk of all-cause mortality compared with placebo [Moderate quality evidence].
- One study with 412 people showed that beta-blockers may increase the risk of cardiac mortality compared with placebo but there was some uncertainty [High quality evidence].
- One study with 412 people showed that beta-blockers may decrease the risk of reinfarction compare with placebo but there was considerable uncertainty [Low quality evidence].
- No evidence on sudden death was identified.
- No evidence on stroke was identified.
- No evidence on revascularisation was identified.
- No evidence on rehospitalisation was identified.
- No evidence on adverse events was identified.
- No evidence on quality of life was identified.

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7.5.1.5 Economic

- One original cost-effectiveness analysis suggested that beta-blockers may be cost effective compared to placebo in people who had an MI (ICER around £1,100 per QALY gained). This analysis was assessed as partially applicable with minor limitations.

7.5.2 Optimal initiation of beta-blocker therapy

7.5.2.1 Is there an optimal time for a beta-blocker to be initiated in people who have had a MI?

For full details see review protocol in Appendix C.

7.5.2.2 Clinical evidence

Two studies were included in this review.[78,388] Evidence from these studies is summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix D, forest

plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J. A summary of the included studies is shown in Table 110.

The previous guideline, CG48, recommended treatment with a beta-blocker should be offered to all people after an MI and suggests that treatment should be initiated as soon as possible when the person is clinically stable and titrated upwards to the maximum tolerated dose. At the time of publication of CG48, no RCTs were found comparing different times for initiating beta-blocker therapy after an acute MI. As no RCTs were identified, the recommendations were based on a separate analysis of RCTs included in a meta-analysis by Freemantle et al. (1999).[151] This study found no reason to delay treatment with a beta-blocker and that early initiation will lead to a greater period when benefits may be accrued from treatment. Given the lack of data to support the recommendations in CG48 and the change in acute management strategies to favour primary PCI, the update of CG48 has reviewed this question.

Of the 2 studies included in this review, only 1 randomised people to different times of initiating beta-blocker treatment.[387,388] Conversely, in the study by Califf et al (2009), the results on beta-blockers are taken from a subgroup analysis of people in a study (VALIANT study) that compared an ARB with an ACE inhibitor (valsartan and captopril).[78,78] Physicians were encouraged to prescribe beta-blockers because of previous evidence of benefit and results from these people were then categorised according to whether beta-blocker treatment was initiated: i) both before randomisation and at discharge, ii) before randomisation, iii) at discharge, or iv) neither time point (no beta-blocker use). A multivariate Cox-model was performed, adjusting for 38 predictors of mortality, to calculate long-term survival in each of the 4 groups. These results are presented in this review. However, they must be viewed with caution since a large number of covariates can increase the risk of false positive conclusions.[437,438]

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Table 110: Summary of included studies

Study	Intervention/ comparison	Population	Outcomes	Comments
Califf et al 2009[78,78] VALIANT	Subgroup analysis from an RCT of valsartan versus captopril versus valsartan plus captopril. Beta-blocker use before/after randomisation, at discharge or not at all compared (but not randomised) Median interval from MI symptoms to randomisation was 4.9d MI less than 4.9 days versus time at discharge	People who had an MI (direct population) and left ventricular systolic dysfunction or heart failure or both (<25% heart failure). LVSD: Ejection fraction 33%-34%. Chronic obstructive pulmonary disease: 7-10%. Comparing 2 of 4 groups, before randomisation versus discharge. n=2,188	Survival. • HR (over 45 days), adjusted for predictors of mortality (based on multivariate Cox model). • Comparing before randomisation versus discharge.	• Physicians encouraged to prescribe beta-blockers. • Beta-blocker use was recorded at randomisation (median 4.9 days after randomisation) and at each study visit thereafter; specific drug used, dose and adherence not recorded. • People not randomly assigned to beta-blockers and major differences between groups receiving or not receiving treatment • Provided outcome that relation between BB use at discharge and survival over 45 days was the same in people with a LVEF over 40% and those with a LVEF under 40% (chi-square = 0.36, p =0.55)
Roberts et al 1991 [387,388] TIMI II-B	Immediate (as soon as possible after initiating recombinant tissue-type plasminogen activator (rt-PA) versus delayed (6-8 days) beta-blocker therapy 2 hours versus 6-8 days	People who had an MI (direct population) Normal LV function = average ejection fraction at discharge was 50%, n=1,434 Number of people with COPD not stated	1 year • Global left ventricular ejection fraction. • Mortality. • Reinfarction (fatal, non-fatal or both). • Severe ischaemic event.	• RCT; ITT analysis

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Table 111: GRADE profile: beta-blocker (early initiation- 2 hours) versus beta-blocker (late initiation - 6-8 days)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early initiation	Late initiation	Relative (95% CI)	Absolute		
Survival[78,78]												
1	Randomised trial	Very serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	-	-	HR 1.03 (0.83 to 1.27)	-	VERY LOW	CRITICAL
Death - at 6 days[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	None	17/720 (2.4%)	17/714 (2.4%)	RR 0.99 (0.51 to 1.93)	0 fewer per 1000 (from 12 fewer to 22 more)	VERY LOW	CRITICAL
Death - at 6 weeks[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	None	26/720 (3.6%)	25/714 (3.5%)	RR 1.03 (0.6 to 1.77)	1 more per 1000 (from 14 fewer to 27 more)	VERY LOW	CRITICAL
Death - at 1 year[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	None	34/720 (4.7%)	35/714 (4.9%)	RR 0.96 (0.61 to 1.53)	2 fewer per 1000 (from 19 fewer to 26 more)	VERY LOW	CRITICAL
Fatal or non-fatal reinfarction - at 6 days[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[f]	None	19/720 (2.6%)	36/714 (5%)	RR 0.52 (0.3 to 0.9)	24 fewer per 1000 (from 5 fewer to 35 fewer)	LOW	IMPORTANT
Fatal or non-fatal reinfarction - at 6 weeks[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[f]	None	32/720 (4.4%)	51/714 (7.1%)	RR 0.62 (0.4 to 0.96)	27 fewer per 1000 (from 3 fewer to 43	LOW	IMPORTANT

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Quality assessment							No of patients		Effect		Quality	Importance
										fewer)		
Fatal or non-fatal reinfarction - at 1 year[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[g]	None	60/720 (8.3%)	67/714 (9.4%)	RR 0.89 (0.64 to 1.24)	10 fewer per 1000 (from 34 fewer to 23 more)	LOW	IMPORTANT
Severe ischaemic event - less than 6 days[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[f]	None	2/720 (0.28%)	10/714 (1.4%)	RR 0.2 (0.04 to 0.9)	11 fewer per 1000 (from 1 fewer to 13 fewer)	LOW	IMPORTANT
Severe ischaemic event - at 6 weeks[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	Serious[g]	None	92/720 (12.8%)	102/714 (14.3%)	RR 0.89 (0.69 to 1.16)	16 fewer per 1000 (from 44 fewer to 23 more)	LOW	IMPORTANT
Severe ischaemic event – at 1 year[387,388]												
1	Randomised trial	Serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	170/720 (23.6%)	170/714 (23.8%)	RR 0.99 (0.82 to 1.19)	2 fewer per 1000 (from 43 fewer to 45 more)	MODERATE	IMPORTANT
Quality of life												
0	No evidence available.	-	-	-	-	-	-	-	-	-	–	-

(a) Participants were not randomly assigned to beta-blocker treatments, specific drug and dose were not recorded for beta-blocker use. The results are a subgroup analysis from an RCT, VALIANT. Participants were divided into their timing of initiating treatment and were not matched for baseline characteristics.

