

## Emerging Role of Angiotensin-Converting Enzyme Inhibitors in Cardiac and Vascular Protection

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**A**ngiotensin-converting enzyme (ACE) inhibitors are commonly used drugs in the management of a variety of cardiovascular diseases. They are effective antihypertensive agents.<sup>1-3</sup> Early studies have demonstrated reductions in mortality and symptoms of heart failure in patients with severe congestive heart failure.<sup>4</sup> More recently, clinical trials have demonstrated reductions in mortality and in hospitalizations for heart failure when these agents were used in patients with moderate left ventricular dysfunction, with and without overt heart failure, further expanding the clinical value of these drugs in the management of patients with cardiac diseases. These benefits have been observed consistently in several trials,<sup>5-7</sup> in patients with ischemic and nonischemic causes for the left ventricular dysfunction and with or without recent myocardial infarction. The reductions in progressive heart failure and mortality in these patients are at least partly related to a beneficial effect on left ventricular remodeling and reductions in left ventricular enlargement.<sup>8-10</sup> Other potential beneficial effects of these agents, such as regression of left ventricular hypertrophy and retardation of the rate of loss of renal function in patients with diabetic nephropathy, have been brought into focus by recent trials and also by experimental studies that explore their mechanisms of action.

A new and important potential role for ACE inhibitors is suggested by the recent trials in patients with low ejection fraction, which documented a significant reduction in major ischemic events such as myocardial infarction, unstable angina, and the need for coronary revascularization procedures. In addition, parallel epidemiological, genetic, and experimental studies suggest that the renin-angiotensin-aldosterone system may have a role in the development of coronary artery disease

and its clinical sequelae not only in patients with left ventricular dysfunction or overt heart failure but also in other high-risk patients.

This article will summarize several independent and complementary lines of evidence suggesting that ACE inhibitors may reduce the risk of ischemic events in patients at high risk of developing major vascular events.

### Biological Rationale for the Cardioprotective Effects of ACE Inhibitors in Preventing Myocardial Ischemia and Infarction

The renin-angiotensin-aldosterone system is complex and acts as a circulating hormonal system, a local endogenous tissue hormonal system with autocrine and paracrine effects, and a neurotransmitter and neuromodulator. Current experimental evidence suggests that ACE inhibitors reduce the risk associated with atherosclerotic cardiovascular disease through multiple mechanisms (Table 1). These can be classified into "cardioprotective" effects, referring to the benefits in overall cardiac hemodynamics, energetics, electrical stability, and the reduction in left ventricular mass, and "vasculoprotective" effects, related to direct antiproliferative effects, possible antiatherogenic properties, and favorable effects on thrombotic mechanisms and on arterial compliance and tone. ACE inhibitors probably exert these protective effects by blocking both circulating and tissue renin-angiotensin systems.

The cardioprotective effects of ACE inhibitors are well documented<sup>11</sup> (Table 1) and can be summarized as follows.

### Restoring the Balance Between Oxygen Supply and Demand

Angiotensin II is a potent direct systemic and coronary vasoconstrictor that increases myocardial inotropy by its ability to raise the cytosolic  $\text{Ca}^{2+}$  concentration in the myocardium<sup>11-16</sup> and therefore adversely affects the balance between myocardial oxygen supply and demand. Gavras and Gavras<sup>17</sup> reported that infusion of angiotensin II in rabbits resulted in myocardial infarction. Inhibition of the enzyme that converts angiotensin I to angiotensin II reduces the loading conditions of the heart (by reducing preload and afterload), thereby decreasing ventricular wall stress. ACE inhibitors also reduce left ventricular dilatation by reducing early infarct expansion and ventricular remodeling after experimental<sup>18</sup> and human infarction.<sup>8-10</sup> This reduction in

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**TABLE 1. Cardioprotective and Vasculoprotective Effects of Angiotensin-Converting Enzyme Inhibitors**

<b>Cardioprotective effects</b>
Restoring the balance between myocardial oxygen supply and demand
Reduction in left ventricular preload and afterload
Reduction in left ventricular mass
Reduction in sympathetic stimulation
Beneficial effect on reperfusion injury*
<b>Vasculoprotective effects</b>
Direct antiatherogenic effect*
Antiproliferative and antimigratory effects on smooth muscle cells, neutrophils and mononuclear cells
Improvement and/or restoration of endothelial function
Protection from plaque rupture*
Antiplatelet effects
Enhancement of endogenous fibrinolysis*
Antihypertensive effects
Improvement in arterial compliance and tone
*Not demonstrated conclusively in humans.

ventricular dilatation also reduces wall stress and thus myocardial oxygen demand. Blockade of angiotensin II-mediated coronary vasoconstriction and the resulting increase in coronary blood flow, demonstrated in animals and in human subjects,<sup>19-28</sup> contribute to increased oxygen supply. The net effect of these actions is a decrease in myocardial oxygen demand and an increase in myocardial oxygen supply. This beneficial effect is maintained by the absence of reflex tachycardia, which may occur with other vasodilators. Improved cardiac hemodynamics and improved energy supply to the myocardium have been demonstrated in human subjects treated with ACE inhibitors in the setting of acute and chronic heart failure and acute and chronic myocardial ischemic damage.<sup>29-34</sup> ACE inhibitors also cause regression of left ventricular hypertrophy with an associated improvement in ventricular relaxation (see below). They also increase arterial compliance.<sup>35</sup> These are important mechanisms of improving the balance of myocardial oxygen supply and demand and coronary reserve in patients with left ventricular hypertrophy, such as those with hypertensive heart disease, but also those with compensatory hypertrophy after myocardial infarction.<sup>36</sup>

