Efficacy of Zofenopril Compared With Placebo and Other Angiotensin-converting Enzyme Inhibitors in Patients With Acute Myocardial Infarction and Previous Cardiovascular Risk Factors: A Pooled Individual Data Analysis of 4 Randomized, Double-blind, Controlled, Prospective Studies

Claudio Borghi, MD,* Stefano Omboni, MD,† Giorgio Reggiardo, BSc,‡ Stefano Bacchelli, MD,* Daniela Degli Esposti, MD,* and Ettore Ambrosioni, MD* on behalf of the SMILE Working Project

Abstract: In the Survival of Myocardial Infarction Long-term Evaluation (SMILE) 1, 3, and 4 studies, early administration of zofenopril in acute myocardial infarction showed to be prognostically beneficial versus placebo or ramipril. The SMILE-2 showed that both zofenopril and lisinopril are safe and showed no significant differences in the incidence of major cardiovascular (CV) complications. In this pooled analysis of individual data of the SMILE studies, we evaluated whether the superior efficacy of zofenopril is maintained also in patients with ≥1 CV risk factor (CV+, n = 2962) as compared to CV− (n = 668). The primary study end point was set to 1-year combined occurrence of death or hospitalization for CV causes. The risk of CV events was significantly reduced with zofenopril versus placebo either in the CV+ (−37%; hazard ratio: 0.63; 95% confidence interval: 0.51–0.78; P = 0.0001) or in the CV− group (−55%; hazard ratio: 0.45; 0.26–0.78; P = 0.004). Also, the other angiotensin-converting enzyme inhibitors reduced the risk of major CV outcomes, though the reduction was not statistically significant versus placebo (CV+: 0.78; 0.58–1.05; P = 0.107; CV−: 0.71; 0.36–1.41; P = 0.334). The benefit was larger in patients treated with zofenopril than other angiotensin-converting enzyme inhibitors, with a statistically significant difference for CV+ (0.79; 0.63–0.99; P = 0.039) versus CV− (0.62; 0.37–1.06; P = 0.081). In conclusion, zofenopril administered to patients after acute myocardial infarction has a positive impact on prognosis, regardless of the patient’s CV risk profile.

Key Words: acute myocardial infarction, drug therapy, angiotensin-converting enzyme inhibitors, cardiovascular risk

INTRODUCTION

The Survival of Myocardial Infarction Long-term Evaluation (SMILE) project is a comprehensive program of 4 randomized controlled studies aimed to evaluate the efficacy and safety profile of zofenopril in post–acute myocardial infarction (AMI) patients compared with that of placebo or other angiotensin-converting enzyme (ACE) inhibitors (ramipril and lisinopril) in preventing cardiovascular (CV) events.1–4 In the SMILE-1 study, 1556 patients were enrolled within 24 hours after the onset of symptoms of AMI, and they were randomly assigned in a double-blind balanced fashion to receive either placebo or zofenopril for 6 weeks. The incidence of death or severe congestive heart failure during the study was 34% lower with zofenopril.1 The SMILE-2 study was the first direct comparative study between 2 ACE inhibitors in post-AMI.2 Overall, 1024 thrombolysed patients with AMI were randomized to receive one or the other drug starting within 12 hours of completion of thrombolytic therapy and continuing for 6 weeks. The primary study end point was the incidence of severe hypertension, which was slightly but significantly lower with zofenopril than with lisinopril (6.7% vs. 9.8%). In this study, the 6-week mortality rate was not significantly different between
the study groups. The anti-ischemic effects of zofenopril were documented in the SMILE-3 study which included 349 post-AMI patients with preserved left ventricular function. The risk of combined occurrence of significant ST-T abnormalities on ambulatory electrocardiography, electrocardiography abnormalities or symptoms of angina during standard exercise test, recurrence of AMI, and need for revascularization procedures for angina was 44% lower under zofenopril than under placebo.

