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Six-Month Effects of Early Treatment With Lisinopril and Transdermal Glyceryl Trinitrate Singly and Together Withdrawn Six Weeks After Acute Myocardial Infarction: The GISSI-3 Trial

GRUPPO ITALIANO PER LO STUDIO DELLA SOPRAVVIVENZA NELL'INFARTO MIOCARDICO*

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Objectives. **This 6-month follow-up analysis sought to assess whether the early reduction of mortality obtained with a 6-week treatment course of lisinopril or glyceryl trinitrate, or both, in unselected patients with acute myocardial infarction outlasts therapy and is still present after 6 months. The primary outcome of the 6-month follow-up was the combined end point of mortality and severe left ventricular dysfunction.**

Background. **The assumption was that the early benefit on remodeling processes may be maintained over a longer period of time, even in the absence of treatment.**

Methods. **A total of 19,394 patients with acute myocardial infarction were randomized within 24 h of onset of symptoms to a 6-week treatment course of oral lisinopril or open control and, according to a 2 × 2 factorial design, to glyceryl trinitrate or open control. Randomized treatments were stopped after 6 weeks in the absence of specific indications, and the patients were followed up for 6 months.**

Results. **At 6 months, among patients randomized to lisinopril, 18.1% died or developed severe ventricular dysfunction versus 19.3% of those randomized to no lisinopril (2p = 0.03). No difference was found between patients with and without glyceryl trinitrate therapy (18.4% vs. 18.9%, 2p = 0.39).**

Conclusions. **Although the systematic administration of glyceryl trinitrate started early and continued for 6 weeks after acute myocardial infarction does not yield evidence of benefit, early treatment with lisinopril appears to improve prognosis. This effect seems to carry over the first 6 months from randomization, even after treatment withdrawal.**

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The report of the 6-month results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-3 trial (1) does not simply represent an account of the medium-term consequences of a randomized treatment started in the very early phase of acute myocardial infarction, as has been the case for previous GISSI trials (2,3). According to the study protocol (4), the 6-month follow-up was planned to answer a specific question not formally addressed by other trials: Does a very early exposure to angiotensin-converting enzyme inhibitors or glyceryl trinitrate express itself better or exclusively during treatment (6 weeks after acute myocardial infarction) or as a medium-term benefit measurable at 6 months after treatment discontinuation? To formally test this hypothesis, which relied largely on the attenuation of the remodeling processes after acute myocardial infarction (5,6), randomized treatments (lisinopril and transdermal glyceryl trinitrate) were stopped after 6 weeks. According to the study protocol, outcome events were also different, mortality being the primary end point for the 6-week treatment hypothesis and the combination of mortality plus severe left ventricular dysfunction (1,7) representing the primary end point for the 6-month evaluation. Therefore, after the report on the 6-week results on mortality, which have recently been confirmed by the results of International Study of Infarct Survival (ISIS)-4 (8) and Chinese Cardiac Study (CCS)-1 (9), the present study is focused on the combined end point of mortality and severe left ventricular dysfunction at 6 months.

Methods

Patients. The GISSI-3 protocol has been fully described elsewhere (1,4). In brief, patients admitted to the participant coronary care units were eligible for central randomization: 1) if they presented chest pain accompanied by elevation or depression of the ST segment of at least 1 mm in one or more peripheral leads or of at least 2 mm in one or more precordial leads; 2) if they had been admitted to the coronary care units within 24 h of symptom onset; and 3) if they had no clear contraindications to the study treatments. No age restriction was imposed. Patients were ineligible for randomization (4) if

*A complete list of investigators and participating centers appears in reference 1. Organizational information for GISSI-3 is provided in the Appendix. The GISSI-3 trial is endorsed by the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO), Florence and the Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy. Zeneca Pharmaceutical, Milan supplied the lisinopril, Schwarz Pharma, Milan supplied the intravenous and transdermal glyceryl trinitrate, and both companies provided financial support for this study.

