REVIEW

Angiotensin-Converting Enzyme Inhibition: Beyond Blood Pressure Control—The Role of Zofenopril

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ABSTRACT

The extensive use of angiotensin-converting enzyme inhibitors (ACEIs) as antihypertensive agents and the huge amount of data collected in clinical trials and post-marketing studies has allowed the extending of the indication of ACEIs beyond blood pressure control. Current guidelines recommend ACEIs in symptomatic patients with heart failure with reduced ejection fraction to decrease the risk of heart failure hospitalization, and also in patients after acute myocardial infarction (AMI) with ST-elevation with or without post-AMI ventricular dysfunction. Analyzing the association between the choice of an ACEI after AMI with the risk of mortality and re-infarction, a class effect, rather than the superiority of some agents, has been described. The focus of this review is centered on the role of ACEIs in addition to and beyond blood pressure control. It summarizes clinical evidence on the use of these agents in cardiovascular diseases, with a specific interest in the experience with zofenopril, which presents a peculiar pharmacological profile that may contribute to additional clinical benefits in some identifiable populations of patients. Indeed, the presence of a sulfhydryl group in its structure confers on zofenopril high anti-oxidant and anti-ischemic properties involving the activation of the H_2S system, resulting in a cardioprotective effect. The efficacy and safety of zofenopril have been extensively evaluated and proved in the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) program in numerous clinical settings. The pharmacological features and ancillary characteristics of zofenopril with potent cardioprotective effects seem to differentiate it from other ACEIs and to confer further benefits to patients.

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Key Summary Points

Angiotensin-converting enzyme inhibitors (ACEIs) are currently recommended for managing arterial hypertension, the progression of chronic renal disease, post-myocardial infarction, congestive heart failure, and type 2 diabetes mellitus.

In patients with acute or chronic coronary syndrome and heart failure ACEIs appear to provide several benefits beyond blood pressure control.

Among the various drugs of this class, zofenopril, a lipophilic, sulfhydryl group-containing ACEI, seems to contribute to additional clinical benefits in some identifiable populations of subjects.

The clinical efficacy and safety of zofenopril has been evaluated in more than 3,600 post-acute myocardial infarction patients with or without left ventricular dysfunction in the four randomized controlled trials of the SMILE program.

The pharmacological characteristics and ancillary features of zofenopril with potent cardioprotective activity seem to differentiate it from other ACEIs and to confer further benefits to patients.

INTRODUCTION

Given the consolidated clinical experience in the use of therapies blocking the renin-angiotensin system (RAS), angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II-receptor blockers (ARBs) have become a first-line strategy for managing arterial hypertension, the progression of chronic renal disease, post-myocardial infarction, congestive heart failure, and type 2 diabetes mellitus [1, 2]. These results have been generated by a large number of randomized clinical trials and observational post-surveillance studies that have demonstrated the clinical efficacy of RAS blockade in daily practice and in patients with presumed RAS activation and without hypertension [2]. The focus of this review is centered on the role of ACEIs beyond blood pressure (BP) control and summarizes the clinical evidence on the use of these agents in patients with different settings of cardiovascular diseases (CVDs). Specific attention is paid to the experience with zofenopril because of its peculiar pharmacological properties, mainly related to the sulfhydryl group present in its molecular structure. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RAS INVOLVEMENT IN CVD

The RAS is one of the main physiological system responsible for homeostatic control of arterial pressure, electrolyte balance, organ perfusion, and extracellular volume. Its modulation has several important effects that mainly involve CVDs and renal disease [3]. The pathway is initiated by renin which cleaves the N-terminal portion of angiotensinogen to form the biologically inactive decapeptide angiotensin I [4]; this inactive peptide is then hydrolyzed by ACE which removes the C-terminal dipeptide in order to form the octapeptide angiotensin II, biologically active as a vasoconstrictor [4]. Angiotensin II is the primary effector of a variety of RAS-induced physiological and pathophysiological actions. It interacts with 4 receptor subtypes expressed in the CV system (vasoconstriction, increased BP, increased cardiac contractility, vascular and cardiac hypertrophy), kidney (renal tubular sodium reabsorption, inhibition of renin release), sympathetic nervous system, and adrenal cortex (stimulation of aldosterone synthesis), as well as in the lung and the gut where it plays a remarkable role in fluid balance and respiratory function [5, 6].
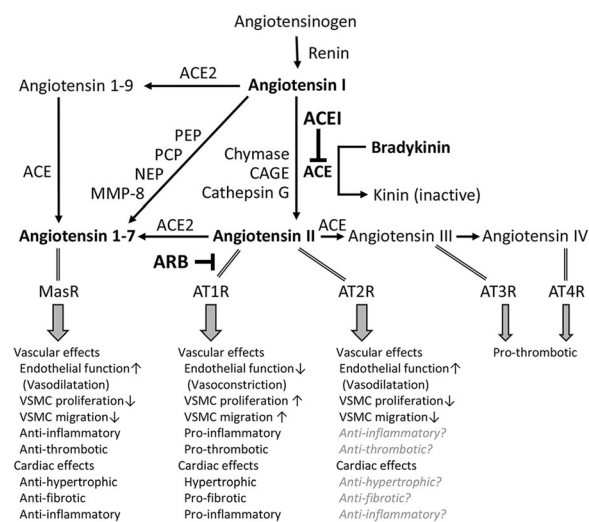
Therefore, a dysregulation of RAS is reported not only in essential hypertension and in the

response of CV and renal tissue to hypertensive and non-hypertensive injury but also in many other CV disorders [4]. Angiotensin II is involved in the development of both vascular and cardiac hypertrophy and remodeling, vascular damage, renal damage, and atherosclerosis with a mechanism that is only partially dependent on elevated BP values. [4]. In congestive heart failure (HF), the reduced cardiac function and the renal under-perfusion related to a reduced effective intravascular volume are responsible for renin hypersecretion and secondary aldosteronism, contributing to pulmonary congestion and development of edema. In these patients, angiotensin II increases peripheral vascular resistance (cardiac afterload) and enhances progressive ventricular

