Evidence-based Clinical Practice Guideline

Prophylaxis for patients who have experienced a myocardial infarction: drug treatment, cardiac rehabilitation and dietary manipulation.

North of England Evidence-based Guidelines Development Project

Centre for Health Services Research
University of Newcastle upon Tyne

Medicines Evaluation Group
Centre for Health Economics
University of York

Executive Summary

Ischaemic heart disease may be broadly defined to include myocardial infarction, angina, coronary atherosclerosis and heart failure: often these conditions coexist in patients. Ischaemic heart disease is the most common cause of death, accounting for about a quarter of all mortality in England and Wales. A general practitioner with a list of 2000 patients would expect on average 5 deaths, 12 hospitalisations and to have 50 patients making 130 primary care consultations for ischaemic heart disease each year. Epidemiological studies in patient populations following myocardial infarction feature post-hospital discharge mortality rates of 5-10% per year.

Evidence for treatments to prolong life in patients with prior myocardial infarction, and in those complicated by diabetes and heart failure have been reviewed and explored by the North of England Guideline Group.

Mortality rates are measured consistently in trials and a rigorous analysis of the propensity of the different treatments to improve survival has been possible. Although non-fatal myocardial infarction rates are often recorded, other important aspects of treatments including tolerability, side-effect profiles, influence upon quality-of-life and costs are less consistently reported in trials.

Interpreting the evidence from trials presents two difficulties. First, patients included in the trials of different drugs are at different levels of underlying risk of further ischaemic disease and death making comparisons of trial-based absolute gains in survival hard to interpret. Second, the findings of trials already have a drug sequence implicit in them; i.e. the trials do not present simple head-to-head comparisons of alternative treatments.

A ‘profile’ approach and a ‘modelling’ approach were used to explore the interpretation of trial findings. Although quite different in presentation and assumptions both support the inference that a range of treatments are both effective and cost-effective in patients with prior myocardial infarction when sequenced appropriately.

For patients with uncomplicated previous myocardial infarction, treatment should be offered to patients, initially with a beta-blocker and aspirin, and then with a statin and an ACE inhibitor. Referral for cardiac rehabilitation (with a substantial exercise component) should be offered, if not initiated, in hospital.

For patients with previous myocardial infarction and heart failure, treatment should be offered to patients, initially with ACE inhibitor, and then a beta-blocker. Patients with moderate to severe heart failure should additionally be offered spironolactone.

There is evidence to suggest value in a ‘Mediterranean diet’ in patients with prior myocardial infarction and insulin therapy in the post-acute phase in patients with diabetes, although it has not been possible to assess the cost-effectiveness of these interventions.

Recommendations

All recommendations are for patients who have survived a myocardial infarction and are made with the aim of decreasing subsequent premature mortality. **Recommendations for drug treatment are made assuming that clinicians will take account of both patient tolerability and compliance and the indications, contra-indications and cautions as listed in the British National Formulary (BNF) or Summary of Product Characteristics.** Within three of the drug groups discussed in this guideline (beta-blockers, ACE inhibitors, statins) not all drugs have a licence for the indications discussed in the guideline. To achieve the benefits described within this guideline, drugs should be used in dosages as close as possible to those used in the trials described.

In reaching treatment decisions clinicians will need to appropriately share the information within the guideline to allow patients to be appropriately informed about, and involved in, decision making about their care.

Strength of recommendations are:

A: directly based on category I evidence (meta-analysis of randomised controlled trials or at least one randomised controlled trial)

B: directly based on category II evidence (at least one controlled study without randomisation or one other type of quasi-experimental study) or extrapolated recommendation from category I evidence

C: directly based on category III evidence (non-experimental descriptive studies) or extrapolated recommendation from category I or II evidence

D: directly based on category IV evidence (expert committee reports or opinions and/or clinical experience of respected authorities) or extrapolated recommendation from category I, II or III evidence

Drug treatment

Patients with prior myocardial infarction who do not have heart failure

Which drugs?

- All patients should be offered long term treatment firstly with a beta-blocker and an antiplatelet drug (aspirin), and then with a statin and an ACE inhibitor. This sequencing of initiation reflects the evidence from trials and estimates of cost-effectiveness (A). Not all ACE inhibitors or statins have a licence for this indication.

- The precise lower limit of the level of cholesterol that should be treated is unclear. Across the statin trials considered, the lower limit of the range of cholesterol values defining entry into the trials varied; one large trial enrolled patients with serum cholesterols down to 4 mmol/l. Licence indications currently suggest a lower limit of 4.8 mmol/l or 5.5 mmol/l depending on the drug used. (D).

- Beta-blockers and ACE inhibitors will also be considered for the management of symptoms (e.g. in stable angina) or risk factors (e.g. hypertension) (D).

- Calcium channel blockers, nitrates, and potassium channel activators have no effect on premature mortality making their role the management of symptoms and risk factors (principally hypertension) (A). They should therefore only be used in those patients who are intolerant of beta-blockers and ACE inhibitors (D). Given their effect on non-fatal myocardial infarction, verapamil or diltiazem should then be considered initially (B). Subsequent necessary treatment with other calcium channel blockers, nitrates or potassium channel activators is then appropriate (D).

When to start drug treatment

The recommended starting points for drug treatments are based on the initiation points in the trials.

- Beta-blockers, antiplatelet drugs (aspirin) and ACE inhibitors should be initiated whilst patients are in hospital as there is evidence to support benefit following early initiation. If this does not happen then primary care clinicians should initiate them as soon after discharge as possible (A).

- Although there is no evidence of the long-term benefit from the use of statins initiated prior to 12 weeks post-infarct, many patients will have been taking statins prior to admission or will have them initiated in hospital. All patients discharged from hospital who are not already taking a statin should be assessed and have treatment initiated 12 weeks after a myocardial infarction (A).

Monitoring treatment

- Patients being considered for treatment with a statin should have an initial serum cholesterol measurement both to exclude familial lipid disorders and to identify those patients with a serum cholesterol level that does not need treating. Once these have been excluded, further measurement allows an assessment of response to treatment and informs the assessment of compliance with treatment. The frequency of such monitoring is unclear; the National Service Framework for Coronary Heart Disease suggests annually. (D)

- Patients being considered for treatment with ACE inhibitors should have their renal function checked prior to initiation and after each significant dose increase. (D)

Continuation of treatment

- Based on the evidence from the trials, treatment should continue long term (D).

- The treatment durations, for which there is at least one trial that provides direct support, are three and a half years for antiplatelet drugs (aspirin), four years for beta-blockers and ACE inhibitors and six years for statins. In the absence of a clear reason to stop treatment it seems reasonable to continue treatment indefinitely (D).

Patients with prior myocardial infarction who have diabetes

- There is evidence that intensive insulin therapy initiated soon after admission for acute myocardial infarction reduces mortality (B). To achieve the benefits demonstrated in the single trial in this area involves 4 daily insulin injections continuing for at least three months (B).

Patients with prior myocardial infarction and heart failure

- Patients with prior myocardial infarction and heart failure are a relatively ill group of patients and care is required when initiating drug treatments (D).

- All patients should be offered long term treatment with an ACE inhibitor and then a beta-blocker (not all beta-blockers have a licence for this indication). In addition they should be treated with an antiplatelet drug (aspirin). Patients who have moderate or severe heart failure (New York Heart Association (NYHA) grade 3 or 4) should be treated with spironolactone. All of these treatments are cost effective (A).

- Patients are likely to continue to need symptomatic treatment with a loop diuretic (D). In patients with mild symptoms of heart failure (NYHA grade 1 or 2) it is unclear whether spironolactone decreases premature mortality. It may represent a reasonable choice of adjuvant symptomatic therapy (D).

- As patients with heart failure were almost always excluded from trials there is no evidence on which to recommend the use of statins in such patients. Statin use will be influenced by clinical and practical considerations, such as whether patients were treated with them prior to developing heart failure (D).

When to start drug treatment

The recommended starting points for drug treatments are based on the initiation points in the trials.

- ACE inhibitors and antiplatelet drugs (aspirin) should be initiated whilst patients are in hospital as there is evidence to support benefit following early initiation. If this does not happen then primary care clinicians should initiate them as soon after discharge as possible (A).

- Beta-blockers can be initiated at any point. Treatment should start with low doses and should be slowly increased, for example at fortnightly intervals, over a period of up to 12 weeks (A).

- Given the limited experience initiating beta-blockers it is currently unclear whether this can be done safely in primary care. Whilst the BNF recommends hospital supervision it seems possible that there are a group of patients with heart failure for whom general practitioners (based on their knowledge of the patient's clinical condition) may feel able to initiate treatment in primary care. Unfortunately the characteristics of this patient group are not currently clear. Discussion at a local level may inform appropriate methods of treatment initiation (D).

- Spironolactone can be initiated at any point. In patients with moderate to severe symptoms of heart failure (NYHA grade 3 or 4), given the time involved in achieving full dosages of beta-blockers, it seems reasonable to consider initiating spironolactone before beta-blockers (D).

Monitoring treatment

- Patients being considered for treatment with ACE inhibitors should have their renal function checked prior to initiation and after each significant dose increase (D).

- Patients being treated with spironolactone should have their serum potassium monitored (D).

Continuation of treatment

- Based on the evidence from the trials, treatment should continue long term (D). The treatment durations, for which there is at least one trial that provides direct support, are three and a half years for ACE inhibitors, two and a half years for beta-blockers and two years for spironolactone. In the absence of a clear reason to stop treatment it seems reasonable to continue treatment indefinitely (D).

Non-drug treatment

Rehabilitation

- Patients should be offered enrolment in a rehabilitation programme that has a prominent exercise component within it (A). Although many of the trials imposed upper age limits for recruitment, the guideline development group felt that in a service setting it was more appropriate to be guided by functional ability and patient preference (D).

Diet

- Given the nature of the available evidence of the effectiveness of dietary manipulation as a strategy for secondary prophylaxis it is not possible to recommend specific dietary manipulation (B).

Preface

This document describes the methods, process and recommendations of the North of England Evidence-based Guideline on the primary care management of patients who have survived a myocardial infarction. It describes explicitly the evidence used to support each recommendation made, and is intended to form the source document from which summaries can be drawn for use in daily practice.

We have continued to develop our methods of guideline development and faced particular complexities when tackling this guideline due to its broad clinical scope. We have continued to adapt meta-analysis and cost-effectiveness concepts to the task.

This guideline was developed over a period of 12 months between March 1999 and February 2000. The group members committed both time and enthusiasm to the task and we are immensely grateful to them for this. Guidelines evoke differing responses. However, we intend this guideline to be viewed in the following way:

Medical practitioners should regard this guideline as a useful reference tool: not the rulings of philosopher kings, but the attempt of thoughtful people to share their knowledge - albeit imperfect - with other people.[*]

[*] Adapted from:

Tong, R. The epistemology and ethics of consensus: uses and misuses of 'ethical' expertise. *Journal of Medicine and Philosophy* 1991;16**:**409-426.

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Methods

Aim of the guideline

The aim of this guideline is to provide evidence-based recommendations to guide health care professionals in the appropriate primary care management of secondary prophylaxis for patients who have previously experienced a myocardial infarction (MI).

The development group assumes that health care professionals will use general medical knowledge and clinical judgement in applying the general principles and specific recommendations of this document to the management of individual patients. Recommendations may not be appropriate for use in all circumstances. Decisions to adopt any particular recommendation must be made by the practitioner in the light of circumstances presented by individual patients and available resources. In reaching treatment decisions clinicians will need to appropriately share the information within the guideline to allow patients to be appropriately informed about, and involved in, decision making about their care.

Within this guideline we have (in the appendices) reported the diagnostic criteria used in studies included in our review to allow clinicians to judge how closely these apply to the individual patients whom they will manage.

This guideline is concordant with the National Service Framework (NSF) for Coronary Heart Disease. It provides a firm evidence base for clinical actions and for the principles of relevant audit criteria within the NSF. By its nature, the NSF specifies the audit criteria to a greater level of detail than the guideline. The recommendations within the guideline differ from the content of the NSF only in the area of initiating statins where the guideline offers recommendations based strictly on the evidence.

Responsibility and support for guideline development

Source of funding

The Department of Health of England and Wales funded the development of this guideline.

Guideline development group

The guideline development group was composed of four types of members: relevant health care professionals; a patient/carer representative; specialist resources; and a specialist small-group leader.

It was important that the health care professionals represented the appropriate sectors (Russell et al., 1993). The sectors approached were general practitioners, cardiologists, nurses and health authority representatives. These group members were invited to ensure adequate relevant discussion of the evidence, of areas where there was no evidence, and of the subsequent recommendations in the guideline. Unfortunately, the nurse member of the group was unable to attend the first three meetings and left the group.

The research team consisted of the specialist resources (NF and JM) and the development group leader (ME). The specialist resources were a health services researcher and a health economist. The research team was responsible for reviewing and summarising the literature on clinical effectiveness, safety, quality of life and health economics and feeding this information back to the group. The group leader had the role of ensuring that the group worked effectively. The research team was responsible for the drafting of the guideline and the resourcing of the guideline development group.

The members of the development group were (in alphabetical order):

John Cleland	*Professor of Cardiology, Castle Hill Hospital, Hull*
Martin Eccles	*Professor of Clinical Effectiveness, University of Newcastle upon Tyne, and small group leader*
Nick Freemantle	*Reader in Epidemiology & Biostatistics, University of York and Specialist Resource*
Eve Knight	*British Cardiac Patients' Association, Bromley, Kent*
Keith MacDermott	*General Practitioner, York*
James Mason	*Senior Research Fellow, University of York and Specialist Resource*
Basil Penney	*General Practitioner, Darlington, Co Durham*
Colin Pollock	*Medical Director, Wakefield Health Authority*
Wendy Ross	*General Practitioner, Walker, Newcastle upon Tyne*
Jane Skinner	*Consultant Community Cardiologist, Royal Victoria Infirmary, Newcastle*
Malcolm Thomas	*General Practitioner, Guide Post, Northumberland*

The group met on seven occasions during a weekday afternoon. All group members were offered reimbursement for their travelling expenses and locum costs.

Declaration of Competing Interest

The following people have declared no competing interests in relation to the guideline. Martin Eccles, Eve Knight, Keith MacDermott, Basil Penney, Malcolm Thomas.

The following competing interests were declared.

John Cleland has received honorariums and money for research from a number of companies who make beta-blockers and ACE inhibitors. He is about to embark upon a study funded by the Veterans Administration comparing Warfarin, Aspirin and Clopidogrel in patients with Heart Failure and is on the Steering Committee of this study.

Nick Freemantle has held an unrestricted grant from SmithKline Beecham to investigate the effectiveness of beta-blockers in secondary prevention. He is advising Servier Laboratories on the design and conduct of a randomised trial of ACE inhibitors in elderly people with diastolic heart failure. He holds a grant from Servier Laboratories for data management and analysis of a large European survey on the treatment of heart failure. He holds a grant from Orion Pharma/Abbott Pharmaceuticals, who have an investigational inotropic agent. Has held a number of grants from the Department of Health on the investigation of cardiovascular drugs and their implementation in practice.

James Mason has worked for several companies who manufacture drugs for cardiovascular disease, either as an invited speaker or consultant. None of the work was in the field of cardiovascular disease. Has been involved in a variety of projects funded by the Department of Health.

Colin Pollock has been involved on a paid consultancy basis on an NHS Advisory Panel for Janssen-Cilag. Has also, on an ad hoc consultancy basis, provided advice to Ted Butler Associates which is an independent healthcare research company which often works with most major pharmaceutical industry companies in the UK.

Wendy Ross is a member of the Newcastle & North Tyneside District Drug & Therapeutics Committee, which is responsible for developing the district formulary.

Jane Skinner has received a fee from a journal to write a review of post MI care.

Additional Staff

The following personnel made a substantial contribution to the functioning of the guidelines development group and to the development of the practice guideline. They are listed in alphabetical order:

Anne Burton	*Administrative support, University of York*
Jane Harrison	*Designing and implementing electronic searches, University of York*

Evidence identification and overview

The search strategy

The aim of this review was to identify and synthesise relevant published and unpublished evidence to allow recommendations to be evidence-based wherever possible (West, 1992). The search was carried out using the electronic databases MEDLINE, EMBASE, SIGLE and the Cochrane Controlled Trial Register, attempting to locate systematic reviews and meta-analyses, randomised trials, quality of life studies and economic studies using a combination of subject heading and free text searches. We made extensive use of high quality recent review articles and bibliographies, as well as contact with subject area experts. New searches were concentrated in areas of importance to the guideline development process, for which existing systematic reviews were unable to provide valid or up to date answers. The expert knowledge and experience of group members also backed up the search strategy.

Electronic searches used an optimally sensitive search strategy based on a combination of text and index terms to locate randomised trials of treatments relevant to the guideline. Where data necessary for our analyses, or which described the context of a trial, were not reported, we wrote to authors and sponsoring agencies (predominantly the pharmaceutical industry), reminding non-responders after approximately one month. We are most grateful to investigators and sponsors who provided unpublished information to aid our work.

Overview of the literature

Once the clinical questions had been identified by the guidelines development group, we assessed the quality of relevant studies retrieved and their ability to provide valid answers. Assessment of study quality concentrated on questions of internal validity (the extent to which the study measured what it intended to measure), external validity (the extent to which study findings could be generalised to other treatment settings) and construct validity (the extent to which measurement corresponded to theoretical understanding of a disease) (Cook & Campbell 1979). The specific dimensions of quality examined in each study are reported below (Eccles et al 1998a).

Quality Criteria for Randomised Trials

Appropriateness of inclusion and exclusion criteria
Concealment of allocation
Blinding of Patients
Blinding of Health Professionals
Objective/ blind method of data collection
Valid/ blind method of data analysis
Completeness and length of follow up
Appropriateness of outcome measures
Statistical power of results

Once individual papers had been checked for methodological rigour and clinical significance, the information was synthesised. Pharmaceutical studies often have an insufficient sample size to identify significant outcomes with confidence (Bland 1985), so where appropriate, the results of randomised studies were combined using meta-analytic techniques (DerSimonian & Laird 1986; Smith et al 1995). Papers were categorised according to study design, reflecting susceptibility to bias. Questions were answered using the best evidence available. When considering a question of the effect of an intervention, if the question could be answered by category I evidence provided by a meta-analysis or randomised controlled trial, then studies of weaker design (controlled studies without randomisation) were not reviewed. Where studies were of poor quality, or contained patient groups considered *a priori* likely to have different responses, the effects of inclusion or exclusion were examined in sensitivity analyses. No trials that met our inclusion criteria were excluded from the primary analyses. However, where data on relevant outcomes included were not available, these studies could not be incorporated, thus leading to the potential for publication bias.

Evidence categories were adapted from the US Agency for Health Care Policy and Research Classification (AHCPR, 1992). This categorisation is most appropriate to questions of causal relationships. Potentially, six categories are available:

Categories of evidence

Ia:	evidence from meta-analysis of randomised controlled trials
Ib:	evidence from at least one randomised controlled trial
IIa:	evidence from at least one controlled study without randomisation
IIb:	evidence from at least one other type of quasi-experimental study
III:	evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV:	evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Strength of recommendation

Recommendations were graded A to D as shown below. The guideline distinguishes between the category of evidence and the strength of the associated recommendation. It is possible to have methodologically sound (category I) evidence about an area of practice that is clinically irrelevant or has such a small effect that it is of little practical importance and would attract a lower strength of recommendation. More commonly, a statement of evidence would only cover one part of an area in which a recommendation has to be made or would cover it in a way that conflicts with other evidence. In order to produce comprehensive recommendations, the group had to extrapolate from the available evidence. This may lead to weaker levels of recommendation (B, C or D) based upon evidence category I statements. It is not assumed that guideline group members will always be able to reach

agreement on the interpretation of research evidence, and the nature of such disagreement is reflected in the text of the guideline.

Strength of recommendation

A	directly based on category I evidence
B	directly based on category II evidence **or** extrapolated recommendation from category I evidence
C	directly based on category III evidence **or** extrapolated recommendation from category I or II evidence
D	directly based on category IV evidence **or** extrapolated recommendation from category I, II or III evidence

Areas without evidence

It was accepted that there would be areas without evidence where recommendations had to be made and that consensus would be required to deal with these areas. Where this process identified important unanswered research questions, these were recorded at the end of the relevant section of the guideline.

Describing results: binary outcomes

Meta-analysis of binary data, such as the number of deaths in a randomised trial, enables the results of a group of trials to be expressed in a number of ways. These are primarily odds ratios, risk ratios (also known as relative risks) and risk differences. If binary data on mortality from a trial are expressed in a 2x2 table:

	Dead	Alive
Intervention Group	A	B
Control	C	D

Odds ratios are defined as: $\frac{A}{B} \Big/ \frac{C}{D}$

In other words, the odds ratio is the odds of death in the intervention group (number of deaths divided by the number of survivors) divided by the odds of death in the control group.

Risk Ratios are defined as: $\frac{A}{A+B} \Big/ \frac{C}{C+D}$

The risk ratio is the risk of death in the intervention group (number of deaths in the intervention group divided by the total number allocated to the intervention) divided by the risk of death in the control group. Trials sometimes refer to relative risk reductions (RRRs) which are calculated as one - Risk Ratio.

Risk Differences are defined as: $\frac{A}{A+B} - \frac{C}{C+D}$

The Risk Difference is the risk of death in the intervention group (number of deaths in the intervention group divided by the total number allocated to the intervention) minus the risk of death in the control group.

Worked Example:

In a trial of an ACE inhibitor in patients with heart failure there were 452 deaths among 1,285 patients randomised to receive enalapril, and 510 deaths among 1,284 allocated to control at endpoint (SOLVD, 1991). In a two x two table this is:

SOLVD	Dead	Alive
Intervention Group	452	833
Control	510	774

providing an odds ratio of 0.82, a risk ratio of 0.89, and a risk difference of -0.045 (or a 4.5% reduction in the risk of death).

Each measure has advantages and disadvantages. The *Odds Ratio* is a statistically robust measure, but is hard to interpret clinically. The *Risk Ratio* is superficially easier to interpret, and both odds ratios and risk ratios may be particularly useful when attempting to combine studies which are estimating the same common underlying effect, but in which both severity of condition and length of follow up may vary substantially. This is because *Risk Ratios* and *Odds Ratios* express the relationship between rates, rather than those rates in absolute terms. Neither measure is sufficient for clinical decision making alone: an odds ratio or risk ratio apparently showing a large effect from an intervention will not lead to large benefits in practice where the events are rare, and an apparently small effect may have a substantial impact where events are very common. Odds ratios and 95% confidence intervals for individual trials cannot be estimated where there are no events in either the intervention or control groups. Although such studies are not included in figures, they are included in the estimation of overall pooled results using meta-analysis (Smith et al 1995).

Risk Differences are not very helpful for exploring common underlying effects, but are very useful for describing the practical importance of the effects of an intervention in practice. Similarly, *Number Needed to Treat* (NNT) is used to describe absolute benefits (NNT is simply the inverse of the risk difference) and is an expression for the number of patients that would have to receive the treatment of interest to achieve, all things being equal, the benefit described in the trial or meta-analysis. A standard problem with the risk difference and number needed to treat is that they are often derived from trials that have different lengths of follow up. One of the main potential advantages of the risk difference is that it enables the practical value of interventions to be assessed and compared with alternative treatment strategies. Thus the incidence risk difference is used to estimate treatment effects across a common time frame, for example the number of deaths avoided as a result of treating 1,000 patients for a year (Freemantle et al, 2000).

A *Confidence Interval* (CI) for a treatment effect estimated in a trial is the interval in which the underlying population treatment effect is assumed to lie, with a specified probability. The specified probability is arbitrary: 95% is the most commonly chosen value, meaning that the true underlying treatment effect is assumed to lie within the interval 19 times out of 20. In figures describing groups of studies combined by meta-analysis, the point estimate of effect from each study is indicated, as are the 95% confidence intervals which are denoted by horizontal lines; the shorter the line, the narrower the confidence intervals and the greater the precision of measurement in the study. The best and most likely estimate of effect is the point estimate at the centre of the confidence interval range.

Binary versus continuous outcomes

Often, in randomised clinical trials, the effectiveness of treatments can best be expressed by a binary outcome; for example alive or dead. In these cases odds ratios are useful for describing underlying treatment effects, and risk differences or numbers needed to treat are useful for describing the absolute size of the effect of treatment in the trial populations. However, many outcomes are not amenable to this binary approach, and are better considered as continuous measures.

Meta-analysis of continuous data

Meta-analysis of continuous data can provide particular challenges. The approach of dichotomising data that are naturally continuous (for example into treatment failures and successes) is to be

discouraged. It is often arbitrary, may result in pooling different scores based on different cut-offs in different studies or cut-offs that have been identified with knowledge of the data and thus show the data in a particular light. Similarly, it may exaggerate small differences in effect, and more fundamentally the approach explains the data poorly.

Standardisation

Where studies use a common outcome measure, meta-analysis can combine these to calculate a summary weighted mean difference comparing treatment and control groups. When there are concerns that measurement between studies is not undertaken using a common metric, standardised scores are calculated for each trial. Examples might be where different but related instruments are used to estimate the same common underlying effect in patients with schizophrenia, or where there is likelihood of poor inter-rater reliability in the use of instruments. The approach, advocated by Hedges (Hedges & Olkin 1985, Hedges 1992), in which the standard deviation for each study is based upon a weighted mean of the intervention and control group variances, is used.

Studies examining different doses

Sometimes trials examine multiple dose regimens compared with a single control group. These phase II or early phase III trials were designed to examine the most appropriate dosage of a drug and may include several groups that received doses within the range at which the drug was ultimately licenced. It is important that such comparisons are not considered separately in the analyses, since they share a single control group and the resulting confidence intervals will be unduly narrow. In order to include all relevant information without undue statistical precision, an average effect is estimated for the range of therapeutic doses available, and the appropriate degrees of freedom applied. For continuous data the population variance is estimated from all the randomised subjects, regardless of the dosage that they receive.

Naturalistic studies

Double-blind randomised trials are occasionally criticised for inadequately representing treatment in the real world. In other words, trials that use a well defined population without co-morbidity, limit treatment options and make both the doctor and patient blind to what the treatment is, may provide different results from those realised in practice. The evaluation of pharmaceuticals is best undertaken using a series of experimental studies. This is reflected in phase II and III studies (small-scale dose ranging and licensing). Studies in phase IV may relax some of the requirements of the earlier trials in order to better reflect the real world: these may include relaxation of blinding, limiting clinical strategies such as choice of drug after initial randomisation and co-morbidity. Such studies have been described as ‘contaminated with the real world’ (Freemantle & Drummond 1997) and it may be difficult to work out what is being estimated (particularly with, say, strong patient or doctor preferences for one treatment). However, when examined with the earlier phase III trials, they may add useful information.

Meta-regression Analysis

Where a number of trials examine the same underlying question, techniques may be used to construct regression models to provide the best estimate of the predictive value of a factor (Smith, 1995). For example, this approach may be used to provide best estimates of the predictive value of whether cholesterol level predicts outcome in trials of statins.

Economic Analysis

A methodology for conducting economic analyses to assist in reaching recommendations for the efficient use of health service resources has been developed (Mason et al, 1999) and applied in a series of primary care evidence-based guidelines. This guideline involves a systematic appraisal of effectiveness, compliance, quality-of-life, safety and health service resource use and costs of a medical intervention provided in the British health care setting. These being the most current, pertinent and complete data available, the economic analysis attempts a robust presentation showing the possible bounds of cost-effectiveness that may result. The range of values used to generate cost-

effectiveness estimates reflects the available evidence and the concerns of the guideline development group. Recommendations are graded reflecting the certainty with which the costs and consequences of a medical intervention can be assessed. This practice reflects the desire of group members to have simple, understandable and robust information based on good data.

It was not thought helpful to present an additional systematic review of previous economic analyses that have adopted a variety of differing perspectives, analytic techniques and baseline data. However, the economic literature was reviewed to compare guideline findings with representative published economic analyses and to interpret any differences in findings when these occurred. A commentary is included when the group feels this aids understanding.

External review of the guideline

We are grateful to the following external reviewer, whose comments had scope to influence the style and content of the guideline. However, the guideline remains the responsibility of the development group.

Dr P Adams, Consultant Cardiologist, Royal Victoria Infirmary, Newcastle upon Tyne.

Scheduled review of the guideline

This guideline should be reviewed no later than 3 years after its completion.

GUIDELINE

Aim

The aim of this guideline is to provide evidence-based recommendations to guide health care professionals in the appropriate primary care management of secondary prophylaxis for patients who have previously experienced a myocardial infarction (MI).

The development group assumes that health care professionals will use general medical knowledge and clinical judgement in applying the general principles and specific recommendations of this document to the management of individual patients. Recommendations may not be appropriate for use in all circumstances. Decisions to adopt any particular recommendation must be made by the practitioner in the light of circumstances presented by individual patients and available resources. In reaching treatment decisions clinicians will need to appropriately share the information within the guideline to allow patients to be appropriately informed about, and involved in, decision making about their care.

Within this guideline we have (in the appendices) reported the diagnostic criteria used in studies included in our review to allow clinicians to judge how closely these apply to the individual patients whom they will manage.

This guideline is concordant with the National Service Framework (NSF) for Coronary Heart Disease, which provides the general framework for the monitoring of patients with coronary heart disease. This guideline provides a firm evidence base for clinical actions and for the principles of relevant audit criteria within the NSF. By its nature, the NSF specifies the audit criteria to a greater level of detail than the guideline. The recommendations within the guideline differ from the content of the NSF only in the area of initiating statins where the guideline offers recommendations based strictly on the evidence.

Scope

The scope of this first edition of the guideline is necessarily limited to addressing key areas of current clinical uncertainty. Our focus is on the provision of recommendations for the primary care management of secondary prophylaxis for patients who have experienced an MI.

There have been a number of recent developments in secondary prophylaxis for patients who have experienced an MI.

- Several new treatments have become available over the last decade. The cholesterol lowering statins have been widely studied and promoted. The use of beta-blockers in patients with heart failure has been the subject of considerable research over the last few years. Angiotensin converting enzyme (ACE) inhibitors have been evaluated in patients who experienced an acute MI (both with and without signs of left ventricular dysfunction or heart failure) and in patients with heart failure (many of whom have previously experienced an MI). There is continued interest and controversy concerning the role of antiplatelet agents in this patient group. Calcium channel blockers and, to a lesser extent, potassium channel activators, have both been evaluated in large scale mortality trials as has the effect of nitrates on major morbidity and mortality. Non-drug treatments, in particular dietary measures and rehabilitation, have been the subject of considerable interest and the dietary measures have been subjected to large-scale research.
- Given the range of treatments available, it is increasingly important to examine the value of each and the extent to which treatments might be complementary. Thus, the aim of this guideline is to provide evidence-based guidance on the value of different treatment options and their prioritisation.

In light of these developments, the guideline will address a number of related questions.

1. What are the benefits in mortality and major morbidity from treatment with statins, beta-blockers, ACE inhibitors, antiplatelet agents, calcium channel blockers, potassium channel activators, cardiac rehabilitation, and Mediterranean diet or polyunsaturated fatty acids in patients who have experienced an MI?
2. What are the benefits in identifiable major subgroups of patients who have experienced an MI? (The main clinical area examined here is the subgroup of patients who develop heart failure following an MI).