Finally, a 30% reduced risk of 1-year combined occurrence of death or hospitalization for CV causes was observed in 365 post-AMI patients with left ventricular dysfunction (LVD) treated with zofenopril versus 351 patients treated with ramipril, both combined with acetylsalicylic acid (ASA) in the SMILE-4 study. 4

The results of the 4 SMILE studies were an important source of additional information regarding subpopulations of patients. For this aim, the individual data were first included in a previous pooled analysis5 where the cumulative efficacy of zofenopril on CV mortality and morbidity in post-AMI patients was evaluated by increasing the robustness of the evidence related to the prevention of major CV events. The SMILE project further encompassed in-depth analyses of patient subgroups such as patients with diabetes6,7 or hypertension.8,9

It is generally known that CV risk factors and comorbidities before AMI are strongly predictive of unfavorable prognosis after AMI10,11. Hence, further analyses of the SMILE data were planned to investigate the efficacy of zofenopril versus placebo and other ACE inhibitors, by focusing on the subgroup of patients with at least one additional CV risk factor. The selection of these patients was based on the presence of one or more of the following factors: previous angina pectoris or congestive heart failure, arterial hypertension, diabetes mellitus, hypercholesterolemia, peripheral arterial occlusive disease, coronary artery bypass graft surgery, percutaneous coronary intervention, recent ST-elevation myocardial infarction (STEMI), or non–ST-segment elevation myocardial infarction (NSTEMI), with or without signs and symptoms of heart failure.

In this article, we report the results of the pooled analysis of the 4 SMILE studies in these patients at higher risk, specifically aiming at comparing the efficacy of zofenopril versus that of placebo, lisinopril, and ramipril in terms of prevention of major CV outcomes.

METHODS

Study Design and Population

The 4 double-blind, randomized, parallel-group SMILE studies, compared the efficacy and safety of zofenopril with that of placebo (SMILE-1 and 3),1,3 lisinopril (SMILE-2),2 or ramipril (SMILE-4)4 in European men and nonpregnant women with AMI. Inclusion criteria were as follows: (1) AMI diagnosis within less than 24 hours, not eligible for thrombolytic therapy for late hospital admission or contraindication to systemic fibrinolysis (SMILE-1);1 (2) a confirmed diagnosis of AMI and a previous thrombolytic treatment within 12 hours from the onset of AMI clinical symptoms (SMILE-2); (3) a recent AMI (within 6 ± 1 week) with preserved left ventricular ejection fraction (>40%), treated with thrombolytic therapy and ACE inhibitors (SMILE-3); and (4) early myocardial infarction (<24 hours), treated or not with thrombolysis, with primary percutaneous transluminal angioplasty or coronary artery bypass graft, and with clinical and/or echocardiographic evidence of LVD (SMILE-4).4 All studies were conducted according to 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.

Treatments

Eligible patients were double-blind randomly allocated to treatment with zofenopril or a comparator (placebo, lisinopril, or ramipril), in addition to standard recommended therapy for AMI. Treatments and randomization procedures were described in the original studies. Briefly, the first zofenopril dosing was 7.5 mg twice daily on days 1 and 2, followed by 15 mg twice daily on days 3 and 4, and 30 mg twice daily from day 5 onward. Uptitration was allowed if systolic blood pressure remained >100 mm Hg and if there were no signs or symptoms of hypotension. Similarly, uptitration scheme dosing was applied to lisinopril (up to 10 mg once daily) and ramipril (up to 5 mg twice daily). For all studies, duration of treatment and follow-up periods overlapped, except for the SMILE-1 Study. In this trial, the patients stopped the double-blind treatment with the study medication after 6 weeks, and continued AMI therapy with their other medications for additional 48 weeks.

