The prognostic value of predischARGE quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 Trial

Gruppo Italiano per lo Studio della Sopravvivenza Nell’infarto Miocardico (see Appendix)

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Background Left ventricular dilatation and a low ejection fraction after acute myocardial infarction are independent indicators of a poor prognosis. ACE inhibitors have been shown to decrease left ventricular dilatation after myocardial infarction. In the GISSI-3 trial, patients were randomly assigned, within 24 h of onset of myocardial infarction symptoms, to 6 weeks of treatment with lisinopril, nitroglycerin, both or neither, in an open, 2 x 2 factorial design. The study showed that early treatment in relatively unselected patients with lisinopril decreases mortality at 6 weeks and severe left ventricular dysfunction. We assessed (1) the prognostic value of pre-discharge 2-D echocardiographic variables, and (2) the effects of lisinopril on the progression of left ventricular dilatation.

Methods and results 2-D echocardiograms were available pre-discharge in 8619 GISSI-3 trial patients discharged alive. In 6405 of these patients, a 2-D echocardiographic study was also available at 6 weeks, and at 6 months. Pre-discharge end-diastolic and end-systolic volumes, and ejection fraction predicted 6-month mortality and non-fatal clinical congestive heart failure (P<0.01). The increase in left ventricular volumes over time was significantly reduced by 6 weeks' lisinopril treatment in patients with wall motion asynergy pre-discharge of ≥27%. Patients with wall motion asynergy <27% showed no dilatation and lisinopril did not affect volumes at 6 months. Patients randomized to lisinopril also had smaller volumes after withdrawal of treatment at 6 weeks. Lisinopril did not affect left ventricular ejection fraction.

Conclusions 2-D echocardiography independently contributes to pre-discharge risk stratification in terms of 6-month mortality and clinical heart failure after myocardial infarction, and early, short-term treatment with lisinopril in unselected myocardial infarction patients attenuates left ventricular dilatation; an effect evident in patients with larger infarcts. These results probably only partly explain the effect of lisinopril on total mortality concentrated in the first week after infarction. (Eur Heart J 1996; 17: 1646-1656)

Key Words: Myocardial infarction, 2-D echocardiography, left ventricular remodelling, ACE inhibition.

Introduction

Acute myocardial infarction can initiate a dynamic process of changing left ventricular size, shape and myocardial architecture which can profoundly affect left ventricular function and, thereby, prognosis[1-5]. This process, frequently called ventricular remodelling, involves acutely and chronically both the infarcted and non-infarcted zones of the left ventricle, and affects wall thickness and structure, as well as chamber size, shape and function.

Quantitative two-dimensional echocardiography has been used to provide prognostic information and knowledge about the mechanisms and temporal sequence of left ventricular remodelling after myocardial
infarction. Angiotensin converting enzyme (ACE) inhibitors decrease mortality and morbidity in myocardial infarction patients, either selected a few days after the acute event in the presence of left ventricular dysfunction and treated for several years, or in relatively unselected patients started on the treatment the day after the myocardial infarction and treated for a few weeks.

Previous echocardiographic studies have reported the effects of ACE inhibition on myocardial infarction patients with left ventricular dysfunction, started on treatment a few days to months after the event in patients with early signs of a high-risk of post-myocardial infarction left ventricular remodelling, started on treatment within a day or so after the event. Only the CONSENSUS II trial studied 428 patients with early signs of a high-risk of post-myocardial infarction left ventricular remodelling, started on treatment within a day or so after the event. The pre-defined aim of the quality control examinations randomly selected from those performed on videotape and analysed at each participating centre. End-diastolic and end-systolic left ventricular long axis (L) and the orthogonal septolateral transverse axis (T) at the mid point of the long axis were measured. End-diastolic and end-systolic left ventricular volumes (LVV) were then computed according to an algorithm previously reported by Wyatt et al., that relates the left ventricle to a biplane ellipsoidal figure, using the formula LVV = π/6 × AP × T × L. The ejection fraction was then calculated.

