

Appendices

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Appendix A – 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).

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- 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).

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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

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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.

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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.

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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
- Guideline development methods – information for National Collaborating Centres and Guideline Developers.

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 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults, September 2004.
- Type 2 diabetes – management of blood pressure and blood lipids, October 2002.
- Type 2 Diabetes - management of blood glucose, September 2002.
- Hypertension – management of hypertension in adult patients in primary care, August 2004.
- Chronic heart failure – management of chronic heart failure in adults in primary and secondary care, October 2003.
- Hyperlipidaemia – identification and management of hyperlipidaemia as part of cardiovascular risk assessment in primary care (ongoing)

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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).

Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome, July 2004.

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 B – 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. (Oldridge, N. et al 1993), (Joliffe, J. A. et al 2003), (Taylor, R. S. et al 2004), (Clark, A. M. et al 2005) (Beswick, A. D. et al 2004)

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 (Department of Health 2000)

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 (Bethell, H. J. et al 2001) (Betell, H. J. N. et al 2000). 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 (Beswick, A. D., Rees, K., Griebisch, I. et al 2004)

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 ((Beswick, A. D., Rees, K., Griebisch, I. et al 2004) (Evans, J. A., Turner, S. C., and Bethell, H. J. N. 2002),(Betell, H. J. N., Turner, S. C., Flint, E. J. et al 2000)

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 (Beswick, A. D., Rees, K., Griebisch, I. et al 2004), (Betell, H. J. N., Turner, S. C., Flint, E. J. et al 2000) (Lewin, B. et al 1992)

The wider economic benefits of CR are believed to derive primarily from reduced secondary utilization of inpatient medical resources. Studies from USA (Ades, P. A., Pashkow, F. J., and Nestor, J. R. 1997), (Oldridge, N., Furlong, W., Feeny, D. et al 1993), Australia (Hall, J. P. et al 2002) and Sweden (Levin, L. A., Perk, J., and Hedback, B. 1991) 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.

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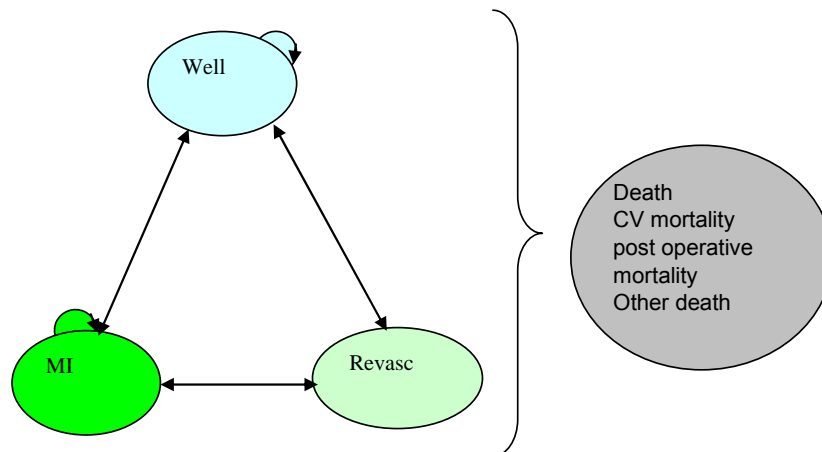
In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states. Figure 1 shows a schematic representation of the patients' 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



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 (Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003), (Clark, A. M., Hartling, L., Vandermeer, B. et al 2005) The probabilities of having revascularisation were taken from another meta-analysis (Taylor, R. S., Brown, A., Ebrahim, S. et al 2004). 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 (Eagle, K. A. et al 2004).

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) (Government

Actuaries Department 2006), (Office for National Statistics 2006).. 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 1 Probabilities for a 65-year-old man without Cardiac rehabilitation

Parameter	Annual probability	Source
Well to Rev	0.062	(Taylor, R. S., Brown, A., Ebrahim, S. et al 2004)
Well to MI	0.096	(Clark, A. M., Hartling, L., Vandermeer, B. et al 2005)
Well to death	0.093	(Clark, A. M., Hartling, L., Vandermeer, B. et al 2005), (Office for National Statistics 2006)
Revascu to MI	0.009	(Henderson, R. A. et al 2003)
Revascu to post op death	0.008	(Eagle, K. A., Guyton, R. A., Davidoff, R. et al 2004)
Revascu to another revascu	0.030	(Taylor, R. S., Brown, A., Ebrahim, S. et al 2004)
Well after revascu to death	0.042	(Henderson, R. A., Pocock, S. J., Clayton, T. C. et al 2003),

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		(Office for National Statistics 2006)
Mi to revascu	0.062	(Taylor, R. S., Brown, A., Ebrahim, S. et al 2004)
MI to MI	0.062	(Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003)
MI to death	0.094	(Joliffe, J. A., Rees, K., Taylor, R. S. et al 2003), (Office for National Statistics 2006)

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Treatment effects:

The effectiveness of CR defined as the reduction in relative risks of mortality and non fatal reinfaction was obtained from systematic (Clark, A. M., Hartling, L., Vandermeer, B. et al 2005) and for revascularisation from (Taylor, R. S., Brown, A., Ebrahim, S. et al 2004). Data on the effectiveness of the strategies aimed at increasing uptake and compliance were obtained from an HTA report (Beswick, A. D., Rees, K., Griebisch, I. et al 2004)

Table 2 Relative risks of CR (base case analysis)

Outcome	Mean	Lower CI	Upper CI	Source
Revascularisation	0.85	0.65	1.12	(Taylor, R. S., Brown, A., Ebrahim, S. et al 2004)
MI	0.83	0.74	0.94	(Clark, A. M., Hartling, L., Vandermeer, B. et al 2005)
Post operative death	1	1	1	Assumption
Death	0.85	0.77	0.94	(Clark, A. M., Hartling, L., Vandermeer, B. et al 2005)

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

Intervention	Results	Source
Letters	87% intervention group Compared to 57% in control p=0.0025	(Beswick, A. D., Rees, K., Griebisch, I. et al 2004)
Telephone+ HCP	57% vs. 27% in those who did not get the intervention.	(Beswick, A. D., Rees, K., Griebisch, I. et al 2004)

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 (National Institute for Health & Clinical Excellence. 2006b).

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 (Department of Health Reference Costs 2005 2005). 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 (National Institute for Health and Clinical Excellence. 2006). The cost of CR was taken from a review (Beswick, A. D.,

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Rees, K., Griebisch, I. et al 2004) and included staff costs, equipment, and that of recruiting patients to CR. Costs of acute MI (non-fatal reinfaction) were assumed to be the same as those of patients treated with thrombolysis, which includes the cost of hospitalisation (Hartwell, D. et al 2005). 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 (Beswick, A. D., Rees, K., Griebisch, I. et al 2004). The actual unit costs were taken from the Personal Social Services Research Unit PSSRU (PSSRU 2005).

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 (Beswick, A. D., Rees, K., Griebisch, I. et al 2004) 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 (PSSRU 2005)

Table 4 Costs of health states

Parameter	2005 UK £ pa			Source
	Mean	Lower	Upper	
No event	£171	£86	£342	(National Institute for Health & Clinical Excellence. 2006a)
Rev	£8,676	£4,338	£17,352	NHS ref cost
Post Rev	£500	£250	£1,000	assumption
MI	£4,448	£2,224	£8,896	(Hartwell, D., Colquitt, J., Loveman, E. et al 2005)
MI (subsequent)	£500	£250	£1,000	(National Institute for Health and Clinical Excellence. 2006)
Rev2	£8,676	£4,338	£17,352	NHS ref cost
Post Rev2	£500	£250	£1,000	assumption
post OPD	£0	£0	£0	
Death	£0	£0	£0	

Table 5, other resources

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

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. (National Institute for Health & Clinical Excellence. 2006b)

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 (Harvard CEA Registry 1997)

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

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by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England (Department of Health 1998)

One study (Oldridge, N., Furlong, W., Feeny, D. et al 1993), 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 in sensitivity analysis. The weight attached to death was zero

Table 6 Health state utility weights

Health State	Utility	Mean	Lower limit	Upper limit	Source
No event	1.00	1.00	-	-	
Rev	0.80	0.80	0.70	0.90	(Palmer, S., Sculpher, M., and Philips, Z. 2004)
Post Rev	0.88	0.88	0.70	0.90	(Harvard CEA Registry 1997)
MI	0.76	0.76	0.70	0.90	(Harvard CEA Registry 1997)
MI (subsequent)	0.88	0.88	0.70	0.90	assumption
Rev2	0.80	0.80	0.70	0.90	same as Rev 1
Post Rev2	0.88	0.88	0.70	0.90	same as Rev 1
post OPD	0.00	0.00	0.00	0.00	
Death	0.00	0.00	0.00	0.00	

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Table 7 Utility weight by age

Age group	Age utility weight	Source
45-54	0.85	(Department of Health 1998)
55-64	0.79	
65-74	0.78	
75+	0.73	

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

$$\text{ICERs} = (\text{cost of CR} - \text{cost of no CR}) / (\text{QALY of CR} - \text{QALY of no CR})$$

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.

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- iv) ICERs are recalculated excluding any drugs subject to extended dominance. (Palmer, S., Sculpher, M., and Philips, Z. 2004)

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 Cardiac Rehabilitation vs. no Cardiac Rehabilitation.

The base case results are presented in table 8a and b for 65-year-old men and women respectively. This suggests that CR is cost-effective for this population. The ICER of CR compared with no CR is about £7,860 and £8,360 per QALY gained for men and women respectively, which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

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

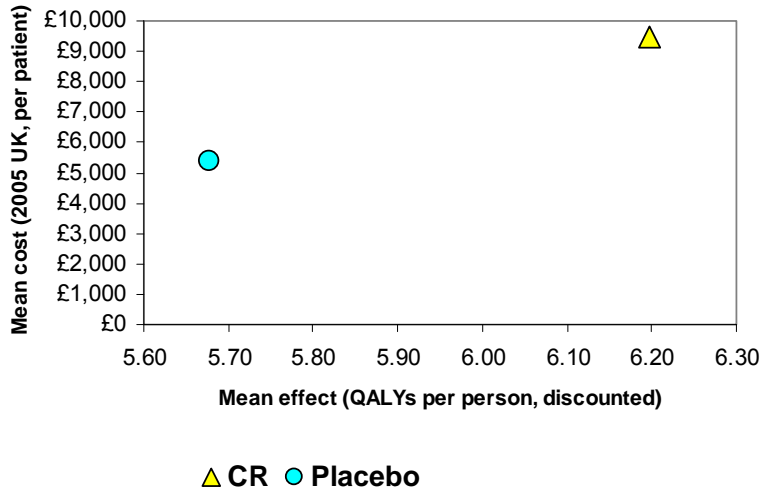
	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	5359.497	5.677295			
CR	9449.575	6.197696	4090.078	0.520401	7859.471

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

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	5773.631	6.088688			
CR	10135.59	6.610674	4361.962	0.521986	8356.474

Figure 2

Cost effectiveness plane, CR compared to no CR in post MI patients



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 £ 8,000/QALY. The strategy of using phone calls and home visits by a HCP compared to sending letters is about £ 8,400/QALY gained which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

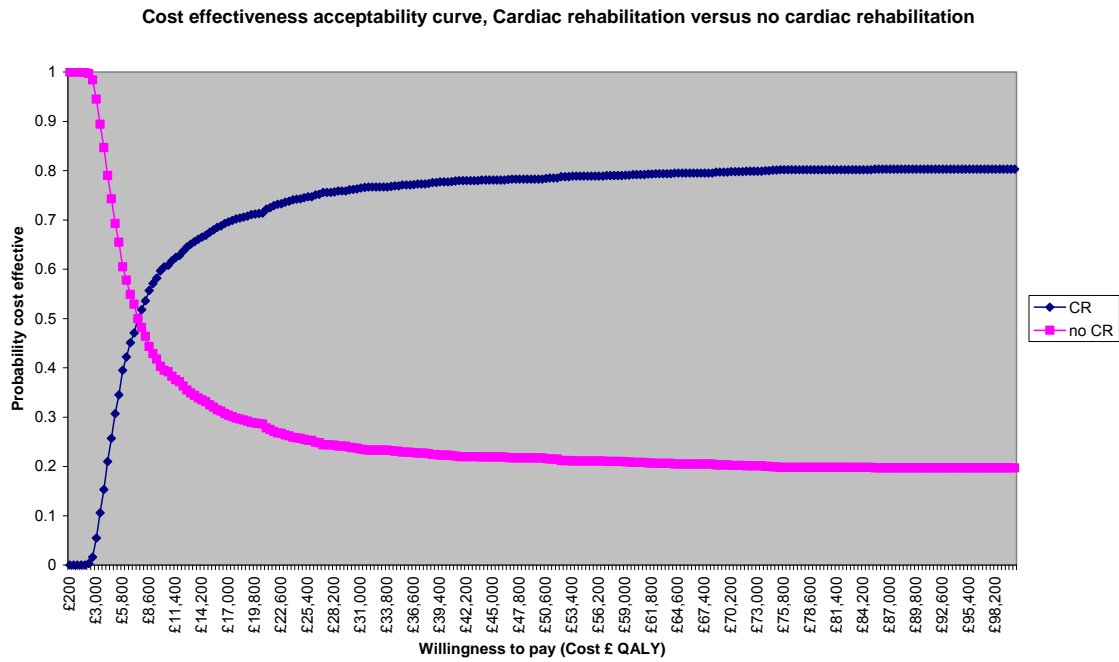
Table 9 Incremental cost effectiveness of the methods used to increase uptake of CR after an MI,

Strategy	Costs	QALY	Incre costs	Incre QALYs	ICER (£/QALY)
Usual care	£6,995,529	5885			
Letters	£7,844,705	5992	£849,176	106	£7,999
Phone + HCP	£8,896,943	6117	£1,052,239	125	£8,425

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.

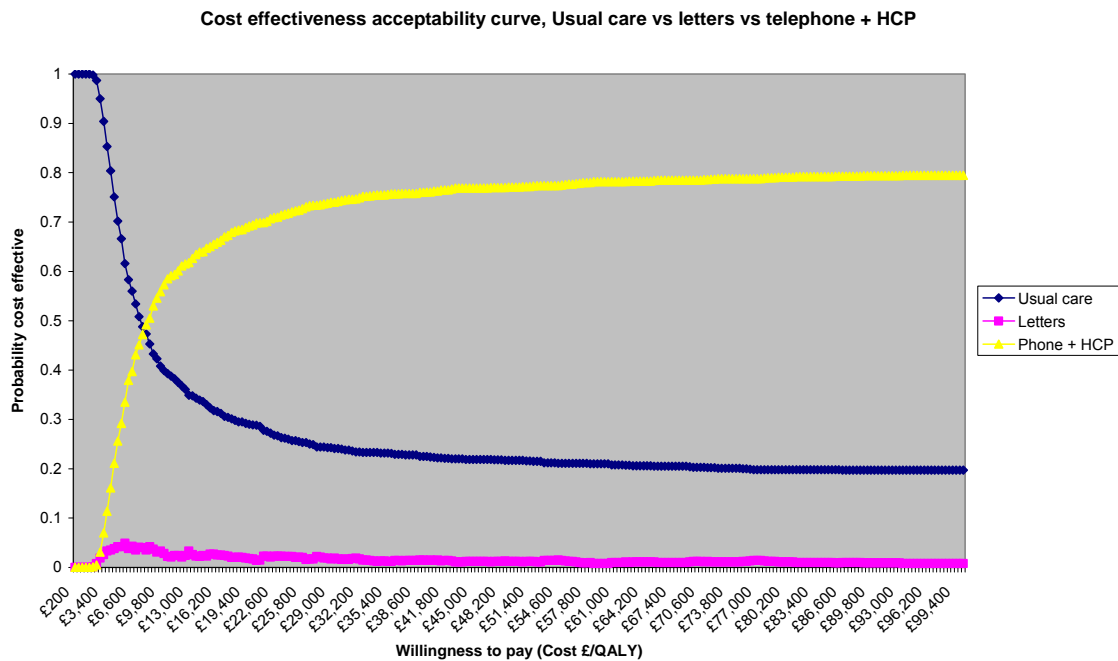
The CEACs demonstrate that CR is highly cost effective. The probability that CR is cost effective increases as the willingness to pay increases. If the NHS is willing to pay up to £10,000 for an additional QALY, the probability that CR is cost effective is around 60%, increasing to 71% if the maximum willingness to pay is £20,000.

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 willing to pay upto £10,000 for an additional QALY, the probability that phone calls plus home visits by a HCP is cost effective is around 57%, increasing to 69% if the maximum willingness to pay is £20,000.

Figure 4



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. We did a threshold analysis to find the point at which CR becomes cost ineffective due to loss in quality of life. The model estimates that a loss in quality of life due to CR of more than 3.5% will make CR cost ineffective. Thus the model is

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sensitive to this assumption. 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 £5,400/QALY and when the upper CI is used the ICERs rise to about £19,730/QALY which is borderline cost effective.

QALY gain due to CR

The model is not sensitive to changes in additional QALYs as a result of CR. The base case model assumed that there was no difference in QALYs between those who participate in CR and those that do not. We used a multiplier of 0.052 reported by Oldridge et al in the sensitivity analysis. The estimated ICERs decrease by almost half to about £4,940 per QALY gained. The model is robust to this assumption since we retrain the original conclusion..

Adherence to CR

The base case model assumed that patients will adhere to CR 100% However studies have shown that compliance rates are high in the first year and fall in subsequent years. The average for the first year is between 60 to 70% in the first 12 months, falling to between 45% to 70% after 3 years. We tested for adherence in our model. The model appears to be slightly sensitive to this

assumption since compliance rates below 40% are not cost effective. For instance 40% compliance has an estimated ICER of about £20,000

Cost of CR

The results were sensitive to changes in the cost of rehabilitation but remained robust. The ICER ranged from about £2,320/QALY if the lowest cost per patient per year of £140 cited by Taylor et al is used to about £12,890/QALY when the cost is assumed to be about £800/patient per year cited by Beswich et al. 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 £8,980/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, the results of the model remain robust with an estimated ICER of

about £6,780/QALY. If the discount rate was raised to 6%, the ICERs slightly increased to £8,680/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 1% increase in uptake, the ICERs compared to usual care increased to about £15,000/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 100% increase in the uptake of CR letters the ICERs for letters compared to HCP + phone increased to about £11,000/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. We did a threshold analysis to find the point at which this intervention ceases to be cost effective. The model estimates that when the efficacy of phone call plus home visits by a HCP was assumed to result in an increase in uptake of CR of less than 55% then phone calls plus home visits by a HCP will not be cost effective at a willingness to pay value of £20,000/QALY. For instance if the strategy of HCP + phone resulted in increase of 50% in uptake of CR, letters will dominate them. Thus the model is sensitive to this assumption, but the analysis is speculative since the ranges used in sensitivity analysis are arbitrary.

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

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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. Studies have shown that participation rates ranges between 14-50%. In The base case model assumed a 40% participation rate. We varied the participation rate between 14% to 85%. The ICERs were below £10,000/QALY for all comparisons thus the model remained robust to this assumption

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 (Henderson, R. A. et al 1998) 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

RR of non CVD death	ICER (cost/QALY)
0.5	£10,120
1	£8,980
4	£6,940
8	£6,070

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 £8,980/QALY. Overall the model was robust to this assumption

Sensitivity analysis for Age and sex

Age	ICER (cost/QALY)	ICER (cost/QALY)
	Males	Females
55	£7,670	£8,210
65	£7,680	£8,360
75	£7,110	£7,610
85	£6,790	£7,050

Interpretation

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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.

Sensitivity analysis for efficacy of CR

Parameter	ICER (cost/QALY lower 95% CI)	ICER (cost/QALY upper 95% CI)
Revascularisation	£8,550	£7,330
MI	£7,300	£8,580
Death	£5,410	£19,730

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 £5,410/QALY and when the upper CI is used the ICERs rise to about £19,730/QALY.

Sensitivity analysis for reduction in quality of life due to CR

Reduction in QoL due to CR	ICER (Cost/QALY)
1%	£9,440
3%	£15,830
3.5%	£19,040
4%	£23,900

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Interpretation

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 1-4%. CR will cease to be cost effective at £20,000/QALY threshold if it resulted in quality of loss of more than 3.5%. 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

Additional QALYs due to CR	ICER (cost/QALY)
1%	£7,060
5.2%	£4,940
10%	£3,680

Interpretation

The model is not sensitive to changes in additional QALYs as a result of CR. The base case model assumed that there was no difference in QALYs between those who participate in CR and those that do not. We assumed there would be an increase in QALY due to CR ranging from 1% to 10%. The estimated ICERs ranged from £7,060 per QALY gained for a 1% increase in QALY to about £3,680 for a 10% increase in QALY due to CR

Sensitivity analysis for compliance to CR

Compliance rate	ICER (cost/QALY)
50%	£15,720
40%	£19,650

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35%	£22,460
30%	£26,200

Interpretation

The base case model assumed that patients will adhere to CR 100%. However studies have shown that compliance rates are high in the first year and fall in subsequent years. The average for the first year is between 60 to 70% in the first 12 months, falling to between 45% to 70% after 3 years. We tested for adherence in our model. The model appears to be slightly sensitive to this assumption since compliance rates below 40% are not cost effective. For instance 40% compliance has an estimated ICER of about £20,000

Sensitivity analysis for Cost of CR

Cost of CR/patient/year	ICER (cost/QALY)
£140	£2,320
£300	£4,880
£600	£9,680
£800	£12,890

Interpretation

The results were sensitive to changes in the cost of rehabilitation but remained robust. The ICER ranged from about £2,320/QALY if the lowest cost per patient per year of £140 cited by Taylor et al is used to about

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£12,890/QALY when the cost is assumed to be about £800/patient per year.

As the cost of rehabilitation increases the ICER become less favourable

Sensitivity analysis for Cost of CVD events and procedures

Parameter	ICER Lower costs (50% less) (cost/QALY)	ICER Upper costs (100% more) (cost/QALY)
Revascularisation	£7,920	£7,750
MI	£7,730	£7,920
Subsequent MI	£7,790	£7,990

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 £8,000/QALY.

Sensitivity analysis for discounting

Discount rate	ICER (cost/QALY)
0%	£6,780
6%	£8,680

Interpretation

The impact of the discounting was also explored. Assuming that there was no discounting, the results of the model remain robust with an estimated ICER of about £6,780/QALY. If the discount rate was raised to 6%, the ICERs slightly increased to £8,680/QALY. Thus the model was not sensitive to this parameter

Sensitivity analysis for baseline uptake of CR

Baseline uptake	Letters vs. usual care	Phone call plus home visit by HCP vs. Letters
14%	£8,257	£9,474
60%	£7,952	£8,236
85%	£7,925	£8,125

Interpretation

The model was not sensitive to assumptions about baseline uptake of cardiac rehabilitation. Studies have shown that participation rates ranges between 14-50%. In The base case model assumed a 40% participation rate. We varied the participation rate between 14% to 85%. The ICERs were below £10,000/QALY for all comparisons thus the model remained robust to this assumption

Sensitivity analysis for efficacy of letters

Efficacy of letters	Letters vs. usual care	Phone call plus home visit by HCP vs. Letters
1%	£14,969	£8,167
10%	£8,570	£8,195
20.%	£8,214	£8,232
80.00%	£7,948	£8,953
100%	£7,930	£10,943

Interpretation

When assumptions about the efficacy of letters were changed the model remained robust. When letters were assumed to result in a modest 1% increase in uptake, the ICERs compared to usual care increased to about £15,000/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

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when the efficacy of letters was assumed to result in a 100% increase in the uptake of CR letters the ICERs for letters compared to HCP + phone increased to about £11,000/QALY

Sensitivity analysis for efficacy of phone plus HCP

Efficacy of phones	Letters vs. usual care	Phone call plus home visit by HCP vs. Letters
50 %	£7,998	Dominated by letters
60 %	£7,998	£11,629
80 %	£7,998	£9,029

Interpretation

In the base case model phone calls plus home visits by a HCP resulted in 111% increase in uptake of CR. We did a threshold analysis to find the point at which this intervention ceases to be cost effective. The model estimates that when the efficacy of phone call plus home visits by a HCP was assumed to result in an increase in uptake of CR of less than 55% then phone calls plus home visits by a HCP will not be cost effective at a willingness to pay value of £20,000/QALY. For instance if the strategy of HCP + phone resulted in increase of 50% in uptake of CR, letters will dominate them. Thus the model is sensitive to this assumption, but the analysis is speculative since the ranges used in sensitivity analysis are arbitrary.

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 (Al-Mallah, M. H. et al 2006) which meta-analysed data from six trials (Braunwald, E. et al 2004), (Nissen, S. E. et al 2004), (Fox, K. M. and EUROpean, trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators 2003), (Arnold, J. M. O. et al 2003), (MacMahon, S. et al 2000) and (Pitt, B. et al 2001).

