Evolving concept of cardioprotection in myocardial infarction: from SMILE-1 to SMILE-5

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INTRODUCTION

The renin–angiotensin–aldosterone system (RAAS) is a central regulator of cardiovascular (CV) and renal function and plays a key role in the pathophysiology of various CV and renal diseases [1, 2]. The RAAS consists of a series of enzymatic reactions culminating in the generation of angiotensin II (Ang-II) in plasma and in various tissues, including the vessels, the heart and the kidney. Ang-II mediates most of the biological actions of RAAS through an interaction with two different types of G-protein coupled receptors — AT1 and AT2 — that can have opposing effects [1, 2]. The importance of Ang-II is supported by the widespread clinical use of angiotensin-converting enzyme (ACE) inhibitors in a wide array of CV and renal diseases. However, the RAAS is far more complex than previously understood, and several new aspects have been recently identified that have potential clinical implications. First, tissue Ang-II may be generated by non-ACE-mediated enzymes, particularly in several conditions associated with an increased CV disease risk (e.g. acute myocardial infarction [AMI]) [3]. Second, ACE can cleave and inactivate other peptides such as bradykinin, a family of potent vasodilators that counterbalance the effects of Ang-II. Importantly, all these mechanisms can be involved in the overall effects of drugs inhibiting RAAS and could help explain some aspects of the complexity of their therapeutic profile.

Since their discovery more than 25 years ago, ACE inhibitors have been widely used for the treatment of CV diseases for their important cardioprotective and vasculoprotective properties [1–3]. Clinical data has demonstrated that ACE inhibitors are very effective at reducing blood pressure in a large proportion of patients with hypertension (HBP) [1, 2] when given alone or in combination. ACE inhibitors improve the clinical prognosis of patients with congestive heart failure (CHF) and AMI, particularly when complicated by overt left ventricular (LV) dysfunction [4], although their efficacy may be limited in postmyocardial patients with preserved LV function [5, 6]. ACE inhibitors are also the treatment of choice for many patients with types 1 and 2 diabetes, particularly when complicated by renal disease or proteinuria.

Among the different ACE inhibitors, the efficacy of zofenopril has been proven in a wide population of patients with HBP and coronary heart disease, in particular AMI [4]. The clinical efficacy of zofenopril has been extensively studied in many subpopulations of high-risk patients where it has proven to be very effective, compared to both placebo and active treatments. Treatment with zofenopril is associated with a favourable tolerability profile as a consequence of its unique mechanism of action, which might also contribute to the additional benefits beyond ACE inhibition that have been described in patients treated with zofenopril.

PHARMACOLOGICAL PROFILE OF ZOFENOPRIL
General issues

Many ACE inhibitors have been discovered and marketed. They are characterised by different aspects: chemical structure, functional group, prodrug nature, potency, additional pharmacological properties and clinical pharmacokinetic profile. Zofenopril differs from other ACE inhibitors in being highly lipophylic, which allows it to reach tissue ACE [7]. Also, it is converted into the active form (zofenoprilat) both in serum and different tissues [7, 8], whereas the other ACE inhibitors are activated mainly in serum and in the kidney. For this reason, zofenopril has several 'pleiotropic' properties: prevention of endothelial dysfunction, reversal of nitrate tolerance, anti-ischaemic, anti-inflammatory and antiatherogenic effects, enhanced angiogenesis and reversal of apoptosis. The ability of zofenopril to inhibit cardiac ACE was first evaluated *in vitro* and in comparison with several other ACE inhibitors [9, 10], and was demonstrated to be more potent than any other tested compound. This could result from the combination of a greater extent of cardiac uptake and a greater rate of conversion to its active inhibitor by local cardiac esterases. The tissue ACE inhibitory activity of

