Effects of the Early Administration of *Zofenopril* on Onset and Progression of Congestive Heart Failure in Patients With Anterior Wall Acute Myocardial Infarction

Claudio Borghi, MD, Ettore Ambrosioni, MD, and Bruno Magnani, MD, on behalf of the SMILE Study Investigators*

Chronic congestive heart failure (CHF) is a common disease responsible for a high mortality and morbidity whose clinical course can be improved by angiotensin-converting-enzyme (ACE) inhibition. However, limited data are available on the effects of ACE inhibitors on the onset and progression of CHF in patients with acute myocardial infarction (AMI). The present study was performed as a substudy of the Survival of Myocardial Infarction Long-term Evaluation trial and involved 1,146 patients with anterior wall AMI not undergoing thrombolysis with the exclusion of patients with prior history or clinical signs of CHF on admission. Patients were randomly allocated to treatment with zofenopril (7.5 to 30 mg twice daily) or placebo for a cumulative period of 6 weeks. The prevalence of CHF, either mild to moderate or severe, has been the main objective and has been evaluated 6 weeks and 1 year after AMI. The overall prevalence of CHF was not reduced by zofenopril after both 6 weeks and 12 months. Conversely the prevalence of severe CHF (1.6% vs 2.6%: risk reduction 55.5%; 95% confidence interval 9 to 63; p = 0.0325) and the combined occurrence of death or severe CHF (4.8% vs 8.2%: risk reduction 59%; 95% confidence interval 11 to 71; p = 0.024) were reduced after 6 weeks of treatment with zofenopril. Moreover, the percentage of patients experiencing a deterioration to severe CHF after 1 year was significantly reduced with zofenopril (11.0% vs 24.3%; p = 0.001). In conclusion, the early administration of zofenopril to patients with AMI attenuates the progression of the clinical symptoms of CHF and its clinical consequences, suggesting that ACE inhibitors should be regarded as a suitable strategy for the prevention and treatment of CHF in patients with AMI.

(Am J Cardiol 1996;78:317–322)

Limited data are available on the effects of the early administration of angiotensin-converting enzyme inhibitors (ACE) on the onset and progression of congestive heart failure (CHF) in patients with acute myocardial infarction (AMI) not selected on the basis of left ventricular function.[1] In the CONSENSUS II study[2] as well as in the recently published GISSI 3 and ISIS IV studies[3,4] the early administration of an ACE inhibitor to patients with AMI did not result in any sizeable clinical benefit to CHF. These studies, however, reported the results achieved in large, unselected populations of patients including many subjects with a very low risk of developing ventricular remodeling and CHF. Accordingly, it is appropriate to investigate the effects of ACE inhibitors (started within 24 hours of an AMI) in patients with high risk of cardiovascular events. Since an anterior location of AMI is often associated with a greater degree of ventricular dysfunction[5] and the worst outcome in terms of mortality and occurrence of CHF,[6] it seemed a reasonable proposition to test the efficacy of early ACE inhibition in preventing CHF in patients with anterior wall AMI. The research was planned as a substudy of the Survival of Myocardial Infarction Long-term Evaluation (SMILE) trial,[7] which primarily tested the ability of the early administration of zofenopril calcium to reduce the short- and long-term occurrence of major cardiovascular events in patients with anterior wall AMI with no thrombolytic treatment.

METHODS

The SMILE trial was a randomized, double-blind, placebo-controlled trial in 1,556 patients with AMI located anteriorly who were not eligible for thrombolytic treatment; they were enrolled at 154 centers in Italy (see Appendix). The study was conducted in agreement with the Declaration of Helsinki (Hong Kong Revision 1989) and was approved by the Institutional Review Board of the University of Bologna as well as by the local ethical committees when required. All the patients provided informed consent before randomization.

In the SMILE trial, patients of either sex, aged 18 to 80 years, were eligible for enrollment if (1) they presented to the intensive care unit within 24 hours from onset of typical chest pain associated with electrocardiographic signs of definite anterior wall myo-

From the Department of Internal Medicine and Department of Cardiology, University of Bologna, Bologna, Italy. This study was supported by a grant from Bristol-Myers Squibb Institute for Pharmaceutical Research, which was not involved in the acquisition or management of data and did not have access to unblinded information. Manuscript received December 11, 1995; revised manuscript received and accepted March 4, 1996.

Address for reprints: Claudio Borghi, MD, Clinica Medica 3°, Policlinico S. Orsola, Via Massarenti 9, 40138 Bologna, Italy.

*A list of the participants in the SMILE study are given in the Appendix.

