THE RECENT DEVELOPMENTS ON ACE INHIBITORS- A REVIEW

Shashikant R Pattan*, Prerana A Chavan¹, Nachiket S Dighe¹, V A Kothiwale², S V Hiremath³, M B Sanikop⁴, S P Bhosle⁵, R.K.Godge¹ and J.G.Bagi³

1-Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, MS, India, 413736.
2-Department of Medicine, K.L.E.University, Belgaum, Karnataka, India.
3-Department of Pharmacology, J.N.Medical College, K.L.E.University, Belgaum, Karnataka, India.
4-Department of Anatomy, D.Devaraj Urs University, Kolar, Karnataka.
5-S. V. M. College of Engineering, Chincholi (Nashik), M.S. India.

Summary
Hypertension is controlled by many hypothesis and pharmacological efforts. ACE inhibitor are found to be more effective and safe for secondary hypertension. ACE inhibitor have found to reduce the progress of Diabetic neuropathy. In the present review we have attempted to focus the medicinal importance of ACE inhibitors, their side effects and mechanism of action. The research of ACE inhibitors have inspired all the physicians, pharmacists as it will be the major route of treatment for hypertension.

Key-words: ACE inhibitor, Angiotensin, Hypertension, Proteinurea.

*Address for correspondence
Dr. Shashikant R. Pattan
Principal,
Pravara Rural College of Pharmacy, Pravaranagar
A/P Loni Bk.
Tal-Rahata, Dist-Ahmednagar
M.S. India 413736
Mob: +91-9423787413
E-mail: shashipattan@yahoo.com

Introduction
Hypertension is a chronic medical condition in which the blood pressure is elevated. It is shortened to HT, HTN or HPN. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.1 Hypertension can be classified as either essential (primary) or secondary. 2 It is common. About 90-95% of hypertension is essential hypertension. 2-5 Secondary hypertension indicates that the high blood pressure is a result of (i.e., secondary to) another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma).
Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated.

### History

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1956</td>
<td>Leonard T. Skeggs and his colleagues discovers angiotensin converting enzyme (ACE) in plasma</td>
</tr>
<tr>
<td>2.</td>
<td>1965</td>
<td>Brazilian scientist Sergio Ferreira reported a 'bradykinin potentiating factor (BPFs) present in the venom of bothrops jararaca, a South American pit viper. Dr SH Ferreira then proceeded to John Vane's laboratory as a Post-Doc with his already isolated BPFs. The conversion of the inactive angiotensin I to the potent angiotensin II was thought to take place in the plasma.</td>
</tr>
<tr>
<td>3.</td>
<td>1967</td>
<td>Kevin K. F. Ng and John R. Vane showed that the plasma (ACE) was too slow to account for the conversion of angiotensin I to angiotensin II in vivo.</td>
</tr>
<tr>
<td>4.</td>
<td>1975</td>
<td>David Cushman, Miguel Ondetti and Colleagues used peptide analogues to study the structure of ACE, using carboxypeptidase A as a model. Their discoveries led to the development of captopril, the first orally-active ACE inhibitor.</td>
</tr>
<tr>
<td>5.</td>
<td>1991</td>
<td>Japanese Scientists created the first ever milk-based ACE inhibitor in the form of a fermented milk drink, using specific cultures to liberate the IPP from the dairy protein.</td>
</tr>
</tbody>
</table>

### Table 1 History

ACE inhibitors disrupt the RAAS by preventing the conversion of AT-I to AT-II. As a result, ACE inhibitors are used widely to treat hypertension. These agents reduce proteinuria and delay progression of renal disease in patients with diabetic nephropathy or nondiabetic kidney disease. Nevertheless, the use of ACE inhibitors has limitations. Some patients taking ACE inhibitors develop a reactive and persistent increase in ATII levels as a result of a compensatory stimulation of ACE independent pathways of production in tissues, a phenomenon known as AT II escape. These increased local levels of ATII may cause further target organ damage through effects at the AT, receptor. Inhibition of ACE, a nonspecific enzyme, also prevents the catabolism of other biologically active peptides, such as bradykinin, substance P, and prostaglandins. Although these vasodilators may augment the antihypertensive effect, they may also be responsible for some of the more troublesome side effects of ACE-inhibitor therapy-cough and angioedema. The cough associated with ACE-inhibitor use is sufficiently bothersome to lead to treatment discontinuation in -60% of patients who develop it.
Role of ACE in Renin - Angiotensin - Aldosterone system:

Figure 2: The Renin-Angiotensin-Aldosterone System.
ACE = Angiotensin converting enzyme
AT₁ and AT₂ = angiotensin subtype I and II

Fig. 1: Role of ACE in Renin-Angiotensin-Aldosterone system

Pharmacological effects of ACE inhibitors

With ACE inhibitor use, the effects of angiotensin II are prevented, leading to decreased blood pressure. The effects of angiotensin II are vasoconstriction (narrowing of blood vessels), which may lead to increased blood pressure and hypertension, constriction of the efferent arterioles of the kidney, leading to increased perfusion pressure in the glomeruli, ventricular remodeling of the heart, which may lead to ventricular hypertrophy and CHF stimulation of the adrenal cortex to release aldosterone, a hormone that acts on kidney tubules to retain sodium and chloride ions and excrete potassium. Sodium is a "water-holding" molecule, so water is also retained, which leads to increased blood volume, hence an increase in blood pressure. Stimulation of the posterior pituitary to release vasopressin (also known as anti-diuretic hormone (ADH)) which also acts on the kidneys to increase water retention. Decrease renal protein kinase C.