Interventions falling outside scope of this guideline

We acknowledge that the choice of primary care drug treatments to prevent subsequent mortality and major morbidity is only one of the uncertainties faced by clinicians and patients. Relevant areas that were identified during the guideline development process but are not covered by this guideline are:

Areas beyond the scope of this guideline

- Smoking cessation programmes
- Symptomatic management of angina
- Exercise programmes in heart failure
- Dietary regimes other than those identified above
- Identification and referral to secondary care for worsening symptoms of cardiovascular disease

The guideline development group assumes that clinicians will give full consideration to these options when deciding relevant management with patients.

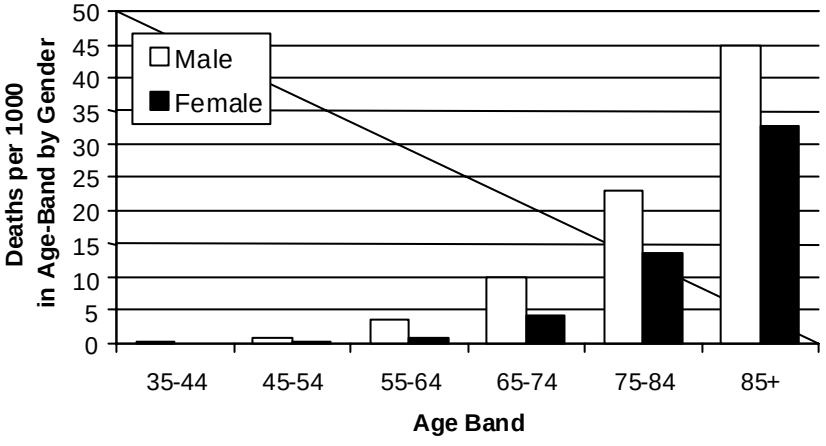
Introduction

Definitions of the diagnosis of an acute myocardial infarction (MI) vary. Chest pain compatible with infarction is the usual reason for hospital admission and a heart attack is diagnosed with the presence of one or more of electrocardiographic changes with development of Q-waves, bundle branch block, ST segment elevation or depression over 24 hours and increased activity of cardiac enzymes or other biochemical tests.

National mortality and health service data are unable to differentiate between first or subsequent ischaemic events, making a demographic profile of those who have already experienced an MI problematic. Patients experiencing an MI may also develop heart failure. Thus, ischaemic heart disease may be broadly defined to include MI, angina, coronary atherosclerosis and heart failure (ICD-9 codes 410-414 and 428). The interaction of these conditions is illustrated by a study of 6,676 patients considered for enrolment to the Trandolapril Cardiac Evaluation trial (TRACE, 1995a, 1995b). Immediately following confirmed acute MI, 37% of patients demonstrated a low wall motion index (equivalent to a left ventricle ejection fraction less than or equal to 35%). Additionally, 39% had previous angina, 27% a previous MI, 23% a history of systemic hypertension and 55% a history of heart failure. These figures may be slightly inflated since 4% of patients contributed data for more than one infarct.

Ischaemic heart disease is the most common cause of death, accounting for 24% of all mortality in England and Wales in 1997 (Office for National Statistics, 1998). The likelihood of dying from ischaemic heart disease increases with age and remains more common in men (Figure 1). A general practitioner with a typical list of 2000 patients would expect an average of five deaths a year from this cause.

Figure 1: Age and Gender Specific Death Rate per annum:
Ischaemic Heart Disease (ICD 410-4, 428)
England and Wales, 1997



Over the last 25 years, mortality from ischaemic heart disease has fallen by approximately 40% (Office for National Statistics, 1998). Possible explanations for this decline include the increasing uptake and improvement of a range of drugs and surgical techniques, although a 40% reduction in smoking in adults reported during the same period is likely to have been important (OPCS, 1994; Joint Surveys Unit, 1998).

Epidemiological studies, following patients surviving a first heart attack, have demonstrated average mortality rates of 5-10% per year in those patients aged 50 to 70. This can be compared with an average mortality rate in the population in this age group of 1% per year. Survival following infarct does not appear to vary significantly by diagnosis of definite or probable infarction or by gender, although prognosis worsens with increasing age. Multivariate analyses conducted in these studies

identified few important prognostic risk factors. Exceptions are increasing ventricular dysfunction and recurrent MI indicating poorer prognosis; and moderate (compared to occasional) alcohol consumption associated with a better prognosis (Rouleau et al, 1996; Galatius et al, 1998; TRACE, 1995a, 1995b; Launbjerg et al, 1991; Muntwyler et al, 1998). It may be helpful to consider potential confounding from these factors when comparing the findings of trials.

In 1994, there were approximately 300,000 hospital admissions in England for ischaemic heart disease requiring two million bed days. Ischaemic heart disease accounted for nearly 4% of all NHS admissions (Department of Health, 1996). A general practitioner with a list of 2000 patients would expect an average of 12 hospitalisations and to have about 50 patients making 130 primary care consultations for ischaemic heart disease each year (McCormick et al, 1995).

Seven classes of drugs are potentially available to treat ischaemic heart disease, including antiplatelet drugs, beta-blockers, calcium channel blockers, potassium channel activators, drugs affecting the renin-angiotensin system, nitrates and lipid lowering agents, although these drugs are also used in a range of other indications. Primary care prescribing of these drugs in the NHS cost £814 million in 1998 (Table 1), although the proportion used in ischaemic heart disease, or for patients with prior MI is uncertain.

Substantial differences are observable not only when comparing the costs of classes of drug but also within classes. These variations are seen in the costs of proprietary and generic forms, modified release products, combination products (e.g. a diuretic combined with a calcium channel blocker) and different uses for the same drug, requiring different doses (e.g. following an MI and for hypertension).

The acquisition costs of drugs form only a part of the total health service costs of care for ischaemic heart disease. Applying Department of Health reference costs, inpatient admissions alone for ischaemic heart disease can be estimated to have cost the NHS £450 million in 1997.

Table 1: Prescribing of drugs used in ischaemic heart disease, England 1998

BNF Section	Class	No. of Scripts (millions)	Reimbursed cost, £ (millions)	Cost/script, £
2.4.0	Beta-blockers	15.30	76.42	4.99
2.5.5	Renin-angiotensin system drugs	13.34	238.32	17.86
2.5.5.1	Angiotensin-converting enzyme inhibitors	12.28	209.30	17.04
2.5.5.2	Angiotensin-II receptor antagonists	1.06	29.01	27.31
2.6.1	Nitrates	8.39	67.01	7.99
2.6.2	Calcium Channel Blockers	13.85	224.62	16.22
2.6.3	Potassium Channel Activators	0.47	7.25	15.47
2.9.0	Antiplatelet drugs	12.16	10.36	0.85
2.12.0	Lipid lowering drugs	5.98	189.70	31.74
	Statins	4.98	170.28	34.17
	Omega-3 Marine Triglycerides	0.03	1.03	35.21
	Other Lipid lowering drugs	0.96	18.39	19.10

* Data provided by the Prescription Pricing Authority.

There is genuine uncertainty about how to prioritise or sequence available drugs to patients presenting with a prior MI, reflected in variations in prescribing rates for these drugs reported in surveys of primary care (Smith & Channer, 1995; Viskin & Barron, 1996; Houghton & Cowley, 1997; Lough et al, 1998). The objective of this guideline is to examine and present the evidence concerning the appropriate sequencing of drugs and other interventions for secondary prophylaxis in patients with a prior MI, and to identify whether this differs according to prognostic risk factors (principally heart failure). Incremental health benefits and health care costs, for each treatment initiated, are presented as the available data permits.

Statins in patients with prior MI

Statements

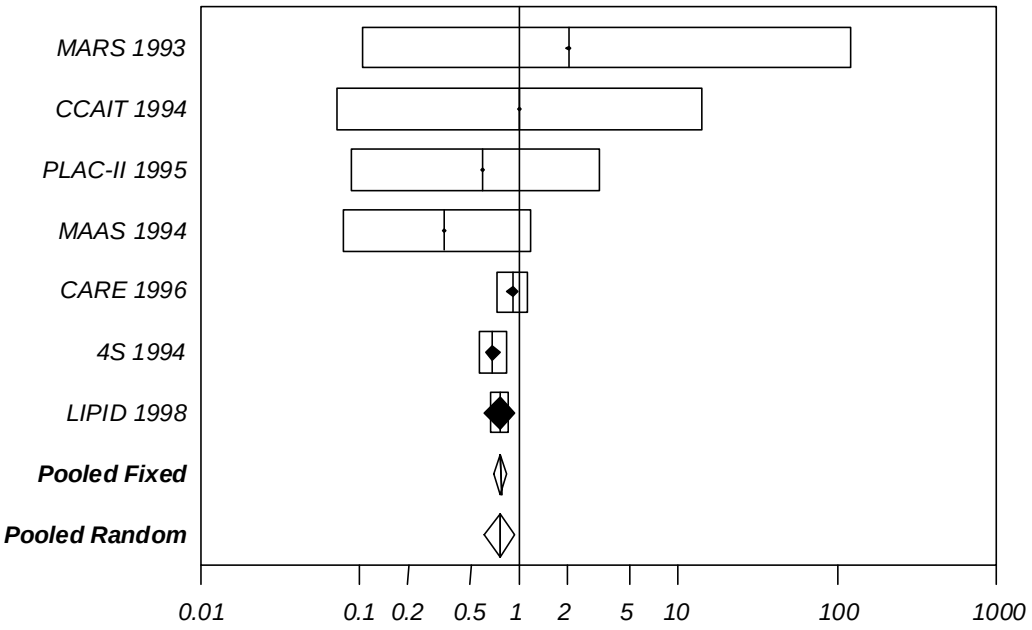
- *Based on the data from randomised controlled trials in 1,000 patients who have experienced an MI, treatment with statins for a year will avoid about four deaths, six non-fatal MIs and two strokes. These benefits appear similar regardless of initial cholesterol level (Ia).*
- *Most of the evidence comes from trials of pravastatin and simvastatin (Ib)*
- *Most trials started statins 12 weeks after myocardial infarction (Ia)*
- *The effectiveness of statins in patients who develop heart failure in addition to MI has not been adequately assessed (Ia).*
- *None of the studies considered included patients with an initial cholesterol <4 mmol/l (Ia).*

Statins have been researched in a range of situations, including primary prevention and atherosclerosis. Potential benefits of treatment in different patient groups are likely to vary according to baseline risk and other possible confounding issues. Further, it is likely that potential benefits will accrue only with sustained use, so we searched for unconfounded trials of statins in which at least 50% of patients had experienced a heart attack and in which average follow up was a minimum of one year.

Seven trials were located that met the entry criteria (LIPID 1998, MAAS 1994, CCAIT 1994, MARS 1993, CARE 1996, 4S 1994, PLAC-II 1995). There were 1,975 deaths among the 18,727 patients randomised in these trials, and average follow up ranged from two to 6.1 years. Three different agents were used and overall, 71% of patients were randomised into trials that examined the effectiveness of pravastatin, 26% to simvastatin, and 3% to lovastatin. Patients with heart failure were excluded in all but two small trials (MARS 1993, PLAC-II 1995). Patient population showed average to moderately elevated cholesterol levels (Included trials are described in Appendix 1.) though the largest and most recent trial (LIPID 1998) enrolled patients with cholesterol levels down to 4 mmol/l.

Statins were associated with a 24% reduction in the odds of all cause mortality (95% CI: 16% to 30%) using a fixed effects model. Substantial variability in the effect observed in different trials is reflected in the greater uncertainty in the random effects model: reduction in the odds of mortality of 24% (95% CI: 5% to 40%). The odds ratios for individual trials, 95% confidence intervals and pooled fixed and random effects estimators are described in Figure 2.

Figure 2. Effect of statins on the odds of all cause mortality by fixed and random effects, with 95% confidence intervals



Although the reduction in the odds of death is substantial, the absolute benefits observed appear moderate. Treating 1,000 patients who have experienced an MI with a statin for a year will avoid about four deaths (95% CI: 2 to 6 deaths). Additionally, six non-fatal MIs (95% CI: 2 to 10) and two non-fatal strokes (95% CI: 1 to 3) will also be avoided.

We did not observe a convincing relationship between enrolment cholesterol levels and mortality reduction in these patients. Absolute benefits in the large LIPID (1998) trial did not differ beyond that which might be expected by chance with cholesterol level. Similarly, baseline cholesterol level did not predict outcome in these trials in a meta regression model, although the small number of trials and reliance upon summary data may obscure moderate differences that may be observed in an individual patient level analysis. In addition, no relationship between length of follow up and outcome was identified although all trials were of patients receiving long term treatment.

Across all the trials the lower limit of the range of cholesterol values defining eligibility varied. At least one study enrolled patients with cholesterol values down to 4 mmol/l. However, licence indications suggest a lower limit of 4.8 mmol/l for pravastatin and 5.5 mmol/l for simvastatin.

The LIPID trial (1998) included over half of the patients contributing to the analyses above. Benefits were observed across a range of secondary outcomes, including absolute reductions of 2.4% in coronary artery bypass surgery, 0.9% in percutaneous transluminal coronary angioplasty and 2.3% in hospitalisations for unstable angina. There were no differences in the incidence of cancers, accidents, violence, or attempted suicide, neither was there any difference in the rate of discontinuation of either pravastatin or placebo.

Beta-blockers for unselected patients with prior MI

Statements

- *Based on the data from randomised controlled trials, in 1,000 unselected patients who have experienced an MI, treatment with a beta-blocker for a year will avoid about thirteen deaths and eight non-fatal MIs (Ia).*
- *Potential benefits from beta-blockers may be achieved through early initiation of therapy. However, these will continue to accrue over long-term use (Ia).*
- *Based on the data from randomised controlled trials, in 1,000 patients treated for a year with a beta-blocker, in about twelve of those who discontinue therapy, the discontinuation is attributable to the drug (Ia).*
- *Beta-blockers with intrinsic sympathomimetic activity are associated with a near significant reduction in therapeutic effect compared with agents without this characteristic (Ia).*
- *Most evidence for long term beta-blocker use comes from trials of propranolol, timolol and metoprolol (Ib).*

Beta-blockers have a long established role in the management of patients who have experienced an MI. However, newer drugs and acute treatments have been developed since beta-blockers first became available and beta-blockers are sometimes perceived to have poor tolerability.

We updated previous work examining the effectiveness and tolerability of beta-blockers in patients who have experienced a prior MI (Freemantle et al 1999). Trials divide into those that address short-term treatments and those in which therapy is continued long term.

We searched for unconfounded trials of beta-blockers in patients who had experienced an MI. These were divided into those in which treatment was for up to six weeks after an index event or those in which treatment was for a longer period. For the longer term trials, therapy could have been commenced either immediately post MI, with or without initial intravenous therapy, or could have been initiated some time after the index event.

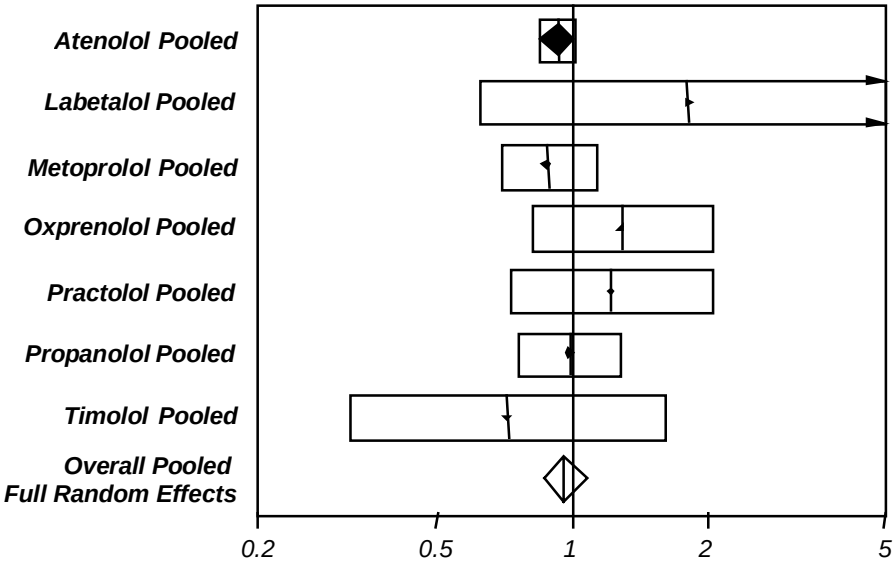
Short Term Trials

We identified 51 trials in which 29,260 patients were randomised to beta-blockers or control. Overall there were 3,062 deaths. Only 45 trials actually observed any deaths. Thirty-two trials included initial intravenous treatment. All cause mortality alone was reported reliably in trials. (Short term trials of beta-blockers are described in Appendix 2.)

The short term use of beta-blockers was associated with a 5% reduction in the odds of death not statistically significant at conventional levels (95% CI: –2% to 12%), by fixed effects model. The random effects estimate was similar, suggesting a 4% reduction in the odds of death (95% CI: –8% to 15%). The summary effect of beta-blockers, by drug, on all cause mortality is described in Figure 3.

Treating 1,000 patients with beta-blockers for up to six weeks post MI will avoid about four deaths (95% CI: -2 to 10). The use of beta-blockers in short term therapy immediately post MI is associated with a small, and statistically uncertain, reduction in mortality.

Figure 3: Short term effect of beta-blockers on all cause mortality: odds ratios and 95% confidence intervals.



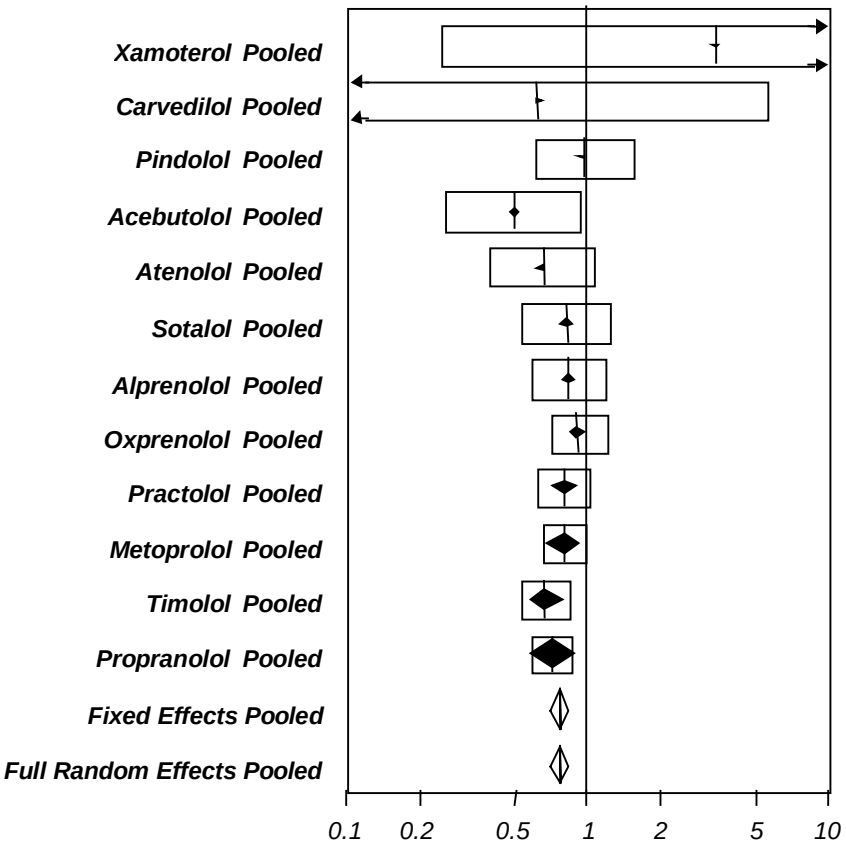
Long Term Trials

Long term trials were defined as those in which treatment was longer than six weeks after an index event. Included trials could have commenced soon after MI, and may have included initial treatment with intravenous therapy. Similarly, trials met the entry criteria if they included patients who had experienced an MI at some time in the past. Altogether, 32 trials were identified in which 24,974 patients were randomised to treatment or control and a total of 2,415 deaths were observed. Mortality was reported reliably in the included trials. Non-fatal re-infarction was also reported in 22 trials. (Included trials are described in Appendix 3.)

Overall, treatment with beta-blockers was associated with a 24% reduction in the odds of death (95% CI: 17% to 30%) for both fixed and random effects approaches (see Figure 4).

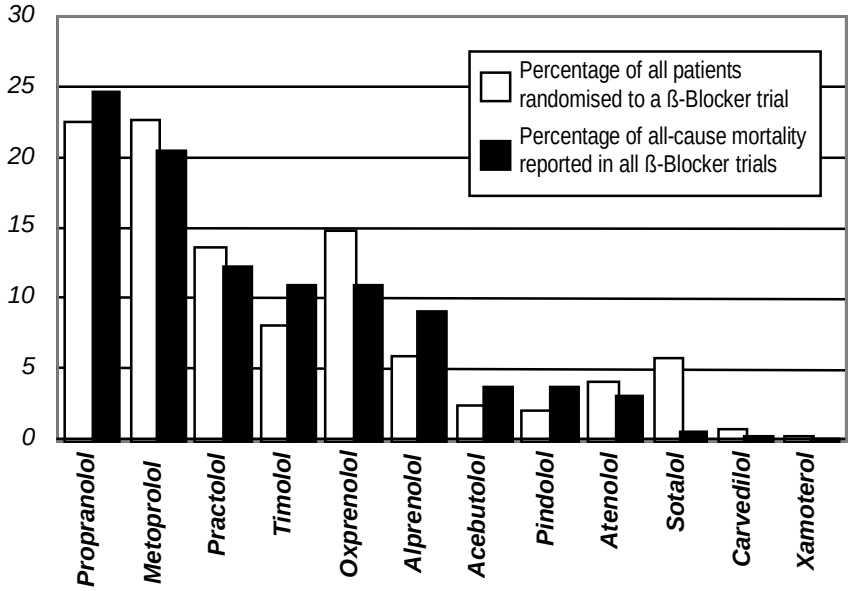
Similarly, beta-blockers were associated with a 24% reduction in the odds of non-fatal re-infarction (95% CI: 15% to 33%) by fixed effects model, and a 24% reduction in the odds of non-fatal re-infarction (95% CI: 11% to 36%) by random effects model. Treating 1000 patients with a beta-blocker for a year will avoid 13 deaths (95% CI: seven to 18), and eight non-fatal MIs (95% CI: 2 to 14).

Figure 4: Long term effect of beta- blockers on all cause mortality: odds ratios and 95% confidence intervals.



The most commonly used drugs in the trials were propranolol and metoprolol (see Figure 5), both of which achieved a statistically significant reduction in mortality, as did timolol. We examined the influence of a number of factors on the results of trials, using a full mixed regression model (Freemantle et al 1999), including the effect of initial intravenous treatment, which was associated

Figure 5: Deaths and numbers randomised by beta-blocking agent in long terms trials



with an odds ratio 0.87 (95% CI: 0.62 to 1.23). In other words, initial intravenous treatment was associated with a non-significant benefit. As patients soon after MI are at a particularly raised risk of an additional event, early initiation by intravenous or oral therapy would maximise the opportunity for a patient to benefit from therapy. However, unlike some other treatments where effectiveness is dependent upon early initiation (such as thrombolytic therapy), there is no evidence, for beta blockade, that effectiveness is dependent upon early initiation.

We also examined the predictive effect of cardio-selectivity, a characteristic of some β-blocking agents, on outcome. The odds ratio for this factor was 1.07 (95% CI: 0.86 to 1.37), a non-significant reduction in benefits from presence of cardio-selectivity, though the confidence intervals are wide and this effect is likely to be attributable to chance alone, or confounding with another factor. The odds ratio describing the effect of intrinsic sympathomimetic activity was 1.21 (95% CI: 0.98 to 1.50), a near significant trend towards reduced efficacy of borderline statistical significance (p= 0.077). Finally, since the use of other drugs constituting standard care has increased over time, we conducted a nested regression model, examining whether benefits reduced over time in both the short and long term trials before or after the historically median trial in both groups of trials. The odds ratio for publication date based upon lying before or after the median trial was 0.98 (95% CI: 0.84 to 1.13). In other words, the analysis provided no evidence to support the notion that benefits previously achieved by β-blocking agents alone are increasingly achieved through other treatment modalities.

The tolerability of different beta-blockers was examined through meta analysis of discontinuation rates. Twenty-five long term trials reported rates of discontinuation of therapy. Overall there were 5,151 withdrawals from treatment among 21,954 patients randomised. For 1,000 patients treated with a beta–blocker for one year, in about 12 of those who discontinue treatment, the discontinuation is attributable to the beta-blocker (95% CI: 6 to 18).

Angiotensin converting enzyme inhibitors (ACE inhibitors) in patients with prior MI

ACE inhibitors in unselected patients

Statement

- *ACE inhibitors are associated with a small reduction in mortality in short-term use immediately after acute MI. Based on the data from randomised controlled trials, in 1,000 patients who have experienced an MI, treatment with an ACE inhibitor for a year will avoid about two deaths (Ia).*

- *In longer term use in patients at raised cardiovascular risk, ACE inhibitors are associated with a moderate reduction in mortality. Based on one large randomised controlled trial, if 1,000 patients are treated for one year 4 deaths will be avoided (Ib).*

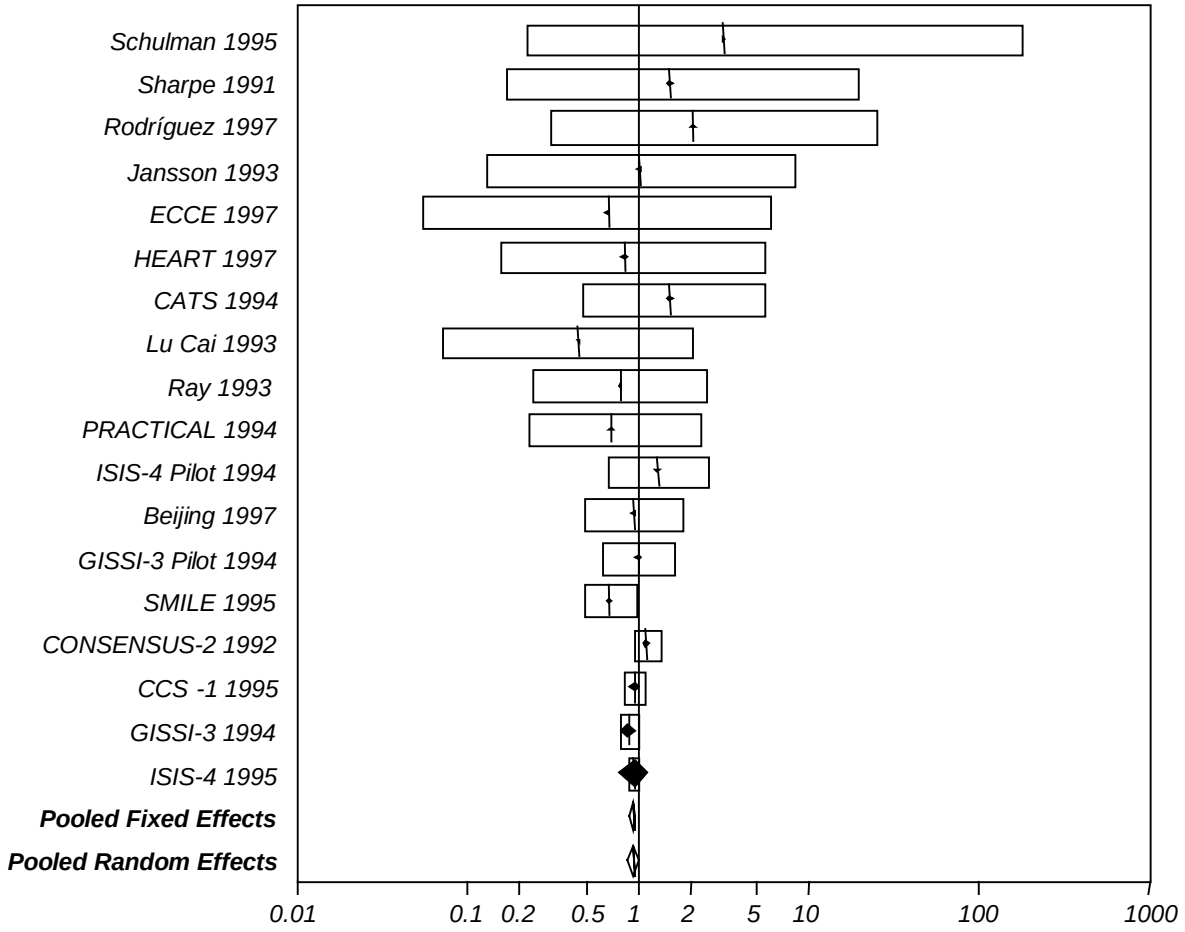
There is considerable interest in the potential benefits from ACE inhibitors in patients who have experienced an MI. We searched for trials of ACE inhibitors in unselected patients who had experienced an MI. Overall, we located 22 trials including 102,476 patients. The only consistently reported outcome in these trials was mortality and there were 7,914 deaths in the trials.

Trial follow up varied from 3 days to 19 months. However, the majority of patients were randomised in ISIS-4 or GISSI-3, in which follow up was five and six weeks respectively. The characteristics of the included trials are described in Appendix 4. Treatment with an ACE inhibitor was associated with a 7% reduction in the odds of death (95% CI: 2% to 11%) by fixed effects model, and a 7% reduction in the odds of death (95% CI: –1% to 14%) by random effects model (Figure 6). If 1,000 patients are treated for one month immediately after MI, 1.6 deaths will be avoided (95% CI: 0.4 to 2.8).

Because of the limited information collected in the case report forms for the large trials (ISIS-4 1995; GISSI-3 1994) remarkably little is known about the characteristics of patients treated with ACE inhibitors; it is unclear if benefits are concentrated in a particular subgroup of patients, or if the treatment period was insufficient for benefits to accrue. In two moderately-sized, longer term trials (SMILE 1995; Beijing 1997) benefits were inconsistent, although the patient event rate was twice that in SMILE (1995) compared with Beijing (1997) and the trials are not powered to exclude the play of chance in the difference in results observed.

The HOPE (2000) trial examined the effect of ramipril vs. placebo in patients at raised risk of cardiovascular events but excluding those with left ventricular systolic dysfunction and an ejection fraction of < 40%. HOPE enrolled 9,297 patients, 53% of whom had experienced a prior MI, with an average follow up of 5 years. Treatment with an ACE inhibitor in HOPE was associated with a 17% reduction in the odds of death (95% CI: 5% to 27%): for 1,000 patients treated for one year 4 deaths were avoided (95% CI: 1 to 6).

Figure 6: Effect of ACE inhibitors on all cause mortality immediately post myocardial infarction in unselected patients: odds ratios and 95% confidence intervals.



