

THE EFFECT OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR ZOFENOPRIL ON MORTALITY AND MORBIDITY AFTER ANTERIOR MYOCARDIAL INFARCTION

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FOR THE SURVIVAL OF MYOCARDIAL INFARCTION LONG-TERM EVALUATION (SMILE) STUDY INVESTIGATORS*

Abstract *Background.* Left ventricular dilatation and neuroendocrine activation are common after acute anterior myocardial infarction. Long-term treatment with an angiotensin-converting-enzyme (ACE) inhibitor may improve outcome by attenuating these processes. We investigated whether the ACE inhibitor zofenopril, administered for six weeks after anterior myocardial infarction, could improve both short-term and long-term outcome.

Methods. A total of 1556 patients were enrolled within 24 hours after the onset of symptoms of acute anterior myocardial infarction, and they were randomly assigned in a double-blind fashion to receive either placebo (784 patients) or zofenopril (772 patients) for six weeks. At this time we assessed the incidence of death or severe congestive heart failure. The patients were reexamined after one year to assess survival.

Results. The incidence of death or severe congestive heart failure at six weeks was significantly reduced in the

zofenopril group (55 patients, 7.1 percent), as compared with the placebo group (83 patients, 10.6 percent); the cumulative reduction in the risk of death or severe congestive heart failure was 34 percent (95 percent confidence interval, 8 to 54 percent; $P=0.018$). The reduction in risk was 46 percent (95 percent confidence interval, 11 to 71 percent; $P=0.018$) for severe congestive heart failure and 25 percent (95 percent confidence interval, -11 to 60 percent; $P=0.19$) for death. After one year of observation, the mortality rate was significantly lower in the zofenopril group (10.0 percent) than in the placebo group (14.1 percent); the reduction in risk was 29 percent (95 percent confidence interval, 6 to 51 percent; $P=0.011$).

Conclusions. Treatment with zofenopril significantly improved both short-term and long-term outcome when this drug was started within 24 hours after the onset of acute anterior myocardial infarction and continued for six weeks. (N Engl J Med 1995;332:80-5.)

THE outcome of patients with acute myocardial infarction has been improved by the early administration of drugs such as thrombolytic agents, beta-blockers, and aspirin.¹⁻⁵ The use of angiotensin-converting-enzyme (ACE) inhibitors has also been reported to be beneficial in patients after acute myocardial infarction,^{6,7} and the benefit seems to be greatest in patients with congestive heart failure⁸ or asymptomatic ventricular dysfunction.^{9,10} Ventricular dysfunction is an important prognostic indicator after myocardial infarction.^{11,12} ACE inhibitors may function in part by affecting the process of ventricular remodeling.¹³ Recently, the third study by the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3)¹⁴ showed that early treatment with an ACE inhibitor reduced mortality at six weeks when given to a large, unselected population of patients with myocardial infarction. These results have been supported by preliminary data from the fourth International Study of Infarct Survival¹⁵ but not by the results of the second Cooperative New Scandinavian Enalapril Survival Study.¹⁶ We wanted to address the question of the efficacy of an ACE inhibitor in patients at high risk for death and congestive heart failure. We chose patients with anterior myocardial infarctions, because they often have a substantial degree of ventricular dysfunction¹⁷ and a worse outcome in terms of these events.¹⁸

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Accordingly, the Survival of Myocardial Infarction Long-Term Evaluation trial was planned to test the hypothesis that oral administration of an ACE inhibitor, zofenopril, to patients with acute anterior myocardial infarction who were not undergoing thrombolysis would improve their clinical outcome by reducing the incidence of major cardiovascular events. We were particularly interested in whether a short (six-week) course of drug therapy would have a sustained beneficial effect over the subsequent year.

METHODS

Organization of the Study

The study was a randomized, double-blind, placebo-controlled trial involving 1556 patients with acute anterior myocardial infarctions who were not eligible for thrombolytic therapy and who were enrolled at 154 centers in Italy (listed in the Appendix). The study was conducted in accordance with the Declaration of Helsinki (1989) and was approved by the institutional review board of the University of Bologna as well as by the local ethics committees when required. All the patients provided informed consent.