Fig. 1 Renin-angiotensin system and related molecules. Many molecules influence the effects of renin-angiotensin system activation. Angiotensin II and AT1R are key molecules of the major harmful pathway in the cardiovascular system. Counteracting pathways with cardiovascular protective property also exist. There are controversies about the effects of AT2R signaling, which are indicated in *gray italic* [3]. *ARB* angiotensin receptor blocker, *AT1R* angiotensin type one receptor, *AT2R* angiotensin type two receptor, *AT3R* angiotensin type three receptor, *AT4R* angiotensin type four receptor, *CAGE* chymostatin-sensitive angiotensin-II-generating enzyme, *MasR* Mas receptor, *MMP-8* matrix metalloproteinase-8, *NEP* neutral endopeptidase, *PCP* prolyl carboxypeptidase, *PEP* prolyl endopeptidase, *RAS* renin-angiotensin system, *VSMC* vascular smooth muscle cell

dysfunction contributing to the progression of heart failure [4].

ACEI and ARB medications both target RAS, and are recommended in the treatment of several types of CVD (Fig. 1). However, the optimal choice between these two groups of medications for the prevention of CVD is not well established [3].

ACEIs prevent the conversion of angiotensin I to angiotensin II by competing with angiotensin I for the active site of ACE. The reduction of angiotensin II formation decreases vasoconstriction and aldosterone secretion and increases plasma renin. As a consequence, ACEIs can lower BP, total peripheral resistance, and sodium and water retention [7]. ACEIs also reduce both preload and afterload through arterial and venous dilation. These hemodynamic effects are particularly beneficial in the presence of left ventricular dysfunction (LVD) [8]. One disadvantage of ACEIs is that the presence of non-ACE pathways results in continued low-level production of angiotensin II, despite the inhibition of ACE. ARBs are selective ligands of AT1 receptors; these drugs achieve their clinical goals bypassing the limitations of ACE escape phenomena and non-ACE sources of angiotensin II formation, despite the increased blood angiotensin II levels due to blockade of AT1-mediated receptor internalization (Fig. 1) [3, 9].

ROLE OF ACEIS IN CVD ACCORDING TO CURRENT GUIDELINES

ACEIs are widely prescribed to manage hypertension, and are recommended in recent guidelines (level of recommendation IA) as the basis of antihypertensive strategies, given their ability to reduce BP and CV events in randomized clinical trials [10]. The potency of ACE inhibition is influenced by the affinity of the drug to the zinc ($Zn++$) ligand of ACE. There are three distinct chemical classes of ACEIs (Table 1): (1) sulfhydryl containing ACEIs (i.e., captopril, zofenopril) which strongly bind the $Zn++$ ligand, but disulfide formation limits their half-life; (2) drugs containing a carboxyl

Table 1 Angiotensin-converting enzyme inhibitors currently indicated for the treatment of cardiovascular patients

Drug	Molecular structure	Absorption (%)	Half-life (h)	Metabolism	Main route of elimination	Approved indications	Hypertension		Heart failure	
							Initial daily dose (mg)	Maximal daily dose (mg)	Initial daily dose (mg)	Initial daily dose (/ mg)
Benazepril	Dicarboxylic group	37	10–11	+ (benazeprilat)	Renal	Hypertension	10	40	–	–
Captopril	Sulfhydryl group	60–75	2	+	Renal	Hypertension, heart failure, post-AMI patients with LVD, type 1 diabetic nephropathy	12.5 (tid)	150 (tid)	6.25 (tid)	150 (tid)
Cilazapril	Dicarboxylic group	45–85	1.5–2.0	+ (cilazaprilat)	Renal	Hypertension and heart failure	1–1.25	5	0.5	5
Enalapril	Dicarboxylic group	60	11–14	+ (enalaprilat)	Renal	Hypertension and heart failure (or asymptomatic LVD)	5	40	2.5 (bid)	20 (bid)
Fosinopril	Phosphonate group	36	12	+ (fosinoprilat)	Renal and hepatic	Hypertension and heart failure	10	40	5–10	40
Lisinopril	Dicarboxylic group	25	12	–	Renal	Hypertension, heart failure and post-AMI hemodynamically stable patients	10	40	2.5–5	40
Moexipril	Dicarboxylic group	13	2–9	+ (moexiprilat)	Renal	Hypertension	7.5	30	–	–
Perindopril	Dicarboxylic group	65–75	1.2	+ (perindoprilat)	Renal	Hypertension and stable CAD patients	4	16	–	–
Quinapril	Dicarboxylic group	50–80	2.3	+ (quinaprilat)	Renal	Hypertension and heart failure	10–20	80	5 (bid)	20 (bid)

Table 1 continued

Drug	Molecular structure	Absorption (%)	Half-life (h)	Metabolism	Main route of elimination	Approved indications	Hypertension		Heart failure	
							Initial daily dose (mg)	Maximal daily dose (mg)	Initial daily dose (mg)	Initial daily dose (/mg)
Ramipril	Dicarboxylic group	50–60	13–17	+ (ramiprilat)	Renal	Hypertension, heart failure (post-AMI), high risk CV patients	2.5	20	2.5 (bid)	5 (bid)
Trandolapril	Dicarboxylic group	40–60	16–24	+ (trandolaprilat)	Hepatic	Hypertenion and post-AMI (CHF or asymptomatic LVD patients)	1–2	4	1	4
Zofenopril	Sulfhydryl group	78	5.5	+ (zofenoprilat)	Renal	Hypertension and post-AMI (< 24-h)	15	60	–	–

Drug	Post-AMI		Other indication	
	Initial daily dose (mg)	Maximal daily dose (mg)	Initial daily dose (mg)	Maximal daily dose (mg)
Benazepril	–	–	–	–
Captopril	6.25 (tid)	50 (tid)	–	25 (tid)
Cilazapril	–	–	–	–
Enalapril	–	–	–	–
Fosinopril	–	–	–	–
Lisinopril	5	10	–	–
Moexipril	–	–	–	–
Perindopril	–	–	4	8
Quinapril	–	–	–	–
Ramipril	–	–	2.5	10
Trandolapril	1	4	–	–

Table 1 continued

Drug	Post-AMI		Other indication	
	Initial daily dose (mg)	Maximal daily dose (mg)	Initial daily dose (mg)	Maximal daily dose (mg)
Zofenopril	7.5 (bid)	30 (bid)	–	–

AMI acute myocardial infarction, *CAD* coronary artery disease, *CV* cardiovascular, *CHF* congestive heart failure, *LVD* left ventricular dysfunction, *bid* twice-a-day, *tid* three-times-a-day

group (i.e., enalapril, lisinopril, ramipril) that binds to side chains of the enzyme within the active moiety for improved potency and duration of action; and (3) drugs composed of phosphorus-containing ACEIs (i.e., fosinopril) [11, 12]. Although direct ACEIs comparisons among available agents are rare, a Cochrane review has demonstrated that there are no clinically meaningful differences in BP-lowering efficacy between different ACEIs [13].

