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Efficacy of Ace Inhibition with Zofenopril, Lisinopril, or Ramipril in Postacute Myocardial Infarction Patients With or Without Metabolic Syndrome: A Pooled Individual Data Analysis of Four Randomized, Double-Blind, Controlled, Prospective Studies

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Abstract

Background: The metabolic syndrome (MS) is a clustering of different cardiovascular (CV) risk factors, which further enhances the risk of death and CV complications in post-acute myocardial infarction (AMI) patients. In the present meta-analysis of individual data of the four randomized, prospective SMILE studies, we evaluated the efficacy of zofenopril vs. lisinopril, ramipril, and placebo on 1-year CV morbidity and mortality, according to the presence (+) or absence (−) of the MS.
Methods: 2203 (63.2%) of the 3488 patients were classified as MS+, 1285 (36.8%) as MS−. Five hundred two MS+ and 380 MS− were treated with placebo, 1134 and 608 with zofenopril 30–60 mg/die, 340 and 175 with lisinopril 5–10 mg/die, and 227 and 122 with ramipril 10 mg/die. Treatment was continued for 6 to 48 weeks.
Results: The 1-year risk of a major CV event was similar ($P = 0.420$) in MS+ (18.1%) and MS− (18.0%) patients [HR and 95% confidence interval: 0.92 (0.76–1.12)]. After accounting for MS+/MS−, the 1-year risk of CV events vs. placebo was significantly lower under zofenopril [0.79 (0.63–0.97); $P = 0.028$] and lisinopril [0.65 (0.47–0.89); $P = 0.007$], but larger under ramipril [2.57 (1.94–3.93); $P = 0.0001$]. Treatment with zofenopril was associated with a statistically significant ($P = 0.0001$) reduction in CV risk as compared with the other angiotensin-converting enzyme inhibitors [MS+: 0.52 (0.42–0.66); MS−: 0.52 (0.38–0.73)].
Conclusions: In post-AMI patients with MS, zofenopril treatment is associated with a clinically relevant reduction in long-term CV morbidity and mortality, compared with placebo, with an efficacy similar to lisinopril, but better than ramipril.

Keywords: acute myocardial infarction, drug therapy, angiotensin-converting enzyme inhibitors, metabolic syndrome

Introduction

The metabolic syndrome (MS) is characterized by the clustering of different cardiovascular (CV) risk factors, such as abdominal obesity, atherogenic dyslipidemia, insulin resistance or glucose intolerance, and blood pressure (BP) elevation.[1–3] Approximately 25% of the general population worldwide has MS, but this condition occurs in nearly 50% of unselected patients with acute myocardial infarction (AMI).[3,4]

MS increases by two- to three-fold the risk of developing CV diseases[5–7] and it has been estimated that 63% of deaths from CV diseases, chronic kidney disease, and diabetes worldwide can be attributable to the combined effect of elevated BP and

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glucose, serum cholesterol, and body mass index (BMI).[8] In patients with AMI, the concomitant presence of MS further enhances the risk of death and CV complications.[9]

Several studies showed that both hyperglycemia and hyperinsulinemia, which characterize patients with MS, activate the renin angiotensin system (RAS) by increasing the expression of angiotensinogen, angiotensin II, and vascular angiotensin (AT)1 receptors, leading to an exaggerated activation of the RAS, a condition particularly harmful in patients with AMI.[10] This suggests that angiotensin-converting enzyme (ACE) inhibition may play a relevant role in the prevention of CV complications in post-AMI patients with MS.[11,12] In a *post-hoc* analysis of the double-blind, randomized, placebo-controlled prospective SMILE-1 (Survival of Myocardial Infarction Long-term Evaluation) study, we have documented a 69% significantly reduced incidence of all causes of death and severe congestive heart failure after 6 weeks of treatment with the ACE inhibitor, zofenopril, and a 29% significantly reduced risk of mortality over 1 year, in the subgroup of patients with MS.[13] Zofenopril was effective also in patients without MS, but the amount of relative risk reduction was less than in patients free from MS.

