

# Effects of Angiotensin-Converting Enzyme Inhibition With Perindopril on Left Ventricular Remodeling and Clinical Outcome

## Results of the Randomized Perindopril and Remodeling in Elderly With Acute Myocardial Infarction (PREAMI) Study

The PREAMI Investigators\*

**Background:** Angiotensin-converting enzyme inhibitors reduce mortality and remodeling after myocardial infarction in patients with left ventricular dysfunction.

**Methods:** Perindopril and Remodeling in Elderly With Acute Myocardial Infarction (PREAMI), a double-blind, randomized, parallel-group, multicenter, placebo-controlled study, determined whether similar benefits occur in elderly postinfarction patients with preserved left ventricular function. A total of 1252 patients 65 years or older with a left ventricular ejection fraction of 40% or higher and recent acute myocardial infarction were randomized to receive perindopril erbumine or placebo (8 mg/d) for 12 months. The combined primary end point was death, hospitalization for heart failure, or left ventricular remodeling. Secondary end points included cardiovascular death, hospitalization for reinfarction or angina, and revascularization.

**Results:** The primary end point occurred in 181 patients (35%) taking perindopril and 290 patients (57%) taking placebo, with a significant absolute risk reduc-

tion of 0.22 (95% confidence interval, 0.16 to 0.28;  $P < .001$ ). A total of 126 patients (28%) and 226 patients (51%) in the perindopril and placebo groups, respectively, experienced remodeling. The mean increase in left ventricle end-diastolic volume was 0.7 mL with perindopril compared with 4.0 mL with placebo ( $P < .001$ ). In the perindopril group, 40 deaths (6%) and 22 hospitalizations (4%) for heart failure occurred, whereas 37 deaths (6%) and 30 hospitalizations (5%) occurred in the placebo group. Treatment did not affect death, whereas the hospitalization rate for heart failure was slightly reduced (absolute risk reduction, 0.01; 95% confidence interval, -0.01 to 0.02). No treatment effect on other secondary end points was detected.

**Conclusion:** We found that 1-year treatment with 8 mg/d of perindopril reduces progressive left ventricular remodeling that can occur even in the presence of small infarct size, but it was not associated with better clinical outcomes.

*Arch Intern Med.* 2006;166:659-666

**A**CUTE MYOCARDIAL INFARCTION (AMI) leads to progressive changes in ventricle size, shape, and function, a process often referred to as remodeling.<sup>1</sup> Quantitative 2-dimensional echocardiography (ECHO) provides useful information on the temporal sequence of remodeling that, together with age, is the strongest indicator of poor prognosis.<sup>2</sup>

Studies on long-term angiotensin-converting enzyme (ACE) inhibition documented effective prevention of left ventricular (LV) remodeling in patients with LV dysfunction,<sup>2-5</sup> whereas only moderate effects occurred in patients with normal or abnormal LV function.<sup>1,6</sup> These studies included mainly relatively young patients with LV dysfunction; however, patients with AMI and preserved LV function admitted to in-

ternal medicine departments (approximately 40% of the hospital admissions for AMI) are more often older than 65 years<sup>7-9</sup> (**Table 1**). Thus, little direct evidence exists for this important subset of AMI patients, who are at higher risk of cardiovascular morbidity and mortality. Because of this gap in our knowledge, these patients may be less likely to receive a potentially valuable treatment (eg, thrombolytic agents or other interventions).<sup>10,11</sup> This patient population was studied in the Perindopril and Remodeling in Elderly With Acute Myocardial Infarction (PREAMI) study, which was designed to test whether ACE inhibition with 8 mg/d of perindopril erbumine in elderly patients with AMI and preserved LV function would attenuate remodeling and reduce the occurrence of heart failure (HF) and death.

\*Author: The author for the PREAMI Investigators is Roberto Ferrari, MD, PhD.

Group Information: The PREAMI Investigators and their affiliations are listed at the end of this article.

**Table 1. Most Representative Echocardiographic Studies in Patients With AMI and Left Ventricular Remodeling**

| Study                     | Mean Age, y | Treatment                    | No. of Patients | Interval Between AMI and Start of Treatment | Follow-up | Mean EF at Baseline, % | Mean % Increase of LVEDV During Follow-up | Difference in LVEDV Increase Between Drug and Placebo |
|---------------------------|-------------|------------------------------|-----------------|---|-----------|------------------------|---|---|
| CONSENSUS II <sup>6</sup> | 66          | Enalapril maleate, 20 mg     | 428             | 5 d   | 6 mo      | 45                     | 7.7                                       | 2 mL/m <sup>2</sup>                                   |
| SAVE <sup>2</sup>         | 59          | Captopril, 150 mg            | 512             | 11 d  | 2 y       | 31                     | 2.0                                       | 3 cm <sup>2</sup> *                                   |
| SOLVD <sup>3</sup>        | 59          | Enalapril maleate, 10 mg     | 301             | 1 mo  | 1 y       | 29                     | 2.8                                       | 9 mL  |
| GISSI-3 <sup>1</sup>      | 59          | Lisinopril, 10 mg, ± nitrate | 6405            | 24 h  | 6 mo      | 47                     | 1.4                                       | 0.7 mL  |
| FAMIS <sup>4</sup>        | 60          | Fosinopril sodium, 20 mg     | 285             | <9 h  | 2 y       | 50                     | 10.8                                      | 2.2 mL/m <sup>2</sup>                                 |
| VALIANT <sup>5†</sup>     | 63          | Captopril, 50 mg             | 204             | 5 d   | 20 mo     | 39                     | 2.1                                       | NA  |

Abbreviations: AMI, acute myocardial infarction; CONSENSUS, Cooperative New Scandinavian Enalapril Survival Study; EF, ejection fraction; FAMIS, Fosinopril in Acute Myocardial Infarction Study; GISSI-3, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; LVEDV, left ventricular end-diastolic volume; NA, not applicable; SAVE, Survival and Ventricular Enlargement; SOLVD, Studies of Left Ventricular Dysfunction; VALIANT, Valsartan in Acute Myocardial Infarction.

