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ORIGINAL ARTICLE

Serum cholesterol levels on admission and survival in patients with acute myocardial infarction treated with zofenopril: a post hoc analysis of the Survival of Myocardial Infarction Long-term Evaluation trial

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ABSTRACT

To evaluate the clinical efficacy of early angiotensin-converting enzyme (ACE) inhibition by zofenopril in patients with anterior myocardial infarction and normal or high plasma low density lipoprotein-cholesterolaemia. Post hoc analysis of the Survival of Myocardial Infarction Long-Term Evaluation study, a double-blind, clinical trial including 1400 patients with anterior myocardial infarction, randomized to zofenopril (n = 699, 66% hypercholesterolemics) or placebo (n = 701, 64% hypercholesterolemics) for 6 weeks. The rate of the primary end-point (6-week combined occurrence of death and severe congestive heart failure) was 8.1% in hypercholesterolemic and 6.4% in normocholesterolemic patients ($P < 0.03$). The favourable effect of treatment with zofenopril was enhanced in hypercholesterolemics patients when compared with normocholesterolemics (RRR = 43%, $P = 0.034$ vs. 25%, $P = 0.19$). One-year mortality was 10% in hypercholesterolemic patients vs. 7.5% in normocholesterolemic patients ($P = 0.037$), equally reduced in both hypercholesterolemic and normocholesterolemics patients by zofenopril. The presence of hypercholesterolaemia in patients with anterior myocardial infarction could be associated with more favourable effects of early ACE-inhibition.

INTRODUCTION

Hypercholesterolaemia is an independent risk factor for coronary artery disease [1] and its pharmacological treatment is associated with a significant reduction in cardiovascular morbidity and mortality [2]. In recent years, thanks to the development of highly effective lipid-lowering drugs, outcome of patients with hypercholesterolaemia has significantly improved, even though it is still far from what is suggested by scientific evidence [2,3]. Hypercholesterolaemia also negatively affects the prognosis of patients with acute myocardial infarction or coronary artery disease in whom its prevalence is particularly high [4]. This might be indirectly related to the greater severity of the atherosclerotic disease that affects hypercholesterolemic patients as well as to activation of the tissue renin–angiotensin system (RAS). Several lines of evidence support a synergistic increase in endothelial dysfunction and cardiovascular risk by augmented angiotensin II and low density lipoprotein (LDL) levels [5,6]. LDL and oxidized LDL upregulate AT1 receptor gene expression and receptor density in vascular cells, thus promoting atherosclerosis [7]. This lipoprotein–neurohumoral interaction is only partly modifiable by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) or other lipid-lowering drugs [6]. On the other hand, a body of

evidence is now supporting the hypothesis that angiotensin-converting enzyme (ACE) inhibitors may have an important role in blocking or slowing down the development and progression of atherosclerosis [8,9], particularly in high-risk coronary patients with lipid disorders [10,11]. This supports the hypothesis that RAS blockade might be more effective in presence of hypercholesterolaemia, particularly in those clinical conditions where the degree of RAS activation can affect the clinical outcome.

Although it is well known that early treatment with ACE-inhibitors of patients with acute myocardial infarction greatly improves their in-hospital and long-term survival [12–18], a literature search of Medline, Embase® and Micromedex® databases (key words: *ACE-inhibitors*, *death*, *hypercholesterolaemia*, *myocardial infarction*, *prognosis*, *survival*; years searched: 1970–2007) does not provide specific evidence on the effect of ACE-inhibitors in patients with acute myocardial infarction and high serum cholesterol.

To answer this question, a post hoc analysis of data of the Survival of Myocardial Infarction Long-term Evaluation (SMILE) Study was carried out in the subgroup of patients with hypercholesterolaemia. The main SMILE Study showed the beneficial effects of the treatment with the sulfhydryl-containing ACE-inhibitor zofenopril on mortality and morbidity of patients with non-thrombolysed anterior acute myocardial infarction [15].

