

# Early Treatment With Zofenopril and Ramipril in Combination With Acetyl Salicylic Acid in Patients With Left Ventricular Systolic Dysfunction After Acute Myocardial Infarction: Results of a 5-Year Follow-up of Patients of the SMILE-4 Study

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**Abstract:** The SMILE-4 study showed that in patients with left ventricular dysfunction (LVD) after acute myocardial infarction, early treatment with zofenopril plus acetyl salicylic acid is associated with an improved 1-year survival, free from death or hospitalization for cardiovascular (CV) causes, as compared to ramipril plus acetyl salicylic acid. We now report CV outcomes during a 5-year follow-up of the patients of the SMILE-4 study. Three hundred eighty-six of the 518 patients completing the study (51.2%) could be tracked after the study end and 265 could be included in the analysis. During the 5.5 ( $\pm 2.1$ ) years of follow-up, the primary endpoint occurred in 27.8% of patients originally randomized and treated with zofenopril and in 43.8% of patients treated with ramipril [odds ratio (OR) and 95% confidence interval, 0.65 (0.43–0.98),  $P = 0.041$ ]. Such a result was achieved through a significantly larger reduction in CV hospitalization under zofenopril [OR: 0.61 (0.37–0.99),  $P = 0.047$ ], whereas reduction in mortality rate with zofenopril did not achieve statistical significance versus ramipril [OR: 0.75 (0.36–1.59),  $P = 0.459$ ]. These results were in line with those achieved during the initial 1-year follow-up. Benefits of early treatment of patients with LVD after acute myocardial infarction with zofenopril are sustained over many years as compared to ramipril.

**Key Words:** acute myocardial infarction, left ventricular dysfunction, angiotensin-converting enzyme inhibitors, zofenopril, ramipril, acetyl salicylic acid

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## INTRODUCTION

The SMILE-4 study was specifically designed to investigate the efficacy and safety of early administration of zofenopril and ramipril plus acetyl salicylic acid (ASA) in patients with acute myocardial infarction (AMI) complicated by left ventricular systolic dysfunction (LVD) and treated with daily 100 mg aspirin.<sup>1</sup> The combination of angiotensin-converting enzyme (ACE) inhibitors and ASA is recommended to treat acute infarction and ischemic heart disease.<sup>2</sup> In patients with heart failure, a daily dose of 80–100 mg ASA is used to decrease the risk of atherothrombosis, without interfering with hemodynamic, neurohumoral, or renal functions. ASA prevents thromboxane A<sub>2</sub> synthesis by platelets and reduces prostaglandin production by cyclooxygenase in the vascular endothelium.<sup>3,4</sup> Similarly, in the early phase of myocardial infarction (MI), ACE inhibitors are recommended for their effect on renin–angiotensin system. In addition, they favor prostacyclin production by delaying bradykinin breakdown.<sup>5</sup> This bradykinin-induced prostacyclin stimulating effects by ACE inhibitors is apparently counteracted by the inhibition of prostacyclin production by ASA, thus generating some concerns about the opportunity to concomitantly use ACE inhibitors and ASA, particularly for long-term treatment of post-MI.<sup>6</sup> A retrospective analysis indicated that a negative interaction between aspirin and ACE inhibitors may reduce the beneficial effects of ACE inhibitors in patients with heart failure.<sup>7</sup> However, in patients with stable LVD, no interactions among aspirin, ACE inhibitors, and overall survival were observed.<sup>8</sup> Preclinical data on experimental animal models suggested that ACE inhibitors may have a different response to cyclooxygenase inhibition.<sup>9</sup> Captopril and zofenopril with their sulfhydrylic group maintain a cardiovascular (CV) protective effect even in the presence of cyclooxygenase inhibitors differentially to enalapril,<sup>9</sup> ramipril,<sup>10</sup> or lisinopril.<sup>11</sup> Sulfhydryl ACE inhibitors might have a cardioprotective mechanism of

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action, which only in part includes a prostaglandin-mediated mechanism. In the Valsartan in Acute Myocardial Infarction (VALIANT) study in which 92% patients were treated with aspirin or other antiplatelet agents, captopril had similar outcomes than valsartan or placebo.<sup>12</sup> Similarly, in the SMILE-4 study, zofenopril treatment plus ASA compared with ramipril plus ASA significantly reduced the CV hospitalization by 36% without affecting the mortality rate. Drug safety profile was comparable between treatments.<sup>1</sup> This follow-up study was aimed to evaluate whether benefits of early treatment after AMI with zofenopril plus ASA compared with ramipril plus ASA in patients previously enrolled in the SMILE-4 study were sustained over the long term.

