Post Myocardial Infarction

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

Full guideline: Appendices

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Appendix A – Audit Criteria

Audit criteria will be available upon publication.
Appendix B – Scope

Guideline title
   Post MI: secondary prevention in primary and secondary care for patients following a myocardial infarction.

Short title
   Post MI : secondary prevention

1. Background

The National Institute for Clinical Excellence (‘NICE’ or ‘the Institute’) has commissioned the National Collaborating Centre for Primary Care to develop a clinical guideline on secondary prevention for patients following a myocardial infarction in primary and secondary care (post MI), as part of updating the existing inherited NICE guideline ‘Prophylaxis for patients who have experienced a myocardial infarction’ (inherited Guideline A, April 2001) for use in the NHS in England and Wales. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.
The Institute’s clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

2. Clinical need for the guideline

The 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. From these statistics, the British Heart Foundation (2004) have 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, the number of people who have had an MI at some point in their lives is 838,000 for men, and about 394,000 for women. This gives a total of over 1.2 million cases (British Heart Foundation, 2004).

MI is a complication of coronary heart disease (CHD). CHD is a preventable disease. The death rate from CHD has been falling since the early 1970s, and 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 CHD 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 under 75 are nearly three times higher than in women (Department of Health, 2003).
- 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).
Management

Cardiac rehabilitation programs 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).

A number of drugs have been shown to improve outcome after MI.

3. The guideline

The guideline development process is described in detail in two booklets that are available from the NICE website (see ‘Further information’). The guideline development process – an overview for stakeholders, the public and the NHS describes how organisations can become involved in the development of a guideline. Guideline development methods – information for National Collaborating Centres and guideline developers provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government (see Appendix).

The areas that will be addressed by the guideline are described in the following sections.

4. Population

Groups that will be covered

Adult patients (≥ 18 years) who have had an MI. The following groups are included:

a) patients following the early acute phase, which can be defined as 48 hours after admission, providing the patient is stable
b) patients who are identified as having had a proven MI at some point in the past.

Groups that will not be covered

a) Patients that have had a non-spontaneous MI (for example, a periprocedural MI, which may occur after percutaneous coronary intervention).

b) Patients who have had a non-atherosclerotic-induced MI, which is an MI in patients without underlying coronary artery disease.

5. Healthcare setting

a) The guideline will cover the care received from healthcare professionals who have direct contact with, and make decisions concerning, the care of people who have survived the early acute phase of an MI.

b) The guideline will address care in primary and secondary and, where appropriate, tertiary centres.

c) The management of patients in accident and emergency departments will not be considered.

d) The guideline will also be relevant to the work, but will not cover the practice, of those working in the occupational health services and voluntary sector.

6. Clinical management of secondary prevention

Areas that will be covered

a) The guideline will cover the management of MI following the early acute phase.

b) The guideline will cover pharmacological intervention including commencement of treatment and drug combination, monitoring of treatment and duration of treatment. The guideline will advise on the use of the following classes of drugs within the licensed indications for secondary prevention. This will include advice for those with and without left ventricular dysfunction:

i. antiplatelet drugs including aspirin
ii. beta-adrenoreceptor blocking drugs

iii. lipid modifying drugs with specific reference to the additional advice for patients post MI and incorporating the statins technology appraisal and cross referencing to the hyperlipidaemia guideline.

iv. omega-3-acid ethyl esters

v. a. angiotensin-converting enzyme inhibitors
   b. angiotensin II receptor blockers

vi. calcium channel blockers

vii. potassium channel activators

viii. eplerenone

ix. vitamin K antagonists

Drugs that are subject to NICE Technology Appraisal (section 6) will be cross-referred to as appropriate.

Recommendations on treatment options will be based on the best evidence available to the guideline development group. Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use the Summary of Product Characteristics/British National Formulary for information about possible side-effects and to inform their decisions for individual patients.

c) The guideline will include detection and identification of, and secondary prevention in, patients with left ventricular systolic dysfunction post MI, sign-posting, where appropriate, to the heart failure guideline and subsequent updates, and Technology Appraisals.

d) The guideline will advise on the optimal control of blood pressure post MI sign-posting to the hypertension guideline where appropriate.
e) The guideline will cover the criteria for referral for assessment for possible coronary revascularisation.

f) The guideline will cover cardiac rehabilitation. Cardiac rehabilitation is defined as the sum of activities required to influence favourably the underlying cause of the disease, as well as to ensure the patients the best possible physical, mental and social conditions so that they may, by their own efforts, preserve, or resume when lost, as normal a place as possible in the life of the community (WHO definition, 1993).

g) The guideline will cover methods for the routine assessment and recording of each individual patient’s rehabilitation needs and the provision of an individualized rehabilitation plan for each patient.

h) The guideline will cover exercise, education sessions, and resumption of physical, sexual, social and vocational activities and psychological aspects of rehabilitation.

i) The guideline will include advice on the following ongoing lifestyle modifications for people following an MI:

i. diet

ii. exercise and regular physical activity

iii. alcohol consumption

iv. smoking cessation will be cross referred to the Technology Appraisal ‘Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation’, April 2002.

j) The guideline will pay particular attention to the clinical needs of groups which may be at risk of being excluded from secondary prevention following MI, including:

i. black and minority ethnic groups

ii. older people

iii. lower socio-economic groups
iv. women

v. rural communities.
Areas that will not be covered

a) Diagnosis of an MI either acutely or retrospectively.

b) Interventions specific to the early phase of the acute MI including (but not exclusively):

i. re-perfusion strategies in ST elevation infarcts

ii. conservative versus invasive management in non-ST elevation infarcts including angiography.

c) Different methods of assessment of cardiac status before possible coronary revascularisation.

d) 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.

e) The additional management of chronic heart failure which would be more appropriately placed in revisions of the chronic heart failure guideline.

f) Symptom control such as the management of angina.

7. Status

Scope

This is the final scope.

Guideline

The development of the guideline recommendations will begin in November 2004.
8. Further information

Information on the guideline development process is provided in:

- The guideline development process – an overview for stakeholders, the public and the NHS

These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information on the progress of the guideline will also be available from the website.

9. Relevant NICE publications

*Clinical Guidelines:*

- Type 2 diabetes – management of blood pressure and blood lipids, October 2002.
- Type 2 Diabetes - management of blood glucose, September 2002.
- Hyperlipidaemia – identification and management of hyperlipidaemia as part of cardiovascular risk assessment in primary care (ongoing)
- Obesity – the prevention, identification, evaluation, treatment and weight maintenance of overweight and obesity in adults (ongoing).
- Familial hypercholesterolaemia - identification and management (ongoing)
Technology Appraisals:

Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation, April 2002.

Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events, (ongoing).


Statins for the prevention of coronary events in patients at increased risk of developing CHD or those with established CHD (ongoing).

Angina and myocardial infarction - myocardial perfusion scintigraphy, November 2003.

Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias - review of guidance no 11, (ongoing).
Appendix C – Health Economic Modelling

1.1 Economic analysis of cardiac rehabilitation

1.1.1 Introduction

Cardiac rehabilitation (CR) after an acute myocardial infarction (MI) is a recommended therapy with established clinical effectiveness. It comprises mainly of supervised exercise training, relaxation and education. There is evidence that CR reduces the risk of total and cardiac related mortality, subsequent revascularizations, occurrence of non-fatal MI, improvements in work and physical capacity and perceived quality of life. {280}, {1360},{6}, {5103} {3058}

In England the National Service Framework for Coronary heart disease (NSF-CHD) identifies patients who have survived acute MI and those who have undergone Coronary artery bypass graft (CABG) and percutaneous transluminal coronary angiography (PTCA) as initial priorities for CR {1371}

The provision of exercise-based CR in the United Kingdom (UK) has increased since the early 1990s. The British Cardiac Society Working Party Report showed that 99 programmes were in place 1989 {5281} {5283}. By 1997 their numbers had tripled. By year 2000 in England alone 220 centres were identified in a survey of implementation of the NSF-CHD but concluded that there is still scope for improving services so that those in need are offered rehabilitation {3058}

Although CR is considered effective in quickening recovery and improving prognosis, not all patients participate in a CR programme. Surveys in UK have given diverse estimates of uptake, ranging between 14-59% after MI {3058} {5282},{5283}

Costs of CR services vary by format of delivery. The most recent survey the British Association of cardiac rehabilitation (BACR) and the British Heart Foundation (BHF)
suggest that costs per patient vary widely between £50-£712 depending on level of staffing, equipment used and intensity of the programme. In all cases staff costs ranged between 64-80% of the total {3058}, {5283} {11}.

The wider economic benefits of CR are believed to derive primarily from reduced secondary utilization of inpatient medical resources. Studies from USA {21}, {280}, Australia {2919} and Sweden {297} have shown that CR is cost effective. However, there are no cost effectiveness studies of CR in the UK.

This study had two objectives. The first was to assess the cost effectiveness of comprehensive CR compared to no CR. A second objective was to assess the comparative cost effectiveness of some of the methods used to increase uptake of CR after an MI. The methods considered were firstly the use of telephone calls together with home visits carried out by a healthcare professional (HCP), and secondly invitation letters. Costs relevant to the National Health Service (NHS) were considered.
1.1.2 Methods

Population and sub-groups
The model considered a cohort of patients who had had a recent MI. The trial evidence that the model is based on included relatively few older (>65) or black patients, so the results may not be reliable for these groups.

Interventions compared
The analysis assessed the costs and effects of CR compared with no CR. Additionally it assessed using the output from the CR model, the cost effectiveness of two methods of increasing uptake and adherence compared to ‘current practice/usual care’, i.e. current uptake of CR. These two methods were firstly the use of phone calls together with home visits by a HCP, in which the HCP was assumed to make contact over the phone four times, each followed by a home visit and secondly the use of two consecutive invitation letters to a CR programme over a period of 6 weeks.

Outcomes
The treatment effects were measured in terms of reduction of CVD events: non-fatal MI, revascularisation CVD-related deaths and other deaths. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life Years (QALYs), where one QALY represents one year of healthy life.

Model structure and assumptions
A Markov model was developed to evaluate the incremental costs and effects of lifetime intervention with CR in secondary prevention of cardiovascular disease (CVD) events in post MI patients from a UK NHS perspective.

In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states. Figure 1 shows a schematic representation of the patients’ pathways. All patients start in the event-free health state. During each six-month cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, revascularisation and death) while the remainder stay in the event free state. Patients can experience more than one non-fatal event in subsequent periods of the model.
The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (six months). For illustration, the equivalent annual transition probabilities for a 65-year-old patient receiving no-CR are shown in Table 1. The probabilities are derived from the placebo arms of the meta-analysis of CR trials.

The model was run first assuming that the cohort was to receive no CR. The model was then re-run assuming that the cohort all received CR and complied 100%. Transition probabilities were adjusted to reflect the expected reduction in CVD events and revascularisations. Health care costs and QALYs were then estimated for each option by weighting the time spent in the various states by mean costs and ‘utilities’ (health-related quality of life) of the health states. The cost and utility data used in the model are described below.

The time horizon modelled is lifetime, with an assumed upper age of 100, by which time most of the cohort have died.

**Figure 1: Economic Model Structure**

![Economic Model Structure Diagram]

**Baseline risks:**
The risks of secondary or subsequent events, following an MI or revascularisation are shown in Table 1. Probabilities of having a re-infarction, and death were taken from the placebo arm of two recent meta-analyses \{1360\}, \{5103\}. The probabilities of having revascularisation were taken from another meta-analysis \{6\}. The incidence of MI following revascularisation was taken from Rita 2 and probability of post operative death was taken from the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery \{3123\}.

Non-CVD related mortality by age and sex was taken from the life tables for England and Wales prepared by the Government Actuaries Department (GAD) and from the Office for National Statistics (ONS) \{5288\}, \{5290\}. In the base case model we assumed that the post MI cohort had a 2 fold increase in risk of non-CVD death compared with the general population, because they are a high risk population (expert opinion). However, we tested this assumption in the sensitivity analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Annual probability</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well to Rev</td>
<td>0.062</td>
<td>{6}</td>
</tr>
<tr>
<td>Well to MI</td>
<td>0.096</td>
<td>{5103}</td>
</tr>
<tr>
<td>Well to death</td>
<td>0.093</td>
<td>{5103}, {5290}</td>
</tr>
<tr>
<td>Revascu to MI</td>
<td>0.009</td>
<td>{5277}</td>
</tr>
<tr>
<td>Revascu to post op death</td>
<td>0.008</td>
<td>{3123}</td>
</tr>
<tr>
<td>Revascu to another revascu</td>
<td>0.030</td>
<td>{6}</td>
</tr>
<tr>
<td>Well after revascu to death</td>
<td>0.042</td>
<td>{5277}, {5290}</td>
</tr>
<tr>
<td>Mi to revascu</td>
<td>0.062</td>
<td>{6}</td>
</tr>
<tr>
<td>Mi to MI</td>
<td>0.062</td>
<td>{1360}</td>
</tr>
<tr>
<td>Mi to death</td>
<td>0.094</td>
<td>{1360}, {5290}</td>
</tr>
</tbody>
</table>
Treatment effects:

The effectiveness of CR defined as the reduction in relative risks of mortality and non fatal reinfaction was obtained from systematic {5103} and for revascularisation from {6}. Data on the effectiveness of the strategies aimed at increasing uptake and compliance were obtained from an HTA report {3058}

Table 2 Relative risks of CR (base case analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularisation</td>
<td>0.85</td>
<td>0.65</td>
<td>1.12</td>
<td>{6}</td>
</tr>
<tr>
<td>MI</td>
<td>0.83</td>
<td>0.74</td>
<td>0.94</td>
<td>{5103}</td>
</tr>
<tr>
<td>Post operative death</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Assumption</td>
</tr>
<tr>
<td>Death</td>
<td>0.85</td>
<td>0.77</td>
<td>0.94</td>
<td>{5103}</td>
</tr>
</tbody>
</table>

Table 3 Relative risks of Letters and phone calls (base case analysis)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Results</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letters</td>
<td>87% intervention group</td>
<td>{3058}</td>
</tr>
<tr>
<td></td>
<td>Compared to 57% in control p=0.0025</td>
<td></td>
</tr>
<tr>
<td>Telephone+ HCP</td>
<td>57% vs. 27% in those who did</td>
<td>{3058}</td>
</tr>
<tr>
<td></td>
<td>not get the intervention.</td>
<td></td>
</tr>
</tbody>
</table>

Cost data

The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of CVD and hospitalisations. Costs were calculated using cost weights for each of the states
of the model, multiplied by the time spent in each state. Costs are at 2005 prices. As per current NICE guidance, an annual discount rate of 3.5% was used for both costs and health benefits {5292}.

The costs of health states used in the model are shown in Table 4. Costs for revascularization which includes hospitalisation were taken from the NHS reference cost 2005 {5293}. It was assumed that 67% of patients will have PCI and 33% will have CABG and the costs were weighted to reflect this (expert opinion). The cost of the well states was assumed to be the outpatient cost which includes the costs of medication and monitoring costs, these were taken from the NICE hypertension guideline 2006 {5256}. The cost of CR was taken from a review {3058} and included staff costs, equipment, and that of recruiting patients to CR. Costs of acute MI (non-fatal reinfection) were assumed to be the same as those of patients treated with thrombolysis, which includes the cost of hospitalisation {5276}. The cost of death was zero.

The costs of each strategy used to increase uptake, invitation letters or phone call contacts followed by home visits, were calculated from resource use identified in the HTA {3058}. The actual unit costs were taken from the Personal Social Services Research Unit PSSRU {5294}.

The cost of invitation letters were calculated assuming that letters inviting participants to a CR programme were sent twice, soon after discharge and 3 weeks later. It was assumed that the letters were sent by a medical secretary, and also that 30 minutes work was required to type and send each letter.

For the HCP and phone calls {3058} estimated there would be about four visits and a phone call made before each visit. Contact by the HCP was assumed to last 30 minutes and the phone call about 11 minutes. Duration for the phone call and staff costs were taken from the PSSRU {5294}.
Table 4 Costs of health states

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2005 UK £ pa</th>
<th></th>
<th></th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>No event</td>
<td>£171</td>
<td>£86</td>
<td>£342</td>
<td>{5201}</td>
</tr>
<tr>
<td>Rev</td>
<td>£8,676</td>
<td>£4,338</td>
<td>£17,352</td>
<td>NHS ref cost</td>
</tr>
<tr>
<td>Post Rev</td>
<td>£500</td>
<td>£250</td>
<td>£1,000</td>
<td>assumption</td>
</tr>
<tr>
<td>MI</td>
<td>£4,448</td>
<td>£2,224</td>
<td>£8,896</td>
<td>{5276}</td>
</tr>
<tr>
<td>MI (subsequent)</td>
<td>£500</td>
<td>£250</td>
<td>£1,000</td>
<td>{5256}</td>
</tr>
<tr>
<td>Rev2</td>
<td>£8,676</td>
<td>£4,338</td>
<td>£17,352</td>
<td>NHS ref cost</td>
</tr>
<tr>
<td>Post Rev2</td>
<td>£500</td>
<td>£250</td>
<td>£1,000</td>
<td>assumption</td>
</tr>
<tr>
<td>post OPD</td>
<td>£0</td>
<td>£0</td>
<td>£0</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>£0</td>
<td>£0</td>
<td>£0</td>
<td></td>
</tr>
</tbody>
</table>

Table 5, other resources

<table>
<thead>
<tr>
<th>Resource use</th>
<th>Hourly rates</th>
<th>Contact time</th>
</tr>
</thead>
<tbody>
<tr>
<td>social worker</td>
<td>£38.00</td>
<td>30 minutes per visit X 4</td>
</tr>
<tr>
<td>visiting costs</td>
<td>£1.20</td>
<td>4 visits</td>
</tr>
<tr>
<td>rehabilitation nurse</td>
<td>£21.00</td>
<td>11 minutes once</td>
</tr>
<tr>
<td>Secretaries</td>
<td>£14.00</td>
<td>30 minutes to write a letter and post it on two occasions</td>
</tr>
<tr>
<td>postage first class+</td>
<td>£0.40</td>
<td>twice</td>
</tr>
<tr>
<td>paper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cost per minute of</td>
<td>£0.04</td>
<td></td>
</tr>
<tr>
<td>phone call</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quality of life (Utility):
In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the Quality Adjusted Life Year (QALY) approach. This requires estimates of survival and quality of life associated with each health state included in the model.\{5292\}

The utility values used in the model are shown in Tables 6 and 7. The values were taken from literature or the Harvard cost effectiveness registry database \{5286\}

Utilities were adjusted to reflect the fact that health related quality of life in the general population decreases with age (i.e. multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England \{5287\}

One study \{280\}, found that there was a difference of 0.052 QALYs between patients who participated in CR and those who did not using the time trade off method. This factor was applied to all the well states in the CR arm to take account of this difference in quality of life. The weight attached to death was zero

<table>
<thead>
<tr>
<th>Health State</th>
<th>Utility</th>
<th>Mean</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>No event</td>
<td>1.00</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Rev</td>
<td>0.80</td>
<td>0.80</td>
<td>0.70</td>
<td>0.90</td>
<td>{5284}</td>
</tr>
<tr>
<td>Post Rev</td>
<td>0.88</td>
<td>0.88</td>
<td>0.70</td>
<td>0.90</td>
<td>{5286}</td>
</tr>
<tr>
<td>MI</td>
<td>0.76</td>
<td>0.76</td>
<td>0.70</td>
<td>0.90</td>
<td>{5286}</td>
</tr>
<tr>
<td>MI (subsequent)</td>
<td>0.88</td>
<td>0.88</td>
<td>0.70</td>
<td>0.90</td>
<td>assumption</td>
</tr>
</tbody>
</table>
Table 7 Utility weight by age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Age utility weight</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-54</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

Cost effectiveness

The results of cost-effectiveness analysis are usually presented as Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of CR per additional QALY gained compared with no CR

\[ \text{ICERs} = \frac{\text{cost of CR} - \text{cost of no CR}}{\text{QALY of CR} - \text{QALY of no CR}} \]

Where more than two interventions are being compared, the ICERs are calculated using the following process:

i) The drugs are ranked in terms of cost (from the cheapest to the most expensive).

ii) If a drug is more expensive and less effective than the previous one, then it is said to be ‘dominated’ and is excluded from further analysis.

iii) ICERs are calculated for each drug compared with the next most expensive non-dominated option. If the ICER for a drug is higher than that of the next more
effective strategy, then it is ruled out by ‘extended dominance’. This means that there is some mixture of two other strategies that is more effective and less expensive.

iv) ICERs are recalculated excluding any drugs subject to extended dominance. {5284}

**Sensitivity analysis**

The model includes a base case analysis supplemented with both deterministic and probabilistic sensitivity analysis. In the probabilistic sensitivity analysis all parameters in the model were allowed to vary simultaneously according to an assumed distribution reflecting the degree of uncertainty over the parameter value.
1.1.3 Results

The tables 8 & 9 below present the analysis of the incremental cost effectiveness ratio (ICER) for the base-case analysis of

a) CR versus no CR in post MI patients.

b) the comparative cost effectiveness of the methods used to increase uptake of CR after an MI

a) Cost effectiveness of CR vs. no CR.

The base case results are presented in table 8 for 65-year-old men. This suggests that CR is cost-effective for this population. The ICER of CR compared with no CR is about £4,900 per QALY gained, which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

Table 8 Incremental cost effectiveness of CR vs. No CR, base case results for 65 year old men.

<table>
<thead>
<tr>
<th></th>
<th>Cost (£)</th>
<th>Effect (QALYs)</th>
<th>Incremental cost (£)</th>
<th>Incremental effect (£)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£5,359</td>
<td>5.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>£9,450</td>
<td>6.54</td>
<td>£4,090</td>
<td>0.84</td>
<td>£4,865</td>
</tr>
</tbody>
</table>
Cost effectiveness plane, CR compared to no CR in post MI patients

Figure 2

b) The comparative cost effectiveness of the methods used to increase uptake of CR after an MI

None of the strategies were ruled out on the basis of dominance. The base case model shows that the strategy of sending letters compared to usual care to increase uptake of CR is about £5,000/QALY. The strategy of using phone calls and home visits by a HCP compared to sending letters is about £5,200/QALY gained which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

Table 9 Incremental cost effectiveness of the methods used to increase uptake of CR after an MI,

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs</th>
<th>QALY</th>
<th>Incre costs</th>
<th>Incre QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care</td>
<td>£6,995,529</td>
<td>6031</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letters</td>
<td>£7,844,705</td>
<td>6202</td>
<td>£849,176</td>
<td>172</td>
<td>£4,951</td>
</tr>
<tr>
<td>Phone +</td>
<td>£8,896,943</td>
<td>6404</td>
<td>£1,052,239</td>
<td>202</td>
<td>£5,215</td>
</tr>
</tbody>
</table>

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices
While the results of the ICER can be used to determine the optimal decision based on a comparison of mean costs and QALYs, they do not incorporate the uncertainty surrounding this decision. Figure 3 presents the base-case results in the form of cost effectiveness acceptability curves (CEACs) for CR versus no CR. Figure 4 shows the comparison between the three strategies of increasing uptake of CR. These curves detail the probability that each strategy is cost effective over a range of potential maximum values that the NHS is prepared to pay for an additional QALY.

The CEACs demonstrate that CR is highly cost effective. The probability that CR is cost effective increases as the willingness to pay increases. If the NHS is willing to pay up to £5,000 for an additional QALY, the probability that CR is cost effective is around 52%, increasing to 77% if the maximum willingness to pay is £10,000. At a threshold of £20,000/QALY the probability that CR is cost effective is 86%.

Figure 3

In figure 4, the CEACs demonstrate that either the strategy of phone calls plus home visits by a HCP or the strategies of sending letters are cost effective. However by comparison, the
strategy of using phone calls plus home visits by a HCP is the optimal strategy. If the NHS is prepared to pay £5,000 for an additional QALY, the probability that phone calls plus home visits by a HCP is cost effective is around 48%, increasing to 85% if the maximum willingness to pay is £20,000.

**Figure 4**

![Cost-Effectiveness acceptability curves doing nothing vs. letters vs. phone + HCP](image)

**Other sensitivity Analysis**

Sensitivity analysis was done to explore the robustness of the base case results, including the impact of age, costs of CR and CVD events, quality of life, and efficacy of CR. The model was robust to changes in assumptions about the different parameters except for quality of life.

**Quality of life loss due to CR**

The impact of cardiac rehabilitation on quality of life was tested. It was assumed that that cardiac rehabilitation will result in disutility or a loss in quality of life. Arbitrary figures were used ranging between 1-8%. CR will cease to be cost effective at £20,000/QALY threshold if it resulted in quality of loss of 7.3% and more. This is an unlikely scenario unless CR is provided to very high risk patients whose health is made worse by participating in CR.
Efficacy of CR

The efficacy of CR was tested using the upper and lower confidence intervals. When the lower confidence interval is used, the ICERs are expected to improve and when the upper confidence interval the ICERs is expected to worsen. The model remained robust when both upper and lower confidence intervals were used. Impact of CR on mortality appears to have a bigger impact on the ICERs. When the lower CI is used the ICERs fall to about £4000/QALY and when the upper CI is used the ICERs rise to about £7400/QALY.

QALY gain due to CR

The model is not sensitive to changes in additional QALYs as a result of CR. The base case model used a multiplier of 0.052 reported by Oldridge et al. If the multiplier is reduced to 0.001 the ICERs increase to about £7,600/QALY and if the multiplier is raised to 0.1 or doubled, the ICERs fall by almost half, but the model remains robust.

Cost of CR

The results were sensitive to changes in the cost of rehabilitation but remained robust. The ICER ranged from about £1,400/QALY if the lowest cost per patient per year of £140 cited by Taylor et al is used to about £10,000/QALY when the cost is assumed to be about £1,000/patient per year. As the cost of rehabilitation increases the ICER become less favourable

RR of non CVD death

The model assumed that patients after MI have a two fold increased risk of dying from any other causes than the general population. We tested this assumption in sensitivity analysis. When we assumed that there was no difference in non CVD mortality between the general population and the post MI patients the ICERs increased slightly to £5,300/QALY. Overall the model was robust to this assumption

Age and sex
Age and sex did not affect the results. However it should be acknowledged that the efficacy data available is mainly for middle aged men usually aged upto 65. Only mortality data was available a by age and sex in our model.

Discounting

The impact of the discounting was also explored. Assuming that there was no discounting at all, the results of the model remain robust with an estimated ICER of £4,500/QALY. If the discount rate was raised to 6%, the ICERs slightly increased to £5,100/QALY. Thus the model was not sensitive to this parameter.

**Efficacy of letters**

When assumptions about the efficacy of letters were changed the model remained robust. When letters were assumed to result in a modest 0.5% increase in uptake, the ICERs compared to usual care increased 3 fold rising to £13,700/QALY. The ICERs of phone call plus home visit by a HCP improved as the efficacy of letters worsens, and worsens as the efficacy of letters improves. For instance when the efficacy of letters was assumed to result in a 20% increase in the uptake of CR the ICERs were about £5,100 and when the efficacy of letters increased to 100% the ICERs increased to £6,800/QALY

**Efficacy of phone calls plus home visit by HCP**

In the base case model phone calls plus home visits by a HCP resulted in 111% increase in uptake of CR. When the efficacy of phone call plus home visits by a HCP was assumed to result in 50% increase in uptake of CR, letters became the optimal strategy dominating phone calls plus home visits by a HCP. When phone calls plus home visits by a HCP was assumed to result in 60% or more in uptake of CR it became the optimal strategy.

**HCP used**

The HCP used in the base case model was a social worker. The impact of using another HCP assuming the same efficacy observed in the social worker trial was tested. We tested the use of a healthcare assistant whose wages are half those of the social worker. The ICER when letters were compared with phone calls plus home visits by a HCP improved slightly. Other health care professionals considered were community physiotherapist and a practice nurse.
The results remained robust, suggesting that the type of health care professional used to increase the uptake of CR does not matter much.

**Baseline uptake of CR**

The model was not sensitive to assumptions about baseline uptake of cardiac rehabilitation. However the ICERs doubled when the baseline uptake was assumed to be as low as 1% with estimated ICERs of about £8,300 for letters compared with usual care and £18,900 for phone calls plus home visits by a HCP compared with letters. However the model remained robust.

### 1.1.4 Limitations of the model

The assumptions about mortality and revascularisation were simplified, assuming that mortality was the same in the first year post MI and subsequent years. Study {5278} demonstrated that mortality may be greater than 6 fold in the first year post MI compared to subsequent years. Revascularisation rates may also differ in the first year post MI compared to subsequent years.

The model does not consider the effect of gender. In particular, most studies of effectiveness from which the data for this model were taken were conducted in predominantly male populations. Therefore these results ought to be interpreted with caution when being generalized to women.

Lack of long term data on clinical endpoints. The follow up in the trials were averaging upto 5 years. Benefits beyond the trial period are not fully known. The model assumed that the benefits observed during the trial period will persist for lifetime. This might not necessarily be true.

Efficacy of interventions used to increase uptake of CR were drawn from very small studies of less than 100 patients in each study. These small studies might not give reliable estimates of effectiveness of these interventions.

Finally, reliable utility data for these patients are lacking. Utility weights were taken from the literature and the estimates were crude, and in some cases, old. Although we believe that the assumptions we used around health state utilities were reasonable, the model showed that the
cost-effectiveness of rehabilitation is not dependent on assumptions about health state utilities.

# 1.1.5 Conclusions

The results suggest that CR is highly cost effective when compared to no CR with 86% probability that CR is cost effective. These results are robust in sensitivity analysis except for quality life.

The results also showed that methods of increasing uptake of CR are cost effective. The ICERs were below £20,000/QALY for all comparisons in the base case model. The optimal strategy is the use of a phone plus a HCP. This result is sensitive to the efficacy of phone plus HCP. The model also shows that the HCP delivering CR does not matter much because the model remains robust in sensitivity analysis.

## 1.1.6 ADDITIONAL INFORMATION: SENSITIVITY ANALYSIS

### Sensitivity analysis for relative risk of non-CVD death

<table>
<thead>
<tr>
<th>RR of non CVD death</th>
<th>ICER (cost/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>£5,630</td>
</tr>
<tr>
<td>1</td>
<td>£5,270</td>
</tr>
<tr>
<td>4</td>
<td>£4,490</td>
</tr>
<tr>
<td>8</td>
<td>£4,100</td>
</tr>
</tbody>
</table>

**Interpretation**

The model assumed that patients after MI have a two fold increased risk of dying from any other causes than the general population. We tested this assumption in sensitivity analysis. When we assumed that there was no difference in non CVD mortality between the general population and the post MI patients the ICERs increased slightly to £5,300/QALY. Overall the model was robust to this assumption.
Age & ICER (cost/QALY)

<table>
<thead>
<tr>
<th>Age</th>
<th>ICER (cost/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>£4,770</td>
</tr>
<tr>
<td>65</td>
<td>£4,860</td>
</tr>
<tr>
<td>75</td>
<td>£4,650</td>
</tr>
<tr>
<td>85</td>
<td>£4,490</td>
</tr>
</tbody>
</table>

**Interpretation**

Age and sex did not affect the results. However it should be acknowledged that the efficacy data available is mainly for middle aged men usually aged upto 65. Only mortality data was available by age and sex in our model.

**Sensitivity analysis for efficacy of CR**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICER (cost/QALY lower 95% CI)</th>
<th>ICER (cost/QALY upper 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularisation</td>
<td>£4,670</td>
<td>£4,980</td>
</tr>
<tr>
<td>MI</td>
<td>£4,620</td>
<td>£5,170</td>
</tr>
<tr>
<td>Death</td>
<td>£3,880</td>
<td>£7,370</td>
</tr>
</tbody>
</table>

**Interpretation**

The efficacy of CR was tested using the upper and lower confidence intervals. When the lower confidence interval is used, the ICERs are expected to improve and when the upper confidence interval the ICERs is expected to worsen. The model remained robust when both upper and lower confidence intervals were used. Impact of CR on mortality appears to have a bigger impact on the ICERs. When the lower CI is used the ICERs fall to about £4000/QALY and when the upper CI is used the ICERs rise to about £7400/QALY.

**Sensitivity analysis for reduction in quality of life due to CR**

Reduction in QoL due to CR | ICER (Cost/QALY)

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The impact of cardiac rehabilitation on quality of life was tested. It was assumed that that cardiac rehabilitation will result in disutility or a loss in quality of life. Arbitrary figures were used ranging between 1-8%. CR will cease to be cost effective at £20,000/QALY threshold if it resulted in quality of loss of 7.3% and more. This is an unlikely scenario unless CR is provided to very high risk patients whose health is made worse by participating in CR.

Sensitivity analysis for additional QALYs due to CR

<table>
<thead>
<tr>
<th>Additional QALYs due to CR</th>
<th>ICER (cost/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>£7,640</td>
</tr>
<tr>
<td>0.02</td>
<td>£6,300</td>
</tr>
<tr>
<td>0.1</td>
<td>£3,630</td>
</tr>
</tbody>
</table>

Interpretation

The model is not sensitive to changes in additional QALYs as a result of CR. The base case model used a multiplier of 0.052 reported by Oldridge et al. If the multiplier is reduced to 0.001 the ICERs increase to about £7,600/QALY and if the multiplier is raised to 0.1 or doubled, the ICERs fall by almost half, but the model remains robust.

Sensitivity analysis for Cost of CR

<table>
<thead>
<tr>
<th>Cost of CR/patient/year</th>
<th>ICER (cost/QALY)</th>
</tr>
</thead>
</table>
Interpretation

The results were sensitive to changes in the cost of rehabilitation but remained robust. The ICER ranged from about £1,400/QALY if the lowest cost per patient per year of £140 cited by Taylor et al is used to about £10,000/QALY when the cost is assumed to be about £1,000/patient per year. As the cost of rehabilitation increases the ICER become less favourable.

Sensitivity analysis for Cost of CVD events and procedures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICER Lower costs (50% less) (cost/QALY)</th>
<th>ICER Upper costs (100% more) (cost/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularisation</td>
<td>£4,900</td>
<td>£4,800</td>
</tr>
<tr>
<td>MI</td>
<td>£4,900</td>
<td>£4,790</td>
</tr>
<tr>
<td>Subsequent MI</td>
<td>£4,820</td>
<td>£4,950</td>
</tr>
</tbody>
</table>

Interpretation

The model is not sensitive to outcome costs. The mean costs were reduced by 50% and increased by 100% and the results remained robust, all below £5000/QALY.

Sensitivity analysis for baseline uptake of CR

<table>
<thead>
<tr>
<th>Baseline uptake</th>
<th>Letters vs. usual care</th>
<th>Phone call plus home visit by HCP vs. Letters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>£8,316</td>
<td>£18,864</td>
</tr>
</tbody>
</table>
10% £5,210 £6,265
15% £5,095 £5,798
50% £4,934 £5,145
70% £4,914 £5,065
85% £4,905 £5,029

Interpretation

The model was sensitive to assumptions about baseline uptake of cardiac rehabilitation. The ICERs doubled when the baseline uptake was assumed to be as low as 1% with ICERs of £8316 for letters compared with usual care and £18864 for phone calls plus home visits by a HCP compared with letters. However the model remained robust.

Sensitivity analysis for efficacy of letters

<table>
<thead>
<tr>
<th>Efficacy of letters</th>
<th>Letters vs. usual care</th>
<th>Phone call plus home visit by HCP vs. Letters</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05%</td>
<td>£13,666</td>
<td>£5,055</td>
</tr>
<tr>
<td>1.00%</td>
<td>£9,266</td>
<td>£5,056</td>
</tr>
<tr>
<td>20.00%</td>
<td>£5,085</td>
<td>£5,096</td>
</tr>
<tr>
<td>60.00%</td>
<td>£4,938</td>
<td>£5,277</td>
</tr>
<tr>
<td>100.00%</td>
<td>£4,909</td>
<td>£6,774</td>
</tr>
</tbody>
</table>

Interpretation

When assumptions about the efficacy of letters were changed the model remained robust. When letters were assumed to result in a modest 0.5% increase in uptake, the ICERs compared to usual care increased 3 fold rising to £13,700/QALY. The ICERs of phone call plus home visit by a HCP improved as the efficacy of letters worsens, and worsens as the efficacy of letters improves. For instance when the efficacy of letters was assumed to result in a 20% increase in the uptake of CR the ICERs were about £5,100 and when the efficacy of letters increased to 100% the ICERs increased to £6,800/QALY.
Sensitivity analysis for efficacy of phone plus HCP

<table>
<thead>
<tr>
<th>Efficacy of phones</th>
<th>Letters vs. usual care</th>
<th>Phone call plus home visit by HCP vs. Letters</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 %</td>
<td>£4,951</td>
<td>dominated</td>
</tr>
<tr>
<td>60 %</td>
<td>£4,951</td>
<td>£7,198</td>
</tr>
<tr>
<td>100 %</td>
<td>£4,951</td>
<td>£5,293</td>
</tr>
<tr>
<td>150 %</td>
<td>£4,951</td>
<td>£5,077</td>
</tr>
</tbody>
</table>

Interpretation

In the base case model phone calls plus home visits by a HCP resulted in 111% increase in uptake of CR. When the efficacy phone calls + home visits by a HCP was assumed to result in 50% increase in uptake of CR, letters became the optimal strategy dominating phone calls + home visits by a HCP. When phone calls + home visits by a HCP was assumed to result in 60% or more increase in uptake of CR it became the optimal strategy.
1.2 Economic analysis of ACE inhibitors in low risk patients with preserved LVDF

An additional analysis was undertaken to examine the cost effectiveness of treatment with ACE inhibitors compared to placebo in patients with preserved left ventricular dysfunction. The analysis used effectiveness data from a meta-analysis (5215) which meta-analysed data from six trials (1770), (2334), (3128), (3251), (5279) and (5280).

1.2.1 Methods

Population and sub-groups
The model considered a cohort of low risk post MI patients with preserved left ventricular dysfunction. Low risk is defined as the population who met the inclusion criteria of the meta-analysis (5215) seen in primary and secondary care.

Interventions compared
The analysis assessed lifetime costs and effects of ACE inhibitors compared with placebo.

Outcomes
The treatment effects were measured in terms of reduction of cardiovascular events: non-fatal MI, revascularisation, unstable angina, heart failure, cardiovascular -related deaths and other deaths. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life Years (QALYs).

Model structure and assumptions
A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment with ACE inhibitors in secondary prevention of CVD events in low risk post MI patients from a UK NHS perspective.

In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states. Figure 1 shows a schematic representation of the patients' pathways. All patients start in the event-free
health state. During each six-month cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, heart failure, unstable angina, revascularisation and death) while the remainder stay in the event free state. Patients can experience more than one non-fatal event in subsequent periods of the model.

The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (six months). For illustration, the equivalent annual transition probabilities for a 65-year-old patient on placebo are shown in Table 1. The probabilities are derived from the placebo arm of the meta-analysis (5215).
The model was run first assuming that the cohort was to receive placebo. The model was then re-run assuming that the cohort all received ACE inhibitors and complied 100% with transition probabilities adjusted to reflect the expected reduction in CVD events and revascularisations. Health care costs and QALYs were then estimated for each option by weighting the time spent in the various states by mean costs and ‘utilities’ (health-related quality of life) of the health states. The cost and utility data used in the model are described below.

The time horizon modelled is lifetime, with an assumed upper age of 100, by which time most of the cohort have died.

Table 1 Annual probabilities for an untreated 65 year old men

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Annual probability</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well to REV</td>
<td>0.0189</td>
<td></td>
</tr>
<tr>
<td>Well to MI</td>
<td>0.01008</td>
<td></td>
</tr>
<tr>
<td>Well to unstable angina</td>
<td>0.01196</td>
<td></td>
</tr>
<tr>
<td>Well to heart failure</td>
<td>0.00328</td>
<td></td>
</tr>
<tr>
<td>Well to DEATH</td>
<td>0.0426298</td>
<td></td>
</tr>
<tr>
<td>Rev to MI</td>
<td>0.0189</td>
<td>{5284}</td>
</tr>
<tr>
<td>Rev to unstable angina</td>
<td>0.0189</td>
<td>assumed to be the same as MI</td>
</tr>
<tr>
<td>Rev to heart failure</td>
<td>0.00945</td>
<td>of MI</td>
</tr>
<tr>
<td>Rev to DEATH</td>
<td>0.0426298</td>
<td>{5277} {5290}</td>
</tr>
<tr>
<td>MI to REV</td>
<td>0.0189</td>
<td></td>
</tr>
<tr>
<td>MI to MI</td>
<td>0.01008</td>
<td></td>
</tr>
<tr>
<td>MI to unstable angina</td>
<td>0.01196</td>
<td></td>
</tr>
<tr>
<td>MI to heart failure</td>
<td>0.00328</td>
<td></td>
</tr>
<tr>
<td>MI to DEATH</td>
<td>0.0426298</td>
<td></td>
</tr>
<tr>
<td>Unstable angina to REV</td>
<td>0.0189</td>
<td>same as MI</td>
</tr>
<tr>
<td>Unstable angina to MI</td>
<td>0.01008</td>
<td>same as MI</td>
</tr>
<tr>
<td>Unstable angina to heart failure</td>
<td>0.01196</td>
<td>same as MI</td>
</tr>
<tr>
<td>Unstable angina to DEATH</td>
<td>0.0426298</td>
<td>same as MI</td>
</tr>
<tr>
<td>Heart failure to MI</td>
<td>0.023</td>
<td>{3393}</td>
</tr>
<tr>
<td>Heart failure to unstable angina</td>
<td>0.023</td>
<td>{3393}</td>
</tr>
</tbody>
</table>
Heart failure to heart failure \(0.0545\) \{3393\}
Heart failure to DEATH \(0.0915098\) \{3393\} \{5290\}

Key:

MI: myocardial infarction
UNA: unstable angina
REV: revascularisation

1.2.1.1 Baseline risks:

The risk of secondary or subsequent events, following an MI, unstable angina, heart failure and revascularisation were taken from the placebo arm of the meta-analysis \{5215\}. The incidence of MI following revascularisation was taken from \{5277\}.

Non-CVD related mortality by age and sex was taken from the life tables for England and Wales prepared by the Government Actuaries Department (GAD) \{5288\} and from data on the proportion of deaths due to CVD-related causes from the Office for National Statistics \{5290\}. In the base case model we assumed that the post MI cohort had a 2 fold increase in risk of non-CVD death compared with the general population, because they are a high risk population (expert opinion).

Table Error! No text of specified style in document.-2 Baseline non CVD related death
The effectiveness of ACE inhibitors defined as the reduction in relative risks of mortality, heart failure, revascularisation and non fatal reinfaction was obtained from the meta-analysis {5215}.

<table>
<thead>
<tr>
<th>COMPARATOR</th>
<th>Relative risks</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERVENTION</td>
<td></td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularisation</td>
<td>0.93</td>
<td>0.87</td>
<td>1.00</td>
</tr>
<tr>
<td>MI</td>
<td>0.84</td>
<td>0.75</td>
<td>0.94</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.93</td>
<td>0.83</td>
<td>1.05</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.71</td>
<td>0.59</td>
<td>0.86</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.87</td>
<td>0.81</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Cost data

The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of CVD and hospitalisations. Costs were calculated using cost weights for each of the states of the model, multiplied by the time spent in each state. Costs are at 2005 prices. As per current NICE guidance, an annual discount rate of 3.5% was used for both costs and health benefits {5292}.

The costs of health states used in the model are shown in Table Error! No text of specified style in document.-4. Costs for revascularization which includes hospitalisation were taken from the NHS reference cost 2005.{5293} It was assumed that 67% of patients will have PCI and 33% will have CABG and the costs were weighted to reflect this (expert opinion). The cost of the well states was assumed to be the outpatient cost which includes the costs of medication and monitoring costs were taken from the Statin HTA {5201}. The subsequent costs of MI and unstable angina were assumed to be the same and were taken from the NICE hypertension guideline 2006 {5256}. Costs of acute MI (non-fatal reinfaction) were assumed to be the same as those of patients on thrombolysis, which
includes the cost of hospitalisation, \( (5276) \). The cost of death was zero. Costs of drugs were taken from the drug tariff \( (5289) \).

Cost of heart failure was taken from the NHS reference cost 2005,\( (5293) \) and subsequent costs after heart failure were assumed to be the same as those seen in subsequent MI patients (expert opinion). Costs of events were reduced by 50\% and doubled in sensitivity analysis.

Table **Error! No text of specified style in document.**-4 Costs of health states

<table>
<thead>
<tr>
<th></th>
<th>2005 UK £ pa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>No event</td>
<td>£171</td>
</tr>
<tr>
<td>Rev</td>
<td>£8,676</td>
</tr>
<tr>
<td>Post Rev</td>
<td>£500</td>
</tr>
<tr>
<td>MI</td>
<td>£4,448</td>
</tr>
<tr>
<td>MI (subsequent)</td>
<td>£500</td>
</tr>
<tr>
<td>Rev2</td>
<td>£8,676</td>
</tr>
<tr>
<td>Post Rev2</td>
<td>£500</td>
</tr>
<tr>
<td>post OPD</td>
<td>£0</td>
</tr>
<tr>
<td>Death</td>
<td>£0</td>
</tr>
</tbody>
</table>

Quality of life (Utility):

In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the Quality Adjusted Life Year (QALY) approach. This requires estimates of survival and quality of life associated with each health state included in the model.\( (5292) \)

The utility values used in the model are shown in Table **Error! No text of specified style in document.**-5 and Table **Error! No text of specified style in document.**-6. The values were taken from literature or the Harvard cost effectiveness registry database.\( (5286) \)

Utilities were adjusted to reflect the fact that health related quality of life in the general population decreases with age (i.e. multiply the disease utility weight by age utility weight).
Age utility weights were taken from the Department of Health, Health Survey for England (5287)

<table>
<thead>
<tr>
<th>Health State (subsequent)</th>
<th>Utility</th>
<th>Mean</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>No event</td>
<td>1.00</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Rev</td>
<td>0.80</td>
<td>0.80</td>
<td>0.70</td>
<td>0.90</td>
<td>(5284)</td>
</tr>
<tr>
<td>Post Rev</td>
<td>0.88</td>
<td>0.88</td>
<td>0.70</td>
<td>0.90</td>
<td>(5286)</td>
</tr>
<tr>
<td>MI</td>
<td>0.76</td>
<td>0.76</td>
<td>0.70</td>
<td>0.90</td>
<td>(5286)</td>
</tr>
<tr>
<td>Rev2</td>
<td>0.80</td>
<td>0.80</td>
<td>0.70</td>
<td>0.90</td>
<td>same as Rev 1</td>
</tr>
<tr>
<td>Post Rev2</td>
<td>0.88</td>
<td>0.88</td>
<td>0.70</td>
<td>0.90</td>
<td>same as Rev 1</td>
</tr>
<tr>
<td>post OPD</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

1.2.1.2 Cost effectiveness

The results of cost-effectiveness analysis are presented as Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of ACE inhibitors per additional QALY gained compared with placebo.

\[
\text{ICERs} = (\text{cost of ACE inhibitors} - \text{cost of placebo}) / (\text{QALY of ACE inhibitors} - \text{QALY of placebo})
\]

Sensitivity analysis

The model includes a base case analysis supplemented with both deterministic and probabilistic sensitivity analysis. The impact of utility, costs of revascularisation, cost of ACE inhibitors and baseline risks for mortality, revascularisation second MI, heart failure and unstable angina were assessed.
1.2.2 Results

The base case results are presented for 65-year-old low risk men and women post MI with preserved left ventricular dysfunction. The results suggest ACE inhibitors are cost-effective with an estimated ICER of about £3,400/QALY gained for men and about £3,700 for women compared with placebo which is well below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

<table>
<thead>
<tr>
<th></th>
<th>Effect (QALYs)</th>
<th>Incremental cost (£)</th>
<th>Incremental effect (£)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£3,847</td>
<td>7.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>£5,633</td>
<td>8.24</td>
<td>£1,786</td>
<td>0.52</td>
</tr>
</tbody>
</table>

### Table

<table>
<thead>
<tr>
<th></th>
<th>Effect (QALYs)</th>
<th>Incremental cost (£)</th>
<th>Incremental effect (£)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£4,265</td>
<td>8.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>£6,176</td>
<td>8.92</td>
<td>£1,911</td>
<td>0.52</td>
</tr>
</tbody>
</table>

### Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was also done, where all parameters are assigned a distribution and are allowed to vary at the same time. The results are reported below in the form of cost effectiveness acceptability curves (CEACs). These curves detail the probability
that each strategy is cost effective over a range of potential maximum willingness to pay values that the NHS can afford to pay for an additional QALY.

The CEACs demonstrate that ACE inhibitors are cost effective when compared to placebo. The probability that ACE inhibitors are cost effective is around 70% at £20,000/QALY threshold. As expected the probability that an intervention is cost effective improves as the willingness to pay increases. Thus for a threshold of £5,000/QALY the probability that ACE inhibitors are cost effective is 59%, while at £30,000/QALY the probability increases to 72%.

**Figure 2, Cost effectiveness acceptability curve**

Deterministic sensitivity analysis
A range of univariate sensitivity analyses were conducted to assess the impact of different input parameters on the base case results. Detailed results for all parameters are shown in the appendix.

Quality of life
The base case model assumed that the side effect profile of ACE inhibitors was the same as in the placebo arm. However when it was assumed that ACE inhibitors will result in loss of quality due to side effects of more than 2.1%, then ACE inhibitors would no longer be cost effective at £20,000/QALY threshold. For instance if the loss in quality of due to side effects are assumed to be about 2.5% the estimated ICERs is about £230,200/QALY. If the
loss was 3% ACE inhibitors are dominated by placebo. Overall the result is sensitive to
loss in quality of life due side effects of treatment.

Health state utilities were arbitrarily reduced and increased by 0.2. This did not affect the
base case conclusions suggesting the model was is not sensitive to changes in health
state utilities. The ICERs ranged between £3,370 to about £3,480/QALY.

Costs
Cost of events (cost of treating MI, heart failure, revascularizations, and unstable angina)
were increased by 100% and reduced by 50%. The model remained robust with ICERs
remaining ranging between about £3,300/QALY and £3,400/QALY in all cases examined.

Worse case scenario
A worse case scenario was examined were the cost of events were doubled, and treatment
effects were set at their upper limit of the 95% confidence interval. In this case the ICERs
increased to about £8,400/QALY. This is still within acceptable limits of what is usually
considered affordable by the NHS. Thus the model is robust to the worse case scenario
assumption.

Efficacy
Assumptions about the efficacy of treatment were tested using the 95% confidence
interval. The model was robust in all cases when either the lower or the upper 95%
confidence interval was used. When the upper 95% CI was used, the ICERs increased to
about £6,100/QALY but were still within the range considered affordable by NHS.