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they were at high risk of developing further serious hemodynamic deterioration after treatment with vasodilators (systolic blood pressure at entry ≤100 mm Hg) and if they had a history of clinically relevant renal dysfunction (serum creatinine >177 μmol/liter or proteinuria >500 mg per 24 h, or both).

Patients were randomly assigned to oral lisinopril (5 mg at randomization, 5 mg after 24 h, 10 mg after 48 h, then 10 mg once daily for 6 weeks) or open control. Subjects with systolic blood pressure between 100 and 120 mm Hg at randomization or in the first 3 days could be given a lower dose of lisinopril (2.5 mg). Patients were also randomly assigned to glyceryl trinitrate or open control. Glyceryl trinitrate was administered during the first 24 h by intravenous infusion. After 24 h, the intravenous infusion was replaced with a transdermal patch providing 10 mg of glyceryl trinitrate daily. The patch was applied early every morning and removed at bedtime to provide a 10-h nitrate-free interval so as to minimize pharmacologic tolerance.

Mortality and severe left ventricular dysfunction were assessed after 6 weeks of treatment to check for possible effects of the study treatments. In the absence of specific indications (i.e., hypertension, angina, congestive heart failure), treatment was then stopped at the 6-week visit, and the patients were followed up to 6 months from randomization to determine whether the benefit shown with an early 6-week treatment was maintained after drug withdrawal. This was assessed by means of a combined end point that consisted of death, clinical heart failure or left ventricular dysfunction (1,10).

To minimize the potential bias arising from the open design, a conservative criterion was adopted to define clinical heart failure after discharge, namely, the presence of New York Heart Association functional class III or IV. Extensive left ventricular damage was identified by the presence of a left ventricular ejection fraction of 35% or less on two-dimensional echocardiography; if the ejection fraction was not available, extensive left ventricular damage was deemed present if ≥45% of myocardial segments appeared injured at echocardiography (10). The criteria for central quality control of the echo recordings have been described elsewhere (1).

The participating coronary care units were also asked to report all clinically relevant events (postinfarction angina, reinfarction, sustained ventricular tachycardia, revascularization procedures) occurring following trial admission. Information on survival of patients not traced by the coronary care units was obtained by telephone or through census offices.

Statistical methods. The data on the combined end point were analyzed according to the intention to treat principle using the same comparisons adopted for the 6-week period (i.e., lisinopril vs. no lisinopril, transdermal glyceryl trinitrate vs. no transdermal glyceryl trinitrate, lisinopril plus transdermal glyceryl trinitrate vs. neither, in the overall population, and in the prespecified populations of elderly patients and women).

The chi-square statistic was used for significance testing on categoric variables. The results are presented in terms of Mantel-Haenszel-Peto odds ratios with their 95% confidence intervals. All p values are two-tailed.

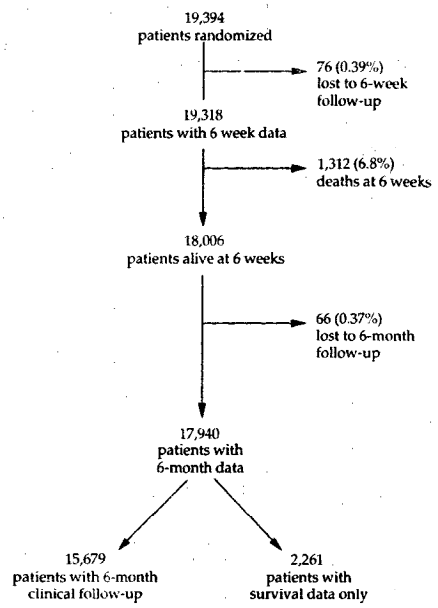

Figure 1. Flowchart for GISSI-3 trial.

Results

A comprehensive picture of the patient population is provided in the flowchart of Figure 1. The previous report on 6-week follow-up (1) concerned 18,895 patients (97.4% of the randomized population) for whom complete clinical data were available at that time. Because a substantial proportion of patients reported as lost to follow-up were subsequently traced (423 of 499), the present report includes information on the 6-month survival of 17,940 (99.7%) patients, of the 18,006 still alive at 6 weeks: 15,679 patients were evaluated clinically by the responsible cardiologists, but for 2,261 patients only survival data obtained through the census offices were available.