ACE inhibitors in selected patients with prior MI and heart failure

Statement

- *Long term treatment with ACE inhibitors is associated with a substantial reduction in all cause mortality in selected patients with signs of heart failure who have recently experienced an MI. Based on the data from randomised controlled trials treating 1,000 patients with heart failure with ACE inhibitors for a year, commencing soon after an index MI, will avoid 18 deaths (Ia).*

- *ACE inhibitors may also reduce the incidence of non-fatal MI (Ia).*

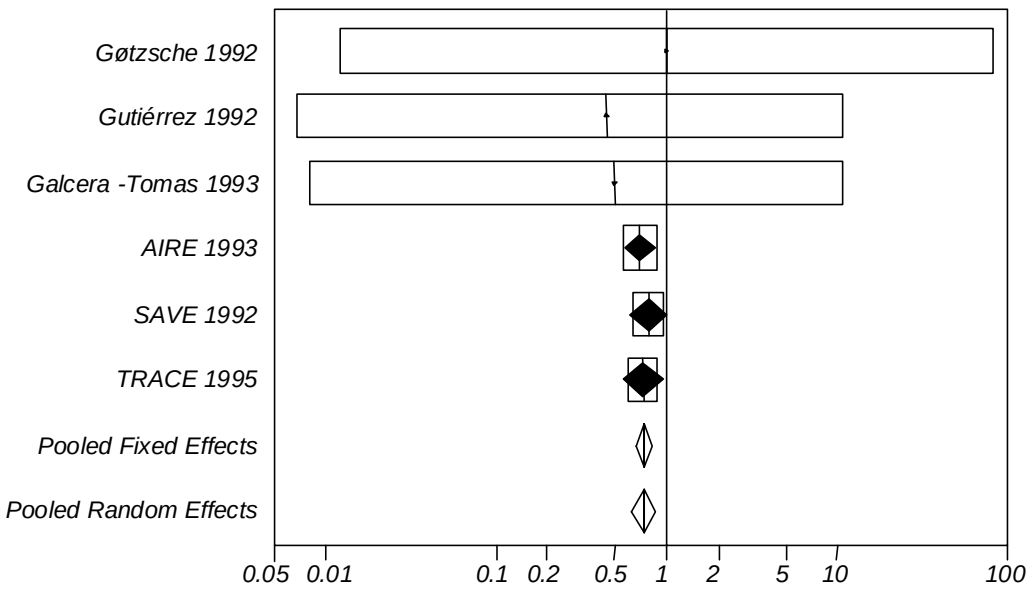
- *The tolerability of ACE inhibitors in the trials was very similar to that achieved with placebo (Ia).*

Many patients develop signs of heart failure in the period after acute MI. During recruitment screening for the TRACE trial (1995a), in 7,001 consecutive episodes of acute MI in 6,676 patients evaluated, 2,606 (39%) had an ejection fraction <35% immediately following MI. We identified six trials that examined the effect of ACE inhibitors in patients who have experienced acute MI and who developed signs of heart failure. These trials included 6,093 patients, in which there were 1,576 deaths. Follow up ranged from two weeks in one small trial to 42 months. All but one have at least six months follow up. Again, only mortality is reported reliably. (Included trials are described in Appendix 5.)

ACE inhibitors were associated with a 26% reduction in the odds of death (95% CI: 17% to 34%) by fixed effects method, and a 26% reduction in the odds of death (95% CI: 14% to 38%) by random effects method (See Figure 7). Treating 1,000 patients with heart failure with ACE inhibitors for a year, commencing soon after index MI, will avoid 18 deaths (95% CI: 8 to 28).

In the TRACE trial (1995b) there was a non-significant reduction in the incidence of fatal or non-fatal re-infarctions (hazard ratio 0.86, 95% CI: 0.66 to 1.13). The increase in annual withdrawal in the three major trials, comparing angiotensin converting inhibitors with placebo, is less than one in a thousand (p=0.047).

Figure 7: Effect of ACE inhibitors on all cause mortality immediately post myocardial infarction in selected patients: odds ratios and 95% confidence intervals.



ACE inhibitors in patients with heart failure (but not necessarily with prior MI)

Statement

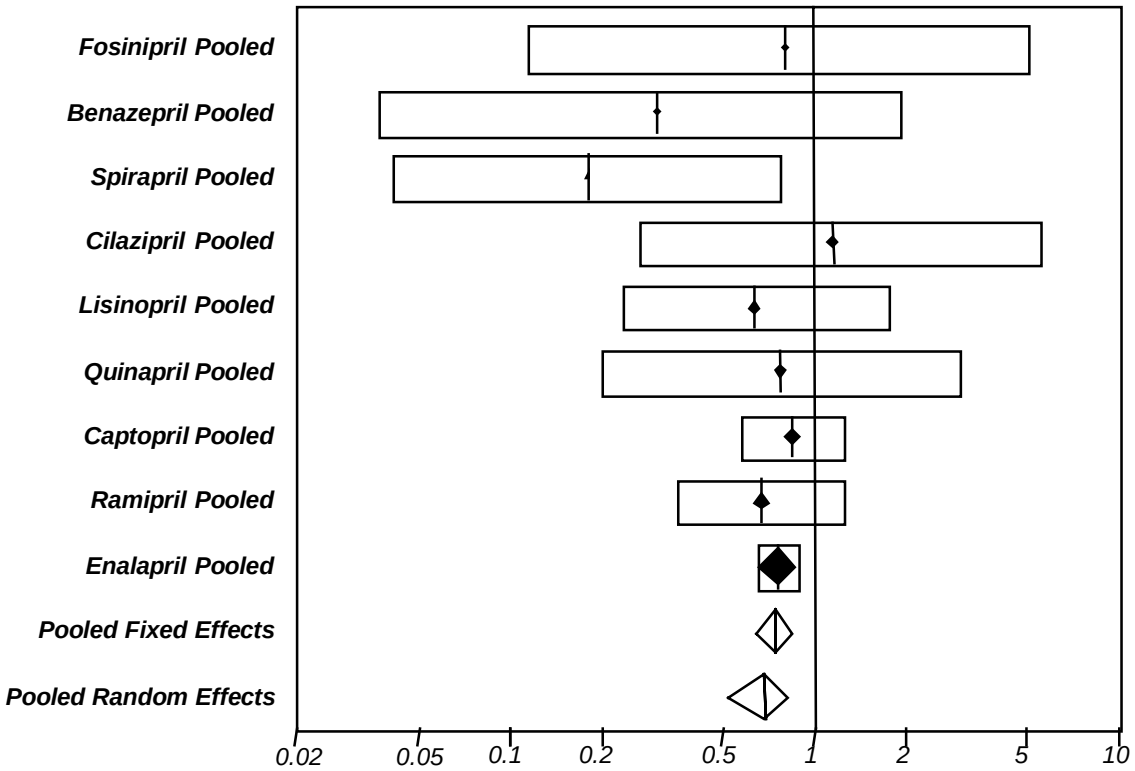
- *Long term treatment with ACE inhibitors is associated with a substantial reduction in all cause mortality in patients with symptoms of heart failure and reduced left ventricular function who may or may not have experienced an MI. Based on the data from randomised controlled trials treating 1,000 patients for one year will avoid about 15 deaths (Ia).*

There has been a substantial programme of research into the effectiveness of ACE inhibitors in patients who have left ventricular dysfunction and heart failure. In the SOLVD treatment trial (1991) (the largest trial of ACE inhibitors for heart failure), two-thirds of patients had previously experienced an MI, although they were ineligible for the trial if this event had been experienced less than a month prior to randomisation. These data provide a further insight into the appropriate treatment of patients in primary care who have experienced an MI.

We searched for unconfounded trials of ACE inhibitors with at least two months of follow up, in which the comparator was either placebo or open (non intervention) control. We located 49, in which 8,818 patients were randomised to treatment or control. Only all cause mortality was reported reliably and there were 1,418 deaths in these trials (see Appendix 6).

Overall, treatment with an ACE inhibitor led to a 26% reduction in the odds of death in the trials (95% CI: 16% to 35%) by fixed effects model, and a 31% reduction in the odds of death (95% CI: 18% to 47%) by random effects model. The reduction, by drug, in the odds of death is presented in Figure 8.

Figure 8: Effect of ACE inhibitors on all cause mortality in selected patients who may, or may not, have experienced a myocardial infarction: odds ratios and 95% confidence intervals.



This observed reduction in the odds of death attributable to treatment with an ACE inhibitor is remarkably similar in patients with heart failure who may have experienced an MI and in selected patients, with signs of heart failure, post MI. Treating 1,000 patients for one year led to the avoidance

of 15 deaths in the trials (95% CI: three to 26). In general, only all cause mortality was reported adequately, but the SOLVD treatment trial (1991) (which included over ¼ of patients randomised) also reported adherence to treatment and hospitalisation rates. Although the majority of patients reported side effects during the trial, the difference between rates for enalapril and placebo was only 5% in favour of placebo. More than two-thirds of patients were hospitalised during the follow up period (average 41.4 months), but allocation to the enalapril group was associated with a 5% reduction in the all-cause rates of first hospitalisation in this period (p=0.006).

ACE inhibitors and beta-blockers combination therapy in patients who have heart failure (who may, or may not, have experienced an MI)

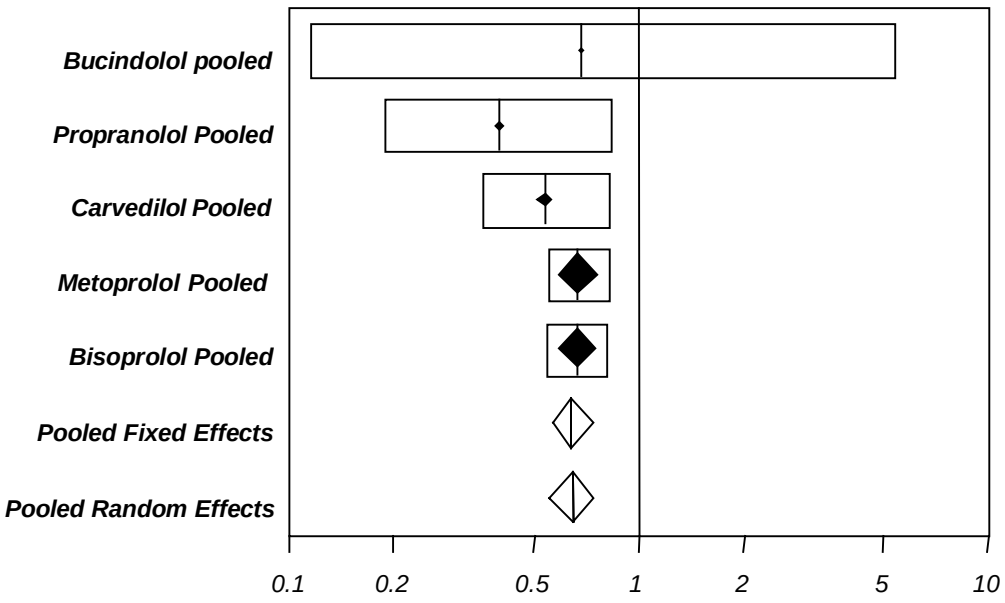
Statement

- *Beta-blockers are associated with a substantial reduction in all cause mortality in patients with symptoms of heart failure being treated with an ACE inhibitor, who may or may not have experienced an MI. Based on the data from randomised controlled trials treating 1,000 patients with heart failure for one year with beta-blockers will avoid 35 deaths (Ia).*

For many years beta-blockers have been contraindicated in patients who have heart failure. Several large trials that examined the effectiveness of beta-blockers in addition to conventional (ACE inhibitor) treatment in patients with heart failure have been completed recently (Cleland et al 1999). We searched for unconfounded trials comparing the effectiveness of beta-blockers and placebo or open control in patients with heart failure and overall, we located 27 trials including 10,502 patients. There were 1,172 deaths in these trials. Only mortality was reported reliably across the group of trials. (The trials are described in Appendix 7.).

Overall, allocation to beta-blockers was associated with a 35% reduction in the odds of death (95% CI: 27% to 43%) by fixed effects approach, and a 35% reduction in the odds of death (95% CI: 25% to 45%) by random effects approach. The effect of beta-blockers on the odds of death in the trials is presented in Figure 9.

Figure 9: Reduction in the odds of death attributable to beta-blockers in patients with heart failure treated conventionally, and 95% confidence intervals



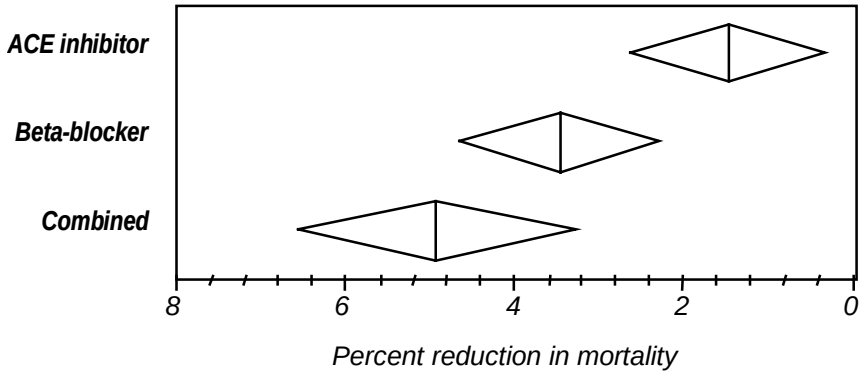
Treating 1,000 patients with heart failure for one year with beta-blockers will avoid 35 deaths (95% CI: 23 to 46). There was no difference in tolerability between those taking a beta-blocker and those taking placebo. Treating 1,000 patients for one year will lead to five more patients discontinuing treatment (95% CI: -19 to 30).

In CIBIS-II (1999) most mortality benefits for bisoprolol were observed for sudden death (4% versus 6%, p = 0.0011), though hospitalisation for worsening heart failure was also substantially reduced (12% versus 18%, p = 0.0001).

Since the majority of patients randomised in these trials were being treated with an ACE inhibitor the benefits observed for beta-blockers may be considered as additional to those achieved with ACE inhibition (Cleland et al 1999). The annual risk in the control group of the beta-blocker trials (12%) is similar to that in the intervention group in the ACE inhibitor trials (10%), so it is reasonably simple to add together the absolute annual benefit from the meta-analyses of trials of ACE inhibitors and beta-blockers in comparable patients, and the variance estimates.

Extrapolating from the trials, if 1,000 patients with heart failure are treated for one year with an ACE inhibitor, 15 deaths will be avoided (95% CI: three to 26). Similarly, if 1,000 patients are treated with a beta-blocker, 35 deaths will be avoided (95% CI: 23 to 46). The best estimate for the benefits of treatment with both an ACE inhibitor and a beta-blocker suggests that if 1000 patients are treated for a year, 49 deaths will be avoided (95% CI: 38 to 61) (see Figure 10).

Figure 10: Annual reduction in the rate of death in patients with heart failure treated with an ACE inhibitor, a beta-blocker, or combination



Spironolactone in patients with severe heart failure

Statement

- *Spironolactone is associated with a decrease in all cause mortality among patients with moderate to severe heart failure treated optimally with ACE inhibitors (Ib).*

The recent publication of a large trial compares spironolactone and placebo in patients with severe heart failure who are optimally treated with an ACE inhibitor (see Appendix 8 for details). The RALES trial (Pitt et al, 1999) is of considerable interest since a substantial attributable reduction in all cause mortality was observed. The trial examined the effect of spironolactone 25mg daily, a dose established in a previous small dose ranging study (Pitt et al, 1995). Patients had severe symptoms, having a New York Heart Association (NYHA) grade IV classification at some time in the 6 months preceding enrolment to be included (see Appendix 8). Some 70% had improved and were in NYHA grade III at time of entry. In all 1,663 patients were included, and after 24 months mean follow up an 11.3% reduction in all cause mortality favoured spironolactone. Thus if 1,000 patients were treated for one year 57 deaths would be avoided (95% CI: 26 to 87).

Antiplatelet therapy with aspirin or alternative agents in patients with prior MI

Statements

- *Antiplatelet therapy is associated with a reduction in all cause mortality and non-fatal MI in patients who have experienced a previous MI (Ia).*
- *There is no evidence that any alternative antiplatelet agent is more effective than aspirin in this patient group; the majority of evidence comes from trials of aspirin (Ib).*
- *There is some evidence from sub group analyses of major trials that the benefits of aspirin and ACE inhibitors are not completely additive in patients with heart failure (Ia).*

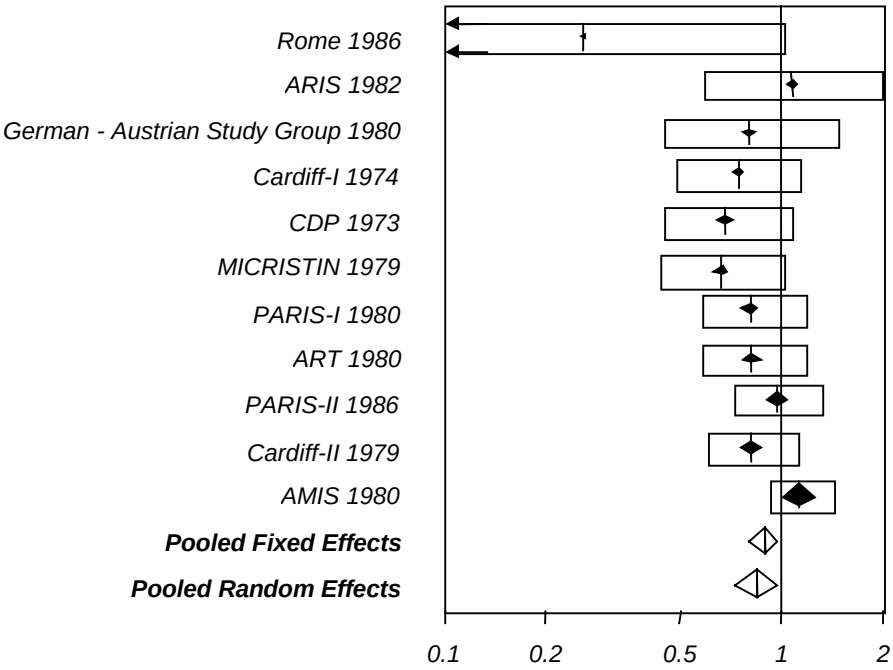
We examined the evidence for the use of antiplatelet therapy with aspirin or an alternative agent in patients who had previously experienced an MI, including trials of prolonged antiplatelet therapy (at least one month), in line with our previous work (Eccles et al 1998). We identified 11 trials in which 18,574 patients were randomised and 1,783 deaths reported. (See Appendix 9.) Three different antiplatelet agents were used: aspirin; sulphinpyrazone; and dipyridamole (although only used without aspirin supplementation in one small trial). We examined all cause mortality, non-fatal stroke and non-fatal MI.

Overall, antiplatelet therapy was associated with a reduction in all cause mortality in the trials; odds ratio 0.89 (95% CI: 0.80 to 0.98) by fixed effects, and odds ratio 0.86 (95% CI: 0.73 to 0.98) by random effects (see Figure 11). Disturbingly, the largest trial (AMIS 1980) demonstrated an excess mortality in the intervention group, though this may best be explained simply by the play of chance. If 1,000 patients are treated for one year with an antiplatelet agent, three deaths will be avoided (95% CI: – 1 to 7) by fixed effects, or seven deaths will be avoided (95% CI: 1 to 13) by random effects. The difference in the estimated benefit depending upon the model used indicates the relative uncertainty for the effect of antiplatelet therapy when compared with other drug groups examined in this guideline.

All the trials of aspirin in Appendix 10 used medium doses of aspirin. However, previous work across a range of clinical conditions (including prior MI) (Eccles et al 1998), demonstrated that effectiveness was not influenced by dose but side effects potentially were and recommended a dose of 75mg.

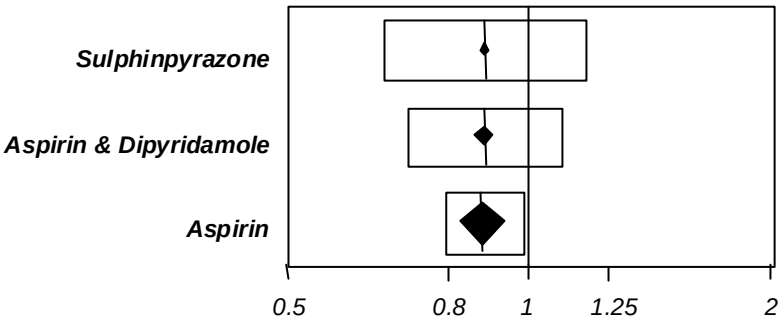
More consistent results were observed for the outcome non-fatal stroke. In all, eight trials reported this outcome and antiplatelet therapy reduced the incidence of non-fatal stroke; odds ratio 0.59 (95% CI: 0.44 to 0.80) by fixed effects, and 0.59 (95% CI: 0.40 to 0.84) by random effects. Thus, if 1,000 patients are treated for one year, two non-fatal strokes will be avoided (95% CI: 1 to 4). Similarly, across all 11 trials, antiplatelet therapy was associated with a reduction in the incidence of non-fatal MI; odds ratio 0.69 (95% CI: 0.61 to 0.79) by fixed effects, or odds ratio 0.68 (95% CI: 0.59 to 0.80) by random effects. If 1000 patients are treated for one year with an antiplatelet agent, eight non-fatal MIs will be avoided (95% CI: 5 to 11).

Figure 11. Effects of prolonged antiplatelet therapy upon all cause mortality in patients with previous MI - odds ratios and 95% confidence intervals



We examined the evidence from relevant trials on the choice of antiplatelet agent. Only one trial (PARIS-1, 1980), provided evidence from a direct comparison of dipyridamole and aspirin combined, aspirin and control. Additionally, CAPRIE (1996) provides evidence on the comparative effects of clopidogrel and aspirin. Pooling the 11 antiplatelet trials that compared prolonged antiplatelet therapy against control in patients with previous MI by each drug provided similar results, although aspirin provides the greatest precision as most patients were allocated in trials of aspirin. The pooled effects of different antiplatelet agents on the odds of death are described in Figure 12.

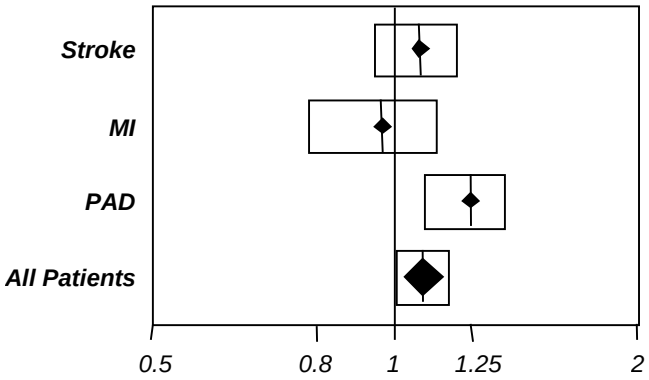
Figure 12. Effects of prolonged antiplatelet therapy upon all cause mortality in patients with previous MI by antiplatelet agent: odds ratios and 95%confidence intervals.



In the one directly randomised comparison between aspirin and the combination of aspirin and dipyridamole, no difference was observed in all cause mortality (odds ratio 0.96, 95% CI: 0.69 to 1.34).

Clopidogrel has recently been licenced in the UK for use as an antiplatelet agent. The CAPRIE trial (1996) compared clopidogrel 75 mg with aspirin 325 mg in 19185 patients with prior stroke, MI or peripheral artery disease with a mean follow up 1.91 years. Overall, clopidogrel was associated with a slight reduction in vascular events (see Figure 13) although not in the subgroup with prior MI as the index event.

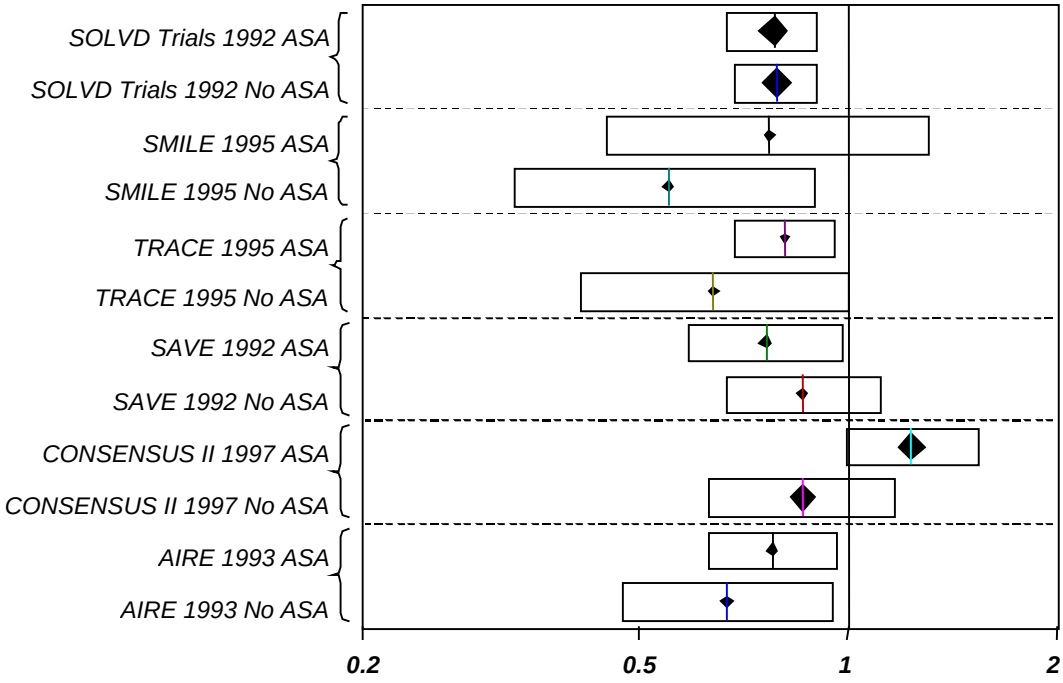
Figure 13. Vascular events in CAPRIE trial comparing clopidogrel and aspirin in pre-defined subgroups by index event: odds ratios and 95% confidence intervals



However, there was no difference in all cause mortality between those allocated to clopidogrel and those allocated to aspirin, odds ratio 0.98 (95% CI: 0.87 to 1.10). Similar rates of side effects and withdrawal from therapy were observed for aspirin and clopidogrel in the trial.

There have been concerns expressed that aspirin and ACE inhibitors do not have a strictly additive effect (in statistical terms, there is a negative interaction between the two agents) (CONSENSUS II 1997). We looked for evidence to support this hypothesis in major trials of angiotensin converting enzyme inhibitors, which reported these data. Data are available in the SOLVD treatment and prevention trials for the outcome of MI or hospitalisation for unstable angina (Yusuf et al, 1992), in SMILE (1995) for all cause mortality or severe heart failure, and in TRACE (1995), SAVE (1992), AIRE (1993) and CONSENSUS II (1997) for all cause mortality. Patients on aspirin did appear to gain less benefit from angiotensin converting enzyme inhibitors in a number of the trials, but only CONSENSUS II (1997), which demonstrated no overall benefit for ACE inhibitors, appears to demonstrate a harmful effect associated with aspirin (see Figure 14). Subgroup analyses, especially those conducted ad hoc examining the possibility of interactions are difficult to interpret. However, the benefits in patients with signs of heart failure taking an aspirin and angiotensin converting enzyme inhibitor after MI in TRACE (1995) suggest that optimal treatment for this patient group probably does include the use of aspirin.

Figure 14. Patients taking angiotensin converting enzyme inhibitors by subgroup with or without aspirin: relative risk and 95% confidence intervals (outcomes presented vary: see text)



Insulin glucose infusion followed by subcutaneous insulin in patients with diabetes with prior MI

Statement

- *There is evidence that rigorous control of diabetes post myocardial infarction lowers mortality (Ib).*

We identified a single trial that described the effectiveness of rigorous insulin control in patients with raised blood sugar post myocardial infarction (Malmberg, 1997). The characteristics of the trial are described in Appendix 10. The intervention (insulin - glucose infusion for at least 24 hours followed by subcutaneous insulin 4x daily for at least 3 months) led to a substantial benefit achieving a hazard ratio of 0.72 (95% CI: 0.55 to 0.92) for all cause mortality, and an absolute risk reduction of 11% (3% to 18%). Based on this trial if 1,000 patients were treated for one year 30 deaths would be avoided (95% CI: 9 to 53).

Treatment with calcium channel blockers

Patients with prior MI

Statements

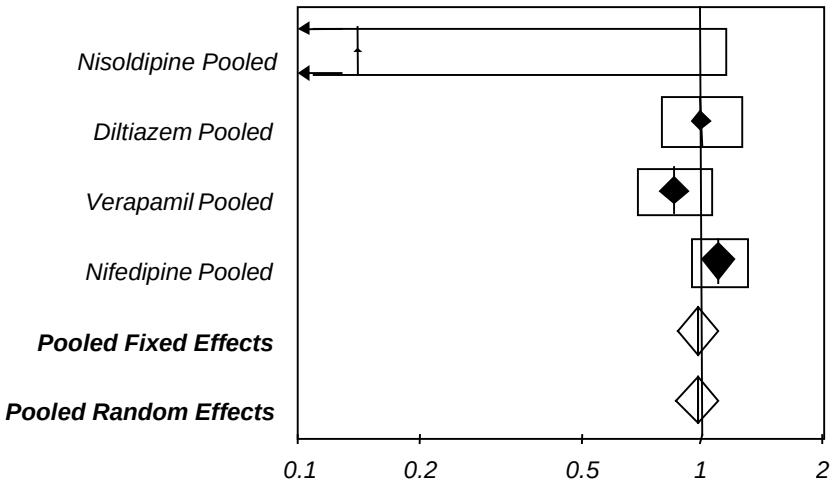
- *Calcium channel blockers are not associated with a reduction in mortality in patients with MI, with the exception of verapamil. However, even for verapamil the observed effect may simply be due to the play of chance (Ia).*

- *Several calcium channel blockers are associated with a reduction in non-fatal MI, though this effect is hard to interpret in the absence of an effect upon mortality (Ia).*

There has been considerable interest in the use of calcium channel blockers in patients who have experienced an MI. We searched for unconfounded trials in which patients who had experienced an MI were treated with calcium channel blockers or control. Trials were only included if treatment had continued for at least one day, and treatment may have been introduced intravenously. We identified 21 trials in which 19,451 were randomised to calcium channel blockers or control. There were 1,549 deaths in these trials (see Appendix 11).

