3.0 REVIEW OF LITERATURE

3.1 HYPERTENSIVE VASCULAR DISEASE

An elevated arterial pressure is probably the most important public health problem in developed countries. It is common, asymptomatic, readily detectable, usually easily treatable, and often leads to lethal complications if left untreated. Its impact is greatest for stroke and end-stage renal failure. It is also one of the contributing factors for the development of coronary artery disease. Although our understanding of the pathophysiology of the elevated arterial pressure has increased, in 90-95% of cases the etiology is still largely unknown. As a consequence, in most cases the hypertension is treated nonspecifically, resulting in a large number of minor side effects and a relatively high (50-60%) noncompliance rate.

3.1.1 Prevalence

The prevalence of hypertension depends on both the racial composition of the population studied and the criteria used to define the condition. Community surveys carried out in India in different geographical locations, often with small population samples, have reported prevalence rates of 2.5% to 3.5% in rural and 4% to 18% in urban populations, and 7.5% in slum areas.

The various forms of hypertension are outlined in Table A and their relative frequencies are given in Table B.

3.1.2 Essential Hypertension

Patients with arterial hypertension and no definable cause are said to have primary, essential, or idiopathic hypertension. Undoubtedly, the primary difficulty in uncovering the mechanism(s) responsible for the hypertension in these patients is attributable to the variety of systems that are involved in the regulation of arterial pressure – peripheral and
### TABLE A: CLASSIFICATION OF ARTERIAL HYPERTENSION

**SYSTOLIC HYPERTENSION WITH WIDE PULSE PRESSURE**

| I. | Decreased compliance of aorta (arteriosclerosis) |
| II | Increased stroke volume |
| A. | Aortic regurgitation |
| B. | Thyrotoxicosis |
| C. | Hyperkinetic heart syndrome |
| D. | Fever |
| E. | Arteriovenous fistula |
| F. | Patent ductus arteriosus |

**SYSTOLIC AND DIASTOLIC HYPERTENSION (INCREASED PERIPHERAL VASCULAR RESISTANCE)**

| I. | Renal |
| A. | Chronic pyelonephritis |
| B. | Acute and chronic glomerulonephritis |
| C. | Polycystic renal disease |
| D. | Renovascular stenosis or renal infarction |
| E. | Most other severe renal diseases (arteriolar nephrosclerosis, diabetic nephropathy, etc.) |
| F. | Renin-producing tumors |

| II | Endocrine |
| A. | Oral contraceptives |
| B. | Adrenocortical hyperfunction |
| 1. | Cushing's disease and syndrome |
| 2. | Primary hyperaldosteronism |
| 3. | Congenital or hereditary adrenogenital syndromes |
| (17α-hydroxylase and 11β-hydroxylase defects) |
| C. | Pheochromocytoma |
| D. | Myxedema |
| E. | Acromegaly |

| III. | Neurogenic |
| A. | Psychogenic |
| B. | Diencephalic syndrome |
| C. | Familial dysautonomia (Riley-Day) |
| D. | Polyneuritis (acute porphyria, lead poisoning) |
| E. | Increased intracranial pressure (acute) |
| F. | Spinal cord section (acute) |

| IV | Miscellaneous |
| A. | Coarctation of aorta |
| B. | Increased intravascular volume (excessive transfusion, polycythemia vera) |
| C. | Polyarteritis nodosa |
| D. | Hypercalcemia |
| E. | Medications, e.g., glucocorticoids, cyclosporine |

| V. | Unknown etiology |
| A. | Essential hypertension (>90% of all cases of hypertension) |
| B. | Toxemia of pregnancy |
| C. | Acute intermittent porphyria |
TABLE B: RELATIVE FREQUENCIES OF EXISTENCE OF VARIOUS TYPES OF HYPERTENSION

<table>
<thead>
<tr>
<th>TYPE OF HYPERTENSION</th>
<th>FREQUENCY (% IN GENERAL POPULATION)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
<td>92-94</td>
</tr>
<tr>
<td>Renal hypertension</td>
<td></td>
</tr>
<tr>
<td>Parenchymal</td>
<td>2-3</td>
</tr>
<tr>
<td>Renovascular</td>
<td>1-2</td>
</tr>
<tr>
<td>Endocrine hypertension</td>
<td></td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>0.3</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Oral contraceptive-induced</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Central adrenergic, renal, hormonal, and vascular – and to complexity of the interrelations of these systems. It is still uncertain whether these individual abnormalities are primary or secondary, varying expressions of a single disease process or reflective of separate disease entities, the accumulating data increasingly support the latter hypothesis. Thus, the distinction between primary and secondary hypertension has become blurred, and the approach to both the diagnosis and therapy of hypertensive patients has been modified. Individuals in whom a specific structural organ or gene defect is responsible for hypertension are defined as having a secondary form of hypertension. In contrast, individuals in whom generalized or functional abnormalities may be the cause of hypertension, even if the abnormalities are discrete, are defined as having essential hypertension.

3.1.3 Genetic Considerations

Genetic factors have long been assumed to be important in the genesis of hypertension. Most studies support the concept that the inheritance is probably multifactorial or that a number of different genetic defects each having an elevated blood pressure as one of their phenotypic expressions. Finally, both monogenic defects (e.g., glucocorticoid-
remediable aldosteronism and Liddle's syndrome) and susceptibility genes (e.g., the angiotensinogen and alpha adducin genes) have now been reported which have as one of their consequences as increased arterial pressure.

3.1.4 Environmental

A number of environmental factors have been implicated in the development of hypertension, including salt intake, obesity, occupation, alcohol intake, family size, and crowding.

3.1.5 Salt Sensitivity

This factor illustrates the heterogeneous nature of the essential hypertensive population, in that the blood pressure in only approximately 60% of hypertensives is particularly responsive to the level of sodium intake.

3.1.6 Role of Renin

The end product of the action of renin on its substrate is the generation of the peptide angiotensin II (A-II). The response of target tissues to this peptide is uniquely determined by the prior dietary electrolyte intake. Sodium intake normally modulates adrenal and renal vascular responses to A-II. The range of plasma renin activities observed in hypertensive subjects is broader than in normotensive individuals. In consequence, some hypertensive patients have been defined as having low-renin and others as having high-renin essential hypertension.

Low-renin essential hypertension

Approximately 20% of patients who by all other criteria have essential hypertension have suppressed plasma renin activity. Though these patients are not hypokalemic, they have been reported to have expanded extracellular fluid volumes, and it has been suggested but not proved that they have sodium retention and renin suppression due
to excessive production of an unidentified mineralocorticoid. On the other hand, some, but not all, studies have suggested that the adrenal cortex of some of these patients have an increased sensitivity to A-II as the underlying mechanism.

3.1.7 Nonmodulating Essential Hypertension

Another subset of hypertensive patients has an adrenal defect opposite to that observed in some low-renin patients — a reduced adrenal response to sodium restriction. In these individuals, sodium intake does not modulate either adrenal or renal vascular responses to A-II. Hypertensives in this subset have been termed nonmodulators because of the absence of the sodium-mediated modulation of target tissue responses to A-II. They also are more insulin-resistant than other hypertensive patients. Furthermore, the nonmodulation characteristic appears to be genetically determined.

*High-renin essential hypertension*

It has been suggested that plasma renin plays an important role in the pathogenesis of the elevated arterial pressure in these patients. It has also been proposed that elevated renin levels and blood pressure may both be secondary to an increase in adrenergic system activity.

3.1.8 Sodium Ion versus Chloride or Calcium

Most studies assessing the role of salt in the hypertensive process have assumed that it is the sodium ion that is important. However, some investigators have suggested that the chloride ion may be equally important. Calcium has also been implicated in the pathogenesis of some forms of essential hypertension. It has been postulated that salt loading in combination with a defect in the kidney’s ability to excrete salt may lead to a secondary increase in circulating natriuretic factors. One of these factors, the so-called digitalis-like natriuretic factor, inhibits ouabain-sensitive Na+, K+-ATPase and thereby leads to
intracellular calcium accumulation and a hyperreactive vascular smooth muscle.

3.1.9 Cell Membrane Defect

This hypothesis derives most of its data from studies on circulating blood elements, particularly red blood cells, in which abnormalities in the transport of sodium across the cell membrane have been documented. It is assumed that this abnormality in sodium transport reflects an alteration in the cell membrane.

3.1.10 Insulin Resistance

Insulin resistance and/or insulinemia have been suggested as being responsible for arterial pressure in some patients with hypertension. Hyperinsulinemia can increase arterial pressure by one or more of four mechanisms. An underlying assumption in each case is that some, but not all, of the target tissues of insulin are resistant to its effects. Specifically, tissues involved in glucose homeostasis are resistant (thereby producing the hyperinsulinemia), while, tissues involved in the hypertensive process are not. First, hyperinsulinemia produces renal sodium retention (at least acutely) and increases sympathetic activity. Either or both of these effects could lead to an increase in arterial pressure. Another mechanism is vascular smooth-muscle hypertrophy secondary to the mitogenic action of insulin. Third, insulin also modifies ion transport across the cell membrane, thereby potentially increasing the cytosolic calcium levels of insulin-sensitive vascular or renal tissues. This mechanism would increase arterial pressure for reasons similar to those described above for the membrane-defect hypothesis. Finally, insulin resistance may be a marker for another pathologic process, e.g., nonmodulation, which could be the primary mechanism increasing blood pressure. It is important to point out however, that the role of insulin in controlling arterial pressure is only vaguely understood, and, therefore, its potential as a pathogenic factor in hypertension remains unclear.
3.1.11 Factors that Modify the Course of Essential Hypertension

Age, race, sex, smoking, alcohol intake, serum cholesterol, glucose intolerance, and weight may all alter the prognosis of this disease. At all ages and in both white and non-white populations, females with hypertension fare better than males up to the age of 65, and the prevalence of hypertension in pre-menopausal females is substantially less than that in age-matched males or post-menopausal women, yet, compared with their normotensive counterparts, females with hypertension run the same relative risk of a morbid cardiovascular event as males do. Accelerated atherosclerosis is an invariable companion of hypertension. Thus, it is not surprising that independent risk factors associated with the development of atherosclerosis, such as an elevated serum cholesterol, glucose intolerance, and/or cigarette smoking, significantly enhance the effect of hypertension on mortality rate regardless of age, sex, or race. There is also no question that a positive correlation exists between obesity and arterial pressure.

3.1.12 Natural History

Because essential hypertension is a heterogeneous disorder, variables other than the arterial pressure modify its cause. Thus, the probability of developing a morbid cardiovascular event with a given arterial pressure may vary as much as 20-fold depending on whether associated risk factors are present. Even individuals who have relatively mild disease — i.e., without evidence of end-organ damage — that is left untreated for 7-10 years have a high risk of developing significant complications. Nearly 30% will exhibit atherosclerotic complications, and more than 50% will have end-organ damage related to hypertension itself, such as cardiomegaly, congestive heart failure, retinopathy, cerebrovascular accident, and/or renal insufficiency. Thus, even in its mild forms, hypertension is a progressive and lethal disease if left untreated.
3.1.13 Secondary Hypertension

Nearly all the secondary forms of hypertension are related to an alteration in hormone secretion and/or renal function.

(i) Renal hypertension

Hypertension produced by renal disease is the result of either (1) a derangement in the renal handling of sodium and fluids leading to volume expansion or (2) an alteration in renal secretion of vasoactive materials resulting in a systemic or local change in arteriolar tone. The main subdivisions of renal hypertension are renovascular hypertension, including preeclampsia and eclampsia, and renal parenchymal hypertension. A simple explanation for renal vascular hypertension is that decreased perfusion of renal tissue due to stenosis of main or branch renal artery activates the renin-angiotensin system. Activation of the renin-angiotensin system has also been offered as an explanation for the hypertension in both acute and chronic renal parenchymal disease.

