# Effects of the Early ACE Inhibition in Diabetic Nonthrombolyzed Patients With Anterior Acute Myocardial Infarction

CLAUDIO BORGHI, MD
STEFANO BACCHELLI, MD
DANIELA DEGLI ESPOSTI, MD
ETTORE AMBROSIONI, MD
ON BEHALF OF THE SMILE STUDY INVESTIGATORS

**OBJECTIVE** — The aim of the present study was to evaluate the clinical efficacy of the ACE inhibitor zofenopril in a cohort of diabetic patients with nonthrombolyzed anterior acute myocardial infarction who were enrolled in the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) trial.

**RESEARCH DESIGN AND METHODS** — Among the overall population of 1,512 patients, 303 (20.0%) had diabetes. The primary end point of this study was the effect of treatment on the 6-week combined occurrence of death and severe congestive heart failure (CHF). Secondary end points included the evaluation of the 6-week rate of major cardiovascular events as well as the 1-year survival rate.

**RESULTS** — After 6 weeks of double-blind treatment, zofenopril significantly reduced both the incidence of the primary end point (8.6 vs. 18.3%; $P = 0.019$) and the 6-week incidence of severe CHF (0 vs. 7.3%; $P = 0.001$) in diabetic patients, and the effect was greater than that observed in nondiabetic patients. Conversely, 1-year mortality was significantly reduced among nondiabetic patients (9.1 vs. 13.8%; $P = 0.010$), whereas in the diabetic population, the decrease did not reach statistical significance (13.7 vs. 16.5%; $P = 0.52$).

**CONCLUSIONS** — The present data suggest that the clinical outcome of patients with diabetes and myocardial infarction can be significantly improved by early treatment with zofenopril. The lesser effect on 1-year mortality seems to suggest that long-term treatment is probably needed to maintain the benefits of the early ACE inhibition in patients with diabetes.

*Diabetes Care* **26:1862–1868, 2003**

In-hospital and long-term mortality rates after acute myocardial infarction (AMI) are twice as high among individuals with diabetes as in those without diabetes, even after adjustment for confounding factors (1–9). This has very important clinical implications because ~30% of patients with AMI who are hospitalized have diabetes compared with a diabetes prevalence of 6–8% in the general population (7). In the past 10–15 years, the prognosis of patients with myocardial infarction (MI) has been considerably improved by the widespread use of highly effective therapeutic agents and invasive procedures of revascularization (i.e., primary percutaneous transluminal coronary angiography) that have, however, only slightly reduced the gap between diabetic and nondiabetic patients (2–4,6). This suggests the importance of a more aggressive therapeutic approach in this high-risk population of patients, particularly during the early phases of MI.

Many studies have demonstrated that the clinical outcome of patients with AMI can be significantly improved by routine administration of drugs that prevent the onset and progression of left ventricular (LV) dysfunction, which occurs as a function of extensive myocardial injury (10) and is a powerful predictor of mortality after MI and a recognized precursor of congestive heart failure (CHF) (11,12). The risk of development of LV dysfunction after MI is increased in patients with diabetes, in whom the presence of some specific structural, functional, and metabolic abnormalities can promote the processes of LV remodeling (13). In addition, recent data have shown that the concomitant presence of diabetes and ischemic heart disease can accelerate the progression of CHF in patients with overt LV systolic dysfunction (14). These data provide an explanation for the higher incidence of CHF and the excess mortality that has been observed in patients with diabetes after MI, even when the data are adjusted for infarct size (15–17).

