

**Review Article**

## **Role of ACE Inhibitors In Atherosclerosis**

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### **Abstract**

Angiotensin converting enzyme (ACE) inhibitors are an important class of antihypertensive drugs which have been used in the treatment of cardiovascular diseases where hypertension is the main risk factor. In hypertensive patients, it has been observed that there is formation of atherosclerotic plaques. Circulating and local renin angiotensin system (RAS) have been involved in atherosclerotic process on the basis of experimental data showing the presence and specific actions of the components of this system in the vascular wall particularly, angiotensin II which participate in atherogenesis. ACE inhibitors prevent angiotensin II induced vascular proliferation and thereby suppress the development of atherosclerosis in animals. It is also seen that blood pressure effects of ACE inhibitors could play a role in the antiatherosclerotic effect of these drugs. Other mechanisms involved could be blockade of the renin angiotensin system on sympathetic nervous activity, regulation of vascular growth factors and insulin sensitivity. Oxidative stress also plays an important part in the pathogenesis of hypertension and atherosclerosis. ACE inhibitors have been shown to have anti-oxidant activity and by their antihypertensive action, they can prevent atherosclerosis also. In this review, maximum information related to ACE inhibitors, hypertension and atherosclerosis has been compiled for the benefit of physicians and patients.

**Keywords:** Angiotensin converting enzyme inhibitors, hypertension, atherosclerosis.

### **1. Introduction**

Coronary heart disease is the narrowing or blockage of the coronary arteries, usually caused by atherosclerosis. It is the leading cause of death for both men and women and accounts for approximately 600,000 deaths every year. Cardiovascular deaths account for 18.8% in India. About 25 % of deaths in the age group of 25-69 years occur because of heart diseases. Other causes of deaths are respiratory diseases such as asthma, tuberculosis, malignant tumours, digestive diseases and diarrhoeal diseases.<sup>1</sup>

It is estimated that by 2020 cardiovascular disease will be the cause of over 40 percent deaths in India as compared to 24 per cent in 1990. With over 3 million deaths owing to cardiovascular diseases every year, India is set to be the heart disease capital of the world. The main reasons for this epidemic is lifestyle changes such as sedentary jobs, improvement in socioeconomic status leading unhealthy diets rich in fats, high stress jobs and addictions like smoking and tobacco chewing.

ACE inhibitors are important antihypertensive drugs. Long term ACE inhibition significantly reduced the rate of death, myocardial infarction and stroke and reduced the intima to media ratio of carotid arteries in patients at high risk for cardiovascular events<sup>2</sup>. ACE inhibitors ameliorate vasoconstriction, increase the bioactivity of NO and can inhibit vascular superoxide production at its source. ACE inhibitors have achieved widespread usage in the treatment of cardiovascular<sup>3</sup> and

renal disease. They alter the balance between the vasoconstrictive, salt retentive, and hypertrophic properties of angiotensin II (Ang II) and the vasodilatory and natriuretic properties of bradykinin and alter the metabolism of a number of other vasoactive substances. They differ in the chemical structure of their active moieties, in potency, in bioavailability, in plasma half life, in route of elimination, in their distribution and affinity for tissue bound ACE. They have proven effective in the treatment of hypertension<sup>4</sup>, they decrease mortality in congestive heart failure and left ventricular dysfunction after myocardial infarction, and they delay the progression of diabetic nephropathy.

## 2. Classification of ACE Inhibitors<sup>5</sup>

### 2.1. On the basis of the chemical moiety

**Table 1. Classification of ACE on the basis of the chemical moiety**

Sulphydrul containing agents	Captopril Zofenopril
Dicarboxylate containing agents	Enalapril Ramipril Quinapril Perindopril Lisinopril Benazepril
Phosphonate-containing agents	Fosinopril
Naturally occurring agents	Casokinins and lactokinins are breakdown products of casein. Lactotriptides Val-Pro-Pro and Ile-Pro-Pro are produced by the Probiotic Lactobacillus helveticus or derived from casein.