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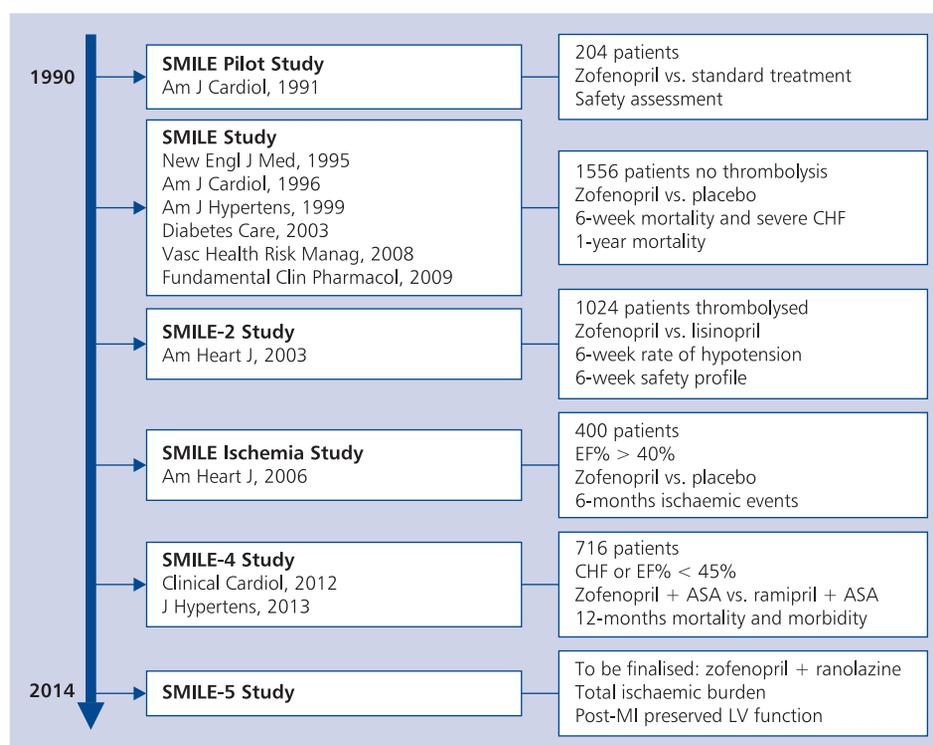
Figure 1. Overall structure of the SMILE project; CHF — congestive heart failure; EF — ejection fraction; ASA — acetylsalicylic acid; MI — myocardial infarction; LV — left ventricular

zofenopril was also evaluated *ex vivo* in the same rat model where, despite no differences in the extent of blockade of serum ACE, some relevant differences were found in the capacity of different compounds to blockade ACE at the tissue level [8]. In particular, in the aorta, the inhibitory activities of zofenopril persist for more than four days, while the other tested compounds are shorter acting, demonstrating a long-lasting antihypertensive action. These properties are responsible for a high degree of favourable pharmacological interaction with the mechanisms responsible for CV diseases, and make this drug potentially suitable for the prevention and treatment of several CV diseases.

PHARMACOLOGICAL PROPERTIES AND CORONARY ARTERY DISEASE

Zofenopril has been extensively tested in preclinical models of ischaemic heart disease to test its cardioprotective properties. Such an effect has been demonstrated in *in vitro* studies and seems to be modulated through the ATP-sensitive potassium channels [11]. The actions of zofenopril are summarised by its free radical scavenging activity, increased heart contractile function, and reduced lactate dehydrogenase release in a rat model of global ischaemia [11].

In recent years, several investigators have explored the anti-ischaemic and cardioprotective actions of ACE inhibitors. There are significant differences among the various ACE

inhibitors in their capacity to exert a cardioprotective effect [12]. In particular, cardioprotective activity has been mainly described for ACE inhibitors containing a sulfhydryl group such as captopril and zofenopril. In fact, the sulfhydryl moiety of zofenopril allows a scavenger of radical oxygen species [11, 13]. Accordingly, the availability of nitric oxide at the vascular endothelial level is enhanced. The benefit on the CV system of sulfhydryl-containing ACE inhibitors has been clearly documented and can be mainly related to the antioxidant activity due to their chemical structure.

Other data suggests that zofenopril may also have relevant antiatherosclerotic activity that may significantly contribute to the clinical efficacy of the drug in the prevention of CV diseases. In fact, the antioxidant activity of zofenopril has been also confirmed against LDL [14].