MATERIAL AND METHODS

Study population

The SMILE Study included 1556 patients admitted to 154 Italian coronary care units who were randomized to study treatment with zofenopril or placebo in addition to standard recommended pharmacological treatment. Details of the study protocol have been largely described elsewhere [15]. Main SMILE study inclusion criteria were: (i) male or female gender; (ii) age 18–80 years; (iii) admittance to the intensive care unit within 24 h of the onset of chest pain typically associated with electrocardiographic signs of myocardial infarction of the anterior wall and (iv) no eligibility for thrombolytic therapy because of late admission to the intensive care unit or individual contraindications to systemic fibrinolysis.

Patients were excluded from the study if they had: (i) cardiogenic shock (Killip class 4) on admission; (ii) systolic blood pressure on admission below 100 mmHg; (iii) serum creatinine concentration above 2.5 mg/dL; (iv) history of congestive heart failure; (v) current treatment with an ACE-inhibitor; (vi) contraindications to the use of ace-inhibitors or (vii) were unable or unwilling to give informed consent. All potentially eligible patients received standard therapy including analgesic agents, beta-blockers, nitrates, calcium antagonists, aspirin, diuretics and anticoagulants as indicated.

In the present post hoc analysis, two separate subgroups of hypercholesterolemic and normocholesterolemic patients were considered. Patients were retrospectively classified as having hypercholesterolaemia in the presence of fasting plasma LDL-cholesterol ≥160 mg/dL at the baseline evaluation before randomization in the study. This is the first-level cut-off suggested by the most recent international guideline for dyslipidaemia diagnosis and management to detect hypercholesterolaemias [19,20].

Study design

The initial dose of study medication was 7.5 mg and was repeated after 12 h and progressively doubled up to the final dose of 30 mg twice daily if systolic blood pressure remained above 100 mmHg and there were no signs or symptoms of hypotension. Patients who were unable to tolerate the dose of 7.5 mg were withdrawn from the study, but included in the intention-to-treat analysis. The local investigators were aware of serum cholesterol levels, but this did not change the treatment protocol throughout the study. Patients were seen while they were in the hospital (7–15 days), after 4 weeks and at the end of the treatment period (6 weeks) during which time they could be treated with any other drug except ACE-inhibitors. On completion of the 6 week double-blind period, the patients stopped taking the study medications, but continued treatment in an open-label fashion for approximately 11 months when their vital status was blindly evaluated. Vital status was determined by means of a questionnaire or by family members, medical personnel and registry officers. Plasma lipid pattern was measured just before the first zofenopril administration with standardized enzymatic methods. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of the University of Bologna as well as by the local ethics committees when required. All patients provided written informed consent prior to inclusion into the study.

Study end-points

The primary study end-point was the combined occurrence of death or severe congestive heart failure during the 6 week of treatment with zofenopril or placebo, both

given in addition to conventional treatment. Death or presence of severe congestive heart failure was considered as a single event for each patient and their prevalence was calculated according to whichever occurred first.

Patients were considered to have severe congestive heart failure if after randomization they had at least three of the following: (i) third heart sound; (ii) bilateral pulmonary rates; (iii) radiological evidence of pulmonary congestion (above grade II on the scale of Madsen) [21] or (iv) peripheral oedema, despite the concomitant administration of digoxin, diuretics and vasodilators other than ACE-inhibitors and necessitating open-label treatment with an ACE-inhibitor. Clinical signs of severe congestive heart failure during follow-up were categorized according to the New York Heart Association functional classification [22]. Predefined secondary end-point was the effect of 6-week double-blind treatment on cumulative 1 year survival.

Statistical analysis

The present study is a post hoc analysis of the main SMILE Study carried out on hypercholesterolemic and normocholesterolemic patients. The baseline characteristics and the distribution of the various parameters for the hypercholesterolemic and normocholesterolemic patients were compared using a chi-squared test for categorical variables (with Yates' continuity correction where appropriate) and a standard normal *t*-test for continuous variables. Risk reductions and corresponding 95% CI were calculated for both the primary and secondary end-points in hypercholesterolemic patients. The chi-squared analysis was applied to data with the Mantel-Haenzsel extension for the comparisons between the two treatment groups. Time-to-event curves for mortality were drawn using Kaplan–Meier estimates. For the primary end-point, a comparison was made of hypercholesterolemic and normocholesterolemic patients. All analyses were performed on an intention-to-treat basis and all *P* values are two-tailed.