## MATERIALS AND METHODS

### Study Population

In the SMILE-4 study, the first patient was enrolled in March 2005, whereas the last patient was completed in July 2009. In 2012, the study investigators agreed that patients randomized and followed up in the main SMILE-4 study, who could be tracked after the study end and consented to provide information on their current status during a visit at the center, could be included in an observational retrospective follow-up study.<sup>1</sup> This consisted of 3 phases. Between June and July 2012, a phone survey was carried out among all participating centers to know their availability in participating in the follow-up study and whether it was still possible to contact the patients originally enrolled in the trial. At that time, it was estimated that 386 of the 518 patients who terminated the study could be tracked and contacted. A second (feasibility) phase took place between September 2012 and February 2013, when a clinical monitor visited the centers to check the availability of patients: at the end of this phase, it was estimated that 290 patients could be tracked, and thus, the study protocol could be submitted to local Ethics Committees of the consenting centers. The countries involved in the original SMILE-4 interventional study were Italy (27 sites, 153 patients completed), Russia (12 sites, 154 patients), Ukraine (7 sites, 38 patients), Romania (9 sites, 118 patients), Portugal (3 sites, 4 patients), Turkey (4 sites, 27 patients), Spain (2 sites, 20 patients), and Greece (2 sites, 4 patients). Centers from Portugal, Turkey, and Greece did not take part in the SMILE-4 follow-up study. Centers from Spain did not obtain approval for the study. Eleven of the original 27 sites in Italy, 4 of 12 in Russia, 2 of 27 in Ukraine, and 4 of 9 in Romania refused to participate or did not obtain approval from their Ethics Committees. As the main study, the follow-up trial was coordinated by the Internal Medicine Unit of the University of Bologna (Italy), whose Ethics Committee gave approval for conduction of the observational study in June 2013. The original double-blind SMILE-4 study was registered in the EU Clinical Trials Register (EudraCT number: 2004-001150-88) and in the Italian Ministry of Health Register (code: GUIDOTT\_III\_2004\_001). Given the observational nature of the follow-up study, this did not require any further registration. During the follow-up, the first patient was visited in May 2014 and the last in December 2014.

The main SMILE-4 study enrolled male and nonpregnant female patients aged 18–85 years with a confirmed diagnosis of ST Elevation MI (STEMI) or Non-ST Elevation MI (NSTEMI) in the 24 hours preceding the enrollment and with clinical and/or echocardiographic LVD evidence. Patients with percutaneous transluminal coronary angioplasty or a coronary artery bypass graft were also included. The main exclusion criteria were as follows: severe hypotension, a history of renal artery stenosis, significant valve disease, current treatment with ACE inhibitors, angiotensin-receptor blockers (ARBs) or ASA, hypersensitivity to these drugs, a history of stroke, renal failure, severe liver impairment, hematologic diseases, or other significant clinical conditions. Anticoagulant treatment was allowed only during the acute phase of the infarction.

The follow-up study was performed following the Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the University of Bologna (coordinating center) and by the local ethics committees of each participating center (a list of centers is available in the acknowledgments). Written informed consent was obtained from each patient before enrollment.