To our knowledge, there are currently no other published prospective studies evaluating the impact of ACE inhibition on the prevention of CV complications in post-AMI patients with MS. To fill such gap of evidence, we settled to carry out a retrospective individual patient data analysis of the four randomized SMILE trials. These studies evaluated the long-term efficacy of zofenopril vis-à-vis that of placebo, lisinopril, or ramipril in post-AMI patients, showing the good cardioprotective efficacy of the drug.[14–17] In the present analysis, we tested whether a difference exists in the cumulative efficacy of zofenopril vs. the other ACE inhibitors and placebo on CV morbidity and mortality according to the presence of MS.

Methods

Study population

The SMILE studies had a double-blind, randomized, parallel-group design. The SMILE-1 and 3 studies compared the efficacy and safety of zofenopril with that of placebo,[14,16] the SMILE-2 that of zofenopril vs. lisinopril[15] and the SMILE-4 that of zofenopril in combination with acetylsalicylic acid (ASA) vs. ramipril plus ASA.[17] Patients were enrolled into the study if complying with the following inclusion criteria: (1) early AMI (<24 hr), not eligible for thrombolytic therapy because of late admission to the intensive care unit or with contraindication to systemic fibrinolysis (SMILE-1),[14] (2) confirmed diagnosis of AMI and a prior thrombolytic treatment within 12 hr of the onset of clinical symptoms of AMI (SMILE-2)[15]; (3) recent AMI (within 6 ± 1 weeks) with preserved left ventricular ejection fraction (>40%), treated with a thrombolytic treatment and with ACE inhibitors (SMILE-3)[16]; and (4) early myocardial infarction (<24 hr), treated or not with thrombolysis, with primary percutaneous transluminal angioplasty or coronary artery bypass graft, and with clinical and/or echocardiographic evidence of left ventricular dysfunction (SMILE-4).[17] All studies complied with the Guidelines for Good Clinical Practice and the Declaration of Helsinki and were approved by the Ethics Committee of each participating center. Written informed consent was obtained from each patient before enrollment. All studies excluded pregnant women and breast-feeding mothers.

Study design and treatments

Eligible patients were randomized double-blind to treatment with placebo, zofenopril, lisinopril, or ramipril, in addition to standard recommended therapy for AMI. No run-in period was foreseen before randomization, except for the SMILE-4 study. In this study, eligible patients entered a 4-day open-label phase before randomization and were given zofenopril according to the following uptitration scheme[17]: 7.5 mg twice daily on day 1 and 2, 15 mg twice daily on day 3 and 4, and 30 mg twice daily on day 5 onward. Uptitration was allowed if systolic BP remained >100 mmHg and if there were no signs or symptoms of hypotension. The doses of the active comparators were also uptitrated: up to 10 mg once daily for lisinopril and up to 5 mg twice daily for ramipril. Randomized treatment was continued for 6 to 48 weeks and patients were seen at enrollment and every 1 to 6 months, depending on the study. For all studies, duration of treatment and follow-up periods overlapped, the only exception being represented by the SMILE-1 study. In this trial, on completion of the 6-week double-blind treatment period, the patients stopped taking the study medication, but continued treatment with their other medications for additional 48 weeks.

Statistical analysis

For the purpose of the present retrospective analysis, the primary study endpoint was set as the composite outcome of 1-year death or hospitalization for CV causes, after weighing for the number of subjects contributing from each study. The analysis was based on the intention-to-treat population, consisting of all randomized patients treated with at least one dose of study medication and providing at least once the measure of the primary efficacy assessment, even in case of protocol violation or premature withdrawal from the study. The efficacy endpoint was compared across treatments, separately for MS+ and MS− patients. A diagnosis of MS was based on the harmonized definition proposed by the International Diabetes Federation and the American Heart Association, National Heart, Lung, and Blood Institute.[18] Accordingly, a patient was defined as MS+ when at least three out of the following five risk factors were present: (1) elevated waist circumference (≥102 cm males and ≥88 females); (2) elevated triglycerides (≥150 mg/dL) or under specific lipid-lowering pharmacological treatment; (3) reduced high-density lipoprotein (HDL) cholesterol (<40 mg/dL in males and <50 mg/dL in females) or under specific lipid-lowering pharmacological treatment; (4) elevated office BP (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or under antihypertensive drug treatment; (5) elevated fasting glucose (≥100 mg/dL) or treated with antidiabetic drugs. Since waist circumference was not available from the studies, central obesity was defined according to a BMI ≥25 kg/m^2.