\*Left ventricular end-diastolic cavity area.

†Only patients treated with captopril.

## METHODS

### STUDY DESIGN

The design of the trial has been described previously.<sup>12</sup> The PREAMI study is a double-blind, randomized, parallel-group, multicenter study comparing perindopril with placebo in patients 65 years or older who survived an AMI (defined according to the recommendation of the American College of Cardiology and European Society of Cardiology, as reported in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI-3] study)<sup>13</sup> with preserved ejection fraction ( $\geq 40\%$ ) and optimal apical 4- and 2-chamber views of the LV recorded for at least 5 complete cardiac cycles. Ethics committees of the participating centers gave their approval. All patients gave their written informed consent, and the principles of the Declaration of Helsinki were applied. Exclusion criteria included (1) severe HF (New York Heart Association class IV and need for intravenous inotropic support); (2) coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; (3) severe hypotension (systolic arterial pressure  $\leq 100$  mm Hg); and (4) serum creatinine level greater than 2.0 mg/dL ( $>176.8$   $\mu\text{mol/L}$ ).

The primary end point was a composite of (in hierarchical order) death, hospitalization for HF, and LV remodeling (considered as  $\geq 8\%$  increase in LV end-diastolic volume [LVEDV] measured by ECHO). Secondary end points included the primary objective considered separately, an increase in LVEDV (considered as a quantitative variable), cardiovascular death, hospitalization for reinfarction or angina (documented by symptoms and electrocardiographic signs), and incidence of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

The centralized randomization was performed at a mean  $\pm$  SD of  $11 \pm 4$  days from AMI. The randomization code was previously developed using a computer random-number generator to select random permuted blocks (fixed length of 4 without stratification). Patients were allocated at a ratio of 1:1 to receive either perindopril or placebo at an oral dose of 2 mg on the day of randomization, 4 mg on the day after and for 1 month, and then 8 mg until month 12. If this dose was not tolerated, it could be reduced to 4 mg/d. Angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists,  $\alpha$ -blockers, and any inotropic drug (apart from digoxin) were prohibited unless acute conditions required their administration. In the following 12-month follow-up phase, 5 visits were performed (at months 1, 3, 6, 9, and 12). At each visit, blood pressure, heart rate, physical examination results, and information on con-

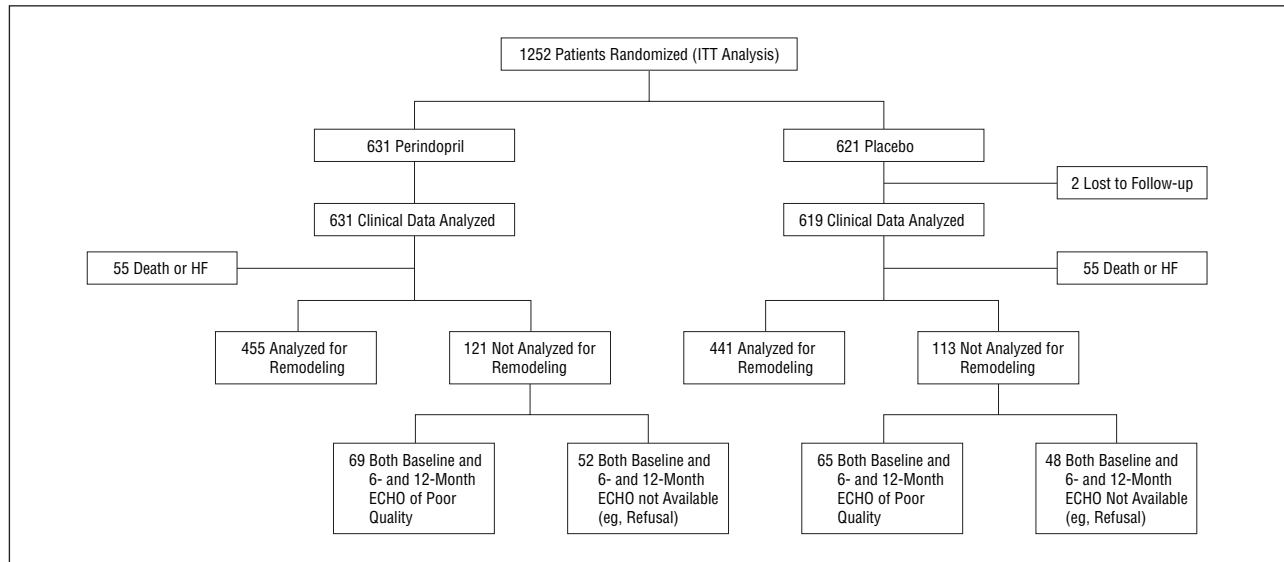
comitant therapy were recorded. Standard laboratory tests, electrocardiograms, and ECHO studies were performed before randomization and then at months 6 and 12.

### ECHO MEASUREMENT OF REMODELING

Two-dimensional ECHO studies were recorded on 0.5-in videotapes and submitted to a core laboratory for a centralized assessment of quantitative analysis after quality control. Wall motion (WM) asynergy analysis in a 16-segment model of the LV was performed using a semiquantitative visual grading system proposed by the American Society of Echocardiography.<sup>14</sup> The percentage of WM asynergy, as an index of the extent of ischemic damage, was obtained by dividing the number of akinetic, dyskinetic, and aneurysmal segments (segmental score  $\geq 3$ ) by the total number of evaluated segments.<sup>15,16</sup> Selected images were then digitized to obtain endocardial contours and LV cavity volumes at end diastole and end systole from 2 apical orthogonal views (4- and 2-chamber views). The modified Simpson rule was used to obtain biplane LV volumes, from which EF was derived using the standard formula.<sup>14,15</sup> All measurements were obtained in a blinded fashion by a single experienced operator from 3 cardiac cycles, and the mean values were considered for analysis.<sup>16</sup> The interobserver variability, measured by the intraclass correlation coefficient in 76 randomly selected patients (according to the approach of Donner et al<sup>17</sup> with  $\alpha = .05$  and a power of 80% to detect reliability  $>95\%$ ), was rather low (2.0%; 95% confidence interval [CI], 1.3%-3.1%; and 1.5%; 95% CI, 0.9%-2.3%; for LVEDV and LV end-systolic volume [LVESV], respectively), as was the intraobserver variability (1.0%; 95% CI, 0.7%-1.7%; and 0.7%; 95% CI, 0.5%-1.1%; for LVEDV and LVESV, respectively).