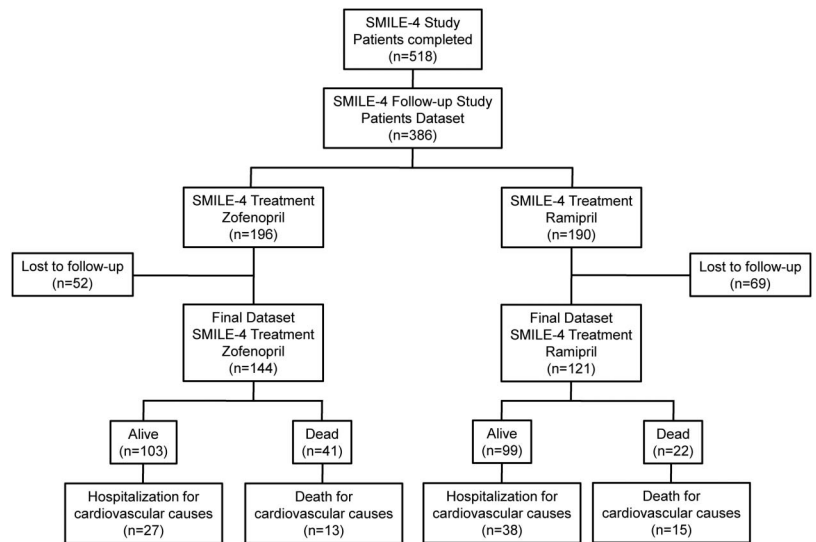
### Study Design

The original SMILE-4 study was a phase III b randomized, double-blind, parallel group study. Briefly, eligible patients were treated with open-labeled zofenopril for 4 days in an uptitration scheme plus an evening dose of 100 mg ASA. On days 1 and 2, patients received zofenopril 7.5 mg twice daily plus an evening dose of ASA 100 mg. On days 3 and 4, the zofenopril dose was doubled (15 mg twice daily), whereas the dose of ASA remained unchanged. On day 5, patients were randomized 1:1 to receive zofenopril 30 mg twice daily plus ASA 100 mg once daily or ramipril 5 mg twice daily plus ASA 100 mg once daily for 12 months. Zofenopril and ramipril were supplied as identical oral tablets (overencapsulation technique). In the event of severe hypotension (systolic blood pressure <90 mm Hg) or any other clinically relevant adverse event, treatment was discontinued and the patient was withdrawn from the study. The study medications were administered in combination with standard recommended treatments for AMI, excluding other ACEIs, ARBs, and antiplatelet drugs other than ASA, clopidogrel, or ticlopidine. Concomitant chronic anticoagulant treatment was allowed in the acute phase of myocardial infarction (MI) and in case of a specific indication or in patients who reached a study endpoint. Patients were followed up for 12 months. Further details on the original study protocol and procedures are available in the main study publication.<sup>1</sup>

In the SMILE-4 follow-up study, information on patients' status (current medication and CV outcomes—only if requiring hospitalization) was collected during a visit at the center.

### Statistical Analysis

As in the SMILE-4 study, the primary outcome was the combined occurrence of death or hospitalization for CV causes (congestive heart failure, AMI, angina, or a decline in the left ventricular ejection fraction >15%) in patients originally randomized to zofenopril and ramipril. The survival



**FIGURE 1.** Flow diagram of the patients throughout the study.

analysis started on the date of entry into the SMILE-4 study. Baseline characteristics and variables distribution were compared using a  $\chi^2$  test for categorical variables and Student's *t* test for continuous variables. Differences in CV mortality and morbidity rate were assessed in a logistic regression model as estimated odds ratio (OR) and 95% confidence interval. To compare treatment group, the  $\chi^2$  analysis was applied to data with the Mantel–Haenszel extension. Time-to-event curves were drawn using Kaplan–Meier estimates, and the survival analysis was performed according to the log-rank statistics.

All *P* values are 2-tailed, and the minimum level of statistical significance was set at *P* < 0.05. Data management and statistical analysis was carried by a team under the supervision of the study coordinators.

## RESULTS

### Patient Population

Of the 518 patients terminating the original study, 386 were tracked after the study end and consented to participate in the follow-up study: 196 were originally randomized to zofenopril and 190 to ramipril. During the study, 121 patients (52 in the zofenopril group and 69 in the ramipril group; *P* = 0.038) were lost to follow-up. Thus, the full analysis set included 265 patients: 144 of the former zofenopril and 121 of the former ramipril group (Fig. 1).

No differences were observed between the 2 groups in demographic and clinical characteristics, except for a larger proportion of patients previously submitted to a percutaneous transluminal coronary angioplasty (*P* = 0.021) (Table 1), consistently with the original study.<sup>1</sup>

### Concomitant Treatments During the Study

A total of 149 patients (56.2%) were still taking an ACE inhibitor during the follow-up. Forty-three (28.9%) patients were treated with the originally assigned treatment, 52 (34.9%) switched to the other randomized drug, whereas in 54 patients (36.2%), ACE inhibitors different from

zofenopril or ramipril were administered. As summarized in Table 2, apart from ACE inhibitors, the most common concomitant CV drugs were antithrombotic agents (65.7%), lipid-lowering drugs (51.3%), and beta-blockers (43.4%). No difference (*P* = 0.610) was observed in the distribution of concomitant CV treatments between 2 groups.