Recruitment of Patients

The enrollment phase of the trial began in January 1991 and ended in November 1992. Patients of either sex who were 18 to 80 years of age were eligible if they presented to the intensive care unit within 24 hours of the onset of chest pain typically associated with electrocardiographic signs of myocardial infarction of the anterior wall and if they were not eligible for thrombolytic therapy because of late admission to the intensive care unit or contraindications to systemic fibrinolysis.^{4,8}

Acute anterior myocardial infarction was considered to have occurred if the electrocardiogram showed progressive changes in the ST segments or T waves in at least two contiguous precordial leads with or without new abnormal Q waves. Patients were excluded from the study if they were in cardiogenic shock (Killip class 4) on admission, had a systolic blood pressure below 100 mm Hg (measured with the patient supine) on admission, had a serum creatinine concentration above 2.5 mg per deciliter (221 μmol per liter), had a history of

congestive heart failure, were being treated with ACE inhibitors, had contraindications to the use of ACE inhibitors, or were unable or unwilling to give informed consent. All potentially eligible patients received standard therapy including analgesic agents, beta-blockers, nitrates, calcium antagonists, aspirin, inotropic drugs, diuretic agents, and anticoagulants as indicated.

Randomization, Titration, and Follow-up

The study drug, zofenopril (Bristol-Myers Squibb, Princeton, N.J.), is a new short-acting ACE inhibitor that contains a sulfhydryl group and is an analogue of captopril; its characteristics have been extensively reviewed.¹⁹⁻²² The patients were randomly assigned with the use of fixed blocks to receive zofenopril or placebo, and the details of the randomization procedures have been published elsewhere.²³ The initial dose of medication was 7.5 mg. The dose was repeated after 12 hours and progressively doubled — as long as systolic blood pressure remained above 100 mm Hg and there were no signs or symptoms of hypotension — until the final target dose of 30 mg twice daily was reached. Patients who were unable to tolerate the dose of 7.5 mg were withdrawn from the study but included in the intention-to-treat analysis. Patients were seen while they were in the hospital (7 to 15 days), after 4 weeks, and at the end of the treatment period (mean, 6 weeks \pm 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 the study medications but continued treatment with their other medications for a mean of 48 \pm 4 additional weeks, at which time vital status was blindly evaluated. Vital status was determined by means of a questionnaire for 1249 patients and by family members, medical personnel, and registry offices for 307 patients.

End Points

The primary end point was the occurrence of death or severe congestive heart failure during the treatment period. The two were tabulated as a single event, according to which one occurred first.

Patients were considered to have severe congestive heart failure if after randomization they had at least three of the following: third heart sound, bilateral pulmonary rales, radiologic evidence of pulmonary congestion (a score above grade II on the scale of Madsen et al.),²⁴ or peripheral edema, despite the concomitant administration of digoxin, diuretics, and vasodilators other than ACE inhibitors and necessitating open-label treatment with an ACE inhibitor. Clinical signs of mild-to-moderate congestive heart failure during follow-up were categorized according to the New York Heart Association classification (I through IV).

The causes of death were classified by the principal investigators and reviewed by an end-points committee acting on the basis of a blinded review. All deaths occurring during the trial were classified as due to cardiac or noncardiac causes. Cardiac causes included progressive heart failure, sudden death, recurrent myocardial infarction, and cardiac rupture. Noncardiac causes included cerebrovascular events, pulmonary embolism, and nonvascular causes. Progressive heart failure was classified on the basis of pump failure and the occurrence of cardiogenic shock. Sudden death was defined as sudden, unexpected death occurring within one hour after the onset of new symptoms.

Secondary prospectively defined end points for the study included the effect of six weeks of treatment on the occurrence of clinical signs of mild-to-moderate congestive heart failure, nonfatal recurrent myocardial infarction, and angina, and cumulative one-year mortality.