### Reduction in Left Ventricular Mass

Increased left ventricular mass has been identified as an independent risk factor for coronary heart disease in general and is associated with increased cardiac mortality and morbidity.<sup>37-39</sup> While left ventricular hypertrophy occurs primarily in hypertensive individuals, the Framingham Heart Study suggested an association between left ventricular mass and cardiovascular mortality in the general population.<sup>40</sup> ACE inhibitors have been consistently shown to be effective in reducing left ventricular mass in animal models and in hypertensive subjects.<sup>41-46</sup> Prevention and regression of ventricular hypertrophy is related in part to reduced afterload, inhibition of myocardial smooth muscle cell hypertro-

phy,<sup>11</sup> and restructuring of the elastic and collagen fibers of the myocardium, limiting the remodeling process.<sup>47,48</sup> Recent experimental evidence<sup>49</sup> suggests that load-independent mechanism(s) could also play a role in regression of left ventricular mass with ACE inhibitor therapy. For example, rats with left ventricular hypertrophy produced by banding of the abdominal aorta, when treated with the high-affinity binding ACE inhibitor ramipril, exhibited a reduction in left ventricular mass, even when the drug was used in doses too low to reduce blood pressure. These findings were attributed to a direct inhibition of cardiac tissue ACE, resulting in blockade of the angiotensin II-mediated myocyte hypertrophy. Both circulating and locally (cardiac) produced angiotensin II appear to affect cardiac growth, although the precise contributions of these two sources of angiotensin II are not yet entirely clear. Proof for the direct involvement of angiotensin II in the development of cardiac hypertrophy is strengthened by recent experimental studies in spontaneously hypertensive rats with marked cardiac hypertrophy in which both renin and angiotensinogen mRNA are increased in the myocardium compared with that in normotensive rats.<sup>50</sup> Similarly, angiotensinogen gene expression is also transiently increased in the hypertrophied region of the left ventricular myocardium after coronary occlusion.<sup>51,52</sup> Therefore, angiotensin II contributes to an increase in left ventricular mass by directly promoting myocyte growth as well as by stimulating vascular smooth muscle cell growth and proliferation (see below). Aldosterone may also contribute to an increase in left ventricular mass<sup>53,54</sup> by increasing myocardial collagen content.<sup>54</sup> The combined effect of activation of the renin-angiotensin-aldosterone system is therefore an increase in left ventricular mass related to cardiac myocyte hypertrophy, increase in the mass of the extracellular collagen matrix, and hypertrophy of vessel walls. Production of both angiotensin II and aldosterone is inhibited by ACE inhibitors, resulting in reductions in left ventricular mass.

While extensive and consistent evidence is available showing the efficacy of ACE inhibitors in reducing left ventricular mass in humans, a clear reduction in cardiovascular events associated with this effect is not yet clearly established. Early findings regarding the mechanisms involved in ACE inhibitor-mediated reduction in left ventricular mass are based largely on experimental work in animal models and cell cultures and require further confirmation including assessment of how relevant they are in human subjects, since the distribution of ACE in cardiac tissue and vascular wall is known to be subject to great interspecies variability.

### Neurohormonal Effects

Angiotensin II activates both the central and the peripheral sympathetic nervous systems.<sup>55-59</sup> It is an important regulator of noradrenaline release from sympathetic nerve terminals by its action on prejunctional receptors, and it may therefore modulate local cardiac and vascular sympathetic activity.<sup>60,61</sup> Inhibition of this effect of angiotensin II could also potentially account for a reduction in cardiovascular ischemic events. Caution is suggested in the interpretation of the results of these experimental studies, since the importance of this mechanism in humans is not entirely clear. Data in

humans are conflicting: one recent small study by Goldsmith et al<sup>62</sup> suggests that in patients with compensated congestive heart failure, ACE inhibitor therapy might not significantly affect plasma noradrenaline or systemic venous norepinephrine spillover, whereas data from the Studies of Left Ventricular Dysfunction (SOLVD) indicate a significant drop in plasma norepinephrine that is most marked in patients with initially greater elevations of plasma norepinephrine.<sup>63</sup> Similarly, Gilbert and coworkers<sup>64</sup> found that lisinopril lowered cardiac adrenergic drive and increased  $\beta$ -receptor density in subjects with heart failure with increased cardiac adrenergic drive, suggesting that cardiac antiadrenergic properties contribute to the efficacy of ACE inhibitors in subjects with heart failure. The importance of the antiadrenergic properties of ACE inhibitors in humans in the absence of heart failure is even less clear.

### Other Effects

Other potential cardioprotective actions of ACE inhibitors in acute ischemia are suggested primarily by experimental studies in animals and include a reduction in infarct size in some but not all studies,<sup>65-72</sup> a beneficial effect on reperfusion injury including improvement of contractility of the stunned myocardium,<sup>65,70,71</sup> reduction in reperfusion arrhythmias and the potential to reduce other ventricular arrhythmias,<sup>73-75</sup> and possibly (still controversial) beneficial effects related to an antioxidant (free scavenger) action.<sup>76,77</sup> These effects have been studied primarily in experimental animal preparations. Their importance in acute ischemic syndromes in human subjects remains unclear.

The vascular protective effects (Table 1) of ACE inhibitors have recently received considerable attention and can be summarized as follows.

### Direct "Antiatherogenic" Effect

A direct "antiatherogenic" action of these drugs has been shown in several animal models of atherosclerosis related to cholesterol-mediated endothelial injury<sup>78-81</sup> and in models of accelerated atherosclerosis after mechanical endothelial damage (balloon endothelial injury)<sup>82,83</sup> or immune mechanism-mediated endothelial damage (allograft vasculopathy).<sup>84</sup> The direct "antiatherogenic" action of ACE inhibitors observed in these experiments is related to complex effects mediated by these agents, including an antiproliferative and antimitogenic action, beneficial effects on endothelial function, possible plaque-stabilizing effects, antithrombotic effects, the action of these agents on the sympathetic nervous system, and possible antioxidant properties.

Chobanian and coworkers<sup>78,79</sup> studied the effects of captopril in the normotensive Watanabe heritable hyperlipidemic (WHHL) rabbit, an experimental model in which other blood pressure-lowering drugs such as propranolol, nifedipine, and verapamil failed to inhibit the development of atherosclerotic lesions. Captopril reduced the total aortic intimal surface covered with atherosclerotic lesions and decreased the cellularity and cholesterol content of atherosclerotic plaques and increased their extracellular matrix. It appears, therefore, that in addition to a reduction in the anatomic extent of atherosclerotic lesions, captopril had potentially stabilizing effects on the atherosclerotic lesions, which may be associated with less propensity to rupture. Similar

results were reported by Aberg and Ferrier<sup>80</sup> in the cholesterol-fed cynomolgus monkey model of atherosclerosis. Rolland and coworkers<sup>81</sup> demonstrated a reduction in the atherosclerotic lesion size, a decrease in the lipid-laden macrophages, and less fragmentation of the arterial elastic tissue in the Pitman-Moore minipig treated with the ACE inhibitor perindopril and receiving a high-fat diet. The atherosclerotic lesions that developed in perindopril-treated animals appeared more "stable" (less prone to rupture) and had improved viscoelastic properties, favoring improved arterial flow.