RESULTS

Patients

A cumulative population of 1400 patients with a duplicate measurement of cholesterol levels at randomization in the SMILE trial were included in this study. Seven hundred and forty-nine (53.5%) were hypercholesterolemic and 651 (46.5%) normocholesterolemic. Placebo and zofenopril treatments were equally distributed within hypercholesterolemics ($n = 384$ for placebo and $n = 365$ for zofenopril) and normocholesterolemics ($n = 317$ for placebo and $n = 334$ for zofenopril).

The hypercholesterolemic and normocholesterolemic groups were comparable for baseline clinic characteristics with the exception of hypertension that was present in the 36% of normocholesterolemic vs. the 42% of hypercholesterolemic patients ($P < 0.05$) (*Table I*). No differences in baseline characteristics were observed between hypercholesterolemic and normocholesterolemic patients allocated to placebo or zofenopril treatment. Physical activity, dietary habits and smoking habit did not significantly change during the study between the considered groups. In particular, concomitant drug treatment was comparable in normocholesterolemic and hypercholesterolemic groups, with an expected and progressive increase in the use of antiplatelet agents and beta-blockers over time (*Table II*). Non-cardiovascular drugs were assumed in a significant way by normocholesterolemic and hypercholesterolemic patients, as well.

Primary outcome measures

During the 6 weeks of double-blind treatment, the cumulative rate of primary end-point was 8.1% in hypercholesterolemic and 6.4% in normocholesterolemic patients ($P = 0.03$). Risk ratio at baseline was 1.53 (95% CI: 1.13–2.9; $2P = 0.028$). The absolute difference was more evident in patients treated with placebo (10.1% vs. 7.8%, $P < 0.002$ than in those undergoing

Table I Baseline characteristics of study population.

	NC ($n = 651$)	HC ($n = 749$)	*P* value
Age (years, mean ± SD)	65 ± 10	63 ± 10	NS
Gender ratio (male/female, %)	70/30	82/18	NS
Body weight (kg, mean ± SD) (range)	73 ± 11 (57–94)	73 ± 10 (56–92)	NS
Current smokers (%)	43	43	NS
Diabetes mellitus (%)	23	21	NS
Hypertension (%)	36	42	<0.05
SBP (mmHg, mean ± SD)	134 ± 19	138 ± 20	<0.05
DBP (mmHg, mean ± SD)	82 ± 10	85 ± 11	<0.05
HR (mmHg, mean ± SD)	81 ± 18	82 ± 15	NS
Total cholesterol (mg/dL)	173 ± 14	238 ± 27	<0.001
LDL-cholesterol (mg/dL)	128 ± 11	174 ± 9	<0.001
HDL-cholesterol (mg/dL)	43 ± 9	44 ± 8	NS
Triglycerides (mg/dL)	154 ± 13	148 ± 26	NS

NC, normocholesterolemics; HC, hypercholesterolemics; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LDL, low density lipoprotein; HDL, high density lipoprotein.

Table II Percentage distribution of concomitant drug treatments at baseline and after 6 weeks in patients with (HC) and without (NC) hypercholesterolaemia.

	NC (n = 651)		HC (n = 749)	
	Baseline	End of treatment	Baseline	End of treatment
Antiplatelet agents	45	87	41	89
Calcium channel blockers	12	12	14	12
β-blockers	45	84	41	85
Diuretics	8	9	11	14
Lipid-lowering drugs	0	7	0	11

NC, normocholesterolemics; HC, hypercholesterolemics.