The formula was chosen for three main reasons: (a) it requires only simple linear measurements (b) it is derived from a biplane left ventricular model, and (c) it allows simple information to be obtained from the ventricular shape. However, it should be taken into account that the formula tends to underestimate left ventricular volumes. Segmental wall motion was assessed by an 11 segment model modified from Edwards et al. to consider the apex as a single segment. Using this model, the percentage of akinetic-dyskinetic segments and visualized segments, i.e. the percentage of the extent of wall motion asynergy (WMA %) was calculated as a rough indicator of the extent of ischaemic damage. Wall motion asynergy at pre-discharge was used to assess the impact of lisinopril on left ventricular structure and function over time.

Quality control was performed by central reading a videotaped sample of 526 echocardiographic examinations randomly selected from those performed at 6 weeks. The pre-defined aim of the quality control
was to assess the agreement between peripheral and central reading on the attribution of a patient to one of the classes of left ventricular ejection fraction, \( \leq 35\% \) and \( >35\% \) in order to calculate the combined end-point\(^{[31]} \). We chose not to eliminate any data from analysis even if deemed unacceptable by quality control. In view of the present analysis, the agreement was also analysed in terms of continuous values of the echo variables according to Bland and Altman\(^{[36]} \).

**Statistical methods**

Two different analyses were performed, one (a) focused on the prognostic value of pre-discharge 2-D echocardiography, and the other (b) on the effects of lisinopril over time on 2-D echocardiographic variables.

**Pre-discharge echo as prognostic factor**
The relationship between pre-discharge left ventricular volumes and ejection fraction and 6-month mortality were examined by both univariate (unadjusted) and multivariate (adjusted) analysis. These analyses were performed on 8606 patients, since 13 patients were lost to 6-month follow-up.

For the univariate analysis, patients were stratified into quartiles based on left ventricular end-diastolic and end-systolic volumes, and ejection fraction. For each of these variables, the number of deaths and of patients with non-fatal late clinical congestive heart failure (i.e. NYHA class 3 or 4 occurring after discharge) in each quartile were computed and compared by a Pearson chi-squared test to assess statistical significance.

Multivariate analysis was performed using a Cox proportional hazard model to assess the independent prognostic weight of left ventricular volumes and ejection fraction in terms of 6-month mortality. The model includes baseline clinical risk factors: age >70 years, female sex, previous myocardial infarction, history of diabetes mellitus and hypertension, anterior myocardial infarction, Killip class >1, heart rate >100 beats \( \text{min}^{-1} \) and systolic blood pressure \( \leq 120 \text{mmHg} \) at randomization. The dependent variable was time to death and to non-fatal late clinical congestive heart failure. Left ventricular volumes and ejection fraction were added individually as continuous variables. Relative risks were expressed as increments for a change of 10 units of each echocardiographic variable. Improvement of goodness of fit for the models obtained adding left ventricular volumes and ejection fraction individually was evaluated by the likelihood ratio test which was asymptotically distributed as a chi-square with one degree of freedom\(^{[37]} \).

**Effects of lisinopril over time on 2-D echocardiographic variables**

Left ventricular volumes, and ejection fraction of the 6405 patients with 2-D echocardiograms available at pre-discharge, 6 weeks and 6 months were analysed in terms of within- and between-patient changes over time.

Randomized treatment (i.e. lisinopril and no lisinopril), and wall motion asynergy (<27% and \( \geq 27\% \)) at pre-discharge were introduced in the model as between-patient factors. A Repeated Measures Analysis of Variance was performed using the GLM procedure of the SAS program\(^{[38,39]} \), which enables main effects to be evaluated (i.e. time, treatment, wall motion asynergy, and their two- and three-way interactions). Within-patient comparisons between two subsequent time points were also performed, in order to test for the effects on left ventricular volumes and ejection fraction of the 6-week lisinopril treatment (pre-discharge vs 6 weeks) and for the effects of lisinopril withdrawal (6 weeks vs 6 months).

