The Survival Benefit of Angiotensin-Converting Enzyme Inhibitors Used Within 16 Days of Myocardial Infarction

A Meta Analysis

A sub-thesis submitted in partial fulfilment for the degree of Master of Population Health of The Australian National University.

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August 1995
Declaration

I declare that this sub-thesis is my own work, and that all sources used have been acknowledged.

Acknowledgments

I acknowledge the support and encouragement of my supervisors, Professor Bob Douglas, Professor Chris Silagy and Dr Wayne Smith. I also thank Professor Charles McGilchrist and Dr Ross Cunningham for statistical advice.
Abstract

1.1 Objectives

This thesis reviews the technique of meta analysis applied to randomised controlled trials in medicine and employs the new technique of mixed models to account for heterogeneity of effects amongst trials. Mixed models are used to analyse the survival benefits of angiotensin-converting enzyme (ACE) inhibitors commenced within 16 days of myocardial infarction. Optimum treatment population, regime and duration of treatment are addressed. The treatment group receives an ACE inhibitor in addition to standard treatment whereas the control group receives standard treatment only.

My interest in this project was inspired by my work in drug evaluation, an area in which meta analysis is becoming more important.

1.2 Data Sources

Published trials were identified by a systematic search of Medline, Embase, Current Contents, Dialog, Biosis and Scisearch, and bibliographies from reviews and clinical trial reports. An attempt to identify unpublished trials was made by discussions with colleagues; however, none were found.

1.3 Data Selection

Fourteen randomised placebo-controlled trials involving 107,005 subjects were included in the analyses.
1.4 Data Extraction

Data were extracted from the trial reports by the author.

1.5 Data Synthesis

The outcomes of interest were cardiovascular deaths and total deaths. Pooled odds ratios were obtained using a mixed logistic regression model with trial as a random effect and treatment as a fixed effect. There was significant heterogeneity of effect amongst trials; thus, the mixed model approach was appropriate. The mixed model was then used to examine trial covariates. For all-cause deaths, the mixed model demonstrated that significant factors in the heterogeneity of effect amongst trials were time of commencing treatment, percentage of subjects with heart failure and duration of treatment.

For ACE inhibitor treatment begun within 48 hours of myocardial infarction, the pooled odds ratio for death (any cause) was 0.94 (95% CI: 0.90-0.98), and for treatment begun after this time but within 16 days, the pooled odds ratio was 0.75 (95% CI: 0.66-0.84).

If 25% of the subjects treated with ACE inhibitors after infarction had heart failure, the odds ratio for all-cause mortality was 0.84 (95% CI: 0.77-0.91; however, if 75% of the subjects had heart failure, then the odds ratio was 0.70 (95% CI: 0.57-0.85) which implies that subjects with heart failure derive greater benefit from ACE inhibitor treatment after myocardial infarction.
It was also found that the longer the duration of treatment, the greater the survival benefit as a result of ACE inhibitor treatment after myocardial infarction. The odds ratio for all-cause deaths was 0.92 (95% CI: 0.88-0.95) for one month's treatment, whereas it was 0.79 (95% CI: 0.72-0.87) for 12 months' treatment.

Age, sex and duration of follow-up did not appear to influence the odds ratio for all-cause mortality.

Data on cardiovascular deaths was provided for only four trials; thus, there was insufficient information to draw any conclusions in regard to the pooled odds ratio for cardiovascular deaths.

1.6 Summary of Findings

ACE inhibitors significantly improve survival after myocardial infarction. The benefits are greater if there is some degree of heart failure after infarction and if treatment is not begun until at least 24 hours after the infarction. The benefits are also greater the longer the duration of ACE inhibitor treatment.

The value of the mixed model method employed here in meta analysis is to identify sources of heterogeneity in outcomes amongst trials as a prelude to sub-group analysis. The method provides an expeditious means of identifying trends and providing policy and research directions without the need to resort to individual patient data from trialists. However, sub-group analysis using individual patient data is also needed for the proper development of clinical practice guidelines.
1.7 Future Directions

Future directions include the confirmation of the effects of advanced age, baseline heart failure and duration of treatment by sub-group analysis, the examination of other endpoints, in particular reduction in the incidence of congestive cardiac failure and re-infarction, to gain some insight into the reasons for the survival benefits of ACE inhibitors, and examination of other covariates such as dose and type of ACE inhibitor, whether short-acting or long-acting.
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Part A: The Technique of Meta Analysis

1. What is Meta Analysis?

1.1 Definition

Meta analysis is a technique for quantitatively combining the results of clinical trials. The method has been proposed to overcome the subjective nature of traditional reviews (1). In analysing clinical trials the difference between treated and control groups in the effect measure is determined. If this difference differs only randomly from zero it is very likely that the intervention has done nothing. In meta analysis the total of the differences between treated and control groups for several clinical trials is obtained. If this total difference also only randomly differs from zero it is likely that the intervention has done nothing. This is the basic principle of meta analysis.

Odds Ratio

For dichotomous outcome data which are the subject of the analysis in Part B, the result of a meta analysis is usually expressed as an odds ratio which is computationally easier to obtain than a relative risk. The assumption is then made that the odds ratio is approximately equal to the relative risk. This assumption holds true only if the baseline risk is low. If the baseline risk is high, then for treatments showing benefit (relative risk and odds ratio less than one), the relative risk is greater than the odds ratio; thus, the odds ratio underestimates the relative risk (and overestimates the strength of association).
1.2 Uses

Meta analysis is being used to justify new research (in grant applications), develop clinical guidelines and assist health policy and the development of health services.

1.3 Important Steps

Important steps in a meta analysis are the identification of all relevant trials and the abstraction of the relevant data from them. There is a tendency to publish only interesting, usually positive, results ("publication bias"). Thus, clinical trial registers, institutional ethics committees' records and other sources need to be searched to find the uninteresting trials, and uninteresting results.

Identification of relevant studies is becoming easier with the development of clinical trial registers. However, the sharing of data needs to be encouraged since, even if relevant trial reports can be found, they often do not contain all the information needed for a meta analysis and trial investigators are often reluctant to provide the information.

Studies entered in a meta analysis must be sufficiently similar in design, population, intervention and outcome measures to allow meaningful interpretation of the combined result (1). Advances in diagnostic and therapeutic methods should be considered if the trials being pooled were done in different eras (2).

1.4 When Most Appropriate

Meta analysis is most appropriate when a particular intervention is of moderate rather than dramatic benefit but nevertheless the intervention has public health
importance. When the benefit is moderate individual studies typically point in a favourable direction; however, they do not reach statistical significance.

1.5 Avoidance of Bias

Since in meta analysis moderate effects are being investigated rather than dramatic effects, bias may have a large impact on the result (3). Bias can occur at two levels: trial level and meta analysis level.

Randomisation, avoidance of exclusions after trial entry and blinding are important factors in overcoming bias at the trial level. Schulz et al (4) found, in a study of the Cochrane Pregnancy and Childbirth Database, that trials with inadequate concealment of treatment allocation and trials that were not double-blind exaggerated odds ratios in favour of treatment effect by 41% and 17% respectively. Mengersen et al (5) showed, in a meta analysis of cohort and case-control studies of passive smoking and lung cancer, that bias may change estimates of differences in risk between treatment and control groups by as much as 50%.

At trial level, selection and measurement biases can be avoided by including, in the meta analysis, only randomised controlled trials with double-blinding and objective outcome measures. Intention-to-treat analysis, which includes all patients randomised, overcomes bias due to deliberately omitting subjects with poor compliance. Misclassification bias (with respect to diagnosis and covariates) is avoided with robust diagnostic methods; however, if such bias occurs in randomised trials, it would be expected to be equal in the treatment and placebo groups.
At meta analyst level, selection bias is avoided by a thorough search for all the relevant trials, and the use of at least two people independently to decide which trials should be included in the analysis, and to extract the relevant data from each trial. Measurement bias is avoided by sound pooling methods, explanation of heterogeneity between trials and the use of sensitivity analysis.

1.6 How to Combine Information

Results can be combined using either fixed or random effects methods. An important consideration is why trials differ in their results. There are three reasons:

(a) sampling error within each trial
(b) random variation between trials, and
(c) trial characteristics (covariates).

The method used to combine trials should account for each of these sources of variation. A fixed-effects method without covariates such as the Peto Method (6) only accounts for (a); a random-effects method without covariates such as the DerSimonian and Laird Method (7) accounts for (a) and (b); whilst a random-effects method with covariates (regression) accounts for (a), (b) and (c).

In the fixed-effects methods inference is conditional on the studies actually done, and all trials in the meta analysis are assumed to be estimating the same true effect of a fixed intervention, for example, ACE inhibitor treatment (8). Effect size estimates differ only as a result of sampling variability (within-trial variation). Between-trial variation is assumed to be zero, and only within-trial variation is used to obtain standard errors and 95% confidence intervals.
In the random-effects methods inference is based on the assumption that the studies are a random sample from a hypothetical population of studies (8), and that each trial is estimating a different effect (related to differences between trials in subjects, methods and outcome measures). Effect size estimates differ as a result of both sampling variability within trials and variability between trials. The standard errors and 95% confidence intervals reflect both within-trial and between-trial differences.

When between-trial variation is minimal the fixed- and random-effects methods produce similar results. However, when there is significant between-trial variation (heterogeneity), the standard errors are greater and hence the confidence intervals for the effect estimates are wider for random-effects methods compared with fixed-effects methods. The random-effects methods give more realistic results if there is between-trial variation.

**Peto Method**

The Peto Method, which is widely used in practice, is a fixed-effects method. The pooled odds ratio (OR) is estimated as

\[
\ln \text{OR} = \frac{\sum(O_i - E_i)}{\sum V_i}
\]

with standard error, \(se(\ln \text{OR}) = 1/\sqrt{\sum V_i}\)

where

- \(O_i\) = Observed number of deaths in the ACE inhibitor group in the ith trial
- \(E_i\) = Expected number of deaths in the ACE inhibitor group in the ith trial if there were no treatment effect, and
- \(V_i\) = Variance of the difference \((O_i - E_i)\).
Heterogeneity of effect between trials is tested by a chi-square test on the statistic

\[ Q = \sum_{i} (O_i - E_i)^2 / V_i - \sum (O_i - E_i)^2 / \Sigma V_i. \]

This tests the hypothesis that the degree of heterogeneity is no greater than that due to random variation.

**DerSimonian and Laird Method**

The DerSimonian and Laird Method, also widely used, is a random-effects method. The pooled odds ratio (OR) is estimated as

\[ \ln OR = \sum_{i} (w_i \ln OR_i) / \Sigma w_i \]

with standard error, \( se (\ln OR) = 1 / \sqrt{\Sigma w_i} \), where

- \( OR_i = \) Odds Ratio for the \( i \)th trial
- \( w_i = 1 / (\text{within-study variance} + \text{between-study variance}) \).

Both the Peto and the DerSimonian and Laird methods are supported by the Cochrane Collaboration, an international consortium promoting and supporting meta analyses of randomised controlled trials in medicine.

**Regression**

The conventional meta analysis techniques have been criticised because they average the outcomes of the trials included (9,10). Even if the average differs from zero, trial results could be either favourable, indifferent or unfavourable. Averaging may be satisfactory if the trials are homogeneous; however, it can mislead when there is significant between-trial
An important issue is why heterogeneity has occurred. Heterogeneous results amongst trials may relate to several factors, for example, differences in trial populations or treatment regimes and differences in the quality of the studies. These factors are referred to as explanatory variables or covariates. Some important covariates are age, sex, diagnosis, stage of disease, dose, timing and duration of treatment, and randomisation and blinding technique.

The use of regression enables covariates relating to each trial to be studied as a means of identifying causes of heterogeneity. Traditionally regression has been applied with all variables as fixed effects. Recent developments in statistics have allowed study of mixed models, which contain both fixed and random effects. Covariates relating to the trials are entered as fixed effects, and trial is entered as a random effect. The extent of heterogeneity amongst trials is determined by the trial variable.

Regression models can handle continuous, ordered and polytomous outcome variables as well as odds ratios from dichotomous outcome data. For example, person-time incidence rates could be studied (11).

Regression uses maximum likelihood to estimate effects. The effect estimates obtained are similar to the other methods if there is no adjustment for covariates.

A random-effects regression is presented in Part B of this sub-thesis.
Bayesian Meta Analysis

The methods so far discussed adopt the frequentist approach of statistical inference which tests the hypothesis that there is a difference between treatment and control groups with a specified level of certainty (usually 95%). The Bayesian approach, rather than testing a hypothesis that one treatment is superior, directly estimates the treatment effect by combining prior knowledge with the current trial results (12).

DuMouchel (13,14) has developed the Bayesian method to incorporate a random trial effect, in what he calls a hierarchical Bayes linear model. There are two levels of variation in the model, the within-trial variation and the between-trial variation: Thus, the model has a similar structure to a mixed regression model. Prior distributions of the covariate coefficients and the between-trial variation are used in estimating treatment effects. The model can account for uncertainty in the between-trial variability, unlike the frequentist regression approach. An important issue is what to choose for the prior distributions. The practical use of the method is limited by the absence of reliable prior information on treatment effects (15).

1.7 Sub-Group Analysis

Regression is simply an efficient technique for looking at sub-groups. Hence, as in any sub-group analysis, some caution is needed. The numbers of patients and events in each group may be low; thus, effects due to chance may come out as significant. If too many sub-groups are analysed the chance of obtaining a significant result in any one analysis is increased.
Specification of sub-group analyses *a priori* reduces the risk of being misled by a significant sub-group analysis result. In any case the use of sub-group analysis should be regarded as exploratory rather than confirmatory (16).

2. **Three Significant Meta Analyses**

The technique of meta analysis has been applied to medicine for about 15 years. Three significant analyses which demonstrate the development of the technique are:

(a) Yusuf, S et al (17) - Beta Blockers During and After Myocardial Infarction (1985)

(b) AntiPlatelet Trialists' Collaboration (ATC) (18) - Secondary Prevention of Vascular Disease by Prolonged AntiPlatelet Treatment (1988), and

(c) Law, MR et al (19,20) - Serum Cholesterol Reduction and Ischaemic Heart Disease (1994).

There are parallels between these studies and the meta analysis I will present in Part B.

2.1 **Randomised Controlled Trials**

The three meta analyses pool randomised controlled trials as I have done. The Law study also pools cohort studies; however, the pooling of cohort studies is outside the scope of this review. In this review the emphasis has been placed on randomised controlled trials so that the quality of trials does not become a significant issue.
The three analyses were ideal candidates for meta analysis. They examine an intervention which is of only moderate benefit, but still of public health significance. Individual studies were favourable but did not achieve statistical significance, in respect of the intervention.

2.2 Intention-To-Treat Analysis

Intention-to-treat analyses were used. This type of analysis reduces the risk of bias due to differential withdrawal rates in the treatment and control groups. My meta analysis also uses intention-to-treat analysis.

2.3 Search Strategy

An appropriate search strategy to obtain all the relevant studies for the meta analysis was given for the Yusuf and ATC studies but not for the Law study. The strategy included use of literature data bases and reference lists of papers retrieved, and inquiry of colleagues: I have adopted the same approach in my study.

2.4 Pooling Technique

Yusuf and the ATC pooled studies using the Peto method whereas the Law study used fixed-effect logistic regression. The regression gave the same result as the Peto method when trials were weighted by size (21). However, the significance of the regression approach was that it identified mean change in total serum cholesterol from baseline as a factor in explaining the heterogeneity amongst trials. Law et al found that the best model weighted trials by the mean difference in total serum cholesterol concentration between treated and control groups.
I used regression in my analysis to identify causes of heterogeneity.

**2.5 Mortality As Effect Measure**

All studies used mortality as one of the effect measures as I have in my meta analysis.

