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Clinical Investigations

PREVENTION

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)

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ABSTRACT

Background: Angiotensin-converting enzyme inhibitors (ACEIs) are largely employed for treating patients with left ventricular dysfunction (LVD), but their efficacy may be negatively affected by concomitant administration of acetylsalicylic acid (ASA), with some difference among the different compounds.

Hypothesis: The interaction between ASA and the two ACEIs zofenopril and ramipril may result in a different impact on survival of cardiac patients, due to differences in the pharmacological properties of the two ACEIs.

Methods: This phase IIIb, randomized, double-blind, parallel-group, multicenter, European study compared the safety and efficacy of zofenopril (60 mg/day) and ramipril (10 mg/day) plus ASA (100 mg/day), in 771 patients with LVD (clinical signs of heart failure or a left ventricular ejection fraction <45%) following acute myocardial infarction (AMI). The primary study end point was 1-year combined occurrence of death or hospitalization for cardiovascular causes.

Results: In the intention-to-treat population, the primary outcome was significantly reduced by zofenopril (n = 365) vs ramipril (n = 351) (odds ratio [OR]: 0.70, and 95% confidence interval [CI]: 0.51-0.96; $P = 0.028$) as a result of a decrease in cardiovascular hospitalization (OR: 0.64,95% CI: 0.46-0.88; $P = 0.006$). Mortality rate was not significantly different between the 2 treatments (OR: 1.51, 95% CI: 0.70-3.27; $P = 0.293$). Blood pressure values did not significantly change during the 1-year follow-up. N-terminal pro-brain natriuretic peptide levels were progressively reduced during the study, with no statistically significant between-treatment differences. Proportion of patients with deterioration of renal function during the study was similar between the 2 groups. Drug safety profile was comparable between treatments.

Conclusions: In patients with LVD following AMI, the efficacy of zofenopril associated with ASA was superior to that of ramipril plus ASA, indicating some important clinical implications for the future use of ACEIs in patients with LVD or overt heart failure.

Trial registration: EudraCT Number: 2004-001150-88 (www.clinicaltrialsregister.eu); Italian Ministry of Health Code: GUID OTT_III_2004_001 (https://oss-sper-clin.agenziafarmaco.it).

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Introduction

A combination of an angiotensin-converting enzyme inhibitor (ACEI) and acetyl salicylic acid (ASA) is a widely used treatment in patients with both heart failure and ischemic heart disease.[1] However, the safety of such an association has been questioned because both drugs interfere with a prostaglandin-mediated pathway.[2] To date there is conflicting evidence on the possible negative interaction between ASA and ACEIs on survival of cardiac patients.[1,3–6] Some meta-analyses seem to suggest an antagonistic interaction between the 2 drugs, with reduced efficacy of ACEIs on morbidity and mortality.[7,8]

The differences in the results of the studies investigating the effects of the combination of ACEI plus ASA are basically post hoc or retrospective, with some differences in study design, choice of the evaluation parameter, patient characteristics and inclusion criteria, and type and the dosage of each selected treatment.[2] In addition, some differences in the pharmacological profile of ACEIs can affect the extent of interaction with ASA.[9–12] Given the controversy, current guidelines suggest that further prospective studies are required in this field.[13,14]

The objective of this prospective, double-blind, randomized, parallel group study was to investigate the efficacy and safety of early administration of the ACEIs zofenopril and ramipril plus ASA in patients with acute myocardial infarction (AMI) complicated by left ventricular systolic dysfunction (LVD).

Methods

Study Population

Male and non-pregnant female patients aged 18 to 85 years with a confirmed diagnosis of ST-elevation myocardial infarction (STEMI) or non–ST-elevation myocardial infarction (NSTEMI) in the 24 hours preceding the enrollment (not treated with primary percutaneous transluminal angioplasty [PTCA], treated or not with thrombolysis, and recommended pharmacologic treatment) and with clinical and/or echocardiographic evidence of LVD (Killip class >1, plus 3rd heart sound or pulmonary congestion on chest x-ray, and/or a left ventricular ejection fraction [LVEF] <45%) were enrolled in this study. The protocol was amended to also allow inclusion of patients treated with PTCA or a coronary artery bypass graft, representing the majority of eligible patients.