The relative risk of the composite endpoint was separately estimated for MS+ and MS− and for each treatment group using a time-dependent Cox proportional hazard regression model. Adjustments were made for gender (males vs. females) and age (<65 years vs. ≥65 years). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, and survival

Table 1. Absolute (*n*) and Relative (%) Frequencies of Individual Components of the Metabolic Syndrome According to the Type of Treatment

	Placebo (n = *882*)	*Zofenopril* (n = *1742*)	*Lisinopril* (n = *515*)	*Ramipril* (n = *349*)	P *value across treatments*
Obesity (BMI ≥25 kg/m^2)	523 (59.3)	1198 (68.8)	364 (70.7)	250 (71.6)	0.001
Elevated triglycerides (≥150 mg/dL) or under specific lipid-lowering pharmacological treatment	334 (37.9)	684 (39.3)	213 (41.4)	125 (35.8)	0.261
Reduced HDL cholesterol (<40 mg/dL in males and <50 mg/dL in females) or under specific lipid-lowering pharmacological treatment	323 (36.6)	652 (37.4)	191 (37.1)	143 (41.0)	0.653
Elevated office BP (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or under antihypertensive drug treatment	584 (66.2)	1205 (69.2)	321 (62.3)	260 (74.5)	0.001
Elevated fasting glucose (≥100 mg/dL) or treated with antidiabetic drugs	628 (71.2)	1337 (76.8)	417 (81.0)	248 (71.1)	<0.001
Concomitant presence of at least three risk factors for MS	502 (56.9)	1134 (65.1)	340 (66.0)	227 (65.0)	<0.001

P values refer to the statistical significance of the difference across the four treatment groups.
BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; MS, metabolic syndrome.

curves were drawn. This analytical approach was followed because the duration of the observation varied across studies. Additionally, a survival analysis with Log Rank (Mantel–Cox) test was run by considering events at the time of their occurrence, without applying any missing handling procedure.

Homogeneity of patients' baseline characteristics were compared by a Chi-square test (discrete variables) or a Student *t*-test (continuous variables). The minimum level of statistical significance is $P < 0.05$ throughout the article. Data are summarized as mean ± SD or as mean and 95% CI or as absolute (*n*) and relative (%) frequencies.

Results

Patient population

A total of 3645 patients from the four SMILE studies were eligible for the inclusion in the present individual pooled data analysis. However, 157 patients were excluded from the analysis because the number of individual components for the definition of the MS was less than three and thus insufficient to define the presence or absence of MS. Two thousand two hundred and three patients (63.2%) were classified as MS+ and 1285 (36.8%) as MS–. As far as MS+ patients are regarded, 502 were treated with placebo (22.8%), 1134 with zofenopril (51.5%), 340 with lisinopril (15.4%), and 227 with ramipril (10.3%). In the MS– subgroup, 380 patients received placebo (29.6%), 608 zofenopril (47.3%), 175 lisinopril (13.6%), and 122 ramipril (9.5%). No statistically significant difference ($P = 0.924$) was observed for the distribution of treatments between the two study subgroups.

Main demographic and clinical features of the population, including the distribution of the single components of the MS according to treatment group, is summarized in Table 1. The prevalence of hypertriglyceridemia and HDL hypocholesterolemia was balanced across the four treatment groups, whereas some heterogeneity was observed for other MS components such as obesity, hypertension, and hyperglycemia. MS was more common ($P < 0.001$) in patients treated with active drugs (65.3%) than in those treated with placebo (56.9%).

CV outcomes in MS+ vs. MS–

As shown in Table 2, patients with MS+ were older, less often of a male gender, and presented with higher values of

Table 2. Demographic and Clinical Characteristics According to the Presence (MS+) or Absence of the Metabolic Syndrome (MS–)

	MS+ (n = *2203*)	*MS–* (n = *1285*)	P *value between groups*
Age (years)	61.0 ± 10.5	61.7 ± 11.1	0.036
Males	1612 (73.2)	1038 (80.8)	<0.001
NSTEMI	592 (26.9)	314 (24.4)	0.113
BMI (Kg/m^2)	28.0 ± 3.6	25.1 ± 3.3	<0.001
Blood glucose (mg/dL)	149.8 ± 66.0	119.7 ± 57.1	<0.001
Serum HDL cholesterol (mg/dL)	42.2 ± 13.0	50.5 ± 15.5	<0.001
Serum triglycerides (mg/dL)	177.4 ± 110.1	109.9 ± 49.7	<0.001
SBP (mmHg)	141.6 ± 20.7	127.6 ± 19.4	<0.001
DBP (mmHg)	85.2 ± 12.2	78.5 ± 11.3	<0.001

Data are shown as absolute (*n*) and relative (%) frequencies for categorical variables and as mean ± SD for continuous variables. *P* values refer to the statistical significance of the difference between the two groups.
DBP, diastolic blood pressure; NSTEMI, non ST-segment elevation myocardial infarction; SBP, systolic blood pressure.