### 2.2. Dosage of ACE inhibitors

**Table 2. ACE inhibitors dosages for hypertension**

Name	Dosage			
	Equivalent daily dose	Start	Usual	Maximum
Benazepril	10 mg	10 mg	20-40 mg	80 mg
Captopril	50 mg (25 mg bid)	12.5-25 mg bid-tid	25-50 mg bid-tid	450 mg/d
Enalapril	5 mg	5 mg	10-40 mg	40 mg
Fosinopril	10 mg	10 mg	20-40 mg	80 mg
Lisinopril	10 mg	10 mg	10-40 mg	80 mg
Moexipril	7.5 mg	7.5 mg	7.5-30 mg	30 mg
Perindopril	4 mg	4 mg	4-8 mg	16 mg
Quinapril	10 mg	10 mg	20-80 mg	80 mg
Ramipril	2.5 mg	2.5 mg	2.5-20 mg	20 mg
Trandolapril	2 mg	1 mg	2-4 mg	8 mg

### 2.3. Adverse effects, contra-indications and special precautions of ACE inhibitors<sup>6</sup>

**Table 3 Adverse effects, contra-indications and special precautions of ACE inhibitors**

Drug	Adverse effects	Contra-indications	Special Precautions
Captopril	Dry cough, skin rash, loss of taste, hyperkalaemia vertigo, headache, nausea, vomiting, hypotension, fatigue, Neutropenia, proteinuria, anemia.	Aortic stenosis, renal dysfunction, Hypersensitivity	Bilateral renal artery Stenosis--renal failure may occur, Anesthesia. Sodium depletion should be corrected before starting therapy
Enalapril	Skin rash, dry cough, headache, nausea, diarrhoea, dizziness, fatigue.	Aortic stenosis, hypersensitivity.	Children in severe heart failure. Hypotension may occur, renal dysfunction, surgery, and anesthesia.
Lisinopril	Dizziness, cough, hyperkalaemia, headache, hypotension, angioedema.	Children, aortic stenosis, outflow obstruction, hypersensitivity.	In severe cardiac failure it may lead to oliguria and rarely acute renal failure. Renal dysfunction. It may cause hypotension during anesthesia or major surgery.

Ramipril	Renal dysfunction, cough, hyperkalaemia, angioedema, nausea.	Bilateral renal artery stenosis, hypersensitivity	Renal dysfunction, severe CHF, impaired hepatic function, children, surgery, anaesthesia
Trandolapril	Tachycardia, arrhythmias, angina, transient ischaemic attacks, cerebral haemorrhage, myocardial infarction, skin reaction (Stevens-Johnson Syndrome, toxic epidermal necrosis) dry mouth	Bilateral renal artery stenosis, hypersensitivity.	Renal dysfunction, severe CHF, impaired hepatic function, children, surgery, and anaesthesia.
Perindopril	Anorexia, nausea vomiting, skin rash, cough, proteinuria, fatigue, angio-neurotic oedema, decrease in hemoglobin, sleep disturbances.	Children	-
Benazepril	Head ache, dizziness, fatigue, cough, somnolence, nausea, postural dizziness, angioedema, hypotension, transient elevations in BUN and serum creatinine, palpitations, constipation, gastritis, rash, pruritus, anxiety, musculo-skeletal pain, UT infection, leucopenia, serum potassium elevation, flushing and peripheral edema.	Hypersensitivity to benazepril or any other ACE inhibitor, history of angioedema.	Symptomatic hypotension may occur especially in patients who have been volume and/or salt depleted. Renal diseases & renal artery stenosis.
Fosinopril	Hyper kalaemia, chronic cough, hypersensitive crisis, conduction disorder, elucidation, dizziness, brady cardia. Memory disturbance, numbness, tumor, mood change. diarrhea, nausea, vomiting, flatulence, abdominal distension.	Hypersensitivity to drug and its components.	Periodic WBC monitoring may be required

### 3. Ace Inhibitors: Indications

#### 3.1. Hypertension<sup>7</sup>

Guidelines for the pharmacologic management of hypertension issued by the World Health Organization and the International Society of Hypertension place ACE inhibitors with diuretics and beta blockers as first-line therapy.

