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Potential role of angiotensin converting enzyme inhibitors in the treatment of atherosclerosis

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Recent clinical data from the SOLVD (Studies on Left Ventricular Dysfunction) and SAVE (Survival and Ventricular Enlargement) studies have shown a significant reduction in ischaemic events with ACE inhibition. When the results of the two SOLVD and the SAVE trials were combined, the overall risk reduction in myocardial infarction with long-term ACE inhibitor treatment was 23% ($P < 0.001$) and the overall risk reduction for hospitalizations for unstable angina 15%. The time frame of the clinical effects suggests that ACE inhibitors may be working through an antiatherosclerotic mechanism, and genetic, epidemiological and mechanistic data suggest that the renin-angiotensin-aldosterone system may play a role in the atherosclerotic process. Genetic and epidemiological evidence has shown that an activated renin-angiotensin aldosterone system is associated with a higher incidence of myocardial infarction, and mechanistic studies have demonstrated that ACE inhibition can produce antiatherosclerotic effects in animal models. The antiatherosclerotic effects of ACE inhibitors may be mediated at one of several steps in the atherosclerotic pathway: blocking plaque formation, plaque rupture, or thrombus formation.

Introduction

ACE (angiotensin converting enzyme) inhibitors have clinical benefits far broader in scope than originally anticipated. Initially, recognition of angiotensin II's powerful vasoconstrictor activity led to the use of ACE inhibitors as antihypertensive agents. Early clinical studies documented the efficacy of ACE inhibitors in reducing systolic and diastolic blood pressure, even in patients with low renin values[1–3]. Subsequently, ACE inhibitors were shown to produce beneficial effects in patients with heart failure as well. In CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), enalapril reduced mortality and symptoms of heart failure in patients with severe congestive heart failure[4].

The clinical applications of ACE inhibitors were further broadened to include patients with systolic left ventricular dysfunction, with or without overt heart failure. In SOLVD (Studies on Left Ventricular Dysfunction) and SAVE (Survival and Ventricular Enlargement), patients with left ventricular dysfunction also showed a significant reduction in mortality associated with heart failure[5–7], but more intriguing was the significant decrease in ischaemic events observed in these studies among patients receiving ACE inhibitors. In both SOLVD and SAVE, not only was mortality significantly reduced, but ischaemic events, such as myocardial infarction, hospitalizations for unstable angina, and the need for revascularization procedures, were reduced with ACE inhibitor treatment[8,9].

Since the renin-angiotensin-aldosterone system has multiple actions on the cardiovascular system, there are several potential mechanisms by which ACE inhibitors could have produced the reduction in ischaemic events observed in these studies. The clinical data suggest the direct haemodynamic effects of ACE inhibitors alone cannot fully explain the results. The time frame of the clinical effects suggests that ACE inhibitors may be working through antiatherosclerotic or antithrombotic mechanisms. As a result, renewed interest in exploring the complex relationship between the renin-angiotensin-aldosterone system and atherosclerosis has emerged.

The purpose of this article is to review both the clinical and experimental evidence suggesting a link between the renin-angiotensin-aldosterone system and the atherosclerotic process. The data from three recent, large, long-term clinical trials involving over 9000 patients (SOLVD Treatment and Prevention, and SAVE) in which ACE inhibitors significantly reduced ischaemic events such as myocardial infarction will be reviewed. Parallel epidemiological, genetic and experimental studies linking the renin-angiotensin-aldosterone system and the antiatherosclerotic process will also be covered. Although much of the data suggesting that ACE inhibitors may have an antiatherosclerotic effect are preliminary, if confirmed in further clinical trials, ACE inhibitors may have yet another clinical application. Patients without left ventricular dysfunction, who have or are high-risk candidates for coronary artery disease, may also benefit from ACE inhibition. Thus this review may provide a glimpse into the next chapter of clinical applications for ACE inhibitors: their role in the secondary and possibly primary prevention of ischaemic heart disease.

Clinical evidence supporting antiatherosclerotic effect of ACE inhibitors

Three recent, large clinical trials demonstrated that ACE inhibitors reduced mortality in patients with left ventricu-

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lar dysfunction when administered long-term. Moreover, treatment with ACE inhibitors also markedly decreased the risk of coronary ischaemic events including myocardial infarction, hospitalizations for unstable angina, and the need for revascularization procedures.

In the SOLVD studies, patients with moderate left ventricular dysfunction (left ventricular ejection fraction ≤0·35) were treated with enalapril or placebo. Patients with a history of congestive heart failure entered the Treatment Trial[5] and those without overt heart failure entered the Prevention Trial[6]. While most of the patients in the SOLVD trial had a history of previous myocardial infarction, no patients with myocardial infarction within the previous month or with current unstable angina were allowed to participate. In both trials, the average follow-up time exceeded 36 months.