TABLE 1 Comparability of Study Groups at Baseline

Variable	Placebo (n = 586)	Zofenopril (n = 560)
Mean age (yr) (mean ± SD)	64 ± 5	64 ± 4
Men/women (no., %)	433/153 (74/26)	403/157 (72/28)
Clinical history at admission (no., %)		
Previous myocardial infarction	83 (14)	78 (14)
Diabetes mellitus	119 (20)	110 (20)
Hypertension	239 (41)	224 (40)
Angina pectoris	190 (32)	178 (32)
Mean ± SD hours to hospitalization	9.2 ± 1	9.1 ± 1
Mean ± SD hours to randomization	14.9 ± 1	15 ± 1
Characterization of index MI (n, %)		
Q-wave	489 (83)	470 (84)
non–Q-wave	97 (17)	90 (16)
Medication use within 24 hours of randomization (no., %)		
Antiplatelets agents	334 (57)	308 (55)
β blockers	116 (20)	103 (18)
Calcium antagonists	67 (11)	61 (11)
Digoxin	8 (1)	9 (2)
Diuretics	53 (9)	50 (9)
Nitrates	258 (44)	245 (44)

MI = myocardial infarction.

cardial infarction, and if (2) they were unable to receive thrombolytic treatment because of late admission to unit or had individual contraindications to systemic fibrinolysis.[8,9]

Patients were excluded from the present evaluation if they had 1 of the following symptoms on admission: (1) clinical signs of CHF, (2) supine systolic blood pressure <100 mm Hg, (3) serum creatinine level >2.5 mg/dl, (4) previous history of CHF, (5) current treatment with ACE inhibitors, (6) contraindications to the use of ACE inhibitors, and (7) inability or refusal to give informed consent. All potentially eligible patients received standard therapy including analgesic agents, β blockers, nitrates, calcium antagonists, aspirin, inotropic drugs, diuretic agents, and anticoagulants as indicated.

The study drug, zofenopril calcium (Bristol Myers-Squibb Company, Princeton, New Jersey), is a new short-acting sulfhydryl-containing ACE inhibitor, prodrug ester analog of captopril. Its pharmacologic characteristics have been extensively reviewed[10,11] and the drug is safe and well tolerated.[12] Zofenopril actively inhibits circulating as well as cardiac and vascular converting enzymes,[10,11] with a substantial capacity to enhance coronary blood flow[13] and contractile function of stunned myocardium independently of prostaglandin metabolism.[14]

The patients were randomly assigned according to fixed blocks of treatment to receive zofenopril or placebo; the randomization procedure has been published elsewhere.[15] The initial dose of the study medication was 7.5 mg and was repeated after 12 hours if tolerated. The dose of 7.5 mg twice daily was maintained for a cumulative period of 2 days, and then progressively doubled to the final target dose of 30 mg twice daily if systolic blood pressure was >100 mm Hg and no signs or symptoms of hypotension occurred. Patients unable to tolerate the dose of 7.5 mg were withdrawn from the study. Patients were seen while they were in the hospital (7 to 15 days), after 4 weeks, and at the end of the double-blind treatment period (6 weeks ± 3 days) during which time they could be treated with any other drug except ACE inhibitors. On completion of the 6-week, double-blind period, the patients stopped taking study medications but continued their concomitant treatment for an average period of 48 ± 4 additional weeks when the occurrence of CHF was blindly evaluated. According to the study protocol, patients who developed CHF during the trial were initially treated with conventional therapy including digoxin, diuretics, and nitrates. If the symptoms of heart failure persisted, treatment with an ACE inhibitor was initiated.

The primary objective of this SMILE substudy was to investigate the 6-week occurrence of either mild to moderate or severe CHF in patients treated with zofenopril. The prospectively defined secondary end point was to investigate the prevalence of CHF after 1 year of follow-up in the same group of patients.

After randomization during the in-hospital period, mild to moderate CHF was defined by the presence of ≥3 of the following symptoms: third heart sound; bilateral pulmonary rales; radiologic evidence of pulmonary congestion (a score above grade II on the scale of Madsen et al[16]); or peripheral edema that improved after pharmacologic treatment (no ACE inhibitors). Severe CHF was defined by the need for an open-label treatment with an ACE inhibitor for the presence of mild to moderate CHF, despite concomitant administration of digoxin, diuretic agents, and vasodilators other than ACE in-