ACE inhibitors have demonstrated the capacity to improve the clinical outcome of patients with different cardiovascular diseases, including AMI with or without overt LV dysfunction and CHF (18–23). The role of ACE inhibition in patients with AMI and diabetes has been indirectly analyzed by post hoc analysis of some large clinical trials performed in different populations of patients. Among the studies in which ACE inhibitors have been administered within 24 h of the onset of symptoms in an unselected population of patients with MI, only the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) reported a significantly higher benefit in terms of mortality and incidence of CHF in diabetic patients compared with

From the Department of Internal Medicine, University of Bologna, Bologna, Italy.
Address correspondence and reprint requests to Claudio Borghi, MD, Divisione di Medicina Interna-Ambrosioni, Policlinico S. Orsola Via Massarenti 9, 40138 Bologna, Italy. E-mail: claudio@med.unibo.it.
Received for publication 19 November 2002 and accepted in revised form 25 January 2003.
C.B. and E.A. have received honoraria from the Menarini Company for speaking engagements on ACE inhibitors.
**Abbreviations:** AMI, acute myocardial infarction; CHF, congestive heart failure; GISSI-3, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; LV, left ventricular; MI, myocardial infarction; NNT, number needed to treat; SMILE, Survival of Myocardial Infarction Long-term Evaluation; TRACE, Trandolapril Cardiac Evaluation.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—*Baseline characteristics of 1,512 patients with and without diabetes***

| | Diabetes ($N$ = 303) | No diabetes ($N$ = 1,209) | Significance ($P$ value) |
|---|---|---|---|
| Mean age (years) | 66.5 | 63.6 | <0.001 |
| Ratio of men to women (%) | 60.4/39.6 | 75.7/24.3 | <0.001 |
| Current smokers (%) | 28.7 | 43.8 | <0.001 |
| Clinical history at admission (%) | | | |
| Previous MI | 17.2 | 14.3 | NS |
| Hypertension | 51.2 | 35.5 | <0.001 |
| Hours to randomization (%) | | | |
| <6 | 36.8 | 42.8 | 0.96 |
| 6–12 | 34.4 | 28.8 | |
| >12 | 28.8 | 28.4 | |
| Killip Class on admission >1 (%) | 22.8 | 12.3 | <0.001 |
| Peak creatine kinase level (unit × $10^{-3}$) | 1.44 ± 1.2 | 1.50 ± 1.2 | 0.23 |
| Mean systolic blood pressure (mmHg) | 133.8 ± 2 | 132.1 ± 17 | 0.12 |
| Mean diastolic blood pressure (mmHg) | 81.5 ± 12 | 81.8 ± 10 | 0.12 |
| Use of drugs (%) | | | |
| Antiplatelet agents | 52.5 | 54.3 | 0.47 |
| β-Blockers | 16.5 | 20.3 | 0.07 |
| Calcium channel blockers | 10.9 | 9.7 | 0.33 |
| Diuretics | 26.1 | 15.1 | <0.001 |
| Nitrates | 49.5 | 41.5 | 0.012 |
| Inotropic agents | 9.9 | 5.5 | 0.006 |
| Anticoagulants | 80.9 | 78.4 | 0.61 |

Data are means ± SE unless otherwise indicated.

nondiabetic patients (24). In the Survival and Ventricular Enlargement (SAVE) (25) and Trandolapril Cardiac Evaluation (TRACE) (26) studies, the benefit of ACE inhibition was reported to be increased in the selected population of diabetic patients with AMI complicated by LV dysfunction and/or CHF and treated from days to weeks after onset of symptoms. However, in all these studies, although the extent of the absolute survival benefit of ACE inhibition was greater in patients with diabetes, the difference between patients with and without diabetes did not achieve formal statistical significance. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) trial (19) was performed in a selected population of patients with anterior AMI who were not undergoing thrombolysis and were treated early after onset of symptoms in order to gather additional information about the role of ACE inhibitors in diabetic patients with AMI. Accordingly, the aim of the present study was to compare the clinical efficacy of the ACE inhibitor zofenopril in patients with and without diabetes who were enrolled in the SMILE study.