#### 3.2. Congestive Heart Failure<sup>8,9,10,11</sup>

ACE inhibitors are first-line therapy in patients with left ventricular systolic dysfunction. All patients with systolic dysfunction, even if they are asymptomatic, should be considered for treatment with an ACE inhibitor.

#### 3.3. Myocardial Infarction<sup>12,13,14,15</sup>

In 1996 and 1999, the American Heart Association recommended the administration of an ACE inhibitor to all patients presenting with acute anterior myocardial infarction and/or clinical heart failure in the absence of hypotension or other contraindications. The guidelines recommend starting within the first 24 hours and continuing therapy indefinitely for anterior infarctions and left ventricular dysfunction are given.

#### 3.4. Diabetes Mellitus<sup>16,17,18</sup>

ACE inhibitors slow the onset of diabetic nephropathy in patients with microalbuminuria and type 1 diabetes.

#### 3.5. Renal Insufficiency<sup>19</sup>

ACE inhibitors in nondiabetic patients with nephropathy are more effective than other antihypertensives at slowing progression to end-stage renal disease.

### 4. Activation of the Renin-Angiotensin System (RAS) in Atherosclerosis

Activation of the Renin Angiotensin System (RAS) may exert numerous adverse effects on the cardiovascular system (i.e. arterial hypertension, chronic renal failure and, potentially, atherosclerosis). Traditionally, the RAS has been described as an endocrine system in which renin of renal origin acts on angiotensinogen (an acute protein of hepatic origin to produce angiotensin I in the plasma, which in turn is converted by pulmonary endothelial Angiotensin converting enzyme (ACE) to ANGII. The latter is considered to be the main mediator of the physiological action of the RAS. Alternatively, ANGII can be produced directly by conversion of angiotensinogen by the tissue plasminogen activator (tPA), cathepsin G and tonin or by hydrolysis of angiotensin I by chymase and cathepsin G. The importance of local tissue RAS, other

Angiotensin peptides (i.e. Angiotensin III and IV) and the interaction with other systems such as the endogenous kallikrein-kinogen-kinin system is seen. ANGII mediates its physiological effects by binding to specific receptors located on the cell membrane of various cell types that are all vascular cells. It has also been recognized that although the majority of ANGII actions are exerted through AT1 receptors, a seven-transmembrane domain G-protein-coupled receptor, which is strongly expressed on vascular smooth muscle cells (VSMCs), other specific cell surface receptors, including AT2 and AT4 receptors, and angiotensin(1-7) are also involved in the actions of angiotensin peptides.<sup>20,21</sup>

The effects of ANGII include the following (i) vasoconstriction (ii) VSMC migration, proliferation and hypertrophy (iii) increased extra cellular matrix (ECM) formation (iv) release of thromboxane A2 and (v) enhanced matrix metalloproteinase (MMP) production. More recent findings show (i) effects on plasminogen activator inhibitor-1 (PAI-1) synthesis (ii) activation NAD(P)H oxidases (iii) release of proinflammatory mediators, such as interleukin-6 (IL-6). Clinical consequences of these effects include an increase in blood pressure, myocardial and vascular hypertrophy and remodelling, and, potentially, plaque growth and rupture.

ANGII activates intracellular signaling pathways that promote atherosclerosis through the formation of reactive oxygen species (ROS), inflammation, growth, oxidation of LDL, endothelial dysfunction matrix degradation and thrombosis.<sup>22,23</sup> ROS formation seems to be pivotal for the cross-link to inflammatory processes which contribute to atherosclerotic plaque formation. ANGII stimulation leads to an AT1/NAD(P)H oxidase-dependent formation of ROS. These oxygen radicals are known activators of cytoplasm signaling cascades, such as nuclear factor (NF)-B, mitogen-activated protein (MAP) kinases and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Together, these mechanisms may enhance oxidative stress within the vessel wall and leads to the activation of redox-sensitive genes, such as those coding for proinflammatory cytokines like IL-6.