The main exclusion criteria were: severe hypotension (systolic blood pressure [SBP] <90 mm Hg), history of renal artery stenosis, significant valvular disease, current treatment with ACEIs, angiotensin-receptor blockers (ARBs) or ASA, hypersensitivity to these drugs, history of stroke (previous 3 months), renal failure (serum creatinine >2.5 mg/dL), severe liver impairment (serum transaminases 3 times the upper normal limit), hematologic diseases, or other significant clinical conditions. Anticoagulant treatment was allowed only during the acute phase of the infarction.

Study Design

This was a phase IIIb randomized, double-blind, parallel-group study, involving patients with acute myocardial infarction (MI) and LVD. The study was conducted at 79 Hospitals in 8 different European countries and coordinated by the Internal Medicine Unit of the University of Bologna (Italy). The study was performed following the Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was reviewed and approved by the ethics committee of each participating center. Written informed consent was obtained from each patient before enrollment.

Study Protocol

Eligible patients entered a 4-day open-label phase when zofenopril was administered to all patients according to an up-titration scheme. This choice was based on ethical and regulatory reasons, based on previous evidence of efficacy and safety of the early zofenopril treatment in patients with anterior AMI.[15] On days 1 and 2, patients received 7.5 mg zofenopril twice daily plus an evening dose of 100 mg ASA. 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 double-blind (using a centralized, computer-generated, randomization list) to receive 30 mg zofenopril twice daily plus 100 mg ASA once daily, or 5 mg ramipril twice daily plus 100 mg ASA once daily for 12 months. Originally the study design foresaw 4 treatment arms with 2 different doses of ASA (100 and 325 mg once daily). Because patients submitted to primary PTCA were treated with clopidogrel, which cannot be combined with high-dose aspirin according to recent studies and recommendations,[16,17] the protocol was amended, deleting from the study design the 325 mg ASA arm. The amendment was submitted to and approved by ethics committees in April 2005 (no patient enrolled before the amendment received 325 mg ASA).

The first patient was enrolled in March 2005, and the last patient was completed in July 2009. Zofenopril and ramipril were supplied as identical oral tablets (overencapsulation technique). In the event of severe hypotension (SBP <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 MI, and in case of a specific indication or in patients who reached a study end point. Patients were seen at enrollment (visit 1), at randomization (visit 2, 5 days after enrolment), and after 1, 6, and 12 months (visits 3, 4, and 5). Blood pressure and heart rate were measured on each visit before the morning drug dose or in case of suspected hypotension. A physical examination, a 12-lead electrocardiogram, and laboratory tests (hematology, clinical chemistry, and urinalysis) were performed at visit 1. These tests were repeated at visit 2 and at study end. An echocardiogram was performed, blood samples were drawn (centralized estimation of N-terminal pro-brain natriuretic peptide [NT-proBNP]), and occurrence of concomitant diseases, adverse events, use of concomitant medications, and compliance to study drugs were checked at each study visit.

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Statistical Analysis

The primary study end point was the comparison between zofenopril- and ramipril-treated patients at the 1-year combined occurrence of cardiovascular mortality or hospitalization for cardiovascular causes (congestive heart failure, AMI, angina, or a decline in LVEF >15%). Secondary study end points were hospitalization for cardiovascular causes, changes in LVEF, left ventricular end-diastolic and end-systolic volumes, plasma NT-proBNP levels and blood pressure, overall incidence of noncardiovascular adverse events, severe hypotension, and deterioration of renal function (decline >15% of glomerular filtration rate or glomerular filtration rate [GFR], Cockroft-Gault formula). The primary and secondary end points were confirmed by an independent end point and safety committee that directly reviewed patients' records in a blinded fashion. Data management and statistical analysis were carried out by a team under the supervision of the study coordinators.