RR of non CVD death, age and sex
The model was also robust to assumptions about age and sex. The estimated ICERs
ranged between about £3,000/QALY for a 85 year old men to about and about
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£5,000/QALY for a 55 year old men. For women it ranged between £4,000/QALY for an 85 year old to about £5,500/QALY for 55 year old women. There was no big difference between sexes; ICERs were more favourable to men than women.

1.2.3 Limitations of the model

The model was based on various assumptions that could possibly bias the results.

The first limitation of the model arises because of the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends only on their current health state (there is no longer ‘memory’ in the model). Thus the probability of heart failure for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. Similarly, a patient’s health outcome and health care costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost-effective than they may be in reality. So the model is conservative in this respect.

A second potentially important limitation of the model is the lack of utility data for the side effects of the drug. However sensitivity analysis was done, assuming that ACE inhibitors would result in loss of quality of life. Assuming a loss in quality of life greater than 2.1%, ACE inhibitors will no longer be cost effective at £20,000/QALY threshold suggesting that the side effects profile of ACE inhibitors affects the model results yet there is no quality of life data that is available.

There is also lack of outcome data by age and sex and non white population. This implies that it is difficult to predict the relative cost-effectiveness of ACE inhibitors in these sub-groups. There is also lack of standard errors needed for the probabilistic sensitivity analysis. In the model we assumed the standard errors were a tenth of the observed mean values used in the base case model which might not always be the case.

Another limitation of the model relates to the treatment of withdrawals and non-concordance with treatment. Since the treatment effects are based on ‘intention-to-treat’
analyses, the impact of withdrawals and non-concordance from the trials is already included in the model. However, the model continues to attribute drug costs for all patients throughout their lifetime. This is a conservative assumption that will tend to underestimate the cost-effectiveness of treatment.

1.2.4 Conclusions
The use of ACE inhibitors in low risk patients with preserved left ventricular function is cost effective. This result is largely robust in sensitivity analysis. The model is sensitive to assumptions about loss of quality of life due to treatment side effects.
1.2.5 ADDITIONAL INFORMATION: SENSITIVITY ANALYSIS

**Sensitivity analysis; quality of life loss due to side effects**

<table>
<thead>
<tr>
<th>% loss of QoL due to treatment side effects</th>
<th>Cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>£5,650</td>
</tr>
<tr>
<td>2%</td>
<td>£16,160</td>
</tr>
<tr>
<td>2.1%</td>
<td>£20,000</td>
</tr>
<tr>
<td>2.5%</td>
<td>£230,200</td>
</tr>
<tr>
<td>3%</td>
<td>DOMINATED</td>
</tr>
</tbody>
</table>

**Interpretation:**

The base case model assumed that the side effect profile of ACE inhibitors was the same as in the placebo arm. However when it was assumed that ACE inhibitors will result in loss of quality due to side effects of more than 2.1%, then ACE inhibitors would no longer be cost effective at £20,000/QALY threshold. For instance if the loss in quality of due to side effects are assumed to be about 2.5% the estimated ICERs is about £230,200/QALY. If the loss was 3% ACE inhibitors are dominated by placebo. Overall the result is sensitive to loss in quality of life due side effects of treatment.

**Sensitivity analysis; health state utilities ± 0.2**

<table>
<thead>
<tr>
<th>Health state</th>
<th>(-0.2) cost/QALY</th>
<th>(+ 0.2) cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularisation</td>
<td>£3,420</td>
<td>£3,420</td>
</tr>
<tr>
<td>Post Revascularisation</td>
<td>£3,520</td>
<td>£3,370</td>
</tr>
<tr>
<td>MI</td>
<td>£3,420</td>
<td>£3,430</td>
</tr>
<tr>
<td>Post MI</td>
<td>£3,400</td>
<td>£3,440</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>£3,420</td>
<td>£3,430</td>
</tr>
<tr>
<td>Post unstable angina</td>
<td>£3,480</td>
<td>£3,370</td>
</tr>
<tr>
<td>Heart failure</td>
<td>£3,420</td>
<td>£3,430</td>
</tr>
<tr>
<td>Post HF</td>
<td>£3,390</td>
<td>£3,450</td>
</tr>
</tbody>
</table>

**Interpretation:**

Health state utilities were arbitrarily reduced and increased by 0.2. This did not affect the base case conclusions suggesting the model was is not sensitive to changes in health state utilities. The ICERs ranged between £3,370 to about £3,480/QALY.
**Sensitivity analysis cost of CVD events/health state costs**

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost of events (cost/QALY)</th>
<th>50% less</th>
<th>100% more</th>
</tr>
</thead>
<tbody>
<tr>
<td>No event</td>
<td>£3,320</td>
<td>£3,630</td>
<td></td>
</tr>
<tr>
<td>Revascularisation</td>
<td>£3,430</td>
<td>£3,420</td>
<td></td>
</tr>
<tr>
<td>Post Revascularisation</td>
<td>£3,380</td>
<td>£3,510</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>£3,450</td>
<td>£3,370</td>
<td></td>
</tr>
<tr>
<td>MI (subsequent)</td>
<td>£3,440</td>
<td>£3,400</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>£3,430</td>
<td>£3,420</td>
<td></td>
</tr>
<tr>
<td>Unstable angina subsequent</td>
<td>£3,390</td>
<td>£3,480</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>£3,440</td>
<td>£3,370</td>
<td></td>
</tr>
<tr>
<td>Post HF</td>
<td>£3,440</td>
<td>£3,400</td>
<td></td>
</tr>
</tbody>
</table>

Interpretation:

Cost of events (cost of treating MI, heart failure, revascularizations, and unstable angina) were increased by 100% and reduced by 50%. The model remained robust with ICERs remaining ranging between about £3,300/QALY and £3,400/QALY in all cases examined.

**Sensitivity analysis; worse case scenario 1, doubling the cost of events and using upper confidence limit of the 95% CI**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cost (£)</th>
<th>Effect (QALYs)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£7,690</td>
<td>7.7193</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>£9,530</td>
<td>7.9394</td>
<td>£8,360</td>
</tr>
</tbody>
</table>

Interpretation:

A worse case scenario was examined were the cost of events were doubled, and treatment effect was set at its upper limit of the 95% confidence interval. In this case the ICERs increased £8,400. This is still within acceptable limits of what is usually considered affordable by the NHS. Thus the model is sensitive to the worse case scenario assumption.

**Sensitivity analysis; efficacy of ACE inhibitors treatment**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
</table>

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Interpretation:

Assumptions about the efficacy of treatment were tested using the 95% confidence interval. The model was robust in all cases when either the lower or the upper 95% confidence interval was used. When the upper 95% CI was used, the ICERs increased to about £6,100/QALY but were still within the range considered affordable by NHS.

**Sensitivity analysis; relative risk of non CVD death**

<table>
<thead>
<tr>
<th>Relative risk of non CVD death</th>
<th>cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£4,060</td>
</tr>
<tr>
<td>2</td>
<td>£3,420</td>
</tr>
<tr>
<td>4</td>
<td>£2,960</td>
</tr>
<tr>
<td>8</td>
<td>£2,540</td>
</tr>
</tbody>
</table>

Interpretation:

Then model was robust to assumptions about the relative risk of death from other causes between the post MI cohort and the general population. The base case assumed a relative risk of 2. When it was assumed that there was no difference in mortality from other causes between the general population and the post MI cohort, the ICERs slightly increased to about £4,100/QALY.

**Sensitivity analysis; age and sex**

<table>
<thead>
<tr>
<th>Age</th>
<th>cost/QALY (Males)</th>
<th>cost/QALY (Females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>£4,740</td>
<td>£5,520</td>
</tr>
<tr>
<td>65</td>
<td>£3,420</td>
<td>£4,060</td>
</tr>
<tr>
<td>75</td>
<td>£2,990</td>
<td>£3,790</td>
</tr>
<tr>
<td>85</td>
<td>£2,890</td>
<td>£4,040</td>
</tr>
</tbody>
</table>

Interpretation:

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices
The model was also robust to assumptions about age and sex. The estimated ICERs ranged between about £3,000/QALY for a 85 year old men to about £5,000/QALY for a 55 year old men. For women it ranged between £4,000/QALY for an 85 year old to about £5,500/QALY for 55 year old women. There was no big difference between sexes; ICERs were more favourable to men than women.
1.3  Beta blockers economic model results

An additional analysis was undertaken which examined the cost effectiveness of a “new” generation beta blocker carvedilol in selected in post MI patients. Only one trial {368} was identified which compared carvedilol with placebo. An economic analysis was performed using data from this trial and the results are presented below.

1.3.1 Methods

Population and sub-groups
The model considered post MI patients with left ventricular dysfunction who met the inclusion criteria of the Carvedilol Post Infarct Survival Control in left ventricular Dysfunction (CAPRICORN) trial {368}. The model was run separately for different cohorts, defined by age (65, 75 and 85) and sex. The base case analysis is presented for 65-year-old men and women. However the trial evidence that the model this is based on included relatively few women (27%) or black patients, so the results may not be reliable for these sub-groups.

Interventions compared
The analysis assessed the costs and effects of carvedilol compared with placebo.

Outcomes
The treatment effects were measured in terms of prevention of cardiovascular events: non-fatal MI, hospital admission for heart failure, and cardiovascular-related deaths. Other cardiovascular events, including onset of stable or unstable angina, stroke, and peripheral vascular disease were not modelled, as they were not reported in the trial. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life Years (QALYs), where one QALY represents one year of healthy life.

Model structure and assumptions
A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment with third generation beta blockers for post MI patients with left ventricular dysfunction seen in primary care from a UK NHS perspective.
In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states. Figure 1 shows a schematic representation of the patients’ pathways. All patients start in the event-free health state. During each six-month cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, heart failure, or death) while the remainder remains in the event free state. Patients can experience more than one non-fatal event in subsequent periods of the model.

Figure Error! No text of specified style in document.-2 Model structure for third generation beta blockers

The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (six months). These transition probabilities are adjusted for each subgroup by age and sex. For illustration, the equivalent annual transition probabilities for untreated 65-year-old men are shown in Table 1.

The model was run first assuming that the cohort received no intervention (placebo). The model was then re-run for the treatment arm with transition probabilities adjusted to reflect the expected reduction in CVD events from the clinical trial data. Health care costs and QALYs are then estimated for each option by weighting the time spent in the various states by mean costs and ‘utilities’ (health-related quality of life) of the health states. The cost and utility data used in the model are described below.
The time horizon modelled is lifetime, with an assumed upper age limit of 100, by which time most of the cohort have died.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Annual probability</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well to MI</td>
<td>0.0480</td>
<td>(368)</td>
</tr>
<tr>
<td>Well to heart failure</td>
<td>0.1120</td>
<td>(368)</td>
</tr>
<tr>
<td>Well to death</td>
<td>0.1268</td>
<td>(368)</td>
</tr>
<tr>
<td>MI to MI</td>
<td>0.0480</td>
<td>(368)</td>
</tr>
<tr>
<td>MI to heart failure</td>
<td>0.1120</td>
<td>(368)</td>
</tr>
<tr>
<td>MI to death</td>
<td>0.1268</td>
<td>(368)</td>
</tr>
<tr>
<td>heart failure to heart failure</td>
<td>0.1120</td>
<td>(368)</td>
</tr>
<tr>
<td>heart failure to MI</td>
<td>0.0480</td>
<td>(368)</td>
</tr>
<tr>
<td>heart failure to death</td>
<td>0.2118</td>
<td>(5291)</td>
</tr>
</tbody>
</table>

1.3.1.1 Baseline risks:

The probabilities of secondary cardiovascular events were taken from the placebo arm of the CAPRICORN trial (368) Non-cardiovascular related mortality by age and sex was taken from the life tables for England and Wales prepared by the Government Actuaries Department (GAD) (5288) In the base case model we assumed that post MI cohort is at increased risk of non-cardiovascular death (2 fold risk) compared with the general population (expert opinion).

<table>
<thead>
<tr>
<th>All cause</th>
<th>Circulatory (ICD: I00-I99)</th>
<th>Non-circulatory as proportion of all deaths (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>45</td>
<td>527.090 37,041</td>
<td>35,607</td>
</tr>
<tr>
<td>55</td>
<td>27,117 17,649</td>
<td>9,300</td>
</tr>
<tr>
<td>65</td>
<td>87,367 88,404</td>
<td>35,607</td>
</tr>
<tr>
<td>75</td>
<td>51,329 109,488</td>
<td>20,816</td>
</tr>
</tbody>
</table>

Relative risk of death from non-circulatory causes in cohort compared with general population: 2

Estimated non-circulatory deaths for post MI cohort

<table>
<thead>
<tr>
<th>Annual probability of death in age band</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
</tr>
<tr>
<td>45</td>
</tr>
<tr>
<td>55</td>
</tr>
<tr>
<td>65</td>
</tr>
<tr>
<td>75</td>
</tr>
<tr>
<td>85</td>
</tr>
</tbody>
</table>


Source: http://www.gad.gov.uk/Life_Tables/Interim_Wk_tables.htm

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 55 of 248
Treatment effects:
The relative treatment effects of third generation beta blockers were taken from the CAPRICON trial (368).

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>Relative risks</th>
<th>Lower CL</th>
<th>Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>0.59</td>
<td>0.39</td>
<td>0.90</td>
</tr>
<tr>
<td>heart failure</td>
<td>0.86</td>
<td>0.67</td>
<td>1.09</td>
</tr>
<tr>
<td>Death</td>
<td>0.75</td>
<td>0.58</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Cost data:
The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of CVD disease. Costs were calculated using cost weights for each of the states of the model, multiplied by the time spent in each state. Costs are at 2005/06 prices. As per current NICE guidance, an annual discount rate of 3.5% was used for both costs and health benefits. (5292)

The cost of health states used in the model are shown in Table No text of specified style in document.-12. Costs of acute MI (non-fatal reinfaction) were assumed to be the same as those of patients on thrombolysis, which includes the cost of hospitalisation.
Hartwell 2005 {5276}. Costs of heart failure were taken from NHS reference costs.
Subsequent MI costs were taken from NHS hypertension guideline 2006.{5256} 
Subsequent heart failure costs were assumed to be the same as those of MI (expert opinion)

Drug costs were taken from the prices quoted in the Drug Tariff, {5289} based on the usual
dose for post MI patients. In the base case model a conservative approach was taken,
using the most expensive dose of carvedilol 25mg and the use of the smaller dose of
6.25mg was tested in sensitivity analysis.

<table>
<thead>
<tr>
<th>Health state</th>
<th>£ Cost/year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>£4,448</td>
<td>{5276}</td>
</tr>
<tr>
<td>Subsequent MI costs</td>
<td>£500</td>
<td>{5256}</td>
</tr>
<tr>
<td>Heart failure</td>
<td>£2,350</td>
<td>{5293}</td>
</tr>
<tr>
<td>Post heart failure costs</td>
<td>£500</td>
<td>assumption</td>
</tr>
<tr>
<td>Death</td>
<td>£0</td>
<td>{5284}</td>
</tr>
</tbody>
</table>

Table Error! No text of specified style in document.-12 Costs of health states

Source: Prescription Pricing Authority (PPA) February 2006.

1.3.1.2 Quality of life (Utility):

In the NICE reference case, the value of health outcomes – including beneficial and
harmful impacts of treatment on mortality and morbidity – is estimated using the Quality
Adjusted Life Year (QALY) approach. This requires estimates of survival and quality of life
associated with each health state included in the model {5292}.

The utility estimates for MI was taken from study {5284}, heart failure and post MI were
taken from the Harvard cost effectiveness registry {5286}. Post heart failure was assumed
to be the same as heart failure state.

Utilities were adjusted to reflect the fact that health related quality of life in the general
population decreases with age (i.e. multiply the disease utility weight by age utility weight).
Age utility weights were taken from the Department of Health, Health Survey for England (1996) \( {5287} \).

The base case model assumed that there was no loss in quality of life due to treatment side effects. This assumption was tested in the sensitivity analysis, assuming that treatment resulted in a reduction in quality of life of up to 10%.

<table>
<thead>
<tr>
<th>Health state</th>
<th>Utility weight</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>0.80</td>
<td>( {5284} )</td>
</tr>
<tr>
<td>Post MI</td>
<td>0.88</td>
<td>( {5286} )</td>
</tr>
<tr>
<td>heart failure</td>
<td>0.71</td>
<td>( {5286} )</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>( {5286} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group</th>
<th>Age utility weight</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-54</td>
<td>0.85</td>
<td>( {5287} )</td>
</tr>
<tr>
<td>55-64</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

**Cost effectiveness:**

The results of cost-effectiveness analysis are usually presented as Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of using one drug (X) per additional QALY gained compared with no intervention or another drug (Y):

\[
\text{ICERs} = \frac{\text{cost of X} - \text{cost of Y}}{\text{QALY of X} - \text{QALY of Y}}
\]

**Sensitivity Analysis:**

The model includes a base case analysis supplemented with both univariate deterministic and probabilistic sensitivity analyses to test the impact of uncertainty over various model parameters and assumptions.
1.3.2 Results

The base case results are presented in tables Table Error! No text of specified style in document.-16 and Table Error! No text of specified style in document.-17 for 65-year-old men and women post MI with left ventricular dysfunction. 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 well below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

### Table 16 Base case results 65 year old male

<table>
<thead>
<tr>
<th></th>
<th>Cost (£)</th>
<th>Effect (QALYs)</th>
<th>Incremental cost (£)</th>
<th>Incremental effect (£)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£2,414</td>
<td>3.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>£3,286</td>
<td>4.20</td>
<td>£872</td>
<td>0.80</td>
<td>£1,091</td>
</tr>
</tbody>
</table>

### Table 17 Base case results 65 year old female

<table>
<thead>
<tr>
<th></th>
<th>Cost (£)</th>
<th>Effect (QALYs)</th>
<th>Incremental cost (£)</th>
<th>Incremental effect (£)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£2,533</td>
<td>3.54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>£3,439</td>
<td>4.36</td>
<td>£906</td>
<td>0.82</td>
<td>£1,102</td>
</tr>
</tbody>
</table>

Figure 3 Base case results 65-year-old male, Cost effectiveness plane
Figure Error! No text of specified style in document. Base case results 65-year-old female, Cost effectiveness plane

Probabilistic sensitivity analysis
A probabilistic sensitivity analysis was also done, where all parameters are allowed to vary at the same time. The results are reported below in the form of cost effectiveness acceptability curves (CEACs). These curves detail the probability that each strategy is cost effective over a range of potential maximum willingness to pay values that the NHS can afford to pay for an additional QALY.

The CEACs demonstrate that beta blockers are cost effective when compared to placebo. The probability that beta blockers are cost effective is around 93% at £20,000/QALY threshold. Even at lower thresholds such as £5,000/QALY beta blockers are still highly cost effective with a 90% probability of being cost effective. This suggest that beta blocker treatment in patients with left ventricular dysfunction is value for money.

**Figure 3-4, Cost effectiveness acceptability curve**

![Cost effectiveness acceptability curve](image)

**Deterministic sensitivity analysis**

A range of univariate sensitivity analyses were conducted to assess the impact of different input parameters on the base case results. Detailed results for all parameters are shown in the appendix. The following parameters were tested costs of drugs, cost of events, discount rate, utility, age, and relative risk of non-CVD deaths and efficacy of treatment.

**Efficacy of treatment**
The results are not sensitive to uncertainty over the magnitude of treatment effects estimated from the CAPRICON trial (368). When the relative risks of carvedilol compared with no intervention were increased to their upper 95% confidence limits and reduced to their lower 95% confidence limits the results remained robust. The ICERs ranged between about £800/QALY to about £1500/QALY when both lower and upper confidence intervals are used.

**Relative risk of non CVD death**
Relative risk of non CVD mortality does not affect the conclusions of the model. If it's assumed that patients post MI have the same risk of dying from non circulatory causes as the general population, the ICERs increase by £20 to £1110. If it was assumed that post MI patients have a six fold increase in risk of dying from non circulatory causes, the ICERs slightly fell by £60 to £1030/QALY. This suggests that the model is robust to this assumption.

**Quality of life due to treatment side effects**
The model is robust assumptions about loss of quality of life as a result of treatment side effects. If it was assumed that beta blocker treatment would result in a 1% loss in quality of life, the estimated ICERs would be about £1090/QALY and if the loss was assumed to be as big as 10%, the ICERs will increase four fold to £4360/QALY, still within the range considered affordable by NHS.

**Health state utilities**
The results are not sensitive to assumptions about the health state utilities used in the base case model. When the observed health state utilities were arbitrarily reduced by 0.2, the model remained robust. When they increased by 0.2 the results did not change. The ICERs ranged between about £1100 to about £1200/QALY.

**Cost of health states**
The model is not sensitive to assumptions about the health state costs. When they were doubled or reduced by 50% the ICERs ranged between about £1,000/QALY to about £1,300/QALY.
Age and sex
The model is robust to assumptions about age and sex. However it should be noted that efficacy data by age and sex is not available except for baseline mortality. The trial data mainly had male population aged between 60-65 years. For ages below 55 and above 70 and to females the results need to be interpreted with caution.

Worse case scenarios
A worse case scenario was examined were the cost of events were doubled, and treatment effect was set at its upper 95% confidence interval. In this case the ICERs increased by ten fold, to about £11,000/QALY. This however was still within the range of what is considered affordable by the NHS. Thus in this worse case scenario, the model remained robust.

Another scenario was tested where in addition to doubling the costs of events and using the upper 95% confidence interval for treatment effect, it was also assumed that ACE inhibitors will result in a 1% loss in quality of life due to side effects of treatment. The ICER increased to about £55,000/QALY. The model was not robust to this worse case scenario. It is however important to note that this is an unlikely scenario since the cost of events/health states are not as high as suggested in this assumption and the efficacy of beta-blockers is not as low as again suggested in this assumption.

1.3.3 Limitations of the model
The model was based on various assumptions that could possibly bias the results.

The first limitation of the model arises because of the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends only their current health state (there is no longer ‘memory’ in the model). Thus the probability of heart failure for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. Similarly, a patient’s health outcome and health care costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost-effective than they may be in reality. So the model is conservative in this respect.
A second potentially important limitation of the model is the lack of utility data for the side effects of the drug. However exploratory sensitivity analysis was done assuming that carvedilol would result in loss of quality of life of upto 10%, but the results remained robust. This suggests that side effects profile might not affect the base case conclusions.

There is also lack of outcome data by age and sex and non white population. This implies that it is difficult to predict the relative cost-effectiveness of third generation beta blockers in these sub-groups. There is also lack of standard errors needed for the probabilistic sensitivity analysis. In the model we assumed the standard errors were a tenth of the observed mean values used in the base case model which might not always be the case.

Another limitation of the model relates to the treatment of withdrawals and non-concordance with treatment. Since the treatment effects are based on ‘intention-to-treat’ analyses, the impact of withdrawals and non-concordance from the trials is already included in the model. In CAPRICON {368} 20% of patients were permanently withdrawn from treatment. However, the model continues to attribute drug costs for all patients throughout their lifetime. This is a conservative assumption that will tend to underestimate the cost-effectiveness of treatment.

### 1.3.4 Conclusions

This analysis suggests that treatment with third generation beta blockers is cost effective. This result is robust for all the parameters tested in sensitivity analysis including a worse case scenario.
### 1.3.5 ADDITIONAL INFORMATION: SENSITIVITY ANALYSIS

All sensitivity analysis applies to 65 year old men

Sensitivity analysis, efficacy of beta blocker treatment (95% CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICER for Lower 95% CI</th>
<th>ICER for Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>£880</td>
<td>£1,420</td>
</tr>
<tr>
<td>Heart failure</td>
<td>£790</td>
<td>£1,530</td>
</tr>
<tr>
<td>Mortality</td>
<td>£1,060</td>
<td>£1,530</td>
</tr>
</tbody>
</table>

Interpretation:

The model is stable to assumptions about the efficacy of treatment. The ICERs ranges between about £800/QALY to about £1500/QALY when both lower and upper confidence intervals are used.

Sensitivity analysis, quality of life loss due to treatment side effects

<table>
<thead>
<tr>
<th>Quality of life loss due to treatment side effects</th>
<th>cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>£1,180</td>
</tr>
<tr>
<td>2%</td>
<td>£1,180</td>
</tr>
<tr>
<td>5%</td>
<td>£1,750</td>
</tr>
<tr>
<td>10%</td>
<td>£4,360</td>
</tr>
</tbody>
</table>

Interpretation:
The model is robust assumptions about loss of quality of life as a result of treatment side
effects. If it was assumed that beta blocker treatment would result in a 1% loss in quality of
life, the estimated ICERs would be about £1090/QALY and if the loss was assumed to be
as big as 10%, the ICERs will increase four fold to £4360/QALY, still within the range
considered affordable by NHS.

Sensitivity analysis; health state utilities ± 0.2

<table>
<thead>
<tr>
<th>Health state</th>
<th>(0.2 less)</th>
<th>cost/QALY</th>
<th>(0.2 more)</th>
<th>cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>£1,090</td>
<td>£1,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>well post MI</td>
<td>£1,100</td>
<td>£1,090</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>£1,090</td>
<td>£1,090</td>
<td></td>
<td></td>
</tr>
<tr>
<td>well post heart failure</td>
<td>£1,180</td>
<td>£1,020</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interpretation:

The results are not sensitive to assumptions about the health state utilities used in the
base case model. When the observed health state utilities were arbitrarily reduced by 0.2,
the model remained robust. When they increased by 0.2 the results did not change. The
ICERs ranged between about £1100 to about £1200/QALY.

The model is very robust to all assumptions tested with ICERs remaining the same as in
the base case or differing very slightly as shown in the table above.
Sensitivity analysis; relative risk of non CVD death

<table>
<thead>
<tr>
<th>Relative risk of non CVD mortality</th>
<th>ICER (Cost/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£1,110</td>
</tr>
<tr>
<td>2</td>
<td>£1,090</td>
</tr>
<tr>
<td>4</td>
<td>£1,060</td>
</tr>
<tr>
<td>6</td>
<td>£1,030</td>
</tr>
</tbody>
</table>

Interpretation:
Relative risk of non CVD mortality does not affect the conclusions of the model. If its assumed that patients post MI have the same risk of dying from non circulatory causes as the general population, the ICERs increase by £20 to £1110. If it was assumed that post MI patients have a six fold increase in risk of dying from non circulatory causes, the ICERs slightly fell by £60 to £1030/QALY. This suggests that the model is robust to this assumption.

Sensitivity analysis; health state costs

<table>
<thead>
<tr>
<th>Health state</th>
<th>50% less (cost/QALY)</th>
<th>100% more (cost/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WELL</td>
<td>£1,010</td>
<td>£1,260</td>
</tr>
<tr>
<td>MI (ACUTE)</td>
<td>£1,150</td>
<td>£980</td>
</tr>
<tr>
<td>Well post MI</td>
<td>£1,080</td>
<td>£1,110</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>£1,100</td>
<td>£1,070</td>
</tr>
</tbody>
</table>
Well post heart failure £970 £1,330

Interpretation:

The model is not sensitive to assumptions about the health state costs. When they were doubled or reduced by 50% the ICERs ranged between about £1,000/QALY to about £1,300/QALY.

Sensitivity analysis; Age and sex

<table>
<thead>
<tr>
<th>AGE</th>
<th>MALE cost/QALY</th>
<th>FEMALE cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>£1,070</td>
<td>£1,080</td>
</tr>
<tr>
<td>65</td>
<td>£1,090</td>
<td>£1,100</td>
</tr>
<tr>
<td>75</td>
<td>£1,110</td>
<td>£1,120</td>
</tr>
<tr>
<td>85</td>
<td>£1,070</td>
<td>£1,080</td>
</tr>
</tbody>
</table>

Interpretation:

The model is robust to assumptions about age and sex. However it should be noted that efficacy data by age and sex is not available except for baseline mortality. The trial data mainly had male population aged between 60-65 years. For ages below 55 and above 70 and to females the results need to be interpreted with caution.

Sensitivity analysis; Worse case scenario 1, costs of health state doubled, treatment effects set the upper limit of the 95% CI
Cost | Effect (QALYs) | ICER (£/QALY)
---|---|---
Placebo | £4830 | 3.402509
Beta Blockers | £5500 | 3.4643036 | £10870

**Interpretation:**

A worse case scenario was examined where the cost of events were doubled, and treatment effect was set at its upper 95% confidence interval. In this case the ICERs increased by ten fold, to about £11,000/QALY. This however was still within the range of what is considered affordable by the NHS. Thus in this worse case scenario, the model remained robust.

Sensitivity analysis; Worse case scenario 2, costs of health states doubled, treatment effects set at the upper limit of the 95% CI, 1% loss in quality of life due to treatment side effects

<table>
<thead>
<tr>
<th>Cost (£)</th>
<th>Effect (QALYs)</th>
<th>Incremental cost (£)</th>
<th>Incremental effect (£)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>£4,828</td>
<td>3.402509</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>£5,499</td>
<td>3.4148236</td>
<td>£671.42</td>
<td>0.0123147</td>
</tr>
</tbody>
</table>

Another scenario was tested where in addition to doubling the costs of events and using the upper 95% confidence interval for treatment effect, it was also assumed that ACE inhibitors will result in a 1% loss in quality of life due to side effects of treatment. The ICER increased to about £55,000/QALY.
model was not robust to this worse case scenario. It is however important to note that this is an unlikely scenario since the cost of events/health states are not as high as suggested in this assumption and the efficacy of beta-blockers is not as low as again suggested in this assumption.
Appendix D – Clinical Evidence Extractions

Evidence Extractions

Question: What is the effectiveness of changing dietary regime from the pre-infarct diet?

Grading: 1++  
High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number 26

Shekelle P; Morton S; Hardy M;
Effect of supplemental antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease
2003  
Study Type: Systematic Review

Patient Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect

The available scientific studies offer little evidence that supplementation with vitamin C, vitamin E, or coenzyme Q10 has any benefit on secondary prevention in secondary prevention of cardiovascular disease.

Reference number 27

Wang C; Chung M; Lichtenstein A; Balk E; Kupelnick B; DeVine D; Lawrence A; Lau J;
Effects of omega-3 fatty acids on cardiovascular disease
2004  
Study Type: Systematic Review

Patient Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect

Evidence from secondary prevention studies supports the hypothesis that consumption of omega-3 fatty acids (EPA, DHA, ALA), fish, and fish oil reduces all-cause mortality and various cardiovascular disease outcomes such as sudden death and MI, although the evidence is strongest for fish or fish oils.
Grading:  **1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias**

Reference number 1482

de Lorgeril M; Salen P; Martin JL; Monjaud I; Delaye J; Mamelle N;
Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study.[see comment]

1999 99 Circulation  pgs 779 785

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Randomised Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Post MI patients &lt; 70 years</td>
</tr>
<tr>
<td>Characteristics</td>
<td>The experimental group were advised to eat more bread, fruit and vegetables, fish, and less meat, and to replace butter and cheese with rapeseed margarine Controls: no advice</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diet change versus no diet change</td>
</tr>
<tr>
<td>Study Length</td>
<td>46 months</td>
</tr>
<tr>
<td>Outcomes</td>
<td>All-cause mortality, cardio-vascular deaths</td>
</tr>
<tr>
<td>Funding</td>
<td>Not listed</td>
</tr>
<tr>
<td>Effect</td>
<td>Mean follow for survival in the control group was 44.9 month and 46.7 months in the experimental group. All-cause and cardiovascular (P = 0.01) mortality and the combination of recurrent MI and cardiac death were reduced in the treatment group (P = 0.0001).</td>
</tr>
</tbody>
</table>

Reference number 2070

Liem A; Reynierse-Buitenwerf GH; Zwinderman AH; Jukema JW; van V;
Secondary prevention with folic acid: Effects on clinical outcomes

2003 41 Journal of the American College of Cardiology  pgs 2105 2113

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Randomised Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Stable CAD (MI, coronary artery lesions, PCI, CABG Age Treatment: 64.9±9.9 years Control: 65.5±9.7 years Male gender Treatment: 76% Control: 80%</td>
</tr>
<tr>
<td>Characteristics</td>
<td>folic acid (0.5 mg/day)</td>
</tr>
<tr>
<td>Comparison</td>
<td>No treatment</td>
</tr>
<tr>
<td>Study Length</td>
<td>24 months</td>
</tr>
<tr>
<td>Outcomes</td>
<td>all-cause mortality and a composite of vascular events</td>
</tr>
<tr>
<td>Funding</td>
<td>Not listed</td>
</tr>
<tr>
<td>Effect</td>
<td>All-cause mortality and a composite of vascular events was found to be in 31 (10.3%) patients in the folic acid group, and in 28 (9.6%) patients in the control group (relative risk 1.05; 95% CI: 0.63 to 1.75).</td>
</tr>
</tbody>
</table>

Reference number 179

Morris CD; Carson S;
Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force.[see comment]. [Review] [65 refs]

2001 139 Annals of Internal Medicine  pgs 56 70

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Systematic Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
<td></td>
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<tr>
<td>Intervention</td>
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<tr>
<td>Comparison</td>
<td></td>
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<tr>
<td>Study Length</td>
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<tr>
<td>Outcomes</td>
<td></td>
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<tr>
<td>Funding</td>
<td></td>
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<tr>
<td>Effect</td>
<td>Randomised controlled trials of specific supplements failed to demonstrate a consistent or</td>
</tr>
</tbody>
</table>

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices  Page 72 of 248
significant effect on incidence of, or death from, cardiovascular disease.

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

Reference number: 1771

Burr ML; Fehily AM; Gilbert JF; Rogers S; Holliday RM; Sweetnam PM; Elwood PC; Deadman NM;

Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). [see comment]

1989 2  Lancet  pgs 757 761

**Study Type:** Randomised Controlled Trial

**Patient Characteristics**

Recent male post MI patients > 70

**Intervention**

Three dietary regimes were compared: fat advice (to eat less fat), fibre advice (to eat more cereal fibre) and fish advice (to eat at least two portions of oily fish a week)

**Comparisons**

Dietary advice

**Study Length**

2 years

**Outcomes**

Re-infarction, death

**Funding**

Not listed

**Effect**

The 2 year incidence of reinfarction plus death from ischaemic heart disease was not significantly affected by any of the dietary regimes.
Question: What is the effectiveness of low/moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?

Grading: 2+ \textit{Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a}

Reference number 224
de Vreede Swagemakers JJ; Gorgels AP; Weijenberg MP; Dubois-Arbouw WJ; Golombeck B; van R; Knottnerus A; Wellens HJ; Risk indicators for out-of-hospital cardiac arrest in patients with coronary artery disease

1999 52 Journal of Clinical Epidemiology pgs 601 607

Study Type: Case-Control
Patient Characteristics
Intervention
Comparisons Alcohol (glasses per week) 0 1-6 7-21 >21
Study Length Retrospective
Outcomes SCA
Funding Wijnand M. Pon Foundation Leusden Research Cardiol Foundation Maasrict NL
Effect Multiple logistic regression analysis, with SCA as the dependent variable, and two sets of independent variables found that alcohol consumption of 1-21 glasses per week (1-26 units/week) was negatively associated with SCA. Thus, alcohol consumption (1-21 glasses per week) (1-26 units/week) seems to protect patients with CAD from SCA (OR 0.05, 95% CI 0.2-

Reference number 642
Muntwyler J; Hennekens CH; Buring JE; Gaziano JM; Mortality and light to moderate alcohol consumption after myocardial infarction

1998 352 Lancet pgs 1882 1885

Study Type: Cohort
Patient Characteristics
Intervention
Comparisons Number of alcoholic drinks Rarely/ never (n= 1125) 1-4/month (n= 1227) 2-6/week (n= 1390) 1/day (n= 1424) > 2/day (n= 192)
Study Length 5 years
Outcomes Total mortality Cardiovascular death
Funding NHLBI USA Theodor und Ida Herzog-Egli Foundn Switzerland
Effect After multivariate adjustment, the total mortality risk in men who drank two to six drinks per week (4-13 units/wk) was significantly lower by 28% (95% CI 11-42) compared with men who never or rarely drank. Patients who reported drinking one alcoholic drink per day (17 units/wk) had a significantly decreased risk (21%, 95% CI 4-36). For death due to cardiovascular diseases, the risk reduced up to an alcohol intake of two to six drinks per week.
Study Type: Cohort
Patient: 455 post MI patients and 200 angina patients

Characteristics: Alcohol consumption lifelong teetotallers (n= 43), ex-drinkers (n= 59), occasional drinkers (< 1 drink per month, n= 199) light drinkers (1-15 units per week, n= 230) moderate drinkers (16-42 units per week, n= 104), heavy drinkers (> 42 units per week, n= 20). Men in the heavy drinking group were combined with the moderate drinking group because of the small numbers.

Study Length: Mean follow-up 12.8 years
Outcomes: All cause mortality  CVD mortality  Non CVD mortality
Funding: Not listed

Effect: There was little difference in risk of CHD, cardiovascular, non-cardiovascular, and all cause mortality between lifelong teetotallers, occasional drinkers (1-2 units/month), and light drinkers (1-15 units/wk). In the patients with previous MI, there was no difference in outcome between lifelong teetotallers, occasional drinkers, and light drinkers. Ex-drinkers showed a significant increase in cardiovascular mortality (marginal) and all cause mortality compared with lifelong teetotallers.

Grading: 2- Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk

Reference number 46
Aguilar D;Skali H;Moye LA;Lewis EF;Gaziano JM;Rutherford JD;Hartley LH;Randall OS;Geltman EM;Lamas GA;Rouleau JL;Pfeffer MA;Solomon SD;
Alcohol consumption and prognosis in patients with left ventricular systolic dysfunction after a myocardial infarction. Journal of the American College of Cardiology 2002 43 2015 2021

Study Type: Cohort
Patient: Left ventricular dysfunction after MI, with a LV ejection fraction of 40% or less, 21-80 years of age
Characteristics: 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).

Study Length: 2 years
Outcomes: Development of symptomatic heart failure (HF), need for hospitalization for HF, endpoints that only occurred 90 days after enrolment
Funding: Not listed

Effect: Compared with non drinkers, the unadjusted HR for the development of HF was lower in the light-to-moderate drinkers (2-22 units/wk) (HR 0.70, 95% CI 0.53-0.91). After adjustment for baseline characteristics, the difference was no longer statistically different (HR 0.93, 95% CI 0.80-1.08).

Reference number 2944
De Lorgeril, M.; Salen, P.; martin, J.L.; Boucher, F.; Paillard, F.; De Leiris, J.

Study Type: Cohort
Patient: Participants of Lyon Diet Heart Study post MI, <70 years of age, male
Characteristics: Quartiles of ethanol consumption  Zero percent of energy intake per day derived from ethanol (non-drinkers) was quartile 1 (44 patients), <5.4% of total energy intake per day was quartile 2 (37 patients), >5.41% but <9.84% of total energy intake per day was quartile 3 (44 patients), and >9.84% of energy was quartile 4 (38 patients).

Study Length: 4 years
Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 75 of 248
Clinical complications

Not listed

There were 36, 34, 18 and 16 complications in the quartiles 1, 2, 3, and 4, respectively.

Multivariate risk ratios of CVD complications according to wine ethanol intake:
- Quartile 1: 0, 0 units/wk
- Quartile 2: 0.74 (CI 95% 0.40-1.38) 8 units/wk
- Quartile 3: 0.41 (0.20-0.83) 19 units/wk
- Quartile 4: 0.48 (0.24-0.96) 53 units/wk.
**Question:** What is the effectiveness of regular physical activity versus a sedentary lifestyle to improve outcome in patients after MI?

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

**Reference number:** 367

Naughton J; Dorn J; Imamura D;  
Outcomes measurement in cardiac rehabilitation: the National Exercise and Heart Disease Project

2000  4  Journal of Rehabilitation Outcomes Measurement  pgs 64  75

**Study Type:** Randomised Controlled Trial

**Patient Characteristics:**  
Male (age range 35-64 years) post MI (≥ 8 weeks but < 2 years). Ability to exercise minimum of 3 METS and resting diastolic BP < 100 mm Hg. Exclusions: uncontrolled diabetes, coexisting CVD, terminal disease, heart block, emotional or physical impairment  
Mean age Exercise group: 51.5±7.4 years  
Control group: 52.1±7.4 years

**Intervention:**  
Exercise: 8 weeks brisk activity (1 hour per day, 3 times per week) then 34 months of exercise for 40 minutes 3 times per week

**Comparison:** Primary outcome: mortality

**Study Length:** 3, 5, 10, 15, 19 years.

**Outcomes:**  
Mortality

**Funding:** NIHR NHLBI

**Effect:**  
At 3 years follow up, the exercise group's cumulative mortality = 15 (4.6%) compared with controls = 24 (7.3%). Observed effectiveness = 37% (95% CI -15, 68; p = 0.22). Cardiovascular deaths in exercise group = 14 (4.3%) compared with 20 (6.1%) in control group. Observed effectiveness = 29% (95% CI -33, 66; p < 0.40). MI deaths in exercise group = 1 (0.3%) compared with 8 (2.4%) in control group. Observed effectiveness = 87% (95% CI 22, 98; p < 0.047).  
Long term follow up: all cause mortality relative risk (95% CI) at 3, 5, 10, 15 and 19 years were 0.69 (0.39, 1.25), 0.84 (0.55, 1.28), 0.95 (0.71, 1.29), 1.02 (0.79, 1.32) and 1.09

**Reference number:** 801

Shaw LW;  
Effects of a prescribed supervised exercise program on mortality and cardiovascular morbidity in patients after myocardial infarction. The National Exercise and Heart Disease Project

1981  48  American Journal of Cardiology  pgs 39  46

**Study Type:** Randomised Controlled Trial

**Patient Characteristics:**  
Patients from 5 centres were recruited for this study. Patients had documented AMI within 1-3yrs of admission to the study. Subjects were all men.  
Mean age (yrs ± SEM):  Int gp: 51.5 ± 0.4  
Cont gp: 52.0 ± 0.4

**Intervention:**  
During the first 8wks, the participants attended to exercise laboratory 1hr/day, 3days/week. They exercised for a total of 24min, by exercising for 4min on each of the 6 stationary devices & resting for 2min after use of each device. The workload on each device was set to yield the target heart rate early in each 4min exercise period. Thereafter the exercise program was conducted in a gym without ECG monitoring. It consisted of supervised physical activities designed to yield the prescribed target heart rate. The activities included 15min of continuous jogging, cycling or swimming followed by 25min of games.

**Comparison:** Not reported

**Study Length:** 3 yrs

**Outcomes:**  
Mortality, Nonfatal infarction, Suspected infarctions, Other events All, recurrent MI,

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices  Page 77 of 248
Grant from the Rehab. Services Admin of the Dept of Health, Education & Welfare. US.

All deaths  Intervention group: 15/323 (4.6%)  Control group: 24/328 (7.3%)  P=NS  Subtotal of all Cardiovascular deaths (including AMI & other definite)  Intervention group: 6/323 (1.9%)  Control group: 14/328 (4.3%)  P=0.13  Of which AMI deaths  Intervention group: 1/323 (0.3%)  Control group: 8/328 (2.4%)  P=0.05  Other definite (6 from arrhythmias, 2 from congestive cardiac failure, 1 from cardiacogenic shock & 2 from cerebrovascular accidents)  Intervention group: 5/323  Control group: 6/328  Sudden death  Intervention group: 8/323  Control group: 6/328  Indeterminate cause  Intervention group: 1/323  Control group: 4/328  

Difference in mortality between smokers/non-smokers: Smokers: 9.4%  Non-smokers: 2.1%  P=NS  Nonfatal infarction: Intervention group: 15/323  Control group: 11/328  Suspected infarctions:  Intervention group: 3/323  Control group: 2/328  Other events:  Intervention group: 25/323  Control group: 25/328  All recurrent MI:  Intervention group: 17/323 (5.3%)  Control group: 23/328 (7.0%)  P=0.4  Total hospitalisations for reasons other than MI:  Intervention group: 92/323 (28.5%)  Control group: 90/328 (27.4%)  P=0.04.

Grading:  

Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a

Reference number 469

Blumenthal JA;Babyak MA;Carney RM;Huber M;Saab PG;Burg MM;Sheps D;Powell L;Taylor CB;Kaufmann PG; Exercise, depression, and mortality after myocardial infarction in the ENRICHD trial 2004 36 Medicine & Science in Sports & Exercise  pgs 746  755

Study Type: Cohort
Patient recent MI patients with perceived lack of social support and/or symptoms depression  Age  No
Characteristics exercise group: 61.1±12.7 years  Exercise group: 59.5±11.8 years
Intervention Self reported exercise
Comparisons Self reported exercising group and non-exercising group
Study Length 6 month after enrolment and each year up to 4 years
Outcomes Mortality, probability of survival
Funding NHLBI
Effect At 6 months, 982 (47.2%) patients reported that they had exercised regularly since their acute MI  During up to 4 years follow-up, 187 patients had died, 5.7 % of exercisers compared with 12.0% of non-exercisers  After statistical adjustment for medical and demographics, regular exercise was found to be significantly associated with increased probability of survival (hazard ratio = 0.62, 95% CI = 0.44-0.86, P < 0.004). After adjustment for modification of diet, counselling sessions, smoking and participation in cardiac rehabilitation, regular exercise remained statistically associated with survival (hazard ratio = 0.69, 95% CI = 0.49-0.98, P = 0.037). The rate of non-fatal MI amongst the exercisers was 6.5% compared with 10.5% for non-exercisers. Exercise was significantly associated with reduced likelihood of non-fatal MI (hazard ratio = 0.72, 95% CI = 0.52-0.99, P = 0.044).

Grading:  

Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk

Reference number 2908

Wilhelmsen L;Sanne H;Elmfeldt D;Grimby G;Tibblin G;Wedel H; A controlled trial of physical training after myocardial infarction. Effects on risk factors, nonfatal reinfarction, and death 1975 4 Preventive Medicine  pgs 491  508

Study Type: Cohort
Myocardial infarction: full guideline DRAFT (August 2006) – Appendices  Page 78 of 248
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Post MI patients</th>
<th>Age: not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>3 months after MI, patients in the treatment group were advised about the benefit of regular exercise and were encouraged to attend an exercise programme. (3 half hour supervised training sessions per week)</td>
<td></td>
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<tr>
<td>Comparisons</td>
<td>Exercise program versus no exercise</td>
<td></td>
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<tr>
<td>Study Length</td>
<td>1 year, 4 year follow up</td>
<td></td>
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<tr>
<td>Outcomes</td>
<td>All-cause mortality, cardio-vascular deaths</td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>Not listed</td>
<td></td>
</tr>
<tr>
<td>Effect</td>
<td>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. However, at four year follow up, there were no significant differences found in all-cause mortality or cardiovascular deaths.</td>
<td></td>
</tr>
</tbody>
</table>
Question: What is the level of physical activity which increases physical work capacity versus physical activity which does not increase physical work capacity?

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

Dorn J, Naughton J, Imamura D, Trevisan M; Results of a multicenter randomized clinical trial of exercise and long-term survival in myocardial infarction patients: the National Exercise and Heart Disease Project (NEHDP)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>As above</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Age (yrs ± SD): 51.5 ± 7.4</td>
</tr>
<tr>
<td>Intervention</td>
<td>Work capacity (metabolic equivalents (METs) ±SD): Intervention group: 7.8 ± 2.1 Control group: 7.8 ± 2.2 Men with documented MI after 8 weeks but before 3 years I before enrollment. Subjects with the ability to exercise at an intensity level of 3 METs and a suprime resting diastolic blood pressure of 100mm Hg. Excluded: Patients with other significant</td>
</tr>
<tr>
<td>Comparisons</td>
<td>As above</td>
</tr>
<tr>
<td>Study Length</td>
<td>3, 5, 10, 15, 19 years.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mortality</td>
</tr>
<tr>
<td>Funding</td>
<td>NHLBI</td>
</tr>
<tr>
<td>Effect</td>
<td>Secondary analysis of the NEHDP. Long term follow up: age adjusted all-cause mortality (95% CI) at 3, 5, 10, 15 and 19 years were 0.86 (0.76-0.98), 0.91 (0.82-1.00), 0.88 (0.83-0.95), 0.89 (0.84-0.95) and 0.92 (0.87-0.97), respectively. Long term follow up: age adjusted CVD mortality (95% CI) at 3, 5, 10, 15 and 19 years were 0.87 (0.74-1.02), 0.91 (0.81-1.03), 0.89 (0.82-0.96), 0.89 (0.82-0.96) and 0.93 (0.87-0.99), respectively.</td>
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</table>

Reference number 596
CI) at 3, 5, 10, 15 and 19 years were 0.86 (0.76-0.98), 0.91 (0.82-1.00), 0.88 (0.83-0.95), 0.89 
(0.84-0.95) and 0.92 (0.87-0.97), respectively. Long term follow up: age adjusted CVD 
mortality (95% CI) at 3, 5, 10, 15 and 19 years were 0.87 (0.74-1.02), 0.91 (0.81-1.03), 0.89 
(0.82-0.96), 0.89 (0.82-0.96) and 0.93 (0.87-0.99), respectively

Funding
Supported by a National Heart, Lung & Blood Institute First Independent Research Support in 
Transition award.

Effect

Reference number 2948
Holmback AM; Sawe U; Fagher B;
Training after myocardial infarction: lack of long-term effects on physical capacity and psychological variables
1994 75 Arch Phys Med Rehabil pgs 551 554

Study Type: Randomised Controlled Trial
Patient All acute MI patients under 65 years and attending the Hospital Post-MI Clinic. Median age: 55 years. Total age range (years)-
Characteristics
Intervention Program was designed and supervised by a physiotherapist. It started weeks post MI and patients trained over a 12 week period for at least 45 min (effective time) twice a week with interval training involving large muscle groups.

Comparison Received regular medical care with no special emphasis on exercise.

Study Length 1 year post MI
Outcomes Maximal Physical Capacity (MPC) (after 1 year testing):
Mean exercise capacity:
Return to work:

Funding Malmohus county council. No commercial party had a direct financial interest in the results of the research.

Effect MPC in intervention group: increased non significantly, average of 10% or 12 W (95% CI: 2 to 22W) over baseline.
MPC in control group: increased nonsignificant, average of 2% or 1W (CI: -8 to 10W) over baseline. Intergroup difference: not significant.
Mean exercise capacity: intervention group: 172W (SD 33) control group 144W (SD 29). Return to work: After 1year follow up median time of work return: not significant, intervention group: 16 weeks (interquartile range 12 to 30 weeks), control group 12weeks (interquartile range 9 to 23 weeks).