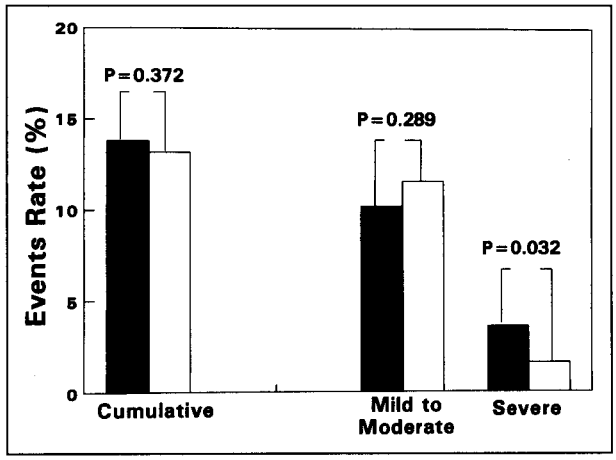

FIGURE 1. Six-week occurrence of various degrees of congestive heart failure in patients treated with placebo *(closed bars)* or zofenopril *(open bars).*

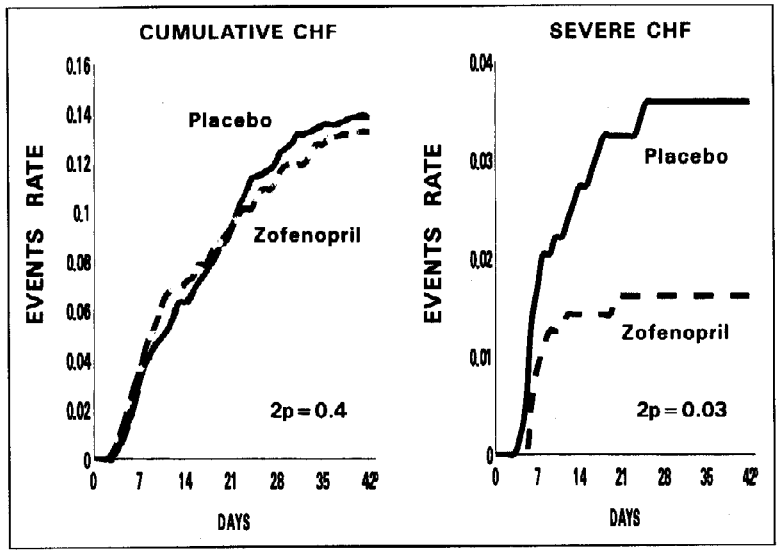

FIGURE 2. Curves showing the proportion of patients with cumulative or severe congestive heart failure (CHF) during the double-blind phase of the study. 2p = 2-tailed p value.

hibitors. During the follow-up phase of the study, symptoms of CHF were defined by the same cardiologist responsible for evaluating the patient during the double-blind phase of the trial and according to New York Heart Association functional classification.

Statistical analysis: The results of the study were analyzed by an independent data coordinating center, and no formal interim analysis was undertaken during the course of the trial. The difference in the cumulative prevalence of mild to moderate and severe CHF at 6 weeks was the main comparison between the 2 treatment groups. All analyses were performed on an intention-to-treat basis and p values were reported as 2-tailed. The comparability of baseline characteristics in the 2 treatment groups was ascertained by chi-square test for categorical variables (with Yates' continuity correction where appropriate) and a standard normal *t* test for continuous variables. The chi-square analysis was applied to data with the Mantel-Haenszel extension for comparisons between the 2 treatment groups. A p value <0.05 was considered statistically significant. Kaplan-Meier estimates for the distribution of time from randomization to event were computed both for cumulative and severe CHF. The log rank test was used for comparison of the 2 groups (zofenopril and placebo).

RESULTS

From January 1991 to November 1992, a population of 1,556 patients were enrolled in the SMILE trial from a total of 154 Italian coronary care units. From the initial patient population we excluded 410 subjects with clinical signs of CHF before randomization. In all, 1,146 patients were evaluated in this substudy and all of them have been followed-up according to the time schedule. There were 560 patients in the zofenopril group and 586 patients in the placebo group and both groups were comparable at baseline with regard to demographic characteristics, clinical data, and distribution of concomitant pharmacologic treatments (Table I).