**TABLE 1.** Baseline Demographic Characteristics of the Patients of the Intention-to-Treat Population (n = 265)

Characteristics	Zofenopril	Ramipril	<i>P</i>
	(n = 144)	(n = 121)	
Age, yr	60.7 ± 10.6	60.5 ± 10.4	0.898
Sex			
Male	103 (71.5)	96 (79.3)	0.143
Female	41 (28.5)	25 (20.7)	
BMI, kg/m <sup>2</sup>	27.5 ± 3.6	27.2 ± 3.4	0.555
Diabetes	30 (21.1)	21 (18.4)	0.590
Treated hypercholesterolemia	31 (28.7)	22 (26.5)	0.737
Treated hypertension	97 (71.3)	68 (60.7)	0.078
Peripheral arterial occlusive disease	8 (5.7)	5 (4.2)	0.577
Previous MI	25 (17.6)	22 (18.2)	0.903
Angina pectoris	52 (36.1)	39 (32.5)	0.539
Previous PTCA	9 (6.3)	1 (0.8)	0.021
Previous CABG	3 (2.1)	1 (0.8)	0.403
Congestive heart failure	11 (7.7)	9 (7.5)	0.940
NT-proBNP, pg/mL	1406.6 ± 1776.8	1169.4 ± 1127.2	0.247
LVEF, %	42.7 ± 6.9	44.0 ± 6.6	0.129
SBP, mm Hg	129.1 ± 16.9	127.9 ± 14.1	0.518
DBP, mm Hg	77.1 ± 9.8	76.1 ± 9.5	0.435
HR, bpm	68.9 ± 7.9	67.5 ± 9.1	0.182

Data are shown as mean ± SD or as absolute numbers and percentages (in brackets). *P*-values refer to the statistical significance of the between-group difference.

BMI, body mass index; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; MI, Myocardial Infarction; NT-proBNP, N-terminal pro brain natriuretic peptide; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure.

**TABLE 2.** Concomitant CV Drug Treatments During the Follow-up Period in the 2 Study Groups (Intention-To-Treat Population)

Relevant Concomitant CV Treatments	Zofenopril (n = 144)	Ramipril (n = 121)
ACE inhibitors	77 (53.5)	72 (59.5)
ARBs	13 (9.0)	8 (6.6)
Beta-blockers	56 (38.9)	59 (48.8)
Calcium channel blockers	16 (11.1)	12 (9.9)
Diuretics	33 (22.9)	28 (23.1)
Nitrates	12 (8.3)	20 (16.5)
Antiarrhythmic drugs	1 (0.7)	4 (3.3)
Antithrombotic agents	85 (59.0)	89 (73.6)
Lipid-lowering drugs	63 (43.8)	73 (60.3)
Other CV drugs	8 (5.6)	6 (5.0)

Data are shown as absolute numbers and percentages (in brackets).

**CV Death or Hospitalization**

During the average 5.5 ± 2.1 years of follow-up, CV death or hospitalization occurred in 40 of 144 patients originally randomized and treated with zofenopril (27.8%) and in 53 of 121 patients treated with ramipril (43.8%). This accounted for a 35% significantly higher chance of surviving without events in patients taking zofenopril in the early phase of AMI and continuing it for at least 1 year [OR and 95% CI, 0.65 (0.43–0.98), P = 0.041]. The average survival time significantly differed between 2 treatment groups, in favor of zofenopril [6.8 (6.4–7.2) versus 6.5 (6.0–7.0) years with ramipril, P = 0.037 log-rank test, Fig. 2A].

