Commentary

How long should angiotensin-converting enzyme inhibitors be given to patients following myocardial infarction: implications of the HOPE trial

Vernon VS Bonarjee and Kenneth Dickstein

Central Hospital in Rogaland, Armauer Hansensvei, Stavanger, Norway

Correspondence: Vernon VS Bonarjee, vernonbonarjee@rl.telia.no

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Abstract

Long-term treatment with angiotensin-converting enzyme inhibitors reduces post-infarction morbidity and mortality in patients with left ventricular (LV) systolic dysfunction or symptomatic heart failure. Until recently, the effect of such treatment in patients with preserved LV function has not been known. The results from the Heart Outcome Prevention Evaluation trial have indicated that long-term treatment with ramipril leads to a significant reduction in cardiovascular events in patients with atherosclerotic disease, including those with prior myocardial infarction and preserved LV function. These results suggest that long-term angiotensin-converting enzyme inhibition should also be considered in post-infarction patients with normal cardiac function.

Keywords angiotensin-converting enzyme inhibitors, heart failure, left ventricular dysfunction, myocardial infarction, renin–angiotensin system

Heart failure is commonly caused by coronary disease [1] and accounts for a substantial part of post-infarction morbidity and mortality. Prevention and treatment of heart failure is, therefore, an integral part of post-infarction therapy.

The benefit of angiotensin-converting enzyme (ACE) inhibitors in heart failure is well documented [2–4]. Sharpe *et al* demonstrated in 1986 that post-infarction treatment with the ACE inhibitor captopril attenuated left ventricular (LV) remodeling [5]. The effect was more pronounced with treatment initiated within the first 24 hours [6]. Several large clinical trials have subsequently demonstrated a reduction in mortality and morbidity with ACE inhibition following myocardial infarction [7–9]. The evidence has been strongest following prolonged treatment (6–60 months) in patients with LV dysfunction [10,11] or with symptomatic heart failure [12]. In unselected patients [7,8], however, there has been no clinical evidence to support a treatment effect beyond 6 weeks.

The renin–angiotensin system (RAS) plays an important role in the initiation and progression of atherosclerosis [13]. Clinical data exists that indicates an effect of ACE inhibitors in the prevention of myocardial infarction and unstable angina [10,14]. The recently completed Heart Outcome Prevention Evaluation (HOPE) trial included patients with coronary artery disease, stroke, peripheral vascular disease, or diabetics with additional cardiovascular risk factors. Over 50% of the patients in the HOPE study had suffered a myocardial infarction, but none had symptomatic heart failure [15]. In the trial, ramipril treatment (lasting an average of 4.5 years) caused a significant reduction in cardiovascular events. This supports the use of chronic ACE-inhibitor therapy in a wider range of post-infarction patients, independent of cardiac status.

ACE = angiotensin-converting enzyme; AIRE = Acute Infarction Ramipril Efficacy; CI = confidence interval; CONSENSUS = Cooperative New Scandinavian Enalapril Survival Study; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardico; HOPE = Heart Outcome Prevention Evaluation trial; ISIS = International Study of Infarct Survival; LV = left ventricular; RAS = renin–angiotensin system; SAVE = Survival and Ventricular Enlargement trial; SOLVD = Studies of Left Ventricular Dysfunction; TRACE = Trandolapril Cardiac Evaluation.

Table 1

Post-infarction angiotensin converting enzyme-inhibitor trials

	Unselected post-infarction patients			Post-infarction patients with left ventricular dysfunction			
Trial [Reference no]	CONSENSUS II [16]	GISSI-3 [8]	ISIS-4 [7]	SAVE [10]	AIRE [12]	SMILE [9]	TRACE [11]
Drug	Enalapril	Lisinopril	Captopril	Captopril	Ramipril	Zofenopril	Trandolapril
Number of patients	6090	19,394	58,050	2231	2006	1556	1749
Target dose	20 mg × 1	10 mg × 1	50 mg × 2	50 mg × 3	5 mg × 2	30 mg × 2	4 mg × 1
Inclusion criteria	AMI consecutively	AMI consecutively	AMI consecutively	LVEF < 40%	Signs or symptoms of heart failure	Anterior wall AMI without thrombolytics	Low wall motion index score
Follow-up time	1.5–6 months (trial stopped)	6 weeks	5 weeks	24–60 months	6–30 months	6 weeks	24–50 months
Mortality reduction	P: 10.2% T: 11.0%	P: 7.1% T: 6.3%	P: 7.7% T: 7.2%	P: 25% T: 20%	P: 23% T: 17%	P: 10.6% T: 7.1%	P : 42.3% T: 34.7%
Risk reduction (95% CI)	−10 % (−29 to 7%)	12% (1% to 21%)	7% (1% to 13%)	19% (3% to 32%)	27% (11% to 40%)	25% (−11% to 60%	22% (9% to 33%)
Level of significance	$P = 0.26$	$P = 0.03$	$P = 0.02$	$P = 0.019$	$P = 0.002$	$P = 0.19$	$P = 0.001$

SMILE, Survival of Myocardial Infarction Long-Term Evaluation; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; P, placebo; T, treatment; CI, confidence interval.