Statistical Analysis

The study was planned to include 1500 patients on the basis of an expected mortality rate of 12 percent at six weeks and an expected rate of severe congestive heart failure of 5 percent in the placebo group, a 30 percent reduction in the occurrence of death or severe congestive heart failure in the zofenopril group as compared with the placebo group, a dropout rate of 1 percent, a statistical power of at least 80 percent, and a significance level of 5 percent (two-tailed test). The results were analyzed by an independent data-coordinating

center. No formal interim analysis was undertaken during the course of the trial. The cumulative prevalence of death or severe congestive heart failure at six weeks was the main outcome variable compared in the two treatment groups. All analyses were performed on an intention-to-treat basis, and all P values are two-tailed. For the comparison of the zofenopril and placebo groups with respect to end points, risk reductions and corresponding 95 percent confidence intervals were determined. The chi-square test with the Mantel-Haenszel extension was used for the comparisons between the two groups. Follow-up data collected after one year were analyzed according to the original group assignment. Life-table curves were calculated and the survival analysis was performed with the use of the Lee-Desu statistics for group comparisons.

RESULTS

From January 1991 to November 1992, a total of 20,261 patients were admitted to the 154 coronary care units in the study; 1556 patients were enrolled in the trial and randomly assigned to one of the treatment groups. The diagnosis of acute myocardial infarction was confirmed in 96.1 percent of the patients who underwent randomization; 3.6 percent had acute coronary syndromes, and the remaining 0.3 percent were given other diagnoses. The base-line clinical characteristics of the two groups of patients are shown in Table 1.

Primary Outcome Measures

During the six weeks of treatment, death or severe congestive heart failure occurred in 83 of the 784 patients in the placebo group (10.6 percent) and in 55 of the 772 patients in the zofenopril group (7.1 percent) (Fig. 1); the reduction in the risk of a major cardiovas-

Table 1. Characteristics of the Patients at Base Line, According to Treatment Group.

CHARACTERISTIC	PLACEBO GROUP (N = 784)	ZOFENOPRIL GROUP (N = 772)
Mean age (yr)	64.3	63.9
Age >70 yr (%)	31	29
Sex (%)		
Male	73	72
Female	27	28
Previous myocardial infarction (%)	13	13
History of diabetes (%)	21	20
History of hypertension (%)	40	39
Current smoker (%)	41	41
History of angina (%)	33	32
Mean hours to hospitalization	9	9
Mean hours to randomization	15	15
Killip class (%)		
1	86	85
>1	14	15
Characterization of index myocardial infarction (%)		
Q wave	52	53
ST elevation	65	67
Medication use within 24 hr of randomization (%)		
Antiplatelet agents	55	53
Beta-blockers	21	18
Calcium-channel blockers	10	10
Digitalis	6	7
Diuretics	19	17
Nitrates	44	43

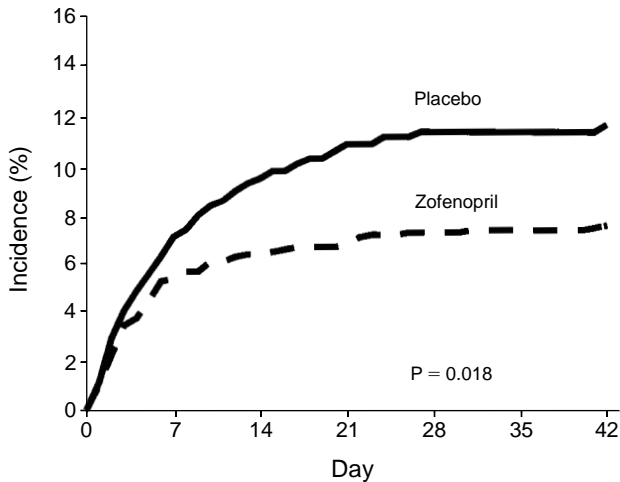


Figure 1. Incidence of Death or Severe Congestive Heart Failure during Six Weeks of Treatment with Zofenopril or Placebo in Patients with Acute Myocardial Infarction.

