THIS IS WHY
with Dr. Busti

Title

GISSI-3 (1994): Early Lisinopril After Acute Myocardial Infarction

Reference

Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction.* Lancet. 1994;343:1115-1122. PMID: 7910229.

Background / Rationale

Before GISSI-3, thrombolysis and aspirin were already established in acute MI, but many patients still developed death, heart failure, and adverse ventricular remodeling. Earlier ACE inhibitor data in acute MI were mixed, and GISSI-3 was designed to test whether starting lisinopril early after MI could improve short-term mortality and ventricular outcomes in a broad, relatively unselected AMI population; it also tested routine nitrate therapy in parallel.

PICOTS

P (Population)

Patients with suspected acute myocardial infarction presenting within 24 hours of symptom onset, enrolled from 200 coronary care units in Italy; patients needed no clear indication for or against study treatments. Severe heart failure/Killip class IV and high risk for hemodynamic compromise with vasodilators were excluded.

I (Intervention)

Early oral lisinopril started within 24 hours of symptom onset, typically 2.5-5 mg initially then titrated to 10 mg daily, given for 6 weeks. In the factorial design, some patients also received nitrate therapy.

C (Comparator)

Open control without lisinopril; separately, nitrate vs no nitrate in a 2×2 factorial design.

O (Outcome)

Primary outcomes: all-cause mortality and a combined endpoint of death plus heart failure or severe LV dysfunction. Secondary outcome: change in left ventricular ejection fraction.

T (Timing)

Randomization within 24 hours of symptom onset; treatment for 6 weeks; follow-up reported at 6 weeks and 6 months.

S (Setting)
Multicenter coronary care units in Italy.

Objective / Purpose

To determine whether early treatment with lisinopril and/or glyceryl trinitrate after acute MI reduces 6-week mortality and ventricular dysfunction, and whether any benefit persists to 6 months.

Study Design & Methods

Design
Large, multicenter, randomized, open-label, controlled 2×2 factorial trial with central randomization.

Participants
19,394 patients were randomized between June 1991 and July 1993 from 200 Italian coronary care units. Screened patients numbered >43,000 in the ACC summary.

Intervention
Lisinopril, nitrate therapy, both, or neither for 6 weeks. Nitrates consisted of IV glyceryl trinitrate for 24 hours followed by transdermal GTN or oral isosorbide mononitrate.

Sample size
19,394 randomized.

Baseline characteristics
Accessible web sources confirm that 22% were women and that background contemporary therapy included aspirin in 84%, thrombolytics in 72%, and beta-blockers in 31%. More granular baseline demographics were not fully available in the accessible sources reviewed.

Outcomes (Endpoints)

Primary

- All-cause mortality at 6 weeks
- Combined endpoint of death plus heart failure/severe LV dysfunction at 6 weeks

Secondary

- Change in left ventricular ejection fraction

- Six-month follow-up analysis of mortality plus severe LV dysfunction after discontinuation of study therapy at 6 weeks

Results / Key Findings

- Overall 6-week mortality in the trial was 6.7%.
- Lisinopril reduced 6-week mortality versus no lisinopril: 6.3% vs 7.1%, an 11% relative reduction (OR 0.88, 95% CI 0.79-0.99; p=0.03).
- Lisinopril also reduced the combined endpoint at 6 weeks: 15.6% vs 17.0% (p=0.009; OR 0.90, 95% CI 0.84-0.98).
- Routine nitrate therapy did **not** significantly improve 6-week mortality: 6.5% vs 6.9% (p=0.28), and did not significantly improve the combined endpoint: 15.9% vs 16.7% (p=0.12).
- At 6 months, the combined endpoint remained lower with prior lisinopril assignment: 18.1% vs 19.3% (p=0.03), suggesting persistence of early benefit after the 6-week treatment course ended.
- Predefined higher-risk groups appeared to derive particular benefit for the combined endpoint, and later follow-up/commentary highlighted diabetes, anterior MI, and higher Killip class as groups with greater absolute benefit.
- **Adverse effects:** Hypotension was an important safety issue with early ACE inhibition in this era; accessible commentary on GISSI-3 notes persistent hypotension, and to a lesser extent renal dysfunction, as key treatment-limiting concerns. Exact main-trial adverse-event percentages were not clearly available in the accessible sources reviewed.

Number Needed to Treat (NNT)

Event rates
Lisinopril 6-week mortality: 6.3%
No lisinopril 6-week mortality: 7.1%

Absolute Risk Difference (ARD)
7.1% - 6.3% = 0.8% absolute risk reduction = 0.008.

Formula
NNT = 1 / 0.008 = 125.