Lisinopril versus no lisinopril. The results in terms of the combined end point of mortality and severe ventricular dysfunction, which was the main outcome measure of the study at 6 months, are reported in Table 1 together with the corresponding 6-week figures. Among patients randomized to receive lisinopril, 18.1% died or developed severe ventricular dysfunction within 6 months (1,743 of 9,646) versus 19.3% among those not treated with lisinopril (1,866 of 9,672). The difference (6.2% reduction in the combined end point) was statistically significant (2p = 0.03). Among lisinopril-allocated patients there were 123 fewer events than in the no-lisinopril group; such a reduction was distributed equally among the different components of the combined end point: −46 deaths, −37 patients with clinical heart failure, −40 patients with severe left ventricular dysfunction (defined as an ejection fraction ≤35% or as a dyskinesia score ≥45% in the small group of patients in whom ejection fraction was not measured).

Although the difference in terms of mortality was lower at

Table 1. Six-Week and Six-Month Combined End Point Rates in Lisinopril and No-Lisinopril Groups

	6 Weeks				6 Months			
	Lisinopril (n = 9,646)	No Lisinopril (n = 9,672)	OR (95% CI)	p Value (two-tailed)	Lisinopril (n = 9,646)	No Lisinopril (n = 9,672)	OR (95% CI)	p Value (two-tailed)
Total events	1,495 (15.5)	1,629 (16.8)	0.89 (0.79–0.99)	0.04	1,743 (18.1)	1,866 (19.3)	0.92 (0.86–0.99)	0.03
Deaths	619 (6.4)	693 (7.2)			882 (9.1)	928 (9.6)		
CHF	366 (3.8)	354 (3.7)			521 (5.4)	558 (5.8)		
EF ≤35%	451 (4.7)	530 (5.5)			320 (3.3)	358 (3.7)		
AD score ≥45%	59 (0.6)	52 (0.5)			20 (0.2)	22 (0.2)		

Data presented are number (%) of patients or odds ratio (OR) with 95% confidence interval (CI). AD = akinesia/dyskinesia; CHF = congestive heart failure; EF = ejection fraction.

6 months with respect to the corresponding 6-week figures (8 lives saved per 1,000 treated patients at 6 weeks vs. 5 per 1,000 at 6 months), the incidence rate of patients with clinical heart failure was slightly lower at 6 months among lisinopril-allocated patients than among control subjects (5.4% vs. 5.8% respectively), while no difference was present at 6 weeks (3.8% vs. 3.7%).

The benefit of lisinopril treatment at 6 weeks was confirmed for the elderly and in women after 6 months (Table 2). There was a significant reduction of the combined end-point rate among patients over 70 allocated to lisinopril with respect to those allocated to no lisinopril (30.6% vs. 33.8%, 9.5% reduction, 2p = 0.01). The pattern for women was similar; the combined end-point rate was 25.4% among women allocated to lisinopril versus 28.0% among women allocated to no lisinopril (9.3% reduction, 2p = 0.05).

There were no significant differences between patients allocated to lisinopril or no lisinopril in rates of reinfarction, postinfarction angina, sustained ventricular tachycardia and revascularization procedures (percutaneous transluminal angioplasty, coronary artery bypass surgery) (Table 3).

Transdermal glyceryl trinitrate versus no glyceryl trinitrate. Table 4 presents the 6-month combined end-point results for the glyceryl trinitrate versus no–glyceryl trinitrate groups. At 6 months no significant difference in benefit was seen in the combined end point between the group of patients allocated to receive 6 weeks of transdermal glyceryl trinitrate treatment and control subjects (18.4% vs. 18.9%, 2p = 0.39).