Reference number 1350
Marchionni N; Fattirolli F; Fumagalli S; Oldridge N; Del Lungo F; Morosi L; Burgisser C; Masotti G;
Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial
2003 107 Circulation pgs 2201 2206
Study Type: Randomised Controlled Trial
Patient Patients older than 45yrs referred to CR unit by 4 of the 6 intensive care units in the Florence area for functional evaluation 4 to 6wks after MI over a 48mth period. Baseline characteristics were different between the 3 age groups therefore these groups are examined separately in this trial. Age (yrs): 45-65 groups: 57 ± 0.6 66-75 groups: 70 ± 0.3 >75 groups: 80 ± 0.3 Males (%): 45-65 groups: 85.6 66-75 groups: 66.7 >75 groups: 60 3 age groups predefined as middle age (45-65yrs), old (66 to 75 yrs) and very old (>75yrs). Excluded: Patients with severe cognitive impairment or physical disability, left ventricular ejection fraction <35%, contraindications to vigorous physical exercise, eligibility for myocardial revascularisation because of low-effort myocardial ischemia, refusal or living too far from the CR unit.

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 81 of 248
The American College of Sports Medicine guidelines were used for exercise prescription. Hosp CR programme consisted of 40 exercise sessions: 24 sessions (3/wk) of endurance training on a cycle ergometer (5min warm-up, 20min training at constant workload, 5min cool down & 5min post-exercise monitoring) plus 16 (2/wk) 1hr sessions of stretching & flexibility exercises. Exercise intensity was set at 70% to 85% of heart rate attained during baseline symptom-limited exercise test. Patients received cardiovascular risk factor management counselling twice per week & were invited to join a monthly support group with family members. Home CR patients participated in 4 to 8 supervised instruction sessions in the CR unit, where they were taught necessary precautions & how to perform their training at home. Patients received cardiovascular risk factor management counselling at each in hospital session & were invited to join a monthly family oriented support group. After the instruction phase, patients received an exercise prescription similar to that of the Hosp CR group, a wrist-watch digital pulse monitor, a cycle ergometer & a log book to record the heart rate attained during each exercise session & reasons for not finishing or missing a session. A physical therapist made home visits every week to adjust if necessary the exercise prescription, to enhance adherence with intervention & to record the number of completed sessions & distance cycled.

Comparisons
No CR patients attended a single structured education session on cardiovascular risk factor management with no exercise prescription & were referred back to their family physicians.

Study Length
14 months

Outcomes
Total Work Capacity (TWC), Sickness Impact Profile (SIP) & Health Related Quality of Life (HRQL).

Funding
National Research Council (CNR), the University of Florence & the Regional Government of Tuscany, Italy.

Effect
Baseline TWC was lower in older patients in each study arm but similar within each age group by treatment assignment. Baseline SIP scores were similar across age groups, but in middle-aged and very old patients they were higher (i.e., worse) in the Hosp CR than in the other study arms. TWC improved in Hosp CR & Home CR groups but not in controls with no sig. difference between Hosp CR & Home CR. Significant treatment time interactions confirmed a greater effect of both active interventions compared with control middle aged & old patients but not in very old patients, which suggests a lower enhancement in TWC at older age. No sig. age treatment interaction was found for changes in TWC, which suggests that the 2 active interventions were equally less effective in older patients. Despite this, at 2mths, TWC had improved sig. in very old patients with both interventions. Complications were similar across treatment & age groups. In middle aged & old patients, HRQL improved sig. over the entire study duration regardless of treatment assignment, whereas in very old patients, HRQL improved significantly with active treatment but not with no CR.

Reference number 664
Oberman A; Fletcher GF; Lee J; Nanda N; Fletcher BJ; Jensen B; Caldwell ES; Efficacy of high-intensity exercise training on left ventricular ejection fraction in men with coronary artery disease (the Training Level Comparison Study)
1995 76  American Journal of Cardiology

Study Type: Randomised Controlled Trial
Patient Characteristics
Subjects were men aged between 30 to 64 yrs. Enrolled at 1 of 5 centers in the US during 1976. Age (yrs ± SD): Int gp: 51.5 ± 7.4  Cont gp: 52.1 ± 7.2  Work capacity (metabolic equivalents (METs) ± SD): Int gp: 7.8 ± 2.1  Cont gp: 7.8 ± 2.2  Men with documented MI ³8wks but <3yrs before being enrolled. Subjects with the ability to exercise at an intensity level ³3 METs & a surprin resting diastolic blood pressure <100mm Hg. Excluded: Patients with other sig coexisting CVD or other disease likely to be fatal in the near future.

Intervention
An exercise prescription was developed on the basis of each patient’s MSET (multistage graded exercise test) results. An exercise target heart rate guided the prescription & was determined as Myocardial infarction: full guideline DRAFT (August 2006) – Appendices  Page 82 of 248
85% of the peak heart rate achieved on the test. This gp performed brisk physical activity in the laboratory for 8wks, exercising 1hr per day, 3 days per week. Patients were supervised & underwent continuous ECG monitoring. Each individual exercised for 4min on each of 6 stationary machines with a 2min rest interval between machines. Attainment of the target heart rate was the goal for every 4min exercise period. Exercise was stopped if patients experienced any adverse signs or symptoms or ECG abnormalities. After 8wks, subjects exercised in a gym or swimming pool without ECG monitoring, although exercise heart rates were periodically checked. Activities consisted of 15min of continuous jogging, cycling or swimming, followed by 25min of recreational games. The activities were performed at an intensity level enabling each participant to reach his individual prescribed target heart rate. The men were encouraged to attend 3 sessions per week but in some situations were allowed to exercise on their own. There was no formal education/targeting provided regarding other lifestyle habits.

Patients were encouraged to maintain normal routines but not to participate in any regular exercise program.

### Study Length

The original clinical trial was terminated on 1st Dec 1995, with morbidity & mortality follow-up completed on 31st May 1979.

### Outcomes

As of 31st Dec 1995. No of patients deceased: Risk of all-cause mortality in int gp compared with cont gp at average 3, 5, 10, 15 & 19 yrs follow up periods: Risk of CVD mortality in int gp compared with cont gp at average 3, 5, 10, 15 & 19 yrs follow up periods: RR of all-cause mortality according to PWC change at various follow up period: The NEHDP -

### Funding

Supported by a National Heart, Lung & Blood Institute First Independent Research Support in Transition award.

### Effect

As of 31st Dec 1995. No of patients deceased: Int gp: 162/315 (51.4%) Cont gp: 150/319 (47%) Deaths due to CVD: Int gp: 64.2% Cont gp: 72.7% Of which are stroke deaths: Int gp: 2 Cont gp: 7 RR: 0.32 CI: 0.07-1.66 P=0.16 Cause of death unknown: n=29 Risk of all-cause mortality in int gp compared with cont gp: 3 Years – RR: 0.69 CI: 0.39-1.25 5 Years – RR: 0.84 CI: 0.55-1.28 10 Years – RR: 0.95 CI: 0.71-1.29 15 Years – RR: 1.02 CI: 0.79-1.32 19 Years – RR: 1.09 CI: 0.87-1.36 Risk of CVD mortality in int gp compared with cont gp: 3 Years – RR: 0.73 CI: 0.37-1.43 5 Years – RR: 0.98 CI: 0.60-1.61 10 Years – RR: 1.21 CI: 0.79-1.60 15 Years – RR: 1.14 CI: 0.84-1.54 19 Years – RR: 1.16 CI: 0.88-1.52 Younger men, cigarette smokers & those with a low initial PWC (<7METs) generally derived more benefits from the exercise program than men who were older, non-smokers or had a high PWC. Only stat sig difference in effectiveness of the program were between smokers & nonsmokers at the 10yr follow up period. Non Smokers- Int gp: 64/220 (29.7%) Cont gp: 57/238 (24%) Diff: 17.5% P<0.01 Secondary analysis found that each single-stage (1 MET) increase in PWC of the MSET was associated with a reduction in all-cause mortality risk in the range of 8% to 14% depending on the time period examined. The age-adjusted RRs were sig at every follow up period except 5yr. CVD mortality risks were similar to those observed for all-cause mortality. Patients were evaluated at 2 & 5mths after randomisation and semi-annually thereafter. This study focuses on long-term mortality follow up of patients in the original trial, National Exercise & Heart Disease Project (NEHDP). After 19yrs of follow up 7cont & 2 exercise gp subjects died of stoke, resulting in RR in favour of the exercise program subjects. Initially, enrolment in the int gp appeared to offer survival benefits compared with cont gp assignment although none of the RR were stat. sig. At 3yrs of follow up, exercisers were at an ~30% lower risk of death than men in the cont gp. Death due to CVD, there was a benefit in favour of the int gp was detected only in the earliest yrs of the study. A nonsig elevated risk for CVD death associated with int go assignment became evident at yr 10 & levelled off thereafter.
Shaw LW; Effects of a prescribed supervised exercise program on mortality and cardiovascular morbidity in patients after myocardial infarction. The National Exercise and Heart Disease Project

1981 48 American Journal of Cardiology pgs 39 46

Study Type: Randomised Controlled Trial

Patient Characteristics

Patients from 5 centres were recruited for this study. Patients had documented AMI within 1-3 years of admission to the study. Subjects were all men.

Intervention

Mean age (yrs 1± SEM):
- Intervention group: 51.51±0.4
- Control group: 52.01±0.4

During the first 8 weeks, the participants attended to exercise laboratory 1hr/day, 3days/week. They exercised for a total of 24min, by exercising for 4min on each of the 6 stationary devices & resting for 2min after use of each device.

Comparisons

Not reported

Study Length 3 yrs

Outcomes

Primary outcome: mortality:
- Nonfatal infarction:
- Suspected infarctions:

Other events:
- All recurrent MI:
- Total hospitalisations for reasons other than MI:

Meaningful differences in mortality and morbidity were not noted:

- All deaths: Intervention group: 15/323 (4.6%) Control group: 24/328 (7.3%) P = not significant.
- Subtotal of all Cardiovascular deaths (including AMI & other definite) Intervention group: 6/323 (1.9%) Control group: 14/328 (4.3%) P = 0.13  of which AMI deaths Intervention group: 1/323 (0.3%) Control group: 8/328 (2.4%) P = 0.05. Other definite 6 from arrhythmias, 2 from congestive cardiac failure, 1 from cardiogenic shock and 2 from cerebrovascular accidents)
- Intervention group: 5/323 Control group: 6/328 Sudden death Intervention group: 8/323 Control group: 6/328

Total hospitalisations for reasons other than MI: Intervention group: 92/323 (28.5%) Control

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

Reference number 2910

Dubach P;Myers J;Dziekan G;Goebbel U;Reinhart W;Vogt P;Ratti R;Muller P;Miettunen R;Buser P; Effect of exercise training on myocardial remodeling in patients with reduced left ventricular function after myocardial infarction: application of magnetic resonance imaging

1997 95 Circulation pgs 2060 2067

Study Type: Randomised Controlled Trial

Patient Characteristics

Rehabilitation center for 2 months, training program consisting of two 1 hour sessions of walking daily, along with 4 monitored 45 minute sessions of stationary cycling weekly

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 84 of 248
Exercise training vs usual care

**Comparisons**  
Exercise training vs usual care

**Study Length**  
2 months

**Outcomes**  
Maximal exercise oxygen uptake Ejection fraction Diastolic, systolic volume Myocardial wall thickness

**Funding**  
Schweizerische Herz-Stiftung Switzerland Roche Research Foundation

**Effect**  
Oxygen uptake increased 26% at maximal exercise (19.7±3 to 23.9±5, P < 0.05) and 39% at the lactate threshold (P < 0.01) in the exercise group, whereas control values did not change. No differences were observed within or between groups in MRI measures of end-diastolic (187±47 pre versus 196±35 mL post in the exercise group and 179±52 pre versus 180±51 mL post in the control group), end-systolic volume (118±41 pre versus 121±33 mL post in the exercise group and 119±54 pre versus 116±56 mL post in the control group), ejection fraction (38.0±9 pre versus 38.2±10% post in the exercise group and 37.0±10 pre versus 38.3±13% post in the control group). Myocardial wall thickness measurements at end diastole and end systole and their difference in 80 myocardial segments determined by MRI yielded no significant interactions.
**Question:** What is the effectiveness of comprehensive cardiac rehabilitation versus standard care with no cardiac rehabilitation to improve outcome in patients after MI?

**Grading:** 1++  *High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias*

<table>
<thead>
<tr>
<th>Reference number</th>
<th>710</th>
</tr>
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<tbody>
<tr>
<td><strong>Beswick AD; Rees K; Griebsch I; Taylor FC; Burke M; West RR; Victory J; Brown J; Taylor RS; Ebrahim S;</strong></td>
<td></td>
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<tr>
<td>Provision, uptake and cost of cardiac rehabilitation programmes: Improving services to under-represented groups</td>
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<tr>
<th>Study Type</th>
<th>Systematic Review</th>
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<tr>
<td>Patient</td>
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<tr>
<td>Characteristics</td>
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<tr>
<td>Intervention</td>
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<tr>
<td>Comparisons</td>
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<td>Study Length</td>
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<td>Outcomes</td>
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<td>Funding</td>
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<td>Effect</td>
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</table>

2004 8  *Health Technology Assessment (Winchester, England)*  pgs  82

All studies reported that there was benefit of intervention to improve uptake (healthcare led-professional interventions at the patient level, trained lay volunteers, coordination of referral post-discharge care at the service level, written or aural motivational communications) This may be indicative of publication bias. For adherence, the authors of the HTA stated that they found few studies of sufficient quality to make specific recommendations of methods to improve adherence to cardiac rehabilitation. Their opinion was that the most promising approach was the use of self management techniques based around individualised assessment, problem solving, goal setting and follow-up.

<table>
<thead>
<tr>
<th>Reference number</th>
<th>1358</th>
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</thead>
<tbody>
<tr>
<td><strong>Brown A; Taylor R; Noorani H; Stone J; Skidmore B;</strong></td>
<td></td>
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<tr>
<td>Exercise-based cardiac rehabilitation programs for coronary artery disease: a systematic clinical and economic review</td>
<td></td>
</tr>
</tbody>
</table>

2003 34  *Ottawa*  pgs

Cardiac rehabilitation programs that include exercise, both exercise-only (EX CR) and comprehensive care programs (CCR), have beneficial effects on cardiac mortality (RR: 0.73, 95% CI 0.56-0.96 and 0.80, 95% CI 0.65-0.99, respectively). However, with respect to total mortality, exercise-only programs show a statistically significant reduction, whereas the comprehensive care programs showed a trend in that direction (RR: 0.76, 95% CI 0.59-0.98 and 0.87, 95% CI 0.74-1.04, respectively). There was no effect with either intervention on non-fatal MI, CABG, or PTCA. For HRQoL, few studies showed intervention improved HRQoL compared
For the exercise only intervention, the pooled effect estimate for total mortality showed a 27% reduction in all cause mortality (random effects model OR 0.73 (0.54-0.98)). Similarly, comprehensive cardiac rehabilitation reduced all cause mortality compared to usual care, but to a lesser, and non-significant, degree (13% OR 0.87 (0.71-1.05)). Total cardiac mortality was reduced by 31% (random effects model OR 0.69 (0.51-0.94)) and 26% (random effects model OR 0.74 (0.57-0.96)) in the exercise only and comprehensive cardiac rehabilitation intervention groups respectively when compared to usual care. There was no significant effect of either intervention on sudden cardiac deaths, non-fatal reinfarctions, or revascularization. Overall for HRQoL, in the RCTs with an exercise only intervention, there were small changes or no change in HRQoL measures. In the RCTs examining comprehensive cardiac rehabilitation intervention, most showed small and variable effects in HRQoL measures.

Grading: 1+  
Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
Reference number: 2948

Holmback AM; Sawe U; Fagher B; 
Training after myocardial infarction: lack of long-term effects on physical capacity and psychological variables
1994 75 Arch Phys Med Rehabil pgs 551-554

Study Type: Randomised Controlled Trial
Patient Characteristic: All acute MI patients under 65 years and attending the Hospital Post-MI Clinic. Median age: 55yrs Total age range (yrs) - Int gp: 38-65 Cont gp: 43-63 Gender: nearly all males
Intervention: Program was designed and supervised by a physiotherapist. It started 8 weeks post MI and patients trained over a 12 week period for at least 45 minutes (effective time) twice a week with interval training involving large muscle groups: bicycling (10 minutes), calisthenics (10 minutes) and jogging (15min) ending with relaxation (10min). During the initial sessions heart rate amounted to 70% to 85% of peak heart rate at the bicycle test; the workload was then individually adjusted to obtain the desired max. heart rate if possible. On completion of the course, patients were encouraged to maintain their fitness by continuing on their own with
Comparisons: Received regular medical care with no special emphasis on exercise.
Study Length: 1 year post MI
Outcomes: Maximal Physical Capacity (MPC) (after 1 year testing): Mean exercise capacity:
Return to work: The research was supported by Malmohus county council. No commercial party had a direct financial interest in the results of the research.
Effect: MPC in intervention gp: increased non significant. By an average of 10% or 12W (95% CI: 2 to 22W) over baseline. MPC in control group: increased non significant. By an average of 2% or 1W (CI: -8 to 10W) over baseline. Intervention group difference: not significant. Mean exercise capacity: Intervention group: 172W (SD 33) Control group: 144W (SD 29). Return to work: After 1 year follow up median time of work return: not significant Intervention group: 16
weeks (interquartile range 12 to 30 weeks) Control group: 12 weeks (interquartile range 9 to 23 weeks). Number of patients that resumed at least part-time work: Intervention group: 23/30 (77%) Control group: 27/32 (84%) There was a weak tendency of earlier return to work in those subjects who were least fit.

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

Reference number 2950

Stahle A; Lindquist I; Mattsson E; Important factors for physical activity among elderly patients one year after an acute myocardial infarction


Study Type: Randomised Controlled Trial
Patient post MI patients ≥ 65 years
Characteristics
Intervention Supervised outpatient training program (50 min, 3x per week for 3 months)
Comparisons Exercise training versus usual care
Study Length 12 months
Outcomes Self-motivation Outcome expectation Efficacy expectation Physical activity
Funding Nat. Asn. Heart & Lung Foundn Swedish Heart & Lung Foundn Swedish Foundn Health Care Sciences Allergy Re-search King Gustaf V & Queen Victoria Foundn Swedish Nat. Center for Research in Sports
Effect No significant difference for: Self-motivation Outcome expectation Efficacy expectation 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, SMI, activity level before admission, and group (intervention and controls) found that group and activity before admission were the only variables that predicted high activity at 12 months (RR = 0.74, P < 0.001).

Grading: 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias and a

Reference number 1020

Dugmore LD; Tipson RJ; Phillips MH; Flint EJ; Stentiford NH; Bone MF; Ittler WA; Changes in cardiorespiratory fitness, psychological wellbeing, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme

1999 81 Heart (British Cardiac Society) pgs 359 366

Study Type: Cohort
Patient Post MI patients 36 good prognosis patients & their matched controls (ages 51.6±1.28 & 52.9±1.35 years, respectively) 26 poor prognosis patients & their matched controls (ages 59.6±1.4 & 59.5±1.36 years, respectively)
Characteristics
Intervention Exercise program: 3x per week for a 12 month period-aerobic & local muscular endurance training Each patient’s training program was individually designed based on results of regular
Comparisons Exercise program for 12 months & no exercise program
Study Length 12 month then follow up at 5 years
Outcomes Cardio-respiratory fitness, psycho-logical profiles, quality of life scores, mortality, full time employment return, non- fatal reinfarction
Funding Not listed
Effect At 12 months, treatment group had significant improvements compared with matched controls in cardio respiratory fitness (P < 0.01-0.001), psychological profiles (P < 0.05-0.001) & quality of life scores (P < 0.001) 5 years later by questionnaire and interview. 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. The exercising groups suffered significantly fewer non-fatal reinfarctions (8%) compared with controls (22%) (P < 0.05). Compared with controls, the exercisers visited their general practitioners less frequently (P < 0.01), returned to work earlier (P < 0.05), and reported less angina (P < 0.001).
Question: What is the effectiveness of an individualised cardiac rehabilitation programme versus a non-individualised cardiac programme to improve outcome in patients after MI?

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

Reference number 442

Mayou RA; Thompson DR; Clements A; Davies CH; Goodwin SJ; Normington K; Hicks N; Price J; Guideline-based early rehabilitation after myocardial infarction. A pragmatic randomised controlled trial

2002 52 Journal of Psychosomatic Research pgs 89 95

Study Type: Randomised Controlled Trial

Patient Characteristics

Intervention: Intervention based on national guidelines. Patients seen 2-4 times in hospital, given information sheets (return to ADL and secondary prevention) and a relaxation tape. Following discharge, patients were telephoned to review goals and to discuss any problems.

Comparisons: Usual care, advice from medical and nursing staff. Access to standard booklets and medical outpatient clinic.

Study Length: 12 months

Outcomes: HAD and Dartmouth COOP scales and questions about activities and belief.

Funding: British Heart Found.

Effect: Primary outcome At 3 months Significant improvement in the Dartmouth COOP score in intervention group (59% versus 33%; OR 0.34, 95% CI 0.16-0.73). Subsidiary outcomes At 1 month No significant differences between groups measured by HAD or COOP scores. Significantly less intervention patients had further treatment needs (25% versus 74%; OR 0.12, 95% CI 0.05-0.27). At 3 months Significant improvement in the HAD score in intervention group (median score 5 (2.75-8.25) versus 8 (5-12), P = 0.002). At 1 year No significant differences between groups measured by HAD or COOP scores. No significant further improvement seen in intervention group, while control group improved.

Grading: 4 Expert opinion, formal consensus

Reference number 45

Benzer W; Oldridge NB; Current concepts in cardiac rehabilitation medical considerations and outcomes evaluations

2001 4 Journal of Clinical & Basic Cardiology pgs 211 219

Study Type: Reviews and Reports

Funding: Not listed

Effect: Cardiac rehabilitation should not be considered to be exercise training, but rather as a program based on the individual’s requirements.

Reference number 2987

DeBusk RF; How to individualize rehabilitation after myocardial infarction

1977 32 Geriatrics pgs 77 79
Determining functional capacity is useful in formulating individual guidelines for physical activity within the hospital and during the early home phase of rehabilitation.
Question: Are there any patients after MI in whom the exercise component of cardiac rehabilitation is not safe?

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

Reference number 631

Giannuzzi P; Temporelli PL; Corra U; Gattone M; Giordano A; Tavazzi L;
Attenuation of unfavorable remodeling by exercise training in postinfarction patients with left ventricular dysfunction: results of the Exercise in Left Ventricular Dysfunction (ELVD) trial.

1997 Circulation pgs 1790 1797

Study Type: Randomised Controlled Trial
Patient Characteristics: <40% ejection fraction after a first Q-wave myocardial infarction

Intervention: 6 month exercise training program 30-minute bicycle ergometry at least 3x per week for 2 months, thereafter continuation of exercise program (30 minute bicycle ergometry 3x per week

Comparison: Exercise training vs usual care

Study Length: 6 months

Outcomes: Work capacity  Left ventricular volumes  Ejection fraction

Funding: Minist-ero della Sanitá, Rome, Italy. S. Maug-eri Found-ation, Pavia, Italy

Effect: Significant increase in work capacity observed only in the training group (from 4.462±1.095 to 5.752±1.749 kilopond-meters [Kp-m], P < 0.01), not in the control group (from 4.375±1.143 to 4.388±1.199 Kp-m). Left ventricular volumes increased in the control group (end-diastolic volume, from 94±26 to 99±27 mL/m2, P < 0.01; end-systolic volume, from 62±20 to 67±23 mL/m2, P< 0.01) but not in the training group (end-diastolic volume, from 93±28 to 92±28 mL/m2, P = NS; end-systolic volume, from 61±22 to 57±23 mL/m2, P = NS). Ejection fraction 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 = NS).

Reference number 1350

Marchionni N; Fattirolli F; Fumagalli S; Oldridge N; Del LF; Morosi L; Burgisser C; Masotti G;
Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: results of a randomized, controlled trial

2003 Circulation pgs 2201 2206

Study Type: Randomised Controlled Trial
Patient Characteristics: post MI patients 3 age groups: middle aged (45-65 years) old (66-75 years) very old (> 75 years)

Intervention: hospital-based cardiac rehabilitation (Hos-CR) home-based cardiac rehabilitation (Home-CR) no cardiac rehabilitation (no CR)

Comparison: 3 interventions in each age group

Study Length: 14 months

Outcomes: Total work capacity (TWC) HRQoL


Effect: TWC improved in the Hosp-CR and Home-CR groups but not in the controls. Treatment-time interactions showed a greater effect of both interventions compared with controls in middle aged (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 Hosp-CR and Home-CR treatment (P = 0.013 and P < 0.035, respectively) but not with no CR (P = 0.079).
Contraindications to exercise training experienced a MI complicated by HF, 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 shuffle walking test. ST segment depression $\geq$ 1 mm on resting ECG. Undergone exercise testing with marked ST depression $\geq$ 2 mm or angina at < 5 METS (for example, 3 minutes of a Bruce protocol).

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Cohort</th>
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<tbody>
<tr>
<td>Patient Characteristics</td>
<td>74 patients with LVEF $\geq$ 45% (Group H) 35 patients with 35% $\leq$ LVEF $&lt;$ 45% (Group M) 17 patients with LVEF $&lt;$ 35% (Group L)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Exercise program consisting of walking, cycling on an ergometer and aerobic dance (50-90 min/session), 3-5 sessions per week for 3 months.</td>
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<tr>
<td>Comparisons</td>
<td>LVEF</td>
</tr>
<tr>
<td>Study Length</td>
<td>3 months</td>
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<tr>
<td>Outcomes</td>
<td>Exercise capacity  Peak work rate  Rest heart rate  LV end-diastolic dimension</td>
</tr>
<tr>
<td>Funding</td>
<td>Not listed</td>
</tr>
<tr>
<td>Effect</td>
<td>After 3 months of exercise training, exercise capacity significantly in all 3 groups. Peak Vo2 increased from 1355±321 to 1575±336 ml/min (P $&lt;$ 0.01) in Group H, from 1278±332 to 1464±406 ml/min (P $&lt;$ 0.01) in Group M, and from 1248±369 to 1454±424 ml/min in Group L (P $&lt;$ 0.01). Similarly, peak work rate increased from 122±35 to 144±34 W (P $&lt;$ 0.05) in group H, from 177±42 to 137±12 W in Group M (P $&lt;$ 0.05), and from 107±58 to 129±56 W (P $&lt;$ 0.01) in group L. Rest heart rate reduced from 75±13 to 72±11/ min (P $&lt;$ 0.05) in group H, from 76±13 to 72±12/min in Group M (P $&lt;$ 0.05), and from 80±15 to 75±10/min (NS) in group L. At 35±8 months follow-up there were no significant differences in the incidence of cardiac events among the 3 groups. There was also no significant change in LV end-diastolic dimension in each group.</td>
</tr>
</tbody>
</table>

**Question:** What approach to patient engagement best aids access to cardiac rehabilitation, particularly in reference to em, op, seg, women, those from rural communities, and those with mental and physical health co-morbidities?

**Grading:** 1+++  High-quality meta-analyses, systematic reviews of
**RCTs, or RCTs with a very low risk of bias**

**Reference number** 3058

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Beswick AD;Rees K;Griebsch I;Taylor FC;Burke M;West RR;</th>
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<tbody>
<tr>
<td>2004</td>
<td>Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups</td>
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<tr>
<td>Patient Characteristics</td>
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<tr>
<td>Intervention</td>
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<td>Comparisons</td>
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<td>Outcomes</td>
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</table>

**Effect**

All studies reported that there was benefit of intervention to improve uptake (healthcare led-professional interventions at the patient level, trained lay volunteers, coordination of referral post-discharge care at the service level, written or aural motivational communications) This may be indicative of publication bias. For adherence, the authors of the HTA stated that they found few studies of sufficient quality to make specific recommendations of methods to improve adherence to cardiac rehabilitation. Their opinion was that the most promising approach was the use of self management techniques based around individualised assessment, problem solving, goal setting and follow-up.

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

**Reference number** 3064

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Hughes AR;Gillies F;Kirk AF;Mutrie N;Hillis WS;MacIntyre PD;</th>
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<tbody>
<tr>
<td>2002</td>
<td>Exercise consultation improves short-term adherence to exercise during phase IV cardiac rehabilitation: a randomized, controlled trial</td>
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<th>Study Type:</th>
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<td>Patient Characteristics</td>
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<td>Intervention</td>
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<td>Comparisons</td>
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<td>Outcomes</td>
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<td>Funding</td>
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**Effect**

Using Mann-Whitney tests, leisure activity at baseline was similar between intervention and control groups (95% CI -325, 105.1). In the intervention group, leisure physical activity increased by 29.5% (123/417.5) analysed by Wilcoxon signed rank test.
Question: What education and/or information best aids patients after MI to (i) reduce their risk of subsequent cardiac problems (ii) return to a full and normal life (daily activities, driving, exercise, employment, leisure activities, sexual activities)

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number: 1289

Scottish Intercollegiate Guidelines Network (SIGN).

Cardiac rehabilitation

2002 57 SIGN pgs

Study Type: Guideline

Patient Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect

Recommends that comprehensive cardiac rehabilitation should be delivered by healthcare staff using established principles of adult education and behavioural change.

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

Reference number: 11

Lewin B; Robertson IH; Cay EL; Irving JB; Campbell M;

Effects of self-help post-myocardial-infarction rehabilitation on psychological adjustment and use of health services.

1992 339 Lancet pgs 1036 1040

Study Type: Randomised Controlled Trial

Patient Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect

Repeated measures 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). 'Distressed' post MI patients. Repeated measures analysis 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). The intervention group made fewer visits to their GP at 6 month (P < 0.0001) and at 12 months (P < 0.05).

Reference number: 442

Mayou RA; Thompson DR; Clements A; Davies CH; Goodwin SJ; Normington K; Hicks N; Price J; Guideline-based early rehabilitation after myocardial infarction. A pragmatic randomised controlled trial

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 95 of 248
<table>
<thead>
<tr>
<th>Study Type:</th>
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<td>Patient Post MI &lt; 70 years</td>
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<tr>
<td>Characteristics</td>
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<tr>
<td>Intervention</td>
<td>Intervention based on national guidelines. Patients seen 2-4 times in hospital, given information sheets (return to ADL and secondary prevention) and a relaxation tape. Following discharge, patients were telephoned to review goals and to discuss any problems.</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Usual care, advice from medical and nursing staff. Access to standard booklets and medical outpatient clinic.</td>
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<td>Study Length</td>
<td>12 months</td>
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<tr>
<td>Outcomes</td>
<td>HAD and Dartmouth COOP scales and questions about activities and belief.</td>
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<td>British Heart Found.</td>
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</table>

Primary outcome At 3 months Significant improvement in the Dartmouth COOP score in intervention group (59% versus 33%; OR 0.34, 95% CI 0.16-0.73). Subsidiary outcomes At 1 month No significant differences between groups measured by HAD or COOP scores. Significantly less intervention patients had further treatment needs (25% versus 74%; OR 0.12, 95% CI 0.05-0.27). At 3 months Significant improvement in the HAD score in intervention group (median score 5 (2.75-8.25) versus 8 (5-12), P = 0.002). At 1 year No significant differences between groups measured by HAD or COOP scores. No significant further improvement seen in intervention group, while control group improved.

**Reference number** 1289

Scottish Intercollegiate Guidelines Network (SIGN); Cardiac rehabilitation

<table>
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<tr>
<th>Study Type:</th>
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Contraindications to exercise training experienced a MI complicated by HF, 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 shuffle 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).

**Reference number** 2967

Van Horn E; Fleury J; Moore S; Family interventions during the trajectory of recovery from cardiac event: an integrative literature review

2002 31 Heart and Lung: Journal of Acute and Critical Care

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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 interventions included educationally oriented discussion, physical conditioning, or home visits or telephone calls made by registered nurses. Two studies (Dracup, Buls) found that family intervention decreased anxiety in the spouse. One study found that anxiety was also decreased in the patient (Buls). One study showed that wives' perception of the husbands' cardiac efficacy improved when the wives' observed the husbands' treadmill test and also utilised it themselves (Taylor). Two studies found no positive effect of family intervention on the Family APGAR scale (Gortner, Gillis). A study measuring the effect of family intervention with a social network and social support scale showed no effect of family intervention (Fridlund). A study training spouses on CPR found that perceived control on the Family Control Attitudes Scale increased significantly (Moser).
Question: What psychological and social (carers) support best aids people after MI to reduce their risk of subsequent cardiac problems and to promote their return to a full and normal life?

Grading: 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a

Reference number: 2999

O'Rourke A; Hampson SE; Psychosocial outcomes after an MI: an evaluation of two approaches to rehabilitation

1999 4 Psychology Health & Medicine pgs 393 402

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Consecutive first time post MI patients, age &lt; 76 years, speak / read English.</td>
</tr>
<tr>
<td>Characteristics</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>Hospital 1</td>
<td>Edinburgh Heart Manual  Self-help rehabilitation program incorporating education, exercise and stress management components with follow-ups at 1, 3 and 6 weeks post MI by a trained facilitator.</td>
</tr>
<tr>
<td>Hospital 2</td>
<td>Usual care</td>
</tr>
<tr>
<td>Study Length</td>
<td>6 months</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Significant Others Scale (SOS)  Recovery Locus of Control Scale (RLOC)  Generalised Self-Efficacy Scale (GSES)  Illness Perception Questionnaire (IPQ)  Hospital Anxiety and Depression Scale (HAD)  Health Service Utilization.</td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>Not listed</td>
</tr>
<tr>
<td>Effect</td>
<td></td>
</tr>
<tr>
<td>There was a significant interaction between group (hospital 1 versus hospital 2) and time (baseline versus 6 months) for perceptions of control over the illness (F(1,45) = 4.14, P &lt; 0.05, effect size 0.08) and depression (F(1,53) = 6.55, P &lt; 0.01, effect size 0.11). 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. No significant differences were found between groups for either hospital admissions or GP contact.</td>
<td></td>
</tr>
</tbody>
</table>
**Question:** What is the incidence of sexual dysfunction in patients after MI and how can patients be identified who would require referral to a specialist unit?

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

Reference number 3051

Conti, A.R. Pepine, C.J. Sweeney, M.

Efficacy and safety of sildenafil citrate in the treatment of erectile dysfunction in patients with ischemic heart disease.

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparisons</th>
<th>Study Length</th>
<th>Outcomes</th>
<th>Funding</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Systematic Review</td>
<td>Male IHD / ED</td>
<td>Sildenafil (5-200 mg)</td>
<td>Placebo</td>
<td>Up to 6 months</td>
<td>Sexual function, Adverse events</td>
<td>Not listed</td>
<td>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 &lt; 0.0001). On the 5 sexual function domains, scoring was significantly higher in the treatment group than the placebo group (P &lt; 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, 5.6-19.1; P &lt; 0.0001 for treatment effect).</td>
</tr>
</tbody>
</table>

Reference number 220

DeBusk RF; Pepine CJ; Glasser DB; Shpilsky A; DeRiesthal H; Sweeney M;

Efficacy and safety of sildenafil citrate in men with erectile dysfunction and stable coronary artery disease.

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparisons</th>
<th>Study Length</th>
<th>Outcomes</th>
<th>Funding</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Randomised Controlled Trial</td>
<td>Male CAD / ED</td>
<td>Sildenafil (25-100 mg)</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>Sexual function, Adverse events</td>
<td>Not listed</td>
<td>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 &lt; 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).</td>
</tr>
</tbody>
</table>

Reference number 59

Olsson AM; Persson CA; Swedish S;

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 99 of 248
Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men with cardiovascular disease

Randomised Controlled Trial

CVD / ED Male 18% MI intervention 20% MI placebo

Sildenafil (25-100 mg)

Placebo

12 weeks

Sexual function Adverse events

Pfizer

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 < 0.0001). 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 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 (data not shown).
**Question:** What is the effectiveness of adding ACEI versus placebo to improve outcome in...

**Grading:** 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

**Reference number:** 5198

Bonaa KH; Njolstad I; Ueland PM; Schirmer H; Tverdal A; Steigen T; Wang H; Nordrehaug JE; Arnesen E; Rasmussen

Homocysteine lowering and cardiovascular events after acute Myocardial Infarction

**Study Type:** Randomised Controlled Trial

**Patient Characteristics:**
- Inclusion criteria: Men and women (26%) aged 30 to 85 years of age (mean 63 years) with acute MI within 7 days before randomisation
- Concomitant therapy: Aspirin: 89%
- Diuretics: 18%
- Beta blockers: 91%
- ACEs: 32%
- ARBs: 5%
- Statins: 81%
- Warfarin: 12%

**Exclusion criteria:** Coexisting disease associated with a life expectancy of less than 4 years, prescribed treatment with B vitamins or untreated B vitamin deficiency or inability to follow the protocol, as judged by the investigator.

**Intervention:**
- Folic acid 0.8 plus 0.4 mg vitamin B12 mg plus 40 mg vitamin B6 once daily
- Placebo 943 patients
- 40 mg vitamin B6 once daily
- 934 patients
- Folic acid 0.8 mg plus 0.4 mg vitamin B12 once daily
- 953 patients

**Study Length:** Median follow-up 40 months (mean 36 months)

**Outcomes:**
- Primary: Composite of new nonfatal myocardial infarction and fatal myocardial infarction, fatal and nonfatal stroke or sudden death attributed to CHD
- Secondary: Myocardial infarction, unstable angina pectoris requiring hospitalization
- Stroke: CABG, PCI, Death from any cause

**Results presented for the folate combination versus placebo:**

- **Primary:** Composite of new nonfatal myocardial infarction and fatal myocardial infarction, fatal and nonfatal stroke or sudden death attributed to CHD: 201/937 (21.5%) folic acid plus vitamin B12 mg plus B6 versus 172/943 (18.2%) placebo RR of 1.22 (95% CI 1.00 to 1.50, P = 0.05).
- **Secondary:** Myocardial infarction: 182/937 (19.4%) folic acid plus vitamin B12 mg plus B6 versus 153/943 (16.2%) placebo RR of 1.23 (95% CI 0.99 to 1.52, P = 0.06).

**Effect:**

Results presented for the folate combination versus placebo

- **Primary:** Composite of new nonfatal myocardial infarction and fatal myocardial infarction, fatal and nonfatal stroke or sudden death attributed to CHD: 201/937 (21.5%) folic acid plus vitamin B12 mg plus B6 versus 172/943 (18.2%) placebo RR of 1.22 (95% CI 1.00 to 1.50, P = 0.05).

**Reference number:** 3093

Pfeffer MA; McMurray JJ; Velazquez EJ; Rouleau JL; Kober L; Maggioni AP; Solomon SD; Swedberg K; Van de VF; White H; Leimberger JD; Henis M; Edwards S; Zelenkofske S; Sellers MA; Califf RM;

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices
Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or

Primary outcome: all cause mortality. Secondary outcomes: CV death or MI, CV death or HF death, death from HF, CV causes or MI, Death from CV causes, MI, HF, resuscitation after cardiac arrest or stroke, hospitalization for MI or HF, tolerability.

Funding: Novartis Pharm.

Effect: Primary outcome: all cause mortality valsartan 979 (19.9%), valsartan + captopril 941 (19.3%), captopril 958 (19.5). Hazard ratio valsartan versus captopril: 1.00 (97.5% CI 0.90-1.11, P = 0.98). Hazard ratio valsartan + captopril versus captopril: 0.98 (97.5% CI 0.89-1.09, P = 0.73).

Secondary outcomes: Valsartan versus captopril hazard ratios Death from CV causes 0.98 (97.5% CI 0.87 to 1.09, P = 0.62). Death from CV causes or MI 0.95 (97.5% CI 0.87 to 1.05, P = 0.25). Death from CV causes or HF 0.97 (97.5% CI 0.90 to 1.05, P = 0.51). Death from CV causes, MI or HF 0.95 (97.5% CI 0.88 to 1.03, P = 0.20). Death from CV causes, MI, HF, resuscitation after cardiac arrest or stroke 0.96 (97.5% CI 0.89 to 1.04, P = 0.25).

Valsartan + captopril versus captopril Death from CV causes 1.00 (97.5% CI 0.89 to 1.11, P = 0.95). Death from CV causes or MI 0.96 (97.5% CI 0.88 to 1.09, P = 0.40). Death from CV causes or HF 1.00 (97.5% CI 0.92 to 1.09, P = 0.94). Death from CV causes, MI or HF 0.97 (97.5% CI 0.89 to 1.05, P = 0.37). Death from CV causes, MI, HF, resuscitation after cardiac arrest or stroke 0.96 (97.5% CI 0.89 to 1.04, P = 0.26). Hospitalization for MI or HF Valsartan group 919 patients (18.7%) had a total of 1447 hospitalizations. Valsartan + captopril group 834 patients (17.1%) had a total of 1297 hospitalizations. Valsartan group 945 patients (19.3%) had a total of 1437 hospitalizations. Valsartan versus captopril group P = 0.50 for comparison of proportion of patients and P = 0.51 for comparison of admissions. Valsartan + captopril group versus captopril group P = 0.005 for comparison of proportion of patients and P = 0.007 for comparison of admissions. Tolerability Proportion of patients no longer taking medication at 1 year: valsartan group 15.3%, valsartan + captopril group 19.0% captopril group 16.8%. Valsartan + captopril group versus captopril group P = 0.007. Mean doses of patients taking medication at 1 year: valsartan group 116±53 mg, valsartan + captopril group, valsartan 116±53 mg, captopril 107±53 mg, captopril group 117± 53 mg. Discontinuation reasons Hypotension Valsartan 70/4885 (1.4%)* Valsartan+captopril 90/4862 (1.9%)* Captopril 41/4879 (0.8%) Cough Valsartan 70/4885 (1.4%)* Valsartan+captopril 90/4862 (1.9%)* Captopril 41/4879 (0.8%) Rash Valsartan 30/4885 (1.4%)* Valsartan+captopril 101/4862 (2.1%) Captopril 122/4879 (2.5%) Angiodema Valsartan 9/4885 (0.2%)* Valsartan+captopril 0.2/4862 (1.9%) Captopril 13/4879 (0.3%) Taste disturbance Valsartan 9/4885 (0.2%)* Valsartan+captopril 16/4862 (0.3%) Captopril 21/4879 (0.4%) * the difference from the captopril group is significant at P < 0.05 Note: Valsartan is licensed in the UK for post MI patients with LV dysfunction.

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

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 102 of 248
Arnold JMO; Yusuf S; Young J; Mathew J; Johnstone D; Avezum A; Lonn E; Pogue J; Bosch J; Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study

Study Type: Randomised Controlled Trial

Patient Characteristics 
Men & women at least 55 years, mean age 66 years, 26.7% women Before random assignment, all eligible participants entered a run-in phase, during which 2.5 mg of ramipril was administered daily for 7 days, followed by a matching placebo for 10 to 14 days. History of CAD, stroke, PAD or diabetes plus one CV risk factor, 80.6% previous CV event, 53% previous MI, 43.4% PAD, 10.8% stroke or transient ischemic attack, 38.3% diabetes mellitus, hypertension history 46.5%, dyslipidemia 65.8%. Trial entry: 76.8% subjects taking antplatelet agent, 28.9% lipid-lowering agent, 39.5% beta blocker, 47.0% calcium channel blocker, 15.1% diuretic. Exclusions: HF, LVEF < 0.40, taking ACE inhibitor, uncontrolled hypertension, overt nephropathy, MI / stoke within 4 weeks recruitment, hyper-sensitivity to ACE

Study Length: 4.5 years

Outcomes 
Primary: composite MI / stroke / death from CV causes. Secondary: hospitalisations for HF and unstable angina, worsening angina, heart failure rate (composite of heart failure requiring hospitalisations, fatal heart failure, heart failure signs and symptoms and heart failure requiring open label ACEIs)

Funding: MRC Canada, Hoechst-Marion Roussel, Astra-Zeneca, King Pharm., Natural Source Vit E Assn and Negma, Heart and Stroke Foundn of Ontario

Effect: Mean follow-up 4.5 years: there were 482 (10.4%) patients with clinical MI and unexpected CV deaths in ramipril group compared with 604 (12.9%) in the placebo group (RRR 21%, 95%CI 11 to 30; P < 0.0003). Ramipril reduced heart failure rate from 11.5% to 9% (RR 0.77; 95%CI 0.68 to 0.87; P < 0.0001). Ramipril patients had a reduced RR of nonfatal MI of 23% (9 to 34); P < 0.0019, either Q-wave MI (18%, 9 to 38) or non-Q-wave MI (24%, 8 to 37), ramipril 5.6% versus placebo 7.2%. Risk reductions in MI were documented in subjects taking or not taking beta blockers, lipid lowering and / or antplatelet agents. Ramipril had no effect on hospitalizations for unstable angina or heart failure hospitalizations but reduced worsening and new angina (27.2% versus 30.0%, RRR, 12%; (5 to 18) P < 0.0014, and coronary revascularization (12.5% versus 14.8%; RRR, 18%; (8 to 26) P < 0.0005.

Reference number: 3251

Arnold JMO; Yusuf S; Young J; Mathew J; Johnstone D; Avezum A; Lonn E; Pogue J; Bosch J; Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study

Study Type: Randomised Controlled Trial

Patient Characteristics 
Men & women at least 55 years, mean age 66 years, 26.7% women. Before random assignment, all eligible participants entered a run-in phase, during which 2.5 mg of ramipril was administered daily for 7 days, followed by a matching placebo for 10 to 14 days. History of CAD, stroke, PAD or diabetes plus one CV risk factor, 80.6% previous CV event, 53% previous MI, 43.4% PAD, 10.8% stroke or transient ischemic attack, 38.3% diabetes mellitus, hypertension history 46.5%, dyslipidemia 65.8%. Trial entry: 76.8% subjects taking antplatelet agent, 28.9% lipid-lowering agent, 39.5% beta blocker, 47.0% calcium channel blocker, 15.1% diuretic. Exclusions: HF, LVEF < 0.40, taking ACE inhibitor, uncontrolled hypertension, overt nephropathy, MI / stoke within 4 weeks recruitment, hyper-sensitivity to ACE

Study Length: 4.5 years

Outcomes 
Primary: composite MI / stroke / death from CV causes. Secondary: hospitalisations for HF and unstable angina, worsening angina, heart failure rate (composite of heart failure requiring hospitalisations, fatal heart failure, heart failure signs and symptoms and heart failure requiring open label ACEIs)

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Reference number: 1770

Braunwald E; Domanski MJ; Fowler SE; Geller NL; Gersh BJ; Hsia J; Pfeffer MA; Rice MM; Rosenberg YD; Rouleau JL; PEACE T; Angiotensin-converting-enzyme inhibition in stable coronary artery disease.

Study Type: Randomised Controlled Trial

Patient Characteristics 
50 years or older, mean age 65 years, women 18%. CAD at least 1 of following: MI at least 3 months prior to recruitment 55%, CABG / PTCA at least 3 months prior to recruitment, obstruction greater / equal to 50% of luminal diameter of 1 native vessel, LVEF < 40%, toleration medication & successful completion of run-in phase, compliance. Diabetes mellitus 17%. Exclusions: current ACE / ARB usage, hospitalization for unstable angina 2 months prior, valvular HD requiring surgery, CADG / PTCA within 3 months prior, planned revascularisation, serum creatinine > 2.0 mg/dl, serum K > 5.5 mmol/l, limited 5 year survival chance, psychosocial risk adherence, no consent, female not using contraception, involved in non FDA / HP Canadian NHW approved trial. There was a 4 week run-in period. The participants was instructed to take 2 mg of trandolapril daily, and they recruited if they compliant and tolerated

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 103 of 248
the treatment. The median follow-up was 4.8 years. There were 9297 patients enrolled with documented.

**Intervention**
Trandolapril, target dose 4 mg OD

**Comparisons**
Matching placebo

**Study Length**
7 years, median 4.8 years

**Outcomes**
Primary: composite of death from CV causes, non fatal MI, coronary revascularisation  Other: combination of CV death, nonfatal MI, revascularisation, unstable angina, HF, stroke, PAD, cardiac arrhythmia

**Funding**
NHLB Inst., Knoll Pharm., Abbott Labs.

The incidence of the primary endpoint (composite of death from CV causes, non fatal MI, or coronary revascularization was 21.9% in the Trandolapril group compared with 22.5% in the placebo group (HR in Trandolapril group 0.96, 95% CI 0.88 to 1.06, P = 0.45). Drop out: 3 in treatment and 8 in placebo did not return for a follow-up visit. Compliance: Treatment, at 1 year: 81.9% on treatment, at 2 years: 78.5%, at 3 years: 74.5%. Among patients in placebo, 1.5% were receiving ACEI at 1 year, 4.6% at 2 years and 8.3% at 3 years. 68.6% of treatment group and 77.7% of placebo group were taking target dose 4 mg placebo / placebo per day.

Side effects: The rates of cough (39.1% versus 27.5% P = 0.01 and syncope (4.8% versus 3.9% P = 0.04) were greater in the Trandolapril group compared with the control group.

### Reference number 3228

Flather MD;Yusuf S;Kober L;Pfeffer M;Hall A;Murray G;Ball S;Pogue J;Moye L;Braunwald E;
Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients
2000 355 Lancet  pgs 1575 1581

**Study Type:** Systematic Review

MRC Canada, Hoechst-Marion Roussel, Sqibb, Merck Frosst Canada, Merck Sharpe & Dohme UAS, Bristol Myers, Zeneca.

Median treatment duration in SAVE, AIRE and TRACE was 31 (IQR 19-41) months. Treatment was associated with a reduction of mortality in the three post MI trials, SAVE 1992, AIRE 1993 and TRACE 1995 (N = 5966, treatment deaths 702/2995 (23.4%) versus placebo deaths 866/297 (29.1%), OR 0.74, 95% CI 0.66 to 0.83). Similarly, readmission for heart failure (treatment 11.9% versus placebo 15.5%, OR 0.73, 95% CI 0.63 to 0.85), recurrent myocardial infarction (treatment 10.8% versus placebo 13.2%, OR 0.80, 95% CI 0.69 to 0.94), or the composite of these events (treatment 35.5% versus placebo 41.9%, OR 0.75, 95% CI 0.67 to 0.83) were reduced. Combining all five trials (SAVE 1992, AIRE 1993 and TRACE 1995 + SOLVD 1991 / 1992) the treatment decreased mortality (N = 12 763), treatment deaths 1467/6391 (23.0%) versus placebo deaths 1710/6372 (26.8%), OR 0.80, 95% CI 0.74 to 0.87). Treatment also reduced readmission for heart failure (treatment 13.7% versus placebo 18.9%, OR 0.67, 95% CI 0.61 to 0.74), re-infarction (treatment 8.9% versus placebo 11.0%, OR 0.79, 95% CI 0.70 to 0.89), or the composite of these events (treatment 33.8% versus placebo 41.0%, OR 0.72, 95% CI 0.67 to 0.78).