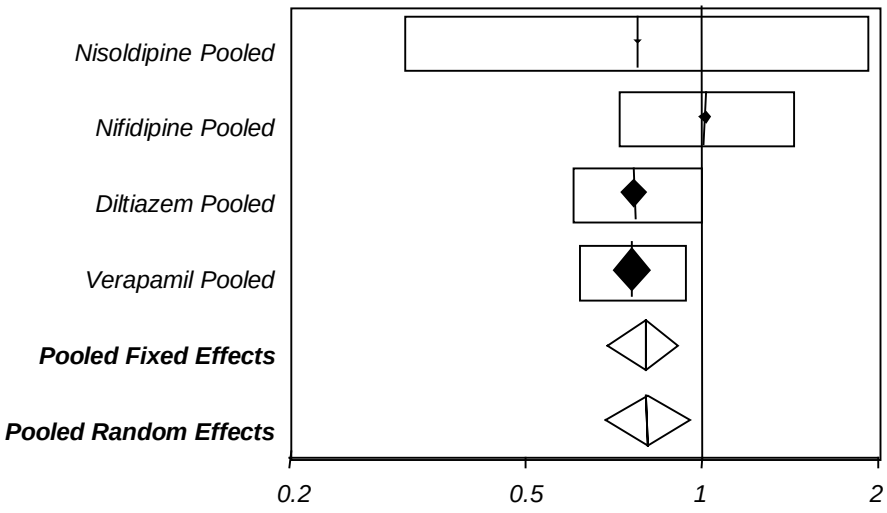
Treatment with a calcium channel blocker was not related to a reduction in all cause mortality (odds ratio 0.99, 95% CI: 0.89 to 1.10, by fixed effects; odds ratio 0.99, 95% CI: 0.87 to 1.12, by random effects) (see Figure 15). The data provide some limited support for the enhanced effect of verapamil rather than alternative calcium channel blockers, which are not a homogenous pharmacological group. Verapamil has been evaluated in a substantial programme of research (see Appendix 11). Overall, verapamil was evaluated in six trials, and in 6,453 patients there were 470 deaths. Although statistically uncertain, the absolute effect from verapamil on all cause mortality was similar to that achieved by other interventions. The effect of calcium channel blockers on non-fatal MI was reported in 14 trials (see Appendix 11).

Figure 15. Effects of calcium channel blockers upon all cause mortality in patients who have experienced a myocardial infarction - odds ratios and 95% confidence intervals



Treatment with a calcium channel blocker was associated with a benefit in reducing non-fatal MI; odds ratio 0.80 (95% CI: 0.70 to 0.92) by fixed effects; odds ratio 0.81 (95% CI: 0.69 to 0.96) by random effects (see Figure 16). If 1000 patients are treated with a calcium channel blocker for a year, 10 non-fatal MIs will be avoided, (95% CI: two to 19). The absence of an effect upon mortality in the trials, coupled with a reduction in non-fatal MI, raises questions about the effects of calcium channel blockers in this group of patients, as some mortality reduction would be expected from this effect.

Figure 16. Effects of calcium channel blockers upon non-fatal MI in patients who have previously experienced an MI: odds ratios and 95% confidence intervals



Calcium channel blockers in patients with heart failure

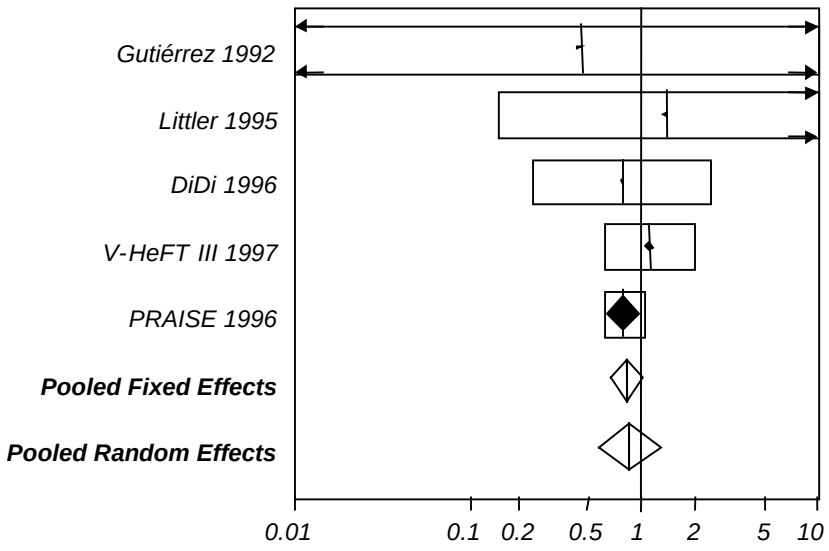
Statement

- *Calcium channel blockers do not lead to a statistically significant reduction in mortality in trials in patients with heart failure. Further data are required to provide greater certainty on the effects of calcium channel blockers in this patient group (Ia).*

There has been some research interest in the use of calcium channel blockers in patients with heart failure. We searched for unconfounded trials of calcium channel blockers compared with control patients, in which treatment was for a period of at least two months. We located nine trials including 2,163 patients. All cause mortality was the only outcome reported reliably and there were 436 deaths. (Included trials are described in Appendix 12.) Calcium channel blockers in patients with heart failure were associated with a non-significant reduction in the odds of death; Odds Ratio 0.83 (95% CI: 0.67 to 1.04) by fixed effects; Odds Ratio 0.86 (95% CI: 0.59 to 1.29) by random effects (see Figure 17).

Thus, on the basis of available data, the effect of calcium channel blockers on mortality in patients with heart failure is uncertain. If 1000 patients with heart failure are treated with a calcium channel blocker for one year, 11 deaths will be avoided (95% CI: -1.5 deaths to 37 deaths).

Figure 17. Effects of calcium channel blockers upon all cause mortality in patients with heart failure – odds ratios and 95% confidence intervals



Potassium channel activators and nitrates in patients with prior MI

Statements

- *There is no evidence to support the use of nicorandil, a potassium channel activator, in patients with prior MI, to prevent mortality or major morbidity (Ib).*

- *Two very large trials in patients post MI found no evidence for the routine use of nitrates in patients who have experienced an MI if the aim is to prevent mortality or major morbidity (Ib).*

Nicorandil, a potassium channel activator, is licenced in the UK for the prophylaxis and treatment of angina. We searched for trials of nicorandil in patients with MI. Only one trial, including just 70 patients was identified (Kobayashi et al, 1998) and this was too small to provide evidence for any beneficial effect of nicorandil in patients with MI.

Two large trials (see Appendix 4) provide good evidence of the effects of nitrates on mortality in MI. GISSI-3 (1994) examined the effectiveness of transdermal GTN 10 mg daily, lisonopril 5-10 mg and open control in 19,394 patients in a factorial designed trial. GTN had no effect on survival; odds ratio 0.94 (95% CI: 0.84 to 1.05). Similarly, ISIS-4 (1995) compared one month captopril, one month oral mononitrate (30-60 mg once daily), intravenous magnesium sulphate and control in 58,050 patients with acute MI in a factorial design trial. No survival benefits for treatment with nitrates were identified (odds ratio 0.97 (95% CI: 0.91 to 1.03).

Cardiac rehabilitation

Statement

- *There is good evidence that cardiac rehabilitation that includes an exercise component is associated with a reduction in mortality and major morbidity in patients post myocardial infarction. Based on the data from randomised controlled trials if 1,000 patients were treated with cardiac rehabilitation commencing soon after myocardial infarction, and followed up for between 3 months and 5 years, 24 deaths will be avoided (Ia).*

- *The importance of different components of cardiac rehabilitation is poorly understood, although the trials included in the overview provided consistent results (Ia).*

Cardiac rehabilitation is often considered a standard component of care post myocardial infarction. We evaluated the evidence for the effectiveness of this intervention, focusing particularly on outcomes for mortality and major morbidity. We searched for unconfounded randomised trials of cardiac rehabilitation programmes post MI that compare rehabilitation to normal care with at least 2 months follow up. Although many trials used a multi-faceted intervention including a range of components of rehabilitation, we selected only those that included an exercise programme. Although we aimed to assess outcomes of mortality, re-infarction, exercise duration and quality of life, only mortality was reported reliably, with limited data on non-fatal myocardial infarction.

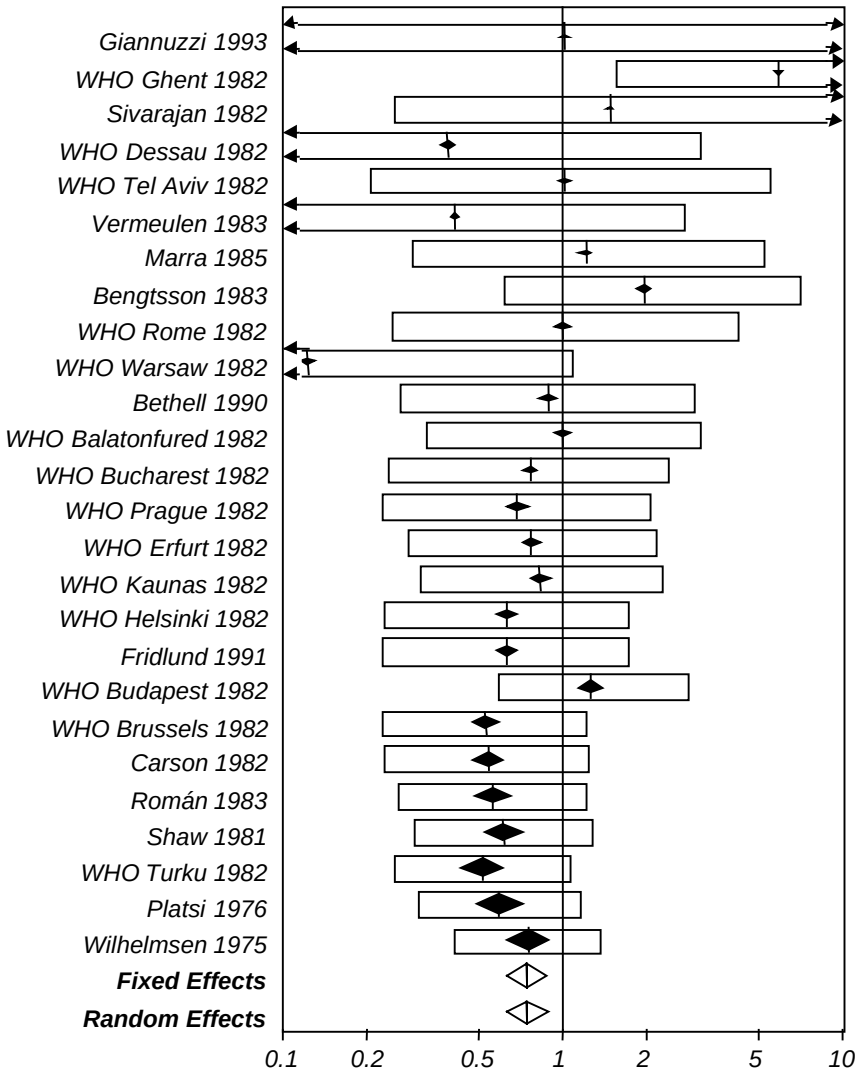
Overall we identified 28 trials that met the entry criteria (see Appendix 13). These trials included 4,972 patients among whom there were 626 deaths. Fourteen comparisons were individual country centres in a WHO trial in the late 1970s. All the trials featured an open design and some had methodological challenges that limit their reliability and validity. For example, Platsi (1976) in which there was a 12 week gap between randomisation and inclusion in the rehabilitation programme, and some patients were excluded after randomisation because they were not considered capable of the rehabilitation programme. However most trials were of an acceptable methodological standard.

Overall cardiac rehabilitation was associated with a substantial reduction in the odds of death in the trials. The fixed effects odds ratio was 0.74 (95% CI: 0.62 to 0.88), and the random effect odds ratio was 0.74 (95% CI: 0.62 to 0.89). The similarity between the pooled fixed and full random effects estimates indicates substantial consistency in the results of the trials included (See Figure 18).

Since cardiac rehabilitation is normally an intervention that is delivered most intensively in the period soon after myocardial infarction, the estimates of absolute benefit presented are not adjusted for the period of treatment or follow up. Thus while providing an indication of the likely magnitude of benefits, the results per 1,000 patients treated may not be comparable to estimates for other interventions. Thus if 1,000 patients were treated with cardiac rehabilitation commencing soon after myocardial infarction, and followed up for between 3 months and 5 years, 24 deaths will be avoided (95% CI: 3 to 45).

Only limited data are available on the effect of cardiac rehabilitation on non fatal myocardial infarction (see Appendix 13). However, these are broadly in line with the results for all cause mortality. Overall, cardiac rehabilitation led to a non significant reduction in the odds of death of non fatal myocardial infarction of 0.79 (95% CI: 0.60 to 1.04) by fixed effects, and 0.78 (95% CI: 0.56 to 1.05) with random effects.

Figure 18. Effect of cardiac rehabilitation on all cause mortality post MI. Reduction in the odds of death, and 95% confidence intervals.



Mediterranean diet

Statement

- *Dietary changes in line with a Mediterranean type diet (in particular the avoidance of meat and dairy products and an increase in the consumption of fatty fish) appear to reduce mortality. Based on the data from randomised controlled trials implementing dietary advice on Mediterranean Diet for 1,000 people for one year would lead to the avoidance of 18 deaths. This finding is in line with evidence that describes the effect of therapeutic doses of poly-unsaturated fatty acids (Ia).*

- *There is an issue about the generalisability of the trials in this area (Ib)*

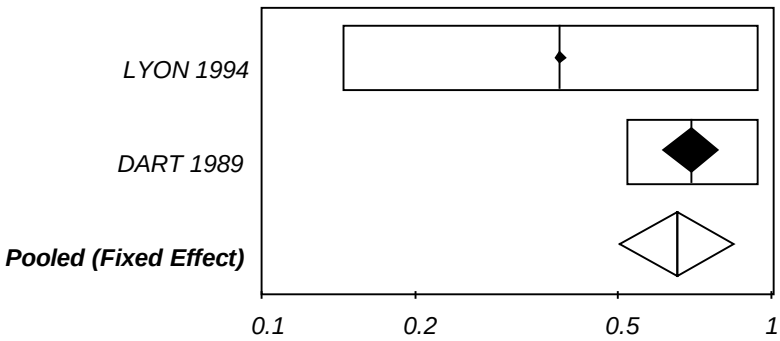
The effect of changing dietary intake in patients at raised risk of cardiovascular events is of some interest in patients with prior myocardial infarction. In particular, the beneficial effects of a Mediterranean diet reported in observation studies (Kafatos 1997) have indicated the importance of further evaluation in experimental studies.

We searched for randomised trials of dietary changes emphasising increased consumption of fatty fish (Mediterranean style diet) in which patients had to have previously experienced a MI. We located just two trials that met these inclusion criteria (see Appendix 14). Together these trials included 2,638 patients allocated to dietary advice or control, among whom 252 deaths were observed.

There are some issues about the quality and interpretation of the findings from these trials. Both trials used an open study design. A single clinical team delivered the Lyon study intervention (LYON 1994) and thus the results may not be extrapolated to others attempting to deliver the same intervention. DART (1989) included several comparisons of different interventions in a factorial design, although only dietary changes featuring an increase in the consumption of fatty fish had an effect of statistical or practical importance. The DART (1989) study findings presented here assume only increased consumption of fatty fish effects mortality and thus discounts potential confounding due to multiple comparisons. After 2 years follow-up 22% of the fatty fish randomised group were taking maxepa capsules as a partial or complete substitute.

Overall allocation to an intervention promoting the Mediterranean style diet was associated with a significant reduction in the odds of death (odds ratio 0.65, 95% CI: 0.50 to 0.85 by fixed effects) (see Figure 19). Implementing dietary advice on Mediterranean Diet for 1,000 people for one year would lead to the avoidance of 18 deaths (95% CI: 7 to 28).

Figure 19. The effect of Mediterranean Diet on all cause mortality: odds ratio and 95% confidence intervals



Allocation to Mediterranean style diet was not associated with a reduction in the risk of non fatal myocardial infarction (odds ratio 1.09, 95% CI: 0.74 to 1.62), indeed a small and non significant increase in the odds of non fatal myocardial infarction was observed in the Mediterranean Diet patients.

These findings appear in line with the recent results from the GISSI Prevenzione trial (1999), in which poly-unsaturated fatty acids were associated with a small but significant reduction in the risk of death in patients who had previously experienced a myocardial infarction.

Valuing alternative treatments

Interpreting the findings from trials

For a GP and a patient trying to resolve appropriate long term therapy following myocardial infarction the problem posed is: how should treatments be sequenced or combined? The recommendations of this guideline are intended to inform such decisions. However, the data from trials present two fundamental problems.

First, patients included in the trials of different drugs are at different levels of underlying risk of further fatal ischaemic heart disease (approximated as the mortality rates found in trial control groups). Thus for two different drugs achieving the same relative reduction in mortality during the same period of time, one drug may appear to generate greater survival benefits although both may be equally effective. It is inappropriate, when trying to quantify benefits of different drugs to a new patient, to compare the trial-based absolute benefits of improved survival since these are obtained from different patients at different underlying risk.

Second, the findings of trials already have a drug sequence implicit in them. In major trials of beta-blockers the most common co-therapies are diuretics, nitrates and digitalis. A similar pattern of co-therapy (although inconsistently reported) is suggested for the trials of antiplatelet drugs, which were conducted during the same period. Hence findings for both beta-blockers and antiplatelet drugs in patients following myocardial infarction can be thought of as preventative therapies in addition to medical management. In major trials of the statins, the majority of patients received aspirin and substantial proportions of patients received beta-blockers, ACE inhibitors, calcium channel blockers or some combination. A similar pattern emerges for the use of ACE inhibitors in patients at raised cardiovascular risk in the HOPE trial. Consequently findings for ACE inhibitors and statins in patients post myocardial infarction are compared with medical management including the use of beta-blockers and aspirin. It is unclear how large the benefits might be of giving a patient a statin or ACE inhibitor instead of a beta-blocker since such a head-to-head trial does not exist. It is more appropriate to consider adding treatments in the order that is implicit in the trials.

For patients with previous myocardial infarction and heart failure, virtually all patients in trials of beta-blockers received an ACE inhibitor. Only a minority of patients in trials of ACE inhibitors received a beta-blocker. In the one trial to date of spironolactone, nearly all patients received an ACE inhibitor but few a beta-blocker. Thus the trials present the value of using an ACE inhibitor in patients with previous myocardial infarction and heart failure, and of adding either a beta-blocker or spironolactone to this.

Comparison between drugs is complicated further by differences in the type of disease and point in the disease process when patients are enrolled. To explore the effect of beta-blockers it has been necessary to analyse separately post-acute phase short-term trials and long term follow-up trials. Trials of ACE inhibitors can be grouped into four categories:

1 Trials of (unselected) patients with previous myocardial infarction (who may or may not have heart failure). The major trials are short term, starting immediately after an acute episode.

2 One long term trial of patients at raised cardiovascular risk (HOPE 2000). Most patients had a history of cardiovascular disease, about half of patients had a previous myocardial infarction and none had heart failure

3 Trials in selected patients with prior myocardial infarction and heart failure

4 Trials in patients with heart failure some of whom may have had a previous myocardial infarction.

These have all been presented since they help to explore the effect of treatment. However, in the sections that follow category 2 is used to best represent patients with previous myocardial infarction, and category 3 for those who additionally have heart failure. Spironolactone has only been trialed in patients with severe heart failure without specific reference to myocardial infarction and so provides less direct evidence than that available for ACE inhibitors. Similarly beta-blockers have been trialed in patients with heart failure who may or may not have experienced myocardial infarction. Evidence from trials of beta-blockers in uncomplicated myocardial infarction enhances the plausibility that patients with both myocardial infarction and heart failure benefit, as do those with heart failure.

Calcium channel blockers and potassium channel activators are not considered further since their ability to improve survival is not established.

Given that the trials do not provide the simple head-to-head results in comparable patients that might be hoped for, one response is to provide a profile of the important attributes of treatments (in this instance effectiveness, tolerability, and cost), with interpretation reflecting the characteristics of the trials, to see if this presents clear indications about how to use available treatments.

The profile approach

Statements

- *In patients with previous myocardial infarction, beta-blockers and aspirin are effective. Statins or ACE inhibitors when used in addition to these treatments are also effective. (Ia)*
- *In patients with previous myocardial infarction and heart failure ACE inhibitors are effective. When used in addition, spironolactone (in severe patients) or a beta-blocker are also effective. (Ia)*
- *All available evidence-based treatments provide benefits at acceptable cost (IV)*

Mortality rates are measured consistently in trials and a rigorous analysis of the propensity of the different treatments to improve survival has been possible. One measure of co-morbidity that is also measured reasonably consistently in trials is non-fatal myocardial infarction and it is notable that this outcome broadly correlates with mortality data, reflecting an influence of treatments upon the underlying process of ischaemic heart disease (Table 1). Other aspects of treatments important to patients include tolerability, side-effect profiles and influence upon quality-of-life. These other aspects of treatment are less consistently reported in trials.

It is apparent that the various treatments offer similar improvements in survival in relative terms (Table 2). The absolute benefits (expressed as incident rate differences) are very different reflecting different baseline risk. It should not generally be presumed that the relative reduction in mortality achieved by a drug in patients at one level of risk would be achieved by patients at another level of risk. However, there is some evidence to support this assumption in drug treatments following myocardial infarction. Stratification of results by prognostic risk markers in the largest trials (LIPID, 1998; BHAT, 1982; HOPE, 2000; Pitt 1999) provides evidence of similar relative reductions in mortality across risk strata. A cautious interpretation of the trials is that the drugs demonstrate similar effectiveness albeit in different patient groups and are similarly well tolerated. It is likely but not certain that all of beta-blockers, antiplatelet drugs, ACE inhibitors and statins will work (on average) similarly well in individual patients with previous myocardial infarction with two major caveats:

- Exclusions from trials of statins were extensive with the consequence that nothing is known about how well these drugs work in patients at higher risk.
- Reflecting the sequencing of drugs in trials the values for statins and ACE inhibitors should be considered as benefits in addition to appropriate first-line use of antiplatelet drugs and beta-blockers.

For patients with heart failure in addition to previous myocardial infarction it is possible to say that ACE inhibitors, beta-blockers and spironolactone offer worthwhile benefits with the following caveats:

- Spironolactone has only been trialed in patients with severe heart failure. Benefits in less severe patients and patients with myocardial infarction in particular are unknown.
- Reflecting the sequencing of drugs in trials the value of beta-blockers and spironolactone should be considered as benefits resulting in addition to appropriate first-line use of ACE inhibitors.

No useful quality-of-life data has been identified from trials relating directly to patients who have previously experienced a myocardial infarction.

Table 2: Comparison of summary findings from trials

	Reduction in all cause mortality 1-Odds Ratio [1]		Reduction in all cause mortality Incident rate difference [2]		Reduction in non-fatal MI Incident rate difference [2]		Reduction in non-fatal stroke Incident rate difference [2]		Withdrawal from treatment % above placebo	
Patients with myocardial infarction										
Beta-blockers	24%	(17% to 30%)	13	(7 to 18)	8	(2 to 14)	NR		1.2%	(0.6% to 1.8%)
ACE Inhibitors	17%	(5% to 27%)	4	(1 to 6)	5	(2 to 7)	3	(1 to 5)	1.7%	(-0.2% to 3.5%)
Statins	24%	(5% to 40%)	4	(2 to 6)	6	(2 to 10)	2	(1 to 3)	NR	
Antiplatelet drugs	16%	(2% to 27%)	7	(1 to 13)	8	(5 to 11)	2	(1 to 4)	NS	
Cardiac Rehabilitation	26%	(11% to 38%)	9	(3 to 16)	NR		NR		NR	
Mediterranean Diet	21%	(6% to 35%)	6	(1 to 10)	NS		NS		NR	
Patients with myocardial infarction and heart failure										
Insulin	36%	(11% to 55%)	31	(2 to 60)	NR		NR		NR	
Patients with myocardial infarction and heart failure										
Beta-blockers	35%	(25% to 45%)	35	(23 to 46)	NR		NR		5%	(-19% to 30%)
ACE Inhibitors	26%	(14% to 34%)	18	(8 to 28)	NS		NR		NR	
Spironolactone	38%	(24% to 49%)	57	(26 to 87)	NS		NS		5%	(2% to 9%)

1 The odds ratios presented are random effects estimates, 95% confidence intervals are shown in brackets

2 Incident rates are calculated as the reduction in the number of events for 1000 patients treated for 1 year when comparing treatment with placebo (see text for explanation)

NR: not reported consistently; NS: data not reported consistently or in a form permitting quantitative summary but indicating no significant difference between treatment and placebo

Since resources are limited, the additional benefits of each new treatment should be set against their costs. Some major trials for some drugs report reductions in hospitalisations during the trial follow-up period: subsequent economic analyses offset the costs of the drugs with savings due to reductions in admissions. Unfortunately these savings are not reported consistently for different drugs. One approach might be to offset drug cost only where trial data is available to demonstrate this. However, savings achieved are affected by the underlying risk of patients enrolled in a trial in the same manner as mortality data are. The various drugs are predicted to achieve similar relative reductions in mortality and morbidity and it is plausible that reductions in hospitalisations will be similar for all of the drugs for new patients being treated. A potential criticism of analysing reductions in hospitalisations measured in trials is that morbidity may have been delayed during the trial period but that patients still have a chronic disease that will progress in time. Additionally, although a drug may achieve additional survival, health care costs tend to increase with age. Consequently it is uncertain whether resource savings achieved in trials of cardiovascular disease are permanent or only temporary. Analysis restricted to using comparable data for all treatments means using just the acquisition costs of the drugs. It is recognised that the net cost of treatments may be overestimated by leaving out reductions in hospitalisation, but that this is likely to be a consistent bias that will not alter their relative costs.

All drugs included in major trials have been costed. Drug treatments for patients with previous myocardial infarction (Appendix 15) and previous myocardial infarction with heart failure (Appendix 16) were costed using the dosing schedules found in the trials. Assuming a common class effect for the effectiveness and tolerability of drugs, the cheapest (based on comparative costs as of November 1999) are shown in Table 3. It is recognised that there is a potential impact on compliance when trading-off cost and frequency of dosing; this is reflected by showing the cheapest once or twice daily dose where this is more expensive than a cheaper but more frequent dose requirement.

Subcutaneous insulin infusion, as a prophylactic treatment for patients with diabetes and prior myocardial infarction, is not a licenced indication in England. Mediterranean diet-type interventions are problematic since patients may bear considerable costs in dietary modification and the trial interventions involved considerable investment by the trialists for which the required resources are unclear. Both of these interventions have been left uncosted although both interventions appear effective. National published data provide a cost for (non-elective) cardiac rehabilitation of £3,035 per person (IQR: £1,705 to £3,503; HRG Code S23, 1998 data).

Considering the acquisition costs of drugs for patients with previous myocardial infarction it is clear that beta-blockers and aspirin are not only effective first line treatment but also very good value for money. Similarly all treatments with patients additionally with heart failure appear good value. In the light of the apparent survival gains, none of the available treatments shown present an unacceptable cost.

In summary GPs and patients are presented with an array of effective drugs for patients post myocardial infarction, with or without complicating heart failure. The value of these should be discussed with patients, and if appropriate, initiated and continued if tolerated.

Table 3: Comparative cost of drug treatments for patients with previous myocardial infarction

Drug class	Drug [1]	Daily Dose [2]	Cost/year [3]
Patients with myocardial infarction			
ACE Inhibitors	ramipril (tritace)	5mg twice daily	249
Antiplatelet drugs	aspirin (generic)	75mg once daily	2
Beta-blockers	propranolol (generic)	80mg three times daily	8
	metoprolol (betaloc)	100mg twice daily	45
Statins	pravastatin (lipostat)	40mg once daily	387
	simvastatin (zocor)	20-40mg once daily	387
Patients with myocardial infarction and heart failure			
ACE Inhibitors	captopril (generic)	25-50mg three times daily	36
	ramipril (tritace)	2.5-5mg twice daily	241
Beta-blockers	propranolol (generic)	40mg three times daily	4
	bisoprolol (emcor/monocor)	5-10mg once daily	118
Spironolactone	spironolactone (generic)	25mg once daily	22

1 For a full listing of the doses and costs of drugs, by drug class, with trial evidence for treatment in patients with myocardial infarction or myocardial infarction and heart failure see Appendices 15 and 16 respectively.

2 Doses shown are the target doses used in trials. Where a dose range has been reported the cost has been calculated by weighting the proportions of each dose used, see Appendices 15 and 16. Where the cheapest form of a drug represents the most convenient (once daily dosing) this is listed exclusively. Where there is a trade-off between more convenient dosing and cost, several forms are listed.

3 Reimbursed cost to prescribe the cheapest priced form of the drug for one year. Source of cost (eMIMS, Nov. 1999). Drug costs vary over time and this table illustrates the relative positioning of drugs based on costs as of November 1999. Practitioners may wish to consult an up to date formulary.

Limitations of the profile approach

A criticism of limiting the discussion to the effects measured during trials is that they may not describe benefits helpfully to patients. For example patients may be interested to know how much longer they are likely to live by taking a (primarily) preventative treatment. Survival gains are considerably truncated by considering only the period of trial follow-up. Furthermore in trying to summarise the costs and benefits of different treatments in a profile we may in fact be running an internal and implicit modelling process where we weigh alternatives up and try to make ‘sensible’ recommendations. This process may be particularly strained when the available trials have failed to deliver simple and interpretable comparisons, as is the case for this guideline. Advocates of the modelling approach argue that it is best to use explicit assumptions to put the evidence together to explore value-for-money and to try to explore thoroughly the assumptions made to see if findings are robust. A modelling approach is presented and its limitations explored.

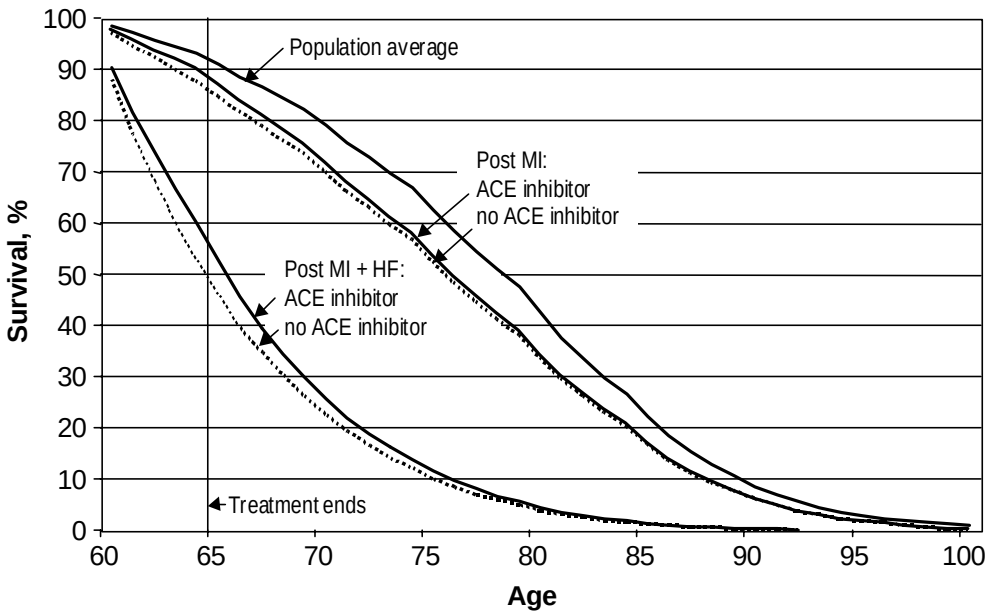
The modelling approach

Statements

- *In patients with previous myocardial infarction, beta-blockers and aspirin are effective. Statins or ACE inhibitors when used in addition to these treatments are also effective. (I)*
- *In patients with previous myocardial infarction and heart failure ACE inhibitors are effective. In addition, spironolactone (in moderate or severe patients) or a beta-blocker are also effective. (I)*
- *All available treatments are estimated to be cost-effective (III)*

The purpose of modelling is to help make meaningful comparisons between available treatments. This involves extrapolating survival gains over the remaining life expectancy of patients. This is achieved by taking the survival rates from the control groups of trials (untreated patients) and modelling their continued survival, adjusted for age, as a hypothetical cohort of patients until all are deceased. In the analyses that follow the modelled treatment group are similar to the control group with the exception that their survival is improved for a treatment period of five years reflecting the relative risk reduction seen in trials (Appendix 17). That is the decision to provide a treatment for the next five years is being explored. For example, the modelled survival curves from trials of ACE inhibitors including patients with previous myocardial infarction (MI) and with or without heart failure (HF) are shown in Figure 20. For reference the population average survival curve is shown.