With respect to the high risk populations, although the 6.2% reduction in the combined end point observed in women was not statistically significant (2p = 0.22), a significant reduction in terms of combined end point was confirmed among elderly patients allocated to glyceryl trinitrate with respect to no–glyceryl trinitrate group (30.9% vs. 33.5%, 7.8% reduction, 2p = 0.04) (Table 5).

The 6-month rates of sustained ventricular tachycardia, reinfarction, postinfarction angina and revascularization procedures did not differ significantly between glyceryl trinitrate and no–glyceryl trinitrate group-allocated patients (Table 3).

Lisinopril plus transdermal glyceryl trinitrate versus neither. The combined end point rates for control subjects, glyceryl trinitrate alone, lisinopril alone and the combination

Table 2. Six-Month Combined End Point Rates by Age and Gender in Lisinopril and No-Lisinopril Groups

	Lisinopril	No Lisinopril	OR (95% CI)	Total (%)	p Value (two-tailed)
Patients >70 yr					
Total events	790/2,585 (30.6)	896/2,649 (33.8)	0.86 (0.77–0.97)	1,686/5,234 (32.2)	0.01
Deaths	518 (20.0)	545 (20.6)			
CHF	196 (7.6)	258 (9.7)			
EF ≤35%	70 (2.7)	88 (3.3)			
AD score ≥45%	6 (0.2)	5 (0.2)			
Women					
Total events	544/2,144 (25.4)	598/2,132 (28.0)	0.87 (0.76–1.00)	1,142/4,276 (26.7)	0.05
Deaths	323 (15.1)	360 (16.9)			
CHF	165 (7.7)	184 (8.6)			
EF ≤35%	51 (2.4)	49 (2.3)			
AD score ≥45%	5 (0.2)	5 (0.2)			

Data presented are number (%) of patients, unless otherwise indicated. Abbreviations as in Table 1.

Table 3. Six-Month Clinical Events

	GTN (n = 9,663)	No GTN (n = 9,655)	OR (95% CI)	Lisinopril (n = 9,646)	No Lisinopril (n = 9,672)	OR (95% CI)
Reinfarction	445 (4.6)	451 (4.7)	0.99 (0.86–1.13)	454 (4.7)	442 (4.6)	1.03 (0.90–1.18)
Postinfarction angina	2,612 (27.0)	2,726 (28.2)	0.94 (0.88–1.00)	2,701 (28.0)	2,637 (27.3)	1.04 (0.97–1.11)
Sustained VT	219 (2.3)	251 (2.6)	0.87 (0.72–1.04)	224 (2.3)	246 (2.5)	0.91 (0.76–1.09)
Angioplasty	379 (3.9)	374 (3.9)	1.01 (0.88–1.17)	383 (4.0)	370 (3.8)	1.04 (0.90–1.20)
Bypass surgery	437 (4.5)	446 (4.6)	0.98 (0.85–1.12)	463 (4.8)	420 (4.3)	1.11 (0.97–1.27)

Data presented are number (%) of patients, unless otherwise indicated. GTN = glyceryl trinitrate; VT = ventricular tachycardia; other abbreviations as in Table 1.

of lisinopril plus glyceryl trinitrate are shown in Table 6. The combination of lisinopril and transdermal glyceryl trinitrate produced an 8.7% reduction in the combined end point events rate compared with the control group (17.8% vs. 19.5%, 2p = 0.03).

The combination of lisinopril and transdermal glyceryl trinitrate was associated with an even greater effect on the combined end point both in elderly patients (29.2% vs. 35.2%, 17% reduction, 2p = 0.001) and in women (24.9% vs. 29.3%, 15% reduction, 2p = 0.02) (Table 7).