### Reference number 3128

Fox KM;EURopean t;
Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease:
Myocardial infarction: full guideline DRAFT (August 2006) – Appendices  Page 104 of 248
randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study).

### Study Type:
Randomised Controlled Trial

### Patient Characteristics
Age > 18, mean age 60 years, 15% female. Run-in period: for 2 weeks participants were given 4 mg of perindopril once daily in the morning in addition to their normal medication. If 4 mg was tolerated, perindopril was increased to 8 mg once daily in the morning for 2 weeks. Patients aged 70 years or older were given 2 mg daily in the first week, followed by 4 mg daily in the second week, and 8 mg daily in the last 2 weeks. Documented CAD, post MI < 3 months 64%, PCI or CABG < 6 months, 55%, narrowing of at least one main coronary artery, history of chest pain, positive electro-cardiogram, echo or nuclear stress test. Diabetes mellitus 12%. Most patients used antiplatelet agent > 90%. Exclusions: HF, planned revascularization, hypertension, uncontrolled hyper-tension, recent ACE / ARB use, renal in-sufficiency creatinine > 150 micromol/L serum K > 5.5 mmol/L.

### Intervention
Perindopril 8mg OD

### Comparisons
Matched placebo

### Study Length
Average 4.2 years follow-up

### Outcomes
Primary: composite of CV death, non-fatal MI, cardiac arrest with successful resuscitation
Secondary: the composite of total mortality, non fatal MI, hospital admission for unstable angina, cardiac arrest with successful resuscitation, plus these individual components, revascularisation, stroke, admission for HF

### Funding
Servier, France

### Effect
Perindopril treatment was associated with reduction in primary endpoint 20% RRR (95%CI 9-29, P = 0.0003), 1.9% absolute risk reduction. Perindopril was associated with reductions in all secondary endpoints, although some were not statistically significant (not significant: unstable angina, total mortality, cardiovascular mortality, cardiac arrest, stroke, revascularization). See Figure 3, Table 1. Of note, perindopril treatment resulted in a 14% reduction in the composite outcome of total mortality, non-fatal MI, unstable angina and cardiac arrest (95% CI 6 to 21, P = 0.0009).

### Reference number
3402

Granger CB;McMurray JJ;Yusuf S;Held P;Michelson EL;Olofsson B;Ostergren J;Pfeffer MA;Swedberg K; Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial

### Study Type:
Randomised Controlled Trial

### Patient Characteristics
Inclusion criteria: Aged 18 years or older, male and female (68% male in treatment group, 68% male in placebo group), symptomatic HF of at least 4 weeks duration, LVEF\(\leq\)40%, previous intolerance to ACE inhibitors

### Intervention
Candesartan 32 mg daily, 1011 patients

### Comparisons
Placebo 1014 patients

### Study Length
Median follow-up 33.7 months

### Outcomes
Primary: Composite of unplanned hospital admission for the manage-ment of worsening CHF or CV death. Secondary: CV death, hospital admission for CHF or MI, CV death, hospital admission for CHF, MI or stroke.

### Funding
Astra-Zeneca R&D, Molndal, Sweden

### Effect
Primary Composite of unplanned hospital admission for the management of worsening CHF or CV death: candesartan versus placebo HR 0.70 95%CI 0.60 to 0.81 P < 0.001
Secondary CV death: candesartan versus placebo HR 0.80 95%CI 0.66 to 0.96 P = 0.02
Hospital admission for CHF: candesartan versus placebo HR 0.61 95%CI 0.51 to 0.73 P < 0.001
CV death, hospital admission for CHF or MI: candesartan versus placebo HR 0.72 95%CI 0.62 to
0.83 P < 0.001 CV death, hospital admission for CHF, MI or stroke: candesartan versus placebo HR 0.74 95%CI 0.64 to 0.85 P < 0.001 CV death, hospital admission for CHF, MI, stroke or coronary revascularization: candesartan versus placebo HR 0.76 95%CI 0.66 to 0.87 P < 0.001 Discontinuation reasons Hypotension Candesartan 37/1013 (1.4%)** Placebo 9/1015 (0.8%) Intolerance due to previous hypotension: Candesartan 13/143 (9.1%) Placebo 5/113 (4.2%) Cough Candesartan 2/4885 (0.2%) Placebo 4/4879 (0.4%) Intolerance due to previous cough: Candesartan 2/704 (0.3%) Placebo 4/751 (0.5%) Increase in creatinine: Candesartan 62/4885 (6.1%)** Placebo 27/4879 (2.7%) Intolerance due to previous renal dysfunction: Candesartan 31/134 (23.1%) Placebo 12/100 (12%) Angioedema: Candesartan 1/4885 (0.1%) Placebo 0/4879 Intolerance due to previous angioedema / anaphylaxis Candesartan 1/28 (2.6%) Placebo 0/44 (0.4%) Hyperkalaemia Candesartan 19/4885 (1.9%)* Placebo 3/4879 (0.3%) Intolerance due to previous hyperkalaemia: Candesartan 8/134 (13.6%) Placebo 1/100 (1.0%) * the difference from the candesartan group is significant at P = 0.0005 ** the difference from the candesartan group is significant at P < 0.0001.

Reference number 3183

Investigators H.O.P.E.;
Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study
2001 104 Circulation pgs 522 526

Study Type: Randomised Controlled Trial

Patient Characteristics
Men & women at least 55 years, mean age 66 years, 26.7% women Before random assignment, all eligible participants entered a run-in phase, during which 2.5 mg of ramipril was administered daily for 7 days, followed by a matching placebo for 10 to 14 days History of CAD, stroke, PAD or diabetes plus one CV risk factor, 53% previous MI, 43.4% PAD, 10.8% stroke or transient ischemic attack, 38.3% diabetes mellitus, hypertension history 46.5%, dyslipidemia 65.8%. Trial entry: 76.8% subjects taking antiplatelet agent, 28.9% lipid-lowering agent, 39.5% beta blocker, 47.0% calcium channel blocker, 15.1% diuretic Exclusions: HF, LVEF < 0.40, taking ACE inhibitor, uncontrolled hypertension, overt nephropathy, MI / stroke within 4 weeks recruitment, hyper-sensitivity to ACE

Intervention
Ramipril, 10 mg OD

Comparisons Matching placebo

Study Length 4.5 years

Outcomes Primary: composite MI / stroke / death from CV causes Secondary: hospitalisations for HF and unstable angina, worsening angina, heart failure rate (composite of heart failure requiring hospitalisations, fatal heart failure, heart failure signs and symptoms and heart failure requiring open label ACEIs)

Funding MRC Canada, Hoechst-Marion Rousses, Astra-Zeneca, King Pharm., Natural Source Vit E Assn and Negma, Heart and Stroke Foundn of Ontario

Effect Mean follow-up 4.5 years: there were 482 (10.4%) patients with clinical MI and unexpected CV deaths in ramipril group compared with 604 (12.9%) in the placebo group (RRR 21%, 95%CI 11 to 30; P < 0.0003). Ramipril reduced heart failure rate from 11.5% to 9% (RR 0.77; 95%CI 0.68 to 0.87; P < 0.0001). Ramipril patients had a reduced RR of nonfatal MI of 23% (9 to 34); P < 0.0019, either Q-wave MI (18%, -9 to 38) or non-Q-wave MI (24%, 8 to 37), ramipril 5.6% versus placebo 7.2%. Risk reductions in MI were documented in subjects taking or not taking beta blockers, lipid lowering and / or antiplatelet agents. Ramipril had no effect on hospitalizations for unstable angina or heart failure hospitalizations but reduced worsening and new angina (27.2% versus 30.0%; RRR, 12%; (5 to 18) P < 0.0014, and coronary revascularization (12.5% versus 14.8%; RRR, 18%; (8 to 26) P < 0.0005.

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 106 of 248
Grading: 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Reference number 1764

Kondo J;Sone T;Tsuboi H;Mukawa H;Morishima I;Uesugi M;Kono T;Kosaka T;Yoshida T;Numaguchi Y;Matsui H;Murohara T;Okumura K;
Effects of low-dose angiotensin II receptor blocker candesartan on cardiovascular events in patients with coronary artery disease.[see comment]

2003 146 American Heart Journal pgs 1022 1027

Study Type: Randomised Controlled Trial
Patient Characteristics
  Inclusion criteria: Male and female (74% male in treatment group, 77% male in placebo group), history of coronary intervention. Patients with a history of coronary intervention and no significant coronary stenosis on follow up after intervention (MI: treatment group 67%, placebo group 70%). Exclusion criteria: Congestive heart failure EF < 0.40, receiving dialysis, Intervention
  Candesartan 4 mg daily, 203 patients
Comparisons
  Placebo, no tablet given, 203 patients
Study Length
  Mean follow-up 24 months
Outcomes
  Primary Composite of revascularisation, nonfatal MI, CV death  Secondary Composite of worsening angina, congestive heart failure
Funding
  Not listed
Effect
  Composite of revascularization, nonfatal MI, CV death: 12/194 recruits candesartan group versus 25/203 recruits control group, P = 0.03. Composite of worsening angina, congestive heart failure 9/194 recruits candesartan group versus 16/203 recruits control group, P = 0.14. Note: Candesartan is not licensed in the UK for post MI patients.
Question: What is the effectiveness of adding ACEI versus ARBs to improve outcome in...

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Dickstein K; Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group; Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II

2002 360 Lancet pgs 752 760

Study Type: Randomised Controlled Trial

Reference number: 3134

Patent

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number: 3134

Study Type: Randomised Controlled Trial

Inclusion criteria: At least 50 years mean 67.5±9.8 years, men and women, MI (at least 2 of the following: history chest pain > 20 min, ST elevation on electrocardiograph, or an increase in cardiac markers). MI patients with signs and symptoms of HF during the acute phase (defined as treatment with diuretic or intravenous vasodilator therapy for HF, pulmonary rates, third heart rate sound, persistent sinus tachycardia > 100 bpm, or radiographic evidence of pulmonary congestion). Patients with acute MI and EF < 35% or LV end-diastolic dimension > 65 mm and/or new Q-wave anterior-wall acute MI, or previous pathological Q-waves in the anterior wall. Patients enrolled within 10 days of onset of symptoms (median 3 days). Exclusion criteria: Supine systolic arterial blood pressure < 100 mm Hg at randomization, current receipt ACE inhibitor or angiotensin II antagonist, unstable angina, haemodynamically significant dysrhythmia, haemodynamically significant stenotic valvular heart disease, and planned revascularization.

Patient

Losartan 12.5 mg once daily titrated to 50 mg daily as tolerated, 2551 patients

Captopril 12.5 mg three times daily to 50 mg three times daily as tolerated, 2733 patients

Study Length

Follow-up: average 2.7 years (0.9)

Intervention

Comparison

Study Length

Outcomes

Primary outcome: all cause mortality Secondary outcomes: sudden cardiac death / resuscitated cardiac arrest, MI (fatal / non fatal), MI / total mortality, CV death, Stroke (fatal / non fatal), CABG, PTCA, revascular-isation, first all cause admission, first admission for HF, cardio-vascular admission, non-cardio-vascular admission, tolerability.

Primary outcome: all cause mortality 499 (18.2%) versus captopril 447 (16.4%), relative risk (95% CI) 1.13 (0.99-1.28) P = 0.069. Secondary outcomes: sudden cardiac death / resuscitated cardiac arrest losartan 239 (8.7%) versus captopril 203 (7.4%), relative risk (95% CI) 1.19 (0.99-1.43) P = 0.072, MI (fatal / non fatal) losartan 384 (14.0%) versus captopril 379 (13.9%), relative risk (95% CI) 1.03 (0.89-1.18) P = 0.722, MI / total mortality losartan 746 (27.2%) versus captopril 689 (25.2%), relative risk (95% CI) 1.10 (0.99-1.22) P = 0.085, CV death losartan 420 (15.3%) versus captopril 363 (13.3%), relative risk (95% CI) 1.17 (1.01-1.34) P = 0.032, Stroke (fatal / non fatal) losartan 140 (5.1%) versus captopril 132 (4.8%), relative risk (95% CI) 1.07 (0.84-1.36) P = 0.587, CABG losartan 404 (14.7%) versus captopril 375 (13.7%), relative risk (95% CI) 1.09 (0.95-1.26) P = 0.228. PTCA losartan 466 (17.0%) versus captopril 493 (18.0%), relative risk (95% CI) 0.94 (0.83-1.07) P = 0.358, revascularization losartan 845 (30.8%) versus captopril 827 (30.3%), relative risk (95% CI) 1.03 (0.93-1.13) P = 0.620, first all cause admission losartan 1806 (65.8%) versus captopril 1774 (64.9%), relative risk (95% CI) 1.03 (0.97-1.10) P = 0.362, first admission for HF losartan 306 (11.2%) versus captopril 265 (9.7%), relative risk (95% CI) 1.16 (0.98-1.37) P = 0.072, cardiovascular admission losartan 1480 (53.9%) versus captopril 1421 (52.0%), relative risk (95% CI) 1.06 (0.99-1.14) P = 0.108, non-cardiovascular admission losartan 855 (32.3%) versus captopril 905 (33.1%), relative risk (95%...
CI: 0.98 (0.90-1.08) P = 0.719. Tolerability: Losartan was better tolerated than captopril. Discontinuation due to adverse experience: Losartan 202 (7.0%) versus captopril 387 (14.0%), relative risk (95% CI) 0.94 (0.42-0.59) P < 0.0001. Discontinuation reasons: Hypotension Losartan 47/2744 (1.7%) Captopril 61/2733 (2.2%) Cough Losartan 28/2744 (0.4%)*** Captopril 113/2733 (8%) Rash Losartan 3/2744 (1.0%)** Captopril 18/2733 (0.7%) Angioedema Losartan 4/2744 (0.1%)* Captopril 14/2733 (0.5%) Taste disturbance Losartan 1/2744 (0.0%)*** Captopril 17/2733 (0.5%) * the difference from the captopril group is significant at P = 0.0.19 ** the difference from the captopril group is significant at P = 0.008 *** the difference from the captopril group is significant at P < 0.0001 Note: Losartan is not licensed in the UK for post MI patients.
Question: What is the effectiveness of adding aspirin versus placebo to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number 1784

Baigent C; Sudlow C; Collins R; Peto R; Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

2002 324 British Medical Journal

Study Type: Systematic Review

Patient Characteristics

Intervention Aspirin, dipyridamole, sulfinpyrazone 9984 patients

Comparison Placebo 10022 patients

Study Length

Outcomes


Effect

For post MI patients treated for a mean duration of 27 months, treatment resulted in 36 (SE 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 bleeds due to antiplatelet therapy was calculated as approximately 1 patient per 1000 per year.

Reference number 3740

Chan FK; Ching JY; Wong VW; Leung VK; Kung NN; Hui AJ; Wu JC; Leung WK; Lee VW; Lee KK; Lau JY; To KF; Chan HL; Sung JJ

Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding

2005 352 New england Journal of Medicine

Study Type: Randomised Controlled Trial

Patient Characteristics

Inclusion criteria: Previous upper GI bleeding, treated and endoscopy performed 8 weeks post eradication therapy. Endoscopically confirmed ulcer healing, negative test for H. pylori

Exclusion criteria: Use of NSAIDs, Cox-2 inhibitors, anticoagulants, other antiplatelets, or corticosteroids, history gastric surgery, aspirin or clopidogrel allergy, presence of erosive esophagitis, gastric-outlet obstruction, renal failure requiring dialysis, terminal illness, or cancer

Intervention

Clopidogrel 75 mg daily plus esomeprazole placebo twice daily

Comparison

Aspirin 80 mg daily plus esomeprazole 20mg twice daily

Study Length

12 months

Outcomes

Primary recurrent ulcer bleeding Secondary lower GI bleeding

Funding Division Gastro-enterology and Haepatology at the Chinese University of Hong Kong

Effect

Recurrent bleeding: 13/161 clopidogrel, 1/159 aspirin plus esomeprazole Cumulative incidence of recurrent bleeding: clopidogrel 8.6% (95%CI 4.1 to 13.1%) versus aspirin plus esomeprazole 0.7% (95%CI 0 to 2%), P = 0.001 Cumulative incidence of lower GI bleeding: clopidogrel 4.6% (95%CI 1.7 to 7.9%) versus aspirin plus esomeprazole 4.6% (95%CI 1.3 to

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

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices
A randomized, controlled trial of aspirin in persons recovered from myocardial infarction

Study Type: Randomised Controlled Trial
Inclusion criteria: post MI, men and women (12%), aged between 30-69 years, mean age 54 years, > 85% patients recruited 6 month post MI, interval between infarct and entry to trial: mean 25 months (range 2 -60 months)   Exclusion criteria: Anticoagulation, aspirin dipyridamole or sulfipyrazone therapy, severe ulcer disease, sensitivity to aspirin, previous cardiovascular therapy.

Intervention: Aspirin 1000 mg once daily  2267 patients
Comparisons: Placebo   2257 patients
Study Length: 3 years months, mean follow-up 38 months
Outcomes: Primary Total mortality Secondary CHD mortality (MI + sudden death), coronary incidence (CHD mortality or non-fatal MI), fatal or non-fatal stroke.

Effect: Total mortality: treatment 10.8% versus 9.7% placebo, not significant  CHD mortality: treatment 8.7% versus 8.0% placebo, not significant  Sudden death: treatment 2.7% versus 2.0% placebo, not significant  Coronary incidence: treatment 14.1% versus 14.8% placebo, not significant  Symptoms suggestive of peptic ulcer, gastritis, or erosion of gastric mucosa: treatment 23.7% versus 14.9% placebo, Z value 7.52, significant.

Aspirin in coronary heart disease. The Coronary Drug Project Research Group

Inclusion criteria: MI patients who survived 4-6 weeks post infarct, male, age 45-70 years
Exclusion criteria: none listed

Intervention: Aspirin 324 mg three times daily  758 patients
Comparisons: Placebo  771 patients
Study Length: Mean follow-up 22 months
Outcomes: Primary Mortality Secondary Coronary death, sudden coronary death, nonfatal MI
Funding: Not listed
Effect: Mortality: treatment 5.8% versus placebo 8.3%, Z value - 1.9  Coronary death: treatment 4.6% versus placebo 6.4%, Z value - 1.49  Sudden coronary death: treatment 2.6% versus placebo 3.2%, Z value 0.70 Nonfatal MI: treatment 3.6% versus placebo 2.2%, Z value 0.48  Upper GI irritation: treatment 12.5% versus placebo 6.3%, Z value 4.08.

Secondary prevention of myocardial infarction. Comparison of acetylsalicylic acid, phenprocoumon and placebo. A multicenter two-year prospective study

Inclusion criteria: acute MI patients who survived 4-6 weeks, age 45 to 70 years, male and female (21.5%)   Exclusion criteria: contraindications to aspirin

Intervention: Aspirin 1500mg   317 patients
Comparisons: Placebo  309 patients
Study Length: Mean follow-up 24 months
Outcomes: Primary  Coronary death (fatal MI + sudden death), coronary events (non fatal MI, fatal MI + sudden death  Secondary  Stomach complaints / ulcer

Reference number 1161
Reference number 1151
Reference number 1163
Funding  Not listed
Effect Coronary death (fatal MI + sudden death): aspirin 13/317 versus placebo 22/309, P < 0.05
Coronary events (non fatal MI, fatal MI + sudden death ): aspirin 24/317 versus placebo 37/309, P < 0.05
Stomach complaints / ulcer: aspirin 20/317 versus placebo 12/309.

Reference number 557

Elwood PC CABMSPW;
A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction
1974 1 British Medical Journal pgs 436 440
Study Type: Randomised Controlled Trial
Patient characteristics: Inclusion criteria: post MI, men under 65 years, mean age 56 years, interval between infarct and entry to trial: mean 70 days (range ½ -6 months) Exclusion criteria: Anticoagulation therapy, evidence of peptic ulcer.
Intervention: Aspirin 300mg once daily  615 patients
Comparisons: Placebo  624 patients
Study Length: 1 year
Outcomes: Mortality
Funding: Not listed
Effect: Mortality: treatment 8.3% versus 10.9% placebo, not significant.

Reference number 1162

Elwood PC;Sweetnam PM;
Aspirin and secondary mortality after myocardial infarction
1979 2 Lancet pgs 1313 1315
Study Type: Randomised Controlled Trial
Patient characteristics: Inclusion criteria: post MI, men and women (15%), mean age 56 years, interval between infarct and entry to trial: < 6 weeks 50%, 6-13 weeks 26%, 14 weeks > 24%, mean interval 10 months Exclusion criteria: Anticoagulation therapy, evidence of peptic ulcer, sensitivity to aspirin.
Intervention: Aspirin 300mg three times daily  847 patients
Comparisons: Placebo  878 patients
Study Length: 1 year
Outcomes: Mortality, Cardiovascular mortality, non-fatal MI, total mortality plus non-fatal vascular events
Funding: Not listed
Effect: Mortality: treatment 14.8% versus 12.3% placebo, not significant, cardiovascular mortality: treatment 11.6% versus 13.9% placebo, not significant, non-fatal MI treatment 7.1% versus 10.9% placebo, P < 0.05, total mortality plus vascular events treatment 27.4% versus 35.8% placebo, P < 0.05 Withdrawal due to bleeding: treatment 8/847 patients versus 4/878 placebo Authors state that the study was underpowered with respect to recruitment to detect a 25% reduction as significant at P < 0.05.

Reference number 1052

Verheugt FW;van d;Funke-Kupper AJ;Sterkman LG;Galema TW;Roos JP;
Effects of early intervention with low-dose aspirin (100 mg) on infarct size, reinfarction and mortality in anterior wall acute myocardial infarction
1990 66 American Journal of Cardiology pgs 267 270
Study Type: Randomised Controlled Trial
Patient characteristics: Inclusion criteria: First anterior wall acute MI < 12 h (ST-segment elevation > 2 mm in precordial leads in absence of precordial Q wave), men and women (26%), age range 27 to 91 years, mean aspirin 61 years, placebo 64 years Exclusion criteria: contraindication to aspirin

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 112 of 248
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Aspirin 100 mg once daily  50 patients</th>
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<tr>
<td>Comparisons</td>
<td>Placebo  50 patients</td>
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<td>Outcomes</td>
<td>Primary Infarct size  Secondary Death, reinfarction, unstable angina, revascularisation</td>
</tr>
<tr>
<td>Funding</td>
<td>Not listed</td>
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<tr>
<td>Effect</td>
<td>Infarct size assessed as 72 hour cumulative lactate dehydrogenase release: treatment 1431±782 U/l versus placebo 1592±1082 U/l (P = 0.35)  Mortality: treatment 10/50 versus placebo 12/50, not significant  Reinfarction: treatment 2/50 versus placebo 9/50 (P &lt; 0.03)  Unstable angina: treatment 14/50 versus placebo 11/50, not significant  CABG/PTCA: treatment 2/50 versus placebo 1/50, not significant.</td>
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</table>
Question: What is the effectiveness of adding aspirin versus clopidogrel to improve outcome in patients after MI?

Grading: 1++  
High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number 3730

Gent M;
A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)

1996  348  Lancet  pgs 1329 1339

Study Type: Randomised Controlled Trial

Patient Characteristics
Inclusion criteria: MI onset ≤ 35 days before randomization, two of a) characteristic ischaemic pain for 20 min, b) elevation of CK, CK-MB, LDL or AST to 2x upper limit of laboratory normal with no other explanation, c) development of new ≥ 40 Q waves in

Intervention  Clopidogrel 75 mg once daily  3143 patients MI subgroup  3233 patients stroke subgroup  3233 patients PAD subgroup

Comparisons  Aspirin 325 mg once daily  3159 patients MI subgroup  3198 patients stroke subgroup  3229 patients PAD subgroup

Study Length  Mean follow-up 1.91 years

Outcomes  Primary Incidence of first occurrence of ischemic stroke, MI or vascular death

Funding  Sanofi, Bristol-Myers Squibb

Effect  RR reduction of primary outcome measure for post MI patient subgroup: clopidogrel versus aspirin = -3.7% (-22 to 12.0), P = 0.66. Clopidogrel 291/3159 versus aspirin 283/3159. RR reduction of primary outcome measure for stroke patient subgroup: clopidogrel versus aspirin = 7.3% (-5.7 to 18.7), P = 0.26. Clopidogrel 433/3233 versus aspirin 461/3198. RR reduction of primary outcome measure for PAD patient subgroup: clopidogrel versus aspirin = 23.8% (8.9 to 36.2), P = 0.0028. Clopidogrel 433/3233 versus aspirin 461/3198. RR reduction of primary outcome measure for ALL patient subgroup: clopidogrel versus aspirin = 8.7% (0.3 to 16.5), P = 0.043. Clopidogrel 939/9599 versus aspirin 1021/9586.

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

Reference number 2278

Sabatine MS;Cannon CP;Gibson CM;López-Sendón JL;Montalescot G;Téroux P;Claeys MJ;Cools F;Hill KA;Skene AM;McCabe CH;Braunwald E;
Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation

2005  352  New England Journal of Medicine  pgs 1179 1189

Study Type: Randomised Controlled Trial

Patient Characteristics
Inclusion criteria: enrolled within 12 h after onset ST-elevation MI, aged 18 to 75 years, mean
57 years, men and women (20%), scheduled to receive a fibrinolytic agent, an anticoagulant (if a fibrin-specific lytic agent was prescribed), aspirin and undergo angiography 48 to 192 hours
after the start of study medication  Exclusion criteria: treatment with clopidogrel within 7 days
before enrolment or planned treatment with Clopidogrel or a glycoprotein 11b/11a inhibitor
before angiography, contraindications to fibrinolytic therapy, planned angiography within 48 h
in the absence of a new clinical indication, cardiac shock, prior CABG, weight 67 kg or less and
receipt of more than 4000-U bolus of unfractionated heparin, weight more than 67 kg and
receipt of more than 5000-U bolus of unfractionated heparin, or receipt of more than standard
dose of low-molecular-weight heparin

Intervention  Clopidogrel 300 mg loading dose, followed by 75 mg once daily  Aspirin  Fibrinolytic agent
1752 patients

Comparisons  Clopidogrel placebo  Aspirin  Fibrinolytic agent  1739 patients

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices  Page 114 of 248
**Study Length**
30 days

**Outcomes**
Primary  Composite occluded infarct related artery on angiography, death or recurrent MI before angiography  Composite death from CV causes, recurrent MI, recurrent ischemia requiring revascularisation at 30 days  Secondary

**Funding**
Sanofi-Aventis, Bristol-Myers Squibb

**Effect**
Before angiography  Rates of the primary efficacy endpoint 21.7% in placebo group and 15.0% in clopidogrel group: 36% odds reduction with clopidogrel therapy (95% CI 24 to 47%, P < 0.001)  At 30 days  Primary endpoint: clopidogrel therapy odds reduction = 20%, P < 0.03

There was no significant difference in major or minor bleeding between the two treatment
Question: What is the effectiveness of adding aspirin versus aspirin and clopidogrel to improve outcome in...

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number 5183

Bhatt DL; Fox KA; Hacke W; Berger PB; Black HR; Boden WE; Cacoub P; Cohen EA; Creager MA; Easton JD; Flather MD; Haffner SM; Hamm CW; Hankey GJ; Johnston SC; Mak KH; Mas JL; Montalescot G; Pearson TA; Steg PG; Steinhubl SR; Weber MA; Brennan DM; Fabry-Ribaudo L; Booth J; Topol E

Clopidogrel and aspirin versus aspirin alone for the prevention of Atherothrombotic events 2006 354 New England Journal of Medicine pgs

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Aged 45 years or older and one of the following conditions: Multiple atherothrombotic risk factors (such as diabetes, diabetic nephropathy, ankle-brachial < 0.9, asymptomatic carotid stenosis ≥ 70% of luminal diameter, ≥ 1 carotid

Intervention

Comparisons Placebo once daily plus aspirin 75 mg once daily  7801 patients

Study Length Median follow-up 28 months

Outcomes Primary Composite of myocardial infarction, stroke (of any cause), or death from cardio-vascular causes (including haemorrhage). Secondary Composite of myocardial infarction, stroke (of any cause), death from cardio-vascular causes, hospitalisation for unstable angina, transient ischaemic attack, or revascularisation: 1301/7802 (16.7%) clopidogrel plus aspirin versus 1395/7801 (17.9%) placebo plus aspirin, RR of 0.92 (95% CI 0.82 to 0.98, P = 0.04). Death from any cause: 371/7802 (4.8%) clopidogrel plus aspirin versus 374/7801 (4.8%) placebo plus aspirin, RR of 0.99 (95% CI 0.86 to 1.14, P = 0.90). Death from cardiovascular causes: 238/7802 (3.1%) clopidogrel plus aspirin versus 229/7801 (2.9%) placebo plus aspirin, RR of 1.04 (95% CI 0.87 to 1.25, P = 0.68). Nonfatal MI: 147/7802 (1.9%) clopidogrel plus aspirin versus 1.59/7801 (2.0%) placebo plus aspirin, RR of 0.92 (95% CI 0.74 to 1.16, P = 0.48). Nonfatal ischaemic stroke: 132/7802 (1.7%) clopidogrel plus aspirin versus 160/7801 (2.1%) placebo plus aspirin, RR of 0.82 (95% CI 0.66 to 1.04, P = 0.10). Nonfatal stroke: 149/7802 (1.9%) clopidogrel plus aspirin versus 185/7801 (2.4%) placebo plus aspirin, RR of 0.80 (95% CI 0.65 to 0.997, P = 0.05). Hospitalisation for unstable angina, transient ischaemic attack or revascularisation: 886/7802 (11.1%) clopidogrel plus aspirin versus 957/7801 (12.3%) placebo plus aspirin, RR of 0.90 (95% CI 0.82 to 0.98, P = 0.02). Subgroup analysis Documented CV disease ‘symptomatic’ Enrolled with multiple vascular risk factors ‘asymptomatic’ (some of whom had a reported history of cardiovascular events – 10.4% prior MI, 5.8% prior stroke, 5.2% prior TIA, 7.7% had undergone PCI and 9.8% prior CABG although did not meet the criteria for established cardiovascular disease as defined in the study) Primary endpoint: Among 3284 asymptomatic patients, there was a 20% relative increase in primary events with clopidogrel plus aspirin compared with placebo plus aspirin (6.6% versus 5.5% respectively, P = 0.20) Among 12153 symptomatic patients there was a marginal significant

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 116 of 248
reduction in the primary endpoint with clopidogrel plus aspirin compared with placebo plus aspirin (6.9% versus 7.9% respectively, P = 0.046). Death from all causes and cardiovascular cause: Among 3284 asymptomatic patients, there was a significant increase in death from any cause with clopidogrel plus aspirin compared with placebo plus aspirin (5.4% versus 3.8% respectively, P = 0.04), as well as a significant increase in the rate of death from cardiovascular disease with clopidogrel plus aspirin compared with placebo plus aspirin (3.9% versus 2.2% respectively, P = 0.01) In contrast, the addition of clopidogrel had no significant effect on death from cardiovascular causes in the symptomatic subgroup. Safety end points Severe bleeding: 130/7802 (1.7%) clopidogrel plus aspirin versus 104/7801 (1.3%) placebo plus aspirin, RR of 1.25 (95% CI 0.97 to 1.61, P = 0.09). Fatal bleeding: 26/7802 (0.3%) clopidogrel plus aspirin versus 17/7801 (0.2%) placebo plus aspirin, RR of 1.53 (95% CI 0.83 to 2.82, P = 0.17). Primary intracranial haemorrhage: 26/7802 (0.3%) clopidogrel plus aspirin versus 27/7801 (0.3%) placebo plus aspirin, RR of 0.96 (95% CI 0.56 to 1.65, P = 0.89). Moderate bleeding: 164/7802 (2.1%) clopidogrel plus aspirin versus 101/7801 (1.3%) placebo plus aspirin, RR of 1.62 (95% CI 1.27 to 2.1, P < 0.001). Subgroup analysis Severe bleeding: Symptomatic patients: Clopidogrel plus aspirin: 2% Placebo plus aspirin 1.2% (P = 0.07) Symptomatic patients: Clopidogrel plus aspirin: 1.6% Placebo plus aspirin 1.4% (P = 0.39) Moderate bleeding: Asymptomatic patients: Clopidogrel plus aspirin: 2.2%. Placebo plus aspirin 1.4% (P = 0.08) Symptomatic patients: Clopidogrel plus aspirin: 2.1% Placebo plus aspirin 1.3% (P < 0.001).

Reference number 1822
Yusuf S;Zhao F;Mehta SR;Chrolavicius S;Tognoni G;Fox KK;
Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment
2001 345 New England Journal of Medicine pgs 494 502

Study Type: Randomised Controlled Trial
Patient Inclusion criteria: Hospitalised within 24 h of onset of symptoms of acute coronary syndromes without ST elevation Exclusion criteria: contraindications to antiplatelet / anticoagulant therapy, high risk for bleeding or heart failure, taking oral coagulants, revascularization in previous 3 months, received intravenous glycoprotein IIb / IIIa receptor inhibitors in previous 3

Intervention Clopidogrel 300 mg immediately followed by 75 mg daily plus aspirin 6259 patients

Comparisons Placebo plus aspirin 6303 patients

Study Length 3 to 12 months, mean duration of treatment 9 months, no patient < 3 months

Outcomes Primary Death from CV causes non fatal MI or stroke. Death from CV causes, nonfatal MI, stroke or refractory ischemia Reinfarction Secondary Revascularization

Funding Not listed

Effect Death from CV causes, non fatal MI or stroke: clopidogrel 582/6259 (9.3%) versus placebo 719/6303 (11.4%), RR 0.80 (95%CI 0.72 to 0.90, P < 0.001) Death from CV causes, nonfatal MI, stroke or refractory ischemia: clopidogrel 1035/6259 (16.5%) versus placebo 1187/6303 (18.8%), RR 0.86 (95%CI 0.79 to 0.94, P < 0.001) Reinfarction: clopidogrel 85/6259 (1.4%) versus placebo 126/6303 (2.0%), RR 0.69 (95%CI 0.52 to 0.90, P < 0.007) Slightly fewer patients in the clopidogrel group underwent revascularization: 36% versus placebo 36.5% Major bleeding was significantly higher in clopidogrel group (3.7%) versus placebo (2.7%), RR 1.38 95% CI 1.13 to 1.67, P = 0.001. but there were not significantly more patients with episodes of life-threatening bleeding or hemorrhagic strokes (Clopidogrel 2.2% versus placebo 1.8%, RR 1.21, 95%CI 0.95 to 1.56).

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
Reference number 2278
Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 117 of 248
Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation


Study Type: Randomised Controlled Trial

Patient Characteristics
Inclusion criteria: enrolled within 12 h after onset ST-elevation MI, aged 18 to 75 years, mean 57 years, men and women (20%), scheduled to receive a fibrinolytic agent, an anticoagulant (if a fibrin-specific lytic agent was prescribed), aspirin and undergo angiography 48 to 192 hours after the start of study medication. Exclusion criteria: treatment with clopidogrel within 7 days before enrolment or planned treatment with Clopidogrel or a glycoprotein 11b/11a inhibitor before angiography, contraindications to fibrinolytic therapy, planned angiography within 48 h in the absence of a new clinical indication, cardiac shock, prior CABG, weight 67 kg or less and receipt of more than 4000-U bolus of unfractionated heparin, weight more than 67 kg and receipt of more than 5000-U bolus of unfractionated heparin, or receipt of more than standard dose of low-molecular-weight heparin.

Intervention
Clopidogrel 300 mg loading dose, followed by 75 mg once daily. Aspirin. Fibrinolytic agent.

Comparisons
Clopidogrel placebo  Aspirin  Fibrinolytic agent  1739 patients

Study Length
30 days

Outcomes
Primary Composite occluded infarct related artery on angiography, death or recurrent MI before angiography. Composite death from CV causes, recurrent MI, recurrent ischemia requiring revascularisation at 30 days. Secondary

Funding
Sanofi-Aventis, Bristol-Myers Squibb

Effect
Before angiography Rates of the primary efficacy endpoint 21.7% in placebo group and 15.0% in clopidogrel group: 36% odds reduction with clopidogrel therapy (95% CI 24 to 47%, P < 0.001). At 30 days Primary endpoint: clopidogrel therapy odds reduction = 20%, P < 0.03. There was no significant difference in major or minor bleeding between the two treatment
**Question:** What is the effectiveness of adding a beta blocker versus placebo to improve outcome in...

**Grading:** 1++ *High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias*

**Reference number** 3841

Chen ZM; Jiang LX; Chen YP; Xie JX; Pan HC; Peto R; Collins R;
Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction: randomised placebo-controlled trial

**Study Type:** Randomised Controlled Trial

**Patient Characteristics**
- Inclusion criteria: Post MI recruited within 24 h of suspected acute MI onset (ST elevation (87%), left bundle block (6%), or ST depression (7%)). Mean age ± SD = 61 ± 11 years, male and female (28%). Patients with hypertension: 8% Exclusion criteria

**Intervention**
- Immediately: 162 mg aspirin plus 75 mg clopidogrel Subsequently: 162 mg aspirin plus 75 mg clopidogrel once daily for up to 4 weeks (or, if earlier, until hospital discharge or death) 22,961 patients

**Comparisons**
- Immediately: 162 mg aspirin plus placebo Subsequently: 162 mg aspirin plus placebo once daily for up to 4 weeks (or, if earlier, until hospital discharge or death) 22,891 patients

**Study Length**
- Up to 4 weeks

**Outcomes**
- Primary Composite of death, reinfarction, or stroke. Death from any cause. Secondary Reinfarction Stroke Cardiogenic shock Heart failure Presumed cardiac rupture Ventricular fibrillation Other cardiac arrest Pulmonary embolism

**Study Length**
- Up to 4 weeks

**Outcomes**
- Primary Composite of death, reinfarction, or stroke: 2121/22961 (9.2%) treatment versus 2310/22891 (10.1%) placebo, OR of 0.91 (95% CI 0.86 to 0.97, P = 0.002). About 2 weeks of clopidogrel therapy associated with 9 (SE 3) fewer patients with death, reinfarction or stroke in hospital per 1000 allocated treatments. Death from any cause: 1726/22961 (7.5%) treatment versus 1845/22891 (8.1%) placebo, OR of 0.93 (95% CI 0.87 to 0.99, P = 0.03). Arrhythmia: 432/22961 (1.9%) treatment versus 454/22891 (2.0%) placebo. Asystole: 642/22961 (2.8%) treatment versus 697/22891 (2.0%) placebo. Cardiac rupture: 188/22961 (0.8%) treatment versus 210/22891 (0.9%) placebo. Cardiogenic shock: 503/22961 (2.2%) treatment versus 562/22891 (2.5%) placebo. Reinfarction: 133/22961 (0.5%) treatment versus 101/22891 (0.4%) placebo. Stroke: 72/22961 (0.3%) treatment versus 87/22891 (0.4%) placebo. Other: 92/22961 (0.4%) treatment versus 103/22891 (0.4%) placebo. Secondary Reinfarction: Died, any cause: 209/22961 (0.9%) treatment versus 223/22891 (1.0%) placebo, OR of 0.93 (95% CI 0.77 to 1.13, P = 0.46). Survived: 270/22961 (1.2%) treatment versus 330/22891 (1.4%) placebo, OR of 0.81 (95% CI 0.69 to 0.95, P = 0.01). All: 479/22961 (2.1%) treatment versus 553/22891 (2.4%) placebo, OR of 0.86 (95% CI 0.76 to 0.97, P = 0.02). Allocation to clopidogrel produced 14% (95% CI 3-4) proportional reduction in the risk of any reinfarction. Stroke: Ischaemic (or unknown): 164/22961 (0.7%) treatment versus 194/22891 (0.8%) placebo, OR of 0.84 (95% CI 0.68 to 1.03, P = 0.10). Haemorrhagic: 53/22961 (0.2%) treatment versus 56/22891 (0.2%) placebo, OR of 0.98 (95% CI 0.67 to 1.42, P = 0.90). Died, any cause: 90/22961 (0.4%) treatment versus 108/22891 (0.5%) placebo, OR of 0.83 (95% CI 0.63 to 1.10, P = 0.19). Survived: 127/22961 (0.6%) treatment versus 142/22891 (0.6%) placebo, OR of 0.89 (95% CI 0.70 to 1.13, P = 0.33). All: 217/22961 (0.9%) treatment versus 228/22891 (1.0%) placebo, OR of 0.88 (95% CI 0.72 to 1.08, P = 0.30).
250/22891 (1.1%) placebo, OR of 0.86 (95% CI 0.72 to 1.03, P = 0.11). Cardiogenic shock: 983/22961 (4.3%) treatment versus 1043/22891 (4.6%) placebo, OR of 0.94 (95% CI 0.86 to 1.02, P = 0.15). Heart failure: 3033/22961 (13.2%) treatment versus 3093/22891 (13.5%) placebo, OR of 0.97 (95% CI 0.92 to 1.03, P = 0.34). Presumed cardiac rupture: 209/22961 (0.9%) treatment versus 224/22891 (1.0%) placebo, OR of 0.93 (95% CI 0.77 to 1.12, P = 0.45).

Ventricular fibrillation: 624/22961 (2.7%) treatment versus 655/22891 (2.9%) placebo, OR of 0.95 (95% CI 0.85 to 1.06, P = 0.35). Other cardiac arrest: 867/22961 (3.8%) treatment versus 913/22891 (8.1%) placebo, OR of 0.94 (95% CI 0.86 to 1.04, P = 0.24). Pulmonary embolism: 32/22961 (0.1%) treatment versus 33/22891 (0.1%) placebo, OR of 0.97 (95% CI 0.59 to 0.91, P = 0.03). Safety Bleeding: Fatal: 73/22961 (0.32%) treatment versus 74/22891 (0.32%) placebo, excess per 1000 (SE) = -0.1 (0.5), P = 0.35. Cerebral: 39/22961 (0.17%) treatment versus 41/22891 (0.18%) placebo. Non-cerebral: 36/22961 (0.16%) treatment versus 37/22891 (0.16%) placebo. Non-fatal: 61/22961 (0.27%) treatment versus 51/22891 (0.22%) placebo, excess per 1000 (SE) = 0.4 (0.5), P = 0.35. Cerebral: 16/22961 (0.07%) treatment versus 15/22891 (0.07%) placebo. Transfused: 46/22961 (0.20%) treatment versus 36/22891 (0.16%) placebo. Any: 134/22961 (0.58%) treatment versus 125/22891 (0.55%) placebo, excess per 1000 (SE) = 0.4 (0.7), P = 0.59. Additional drug therapy during hospital stay: Non-study antiplatelet therapy: 10% patients Anticoagulation therapy (chiefly heparin): 75%.

Dargie HJ:
Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial.

2001 357  Lancet pg 1385 1390

Study Type: Randomised Controlled Trial

Patient Characteristics
Inclusion criteria Confirmed MI occurring within the previous 21 days, aged > 18 years, mean age 63 years (25-90), male and female (27%), LV ejection fraction ≤ 40% (mean directly by 2D electrocardiography, radionuclide or contrast ventriculography) or indirectly by wall motion score index ≤ 1.3, concurrent treatment with ACE inhibitor for > 48 h with the dose being stable for > 24 h unless proven intolerance of ACE inhibitors. Exclusion criteria Continued requirement for IV inotropic therapy or uncontrolled heart failure, ongoing or expected need for b-blockage, complicating clinical conditions including unstable angina, uncorrected significant valve disease, hypotension < 90 mmHg, bradycardia < 60 bpm., uncontrolled hypertension, unstable IDDM, significant pulmonary, hepatic or renal impairment, ongoing therapy with inhaled beta-2 agonists or steroids, rate-limiting calcium channel blockers, antiarrythmics (except amiodarone), immunosuppressive agents, pregnancy, continuing lactation or planned pregnancy, inability or unwillingness to give informed consent.

Intervention Carvediol Up-titration phase to 25 mg Initial dose 6.25 mg, if tolerated continued on a twice daily basis. If not tolerated, same dose was re-administered 12 h later. If again not tolerated two further attempts to introduce drug were made, but at the lower dose of 3.123 mg. If that dose was not tolerated patients were followed up off study medication. Following successful initial dosing, patient returned to outpatients at 3-10 day intervals for up-titration to target of 25 mg or maximum dose tolerated. Up-titration phase lasted approximately 4 to 6 weeks and dose of ACE inhibitor was not altered. 975 patients

Comparisons Placebo 984 patients

Study Length Mean follow-up 1.3 years. Minimum time 3 months

Outcomes Primary All cause mortality Composite of all cause mortality or cardiovascular-cause hospital admission Secondary Sudden death Hospitalization for heart failure

Funding None listed

Effect Primary All cause mortality Treatment 116/975 (12%) versus placebo 151/984 (15%). Hazard ratio 0.77 (95%CI 0.60 to 0.98), P = 0.031. Composite of all cause mortality or cardiovascular-
cause hospital admission  Treatment 340/975 (35%) versus placebo 367/984 (37%). Hazard ratio 0.92 (95%CI 0.80 to 1.07), P = 0.296. Secondary  Sudden death  Treatment 51/975 (5%) versus placebo 69/984 (7%). Hazard ratio 0.74 (95%CI 0.51 to 1.06), P = 0.098. Hospitalization for heart failure  Treatment 118/975 (12%) versus placebo 138/984 (14%). Hazard ratio 0.86 (95%CI 0.67 to 1.09), P = 0.215. Other  Cardiovascular-cause mortality  Treatment 104/975 (11%) versus placebo 139/984 (14%). Hazard ratio 0.75 (95%CI 0.58 to 0.96), P = 0.024. Death due to heart failure  Treatment 18/975 (2%) versus placebo 30/984 (3%). Hazard ratio 0.60 (95%CI 0.33 to 1.07), P = 0.083. Non-fatal MI  Treatment 34/975 (3%) versus placebo 57/984 (6%). Hazard ratio 0.59 (95%CI 0.39 to 0.90), P = 0.014. All cause mortality or non-fatal MI  Treatment 139/975 (14%) versus placebo 192/984 (20%). Hazard ratio 0.71 (95%CI 0.57 to 0.89), P = 0.002.

Reference number 3755

Freemantle N;Cleland J;Young P;Mason J;Harrison J;  
Beta-blockade after myocardial infarction: systematic review and meta regression analysis

1999 318 BMJ  pg 1730 1737

Study Type: Systematic Review  
Patient Characteristics  
Post MI patients Acute phase, long term therapy  
Intervention  
β blockers  
Comparisons  
placebo  
Study Length  
Short term trials: up to 6 weeks after onset of pain (51 RCTs)  
Long term trials: 6 weeks to 48 months (31 RCTs)  
Outcomes  
Mortality  
Reinfarction  
Funding  
Not listed  
Effect  
Short term trials: Overall 3062/29260 died (10.1%). Of the 51 RCTs identified, only 45 observed deaths in either in treatment or placebo groups. The quality of group of trials may be influenced by the small numbers of patients recruited in some of the trials and also the small numbers of deaths. Pooled random effects odds ratio: 0.96 (95%CI 0.85 to 1.08), a 4% reduction in odds of death. Equates to an annual reduction of 0.4 deaths in 100 patients for treatment up to six weeks, not significant (-0.2 to 10). 50 patients would require treatment to avoid one death (100 to ∞). Long term trials: Overall 2415/24975 died (9.7%) in 31 trials. Pooled random effects odds ratio: 0.77 (0.69 to 0.85), a 23% reduction in odds of death. Equates to an annual reduction of 1.2 deaths in 100 patients (0.6 to 1.7). 84 patients would require treatment to avoid one death. 
For reinfarction (22 trials): annual reduction in reinfarction of 0.9 events in every 100 (0.3 to 1.6), 107 patients would need to be treated to avoid one non-fatal infarction. 
Predictors of benefit: initial intravenous dose of β blocker on mortality in long term trials Applying covariate term in the analysis suggested no additional benefit among patients treated in this manner, odds ratio 0.87 (95%CI 0.61 to 1.22). Equally this analysis indicated that there is no reason to delay treatment with a β blocker. Early initiation will lead to a greater period when benefits may be accrued from treatment. 
Choice of drug 
Individually, only four drugs achieved a reduction in the odds of death: Propranolol: OR 0.71 (95%CI 0.59 to 0.85). Timolol: OR 0.59 (95%CI 0.46 to 0.77). Metoprolol: OR 0.80 (95%CI 0.66 to 0.96). Acebutolol: OR 0.49 (95%CI 0.25 to 0.93). Acebutolol is supported by a single moderately sized study (open to considerable measurement error). RCTs including propranolol, timolol and metoprol include 63% of the available evidence on the long term effect of β blockade in post MI patients. Other β blockers that did not show a reduction in odds of death: Atenolol, Labetalol, Oxprenolol, Pindolol, Practolol.

Reference number 3783

Ko DT;Hebert PR;Coffey CS;Sedrakyan A;Curtis JP;Krumholz HM;  
Myocardial infarction: full guideline DRAFT (August 2006) – Appendices  Page 121 of 248
### Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction

**Study Type:** Systematic Review  
**Patient** Post MI patients, RCTs that enrolled ≥ 100 patients and ≥ 6 months of follow-up.  
**Characteristics**  
**Intervention** β blockers  
**Comparisons** placebo  
**Study Length** Follow-up range: 6 to 59 months  
**Outcomes**  
- Adverse effects: Fatigue: 10 trials, 17,682 patients  
- Sexual dysfunction: 6 trials, 14,897 patients  
- Depressive symptoms: 7 studies, 10,662 patients  

**Funding** Not stated

**Effect**  
- **Fatigue:** Weighted event rates: β blockers 34% versus placebo 30%. RRI (95%CI) = 15% (2 to 26). Withdrawal because of fatigue: β blockers 1.8% versus placebo 0.5%. RRI (95%CI) = 163% (16 to 494).  
- **Sexual dysfunction:** Weighted event rates: β blockers 19% versus placebo 17%. RRI (95%CI) = 10% (-4 to 25), not significant. Withdrawal because of sexual dysfunction: β blockers 1.2% versus placebo 0.3%. RRI (95%CI) = 397% (203 to 716).  
- **Depressive symptoms:** Withdrawal because of depressive symptoms: β blockers 21.7% versus placebo 20.5%. RRI (95%CI) = 12% (-11 to 41), not significant.
**Question:** What is the effectiveness of adding vitamin K antagonist (warfarin) versus placebo to improve outcome in patients after an MI?