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 (Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006) seen in primary and secondary care.

Interventions compared

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

Outcomes

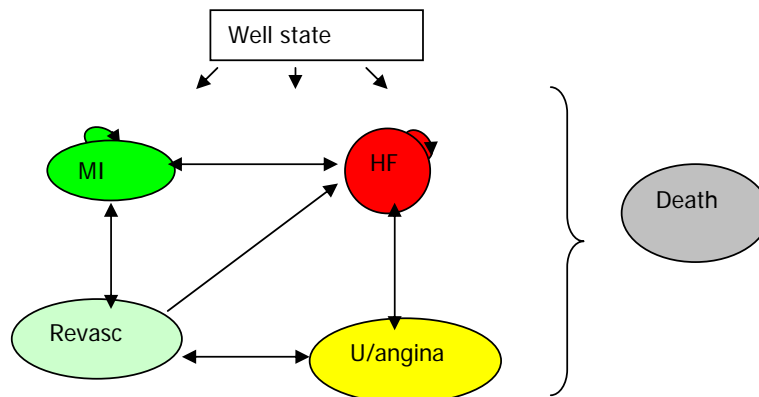
The treatment effects were measured in terms of reduction of cardiovascular events: non-fatal MI, revascularisation, unstable angina, heart failure, cardiovascular -related deaths and other deaths. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life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

Figure 1 Model structure for the cost effectiveness of ACE inhibitors in low risk patients with preserved LVDF compared to placebo



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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 (Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006).

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

Parameter	Annual probability	Source (Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006)
Well to REV	0.0189	(Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006)
Well to MI	0.01008	(Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006)
Well to unstable angina	0.01196	(Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006)
Well to heart failure	0.00328	(Al-Mallah, M. H., Tleyjeh, I M.,

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Well to DEATH	0.0426298	Abdel-Latif, A. A. et al 2006) (Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006) (Office for National Statistics 2006)
Rev to MI	0.0189	(Palmer, S., Sculpher, M., and Philips, Z. 2004)
Rev to unstable angina	0.0189	assumed to be the same as MI
Rev to heart failure	0.00945	assumed to be half of MI (Henderson, R. A., Pocock, S. J., Clayton, T. C. et al 2003) (Office for National Statistics 2006)
Rev to DEATH	0.0426298	(Palmer, S., Sculpher, M., and Philips, Z. 2004)
MI to REV	0.0189	(Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006)
MI to MI	0.01008	(Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006)
MI to unstable angina	0.01196	(Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006)
MI to heart failure	0.00328	(Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006)
MI to DEATH	0.0426298	(Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006) (Office for National Statistics 2006)
Unstable angina to REV	0.0189	same as MI

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Unstable angina to MI	0.01008	same as MI
Unstable angina to heart failure	0.01196	same as MI
Unstable angina to DEATH	0.0426298	same as MI
Heart failure to MI	0.023	(SOLVD Investigators 1992)
Heart failure to unstable angina	0.023	(SOLVD Investigators 1992)
Heart failure to heart failure	0.0545	(SOLVD Investigators 1992)
Heart failure to DEATH	0.0915098	(SOLVD Investigators 1992) (Office for National Statistics 2006)

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 (Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006). The incidence of MI following revascularisation was taken from (Henderson, R. A., Pocock, S. J., Clayton, T. C. et al 2003).

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) (Government Actuaries Department 2006) and from data on the proportion of deaths due to CVD-related causes from the Office for National Statistics (Office for National Statistics 2006). 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).

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Table a Baseline non CVD related death

Deaths by age, sex and underlying cause, 2004 registrations, England and Wales

	All cause ICD10: A00-R99		Circulatory ICD: 100-199		Non-circulatory as proportion of all deaths (p)	
	M	F	M	F	M	F
	45	12,417	8,139	3,930	1,362	0.68
55	27,117	17,649	9,330	3,541	0.66	0.80
65	52,709	37,041	19,783	11,304	0.62	0.69
75	87,367	88,404	35,607	35,958	0.59	0.59
85	51,329	109,488	20,816	46,470	0.59	0.58

Source: <http://www.statistics.gov.uk/STATBASE/Expodata/Spreadsheets/D8986.xls>

All cause mortality, estimated from life tables, 2002-4, England

	Annual probability of death in age band	
	M	F
45	0.0037	0.0025
55	0.0093	0.0059
65	0.0236	0.0154
75	0.0537	0.0406
85	0.0870	0.0807

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

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

2

Estimated non-circulatory deaths for post MI cohort

	Annual probability of death in age band	
	M	F
45	0.51%	0.41%
55	1.23%	0.94%
65	2.95%	2.14%
75	6.37%	4.82%
85	10.35%	9.30%

Treatment effects:

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 (Al-Mallah, M. H., Tleyjeh, I M., Abdel-Latif, A. A. et al 2006).

Table b Relative risks of treatment (base case analysis)				
		COMPARATOR		
		Relative risks		
INTERVENTION		Mean	Lower	Upper
			95% CI	95% CI
ACE inhibitors	Revascularisation	0.93	0.87	1.00
	MI	0.84	0.75	0.94
	Unstable angina	0.93	0.83	1.05
	Heart failure	0.71	0.59	0.86
	Mortality	0.87	0.81	0.94

Cost data

The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the

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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 (National Institute for Health & Clinical Excellence. 2006b).

The costs of health states used in the model are shown in Table 2c. Costs for revascularization which includes hospitalisation were taken from the NHS reference cost 2005.(Department of Health Reference Costs 2005 2005) 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 (National Institute for Health & Clinical Excellence. 2006a). The subsequent costs of MI and unstable angina were assumed to be the same and were taken from the NICE hypertension guideline 2006 (National Institute for Health and Clinical Excellence. 2006). 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, D., Colquitt, J., Loveman, E. et al 2005). The cost of death was zero. Costs of drugs were taken from the drug tariff (Prescription Pricing Authority 2006)

Cost of heart failure was taken from the NHS reference cost 2005,(Department of Health Reference Costs 2005 2005) 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 c Costs of health states

	2005 UK £ pa			Source
	Mean	Lower	Upper	
No event	£171	£86	£342	(National Institute for Health & Clinical Excellence. 2006a)
Rev	£8,676	£4,338	£17,352	(Department of Health Reference Costs 2005 2005)
Post Rev	£500	£250	£1,000	assumption (Hartwell, D., Colquitt, J., Loveman, E. et al 2005)
MI	£4,448	£2,224	£8,896	(National Institute for Health and Clinical Excellence. 2006)
MI (subsequent)	£500	£250	£1,000	(Department of Health Reference Costs 2005 2005)
Rev2	£8,676	£4,338	£17,352	assumption
Post Rev2	£500	£250	£1,000	
post OPD	£0	£0	£0	
Death	£0	£0	£0	

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.(National Institute for Health & Clinical Excellence. 2006b)

The utility values used in the model are shown in Table 2d and Table 2e. The values were taken from literature or the Harvard cost effectiveness registry database (Harvard CEA Registry 1997)

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 (Department of Health 1998)

Health State	Utility	Mean	Lower limit	Upper limit	Source
No event	1.00	1.00	-	-	
Rev	0.80	0.80	0.70	0.90	(Palmer, S., Sculpher, M., and Philips, Z. 2004)
Post Rev	0.88	0.88	0.70	0.90	(Harvard CEA Registry 1997)
MI	0.76	0.76	0.70	0.90	(Harvard CEA Registry 1997)
MI (subsequent)	0.88	0.88	0.70	0.90	assumption
Rev2	0.80	0.80	0.70	0.90	same as Rev 1
Post Rev2	0.88	0.88	0.70	0.90	same as Rev 1
post OPD	0.00	0.00	0.00	0.00	
Death	0.00	0.00	0.00	0.00	

Age group	Age utility weight	Source
45-54	0.85	(Department of Health 1998)
55-64	0.79	
65-74	0.78	
75+	0.73	

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 suggests 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 f Base case results 65 year old male

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£3,847	7.72			
ACE inhibitors	£5,633	8.24	£1,786	0.52	£3,424

Table g Base case results 65 year old female

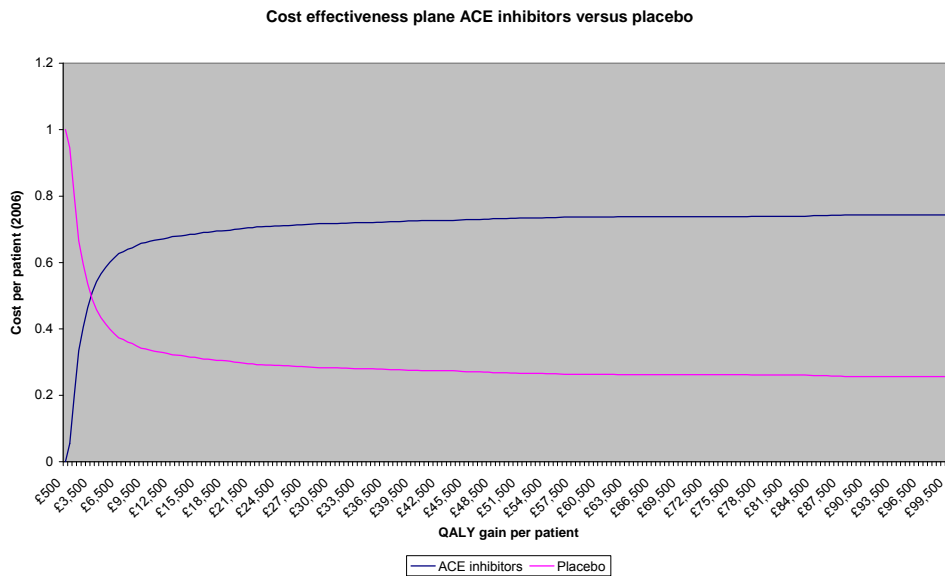
	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£4,265	8.40			
ACE inhibitors	£6,176	8.92	£1,911	0.52	£3,707

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

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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 where 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 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.

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.

1.2.3 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. The model is sensitive to assumptions about loss of quality of life due to assumed treatment side effects.

1.2.5 ADDITIONAL INFORMATION: SENSITIVITY ANALYSIS

Sensitivity analysis; quality of life loss due to side effects

% loss of QoL due to treatment side effects	Cost/QALY
1%	£5,650
2%	£16,160
2.1%	£20,000
2.5%	£230,200
3%	DOMINATED

Interpretation:

The base case model assumed that the side effect profile of ACE inhibitors was the same as in the placebo arm. However when a threshold analysis was done, if ACE inhibitors treatment resulted in loss of quality 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. This however should be interpreted with caution since there was no published evidence supporting the idea that ACE inhibitor treatment resulted in side effects that were significantly different from placebo.

Sensitivity analysis; health state utilities \pm 0.2

Health state	(-0.2) cost /QALY	(+ 0.2) cost/QALY
Revascularisation	£3,420	£3,420
Post Revascularisation	£3,520	£3,370
MI	£3,420	£3,430
Post MI	£3,400	£3,440
Unstable angina	£3,420	£3,430
Post unstable angina	£3,480	£3,370
Heart failure	£3,420	£3,430
Post HF	£3,390	£3,450

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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

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

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

	Cost (£)	Effect (QALYs)	ICER (£/QALY)
Placebo	£7,690	7.7193	
ACE inhibitors	£9,530	7.9394	£8,360

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Interpretation:

A worse case scenario was examined where 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

Outcome	Lower 95% CI	Upper 95% CI
Revascularisation	£3,270	£3,600
MI	£3,320	£3,540
Unstable angina	£3,280	£3,600
Heart failure	£3,330	£3,550
Mortality	£2,600	£6,090

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

Relative risk of non CVD death	cost/QALY
1	£4,060
2	£3,420
4	£2,960
8	£2,540

Interpretation:

The 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

Age	cost/QALY (Males)	cost/QALY (Females)
55	£4,740	£5,520
65	£3,420	£4,060
75	£2,990	£3,790
85	£2,890	£4,040

Interpretation:

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 (Dargie, H. J. 2001) 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 (Dargie, H. J. 2001). 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.

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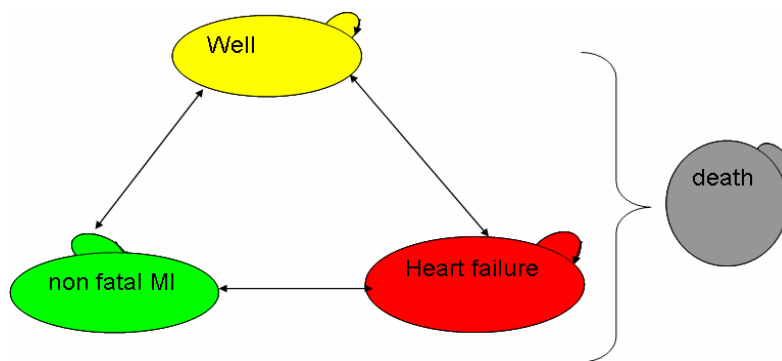
Model structure and assumptions

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.

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 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

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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.

Parameter	Annual probability	Source
Well to MI	0.0480	(Dargie, H. J. 2001)
Well to heart failure	0.1120	(Dargie, H. J. 2001)
Well to death	0.1268	(Dargie, H. J. 2001)
MI to MI	0.0480	(Dargie, H. J. 2001)
MI to heart failure	0.1120	(Dargie, H. J. 2001)
MI to death	0.1268	(Dargie, H. J. 2001)
heart failure to heart failure	0.1120	(Dargie, H. J. 2001)
heart failure to MI	0.0480	(Dargie, H. J. 2001)
heart failure to death	0.2118	{Davies, 2001 5291 /id}

1.3.1.1 Baseline risks:

The probabilities of secondary cardiovascular events were taken from the placebo arm of the CAPRICORN trial (Dargie, H. J. 2001) 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) (Government Actuaries Department 2006) In the base case model we

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assumed that post MI cohort is at increased risk of non- cardiovascular death (2 fold risk) compared with the general population (expert opinion).

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Table 2 Baseline non-CVD related death

Deaths by age, sex and underlying cause, 2004 registrations, England and Wales

	All cause ICD10: A00-R99		Circulatory ICD: I00-I99		Non-circulatory as proportion of all deaths (p)	
	M	F	M	F	M	F
	45	12,417	8,139	3,930	1,362	0.68
55	27,117	17,649	9,330	3,541	0.66	0.80
65	52,709	37,041	19,783	11,304	0.62	0.69
75	87,367	88,404	35,607	35,958	0.59	0.59
85	51,329	109,488	20,816	46,470	0.59	0.58

Source: <http://www.statistics.gov.uk/STATBASE/Expodata/Spreadsheets/D8986.xls>

All cause mortality, estimated from life tables, 2002-4, England

	Annual probability of death in age band	
	M	F
45	0.0037	0.0025
55	0.0093	0.0059
65	0.0236	0.0154
75	0.0537	0.0406
85	0.0870	0.0807

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

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

2

Estimated non-circulatory deaths for post MI cohort

	Annual probability of death in age band	
	M	F
45	0.51%	0.41%
55	1.23%	0.94%
65	2.95%	2.14%
75	6.37%	4.82%
85	10.35%	9.30%

Treatment effects:

The relative treatment effects of third generation beta blockers were taken from the CAPRICON trial (Dargie, H. J. 2001).

Table 3 Relative risks of third generation beta blockers (base case analysis)				
INTERVENTION		Relative risks		
		Mean	Lower CL	Upper CL
Beta blockers	MI	0.59	0.39	0.90
	heart	0.86	0.67	1.09

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failure			
Death	0.75	0.58	0.96

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. (National Institute for Health & Clinical Excellence. 2006b)

The cost of health states used in the model are shown in Table 4. Costs of acute MI (non-fatal reinfarction) were assumed to be the same as those of patients on thrombolysis, which includes the cost of hospitalisation Hartwell 2005 (Hartwell, D., Colquitt, J., Loveman, E. et al 2005). Costs of heart failure were taken from NHS reference costs. Subsequent MI costs were taken from NHS hypertension guideline 2006.(National Institute for Health and Clinical Excellence. 2006) 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, (Prescription Pricing Authority 2006) 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.

Health state	£ Cost/year	Source
MI	£4,448	(Hartwell, D., Colquitt, J., Loveman, E. et al 2005)
Subsequent MI costs	£500	(National Institute for Health and Clinical Excellence. 2006)
Heart failure	£2,350	(Department of Health Reference Costs 2005 2005)
Post heart failure costs	£500	assumption
Death	£0	(Palmer, S., Sculpher, M., and Philips, Z. 2004)

Drug	Cost per year (£)	
	Drug used in the model (25mg)	6.25 mg
Carvedilol	£113.67	£81.08

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 (National Institute for Health & Clinical Excellence. 2006b).

The utility estimates for MI was taken from study (Palmer, S., Sculpher, M., and Philips, Z. 2004), heart failure and post MI were taken from the Harvard cost effectiveness registry (Harvard CEA Registry 1997). 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) (Department of Health 1998).

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 6 Health state utility weights		
Health state	Utility weight	Source
MI	0.80	(Palmer, S., Sculpher, M., and Philips, Z. 2004)
Post MI	0.88	(Harvard CEA Registry 1997)
heart failure	0.71	(Harvard CEA Registry 1997)
Death	0	(Harvard CEA Registry 1997)

Table 7 Utility weight by age		
Age group	Age utility weight	Source
45-54	0.85	(Department of Health 1998)
55-64	0.79	
65-74	0.78	
75+	0.73	

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):

$$\text{ICERs} = (\text{cost of X} - \text{cost of Y}) / (\text{QALY of X} - \text{QALY of Y})$$

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 4 and Table 5 for 65-year-old men and women post MI with left ventricular dysfunction. The results suggests 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 4 Base case results 65 year old male

	Effect Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£2,414	3.40			
Beta Blockers	£3,286	4.20	£872	0.80	£1,091

Table 5 Base case results 65 year old female

	Effect Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£2,533	3.54			
Beta Blockers	£3,439	4.36	£906	0.82	£1,102

Figure 3 Base case results 65-year-old male, Cost effectiveness plane

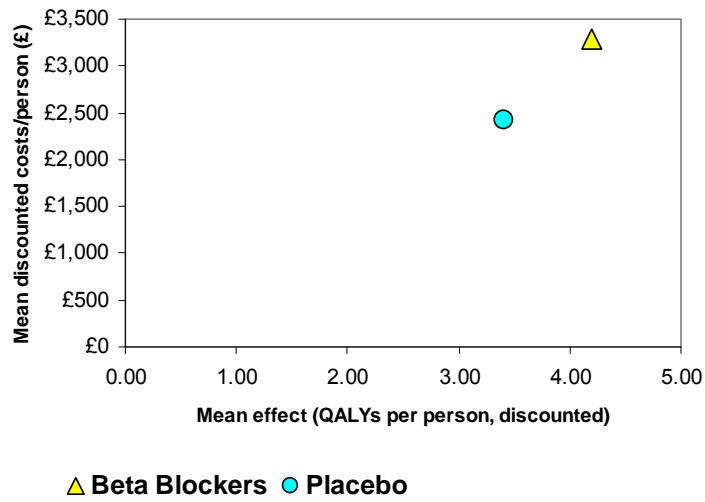
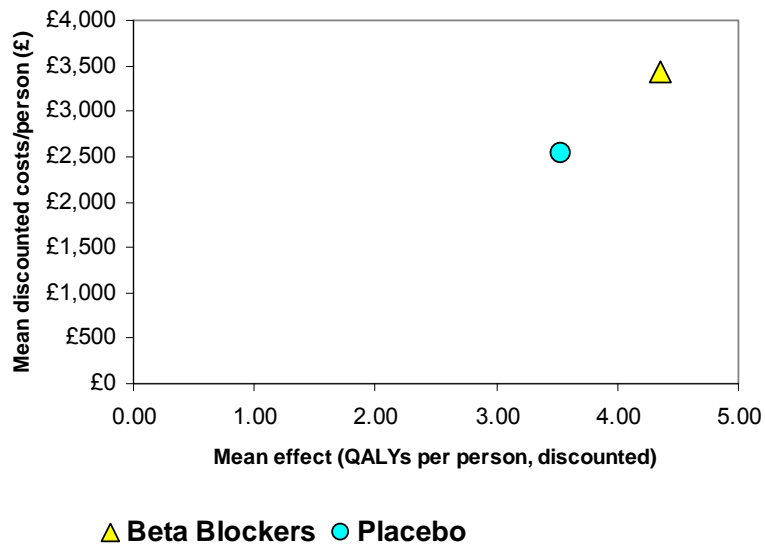


Figure 4 Base case results 65-year-old female, Cost effectiveness plane



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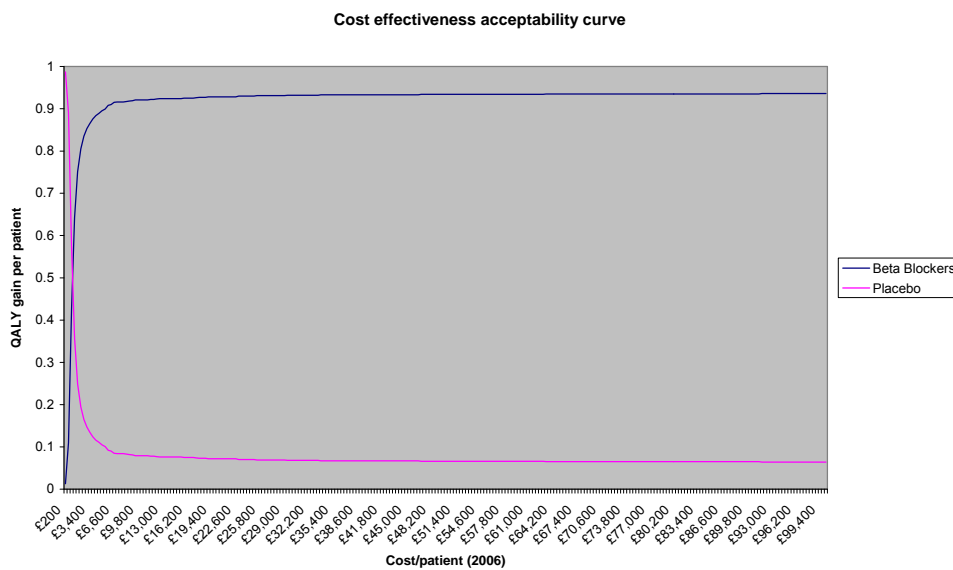
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Probabilistic sensitivity analysis

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



Deterministic sensitivity analysis

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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 (Dargie, H. J. 2001). 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 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.

Quality of life loss 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.

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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 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.

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

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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.

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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 (Dargie, H. J. 2001) 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)

	ICER for Lower Outcome 95% CI	ICER for Upper 95% CI
MI	£880	£1,420
Heart failure	£790	£1,530
Mortality	£1,060	£1,530

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

Quality of life loss due to treatment side effects	cost/QALY
1%	£1,180
2%	£1,180
5%	£1,750
10%	£4,360

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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 \pm 0.2

Health state	(0.2 less) cost/QALY	(0.2 more) cost/QALY
MI	£1,090	£1,100
well post MI	£1,100	£1,090
Heart failure	£1,090	£1,090
well post heart failure	£1,180	£1,020

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

Relative risk of non CVD mortality	ICER (Cost/QALY)
1	£1,110
2	£1,090
4	£1,060
6	£1,030

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

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Cost of health state	50% less (cost/QALY)	100% more (cost/QALY)
WELL	£1,010	£1,260
MI (ACUTE)	£1,150	£980
Well post MI	£1,080	£1,110
Heart Failure	£1,100	£1,070
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

AGE	MALE cost/QALY	FEMALE cost/QALY
55	£1,070	£1,080
65	£1,090	£1,100
75	£1,110	£1,120
85	£1,070	£1,080

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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 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.

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

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£4,828	3.402509			
Beta Blockers	£5,499	3.4148236	£671.42	0.0123147	£54,522

Interpretation:

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.

1.4 *Economic analysis of omega-3 fatty acid supplementation compared to no supplements for patients following MI*

1.4.1 Introduction

During validation of the Post Myocardial Infarction guideline some questions were raised about the robustness of the evidence of effectiveness and cost-

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effectiveness for the recommendation on use of omega-3 fatty acid supplements. NICE's Guidance Executive has asked the NCC and GDG to reconsider this evidence and do a further economic analysis on the cost-effectiveness of omega-3 fatty acids.

1.4.2 Clinical evidence

The recommendation in the draft guideline was based on the GISSI-P trial (GISSI Prevenzione Investigators. 1999), which found a reduced incidence of cardiovascular deaths in patients recruited within 3 months of an acute MI treated with an omega-3-acid ethyl ester supplement (850-882mg EPA and DHA as ethyl esters in the average ratio of EPA/DHA of 1:2).