Mortality and hospital admissions for heart failure were significantly reduced in both trials among patients taking enalapril[5,6]. Furthermore, enalapril reduced ischaemia-related events in both trials by 22%[8]. In the SOLVD Treatment Trial, the risk reduction for myocardial infarction with enalapril was 23% ($P = 0·02$), and the risk reduction in hospitalizations for unstable angina with enalapril was 27% ($P = 0·001$). Similar results occurred in the Prevention Trial. A 24% risk reduction in myocardial infarction ($P = 0·01$) and a 14% risk reduction in hospitalizations for unstable angina ($P = 0·05$) were observed. Combining the Treatment and Prevention trials, a 20% risk reduction in hospitalizations for unstable angina was apparent[9].

Interestingly, when subgroups were analysed, the reductions in ischaemic events were observed both among patients with and without overt congestive heart failure, thus in patients presumably with and without elevated serum renin levels[10].

In SAVE, patients with left ventricular dysfunction (left ventricular ejection fraction ≤ 0·40) were randomized to treatment with captopril or placebo 3 to 16 days following myocardial infarction[7]. These patients were asymptomatic or had only mild heart failure, and treatment lasted an average of 42 months. Overall, among patients treated with captopril, there was a significant reduction in mortality, and a significant diminution of major ischaemic events, including the incidence of myocardial infarction and revascularization procedures. The statistics showed a 25% risk reduction in myocardial infarction ($P = 0·015$), and a 24% risk reduction in the need for revascularization procedures.

Table 1 Risk reduction for myocardial infarction

	SOLVD Treatment Trial	SOLVD Prevention Trial	SAVE
Sample size	2569	4228	2231
ACE inhibitor used	Enalapril	Enalapril	Captopril
Duration of follow-up (years)	41.4	37.4	42
Myocardial infarction, risk reduction (%)	23	24	25
Unstable angina, risk reduction (%)	27	14	NA*
Revascularization procedures, risk reduction (%)	NA	NA	24

*Not available.

When the results of the two SOLVD and the SAVE trials were combined[9], the overall risk reduction in myocardial infarction with long-term ACE inhibitor treatment was 23% ($P < 0·001$) and the overall risk reduction for hospitalizations for unstable angina was 15%. Table 1 summarizes the risk reduction for myocardial infarction in the SOLVD and SAVE trials.

The mechanism by which ACE inhibitors produced this reduction in ischaemic events remains uncertain. Since the renin-angiotensin-aldosterone system has a broad scope of activity related to the regulation of the cardiovascular system, there are a number of points at which ACE inhibitors could interfere with the progression of heart failure.

It is difficult to account for these beneficial clinical results based solely on the immediate haemodynamic effects of ACE inhibitors, such as reduced myocardial oxygen demand, preload, or afterload. Benefits associated with immediate haemodynamic effects would be expected to occur immediately. During the first 6 months of the SOLVD trials and the SAVE trial, there was little difference in the incidence of myocardial infarction between treatment groups. The differences between treatment group and

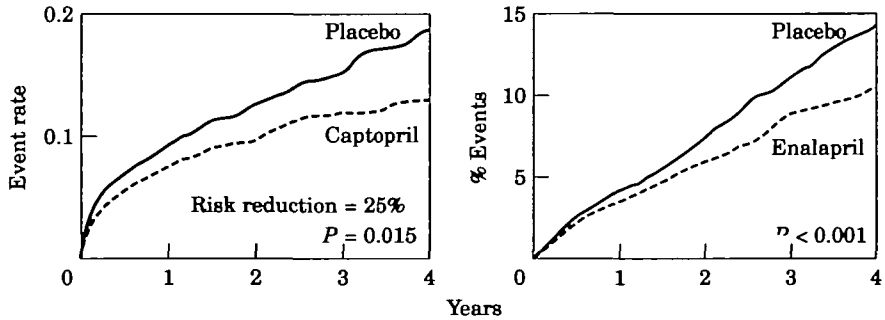

Figure 1 Cumulative incidence of myocardial infarction in the combined Studies of Left Ventricular Dysfunction (SOLVD) and incidence of recurrent myocardial infarction in the Survival and Ventricular Enlargement trial (SAVE). (Adapted with permission from[8] Lancet, 1992 and[7] The New England Journal of Medicine, 327: 673; 1992.)