### SAMPLE SIZE

The expected rate of events in the control group was derived from the GISSI-3 study<sup>1</sup>: the available 6-month figures for mortality, hospitalization, and remodeling in patients older than 65 years were projected in a conservative way, considering 6.0%, 14.3%, and 29.5% for 12-month mortality, hospitalization for HF, and remodeling, respectively. According to the Moyé approach<sup>18</sup> and considering a 25% loss of follow-up or unreadable echocardiographic tapes, 1250 patients were needed for a 20% or greater relative reduction in the probability of occurrence of the primary end point at month 12 (1-tailed test), with 90% power and  $\alpha = .05$ .



**Figure 1.** Patient distribution. ECHO indicates echocardiography; HF, heart failure; and ITT, intention to treat.

## STATISTICAL ANALYSIS

We used the intention-to-treat principle applied to all randomized patients, considering the actual randomization code assigned. The primary end point was analyzed by the Moyé approach, which allows a combined evaluation of both the time-related (death or hospitalization for HF) and the fixed-time (remodeling) events.<sup>18</sup> This model provides for each group a score derived from the end point occurrence, their hierarchical order, and the time to occurrence of end point. The sum of the scores in the 2 treatment groups was compared by the Wilcoxon test.

For the separate analyses on death or HF, the event-free survival was estimated according to the Kaplan-Meier method and compared between the 2 treatment groups by the log-rank test.<sup>19</sup> The Cox regression model was used to evaluate the treatment effect, adjusting for different confounding or prognostic factors (sex and age, previous history of AMI, hypertension, diabetes, and other risk factors). For remodeling, logistic regression was performed. Moreover, an explorative analysis was performed to evaluate possible differences of the treatment in particular subgroups (the previously defined factors). For the analysis of ECHO parameters, a linear mixed model was adopted.<sup>20</sup> The statistical tests were 2-tailed and conducted at the .05 significance level using the statistical package R language (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### PATIENT POPULATION

Between September 18, 1998, and November 19, 2003, 1252 patients were randomized (631 to perindopril and 621 to placebo) from 109 centers in 5 European countries. Only 2 patients in the placebo group were lost to follow-up. Validated ECHO studies at prerandomization and during follow-up were obtained for 441 patients in the placebo group and 455 in the perindopril group (**Figure 1**). Mean  $\pm$  SD patient age was  $73 \pm 6$  years, and 436 (35%) were women. A total of 128 patients (10%) had a previous AMI, 39 (3%) had previous revascularization, 300 (24%) had diabetes mellitus, 728 (58%) had hypertension, and 357 (29%) had hyperlipidemia. A total

of 533 patients (43%) underwent thrombolysis, 479 (90%) within 6 hours of AMI. Infarct sizes were limited: mean  $\pm$  SD WM asynergy was  $13\% \pm 13\%$ , and creatine phosphokinase level was  $1243 \pm 1052$  U/L. The LV function was well preserved, with a mean  $\pm$  SD ejection fraction of  $59.1\% \pm 7.7\%$  and LVEDV and LVESV of  $80 \pm 23$  mL and  $34 \pm 14$  mL, respectively. No differences occurred in the baseline characteristics between the 2 groups (**Table 2**). The use of concomitant medications increased markedly after AMI and remained as such until the end of the study (**Table 3**).

A statistically significant difference occurred in blood pressure between the 2 groups after randomization: the values of systolic arterial pressure/diastolic arterial pressure were lower in the treated than in the placebo group (mean systolic arterial pressure/diastolic arterial pressure, 134/78 and 137/79 mm Hg, respectively) ( $P = .04$  and  $P = .004$  for systolic arterial pressure and diastolic arterial pressure, respectively). Heart rate did not change during the study. Treatment was well tolerated: at 1 year, 74% and 76% of patients assigned to perindopril and placebo, respectively, were taking study medication. Almost all patients assigned to perindopril erbumine were taking 8 mg/d, and only 6% had their dosages decreased to 4 mg/d at 1 year. Reasons for permanent treatment withdrawal are reported in **Table 4**.

### END POINTS

Perindopril induced a significant absolute risk reduction of 0.22 (95% CI, 0.16-0.28;  $P < .001$ ) in the combined primary end point (death, hospitalization for HF, or remodeling) (**Figure 2**) that occurred in 181 patients (35%) in the perindopril group and 290 (57%) in the placebo group (the relative risk reduction was 0.38 [95% CI, 0.29-0.46];  $P < .001$ ). A total of 126 patients (28%) and 226 patients (51%) in the perindopril and placebo groups, respectively ( $P < .001$ ), experienced remodeling (**Figure 3**). In the perindopril group, 40 deaths and 22 hospitalizations for HF (6% and 4%, respectively) occurred, whereas 37 deaths and 30 hospitaliza-