ACE-inhibition (5.9% vs. 4.6%, $P = 0.06$). The event rate was 50% higher in patients with overt hypercholesterolaemia (LDL-cholesterol >160 mg/dL) than in normocholesterolemics (*Figure 1*). During the 6 weeks of double-blind treatment, death or severe congestive heart failure occurred in 39/384 of hypercholesterolemic patients randomized to placebo (10.1%) and in 21/364 of those randomized to zofenopril (5.9%) (*Figure 2a*). The relative risk reduction (RRR) in death and congestive heart failure with zofenopril was 43% as compared with placebo (95% CI: 3–57%; $2P = 0.034$). The beneficial effect associated with ACE-inhibition observed in hypercholesterolemic patients significantly exceeded that observed in normocholesterolemic patients (25%; 95% CI: −18 to 43%; $2P = 0.19$) (*Figure 2b*). Kaplan–Meier estimate of the 6-week cumulative incidence of primary end-point in patients with normal or high cholesterol levels confirmed the significantly greater benefit of zofenopril treatment in hypercholesterolemic patients ($P = 0.046$) (*Figure 3*).

Investigating the effects of zofenopril in the small population of hypercholesterolemic (11%) and normocholesterolemic patients (7%), we observed a trend towards a lesser difference in terms of RRR of primary end-point between the two samples with different lipid profile (hypercholesterolemics = 31%; 95% CI: −12 to 65% vs. normocholesterolemics = 21%; 95% CI: −23 to 71%). The difference did not achieve statistical significance.

One-year mortality

The 1-year mortality rates for patients with normal and high cholesterol levels treated with placebo or ACE-inhibition are shown in *Figure 4*. Hypercholesterolemic patients receiving placebo for 6 weeks were more likely to die at 1 year than patients with normal cholesterol

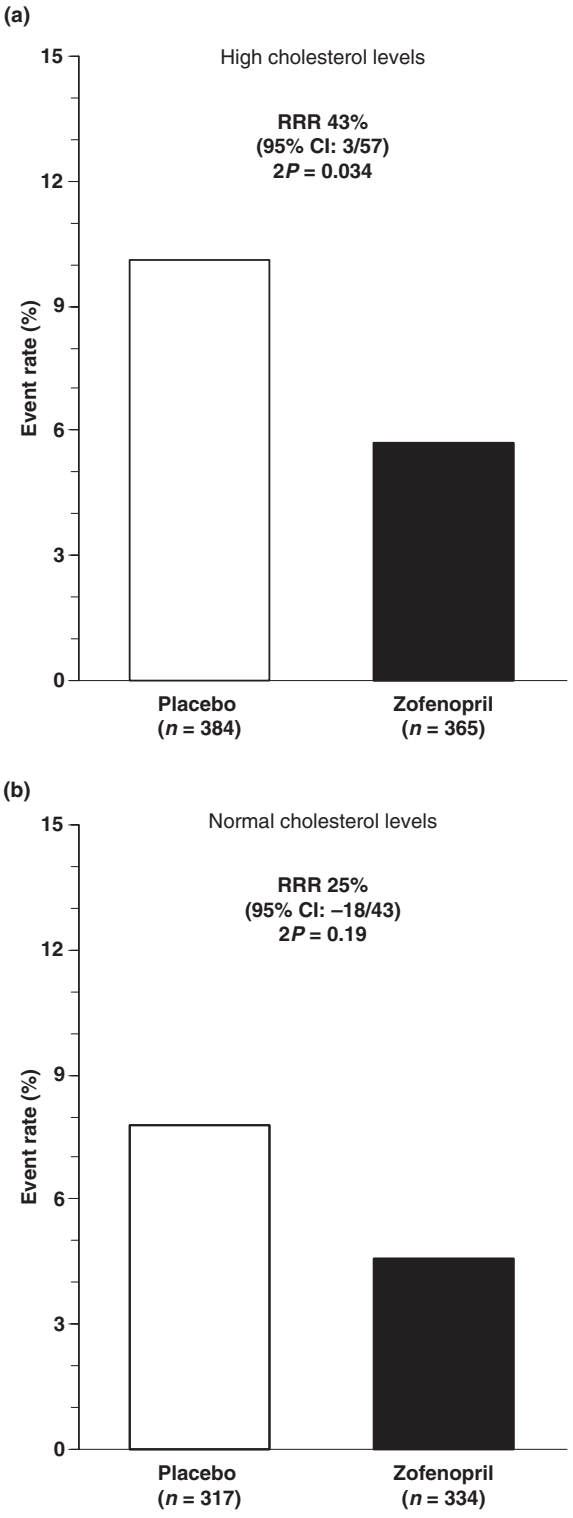

Figure 1 Combined occurrence of death and severe congestive heart failure and relative risk reduction (RRR) in hypercholesterolemic (a) and normocholesterolemic (b) patients after 6 weeks of treatment with zofenopril or placebo.