(b) A multivariate Cox model was used to determine the relationship between the use of BB and outcomes. Predictors were adjusted for various covariates incl: age, weight, BMI, Q wave, MI, medical history. Survival models can be viewed as consisting of 2 parts: the underlying hazard function, describing how the hazard (risk) changes over time; and the effect parameters, describing how the hazard varies in response to explanatory covariates. This model relies on the assumption that the factors investigated have a constant impact on the hazard or risk over time. If time-dependent variables are included without appropriate modelling, the PH assumption is violated. As a result, misleading effect estimates can be derived. It is unclear if Califf et al. checked whether the factors have a constant impact on the hazard over time. Furthermore, the results were adjusted for 38 predictors of mortality and this high number can increase the risk of false positive conclusions.

(c) 95% CI crosses line of no effect and 1 MID (1.25).

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(d) Unclear on how they randomised, performed allocation concealment or if investigators or participants were blinded to the treatment.
(e) 95% CI crosses 2 MIDs (0.75 and 1.25).
(f) 95% confidence intervals crossed 1 MID (0.75) .
(g) 95% confidence intervals crossed 1 MID (0.75) and line of no effect (1).

7.5.2.3 Economic evidence

Published literature

No relevant economic evaluations comparing early with late initiation of beta-blockers that met the inclusion criteria were identified. See also the study selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix M to aid consideration of cost effectiveness.

7.5.2.4 Evidence statements

7.5.2.4.1 Clinical

Long-term survival (less than 4.9 days of MI versus discharge)

- One study of 2118 people showed that there was no difference in the outlook for survival in those treated early with beta-blockers compared with those treated late after a myocardial infarction (Very low quality evidence).

All-cause mortality (2 hours versus 6-8 days after an MI)

- In 1 study with 1434 people there was too much uncertainty to determine whether there was a difference in the risk of all-cause mortality within 6 days in people treated with beta-blockers early versus late (Very low quality evidence).
- In 1 study with 1434 people there was too much uncertainty to determine whether there was a difference in the risk of all-cause mortality within 6 weeks in people treated with beta-blockers early versus late (Very low quality evidence).
- In 1 study with 1434 people there was too much uncertainty to determine whether there was a difference in the risk of all-cause mortality within 1 year in people treated with beta-blockers early versus late (Very low quality evidence).

Reinfarction (fatal and non-fatal) (2 hours versus 6-8 days after an MI)

- One study with 1434 people showed that early beta-blocker treatment reduces the risk of reinfarction within 6 days of treatment compared with late beta-blocker treatment, but there was some uncertainty (Low quality evidence).
- One study with 1434 people showed that early beta-blocker treatment reduces the risk of reinfarction within 6 weeks of treatment compared with late beta-blocker treatment, but there was some uncertainty (Low quality evidence).
- In 1 study with 1434 people there was no difference in the risk of reinfarction after 1 year in people treated early with beta-blockers compared with those treated late, but there was some uncertainty (Low quality evidence).

Severe ischaemic event (2 hours versus 6-8 days after an MI)

- One study with 1434 people there was no difference in the risk of a severe ischaemic event within 6 days in people treated early compared with late beta-blocker treatment, but there was some uncertainty (Low quality evidence).

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- In 1 study with 1434 people there was no difference in the risk of a severe ischaemic event after 6 weeks in people treated early with beta-blockers compared with those treated late, but there was some uncertainty (Low quality evidence).
- One study with 1434 people showed that initiating beta-blocker treatment early versus late are equally effective on the risk of a severe ischaemic event after 1 year of treatment (Moderate quality evidence).

Additional outcomes: (less than 4.9 days of MI versus discharge)

- Califf et al. stated that the relation between beta-blocker use at discharge and survival over45 days was the same in peoplewith a LVEF over 40% and those with a LVEF under 40% (chi-square = 0.36, p =0.55).[78,78]
- The group who received beta-blockers both pre-randomisation and at discharge had the best survival curve, followed by those who initiated beta-blockers between randomisation and discharge.[78,78]

7.5.2.5 Economic

No relevant economic evaluations were identified.

7.5.3 Recommendations and link to evidence

Recommendation	80. Offer people a beta-blocker as soon as possible after an MI, when the person is haemodynamically stable. [new 2013]
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant).
Trade-off between clinical benefits and harms	Two studies were identified that addressed the question of when is the best time to initiate beta-blockers. One study showed that starting treatment within 2 hours reduced the risk of reinfarction and severe ischaemic events compared with starting 6 days later. The benefits were still evident after 12 months for reinfarction and after 6 weeks for severe ischaemic events. No benefit was evident at 12 months for severe ischaemic events. No benefit was detected for the risk of all-cause mortality. The other study showed no difference in the long-term risk of mortality if treatment is initiated before discharge versus 4.9 days after discharge. No data on adverse events were found. However, the GDG commented that the review of beta-blockers compared to placebo provided insight into the magnitude of potential adverse events. There was an increased risk of adverse events in people treated with beta-blockers in the review. However, they were not considered severe and mostly manageable. For this reason, the GDG felt that beta-blocker treatment