Yusuf obtained the mortality for two follow-up periods: less than or equal to one week, and greater than one week after beginning treatment. Law obtained the incidence of ischaemic heart disease events but not mortality for three follow-up periods: less than or equal to 2 years, 2.1 to 5 years, and 5.1 -12 years after beginning treatment. Time since randomisation for the Law meta analysis was also used as an explanatory variable in the logistic regression. This analysis demonstrated increasing benefit with increasing time since randomisation (21). The ATC study combined trials with follow-up periods from three months to six years but did not account for the different risks resulting from the different follow-up periods. This may lead to bias in estimates of effects.

In my analysis I have included follow-up time as a covariate.

**2.6 Pooling of Total Mortality**

The overall results based on total mortality for each meta analysis are given in Table 1.
### TABLE 1. POOLING OF THE ODDS RATIOS OF TOTAL MORTALITY FOR EACH META ANALYSIS

<table>
<thead>
<tr>
<th>Meta Analysis</th>
<th>Subjects Randomised</th>
<th>Pooled Odds Ratio (95% CI)</th>
<th>Heterogeneity of Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yusuf et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week oral</td>
<td>3,611</td>
<td>0.93 (0.74-1.18)</td>
<td>not significant</td>
</tr>
<tr>
<td>1 week iv then oral</td>
<td>11,309</td>
<td>0.94 (0.76-1.14)</td>
<td>' ' '</td>
</tr>
<tr>
<td>&gt; 1 week</td>
<td>20,312</td>
<td>0.77 (0.70-0.85)</td>
<td>' ' '</td>
</tr>
<tr>
<td>ATC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29,073</td>
<td>0.85 (vasc)^1 (0.77-0.93)</td>
<td>not significant</td>
</tr>
<tr>
<td></td>
<td>29,073</td>
<td>0.93 (non-vasc)^1 (0.78-1.13)</td>
<td>' ' '</td>
</tr>
<tr>
<td>Law et al^2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46,254</td>
<td>0.96 (0.90-1.02)</td>
<td>significant</td>
</tr>
</tbody>
</table>

Table 1 Notes

1. Results are for vascular and non-vascular mortality; total mortality was not provided.

2. In the Law meta analysis the pooled odds ratios are per 0.6 mmol/L reduction in serum cholesterol concentration.
Significant features of these results are:

* Yusuf et al study: the odds of death were significantly reduced in the beta blocker group for periods of treatment greater than one week, but not for shorter periods.

* ATC study: the odds of cardiovascular death, but not non-cardiovascular death, were significantly reduced in the antiplatelet group. This result implies that antiplatelet treatment also reduced total mortality; however, this question could not be answered directly from the data in the report.

* Law et al study: the odds of death were not significantly reduced by reduction in serum cholesterol concentration. However, the odds of cardiovascular death were significantly reduced in the group receiving cholesterol-lowering treatment (odds ratio 0.90, 95% confidence interval 0.84-0.97). The authors believed that there were too few deaths from causes other than cardiovascular disease and that the follow-up period was insufficient (mean 4.6 years) to achieve a significant result for total mortality.

* Heterogeneity of effect on the mortality endpoint was not a problem for the Yusuf and ATC analyses but was a problem in the Law analysis. Heterogeneity for the Law study became non-significant when adjustments were made using logistic regression for the average extent of cholesterol reduction achieved and the duration of treatment.

Heterogeneity of effects was also a problem with my study.
2.7 Sub-Group Analysis

Sub-group analysis was done in each meta analysis.

The Yusuf study examined beta-blockers with and without intrinsic sympathomimetic activity (ISA) obtaining a significant reduction in the odds of death in the group treated with non-ISA beta-blockers but not in the group treated with ISA beta-blockers. This result has been challenged as being possibly due to chance, and has not influenced treatment guidelines at the present time.

The ATC study examined the type of antiplatelet treatment used (high- and medium-dose aspirin, aspirin plus dipyridamole, and sulphipyrazone) and found that all types of antiplatelet treatment, when compared with placebo, produced significant reductions in the odds of death; however, when the treatments were compared with each other there was no difference in the odds of death. The authors argued that the numbers randomised were insufficient to achieve significant results for the active treatment comparisons: there were 703 subjects randomised for the aspirin-sulphipyrazone comparison, and 3,194 for the aspirin-aspirin+dipyridamole comparison.

The Law study examined the sub-groups, drug treatment and dietary treatment, and the sub-groups, ischaemic heart disease and no ischaemic heart disease at baseline. There were no differences in the odds of death from any cause between drug and diet treatment; however, the odds of non-cardiovascular death were increased compared with placebo in those receiving drug therapy to lower serum cholesterol (odds ratio 1.20, 95% confidence interval 1.02-1.40). The odds of death from any cause were reduced compared with placebo in subjects with ischaemic heart disease at baseline (odds ratio 0.90,
95% confidence interval 0.84-0.97).

These results, even though they have been obtained by sub-group analysis a posteriori have influenced treatment guidelines. There is an awareness amongst prescribers of a possible increase in non-cardiovascular deaths from cholesterol-lowering therapy with drugs, and cholesterol-lowering therapy is specifically directed at those patients with existing ischaemic heart disease (secondary prevention).

In my meta analysis regression was used to predict effects in sub-groups.

2.8 Policy Implications

All studies have had a significant impact on clinical practice. The Yusuf and ATC results which were not marred by the problem of heterogeneity of effects have been almost universally accepted.

Law et al argue for serum cholesterol-lowering in both primary and secondary prevention of ischaemic heart disease. The Law data do not support the primary prevention indication since a non-significant difference in the odds of death between treatment and control groups was obtained (odds ratio 1.06, 95% confidence interval 0.97-1.17).

Whilst serum cholesterol-lowering for secondary prevention has been generally accepted, serum cholesterol-lowering for primary prevention has not, some meta analyses (including Law's) supporting it and others not supporting it. Silberberg (22) argues that these different interpretations arise from selective inclusion of trials and choice of trial weights for the meta analysis. This illustrates a danger of meta
analysis. The Law meta analysis appears to be the most rigorous since it weights trials on the extent of serum cholesterol reduction and considers the duration of treatment.

2.9 Implications For My Study

I have considered the techniques in these three meta analyses and applied them to the meta analysis in Part B of this review.

I have restricted my meta analysis to randomised controlled trials to reduce bias due to selection and confounding, I have applied intention-to-treat analysis to overcome bias from the deliberate omission of subjects with poor compliance, and I have used mortality as the effect measure because it is easy to assess and is a clinically-relevant endpoint.

I have adopted a similar three-stage search strategy of use of the literature databases, thence use of the reference lists of papers retrieved, and finally enquiry of colleagues.

For pooling trials I used a new technique of mixed models, a random effects approach which can incorporate several covariates. This technique allows sub-groups to be examined efficiently, and reasons for heterogeneity of effects to be identified. A priori hypotheses were made with respect to the covariates of interest.
Part B: Application to the Use of ACE Inhibitors in Myocardial Infarction

1. Introduction

1.1 Development of Heart Failure After Myocardial Infarction

After a myocardial infarction the sympathetic nervous system and the renin-angiotensin system become activated. The activation of these systems is maximal within the first 72 hours and has resolved by 7-10 days (23,24). Plasma levels of noradrenaline and angiotensin II become elevated. The activation is greatest in patients with left ventricular dysfunction (24). These hormones increase systemic vascular resistance and consequently left ventricular pre-load and after-load. Greater stress is placed on the left ventricular wall causing thinning and elongation of the infarcted area. Meanwhile, the remaining viable myocardium hypertropies to compensate for the lost myocardium. Thus, a process of left ventricular remodelling ensues. This process begins within two weeks of infarction and may continue for six months (25,26).

Remodelling reduces myocardial function and progressively leads to congestive cardiac failure in approximately 20% of patients after myocardial infarction (26). The underlying ischaemia contributes to the diminution in cardiac function by a vicious cycle where diminished cardiac function leads to further ischaemia.

Congestive cardiac failure has a poor prognosis. This was clearly demonstrated in early studies (27,28), and confirmed in a study by Stevenson et al (29) since the
introduction of thrombolysis. In this study the mortality rate at three years in patients with congestive cardiac failure following myocardial infarction was 55.4% compared with 17.4% in those without congestive cardiac failure.

1.2 ACE Inhibitors After Myocardial Infarction

Angiotensin-converting enzyme (ACE) inhibitors are potent vasodilators. It was hypothesised that ACE inhibitors would limit ventricular enlargement after myocardial infarction by reducing afterload (30-2). Clinical trials have been designed to test, firstly, whether ACE inhibitors limited ventricular enlargement post-myocardial infarction, and secondly, whether they improved survival.

There have been several large randomised controlled trials of the survival benefit of ACE inhibitors after myocardial infarction. Some studies have demonstrated a benefit (25,33,34,35) whilst others (36) have not. Key issues appear to be the time of commencement of the ACE inhibitor after infarction, the initial dose and route of administration, and the degree of left ventricular dysfunction.

Beneficial Effects

Several mechanisms of action have been proposed for the beneficial effects of ACE inhibitors after myocardial infarction.

Firstly, ACE inhibitors inhibit the activation of the sympathetic nervous system and the renin-angiotensin system (33,36,37). As a consequence, plasma levels of noradrenaline and angiotensin II are reduced and less stress is placed on the left ventricular wall. The left
ventricular remodelling process is thereby attenuated, improving cardiac output and reducing the development of congestive cardiac failure (33,35,38).

Secondly, ACE inhibitors have an anti-ischaemic effect by virtue of their vasodilatory action. Coronary blood flow is thereby increased, and there is less risk of the infarcted area expanding; thus, attenuating left ventricular remodelling and breaking the vicious cycle of ischaemia causing diminished cardiac function which in turn causes more ischaemia. This effect is supported by the SAVE (33), SOLVD (39,40) and AIRE (35) studies which demonstrated a reduced recurrence rate of myocardial infarction in patients treated with ACE inhibitors.

Thirdly, ACE inhibitors exert an anti-arrhythmic effect. This proposal is supported by the reduced incidence of ventricular arrhythmias in subjects treated with the ACE inhibitor, zofenopril, compared with those treated with placebo in the SMILE pilot study (41). The anti-arrhythmic effect may be due to better myocardial perfusion as a result of vasodilation induced by the ACE inhibitor.

Finally, ACE inhibitors may prevent atherosclerotic plaque formation, plaque rupture and thrombosis after plaque rupture. Angiotensin II stimulates platelet-derived growth factor and the migration of neutrophils and macrophages into blood vessel walls, and is also believed to increase lipid uptake into vessel walls (42). These processes lead to atherosclerosis, and may be curbed by an ACE inhibitor. Stimulation of the renin-angiotensin system, because it increases vasomotor tone, has the potential to increase plaque rupture. This process could also be curbed with the use of an ACE inhibitor.
Adverse Effects

On the other hand, there are two proposed mechanisms for the failure of ACE inhibitors to improve survival after myocardial infarction.

Firstly, ACE inhibitors reduce blood pressure and, hence, myocardial perfusion. The corresponding increased ischaemia increases the risk of infarct extension, and the risk of re-occlusion in situations where thrombolytic treatment has been used to re-open occluded coronary vessels (23). The hypotensive effect will be more pronounced if a more potent or faster-acting ACE inhibitor is used, a larger initial dose is employed or the ACE inhibitor is given by the intravenous route.

Secondly, angiotensin II stimulates myocardial protein synthesis early after myocardial infarction, and this may be important in stimulating the healing process, in particular compensatory cardiac muscle cell proliferation (36). If this process is blocked by use of an ACE inhibitor, healing is thereby reduced. (It could be argued that blocking the healing process is a good thing, because healing may cause potentially damaging left ventricular remodelling).

Optimal Commencement Time

There appears to be an optimal time after infarction when the beneficial effects of ACE inhibition take over from the adverse effects. The SAVE study (33), which began ACE inhibitor treatment not earlier than three days after myocardial infarction, showed survival benefits; whereas the CONSENSUS II study (36), which began treatment within 24 hours of infarction, did not show survival benefits. Why?
To achieve maximal inhibition of the renin-angiotensin system treatment must begin within 72 hours, and to have an impact on left ventricular remodelling ACE inhibitor treatment must begin within two weeks of an infarction (23,24). However, soon after infarction, the myocardium is sensitive to the hypotensive insult induced by ACE inhibitors. The duration of the sensitive period varies from case to case and could be as long as 48 hours. It may be possible to identify the sensitive period with the use of a small test dose of an ACE inhibitor. The optimal timing for stimulation of myocardial protein synthesis after infarction is unknown. Thus, there are several factors determining the optimal commencement time of ACE inhibitors after myocardial infarction.

**Left Ventricular Dysfunction**

Having determined an optimum time to begin ACE inhibitor treatment, there are other factors which are believed to influence the magnitude of any survival benefit. Greater survival benefits have been postulated if there is some evidence of left ventricular dysfunction following infarction. The SAVE (33) and AIRE (35) studies demonstrated a greater survival benefit in subjects with left ventricular dysfunction; whereas the CONSENSUS II study (36), which did not specifically select subjects with left ventricular dysfunction, did not demonstrate survival benefits.

There is greater sympathetic and renin-angiotensin system activation in patients with left ventricular dysfunction compared with other patients, and, therefore, curbing the activity of these systems in such patients would be expected to have a greater impact (33,35).
Ischaemia

Greater survival benefits from ACE inhibitors have also been postulated where thrombolysis has either failed or has not been used after infarction (35). In such situations ischaemia persists longer than in other situations; thus, it is presumed that the anti-ischaemic effect of ACE inhibitors has a greater impact.

Optimum Duration of Treatment

Another factor to be determined is the optimum duration of treatment with ACE inhibitor after myocardial infarction. There is evidence that, if the ACE inhibitor is used only in the first critical weeks after infarction when the events previously described are occurring, the survival benefits will persist for at least 12 months.

In the SMILE study (25), only six weeks treatment with an ACE inhibitor was given; however, the survival benefit of zofenopril over placebo was maintained at 12 months of follow-up. The benefits of ACE inhibitor treatment in this study appear to derive from events occurring immediately after the infarction, in particular renin-angiotensin system activation and left ventricular remodelling.

On the other hand, the SAVE study with captopril did not demonstrate survival benefits until after 12 months' treatment, and the CONSENSUS II study with enalapril had not demonstrated any survival benefits at six months when it was terminated.

If ACE inhibitors have anti-ischaemic and anti-plaque effects then additional survival benefits could be expected from longer treatment.
Questions

ACE inhibitor studies to date raise several questions:

* Should treatment be started as soon as possible after infarction or delayed for 24-48 hours?

* What is the optimum duration of treatment?

* What is the optimum treatment population?

* What is the optimum dose?

* Why do ACE inhibitors improve survival in some patients and not in others?

2. Objective

The objective of this review is to determine the survival benefit of ACE inhibitors when used early (within 16 days) after myocardial infarction, and to determine the optimum treatment regime, duration of treatment and treatment population. The outcomes of interest are cardiovascular deaths and total deaths.

Hypotheses

* ACE inhibitors diminish survival if started earlier than 24 hours after a myocardial infarction.

* ACE inhibitors have a greater impact on the survival of subjects with some degree of left ventricular dysfunction than no left ventricular dysfunction after myocardial infarction.
* ACE inhibitors have a greater impact on survival after myocardial infarction if used in subjects under the age of 70 years than if used in subjects 70 years and over.

* ACE inhibitors after myocardial infarction have an equal impact on survival for males and females.

* A treatment duration of at least one month is needed for ACE inhibitors to improve survival after myocardial infarction.

3. Criteria for Considering Trials for This Review

Study Design

Randomised placebo-controlled trials.

Types of Participants

Patients within 16 days of a myocardial infarction.

Myocardial infarction is defined as typical symptoms with:

* ST elevation and/or T-wave inversion on electrocardiogram (ECG), or

* changes in Q waves on serial ECGs, or

* elevation of myocardial enzymes.

Intervention

ACE inhibitor.
Outcome Measures

Cardiovascular mortality and total mortality.

4. Search Strategy for Identification of Trials

Published trials were identified by a systematic search of Medline, Embase, Current Contents, Biosis and Scisearch.