## RESEARCH DESIGN AND METHODS

— The SMILE study was a randomized, double-blind, placebo-controlled study of patients with anterior AMI. The aim of the study was to evaluate the efficacy of zofenopril in reducing the morbidity and mortality of patients with anterior AMI not undergoing thrombolysis and treated within 24 h of onset of symptoms. The complete protocol of the SMILE study has been published in more detail elsewhere (19,27). A total of 1,556 patients with an anterior AMI were enrolled at 154 centers in Italy. Men and women aged 18–80 years were eligible for the study if they presented to the intensive care unit within 24 h of onset of typical chest pain associated with electrocardiographic signs of definite anterior wall MI and if they were not eligible for thrombolytic treatment because of late admission to the intensive care unit or individual contraindications to systemic fibrinolysis (28,29). Patients were excluded from the study if one of the following was present: Killip Class IV on admission, severe hypotension on admission (systolic blood pressure <100 mmHg), serum creatinine level >2.5 mg/dl, previous history of CHF, current treatment with or contraindications to ACE inhibitors, or inability or refusal to give informed consent. All potentially eligible patients received standard therapy including analgesic agents, β-blockers, nitrates, calcium channel blockers, aspirin, inotropic drugs, diuretics, and anticoagulants as indicated.

Eligible patients were administered the study drug zofenopril calcium (Bristol Myers-Squibb, Princeton, NJ) or placebo at the initial dose of 7.5 mg, which was repeated after 12 h and progressively doubled to the final target dose of 30 mg b.i.d. if systolic blood pressure was >100 mmHg and no signs or symptoms of hypotension occurred. Patients who were unable to tolerate the dose of 7.5 mg were withdrawn from the study. Patients were seen during the in-hospital phase and after 6 weeks (±3 days) of double-blind treatment. Upon completion of the 6-week double-blind period, the study medication was stopped and patients were maintained on their conventional therapy for 48 ± 4 additional weeks and then blindly evaluated for survival status.

The primary end point of the SMILE study was composite and aimed at evaluating the effect of zofenopril in addition to conventional treatment on the combined occurrence of death or severe CHF during a 6-week observation period. Death or presence of severe CHF was considered a single event for each patient and prevalence was calculated according to occurrence of the first event. Predefined secondary end points were the 6-week occurrence of clinical signs of mild to moderate CHF, recurrent MI, and angina. In addition, we have evaluated the effect of a 6-week double-blind treatment on cumulative 1-year survival. Either severe or mild to moderate CHF included in the definition of study end points was defined elsewhere in more detail (19,27). In particular, mild to moderate CHF was defined during the in-hospital period by the presence, after randomization, of three or four of the following clinical and radiological signs: third-degree heart sound, bilateral pulmonary rales, radiological pulmonary congestion, and peripheral edema. During the follow-up phase of the study, the presence of clinical signs of mild to moderate CHF was defined according to the New York Heart Association classification. Severe CHF was defined by the need for open-label treat-

**Table 2—*Baseline characteristics of patients with and without diabetes randomized to placebo or zofenopril***

| | Diabetes | | No diabetes | |
|---|---|---|---|---|
| | Placebo ($n$ = 164) | Zofenopril ($n$ = 139) | Placebo ($n$ = 602) | Zofenopril ($n$ = 607) |
| Mean age (years) | 66.4 ± 8.4 | 66.6 ± 9.0 | 63.9 ± 10.7 | 63.4 ± 10.9 |
| Ratio of men to women (%) | 62.8/37.2 | 57.6/42.4 | 75.7/24.3 | 75.8/24.2 |
| Current smokers (%) | 31.7 | 25.0 | 43.1 | 44.6 |
| Clinical history at admission (%) | | | | |
| Previous MI | 28.0 | 18.1 | 26.3 | 17.2 |
| Hypertension | 51.3 | 51.1 | 36.7 | 34.4 |
| Hours to randomization (%) | | | | |
| <6 | 35.8 | 38.0 | 41.7 | 43.8 |
| 6–12 | 36.4 | 32.1 | 30.1 | 27.5 |
| >12 | 27.8 | 29.9 | 28.2 | 28.7 |
| Killip Class on admission >I (%) | 21.9 | 23.7 | 12.3 | 12.3 |
| Peak creatine kinase level (units × $10^{-3}$) | 1.44 ± 1.2 | 1.5 ± 1.2 | 1.51 ± 1.3 | 1.50 ± 1.3 |
| Mean systolic blood pressure (mmHg) | 133.8 ± 11 | 132.1 ± 9 | 132.1 ± 10 | 133.8 ± 10 |
| Mean diastolic blood pressure (mmHg) | 82.1 ± 9 | 81.3 ± 10 | 81.7 ± 9 | 81.5 ± 10 |
| Use of drugs (%) | | | | |
| Antiplatelet agents | 53.0 | 51.8 | 55.6 | 53.0 |
| β-Blockers | 15.2 | 18.0 | 22.1 | 18.5 |
| Diuretics | 24.4 | 28.1 | 16.1 | 14.2 |
| Nitrates | 48.8 | 50.4 | 41.9 | 41.2 |
| Inotropic agents | 11.0 | 8.6 | 4.7 | 6.4 |
| Anticoagulants | 78.0 | 84.2 | 80.9 | 75.9* |