**Table 2. Baseline Characteristics\***

| Characteristic                                | Perindopril Erbumine<br>(n = 631) | Placebo<br>(n = 621) | P Value |
|---|-----------------------------------|----------------------|---------|
| Age, mean (SD), y                             | 72 (6)                            | 73 (5)               | .07     |
| Female sex                                    | 219 (35)                          | 217 (35)             | .95     |
| Weight, mean (SD), kg                         | 73 (11)                           | 72 (11)              | .57     |
| Body mass index,† mean (SD)                   | 27 (4)                            | 26 (4)               | .43     |
| Heart rate, mean (SD), beats/min              | 67 (10)                           | 67 (11)              | .87     |
| Systolic arterial pressure, mean (SD), mm Hg  | 126 (15)                          | 125 (14)             | .80     |
| Diastolic arterial pressure, mean (SD), mm Hg | 74 (9)                            | 74 (9)               | .19     |
| NYHA class                                    |                                   |                      | .18     |
| I   | 483 (77)                          | 501 (81)             |         |
| II  | 140 (22)                          | 112 (18)             |         |
| III   | 8 (1)                             | 7 (1)                |         |
| Wall motion asynergy, mean (SD), %            | 12 (13)                           | 13 (12)              | .30     |
| CPK release, mean (SD), U/L                   | 1249 (1058)                       | 1237 (1046)          | .85     |
| LVEDV, mean (SD), mL                          | 81 (23)                           | 79 (23)              | .23     |
| LVESV, mean (SD), mL                          | 34 (14)                           | 33 (14)              | .25     |
| Ejection fraction, mean (SD), %               | 59 (8)                            | 59 (8)               | .38     |
| Thrombolysis given                            | 272 (43)                          | 261 (42)             | .99     |
| Previous medical history                      |                                   |                      |         |
| Myocardial infarction                         | 66 (11)                           | 62 (10)              | .22     |
| Revascularization                             | 19 (3)                            | 20 (3)               | .82     |
| Stroke or transient ischemic attack           | 35 (6)                            | 42 (7)               | .15     |
| Heart failure                                 | 11 (2)                            | 7 (1)                | .18     |
| Peripheral vascular disease                   | 49 (8)                            | 37 (6)               | .40     |
| Hypertension‡                                 | 373 (59)                          | 355 (57)             | .44     |
| Diabetes mellitus                             | 157 (25)                          | 143 (23)             | .48     |
| Hyperlipidemia§                               | 175 (28)                          | 182 (29)             | .63     |
| Smoker  | 266 (42)                          | 256 (41)             | .98     |
| Current smoker                                | 122 (19)                          | 120 (19)             | .85     |

Abbreviations: CPK, creatine phosphokinase; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.

\*Data are presented as number (percentage) of patients unless otherwise indicated.

†Calculated as weight in kilograms divided by height in meters squared.

‡Known history of hypertension or receiving antihypertensive treatment.

§Known history of hyperlipidemia or receiving lipid-lowering therapy.

**Table 3. Concomitant Therapy**

| Therapy                  | Perindopril, %          |                        |                           | Placebo, %              |                        |                           |
|--------------------------|-------------------------|------------------------|---------------------------|-------------------------|------------------------|---------------------------|
|                          | Before AMI<br>(n = 631) | After AMI<br>(n = 631) | At 12 Months<br>(n = 528) | Before AMI<br>(n = 621) | After AMI<br>(n = 621) | At 12 Months<br>(n = 521) |
| Anti-thrombotics         | 19                      | 98                     | 94                        | 18                      | 98                     | 93                        |
| β-Blockers               | 13                      | 70                     | 65                        | 11                      | 72                     | 66                        |
| Lipid-lowering agents    | 10                      | 49                     | 54                        | 10                      | 52                     | 56                        |
| Nitrates                 | 13                      | 82                     | 64                        | 13                      | 82                     | 65                        |
| Calcium channel blockers | 21                      | 19                     | 27                        | 25                      | 22                     | 32                        |
| Diuretics                | 17                      | 28                     | 28                        | 15                      | 26                     | 26                        |
| ACE inhibitors*          | 24                      | 77                     | 8                         | 24                      | 79                     | 8                         |

Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction.

\*ACE inhibitors were withdrawn at least 24 hours before randomization.

tions for HF occurred in the placebo group (6% and 5%, respectively). Death was not affected by treatment, whereas the hospitalization rate for HF only slightly decreased (absolute risk reduction, 0.01; 95% CI, -0.01 to 0.02).

The mean increase in LVEDV was higher in the placebo than in the perindopril group (mean difference in LVEDV from month 12 vs prerandomization assessment, 4.0 vs 0.7 mL;  $P < .001$ ) (Figure 3). In the placebo

group, the main increase in LVEDV occurred within 6 months after AMI (3.4 mL), with a further increase of 0.6 mL thereafter. Hypertension was the most interesting significant predictor of LV remodeling (odds ratio, 1.4; 95% CI, 1.0-1.9;  $P = .05$ ).

The other secondary end points, such as cardiovascular death, hospitalization for subsequent AMI or angina, or revascularization, were infrequent and not modi-

**Table 4. Reasons for Permanent Treatment Withdrawal**

| Reason               | Perindopril, %<br>(n = 631) | Placebo, %<br>(n = 621) |
|----------------------|-----------------------------|-------------------------|
| Cough                | 1.6                         | 0.5                     |
| Study end points     | 9.0                         | 8.0                     |
| Other adverse events | 1.9                         | 2.6                     |
| Refusal to continue  | 12.0                        | 11.6                    |
| Other reasons        | 0.6                         | 1.3                     |
| <b>Total</b>         | <b>25.2</b>                 | <b>24.0</b>             |

fied by treatment (64 [5.1%], 142 [11.3%], and 148 [11.8%], respectively). Combined analysis of the most important cardiovascular events (ie, cardiovascular death, hospitalization for HF, stroke, and subsequent AMI [73 (12%) and 83 (13%) in the perindopril and placebo groups, respectively]) showed an absolute risk reduction of 0.01 (95% CI, -0.01 to 0.04;  $P = .37$ ). The beneficial effect of perindopril on remodeling was consistent across all predefined subgroups (**Figure 4**).