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	should still be recommended. No evidence from RCTs was found to help us make a recommendation on the treatment of beta-blockers in those who had undergone primary PCI and the GDG therefore did not wish to make any changes to the recommendation in line with changes to current acute management. The GDG therefore considered that, despite the lack of data relating to adverse events at the time of initiating beta-blockers, the benefits of initiating beta-blockers early on the incidence of reinfarction and severe ischaemic events, outweighed potential adverse events. The group felt that it was unlikely that the difference between early and late initiation would have significant effects on the incidence of adverse events.
Economic considerations	No economic evidence was identified to compare different timings of initiation of beta-blockers. However, given the small unit cost of beta-blockers and the potential for health benefit associated with early initiation as identified in the clinical review, initiating the treatment earlier would be cost-saving as it would add a negligible drug cost but would prevent further costly events such as reinfarctions.
Quality of evidence	Overall, the quality of the evidence was generally graded as low, ranging from very low to moderate. Both studies lacked details regarding the population, specifically the type of acute management and the type of MI experienced. Given the date of publication, participants in 1 study may have undergone PCI but not in the other. The GDG noted that this was particularly limiting given changes in acute management since the previous guideline, CG48. Additionally, the GDG highlighted that as well as changes in acute management (for example. PCI), pharmacological therapies such as ACE inhibitors, statins and dual antiplatelet therapy would not have been given to people in older studies, therefore it was important to consider differences in acute management and secondary prevention when interpreting the results of the older study. Furthermore, people were not randomised in 1 study and they provided adjusted hazard ratios which may introduce bias. In the other study, beta-blockers were administered intravenously within 2 hours of the MI. This is no longer accepted practice. The GDG noted that neither study included in this review was included in the previous guideline, CG48, as no formal review was conducted on the initiation of beta-blockers. Therefore, the original recommendation was based upon the results of a single systematic review. This review was not included in the current question as higher quality evidence (RCTs) to answer the question was identified and included. No economic evidence was found on this question. The economic evidence was based on an original model with partial applicability and minor limitations.
Other considerations	The GDG did not feel that there were any important equity considerations in the initiation of beta-blockers but highlighted that it was important to consider medical contraindications when initiating beta-blockers in a person who has had an MI. For example, the GDG noted that the current practice of some clinicians would be to avoid beta-blocker therapy in some populations, such as those with stable airways disease, despite evidence that the treatment could be tolerated.

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Recommendation	81. Communicate plans for titrating beta-blockers up to the maximum tolerated or target dose, for example, in the discharge summary. [new 2013]
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant).
Trade-off between clinical benefits and harms	The current review did not aim to identify evidence relating to the titration of beta-blockers, however the GDG felt that it was important to highlight the need to ensure full titration of beta-blockers to ensure optimal effectiveness. The risk of not achieving full titration would be that a person may not receive the full benefits of the beta-blockers outlined in the following recommendations. If people were left at a lower dose they would also be at a decreased risk of suffering from adverse effects but the GDG felt the benefits of the drug outweighed the risks and therefore a maximum tolerated or target dose should be aimed for. Given this, the GDG did not feel that it would be appropriate to recommend a time for completion of full titration and the group noted that clinical practice currently varies depending on the starting dose given. However, it was agreed that changes in acute management have meant that the context of care has now changed. Given the shorter period of acute care associated with current clinical practice and the increased likelihood that care will be continued in a community setting, it was considered important to highlight the need to ensure full titration. The GDG felt that an example of how this could be achieved effectively would be via the discharge summary.
Economic considerations	No economic evidence was identified to compare titration regimens with beta-blockers. It is likely that the difference in cost between titration strategies is minimal given the low unit cost of beta-blockers.
Quality of evidence	This recommendation was based upon informal consensus of the GDG.
Other considerations	The GDG noted that the titration of beta-blockers should be conducted in line with recommendations from the British National Formulary (BNF). The GDG identified this recommendation as a key priority for implementation. It was felt, as for the recommendation on ACE inhibitor titration, titration of beta-blockers to the maximum tolerated or target dose may not be achieved consistently in clinical practice, particularly given changes in acute management, and that arrangements should be made to ensure that this is the case.

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Recommendation	82. Continue a beta-blocker for at least 12 months after an MI in people

	without left ventricular systolic dysfunction or heart failure. [new 2013]
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant).
Trade-off between clinical benefits and harms	Evidence in people who had an MI without LVSD was limited, of the data available on those who had treatment initiated within 72 hours of the MI, the effects of beta-blockers (up to 24 months) on all-cause mortality, cardiac mortality, and reinfarction was unclear but they reduce the risk of sudden death. Beta-blockers were, however, associated with an increased risk of adverse events in people without LVSD. Data in people without LVSD but whose treatment was initiated in the sub-acute period (greater than72 hours to 12 months following an MI) showed a clear benefit of beta-blocker treatment (up to 22 months) on all-cause mortality, sudden death, cardiac mortality and reinfarction. It was also associated with an increased risk of adverse events, including a decrease in sexual function. No evidence was found on stroke, rehospitalisation or quality of life. The GDG felt that the side-effects of beta-blockers were generally not severe and were manageable; therefore they felt the potential benefits of providing treatment with a beta-blocker treatment for at least 12 months outweighed the generally accepted risks. The majority of the evidence was from studies that treated people up to 12 months, only 2 small studies continued treatment for 22-24 months. Furthermore, although the previous guideline, CG48, recommended indefinite treatment with beta-blockers, following an MI, there was no evidence identified in the current review to suggest a further benefit of indefinite treatment with beta-blockers. The GDG therefore agreed to recommend treatment for at least 12 months in people without LVSD who had an MI. This is in contrast to the recommendation for those who have LVSD which states that beta-blockers should be continued indefinitely. The GDG agreed that people without LVSD have a lower baseline risk, therefore, indefinite use of beta-blockers may not be necessary. Furthermore, the data were mostly on those who were treated medically not with primary PCI, therefore, given the better outcomes in people who receive current treatment and because this is a lower risk population, the GDG were less confident recommending the indefinite use of beta-blockers. The GDG acknowledged that there was no evidence to support routine withdrawal of treatment in those people currently being treated with beta-blockers for longer than 12 months following an MI.
Economic considerations	No economic evidence was about people without LVSD who had an MI. The GDG considered the unit costs of beta-blockers together with the results of the clinical review and concluded that the low cost of these drugs would be offset by even a

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	small increase in health benefits in this population.
Quality of evidence	The quality of evidence on people with and without LVSD was graded from very low to moderate quality. The results from the ten studies on people who had an MI and without LVSD, were mostly imprecise that is the 95% confidence interval was wide and crossed 1 or 2 minimal important differences (0.75 or 1.25). In contrast, the results from the 1 study on those whose treatment had been initiated between 72 hours and 12 months of the MI, showed greater precision with tighter confidence intervals. The results showed a clear benefit of beta-blockers on clinical outcomes within 22 months of treatment. Detail on methodology was generally insufficient, that is randomisation and allocation concealment. Most studies recruited a small number of participants and few events were recorded. The study with the largest participant numbers gave beta-blockers for only for 15 days and the study that had the longest follow-up (24 months) had very small participant numbers. It is also unclear when the events took place, so it was difficult for the GDG to make long-term recommendations. No evidence was available on people who have undergone primary PCI and healthcare professionals should consider that there is no compelling evidence to support the indefinite use of beta-blockers in this population. No economic evidence was available on this population.
Other considerations	This recommendation represents a change in the advice to give all people who had an MI and have normal LV function a beta-blocker indefinitely. The GDG felt that after 12 months after the MI the evidence was much weaker in the context of changes in acute management, and consideration could be given to discontinuing betablockers at this stage. The clinician should consider the risks and benefits of continuing treatment for the individual, taking into account the extent of coronary disease or evidence of ischaemia, concurrent conditions, and any adverse effects when discussing this balance with the person who has had an MI. The GDG felt that this was an important area in which further research should be carried out, to identify whether there are any additional benefits of treatment greater than 12 month in those with preserved LV function. A research recommendation was therefore made for an RCT on long term (greater than 12 months) versus 12 months of beta-blocker treatment (see Appendix N).