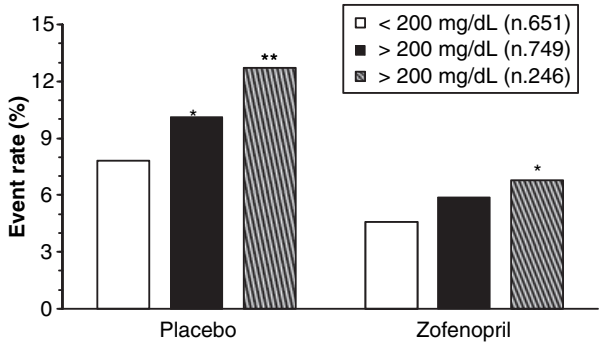

Figure 2 Combined occurrence of death and severe congestive heart failure at 6 weeks (primary end-point) in patients with different levels of baseline serum LDL-cholesterol and treated with placebo and zofenopril. (*2P = 0.02; **2P = 0.01).

levels (13.1% vs. 10.8%; P = 0.037). Zofenopril treatment reduced the 1-year mortality to the same extent in both hypercholesterolemic and normocholesterolemic patients and the reduction did not achieve statistical significance in either group probably because of the limited sample size (*Figure 4*).

Blood pressure profile

At the end of the 6-week treatment period, supine systolic and diastolic blood pressure changes were not significantly different in both hypercholesterolemic and norocholesterolemic patients ($P > 0.05$). Zofenopril treatment resulted in a slightly greater decrease in blood pressure in both hypercholesterolemic and normocholesterolemic patients when compared with placebo, but the difference did not achieve statistical significance (data not shown). Heart rate was comparably reduced in the zofenopril and placebo group (data not shown). The extent of blood pressure control was largely comparable in hypercholesterolemic and normocholesterolemic patients thereby excluding any interaction with the major study outcome and lipid profile.

Serum cholesterol levels

During the 6 weeks of double-blind treatment, LDL-cholesterol levels decreased in both subgroups of patients with normal (133 ± 11 vs. 122 ± 18; $P < 0.001$) or high cholesterol levels (188 ± 17 vs. 165 ± 14; $P < 0.001$) despite a marginal use of statins. The decrease was slightly enhanced in hypercholesterolemic patients irrespective of treatment allocation probably because of the greater proportion of patients undergoing lipid-lowering therapy (*Table II*).

