

# ACE-INHIBITORS AND CARDIOPROTECTION OPEN ISSUES AND FUTURE SOLUTIONS

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### Pharmacodynamics of Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors: From Laboratory to Clinical Practice

Prof Krzysztof Narkiewicz

The current management of patients with hypertension, especially those with a high risk of coronary artery disease should take into account the role of angiotensin II in the development of hypertension and cardiovascular disease.

There are several ways that the RAAS might contribute to high cardiovascular risk. However, the RAAS might affect several other mechanisms underlying both the development of hypertension and the development of cardiovascular disease. This includes the effect on the endothelial function, the increased risk of inflammation, the effect on lipids, which are a very important component of cardiovascular risk and the effect on fibrinolysis. All these factors may contribute to both cardiovascular morbidity and mortality.

The new 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines<sup>1</sup> stress that the role of target organ damage assessment is not only evident cardiovascular

disease, but the subclinical evidence of target organ damage which in the vast majority of patients would put them in the category of high cardiovascular risk.

The activation of the RAAS contributes to the development of target organ damage and it is inter-related with other mechanisms that contribute to target organ damage. For example, the positive relationship between the RAAS and the sympathetic nervous system, the effect of inflammation (oxidative stress) on endothelial dysfunction and the input of insulin and leptin resistance (which are important in terms of sodium handling and volume retention). To date, the evidence is that the RAAS contributes to target organ damage, which includes both blood pressure dependent and blood pressure independent mechanisms that are of clinical importance.

A large amount of research has been performed to discover the most effective way to inhibit the RAAS and this has indicated that there are several ways that the RAAS can be potentially blocked;<sup>2</sup> angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and renin inhibitors (the newest component in terms of clinical management). There is no doubt that blocking the RAAS provides substantial clinical benefit.

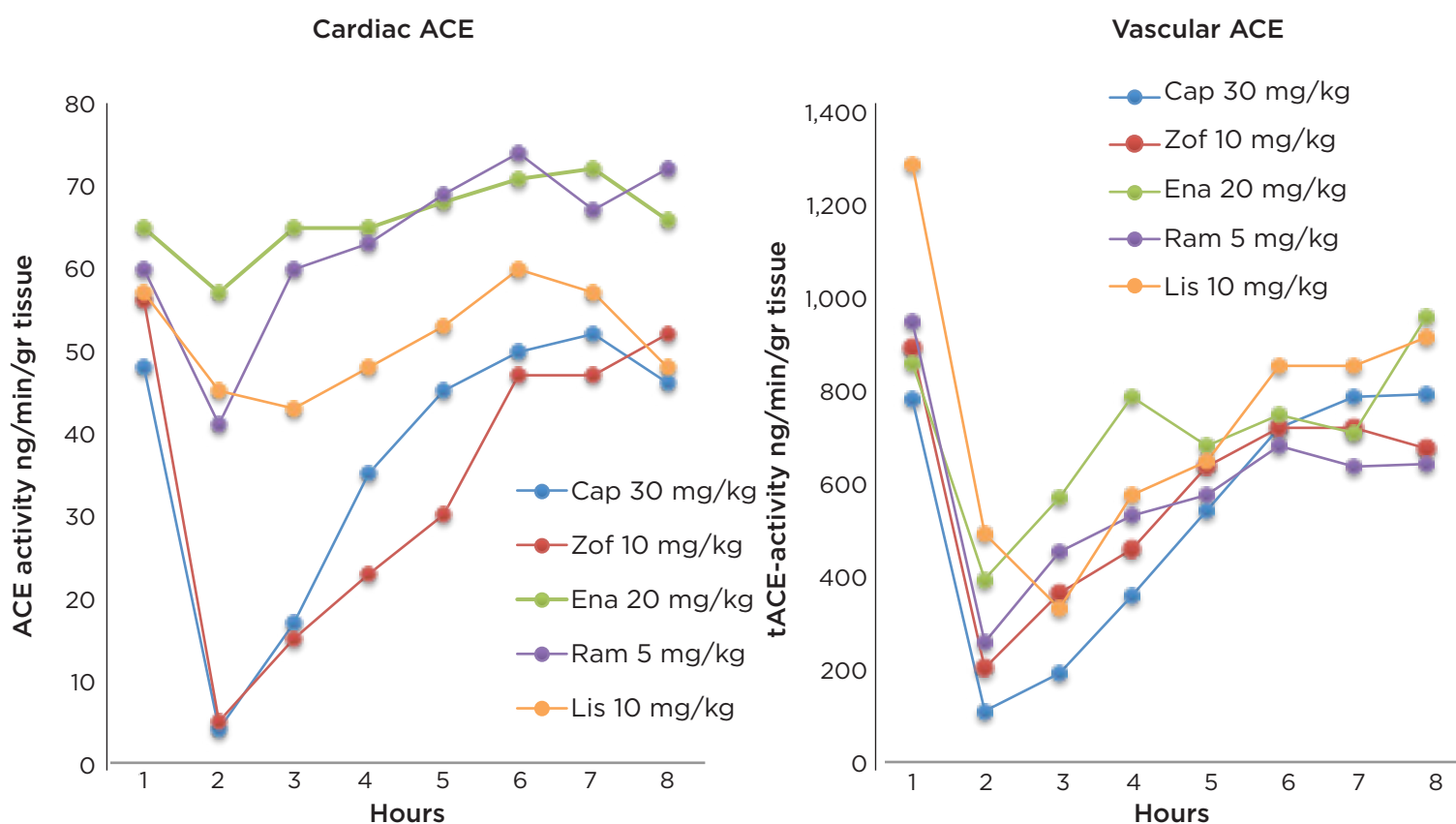
The evidence base for this is comprehensive; ACE inhibitors have been used successfully for decades and effective innovative drugs are becoming available, in addition there is increased understanding of the pathophysiology and pharmacology, all of which contribute to improved management of high risk patients.

The ESH/ESC guidelines present the various types of asymptomatic organ damage (left ventricular hypertrophy, asymptomatic atherosclerosis, micro albuminuria, renal dysfunction) various clinical cardiovascular (CV) events (previous stroke, previous myocardial infarction [MI] angina pectoris, heart failure, aortic aneurysm, atrial fibrillation prevention, atrial fibrillation ventricular rate control, end stage renal disease/proteinuria, peripheral artery disease) and other co-morbidities (isolated systolic hypertension [elderly], metabolic syndrome, diabetes mellitus). In many of these conditions ACE inhibitors are listed in the guidelines as the drugs of preferred choice. There is increasing evidence suggesting that ACE inhibitors could be beneficial in patients at risk of coronary artery disease, they not

only provide management for hypertension, but also for congestive heart failure and more recently for different stages of coronary artery disease, including acute coronary events.<sup>3</sup>

ACE inhibitors differ in chemical structure and functional group (primarily the sulfhydryl [SH] group), prodrug nature, potency and duration of effect. Different structural profiles may include additional pharmacological properties which may provide significant benefits as well as different clinical pharmacokinetic profiles.

The ACE inhibitors captopril and Zofenopril are at the top of the SH-group. Captopril provides several benefits but has the disadvantage of having a short mode of action. Zofenopril is the most recent drug in the ACE inhibitor group. The major difference of Zofenopril compared with other drugs is that Zofenopril is converted into the active form (zofenoprilat) both in serum and different tissues, especially the cardiac tissue. It is highly lipophilic which possibly provides important benefits in terms of the reduction of the activity of the RAAS and there is evidence<sup>4</sup> of increased



**Figure 1. Inhibition of tissue ACE activity over time after equivalent oral doses of Zofenopril and ramipril.**  
Cushman DW et al.<sup>6</sup>

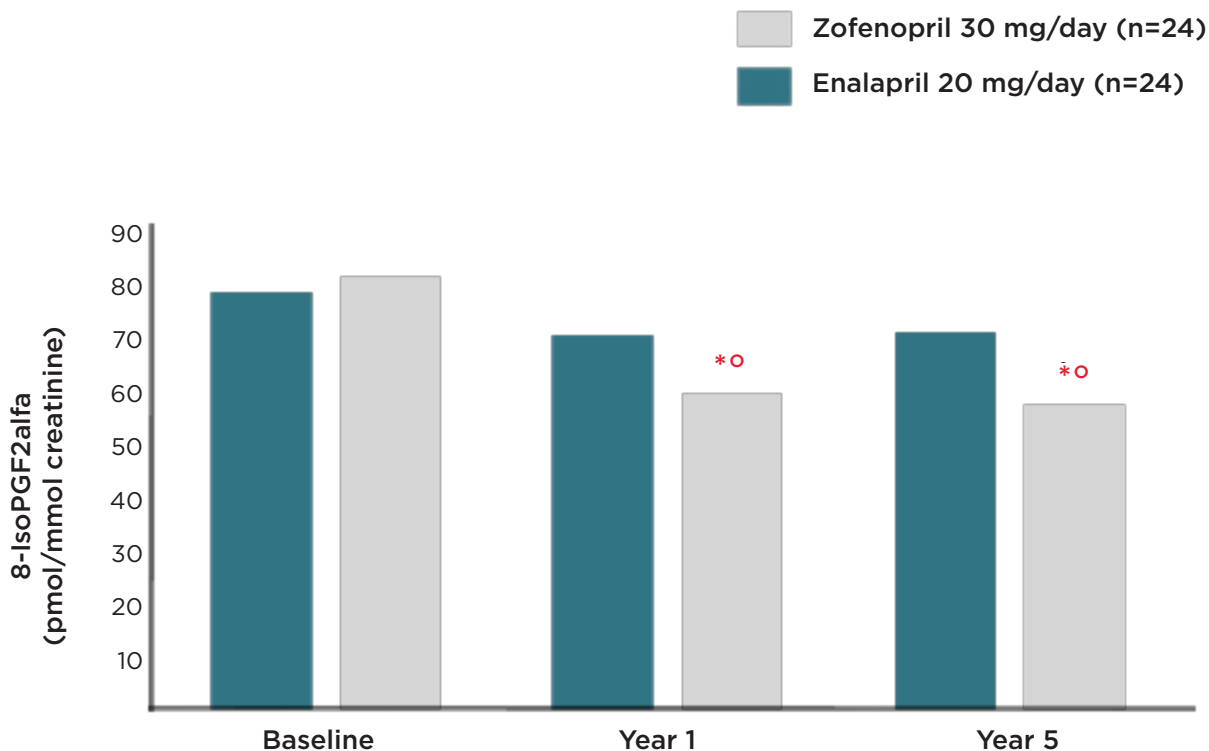
cardiac uptake, and a greater rate of conversion to its active inhibitor by local cardiac esterases. In contrast to captopril and many other ACE inhibitors, Zofenopril has a long mode of action.