Data are means ± SE unless otherwise indicated. *P = 0.036 vs. placebo.

ment with an ACE inhibitor for presence of the same criteria as described above despite the concomitant administration of a positive inotropic drug, diuretic agents, and vasodilators other than ACE inhibitors.

The presence of diabetes, either type 1 or 2, was defined as previous clinical diagnosis of the disease, current treatment with insulin, oral hypoglycemic agents, or diet alone, or the presence of fasting serum glucose levels >130 mg/dl 1 week after the index infarction. In addition, according to the SMILE study protocol (27), serum glucose was also measured after 2 weeks or at discharge, and at the study termination (6 ± 1 weeks), and 95% of the patients classified as diabetics had at least one of the major criteria reported above confirmed in any of the following controls. This information was available for 1,512 (97.2%) of the patients cumulatively randomized in the SMILE study; for all of these patients, complete information about the study end points has been recorded.

### Statistical analysis

The current study is a post hoc analysis of the effects of diabetes on the efficacy of zofenopril in decreasing morbidity and mortality after anterior AMI. The baseline characteristics and the distribution of the various parameters for the placebo and treatment groups were compared using the $\chi^2$ test for categorical variables (with Yates' continuity correction where appropriate) and standard normal Student's $t$ test for continuous variables. All analyses were performed on an intention-to-treat basis and $P$ values are reported as two tailed. The $\chi^2$ analysis was applied to data with the Mantel-Haenszel extension for comparison between the two treatment groups. Time-to-event curves for mortality were drawn using Kaplan-Meier estimates, and the survival analysis was performed with the use of the Lee-Desu statistic for group comparisons. A secondary confirmatory analysis of data has been performed on diabetic patients with serum glucose levels >126 mg/dl and classified according to American Diabetes Association (ADA) criteria. Because the two analyses have reached the same conclusions, we have decided to base our inference on protocol criteria.

### Ethical aspects

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 patients provided informed consent before randomization.

## RESULTS

### Patients

Of the 1,512 patients who entered the study, 303 (20.0%) were classified as having diabetes. Of these, 57 (18.8%) had type 1 diabetes and 213 (70.3%) had type 2 diabetes; in 33 patients (10.9%), the diagnosis was not specified. No significant differences have been found in the prevalence of diabetes between the patients treated with zofenopril ($n$ = 139; 18.6%) and those treated with placebo ($n$ = 164; 21.4%). The baseline characteristics of patients with and without diabetes and those treated with zofenopril or placebo are shown in Tables 1 and 2. The overall diabetic population was older than the nondiabetic population and comprised a greater proportion of women and patients with a history of hypertension. Moreover, a greater percentage of the diabetic population presented with a Killip Class II and III on hospital admission. Smoking was more common in patients without diabetes. During the double-blind treat-