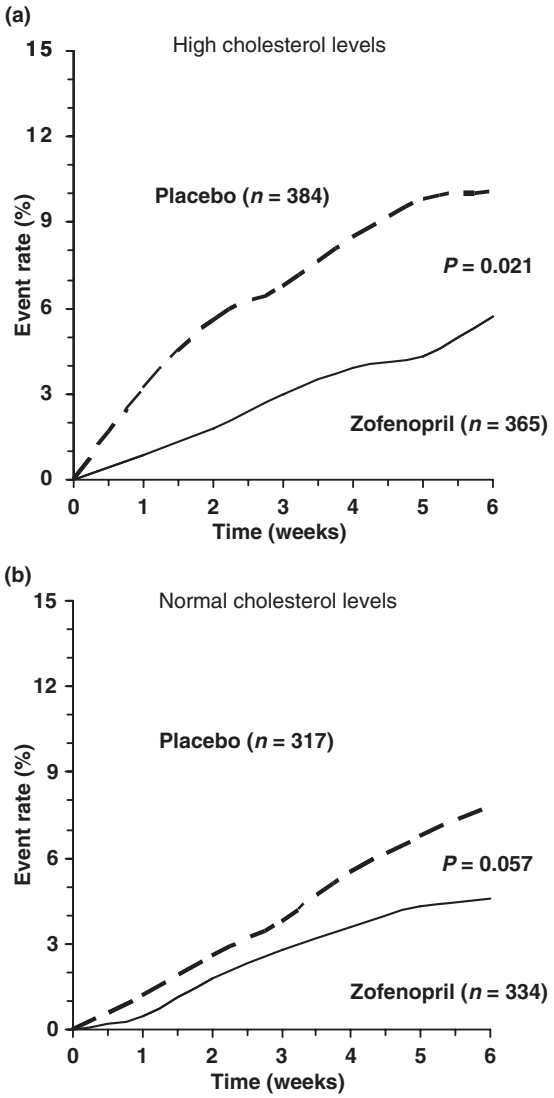

Figure 3 Kaplan–Meier estimate of the rate of combined occurrence of death and severe congestive heart failure in hypercholesterolemic (a) and normocholesterolemic (b) patients after 6 weeks of treatment with zofenopril or placebo.

DISCUSSION

Although the beneficial effects of early ACE-inhibition in patients surviving myocardial infarction have been extensively studied in patients with another important metabolic disease as diabetes, we need larger evidence on the effect of ACE-inhibitors in hypercholesterolemic patients with definite coronary syndrome or at high risk for coronary disease.

The results of the HOPE [10], EUROPA [11] and PEACE [22] trials respectively carried out with ramipril,

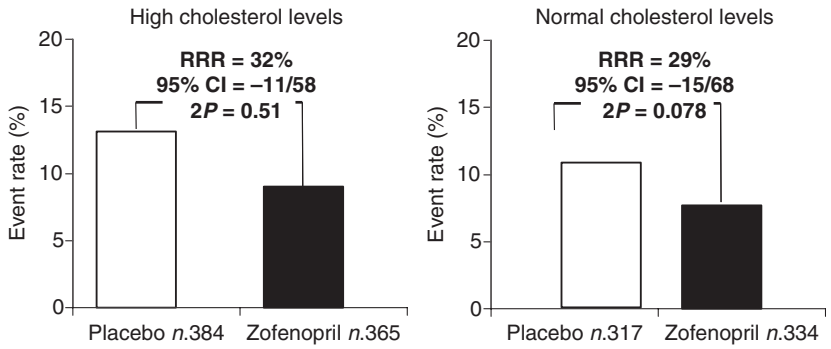

Figure 4 Mortality after 1-year of follow-up in patients with high or normal cholesterol levels and treated with placebo or zofenopril.

perindopril and trandolapril have not been analysed according to baseline patient cholesterolaemia. However, the results of the PEACE trial, which included a large proportion of patients treated with statins in comparison with EUROPA and HOPE, do not support any additional benefit for ACE-inhibitors. This was probably because of the lesser degree of local RAS activation associated with the better control of cholesterolaemia.

These lines of recent evidence have induced our research unit to re-analyse the data of the SMILE study to asses if the prognostic advantages associated with the early ACE-inhibition after an acute myocardial infarction [15] are modulated by the basal cholesterolaemia. This post hoc analysis of the SMILE study confirms that myocardial infarction is associated with a worse prognosis in patients with hypercholesterolaemia than in those with normal cholesterol levels. In particular, the combined occurrence of death and severe congestive heart failure in the placebo group was almost 30% higher in hypercholesterolemic than in normocholesterolemic patients. Our data also highlight the importance of early (<24 h) ACE-inhibition in hypercholesterolemic patients to improve their negative outcome. As a matter of fact, a 6-week treatment with zofenopril in these patients reduced the risk of death plus severe congestive heart failure by 43%, while 1-year mortality decreased by 32%.