While these experiments are important and suggest potential benefits for the use of ACE inhibitors in ischemic cardiovascular diseases beyond their hemodynamic effects, these findings should be interpreted cautiously. The plaques produced in animals receiving high-cholesterol or high-fat diets are likely to differ from those observed in human atherosclerosis. The clinical impact of the potential to stabilize the plaque remains unclear, and direct proof that ACE inhibitors can retard the progression of atherosclerosis in humans is not available.

Powell and coworkers<sup>82</sup> demonstrated that administration of the ACE inhibitor cilazapril prevented myointimal proliferation and preserved lumen integrity in carotid arteries of normotensive rats after endothelial denudation by balloon injury. Similar effects have also been reported in the atherosclerotic rabbit iliac model.<sup>83</sup> Increases in the messenger RNA for ACE and angiotensinogen have been demonstrated in the proliferating tissue of balloon-injured vessels in rats.<sup>85</sup> However, important interspecies differences exist in the distribution of ACE in the arterial wall, and some investigators reported no benefit or only modest effects associated with the use of ACE inhibitors in other animal models of restenosis.<sup>86-88</sup> Furthermore, in two recent clinical trials, cilazapril had no effect on the incidence of restenosis after balloon angioplasty in humans.<sup>89,90</sup> Differences in the timing and dosage of cilazapril in these trials compared with the studies in the rat model reported by Powell et al could be important, and further studies appear warranted.

### Antiproliferative and Antimigratory Effects

Data from both in vitro and in vivo studies<sup>91-97</sup> show that angiotensin II can produce vascular smooth muscle cell growth and proliferation, a mechanism important in the genesis and progression of atherosclerotic lesions. In animal models, angiotensin II acts by the induction of proto-oncogenes *c-fos*,<sup>98-100</sup> *c-myc*,<sup>97,101</sup> and *c-jun*.<sup>102,103</sup> and induces the expression of several growth factor genes, such as the genes encoding for the  $\alpha$ -chain of platelet-derived growth factor, transforming growth factor- $\beta$ , and thrombospondin.<sup>97,104-106</sup> Early activation of these proto-oncogenes followed by sequential activation of growth factor genes (and possibly other genes involved in cell growth) ultimately result in vascular smooth muscle cell growth. In addition to the trophic effect on vascular smooth muscle cells, angiotensin II has been shown to release an endothelial neutrophil chemoattractant (which is as yet unidentified), leading to neutrophil accumulation.<sup>107</sup> Recent experiments in spontaneously hypertensive rats demonstrated decreased subendothelial accumulation of mononuclear macrophages after treatment with cilazapril.<sup>108,109</sup> These



cells are all involved in the development of atherosclerotic lesions, and by decreasing their migration, ACE inhibitors could prevent lesion formation.<sup>110</sup> In contrast to these antiproliferative and antimigratory effects, an enhancement of endothelial cell migration has been demonstrated with ACE inhibitors and decreases in angiotensin II that may contribute to improved endothelial function and might therefore exert an antiatherosclerotic action.<sup>111</sup>

### Improvement and/or Restoration of Endothelial Function

ACE inhibitors have been shown to improve or restore endothelial function in different animal models such as the spontaneously hypertensive rat,<sup>109</sup> the hypercholesterolemic rabbit,<sup>112</sup> in other normotensive animals,<sup>113</sup> and in experimental heart failure models.<sup>114</sup> This effect of ACE inhibitors appears to be mediated primarily by bradykinin accumulation. Since ACE is identical to the kininase II of the kallikrein-kinin system that inactivates bradykinin,<sup>115</sup> it leads to the accumulation of kinins (potentiation of bradykinin effects). Bradykinin has a direct vasodilator effect and acts also by release of the potent arteriolar dilator nitric oxide (NO or endothelium-derived relaxing factor [EDRF]) and prostacyclin (PGI<sub>2</sub>) from endothelial cells (complex interactions with the prostaglandin system). EDRF is a potent coronary vasodilator and has other beneficial effects on endothelial function and integrity: it inhibits platelet adhesion and aggregation, smooth muscle cell mitogenesis, and proliferation and could thereby play an important role in preventing the development of proliferative atherosclerotic lesions in response to vascular injury.<sup>116</sup> Bradykinin may also cause vasodilatation by interfering with eicosanoid metabolism and by increasing synthesis of a vasodilator prostanoid.<sup>117</sup> Improved endothelial function and vascular reactivity could also be mediated by inhibition of the angiotensin II stimulation of endothelial production of endothelin.<sup>118</sup>

Aldosterone may also be implicated in endothelial dysfunction, as evidenced by studies in patients with primary aldosteronism and correction of the endothelial function abnormalities after removal of the aldosterone-producing tumor.<sup>119</sup> The relevance of these observations to other patients is unclear, since aldosterone levels are considerably increased in the presence of aldosterone-producing tumors and similar levels of aldosterone increase have generally not been measured in patients after myocardial infarction, heart failure, and other ischemic syndromes.

### Protection From Plaque Rupture

ACE inhibitors may also play a role in reducing the propensity for plaque rupture by several mechanisms. We discussed earlier the morphological changes in plaques associated with the use of ACE inhibitors in animal models of atherosclerosis and how these changes could potentially contribute to "plaque stabilization." Other mechanisms of preventing plaque rupture may be mediated through direct inhibition of angiotensin II-mediated vasoconstriction, effects on endothelin or on serum and tissue magnesium: Angiotensin II stimulates release of endothelin. Endothelin is one of the most potent coronary vasoconstrictors, and its local release might, in the presence of a susceptible atherosclerotic

lesion, accelerate plaque rupture.<sup>118,120</sup> Inhibition of angiotensin II could potentially block this effect. Hypomagnesemia has been shown to cause an increase in coronary vascular reactivity<sup>121</sup> and could potentially accelerate plaque rupture. Individuals living in areas with low magnesium levels have been shown to have a high incidence of myocardial infarction, and experimental hypomagnesemia has led to coronary artery spasm.<sup>122</sup> ACE inhibitors increase serum and tissue magnesium and could therefore have beneficial effects.

Definitive proof that ACE inhibitors provide protection from plaque rupture is not yet available.