Study End Point

Because all the 4 SMILE studies provided information on fatal and nonfatal CV events, the primary study end point of this retrospective analysis was set to the 1-year combined occurrence of death or hospitalization for CV causes. The efficacy end point was calculated after weighing for the number of subjects contributing from each study. The primary objective of this post-hoc analysis was the comparison between zofenopril, placebo, and the other ACE inhibitors (lisinopril and ramipril) for the occurrence of major CV events in the 2 subgroups of patients with and in those without at least one additional CV risk factor. The presence of CV risk factors was confirmed in case of a positive medical history for at least one of the following: angina pectoris, previous AMI, congestive heart failure, coronary revascularization, peripheral arterial occlusive disease, arterial hypertension, diabetes mellitus, and hypercholesterolemia.

Statistical Analysis

The analysis was performed on the intention-to-treat population, made up of all randomized patients treated with at least one 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. To assess the study objectives, for each study subgroup (CV+ and CV−) 3 treatment groups were considered: zofenopril-treated patients, placebo-treated patients, and those
treated with the other ACE inhibitors pooled together (lisinopril or ramipril). The choice of pooling together the 2 active comparators (lisinopril and ramipril) was made to increase the size of patients in each subgroup, and thus, the power of the results. However, for exploratory reasons, the main outcomes were also computed and compared separately by the type of ACE inhibitors. The baseline characteristics and the distribution of variables in the study populations and subgroups were compared using χ² test for categorical variables and analysis of variance for continuous variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a Cox proportional hazard regression model. To account for the different durations of follow-up among the 4 studies, the relative risk of CV morbidity and mortality was assessed using a time-dependent Cox regression model and corresponding survival curves were drawn. In addition, 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.

All P values are 2-sided and the minimum level of statistical significance was set at P < 0.05. Data are shown as mean ± SD or as mean and 95% CI or as absolute (n) and relative (%) frequencies.

RESULTS

Patient Characteristics
Among 3630 available patients, 1556 (43%) were enrolled in the SMILE-1, 1024 (28%) in the SMILE-2, 334 (9%) in the SMILE-3, and 716 (20%) in the SMILE-4 Study. Of these patients, 2962 (81.6%) had at least one CV risk factor (CV+), whereas 668 (18.4%) did not. Among CV+ patients, 769 (26.0%) were treated with placebo, 1493 (50.4%) with zofenopril, and 700 (23.6%) with lisinopril (n = 437) or ramipril (n = 263). In the CV− subgroup, 182 (27.2%) patients received placebo, 315 (47.2%) zofenopril, and 171 (25.6%) lisinopril (n = 83) or ramipril (n = 88).

Baseline characteristics according to the study and treatment group, including also main CV risk factors for CV+ patients, are summarized in Table 1. Some heterogeneity across the 3 treatment groups was observed. In particular, the prevalence of hypertension was significantly larger in actively treated patients than in those receiving placebo, whereas the prevalence of previous CV disease was significantly more common under placebo.

Significantly more CV+ (578, 19.5%) than CV− patients (102, 15.3%) reported a major CV event during the 1-year follow-up [HR: 1.27 (95% CI: 1.09–1.41); P = 0.005 Cox regression analysis]. Event-free survival rate was larger (Figure 1) and survival time was longer in CV+ patients [9.9, (9.8–10.1) months] than in CV+ patients [9.9, (9.8–10.1) months, P = 0.001 log-rank test].

FIGURE 1. Cumulative survival without events during 1-year of follow-up in patients with at least one CV risk factor (CV+, n = 2962) and in those with no previous CV risk factors (CV−, n = 668) of the SMILE program. P value is from the Cox regression analysis.
CV Outcomes According to the Type of Treatment in CV+ Patients

A larger proportion of CV+ patients treated with placebo (181, 23.5%) than with zofenopril (250, 16.7%) had a major CV event, with a significant risk reduction under active treatment [HR: 0.63 (95% CI: 0.51–0.78); P = 0.0001 Cox regression analysis]. Also, lisinopril and ramipril reduced CV morbidity and mortality when compared with placebo (147 patients, 21.0% with CV events), but the reduction was not statistically significant [HR: 0.78 (0.58–1.05); P = 0.107]. A larger benefit was observed with respect to placebo under lisinopril [HR: 0.37 (0.26–0.53); P = 0.0001] than under ramipril [HR: 2.06 (1.53–2.78); P = 0.0001].

