Zofenopril and ramipril in patients with left ventricular systolic dysfunction after acute myocardial infarction: A propensity analysis of the Survival of Myocardial Infarction Long-term Evaluation (SMILE) 4 study

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Abstract

Introduction: This was a propensity score analysis of the prospective, randomized, double-blind Survival of Myocardial Infarction Long-term Evaluation (SMILE) 4 study in which one-year treatment with zofenopril 60 mg plus acetylsalicylic acid (ASA) 100 mg gave superior results compared to ramipril 10 mg plus ASA in terms of death or hospitalization for cardiovascular causes in patients with acute myocardial infarction (AMI) complicated by left ventricular dysfunction (LVD). Materials and methods: A total of 716 patients of the intention-to-treat population were divided into homogeneous propensity quintiles (Q) using a logistic regression model (QI: best risk profile; QV: worst risk profile). Results: Treatment was associated with a similar low rate of major cardiovascular events in any Q. However, the efficacy of zofenopril was better than that of ramipril in QII, QV, and particularly QIII (odds ratio (OR) and 95% confidence interval: 0.43 (0.21–0.87), p<0.05). This result was primarily attributed to a decrease in the risk of cardiovascular hospitalization, particularly striking in the QIII (OR: 0.40, 0.19-0.85; p<0.05). Mortality rate did not significantly differ between the two treatments in any Q. Conclusions: In the SMILE-4 study the propensity analysis confirmed the efficacy of zofenopril in the prevention of long-term cardiovascular outcomes irrespective of the cardiovascular risk profile of post-AMI patients.

Keywords
Acute myocardial infarction, left ventricular dysfunction, angiotensin-converting enzyme inhibitors, acetylsalicylic acid, propensity analysis

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Introduction

The propensity score analysis allows us to objectively measure the probability of a patient being in a treatment group or in another based on his/her baseline clinical and demographic features, and thus to balance two non-equivalent groups on observed potentially confounding variables, to get more accurate estimates of the effects of a treatment on which the two groups differ.1–5 The propensity score approach has been applied in many fields, including cardiovascular research, and it is having an
increasing role as a potentially useful method of data analysis to estimate treatment effects when potential bias may be present.

The prospective, double-blind, randomized Survival of Myocardial Infarction Long-term Evaluation (SMILE) 4 study showed the superiority of one-year treatment with zofenopril 60 mg plus acetylsalicylic acid (ASA) 100 mg vs ramipril 10 mg plus ASA in the prevention of major cardiovascular outcomes in patients with acute myocardial infarction (AMI) complicated by left ventricular dysfunction (LVD). In the present article we report on the outcomes of the retrospective propensity score analysis of the SMILE-4 data. This analysis was performed to further investigate the cardiovascular risk reduction profile of zofenopril in the clinical setting of the SMILE-4 study and to increase the power of the study, by correcting for some potential confounding factors, in an attempt to re-evaluate the study results at the light of the primary impact of the therapy rather than of factors related to the study population.

Materials and methods

Study design

The full methodology of the SMILE-4 study has been detailed elsewhere. In short, male and non-pregnant female patients aged 18–85 years with a confirmed diagnosis of ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) in the 24-hour period preceding enrolment (treated or not with primary percutaneous transluminal coronary angioplasty (PTCA), treated or not with thrombolysis and recommended pharmacologic treatment) and with clinical and/or echocardiographic evidence of LVD were enrolled in 79 hospitals in eight different countries. The study was conducted in accordance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of the University of Bologna as well as by the local ethics committees when required (see acknowledgments for a list members of the SMILE-4 working party by country). Written informed consent was obtained from each patient before enrolment. The SMILE-4 study (protocol MEN/03/ZOF-CHF/001) was registered with EudraCT Number 2004-001150-88 (www.clinicaltrialsregister.eu) and with the Italian Ministry of Health Code: GUIDOTT_III_2004_001 (https://oss-sper-clin.agenziafarmaco.it).