A non-parametric Friedman test was used to compare wall motion asynergy changes with time within patients. A non-parametric Mann–Whitney test was used to compare wall motion asynergy in lisinopril and no-lisinopril patients at each time\(^{[40]} \). In order to compare different patient populations for baseline clinical characteristics, we used a chi-squared for trends\(^{[41]} \). Data are presented as mean ± standard error of the mean for continuous variables and as median (25th and 75th percentiles) for wall motion asynergy.

**Results**

Baseline clinical characteristics of the 8606 patients with a 2-D echocardiogram at pre-discharge and those of 6405 survivors at 6 months with complete 2-D echocardiographic data were more favourable, as expected, than those of the patients with confirmed myocardial infarction, discharged alive (n=16958). No difference was shown within the 6-month echocardiographic sub-population between lisinopril and no-lisinopril groups (Table 1).

Two-dimensional echocardiograms were obtained at a median time of 9 days after the index myocardial infarction (pre-discharge), at 46 days (6-week follow-up visit), and at 190 days (6-month follow-up visit).

Pre-discharge echo as prognostic factor (n=8606)

Pre-discharge quartiles of end-diastolic volume, end-systolic volume and ejection fraction predicted 6-month mortality and non-fatal late clinical congestive heart failure \((P<0.01)\) (Fig. 1). Overall, the cumulated number of events at 6 months was 600/8606 patients \((7.0\%)\), 263 deaths and 337 non-fatal late clinical congestive heart failures.

Independently of lisinopril treatment, patients with wall motion asynergy <27% at pre-discharge showed lower 6-month mortality (2.2%; 173/7810) than patients with wall motion asynergy \( \geq 27\% \) \((6.6%; 222/3358)\) \((P<0.001)\) (11168 patients with wall motion asynergy at pre-discharge available). Multivariate regression models showed that echocardiographic variables independently predicted 6-month mortality and non-fatal late clinical congestive heart failure. Adjusted relative
Eur Heart J, Vol. 17, November 1996

Table 1 Baseline characteristics of patient populations (%)

<table>
<thead>
<tr>
<th></th>
<th>Confirmed MI discharged alive</th>
<th>Echo pre-discharge subpopulation</th>
<th>6-month echo subpopulation</th>
<th>2P for trend</th>
<th>6-month echo subpopulation</th>
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<tr>
<td></td>
<td>n=16958</td>
<td>n=8606</td>
<td>n=6405</td>
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<td>n=3186</td>
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<td>Females</td>
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<td>≤6</td>
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<td>0.5</td>
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<tr>
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<td>0</td>
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<td>Site of infarction</td>
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<td>Anterior</td>
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<td>Infero-posterior</td>
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<td>ns</td>
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<td>Non Q</td>
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<td>7.8</td>
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<td>2.6</td>
<td>2.1</td>
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<td>Heart rate at randomization</td>
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<tr>
<td>&lt;60 beats . min⁻¹</td>
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<td>12.0</td>
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<td>60-79 beats min⁻¹</td>
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<td>50.6</td>
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<td>51.4</td>
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<td>80-100 beats . min⁻¹</td>
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<td>33.0</td>
<td>32.1</td>
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<td>32.7</td>
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<tr>
<td>&gt;100 beats . min⁻¹</td>
<td>3.4</td>
<td>4.5</td>
<td>3.6</td>
<td>&lt;0.01</td>
<td>3.6</td>
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<td>Systolic blood pressure at randomization</td>
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<td>100-120 mmHg</td>
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<td>38.8</td>
<td>38.8</td>
<td>ns</td>
<td>39.4</td>
</tr>
<tr>
<td>121-150 mmHg</td>
<td>46.4</td>
<td>46.8</td>
<td>46.8</td>
<td>ns</td>
<td>46.2</td>
</tr>
<tr>
<td>&gt;150 mmHg</td>
<td>14.6</td>
<td>14.4</td>
<td>14.4</td>
<td>ns</td>
<td>14.4</td>
</tr>
<tr>
<td>Previous MI</td>
<td>13.2</td>
<td>12.4</td>
<td>11.1</td>
<td>&lt;0.001</td>
<td>11.5</td>
</tr>
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<td>Previous angina</td>
<td>33.9</td>
<td>34.1</td>
<td>33.4</td>
<td>ns</td>
<td>34.2</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>29.2</td>
<td>28.1</td>
<td>27.6</td>
<td>&lt;0.05</td>
<td>28.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15.0</td>
<td>14.2</td>
<td>13.7</td>
<td>&lt;0.05</td>
<td>13.7</td>
</tr>
<tr>
<td>Recommended treatments</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV beta-blockers</td>
<td>31.3</td>
<td>32.3</td>
<td>32.9</td>
<td>&lt;0.05</td>
<td>32.2</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>72.9</td>
<td>74.1</td>
<td>74.9</td>
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</tr>
<tr>
<td>Aspirin</td>
<td>84.9</td>
<td>85.8</td>
<td>86.4</td>
<td>&lt;0.01</td>
<td>86.3</td>
</tr>
</tbody>
</table>