**CV Death**

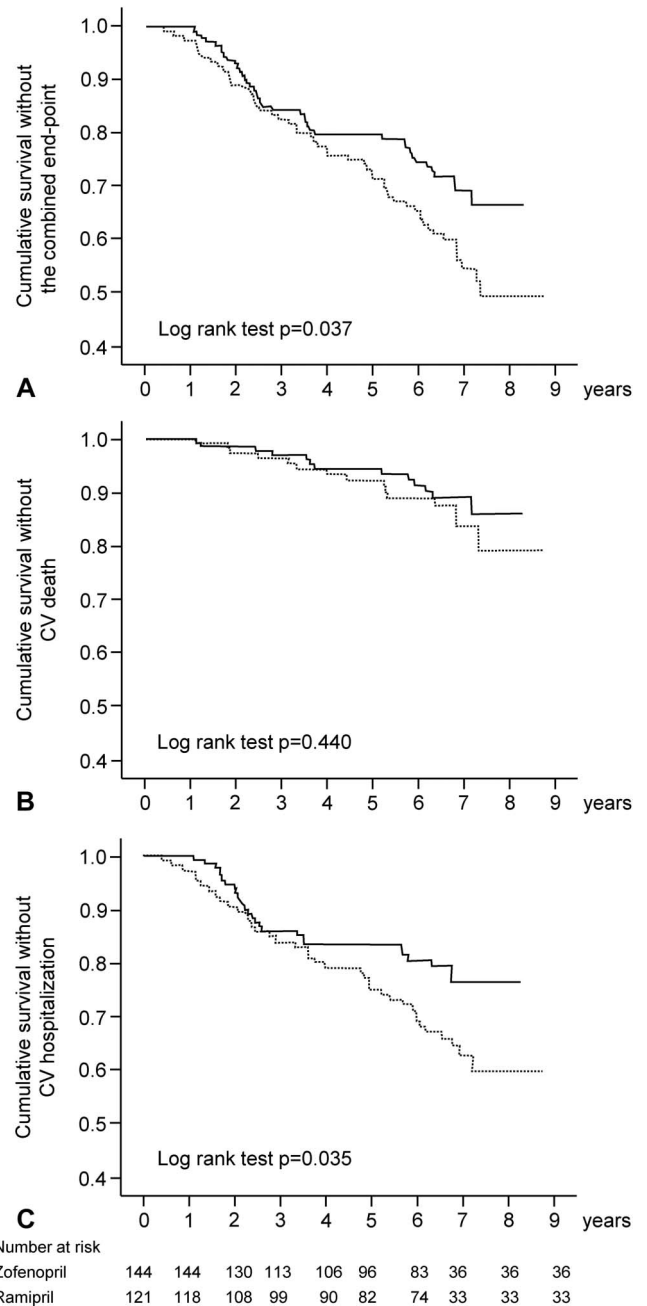
As shown in Table 3, during the follow-up, the number of deaths was low and did not significantly differ among the 2 groups (P = 0.459). Thirteen deaths (9.0%) were reported in patients originally assigned to zofenopril and 15 (12.4%) in patients formerly randomized to ramipril. The risk of CV death was 0.75 (0.36–1.59). Time of death was also similar in the zofenopril [7.8 (7.5–8.0) years] and ramipril group [8.0 (7.6–8.3), P = 0.440 log-rank test, Fig. 2B].

**Hospitalizations for CV Causes**

The hospitalization reasons and their distribution are described in Table 3. The rate of hospital admissions for CV causes was significantly (P = 0.047) reduced by 39% [OR = 0.61 (0.37–0.99)] in patients formerly receiving zofenopril (27 of 144, 18.8%) as compared to those receiving ramipril (38 of 121, 31.4%). The average time to hospitalization was 7.1 (6.–7.5) years in the zofenopril and 6.8 (6.3–7.3) years in the ramipril group (P = 0.035 log-rank test, Fig. 2C).

**DISCUSSION**

This study described the 5-year follow-up of the SMILE-4 study. In patients originally treated after AMI with zofenopril plus ASA, a significant reduction in the combined risk of CV deaths or hospitalizations was still observed over



**FIGURE 2.** Incidence of CV mortality or hospitalization for CV causes (A), CV death (B), or CV hospitalization (C) during the follow-up in patients originally randomized and treated with zofenopril (continuous lines, n = 144) or ramipril (dashed lines, n = 121). Data refer to the intention-to-treat population. P-value from the log-rank statistics.

5 years as compared to those originally treated with ramipril plus ASA. The rate and time of hospitalization were significantly reduced with zofenopril, whereas CV deaths and the time of occurrence were similar with the 2 ACE inhibitors. These results are consistent with findings of the original SMILE-4 study after 1 year of follow-up. Compared

**TABLE 3.** Absolute and Relative Frequency (%) of Causes of CV Death and of Major CV Events Requiring Hospitalization During the Follow-up