### Antithrombotic Effects

Recent evidence suggests that ACE inhibitors can also affect arterial thrombosis by effects on platelets and on the endogenous fibrinolytic system. Several investigators<sup>123,124</sup> have demonstrated that captopril inhibits platelet aggregation. This reduces the release of vasoconstrictors (such as thromboxane A<sub>2</sub>) from platelets and of stimulators of smooth muscle cell proliferation (such as platelet-derived growth factor). It has been demonstrated that human platelets possess angiotensin II receptors. The action of ACE inhibitors on the platelets could be related to angiotensin II blockade. Platelet aggregation may also be suppressed through increased prostacyclin and EDRF, induced by elevated bradykinin levels, as well as by an increase in serum magnesium.

In vitro studies have demonstrated that angiotensin II selectively induces the production and secretion of plasminogen activator inhibitor-1 (PAI-1) in endothelial cells<sup>125</sup> and in cultured astrocytes.<sup>126</sup> PAI-1 is the most important physiological inhibitor of tissue-type plasminogen activator (TPA) in plasma,<sup>127</sup> and elevated levels have been implicated in the pathogenesis of thromboembolic disease.<sup>128</sup> A recent small investigation in human subjects demonstrated a rapid and significant increase in PAI-1 after the infusion of angiotensin II.<sup>129</sup> This effect appeared to be dose related and occurred in both normotensive and hypertensive subjects. These findings suggest that angiotensin II may be prothrombotic at least in part by increasing plasma levels of PAI-1, thereby reducing the activity of the fibrinolytic system. An important action of ACE inhibitors may be to improve endogenous fibrinolytic function among patients at high risk for ischemic events. These early observations, which are derived from a small number of individuals tested, require further confirmation in larger studies and suggest a potentially important link between the renin-angiotensin system and risk for thrombosis.

### Antihypertensive Effects

The antihypertensive action of ACE inhibitors by itself is likely to contribute to their ability to reduce coronary heart disease and strokes. The link between hypertension and atherosclerosis is well established.<sup>130</sup> Epidemiological studies demonstrate that elevations in blood pressure levels are associated with increased risk of coronary artery disease and that this risk is "continuous," even within ranges considered to be "normotensive."<sup>131</sup> Antihypertensive therapy has been shown to reduce the anatomic extent of atherosclerosis,<sup>130</sup> the risk of stroke, and to a lesser extent, the risk of coronary heart disease.<sup>132</sup> ACE inhibitors are effective blood

pressure-lowering agents<sup>1-3</sup> and have no adverse metabolic effects on lipids and blood glucose levels.<sup>133-137</sup> Therefore, it is theoretically possible that ACE inhibitors could reduce the risk of coronary heart disease to a greater extent than that seen with moderate to high doses of diuretics (which have been extensively evaluated) because of the lack of adverse metabolic effects and their special "antiatherosclerotic" properties. This hypothesis remains unproven, however, and is currently being evaluated in large randomized trials. The results of the SOLVD and of the Survival and Ventricular Enlargement Trial (SAVE) (see below), as well as the antiatherogenic effect of ACE inhibitors in the normotensive animal models of atherosclerosis, however, suggest that a reduction in major ischemic events may be expected to occur with ACE inhibitor therapy and that the magnitude of benefit may be larger than that expected purely from a blood pressure-lowering effect. Therefore, it is likely that other mechanisms of action may also be relevant.

### **Epidemiological and Genetic Studies: Link Between the Renin-Angiotensin System and the Risk for Myocardial Infarction**

Several epidemiological studies have examined the relation between plasma renin levels in hypertensive patients and the risk for ischemic events. Early studies reported conflicting results,<sup>138,139</sup> and conclusions from these investigations are limited by methodological shortcomings, such as selection bias, retrospective analysis, and differences in the laboratory assays used for measuring plasma renin activity. The best epidemiological evidence for an association between plasma renin levels and the risk for subsequent myocardial infarction is provided by a recent prospective cohort study, in which Alderman and coworkers<sup>140</sup> report findings in 1717 subjects with mild and moderate hypertension followed for a mean of 8.3 years. The risk of myocardial infarction was increased 5.3-fold among subjects with high versus those with low renin profiles (95% CI, 3.4 to 8.3), and this effect was independent of other established cardiovascular risk factors, such as age, sex, race, smoking status, cholesterol and glucose levels, and systolic and diastolic blood pressure levels. This association between elevated renin levels and myocardial infarction may be causal or secondary to preexisting underlying cardiovascular disease resulting in an activated renin-angiotensin system.<sup>141</sup> Moreover, it is not clear whether these observations are generalizable to individuals without high blood pressure. A recent prospective study by Meade et al<sup>142</sup> failed to demonstrate an independent association between plasma renin levels and the risk for myocardial infarction in normotensive individuals. This study does not necessarily contradict the findings by Alderman et al, since among men whose systolic blood pressures were in the highest third of the distribution, there may have been an association between plasma renin activity and subsequent coronary events.

Cambien and coworkers<sup>143</sup> have recently reported that the ACE-DD genotype, which identifies individuals with higher levels of circulating ACE, was more prevalent in middle-aged men with previous myocardial infarction ( $n=610$ ) than in a case-matched control group

( $n=733$ ;  $P=.007$ ), raising the interesting possibility of ACE as a genetic predictor of coronary disease and its sequelae. The ACE-DD genotype appeared to be an independent risk factor for myocardial infarction after adjustment for the presence of other known coronary risk factors such as smoking, dyslipidemia, and hypertension. It is of particular interest that, although for the entire study population the ACE-DD genotype was associated with only a modest increase in the risk for myocardial infarction (odds ratio of 1.34), in a subgroup analysis of patients without other risk factors, the risk of myocardial infarction was increased more markedly (odds ratio of 3.2). Therefore, it appears that patients who are homozygous for the deletion polymorphism represent a group at considerably increased risk for myocardial infarction, even in the absence of other risk factors. While this observation awaits further confirmation, it may provide us with clues as to why certain individuals with no or very few conventional risk factors for coronary artery disease develop myocardial infarction. It also supports a role for the renin-angiotensin system in the pathogenesis of coronary artery disease and its complications. The same group of investigators also demonstrated an excess of both ACE-DD (odds ratio, 2.6;  $P=.02$ ) and ACE-ID (odds ratio, 1.9;  $P=.08$ ) genotypes among individuals with a parental history of myocardial infarction compared with age-matched controls.<sup>144</sup>

The ACE-DD genotype has also been associated with hypertrophic cardiomyopathy and with sudden death in families with this disease,<sup>145</sup> and a recent study showed an increased frequency of this genotype in patients undergoing cardiac transplantation for ischemic or idiopathic dilated cardiomyopathy.<sup>146</sup>

These studies suggest a link between activation of the renin-angiotensin system and increased cardiac hypertrophy, vascular hypertrophy, and atheroma development and rupture. Consequently, ACE inhibitors could potentially reduce myocardial ischemic events.