ZOFENOPRIL AND ACUTE MYOCARDIAL INFARCTION: THE SMILE PROJECT

The early activation of RAAS is a typical feature of patients with AMI and is responsible for the progression toward HF. So ACE inhibitors have some significant clinical benefits in reducing mortality and morbidity after MI whether used alone or in combination with aspirin [15, 16]. Among the different studies of ACE-inhibitors, the SMILE project was a large clinical programme aimed at investigating the efficacy of zofenopril for the treatment of patients with AMI (Fig. 1). Zofenopril

has been reported to be highly effective in animal models of experimental ischaemia and patients with MI and coronary artery disease. For this reason, the marked cardioprotective effect of zofenopril justifies the use of this drug in the setting of AMI [10–14]. The SMILE programme has involved several populations of patients with AMI and has been designed to test the hypothesis that the unique pharmacological profile of zofenopril could provide some benefit beyond ACE inhibition, in terms of CV event prevention. Very recently, the SMILE programme has been implemented with the possibility of a new randomised clinical trial (SMILE-5) investigating the combined anti-ischaemic effects of zofenopril and ranolazione in patients with preserved LV function after MI (Fig. 1).

SAFETY PROFILE OF ZOFENOPRIL IN PATIENTS WITH MYOCARDIAL INFARCTION: THE SMILE PILOT TRIAL

The primary outcome of the SMILE pilot study was safety, and included 200 patients randomly allocated to treatment with zofenopril or conventional therapy (not including ACE inhibitors) within 24 h of the onset of symptoms of AMI who were not treated with thrombolysis [17]. After 12 months of follow-up, the combined occurrence of death, non-fatal CV events and severe adverse events (primary end-point) was significantly reduced in patients treated with zofenopril. Cumulative mortality was also reduced by early zofenopril, but the difference with placebo therapy did not achieve statistical significance (7.8% vs. 10.7%). Among the secondary end-points, the in-hospital incidence of acute LV failure and ventricular arrhythmias decreased by 63% and 39% respectively, among zofenopril-treated patients. Also the incidence of anginal episodes reduced both acutely (68% reduction) and over the long term (56% reduction). LV size decreased and ejection fraction (EF) increased in patients who received zofenopril, and the improvement was greater among patients with poorer ventricular function (EF less than 40%).

Early administration of ACE inhibitors may therefore constitute a safe form of therapy for patients with AMI, particularly when the event is complicated by clinical signs or evidence of ventricular dysfunction. These findings support the importance of a larger trial aimed at assessing the effects of zofenopril on mortality and morbidity in patients with MI.

EFFECTS OF ZOFENOPRIL ON MORTALITY AND HEART FAILURE: THE SMILE TRIAL

The SMILE trial was designed to test the hypothesis that the administration of zofenopril (15–60 mg twice daily or a placebo) administered within 24 h of the onset of symptoms for six weeks would improve the clinical outcome of 1,556 high-risk patients with acute anterior MI not receiving thrombolysis. At this time we assessed the incidence of death or severe CHF. The patients were re-examined after one year to assess survival [17, 18]. The primary end-point of the SMILE study was the
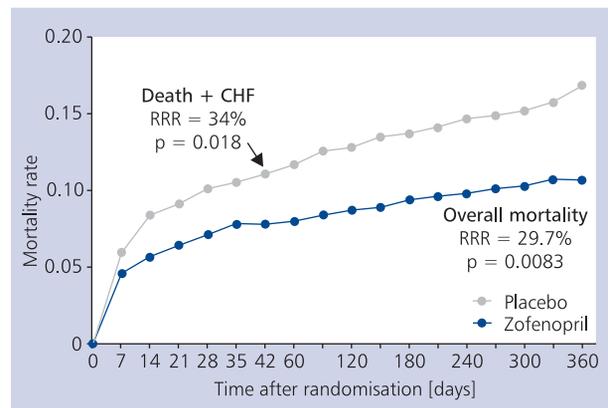

Figure 2. Primary end-point and long-term survival in the SMILE study (from [18]); CHF — congestive heart failure; RRR — relative risk reduction
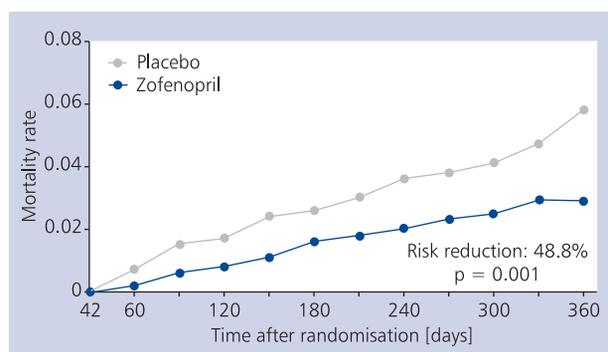