Epidemiological and clinical studies have shown that ACE inhibitors reduce the progress of diabetic nephropathy independently from their blood pressure-lowering effect. This action of ACE inhibitors is utilised in the prevention of diabetic renal failure. ACE inhibitors have been shown to be effective for indications other than hypertension even in patients with normal blood pressure. The use of a maximum dose of ACE inhibitors in such patients (including for prevention of diabetic nephropathy, congestive heart failure, prophylaxis of cardiovascular events) is justified because it improves clinical outcomes, independent of the blood pressure lowering effect of ACE inhibitors. Such therapy, of course, requires careful and gradual titration of the dose to prevent the effects of rapidly decreasing blood pressure (dizziness, fainting, etc.).
Adverse Effects of ACE inhibitors

| Renal impairment | It is a significant adverse effect of all ACE inhibitors. Some suggest that it is associated with their effect on angiotensin II-mediated homeostatic functions such as renal blood flow. Renal blood flow may be affected by angiotensin II because it vasoconstricts the efferent arterioles of the glomeruli of the kidney, thereby increasing glomerular filtration rate (GFR). Hence, by reducing angiotensin II levels, ACE inhibitors may reduce GFR, a marker of renal function. Specifically, ACE inhibitors can induce or exacerbate renal impairment in patients with renal artery stenosis. This is especially a problem if the patient is also concomitantly taking an NSAID and a diuretic. When the three drugs are taken together, there is a very high risk of developing renal failure.17 |
| Hyperkalemia | Suppression of angiotensin II leads to a decrease in aldosterone levels. Since aldosterone is responsible for increasing the excretion of potassium, ACE inhibitors ultimately cause retention of potassium. |
| Angioedema | Due to increased bradykinin levels. There appears to be a genetic predisposition towards this adverse effect in patients who degrade bradykinin more slowly than average.18 |
| congenital malformations, stillbirths, and neonatal deaths | ACE inhibitors taken during the first trimester have been reported to cause it. |
| hypotension, renal dysplasia, anuria/oliguria, oligohydramnios, intrauterine growth retardation, pulmonary hypoplasia, patent ductus arteriosus, and incomplete ossification of the skull. | These are the commonly reported fetal abnormalities. |

Table 2: Adverse Effects of ACE inhibitors

ACE inhibitors can be divided into three groups based on their molecular structure:

A) Sulfhydryl-containing agents

<table>
<thead>
<tr>
<th>Captopril</th>
</tr>
</thead>
</table>
| \[
\text{HS} \quad \text{CO} \\
\text{N} \quad \text{OH}
\] |
B) Dicarboxylate-containing agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td><img src="image" alt="Enalapril structure" /></td>
</tr>
<tr>
<td>Benazepril</td>
<td><img src="image" alt="Benazepril structure" /></td>
</tr>
<tr>
<td>Lisinopril</td>
<td><img src="image" alt="Lisinopril structure" /></td>
</tr>
<tr>
<td>Ramipril</td>
<td><img src="image" alt="Ramipril structure" /></td>
</tr>
<tr>
<td>Quinapril</td>
<td><img src="image" alt="Quinapril structure" /></td>
</tr>
<tr>
<td>Perindopril</td>
<td><img src="image" alt="Perindopril structure" /></td>
</tr>
</tbody>
</table>
C) Phosphonate-containing agents

ACEI equivalents

The ACE inhibitors have different strengths with different starting dosages. Dosage should be adjusted according to the clinical response. 19-21

ACE inhibitors dosages for hypertension

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

Note: bid = 2 times a day, tid = 3 times a day, d = daily

Table 3: ACEI equivalents

Contraindications and precautions 22-23

The ACE inhibitors are contraindicated in patients with:

- Previous angioedema associated with ACE inhibitor therapy
- Renal artery stenosis (bilateral, or unilateral with a solitary functioning kidney)
- Hypersensitivity to ACE inhibitors
- ACE inhibitors should be used with caution in patients with:
  - Impaired renal function
  - Aortic valve stenosis or cardiac outflow obstruction
  - Hypovolemia or dehydration
  - Hemodialysis with high flux polyacrylonitrile membranes
ACE inhibitors are ADEC Pregnancy category D, and should be avoided in women who are likely to become pregnant. In the U.S., ACE inhibitors are required to be labelled with a "black box" warning concerning the risk of birth defects when taking during the second and third trimester. It has also been found that use of ACE inhibitors in the first trimester is also associated with a risk of major congenital malformations, particularly affecting the cardiovascular and central nervous systems. Potassium supplementation should be used with caution and under medical supervision owing to the hyperkalemic effect of ACE inhibitors.

Conclusions

Secondary hypertension and it’s management has become challenging. ACE inhibitors have created interest amongst the physician and pharmacists. Though ACE was discovered in 1956, a very little research work has been carried out. In 1975 Captopril the first orally active ACE inhibitor was developed. Now medicinal chemist have designed various inhibitors based on molecular structure and chemical entity attached. This has led to discover many more ACE inhibitors with promising absorption, lipophilic characters and other physico-chemical properties. There is a better scope for the search of these ACE inhibitors.

References