Recommendation	**83. Continue a beta-blocker indefinitely in people with left ventricular systolic dysfunction. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but

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	clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant).
Trade-off between clinical benefits and harms	Limited evidence was found on the use of beta-blockers in people with left ventricular dysfunction but without heart failure. Two trials were identified in a population who had an MI (that is, who had an MI between 72 hours and 12 months earlier). The results from the larger trial shows beta-blockers may reduce the risk of all-cause mortality, sudden death, cardiac death, and reinfarction. These benefits were detected after 30 days and for up to 24 months. These gains, however, need to be weighed up against the increased risk of adverse events. No data were available on the risk of stroke, re-hospitalisation or quality of life. Beta-blockers had unclear effects on the risk of revascularisation and bradycardia. The GDG felt that the side-effects of beta-blockers were not severe and were manageable; therefore they felt the benefits of providing treatment with a beta-blocker outweighed any potential harms. The previous guideline, CG48, recommended indefinite treatment with beta-blockers, following an MI for people with left ventricular dysfunction. The GDG felt that, weighing up the evidence of benefit and potential harm, long-term treatment with beta-blockers could still be considered beneficial. This is in contrast to the recommendation for those without LVSD that states beta-blockers should be continued for at least 12 months. The GDG agreed that the baseline risk in people with LVSD is higher than in those without LVSD. Therefore, the benefits of beta-blockers are potentially greater in this group and there is no reason to think that the benefits would end after 24 months. One caveat regarding the data on the long-term use of beta-blockers is that most people were treated medically, not with primary PCI. The GDG were, therefore, less sure about the benefits of continuing indefinitely but in the absence of evidence they felt it was better to continue with the existing recommendation that those with LVSD are given it indefinitely. Therefore, the GDG agreed to recommend that beta-blockers should be continued indefinitely in this population.
Economic considerations	No economic studies were identified which compared different durations of treatment with beta-blockers in people with left ventricular dysfunction. However the original economic model conducted in the previous guideline, CG48, showed that a lifetime treatment with beta-blockers was cost-effective compared to placebo in 65-year-old men and women post MI with left ventricular dysfunction. The estimated ICER was around £1,100 per QALY gained. Although there was some concern over the applicability of this model to the current practice as the baseline risk of further events is lower compared to the past due to better care, the GDG thought this decrease in cost-effectiveness of beta-blockers could be offset by a decrease in their costs as they are now available as generics. Therefore the GDG concluded that indefinite treatment with beta-blockers in people with left ventricular dysfunction is cost-effective.

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Quality of evidence	The quality of evidence on people with and without LVSD was graded from very low to moderate quality. The GDG acknowledged that indirect data on people with LVSD were only available from those who had an MI who had treatment initiated between 72 hours and 12 months of the MI. However, the GDG felt that it was appropriate to extrapolate from this group to those who had received treatment within 72 hours of an MI. In the large trial, the benefits of beta-blocker treatment were evident after 30 days and from 30 days up to 24 months of treatment. The results showed some imprecision, that is the 95% CI crossed 1 MID but the estimate of the effect was large. It was unclear whether there was allocation concealment. In contrast, the findings from the small trial showed serious imprecision. The participant numbers were small and few events were recorded. The study was much older than the larger trial. The economic evidence was based on an original model with partial applicability and minor limitations.
Other considerations	The GDG also took into account the strong evidence for benefit of beta-blocker in people with heart failure including those with a previous MI when considering this recommendation.

7.5.3.1 People who have had an MI in the past

Recommendation	**84. Offer all people who have had an MI more than 12 months ago, who have left ventricular systolic dysfunction, a beta-blocker whether or not they have symptoms. For people with heart failure plus left ventricular dysfunction, manage the condition in line with 'Chronic heart failure' (NICE clinical guideline 108). [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant).
Trade-off between clinical benefits and harms	One paper was identified on people who had an MI in the past. The results showed beta-blockers increased the risk of all-cause mortality and cardiac death but decreased the risk of reinfarction. No other outcomes were reported. Because the evidence was low quality and because no other outcomes were reported, the GDG decided to extrapolate from the data on people with left ventricular systolic dysfunction, who receive treatment shortly after the MI, particularly as this data was from a population who received treatment between 72 hours and 12 months after the MI. Therefore, the GDG recommended that treatment with a beta-blocker should be offered indefinitely.

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	People who had an MI and who have heart failure, as well as left ventricular dysfunction, should be treated in line with NICE clinical guideline 108 'Chronic Heart Failure'.
Economic considerations	No economic studies were identified in this specific population. However the original economic model conducted in the previous guideline, CG48, showed that treatment with beta-blockers was cost-effective compared to placebo in 65-year-old men and women post MI with left ventricular dysfunction. The estimated ICER was around £1,100 per QALY gained. Although there was some concern over the applicability of this model to the current practice as the baseline risk of further events is lower compared to the past due to better care, the GDG thought this decrease in cost-effectiveness of beta-blockers could be offset by a decrease in their costs as they are now available as generics. The GDG concluded that treatment with beta-blockers is likely to be cost-effective also in people with left ventricular dysfunction independently from their symptoms.
Quality of evidence	The evidence identified was graded as low quality. The group agreed and felt that the evidence was unlikely to influence their decision. The data were a subgroup analysis on male participants in an RCT who had an MI between 1 and 90 months prior to starting treatment. The participants were not randomised to different starting dates, so treatment was likely to have been delayed by the clinicians for a reason. The LV status of the participants was unclear so the population was deemed indirect for this recommendation on people with LV dysfunction. The paper was published in 1962, all in men with a wide age range. No details were provided on methods of randomisation or allocation concealmentand the findings are from only 1 study and acute treatment is not reflective of current practice (that is primary PCI). No economic evidence was found on this question.
Other considerations	There were no other considerations.

Recommendation	**85. Do not offer people without left ventricular systolic dysfunction or heart failure, who have had an MI more than 12 months ago, treatment with a beta-blocker unless there is an additional clinical indication for a beta-blocker. [new 2013]**
Relative values of different outcomes	The GDG discussed the importance and relevance of various outcomes in assessing treatments in the context of secondary prevention of MI. For heart disease, mortality is clearly of greatest concern. The GDG focussed on total mortality, but also considered sudden death and cardiac mortality. However, quality of life was considered of critical importance as well, given that many people receive treatment to prevent relatively few deaths. Other events of concern in people after an MI, of lesser importance to mortality, but clearly important outcomes for the person who has had an MI and society, were stroke, reinfarction and revascularisation. Rehospitalisation was considered a relevant outcome by the GDG. It was clearly undesirable and in addition had significant economic impact. The adverse effects of treatment, which impact on quality of life (which was not always measured) were also considered relevant).