Effects of lisinopril over time on 2-D echocardiographic variables (n=6405).

At pre-discharge, end-diastolic volume was 94.7±0.6 ml in the no-lisinopril patients, similar to that of lisinopril-treated patients (94.4±0.6 ml). At 6 weeks, end-diastolic volume increased in the no-lisinopril to 95.1±0.6 ml, while it decreased in lisinopril-treated subjects to 93.9±0.6 ml. At 6 months, end-diastolic volume increased to a similar extent in both groups, and therefore, the lisinopril-treated patients showed slightly smaller end-diastolic volumes (95.4±0.6 ml) as compared to those of the no-lisinopril patients (96.4±0.6 ml). The difference observed between treatments within patients was statistically significant (interaction time × treatment: P=0.0155, Table 2).

A similar trend was observed for end-systolic volume, although the differences were smaller and did not reach statistical significance (interaction time × treatment: P=0.2042, Table 2).

End-diastolic and end-systolic volumes were significantly larger for patients with wall motion asynergy ≥27% as compared to the patients with wall motion asynergy <27% (interaction time × wall motion asynergy ≥27%).
Figure 1 Pre-discharge echocardiographic variables in quartiles vs 6-month mortality (●) plus non-fatal late congestive heart failure (CHF) (□). Data refer to 8606 myocardial infarction patients discharged alive.

Table 2 Repeated Measures Analysis of Variance in 6405 patients with complete echocardiographic data at pre-discharge, 6 weeks and 6 monthly

<table>
<thead>
<tr>
<th>Univariate between patients test</th>
<th>EDV 2P</th>
<th>ESV 2P</th>
<th>EF 2P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>0.1921</td>
<td>0.4619</td>
<td>0.8340</td>
</tr>
<tr>
<td>WMA</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Treatment × WMA</td>
<td>0.6683</td>
<td>0.5963</td>
<td>0.4156</td>
</tr>
</tbody>
</table>

Contrasts (within patients)

(1) Pre-discharge vs 6 week
- Time effects: 0.0310 0.7160 0.0001
- Treatment: 0.0051 0.0810 0.4368
- WMA: 0.0001 0.0116 0.0037
- Treatment × WMA: 0.0017 0.0305 0.2551

(2) 6 week vs 6 months
- Time effects: 0.0001 0.0001 0.0048
- Treatment: 0.0952 0.9534 0.9976
- WMA: 0.0031 0.0020 0.6331
- Treatment × WMA: 0.4878 0.7260 0.7251

EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; WMA = wall motion asynergy.

