

REVIEW ARTICLES

A Remarkable Medical Story: Benefits of Angiotensin-Converting Enzyme Inhibitors in Cardiac Patients

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The development of angiotensin-converting enzyme inhibitors (ACE inhibitors) has been one of the most remarkable stories in the treatment of cardiovascular diseases. Angiotensin converting enzyme inhibitors have several acute and sustained hemodynamic effects that are beneficial in the presence of left ventricular (LV) dysfunction. They increase cardiac output and stroke volume and reduce systemic vascular resistance as well as pulmonary capillary wedge pressure. The hemodynamic benefits are associated with improvement in the signs and symptoms of congestive heart failure (CHF) as well as decreased mortality, regardless of the severity of CHF. In patients with asymptomatic LV dysfunction, therapy with ACE inhibitors prevented the development of CHF and reduced hospitalization and cardiovascular death. They also increase survival when administered early after an acute myocardial infarction (MI). Most recently, ACE inhibition was associated with improved clinical outcomes in a broad spectrum of high-risk patients with preserved LV function. The mechanism of ACE inhibitors benefits is multifactorial and includes prevention of progressive LV remodeling, prevention of sudden death and arrhythmogenicity and structural stability of the atherosclerotic process. Evidence suggests that ACE inhibitors are underutilized in patients with cardiovascular diseases. Efforts should be directed to prescribe ACE inhibitors to appropriate patients in target doses. It is reasonable to believe that ACE inhibitors have a class effect in the management of LV dysfunction with or without CHF and acute MI. Whether the same is true for ACE inhibitors in the prevention of ischemic events is not known yet. (J Am Coll Cardiol 2001;37:1757-64) © 2001 by the American College of Cardiology

The development of angiotensin-converting enzyme (ACE) inhibitors has been one of the most remarkable stories in the treatment of cardiovascular diseases. In the 1960s and 1970s, neurohormonal activation was considered a necessary mechanism to insure survival for patients with left ventricular (LV) dysfunction. However, this was proven to be incorrect, and blockade of the renin-angiotensin system and other neurohormonal systems proved to be of great benefit for patients with LV dysfunction. The first step in the development of ACE inhibitors was to document their hemodynamic properties. Hemodynamic improvement correlated with symptomatic improvement, and by the early 1980s the role of ACE inhibitors expanded from use in hypertension to symptomatic therapy for patients with congestive heart failure (CHF). In the 1980s and early 1990s, it was demonstrated that ACE inhibitors provided a survival benefit for patients with LV dysfunction by attenuating the progressive process of LV remodeling. Moreover, ACE inhibitors have been shown to improve outcome for patients when administered in the early postinfarction

period. Most recently, ACE inhibition has been associated with improvement in the clinical outcomes in a broad spectrum of high-risk patients with preserved LV function.

This review discusses the magnitude of ACE inhibitors benefit in various cardiac patients. It also describes the mechanism of action and appropriate dosing of these agents.

BENEFITS OF ACE INHIBITORS SEEN IN PATIENTS WITH CHF

Effects on hemodynamics. Angiotensin-converting enzyme inhibitors have several acute and sustained hemodynamic effects that are particularly beneficial in the presence of LV dysfunction. The hemodynamic effects of oral captopril in patients with CHF were examined by several investigators (1-4). A single dose of captopril increased cardiac output and stroke volume and reduced systemic and pulmonary vascular resistance as well as pulmonary capillary wedge pressure (1,4). Hemodynamic benefits were observed at 30 min, peaked at 90 min and persisted for at least 6 h (1). These favorable hemodynamic changes were sustained after eight weeks of continuous therapy. Enalapril produced comparable effects (5,6), and the benefits were maintained with long-term therapy. The hemodynamic and hormonal effects of ramipril compared with captopril were studied in

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
CAD	=	coronary artery disease
CHF	=	congestive heart failure
CONSENSUS	=	Cooperative North Scandinavian Enalapril Survival Study
GISSI	=	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico trial
HOPE	=	Heart Outcomes Prevention Evaluation
LV	=	left ventricular
MI	=	myocardial infarction
NYHA	=	New York Heart Association
SAVE	=	Survival And Ventricular Enlargement study
SMILE	=	Survival of Myocardial Infarction Long-term Evaluation
SOLVD	=	Studies Of Left Ventricular Dysfunction

patients with moderate to severe heart failure (7). Compared with 12.5 mg of captopril, 5 mg of ramipril was associated with slower onset of action; however, the benefits were maintained for a longer duration (7). With 10 mg of ramipril, both hemodynamic and hormonal benefits were observed quicker and maintained for an even longer duration (7). Similar hemodynamic benefits were demonstrated using the ACE inhibitors fosinopril and lisinopril (8–10).