There are many other trials of omega-3 fatty acids, dietary and supplemental, in various patient populations at different levels of cardiovascular risk. A Cochrane review (Hooper, L. et al 2004) found significant heterogeneity in these data, essentially due to one large study in patients with angina (Burr, M. L. et al 2003) When this study was taken out, the heterogeneity was removed and the meta-analysis suggested a significant reduction in mortality with omega 3, largely due to two studies in patients recruited shortly after acute myocardial infarction DART1(Burr, M. L. et al 1989) and (GISSI Prevenzione Investigators. 1999) The negative effects of DART2 appeared to offset the positive effects in DART1 and GISSI-P.

(Hooper, L., Griffiths, E., Abrahams, B. et al 2004) considered various possible explanations for this difference and concluded:

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“It may be that the effect of omega 3 fats on cardiovascular disease is smaller than previously thought (if indeed the effect does exist).

Alternatively it may be that effects in those who have had a myocardial infarction are protective of death, but the effects in men with angina and no infarction are not...” (p16 Hooper et al 2004)

The researchers on the DART1 and DART2 studies suggested that the effect might be due to interaction between fish oil and medication in angina patients (Burr, Dunstan and George 2005). Other hypotheses are that the benefits of omega-3 could be due to promotion of electrical stability, reduced platelet thrombogenicity or avoidance of damage from unstable plaques in the early post-MI period.

1.4.3 Cost-effectiveness evidence

Two cost-effectiveness analyses based on GISSI-P were available to the GDG – one from a company submission Salvoy 2004, (Innovus Research (UK) Ltd. 2004) and another from a published study (Franzosi, M. G. et al 2004), part funded by another company (Pharmacia & Upjohn). The Solvay submission estimated an incremental cost effectiveness ratio (ICER) of £15,189 over the four-year trial period, and £3,717 per QALY extrapolated over the patients' lifetimes. Though generally of good methodological quality, the Solvay submission did not report the sensitivity of their findings to the effectiveness data or assumptions.

The published analysis by Franzosi and colleagues (Franzosi, M. G., Brunetti, M., Marchioli, R. et al 2004) used rather more conservative assumptions, and estimated an ICER of 24,603 euros per life year gained (LYG) (with a range of 15,721 to 52,524 euros for a best-case and worst-case analysis). It is unclear whether this estimate would lie below the NICE threshold of £20-30,000 per QALY.

Another cost-effectiveness analysis based on the GISSI-P trial has since been published Lamotte et al (Lamotte, M. et al 2006). This analysis, also funded by Solvay, presented results from the perspective of the Australian, Canadian, German, Polish and Belgian health care systems. It used a different modelling approach to that in the Solvay submission, but arrived at similar results (5,346 to 8,315 euro per LYG, compared with £2,812 per LYG in the submission). Lamotte et al estimated that treatment would still be cost-effective (relative to the five countries' maximum willingness-to-pay), if the risk of cardiovascular death with treatment were up to 24% to 40% higher than observed in GISSI-P. They also conducted a probabilistic sensitivity analysis, in which they estimated the impact of uncertainty over the relative risk reductions, as reflected in the 95% confidence intervals from the GISSI-P trial. According to this analysis, the probability that supplementation is cost-effective was estimated at around 98%. However, this did not allow for uncertainty over other model assumptions or parameters. For example, the model assumed that patients dying in the study period lost 12-13 years of life and this was not tested in sensitivity analysis.

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On balance the current evidence suggests that omega-3 supplements may be a cost-effective intervention for patients after MI. However, there is considerable uncertainty over this finding. In particular, it was unclear whether the cost-effectiveness of supplements is robust to different methods of estimating their clinical effectiveness.

1.4.4 Aim for further economic analysis

To estimate the cost-effectiveness of omega-3 fatty acid supplementation for patients following MI who cannot comply with dietary recommendations.

1.4.5 Methods for economic analysis

Population

Patients who have had an MI within 3 months and who are unable to eat sufficient oily fish of 2-4 portions per week to meet the recommended intake of approximately 3.5g eicosapentaenoic acid (EPA) and 2.5g decosahexaenoic acid (DHA) per week. Subgroup analysis was performed to estimate the cost-effectiveness of supplementation for people who partially comply with the recommended dietary intake of oily fish.

Intervention

The analysis compared increased intake of omega-3 fatty acids from supplemental sources compared with no supplementation. The supplements considered were:

- 1g per day omega-3-acid ethyl esters (460mg EPA, 380mg DHA per capsule) (Omacor)
- 3g per day omega-3-marine triglycerides (170mg EPA, 115mg DHA per capsule) (Maxepa)

Both of the above options provide the recommended levels of EPA and DHA, assuming no dietary intake. The cost-effectiveness of supplements for patients who partially meet the recommended dietary intake of oily fish was estimated by assuming that patients use half the above doses: one capsule every other day for Omacor; or for Maxepa, instead of taking the supplements twice a day they will take them once a day.

The use of other over-the-counter supplements was not considered due to potential concerns about contamination in unlicensed products. The Cochrane review (Hooper, L., Griffiths, E., Abrahams, B. et al 2004) discusses potential concerns over cancers and neurological deficits that could

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possibly be increased due to dioxin and PCB contamination of fish oils. Although they found no direct evidence for this in the RCT or cohort data, they note that there is a lack of data on important outcomes. They conclude “independent analysis of the levels of toxins in named brands of fish oil supplements and oily fish sold for food should be more widely available” (p20 Hooper et al 2004).

Source of effectiveness data

In the absence of evidence of a difference in effect between dietary and supplemental sources of omega-3 fats, we assume equivalence (at equivalent doses of EPA/DHA). Thus evidence from trials of dietary or supplemental sources was pooled where relevant. Thus estimates of effectiveness for the base case analysis were taken from a meta-analysis of the results of DART 1 (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989) and GISSI-P trials.(GISSI Prevenzione Investigators. 1999) In addition data from GISSI-P and DART 1 was considered in the sensitivity analysis. This is based on the hypothesis that the effect observed in these trials is specific to patients who have recently had an MI, and that the results of the other main trial DART2 (Burr, M. L., shfield-Watt, P. A., Dunstan, F. D. et al 2003) are not relevant to this population.

The outcomes considered were total deaths, non-fatal MI, non-fatal stroke and revascularisations. Other outcomes such as heart failure, peripheral artery disease were not considered because very few events were recorded in both trials.

Table 1. Treatment effect used in the model

Outcome	Meta-analysis (Base model)			GISSI-P alone			DART1 alone		
	Mean	Lower CL	Upper CL	Mean	Lower CL	Upper CL	Mean	Lower CL	Upper CL
	MI	1.14	0.75	1.74	0.96	0.80	1.14	1.49	0.97
STROKE	1.22	0.91	1.64	1.19	0.88	1.61	2.51	0.49	12.89
Revascu	1.05	0.97	1.13	1.05	0.97	1.13	1.05	0.97	1.13
CVD									
death	0.79	0.67	0.93	0.84	0.72	0.97	0.70	0.53	0.91
Total									
mortality	0.81	0.68	0.96	0.86	0.77	0.97	0.71	0.55	0.92

The company submission used the results of a four way analysis from the GISSI-P trial, and for our base model, we used the same results from the meta-analysis and did sensitivity analysis to estimate the impact of uncertainty over the treatment effects (as reflected in the 95% confidence intervals estimated from the meta-analysis) and various other model parameters.

The model was not adjusted for non-compliance. We assumed compliance issues were accounted for in the intention-to-treat results. Assuming 100% compliance tend to over-estimate costs, thus our model is conservative biasing the results against treatment.

The Cochrane review (Hooper, L., Griffiths, E., Abrahams, B. et al 2004) found no evidence of long-term side effects of omega-3. However, they did find that increased omega-3 intake was significantly associated with drop outs due to side effects and gastrointestinal (GI) side effects. The model included a loss of quality-of-life due to GI side effects, based on the estimated incidence in the Cochrane review, pooling results across all levels of cardiovascular risk. This assumes that the rates of such side effects do not differ for the post-MI population.

Estimation of costs and effects

The costs and effects of treatment were estimated over a lifetime horizon using a cohort Markov modelling approach. We used a twelve-month model cycle length. This period was deemed sufficiently short to ensure that it is unlikely that patients would experience two events within the same cycle.

Baseline non-CVD mortality rates in the absence of additional omega-3 were estimated by age from population data for England and Wales. That is Governments Actuary's Department and Office for National Statistics (Government Actuaries Department 2006) (Office for National Statistics 2006) and adjusted for assumed increased risks following a first MI. Incidence rates for CVD mortality, non-fatal MI and stroke following a first MI, in the absence of treatment, were estimated from the observed rates in the trial control groups. Estimates for sensitivity analysis were also taken from a cohort study by Kaplan 2002 (Kaplan RC, Heckbert SR Furberg CD Psaty BM. 2002), in which 2677 patients were followed up for an average of 3.4 years after an MI. The Kaplan data was also used to estimate the distribution of CVD death, non-fatal MI and non-fatal stroke by age, and the proportion of these events that occurred in the first year after an initial MI. Risks of stroke following a first stroke were estimated from a cohort study by Hardie et al 2004 (Hardie K, Hankey GJ Jamrozik K Broadhurst RJ Anderson C. 2004). The incidence of revascularisation by age was estimated from Johansen et al 1998 (Johansen H, Nair C Taylor G. 1998).

It has been reported that the survival benefits of omega-3 following myocardial infarction appear early and do not persist in the longer term Ness et al 2002 (Ness, A. R. et al 2002). In the base case analysis we assumed that treatment effects do not persist beyond the longest trial period (3.5 years for

GISSI-P), and that supplements are only used for this time. We tested these assumptions in sensitivity analysis.

Costs were estimated from the perspective of the NHS and discounted at an annual rate of 3.5% in accordance with NICE guidance (National Institute for Health & Clinical Excellence. 2006b).. The cost of omega-3 supplements were taken from the BNF (British National Formulary 2007). The cost for non-fatal MI and strokes were based on those reported in the NICE technology appraisal of statins Ward et al 2005 (National Institute for Health & Clinical Excellence. 2006a), adjusted for inflation.

Outcomes were estimated in the form of quality adjusted life years (QALYs). The quality of life ('utility') associated with various health states in the post-MI population was also taken from the NICE statin technology appraisal (National Institute for Health & Clinical Excellence. 2006a) Utility was adjusted for age, using estimates from a representative general population sample in the Health survey of England 1996 (Department of Health 1998). QALYs were discounted at 3.5% per annum.

Cost effectiveness

The results of cost-effectiveness analysis are presented as Incremental Cost-Effectiveness Ratios (ICERs), which estimate the additional cost per additional QALY gained using Omega 3 supplements compared with no supplements.

Sensitivity Analysis

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

1.4.6 Results

The base case results are presented for patients aged 55 years in Table 2.

These suggest that for post-MI patients who do not comply with dietary advice to eat 2-4 portions of oily fish per week, omega-3-acid ethyl esters supplements are cost-effective, with an estimated ICER of about £12,500 per QALY.

Table 2. Base case results for omega-3-acid ethyl esters supplements compared with no supplements in 55 year old patients after MI who do not comply with dietary recommendations

	<i>Cost</i> (£)	<i>Effect</i> (QALYs)	<i>Incremental</i> <i>cost</i> (£)	<i>Incremental</i> <i>effect</i> (£)	<i>ICER</i> (£/QALY)
No supplements	£14,164	9.10	-	-	-
Supplements	£15,237	9.19	£1,073	0.09	£12,480

The supplements are estimated to be rather less cost-effective for younger patients and more cost-effective for older patients (see Table 3 below).

Table 3. Estimated cost-effectiveness by age – base case assumptions

Age	No supplements		Supplements		<i>ICER</i> (£/QALY)
	<i>Cost</i> (£)	<i>Effect</i> (QALYs)	<i>Cost</i> (£)	<i>Effect</i> (QALYs)	
45	£16,529	11.64	£17,653	11.70	£19,424
55	£14,164	9.10	£15,237	9.19	£12,480
65	£11,535	6.51	£12,592	6.66	£7,020
75	£8,694	4.03	£9,704	4.24	£4,639

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It will be more cost-effective from an NHS perspective if some or all of the recommended intake of omega 3 fatty acids could be obtained from dietary sources. For example, if only half the quantity of supplements is required, the estimated ICER for a 55 year old falls to £9,267 per QALY.

Duration of treatment costs and effects

In the base model we assumed that the benefits and costs of supplementation persist for 3.5 years, as this was the longest duration of demonstrated effectiveness (GISSI Prevenzione Investigators. 1999). The duration of the other included trial (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989) was two years, and a long-term follow-up study found that treatment effects did not persist beyond two years (Ness, A. R., Hughes, J., Elwood, P. C. et al 2002). If we assume that treatment costs and effects only last for two years, omega 3 supplementation appears to be less cost-effective (Table 4). At age 55 the estimated ICER is £23,400, which is above the £20,000 threshold.

Conversely, if we assume that treatment effects and costs persist for life, supplementation appears to be more cost-effective: £6,600 per QALY for 55 year olds.

Clearly if the benefit of omega 3 is of limited duration, it will not be cost-effective to continue using, and paying for, supplements beyond this period. If

we assume that the benefits will cease at 3.5 years and costs will persist for life – that is that people continue to receive omega 3 supplements but they do not derive any benefit from them - omega-3-acid ethyl esters supplements would only appear to be cost-effective for older patients (age 65 and over).

Table 4. Sensitivity to duration of treatment costs and effects

Costs	ICER (£/QALY)			
	2 years	3.5 years	Lifetime	Lifetime
Effects	2 years	3.5 years	3.5 years	Lifetime
Age 45	£44,088	£19,424	£53,077	£8,343
Age 55	£23,429	£12,480	£29,950	£6,584
Age 65	£10,829	£7,020	£13,590	£5,065
Age 75	£6,495	£4,639	£7,069	£3,912

Source of effectiveness data

The base model used estimates of treatment effects from a meta-analysis of DART 1 and GISSI-P trials. When we considered results of the GISSI-P trial alone, the ICERs increased slightly (Table 5). Treatment remained cost-effective with the GISSI-P data, except for the 45 year old group, for whom the estimated ICER was above the £20,000 per QALY threshold. The results using the DART1 data alone were very similar to those using the pooled data.

Table 5. Sensitivity to source of effectiveness estimates

	<i>ICER (£/QALY)</i>		
	<i>DART1</i>	<i>GISSI-P</i>	<i>Pooled</i>
Age 45	£19,640	£27,393	£19,424
Age 55	£12,206	£16,603	£12,480
Age 65	£7,337	£8,834	£7,020
Age 75	£5,157	£5,596	£4,639

Uncertainty over the size of treatment effects

The robustness of the results to uncertainty over the size of treatment effects was assessed using the upper and lower 95% confidence intervals from the meta-analysis (Table 6). The model results remained robust when the treatment effects were improved (set to their lower confidence interval) and worsened (upper confidence interval) for all outcomes except for all cause mortality. When the upper 95% confidence limits were used for all cause mortality, omega-3-acid ethyl esters supplements were no longer cost effective at the £20,000/QALY threshold. The estimated ICER was about £130,700 per QALY for a person aged 55 years, £37,800 for a 65 year old and £20,400 for a 75 year old.

Table 6. Sensitivity to upper and lower confidence limits of treatment effects:
age 55

	<i>Relative risks</i>		<i>ICER (£/QALY)</i>	
	Mean	95% CI	Lower limit	Upper limit
Non-fatal MI	1.14	(0.75 to 1.74)	£11,672	£13,792
Non-fatal stroke	1.22	(0.91 to 1.64)	£11,174	£14,533
Revascularisation	1.05	(0.97 to 1.13)	£12,067	£12,885
All cause mortality	0.81	(0.68 to 0.96)	£7,472	£130,705

Outcomes included in model

In the meta-analysis, only all cause mortality was found to be significantly different between treatment groups. If we assume no effect for the other outcomes (non-fatal MI, non-fatal stroke and revascularisation) and model mortality alone, the results become slightly more favourable (Table 7). Thus the model results are largely driven by the treatment effect on all cause mortality.

Table 7. Sensitivity to inclusion of non-fatal outcomes (MI, stroke and revascularisation)

	<i>ICER (£/QALY)</i>	
	<i>All outcomes</i>	<i>All cause mortality only</i>
Age 45	£19,424	£16,327
Age 55	£12,480	£11,021
Age 65	£7,020	£6,253
Age 75	£4,639	£4,111

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Source of baseline event rates

In the base case model, the annual risks of cardiovascular disease events (non-fatal MI, non-fatal stroke, revascularisation and cardiovascular disease-related mortality) in the absence of supplements was taken from the rates observed in the control groups of the included trials (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989) and (GISSI Prevenzione Investigators. 1999) These included 6,676 patients followed up for an average of 3.3 years. Estimates from a cohort study (Kaplan RC, Heckbert SR Furberg CD Psaty BM. 2002) gave rather higher ICERs (less cost-effective) (Table 8). Supplements still appeared to be cost-effective for people aged 55 and older, but not for 45 year olds (based on the £20,000 per QALY cost-effectiveness threshold).

Table 8. Sensitivity to source of baseline cardiovascular disease risks (MI, stroke, revascularisation, cardiovascular disease-related death)

	ICER (£/QALY)	
	<i>DART1 & GISSI-P controls</i>	Kaplan cohort study
Age 45	£19,424	£24,641
Age 55	£12,480	£15,136
Age 65	£7,020	£8,654
Age 75	£4,639	£6,110

Relative Risk of non cardiovascular disease mortality

Packham C et al (Packham C Gray D Silcocks P Hampton J 2000) and Robinson M et al {Robinson, 2005 5309 /id} estimated that the relative risk of dying from non cardiovascular disease in a cohort of patients with coronary heart disease compared with the general population lies between 2 and 8. We used a conservative estimate of 2 for the base case model. If we assume that there is no difference in non cardiovascular mortality between the general population and those with coronary heart diseases, the ICERs rise and treatment no longer appears to be cost-effective for younger patients (Table 9). When the risk is assumed to be around 4, the ICERs fall.

Table 9. Sensitivity to assumed relative risk of non-cardiovascular disease mortality

	<i>ICER (£/QALY)</i>		
	<i>RR=1</i>	<i>RR=2</i>	<i>RR=4</i>
Age 45	£24,004	£19,424	£14,417
Age 55	£15,856	£12,480	£9,177
Age 65	£8,469	£7,020	£5,541
Age 75	£5,345	£4,639	£3,943

Cost of supplements

The base model used Maxepa, which was used in the DART1 trial and costs about £150 a year. We also tested the use of the supplement used in the

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GISSI-P trial (Omacor), which is slightly more expensive (£181 a year). The model results remained cost effective, although for younger patients the estimated ICER was very close to the £20,000 per QALY threshold (Table 10). If we assume clinical equivalence between these supplements, it will not be cost-effective to use the more expensive product.

Table 10. Sensitivity to price of supplements

	ICER (£/QALY)	
	<i>Maxepa</i> £150 pa	<i>Omacor</i> £181 pa
Age 45	£19,424	£21,472
Age 55	£12,480	£13,843
Age 65	£7,020	£7,772
Age 75	£4,639	£5,119

Impact of treatment side effects

The base model assumes that there is a 0.07% loss in quality of life due to treatment side effects. This is probably an over-estimate, as it is based on the assumption that the additional 5% of patients who reported gastrointestinal (GI) side effects in omega-3-acid ethyl esters supplement trials (Hooper et al 2004) all experience a permanent loss of quality of life of 1.4%, which is an estimate for of the quality of life loss due to “nausea, vomiting or diarrhoea for 5 days” Anderson 1985 (Anderson JP, Moser RJ. 1985). In reality many of these patients would have only experienced transient effects, and those with longer lasting or more serious effects would have been likely to stop taking the supplements.

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The Hooper review (Hooper, L., Griffiths, E., Abrahams, B. et al 2004) found that there were significantly more drop outs due to side effects with omega 3 than in the control groups, although overall drop out rates were not significantly different. Any loss of effectiveness due to drop outs is included in the model through the intention-to-treat estimates of treatment effects. No adjustment is made for the reduced cost of supplements due to drop outs, but if anything this will tend to bias the model against supplementation.

In addition to the quality of life loss, the base case model assumes that an additional GP visit (cost £24) is required per patient per year to treat side effects. This is also likely to be conservative, since only a minority of patients report side effects and these appear to be relatively minor in nature.

Assumptions about the cost and quality of life loss due to side effects made little difference to the base case results, which still showed that omega-3-acid ethyl esters supplements were cost effective, except possibly for younger patients with particularly high treatment costs for side effects (2 or 3 additional GP visits for every patient each year) – see Table 11.

Table 11. Sensitivity to cost and quality of life loss due to side effects

	<i>ICER (£/QALY)</i>					
Quality of life loss	0.001%			0.07%		
	1	2	3	1	2	3
Extra GP visits						
Age 45	£16,248	£22,068	£27,889	£19,424	£26,383	£33,342
Age 55	£11,264	£14,730	£18,196	£12,480	£16,319	£20,159
Age 65	£6,713	£8,268	£9,822	£7,020	£8,645	£10,271
Age 75	£4,543	£5,281	£6,019	£4,639	£5,393	£6,147

Discounting

NICE (National Institute for Health & Clinical Excellence. 2006b) recommends we discount both cost and benefits at 3.5% per annum. We tested three different scenarios: no discounting, 3.5% for effects and 6% for costs, and 6% for both costs and effects. The model was not sensitive to assumptions (Table 12).

Table 62. Sensitivity to discount rates for costs and effects (QALYs)

	<i>ICER (£/QALY)</i>			
Costs	0%	3.5%	6%	6%
Effects	0%	3.5%	3.5%	6%
Age 45	£15,301	£19,424	£16,818	£22,924
Age 55	£10,170	£12,480	£11,068	£14,366
Age 65	£6,041	£7,020	£6,350	£7,781
Age 75	£4,173	£4,639	£4,269	£4,990

Health state utilities

The health state utilities used in the model were obtained from the literature. We tested the assumption that the mean health state utilities were 0.2 less or more than the ones we got from the literature. The model was not sensitive to this assumption.

Table 13. Sensitivity to health state utility values: age 55

Health State	Utility values (0-1)		ICER (£/QALY)	
	Base case	Range	Lower limit	Upper limit
MI (year one)	0.76	(0.56 to 0.96)	£12,654	£12,310
Post MI	0.88	(0.68 to 1.00)	£13,389	£11,991
Stroke (year one)	0.63	(0.43 to 0.83)	£12,550	£12,410
Post stroke	0.63	(0.43 to 0.83)	£13,004	£11,996
Revascularisation (year one)	0.80	(0.60 to 1.00)	£12,685	£12,281
Post revascularisation	0.88	(0.68 to 1.00)	£14,259	£11,610

Costs of cardiovascular disease events

The costs of cardiovascular disease events do not affect the model results. When the costs were increased by 100% or reduced by 50%, the ICERs changed very little (Table14).

Table 14. Sensitivity to cost of cardiovascular disease events

Health State	Costs (£ pa)		ICER (£/QALY)	
	Base case	Range	Lower limit	Upper limit
MI (year one)	£4,537	(£2,268 to £9,074)	£12,280	£12,879
Post MI	£510	(£255 to £1,020)	£12,368	£12,703
Stroke (year one)	£8,207	£16,414)	£12,333	£12,772
Post stroke	£2,206	(£1,103 to £4,413)	£12,193	£13,054
Revascularisation (year one)	£3,082	(£1,541 to £6,163)	£12,322	£12,795
Post revascularisation	£510	(£255 to £1,020)	£12,275	£12,889

1.4.7 Discussion

Our results are broadly consistent with other published economic evaluations.

(Franzosi, M. G., Brunetti, M., Marchioli, R. et al 2004) and (Lamotte, M.,

Annemans, L., Kawalec, P. et al 2006) all concluded that omega 3

supplements were cost effective compared with no supplements.

The submission by Solvay 2004 (Innovus Research (UK) Ltd. 2004) estimated an incremental cost effectiveness ratio (ICER) of £15,189 over the four-year trial period, and £3,717 per QALY extrapolated over the patients' lifetimes.

Their estimated ICERs are comparable with ours which we estimated to be £12,500 over 3.5 years and £6,600/QALY over lifetime. If we use the same effectiveness data (GISSI-P alone) and drug costs (Omacor) as used in the

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Solvay analysis, our model gives an estimate ICER of £18,500 per QALY for a 55 year old.

The Solvay model was of good methodological quality. Their main limitation was that they did not report the sensitivity of their findings to the effectiveness data or assumptions. Our results were highly sensitive to uncertainty over the treatment effects: at the upper 95% confidence limit for the relative risk of total mortality, omega 3 supplementation was not cost-effective, with an ICER of over £130,000 per QALY.