Discussion

End-diastolic volume, end-systolic volume and ejection fraction values, calculated in the 8606 GISSI-3 patients discharged alive, were predictive of 6-month mortality and of non-fatal late clinical congestive heart failure, confirming the prognostic clinical importance of pre-discharge echocardiographic variables in post-myocardial infarction patients. Furthermore, our regression model adjusted for the main clinical-epidemiological variables at entry suggested that echocardiographic variables have independent prognostic value and confirmed that the best echocardiographic predictor of 6-month mortality was left ventricular ejection fraction.

The increase in end-diastolic volume after myocardial infarction was significantly prevented by 6 weeks of lisinopril treatment, started within 24 h of symptom onset. Subsequently, after treatment withdrawal, end-diastolic volume dilated both in the patients who received and in those who did not receive 6-week lisinopril treatment. However, left ventricular end-diastolic volume in lisinopril-treated patients at 6 months was still significantly lower than that of patients with larger infarcts, lisinopril reduced the dilation observed during the 6 weeks of treatment in the no-lisinopril group (Figs 2 and 3); the left ventricle began to dilate after lisinopril withdrawal. The difference between lisinopril and no-lisinopril treated patients was statistically significant (interaction time × treatment × wall motion asynergy: P=0.0015, Table 2). A similar trend was observed for end-systolic volume (Fig. 3), with a borderline statistically significant difference between lisinopril and no-lisinopril groups (interaction time × treatment × wall motion asynergy: P=0.0596, Table 2). Patients with wall motion asynergy at pre-discharge <27% showed no dilation and lisinopril did not affect volumes (Figs 2 and 3). Left ventricular ejection fraction increased significantly over time (P=0.0001), and was significantly lower in patients with wall motion asynergy ≥27% than in those with wall motion asynergy <27% (interaction time × wall motion asynergy: P=0.0128, Table 2, Fig. 4). However, treatment had no effect on ejection fraction over time. Wall motion asynergy decreased significantly (P<0.0001) during the follow-up without difference between lisinopril and no-lisinopril treated patients at any time (Table 3).
patients allocated no lisinopril in whom dilatation was progressive over time.

The difference in end-diastolic volume between lisinopril and patients allocated no lisinopril was significant in larger infarcts (i.e. wall motion asynergy ≥27%), while smaller infarcts (i.e. wall motion asynergy <27%) did not show any major changes during the follow-up, regardless of treatment. This finding is in agreement with previous data showing that ventricular remodelling may be observed mainly in infarctions of at least moderate size.\(^\text{121}\)

A similar trend over time was observed for end-systolic volumes, even though the difference between lisinopril and no-lisinopril treated patients did not reach statistical significance.

At variance with other studies\(^\text{4,20,24}\), ejection fraction was not modified by lisinopril, suggesting that the main effect of lisinopril in our study was to reduce left ventricular enlargement. However, similar results have been obtained by others\(^\text{25,28}\). The absolute differences in left ventricular volumes between lisinopril and no-lisinopril groups were very small (<5 ml), but statistically significant in patients with larger infarcts. These are probably reliable estimates of the real effects of lisinopril in a large population of patients with moderate size myocardial infarction. The large number of participating centres and the peripheral analysis of 2-D echocardiograms may have increased within- and between-patient variability, as shown by quality control results. In fact, quality control analysis showed that: (a) there was a good agreement between observers (i.e. the mean of the differences was always around zero), (b) the differences were not related to the mean value of the variable itself (no transformation of the data was
needed), and (c) the confidence intervals of the differences were relatively large (i.e. a considerable random variability was present, as expected from analyses performed in 200 different Cardiology Centres).

The differences found in the GISSI-3 echocardiographic study were of the same order of magnitude or slightly smaller than those observed in the three largest studies published up to now, SAVE[29], CONSENSUS II[28], and the SOLVD echocardiographic substudy[25], where patients were treated for long periods of time (i.e. 4 months to 3 years).