Post-infarction trials with converting enzyme inhibitors

Post-infarction ACE-inhibitor trials may be divided into two main categories (Table 1). In one trial, patients with acute myocardial infarction were included consecutively, irrespective of cardiac function [7,8,16]. In the other, patients were selected and included only if they had heart failure [12], LV dysfunction [10,11], or a transmural anterior wall infarction [9]. The Fourth International Study of Infarct Survival (ISIS-4) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardico (GISSI-3), in which all post-infarction patients were randomized, demonstrated a marginal but statistically significant mortality reduction at 5 and 6 weeks, respectively. There has been no data showing an effect of long-term treatment in unselected patients. Some patients were followed-up for 6 months in the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II), but this trial was terminated prematurely because, based on an interim analysis, the chances of demonstrating a treatment effect were considered unlikely.

The average duration of treatment in the Acute Infarction Ramipril Efficacy (AIRE), the Trandolapril Cardiac Evaluation (TRACE), and the Survival and Ventricular Enlargement (SAVE) trials were 15, 27, and 42 months, respectively. A highly significant reduction in mortality was observed during this period (Table 1). There is therefore sufficient evidence to state that long-term ACE-inhibitor therapy for up to 5 years provides a continuous, cumulative benefit in patients with post-infarction heart failure or LV dysfunction.

The RAS in cardiovascular disease

Neurohormonal activation in heart failure

Myocardial infarction results in ischemia and necrosis of myocytes, causing myocardial dysfunction and a reduction in cardiac output. This activates several compensatory mechanisms, including neurohormonal activation, in an effort to maintain adequate perfusion of vital organ systems. Neurohormonal activation, primarily of the sympathetic nervous system and the RAS, counteracts myocardial dysfunction initially, but may eventually aggravate the underlying pathophysiology, causing a further deterioration of cardiac function. Results from clinical trials in patients with heart failure have demonstrated lower mortality and improved morbidity with converting-enzyme inhibition [2–4], as well as with beta-blockers [17,18]. This indicates that neurohormonal activation is important in the pathophysiology of heart failure and contributes to the progression of this condition.

Autocrine and paracrine activity of the RAS

The RAS was previously conceived to be an endocrine system regulating the circulation. It has subsequently been demonstrated that the RAS not only has endocrine activity, but also operates as autocrine and paracrine systems, acting at multiple sites (including cardiac, vascular, and renal tissues) [19]. All components of the RAS, and angiotensin II receptor subtypes 1 and 2, have been identified in cardiac tissue [20]. Markedly increased ACE immunoreactivity has been demonstrated in human myocytes adjacent to infarct scars [21]. The major effect of ACE inhibition in cardiac disorders may therefore not be

due to inhibition of systemic angiotensin production, but due to reduced tissue angiotensin II activity.

RAS and remodeling

The change in size, shape, and function of the myocardium following infarction, a process termed 'remodeling', is modulated by angiotensin II. Necrotic myocytes release a number of cytokines, including transforming growth factor β_1, which initiates the infiltration and activation of inflammatory cells, such as neutrophils, monocytes, and macrophages. Tissue fibroblasts proliferate and transform into myofibroblasts. The intercellular collagen is first degraded by matrix metalloproteinases, resulting in myocyte slippage and expansion of the infarcted area. During the later phase, there is new collagen deposition and the formation of scar tissue. Activated inflammatory cells as well as myofibroblasts have abundant angiotensin II receptor subtype 1 receptors. They also express ACE activity and provide a local source of angiotensin II production that is independent of systemic angiotensin II [22]. Angiotensin II, therefore, plays an important role in LV remodeling after infarction. This has been confirmed by clinical studies demonstrating reduced LV volumes with ACE inhibition following infarction [6,23]. Moreover, the process of new collagen deposition and scar formation may, in some cases, affect distant non-infarcted myocardium, resulting in inappropriate fibrosis and combined systolic and diastolic dysfunction [24]. Reduced angiotensin II concentrations may prevent this occurring. Treatment with the ACE inhibitor enalapril has been shown to preserve regional wall motion in the non-infarcted region in patients with anterior wall myocardial infarction [25]. Aldosterone is also operative in this pathological production of fibrous tissue [26]