Our model slightly differed from the Solvay model (Innovus Research (UK) Ltd. 2004). We included the outcome of revascularisation while their model did not. However, this made little difference to the results. Our base model used pooled treatment effects from (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989) and (GISSI Prevenzione Investigators. 1999), while the Solvay submission used data from (GISSI Prevenzione Investigators. 1999) alone. We tested this in sensitivity analysis and this did not change model results. We also modelled loss of quality of life of due to treatment side effects which the Solvay model did not consider. Again, this made little difference to the results. Despite these identified methodological differences, our conclusions are similar.

Our analysis had some weakness especially with regards to lack of data on relative treatment effects for under-55s and over 75 year olds. This means that it is difficult to predict the relative cost-effectiveness of omega-3-acid ethyl esters in these age groups. Most of the efficacy data relates to mainly middle aged men 60-75 years. As such extrapolating this evidence to longer-term outcomes (cardiovascular disease events) is more difficult for these age groups.

The model also assumes that a patient's health outcome and health care costs incurred are assumed to depend only on their current health state. This is 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.

1.4.8 Conclusions

Our analysis found that omega-3-acid ethyl esters supplements are cost effective when compared with no supplements in patients soon after MI. Using the best available data and assumptions, we estimated ICERs of about £12,500. This result was sensitive to uncertainty over the size of treatment effects - supplements did not appear to be cost-effective at the upper confidence limit for the relative risk of mortality.

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These results depend on the assumption that treatment effects do not persist beyond the longest trial period, 3.5 years for the GISSI-P trial,(GISSI Prevenzione Investigators. 1999) and that supplements are not continued after this time. DART1, (Burr, M. L., Fehily, A. M., Gilbert, J. F. et al 1989)was of shorter duration (2 years), and benefits were not observed to continue beyond this in a follow-up study Ness et al 2002 (Ness, A. R., Hughes, J., Elwood, P. C. et al 2002). Although this was beyond the intervention time, and while there were still differences in fish intake between the two groups, the differences were less than during the trial period (Ness, A. R., Hughes, J., Elwood, P. C. et al 2002) If we assume that treatment costs and effects only last for two years, supplements are of borderline cost-effectiveness (£23,400 per QALY).

We assumed clinical equivalence for dietary and supplemental sources of omega 3 supplements, provided that the patient consumes the correct quantities of omega 3 fatty acids. From an NHS perspective, it will clearly be more cost-effective for patients to obtain this from dietary sources. But if a patient is unable to do this, provision of supplements does appear to be a cost-effective use of NHS resources. We assumed use of the cheapest available supplement with the correct quantities of EPA and DHA (Maxepa). Although the other such supplement (Omacor) also appears to be cost-

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effective compared with no supplementation, it will not be cost-effective compared with the cheaper alternative (assuming clinical equivalence between these products).

Finally, the validity of this analysis depends on acceptance of the proposition that the benefits of omega 3 are confined to people with a recent MI. We only included effectiveness data from the two trials in this population (DART1 and GISSI-P). If we were to broaden this evidence base to include the DART2 trial in angina patients, omega-3 supplementation would not appear to be effective or cost-effective.

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Evidence Extractions

Question: What is the effectiveness of adding ACEI versus placebo to improve outcome in...

1

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

Reference number 3093

Pfeffer MA;McMurray JJ;Velazquez EJ;Rouleau JL;Kober L;Maggioni AP;Solomon SD;Swedberg K;Van de

WF;White H;Leimberger JD;Henis M;Edwards S;Zelenkofske S;Sellers MA;Califf RM;

Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or

2003 349 New England Journal of Medicine

pgs 1893 1906

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: At least 18 years mean (valsartan 65.0± 11.8 years, captopril 65.4, valsartan

Characteristics plus captopril 64.9±11.8 years). Men and women (31.1%). MI complicated by clinical or

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Intervention Valsartan 20 mg initially, dose increased in 4 steps, goal of step 3: 80 mg valsartan twice daily during initial hospitalization, step 4: by 3 month visit 160 mg twice daily: 4909 patients.

Comparisons Captopril 6.25 mg initially, goal of step 3: 25 mg captopril three times daily during initial hospitalization, step 4: by 3 month visit 50 mg three times daily: 4909 patients.

Study Length Follow-up: average 24.7 months years.

Outcomes Primary outcome: all cause mortality. Secondary outcomes: Death from CV causes, or MI or 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

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had a total of 1447 hospitalizations. Valsartan + captopril group 834 patients (17.1%) had a total of 1297 hospitalizations. Captopril 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%). Key: * 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

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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

2003 107 Circulation

pgs 1284 1290

Study Type: Randomised Controlled Trial

Patient Men & women at least 55 years, mean age 66 years, 26.7% women. Before random

Characteristics 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 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 F:\Post MI appendices-Final Version-08-05-07.doc

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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 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.

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.

2004 351 New England Journal of Medicine **pgs** 2058 2068
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Patient	50 years or older, mean age 65 years, women 18%. CAD at least 1 of following: MI at least 3
Characteristics	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 the treatment. The median follow-up was 4.8 years. There were 9297 patients enrolled with
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.
Effect	The incidence of the primary endpoint (composite of death from CV causes, non fatal MI, or

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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

Patient

Characteristics

Intervention

Comparisons

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Outcomes**Funding**

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

Effect

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

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randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study).[see comment]

2003 362 Lancet

pgs 782 788

Study Type: Randomised Controlled Trial

Patient Age > 18, mean age 60 years, 15% female. Run-in period: for 2 weeks participants were given 4

Characteristics 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, hypotension, uncontrolled hyper-tension, recent ACE / ARB use, renal insufficiency 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

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revascularisation, stroke, admission for HF.

Funding Servier, France.

Effect Perindopril treatment was associated with reduction in primary endpoint 20% RRR (95% CI 9 to 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

2003 362

pgs 772 776

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Aged 18 years or older, male and female (68% male in treatment group, 68%

Characteristic male in placebo group), symptomatic HF of at least 4 weeks duration, LVEF≤40%, previous
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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 management 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

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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%).

Key: * 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 Men & women at least 55 years, mean age 66 years, 26.7% women. Before random

Characteristics 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 antiplatelet agent, 28.9%

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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

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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 Inclusion criteria: Male and female (74% male in treatment group, 77% male in placebo

Characteristics 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.

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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...

3

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

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Study Type: Randomised Controlled Trial

Patient Characteristics Inclusion criteria: At least 50 years mean 67.5±9.8 years, men and women, MI (at least 2 of the following: history of 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 rales, 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.

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

Comparisons 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).

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cardiac arrest, MI (fatal / non fatal), MI/total mortality, CV death, stroke (fatal / non fatal),

CABG, PTCA, revascularisation, first all cause admission, first admission for HF, cardio-vascular admission, non-cardio-vascular admission, tolerability.

Funding Merck, Sharpe and Dohme Re-search Labs., USA.

Effect Primary outcome: all cause mortality: losartan 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 = 0.0.72, 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.

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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 (0.8%), Rash: Losartan 3/2744(1.0%)** Captopril 18/2733(0.7%), Angioedema: Losartan 4/2744(0.1%)* Captopril 142/2733(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: Is there an optimum time for ACEI to be administered in the nonacute phase?

6

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

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;

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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 Exclusion criteria: Need of ACEI for CHF, serum creatinine \geq 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 Delayed, late (14 day ramipril).

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

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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 is the effectiveness of adding aspirin versus placebo to improve outcome in patients after MI?

7

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
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Study Type: Systematic Review

Patient: Previous MI.

Characteristics

Intervention: Aspirin, dipyridamole, sulfapyrazone. 9984 patients.

Comparisons: Placebo: 10022 patients.

Study Length

Outcomes

Funding: MRC UK, Stroke Assn., BHF, Imperial Cancer Res. Fund, EU Biomed Program, Well-come, Chest Heart & Stroke Scotl.

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
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Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Previous upper GI bleeding, treated and endoscopy performed 8 weeks post

Characteristics 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.

Comparisons 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

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Reference number 1161

A randomized, controlled trial of aspirin in persons recovered from myocardial infarction

1980 243 JAMA

pgs 661 669

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: post MI, men and women (12%), aged between 30-69 years, mean age 54

Characteristics 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

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.

Funding NHLB Institute.

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.

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Reference number 1151

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

1980 62 Circulation

pgs V59 V62

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: MI patients who survived 4-6 weeks post infarct, male, age 45-70 years.

Characteristics 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.

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Breddin K;Loew D;Lechner K;Uberla K;Walter E;

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

1979 41 Thrombosis & Haemostasis **pgs** 225 236

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: acute MI patients who survived 4-6 weeks, age 45 to 70 years, male and

Characteristics 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.

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 .

infarction

1974 1 British Medical Journal **pgs** 436 440

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: post MI, men under 65 years, mean age 56 years, interval between infarct and

Characteristics 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;

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Study Type: Randomised Controlled Trial

Patient Inclusion criteria: post MI, men and women (15%), mean age 56 years, interval between infarct

Characteristics 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;

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Study Type: Randomised Controlled Trial

Patient Inclusion criteria: First anterior wall acute MI < 12 h (ST-segment elevation > 2 mm in

Characteristics 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.

Intervention Aspirin, 100 mg once daily, 50 patients.

Comparisons Placebo: 50 patients.

Study Length 3 months.

Outcomes Primary: Infarct size. Secondary: Death, reinfarction, unstable angina, revascularisation.

Funding Not listed.

Effect 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 < 0.03). Unstable angina: treatment 14/50 versus placebo 11/50, not significant. CABG/PTCA: treatment 2/50 versus placebo 1/50, not significant.

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Question: What is the effectiveness of adding aspirin versus clopidogrel to improve outcome in patients after MI?

8

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 Inclusion criteria: MI onset \leq 35 days before randomization, two of a) characteristic ischaemic

Characteristics 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 \geq 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.

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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;Lopez-Sendon JL;Montalescot G;Theroux 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

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Study Type:	Randomised Controlled Trial
Patient	Inclusion criteria: enrolled within 12 h after onset ST-elevation MI, aged 18 to 75 years, mean
Characteristics	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.
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.
Funding	Sanofi-Aventis, Bristol-Myers Squibb.

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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...

9

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

Reference number 5183

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Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Aged 45 years or older and one of the following conditions: Multiple

Characteristics atherothrombotic risk factors such as diabetes, diabetic nephropathy, ankle-brachial < 0.9, asymptomatic carotid stenosis \geq 70% of luminal diameter, \geq 1 carotid.

Intervention Clopidogrel 75 mg once daily plus aspirin 75 mg once daily: 7802 patients.

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 cardiovascular causes (including haemorrhage). Secondary: Composite of myocardial infarction, stroke (of any cause), death from cardiovascular causes, hospitalisation.

Funding Sanofi-Aventis, Bristol-Myers Squibb.

Effect Primary: First occurrence of composite of myocardial infarction, stroke (from any cause) or death from cardiovascular causes: 534/7802 (6.8%) clopidogrel plus aspirin versus 573/7801 (7.3%) placebo plus aspirin, RR of 0.93 (95% CI 0.83 to 1.05, P = 0.22). Secondary: Composite of myocardial infarction, stroke, death from cardiovascular causes, hospitalisation for unstable

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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 159/7801 (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 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

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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: Asymptomatic 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

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Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Hospitalised within 24 h of onset of symptoms of acute coronary syndromes

Characteristics 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

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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;Lopez-Sendon JL;Montalescot G;Theroux 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 Inclusion criteria: enrolled within 12 h after onset ST-elevation MI, aged 18 to 75 years, mean

Characteristics 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

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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.
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.
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...

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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

2005 366

pgs 1607 1621

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Post MI recruited within 24 h of suspected acute MI onset (ST elevation

Characteristics (87%), left bundle block (6%), or ST depression (7%)). Mean age \pm SD = 61 \pm 11 years, male and female (28%). Patients with hypertension: 8%.

Intervention Immediately: 162 mg aspirin plus 75 mg clopidogrel. Subsequently: 162 mg aspirin plus 75 mg

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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.

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

Effect 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

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(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 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 0.91.57, 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 = 0.92. 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:

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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%.

Reference number 368

Dargie HJ;

Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the

CAPRICORN randomised trial.

2001 357 Lancet

pgs 1385 1390

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Confirmed MI occurring within the previous 21 days, aged > 18 years, mean
Characteristics age 63 years (25-90), male and female (27%), LV ejection fraction \leq 40% (mean directly by 2D
electrocardiography radionuclide or contrast ventriculography) or indirectly by wall motion score
index \leq 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 β -blockage,
complicating clinical conditions including unstable angina, uncorrected significant valve
disease, hypotension < 90 mmHg, bradycardia < 60 bpm., uncontrolled hypertension, unstable

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agonists or steroids, rate-limiting calcium channel blockers, antiarrhythmics (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

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(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

pgs 1730 1737

Study Type: Systematic Review

Patient Post MI patients. Acute phase, long term therapy.

Characteristics

Intervention β blockers

Comparisons placebo.

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months (31 RCTs).

Outcome

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

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timolol and metoprol include 63% of the available evidence on the long term effect of β

blockage 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;

Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction

2002 288 JAMA

pgs 351 357

Study Type: Systematic Review

Patient Post MI patients, RCTs that enrolled \geq 100 patients and \geq 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.

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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: Is there an optimum time for beta-blockers to be initiated in unselected patients after MI?

II

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

pjs

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Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect

Meta-analysis of 22 trials (10634 patients) reporting this outcome (OR 0.78, 95% CI 0.67 to 0.90). There was significant heterogeneity of effects in 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 (ENRICH, 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). 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). 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

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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 to 1.15). Cardiac mortality was reported in 4 trials where weak evidence of a reduction in the number of deaths was seen in the intervention group (pooled effect estimate OR 0.62, 95% CI 0.38 to 0.99), and of a 31% reduction in non-fatal myocardial infarction in the intervention group in the 8 trials (3990 patients) reporting this outcome (OR 0.69, 95% CI 0.52 to 0.92). One of these 8 trials recruited patients with identified levels of psychopathology prior to randomisation (Stern). 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*

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Study Type: Randomised Controlled Trial

Patient Post MI< 65 years.

Characteristics

Intervention Session lasted 30-40 minutes, was conducted by a psychologist during the hospital stay. 1st session/ Individualised according to Illness Perception Questionnaire. Explained pathophysiology of MI, examined patient's belief, addressed misconceptions.

Comparisons Usual care from rehabilitation nurses.

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.

versus placebo to improve outcome in...

12

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

pgs

Study Type: Guideline

Patient Post MI.

Characteristics

Intervention Calcium channel blockers.

Comparisons Mortality, Non-fatal MI.

Study Length

Outcomes

Funding NHS.

Effect Mortality: treatment versus placebo OR of 0.99 (95% CI 0.89 to 1.10 not significant) fixed

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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 **pgs** 779 785

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Post MI patients recruited during hospitalization from day 7 to 15 after

Characteristics admission. Aged under 75 years. Male and female (20%). Exclusion criteria: Heart failure, systolic blood pressure below 90 mmHg.

Intervention Verapamil 120 mg three times daily: 878 patients.

Comparisons Placebo: 897 patients.

Study Length 18 months.

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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. 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 heart failure immediately before randomisation.

Reference number 3832

Pitt B;Byington RP;Furberg CD;Hunninghake DB;Mancini GB;Miller ME;Riley W;

Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT

Investigators

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Study Type:	Randomised Controlled Trial
Patient Characteristics	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 \leq 30% diameter stenosis and the presence of \geq 1 lesion with 5% to 20% stenosis that was not in a vessel with a \leq 60% lesion. Diastolic BP <95 mmHg, total cholesterol <325 mg/dl, fasting blood glucose of <200 mg/dl. Patient population, Post MI: 45%, Stroke 3%, Angina 68%.
Intervention	Amlodipine 5 mg QD, after 2 weeks increased to 10 mg if tolerated 417 patients.
Comparisons	Placebo: 408 patients.
Study Length	36 months.
Outcomes	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-grapgy. 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,
Funding	Pfizer.
Effect	Primary outcome: Mean 3 year change in minimum diameter in segments of \leq 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

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versus amlodipine 0.013 mm increase ($P < 0.007$). 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).

Question: What is the effectiveness of adding potassium channel activators versus placebo to improve outcome in patients after MI?

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

Reference number 3817

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randomised trial

2002 359

PDFS 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 angiogram: 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: Nicorandil 10 mg twice daily thereafter 20 mg twice daily: 2565 patients.

Comparisons: 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

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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 omega 3 supplements versus placebo to improve outcome in patients after MI?

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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

Patient Inclusion criteria: Post MI (≤ 3 months), mean days since diagnosis \pm SD = 25 ± 21 days, male

Characteristics and female (15%), no age limit (mean age \pm SD = 59 ± 10 years), mean ejection fraction \pm 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,

Intervention n-3 polyun-saturated fatty acids (PUFA) 1g gelatine capsule containing 850-882 mg eicosa-pentanoic acid (EPA) and docisa-hexaenoic acid (DHA) as ethyl esters in the average ratio of EPA/DHA 1.2/1: 2836 patients.

Comparisons 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-

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death, Sudden death, Other deaths, CHD death and non fatal MI Fatal and non-fatal stroke.

Finding

Bristol-Myers Squibb, Pharmacia-Upjohn, Soicetà 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

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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%, GI disturbances: treatment group 4.9%. 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?

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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 Inclusion criteria: Men aged below 45 years post MI (interval between acute event and study

Characteristics entry had to be 3 to 6 months). Whole serum cholesterol value of > 5.2 mmol/l and / or
triglycerides values \geq 1.6 mmol/l. Patients fulfilling the inclusion criteria were first treated with
diet for 3 months (pre-treatment period). Patients were given a dietary instruction sheet and saw
a nutritionist. Exclusion criteria: Severe hyperlipidemia (cholesterol > 10 mmol/l and or
triglycerides \geq 8 mmol/l), severe hypertension resistant to medication, diabetes mellitus,
impaired renal function (creatinine \geq 150 μ mol/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%.

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Comparisons	Placebo: 45 patients.
Study Length	5 years.
Outcomes	Coronary events (reinfarction, CABG, PTCA, sudden death, cardiovascular death). Plasma lipid concentration.
Funding	Boehringer, Mann-heim, GmbH, Karolinska Institutue, Swedish Heart-Lung Found., Sera-firmer Found., Eirs Found.
Effect	<p>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.</p>

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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?

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

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Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Patients with acute coronary syndrome in preceding 10 days (median 7 days).

Characteristics 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 renal 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.

Comparisons 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.

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). Cardiovascular death: 83/2265 (5.4%) 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 1.20, P = 0.60). 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

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6% to 62 mg/dl (1.61 mmol/l) at month 4 following increase to 80 mg simvastatin. 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

pgs 1425 1435

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Patient Inclusion criteria: Men and women (19%), age range 35 to 75 years (mean±SD = 61±9 years),

Characteristics 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: 46.4%, Atorvastatin 10 mg: 46.7%, 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 mmol/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 hypothyroidism, 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%,

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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 daily, 5006 patients.

Comparisons Atorvastatin: 80 mg once daily, 4958 patients.

Study Length Median 4.9 years (up to 6 years).

Outcomes Primary: Major cardiovascular 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 cardiovascular event, any coronary

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

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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 0.1.15, 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

event, 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

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(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 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

2004 350

New England Journal of Medicine

pjs 1495 1504

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Patient Inclusion criteria: Patients hospitalized for acute coronary syndrome in preceding 10 days

Characteristics (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 (6.22 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 haepatobilliary 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. Concomittant 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 year.

Intervention Pravastatin 40 mg once daily: 2063 patients.

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Study Length	Mean follow up 24 months (18 to 36 months).
Outcomes	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.
Funding	Bristol Myers-Squibb, Sanko
Effect	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 < 0.001).LDL-C median change among 2985 patients who had not previously received statin therapy: Note: absolute values not reported.

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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% Atovastatin 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%, Atovastatin 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?

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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 **pgs** e2 e8

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Patients were enrolled within 24 hours of symptoms of acute coronary

Characteristics 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%. Concomittant 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.

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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

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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;Schechtman 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

Patient Inclusion criteria: Men with documented coronary artery disease (defined as a history of MI, F:\Post MI appendices-Final Version-08-05-07.doc

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angiogenic 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 Gemfibrozil 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	Primary: Composite of nonfatal MI or death from coronary heart disease (fatal MI, sudden death, death due to CHF, death as a complication of invasive cardiac procedures). Secondary: Composite of nonfatal MI, death from coronary heart disease or confirmed stroke. Stroke. Death from any cause. Transient ischaemic attack. Revascularisation. Hospitalisation for unstable angina. Hospitalisation for CHF. Carotid end-arterectomy.
Funding	Co-operative Studies Program of Dept. Veterans Affairs Office Research 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 =

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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 1.1.20, 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:

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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: 113 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: 68/1264 (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*

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Study Type: Randomised Controlled Trial

Patient Inclusion criteria: Post MI men aged 30 to 64 years (at least 3 months post infarction). Exclusion

Characteristics criteria: Patients with cardiac failure which required treatment with digoxin and / or diuretics.
Patients with diabetes mellitus. Concomitant drug therapy: Not detailed.

Intervention Clofibrate, 1.8 g once daily, 1103 patients. Niacin, 3 g once daily, 1119 patients.

Comparisons Placebo: 2789 patients.

Study Length 5 years (all surviving patients in the study for at least 54 months).

Outcomes Primary: All cause mortality. Secondary: Individual components of all cause mortality, nonfatal MI, coronary death or nonfatal MI, definite pulmonary embolism (fatal or nonfatal), definite or suspected fatal or nonfatal pulmonary embolism or thrombo-phlebitis, fatal or nonfatal stroke or intermittent cerebral ischaemic attack, any definite or suspected fatal or nonfatal cardiovascular event.

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

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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

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(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: 86/1103 (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) = 16.3 mg/dl (0.34 mmol/l), mean decrease of 6.5% from
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placebo group) = 1.5 mEq/100 ml, mean decrease of 22.3% from baseline level. Niacin: 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. Flushing: 987/1065 (92.0%) Niacin versus 115/2695 (4.3%) 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.

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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

Patient Inclusion criteria: Men & women (8%) aged 45-74 yrs (mean±SD = 60±7 years, history of MI ≥ 6

Characteristics months but < 5yrs 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.

Comparisons Placebo: 1542 patients.

Study Length Mean length of follow up was 6.2 years.

Outcomes Primary: Composite of fatal MI, nonfatal MI or sudden death. Secondary: Composite of hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft. Cardiac Mortality. Noncardiac mortality. Stroke.

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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)
Bezafibrate: 234/1548 (12.0%) Placebo: 225/1542 (19.7%) RR = 39.5%, P = 0.02. HDL-C <35

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Placebo: 382/1542 (15.5) RR = 12.4%, P = 0.46. ≥ 150 mg/dl (1.7 mmol/l) Bezafibrate:
420/1548 (18.5%) Placebo: 436/1542 (19.4%) RR = 4.5%, P = 0.56. ≥ 175 mg/dl (2.0 mmol/l)
Bezafibrate: 294/1548 (17.2%) Placebo: 286/1542 (22.2%) RR = 22.6%, P = 0.09. ≥ 200 mg/dl
(2.26 mmol/l) Bezafibrate: 184/1548 (13.0%) Placebo: 162/1542 (22.3%) RR = 41.8%, P =
0.02. HDL-C ≥ 35 mg/dl (0.9 mmol/l) & triglycerides < 150 mg/dl (1.7 mmol/l) Bezafibrate:
560/1548 (12.0%) Placebo: 518/1542 (12.2%) RR = 1.6%, P = 0.77. ≥ 150 mg/dl (1.7 mmol/l)
Bezafibrate: 183/1548 (11.2%) Placebo: 193/1542 (12.2%) RR = 8.5%, P = 0.59. ≥ 175 mg/dl
(2.0 mmol/l) Bezafibrate: 113/1548 (12.7%) Placebo: 99/1542 (15.2%) RR = 16.8%, P = 0.45. \geq
200 mg/dl (2.26 mmol/l) Bezafibrate: 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 benzafibrate group and 1 patients in the placebo group.

Question: What is the effectiveness of adding vitamin K antagonist
(warfarin) versus placebo to improve outcome in patients after
an MI?

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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

Study Type: Systematic Review

Patient Established coronary artery disease, MI, unstable angina, CABG surgery.

Characteristics

Intervention

Comparisons

Study Length At least 3 months.

Outcomes

Funding Medical Research Council Canada.

Effect 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 =

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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 264

Smith P;

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Study Type:	Randomised Controlled Trial
Patient	Inclusion criteria: acute MI < 75 years, stratified for chronic beta blocker usage. Exclusion
Characteristics	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.
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 19% to 54%, P = 0.0007). Stroke: treatment 19/607 versus placebo 44/607 RR of 55% (95% CI 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.