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Trade-off between clinical benefits and harms	One paper was identified on people who had an MI in the past although LV status is clear. The results showed beta-blockers increased the risk of all-cause mortality, cardiac death but decreased the risk of reinfarction. No other outcomes were reported. Because the evidence was moderate to low quality and because no other outcomes were reported, the GDG decided to extrapolate from the data on people without left ventricular systolic dysfunction, who have had an MI and who have received treatment between 72 hours and 21 months after the MI. Additionally, the previous guideline, CG48, recommended that people who have had an MI in the past should not be offered treatment with a beta-blocker. This recommendation is in line with the previous recommendation which suggests consideration may be given to discontinuing betablockers in certain circumstances after 12months of treatment. Given the weak evidence of benefit in people with normal LV function, the GDG felt that starting this treatment in people who presented more than 12 months after their MI was not to be recommended, unless there are additional clinical indications, such as hypertension, or other features as discussed in the previous recommendation.
Economic considerations	No economic evidence was found in this population. The GDG considered the unit costs of beta-blockers together with the results of the clinical review and concluded that despite the low cost of these drugs, there is no evidence of their benefits to conclude that beta-blockers are cost-effective in this population.
Quality of evidence	The evidence identified was graded as low quality. The group agreed and felt that the evidence was unlikely to influence their decision. The data were a subgroup analysis on male participants in an RCT who had an MI between 1 and 90 months prior to starting treatment. The participants were not randomised to different starting dates, so treatment was likely to have been delayed by the clinicians for a reason. The LV status of the participants was unclear so the population was deemed indirect for this recommendation on people without LV dysfunction. The paper was published in 1962, all in men with a wide age range. No details were provided on methods of randomisation or allocation concealment and the findings are from only 1 study and no treatment would have been reflective of current practice. No economic evidence was found on this question.
Other considerations	The GDG also took into account the strong evidence for benefit of beta-blocker in people with heart failure including those with a previous MI when considering this recommendation.

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7.6 Vitamin K antagonists

Recommendations relating to the use of warfarin for the secondary prevention of MI have been removed from the guideline update, as as due to the availability of a range of alternative antiplatelet agents, the use of vitamin K antagonists in secondary prevention is very unlikely to be considered (see Chapter 7.4).

Recommendations relating to the use of antiplatelet agents in those with an additional indication for anticoagulation can be found in 7.4.8.1.1.1.

7.7 Calcium channel blockers

7.7.1 Clinical effectiveness of calcium channel blockers

7.7.1.1 Clinical evidence

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).[310]

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.[302 109] 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 [302]. 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).[302]

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.[109]

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 [57,58] although there was a reduction in revascularisation, and the combination endpoint of non-fatal reinfarction or revascularisation.[57,58]

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.[364,368] 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.[364,368]

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.

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.

7.7.1.2 Economic evidence

7.7.1.2.1 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 [82] 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 [83] 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 [128] 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.

7.7.1.3 Evidence statements

7.7.1.3.1 Clinical

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++).

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+).

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+).

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++).

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+).

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++).

7.7.1.3.2 Economic

Three non-UK studies found that treatment with calcium channel blockers compared to placebo in patients with angiographically documented CHD is cost effective.

7.7.2 Summary of recommendations

86. Do not routinely offer calcium channel blockers to reduce cardiovascular risk after an MI. [2007]

87. 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. [2007]

88. 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, use amlodipine, and avoid verapamil, diltiazem and short-acting dihydropyridine agents in line with 'Chronic heart failure' (NICE clinical guideline 108). [2007]

7.8 Potassium channel activators

7.8.1.1 Clinical effectiveness of potassium channel activators

7.8.1 Clinical evidence

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.[310]

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).[203] However, the frequency of the secondary outcome of CHD death or non-fatal MI was similar in the two groups [203] 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/ [203]

7.8.1.1 Evidence statements

7.8.1.1.1 Clinical

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

7.8.2 Summary of recommendations

89.Do not offer nicorandil to reduce cardiovascular risk in patients after an MI. [2007]

7.9 Aldosterone antagonists in patients with heart failure and LV dysfunction

7.9.1 Clinical effectiveness of aldosterone antagonists

7.9.1.1 Clinical evidence

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%).[366,368] 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.[366,368]

There was an increased risk of serious hyperkalaemia 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 .[366,368]

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.[308] 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 effectiveness 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.

7.9.1.2 Economic evidence

7.9.1.2.1 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.[366,368] 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 [361] 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 [460,461] 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.

7.9.1.3 Evidence statements

7.9.1.3.1 Clinical

The only large trial of an aldosterone antagonist in early post MI patients with left ventricular systolic dysfunction (ejection fraction of less than or equal to 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++).

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++).

7.9.1.3.2 Economic

Treatment with aldosterone antagonist, eplerenone is cost effective, compared with placebo in patients early after MI with left ventricular systolic dysfunction.

7.9.2 Summary of recommendations

90. For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, initiate treatment with an aldosterone antagonist licensed for post-MI treatment within 3–14 days of the MI, preferably after ACE inhibitor therapy. [2007]

91. 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. [2007]

92. 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 108). [2007]

93. Monitor renal function and serum potassium before and during treatment with an aldosterone antagonist. If hyperkalaemia is a problem, halve the dose of the aldosterone antagonist or stop the drug. [2007]

7.10 Statins and other lipid lowering agents

94. 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) and 'Lipid modification' (NICE clinical guideline 67). [2007]

Recommendations regarding the use of statins and other lipid lowering agents have been removed from the update of the guideline. Recommendations on the use of statins and other lipid lowering agents can be found in NICE clinical guideline CG67 'Lipid modification' and 'Statins for the prevention of cardiovascular events (NICE technology appraisal guidance 94).

7.11 Monitoring guidance

This section details the guidance for initiation, titration and monitoring of ACE inhibitors and epelenone treatment in people after MI. The GDG considered that this specific information for these therapies was required in people who had an MI.

Table 112: Initiation, titration and monitoring of ACE inhibitors in people who had an MI

Doses
ACE inhibitors should be started at an appropriate dose and titrated upwards until the optimum or target dose* is reached (see Chapter 7).
Which ACE inhibitor and target dose*

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Doses

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[a]	6.25mg tds	50ng tds
Lisinopril	2.5 mg – 5mg od	5 – 10mg od
Ramipril[b]	1.25 mg – 2.5mg bd	5mg bd
Trandalopril[a]	0.5mg od	4mg od
Enalapril[c]	2.5mg od	20mg od or 10mg bd
Perindopril[d]	4mg od	8mg od

NB. These are the licensed recommended doses for people who had an MI, and may differ from those for people with symptomatic heart failure. In people with asymptomatic LV systolic dysfunction aim for the target dose recommended in those with symptomatic heart failure and LV systolic dysfunction (refer to NICE Clinical guideline 108 'Chronic Heart Failure').