Double-blind treatment: During the 6 weeks of double-blind treatment, clinical signs of CHF occurred in 81 of the 586 patients (13.6%) in the placebo group and in 74 of the 560 (13.2%) undergoing zofenopril treatment (Figures 1 and 2), and no difference was observed between the 2 groups. The number of patients with mild to moderate CHF was comparable even though a slight but not significant increase was observed in the group treated with zofenopril (65 patients; 11.6%) versus controls (60 patients; 10.2%). Conversely, the prevalence of severe CHF was significantly decreased in patients receiving ACE inhibition (Figures 1 and 2). Within the group of 30 patients (2.6%) who experienced a severe CHF, 9 (1.6%) were in the zofenopril group and 21 (3.6%) were in the placebo group, and this difference between groups was statistically significant (risk reduction 56%; 95% confidence interval 9 to 63; p = 0.0325). The lesser occurrence of severe CHF was associated with a trend toward a reduction in cumulative 6-week mortality (Figure 3) even though the figures did not allow any conclusion based on statistical inference. The beneficial effect of zofenopril administration was confirmed by data summarizing the 6-week combined occurrence of major cardiovascular events, i.e., death or severe CHF. In the group of patients actively treated with the zofenopril, the combined occurrence of death or severe CHF was reduced significantly compared with placebo (28 patients [4.8%] vs 48 patients [8.2%]; risk reduction 59%; 95% confidence interval 11 to 71; p = 0.024).

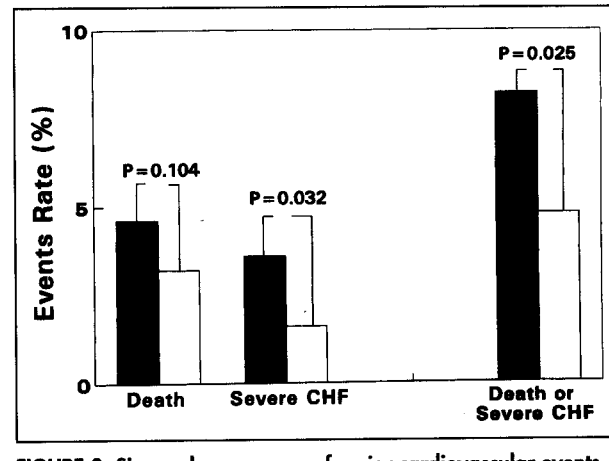

FIGURE 3. Six-week occurrence of major cardiovascular events (death or severe congestive heart failure [CHF]) in patients treated with placebo *(closed bars)* or zofenopril *(open bars).*

TABLE II Concurrent Treatments After Six Weeks of Double-Blind Treatment

Treatment	Placebo (n = 586)	Zofenopril (n = 560)
Digitalis	49 (8)	39 (7)
Diuretics	73 (12)	66 (12)
Calcium antagonists	65 (11)	66 (12)
β blockers	77 (13)	73 (13)
Aspirin	321 (55)	270 (53)
Nitrates	153 (26)	134 (24)
Vasodilators	10 (2)	7 (1)
Noncardiovascular drugs	56 (10)	62 (11)
Coronary angioplasty	27 (5)	25 (5)
Coronary bypass	16 (3)	12 (2)

Values are expressed as number (%).

With regard to concomitant pharmacologic treatment during the 6 weeks of double-blind treatment, the data are summarized in Table II. The clinical differences observed between the 2 groups of patients cannot be accounted for by differences in drug therapy or in the rate of surgical procedures.

Long-term observation: After 1 year of follow-up, the occurrence of clinical signs of CHF was not different between patients treated with zofenopril and those given placebo (Table III). However, by considering the 2 groups of patients according to the New York Heart Association classification, we observed a significant difference in the severity of CHF (Table III). Again, the differences between the 2 groups of patients cannot be explained in terms of differences in the concomitant pharmacologic and/or surgical treatment (Table IV). In particular, the use of open-label ACE inhibitors was not different between patients treated with zofenopril and those given placebo.

Concerning compliance with treatment, the percentage of patients taking their assigned study medication at the last study visit was similar in the placebo (78.1%) and the zofenopril group (77.3%; p = NS). Of these patients, 86.4% in the placebo group and 79.9% in the zofenopril group reached the target daily dose of 60 mg after randomization. Owing to the short period of follow-up and the marginal proportion of events, a small percentage of patients complained of adverse effects during the double-blind phase of the trial; none of the common adverse effects of ACE inhibitors were reported as significantly increased in patients treated with zofenopril.

TABLE III One-year Occurrence of Congestive Heart Failure and New York Heart Association Class Distribution in Patients Treated for Six Weeks With Placebo or Zofenopril

	Placebo (n = 586)	Zofenopril (n = 560)	p Value
Cumulative CHF	87 (15)	86 (15)	0.813
NYHA class			
I	2 (2)	7 (8)	0.021
II	41 (47)	46 (53)	0.128
III	24 (28)	23 (27)	0.743
IV	20 (23)	9 (11)	0.001
Total	87 (100)	86 (100)	

Values are expressed as number (%).
CHF = congestive heart failure; NYHA = New York Heart Association.