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Van Bergen PFMM;Jonker JJC;Van der Meer FJM;Azar AJ;Meeter K;Deckers JW;Colly LP;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 Inclusion criteria: Hospital survivors of MI within 6 weeks after hospital discharge, cardiac

Characteristics enzyme rises at least twice the normal upper limit, male and female (20%), mean age: 61 years. Exclusion criteria: indication for oral anticoagulant treatment.

Intervention Nicoumalone or phenpro-coumon decision made 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.

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
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(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).

Question: What is the effectiveness of adding vitamin K antagonist (warfarin) versus aspirin to improve outcome in patients after an MI?

20

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

pjs 2058 2067

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Patient Established coronary artery disease, MI, unstable angina, CABG surgery.

Characteristics

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Intervention

Comparisons

Study Length At least 3 months

Outcomes

Funding Medical Res. Council Canada.

Effect 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

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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 i;
Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial.

2002 360 Lancet **pgs** 109 113

Study Type: Randomised Controlled Trial

Patient Inclusion criteria: acute MI (88%) or unstable angina within preceding 8 weeks, mean age 61

Characteristics 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.

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patients. Oral anti-coagulants (phenprocoumon or acenocoumon with a target INR of 2.0 to 2.5)

plus aspirin 100 mg daily, 332 patients.

Comparisons Aspirin 100 mg daily, 336 patients.

Study Length Mean follow-up \leq 26 months.

Outcomes Primary: Composite of death, nonfatal MI or stroke. Secondary: All-cause mortality, bleeding.

Funding Praeven-tiefonds NL, NL National Health Ins. Fund Council, NL Heart Found.

Effect Composite of death, nonfatal MI or stroke: 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 versus aspirin 31/336 (9%), HR = 0.50 (95%CI 0.27 to 0.92). All-cause mortality: 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 versus aspirin 15/336 (4%), HR = 0.60 (95%CI 0.26 to 1.36). Vascular death, MI or stroke: 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). Vascular death: 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: 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). Revascularization (CABG/PTCA): 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). All stroke: Coumadin 0/325 versus aspirin 5/336 (1%), Coumadin plus aspirin 1/325 (0.3%) versus aspirin 5/336 (1%), HR = 0.20 (95%CI 0.02 to 1.7). Major

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(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). Minor bleeding: 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?

21

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

pjs 1622 1632

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Patient	Inclusion criteria: Post MI recruited within 24 h of suspected acute MI onset (ST elevation
Characteristics	(87%), left bundle block (6%), or ST depression (7%)). Mean age \pm SD = 61 \pm 11 years, male and female (28%). Patients with hypertension: 8%.
Intervention	Immediately: 5 mg metoprolol iv over 2-3 min, if heart rate was above 50 bpm and systolic blood pressure above 90 mm Hg, 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

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(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 342/22923 (1.5%) 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 (2.5%) 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 5.4% versus placebo
2.2%, OR = 2.41(95% CI 2.19 to 2.65, P = 0.0001).

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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** 396

Study Type: Randomised Controlled Trial

Patient Inclusion criteria 3-21 days post MI, men and women (approx 22%), aged 21 to 85 years, mean

Characteristics 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 < 4 years, liver disease, renal disease, anaemia,

thrombocytopenia, haematuria, uncontrolled hypertension, scheduled CABG, patients requiring

long term warfarin therapy for thromboembolism.

Intervention Warfarin 3 mg plus aspirin 80 mg: 3382 patients. Warfarin 1 mg plus aspirin 80 mg: 2028

Comparisons Aspirin 160 mg: 3393 patients.

Study Length Median follow-up 14 months, maximum 33 months.

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mortality, non fatal MI, ischemic stroke, CV death, spontaneous major haemorrhage.

Funding Du Pont Merck Pharm. Co.

Effect 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. 1 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.

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

Study Type: Randomised Controlled Trial

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Characteristics 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,

Intervention Aspirin 81 mg daily plus warfarin INR 1.5 to 2.5 IU: 2522 patients.

Comparisons Aspirin 162 mg daily: 2537 patients.

Study Length Median follow-up 2.7 years.

Outcomes Primary: All-cause mortality. Secondary: Recurrent MI, stroke, major haemorrhage.

Funding DuPont Pharm., Bayer Pharm., Co-op. Studies Program Dept. Veterans Affairs Office Res. & Develop.

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

Reference number 3729

Hurlen M;Abdelnoor M;Smith P;Erikssen J;Arnesen H;

Warfarin, aspirin, or both after myocardial infarction.

2002 347 New England Journal of Medicine

pgs 969 974

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Patient Inclusion criteria: hospitalized for acute MI, < 75 years, mean age 60 years, male and female

Characteristics (approx. 26%).

Exclusion criteria: History of serious spontaneous bleeding on any of study drugs, heamorrhagic diathesis, any other contraindications.

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.

Comparisons 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

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= 0.20). Reinfarction: aspirin 117/1206 (9.7%) warfarin 90/1216 (7.4%) 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 eplerenone versus placebo to improve outcome in patients after MI ?

23

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

Patient Inclusion criteria: Post MI with LV dysfunction and heart failure. LV dysfunction documented as

Characteristics LV ejection fraction \leq 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:

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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 infarction: 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
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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 0.86 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 0.80 (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 29843/3313 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

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(no. of episodes): 73/3319 treatment versus 54/3313 placebo, ratio of 0.92 (P = 0.11).

Ventricular arrhythmia (no. of episodes): 58/3319 treatment versus 63/3313 placebo, ratio of

0.92 (P = 0.69). Safety: 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

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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 \geq 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 difference between treatment and placebo reported for the following: \geq 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*

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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 Inclusion criteria: Post MI patients recruited during hospitalization for enzyme confirmed MI.

Characteristics Aged 25 to 75 years. Mean age \pm SD = 58 \pm 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 followed for a minimum of 12 months, mean follow-up 25 months, maximum of 54 months.

Outcomes Mortality. Death from cardiac causes. Nonfatal MI.

Funding Tanabe Seiyaku Co Ltd, Marion Laboratories.

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). Interactions: The presence or absence of pulmonary congestion was found to have a significant

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interaction was noted between pulmonary congestion and diltiazem with death from cardiac causes as the endpoint (two sided P value = 0.0042). 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). 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: Are there stable patients after MI who a) benefit prognostically from revascularisation b) those who don't benefit prognostically

26

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

Reference number 3081

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2003 National Institute for Health and Clinical Excellence

pgs

Study Type: Guideline

Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect

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

pgs

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Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect

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

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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.;

Coronary angioplasty : guidelines for good practice and training

2000 83 Heart

pgs 224 235

Study Type: Randomised Controlled Trial

Patient Post MI patients: 3 age groups: middle aged (45-65 years), old (66-75 years), very old (> 75

Characteristics years).

Intervention Hospital-based cardiac rehabilitation (Hos-CR), home-based cardiac rehabilitation (Home-CR), no cardiac rehabilitation (no CR).

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Study Length 14 months.

Outcomes Total work capacity (TWC), HRQoL.

Funding National Research Council Florence Un. Reg. Gov. Tuscany Italy.

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).

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

2004 American College of Cardiology website

pgs

Study Type: Systematic Review
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Characteristics

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Intervention

Comparisons

Study Length

Outcomes

Funding

Effect

Question: What is the effectiveness of comprehensive cardiac rehabilitation versus standard care with no cardiac rehabilitation to improve outcome in patients after MI ?

30

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Reference number 710

Beswick AD;Rees K;Griebsch I;Taylor FC;Burke M;West RR;Victory J;Brown J;Taylor RS;Ebrahim S;

Provision, uptake and cost of cardiac rehabilitation programmes: Improving services to under-represented groups

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

Study Type: Systematic Review

Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding DOH

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

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Reference number 1358

Brown A;Taylor R;Noorani H;Stone J;Skidmore B;

Exercise-based cardiac rehabilitation programs for coronary artery disease: a systematic clinical and economic review

2003 34 Ottawa

pgs

Study Type: Systematic Review

Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect 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 to 0.96 and 0.80, 95% CI 0.65 to 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 F:\Post MI appendices-Final Version-08-05-07.doc

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with usual care.

Reference number 1360

Joliffe JA;

Exercise-based rehabilitation for coronary heart disease

2003

Cochrane Library

pgs

Study Type: Systematic Review

Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect 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,

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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 All acute MI patients under 65 years and attending the Hospital Post-MI Clinic. Median age: 55

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all males.

Intervention	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.
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.
Funding	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 group: increased non significantly by an average of 10% or 12W (95% CI: 2 to 22W) over baseline. MPC in control group: increased non significantly 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.

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Reference number 2950

Stahle A;Lindquist I;Mattsson E;

Important factors for physical activity among elderly patients one year after an acute myocardial infarction

2000 32 Scand J Rehabil Med

pgs 111 116

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

Characteristics 52.9±1.35 years, respectively). 26 poor prognosis patients & their matched controls (ages 59.6±1.4 & 59.5±1.36 years, respectively).

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 exercise tests.

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Study Length	12 month then follow up at 5 years.
Outcomes	Cardiorespiratory fitness, psychoogical profiles, quality of life scores, mortality, full time employment return, non-fatal reinfarction.
Funding	Not listed.
Effect	At 12 months, the treatment group had significant improvements compared with matched controls in cardiorespiratory 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: Are there any patients after MI in whom the exercise component of cardiac rehabilitation is not safe?

33

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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 96 Circulation

pgs 1790 1797

Study Type: Randomised Controlled Trial

Patient <40% ejection fraction after a first Q-wave myocardial infarction

Characteristics

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

Comparisons Exercise training vs usual care

Study Length 6 months

Outcomes Work capacity Left ventricular volumes Ejection fraction

Funding Minist-ero della Sanità, 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

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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 107 Circulation **pgs** 2201 2206

Study Type: Randomised Controlled Trial

Patient Post MI patients: 3 age groups: middle aged (45-65 years), old (66-75 years), very old > 75

Characteristics

Intervention Hospital-based cardiac rehabilitation (Hos-CR), home-based cardiac rehabilitation (Home-CR), no cardiac rehabilitation (no CR).

Comparisons 3 interventions in each age group.

Study Length 14 months.

Outcomes Total work capacity (TWC), HRQoL.

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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).

Reference number

Scottish Intercollegiate Guidelines Network (SIGN).;

Cardiac rehabilitation

2002 57

pgs

Study Type: Guideline

Patient

Characteristics

Intervention

Comparisons

Study Length

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Finding

Effect 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).

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

Reference number 312

Otsuka Y;Takaki H;Okano Y;Sato T;Aihara N;Matsumoto T;Yasumura Y;Morii I;Goto Y;

Exercise training without ventricular remodeling in patients with moderate to severe left ventricular dysfunction early after acute myocardial infarction

2003 87 International Journal of Cardiology **pgs** 237 244

Study Type: Cohort

Patient 74 patients with LVEF $\geq 45\%$ (Group H), 35 patients with $35\% \leq$ LVEF $< 45\%$ (Group M), 17

Characteristics patients with LVEF $< 35\%$ (Group L).

Intervention Exercise program consisting of walking, cycling on an ergometer and aerobic dance (50-90 min/session), 3-5 sessions per week for 3 months.

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Study Length 3 months.

Outcomes Exercise capacity. Peak work rate. Rest heart rate. LV end-diastolic dimension.

Funding Not listed.

Effect After 3 months of exercise training, exercise capacity increased significantly in all 3 groups. Peak Vo₂ increased from 1355±321 to 1575±336 ml/min (P < 0.01) in Group H, from 1278±332 to 1464±406 ml/min (P < 0.01) in Group M, and from 1248± 369 to 1454±424 ml/min in Group L (P < 0.01). Similarly, peak work rate increased from 122±35 to 144±34 W (P < 0.05) in group H, from 177±42 to 137±12 W in Group M (P < 0.05), and from 107±58 to 129±56 W (P < 0.01) in group L. Rest heart rate reduced from 75±13 to 72±11/ min (P < 0.05) in group H, from 76±13 to 72±12/min in Group M (P < 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

Question: What is the effectiveness of an individualised cardiac rehabilitation programme versus a non-individualised cardiac programme to improve outcome in patients after MI?

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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 **pjs** 89 95

Study Type: Randomised Controlled Trial

Patient Post MI < 70 years.

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 Foundation.

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.

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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

Study Type: Reviews and Reports

Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding Not listed.

Effect Determining functional capacity is useful in formulating individual guidelines for physical activity within the hospital and during the early home phase of rehabilitation.

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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)

35

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

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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

1992 339 Lancet

pgs 1036 1040

Study Type: Randomised Controlled Trial

Patient Consecutive post MI patients, age < 80 years, speak / read English, no history of severe mental

Characteristics illness, dementia, uncontrolled arrhythmias or HF.

Intervention Edinburgh Heart Manual: Self-help rehabilitation program incorporating education, exercise

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Comparisons Standard care. Equal amount of facilitator's time and a package of educational leaflets (BHF, Scot Health Ed Group, Flora Project).

Study Length 12 months.

Outcomes Hospital Anxiety and Depression Scale (HAD) and the General Health Questionnaire (GHQ), Health Service Utilization.

Funding Chief Scientist Office, Scot Office of Scot Home and health Dept, BHF.

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

2002 52 Journal of Psychosomatic Research **pgs** 89 95

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Patient	Post MI < 70 years.
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.

Reference number 1289

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Study Type: Guideline

Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect 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

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Study Type: Systematic Review

Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect 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

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Question: What are the information and support needs for patients at different points in the care pathway?

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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

1999 18 Health Psychology

pgs 506 519

Study Type: Metaanalysis

Patient MI, CABG, PTCA < 6 months.

Characteristics

Intervention Psycho-educational and/or stress management.

Comparisons Usual care.

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Outcomes**Funding** Netherlands Organ. Scientific Res.**Effect** 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

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?

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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;

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Study Type:	Cohort
Patient	Consecutive first time post MI patients, age < 76 years, speak / read English.
Characteristics	
Intervention	Hospital 1: 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.
Comparisons	Hospital 2: Usual care.
Study Length	6 months.
Outcomes	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.
Funding	Not listed.
Effect	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 ($F(1,45) = 4.14, P < 0.05$, effect size 0.08) and depression ($F(1,53) = 6.55, P < 0.01$, 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.

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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?

38

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

1999 83 Am J Cardiol

pgs 29C 34C

Study Type: Systematic Review

Patient Male, IHD / ED.

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Intervention Sildenafil (5-200 mg).

Comparisons Placebo.

Study Length Up to 6 months.

Outcomes Sexual function, adverse events.

Funding Not listed.

Effect The mean end of treatment scores for achieving an erection and maintaining an erection were significantly higher in the sildenafil group than for the placebo group ($P < 0.0001$). On the 5 sexual function domains, scoring was significantly higher in the treatment group than the placebo group ($P < 0.0001$). At the end of treatment, improved erections were reported by 70% of patients with ischaemic heart disease who received sildenafil and by 20% of those in the placebo group (OR 10.3; 95% CI, 5.6-19.1; $P < 0.0001$ for treatment effect).

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

2004 93 American Journal of Cardiology **pages** 147 153

Study Type: Randomised Controlled Trial

Patient Male CAD / ED.

Characteristics

Intervention Sildenafil (25-100 mg).
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Study Length 12 weeks.

Outcomes Sexual function. Adverse events.

Funding Not listed.

Effect After 12 weeks of treatment, the mean end of treatment scores for achieving an erection and maintaining an erection were significantly higher in the sildenafil group than for the placebo group ($P < 0.01$). Larger percentages of sildenafil treated patients reported improved erections (64%) and improved intercourse (65%) compared with placebo-treated patients (21% and 19%,

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

Reference number 59

Olsson AM;Persson CA;Swedish S;

Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men with cardiovascular disease

2001 55 International Journal of Clinical Practice **pgs** 171 176

Study Type: Randomised Controlled Trial

Patient CVD / ED, Male, 18% MI intervention, 20% MI placebo.

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Intervention	Sildenafil (25-100 mg).
Comparisons	Placebo.
Study Length	12 weeks.
Outcomes	Sexual function Adverse events.
Funding	Pfizer.
Effect	<p>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 ($P < 0.0001$).</p> <p>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).</p>

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

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

Reference number 3058

Beswick AD;Rees K;Gribsch I;Taylor FC;Burke M;West RR;

Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups

2004 8 Health Technology Assessment **pgs**

Study Type: Systematic Review

Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding DOH

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
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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

Hughes AR;Gillies F;Kirk AF;Mutrie N;Hillis WS;MacIntyre PD;

Exercise consultation improves short-term adherence to exercise during phase IV cardiac rehabilitation: a randomized, controlled trial

2002 22 Journal of Cardiopulmonary Rehabilitation **pgs** 421 425

Study Type: Randomised Controlled Trial

Patient Intervention MI/CABG: 12/4, Control MI/CABG: 8/7.

Characteristics

Intervention Exercise consultation plus exercise leaflet.

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Study Length 4 weeks.

Outcomes Scottish Physical Activity Questionnaire. Measuring occupational and leisure physical activity.

Funding Not listed.

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

41

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

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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.

pgs

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

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Study Type: Randomised Controlled Trial

Patient Post MI patients < 70 years.

Characteristics

Intervention 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.

Comparisons Diet change versus no diet change.

Study Length 46 months.

Outcomes All-cause mortality, cardio-vascular deaths.

Funding Not listed.

Effect 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).

Reference number 2070

Liem A;Reynierse-Buitenwerf GH;Zwinderman AH;Jukema JW;van V;

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Study Type: Randomised Controlled Trial

Patient: Stable CAD, MI, coronary artery lesions, PCI, CABG. Age: Treatment: 64.9±9.9 years, Control:

Characteristics: 65.5±9.7 years. Male gender Treatment: 76%, Control: 80%.

Intervention: Folic acid (0.5 mg/day).

Comparisons: No treatment.

Study Length: 24 months.

Outcome: All-cause mortality and a composite of vascular events.

Funding: Not listed.

Effect: 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).

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

2006 354

New England Journal of Medicine

pgs 1 11

Study Type: Randomised Controlled Trial

Patient: Inclusion criteria: Men and women (26%), aged 30 to 85 years of age (mean 63 years) with
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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: 937 patients.

Comparisons 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.

Funding Norwegian Res Council. Council. Health and Rehab., Norwegian Council CV disease, Northern Norway Reg health Authority, Norwegian Red Cross, Found. Promote Res. Into Functional Vitamin B12 Deficiency.

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). 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). Fatal myocardial infarction: 68/937 (7.3%)

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to 1.69, P = 0.34). Nonfatal myocardial infarction: 132/937 (14.1%) folic acid plus vitamin B12 mg plus B6 versus 104/943 (11.0%) placebo RR of 1.30 (95% CI 1.00 to 1.68, P = 0.05). Stroke: 21/937 (2.2%) folic acid plus vitamin B12 mg plus B6 versus 27/943 (2.9%) placebo RR of 0.87 (95% CI 0.47 to 1.47, P = 0.52). Death from any cause: 104/937 (11.1%) folic acid plus vitamin B12 mg plus B6 versus 89/943 (9.4%) placebo RR of 1.21 (95% CI 0.91 to 1.61, P = 0.19). Unstable angina pectoris requiring hospitalization: 125/937 (13.3%) folic acid plus vitamin B12 mg plus B6 versus 132/943 (14.0%) placebo RR of 0.93 (95% CI 0.73 to 1.19, P = 0.57). CABG: 138/937 (14.7%) folic acid plus vitamin B12 mg plus B6 versus 157/943 (16.6%) placebo RR of 0.89 (95% CI 0.71 to 1.13, P = 0.34). PCI: 257/937 (27.4%) folic acid plus vitamin B12 mg plus B6 versus 290/943 (30.8%) placebo RR of 0.86 (95% CI 0.72 to 1.02, P = 0.08).

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

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Patient

Characteristics

Intervention

Comparisons

Study Length

Outcomes

Funding

Effect Randomised controlled trials of specific supplements failed to demonstrate a consistent or 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

pjs 757 761

Study Type: Randomised Controlled Trial

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Characteristics

Intervention Three dietary regimes were compared: fat advice, fibre advice and fish advice. Patients were advised to eat at least two weekly portions (220 to 400 g) of oily fish (mackerel, herring, kipper, pilchard, sardine, salmon or trout). Fat advice was to reduce fat intake to 30% of total energy and to increase the polyunsaturated fat / saturated fat ratio to 1.0. Fibre advice (to eat more cereal fibre). Patients in the oily fish advice group who could not tolerate oily fish were given omega-3- acid ethyl esters capsules; 3 x 0.5 g per day supplying 2.5 g of eicosapentaenoic acid per week.

Comparisons No dietary advice

Study Length 2 years.

Outcomes Mortality, ischaemic heart disease events.

Funding Not listed

Effect Advice to eat oily fish was associated with a reduction in all cause mortality compared with no dietary advice after adjustment for confounders (RR = 0.71, 95%CI 0.54 to 0.92). There was no reduction in ischaemic heart disease events in the oily fish advice group compared with the group given no advice (RR 0.84, 95% CI 0.67 to 1.07). There was no reduction in ischaemic heart disease events in the oily fish advice group compared with the group given no advice (RR 0.84, 95% CI 0.67 to 1.07). Patients given oily fish advice had a lower mortality than patients within other dietary groups although these were not statistically significant. Advice to eat less fat as well as advice to eat more fibre was not associated with any reduction in mortality or ischaemic hear disease compared with no diet advice.

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Question: What is the effectiveness of regular physical activity versus a sedantary lifestyle to improve outcome in patients after MI?

43

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 Male (age range 35-64 years), post MI (≥ 8 weeks but < 2 years). Ability to exercise to minimum

Characteristics 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.
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40 minutes 3 times per week.

Comparisons Controls.

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 control's = 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

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Patient	Patients from 5 centres were recruited for this study. Patients had documented AMI within 1-3yrs
Characteristics	of admission to the study. Subjects were all men. Mean age (yrs \pm SEM): Intervention group: 51.5 \pm 0.4, Control group: 52.0 \pm 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.
Comparisons	Not reported.
Study Length	3 yrs.
Outcomes	Mortality, nonfatal infarction, suspected infarctions, other events. all, recurrent MI. Total hospitalisations for reasons other than MI.
Funding	Grant from the Rehab. Services Admin of the Dept of Health, Education & Welfare. US.
Effect	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 cardiogenic shock & 2 from cerebrovascular accidents) Intervention

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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: 2+ 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 **ppgs** 746 755

Study Type: Cohort

Patient Recent MI patients with perceived lack of social support and/or symptoms depression. Age: No

Characteristic exercise group: 61.1±12.7 years, Exercise group: 59.5±11.8 years.

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

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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

Patient Post MI patients. Age: not reported.

Characteristics

Intervention 3 months after an 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)

Comparisons Exercise program versus no exercise.

Study Length 1 year, 4 year follow up.

Outcome All-cause mortality, cardiovascular deaths.

Funding Not listed.

Effect 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.

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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** Subjects recruited into the Physicians' Health Study, male, post MI.**Characteristics****Intervention****Comparisons** Number of alcoholic drinks: Rarely/never (n= 1125), 1-4/month (n= 1227), 2-6/week (n= 1390),

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Study Length 5 years.

Outcome 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.

Reference number 611

Shaper AG;Wannamethee SG;

Alcohol intake and mortality in middle aged men with diagnosed coronary heart disease

2000 83 Heart (British Cardiac Society)

pgs 394 399

Study Type: Cohort

Patient 455 post MI patients and 200 angina patients.

Characteristics

Intervention

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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

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;

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Study Type: Cohort

Patient Left ventricular dysfunction after MI, with a LV ejection fraction of 40% or less, 21-80 years of

Characteristic

Intervention

Comparisons 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

Reference number 2944

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

Wine drinking and risks of cardiovascular complications after recent myocardial infarction

2002 106 Circulation

pgs 1465 1469

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Patient	Participants of Lyon Diet Heart Study post MI, <70 years of age, male.
Characteristics	
Intervention	
Comparisons	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.
Outcomes	Clinical complications.
Funding	Not listed.
Effect	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 level of physical activity which increases physical work capacity versus physical activity which does not increase

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

Reference number 596

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)

1999 100 Circulation

pgs 1764 1769

Study Type: Randomised Controlled Trial

Patient Subjects were men aged between 30 to 64 yrs. Enrolled at 1 of 5 centres in the US during

Characteristics 1976.

Age (yrs \pm SD):

Intervention group: 51.5 \pm 7.4,

Control group: 52.1 \pm 7.2. Work capacity (metabolic equivalents (METs) \pm SD): Intervention

group: 7.8 \pm 2.1, Control group: 7.8 \pm 2.2. Men with documented MI after 8 weeks but before 3

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and a surprise resting diastolic blood pressure of 100mm Hg.

Excluded: Patients with other significant coexisting CVD or other disease likely to be fatal in the

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 85% of the peak heart rate achieved on the test (see comments).