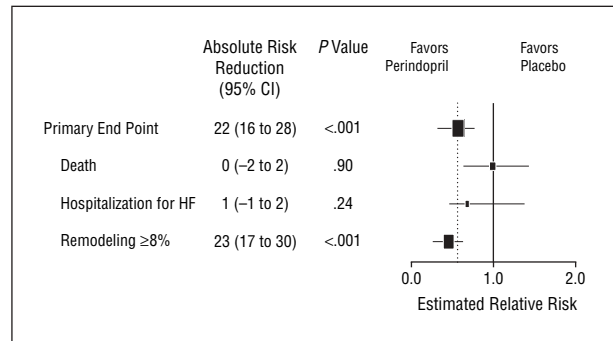
### COMMENT

The results of the PREAMI study generate novel pathophysiologic and therapeutic information. On pathophysiologic grounds, in elderly post-AMI patients, progressive LV remodeling can occur even in the presence of small infarct sizes. Administration of 8 mg/d of perindopril erbumine for 12 months (which was well tolerated despite the advanced age of the patients) led to a highly significant absolute risk reduction ( $>0.20$ ) in the combined primary end point. This result was due to LV remodeling reduction.

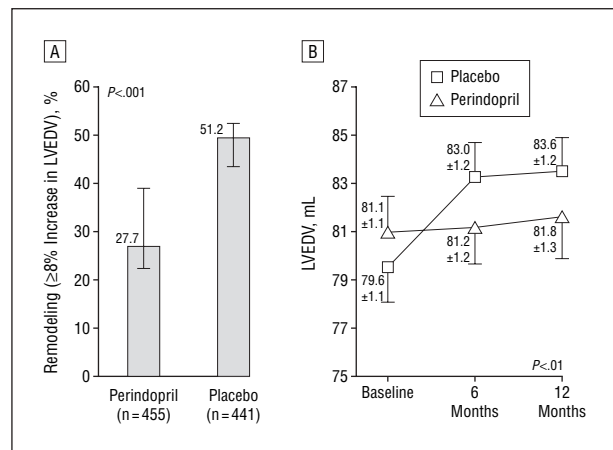
Advanced age appears to be an important determinant for LV remodeling. Despite normal prerandomization LV ejection fraction, the untreated elderly post-AMI patients underwent progressive LV dilation of a magnitude similar to that reported in other studies that enrolled younger patients but with larger infarct areas and greater LV dysfunction.<sup>1-3,6</sup> In PREAMI, the absolute increases in LVEDV in the placebo group were 3.4 and 4.0 mL at 6 and 12 months, respectively. These findings provide the first prospectively generated data on this topic.

The largest available data set on LV remodeling in post-AMI patients derives from the GISSI-3 trial, which involved more than 6000 patients younger than 65 years. Only patients with WM asynergy of 27% or greater underwent remodeling (with a mean increase in LVEDV of approximately 4.5 mL, which was reduced by lisinopril). Notably, the authors concluded that LV remodeling is mainly seen in at least moderate-sized AMI.<sup>1</sup> The mean WM asynergy index of the PREAMI patients was rather small (only 12.5%), probably due to widespread use of recommended treatments in the acute phase and to the strict selection criteria of the study. At the same time, the PREAMI patients were much older (mean age, 73 years). Thus, advanced age appears to be a major determinant for LV remodeling, in addition to and after the size of the infarcted area.

On therapeutic grounds, PREAMI shows that perindopril in this elderly population attenuates LV dilation. Re-



**Figure 2.** Effect of treatment on primary end point. Size of squares is proportional to the number of patients in that group. Dashed line indicates overall relative risk. CI indicates confidence interval; HF, heart failure.