ACEIs are the mainstay not only for hypertension management but also for other CVD, including HF, LVD, and acute myocardial infarction (AMI) (Table 2). In HF, ACEIs decrease total peripheral resistance, pulmonary vascular resistance, pulmonary capillary wedge pressure, and mean arterial and right atrial pressures, thus resulting in reduced mortality, regardless of HF severity [7, 8]. In these patients, the use of ACEIs has been shown to increase cardiac index, cardiac output, stroke volume, and exercise tolerance [7]. Many pieces of evidence indicate that BP control delays the onset of HF and, in some cases, contributes to prolonging life, and this also applies to hypertensive patients treated with ACEIs with or without a history of myocardial infarction, especially in older people [14]. As per current guidelines, an ACEI is recommended in addition to a beta-blocker for symptomatic patients with HF with reduced left ventricular ejection fraction (LVEF) to reduce the risk of HF hospitalization and death (recommendation 1A) [15]. A meta-analysis of three randomized trials (SAVE, Survival and Ventricular Enlargement; AIRE, Acute Infarction Ramipril Efficacy; and TRACE, trandolapril in patients with reduced LVD after acute myocardial infarction), including 5966 patients with LVD or HF, have indicated that administration of ACEIs after AMI provides clear benefit and lead to substantial reductions in mortality and morbidity in high-risk patients [16]. Indeed, the proportion of patients readmitted for HF resulted was reduced by 27% with ACEIs [11.9% in the ACEI group vs. 15.5% of the control group; hazard ratio (HR) 0.73 95% CI 0.63–0.85, $p < 0.0001$], while the combination of death or hospital admission for HF occurred in 30.5% of the ACEI group and 37.0% of the control group [17]. ACEIs are also

Table 2 Current recommendations of the European Society of Cardiology for the use of angiotensin converting enzyme inhibitors in patient with cardiovascular disease

	Class of recommendation	Level of evidence
Recommendations for treating arterial hypertension [10]		
Among all antihypertensive drugs, ACEIs, ARBs, BBs, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and are thus indicated as the basis of antihypertensive treatment strategies	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACEI or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used	I	A
It is recommended that if BP is not controlled with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC	I	A
Recommendations for treating patients with symptomatic HF with reduced ejection fraction [15]		
An ACEI is recommended, in addition to a BB, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
A BB is recommended, in addition to an ACEI, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death	I	A
An MRA is recommended for patients with HFrEF who remain symptomatic despite treatment with an ACEI and a BB to reduce the risk of HF hospitalization and death	I	A
Recommendations for treating chronic coronary syndrome [18]		
ACEIs (or ARBs) are recommended if a patient has other conditions (e.g., HF, hypertension, or diabetes)	I	A
ACEIs should be considered in CCS patients at very high risk of CV events	IIa	A
Recommendations for treating STEMI [22]		
ACEIs are recommended, starting within the first 24-h of STEMI in patients with evidence of HF, LVSD, diabetes, or anterior AMI	I	A
An ARB, preferably valsartan, is an alternative to ACEIs in patients with HF and/or LVSD, particularly those who are intolerant to ACEIs	I	B
ACEIs should be considered in all patients in the absence of contraindications	IIa	A

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BP* blood pressure, *BB* beta-blocker, *CCB* calcium channel blocker, *CCS* chronic coronary syndrome, *CV* cardiovascular, *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *LVSD* left ventricular systolic dysfunction, *MRA* mineralocorticoid receptor antagonist, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *SPC* single-pill combination, *STEMI* ST-segment elevation myocardial infarction

indicated in patients with asymptomatic LV systolic dysfunction in order to minimize the risk of development of HF, and consequent hospitalization, and death [15].

In patients affected by coronary artery disease (CAD) with preserved systolic ventricular function, the evidence for routine administration has been conflicting. A metanalysis by Al-Mallah et al. reported a modest benefit of ACEIs on the prognosis of patients with CAD associated with preserved LV systolic function [17]. Data from more than 33,000 patients indicated that ACEIs therapy, when added to conventional therapy (aspirin, beta-blockers, and statins), was associated with a decrease in the rate of CV mortality (risk reduction or RR 0.83, 95% CI 0.72–0.96, $p = 0.01$), nonfatal MI (RR 0.84, 95% CI 0.75–0.94, $p = 0.003$), all-cause mortality (RR 0.87, 95% CI 0.81–0.94, $p = 0.0003$), and coronary revascularization (RR 0.93, 95% CI 0.87–1.00, $p = 0.04$) [17]. Not all trials, however, described an effective advantage in the use of ACEIs in this setting; hence, current guidelines generally do not recommend ACEIs in chronic coronary syndrome patients without HF or high CV risk, unless with coexisting hypertension, LVEF $\leq$ 40%, diabetes, or chronic kidney disease. In these latter cases, ACEIs should be considered (level of recommendation IIA) [18].