Six-month prescriptions of cardiovascular drugs. The overall picture of the prescription patterns at 6 months is presented in Table 8, which includes data on trial treatments as well as on the other cardiovascular drugs. The information available for the 15,679 patients who underwent a clinical visit at 6 months is presented according to the four-way scheme to allow a more thorough evaluation of the possible confounding by unbalanced distributions. A higher proportion of patients randomized to either lisinopril or nitrates appear to have been exposed to the originally allocated drug. The main indications for angiotensin-converting enzyme inhibitors at 6 months were hypertension (48.6%) and clinical heart failure/left ventricular dysfunction (34%), whereas the main indications for nitrates at 6 months were angina (48.1%) and left ventricular dysfunction (15.4%). As expected, a slightly lower proportion of lisinopril-allocated patients appear to have been exposed to therapeutic classes (mainly calcium antagonists and beta-adrenergic blocking agents) whose indications are partially overlapping with those of angiotensin-converting enzyme inhibitors.

Of the patients with angiotensin-converting enzyme inhibitors prescribed at 6 months, 47.7% of the patients allocated to lisinopril were receiving angiotensin-converting enzyme inhibitors since the 6-week visit versus and 30.3% of those allocated to no lisinopril. A similar trend was found for glyceryl trinitrate, where 49.8% of the patients allocated to this drug who were treated with nitrates at 6 months had actually been consuming nitrates since the 6-week visit versus 41.0% of no–glyceryl trinitrate-allocated patients.

Six-month outcome of patients with or without left ventricular failure/dysfunction at 6 weeks. Table 9 shows the total mortality rate and the rate of patients with severe heart failure (functional classes III and IV) between 6 weeks and 6 months stratified by the presence at 6 weeks of signs or symptoms of left ventricular failure or dysfunction, or both. Total mortality and severe heart failure rates among patients with asymptomatic depressed left ventricular ejection fraction (≤35%) or marked regional wall motion abnormalities (≥45%) was over twice that among patients classified at 6 weeks as patients with no complications. The presence of symptoms of heart failure at 6 weeks appears to be even more predictive of an unfavorable prognosis.

Table 4. Six-Week and Six-Month Combined End Point Rates in Glyceryl Trinitrate and No–Glyceryl Trinitrate Groups

	6 Weeks				6 Months			
	GTN (n = 9,663)	No GTN (n = 9,655)	OR (95% CI)	p Value (two-tailed)	GTN (n = 9,663)	No GTN (n = 9,655)	OR (95% CI)	p Value (two-tailed)
Total events	1,524 (15.8)	1,600 (16.6)	0.94 (0.87–1.02)	0.13	1,782 (18.4)	1,827 (18.9)	0.97 (0.90–1.04)	0.39
Deaths	639 (6.6)	673 (7.0)			895 (9.3)	915 (9.5)		
CHF	357 (3.7)	363 (3.8)			548 (5.7)	531 (5.5)		
EF ≤35%	483 (5.0)	498 (5.2)			318 (3.3)	360 (3.7)		
AD score ≥45%	45 (0.5)	66 (0.7)			21 (0.2)	21 (0.2)		

Data presented are number (%) of patients, unless otherwise indicated. Abbreviations as in Tables 1 and 3.

Table 5. Six-Month Combined End Point Rates by Age and Gender in Glyceryl Trinitrate and No–Glyceryl Trinitrate Groups

	GTN	No GTN	OR (95% CI)	Total	p Value (two-tailed)
Patients >70 yr					
Total events	802/2,599 (30.9)	884/2,635 (33.5)	0.88 (0.79–0.99)	1,686/5,234 (32.2)	0.04
Deaths	509 (19.6)	554 (21.0)			
CHF	214 (8.2)	240 (9.1)			
EF ≤35%	73 (2.8)	85 (3.2)			
AD score ≥ 45%	6 (0.2)	5 (0.2)			
Women					
Total events	558/2,156 (25.9)	584/2,120 (27.6)	0.92 (0.80–1.05)	1,142/4,276 (26.7)	0.22
Deaths	327 (15.2)	356 (16.8)			
CHF	178 (8.3)	171 (8.1)			
EF ≤35%	48 (2.2)	52 (2.5)			
AD score ≥ 45%	5 (0.2)	5 (0.2)			

Data presented are number (%) of patients, unless otherwise indicated. Abbreviations as in Tables 1 and 3.