The study was planned to enroll 896 patients (448 per treatment group), with an expected 1-year event rate of 15% under zofenopril and 25% under ramipril. The sample size estimation was based on a 2-sided χ^2 test, with a 90% power and a 5% significance level. A 25% drop-out rate was taken into account to obtain at least 672 evaluable patients (336 per treatment group). Event rates for sample size estimation were assumed from the Survival of Myocardial Infarction Long-term Evaluation group-1 study (SMILE-1) for zofenopril (10% rate of major cardiovascular events after 6 weeks in 772 patients)[15] and from the Acute Infarction Ramipril Efficacy study (AIRE) for ramipril (28% of patients with any event in 1.104 patients, of whom 86% treated with 5 mg twice-daily).[18]

Evaluation of the efficacy end points was carried out in the intention-to-treat population (patients treated with at least 1 dose of study medication and documenting at least once the measure of the primary efficacy assessment, even in case of protocol violation or premature withdrawal from the study).

The baseline characteristics and the distribution of variables in the zofenopril and ramipril populations were compared using a χ^2 test for categorical variables and Student *t* test for continuous variables. A logistic regression model was used to assess the difference between treatment groups with respect to cardiovascular mortality and morbidity rate, calculating the estimated odds ratio (OR) and the corresponding 95% confidence interval (CI). To account for possible confounding factors, the analysis was also adjusted for age, gender, GFR, LVEF, Killip class, revascularization, diabetes, metabolic syndrome, hypercholesterolemia, low high-density lipoprotein HDL, STEMI vs NSTEMI, NT-proBNP, and heart rate. The χ^2 analysis was applied to data with the Mantel-Haenszel extension for the comparison between the 2 treatment groups. Time-to-event curves were also 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 $P < 0.05$.

Results

Patient Population

Overall, 871 patients were enrolled into the study, and 771 were randomized to treatment (389 patients to zofenopril and 382 patients to ramipril) (Figure 1). Of the randomized patients, 64 (17%) receiving zofenopril and 58 (15%) receiving ramipril were prematurely withdrawn from the study (a drop-out frequency lower than the 25% planned). The number of patients included in the intention-to-treat population was 716 (365 treated with 60 mg zofenopril and 351 with 10 mg ramipril). Treatment compliance (subjects taking ≥75% of drug dose) was high and comparable between groups (zofenopril 96%, ramipril 96%, ASA zofenopril group 97%, ASA ramipril group 96%).

At baseline there were no significant differences in demographic and clinical characteristics between the treatment groups, except for the proportion of patients with hypertension ($P = 0.033$), previous PTCA ($P = 0.044$) and LVEF <40% ($p = 0.009$) (table 1).

Primary Outcome Measure

During the 12 months of double-blind randomized treatment, cardiovascular death or hospitalization occurred in 128/351 patients in the ramipril (37%) and in 105/365 patients in the zofenopril group (29%) (Figure 2A). Treatment with zofenopril was associated with a 30% significantly ($P = 0.028$) lower risk of achieving the combined end point (OR: 0.70, 95% CI: 0.51-0.96). Risk estimate did not differ after adjustment for confounding factors (OR: 0.68, 95% CI: 0.49-0.95); [$P = 0.024$]. The distribution of fatal and nonfatal cardiovascular events is reported in Table 2.

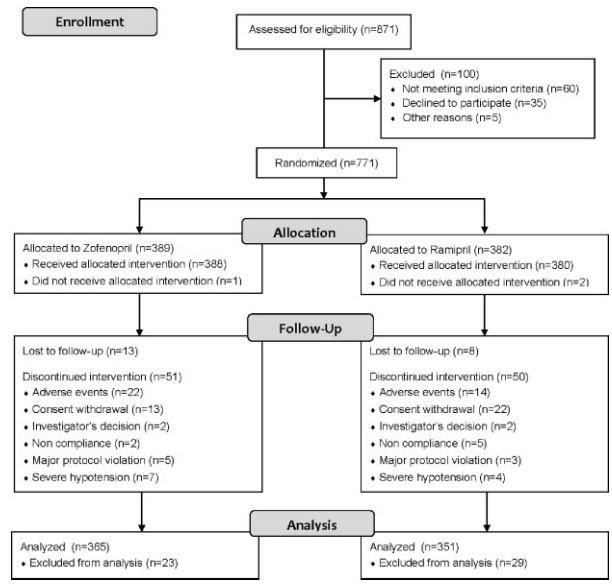

Figure 1. Flow diagram of the patients throughout the study. Analyzed patients refer to those treated with at least 1 dose of study medication and who had documented at least once the measure of the primary efficacy assessment, even in case of protocol violation (intention-to-treat population).