(a) Licensed for use in people following MI with left ventricular dysfunction.
(b) Licensed for use following myocardial infarction in people with clinical evidence of heart failure and also susceptible people over 55 years, prevention of MI, stroke, cardiovascular death or need of revascularisation procedures.
(c) Licensed for use in people for prevention of symptomatic heart failure in people with left ventricular dysfunction (this may include people with MI in the past).
(d) Licensed for reduction of risk of cardiac events in people with a history of myocardial infarction and/or revascularisation.

How to use

- Avoid in people with known severe renal artery stenosis.
- Check renal function (creatinine) and serum electrolytes (particularly potassium), and blood pressure at baseline.
- Seek specialist advice in people 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).
- Monitor renal function (creatinine) and serum electrolytes, and blood pressure before starting an ACE inhibitor. Monitor thereafter until treated with a stable dose, and then at least annually. More frequent monitoring should be considered in people at risk of deterioration in renal function and or of developing hyperkalaemia, or during an intercurrent illness, particularly where associated with a risk of dehydration.

Recommendations on the initiation and titration of ACE inhibitors can be found in Chapter 7.

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 and calcium antagonists if for hypertension and diuretics if for hypertension or if not needed for congestion).
- If these measures do not resolve the problem, stop the ACE inhibitor and seek further 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 volume overload, 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. If after 1 further week, serum creatinine persistently > 30% above baseline, seek specialist

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Doses
advice. Continue to monitor renal function at least once weekly. • 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 volume overload, 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. Continue to monitor renal function at least weekly, until stable or resolved. • If serum creatinine increases > 100% from baseline, or serum creatinine is > 350 micromol/l stop the ACE inhibitor and seek specialist advice. Continue to monitor renal function at least once weekly, until stable of resolved. • 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 advise against the use of potassium rich foods and '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 urgent advice. 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.

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Table 113: 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 [368,369].

8 Coronary revascularisation

8.1.1 Clinical effectiveness of coronary revascularisation

8.1.1.1 Clinical evidence

The Coronary Heart Disease National Service Framework [119] 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 (for example. 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:
  - 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
  - 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 exercise testing included in the extract from the Coronary Heart Disease National Service Framework [119] 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).[362] 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.[472,479] 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.[472,479] 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.[472,479]

The systematic review [362] identified an earlier systematic review which examined the effectiveness of PCI compared to medical treatment in patients with non-acute coronary disease.[73] 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.[144 385 367,368] 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 [472,479] 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 [362] 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 [111,112]. 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.[111,112] (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 ischaemia-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 ischaemia-guided strategy, and 4.7% for the revascularisation strategy ($P < 0.01$ for the angina guided strategy versus revascularisation).[111,112]

The authors of the most recent systematic review [362] 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.

8.1.1.2 Economic evidence

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.

8.1.1.3 Evidence statements

8.1.1.3.1 Clinical

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++).

8.1.2 Summary of recommendations

95. Offer everyone who has had an MI a cardiological assessment to consider whether coronary revascularisation is appropriate. This should take into account comorbidity. [2007]

9 Selected patient subgroups

9.1 Patients with hypertension

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 clinical guideline 127 'Hypertension'.

9.1.1 Recommendations for patients with hypertension

96. Treat hypertension in line with 'Hypertension' (NICE clinical guideline 127). [2007, amended 2013]

9.2 Patients with left ventricular dysfunction

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. 108.

9.2.1 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 Chapter 7;

- ACE inhibitors and angiotension II receptor blockers Section 7.3
- Beta-blockers Section 7.5
- Aldosterone antagonists Section 7.9
- Calcium channel blockers Section 7.7.
- Other drug treatments are the same for patients with and without LV systolic dysfunction.

9.2.2 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 6.

9.2.3 Cross referenced implantable cardioverter defibrillators

97. 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).[2007]

9.3 Patients with an MI in the past (more than 12 months ago)

9.3.1 Cross referenced recommendations for patients with a proven MI in the past (more than 12 months ago)

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 5).

Comprehensive cardiac rehabilitation (Chapter 6) 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.

10 Communication of diagnosis and advice

10.1.1.1 Clinical evidence

The guideline development group considered that explicit communication between specialist and generalist care is a pre-requisite for implementation 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.

10.1.2 Summary of recommendations

98. After an acute MI, ensure that the following are part of every discharge summary:

- **confirmation of the diagnosis of acute MI**
- **results of investigations**
- **incomplete drug titrations[d]**
- **future management plans**
- **advice on secondary prevention. [2007, amended 2013]**

99. Offer a copy of the discharge summary to the patient. [2007]

[d] Recommendation amended to reflect new recommendations in the current guideline, highlighting the importance of including details of incomplete titrations in the discharge summary.

11 Acronyms and abbreviations

Acronym	Definition
ACA	Available case analysis
ACB	Aortocoronary bypass
ACE	Angiotensin-converting-enzyme
ACEi	Angiotensin-converting-enzyme inhibitor
ACS	Acute coronary syndromes
ADP	Adenosine diphosphate
AF	Atrial fibrillation
ALA	α-linolenic acid
AE	Adverse events
ALT	Alanine transaminase
ARB	Angiotensin receptor blocker
ARVD	Arrhythmogenic right ventricular dysplasia
AST	Aspartate transaminase
AV	Atrioventricular
BB	Beta-blocker
BMI	Body mass index
BMS	Bare metal stent
BNF	British National Formulary
BPM	Beats per minute
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CHF	Chronic heart failure
CG	Clinical guideline
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CR	Cardiac rehabilitation
CRP	Cardiac rehabilitation programme
CV	Cardiovascular
CVD	Cardiovascular disease
EBQ	Evidence based question
ECG	Electrocardiogram
EF	Ejection fraction
EPA	Eicosapentaenoic acid
DAPT	Dual antiplatelet therapy
DES	Drug eluting stent
DHA	Docasahexaenoic acid
DSA	Deterministic sensitivity analysis
ECHO	Echocardiography
GDG	Guideline development group
GI	Gastrointestinal