When the efficacy of zofenopril was compared with that of the other ACE inhibitors, HR was 0.79 (0.63–0.99; P = 0.039). As shown in Figure 2 (left panel), 1-year survival rate without any major CV event was significantly higher under active treatments than under placebo, with lisinopril showing an efficacy closer to that of zofenopril, and ramipril similar to that of placebo (Figure 3, left panel).

CV Outcomes According to the Type of Treatment in CV− Patients

In the CV− group, 33 patients (10.5%) treated with zofenopril and 32 patients (17.6%) under placebo reported a CV event during the 1-year of follow-up. The risk of mortality and morbidity was significantly reduced under treatment with zofenopril [HR: 0.45 (0.26–0.78); P = 0.004]. The treatment with other ACE inhibitors reduced the risk of CV events in comparison with placebo [HR: 0.71 (0.36–1.41)], but the difference was not statistically significant (P = 0.334). Survival rates with respect to placebo were much better under lisinopril [0.72 (0.34–1.50); P = 0.375] than under ramipril [1.97 (1.08–3.57); P = 0.025].

Zofenopril reduced the risk of major CV outcomes compared with lisinopril and ramipril, but the between-treatment difference was not statistically significant [HR: 0.62 (0.37–1.06); P = 0.081]. Cumulative survival rates were significantly higher under ACE inhibitor treatment than under placebo (Figure 2, right panel), particularly for zofenopril and lisinopril (Figure 3, right panel).

DISCUSSION

In this pooled individual data analysis of the SMILE studies, the proportion of post-AMI patients with at least one CV risk factor (CV+) was quite large (82%), and the impact on risk reduction in major CV events by treatment with ACE inhibitors versus placebo was particularly evident in these patients. The major finding of this post-hoc study was the superior clinical efficacy of zofenopril compared with placebo and the other ACE inhibitors (in particular ramipril). The reduction of CV events at 1 year versus placebo was more marked in CV+ and larger than that of lisinopril and ramipril in CV− patients. Zofenopril treatment determined

FIGURE 2. Cumulative survival without events during 1-year of follow-up in CV+ patients treated with placebo (n = 769), zofenopril (n = 1493), or other ACE inhibitors (n = 700), and in CV− patients (n = 182 placebo, n = 315 zofenopril, and n = 171 other ACE inhibitors). P values are from the Cox regression analysis.

FIGURE 3. Cumulative survival without events during 1-year of follow-up in CV+ patients treated with placebo (n = 769), zofenopril (n = 1493), lisinopril (n = 437), or ramipril (n = 263), and in CV− patients (n = 182 placebo, n = 315 zofenopril, n = 83 lisinopril, and n = 88 ramipril). P values are from the Cox regression analysis.
a longer survival time without CV events than the other ACE inhibitors in CV+ patients. The sample size reached in this pooled analysis, constituted by 2962 patients at high CV risk, notably strengthened the value of the results.

The role of ACE inhibition in post-AMI patients with 1 or more CV risk factors was extensively underpinned in several trials, and the clinical development highlighted the different characteristics of the various ACE inhibitors. The importance of tissue selectivity among ACE inhibitors was already observed for its influence on lipophilicity, potency, binding affinity, and level of tissue retention. Zofenopril showed significant benefits because of its distinguishing pharmacological and clinical features as an anti-ischemic drug suitable for high CV risk patients: high lipophilicity, selective cardiac ACE inhibition, antioxidant activity, and cardioprotective and vasculoprotective properties. The antiremodelling effect after AMI of zofenopril, compared with placebo and ramipril, enables it to prevent the increase of LV mass and end-diastolic volume, altered hemodynamic parameters, wall thickness, and chamber diameter. Moreover, the zofenopril treatment significantly reduced the postischemic contractile dysfunction of myocardium after ischemia relief. These hallmarks of zofenopril may contribute to explain the positive results achieved in post-AMI high CV risk patients.