The SAVE echocardiographic study included 512 myocardial infarction patients at baseline and 420 survivors at one year follow-up and the absolute difference of end-diastolic and end-systolic areas between captopril and placebo was around 3 cm$^2$ at one year[29]. However, despite this small absolute difference in left ventricular size, attenuation of left ventricular enlargement was associated to a reduction of adverse cardiovascular events after myocardial infarction.

In the 428 patients considered by the CONSENSUS II Multi-Echo Study Group[28], the absolute difference in left ventricular end-diastolic volume index between enalapril and placebo was around 3 ml m$^{-2}$ at 6 months after myocardial infarction. The CONSENSUS II trial, however, showed that early administration of intravenous enalapril to all eligible patients with myocardial infarction followed by oral enalapril, did not improve survival during the 180 days after the index event[28], even though left ventricular dilation was attenuated by enalapril.

The SOLVD echocardiographic substudy, although not specifically dealing with post-myocardial infarction patients, showed differences at 4 months of about 10 ml in end-diastolic volumes when enalapril was compared to placebo in patients with congestive heart failure, mostly of cardiac ischaemic origin[25].

A study on 99 haemodynamically stable patients, at risk for left ventricular dilatation treated with captopril between 6 and 24 h after onset of symptoms of myocardial infarction, showed a significant and progressive reduction of left ventricular enlargement over 12 months. Our time course of an effect by lisinopril (given for only 1-5 months) on left ventricular volumes, although less marked, is comparable to that observed by these authors[26]. Other studies have shown by 2-D echocardiography that ACE inhibition attenuates left ventricular enlargement after myocardial infarction[20–24,27]. In general, smaller studies tended to report greater effects, possibly due to patient selection and to a more controlled data collection (i.e. monocentric studies vs multicentric).

In the GISSI-3 echo study population, infarct size, as assessed by wall motion asynergy, was relatively small with a median of 18%. This infarct size index is smaller than that observed at pre-discharge examination in the GISSI-1 echocardiographic study, testing streptokinase vs conventional treatment, which ranged from 20% in the treated group to 24% in the controls[34]. This relatively small wall motion asynergy was probably related to the large use of the recommended treatments.
in the acute phase (i.e. thrombolysis, aspirin and beta-blockade), and to the lower severity of the disease in the GISSI-3 population.

Interestingly, spontaneous reduction of wall motion asynchrony was also observed during follow-up, independently of lisinopril treatment. These results suggest late recovery of stunned and/or hibernated myocardium and confirm in a large population experimental data[43] and recent clinical observations made in selected patients[44,45].

The beneficial effects on left ventricular volumes shown in GISSI-3 after early, short-term treatment with lisinopril do not fully explain the significant 11% reduction in mortality, which occurred mostly in the first week of treatment, before any echo measurement had been performed[45]. The early mortality reduction by ACE inhibitors has now been confirmed by other trials[18,19] besides GISSI-3. Probably, other mechanisms (e.g. reduction of neurohumoral activation, early reduction of infarct expansion not measurable with an index such as wall motion asynchrony) can explain this early benefit[46]. Indeed, the reduction in left ventricular volumes was observed in a subpopulation of low-risk patients, survivors at 6 months. Similar findings have been reported by CONSENSUS II, for example, where enalapril did not reduce overall mortality.

In conclusion, our results support the contention that a predischarge 2-D echocardiographic study should be performed systematically in all patients with myocardial infarction, both for prognostic stratification and for the selection of patients for whom a more prolonged ACE inhibitor treatment is recommended.

Left ventricular enlargement was significantly prevented by 6-week lisinopril treatment. Accordingly, early lisinopril treatment given for 6 weeks to all eligible patients with myocardial infarction could be considered as a part of a systematic strategy of prevention of post-infarction left ventricular remodelling[46].

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References

**Appendix**

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