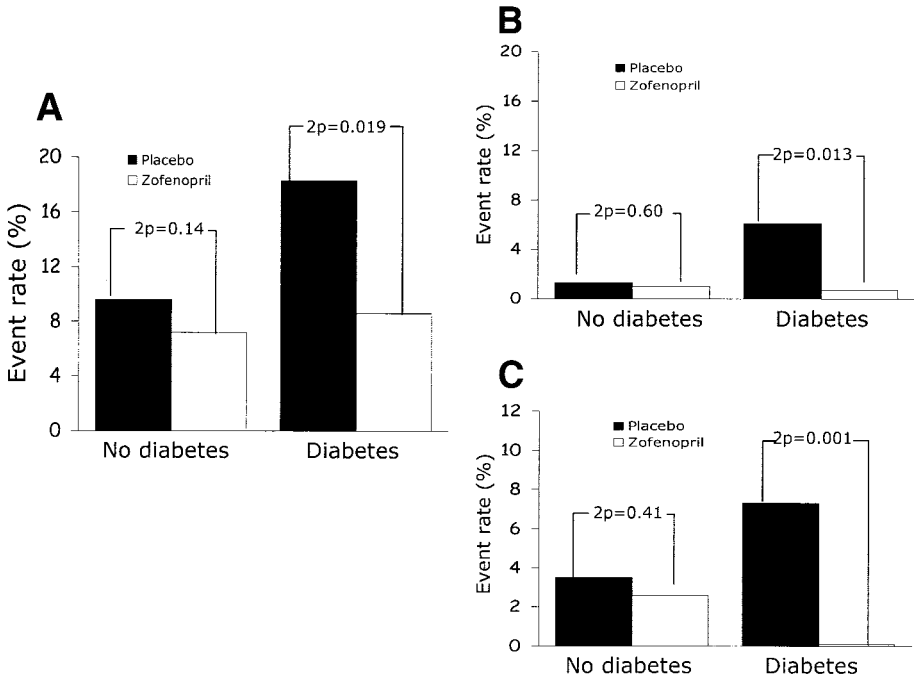


**Figure 1**—*Combined occurrence of death and severe CHF (*A*), early (<24 h) death rate (*B*), and rate of severe CHF (*C*) during the 6 weeks of follow-up in diabetic and nondiabetic patients.*

ment, use of diuretics, inotropic agents, and nitrates was significantly greater in the diabetic patients than the nondiabetic individuals.

Within the diabetic and nondiabetic populations, the subgroups of patients treated with zofenopril or placebo were largely comparable at baseline (Table 2). There was only a slight, but significant, lesser use of anticoagulant agents among nondiabetic patients treated with zofenopril. There was no evidence that diabetes significantly changed the total exposure to the ACE inhibitor during the whole double-blind treatment period, appreciably affected compliance with the study drug, or affected the rate of dropout in either treatment group.

## Primary end point

During the 6 weeks of double-blind treatment, death or severe CHF occurred in 42 of the 303 patients with diabetes (13.9%) and in 102 of the 1,209 patients without diabetes (8.4%); there was a 39% increase in the relative risk (1.39, 95% CI 1.1–1.7; $P < 0.001$) of reaching the primary end point. The effects of treatment on the primary end point of the study are reported in Fig. 1*A*. The proportion of patients who reached the primary end point of death and severe CHF was significantly reduced in the diabetic population treated with zofenopril (8.6%, 95% CI 4.6–14.9%) when compared with placebo (18.3%, 12.8–25.2%; $P = 0.019$). The absolute difference in the event rate was 9.7 ± 3.8% (2.1–17.2%), which yields a number needed to treat (NNT) of 10 (95% CI 6–48) for treatment with zofenopril. In the nondiabetic population, the combined primary end point occurred in 7.2% (5.4–9.7%) of the patients treated with zofenopril and in 9.6% (7.4–12.3%) of those treated with placebo with an absolute 2.4% reduction in the event rate, which did not achieve a formal statistical significance, probably because of the limited event rate.

Concerning the rate of events that compose the primary end point, at the end of the 6-week treatment period, the cumulative mortality was significantly higher in diabetic patients (10.2%) than in nondiabetic patients (5.9%; $P = 0.01$). Treatment with zofenopril was consistently associated with a trend toward a nonsignificant reduction in mortality rate in both diabetic (8.6 vs. 11.6%) and nondiabetic patients (6.6 vs. 5.1%). Conversely, in diabetic patients treated with zofenopril, a statistically significant decrease in mortality occurred within the first 24 h after randomization compared with patients treated with placebo (0.7%, 0–3.4% vs. 6.1%, 3.0–11.2%; $P = 0.013$) (Fig. 1*B*). No treatment effects have been observed in the early mortality rate in nondiabetic patients (1.0 vs. 1.3%).