Figure 3. Long-term survival after withdraval of double-blind treatment with zofenopril or placebo in the SMILE study

combined occurrence of death or severe CHF (defined as a new onset of HF requiring open-label treatment with ACE inhibitors despite the administration of digoxin, diuretics and vasodilators) and occurred in 10.6% of patients in the placebo vs. 7.1% of patients in the zofenopril group (relative risk reduction [RRR]: 34%; 95% confidence interval [CI]: 8–54). These results have been confirmed by the GISSI-3 [19] and the ISIS-4 studies [20], and in all three studies most of the benefit of ACE inhibition has been observed within the first 24 h after randomisation. In the SMILE study, the incidence of death or severe CHF at six weeks was significantly reduced in the zofenopril group (55 patients, 7.1%), compared to the placebo group (83 patients, 10.6%). The cumulative reduction in the risk of death or severe CHF was 34% (95% CI: 8–54%; p = 0.018). The reduction in risk for severe CHF was 46% (95% CI: 11–71%; p = 0.018), and for death was 25% (95% CI: –11% to 60%; p = 0.19). After one year of observation, the mortality rate was significantly lower in the zofenopril group (10.0%) than in the placebo group (14.1%); the reduction in risk was 29% (95% CI: 6–51%; p = 0.011) (Fig. 2). A detailed analysis of the survival rate showed a progressive separation
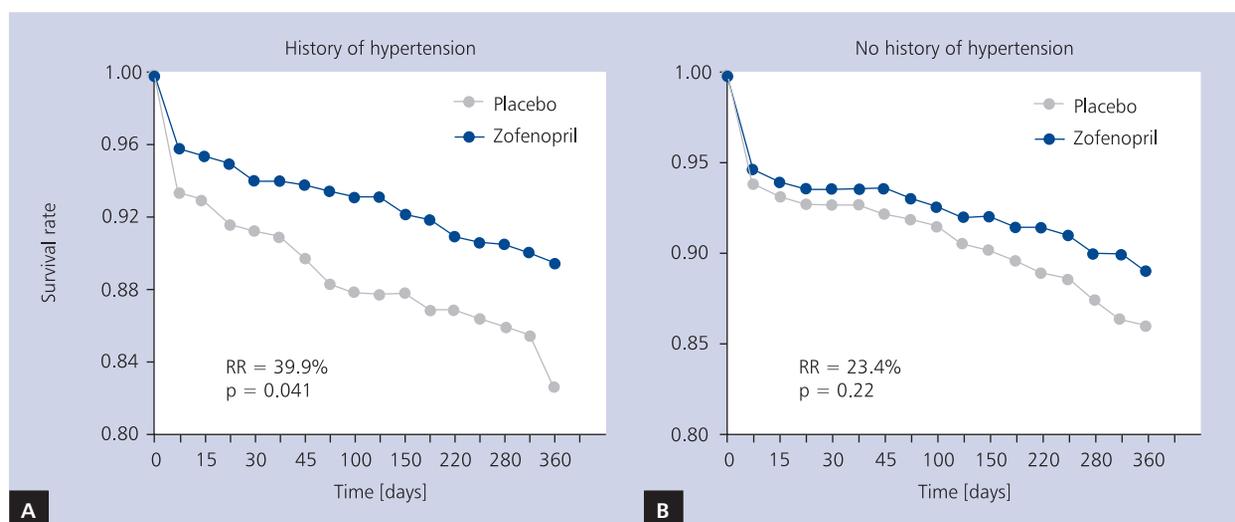
Figure 4. One-year survival in patients with acute myocardial infaction and history of hypertension (**A**) or no history of hypertension (**B**) treated with zofenopril or placebo (from [21]); RR — relative risk

of the two curves that was maintained after withdrawal of double-blind treatment as a 'legacy effect' of zofenopril treatment resulting from its anti-ischaemic and cardioprotective effects (Fig. 3).