### **Evidence From Randomized Clinical Trials**

The role of ACE inhibitors in preventing the clinical sequelae of atherosclerotic cardiac disease has been evaluated in various patient populations: those with reduced left ventricular ejection fraction, with and without recent myocardial infarction, in the acute phase of myocardial infarction, after coronary angioplasty, and with chronic stable angina.

### **Long-term Trials in Patients With Heart Failure and Low Ejection Fraction**

Three recent large randomized trials in patients with low left ventricular ejection fraction followed over a period of >3 years reported significant reductions in myocardial infarction with the use of ACE inhibitors: The SOLVD trials included patients with left ventricular ejection fraction of  $\leq 0.35$ . Patients with congestive heart failure entered the Treatment Trial,<sup>5</sup> and those without overt heart failure and receiving no therapy for heart failure entered the Prevention Trial.<sup>6</sup> Patients in both trials had not sustained a recent myocardial infarction in the month before enrollment, nor did they have unstable angina or any clear indications for revascularization at study entry. The SAVE trial<sup>7</sup> enrolled patients within 3 to 16 days after myocardial infarction

**TABLE 2. Characteristics of Large Randomized Studies of Angiotensin-Converting Enzyme Inhibitors in Patients With Low Ejection Fractions**

	SOLVD Treatment Trial	SOLVD Prevention Trial	SAVE	AIRE
Sample size	2569	4228	2231	2006
Design	Prospective double-blind	Prospective double-blind	Prospective double-blind	Prospective double-blind
ACE inhibitor used	Enalapril	Enalapril	Captopril	Ramipril
Patient population*				
Mean age, y	60.8	59.1	59.4	64.9
Sex ratio, M/F, %	80.4/19.6	88.6/11.4	82.5/17.5	74/26
Recent MI	No	No	Yes	Yes
Mean LVEF, %	25	28	31	Not available
LVEF inclusion threshold, %	<35	<35	<40	Not available
Symptomatic heart failure	Yes	No	No	Yes
Ischemic heart disease, %	71.1	83.2	100	100
Duration of follow-up, mo	41.4	37.4	42	15

SOLVD indicates Studies of Left Ventricular Dysfunction; SAVE, Study of Survival and Ventricular Enlargement; AIRE, The Acute Infarction Ramipril Efficacy Study; ACE, angiotensin-converting enzyme; MI, myocardial infarction; and LVEF, left ventricular ejection fraction.

\*All relevant clinical patient characteristics were similar in the placebo and treatment groups.

with left ventricular ejection fraction of  $\leq 0.40$  who were asymptomatic or had only mild heart failure. Patients underwent revascularization procedures before study entry if they had objective evidence of ischemia. In all these three trials, mean duration of treatment was close to or exceeding 40 months. The prolonged duration of treatment is probably essential for the anti-ischemic action of ACE inhibitors to become manifest. Key study characteristics of these trials (and of the Acute Infarc-

tion Ramipril Efficacy [AIRE] Study<sup>147</sup> [see below]) are summarized in Table 2. The main end points in the SOLVD and SAVE trials was mortality. Development of myocardial infarction was a predefined secondary end point in these studies, and data on myocardial infarction were therefore prospectively and systematically collected. A significant risk reduction (RR) in the incidence of myocardial infarction was observed in each of these three long-term trials, and all were of similar

**TABLE 3. Effect of ACE Inhibitors on Myocardial Infarction and on Unstable Angina in Patients With Low Ejection Fraction**

Trial	MI Incidence, No. (%)		Risk Reduction, % (95% CI)	P	Unstable Angina, No. (%)		Risk Reduction, No. (%) (95% CI)	P
	ACE-I	Placebo			ACE-I	Placebo		
SOLVD* Treatment Trial	127 (9.9)	158 (12.3)	23 (2, 39)	.02	187 (14.6)	240 (18.7)	27 (12, 40)	.001
SOLVD* Prevention Trial	161 (7.6)	204 (9.1)	24 (6, 38)	.01	312 (14.8)	355 (16.8)	14 (0, 26)	.05
SAVE†	133 (11.9)	170 (15.2)	25 (5, 40)	.015	135 (12.1)	133 (11.9)	0 (-26, 22)	.93
AIRE‡	81 (8.0)	88 (8.9)	11 (-22, 35)	NS	Not available	Not available	Not available	...
Combined Trials§ (N=11,034)	502 (9.1)	620 (11.3)	21 (11, 30)	<.002	634 (14.1)	720 (15.9)	15 (4, 24)	<.003

ACE indicates angiotensin-converting enzyme; MI, myocardial infarction; and ACE-I, ACE inhibitor.

\*Clinical diagnosis by treating physician of MI confirmed in 94% of patients as having two or three documented classic criteria of characteristic chest pain, typical electrocardiographic changes, and typical enzyme changes or fatal MI documented on death certificates. Unstable angina was defined as new-onset or worsening angina pectoris requiring hospital admission.

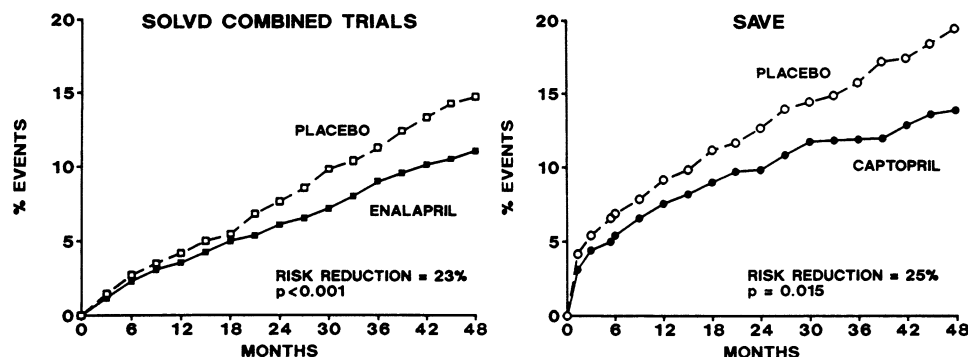
†According to the original protocol criteria (clinically defined MI with predefined typical changes in creatine kinase levels or fatal MI validated by the Mortality Classification Committee), there were 129 cases of recurrent MI in the placebo vs 108 cases in the captopril group. This difference, although it did not reach statistical significance (risk reduction, 19%; 95% CI, -4% to 37%;  $P=.102$ ), is similar to the results summarized in the table using clinical criteria for recurrent MI by clinic physicians.