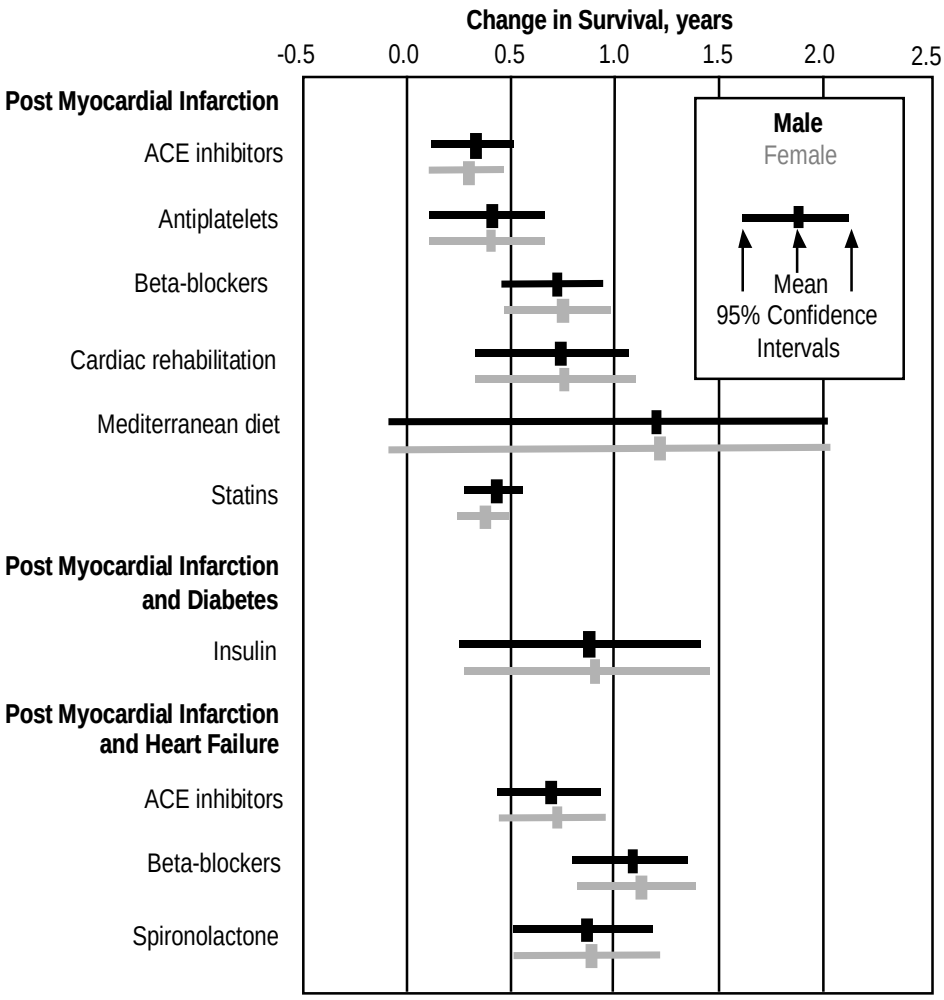
Figure 20: Survival curves extrapolated from trials of patients receiving an ACE inhibitor or placebo. Curves shown are for male patients aged 60 at the start of treatment.



The gain in survival is the area between the treatment and control survival curves. It is notable that patients with heart failure are dying very much more quickly than those without, reflecting more severe underlying disease. Consequently nearly half of the gain attributable to treatment accrues in the modelled 5-year treatment period for patients with heart failure. In patients without heart failure about 80% of the estimated gain from treatment occurs after the 5 year treatment period.

The estimated survival gains for all treatments are tabulated in Appendix 18. Survival gains are similar for different age and gender results: male and female patients aged 65 at the start of treatment are shown in Figure 21.

Figure 21: Estimated survival gains (undiscounted) and 95% confidence intervals. Results shown are for male and female patients aged 65 at the start of treatment*

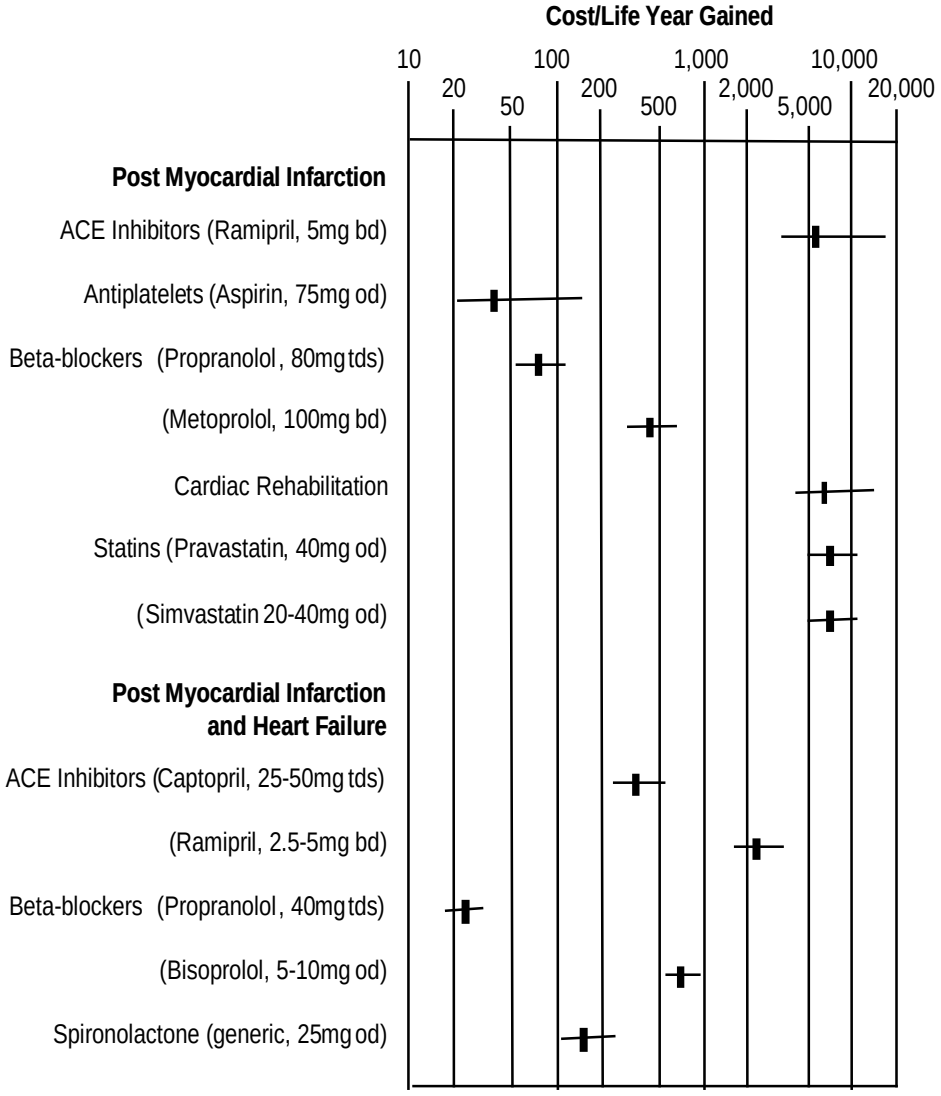


It is notable that predicted survival gains are more similar for the various drugs than the respective incidence rate differences from the trials. The benefit predicted for dietary intervention is not statistically significant due to the cautious use of random effect estimates of relative risk in the modelling process. Treatments are predicted to extend average survival in a patient by between about one quarter and one year of life.

For reasons identified in the previous section, a cautious approach to the cost of drug treatments would simply be to set gain in life expectancy against 5-year cost of prescribing each drug (or in the case of rehabilitation, a one time referral). Costings are not available for Mediterranean diet or insulin interventions. For cardiac rehabilitation the mean cost for inpatient non-elective rehabilitation has been applied. The cost-effectiveness of treatments is shown in Figure 22 for men starting treatment at 65: the findings were not sensitive to age or gender.

* Healthcare decisions can have consequences upon healthcare costs and produce improvements in health that occur many years in the future. It is observable that both individuals and society prefer benefits now and costs later, consequently it is an economic convention to progressively discount costs and benefits as they occur progressively further from the time of decision. When asking by how much a treatment will extend survival it is helpful to the doctor and patient to have this information undiscounted. When considering the cost-effectiveness of treatment alternatives it is usual to discount both future costs and benefits, and commonly this is at a rate of 5% per year.

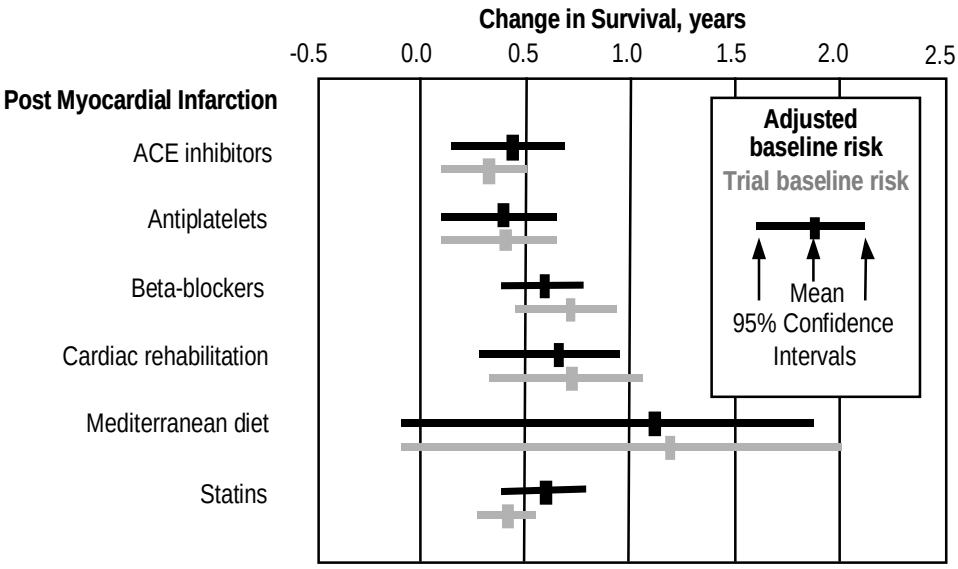
Figure 22: Estimated cost-effectiveness (and 95% confidence intervals) of treatments for patients with prior myocardial infarction: male patients aged 65 at the start of treatment. Future costs and benefits have been discounted at 5%



Reflecting the wide range of costs of treatment, the range of cost-effectiveness of treatments is quite broad. However, the method of estimating costs is conservative and it is apparent that all available treatments fall within accepted bounds of cost-effectiveness. The purpose of the modelling exercise is to provide comparable estimates of cost-effectiveness and Figure 22 gives such a presentation reflecting the patients included in the trials. That is to say we do not know how these cost-effectiveness estimates might change when applied to a new patient with one level of underlying risk rather than the different ones found in the trials of the various treatments.

This can be explored by putting into the model a constant baseline risk for all the treatments and assuming the relative risk reduction for each treatment derived from the trials can be applied. There is some weak evidence to support this step, but nonetheless it is a strong modelling assumption. The consequence of running such a model is that the survival gains become more similar for each of the treatment alternatives (Figure 23).

Figure 23: Estimated survival gains and 95% confidence intervals assuming common underlying risk for all treatments ▬, underlying risk reported in trials ▬, (common underlying risk assumes initial 5% annual all cause mortality in all patients). Results shown are for male patients aged 65 at the start of treatment



This latter model explores the consequence of trying to adjust for different underlying risk in the various trials and suggests that the treatments may in fact have similar effectiveness in terms of prolonging life in any particular risk group. Recalculated cost-effectiveness estimates using this pattern of survival are similar to those shown in Figure 22 and qualitatively the same as estimates based more directly on the trials: this is because the cost-effectiveness estimates are most influenced by the costs of the drugs. Results of this model are tabulated in Appendix 19.

In summary, a modelling approach suggests all available treatments (in Figure 21) demonstrate worthwhile survival gains. Modelling additionally suggests that differences in the survival gains attributed to drugs from trials may be partly explained by differences in the underlying risk of enrolled patients. In patients with previous myocardial infarction beta-blockers, antiplatelet drugs, ACE inhibitors and statins all appear to offer acceptable cost-effectiveness and should be initiated and continued by patients if tolerated, with two caveats:

- Exclusions from trials of statins were extensive with the consequence that nothing is known about how well these drugs work in patients at higher risk.
- Reflecting the sequencing of drugs in trials the values for statins and ACE inhibitors should be considered as benefits in addition to appropriate first-line use of antiplatelet drugs and beta-blockers.

For patients with heart failure in addition to previous myocardial infarction it is possible to say that ACE inhibitors, beta-blockers and spironolactone provide worthwhile survival gains and are cost-effective with the following caveats:

- Spironolactone has only been trialed in patients with severe heart failure. Benefits in less severe patients and patients with myocardial infarction in particular are unknown.
- Reflecting the sequencing of drugs in trials the value of beta-blockers and spironolactone should be considered as benefits in addition to appropriate first-line use of ACE inhibitors.

Limitations of the modelling approach

For trials reported in this guideline, follow-up is generally modest requiring substantial extrapolation to estimate gains in life-expectancy caused by treatment. When extrapolations are conducted these

calculations are not value free. The lower the underlying rate of mortality, the more substantial the extrapolations become and the more speculative the predicted gains due to treatment. Patients who have survived a period of treatment on a particular drug are atypical, unlike healthy people or 'average' patients with the same medical condition. Although analysts strive for face validity and plausibility in their models, extrapolation of survival requires assumptions that cannot be validated.

Audit criteria

The following audit criteria are suitable for use in primary care and are concordant with those within the National Service Framework for Coronary Heart Disease. The baseline population is those patients discharged from hospital having survived a myocardial infarction. The audit criteria require the identification of a sub-set of patients with heart failure.

- Number (and %) of all patients with and without heart failure appropriately taking beta-blockers
- Number (and %) of all patients with and without heart failure appropriately taking aspirin
- Number (and %) of all patients with and without heart failure appropriately taking a statin
- Number (and %) of patients with and without* heart failure appropriately taking an ACE inhibitor
- Number (and %) of patients with heart failure appropriately taking spironolactone
- Number (and %) of all patients (i) offered and (ii) enrolled into a rehabilitation programme

* This criterion is not directly concordant with the NSF due to evidence that has emerged since the NSF was written.

Research questions

The following research questions arose in the course of the guideline development process:

- What are the important elements of cardiac rehabilitation packages?
- What is the effectiveness of cardiac rehabilitation in those patient groups excluded from the trials?
- Which patients with heart failure can have beta-blockers initiated safely in primary care?
- How effective can dietary manipulation be in reducing premature mortality, and what are its resource implications?
- How often do serum lipids need monitoring after initiation of a statin?
- What is the role of statins in patients with heart failure?
- Is spironolactone beneficial in patients with mild (NYHA 1 or 2) heart failure?

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Appendix 1. Included trials that examine the effectiveness of statins

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Proportion with MI	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
4S 1994	Simvastatin: 20-40 mg daily Placebo	Patients aged 35 to 70 years, with history of angina pectoris or acute MI, with fasting serum cholesterol of > 5.5 < 8.0 mmol/l after eight weeks in which they had been given dietary advice.	Secondary hypercholesterolaemia; unstable or Prinzmetal angina; tendon xanthomata; planned CABG or PTCA; MI < six months previously; heart failure requiring treatment; persistent atrial fibrillation; cardiomegaly; haemodynamically important valvular heart disease; history of stroke; impaired hepatic function.	79%	Done	4444	0%	5.4 years	Mortality MI Stroke
CARE 1996	Pravastatin: 40 mg daily Placebo	Patients with previous acute MI in last three to 20 months, aged between 21 and 75 years, with plasma total cholesterol < 6.2 mmol/l, LDL >3 and < 4.5 mmol/l, fasting triglyceride < four mmol/l after at least four weeks of National Cholesterol Education Program Step one diet.	EF < 25%; fasting glucose ≥ 12.2 mmol/l; symptomatic heart failure;	100%	Done	4159	0.02%	5 years	Mortality MI Stroke
CCAIT 1994	Lovastatin: 20-80mg daily to achieve LDL ≤130 mg/dl. Placebo	Patients aged up to 70 years with high risk of coronary progression on angiography. Fasting cholesterol between 5.7 and 7.8 mmol/l.	Previous CABG; angioplasty in previous six months; EF < 40%; left main coronary artery stenosis > 50%; three vessel disease with pre-septal left anterior descending stenosis > 70%; MI or unstable angina within six weeks; co-morbidity.	54%	Done	331	0%	2 years	Mortality Stroke
LIPID 1998	Pravastatin: 40mg daily Placebo	Patients aged 31 to 75 years with diagnosis of acute MI or unstable angina between three and 36 months before study entry. After eight week period of single blind placebo and dietary advice, patients with total cholesterol between four and 7mmols/l, and fasting triglyceride levels less than five mmol/l were eligible.	Clinically significant medical or surgical event with three months, cardiac failure, renal or hepatic disease, current use of any cholesterol lowering drug.	64%	Done	9014	0.01%	6.1 years	Mortality Stroke MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Proportion with MI	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
MAAS 1994	Simvastatin: 20mg daily Placebo	Patients aged 30 to 67 years, who at angiography had ≥2 coronary artery segments arteriographically atheromatous but not totally occluded; angioplasty or bypass surgery not considered necessary; ≥5 segments suitable for quantitative analysis; mean total serum cholesterol 5.5-8.0 Mmol/L; mean successive fasting serum triglyceride concentrations < four mmol/l.	MI or unstable angina within six weeks. Previous CABG, PTCA within three months; heart failure or EF <30%. Diastolic BP > 100mm Hg despite treatment. Fasting plasma glucose concentration > 7.8 mmol/l or diabetes requiring treatment other than diet. Secondary hypercholesterolaemia. Use of lipid lowering agent, oestrogen or steroid within 6 weeks of randomisation	54%	Done	381	0%	4 years	Mortality MI Stroke
MARS 1993	Lovastatin: 80 mg daily Placebo	Patients < 70 years, with coronary artery disease of at least two segments, with at least one showing diameter stenosis of 50% or more (but not total occlusion) and unaltered by PTCA.	Diastolic BP > 115 mm Hg; diabetes mellitus; lipid lowering drugs < two months; candidates for CABG, but not those for PTCA.	60%	Done	270	9.3%	2.2 years	Mortality Stroke
PLAC II 1995	Pravastatin: 10-40 mg/daily Placebo	Patients aged 50-75 years with history of MI or > 50% stenosis of at least one coronary artery. Lipid levels within 60th and 90th percentiles. At least one qualifying extra-cranial carotid lesion.	Plasma triglyceride concentration ≥ 350 mg/dl; untreated hypo or hyperthyroidism; secondary hyperlipidaemia; recent MI (≤ six months); severe or unstable angina; co-morbidity; excessive alcohol consumption.	63.8%	Done	151	Not clear	3 years	Mortality MI Stroke

Appendix 2. Short term trials of beta-blockers in unselected patients who have experienced an MI

Trial	Average Follow Up	Drug Comparison (initial iv)	Blinding	Concealment of Allocation	Loss to Follow up (%)	Objective Outcome/ endpoint	% Heart Failure	Mortality on β-blockers/ total	Mortality among controls/ total
Azancot 1982	1 month	Acebutolol (iv).	Not Blind	Not Clear	0%	Mortality	0%	0/14	0/12
Balcon 1996	28 days	Propranolol	Double	Not Clear	0	Mortality	55%	14/56	15/58
Barber 1976	4 weeks	Practolol	Not Blind	Not Clear	Not Clear	Mortality, re-infarction	Not Clear	10/52	12/47
Campbell 1984	in hospital	Timolol (iv)	Not clear	Not Clear	0	Mortality	Not Clear	1/20	2/19
Clausen 1966	14 days	Propranolol	Not Clear	Not Clear	0	Mortality	Not clear	18/66	19/64
CPRG 1981	8 weeks	Oxprenolol	Double	Not Clear	0%	Mortality, re-infarction	0%	9/177	5/136
Curtis 1991	3.4 days	Propranolol	Double	Not Clear	0	Mortality	Not Clear	0/18	0/12
Dotremont 1968	3-6 weeks	Propranolol	Not blind	Not done	Not clear	Mortality	68.6%	4/36	5/36
Evemy 1978	7 months	Practolol (iv)	Not done	Not Done	Not Clear	Mortality	Not clear	9/46	6/48
Federman 1984	28 days	Timolol (iv)	Not clear	not clear	0%	mortality	0%	1/50	0/50
Fuccella 1968	21 days	Oxprenolol	Not clear	Not clear	14%	Mortality	Not clear	15/106	9/114
Gupta 1982	Not Clear	Propranolol	Not Clear	Not Clear	0	Mortality	Not Clear	0/25	3/25
Gupta 1984	72 hours	Propranolol (iv)	Not blind	Not Clear	Not Clear	Mortality	Not clear	0/15	0/15
Heber 1987	1 year	Labetalol (iv)	Not Done	Not Clear	Not Clear	Mortality	Not Clear	12/83	7/83
Hutton 1979	2 days	Propranolol	Not Clear	Not Clear	0	Mortality	Not clear	0/16	0/13
ICSG 1984	Until discharge from hospital	Timolol	Double	Not Clear	0%	Mortality	57% on therapy for heart failure.	3/73	4/71
ISIS –I 1986	1 year	Atenolol (iv)	Not blind	Not applicable	Not Clear	Mortality	Not Clear	1071/8037	1120/7990
Johansson 1980	6 months	Practolol (iv)/atenolol	Single	Not Done	Not Clear	Mortality	Not Clear	7/25	7/29
Kahler 1968	up to 35 days	Propranolol	double	Not Clear	Not Clear	Mortality, re-infarction	11%	3/38	6/31
Ledwich 1968	7 days	Propranolol	Double	Not Clear	Not Clear	Mortality	Not Clear	2/40	3/40
Lloyd 1988	72 hours	Sotalol (iv)	Not blind	Not Clear	0	Mortality	Not Clear	0/15	0/15
Lombardo 1979	20 days	Oxprenolol	Double	Not Clear	Not Clear	Mortality	0%	8/133	11/127
Macleod 1980	1 week	Practolol IV	Not Clear	Not Clear	0	Mortality	Not clear	1/26	0/26
McMurray 1991	7 days	Xamoterol	Double	Not Clear	0	Mortality	31%	0/25	0/26
MIAMI 1985	15 days	Metoprolol (iv)	Double	Done	2 patients in placebo group	Mortality	23.5	123/2877	142/2901

Trial	Average Follow Up	Drug Comparison (initial iv)	Blinding	Concealment of Allocation	Loss to Follow up (%)	Objective Outcome/ endpoint	% Heart Failure	Mortality on β-blockers/ total	Mortality among controls/ total
Mueller 1980	Until discharge	Propranolol (iv)	Double	Not Clear	Not Clear	Mortality	Not clear	2/35	1/35
Multicentre 1966	28 days	Propranolol	Double	Not Clear	1%	Mortality	11%	15/100	12/95
Nigam 1983	1 week	Propranolol (iv)	Not clear	Not clear	0	Mortality	Not Clear	0/20	0/20
Norris 1968	3 weeks	Propranolol	Double	Done	0	Mortality	Not clear	31/226	24/228
Norris 1978	To discharge	Propranolol (iv)	Not done	Not Done	Not Clear	Mortality to discharge	Not Clear	0/20	0/23
Norris 1984	In hospital	Propranolol (iv)	Not Blind	NA	0	Mortality	Not clear	15/364	14/371
Owensby 1984	3 days	Pindolol (iv)	Not blind	NA	Not Clear	Mortality	Not Clear	1/50	1/50
Peter 1978	To discharge	Propranolol (iv)	Not Done	Not Clear	0	Mortality to discharge	0%	1/47	2/48
Pitt 1976	14 days	Propranolol	Double	Not Clear	0	Mortality	Not Clear	0/9	0/8
Ranganathan 1988	28 days	Timolol (iv)	Double blind iv, followed by open label oral.	Not Clear	2%	Mortality	Not Clear	1/45	3/49
Roberts 1984	36 months	Propranolol (iv)	Single	Not Clear	1 patient	Mortality	4.9%	24/134	20/135
Singh 1985	60 hours	Propranolol (iv)	Not done	Not clear	0%	Mortality	Not Clear	0/8	0/7
Sloman 1967	To discharge	Propranolol (iv)	Not blind	Not Clear	Not Clear	Mortality to discharge	Not Clear	3/26	4/23
Snow 1985	Short term	Practolol	Not Clear	Not Clear	0	Mortality	Not clear	19/76	15/67
Thompson 1979	1 year	Practolol	Double	Not Clear	Not Clear	Mortality	Not Clear	5/72	6/71
TIMI 1989	5 days	15 mg Metoprolol (iv)	Not blind	Not Clear	3.5%	Mortality, re-infarction	1.1%	17/696	17/694
Tonkin 1981	1 year	Timolol	Double	Not Clear	Not Clear	Mortality, re-infarction	Not Clear	1/42	1/46
UKCSG 1985	Until discharge	Timolol	Double Blind	Not Clear	Not Clear	Mortality	Not Clear	4/56	5/55
Van de Werf 1993	10-14 days	Atenolol	Double	Not Clear	0	Mortality, re-infarction	Not Clear	1/100	4/94
von Essen 1982	14 days	Metoprolol (iv)	Double	Not Clear	0	Mortality	Not Clear	1/25	1/26
Waagstein 1975	1 week	Practolol (iv), H87/07, or metoprolol	Double	Not Clear	0	Mortality	Not clear	0/38	0/45
Wilcox 1980b	6 weeks	Oxprenolol.	Double	Done	0	Mortality	28% (withdrawn because of severe heart failure]	14/157	10/158
Yang 1987	14 days	Betaxolol	Double	Not Clear	0%	Mortality	9.4%	0/16	0/15
Yusuf 1980	Followed 10 days re infarct, 1-4 years for mortality	Atenolol (iv)	Not blind	Not clear	Not clear	Mortality, morbidity	6.5%	36/244	44/233

Appendix 3. Long term trials of beta-blockers in unselected patients who have experienced an MI

Trial	Average Follow Up	Drug Comparison (initial iv)	Blinding	Concealment of Allocation	Loss to Follow up (%)	Objective Outcome/ endpoint	% Heart Failure	Mortality on β-blockers/ total	Mortality in controls/ total	Re-infarction on β-blockers	Re-infarction in controls	Withdrawal on β-blockers	Withdrawal in controls
Ahlmark 1974	2 years	Alprenolol	Not Clear	Not Clear	Not Clear	Mortality, re-infarction	Not clear	5/69	11/93	4	15	4	6
Andersen 1979	About one year	Alprenolol	Double	Not Clear	0	Mortality	Not clear	61/238	64/242	-	-	59	49
APSI 1990	318 days	Acebutolol	Double	Done	0	Mortality	49.5	17/298	34/309	-	-	102	109
Aronow 1997 a and b	1 year	Propranolol	Not Clear	Not Clear	Not Clear	Mortality, re-infarction	100%	44/79	60/79	3	5	-	-
Australian/ Swedish 1983	2 years	Pindolol	Double	Not Clear	Not Clear	Mortality, re-infarction	61% LVF	45/263	47/266	12	13	76	50
Baber 1980	9 months	Propranolol	Double	Not Clear	Not Clear	Mortality, re-infarction	Not Clear	28/355	27/365	17	27	82	88
Barber 1967	2 years	Practolol	Not Clear	Not Clear	Not Clear	Mortality, re-infarction	26%	33/207	38/213	-	-	-	-
Basu 1997	6 months	Carvedilol	Double	Not Clear	0%	Mortality, re-infarction	45%	2/75	3/71	4	8	-	-
Beijing 1997	19 months	Atenolol	Open	Not clear	Not clear	Mortality, re-infarction	55%	10/385	24/372	12	7	-	-
BHAT 1982	25 months	Propranolol	Double	Done	0.3%	Mortality	9.2%	138/1916	188/1921	103	121	243	179
EIS 1984	1 year	Oxprenolol	Double	Not Clear	Not clear	Mortality, re-infarction	7.7%	57/853	45/883	36	38	275	275
Hansteen 1982	1 year	Propranolol	Double	Not clear	0%	Mortality, re-infarction	5.9% (on digitalis)	25/278	37/282	16	21	70	72
Hjalmarson 1981	2 years	Metoprolol (iv)	Double Blind for three months then open treatment 2 yr	Not Clear	1.6 %	Mortality(2yr); re-infarction (3 months)	10%	40/698	62/697	35	54	131	131
Julian 1982	12 months	Sotalol	Double	Done	0	Mortality, re-infarction	0	64/873	52/583	37	38	218	121
Kaul 1988	6 months	Propranolol (iv)	Double	Not Clear	0%	Mortality, re-infarction	Not Clear	3/25	3/25	0	4	0	0