The first patient was enrolled in March 2005, and the last patient completed in July 2009. Patients complying with the study eligibility criteria entered a four-day open-label phase, during which zofenopril was administered to all patients according to an up-titration scheme. 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 was kept unchanged. On day 5 patients were randomized 1:1 double-blind (using a centralized, computer-generated randomization list) to receive zofenopril 30 mg twice daily and ASA 100 mg once daily or ramipril 5 mg twice daily and ASA 100 mg once daily for 12 months. The study medications were given in combination with standard recommended treatments for AMI. Patients were seen at enrolment, at randomization and at one, six and 12 months thereafter. A physical examination, a 12-lead electrocardiogram and laboratory tests (haematology, clinical chemistry and urinalysis) were performed at entry, at randomization and at the study end. Laboratory tests included red blood cell count, white blood cell count, platelet count, serum creatinine, blood glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, serum transaminases and urinalysis. Glomerular filtration rate was estimated by the Cockroft-Gault formula. Blood pressure and heart rate were measured, 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.

Statistical analysis

In this post-hoc analysis of the SMILE-4 study we evaluated the probability of receiving different treatments (based on the measured characteristics) with the propensity score. The propensity score is usually estimated by applying a logistic regression analysis, where the outcome is the treatment variable and predictor variables are the covariates. Accordingly, we estimated propensity scores with the observed covariates as predictors, and treatment assignment (dummy coded 0=ramipril, 1=zofenopril) as dependent variable. The selected model included 13 possible patient variables (predictors), as recorded at entry: age (>65 vs ≤65 years), gender, heart rate (>70 vs ≤70 bpm), diagnosis of diabetes, metabolic syndrome, hypercholesterolaemia, low HDL, type of infarction (STEMI vs NSTEMI), revascularization, Killip class (≥2 vs 1), NT-proBNP (>330 vs ≤330 pg/ml), left ventricular ejection fraction (LVEF) (>40 vs ≥40%), GFR (<60 vs >60 ml/min). Such variables were selected because they were considered representative of the individual’s risk level and were available as complete data for all patients. After fitting the model according to a step-wise approach, the patients in the two treatment groups were stratified according to the aforementioned predictors and ranked in five equal-sized strata or quintiles (Qs). The QI represented patients with the best and the QV included those with the worst risk profile; thus, patients inside each Q had a similar overall risk. The choice of five strata was based on
the Cochran method,9 which showed that, in general, five strata are able to remove approximately 90% of the bias due to a single continuous covariate.10 To validate the propensity score model we tested each of the covariates (predictors) in a two-way (two conditions x five strata) analysis of variance, examining the magnitude and significance of the F ratio for the treatment group main effect and the interaction F ratio. If both F ratios were small, balance on the covariate was probably reasonable. However, if either F ratio was large, the model was revised including any covariates with large F ratios that had previously been excluded during the stepwise procedure, and if balance was still questionable, nonlinear and interaction terms were added. We used logistic regression in a similar two-step procedure for assessing the balance of dichotomous categorical variables. To estimate the effects of treatment with a propensity score adjustment, zofenopril and ramipril group means were analysed as the unweighted average of the cell means over the five strata for each group. The appropriateness of the propensity score model was confirmed by the Hosmer-Lemeshow goodness of fit test ($p=0.459$).

The primary study end-point was defined as in the original study as the one-year combined occurrence of cardiovascular mortality or hospitalization for cardiovascular causes. Secondary study end-points, including hospitalization and death for cardiovascular causes, were assessed as well. Efficacy evaluation was carried out in the intention-to-treat population, defined as patients treated with at least one dose of study medication and documenting at least once the measure of the primary efficacy assessment, even in a case of protocol violation or premature withdrawal from the study.

The difference between treatment groups with respect to the primary combined end-point and cardiovascular morbidity and mortality rate, was assessed within each Q of the propensity score, by calculating the estimated odds ratio and the corresponding 95% confidence interval. The Chi-square analysis was applied to data with the Mantel-Haenszel extension for the comparison between the two treatment groups. A logistic regression model was also applied to assess differences between treatments, by accounting for treatment and propensity score group. Survival curves were drawn using Kaplan-Meier estimates and the survival analysis was performed according to survival Cox regression analysis.

All $p$ values are two-tailed and the minimum level of statistical significance was set at $p$ value less than 0.05.