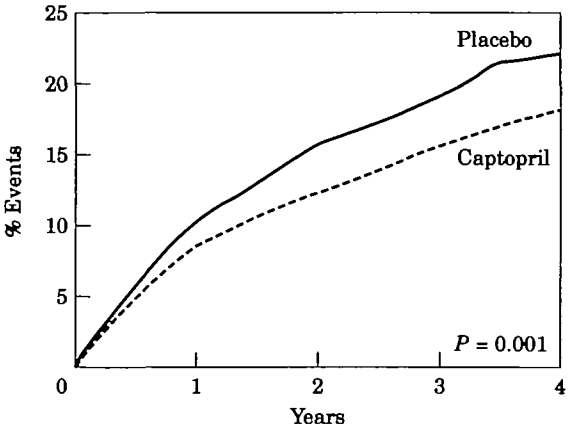

Figure 2 Cumulative incidence of unstable angina in the combined Studies of Left Ventricular Dysfunction (SOLVD). (Adapted with permission from[8] The Lancet, 1992.)

placebo in these studies became apparent only after 6 months and broadened thereafter[8]. Figure 1 depicts the incidence of myocardial infarction over time in the SOLVD and SAVE trials for each treatment group. A similar delay was also observed in SOLVD for the reduction of hospitalizations for angina (Fig. 2). The delay in the reduction of ischaemic events resembled the pattern observed in trials of cholesterol lowering.

In addition, clinical trials have shown that antihypertensive therapies do not appear to provide a similar level of protection. In a recent meta-analysis of 14 randomized clinical trials of antihypertensive therapies, a 5–6 mmHg reduction in diastolic blood pressure was associated with a 14% reduction in coronary heart disease events[11]. However in SOLVD, a reduction in diastolic blood pressure of 4 mmHg yielded a 23% reduction in myocardial infarction, indicating that benefits in addition to blood pressure reduction were most probably involved. Taken together, these clinical results suggest that the beneficial effect of ACE inhibitors may be due to effects over and above direct haemodynamic effects.

The reduction in ischaemic events produced by ACE inhibitors could be due to several mechanisms, including alterations in the remodelling process, anti-adrenergic effects, antiatherosclerotic effects and/or antithrombotic effects. Most likely, several mechanisms are contributing to the clinical results.

In several recent, large studies in acute post myocardial infarction patients (AIRE, ISIS-IV, and GISSI-III), a reduction in reinfarction rates was not observed with ACE inhibitor treatment[12–14], however, all these studies were of relatively short duration. Some previous, small clinical studies have also shown little or no benefit from ACE inhibitors on unstable angina[15,16], however most of these studies were of short duration (6 weeks to 3 months) and therefore would not be expected to exhibit an attenuation of ischaemic events. At least 6 months of treatment was required to demonstrate the positive effects on ischaemic events in SOLVD and SAVE.

Atherosclerosis

Many complex and interrelated processes are involved in the development of atherosclerosis. Build-up of plaque in the coronary arteries leads to coronary artery disease, which may culminate in myocardial infarction, angina, and/or death. Once the clinical signs of ischaemic heart disease, such as myocardial infarction or angina, appear, atherosclerosis is usually well developed and the risk of cardiovascular-associated mortality is greatly increased.

Various risk factors have been identified that are associated with individuals who develop atherosclerosis, and therefore myocardial infarction, compared to the general population. These risk factors include age, sex, genetic traits, cigarette smoking, obesity, hyperlipidaemia, diabetes, and physical inactivity. Hypercholesterolaemia, hypertension, and cigarette smoking may be the most potent risk factors involved in causation of atherosclerosis and are also those that may be reversible[17].

Hypertension is a particularly important risk factor for the development of atherosclerosis. In the Framingham study, the incidence of ischaemic heart disease was more than five times greater in middle-aged men with blood pressures exceeding 160/95 mmHg than normotensive men[17]. Therapeutic reduction of blood pressure clearly reduces the risk of atherosclerosis. In epidemiological studies, a 5 mmHg difference in diastolic pressure was associated with a 21% difference in coronary heart disease events[8]. Similarly, a 5–6 mmHg reduction of diastolic blood pressure with antihypertensive therapy was associated with a 14% reduction in coronary heart disease events[11].

The preponderance of evidence suggests that atherosclerosis arises as a response to injury. The repeated injury to the endothelial cells lining blood vessels caused by hypertension, smoking, or hyperlipidaemia initiates a chain of events resulting in plaque formation. Once the endothelial cells are damaged, the subendothelial tissue is exposed. Platelets adhere, form microthrombi, and release platelet factors, including a potent mitogenic factor. Platelet mitogenic factor initiates the migration and proliferation of smooth muscle cells to the injured site. Circulating monocytes also adhere to the injured site. Over time, a gradual build-up of macrophages, smooth muscle cells, connective tissue, and lipid leads to a thickening of the inner lining of the blood vessels. Blood flow becomes restricted resulting in further injury and eventual ischaemic heart disease.