TABLE IV Concurrent Treatments During One Year of Observation

Treatment	Placebo (n = 586)	Zofenopril (n = 560)	p Value
Digitalis	40 (7)	44 (8)	0.223
Diuretics	76 (13)	75 (13)	0.715
ACE inhibitors	147 (25)	144 (26)	0.284
Calcium antagonists	92 (16)	114 (20)	0.124
β blockers	78 (13)	71 (12)	0.158
Aspirin	461 (78)	456 (81)	0.168
Nitrates	186 (32)	181 (32)	0.419
Anthiarrhythmic drugs	21 (4)	17 (3)	0.413
Noncardiovascular	53 (9)	58 (10)	0.201
Coronary angioplasty	38 (6)	41 (7)	0.780
Coronary bypass	34 (6)	40 (7)	0.959

Values are expressed as number (%).
ACE = angiotensin-converting enzyme inhibitors.

DISCUSSION

ACE inhibitors have been proven to be effective for the treatment of many cardiovascular diseases including arterial hypertension, heart failure, and acute myocardial infarction. The present study demonstrated that the early administration of zofenopril to patients with AMI can prevent the progression of CHF in patients with anterior wall AMI not undergoing thrombolysis. Our findings are largely in agreement with those reported by the SAVE study that reported a lesser rate of hospitalization for CHF and a reduction in mortality rate for CHF in patients with symptomless left ventricular dysfunction treated with captopril.[17] Moreover, the conclusions of the present study are also in keeping with the results of the prevention arm of the SOLVD study that demonstrates the capacity of enalapril to reduce the rate of development of CHF and to increase the median length of time to the development of CHF in asymptomatic patients with reduced left ventricular ejection fraction.[18] Importantly, our results were obtained without pretrial selection of patients according to baseline left ventricular function or individual drug tolerance, and this strategy gives a simple appraisal of the benefit of treatment with zofenopril and increases the relevance of the findings to normal clinical practice.

The reduced progression of CHF to the more severe stages we observed did not result from a proportional reduction in the cumulative prevalence of the disease (Figures 1 and 2). These findings do not agree with the conclusions of the SAVE and SOLVD prevention trials[17,18] that reported a reduction in the cumulative incidence of overt CHF in patients treated with ACE inhibitors, thus arguing that prophylactic therapy with these drugs can interfere with the natural history of CHF. The discrepancies between the various studies could be basically related to the characteristics of the study populations. Indeed, all the patients in SAVE and SOLVD studies

had evidence of left ventricular systolic disfunction at baseline and were therefore likely to have CHF eventually. In addition, most patients showed some clinical sign of CHF either at randomization (>30% of the patients in the SOLVD prevention arm were in New York Heart Association class II) or during the acute phase of the index AMI (about 40% of the patients in the SAVE trial were in Killip class >I during the in-hospital period). This could have increased the power of the treatment with ACE inhibitors to prevent the development of the clinical overt CHF. Conversely, in our study, we enrolled patients who did not undergo thrombolyis and were not selected because of left ventricular dysfunction, with the exclusion of those with a history or clinical signs of CHF. We speculate that in this group, the development of CHF could be primarily related to the initial loss of myocardial tissue, which can be unlikely modified in humans by therapeutic doses of ACE inhibitors. A further possible explanation for the dissimilarities between the present data and the findings of either SAVE or SOLVD could be in the duration of treatment with ACE inhibitors in the studies. In the SAVE and SOLVD trials, patients were actively treated for several years with ACE inhibitors, and this could have reduced the prevalence of cumulative CHF acting through a long-term prevention of the remodeling processes. Again, the failure to demonstrate a reduction in the overall prevalence of CHF in patients treated with zofenopril could be explained by the lesser mortality rate observed in this group of patients (Figure 3), and confirmed after 1 year of follow-up.[7] Interestingly, the absolute reduction in mortality observed after 6 weeks in patients treated with zofenopril strictly corresponded to the excess in the prevalence of mild to moderate CHF (+1.4%) in the same population (Figure 1). We speculate that the improved survival observed in patients undergoing the 6-week treatment with zofenopril may have increased the proportion of patients developing CHF, particularly during the first 2 weeks after randomization when the Kaplan-Meier curves for cumulative CHF (Figure 2) seem to suggest a trend toward a greater event rate in patients treated with zofenopril. This observation could be crucial for the interpretation of the studies evaluating the pharmacologic strategies aimed at preventing the development of CHF in patients with AMI. We suggest that a simple evaluation of the cumulative incidence of CHF may not be representative of the efficacy of the treatment with ACE inhibitors, unless it is interpreted according to concomitant data on mortality and severity of CHF. The same concept could also apply to the results of the other trials where acute administration of ACE inhibitors has not resulted in a significant reduction in cumulative prevalence of CHF.[2–4] In the present study, the combined occurrence of death and severe CHF is significantly reduced despite the lack of any significant reduction in the prevalence of cumulative CHF (Figure 3); thus, treatment with zofenopril must be regarded as a reasonable strategy for the treatment of patients with AMI, particularly when myocardial reperfusion with thrombolytic agents is not appropriate.