The CV comorbidities or risk factors are highly prevalent in post-AMI populations, have a significant impact on patient outcomes, and several interplays among them. Thus, the knowledge of the clinical profiles of ACE inhibitors in these settings is essential. For example, congestive heart failure is frequently evident in post-AMI patients and significantly contributes to a high mortality and morbidity risk; the presence of renal dysfunction is a further negative complication increasing the 1-month and 1-year mortality and adverse cardiac events. In an unselected population of patients with AMI, the treatment with ACE inhibitors was associated with a significant (24%) 1-year reduction of mortality in patients with a history or current signs of heart failure and a decreased by 7% of the risk of reinfarction especially in patients with ST-segment elevation AMI or LVD. Heart failure after acute STEMI is one of the most frequent causes for rehospitalization or postdischarge death at 30 days after heart disease, chest pain, and gastrointestinal complications.

As AMI and ischemic stroke, peripheral artery disease is one of the atherosclerotic manifestations with a significant contribution to CV risk especially in the long-term. Indeed, the 5-year mortality rate caused by peripheral artery disease was showed to be lower than that by stroke but higher than AMI. Moreover, the differences of mortality risk between patients with peripheral artery disease and AMI and patients with stroke and AMI were substantially reduced at 5 years. In a population-based study, the patients with established peripheral artery disease who experienced AMI were at a significantly increased risk of dying during the first year after hospital discharge compared with patients without the disease. Retrospective analysis of registries data showed that preinfarction angina pectoris was independently associated with lower 5-year mortality in patients with STEMI who underwent primary percutaneous coronary intervention.

Regarding hypercholesterolemia, even in case of a low-density lipoprotein cholesterol level, post-AMI patients may still have a residual CV risk due to several types of factors: atherosclerosis, residual dyslipidemia, nonlipid factors, beyond suboptimal implementation of lifestyle therapy, and an appropriate pharmacotherapy. In large clinical trials, ACE inhibitors largely proved to be effective and safe in post-AMI patients as cardioprotective agents against reinfarction even in patients with diabetes and nephropathy. In addition, they showed to be superior to angiotensin receptor blockers in reducing CV mortality, stroke, and new-onset congestive heart failure in high CV risk patients.

Frequently associated with other CV risk factors, antecedent hypertension is often observed in patients with AMI and related to higher mortality and morbidity in the early and long-term after AMI. The combination of diabetes and hypertension in patients with AMI after angioplasty showed a synergistic effect in terms of higher mid-term mortality rate compared with patients with only diabetes or hypertension.

Acute coronary syndromes are known to alter the equilibrium between endothelial apoptosis and endothelial renewal; an in vitro study showed that ACE inhibition reduced the proapoptotic effect of serum on the endothelium and increased endothelial renewal in post-AMI patients. Because of the progressive coronary atherosclerosis and accelerated atherosclerosis in saphenous vein grafts and the increasing population age, the number of patients with previous coronary artery bypass graft and STEMI is increasing as well. These patients perform less frequent acute reperfusion, show less favorable angiographic outcomes after primary angioplasty, and higher mortality. In these patients, several independent risk factors played an important role: previous angina, diabetes and age, use of digitals and diuretics, the combination of diabetes, and older age.

To our knowledge, this is the first study carried on a large population of high CV risk patients after AMI, with a long-term follow-up, which deepened the favorable impact of zofenopril treatment already assessed in other subgroups of patients, and further valued the zofenopril and ACE inhibition treatment in post-AMI patients at high CV risk. Our study also confirms that control of CV risk factors reduces the progression of atherosclerosis and CV events, even under treatment with drugs known to have a favorable impact on prognosis of post-AMI patients. It also highlights the importance of achieving optimal targets for normal risk factors, as indicated in most recent guidelines for diabetes (HbA1c <7%), lipids (Low Density Lipoprotein <70 mg/dL in very high-risk patients and High Density Lipoprotein cholesterol >40 mg/dL in men and >55 mg/dL in women), blood pressure (<140/90 mm Hg), and smoking (total cessation).