A rare form of renal hypertension results from the excess secretion of renin by juxtaglomerular cell tumors or nephroblastomas.

(ii) Endocrine hypertension
(a) Adrenal hypertension

Hypertension is a feature of a variety of adrenal cortical abnormalities. In primary aldosteronism, there is a clear relationship between the aldosterone-induced sodium retention and the hypertension. Primary aldosteronism may be secondary to either a tumor or bilateral adrenal hyperplasia.

The sodium-retaining effect of large amount of glucocorticoids also offers an explanation for the hypertension in severe cases of Cushing's syndrome. Moreover, increased production of mineralocorticoids has also been documented in some patients with Cushing's syndrome.
In patients with pheochromocytoma, increased secretion of epinephrine and norepinephrine by a tumor causes excessive stimulation of adrenergic receptors, which results in peripheral vasoconstriction and cardiac stimulation.

(b) Acromegaly

Hypertension, coronary atherosclerosis, and cardiac hypertrophy are frequent complications of this condition.

(c) Hypercalcemia

The hypertension that occurs in up to one-third of patients with hyperparathyroidism ordinarily can be attributed to renal parenchymal damage due to nephrolithiasis and nephrocalcinosis. However, increased calcium levels can also have a direct vasoconstrictive effect.

(d) Oral contraceptives

In patients receiving these agents who do become hypertensive, the mechanism is likely to be activation of renin-angiotensin-aldosterone system. The estrogen component of oral contraceptive agents stimulates the hepatic synthesis of the renin substrate angiotensinogen, which in turn favors the increased production of A-II and secondary aldosteronism.

(e) Coarctation of the aorta

The hypertension associated with coarctation may be caused by the constriction itself, or perhaps by the changes in renal circulation which result in an unusual form of renal arterial hypertension. The diagnosis of coarctation is usually evident from physical examination and routine X-ray findings.
3.1.14 Effects of Hypertension

Patients of hypertension die prematurely; the most common cause of death is heart disease, with stroke and renal failure also frequent, particularly in patients with significant retinopathy.

(i) Effects on the heart

Cardiac compensation for the excessive work-load imposed by increased systemic pressure is at first sustained by concentric left-ventricular hypertrophy characterized by an increase in wall thickness. Angina pectoris may also occur because of the combination of accelerated coronary artery disease and increased myocardial oxygen requirements as a consequence of the increased myocardial mass.

(ii) Neurologic effects

The neurologic effects of long-standing hypertension may be divided into retinal and central nervous system changes. Because the retina is the only tissue in which the arteries and arterioles can be examined directly, repeated ophthalmoscopic examination provides the opportunity to observe the progress of the vascular effects of hypertension.

Central nervous system dysfunction also occurs frequently in patients with hypertension. Occipital headaches, most often occurring in the morning, are among the most prominent early symptoms of hypertension. Dizziness, light-headedness, vertigo, tinnitus, and dimmed vision or syncope may also be observed, but the more serious manifestations are due to vascular occlusion, hemorrhage, or encephalopathy.

Hypertensive encephalopathy consists of the following symptom complex: severe hypertension, disordered consciousness, increased intracranial pressure, retinopathy with papilledema and seizures. The
pathogenesis is uncertain but is probably not related to arteriolar spasms or cerebral edema.

(iii) Effects on the kidney

Arteriosclerotic lesions of the afferent and efferent arterioles and the glomerular capillary tufts are the most common renal vascular lesions in hypertension and result in a decreased glomerular filtration rate and tubular dysfunction.

3.2 RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) is an important participant in both short- and long-term regulation of arterial blood pressure. Factors that decrease arterial blood pressure, such as decreases in effective blood volume (caused by, for example, a low-sodium diet, diuretics, blood loss, congestive heart failure, liver cirrhosis, or nephrotic syndrome) or reductions in total peripheral resistance (caused by, for example, vasodilators), activate renin release from the kidneys.

Renin is an enzyme that acts on angiotensinogen (renin substrate) to catalyze the formation of the decapeptide angiotensin I. This decapeptide is then cleaved by ACE to yield the octapeptide angiotensin II (A-II). A representation of the biochemical pathways of the RAS is shown in Figure A.

A-II acts via diverse, yet coordinated mechanisms to raise arterial blood pressure toward normal. The peptide acts in several ways to increase total peripheral resistance thereby contributes to short-term regulation of arterial blood pressure. Perhaps more important is the A-II to inhibit excretion of Na\(^+\) and water by the kidneys. A-II-induced changes in renal function play an important role in long-term stabilization of arterial blood pressure in face of large swings in dietary Na\(^+\) intake (Hall et al, 1980). As with its effect on peripheral resistance, the renal actions of A-II also involve multiple interacting mechanisms.
Fig. A: Formation of angiotensin peptides (Jackson, 2001)

The solid arrows show that classical pathways, and the dashed arrows indicate minor alternative pathways.
3.2.1 Components of Renin-Angiotensin System

(i) Renin

The major determinant of the rate of A-II production is the amount of renin released by the kidney. Renin is synthesized, stored, and secreted into the renal arterial circulation by the granular juxtaglomerular cells that lie in the walls of afferent arterioles as they enter the glomeruli. There is morphological and functional evidence that renin is secreted by exocytosis of storage granules, and studies by Friis et al (1999) provide direct evidence of exocytosis in isolated juxtaglomerular cells.

Renin is an aspartyl protease that attacks a restricted number of substrates. Its principal natural substrate is a circulating $\alpha_2$-globulin, angiotensinogen. Renin cleaves the bond between residues 10 and 11 at the amino terminus of this protein to generate angiotensin I. The active form of renin is a glycoprotein that contains 340 amino acids. It is synthesized as a preproenzyme of 406 amino acid residues that is processed to prorenin, a mature but inactive form of the protein (Imai et al, 1983). Prorenin is finally activated by an as yet uncharacterized enzyme that removes 43 amino acids from the amino terminus of prorenin. Similar to other aspartyl proteases, renin has a bilobal structure with a cleft that forms the active site (Inagami, 1989; Sielecki et al, 1989). A truncated, nonsecreted form of renin is expressed in the brain as a result of an alternative promoter within intron I of the renin gene (Lee-Kirch et al, 1999).

Renin and prorenin both are stored in juxtaglomerular cells and, when released, circulate in the blood. The concentration of prorenin in the circulation is approximately tenfold greater than that of the active enzyme. The half-life of circulating renin is approximately 15 minutes.

The physiological status of circulating prorenin is unclear.
(a) Control of renin secretion

The control of secretion of renin from juxtaglomerular cells is controlled predominantly by 3 pathways: two acting locally within the kidney, and the third acting through the central nervous system and mediated by norepinephrine release from renal noradrenergic nerves.

One intrarenal mechanism controlling renin release is called the macula densa pathway (Figure B A). The macula densa lies adjacent to the juxtaglomerular cells and is composed of specialized columnar epithelial cells located in the wall of that portion of the cortical thick ascending limb that passes between the afferent and efferent arterioles of the glomerulus. A change in NaCl reabsorption by the macula densa results in the transmission to nearby juxtaglomerular cells of chemical signals that modify renin release. Increases in NaCl flux across the macula densa inhibit renin release, and decreases in NaCl flux stimulate renin release. The chemical signals mediating the macula densa pathway involve both adenosine (Itoh et al, 1985; Weihprecht et al, 1990) and prostaglandins (Gerber et al, 1981; Greenberg et al, 1993), with the former being released when NaCl transport increases and the latter being released when NaCl transport decreases. In this regard, adenosine, acting via an A1 receptor, inhibits renin release (Jackson, 1991), and prostaglandins stimulate renin release (Jackson et al, 1985).

Several lines of evidence suggest a critical role for inducible cyclooxygenase (COX-2) and neuronal nitric oxide synthetase (nNOS) in the mechanism of macula densa-stimulated renin release. Although constitutive cyclooxygenase (COX-1) is the most abundant cyclooxygenase isoform in the mammalian kidney, inducible COX-2 is the only cyclooxygenase form expressed in the macula densa, and the amount of COX-2 in the macula densa is upregulated by chronic dietary sodium restriction (Harris et al, 1994). Moreover, selective inhibition of COX-2 blocks macula densa-mediated renin release.
(Traynor et al, 1999). Like COX-2, and nNOS is expressed in the macula densa; nNOS expression in the macula densa is upregulated by dietary sodium restriction (Singh et al, 1996), and selective inhibition of nNOS reduces renin release in response to chronic dietary sodium restriction (Beierwaltes, 1997). Together, these findings suggest a biochemical interplay between COX-2 and nNOS in the mechanism of macula densa-mediated renin release. Since nitric oxide reacts with superoxide anion to generate peroxynitrite, and peroxynitrite markedly activates cyclooxygenase activity (Landino et al, 1996), it is conceivable that activation of macula densa-mediated renin release by sodium depletion involves the following events: upregulation nNOS and COX-2 in the macula densa by sodium depletion; increased nitric oxide and hence peroxynitrite, biosynthesis in the macula densa; peroxynitrite-induced activation of COX-2 in the macula densa; increased prostaglandin production in the macula densa; activation of prostaglandin receptors in the juxtaglomerular cells by prostaglandins released from the macula densa. Possible mechanisms by which the macula densa regulates renin release are summarized in figure B B.

Although a change in NaCl by the macula densa is the key event that modulates the macula densa pathway, regulation of this pathway is more dependent on the luminal concentration of Cl· than Na⁺. NaCl transport into the macula densa is mediated by the Na⁺-K⁺-2 Cl· symporter, and the half-maximal concentrations of Na⁺ and Cl· required for transport via this symporter are 2-3 mEq/L and 40 mEq/L, respectively. Since the luminal concentration of Na⁺ at the macula densa is usually much greater than the level required for half-maximal transport, physiological variations in luminal Na⁺ concentrations at the macula densa have little effect on renin release (i.e., the symporter remains saturated with respective Na⁺). On the other hand, physiological changes in Cl· concentration at the macula densa have profound effect on macula densa-mediated renin release (Lorenz et al, 1991).
The second intrarenal mechanism controlling renin release is called the intrarenal baroreceptor pathway (middle of figure 2A). Increases and decreases in blood pressure in the preglomerular vessels inhibit and stimulate renin release, respectively. The immediate stimulus to secretion is believed to be a reduction in the tension within the wall of the afferent arteriole. Increases and decreases in renal perfusion pressure may inhibit and stimulate, respectively, the release of renal prostaglandins, which perhaps mediate in part the intrarenal baroreceptor pathway (Data et al, 1978; Linas, 1984). In fact, in renin-dependent renovascular hypertension, renin secretion and blood pressure are reduced by selective inhibition of COX-2 (Wang et al, 1999). However, biomechanical coupling via stretch-activated ion channels may play an important role in the intrarenal baroreceptor pathway (Carey et al, 1997).

The third mechanism, called the β-adrenergic receptor pathway (bottom of Figure B A), is mediated by the release of norepinephrine from postganglionic sympathetic nerve terminals; activation of β1-receptors on juxtaglomerular cells enhances renin release.