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Table 1. Baseline Demographic Characteristics of the Intention-to-Treat Population (N = 716)

Characteristics	Zofenopril (n = 365)	Ramipril (n = 351)
Age, mean ± SD, y	61 ± 11	61 ± 11
Gender, n (%)		
Male	268 (73)	276 (79)
Female	97 (27)	75 (21)
BMI, mean ± SD, kg/m²	28 ± 4	28 ± 4
Diabetes, n (%)	68 (19)	63 (18)
Treated hypercholesterolemia, n (%)	68 (19)	72 (21)
Treated hypertension, n (%)	237 (65)	200 (57)
Relevant concomitant treatments, n (%)		
ACE-inhibitors	13(4)	3 (1)
Angiotensin II antagonists	4 (1)	1 (1)
β-blockers	199 (55)	177 (50)
α-blockers	24 (7)	28 (8)
Calcium antagonists	8 (2)	13 (4)
Diuretics	73 (20)	74 (21)
Digoxin	—	3 (1)
Nitrates	128 (35)	117 (33)
Antiarrhythmic drugs	14 (4)	9 (3)
Statins	217 (59)	200 (57)
Other lipid lowering drugs	15 (4)	17 (5)
Other cardiovascular drugs	47 (13)	32 (9)
Atrial fibrillation, n (%)	7 (2)	2 (1)
Peripheral arterial occlusive disease, n (%)	17 (5)	18 (5)
Previous myocardial infarction, n (%)	72 (20)	61 (18)
Angina pectoris, n (%)	140 (39)	123 (35)
Prior PTCA, n (%)	26 (7)	13 (4)
Prior CABG, n (%)	6 (2)	6 (2)
Congestive heart failure, n (%)	24 (7)	25 (7)
Killip class on admission, n (%)		
I	116 (31)	120 (34)
II-IV	249 (69)	231 (66)
Infarct location (%)		
Anterior	198 (54)	185 (53)
Posterior	33 (9)	21 (6)
Lateral	26 (7)	26 (7)
Inferoposterior	67 (18)	70 (20)
Other	40 (11)	49 (14)
PTCA performed at entry, n (%)	115 (32)	109 (31)
Thrombolytic therapy performed at entry, n (%)	141 (39)	134 (38)
Type of thrombolytic therapy, n (%)		
Streptokinase	56 (15)	60 (17)
Alteplase	22 (6)	18 (5)
Tenecteplase	42 (12)	36 (10)
Reteplase	9 (2)	6 (2)
Other	12 (3)	14 (4)
Estimated GFR, mean ± SD, mL/min	85 ± 32	89 ± 34
NT-proBNP, median (25th and 95th percentile), pg/mL	1118 (448–2514)	1114 (521–2342)
LVEF mean ± SD, %	42 ± 8	43 ± 7
LVEF ≤40%, n (%)	151 (41)	111 (32)
SBP, mean ± SD, mm Hg	139 ± 24	140 ± 24
DBP, mean ± SD, mm Hg	83 ± 14	83 ± 13
HR, mean ± SD, mm Hg	81 ± 17	79 ± 16

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; GFR, glomerular filtration rate (estimated by Cockroft-Gault formula); HR, heart rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure; SD, standard deviation.

Secondary Outcome Measures

The rate of hospital admission for cardiovascular causes was significantly reduced by 35% in patients receiving zofenopril (88/365, 24%) as compared to those receiving ramipril (117/351, 33%) (OR: 0.64, 95% CI: 0.46-0.88, $P = 0.006$) (Figure 2B). The OR for 1-year risk of cardiovascular hospitalization was 0.65 (95% CI: 0.46-0.91) ($P = 0.012$) after adjustment for covariates.