**Study Limitations**

The retrospective analysis of the SMILE studies, not prespecified in the protocols, represents the most important...
limitation of this study. The 4 SMILE studies had different treatment and observation durations, and different follow-ups, and there was heterogeneity across the patient groups regarding the eligibility to the thrombolytic therapy: non-thrombolyzed (SMILE-1), only thrombolyzed (SMILE-2 and SMILE-3), or both types of patients (SMILE-4). In addition, different study designs, end points, inclusion and exclusion criteria of the protocols, preserved LV ejection fraction or the evidence of LVD, treatment with percutaneous coronary angioplasty, or coronary artery bypass graft of the 4 studies may contribute to the limitations of this post-hoc analysis. Yet, the Cox regression analysis essentially adjusted the differences among the 4 studies taking into account the individual patients’ data in place of the average values.

In addition, the favorable effect of zofenopril might be the results of the specific doses used. The different ACE inhibitors could have not been comparable in terms of dose response in the SMILE studies. However, all the ACE inhibitors were used at the doses proved to be effective in the large randomized trials based on the single drug components: the SMILE-1 for zofenopril,1 Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico-3 for lisinopril,41 and the Acute Infarction Ramipril Efficacy Study for ramipril.42 We acknowledge that in the future direct comparative studies might be planned at higher drug doses for lisinopril or ramipril.

CONCLUSIONS

The high prevalence of at least one CV risk factor in patients with AMI and in the patients enrolled in the 4 SMILE studies attests the importance of an early detection and evaluation of factors that are predictive of negative prognosis in post-AMI patients. A prompt identification of the underlying CV risk factors of recurrent AMI and major CV events, and the appropriate treatment may substantially contribute to a good prognosis of high CV risk patients.

The ACE inhibitors are considered the first-line treatment of high CV risk patients by the worldwide guidelines as the most valuable secondary prevention treatment after AMI. Among the various options, the ACE inhibition carried out with zofenopril may represent an important support for guaranteeing a favorable prognosis of high CV risk patients after AMI.