The three pathways regulating renin release are embedded in a physiological network. Increases in renin secretion enhance the formation of A-II, and A-II stimulates angiotensin subtype 1 (AT₁) receptors on juxtaglomerular cells to inhibit renin release. This feedback system has been termed the short-loop negative feedback mechanism. A-II also increases arterial blood pressure via stimulation of AT₁-receptors. Increases in blood pressure inhibit renin release by: (1) activating high-pressure baroreceptors, thereby reducing renal sympathetic tone; (2) increasing pressure in the preglomerular vessels, and (3) reducing NaCl reabsorption in the proximal tubule (pressure natriuresis), which increases tubular delivery of NaCl to the macula densa. The inhibition of renin release due to A-II-induced increases in blood pressure has been termed the long-loop negative feedback mechanism.
Fig. B: A. A schematic portrayal of the three major physiological pathways regulating renin release (Jackson, 2001).
MD, macula densa; PGI₂, prostaglandin I₂; NE/EPI, norepinephrine/epinephrine.
B. Possible mechanisms by which the macula densa regulates renin release (Jackson, 2001).
ADP, adenosine diphosphate; ADO, adenosine; nNOS, neuronal nitric oxide synthetase; A₁-receptor, adenosine receptor
The physiological pathways regulating renin release can be influenced by a number of pharmacological agents. Loop diuretics stimulate renin release in part by blocking the reabsorption of NaCl at the macula densa. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the formation of prostaglandins and thereby decreases renin release (Fröhlich et al., 1979). ACEIs, AT1-receptor blockers, and renin inhibitors interrupt both the short-and long-loop negative feedback mechanisms and therefore increase renin release.

(ii) Angiotensinogen

The substrate for renin is angiotensinogen, an abundant globular glycoprotein (MW=55,000-60,000Da), containing 13%-14% carbohydrate. High-molecular-weight (350,000-500,000Da) angiotensinogen also circulates in plasma and represents a complex of angiotensinogen with other proteins. The relevant portion of angiotensinogen is the amino terminus, from which angiotensin I is cleaved. Molecular cloning studies (Kageyama et al., 1984) demonstrate that human angiotensinogen contains 452 amino acids and is synthesized as preangiotensinogen which has a 24- or 33-amino acid signal peptide. Angiotensinogen is synthesized primarily in the liver, although mRNA that encodes the protein also is abundant in fat, certain regions of the CNS, and kidney (Campbell & Habener, 1986; Cassis et al., 1988). Angiotensinogen is continuously synthesized and secreted by the liver and its synthesis is stimulated by inflammation, insulin, estrogens, glucocorticoid, thyroid hormone, and A-II (Ben-Ari & Garrison, 1988).

Increases in angiotensinogen levels are associated with essential hypertension (Jeunemaitre et al., 1992), and there is genetic linkage between essential hypertension, angiotensinogen levels, and the angiotensinogen genes (Jeunemaitre et al., 1992; Caulfield et al., 1994, 1995).
(iii) Angiotensin-converting enzyme (ACE; kininase II; dipeptidyl carboxypeptidase)

ACE is an ectoenzyme and a glycoprotein with an apparent MW of 170,000Da. Human ACE contains 1277 amino acid residues and has two homologous domains, each with a catalytic site and a region for binding Zn$^{++}$ (Soubrier et al, 1988; Berstein et al, 1989). ACE has a large amino-terminal extracellular domain, a short carboxyl-terminal intracellular domain and a 17-amino acid hydrophobic stretch that anchors the ectoenzyme to the cell membrane. ACE is rather non-specific and cleaves dipeptide units from substrates with diverse amino acid sequences. Bradykinin is one of the many natural substrates for ACE, and ACE is identical to kininase II, which inactivates bradykinin and other potent vasodilator peptides.

The ACE gene codes for both a somatic and a testis-specific isozymes. The testis ACE is found exclusively in developing spermatids and mature sperm and is encoded by the second half of the ACE gene, driven by a testis-specific promoter. The ACE gene contains, in intron 16, an insertion/deletion polymorphism that explains 47% of the phenotypic variance in serum ACE levels (Rigat et al, 1990). The deletion allele is associated with higher levels of serum ACE and may confer an increased risk of ischemic heart disease (Cambien et al, 1992; Gardemann et al, 1995; Mattu et al, 1995).

(iv) Angiotensin peptides

When given intravenously, angiotensin I is so rapidly converted to A-II that the pharmacological responses of these two peptides are indistinguishable. However, angiotensin I per se is less than 1% as potent as A-II on smooth muscle, heart, and the adrenal cortex. As shown in figure 1, angiotensin III, also called (des-Asp$^1$) A-II or angiotensin (2-8) can be formed either by the action of ACE on (des-Asp$^1$) angiotensin I. Angiotensin III and A-II cause qualitatively similar effects. Angiotensin III is approximately as potent as A-II in stimulating
the secretion of aldosterone; however, angiotensin III is only 25% and 10% as potent as A-II in elevating blood pressure and stimulating the adrenal medulla, respectively (Peach, 1977; Bell et al, 1984).

Angiotensin I can be metabolized to angiotensin (1-7) by the enzymes metalloendopeptidase 24.15, endopeptidase 24.11, and prolylendopeptidase 24.26, and A-II can be converted to angiotensin (1-7) by prolylcarboxypeptidase (Ferraro et al, 1997). ACEIs increase, rather than decrease, tissue and plasma levels of angiotensin (1-7), because angiotensin I levels are increased and diverted away from A-II formation (figure 1) and because ACE contributes importantly to the plasma clearance of angiotensin (1-7) (Yamada et al, 1998). The pharmacological profile of angiotensin (1-7) is distinct from that of A-II. Unlike A-II, angiotensin (1-7) does not cause vasoconstriction, aldosterone release, or facilitation of noradrenergic neurotransmission. Angiotensin (1-7) releases vasopressin, stimulates prostaglandin biosynthesis, elicits depressor responses when microinjected into certain brainstem nuclei, dilates some blood vessels, and exerts a natriuretic action on the kidney. The effects of angiotensin (1-7) may be mediated by a specific angiotensin (1-7) receptor (Tallant et al, 1997).

Putative receptors for angiotensin (3-8), also called angiotensin IV, are detectable in a number of tissues (Swanson et al, 1992), and angiotensin (3-8) stimulates the expression of plasminogen activator inhibitor 1 in endothelial (Kerins et al, 1995) and proximal tubular (Gesualdo et al, 1999) cells. The physiological significance of both angiotensin (1-7) and angiotensin (3-8) remains uncertain.

(v) Angiotensinases

This term is applied to various peptidases that are involved in the degradation and inactivation of angiotensin peptides; none is specific. Among them are aminopeptidases, endopeptidases, and the carboxypeptidases.
3.2.2 Local (Tissue) Renin-Angiotensin Systems

Circulating renin of renal origin acts on circulating angiotensinogen of hepatic origin to produce angiotensin I in the plasma; circulating angiotensin I is converted by plasma ACE and by pulmonary endothelial ACE to A-II; A-II is then delivered to its target organs via the blood stream, where it induces a physiological response.

3.2.3 Extrinsic, Local Renin-Angiotensin Systems

Since ACE is present on the luminal face of vascular endothelial cells throughout the circulation, and since circulating renin of renal origin can be taken up (sequestered) by the arterial wall as well as by other tissues, the conversion of hepatic angiotensinogen to angiotensin I and the conversion of angiotensin I (both circulating and locally produced) to A-II may occur primarily within or at the surface of the blood vessel wall, not in the circulation per se (Danser et al, 1991; 1994).

3.2.4 Intrinsic, Local Renin-Angiotensin Systems

Many tissues – including the brain, pituitary, blood vessels, heart, kidney, and adrenal gland – express mRNAs for renin, angiotensins, angiotensinogen, and/or ACE, and various cultured cell types from these issues produce renin, angiotensinogen, ACE, and/or angiotensins I, II, and III (Dzau, 1993; Phillips et al, 1993). Therefore, it appears that local-angiotensin systems exist independently of the renal/hepatic-based system.

3.2.5 Alternative Pathways for Angiotensin Biosynthesis

Some tissues contain nonrenin angiotensinogen-processing enzymes that convert angiotensinogen to angiotensin I (nonrenin proteases) or directly to A-II (e.g., cathepsin G, tonin) and non-ACE angiotensin I-processing enzyme that convert angiotensin I to A-II (e.g., cathepsin G, chymostatin-sensitive A-II-generating enzyme, heart chymase) (Dzau et al, 1993).
3.2.6 Angiotensin Receptors

The effects of angiotensins are exerted through specific cell surface receptors. Studies by Whitebread et al (1989) and Chiu et al (1989) have identified two subtypes of angiotensin receptors that are now designated AT\(_1\) and AT\(_2\) (Bumpus et al, 1991). Both the AT\(_1\) and AT\(_2\) receptors are members of the G-protein coupled receptor family with seven putative transmembrane regions. The AT\(_1\) receptor is 359 amino acids long, and AT\(_2\) receptor is 366 amino acids long. Most of the biological effects of A-II are mediated by the AT\(_1\) receptor. The AT\(_1\) receptor gene contains a polymorphism (A to C transversion at position 1166) that may be associated with hypertension (Kainulainen et al, 1999).

3.2.7 Functions of the Renin-Angiotensin System

The renin-angiotensin system (RAS) plays a major role in regulating arterial blood pressure over both the short and long term. Moderate changes in plasma concentrations of A-II acutely increase blood pressure; on a molar basis, A-II is approximately 40 times more potent than norepinephrine in this regard. When a single moderate dose of A-II is injected intravenously, systemic blood pressure begins to rise within seconds, rapidly reaches maximum, and returns to normal within minutes. This rapid pressor response to A-II is due to swift increase in total peripheral resistance (TPR) – a response that helps maintain arterial blood pressure in the face of an acute hypotensive challenge (e.g., blood loss, vasodilation). Although A-II directly increases cardiac contractility (via opening voltage-gated Ca\(^{2+}\) in cardiac myocytes) and indirectly increases heart rate (via facilitation of sympathetic tone, enhanced noradrenergic neurotransmission, and adrenal catecholamine release), the rapid increase in arterial blood pressure activates a baroreceptor reflex that decreases sympathetic tone and increases vagal tone.
A-II also causes slow pressor response that helps stabilize arterial blood pressure over the long term. A-II-induced stimulation of endothelin-1 (Laursen et al, 1997) and superoxide anion (Rajagopalan et al, 1997) mediates, in part, the slow pressor response. The effects of A-II on TPR, renal function, and cardiovascular structure are mediated by a number of direct and indirect mechanisms (Figure C).

**Fig C:** Summary of the three major effects of angiotensin-II and the mechanism that mediate them.

### 3.2.8 ACE Inhibitors

ACE inhibitors attenuate or abolish responses to angiotensin I but not to A-II (Fig-1). In this regard, ACE inhibitors are highly selective drugs. They do not interact directly with other components of RAS, and the principal pharmacological and clinical effects of ACEIs seem to arise from suppression of synthesis of A-II. Nevertheless, ACE is an enzyme with many substrates and inhibition of ACE therefore may induce effects unrelated to reducing the levels of A-II. Since ACEIs increase bradykinin levels, and since bradykinin stimulates prostaglandin...
synthesis, bradykinin/or prostaglandins may contribute to the pharmacological effects of ACEIs. It has been demonstrated that blockade of bradykinin receptors in human attenuates the acute blood pressure reduction induced by ACE inhibition (Gainer et al, 1998). Recent studies, however, failed to demonstrate a role for bradykinin in the vascular or cardiac effects of ACEIs (Davie et al, 1999; Campbell et al, 1999; Rhaleb et al, 1999).