The 6-week incidence of severe CHF was slightly, though not significantly, increased (4.0 vs. 3.1%) in patients with diabetes compared with nondiabetic control subjects. Compared with placebo, treatment with zofenopril was associated with a significantly lesser incidence of severe CHF (0%, 0–3.4% vs. 7.3%, 3.9–12.7%; $P = 0.001$) in patients with diabetes (Fig. 1*C*). This difference in the incidence of severe CHF (7.3 ± 2.9%, 3.3–11.1%) accounted for a number needed to treat (NNT) of 14 (9–30). Conversely, the effect of ACE inhibition on the occurrence of severe CHF in the nondiabetic population did not achieve statistical significance.

## Secondary end points

After stratification for the presence of diabetes, there was no evidence of a significantly different distribution between treatments for the 6-week occurrence of angina, nonfatal MI, mild-to-moderate CHF, and any noncardiovascular or cardiovascular event (data not shown).

The 1-year survival rate was significantly reduced in patients with diabetes, in whom mortality was 15.2%, compared with 11.4% in nondiabetic patients ($P = 0.048$). The difference cannot be attributed to differences in the use of concomitant cardiovascular medications (ACE inhibitors, antiplatelet agents, anticoagulant agents, β-blockers, calcium channel blockers, diuretics, and inotropic agents) during the follow-up period as a function of the presence of diabetes (data not shown).

In the nondiabetic population, patients undergoing a 6-week treatment with zofenopril during the double-blind phase of the trial showed a significantly greater chance of long-term survival compared with patients treated with placebo. Indeed, the 1-year mortality rate was 13.8% (11.2–16.9%) in patients treated with placebo and 9.1% (1.0–11.7%) in those treated with ACE inhibitors, yielding a statistically significant difference of 4.7 ± 1.8% (1.1–8.3%; $P = 0.01$). Conversely, in the diabetic population, despite a trend toward an improved survival rate in patients treated with the ACE in-

**Table 3—*Summary of the effects of treatment with ACE inhibitors in diabetic and nondiabetic patients with AMI: results of large-scale randomized clinical trials***

| Study | Patients (*n*) | Drug | Primary outcome | Placebo | ACE inhibitors | Odds ratio | 95% CI | NNT |
|---|---|---|---|---|---|---|---|---|
| Diabetic population | | | | | | | | |
| GISSI-3 | 2,790 | Lisinopril | 6-week mortality | 12.4% | 8.7% | 0.68 | 0.53–0.86 | 27 |
| TRACE | 237 | Trandolapril | 26-month death from any cause | 61% | 45% | 0.64 | 0.45–0.91 | 6 |
| SMILE | 303 | Zofenopril | 6-week death + CHF | 18.3% | 8.6% | 0.47 | 0.32–0.78 | 10 |
| Nondiabetic population | | | | | | | | |
| GISSI-3 | 15,341 | LIsinopril | 6-week mortality | 5.9% | 5.6% | 0.95 | 0.83–1.08 | 333 |
| TRACE | 1,512 | Trandolapril | 26-month death from any cause | 39% | 33% | 0.82 | 0.69–0.97 | 17 |
| SMILE | 1,209 | Zofenopril | 6-week death + CHF | 9.6% | 7.2% | 0.75 | 0.42–0.98 | 42 |

hibitors, we were unable to demonstrate a significant difference in long-term survival. In particular, 27 of 164 patients (16.5%) in the placebo group and 19 of 139 patients (13.7%) in the zofenopril-treated group died. The reduction in relative risk of death was 17%, which did not achieve formal statistical significance, probably again because of the small proportion of events. These findings also have been also confirmed by the Kaplan-Meier estimate of survival, which yielded a significant reduction in the cumulative probability of death associated with ACE inhibitor treatment in nondiabetic patients ($P = 0.012$), whereas no significant difference has been found in patients with diabetes ($P = 0.48$).