When compared with other vasodilators, ACE inhibitors produce a balanced systemic arteriovenous vasodilation. They also decrease salt and water retention by reducing aldosterone synthesis (11). Clinically, these beneficial hemodynamic effects translate into considerable improvement in LV function and symptoms in patients with CHF. Thus, ACE inhibitors improve hemodynamic parameters acutely in patients with CHF, and such improvement persists over time.

Effects on signs and symptoms of CHF. The Captopril Multicenter Group conducted a study designed to test the clinical efficacy and safety of using ACE inhibitor therapy in patients with CHF (12). In this study, patients with heart failure treated with digoxin and diuretic therapy were randomized to receive captopril or placebo for a 12-week period. The study demonstrated that captopril was associated with a lessening of the signs and symptoms of CHF. The symptoms compared were dyspnea, fatigue, orthopnea and edema. Using exercise treadmill testing, captopril resulted in improved exercise capacity when compared with the placebo patients. Captopril was compared with digoxin in the Captopril-Digoxin Multicenter trial (13). The captopril treated group showed significant improvement in exercise time, New York Heart Association (NYHA) functional class and the need for increased diuretics or hospitalization for worsening CHF. Similar results were noted with the once daily ACE inhibitor fosinopril (14). In this study, patients had symptoms that were milder when compared with the symptoms seen in the previous study. Patients

received fosinopril or placebo for six months with concomitant diuretic therapy, but not digitalis. Patients receiving fosinopril had improved exercise treadmill time. They were more likely than the placebo group to show improvement in the amount of dyspnea, fatigue and paroxysmal nocturnal dyspnea as well as a reduction in hospitalizations due to worsening heart failure. These benefits were confirmed in the in fosinopril Efficacy/Safety trial (15).

In patients with severe CHF, therapy with ACE inhibitors will improve peak exercise performance and reduce the symptoms of CHF. In the Cooperative North Scandinavian Enalapril Survival study (CONSENSUS) I trial, patients who had symptoms at rest were randomized to receive the ACE inhibitors enalapril or placebo (16). Patients treated with enalapril were more likely to improve their NYHA classification than placebo-treated patients (42% vs. 22%). Similar results were reported using other ACE inhibitors in patients with NYHA class II to IV CHF (17–19).

Effects on survival. Documentation of the survival benefits of ACE inhibitors is one of the most important advances in the management of LV dysfunction. Angiotensin-converting enzyme inhibitors are now well-established drugs used in the treatment of CHF.

The CONSENSUS I study was the first major mortality trial of ACE inhibitors therapy (16). The study demonstrated a 40% reduction in mortality in patients with severe NYHA class IV symptoms. The mortality at one year was reduced from 52% with placebo to 36% with enalapril. Survival benefits were maintained at a two-year follow-up among those allocated to the ACE inhibitor therapy (20). The Studies Of LV Dysfunction (SOLVD) treatment trial demonstrated that ACE inhibitors could benefit patients with CHF and less severe symptoms—NYHA class II and III symptoms (21). In this study, a total of 2,569 patients with LV ejection fraction $\leq 35\%$ (mean 25%) were randomized to receive either enalapril or placebo and followed for an average of 41 months. Treatment with enalapril reduced the overall risk of death by 16%; mortality was 40% in the placebo-treated group compared with 35% in the enalapril-treated group. Cardiovascular death was reduced by 18%, and the combined end point of death or hospitalization for CHF was reduced by 26%. This translated into the prevention of 50 deaths and 350 hospitalizations for every 1,000 patients with CHF treated with enalapril for three years. The V-HeFT II trial compared a regimen hydralazine/isosorbide dinitrate to enalapril in patients with CHF class II and III NYHA symptoms (22). The study demonstrated a survival advantage with ACE inhibitor therapy; treatment with enalapril was associated with a 28% reduction in the risk of death at two years compared with the vasodilator combination.