(i) Clinical pharmacology

These drugs can be classified into three broad groups based on chemical structure:

(1) sulfhydryl-containing ACEIs structurally related to captopril (e.g., fentiapril, pivalopril, zofenopril, alacepril);

(2) dicarboxyl-containing ACEIs structurally related to enalapril (e.g., lisinopril, benazepril, quinapril, moexipril, ramipril, spirapril, perindopril, pentopril, cilazapril); and

(3) phosphorus-containing ACEIs structurally related to fosinopril.

In general, ACEIs differ with regard to three properties: (1) potency; (2) whether ACE inhibition is due primarily to the drug itself or to conversion of a prodrug to an active metabolite; and (3) pharmacokinetics.

3.3 TREATMENT OF HYPERTENSION

Hypertension is one of the most common conditions treated by clinicians, yet accurate diagnosis and selection of the appropriate treatment can be challenging and recommendations regarding antihypertensive medications continue to evolve. Virtually every patient with a diastolic arterial pressure that persistently exceeds 90 mmHg, or any patient over 65 years of age with a systolic arterial pressure > 160 mmHg, is a candidate for diagnostic studies and for subsequent treatment.
3.3.1 General Measures

Before the diagnosis of hypertension is made and therapy begun, the blood pressure must be carefully measured (Reeves, 1995). Considerations should be given to home and ambulatory recordings since more than 20% of patients with readings repeatedly higher than 140/90 mm Hg in the office are normotensive when multiple out-of-the-office readings are obtained (Pierdomenico et al, 1995).

Nondrug therapeutic intervention is probably indicated in all patients with sustained hypertension and probably in most with labile hypertension. The general measures employed include (1) relief of stress, (2) dietary management, (3) regular aerobic exercise, (4) weight reduction (if needed), and (5) control of other risk factors contributing to the development of arteriosclerosis.

Dietary management has 3 aspects:

1. Because of the documented efficacy of sodium restriction and volume contraction in lowering blood pressure, patients previously were instructed to curtail sodium intake drastically. Some investigators have suggested that this is not necessary. They base their conclusion on two observations: (1) in many patients the blood pressure is not sensitive to the level of sodium intake, and (2) diuretics provide another method of decreasing body sodium stores in individuals whose blood pressure is sodium-sensitive. Some studies have also reported a lowering of arterial pressure related to an increase in potassium and/or calcium intake.

2. Caloric restrictions should be urged for patients who are overweight.

3. A restriction in the intake of cholesterol and saturated fats is recommended, as this diet modification may diminish the incidence of arteriosclerotic complications. Reducing alcohol intake to < 15mL daily is also beneficial. Regular exercise is indicated within the limits of the patient's cardiovascular status. The dietary
management outlined above is aimed at the control of other risk factors.

The lifestyle changes listed (Table C) in the fifth report of the Joint National Committee for the Detection, Evaluation, and Treatment of High Blood Pressure (JNC V, 1993) are indicated for those with either white-coat or persistent hypertension. In the absence of severe hypertension with blood pressure above 210/120 mm Hg, or target organ damage that mandates immediate antihypertensive therapy, these lifestyle modifications should be instituted before drug therapy is begun while the degree of hypertension is being ascertained.

Table C: Lifestyle Modifications for Hypertension Control and/or Overall Cardiovascular Risk

<table>
<thead>
<tr>
<th>Lose weight if overweight.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limit alcohol intake to ≤ 1 oz/d of ethanol (24 oz of beer, 8 oz of wine, or 2 oz of 100-proof whiskey).</td>
</tr>
<tr>
<td>Exercise (aerobic) regularly.</td>
</tr>
<tr>
<td>Reduce sodium intake to less than 100 mmol/d (&lt; 2.3g of sodium or approximately &lt; 6g of sodium chloride).</td>
</tr>
<tr>
<td>Maintain adequate dietary potassium, calcium, and magnesium intake.</td>
</tr>
<tr>
<td>Stop smoking and reduce dietary saturated fat and cholesterol intake for overall cardiovascular health; reducing fat intake also helps reduce caloric intake—important for control of weight and type II diabetes.</td>
</tr>
</tbody>
</table>

3.3.2 Drug Therapy for Hypertension

When drug therapy is instituted, the practitioner has a large number of choices, rationally divided into six major classes: diuretics, peripheral and central adrenergic inhibitors (α-blockers, β-blockers and α-β-blockers), vasodilators, calcium channel blockers (CCBs), and angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (Table D). The direct vasodilators are rarely used alone. The overall pattern of antihypertensive drug use has changed dramatically during recent years. CCBs and ACEIs have become increasingly popular, the former now having replaced diuretics as the most common prescribed agents.
### Table D: Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Volume depleters</th>
<th>Loop diuretics</th>
<th>Potassium savers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Bumetanide</td>
<td>Amiloride</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Furosemide</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Metolazone</td>
<td>Torsemide</td>
<td>Triamterene</td>
</tr>
<tr>
<td>Thiazides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adrenergic inhibitors</th>
<th>Peripheral</th>
<th>Central</th>
<th>α-Receptor</th>
<th>β-Receptors</th>
<th>Combined α-β</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Guanethidine</td>
<td>Clonidine</td>
<td>Doxazosin</td>
<td>Acebutolol</td>
<td>Carvedilol</td>
</tr>
<tr>
<td></td>
<td>Reserpine</td>
<td>Guanabenz</td>
<td>Prazosin</td>
<td>Atenolol</td>
<td>Labetalol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guanphesine</td>
<td>Terazosin</td>
<td>Betaxolol</td>
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<tr>
<td></td>
<td></td>
<td>Methyldopa</td>
<td></td>
<td>Bisoprolol</td>
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<td>Carteolol</td>
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<td></td>
<td>Metoprolol</td>
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<td></td>
<td></td>
<td></td>
<td>Propranolol</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vasodilators</th>
<th>Calcium Channel Blockers</th>
<th>ACE Inhibitors</th>
<th>Angiotensin II Receptor Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Amlodipine</td>
<td>Benazepril</td>
<td>Losartan</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Diltiazem</td>
<td>Captopril</td>
<td>Candesartan</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>Enalapril</td>
<td>Irbesartan</td>
</tr>
<tr>
<td></td>
<td>Isradipine</td>
<td>Fosinopril</td>
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</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>Lisinopril</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nisoldipine</td>
<td>Moexipril</td>
<td></td>
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<tr>
<td></td>
<td>Verapamil</td>
<td>Quinapril</td>
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<tr>
<td></td>
<td></td>
<td>Ramipril</td>
<td></td>
</tr>
</tbody>
</table>

Antihypertensive drugs can also be classified according to their sites or mechanisms of action (Table E).

Whatever drug is chosen to institute therapy will provide about the same overall antihypertensive efficacy to the general population of hypertensive patients, assuming that mid-range doses are prescribed. Almost all hypertensive patients are started on a single drug since most have fairly mild hypertension and few need immediate reductions of blood pressure beyond that provided by a single agent. Parenthetically, combinations of 2 drugs in low doses, neither of which alone provide much antihypertensive efficacy, have been shown to provide full efficacy and fewer adverse effects (Frishman et al, 1994), so that low-dose combinations in a single tablet may increasingly be chosen for initial therapy. As stated in the JNC-V report: “Combining antihypertensive drugs with different modes of action will often allow smaller doses of drugs to be used to achieve control, thereby minimizing the potential for dose-dependent side effects.”
<table>
<thead>
<tr>
<th>Site of action</th>
<th>Drug</th>
<th>Dosage</th>
<th>Indications</th>
<th>Contraindications / Cautions</th>
<th>Frequent or peculiar side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIURETICS</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Renal tubule</td>
<td><strong>Thiazides:</strong></td>
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<tr>
<td></td>
<td>e.g., hydrochlorothiazide</td>
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<td></td>
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<tr>
<td></td>
<td>Oral: 12.5-25mg</td>
<td>Daily</td>
<td>Mild hypertension; as adjunct in treatment of moderate to severe hypertension</td>
<td>Diabetes mellitus, hyperuricemia, primary aldosteronism</td>
<td>Potassium depletion, hyperglycemia, hyperuricemia, hypercholesterolemia, dermatitis, purpura, depression, hypercalcemia</td>
</tr>
<tr>
<td>Loop-acting:</td>
<td><strong>e.g., furosemide</strong></td>
<td>Oral: 20-80mg 2 or 3 times a day</td>
<td>Mild hypertension; as adjunct in severe or malignant hypertension, particularly with renal failure</td>
<td>Hyperuricemia, primary aldosteronism</td>
<td>Potassium depletion, hyperuricemia, hyperglycemia, hypocalcemia, blood dyscrasias, rash, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Potassium-sparing</td>
<td><strong>e.g., spironolactone</strong></td>
<td>Oral: 25mg 2 to 4 times daily</td>
<td>Hypertension due to hypermineralocorticoidism, as adjunct to thiazide therapy</td>
<td>Renal failure</td>
<td>Hyperkalemia, diarrhea, gynecomastia, menstrual irregularities</td>
</tr>
<tr>
<td></td>
<td><strong>triamterene</strong></td>
<td>Oral: 25-100mg Daily</td>
<td></td>
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<tr>
<td></td>
<td><strong>amiloride</strong></td>
<td>Oral: 5-10mg Daily</td>
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</tbody>
</table>
### REVIEW OF LITERATURE