4.1 Medline

The Medline search provided the majority of the trials identified. The Medline search strategy was as follows:

(a) thesaurus "ACE inhibitors" (exploded)
(b) thesaurus "myocardial infarction" (exploded)
(c) "human in tg"
(d) "not review" (1966-93)
(e) "clinical-trial in pt".

A browse was done at point (d) and an additional clinical trial not tagged as such was identified (Mourao,L et al). The search was broad-based for 1994-95, retrieving not only clinical trial reports but also other articles including reviews and letters. The other articles were examined to identify any other relevant clinical trials. The bibliographies of the clinical trial reports were examined to identify other studies. Animal studies were excluded from the search.

4.2 Embase

Embase was searched on "ACE inhibitors" and "myocardial infarction" for the period 1989 to May 1994; resulting in one additional trial being identified (a study by Di Pasquale et al not amongst the Di Pasquale studies found
on Medline); however, this trial did not meet the inclusion criteria since it was not placebo-controlled.

4.3 Other Databases

The other databases were searched from January to June 1995 to identify the more recent published studies. A preliminary report of the TRACE study was found on Medline; however, the final results of this study were obtained from the Dialog search. Current Contents identified the SMILE and CCS trials. Biosis and Scisearch did not provide any new information. The search results are given in Tables 1 and 2.

**TABLE 1. ACE INHIBITORS WITHIN 16 DAYS OF MYOCARDIAL INFARCTION: TRIALS IDENTIFIED FROM MEDLINE "CLINICAL-TRIAL" SEARCH**

<table>
<thead>
<tr>
<th>Source</th>
<th>Items</th>
<th>Trials</th>
<th>Incl or Excl</th>
<th>Reason for Excl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline 1/94-</td>
<td>'41</td>
<td>Flather, M: ISIS-4 Pilot</td>
<td>Incl</td>
<td></td>
</tr>
<tr>
<td>1/95</td>
<td></td>
<td>Bonaduce, D et al</td>
<td>Excl</td>
<td>No data on mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sogaard, P et al: 3 papers</td>
<td>Excl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wright, RA et al</td>
<td>Excl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tohmo, H et al</td>
<td>Excl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Santos, JM et al</td>
<td>Excl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foy, SG et al: PRACTICAL</td>
<td>Incl</td>
<td>Not placebo controlled</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mareev, VIU et al</td>
<td>Excl</td>
<td></td>
</tr>
<tr>
<td>Source</td>
<td>Items</td>
<td>Trials</td>
<td>Incl or Excl</td>
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<tr>
<td>-----------------------------</td>
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<td>-------------------------</td>
<td>--------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Medline 1/94-1/95 (cont)</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Kettunen, RV et al</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GISSI-3</td>
<td>Incl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Di Pasquale, P et al</td>
<td>Excl</td>
<td></td>
<td>No data on mortality</td>
</tr>
<tr>
<td></td>
<td>TRACE</td>
<td>Incl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kyriakidis, M et al</td>
<td>Excl</td>
<td></td>
<td>No data on mortality</td>
</tr>
<tr>
<td></td>
<td>CADS</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECCE</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kingma, JH et al: CATS</td>
<td>Excl</td>
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<td></td>
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<td></td>
<td>Omland, T et al</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lu, CY et al</td>
<td>Incl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medline 1990-93</td>
<td>55</td>
<td>Sigurdsson, A 2 papers</td>
<td>Excl</td>
<td>No data on mortality</td>
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</table>
TABLE 1 (CONT). TRIALS IDENTIFIED FROM MEDLINE "CLINICAL-TRIAL" SEARCH

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<td>Incl</td>
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<td>(cont)</td>
<td>Jansson, JH et al</td>
<td>Excl</td>
<td>No data on mortality</td>
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<tr>
<td></td>
<td>Motwani, JG et al</td>
<td>Excl</td>
<td>&quot;&quot;</td>
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<tr>
<td></td>
<td>Gonzalez-Fernandez, RA</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sogaard, P et al</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ray, SG et al</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galcera-Tomas, J</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pipilis, A et al</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 papers</td>
<td></td>
<td>&quot;&quot;</td>
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</tr>
<tr>
<td></td>
<td>Tranchesi-Junior, B</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borghi, C et al</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kleber, FX et al</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
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<tr>
<td></td>
<td>al Di</td>
<td></td>
<td>&quot;&quot;</td>
<td></td>
</tr>
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<td></td>
<td>Pasquale, P et al</td>
<td>Excl</td>
<td>&quot;&quot;</td>
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<td></td>
<td>Villalpando-Gutierrez, J</td>
<td>Excl</td>
<td>&quot;&quot;</td>
<td></td>
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<tr>
<td></td>
<td>Frost, L et al</td>
<td>Excl</td>
<td>&quot;&quot;</td>
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<tr>
<td></td>
<td>Hargreaves, A D et al</td>
<td>Excl</td>
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</table>
### TABLE 1 (CONT). TRIALS IDENTIFIED FROM MEDLINE "CLINICAL-TRIAL" SEARCH

<table>
<thead>
<tr>
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<th>Reason for Excl</th>
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<td>Medline 1990-93</td>
<td>SAVE</td>
<td>Incl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cont)</td>
<td>Bonaduce,D:</td>
<td>Excl</td>
<td>Mortality not endpt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 papers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CONSENSUS II</td>
<td>Incl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gotzsche,CO et al</td>
<td>Excl</td>
<td>Mortality not endpt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bussmann,WD et al</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nabel,EG et al</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pinzur,SV et al</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ambrosioni,E et al</td>
<td>Incl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oldroyd,KG et al</td>
<td>Excl</td>
<td>Mortality not endpt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sharpe,N et al</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>di Pasquale, P et al</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medline 1989</td>
<td>3 Nil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medline 1982-88</td>
<td>3 Pfeffer,MA et al</td>
<td>Excl</td>
<td>Mortality not endpt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sharpe,N et al</td>
<td>Excl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medline 1966-81</td>
<td>3 Brivet,F et al</td>
<td>Excl</td>
<td>Mortality not endpt</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2. ACE INHIBITORS WITHIN 16 DAYS OF MYOCARDIAL INFARCTION: TRIALS IDENTIFIED FROM OTHER SOURCES (NOT FOUND ON MEDLINE "CLINICAL-TRIAL" SEARCH)

<table>
<thead>
<tr>
<th>Source</th>
<th>Trials</th>
<th>Incl or Excl</th>
<th>Reason for Excl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad Medline search (not restricted to &quot;clinical-trial in pt&quot;)</td>
<td>Mourao, L et al</td>
<td>Excl</td>
<td>No data on mortality</td>
</tr>
<tr>
<td>Bibliography of articles identified by Medline and supplementary Medline search to 5/95</td>
<td>ISIS-4</td>
<td>Incl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hochman, JS et al: CAPTIN</td>
<td>Excl</td>
<td>Incomplete</td>
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<tr>
<td></td>
<td>Jugdutt, B et al</td>
<td>Excl</td>
<td>No data on mortality</td>
</tr>
<tr>
<td></td>
<td>Latini, R: GISSI-3 Pilot</td>
<td>Incl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sigurdsson, A et al</td>
<td>Excl</td>
<td>No data on mortality</td>
</tr>
<tr>
<td>Embase 1989-5/95</td>
<td>Di Pasquale, P et al</td>
<td>Excl</td>
<td>No placebo control</td>
</tr>
<tr>
<td>Current Contents 1/95-6/95</td>
<td>Ambrosini, E et al: SMILE CCS</td>
<td>Incl</td>
<td></td>
</tr>
<tr>
<td>Dialog</td>
<td>TRACE: final results</td>
<td>Incl</td>
<td></td>
</tr>
</tbody>
</table>
Legend (Tables 1 and 2):

CADS  Captopril and Digoxin Study
CATS  Captopril and Thrombolysis Study
CCS  Chinese Cardiac Study
ECCE  Effects of Captopril on Cardiopulmonary Exercise Parameters
GISSI-3  Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
ISIS-4  Fourth International Study of Infarct Survival
PRACTICAL  Placebo-Controlled Randomised ACE Inhibitor Comparative Trial in Cardiac Infarction and LV Function
SMILE  Survival of Myocardial Infarction Long-Term Evaluation
TRACE  Trandolapril Cardiac Evaluation Study

4.4 Unpublished Trials

An attempt to identify unpublished trials was made by discussions with colleagues. No unpublished trials were found.

5. Trials Selected For Meta Analysis

5.1 Trials

Fourteen trials were identified as satisfying the search criteria (Section 3). The trials were:

SAVE (33)
CONSENSUS II (36)
GISSI-3 Pilot (43)
GISSI-3 (34)
Lu,CY et al (44)
PRACTICAL (38)
5.2 Likelihood of Missed Trials

A funnel plot was used to determine the likelihood that relevant trials were missed due, for example, to publication bias. The number of subjects (a measure of precision) versus the odds ratio for each of the 14 included published trials was plotted (Figure 1). Assuming all trials are estimating the same value of effect (fixed effect), the spread of results would be expected to narrow as the precision (number of subjects) increases (11). Thus, if there are no missing trials, the plot should form the shape of an inverted funnel.

A favourable meta analysis of several small magnesium trials was recently refuted by a large trial (ISIS-4, a factorial trial involving treatment with both captopril and intravenous magnesium). Egger and Davey Smith (50) argued that the meta analysis was affected by publication bias, negative studies not being published, and this was shown by a gap in the funnel plot.
Figure 1 is sparse because there were only 14 points; thus, there are dangers in using it for pattern recognition (51). The assumption of fixed effects for this data is also contentious. Nevertheless, an inverted funnel shape can be made out and this provides a rough guide that the trials selected represent most of the relevant trials. There possibly should be more small negative (odds ratio greater than one) trials.
5.3 Data Extracted

The included trials enrolled 107,005 subjects. The trials met the diagnostic criteria for myocardial infarction as stated in Section 3. Since only randomised trials have been considered, any misclassification with respect to the diagnosis of myocardial infarction would be expected to be equal in the ACE inhibitor and placebo groups. The inclusion of patients without infarction, assuming they have a better prognosis, would underestimate any survival benefit in the ACE inhibitor group.

The data extracted from the trials is given in Appendix I, and descriptions of the trials are given in Appendix II.

The number of subjects with each outcome event was extracted, by allocated treatment group, irrespective of compliance, and whether or not the subject was subsequently excluded from treatment or follow-up, so as to allow an intention-to-treat analysis. Data on covariates sufficient to test my a priori hypotheses was collected.

6. Methods of Analysis

6.1 Outcomes of Interest

The outcomes of interest were total mortality and cardiovascular mortality.
6.2 Analysis of Individual Trials

The Cochrane Collaboration software Revman (52) was used to calculate the odds ratios and their 95% confidence intervals for the individual trials.

6.3 Combined Analysis

The data from the individual trials was combined using generalised linear mixed models.

Binomial response variables, the proportion of deaths (any cause) and the proportion of deaths (cardiovascular causes) in the ACE inhibitor and placebo groups, were used to estimate the probability of death (all causes) and the probability of death (cardiovascular causes). The response variables were fitted with a logit link (logistic regression). The corresponding odds ratios were then calculated from the estimates of the odds of death (all-causes and cardiovascular causes) in the ACE inhibitor and placebo groups.

The responses, probability of death (all causes) and probability of death (cardiovascular causes), can vary at two levels, the within-trial level and the between-trial level. Thus an appropriate statistical model will include random effects for between-trial and within-trial variability and fixed effects for the factors of interest (covariates) associated with the trials. This was the approach adopted.

The trial covariates were chosen so that my a priori hypotheses could be tested. The covariates were treatment, time of commencing treatment, age, proportion of subjects over age 70 years, sex, proportion of subjects with heart failure (Killip Class>1, or clinical heart failure), mean duration of treatment and mean
duration of follow-up.

Since the covariates are at the trial level rather than the subject level and relate to trial outcomes rather than individual outcomes the \textit{a priori} hypotheses can be tested only indirectly. The robustness of this approach is examined for the effects of sex and baseline heart failure by sub-group analyses in males, females and those with baseline heart failure.

The models had the following structure:

\[
\text{Probability of death (all-causes and cardiovascular causes)} = \text{Constant} + \text{Effect due to ACE inhibitor treatment} + \text{Effect due other covariate} + \text{Interaction Effect between treatment and other covariate} + \text{Random Between-Trial Error} + \text{Random Within-Trial Error}.\]

The method efficiently pools the between-trial and within-trial error; thus, more realistic standard errors are obtained, and inference is more accurate.

Some trials did not provide data for all covariates. Thus, I examined the impact of one covariate at a time on treatment, and included trial as a random effect.

The mean duration of treatment and the mean duration of follow-up data were skewed. Log transformations of these covariates were taken to overcome this problem.

The impact of quality of trials was tested by removing trials of potentially poorer quality and noting the effect on outcome.
The models were computed with Genstat software (53), which uses the method of Schall (54). Diagnostic plots were done for each model to ascertain whether the model assumptions of constant variance and normality were met. The plots were of residuals versus fitted values, and residuals versus normal variates.

7. Analysis

7.1 Deaths - All Causes

7.11 Analysis of Individual Trials

The odds ratios and 95% confidence intervals for each trial are listed in Table 3, and plotted in figure 2.

The PRACTICAL trial which was a three-arm study involving captopril, enalapril and placebo groups was entered into Revman as two trials. The two trials are not independent since each trial has the same placebo group.

The 14 trials randomised a total of 107,005 subjects in whom there were 12,247 deaths. The largest trial, ISIS-4, accounted for 54.2% of the subjects.
TABLE 3. ODDS RATIOS OF DEATH ANY CAUSE (ACE INHIBITOR VERSUS PLACEBO) OBTAINED USING REVMAN

<table>
<thead>
<tr>
<th>No</th>
<th>Trial</th>
<th>No Deaths/No Subjects</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval of Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ACE Inhib</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>SAVE</td>
<td>228/1115</td>
<td>275/1116</td>
<td>0.79</td>
</tr>
<tr>
<td>2</td>
<td>CONSENSUS II</td>
<td>312/3044</td>
<td>286/3046</td>
<td>1.10</td>
</tr>
<tr>
<td>3</td>
<td>GISSI-3</td>
<td>597/9435</td>
<td>673/9460</td>
<td>0.88</td>
</tr>
<tr>
<td>4</td>
<td>Lu et al</td>
<td>3/43</td>
<td>8/55</td>
<td>0.47</td>
</tr>
<tr>
<td>5</td>
<td>CCS</td>
<td>617/6814</td>
<td>654/6820</td>
<td>0.94</td>
</tr>
<tr>
<td>6</td>
<td>PRACTICAL Captopril</td>
<td>10/75</td>
<td>12/75</td>
<td>0.81</td>
</tr>
<tr>
<td>6</td>
<td>PRACTICAL Enalapril</td>
<td>2/75</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>7</td>
<td>SMILE Pilot</td>
<td>8/101</td>
<td>11/103</td>
<td>0.72</td>
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<tr>
<td>8</td>
<td>SMILE</td>
<td>77/772</td>
<td>111/784</td>
<td>0.67</td>
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<td>9</td>
<td>ISIS-4 Pilot 1</td>
<td>3/133</td>
<td>5/134</td>
<td>0.60</td>
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<td>10</td>
<td>ISIS-4 Pilot 2/3</td>
<td>21/237</td>
<td>14/237</td>
<td>1.54</td>
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TABLE 3 (CONT). ODDS RATIOS OF DEATH ANY CAUSE (ACE INHIBITOR VERSUS PLACEBO) OBTAINED USING REVMAN

<table>
<thead>
<tr>
<th>No</th>
<th>Trial</th>
<th>No Deaths/No Subjects</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval of Odds Ratio</th>
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<td></td>
<td>ACE Inhib / Placebo</td>
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<td></td>
</tr>
<tr>
<td>11</td>
<td>ISIS-4</td>
<td>3480/29028 / 3636/29022</td>
<td>0.95</td>
<td>0.91-1.00</td>
</tr>
<tr>
<td>12</td>
<td>AIRE</td>
<td>170/1014 / 222/992</td>
<td>0.70</td>
<td>0.56-0.87</td>
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<tr>
<td>13</td>
<td>GISSI-3 Pilot</td>
<td>41/509 / 98/1017</td>
<td>0.83</td>
<td>0.57-1.20</td>
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<tr>
<td>14</td>
<td>TRACE</td>
<td>307/876 / 366/873</td>
<td>0.75</td>
<td>0.62-0.91</td>
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<td></td>
<td>POOLED</td>
<td>5876/53271 / 6371/53734</td>
<td>0.92</td>
<td>0.88-0.95</td>
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</table>

Between-trial test for heterogeneity; $\chi^2$ (df=14) = 34.68.
Figure 2. Death (All Causes) Odds Ratios and 95% Confidence Intervals for Included Trials
ACE inhibitor treatment significantly (p<0.05) increased survival compared with placebo in 7 trials, and there was a non-significant result in 8 trials (the PRACTICAL trial being counted twice because of its three treatment arms). The individual odds ratios ranged from 0.21 to 1.54. The trials with these extreme odds ratios were small. Of the three trials with more than 10,000 subjects, two (GISSI-3, ISIS-4) were just significant and the other (CCS) non-significant. Thus, a clear judgement of the survival benefit or otherwise of ACE inhibitors after myocardial infarction cannot be made on the basis of individual analysis; however, there is a suggestion of moderate benefit which may have public health importance. Combined or meta analysis is appropriate.