cular event as defined above was 34 percent (95 percent confidence interval, 8 to 54 percent; $P=0.018$). The reduction in risk was mainly attributable to a decrease in the incidence of severe congestive heart failure requiring open-label treatment with an ACE inhibitor, whereas the relative contribution of death was not statistically significant (Table 2). When we examined the cumulative incidence of death from all causes regardless of whether there was prior congestive heart failure, we found that there were 65 deaths in the placebo group (8.3 percent) as compared with 50 in the zofenopril group (6.5 percent) (Table 3). Thus, the reduction in the risk of death from all causes during the six-week treatment period was 22 percent (95 percent confidence interval, -12 to 48 percent; $P=0.17$) and was almost entirely due to the reduction in cardiovascular mortality in the zofenopril group (reduction in risk, 22 percent; 95 percent confidence interval, -8 to 53 percent; $P=0.08$) (Table 3). There was also a marked difference between the zofenopril group and the placebo group in the number of patients who died within 24 hours after randomization (1 vs. 8 deaths).

Table 2. Incidence of Severe Congestive Heart Failure or Death as the Combined Primary End Point of the Study.

EVENT	PLACEBO GROUP	ZOFENOPRIL	REDUCTION IN RISK	P VALUE
	(N = 784)	GROUP (N = 772)	(95% CI)*	
	no. of patients (%)		%	
Severe congestive heart failure†	32 (4.1)	17 (2.2)	46 (11 to 71)	0.018
Death	51 (6.5)	38 (4.9)	25 (-11 to 60)	0.19
Combined end point	83 (10.6)	55 (7.1)	34 (8 to 54)	0.018

*CI denotes confidence interval.

†At least three of the following had to be present: third heart sound, bilateral pulmonary rales, radiologic evidence of pulmonary congestion, or peripheral edema despite the concomitant administration of digoxin, diuretics, and vasodilators other than ACE inhibitors and necessitating open-label treatment with an ACE inhibitor.

The numbers of deaths due to noncardiac causes were similar in the two treatment groups (Table 3).

Secondary Outcome Measures

During the six weeks of treatment angina occurred in 153 patients (19.5 percent) in the placebo group and in 128 patients (16.6 percent) in the zofenopril group. Thus, the reduction in risk was 18 percent (95 percent confidence interval, -6 to 37; $P=0.08$). After randomization, 23 patients had at least one clinically reported nonfatal myocardial infarction (12 patients in the placebo group and 11 in the zofenopril group). A total of 75 patients (9.6 percent) in the placebo group had clinical signs of mild-to-moderate congestive heart failure after six weeks, as compared with 52 patients (6.7 percent) in the zofenopril group, with a reduction in risk of borderline statistical significance (reduction in risk, 29 percent; 95 percent confidence interval, -2 to 51; $P=0.054$). The use of other medications during the six-week treatment period was comparable in the two groups with the exception of the use of digoxin, which was given less often to patients taking zofenopril than to patients taking placebo (5.8 percent vs. 8.4 percent, $P=0.041$), a finding consistent with the lower inci-

Table 3. Cumulative Incidence of Death from All Causes after Six Weeks of Treatment with Zofenopril or Placebo, Regardless of Whether There Was Prior Congestive Heart Failure.

CAUSE OF DEATH	PLACEBO GROUP	ZOFENOPRIL GROUP	REDUCTION IN RISK
	(N = 784)	(N = 772)	(95% CI)*
	no. of patients (%)		%
Progressive heart failure	19 (2.4)	13 (1.7)	31 (-16 to 67)
Sudden death	11 (1.4)	4 (0.5)	63 (-2 to 89)
Cardiac rupture	10 (1.3)	8 (1.0)	19 (-10 to 41)
Recurrent myocardial infarction	8 (1.0)	5 (0.6)	37 (-20 to 80)
Other cardiac event	12 (1.5)	15 (2.0)	-27 (-34 to 39)
Cerebrovascular event	3 (0.4)	3 (0.4)	—
Noncardiac event	2 (0.3)	2 (0.3)	—
All causes	65 (8.3)	50 (6.5)	22 (-12 to 48)

dence of the clinical manifestations of heart failure in this group (data not shown).