**Results**

**Study population**

The 716 patients of the original SMILE-4 study intention-to-treat population were included in this analysis. For the purpose of the current analysis, the patients were ranked by their estimated propensity score and grouped in Qs. The propensity score was similar for the two treatment groups within each Q (Table 1). Stratifying on the Qs of the propensity score model resulted in residual imbalance between individuals treated with zofenopril vs ramipril patients in the upper (QV) and lower (QI) Qs. After the matching process, the two treatment groups looked balanced for propensity scores (Figure 1).

A statistically significant difference was observed across the five groups for the predictors included in the propensity analysis (Table 1). It should be noted that, with few exceptions, relevant concomitant cardiovascular treatments were equally distributed among the five Qs, either at baseline (Table 1) and at the study end (data not shown).

**One-year combined end-point**

In the whole study population, cardiovascular death or hospitalization occurred in 105 of 365 patients in the zofenopril group (29%) and in 128 of 351 patients in the ramipril group (37%), with a 30% significantly ($p=0.028$) lower risk of achieving the combined end-point with zofenopril (odds ratio and 96% confidence interval: 0.70 (0.51–0.96)). A logistic regression analysis adjusted by the propensity score confirmed the superiority of zofenopril, with results completely overlapping those of the original study (0.70 (0.51–0.96), $p=0.028$).

For the primary study end-point, the rate of major cardiovascular events was similar across the various propensity groups (QI: 34%; QII: 32%; QIII: 32%; QIV: 34%; QV: 32%), but differences in the effect of the two study drugs were observed within each Q of the propensity score (Figure 2). In the QI and QIV the rates of the combined end-point were similar between zofenopril and ramipril. In the QII, QIII and QV, treatment with zofenopril was associated with a lower rate of cardiovascular morbidity and mortality than ramipril, the difference being statistically significant for the QIII (0.43 (0.21–0.87), $p<0.05$).

A survival Cox regression analysis using treatment and propensity score group as predicting variables indicated a significantly overall larger survival rate under zofenopril (0.77 (0.59–0.99), $p=0.045$) and no statistically significant ($p=0.995$) effect of the propensity score in predicting the probability of the outcome at a given time of the observation. The lack of difference in the trend of the overall treatment effect within the Qs (Figure 3) was confirmed by the fact that the cumulative survival curves were superimposable across the five Qs, regardless of the type of treatment (Figure 4).

**One-year rate of hospitalization and death for cardiovascular causes**

In the main study the reduction in the risk of major cardiovascular events was mainly attributable to a decreased risk
of hospitalization for cardiovascular causes (0.64 (0.46–0.88), p=0.006). The same analysis modelled with the propensity score showed similar results (0.64 (0.46–0.90), p=0.009). Hospitalization rates were always lower under zofenopril in any Q, a between-treatment statistically significant difference being observed for the QIII (0.40 (0.19–0.85); p<0.001) (Table 2).

Since few deaths occurred over the one-year observation period, mortality contribution to the primary study endpoint was marginal and the rate of deaths for cardiovascular causes did not significantly differ between treatments in the original study (1.51 (0.70–3.27), p=0.293). This was the case also for the propensity analysis, though a trend to a non-statistically significant larger reduction in mortality with zofenopril was observed (0.66 (0.30–1.43), p=0.291). No between-treatment differences in mortality rates were ever observed in any Q of the propensity score (Table 3).

### Discussion

It is well established that angiotensin-converting enzyme (ACE) inhibitors should be given to patients with an impaired LVEF or those who have experienced heart failure in the early phase of an AMI. The protective effects of ACE-inhibition have been demonstrated independent of...

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**Table 1.** Baseline demographic characteristics of the intention-to-treat population (n=716) stratified by propensity subgroups (quintiles, Q).