In the Acute Infarction Ramipril Efficacy trial, long-term ACE inhibitor therapy was tested in a group of survivors of acute myocardial infarction (MI) with transient signs and symptoms of CHF (23). A total of 2,006 patients were enrolled and randomized to either the ACE inhibitor ramipril group or placebo group within 3 to 10 days after

MI. The active therapy group experienced a 27% reduction in the risk of death after a mean follow-up of 15 months. This benefit was maintained for five years after randomization (24).

Thus, ACE inhibitors had demonstrated efficacy in prolonging life in patients with all degrees of CHF associated with LV systolic dysfunction. They also demonstrated efficacy in preventing death in a population of patients with acute MI and CHF.

BENEFITS SEEN IN ASYMPTOMATIC PATIENTS WITH LV DYSFUNCTION

The benefits of ACE inhibitor therapy on survival in patients with symptomatic CHF prompted investigators to study the effects of ACE inhibitors in patients with asymptomatic LV dysfunction. The Survival And Ventricular Enlargement (SAVE) trial randomized 2,231 patients 3 to 16 days after MI with LV ejection fraction $\leq 40\%$ without symptomatic heart failure to captopril or placebo (25). After an average 3.5 years of follow-up, the captopril group had a 19% reduction in all-cause mortality, a 21% reduction in cardiovascular death, a 22% reduction in the incidence of heart failure requiring hospitalization and a 25% reduction in the incidence of recurrent MI.

The SOLVD prevention trial was designed to determine whether enalapril would reduce mortality and morbidity in a broad spectrum of asymptomatic patients with LV dysfunction (26). In this study, 4,228 patients with an LV ejection fraction $\leq 35\%$ were randomized to receive either enalapril or placebo. None of these patients were on therapy for heart failure. The mean follow-up period was 37 months (15 to 62 months). There was a trend toward a lower rate of overall death noted in the enalapril group with a risk reduction of 8%; cardiovascular death was also reduced by 12%, but it did not reach statistical significance. However, the combined end point of death or the development of CHF was reduced significantly (risk reduction = 29%). In the Trandolapril Cardiac Evaluation (TRACE) trial, patients with documented LV dysfunction after MI were randomized to either trandolapril or placebo within three to seven days of infarction (27). Mortality was significantly reduced from 42.3% in the placebo group to 34.7% in the trandolapril-treated group.

BENEFITS SEEN IN PATIENTS WITH ACUTE MI

For many years it was believed that therapeutically induced hypotension would decrease coronary blood flow and be harmful for patients suffering an acute MI. The CONSENSUS II trial was published in 1992 and reinforced this hypothesis (28). In this trial, enalapril was started within 24 h of acute MI. The initial dose was given intravenously and was associated with a higher risk of early hypotension. Although there was no worsening of heart failure in the patients randomized to ACE inhibitor therapy, there was no significant effect on survival at either one or six months. The lack of survival benefits and an excess of deaths in the

enalapril group who had early hypotension resulted in premature termination of the study.