Discussion

Effects of randomized treatments. The GISSI-3 results at 6 months are substantially consistent with those on mortality at 6 weeks. The early treatment of unselected acute myocardial infarction patients with lisinopril leads to a small but statistically significant benefit in terms of the combined end point of mortality plus severe ventricular dysfunction. Both components of the combined end point contribute to the overall result, which also applies (symmetrically with the observations at 6 weeks) to the predefined higher-risk populations (women and elderly subjects).

With respect to the other main hypothesis tested in the study, no independent beneficial effects are found for glyceryl trinitrate, although the safety of the combination of glyceryl trinitrate and lisinopril is confirmed.

Overall, the results obtained on the combined end point confirm those on mortality of the ISIS-4 trial (8), in which a two-stage assessment was not planned, although the double-blind design implied the discontinuation of the randomized treatments: the findings on survival at the end of the treatment period (at 35 days) are reported unchanged up to 1 year (8). A comparison of these data with those of the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) trial (11), which showed an increasing benefit among patients allocated to zofenopril over 11 months after drug discontinuation, would be difficult because of the rather different characteristics of that population (selected anterior acute myocardial infarction patients not exposed to thrombolysis).

The analysis of the different components of the combined end point suggests some interesting observations, mainly with respect to the effects of an early treatment with angiotensin-converting enzyme inhibitors on mortality and on ventricular function. The difference in terms of mortality was less marked at 6 months than at 6 weeks; in contrast, although after 6 weeks there was no evidence of an effect on the percent of patients with clinical heart failure, a reduction was shown at 6 months among patients taking lisinopril. The improvement in left ventricular function seen at 6 weeks—the smaller fraction of subjects with a depressed ejection fraction (4.7% vs. 5.5%)—in the group randomized to lisinopril has probably determined the lower rate of patients subsequently developing an overt heart failure.

If the mechanisms of the early reduction of mortality are still not clear (12,13), the better profile in terms of ventricular

Table 6. Six-Month Combined End Point Rates for Four-Way Comparison

	Control (n = 4,828)	GTN (n = 4,844)	Lisinopril (n = 4,827)	Lisinopril + GTN (n = 4,819)
Total events	940 (19.5)	926 (19.1)	887 (18.4)	856 (17.8)
OR (95% CI)	1	0.98 (0.88–1.08)	0.93 (0.84–1.03)	0.89 (0.81–0.99)
p value (two-tailed)				0.03
Deaths	467 (9.7)	461 (9.5)	448 (9.3)	434 (9.0)
CHF	275 (5.7)	283 (5.8)	256 (5.3)	265 (5.5)
EF ≤35%	186 (3.9)	172 (3.6)	174 (3.6)	146 (3.0)
AD score ≥45%	12 (0.2)	10 (0.2)	9 (0.2)	11 (0.2)

Data presented are number (%) of patients, unless otherwise indicated. Abbreviations as in Tables 1 and 3.

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Table 7. Six-Month Combined End Point Rates by Age and Gender

	Control	GTN	Lisinopril	Lisinopril + GTN
Patients >70 yr old				
Total events	465/1,322 (35.2)	431/1,327 (32.5)	419/1,313 (31.9)	371/1,272 (29.2)
OR (95% CI)	1	0.89 (0.75–1.04)	0.86 (0.73–1.02)	0.76 (0.64–0.90)
p value (two-tailed)				0.001
Deaths	278 (21.0)	267 (20.1)	276 (21.0)	242 (19.0)
CHF	137 (10.4)	121 (9.1)	103 (7.8)	93 (7.3)
EF ≤35%	49 (3.7)	39 (2.9)	36 (2.7)	34 (2.7)
AD score ≥45%	1 (0.1)	4 (0.3)	4 (0.3)	2 (0.2)
Women				
Total events	306/1,046 (29.3)	292/1,086 (26.9)	278/1,074 (25.9)	266/1,070 (24.9)
OR (95% CI)	1	0.89 (0.74–1.07)	0.84 (0.70–1.02)	0.80 (0.66–0.97)
p value (two-tailed)				0.02
Deaths	187 (17.9)	173 (15.9)	169 (15.7)	154 (14.4)
CHF	89 (8.5)	95 (8.7)	82 (7.6)	83 (7.8)
EF ≤35%	27 (2.6)	22 (2.0)	25 (2.3)	26 (2.4)
AD score ≥45%	3 (0.3)	2 (0.2)	2 (0.2)	3 (0.3)