SMILE demonstrated that treatment with zofenopril, when started within 24 h of the onset of IMA and continued for six weeks, significantly improved both short- and long-term outcomes.

EFFECTS OF ZOFENOPRIL IN HIGH-RISK PATIENT POPULATIONS WITH MYOCARDIAL INFARCTION

In the SMILE study, the effects of zofenopril have been confirmed in some subgroups of high-risk patients such as older patients and those with HBP, diabetes mellitus, previous MI or angina.

Older patients
In the older population, the effects of treatment with zofenopril on cumulative primary and secondary end-points (age > 65 years; placebo 20.5% vs. zofenopril 12.8%; 2p = 0.025) were comparable with those observed in the middle-aged population of patients (age < 65 years; placebo 15.5% vs. zofenopril 10.2%; 2p = 0.025), and no adjustment in drug dosage were specifically required [18].

Patients with arterial hypertension
The extent of the benefit of zofenopril treatment was significantly more evident in patients with a history of HBP compared to the normotensive population (Fig. 4), probably due to the favourable effects of better blood pressure control with zofenopril in patients where HBP complicated MI. In fact, the zofenopril reduced the relative risk of death or severe CHF by 40%, the one year risk of death by 39%, and

was associated with a decrease in the six-week prevalence of mild-to-moderate CHF [21].

Patients with diabetes
The effects of zofenopril treatment in patients with MI have been investigated in a cohort of diabetic patients in the SMILE study [22]. In the diabetic population, a six-week, double-blind treatment with zofenopril significantly reduced both the incidence of the primary end-point (8.6% vs. 18.3%; p = 0.019) and the six-week incidence of severe CHF (0% vs. 7.3%; p = 0.001) compared to a placebo (Fig. 5). This suggests a direct influence of RAAS activation on the clinical prognosis of patients with AMI. Conversely, one-year mortality was significantly reduced among nondiabetic patients (9.1% vs. 13.8%; p = 0.010), whereas in the diabetic population the beneficial effect of zofenopril did not achieve statistical significance (13.7% vs. 16.5%; p = 0.52).

Moreover, zofenopril not only reduced the risk of death until the end of the observation period (12 months) in non-diabetic patients, SMILE also showed that it is important to apply long-term ACE inhibition in diabetic patients surviving an AMI.

Patients with hypercholesterolaemia
During the six weeks of double-blind treatment, the cumulative rate of primary end-point was 8.1% in hypercholesterolaemic (HC) and 6.4% in normocholesterolaemic (NC) patients with anterior MI (p = 0.03) [23]. The one-year mortality rate in HC patients receiving placebo for six weeks was higher than that of NC patients (13.1% vs. 10.8%; p = 0.037). Conversely, treatment with zofenopril was associated with a similar reduction in one-year mortality in both NC and HC patients. However, due to the limited sample size of
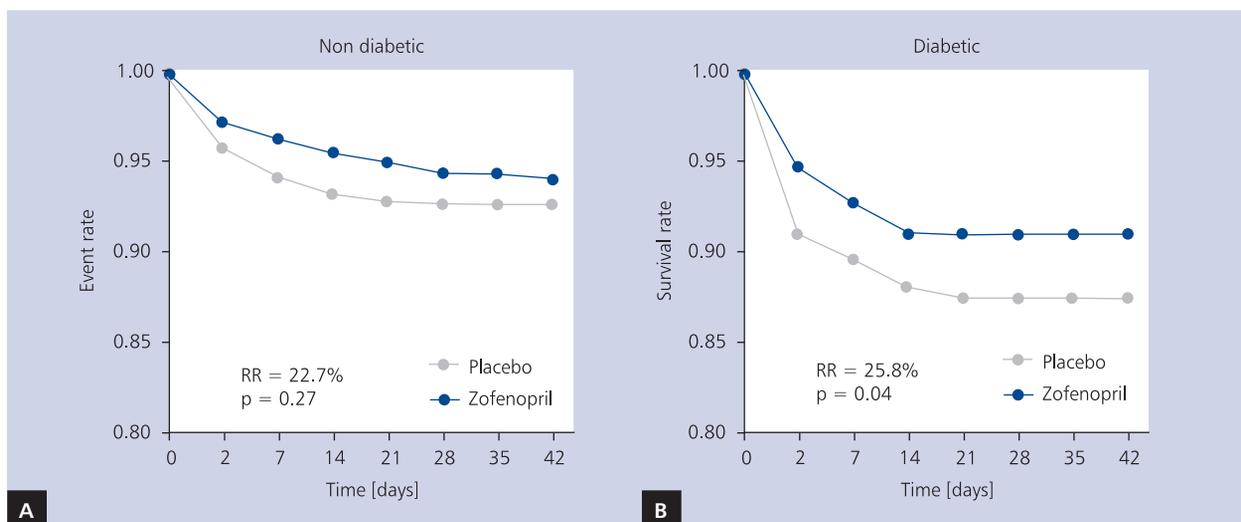
Figure 5. Combined occurrence of death and severe congestive heart failure (primary end-point) during the 6 weeks of duble-
-blind treatment in the nondiabetic (**A**) and diabetic (**B**) population of the SMILE study (from [22]); RR — relative risk