| Characteristics | Propensity group | p-Value for propensity score analysis |
|-----------------|------------------|--------------------------------------|
|                 | QI (n=143) | QII (n=145) | QIII (n=145) | QIV (n=140) | QV (n=143) |
| Age (years, mean±SD) | 63.4±11.2 | 59.8±10.1 | 58.9±10.0 | 58.9±10.4 | 63.0±11.5 | <0.001 |
| Gender (n, %) | | | | | |
| Male | 76 (53.1) | 105 (72.4) | 112 (77.2) | 120 (85.7) | 131 (91.6) | <0.001 |
| Female | 67 (46.9) | 40 (27.6) | 33 (22.8) | 20 (14.3) | 12 (8.4) | |
| BMI (kg/m², mean±SD) | 26.9±3.9 | 27.2±4.3 | 27.7±3.6 | 27.8±3.6 | 28.4±4.1 | 0.025 |
| Diabetes (n, %) | 34 (23.8) | 24 (16.6) | 19 (13.1) | 31 (22.1) | 23 (16.1) | 0.106 |
| Metabolic syndrome (n, %) | 32 (22.4) | 44 (30.3) | 40 (27.6) | 56 (40.0) | 81 (56.6) | <0.001 |
| Hypercholesterolaemia (n, %) | 19 (13.3) | 22 (15.2) | 27 (18.6) | 33 (23.6) | 39 (27.3) | 0.015 |
| Low HDL (n, %) | 100 (70.1) | 110 (75.6) | 102 (70.3) | 84 (60.0) | 95 (66.4) | 0.061 |
| Hypertension (n, %) | 96 (67.0) | 83 (60.6) | 78 (57.4) | 82 (61.2) | 98 (71.0) | 0.063 |
| Peripheral arterial occlusive disease (n, %) | 13 (9.2) | 6 (4.2) | 4 (2.8) | 5 (3.6) | 7 (5.0) | 0.111 |
| Previous myocardial infarction (n, %) | 36 (25.4) | 32 (22.5) | 21 (14.6) | 23 (16.5) | 21 (14.7) | 0.060 |
| Angina pectoris (n, %) | 60 (42.0) | 52 (35.9) | 49 (33.8) | 48 (34.3) | 54 (37.8) | 0.772 |
| Congestive heart failure (n, %) | 18 (12.7) | 12 (8.3) | 6 (4.1) | 9 (6.4) | 4 (2.8) | 0.046 |
| Killip class on admission (n, %) | | | | | |
| I | 28 (19.6) | 49 (33.8) | 51 (35.2) | 52 (37.1) | 56 (39.2) | 0.004 |
| II–IV | 115 (80.4) | 96 (66.2) | 94 (64.8) | 88 (62.9) | 87 (60.8) | 0.001 |
| Thrombolytic therapy performed at entry (n, %) | 39 (27.3) | 48 (33.1) | 65 (44.8) | 53 (37.9) | 69 (48.3) | 0.001 |
| Relevant concomitant treatments (n, %) | | | | | |
| ACE inhibitors | 6 (4.2) | 3 (2.1) | 2 (1.4) | 2 (1.4) | 3 (2.1) | 0.486 |
| Angiotensin II antagonists | 1 (0.7) | 0 (0.0) | 2 (1.4) | 1 (0.7) | 1 (0.7) | 0.738 |
| β-Blockers | 72 (50.3) | 65 (44.8) | 89 (61.4) | 51 (36.4) | 99 (69.2) | <0.001 |
| Calcium antagonists | 11 (7.7) | 7 (4.8) | 16 (11.0) | 8 (5.7) | 10 (7.0) | 0.299 |
| Diuretics | 27 (18.9) | 31 (21.4) | 35 (24.1) | 29 (20.7) | 25 (17.5) | 0.685 |
| Digoxin | 1 (0.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.731 |
| Nitrates | 56 (39.2) | 47 (32.4) | 53 (36.6) | 58 (41.4) | 31 (21.7) | 0.004 |
| Anti-arrhythmic drugs | 6 (4.2) | 8 (5.5) | 5 (3.6) | 3 (2.1) | 1 (0.7) | 0.173 |
| Statins | 74 (51.7) | 70 (48.3) | 93 (64.1) | 88 (62.9) | 92 (64.3) | 0.008 |
| Other lipid-lowering drugs | 9 (6.3) | 4 (2.8) | 7 (4.8) | 6 (4.3) | 6 (4.2) | 0.701 |
| Other cardiovascular drugs | 19 (13.3) | 22 (15.2) | 13 (9.0) | 14 (10.0) | 11 (7.7) | 0.224 |
| Estimated GFR (ml/min, mean±SD) | 67±33.1 | 87±31.0 | 91.6±23.1 | 94.3±31.3 | 95.1±37.1 | <0.001 |
| NT-proBNP (pg/ml, median, 25th and 95th percentile) | 988 (347, 8507) | 824 (354, 5557) | 776 (276, 3852) | 652 (289, 4118) | 853 (500, 5786) | 0.025 |