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Acronym	Definition
GP	General practitioner
GPP	Good practice point
GRP	Guideline review panel
HCP	Healthcare professionals
HF	Heart failure
HR	Hazard ratio
HRQoL	Health related quality of life
HTA	Health technology assessment
ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost effectiveness ratio
INR	International normalised ratio
ITT	Intention to treat
KCQ	Key clinical question
LAD	Left anterior descending
LETR	Linking evidence to recommendations
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
LYG	Life year gained
MD	Mean difference
MET	Metabolic equivalent of task
MI	Myocardial infarction
MID	Minimal important difference
MINAP	Myocardial infarction national audit project
MRI	Magnetic resonance imaging
MSET	Multistage graded test
n	Number
n-3-PUFA	n-3 polyunsaturated fatty acids
NA	Not applicable
NOAC	New oral anticoagulant
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRMI	National registry for myocardial infarction
NRT	Nicotine replacement therapy
NSAID	Non-steroidal anti inflammatory drug
NYHA	New York Heart Association
NSTEMI	Non-ST-segment elevation myocardial infarction
OAC	Oral anticoagulation
OECD	Organisation for economic co-operation and development
OR	Odds ratio
OVE	Occlusive vascular events
PA	Probabilistic analysis

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Acronym	Definition
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
PDE5	Phosphodiesterase type 5
PE	Pulmonary embolism
PTCA	Percutaneous transluminal coronary angioplasty
PTCR	Percutaneous transluminal coronary recanalisation
PWC	Physical work capacity
QALY	Quality adjusted life year
QoL	Quality of life
RAAS	Renin-angiotensin-aldosterone-system
RCT	Randomised controlled trial
RR	Risk ratio or relative risk
RT-PA	Recombinant tissue type plasminogen activator
SD	Standard deviation
SE	Standard error
SIGN	Scottish international guidelines network
SMD	Standardised mean difference
STEMI	ST-segment- elevation myocardial infarction
TA	Technology appraisal
UA	Unstable angina
VF	Ventricular function
Vit	Vitamin
Vs.	Versus

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12 Glossary

Term	Definition
Absolute risk	Measures the probability of an event or outcome occurring (for example, an adverse reaction to the drug being tested) in the group of people under study. Studies that compare two or more groups of patients may report results in terms of the Absolute Risk Reduction.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
ACE inhibitor	A drug which inhibits the angiotensin converting enzyme.
Acute coronary syndrome	A condition in which there is an event in a coronary artery with plaque rupture or erosion, or coronary dissection, with the formation of intracoronary thrombus. A single term which includes both unstable angina and myocardial infarction.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a randomised controlled trial (RCT). The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The extent to which the results of a study or review can be applied to the target population for a clinical guideline.
Appraisal of evidence	Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Balloon angioplasty	A type of percutaneous coronary intervention (vide infra) in which the coronary artery is dilated with a balloon only, without a stent or other device being used.
Bare metal stent	A wire mesh tube (used to widen narrowed arteries during a procedure called balloon angioplasty).
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Beta-blocker	A class of drugs that block beta-adrenergic substances such as adrenaline (epinephrine) in the 'sympathetic' portion of the autonomic (involuntary) nervous system.
Bias	Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually doesn't. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, for example, in the collection, analysis, interpretation, publication or review of research data. For examples see Selection bias, Performance bias, Information bias, Confounding, Publication bias.
Blinding or masking	The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against bias.

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	See also Double blind study, Single blind study, Triple blind study.
Calcium channel blocker	Medicines that slow the movement of calcium into the cells of the heart and blood vessels. This, in turn, relaxes blood vessels, increases the supply of oxygen-rich blood to the heart, and reduces the heart's workload.
Cardiac rehabilitation	A programme for patients with heart disease aimed at ensuring patients preserve or resume best possible health and wellbeing. Usually includes behaviour change and education, lifestyle and medical risk factor management, psychosocial health interventions and cardioprotective therapies.
Cardiovascular event	An acute coronary, cerebrovascular or peripheral vascular event.
Cardiovascular risk	The risk of a cardiovascular event occurring.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	A study that starts with the identification of a group of individuals sharing the same characteristics (for example, people with a particular disease) and a suitable comparison (control) group (for example, people without the disease). All subjects are then assessed with respect to things that happened to them in the past, for example, things that might be related to getting the disease under investigation. Such studies are also called retrospective as they look back in time from the outcome to the possible causes.
Case series	Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical audit	A systematic process for setting and monitoring standards of clinical care. Whereas 'guidelines' define what the best clinical practice should be, 'audit' investigates whether best practice is being carried out. Clinical audit can be described as a cycle or spiral. Within the cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care, and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as efficacy.
Clinical question	This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a focused question.
Clinical trial	A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomised controlled trials.
Cochrane Collaboration	An international organisation in which people find, appraise and review specific types of studies called randomised controlled trials. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the Cochrane Library.

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Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, for example, comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.
Co-morbidity	Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
Community health services	General Practice, ambulance crews, NHS walk-in centres and dental practitioners.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Confidence interval	A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Confounder or confounding factor	Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.
Consistency	The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also Homogeneity.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Coronary artery bypass surgery	Open-heart surgery in which the rib cage is opened and a section of a blood vessel is grafted to a coronary artery to bypass the blocked section of the artery and thus improve the blood supply to the heart.
Coronary heart disease	Happens when a fatty substance builds up in the walls of the coronary arteries, making the space inside narrower. The narrowing of the arteries may mean that they are not supplying enough blood to deliver all the oxygen the

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	heart needs to work properly.
Coronary artery disease	Coronary artery disease is a condition in which atheromatous plaque builds up inside the coronary artery. This leads to a narrowing of the artery which may be sufficient to restrict blood flow and cause myocardial infarction.
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 (CCA)	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	A type of economic evaluation that assesses the different costs and benefits of different health care interventions. In cost effectiveness analysis, the costs and benefits of different treatments are compared. When a new treatment is compared with current care, its additional costs divided by its additional benefits is called the cost effectiveness ratio. Benefits are measured in natural units, for example, cost per additional heart attack prevented.
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 utility analysis	A special form of cost effectiveness analysis where benefit is measured in quality adjusted life years. A treatment is assessed in terms of its ability to extend or improve the quality of life.
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.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Double blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
Drop-out	A participant who withdraws from a trial before the end.
Drug eluting stent	A tiny wire mesh tube used to widen narrowed arteries in a procedure called balloon angioplasty. It is coated in a drug that reduces the chance of the artery narrowing again after surgery.
Economic evaluation	Comparative analysis of alternative courses of action in terms of both their costs and consequences.
Effectiveness	See Clinical effectiveness.
Efficacy	The extent to which a specific treatment or intervention, under ideally controlled conditions (for example, in a laboratory), has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care.
Emergency Department (ED or A&E)	A clinical department in a district general or teaching hospital which has trained staff and equipment able to receive, resuscitate, investigate and initially manage the full spectrum of emergencies. Most units accept patients of all ages, some are restricted to adults, others to children. All should be open at all times and all its facilities should be available at all times.
Epidemiology	Study of diseases within a population, covering the causes and means of prevention.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Event rate	The proportion of patients in a group for whom a specified health event or