Borghi et al. (1993)<sup>5</sup> showed that the use of Zofenopril compared with placebo in patients with acute MI produced a dramatic decrease in ACE activity. When Zofenopril is compared with other ACE inhibitors (including ramipril) vascular ACE inhibition is similar. However, unlike other ACE inhibitors, cardiac ACE inhibition with Zofenopril produces a decrease in the ACE activity and marked long-lasting inhibition sustained for up to 24 hours (Figure 1).<sup>6</sup> This potentially provides benefit in terms of target organ damage. In addition the prevention of cardiac tissue necrosis, which is related to acute coronary ischaemia and acute coronary syndrome, has been shown to be significantly reduced with Zofenopril when compared with a control group ( $p < 0.05$ ).<sup>7</sup>

Zofenopril may have an effect beyond blood pressure control; it has a beneficial vasculoprotective effect on endothelial function that is partly mediated by its action on nitric

oxide (NO). An experimental study using bovine aortic endothelial cells demonstrated that Zofenopril stimulates NO release from these cells to a significantly greater extent ( $p < 0.001$ ) than both captopril and enalapril.<sup>8</sup> Pasini et al. (2007)<sup>9</sup> compared the vasculoprotective effects of Zofenopril with ramipril and atenolol in hypertensive subjects and found endothelium-dependent dilation was significantly increased ( $p < 0.001$ ) in the Zofenopril treated group when compared with the ramipril and atenolol treated groups. These results indicate that Zofenopril has important advantages in reducing endothelial activation.

The role of the SH-group in the improvement of endothelial dysfunction with ACE inhibitors was evaluated in an experimental model of heart failure in myocardial infarcted rats treated with Zofenopril or lisinopril. Following 11 weeks of treatment, the aortas were studied as ring preparations for endothelium dependent and independent dilation. At the end of the study, Zofenopril (but not lisinopril) additionally potentiated the vasodilator effect of endogenous NO after A23187-induced release from the



**Figure 2. Antioxidant activity of ACE inhibitors after 5 years of treatment.**

\* $p < 0.01$  versus respective baseline; ° $p < 0.05$  versus enalapril.

Napoli C et al.<sup>12</sup>

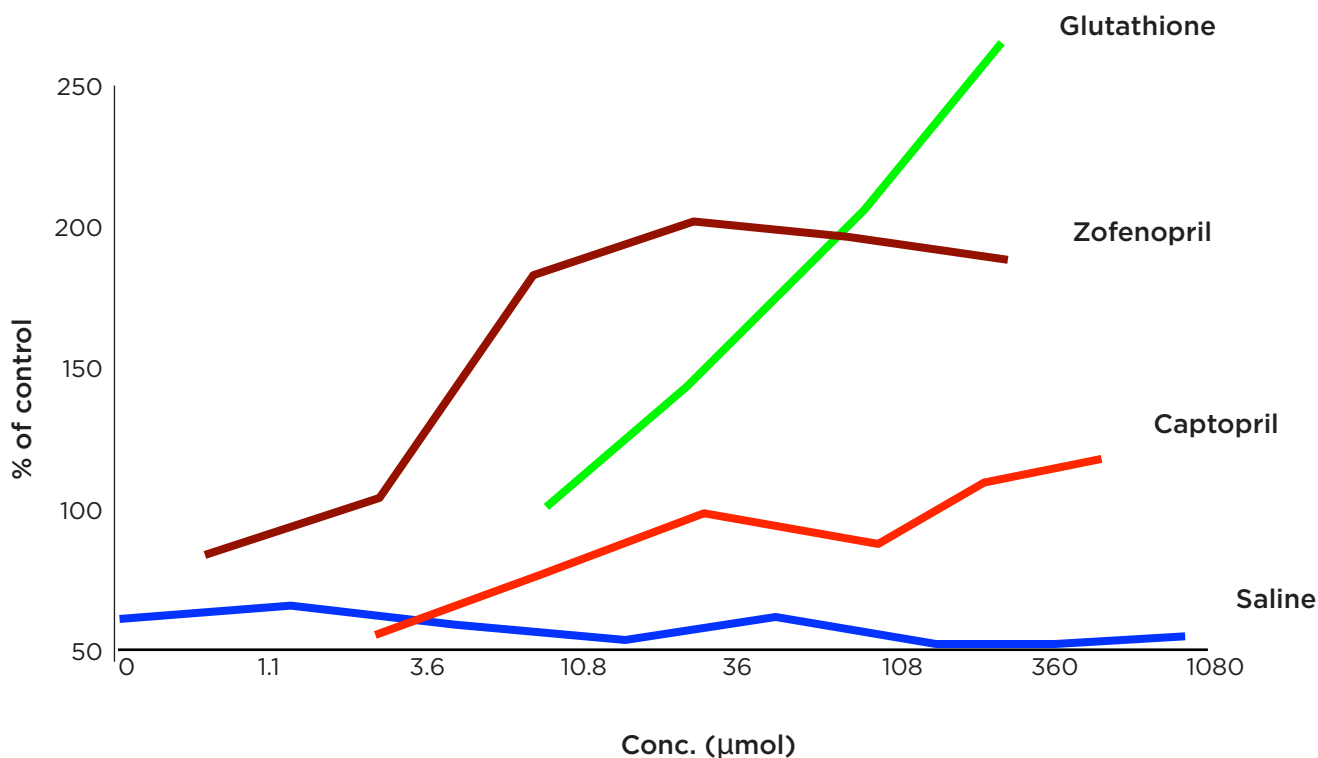
endothelium (+100%).<sup>10</sup> This demonstrates a potential advantage in improvement of endothelial dysfunction through increased activity of NO after release from the endothelium into the vessel wall.

The oxidative stress potentially exposes hypertensive patients to both arterial sclerosis and atherosclerosis. Healthy subjects were compared with: hypertensive subjects before treatment; hypertensive subjects who received 12 weeks of treatment with enalapril; and hypertensive subjects who received 12 weeks treatment of Zofenopril. The results showed that isoprostanes were similar after Zofenopril treatment ( $p < 0.03$ ) compared to the healthy control subjects ( $p < 0.01$ ) whereas enalapril was ineffective.<sup>11</sup> These results are sustained in long-term follow-up, in a randomised, prospective study, 48 newly diagnosed mildly hypertensive patients with no additional risk factors for atherosclerosis (e.g. hyperlipidaemia, smoking habit, family history of atherosclerosis-related diseases or diabetes) were enrolled and randomly assigned to 5 years of treatment with either enalapril 20 mg/day ( $n = 24$ ) or Zofenopril 30 mg/day ( $n = 24$ ).<sup>12</sup> The objective was to evaluate the effect of treatment with Zofenopril and enalapril

on systemic oxidative stress. The isoprostane 8-iso-PGF<sub>2</sub> was measured at baseline and at 1 and 5 years of treatment. The results showed the reduction of 8-iso-PGF<sub>2</sub>a levels were greater in the Zofenopril group, suggesting a sustained antioxidant efficacy (Figure 2). This indicates there is no rebound effect for patients after long-term treatment.

There have been some novel developments in terms of cardiovascular risk; these include reduced platelet accumulation in atherosclerosis. In a rabbit model of atherosclerosis, platelets were labelled to assess their distribution in the atherosclerotic plaque. Zofenopril reduced platelet accumulation in the abdominal aorta and common carotid ( $p < 0.01$ ).<sup>13</sup> The reduced accumulation of labelled platelets induced by Zofenopril indicates less atherosclerotic plaque progression and lower probability of plaque rupture with consequent vessel occlusion, suggesting that Zofenopril may play an important role in the prevention of cardiovascular events.

Ferrari R et al. (1992)<sup>14</sup> assessed the effect of captopril and Zofenopril on reperfusion and determined that Zofenopril influences the release



**Figure 3. Dose response curve of captopril, Zofenopril and glutathione effects on coronary flow of isolated rat hearts.**

*Van Gilst WH et al.<sup>15</sup>*

of lactate and creatinine phosphokinase from the heart. The study concluded that captopril had no effect on the occurrence of oxidative stress during reperfusion, whereas Zofenopril reduced it. The dose response curve of captopril, Zofenopril and glutathione on the coronary flow of isolated rat hearts showed that Zofenopril is considerably more powerful than captopril<sup>15</sup> (Figure 3).