REFERENCES

1. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting enzyme inhibitor zofenopril on the mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med. 1995;332:80–85.
2. Borghi C, Ambrosioni E; Survival of Myocardial Infarction Long-Term Evaluation-2 Working Party. Double-blind comparison between zofenopril and lisinopril in patients with acute myocardial infarction: results of the Survival of Myocardial Infarction Long-Term Evaluation-2 (SMILE-2). Study Am Heart J. 2003;145:80–87.
3. Borghi C, Ambrosioni E; Survival of Myocardial Long-term Evaluation Study Group. Effects of zofenopril on myocardial ischemia in post-myocardial infarction patients with preserved left ventricular function: the Survival of Myocardial Infarction Long-term Evaluation (SMILE)-ISCHEMIA study. Am Heart J. 2007;153:445–450.
4. Borghi C, Ambrosioni E, Novo S, et al; SMILE-4 Working Party. Comparison between zofenopril and ramipril in combination with acetylsalicylic acid in patients with left ventricular systolic dysfunction after acute myocardial infarction: results of a randomized, double-blind, parallel-group, multicenter European study (SMILE-4). Clin Cardiol. 2012;35:416–423.
5. Borghi C, Omboni S, Reggiani G, et al. Cardioprotective role of zofenopril in patients with acute myocardial infarction: a pooled individual data analysis of four randomized, double-blind, controlled, prospective studies. Open Heart. 2015;2:e000220.
6. Borghi C, Bacchelli S, Esposti DD, et al; on behalf of the SMILE Study Investigators. Effects of the early ACE inhibition in diabetic non-thrombolyzed patients with anterior acute myocardial infarction. Diabetes Care. 2003;26:1862–1868.
7. Borghi C, Omboni S, Novo S, et al. Zofenopril and ramipril in combination with acetylsalicylic acid in post-myocardial infarction patients with left ventricular dysfunction: a retrospective analysis of the SMILE-4 study in diabetic patients. Cardiovasc Ther. 2016;34:76–84.
8. Borghi C, Ambrosioni E, Omboni S, et al, on behalf of the SMILE-4 Working Party. Zofenopril and ramipril and acetylsalicylic acid in post-myocardial infarction patients with left ventricular systolic dysfunction: a retrospective analysis in hypertensive patients of the SMILE-4 study. J Hypertens. 2013;31:1256–1264.
9. Borghi C, Bacchelli S, Esposti DD, et al. Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension. SMILE Study Investigators. Survival of Myocardial Infarction Long-term Evaluation. Am J Hypertens. 1999;12:665–672.
10. Taylor GJ, Humphries JO, Mellits ED, et al. Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. Circulation. 1980;62:960–970.
11. Marchioli R, Avanzini F, Barzi F, et al; GISSI-Prevenzione Investigators. Assessment of absolute risk of death after myocardial infarction by use of multiple-risk-factor assessment equations: GISSI-Prevenzione mortality risk chart. Eur Heart J. 2001;22:2085–2103.
12. Dezsi CA. Differences in the clinical effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a critical review of the evidence. Am J Cardiovasc Drugs. 2014;14:167–173.
13. Kalsekar I, Koehler J, Mulvaney J. Impact of ACE inhibitors on mortality and morbidity in patients with AMI: does tissue selectivity matter? Value Health. 2011;14:184–191.
14. Del Corso F, Pareo I, Borghi C. Evolving concept of cardioprotection in myocardial infarction: from SMILE-1 to SMILE-5. Kardiologica Polska. 2013;71:667–674.
15. Ambrosioni E. Defining the role of zofenopril in the management of hypertension and ischemic heart disorders. Am J Cardiovasc Drugs. 2007;7:17–24.
16. Evangelista S, Manzini S. Antioxidant and cardioprotective properties of the sulphydryl angiotensin-converting enzyme inhibitor zofenopril. J Int Med Res. 2005;33:42–54.
17. Napoli C, Sica V, de Negris F, et al. Sulphydryl angiotensin-converting enzyme inhibition induces sustained reduced of systemic oxidative stress and improves the nitric oxide pathway in patients with essential hypertension. Am Heart J. 2004;148:e5.
18. Napoli C, Bruzese G, Ignarro LJ, et al. Long-term treatment with sulphydryl angiotensin-converting enzyme inhibition reduces carotid intima-media thickening and improves the nitric oxide/oxidative stress pathways in newly diagnosed patients with mild to moderate primary hypertension. Am Heart J. 2008;156:1154.e1–1154.e8.
19. Pasini AF, Garbin U, Nava MC, et al. Effect of sulphydryl and non-sulphydryl angiotensin-converting enzyme inhibitors on endothelial function in essential hypertensive patients. Am J Hypertens. 2007;20:443–450.
20. McDonald KM, Carlyle PF, et al. Early ventricular remodeling after myocardial damage and its attenuation by converting enzyme inhibition. Trans Assoc Am Physicians. 1990;103:229–235.
21. McDonald KM, Garr M, Carlyle PF, et al. Relative effects of alpha 1-adrenoceptor blockade, converting enzyme inhibitor therapy, and angiotensin II subtype 1 receptor blockade on ventricular remodeling in the dog. Circulation. 1994;90:3034–3041.
22. Przybylken K, Klener RA. “Cardioprotection” by ACE-inhibitors in acute myocardial ischemia and infarction? Basic Res Cardiol. 1993;88(Suppl.1):139–154.
23. Cacciatore F, Bruzese G, Vitale DF, Liguori A, et al. Effects of ACE inhibition on circulating endothelial progenitor cells, vascular damage,
and oxidative stress in hypertensive patients. *Eur J Clin Pharmacol.* 2011;67:877–883.