Comparisons 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 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.

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

Effect

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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)

1999 100 Circulation

pgs 1764 1769

Study Type: Randomised Controlled Trial

Patient As above.

Characteristics

Intervention As above.

Comparisons As above.

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

Outcomes Mortality.

Funding NHLBI.

Effect 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.

Reference number 2948

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Study Type: Randomised Controlled Trial

Patient All acute MI patients under 65 years and attending the Hospital Post-MI Clinic. Median age: 55

Characteristics years. Total age range (years): Intervention group: 38-65, Control group: 43-63. Gender: nearly all males.

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.

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.

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 nonsignificantly, 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 1 year follow up median time

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Reference number 1350

Marchionni N; Fattiolli 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

Characteristics 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.

Intervention 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
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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

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-

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arms. TWC improved in Hosp CR & Home CR groups but not in controls with no significant 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 significant 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 significantly in very old patients with both interventions. Complications were similar across treatment & age groups. In middle aged & old patients, HRQL improved significantly 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 **pgs** 643 647

Study Type: Randomised Controlled Trial

Patient Subjects were men aged between 30 to 64 yrs. Enrolled at 1 of 5 centers in the US during

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equivalents (METs) \pm SD): Intervention gp: 7.8 ± 2.1 Cont gp: 7.8 ± 2.2 Men with documented MI

≥ 8 wks but < 3 yrs before being enrolled. Subjects with the ability to exercise at an intensity level

≥ 3 METs & a surprise resting diastolic blood pressure < 100 mm 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 85% of the peak heart rate achieved on the test. This gp performed brisk physical activity in the laboratory for 8 wks, exercising 1 hr per day, 3 days per week. Patients were supervised & underwent continuous ECG monitoring. Each individual exercised for 4 min on each of 6 stationary machines with a 2 min rest interval between machines. Attainment of the target heart rate was the goal for every 4 min exercise period. Exercise was stopped if patients experienced any adverse signs or symptoms or ECG abnormalities. After 8 wks, subjects exercised in a gym or swimming pool without ECG monitoring, although exercise heart rates were periodically checked. Activities consisted of 15 min of continuous jogging, cycling or swimming, followed by 25 min 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.

Comparisons

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

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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: 0.07-1.56 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)

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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% lover 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.

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

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Study Type: Randomised Controlled Trial

Patient Patients from 5 centres were recruited for this study. Patients had documented AMI within 1-3

Characteristics years of admission to the study. Subjects were all men.

Mean age (yrs $1\pm$ SEM):

Intervention group: 51.51 \pm 0.4

Control group: 52.01 \pm 0.4

Intervention 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.

Total hospitalisations for reasons other than MI.

Funding Grant from the Rehab. Services Admin of the Dept of Health, Education & Welfare. US.

Effect 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

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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= not significant. 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

**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;Goebbels U;Reinhard 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 Recent MI, and heart failure.

Characteristics

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daily, along with 4 monitored 45 minute sessions of stationary cycling weekly.

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 Herzstiftung 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), or ejection fraction (38.0 ± 9 pre versus $38.2 \pm 10\%$ post in the exercise group and 37.0 ± 10 pre versus $38.3 \pm 13\%$ 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

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Appendix D – Health Economic Extractions

What is the cost effectiveness of Cardiac rehabilitation in Post MI?

Ref ID: 21	Ades PA, Pashkow FJ, Nestor JR. Cost-effectiveness of cardiac rehabilitation after myocardial infarction. J Cardpulm Rehabil 1997; 17(4): 222-231.
Economic study type	CEA, benefit measure was years of life saved (YLS)
Population, country & perspective	Males with a post acute MI below the age of 65 years patient or insurance payer
Intervention	Cardiac rehabilitation + usual care
Comparison(s)	No cardiac rehabilitation (usual care which consisted of thrombolytic therapy coronary bypass surgery, cholesterol lowering drugs and smoking cessation).
Source of effectiveness data	Published review of RCTs
Method of eliciting health valuations (if applicable)	Not applicable
Cost components included	Direct medical costs
Currency and cost year	USA, 1995
Results – cost per patient per alternative	The net cost for MI was \$430 in 1985 and \$940 in 1995. The costs of other common interventions were not stated
Results – effectiveness per patient per alternative	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
Results –incremental cost-effectiveness	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)
Results-uncertainty	Varying the survival rate, the survival probabilities and the rehospitalisation expenses averted
Time horizon & discount rate	3 years 5%
Source of funding	Not stated
Comments	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

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Ref ID: 2919	Hall JP, Wiseman VL, King MT, Ross DL, Kovoov P, Zecchin RP et al. Economic evaluation of a randomised trial of early return to normal activities versus cardiac rehabilitation after acute myocardial infarction. Heart, Lung & Circula 2002; 11(1): 10-18.
Economic study type	Cost consequence analysis. Outcomes were Quality of life (QOL) measures a four measures of return to normal activities (paid and unpaid return to any work and to pre-AMI level of work).
Population, country & perspective	Low-risk patients after acute myocardial infarction (AMI),
Intervention Comparison(s)	6 weeks of standard rehabilitation (REHAB, n = 70) (exercise and counselling times a week) No formal rehabilitation (ERNA, n = 72).
Source of effectiveness data	RCT
Method of eliciting health valuations (if applicable)	Not applicable
Cost components included	Direct medical cost and indirect costs
Currency and cost year	\$AUD, cost year not stated
Results – cost per patient per alternative	\$21.57/Patient/session for 14 sessions on average direct costs excluding hospital overheads \$28.12/Patient/session for 14 sessions on average total hospital costs. 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
Results – effectiveness per patient per alternative	There were no statistically significant differences between the two groups in of the outcomes measured or in the use of other health services
Results –incremental cost-effectiveness	Not done (cost minimisation)
Results-uncertainty	Not done
Time horizon & discount rate	12 months and discounting was not necessary
Source of funding	Public
Comments	Did not state the cost year. Good discussion

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Ref ID: 280	Oldridge N, Furlong W, Feeny D, Torrance G, Guyatt G, Crowe J et al. Economic evaluation of cardiac rehabilitation soon after acute myocardial infarction American Journal of Cardiology 1993; 72(2): 154-161.
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)
Comparison(s)	Usual care (n = 102).
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

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Ref ID: 297	Levin LA, Perk J, Hedback B. Cardiac rehabilitation--a cost analysis. Journal of Internal Medicine 1991; 230(5): 427-434.
Economic study type	Cost consequence analysis
Population, country & perspective	Non-selected post MI patients, societal perspective. Mortality (total & cardiac) Readmission, non-fatal and total cardiac events
Intervention	Comprehensive cardiac rehabilitation programme 147 non-selected MI patients aged less than 65 years (124 men vs. 23 women)
Comparison(s)	Standard care after myocardial infarction (MI) non-selected MI-population aged less than 65 years (n = 158) (134 men vs. 24 women)
Source of effectiveness data	Prospective non- RCT
Method of eliciting health valuations (if applicable)	Not applicable
Cost components included	Both direct and indirect costs (time costs of rehab and lost productivity)
Currency and cost year	SEK 1996
Results – cost per patient per alternative	Rehab group SEK 484260 vs. SEK 557770 usual care and difference was SEK 73,500 in favour of the rehabilitated group
Results – effectiveness per patient per alternative	Mortality (total & cardiac) did not differ between the groups Readmission was less in the rehab 13.7 days vs. 19.3 days in the control p<0.05 They differed in non-fatal reinfarction (17.3 vs. 33.3%), total cardiac events (vs. 53.2%) p=0.001
Results –incremental cost-effectiveness	Not calculated because it was a cost consequence analysis
Results-uncertainty	Remained robust
Time horizon & discount rate	5 yrs, 0 & 10%
Source of funding	Not stated
Comments	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.

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Ref ID: 166	Taylor R, Kirby B. Cost implications of cardiac rehabilitation in older patients. Coronary Artery Disease 1999; 10(1): 53-56.
Economic study type	Review of economic evaluations including costs of the UK cardiac rehabilitation programme
Population, country & perspective	Post-MI patients, Societal cost data for UK and effectiveness data from a Canadian trial
Intervention	Cardiac rehabilitation
Comparison(s)	Usual care
Source of effectiveness data	RCT
Method of eliciting health valuations (if applicable)	N/A
Cost components included	Both direct and indirect patient costs
Currency and cost year	£, 1994/5
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 situation

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Improve outcome in patients after MI ?

No 993

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%

Results- cost: AGE Limited benefit Persistent benefit model

50yrs

Captopril \$ 3209 \$32883

Placebo \$30369 \$ 30369

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60yrs		
Captopril	\$26128	\$27382
Placebo	\$24449	\$24449
70yrs		
Captopril	\$ 20822	\$ 22292
Placebo	\$ 19099	\$ 19099
80yrs		
Captopril	\$16699	\$ 18067
Placebo	\$ 14844	\$ 14844

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	QALYS	QALYS
50yrs		
Captopril	8.13	8.34
Placebo	8.10	8.10
60yrs		
Captopril	6.51	6.85
Placebo	6.33	6.33
70yrs		
Captopril	5.07	5.47
Placebo	4.72	4.72
80yrs		
Captopril	3.96	4.33
Placebo	3.44	3.44

Results-ICER:	AGE	Ltd benefit (\$/QALY)	Persistent benefit model (\$/QALY)
	50yrs	60800	10400
	60yrs	9000	5600
	70yrs	4900	4300
	80yrs	3600	3700

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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

Source of Funding: 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.

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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

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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.

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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	HOPE diabetic subgroup
	CHF 71351	CHF 74650

Results-effectiveness:	HOPE study all patients	HOPE diabetic subgroup
	LYG 11.88	LYG 19.69

Results-ICER:	HOPE study all patients	HOPE diabetic subgroup
	ICER 6005/LYG	3790/LYG

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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

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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)

	Total direct medical	48957	46294	2663 (NS) Direct
nonmedical	1450	1725	-275 (NS)	Indirect costs
49672	2582 (NS)			52525

NS= non significant difference

Results-effectiveness: Expected LYG at the end of the study 0.16

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Costs related to cardiovascular disease only:

	Cost/LYG	Cost/CVE avoided
Direct medical	16600	76100
Direct medical+ direct non medical+	16100	73800

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Direct medical	5400	207300
Direct medical+ direct non medical+	54600	249600

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.

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Study Quality: 1+ 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

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3yr	0.071
3.8yr	0.100

Results-ICER: Follow up cost/LYG

1 yr	euro 4784
2yr	euro 2286
3yr	euro 2763
3.8yr	euro 1550

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.

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No 959

Study Quality: 1+ A South African pharmaco-economic analysis of the acute infarction efficacy (AIRE) study
ramipril

Author: Anderson AN; Moodley I; Kropman K; 2000

Intervention: Ramipril

Comparison: Placebo

Population: Post MI patients with heart failure

Perspective: NHS

Study type: CEA & CUA

Methods: RCT (AIRE study)

Health valuations: NOT STATED (used data from literature)

Cost components: Direct medical

Currency: OTHER (South Africa Rand)

Cost year: 1999

Time horizon: 4yrs

Discount rate: 5%

Results- cost:	Follow up	incremental mean costs	lower limit	upper limit
	1y	1833	1340	2465
	2y	1576	1147	2125
	3.8y	1278	949	1702

Results-effectiveness:	Follow up	LYG
	1y	0.027

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3.8y

0.289

QALYs for <65yrs 0.786

QALYs for >65yrs 0.932

Results-ICER:	FU	cost/LYG	lower limit	upper limit
	1y	67907	49633	91290
	2y	17516	12743	23615
	3.8y	4423	3284	5888

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COST UTILITY RESULTS

Age group	cost/QALY	lower limit	upper limit
<65yrs	5627	4177	7490
>65yrs	4744	3522	6315

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.

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:	Follow up	additional cost
	4years	2491
	20yrs	8723

	Follow up	additional cost/additional survivor
	4years	69126
	20yrs	68142

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4yrs 0.11
20yrs 0.55

Results-ICER:	Follow up	cost/LYG
	4yrs	22887
	20yrs	15799

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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.

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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

Time horizon: 5yrs

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)

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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

	Eligible population	Life year gained
Total population	>3000000	12000
Ischemic heart disease	1400000	5600

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Diabetes	1700000	6800
Peripheral vascular disease	1000000	4000

Results-ICER:

Results	5yr	20yrs
Base case	14700	2800
Low risk	36600	5300
High risk	4000	100
Highest risk	1300	-900 (net saving)

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.

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:	Follow up	cost/patient
	1y	11.42
	2y	12.79
	3.8y	73.77

Results-effectiveness:	Follow up	LYG
	1y	0.027
	2y	0.090

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Results-ICER:	Follow up	cost/LYG
	1y	425.79
	2y	147.90
	3.8y	286.24

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:

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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

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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

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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

Follow up	mean cost (DM)
1y	223
2y	361
3y	860
3.8y	710

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Follow up	LYG
1y	0.027
2y	0.090
3y	0.170
3.8y	0.289

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Follow up	mean cost (DM)	lower limit CI:	upper limit CI
1y	7	-3712	13624
2y	4012	-2402	6863
3y	5056	2203	6438
3.8y	2456	-102	3623

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

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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:	Trandolapril	22 080 500
	Placebo	20 317 300
	Difference	1 763 200

Results-effectiveness:	All-cause mortality	
	Trandolapril	304
	Placebo	369
	Difference	65

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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

BOOTHSTRAP 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.

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Study Quality: 1++ Cost effectiveness in the treatment of heart failure with ramipril: a Swedish sub study of the AIRE study.

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

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Results-ICER:	Follow up	cost/LYS
	1yr	33033
	2yrs	18153
	3.8yrs	14148

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.

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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, reinfaction, 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%

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Aspirin \$91700

Clopidogrel: \$98500

Results-effectiveness: 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.

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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, reinfarction, 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: 2years

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

and 14320 euros/LYG 95%CI [6990-26470] using the probabilistic model.

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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.

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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, reinfarction, 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: 2 years of Clopidogrel: £1359628

Lifetime costs of Clopidogrel: £19199554

2 years of ASA: £1388494

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Results-effectiveness:	QALY gained	Life year Gained	
	Clopidogrel:	12002	14242
	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.

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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, reinfarction, 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

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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

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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

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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.

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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, reinfarction, 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

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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

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.

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, reinfarction, 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

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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-effectiveness: 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

Patients without Diabetes

50 year olds -0.03

60 year olds-0.05

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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

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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

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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

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>65years \$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.

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Study Quality: 1+ A cost-effectiveness analysis of combination antiplatelet therapy for high-risk acute coronary syndromes: clopidogrel plus aspirin versus aspirin alone.

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, reinfarction, 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 including 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

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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, providing details of sources of data, how the data was incorporated as well as a clear model structure.

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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; Hunnink 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

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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.

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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

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Sub-groups

For high risk group there was a reduction in the ICER to about £4939/QALY and low risk 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.

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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 Metoprolol 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

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Discount rate: 5%

Results Metoprolol Kr 118610 (approx £11981) inclusive of indirect costs

Cost/patient: Placebo Kr 137220 (approx £13861) inclusive of indirect costs

Excluding indirect costs

Metoprolol Kr 12310 (approx £1243)

Placebo Kr 17120 (approx £1729)

Results Significant differences were found on the reinfaction, cerebrovascular events, coronary bypass

Effectiveness: surgery and reduced hospitalisation in favor of metoprolol. 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.

Results Results were not synthesized. But metoprolol was deemed cost effective on the basis of reduced

Incremental: rates of adverse events and less cost over the three year follow up.

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.

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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 adrenergic 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, reinfarction, 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\$

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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 65y: 0.31 (3.1%)

High 45yrs: 0.48 (3.8%)

High 55yrs: 0.47 (4.6%)

High 65yrs: 0.44 (5.5%)

Results low-risk group 45yrs: \$23457/LYG-----\$12855/LYG

Incremental: 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

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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.

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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

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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.

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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.

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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.

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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.
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Source of Funding: not stated

Comments: 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.

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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

Study type: CUA

Methods: RCT EPHEBUS 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

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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.

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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;I shak J;Goldberg 2005

R; Tooley J; Willke R; Pitt B;

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

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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%)

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Source Funding: Private

Comments: This study was detailed and used three different data sources to estimate what would happen after the trial period.

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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
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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 cot 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).

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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;Marfisi RM;Tognoni G;Valagussa F;GISSI- 2004
Prevenzione I;

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

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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.

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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 JJC;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

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Cost 1994

Time horizon: 3yrs

Discount rate: 5%

Results Anticoagulation: average Dfl 9878 and total costs are Dfl 17621613

Cost/patient:

Placebo: average Dfl 10784 and total costs are Dfl 19222590

Results Warfarin treatment resulted in

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

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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
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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.

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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

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	Placebo	gemfibrozil
Age 55:	\$13464	\$17428
Age 65:	\$10462	\$14434
Age 75:	\$8284	\$12193

Results-effectiveness:

Life expectancy

	Placebo	Gemfibrozil
Age 55:	22.5	23.15
Age 65:	17.45	18.07
Age 75:	13.36	13.98

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

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Appendix E - Clinical Questions and Search Strategy

Guideline Questions

	Question	Population	Interventions	Comparisons	Outcomes
1.	What is the effectiveness of changing dietary regime from the pre-infarct diet?	patients after MI	fibre, low-saturated fat, low GI, low blood sugar, folate rich, fish oils, plant sterols, anti-oxidant diets,	no change	re-infarction, mortality, revascularisation, stroke, readmission,
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)	patients after MI	patient education/information		(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)
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?	patients after MI	psychological/social support		(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)
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?	patients after MI	incidence and identification of sexual dysfunction		referral
5.	What is the effectiveness of adding ACEI versus placebo to improve outcome in...	(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?	ACEI	Placebo	re-infarction, mortality, revascularisation, stroke, readmission,
6.	What is the effectiveness of adding ARBs versus placebo to improve outcome in.....	(i) patients after MI without LV dysfunction? (ii) patients after MI with LV dysfunction?	ARB	Placebo	re-infarction, mortality, revascularisation, stroke, readmission,
7.	What is the effectiveness of adding ACEI versus ARBs to improve outcome in...	(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?	ACEI	ARB	re-infarction, mortality, revascularisation, stroke, readmission,
8.	What is the effectiveness of adding ACEI plus ARBs versus ACEI to improve outcome in..	patients after MI with LV dysfunction?	ACEI plus ARB	ACEI	re-infarction, mortality, revascularisation, stroke, readmission,
9.	How frequently should renal function tests, including serum potassium, be monitored in patients treated with ACEI and/or ARBs after MI?	patients after MI treated with ACEI and/or ARB	frequency of renal function tests - serum potassium		

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	Question	Population	Interventions	Comparisons	Outcomes
10.	What is the effectiveness of adding aspirin versus placebo to improve outcome in patients after MI?	patients after MI	aspirin	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
11.	What is the effectiveness of adding aspirin versus clopidogrel to improve outcome in patients after MI?	patients after MI	aspirin	clopidogrel	re-infarction, mortality, revascularisation, stroke, readmission,
12.	What is the most effective method of delivering dietary advice?	patients after MI			adherence, compliance, concordance
13.	What is the effectiveness of adding aspirin versus aspirin and clopidogrel to improve outcome in...	(i) patients after NSTEMI (ii) patients after STEMI	aspirin	aspirin and clopidogrel	re-infarction, mortality, revascularisation, stroke, readmission,
14.	What is the effectiveness of adding a beta blocker versus placebo to improve outcome in...	(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?	beta blocker	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
15.	What is the effectiveness of adding vitamin K antagonist (warfarin) versus placebo to improve outcome in patients after an MI?	patients after MI	Warfarin	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
16.	What is the effectiveness of adding vitamin K antagonist (warfarin) versus aspirin to improve outcome in patients after an MI?	patients after MI	warfarin	aspirin	re-infarction, mortality, revascularisation, stroke, readmission,
17.	What is the effectiveness of adding vitamin K antagonist (warfarin) plus aspirin versus aspirin to improve outcome in patients after MI?	patients after MI	warfarin and aspirin	aspirin	re-infarction, mortality, revascularisation, stroke, readmission,
18.	What is the effectiveness of adding vitamin K antagonist (warfarin) plus aspirin versus warfarin to improve outcome in patients after MI?	patients after MI	warfarin and aspirin	warfarin	re-infarction, mortality, revascularisation, stroke, readmission,
19.	What is the effectiveness of adding calcium channel blocker versus placebo to improve outcome in...	(i) patients after MI without LV dysfunction? (ii) patients after MI with LV dysfunction?	calcium channel blocker	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
20.	What is the effectiveness of adding potassium channel activators versus placebo to improve outcome in patients after MI?	patients after MI	potassium channel activators	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
21.	How frequently should renal function, including serum potassium, be monitored in patients post MI treated with eplerenone?	patients after MI treated with eplerenone	frequency of renal function tests - serum potassium		
22.	What is the effectiveness of adding eplerenone versus placebo to improve outcome in patients after MI ?	patients after MI with heart failure and LV dysfunction	eplerenone	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
23.	What is the effectiveness of adding Omega-3-acid ethyl esters versus placebo to improve outcome in patients after MI?	patients after MI	Omega-3-acid ethyl esters treatment	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
24.	What is the effectiveness of low/ moderate alcohol consumption versus high alcohol consumption to	patients after MI	low to moderate alcohol consumption	no alcohol	re-infarction, mortality, revascularisation, stroke,

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	Question	Population	Interventions	Comparisons	Outcomes
	improve outcome in patients after MI?				readmission,
25.	What is the effectiveness of no/ low/moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?	patients after MI	none to moderate alcohol consumption	high alcohol consumption	re-infarction, mortality, revascularisation, stroke, readmission,
26.	What is the effectiveness of low/ moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?	patients after MI	low to moderate alcohol consumption	no alcohol	re-infarction, mortality, revascularisation, stroke, readmission,
27.	What is the effectiveness of adding statins versus placebo to improve outcome in patients after MI?	patients after MI	statins	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
28.	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?	patients after MI	high dose statin	low dose statin	re-infarction, mortality, revascularisation, stroke, readmission,
29.	What is the effectiveness of adding early statin therapy versus delayed statin therapy to improve outcome in patients after MI?	patients after MI	early statin	delayed statin	re-infarction, mortality, revascularisation, stroke, readmission,
30.	What is the effectiveness of adding fibrates or niacin or ezetimibe versus placebo to improve outcome in patients after MI?	patients after MI	fibrates	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
31.	Are there stable patients who don't benefit prognostically from revascularisation	patients after MI with reversible ischaemia without LV dysfunction	revascularisation		re-infarction, mortality, revascularisation, stroke, readmission,
32.	Are there stable patients after MI who a) benefit prognostically from revascularisation b) those who don't benefit prognostically	patients after MI with reversible ischaemia and LV dysfunction	revascularisation		re-infarction, mortality, revascularisation, stroke, readmission,
33.	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)	patients after MI with hypertension	optimal blood pressure		re-infarction, mortality, stroke, readmission,
34.	Does determining LV function versus standard care improve (that is, affect) outcome of patients MI (summarising LV dysfunction effect on drugs/ ICD /rehab)?	patients after MI	determining (testing?) LV dysfunction	standard care	adverse effects
35.	Is there any benefit in giving ACEI at a later stage of treatment in patients with previous MI (later than one year)		late treatment		re-infarction, mortality, revascularisation, stroke, readmission, safety, tolerance
36.	Does a history of proven MI in the past (> 1 year) versus recent MI (< 1 year) change treatment / management / outcome?	i) proven MI in the past > 1 year	treatment for MI < 1 year	treatment for MI > 1 year	re-infarction, mortality, revascularisation, stroke, readmission,
37.	What is the effectiveness of regular physical activity versus a sedentary lifestyle to improve	patients after MI	regular exercise (need to define this) structured	no exercise	re-infarction, mortality, revascularisation, stroke,

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	Question	Population	Interventions	Comparisons	Outcomes
	outcome in patients after MI?		exercise, unstructured exercise, frequency, duration, intensity		readmission,
38.	What is the level of physical activity which increases physical work capacity versus physical activity which does not increase physical work capacity		level of physical activity		physical work capacity, re-infarction, mortality
39.	What is the effectiveness of comprehensive cardiac rehabilitation versus standard care with no cardiac rehabilitation to improve outcome in patients after MI ?	patients after MI	comprehensive cardiac rehab	standard care	re-infarction, mortality, stroke, readmission, resumption of dai activities, return to work, QoL, increased psychological wellbeing
40.	What is the effectiveness of exercise only cardiac rehabilitation versus standard care with no cardiac rehabilitation to improve outcome in patients after MI?	patients after MI	exercise only rehab	standard care	re-infarction, mortality, stroke, readmission, resumption of dai activities, return to work, QoL, increased psychological wellbeing
41.	What is the effectiveness of comprehensive cardiac rehabilitation versus exercise only cardiac rehabilitation to improve outcome in patients after MI?	patients after MI	comprehensive cardiac rehab	exercise only rehab	re-infarction, mortality, stroke, readmission, resumption of dai activities, return to work, QoL, increased psychological wellbeing
42.	What is the effectiveness of an individualised cardiac rehabilitation programme versus a non-individualised cardiac programme to improve outcome in patients after MI?	patients after MI	individualised cardiac rehab	non-individualised cardiac rehab	re-infarction, mortality, stroke, readmission, resumption of dai activities, return to work, QoL, increased psychological wellbeing, patient satisfaction
43.	Are there any patients after MI in whom the exercise component of cardiac rehabilitation is not safe?	patients after MI	risk factors of cardiac rehab		re-infarction, mortality, stroke, readmission,
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?	previous MI - women, ethnic minorities, older people, lower social economic groups, mental and physical health co-morbidities, living in rural communities	access to cardiac rehab		
45.	What is the effectiveness of regular physical activity versus a sedantary lifestyle to improve outcome in patients after MI?	patients after MI	regular exercise (need to define this) structured exercise, unstructured exercise, frequency, duration, intensity	no exercise	re-infarction, mortality, revascularisation, stroke, readmission,
46.	Does a history of proven MI in the past (> 1 year) versus recent MI (< 1 year) change treatment / management / outcome?	i) proven MI in the past > 1 year	treatment for MI < 1 year	treatment for MI > 1 year	re-infarction, mortality, revascularisation, stroke, readmission,

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	Question	Population	Interventions	Comparisons	Outcomes
47.	What is the effectiveness of adding fibrates versus placebo to improve outcome in patients with CHD		Fibrates	placebo	total cholesterol, HDL-C, LDL-C
48.	What is the effectiveness of adding ezetimibe versus placebo to improve outcome in patients with CHD		ezetimibe	placebo	total cholesterol, HDL-C, LDL-C
49.	Is there an optimum time for ACEI to be administered in the nonacute phase?	(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?	Early ACEI	Delayed ACEI	re-infarction, mortality, revascularisation, stroke, readmission,
50.	Is there an optimum time for beta-blockers to be initiated in unselected patients after MI?	unselected patients after MI	timing of beta blocker		re-infarction, mortality, revascularisation, stroke, readmission,
51.	What is the potential harm of adding the following: calcium channel blocker or thiazide diuretic or alpha blocker versus placebo in...	(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?	calcium channel blocker, thiazide diuretic, alpha blocker	standard care	adverse effects
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 & Depression guidelines)				
53.	What are the information and support needs for patients at different points in the care pathway?	patients after MI	patient information and support		
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		Whether to continue ACEI treatment. what are the risk factors?	Discontinue ACEI treatment	Chronic renal failure, mortality, re-infarction
55.	Is there any benefit in initiating beta blockers at a later stage of treatment		beta blocker at later stage		re-infarction, mortality, revascularisation, stroke, readmission,

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The following Guideline sources were searched for each question.