The one-year mortality rates for all patients according to their original treatment assignments are shown in Figure 2. Patients who received zofenopril for six weeks were significantly more likely to survive than patients given placebo. During the year of observation 77 of 772 patients in the zofenopril group (10.0 percent) died, as compared with 111 of 784 patients in the placebo group (14.1 percent), and this difference accounted for a significant reduction in the risk of death (29 percent; 95 percent confidence interval, 6 to 51; $P=0.011$). This reduction in risk cannot be explained by differences in the concomitant pharmaco-

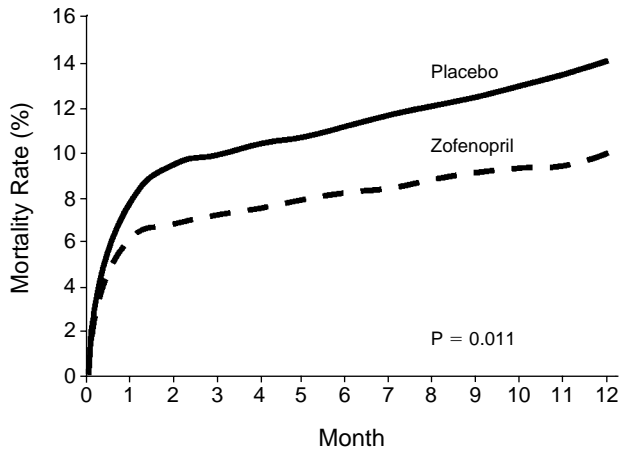


Figure 2. Cumulative Mortality during One Year of Follow-up among Patients with Acute Myocardial Infarction Treated for Six Weeks with Zofenopril or Placebo.

logic or surgical treatment, which was ascertained for over 80 percent of the patients (Table 4).

Analysis of Subgroups

The primary end point was assessed in subgroups defined on the basis of characteristics or treatments known to influence survival after myocardial infarction (Table 5). The beneficial effect of zofenopril therapy was apparent in patients with a previous myocardial infarction and in those concomitantly treated with calcium-channel blockers and nitrates during hospitalization.

Blood-Pressure Profile

The overall prevalence of hypotension, conservatively defined as a systolic blood pressure below 100 mm Hg at any time during the study, was significantly higher in the zofenopril group (132 patients, 17.1 percent) than in the placebo group (70 patients, 8.9 percent, $P < 0.001$). However, the rate of discontinuation of treatment because of symptomatic or severe hypotension (systolic blood pressure, < 90 mm Hg) and the rate of hypotension after the first dose of zofenopril or placebo were similar in patients treated with zofenopril and those given placebo (3.8 percent vs. 2.7 percent and 0.6 percent vs. 0.3 percent, respectively).

Compliance with Treatment and Adverse Events

The number of patients taking their assigned study medication on the last study visit was similar in the placebo group (592 of 784, or 75.5 percent) and the zofenopril group (580 of 772, or 75.1 percent). The target daily dose of 60 mg was achieved in 86.1 percent of patients in the placebo group and 78.8 percent of those in the zofenopril group.

Because of the short follow-up, only a small proportion of patients reported side effects during the trial; 6.8 percent of patients in the placebo group and 8.6

percent of patients in the zofenopril group discontinued treatment permanently. In both groups of patients, the main reason for the discontinuation of treatment was symptomatic or severe hypotension.

DISCUSSION

Although thousands of patients with myocardial infarction have been studied in clinical trials of various ACE inhibitors, important questions remain regarding the use of these agents in this group of patients.^{25,26} In the present study we have demonstrated that the early administration of zofenopril to patients with acute anterior myocardial infarction who were not receiving thrombolytic therapy significantly reduced the combined end point of death or severe congestive heart failure at six weeks. Moreover, we found that six weeks of treatment with zofenopril resulted in long-term improvement in survival. In previous trials of ACE inhibitors for acute myocardial infarction, the drugs were not discontinued after six weeks; rather, patients continued to receive therapy for months or years.