The interaction between hypertension, cardiovascular disease and metabolic factors and the RAAS possibly predisposes patients to diabetes, metabolic syndromes and other abnormalities. The blockade of the system with ACE inhibitors, particularly the in light of the evidence shown by Zofenopril, could provide beneficial effects in terms of the metabolic risk.

In summary, Zofenopril is differentiated from other drugs in its class by the presence of the SH-group due to its ability to reduce oxidative stress. It has high lipophilicity producing high myocardial and vascular uptake that provides improved blockade at the level of the cardiac tissue (increasing coronary flow) and reduced cellular hypertrophy. Zofenopril has a high level of ACE inhibition providing the additional benefits of plasma ACE blockade. Including reduced angiotensin II and increased bradykinin level beyond classic ACE inhibitor levels. This reduces ischaemia and improves left ventricular fraction. Consequently there is an improved CV outcome for the patient.

Zofenopril has been tested in a series of randomised trials looking at the different aspects of ACE inhibition;<sup>16-25</sup> this provides a carefully tested evidence base that demonstrates the beneficial effects of the drug.

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## ACE-Inhibitors Pharmacological Effects: Just a Matter of mmHg?

**Prof Athanasios J. Manolis**

The fundamental questions in the treatment of patients with cardiac disease are:

Are there beneficial effects in blood pressure reduction? Are drugs in all classes the same? Are drugs of the same class equally effective in cardiovascular prevention?

The ESH/ESC hypertension guidelines<sup>1</sup> - choice

of antihypertensive drugs, conclude that the main benefits of antihypertensive treatment are due to lowering the blood pressure per se and are largely independent of the drug employed. Although meta-analyses occasionally claim superiority of one class of drug the outcome largely depends on selection bias of the trials and the largest meta-analyses do not show clinically relevant class differences. The current guidelines reconfirm that the drugs classes: diuretics (thiazides, chlorthalidone, indapamide); beta-blockers; calcium antagonists; ACE-inhibitors and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as a monotherapy or in various combinations with each other. The guidelines propose the combinations between some classes of antihypertensive drugs (ACE-inhibitors or angiotensin receptor blockers plus diuretics or calcium antagonists) produce a pronounced antihypertensive effect, CV protection and optimal tolerability.

Previous clinical trials have shown promising data and excellent results using ACE inhibitors in the treatment of chronic heart failure and post-MI.<sup>17,26-34</sup> ACE inhibitors are the preferred drug in the treatment of most conditions in the cardiovascular continuum (heart failure, LV dysfunction, post-MI, diabetic nephropathy, non-diabetic nephropathy, LV hypertrophy, carotid atherosclerosis, proteinuria/microalbuminuria, atrial fibrillation, metabolic syndrome), and in most of these conditions are the gold standard treatment.

There is continued debate concerning ACE inhibitors and ARBs and which group is the best choice of treatment. Staessen et al.<sup>35</sup> reviewed the outcome of six trials evaluating blood-pressure lowering drugs in 74,524 hypertensive or high risk patients. The review concluded that because ARBs might offer less protection against MI than ACE inhibitors, ACE inhibitors should remain the preferred renin system inhibitor for cardiovascular prevention in ACE inhibitor tolerant patients. The protective attributes of ACE inhibitors are due to the cardioprotective properties of bradykinin. The actions of bradykinin include vascular contraction and relaxation, participation in the process of inflammatory reactions, interaction with central and peripheral neural structures, stimulation of synthesis and release of various vasoactive substances, and enhanced insulin-dependent glucose transport utilisation. Recent studies have shown that the

activation of the  $\beta$ -2 receptor has beneficial effects in terms of both functional and structural cardioprotective actions.<sup>36</sup>

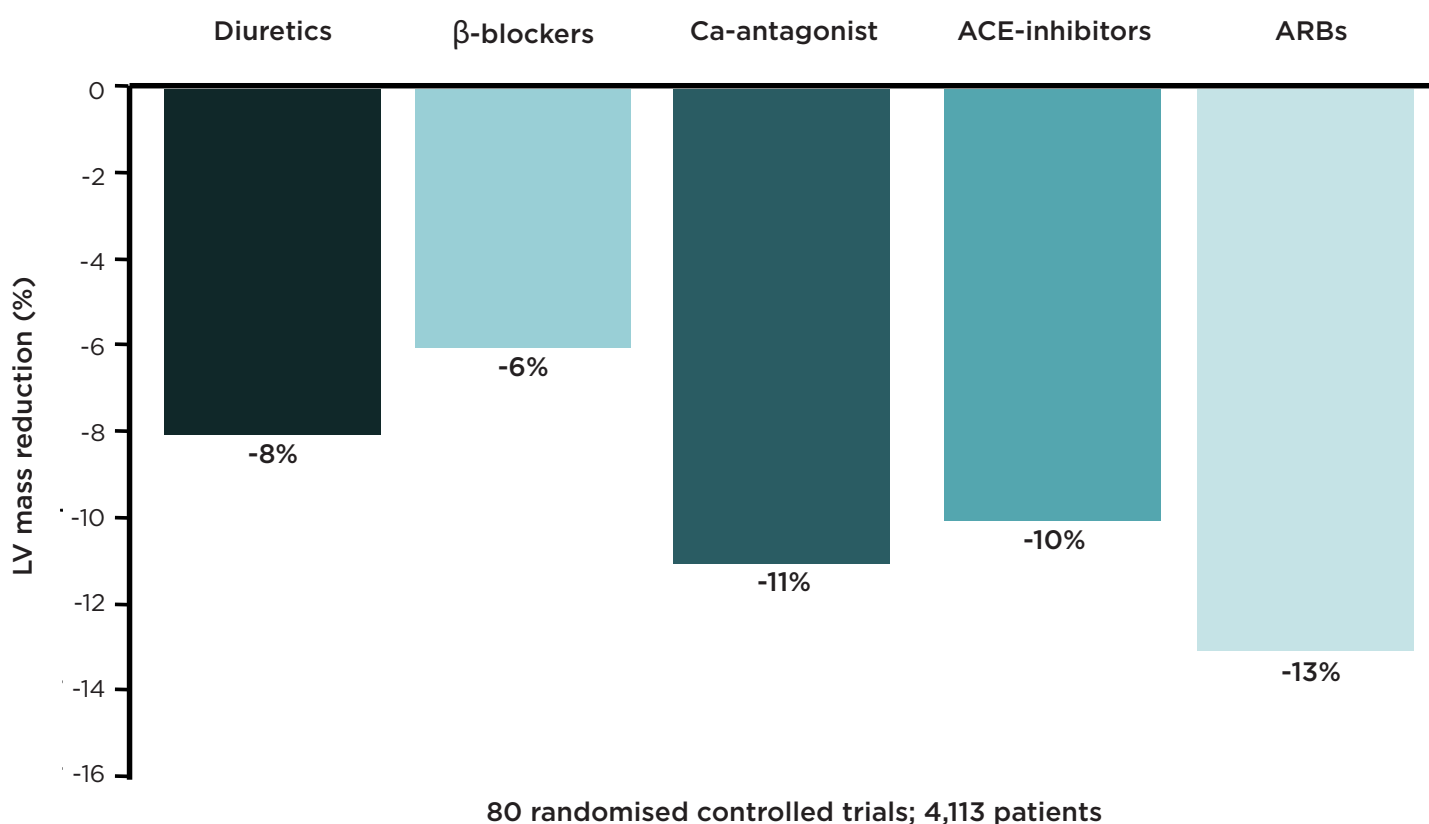
In CV prevention the main target is blood pressure reduction. However, there are drugs that provide beneficial effects beyond blood pressure reduction, mainly in the field of high risk factors, these include; prevention of diabetes, target organ regression and prevention, prevention of atrial fibrillation or coronary artery disease, congestive heart failure, stroke and cognitive dysfunction dementia.

A meta-analysis of randomised, controlled trials of left ventricular hypertrophy (LVH) regression in essential hypertension showed that there are significant differences between the different classes of drugs in the regression of LVH<sup>37</sup> (Figure 4).

The LIFE study<sup>38</sup> showed that in patients with LVH (ascertained by electrocardiography) there was similar blood pressure reduction in both systolic and diastolic measurements in patients receiving atenolol based treatment or losartan

based treatment. However, the primary composite endpoint results showed losartan prevents more cardiovascular morbidity and death than atenolol for a comparable reduction in blood pressure and has greater tolerability.

The ACCOMPLISH study<sup>39</sup> found that treatment with the combination of an ACE inhibitor plus a diuretic, or a calcium channel blocker plus an ACE inhibitor resulted in a similar blood pressure reduction (within 1 mmHg). However, there was a 20% (p=0.0002) risk reduction of cardiovascular events in patients treated with an ACE inhibitor plus a calcium channel blocker. These results clearly show that treatment with an ACE inhibitor plus a calcium channel blocker has beneficial effects beyond blood pressure reduction. Likewise, the ASCOT trial<sup>40</sup> compared amlodipine plus perindopril versus atenolol plus thiazide and the results showed a significant reduction in cardiovascular events in patients who were treated with an ACE inhibitor plus a calcium channel blocker. Furthermore, the results of the CAFÉ trial<sup>41</sup> have shown that despite a similar reduction in the peripheral systolic blood pressure in patients



**Figure 4. Meta-analysis of randomised, controlled trials of the treatment of LVH regression in essential hypertension.**

*Schmieder RE et al.<sup>37</sup>*

treated with an ACE inhibitor plus a calcium channel blocker, and patients treated with a  $\beta$ -blocker plus a diuretic, there was a significant difference in the central systolic blood pressure. This difference was shown in patients treated with the combination of an ACE inhibitor and a calcium channel blocker.

