# Captopril but not mononitrate or intravenous magnesium reduced short-term mortality after suspected myocardial infarction

*ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group.* ***ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected myocardial infarction.*** *Lancet. 1995 Mar 18;345:669-82.*


### Objective

To assess early use of oral captopril, oral mononitrate, and intravenous magnesium sulfate ($MgSO_4$) to reduce mortality in patients with suspected acute myocardial infarction (MI).

### Design

Randomized, double-blind (captopril and mononitrate), controlled trial with 1-year follow-up.

### Setting

1086 hospitals in 31 countries.

### Patients

58 050 patients with suspected acute MI. Exclusion criteria were symptoms lasting > 24 hours, contraindications to study drugs, negligible risk for cardiac death, or other life-threatening disease. Follow-up to discharge was 98%.

### Intervention

Antiplatelet therapy was recommended and fibrinolytics were considered for all patients. Patients were randomly assigned as early as possible in a 2 × 2 × 2 factorial design. Half the patients received captopril (6.25-mg initial dose; 12.5 mg 2 h later; 25 mg 10 to 12 h later, then 50 mg twice/d for 28 d). Half the patients received mononitrate (30 mg initially and after 10 to 12 h, then 60 mg each morning for 28 d). Half the patients received intravenous $MgSO_4$ (8 mmol initial bolus over 15 min and then 72 mmol over 24 h). Other treatments were at the discretion of the treating physician.

### Main Outcome Measures

5-week and 1-year total mortality.

### Main Results

Analysis was by intention to treat. Captopril compared with placebo had a lower mortality rate at 5 weeks (7.19% vs. 7.69% {95% CI for the 0.5% absolute risk reduction [ARR], 0.07 to 0.9; $P = 0.02$; relative risk reduction [RRR], 7%; number needed to treat, 200; CI, 18 to 1366}*) but not at 1 year (11.99% vs. 12.53% {CI for the 0.54% ARR, –0.02% to 1.2%; $P = 0.1$; RRR, 4.3%}*). Neither mononitrate compared with placebo nor $MgSO_4$ compared with open control was associated with a reduction in mortality at either 5 weeks (7.34% vs. 7.54% for mononitrate vs. placebo and 7.64% vs. 7.24% for $MgSO_4$ vs. no treatment) or at 1 year (12.17% vs. 12.35% for mononitrate and 12.44% vs. 12.08% for $MgSO_4$).

### Conclusions

Oral captopril reduced 5-week mortality in patients with suspected acute myocardial infarction. Oral mononitrate or intravenous magnesium sulfate did not reduce either short- or long-term mortality.


*Sources of funding: Bristol-Myers Squibb (captopril); Astra-Hassle (mononitrates); Artesan Pharma and Cassellamed ($MgSO_4$).*

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*Numbers calculated from data in article.

Abstract and Commentary also published in *ACP Journal Club* 1995;123:44.

## Commentary

Several trials have shown that converting enzyme inhibitors (CEI) reduce mortality in patients with heart failure. More recent studies have tested CEIs after acute MI. In the CONSENSUS II trial (1), enalapril was begun intravenously and a nonsignificant higher mortality rate was found, whereas investigators of the more recent GISSI-3 (2) found that oral lisinopril significantly reduced 6-week mortality. Now, the ISIS-4 investigators have also found a significant lower mortality rate at 5 weeks with the use of oral captopril. Hypotension was more common among patients treated with CEIs in each trial. The findings suggest that CEIs begun soon after onset of MI reduce short-term mortality, although care is necessary in starting therapy, especially in patients with systolic blood pressure < 100 mm Hg. Patients at higher risk may have greater mortality reductions from CEI therapy because of their lower ejection fractions, especially patients with either anterior MI or previous MI.

The ISIS-4 investigators found no benefit from nitrate or $MgSO_4$, despite previous meta-analyses predicting that these therapies would substantially improve outcomes. ISIS-4 thus shows a clear-cut failure of meta-analysis that should lead to a re-evaluation of this technique. The cycle of over-optimism, disappointment, and eventual balanced assessment described with new drugs and devices also appears to apply to methodologic innovations such as meta-analysis. Although meta-analysis is valuable for providing a quantitative summary of evidence, numbers alone do not tell the whole story. Design differences among trials should be weighed, as should the results. Evidence from other pathophysiologic, epidemiologic, and therapeutic studies also needs to be considered. In short, meta-analysis should be an adjunct to, not a replacement for, expert judgment in weighing evidence.

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*References*

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