ACE: angiotensin-converting enzyme; BMI: body mass index; DBP: diastolic blood pressure; GFR: glomerular filtration rate (estimated by Cockcroft-Gault formula); HDL: high density lipoprotein; 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.
Figure 1. Frequency distribution of estimated probability (propensity scores) by treatment group (zofenopril vs ramipril).

Figure 2. One-year combined (morbidity and mortality) endpoint of the intention-to-treat population (n=716) stratified by the five propensity subgroups (quintiles (Qs)). Relative (%) frequency of outcomes is shown according to treatment group (zofenopril: open bars; ramipril: full bars) with the odds ratio (OR) and 95% confidence interval (CI). The p-values indicate the statistical significance of the between-treatment difference. NS: not significant.
As a matter of fact, current guidelines recommend starting the ACE-inhibitor in the first 24 h of STEMI or NSTEMI in patients with evidence of heart failure, LVD, diabetes or an anterior infarct. In the recently published SMILE-4 study post-AMI patients with LVD receiving zofenopril, a sulphhydryl-containing...
ACE-inhibitor, in combination with ASA, showed a decreased one-year risk of major cardiovascular complications, the effect being larger than that of ramipril plus ASA. Such superiority was mainly attributable to a larger decrease in the rate of cardiovascular hospitalizations in the zofenopril-treated patients, with no significant differences in cardiovascular mortality.

In this post-hoc analysis of the SMILE-4 study based on propensity data modelling, we confirmed the results of the main study, with the addition of new important findings. The preliminary step of the propensity approach applied to the SMILE-4 study was to verify the homogeneity between the two patient groups: after the matching process, the treatment groups were well balanced and, consequently, comparable on propensity scores. The use of the propensity score as a stratification method yielded new information on how demographic and clinical variables may have influenced the outcome of treatment. Although the rate of major cardiovascular events was constant across the various propensity score groups (Qs), we observed some heterogeneity in the treatment effects: indeed, zofenopril was associated with a greater reduction in the rate of major cardiovascular events (primary study endpoint) and hospitalizations alone (secondary endpoints) in QII, QIII, and QIV, with a statistically significant difference in favour of this drug in the third Q. Mortality rates were similarly affected by both study treatments, irrespective of the propensity group, confirming the finding of the main study. Thus, the propensity score analysis helped in substantiating the main study results, because it allowed us to correct for some potential confounding factors, mainly related to the study population. We can speculate on the origin of the observed superiority of zofenopril over ramipril in individuals at an intermediate risk, but not in the other Qs. Likely, patients in the low, and those in the high, risk category may equally benefit from both ACE-inhibitors, with no specific

Figure 4. Survival function irrespective of treatment (data for zofenopril and ramipril are pooled together) for the five propensity score groups.

Table 2. One-year hospitalization for cardiovascular causes per quintile (Q) of the propensity score.

| Q of the propensity score | Zofenopril (no. events/no. subjects, %) | Ramipril (no. events/no. subjects, %) | OR (95% CI) | p-Value |
|--------------------------|----------------------------------------|--------------------------------------|-------------|---------|
| I                        | 17/65 (26.2)                           | 19/66 (28.8)                         | 0.88 (0.41–1.89) | NS      |
| II                       | 17/71 (23.9)                           | 24/69 (34.8)                         | 0.59 (0.28–1.23) | NS      |
| III                      | 15/71 (21.1)                           | 28/70 (40.0)                         | 0.40 (0.19–0.85) | <0.05   |
| IV                       | 22/71 (31.0)                           | 22/66 (33.3)                         | 0.90 (0.44–1.84) | NS      |
| V                        | 17/70 (24.3)                           | 24/69 (34.8)                         | 0.60 (0.29–1.26) | NS      |

Cl: confidence interval; NS: not significant; OR: odds ratio.