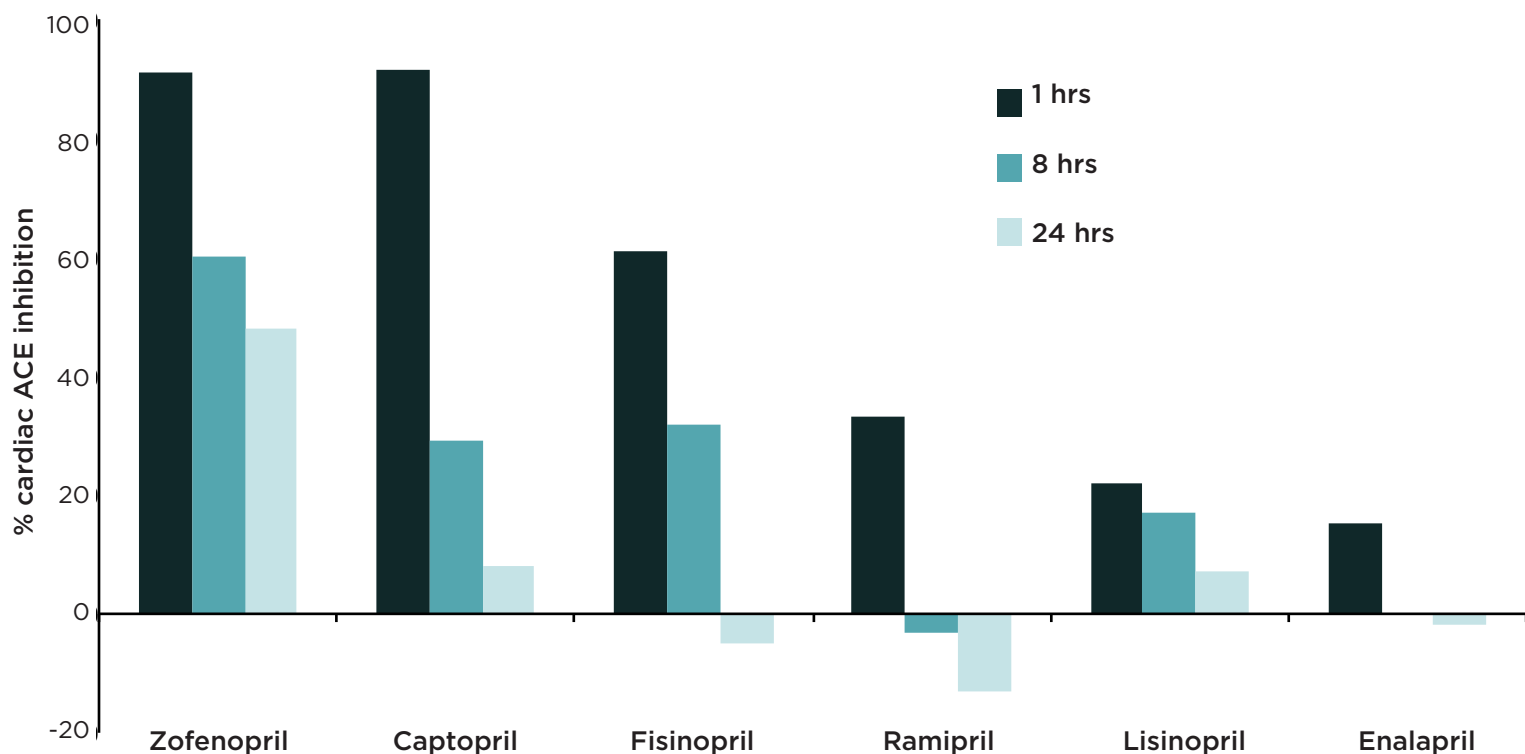
ACE inhibitors have been shown to produce a greater reduction in central aortic pressure compared with other antihypertensive drug classes.<sup>42</sup> In addition, pulse wave velocity (PWV) measured in normotensive patients with diabetes mellitus showed a significant reduction in PWV in patients treated with ACE inhibitors compared with placebo ( $p < 0.003$ ).<sup>43</sup> McEniery et al.<sup>44</sup> compared nebivolol and atenolol and found that atenolol caused an increase in PWV and conversely nebivolol caused a reduction in PWV.

It is clear that in the same class there are differences between drugs. For example, nebivolol when compared with other beta-blockers demonstrates improvements in central blood pressure and sexual dysfunction that are not shown in other beta-blockers. Moreover, nebivolol is one of the preferred beta-blockers in chronic

obstructive pulmonary disease. This is due to its NO-mediated vasodilating properties and beta-1 selectivity, and it does not decrease glucose tolerance as demonstrated by the low occurrence of new onset diabetes in seniors versus placebo.<sup>1</sup>

Two studies; the PEACE trial<sup>45</sup> and the EUROPA trial<sup>46</sup> evaluated patients with coronary artery disease who had experienced a previous MI. Patients in the PEACE trial were treated with either trandolapril or placebo and in the EUROPA trial patients were treated with perindopril. The PEACE study found no difference in cardiovascular events between trandolapril and placebo whereas the EUROPA trial found that perindopril significantly reduced cardiovascular events ( $p = 0.003$ ). An editorial comment on the PEACE trial results<sup>47</sup> stated that *'the possibility that not all ACE inhibitors are equally effective for all indications should also be considered.....I will continue to use ACE inhibitors that have been shown to be effective for this indication in several groups of patients.'*

It is evident that there are distinctions in the mode of action of different ACE inhibitors. Within this class Zofenopril shows promising results.



**Figure 5. Cardiac tissue ACE inhibition by equivalent oral doses of ACE inhibitors.**

*Cushman DW et al.<sup>6</sup>*

In Watanabe heritable hyperlipidaemic rabbits Zofenopril significantly reduced atherosclerosis in the abdominal aorta and common carotid arteries ( $p < 0.05$ ).<sup>13</sup> In addition, cardiac ACE inhibition by equivalent oral doses of ACE inhibitors in spontaneously hypertensive rats showed that Zofenopril has a longer activity in comparison with other ACE inhibitors<sup>6</sup> (Figure 5).

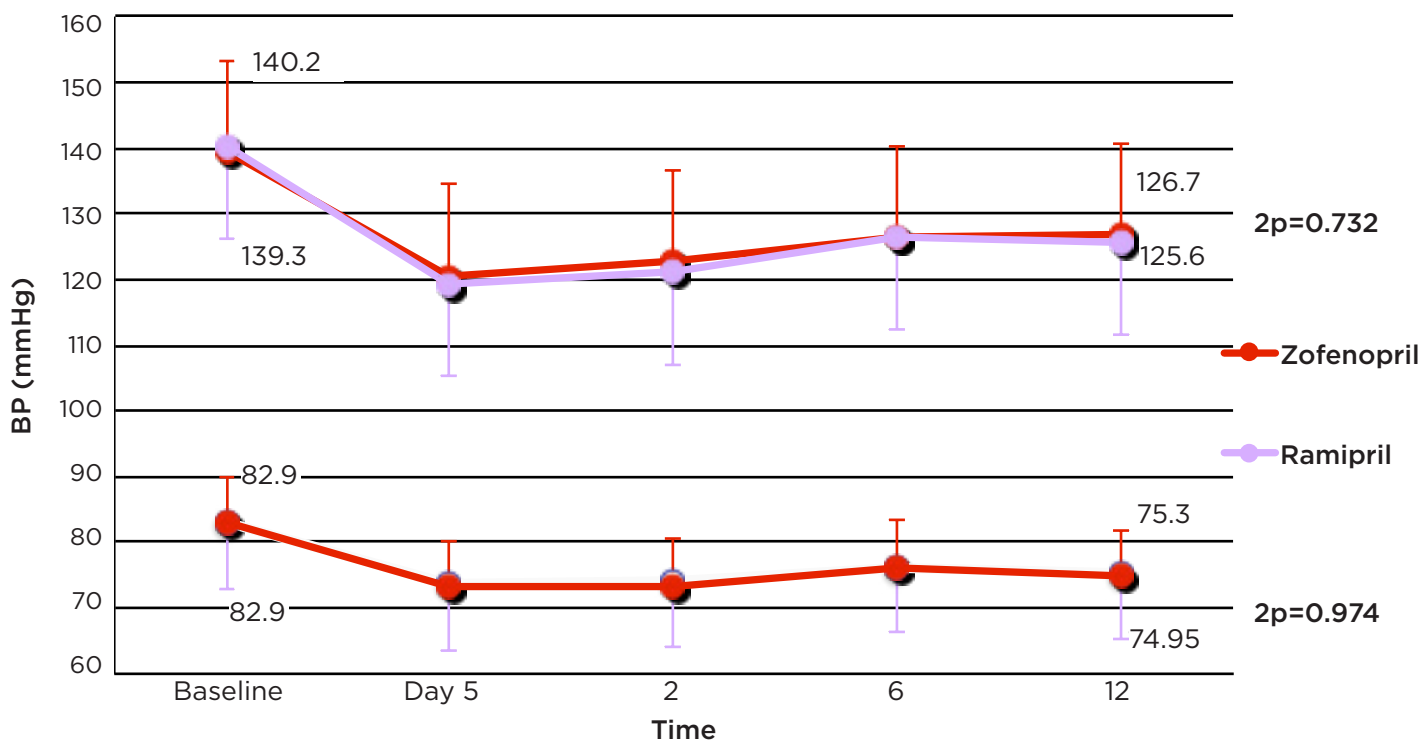
Napoli et al.<sup>11</sup> compared the effect of the two ACE inhibitors enalapril and Zofenopril on low density lipoprotein (LDL). The results of the study found that there were differences in oxidisability, LDL from hypertensive patients had enhanced oxidation compared with control subjects ( $p < 0.05$ ). Following 12 weeks of treatment malondialdehyde levels were significantly reduced by Zofenopril ( $p < 0.05$ ) but not enalapril treatment ( $p = \text{not significant}$ ). This suggests that Zofenopril reduces oxidative stress and improves the NO pathway in patients with essential hypertension.