7.12 Combined Analysis

ACE Inhibitor Treatment Unadjusted for Other Covariates

For deaths (all causes) the mixed model yielded a pooled odds ratio of 0.92 with 95% confidence interval 0.88-0.95. By way of comparison and as a means of validating the mixed model approach the pooled odds ratios were also obtained using the Peto Method and the DerSimonian and Laird Method. The computation was done using Revman for the Peto Method and Excel (55,56) for the DerSimonian and Laird Method. The results are given in Table 4.
TABLE 4. POOLED ODDS RATIOS OF DEATH ALL CAUSES (ACE INHIBITOR VERSUS PLACEBO) BY THREE METHODS

<table>
<thead>
<tr>
<th>Method</th>
<th>Pooled Odds Ratio</th>
<th>95% Confidence Interval of Pooled Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed Model</td>
<td>0.92</td>
<td>0.88-0.95</td>
</tr>
<tr>
<td>Peto Method</td>
<td>0.92</td>
<td>0.88-0.95</td>
</tr>
<tr>
<td>DerSimonian &amp; Laird Method</td>
<td>0.86</td>
<td>0.79-0.94</td>
</tr>
</tbody>
</table>

The methods do not differ significantly since their 95% confidence intervals overlap; however, the DerSimonian and Laird Method produces a lower odds ratio and a wider confidence interval than the other methods. It is noteworthy that the fixed effect Peto Method yields a similar result to the mixed model without adjustment for covariates. This has occurred because there are equal numbers of controls and treatments at the trial level and no confounding between odds ratio and treatment; in other words, treatment is orthogonal to trial. However, this is not the case when other covariates are added to the model.

The pooled odds ratio indicates that ACE inhibitor treatment reduced deaths significantly compared with placebo treatment. However, the variance component associated with the trial term, which represents the between-trial heterogeneity, was significant (p~0.01). It is necessary to add covariates to the model to reduce this heterogeneity before validly inferring benefit from ACE inhibitor treatment.
Impact of Study Quality

Trials which may have been of doubtful quality were removed to assess their impact. There were six unblinded trials (GISSI-3 pilot, GISSI-3, SMILE pilot, ISIS-4 pilots 1 and 2/3, and ISIS-4) and one trial (CCS) where blinding was not specified. The pilot studies were small with wide 95% confidence intervals for their estimates of treatment effect. All of these trials were considered lower quality because of sampling variability as well as open design. GISSI-3, ISIS-4 and CCS were very large trials; thus, their 95% confidence intervals for the estimates of treatment effect were narrower and there was less risk of their open designs producing biased results. But, the GISSI-3 trial also failed to account for exclusions from follow-up and did not have an intention-to-treat analysis, and the CCS trial provided limited information. Two other trials, Lu and TRACE, also provided limited information. These trials were also considered lower quality.

The trials removed were the pilot studies, GISSI-3, CCS, Lu and TRACE. The pooled odds ratio obtained was 0.93 (0.89-0.97) which is not much different from the overall analysis. Thus, the trials of potentially doubtful quality do not appear to have influenced the meta analysis. Heterogeneity between trials remained significant; thus, the quality of trials also does not explain the between-trial heterogeneity.

ACE Inhibitor Treatment Adjusted By Other Covariates

The model was adjusted by adding the covariates of interest and noting their significance and impact on the between-trial variability.
The covariates of interest were as follows:

- Time of Commencing Treatment (com)
  - 0: <= 48 hours after infarction
  - 1: > 48 hours after infarction
- Mean Age (age)
- Percentage of Subjects Aged 70 Years and Over (A70)
- Percentage of Subjects with Heart Failure (Hfail)
- Percentage of Subjects Who Were Male (%males)
- Mean Duration of Treatment (DurT)
- Mean Duration of Follow-Up (DurF).

**Model 1 - Impact of Time of Commencing ACE Inhibitor Treatment (com*treat)**

The effects of com, treat and the interaction com*treat were all significant (p<0.05). The addition of com and com*treat to the model reduced the variance component associated with the trial term so that it became non-significant at the 5% level, suggesting that com and com*treat have explained some of the between-trial heterogeneity. The model for the pooled odds ratio (OR) was:

\[ OR = \exp(-0.06196 - 0.23020(com)) \]

with standard errors 0.02054 for the constant and 0.06342 for the coefficient of com.

The pooled odds ratios obtained from this model are given in Table 5, and a comparison for commencing ACE inhibitor within and beyond 48 hours of infarction is given in figure 3.
TABLE 5. POOLED ODDS RATIOS OF DEATH ALL CAUSES (ACE INHIBITOR VERSUS PLACEBO) ADJUSTED FOR TIME OF COMMENCEMENT OF TREATMENT

<table>
<thead>
<tr>
<th>Time of Commencing Treatment</th>
<th>Pooled Odds Ratio</th>
<th>95% Confidence Interval of Pooled Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 48 hours after infarction</td>
<td>0.94</td>
<td>0.90-0.98</td>
</tr>
<tr>
<td>&gt; 48 hours after infarction</td>
<td>0.75</td>
<td>0.66-0.84</td>
</tr>
</tbody>
</table>

Figure 3. Pooled Odds Ratios for Death (All Causes) for Trials Where ACE Inhibitor Treatment Was Begun Within and Beyond 48 Hours of Myocardial Infarction
The effect of the time of commencing treatment on the pooled odds ratio is dramatic. The odds reduction for all-cause mortality as a result of ACE inhibitor treatment is 25% if the treatment is commenced greater than 48 hours after myocardial infarction compared with only 6% if treatment is commenced within 48 hours.

It is worth noting that, of the subjects who commenced ACE inhibitors within 48 hours of infarction, the majority (86%) commenced ACE inhibitors within 24 hours. Of those who commenced ACE inhibitors beyond 48 hours after infarction, the average time of commencement was approximately 6 days with a range of 3 to 16 days. Thus, the optimal time for commencement of ACE inhibitors appears to lie between one and six days. This result supports my first hypothesis that ACE inhibitors diminish survival benefit if started earlier than 24 hours after a myocardial infarction.

An important factor not considered is that those trials which enrolled patients beyond 48 hours after infarction were treating patients who had survived the critical first days after infarction whereas those enrolling patients within 48 hours of infarction had a higher percentage of patients who died in the critical first days. To examine the impact of this factor individual patient data on the early deaths is needed.

Model 2 - Impact of Mean Age on Response to ACE Inhibitor Treatment (age*treat)

Four trials (3,4,5,11 - Appendix I) were excluded because of lack of data on mean age. One of the excluded trials was the 58,000-subject ISIS-4 trial. For the trials included mean age ranged from 59 to 67 years.
Mean age had no significant impact on the pooled odds ratio.

The four trials excluded represent 84.7% of the subjects in the meta analysis. Thus, the power to detect an age effect is substantially reduced. Furthermore, the pooled odds ratio, unadjusted for covariates, of the trials included was 0.85 (95% confidence interval 0.77-0.93) which is quite different from the corresponding ratio overall, 0.92 (95% confidence interval 0.88-0.95). It is possible that the distribution of mean age is different for included and excluded trials; thus, there is doubt about the insignificant effect of mean age shown by this analysis.

Model 3 - Impact of Percentage of Subjects Aged 70 Years or Over on Response to ACE Inhibitor Treatment (A70*treat)

Seven trials (4, 5, 7, 9, 10, 12, 14 - Appendix I) were excluded because of lack of data on the percentage of subjects over the age of 70 years. In the trials included the percentage of subjects over the age of 70 years varied from 15% to 42%.

The trials excluded represent 17.1% of the subjects in the meta analysis; thus, the power to detect an age-over-70 effect is unlikely to be affected substantially by the exclusions, and the result obtained would be unlikely to change substantially if the excluded trials were included. The unadjusted pooled odds ratio for the trials included was 0.93 (95% confidence interval 0.89-0.97) which is similar to the corresponding ratio overall, 0.92 (95% confidence interval 0.88-0.95).

The interaction A70*treat was significant (p<0.05). The variance component associated with the trial term was
non-significant at the 5% level; thus, the A70 and A70*treat terms have explained some of the between-trial variation. The model for pooled odds ratio (OR) was as follows:

\[ OR = \exp(-0.07084 + 0.013174(A70)) \]

with standard errors 0.02152 for the constant and 0.005001 for the coefficient of A70.

Table 6 lists predictions of the pooled odds ratio obtained from this model.

**TABLE 6. POOLED ODDS RATIOS OF DEATH ALL CAUSES (ACE INHIBITOR VERSUS PLACEBO) ADJUSTED FOR PERCENTAGE OF SUBJECTS 70 YEARS AND OVER**

<table>
<thead>
<tr>
<th>Percentage of Subjects 70 Years and Over</th>
<th>Pooled Odds Ratio</th>
<th>95% Confidence Interval(^1) of Pooled Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0(^2)</td>
<td>0.93</td>
<td>0.89-0.97</td>
</tr>
<tr>
<td>15</td>
<td>1.14</td>
<td>0.97-1.33</td>
</tr>
<tr>
<td>25</td>
<td>1.29</td>
<td>1.00-1.67</td>
</tr>
<tr>
<td>35</td>
<td>1.48</td>
<td>1.04-2.10</td>
</tr>
<tr>
<td>50(^2)</td>
<td>1.80</td>
<td>1.09-2.97</td>
</tr>
</tbody>
</table>

Footnotes: \(^1\) The confidence interval is an estimate based on the standard errors of the constant and coefficient of A70.

\(^2\) Projected - the limits of the data are 15-42%.

The predictions indicate that as the percentage of subjects 70 years and over increases the odds of death
as a result of ACE inhibitor treatment increase. In other words, subjects 70 years and over are worse off as a result of ACE inhibitor treatment after myocardial infarction. A survival benefit is predicted only when there are no patients 70 years and over.

Analysis of Deaths in the Elderly Sub-Group

Six trials provided mortality data for "elderly" (age greater than 65 to 70 years) subjects. This data was used to confirm the result obtained indirectly by use of the trial variable A70.

The odds ratios for death (all causes) in the elderly subject groups of these trials are given in table 7. Age was greater than or equal to 70 years except where indicated.

**TABLE 7. ODDS RATIOS OF DEATH ANY CAUSE (ACE INHIBITOR VERSUS PLACEBO) FOR "ELDERLY" SUBJECTS**

<table>
<thead>
<tr>
<th>No</th>
<th>Trial</th>
<th>No Subjects</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval of Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SAVE (age&gt;=65 yrs)</td>
<td>783</td>
<td>0.77</td>
<td>0.58-0.96</td>
</tr>
<tr>
<td>2</td>
<td>CONSENSUS II</td>
<td>2,538</td>
<td>1.18</td>
<td>ns</td>
</tr>
<tr>
<td>3</td>
<td>GISSI-3</td>
<td>5,124</td>
<td>0.88</td>
<td>0.73-1.03</td>
</tr>
<tr>
<td>8</td>
<td>SMILE (age&gt;=65 yrs)</td>
<td>789</td>
<td>0.61</td>
<td>0.40-0.93</td>
</tr>
<tr>
<td>11</td>
<td>ISIS-4</td>
<td>16,000</td>
<td>1.01</td>
<td>ns</td>
</tr>
<tr>
<td>12</td>
<td>AIRE (age&gt;=65 yrs)</td>
<td>ns</td>
<td>0.65</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td><strong>Pooled Results</strong>¹</td>
<td>25,234</td>
<td>0.97</td>
<td>0.90-1.04</td>
</tr>
</tbody>
</table>
Footnotes (Table 6):¹ Does not include AIRE study because of insufficient data.
² Relative hazard.
ns-not stated.

The pooled odds ratio and its 95% confidence interval indicate that the ACE inhibitor and placebo groups are not significantly different in respect of all-cause mortality in elderly subjects after myocardial infarction; however, there is a trend towards a survival benefit in the ACE inhibitor group. There may be too few elderly subjects in this group of trials to show a treatment effect.

The direct analysis of the impact of advanced age included six trials whereas the indirect analysis included seven trials. Since the results achieved by the two methods are contradictory (one being significant and the other non-significant), doubt remains as to the true effect of advanced age and the ability of the indirect method to predict the impact of this covariate.

My third hypothesis, that ACE inhibitors have a greater impact on survival after myocardial infarction if used in subjects under the age of 70 years than if used in subjects 70 years and over, is not supported.

Model 4 - Impact of Percentage of Subjects With Heart Failure on Response to ACE INhibitor Treatment (Hfail*treat)

Four trials (4,5,6,13 - Appendix I) were excluded because of lack of data on the percentage of subjects with "heart failure", that is, for the purposes of this meta analysis, Killip Class > I or clinical heart failure. The percentage of subjects with heart failure varied from 14% to 100% for trials with this data.
The trials excluded represent 14.4% of the subjects in the meta analysis; thus, the power to show a heart failure effect is not greatly affected, and the result is unlikely to change substantially if the excluded trials were included. Furthermore, the unadjusted pooled odds ratio for the trials included was 0.92 (95% confidence interval 0.87-0.96) which is similar to the corresponding ratio overall, 0.92 (95% confidence interval 0.88-0.95).

The interaction Hfail*treat was significant (p<0.05). The variance component associated with the trial term was non-significant at the 5% level; thus, the Hfail and Hfail*treat terms have explained some of the between-trial variation. The model for pooled odds ratio (OR) was as follows:

$$\text{OR} = \exp(-0.08472 - 0.003697(\text{Hfail}))$$

with standard errors 0.02083 for the constant and 0.001292 for the coefficient of Hfail.

Table 8 lists predictions of the pooled odds ratio obtained from this model. These predictions are plotted in figure 4.
TABLE 8. POOLED ODDS RATIOS OF DEATH ALL CAUSES (ACE INHIBITOR VERSUS PLACEBO) ADJUSTED FOR PERCENTAGE OF SUBJECTS WITH HEART FAILURE

<table>
<thead>
<tr>
<th>Percentage of Subjects with Heart Failure</th>
<th>Pooled Odds Ratio</th>
<th>95% Confidence Interval of Pooled Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0(^2)</td>
<td>0.92</td>
<td>0.87-0.96</td>
</tr>
<tr>
<td>25</td>
<td>0.84</td>
<td>0.77-0.91</td>
</tr>
<tr>
<td>50</td>
<td>0.76</td>
<td>0.66-0.88</td>
</tr>
<tr>
<td>75</td>
<td>0.70</td>
<td>0.57-0.85</td>
</tr>
<tr>
<td>100</td>
<td>0.63</td>
<td>0.48-0.83</td>
</tr>
</tbody>
</table>

Footnotes: \(^1\) The confidence interval is an estimate based on the standard errors of the constant and coefficient of Hfail.