The results of our study are in agreement with accumulating data showing that treatment with ACE inhibitors begun days to weeks after myocardial infarction improves left ventricular function as well as clinical outcome in patients with symptomatic¹¹ or asymptomatic¹² left ventricular dysfunction. The reduction in early mortality (< 24 hours) and the occurrence of major cardiovascular events at six weeks in our study are consistent with the recently reported results of the GISSI-3 study¹⁴ and suggest that the benefit of ACE inhibitors may not be due entirely to an attenuation of ventricular remodeling, which would be expected to occur over a longer period. We suggest that most of the benefit is achieved through a primary cardioprotective effect²⁷⁻²⁹ as well as through the prompt blockade of the deleterious effects of neurohumoral activation.^{30,31} A previous clinical trial involving the intravenous and

Table 4. Treatments Administered to the Patients during One Year of Observation.*

TREATMENT	PLACEBO GROUP (N = 633)	ZOFENOPRIL GROUP (N = 616)	P VALUE
	% of patients		
Digitalis	6.3	8.0	0.25
Diuretics	12.6	13.1	0.79
ACE inhibitors	25.8	26.1	0.20
Calcium-channel blockers	15.9	21.1	0.02
Beta-blockers	13.1	10.4	0.06
Aspirin	79.5	82.7	0.08
Nitrates	32.6	34.3	0.53
Antiarrhythmic drugs	3.7	3.0	0.46
Lipid-lowering agents	4.5	3.0	0.14
Noncardiovascular drugs	9.6	11.0	0.19
Percutaneous transluminal coronary angioplasty	6.5	7.4	0.78
Coronary-artery bypass surgery	5.8	7.1	0.95

*Data were available for 80 percent of the patients.

Table 5. Effects of Zofenopril on the Primary End Point (Death or Severe Congestive Heart Failure) in Subgroups Defined on the Basis of Characteristics or Pharmacologic Treatments Known to Influence the Outcome in Patients with Myocardial Infarction.*

VARIABLE	ZOFENOPRIL GROUP		P VALUE FOR INTERACTION	RR (95% CI)	P VALUE
	PLACEBO GROUP	no. of events/no. of patients (%)			
Sex					
Male	47/571 (8.2)	28/557 (5.0)	NS	0.59 (0.36–0.95)	NS
Female	36/213 (16.9)	27/215 (12.5)		0.70 (0.40–1.21)	NS
Age					
<65 yr	22/389 (5.6)	15/378 (4.0)	NS	0.68 (0.35–1.34)	NS
≥65 yr	61/395 (15.4)	40/394 (10.2)		0.61 (0.40–0.93)	NS
Previous myocardial infarction					
Yes	20/102 (19.6)	4/100 (4.0)	<0.01	0.17 (0.05–0.52)	<0.006
No	63/682 (9.2)	51/672 (7.6)		0.84 (0.57–1.27)	0.38
History of diabetes					
Yes	27/164 (16.5)	10/139 (7.2)	NS	0.39 (0.18–0.84)	NS
No	56/620 (9.0)	45/633 (7.1)		0.77 (0.50–1.17)	NS
History of hypertension					
Yes	40/291 (13.7)	21/275 (7.6)	NS	0.53 (0.30–0.91)	NS
No	43/493 (8.7)	34/497 (6.8)		0.87 (0.52–1.45)	NS
Use of beta-blockers					
Yes	13/161 (8.0)	10/140 (7.1)	NS	0.87 (0.37–2.04)	NS
No	70/623 (11.2)	45/632 (7.1)		0.60 (0.41–0.89)	NS
Use of calcium-channel blockers					
Yes	13/82 (15.8)	2/74 (2.7)	<0.05	0.14 (0.03–0.66)	0.005
No	70/702 (10.0)	53/698 (7.6)		0.74 (0.51–1.07)	0.12
Use of nitrates					
Yes	53/337 (15.7)	27/327 (8.3)	<0.02	0.48 (0.29–0.79)	0.003
No	30/447 (6.7)	28/445 (6.3)		0.93 (0.54–1.58)	0.79
Use of aspirin					
Yes	35/431 (8.1)	26/409 (6.4)	NS	0.77 (0.45–1.30)	NS
No	48/353 (13.6)	29/363 (8.0)		0.55 (0.33–0.89)	NS

*RR denotes relative risk, CI confidence interval, and NS not significant.

oral administration of enalapril to patients with acute myocardial infarction failed to demonstrate any beneficial effect of early treatment with ACE inhibitors.¹⁶ We did not use the intravenous route of administration.