Guidelines sources searched

National electronic Library for Health (NeLH) Guidelines Finder

<http://libraries.nelh.nhs.uk/guidelinesFinder/>

National Guidelines Clearinghouse

<http://www.guideline.gov/>

National Institute for Clinical Excellence (NICE) guidelines & technology appraisals

<http://www.nice.org.uk/page.aspx?o=ourguidance>

Scottish Intercollegiate Guidelines Network (SIGN)

www.sign.ac.uk

Canadian Medical Association (CMA) Infobase

<http://mdm.ca/cpgsnew/cpgs/index.asp>

National Health and Medical Research Council (NHMRC) Australian guidelines

<http://www7.health.gov.au/nhmrc/publications/subjects/clinical.htm>

New Zealand Guidelines Group

<http://www.nzgg.org.nz/index.cfm?screenSize=800&ScreenResSet=yes>

Guidelines International Network

<http://www.g-i-n.net/index.cfm?fuseaction=homepage>

BMJ Clinical Evidence

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<http://www.clinicalevidence.com/ceweb/conditions/index.jsp>

The following databases were searched for all questions:

Medline, Embase, Cinahl, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), CENTRAL, NHS Economic Evaluations Database (NHS EED), Social Science Citation Index. Where relevant to the question PsycINFO, Allied & complementary Medicine (AMED) and PEDro (Physiotherapy Evidence Database) and were also searched

For each question the Medline strategy is given below. This strategy was adapted to run on the other databases searched. Medline, Embase, NHS EED and the Social Science Citation Index (SCCI) were searched for economic literature using the following filters developed by ScHaRR, University of Sheffield. This filter was adapted to run on (SCCI).

Medline economics/quality of life filter

1. exp "costs and cost analysis"/
2. economics/
3. exp economics,hospital/
4. exp economics,medical/
5. economics,nursing/
6. economics,pharmaceutical/

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7. exp "fees and charges"/
8. exp budgets/
9. budget\$.tw.
10. cost\$.tw.
11. (cost\$ adj2 (effective\$ or utilit\$ or benefit\$ or minimi\$)).ab.
12. (economic\$ or pharmacoeconomic\$ or pharmaco-economic\$).ti.
13. (price or pricing).tw.
14. (financial or finance or finances or financed).tw.
15. (fee or fees).tw.
16. (value adj2 (money or monetary)).tw.
17. value of life/
18. quality adjusted life year/
19. quality adjusted life.tw.
20. (qaly\$ or qald\$ or qale\$ or qtime\$).tw.
21. disability adjusted life.tw.
22. daly\$.tw.
23. health status indicators/
24. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

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25. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

26. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sf twelve or shortform twelve or shortform twelve or short form twelve or short form twelve).tw.

27. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sf sixteen or shortform sixteen or shortform sixteen or short form sixteen or short form sixteen).tw.

28. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sf twenty or shortform twenty or shortform twenty or short form twenty or short form twenty).tw.

29. (euroqol or euro qol or eq5d or eq 5d).tw.

30. (hql or hqol or h qol or hrqol or hr qol).tw.

31. (hye or hyes).tw.

32. health\$ year equivalent\$.tw.

33. health utilit\$.tw.

34. (hui or hui1 or hui2 or hui3).tw.

35. disutilit\$.tw.

36. rosser.tw.

37. quality of wellbeing.tw.

38. quality of well being.tw.

39. qwb.tw.

40. willingness to pay.tw.

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41. standard gamble\$.tw.
42. (time trade off or time tradeoff).tw.
43. tto.tw.
44. exp models,economic/
45. *models, theoretical/
46. *models, organizational/
47. economic model\$.tw.
48. markov chains/
49. markov\$.tw.
50. monte carlo method/
51. monte carlo.tw.
52. exp decision theory/
53. (decision\$ adj2 (tree\$ or analy\$ or model\$)).tw.
54. or/1-53
55. (letter or editorial or comment).pt.
56. 54 not 55

Embase economics/quality of life filter

1. exp 'economic aspect'/
2. cost\$.tw.

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3. (cost\$ adj2 (effective\$ or utilit\$ or benefit\$ or minimi\$)).ab.
4. (economic\$ or pharmacoeconomic\$ or pharmaco-economic\$).ti.
5. (price or pricing).tw.
6. (financial or finance or finances or financed).tw.
7. (fee or fees).tw.
8. (value adj2 (money or monetary)).tw.
9. quality adjusted life.tw.
10. (qaly\$ or qald\$ or qale\$ or qtime\$).tw.
11. disability adjusted life.tw.
12. daly\$.tw.
13. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
14. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
15. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sf twelve or shortform twelve or shortform twelve or short form twelve or short form twelve).tw.
16. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sf sixteen or shortform sixteen or shortform sixteen or short form sixteen or short form sixteen).tw.

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17. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sf twenty or shortform twenty or shortform twenty or short form twenty or short form twenty).tw.

18. (euroqol or euro qol or eq5d or eq 5d).tw.

19. (hql or hqol or h qol or hrqol or hr qol).tw.

20. (hye or hyes).tw.

21. health\$ year equivalent\$.tw.

22. health utilit\$.tw.

23. (hui or hui1 or hui2 or hui3).tw.

24. disutilit\$.tw.

25. rosser.tw.

26. quality of wellbeing.tw.

27. quality of well being.tw.

28. qwb.tw.

29. willingness to pay.tw.

30. standard gamble\$.tw.

31. (time trade off or time tradeoff).tw.

32. tto.tw.

33. exp 'mathematical model'/

34. economic model\$.tw.

35. markov\$.tw.

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36. monte carlo method/

37. monte carlo.tw.

38. exp decision theory/

39. (decision\$ adj2 (tree\$ or analy\$ or model\$)).tw.

40. or/1-39

41. (letter or editorial or comment).pt.

Full details of the search strategies are available on request from the National Collaborating Centre for Primary Care.

1.5 Drug therapy

Questions 1-4,6, 52-53. Angiotensin converting enzyme (ACE) & Angiotensin II receptor blockers (ARB)

Medline 1999-May Wk 3 2005 via Ovidweb

Search date: 01/06/05

Update search: May wk 3 2005-May wk 5 2006

Search date: 08/06/06

1. exp myocardial infarction/

2. (infarct\$ or MI or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.

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3. 1 or 2

4. Angiotensin-Converting Enzyme Inhibitors/

5. Captopril/ae, tu

6. lisinopril/ae, tu

7. ramipril/ae, tu

8. enalapril/ae, tu

9. perindopril/ae, tu

10. fosinopril/ae, tu

11. cilazapril/ae, tu

12. (captopril or lisinopril or ramipril ortrandolapril or enalapril or quinapril or perindopril or moexipril or imadipril or fosinopril or cilazapril).ti,ab.

13. angiotensin converting enzyme inhibit\$.ti,ab.

14. (acel or ace inhibit\$.ti,ab.

15. exp Receptors, Angiotensin/

16. losartan/ae, tu

17. (losartan or valsartan or candesartan or eprosartan or irbesartan or olmesartan or telmisartan).ti,ab.

18. (angiotensin adj2 antagonist\$.ti,ab.

19. (angiotensin adj3 receptor\$.ti,ab.

20. (angiotensin adj3 (blocker\$ or blockade)).ti,ab.

21. (arb\$1 or AIIA or AIIIRA).ti,ab.

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22. or/4-18

23. (systematic adj review\$).tw.

24. (published adj studies).ab.

25. (data adj synthesis).tw.

26. (data adj extraction).ab.

27. meta-analysis/

28. meta-analysis.ti,ab.

29. meta-analysis.pt.

30. or/23-29

31. 3 and 22

32. 30 and 31

33. randomized controlled trial.pt.

34. controlled clinical trial.pt.

35. randomized controlled trials.sh.

36. random allocation.sh.

37. double blind method.sh.

38. single blind method.sh.

39. or/33-38

40. clinical trial.pt.

41. exp clinical trials/

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42. (clin\$ adj5 trial\$.ti,ab.
43. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.
44. placebos.sh.
45. placebo\$.ti,ab.
46. random\$.ti,ab.
47. or/40-46
48. 39 or 47
49. 31 and 48
50. 32 or 49
51. animals/
52. humans/
53. 51 not (51 and 52)
54. 50 not 53
55. (comment or letter or editorial).pt.
56. 54 not 55

Question 5. Renal function tests with ACE and/or ARBs

Medline 1966-June wk 2 2005 via Ovidweb

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Search date: 16/06/05

Update search June wk 2 2005-may wk 5 2006

Search date: 08/06/06

1. exp myocardial infarction/
2. (infarct\$ or MI or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.
3. 1 or 2
4. Angiotensin-Converting Enzyme Inhibitors/
5. Captopril/ae, tu
6. lisinopril/ae, tu
7. ramipril/ae, tu
8. enalapril/ae, tu
9. perindopril/ae, tu
10. fosinopril/ae, tu
11. cilazapril/ae, tu
12. (captopril or lisinopril or ramipril ortrandolapril or enalapril or quinapril or perindopril or moexipril or imadipril or fosinopril or cilazapril).ti,ab.
13. angiotensin converting enzyme inhibit\$.ti,ab.
14. (acel or ace inhibit\$).ti,ab.
15. exp Receptors, Angiotensin/

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16. losartan/ae, tu
17. (losartan or valsartan or candesartan or eprosartan or irbesartan or olmesartan or telmisartan).ti,ab.
18. (angiotensin adj2 antagonist\$.ti,ab.
19. (angiotensin adj3 receptor\$.ti,ab.
20. (angiotensin adj3 (blocker\$ or blockade)).ti,ab.
21. (arb\$1 or AIIA or AIIIRA).ti,ab.
22. or/4-18
23. 3 and 22
24. (serum potassium or creatinine).ti,ab.
25. Creatinine/
26. (glomerular filtration rate or gfr).ti,ab.
27. Kidney Function Tests/
28. GLOMERULAR FILTRATION RATE/
29. ((renal or kidney) adj2 (test\$ or assess\$ or evaluat\$ or investigat\$)).ti,ab.
30. or/24-29
31. 23 and 30
32. animal/
33. Humans/
34. 32 not (32 and 33)

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35. 31 not 34

Questions 7-9. Antiplatelets

Medline 1999-Jul wk 1 2005 via Ovidweb

Search date: 20/07/05

Update search: Jul wk 1 2005-May wk 4 2006

Search date: 08/06/06

1. exp myocardial infarction/
2. (infarct\$ or MI or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.
3. 1 or 2
4. Aspirin/
5. aspirin.tw.
6. 4 or 5
7. (clopidogrel or plavix).tw.
8. DIPYRIDAMOLE/
9. (dipyridamole or persantin).tw.

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10. placebo/
11. placebo\$.tw.
12. or/7-11
13. 3 and 6 and 12
14. (aspirin adj2 (intoleran\$ or hypersensitiv\$ or hyper-sensitiv\$ or resistan\$ or allerg\$ or sensitiv\$)).tw.
15. 3 and 14
16. (systematic adj review\$).tw.
17. (published adj studies).ab.
18. (data adj synthesis).tw.
19. (data adj extraction).ab.
20. meta-analysis/
21. meta-analysis.ti,ab.
22. meta-analysis.pt.
23. or/16-22
24. 13 and 23
25. comment.pt.
26. letter.pt.
27. editorial.pt.
28. or/25-27

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29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. randomized controlled trials.sh.
32. random allocation.sh.
33. double blind method.sh.
34. single blind method.sh.
35. or/29-34
36. clinical trial.pt.
37. exp clinical trials/
38. (clin\$ adj2 trial\$).ti,ab.
39. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj2 (blind\$ or mask\$)).ti,ab.
40. placebos.sh.
41. placebo\$.ti,ab.
42. random\$.ti,ab.
43. or/36-42
44. 35 or 43
45. 13 and 44
46. 24 or 45
47. 46 or 15
48. Animals/

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49. Humans/

50. 48 not (48 and 49)

51. 47 not 50

52. 51 not 28

Question 10. Betablockers

Medline 1999-Aug wk 1 2005 via Ovidweb

Search date: 17/08/05

Update search: Aug wk 1 2005-May wk 5 2006

Search date:12/06/06

1. exp myocardial infarction/

2. (infarct\$ or MI or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.

3. 1 or 2

4. adrenergic beta-antagonists/ or acebutolol/ or atenolol/ or bisoprolol/ or celiprolol/ or labetalol/ or metoprolol/ or nadolol/ or oxprenolol/ or pindolol/ or propranolol/ or timolol/

5. (atenolol or metoprolol or acebutolol or propranolol or timolol or bisoprolol or carvedilol or nadolol or oxprenolol or pindolol or nebivolol or labetalol or celiprolol).ti,ab.

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6. (beta adj3 block\$).ti,ab.
7. (b adj3 block\$).ti,ab.
8. (beta adj2 antagonist\$).ti,ab.
9. or/4-8
10. 3 and 9
11. (systematic\$ adj review\$).ab.
12. review.pt.
13. meta-analysis.ab.
14. meta-analysis.pt.
15. meta-analysis.ti.
16. or/11-15
17. 10 and 16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized controlled trials.sh.
21. random allocation.sh.
22. double blind method.sh.
23. single blind method.sh.
24. or/18-23
25. clinical trial.pt.

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26. exp clinical trials/
27. (clin\$ adj5 trial\$).ti,ab.
28. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.
29. placebos.sh.
30. placebo\$.ti,ab.
31. random\$.ti,ab.
32. or/25-31
33. 24 or 32
34. 10 and 33
35. 17 or 34
36. animals/
37. humans/
38. 36 not (36 and 37)
39. 35 not 38
40. (comment or letter or editorial).pt.
41. 39 not 40

Question 11,54. Timing of initiating Betablockers

Medline 1966-Aug wk 2 2005 via Ovidweb

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Appendices Post MI - Final Version

Search date: 24/08/05

Update search: Aug w2 2005-may wk 5 2006

Search date: 12/06/06

1. exp myocardial infarction/
2. (infarct\$ or MI or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.
3. 1 or 2
4. (secondary or post or previous\$ or prior or follow\$ or former\$ or earlier or history).ti,ab.
5. 3 and 4
6. adrenergic beta-antagonists/ or acebutolol/ or atenolol/ or bisoprolol/ or celiprolol/ or labetalol/ or metoprolol/ or nadolol/ or oxprenolol/ or pindolol/ or propranolol/ or timolol/
7. (atenolol or metoprolol or acebutolol or propranolol or timolol or bisoprolol or carvedilol or nadolol or oxprenolol or pindolol or nebivolol or labetalol or celiprolol).ti,ab.
8. (beta adj3 block\$).ti,ab.
9. (b adj3 block\$).ti,ab.
10. (beta adj2 antagonist\$).ti,ab.
11. or/6-10
12. 5 and 11
13. time factors/

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14. time factor\$.ti,ab.
15. (later adj2 (time or stage)).ti,ab.
16. or/13-15
17. 12 and 16
18. animals/
19. humans/
20. 18 not (18 and 19)
21. 17 not 20
22. (letter or comment or editorial).pt.
23. 21 not 22

Question 12-13,29. Calcium Channel blocker & Potassium activators

Medline 1999-aug wk 5 2005 via Ovidweb

Search date: 14/09/05

Update search: Aug wk 5 2005-May wk 5 2006

Search date: 13/06/06

1. exp myocardial infarction/
2. (infarct\$ or MI or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.

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3. 1 or 2

4. calcium channel blockers/ or amlodipine/ or diltiazem/ or felodipine/ or isradipine/ or nicardipine/ or nifedipine/ or nimodipine/ or nisoldipine/ or verapamil/

5. (calcium channel adj (blocker\$ or antagonist)).ti,ab.

6. (nifedipine or amlodipine or diltiazem or verapamil or felodipine or nicardipine or isradipine or lacidipine or lercanidipine or nisoldipine or nimodipine).ti,ab.

7. or/4-6

8. Nicorandil/

9. (potassium channel adj (activator\$ or opener)).ti,ab.

10. (nicorandil or ikorel).ti,ab.

11. or/8-10

12. 7 or 11

13. 3 and 12

14. (systematic\$ adj review\$).ab.

15. review.pt.

16. meta-analysis.ab.

17. meta-analysis.pt.

18. meta-analysis.ti.

19. or/14-18

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20. 13 and 19

21. randomized controlled trial.pt.

22. controlled clinical trial.pt.

23. randomized controlled trials.sh.

24. random allocation.sh.

25. double blind method.sh.

26. single blind method.sh.

27. or/21-26

28. clinical trial.pt.

29. exp clinical trials/

30. (clin\$ adj5 trial\$).ti,ab.

31. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.

32. placebos.sh.

33. placebo\$.ti,ab.

34. random\$.ti,ab.

35. or/28-34

36. 27 or 35

37. 13 and 36

38. 20 or 37

39. animal/

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40. humans/

41. 39 not (39 and 40)

42. 38 not 41

43. (letter or editorial or comment).pt.

44. 42 not 43

Question 14. Omega-3-acid ethyl esters treatment

Medline 1966- Oct wk 2 2005 via Ovidweb

Search date: 25/10/05

Update search Oct wk 2 2005-may wk 5 2006

Search date: 13/06/06

1. Fatty Acids, Omega-3/

2. omega-3.ti,ab.

3. n-3 fatty acid\$.ti,ab.

4. n-3 polyunsaturated fatty acid\$.ti,ab.

5. n-3 pufa.ti,ab.

6. n-3 polyunsaturated fa.ti,ab.

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7. omacor.ti,ab.

8. maxepa.ti,ab.

9. fish oil\$1.ti,ab.

10. or/1-9

11. (supplement\$ or concentrate\$ or dose\$ or capsule\$ or tablet\$ or additive\$ or treatment\$ or therap\$ or intervention\$).ti,ab.

12. dietary supplementation/

13. 11 or 12

14. exp Myocardial Infarction/

15. (infarct\$ or mi or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.

16. 14 or 15

17. 10 and 13 and 16

18. (systematic\$ adj review\$).ab.

19. review.pt.

20. meta-analysis.ab.

21. meta-analysis.pt.

22. meta-analysis.ti.

23. or/18-22

24. 17 and 23

25. randomized controlled trial.pt.

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26. controlled clinical trial.pt.
27. randomized controlled trials.sh.
28. random allocation.sh.
29. double blind method.sh.
30. single blind method.sh.
31. or/25-30
32. clinical trial.pt.
33. exp clinical trials/
34. (clin\$ adj5 trial\$).ti,ab.
35. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.
36. placebos.sh.
37. placebo\$.ti,ab.
38. random\$.ti,ab.
39. or/32-38
40. 31 or 39
41. 17 and 40
42. 24 or 41
43. (letter or editorial or comment).pt.
44. 42 not 43
45. animals/

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46. humans/

47. 45 not (45 and 46)

48. 44 not 47

Question 19-22. Vitamin K antagonists

Medline 1966-July wk 2 2005 via Ovidweb

Search date: 27/05/05

Update search: Jul wk 2 2005-May wk 5 2006

Search date: 13/06/06

1. exp Myocardial Infarction/

2. (infarct\$ or mi or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.

3. 1 or 2

4. Warfarin/

5. ACENOCOUMAROL/

6. warfarin.ti,ab.

7. acenocoumarol.ti,ab.

8. nicoumalone.ti,ab.

9. phenindione.ti,ab.

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10. oral anticoagulant\$.ti,ab.
11. oral anti-coagulant\$.ti,ab.
12. or/4-11
13. 12 and 3
14. (systematic\$ adj review\$).ab.
15. review.pt.
16. meta-analysis.ab.
17. meta-analysis.pt.
18. meta-analysis.ti.
19. or/14-18
20. 13 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized controlled trials.sh.
24. random allocation.sh.
25. double blind method.sh.
26. single blind method.sh.
27. or/21-26
28. clinical trial.pt.
29. exp clinical trials/

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30. (clin\$ adj5 trial\$.ti,ab.

31. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.

32. placebos.sh.

33. placebo\$.ti,ab.

34. random\$.ti,ab.

35. or/28-34

36. 27 or 35

37. 13 and 36

38. 20 or 37

39. animal/

40. human/

41. 39 not (39 and 40)

42. 38 not 41

43. (letter or editorial or comment).pt.

44. 42 not 43

Question 23-24. Eplerenone

Medline 1966-Nov wk 3 2005 via Ovidweb

Search date: 29/11/05

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Update search: Nov wk 3 2005-May wk 5 2006

Search date: 13/06/06

1. exp MYOCARDIAL INFARCTION/
2. (infarct\$ or MI or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.
3. 1 or 2
4. eplerenone.ti,ab.
5. inspra.ti,ab.
6. 4 or 5
7. 3 and 6
8. Animals/
9. Humans/
10. 8 not (8 and 9)
11. 7 not 10
12. (letter or comment or editorial).pt.
13. 11 not 12

Question 15-18. Lipid lowering agents

Medline 1966-Dec wk 4 2005 via Ovidweb

Search date: 10/01/06

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Update search: Dec wk 4 2005-May wk 5 2006

Search date: 13/06/06

1. exp Myocardial Infarction/
2. (infarct\$ or MI or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.
3. 1 or 2
4. Hydroxymethylglutaryl-CoA Reductase Inhibitors/
5. SIMVASTATIN/
6. PRAVASTATIN/
7. (simvastatin or pravastatin or rosuvastatin or fluvastatin or atorvastatin).ti,ab.
8. statin\$1.ti,ab.
9. hmg-coa.ti,ab.
10. or/4-9
11. 3 and 10
12. (systematic adj review\$).tw.
13. (published adj studies).ab.
14. (data adj synthesis).tw.
15. (data adj extraction).ab.
16. meta-analysis/

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17. meta-analysis.ti,ab.
18. meta-analysis.pt.
19. or/12-18
20. comment.pt.
21. letter.pt.
22. editorial.pt.
23. or/20-22
24. 11 and 19
25. randomized controlled trial.pt.
26. controlled clinical trial.pt.
27. randomized controlled trials.sh.
28. random allocation.sh.
29. double blind method.sh.
30. single blind method.sh.
31. or/25-30
32. clinical trial.pt.
33. exp clinical trials/
34. (clin\$ adj5 trial\$).ti,ab.
35. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.
36. placebos.sh.