\(^2\) Projected - the limits of the data are 14-100%.

Figure 4. Impact of Percentage of Subjects With Heart Failure on the Deaths (All Cause) Odds Ratio
The predictions indicate that the greater the percentage of subjects with some degree of heart failure after myocardial infarction the greater the reduction in the odds of death as a result of ACE inhibitor treatment.

Analysis of Deaths in the Heart Failure Sub-Group

Three trials provided mortality data for subjects with baseline heart failure. In the case of the SAVE trial (trial 1), the data refers to subjects with baseline ejection fractions less than or equal to 32%. This data is used to confirm the result obtained indirectly by use of the trial variable Hfail.

The odds ratios for death (all causes) for subjects with baseline heart failure in these trials are given in table 9.

TABLE 9. ODDS RATIOS OF DEATH ANY CAUSE (ACE INHIBITOR VERSUS PLACEBO) FOR SUBJECTS WITH BASELINE HEART FAILURE

<table>
<thead>
<tr>
<th>No</th>
<th>Trial</th>
<th>No Subjects</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval of Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SAVE</td>
<td>1,183</td>
<td>0.76</td>
<td>0.62-0.94</td>
</tr>
<tr>
<td>2</td>
<td>CONSENSUS II</td>
<td>1,109</td>
<td>1.00</td>
<td>ns</td>
</tr>
<tr>
<td>11</td>
<td>ISIS-4</td>
<td>8,070</td>
<td>0.89</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Pooled Results</td>
<td>10,362</td>
<td>0.87</td>
<td>0.78-0.96</td>
</tr>
</tbody>
</table>

Footnotes: ns—not stated.

The pooled odds ratio and its 95% confidence interval indicate that ACE inhibitor treatment significantly reduces all-cause mortality by 13% compared with placebo.
treatment in subjects with heart failure after myocardial infarction.

This supports the indirect result obtained with the trial covariate Hfail; thus, the result is likely to be robust and the indirect method a good predictor in this case. The result supports my second hypothesis that ACE inhibitors have a greater impact on the survival of subjects with some degree of left ventricular dysfunction than no left ventricular dysfunction after myocardial infarction.

Model 5 - Impact of Percentage of Male Subjects on Response to ACE Inhibitor Treatment (%males*treat)

Two trials (4,5 - Appendix I) were excluded because of lack of data on percentage of male subjects. In the included trials percentage of males ranged from 56% to 86%.

The trials excluded represent 12.8% of the subjects in the meta analysis; thus, the power of this analysis is unlikely to be substantially affected by the exclusions, and the result of the analysis is unlikely to change substantially if the excluded trials were included. The unadjusted pooled odds ratio for the trials included was 0.91 (95% confidence interval 0.88-0.95) which is similar to the corresponding ratio overall, 0.92 (95% confidence interval 0.88-0.95).

The percentage of male subjects did not have a significant impact on the pooled odds ratio.

Analysis of Deaths in the Male and Female Sub-Groups

Six trials provided mortality data for males and/or females. This data was used to confirm the result
obtained indirectly by use of the trial variable \( %\text{males} \). The odds ratios for death (all causes) for males are given in table 10, and for females in table 11.

**TABLE 10. ODDS RATIOS OF DEATH ANY CAUSE (ACE INHIBITOR VERSUS PLACEBO) FOR MALES**

<table>
<thead>
<tr>
<th>No</th>
<th>Trial</th>
<th>No Subjects</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval of Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SAVE</td>
<td>1,841</td>
<td>0.78</td>
<td>0.64-0.94</td>
</tr>
<tr>
<td>2</td>
<td>CONSENSUS II</td>
<td>4,447</td>
<td>1.03</td>
<td>ns</td>
</tr>
<tr>
<td>8</td>
<td>SMILE</td>
<td>1,128</td>
<td>0.59</td>
<td>0.36-0.95</td>
</tr>
<tr>
<td>11</td>
<td>ISIS-4</td>
<td>43,043</td>
<td>0.91</td>
<td>ns</td>
</tr>
<tr>
<td>12</td>
<td>AIRE</td>
<td>ns</td>
<td>0.75(^2)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td><strong>Pooled Results(^1)</strong></td>
<td>50,459</td>
<td>0.90</td>
<td>0.84-0.96</td>
</tr>
</tbody>
</table>

**Footnotes:**  
\(^1\) Does not include AIRE study because of insufficient data  
\(^2\) Relative hazard

ns—not stated.

The pooled odds ratio and its 95% confidence interval indicate that ACE inhibitor treatment significantly reduces all-cause mortality by 10% compared with placebo treatment in male subjects after myocardial infarction. This result compares with the non-significant result obtained with the trial variate \( %\text{males} \). The direct method although it included only five trials compared with 12 for the indirect method still contained a substantial proportion of the subjects (the number of male subjects in the five trials is almost half of all subjects included in this review). Thus, the indirect
method appears to have been a poor predictor of the effect of male sex in this instance.

TABLE 11. ODDS RATIOS OF DEATH ANY CAUSE (ACE INHIBITOR VERSUS PLACEBO) FOR FEMALES

<table>
<thead>
<tr>
<th>No</th>
<th>Trial</th>
<th>No Subjects</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval of Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SAVE</td>
<td>390</td>
<td>0.98</td>
<td>0.63-1.53</td>
</tr>
<tr>
<td>2</td>
<td>CONSENSUS II</td>
<td>1,643</td>
<td>1.21</td>
<td>ns</td>
</tr>
<tr>
<td>3</td>
<td>GISSI-3</td>
<td>4,191</td>
<td>0.81</td>
<td>0.62-1.00</td>
</tr>
<tr>
<td>8</td>
<td>SMILE</td>
<td>428</td>
<td>0.70</td>
<td>0.40-1.21</td>
</tr>
<tr>
<td>11</td>
<td>ISIS-4</td>
<td>15,000</td>
<td>0.97</td>
<td>ns</td>
</tr>
<tr>
<td>12</td>
<td>AIRE</td>
<td>ns</td>
<td>0.70²</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td><strong>Pooled Results</strong>¹</td>
<td>21,652</td>
<td>0.95</td>
<td>0.87-1.03</td>
</tr>
</tbody>
</table>

Footnotes: ¹ Does not include AIRE study because of insufficient data ² Relative hazard ns—not stated.

The pooled odds ratio and its 95% confidence interval in Table 11 indicate that the ACE inhibitor and placebo groups are not significantly different in respect of all-cause mortality in females after myocardial infarction; however, there is a trend towards a survival benefit in the ACE inhibitor group. There may be too few female subjects in these trials to show a treatment effect.

My fourth hypothesis, that ACE inhibitors after
myocardial infarction have an equal impact on survival for males and females is not disproved. The direct method produced a significant survival benefit for males and a trend towards benefit in females.

Model 6 - Impact of Mean Duration of Treatment on Response to ACE Inhibitor Treatment (durT*treat)

One trial (4- Appendix I) was excluded because of lack of data on mean duration of treatment. In the other trials mean duration of treatment ranged from one month to 42 months.

The unadjusted pooled odds ratio for the trials included was the same as the corresponding ratio overall, 0.92 (95% confidence interval 0.88-0.95), because of the negligible impact of excluding trial 4 (Lu et al), which contained only 98 subjects (0.1% of the subjects in the meta analysis). The power of the analysis to detect a duration-of-treatment effect is unlikely to be affected substantially by the exclusion of trial 4.

The terms ln(durT) and ln(durT)*treat were significant (p<0.005). These effects are likely to be robust because of the negligible impact on power caused by the exclusion of trial 4. The variance component associated with the trial term was non-significant at the 5% level suggesting that durT and durT*treat have explained some of the between-trial heterogeneity. The model obtained for the pooled odds ratio (OR) was as follows:

$$ OR = \exp(-0.08581-0.05878*\ln(durT)) $$

with standard errors 0.01944 for the constant and 0.01776 for the coefficient of ln(durT).
Table 12 lists predictions of the pooled odds ratio obtained from this model. The predictions are plotted in figure 5.

**TABLE 12. POOLED ODDS RATIOS OF DEATH ALL CAUSES (ACE INHIBITOR VERSUS PLACEBO) ADJUSTED FOR MEAN DURATION OF TREATMENT**

<table>
<thead>
<tr>
<th>Mean Duration of Treatment (months)</th>
<th>Pooled Odds Ratio</th>
<th>95% Confidence Interval$^1$ of Pooled Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5$^2$</td>
<td>0.96</td>
<td>0.91-1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.92</td>
<td>0.88-0.95</td>
</tr>
<tr>
<td>2</td>
<td>0.88</td>
<td>0.84-0.92</td>
</tr>
<tr>
<td>3</td>
<td>0.86</td>
<td>0.81-0.91</td>
</tr>
<tr>
<td>6</td>
<td>0.83</td>
<td>0.77-0.89</td>
</tr>
<tr>
<td>12</td>
<td>0.79</td>
<td>0.72-0.87</td>
</tr>
<tr>
<td>24</td>
<td>0.76</td>
<td>0.68-0.86</td>
</tr>
<tr>
<td>48$^2$</td>
<td>0.73</td>
<td>0.63-0.84</td>
</tr>
</tbody>
</table>

Footnotes: $^1$ The confidence interval is an estimate based on the standard errors of the constant and coefficient of ln(durT).

$^2$ Projected - the limits of the data are 1-48 mths.
The predictions indicate that the longer the treatment duration the greater the reduction in the odds of death as a result of ACE inhibitor treatment after myocardial infarction. The reduction in odds is particularly substantial for mean treatment durations of 12 months or greater. However, the marginal benefits diminish the greater the duration of treatment. Doubling the treatment duration produces an additional odds reduction for death of 3%.

My fifth hypothesis, that a treatment duration of at least one month is needed for ACE inhibitors to improve survival after myocardial infarction, could not be tested directly because no trial had a duration of
treatment less than one month. The model predicts a significant benefit at a duration of treatment of 0.5 months; however, such a prediction may be wrong since it is beyond the limit of the data in the trials.

Model 7 - Impact of Mean Duration of Follow-Up on Response to ACE Inhibitor Treatment (durF*treat)

One trial (4- Appendix I) was excluded because of lack of data on mean duration of follow-up. In the other trials mean duration of treatment ranged from one month to 42 months.

As in model 6, the exclusion of trial 4 has a negligible impact on the power to detect a duration-of-follow-up effect.

The term ln(durF) was significant (p<0.005) but not the interaction term ln(durF)*treat. These are likely to be true effects in view of the power of this analysis. Trial was non-significant at the 5% level; thus, durF explains some of the between-trial heterogeneity. Because there was no interaction between durF and treat, the pooled odds ratio was independent of the mean duration of follow-up.

7.2 Deaths - Cardiovascular Causes

7.21 Analysis of Individual Trials

Four of the 14 trials quoted the number of deaths from cardiovascular causes. The odds ratios and 95% confidence intervals for each trial for this measure are given in Table 13, and plotted in figure 6.
TABLE 13. ODDS RATIOS OF CARDIOVASCULAR DEATH (ACE INHIBITOR VERSUS PLACEBO) OBTAINED USING REVMAN

<table>
<thead>
<tr>
<th>No</th>
<th>Trial</th>
<th>No Deaths/ No Subjects</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval of Odds Ratio</th>
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<tr>
<td></td>
<td></td>
<td>ACE Inhib</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>SAVE</td>
<td>188/1115</td>
<td>234/1116</td>
<td>0.77</td>
</tr>
<tr>
<td>2</td>
<td>CONSENSUS II</td>
<td>299/3044</td>
<td>270/3046</td>
<td>1.12</td>
</tr>
<tr>
<td>6</td>
<td>PRACTICAL</td>
<td>8/75</td>
<td>12/75</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Captopril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PRACTICAL</td>
<td>1/75</td>
<td></td>
<td>0.16</td>
</tr>
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<td></td>
<td>Enalapril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SMILE Pilot</td>
<td>8/101</td>
<td>11/103</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>POOLED</td>
<td>504/4410</td>
<td>527/4340</td>
<td>0.94</td>
</tr>
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</table>

Between-trial test for heterogeneity; $\chi^2$ (df=4) = 17.97.
Figure 6. Cardiovascular Death Odds Ratios and 95% Confidence Intervals for Included Trials
ACE inhibitor treatment significantly (p<0.05) reduced cardiovascular deaths compared with placebo in 2 trials, and there was a non-significant result in 3 trials (the PRACTICAL trial being counted twice because of its three treatment arms).

7.22 Combined Analysis

For cardiovascular deaths the model produced a pooled odds ratio of 0.94 with 95% confidence interval 0.82-1.07. This result is similar to the result obtained by the Peto Method (0.93 with 95% confidence interval 0.81-1.06). The odds ratio estimate from the DerSimonian and Laird Method was lower (0.80 with 95% confidence interval 0.55-1.16).

There were too few trials with data on cardiovascular deaths to examine the impact of covariates.

7.3 Model Diagnostics

The model diagnostic checks were satisfactory for all models fitted. The diagnostic plots are attached as Appendix III.

7.4 Impact of ISIS-4

The very large ISIS-4 trial which provides about half the subjects in this meta analysis was removed to assess its impact.

Model with Treatment Only

Removal of the ISIS-4 trial reduced the pooled odds ratio from 0.92 (95% confidence interval 0.88-0.95) to 0.87 (95% confidence interval 0.82-0.93). Thus, the
ISIS-4 trial does have an impact; however, it is not a significant impact since the 95% confidence interval for odds ratio overall and the ratio without ISIS-4 overlap. Removal of this trial did not alter the between-trial heterogeneity.

Models with Treatment and Other Covariates

Com (time of commencing treatment) remained a significant term and the pooled odds ratios were virtually unchanged when the ISIS-4 trial was removed; thus, the significance of com is quite robust. The ISIS-4 trial commenced treatment within 48 hours of infarction as did ten other trials. The combined information from the ten other trials was sufficient to predict the impact of treatment within 48 hours of infarction, and to conclude that commencement of ACE inhibitor treatment too early after infarction lessens the survival benefit.

Hfail (proportion of subjects with heart failure) and durT (mean duration of treatment) remained significant terms when ISIS-4 was removed; however, the estimates of odds ratio favoured the ACE inhibitor group for lower proportions of heart failure subjects enrolled, and for shorter mean durations of treatment, a situation which is unlikely. The ISIS-4 trial appears to have been of borderline significance because it was unselective in terms of the degree of heart failure (only 14% of subjects enrolled had heart failure), and the duration of treatment (one month) was too short. The meta analysis with ISIS-4 included is reflecting this.
8. Discussion

8.1 A Priori Hypotheses

It is clear from this meta analysis of 14 trials that ACE inhibitors do significantly reduce deaths after myocardial infarction. Overall, the risk reduction was 8% (95% confidence interval 5 to 12%) compared with placebo. However, the trials were heterogeneous in their results; thus, it is inappropriate to quote merely the overall figure for risk reduction.

It was found that, at trial level, the time of commencing treatment after infarction, the proportion of subjects with some degree of heart failure, and the mean duration of treatment significantly alter the risk reduction and explain some of the heterogeneity amongst trials. These trial level results provide an indication that time of commencing treatment, degree of heart failure and duration of treatment may be important at the individual level.