Absolute and relative (%) frequencies of outcomes are shown according to treatment group (zofenopril or ramipril) together with the OR and 95% CI. The p-values indicate the statistical significance of the between-treatment difference.

Table 3. One-year cardiovascular mortality per quintile (Q) of the propensity score.

| Q of the propensity score | Zofenopril (no. events/no. subjects, %) | Ramipril (no. events/no. subjects, %) | OR (95% CI) | p-Value |
|--------------------------|----------------------------------------|--------------------------------------|-------------|---------|
| I                        | 8/73 (11.0)                            | 4/70 (5.7)                           | 2.03 (0.58–7.08) | NS      |
| II                       | 2/73 (2.7)                             | 3/72 (4.2)                           | 0.65 (0.11–4.00) | NS      |
| III                      | 2/73 (2.7)                             | 2/72 (2.8)                           | 0.99 (0.14–7.20) | NS      |
| IV                       | 2/73 (2.7)                             | 1/67 (1.5)                           | 1.86 (0.17–21.0) | NS      |
| V                        | 3/73 (4.1)                             | 1/70 (1.4)                           | 2.96 (0.30–29.1) | NS      |

Cl: confidence interval; NS: not significant; OR: odds ratio.

Absolute and relative (%) frequencies of outcomes are shown according to treatment group (zofenopril or ramipril) together with the OR and 95% CI. The p-values indicate the statistical significance of the between-treatment difference.
advantages of one treatment over the other. Particularly in high risk patients, the class effect could be more important than the specific properties of the pharmacological compounds (in this case zofenopril and ramipril). We also acknowledge that, given the small number of subjects in each Q, the possibility that the between-group difference might be a result of chance cannot be ruled out.

The propensity score analysis represents an alternative to standard adjustment methods (linear or logistic regression) and is a useful tool to provide estimates of the treatment effects and create a direct covariate balance between compared groups, thus removing bias. The propensity analysis is a suitable technique especially for clinical settings where other pretreatment observed covariates (e.g. disease risk factors, concomitant treatments, demographic variables) are present, and it is necessary to reach an unbiased effect assessment of the randomly compared treatments. As well as the estimating of causal effects of treatments coming from large databases, the propensity score analysis can yield clinically relevant information with practical implications. For instance, results from propensity analysis may provide helpful hints for improving treatment efficacy. Matching subjects by propensity analysis may also help refining the intervention strategies. Propensity analysis may help unravelling prognostic factors negatively influencing the drug treatment effect.

In the context of our study, the result of the propensity analysis may have practical clinical implications, because it might help in identifying subjects who could benefit most from treatment with one or the other ACE inhibitor used in the study. It is likely that subjects at intermediate risk might benefit more by early treatment with zofenopril, whereas in other risk classes one or the other treatment may be equally effective.

**Study limitations**

Our study should be interpreted in the context of some potential limitations. First, though the propensity score of the SMILE-4 study provided an adjustment for measured differences between treatment groups, this analysis, by its nature, did not include unmeasured differences. Despite the methodological rigour due to the design of the SMILE-4 trial and the stratification of patients based on the propensity score approach, possible unknown risk factors could have contributed to the generation of cardiovascular outcomes. Second, the propensity score retrospective analysis was not included in the original SMILE-4 study protocol; therefore, potentially significant information could have not been collected at the enrolment phase and/or during the study progress. Third, the relatively limited length of the patient’s follow-up may have reduced the chance of recording some events and, in particular, may explain the low mortality rate; due to this fact, the propensity analysis was not helpful for better exploring the impact of treatments and their possible diversity on cardiovascular deaths.

Fourth, usually the propensity analysis is appropriately applied to observational studies in order to minimize the limitations due to the non-randomized nature of the studies. In the case of our double-blind randomized study this approach might appear to be less useful. However, we think that it helped provide a confirmatory analysis of the main study results.

**Conclusions**

The propensity score analysis of the SMILE-4 study confirmed the good efficacy of zofenopril in the prevention of one-year cardiovascular outcomes. The propensity model was useful to confirm results of the main study by correcting for selection bias and possible unbalance between treatment groups, and to support the view that zofenopril is beneficial regardless of an individual patient’s cardiovascular risk level.

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