	Zofenopril (n = 144)	Ramipril (n = 121)
CV death		
Congestive heart failure	3 (2.1)	4 (3.3)
AMI	6 (4.2)	6 (5.0)
Sudden death	4 (2.8)	5 (4.1)
All causes of CV death	13 (9.0)	15 (12.4)
OR (95% confidence interval)	0.75 (0.36–1.59)	
P	0.459	
Major CV events requiring hospitalization		
Congestive heart failure	5 (3.5)	6 (5.0)
AMI	7 (4.9)	8 (6.6)
Angina pectoris	8 (5.6)	13 (10.7)
Decline in left ventricular ejection fraction >15%	4 (2.8)	5 (4.1)
Revascularization	3 (2.1)	6 (5.0)
Other causes		
All causes of major CV events	27 (18.8)	38 (31.4)
OR (95% confidence interval)	0.61 (0.37, 0.99)	
P	0.047	

OR and corresponding 95% confidence intervals, with corresponding *P* statistics, are also shown.

with the SMILE-4 study,<sup>1</sup> during the 5 years of follow-up, the rates of CV death marginally increased in the zofenopril group (from 5% to 9%) and more consistently in the ramipril group (from 3% to 12%). Conversely, the rate of hospitalization was unchanged in originally ramipril-treated patients (31 vs. 33%) and reduced in originally zofenopril-treated patients (from 24% to 19%). Thus, this follow-up study suggests that early treatment with zofenopril after AMI may offer more favorable sustained effects than early treatment with ramipril.

Our results are in line with those of previous similar long-term trials. The Chinese Cardiac Study (CCS-1) trial on 15,000 patients described lower CV mortality with early captopril treatment versus placebo (10.0% vs. 11.8%, *P* = 0.01) within a median follow-up of 23.4 (±16.9) months.<sup>13</sup> Similarly, in the follow-up of the Survival and Ventricular Enlargement clinical trial, captopril treatment prevented 7.0 (95% CI, 0.5–13.5) combined CV events for every 100 treated patients in the presence of hypertension and 7.5 (2.6–12.5) events in the absence of hypertension. Patients included in the Survival and Ventricular Enlargement study survived an AMI and had left ventricular dysfunction; the mean follow-up lasted 42 (±10 months).<sup>14</sup> After a mean 59 months of follow-up, the results from the Acute Infarction Ramipril Efficacy study indicated that death from all causes occurred in 38.9% of patients assigned to placebo and 27.5% of patients treated with ramipril, with a relative risk reduction of 36% (15%–52%; *P* = 0.002) and an absolute reduction in mortality of 11.4%.<sup>15</sup> At the end of the Acute Infarction Ramipril Efficacy study, 15 months after randomization, all-cause mortalities were 22.6% in the placebo group and 16.9% in the

ramipril group, with an absolute mortality reduction of 5.7% and a relative risk reduction of 27% (11%–40%; *P* = 0.002).<sup>15</sup> The 5-year survival analysis from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI-3) trial suggested that lisinopril treatment improved survival mainly because of a reduction in cardiac rupture, electromechanical dissociation, and pump failure occurring early (within 4 days) from the onset of MI symptoms. The beneficial effects of lisinopril observed at 6 weeks (8 fewer deaths per 1000 treated patients) were maintained up to nearly 5 years (10 fewer deaths per 1000).<sup>16</sup> Thus, the use of ACE inhibitors during the early phases of AMI has proven long-term advantages in terms of clinical outcomes.

In the SMILE-4 follow-up study, we directly compared the long-term effects of 2 ACE inhibitors and described better outcomes in patients previously treated with zofenopril than ramipril. Indeed, these 2 compounds are chemically different: the presence of a sulfhydryl group in the zofenopril structure may confer additional cardioprotective properties to this agent.<sup>17–22</sup> Furthermore, zofenopril has antioxidants features at clinically achievable tissue concentration: in endothelial cells enhances nitric oxide production, attenuates atherosclerotic lesion development, and inhibits cellular adhesion molecule expression.<sup>23–25</sup> These characteristics may be advantageous to control the cardiac hypertrophy, independently of blood pressure-reducing effects.<sup>17</sup> Indeed, the results of the SMILE-ISCHEMIA study supported the beneficial effect of zofenopril in patients with normal left ventricular function and demonstrated lower rate of development and progression of congestive heart failure with the ACE inhibitor treatment.<sup>26</sup> However, during the follow-up of the SMILE-4 study, a relatively small percentage of patients took ACE inhibitors, beta-blockers, and antithrombotic therapy, despite current international guidelines strongly recommend the use of these drugs after MI.<sup>27</sup> Compared with the original SMILE-4 study, the percentage of patients who took beta-blockers decreased while increased those of patients who took ACE inhibitors and ARBs. It is well established that ACE inhibitors should be given to patients with an impaired ejection fraction (<40%) or to those who have experienced heart failure in the early phase. Long-term administration of ACE inhibitors is recommended in all patients with atherosclerosis, but it cannot be considered mandatory in post-STEMI patients who are normotensive, without heart failure, or have neither LVD nor diabetes.<sup>27</sup> Similarly, the benefit of long-term therapy with beta-blockers has been confirmed by a number of clinical trials and clinical practice. Its early use may be associated with a modest benefit in low-risk, hemodynamically stable patients.<sup>27</sup> The antithrombotic therapy with ASA should be used indefinitely in all patients with STEMI because the long-term antiplatelet therapy reduces the yearly risk of serious vascular events by about a quarter.<sup>28</sup> The concerns about the concomitant use of ASA and ACE inhibitors have been partially overcome with data from the VALIANT study and the SMILE-4 study in which ASA did not affect the clinical outcomes of ACE inhibitor treatment.<sup>1,12</sup>