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37. placebo\$.ti,ab.

38. random\$.ti,ab.

39. or/32-38

40. 31 or 39

41. 11 and 40

42. 24 or 41

43. 42 not 24

44. animals/

45. humans/

46. 44 not (44 and 45)

47. 43 not 46

48. limit 47 to english language

49. limit 48 to yr="1999 - 2006"

50. Clofibrlic Acid/

51. Bezafibrate/

52. Procetofen/

53. Gemfibrozil/

54. (bezafibrate\$ or ciprofibrate\$ or fenofibrate\$ or gemfibrozil\$ or
fibrate\$).ti,ab.

55. Niacin/

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56. (niacin or nicotinic acid or acipimox).ti,ab.

57. ezetimibe.ti,ab.

58. or/50-57

59. 3 and 58

60. 59 not 46

61. 59 not 23

62. limit 61 to english language

63. 49 or 62

64. 19 and 62

65. 40 and 62

66. 65 or 64

67. 49 or 66

1.5.1 *Coronary revascularisation*

Question 26-27. What is the prognostic benefit of coronary revascularisation

Medline 1966-Jun wk 2 2005 via Ovidweb

Search date: 21/06/05

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1. exp myocardial infarction/
2. (acute coronary syndrome\$ or acs).ti,ab.
3. (infarct\$ or mi or heart attack\$ or heart arrest\$ or heart event\$).ti,ab.
4. or/1-3
5. exp myocardial revascularization/
6. (revascularisation or revascularization).ti,ab.
7. exp angioplasty, balloon/
8. (balloon adj2 (dilation or catheter\$ or transluminal)).ti,ab.
9. angioplasty.ti,ab.
10. (pci or ptca or ptcra).ti,ab.
11. coronary atherectomy/
12. atherectomy.ti,ab.
13. ((coronary or aortocoronary) adj2 bypass).ti,ab.
14. (cabg or stent\$).ti,ab.
15. stents/
16. or/5-15
17. 4 and 16
18. incidence/
19. Mortality/

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20. Follow-Up Studies/

21. prognos\$.ti,ab.

22. predict\$.ti,ab.

23. course.ti,ab.

24. or/18-23

25. 17 and 24

1.6 Lifestyle

Question 43,51. Regular physical activity

Medline 1966- Wk 3 Nov 2004 via Ovidweb

Search date: 29/11/04

Update search wk3 nov 2004- wk 4 may 2006

Search date: 06/06/06

1. Cardiovascular Diseases/pc, th, rh [Prevention & Control, Therapy, Rehabilitation]

2. Coronary Disease/pc, th, rh [Prevention & Control, Therapy, Rehabilitation]

3. exp Myocardial Infarction/

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4. ((myocardial or infarct\$ or MI or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.
5. or/1-4
6. *Exercise Therapy/
7. ((regular\$ or frequen\$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 exercise\$).ti,ab.
8. ((regular\$ or frequen\$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 physical\$ activ\$).ti,ab.
9. ((regular\$ or frequen\$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 physical training).ti,ab.
10. ((regular\$ or frequen\$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 formal training).ti,ab.
11. ((regular\$ or frequen\$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 aerobic\$).ti,ab.
12. ((phase 4 or phase-4 or phase IV or phase-IV or phase four or phase-four) adj3 (exercise\$ or physical\$ activ\$ or physical training or formal training or aerobic\$)).ti,ab.
13. ((intensive\$ or intensity) adj3 (exercise\$ or physical\$ activ\$ or physical training or formal training or aerobic\$)).ti,ab.
14. (duration adj3 (exercise\$ or physical\$ activ\$ or physical training or formal training or aerobic\$)).ti,ab.
15. (adherence adj3 (exercise\$ or physical\$ activ\$ or physical training or formal training or aerobic\$)).ti,ab.

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16. or/6-15
17. 5 and 16
18. (systematic\$ adj review\$).ab.
19. review.pt.
20. meta-analysis.ab.
21. meta-analysis.pt.
22. meta-analysis.ti.
23. or/18-22
24. 17 and 23
25. randomized controlled trial.pt.
26. controlled clinical trial.pt.
27. randomized controlled trials.sh.
28. random allocation.sh.
29. double blind method.sh.
30. single blind method.sh.
31. or/25-30
32. clinical trial.pt.
33. exp clinical trials/
34. (clin\$ adj5 trial\$).ti,ab.
35. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.

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36. placebos.sh.

37. placebo\$.ti,ab.

38. random\$.ti,ab.

39. or/32-38

40. 31 or 39

41. 17 and 40

42. 24 or 41

43. (letter or editorial or comment).pt.

44. 42 not 43

Question 44-45. Alcohol consumption

Medline 1966-Nov wk 3 2004 via Ovidweb

Search date: 23/12/04

Update search Nov wk 3 2004-May wk 4 2006

Search date: 05/06/06

1. Cardiovascular Diseases/pc, ep [Prevention & Control, epidemiology]
2. Coronary Disease/pc, ep [Prevention & Control, epidemiology]

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3. exp Myocardial Infarction/

4. ((myocardial or infarct\$ or MI or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.

5. or/1-4

6. alcohol drinking/

7. temperance/

8. (alcohol\$ adj2 (consum\$ or drink\$ or intake\$ or beverage\$ or abstinence or abstain\$)).ti,ab.

9. (drink\$ adj2 (non or low or lower or light or occasional\$ or moderat\$ or regular\$ or heavy or heavily)).ti,ab.

10. (temperance or intemperance or teetotal\$).ti,ab.

11. or/6-10

12. 5 and 11

13. (systematic\$ adj review\$).ab.

14. review.pt.

15. meta-analysis.ab.

16. meta-analysis.pt.

17. meta-analysis.ti.

18. or/13-17

19. 12 and 18

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20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized controlled trials.sh.
23. random allocation.sh.
24. double blind method.sh.
25. single blind method.sh.
26. or/20-25
27. clinical trial.pt.
28. exp clinical trials/
29. (clin\$ adj5 trial\$).ti,ab.
30. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.
31. placebos.sh.
32. placebo\$.ti,ab.
33. random\$.ti,ab.
34. or/27-33
35. 26 or 34
36. 12 and 35
37. 19 or 36
38. (letter or editorial or comment).pt.
39. 37 not 38

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Question 41-42. Changing dietary regime

Medline 1966- Nov wk 3 2004 via Ovidweb

Search date: 24/11/04

Update search: Nov wk 3 2004-May wk 4 2006

Search date: 05/06/06

1. Cardiovascular Diseases/pc, dh [Prevention & Control, Diet Therapy]
2. Coronary Disease/dh, pc [Diet Therapy, Prevention & Control]
3. exp Myocardial Infarction/
4. ((myocardial or infarct\$ or MI or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.
5. or/1-4
6. Diet, Fat-Restricted.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. ((reduc\$ or modify or modification or low or lower\$ or decreas\$) adj2 fat\$1).ti,ab.
8. DIET, FAT-RESTRICTED/
9. Fish Oils/

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10. Fatty Acids, Omega-3/
11. ((oily or oil or oils or fatty) adj fish).ti,ab.
12. (omega-3 or omega 3 or n-3 fatty acid\$ or n-3 polyunsaturated fatty acid\$ or pufa).ti,ab.
13. rapeseed oil\$.ti,ab.
14. ANTIOXIDANTS/ad, tu
15. dietary fiber/
16. Folic acid/ad, tu
17. ((antioxidant\$ or anti-oxidant\$ or folate\$) adj (vitamin\$ or supplement\$)).ti,ab.
18. ((fruit\$ or vegetable\$ or fibre\$ or fiber\$ or folate\$) adj3 (high\$ or increas\$)).ti,ab.
19. (mediterranean adj2 diet\$).ti,ab.
20. Diet, Mediterranean/
21. Phytosterols/
22. (phytosterols or plant sterols or stanol esters).ti,ab.
23. ((low\$ or reduc\$ or decreas\$ or modify or modification) adj2 (glycemic diet\$ or glycaemic diet\$)).ti,ab.
24. ((cardioprotect\$ or cardio-protect\$) adj2 diet\$).ti,ab.
25. (diet\$ adj3 (advice or advis\$ or inform\$ or guide\$ or guidance or educat\$)).ti,ab.

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26. (nutrition\$ adj3 (advice or advis\$ or inform\$ or guide\$ or guidance or educat\$)).ti,ab.

27. or/6-26

28. 5 and 27

29. (systematic\$ adj review\$).ab.

30. review.pt.

31. meta-analysis.ab.

32. meta-analysis.pt.

33. meta-analysis.ti.

34. or/29-33

35. 28 and 34

36. randomized controlled trial.pt.

37. controlled clinical trial.pt.

38. randomized controlled trials.sh.

39. random allocation.sh.

40. double blind method.sh.

41. single blind method.sh.

42. or/36-41

43. clinical trial.pt.

44. exp clinical trials/

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45. (clin\$ adj5 trial\$).ti,ab.
46. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.
47. placebos.sh.
48. placebo\$.ti,ab.
49. random\$.ti,ab.
50. or/43-49
51. 42 or 50
52. 28 and 51
53. Epidemiologic Studies/
54. exp case control studies/
55. exp cohort studies/
56. case control.tw.
57. (cohort adj (study or studies)).tw.
58. ((followup or follow-up) adj (study or studies)).tw.
59. ((incidence or concurrent) adj (study or studies)).tw.
60. longitudinal.tw.
61. retrospective.tw.
62. cross sectional.tw.
63. Cross-Sectional Studies/
64. cohort analy\$.tw.

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65. or/53-64

66. 28 and 65

67. 35 or 52 or 66

68. (editorial or comment or letter).pt.

69. 67 not 68

70. animals/

71. humans/

72. 70 not (70 and 71)

73. 69 not 72

1.7 Cardiac Rehabilitation

Question 30-32. Comprehensive cardiac rehabilitation or exercise only rehabilitation

Medline 1999-Nov wk 3 2004 via Ovidweb

Search date: 19/01/05

Update search Nov wk 3 2004-may wk 4 2006

Search date: 06/06/06

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1. CARDIOVASCULAR DISEASES/
2. CORONARY DISEASE/
3. exp MYOCARDIAL INFARCTION/
4. ((myocardial or infarct\$ or mi or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.
5. or/1-4
6. exp Rehabilitation/
7. "Recovery of Function"/
8. activities of daily living/
9. exercise/
10. exercise therapy/
11. rehabilitat\$.ti,ab.
12. (exercise\$ adj2 (rehabilitat\$ or therap\$ or training or program\$ or activit\$ or toleran\$ or prescribe\$ or prescription\$ or structure\$ or unstructure\$ or un-structure\$ or supervise\$ or unsupervise\$ or un-supervise\$ or guided or unguided or dynamic or regime\$)).ti,ab.
13. (physical adj2 (exercise\$ or educat\$ or training or program\$ or activit\$ or regime\$)).ti,ab.
14. (aerobic\$ adj2 (exercise\$ or training or program\$ or activit\$ or regime\$)).ti,ab.
15. (strength\$ adj (exercise\$ or training)).ti,ab.
16. (endurance adj (exercise\$ or training)).ti,ab.

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17. (fitness adj2 (training or program\$ or regime\$)).ti,ab.
18. ((resistance or resistive) adj (exercise\$ or training)).ti,ab.
19. (isometric adj2 (exercise\$ or training or program\$ or activit\$ or regime\$)).ti,ab.
20. ((high\$ frequency or low\$ frequency) adj2 (exercise\$ or training or program\$ or activit\$ or regime\$)).ti,ab.
21. ((high\$ intensi\$ or low\$ intensi\$) adj2 (exercise\$ or training or program\$ or activit\$ or regime\$)).ti,ab.
22. Managed Care Programs/
23. ((multifactor\$ or multifacet\$ or managed care) adj program\$).ti,ab.
24. or/6-23
25. 5 and 24
26. (systematic\$ adj review\$).ab.
27. review.pt.
28. meta-analysis.ab.
29. meta-analysis.pt.
30. meta-analysis.ti.
31. or/26-30
32. 25 and 31
33. (letter or editorial or comment).pt.
34. animals/

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35. humans/

36. 34 not (34 and 35)

37. 32 and 36

38. 37 not 33

Question 33. Safety in the exercise component of comprehensive cardiac rehabilitation

Medline 1966-Jan wk 3 2005 via Ovidweb

Search date: 29/01/05

Update search: Jan wk 3 2005-May wk 4 2006

Search date: 06/06/06

1. CARDIOVASCULAR DISEASES/rh [Rehabilitation]

2. CORONARY DISEASE/rh [Rehabilitation]

3. exp MYOCARDIAL INFARCTION/rh [Rehabilitation]

4. ((myocardial or infarct\$ or mi or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.

5. or/1-4

6. exercise/

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7. exercise therapy/

8. exercise tolerance/

9. (exercise\$ adj2 (rehabilitat\$ or therap\$ or training or program\$ or activit\$ or toleran\$ or prescribe\$ or prescription\$ or structure\$ or unstructure\$ or un-structure\$ or supervise\$ or unsupervise\$ or un-supervise\$ or guided or unguided or dynamic or regime\$)).ti,ab.

10. (physical adj2 (exercise\$ or educat\$ or training or program\$ or activit\$ or regime\$)).ti,ab.

11. (aerobic\$ adj2 (exercise\$ or training or program\$ or activit\$ or regime\$)).ti,ab.

12. (strength\$ adj (exercise\$ or training)).ti,ab.

13. (endurance adj (exercise\$ or training)).ti,ab.

14. (fitness adj2 (training or program\$ or regime\$)).ti,ab.

15. ((resistance or resistive) adj (exercise\$ or training)).ti,ab.

16. (isometric adj2 (exercise\$ or training or program\$ or activit\$ or regime\$)).ti,ab.

17. ((high\$ frequency or low\$ frequency) adj2 (exercise\$ or training or program\$ or activit\$ or regime\$)).ti,ab.

18. ((high\$ intensi\$ or low\$ intensi\$) adj2 (exercise\$ or training or program\$ or activit\$ or regime\$)).ti,ab.

19. or/6-18

20. safety/

21. risk/

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22. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.

23. (negative adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.

24. (undesirable adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.

25. (safe or safety or safely).ti,ab.

26. ((high or higher or greater or increas\$ or rise or raise or raising) adj risk).ti,ab.

27. or/20-24

28. 5 and 19 and 27

29. (letter or editorial or comment or case report).pt.

30. 28 not 29

31. Animals/

32. Humans/

33. 31 not (31 and 32)

Question 34. Individualised comprehensive cardiac rehabilitation

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Medline 1966-Feb wk 4 2005 via Ovidweb

Search date: 08/03/05

Update search: Feb wk 4 2005-May wk 4 2006

Search date: 06/06/06

1. cardiovascular diseases/
2. Coronary Disease/
3. exp myocardial infarction/
4. ((myocardial or infarct\$ or mi or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.
5. or/1-4
6. ((individualis\$ or individualiz\$) adj3 (exercise\$ or rehabilit\$)).ti,ab.
7. (tailor\$ adj3 (exercise\$ or rehabilit\$)).ti,ab.
8. ((menu-based or menubased) adj3 (exercise\$ or rehabilit\$)).ti,ab.
9. (personalis\$ adj3 (exercise\$ or rehabilit\$)).ti,ab.
10. (personaliz\$ adj3 (exercise\$ or rehabilit\$)).ti,ab.
11. or/6-10
12. 5 and 11

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1.7.1 Patient Engagement

Question 40. Patient engagement in comprehensive cardiac rehabilitation

Medline 1966-April wk 4 2005 via Ovidweb

Search date: 07/04/05

Update search April wk 4 2005-May wk 4 2006

Search date: 06/06/06

1. CARDIOVASCULAR DISEASES/
2. CORONARY DISEASE/
3. exp MYOCARDIAL INFARCTION/
4. ((myocardial or infarct\$ or mi or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.
5. or/1-4
6. exp Rehabilitation/
7. "Recovery of Function"/
8. activities of daily living/
9. exercise therapy/
10. (exercise\$ adj3 (rehabilitat\$ or therap\$ or training or program\$)).ti,ab.

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11. rehabilitat\$.ti,ab.
12. Managed Care Programs/
13. ((multifactor\$ or multifacet\$ or managed care) adj program\$.ti,ab.
14. or/6-13
15. (enrollment or enrolment or enrolling or enrolling).ti,ab.
16. participat\$.ti,ab.
17. motivation\$.ti,ab.
18. uptake.ti,ab.
19. referral.ti,ab.
20. (compliance or adherence).ti,ab.
21. (attend\$ or non-attend\$).ti,ab.
22. barrier\$.ti,ab.
23. (engaging or engagement).ti,ab.
24. health services accessibility/
25. Patient Compliance/
26. "Referral and Consultation"/
27. Patient Satisfaction/
28. patient participation/
29. Self Efficacy/
30. Motivation/

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31. or/15-30

32. 5 and 14 and 31

1.7.2 Education & Information

Question 35. Education & information needs of patients

Medline 1966-Feb wk 2 2005 via Ovidweb

Search date: 23/02/05

Update search: Feb wk 2 2005-May wk 5 2006

Search date: 08/06/06

1. Cardiovascular Diseases/nu, pc, rh [nursing, prevention & control, rehabilitation]
2. Coronary Disease/nu, pc, rh [nursing, prevention & control, rehabilitation]
3. exp myocardial infarction/
4. ((myocardial or infarct\$ or mi or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.
5. or/1-4
6. Health Knowledge, Attitudes, Practice/
7. Patient Education/

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8. teaching materials/
9. audiovisual aids/
10. counseling/
11. (Patient adj2 (education\$ or information or knowledge)).ti,ab.
12. ((information or education\$) adj (need or needs)).ti,ab.
13. ((information or education\$) adj (provision or provide or providing or require\$)).ti,ab.
14. (learning adj (need or needs)).ti,ab.
15. (rehab\$ adj2 (information or education\$ or guidance)).ti,ab.
16. (health adj2 (advice or information or guidance)).ti,ab.
17. ((needed or wanted) adj information).ti,ab.
18. ((medicat\$ or diet\$ or physical\$ or activit\$ or exercise\$ or lifestyle\$ or life-style\$) adj2 (information or advice)).ti,ab.
19. (information adj support\$).ti,ab.
20. (cardiac patient learning needs or cplni).ti,ab.
21. (education\$ adj (class or classes)).ti,ab.
22. ((teaching or education\$) adj (material\$ or program\$ or intervention\$ or session\$ or group or groups or individual\$ or one to one or one-to-one)).ti,ab.
23. (counseling or counselling).ti,ab.
24. ((pamphlet\$ or booklet\$ or leaflet\$ or video\$ or cassette\$ or audiotape\$ or audio-tape\$ or handout\$ or hand-out\$ or web or internet) adj2 (information or education\$)).ti,ab.

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25. or/6-24

26. 5 and 25

27. (systematic\$ adj review\$).ab.

28. review.pt.

29. meta-analysis.ab.

30. meta-analysis.pt.

31. meta-analysis.ti.

32. or/27-31

33. 26 and 32

34. randomized controlled trial.pt.

35. controlled clinical trial.pt.

36. randomized controlled trials.sh.

37. random allocation.sh.

38. double blind method.sh.

39. single blind method.sh.

40. or/34-39

41. clinical trial.pt.

42. exp clinical trials/

43. (clin\$ adj5 trial\$).ti,ab.

44. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.

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45. placebos.sh.

46. placebo\$.ti,ab.

47. random\$.ti,ab.

48. or/41-47

49. 40 or 48

50. 26 and 49

51. (letter or editorial or comment).pt.

52. 33 or 50

53. 52 not 51

1.7.3 *Psychological support*

Question 37. Psychological and social support for patients

Medline 1966-Feb wk 4 2005 via Ovidweb

Search date: 03/03/05

Update search Feb wk 4 2005-may wk 5 2006

Search date: 08/06/06

1. Cardiovascular Diseases/

2. Coronary Disease/

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3. exp Myocardial Infarction/
4. ((myocardial or infarct\$ or MI or heart attack or cardiovascular or coronary or cvd or chd or cardiac event\$) adj4 (prevent or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.
5. Counseling/
6. Cognitive Therapy/
7. Psychotherapy, Group/
8. Social Support/
9. Self-Help Groups/
10. (counselling or counseling).ti,ab.
11. ((Cognitive or cognition) adj2 (therap\$ or psychotherap\$)).ti,ab.
12. (group adj (therap\$ or psychotherap\$)).ti,ab.
13. cbt.ti,ab.
14. (social adj (support or network\$)).ti,ab.
15. ((Psychosocial or psychological\$) adj (support\$ or intervention\$ or treatment\$ or rehabilitation)).ti,ab.
16. ((carer or carers spouse or family or families or partner\$) adj2 support\$).ti,ab.
17. ((peer or peers or lay) adj2 support\$).ti,ab.
18. (emotional\$ adj support\$).ti,ab.
19. or/1-4

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20. or/5-18

21. 19 and 20

22. (systematic\$ adj review\$).ab.

23. review.pt.

24. meta-analysis.ab.

25. meta-analysis.pt.

26. meta-analysis.ti.

27. or/22-26

28. 21 and 27

29. randomized controlled trial.pt.

30. controlled clinical trial.pt.

31. randomized controlled trials.sh.

32. random allocation.sh.

33. double blind method.sh.

34. single blind method.sh.

35. or/29-34

36. clinical trial.pt.

37. exp clinical trials/

38. (clin\$ adj5 trial\$).ti,ab.

39. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).ti,ab.

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40. placebos.sh.

41. placebo\$.ti,ab.

42. random\$.ti,ab.

43. or/36-42

44. 35 or 43

45. 21 and 44

46. 28 or 45

47. (letter or editorial or comment).pt.

48. 46 not 47

49. limit 48 to english language

1.7.4 Sexual activity

Question 38. Interventions for sexual dysfunction

Medline 1966-Feb wk 4 2005 via Ovidweb

Search date: 08/03/05

Update search Feb wk 4 2005-May wk 5 2006

Search date: 08/06/06

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1. cardiovascular diseases/
2. coronary disease/
3. myocardial infarction/
4. ((myocardial or infarct\$ or mi or coronary or cardiovascular or chd or cvd or heart attack\$ or cardiac event\$) adj4 (prevent\$ or secondary or post or previous\$ or prior or history or follow\$)).ti,ab.
5. or/1-4
6. exp Sex Disorders/
7. Sexual Dysfunctions, Psychological/
8. libido/
9. ((sexual or psychosexual or psycho-sexual) adj (dysfunction\$ or problem\$ or difficult\$ or dissatisf\$ or concern\$ or disorder\$)).ti,ab.
10. (erectile adj (dysfunction\$ or disorder\$ or problem\$ or difficult\$ or concern\$)).ti,ab.
11. ((premature\$ or pre-mature\$) adj ejaculat\$).ti,ab.
12. (impoten\$ or frigidity or libido or dyspareunia).ti,ab.
13. (sexual adj (activit\$ or intercourse or satisfaction)).ti,ab.
14. coitus/
15. or/6-14
16. incidence/
17. Sex Counseling/

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18. (sildenafil or viagra).ti,ab.
19. piperazines/
20. phosphodiesterase inhibitors/
21. (phosphodiesterase adj3 inhibitor\$.ti,ab.
22. piperazines.ti,ab.
23. (counseling or counselling).ti,ab.
24. Relaxation Techniques/
25. (relaxation adj2 (technique\$ or training or therap\$)).ti,ab.
26. ((stress or anxiety or anxious\$) adj2 (manag\$ or treatment\$ or intervention\$ or control\$ or prevent\$)).ti,ab.
27. or/16-26
28. 5 and 15 and 27

Appendix F – 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)

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- 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

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Appendix G – Omega-3 fatty acids content of various oily fish required to provide approximately 1 g of EPA plus DHA per day

Omega-3 fatty acids (eicosapentaenoic acid, C20:5n-3 (EPA) and docosahexaenoic acid, C22:6n-3 (DHA) content of various oily fish required to provide approximately 1 g of EPA plus DHA per day.	
Fish	Amount required to provide approximately 1 g of EPA plus DHA per day (g)
Canned tuna	340
Fresh tuna	56-200
Herring	56
Mackerel	56-255
Salmon	56-85
Sardines	56-85
Trout	100
<p>Source: P.M. Kris-Etherton, W.S. Harris, L.J. Appel. "Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease." <i>Circulation</i>. 2002;106:2747.</p> <p>The intakes of fish given are very rough estimates because oil content can vary markedly with species, season, diet, packaging and cooking methods</p>	