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Drug</th>
<th>Dosage</th>
<th>Indications</th>
<th>Contraindications / Cautions</th>
<th>Frequent or peculiar side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIADRENERGIC AGENTS</strong></td>
<td></td>
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<tr>
<td>Central</td>
<td>Clonidine</td>
<td>Oral: 0.05-0.6mg</td>
<td>Mild to moderate hypertension, renal disease with hypertension</td>
<td>Postural hypotension, drowsiness, dry mouth, rebound hypertension after abrupt withdrawal, insomnia</td>
<td>Postural hypotension, drowsiness, dry mouth, rebound hypertension after abrupt withdrawal, insomnia</td>
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<tr>
<td></td>
<td></td>
<td>Twice daily</td>
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<td></td>
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<td>Oral: 4-16mg</td>
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<td></td>
<td></td>
<td>Twice daily</td>
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<tr>
<td></td>
<td></td>
<td>Oral: 1-3mg daily</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Oral: 250-1000 mg</td>
<td>Mild to moderate hypertension (oral), malignant hypertension (IV) during MAO inhibitor administration</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>mg twice daily</td>
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<td></td>
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<td>IV: 250-1000mg每4-6h</td>
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<td></td>
<td></td>
<td>Oral: l-3mg daily</td>
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<td>(tolerance may develop)</td>
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<tr>
<td></td>
<td>Guanabenz</td>
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<tr>
<td></td>
<td>Guanfacine</td>
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<tr>
<td></td>
<td>Methylodopa (also acts by blocking sympathetic nerves)</td>
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<tr>
<td>Autonomic Ganglia</td>
<td>Trimethaphan</td>
<td>IV: 1-6mg/min</td>
<td>Severe or malignant hypertension</td>
<td>Postural hypotension, visual symptoms, dry mouth, constipation, urinary retention, impotence</td>
<td>Postural hypotension, visual symptoms, dry mouth, constipation, urinary retention, impotence</td>
</tr>
<tr>
<td>Nerve Endings</td>
<td>Guanethidine</td>
<td>Oral: 10-150mg</td>
<td>Moderate to severe hypertension</td>
<td>Pheochromocytoma, severe coronary artery disease, cerebrovascular insufficiency, diabetes mellitus (on hypoglycemic therapy), glaucoma prostatism</td>
<td>Postural hypotension, bradycardia, dry mouth, diarrhea, impaired ejaculation, fluid retention, asthma</td>
</tr>
<tr>
<td></td>
<td>Guanadrel</td>
<td>Oral: 5-50mg</td>
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<td></td>
<td></td>
<td>Twice daily</td>
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<tr>
<td>Site of action</td>
<td>Drug</td>
<td>Dosage</td>
<td>Indications</td>
<td>Contraindications / Cautions</td>
<td>Frequent or peculiar side effects</td>
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<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>α-receptors</td>
<td>Phentolamine</td>
<td>IV: 1-5mg bolus</td>
<td>Suspected or proved pheochromocytoma</td>
<td>Severe coronary artery disease</td>
<td>Tachycardia, weakness, dizziness, flushing</td>
</tr>
<tr>
<td></td>
<td>Phenoxybenzamine</td>
<td>Oral: 10-50mg Once or twice Daily (tolerance May develop)</td>
<td>Proved pheochromocytoma</td>
<td></td>
<td>Postural hypotension, tachycardia, miosis, nasal congestion, dry mouth</td>
</tr>
<tr>
<td></td>
<td>Prazosin</td>
<td>Oral: 1-10mg Twice daily</td>
<td>Mild to moderate hypertention</td>
<td>Use with caution in the elderly</td>
<td>Sudden syncope, headache, sedation, dizziness, tachycardia, anticholinergic effect, fluid retention</td>
</tr>
<tr>
<td></td>
<td>Terazosin</td>
<td>Oral: 1-20mg Daily</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Doxazosin</td>
<td>Oral: 1-16mg Daily</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>β-receptor</td>
<td>Propranolol</td>
<td>Oral: 10-120mg 2-4 times daily</td>
<td>Mild to moderate hypertension (especially with evidence of hyperdynamic circulation); as adjunct to hydralazine therapy</td>
<td>Congestive heart failure, asthma, diabetes mellitus (on hypoglycemic therapy), during MAO inhibitor administration, COPD, sick sinus syndrome, 2d or 3d degree heart block</td>
<td>Dizziness, depression, bronchospasm, nausea, vomiting, diarrhea, constipation, heart failure, fatigue, Raynaud's phenomenon, hallucinations, hypertriglyceridemia, hypercholesterolemia, psoriasis; sudden withdrawal may precipitate angina or myocardial injury in patients with heart disease Less resting bradycardia than other beta blockers</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>Oral: 25-150mg Twice daily</td>
<td></td>
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<tr>
<td></td>
<td>Nadolol</td>
<td>Oral: 20-120mg daily</td>
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<tr>
<td></td>
<td>Atenolol</td>
<td>Oral: 25-100mg daily</td>
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<tr>
<td></td>
<td>Timolol</td>
<td>Oral: 5-15mg twice daily</td>
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<tr>
<td></td>
<td>Betaxolol</td>
<td>Oral: 10-20mg daily</td>
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<tr>
<td></td>
<td>Carteolol</td>
<td>Oral: 2.5-10mg daily</td>
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<tr>
<td></td>
<td>Pindolol</td>
<td>Oral: 5-30mg twice daily</td>
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<tr>
<td></td>
<td>Acebutolol</td>
<td>Oral: 200-600mg twice daily</td>
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<tr>
<td>Site of action</td>
<td>Drug</td>
<td>Dosage</td>
<td>Indications</td>
<td>Contraindications / Cautions</td>
<td>Frequent or peculiar side effects</td>
</tr>
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<td>---------------</td>
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<td>-----------------------------------------------------------------</td>
<td>----------------------------------------------------</td>
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</tr>
<tr>
<td>a/β-receptors</td>
<td>Labetalol</td>
<td>Oral: 100-600mg twice daily</td>
<td></td>
<td>Similar to beta blockers with more postural effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV: 2 mg/min</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Oral: 12.5-50mg daily or in divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carvedilol</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>VASODILATORS</td>
<td>Hydroalazine</td>
<td>Oral: 10-75mg 4 times daily</td>
<td>As adjunct in treatment of hypertension (oral), malignant</td>
<td>Lupus erythematosus, severe coronary artery disease</td>
<td>Headache, tachycardia, angina</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td>IV or IM: 10-50 mg every 6h (tolerance may</td>
<td>hypertension (IV or IM), renal disease with hypertension</td>
<td></td>
<td>pectoris, anorexia, nausea,</td>
</tr>
<tr>
<td>smooth</td>
<td></td>
<td>develop)</td>
<td></td>
<td></td>
<td>vomiting, diarrhea, lupuslike</td>
</tr>
<tr>
<td>muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>syndrome, rash, fluid retention</td>
</tr>
<tr>
<td></td>
<td>Minoxidil</td>
<td>Oral: 2.5-40mg twice daily</td>
<td>Severe hypertension</td>
<td>Severe coronary artery disease</td>
<td>Tachycardia, aggravates angina,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>marked fluid retention, hair growth on face and body, coarsening of facial features, possible pericardial effusions</td>
</tr>
<tr>
<td></td>
<td>Diazoxide</td>
<td>IV: 1-3 mg/kg up to 150 mg rapidly</td>
<td>Severe malignant hypertension</td>
<td>Diabetes mellitus, hyperuricemia, congestive heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nitroprusside</td>
<td>IV: 0.5-8 (µg/kg) /min</td>
<td>Malignant hypertension</td>
<td></td>
<td>Apprehension, weakness, diaphoresis, nausea, vomiting, muscle twitching, cyanide toxicity</td>
</tr>
<tr>
<td>Site of action</td>
<td>Drug</td>
<td>Dosage</td>
<td>Indications</td>
<td>Contraindications / Cautions</td>
<td>Frequent or peculiar side effects</td>
</tr>
<tr>
<td>----------------</td>
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<td>-------------</td>
<td>----------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>ANGIOTENSIN-CONVERTING ENZYME INHIBITORS</td>
<td>Captopril</td>
<td>Oral: 12.5-75mg twice daily</td>
<td>Mild to severe hypertension, renal artery stenosis</td>
<td>Renal failure (reduction of dose), bilateral renal artery stenosis, pregnancy</td>
<td>Leukopenia, pancytopenia, hypotension, cough, angioedema, urticarial rash, fever, loss of taste, acute renal failure in bilateral renal artery stenosis, hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Benazepril</td>
<td>Oral: 5-40mg daily</td>
<td></td>
<td></td>
<td>Same as captopril, but little evidence for leukopenia, but perhaps increased frequency of cough and angioedema. All can be given once daily, but side effects are reduced if one-half dose is given twice daily. Fosinopril is excreted more in bile than the others.</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td>Oral: 2.5-40mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enalaprilat</td>
<td>IV: 0.625-1.25mg over 5 min every 6-8h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fosinopril</td>
<td>Oral: 10-40mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lisinopril</td>
<td>Oral: 5-40mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quinapril</td>
<td>Oral: 5-80mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>Oral: 1.25-20mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trandolapril</td>
<td>Oral: 1-4mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANGIOTENSIN RECEPTOR ANTAGONISTS</td>
<td>Losartan</td>
<td>Oral: 25-50mg once or twice daily</td>
<td>Mild to severe hypertension, renal artery stenosis</td>
<td>Pregnancy, bilateral renal artery stenosis</td>
<td>Hypotension, acute renal failure in bilateral renal artery stenosis, hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Valsartan</td>
<td>Oral: 80-320mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irbesartan</td>
<td>Oral: 150-300mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of action</td>
<td>Drug</td>
<td>Dosage</td>
<td>Indications</td>
<td>Contraindications / Cautions</td>
<td>Frequent or peculiar side effects</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
<td>------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Vascular</td>
<td>Dihydropyridines:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>smooth muscle</td>
<td>Nifedipine XL</td>
<td>Oral: 30-90mg daily</td>
<td>Mild to moderate</td>
<td>Heart failure 2d or 3d heart block</td>
<td>Tachycardia, flushing, gastrointestinal disturbances, hyperkalemia, edema, headache</td>
</tr>
<tr>
<td></td>
<td>Amlodipine</td>
<td>Oral: 2.5-10mg daily</td>
<td>hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Felodipine XL</td>
<td>Oral: 5-10mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isradipine</td>
<td>Oral: 2.5-10mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td>Oral: 20-40mg 3 times daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzothiazepines:</td>
<td>Diltiazem</td>
<td>Oral: 30-90mg 4 times daily or as CD form 180-300 mg daily</td>
<td>Mild to moderate hypertension</td>
<td>Heart failure 2d or 3d heart block</td>
<td>Same as amlodipine, except no tachycardia or edema, but can cause heart block, constipation and liver dysfunction</td>
</tr>
<tr>
<td>Phenylalkylamine:</td>
<td>Verapamil</td>
<td>Oral: 30-120mg 4 times daily or as SR form 120-480mg daily</td>
<td>Mild to moderate hypertension</td>
<td>Heart failure 2d or 3d heart block</td>
<td></td>
</tr>
</tbody>
</table>
3.3.3 Choice of Initial Therapy for Hypertension (Kaplan & Gifford, 1996)

(i) Diuretics

Low doses of thiazide diuretics, i.e., 12.5mg of hydrochlorothiazide with a potassium-sparing agent, are often effective. The metabolic adverse effects of diuretics are minimized but not eliminated by using such small doses. A loop diuretic should only be used if renal insufficiency is present. Diuretics have an additive, if not synergistic, effect with all of the other classes of drugs for hypertension.

(ii) Peripheral and central-acting adrenergic inhibitors

These agents are not ideal initial drugs because of their adverse-effect profile, and the fact they must be given at least twice daily, except for reserpine, guanphesine and the clonidine patch.

α1-Adrenergic Receptor Blockers: Drugs that produce vasodilation by selective blockade of the α1-Adrenergic Receptor usually do not produce tachycardia and palpitations because they do not interfere with the negative feedback mechanism that controls the release of norepinephrine. These are the only antihypertensive agents that have beneficial effects on both serum lipid levels and glucose metabolism by reducing insulin resistance, which is frequently found in hypertension patients, especially the obese. There are no contraindications to the use of selective α1-Adrenergic Receptor blocking agents, provided that appropriate caution is exercised in warning patients, particularly the elderly, about the possibility of an orthostatic hypotensive response to the initial dose ("first-dose effect").

β-Adrenergic Receptor Blockers: All β-blockers with or without cardioselectivity / intrinsic sympathomimetic activity, are equally potent in reducing blood pressure when given in effective doses.

The combined α-β-Blockers are usually reserved for more severe hypertension.
(iii) Calcium channel blockers (CCBs)

CCBs differ in their action on various vascular beds. Dihydropyrine CCBs are excellent peripheral vasodilators, reducing total peripheral resistance. There are concerns about deleterious cardiac effects of short-acting formulations of various CCBs.

(iv) ACE inhibitors (ACEIs)

Randomized controlled trials have convincingly shown that treatment with an ACE Inhibitor (ACEI) reduces morbidity and mortality for patients with systolic dysfunction (ejection fraction < 40%) with or without congestive heart failure (Pfeffer et al, 1992).

(v) Angiotensin-II receptor blockers

They seem to be equipotent to ACEIs in reducing blood pressure. It is clear from available information that unlike ACEIs, they do not incite cough as an adverse effect but they may cause angioedema.

3.3.4 Therapeutic Uses of ACEIs

ACEIs act by inhibiting short as well as long term effects of Ang-II on cardiovascular system.

(i) They reverse Ang-II mediated vasoconstriction and cause a large drop in arterial pressure.
(ii) They cause natriuresis. ACEIs also affect renal hemodynamics.