This study has some limitations. First, only 37% of the original population of the SMILE-4 study participated at this

follow-up study. However, baseline characteristics were similar to those of the original study and still well distributed in the 2 groups. Second, because a considerable amount of the patients originally participating in the SMILE-4 study was lost to follow-up with no information on the CV outcome, we cannot exclude that, at least at an intermediate period of follow-up, the efficacy of the 2 drugs could be different from that observed in the patients actually included in the final analysis. Third, during the follow-up, 84% of randomized treatments originally assigned to patients was switched to the other ACE inhibitor or changed with different ACE inhibitors or drug classes. Therefore, the long-term beneficial effects of zofenopril seem to be more attributable to its early use after AMI than to other following treatments. The change of therapies during the follow-up may represent a confounding factor and may underestimate the real long-term advantage of early zofenopril use. Fourth, differences in the efficacy of the 2 drugs may be related to the fact that the doses of the 2 comparators may not be situated at the same level of their respective dose-response curves. However, this is unlikely because the doses of zofenopril (60 mg daily) and ramipril (10 mg daily) used in the SMILE-4 study, correspond to the maximum daily maintenance doses recommended by the manufacturers for treating patients with AMI with or without signs and symptoms of heart failure (zofenopril) and for treating patients with symptomatic heart failure (ramipril).

In conclusion, the SMILE-4 follow-up confirms that the early concomitant administration of zofenopril and ASA had long-term major benefits in terms of reduced risk of CV deaths and hospitalization rate than ramipril plus ASA. Further studies are recommended to evaluate head-to-head long-term benefits of early use of different ACE inhibitors after AMI to identify the most favorable therapeutic scheme.