Cumulative incidence of cardiovascular death in the course of the 1 year of follow-up was not significantly different between ramipril (11 deaths, 3% of patients) and zofenopril (17 deaths, 5% of patients) (OR: 1.51, 95%

Table 2. Absolute and Relative Frequency (%) of Causes of Cardiovascular Death and of Major Cardiovascular Events Requiring Hospitalization in the Intention-to-Treat Population (N = 716)

	Zofenopril (n = 365), N (%)	Ramipril (n = 351), N (%)
Cardiovascular death		
Congestive heart failure	4 (1.1)	2 (0.6)
Acute myocardial infarction	6 (1.6)	1 (0.3)
Sudden death	6 (1.6)	6 (1.7)
Cardiac rupture	1 (0.3)	1 (0.3)
Stroke	—	1 (0.3)
All causes of cardiovascular death	17 (4.7)	11 (3.1)
Major cardiovascular events requiring hospitalization		
Congestive heart failure	4 (1.1)	7 (2.0)
Acute myocardial infarction	13 (3.6)	16 (4.6)
Angina pectoris	20 (5.5)	22 (6.3)
Decline in left ventricular ejection fraction >15%	15 (4.1)	28 (8.0)
Revascularization	25 (6.8)	32 (9.1)
Other causes	11 (3.0)	12 (3.4)
All causes of major cardiovascular events	88 (24.1)	117 (33.3)

CI: 0.70-3.27; $P = 0.293$). Adjusted risk of death was slightly lower than the crude estimation (OR: 1.18, 95% CI: 0.51-2.70); $P = 0.704$).

SBP and diastolic blood pressure decreased from baseline, achieving similar values at study end in both groups (zofenopril 126.1 ± 16.5/75.4 ± 9.9 mm Hg vs ramipril 125.6 ± 14.0/75.0 ± 9.0 mm Hg, $P = 0.685$ and $P = 0.604$, respectively). Median NT-proBNP levels (25th and 95th percentile) were progressively reduced during the follow-up, although no statistically significant ($P = 0.456$) between-treatment differences were observed at study end (zofenopril 264, 98.5-677.0 pg/mL vs ramipril 189.0, 77.5-459.8 pg/mL). Improvement in LVEF (increase ≥5%) at the end of treatment was achieved by 65% of zofenopril- and 65% of ramipril-treated patients ($P = 0.862$). A deterioration of renal function was observed during the study in similar ($P = 0.452$) proportions in the zofenopril (20%) and ramipril group (23%).

Concomitant cardiovascular drugs were taken during the study by 96% of patients receiving zofenopril and 94% receiving ramipril. The most common concomitant drugs were lipid-lowering drugs (88% and 90%), followed by β-blockers (76% of zofenopril-treated and 72% of ramipril-treated patients), nitrates (55% and 54%), diuretics (44% and 40%), calcium-channel blockers (13% and 11%), antiarrhythmics (7% and 8%), ARBs (4% and 3%), cardiac glycosides (3% and 2%), other minor cardiac treatments (28% and 26%).

Safety

Assessment of noncardiovascular adverse events was done in 768 patients (388 treated with zofenopril and 380 with ramipril). Overall, 352 (46%) patients reported 784 adverse events (180 patients and 395 events under zofenopril, 172 patients and 389 events under ramipril). Most of the events (83%) were of a mild or moderate intensity; 44% of them