In a study of patients with essential hypertension,<sup>9</sup> differences were observed between Zofenopril, ramipril and atenolol in relation to the molecules related to inflammation (intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion

molecule 1 [VCAM-1] and E-selectin), a significant reduction in these molecules was seen in patients treated with Zofenopril but not in patients treated with ramipril or atenolol. This suggests that through sustained antioxidant activity Zofenopril has advantages in reducing endothelial activation. A further study compared Zofenopril with other ACE inhibitors and found that there was an increase in the release of NO ( $p < 0.01$  versus control;  $p < 0.02$  Zofenopril versus other ACE inhibitors) showing that when compared with other ACE inhibitors, Zofenopril has superior efficacy in improving the endothelin-1/nitric oxide balance in human vascular endothelial cells due to its greater antioxidant properties.<sup>48</sup>

Zofenopril has further potential in the field of diabetes, when compared with enalapril Lupi et al.<sup>49</sup> found that Zofenopril had increased potency in promoting insulin secretion from human pancreatic cells ( $p < 0.05$  versus glucose 22.2 mmol/L;  $p < 0.05$  versus enalapril;  $p < 0.01$  versus glucose 5.5 mmol/L). These results indicate that Zofenopril protects human islets from glucotoxicity.

Not all ACE inhibitors are equivalent, pharmacology classifies ACE inhibitors in three



**Figure 6. Changes in systolic and diastolic blood pressure - Zofenopril compared with ramipril.**  
Borghi C et al.<sup>25</sup>



groups; prodrugs (captopril, lisinopril, Zofenopril), SH-group (captopril, Zofenopril) and high lipophilicity group (quinapril, ramipril, Zofenopril). As a third generation ACE inhibitor Zofenopril has the advantage of demonstrating the properties of all three groups. It is a prodrug and therefore has a long duration of action and is effective in patients with renal and hepatic impairment. In addition it has the SH-group properties of a free radical scavenger and reduces oxidative stress, prevents endothelial dysfunction, has anti-ischaemic, anti-inflammatory and anti-atherogenic effects, reverses apoptosis and increases NO. Furthermore, Zofenopril has high lipophilicity which produces high myocardial and vascular uptake, a high tissue ACE blockade, increases coronary flow and reduces cellular hypertrophy.

Likewise data in human trials show the benefits of using Zofenopril. In post-MI patients Zofenopril was compared with ramipril (SMILE-IV trial).<sup>25</sup> The results concluded that a similar systolic and diastolic blood pressure reduction was seen using either ramipril or Zofenopril but a significant reduction of cardiovascular events was seen in patients treated with Zofenopril (Figure 6).

The primary endpoint of one year CV mortality and hospitalisation for CV causes in the same trial showed there was a significant reduction in those treated with Zofenopril ( $p < 0.05$ ) compared with those treated with ramipril. Furthermore, a retrospective analysis of post-MI patients with left ventricular systolic dysfunction compared Zofenopril and ramipril and acetylsalicylic acid. The results showed that the survival rate was significantly improved in those treated with Zofenopril compared with those treated with ramipril (normotensive patients  $p = 0.631$ ; hypertensive patients  $p = 0.041$ ).<sup>50</sup>

Based on the editorial comments on the SMILE study<sup>25</sup> that emphasised the possibility that not all ACE inhibitors are equally effective for all indications, it appears judicious to use ACE inhibitors that have been shown to be effective for the particular indication as opposed to using other ACE inhibitors that are effective in several groups of patients.

## Zofenopril in Post-MI: Can We SMILE Again?

Prof Claudio Borghi

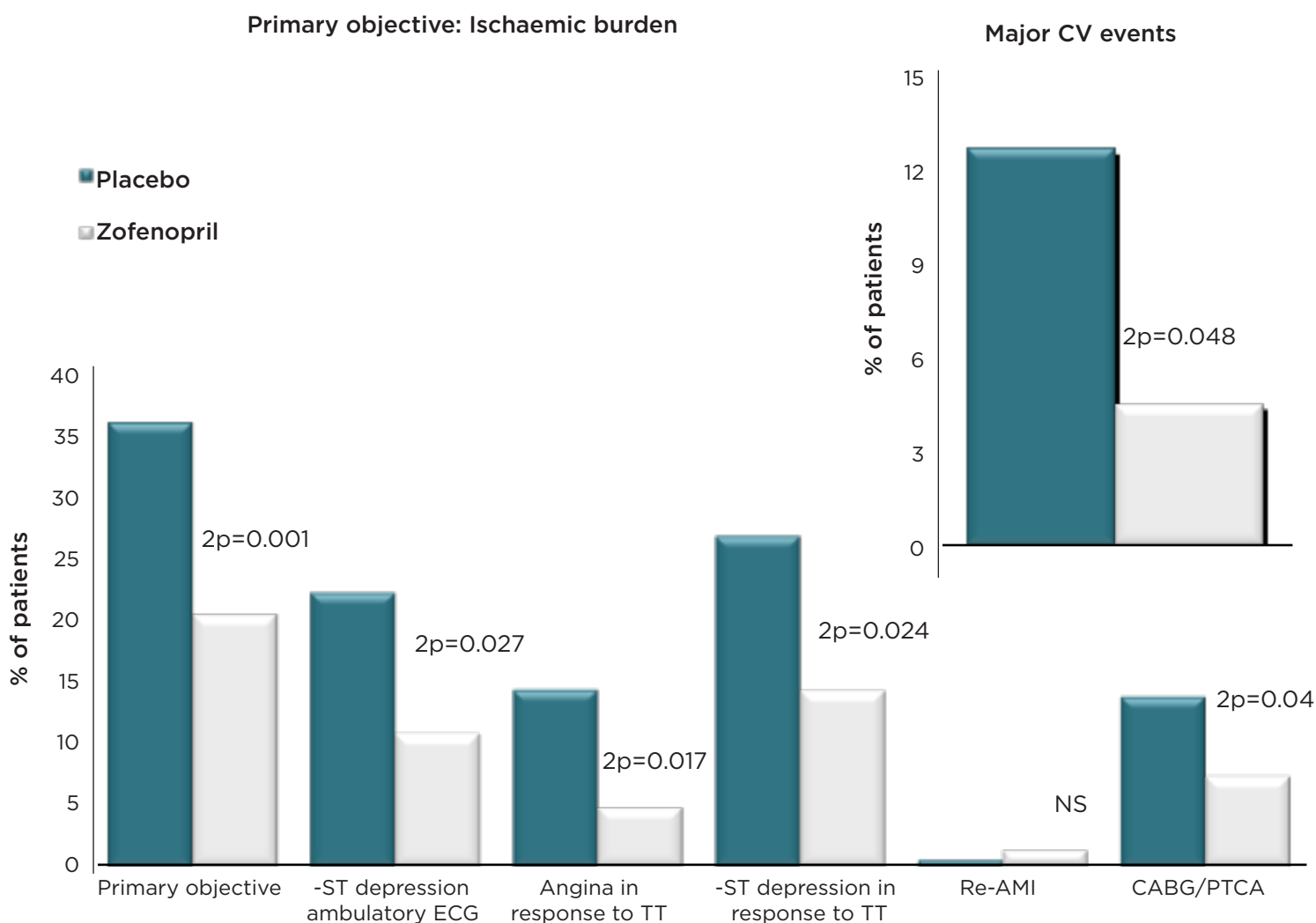
It is a matter of fact that extensive activation of the renin angiotensin system is deeply involved in the pathophysiology of cardiovascular disease. This gives a robust rationale for the successful use of drugs inhibiting the renin angiotensin system in the prevention and treatment of cardiovascular disease. This is particularly true for ACE inhibitors whose clinical efficacy has been clearly demonstrated in several clinical trials<sup>51</sup> and recently emphasised by the publication of two large meta-analyses<sup>52,53</sup> that show the superiority of ACE inhibitors even when compared with other drugs belonging to the inhibition of the same renal angiotensin system.