Trial	Average Follow Up	Drug Comparison (initial iv)	Blinding	Concealment of Allocation	Loss to Follow up (%)	Objective Outcome/ endpoint	% Heart Failure	Mortality on β-blockers/ total	Mortality in controls/ total	Re-infarction on β-blockers	Re-infarction in controls	Withdrawal on β-blockers	Withdrawal in controls
LIT 1987	18 months	Metoprolol	Double	Not Clear	0.2%	Mortality	2.1%	86/1195	93/1200	-	-	381	355
Manger Cats 1983	1 year	Metoprolol	Double	Not Clear	0%	Mortality	Not clear	9/273	16/280	-	-	-	-
Mazur 1984	1.5 years	Propranolol	Not Blind	Not clear	Not Clear	Mortality, re-infarction	Not Clear	5/101	11/103	5	7	-	-
Multicentre Int 1975	Up to 24 months	Practolol	Double	Not Clear	104 (3.4%)	Mortality, re-infarction	0%	102/1533	127/1520	69	89	389	382
NMSG 1981	17 months	Timolol	Double	Not Clear	Not Clear	Mortality	33%	98/945	152/939	88	141	275	219
PROVED 1995	6 months	Xamoterol	Double	Not clear	12 (17%)	Mortality, re-infarction		3/23	1/24	?	?	3	6
Rehnqvist 1980	1 year	Metoprolol	Not Clear	Not Clear	0	Mortality	Not Clear	4/59	6/52	-	-	12	5
Rehnqvist 1984	36 month	Metoprolol	double	Not clear	0%	Mortality, re-infarction	24% (on digitalis)	25/154	31/147	18	31	38	35
Reynolds 1972	1 year	Alprenolol	double	Done	Not Clear	Mortality, re-infarction	Not clear	3/38	3/39	3	2	4	3
Salathia 1985	1 year	Metoprolol(iv)	Double	Not Clear	0.5%	Mortality,	10%	49/416	52/348	-	-	95	66
Schwartz 1992 [high risk/low risk]	22 months	Oxprenolol	High risk group† single blind, low risk group‡ double blind	Not Clear	0	Mortality, re-infarction	2% in high risk group. Not clear for low risk group	2/48† 15/437‡	12/56† 27/432‡	0	2	11†	9†
SSSD 1993	3 years	Metoprolol	Not blind	Not clear	1.9%	Mortality, re-infarction	100%	17/130	9/123	5	6	-	-
Taylor 1982	48 months	Oxprenolol	Double	Done	Not clear	Mortality, re-infarction	0%	60/632	48/471	67	58	185	141
TIARA 1987	24 months	Timolol (iv)	Double	Not Clear	Not Clear	Mortality	Not Clear	7/102	12/98	-	-	-	-
Wilcox 1980a	1 year	Propranolol* or Atenolol#	Double	Done	0	Death	Not Clear	19/127* 17/132#	19/129	-	-	44* 51#	40* 40#
Wilhelmsson 1974	2 years	Alprenolol	double	Not Clear	7%	Mortality	Not clear	7/114	14/116	16	18	8	8
Yusuf 1979	12 months	Atenolol	Double	Not Clear	4 (23%)	Death; ECG signs	Not Clear	1/11	1/11			2	1

Appendix 4. Trials of angiotensin converting enzyme inhibitors in unselected patients who have experienced an MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Baur 1997	Enalapril: 5 to 20 mg daily Placebo	Patients with ECG ST segment elevation due to acute antero-septal or anterior wall infarction, with peak creatine kinase plasma levels ≥ four times upper limit of normal.	History of clinically important renal, hepatic or haematological disorders; haemodynamically significant valvular disease; systolic BP < 100 mm Hg; right sided HF due to pulmonary disease; poor quality Echo.	Double blind	Not clear	71	Not clear	1 year	Death
Beijing 1997	Enalapril: Titrated to max patient tolerance Control	Patients with acute MI according to standard Chinese and WHO criteria, aged < 75 years, with no contraindication to study drugs, possibility of being followed up for extended period	Excluding those not strictly conforming to those standards	Open	Not clear	721	Not clear	19 months	Death
CATS 1994	Captopril: 12.5 to 75mg daily Placebo	Patients with first anterior wall MI presenting < six hours after onset of symptoms, with ≥ one mV ST segment elevation in lead I and a VL and/or two mV ST elevation in two precordial leads of the 12 lead ECG.	Known intolerance to ACEi; systolic BP > 200 mm Hg or < 100 mm Hg; diastolic BP > 120 mm Hg or < 55 mm Hg; severe valvular heart disease; arrhythmias requiring antiarrhythmic therapy; serious systemic or metabolic disease except diabetes; AV conduction disturbances (PR interval ≥0.24s); left bundle branch block; TIA or stroke < six weeks.	Double blind	Done	298	0.3%	3 months	Death
CCS-1 1995	Captopril: 37.5 mg daily Placebo	Patients within 36 hours of the onset of chest pain (with or without ST elevation) if thought to have no clear contraindication to ACEi.	Persistent hypotension (e.g. systolic BP <90 mm Hg); chronic use of high dose diuretics.	Double blind	Done	13634	0	4 weeks	Death
CONSENSUS-II 1992	Enalapril: 1mg enalapril at (iv) over two hours rising to 20mg daily orally Placebo	Patients within 24 hours of onset of chest pain associated with at least one of: a) ST elevation in ≥2 leads; pathologic Q-waves; enzymes.	BP supine <100/60 mm Hg; need for vasopressor agents hemodynamically severe valvular stenosis; untreated 3rd degree atrioventricular block; history of angioedema; sensitivity to ACE inhibitors or recent use (< one week); co-morbidity; poor compliance.	Double blind	Done	6090	0	1.5 to six months	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
ECCE 1997	Captopril (individually titrated): mean dose 46mg/daily at seven days, and 69mg/daily at 28 days Placebo	Patients with acute MI verified by elevation of creatine kinase > 500 units/L and ECG findings, 24 to 72 hours after the onset of pain.	Contraindications to ACE inhibitors, exercise limitation due to concomitant disease or haemodynamic complications of acute MI.	Double blind	Done	208	0	4 weeks	Death
GISSI-3 1994	Lisinopril: 10 mg daily Open control	Patients with chest pain coupled with elevation or depression of the ST segment of at least one mm in one or more peripheral leads of the ECG, or at least two mm in one or more precordial leads; admitted within 24 hours of symptom onset; with no clear contraindication to study treatments (lisinopril and transdermal glyceryl trinitrate.	Severe heart failure; Killip class 4; high risk of further serious haemodynamic deterioration after treatment with vasodilators (systolic BP ≤100 mm Hg; specific contraindications to study drugs – clinically relevant renal failure (serum creatinine > 177 μmol/L; proteinuria > 500 mg per 24 hour, or both) history of bilateral stenosis or the renal arteries; documented allergy to one of the study drugs; serious co-morbidity.	Open	Done	19394	2.6%	6 weeks	Death
GISSI-3 Pilot 1994	Lisinopril: 5 to 10 mg daily	Patients admitted to coronary care units within 24 hours of the onset of chest pain in stable clinical condition.	Systolic BP < 100 mm Hg; renal dysfunction; Killip class 4; demonstrated contraindication to drugs; bilateral stenosis of renal arteries.	Open	Not clear	1015	< 14.2%	3 days	Death
HEART 1997	Ramipril: 0.625 mg daily 10 mg daily Placebo	Patients aged ≥ 21 years with acute MI within 24 hours.	Contraindications to the use of an ACEi; existing ACEi; serum creatinine level of ≥2.5 mg/dL; cardiogenic shock; persistent ischaemia; hypotension.	Double blind	Done	352	0%	14 days	Death
ISIS-4 1995	Captopril: 6.25 to 100 mg daily No treatment	Patients thought to be within 24 hours of the onset of symptoms of suspected acute MI with no clear indications for, or contraindications against ACEi, magnesium or nitrates.	In judgement of clinician, but suggested avoidance in cardiogenic shock, persistent severe hypotension especially with right ventricular infarction or poor peripheral perfusion; severe fluid depletion; negligibly low risk of cardiac death or severe co-morbidity.	Open	Done	58050	3%	5 weeks	Death
ISIS-4 Pilot 1994	Captopril: 37.5 to 100 mg daily Placebo	Patients within 36 hours of the onset of symptoms of suspected acute MI (with or without ST elevation on the presenting ECG).	Contraindications to prolonged use of nitrates or ACEi (for example systolic BP < 90 mm Hg, or large chronic doses of diuretics)	Double blind (phase II programme)	Not clear	741	0.7%	In hospital	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Jansson 1993	Enalapril: 2.5 to 20 mg daily Placebo	Patients > 18 years, admitted with MI within 254 hours of onset of pain. MI confirmed with: ECG ST segment elevation in two or more contiguous leads; new, evolving pathological Q waves; total creatine kinase or other cardiac specific enzymes elevated.	Systolic BP < 100 mm Hg; diastolic BP < 60 mm Hg. Patients with a clear indication or contraindication for ACEi.	Double blind	Not clear	103	Not clear	6 months	Death
Johnson 1997	Ramipril: 10 to 30 mg Placebo	Patients with first Q wave MI and EF > 40%, with no signs of HF.	Significant valvular disease; symptomatic HF; atrial fibrillation; suspected renal artery stenosis; renal insufficiency with serum creatinine > two mg/DL; child-bearing potential; prior use of or allergy to ACEi; contraindication to MRI.	Double blind	Not clear	44	Not clear	3 months	Death
Lu-Cai 1993	Captopril: Dose unclear Placebo	Patients in the early stage of acute MI	Not clear	Double blind Pilot study	Not clear	98	Not clear	In hospital	Death
Nabel 1991	Captopril: IV 2mg oral 25 to 100 mg daily Placebo	Patients within six hours of onset of symptoms of MI.	Chest pain relieved by nitroglycerine or < 20 minutes duration; age > 75 years; contraindications to thrombolytic therapy; contraindications to ACEi; severe co-morbidity; cardiogenic shock (systolic BP < 85 mm Hg; prior Q wave infarction; pregnancy or ability to become pregnant; prior treatment with ACEi < two weeks before.	Double blind	Not clear	38	30%	3 months	Death
PRACTICAL 1994	Captopril: 75 mg daily Enalapril: 15 mg daily Placebo	Patients presenting within 24 hours of the onset of acute MI associated with: ST segment elevation in ≥2 contiguous electrocardiographic leads; or new pathologic Q waves; or elevation of plasma creatine phosphate.	Persistent hypotension (systolic BP < 90 mm Hg); sensitivity to ACEi or use of ACEi within one week; hemodynamically significant valvular stenosis; clinically severe renal or hepatic disorders; clear indication for ACEi treatment.	Double blind (3 group)	Not clear	225	0%	3 months	Death
Ray 1993	Captopril: 37.5 to 75 mg daily Placebo	Patients presenting within 24 hours of the onset of acute MI, aged 40 to 75 years. MI confirmed with ST elevation in two frontal plane leads with ST depression compatible with posterior wall infarction of at least three mm in two precordial leads.	Patients with Norris score < 3.5; systolic BP < 95 mm Hg; history of significant renal or cerebrovascular disease; contraindications to captopril or a definite indication for its use.	Double blind	Not clear	99	9.3%	1 year	Death
Rodríguez 1997	Ramipril: 5 mg daily Placebo	Patients hospitalised with first episode MI within 72 hours of the onset of pain, confirmed with Q waves, creatine phosphate 1500µI/L.	Valvular disease; cardiogenic shock; NYHA IV; arterial systolic pressure < 100 mm Hg; creatinine > two mg/dL.	Double blind	Not clear	55	Not clear	6 months	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Schulman 1995	Enalapril: IV 1mg followed by 5 to 20 mg daily Placebo	Patients with anterior MI presenting within 24 hours of onset of pain with evidence of ≥2 contiguous electrocardiographic leads. BP ≥ 105/65 mm Hg.	Creatinine > 2.5 mg/DL; hepatic, neurologic, or other life threatening diseases. History or ECG indicating prior MI; cardiogenic shock; aortic stenosis; cardiomyopathies.	Double blind	Not clear	43	Not clear	1 month	Death
Sharpe 1991	Captopril: 100 mg daily Placebo	Patients with definite Q wave MI clinically stable 24-48 hours after onset of pain who could tolerate a test dose of 12.5 mg captopril.	Ongoing myocardial ischaemia; atrial fibrillation or other arrhythmias requiring treatment; valvular disease; clinical congestive heart failure; hypotension (systolic BP < 90 mm Hg); chronic lung disease; renal impairment (serum creatinine above 0.20 mmol/L) or other serious co-morbidity.	Double blind	Not clear	100	0%	3 months	Death
SMILE 1995	Zofenopril: 15 to 60 mg daily Placebo	Patients aged 18 to 80 years presenting to intensive care unit < 24 hours of onset of chest pain typically associated with electro-cardiographic signs of MI of the anterior wall and not eligible for intensive care because of late admission to ICU or contraindications to systemic fibrinolysis. MI confirmed by ECG changes in the ST segments or T waves in at least two contiguous precordial leads with or without new abnormal Q waves.	Cardiogenic shock (Killip class 4); systolic BP < 100 mm Hg on admission; serum creatinine concentration > 221µmol/L; history of HF; treated with ACEi; contraindications to ACEi.	Double blind	Not clear	1556	Not clear	1 year	Death
Yoshitomi 1998	Imidapril: iv 2.5 mg infusion over 24 hours oral three to five mg daily Control	Patients with acute MI receiving primary PTCA and stenting within four hours of the onset of pain.	Not clear	Open	Not clear	40	0%	3 months	Death

Appendix 5. Trials of angiotensin converting enzyme inhibitors in selected patients who have experienced an MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
AIRE 1993	Ramipril: 5 to 10 mg daily Placebo	Patients aged > 18 years, with definite MI and clinical evidence of heart failure at some time post MI. MI defined as evolving ECG diagnostic of MI (i.e. progressive changes in the ST segment and T wave compatible with MI, with or without presence of Q waves, and abnormal cardiac enzymes (i.e. creatinine and/or aspartate aminotransferase and/or lactic dehydrogenase ≥ twice normal laboratory range. HF defined as at least one of: evidence of LVF (pulmonary venous congestion with interstitial or alveolar oedema at least one chest X ray; evidence of pulmonary oedema (bilateral post-tussive crackles extending ≥ 1/3 up lung fields in absence of chronic pulmonary disease; auscultatory evidence of a third heart sound with persistent tachycardia.	Severe heart failure (usually NYHA IV); HF of primary valvular or congenital aetiology; unstable angina; recognised contraindication to ACEi,	Double blind	Not clear	1986	0.05%	15 months	Death
Galcera-Tomas 1993	Captopril: Placebo:	Patients within 24 hours of first anterior MI, with ST segment elevation in ≥ three precordial leads, with retrospectively documented Q waves and typical enzyme changes, less than 70 years of age.	Valvulopathy or myocardiopathy; Killip class grade III or IV; clinical or enzymatic evidence of infarct extension.	Double blind	Not clear	43	0%	14 days	Death
Gøtzsche 1992	Captopril: 50 mg daily Placebo	Patients aged ≤ 70 years, randomised on day seven after MI, with at least one of: signs of HF needing diuretics < five days of MI; LV ≤ 45%.	Receiving medication for HF before admission; systolic BP < 100 mm Hg; atrial fibrillation; valvular heart disease; LV aneurysm; serious systemic disease; hepatic or renal impairment (serum creatinine > 150 μmol/L; EF < 25%.	Double blind	Not clear	62	1.6%	6 months	Death
Gutiérrez 1992	Captopril: 25 to 100 mg daily Placebo	Patients admitted to ICU with first MI of any location, with EF < 40%.	Not clear	Double blind	Not clear	20	Not clear	12 months	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
SAVE 1992	Captopril: 12.5 to 150 mg daily Placebo	Patients aged > 21 years and < 80 years, ≥ three days post MI, with EF ≤ 40%.	Failure to undergo randomisation within 16 days of MI; relative contraindication to ACEi or need for ACEi; serum creatinine > 221 µmol/L; other conditions considered to limit survival; unstable course after MI.	Double blind	Done	2231	0.3%	42 months	Death
TRACE 1995	Trandolapril: 1 to four mg daily Placebo	Patients aged > 18 years, hospitalised with MI between two and six days of the onset of pain with EF ≤35%. MI confirmed by chest pain or ECG changes in line with MI, accompanied by an increase to at least twice upper limit of normal value at laboratory of participating hospital.	Absolute or relative contraindication to ACEi or definite need for ACEi; severe uncontrolled diabetes; hyponatraemia (<125 mmol/L Sodium); serum creatinine ≥ 2.3 µmol/L; pregnancy or lactation; acute pulmonary embolism; vascular collagen disease; non-ischaemic obstructive heart disease; unstable angina requiring immediate invasive therapy; severe liver disease; neutropenia; concurrent immunosuppressive or antineoplastic therapy; drug or alcohol abuse; treatment with another investigational drug..	Double blind	Done	1749	Not clear	24 to 50 months	Death

Appendix 6. Trials of angiotensin converting enzyme inhibitors in selected patients who may, or may not, have experienced an MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Ahlner 1988	Enalapril: 10 to 40 mg daily Placebo	Patients with > three months of symptoms of HF, stabilised on conventional therapy and enalapril (target dose 40 mg daily) randomised to continue enalapril or receive placebo.	Acute MI or unstable angina < three months; systolic BP < 90 mm Hg; symptomatic ventricular arrhythmias; stenotic valve disease; hypokalaemia; serum creatinine > 300 μmol/L or severe co-morbidity.	Double blind	Not clear	19	Not clear	8 weeks	Death
Barabino 1991	Captopril: 37.5 to 75 mg daily Placebo:	Patients older than 65 years, with mild to moderate HF (NYHA II to II/IV) on stable therapy with digitalis and or diuretics. Diagnosis based upon clinical findings with exercise intolerance limited by dyspnoea or fatigue, or both, sings of fluid retention, cardiothoracic ratio >0.52.	Severe and irreversible heart failure requiring intravenous inotropic agents; aortic and mitral valve stenosis; MI or stroke < two months; systemic arterial hypotension (SBP < 80 mm Hg): severe pulmonary, hepatic, renal or neurological diseases; concurrent therapy with beta-blockers; unstable angina or history of captopril or ibopamine intolerance; digitalis toxicity; inability to walk on flat corridor for at least 100 m in six minutes.	Double blind for six months, then open	Done	150	1%	1 to 48 months	Death
Brilla 1991	Enalapril : 5 mg daily Control	Patients with severe heart failure (NYHA III – IV) treated with digitalis and diuretics, aged < 70 years.	Systolic BP < 90 mm Hg.	Open	Not clear	40	0%	1 year	Death
Bussmann 1987	Captopril: 36 to 150 mg daily Placebo:	Patients with severe heart failure (NYHA III to IV) who were in a stable condition for ≥ three weeks prior to randomisation.	Not clear	Double blind	Not clear	23	0%	6 months	Death
Cannavà 1990	Enalapril: 10 mg daily Control	Patients with HF (NYHA II to IV), aged 33 to 71 years.	Valvular disease; angina; intermittent claudication; MI < 90 days; systolic BP < 90 mm Hg; treatment with vasodilator.	Open	Not clear	120	Not clear	1 year	Death
CASSIS 1995	Enalapril: 5 to 10 mg daily Spirapril: 1.5 to six mg daily Placebo:	Patients with HF secondary to coronary heart disease or dilated cardiomyopathy; ability to perform exercise tolerance test between two and 14 minutes; EF < 40% or cardiothoracic ratio > 0.55.	Patients with other causes of HF; with MI < one month; uncontrolled hypertension; unstable angina; clinically relevant arrhythmias; hypotension (systolic BP < 90 mm Hg); uncontrolled diabetes; clinically relevant renal, hepatic, gastrointestinal, neurological, haematological disease; a serum creatinine concentration > 180 mmol/L; hypersensitivity to ACEi.	Double blind to four fixed dose groups or placebo	Not Clear	248	0%	12 weeks	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
CCMG 1995	Captopril: 55.5 to 225 mg daily Cilazapril: 0.5 to 2.5 mg daily Placebo:	Patients aged ≥ 18 years, with NYHA II-IV, clinically stable on digitalis and/or diuretics.	MI or stroke < three months; surgery for primary valvular disease or pacemaker implantation indicated; systolic BP < 90 mm Hg; clinically significant disease; previous medication such as positive inotropes (except digitalis), beta-blockers, ACEi all discontinued.	Double blind	Not clear	443	Not clear	3 months	Death
CDMRG 1988	Captopril: 75-150 mg daily Placebo:	Patients aged < 75 years, with EF ≤40%; treadmill exercise limited by dyspnoea or fatigue; with sinus rhythm and heart failure secondary to ischaemic heart disease or primary myocardial disease, or those without significant valvular regurgitation after valvular surgery;	Concomitant therapy with inotropic agents, vasodilators, beta-blockers; Ca antagonists; immunosuppressive agents or other investigational drugs; MI < two months; unstable angina; hypertension (systolic > 160 or diastolic > 95 mm Hg); pulmonary disease.	Double blind	Not clear	300	1.7%	12 weeks	Death
Circio 1995	Delapril: 15 to 60 mg daily Placebo:	Patients aged 25 to 70 years, with NYHA II or III (with symptoms ≥ three months), with a diagnosis of dilative or ischaemic cardiomyopathy.	Acute HF or MI < three months; stroke < six months; hypotension (systolic BP < 90 mm Hg or diastolic BP < 60 mm Hg; resting angina or exercise angina; exercise test that may have been affected by intermittent claudication, symptomatic pulmonary disease, severe neurologic or muscular disease); valvular disease likely to require surgery; severe mitral or aortic stenosis, acute myocarditis; pericarditis; hypertrophic cardiomyopathy; arrhythmias or conduction problems; hyperaldosteronism; renal artery stenosis; haemodialysis or only one functional kidney; renal or hepatic failure; unstable diabetes; collagen disease; hypokalaemia or hyperkalaemia; severe allergic diathesis; family history of angioneurotic oedema.	Double blind 2:1	Not clear	101	1%	8 weeks	Death
Cleland 1985	Enalapril: 20-40 mg daily Placebo:	Patients with chronic HF with NYHA II-IV.	Patients with severe valvular regurgitation; co-morbidity	Double blind	Not clear	20	0	2 months	Death
CMRG 1983	Captopril: 75-150 mg daily Placebo:	Patients aged 30 to 77 years, with chronic HF refractory to digitalis therapy.	Supine systolic BP < 95 mm Hg, angina pectoris requiring frequent nitrate therapy; uncontrolled hypertension; MI < four months; hepatic or renal impairment; uncorrected valvular or pericardial disease.	Double blind	Not clear	92	1.1%	12 weeks	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Colfer 1992	Benazepril: 2-20 mg daily Placebo:	Patients aged > 18 years with NYHA II-IV, resting EF ≤ 35%; receiving digoxin and diuretics.	Use of drugs known to affect BP including vasodilators (including long acting nitrates), beta-blockers, although discontinuation ≥ three days before randomisation allowed.	Double blind 2:1	Not clear	172	1.2%	12 weeks	Death
CONSENSUS one 1987	Enalapril: 2.5 to 40 mg daily Placebo:	Patients with severe HF (NYHA IV) receiving optimal treatment with digitalis and diuretics.	Patients who improved to NYHA III during 14 day placebo period; acute pulmonary oedema; hemodynamically important aortic or mitral valve stenosis; MI < two months; unstable angina; planned heart surgery; right heart failure due to pulmonary disease or serum creatinine concentration above 300μmol/L	Double blind	Done	253	0%	6.7 months	Death
De Bock 1994	Captopril: 50 mg daily Placebo:	Patients aged ≥ 70 years with chronic heart failure (Boston Score > 4) were eligible.	Patients receiving ACE inhibitor, beta-blocker, Ca blocker, amiodarone. Evidence of malignancy, chronic obstructive pulmonary disease, dementia, arterial insufficiency of the legs, inability to walk, creatinine clearance < 20 ml/minute, hemodynamically important valvular disease, or other important co-morbidity.	Double blind	Not clear	50	0%	6 months	Death
Dickstein 1991	Enalapril: Placebo:	Patients in NYHA II-IV with history of MI (> six months previously) and peak oxygen consumption < 25 ml/kg per min.	Patients unable to perform exercise until exhaustion on cycle ergometer	Double blind	Not Clear	41	0%	48 weeks	Death
Dössegger 1993	Cilazapril: 1 to five mg daily Placebo:	Patients with NYHA II-IV HF for > three months stable on digitalis and/or diuretics	MI or stroke < three months; worsening HF < one month; hypertrophic cardiomyopathy; supine systolic BP < 90 mm Hg; co-morbidity.	Double blind 2:1	Not clear	117	0%	12 weeks	Death
Drexler 1989	Cilazapril: 2.5 to five mg daily Placebo:	Patients with NYHA II-IV chronic HF; EF<45%.	Unable to achieve three minutes workload at 25W on supine bicycle exercise.	Double blind	Not clear	21	0%	12 weeks	Death
Enalapril CHF 1987	Enalapril: 5 to 20 mg daily Placebo:	Patients aged 16 to 78 years, with NYHA II to IV HF.	Less than four minutes, and greater than 16 minutes exercise capacity.	Double blind	Not clear	256	0.4%	12 weeks	Death
Farchtein 1986	Enalapril: 10 to 20 mg daily Placebo	Patients taking digoxin and diuretics, in NYHA class one to III, with exercise tolerance of three to nine minutes, and EF < 60%.	Pregnant women or those without adequate contraception; patients needing anti hypertensives or cardiac drugs except digitalis; valvular disease; systolic BP < 60 mm Hg.	Double blind	Not clear	14	7%	14 weeks	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
FHFSG 1995	Fosinopril: 10 to 20 mg daily Placebo:	Patients aged 18 to 75 years, with NYHA II to III, EF ≤35%, treadmill exercise tolerance between two and 16 minutes duration with fatigue or dyspnoea as limiting symptom.	Inability to perform exercise tolerance tests; recent MI or angina; significant obstructive cardiac valvular disease; restrictive or obstructive cardiomyopathy; seated systolic BP < 90 mm Hg; significant chronic obstructive pulmonary disease; severe hepatic or renal dysfunction; atrial fibrillation or flutter requiring digitalis; history of collagen vascular or autoimmune disease; leukopenia or neutropenia; hypersensitivity to ACEi; alcohol or drug abuse; ineffective contraception in premenopausal women.	Double blind	Not clear	241	1.2%	24	Death
Gilbert 1993	Lisinopril: ≤20 mg daily Placebo:	Patients with NYHA II-IV, and EF > 45%	Not clear	Double blind	Not clear	20	0%	3 months	Death
Giles 1990	Lisinopril: 5 to 20 mg daily Placebo:	Patients with heart failure (NYHA II-IV) who were receiving diuretics and digoxin, with clinical diagnosis of HF supported by EF < 45% and/or cardiothoracic ratio ≥ 0.5. Able to exercise on motorised treadmill for between one and 12 minutes with exercise limited by fatigue, dyspnoea or both.	Clinically important renal, hepatic or hematologic disorders; hyperkalaemia; hypokalaemia; MI < three months; stroke < six months; unstable angina; predominant cor pulmonale; hemodynamically significant aortic stenosis; systolic arterial pressure < 80 mm Hg; evidence of digitalis toxicity.	Double blind 2:1	Not clear	193	1.6%	12 weeks	Death
Gordon 1991	Ramipril: Placebo:	EF ≤ 35% exercise duration 4-12 minutes	Not clear	Double blind	Not clear	192	0.5%	12 weeks	Death
Hattori 1997	Cilazapril: 1 to two mg daily Control	Patients with NYHA II to II HF, and EF 35% (± 6%), stable on diuretics and digitalis.	Not clear	Open	Not clear	32	0%	2 months	Death
Jakob 1995	Captopril: 12.5 to 50 mg daily Placebo	Patients with HF (NYHA II to III), aged 18 to 70 years, with idiopathic dilated cardiomyopathy and reduced anaerobic threshold (≤11 $ml.kg^{-1}$, representing mild to moderate limitation of exercise capacity.	Non compliance; exercise test not possible because of severe HF or attendant diseases; ACEi contraindicated; female of child bearing age.	Double blind	Not clear	33	0%	2 months	Death
Keren 1992	Captopril: Dose not clear Placebo:	Patients with NYHA III-IV HF treated with digitalis and furosemide.	MI < six months; primary valvular disease; restrictive cardiomyopathy; chronic pulmonary hepatic or renal disease.	Double blind	Not clear	50	0%	1 year	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Kleber 1992	Captopril: 50 mg daily Placebo:	Clinical diagnosis of HF, NYHA I-III.	NYHA IV, co-morbidity, haemodialysis or peritoneal dialysis for chronic renal failure; connective tissue disease; immunosuppressive therapy; renal artery stenosis; gestation and lactation; significant aortic or mitral stenosis	Double blind for 2.7 years	Not clear	170	0%	3.7 years (2.7 double blind)	Death
Lechat 1993	Perindopril: 2 to four mg daily Placebo:	Patients aged 18 to 75 years, with NYHA II-III HF, exercise capacity of four to 15 minutes not limited by angina.	HF caused by organic non operated valvulopathy or valvulopathy operated on in last year; vasodilator therapy could not be interrupted; unstable angina; cerebrovascular accident or MI < three months; chronic obstructive airways disease; clinically important hepatic or renal dysfunction; paroxysmal arrhythmia; systolic BP < 60 mm Hg or heart rate > 130 or < 60 beats per minute.	Double blind	Not clear	125	2.4%	12 weeks	Death
Lemarie 1992	Ramipril: 5 mg daily Placebo:	Patients with NYHA II-III, with Volume oxygen maximum 10-20 mg/kg/min	Not clear	Double blind	Not clear	85	1.2%	6	Death
Lubsen 1996 (European)	Ramipril: 2.5 to 10 mg daily Placebo:	Patients with chronic HF aged 18 to 80 years with EF ≤40%, or heart size > 600 ml/m^2 in NYHA II or III.	Present use or, or known intolerance to, ACEi.	Double blind	Not clear	500	0% (35 patients excluded due to missing source data)	12 weeks	Death
Lubsen 1996 (South Africa)	Ramipril: 2.5 to 10 mg daily Placebo:	Patients with chronic HF aged 18 to 80 years with EF ≤40%, or heart size > 600 ml/m^2 in NYHA II or III.	Present use or, or known intolerance to, ACEi	Double blind	Not clear	95	1.1%	3 months	Death
Maass 1991	Ramipril: ≤ 10 mg daily Placebo:	Patients with NYHA III-IV	Not clear	Double blind	Not clear	132	0%	16 weeks	Death
MacFadyen 1997	Perindopril: 2 to four mg daily Placebo	Patients with prior MI in NYHA II to III.	Treatment with ACEi < two weeks from randomisation.	Double blind	Not clear	24	0%	8 weeks	Death
Magnani 1986	Captopril: ≤ 75 mg daily Placebo:	Patients with NYHA III-IV	Not clear	Double blind	Not clear	94	0	18 months	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
McGarry 1991	Benazepril: Placebo:	Patients with NYHA II-III; EF < 35%; Exercise duration one to 16 minutes.	Not clear	Double blind	Not clear	61	0	3 months	Death
Nicholls 1984	Enalapril: 10 mg daily Placebo:	Patients aged 55 to 74 years with HF due to coronary artery disease or cardiomyopathy (NYHA II-IIII).	Not clear	Double blind	Not clear	16	0	12 weeks	Death
Northridge 1993	Quinapril: 10 to 20 mg daily Placebo:	Patients with mild HF (NYHA II-III) attending outpatient clinics, with EF < 50%, stable on diuretics.	MI < three months; obstructive valve lesions; limiting angina; exercise capacity limited by any symptom apart from dyspnoea or fatigue; clinically significant hepatic or renal dysfunction; connective tissue disease; supine systolic BP > 160 or < 90 mm Hg; allergy to, or previous failure to respond to ACE I.	Double blind	Not clear	32	0%	8 weeks	Death
Pflugfelder 1993	Quinapril: 10 to 20 mg daily Placebo:	Patients with NYHA II-III HF, EF ≤ 35%, and maximal treadmill exercise time ≤ 15 minutes.	Concurrent therapy with beta-blockers, alternative ACEi, vasodilators, potassium sparing diuretics, calcium channel blockers, flecainide, ecainide, disopyramide. Patients unable to tolerate ≥ 10 mg daily quinapril in ≥ 10 week single blind run in period.	Double blind	Not clear	224	0%	16 weeks	Death
Riegger 1990	Quinapril: 10, 20 or 40 mg daily Placebo:	Patients with NYHA II-III with exercise time ≥ two minutes limited by dyspnoea.	Exercise time limited by factor other than dyspnoea; rapidly deteriorating HF; MI < three months; mitral stenosis; aortic stenosis; obstructive lesions of the left ventricular outflow tract; non ischaemic HF; resting systolic BP < 100 mm Hg; concomitant therapy with vasodilators, beta-blockers, calcium antagonists, other ACE inhibitors or potassium sparing diuretics.	Double blind	Not clear	225	0%	12 weeks	Death
Rucinska 1991a	Enalapril: ≤ 20 mg daily Placebo:	Patients with NYHA II-IV; EF < 40%.	Not clear	Double blind	Not clear	132	1.5%	12 weeks	Death
Rucinska 1991b	Enalapril: ≤ 40 mg daily Placebo:	Patients with NYHA II-III; Volume oxygen maximum 10-25 ml/kg	Not clear	Double blind	Not clear	110	0%	12 weeks	Death
Rucinska 1991c	Lisinopril: ≤ 20 mg daily Placebo:	Patients with NYHA II-III; Volume oxygen maximum 10-25 ml/kg	Not clear	Double blind	Not clear	58	0%	12 weeks	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Santiparplua cha 1992	Enalapril: 5 to 40 mg daily Placebo	Patients with a clinical diagnosis of systolic heart failure.	Considered unlikely to attend for follow up	Double blind	Done	59	17%	12 months	Death
SOLVD 1991	Enalapril: 2.5 to 20 mg daily Placebo:	Patients with HF and EF ≤35%.	Aged > 80 years; hemodynamically serious valvular disease requiring surgery; unstable angina; angina requiring revascularization; MI < one month; severe pulmonary disease; serum creatinine > 177 μmol per litre; co-morbidity.	Double blind	Done	2569	0.1%	41.4 months	Death
Swedberg 1991	Ramipril: ≤ 10 mg daily Placebo:	Patients with NYHA II to III, EF < 40% and enlarged heart size.	Not clear	Double blind	Not clear	223	0	3 months	Death
Uprichard 1994a	Quinapril: 5 to 40 mg daily Placebo:	Patients with NYHA II-III, EF <0.45, exercise duration from four to 10 minutes	Not clear	Double blind	Not clear	208	0%	16 weeks	Death
Uprichard 1994b	Quinapril: 10 to 40 mg daily Placebo:	Patients with NYHA II-III, EF <0.45.	Not clear	Double blind	Not clear	186	0%	12 weeks	Death
Yodfat 1991	Captopril: ≥ 25 mg daily Placebo	Patients in family practice, in NYHA II or III, receiving ≤ 80 mg furosemide daily, with HF caused by coronary heart disease or dilated cardiomyopathy.	MI or cardiac surgery < three months; digoxin or any ACEi; pregnancy; lactation; aortic stenosis; heart blocks; complex ventricular tachyarrythmias; renal insufficiency; leukopenia; chronic lung disease; angina at rest; malignant disease; recurrent dermatoses; collagen disease; cerebrovascular accident or transient ischaemia; chronic treatment with immunosuppressives; NSAIDs; quinidine; H_2 blockers.	Double blind	Not clear	84	0%	12 weeks	Death
Zwehl 1990	Lisinopril: ≤20 mg daily Placebo:	Patients with NYHA II-IV, EF<45% or CT > 0.5. Exercise duration four to 16 minutes.	Not clear	Double blind	Not clear	275	4%	3 months	Death

Appendix 7. Addition of beta-blockers to conventional therapy in patients with heart failure.