There was no evidence that either diabetes or applied treatment had any effect on the monitored secondary end points at one year: angina, nonfatal MI, mild to moderate CHF, stroke, and procedures of revascularization (data not shown).

**CONCLUSIONS** — This post hoc analysis of the SMILE study confirms that MI is associated with a worse outcome in patients with diabetes than in those without diabetes. The early (<24 h), short-term (6 weeks), and long-term mortality rates observed in the SMILE trial were 135, 73, and 34% higher in diabetic patients. In addition, patients with diabetes experienced a 30% increase in short-term incidence of severe CHF, which represents one of the most relevant complications of MI in this population of patients (7,9,16). Moreover, the present data demonstrate that the clinical prognosis for diabetic patients with anterior AMI who do not undergo thrombolysis can be substantially improved by early administration (within 24 h of symptom onset) of an ACE inhibitor. In particular, treatment with zofenopril significantly reduced the 6-week combined incidence of death and severe CHF and was associated with a decrease in the incidence of severe CHF alone and an improvement in the early (<24 h) survival rate. These findings largely confirm the observations provided by similar post hoc analyses of large clinical trials (24,25,26), which have demonstrated a benefit of different ACE inhibitors in diabetic patients with AMI that significantly exceeds that observed in the nondiabetic population (Table 3). A retrospective evaluation of the GISSI-3 study (24), investigating the effects of early ACE inhibition (lisinopril) in a nonselected population of patients with MI, showed a reduction in the 6-week mortality rate in the treated diabetic population comparable to that observed in the SMILE trial (GISSI-3 30.0% vs. SMILE 28.5%) and significantly greater than that reported in patients without diabetes. In a post-hoc analysis of the TRACE study (26), performed in a selected population of patients with MI complicated by LV dysfunction, the treatment with trandolapril was associated with an impressive 60% reduction in the rate of progression to severe CHF in diabetic patients, which was substantially confirmed by our data. In addition, the results of the SMILE study have significantly extended the benefit of ACE inhibition to patients with MI not undergoing thrombolysis, thereby increasing the amount of information about the primary role of renin-angiotensin-aldosterone blockade in patients with diabetes.

The improvement in the clinical outcome observed in the diabetic population of the SMILE trial treated with zofenopril seems to be mainly related to the preventive effect of the drug against the post-MI deterioration of LV function that is expected to occur, to a large extent, in MI patients not undergoing thrombolysis. This can have some important clinical implications, according to the observation that the diabetic ventricle is more prone to maladaptive remodeling, which increases the risk of CHF and cardiogenic shock (13,30). Many of the abnormalities underlying the impaired LV function in patients with diabetes can be effectively improved by ACE inhibition (9), and the results achieved in the diabetic population of the SMILE study, in terms of prevention of severe CHF (event rate 0% with zofenopril vs. 7.3% with placebo), definitely support a primary role for ACE inhibitors in patients with diabetes and AMI.

Another intriguing observation of our study is the demonstration that improvement in early mortality, which has previously been reported in the general population of patients treated with ACE inhibitors during the acute phase of MI (31,32), can reasonably be extended to the diabetic population as well. This can have some important clinical implications. In particular, the in-hospital mortality after MI, which is twice as high among diabetic patients than among those without diabetes (1–9), could be significantly reduced by more extensive and routine use of ACE inhibitors, the beneficial effect of which could result from a mechanism of action more complex than the simple blockade of the RAA system (33).