In the SMILE programme<sup>16-25</sup> the efficacy of ACE inhibitors in has been demonstrated in both chronic disease<sup>24,45,46,54</sup> and acute coronary syndrome either when patients are treated within 24 hours of the onset of symptoms<sup>17-22,32,33,55</sup> or later on when MI is complicated by left ventricular dysfunction.<sup>27,29-31</sup> A huge amount of evidence has been generated from the SMILE program.<sup>16-25</sup> The SMILE program is a long-standing investigative programme to address the role of ACE inhibitors and in particular Zofenopril in the treatment of patients with coronary artery disease and specifically acute MI. The programme started almost 20 years ago with the pilot study.<sup>16</sup> The results of the SMILE-1 trial<sup>17</sup> showed that early treatment with Zofenopril in patients with acute anterior MI was followed by a significant reduction in the combined incidence of severe congestive cardiac failure and death. Most importantly the results of this trial showed that the early benefit observed in this group of patients was extended over one year in terms of reduction of mortality (overall mortality  $p = 0.0083$ ). This clearly supports the mandatory role of ACE inhibition in patients with acute MI. The mechanistic view shows that the benefits shown by Zofenopril in the treatment of patients post-MI can be due to the effect expected from other ACE inhibitors e.g. improvement in blood pressure control, the prevention of left ventricular failure and improvement of left ventricular function. However, the results of this program have clearly

shown that one of the enhanced benefits of Zofenopril treatment in post-MI patients is conceivably due to its anti-ischaemic effect. This has been demonstrated in the SMILE ischaemic study.<sup>56</sup> The primary objective of the study was ischaemic burden. A group of patients with preserved left ventricular function following MI were treated with Zofenopril and compared with patients treated with placebo. The results showed that treatment with Zofenopril displayed a significant reduction in the overall rate of ischaemic burden. The clinical importance of these results is that such a prevention of cardiovascular complications was associated with a significant reduction in major cardiovascular events (Figure 7). This clearly suggests that this mechanism of action (which has not been demonstrated for any other ACE inhibitors) can significantly contribute to the overall benefits of Zofenopril in post-acute MI patients.

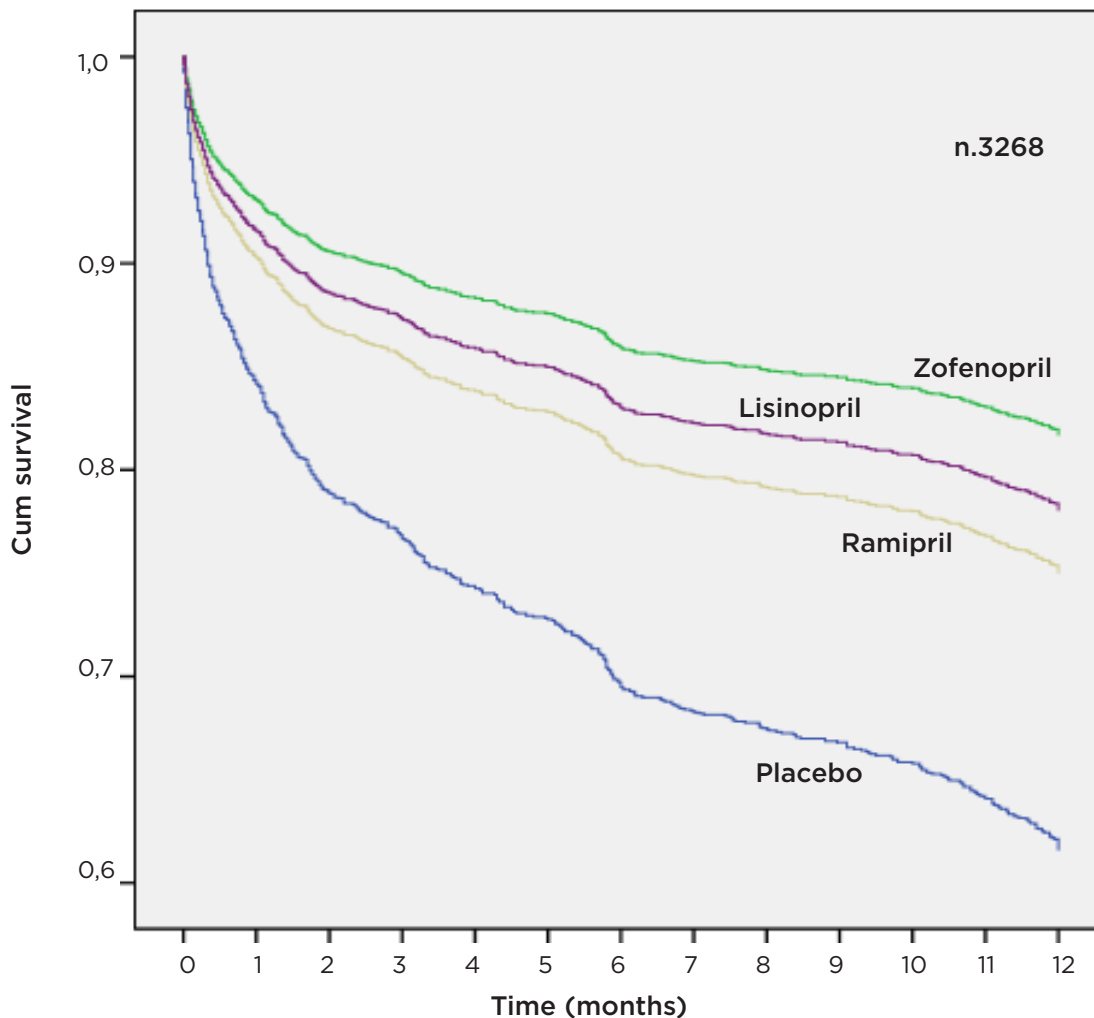
A recent editorial supports the findings of the SMILE ischaemia study by clearly suggesting that the best drugs for the treatment of post-MI patients are those that are able to prevent or effectively treat myocardial ischaemia and not just the symptoms of myocardial ischaemia.<sup>57</sup>

The benefits of Zofenopril treatment seen in the SMILE trial extend to an important sub-group of patients, those with hypertension. The study showed that the reduction of the major cardiovascular endpoint of long-term mortality was more prevalent in Zofenopril treated patients with a history of hypertension ( $p=0.041$ ) compared with placebo.<sup>19</sup> In addition the SMILE trial found that in another subgroup of patients, those with dysmetabolic disease (including patients with diabetes, metabolic syndrome and dyslipidaemia), the extent of reduction of the relative risk of the major category primary endpoint outcome was



**Figure 7. SMILE Ischaemia study: primary objective and clinical outcome.**  
*Borghi C et al.*<sup>56</sup>

Comparison	Hazard ratio (95% CI)
Zofenopril vs placebo	0.36 (0.29-0.45)
Ramipril vs placebo	0.57 (0.43-0.77)
Lisinopril vs placebo	0.49 (0.35-0.70)



**Figure 8. SMILE overall: ACE inhibitors vs. placebo. 1 year adjusted\* event free survival (CV mortality and hospitalisation for CV causes).**

\*Cox Regression model with treatment, age, gender, country and baseline CV risk factor as covariates. SMILE Pooled Analysis<sup>58</sup>

more evident in these patients treated with Zofenopril than in patients without metabolic abnormalities. This is important because it suggests that the benefits observed in the SMILE trial are probably due to Zofenopril's favourable interaction with some of the mechanisms that are responsible for excessive cardiovascular events in patients with high blood pressure and abnormalities of the metabolic profile.

The efficacy of Zofenopril has been compared with other drugs of the same class<sup>58</sup> (Figure 8).

The results of the SMILE pooled analysis, which included over 3,000 patients in the SMILE trials, has confirmed that ACE inhibitors are better than placebo in the treatment of post MI patients. The results also demonstrate that there are some differences between ACE inhibitors. The most striking observation from this huge amount of pooled data is that when Zofenopril is compared with lisinopril and ramipril, event free survival is improved in patients treated with Zofenopril. The difference between Zofenopril and other ACE

inhibitors is that Zofenopril appears to produce superior efficacy. This is an important observation that should be taken into consideration in clinical practice when choosing treatment for post MI patients.