Therapy with ACEIs is also common after AMI. Numerous trials have indicated that mortality and morbidity were reduced when ACEIs were administered in a relatively unselected population of patients in the acute phase of MI ("early") or in patients with evidence of LVD in the subacute phase after MI ("late") [19]. In their metanalysis, Franzosi et al. collected data from large randomized trials which evaluated the efficacy and safety of treatments with ACEIs given in the acute phase of MI (0–36 h from the onset of symptoms) and continued for a short period of follow-up (generally 4–6 weeks) [20]. These trials were CONSENSUS-II, GISSI-3, ISIS-3, and CCS-1, and included a total of 98,496 patients. The main conclusions of the analysis were: (1) ACEI treatment can be started immediately during the acute phase of MI, in association with other routinely recommended treatments (such as thrombolytics, aspirin, and beta-blockers); (2) the benefit occurs during the first few days after MI, suggesting a positive role of tissue remodeling; (3) the benefit is proportionally larger in higher-risk subgroups (those with an anterior site MI or high heart rate); and (4) early benefits would be complementary to that observed later in trials of prolonged ACEI therapy initiated several days or weeks after MI in patients with evidence of HF or LVD [20]. Due to the lack of clinical trials that directly compared the efficacy of different ACEIs treatment after AMI, these drugs are generally assumed to be equally effective [21]. Analyzing the association between the choice of an ACEI after MI with the risk for mortality and reinfarction, a class effect was described rather than a superiority of some agents, when drugs were used in comparable dosages, thus suggesting that it would be more important initiating treatment and continuing treatment at the recommended dosage than choosing a particular agent to achieve long-term benefits [21]. Current guidelines recommend ACEIs after AMI with ST-elevation, starting within the first 24 h of ST-elevation myocardial infarction (STEMI) in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct (level of recommendation IA). They should be considered in all patients with AMI unless specifically contraindicated (level of recommendation IIa) [22].

ACEIs are commonly used in patients with diabetes and/or with renal disease. In a systematic review including 36,917 participants (including 2400 deceased, 766 patients who required dialysis, and 1099 patients in which serum creatinine levels doubled), ACEIs showed higher probabilities of reducing all-cause mortality, use of dialysis, or doubling of serum creatinine levels, and demonstrated renoprotective effects [23]. These observations were confirmed even in chronic renal disease progression when ACEIs decreased BP, and urinary protein excretion slowed the increase in serum creatinine and reduced the risk for end-stage renal disease (ESRD), or for the combined outcome of doubling of the baseline serum creatinine concentration or ESRD by approximately 30% [24].

Table 3 Pharmacological properties of sulphydrylic angiotensin-converting enzyme inhibitors[25]

Pharmacological properties	Clinical effects
Higher lipophilicity and tissue penetration	Effective prevention of CV events
Higher affinity and more persistent binding to tissue ACE (cardiac, renal and vascular)	Effective prevention of CV events
Lesser Bk-dependent effect	Good safety (reduced frequency of hypotension, cough, and renal function deterioration)
Significant antioxidant effect	Significant anti-ischemic effect
Increased release and availability of H2S	Improved CV function

ACE angiotensin-converting enzyme, *BK* bradikinin, *CV* cardiovascular

ZOFENOPRIL: A CARDIOPROTECTIVE ACEI

Zofenopril is a sulfhydryl ACEI featuring a high lipophilicity, long-lasting tissue penetration, selective cardiac ACEI, potent anti-oxidant activities, and good efficacy after a single daily administration (Table 3) [25]. Starting from 1990, its efficacy and safety have been evaluated in the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) project, a large clinical program aimed at investigating the role of zofenopril in the treatment of AMI in several populations of patients to test the hypothesis that its unique pharmacological profile could provide some benefits beyond ACE inhibition, in terms of CV event prevention (Table 4). The first trial was a pilot study that evaluated the safety of zofenopril administration within 24 h of the onset of AMI symptoms and provided some preliminary data of efficacy in terms of combined occurrence of death, non-fatal CV events, and severe adverse events after a 12-month follow-up [26]. A large clinical trial was then designed to determine the efficacy of 6-week zofenopril administration (15–60 mg twice daily) versus placebo in 1556 patients with MI not receiving thrombolysis and treated within 24 h of the onset of symptoms (SMILE-1). The incidence of death or severe congestive HF at 6 weeks (primary end-point) was significantly reduced in the zofenopril group, with risk reduction by 34% (95% CI 8–54%; $p = 0.018$). These positive outcomes were

maintained after 1 year, observing a risk reduction for death of 29% (95% CI 6–51%; $p = 0.011$) [27]. Given the large size of population involved in the SMILE trials, many statistically pre-specified and adequately powered post hoc analyses on specific subgroups could be performed, providing evidence on zofenopril effects in older patients, and in patients with arterial hypertension [28], diabetes [29], hypercholesterolemia [30], metabolic syndrome [31], angina, or previous myocardial infarction or NSTEMI [32]. Zofenopril was then directly compared with two ACEIs in randomized clinical trials carried out in patients with coronary artery disease. In the SMILE-2 study, zofenopril was compared to lisinopril in 1024 patients with acute MI undergoing thrombolysis [33], while in the SMILE-4 study, the main comparison was between zofenopril and ramipril in combination with acetylsalicylic acid (ASA) in patients with post-MI left ventricular dysfunction. In the SMILE 2 trial, zofenopril slightly reduced the incidence of severe hypotension versus lisinopril (10.9% vs. 11.7%, $p = 0.38$), with a significant decrease in the rate of drug-related severe hypotension (6.7% vs. 9.8%, $p = 0.048$) without a difference in mortality or major CV complications [33]. SMILE-4 investigated whether the benefits of zofenopril or ramipril could be affected by a concomitant ASA administration in patients with LV dysfunction after AMI [34]. The occurrence of death or hospitalization for CV cause was significantly reduced with zofenopril (odds ratio: 0.70; 95% CI: 0.51–0.96;