In addition to these clinically relevant observations, our study highlights the importance of long-term ACE inhibition in patients with diabetes surviving AMI. Indeed, a significant reduction in the

1-year mortality rate after the withdrawal of double-blind treatment has only been observed in the nondiabetic population, whereas the extent of reduction observed in patients with diabetes did not reach formal statistical significance. One of the possible reasons for such a shortage in the survival gain of diabetic patients undergoing ACE inhibition could be the small sample size of the diabetic population, which could have reduced the power to achieve a formal statistical significance despite a sizeable treatment effect. Indeed, the absolute reduction in the event rate observed in the SMILE trial (from 16.5 to 13.7%) was superimposable to that observed in the larger (>2,700 patients) diabetic population of the GISSI-3 study (from 16.1 to 12.9%), in which the difference achieved statistical significance (24). However, this explanation could not account for the lesser reduction in relative risk of long-term mortality observed in zofenopril-treated diabetic patients compared with their nondiabetic counterparts (−34 vs. −16.9%). We suggest that this difference can be explained by the negative impact that withdrawal of ACE inhibition after 6 weeks of active treatment could have on survival of diabetic patients. Indeed, the extent of reduction in risk of death observed after 6 weeks of zofenopril treatment was increased after 12 months in the nondiabetic population (from 22.7 to 34.0%) and decreased in the population of patients with diabetes (from 25.8 to 16.9%), thereby suggesting the importance of sustained treatment with ACE inhibitors in diabetic patients with AMI. This is confirmed in the diabetic population of the TRACE study, in which the benefit of the ACE inhibition in terms of survival persisted, along with treatment administration, for a mean follow-up time of 26 months (26).

As expected for a post-hoc analysis of a prospective trial, our study has some weaknesses. The main limitation is the sample size of the study, because any interpretation of the results of a clinical trial based on the analysis of small subgroups of patients should always require some caution. However, the results of our study are largely confirmatory of the evidence reported in the literature and support a larger beneficial effect of ACE inhibitors in diabetic versus nondiabetic patients with MI (24–26). A further methodological limitation of the study lies in its retrospective nature since the paper summarizes the results of a post hoc analysis of the diabetic population of the SMILE data that was not prespecified in the study protocol. However, because no prospective studies on the benefits of ACE inhibition in diabetic patients with MI are either ongoing or planned, we must rely for evidence on agreement among retrospective data, which are, by far, the only data available for analysis. In addition, the study does not provide any information about the extent of glycemic control in diabetic and nondiabetic individuals, in whom modifications in serum glucose could have influenced early mortality, according to the results of the DIGAMI study (34), as well as those of a larger meta-analysis suggesting a relationship between in-hospital mortality and stress hyperglycemia in patients with AMI (35).

In addition to the limitations, our study also has various strengths. It increases the amount of information about the benefit of ACE inhibitors in diabetic patients with MI, and this could have some important clinical implications given the large proportion of diabetic patients who sustain MI compared with the nondiabetic population (13). Our study also provides evidence that ACE inhibition is highly effective in diabetic patients with AMI not undergoing thrombolysis. Patients with diabetes very frequently have impaired recognition of clinical symptoms of MI (36), which can be responsible for a delay in the hospital admission and treatment. This could increase the proportion of patients with diabetes not eligible for thrombolytic treatment, who should be treated aggressively with ACE inhibitors to improve their clinical outcome in terms of mortality and occurrence of CHF. Finally, the SMILE data allow the speculation that treatment with ACE inhibitors should be continued over a long-term period in diabetic patients surviving AMI, irrespective of any preliminary assessment of LV function or the presence of any other prognostic implication. This is an intriguing hypothesis that warrants further prospective investigations in the future.

In conclusion, the present study confirms previous observations demonstrating the striking benefit of early administration of ACE inhibitors in high-risk patients with diabetes and anterior AMI. In addition, the data from the present analysis indicate that the beneficial effects of early ACE inhibition can be extended to patients not undergoing thrombolysis, thereby emphasizing the primary role of ACE inhibitors for the routine treatment of any diabetic patient with AMI.

**Acknowledgments**— This study was supported by a grant from the 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. Additional analysis of data was supported by an educational grant from Menarini Industrie Farmaceutiche, Firenze, which was not involved in the management of data and did not have access to unblinded information.

We thank all the study personnel and particularly Prof. G. Patrizi, Dr. F. Claroni, Dr. S. Collatina, and Dr. Adeoye Olukotun for their continuous support to research.

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