‡Classical clinical criteria were used for defining recurrent MI. All cases presented in the final analysis were validated by a subcommittee of the International Steering Committee.

§Derived from odds ratio calculated by the Mantel-Haenszel method.

¶When the results of the SOLVD and SAVE trials only were combined (trials of long-term ACE-I therapy), the risk reduction in MI rates was 23% (95% CI, 12% to 33%);  $P<.001$ .





Graphs showing cumulative incidence of myocardial infarction in the combined Studies of Left Ventricular Dysfunction (SOLVD) and incidence of recurrent myocardial infarction in the Survival and Ventricular Enlargement Trial (SAVE). In both studies, differences in the incidence of myocardial infarction between ACE inhibitor- and placebo-treated patients started to become apparent after 6 months of therapy and continued to widen thereafter. (Adapted with permission from *The Lancet* and *The New England Journal of Medicine*.)

magnitude (Table 3). For the combined SOLVD and SAVE trials, a highly significant reduction in the risk for myocardial infarction is calculated (Table 3; results of the trials are combined by the Mantel-Haenszel procedure<sup>148</sup>). There were 421 cases of myocardial infarction in the ACE inhibitor-treated patients versus 532 cases of acute myocardial infarction in patients randomized to placebo (RR, 23%; 95% CI, 12% to 33%;  $P < .001$ ). Furthermore, hospitalizations for unstable angina pectoris were significantly reduced in the SOLVD trials (Table 3). There were 187 hospitalizations for unstable angina in enalapril-treated patients in the SOLVD Treatment Trial versus 240 in patients allocated to placebo (RR, 27%; 95% CI, 12 to 40%;  $P = .001$ ). In the Prevention Trial, there were 312 hospitalizations for unstable angina in the enalapril-treated patients versus 355 in patients allocated to placebo (RR, 14%; 95% CI, 0 to 26%;  $P = .05$ ). Overall, combining both arms of the SOLVD trials, 499 (14.7%) patients in the enalapril group were hospitalized for unstable angina compared with 595 (17.5%) in the enalapril group (RR, 20%; 95% CI, 9 to 29%;  $P = .001$ ). In the SAVE trial, the number of hospitalizations was similar in the captopril group: 135 of 1115 patients (12.1%) and in the placebo group: 133 of 1116 patients (11.9%).<sup>149</sup> Combining the results of the SOLVD and the SAVE trials, the risk for hospitalization for unstable angina was reduced significantly in patients treated with ACE inhibitors (RR, 15%; 95% CI, 4, 24;  $P < .003$ ). There was also a 24% risk reduction ( $P < .001$ ) in the need for revascularization procedures (coronary artery bypass surgery [CABG] or percutaneous transluminal coronary angioplasty [PTCA]) in patients treated with captopril in the SAVE trial.<sup>149</sup>

The consistency of the impact of enalapril was examined in a number of subgroups in SOLVD.<sup>150</sup> Reductions in major acute ischemic events were observed in the SOLVD trials among various subgroups defined by age, sex, degree of left ventricular dysfunction (different left ventricular ejection fractions), pathogenesis of left ventricular dysfunction (ischemic versus nonischemic), with and without a history of diabetes, and against a background of different drugs ( $\beta$ -blockers, aspirin, calcium channel blockers). Furthermore, reductions in ischemic events were observed both among patients with overt congestive heart failure, who probably had elevations in plasma renin levels, and in patients without heart failure, who presumably did not have elevated

plasma renin levels in the absence of diuretic therapy.<sup>151</sup> In addition, the observed reduction in ischemic events cannot be explained by the hypotensive actions of ACE inhibitors alone, since the magnitude of risk reduction was substantially larger than that expected from short-term, modest reductions in blood pressure. In a recent meta-analysis of 14 randomized clinical trials of antihypertensive therapy, diastolic blood pressure reductions of 5 to 6 mm Hg for about 4 to 5 years resulted in a 14% reduction in fatal and nonfatal coronary heart disease events.<sup>132</sup> In the combined SOLVD trials, diastolic blood pressure was reduced by an average of 4 mm Hg, and this was associated with a 23% reduction in fatal or nonfatal myocardial infarctions and a 21% reduction in cardiac deaths. Moreover, the risk reductions in ischemic events were similar in patients with different levels of systolic and diastolic blood pressure at baseline. There was a trend toward larger reductions in myocardial infarction and unstable angina among those with a greater reduction in blood pressures; however, these differences did not reach statistical significance. These considerations suggest that the reduction in major ischemic events observed with ACE inhibitor therapy is at least in part due to mechanisms unrelated to the hypotensive effects of these agents.

Analysis of the time course of this observed reduction in ischemic end points may also provide insights into potential mechanisms of action of ACE inhibitors. Both arms of the SOLVD trials, as well as the SAVE trial, found little difference in the incidence of myocardial infarction during the first 6 months after randomization (Figure). Differences were apparent after 6 months of treatment and continued to widen thereafter. A very similar time course of events was noted in the SOLVD trials for hospitalizations for unstable angina. This delay in the reduction of ischemic events resembles the "lag" observed in trials of cholesterol lowering and suggests that the mechanism for this observed anti-ischemic action of ACE inhibitors is unlikely to be related solely to the beneficial hemodynamic effect of the drug, which is observed immediately and which is not expected to increase with time. These observations suggest that ACE inhibitors decrease the incidence of ischemic events, which may be related to multiple mechanisms, including the prevention of the progression of coronary atherosclerosis and/or stabilization of atherosclerotic plaques. Although hemodynamic changes alone are

unlikely to explain the anti-ischemic action of ACE inhibitors, it is possible that the continued reduction in myocardial oxygen consumption related to the effects of these drugs on afterload, preload, left ventricular geometry, and ventricular mass, possibly in conjunction with direct vascular protective effects, leads to reductions in myocardial infarction and unstable angina.