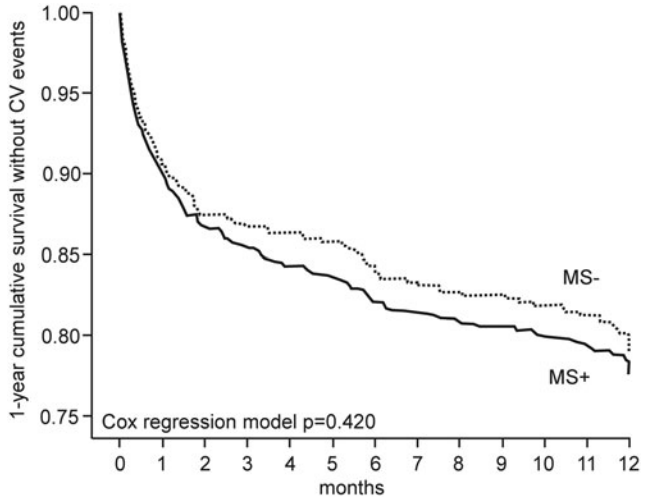

FIG. 1. Cumulative survival without cardiovascular (CV) events during 1 year of follow-up in patients with metabolic syndrome (MS+, $n=2203$) and without metabolic syndrome (MS−, $n=1285$) of the SMILE program. *P* value from the Cox regression analysis.

BMI, blood glucose, serum triglycerides and BP, and lower values of serum HDL cholesterol, as compared with MS−. The mean follow-up time was similar for MS+ and MS− patients (7.1 months). Three hundred ninety nine of 2203 MS+ patients (18.1%) and 231 of 1285 MS− patients (18.0%) reported a major CV event during the 1-year follow-up, with no between-group differences [HR and 95% CI: 0.92 (0.76–1.12), $P=0.420$]. As shown in Figure 1, chance of surviving similarly decreased in the two subgroups during the study. The average survival time according to the Kaplan–Meier analysis was 10.1 (9.9–10.3) months in MS+ and 10.3 (10.0–10.6) months in MS− patients (log rank test $P=0.450$).

CV outcomes according to the type of treatment and MS

When patients were grouped according to the type of treatment, no difference was observed in the prevalence of the composite endpoint between MS+ and MS− patients (Fig. 2). However, in a logistic regression analysis, which accounted for the presence or absence of MS, the 1-year risk of CV events was significantly lower under zofenopril [HR and 95% CI: 0.79 (0.63–0.97); $P=0.028$] and lisinopril [0.65 (0.47–0.89); $P=0.007$], but larger under ramipril [2.57 (1.94–3.93); $P=0.0001$] than under placebo.

As shown in Figure 3, treatment of MS+ patients with zofenopril was associated with a 48% reduction in CV risk as compared with the other ACE inhibitors [HR and 95% CI: 0.52 (0.42–0.66)], with a statistically significant ($P=0.0001$) difference between the two groups in survival rates without events (Fig. 3, left panel). Cumulative survival rates were higher under zofenopril than under the other ACE inhibitors also in MS− patients (Fig. 3, right panel). Treatment with zofenopril was associated with a 48% significantly ($P=0.0001$) larger reduction in the risk of CV than the lisinopril and ramipril pooled together [HR and 95% CI: 0.52 (0.38–0.73)].

CV drug use during the study

Distribution of the use of CV drugs in the MS+ and MS− patients is presented in Table 3. Antithrombotic agents, beta blockers, and nitrates were the most widely employed drugs. Except for angiotensin II receptor blockers and antiarrhythmic drugs, a significantly larger use of CV medications was observed in the MS+ group. This can be expected given the fact that MS patients usually present with several CV comorbidities and risk factors as documented in Table 2.