ACEIs in hypertension: Inhibition of ACE lowers systemic vascular resistance and mean, diastolic, and systolic blood pressures in various hypertensive states. The initial change in blood pressure tends to be positively correlated with plasma renin activity (PRA) and Ang-II plasma levels prior to treatment. However, several weeks into treatment, a greater percentage of patients show a sizeable reduction in blood pressure, and the antihypertensive effect then correlates poorly or not at all with pre-treatment values of PRA.
Renal vessels are exceptionally sensitive to the vasoconstrictor actions of A-II. Increased renal blood flow occurs without an increase in glomerular filtration rate; in fact, the filtration fraction is reduced. Both the afferent and efferent arterioles are dilated. Besides causing systemic arteriolar dilatation, ACEIs increase the compliance of large arteries, which contributes to a reduction of systolic pressure.

**ACEIs in left ventricular systolic dysfunction:** Several large, prospective, randomised, placebo-controlled clinical studies support the usefulness of ACEIs in patients with varying degrees of left ventricular systolic dysfunction (Jackson, 2001). The combined results of these studies strongly indicate that inhibition of ACE in patients with systolic dysfunction prevents or delays the progression of heart failure, decreases the incidence of sudden death and myocardial infarction, decreases hospitalisation, and improves quality of life. Inhibition of ACE commonly reduces afterload and systolic wall stress, and both cardiac output and cardiac index increase, as do indices of stroke work and stroke volume. In heart failure, ACEIs reduce ventricular dilation and tend to restore the heart to its normal elliptical shape. ACEIs may reverse ventricular remodelling via changes in preload/afterload, by preventing the growth effects of A-II on myocytes, and/or by attenuating aldosterone-induced cardiac fibrosis (Grassie et al, 1997).

It is also reported that infusions of enalaprilat into the left coronary arteries of patients with left ventricular hypertrophy significantly improve diastolic function (Friedrich et al, 1994; Kyriakidis et al, 1998).

**ACEIs in acute myocardial infarction:** The beneficial effects of ACEIs in acute myocardial infarction are particularly large in hypertensive (Borghi et al, 1999) and diabetic (Zuanetti et al, 1997; Gustafsson et al, 1999) patients. In high-risk patients (e.g., large infarct, systolic ventricular dysfunction), ACE inhibition should be continued long-term.
**ACEIs in patients who are at high risk of cardiovascular events:** ACEIs tilt the fibrinolytic balance toward a profibrinolytic state by reducing plasma levels of plasminogen activator inhibitor-1 (Vaughan et al, 1997; Brown et al, 1999) and improve endothelial vasomotor dysfunction in patients with coronary artery disease (Mancini et al, 1996). The landmark HOPE study demonstrated that patients who were at high risk of cardiovascular events benefited considerably from treatment with ACEIs (Yusuf et al, 2000).

**ACEIs in chronic renal failure:** Diabetes mellitus accounts for about one-third of all end-stage renal disease (ESRD). It is reported that in patients with type I or type II diabetes mellitus and diabetic nephropathy, regardless of baseline renal function or arterial blood pressure, captopril and other ACEIs prevent or delay the progression of renal disease (Lewis et al, 1993; Ravid et al, 1998; EUCLID study group, 1997). In addition to preventing diabetic nephropathy, ACEIs also may decrease retinopathy progression in type I diabetics (Chaturvedi et al, 1998).

**ACEIs in scleroderma renal crisis:** A few small, observational studies have suggested that captopril markedly improved scleroderma renal crisis otherwise grim prognosis.

### 3.3.5 Adverse Effects of ACEIs

Metabolic side effects are not encountered during long-term therapy with ACEIs. The drugs do not alter plasma concentrations of uric acid and Ca$^{2+}$ (Frohlich, 1989) and may actually improve insulin sensitivity in patients with insulin resistance and decrease cholesterol levels and lipoprotein(a) levels in proteinuric renal disease. Serious untoward reactions to ACEIs are rare, and in general ACEIs are well tolerated.

**Hypotension:** A steep fall in blood pressure may occur following the first dose of an ACEI in patients with elevated PRA. In this regard, care should be exercised in patients who are salt-depleted, in patients being
treated with multiple antihypertensive drugs, and in patients who have congestive heart failure.

**Cough:** In 5% to 20% of patients, ACEIs induce a bothersome, dry cough; it is usually not dose-related, occurs more frequently in women than men, usually develops between 1 week and 6 months after initiation of therapy, and sometimes require cessation of therapy. This adverse effect may be mediated by the accumulation in lungs of bradykinin, substance P, and/or prostaglandins. Once ACEIs are stopped, the cough disappears, usually within 4 days (Israili & Hall, 1992).

**Hyperkalemia:** Despite some reduction in the concentration of aldosterone, significant retention of K⁺ is rarely encountered in patients with normal renal function who are not taking other drugs that cause K⁺ retention. However, ACEIs may cause hyperkalemia in patients with renal insufficiency or in patients taking K⁺-sparing diuretics, K⁺-supplements, β-adrenergic receptor blockers, or NSAIDs (Jackson, 2001).

**Acute-renal failure:** Angiotensin II, by constricting the efferent arteriole, helps maintain adequate glomerular filtration when renal perfusion pressure is low. Consequently, inhibition of ACE can induce acute renal insufficiency in patients with bilateral renal artery stenosis, stenosis of the artery to a single remaining kidney, heart failure, or dehydration due to diarrhea or diuretics. Older patients with congestive heart failure are particularly susceptible ACEI-induced acute renal failure. However, in nearly all patients who receive appropriate treatment, recovery of renal function occurs without sequelae (Wynckel et al, 1998).

**Fetopathic potential:** Although ACE inhibitors are not teratogenic during the early period of organogenesis (first trimester), continued administration of ACEIs during the second and third trimesters can cause oligohydramnios, fetal calvarial hypoplasia, fetal pulmonary
hypoplasia, fetal growth retardation, fetal death, neonatal anuria, and neonatal death. These fetopathic effects may be due in part to fetal hypotension. While ACEIs are not contraindicated in women of reproductive age, once pregnancy is diagnosed, it is imperative that ACEIs be discontinued as soon as possible. If necessary, an alternative antihypertensive regimen should be instituted.

**Skin rash:** ACEIs occasionally cause maculopapular rash that may or may not itch. The rash may resolve spontaneously and may respond to a reduction in doses or a brief course of antihistaminics.

**Proteinuria:** ACEIs have been associated with proteinuria (> 1 gm/day); however, a causal relationship has been difficult to establish.

**Angioneurotic edema:** In 0.1-0.2% of patients, ACEIs induce rapid swelling in the nose, throat, mouth, glottis, lips, larynx, and/or tongue. This untoward effect, called angioneurotic edema, apparently is not dose-related and nearly always develops within the first week of therapy, usually within the first few hours after the initial dose. Airway obstruction and respiratory distress may lead to death. Although the mechanism of angioneurotic edema is unknown, it may involve accumulation of bradykinin, induction of tissue-specific autoantibodies, or inhibition of complement-1-esterase inactivator. Once ACEIs are stopped, angioneurotic edema disappears within hours; meanwhile the patient's airway should be protected, and, if necessary, epinephrine, an antihistamine, and/or a corticosteroid should be administered (Israel & Hall, 1992).

**Dysguesia:** An alteration in or loss of taste can occur in the patients receiving ACEIs.

**Neutropenia:** Neutropenia is a rare, but serious, side effect of ACEIs. Although the frequency of neutropenia is low, it occurs predominantly in hypertensive patients with collagen-vascular or renal parenchymal disease.
Glycosuria: An exceedingly rare and reversible side effect of ACEIs is spillage of glucose in the urine in the absence of hyperglycemia (Cressman et al., 1982).

Hepatotoxicity: Also exceedingly rare and reversible is hepatotoxicity, usually of the cholestatic variety (Hagley et al., 1993).

3.3.6 Drug Interactions

Antacids may reduce the bioavailability of ACEIs; capsaicin may worsen ACEI-induced cough; NSAIDs including aspirin (Guazzi et al., 1998), may reduce the antihypertensive response to ACEIs; and K+-sparing diuretics and K+-supplement may exacerbate ACEI-induced hyperkalemia. ACEIs may increase plasma levels of digoxin and lithium and may increase hypersensitivity reactions to allopurinol.

3.4 PATHOPHYSIOLOGY OF HYPERTENSION IN PATIENTS WITH DIABETES MELLITUS

Patients with diabetes are at an increased risk for becoming hypertensive for many reasons. These include (1) the presence of accentuated pressor response to catecholamine and angiotensin-II, resulting in an increased systemic vascular resistance, renal vascular resistance, increased plasma renin activity, and sodium retention; and (2) hyperinsulinemia, which contributes to increases in sodium retention and systemic vascular resistance, and effects of sodium/potassium adenosine triphosphatase. The presence of insulin potentiates hormonal effects in both vascular smooth muscle cells as well as mesangial cells found in the kidney (Valentino et al., 1991).

Hypertension associated with diabetic nephropathy occurs in approximately 30% of patients diagnosed with type I diabetes mellitus before the age of 21 years, with almost type I patients eventually becoming hypertensive (Krolewsky et al., 1985). These patients are generally hypovolemic secondary to decreased renal responsiveness to natriuretic hormones such as atrial natriuretic peptide. In keeping with
this finding, patients with diabetes display a plasma renin activity that is normal to low, increased peripheral vascular resistance, and the presence of hyperaldosteronism (Christlich et al, 1978).

In contrast to hypertension associated with type I diabetes, the pathogenesis of essential hypertension in patients with type II diabetes is similar to its development in patients who do not have diabetes. The elevated blood pressure may be associated with increased sympathetic nervous system activity, which in part relates to sodium retention and the genesis of insulin resistance that is present in most patients with type II diabetes (Bakris et al, 1992). Thus, a negative cycle develops with the serum insulin causing sodium reabsorption from the renal tubule, and directly stimulating the sympathetic nervous system.

Isolated systolic hypertension is more common in elderly patients with diabetes than in those without it (JNC V). A bifactorial pathogenesis is believed to be involved, with decreased arterial compliance secondary to atherosclerosis leading to a consequent increase in arterial resistance.

A second negative cycle of microvascular complications occurs in the patient with diabetes and hypertension. Diabetic nephropathy leads to hypertension, with the hypertension subsequently accelerating the course of diabetic nephropathy to end-stage renal disease (ESRD) caused by elevated hydrostatic pressure, increases in glomerular ultrafiltration, and glomerular damage (Tuck, 1988). The incidence of an increased urinary albumin concentration (≥ 15 mg/24h) is significantly (p < 0.001) greater among hypertensive than non-hypertensive subjects, independent of the patient’s diabetes mellitus status (Gerber et al, 1992).

It has been demonstrated that clinically significant albuminuria in patients with diabetes, defined as excreted urinary albumin of more than 300 mg/24h, has been associated with a higher mortality rate than in a matched control group (Mogensen, 1984). Moreover, microalbuminuria increases the risk of cardiovascular mortality four-
fold in the patients with type II diabetes (Mattock et al, 1992; Abbott et al, 1994). As diabetic nephropathy progresses, an increase in blood pressure appears to occur simultaneously (NHBPEP, 1994). Although hypertension generally occurs after the onset of albuminuria, it can occur early in the course of diabetic nephropathy, before proteinuria appears.

3.4.1 Diabetic Nephropathy

Pathophysiology

The current treatment for the hypertension patient with diabetes is, in part, based on the patient's current renal status (Mogensen et al, 1983). They have developed a series of 5 stages for defining the development and progression of renal disease in patients with type-I diabetes.