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#### REFERENCES

- Borghi C, Ambrosioni E, Novo S, et al. Comparison between zofenopril and ramipril in combination with acetylsalicylic acid in patients with left ventricular systolic dysfunction after acute myocardial infarction: results of a randomized, double-blind, parallel-group, multicenter, European study (SMILE-4). *Clin Cardiol*. 2012;35:416–423.
- Teo KK, Yusuf S, Pfeffer M, et al; Group ACEIC. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet*. 2002;360:1037–1043.
- Patrono C, Garcia Rodriguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med*. 2005;353:2373–2383.
- De Caterina R, Renda G. Clinical use of aspirin in ischemic heart disease: past, present and future. *Curr Pharm Des*. 2012;18:5215–5223.
- Buczko W, Kramkowski K, Mogielnicki A. Are the endothelial mechanisms of ACE-Is already established? *Pharmacol Rep*. 2006;58(suppl 1):126–131.
- Stys T, Lawson WE, Smaldone GC, et al. Does aspirin attenuate the beneficial effects of angiotensin-converting enzyme inhibition in heart failure? *Arch Intern Med*. 2000;160:1409–1413.
- Ahmed A. Interaction between aspirin and angiotensin-converting enzyme inhibitors: should they be used together in older adults with heart failure? *J Am Geriatr Soc*. 2002;50:1293–1296.
- Aumegeat V, Lamblin N, de Groote P, et al. Aspirin does not adversely affect survival in patients with stable congestive heart failure treated with Angiotensin-converting enzyme inhibitors. *Chest*. 2003;124:1250–1258.
- Przyklenk K, Kloner RA. Angiotensin converting enzyme inhibitors improve contractile function of stunned myocardium by different mechanisms of action. *Am Heart J*. 1991;121:1319–1330.
- Jin ZQ, Chen X. Pretreatment with ramiprilat induces cardioprotection against free radical injury in guinea-pig isolated heart: involvement of bradykinin, protein kinase C and prostaglandins. *Clin Exp Pharmacol Physiol*. 2000;27:257–262.
- Dubey K, Balani DK, Tripathi CB, et al. Adverse interactions of rofecoxib with lisinopril in spontaneously hypertensive rats. *Clin Toxicol (Phila)*. 2005;43:361–373.
- White HD, Aylward PE, Huang Z, et al. Mortality and morbidity remain high despite captopril and/or Valsartan therapy in elderly patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction: results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). *Circulation*. 2005;112:3391–3399.
- Liu L. Chinese Cardiac Study Collaborative G. Long-term mortality in patients with myocardial infarction: impact of early treatment with captopril for 4 weeks. *Chin Med J (Engl)*. 2001;114:115–118.
- Kenchiah S, Davis BR, Braunwald E, et al. Antecedent hypertension and the effect of captopril on the risk of adverse cardiovascular outcomes after acute myocardial infarction with left ventricular systolic dysfunction: insights from the Survival and Ventricular Enlargement Trial. *Am Heart J*. 2004;148:356–364.
- Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. *Acute Infarction Ramipril Efficacy*. *Lancet*. 1997;349:1493–1497.
- Pedrazzini G, Santoro E, Latini R, et al. Causes of death in patients with acute myocardial infarction treated with angiotensin-converting enzyme inhibitors: findings from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-3 trial. *Am Heart J*. 2008;155:388–394.
- Evangelista S, Manzini S. Antioxidant and cardioprotective properties of the sulphhydryl angiotensin-converting enzyme inhibitor zofenopril. *J Int Med Res*. 2005;33:42–54.
- Przyklenk K, Kloner RA. "Cardioprotection" by ACE-inhibitors in acute myocardial ischemia and infarction? *Basic Res Cardiol*. 1993;88(suppl 1):139–154.
- Pasini AF, Garbin U, Nava MC, et al. Effect of sulphhydryl and non-sulphhydryl angiotensin-converting enzyme inhibitors on endothelial function in essential hypertensive patients. *Am J Hypertens*. 2007;20:443–450.
- Frascarelli S, Ghelardoni S, Ronca-Testoni S, et al. Cardioprotective effect of zofenopril in perfused rat heart subjected to ischemia and reperfusion. *J Cardiovasc Pharmacol*. 2004;43:294–299.
- Marzo A, Dal Bo L, Mazzucchelli P, et al. Pharmacokinetic and pharmacodynamic comparative study of zofenopril and enalapril in healthy volunteers. *Arzneimittelforschung*. 2002;52:233–242.
- Grover GJ, Slep PG, Dzwonczyk S, et al. Effects of different angiotensin-converting enzyme (ACE) inhibitors on ischemic isolated rat hearts: relationship between cardiac ACE inhibition and cardioprotection. *J Pharmacol Exp Ther*. 1991;257:919–929.
- Napoli C, Bruzzese G, Ignarro LJ, et al. Long-term treatment with sulphhydryl angiotensin-converting enzyme inhibition reduces carotid intima-media thickening and improves the nitric oxide/oxidative stress pathways

- in newly diagnosed patients with mild to moderate primary hypertension. *Am Heart J.* 2008;156:1154.e1-8.
24. Napoli C, Sica V, de Nigris F, et al. Sulfhydryl angiotensin-converting enzyme inhibition induces sustained reduction of systemic oxidative stress and improves the nitric oxide pathway in patients with essential hypertension. *Am Heart J.* 2004;148:e5.
25. Cominacini L, Pasini A, Garbin U, et al. Zofenopril inhibits the expression of adhesion molecules on endothelial cells by reducing reactive oxygen species. *Am J Hypertens.* 2002;15(10 pt 1):891–895.
26. Borghi C, Ambrosioni E. Survival of Myocardial Infarction Long-term Evaluation Study G. Effects of zofenopril on myocardial ischemia in post-myocardial infarction patients with preserved left ventricular function: the Survival of Myocardial Infarction Long-term Evaluation (SMILE)-ISCHEMIA study. *Am Heart J.* 2007;153:445 e7–445 e14.
27. Task Force on the Management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012;33:2569–2619.
28. Antithrombotic Trialists C, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373:1849–1860.