Table 4 Summary of main characteristics and outcomes of the SMILE Studies

Study	Period of the enrolment	Inclusion criteria	Intervention (n)	Control (n)	Daily zofenopril dose	Control	Treatment duration (weeks)	Post treatment follow-up (weeks)
SMILE Pilot	1988–1989	AMI with lack of indication for a thrombolytic therapy	101	103	15–30 mg	Placebo	48	–
SMILE-1	1991–1992	Anterior AMI not eligible for thrombolytic therapy in the previous 12 h	772	784	15–60 mg	Placebo	6	48
SMILE-2	1998–1999	Thrombolytic treatment within 12 h from AMI and SBP > 100 mmHg	504	520	15–60 mg	Lisinopril 2.5–10 mg daily	6	–
SMILE-3	1998–2001	AMI in the preceding 6 weeks with preserved left ventricular ejection fraction (> 40%), prior thrombolysis and treatment with ACEIs	172	177	15–60 mg	Placebo	24	–
SMILE-4	2005–2009	AMI in the previous 24 h treated or untreated with PTCA, with clinical and/or echocardiographic evidence of left ventricular dysfunction	365	351	15–60 mg plus ASA100 mg daily	Ramipril 10 mg daily plus ASA100 mg daily	48	–
SMILE Overall	1991–2009	The same of the SMILE-1 to -4 study	1808	1822	30–60 mg	Placebo, lisinopril or ramipril	6–48	–

Study	Primary end-point	Main results	Subgroups analysis
SMILE Pilot	Safety of treatment	Good tolerability of zofenopril Similar CV mortality to placebo Reduced hospitalization Improved LVEF	–

Table 4 continued

Study	Primary end-point	Main results	Subgroups analysis
SMILE-1	Occurrence of death or severe congestive heart failure over 6 weeks	Improved short-term 6-weeks) and long-term (1-year) outcome	Superior efficacy of zofenopril compared to placebo, also in subjects with diabetes, hypercholesterolemia, metabolic syndrome, hypertension and NSTEMI
SMILE-2	Occurrence of severe hypotension (SBP < 90 mmHg) at any time	Lower rate of severe hypotension with zofenopril compared to lisinopril	–
SMILE-3	Global ischemic burden (ischemia on 24-h ambulatory ECG, ischemia or angina during treadmill test, recurrent AMI, need for revascularization)	Zofenopril significantly reduced the frequency and severity of exertional and spontaneous cardiac ischemia. It also reduced the risk of CV events	–
SMILE-4	Occurrence of CV mortality or hospitalization for CV causes	Efficacy of zofenopril associated with ASA superior to that of ramipril plus ASA	Superior efficacy of zofenopril compared to ramipril, also in subjects with diabetes, hypercholesterolemia, metabolic syndrome, hypertension and NSTEMI
SMILE Overall	1-year combined occurrence of death or hospitalization for CV causes	Occurrence of CV events was significantly reduced with zofenopril vs. placebo and vs. the other ACEIs	Efficacy superior to placebo and ramipril, but similar to lisinopril in metabolic syndrome. Non-significant trend for superiority of zofenopril vs. other ACEIs in hyperuricemic patients. Zofenopril superior to placebo and the other ACEIs in hypertensive subjects and in those with at least one previous CV risk factor

ACEI angiotensin-converting enzyme inhibitor, *AMI* acute myocardial infarction, *ASA* acetyl salicylic acid, *CV* cardiovascular, *ECG* electrocardiogram, *LVEF* left ventricular ejection fraction, *NSTEMI* non-ST-elevated myocardial infarction, *PTCA* percutaneous transluminal coronary angioplasty, *SBP* systolic blood pressure [26–39]

$p = 0.028$), and this benefit was maintained during 5-year follow-up (Fig. 2) [34, 35]. The same results have been confirmed after a propensity analysis of the population and comparing subpopulations of patients appropriately matched for the main prognostic variables [36]. Finally, the cardioprotective effects of zofenopril were investigated in the SMILE-3 ISCHEMIA trial in 349 patients with preserved LV function after MI. In these patients receiving recommended standard treatment, zofenopril reduced the global burden of myocardial ischemia by decreasing the occurrence of significant ST-T abnormalities on ambulatory electrocardiography (ECG), ECG abnormalities or symptoms of angina during the standard exercise test, MI recurrence and the need for revascularization procedures, in comparison to placebo (20.3% vs. 35.9%, $p = 0.01$) (Fig. 3) [37]. The results were not affected by demography, BP control, and concomitant pharmacological treatment, and supported some primary cardioprotective effect of zofenopril. More recently, the results of the SMILE-ischemia study were corroborated by a post hoc analysis of SMILE 4, stratifying patients by LVEF measured at baseline, and showing a reduction in 1 year and long-term mortality and hospitalization in post-MI with preserved LV function (Fig. 4) [38]. The cardioprotective properties of zofenopril were confirmed in a pooled analysis of the four SMILE studies [39] (Fig. 5).

THE RATIONALE OF THE CARDIOPROTECTIVE PROPERTIES OF ZOFENOPRIL

Zofenopril-mediated cardioprotection during ischemia/reperfusion seems to be associated with an increased H_2S and nitric oxide (NO) signaling. Hydrogen sulfide is a cytoprotective physiological signaling molecule acting in concert with NO and carbon monoxide in order to maintain physiological homeostasis in both the heart and circulation. Experimental evidence indicates that H_2S donors, such as zofenopril, can attenuate the pathological consequences of myocardial ischemia/reperfusion injury and HF, reducing oxidative stress and

inflammation and inhibiting apoptosis [40]. In experimental models, indeed, zofenopril preconditioning enhanced tissue antioxidant defense, thus preventing reactive oxygen species formation, following an ischemic injury during reperfusion. Furthermore, treatment with zofenopril upregulated the expression of antioxidant enzymes, such as Trx-1, GPx-1, and SOD-1, suggesting an enhancement in antioxidant defenses before ischemia that mitigate myocardial reperfusion injury [41]. As summarized in Fig. 6, the enhanced H_2S signaling, alongside the inhibition of angiotensin II formation and bradykinin metabolism, could represent a further explanation of additional beneficial effects provided by zofenopril [40]. In addition, ex vivo animal studies indicated that, at the heart level, where ACE inhibition may prevent ischemic damage, zofenopril produced a more striking and long-lasting ACE inhibition than ramipril and enalapril, and, to a lesser extent, than captopril and fosinopril; 60% of ACE inhibition could persist in the heart at least 8 h after administration, while it was much lower with other ACEIs [41]. Conversely, in the lung, zofenopril showed a lower potency in both inhibiting ACE and reducing bradykinin metabolism [41]; bradykinin accumulation in the airways with zofenopril is lower than that observed with other ACEIs, and this may partially explain the relatively low risk of coughing observed with zofenopril (Fig. 7) [42]. Indeed, a meta-analysis including hypertensive and post-myocardial infarction patients indicated that zofenopril-induced cough was generally of a mild to moderate intensity, occurred significantly ($p = 0.001$) more frequently in the first 3–6 months of treatment (3.0% vs. 0.2% 9–-12 months), and always resolved or improved upon therapy discontinuation [39].