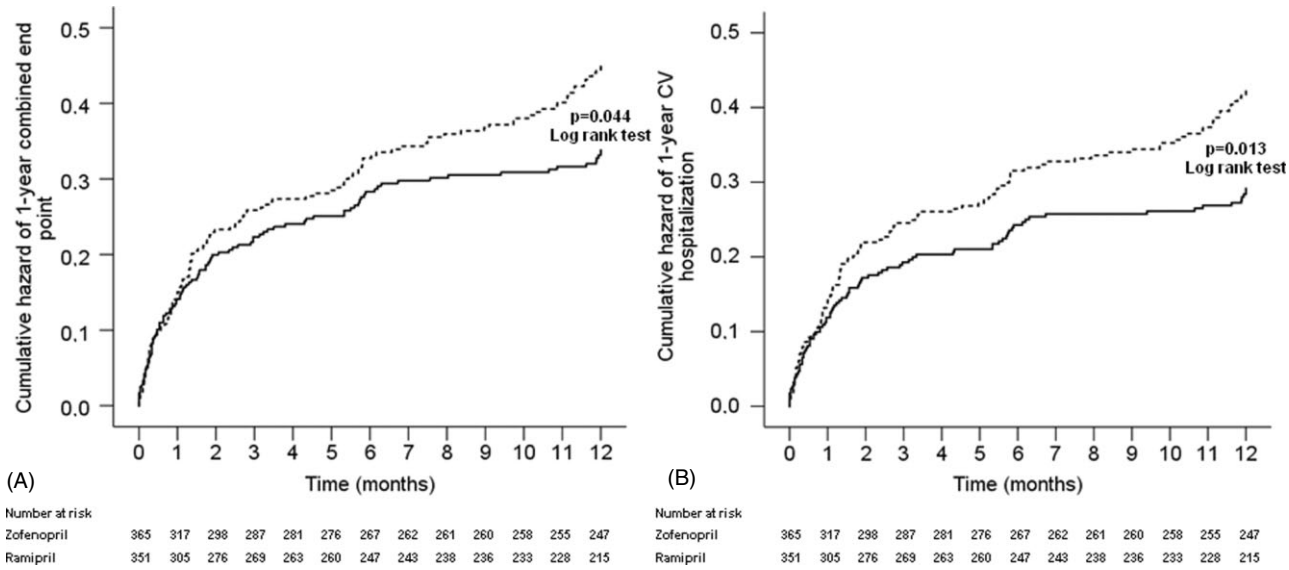

Figure 2. Incidence of the combined primary study end point (cardiovascular [CV] mortality or hospitalization for cardiovascular causes, including congestive heart failure, acute myocardial infarction, angina or decline in left ventricular ejection fraction >15%) (A) and of hospitalization (B) during the 1-year of treatment with zofenopril plus acetylsalicylic acid (ASA) (continuous lines, n = 365) or ramipril plus ASA (dashed lines, n = 351). Data refer to the intention-to-treat population. *P* value from the log-rank statistics.

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were classified as serious. A total of 128 (17%) patients were withdrawn from the study due to adverse events (66 in the zofenopril and 62 in the ramipril group).

Events attributed to study treatment were 48 and occurred in 43 patients. The most common drug-related adverse events were cough, hypotension, asthenia, or vertigo. Gastrointestinal bleeding or ulcers related to concomitant treatment with ASA were reported in 6 patients.

No statistically significant differences were observed between the treatment groups in the distribution of noncardiovascular adverse events.

Discussion

Our results show that zofenopril has a significantly larger effect on prevention of 1-year risk of death or hospitalization than ramipril, although such a superiority is mainly attributed to a larger decreased rate of cardiovascular hospitalizations in the zofenopril-treated patients, with no significant differences in cardiovascular mortality.

Interestingly, the reduction in the risk of major cardiovascular events in the SMILE-4 study, where ASA has been added to ACEI treatment, is similar and consistent with that observed in the previous SMILE trials. In such studies, including 1956 controls and 1941 zofenopril-treated patients, the risk reduction of major cardiovascular events in patients treated early with zofenopril was 29% (30% in the SMILE-4 study).[15,19,20]

Regarding ramipril, we can infer data from the AIRE prospective study,[18] in which 2006 patients with clinical evidence of heart failure at any time after an AMI were treated with ramipril or placebo, starting on the 2nd to 9th day after the infarction, for an average period of 15 months. Approximately 86% of patients were treated with 5 mg ramipril twice daily at the end of the follow-up. In this study, mortality from all causes and the rate of major cardiovascular events were 27% and 19% lower in patients randomized to receive ramipril, respectively. At the end of the study, the relative risk of death was 37% lower with ramipril than placebo in patients receiving ramipril alone and 22% less in those receiving ramipril plus aspirin at randomization. Unfortunately, the difference between the 2 study subgroups did not reach statistical significance, because of the relatively small percentage of patients not taking aspirin at randomization (22%) and because aspirin use after randomization was permitted but not taken into account in the analysis.