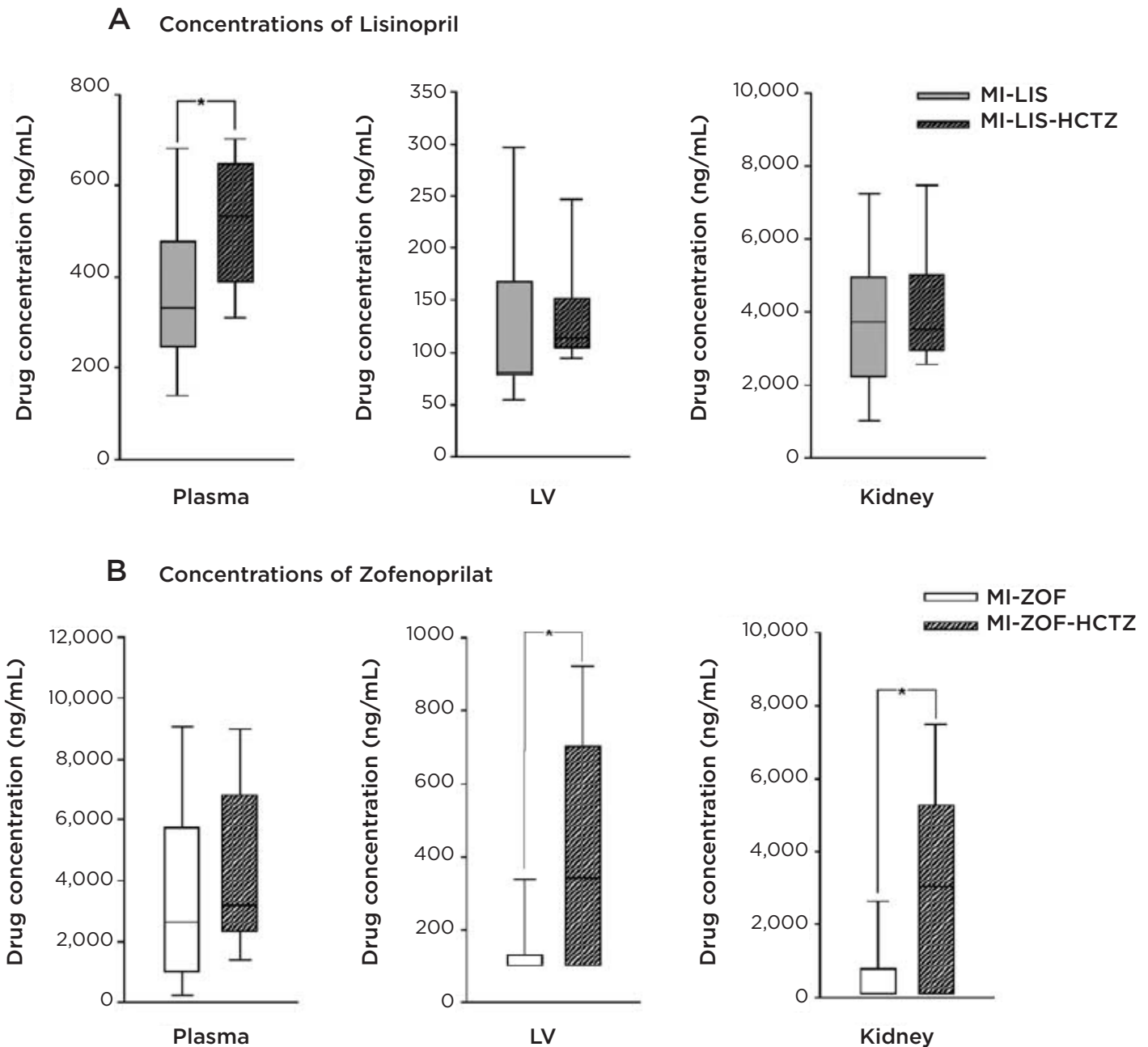
Many of the differences seen when comparing Zofenopril and other ACE inhibitors in terms of clinical outcome have arisen from the results of the SMILE-4 trial.<sup>25</sup> Two different populations of patients were treated with Zofenopril or ramipril in combination with aspirin. The objective was to evaluate the problem of possible interaction between ACE inhibitors and aspirin in patients with acute MI, and particularly in patients where MI was complicated by left ventricular dysfunction. The primary endpoint showed that treatment with Zofenopril was more effective than ramipril ( $p < 0.05$ ) in terms of cardiovascular mortality and hospitalisation for cardiovascular causes. A great proportion of the benefit was due to the reduction in hospitalisation for cardiovascular causes (RR [95% CI] = 0.64 [0.46-0.89]; adjusted  $p = 0.009$ ). The SMILE trial also assessed the difference in benefit between Zofenopril and ramipril in pre-specified subgroups. In patients with hypertension treatment with Zofenopril appears to achieve better results than ramipril. Another very important subgroup is patients with preserved left ventricular function. Despite the clinical signs of congestive heart failure a significant improvement was seen in patients treated with Zofenopril compared with those treated with ramipril. This suggests that the choice of ACE inhibitor should be decided on by the appropriateness to the particular disease characteristics of the patient.

There are differences in the mechanistic action of ACE inhibitors, in particular Zofenopril, in cardiovascular prevention. The four most important properties that differentiate Zofenopril from other ACE inhibitors are: 1) the presence of an SH-group producing an antioxidant effect. 2) High lipophilicity allowing a greater tissue drug concentration. 3) High tissue ACE blockade. 4) A favourable balance between reduced A-II and increased bradykinin levels. Indeed the mechanism of action of Zofenopril appears less dependent on the bradykinin system while it promotes a prominent increase in the NO availability that compensate for the lesser BK activation. The combination of these four properties demonstrates that Zofenopril is very different from other drugs belonging to the same class.

The evidence obtained from the SMILE studies show that when compared with drugs of the same class Zofenopril is firstly, more effective than any other ACE inhibitor in the treatment of post-MI patients complicated by left ventricular dysfunction. Secondly, the efficacy of Zofenopril is less affected in terms of negative interaction by the concomitant administration of aspirin because of the difference in the extent of the bradykinin contribution to the overall mechanism of action of the drug. Thirdly, Zofenopril has additional properties that play a clinical role, particularly the anti-ischaemic effect, which can have some advantage in terms of clinical outcome when compared with other drugs of the same class. Finally, Zofenopril has a more favourable interaction with the concomitant drugs which are usually given in combination with ACE inhibitors, in particular diuretics. This has been demonstrated as a working hypothesis in an experimental situation in which two different ACE inhibitors lisinopril and Zofenopril were given to rats in an attempt to understand the changes in plasma and tissue concentration.<sup>59</sup> The results showed that plasma concentration particularly at the left ventricular level was higher in rats treated with Zofenopril (Figure 9). The ability to achieve higher plasma concentration plays an important role in target organ protection and clinical prognosis.

The SMILE programme is set to continue to further develop understanding of the mechanism of Zofenopril particularly in cardio protection and increase the amount of data concerning the anti-ischaemic effect.

Based on the evidence to date it is clear that ACE inhibitors favourably affect CV outcomes and have a remarkable cardioprotective effect in patients with coronary artery disease. The benefit can be demonstrated from the acute phase of MI and is related to specific drug properties, particularly those seen in Zofenopril. The cardioprotective benefit of ACE inhibitors is enhanced in Zofenopril as a result of its haemodynamic and anti-ischaemic effects. The peculiar mechanism of action of Zofenopril when compared with other ACE inhibitors might improve the treatment of a wide range of patients with coronary artery disease and patients with hypertension with or without left ventricular dysfunction and congestive cardiac failure.



**Figure 9. Plasma, left ventricular and kidney tissue concentrations of different ACE-inhibitors in rats with MI treated or not with hydrochlorothiazide.**

*Westendorp B et al.<sup>59</sup>*

## Panel Discussion

**Question:** In SMILE Zofenopril was used twice a day (30 mg dose) while the advice is to give it once a day. Should Zofenopril be given twice a day at 30 mg or 60 mg once a day?

**Prof Claudio Borghi:** In the SMILE trial we have tried to follow the suggested dose of other ACE inhibitors used in other trials in post MI patients e.g. captopril or enalapril. In these trials the drugs had been given twice a day. In the SMILE trial we needed to have careful control of blood pressure values. Actually we have achieved a good result using the drug twice a day so my suggestion is try to use the drug twice a day for the first 6 weeks and later on the drug can be given once a day.

**Question:** Nebivolol has advantages in terms of organ damage and blood pressure control. Is there an outcome trial with nebivolol?

**Prof Claudio Borghi:** There is the Seniors trial which is a trial where the study population's mean age was 68 whereas in previous trials the mean age was 62. In the Seniors trial we saw that by adding nebivolol at the start of treatment showed a significant reduction of cardiovascular events and in the prevention of coronary artery disease there was a significant reduction even of cardiac death. And there are some promising data for congestive cardiac failure. On the other hand despite what has been seen, beta blockers increase the nuances of diabetes despite that 85% of heart failure patients receive high doses of diuretics there is a reduction of nuances of diabetes instead of an increase of nuances of diabetes

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**Question:** The title of the discussion is also to look for solutions. The question of differences between drugs and different ACE inhibitors, there are mechanistic differences no question about that. But how can we move further than we already have in terms of proving differences because you don't have proof that there are differences in addition to blood pressure we need to be sure that the effect on blood pressure is the same. Now the picture is complicated because we need to be sure that the effect on office blood pressure is the same, out of office blood pressure is the same in other words you have to remove all blood pressure related effects which have prognostic significance, this is going to be a very difficult step.

**Prof Krzysztof Narkiewicz:** This is a very difficult question we had a discussion during the presentation about the guidelines and we stressed the role and the need for a trial in younger patients with stage 1 hypertension because I am convinced that the evidence is overwhelming that the cardiovascular complications need to be caught very early. The data coming from Sweden with 1.2 million subjects observed for many years which indicate that those effects might be observed in the earlier stages of hypertension of the cardiovascular continuum suggests that mild alteration of the mechanism and all the potential benefits will be I think observed in younger patients. It will be extremely important to explore this as it can not only prevent heart endpoints in very high risk older patients but that we can prevent or delay the development of target organ damage. Such a study would provide evidence of the benefit of the newer ACE inhibitors.

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**Question:** Is there any comparison on the efficacy of Zofenopril and ramipril? Of course ramipril is still considered by many cardiologists as the gold standard because of the data.