Trial	Inclusion criteria	Exclusion criteria	Lost to follow up (%)	Concealment of allocation	Blinding	NYHA	Prior MI (%)	Idiopathic cardiomyopathy (%)	Ejection fraction	ACEi (%)	Drug (dose)	Death with BB	Total on BB	Death on control	Total Controls	Follow up (years)	Withdrawl in BB	Withdrawal in Controls
Anderson 1985	Patients with stable chronic symptomatic heart failure caused by idiopathic dilated cardiomyopathy, NYHA II/III, EF<40%.	Advanced heart block and allergy.	4	Not Clear	Not Clear	2.8	0	100	28	NA	Metoprolol (mean daily dose 61 mg)	5	25	6	25	1.58	5	NA
Aronow 1997	Men & women aged 62 years or more, with NYHA II/III, prior MI, EF >40% after two months treatment with ACEi & diuretics.	Valvular heart disease, systolic BP <100 mm Hg, bronchospasm, hepatic disease; renal insufficiency; sinus bradycardia; greater than first degree heart block; severe peripheral arterial disease.	0	Not Clear	Not Clear	2.48	100	0	56.5	100	Propranolol (90 mg daily)	44	79	60	79	2.67	11	0
Australia/New Zealand 1997	Chronic stable heart failure due to ischaemic heart disease with EF<45%. Current NYHA II/III, who had tolerated test dose of carvedilol for two to three weeks (94% tolerated this).	NYHA IV; heart rate below 50 bpm; sick sinus syndrome; second-degree or more heart block; BP <90 mm Hg systolic, or above 160/100 mm Hg; treadmill exercise duration < two min or >18 min, coronary event or procedure.	0	Central allocation	Double blind	1.86	88.67	100	29	85	Carvedilol (12.5 to 50 mg daily)	20	207	26	208	1	41	30
Bristow 1994	Patients with chronic heart failure, EF<40%, max exercise time >16 min.	Active myocarditis; causes of heart failure other than idiopathic or ischaemic cardiomyopathy; active ischaemia; recent MI; symptomatic ventricular tachycardia; heart block; bradycardia (< 50 bpm)>	0	Not Clear	Double blind	2.53	NA	76.74	24.45	NA	Bucindolol (12.5mg to 200mg per day)	4	105	2	34	0.23	12	4
CIBIS 1994	Aged 18-75 with chronic heart failure. NYHA III/IV, EF<40%, and clinically stable	Hypertrophic or restrictive cardiomyopathy with left ventricular diastolic dysfunction. Mitral or aortic valve disease not surgically repaired in last six months. Disabling dysnpnoea at rest, insulin dependent diabetes, asthma, renal insufficiency.	0.2	Central allocation	Double blind	3.05	47.27	36.19	25.4	92.59	Bisoprolol (1.5 to five mg daily)	53	320	67	321	1.9	75	82

Trial	Inclusion criteria	Exclusion criteria	Lost to follow up (%)	Concealment of allocation	Blinding	NYHA	Prior MI (%)	Idiopathic cardiomyopathy (%)	Ejection fraction	ACEi (%)	Drug (dose)	Death with BB	Total on BB	Death on control	Total Controls	Follow up (years)	Withdrawl in BB	Withdrawal in Controls
CIBIS II 1999	Patients aged 18 to 80 years with ischaemic or non-ischaemic heart failure, lvf <35%, dyspnoea on exertion or orthopnoea, or paroxysmal nocturnal dyspnoea. NYHA III/IV, stable for six weeks (3 months post MI), unchanged therapy in last two weeks, treated with ACEi and diuretics (alternative vasodilator if ACEi intolerant).	Uncontrolled hypertension, MI or unstable angina pectoris within three months; PTCA or CABG within six months; stroke within one year; planned PTCA or CABT; obstructive or restrictive cardiomyopathy; ongoing myocarditis; significant organic valvular disease; previous or scheduled heart transplant; congenital heart disease; heart block greater than first degree without pace maker; resting heart rate <60 beats/min, systolic BP < 100mmHg, co-morbidity.	0.2	Central allocation	Double blind	3.2	NA	11.98	≤35%	96%	Bisoprolol (1.25 to 10mg daily)	156	1323	228	1324	1.4	41	28
Currie 1984	Patients with idiopathic dilated cardiomyopathy, no MI or angina, NYHA III for at least three months, sinus rhythm, heart rate > 85 bpm at rest, EF <35% who had completed an open label dose ranging study.	Prior MI	0	Not Clear	Double blind	3	0	100	24.9	0	Metoprolol (mean 130mg daily)	0	5	0	5	0.08	0	0
Eichhorn 1994	Men with non-ischaemic dilated cardiomyopathy, EF < 45%.	Severe renal, hepatic, pulmonary, rheumatologic, endocrine disease; previous MI; constrictive, restrictive or hypertrophic cardiomyopathy; primary valvular disease.	4	Not Clear	Double blind	2.35	0	100	18	100	Metoprolol (100 mg daily)	0	15	0	10	0.5	0	1
Engelmeier 1985	Stable patients with idiopathic dilated cardiomyopathy, EF < 49% or evidence of lvd,	Coronary artery disease; myocarditis; obstructive lung disease; advanced heart block.	4	Not Clear	Double blind	2.4	0	100	17.59	NA	Metoprolol, up to 100 mg daily	2	9	2	16	1.00	2	5
Fisher 1994	Patients with chronic heart failure despite treatment, with documented history of coronary artery disease.	Acute MI or unstable angina in the previous three months, primary valvular disease, greater than first degree heart block, heart rate < 60 bpm, bronchospasm, active neoplastic process.	0	Not Clear	Double blind	2.74	74	0	22.5	94	Metoprolol (mean 87 mg daily).	1	25	2	25	0.5	2	0

Trial	Inclusion criteria	Exclusion criteria	Lost to follow up (%)	Concealment of allocation	Blinding	NYHA	Prior MI (%)	Idiopathic cardiomyopathy (%)	Ejection fraction	ACEi (%)	Drug (dose)	Death with BB	Total on BB	Death on control	Total Controls	Follow up (years)	Withdrawl in BB	Withdrawal in Controls
Gilbert 1990	Patients aged 18 to 80 years, with idiopathic dilated cardiomyopathy, symptomatic heart failure, EF <40%, with 4> exercise> 16 min, diffuse hypokinesis, cardiac chamber dilation, who had tolerated at least one test day of treatment (96%).	Primary valvular disease; coronary artery disease; hypertension; myocarditis; clinically unstable. Bronchial asthma; chronic obstructive lung disease; systolic < 80 mm Hg; advanced heart block; renal, hepatic, hematological or neurological disease;	0	Not clear	Double blind	2.57	0	100	22.46	66.67	Bucindolol (mean 170 mg daily)	0	14	0	9	0.25	1	0
Krum 1995	Patients with chronic heart failure despite treatment, EF <35%, NYHA II/IV, who had tolerated a three week open label exposure to carvedilol titrated to 12.5mg bd (87.5%)	Primary valvular disease; active myocarditis; obstructive hypertrophic or restrictive cardiomyopathy; active angina; MI/stroke in last three months; high degree heart block; chronic obstructive airways disease.	0	Not Clear	Double blind	2.96	NA	63.27	16.5	89.80	Carvedilol 100 mg daily	3	33	2	16	0.27	1	2
Leung 1990	Patients with NYHA II-IV, chronic stable heart failure, sinus rhythm, cardiomegaly with cardiothoracic ratio > 0.5, LVD, EF < 35%.	Patients aged under 18 or over 70 years; with obstructive lung disease; advanced atrioventricular block; significant valvular heart disease.	0	Not Clear	Double blind	3.15	0	100	20	NA	Labetolol (mean dose 275 mg daily)	0	6	0	6	0.15	0	0
MDC 1993	Patients aged 16-75 years, with EF<40%, and symptomatic dilated cardiomyopathy. Systolic blood pressure > 90mm Hg, heart rate >45 BPM who tolerated a 2-7 day period of test low dose metoprolol (96%)	Significant coronary artery disease by angiography, ongoing myocarditis, high doses of tricyclics,	0	Central allocation	Double blind	2.53	0	100	22	79.37	Metoprolol (mean 108 mg daily).	23	194	21	189	1.22	23	31
MERIT 1999	Men & women mean age 40 to 80 years (mean age 64), 48.5% with prior MI, with mean EF 28%, 90% of whom on ACEi, and 7% on ACEi-II.	Acute MI or unstable angina ≤28 days; indication or contraindication for β-blockade; chronic β-blockade; co-morbidity.	Not Clear	Central allocation	Double blind	III/IV	48.5	35	26	100	Metoprolol SR: 12.5 to 200 mg daily I	145	1990	217	2001	1	281	310
Metra 1994	Patients with stable chronic symptomatic heart failure caused by idiopathic dilated cardiomyopathy, NYHA II/III, EF<35%	Coronary artery disease, active myocarditis, valvular disease, hypertension.	0	Not Clear	Double blind	2.73	0	100	19.5	55	Carvedilol (12.5 to 50 mg daily)	0	20	0	20	0.33	0	0

Trial	Inclusion criteria	Exclusion criteria	Lost to follow up (%)	Concealment of allocation	Blinding	NYHA	Prior MI (%)	Idiopathic cardiomyopathy (%)	Ejection fraction	ACEi (%)	Drug (dose)	Death with BB	Total on BB	Death on control	Total Controls	Follow up (years)	Withdrawl in BB	Withdrawal in Controls
Olsen 1995	Aged 18 to 80 years with stable symptomatic heart failure (NYHA II/III), caused by ischaemic or idiopathic dilated cardiomyopathy and EF< 35%, who tolerated seven days of low dose carvedilol (100%).	Valvular heart disease, active myocarditis, active angina, sustained ventricular tachycardia or symptomatic non sustained uncontrolled ventricular tachycardia, 2nd or 3rd degree heart block, exercise duration <3 or >30mins.	0	Not Clear	Double blind	2.5	NA	71.67	19.60	93.33	Carvedilol (mean 80 mg daily)	1	36	0	24	0.25	1	1
Pacher 1995	Patients with congestive heart failure, NYHA II, receiving fosinopril20mg mononitrate, digitalis and furosomide.	Not Clear	0	Not Clear	Double blind	2	NA	NA	24	100	Atenolol 50 mg daily	0	10	0	11	0.08	0	0
Packer 1996	Chronic stable heart failure with EF<35%, who had tolerated two weeks low dose Carvedilol (94.4%)	Major cardiovascular event/surgical procedure <3 months, uncorrected primary valvular disease, active myocarditis; sustained ventricular tachycardia; advanced uncontrolled heart bock; systolic BP >160 or <85 mm Hg; diastolic BP >100 mm Hg; heart rate <68bpm	0	Not Clear	Double blind	2.50	47.62	52.10	22.5	95	Carvedilol (mean 45 mg daily)	22	696	31	398	0.54	77	68
Paolisso 1992	Patients with stable chronic symptomatic heart failure.	Family history of diabetes, obstructive airways disease, advanced heart block.	0	Not Clear	Double blind	3	NA	40	NA	NA	Metoprolol	0	5	0	5	0.08	0	0
Pollock 1990	Patients with dilated cardiomyopathy (ischaemic or non ischaemic), EF < 40%, 4< min exercise <16, who had tolerated at least one day open label treatment with bucindolol 25mg daily/	Pulmonary contraindications or severe illness	0.05	Not Clear	Double blind	1.74	NA	36.84	21.21	NA	Bucindolol (25 mg daily)	0	13	0	7	0.25	1	0
RESOLVD 1997	Patients with clinical signs of heart failure (NHYA II - IV), six min walk distance of 500m or less, EF <40%.	Acute illness, renal impairment, contraindications to study medication.	NA	Central allocation	Double blind	II-IV	NA	31	29	100	Metoprolol (mean 160mg daily)	8	215	17	211	0.38	23	22
Sanderson 1998	Patients with congestive heart failure and EF< 45%.	Valvular heart disease, active myocarditis, active angina, sustained ventricular tachycardia, symptomatic non-sustained ventricular tachycardia, 2nd or 3rd degree atrioventricular block.	0	Not Clear	Double blind	2.60	0	100	29.5	82	Metoprolol (100 mg daily) or celiprolol (200 mg daily)	2	40	0	10	0.25	4	2

Trial	Inclusion criteria	Exclusion criteria	Lost to follow up (%)	Concealment of allocation	Blinding	NYHA	Prior MI (%)	Idiopathic cardiomyopathy (%)	Ejection fraction	ACEi (%)	Drug (dose)	Death with BB	Total on BB	Death on control	Total Controls	Follow up (years)	Withdrawl in BB	Withdrawal in Controls
Sigmund 1996	Men and women with HF (NYHA II-IV). Diagnosis based upon clinical and echocardiographic findings, left and right heart catherterisation, coronary angiography and myocardial biopsy.	Patients not able to perform exercise tests due to end stage heart failure; co-morbidity; contraindications to study drugs; women of childbearing age.	0	Not clear	Double blind	2.80	NA	44	32	83.3	Metoprolol: 50 to 150 mg daily	1	11	3	14	0.25	3	1
Uhlir 1997	Patients aged 18-75 years with mild to moderate heart failure (NYHA II-III) due to ischaemic heart disease or cardiomyopathy, not treated with ACEi. Previous MI. LVEF <40%.	Cardiovascular drugs other than diuretic or digitalis; Systolic BP < 100 or diastolic <50; secondary or malignant hypertension; COAD; BP < 50 bpm; recurrent arrhythmias; > 1st degree heart block; sick sinus syndrome; significant valvular disease; insulin dependent diabetes; obesity; significant renal or hepatic disease; pregnancy or inadequate contraception.	0	Not Clear	Double blind	II-III	100	22.2	NA	0	Nebivolol (2.5 mg or 5mg daily	1	62	0	28	0.27	5	0
Wisenbaugh 1993	Aged 18-65 years, which NYHA II/III, 15%<EF<40%, exercise treadmill four to 12 minutes.	Pulmonary or valvular disease; diastolic BP >105 mm Hg; MI/stroke <6 months; insulin dependent diabetes; severe renal or hepatic disease; women of childbearing age; arrhythmias/atrial fibrillation; ACEi or digoxin; obese.	15	Not Clear	Double blind	2.04	NA	91.67	24	0	Nebivolol	1	11	0	13	0.25	4	1
Woodley 1991	Patients with heart failure and EF <40%, who had tolerated a test dose of bucindolol (98%), who had been on stable heart failure therapy for at least three weeks prior to beginning study, stratified by cause of heart failure.	Patients with active myocarditis; other causes of heart failure; or ischaemic dilated cardiomyopathy; active ischaemia; recent MI; ventricular tachycardia; heart block; bradycardia (<50 bpm).	0	Not Clear	Double blind	2.69	NA	44.90	21.80	50.96	Bucindolol (up to 300 mg daily)	0	29	0	20	0.25	1	0

Appendix 8. Spironolactone in patients with severe heart failure

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Blinding	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Pitt 1999	Spironolactone: 12.5mg to 50mg daily Placebo:	NYHA IV within 6 months, and NYHA III/IV on entry. Diagnosis of HF ≥ 6 weeks before enrollment. EF ≤ 35%, ACE inhibitor treatment (if tolerated) and loop diuretic.	Primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolic heart failure); congenital heart disease; unstable angina; primary hepatic failure; active cancer; any life threatening disease other than HF; awaiting heart transplantation; serum creatinine > 2.5 mg/dl; serum potassium > 5.0 mmol / L.	Double blind	Not clear	1663	0	24 months	Death Hospitalisation

Appendix 9. Prolonged antiplatelet therapy in patients who have previously experienced an MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
AMIS 1980	Aspirin: 1 g daily Placebo	Patients ≥ eight weeks and < five years post MI, aged 30 to 69	History of aspirin intolerance; severe ulcer disease; previous cardiovascular surgery; uncontrolled hypertension; taking aspirin, anticoagulants; dipyridamole; sulfinpyrazone.	Double blind	Not clear	4524	0.2%	3 years	Death Non-fatal MI Non-fatal Stroke
ARIS 1982	Sulphinpyrazone: 400 mg Placebo	Patients ≤ 70 years old, recruited from CCU with diagnosis of MI 15 to 25 days previously. MI confirmed by typical chest pain, ECG changes (pathological Q waves and/or ST elevation with T inversion), two of three enzyme levels above normal upper limit (lactate dehydrogenase, creatine phosphokinase, serum glutamic-oxalacetic transaminase). Killip fitness category I or II.	Severe renal (plasma creatinine > two mg/dl) or hepatic impairment; history of peptic ulceration; heart surgery; hypertension or diabetes requiring drug treatment; continuous anticoagulant or antiaggregant treatment; serious co-morbidity.	Double blind	Not clear	725	0.7%	19.2 months	Death Non-fatal MI Non-fatal Stroke
ART 1982	Sulfinpyrazone: 800 mg daily Placebo	Patients with well documented MI 25 to 35 days prior to randomisation.		Double blind	Not clear	1629	0	16 months	Death Non-fatal MI Non-fatal Stroke
Cardiff-I 1981	Aspirin: 300 mg daily Placebo	Patients recovering from an MI soon after index event, through to more than six months post MI.	Receiving anticoagulation; evidence of peptic ulcer.	Double blind	Not clear	1239	0.4%	13 months	Death Non-fatal MI
Cardiff-II 1979	Aspirin: 900 mg daily Placebo	Patients recovering from acute MI.	Anticoagulation; evidence of peptic ulcer; sensitivity to aspirin.	Double blind	Not clear	1682	0%	12 months	Death Non-fatal MI
CDP 1976	Aspirin: 1 g daily Placebo	Men aged 30 to 64 with ECG documented MI ≥ three months prior to entry, and NYHA I or II.	Previous surgery for coronary artery disease; life limiting disease; contraindication to estrogens; dextrothyroxine.	Double blind	Done	1529	0	22 months	Death Non-fatal MI Non-fatal Stroke

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
German – Austrian Study Group 1980	Aspirin: 1.5 g daily Placebo	Patients aged 45 to 70 years who had survived an MI 30 to 42 days before randomisation. MI defined as ≥ two of: unequivocal serial ECG; chest pain typical of acute MI; increased serum enzyme levels (CPK, LDH, SGOT).	Patients with contraindications to aspirin or phenprocoumon; hypertension (diastolic BP > 110 mm Hg); recent ulceration of GI tract; cerebral ischaemia (in preceding six weeks); severe hepatic or renal insufficiency.	Double blind	Done	626	9.6%	2 years	Death Non-fatal MI Non-fatal Stroke
MICRISTIN 1981	Aspirin: 1.5 g daily Placebo	Patients with previous MI confirmed by ECG changes and enzyme changes.	Previous haemorrhage; asthma; diastolic BP > 110 mm Hg; co-morbidity.	Double blind	Done	1341	1.8%	24 months	Death Non-fatal MI Non-fatal Stroke
PARIS-I 1980	Aspirin (half with dipyridamole): A 972 mg daily D 225 mg daily Placebo	Patients aged 30 to 74 years who had recovered from MI, confirmed by ECG changes, two to 60 months previously.	Previous cardiac or coronary surgery; serious co-morbidity; antiplatelet drugs indicated; aspirin hypersensitivity; unwilling to forego use of aspirin; on anticoagulant therapy; postural hypotension; systolic BP ≥ 200 mm Hg; diastolic BP ≥ 115 mm Hg; women of childbearing potential.	Double blind	Done	2026	0%	41 months	Death Non-fatal MI Non-fatal Stroke
PARIS-II 1986	Dipyridamole & Aspirin: D 225 & A one g daily Placebo	Patients aged 30 to 74 years with history of MI and compatible ECG changes, one to four months from index event, with class I or II NYHA.	Previous cardiac or coronary surgery; serious co-morbidity; antiplatelet drugs indicated; aspirin hypersensitivity; unwilling to forego use of aspirin; on anticoagulant therapy; postural hypotension; systolic BP ≥ 200 mm Hg; diastolic BP ≥ 115 mm Hg; women of childbearing potential.	Double blind	Done	3128	0.3%	23.4 months	Death Non-fatal MI Non-fatal Stroke
Rome 1986	Dipyridamole: Placebo/control	Patients who have experienced an MI	Not clear	Not clear	Not clear	80	0%	72 months	Death Non-fatal MI

Appendix 10. Insulin Glucose Infusion followed by Subcutaneous Insulin Treatment post MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Blinding	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Malmberg 1997	Intervention Group: Insulin - glucose infusion for at least 24 hours with aim to achieve glucose level of 7 to 10 mmol/litre. Subcutaneous insulin 4x daily for at least 3 months Standard Treatment	Suspected MI within 24 hours combined with previously known diabetes mellitus and blood glucose level > 11 mmol/litre, or blood glucose > 11 mmol/litre without history of diabetes mellitus	Inability to participate due to poor health; refusal or residence outside hospital catchment area; enrolment in other studies; previous enrolment in DIGAMI	Open	Done	620	Not clear	3.4 years	Death

Appendix 11. Calcium channel blockers in patients who have experienced an MI.