Furthermore, NF-B activation by ANGII leads to increased expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1, vascular adhesion molecule (VCAM)-1 and E-selectin, and chemoattractant proteins such as monocyte chemoattractant protein (MCP)-1 involved in adhesion and tissue recruitment of inflammatory cells. In addition, ANGII leads to the production of autocrine growth factors such as transforming growth factor (TGF)B-1 and platelet-derived growth factor (PDGF), stimulating cellular hypertrophy and proliferation of smooth muscle cells.<sup>24,25</sup>

Moreover, ANGII has important modulatory effects on vascular lipid metabolism in the vessel wall by enhancing LDL oxidation, involving the stimulation of lipoxygenase and NAD(P)H oxidase in macrophages.<sup>26,27</sup> An additional effect of ANGII is the upregulation of the lectin-like oxidized LDL receptor (LOX) -1 on endothelial cells and macrophages, an effect that may further enhance oxidized LDL infiltration in the vessel wall. The development of atherosclerosis occurs through structural changes of the vessel wall from migration and proliferation of smooth muscle cells up to plaque rupture.<sup>28,29</sup> Finally, ANGII inhibits the fibrinolytic system and enhances thrombosis by increased production of plasminogen activator inhibitor (PAI)-1, tissue factor (TF), and platelet activation and aggregation.<sup>30,31,32,33</sup>

#### 4.1 Hypertension and Oxidative Stress

Hypertension is associated with increased vascular oxidative stress. Oxidative stress promotes vascular smooth muscle cell proliferation and hypertrophy and collagen deposition, leading to thickening of the vascular media and narrowing of the vascular lumen. Increased oxidative stress may damage the endothelium and impair endothelium dependent vascular relaxation and increases vascular contractile activity. All these effects on the vasculature may explain how increased oxidative stress can cause hypertension. It is noted that lowering blood pressure with antihypertensive drugs can reduce oxidative stress also<sup>34,35,36</sup>

Experimental studies have shown that ROS through the production of superoxide anion, can cause important alterations in the cellular signal transduction systems characterized by an enhanced production of inositol triphosphate and reduced production of cyclic GMP in cultured vascular smooth muscle cells (SMC), thus favouring vasoconstriction.<sup>37,38</sup>

#### 4.2 Atherosclerosis and Oxidative Stress

Cardiovascular (CV) events remain the main cause of morbidity and mortality in industrialized societies. Atherosclerosis is a chronic inflammatory disease initiated and perpetuated by a variety of CV risk factors such as smoking, diabetes mellitus, hypertension and elevated plasma low-density lipoprotein (LDL). Atherosclerotic plaques are conglomerates composed of dysfunctional endothelial cells, smooth muscle cells, lipid-laden macrophages and T

lymphocytes. These lipid-laden activated macrophages and T-lymphocytes stimulate their neighbouring cells to erode the collagen and elastic frame work which forms the plaques cap. Myocardial infarction, stroke or sudden cardiac death are the fatal end-points of progressive atherosclerosis and are thought to be the result of these pathological remodelling processes.<sup>39,40,41,42</sup>

According to the theory of oxidative stress, atherosclerosis is the result of the oxidative modification of low density lipoproteins (LDL) in the arterial wall by reactive oxygen species (ROS), from the endothelial cells, macrophages, smooth muscle cells and the adventitial cells. The increased production of ROS reduces the production and consequently the bioavailability of NO, leading to vasoconstriction, platelet aggregation and adhesion of neutrophils to the endothelium. Oxidative stress by hydrogen peroxide ( $H_2O_2$ ) increases phosphorylation of tyrosine kinases, which leads to stronger binding of neutrophils cells on endothelium. Oxidative stress by hydrogen peroxide ( $H_2O_2$ ), increases phosphorylation of tyrosine kinases, which leads to stronger binding of neutrophil cells on endothelium and alteration of vessel permeability. Another mechanism through which oxidative stress by  $H_2O_2$  affects atherogenesis is the production of transcription factors such as nuclear factor  $\kappa B$  (NF- $\kappa B$ ) and activator protein1 (AP-1), which participates in the expression of adhesion molecules, such as vascular cellular adhesion molecules (VCAM-1), intracellular adhesion molecules (ICAM-1), E selectin and other cytokines. The examples of free radicals in biological systems include superoxide anions, alkoxyl, peroxy and hydroxyl radicals, nitric oxide and nitrogen dioxide. ROS initiate processes involved in atherogenesis through several important enzyme systems including xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and nitric oxide synthase.<sup>43,44</sup>