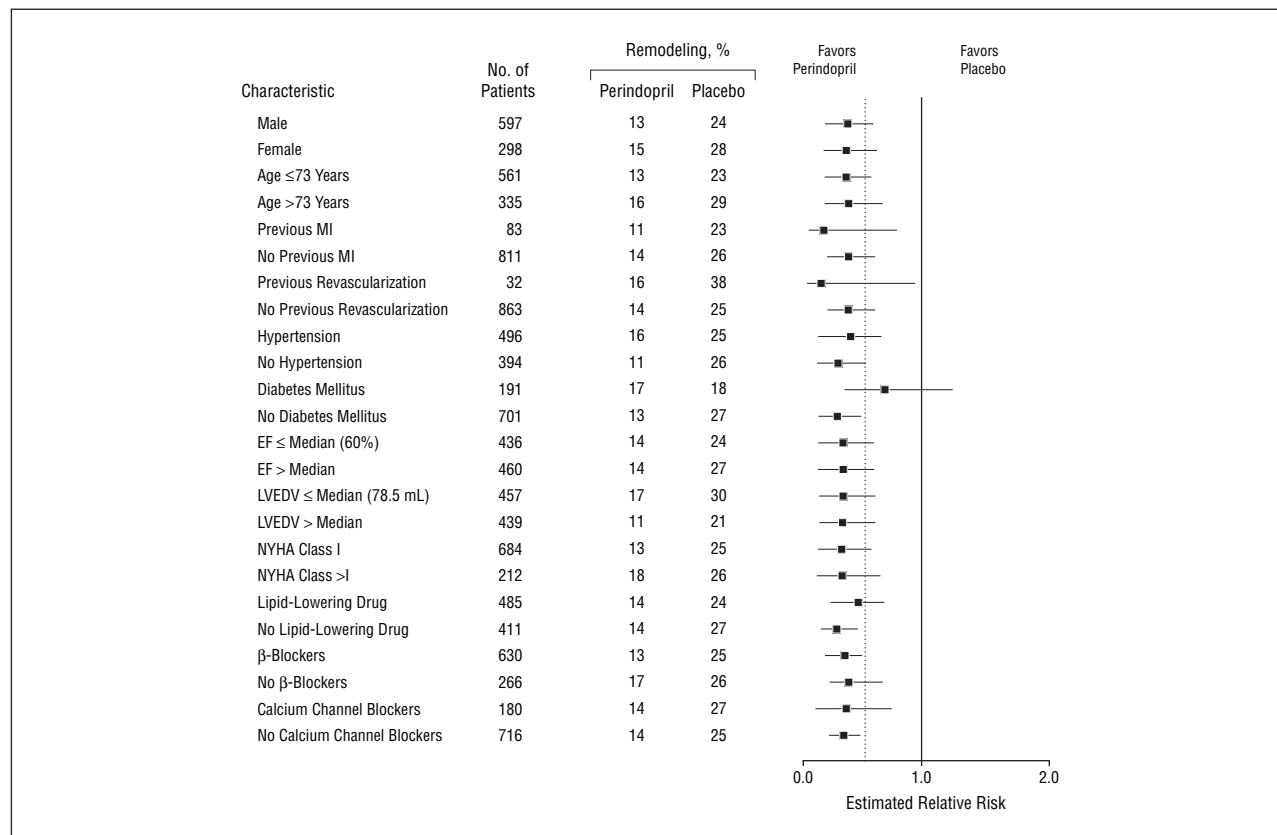


**Figure 3.** Remodeling and left ventricular end-diastolic volume (LVEDV) over time in the 2 groups. A, The LVEDV values are given as mean with standard error (error bars). B, Remodeling was assessed in 896 patients for whom baseline and either month 6 or month 12 echocardiography recordings were available. Remodeling values are given as percentages with 95% confidence intervals (error bars).

modeling occurred less frequently in the intervention arm (28% vs 51%). We defined remodeling as an 8% or greater increase in LVEDV. This definition is not an arbitrary assumption; previous data on ECHO studies (Table 1) suggest a mean 4% LVEDV increase after 6 months to 2 years of follow-up (in younger patients with impaired LV dysfunction). Assuming 4% variability in LVEDV measurements, we considered an increase of 8% or greater to be a suitably conservative cutoff limit; of note, both intraobserver and interobserver variability were rather low.

The difference in LVEDV increase between the placebo and perindopril arms observed in PREAMI (3.3 mL) was highly significant and consistent with that obtained in other studies, even in patients with LV dysfunction,<sup>2,3,6</sup> GISSI-3 included, in which patients with WM asynergy of 27% or greater were enrolled.<sup>1</sup> The greater effects reported in smaller studies can probably be attributed to more restricted patient selection and the more accurate data collection typical of single-center studies.<sup>21-23</sup> The antiremodeling effect of perindopril was responsible for the reduction in the combined primary end point, because mortality and HF hospitalization rates were similar in the 2 arms, as well as the secondary end points. This may be explained by the relatively low morbidity





**Figure 4.** Beneficial effect of treatment on remodeling in predefined subgroups. Dashed line indicates overall relative risk. EF indicates ejection fraction; LVEDV, left ventricular end-diastolic volume; MI, myocardial infarction; and NYHA, New York Heart Association.

and mortality rates in the current study owing to the well-conserved LV function (mean LV ejection fraction, 59%), optimized treatment (including ACE inhibitors after AMI), and the relatively short duration of treatment (12 months). Also in GISSI-3<sup>1</sup> and the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II),<sup>6</sup> no reduction in mortality was detectable despite beneficial effects of ACE inhibition in terms of maintenance of LV volumes. However, in the recent European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA),<sup>24</sup> administration of the same dose of perindopril erbumine (8 mg/d) for a mean duration of 3.7 years in a broad population of approximately 12 000 patients with stable coronary artery disease led to a reduction in the combined primary end point of cardiovascular death, nonfatal MI, and cardiac arrest with successful resuscitation. This effect became evident at 1 year, but differences between the event curves reached significance only after 3 years. Moreover, a subanalysis of EUROPA patients corresponding to the PREAMI population ( $\geq 65$  years, LV ejection fraction  $\geq 40\%$ , and previous AMI) demonstrated a significant relative risk reduction of 36.1% ( $P = .03$ ) for the primary EUROPA end point only after 3 years of treatment.

The mechanisms for the beneficial effects of perindopril on LV remodeling have yet to be defined. They might include reductions in ventricular wall stress, adverse neurohormonal stimulation, and myocardial ischemia. Interestingly, the Perindopril–Thrombosis, Inflammation, Endothelial Dysfunction, and Neurohormonal

Activation Trial,<sup>25</sup> a substudy of the EUROPA trial, has shown that perindopril reduces the rate of endothelial apoptosis. Increased myocyte apoptosis is an important biological component of remodeling, particularly in elderly patients.<sup>26,27</sup> All of these hypotheses are being explored in predefined substudies of PREAMI.

The effect of perindopril on remodeling occurred despite widespread use of  $\beta$ -blockers (71% at randomization), and no interaction occurred among treatments, suggesting that the intrinsic mechanisms of action of  $\beta$ -blockers and ACE inhibitors are complementary and not mutually exclusive. In HF trials, the effect of  $\beta$ -blockers on LV enlargement has been robust, with greater attenuation than in randomized studies with ACE inhibitors.<sup>28</sup>

#### STUDY LIMITATIONS

The choice of the sample size and duration of the PREAMI study resulted in a low rate of HF hospitalizations (4% recorded vs 14% anticipated). Larger and longer studies would be required to generate information on possible beneficial effects in terms of mortality and HF hospitalization.

#### CLINICAL IMPLICATIONS AND CONCLUSIONS

The PREAMI study partially fills the gap about optimal treatment of elderly patients with AMI and preserved LV function. Therefore, the results are of clinical relevance in this important subset of patients for whom therapeutic decision making is still equivocal and incompletely

defined in current practice guidelines.<sup>29</sup> In elderly patients with AMI, LV remodeling can occur despite small infarct size and optimized treatment. Addition of 8 mg/d of perindopril erbumine to optimized treatment counteracts progressive LV dilation. This regimen is well tolerated and might be considered as a standard treatment in this particular clinical setting.