Five hypotheses were made a priori. These hypotheses are re-stated in Table 14 with the corresponding outcomes from this meta analysis. The table provides the outcomes for all-cause mortality only. There was insufficient data to draw conclusions on the other effect measure, cardiovascular mortality.
TABLE 14. EVIDENCE FROM THE META ANALYSIS SUPPORTING THE 
A PRIORI HYPOTHESES

<table>
<thead>
<tr>
<th>No</th>
<th>Hypothesis</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACE inhibitors diminish survival benefit if started earlier than 24 hours after a myocardial infarction</td>
<td>Supported - optimal commencement time 1-6 days after myocardial infarction.</td>
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<tr>
<td>2</td>
<td>ACE inhibitors have a greater impact on the survival of subjects with some degree of left ventricular dysfunction than no left ventricular dysfunction after myocardial infarction</td>
<td>Supported - trial covariate, proportion of subjects with heart failure, significant (p&lt;0.05, figure 4); subject covariate, presence of heart failure, significant on sub-group analysis: odds ratio 0.87 (95% CI: 0.78-0.96).</td>
</tr>
<tr>
<td>3</td>
<td>ACE inhibitors have a greater impact on survival after myocardial infarction if used in subjects under the age of 70 years than if used in subjects 70 years and over</td>
<td>Not Supported - trial covariate, proportion of subjects over age 70 years, significant (p&lt;0.05); subject covariate, age over 70 years, not significant on sub-group analysis.</td>
</tr>
</tbody>
</table>
TABLE 14 (CONT). EVIDENCE FROM THE META ANALYSIS SUPPORTING THE A PRIORI HYPOTHESES

<table>
<thead>
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<th>No</th>
<th>Hypothesis</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>ACE inhibitors after myocardial infarction have an equal impact on survival for males and females</td>
<td>Not Disproved - trial covariate, %males, not significant; subject covariate, male, significant (p&lt;0.05) on sub-group analysis: odds ratio 0.90 (95% CI: 0.84-0.96); insufficient data on females.</td>
</tr>
<tr>
<td>5</td>
<td>A treatment duration of at least one month is needed for ACE inhibitors to improve survival after myocardial infarction</td>
<td>Not Disproved - no data on treatment duration &lt; 1 month. Data suggest at least 12 months treatment before diminishing returns (figure 5).</td>
</tr>
</tbody>
</table>

The results suggest that the optimum treatment population includes subjects with some degree of heart failure; the optimum treatment regime includes commencement of ACE inhibitor beyond 24 hours after infarction; and the optimum duration of treatment is at least 12 months.

8.2 Validity of the Results

Biological and methodological factors provide validity for the results. The results are also supported by current opinion.
Biological Plausibility

Biological processes after myocardial infarction, and mechanisms of ACE inhibitor action were discussed in the Introduction. Soon after infarction, the myocardium is sensitive to the hypotensive insult induced by ACE inhibitors. Thus, ACE inhibitor treatment cannot begin too soon. On the other hand, to achieve maximal inhibition of the renin-angiotensin system, which is a factor in stabilising the infarct, treatment must begin within 72 hours. This supports the hypothesis that ACE inhibitors should not be started sooner than 24 hours after myocardial infarction.

The sympathetic and renin-angiotensin system activation after infarction is greater in patients with left ventricular dysfunction compared with other patients. Curbing the activity of these systems in patients with some degree of left ventricular dysfunction would then be expected to have a greater impact. This supports the greater reduction in mortality in patients with heart failure treated with ACE inhibitors.

It is believed that ACE inhibitors have anti-ischaemic and anti-plaque effects. If this is the case then additional survival benefits could be expected from longer treatment, which supports the hypothesis of greater survival for longer durations of ACE inhibitor treatment.

Methodological Plausibility

The model diagnostic checks were satisfactory. All trials except three fitted the models reasonably well. The three exceptions were ISIS-4 Phase 2/3, PRACTICAL-Enalapril and CONSENSUS II, which were outliers in the three significant models (those involving time of
commencement of ACE inhibitor, proportion of subjects with heart failure and mean duration of treatment). The ISIS-4 Phase 2/3 and PRACTICAL-Enalapril trials were very small (474 and 150 subjects respectively) which may explain their outlier status. The outlier status of the CONSENSUS II trial, which enrolled 6,090 subjects, is more difficult to explain. The premature termination of this trial after six months may have been a factor: a benefit may have been achieved if the trial had been continued for 12 months. Support for this is provided by the SAVE trial which took ten months to show a significant survival benefit for ACE inhibitors.

Sensitivity analysis indicated that the quality of the included trials was not an important issue, the result being the same if trials of doubtful quality were removed. This was expected since only randomised controlled trials were included in this review.

From discussions with colleagues it is unlikely that any important trials have been missed. The meta analysis covered more than 107,000 subjects and 12,000 events (deaths); thus, a chance result is unlikely.

The unadjusted results for the mixed model were similar to results obtained using the traditional methods of Peto, and DerSimonian and Laird.

Current Opinion

A key current issue is whether to give all patients an ACE inhibitor after myocardial infarction or to be selective and give ACE inhibitors only to those patients with some degree of left ventricular dysfunction after myocardial infarction (provided the left ventricular function is not so poor as to cause severe hypotension if an ACE inhibitor were to be given). Current opinion
is to be selective (46,57-65). This is the stance taken by regulatory authorities such as the US Food and Drug Administration and the Australian Therapeutic Goods Administration. There was a greater reduction in the risk of death achieved with ACE inhibitor treatment in the selective trials (SAVE, AIRE, TRACE) compared with the non-selective trials. The three selective trials were significant (p<0.05) whereas only four of the eleven non-selective trials were significant. The meta analysis demonstrated the significant impact of percentage of subjects with some degree of heart failure on the odds of death, which is consistent with this opinion.

Patients developing severe hypotension after a test dose of ACE inhibitor were excluded from the trials examined in the meta analysis. ACE inhibitors are contraindicated in this group of patients.

Another current issue is the time of commencement of ACE inhibitor treatment after infarction. Opinion is to delay the commencement of treatment for 24 hours, or until patients are haemodynamically stable (57,58,62,65,66,67). This opinion is based largely on the negative result of the CONSENSUS II trial. The meta analysis supports this opinion, a 6% reduction in the odds of death being achieved from ACE inhibitor treatment begun within 48 hours of infarction, and a 25% reduction for ACE inhibitor treatment begun later.

A further issue is duration of treatment. Opinion is that long-term treatment is unjustified unless there is congestive cardiac failure (68,58). The meta analysis suggests that the benefits are enhanced the longer the duration of treatment; however, it also suggests that there is a point of diminishing returns which occurs at about 12 months treatment. In the individual trials there were marked differences in time to show a survival benefit, for example, in the SAVE trial 10 months of
continuous captopril treatment was necessary before a significant difference between the captopril and placebo group emerged, and the CONSENSUS II trial had not shown a benefit after six months of enalapril treatment. On the other hand, the AIRE (ramipril) and ISIS-4 (captopril) trials were showing significant survival benefit for ACE inhibitor after only four weeks treatment.

8.3 Limitations

The randomisation was only to ACE inhibitor treatment or no ACE inhibitor treatment. There may be confounding (interaction) amongst the other covariates. Confounding could be detected by multivariate logistic regression; however, there were insufficient degrees of freedom and data to permit this.

The covariate effects were tested at trial level and inference made about outcomes in individuals. Whilst, the trial covariates examined could, in some cases, explain heterogeneity amongst trials, their ability to predict effects in individuals was not robust, except in the case of the covariate Hfail.

The trials were spread over a 10-year period during which thrombolysis was introduced. Thus, there may be an era effect. This could be tested as a trial covariate in the mixed model.

Whilst use of total mortality as the outcome measure provides a good global indication of whether there is a benefit from treatment or not, the use of outcomes other than death may give some insight into why ACE inhibitors reduce mortality after myocardial infarction and provide information on other effects of treatment (3). For example, endpoints related to coronary artery disease
(preventing re-infarction) and development of congestive cardiac failure may be interesting since individual trials such as SAVE and AIRE provide evidence that ACE inhibitors may alter the natural history of coronary artery disease (reduced re-infarctions) and left ventricular dysfunction (reduced development of congestive cardiac failure) (57).

The studies included have different average durations of follow-up; thus, the fields of risk are different. To account for the different fields of risk as a result of the different durations of follow-up, the mean duration of follow-up was included as a trial covariate in the regression model. Surprisingly, there was no interaction between mean duration of follow-up and treatment; however, there was an interaction between mean duration of treatment and treatment. These factors need to be examined in more detail at sub-group level, that is, analysis of outcomes for several ranges of treatment duration and follow-up duration.

Since death is not an uncommon outcome after myocardial infarction, Cox proportional hazards models of times to death may be more appropriate than logistic regression. Whilst the logistic regression coefficient for the treatment effect approximates the corresponding Cox model coefficient for rare conditions this is not the case for common conditions (11). A Cox regression analysis would require individual patient data on survival times.

The impact of the type of ACE inhibitor may be important. For example, in this meta analysis there were six ACE inhibitors, two short-acting (captopril, zofenopril), and four long-acting (enalapril, lisinopril, ramipril, trandolapril). Of the nine studies involving short-acting ACE inhibitors only three were
significant, whereas, of the six studies involving long-acting ACE inhibitors, four were significant. Thus, the more sustained action of the long-acting ACE inhibitors may be a factor in enhancing survival.

The site of the myocardial infarction may also be an important factor. Subjects with anterior infarctions, for example, are believed to have a poorer prognosis.

9. Implications for Policy and Future Research

9.1 Policy

The approach to meta analysis used in this review, that is examining the impact of covariates at trial level, is exploratory. It provides the broad picture of whether a treatment is effective or not, and what the likely factors influencing outcome are. It, therefore, provides the direction for policy and future research. This is true of meta analysis generally (69).

The results can be converted from odds ratios to absolute benefit measures, which are more meaningful in the clinical context. The number of patients who need to be treated to prevent one death, which can be obtained from the reciprocal of the absolute risk reduction, is a meaningful absolute measure (70).

From Table 3 the pooled absolute risk reduction for death as a result of ACE inhibitor treatment is 0.0083 which means that one death is prevented per 120 patients treated. If only the trials where ACE inhibitor treatment commenced beyond 48 hours are considered, the pooled absolute risk reduction is 0.0549, which is a substantial improvement since one death is prevented per 18 patients treated.
In the Australian context, answers to broad questions provided by meta analyses may influence decisions with respect to the listing of procedures in the Medicare Benefits Schedule, and the listing of drugs on the Pharmaceutical Benefits Schedule. A finding of benefit on a meta analysis is a reasonable basis on which to decide the allocation of scarce health resources.

Broad results from meta analysis may also influence drug regulatory decisions by the Therapeutic Goods Administration and the development of Clinical Practice Guidelines by the National Health and Medical Research Council; however, these activities usually require more detailed information, for example, with respect to patient population, dosage and duration of treatment.

The US Food and Drugs Administration has taken regulatory action on the basis of a meta analysis. It approved the use of aspirin to reduce the risk of death and/or non-fatal myocardial infarction in patients with a previous infarction (71).

Meta analysis can provide answers to more specific questions when individual patient data is available, thus, allowing sub-group analysis. More resources are required for sub-group analysis. In the case of the use of ACE inhibitors in myocardial infarction, where there was insufficient published information, sub-group analysis would require the co-operation of several trialists in providing the data and the analysis of over 100,000 records.

A more detailed analysis at sub-group level, which could also be done using the mixed model approach, is needed to test the impact of important prognostic and epidemiological factors. Such information is usually required for drug regulatory decisions and the
development of clinical guidelines. Some factors for analysis are suggested under 9.2 Future Research.

The maximum likelihood estimates for pooled odds ratios obtained from the mixed logistic regression model were very similar to the Peto and DerSimonian and Laird pooled odds ratio estimates. Regression models, unlike Peto and DerSimonian and Laird, have the advantage of examining the impact of covariates on pooled odds ratios. Logistic regression may be an appropriate method for the Cochrane Collaboration to use in the future.

The development of computer software for meta analysis and greater facility to analyse sub-groups from large trials in a meta analysis will increase the use of meta analysis in clinical decision-making as well as in policy areas. For the present, clinicians will continue to rely chiefly on the results of individual clinical trials for the most reliable estimates of treatment effect and the optimum patient population and treatment regimen (2).

9.2 Future Research

Several avenues of investigation remain with respect to the use of ACE inhibitors after myocardial infarction. Investigations are needed at both the trial level and the sub-group level. The mixed model approach employed in this review is appropriate at both levels. Some factors for consideration are:

- Other Covariates
  Site of myocardial infarction e.g. anterior
  Type of ACE inhibitor, whether short-acting or long-acting
  Era effect
  Dosage of ACE inhibitor
- Other Endpoints
  Incidence of heart failure
  Recurrent myocardial infarction
  Stroke
  Hospitalisation for heart failure
  Times to specific events such as death

- Sub-Group Analysis
  Outcomes in various age groups
  Outcomes in males and females
  Outcomes for various ranges of commencement times after infarction to pin-point the sensitive period
  Outcomes for various degrees of cardiac failure
  Outcomes for various ranges of treatment duration and follow-up duration.

It is proposed to examine some of these factors in the McMaster study in which the cooperation of several trialists has been obtained for the provision of individual patient data from the major trials (72).

9.3 Conclusion

In this review the mixed model method has been applied to analysis of outcomes at the trial level. It could also be applied to analysis of outcomes at the sub-group level. The value of the analysis employed here at trial level is to identify sources of heterogeneity in outcomes amongst trials as a prelude to analysis of outcomes in sub-groups. The method provides an expeditious means of identifying trends and providing policy and research directions without the need to resort to individual patient data from trialists. However, sub-group analysis using individual patient data is also needed for the proper development of clinical practice guidelines.
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Appendix I - Data Extracted for Meta Analysis

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</table>
Data Extracted (cont)

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<th>Trial</th>
<th>Trt</th>
<th>Com</th>
<th>%Males</th>
<th>Age</th>
<th>A70</th>
<th>Hfail</th>
<th>DurT</th>
<th>DurF</th>
<th>Tdeath</th>
<th>Cdeath</th>
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<td>64</td>
<td>31</td>
<td>-1</td>
<td>1.5</td>
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<td>1017</td>
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<td>18.7</td>
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<td>18.7</td>
<td>36</td>
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<td>366</td>
<td>-1</td>
<td>873</td>
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</tbody>
</table>

Legend:

Trial Numbers: 1-SAVE, 2-CONSENSUS II, 3-GISSI3, 4-Lu, 5-CCS, 6-PRACTICAL, 7-SMILE Pilot, 8-SMILE, 9-ISIS4 Pilot Phase 1, 10-ISIS4 Pilot Phase 2/3, 11-ISIS4, 12-AIRE, 13-GISSI3 Pilot, 14-TRACE.

Trt  Treatment: 0-Placebo, 1-ACE Inhibitor
Com  Time of Commencing Treatment After Infarct: 0-Within 48 Hours, 1-After 48 Hours
%Males Percentage of Subjects Who Were Male
Age  Mean Age of Subjects (Years)
A70  Percentage of Subjects Aged Over 70 Years
Hfail Percentage of Subjects of Killip Class > I, or with Heart Failure Clinically
DurT Mean Duration of Treatment (Months)
DurF Mean Duration of Follow-Up (Months)
Tdeath Total Deaths (Any Cause)
Cdeath Deaths due to Cardiovascular Causes
-1 Missing Data.
Notes:

1. When the group break-up was not available for %Males, Age, A70 or Hfail (trials 9,11,13,14), it was assumed that both groups were equal, which is the likely situation for randomised trials.

2. Intention-to-treat data was not available for trial 3.

3. The Lu et al study commenced ACE inhibitors "early" after myocardial infarction. I interpreted "early" as being within 48 hours.
Appendix II - Descriptions of Trials Included

Survival and Ventricular Enlargement (SAVE) Study, 1987-90, USA and Canada (33)


Diagnosis: 3-16 days after myocardial infarction (av 11 days in both groups).