After demonstration of the remarkable benefits of ACE inhibitors in patients with acute MI by the SAVE investigators, interest resurfaced to examine their effects in the early post-MI period. A careful oral titration of ACE inhibitors in the immediate postinfarct period was used to avoid the development of hypotension. Subsequently, the benefits of early postinfarction ACE inhibitor therapy were demonstrated in large clinical trials. In the third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trial, patients with acute infarctions were randomized to receive the ACE inhibitor lisinopril, 5 mg initial dose and then 10 mg daily versus placebo (29). Therapy was started within 24 h of acute infarction. At six weeks, mortality and the combined end point of mortality and LV dysfunction were reduced in the ACE inhibitor-treated patients. Benefits were seen despite concomitant therapy with aspirin, thrombolytics and beta-adrenergic blocking agents. In the SAVE trial, clinical benefit was not apparent until after 11 months of therapy and was due to remodeling of noninfarcted myocardium (25). The early benefit of ACE inhibitor therapy in the third GISSI trial suggests that starting ACE inhibitors within 24 h has an effect on the infarcted myocardium either by limiting infarct size or by reducing infarct expansion. The International Study of Infarct Survival (ISIS)-4 trial showed similar results (30). In that trial, oral captopril was administered within 24 h of acute MI. At five weeks, survival of patients receiving captopril was better than that of the placebo group. The benefit was greatest in high-risk patients with prior MI, anterior ST elevation and LV dysfunction. Perhaps the most convincing clinical evidence that early ACE inhibitors therapy affects the infarcted myocardium is from the Survival of Myocardial Infarction Long-term Evaluation (SMILE) trial (31). Patients were randomized to the ACE inhibitors zofenopril or placebo, which was administered for only six weeks after acute MI. At the end of six weeks, the combined end point of death and incidence of CHF were reduced in the zofenopril patients. After one year, mortality was lower in the ACE inhibitor-treated group than it was in the placebo group. The short duration of treatment started early after infarction would not be expected to affect remodeling of noninfarcted myocardium as in the SAVE trial. All patients in the SMILE trial had anterior MI, which is the most likely group to benefit from the effects of early ACE inhibitor therapy on reduction of infarct size and attenuation of myocardial infarct expansion.

Similar benefits of ACE inhibitor therapy after MI were demonstrated using captopril in the Chinese Cardiac study. However, because of the small size of the trial, mortality advantage was not statistically significant (32,33). The Placebo-Controlled Randomized ACE Inhibitor Comparative Trial In Cardiac Infarction and LV Function (PRACTICAL) study compared enalapril versus captopril on LV function and survival after acute MI (34) and

demonstrated comparable benefits of both ACE inhibitors on LV function and attenuation of LV dilation.

The benefits of ACE inhibitors in patients with acute MI complicated by CHF were addressed by the Acute Infarction Ramipril Efficacy trial investigators, as discussed earlier in this review. The timing of initial ACE inhibitor therapy was studied in the Healing and Early Afterload Reducing Therapy (HEART) trial (35). The study compared the benefits of ramipril when administered either early (within 24 h) or late (after two weeks) after the onset of acute MI. Although the trial was terminated prematurely due to the obvious benefits of early administration of ACE inhibitors after MI demonstrated by ISIS-4 and the third GISSI trial, the study demonstrated that ramipril, when started early after MI, attenuated LV remodeling and increased ejection fraction when compared with delayed initiation of ACE inhibitors.

Thus, early administration of ACE inhibitors after acute MI for a few weeks is associated with five lives saved per 1,000 treated (36). Administration of ACE inhibitors at a later time is associated with fewer benefits. The maximum benefits are seen in patients with LV dysfunction with or without overt heart failure. The development of hypotension is associated with increase risk of death and should be avoided (36,28).

BENEFITS SEEN IN HIGH-RISK PATIENTS WITHOUT LV DYSFUNCTION

Results from the SAVE and SOLVD trials demonstrated that ACE inhibitor therapy after MI was associated with a reduction of recurrent MI (25,26,37,38). The benefit was independent of the degree of LV dysfunction and was not evident until 6 to 12 months after the initiation of therapy (25,38). This suggested additional ACE inhibitor benefits not related to hemodynamic effects. Observed benefits could be due to structural effects such as delay of progression of coronary artery disease (CAD) or stabilization of atherosclerotic plaques (39).

The Heart Outcomes Prevention Evaluation (HOPE) study (40) explored whether ACE inhibition with ramipril, 10 mg/day, could prevent cardiovascular events or stroke in high-risk patients without known LV dysfunction or CHF. The study was terminated prematurely because of a clear benefit of ACE inhibitor therapy. Treatment with ramipril was associated with a 22% reduction in the risk of a cumulative primary end point of cardiovascular death, MI or stroke. The relative risk of death from any cause with ramipril was 0.84 ($p = 0.005$) compared with placebo. Therapy with ramipril was also associated with a significant reduction in the rate of revascularization, cardiac arrest and the development of CHF.

While previous trials have proven that ACE inhibitors are effective in patients with LV dysfunction, the HOPE study proved that ACE inhibition is protective in a broad range of patients without baseline LV dysfunction or CHF. Whether prevention of ischemic events by ACE inhibitors

in patients without LV dysfunction is a class effect or whether or not lower-risk patients can benefit from their use is currently under investigation.