Acknowlegment: We are indebted to Professor Gianfranco Patrizi, MD, and Filiberto Claroni, MD, for their continuous research.

APPENDIX

The following persons and study centers participated in the SMILE study (names of participating hospitals are given in the parentheses). Albano Laziale (G. Ruggeri, L. Giamundo); Alessandria (P.A. Ravazzi, G. Taverno, M.C. Ferrara); Ancona I.N.R.C.A. (E. Paciaroni); Ancona "Lancisi" (A. Purcaro); Arienzo (V. Zucconelli); Avellino (D. Rotiroti); Bari (L. Colonna, C. D'Agostino, F. Bovenzi); Barletta (D. Messina, G. Deluca); Battipaglia (G. Mondillo); Belluno (P. Pellegrini, A. Da Rold, G. Soravia); Benevento (S. Lombardi): Bologna "Pizzardi" (D. Bracchetti, P.C. Pavesi, M. Mezzetti); Bologna "S. Orsola" (A. Branzi, G. Melandri); Bologna "Malpighi" (G. Di Biase); Borgosesia (M. Gronda, V. Magnano); Breno (G. Straneo, A.C. Tosin); Brescia (C. Rusconi, A. Gardini); Broni (L. Corradi, B. Albonico, R. Scabrosetti); Brindisi (A. Verrienti, A. Storelli); Busto Arsizio (V. De Petra, E. Cecchetti); Cagliari (A. Cherchi, C. Lai, E. Orani); Caltanisetta (C. Amico, A. Federico, F. Vancheri); Camposanpiero (A. Pantaleoni); Carpi (A. Merighi); Caserta (E. Correale, C. Chieffo, M. Catanzaro); Castelfranco Veneto (C. Cernetti, G.L. Suzzi, F. Canel); Castel Nuovo nè Monti (U. Guiducci, D. Molinari); Castellamare di Stabia (G. Pepe, E. Murena, L. De Vivo); Castrovillari (L. Vigna, C. Caluelli); Catania "S. Luigi Gonzaga" (A. Circo, S. Raciti, R. Bosco, F. Platania); Catania "Vittorio Emanuele II" (F. Casaccio); Catania "Cannizzaro" (A. Galassi, R. Coco, M. Franco); Catania "Garibaldi" (S. Mangiameli); Catanzaro (M. Primerano); Cava dei Tirreni (R. Della Monica); Cento (P. Alboni, F. Ippolito, M. Ribani); Cesena (P. Acito, D. Capelletti); Chiari (C. Bellet, G. Beghelli); Cinisello Balsamo (G. C. Maggi); Cittadella (P. Maiolino, U. Di Lio, A. Calvanese); Codigoro (L. Suriani, V. Di Chiara); Colleferro (S. Sonnino); Como (G. Ferrari); Copertino (G. De Rinaldis); Correggio (S. Signorelli, L. Lusetti); Cuneo (E. Uslenghi, F. Margaria); Desenzano del Garda (B. Lomanto, A. Rossi); Desio (D. Riva, G. Iacuitti, G. Cattò); Domodossola (G. Tirella); Eboli (F. Giovine); Faenza (A. Maresta, L. Pirazzini, F. Tani); Fano (F. Pupita); Ferrara (L. Codecà); Fidenza (L. Andreoli, A. Varacca); Firenze (F. Marchi, P. Battelli, L. Sabatini); Foggia (D. De Matteis, G. Maulucci); Foligno (L. Tini Brunozzi, R. Liberati, C. Pagnotta); Forlì (F. Rusticali, C. Simoni); Fossano (M. Radogna, M. Tallone, R. Conte, A. Airaldi); Fucecchio (A. Ieri, G. Fradella, A. Ferreri); Genova "S. Martino" (F. Basso, R. Delfino, E. Oldoino, G.L. Secchi); Genova "Università" (S. Caponnetto, M.P. Masperone, T. Carazza); Grosseto (T. Lanzetta, A. Cresti); Imola (C. Parchi); Lanciano (L. Di Guglielmo, G. Mastrogiuseppe); La Spezia (G. Ragazzini); Latina (B. De Pasquale); Lavagna (A. Bertulla, R. Bollini); Lecce (F. Bacca): Lecco (V. Locatelli, M. T. Savoia, M. Valsecchi); Legnano (S. Romano, T. Forzani, M. Pagani); Leno (G. Moretti, A. Lanzini, E. Bossoni); Livorno (P. Del Bene, M. Cascone); Lodi (M. Orlandi, A. Masa, G.F. Galloni); Lucca (G. Masini, L. Meli, M. Lazzari, R. Lorenzoni); Lugo (M. Sanguinetti, F. Tomassini); Magenta (A. Maggi, G. Bardelli, R. Ferraresi); Matera (L. Tantalo); Melegnano (G. Colombo, G. Bignamini); Mestre (E. Piccolo, F. di Pede, G. Turiano); Messina (G. Casella, L. Pavia, F. Casella); Messina (F. Consolo, F. Arrigo, M. Giannetto, A. Consolo); Milano (C. Belli, L. Oltrona Visconti, P.A. Merlini); Milano "Policlinico" (A. Lotto, A. Foresti, M. Lettino); Milano (L. Pozzoni, A. Lomuscio); Milano "Fatebenefratelli" (P. Sanna); Mirandola (A. Rigo, S. Pancaldi); Mirano (D. D'Este, P. Allibardi); Modena (G. Mattioli, A.V. Mattioli); Moncalieri (G. Lavezzaro); Monfalcone (M. Palmieri, P. Moratti); Monselice (G. Reffo); Montebelluna (R. Sandri, R. Zamprogno, G. Neri); Monterotondo (E. Checchi); Napoli (O. De Divitiis, S. Di Somma); Napoli (M. Condorelli, B. Trimarco); Napoli (G. Pucciarelli); Napoli (R. Santamaria, R. Spadaro); Nettuno (M. Mostacci, D. Banda); Palermo (G. Barone); Parma (G. Botti, A. Finardi, L. Morozzi); Pavia (C. Montemartini, A. Poli, A. Mussin); Perugia (L. Corea, M. Bentivoglio, G. Bardelli); Pescara (E. D'Annunzio, G. Materazzo); Pescia (L. Papi); Piacenza (U. Gazzola, M. Groppi, A. Rosi); Piazza Armerina (B. Aloisi, M. Farruggio, G. Baiunco); Piera Ligure (D. Sanfelici, V. Tarditi); Piove di Sacco (C. Martines); Pisa "C.N.R." (A. Biagini, R. Tongiani, M.T. Baratto, F. Paoli); Pisa (A. Bigalli, A. Boem, G. Del Carratore); Pistoia (F. Del Citerna, A. Giomi, E. Balli); Polla (T. Di Napoli); Pollena Trocchia (L. Filosa); Pordenone (D. Zanuttini); Porretta (M. Facci, A. Napoli, M. Ongari); Portomaggiore (G. Stabellini, F. Frabetti); Potenza (A. Rizzo); Prato (A. Petrella, L. Bardazzi); Ragusa (G. Licitra); Ravenna (G. Tumiotto, S. Bosi, B. Assirelli); Reggio Calabria (E. Adornato); Riccione (G. Baldacci, P. Del Corso); Rieti (A. De Sanctis, L. Bellagamba, L. Eleuteri, I. Marchese); Rho (G. F. Parenti, F. Ferrari); Roma (F. Ferri); Rossano Calabro (U. Striano, S. Saliturì); Rovigo (P. Zonzin, L. Roncon); Salerno (N. Cirillo, V. Paolillo, S. Angri-

sani); Salerno (B. Ravera, A. Gigantino, U. Bugatti); Sanremo (L. Anselmi); Sarteano (G. Giappichini, G. Bidi); Sassuolo (F. Pedrazzini, E. Bagni, V. Agnoletto); Savignano (M. Di Leo, G. Riva); Savona (E. Martinengo, G. Becchi, S. Varnero); Taranto (C. Montervino, F. Sacco, V. Leone); Teramo (F. Jacovoni, G. Speca, V. Ciampini, G. Marcellini); Termoli (D. Staniscia, A. Cimino); Thiene (F. Dal Prà); Torino (A. Brusca, L. Bergandi, S. Bergerone); Torino (P. Presbitero, B. Bianchini); Tricase (F. Leo, A. Galati); Trieste (F. Camerini, T. Morgera, L. Barbieri); Udine (G.A. Feruglio); Varese (G. Binaghi, A. Cozzi, F. Acquati, S. Caico); Verona (P. Zardini, G.P. Nidasio); Vibo Valentia (V. Rosano, B. Milano, C. Bianco, M. Comito); Vigevano (S. Nava, R. Villani); Viterbo (A. Achilli); Vittoria (G. Sciveres); Voghera (F. Nicrosini, G. Bergognoni, P. Gandolfi, C. Pasotti).