Interpretation
About 125 similar hemodynamically stable acute MI patients would need to be treated with early lisinopril to prevent 1 death by 6 weeks.

Note
This NNT is based on the main-effect mortality comparison in an open-label factorial trial from the thrombolytic era. It is valid as a teaching estimate, but should not be overinterpreted as a modern PCI-era absolute effect size.

Conclusions
Early lisinopril after acute MI produced a modest but statistically significant reduction in 6-week mortality and in the combined endpoint of death plus ventricular dysfunction/heart failure. Routine nitrate therapy did not show a meaningful survival benefit. The trial helped establish early ACE inhibition as part of post-MI care, especially in higher-risk patients.

Location of the Trial
Italy.

Funding
Not clearly stated in the accessible sources reviewed. Unable to verify from provided materials and accessible web sources.

PMID
7910229.

ClinicalTrials.gov ID Number
Not registered / no ClinicalTrials.gov ID available. This predates routine ClinicalTrials.gov registration.

Study Limitations

- Open-label design rather than placebo-controlled, which raises potential performance and ascertainment bias.
- Conducted in the early reperfusion era, before contemporary primary PCI, dual antiplatelet therapy, high-intensity statins, and modern secondary prevention.
- Absolute mortality benefit was modest despite statistical significance.
- Broad “suspected AMI” enrollment improves pragmatism but may blur phenotypic precision by modern standards.

- Main accessible sources do not clearly report full adverse-event rates, limiting precise safety teaching.
- Nitrate comparisons were negative, but background nitrate use outside protocol for specific indications may complicate interpretation.
- Six-week treatment duration does not answer the optimal duration of ACE inhibition for all post-MI phenotypes.
- Generalizability to unstable patients is limited because those at high risk for hemodynamic compromise were excluded.
- Benefit estimates come from a population heavily treated with thrombolysis, not contemporary PCI-dominant systems.
- Some clinically important subgroup observations, such as diabetes, come from retrospective or later analyses rather than the main randomization question.

Current Guidelines or Position Statements

- Contemporary ACS guidelines continue to recommend renin-angiotensin system blockade after MI/ACS in higher-risk patients, especially those with LVEF ≤40%, heart failure, anterior MI/STEMI, hypertension, or diabetes.
- The 2025 ACC/AHA multisociety ACS guideline replaced older STEMI/NSTE-ACS guidance and maintains evidence-based medical therapy as a core component of ACS care.
- The 2023 ESC ACS guideline similarly addresses ACS across the spectrum and continues to incorporate guideline-directed secondary prevention after MI, including RAAS blockade in appropriate patients.

Expert Commentary from Reputable Medical Sources or Experts

- ACC's trial summary interprets GISSI-3 as evidence that lisinopril given early after MI improves mortality and LV dysfunction, while routine nitrate therapy does not.
- A contemporaneous review noted that GISSI-3, ISIS-4, and CCS-1 together supported starting ACE inhibitors early in clinically stable, hemodynamically appropriate MI patients, with much of the mortality benefit occurring early.
- NEJM/Journal Watch commentary on the 6-month follow-up emphasized that the early benefit appeared to persist beyond treatment discontinuation,

supporting the idea that early remodeling effects may matter long after the first hospitalization.

- Modern reviews still cite GISSI-3 as one of the landmark trials establishing post-MI ACE inhibition, but they also point out that evidence in patients with preserved LVEF and no other indication is less robust in the contemporary era.
- The diabetic substudy, summarized by EBM Consult from the Circulation analysis, suggested a larger absolute benefit in patients with diabetes, reinforcing the idea that higher-risk subgroups may gain the most from early ACE inhibition.

Clinical Practice Implications and/or Application

- GISSI-3 helped move ACE inhibitors from a selective heart-failure/remodeling therapy toward earlier routine consideration after MI, provided the patient is hemodynamically stable.
- The trial matters less because the absolute benefit was huge, and more because it showed a reproducible early mortality signal in a very large pragmatic AMI population.
- In practice today, the patients most aligned with guideline-supported use are those post-MI with reduced LVEF, heart failure, anterior MI, diabetes, hypertension, or CKD, assuming blood pressure and renal function permit.
- GISSI-3 also reminds clinicians not to treat “class effects” casually in unstable patients: timing, route, and hemodynamic stability matter, especially given hypotension risk.
- Routine long-course nitrate therapy after MI did not improve survival in this trial, so its use should be symptom- or ischemia-driven rather than reflexive for all post-MI patients.
- For teaching purposes, this is a landmark “practice-shaping” trial, but application should be filtered through modern reperfusion care and contemporary guideline-directed medical therapy.