RAS and atherosclerosis

The RAS not only plays a role in the development of cardiac remodeling and heart failure, but also affects several other aspects of cardiovascular disease including the pathogenesis of atherosclerosis. There is sufficient evidence indicating an important role of the RAS in inducing endothelial dysfunction, and the induction of inflammatory responses in the vessel wall [13]. Experimental studies indicate that angiotensin II-mediated superoxide production in vessel walls plays a crucial role in the early stages of atherosclerosis [27]. It has been demonstrated that human coronary atherosclerotic lesions contain angiotensin II [28], and a study of human coronary arteries indicates that ACE, and not chymase, is the major enzyme in the production of angiotensin II in atherosclerotic lesions [29]. The importance of ACE inhibitors in the progression of coronary disease has also been demonstrated in clinical studies. The SAVE trial demonstrated a 25% reduction in recurrent myocardial infarction [10], and a 23% reduction in myocardial infarction and a 20% reduction in the development of unstable angina was observed in the Studies of Left Ventricular Dysfunction (SOLVD) trial [14]

ACE inhibition and cardiovascular risk reduction

The HOPE trial is the first major clinical trial in which long-term ACE inhibition has been evaluated in patients with coronary artery disease, without heart failure or known LV dysfunction [15]. A total of 9297 patients with atherosclerotic disease, including coronary artery disease, stroke, or peripheral vascular disease, were included in this study. Patients with diabetes mellitus, with at least one additional risk factor such as hypertension, elevated levels of cholesterol, microalbuminuria, or smoking, were also included. There were 4892 cases among these patients who had suffered from a prior myocardial infarction. Patients were randomized to treatment with the ACE inhibitor ramipril ($n = 4645$), or placebo ($n = 4652$), up to a target dose of 10 mg once daily. Results after an average of 4.5 years of treatment demonstrated a highly significant reduction in total mortality (16%; 95% confidence interval [CI], 5–25%), cardiovascular mortality (26%; 95% CI, 13–34%), recurrent myocardial infarction (20%; 95% CI, 10–30%), and stroke (32%; 95% CI, 16–44%). The incidence of heart failure was reduced by 23% (95% CI, 13–33%). Recurrent myocardial infarction, stroke, and cardiovascular death was reduced by 20.9% in the subgroup of patients with prior myocardial infarction.

Implications and limitations of HOPE

The application of the results of the HOPE trial may have substantial clinical implications. It has been suggested that, if only one-half of the eligible patients in developed countries and a quarter of eligible patients in developing countries were treated with ramipril, over 1 million major cardiovascular events would be prevented every year [30]. The results of the HOPE trial have recently been compared with other post-infarction trials [31], and it has been demonstrated that post-infarction ramipril therapy is as cost-effective as other prophylactic treatment, such as the use of lipid-lowering agents.

A literal interpretation of the results of the HOPE trial would suggest that all patients following myocardial infarction should be placed on ACE inhibitors. It must be considered, however, that these results are based on *post hoc* subgroup analysis, and results from such an analysis should be interpreted with appropriate conservatism. Published data does not provide enough detailed information to adequately describe the cohort with prior myocardial infarction. Eighty-five percent of these patients suffered their infarction more than 1 year prior to inclusion. All patients in this study were older than 55 years of age and the results may not apply to a younger population. Data on ejection fraction was available in less than 60% of the

patients, and many of these patients with infarction had co-morbid conditions such as peripheral vascular disease, cerebrovascular disease, hypertension, and diabetes, which may have affected the results. The HOPE trial was performed before the use of current guidelines, which include more sensitive troponin assays [32]. The results may therefore not apply to all patients that are diagnosed with myocardial infarction today. The question of whether uncomplicated myocardial infarction itself represents an indication for long-term ACE inhibition must, therefore, be determined in prospective trials.

Beta-blocker therapy is indicated in most post-infarction patients. The timing and titration of beta-blockers in combination with ACE inhibitors may be a therapeutic challenge. This is an issue that needs to be addressed when considering optimal treatment of patients after a myocardial infarction.

Conclusion

Strong evidence exists suggesting that ACE-inhibitor treatment should be initiated early and continued for years, in patients with heart failure and/or LV dysfunction, following myocardial infarction. Results of the HOPE trial indicate that chronic treatment with ramipril should also be considered in post-infarction patients without heart failure. Whether the results of the HOPE trial also apply for other ACE inhibitors or angiotensin II receptor blockers should be addressed in future studies.

Competing interests

None declared.

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