MECHANISMS OF ACE INHIBITORS BENEFICIAL EFFECTS

The mechanisms of ACE inhibitors benefits are multifactorial. In any particular patient, one or more of the following mechanisms may play an important role in producing clinical benefits.

Prevention of CHF. Loss of myocardium as the result of acute MI or muscle damage seen in nonischemic cardiomyopathy results in a decline in cardiac performance. A series of compensatory mechanisms are activated to maintain cardiac output, including enhanced sympathetic tone and activation of the renin-angiotensin endocrine axis (41,42). Enhanced sympathetic tone leads to increased contractility of the remaining functional myocardium and to an increase in systolic and diastolic wall stress. Increased wall stress stimulates myocyte hypertrophy, which returns wall stress levels towards normal. If the amount of damaged myocardium is limited, compensatory mechanisms can be sufficient to minimize chamber enlargement and LV hypertrophy.

When the amount of damaged myocardium is extensive, the increase in LV filling pressures and resulting chamber distension can exceed the hearts ability to increase LV mass. When hypertrophy is inadequate to compensate for lost myocardium, the increased wall stress continues to stimulate further LV dilation that goes beyond that necessary to maintain cardiac performance. A vicious cycle is initiated in which LV dilation progressively increases wall stress, which stimulates even further increases in LV cavity size. The balance between cavity dilation and maintenance of cardiac function is upset, and progressive LV dilation exceeds that which is compensatory and becomes a pathologic process.

In experimentally induced MI, a progressive increase in LV volume has been demonstrated (42). After coronary ligation resulting in a moderate to large MI, the extent of LV enlargement has been shown to be related not only to infarct size, but also to the duration of time after the infarction. Measurements of pressure-volume relationships showed that, for similar end-diastolic pressures, LV volume progressively increased over time. The progressive volume increase is not due to LV distension. It is due to structural changes in both infarcted and noninfarcted myocardium.

Progressive increases in LV volume can be detected by noninvasive imaging with two-dimensional echocardiography, radionuclide ventriculography and magnetic resonance imaging. Progressive enlargement of the LV is viewed as a continuous process with progressive cardiac chamber enlargement occurring as a precursor to, and subsequently continued during, the clinical manifestation of CHF. Alteration or prevention of progressive ventricular enlargement has an effect on morbidity and mortality.

Several large clinical trials demonstrated that treatment with ACE inhibitors in patients with LV dysfunction would

slow the progression of pump failure (16,21,25-27). Antagonism of neurohormonal activation by ACE inhibitors may slow the rate of deterioration of LV function.

On the cellular level, beside stimulation of myocytes hypertrophy as discussed earlier in the text, elevated renin-angiotensin-aldosterone levels promote fibrosis and collagen deposition that lead to a stiff ventricle and progressive LV dysfunction (43,44). Therapy with ACE inhibitors improved myocyte contractile function (45), prevented non-myocyte cellular proliferation and collagen deposition (45,46) and prevented myocyte hypertrophic response (45,46).

Prevention of ischemic events. There are several mechanisms whereby ACE inhibitors can prevent ischemic events and recurrent acute MI. Activation of the renin-angiotensin system has been shown to be an independent predictor of ischemic events. In a group of mild to moderate hypertensive patients, an elevated renin profile was an independent predictor of future acute MI (47). Moreover, angiotensin II has a proischemic vascular effect by causing vasoconstriction and promoting the growth and migration of vascular smooth muscle cells (48). This causes an increase in smooth muscle cell enzyme, an increase in free radical production and promotes the oxidation of low-density lipoprotein cholesterol contributing to atherosclerotic progression.

Angiotensin-converting enzyme inhibitors are shown to counteract the vasoconstriction of the atherosclerotic coronary arteries. Therapy with ACE inhibitors has been demonstrated to prevent endothelial dysfunction in animal (49-53) as well as human experiments (54-58). The benefits appear to be related to the ability of ACE inhibitors to release local vasodilators such as nitric oxide and bradykinins as well as antagonizing the effects of angiotensin II (59). Additionally, ACE inhibition has been shown to counteract several atherosclerotic processes including thrombosis, low-density lipoprotein oxidation, proliferation of vascular smooth muscle cells and local accumulation of neutrophils (60). Activation of the renin-angiotensin system has prothrombotic effects; ACE inhibitors increase plasma levels of plasminogen activator inhibitor-1 and inhibits endogenous fibrinolysis (61,62). Preliminary data have shown that ACE inhibition improves endogenous fibrinolytic function (63).