Number of Subjects:
- captopril group 1,115
- placebo group 1,116

Subject Characteristics:

* Males
  - captopril group 83%
  - placebo group 82%

* Mean Age (Years)
  - captopril group 59.3
  - placebo group 59.5

* Age > 70 years
  - captopril group 15%
  - placebo group 15%

* Degree of left ventricular dysfunction
  - ejection fraction <= 40% (av 31% in both groups)
  - Killip class > I: 40% of captopril group and 41% of placebo group
  - no overt heart failure
* no overt myocardial ischaemia or hypotension and could tolerate a test dose of captopril 6.25 mg orally

* Thrombolytic Therapy: captopril 34%, placebo 32%

* PTCA: captopril 7%, placebo 17%

* CABG: captopril 10%, placebo 8%

ACE Inhibitor Treatment: captopril

* Initially 6.25-12.5 mg daily

* Increased gradually to a maximum of 50 mg three times daily

Duration: 42 months (average), 24-60 months (range)

Endpoints: total mortality, cardiovascular mortality
Results (Intention-to-treat analysis):

Total Mortality (av follow-up 42 months)

<table>
<thead>
<tr>
<th></th>
<th>Captopril</th>
<th>Placebo</th>
<th>Risk Reduction% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>228/1115</td>
<td>275/1116</td>
<td>19 (3-32) p=0.019</td>
</tr>
<tr>
<td>Age &lt;= 64 years</td>
<td>121/731</td>
<td>131/717</td>
<td>8 (-34-37) age&lt;=55 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13 (-21-37) age 56-64 years</td>
</tr>
<tr>
<td>Age &gt; 64 years</td>
<td>107/384</td>
<td>144/399</td>
<td>25 (4-42)</td>
</tr>
<tr>
<td>Male</td>
<td>191/929</td>
<td>234/912</td>
<td>22 (6-36)</td>
</tr>
<tr>
<td>Female</td>
<td>37/186</td>
<td>41/204</td>
<td>2 (-53-37)</td>
</tr>
<tr>
<td>EF &lt;= 32%</td>
<td>153/584</td>
<td>198/599</td>
<td>24 (6-38)</td>
</tr>
<tr>
<td>EF &gt; 32%</td>
<td>75/531</td>
<td>77/517</td>
<td>6 (-29-32)</td>
</tr>
<tr>
<td>Thrombolitics</td>
<td>48/376</td>
<td>58/355</td>
<td>22 (-14-47)</td>
</tr>
<tr>
<td>No Thrombolitics</td>
<td>180/739</td>
<td>217/761</td>
<td>17 (-1-32)</td>
</tr>
</tbody>
</table>
Cardiovascular Mortality (av follow-up 42 months)

<table>
<thead>
<tr>
<th></th>
<th>Captopril</th>
<th>Placebo</th>
<th>Risk Reduction% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>188/1115</td>
<td>234/1116</td>
<td>21 (5-35) p=0.014</td>
</tr>
<tr>
<td></td>
<td>(16.9%)</td>
<td>(21.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Note - Risk Reduction based on life-table analysis.
Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II), 1990-91, Denmark, Finland, Iceland, Norway, Sweden (36)

**Design:** Randomised, double-blind, placebo-controlled, parallel.

**Diagnosis:** within 24 hours of the onset of chest pain (av. 15 hours in both groups).

**Number of Subjects:**
- enalapril group 3,044
- placebo group 3,046

**Subject Characteristics:**

* Males
  - enalapril group 73%
  - placebo group 74%

* Mean Age (Years)
  - enalapril group 65.7
  - placebo group 65.8

* Age > 70 years
  not stated

* Degree of left ventricular dysfunction
  - none to severe
  - heart failure: enalapril 18%, placebo 19%

* Blood Pressure > 100/60 mmHg (later changed to 105/65)

* Hypotension (systolic blood pressure < 90 mmHg): 11% in both groups at baseline

* Thrombolytic Therapy: 56% in each group
ACE Inhibitor Treatment:

* Initially 1 mg enalaprilat in 100 mL normal saline by intravenous infusion over 2 hours

* Six hours after the infusion, enalapril orally starting at 2.5 mg twice daily and increasing gradually to a maximum of 20 mg daily as tolerated

Duration: 41 to 180 days; 48.5% received 180 days treatment before the trial was prematurely stopped.

Endpoints: total mortality, cardiovascular mortality

Results (Intention-To-Treat) - Total Mortality (48.5% achieved max 6 months follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Placebo</th>
<th>Risk Reduction% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>312/3044</td>
<td>286/3046</td>
<td>-10 (-29-7) p=0.26</td>
</tr>
<tr>
<td></td>
<td>(10.2%)</td>
<td>(9.4%)</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 70 years</td>
<td>88/1756</td>
<td>101/1796</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>(5.0%)</td>
<td>(5.6%)</td>
<td></td>
</tr>
<tr>
<td>Age &gt;= 70 years</td>
<td>223/1288</td>
<td>184/1250</td>
<td>-18</td>
</tr>
<tr>
<td></td>
<td>(17.3%)</td>
<td>(14.7%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>199/2208</td>
<td>196/2239</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>(9.0%)</td>
<td>(8.8%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>113/836</td>
<td>90/807</td>
<td>-21</td>
</tr>
<tr>
<td></td>
<td>(13.5%)</td>
<td>(11.2%)</td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>97/541</td>
<td>108/568</td>
<td>0 (same mortality in each group)</td>
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<tr>
<td></td>
<td>(18%)</td>
<td>(19%)</td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>135/1702</td>
<td>121/1712</td>
<td>-12</td>
</tr>
<tr>
<td></td>
<td>(7.8%)</td>
<td>(7.0%)</td>
<td></td>
</tr>
</tbody>
</table>
Note - Risk Reduction (all subjects) is based on the survival curve; risk reductions for sub-groups are based on mortality rates at the end of the study.

*Life-Table Mortality (%)*

<table>
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<tr>
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<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td>10 days</td>
<td>4.6%</td>
<td>4.3%</td>
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<tr>
<td>1 month</td>
<td>7.2%</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>9.1%</td>
<td>8.2%</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>11.0%</td>
<td>10.2%</td>
<td>1.10 (0.93-1.29)</td>
</tr>
</tbody>
</table>

*Cardiovascular Mortality*

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>299/3044 (9.8%)</td>
<td>270/3046 (8.9%)</td>
<td>1.12 (0.57-1.20)</td>
</tr>
</tbody>
</table>
Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) Pilot Study, 1991-3, Italy (43)

Design: Randomised, open-label, placebo-controlled. Subjects were randomly assigned to one of three treatment groups: lisinopril, nitroglycerin or placebo.

Diagnosis: within 24 hours of suspected acute myocardial infarction.

Number of Subjects:
- lisinopril group 509
- nitrate and placebo group 1,017

Subject Characteristics:

* Males
  - 76% (group break-up not given)

* Mean Age (Years)
  - 64 years, sd 11 years (group break-up not given)

* Age > 70 years
  - 31% (group break-up not given)

* Degree of left ventricular dysfunction
  - not stated

* Systolic Blood Pressure > 100 mmHg

* Thrombolytic Therapy
  - 67% (group break-up not given)
ACE Inhibitor Treatment: lisinopril

* An oral dose of 5 mg per day for the first 2 days
* Subsequently 10 mg orally daily maximum.

Duration: 6 weeks.

Endpoint: total mortality (after 6 weeks follow-up).

Results - Total Mortality (6 weeks)

<table>
<thead>
<tr>
<th></th>
<th>Lisinopril</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>41/509 (8.1%)</td>
<td>98/1017 (9.6%)</td>
<td>0.83 (0.57-1.20)</td>
</tr>
</tbody>
</table>
Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3), 1991-3, Italy (34)

Design: Randomised, open-label, placebo-controlled. In a 2x2 factorial design subjects were randomly assigned to one of four treatment groups: lisinopril alone, nitrates alone, combined therapy, and placebo.

Diagnosis: within 24 hours of suspected acute myocardial infarction (35% less than 6 hours from symptom onset).

Number of Subjects:
- lisinopril group 9,435
- placebo group 9,460
- others randomised 399 (no follow-up)

Subject Characteristics:

* Males
  - lisinopril group 77.7%
  - placebo group 77.9%

* Mean Age (Years)
  not stated

* Age > 70 years
  - lisinopril group 26.8%
  - placebo group 27.4%

* Degree of left ventricular dysfunction
  - none to severe
  - Killip class > 1: lisinopril 14.1%, placebo 14.9%
  (except excluded Killip class 4 subjects)

* Systolic Blood Pressure > 100 mmHg

* Thrombolytic Therapy: lisinopril 71.4%, placebo 71.9%
ACE Inhibitor Treatment: lisinopril

* Initially an oral dose of 2.5-5 mg

* Subsequently 10 mg orally daily maximum (47.5% of subjects received the maximum dose)

* non-protocol treatment with ACE inhibitors was allowed (13.3% of placebo subjects took non-study ACE inhibitors)

**Duration:** 6 weeks.

**Endpoint:** total mortality.

**Results:** Analysis on subjects with follow-up data (97.4% of those randomised)

* **Total Mortality** (6 weeks)

<table>
<thead>
<tr>
<th></th>
<th>Lisinopril</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>597/9435 (6.3%)</td>
<td>673/9460 (7.1%)</td>
<td>0.88 (0.79-0.99) p=0.03</td>
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<tr>
<td>Age &gt; 70 years</td>
<td>354/2532 (14.0%)</td>
<td>404/2592 (15.6%)</td>
<td>0.88 (0.73-1.03)</td>
</tr>
<tr>
<td>Female</td>
<td>225/2103 (10.7%)</td>
<td>269/2088 (12.9%)</td>
<td>0.81 (0.62-1.00)</td>
</tr>
</tbody>
</table>

**Note** - Odds Ratio is based on the survival curve.
LU, CY et al. Treatment of Acute Myocardial Infarction with Oral Captopril: A Randomised Double-Blind Placebo-Controlled Pilot Study (44)

Information obtained from the English Medline abstract:

Design: Randomised, double-blind, placebo-controlled.

Diagnosis: "Early stage" of acute myocardial infarction.

Number of Subjects:
- captopril group 43
- placebo group 55

Subject Characteristics:
not stated in abstract

ACE Inhibitor Treatment: captopril

* Initially 6.25 mg orally daily

* Maximum not stated in abstract but 12.5 mg dose also used.

Duration: Not stated in abstract.

Endpoint: total mortality

Results: Intention-to-treat analysis

<table>
<thead>
<tr>
<th>Captopril</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/43</td>
<td>8/55</td>
<td>0.47 (0.13-1.66)</td>
</tr>
<tr>
<td>(7.0%)</td>
<td>(14.5%)</td>
<td></td>
</tr>
</tbody>
</table>
Placebo-Controlled Randomised ACE Inhibitor Comparative Trial in Cardiac Infarction and LV Function (PRACTICAL) Study, 1992-93, New Zealand (38)

Design: Randomised, double-blind, placebo-controlled, parallel.

Diagnosis: Within 24 hours of myocardial infarction.

Number of Subjects:
- captopril group 75
- enalapril group 75
- placebo group 75

Subject Characteristics:

* Males
- captopril group 56 (75%)
- enalapril group 59 (79%)
- placebo group 58 (77%)

* Mean Age (Years)
- captopril group 64
- enalapril group 63
- placebo group 64

* Age > 70 years
- captopril group 17 (23%)
- enalapril group 21 (28%)
- placebo group 20 (27%)

* Relatively unselected in regard to degree of heart failure

* Thrombolytic Therapy
- captopril group 51 (68%)
- enalapril group 56 (75%)
- placebo group 55 (73%)

* Excluded if persistent hypotension with systolic blood pressure < 90 mmHg, or haemodynamically significant valvular stenosis.

ACE Inhibitor Treatment:

* Either oral captopril 6.25 mg at 2-hour intervals for 3 doses followed by 25 mg three times daily, or oral enalapril 1.25 mg at 2-hour intervals for 3 doses followed by 5 mg three times daily.

Duration: 12 months

Endpoints: total mortality, cardiovascular mortality

Results: Intention-to-treat analysis

* Total Mortality

<table>
<thead>
<tr>
<th></th>
<th>Captopr</th>
<th>Enalapr</th>
<th>Placebo</th>
<th>Odds Ratio wrt Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Captopr</td>
</tr>
<tr>
<td>3 mths</td>
<td>9/75</td>
<td>1/75</td>
<td>7/75</td>
<td>1.32</td>
</tr>
<tr>
<td>follow-up</td>
<td>(12.0%)</td>
<td>(1.3%)</td>
<td>(9.3%)</td>
<td></td>
</tr>
<tr>
<td>12 mths</td>
<td>10/75</td>
<td>2/75</td>
<td>12/75</td>
<td>0.81</td>
</tr>
<tr>
<td>follow-up</td>
<td>(13.3%)</td>
<td>(2.7%)</td>
<td>(16.0%)</td>
<td>(0.33-1.99)</td>
</tr>
</tbody>
</table>
* Cardiovascular Mortality

<table>
<thead>
<tr>
<th></th>
<th>Captopr</th>
<th>Enalapr</th>
<th>Placebo</th>
<th>Odds Ratio wrt Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Captopr</td>
</tr>
<tr>
<td>3 mths follow-up</td>
<td>8/75 (10.7%)</td>
<td>1/75 (1.3%)</td>
<td>7/75 (9.3%)</td>
<td>1.16</td>
</tr>
<tr>
<td>12 mths follow-up</td>
<td>8/75 (10.7%)</td>
<td>1/75 (1.3%)</td>
<td>12/75 (16.0%)</td>
<td>0.63 (0.25-1.62)</td>
</tr>
</tbody>
</table>

* Survival Analysis (survival curves p.1185): Kaplan-Meier estimates of survival curves showed a significantly better survival in the enalapril group compared to the other groups at 3 months and 12 months:

Three months: Mantel-Cox chi-square 6.52, df=2; p=0.038
Twelve months: Mantel-Cox chi-square 7.67, df=2; p=0.022.
Ambrosioni, E et al. Early Treatment of Acute Myocardial Infarction with Angiotensin-Converting Enzyme Inhibition: Safety Considerations (SMILE Pilot Study), 1991, Italy (41)

**Design:** Randomised, open-label, placebo-controlled.

**Diagnosis:** Within 24 hours of the onset of symptoms of myocardial infarction (av 13.7h zofenopril, 12.4h placebo).

**Number of Subjects:**
- zofenopril group 101
- placebo group 103

**Subject Characteristics:**

* Males
  - zofenopril group 88 (86.3%)
  - placebo group 84 (81.6%)

* Mean Age(Yrs)
  - zofenopril group 60.7(sd 9)
  - placebo group 61.1(sd 8)

* Heart Failure (Mean Ejection Fraction)
  - zofenopril group 44%
  - placebo group 45%

* Killip Class > 1
  - zofenopril group 18.8%
  - placebo group 18.2%

* No thrombolytics

* No persistent hypotension (systolic blood press < 100 mmHg)
ACE Inhibitor Treatment: zofenopril calcium orally

* Initially 7.5 mg in two divided doses, then increased to 15-30 mg as tolerated

Duration: 12 months

Endpoint: cardiovascular mortality

Results: Intention-to-treat analysis

Cardiovascular Mortality

<table>
<thead>
<tr>
<th>Zofenopril</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/101 (7.9%)</td>
<td>11/103 (10.7%)</td>
<td>0.72 (0.28-1.85)</td>
</tr>
</tbody>
</table>

**Design:** Randomised (in blocks), double-blind, placebo-controlled, parallel.

**Diagnosis:** Within 24 hours (av 15 hours in both groups) of the onset of anterior myocardial infarction.

**Number of Subjects:**
- zofenopril group 772
- placebo group 784

**Subject Characteristics:**

* Males
  - zofenopril group 72%
  - placebo group 73%

* Mean Age (Yrs)
  - zofenopril group 63.9
  - placebo group 64.3

* Age > 70 Yrs
  - zofenopril group 29%
  - placebo group 31%

* Heart Failure (Killip Class > 1)
  - zofenopril group 15%
  - placebo group 14%

* No thrombolytics

* No persistent hypotension (sys blood pressure < 100 mmHg)
ACE Inhibitor Treatment: zofenopril calcium orally

* Initially 7.5 mg, repeated after 12 hours

* Subsequently progressively doubled until the target dose of 30 mg twice daily was reached.