Interestingly, the beneficial effect of short-term treatment with zofenopril was maintained over time, as reflected by the improved survival at one year. These data raise an important issue concerning the ability of a short course of therapy to improve long-term survival in patients with acute myocardial infarction. The mechanism of the persistent benefit even after therapy had been discontinued remains to be sorted out. Others have shown that early treatment with an ACE inhibitor can improve left ventricular function after myocardial infarction.³²

The current data add to a growing body of evidence supporting the use of an ACE inhibitor such as zofenopril early in the course of acute anterior myocardial infarction. We suggest that the early administration of ACE inhibitors in patients with myocardial infarction can be considered a reasonable strategy in high-risk subgroups, especially in patients with large anterior myocardial infarction.

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APPENDIX

The following persons participated in the SMILE study (in places that had more than one study center; the numbers of study centers are given in parentheses): Albano Laziale: G. Ruggeri, L. Giamundo; Alessandria: P.A. Ravazzi, G. Taverno, M.C. Ferrara; Ancona (two centers): E. Paciaroni, 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 (three centers): D. Bracchetti, P.C. Pavesi, M. Mezzetti, A. Branzi, G. Melandri, G. Di Biase; Borgosesia: M. Gronda, V. Maggiano; 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; Caltanissetta: 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 (four centers): A. Circo, S. Raciti, R. Bosco, F. Platania, F. Casaccio, A. Galassi, R. Coco, M. Franco, 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. Iacuiti, 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 Brunozi, R. Liberati, C. Pagnotta; Forlì: F. Rusticali, C. Simoni; Fossano: M. Mareta, M. Tallone, R. Conte, A. Airaldi; Fucecchio: A. Ieri, G. Fradella, A. Ferreri; Genova (two centers): F. Basso, R. Delfino, E. Oldoino, G.L. Secchi, S. Caponnetto, M.P. Masperone, T. Carazza; Grosseto: T. Lanzetta, A. Cresti; Imola: C. Pardi; Lanciano: L. Di Guglielmo, G. Mastrogioseppe; 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. Paganini; 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 (two centers): G. Casella, L. Pavia, F. Casella, F. Consolo, F. Arrigo, M. Giannetto, A. Consolo; Milano (four centers): C. Belli, L. Oltrona Visconti, P.A. Merlini, A. Lotto, A. Foresti, M. Lettino, L. Pozzoni, A. Lomuscio, 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. Cecchi; Napoli (four centers): O. De Divitiis, S. Di Somma, M. Condorelli, B. Trimarco, G. Pucciarelli, R. Santamaria, R. Spadaro; Nettuno: M. Mo-

stacci, 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; Pescara: L. Papi; Piacenza: U. Gazzola, M. Groppi, A. Rosi; Piazza Armerina: B. Aloisi, M. Farruggio, G. Baiunco; Piana Ligure: D. Sanfelici, V. Tarditi; Pieve di Sacco: C. Martines; Pisa (two centers): A. Biagini, R. Tongiani, M.T. Baratto, F. Paoli, 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. Salituri; Rovigo: P. Zonzin, L. Roncon; Salerno (two centers): N. Cirillo, V. Paolillo, S. Angrisani, 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. Specca, V. Ciampini, G. Marcellini; Termoli: D. Staniscia, A. Cimino; Thiene: F. Dal Prà; Torino (two centers): A. Brusca, L. Bergandi, S. Bergerone, 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; *Scientific Committee*: G.D. Bompiani, F. Camerini, C. Dal Palù, P.F. Fazzini, G. Muesan, P.L. Prati, P. Solinas, A. Zanchetti, P. Zardini; *Operations Group*: S. Bacchelli, G. Botta, F. Claroni, S. Collatina, D. Degli Esposti, S. Liberatore, L.J. Meinert; *Clinical Coordinating Center and Study Monitoring*: N. Bergamini, R. Cosentina; and *End-Points Committee*: F. Rovelli, A. Brusca, F.V. Costa, A. Libretti, P. Marino.

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