**Grading:** 1++ *High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias*

**Reference number** 3746

Anand SS; Yusuf S; Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis

<table>
<thead>
<tr>
<th>Year</th>
<th>Journal</th>
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<tr>
<td>1999</td>
<td>JAMA</td>
<td>2058  2067</td>
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<tr>
<th>Study Type:</th>
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<tr>
<td>Patient Characteristics</td>
<td>Established coronary artery disease, MI, unstable angina, CABG surgery</td>
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<tr>
<td>Intervention</td>
<td>Warfarin, set to a prothrombin time within range of 2.8 to 4.8 International Normalised Ratio (INR) 607 patients Both treatment and control groups advised not to take aspirin</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Placebo 607 patients</td>
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</table>

At least 3 months

Medical Res. Council Canada

For studies that compared high intensity anticoagulant therapy (INR > 2.8) versus control, at total of 5044 patients received anticoagulants and 5012 were randomised to placebo or controls: Odds Reduction for anticoagulants versus control for total mortality = 22% (95%CI 13% to 31%, P < 0.001)  Odds Reduction for anticoagulants versus control for fatal or non fatal MI = 42% (95%CI 34% to 48%, P < 0.001) Odds Reduction for anticoagulants versus control for stroke = 48% (95%CI 33% to 60%, P < 0.001) Major bleeding: relative increase with anticoagulants versus control OR = 6.0 (95%CI 4.4 to 8.2, P < 0.001).  For studies that compared moderate intensity anticoagulant therapy (INR > 2-3) versus control, at total of 1365 patients received anticoagulants: Odds Reduction for anticoagulants versus control for total mortality = 18% (95%CI -6% to 31%, P < 0.10).  Odds Reduction for anticoagulants versus control for fatal or non-fatal MI = 52% (95%CI 37% to 64%, P < 0.001) Odds Reduction for anticoagulants versus control for stroke = 53% (95%CI 19% to 73%, P = 0.02) Major bleeding: relative increase with anticoagulants versus control OR = 7.0 (95%CI 3.3 to 18, P < 0.001).

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

**Reference number** 264

Smith P; Long-term anticoagulant treatment after acute myocardial infarction. The Warfarin Re-Infarction Study

<table>
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<th>Year</th>
<th>Journal</th>
<th>Pages</th>
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<tr>
<td>1992</td>
<td>Annals of Epidemiology</td>
<td>549  552</td>
</tr>
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</table>

**Study Type:** Randomised Controlled Trial

**Patient Characteristics:** acute MI < 75 years, stratified for chronic beta blocker usage

**Exclusion criteria:** none listed

**Intervention:** Warfarin, set to a prothrombin time within range of 2.8 to 4.8 International Normalised Ratio (INR) 607 patients Both treatment and control groups advised not to take aspirin

**Comparisons:** Placebo 607 patients

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices
### Study Length
Mean follow-up 37 months

### Outcomes
- **Primary**: Mortality, reinfarction
- **Secondary**: Stroke, bleeding time

### Funding
Not listed

### Effect
Intention to treat analysis:
- **Mortality**: 94/607 treatment deaths (15%) versus 123/607 placebo deaths RR of 24% (95% CI -4% to -44%, P = 0.0267)
- **Reinfarction**: treatment 86/607 versus placebo 124/607 RR of 34% (95% CI 4% to -54%, P = 0.0007)
- **Stroke**: treatment 19/607 versus placebo 44/607 RR of 55% (95% CI 30% to 30 to -77%, P = 0.0015)
- **Bleeding**: major extracranial bleeding occurred in 8/607 treatment group (1.3% treatment versus 0% placebo, P = 0.005), 7/607 bleeding was associated with peptic ulcer, cancer or nonprotocol intake of antiplatelet drugs.

### Funding
- Ciba-Geigy V, Roche BV, Nycomed BV, Praeven-tiefonds NL, NL Thromb-osis Found.

### Effect
- **Mortality**: 170/1700 treatment deaths (10.0%) versus 189/1704 placebo deaths (11.1%) HR of 0.90 (95% CI 0.73 to 1.11, not significant)
- **Reinfarction**: treatment versus placebo: 114/1700 (6.7%) versus 242/1704 (14.2%) patients, HR of 0.47 (95% CI 0.38 to 0.59)
- **Cerebrovascular event**: treatment versus placebo: 37/1700 (2.2%) versus 62/1704 (3.6%) patients, HR of 0.60 (95% CI 0.40 to 0.90)
- **Vascular event**: treatment versus placebo: 82/1700 (4.8%) versus 135/1704 (7.9%) patients, HR of 0.65 (95% CI 0.55 to 0.76)
- **Major bleeding**: treatment versus placebo: 24/1700 (1.4%) versus 7/1704 (0.4%) patients, HR of 3.87 (95% CI 2.33 to 6.41).

### Reference number
1277

Van Bergen PFMM; Jonker JJC; Van der Meer FJM; Azar AJ; Meeter K; Deckers JW; Tijssen JGP; Van Aken WG; Dunning AJ; Hofman A; Hugenholtz PG; Van der Kooij S; Loeliger EA; Lubsen J; Meade TW; van der Meer J; Miettinen OS; Mitchell JRA; et a;

Effect of long-term oral anticoagulant treatment on mortality and cardiovascular after myocardial infarction

1994 343 Lancet pgs 499 503

**Study Type:** Randomised Controlled Trial

**Patient Characteristics**
- Hospital survivors of MI within 6 weeks after hospital discharge, cardiac enzyme rises at least twice the normal upper limit, male and female (20%), mean age 61 years
- Exclusion criteria: indication for oral anticoagulant treatm

**Intervention**
- Nicoumalone or phenpro-coumon decisionmade at discretion of cardiologist before randomization
- 1700 patients
- Prothrombin time in target range of 2.8-4.8 INR
- Treatment and placebo group did not take aspirin

**Comparisons**
- Placebo 1704 patients

**Study Length**
Mean follow-up 37 months (range 6-76 months)

**Outcomes**
- **Primary**: All cause mortality
- **Secondary**: Recurrent MI, cerebro-vascular event, vascular event, major bleeding
Question: What is the effectiveness of adding vitamin K antagonist (warfarin) versus aspirin to improve outcome in patients after an MI?

Grading: 1++  

*High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias*

**Reference number** 3746

Anand SS; Yusuf S; Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis

1999 282 JAMA pgs 2058 2067

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<td>Study Length:</td>
<td>At least 3 months</td>
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<td>Outcomes:</td>
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<td>Funding:</td>
<td>Medical Res. Council Canada</td>
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<td>Effect:</td>
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For studies that compared high intensity anticoagulant therapy (INR > 2.8) versus control, at total of 5044 patients received anticoagulants and 5012 were randomised to placebo or controls: Odds Reduction for anticoagulants versus control for total mortality = 22% (95%CI 13% to 31%, P < 0.001) Odds Reduction for anticoagulants versus control for fatal or non-fatal MI = 42% (95%CI 34% to 48%, P < 0.001) Odds Reduction for anticoagulants versus control for stroke = 48% (95%CI 33% to 60%, P < 0.001) Major bleeding: relative increase with anticoagulants versus control OR = 6.0 (95%CI 4.4 to 8.2, P < 0.001) For studies that compared moderate intensity anticoagulant therapy (INR > 2-3) versus control, at total of 1365 patients received anticoagulants: Odds Reduction for anticoagulants versus control for total mortality = 18% (95%CI -6% to 31%, P < 0.10) Odds Reduction for anticoagulants versus control for fatal or non-fatal MI = 52% (95%CI 37% to 64%, P < 0.001) Odds Reduction for anticoagulants versus control for stroke = 53% (95%CI 19% to 73%, P = 0.02) Major bleeding: relative increase with anticoagulants versus control OR = 7.0 (95%CI 3.3 to 18, P < 0.001) For studies that compared high / moderate intensity anticoagulant therapy versus aspirin, a total of 1431 patients received anticoagulants and 1440 were randomised to placebo or controls. Anticoagulation treatment: no reduction in the combination of death, fatal or non-fatal MI or stroke compared with aspirin Major bleeding: increased 2.37 times with anticoagulants versus aspirin (95%CI 1.6 to 3.6, P < 0.001).

Grading: 1+  

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

**Reference number** 3749

van Es RF; Jonker JJ; Verheugt FW; Deckers JW; Grobbee DE; Antithrombotics; Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial.

2002 360 Lancet pgs 109 113

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Randomised Controlled Trial</th>
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<tbody>
<tr>
<td>Patient Characteristics:</td>
<td>Inclusion criteria: acute MI (88%) or unstable angina within preceding 8 weeks, mean age 61 years, male and women (23%) Exclusion criteria: planned revascularization, recent intracoronary stenting, thrombocytopenia, anaemia, history of stroke, established indications for treatment with oral anticoagulants, contraindications for the study drugs, serious comorbidity, increased risk of bleeding, inability to adhere to protocol or give written consent</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Oral anti-coagulants (phenprocoumon or acenocoumon with a target INR of 3.0 to 4.0)</td>
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</table>

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 125 of 248
patients Oral anti-coagulants (phenprocoumon or acenocoumon with a target INR of 2.0 to 2.5 plus aspirin 100 mg daily  332 patients

Aspirin 100 mg daily  336 patients

Mean follow-up ≤ 26 months

Comparisons

Composite of death, nonfatal MI or stroke

Primary

- Coumadin 17/325 (5%) versus aspirin 31/336 (9%), HR = 0.55 (95%CI 0.3 to 1.00)
- Coumadin plus aspirin 16/332 (5%) versus aspirin 31/336 (9%), HR = 0.50 (95%CI 0.27 to 0.92)

Secondary

- Coumadin 4/325 (1%) versus aspirin 15/336 (4%), HR = 0.28 (95%CI 0.09 to 0.82)
- Coumadin plus aspirin 9/332 (3%) versus aspirin 15/336 (4%), HR = 0.60 (95%CI 0.26 to 1.36)

All-cause mortality

Primary

- Coumadin 17/325 (5%) versus aspirin 28/336 (8%), HR = 0.61 (95%CI 0.33 to 1.12)
- Coumadin plus aspirin 15/325 (5%) versus aspirin 28/336 (8%), HR = 0.52 (95%CI 0.28 to 0.98)

Secondary

- Coumadin 4/325 (1%) versus aspirin 12/336 (4%), HR = 0.34 (95%CI 0.11 to 1.06)
- Coumadin plus aspirin 15/325 (5%) versus aspirin 12/336 (4%), HR = 0.66 (95%CI 0.27 to 1.62)

Vascular death

Primary

- Coumadin 17/325 (5%) versus aspirin 28/336 (8%), HR = 0.61 (95%CI 0.33 to 1.12)
- Coumadin plus aspirin 15/325 (5%) versus aspirin 28/336 (8%), HR = 0.52 (95%CI 0.28 to 0.98)

Secondary

- Coumadin 4/325 (1%) versus aspirin 12/336 (4%), HR = 0.34 (95%CI 0.11 to 1.06)
- Coumadin plus aspirin 15/325 (5%) versus aspirin 12/336 (4%), HR = 0.66 (95%CI 0.27 to 1.62)

Myocardial infarction

Primary

- Coumadin 13/325 (4%) versus aspirin 14/336 (4%), HR = 0.94 (95%CI 0.44 to 2.00)
- Coumadin plus aspirin 10/325 (3%) versus aspirin 14/336 (4%), HR = 0.70 (95%CI 0.31 to 1.58)

Secondary

- Coumadin 34/325 (10%) versus aspirin 39/336 (14%), HR = 0.90 (95%CI 0.58 to 1.39)
- Coumadin plus aspirin 32/325 (10%) versus aspirin 39/336 (14%), HR = 0.83 (95%CI 0.53 to 1.29)

Revascularization (CABG/PTCA)

Primary

- Coumadin 0/325 versus aspirin 1/336 (0.3%), HR = 1.03 (95%CI 0.21 to 5.08)
- Coumadin plus aspirin 7/332 (2%) versus aspirin 3/336 (1%), HR = 2.35 (95%CI 0.61 to 9.10)

Secondary

- Coumadin 26/325 (8%) versus aspirin 16/336 (5%), HR = 1.68 (95%CI 0.92 to 3.07)
- Coumadin plus aspirin 50/332 (15%) versus aspirin 16/336 (5%), HR = 3.13 (95%CI 1.82 to 5.37).
Question: What is the effectiveness of adding vitamin K antagonist (warfarin) plus aspirin versus aspirin to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number 3842

Chen ZM; Pan HC; Chen YP; Peto R; Collins R;
Early intravenous then oral metoprolol 45852 patients with acute myocardial infarction: randomised placebo-controlled trial

2005 366

Study Type: Randomised Controlled Trial

Patient Characteristics

Inclusion criteria: Post MI recruited within 24 h of suspected acute MI onset (ST elevation (87%), left bundle block (6%), or ST depression (7%)). Mean age ± SD = 61 ± 11 years, male and female (28%). Patients with hypertension: 8%. Exclusion criteria

Intervention

Immediately: 5 mg metoprolol iv over 2-3 min, if heart rate was above 50 bpm and systolic blood pressure above 90 mmHg, then second 5 mg metoprolol iv administered, and similarly for the third ampule. 15 min after these iv doses, 50 mg metoprolol tablet. Subsequently: 200 mg metoprolol slow release once daily for up to 4 weeks (or, if earlier, until hospital discharge or death) 22 929 patients

Comparisons

Immediately: placebo iv over 2-3 min, then second and third iv. 15 min after these iv doses, placebo tablet. Subsequently: placebo once daily for up to 4 weeks (or, if earlier, until hospital discharge or death) 22 923 patients

Study Length

Up to 4 weeks

Outcomes

Primary Composite of death, reinfarction, or stroke. Death from any cause. Secondary Reinfarction Ventricular fibrillation Cardiogenic shock Other cardiac arrest

Funding

Sanofi-Aventis, Bristol-Myers Squibb, Astra-Zeneca, MRC UK, BHF, Cancer Research UK.

Effect

Primary Composite of death, reinfarction, or stroke: 2166/22929 (9.4%) treatment versus 2261/22923 (9.9%) placebo, OR of 0.96 (95% CI 0.90 to 1.01, P = 0.10). Death from any cause: 1774/22929 (7.7%) treatment versus 1797/22923 (7.8%) placebo, OR of 0.99 (95% CI 0.92 to 1.05, P = 0.69). Arrhythmia: 388/22929 (1.7%) treatment versus 498/22923 (2.2%) placebo, OR of 0.78 (95% CI 0.68 to 0.89, P = 0.0002). Shock: 496/22929 (2.0%) treatment versus 384/22923 (1.7%) placebo, OR of 1.29 (95% CI 1.13 to 1.47, P = 0.0002). Neither:

890/22929 (3.9%) treatment versus 915/22923 (4.0%) placebo, OR of 0.97 (95% CI 0.89 to 1.07, P = 0.55). Secondary Reinfarction: Died, any cause: 206/22929 (0.9%) treatment versus 226/22923 (1.0%) placebo, OR of 0.91 (95% CI 0.75 to 1.10, P = 0.33). Survived: 258/22929 (1.1%) treatment versus 298/22923 (1.4%) placebo, OR of 0.75 (95% CI 0.64 to 0.88, P = 0.0005). Any: 464/22929 (2.0%) treatment versus 568/22923 (2.5%) placebo, OR of 0.82 (95% CI 0.72 to 0.89, P = 0.001). Ventricular fibrillation: Died, any cause: 492/22929 (2.1%) treatment versus 600/22923 (2.6%) placebo, OR of 0.82 (95% CI 0.73 to 0.92, P = 0.001). Survived: 89/22929 (0.4%) treatment versus 98/22923 (0.4%) placebo, OR of 0.91 (95% CI 0.68 to 1.12, P = 0.51). Any: 581/22929 (2.6%) treatment versus 698/22923 (3.0%) placebo, OR of 0.83 (95% CI 0.75 to 0.93, P = 0.001). Cardiogenic shock: Died, any cause: 755/22929 (3.3%) treatment versus 628/22923 (2.7%) placebo, OR of 1.20 (95% CI 1.08 to 1.34, P = 0.0006). Survived: 386/22929 (1.7%) treatment versus 257/22923 (1.1%) placebo, OR of 1.50 (95% CI 1.28 to 1.75, P < 0.0001). Any: 1141/22929 (5.0%) treatment versus 885/22923 (3.9%) placebo, OR of 1.30 (95% CI 1.19 to 1.41, P < 0.0001). Other cardiac arrest: Died, any cause: 624/22929 (2.7%) treatment versus 593/22923 (2.6%) placebo, OR of 1.05 (95% CI 0.94 to 1.18, P = 0.38). Survived: 61/22929 (0.3%) treatment versus 39/22923 (0.2%) placebo, OR of 1.55 (95% CI 0.1.05 to 2.30, P = 0.03). Any: 685/22929 (3.0%) treatment versus 632/22923 (2.8%) placebo, OR of 0.83 (95% CI 0.97 to 1.28, P = 0.11). Safety Bradycardia: treatment

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 127 of 248
5.4% versus placebo 2.2%, OR = 2.41 (95% CI 2.19 to 2.65, P = 0.0001).

Grading: 1+  

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

Reference number 3728

CarsADD REFERENCE

Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study (CARS) Investigators.

1997 350 Lancet  pgs 389 396

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Randomised Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
<td>Inclusion criteria: 3-21 days post MI, men and women (approx 22%), aged 21 to 85 years, mean age 59 years  Exclusion criteria: CHF, circulatory shock, unresponsive angina, serious ventricular arrhythmias 24 h before randomization, history bleeding, stroke, previous intracranial haemorrhage, co morbidity with life expectancy &lt; 4 years, liver disease, renal disease, anaemia, thrombocytopenia, haematuria, uncontrolled hypertension, scheduled CABG, patients requiring long term warfarin therapy for thromboembolism</td>
</tr>
<tr>
<td>Intervention</td>
<td>Warfarin 3 mg plus aspirin 80 mg 3382 patients  Warfarin 1 mg plus aspirin 80 mg 2028 patients  Aspirin 160 mg 3393 patients</td>
</tr>
<tr>
<td>Comparisons</td>
<td></td>
</tr>
<tr>
<td>Study Length</td>
<td>Median follow-up 14 months, max. 33 months</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary Composite of reinfarction, nonfatal ischemic stroke or CV death  Secondary All cause mortality, non fatal MI, ischemic stroke, CV death, spontaneous major haemorrhage</td>
</tr>
<tr>
<td>Funding</td>
<td>Du Pont Merck Pharm. Co.</td>
</tr>
<tr>
<td>Effect</td>
<td>Primary endpoint: Aspirin 308/3393 versus 3 mg warfarin plus aspirin 295/3382  RR = 0.95 (95% CI 0.81 to 1.12, P = 0.57)  At 6 months median (IQR) INR = 1.02 (0.98-1.06) for aspirin and INR = 1.19 (1.08-1.44) for 3 mg warfarin plus aspirin  Aspirin 308/3393 versus 1 mg warfarin plus aspirin 237/2028  RR = 1.03 (95% CI 0.87 to 1.11, P = 0.74)  At 6 months median (IQR) INR = 1.04 (1.00-1.09) for 1 mg warfarin plus aspirin  Secondary endpoints: no significant difference in 3 treatment group except: Spontaneous major haemorrhage: Aspirin 30/3393 versus 3 mg warfarin plus aspirin 52/3382  l year life estimates 0.74% (95% CI 0.43 to 1.11) versus 3 mg warfarin plus aspirin 1.4% (95% CI 0.94 to 1.8, P = 0.014 log rank on follow-up) 1 mg warfarin plus aspirin 26/2028, not significant compared with aspirin group.</td>
</tr>
</tbody>
</table>

Reference number 3727

Fiore LD; Ezekowitz MD; Brophy MT; Lu D; Sacco J; Peduzzi P; Combination H; Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study.

2002 105 Circulation  pgs 557 563

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Randomised Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
<td>Inclusion criteria: post MI within previous 14 days, male and female (2%), mean age 64 years  Exclusion criteria: comorbidity giving reduced life expectancy, 2 years, ongoing bleeding / bleeding risk, entered into competing trial, refusal to compete, incompetent to give consent, died prior to randomization, alcohol / drug dependency, hypersensitivity to aspirin / warfarin,</td>
</tr>
<tr>
<td>Intervention</td>
<td>Aspirin 81 mg daily plus warfarin INR 1.5 to 2.5 IU  2522 patients  Aspirin 162 mg daily  2537 patients</td>
</tr>
<tr>
<td>Comparisons</td>
<td></td>
</tr>
<tr>
<td>Study Length</td>
<td>Median follow-up 2.7 years</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary All-cause mortality  Secondary Recurrent MI, stroke, major haemorrhage</td>
</tr>
</tbody>
</table>

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices  Page 128 of 248
Effect
Median INR for warfarin + aspirin group was 1.8 IU (1.4 IU to 2.2 IU). All cause mortality, recurrent MI, stroke: no difference between two treatments. Major bleeding occurred more frequently in warfarin + aspirin group compared with aspirin group (RR 1.78 95% CI 1.27 to 2.72, P < 0.001).

Reference number 3729
Hurlen M; Abdelnoor M; Smith P; Erikssen J; Arnesen H; Warfarin, aspirin, or both after myocardial infarction.

Study Type: Randomised Controlled Trial

Patient Characteristics

Inclusion criteria: hospitalized for acute MI, < 75 years, mean age 60 years, male and female (approx. 26%) Exclusion criteria: History of serious spontaneous bleeding on any of study drugs, hemorrhagic diathesis, any other contraindications to th

Intervention
Warfarin with a target INR 2.8 to 4.2 1218 patients Warfarin with a target INR 2.0 to 2.5 plus aspirin 75 mg daily 1208 patients

Comparison
Aspirin 160 mg daily 1206 patients

Study Length
Mean follow-up 1445 days (about 4 years)

Outcomes
Primary Composite of death, nonfatal MI or thrombo-embolic stroke Secondary death, nonfatal MI, thrombo-embolic stroke, bleeding

Funding
Norwegian Council on CV Disease

Effect
Composite of death, nonfatal MI or thrombo-embolic stroke: Both warfarin groups (warfarin alone 16.7%, warfarin + aspirin 15.0%) lower rates of the first composite event compared with aspirin alone group 20%: aspirin 241/1206 (20.0%) warfarin 203/1216 (16.0%) warfarin + aspirin 81/1208 (15.0%) RR warfarin + aspirin (15%) versus aspirin (20%) = 0.71 (95%CI 0.60 to 0.83, P = 0.001) RR warfarin (16.7%) versus aspirin (20%) = 0.81 (95%CI 0.69 to 0.95, P = 0.03) RR warfarin plus aspirin (15%) versus warfarin (16.7%) = 0.87 (95%CI 0.73 to 1.03, P = 0.18) For total cumulative events (death, nonfatal MI or thromboembolic stroke): aspirin 295/1206 (24.5%) warfarin 236/1216 (19.4%) warfarin + aspirin 210/1208 (17.4%) RR warfarin + aspirin versus aspirin = 0.65 (95%CI 0.53 to 0.80, P < 0.001) RR warfarin versus aspirin = 0.75 (95%CI 0.61 to 0.91, P = 0.003) RR warfarin plus aspirin versus warfarin = 0.87 (95%CI 0.71 to 1.08, P = 0.20) Reinfarction: aspirin 117/1206 (9.7%) warfarin 90/1216 (7.4%) RR warfarin + aspirin 69/1208 (5.7%) RR warfarin + aspirin versus aspirin = 0.56 (95%CI 0.41 to 0.78, P < 0.001) RR warfarin versus aspirin = 0.74 (95%CI 0.55 to 0.98, P = 0.03). Thromboembolic stroke: aspirin 32/1206 (2.7%) warfarin 17/1216 (1.4%) warfarin + aspirin 17/1208 (1.4%) RR warfarin + aspirin versus aspirin = 0.52 (95%CI 0.28 to 0.98, P = 0.03) RR warfarin versus aspirin = 0.52 (95%CI 0.28 to 0.97, P = 0.03). Death: aspirin 92/1206 (24.5%) warfarin 96/1216 (19.4%) warfarin + aspirin 95/1208 (17.4%) The three groups did not differ for overall mortality Bleeding: Both warfarin groups had higher rates for nonfatal bleeding compared with aspirin alone group Warfarin + aspirin 2% versus aspirin 0.7% Warfarin 3% versus aspirin 0.7% Episodes of major, nonfatal bleeding were observed in 0.62% of patients per treatment year in both groups receiving warfarin compared with 0.17% patients receiving aspirin (P < 0.001).
**Question:** What is the effectiveness of adding calcium channel blocker versus placebo to improve outcome in...

**Grading:** 1++ **High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias**

Reference number 1290

National Institute for Clinical Excellence;
A Prophylaxis for patients who have experienced a myocardial infarction

2001 National Institute for Clinical Excellence

**Study Type:** Guideline

**Patient Characteristics**

Intervention: Calcium channel blockers

Comparisons: Mortality Non-fatal MI

**Study Length**

Outcomes: NHS

Mortality: treatment versus placebo OR of 0.99 (95% CI 0.89 to 1.10 not significant) fixed effects. OR of 0.99 (95% CI 0.87 to 1.12 not significant) random effects. Non-fatal MI: treatment versus placebo OR of 0.80 (95% CI 0.70 to 0.92) fixed effects. OR of 0.81 (95% CI 0.69 to 0.96) random effects. 1000 patients treated for 1 year, 10 non-fatal MIs avoided (95% CI 2 to 19).

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

Reference number 57

Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II--DAVIT II)

1990 66 American Journal of Cardiology

**Study Type:** Randomised Controlled Trial

**Patient Characteristics**

Inclusion criteria: Post MI patients recruited during hospitalization from day 7 to 15 after admission Aged under 75 years. Male and female (20%).

Exclusion criteria: Heart failure, systolic blood pressure below 90 mmHg, second a

**Intervention**

Verapamil 120 mg three times daily 878 patients

**Comparisons**

Placebo 897 patients

**Study Length**

18 months

**Outcomes**

Total mortality First major event (first reinfarction or death) Cardiac death Sudden death

First reinfarction First cardiac event (first reinfarction or cardiac death)

Funding

Knoll, Germany

**Effect**

Total mortality: 95/878(11.1%) treatment versus 119/897 (13.8%) placebo, HR of 0.80 (95% CI 0.61 to 1.05, P = 0.11). First major event (first reinfarction or death): 146/878(18.0%) treatment versus 180/897 (21.6%) placebo, HR of 0.80 (95% CI 0.66 to 0.99, P = 0.03).

Cardiac death: 84/878(9.9%) treatment versus 107/897 (12.3%) placebo, HR of 0.79 (95% CI 0.59 to 1.05, P = 0.10). Sudden death: 46/878(5.6%) treatment versus 63/897 (7.4%) placebo, HR of 0.74 (95% CI 0.50 to 1.07, P = 0.10). First reinfarction: 84/878(11.0%) treatment versus 107/897 (13.2%) placebo, HR of 0.77 (95% CI 0.58 to 1.03, P = 0.04). First cardiac event (first reinfarction or cardiac death): 137/878(17.0%) treatment versus 170/897 (20.2%) placebo, HR of 0.80 (95% CI 0.64 to 1.00, P = 0.03). Patients without heart failure had a significantly better prognosis than patients with heart failure (Table 2, Figure 3, Appendix). Treatment with verapamil did not confer any benefit on patients with heart failure compared with placebo. Thus the overall benefit of verapamil was found in patients without Myocardial infarction: full guideline DRAFT (August 2006) -- Appendices Page 130 of 248
Reference number 3832

Pitt B; Byington RP; Furberg CD; Hunninghake DB; Mancini GB; Miller ME; Riley W; Investigators
Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Randomised Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
<td>Inclusion criteria: Men and women (20%), 30-80 years mean age 57 years, with angiographic evidence of CAD, angiographic evidence of 1 focal coronary lesion ≤30% diameter stenosis and the presence of ≥1 lesion with 5% to 20% stenosis that was not in a vessel with a ≤60% lesion. Diastolic BP &lt;95 mmHg, total cholesterol &lt;325 mg/dl, fasting blood glucose of &lt;200 mg/dl. Patient population Post MI: 45%Stroke 3%Angina 68%</td>
</tr>
<tr>
<td>Intervention</td>
<td>Amlodipine 5 mg QD, after 2 weeks increased to 10 mg if tolerated 417 patients</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Placebo 408 patients</td>
</tr>
<tr>
<td>Study Length</td>
<td>36 months</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary Reduction in the progression of early athlero-sclerotic segments as measured by change in mean minimal diameter with quantitative coronary angiography Secondary Reduction in progression of athlero-sclerosis as assessed with B-mode ultrasono-grappy. Progression based on mean of 3 year regression slopes of the maximum IMT measurements estimated in each of the separate wall segments All-cause mortality, reinfarction, stroke, congestive heart failure, unstable angina, CABG, other major procedure (angioplasty, stenting, Pfizer</td>
</tr>
<tr>
<td>Funding</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Effect</td>
<td>Primary outcome: Mean 3 year change in minimum diameter in segments of ≤30% stenosis Amlodipine and placebo had nearly identical average reductions in minimal diameter: 0.95 mm versus 0.84 mm, respectively (P = 0.38) Secondary outcomes: Progression of carotid athlero-sclerosis Amlodipine reduced progression: placebo group 0.033 mm increase in IMT versus amlodipine 0.013 mm increase (P &lt; 0.007) Mortality: 6/417 treatment versus 8/408 placebo, HR of 0.74 (95% CI 0.28 to 2.12, not significant) Reinfarction: 19/417 treatment versus 20/408 placebo, HR of 0.94 (95% CI 0.50 to 1.76, not significant) Stroke: 5/417 treatment versus 5/408 placebo, HR of 0.74 (95% CI 0.28 to 2.12, not significant) Congestive heart failure: 1/417 treatment versus 5/408 placebo, HR of 0.20 (95% CI 0.02 to 1.67, not significant) Unstable angina: 60/417 treatment versus 85/408 placebo, HR of 0.67 (95% CI 0.48 to 0.93) CABG: 17/417 treatment versus 29/408 placebo, HR of 0.57 (95% CI 0.31 to 1.03 not significant) Other major procedures: 40/417 treatment versus 67/408 placebo HR of 0.56 (95% CI 0.38 to 0.83).</td>
</tr>
</tbody>
</table>
Question: What is the effectiveness of adding potassium channel activators versus placebo to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number: 3817

IONA Study Group; Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial

2002 pgs 1269 1275

Study Type: Randomised Controlled Trial

Patient Characteristics
History of clearly established coronary artery disease (either had MI, previous CABG or CHD by angiography) or positive exercise test with additional risk factors (see methodology in the paper).

Men older than 45 years and woman older than 55 years, mean age 67 years

Previous MI: 66% Previous CABG: 23% Previous PTCA: 15% Previous angigram: 60% Previous stroke: 5% History of PVD: 12% History of LVD: 9% Diabetes: 9% Hypertension: 47% Current smokers: 17% Hospital admission for transient ischaemic attack: 2%

Intervention Comparison
Nicorandil 10 mg twice daily thereafter 20 mg twice daily 2565 patients

Placebo 2561 placebo

Study Length Mean follow-up 1.6 years

Outcomes
Primary Composite of coronary heart disease death, non-fatal MI, or unplanned hospital admission for cardiac chest pain
Secondary Coronary heart disease death or non-fatal MI
Others Acute coronary syndromes, all CV events (CV mortality, non-fatal MI

Funding Merck Pharm, Aventis Pharma, Chugai Pharm. Co

Effect
Primary Composite of coronary heart disease death, non-fatal MI, or unplanned hospital admission for cardiac chest pain: nicorandil 337/2565 (13.1%) versus placebo 398/2561 (15.5%), HR of 0.83 (95% CI 0.72 to 0.97), P = 0.014

Secondary Coronary heart disease death or non-fatal MI: nicorandil 107/2565 (4.2%) versus placebo 134/2561 (5.2%), HR of 0.79 (95% CI 0.61 to 1.02), P = 0.068

Others Coronary heart disease death: nicorandil 60/2565 (2.3%) versus placebo 73/2561 (2.9%) Non fatal MI: nicorandil 56/2565 (2.1%) versus placebo 72/2561 (2.8%)

Unstable angina: nicorandil 56/2565 (2.1%) versus placebo 73/2561 (2.9%)

Definite angina: nicorandil 115/2565 (4.5%) versus placebo 127/2561 (5.0%)

Presumed angina: nicorandil 128/2565 (4.0%) versus placebo 153/2561 (6.0%)

Stroke or hospital admission for transient ischaemic stroke: nicorandil 37/2565 (1.4%) versus placebo 40/2561 (1.6%)

Coronary heart disease death or non-fatal MI or unstable angina: nicorandil 156/2565 (6.1%) versus placebo 195/2561 (7.6%), HR of 0.79 (95% CI 0.64 to 0.98), P = 0.028

All CV events: nicorandil 378/2565 (14.7%) versus placebo 436/2561 (17.0%), HR of 0.86 (95% CI 0.86 to 0.98), P = 0.027

All-cause mortality: nicorandil 111/2565 (4.3%) versus placebo 129/2561 (5.0%), HR of 0.85 (95% CI 0.66 to 1.10), P = 0.222.
Question: What is the effectiveness of adding eplerenone versus placebo to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number: 3804
Pitt B; Remme W; Zannad F; Neaton J; Martinez F; Roniker B; Bittman R; Hurley S; Kleiman J; Gatlin M; Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial
2003 348 New England Journal of Medicine pgs 1309 1321
Apr 3

Study Type: Randomised Controlled Trial

Inclusion criteria: Post MI with LV dysfunction and heart failure. LV dysfunction documented as LV ejection fraction ≤ 40% on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute MI, mean ejection fraction; 33%. Heart failure as documented by the presence of pulmonary rates, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound (90%). Diabetic Patients: Documented LV dysfunction, however, symptoms did not have to be demonstrated, since diabetics have increased risk of CV events similar to non-diabetic patients with symptoms of heart failure (32%). Patients with hypertension: 61%. Mean age 64 years, male and female (29%). Patients received optimal medical therapy, which could include ACE inhibitors or ARBs (87%), diuretics (60%) and β blockers (75%), aspirin (88%) as well as coronary reperfusion. Exclusion criteria: Use of potassium-sparing diuretics, serum creatinine concentration ≥ 2.5 mg per decilitre (220 µmol per litre), and a serum potassium concentration was > 5.0 mmol per litre before randomization.

Intervention
Initially 25 mg per day for four weeks, then titrated up to 50 mg. Mean dose-equivalent of study medication was 42.6 mg. If serum potassium concentration was > 5.5 mmol per litre, dose of study drug was reduced or temporarily discontinued until serum potassium concentration fell below 5.5 mmol per litre. Randomised 3-14 days post infarct 3319 patients

Comparisons
Placebo 3313 patients

Study Length
Mean follow-up 16 months (range 0 to 33)

Outcomes
Primary Death from any cause Death from CV causes or first hospitalisation for a CV event, including heart failure, recurrent acute MI, stroke, or ventricular arrhythmia. Secondary Death from any cause or any hospitalisation (number of patients) Death from CV causes: (number of patients) Sudden death from cardiac causes Acute MI death Heart failure death Stroke death Other death Any hospitalisation (no. of patients) Hospitalisation for CV events (no. of patients): Acute MI hospitalisations (no. of patients) Heart failure hospitalisations (no. of patients) Stroke hospitalisations (no. of patients) Ventricular arrhythmia hospitalisations (no. of patients): Any hospitalisation (no. of episodes): Hospitalisation for CV events (no. of episodes): Acute MI (no. of episodes) Heart failure (no. of episodes) Stroke (no. of episodes) Ventricular arrhythmia (no. of episodes)

Funding
Pharmacia

Effect
Primary Death from any cause: 478/3319 treatment deaths versus 554/3313 placebo deaths, RR of 0.85 (95% CI 0.75 to 0.96, P = 0.008). Death from CV causes or first hospitalisation for a CV event: 885/3319 treatment deaths or events versus 554/3313 placebo deaths or events, RR of 0.87 (95% CI 0.79 to 0.95, P = 0.002). Secondary Death from any cause or any hospitalisation (number of patients): 1730/3319 treatment versus 1829/3313 placebo, RR of 0.92 (95% CI 0.85 to 0.99, P = 0.004).
0.92 (95% CI 0.86 to 0.98, P = 0.02). Death from CV causes: (number of patients): 407/3319
treatment versus 483/3313 placebo, RR of 0.83 (95% CI 0.72 to 0.94, P = 0.005). Sudden
death from cardiac causes: 162/3319 treatment versus 201/3313 placebo, RR of 0.79 (95% CI
0.64 to 0.97, P = 0.03). Acute MI death: 78/3319 treatment versus 94/3313 placebo, RR of
0.82 (95% CI 0.61 to 1.10, P = 0.19). Heart failure death: 104/3319 treatment versus 127/3313
placebo, RR of 0.802 (95% CI 0.62 to 1.04, P = 0.10). Stroke death: 26/3319 treatment
versus 28/3313 placebo, RR of 0.91 (95% CI 0.53 to 1.55, P = 0.73). Other death: 37/3319
treatment versus 33/3313 placebo, RR of 0.91 (95% CI 0.81 to 1.01, P = 0.99).

Any hospitalisation (no. of patients): 1493/3319 treatment versus 1526/3313 placebo, RR of 0.95
(95% CI 0.89 to 1.02, P = 0.20). Hospitalisation for CV events (no. of patients): 606/3319
treatment versus 649/3313 placebo, RR of 0.91 (95% CI 0.81 to 1.01, P = 0.09). Acute MI
hospitalisations (no. of patients): 224/3319 treatment versus 229/3313 placebo, RR of 0.97
(95% CI 0.85 to 0.99, P = 0.71). Heart failure hospitalisations (no. of patients): 345/3319
treatment versus 391/3313 placebo, RR of 0.85 (95% CI 0.74 to 0.99, P = 0.03). Stroke
hospitalisations (no. of patients): 70/3319 treatment versus 51/3313 placebo, RR of 0.95 (95% CI
0.65 to 1.39, P = 0.79). Ventricular arrhythmia hospitalisations (no. of patients): 52/3319
treatment versus 54/3313 placebo, RR of 0.95 (95% CI 0.65 to 1.39, P = 0.79).

Any hospitalisation (no. of episodes): 2815/3319 treatment versus 2984/3313 placebo, Ratio of
0.94 (P = 0.12). Hospitalisation for CV events (no. of episodes): 876/3319 treatment versus
1004/3313 placebo, RR of 0.87 (P = 0.12). Acute MI (no. of episodes): 268/3319 treatment
versus 269/3313 placebo, Ratio of 0.99 (P = 0.96). Heart failure (no. of episodes): 477/3319
treatment versus 618/3313 placebo, Ratio of 0.77 (P = 0.002). Stroke (no. of episodes):
73/3319 treatment versus 54/3313 placebo, Ratio of 0.92 (P = 0.11). Ventricular arrhythmia

Blood pressure After week 1, the mean systolic and diastolic blood pressure increased in both
groups from baseline to each time point throughout the remainder of trial. The magnitude in
these increases in the eplerenone group was significantly smaller than in placebo group. At 1
year, mean BP increased by 8/4 mm Hg in the placebo group and by 5/3 mm Hg in the
eplerenone (P < 0.01). Serum creatinine concentration At 1 year: serum creatinine
concentration increased by 0.02 mg per decilitre (1.8 µmol per litre) in the placebo group and
by 0.06 mg per decilitre (5.3 µmol per litre) in the eplerenone group (P < 0.001). Potassium
levels At 1 year: potassium levels increased by 0.2 mmol per litre in the placebo group and by
0.3 mmol per litre (5.3 µmol per litre) in the eplerenone group (P < 0.001). Serious
hyperkalemia (serum potassium concentrations ≥ 6.0 mmol per litre) occurred in 5.5% of
patients in eplerenone group, as compared with 3.9% in placebo group (P < 0.002). For those
patients with serious hyperkalemia, the incidence of greater elevation in potassium level was
similar in the eplerenone group (0.6% with concentrations ≥ 7 µmol per litre and 0.2% with
concentrations ≥ 8 µmol per litre ) and in the placebo group (0.5% with concentrations ≥ 7 µmol
per litre and 0.1% with concentrations ≥ 8 µmol per litre ). 15 patients in the eplerenone group
and 3 patients in placebo group were hospitalized for condition, 1 death in placebo group was
attributed to it. For patients with baseline creatinine clearance < 50 ml per minute, the
incidence of serious hyperkalemia was 10.1% in eplerenone group versus 5.9% in placebo
group (P = 0.006). For patients with baseline creatinine clearance > 50 ml per minute, the
incidence of serious hyperkalemia was 4.6% in eplerenone group versus 3.5% in placebo group
(P = 0.04). Significant adverse events: eplerenone versus placebo Dyspnoea: treatment
243/3307 (7.3%) versus placebo 307/3301 (9.3%) (P = 0.004). Hyperkalemia: treatment
113/3307 (3.4%) versus placebo 66/3301 (2.0%) (P < 0.001). Serious hyperkalemia (serum
potassium ≥ 6 mmol per litre): treatment 180/3251 (5.5%) versus placebo 126/3251 (3.9%) (P =
0.002). Hypokalemia: treatment 15/3307 (0.5%) versus placebo 49/3301 (1.5%) (P < 0.001).
Serious hypokalemia: (serum potassium < 3.5 mmol per litre): treatment 273/3251 (8.4%) versus
placebo 424/3251 (2.0%) (P < 0.001). Hypoglycemia: treatment 20/3307 (0.6%) versus
placebo 35/3301 (1.1%) (P = 0.04). Gastrointestinal disorder: treatment 659/3307 (19.9%) versus placebo 583/3301 (17.7%) (P = 0.02). No significant different between treatment and placebo reported for the following: ≥ 1 event, CV disorder, cough, pneumonia, metabolic or nutritional disorder, hyperuricemia, neoplasm, urinary tract disorder, disorder of skin or appendages, musculoskeletal disorder, nervous system disorder, psychiatric disorder, endocrine disorder, impotence and gynecomastia (men), breast pain (woman).

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

**Reference number** 5108

Barnes BJ; Howard PA; Eplerenone: a selective aldosterone receptor antagonist for patients with heart failure.

2005 39 Annals of Pharmacotherapy  pgs 68 76

**Study Type:** Randomised Controlled Trial

**Patient Characteristics**  
Inclusion criteria: Post MI patients recruited during hospitalization for enzyme confirmed MI  
Aged 25 to 75 years. Mean age ± SD = 58 ± 10 years. Male and female (20%).

Exclusion criteria: Ongoing cardiogenic shock or symptomatic

**Intervention**  
Diltiazem 60 mg four times daily  1232 patients

**Comparisons**  
Placebo  1234 patients

**Study Length**  
Patients were for followed for a min-imum of 12 months, mean follow-up 25 months, max-imum of 54 months

**Funding**  
Tanabe Seiykaku Co Ltd  Marion Laboratories

**Outcomes**  
Mortality  
Death from cardiac causes  
Nonfatal MI

**Effect**  
Total mortality: 166/1232 (13.5%) treatment versus 167/1234 (13.5%) placebo, HR of 1.02 (95% CI 0.82 to 1.27, not significant). Death from cardiac causes: 127/1232 (10.3%) treatment versus 124/1234 (10.0%) placebo. Nonfatal MI: 103/1232 (8.4%) treatment versus 110/1234 (8.9%) placebo. Combination of death from cardiac causes and nonfatal MI: 202/1232 (16.4%) treatment versus 226/1234 (18.3%) placebo, HR of 1.02 (95% CI 0.90 to 1.08, not significant). Adverse outcomes: See Table 1 (Appendix)  

Interactions: The presence or absence of pulmonary congestion was found to have a significant interaction with (P < 0.01, two sided P value = 0.0042) with treatment assignment. Figure 1 (Appendix) shows the bidirectional interaction according to treatment assignment in patients with and without pulmonary congestion. A similar interaction was noted between pulmonary congestion and diltiazem with death from cardiac causes as the endpoint (two sided P value = 0.0042). Figure 2 (Appendix) shows a dose response effect in the hazard ratios for first occurrence diltiazem as compared with placebo, with increasing grades of severity for the covariants pulmonary congestion and radionucleotide ejection fraction. In 1909 patients without pulmonary congestion, diltiazem was associated with a reduced number of cardiac events (death from cardiac causes, or nonfatal MI): HR = 0.77 (95% CI 0.61 to 0.98), Figure 2. In 490 patients with pulmonary congestion, diltiazem was associated with an increased number of cardiac events: HR = 1.41 (95% CI 1.01 to 1.96).
Question: What is the effectiveness of adding omega 3 supplements versus placebo to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number 3787

ADD AUTHORS

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial.

1999 354 Lancet pgs 447 455

Study Type: Randomised Controlled Trial

Inclusion criteria: Post MI (≤ 3 months), mean days since diagnosis ± SD = 25±21 days, male and female (15%), no age limit (mean age ± SD = 59±10 years), mean ejection fraction ± SD = 53±11). Exclusion criteria: Contraindications to n-3 polyunsaturated fatty acids, known congenital defects in coagulation, unfavourable outlook (e.g., overt congestive heart failure, cancers).

Intervention n-3 polyunsaturated fatty acids (PUFA) 1g gelatine capsule containing 850-882 mg eicosapentaenoic acid (EPA) and docis-hexaenoic acid (DHA) as ethyl esters in the average ratio of EPA/DHA 1.2/1 2836 patients

Comparison No supplementation 2828 patients

Study Length 42 months

Outcomes

Primary Composite of death, non fatal MI, and non-fatal stroke Composite of CV death, non-fatal MI, and non-fatal stroke Secondary All fatal events CV deaths Cardiac death Coronary death Sudden death Other deaths CHD death and non fatal MI Fatal and non-fatal stroke

Funding Bristol-Myers Squibb, Pharmacia-Upjohn, Societá Prodotti Antibiotici, Pfizer

Effect

Four-way analysis Primary Composite of death, non fatal MI, and non-fatal stroke: Treatment 356/2836 (12.3%) versus control 414/2828 (14.6%), RR = 0.85 (95% CI 0.74 to 0.98). Composite of CV death, non-fatal MI, and non-fatal stroke: Treatment 262/2836 (9.2%) versus control 414/2828 (11.4%), RR = 0.80 (95% CI 0.68 to 0.95). Secondary All fatal events: Treatment 236/2836 (8.3%) versus control 293/2828 (10.4%), RR = 0.80 (95% CI 0.67 to 0.95). CV deaths: Treatment 136/2836 (4.8%) versus control 193/2828 (6.8%), RR = 0.70 (95% CI 0.56 to 0.87). Cardiac death: Treatment 108/2836 (3.8%) versus control 165/2828 (5.8%), RR = 0.65 (95% CI 0.51 to 0.82). Coronary death: Treatment 100/2836 (3.5%) versus control 151/2828 (5.3%), RR = 0.65 (95% CI 0.51 to 0.84). Sudden death: Treatment 55/2836 (1.9%) versus control 99/2828 (3.5%), RR = 0.55 (95% CI 0.40 to 0.76). Other deaths: Treatment 100/2836 (3.5%) versus control 100/2828 (3.5%), RR = 0.99 (95% CI 0.75 to 1.30). Non-fatal CV events: Treatment 140/2836 (4.9%) versus control 144/2828 (5.1%), RR = 0.96 (95% CI 0.76 to 1.21). CHD death and non fatal MI: Treatment 196/2836 (6.9%) versus control 259/2828 (9.2%), RR = 0.75 (95% CI 0.62 to 0.90). Fatal and non-fatal stroke: Treatment 54/2836 (1.9%) versus control 41/2828 (1.5%), RR = 1.30 (95% CI 0.87 to 1.96). Two-way analysis Primary Composite of death, non fatal MI, and non-fatal stroke: Treatment 715/5666 (12.6%) versus control 785/5668 (13.9%), RR = 0.90 (95% CI 0.82 to 0.99). Composite of CV death, non-fatal MI, and non-fatal stroke: Treatment 547/5666 (9.7%) versus control 608/5668 (10.8%), RR = 0.89 (95% CI 0.80 to 1.10). Secondary All fatal events: Treatment 472/5666 (8.3%) versus control 545/5668 (10.4%), RR = 0.86 (95% CI 0.76 to 0.97). CV deaths: Treatment 291/5666 (5.1%) versus control 348/5668 (6.2%), RR = 0.83 (95% CI 0.71 to 0.97). Cardiac death:
Treatment 228/5666 (4.0%) versus control 292/5668 (5.2%), RR = 0.78 (95% CI 0.65 to 0.92).
Coronary death: Treatment 214/5666 (3.8%) versus control 265/5668 (4.7%), RR = 0.80 (95% CI 0.67 to 0.96). Sudden death: Treatment 122/5666 (2.2%) versus control 164/5668 (2.9%), RR = 0.74 (95% CI 0.58 to 0.93). Other deaths: Treatment 378/5666 (3.3%) versus control 197/5668 (2.9%), RR = 0.91 (95% CI 0.74 to 1.11).

Non-fatal CV events: Treatment 287/5666 (5.1%) versus control 291/5668 (5.1%), RR = 0.98 (95% CI 0.83 to 1.15). CHD death and non-fatal MI: Treatment 196/5666 (6.9%) versus control 259/5668 (9.2%), RR = 0.75 (95% CI 0.62 to 0.90).

Fatal and non-fatal stroke: Treatment 54/5666 (1.9%) versus control 41/5668 (1.5%), RR = 1.30 (95% CI 0.87 to 1.96).

Side Effects: Nausea: treatment group 1.4% vs control group 0.9%. GI disturbances: treatment group 4.9% vs control group 3.2%

More than 70% of patients reported eating fish at least once a week at the start of the RCT in both the treatment and placebo groups (no difference between the groups). At 42 months, this had risen to 82% in both groups. The type of fish was not stipulated. At the start of the RCT, the percentage of patients prescribed cholesterol-lowering drug therapy in the treatment and control groups was 4.4% and 5.1%, respectively. At 42 months the percentage rose in the treatment and the control groups to 46.0% and 44.4%, respectively.
Question: What is the effectiveness of adding statins versus placebo to improve outcome in patients after MI?