subjects in each group, the reduction did not achieve statistical significance.

Patients with metabolic syndrome
Of the 1,418 patients included in a *post-hoc* analysis of the SMILE trial, 686 (48.3%) were metabolic syndrome (MS) positive (as defined by the third Adult Treatment Panel of the National Cholesterol Educational Programme) [24] and 732 were MS negative. During the six weeks of treatment, the rates of death and severe CHF were lower in MS-positive patients treated with zofenopril compared to a placebo (p = 0.017). The same was true for long-term mortality after one year, although the difference did not achieve statistical significance. The benefit earned by zofenopril in these patients can be explained by the overexpression of AT1 receptors for Ang-II [25]. These results suggest the importance of persistent RAAS blockade with a drug such as zofenopril in patients with metabolic risk factors (obesity, diabetes, impaired glucose tolerance and MS).

Patients with angina, previous myocardial infarction or nstemi
Subgroup analysis of the SMILE study revealed that zofenopril has a clinically significant benefit in patients with angina or suffering a previous MI before the index infarction [17, 18]. In fact, this drug improved both short-term and long-term outcomes when it was started within 24 h of the onset of acute anterior MI and continued for six weeks. Also in patients with non-ST-segment elevation MI (NSTEMI) [26], zofenopril reduced the incidence of the primary end-point, the six-week incidence of severe CHF, and the one-year mortality. Moreover, the results of the SMILE-ISCHAEMIA trial support the cardioprotective role of zofenopril when given to patients with normal LV function after AMI [27].

Safety aspects of zofenopril treatment in patients with myocardial infarction
in addition to its beneficial effect in patients with AMI, treatment with zofenopril showed an acceptable safety profile. The cumulative rate of serious adverse events was slightly lower in patients treated with zofenopril (15.7% vs. 17.3%) with a nonsignificant increase in the rate of severe hypotension (systolic blood pressure < 100 mm Hg; 3.9% vs. 2.7%). No cases of angioedema were observed, and no relevant changes in haematological variables were observed in either group.