So far there has been a controversy on the possible counteraction of ACEI efficacy by aspirin in patients with ischemic heart disease or heart failure.[2,5] Most of the studies were retrospective analyses or used hemodynamic end points, and with the exception of a well-designed and performed meta-analysis and a pooled analysis of 3 large randomized trials,[7,8] none produced results strong enough to contraindicate the aspirin-ACEI association or to prove the clinical relevance of this interaction.[1,3,6,7,21] Probably, the differences in clinical efficacy among ACEIs, when combined with ASA, might be related to differences in their pharmacological features. There is evidence from small experimental animal studies that sulfhydryl-containing ACEIs, such as captopril or zofenopril, maintain their cardiovascular protective effects even in presence of cyclooxygenase inhibitors,[9,12] whereas this is not the case for enalapril,[9] ramipril,[10,11] or lisinopril.[22] In addition, a direct comparison between zofenopril and ramipril showed a lower accumulation of bradykinin and prostaglandins at the lung level in animals treated with zofenoprilat.[23,24] This means that a sulfhydryl ACEI might have a cardioprotective mechanism of action, which only in part includes a prostaglandin-mediated mechanism largely influenced by indomethacin or ASA. An indirect demonstration of the possible validity of our assumption may come from the Valsartan in Acute Myocardial Infarction (VALIANT) study,[19,25] in which the 1-year rate of death from cardiovascular cause with captopril (25%) was very close to that observed in our study (29%). In the VALIANT study, 92% of patients were treated with aspirin or other antiplatelet agents.[26]

In our study the incidence of adverse events observed with zofenopril was comparable to that observed with the reference drug, ramipril, and both drugs showed a tolerability profile that was largely consistent with previous clinical observations based on treatment of post-MI with the same active principles.[15,18]

We must acknowledge a number of important limitations of our study. First, the dose of ASA (100 mg once daily) might have not been sufficient to observe a clear benefit or to unmask a possible drug-drug interaction with the ACEIs. However, the available evidence indicates that the lowest effective and safe daily dose of aspirin for the long-term prevention of serious vascular events in high-risk patients is in the range of 75 to 100 mg.[16,26] We could not use a higher dose of ASA, because patients could have been treated with clopidogrel or ticlopidine following PTCA, and current evidence and guidelines do not recommend dosages higher than 100 mg/d in the presence of these drugs.[16,17] Second, we cannot exclude that the use of lower or higher doses of ASA than those selected for our study (eg, 75 mg or 300 mg) could have led to different results in terms of outcomes. Third, approximately one-third of the patients performed a PTCA or received thrombolytic therapy at entry, but the distribution of such patients was well balanced between treatments, thus excluding a possible bias. Fourth, the fact that all patients were treated with zofenopril at entry might have favored this drug at the expense of ramipril. However, this was a mandatory ethical choice, because previous evidence from the SMILE program indicates that zofenopril has a clear prognostic benefit when used in the early phase of MI, whereas such an evidence is not available for ramipril.[15,18] Fifth, the combined study end point was statistically significant, but this was mainly due to a 35% reduced hospitalization rate in the zofenopril group, because mortality was not significantly different between the 2 groups, probably because of the relatively short duration of the observation period. Sixth, some prognostic factors at baseline were unevenly distributed in the 2 populations, but a logistic regression analysis adjusted for confounding factors gave results similar to those obtained by unadjusted analysis. Seventh, we did not assess platelet function or specifically address possible pharmacological mechanisms explaining the interaction between ASA and the ACEIs used in this study. This was beyond the study aim, and it could

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be the objective of future studies. Finally, it is important to recognize that our study had no control group with ACE-inhibitors and no ASA, and equally important no control group with no active treatment.

Conclusion

The results of the SMILE-4 trial showed that differences in clinical efficacy may exist when different ACEIs are combined with ASA. In particular, our study showed a more favorable impact of zofenopril than ramipril on major cardiovascular events and in a relatively long-term period of 1 year.

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Appendix: SMILE-4 Working Party

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