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

Reference number 1806

Ericsson CG; Hamsten A; Nilsson J; Grip L; Svane B; de FU; Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients

1996 347 Lancet pgs 849 853

Study Type: Randomised Controlled Trial

Patient Characteristics

Inclusion criteria: Men aged below 45 years post MI (interval between acute event and study entry had to be 3 to 6 months). Whole serum cholesterol value of > 5.2 mmol/l and / or triglycerides values ≥ 1.6 mmol/l. Patients fulfilling the inclusion criteria were first treated with diet for 3 months (pre-treatment period). Patients were given dietary instruction sheet and saw a nutritionist. Exclusion criteria: Severe hyperlipidemia (cholesterol > 10 mmol/l and or triglycerides ≥ 8 mmol/l), severe hypertension resistant to medication, diabetes mellitus, impaired renal function (creatinine ≥ 150 µmol/l) necessitating lowering of the bezafibrate dose, chronic liver disease, chronic alcoholism, symptomatic gallbladder disease, connective tissue disease or arthritis, psychiatric disease, any form of cancer, participation in other clinical trials. Concomitant drug therapy at baseline: Aspirin: 11% Beta blockers: 99% Diuretics: 19% ACE inhibitors: 0% Calcium channel blockers: 19% Long acting nitrates: 27% Concomitant drug therapy at end of study: Aspirin: 45% ACE inhibitors: 5%

Intervention

Bezafibrate 200mg three times a day 47 patients

Comparison

Placebo 45 patients

Study Length

5 years

Outcomes

Coronary events (reinfarction, CABG, PTCA, sudden death, cardiovascular death). Plasma lipid concentration.

Funding


Effect

Coronary events (reinfarction, CABG, PTCA, sudden death, cardiovascular death): Bezafibrate: 3/47 (one reinfarction then death, one sudden death, one reinfarction plus CABG) Placebo: 11/45 (three reinfarction, one reinfarction plus CABG, four CABF, three PTCA) P < 0.019 by log-rank test. Plasma lipid levels Cholesterol at baseline (mmol/l): Bezafibrate: 6.87 (6.42 to 7.69) Placebo: 6.90 (6.21 to 7.27) HDL-C at baseline (mmol/l): Bezafibrate: 0.89 (0.82 to 0.96) Placebo: 1.0 (0.91 to 1.10) LDL-C at baseline (mmol/l): Bezafibrate: 4.66 (3.99 to 5.19) Placebo: 4.62 (4.19 to 5.00) VLDL-C at baseline (mmol/l): Bezafibrate: 1.10 (0.93 to 1.47) Placebo: 0.86 (0.76 to 1.02) Total triglycerides at baseline (mmol/l): Bezafibrate: 2.44 (2.11 to 3.07) Placebo: 1.98 (1.84 to 1.69) VLDL triglycerides at baseline (mmol/l): Bezafibrate: 1.85 (1.30 to 2.22) Placebo: 1.43 (1.28 to 1.69) Mean % change during follow-up relative to baseline (95% CI) Cholesterol: Bezafibrate: -13.97 (-17.09 to -9.13) Placebo: -0.78 (-6.57 to 4.47) P < 0.001 HDL-C: Bezafibrate: 8.64 (1.02 to 16.37) Placebo: -0.78 (-6.57 to 4.47) P = 0.02 LDL-C: Bezafibrate: -3.49 (-9.71 to 2.88) Placebo: -2.19 (-7.05 to 2.61) P = 0.551 VLDL-C: Bezafibrate: -35.94 (-49.74 to 25.26) Placebo: 1.54 (-14.35 to 7.22) P < 0.001 Total triglycerides: Bezafibrate: -26.28 (-39.20 to -17.67) Placebo: 2.69 (-8.05 to 10.79) P < 0.001 VLDL triglycerides: Bezafibrate: -26.07 (-42.03 to -16.80) Placebo: 7.95 (-6.89 to 31.94) Discontinuation from study One patient withdrew from the placebo group because of gastrointestinal complaints and one patient from the bezafibrate group who had pre-existing glomerulonephritis was withdrawn because of progression of renal dysfunction.
Question: What is the effectiveness of adding high dose statin (more potent cholesterol lowering) versus low dose statin (less potent cholesterol lowering) to improve outcome in patients after MI?

Grading: 1++  High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number: 3806

de Lemos JA; Blazing MA; Wiviott SD; Lewis EF; Fox KA; White HD; Rouleau JL; Pedersen TR; Gardner LH; Mukherjee R; Ramsey KE; Palmisano J; Bilheimer DW; Pfeffer MA; Califf RM; Braunwald E;

Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial

2004 292 JAMA pgs 1307 1316

Study Type: Randomised Controlled Trial

Patient Characteristics

- Inclusion criteria: Patients with acute coronary syndrome in preceding 10 days (median 7 days).
- Total cholesterol of level of 250 mg/dl or lower (6.48 mmol/l). Non ST-segment elevation acute coronary syndrome: 60%MI with ST-segment elevation: 40%
- Male and female (24%), between the ages of 21 to 80 years, mean (IQR) = 61 (53-69) years. Other baseline characteristics:
  - Diabetes Mellitus: 24%
  - Systemic Hypertension: 50%
  - Participation in Phase A: 58%
  - Exclusion criteria: On statin therapy at time of randomisation. Participation in any other clinical trial.
  - Planned coronary revascularization disease or cardiac transplantation, severe real or hepatic Concomitant therapy at baseline
  - Aspirin: 98%
  - Beta blockers: 90%
  - ACE inhibitors: 72%

Intervention

- Early intensive therapy Simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter 2265 patients
- Delayed conservative therapy Placebo for 4 months followed by Simvastatin 20 mg once daily thereafter 2232 patients

Study Length

- At least 6 months and up to 24 months
- Median follow up 721 days

Outcomes

- Primary Composite of cardiovascular death, nonfatal MI, readmission for acute coronary syndrome and stroke. Secondary All cause mortality. New onset CHF. Revascularisation due to documented ischaemia.

Funding

- Merck and Company

Effect

- Primary outcome Composite of cardiovascular death, nonfatal MI, readmission for acute coronary syndrome and stroke: 309/2265 (14.4%) Simvastatin 40/80 mg versus 343/2232 (16.7%)
  - Simvastatin placebo: 20 mg, HR of 0.89 (95% CI 0.76 to 1.04, P = 0.14).
  - Simvastatin 40/80 mg versus 109/2232 (4.1%) Simvastatin placebo: 20 mg, HR of 0.75 (95% CI 0.51 to 1.00, P = 0.05).
  - Nonfatal MI: 151/2265 (7.1%) Simvastatin 40/80 mg versus 155/2232 (7.47%) Simvastatin placebo: 20 mg, HR of 0.96 (95% CI 0.71 to 1.21, P = 0.74).
- Readmission for acute coronary syndrome: 309/2265 (14.4%) Simvastatin 40/80 mg versus 343/2232 (16.7%) Simvastatin placebo: 20 mg, HR of 0.99 (95% CI 0.80 to 1.22, P = 0.90).
- Stroke: 103/2265 (5.0%) Simvastatin 40/80 mg versus 102/2232 (4.9%) Simvastatin placebo: 20 mg, HR of 0.99 (95% CI 0.76 to 1.31, P = 0.97).
- Secondary outcomes All cause mortality: 104/2265 (5.4%) Simvastatin 40/80 mg versus 130/2232 (6.7%) Simvastatin placebo: 20 mg, HR of 0.79 (95% CI 0.61 to 1.02, P = 0.08).
- New onset CHF: 72/2265 (3.7%) Simvastatin 40/80 mg versus 98/2232 (5.0%) Simvastatin placebo: 20 mg, HR of 0.72 (95% CI 0.53 to 0.98, P = 0.04).
- Revascularisation due to documented ischaemia: 119/2265 (5.9%) Simvastatin 40/80 mg versus 124/2232 (6.2%) Simvastatin placebo: 20 mg, HR of 0.93 (95% CI 0.73 to 1.19), P = 0.61.
0.73 to 1.20, P = 0.60). Plasma lipid levels See Table 1 in appendix of narrative. Simvastatin placebo/20 mg: Median LDL-C levels increased 11% during the 4 month placebo period from 111 mg/dl (2.87 mmol/l) to 124 mg/dl (3.2 mmol/l), then decreased to 77 mg/dl (1.99 mmol/l at month 8 after the initiation of simvastatin 20 mg (31% change from baseline). Simvastatin 40/80 mg: Median LDL-C levels decreased by 39% to 68 mg/dl (1.61 mmol/l) over the first month of simvastatin 40 mg then decreased an additional 6% to 62 mg/dl (1.61 mmol/l) at month 4 following increase to 80 mg simvastatin. Changes in total cholesterol, HGL-C and triglycerides are shown in Table 3 (Appendix). Safety Alanine aminotransferase or aspartate aminotransferase >3 x upper limit of normal at 2 consecutive measurements:19/2232 (0.9%) Simvastatin 40/80 mg versus 8/2068 (0.4%) Simvastatin placebo/20 mg (P = 0.05).Creatine kinas >10 x upper limit of normal at 2 consecutive measurements:9/2263 (0.4%) Simvastatin 40/80 mg versus 1/2230 (0.04%) Simvastatin placebo/20 mg (P = 0.02). Simvastatin 40/80 patient group: levels were high while taking 80 mg simvastatin. 3/9 with myopathy had creatine kinas levels > 10 000 units/l and met the criteria for rhabdomyolysis. Of these 3 patients, 1 had contrast media renal failure and 1 patient was receiving concomitant verapamil (inhibitor of CYP3A4). In addition, 1 patient receiving 80 mg simvastatin had a creatine kinase level 10 x the upper limit of normal without muscle symptoms, which was associated with alcohol abuse. Rates of discontinuation due to adverse muscle-related events: Simvastatin 40/80 mg: 41/2263 (1.8%)Simvastatin placebo/20 mg: 34/2230 (1.5%) (P = 0.49).

Reference number 74
LaRosa JC;Grundy SM;Waters DD;Shear C;Barter P;Fruchart JC;Gotto AM;Greten H;Kastelein JJ;Shepherd J;Wenger NK;Treating t; Intensive lipid lowering with atorvastatin in patients with stable coronary disease. 2005 352 New England Journal of Medicine

Study Type: Randomised Controlled Trial

Inclusion criteria: Men and women (19%), age range 35 to 75 years (mean±SD = 61±9 years), with clinically evident coronary heart disease defined as one or more of the following: Previous MI: Atorvastatin 80 mg: 59.0% Atorvastatin 10 mg: 57.7% Previous or current angina with objective evidence of atherosclerotic coronary heart disease: Atorvastatin 80 mg: 81.8% Atorvastatin 10 mg: 81.8% History of coronary revascularisation: Angioplasty: Atorvastatin 80 mg: 53.8% Atorvastatin 10 mg: 54.3% Bypass Atorvastatin 80 mg: 53.8% Atorvastatin 10 mg: 54.3% Previous or current angina with objective evidence of atherosclerotic coronary heart disease: Atorvastatin 80 mg: 81.8% Atorvastatin 10 mg: 81.8% History of coronary revascularisation: Angioplasty: Atorvastatin 80 mg: 53.8% Atorvastatin 10 mg: 54.3% Bypass Atorvastatin 80 mg: 53.8% Atorvastatin 10 mg: 54.3% Other baseline characteristics: Diabetes Mellitus: 15% Systemic Hypertension: 54% PAD: 12% CHF: 8% Arrhythmia: 18% Run in period Patients with LDL-C between 130 and 250 mg/dl (3.4 mmol/l and 6.5 mmol) and triglycerides of 600 mg/dl or less (6.8 mol/l) entered an 8 week run in period of open label treatment with 10 mg atorvastatin. At the end of the run-in phase patients with an LDL cholesterol of less than 130 mg/dl (3.4 mmol/l) were randomized to the study. Baseline lipids (mg/dl) mmol/lLDL cholesterol: Atorvastatin 80 mg: 97±18 (2.5±0.5 mmol/l) Atorvastatin 10 mg: 98±18 (2.5±0.5 mmol/l) Total cholesterol: Atorvastatin 80 mg: 175±24 (4.5±0.6 mmol/l) Atorvastatin 10 mg: 175±24 (4.5±0.6 mmol/l) Triglycerides: Atorvastatin 80 mg: 151±70 (1.7±0.8 mmol/l) Atorvastatin 10 mg: 151±72 (1.7±0.8 mmol/l) HDL cholesterol Atorvastatin 80 mg: 47±11 (1.2±0.3 mmol/l) Atorvastatin 10 mg: 47±11 (1.2±0.3 mmol/l) Exclusion criteria: Hypersensitivity to statins, acute liver disease or hepatic dysfunction defined as aspartate aminotransferase > 1.5 times the upper limit of normal, women who were pregnant or breastfeeding, uncontrolled diabetes mellitus, uncontrolled hyphothyroidism, uncontrolled hypertension, an MI, coronary revascularization or severe/unstable angina within 1 month of screening, any planned procedure for the treatment of atherosclerosis, ejection fraction < 30%, haemodynamically important valvular disease, GI disease limit drug absorption or partial ileal bypass, any nonskin malignancy, malignant melanoma or other survival limiting disease, unexplained creatine phosphokinase levels > 6 times upper limit of normal, concurrent therapy with lipid regulating drugs not in study protocol, history of alcohol abuse, participation
in another trial concurrently or within 30 days before screening.

**Intervention**
- Atorvastatin 10 mg once daily5006 patients
- Atorvastatin 80 mg once daily4958 patients

**Comparisons**
- Atorvastatin 10 mg versus 80 mg
- Median 4.9 years (up to 6 years)

**Outcomes**
- Primary Major cardio-vascular event (death from CHD, nonfatal non-procedural MI, resuscitation after cardiac arrest or fatal or nonfatal stroke). Secondary Major coronary event (death from CHD, nonfatal non-procedural MI, or resuscitation after cardiac arrest). Cerebrovascular event, hospitalisation for CHF, PAD, death from any cause, any cardio-vascular event, any coronary event.

**Funding**
- Pfizer

**Effect**

Primary outcome Major cardiovascular event: 548/5006 (10.9%) Atorvastatin 10 mg versus 434/4995 (8.7%) Atorvastatin 80 mg, HR of 0.78 (95% CI 0.69 to 0.89, P < 0.001). Absolute RR = 2.2% (22% relative RR). Death from CHD: 127/5006 (2.5%) Atorvastatin 10 mg versus 101/4995 (2.0%) Atorvastatin 80 mg, HR of 0.80 (95% CI 0.61 to 1.03, P = 0.09).

Nonfatal non-procedural MI: 308/5006 (6.2%) Atorvastatin 10 mg versus 243/4995 (4.9%) Atorvastatin 80 mg, HR of 0.78 (95% CI 0.66 to 0.93, P = 0.004). Resuscitation after cardiac arrest: 26/5006 (0.5%) Atorvastatin 10 mg versus 25/4995 (0.5%) Atorvastatin 80 mg, HR of 0.96 (95% CI 0.56 to 1.67, P = 0.89). Fatal or nonfatal stroke: 155/5006 (3.1%) Atorvastatin 10 mg versus 117/4995 (2.3%).

Atorvastatin 80 mg, HR of 0.75 (95% CI 0.59 to 0.96, P = 0.02). Secondary outcomes Major coronary event: 418/5006 (8.3%) Atorvastatin 10 mg versus 334/4995 (6.7%) Atorvastatin 80 mg, HR of 0.80 (95% CI 0.69 to 0.92, P = 0.002). Cerebrovascular event (fatal or nonfatal stroke or transient ischemic attack): 250/5006 (5.0%) Atorvastatin 10 mg versus 196/4995 (3.9%).

Atorvastatin 80 mg, HR of 0.77 (95% CI 0.64 to 0.93, P = 0.007). Hospitalisation for CHF: 164/5006 (3.3%) Atorvastatin 10 mg versus 122/4995 (2.4%) Atorvastatin 80 mg, HR of 0.75 (95% CI 0.59 to 0.93, P = 0.01). PAD (as defined as any new diagnosis of PAD, any admission related to its treatment, or any incidental discovery of plaques or stenosis): 282/5006 (5.6%) Atorvastatin 10 mg versus 275/4995 (5.5%) Atorvastatin 80 mg, HR of 0.97 (95% CI 0.83 to 1.15, P = 0.76). Death from any cause: 282/5006 (5.6%) Atorvastatin 10 mg versus 284/4995 (5.7%) Atorvastatin 80 mg, HR of 1.02 (95% CI 0.75 to 1.17, P = 0.92). Any cardiovascular event: 1677/5006 (33.8%) Atorvastatin 10 mg versus 1405/4995 (28.1%) Atorvastatin 80 mg, HR of 0.81 (95% CI 0.75 to 0.87, P < 0.001). Any coronary event (as defined as a major coronary event, revascularization procedure, procedure-related MI, or documented angina): 1326/5006 (26.5%) Atorvastatin 10 mg versus 1078/4995 (21.6%) Atorvastatin 80 mg, HR of 0.79 (95% CI 0.73 to 0.86, P < 0.001).

Plasma lipid levels Mean LDL-C levels during the study were 77mg/dl (2.0 mmol/l) for 80 mg atorvastatin patients and 101 mg/dl (2.6 mmol/l) for 10 mg atorvastatin. Total cholesterol levels and triglycerides levels decreased significantly to week 12 in the group given 80 mg atorvastatin (P < 0.001) for both comparisons, and levels remained stable during the treatment period. Both doses of atorvastatin produced non significant increases over baseline in HDL cholesterol, with no significant difference between the groups during the course of the study. Safety Adverse events: 289/5006 (5.8%) Atorvastatin 10 mg versus 406/4995 (8.1%) Atorvastatin 80 mg (P < 0.001). Myalgia: 234/5006 (4.7%) Atorvastatin 10 mg versus 241/4995 (4.8%) Atorvastatin 80 mg (P = 0.72). Persistent elevation in alanine aminotransferase, aspartate aminotransferase, or both (defined as two consecutive measurements obtained 4 to 10 days apart that were more than three times the upper limit of normal range): 9/5006 (0.2%) Atorvastatin 10 mg versus 60/4995 (1.2%) Atorvastatin 80 mg (P < 0.001). There were no persistent elevations in creatine kinase. Five cases of rhabdomyolysis were reported (two in the group given 80 mg of atorvastatin and three in the group given 10 mg atorvastatin).

**Grading:** 1+ Well-conducted meta-analyses, systematic reviews of Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 141 of 248
RCTs, or RCTs with a low risk of bias

Reference number: 3802

Cannon CP; Braunwald E; McCabe CH; Rader DJ; Rouleau JL; Belder R; Joyal SV; Hill KA; Pfeffer MA; Skene AM; Intensive versus moderate lipid lowering with statins after acute coronary syndromes

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Randomised Controlled Trial</th>
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<tbody>
<tr>
<td>Patient</td>
<td></td>
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<tr>
<td>Inclusion criteria:</td>
<td>Patients hospitalized for acute coronary syndrome in preceding 10 days (median 7 days). Unstable angina: 29%MI without ST-segment elevation: 36%MI with ST-segment elevation: 35%Male and female (22%), at least 18 years, mean±SD = 58±11 years). Patients had to be in a stable condition, and were enrolled after percutaneous revascularization procedure if planned (69%). One quarter of patients were taking statins at index event. Patients had to have a total cholesterol level of 240 mg/dl or less (5.22 mmol/l) measured within first 24 hours after onset of acute coronary syndrome, or up to 6 months earlier if no sample had been obtained during first 24 hours. Patients receiving long term lipid-lowering therapy at the time of their index acute coronary syndrome had to have a total cholesterol level of 200 mg/dl (5.18 mmol/l) or less at time of screening. Exclusion criteria: Coexisting condition that shortened expected survival to less than 2 years. On statin therapy at a dose of 80 mg per day at index event or fibrate therapy, or niacin therapy that could not be discontinued before randomization. Treatment with strong inhibitors of cytochrome P-450 3A4 within 1 month of randomization, or likelihood of requiring such therapy. Undergone PCI within previous 6 months, or CABG within previous 2 months before randomization. Having factors that may prolong QT interval. Obstructive hepatico-biliary disease or other serious liver disease. Unexplained elevation in the creatine kinase level 3 times the upper limit of normal that was not related to MI. Creatinine level of more than 2.0 mg/dl. Concomitant therapy during RCT: Aspirin: To 93%Warfarin To 8%Beta blockers: To 85%Antiplatelets (clopidogrel / ticlodipine): To 72% initially and 20% at one year ACE inhibitors: 69%Angiotensin II blockers: to 69% then 14% at one years 14%</td>
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<tr>
<td>Characteristics</td>
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<tr>
<td>Study Length</td>
<td>Mean follow up 24 months (18 to 36 months)</td>
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<tr>
<td>Outcomes</td>
<td>Primary Composite of death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation with CABG or PCI (if these were performed at least 30 days after randomisation), or stroke. Secondary Composite of death from coronary heart disease, nonfatal MI, or stroke</td>
</tr>
<tr>
<td>Intervention</td>
<td>Pravastatin 40 mg once daily 2063 patients</td>
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<tr>
<td>Comparison</td>
<td>Atorvastatin 80 mg once daily 2099 patients</td>
</tr>
<tr>
<td>Funding</td>
<td>Bristol Myers-Squibb, Sanko</td>
</tr>
<tr>
<td>Effect</td>
<td>Primary outcome Composite of death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation with CABG or PCI (if these were performed at least 30 days after randomisation), and stroke:544/2063 (26.4%) Pravastatin versus 470/2099 (22.4%) Atorvastatin, HR of 0.84 (95% CI 0.74 to 0.95, P = 0.005).Death from any cause: non significant reduction (28%, P = 0.06) with intensive (atorvastatin) therapy. MI: Non significant reduction (13%, P = 0.07) with intensive (atorvastatin) therapy. Unstable angina requiring rehospitalisation: Significant reduction (29%, P = 0.02) with intensive (atorvastatin) therapy. Revascularisation: Significant reduction (14%, P = 0.04) with intensive (atorvastatin) therapy. Secondary outcome Composite of death from coronary heart disease, nonfatal MI, or stroke: Risk reduction of 14% (P = 0.029) in intensive (atorvastatin) treatment group compared with pravastatin group. Plasma lipid levels at randomization median LDL-C levels were 106 (2.74 mmol/l) mg/dl before treatment. At follow-up: Pravastatin group: 95 mg/dl (IQR 79 to 113 mg/dl), (2.74 mmol/l IQR 2.04 to 2.92 mmol/l) Atorvastatin group: 62 mg/dl (IQR 50 to 79 mg/dl) (1.60 mmol/l IQR 1.29 to 2.04 mmol/l) (P &lt; 0.001).LDL-C median change among 2985</td>
</tr>
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Myocardial infarction: full guideline DRAFT (August 2006) – Appendices
patients who had not previously received statin therapy: Note: absolute values not reported.
Pravastatin group: 22% at 30 days post randomisation Atorvastatin group: 51% at 30 days post randomization (P < 0.001).
Median HDL-C increases: Note: absolute values not reported.
Pravastatin group: 8.1% at 30 days post randomisation Atorvastatin group: 6.5% at 30 days post randomization (P < 0.001).
Rates of discontinuation Pravastatin discontinuation rate 21.4% versus Atorvastatin 22.8% at one year (P = 0.38), and 33% and 30.4%, respectively, at 2 years (P = 0.22).
Dosage changes Pravastatin group: 8% of patients had a dose increase to 80 mg.
1.4% of patients had a dose decrease to 20 mg. Atorvastatin group: 1.9% of patients had a dose decrease to 20 mg (due to side effects or liver function abnormalities).
Safety
Elevation in alanine aminotransferase levels: Pravastatin group: 1.1% Atorvastatin group: 3.3% (P < 0.001).
Investigator discontinuation of study medication due to myalgias, muscle aches or elevations in creatine kinase levels: Pravastatin group: 2.7% Atorvastatin group: 3.3% (P = 0.23).
No cases of rhabdomyolysis in either group.
Question: What is the effectiveness of adding early statin therapy versus delayed statin therapy to improve outcome in patients after MI?

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

Reference number 5146

Thompson PL; Meredith I; Amerena J; Campbell TJ; Sloman JG; Harris PJ; Pravastatin i;
Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial

2004 148 American Heart Journal  pg  e2

Study Type: Randomised Controlled Trial

Inclusion criteria: Patients were enrolled within 24 hours of symptoms of acute coronary syndrome (electro-cardiographic changes suggestive of unstable angina pectoris or acute MI)

Final diagnosis Acute MI: 65% Unstable angina pectoris: 30% Other: 5% Male and female (24%),
between the ages of 21 to 85 years. Other baseline characteristics: Diabetes Mellitus: 14% PAD:
43% Concomitant therapy at baseline: Antiplatelet agent: 26% Anticoagulant: 3% Beta
blockers: 16% Calcium antagonists: 16% ACE inhibitors: 18% Vasodilator including
nitrates: 16% Non statin lipid lowering agent: 2%

Intervention Pravastatin 20 or 40 mg once daily 1710 patients Pravastatin 20 mg: 720 patients Pravastatin
40 mg: 990 patients

Comparisons Placebo 1698 patients

Study Length 4 weeks

Outcomes Primary Composite of all cause mortality, nonfatal MI, readmission for unstable angina pectoris.

Secondary New unstable angina.

Funding Bristol-Myers Squibb

Effect Primary outcome Composite of all cause mortality, nonfatal MI, readmission for unstable angina pectoris: 199/1710 (11.6%) Pravastatin versus 211/1698 (12.4%) Placebo, RR of 0.94
(95% CI 0.72 to 1.13, P = 0.48). Absolute risk reduction of 0.8% (95% CI -1.4% to 3.0%). Fatal
MI: 13/1710 (0.8%) Pravastatin versus 15/1698 (0.9%) Placebo, not significant. Nonfatal
MI: 13/1710 (0.8%) Pravastatin versus 15/1698 (0.9%) Placebo, not significant. Death excluding
fatal MI: 11/1710 (0.6%) Pravastatin versus 22/1698 (1.3%) Placebo, not significant.

Readmission for unstable angina pectoris: 81/1710 (0.6%) Pravastatin versus 89/1698 (1.3%)
Placebo, not significant. Secondary outcomes New unstable angina: 81/1710 (0.6%) Pravastatin
versus 89/1698 (1.3%) Placebo, not significant. Plasma lipid levels Baseline serum lipids Total
cholesterol mean±SD: Pravastatin: 5.62±1.2 mmol/l Placebo: 5.69±1.1 mmol/l not significant
Levels were not reported at end of study (4 weeks). Safety Elevation in alanine aminotransferase
or aspartate transaminase levels greater than 3 times the upper limit of normal: Pravastatin:
7/1710 (1.5%) Placebo: 5/1698 (1.1%) not significant. Elevation in creatine kinase levels greater
than 10 times the upper limit of normal with suspected or diagnosed myopathy: Pravastatin:
0/1710 Placebo: 0/1698.
Question: What is the effectiveness of adding fibrates or niacin or ezetimibe versus placebo to improve outcome in patients after MI?

Grading: 1++

High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number: 5160

Rubins HB; Robins SJ; Collins D; Fye CL; Anderson JW; Elam MB; Faas FH; Linares E; Schaefer EJ; Schectman G; Wilt TJ; Wittes J.

Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group

1999 341 New England Journal of Medicine pgs 410 418

Study Type: Randomised Controlled Trial

Characteristics

Inclusion criteria: Men with documented coronary artery disease (defined as a history of MI, angina corroborated by objective evidence of ischaemia, coronary revascularization, or angiographic evidence of stenosis > 50% luminal diameter in one or major coronary arteries).

Prior MI: 61%. Time since most recent MI mean±SD = 6±6 years CABG or PCI: 57%. Other baseline characteristic Hypertension: 57%. Diabetes: 25%. CHF: 8%. Aged less than 74 years, mean±SD = 64±7 years An HDL-C level of 40 mg/dl (1.0 mmol/l) or less. LDL-C of 140 mg/dl (3.6 mmol/l) or less. Triglyceride level of 300 mg/dl (3.4 mmol/l) or less. Exclusion criteria: Serious coexisting condition. Concomitant drug therapy at baseline: Aspirin: 82%. Beta blockers: 43%. Nitrates: 46%. ACE inhibitors: 21%. Calcium channel blockers: 53%

Intervention

Gemfibrozil slow release 1200 mg once daily, then Gembrozil 600 mg twice daily (when manufacturer ceased production). 1264 patients

Comparisons

Placebo 1267 patients

Study Length

Median follow up 5.1 years (range 0 to 6.9 years)

Outcomes


Funding

Co-operative Studies Program of Dept. Veterans Affairs Office Re-search and Development, Parke-Davis

Effect

Primary outcomes Composite of nonfatal MI or death from coronary heart disease: 275/1264 (21.7%) Gemfibrozil versus 219/1267 (17.3%) placebo, RR of 0.78 (95% CI 0.65 to 0.93, P = 0.006). Composite of nonfatal MI or death from coronary heart disease (excluding silent MI): 195/1264 (15.4%) Gemfibrozil versus 241/1267 (19.0%) placebo, RR of 0.79 (95% CI 0.66 to 0.96, P = 0.02). Secondary outcomes Composite of nonfatal MI, death from coronary heart disease or confirmed stroke: 258/1264 (20.4%) Gemfibrozil versus 330/1267 (26.0%) placebo, RR of 0.76 (95% CI 0.64 to 0.89, P < 0.001). Nonfatal MI: 146/1264 (11.6%) Gemfibrozil versus 184/1267 (14.5%) placebo, RR of 0.77 (95% CI 0.62 to 0.96, P = 0.02). Death due to CHD: 93/1264 (7.4%) Gemfibrozil versus 118/1267 (9.3%) placebo, RR of 0.78 (95% CI 0.59 to 1.02, P = 0.07). Death from any cause: 198/1264 (15.7%) Gemfibrozil versus 207/1267 (17.4%) placebo, RR of 0.89 (95% CI 0.73 to 1.08, P = 0.23). Investigator-designated stroke: 64/1264 (5.1%) Gemfibrozil versus 88/1267 (6.9%) placebo, RR of 0.81 (95% CI 0.52 to 0.98, P =
0.04). Confirmed stroke: 58/1264 (4.6%) Gemfibrozil versus 76/1267 (6.0%) placebo, RR of 0.75 (95% CI 0.53 to 1.06, P = 0.10). Transient ischaemic attack: 22/1264 (1.7%) Gemfibrozil versus 53/1267 (4.2%) placebo, RR of 0.61 (95% CI 0.25 to 0.67, P < 0.001). Revascularisation: 266/1264 (21.0%) Gemfibrozil versus 287/1267 (22.7%) placebo, RR of 0.91 (95% CI 0.77 to 1.08, P = 0.29). CABG: 164/1264 (13.0%) Gemfibrozil versus 173/1267 (13.7%) placebo, RR of 0.94 (95% CI 0.76 to 1.17, P = 0.60). PTCA: 120/1264 (9.5%) Gemfibrozil versus 241/1267 (19.0%) placebo, RR of 0.79 (95% CI 0.68 to 1.01, P = 0.06). Peripheral vascular surgery: 19/1264 (1.5%) Gemfibrozil versus 28/1267 (2.2%) placebo, RR of 0.67 (95% CI 0.37 to 1.20, P = 0.18). Carotid endarterectomy: 16/1264 (1.3%) Gemfibrozil versus 44/1267 (3.5%) placebo, RR of 0.55 (95% CI 0.40 to 0.78, P < 0.001). Hospitalisation for unstable angina: 457/1264 (36.2%) Gemfibrozil versus 453/1267 (35.8%) placebo, RR of 1.04 (95% CI 0.88 to 1.14, P = 0.95). Hospitalisation for CHF: 134/1264 (10.6%) Gemfibrozil versus 168/1267 (13.3%) placebo, RR of 0.78 (95% CI 0.62 to 0.98, P = 0.04). Plasma lipid levels: One year after randomization Mean HDL-C: Gemfibrozil: 34 mg/dl (0.9 mmol/l) Placebo: 32 mg/dl (0.8 mmol/l) P < 0.001. Mean cholesterol: Gemfibrozil: 170 mg/dl (4.4 mmol/l) Placebo: 177 mg/dl (4.6 mmol/l) P < 0.001. Mean triglycerides: Gemfibrozil: 115 mg/dl (1.3 mmol/l) Placebo: 166 mg/dl (1.9 mmol/l) P < 0.001. Mean LDL-C: Gemfibrozil: 113 mg/dl (2.9 mmol/l) Placebo: 129 mg/dl (2.9 mmol/l) Not significant. Safety Dyspesia: Gemfibrozil: 506/1264 (40%) Placebo: 431/1267 (34%) P = 0.002. Biliary disease: Gemfibrozil: 88/1264 (7%) Placebo: 89/1267 (7%) Not significant. Abdominal surgery: Gemfibrozil: 88/1264 (5.4%) Placebo: 54/1267 (4.3%) P = 0.19. Discontinuation by physician due to concern about safety or adverse event: Gemfibrozil: 19/291 (7%) Placebo: 15/277 (5%) Not significant.

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

Reference number 5177

Clofibrate and niacin in coronary heart disease

1975 231 JAMA pgs 360 381

Study Type: Randomised Controlled Trial
Patient Inclusion criteria: Post MI men aged 30 to 64 years (at least 3 months post infarction). Exclusion criteria: Patients with cardiac failure which required treatment with digoxin and / or diuretics. Patients with diabetes mellitus. Concomitant drug therapy Not detailed

Intervention

Comparison

Study Length

Outcomes

Funding Nat. Heart and Lung Inst.

Effect Results were analysed using the z test (comparison of 2 means of large groups). A z value of greater than 1.96 or less than -1.96 usually is considered significant (P < 0.05). However, the authors noted that for long term RCT it is more appropriate to consider z values > 2.58 or z < -2.58, (P < 0.01) or even z values > 2.81 or z < -2.81, (P < 0.005) as significant. A negative z value denotes an event rate in a drug group that is lower than the placebo group. Clofibrate Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 146 of 248
versus placebo Primary outcome: All cause mortality: 221/1103 (20.0%) Clofibrate versus 583/2789 (20.9%) placebo, z = 0.60, not significant. Secondary outcomes: All cardiovascular mortality: 191/1103 (17.3%) Clofibrate versus 528/2789 (18.8%) placebo, z = -1.17, not significant. Mortality cause unknown: 7/1103 (0.6%) Clofibrate versus 13/2789 (0.5%) placebo, z = 1.27, not significant. Coronary heart disease mortality: 156/1103 (14.1%) Clofibrate versus 452/2789 (16.2%) placebo, z = -1.60, not significant. Sudden cardiovascular death: 93/1103 (8.4%) Clofibrate versus 269/2789 (9.6%) placebo, z = -1.17, not significant. All cancer deaths: 7/1103 (0.6%) Clofibrate versus 16/2789 (0.6%) placebo, z = 0.22, not significant. Other non cardiovascular death: 16/1103 (1.5%) Clofibrate versus 26/2789 (0.9%) placebo, z = 1.41, not significant. Non fatal MI: 128/1103 (11.6%) Clofibrate versus 339/2789 (12.2%) placebo, z = -0.48, not significant. Coronary death or nonfatal MI: 263/1103 (23.8%) Clofibrate versus 731/2789 (26.2%) placebo, z = -1.53, not significant. Definite pulmonary embolism (fatal or nonfatal): 20/1103 (1.8%) Clofibrate versus 30/2789 (1.1%) placebo, z = 1.84, not significant. Definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis: 57/1103 (5.2%) Clofibrate versus 91/2789 (3.3%) placebo, z = 2.80, significant (P < 0.01). Fatal or nonfatal stroke or intermittent cerebral ischaemic attack: 117/1103 (10.6%) Clofibrate versus 271/2789 (9.7%) placebo, z = 0.84, not significant. Any definite or suspected fatal or nonfatal cardiovascular event: 929/1103 (84.2%) Clofibrate versus 2251/2789 (80.7%) placebo, z = 2.56, significant (P < 0.01). Niacin versus placebo Primary outcome: All cause mortality: 237/1103 (21.2%) Clofibrate versus 583/2789 (20.9%) placebo, z = 0.19, not significant. Secondary outcomes: All cardiovascular mortality: 210/1103 (18.9%) Niacin versus 528/2789 (18.8%) placebo, z = -1.12, not significant. Mortality cause unknown: 3/1103 (0.3%) Niacin versus 13/2789 (0.5%) placebo, z = -0.88, not significant. Coronary heart disease mortality: 178/1103 (15.9%) Niacin versus 452/2789 (16.2%) placebo, z = -1.23, not significant. Sudden cardiovascular death: 118/1103 (10.5%) Niacin versus 269/2789 (9.6%) placebo, z = 0.85, not significant. All cancer deaths: 7/1103 (0.6%) Niacin versus 16/2789 (0.6%) placebo, z = 0.19, not significant. Other non cardiovascular death: 17/1103 (1.5%) Niacin versus 26/2789 (0.9%) placebo, z = 1.59, not significant. Non fatal MI: 100/1103 (8.9%) Niacin versus 339/2789 (12.2%) placebo, z = -2.88, significant (P < 0.005). Coronary death or nonfatal MI: 255/1103 (22.8%) Niacin versus 731/2789 (26.2%) placebo, z = -2.23, significant (P < 0.01). Definite pulmonary embolism (fatal or nonfatal): 11/1103 (1.0%) Niacin versus 30/2789 (1.1%) placebo, z = -0.26, not significant. Definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis: 44/1103 (3.9%) Niacin versus 91/2789 (3.3%) placebo, z = 1.04, not significant. Fatal or nonfatal stroke or intermittent cerebral ischaemic attack: 36/1103 (7.7%) Niacin versus 271/2789 (9.7%) placebo, z = -1.99, not significant. Any definite or suspected fatal or nonfatal cardiovascular event: 875/1103 (78.2%) Niacin versus 2251/2789 (80.7%) placebo, z = -1.78, not significant. Plasma lipid values: Clofibrate: Mean decrease of cholesterol levels (after correcting for lipid changes in the placebo group) = 16.3 mg/100 ml, mean decrease of 6.5% from baseline level. Mean decrease of triglyceride levels (after correcting for lipid changes in the placebo group) = 1.5 mEq/100 ml, mean decrease of 22.3% from baseline level. Clofibrate: Mean decrease of cholesterol levels (after correcting for lipid changes in the placebo group) = 26.2 mg/100 ml (0.67 mmol/l), mean decrease of 9.9% from baseline level. Mean decrease of triglyceride levels (after correcting for lipid changes in the placebo group) = 1.8 mEq/l, mean decrease of 26.1% from baseline level. Side Effects Clofibrate: Decreased libido or potentia: 150/1065 (14.1%) Clofibrate versus 269/2695 (10.0%) placebo, z = 3.60, P < 0.005. Increase in appetite: 56/1065 (5.3%) Clofibrate versus 84/2695 (3.1%) placebo, z = 3.60, P < 0.005. Niacin: Combination of diarrhoea, nausea, vomiting, black tarry stools, stomach
pain: 230/1065 (21.4%) Niacin versus 385/2695 (14.3%) placebo, z = 5.36, P < 0.005.

Flushed: 987/1065 (92.0%) Niacin versus 115/2695 (1.5%) placebo, z = 53.42, P < 0.005.

Itching of skin: 525/1065 (48.9%) Niacin versus 167/2695 (6.2%) placebo, z = 30.53, P < 0.005.

Urticaria: 77/1065 (7.2%) Niacin versus 40/2695 (1.5%) placebo, z = 9.09, P < 0.005.

Other type of rash: 212/1065 (19.8%) Niacin versus 159/2695 (5.9%) placebo, z = 12.94, P < 0.005.

Pain or burning when urinating: 103/1065 (9.6%) Niacin versus 32/2695 (1.2%) placebo, z = 3.68, P < 0.005. Decrease in appetite: 44/1065 (4.1%) Niacin versus 40/2695 (1.5%) placebo, z = 4.81, P < 0.005.

Unexpected weight loss: 29/1065 (2.7%) Niacin versus 24/2695 (0.3%) placebo, z = 4.14, P < 0.005.

Excessive sweating: 36/1065 (3.4%) Niacin versus 49/2695 (1.8%) placebo, z = 2.95, P < 0.005.

Reference number 5167

Behar S; Brunner D; Kaplinsky E; Mandelzweig L; Benderly M;
Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: The bezafibrate infarction prevention (BIP) study

2000 102 Circulation pgs 21 27

Study Type: Randomised Controlled Trial

Inclusion criteria: Men & women (8%) aged 45-74 yrs (mean±SD = 60±7 years, history of MI ≥ 6 months but < 5 yrs before enrolment into the study and/or stable angina pectoris confirmed by coronary angiography, &/or radionuclear studies or standard exercise tests. Prior MI: 78%.

Prior Angina: 57%

A serum lipid profile of: total cholesterol between 180 to 250 mg/dl (4.7 to 6.4 mmol/l), LDL-C ≤ 180 mg/dl (4.7 mmol/l) or ≤ 160 mg/dl (4.1 mmol/l), for patient < 50yrs) (HDL-C ≤ 45 mg/dl (1.16 mmol/l), triglycerides ≤ 300 mg/dl (3.4 mmol/l). Exclusion criteria: Insulin dependent diabetes mellitus, severe heart failure, unstable angina pectoris, hepatic or renal failure, known severity to bezafibrate, or current use of lipid modifying drugs.

Intervention

Bezafibrate retard 400 mg once daily 1548 patients

Comparison

Placebo 1542 patients

Study Length

Mean length of follow up was 6.2 years.


Funding

None listed

Effect

Primary outcome Composite of fatal MI, nonfatal MI or sudden death: 211/1548 (13.6%)

Bezafibrate versus 232/1542 (15.0%) Placebo, RR = - 9.4%, P = 0.26. Non fatal MI: 150/1548 (9.7%) Bezafibrate versus 172/1542 (15.0%) Placebo, RR = - 12.8%, P = 0.18. Fatal MI: 18/1548 (1.2%) Bezafibrate versus 17/1542 (1.1%) Placebo, P = 0.87. Sudden death: 43/1548 (2.8%) Bezafibrate versus 43/1542 (2.8%) Placebo, P = 0.98. Secondary outcomes Composite of hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft: 311/1548 (20.1%) Bezafibrate versus 327/1542 (21.2%) Placebo, P = 0.44. Hospitalisation for unstable angina: 76/1548 (4.9%) Bezafibrate versus 82/1542 (5.3%)

Placebo, P = 0.61. Percutaneous transluminal coronary angioplasty: 91/1548 (5.9%) Bezafibrate versus 88/1542 (5.7%) Placebo, P = 0.84. Coronary artery bypass graft: 144/1548 (9.3%)

Bezafibrate versus 157/1542 (10.2%) Placebo, P = 0.41. Mortality: 161/1548 (10.4%) Bezafibrate versus 152/1542 (9.9%) Placebo, P = 0.62. Cardiac mortality: 95/1548 (6.1%) Bezafibrate versus 157/1542 (5.7%) Placebo, P = 0.61. Noncardiac mortality: 66/1548 (4.3%) Bezafibrate versus 64/1542 (4.2%) Placebo, P = 0.87. Stroke: 72/1548 (4.6%) Bezafibrate versus 77/1542 (5.0%)

Placebo, P = 0.36. Ischemic stroke: 59/1548 (3.3%) Bezafibrate versus 69/1542 (4.5%) Placebo, P = 0.38. All outcomes: 522/1548 (33.7%) Bezafibrate versus 559/1542 (36.3%) Placebo, RR = - 6.6%, P = 0.14. Plasma lipid levels: cumulative probability of primary endpoints at 6.2 years of follow up: Triglycerides: < 150 mg/dl (1.7 mmol/l) Bezafibrate: 938/1548 (12.6%) Placebo: 901/1542 (13.7%) RR = 7.9%, P = 0.43. ≥ 150 mg/dl (1.7 mmol/l) Bezafibrate: 603/1548
(16.3%) Placebo: 629/1542 (17.1%) RR = 4.6, P = 0.48
≥ 175 mg/dl (2.0 mmol/l) Bezafibrate: 407/1548 (15.9%) Placebo: 385/1542 (20.3%) RR = 21.6%, P = 0.07
≥ 200 mg/dl (2.26 mmol/l) Bezafrivate: 234/1548 (12.0%) Placebo: 225/1542 (19.7%) RR = 39.5%, P = 0.02
HDL-C < 35 mg/dl (0.9 mmol/l) & and triglycerides < 150 mg/dl (1.7 mmol/l) Bezafrivate: 378/1548 (13.5%) Placebo: 382/1542 (15.5) RR = 12.4%, P = 0.46
≥ 150 mg/dl (1.7 mmol/l) Bezafrivate: 420/1548 (18.5%) Placebo: 436/1542 (19.4%) RR = 4.5%, P = 0.56
≥ 200 mg/dl (2.26 mmol/l) Bezafrivate: 294/1548 (17.2%) Placebo: 286/1542 (22.2%) RR = 22.6%, P = 0.09
Placebo: 184/1548 (13.0%) Placebo: 162/1542 (22.3%) RR = 41.8%, P = 0.02
≥ 35 mg/dl (0.9 mmol/l) & triglycerides < 150 mg/dl (1.7 mmol/l) Bezafrivate: 560/1548 (12.0%) Placebo: 518/1542 (12.2%) RR = 1.6%, P = 0.77
≥ 150 mg/dl (1.7 mmol/l) Bezafrivate: 183/1548 (11.2%) Placebo: 193/1542 (12.2%) RR = 8.5%, P = 0.59
≥ 175 mg/dl (2.0 mmol/l) Bezafrivate: 113/1548 (12.7%) Placebo: 99/1542 (15.2%) RR = 16.8%, P = 0.45
≥ 200 mg/dl (2.26 mmol/l) Bezafrivate: 50/1548 (8.2%) Placebo: 63/1542 (17.8%) RR = 35.9%, P = 0.33

Safety
The overall incidence of any adverse event was 69% in both groups, and the frequency of each type adverse event was similar in both groups. 7 patients in the placebo group and 5 patients in the bezafibrate group complained of muscular pains during follow up. Creatine phosphokinase levels exceeding twice the upper normal limit was recorded in 4 patients in the bezafibrate group and 1 patients in the placebo group.
Question: Are there stable patients after MI who a) benefit prognostically from revascularisation b) those who don’t benefit prognostically

Grading: 1++  High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number: 3081

National Institute for Clinical Excellence;
Guidance on coronary artery stents in the treatment of ischaemic heart disease
2003 National Institute for Health and Clinical Excellence

Study Type: TA

Reference number: 3083

Pignone M;Rihal C;Bazian Ltd.;
Secondary prevention of ischaemic cardiac events: What are the effects of surgical treatments?
2002 Clinical Evidence 2005

Study Type: Systematic Review

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparisons</th>
<th>Study Length</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

CABG versus medical treatment alone  CABG reduced deaths at 5 and 10 years (death at 5 years: RR 0.61 95% CI 0.48 to 0.77; death at 10 years: RR 0.83 95% CI 0.70 to 0.98). Effects in people with reduced versus normal LV dysfunction Relative benefits were similar in people with normal versus reduced LV dysfunction (normal LV dysfunction: death OR 0.61 95% CI 0.46 to 0.81 versus reduced LV dysfunction: death OR 0.59 95% CI 0.39 to 0.91). It was noted that the absolute benefit of CABG was greater in the LV dysfunction group because the baseline risk of death was greater. Effects in people with different numbers of diseased vessels Statistically lower mortality for CABG versus medical treatment in three vessel and left main stem disease (RR with single vessel disease 0.85, 95% CI 0.22 to 1.33, two vessel disease 0.84, 95% CI 0.54 to 1.32, three vessel disease 0.58, 95% CI 0.42 to 0.80, left main stem 0.32, 95% CI 0.15 to 1.70). PTCA versus medical treatment alone PTCA versus medical treatment improved angina compared with medical treatment alone (RR 0.70 95% CI 0.50 to 0.98), but was associated with a higher rate of coronary artery bypass grafting (RR 1.59 95% CI 1.09 to 2.32). CABG or PTCA versus medical treatment: Effects in asymptomatic people Revascularisation versus medical treatment alone reduction of death or MI at 2 years was 4.7% with revascularization versus 8.8% with symptom guided treatment versus 12.1% with symptom plus electrocardiogram guided treatment.

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

Reference number: 3077

Joint Working Group on Coronary Angioplasty of the British Cardiac Society.;British Cardiovascular Intervention Society.;
Myocardial infarction: full guideline DRAFT (August 2006) – Appendices
Coronary angioplasty: guidelines for good practice and training

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Randomised Controlled Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient: post MI patients, 3 age groups: middle aged (45-65 years), old (66-75 years), very old (&gt; 75 years)</td>
<td></td>
</tr>
<tr>
<td>Characteristics:</td>
<td></td>
</tr>
<tr>
<td>Intervention: hospital-based cardiac rehabilitation (Hos-CR), home-based cardiac rehabilitation (Home-CR), no cardiac rehabilitation (no CR)</td>
<td></td>
</tr>
<tr>
<td>Comparisons: 3 interventions in each age group</td>
<td></td>
</tr>
<tr>
<td>Study Length: 14 months</td>
<td></td>
</tr>
<tr>
<td>Outcomes: Total work capacity (TWC), HRQoL</td>
<td></td>
</tr>
<tr>
<td>Funding: National Research Council Florence University, Regional Government Tuscany Italy</td>
<td></td>
</tr>
<tr>
<td>Effect: Treatment-time interactions showed a greater effect of both interventions compared with controls in middle aged (P = 0.002) and old patients (P &lt; 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 Hosp-CR and Home-CR treatment (P = 0.013 and P &lt; 0.035, respectively) but not with no CR (P = 0.079).</td>
<td></td>
</tr>
</tbody>
</table>

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

Reference number: 3123

Eagle KA; Guyton RA; Davidoff R; Edwards FH; Ewy GA; Gardner TJ; Hart JC; Herrmann HC; Hillis LD; Hutter AM; Lytle BW; Marlow RA; Nugent WC; Orszulak TA; ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft S

Study Type: Systematic Review
Question: Is there and optimum time for beta-blockers to be initiated in unselected patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Reference number 2994

Rees K; Bennett P; West R; Davey SG; Ebrahim S;
Psychological interventions for coronary heart disease
2004

Meta-analysis of 22 trails (10634 patients) reporting this outcome (OR 0.78 95% CI 0.67, 0.90). There was significant heterogeneity of effects some of these clinical outcomes, and there was evidence of publication bias for the non-fatal myocardial infarction findings. The evidence was dominated by two large trials (ENRICHD, Jones), both of which produced null findings for all clinical outcomes. Anxiety was measured in only 9 trials. A small but statistically significant reduction in anxiety with the intervention was seen, where the SMD was -0.08 (-0.16, -0.01), see Figure 4. 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) random effects model), see Figure 5. Several studies reported composite measures for anxiety, depression and mental health, and these form a separate category. For the 5 trials overall (347 patients) there is a significant beneficial reduction (SMD -0.22 (-0.44, -0.01)). Eighteen trials were identified that included some form of stress management (SM). Results were presented on 18 trials with any stress management intervention +/- other rehabilitation versus usual care/other rehabilitation. There was no strong evidence of effect of SM on total mortality in the 10 trials (3425 patients) reporting this as an outcome (OR 0.88, 95% CI 0.67, 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 (pooled effect estimate OR 0.62(0.38, 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, 0.92). One of these 8 trials recruited patients with identified levels of psychopathology prior to randomisation (Stern). Only one of these 8 trials examined the effects of a stress management intervention without the influence of other rehabilitation interventions (Jones). 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) - random effects model). Results are dominated by one large trial (Jones) which showed a null effect, and hence significant heterogeneity between studies (SMD -0.3 (-0.48, -0.13) random effects model). 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)).