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Branagan 1986	Nifedipine: 40 mg daily for three days Placebo	Patients admitted to CCU < six hours of onset of chest pain lasting > 15 minutes.	> 70 years old; women capable of child-bearing; heart rate > 110 beats or < 60 per minute; complete heart block; HF requiring diuretic therapy(greater than frusemide 40 mg) or vasodilator, inotropic or mechanical support; systolic BP < 85 mm Hg; ventricular fibrillation as initial rhythm; already treated with nifedipine.	Double blind	Not clear	98	Not clear	1 month	Death
CARES 1996	Diltiazem: 180 mg daily Placebo	Patients < 75 years or in good clinical condition, symptoms suggesting acute MI for ≥20 minutes and ≤6 hours in relation to streptokinase infusion, ST segment elevation ≥1.5mm observed in ≥2 contiguous leads of the conventional 12 lead ECG. MI confirmed through two of: pain; Q waves; creatine kinase myocardial band or creatine phosphokinase elevation ≥ twice normal values.	Contraindication to streptokinase; cardiogenic shock; bradycardia < 55 beats per minute with/without atrioventricular block; hypotension < 90 mm Hg.	Double blind	Not clear	101	Not clear	10 Days	Death MI
Crea 1985	Verapamil: IV 10 to 40 mg followed by 240 mg daily Placebo	Patients admitted to CCU within 12 hours of onset of symptoms. MI confirmed by history of prolonged chest pain, ECG changes and serum creatine kinase elevation.	> 75 years; systolic BP < 90 mm Hg; heart rate < 55 betas/minute; severe hypertension requiring IV vasodilators; PR interval > 0.3 seconds, second and third degree atrioventricular block; interventricular conduction defects (QRS interval longer than 0.1 seconds); severe HF; syncope or cardiac arrest before admission.	Single blind	Not clear	17	Not clear	10 days	Death MI
CRIS 1996	Verapamil: 360 mg daily Placebo	Patients aged 30 to 75 years who survived five days after acute MI, randomised between seven and 21 days post index event.	Severe HF (NYHA III & IV); Wolff-Parkinson-White syndrome; allergy to verapamil; participation in another trial; cardiac surgery; implanted pacemaker; right ventricular failure with pulmonary hypertension; co-morbidity; women before menopause; heart rate < 50 beats per minute; systolic arterial pressure < 90 mm Hg or > 190 mm Hg; diastolic BP > 110 mm Hg; long term treatment with calcium channel blockers or beta-blockers.	Double blind	Not clear	1073	0.5%	23.5 months	Death MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
DAVIT I 1984	Verapamil: 0.1 mg /kg IV then 360 mg daily Placebo	Patients with acute MI, ECG changes compatible with Q-wave or non Q-wave MI, significant elevation of cardiac serum enzymes. Treatment commenced in all those without exclusions in CCU, but stopped when not confirmed by ECG and serum changes.	HF; cardiac arrest; sinoatrial and atrioventricular block; QRS ≥ 0.12 seconds; valvular heart disease; post operative MI; other severe invalidating diseases.	Double blind	Not clear	1436	Not clear	6 months	Death MI
DAVIT II 1990	Verapamil: 360 mg daily Placebo	Patients < 76 years, with acute MI, ECG changes compatible with Q-wave or non Q-wave MI, significant elevation of cardiac serum enzymes. Treatment commenced in all those without exclusions, but stopped when not confirmed by ECG and serum changes.	HF not controlled with furosemide ≤160 mg daily; cardiac arrest; sinoatrial and atrioventricular block; QRS ≥ 0.12 seconds; valvular heart disease; post operative MI; other severe invalidating diseases.	Double blind	Not clear	1775	Not clear	16 months	Death MI
DEFIANT 1992	Nisoldipine: 20 mg daily Placebo	Patients < 75 years with recent MI (8 to 35 days previously) without overt heart failure. MI confirmed by two of: typical chest pain lasting ≥ 30 minutes; cardiac enzymes above twice the normal upper limit; ECG typical of acute MI.	Patients who received positive inotropic drugs (except digitalis) in the acute phase of MI; overt HF; post-infarction angina; atrial fibrillation or flutter; primary valvular disease except mild functional mitral regurgitation and aortic stenosis (peak Doppler velocity more than $2m.s^{-1}$ across aortic valve; dilated or hypertrophic cardiomyopathy; known contra-indication for calcium channel blocking agents; severe hepatic, renal or pulmonary disease and any other condition likely to predict severely impaired life expectancy; coronary bypass surgery < three months; PTCA < seven days; potentially child-bearing women; unable to perform bicycle exercise testing after discharge; systolic BP <100 or > 160 mm Hg; diastolic BP < 100 mm Hg; poor quality Echo.	Double blind	Not clear	135	Not clear	4 weeks	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
DEFIANT II 1997	Nisoldipine 20 to 40 mg daily Placebo	Patients tolerating a single blind run in of 20 mg nisoldipine daily for three to five days, < 10 days from index MI. Diagnosis based upon two of: typical chest pain ≥ 30 minutes duration; cardiac enzymes twice the upper limit of normal; ECG typical of acute MI. EF 25% τo 50%. Stable condition without evidence of overt HF.	Digitalis, calcium antagonists, long acting nitrates, ACEi, other peripheral vasodilators < 48 hours; Positive inotropic agents other than digitalis since index MI, or required treatment with antidepressants or neuroleptics; HF; post-infarct angina; atrial fibrillation or flutter; primary valve disease other than mild aortic sclerosis (peak transaortic Doppler velocity < $2m.s^{-1}$ or mild functional mitral regurgitation; hypertrophic cardiomyopathy; persistent atrioventricular block or other significant abnormality of conduction; significant renal, hepatic, pulmonary, gastrointestinal, haematological or psychiatric disease; known contraindication to calcium blockers; CABG < three months or PTCT< three day. Significant hypotension (systolic BP <100 mm Hg) or hypertension (resting BP > 200/114; women of childbearing age; difficulties in performing exercise test.	Double blind	Done	542	Not clear	6 months	Death MI
DRSG 1986	Diltiazem: 360 mg daily until discharge or 14 days elapsed Placebo	Patients with acute non-Q-wave MI documented by elevated MB creatine kinase activity in plasma in ≥2 samples taken ≥ four hours apart and either: ischaemic chest pain for ≥ 30 minutes or new ST-segment elevation or depression of ≥ 0.1 mV or new T-wave inversion in ≥ two inferior leads (II, III, or a VF), the anterior precordial leads (V_{1-4}), or the lateral leads (I, aVL, or V_{5-6}), or both the ST changes and the T-wave inversions.	New or presumably new Q waves of 30 ≥ msec in duration, R/S ratio or one or greater in V_2 along with a 40-msec R wave in V_1, a 50% loss of R wave ≥ two contiguous leads, or ST-T changes limited to leads with pre-existing Q waves; conduction disturbances that would mask the development of Q waves; bradycardia (<50 beats/min); second or third degree atrioventricular block; cardiogenic shock or sustained hypotension of 100 mm Hg or less; therapy with a calcium channel blocker other than investigational agents, oral anticoagulants or full dose heparin that could not be discontinued; CABG < three months; serious co-morbidity; pregnancy.	Double blind	Not clear	576	Not clear	14 days	Death MI
Erbel 1988	Nifedipine: 20 mg sublingually followed by 0.2 mg iv followed by 60 mg daily Placebo	Patients admitted to emergency ward < six hours after onset of acute MI. Confirmed by: acute chest pain > 30 minutes; persistent ST segment elevation of > 0.3 mV in leads V_1 to V_6 or 0.2 mV in leads I to III, aV_L or aV_F.	Long period of resuscitation; allergic reactions to streptokinase; previous CVA; surgery < 10 days; history of acute peptic ulcer; history of bleeding problems.	Double blind	Not clear	149	Not clear	1 month	Death MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Gottlieb 1988	Nifedipine: 10 to 30 mg daily Placebo	Patients admitted to CCU, aged between 30 and 75 years with acute MI within 21 hours; Killip class I or II, with EF > 35%; MI defined as typical ischaemic chest pain ≥ 30 minutes; with ECG changes of ST segment elevation > one mm, new Q waves, or persistent T wave inversions ≥ two leads. Enzymatic confirmation not required.	Systolic BP < 100 mm Hg; symptomatic cerebrovascular disease; P-R interval > 0.24 seconds; higher degree atrioventricular block without a pacemaker in place; pulmonary oedema; cardiogenic shock; taking calcium antagonist.	Double blind	Not clear	132	Not clear	6 weeks	Death MI
Gupta 1985	Verapamil: 160mg daily Control	Patients reporting within eight hours of onset of symptoms of acute anterior MI confirmed by history, clinical examination, ECG abnormalities and SGOT estimation.	> 70 years; LVF or HF (except minimum basal crepitations); atrioventricular or interventricular conduction disturbances; heart rate < 60 beats per minute; systolic cuff pressure < 100 mm Hg; chronic obstructive lung disease; already on beta-blockers or verapamil; inferior or posterior infarction or posterior extension.	Open	Not clear	50	Not clear	21 days	Death MI
MDPT 1988	Diltiazem: 240 mg daily Placebo	Patients aged 25 to 75 years, admitted to CCU with documented acute MI. In patients with chest pain and ECG changes suggestive of an acute coronary event, enzyme confirmation was required. Enzyme confirmation included any of: the presence of an MB isoenzyme fraction > 4% of the total creatine kinase level or a qualitatively positive MB isoenzyme band; an elevation of total lactic dehydrogenase in the serum with abnormal reversal of the ratio of lactic dehydrogenase one to 2; an elevation of two or more of the serum enzymes creatine kinase, aspartate transaminase, total lactic dehydrogenase to ≥ two times upper limit of normal.	Ongoing cardiogenic shock or symptomatic hypotension; pulmonary hypertension with right ventricular failure; second or third degree atrioventricular block; a resting heart rate < 50 beats/Minute; history of symptoms consistent with sinus-node dysfunction; a history of adverse reaction to diltiazem; inadequate contraception; Wolff-Parkinson-White syndrome; other conditions indicating calcium channel blockers or reduced likelihood of survival for trial; a qualifying MI due to non-atherosclerotic causes.	Double blind	Not clear	2466	Not clear	Mean 25 months	Death MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Muller 1984	Nifedipine: 40 mg daily (reducing to 10mg or 0 in headache) Placebo	Patients < six hours since the onset of chest pain lasting ≥ 45 minutes, with new (or presumed new) ST segment elevation or depression of at least 0.1 mV or new Q waves ≥ 30 msec width and 0.2 mV depth in one of the following lead combinations: ≥2 of the three diaphragmatic leads (II, III, aVF); or ≥2 of six precordial leads; or I and aVL.	Left bundle branch block; systolic arterial pressure < 110 mm Hg; previous CABG; co-morbidity; cardiogenic shock; prior MI < 21 days; childbearing potential.	Double blind	Not clear	181	Not clear	6 months	Death
Rossi 1979	Verapamil: dose not clear Placebo	Patients with recent transmural MI undergoing programme of physical rehabilitation, who commenced study drugs 14 days after onset of symptoms.	Latent or manifest cardiac insufficiency; ventricular and supraventricular arrhythmias; intraventricular conduction disturbances; fall in BP or heart rate during exercise; arterial insufficiency of legs; unstable angina or angina at rest; renal or hepatic insufficiency; insulin-dependent diabetes; anaemia; chronic bronchitis; pulmonary emphysema.	Double blind	Not clear	40	Not clear	2 months	Death
Sirnes 1984	Nifedipine: 40 to 50 mg daily Placebo	Patients aged between 36 and 75 years, presenting within 12 hours of onset with suspected acute MI with severe central chest pain ≥ 30 minutes, or ECG suggesting AMI (not previously recognised ST segment elevation >0.2mV in precordial leads or > 0.1 mV in extremity leads, or a Q wave ≥0.04 sec that had not previously been recognised.	Use of calcium channel blockers within 48 hours; other serious disease.	Double blind	Not clear	227	Not clear	6 weeks	Death
SPRINT 1988	Nifedipine: 30 mg daily Placebo	Patients aged 30 to 74 years with recent acute MI with severe pain in the region of the sternum, precordium or upper abdomen lasting for ≥1hour unless relieved by major analgesics; unequivocal ECG findings (Minnesota Code interpretations) and elevated serum levels (≥ 1.5 times upper normal limit) of SCOT, CPK, CPK-MB or of two of SGOT, CPK, and LDH.	Requiring calcium antagonists; Prinzmetal's variant angina; non-coronary heart disease; previous cardiac surgery or pacemaker implantation; severe pulmonary hypertension; uncontrollable HF preceding index MI; persistent hypotension (systolic BP < 90 mm Hg; complete left bundle branch block or Wolff Parkinson White syndrome; cerebrovascular accident; malignant disease; renal or hepatic failure; alcoholism or psychiatric diagnosis; known sensitivity to nifedipine.	Double blind	Not clear	2276	Not clear	10 months	Death MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
SPRINT-II 1993	Nifedipine: 60 mg daily Placebo	Patients aged 50 to 79 years with suspected MI titrated on nifedipine or placebo within 48 hours of admission.	Patients excluded at six days if did not meet: established diagnosis of MI; previous MI; anginal syndrome in month prior to index event; history of hypertension; NYHA II or above; anterior site of index MI; maximal level of serum lactate dehydrogenase at least three times upper limit of normal.	Double blind	Not clear	1358	Not clear	6 months	Death
Walker 1988	Nifedipine: 60 mg daily Placebo	Patients with acute MI confirmed by increase in creatine kinase MB to > 30 IU/L in a patient with central chest pain ≥30 min that appeared to be cardiac origin, regardless of ECG changes	Patients ≥ six hours after onset of pain; aged > 75 years; systolic BP ≤ 85 mm Hg.	Double blind	Not clear	434	Not clear	In hospital	Death MI
Wilcox 1986	Nifedipine: 40 mg daily Placebo	Patients aged 18 to 70 years, admitted to CCU < 24 hours of onset of chest pain due to suspected acute MI.	Pregnancy or ability to become pregnant; arterial BP < 100 mm Hg systolic or 50 mm Hg diastolic; pulse > 120 beats per minute; severe HF requiring vasodilator or intravenous inotropic support; serious renal or hepatic dysfunction; current treatment with calcium channel blocking drugs.	Double blind	Not clear	4491	0%	28 days	Death
Zannad 1988	Diltiazem: 10 mg iv followed by 15 mg/hr iv infusion for 72 hours, followed by 240 mg daily for 21 days Placebo	Patients with clinical, ECG and enzymatic evidence of acute MI. Required: chest pain, epicardial injury pattern and pathological Q waves, < six hours since onset of pain, no history of previous MI	HF; aged ≥75 years; beta-blocker, amiodarone or calcium channel blocker.	Double blind	Not clear	34	0	3 weeks	Death

Appendix 12. Calcium channel blockers in patients with heart failure.

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
DiDi 1996	Diltiazem: 180 mg daily Placebo	Patients aged 18 to 70 years with idiopathic dilated cardiomyopathy diagnosed < six months and EF < 50%, independent of symptomatic status.	History of hypertension or systolic BP > 160 mm Hg and or diastolic BP > 95 mm Hg; valvular or congenital heart disease, except for 1st or 2nd degree mitral or tricuspid regurgitation by ventriculography; clinical or histological signs of ongoing myocarditis; concomitant coronary artery disease diagnosed by evidence of any coronary stenosis ≥50%; insulin-dependent diabetes; systemic disease; pregnancy; severe liver or kidney disease; co-morbidity.	Double blind	Not clear	186	1.6%	2 years	Death
Dunselman 1989	Felodipine: 10 to 20 mg daily Placebo	Patients with HF (NYHA III) and MI > three months previously, EF < 40%, maximal oxygen consumption < 15ml kg^{-1}, in sinus rhythm and taking digitalis and diuretics for ≥ two months.	Not clear	Double blind	Not clear	23	0%	8 weeks	Death
Gutiérrez 1992	Nifedipine: 30 mg daily Placebo	Patients admitted to ICU with first MI of any location, with EF < 40%.	Not clear	Double blind	Not clear	20	Not clear	12 months	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Littler 1995	Felodipine ER: 5 mg daily Placebo	Patients aged 18 to 75 years, with EF ≤ 40%, stable HF for two months (NYHA II to III), and two to 12 minutes exercise tolerance stopped because of dyspnoea or fatigue despite treatment for ≥ two months with ACEi, diuretic or digoxin, or any combination of these drugs	HF due to stenotic valve lesions, primary mitral or aortic insufficiency or non cardiac causes; exercise limited by claudication; unstable angina; MI, CABG or PTCA < three months; significant obstructive pulmonary disease limiting exercise capacity; uncontrolled atrial or ventricular arrhythmia < four weeks; systolic BP < 100 mm Hg; diastolic BP > 114 mm Hg; medication with vasodilators which could not be withdrawn two weeks before entry (use of long acting nitrates permitted if prescribed for angina and the dose was not changed during the study); severe concomitant disease interfering with assessment; primary liver or renal disorder (creatinine > 200 μmol/L); abnormal laboratory findings suggestive of unstable disease; known intolerance to dihydropyridines; child bearing potential; conditions associated with poor compliance.	Double blind	Not clear	252	Not clear	21 weeks	Death
PRAISE 1996	Amlodipine: 5 to 10 mg daily Placebo	Patients with HF and dyspnoea or fatigue at rest or on minimal exertion (NYHA IIB or IV), and EF < 30% despite treatment with digoxin, diuretics and ACEi. Treatment with nitrates was permitted.	Treatment with vasodilators, uncorrected primary valvular disease; active myocarditis; constrictive pericarditis; cardiac arrest or sustained ventricular tachycardia or fibrillation < one year; unstable angina or acute MI < one month; cardiac revascularisation procedure or stroke < three months; severe pulmonary renal or hepatic disease; systolic BP < 85 mm Hg or > 159 mm Hg; diastolic BP > 89 mm Hg; serum creatinine > 2.7 μmol/L; potassium < 3.5 or > 5.5 mmol/L; treatment with beta-blocker, calcium channel blocker or class IC antiarrhythmic agents.	Double blind	Not clear	1153	0%	13.8	Death MI
Russo 1998	Felodipine: 5 mg daily Placebo	Patients with ischaemic, dilated cardiomyopathy and mild stable HF, treated chronically with enalapril.	Acute MI ≤ 12 months; unstable angina; arterial hypertension; atrial fibrillation; severe ventricular arrhythmias; renal failure; recent acute cardiac decompensation; peripheral oedema; valvular disease or significant mitral regurgitation; poor ECG recordings.	Double blind	Not clear	23	0%	12 months	Death

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Random allocation	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
V-HeFT III 1997	Felodipine: 5 to 10 mg daily Placebo	Male patients aged > 18 years with HF including limited exercise function caused by dyspnoea or fatigue, taking a clinically effective dose of ACEi, who satisfied one of: radiographic cardiothoracic ratio of ≥0.55; echocardiographic LV internal dimension at end diastole >2.7 cm/m^2; resting EF ≤ 0.45.	Clinically important renal, hepatic or hematologic disorders (serum creatinine > 3.0 mg/dL; serum potassium < 3.5 or > 5.5 mEq/L; abnormal liver enzymes twice upper limit of normal); severe chronic obstructive bronchopulmonary disease; inability to perform an exercise test owing to causes other than HF; symptomatic hypotension; aortic or mitral stenosis; hypertrophic cardiomyopathy; severe aortic or mitral valvular regurgitation; severe hypertension; hemodynamically significant pericardial disease; severe angina; MI, CABG or angioplasty < three months; cerebrovascular accident < six months; symptomatic or life-threatening arrhythmias; allergy or intolerance to Ca antagonists; use of beta-blockers, long acting nitrates, other vasodilators (except ACEi) < four weeks; significant co-morbidity.	Double blind	Not clear	450	Not clear	18 months	Death
Vries 1995	Lacidipine: 4 mg daily Placebo	Patients with stable but symptomatic HF (NYHA II to III), despite treatment with ACEi, digoxin and diuretics for > six weeks. Peak oxygen uptake during cardiopulmonary exercise tests > 10 and < 20 ml/kg. EF < 40% and cardiothoracic ratio on chest x-ray > 0.52, or left ventricular end-diastolic diameter on echo > 55 min.	Active myocarditis; obstructive cardiomyopathy; aortic stenosis or insufficiency; hypotension; recent MI, coronary angioplasty or cardiac surgery; permanent pacemaker; symptomatic arrhythmia; severe pulmonary disease; relevant hepatic, haematological or renal disease; psychiatric illness; known intolerance of study drug; unable to perform exercise tests or discontinued exercise tests for reasons other than dyspnoea of cardiac origin or fatigue.	Double blind	Not clear	25	0%	8 weeks	Death
Walsh 1997	Amlodipine: 10 mg daily Placebo	Patients with HF (NYHA II-III).	MI < three months.	Double blind	Not clear	32	Not clear	8 weeks	Death

Appendix 13. Cardiac Rehabilitation in patients who have previously experienced an MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Blinding	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Bengtsson 1983	3 month exercise, counselling and social measures programme. Usual Care	Patients < 65 years with MI randomised in hospital.	Severe cardiovascular disease or HF; orthopaedic states; diabetes mellitus with retinopathy; hyperthyroidism; hypothyroidism; hyperparathyroidism; mental illness; living more than 50km from hospital.	Open	Not clear	171	3%	14 months	Death Re-infarction
Bethell 1990	3 month circuit training course, 3x weekly. Usual care	Male patients < 65 years, with positive diagnosis of MI.	Live > 25 miles from hospital; medical or orthopaedic problems precluding exercise; insulin dependent diabetes; atrial fibrillation.	Open	Done	229	1.7%	12 weeks	Death
Carson 1982	Twice weekly exercise classes in hospital gym for 12 weeks, on circuit training basis. Advised to continue exercise after this. Usual care	Men with confirmed MI who survived to 6 weeks.	>70 years; HF; Cardio-thoracic ratio > 59%; severe chronic obstructive lung disease; hypertension requiring treatment; diabetes requiring insulin; disabling angina during convalescence; orthopaedic or medical disorders likely to impede progress in the gym; personality disorders likely to render patient unsuitable for the course;	Open	Not clear	303	Not clear	3 years	Death Re-infarction
Dubach 1997	High altitude rehabilitation programme including exercise and dietary intervention. Usual care	Men < 65 years with recent MI and HF, in stable condition.	Not clear	Open	Not clear	25	0	2 months	Death Re-infarction
Fridlund 1991	Multidisciplinary rehabilitation programme including exercise and psychological interventions including one 2 hour meeting post discharge for 6 months. Usual Care	Patients ≤ 65 years with MI, living independently in the Health Care District after discharge able to take part in rehabilitation programme.	Cerebral or cardiac disorders or alcohol abuse.	Open	Not clear	178	Not clear	1 year	Death Re-infarction (during rehab period only)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Blinding	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Giannuzzi 1993	6 month exercise training programme – 30 min 3x weekly bicycle ergometry – 2 months in hospital, 4 months at home with supervision every 2 weeks Usual Care	Males who survived first anterior Q wave AMI within 4 to 8 weeks, in NYHA I / II.	HF or rest EF < 25%; low work capacity; angina at low level exercise; exertional angina uncontrolled by medical therapy; high risk of exertional scintigraphic pattern defined by multiple perfusion defects or EF decrease to <35%; practical reasons for not attending.	Open	Not clear	103	Not clear	6 months	Death
Marra 1985	About 8-9 weeks in which participants undertook exercise 4x weekly, including cycling. Usual Care including recommendations for regular exercise	Patients aged 35 to 65 years, with confirmed AMI with a positive stress test.	NYHA IV; angina at rest; Lown grade 4 ventricular arrhythmias; HF; severe hypertension.	Open	Not clear	167	3.6%	55 months	Death Re-infarction
Platsi 1976	Supervised exercise programme involving home sessions and monthly hospital gym supervision for 12 months. Usual Care	Patients < 65 years who had survived a MI 6 weeks previously	Patients with severe motor invalidity (hemiplegia, amputation of the lower extremities); psychiatric cases with uncertain co-operation; severe HF.	Open	Not done	380	Not clear	29 months	Death Re-infarction
PRECOR 1991	Exercise programme including 6 weeks of 3x training sessions weekly and recommendations on control of cardiovascular risk factors. Usual Care	Male patients , 65 years, with confirmed MI and no major irreversible complication or disability.	Recent stroke; disability of lower limbs; uncontrolled HF; severe rhythm disturbances; Hypertension (systolic > 180 mm Hg); severe angina pectoris; abnormalities triggered by the baseline exercise test(systolic BP > 250 mm Hg); severe hypotension; atrioventricular block > 2nd degree; complex ventricular premature beat; left bundle branch block; chest pain or low heart rate on exercise.	Open	Not clear	182	0	2 years	Death Re-infarction
Román 1983	Long term 3x weekly half-hour exercise sessions (average 42 months participation). Usual care	Patients who survived an acute MI randomised after 48 hours, considered capable of undertaking programme.	Severe arrhythmias; atrial flutter; partial or complete AV block; cardiomegaly; left-ventricular aneurysm; persistent HF; severe diastolic hypertension; angina post MI.	Open	Not clear	193	Not clear	9 years	Death Re-infarction

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Blinding	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
Shaw 1981	Medically supervised, regular physical activity continuing either in a gymnasium or unsupervised at home. Usual care	Documented MI in previous 3 years who attended a low-level exercise screening programme. Male.	Female; those not adhering to the pre-randomisation period.	Open	Not clear	651	6.5%	3 years	Death Re-infarction
Sivarajan 1982	Rehabilitation, with or without teaching/counselling, undertaken at home and under supervision. Usual Care	Patients with confirmed MI	> 70 years; prolonged complications; physical limitations; non-cardiac diseases; Other cardiac diseases; Distance > 50 miles; Communications; Massive obesity; psychological problems.	Open	Not clear	258	Not clear	6 months	Death
Vermeulen 1983	Rehabilitation programme including exercise and psychological counselling. Usual Care	Men ≤55 years, 4 to 6 weeks post MI, able to undertake an exercise programme.	Not clear	Open	Not clear	98	Not clear	5 years	Death Re-infarction
WHO 1982	Range of exercise programmes in different centres, including health promotion advice and counselling Usual Care	Men < 65 years on 28th day post MI.	Not clear	Open	Not clear	1780	Not clear	3 years	Death
Wilhelmsen 1975	3 half hour sessions of supervised exercise weekly with no time limit Usual care	Patients <58 years old, with confirmed prior MI, 3 months post index event.	Not clear	Open	Not clear	315	1.6%	4 years	Death Re-infarction

Appendix 14. Mediterranean style diet in patients who have previously experienced an MI

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Blinding	Concealment of allocation	Number in trial	Loss to follow up	Follow up	Outcome measures
DART 1989	Dietary change: Increase in consumption of fatty fish to at least 2 weekly portions of 200-400 g (with or without advice on increased fibre and reduced fat intake), with 'Maxepa' capsules distributed to those who did not tolerate. Visited at home by dietician. No fish advice	Men < 70 years old, admitted to hospital with WHO defined AMI.	Diabetes; awaiting cardiac surgery; already intending to eat one of intervention diets.	Open	Not clear	2033	Not clear	24 months	Death Non fatal MI
LYON 1994	Dietary change: Mediterranean type diet emphasising fatty fish and olive type oils, reducing meat consumption and encouraging fruit and vegetables. No advice	Patients < 70 years old, who had survived a MI < 6 months previously.	NYHA III/IV HF; systolic > 180 mm Hg, diastolic > 110 mm Hg; inability to complete an exercise test due to recurrent angina; ventricular arrhythmias; atrioventricular block; unstable after angioplasty or bypass surgery. Considered unlikely to survive.	Single	Not clear	605	0.5%	27 months	Death Non fatal MI

Appendix 15. Costs (£) of therapies at doses found in trials: myocardial infarction

	Drug	Trial(s)+	Drug name	Daily dose	tabs/pkt	cost/pkt	cost/day	cost/year
ACE Inhibitors	**ramipril**	HOPE	Tritace	5mg bd	28	9.55	0.68	249.15
Antiplatelet drugs	**aspirin**	*	Non-proprietary	75mg od	100	0.46	0.005	1.68
			Angettes 75	75mg od	28	0.94	0.03	12.26
			Caprin / Nu-seals	75mg od	56	3.08	0.06	20.09
			Disprin CV	100mg od	28	1.68	0.06	21.92
			Postmi 75	75mg od	26	1.55	0.06	21.77
	clopidogrel	CAPRI	Plavix	75mg od	28	35.51	1.27	463.22
Beta-Blockers	**propranolol**	BHAT	Non-proprietary	80mg tds	20	0.14	0.02	7.67
			Inderal	80mg tds	60	2.35	0.12	42.92
	metoprolol	LIT, Hjalmarson	Non-proprietary	100mg bd	20	1.31	0.13	47.85
			Betaloc	100mg bd	100	6.13	0.12	44.78
			Lopresor	100mg bd	56	6.68	0.24	87.14
	timolol	Norwegian M/C	Betim	10mg bd	30	2.45	0.16	59.66
			Blocadren	10mg bd	60	5.13	0.17	62.46
Calcium Channel Blockers	**verapamil**	CRIS, DAVIT I, DAVIT II	Non-proprietary	120mg tds	20	0.59	0.09	32.32
			Cordilox	120mg tds	100	13.7	0.41	150.12
			Securon	120mg tds	60	7.67	0.38	140.07
	diltiazem	MDPT	Non-proprietary	60mg qds	100	4.03	0.16	58.88
			Tildiem	60mg qds	90	10.35	0.46	168.02
	nifedipine	Wilcox, Sprint, Sprint II	Adalat	10mg qds	90	7.74	0.34	125.65
Statins	**pravastatin**	LIPID, CARE	Lipostat	40mg od	28	29.69	1.06	387.03
	simvastatin	4S	Zocor	20mg od (63%)	28	29.69	1.06	387.03
				40mg od (37%)	28	29.69		
Omega-3 marine triglycerides	**O-3MT**	GISSI - P	Maxepa	1000mgx5 bd	200	28.57	1.43	521.40

+ od: once daily; bd: twice daily; tds: three times daily; qds: four times daily. The major trials for each drug are used to provide evidence-based dosing regimens. Where dose ranges received by patients are reported these are used to weight the cost of treatment..

- Myocardial infarction trial doses are 300-1000mg. A recent North of England guideline explored dose and recommended 75md od in these patients
- Source of cost (eMIMS, Nov. 1999). Drug costs vary over time and this table illustrates the relative positioning of drugs based on costs as of November 1999.

Appendix 16. Costs (£) of therapies at doses found in trials: myocardial Infarction and heart failure

	Drug	Trial(s)+	Drug name	Daily dose	tabs/pkt	cost/pkt	cost/day	cost/year
ACE inhibitors	**captopril**	SAVE	Non-proprietary	25mg tds (21%)	56	1.35	0.10	36.46
				50mg tds (79%)	56	2.00		
			Capoten	25mg tds (21%)	56	12.03	1.00	366.32
				50mg tds (79%)	56	20.50		
	ramipril	AIRE	Tritace	2.5mg bd (15%)	28	7.51	0.66	241.17
				5mg bd (85%)	28	9.55		
	trandolapril	TRACE	Gopten / Odrik	2md bd	28	12.28	0.88	320.38
Beta-blockers	**propranolol**	Aronow, 1997	Non-proprietary	40mg tds	20	0.07	0.01	3.84
			Inderal	40mg tds	100	2.4	0.07	26.30
	metoprolol	MERIT-HF	*					
	carvedilol	Packer, 1996	Eucardic	25mg bd	28	13.15	0.94	343.07
	bisoprolol	CIBIS-II	Emcor / Monocor	10mg od	28	9.61	0.32	118.51
				5mg od	28	8.56		
Calcium Channel Blockers	**amlodipine**	PRAISE	Istin	10mg od	28	17.7	0.63	230.89
	diltiazem	DiDi	Non-proprietary	60mg qds	100	4.03	0.16	58.88
			Tildiem	60mg qds	90	10.35	0.46	168.02
	felodipine	V-HeFT III	Plendil	5mg bd	28	8.12	0.58	211.85
Spironolactone	**spironolactone**	RALES	Spironolactone	25mg od	100	5.95	0.06	21.73
			Aldactone	25mg od	100	9.88	0.10	36.06

+ od: once daily; bd: twice daily; tds: three times daily; qds: four times daily. The major trials for each drug are used to provide evidence-based dosing regimens. Where dose ranges received by patients are reported these are used to weight the cost of treatment.

- Metoprolol CR/XL is not licenced in the UK at the time of writing

Source of cost (eMIMS, Nov. 1999). Drug costs vary over time and this table illustrates the relative positioning of drugs based on costs as of November 1999.

Appendix 17: Estimated Relative Risk Ratios for treatments (Dersimeon and Laird)

	RR mean	C.I.-	CI+
Post Myocardial Infarction			
ACE inhibitors	0.848	0.757	0.951
Antiplatelet drugs	0.863	0.770	0.967
Beta-blockers	0.793	0.726	0.866
Mediterranean diet	0.613	0.363	1.035
Cardiac rehabilitation	0.772	0.666	0.896
Statins	0.789	0.719	0.866
Post Myocardial Infarction & Diabetes			
Insulin	0.758	0.619	0.927
Post Myocardial Infarction & Heart Failure			
ACE inhibitors	0.806	0.742	0.877
Beta-blockers	0.703	0.634	0.778
Spironolactone	0.753	0.668	0.848

Appendix 18: Estimated Survival gains (years) for treatments stratified by age and gender

	Male, 55			Male, 65			Male,75			Female, 55			Female, 65			Female, 75		
	Mean	95% CI -	95% CI +	Mean	95% CI -	95% CI +	Mean	95% CI -	95% CI +	Mean	95% CI -	95% CI +	Mean	95% CI -	95% CI +	Mean	95% CI -	95% CI +
Post Myocardial Infarction																		
ACE inhibitors	**0.26**	0.08	0.42	**0.31**	0.10	0.50	**0.40**	0.13	0.64	**0.25**	0.08	0.41	**0.28**	0.09	0.45	**0.36**	0.11	0.57
Antiplatelet drugs	**0.40**	0.09	0.68	**0.38**	0.09	0.65	**0.39**	0.09	0.67	**0.42**	0.10	0.71	**0.38**	0.09	0.65	**0.38**	0.09	0.65
Beta-blockers	**0.76**	0.49	1.01	**0.70**	0.45	0.93	**0.65**	0.42	0.88	**0.79**	0.51	1.05	**0.72**	0.46	0.96	**0.67**	0.42	0.89
Cardiac rehabilitation	**0.77**	0.35	1.15	**0.71**	0.32	1.06	**0.70**	0.31	1.05	**0.81**	0.37	1.20	**0.73**	0.33	1.09	**0.70**	0.31	1.04
Mediterranean diet	**1.25**	-0.11	2.11	**1.18**	-0.10	2.00	**1.20**	-0.10	2.08	**1.31**	-0.11	2.21	**1.19**	-0.10	2.02	**1.17**	-0.10	2.01
Statins	**0.32**	0.20	0.42	**0.41**	0.26	0.55	**0.54**	0.34	0.73	**0.30**	0.19	0.40	**0.35**	0.22	0.47	**0.48**	0.30	0.64
Post Myocardial Infarction & Diabetes																		
Insulin	**0.92**	0.27	1.50	**0.85**	0.25	1.40	**0.79**	0.23	1.30	**0.94**	0.28	1.54	**0.88**	0.26	1.44	**0.81**	0.23	1.33
Post Myocardial Infarction & Heart Failure																		
ACE inhibitors	**0.73**	0.46	0.98	**0.67**	0.42	0.91	**0.62**	0.39	0.84	**0.75**	0.47	1.01	**0.70**	0.44	0.94	**0.64**	0.40	0.87
Beta-blockers	**1.15**	0.84	1.43	**1.07**	0.78	1.33	**0.98**	0.72	1.24	**1.18**	0.86	1.47	**1.10**	0.81	1.38	**1.01**	0.74	1.27
Spironolactone	**0.88**	0.52	1.22	**0.84**	0.50	1.17	**0.78**	0.46	1.09	**0.89**	0.53	1.24	**0.86**	0.51	1.20	**0.81**	0.48	1.13

Appendix 19: Estimated cost-effectiveness of treatments post myocardial infarction

Future costs and benefits are discounted at 5%
Model 1: estimates based on 5 years of treatment and trial estimates of underlying risk of death
Model 2: estimates based on 5 years of treatment and common underlying risk of death
(see text for other modelling assumptions).

Post Myocardial Infarction		Model 1 Cost (£)/Life Year Gained	95% CI-	95% CI+	Model 2 Underlying all cause mortality rate at age 65 years	Cost (£)/Life Year Gained	95% CI-	95% CI+
Post Myocardial Infarction								
ACE Inhibitors	(Ramipril, 5mg bd)	5580	3470	17400	5%	3970	2460	12400
Antiplatelet drugs	(Aspirin, 75mg od)	35	21	150	5%	35	21	151
Beta-blockers	(Propranolol, 80mg tds)	73	54	113	5%	93	70	144
	(Metoprolol, 100mg bd)	409	305	638	5%	523	393	812
Cardiac Rehabilitation		6420	4310	14200	5%	7400	4990	16300
Statins	(Pravastatin, 40mg od)	6670	4990	10500	5%	4410	3290	6990
	(Simvastatin 20-40mg od)	6670	4990	10500	5%	4410	3290	6990
Post Myocardial Infarction & Heart Failure								
ACE Inhibitors	(Captopril, 25-50mg tds)	327	242	522	15%	320	235	511
	(Ramipril, 2.5-5mg bd)	2190	1620	3500	15%	2140	1580	3420
Beta-blockers	(Propranolol, 40mg tds)	23	18	31	15%	22	18	31
	(Bisoprolol, 5-10mg od)	673	538	920	15%	663	529	907
Spironolactone	(generic, 25mg od)	147	106	248	15%	151	110	251