COMPARISON BETWEEN DIFFERENT ACE INHIBITORS IN PATIENTS WITH AMI: THE SMILE-2 STUDY
The SMILE-2 trial was carried out with the primary aim of comparing two ACE inhibitors to test their relative safety and efficacy in MI patients who did receive thrombolytic therapy [28]. This study compared the safety and efficacy of zofenopril and lisinopril in 1,024 thrombolysed patients with AMI. Patients aged 18 to 75 years were randomised to receive oral zofenopril (30–60 mg/day) or lisinopril (5–10 mg/day), starting within 12 h of completion of thrombolytic therapy and continuing for 42 days. The primary study end-point was the incidence of severe hypotension (systolic blood pressure < 90 mm Hg), either cumulative or drug-related. Secondary end-points included additional safety and efficacy parameters. The overall incidence of severe hypotension was slightly more reduced with zofenopril (10.9%) than with lisinopril (11.7%, p = 0.38). The incidence of drug-related severe hypotension was slightly but significantly lower with zofenopril than with lisinopril (6.7% vs. 9.8%, 2-tailed p = 0.048). The six-week mortality rate was 3.2% in the zofenopril group and 4.0% in the lisinopril group (p = 0.38), and no significant differences were observed in the
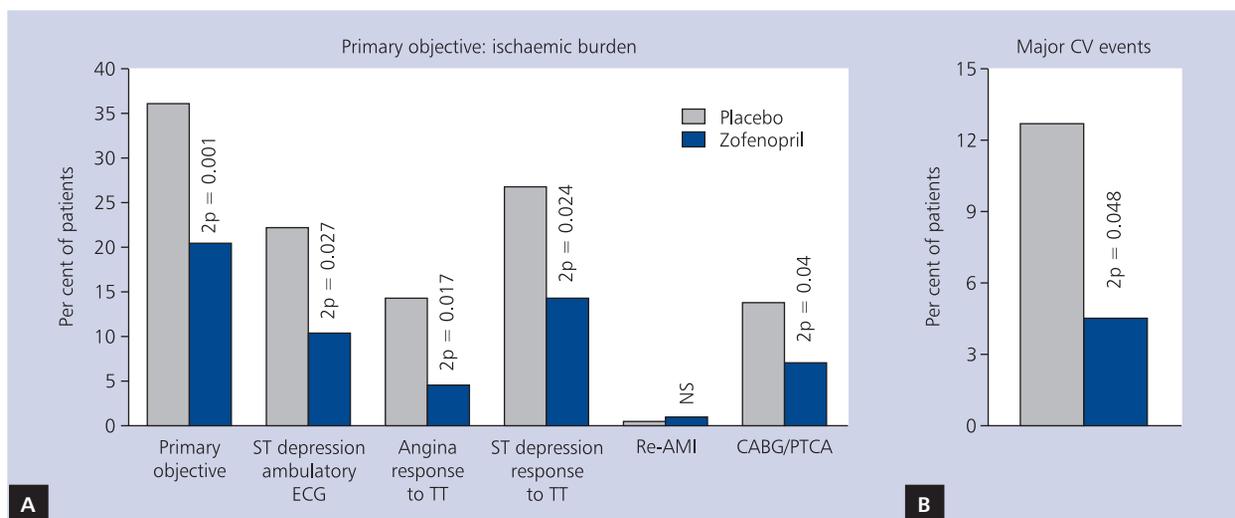
Figure 6. Effect of zofenopril and placebo on the cumulative ischaemic burden (primary end-point) (**A**) and occurrence of major cardiovascular complications events (**B**) in the SMILE-ISCHAEMIA study (from [27]); ECG — electrocardiography; TT — treadmil test; AMI — acute myocardial infarction; CABG — coronary artery bypass grafting; PTCA — percutaneous transluminal coronary angioplasty

incidence of major CV complications or any safety variables between the two ACE inhibitors. The difference between the two treatments was already evident after 48 h (p < 0.041) and still evident at five days (p < 0.033) from randomisation; this may have some important clinical implications, since it could reduce the proportion of patients withdrawn from ACE inhibition during the early phase of MI owing to a severe and potentially dangerous hypotensive response.

The SMILE-2 study demonstrates that both zofenopril and lisinopril are safe and associated with a rather low rate of severe hypotension when given in accordance with a dose-titrated scheme to thrombolysed patients with acute MI. These findings could have a positive clinical impact and increase the proportion of patients with acute MI who can be safely treated with ACE inhibitors.

ANTI-ISCHAEMIC EFFECTS OF ZOFENOPRIL IN PATIENTS WITH CORONARY HEART DISEASE: THE SMILE-3-ISCHAEMIA STUDY

The aim of SMILE-3-ISCHAEMIA was to investigate the cardioprotective effects of the ACE inhibitor zofenopril in post-MI patients with preserved LV function. Three hundred and forty-nine post-MI patients with preserved LV function (LVEF > 40%) were treated for six months with zofenopril 30 to 60 mg (n = 177) or a placebo (n = 172) according to a double-blind, randomised study design. The primary end-point of the study was to investigate whether the ACE inhibitor zofenopril reduces the 'global ischaemic burden' (occurrence of significant ST-T abnormalities on ambulatory electrocardiography [ECG], ECG abnormalities or symptoms of angina during standard exercise test, recurrence of MI,