**Prof Claudio Borghi:** Basically I think there is some evidence in the basic literature, there are some comparisons that seem to suggest that what we have shown and what we have supposed from the clinical point of view can be confirmed in an experimental setting. We have published a paper after the publication of SMILE-4 at the very beginning of this year in which we have extrapolated from our population of out-patients with chronic heart failure patients treated with Zofenopril, patients treated with ramipril and we have found over ten years follow-up the difference in survival in patients treated with Zofenopril compared with patients treated with ramipril. So I think the basic is probably if we talk about the treatment of hypertension the two drugs behave in exactly the same way but if we talk about the protection of organ damage and in particular we talk about the possibility to protect the myocardium in any condition related to myocardial ischaemia there are some differences between the two drugs and all the data we have and the literature seems to report exactly the same way.

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## REFERENCES

1. Mancia G et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159-219.
2. Verdecchia P et al. The renin-angiotensin system in the development of cardiovascular disease: role of aliskiren in risk reduction. *Vasc Health Risk Manag*. 2008;4(5):971-81.
3. Khalil ME et al. A remarkable medical story: benefits of angiotensin-converting enzyme inhibitors in cardiac patients. *J Am Coll Cardiol*. 2001;37(7):1757-64.
4. Grover GJ et al. Effects of different angiotensin-converting enzyme (ACE) inhibitors on ischemic isolated rat hearts: relationship between cardiac ACE inhibition and cardioprotection. *J Pharmacol Exp Ther*. 1991;257(3):919-29.
5. Borghi C et al. Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. *J Clin Pharmacol*. 1993;33(1):40-5.
6. Cushman DW et al. Differentiation of angiotensin-converting enzyme (ACE) inhibitors by their selective inhibition of ACE physiologically important target organs. *Am J Hypertens*. 1989;2(4):294-306.
7. Frascarelli S et al. Cardioprotective effect of zofenopril in perfused rat heart subjected to ischemia and reperfusion. *J Cardiovasc Pharmacol*. 2004;43(2):294-9.
8. Scribner AW et al. The effect of angiotensin-converting enzyme inhibition on endothelial function and oxidant stress. *Eur J Pharmacol*. 2003;482(1-3):95-9.
9. Pasini AF et al. Effects of sulfhydryl and non-sulfhydryl angiotensin-converting enzyme inhibitors on endothelial function in essential hypertensive patients. *Am J Hypertens*. 2007;20(4):443-50.
10. Buikema H et al. Comparison of zofenopril and lisinopril to study the role of the sulfhydryl-group in improvement of endothelial dysfunction with ACE-inhibitors in experimental heart failure. *Br J Pharmacol*. 2000;130(8):1999-2007.
11. Napoli C et al. Sulfhydryl angiotensin-converting enzyme inhibition induces sustained reduction of systemic oxidative stress and improves the nitric oxide pathway in patients with essential hypertension. *Am Heart J*. 2004;148(1):e5.
12. Napoli C et al. Long-term treatment with sulfhydryl 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(6):1154.e1-8.
13. Napoli C et al. Beneficial effects of ACE-inhibition with zofenopril on plaque formation and low-density lipoprotein oxidation in watanabe heritable hyperlipidemic rabbits. *Gen Pharmacol*. 1999;33(6):467-77.
14. Ferrari R et al. Protection of the ischemic myocardium by the converting-enzyme inhibitor zofenopril: insight into its mechanism of action. *J Cardiovasc Pharmacol*. 1992;20(5):694-704.
15. van Gilst WH. Captopril-induced increase in coronary flow: an SH-dependent effect on arachidonic acid metabolism? *J Cardiovasc Pharmacol*. 1987;9 suppl 2:S31-6.
16. Ambrosioni E et al. Early treatment of acute myocardial infarction with angiotensin-converting enzyme inhibition: safety considerations. SMILE pilot study working party. *Am J Cardiol*. 1991;68(14):101D-110D.
17. Ambrosioni E et al. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The survival of myocardial infarction long-term evaluation (SMILE) study investigators. *N Engl J Med*. 1995;33(2):80-5.
18. Borghi C et al. Effects of the early administration of zofenopril on onset and progression of congestive heart failure in patients with anterior wall acute myocardial infarction. The SMILE study investigators. *Survival of myocardial infarction long-term evaluation*. *Am J Cardiol*. 1996;7(8):317-22.
19. Borghi C 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(7):665-72.
20. Borghi C et al. Effects of the early ACE inhibition in diabetic nonthrombolized patients with anterior acute myocardial infarction. *Diabetes Care*. 2003;26(6):1862-8.
21. Borghi C et al. Effects of early treatment with zofenopril in patients with myocardial infarction and metabolic syndrome: the SMILE study. *Vasc Health Risk Manag*. 2008;4(3):665-71.
22. Borghi C et al. 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. *Fundam Clin Pharmacol*. 2009;23(5):641-18.
23. Borghi C et al. 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(1):80-7.
24. Borghi C et al. Effects of early angiotensin-converting enzyme inhibition in patients with non-ST-elevation acute anterior myocardial infarction. *Am Heart J*. 2006;152(3):470-7.
25. Borghi C et al. Comparison between zofenopril and ramipril in combination with acetylsalicylic acid in patients with left ventricular systolic dysfunction after acute myocardial infarction: result of a randomized, double-blind, parallel-group, multicenter. European study (SMILE-4). *Clin Cardiol*. 2012;35(7):416-23.
26. The Consensus trial study group. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative North Scandinavian enalapril survival study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316:1429-53.
27. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med*. 1991;325:293-302.
28. Packer M et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100(23):2312-8.
29. 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;(8875):821-8.
30. Pfeffer MA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327:669-77.
31. Køber L et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril cardiac evaluation (TRACE) Study Group. *N Engl J Med*. 1995;333:1670-6.

32. 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 sopravvivenza nell'infarto miocardico. *Lancet*. 1994;7343(8906):1115-22.
33. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (fourth international study of infarct survival) Collaborative group. *Lancet*. 1995;345(8951):669-85.
34. Swedberg K et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the cooperative new Scandinavian enalapril survival study II (CONSENSUS II). *N Engl J Med*. 1992;327(10):678-84.
35. Staessen JA et al. Implications of recently published trials of blood pressure-lowering drugs in hypertensive or high-risk patients. *Hypertension*. 2010;55(4):819-31.
36. Manolis AJ. Cardioprotective properties of bradykinin: role of the B(2) receptor. *Hypertens Res*. 2010;33(8):772-7.
37. Schmieder RE et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med*. 2003;115(1):41-6.
38. Dahlöf B et al. Cardiovascular morbidity and mortality in the Losartan Intervention for endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*. 2002;359(9311):995-1003.
39. Jamerson K et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in High-Risk Patients. *N Engl J Med*. 2008;359:2417-28.
40. Dahlöf B et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366(9489):895-906.
41. Williams B et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the conduit artery function evaluation (CAFÉ) study. *Circulation*. 2006;113(9):1213-25.
42. Morgan T et al. Effect of different antihypertensive drug classes on central aortic pressure. *Am J Hypertens*. 2004;17(2):118-23.
43. Manolis AJ et al. Arterial compliance in diabetic normotensive patients after angiotensin-converting enzyme inhibition therapy. *Am J Hypertens*. 2005;18(1):18-22.
44. McEniery CM et al. Nebivolol increases arterial distensibility in vivo. *Hypertension*. 2004;44(3):305-10.
45. Braunwald E et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058-68.
46. Fox KM et al. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362(9386):782-8.
47. Pitt B. ACE inhibitors for patients with vascular disease without left ventricular dysfunction-may they rest in PEACE? *N Engl J Med*. 2004;351(20):2115-17.
48. Desideri G et al. Different effects of angiotensin converting enzyme inhibitors on endothelin-1 and nitric oxide balance in human vascular endothelial cells: evidence of an oxidant-sensitive pathway. *Mediators Inflamm*. 2008;2008:305087.
49. Lupi R et al. The direct effects of the angiotensin-converting enzyme inhibitors, zofenoprilat and enalaprilat, on isolated human pancreatic islets. *Eur J Endocrinol*. 2006;1542(2):355-61.
50. Borghi C et al. Zofenopril and ramipril and acetylsalicylic acid in postmyocardial infarction patients with left ventricular systolic dysfunction: a retrospective analysis in hypertensive patients of the SMILE-4 study. *J Hypertens*. 2013;31(6):1256-64.
51. McMurray JJ. ACE inhibitors in cardiovascular disease - unbeatable? *N Engl J Med*. 2008;358(15):1615-6.
52. Savarese G et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol*. 2013;61(2):131-42.
53. van Vark LC et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. *Eur Heart J*. 2012;33(16):2088-97.
54. Verma J et al. Plasma renin activity predicts cardiovascular mortality in the heart outcomes prevention evaluation (HOPE) study. *Eur Heart J*. 2011;32(17):2135-42.
55. Oral captopril versus placebo among 14,962 patients with suspected acute myocardial infarction: a multicentre, randomized, double blind, placebo controlled clinical trial. Chinese Cardiac study (CCS-1) Collaborative Group. *Chin Med J (Engl)* 1997;110(11):834-8.
56. Borghi C et al. 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(3):445.e7-14.
57. Stone PH. Ischemia dictates outcome, not symptoms. *J Am Coll Cardiol*. 2013;61(7):712-3.
58. SMILE Pooled Analysis, *J Am Coll Cardiol* 2013 (abstract).
59. Westendorp B et al. Hydrochlorothiazide increases plasma or tissue angiotensin-converting enzyme-inhibitor drug levels in rats with myocardial infarction: differential effects on lisinopril and zofenopril. *Eur J Pharmacol*. 2005;527(1-3):141-9.

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