To our knowledge, the SMILE study is the first clearly showing a prognostic benefit of early ACE-inhibitor treatment in patients with acute anterior myocardial infarction and hypercholesterolaemia. It also suggests that treatment with ACE-inhibitors should be continued at least over 1-year in hypercholesterolemic patients surviving acute myocardial infarction to achieve maximal benefit in terms of cardiovascular protection. We can hypothesize that the beneficial effect of ACE-inhibition and, in particular, of zofenopril treatment in our patients may be related to the prompt blockade of the deleterious effects of neurohumoral activation, which is involved in the development of endothelial dysfunction, coronary vasoconstriction and myocardial ischaemia [5,24–26]. In particular, as the presence of hypercholesterolaemia has been associated with an over-expression of angiotensin II receptors of the AT_1 type [6,7,27] as well as with an increased affinity of such receptors for circulating and locally released angiotensin II [28], we suggest that the use of an ACE-inhibitor would result in a greater benefit in those patients who are expected to be more sensitive to the negative effects of RAS activation as might be those with hypercholesterolaemia. A small trial comparing the effects of felodipine with those of the angiotensin II receptor blocker (ARB) candesartan in patients with hypercholesterolaemia reported a significantly greater improvement in endothelium-dependent vasodilation with the ARB [29]. The results of this post hoc analysis of the SMILE trial seem to support a role for drugs blocking the RAS in the treatment of patients with hypercholesterolaemia thus increasing the extent of interaction between the different risk factors for cardiovascular disease.

In the SMILE trial, the proportion of patients treated with statins was pretty small (<10%) as the study was conducted before the evidence supporting a role for lipid-lowering drugs in patients with acute coronary syndromes were available. However, a post hoc analysis carried out investigating the effects of zofenopril in the small population of hypercholesterolemic and normocholesterolemic patients undergoing statin treatment showed a trend towards a lesser difference in terms of RRR of primary endpoint between the two samples with different lipid profile. These results slightly differ from those observed in the general population and are indirectly in agreement with the main study hypothesis that ACE-inhibitors can be more effective in patients with hypercholesterolaemia showing an exaggerated expression of tissue RAS that can be downregulated by statin treatment.

As might be expected from a post hoc analysis of an 'aged' prospective randomized trial, our results suffer also from some weakness. First, our study included only 1400 of the original 1556 patients of the main SMILE study and in particular those having a baseline determination of lipid profile before the enrolment in the study. This means that it might have been underpowered to achieve additional study goals particularly in terms of differences in the effect of ACE-inhibition on 1-year mortality. However, the amount of RRR for the primary end-point was clinically relevant, statistically significant and similar to that observed in the whole study population [15] and in the different subgroups previously analysed (patients with diabetes and hypertension) [30,31]. Moreover, the amplitude of the confidence intervals for the RRR of the primary endpoint was not different between the subgroup of patients with high serum cholesterol and the main study group (54 vs. 43%). Secondly, we classified hypercholesterolemic patients only on the basis of LDL-cholesterolaemia, without considering the eventual diagnosis of familial dyslipidaemia that could strongly influence the patient prognosis also independently of the LDL-cholesterol plasma level. Thirdly, only a small proportion of patients were treated with lipid-lowering drugs during the period of follow-up, consistent with the rate of prescription of such drugs in the mid 1990s when the study was conducted. However, the main objective of the study was to assess the extent of interaction among serum cholesterol levels, ACE-inhibition and clinical prognosis in patients with acute myocardial infarction irrespective of the influence of lipid-lowering drugs. Finally, the practical importance of this study could be questioned given the contemporary and aggressive approach to lipid lowering in patients who present with acute coronary syndromes. However, the results of this post hoc analysis of the SMILE trial are mainly focused on the demonstration that hypercholesterolemics is associated with a functional activation of the RAS that further emphasizes the importance of effective lipid-lowering treatment in patients with acute coronary syndrome.

In conclusion, the results of our retrospective analysis of the SMILE Study suggest the possibility that high cholesterol levels might negatively affect the clinical prognosis of patients with acute myocardial infarction. Moreover, in our selected population of patients with acute myocardial infarction, the early treatment with ACE-inhibitors seems to be more effective in subjects affected by hypercholesterolaemia.

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