Discussion

The results of our pooled individual data analysis of the four randomized prospective SMILE studies demonstrated that treatment of AMI patients with ACE inhibitors is effective in reducing the 1-year risk of major CV events, in both MS+ and MS− patients. Together with the previous *post-hoc* publication of the SMILE-1 study, this is one of the first evidences from randomized controlled studies of the prognostic benefit of ACE inhibition in MS patients with AMI. Recently, one prospective, although observational study, showed that chronic ACE inhibition therapy of MS+ patients can reduce the risk of periprocedural myocardial infarction compared with the ACE inhibitor naive group.[19] All these findings taken together strengthen the recommendations of current guidelines, which indicate that ACE

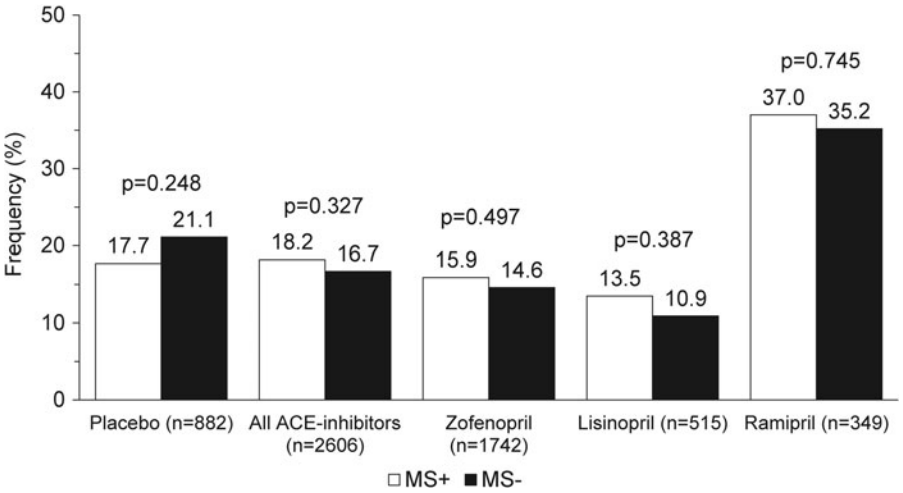

FIG. 2. One-year incidence of CV morbidity and mortality in MS+ and MS− patients treated with placebo, zofenopril, lisinopril, or ramipril. *P* values refer to between-group comparison by Chi-square test. Symbols as in the preceding figure.

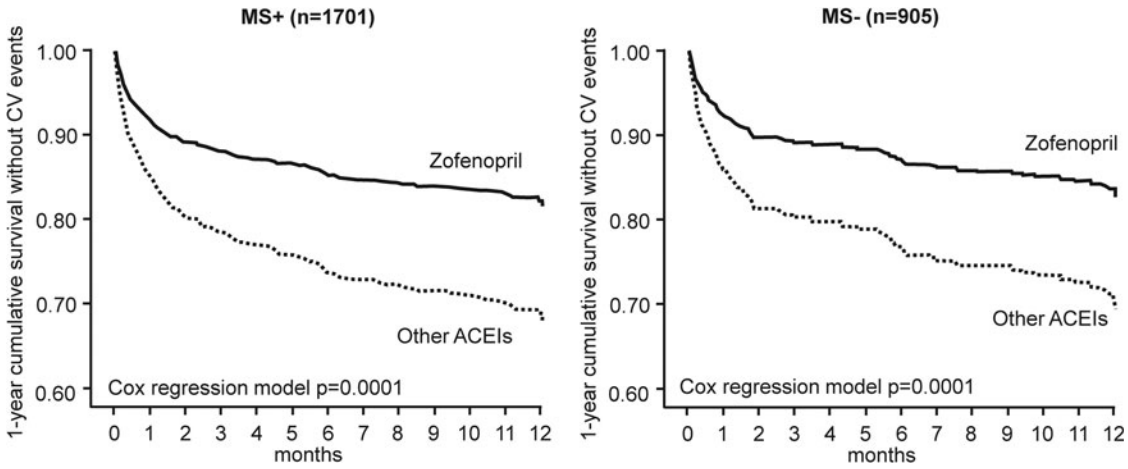

FIG. 3. Cumulative survival without CV events during 1 year of follow-up in MS+ patients treated with zofenopril ($n=1134$) or other angiotensin-converting enzyme (ACE) inhibitors ($n=567$), and in MS− patients ($n=608$ zofenopril and $n=297$ other ACE inhibitors). *P* values are from the Cox regression analysis. Symbols as in preceding figures.