The recent AIRE study<sup>147</sup> randomized 2006 patients within 3 to 10 days after acute myocardial infarction who exhibited transient or persistent symptoms or signs of heart failure to treatment with the ACE inhibitor ramipril or to placebo. Patients were followed for an average of 15 months (minimum duration of follow-up was 6 months). A highly significant and substantial reduction in all-cause mortality, the primary study end point, was demonstrated (RR, 27%; 95% CI, 11% to 40%;  $P=.002$ ), and this benefit was apparent earlier and reached statistical significance after a much shorter duration of follow-up than in the SAVE trial. Reinfarction rates were recorded prospectively. While a trend toward fewer acute myocardial infarcts was noted in patients treated with ramipril, this was not statistically significant: there were 81 recurrent infarcts (8%) in ramipril-treated patients versus 88 (9%) in patients allocated to placebo. These results do not necessarily contradict the results of the SOLVD and SAVE trials. The number of validated recurrent myocardial infarcts in the AIRE study was relatively small, largely due to the much shorter average follow-up period. The favorable trends observed are consistent with the observations made after a similar duration of follow-up in the SOLVD and SAVE trials. Even though the duration of treatment and follow-up in the AIRE study is relatively short, if these results are combined with the SOLVD and SAVE trials, the reduction in myocardial infarction risk still remains highly significant (Table 3).

Other randomized clinical trials in patients with reduced left ventricular ejection fraction contribute only little information regarding the effects of ACE inhibitors on ischemic events because of the small number of patients randomized and the short duration of follow-up. The Collaborative Group on ACE Inhibitor Trials reported a summary of 35 clinical trials of ACE inhibitors in patients with chronic heart failure and/or left ventricular dysfunction (R. Garg, S. Yusuf, personal communication). Trials other than the SOLVD trials were small and of short duration (generally only for 3 to 6 months). Overall, a significant reduction in the incidence of myocardial infarction was noted, but most end points were derived from the SOLVD trials (RR, 19%; 95% CI, 0% to 35%). In trials other than SOLVD, 2023 patients were randomized to receive an ACE inhibitor and 1568 to the control group. There were 26 myocardial infarcts in the ACE inhibitor-treated group (1.3%) versus 24 in the control group (1.5%). The evidence provided by the SOLVD and SAVE trials suggests the intriguing possibility that the reduction in ischemic events may occur in a broader group of high-risk patients such as those with preserved left ventricular ejection fraction. However, such patients may not have significant increases in the systemic levels of renin<sup>152</sup> and angiotensin, although activation of the local tissue angiotensin system may occur in response to atherosclerotic vascular injury. It is important, therefore, to

provide direct proof of potential benefits of ACE inhibitors in such patients.

### Trials in Acute Myocardial Infarction

The CONSENSUS II trial<sup>153</sup> randomized 6090 patients with acute myocardial infarction presenting within 24 hours of onset of symptoms to treatment with enalapril intravenously followed by oral therapy administered for 6 months versus placebo. No benefit was noted with regard to mortality (6-month mortality was 10.2% in the placebo and 11.0% in the enalapril group) or reinfarction (6-month reinfarction rates were 9% [total number 268] in the placebo and 9% [total number 271] in the enalapril group). These results do not necessarily contradict the observations from the SOLVD and SAVE trials, which did not observe differences in ischemic events until after about 6 months of treatment.

The value of ACE inhibitors initiated early in the setting of acute myocardial infarction (within 24 hours of onset of symptoms) was more recently evaluated in three very large trials: the fourth International Study of Infarct Survival (ISIS-4),<sup>154</sup> the third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3),<sup>155</sup> and the Chinese Captopril Trial.<sup>156</sup> Preliminary results of the mortality data from these trials were recently presented. The ISIS-4 investigators reported that 2062 of 29 022 patients (7.1%) treated with captopril within 24 hours of the onset of symptoms died within 35 days of sustaining an acute myocardial infarction versus 2213 of 29 021 patients (7.6%) allocated to placebo (absolute risk reduction,  $5.2 \pm 2.2$  per 1000;  $P<.02$ ). This benefit appeared to widen with time and was estimated at  $6.5 \pm 2.8$  after 6 months of follow-up. In the GISSI-3 trial, after 42 days of follow-up there were 597 deaths in 9435 patients (6.3%) treated with lisinopril compared with 673 deaths in 9460 patients randomized to placebo (7.1%) ( $P=.03$ ). Although the benefits observed with the early use of ACE inhibitors in these very large clinical trials were small, it is important to emphasize that the reduction in mortality occurred in the presence of other interventions proven to improve the early outcome of these patients, such as thrombolytic therapy and  $\beta$ -blockers; the eligibility criteria for these studies were wide, and duration of treatment was only a few weeks. The Chinese Captopril Trial is not yet completed, but preliminary results indicate a favorable trend. Table 4 shows the results of these large trials, summarizing data from more than 90 000 patients randomized to ACE inhibitor therapy or placebo in the early phases of acute myocardial infarction. A small but statistically and clinically significant benefit is observed. The benefits, however, appear to be larger (about 10 lives prolonged for every 1000 patients treated) in high-risk patients (eg, those with anterior infarction, previous infarction, or heart failure at entry).

These trials provide convincing evidence for the benefit of treatment with ACE inhibitors early in the course of acute myocardial infarction, which is likely to be due to hemodynamic effects. However, they do not address whether further major ischemic events will be prevented by these drugs because of their short duration of treatment.



**TABLE 4. ACE Inhibitors in Suspected Acute Myocardial Infarction: Short-term Mortality in Large Trials**

Trial	ACE-I	Duration of Follow-up, d	Deaths/No. of Patients on ACE-I (% Deaths)	Deaths/No. of Patients on Placebo (% Deaths)	Odds Ratio (95% CI)	P
ISIS-4*	Captopril	35	2062/29 022 (7.1%)	2213/29 021 (7.6%)	0.93 (0.87, 0.99)	.02
GISSI-3	Lisinopril	42	597/9435 (6.3%)	673/9460 (7.1%)	0.88 (0.79, 0.99)	.03
Chinese Captopril Trial*	Captopril	28	572/6321 (9.0%)	610/6308 (9.7%)	0.93 (0.87, 0.99)	NS
Consensus II	Enalapril	30	219/3044 (7.2%)	192/3046 (6.3%)	1.15 (0.94, 1.41)	NS
Combined Trials		28-42	3450/47 822 (7.2%)	3688/43 503 (8.5%)	0.93 (0.89, 0.98)	.004

ACE indicates angiotensin-converting enzyme; ACE-I, ACE inhibitor. Addition of results of seven smaller trials of ACE-I in acute myocardial infarction (129 deaths/1816 ACE-I-treated vs 138 deaths/1837 placebo-allocated patients) does not significantly change the combined estimate of ACE effect; for all combined trials, odds ratio=0.94 (95% CI, 0.89, 0.99); *P* (two-tailed)=.01.