Duration: 6 weeks

Endpoints: total mortality and cardiovascular mortality after 12 months follow-up.

Results: Intention-to-treat analysis

* Total Mortality

<table>
<thead>
<tr>
<th></th>
<th>Zofenopril</th>
<th>Placebo</th>
<th>Risk Reduction% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Weeks</td>
<td>50/772 (6.5%)</td>
<td>65/784 (8.3%)</td>
<td>25 (-12-48) p=0.17</td>
</tr>
<tr>
<td>One year</td>
<td>77/772 (10.0%)</td>
<td>111/784 (14.1%)</td>
<td>29 (6-51) p=0.01</td>
</tr>
</tbody>
</table>

* Cardiovascular Mortality

<table>
<thead>
<tr>
<th></th>
<th>Zofenopril</th>
<th>Placebo</th>
<th>Risk Reduction (95% Conf Int)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Weeks</td>
<td>48/772 (6.2%)</td>
<td>63/784 (8.0%)</td>
<td>22 (-8-53) p=0.08</td>
</tr>
<tr>
<td>One year</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns: not stated.
* Survival Analysis

Survival curve to 12 months provided – Fig 2, p.83.

* Sub-Group Analysis – Death or Severe Congestive Heart Failure1 (1 year follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Zofenopril</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>55/772</td>
<td>83/784</td>
<td>0.67 (0.46-0.92)</td>
</tr>
<tr>
<td></td>
<td>(7.1%)</td>
<td>(10.6%)</td>
<td>p=0.018</td>
</tr>
<tr>
<td>Male</td>
<td>28/557</td>
<td>47/571</td>
<td>0.59 (0.36-0.95)</td>
</tr>
<tr>
<td></td>
<td>(5.0%)</td>
<td>(8.2%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27/215</td>
<td>36/213</td>
<td>0.70 (0.40-1.21)</td>
</tr>
<tr>
<td></td>
<td>(12.5%)</td>
<td>(16.9%)</td>
<td></td>
</tr>
<tr>
<td>Age&lt;65 yr</td>
<td>15/378</td>
<td>22/389</td>
<td>0.68 (0.35-1.34)</td>
</tr>
<tr>
<td></td>
<td>(4.0%)</td>
<td>(5.6%)</td>
<td></td>
</tr>
<tr>
<td>Age&gt;=65 yr</td>
<td>40/394</td>
<td>61/395</td>
<td>0.61 (0.40-0.93)</td>
</tr>
<tr>
<td></td>
<td>(10.2%)</td>
<td>(15.4%)</td>
<td></td>
</tr>
</tbody>
</table>

1. At least three of: third heart sound, bilateral pulmonary rales, pulmonary congestion on X-ray, peripheral oedema despite digoxin, diuretics and vasodilators other than ACE inhibitors and necessitating open-label ACE inhibitor.
Fourth International Study of Infarct Survival (ISIS-4)  
Pilot, 1988-91, UK and Poland (23)

Design: Randomised, open-label, placebo-controlled.

There were three phases:

1. 3-way study. Subjects were randomised to either captopril, controlled-release isosorbide-5-mononitrate (mononitrate) or placebo.

2. 2x2 factorial study. Half of all the subjects were randomised to captopril and the other half to captopril-placebo. Half the subjects were also randomised to mononitrate and half to mononitrate-placebo.

3. 2x2x2 factorial study. Subjects were randomised as per phase 2 and then two-thirds of all subjects were randomised to intravenous magnesium sulphate and one-third to matching placebo.

<table>
<thead>
<tr>
<th>Diagnosis:</th>
<th>Phase 1</th>
<th>Phase 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected acute myocardial infarction</td>
<td>within 36h</td>
<td>within 24h</td>
</tr>
<tr>
<td></td>
<td>(av 16h)</td>
<td>(av 11h)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Subjects:</th>
<th>Phase 1</th>
<th>Phase 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>captopril group</td>
<td>133</td>
<td>237</td>
</tr>
<tr>
<td>placebo group</td>
<td>134</td>
<td>237</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject Characteristics: Phase 1</th>
<th>Phase 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Males</td>
<td></td>
</tr>
<tr>
<td>captopril</td>
<td>78%</td>
</tr>
<tr>
<td>placebo</td>
<td>82%</td>
</tr>
<tr>
<td>* Av Age (Yrs)</td>
<td></td>
</tr>
<tr>
<td>captopril</td>
<td>61</td>
</tr>
<tr>
<td>placebo</td>
<td>62</td>
</tr>
</tbody>
</table>
Subject Characteristics: Phase 1 (cont)  Phase 2/3

* Thrombo-lytics  captopril  88%  61%
placebo  88%  58%

* Heart Failure  captopril  35%\(^1\)  19%\(^1\)
placebo  35%\(^1\)  19%\(^1\)

Note 1. The percentage for all subjects (captopril and placebo) but not the captopril-placebo break-up was available; thus, it was assumed that the percentages were the same in each group.

ACE Inhibitor Treatment: captopril (oral)

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Initial</td>
<td>6.25 mg, 12.5 mg 2h later</td>
<td>6.25 mg, 12.5 mg 2h later, 25 mg 8-12h</td>
</tr>
<tr>
<td>* Subsequent</td>
<td>12.5 mg tid</td>
<td>50 mg bd</td>
</tr>
</tbody>
</table>

Duration: 28 days

Endpoint: total mortality

Results: Intention-to-treat analysis

Total Mortality

<table>
<thead>
<tr>
<th></th>
<th>Captopril</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>3/133</td>
<td>5/134</td>
<td>0.60 (0.15-2.46)</td>
</tr>
<tr>
<td></td>
<td>(2.3%)</td>
<td>(3.7%)</td>
<td></td>
</tr>
<tr>
<td>Phase 2/3</td>
<td>21/237</td>
<td>14/237</td>
<td>1.54 (0.77-3.06)</td>
</tr>
<tr>
<td></td>
<td>(8.9%)</td>
<td>(5.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Design: Randomised (2x2x2 factorial), open-label, placebo-controlled.

Diagnosis: Up to 24 hours (median 8 hours) after the onset of suspected acute myocardial infarction

Number of Subjects:
- captopril group 29,028
- placebo group 29,022

Subject Characteristics:

* Males: 74% (group break-up not provided)

* Mean Age (Years)
  not stated

* Age > 70 years: 28% (group break-up not provided)

* Clinical Heart Failure: 14% (group break-up not provided)

* Hypotension
  - systolic blood pressure < 100 mmHg: 2%
  - no cardiogenic shock or persistent severe hypotension

* Thrombolytic Therapy: 70%

ACE Inhibitor Treatment: captopril

* Initially 6.25mg orally daily

* 12.5 mg 2 hours later, 25 mg 10-12 hours later and
then titrated up to 50 mg twice daily

Duration: 28 days

Endpoint: total mortality

Results: Intention-to-treat analysis

The other study treatments (mononitrate and magnesium) did not alter the results obtained with captopril.

* Total Mortality

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Deaths (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>Absolute Risk Reduction (lives saved per 1,000 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Captopril</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>5-weeks</td>
<td>7.19</td>
<td>7.69</td>
<td>0.93 (0.87-0.99)</td>
</tr>
<tr>
<td>6 mths</td>
<td>9.87</td>
<td>10.53</td>
<td>0.93 (CI: insuff info)</td>
</tr>
<tr>
<td>12 mths</td>
<td>11.99</td>
<td>12.53</td>
<td>0.95 (0.91-1.00)</td>
</tr>
</tbody>
</table>

Note: 5-week mortality is based on simple comparison of percentages whereas 6-month and 12-month mortality are based on a time-to-death comparison using the log rank method.
* Sub-Group Analysis of Mortality (at 5 weeks)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Captopril (N, %)</th>
<th>Placebo (N, %)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>2088/29028 (7.19%)</td>
<td>2231/29022 (7.69%)</td>
<td>0.93 (0.87-0.99) p=0.02</td>
</tr>
<tr>
<td>Male</td>
<td>1267/21518 (5.9%)</td>
<td>1384/21525 (6.4%)</td>
<td>0.91 not sig</td>
</tr>
<tr>
<td>Female</td>
<td>820/7504 (10.9%)</td>
<td>844/7496 (11.3%)</td>
<td>0.97 not sig</td>
</tr>
<tr>
<td>Age &lt; 60 yr</td>
<td>293/11699 (2.5%)</td>
<td>350/11706 (3.0%)</td>
<td>0.83 not sig</td>
</tr>
<tr>
<td>Age 60-69 yr</td>
<td>610/9313 (6.5%)</td>
<td>705/9294 (7.6%)</td>
<td>0.85 sig at p=0.05</td>
</tr>
<tr>
<td>Age 70+ yr</td>
<td>1182/8002 (14.8%)</td>
<td>1176/7998 (14.7%)</td>
<td>1.01 not sig</td>
</tr>
<tr>
<td>Sys BP &lt; 100 mmHg</td>
<td>96/674 (14.2%)</td>
<td>83/667 (12.4%)</td>
<td>1.17 not sig</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>585/4029 (14.5%)</td>
<td>645/4041 (16.0%)</td>
<td>0.89 not sig</td>
</tr>
<tr>
<td>Thrombolysics</td>
<td>1284/19917 (6.4%)</td>
<td>1387/19783 (6.9%)</td>
<td>0.91 not sig</td>
</tr>
</tbody>
</table>
Acute Infarction Ramipril Efficacy (AIRE) Study, 1991-92, UK, Sweden, Ireland, South Africa, Argentina, Netherlands, Belgium, Germany, Denmark, Austria, Finland, Italy, Luxembourg, Switzerland (35)

Design: Randomised, double-blind, placebo-controlled, parallel. Randomisation was in blocks of 10 patients and stratified by centre.

Diagnosis: 3-10 days after myocardial infarction (av 5.4 days in both groups)

Number of Subjects:
- ramipril group 1,014
- placebo group 992

Subject Characteristics:

* Males
  - ramipril group 73%
  - placebo group 74%

* Mean Age (Years)
  - ramipril group 64.9 (sd 10.8)
  - placebo group 65.1 (sd 10.8)

* Age > 70 years
  not stated

* Thrombolytics
  - ramipril group 59%
  - placebo group 56%

* Degree of left ventricular dysfunction - clinical evidence of heart failure, defined by:
  - evidence of left ventricular failure (pulmonary venous congestion with interstitial or alveolar
oedema on at least one chest X-ray), or
- evidence of pulmonary oedema (bilateral post-tussive crackles extending at least one-third of the way up the lung fields in the absence of chronic pulmonary disease, or
- auscultatory evidence of a third heart sound with persistent tachycardia.

* No severe heart failure (breathlessness on talking or undressing not attributable to primary pulmonary pathology and unresponsive to non-ACE inhibitor treatment, usually NYHA grade IV), or heart failure of primary valvular or congenital aetiology.

**ACE Inhibitor Treatment:** ramipril orally

* Initially 1.25-2.5 mg daily
* Increased gradually to a maximum of 5 mg twice daily

*Duration:* 15 months (average), 6 (minimum); maximum not stated.

**Endpoint:** total mortality
Results (Intention-to-Treat):

* Total Mortality

<table>
<thead>
<tr>
<th></th>
<th>Ramipril</th>
<th>Placebo</th>
<th>Risk Reduction% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>170/1004 (17%)</td>
<td>222/982 (23%)</td>
<td>27 (11-40) p=0.002</td>
</tr>
<tr>
<td>Age &lt;= 64 years</td>
<td>ns</td>
<td>ns</td>
<td>0.95 rel hazard</td>
</tr>
<tr>
<td>Age &gt; 64 years</td>
<td>ns</td>
<td>ns</td>
<td>0.65 rel hazard</td>
</tr>
<tr>
<td>Male</td>
<td>ns</td>
<td>ns</td>
<td>0.75 rel hazard</td>
</tr>
<tr>
<td>Female</td>
<td>ns</td>
<td>ns</td>
<td>0.70 rel hazard</td>
</tr>
</tbody>
</table>

ns: not stated.
Chinese Cardiac Study (CCS-1), 1990-95, China (6)

Design: Randomised, placebo-controlled, parallel; blinding not stated.

Diagnosis: Within 36 hours of suspected myocardial infarction.

Number of Subjects:
- captopril group 6814
- placebo group 6820

Subject Characteristics:

* Age/Sex break-up not stated

* Relatively unselected in regard to degree of heart failure

* Thrombolytic Therapy - 27%

* Excluded if persistent hypotension with systolic blood pressure < 90 mmHg, or chronic use of large doses of diuretics.

ACE Inhibitor Treatment: captopril orally

* Initially 6.25 mg

* 12.5 mg 2 hours later, then 12.5 mg three times daily.

Duration: 1 month

Endpoint: total mortality
Results (Intention-to-Treat):

* Total Mortality (at one month)

<table>
<thead>
<tr>
<th>Captopril</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>Absolute Risk Reduction (lives saved per 1,000 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>617/6814</td>
<td>654/6820</td>
<td>0.94 (0.84-1.05)</td>
<td>5.3 (sd 5.0)</td>
</tr>
</tbody>
</table>
Trandolapril Cardiac Evaluation (TRACE) Study, 1990-94, Denmark (48,49)

**Design:** Randomised, double-blind, placebo-controlled.

**Diagnosis:** Within 3 to 7 days of myocardial infarction.

**Number of Subjects:**
- trandolapril group 876
- placebo group 873

**Subject Characteristics:**

* Mean age 67.3 years (group break-up not given)

* Male subjects(%): 67.2 (group break-up not given)

* Wall motion index <= 1.2 (approximates to a left ventricular ejection fraction <= 35%)

* Subjects with "heart failure"(%): 18.7 (group break-up not given and "heart failure" not defined)

* Thrombolytic Therapy - 45% (group break-up not given)

* Subjects with residual ischaemia were not excluded; however, subjects were excluded if an open test dose of 0.5 mg trandolapril was not tolerated.

**ACE Inhibitor Treatment:** trandolapril orally

* Initially 1 mg daily for 2 days

* If tolerated, the dose was increased to 2 mg orally daily on the third day after randomisation and then 4 mg orally daily after 4 weeks.
Duration: 4 years

Endpoint: total mortality

Results (Intention-to-Treat): Total Mortality (at 4 years)

<table>
<thead>
<tr>
<th>Trandolapril</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>Absolute Risk Reduction (lives saved per 1,000 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>307/876 (35.1%)</td>
<td>366/873 (41.9%)</td>
<td>0.78 (0.67-0.91)</td>
<td>68.7</td>
</tr>
</tbody>
</table>

p=0.00065
APPENDIX III. MODEL DIAGNOSTICS. MODELS FOR DEATH (ALL CAUSES)

Unadjusted Model

Residuals vs. Fitted values

Normal probability plot of residuals
Model 1 - Impact of com*treat

Residuals vs. Fitted values

Normal probability plot of residuals
Model 2 - Impact of age*treat

Residuals vs. Fitted values

Normal probability plot of residuals
Model 3 - Impact of A70*treat

Residuals vs. Fitted values

Normal probability plot of residuals
Model 4 - Impact of Hfail*treat
Residuals vs. Fitted values

Normal probability plot of residuals
Model 5 - Impact of %males*treat

Residuals vs. Fitted values

Normal probability plot of residuals
Model 6 - Impact of durT*treat

Residuals vs. Fitted values

Normal probability plot of residuals
Model 7 - Impact of durF*treat

Residuals vs. Fitted values

Normal probability plot of residuals
Unadjusted Model - Sub-group age>70

Residuals vs. Fitted values

Normal probability plot of residuals
Unadjusted Model - Sub-group heart failure

Residuals vs. Fitted values

Normal probability plot of residuals
Unadjusted Model - Sub-group males

Residuals vs. Fitted values

Normal probability plot of residuals
Unadjusted Model - Sub-group females

Residuals vs. Fitted values

Normal probability plot of residuals
MODELS FOR DEATH (CARDIOVASCULAR)

Unadjusted Model

Residuals vs. Fitted values

Normal probability plot of residuals