and need for revascularisation procedures for angina) in patients with preserved LV systolic function after a thrombolysed MI. The primary end-point occurred in 20.3% of zofenopril-treated and 35.9% of placebo-treated patients (p = 0.001) (Fig. 5) despite no differences in blood pressure control, LV function, and concomitant therapy. ST-T depression during ambulatory ECG occurred in 22.7% of patients treated with placebo and 10.7% of those undergoing ACE-inhibition treatment (p = 0.027). ST-T depression in response to exercise test occurred in 14.2% and 26.7% of patients treated with zofenopril or placebo, respectively (p = 0.024), with a lower proportion of zofenopril-treated patients who complained of anginal pain (4.7% vs. 14.3%; p = 0.017), significant ST depression (14.2% vs. 26.7%; p = 0.024), and major ventricular arrhythmias (3.8% vs. 10.5%; p = 0.048). The rate of major CV events was reduced in patients treated with ACE inhibitor, with a lower rate of development and progression of CHF.

The results of the SMILE-ISCHAEMIA study support the cardioprotective role of zofenopril when given to patients with normal LV function after AMI [27].

ACE INHIBITORS, ZOFENOPRIL AND INTERACTION WITH ASA: THE SMILE-4 STUDY

The SMILE-4 study is a double-blind, prospective trial directly investigating whether the clinical benefit of the ACE inhibitors zofenopril and ramipril can be influenced by the concomitant administration of acetylsalicylic acid (ASA). Several lines of evidence have suggested the possibility that the clinical benefit of ACE inhibitors might be significantly reduced by the concomitant administration of ASA, particularly in subjects with LV dysfunction and CHF by the inhibition of ASA on
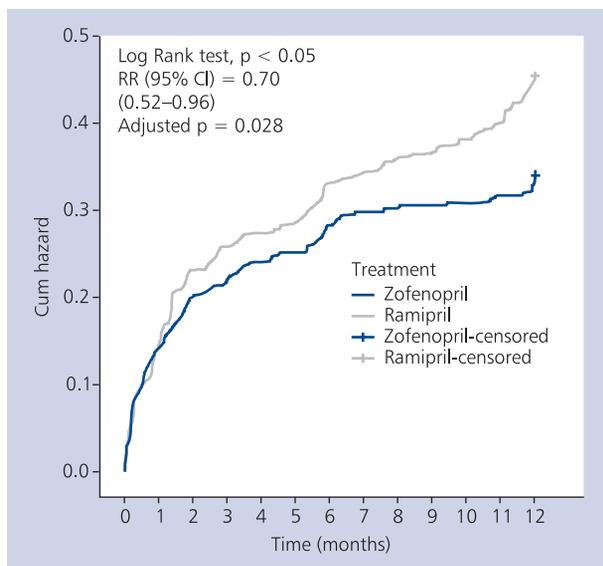
Figure 7. Combined incidence of death and hospitalisation for cardiovascular causes (primary end-point) in patients with post-myocardial infarction left ventricular dysfunction in the SMILE-4 study (from [30]); RR — relative risk

the bradykinin system [29]. This randomised, double-blind, parallel-group, multicentre, 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 LV dysfunction (clinical signs of HF or a LVEF < 45%) following AMI. The primary study end-point was one-year combined occurrence of death or hospitalisation for CV causes. 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; 95% CI: 0.51–0.96; p = 0.028) as a result of a decrease in CV hospitalisation (OR: 0.64; 95% CI: 0.46–0.88; p = 0.006) (Fig. 6). Mortality rate was not significantly different between the two treatments (OR: 1.51; 95% CI: 0.70–3.27; p = 0.293). Blood pressure values did not significantly change during the one-year follow-up. The benefit of zofenopril treatment was more evident in the subgroup of patients with a history of hypertension or elevated blood pressure values at randomisation [31]. These findings confirm those previously reported in the SMILE study, and suggest the primary role of zofenopril in patients with elevated blood pressure values complicating AMI.

Overall, the SMILE-4 study shows how in patients with LV dysfunction 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 ACE inhibitors in patients with LV dysfunction or overt HF (Fig. 7) [30].

Conflict of interest: *none declared*

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