Prevention of sudden death. In addition to reduction of cardiac death by prevention of the development and progression of CHF, the reduction of sudden death demonstrated in clinical trials suggests an additional mechanism of benefit (22,27,64-66). The mechanism by which ACE inhibitors prevents sudden death is not well understood. Sudden death is likely to be due to sudden ischemia or arrhythmic events (67). Neurohormonal modulation by ACE inhibitors may reduce sudden vasoconstriction and, thus, arrhythmogenesis. In isolated perfused rat hearts, ACE inhibitors increased glycogen, adenosine triphosphate and coronary flow and decreased the incidence of ventricular fibrillation (68). These benefits have been attributed to both blockade of angiotensin II production and inhibition of bradykinin breakdown, which may stimulate the production

of various vasodilators like prostaglandins and nitric oxide (69).

Additionally, ACE inhibitors may suppress the release of catecholamines (70), decrease calcium overload (71,72) and suppress endogenous endothelin secretion, which may account for less ventricular dysfunction and arrhythmias (73). Recently, it was found that patients carrying the ACE DD genotype with angiotensin II type 1C allele are at a higher risk for malignant ventricular arrhythmias (74).

After acute MI. Animal experiments suggest several mechanisms that could explain the early post-MI ACE inhibitor benefits. In canine experimental infarctions, captopril started after coronary artery occlusion increased endocardial blood flow, which resulted in reduced infarct size (75). Similar results were demonstrated in patients who received ACE inhibitor therapy after infarction, and infarct size was reduced (76).

Angiotensin-converting enzyme inhibitor therapy may benefit patients in the early post-infarction period by yet another mechanism. Infarct expansion (a thinning and dilation of infarcted tissue), which leads to increased mortality, LV chamber enlargement and aneurysm formation, is attenuated when captopril is started less than 24 h after acute MI (77). In experimental rat MI, treatment with ACE inhibitors reduced the extent of infarct expansion when measured two weeks after infarction (78). Angiotensin-converting enzyme inhibition was started 2 h after infarction, which is too late in rats to have any effect on infarct size. Reduction of infarct expansion has the potential to reduce the risk of cardiac rupture, which is a rare and usually fatal condition (79). However, it will benefit more patients by reducing the extent of LV dilation (42,80-83). While some degree of LV dilation will result from loss of myocardium due to the acute infarction to compensate for the loss of functioning myocardium, infarct expansion will result in further cardiac dilation that goes beyond what is compensatory. An expanded infarct can result in an LV cavity size 20% to 40% over compensatory dilation (84). Left ventricular infarct expansion is associated with increased mortality and acts as a stimulus for remodeling of noninfarcted myocardium resulting in more cardiac dilation.

UTILIZATION AND DOSING OF ACE INHIBITORS

Despite the overwhelming evidence of the effectiveness of ACE inhibitors in the management of patients with LV dysfunction, there is evidence that they are used in too few patients and often at suboptimal doses (85-87). Underutilization may result from concerns for adverse effects. Several large clinical trials showed that ACE inhibitors are safe and exceptionally well-tolerated by most patients, and the side effects are generally reversible after discontinuation of the medication. Thus, a trial of ACE inhibitors is warranted in all candidates unless specific contraindications exist. Angiotensin-converting enzyme inhibitors should be started at low doses and titrated to their proven effective dose. The Assessment of Treatment with Lisinopril And Survival

Table 1. The Doses of the Various ACE Inhibitors in the Treatment of LV Dysfunction and Hypertension (Different Agents May Have Different Specific Indications)

Drug	LV Dysfunction		Hypertension	
	Initial Dose	Target Dose	Initial Dose	Maximum Dose
Captopril	12.5 mg TID	50 mg TID	25 mg BID or TID	450 mg/day
Enalapril	2.5 mg BID	20 mg BID	5 mg OD	40 mg/day
Fosinopril	10 mg OD	40 mg OD	10 mg OD	80 mg/day
Lisinopril	5 mg OD	20 mg OD	10 mg OD	40 mg/day
Quinapril	5 mg BID	20 mg BID	10 mg OD	80 mg/day
Ramipril	2.5 mg BID	5 mg BID	2.5 mg OD	20 mg/day
Trandolapril	1 mg OD	4 mg OD	1 mg OD	8 mg/day

ACE = angiotensin-converting enzyme; BID = twice a day; LV = left ventricular; OD = once daily; TID = three times a day.