**Stage 1**: It is characterized by early hypertrophy of renal tissue with the occurrence of hyperfunction, manifested as an increased glomerular filtration rate (GFR), an increase in urinary albumin excretion (UAER) secondary to vigorous exercise may also be present in stage 1. The abnormalities in this stage are generally present at the time of initial diagnosis of type I diabetes.

**Stage 2**: It includes the presence of glomerular lesions without any clinically appreciable disease. This stage occurs after 2-3 years after initial diagnosis, there are generally no laboratory signs of renal disease such as albuminuria.

**Stage 3**: It is defined as incipient diabetic nephropathy and presence 7-15 years of initial diagnosis of type I diabetes mellitus. The primary laboratory abnormality present in this stage of nephropathy is an increased baseline urinary albumin excretion, as measured by radio-immuno assay. The amount of albumin excreted in the urine during this stage ranges from 15-300 μG/min and has been termed microalbuminuria (Mogensen et al, 1983; Selby et al, 1990). It is a
stage in which effective pharmacologic intervention may have the most beneficial effect (Gerber et al, 1992; Mogensen et al, 1983). The FR at this stage is generally normal or slightly elevated. Whether the presence of hypertension is the major cause of the increased albumin excretion, or the albuminuria itself possibly produces an increase in systemic blood pressure, remains unclear (Mogensen et al, 1983).

Stage 4: In stage 4 (overt) diabetic nephropathy, either a persistent proteinuria (> 0.3-0.5 g/24h) or clinical nephropathy exists. At this point, GFR is normal or slightly decreased, with a continual decline occurring over time. Once a patient has reached this stage of nephropathy, interventions can slow, but cannot reverse, the progression to renal failure (stage 5). Approximately 75% of patients entering this stage will develop end-stage renal disease (ESRD) within 10 years (Krolewski et al, 1985).

It should be noted that similar, albeit shorter durations of the stages are present in the patients with type II diabetes mellitus as well (Hoelscher et al, 1995).

3.4.2 Treatment of Hypertension in Patients with Diabetes Mellitus

Diabetes and hypertension frequently co-exist with approximately 3 million patients diagnosed with both disorders (Houston, 1989). These two conditions occur together more frequently than alone, and are believed to be inter-related (CONSENSUS, 1993). The combination of hypertension and diabetes mellitus reduces life expectancy by approximately 33%, with about 75% of these patients eventually experiencing cardiovascular abnormalities. The most appropriate antihypertensive agent to use in this patient population and the point at which treatment should be started are two questions that remain unanswered. Some clinicians argue that patients with diabetes should begin treatment at blood pressures that would be considered normal or high-normal to prevent the accelerated decline in renal function. Others feel that treatment should not begin in these borderline patients.
unless microalbuminuria is present. The JNC-V report states that the goal blood pressure for patients with diabetes mellitus should be no more than 130/85 mm Hg.

There is a positive correlation between glucose concentrations and systolic blood pressure. The metabolic abnormalities associated with diabetes may also produce, or worsen, the co-existing hypertension (Tuck, 1988). The incidence of glucose intolerance, dyslipidemia, insulin resistance, and hyperinsulinemia is higher in hypertensive patients than in normotensive patients. This phenomenon depends on the type of diabetes (occurs more frequently in type II than in type I), length of disease, presence of albuminuria and renal insufficiency, race, sex, age, and weight. Because of the increased risk of cardiovascular, renal, cerebrovascular, and ocular complications in the patient with diabetes and hypertension, aggressive treatment is indicated to control blood pressure and blood glucose concentrations, as well as other risk factors.

(A) NON-PHARMACOLOGIC TREATMENT

This includes weight reduction, exercise, sodium restriction (< 6 g/day) (NHBPEP, 1993), smoking cessation, and decreased alcohol intake. These lifestyle modifications alone improve glucose use and insulin sensitivity.

(B) PHARMACOLOGIC TREATMENT

Hypertension in patients with diabetes contributes to the development of coronary artery disease (CAD), stroke, ESRD, and retinopathy, and therefore should be recognized and treated early and aggressively (NHBPEP, 1994). Drug selection is important, and several factors should be considered. Several antihypertensive agents have detrimental effects on glucose control and insulin sensitivity (Table F) (Bakris et al, 1992; Houston, 1989; CONSENSUS, 1993; NHBPEP, 1994; Rossing et al, 1994).
The ultimate goals of treatment in patients with diabetes and hypertension should include: (1) correcting hemodynamic and physiological abnormalities; (2) decreasing risk factors for CAD; (3) stabilizing or improving already existing proteinuria and renal insufficiency and preventing progression to ESRD; (4) producing minimal adverse effects from antihypertensive therapy; (5) improving, or at least not worsening, other concomitant medical problems; and (6) maintaining or improving the patient's quality of life.

Table F: Effects of Various Classes of Antihypertensive Agents

<table>
<thead>
<tr>
<th>Antihypertensive drug class</th>
<th>Glucose homeostasis</th>
<th>Insulin sensitivity</th>
<th>Lipid metabolism</th>
<th>Albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>thiazides</td>
<td>Worsened</td>
<td>Worsened</td>
<td>Worsened</td>
<td>Worsened</td>
</tr>
<tr>
<td>indamapide</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Improved</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Worsened</td>
<td>Worsened</td>
<td>Worsened</td>
<td>0</td>
</tr>
<tr>
<td>ACEIs</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>CCBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>verapamil/diltiazem</td>
<td>0</td>
<td>0/Improved</td>
<td>0</td>
<td>Improved</td>
</tr>
<tr>
<td>nifedipine</td>
<td>0/Worsened</td>
<td>0/Worsened</td>
<td>0</td>
<td>Worsened</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>0</td>
<td>Improved</td>
<td>Improved</td>
<td>0</td>
</tr>
</tbody>
</table>

0 = No effect

3.5 DEGENERATIVE JOINT DISEASE

Degenerative joint disease is a disorder of cartilage and bone characterized by cartilage loss and bony overgrowth. Other names used are osteoarthritis (OA), when it affects the peripheral joints and spondylosis or spondylitis when it affects the spine.

3.5.1 CLASSIFICATION

(1) Primary osteoarthritis
   (A) Localized OA
   (B) Generalized OA (3 or more joint groups involved)
   (C) Erosive OA (rare)
(2) Secondary osteoarthritis

(A) Mechanical
   (i) Congenital and developmental disorders such as hip dysplasias, slipped femoral epiphysis
   (ii) Post traumatic

(B) Post inflammatory and /or infective arthritis such as rheumatoid arthritis, septic arthritis

(C) Neuropathic joint disease: Diabetes, tabes dorsalis, syringomyelia, leprosy, meningomyelocele

(D) Endocrine causes: Acromegaly, Cushing's syndrome

(E) Metabolic causes: Gout, pseudogout, ochronosis, Wilson's disease, hemochromatosis

(F) Prior bone disorders like Paget's disease, osteonecrosis

(G) Iatrogenic causes including intraarticular steroids

3.5.2 PATHOLOGY

Despite the diverse etiological factors, certain histological, biochemical, and metabolic changes in OA are similar.

The articular cartilage is the site of primary pathology. It loses its glossy appearance and becomes pitted and fibrillated. Focal and diffused erosions of the cartilage take place with subsequent thinning and complete denudation. The underlying articular bone becomes sclerosed. Reactive proliferation of new bone and cartilage at the joint periphery leads to osteophyte formation. Biochemical changes in the articular cartilage include increase in water content, alteration of the ratio of chondroitin sulphate to keratin sulphate decrease glycosammonioglycan concentration, and disruption of proteoglycan aggregation. There is a progressive loss of chondrocytes.

3.5.3 PATHOGENESIS

The exact pathogenesis of OA is not known. It was thought to be due to normal ageing, accelerated ageing, or secondary to wear and tear of the joint. A dogma existed that the cartilage cannot repair itself and that
chondrocytes are effete cells which cannot replicate or synthesize or repair cartilage damage (Chandrasekaran, 1999).

Recent studies have shown that chondrocytes utilize anaerobic glycolysis for energy production even though the cartilage has no blood vessels, nerve supply or lymphatic drainage. They have been found to synthesize the matrix component like collagens and proteoglycans and enzymes like collagenase. Interleukin-1, tumor necrosis factor-alpha (TNF-α), insulin-like growth factor-1 (IGF-1) and transforming growth factor-beta (TGF-β) have been found to play an important part in articular cartilage metabolism and in matrix protein synthesis and degradation. Drugs have been directed against these to prevent rather than to treat OA.

Glycosyltransferases are enzymes which are required in the synthesis of prostaglandins (PG) by chondrocyte. Studies in animal models have shown that salicylates and indomethacin significantly suppress glycosyltransferase enzyme, thus inhibiting PG synthesis. Ketoprofen, ibuprofen, tenoxicam, tiaprofenic acid and diclofenac sodium have no effect on this enzyme and thus may not inhibit PG synthesis.

3.5.4 CLINICAL FEATURES

The onset of symptoms is usually insidious. In most patients a limited number of joints are involved. Joint pain is the initial symptom; the pain comes on with use and is relieved by rest. As the disease progresses, pain occurs even at rest. The pain may originate from the periosteum, trabecular microfracture, intraarticular ligament disease, capsular distension, periarticular tendon and fascia inflammation, muscle spasm, and release of PG from secondarily inflamed synovium.

The most common sites of involvement in primary OA are the distal interphalangeal and first carpometacarpal joints of the hand, first metatarsophalangeal joint of the foot, the hips, knees, and lumbar and cervical spines. Joints usually not involved are the metacarpophalangeal joints, wrists, elbows and shoulders. Physical
examination usually reveals localized area of tenderness, pain on motion, and joint crepitus. Joint enlargement occurs in the later stages of the disease, and is due to bone proliferation, spurs and synovitis.

3.5.5 MANAGEMENT

The main objectives are relief of symptoms (pain), preservation and restoration of function (mobility) of the failing joint and arresting the process of cartilage destruction (minimizing disability) (Chandrasekarn, 1999; Brandt, 2001). The vigor of the therapeutic intervention should be dictated by the severity of the condition in the individual patient. For those with mild disease, reassurance, instruction in joint protection, and an occasional analgesic may be all that is required; for those with more severe OA, especially of the knee or hip, a comprehensive program comprising a spectrum of nonpharmacologic measures supplemented by an analgesic and/or NSAID is appropriate (Brandt, 2001).

(A) GENERAL MEASURES

Correction and/or prevention of causative/predisposing factors. This should be done very early. The benign nature of the disease and its course should be explained and the need for exercises should be stressed. Weight reduction should be encouraged. Excessive and wrong usage of the joint should be prevented. Stressful activities like kneeling and squatting (for knee OA) and heavy weight lifting (for lumbar spine OA) should be avoided.

(B) NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)

The antiinflammatory, analgesic, and antipyretic drugs are a heterogenous group of compounds, often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions and side effects.
There has been substantial progress in elucidating the mechanism of action of NSAIDs. Inhibition of cyclooxygenase (COX), the enzyme responsible for the biosynthesis of prostaglandins and certain related autacoids, generally is thought to be a major facet of the mechanism of NSAIDs.

**Mechanism of action of NSAIDs**

NSAIDs has been known to inhibit the biosynthesis of prostaglandins (PGs) that may contribute to their therapeutic effect (Abramson & Weissman, 1989; Vane, 1994).