Policy and Safety Monitoring Board: A. Reale, G.A. Feruglio, J.W. Kennedy, A. Maseri.

Data Coordinating Center and Biostatistics: A. Bignamini, L. Peracino for Hyperphar-Milan-Italy.

Scientific Committee: G. D. Bompiani, F. Camerini, C. Dal Palù, P. F. Fazzini, G. Muiesan, P. L. Prati, P. Solinas, A. Zanchetti, P. Zardini.

Operations Group: S. Bacchelli, G. Botta, S. Collatina, D. Degli Esposti, S. Liberatore, L.J. Meinert, O.Y. Olukotun.

1. Borghi C, Bacchelli S, Degli Esposti D, Ambrosioni E. Early and late angiotensin-converting-enzyme inhibition in acute myocardial infarction. *Am J Cardiol* 1993;72:169G–174G.

2. Swedberg K, Held P, Kiekshus J, Rasmussen K, Ryden L, Wedel H, on behalf of the CONSENSUS II Study group. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. *N Engl J Med* 1992;327:678–684.

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

4. ISIS 4 Collaborative Group. ISIS 4: a randomised factorial trial assessing early oral captopril, oral mononitrates, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669–682.

5. Pye M, Oldroyd KG, Ray SG, Christie J, Ford I, Cobbe SM, Dargie HJ. Effects of early captopril administration on left ventricular dilatation after acute myocardial infarction (abstr). *Circulation* 1990;82(suppl III):III–674.

6. Stone PH, Raabe DS, Jaffe AS, Gustafson N, Muller JE, Turi ZG, Rutherford JD, Poole KW, Passamani E, Willerson JT, Sobel BE, Robertson T, Braunwald E, for the MILIS Group. Prognostic significance of location and type of myocardial infarction: independent adverse outcome associated with anterior location. *J Am Coll Cardiol* 1988;11:453–46.

7. Ambrosioni E, Borghi C, Magnani B, for the Survival of Myocardial Infarction Long-Term Evaluation Study Investigators. The effects of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995;332:80–85.

8. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS 1. *Lancet* 1988;2:349–360.

9. Gruppo Italiano per lo Studio della Streptokinasi nell'Infarto (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:397–402.

10. DeForrest JM, Waldron TL, Krapcho J, Turk C, Rubin B, Powell JR, Cushman DW, Petrillo EW. Preclinical pharmacology of zofenopril, an inhibitor of angiotensin I converting enzyme. *J Cardiovasc Pharmacol* 1989;13:887–894.

11. Cushman DW, Wang FL, Fung WC, Harvey CM, DeForrest JM. Differentiation of angiotensin converting enzyme (ACE) inhibitors by their selective inhibition of ACE in physiologically important target organs. *Am J Hypertens* 1989;2:294–307.

12. Ambrosioni E, Borghi C, Magnani B, for the 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.

13. Van Gilst WH, Scholtens E, De Graeff PA, De Langen CDJ, Wesseling H. Differential influences of angiotensin converting enzyme inhibitors on the coronary circulation. *Circulation* 1988;77(suppl I):1–24.

14. Westlin W, Mullane K. Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging free radicals? *Circulation* 1984;71(suppl I):I-30–1-39.

15. Ambrosioni E, Borghi C, Magnani B. Survival of Myocardial Infarction Long term Evaluation (SMILE) study: rationale, design, organization and outcome definitions. *Controlled Clin Trials* 1994;15:201–210.

16. Madsen EB, Gilpin E, Slutsky RA, Ahnve S, Henning H, Ross J Jr. Usefulness of chest x-ray for predicting abnormal left ventricular function after acute myocardial infarction. *Am Heart J* 1984;108:1431–1436.

17. Pfeffer MA, Braunwald E, Moyè LA Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992;327:669–677.

18. The SOLVD Investigators. Effects of enalapril on mortality and development of heart failure in asymptomatic patients with reduced ventricular ejection fraction. *N Engl J Med* 1992;327:685–691.