**Accepted for Publication:** August 28, 2005.

**Correspondence:** Roberto Ferrari, MD, PhD, Department of Cardiology, Arcispedale S. Anna, University of Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy (fri@unife.it).

**Author Contributions:** The Steering Committee and the Statistical Committee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**PREAMI Committees:** *Steering:* R. Ferrari, MD, PhD (Chairman), Ferrara, Italy; M. Chiariello, MD, PhD, Naples, Italy; G. L. Nicolosi, MD, Pordenone, Italy; W. J. Remme, MD, PhD, Rhon, the Netherlands; L. Tavazzi, MD, Pavia, Italy. *Safety:* C. Rapezzi, MD (Chairman), Bologna, Italy; M. Scherillo, MD, Naples, Italy; M. G. Valsecchi, MSc, PhD, Milan, Italy. *Statistical:* A. Decarli, MSc, PhD (Chairman), Milan, Italy; G. Parrinello, MSc, PhD, Brescia, Italy. *End Point:* C. Ceconi, MD (Chairman), Ferrara, Italy; E. Pasini, MD, Gussago, Italy.

**PREAMI Investigators:** *Greece:* D. Cokkinos, MD, PhD, D. Kremastinos, MD, PhD, P. Toutouzas, MD, PhD, I. Nanas, MD, I. Fotiadis, MD, F. Kardaras, MD, I. Karidas, MD, P. Skoufas, MD, and I. Vassiliadis, MD, Athens; P. Vardas, MD, PhD, and G. Nikolaidis, MD, Iraklion; V. Pyrgakis, MD, Korinth; S. Fousas, MD, Piraeus; K. Papadopoulos, MD, PhD, Thessaloniki; S. Zobelos, MD, Kalamata; A. Tyrologos, MD, Kavala; and K. Siogas, MD, Ioanina. *Hungary:* A. János, MD, DSc, and A. Vértes, MD, Budapest; G. Veress, MD, CSc, Balatonfüred; P. Polgár, MD, PhD, Nyíregyháza; L. Nagy, MD, PhD, Szombathely; and M. Sereg, MD, Székesfehérvár. *Italy:* A. Battaglia, MD, Palermo; M. Mariani, MD, Pisa; S. Polimeno, MD, M. Chiariello, MD, PhD, M. Giasi, MD, N. Mininni, MD, and B. Trimarco, MD, Naples; A. Boccanelli, MD, F. Barilla, MD, F. Fedele, MD, and E. Giovannini, MD, Rome; G. D'Angelo, MD, Oliveto Citra; C. Brunelli, MD, Genoa; E. Capponi, MD, Gubbio; A. Capucci, MD, Piacenza; S. Ceravolo, MD, Bergamo; G. Corsini, MD, Caserta; J. Dalle Mule, MD, and M. C. Brunazzi, MD, Pieve di Coriano; I. De Luca, MD, Bari; P. Delise, MD, Feltre; G.B. Braschi, MD, Trapani, A. Giordano, MD, Gussago; G. Giuffrida, MD, Catania; R. Leghissa, MD, Imola; S. Mandorla, MD, Perugia; E. Renaldini, MD, Manerbio; A. Zoni, MD, Parma; M. Orlandi, MD, Lodi; G. Tartarini, MD, Pontedera; P. Pascotto, MD, Mirano; R. P. Dabizzi, MD, Prato; W. Pitscheider, MD, Bolzano; M. Polimeni, MD, Polistena; C. Rapezzi, MD, Bologna; L. Di Leo, MD, Salerno; A. Raviello, MD, Mestre; G. Rosato, MD, Avellino; G. Rovelli, MD, Rho; M. Sanguinetti, MD, Lugo; A. Sanna, MD, Cagliari; N. Moio, MD, Pozzuoli; L. Tavazzi, MD, Pavia; F. Valagussa, MD, Monza; G. Finocchi, MD, Vicenza; G. Risica, MD, Venice; G. L. Nicolosi, MD, Pordenone; E. Bellone, MD, Pinerolo; L. Scarpino, MD, Gorizia; P. Terrosu, MD, Sassari; C. Rusconi, MD, Brescia;

S. Paparoni, MD, Teramo; F. Bacca, MD, Lecce; S. Mangiameli, MD, Catania; G. Ferrari, MD, Como; N. Picchione, MD, Firenze; C. A. Generali, MD, Urbino; and R. Ferrari, MD, PhD, Ferrara. *Romania:* I. Bruckner, MD, PhD, M. Dorobanțu, MD, PhD, M. Cintează, MD, PhD, and A. Ioan, MD, PhD, Bucharest; R. Căpăneanu, MD, PhD, and N. Olinic, MD, PhD, Cluj; G. Georgescu, MD, PhD, and M. Datcu, MD, PhD, Iași; D. D. Ionescu, MD, PhD, Craiova; I. Manițiu, MD, PhD, Sibiu; K. Babeș, MD, Oradea; E. Carasca, MD, PhD, and A. Matei, MD, Târgu-Mureș; A. Tase, MD, Pitești; and B. Mănescu, MD, Brăila. *Spain:* J. M. Ayuela Azcárate, MD, Burgos; E. Simarro Martín, MD, PhD, Oviedo; J. Olagüe de Ros, MD, Valencia; F. Noriega Peiro, MD, PhD, Vigo; E. González Valencia, MD, PhD, Malaga; J. Caparrós Valderrama, MD, and M. Martínez, MD, Seville; J. Bruguera Cortada, MD, Barcelona; L. Jodar Lorente, MD, Manresa; J. J. García Guerrero, MD, PhD, Badajoz; J. L. Blanco Coronado, MD, PhD, and R. Sola Casado, MD, Almeria; A. Amaro Cendón, MD, Santiago de Compostela; and C. Pascual, MD, Leon. **Study Organization:** Salvatore Maugeri Foundation IRCCS (Istituti di Ricovero e Cura a Carattere Scientifico [Healthcare and Research Scientific Institute]), Cardiovascular Research Center, Gussago, Brescia, Italy. *Data Management:* K. Papa, MSc. *Quality Assurance:* P. Bernocchi, MSc, PhD. *Secretarial Activities:* S. Brognoli, J. Gimbatti. **ECHO Substudy:** G. L. Nicolosi, MD (Chairman), Pordenone, Italy. *Core ECHO Laboratory:* Salvatore Maugeri Foundation IRCCS, Cardiovascular Research Center, Gussago, Brescia, Italy; S. Golcea, MD. *ECHO Quality Control:* G. La Canna, MD, Milan, Italy; D. Mele, MD, Ferrara, Italy.