CONCLUSIONS

The pharmacological features of zofenopril provide cardioprotective, anti-ischemic, and anti-oxidant effects that differentiate it from other ACEIs. Zofenopril was evaluated as an early treatment after AMI, showing both short- and long-term benefits, and it has been
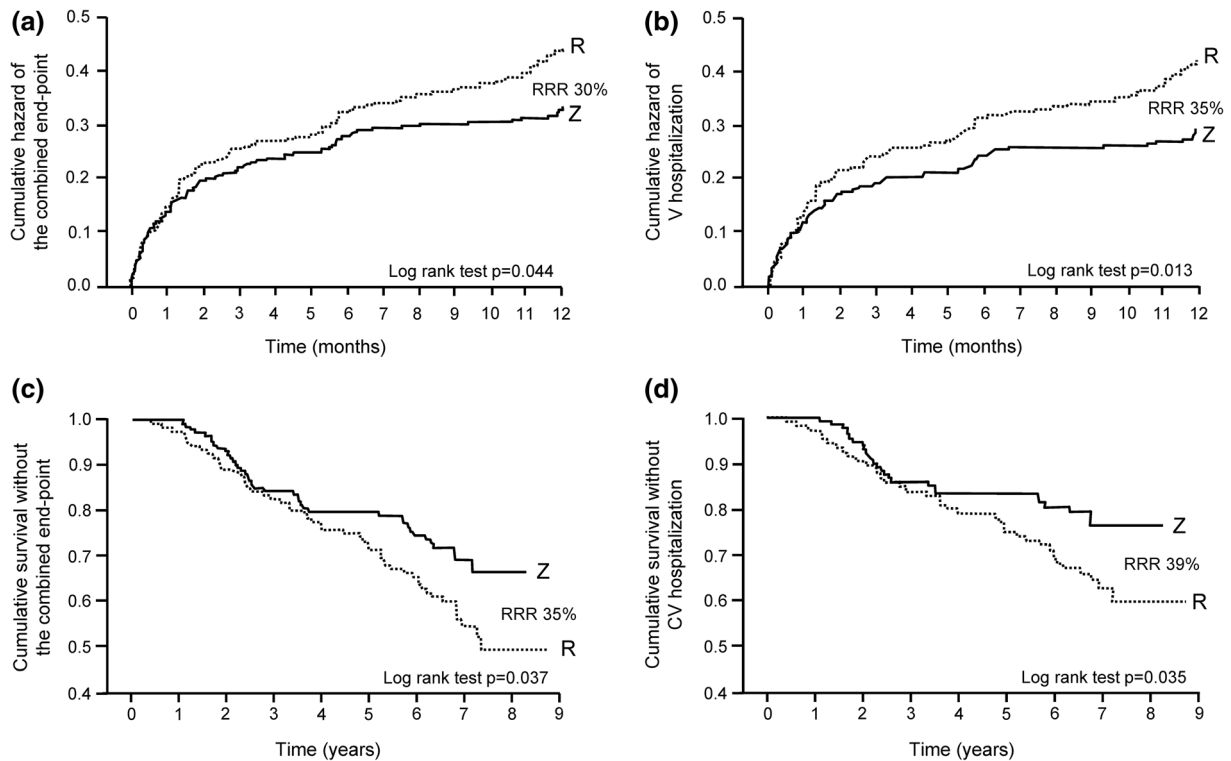
Fig. 2 **a** Incidence of the combined end-point (cardiovascular mortality or hospitalization for cardiovascular causes) and **b** of hospitalization during the 1-year of treatment with ramipril plus acetylsalicylic acid (*n* = 351, *dashed lines*) or zofenopril plus acetylsalicylic acid (*n* = 365, *continuous lines*) in the SMILE-4 Study. **c** Incidence of the combined endpoint and **d** hospitalization during the follow-up in patients originally randomized and treated with zofenopril (*continuous lines*, *n* = 144) or ramipril (*dashed lines*, *n* = 121) in the SMILE-4 Study. *p* values from the log-rank statistics [34, 35]. *RRR* relative risk reduction, *R* ramipril, *Z* zofenopril
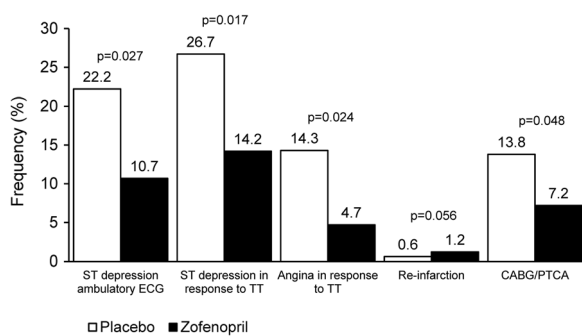
Fig. 3 Occurrence (%) of the different primary endpoints of the study after 6 months of treatment with placebo (*n* = 177, *open bars*) or zofenopril (*n* = 172, *full bars*) in the patients of the SMILE-3 Study [37]. *TT* treadmill test, *CABG* coronary artery bypass graft, *PTCA* percutaneous transluminal coronary angioplasty. *p* values refer to the statistical significance of the between-treatment difference