\*Analysis of the Chinese Captopril Trial and the ISIS-4 Trial are not fully complete, and the numbers in this table are based on preliminary reports.

### Trials After PTCA

ACE inhibitors have the theoretical potential to prevent restenosis after PTCA because of the demonstrated potent antiproliferative action of these drugs on vascular smooth muscle cells and supportive data from animal studies. In the MERCATOR trial,<sup>89</sup> 693 patients were randomized to receive cilazapril or placebo started on the day of angioplasty and continued for 6 months. There was no effect on angiographic restenosis and clinical events at 6 months. Similar results were reported with higher doses of cilazapril in the MARCATOR<sup>90</sup> study. These results contrast with the efficacy of cilazapril in the prevention of restenosis after balloon injury in the rat carotid artery model<sup>82</sup> and the atherosclerotic rabbit iliac artery model.<sup>83</sup> In the animal model, treatment was initiated before PTCA, whereas in the above clinical trials, treatment was initiated after PTCA. It is likely that the very potent and complex wound-healing process after angioplasty may differ in its responsiveness to ACE inhibitors compared with coronary artery disease not affected by invasive interventions. Furthermore, although the relatively short duration of therapy and follow-up of 6 months may have been adequate to evaluate the effects on restenosis, it may have been too short to detect differences in progression of native vessel atherosclerosis. This possibility is supported by the long-term follow-up in the MERCATOR trial, which indicated a trend toward fewer clinical cardiac end points, such as death, myocardial infarction, and coronary revascularization after 12 months of follow-up in cilazapril-treated patients.<sup>157</sup>

### Trials in Stable Angina Pectoris

Several small trials assessing the effects of ACE inhibitors on severity of angina pectoris and/or on myocardial ischemia have reported conflicting results,<sup>158-166</sup> with benefit in some patients and no benefit or even exacerbation of angina in others, indicating that ACE inhibitors do not have consistent antianginal effects in short-term studies. Although reductions in the incidence of myocardial infarction and cardiac death are not expected to become apparent in these small

studies on the basis of sample size alone (limited power), it is also of note that these were again investigations characterized by a short duration of therapy (6 weeks to <6 months) and therefore cannot answer questions related to the long-term efficacy of ACE inhibitor therapy in preventing major acute ischemic events by mechanisms other than acute hemodynamic changes. Sogaard et al<sup>166</sup> evaluated the effects of captopril on spontaneous, ambulatory ST-segment depression and on exercise-induced ST-segment depression in patients with recent myocardial infarction and left ventricular dysfunction. Both ambulatory and exercise-induced ischemia were significantly decreased by treatment with captopril. Statistically significant differences in ambulatory ST-segment depression between captopril- and placebo-treated patients became apparent after 3 months of therapy and continued to widen thereafter, being more pronounced at 6 months, while differences in exercise-induced ischemia occurred only after 6 months of therapy. These results can be explained by a continued improvement in the balance between myocardial oxygen demand and supply related to myocardial remodeling resulting in decreased left ventricular volume, concomitant reduction in both preload and afterload, and increased coronary perfusion and peripheral arterial compliance. The time course of the observed changes also suggests the possibility of other anti-ischemic effects, such as direct effects of ACE inhibition on vascular remodeling, antithrombotic effects, and effects on platelet and fibrinolytic activity.

### Current Ongoing Trials

Several studies are currently under way examining the "anti-ischemic" and "antiproliferative" effects of ACE inhibitors. These studies vary in design (ie, examination of lesion development or progression by angiographic or ultrasound measures or impact on clinical end points) and consequently sample size and duration of follow-up. Key aspects of these trials are summarized in Table 5.

### Conclusions

In summary, there is promising information indicating a potential role for ACE inhibitors in reducing

**TABLE 5. Summary of Major Ongoing Long-term Trials Examining the Effects of ACE Inhibitors on Atherosclerotic Disease Progression or Ischemic Events in Patients Without Heart Failure or Low Ejection Fraction**

Trial	ACE Inhibitor	Primary Outcome	Projected Sample Size	Duration of Treatment	Contact Investigator
HOPE	Ramipril	Composite end point: cardiovascular death, myocardial infarction, and stroke	8000-9000	3.5 years	S. Yusuf T. Montague P. Sleight The Canadian Cardiovascular Collaboration
SECURE	Ramipril	B-mode ultrasound measures of carotid atherosclerosis	700	3.5 years	E. Lonn S. Yusuf
QUIET	Quinapril	A. Quantitative coronary angiographic measures of CAD progression  B. Cardiac ischemic end points*	1775	3 years	B. Pitt
SCAT	Enalapril	Quantitative coronary angiographic measures of CAD progression	468	5 years	K. Teo T. Montague
PART	Ramipril	B-mode ultrasound measures of carotid atherosclerosis	600	4 years	N. Sharpe S. McMahon

ACE indicates angiotensin-converting enzyme; HOPE, Heart Outcomes Prevention Evaluation; SECURE, Study to Evaluate Carotid Ultrasound Changes with Ramipril and Vitamin E; QUIET, The Quinapril Ischemic Event Trial; SCAT, Simvastatin and Enalapril Coronary Atherosclerosis Trial; PART, Prevention of Atherosclerosis with Ramipril Therapy; and CAD, coronary artery disease.

\*Composite end point including cardiovascular death, nonfatal myocardial infarction, coronary revascularization procedures (coronary artery bypass graft surgery, angioplasty, atherectomy), and hospitalization for unstable angina pectoris.

myocardial hypertrophy, vascular hypertrophy, atherosclerosis progression, plaque rupture, and thrombosis after plaque rupture. These effects may be expected to reduce the risk for major cardiovascular ischemic events. This possibility is supported by the results of several large trials in patients with left ventricular dysfunction.

It is presently not clear, however, whether this benefit is limited to patients with reduced left ventricular ejection fraction. Furthermore, mechanisms of action underlying these observed effects are not entirely clear. This potentially important action of ACE inhibitors should be further investigated both by experimental studies to further elucidate the mechanism of action of these drugs and by clinical trials in different populations of patients at high risk for cardiovascular events. If ACE inhibitors can be definitively shown to reduce the risk of major ischemic events, these drugs will be an important intervention in high-risk individuals.

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