**Financial Disclosure:** R. Ferrari, M. Chiariello, G. L. Nicolosi, W. J. Remme, and L. Tavazzi received honoraria from Salvatore Maugeri Foundation (Brescia, Italy) on behalf of the sponsor.

**Funding/Support:** This study was supported by Stroder, Florence, Italy, and Servier Italia, Rome, Italy.

## REFERENCES

- Nicolosi GL, Latini R, Marino P, et al; Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. 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. *Eur Heart J*. 1996;17:1646-1656.
- St John Sutton M, Pfeffer MA, Plappert T, et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction: the protective effects of captopril. *Circulation*. 1994;89:68-75.
- Greenberg B, Quinones MA, Koilpillai C, et al; SOLVD Investigators. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of the SOLVD echocardiography substudy. *Circulation*. 1995;91:2573-2581.
- Borghesi C, Marino P, Zardini P, et al; FAMIS Working Party. Post acute myocardial infarction: the Fosinopril in Acute Myocardial Infarction Study (FAMIS). *Am J Hypertens*. 1997;10:247S-254S.
- Solomon SD, Skali H, Anavekar NS, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. *Circulation*. 2005;111:3411-3419.
- Bonarjee VV, Carstensen S, Caidahl K, Nilsen DW, Edner M, Berning J; CONSENSUS II Multi-Echo Study Group. Attenuation of left ventricular dilatation after acute myocardial infarction by early initiation of enalapril therapy. *Am J Cardiol*. 1993; 72:1004-1009.
- Flather MD, Yusuf S, Kober L, et al; ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or

- left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet*. 2000;355:1575-1581.
8. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation*. 1998;98:2282-2289.
  9. Diller PM, Smucker DR, David B, Graham RJ. Congestive heart failure due to diastolic or systolic dysfunction: frequency and patient characteristics in an ambulatory setting. *Arch Fam Med*. 1999;8:414-420.
  10. Holmes DR Jr, White HD, Pieper HKS, Ellis SG, Califf RM, Topol EJ. Effect of age on outcome with primary angioplasty versus thrombolysis. *J Am Coll Cardiol*. 1999;33:412-419.
  11. Latini R, Nicolosi G, Maggioni AP, et al; GISSI-3 Investigators. The beneficial effect of lisinopril on left ventricular remodeling after a first myocardial infarction is modulated by age: the GISSI-3 Echo database [abstract]. *J Am Coll Cardiol*. 1996;27(2)(suppl 1):281A.
  12. PREAMI Investigators. PREAMI: Perindopril and Remodelling in Elderly with Acute Myocardial Infarction: study rationale and design. *Cardiovasc Drugs Ther*. 2000;14:671-679.
  13. GISSI-3 study protocol on the effects of lisinopril, of nitrates, and of their association in patients with acute myocardial infarction. *Am J Cardiol*. 1992;70:62C-69C.
  14. Schiller NB, Shah PM, Crawford M, et al; American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr*. 1989;2:358-367.
  15. Giannuzzi P, Temporelli PL, Bosimini E, et al. Heterogeneity of left ventricular remodeling after acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-3 Echo substudy. *Am Heart J*. 2001;141:131-138.
  16. Bosimini E, Giannuzzi P, Temporelli PL, et al. Electrocardiographic evolutionary changes and left ventricular remodeling after acute myocardial infarction: results of the GISSI-3 Echo substudy. *J Am Coll Cardiol*. 2000;35:127-135.
  17. Donner A, Eliasziw M. Sample size requirements for reliability studies. *Stat Med*. 1987;6:441-448.
  18. Moyé LA. Analysis of clinical trial involving a combined mortality and adherence dependent interval censored endpoint. *Stat Med*. 1992;11:1705-1717.
  19. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer*. 1977;35:1-39.
  20. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of diseases. *J Natl Cancer Inst*. 1959;22:719-748.
  21. Sharpe N, Murphy J, Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet*. 1988;1:255-259.
  22. Sharpe N, Smith H, Murphy J, et al. Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition. *Lancet*. 1991;337:872-876.
  23. Ambrosioni E, Borghi C, Magnani B. SMILE Pilot Study Working Party. Early treatment of acute myocardial infarction with angiotensin-converting enzyme inhibition: safety considerations. *Am J Cardiol*. 1991;68:101D-110D.
  24. European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (EUROPA). *Lancet*. 2003;362:782-788.
  25. Scientific Committee of the PERTINENT Sub-Study. PERTINENT—Perindopril-Thrombosis, Inflammation, Endothelial Dysfunction and Neurohormonal Activation Trial: a sub-study of the EUROPA study. *Cardiovasc Drugs Ther*. 2003;17:83-91.
  26. Nian M, Lee P, Khaper N, Liu P. Inflammatory cytokines and postmyocardial infarction remodeling. *Circ Res*. 2004;94:1543-1553.
  27. Baines CP, Molkentin JD. STRESS signaling pathways that modulate cardiac myocyte apoptosis. *J Mol Cell Cardiol*. 2005;38:47-62.
  28. Khattar RS. Effects of ACE-inhibitors and beta-blockers on left ventricular remodeling in chronic heart failure. *Minerva Cardioangiol*. 2003;51:143-154.
  29. Antman EM, Anbe DT, Armstrong PW, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation*. 2004;110:e82-e292.