Data presented are number (%) of patients, unless otherwise indicated. Abbreviations as in Tables 1 and 3.

function at 6 months could be explained by the expected favorable influence of angiotensin-converting enzyme inhibitor treatment on left ventricular remodeling processes. In this sense, the analysis of the echocardiographic examinations included in the GISSI-3 protocol suggests that patients randomized to lisinopril may be protected against the left ventricular dilation that follows acute myocardial infarction. Smaller left ventricular volumes were observed at the 6-month follow-up visit among patients allocated to lisinopril compared to control subjects even following drug withdrawal (14).

Both the findings and the hypotheses must certainly be read now in the overall context of the results of the Survival and Ventricular Enlargement (SAVE) (15), Acute Infarction Ramipril Efficiency (AIRE) (16), and Trandolapril Cardiac Evaluation (TRACE) (17) trials, which recommend angiotensin- converting enzyme inhibitor treatment in patients with clinical signs of congestive heart failure or even in those with asymptomatic left ventricular dysfunction. In GISSI-3, many patients with left ventricular dysfunction assigned to lisinopril treatment were maintained on the drug, and several control patients started angiotensin-converting enzyme inhibitor agents after 6 weeks.

Different patterns of medication use. The issue of the possible impact on outcome of the treatments prescribed between 6 weeks and 6 months should be evaluated by considering Table 8. Nonstrict adherence to the withdrawal recommendations was to some extent expected, mainly in the lisinopril-treated group: An angiotensin-converting enzyme inhibitor treatment began to be recommended for heart failure/ventricular dysfunction during the trial period (late 1992), and the protocol had already explicitly stressed the priority of guaranteeing that patients receive the best treatments (as soon as the related evidence was available) rather than strict compliance with the withdrawal rule planned by the GISSI-3 protocol. A letter concerning this point was also sent to the investigators to alert them in as timely a way as possible to the results and the implications of the SAVE trial (14). On the other hand, it is reasonable that continuation of angiotensin-converting enzyme inhibitor treatment could be considered a useful option for hypertensive patients. Analysis at 6 months of

Table 8. Patients Taking Cardiovascular Drugs at 6-Month Follow-Up by Trial Treatment*

Drug	Control (n = 3,902)	GTN (n = 3,920)	Lisinopril (n = 3,923)	Lisinopril + GTN (n = 3,934)
ACE inhibitors	662 (17.0)	614 (15.7)	1,334 (34.0)	1,410 (35.8)
Nitrates	1,251 (32.1)	1,652 (42.1)	1,093 (27.9)	1,672 (42.5)
Digoxin	249 (6.4)	272 (6.9)	250 (6.4)	249 (6.3)
Diuretics	540 (13.8)	531 (13.5)	514 (13.1)	470 (11.9)
Ca antagonists	1,073 (27.5)	1,076 (27.4)	930 (23.7)	911 (23.2)
Beta-blockers	1,185 (30.4)	1,112 (28.4)	1,011 (25.8)	957 (24.3)
Aspirin	2,042 (52.3)	2,019 (51.5)	2,046 (52.2)	1,972 (50.1)

*For 15,679 patients; patients taking different classes of drugs are counted more than once. Data presented are number (%) of patients. ACE = angiotensin-converting enzyme; Ca = calcium; GTN = glyceryl trinitrate.