(ATLAS) study indicated that a high dose of the ACE inhibitors lisinopril was superior to a low dose in reducing the risk of major clinical events in patients with CHF (88). A similar dosing effect was seen in patients after MI treated with ramipril (35). In patients with acute MI, ACE inhibitors should be administered early after infarction (within 24 h from onset of symptoms) and then continued indefinitely in the presence of LV dysfunction. With the recent publication of the HOPE trial, all post-MI patients or patients who are at high risk for CAD should be treated with ACE inhibitors indefinitely, even with normal LV function.

Table 1 summarizes the initial and the target doses of various ACE inhibitors. The initial dose should be lower if the patient's serum sodium concentration is <135 mmol/L, which indicates a high level of plasma renin activity, or if serum creatinine is $\geq 250 \mu\text{mol/L}$ (approximately 3.0 mg/dl). Mild, asymptomatic hypotension and mild azotemia are acceptable side effects of therapy with ACE inhibitors and are an indication to reduce the diuretic dose if the patient is not volume overloaded. Particular attention should be practiced to avoid the development of hypotension in patients with an acute MI, as hypotension may adversely affect the remodeling process in the immediate post-infarction period and can lead to increased mortality. Progressive deterioration of renal function or the development of a significant hyperkalemia or hypotension should prompt an immediate discontinuation of the therapy. Angioedema is a rare, but life-threatening, complication of ACE inhibitor therapy and should be an absolute contraindication to future use of all ACE inhibitors. Angiotensin-converting enzyme inhibitors should be avoided in pregnant women since they are associated with adverse fetal effects (89).

Angiotensin-converting enzyme inhibitors tend to conserve potassium by reducing the secretion of aldosterone. Consequently, hypokalemia induced by diuretics can often be prevented without the need for supplemental potassium or a potassium-sparing diuretic. Accordingly, ACE inhibitors should not be instituted at a time when the serum potassium is $>5.5 \text{ mmol/L}$. Caution should be practiced about stopping ACE inhibitors because of cough. Alternative causes of cough, including worsening heart failure, should be considered before discontinuing an ACE inhibitor. If the cough is intolerable for the patient and no other

cause is identified, then switching to another ACE inhibitor, such as fosinopril, may be beneficial rather than avoiding all ACE inhibitors (90).

FUTURE USE OF ACE INHIBITORS

Several large clinical trials demonstrated similar benefits of various ACE inhibitors in patients with LV dysfunction or CHF. Thus, it is reasonable to believe that ACE inhibitors have a class effect in the management of LV dysfunction with or without CHF. Similarly, ACE inhibitors benefits after MI should be considered a class effect. Whether the same is true for ACE inhibitors in the prevention of ischemic events is not clear. Data from the SAVE and SOLVD trials demonstrated that both captopril and enalapril are effective in preventing ischemic events in patients with LV systolic dysfunction. On the other hand, ramipril is the only ACE inhibitor so far shown to prevent ischemic events in patients without LV dysfunction. Moreover, the benefit of ACE inhibitors in patients at a lower risk than the HOPE population has not been established.

Currently, two ongoing clinical investigations are intending to answer some of these questions. First the Prevention of Events with ACE Inhibition (PEACE) trial (91) is investigating whether trandolapril can prevent MI and cardiovascular events in patients with CAD and normal baseline ejection fraction. Second, the European Trial of Reduction of Cardiac Events with Perindopril in Stable CAD (EUROPA) (92) is assessing whether perindopril can prevent MI, unstable angina and cardiovascular events in patients with stable CAD and no CHF; patients with LV dysfunction are not excluded.

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