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

Reference number 1346

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 152 of 248
Session lasted 30-40 minutes, was conducted by a psychologist during the hospital stay. 1st session Individual-ised according to Illness Perception Questionnaire. Explained pathophysiology of MI, examined patient's belief, addressed misconceptions. 2nd

Comparisons

Study Length 3 months

Outcomes Illness Perception Questionnaire (IPQ), Return to work

Funding Heart Found. NZ

Effect At 3 months, there was a significant success in changing patient’s belief to a more positive and controllable view of MI, as determined by the IPQ, compared to control patients. The intervention group had a shorter delay in return to work rate compared with control.

Reference number 3379

Pfeffer MA; Greaves SC; Arnold JM; Glynn RJ; LaMotte FS; Lee RT; Menapace FJ; Rapaport E; Ridker PM; Rouleau JL; Solomon SD; Hennekens CH;

Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial

1997 95 Circulation

Study Type: Randomised Controlled Trial

Patient Post MI < 65 years

Characteristics Session lasted 30-40 minutes, was conducted by a psychologist during the hospital stay. 1st session Individual-ised according to Illness Perception Questionnaire. Explained pathophysiology of MI, examined patient’s belief, addressed misconceptions. 2nd

Comparisons

Study Length 3 months

Outcomes Illness Perception Questionnaire (IPQ), Return to work

Funding Heart Found. NZ

Effect At 3 months, there was a significant success in changing patient’s belief to a more positive and controllable view of MI, as determined by the IPQ, compared to control patients. The intervention group had a shorter delay in return to work rate compared with control.

Improvements were 2.4±8.8 units, 3.9±8.2 units and 4.8±10.0 units for placebo, low dose ramipril and high dose ramipril, respectively, P = 0.47 for trend. Regression model of early change in EF demonstrated by ramipril demonstrated a significant improvement with the use of ramipril (P = 0.011). Akinesis / dyskinesis decreased in all groups. Late phase Continued reduction in the proportion of the LV that was assessed as either akinetic or dyskinetic in all groups. However, only the group who received ramipril for the first time during the late period (placebo to full dose) showed a statistically significant improvement in wall motion (P = 0.02).

Reference number 3379

Pfeffer MA; Greaves SC; Arnold JM; Glynn RJ; LaMotte FS; Lee RT; Menapace FJ; Rapaport E; Ridker PM; Rouleau JL; Solomon SD; Hennekens CH;

Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial

1997 95 Circulation

Study Type: Randomised Controlled Trial

Patient Men and women (22%), > 21 years with MI within 24 hours post MI. Mean age 60.6 years.

Characteristics Need of ACEI for CHF, serum creatinine ≥ 2.5 mg/dl, presence of major complication of infarction that was not stabilized before infarction (e.g. cardiac shock, persistent ischemia, or unstable rhythm), systolic blood pressure > 100 mm HG, or failure to complete all pre-randomization evaluations within 24 hours from the onset of chest pain.

Intervention

Early (1 day) ramipril 3 groups 117 recruits early placebo/late full dose ramipril group 116 recruits early low 0.625 mg ramipril/late low 0.625 mg ramipril 119 recruits early full dose ramipril/late full dose ramipril. Ramipril highest achievable dose in early phase, first 14 days up to 10 mg (full dose). Initial dose 1.25 mg ramipril 2.5 mg at 12 hours, subsequently titrated up to 10 mg ramipril in 24 hour intervals.

Comparisons

Study Length 90 days

Outcomes LV Ejection fraction (LVEF) Akinesis and dyskinesis (% LV that was non-contractile)

Funding Hoechst Marion Roussel, Upjohn

Effect First 14 days LVEF increased in all 3 groups, but greatest in the full dose ramipril group. Improvements were 2.4±8.8 units, 3.9±8.2 units and 4.8±10.0 units for placebo, low dose ramipril and high dose ramipril, respectively, P = 0.47 for trend. Regression model of early change in EF demonstrated by ramipril demonstrated a significant improvement with the use of ramipril (P = 0.011). Akinesis / dyskinesis decreased in all groups. Late phase Continued reduction in the proportion of the LV that was assessed as either akinetic or dyskinetic in all groups. However, only the group who received ramipril for the first time during the late period (placebo to full dose) showed a statistically significant improvement in wall motion (P = 0.02).
Question: What are the information and support needs for patients at different points in the care pathway?

Grading: 1++  

**High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias**

Reference number: 2964

Dusseldorp E; Van ET; Maes S; Meulman J; Kraaij V;  
A meta-analysis of psychoeducational programs for coronary heart disease patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Psycho-educational and/or stress management</td>
<td></td>
</tr>
</tbody>
</table>

**Funding**: Nether-lands Organ. Scientific Res.

Cardiac mortality  For the long term, the odds of surviving were 1.52 times higher for the treatment group (34% reduction in mortality) than for the control group. For the partial success cluster, the odds of surviving were 1.44 times higher for the treatment group (31% reduction in mortality). MI recurrence  The odds ratios reflect a 20% (total term), 26% (medium term) and 29% (long term) reduction in recurrence of MI. Depression and anxiety  No significant favourable results were found.
Appendix E – Health Economic Extractions
What is the cost effectiveness of Cardiac rehabilitation in Post MI?

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic study type</td>
<td>CEA, benefit measure was years of life saved (YLS)</td>
</tr>
<tr>
<td>Population, country &amp; perspective</td>
<td>Males with a post acute MI below the age of 65 years patient or insurance payer</td>
</tr>
<tr>
<td>Intervention</td>
<td>Cardiac rehabilitation + usual care</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>No cardiac rehabilitation (usual care which consisted of thrombolytic therapy, coronary bypass surgery, cholesterol lowering drugs and smoking cessation).</td>
</tr>
<tr>
<td>Source of effectiveness data</td>
<td>Published review of RCTs</td>
</tr>
<tr>
<td>Method of eliciting health valuations (if applicable)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cost components included</td>
<td>Direct medical costs</td>
</tr>
<tr>
<td>Currency and cost year</td>
<td>USA, 1995</td>
</tr>
<tr>
<td>Results - cost per patient per alternative</td>
<td>The net cost for MI was $430 in 1985 and $940 in 1995. The costs of other common interventions were not stated</td>
</tr>
<tr>
<td>Results - effectiveness per patient per alternative</td>
<td>Cumulative all-cause mortality in the rehabilitation group was reduced by 21.2% at the end of year 1, by 22.9% at the end of 2 years and 16.9% at the end of 3 years of follow-up</td>
</tr>
<tr>
<td>Results - incremental cost-effectiveness</td>
<td>The cost per year of life saved was $2,130 in 1985 and the cost per year of life saved (projected) was $4,950 in 1995 (at a 5% discount rate)</td>
</tr>
<tr>
<td>Results - uncertainty</td>
<td>Varying the survival rate, the survival probabilities and the rehospitalisation expenses averted</td>
</tr>
<tr>
<td>Time horizon &amp; discount rate</td>
<td>3 years 5%</td>
</tr>
<tr>
<td>Source of funding</td>
<td>Not stated</td>
</tr>
<tr>
<td>Comments</td>
<td>Quantities and costs were reported separately. The authors based their analysis of effectiveness on studies with a randomised design, but it is not clear whether these were identified through a systematic search of the medical literature. It should be noted that estimated benefits are unlikely to be generalisable to females of the same age. As acknowledged by the authors, adjustment for quality of life could have been made</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Economic study type</td>
<td>Cost consequence analysis. Outcomes were Quality of life (QOL) measures and four measures of return to normal activities (paid and unpaid return to any work and to pre-AMI level of work).</td>
</tr>
<tr>
<td>Population, country &amp; perspective</td>
<td>Low-risk patients after acute myocardial infarction (AMI),</td>
</tr>
<tr>
<td>Intervention Comparison(s)</td>
<td>6 weeks of standard rehabilitation (REHAB, n = 70) (exercise and counselling 4 times a week)</td>
</tr>
<tr>
<td></td>
<td>No formal rehabilitation (ERNA, n = 72).</td>
</tr>
<tr>
<td>Source of effectiveness data</td>
<td>RCT</td>
</tr>
<tr>
<td>Method of eliciting health valuations (if applicable)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cost components included</td>
<td>Direct medical cost and indirect costs</td>
</tr>
<tr>
<td>Currency and cost year</td>
<td>$AUD, cost year not stated</td>
</tr>
<tr>
<td>Results – cost per patient per alternative</td>
<td>$21.57/Patient/session for 14 sessions on average direct costs excluding hospital overheads</td>
</tr>
<tr>
<td></td>
<td>$28.12/Patient/session for 14 sessions on average total hospital costs.</td>
</tr>
<tr>
<td></td>
<td>The net cost that could be saved by the health service by targeting rehabilitation to high-risk patients was approximately $300 (Australian, 1999) per low-risk patient</td>
</tr>
<tr>
<td>Results – effectiveness per patient per alternative</td>
<td>There were no statistically significant differences between the two groups in any of the outcomes measured or in the use of other health services</td>
</tr>
<tr>
<td>Results - incremental cost-effectiveness</td>
<td>Not done (cost minimisation)</td>
</tr>
<tr>
<td>Results-uncertainty</td>
<td>Not done</td>
</tr>
<tr>
<td>Time horizon &amp; discount rate</td>
<td>12 months and discounting was not necessary</td>
</tr>
<tr>
<td>Source of funding</td>
<td>Public</td>
</tr>
<tr>
<td>Comments</td>
<td>Did not state the cost year. Good discussion</td>
</tr>
</tbody>
</table>

**Economic study type**
CUA, QALYs, cost/QALY

**Population, country & perspective**
Patients with AMI and mild to moderate anxiety or depression, or both
Perspective not stated but appears to be societal

**Intervention**
Comprehensive cardiac rehabilitation intervention (n = 99)
Usual care (n = 102).

**Comparison(s)**

**Source of effectiveness data**
RCT and review of literature

**Method of eliciting health valuations (if applicable)**
TTO

**Cost components included**
Direct medical and indirect patient costs

**Currency and cost year**
US$ 1991

**Results - cost per patient per alternative**
$480/patient. During 1-year follow-up

**Results - effectiveness per patient per alternative**
Rehabilitation patients had fewer "other rehabilitation visits" (p < 0.0001) and gained 0.052 quality-adjusted life-year more than did the group with usual care

**Results - incremental cost-effectiveness**
$9,200/quality-adjusted life-year gained with cardiac rehabilitation during the year of follow-up

**Results-uncertainty**

**Time horizon & discount rate**
12 months and 5%

**Source of funding**
Not stated

**Comments**
Generally a good paper
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Economic study type</td>
<td>Cost consequence analysis</td>
</tr>
<tr>
<td>Population, country &amp; perspective</td>
<td>Non-selected post MI patients, societal perspective. Mortality (total &amp; cardiac) Readmission, non-fatal and total cardiac events</td>
</tr>
<tr>
<td>Intervention</td>
<td>Comprehensive cardiac rehabilitation programme 147 non-selected MI patients aged less than 65 years (124 men vs. 23 women) Standard care after myocardial infarction (MI) non-selected MI-population aged less than 65 years (n = 158) (134 men vs. 24 women)</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td></td>
</tr>
<tr>
<td>Source of effectiveness data</td>
<td>Prospective non-RCT</td>
</tr>
<tr>
<td>Method of eliciting health valuations (If applicable)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cost components included</td>
<td>Both direct and indirect costs (time costs of rehab and lost productivity)</td>
</tr>
<tr>
<td>Currency and cost year</td>
<td>SEK 1996</td>
</tr>
<tr>
<td>Results - cost per patient per alternative</td>
<td>Rehab group SEK 484260 vs. SEK 557770 usual care and difference was SEK 73,500 in favour of the rehabilitated group</td>
</tr>
<tr>
<td>Results - effectiveness per patient per alternative</td>
<td>Mortality (total &amp; cardiac) did not differ between the groups Readmission was less in the rehab 13.7 days vs. 19.3 days in the control p&lt;0.05 They differed in non-fatal reinfaction (17.3 vs. 33.3%), total cardiac events (39.1 vs. 53.2%) p=0.001</td>
</tr>
<tr>
<td>Results - incremental cost-effectiveness</td>
<td>Not calculated because it was a cost consequence analysis</td>
</tr>
<tr>
<td>Results - uncertainty</td>
<td>Remained robust</td>
</tr>
<tr>
<td>Time horizon &amp; discount rate</td>
<td>5 yrs, 0 &amp; 10%</td>
</tr>
<tr>
<td>Source of funding</td>
<td>Not stated</td>
</tr>
<tr>
<td>Comments</td>
<td>Even though the study was not controlled it looked at two real life clinical situations, which make the results more useful for the case for comprehensive rehabilitation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Economic study type</th>
<th>Review of economic evaluations including costs of the UK cardiac rehabilitation programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population, country &amp; perspective</td>
<td>Post-MI patients, Societal cost data for UK and effectives data from a Canadian trial</td>
</tr>
<tr>
<td>Intervention</td>
<td>Cardiac rehabilitation</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>Usual care</td>
</tr>
<tr>
<td>Source of effectiveness data</td>
<td>RCT</td>
</tr>
<tr>
<td>Method of eliciting health valuations (if applicable)</td>
<td>N/A</td>
</tr>
<tr>
<td>Cost components included</td>
<td>Both direct and indirect patient costs</td>
</tr>
<tr>
<td>Currency and cost year</td>
<td>£, 1994/5</td>
</tr>
</tbody>
</table>
| Results - cost per patient per alternative | £140.00 excluding the indirect costs  
£207 including indirect costs |
| Results - effectiveness per patient per alternative | Life year gained per patient 0.022  
QALY gained 0.052 |
| Results - incremental cost-effectiveness | £6400/life year gained  
£2700/QALY gained |
| Results - uncertainty | Not done |
| Time horizon & discount rate | 12 weeks & 5% |
| Source of funding | Not stated |
| Comments | Did not state where they derived the cost data from, but gives insight into the UK situation |

**What is the effectiveness of adding ACEI versus placebo to improve outcome in patients after MI?**

**Study Quality:**  
1+ Cost-effectiveness of captopril therapy after myocardial infarction.[see comment]

**Author:**  
Tsevat J; Duke D; Goldman L; Pfeffer MA; Lamas GA; Soukup JR; Kuntz KM; Lee TH; 1995
**Intervention:** Captopril  
**Comparison:** Placebo  
**Population:** Post MI patients with LVD  
**Perspective:** NHS  
**Study type:** CUA  
**Methods:** RCT (SAVE study)  
**Health valuations:** TTO, interviewed 82 patients  
**Cost components:** direct medical  
**Currency:** US$  
**Cost year:** 1991  
**Time horizon:** Lifetime  
**Discount rate:** 5%  

<table>
<thead>
<tr>
<th>AGE</th>
<th>Limited benefit</th>
<th>Persistent benefit model</th>
</tr>
</thead>
<tbody>
<tr>
<td>50yrs</td>
<td>Captopril</td>
<td>$3209</td>
</tr>
<tr>
<td>Placebo</td>
<td>$30369</td>
<td>$30369</td>
</tr>
<tr>
<td>60yrs</td>
<td>Captopril</td>
<td>$26128</td>
</tr>
<tr>
<td>Placebo</td>
<td>$24449</td>
<td>$24449</td>
</tr>
<tr>
<td>70yrs</td>
<td>Captopril</td>
<td>$20822</td>
</tr>
<tr>
<td>Placebo</td>
<td>$19099</td>
<td>$19099</td>
</tr>
<tr>
<td>80yrs</td>
<td>Captopril</td>
<td>$16699</td>
</tr>
</tbody>
</table>
Placebo     $ 14844     $ 14844
## Results-effectiveness:

<table>
<thead>
<tr>
<th>AGE</th>
<th>Limited benefit</th>
<th>Persistent benefit model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QALYS</td>
<td>QALYS</td>
</tr>
<tr>
<td>50yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>8.13</td>
<td>8.34</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.10</td>
<td>8.10</td>
</tr>
<tr>
<td>60yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.51</td>
<td>6.85</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.33</td>
<td>6.33</td>
</tr>
<tr>
<td>70yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>5.07</td>
<td>5.47</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.72</td>
<td>4.72</td>
</tr>
<tr>
<td>80yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>3.96</td>
<td>4.33</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.44</td>
<td>3.44</td>
</tr>
</tbody>
</table>

## Results-ICER:

<table>
<thead>
<tr>
<th>AGE</th>
<th>Ltd benefit ($/QALY)</th>
<th>Persistent benefit model ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50yrs</td>
<td>60800</td>
<td>10400</td>
</tr>
<tr>
<td>60yrs</td>
<td>9000</td>
<td>5600</td>
</tr>
<tr>
<td>70yrs</td>
<td>4900</td>
<td>4300</td>
</tr>
<tr>
<td>80yrs</td>
<td>3600</td>
<td>3700</td>
</tr>
</tbody>
</table>

## Results-Uncertainty:

For 60-80 years the results are robust to changes in utilities, discount rate, and costs and sensitive in the 50 year olds for the limited benefit model. The persistent benefit model was stable but sensitive to mainly utility changes for the 50 year olds. Worst case analysis showed that the >60yrs results still favour Captopril and for less than
60 years results are not stated

**Comments:** Analysed the results using two models. A) Limited benefit model: assumed mortality will be the same between the intervention post-trial periods. B) Persistent benefit model: assumed differences observed during the trial period will persist for the remaining life time. They also analysed their results by subgroups of age. Appropriate analytical methods were used, and sources of data documented. Data was incorporated as point estimates and parameters subjected to sensitivity analysis.
Study Quality: 1+  The cost and cardioprotective effects of enalapril in hypertensive patients with left ventricular dysfunction

Author: Cook JR; Glick HA; Gerth W; Kinosian B; Kostis JB; 1998

Intervention: Enalapril

Comparison: Placebo

Population: Patients with elevated blood pressure and LVD

Perspective: SOCIETAL (only direct medical costs were collected)

Study type: CEA & CUA

Methods: RCT (SOLVD study)

Health valuations: From literature

Cost components: Direct medical

Currency: US$

Cost year: 1996

Time horizon: life time projection and the 3 year trial observational period

Discount rate: 5%

Results - cost: Enalapril Placebo

$8499  $9156

Results -effectiveness: Outcome Enalapril Placebo

Years gained 2.84 2.68

QALYs 1.74 1.62

Results -ICER: not calculated. Enalapril dominated placebo i.e. it costs less and results in more health benefits

Results - Uncertainty: results were very robust and the CEACs showed that there was a less than 10% chance that enalapril treatment will increase the costs compared to placebo. Lifetime projection showed that 94% of the cases enalapril will dominate
Source of Funding: not stated

Comments: placebo reported results of the treatment trial and prevention trial. This report focuses on the prevention trial results. They used standard methodology in their modelling. Sources of effectiveness and cost data well referenced. Data was incorporated as point estimates and subjected to probabilistic sensitivity analysis as well as univariate.
**Study Quality:** 1+  
Cost-effectiveness of ramipril in patients at high risk for cardiovascular events: a Swiss perspective

**Author:** Aurbach A; Russ W; Battegay E; Bucher HC; Brecht JG; Schadlich PK; Sendi P; 2004

**Intervention:** Ramipril

**Comparison:** Placebo

**Population:** Patients with increased risk of cardiovascular events

**Perspective:** NHS

**Study type:** CEA,

**Methods:** RCT (HOPE study)

**Health valuations:** NOT APPLICABLE

**Cost components:** direct medical

**Currency:** OTHER (Swiss Franc) CHF

**Cost year:** 2001

**Time horizon:** 4.5yrs

**Discount rate:** 5%

**Results- cost:**  
HOPE study all patients: CHF 71351  
HOPE diabetic subgroup: CHF 74650

**Results-effectiveness:**  
HOPE study all patients: LYG 11.88  
HOPE diabetic subgroup: LYG 19.69

**Results-ICER:**  
HOPE study all patients: ICER 6005/LYG  
HOPE diabetic subgroup: ICER 3790/LYG

**Results-Uncertainty:** did both deterministic and probabilistic sensitivity analysis. Results were sensitive to cost of drug

**Source of Funding:** Private (Aventis Pharma)
**Comments:** well reported using standard methodology. Data incorporated as point estimates and subjected to sensitivity analysis. Used CEACs to quantify the uncertainty surrounding the ICER. Also did a best case and worst case analysis.
Study Quality: 1+ The cost-effectiveness of ramipril in the treatment of patients at high risk of cardiovascular events: a Swedish sub-study to the HOPE study

Author: Bjorholt I; Andersson FL; Kahan T; Ostergren J; 2002

Intervention: Ramipril

Comparison: Placebo

Population: Patients at high risk of cardiovascular events

Perspective: NHS

Study type: CEA

Methods: RCT (HOPE study)

Health valuations: base case results did not consider quality of life, but in sensitivity analysis they did using TTO

Cost components: direct medical for base case and direct medical and non medical + indirect costs

Currency: OTHER (SKr)

Cost year: 1999

Time horizon: 4.5 years

Discount rate: 3%

Results- cost: Total category Ramipril Placebo difference (Mean SEK)

<table>
<thead>
<tr>
<th></th>
<th>Total direct medical</th>
<th>Ramipril</th>
<th>Placebo</th>
<th>difference (Mean SEK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct nonmedical</td>
<td>1450</td>
<td>1725</td>
<td>-275 (NS)</td>
<td>52525</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>2582 (NS)</td>
<td></td>
<td></td>
<td>49672</td>
</tr>
</tbody>
</table>

NS = non significant difference

Results-effectiveness: Expected LYG at the end of the study 0.16

Cardiovascular events avoided 3.8%

Results-ICER: BASE CASE RESULTS
### Costs related to cardiovascular disease only:

<table>
<thead>
<tr>
<th>Cost/LYG</th>
<th>Cost/CVE avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct medical</td>
<td>16600</td>
</tr>
<tr>
<td>Direct medical + direct non medical</td>
<td>16100</td>
</tr>
</tbody>
</table>


Costs related to all diseases

<table>
<thead>
<tr>
<th></th>
<th>Cost/LYG</th>
<th>Cost/CVE avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct medical</td>
<td>5400</td>
<td>207300</td>
</tr>
<tr>
<td>Direct medical +</td>
<td>54600</td>
<td>249600</td>
</tr>
<tr>
<td>direct non medical+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using QoL weights

SEK 26600/QALY
SEK 333300/QALY if future costs are included

**Results-Uncertainty:** the results were sensitive to life expectancy assumptions and QALYs. The primary analysis focused on the health service provider perspective. Additional analysis was done from societal perspective which included direct medical + direct non medical + indirect costs.

**Source of Funding:** Private (Astra Zeneca and Aventis)

**Comments:** base case used the health care perspective, but considered societal in further analysis. Data was incorporated as point estimates from the HOPE study appropriate modelling methods were used.
Study Quality: Cost-effectiveness of the treatment of heart failure with ramipril: a Spanish analysis of the AIRE study

Author: Hart WM; Rubio-Terres C; Pajuelo F; Juanatey JR; 2002

Intervention: Ramipril

Comparison: Placebo

Population: Post MI with heart failure

Perspective: NHS

Study type: CEA

Methods: RCT (AIRE study)

Health valuations: NOT APPLICABLE

Cost components: Direct medical

Currency: EURO

Cost year: 2000

Time horizon: 4 yrs

Discount rate: 6%

Results- cost: Follow up add cost on ramipril

1 yr euro 129.2

2yr euro 197.6

3yr euro 435.5

3.8yr euro 399.2

Results-effectiveness: Follow up incremental LYG

1 yr 0.027

2yr 0.059

3yr 0.071
Results-ICER:

<table>
<thead>
<tr>
<th>Follow up</th>
<th>cost/LYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr</td>
<td>euro 4784</td>
</tr>
<tr>
<td>2 yr</td>
<td>euro 2286</td>
</tr>
<tr>
<td>3 yr</td>
<td>euro 2763</td>
</tr>
<tr>
<td>3.8 yr</td>
<td>euro 1550</td>
</tr>
</tbody>
</table>

Results-Uncertainty: Two-way sensitivity analysis varying the length of stay and discount rate was done. Results were robust.

Source of Funding: Private (Aventis Pharma)

Comments: The study was well reported. Data sources well referenced and incorporated as point estimates. Appropriate methods were used.
<table>
<thead>
<tr>
<th>Study Quality:</th>
<th>A South African pharmaco-economic analysis of the acute infarction ramipril efficacy (AIRE) study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author:</td>
<td>Anderson AN; Moodley I; Kropman K; 2000</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Ramipril</td>
</tr>
<tr>
<td>Comparison:</td>
<td>Placebo</td>
</tr>
<tr>
<td>Population:</td>
<td>Post MI patients with heart failure</td>
</tr>
<tr>
<td>Perspective:</td>
<td>NHS</td>
</tr>
<tr>
<td>Study type:</td>
<td>CEA &amp; CUA</td>
</tr>
<tr>
<td>Methods:</td>
<td>RCT (AIRE study)</td>
</tr>
<tr>
<td>Health valuations:</td>
<td>NOT STATED (used data from literature)</td>
</tr>
<tr>
<td>Cost components:</td>
<td>Direct medical</td>
</tr>
<tr>
<td>Currency:</td>
<td>OTHER (South Africa Rand)</td>
</tr>
<tr>
<td>Cost year:</td>
<td>1999</td>
</tr>
<tr>
<td>Time horizon:</td>
<td>4yrs</td>
</tr>
<tr>
<td>Discount rate:</td>
<td>5%</td>
</tr>
<tr>
<td>Results- cost:</td>
<td>Follow up</td>
</tr>
<tr>
<td></td>
<td>1y</td>
</tr>
<tr>
<td></td>
<td>2y</td>
</tr>
<tr>
<td></td>
<td>3.8y</td>
</tr>
<tr>
<td>Results-effectiveness:</td>
<td>Follow up</td>
</tr>
<tr>
<td></td>
<td>1y</td>
</tr>
<tr>
<td></td>
<td>2y</td>
</tr>
<tr>
<td></td>
<td>3.8y</td>
</tr>
</tbody>
</table>
QALYs for <65yrs  0.786
QALYs for >65yrs  0.932

<table>
<thead>
<tr>
<th>Results-ICER:</th>
<th>FU</th>
<th>cost/LYG</th>
<th>lower limit</th>
<th>upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y</td>
<td>67907</td>
<td>49633</td>
<td></td>
<td>91290</td>
</tr>
<tr>
<td>2y</td>
<td>17516</td>
<td>12743</td>
<td></td>
<td>23615</td>
</tr>
<tr>
<td>3.8y</td>
<td>4423</td>
<td>3284</td>
<td></td>
<td>5888</td>
</tr>
</tbody>
</table>
COST UTILITY RESULTS

<table>
<thead>
<tr>
<th>Age group</th>
<th>cost/QALY</th>
<th>lower limit</th>
<th>upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65yrs</td>
<td>5627</td>
<td>4177</td>
<td>7490</td>
</tr>
<tr>
<td>&gt;65yrs</td>
<td>4744</td>
<td>3522</td>
<td>6315</td>
</tr>
</tbody>
</table>

**Results-Uncertainty:** Results were robust in sensitivity analysis as shown by the confidence intervals.

**Source of Funding:** Private (Hoechst Marion Russell)

**Comments:** Used QoL weights from the literature and referenced their sources. Data incorporated as point estimates and appropriate methodology was used. Stratified their results according to age and as expected the ICERs were favourable for the elderly than the younger patients.
No: 953

**Study Quality:** 1+  Economic aspects of treatment with captopril for patients with asymptomatic left ventricular dysfunction in The Netherlands.

**Author:** Michel BC; Al MJ; Remme WJ; Kingma JH; Kragten JA; van Nieuwenhuizen R; van Hout AB; 1996

**Intervention:** Captopril

**Comparison:** Placebo

**Population:** Post MI with LVD

**Perspective:** SOCIETAL (but only direct medical costs are reported)

**Study type:** CEA

**Methods:** RCT (SAVE & SOLVD study)

**Health valuations:** NOT APPLICABLE

**Cost components:** Direct medical

**Currency:** OTHER (DFI Netherlands)

**Cost year:** not stated

**Time horizon:** 4yr and 20 year extrapolation

**Discount rate:** 5%

**Results- cost:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Additional cost</th>
<th>Additional survivor</th>
</tr>
</thead>
<tbody>
<tr>
<td>4yrs</td>
<td>2491</td>
<td></td>
</tr>
<tr>
<td>20yrs</td>
<td>8723</td>
<td></td>
</tr>
</tbody>
</table>

**Results-effectiveness:**

<table>
<thead>
<tr>
<th>Time</th>
<th>LYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>4yrs</td>
<td>0.11</td>
</tr>
<tr>
<td>Follow up</td>
<td>cost/LYG</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>4yrs</td>
<td>22887</td>
</tr>
<tr>
<td>20yrs</td>
<td>15799</td>
</tr>
</tbody>
</table>
Results-Uncertainty: both univariate and multivariate sensitivity analysis were done. Univariate showed that results were sensitive to cost of the drug and the occurrence and prevention of heart failure.

Source of Funding: not stated

Comments: Data was incorporated as point estimates and appropriate methods of modelling were used. Sources of both effectiveness and cost data were described and referenced. Sensitivity analysis was done and caveats of the study well discussed.
No 948

Study Quality: 1 Clinical and economic benefits of ramipril: an Australian analysis of the HOPE study. [see comment]

Author: Smith MG; Neville AM; Middleton JC; 2003

Intervention: Ramipril

Comparison: Placebo

Population: Patients at high risk of cardiovascular diseases

Perspective: NHS

Study type: CEA

Methods: RCT (HOPE study)

Health valuations: NOT APPLICABLE

Cost components: Direct medical

Currency: AU$

Cost year: not stated

Discount rate: 5%

Results- cost: not given

Results-effectiveness: outcome number avoided (95%CI) over 5yrs

Stroke 9188 (4305 to 14317)
MI 14658 (6765 to 22801)
Revascularisation 14317 (4925 to 23678)
Cardiovascular related mortality 12534 (6156 to 18655)

Results-ICER: cost/LYS (95%CI)

A$17214 (8338 to 39536)
Results-Uncertainty: Both a univariate and Monte Carlo sensitivity analysis was done. The results were sensitive to risk of cardiovascular death, cost and risk of revascularisation mainly. Structural assumption about the similarity between the Australian population to that used in the HOPE were similar were tested, so was the effect of blood pressure reduction and results remained robust.

Source of Funding: not stated, but the author worked for Aventis Pharma

Comments: Did not provide detailed costs data. Used appropriate methodology for incorporating data. They used probabilistic sensitivity analysis to quantify the confidence intervals around the ICER and their findings were robust.
Study Quality: 1+ Cost effectiveness of ramipril treatment for cardiovascular risk reduction

Author: Malik IS; Bhatia VK; Kooner JS; 2001

Intervention: Ramipril

Comparison: Placebo

Population: Patients with different risks of mortality. Mortality risks are classified as low (1%), medium (2.44%) high (4.5%) and highest (7%)

Perspective: NHS

Study type: CEA

Methods: RCT (HOPE, AIRE studies)

Health valuations: NOT APPLICABLE

Cost components: direct medical

Currency: £

Cost year: 1999-2000

Time horizon: 5 yrs to lifetime

Discount rate: 6%

Results- cost: not given

Results-effectiveness: authors estimated number of lives gained per year for those on ramipril as well as those eligible for treatment using HOPE study results

<table>
<thead>
<tr>
<th>Eligible population</th>
<th>Life year gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>&gt;3000000</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1400000</td>
</tr>
<tr>
<td>Stroke</td>
<td>600000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1700000</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1000000</td>
</tr>
</tbody>
</table>
Results-ICER:  

<table>
<thead>
<tr>
<th></th>
<th>5yr</th>
<th>20yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>14700</td>
<td>2800</td>
</tr>
<tr>
<td>Low risk</td>
<td>36600</td>
<td>5300</td>
</tr>
<tr>
<td>High risk</td>
<td>4000</td>
<td>100</td>
</tr>
<tr>
<td>Highest risk</td>
<td>1300</td>
<td>-900 (net saving)</td>
</tr>
</tbody>
</table>

Results-Uncertainty: Results were sensitive to drug cost and cost savings (arising from reduction in events) using arbitrary figures of 50 to 200% of the baseline values.

Source of Funding: Charitable

Comments: The study was well reported using standard methodology including a half year correction factor for the occurrence of events. Data was incorporated as point estimates and sources well referenced. A detailed sensitivity analysis was done.
No 941

**Study Quality:** 1+  Cost-effectiveness of ramipril therapy for patients with clinical evidence of heart failure after acute myocardial infarction

**Author:** Martinez C; Ball SG; 1995

**Intervention:** Ramipril

**Comparison:** Placebo

**Population:** Patients with heart failure after MI

**Perspective:** NHS

**Study type:** CEA

**Methods:** RCT (AIRE study)

**Health valuations:** NOT APPLICABLE

**Cost components:** Direct medical

**Currency:** £

**Cost year:** 1993

**Time horizon:** 4 yrs

**Discount rate:** 6%

**Results- cost:**

<table>
<thead>
<tr>
<th>Follow up</th>
<th>cost/patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y</td>
<td>11.42</td>
</tr>
<tr>
<td>2y</td>
<td>12.79</td>
</tr>
<tr>
<td>3.8y</td>
<td>73.77</td>
</tr>
</tbody>
</table>

**Results-effectiveness:**

<table>
<thead>
<tr>
<th>Follow up</th>
<th>LYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y</td>
<td>0.027</td>
</tr>
<tr>
<td>2y</td>
<td>0.090</td>
</tr>
<tr>
<td>3.8y</td>
<td>0.289</td>
</tr>
</tbody>
</table>

**Results-ICER:**

Follow up cost/LYG
<table>
<thead>
<tr>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y</td>
<td>425.79</td>
</tr>
<tr>
<td>2y</td>
<td>147.90</td>
</tr>
<tr>
<td>3.8y</td>
<td>286.24</td>
</tr>
</tbody>
</table>

**Results-Uncertainty:** did a two way sensitivity analysis and results were not sensitive to changes in LYG and hospitalisation costs

**Source of Funding:** not stated

**Comments:**
No 982

**Study Quality:** 1+ Economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events

**Author:** Backhouse ME; Richter A; Gaffney L; 2000

**Intervention:** Ramipril

**Comparison:** Placebo

**Population:** Patients at high risk of cardiovascular events

**Perspective:** NHS

**Study type:** CEA

**Methods:** RCT (HOPE study)

**Health valuations:** NOT APPLICABLE

**Cost components:** direct medical

**Currency:** £

**Cost year:** 1999

**Time horizon:** 5yrs

**Discount rate:** 6%

**Results-cost:** cost/patient

- Ramipril: 1426
- Placebo: 808

**Results-effectiveness:** life year gained (LYG)

- Ramipril: 7.68
- Placebo: 7.57

**Results-ICER:** £5544/LYG
Results-Uncertainty: Results were not sensitive to assumptions about the timing of the occurrence of events (half cycle correction factor), but rather to assumptions about life expectancy beyond the 5 year trial period. This also dependant on age. (structural assumption being tested in patients stratified by age)

Source of Funding: not stated

Comments: Did a sensitivity analysis focusing on structural assumptions and a subgroup stratified by age. Data incorporated as point estimates using appropriate methodology
No 991

Study Quality: 1+ Cost-effectiveness analysis of ramipril in heart failure after myocardial infarction: economic evaluation of the Acute Infarction Ramipril Efficacy (AIRE) Study for Germany from the perspective of statutory health insurance

Author: Schadlich PK; Huppertz E; Brecht JG; 1998

Intervention: Ramipril

Comparison: Placebo

Population: Post MI patients with heart failure

Perspective: NHS

Study type: CEA

Methods: RCT (AIRE study)

Health valuations: NOT APPLICABLE

Cost components: direct medical

Currency: OTHER deutschmarks (DM)

Cost year: 1993/1995

Time horizon: 3.8 yrs

Discount rate: 5%

Results- cost: Incremental costs of adding ramipril

<table>
<thead>
<tr>
<th>Follow up</th>
<th>mean cost (DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y</td>
<td>223</td>
</tr>
<tr>
<td>2y</td>
<td>361</td>
</tr>
<tr>
<td>3y</td>
<td>860</td>
</tr>
<tr>
<td>3.8y</td>
<td>710</td>
</tr>
</tbody>
</table>

Results-effectiveness:

| Follow up | LYG |

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 187 of 248
<table>
<thead>
<tr>
<th>Year</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y</td>
<td>0.027</td>
</tr>
<tr>
<td>2y</td>
<td>0.090</td>
</tr>
<tr>
<td>3y</td>
<td>0.170</td>
</tr>
<tr>
<td>3.8y</td>
<td>0.289</td>
</tr>
</tbody>
</table>
Results-ICER: Cost/LYG

<table>
<thead>
<tr>
<th>Follow up</th>
<th>mean cost (DM)</th>
<th>lower limit CI</th>
<th>upper limit CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y</td>
<td>7</td>
<td>-3712</td>
<td>13624</td>
</tr>
<tr>
<td>2y</td>
<td>4012</td>
<td>-2402</td>
<td>6863</td>
</tr>
<tr>
<td>3y</td>
<td>5056</td>
<td>2203</td>
<td>6438</td>
</tr>
<tr>
<td>3.8y</td>
<td>2456</td>
<td>-102</td>
<td>3623</td>
</tr>
</tbody>
</table>

Negative ICERS indicate savings from ramipril use

Results-Uncertainty: Tested for both methodological and parameter uncertainty. They used Weibull and Kaplan-Mier to quantify the LYG, and a Monte Carlo simulation. Ramipril was found to be cost effective, dominating the alternative in 5% of the cases. 99% of the cases the ICER ranged between -DM2500 to DM8500. Results are sensitive to hospitalisation too.

Source of Funding: Private (Hoechst Marion Russell Germany)

Comments: gave detailed description of the methods including an appendix
Study Quality: 1++ The economics of TRACE: a cost-effectiveness analysis of trandolapril in post infarction patients with left ventricular dysfunction

Author: LePen C; Lilliu H; Keller T; Fiessinger S; 1998

Intervention: Trandolapril

Comparison: Placebo

Population: Post MI patients with LVD

Perspective: NHS

Study type: CEA

Methods: RCT (TRACE study)

Health valuations: NOT APPLICABLE

Cost components: direct medical

Currency: OTHER (French Francs)

Cost year: 1996

Time horizon: 2 years

Discount rate: 5%

Results- cost:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trandolapril</td>
<td>22 080 500</td>
</tr>
<tr>
<td>Placebo</td>
<td>20 317 300</td>
</tr>
<tr>
<td>Difference</td>
<td>1 763 200</td>
</tr>
</tbody>
</table>

Results-effectiveness: All-cause mortality

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trandolapril</td>
<td>304</td>
</tr>
<tr>
<td>Placebo</td>
<td>369</td>
</tr>
<tr>
<td>Difference</td>
<td>65</td>
</tr>
</tbody>
</table>

Mean life expectancy 5.52 years in each group.

Results-ICER: Using raw data from the trial
Cost/life year saved was FF27100

Using the life expectancy at the end of trial discounting both benefits and costs

FF6950/LYS

BOOTSTRAP results (95% CI)

FF8410 (7990 to 8840)

Results-Uncertainty: the results are robust in sensitivity analysis. Bootstrap results showed that 7.4% of the cases trandolapril dominated placebo and 92.6% of the cases the ICER was positive but still within the acceptable ranges of cost/LYG.

Source of Funding: Private (Hoechst Marion)

Comments: The study was well reported. They tested for methodological uncertainty using different methods to estimate the cost effectiveness (student's T distribution, bootstrap method). Appropriate modelling methods were used. Data sources were referenced, and data was incorporated as point estimates. Probabilistic and univariate sensitivity analysis were done and results were robust.
No 986


Author: Erhardt C; Ball Sanderson F; Bergentoft P; Martinez C; 1997

Intervention: Ramipril

Comparison: Placebo

Population: Post MI patients with heart failure

Perspective: NHS

Study type: CEA

Methods: RCT (AIRE study)

Health valuations: NOT APPLICABLE

Cost components: direct medical

Currency: OTHER (SEK)

Cost year: 1993

Time horizon: 3.8yrs

Discount rate: 5%

Results- cost: Follow up cost/patient

1yr 991
2yrs 1579
3.8yrs 2826

Results-effectiveness: Follow up life saved

1yr 0.03
2yrs 0.09
3.8yrs 0.22

Results-ICER: Follow up cost/LYS
Results-Uncertainty: findings were reported to be robust to many variables (which were not mentioned) including number of live years saved. The model was sensitive to hospital costs.

Source of Funding: Private (Astra hassle and Hoechst Marion Russell)

Comments: Tested methodological uncertainty by using both the Weibull method of estimating survival and the Kaplan-Mier method. Did a two-way sensitivity analysis to test parameter uncertainty. Results were reported in two parts. First with only cost discounted and secondly with both costs and effects discounted. In line with NICE recommendations only results reporting discounting for both cost and benefits have been abstracted.
8 What is the effectiveness of adding aspirin versus clopidogrel to improve outcome in patients after MI?

No 1108

Study Quality: 1+Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis

Author: Schleinitz MD; Weiss JP; Owens DK; 2004

Intervention: Clopidogrel

Comparison: Aspirin

Population: Patients at Risk of Ischemic Events. These included three set of patients, those with prior peripheral vascular disease, prior stroke, prior MI.

Perspective: SOCIETAL

Study type: CUA, using a markov decision model. Outcomes were stroke, reinfection, mortality, hemorrhagic events

Methods: RCTs, CAPRIE trial for base case, European stroke prevention study, and observational studies

Health valuations: From literature

Cost components: direct medical costs derived from literature, Medicare DRGs, wholesale prices for medication

Currency: US$

Cost year: 2002 (using GDP deflator)

Time horizon: Lifetime

Discount rate: 3%

Results- cost: lifetime costs

Aspirin: $91700

Clopidogrel: $98500
Results-efficacy: Life expectancy in QALYs

Aspirin: 11.09
Clopidogrel: 10.83

Results-ICER: not calculated. Aspirin dominates clopidogrel

Results-Uncertainty: results were sensitive to the cost and effectiveness of clopidogrel. Even in probabilistic sensitivity analysis, aspirin remained dominant in 88% of the cases.

Source of Funding: Charitable

Comments: The study was well reported with details of how the data was obtained and used in the model. The authors stated they were considering a societal perspective; however, only direct medical costs were included. A detailed breakdown of the cost items was not provided since most of the data were obtained from published studies. This reduces the possibility of replicating the study.
No 1094

**Study Quality:** 1+  Cost-effectiveness analysis of clopidogrel versus aspirin in patients with atherothrombosis based on the CAPRIE trial

**Author:** Annemans L; LaMotte M; Levy E; Lenne X;  2003

**Intervention:** Clopidogrel

**Comparison:** Aspirin

**Population:** Patients with vascular disease with recent stroke, myocardial infarction (MI) or symptomatic peripheral arterial disease

**Perspective:** NHS, Belgium

**Study type:** CEA, markov model stroke, vascular and other death, reinfaction, costs, ICERs

**Methods:** RCT CAPRIE study, and Saskatchewan database

**Health valuations:** NOT APPLICABLE

**Cost components:** Direct medical costs derived from literature and Diagnosis-related group (DRG)

**Currency:** EURO

**Cost year:** 2002

**Time horizon:** 2 years

**Discount rate:** 3%

**Results- cost:**

- Clopidogrel: Euro 12612 000
- Aspirin: Euro 11753 000

**Results-effectiveness:**

- Clopidogrel: 12158 life years
- Aspirin: 12084 life years

**Results-ICER:**

- Euro 13390/LYG using the deterministic model
- 14320 euros/LYG 95% CI [6990-26470] using the probabilistic model.

Using a willingness to pay threshold figure of 20000 euros/LYG clopidogrel is 86% cost effective.

**Results-Uncertainty:** results were robust in both deterministic and probabilistic sensitivity analysis. They
examined the impact of discount rate (0-6%), cost of adverse and ischemic events and assumptions about life expectancy plus or minus 50%. Monte Carlo probabilistic analysis was done using beta distribution for effects and triangular for costs.

Source of Funding: Private

Comments: The study did not quote the actual effectiveness parameters entered into the model, and some of the cost estimates were from expert opinion. These costs were not examined in sensitivity analysis. Also the study combined together all patients with atherothrombosis which makes it difficult to attribute the results to the population of interest Post MI patients.
No 1101

Study Quality: 1++ Modeling the long term cost effectiveness of clopidogrel for the secondary prevention of occlusive vascular events in the UK

Author: Karnon J; Brennan A; Pandor A; Fowkes G; Lee A; Gray D; Coshall C; Nicholls C; Akehurst R; 2005

Intervention: Clopidogrel (75 mg/day) for 2 years followed by ASA (325 mg/day, average) for their remaining lifetime.

Comparison: ASA alone (325 mg/day, average) for life.

Population: Patients who were at risk of secondary occlusive vascular events OVEs (non-fatal myocardial infarction, non-fatal stroke or vascular death) who met the inclusion criteria of the CAPRIE study

Perspective: NHS

Study type: CUA, reinfaction, stroke, vascular death, ICERs,

Methods: RCT, CAPRIE study and data from the NHAR UK. London stroke register, Edinburgh Claudication study

Health valuations: derived from literature

Cost components: direct medical costs of treatment and procedures. Costs were derived from the literature, and BNF.

Currency: £

Cost year: 2002

Time horizon: lifetime-40 years

Discount rate: 6%

Results- cost:

<table>
<thead>
<tr>
<th>2 years of Clopidogrel:</th>
<th>£1359628</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime costs of Clopidogrel:</td>
<td>£19199554</td>
</tr>
<tr>
<td>2 years of ASA:</td>
<td>£1388494</td>
</tr>
<tr>
<td>Lifetime costs of ASA:</td>
<td>£18380509</td>
</tr>
</tbody>
</table>

Results-effectiveness:

<table>
<thead>
<tr>
<th>QALY gained</th>
<th>Life year Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel:</td>
<td>12002</td>
</tr>
<tr>
<td></td>
<td>14242</td>
</tr>
</tbody>
</table>

Myocardial infarction: full guideline DRAFT (August 2006) – Appendices
ASA: 11964 14199

Results-ICER:  
Cost/QALY: £18888  
Cost/LYG: £21489

Clopidogrel would be cost effective in 60% of the cases at £30000/QALY.

Results-Uncertainty: results were not sensitive to all input parameters except for the mean annual risk of vascular events and the relative risk of vascular death. Probabilistic sensitivity analysis showed that clopidogrel is cost effective in 60% of the cases at a threshold value of £30000/QALY.

Source of Funding: Private

Comments: This study is well reported and the authors were very clear in the methodology used and the sources of their input parameters. The only problem however is that their results can not be generalized to the Post MI population per se as they did not report the three conditions separately, stroke, PAD and Post MI.
No 1100

**Study Quality:** 1++ Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.

**Author:** Jones L; Griffin C; Palmer S; Main C; Orton V; Sculpher M; Sudlow C; Henderson R; Hawkins, N; Riemsma R; 2004

**Intervention:** Clopidogrel

**Comparison:** ASA

**Population:** Patients who experienced an MI

**Perspective:** NHS

**Study type:** CUA, reinfection, stroke, cardiovascular and other death, ICERs

**Methods:** CAPRIE and the NHAR

**Health valuations:** form literature

**Cost components:** direct medical costs hospitalisation, procedures, adverse events and drug costs. Cost data was derived from literature and DRGs, BNF

**Currency:** £

**Cost year:**

**Time horizon:** 40 years (lifetime)

**Discount rate:** 3.5%

**Results- cost:** Results were presented in four scenarios. Two of the scenario considered life treatment including or excluding treatment effect on vascular death. The other two considered 2 year treatment period including or excluding treatment effects on vascular death.

Scenario 1. Life with non vascular death

Clopidogrel: £25773

ASA: £18286

Scenario 2. Life with vascular death
Clopidogrel: £25585  
ASA: £18285

Scenario 3. 2 years with non vascular death  
Clopidogrel: £19202  
ASA: £18284

Scenario 4.2 years with vascular death  
Clopidogrel: £19078  
ASA: £18182

Results-effectiveness:

Scenario 1. Life with non vascular death  
Clopidogrel: 9.10 QALYS  
ASA: 8.86 QALYS

Scenario 2. Life with vascular death  
Clopidogrel: 8.94 QALYS  
ASA: 8.86 QALYS

Scenario 3. 2 years with non vascular death  
Clopidogrel: 8.95 QALYS  
ASA: 9.90 QALYS

Scenario 4.2 years with vascular death  
Clopidogrel: 8.91 QALYS  
ASA: 8.87 QALYS

Results-ICER:  
Scenario 1. Life with non vascular death  
£31400/QALY.
Probability that clopidogrel is cost effective WTP was £10000/QALY is 0% and 48% at £30000/QALY

Scenario 2. Life with vascular death

£94446/QALY

Probability that clopidogrel is cost effective WTP was £10000/qaly is 0% and 25% at £30000/QALY

Scenario 3. 2 years with non vascular death

£17081/QALY

Probability that clopidogrel is cost effective WTP was £10000/qaly is 17% and 71% at £30000/QALY

Scenario 4.2 years with vascular death

£21448/QALY

Probability that clopidogrel is cost effective WTP was £10000/qaly is 12% and 61% at £30000/QALY

Results-Uncertainty: Results were sensitive to the efficacy of the treatment (if RR observed in CAPRIE were used, which showed increased risk of events with clopidogrel, aspirin would dominate clopidogrel. Results were also sensitive to the inclusion or exclusion of vascular death in the model.

Source of Funding: Public

Comments: Two studies that are relevant for Post MI patients which were included in the HTA have been individually appraised. The authors did an extended economic model focusing on stroke, PAD, MI. Only results of the model reporting on Post MI patients have been reported. The model was well reported with references of the sources of data. The base case analysis included or excluded the effect of the treatment on vascular death in the short and long-term model.
What is the effectiveness of adding aspirin versus aspirin and clopidogrel to improve outcome in patients after MI?