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	outcome is observed. Thus, if out of 100 patients, the event is observed in 27, the event rate is 0.27 or 27%. Control Event Rate (CER) and Experimental Event Rate (EER) are the terms used in control and experimental groups of patients respectively.
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria	See Selection criteria.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
External validity	The degree to which the results of a study hold true in non-study situations, for example, in routine clinical practice. May also be referred to as the generalisability of study results to non-study patients or populations.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Forest plot	A graphical display of results from individual studies on a common scale, allowing visual comparison of results and examination of the degree of heterogeneity between studies.
GRADE / GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Hazard ratio	The number of times more (or less) likely a participant is to suffer the event at a particular point in time if they are receiving the experimental versus the control intervention
Haemodynamic	Relating to the circulation of the blood, usually describes the mechanical effects of the circulatory system such as the pressure in a chamber or vessel.
Health economics	A field of conventional economics which examines the benefits of healthcare interventions (for example, medicines) compared with their financial costs.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heart failure	Heart failure is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. It is cause by structural or functional abnormalities of the heart. Some patients have heart failure due to impaired contraction of the left ventricular, known as left ventricular systolic dysfunction (LVSD).
Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
High fibre diet	A diet which is high in dietary fibre.
Homogeneity	This means that the results of studies included in a systematic review or

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	meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also Consistency.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria	See Selection criteria.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
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 for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention to treat analysis	An analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment. Intention-to-treat analyses are favoured in assessments of clinical effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the treatment is used in practice.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy, etc.
Ischaemia	Insufficient blood supply to an organ or tissue.
Left ventricular systolic dysfunction	'See heart failure'.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible for example, because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also Systematic review & Heterogeneity.
Methodology	The overall approach of a research project, for example, the study will be a randomised controlled trial, of 200 people, over one year.
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Number needed to treat	The number of patients that who on average must be treated to prevent a

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(NNT)	single occurrence of the outcome of interest.
Non-ST elevation myocardial infarction (NSTEMI)	A mild heart attack, which happens when a part of the heart doesn't get as much oxygen as it needs, so the heart is damaged
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (for example, whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar. See also Relative risk, Risk ratio.
Outcome	The end result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Percutaneous coronary intervention	The management of coronary artery occlusion by any of various catheter-based techniques, such as percutaneous transluminal coronary angioplasty, atherectomy, angioplasty using the excimer laser and implantation of coronary stents and related devices.
Peripheral arterial disease	In peripheral arterial disease, the arteries that carry blood to the legs or arms are narrowed or blocked.
Physical work	An activity which involves increased energy expenditure.
Pilot study	A small scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full scale study begins.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the control group in a clinical trial which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Power	See Statistical power.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by General Practitioners, nurses and other healthcare professionals, dentists, pharmacists and opticians.

Probability	How likely an event is to occur, for example, how likely a treatment or intervention will alleviate a symptom.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Psychoeducational 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 or reduce distress.
Publication bias	Studies with statistically significant results are more likely to get published than those with non-significant results. Meta-analyses that are exclusively based on published literature may therefore produce biased results. This type of bias can be assessed by a funnel plot.
P value	If a study is done to compare two treatments then the P value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the P-value was P=0.03. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of P is below 0.05 (that is, less than 5%) the result is seen as statistically significant. Where the value of P is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the confidence interval.
Qualitative research	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, for example, a patient's description of their pain rather than a measure of pain. In healthcare, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as focus groups and in depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
Quality adjusted life years (QALYS)	A measure of health outcome. QALYS are calculated by estimating the total life-years gained from a treatment and weighting each year with a quality of life score.
Quality of life	See 'Health-related quality of life'.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Random allocation or Randomisation	A method that uses the play of chance to assign participants to comparison groups in a research study, for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.
Randomised controlled trial	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy

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	treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)
Relative risk	A summary measure which represents the ratio of the risk of a given event or outcome (for example, an adverse reaction to the drug being tested) in one group of subjects compared to another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for risk ratio.
Reliability	Reliability refers to a method of measurement that consistently gives the same results. For example someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession – and if their assessments tend to agree then the method of assessment is said to be reliable.
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review	Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.
Risk ratio	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term relative risk is sometimes used as a synonym of risk ratio.
Sample	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
Sampling	Refers to the way participants are selected for inclusion in a study.
Secondary care	Care provided in hospitals.
Selection bias	Selection bias has occurred if: the characteristics of the sample differ from those of the wider population from which the sample has been drawn OR there are systematic differences between comparison groups of patients in a study in terms of prognosis or responsiveness to treatment.
Semi-structured interview	Structured interviews involve asking people pre-set questions. A semi-structured interview allows more flexibility than a structured interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.
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. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.

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	Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. 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).
Significance (statistical)	A result is deemed conventionally statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Single blind study	A study in which either the subject (patient/participant) or the observer (clinician/investigator) is not aware of which treatment or intervention the subject is receiving.
Specific indication	When a drug or a device has a specific remit to treat a specific condition and is not licensed for use in treating other conditions or diseases.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical power	The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a P value of less than 5% in a statistical test (that is, a statistically significant treatment effect) if there really was an important difference (for example, 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also P value.
Structured exercise	A planned exercise programme which aims to meet the needs of an individual patient.
Structured interview	A research technique where the interviewer controls the interview by adhering strictly to a questionnaire or interview schedule with pre-set questions.
Study population	People who have been identified as the subjects of a study.
Study quality	See Methodological quality.
Study type	The kind of design used for a study. Randomised controlled trial, case-control study, cohort study are all examples of study types.
ST-elevation myocardial infarction	ST-segment-elevation myocardial infarction (also known as STEMI) is a type of heart attack. A heart attack is caused by narrowing and blockage of the main blood vessel (the coronary artery) that delivers blood to the heart. One of the treatments involves widening of the narrowed coronary artery in a procedure called percutaneous coronary intervention (sometimes called balloon angioplasty or stenting).
Stroke	When the normal blood supply to part of the brain is cut off and there is death of brain tissue..
Sub-group analysis	An analysis in which the intervention effect is evaluated in a defined subset of the participants in the trial, or in complementary subsets, such as by sex or in age categories.
Survey	A study in which information is systematically collected from people (usually from a sample within a defined population).
Systematic	Methodical, according to plan; not random.

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Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.
Target population	The people to whom guideline recommendations are intended to apply. Recommendations may be less valid if applied to a population with different characteristics from the participants in the research study – for example, in terms of age, disease state, social background.
Titration	The administration of small incremental doses of a drug until either the target dose or the maximum tolerated dose has been reached.
Treatment allocation	Assigning a participant to a particular arm of the trial.
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.
Validity	Assessment of how well a tool or instrument measures what it is intended to measure. See also External validity, Internal validity.
Variable	A measurement that can vary within a study, for example, the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature which can be assessed or measured.

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13 Reference list

Appendices A – Q are in a separate file

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