24. Kim CS, Kim MJ, Kang YU, et al. Influence of renal dysfunction on clinical outcomes in patients with congestive heart failure complicating acute infarction. *Int Heart J.* 2013;54:304–310.

25. Milonas C, Jernberg T, Linback J, et al. Effect of angiotensin-converting enzyme inhibition on one-year mortality and frequency of repeat acute myocardial infarction in patients with acute myocardial infarction. *Am J Cardiol.* 2010;105:1229–1234.

26. Brawn JR, Conley SM, Niles NW. Predicting readmission or death after acute ST-elevation myocardial infarction. *Clin Cardiol.* 2013;36:570–575.

27. Caro J, Migliaccio-Walle K, Ishak KJ, et al. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord.* 2005;5:14.

28. Vaartjes I, van Dis I, Grobbee DE, et al. The dynamics of mortality in follow-up time after acute myocardial infarction, lower extremity arterial disease and ischemic stroke. *BMC Cardiovasc Disord.* 2010;10:57.

29. Spencer FA, Lessard D, Doubeni C, et al. Treatment practices and outcomes of patients with established peripheral arterial disease hospitalized with acute myocardial infarction in a community setting. *Am Heart J.* 2007;153:140–146.

30. Reiter R, Henry TD, Traverse JH. Preinfarction angina reduces infarct size in ST-elevation myocardial infarction treated with percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2013;6:52–58.

31. Taniguchi T, Shiomi H, Toyota T, et al. Effect of preinfarction angina pectoris on long-term survival in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention. *Am J Cardiol.* 2014;114:1179–1186.

32. Colantonio LD, Bittner V. Managing residual risk after myocardial infarction among individuals with low cholesterol levels. *Cardio Clin.* 2015;33:299–308.

33. Vijan SG. Angiotensin-converting enzyme inhibitors (ACEIs), not angiotensin receptor blockers (ARBs) are preferred and effective mode of therapy in high cardiovascular risk patients. *J Indian Med Assoc.* 2009;107:178–182.

34. Sawhney JP. Angiotensin converting enzyme inhibitors in acute myocardial infarction - a review. *Indian Heart J.* 2011;63:71–78.

35. Pedrinelli R, Ballo P, Fiorentini C, et al. Hypertension and acute myocardial infarction: an overview. *J Cardiovasc Med (Hagerstown).* 2012;13:194–202.

36. Lee MG, Jeong MH, Lee KH, et al. Prognostic impact of diabetes mellitus and hypertension for mid-term outcome of patients with acute myocardial infarction who underwent percutaneous coronary intervention. *J Cardiol.* 2012;60:257–263.

37. Cangiano E, Marchesini J, Campo G, et al. ACE inhibition modulates endothelial apoptosis and renewal via endothelial progenitor cells in patients with acute coronary syndromes. *Am J Cardiovasc Drugs.* 2011;11:189–198.

38. Welsh RC, Granger CB, Westerhout CM, et al. Prior coronary artery bypass graft patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2010;3:343–351.

39. Mitrovic PM, Stefanovic B, Vasiljevic Z, et al. In-hospital and long-term prognosis after myocardial infarction in patients with prior coronary artery bypass surgery; 19-year experience. *Scientific World J.* 2009;9:1023–1030.

40. Piepoli MF, Hoes AW, Agewall S, et al; Authors/Task Force Members. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular prevention & Rehabilitation (EACPR). *Eur Heart J.* 2013;37:2315–2381.

41. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo studio della sopravvenienza dell’infarto miocardico. *Lancet.* 1994;343:1115–1122.

42. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet.* 1993;342:821–828.