#### 4.3 Ace-Inhibitors in Relation to Atherosclerosis<sup>45,46,47</sup>

Pro-oxidative and proinflammatory mechanisms are important in the pathogenesis of atherosclerosis and it has been studied that quinapril is beneficial in the prevention of atherosclerosis related diseases. Inhibitors of the RAS, such as ACE inhibitors have powerful anti-inflammatory and antioxidant effects within the vasculature. Angiotensin converting enzyme inhibitors reduce the risk of major coronary events like cardiovascular death, myocardial infarction, resuscitated cardiac arrest by 20% when compared with placebo in patients with stable coronary artery disease (CAD). These cardiovascular benefits are attributed to blood pressure lowering effect of the drug and the direct cardioprotective vascular effect. In this regard, the action of perindopril has been studied which is known to reduce arterial hypertrophy, arterial stiffness and improve arterial elasticity.<sup>48</sup>

The vascular action of ACE inhibitors has been associated with their inhibition of angiotensin II formation. Angiotensin II causes vasoconstriction via stimulation of smooth muscles AT1 receptor. Angiotensin has also been shown to be a strong stimulus for the expression of endothelin within endothelial cells and smooth muscles cells. Part of the Angiotensin II induced vasoconstriction is due to stimulation of the release of endothelin I from endothelial and smooth muscle cells

By inhibiting angiotensin II formation, ACE inhibition may also beneficially influence inflammatory processes within the vascular wall. Another important aspect of ACE inhibitors relates to the fact that the ACE and the enzyme endothelial kininase II are the same. Inhibition of kininase II leads to increased formation of bradykinin which stimulates the bradykinin  $B_2$  receptor, inducing the release of vasodilator substances such as nitric oxide (NO), endothelium-derived hyperpolarizing factor, and prostacyclin.<sup>49,50</sup> The production of NO, endothelium- derived hyperpolarizing factor and prostacyclin causes vascular smooth muscle cell relaxation through distinct mechanisms such as generation of cGMP, activation of  $BK_{Ca}$  channels, and generation of cAMP, respectively.<sup>51</sup>

The action of ACE inhibitors to increase endothelial NO and prostacyclin production may, in part, explain the vasodilator, antithrombotic and antiproliferative effects of ACE inhibitors. Inhibition of renin angiotensin system by ACE inhibitors have reduced the activity NAD(P)H oxidase, improves endothelial dysfunction and leads to reduction of cardiovascular events in patients with arterial hypertension and hypercholesterolemia as well as in high risk patients. ACE Inhibitors cause vasodilatation of coronary and peripheral arteries through increased levels of plasma bradykinin.<sup>52</sup>

#### 4.4 Ace Inhibitors as Antioxidants<sup>53,54</sup>

ACE inhibitors limits the stimulation of vascular NAD(P)H oxidase, thereby preventing the increased superoxide flux associated with activation of the renin angiotensin system. Because superoxide reacts with NO, ACE inhibition should

improve NO bioactivity shown by patients with coronary artery disease and some experimental models of hypertension. NO is known to inhibit the activity of NAD (P)H oxidase, another predictable effect of ACE inhibitors would be to reduce the levels of superoxide in the vascular wall. ACE inhibition inhibit lipid peroxidation through reduced formation of peroxynitrite. Because superoxide is the principal source of  $H_2O_2$ , ACE inhibitors limit smooth muscle proliferation. ACE inhibitors limit the production of  $H_2O_2$ , the formation of  $H_2O_2$ -derived oxidants such as hydroxyl radical and hypochlorous acid (HOCl) are also reduced by ACE inhibitors. By affecting the free radical mechanism and oxidative stress, Angiotensin Converting Enzyme inhibitors have an important role in preventing hypertension as well as atherosclerosis as these are the main risk factors for coronary heart diseases.<sup>55,56</sup>

## 5. Conclusion and Future Outlook

The antioxidant activity of ACE Inhibitors seems to be responsible for its anti-atherosclerotic activity. There is need to explore other mechanisms also for its anti-atherosclerotic activity.

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