confirmed as a feasible and effective therapy in many subgroups of patients with CV and metabolic comorbidities. Therefore, as well as other ACEIs, zofenopril is recommended for the management of CVD, including HF, AMI, and LVD, beyond BP control. As per current guidelines, ACEIs are recommended in symptomatic patients with HF with reduced LVEF to reduce the risk of HF hospitalization and in patients after AMI with ST-elevation. Since the effect in reducing the risk of mortality and reinfarction is not specifically associated with a single agent, and is rather described as a class effect, the choice of ACEI therapy can be addressed by the ancillary characteristics of each agent that may confer further benefits to patients.
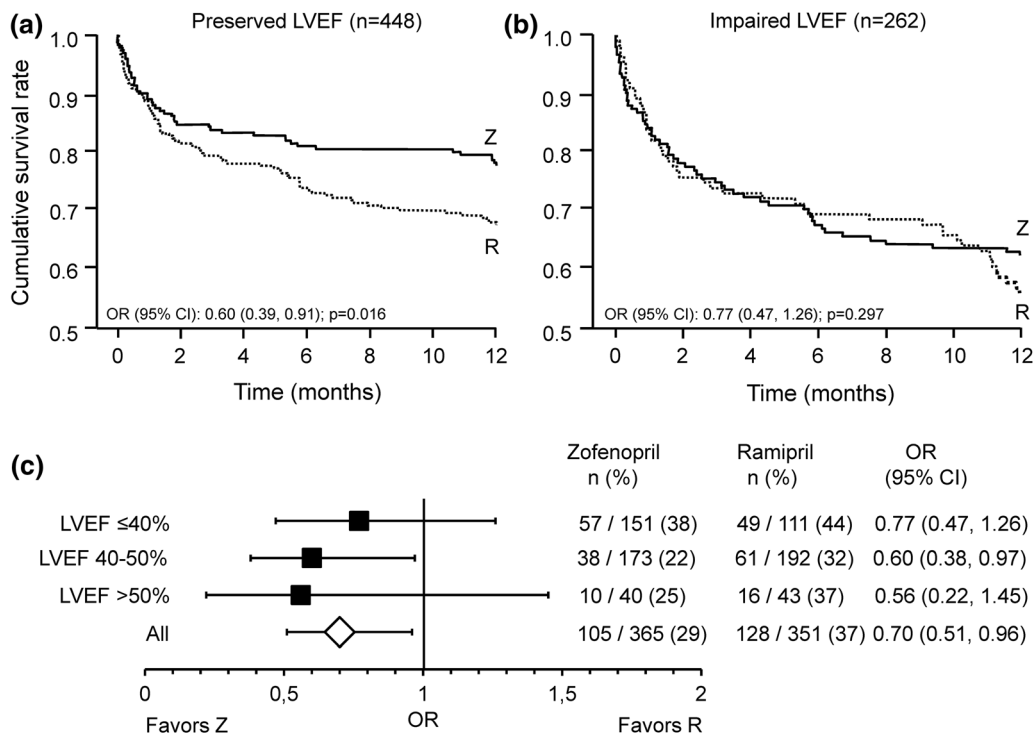
Fig. 4 Cumulative survival without events during 1 year in patients (**a**) with preserved systolic function (left ventricular ejection fraction > 40%) and (**b**) with impaired systolic function (left ventricular ejection fraction ≤ 40%) treated with zofenopril (*continuous line*) or ramipril (*dotted line*). **c** Odds ratio and 95% confidence interval for 1-year combined occurrence of cardiovascular mortality or hospitalization for cardiovascular causes according to ranges of left ventricular ejection fraction [38]. *CI* confidence interval, *LVEF* left ventricular ejection fraction, *OR* odds ratio, *R* ramipril, *Z* zofenopril
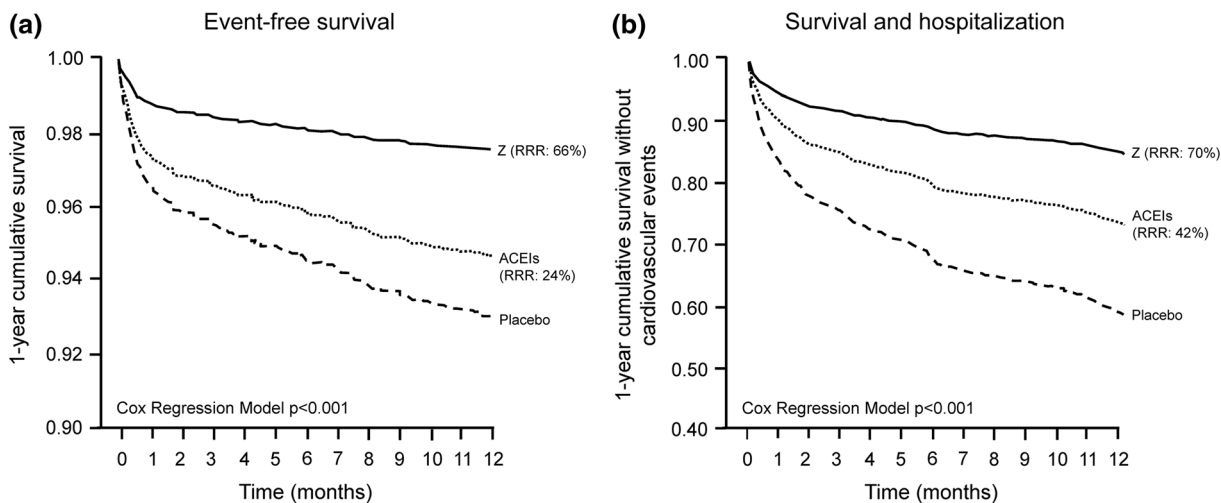