No 1102

**Study Quality:** 1+ Using clopidogrel in non-ST-segment elevation acute coronary syndrome patients: A cost-utility analysis in Spain

**Author:** Latour-Perez J; Navarro-Ruiz A; Ridao-Lopez M; Cervera-Montes M; 2004

**Intervention:** Clopidogrel + aspirin

**Comparison:** Aspirin alone

**Population:** Patients with non-ST-segment elevation acute coronary syndrome

**Perspective:** SOCIETAL

**Study type:** CUA, stroke, reinfaction, death, refractory ischemia, bleeding, ICERs.

**Methods:** RCT, CURE study, the Framingham study, and the Spanish age-sex-specific mortality rates

**Health valuations:** NOT STATED, values derived from literature

**Cost components:** direct medical cost, treatment and cost of procedures derived from DRGs and Spanish Ministry of Health

**Currency:** EURO

**Cost year:** 1999

**Time horizon:** lifetime

**Discount rate:** 3%

**Results- cost:** Clopidogrel + ASA: euro 24806

Aspirin: euro 23962

**Results- effectiveness:** Clopidogrel + ASA: 8.77 QALYs

ASA: 8.70 QALYs

**Results- ICER:** Euro 12221 95% CI (8392-28041) for men

Euro 10299 for women
Results were presented according to age and base baseline risk of events. The base case results shown above were of a 64 year old medium risk case.

For 40 year old

- Low risk: 10846 euros/QALY
- Medium risk: 7778 euros/QALY
- High risk: 5272 euros/QALY

For 80 year old

- Low risk: 37726 euros/QALY
- Medium risk: 23803 euros/QALY
- High risk: 9831 euros/QALY

**Results-Uncertainty:** a one way, two way and probabilistic sensitivity analysis was done. Main attention was given to the effect of age, sex and baseline risk. Results were sensitive to age of the patient, the base risk of cardiovascular events, and the precision of the estimated effectiveness of clopidogrel.

**Source of Funding:** not stated

**Comments:** The study was well reported used standard acceptable methodology. They did an elaborate sensitivity analysis and sub-group analysis which were helpful. The authors concluded that clopidogrel is cost effective in non-ST-segment elevation, however in the results section authors reported results stratified by men and women in the base case, but it’s not clear in the paper which figures or results applied to men.
No  1103

Study Quality: 1+ The long-term cost-effectiveness of clopidogrel plus aspirin in patients undergoing percutaneous coronary intervention in Sweden

Author: Lindgren P, Stenestrand U; Malmberg K; Jonsson B; 2005

Intervention: Clopidogrel + Aspirin

Comparison: Aspirin

Population: Patients with unstable coronary artery disease (CAD) undergoing PCI in Sweden

Perspective: SOCIETAL

Study type: CEA, reinfaction, cardiovascular and other death

Methods: RCT, PCI-CURE study, Swedish Register of Heart and Intensive care Admissions (RIKS-HIA)

Health valuations: NOT APPLICABLE

Cost components: direct medical costs and indirect costs, Costs were derived from DRGs and literature

Currency: EURO

Cost year: 2004. Converted using PCI

Time horizon: lifetime

Discount rate: 3%

Results - cost: Aspirin + Clopidogrel:

Direct costs = 2726 euros

Indirect = 282 euros

Total = 3132 euros

Patients with Diabetes

50 year olds - 16 euros

60 year olds - 72 euros

80 year olds - 374 euros
Patients without Diabetes

50 year olds - 211 euros
60 year olds - 261 euros
80 year olds - 430 euros

Aspirin

Direct costs = 2277 euros
Indirect = 523 euros
Total = 2799 euros

**Results-effective**: Aspirin + Clopidogrel: 14.16 years
Aspirin alone: 14.12 years
Difference 0.04 years

Patients with Diabetes

50 year olds - 0.03
60 year olds - 0.04
80 year olds - 0.09

**Results-ICER**: Direct medical costs: 10993 euros/LYG
Total costs: 8127 euros/LYG
Cost utility was done in sensitivity analysis. 6506 euros/QALY

Patients with Diabetes
50 year olds - dominance
60 year olds - 1969 euros/LYG
80 year olds - 3961 euros/LYG

Patients without Diabetes
50 year olds - 7243 euros/LYG
60 year olds - 6929 euros/LYG
80 year olds - 4609 euros/LYG

In sensitivity analysis they considered post MI patients that occurred 7 days after admission and combination therapy dominated aspirin alone.

Results-Uncertainty: the model was robust to changes in variables such as costs and discounting.

Source of Funding: Private

Comments: Methodologically the paper was well reported. Sources of effectiveness and cost data were clearly reported and both deterministic and probabilistic sensitivity analysis was done. They also did a sub-group analysis in which the conclusions remained the same with either age or diabetes mellitus. ICERs were more favorable for the younger patients aged 50 years with diabetes mellitus and less favorable for the 70 year olds with or without diabetes. Their model predicted fewer/less events than the CURE study did making their estimates more conservative. Their results can not be generalized to the post MI population.
Study Quality: 1+ Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation

Author: Weintraub WS; Mahoney EM; Lamy A; Culler S; Yuan Y; Caro J; Gabriel S; Yusuf S; CURE S; 2005

Intervention: Clopidogrel + ASA

Comparison: ASA/placebo

Population: Patients who had experienced an acute coronary syndrome (ACS) without ST-segment elevation

Perspective: NHS

Study type: CEA, outcomes were death, stroke, and myocardial infarction, ICERs

Methods: RCT CURE study, observational data from the Saskatchewan and Framingham Heart study

Health valuations: NOT APPLICABLE

Cost components: direct medical costs (hospitalisations) and medication costs. These costs were derived from DRGs, Medicare and MEDSTAT data base.

Currency: US$

Cost year: 2001

Time horizon: 12 months

Discount rate: 3%

Results-cost: Using Medicare DRG costs

Clopidogrel: $13019
Placebo: $12578

Using MEDSTAT (private reimbursement) costs

Clopidogrel: $17924
Placebo: $17586

Results-effectiveness: Total number of events using Framingham data
Clopidogrel: 0.5327
Placebo: 0.6026
LYG with clopidogrel: 0.0699

Total number of events using Saskatchewan data
Clopidogrel: 0.3910
Placebo: 0.4592
LYG with clopidogrel: 0.0682

**Results-ICER:**

Using Framingham data
Medicare costs: $9144/LYG and 92.8% probability of being cost effective at $50000/LYG

Using MEDISTAT costs: $7654/LYG and 93.4% probability of being cost effective at $50000/LYG

Using Saskatchewan data
Medicare costs: $9343/LYG and 97% probability of being cost effective at $50000/LYG

Using MEDISTAT costs: $7833/LYG and 97.6% probability of being cost effective at $50000/LYG

**Sub-groups**

Using Framingham database

- <65 years  $5022/LYG
- >65 years  $7569/LYG
- Male  $2362/LYG
- Female  $70396/LYG
- Diabetes  $9857/LYG
- No diabetes  $5583/LYG
- Prior MI  $1404/LYG
- No prior MI  $14171/LYG
Results-Uncertainty: Results remained robust in sensitivity analysis even when baseline data from the Saskatchewan database was used.

Source of Funding: not stated

Comments: The authors were very detailed in their reporting of the methods they used. For costing they used three different credible methods and for effectiveness data they used the CURE trial and two observational databases the Framingham and Saskatchewan to estimate life expectancy, which yielded comparable results.

Author: Schleinitz MD, Heidenreich PA; 2005

Intervention: Clopidogrel, 75 mg/d, plus Aspirin, 325 mg/d, for 1 year,

Comparison: Aspirin alone

Population: Patients with unstable angina and electrocardiographic changes or non-Q-wave myocardial infarction over a lifetime

Perspective: SOCIETAL

Study type: CUA, reinfaction, stroke, mortality, quality-adjusted life-years (QALYs), hemorrhagic events & ICERs

Methods: RCT, CURE study

Health valuations: derived the values from the literature

Cost components: direct medical costs incurred during hospitalisation incusing nursing care and procedures, wholesale price for medications. Used a GDP deflator to update costs to 2002.

Currency: US$

Cost year: 2002

Time horizon: lifetime

Discount rate: 3%

Results- cost: Patients treated with aspirin alone costs $127700

Addition of clopidogrel costs $129300

Results- effectiveness: Patients treated with aspirin alone lived 9.51 QALYs

Addition of clopidogrel increased life expectancy to 9.61 QALYs

Results-ICER: The incremental cost-effectiveness ratio for clopidogrel plus aspirin compared with aspirin alone was 15,400 dollars per QALY.
Duration of therapy

The marginal costs of the second year of therapy was $31600/QALY,

Third year $61300/QALY

Fourth year $136500/QALY

Fifth year $730000/QALY

Before the end of the third year the efficacy of clopidogrel was reduced by about 25% in the model.

Results-Uncertainty: results were not sensitive to changes in risk reduction and costs of clopidogrel in both deterministic and one way sensitivity analysis.

Source of Funding: Public

Comments: This analysis may not apply to patients with severe heart failure, those undergoing long-term anticoagulant therapy or those recently managed with revascularization. The study did not focus on a particular ACS which might limit its applicability to the Post MI population. Otherwise the study was well reported, proving details of sources of data, how the data was incorporated as well as a clear model structure.
No 1099

**Study Quality:** 1+ Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease

**Author:** Gaspoz J; Coxson PG; Goldman PA; Williams LW; Kuntz KM; Hunnik M; Goldman L; 2002

**Intervention:** Aspirin, clopidogrel,

**Comparison:** Aspirin or aspirin + clopidogrel

**Population:** Patients aged 35 to 84 years in which CHD developed and evaluated over a 25 year period.

**Perspective:** THIRD PAYER

**Study type:** Deterministic decision analysis, CUA. The outcomes were deaths from coronary/non coronary, MIs

**Methods:** Framingham heart study, Scandinavian Simvastatin Survey, CURE study, CAPRIE and Antiplatelets T Collaborators

**Health valuations:** Literature

**Cost components:** direct medical costs including drug costs and costs of side effects like gastrointestinal. Costs were derived from literature (refs given) and National medical expenditure survey.

**Currency:** US$

**Cost year:** 2000

**Time horizon:** 25 years

**Discount rate:** 3%

**Results- cost:** Incremental costs are estimated over the 30 year period in millions.

- Aspirin (ASA) for all eligible patients: $8000 000
- Addition of Clopidogrel for those that are not eligible for ASA: $14 000 000
- Clopidogrel alone for all patients: $156 000 000
- Clopidogrel for all + Aspirin for all eligible: $182000 000

**Results-effectiveness:** Incremental QALYs

- Aspirin (ASA) for all eligible patients: 682000 QALYs
Addition of Clopidogrel for those that are not eligible for ASA: 456000 QALYs
Clopidogrel alone for all patients: 632 000 QALYs
Clopidogrel for all + Aspirin for all eligible: 1437 000 QALYs

Results-ICER:  
Aspirin (ASA) for all eligible patients: $1100/QALY
Addition of Clopidogrel for those that are not eligible for ASA: $31000/QALY
Clopidogrel alone for all patients: $250000/QALY
Clopidogrel for all + Aspirin for all eligible: $130000/QALY

Results-Uncertainty: results were sensitive to the effect of the intervention on revascularisation. Aspirin and clopidogrel will save money if they reduced the rate of revascularisation as much as they did on MI. The cost of clopidogrel was also assessed but the results were not reported as they did not change the conclusions.

Source of Funding: Charitable

Comments: This is a detailed study but does not focus on a particular disease area of CHD, limiting its relevance to post MI patients. Baseline event rates and costs differ for subtypes of CHD which might alter cost effectiveness conclusions. Thus the generalisability of these results to the post MI patients is not clear.
No 1104

**Study Quality:** ++ Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation

**Author:** Main C; Palmer S; Griffin S; Jones L; Orton V; Sculpher M; 2004

**Intervention:** Clopidogrel + ASA

**Comparison:** ASA

**Population:** patients with non-ST-elevation ACS

**Perspective:** NHS

**Study type:** CUA, death from cardiovascular causes, non-fatal myocardial infarction or stroke

**Methods:** CURE study, PRAIS-UK and NHAR

**Health valuations:** Quality of life weights were derived from the literature

**Cost components:** Direct medical costs of treatment, procedures and side effects. Costs data was derived from the literature, BNF and NHS reference costs

**Currency:** £

**Cost year:** 2002

**Time horizon:** lifetime

**Discount rate:** 6% for costs and 1.5% for benefits

**Results- cost:** Clopidogrel + ASA: £12695

ASA: £12225

**Results-effectiveness:** Clopidogrel + ASA: 8.2795 QALYS

ASA: 8.2022 QALYS

**Results-ICER:** £6078/QALY

Probability of being cost effective at £10000 and £30000 WTP is 32% and 21% respectively.

Sub-groups

For high risk group there was a reduction in the ICER to about £4939/QALY and low risk 

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the ICER increased to £8734/QALY.

The Assessment Group explored the cost effectiveness of using clopidogrel for periods shorter than 1 year. The ICER for 1 month of treatment with clopidogrel compared with standard care alone was calculated to be £824 per QALY with a 6% probability that clopidogrel is cost effective at £30000/QALY. 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 £30000/QALY.

Results-Uncertainty: The results were most sensitive to the inclusion of additional strategies which assessed alternative treatment durations with clopidogrel for example reducing the treatment duration to 5 years more than doubled the ICERs to about £15000/QALY. Although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk. Discount rate and impact of the cost of stroke did not affect the baseline ICER.

Source of Funding: Public

Comments: One paper and a company submission met the inclusion criteria for this HTA. The results are in agreement and indicate that there is a benefit in the short term and the ICERs are favorable, the ICERs becomes less favorable in the long-term but remain within acceptable range of cost effectiveness. Authors did a sub-group analysis stratifying results according to low or high risk defined as patients with at least one of the following over 70years, those with an ST- depression on an ECG and diabetes.
10 What is the effectiveness of adding a beta blocker versus placebo to improve outcome in patients after MI?

No  1224

**Study Quality:** Economic consequences of post infarction prophylaxis with beta blockers: cost effectiveness of Metoprolol

**Author:** Olsson G; Levin L; Rehnqvist N; 1987

**Intervention:** Metoprolol (Beta-blocker) 100mg. twice daily treatment started 2 weeks after acute onset of

**Comparison:** Placebo

**Population:** Post infarction patients <70 years of age

**Perspective** Swedish societal perspective

**Study** CEA, mortality, reinfarction, readmissions, cerebrovascular events, and revascularisation

**Methods:** Randomised Controlled Trial (RCT) of the Stockholm Metropolol study (66% post MI patients)

**Health valuations:** N/A

**Cost components:** costs relates to the health service costs of medication, concomitant medication (digitalis, diuretics), inpatient care, and outpatient clinic & indirect costs sick leave or early retirement

**Currency:** Swedish Kroner (SEK).

**Cost** 1985

**Time horizon:** 3 years

**Discount rate:** 5%

**Results** Metropolol Kr 118610 (approx £11981) inclusive of indirect costs
**Cost/patient:** Placebo  Kr 137220 (approx £13861) inclusive of indirect costs

Excluding indirect costs

Metropolol  Kr 12310 (approx £1243)

Placebo  Kr 17120 (approx £1729)

**Results**

Significant differences were found on the reinfection, cerebrovascular events, coronary bypass surgery and reduced hospitalisation in favor of metropolol. There were no significant differences between treatment groups in terms of mortality both total and cardiac, readmission for heart failure, arrhythmias, angina pectoris and leg amputations.

**Effectiveness**

Results were not synthesized. But metropolol was deemed cost effective on the basis of reduced rates of adverse events and less cost over the three year follow up.

**Incremental Results**

only discounting was assessed and the results were robust.

**Uncertainty:**

Source Funding: not stated

Comments: There was no sensitivity analysis done except for discounting which did not affect the results. They used hospital billing data for costs of inpatient care, this may still be fine given that the healthcare system is state funded or "socialized medicine" They could have done better by synthesizing the results to estimate a cost/LYG or cost/QALY which is more informative to the decision maker.
No 1220

**Study Quality:** 1+  Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction

**Author:** Goldman L; Sia ST; Cook EF; Rutherford JD; Weinstein MC; 1988

**Intervention:** Beta adrenegernic antagonist started at the end of hospitalisation and continued long-term thereafter

**Comparison:** Placebo

**Population:** Low-risk group, medium-risk group, and high-risk group men aged 45, 55 or 65 years

Risk was defined by estimated cardiac mortality in the 15 year period after MI. First year mortality was estimated to be different from mortality of subsequent years

- High risk: first year mortality =13% and subsequent risk for 2-15 years =7.5%
- Medium risk: first year mortality =7.5% and subsequent risk for 2-15 years =5%
- Low risk: first year mortality =1.5% and subsequent risk for 2-15 years =1.5%

**Perspective** Third payer

**Study** CEA, mortality, revascularisation, reinfaction, costs

**Methods:** Pooled meta-analysis of trial data on beta-blockers and observational studies.

**Health valuations:** N/A

**Cost components:** Costs of drugs excluding follow up outcome costs and costs of side effects.

**Currency:** US$

**Cost** 1987

**Time horizon:** Lifetime

**Discount rate:** 5%
Results

Cost/patient: not given

Results effectiveness: Incremental life expectancy (% change) assuming the benefits observed in 6 years of treatment will be lost gradually

Low 45yrs: 0.11 (0.4%)
Low 55yrs: 0.10 (0.5%)
Low 65yrs: 0.09 (0.7%)

Medium 45yrs: 0.34 (2%)
Medium 55yrs: 0.34 (2.6%)
Medium 65yrs: 0.31 (3.1%)

High 45yrs: 0.48 (3.8%)
High 55yrs: 0.47 (4.6%)
High 65yrs: 0.44 (5.5%)

Results Incremental: Low-risk group 45yrs: $23457/LYG----------------$12855/LYG
Low-risk group 55yrs: $23446/LYG----------------$13068/LYG
Low-risk group 65yrs: $23417/LYG----------------$13571/LYG

Medium-risk group 45yrs: $5890/LYG-----------$3567/LYG
Medium-risk group 55yrs: $5884/LYG----------$3618/LYG
Medium-risk group 65yrs: $5871/LYG-----------$3737/LYG

High-risk group 45yrs: $3623/LYG---------------$2327/LYG
High-risk group 55yrs: $3619/LYG--------------$2357/LYG
High-risk group 65yrs: $3609/LYG--------------$2427/LYG

NOTE: The first figures are for a conservative model which assumed that treatment
benefits will persist for 6 years when treatment is being given. Once the treatment is stopped, the benefits are lost immediately.

Figures after the dotted lines are for the best guess model which assumes that the benefits observed during the 6 years will be lost gradually once the treatment is stopped.

**Results Uncertainty:** Univariate sensitivity analysis was done and results were robust to assumptions about the baseline mortality despite a tendency of less favorable ICERs when mortality risk was reduced. Costs of beta Blockers was almost doubled and made ICERs less favorable but they remained cost effective.

**Source Funding:** Not stated

**Comments:** Authors did not include the outcome costs/savings as a result of the intervention and costs of treating side-effects of therapy. The assumption they made that these will cancel out each other was too strong. However it is more likely that the cost savings from reduced adverse outcomes may outweigh the cost of treating adverse events. They also applied the same magnitude of relative mortality reduction to the various age and mortality groups. They stated that they did a meta-analysis but the study inclusion criteria for the pooled estimates of efficacy are not fully known making the validity of the pooled estimates uncertain. Overall this study needs to be interpreted with caution.
What is the effectiveness of adding calcium channel blocker versus placebo to improve outcome after MI?

**No 1263**

**Study Quality:** + Economic benefits of amlodipine treatment in patients with coronary artery disease

**Author:** Casciano R; Doyle JJ; Chen J; Arikian S; Casciano J; Kugel H; Arocho R; 2002

**Intervention:** Amlodipine

**Comparison:** Placebo

**Population:** Patients with CAD in the USA

**Perspective** Third-party payer

**Study type:** CC A, and outcomes were CABG, PCTA, stroke, heart failure, mortality, unstable angina and MI

**Methods:** RCT, PREVENT study and the NASHES III data set in USA

**Health valuations:** N/A

**Cost components:** direct medical costs were inpatient costs, physician services and follow-up costs. DRGs, the Medicare-based physician fee schedule, and the Redbook

**Currency** US$

**Cost year** 1999

**Time horizon:** 3 years

**Discount rate** 3%

**Results cost** expected per patient costs over the 3-year period of the analysis was $14,117 for amlodipine and $16,683 for placebo

**Results effectiveness:** The use of amlodipine to prevent the progression of coronary artery disease (CAD) was both effective in reducing hospitalisation and the episodes of revascularisation. There were about 200 vs. 300 CVD related hospitalisation during the three-year follow up.

**Results incremental:** not done it was cost-consequences analysis was conducted
Results Uncertainty: The estimated costs were robust to variations carried out in all the sensitivity analyses. None of the alternative scenarios favored placebo patients.

Source Funding: Private

Comments: The study was well reported with appropriate methods. It appears that all the relevant categories of costs have been included in the study. Details on the cost data were reported and the price year was given. Sensitivity analysis was done, both univariate and a Monte Carlo simulation varying the cost data within +/- 10% of the initial values and probability values within the 95% confidence intervals. The study could have been improved by synthesizing benefits and costs and also considering quality of life issues.
Study Quality: + A cost-effectiveness evaluation of amlodipine usage in patients with coronary artery disease in Sweden

Author: Doyle JJ; McGuire A; Arocho R; Arikian S; Casciano J; Svangren P; Kim R; Kugel H; 2002

Intervention: Amlodipine

Comparison: Placebo

Population: Patients with CAD in Sweden

Perspective: Swedish health care system

Study type: CEA, hospitalisation for angina, hospitalisation for MI, hospitalisation for CHF, PTCA, CABG, death

Methods: PREVENT study and authors assumptions adjusted according to Swedish data

Health valuations: N/A

Cost components: Direct medical costs with resource consumption estimated by experts using Delphi techniques. Costs were derived from General Hospitals and Pharmaceuticals Specialties in Sweden

Currency: Swedish Kroner (SEK)

Cost year: 2000

Time horizon: 3 years

Discount rate: 3%

Results cost: 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. These results were robust to all variations carried out in the sensitivity analyses

Results effectiveness: patients given amlodipine experienced 469 hospitalizations per 1000 patients while placebo had 647/1000. 18% fewer hospitalizations attributable to amlodipine.

Results incremental: not calculated because the treatment was dominant over placebo, that is, it was more effective and less costly. Treatment with amlodipine was effective in reducing hospitalisation events. It also resulted in cost-savings from the perspective of the Swedish health care system. i.e. a cost saving of SEK 4300/hospitalisation avoided

Results Uncertainty: the model was robust in both univariate and multivariate sensitivity analysis
Source of Funding: Private

Comments: The study was well reported using appropriate methodology. Key assumptions of the model were tested in sensitivity analyses. It appears that all the relevant categories of costs have been included in the analysis. The authors noted that hospitalisation costs used in the analysis were average estimates and great variation may exist due to the length of stay, type of treatment and type of hospital. However to better evaluate the benefits of amlodipine quality-of-life issues should have been addressed.
Ref No1264

Study Quality: + The economic efficiency of amlodipine in the treatment of coronary atherosclerosis: an analysis based on the PREVENT study

Author: Cathomas G; Erne P; Schwenkglenks M; Szucs TD; 2002

Intervention: amlodipine

Comparison: placebo

Population: Patients with angiographically documented coronary heart disease (CHD) in Switzerland

Perspective Health insurance companies

Study type: CEA. Fatal myocardial infarction, stroke, vascular deaths and bleedings per 1,000 patients

Methods: PREVENT study

Health valuations: N/A

Cost components: Direct medical costs

Currency Swiss francs (Sfr)

Cost year not stated

Time horizon: 3 years

Discount rate 5%

Results cost The total costs per 100 patients were Sfr 639,323 for amlodipine and Sfr 505,672 for placebo. The additional costs (Sfr 133,651) observed in the amlodipine group mainly arose from the high initial drug costs

Results effectiveness: The annual mortality rates were 4.5% in the amlodipine group and 6.2% in the placebo group, but this difference was not statistically significant, (p=0.57) The adjusted life expectancy calculated using the DEALE approach was 18.43 years. Thus, the discounted life-years gained due to amlodipine therapy over placebo was 0.083 years per patient

Results incremental: cost per life-year gained was Sfr 14,650.

Results Uncertainty there was little sensitivity analysis done which was robust.

Source of Funding: not stated
PREVENT study showed that there was no statistically significant difference in terms of survival between the amlodipine and placebo groups. A sensitivity analysis to investigate the effects of varying the difference in fatal events between the treatment groups would have been useful. Quality of life issues were not discussed. It appears that all the relevant categories of cost have been included in the analysis. The unit costs and the quantities of resources used were sometimes reported separately. The sources of the data for both costs and resource consumption were reported. The costs were treated deterministically, although sensitivity analyses were conducted on those categories of costs that appeared to be more subject to uncertainty. Appropriate discounting was performed. The price year was not mentioned, the economic analysis was conservative, as potential cost-savings due to lower hospitalisation episodes and fewer rehabilitation measures were not accounted for in the analysis.
What is the effectiveness of adding eplerenone versus placebo to improve outcome in patients after MI?

No 1354

Study Quality: 1+ Scottish medicines Consortium new product assessment form submission:

Author: Pfizer Ltd

Intervention: Eplerenone

Comparison: Placebo

Population: Post MI patients with left ventricular dysfunction and heart failure (LVDF)

Perspective NHS

Methods: RCT EPHESUS study

Health valuations: NOT STATED

Cost components: direct medical costs (DRG related)

Currency £

Cost year 2002

Time horizon: 16 months

Discount rate 6%

Results cost Eplerenone: £3400

Placebo: 2768

Difference: £632

Results effectiveness: QALY lost
Eplerenone: 0.41

Placebo: 0.48

Difference: 0.07

Results incremental: £9048/QALY gained

Results Uncertainty: Results were stable in sensitivity analysis. There is a 92% chance that Eplerenone is cost effective using a willingness to pay threshold of £20000/QALY.

Source Funding: Private (stakeholder submission)

Comments: This was a stakeholder submission by Pfizer. The submission document had a checklist at the end. The document does not show disaggregated resource use, but it appears the original documents had the information and is referred to on the checklist. In the absence of any other published economic evaluation from the UK perspective, these results can be relied upon as they compare favorably with other drug interventions used for patients post MI.
No 1339

Study Quality: 1+ Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure.

Author: Weintraub WS Zhang Z; Mahoney EM; Kolm P; Spertus JA; Caro J; Ishak J; Goldberg R; Tooley J; Willke R; Pitt B; 2005

Intervention: Eplerenone

Comparison: Placebo

Population: Post MI patients with LDV and HF

Perspective: THIRD PAYER

Study type: CEA

Methods: RCT and observational data from Framingham, Saskatchewan database & Worcester Heart Attack Registry

Health valuations: NOT APPLICABLE

Cost components: Direct medical costs using DRG as used in the Medicare Program

Currency: US$

Cost year: 2001

Time horizon: 16 months and lifetime

Discount rate: 3%

Results cost:

Eplerenone $13494
Placebo $12104
Difference $1391 (95% CI 695-$2165)

Results effectiveness:

QALYs lost

Framingham 0.3940 compared to placebo 0.4616

Saskatchewan 0.2253 compared to placebo 0.2682
Worcester 0.4528 compared to placebo 0.5435

**Results incremental:** Assuming no added costs from life years saved

- Framingham: $21072/QALY
- Saskatchewan: $30349/QALY
- Worcester: $17374/QALY

Assuming added costs from life years saved are included

- Framingham: $29469/QALY
- Saskatchewan: $43301/QALY
- Worcester: $23724/QALY

Subgroups using Framingham data. Cost per life year gained

- Base case: $13718 and 96.6% probability that eplerenone is cost effective
- Age <65 years: $13709 (92.1%)
- Age >65 years: $15409 (87.3%)
- Male: $16903 (89.6%)
- Female: $11873 (91.7%)
- Diabetes: $42160 (55.2%)
- Non-Diabetics: $10999 (99%)
- Prior MI: $21279 (78.4%)
- No previous MI: $10818 (97.3%)

**Results Uncertainty:** Results were robust in probabilistic sensitivity analysis for the different sources of data used. The results also remained cost effective for different subgroups.

**Source Funding:** Private

**Comments:** This study was detailed and used three different data sources to estimate what would happen after the trial period.
14 What is the effectiveness of adding omega 3 supplements versus placebo to improve outcome in patients after MI?

No 1315

Study Quality: 1+  Cost-effectiveness Analysis of Omacor for Myocardial infarction Survivors in the UK, 2004

Author:

Intervention: n3- PUFA

Comparison: No supplement

Population: Post MI patients

Perspective: NHS

Study type: CUA

Methods: RCT, GISSI-P trial

Health valuations: taken from literature and references given

Cost components: direct medical costs of drugs and events with assumptions spelt out clearly

Currency: £

Cost year: 2003

Time horizon: four years and lifetime

Discount rate: 3.5%

Results cost:

4 year results: £1789148 vs £1140143

Lifetime model: £6471024 vs £5700588

Results effectiveness:

4 year results: 2839 vs 2797 QALYs

Lifetime model: 9309 vs 9102 QALYs
Results incremental: 4 year results: 15189/QALY

Lifetime model: 3717/QALY

Results Uncertainty: The results of the model were sensitive but remained robust to the assumptions about costs, discount rates and proportions of patients receiving post MI treatment.

Source of Funding: Private

Comments: They provided results for other comparisons including Vitamin E, and a combination of Vitamin E with n3-PUFA. Results were presented using life years gained and death avoided. For the purpose of this review only the results which use the NICE reference case were considered, that is the QALY utility results. Only results of n3-PUFA compared to placebo were used and other comparators were not included because they were not relevant. This study was appropriately reported using standard methods. However the sources of subsequent MI costs and those of stroke were not clear. They assessed these in sensitivity analysis but again failed to give specify the source of the ranges used (200% increase).
Study Quality: 1+  Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione Trial

Author: Franzosi MG; Brunetti M; Marchioli R; Marcisi RM; Tognoni G; Valagussa F; GISSI-Prevenzione I; GISSI-Prevenzione 2004

Intervention: n3-PUFA

Comparison: No supplements

Population: Post MI patients with no age restriction

Perspective: THIRD PAYER

Study type: CEA

Methods: RCT, GISSI-P trial

Health valuations: NOT APPLICABLE

Cost components: direct medical costs using Italian reimbursement DRGs rates. They used resource consumption data from the trial reports.

Currency: EURO

Cost year: 1999

Time horizon: 42 months (3.5 years)

Discount rate: 5%

Results cost: n3-PUFA euro 5223

Placebo euro 4406

Results effectiveness: n-3-PUFA resulted in significant in the primary combined endpoint including mortality. See the clinical evidence report. This translated to 0.0332 (95% CI 0.0303-0.361) life years gained

Results incremental: Base case results Euro 24603/LYG
Best case scenario: euro 15721/LYG

Worse case scenario: euro 52524/LYG

Results Uncertainty

Costs of n3-PUFA, best worst case scenarios were tested in sensitivity analysis. The results were most sensitive to cost of n3-PUFA but remained cost effective especially that they modelled an expected price fall. The worst case scenario will change the conclusion about cost effectiveness if the payer was willing to pay upto US$50000.

Source of Funding:

Private

Comments:

This paper was well reported. They could have done better buy reporting the impact of the treatment on quality of life. The authors compared their results with those of other interventions.
19 What is the effectiveness of adding vitamin K antagonist versus placebo to improve outcome in patients after MI?

No 1198

Study Quality: 1+ Costs and effects of long-term oral anticoagulant treatment after myocardial infarction

Author: Van Bergen PFMM; Jonker JJ C; van Hot BA; van Domburg RT; Azar AJ; Hofman, 1995

Intervention: Warfarin

Comparison: Placebo

Population: non selected Post MI patients,

Perspective SOCIETAL

Study CEA

Methods: REVIEW of the ASPECT trial data

Health valuations: NOT APPLICABLE

Cost components: Stated societal perspective but only collected direct medical costs related to major cardiologic events, anticoagulation treatment, hospital readmissions obtained from the Dutch Hospitals

Currency: Dutch Dfl

Cost 1994
**Time horizon:** 3yrs

**Discount rate:** 5%

**Results**

Anticoagulation: average Dfl 9878 and total costs are Dfl 17621613

Placebo: average Dfl 10784 and total costs are Dfl 19222590

**Effectiveness:**

- a 10% (95% CI: -11% to 27%) reduction of death
- 53% (95% CI: 41% to 62%) reduction of recurrent MI
- 40% (95% CI: 10% to 60%) reduction of cerebrovascular events

and an increase in the relative risk of bleeding complications of 3.9 (95% CI: 2.3 to 6.4).

**Results Incremental:** Authors did not synthesise costs and benefits; therefore it is a cost minimisation study. The total costs of warfarin were $519.00 cheaper for the warfarin arm.

**Results Uncertainty:** Results of sensitivity analysis shows that changes in costs of the main variables will not affect the conclusions.

**Source Funding:** Public/private

**Comments:** Although the study showed cost savings as a result of warfarin treatment, there was a 400% increase in major bleeding events which was not incorporated in the model and thus weakens the model results.
20 What is the effectiveness of adding vitamin K antagonist versus aspirin to improve outcome in patients after MI?

No 1197

**Study Quality:** 1+ A cost-effectiveness analysis of aspirin versus oral anticoagulants after acute myocardial infarction in Italy: equivalence of costs as a possible case for oral anticoagulants

**Author:** Gianetti J; Gensini G; De CR; 1998

**Intervention:** Aspirin

**Comparison:** Warfarin

**Population:** Patients having had an acute myocardial infarction

**Perspective** NHS, Italy

**Study** CEA, re-infarction, PCTA, CABG, major bleeding, cerebrovascular events, AV Thromboembolism

**Methods:** RCT ASPECT study, APT collaboration

**Health valuations:** NOT APPLICABLE

**Cost components:** Direct medical and treatment costs. Costs were derived from literature and DRGs. Treatment costs were estimated for two DRG pricing schemes: the mean price and the daily price multiplied by mean length of stay

**Currency:** OTHER (Italian Lira) and European currency

**Cost** 1994

**Time horizon:** 3 years

**Discount rate:** no discounting was done

**Results Cost/ patient:** The total cost of therapy per patient/year, was ECU277.56 (warfarin) and ECU62.53 (aspirin). The cost of morbidity per patient per year, using DRG mean total costs, was ECU1,873.32 (warfarin) and ECU2,125.4 (aspirin). The cost of morbidity per patient per year, using the product of DRG mean cost per day and mean length of stay, was ECU1,848.06 (warfarin) and ECU2,074.01 (aspirin)
Results Effectiveness: Results are presented graphically as aspirin/warfarin efficacy ratio. This was found to be close to 0.68.

Results Incremental: Results were not synthesized therefore it was a cost minimisation analysis. The total cost per patient per year, using DRG mean total costs, was ECU2,150.8 or $2,731.4 (warfarin), and ECU2,187.9 or $2,778.9 (aspirin). The total cost per patient per year, using the product of DRG mean cost per day and mean length of stay, was ECU2,125.2 or $2,699.0 (warfarin), and ECU2,136.6 or $2,713.9 (aspirin).

Results Uncertainty: Two way sensitivity analyses was done on the efficacy of warfarin/aspirin and the cumulative costs of both drugs. Results were sensitive to variations in the aspirin-warfarin efficacy ratio. Warfarin is no longer the cost-effective strategy in Italy once an efficacy ratio of approximately

Source Funding: not stated

Comments: The study was well reported but had some weaknesses which were identified. The authors reported aspirin-warfarin efficacy ratio of about 0.68 which was based on indirect comparisons. This showed that warfarin was as cheap and effective as aspirin. Recent data WARIS 11 has shown an efficacy ratio of 0.81. Using this recent data it would appear cumulative costs of Aspirin are cheaper than those of Warfarin. The study did not report on the true variability of cost items and only an arbitrary value of 5% was imposed.
Health Economics Extraction for Question 15 Statins and Fibrates

No 1453

**Study Qualities:** 1+ Cost-effectiveness of gemfibrozil for coronary heart disease patients with low levels of high-density lipoprotein cholesterol: the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial

**Author:** Nyman JA; Martinson MS; Nelson D; Nugent S; Collins D; Wittes J; Fye CL; Wilt TJ; Robins SJ; Bloomfield R; VA-HIT Study Group; 2002

**Intervention:** Gemfibrozil

**Comparison:** Placebo

**Population:** Patients with coronary heart disease, low HDL-C levels, and low LDL-C levels

**Perspective:** THIRD PAYER

**Study type:** CUA/CEA

**Methods:** RCT, VA-HIT trial. A markov model was used

**Health valuations:** NOT STATED used values from time trade off (ref 8) from the paper

**Cost components:** Direct medical costs. Sources of costs were documented including DRGs

**Currency:** US$

**Cost year:** 1998

**Time horizon:** lifetime

**Discount rate:** Did not discount base case results but used 0%, 3% & 5% in sensitivity analysis

**Results- cost:** Results were reported for 55, 65 and 75 year old males reflecting the population of the trial. Also results were reported according to the price of gemfibrozil used.

1) Negotiated price by VA was $46.75/yr
2) Wholesale price $956.96/yr

Using negotiated prices for all age groups treatment with gemfibrozil results in savings

Placebo  gemfibrozil

Age 55:  $13464  $17428
Myocardial infarction: full guideline DRAFT (August 2006) – Appendices Page 241 of 248

DRAFT FOR CONSULTATION

Age 65: $10462 $14434
Age 75: $8284 $12193

Results-effectiveness:

Life expectancy

<table>
<thead>
<tr>
<th>Age</th>
<th>Placebo</th>
<th>Gemfibrozil</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>22.5</td>
<td>23.15</td>
</tr>
<tr>
<td>65</td>
<td>17.45</td>
<td>18.07</td>
</tr>
<tr>
<td>75</td>
<td>13.36</td>
<td>13.98</td>
</tr>
</tbody>
</table>

Results-ICER: Reported for both cost effectiveness and cost utility

Age 55: $6607/LYG
Age 65: $6403/LYG
Age 75: $6305/LYG

Cost utility results

Age 55: $7480/QALY
Age 65: $7217/QALY
Age 75: $7239/QALY

Results-Uncertainty: Results remained robust to assumptions about discounting used 0-5% and age. Utility did not affect the results as well.

When discounting was done at 5% ICERs ranged from about $12000/QALY for an 85 year old to about $17000 for a

Source of Funding:Charitable

Comments: this was a detailed study which used appropriate methodology. They showed that gemfibrozil was cost effective for men in the various age groups considered.
### Guideline Questions

<table>
<thead>
<tr>
<th>Questions</th>
<th>Population</th>
<th>Interventions</th>
<th>Co</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the effectiveness of changing dietary regime from the pre-infarct diet?</td>
<td>patients after MI</td>
<td>fibre, low-saturated fat, low GI, low blood sugar, folate rich, fish oils, plant stenols, antioxidant diets,</td>
<td></td>
</tr>
<tr>
<td>2. What education and/or information best aids patients after MI to (i) reduce their risk of subsequent cardiac problems (ii) return to a full and normal life (daily activities, driving, exercise, employment, leisure activities, sexual activities</td>
<td>patients after MI</td>
<td>patient education/information</td>
<td></td>
</tr>
<tr>
<td>3. What psychological and social (carers) support best aids people after MI to reduce their risk of subsequent cardiac problems and to promote their return to a full and normal life?</td>
<td>patients after MI</td>
<td>psychological/social support</td>
<td></td>
</tr>
<tr>
<td>4. What is the incidence of sexual dysfunction in patients after MI and how can patients be identified who would require referral to a specialist unit?</td>
<td>patients after MI</td>
<td>incidence and identification of sexual dysfunction</td>
<td></td>
</tr>
<tr>
<td>5. What is the effectiveness of adding ACEI versus placebo to improve outcome in...</td>
<td>(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?</td>
<td>ACEI</td>
<td></td>
</tr>
<tr>
<td>6. What is the effectiveness of adding ARBs versus placebo to improve outcome in.....</td>
<td>(i) patients after MI without LV dysfunction? (ii) patients after MI with LV dysfunction?</td>
<td>ARB</td>
<td></td>
</tr>
<tr>
<td>7. What is the effectiveness of adding ACEI versus ARBs to improve outcome in...</td>
<td>(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?</td>
<td>ACEI plus ARB</td>
<td></td>
</tr>
<tr>
<td>8. What is the frequency of renal function tests, including serum potassium, be monitored in patients treated with ACEI and/or ARBs after MI?</td>
<td>patients after MI treated with ACEI and/or ARB</td>
<td>frequency of renal function tests - serum potassium</td>
<td></td>
</tr>
<tr>
<td>9. How frequently should renal function tests, including serum potassium, be monitored in patients treated with ACEI and/or ARBs after MI?</td>
<td>patients after MI treated with ACEI and/or ARB</td>
<td>frequency of renal function tests - serum potassium</td>
<td></td>
</tr>
<tr>
<td>10. What is the effectiveness of adding aspirin versus placebo to improve outcome in patients after MI?</td>
<td>patients after MI aspirin</td>
<td>placebo</td>
<td></td>
</tr>
<tr>
<td>11. What is the effectiveness of adding aspirin versus clopidogrel to improve outcome in patients after MI?</td>
<td>patients after MI aspirin</td>
<td>clo</td>
<td></td>
</tr>
<tr>
<td>12. What is the most effective method of delivering dietary advice?</td>
<td>patients after MI</td>
<td></td>
<td></td>
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### Questions

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<tr>
<td>13. What is the effectiveness of adding aspirin versus aspirin and clopidogrel to improve outcome in...</td>
<td>(i) patients after NSTEMI (ii) patients after STEMI</td>
<td>aspirin and clopidogrel</td>
<td>pla</td>
</tr>
<tr>
<td>14. What is the effectiveness of adding a beta blocker versus placebo to improve outcome in...</td>
<td>(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?</td>
<td>beta blocker</td>
<td>pla</td>
</tr>
<tr>
<td>15. What is the effectiveness of adding vitamin K antagonist (warfarin) versus placebo to improve outcome in patients after an MI?</td>
<td>patients after MI</td>
<td>Warfarin</td>
<td>pla</td>
</tr>
<tr>
<td>16. What is the effectiveness of adding vitamin K antagonist (warfarin) versus aspirin to improve outcome in patients after an MI?</td>
<td>patients after MI</td>
<td>warfarin and aspirin</td>
<td>pla</td>
</tr>
<tr>
<td>17. What is the effectiveness of adding aspirin versus aspirin to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>warfarin and aspirin</td>
<td>pla</td>
</tr>
<tr>
<td>18. What is the effectiveness of adding calcium channel blocker versus placebo to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>calcium channel blocker</td>
<td>pla</td>
</tr>
<tr>
<td>20. What is the effectiveness of adding potassium channel blockers versus placebo to improve outcome in patients after MI?</td>
<td>patients after MI treated with eplerenone</td>
<td>potassium channel blockers</td>
<td>pla</td>
</tr>
<tr>
<td>21. How frequently should renal function, including serum potassium, be monitored in patients post MI treated with eplerenone?</td>
<td>patients after MI with heart failure and LV dysfunction</td>
<td>eplerenone</td>
<td>pla</td>
</tr>
<tr>
<td>22. What is the effectiveness of adding omega 3 supplements versus placebo to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>Omega 3</td>
<td>pla</td>
</tr>
<tr>
<td>23. What is the effectiveness of low/ moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>low to moderate alcohol consumption</td>
<td>pla</td>
</tr>
<tr>
<td>24. What is the effectiveness of no/ low/moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>none to moderate alcohol consumption</td>
<td>pla</td>
</tr>
<tr>
<td>25. What is the effectiveness of low/ moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>low to moderate alcohol consumption</td>
<td>pla</td>
</tr>
<tr>
<td>27. What is the effectiveness of adding early statin therapy versus delayed statin therapy to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>early statin</td>
<td>pla</td>
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<tr>
<td>30. What is the effectiveness of adding fibrates or niacin or ezetimibe versus placebo to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>fibrates</td>
<td>placebo</td>
</tr>
<tr>
<td>31. Are there stable patients who don’t benefit prognostically from revascularisation a) benefit prognostically from revascularisation b) those who don’t benefit prognostically with reversible ischaemia and LV dysfunction</td>
<td>patients after MI with reversible ischaemia and LV dysfunction</td>
<td>revascularisation</td>
<td></td>
</tr>
<tr>
<td>32. What is the optimal target blood pressure for patients after MI with hypertension? Assuming a patient is treated with ACEI and or ARB and a beta blocker already (and in LV dysfunction and HF eplerenone)</td>
<td>patients after MI with hypertension</td>
<td>optimal blood pressure</td>
<td></td>
</tr>
<tr>
<td>33. Does determining LV function versus standard care improve (that is, affect) outcome of patients MI (summarising LV dysfunction effect on drugs/ICD/rehab)?</td>
<td>patients after MI</td>
<td>determining (testing?)</td>
<td>LV dysfunction</td>
</tr>
<tr>
<td>34. Is there any benefit in giving ACEI at a later stage of treatment in patients with previous MI (later than one year)</td>
<td>i) proven MI in the past &gt; 1 year</td>
<td>treatment for MI &lt; 1 year</td>
<td>late treatment</td>
</tr>
<tr>
<td>35. What is the level of physical activity which increases physical work capacity versus physical activity which does not increase physical work capacity?</td>
<td>patients after MI</td>
<td>regular exercise (need to define this)</td>
<td>level of physical activity</td>
</tr>
<tr>
<td>36. What is the effectiveness of comprehensive cardiac rehabilitation versus standard care with no cardiac rehabilitation to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>comprehensive cardiac rehab</td>
<td></td>
</tr>
<tr>
<td>37. What is the effectiveness of exercise only cardiac rehabilitation versus standard care with no cardiac rehabilitation to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>exercise only rehab</td>
<td></td>
</tr>
<tr>
<td>38. What is the effectiveness of an individualised cardiac rehabilitation programme versus a non-individualised cardiac programme to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>individualised cardiac rehab</td>
<td></td>
</tr>
<tr>
<td>39. Are there stable patients who don’t benefit prognostically from revascularisation a) benefit prognostically from revascularisation b) those who don’t benefit prognostically with reversible ischaemia and LV dysfunction</td>
<td>patients after MI with reversible ischaemia and LV dysfunction</td>
<td>revascularisation</td>
<td></td>
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<tr>
<td>43. Are there any patients after MI in whom the exercise component of cardiac rehabilitation is not safe?</td>
<td>patients after MI</td>
<td>risk factors of cardiac rehab</td>
<td></td>
</tr>
<tr>
<td>44. What approach to patient engagement best aids access to cardiac rehabilitation, particularly in reference to em, op, seg, women, those from rural communities, and those with mental and physical health co-morbidities?</td>
<td>previous MI - women, ethnic minorities, older people, lower social economic groups, mental and physical health co-morbidities, living in rural communities</td>
<td>access to cardiac rehab</td>
<td></td>
</tr>
<tr>
<td>45. What is the effectiveness of regular physical activity versus a sedentary lifestyle to improve outcome in patients after MI?</td>
<td>patients after MI</td>
<td>regular exercise (need to define this) structured exercise, unstructured exercise, frequency, duration, intensity</td>
<td></td>
</tr>
<tr>
<td>46. Does a history of proven MI in the past (&gt; 1 year) versus recent MI (&lt; 1 year) change treatment / management / outcome?</td>
<td>i) proven MI in the past &gt; 1 year</td>
<td>treatment for MI &lt; 1 year</td>
<td></td>
</tr>
<tr>
<td>47. What is the effectiveness of adding fibrates versus placebo to improve outcome in patients with CHD</td>
<td>Fibrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48. What is the effectiveness of adding ezetimibe versus placebo to improve outcome in patients with CHD</td>
<td>ezetimibe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>49. Is there an optimum time for ACEI to be administered in the nonacute phase?</td>
<td>(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?</td>
<td>Early ACEI</td>
<td>Del</td>
</tr>
<tr>
<td>50. Is there and optimum time for beta-blockers to be initiated in unselected patients after MI?</td>
<td>unselected patients after MI</td>
<td>timing of beta blocker</td>
<td></td>
</tr>
<tr>
<td>51. What is the potential harm of adding the following: calcium channel blocker or thiazide diuretic or alpha blocker versus placebo in...</td>
<td>(i) patients after MI with LV dysfunction in whom further blood pressure lowering is warranted? (ii) patients after MI without LV dysfunction in whom further blood pressure lowering is warranted?</td>
<td>calcium channel blocker, thiazide diuretic, alpha blocker</td>
<td></td>
</tr>
<tr>
<td>52. What is the incidence of anxiety and depression in patients after MI and how can patients be identified? (can be cross-referenced to the Anxiety &amp; Depression guidelines)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53. What are the information and support needs for patients at different points in the care pathway?</td>
<td>patients after MI</td>
<td>patient information and support</td>
<td></td>
</tr>
<tr>
<td>54. At what level of renal function do the risks of therapy with ACEIs outweigh the benefits in patients after MI with poor renal function?</td>
<td></td>
<td>Whether to continue ACEI treatment. what are the risk factors?</td>
<td></td>
</tr>
<tr>
<td>55. Is there any benefit in initiating beta blockers at a later stage of treatment?</td>
<td></td>
<td>beta blocker at later stage</td>
<td></td>
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Search Strategy

The search strategy will be available in the final draft.
Appendix G – National Service Framework for Coronary Heart Disease definition of phases of comprehensive cardiac rehabilitation

Phase 1: before discharge from hospital

• assessment of physical, psychological needs for cardiac rehabilitation

• negotiation of a written individual plan for meeting these identified needs

• individual advice on lifestyle (smoking cessation, diet, physical activity, alcohol consumption, sexual activity and employment

• prescription of effective medication and education about its use, benefits and harms

• involvement of relevant informal carer(s)

• provision of information about cardiac support groups

• provision of locally relevant written information about cardiac rehabilitation

Phase 2: early post-discharge period

• comprehensive assessment of cardiac risk, including physical, psychological and social needs for cardiac rehabilitation; and a review of the initial plan for meeting these needs

• provision of lifestyle advice and psychological interventions according to the agreed plan from a relevantly trained therapist who has access to support from a cardiologist

• maintain involvement of relevant informal carer(s)
- review information with cardiac support groups
- offer resuscitation training for family carers

Phase 3: four weeks after acute cardiac event, as early post-discharge period plus
- structured exercise sessions to meet the assessed needs of individual patients
- maintain access to relevant advice and support from people trained to offer advice about exercise, relaxation, psychological interventions, health promotion and vocational advice

Phase 4: long-term maintenance of changed behaviour
- long-term follow up in primary care
- offer involvement with local cardiac support groups
- referral to specialist cardiac, behavioural (exercise, smoking cessation) or psychological services as clinically indicated