Table 9. Six-Month Mortality and Heart Failure Rates in Patients With/Without Signs or Symptoms of Left Ventricular Dysfunction

Status at 6 wk (n = 2,756)*	Status at 6 mo	
	Deaths	CHF
Symptomatic heart failure (n = 720)	94 (13.1)	119 (16.5)
Asymptomatic left ventricular dysfunction (n = 1,092)	46 (4.2)	92 (8.4)
No complications (n = 13,429)	196 (1.5)	294 (2.2)

*Asymptomatic patients without echocardiography. Data presented are number (%) of patients. CHF = congestive heart failure; LVD = left ventricular dysfunction.

the section of the data collection forms concerning treatment indications confirms this hypotheses. Overall, however, the prescription burden of cardiovascular drugs appears similar in the two populations.

Outcome profile of patients with or without signs and symptoms of left ventricular dysfunction. The 6-month follow-up period planned by the GISSI-3 study made it possible to confirm the prognostic relevance of left ventricular dysfunction detected echocardiographically after myocardial infarction. Total mortality and severe heart failure (functional classes III or IV) rates appeared to be higher among the patients with asymptomatic depressed left ventricular ejection fraction or marked regional wall motion abnormalities at 6 weeks. However, the presence of clinical symptoms of heart failure appeared to be the strongest predictor of a poor prognosis.

Conclusions. Although the systematic administration of glyceryl trinitrate started early and continued for 6 weeks after an acute myocardial infarction does not provide an appreciable clinical advantage, early treatment with lisinopril of an unselected population of patients with acute myocardial infarction with no treatment contraindications appears to improve their prognosis with respect to mortality and severe left ventricular dysfunction, and this effect seems to carry over the first 6 months from randomization, even after treatment withdrawal. The mortality reduction is mostly obtained in the first few days of lisinopril treatment (12,13), but the improvement in terms of ventricular function (clinical and/or instrumental) becomes more evident at a later stage (i.e., at the 6-month follow-up visit).

Further, with respect to the other prespecified analyses, the combination of glyceryl trinitrate and lisinopril is confirmed to be safe and suggestive of some additive beneficial effect. Similarly, the data presented here seem to confirm the favorable profile of mortality and severe left ventricular dysfunction obtained in elderly patients and in women with lisinopril treatment.

These observations fit the recommendations on the use of angiotensin-converting enzyme inhibitors in the acute and postacute phase of acute myocardial infarction, formulated in an international meeting of the investigators actively involved in the main published angiotensin-converting enzyme inhibitor trials (13).

Appendix

Study Organization

Steering Committee. C. De Vita, P. F. Fazzini, E. Geraci, L. Tavazzi, G. Tognoni and C. Vecchio (Chairman). **Safety and Data Monitoring Committee.** R. Boeri, G. D'Amico, U. Loi, E. Marubini, L. Pagliaro and F. Rovelli (Chairman). **Scientific and Organizing Secretariat.** M. G. Franzosi, R. Latini, A. P. Maggioni, F. Mauri and A. Volpi. **Data Management and Analysis.** S. Barlera, E. Negri, E. Nicolis, E. Santoro and L. Santoro. **Clinical Data ECG Coding and Echocardiographic Data Revision.** A. Ascione, E. Bonfanti, T. Capello, A. Casati, A. Corato, E. Gardinale, M. Negrini, A. Nobili, L. Staszewsky, M. Tavanelli, D. Torta and G. Zuanetti. **Echocardiogram Quality Control Group.** G. Gambelli, L. Moroni, J. J. Pellanda and F. Pietropaolo. **Regional Clinical Monitors.** E. Balli, A. Barbieri, S. Bechi, M. Carrone, M. Catanzaro, L. Fasciolo, C. Fresco, A. Ghiani, G. Iacuitti, A. Ledda, G. Levantesi, L. Moroni, P. Pasini, P. Peci, F. Pizzetti, A. Sagone, F. Turazza, A. Villella and M. Villella. **Scientific Committee for Side Projects.** N. Braggio, M. Disertori, S. Frezzati, S. Garattini, P. Marino, A. Maseri, G. Mazzotta, G. Nicolosi, S. Pirelli, G. P. Sanna and F. Valagussa. **International Advisory Board.** H. J. Dargie, R. Peto, S. Pocock, P. Sleight and S. Yusuf.

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