Fig. 5 a Cumulative survival and **b** cumulative survival without cardiovascular events during 1-year of follow-up in patients treated with placebo (*n* = 951, *dashed lines*), other angiotensin-converting enzyme inhibitors (lisinopril or ramipril, *n* = 871, *dotted lines*) and zofenopril (*n* = 1808, *continuous line*) in the SMILE program. The relative risk reduction versus placebo is indicated. *p* values from a Cox regression model [39]. *Z* zofenopril, *ACEI* angiotensin-converting enzyme inhibitor, *RRR* relative risk reduction
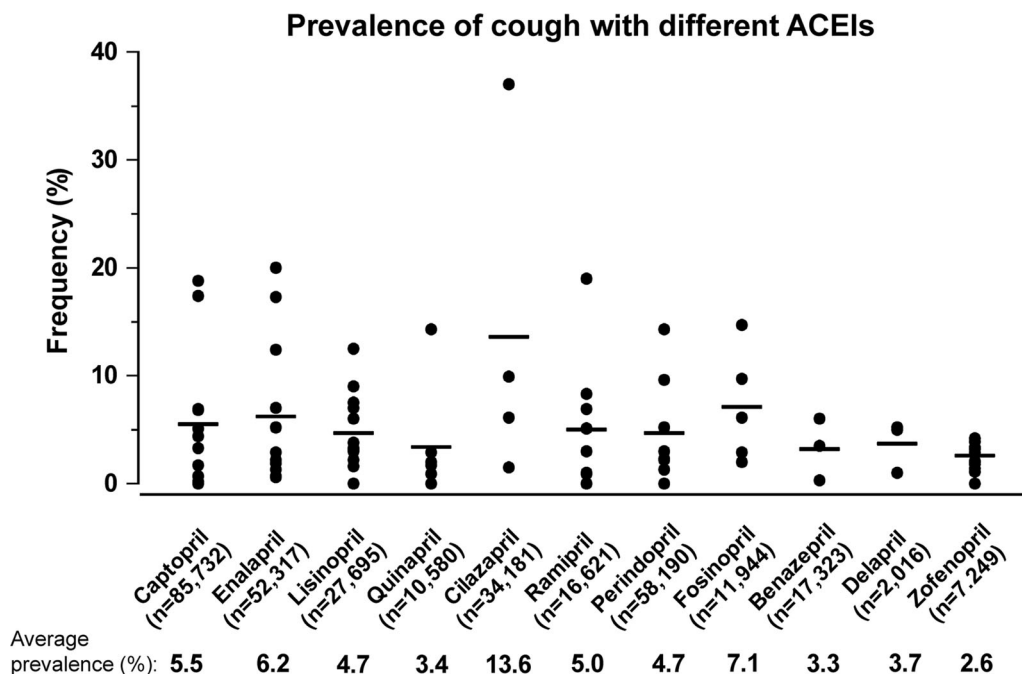
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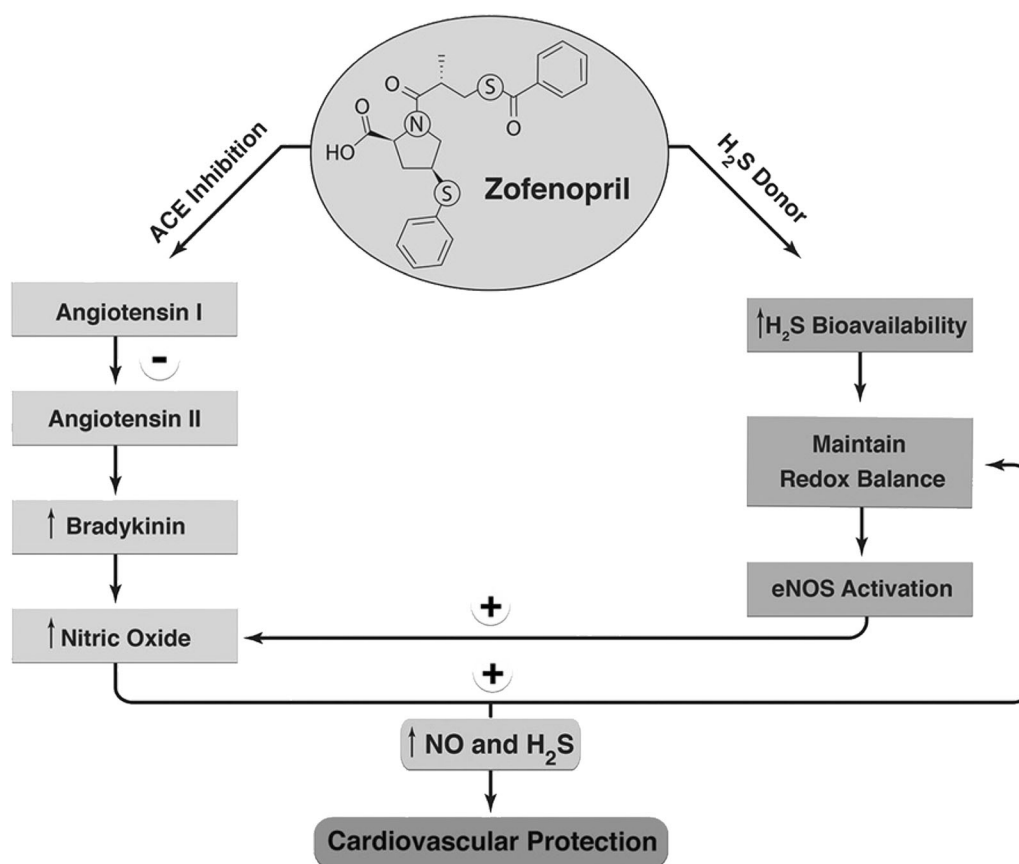
Fig. 6 Effect of zofenopril on hydrogen sulfide and nitric oxide bioavailability. By inhibiting myocardial angiotensin-converting enzyme activity, zofenopril reduces the generation of angiotensin II and increases levels of bradykinin. Bradykinin, through stimulation of endothelial B2 receptors, promotes the release of nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor, which in turn leads to cardioprotection. On the other hand, zofenopril, by releasing hydrogen sulfide, enhances tissue antioxidant defense, and promotes activation of endothelial nitric oxide synthase, leading to increased levels of nitric oxide. Therefore, angiotensin-converting enzyme inhibition, hydrogen sulfide, and nitric oxide account for zofenopril-mediated cardioprotective effects [40]. *ACE* angiotensin-converting enzyme, *BK* bradykinin, *EDHF* endothelium-derived hyperpolarizing factor, *eNOS* endothelial nitric oxide synthase, *H2S* hydrogen sulfide, *NO* nitric oxide

Fig. 7 Prevalence of cough with different ACEIs in double-blind randomized and post-marketing studies and meta-analyses [42]. *ACEI* angiotensin-converting enzyme inhibitor

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