Experimental evidence supporting antiatherosclerotic effect of ACE inhibitors

The first evidence suggesting that the renin-angiotensin aldosterone system plays a role in atherosclerosis was through epidemiological studies. Early studies examined the interrelationship of renin and hypertension and showed that high renin values predicted myocardial infarction, stroke, and death[8,18,19]. In 1717 patients with mild to moderate hypertension followed for a mean of 8·3 years, the risk of myocardial infarction was increased 5·3 fold among patients with high renin values. Although an association was clear, a cause and effect relationship could not be proven with epidemiological data.

Recent genetic studies have corroborated the epidemiological evidence implicating the renin-angiotensin aldosterone system in the atherosclerotic process. Genetic studies have shown that individuals with the ACE-DD genotype have higher than normal levels of circulating ACE. This genotype was found to be more prevalent in men with a history of myocardial infarction than in a case-matched control group[20], suggesting that activation of the renin-angiotensin-aldosterone system is a new, independent risk factor for myocardial infarction.

Experimental studies in animal models have also provided data linking the renin-angiotensin-aldosterone system with atherosclerosis. In animal models of atherosclerosis, ACE inhibitors have been shown to exert direct antiatherogenic effects. Two experimental models of atherosclerosis have been widely used in studying atherosclerosis, one involves high cholesterol diets and the other employs mechanical damage to the lining of arteries with balloon catheters. In the normotensive hyperlipidaemic rabbit model of atherosclerosis, captopril reduced the extent of atherosclerotic lesions in the aorta[21,22], whereas other blood pressure lowering drugs, such as propranolol, nifedipine, and verapamil had no beneficial effects on plaque formation in this model. A reduction in the size of atherosclerotic lesions was also reported with the use of ACE inhibitors in the cholesterol-fed monkey model[23] of atherosclerosis and the high-fat minipig model[24]. In the experimental model of atherosclerosis involving mechanical injury to the arteries, the ACE inhibitor cilazapril preserved carotid artery integrity after balloon injury in normotensive rats[25]. While evidence in experimental models suggests an antiatherosclerotic effect, two recent clinical trials using cilazapril did not reduce the incidence of restenosis in humans after balloon angioplasty[26,27]. Restenosis is, however, a complex process and may not be directly related to atherosclerosis.

Although evidence is preliminary, several mechanistic studies suggest the involvement of an activated renin-angiotensin-aldosterone system in the atherosclerotic process: angiotensin II, bradykinin, and aldosterone have been shown to be involved in several processes critical to the chain of events culminating in atherosclerosis (Table 2). The renin-angiotensin-aldosterone system is involved in three processes that may affect atherosclerosis: plaque formation, plaque rupture, and thrombosis. These three processes will be reviewed in the following sections.

Table 2 Antiatherosclerotic mechanisms of ACE inhibitors

Plaque formation
Prevent proliferative responses to vascular injury
Preserve endothelial function
Prevent smooth muscle cell mitogenesis
Prevent uptake of lipids into endothelium
Plaque rupture
Plaque stabilization
Decrease cellularity and cholesterol content of plaque
Inhibit vasoconstriction or vasospasm
Thrombus formation
Prevent platelet aggregation
Prevent thrombus formation
Prevent release of PAI
Increase magnesium levels in blood

PAI = plasminogen activator inhibitor.

PLAQUE FORMATION

Once endothelial damage has occurred, angiotensin II can stimulate the migration of neutrophils and macrophages into the vascular wall[28]. Angiotensin II has also been shown to stimulate vascular smooth muscle growth and proliferation. These proliferative and migratory changes occur following induction of certain proto-oncogenes, cytokines, and the expression of several growth factor genes, such as platelet growth factor[9], by angiotensin II. The accumulation of various cells and cell matrix results in arterial wall thickening and eventual plaque formation. Use of ACE inhibitors prevents the proliferative response to vascular injury, effects that have been demonstrated in both in vivo and in vitro experimental studies. In animal studies, subendothelial accumulation of mononuclear macrophages was decreased in spontaneously hypertensive rats treated with cilazapril[9].