inhibitors and angiotensin II-AT1 receptor blockers as the preferred treatment for high-risk patients.[20,21]

Interestingly, the effects of zofenopril and lisinopril in MS+ patients were significantly better than those of ramipril. This is not surprising, since the DREAM study has documented that among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of ramipril for 3 years does not significantly reduce the incidence of diabetes or death.[22] At least for zofenopril, we can speculate that its superiority to ramipril may be related to some primary protective effects against the deterioration of left ventricular function and the progression of the atherosclerotic disease that follows myocardial ischemia, which have been demonstrated in animal studies.[23,24]

In our study, the prevalence of MS in post-AMI patients was consistent, confirming the impact of metabolic abnormalities in post-AMI patients. However, the absolute prevalence found in our study (63.2%) was larger than that observed in previous studies. This finding might be explained by differences in the criteria used for classifying the patients as MS and by the inherent characteristics of patients enrolled in the different studies.[4,25,26] It must be acknowledged that, unlike other studies, we applied the most recent and rigorous criteria recommended by harmonized guidelines and we performed a randomized controlled study.[18]

Some limitations of our pooled individual data analysis need also to be discussed. The present is a *post-hoc* analysis of four studies with a quite similar design, but with some differences in the inclusion criteria, and treatment duration and follow-up, which might have biased the study results, particularly when direct comparisons between different active drug treatments were attempted. However, we chose to run a pooled individual data analysis and we adjusted comparisons for confounding variables. Additionally, our results in the two MS+ and MS− subgroups were consistent with those observed for the whole pooled population, which were recently published.[27] We did not observe an increased risk of morbidity and mortality among MS+ patient treated with placebo with respect to MS− patients, as shown in previous observational studies.[9,28,29] This might be due to the fact that patients assigned to placebo in the SMILE-1 and 3 studies were also treated with CV drugs, which might have unmasked the long-term adverse prognostic effect of MS. As a matter of fact, in our pooled analysis we showed that MS+ were more intensively treated with CV medications than MS− patients, a finding which can be expected given the larger prevalence of CV comorbidities and risk factors in MS+ patients. Finally, we used BMI as a surrogate of waist circumference for defining abdominal obesity, which might not have allowed an accurate estimation of central

Table 3. Concomitant Cardiovascular Drug Treatments During the Follow-up Period According to the Presence (MS+) or Absence of the Metabolic Syndrome (MS−)

	MS+ (n=2203)	*MS− (n=1285)*	P *value between groups*
ACE inhibitors	49 (3.8)	22 (1.0)	<0.001
Angiotensin II receptor blockers	5 (0.4)	3 (0.1)	0.132
Beta blockers	1024 (79.7)	638 (29.0)	<0.001
Calcium channel blockers	254 (19.8)	124 (5.6)	<0.001
Diuretics	501 (39.0)	239 (10.8)	<0.001
Nitrates	1008 (78.4)	787 (35.7)	<0.001
Antiarrhythmic drugs	104 (8.1)	149 (6.8)	0.144
Antithrombotic agents (including ASA)	1235 (96.1)	1817 (82.5)	<0.001
Lipid-lowering drugs	587 (45.7)	441 (20.0)	<0.001
Other cardiovascular drugs	169 (13.1)	248 (11.3)	0.096

Data are shown as absolute (*n*) and relative (%) frequencies. *P* values refer to the statistical significance of the difference between the two groups.

ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid.

obesity. However, previous evidence exists that the use of BMI does not negatively affect the assessment of the prevalence and prognostic impact of this condition in the general population.[30]

In conclusion, our pooled individual data analysis of the four randomized prospective SMILE studies demonstrates the striking benefit of ACE inhibitors in post-AMI patients with MS, supporting the use of such class of drugs for the routine treatment of such patients. A larger protective effect of zofenopril and lisinopril than ramipril suggests that not all ACE inhibitors may be equally effective for this purpose.

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Author Disclosure Statement

Conflict of interest of Prof. Claudio Borghi: consultancy for Boheringer Ingelheim, Menarini International, Sanofi, Amgen, Takeda, Novartis, Ely Lilly, and Servier. None of the other authors have any conflicts of interest to disclose.

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