ACE inhibitors also affect plaque formation by preserving endothelial function. Patients with coronary atherosclerosis have been found to have evidence of endothelial dysfunction[29,30]. Various animal models of atherosclerosis have also demonstrated endothelial dysfunction[9], characterized by a lack of vasodilation to various endothelial dependent vasodilators. In animals fed an atherosclerotic diet with an ACE inhibitor, endothelial dysfunction was prevented, as shown by a normal response to acetylcholine-induced vasodilation[31]. The effect of ACE inhibitors on endothelial function may be mediated by bradykinin accumulation. Bradykinin causes the release of endothelium-derived relaxing factor and prostacyclin. Endothelium-derived relaxing factor exerts potent effects on endothelial function by inhibiting platelet adhesion and aggregation, smooth muscle cell mitogenesis, and proliferation[9]. Aldosterone may also be implicated in endothelial dysfunction, since patients with primary aldosteronism have endothelial function abnormalities which can be reversed by removing the aldosterone-producing tumour[9].

Plaque formation can also be affected by uptake of lipids. Angiotensin II has also been shown to enhance oxidation and the uptake of lipids into the endothelium[32] and thus ACE inhibitors would prevent oxidation and accumulation of low density lipoprotein-cholesterol (LDL-C) in the endothelium. Aldosterone also appears to be implicated in atherosclerosis. Aldosterone levels are inversely correlated to serum high density lipoprotein cholesterol levels[33]. The effects mentioned above illustrate possible ways the renin-angiotensin-aldosterone system is involved in plaque formation.

PLAQUE RUPTURE

Once plaque is formed, the renin-angiotensin-aldosterone system may contribute to its destabilization. Use of ACE inhibitors in animal models of atherosclerosis has resulted not only in a decrease in the area of plaque, but also a decrease in the cellularity macrophage accumulation cholesterol content, and an increase in the extracellular

matrix of atherosclerotic plaques[21,22]. ACE inhibitors thus have a stabilizing effect on atherosclerotic lesions.

Direct vasoconstriction or spasms of the coronary arteries could also result in plaque rupture. Angiotensin II has direct coronary vasoconstrictor activity and indirect vasoconstrictor activity through its ability to stimulate endothelin and catecholamine release[9]. Endothelin is one of the most potent coronary vasoconstrictors. ACE inhibitors thereby prevent coronary vasoconstriction that could lead to plaque rupture.

THROMBUS FORMATION

Prevention of thrombus formation by ACE inhibitors, in conjunction with the atherosclerotic plaque, may also account for the beneficial effects of these compounds in ischaemic heart disease. Following injury to endothelial cells, platelets adhere to the injured area resulting in vasoconstriction and smooth muscle proliferation. Platelet aggregation has been shown to be inhibited by captopril[34,35].

Angiotensin II may also play a role in thrombus formation following plaque rupture. Angiotensin II has been shown to stimulate the release of plasminogen activator inhibitor (PAI) in both experimental and clinical studies[36,37]. By preventing release of PAI, ACE inhibitors would enhance thrombolysis and prevent thrombus formation. When plaque rupture is accompanied by complete thrombus formation, myocardial infarction may ensue whereas with ACE inhibitors and decreased PAI release, thrombus formation may not be complete, thereby preventing infarction.

Hypomagnesaemia has also been postulated to play a role in atherosclerosis, by increasing platelet aggregation and vasoconstrictor activity. ACE inhibitors have been shown to increase magnesium levels in the blood[9].

In conclusion, clinical data have demonstrated that an activated renin-angiotensin-aldosterone system may have a role in the progression of ischaemic heart disease. In turn, ACE inhibitors may influence the course of the disease process not only through direct haemodynamic effects, but also through alterations in a number of other protective processes (Table 2). Epidemiological, genetic, and mechanistic data suggest that ACE inhibitors may have an antiatherosclerotic effect. Most likely, a number of different mechanisms may be working in concert to produce the positive beneficial effects on mortality, incidence of myocardial infarction, and other ischaemic events seen in large-scale clinical trials with ACE inhibitors. Until now, use of ACE inhibitors has been limited to patients with hypertension, severe congestive heart failure, or left ventricular dysfunction. Long-term studies to evaluate the effect of ACE inhibitors in preventing atherosclerosis have been initiated, including QUIET (quinapril), HOPE (ramipril), SECURE (ramipril), SCAT (enalapril), and PART (ramipril). QUIET will evaluate atherosclerotic progression and confirmed ischaemic events in patients with normal left ventricular function who have undergone angioplasty. HOPE will evaluate mortality and the progression of coronary atherosclerosis in patients with coronary artery disease but not heart failure. However, if the antiatherosclerotic effects of ACE inhibitors are confirmed in patients without left ventricular dysfunction, the clinical benefits of ACE inhibitors may be broadened further to include the secondary and possibly primary prevention of ischaemic heart disease.

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