The mechanism by which varying NSAIDs interfere with PG biosynthesis are outlined below:

The first enzyme in the PG synthetic pathway is the prostaglandin endoperoxide synthetase, or fatty acid cyclooxygenase. This enzyme converts arachidonic acid to the unstable intermediates PGG$_2$ and PGH$_2$. It is now appreciated that there are two forms of cyclooxygenase, termed COX-1 and COX-2 (Vane et al, 1998). COX-1 is a constitutive isoform found in most normal cells and tissues, while COX-2 is induced in settings of inflammation by cytokines and inflammatory mediators (Seibert et al, 1997). However, COX-2 is also is constitutively expressed in certain areas of kidney and brain (Breder et al, 1995; Harris et al, 1994). Importantly, COX-1, but not COX-2, is constitutively expressed in the stomach. This accounts for the markedly reduced occurrence of gastric toxicity with the use of selective inhibitors of COX-2.

**Classification of NSAIDs**

Classification of NSAIDs based on chemical classes is given in Table G.
Table G: Chemical classification of NSAIDs

**Non-selective COX inhibitors**

*Salicylic acid derivatives*
- Aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, olsalazine

*Para-aminophenol derivatives*
- Acetaminophen

*Indole and indene acetic acids*
- Indomethacin, sulindac

*Heteroaryl acetic acids*
- Tolmetin, diclofenac, ketorolac

*Arylpropionic acids*
- Ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin

*Anthranilic acids (fenamates)*
- Mefenamic acid, meclofenamic acid

*Enolic acids*
- Oxicams (piroxicam, meloxicam)

*Alkanones*
- Nabumetone

**Selective COX-2 Inhibitors**

*Diaryl-substituted furanones*
- Rofecoxib

*Diaryl-substituted pyrazoles*
- Celecoxib

*Indole acetic acids*
- Etodolac

*Sulfonanilides*
- Nimesulide

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*Effects of NSAIDs on blood pressure*

General considerations:

If deficiency of PG synthesis were a feature of essential hypertension the blood pressure raising effect of indomethacin would have been less in hypertensive than in nonhypertensive individuals. In some randomized, controlled studies, indomethacin has increased blood pressure in normotensive individuals (Staessen *et al.*, 1983; Hardy *et al.*, 1988), as well as in hypertensive patients (Beckmann *et al.*, 1988; Gerber *et al.*, 1990); however, in others indomethacin and other NSAIDs failed to increase blood pressure (Pedrinelli *et al.*, 1982; Cinquegrani & Liang, 1988; Wright *et al.*, 1989). The disparities between the studies could be related to many factors, such as variations in drug doses and selection of patients, differences in sodium balance, and previous and
ongoing therapy. Moreover, since blood pressure changes – when they occur – are usually small, the sample size of several studies may have been insufficient to detect a rise in blood pressure.

Pope and co-workers (1993) performed a meta-analysis of the effects of NSAIDs on blood pressure. A total of 1324 patients with a mean age of 46 years could be evaluated, 92% of whom were hypertensive. The data from the analysis showed that, in the normotensive patients, NSAIDs induced virtually no change in blood pressure; this was true even after adjusting for dietary salt intake. In hypertensive patients, on the other hand, mean arterial pressure increased, after adjusting for salt intake, by almost 4 mm Hg; this effect was most pronounced with naproxen and indomethacin, while sulindac, aspirin and ibuprofen had the least effect.

Later on, another, and more rigid, meta-analysis was published by Johnson and co-workers (1994). They found that NSAIDs increased mean blood pressure by 5 mm Hg.

In a study by Walter et al. (1981), aspirin was given for a prolonged period. They found that aspirin increased both systolic and diastolic blood pressure during the first 6 months treatment, but thereafter blood pressure decreased to almost baseline levels. It seems that long-term suppression of PG synthesis does not necessarily lead to a sustained elevation of blood pressure.

Sub-groups at risk:

In view of the fact that NSAIDs are so frequently prescribed for older patients, this section of the population can be expected to run a greater risk. Chrischilles & Wallace (1993) found that among elderly people who were treated with antihypertensive drugs, those who also used NSAIDs had a greater likelihood of having systolic blood pressure greater than 140 mm Hg.
Interference with antihypertensive treatment:

Johnson and associates (1994) have found that NSAIDs antagonized the antihypertensive effect of several drug categories. Statistical significance, however, was achieved only for the interaction with beta blockers. Yet, several papers suggest that NSAIDs may partially attenuate the efficacy of diuretics, beta blockers, alpha blockers and ACE inhibitors (Watkins et al, 1980; Chalmers et al, 1984; Koopmans et al, 1986; Oates, 1988). Nevertheless, the effect tend to be small and not always significant, although life-threatening increases in blood pressure occasionally been reported (Oates, 1988; Salvetti et al, 1987; Schoenfeld, 1989). Moreover, the different NSAIDs appear not to be uniform in this effect, as the risks associated with the use of sulindac and perhaps aspirin (Chalmers et al, 1984) seem to be lower than those for other NSAIDs (Wong et al, 1986; Radack & Deck, 1987). The explanation for the latter is not yet clear, but it may be related to the fact that the kidney metabolises the active sulfide metabolite of the sulindac back to its pro-drug (Sedor et al, 1984) taken together available data strongly suggest that the effect of several antihypertensive agents may be attenuated by NSAIDs.

Mechanisms by which NSAIDs may increase blood pressure:

When, in normotensive individuals, PG synthesis is inhibited acutely by intravenous infusion of indomethacin, blood pressure rises due to an increase in total peripheral vascular resistance with a concomitant decline in heart rate and cardiac output (Wennmalm, 1978). In addition, the vasoconstrictor response to exogenous angiotensin-II is potentiated during short-term indomethacin treatment (Negus et al, 1976). It should be stressed that, in addition to the direct effect on the vasculature, NSAIDs could modify blood pressure regulation through a variety of mechanisms (Clive & Stoff, 1984). Although PGs contribute little, if anything, to the control of renal function in healthy euvoletic humans, both renal blood flow and glomerular filtration rate become
progressively dependent upon PG synthesis under conditions of volume depletion or reduced renal perfusion pressure.

At the moment the precise mechanisms by which NSAIDs raise blood pressure remain obscure. While there is evidence for both an effect on the vasculature and for interference with volume control, the impact of these respective mechanisms and possible interplay between them still need further investigation (de Leeuw, 1996). At the present time, it is important for the practising clinician to remember that there is a lot of circumstantial evidence that NSAIDs - with the possible exception of sulindac and aspirin- may, at least in the short term, increase blood pressure.

3.5.6 NON-Steroidal ANTI-INFLAMMATORY DRUGS & HYPERTENSION

The risk in perspective:

Non-steroidal anti-inflammatory drugs (NSAIDs) block the synthesis of prostaglandins (PGs), and thus may interfere with circulatory control. Also, there is insufficient information regarding whether there are any special subgroups in the population who are at risk of developing hypertension during exposure to NSAIDs. Some data suggest that elderly people and patients with pre-existing hypertension carry an increased risk, notably when they are receiving antihypertensive treatment (de Leeuw, 1996).

Prostaglandins and the cardiovascular system:

In vitro data and results obtained in experimental animals suggest that PGs have a number of actions on the cardiovascular system. Among others, they modulate the vasoconstrictor and antiuretic effects of pressor hormones, in particular the renin angiotensin system (RAS). For instance, the release of PGs is enhanced when angiotensin-II (A-II) is infused into the renal arteries of dogs, with subsequent blunting of its vasoconstrictor and sodium-retaining effects (McGiff et al, 1970). Although this has not been formally demonstrated in humans, it is
likely that a similar mechanism operates, especially under conditions where the RAS is activated, such as congestive cardiac failure or renal artery stenosis. Angiotensin-dependent PG release may be relevant for the maintenance of renal function. Indeed, by opposing the action of angiotensin on pre-glomerular (but not post-glomerular) vessels, PGs prevent a drop in intra-glomerular pressure, thereby maintaining glomerular filtration at an optimal level.

Other effects of PGs include augmentation of the effects of the kallikrein-kinin system, mediation of renin release in response to a fall in renal blood flow or renal perfusion pressure at moderation of adrenergic vasoconstriction (Quilley & McGiff, 1994).

Prostaglandins in hypertension:

To elucidate the potential role of PGs in the initiation or maintenance of hypertension, the urinary excretion of either primary PGs or stable metabolites are measured. While the former is presumed to reflect intrarenal synthesis of PGs, the later is often is taken as an index of systemic production (de Leeuw, 1996). Papanicolaou and associates (1976) found an inverse relationship between the excretion of PGE and blood pressure as well as between PG excretion and the duration of hypertension.

It remains speculative, however, whether reduced excretion of PGs reflects a primary abnormality in hypertension. Apart from deficient synthesis of antihypertensive prostanoids, in some hypertensive patients at least, the formation of pro-hypertensive PGs may be enhanced (Hornyeh et al, 1983). Therefore, the question is which type of PG is involved in the pathophysiology of human hypertension remains unresolved and probably must await studies with specific PG antagonist. Administration of exogenous prostanoids is unlikely to provide information regarding the extent to which these substances are involved in normal cardiovascular control, since intravenous infusion is
relevant only for those PGs that escape metabolic degradation upon passage through the lungs.

Perhaps the most popular approach at the present time is to study the effect of NSAIDs. However, these compounds lack specificity with respect to individual PGs. Thus, blocking the arachidonic acid pathway will not only reduce the formation of antihypertensive PGs such as PGE$_2$ and prostacyclin, but also that of prohypertensive PGs like PGH$_2$ and thromboxane A$_2$. Furthermore, there are several biochemical pathways involved in arachidonic acid metabolism that may cloud the effects of simply inhibiting cyclooxygenase (Quilley & McGiff, 1994).

3.6 DRUGS USED IN THE PRESENT STUDY

3.6.1 ACEIs Used in the Present Study

Two ACEIs were used in the present study namely enalapril and lisinopril.

(i) Enalapril

**Chemical Structure:**

![Chemical Structure of Enalapril](image)

**Description**

Enalapril maleate is the salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-[1-(ethoxycarbonyl) -3-phenylpropyl]-L-alanyl] -L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is C$_{20}$H$_{28}$N$_2$O$_5$·C$_4$H$_4$O$_4$. 

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Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.

Clinical Pharmacology

Enalaprilat, an angiotensin-converting enzyme (ACE) inhibitor when administered intravenously, is the active metabolite of the orally administered pro-drug, enalapril maleate. Enalapril is poorly absorbed orally.

Mechanism of Action

Intravenous enalaprilat, or oral enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalapril remains to be elucidated.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension. Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin
hypertensive population) has a smaller average response to enalapril monotherapy than non-black patients.

**Pharmacokinetics and Metabolism**

Following oral administration of enalapril, peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60 percent. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Excretion of enalapril is primarily renal. Approximately 94 percent of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40 percent of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat.

**Pharmacodynamics**

**Hypertension:** Administration of enalapril to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients.

In most patients studied, after oral administration of a single dose of enalapril, onset of antihypertensive activity was seen at one hour with peak reduction of blood pressure achieved by four to six hours.

At recommended doses, antihypertensive effects have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval.
In some patients achievement of optimal blood pressure reduction may require several weeks of therapy.

The antihypertensive effects of enalapril have continued during long term therapy. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure.

**Heart Failure:** In trials in patients treated with digitalis and diuretics, treatment with enalapril resulted in decreased systemic vascular resistance, blood pressure, pulmonary capillary wedge pressure and heart size, and increased cardiac output and exercise tolerance. Heart rate was unchanged or slightly reduced, and mean ejection fraction was unchanged or increased. There was a beneficial effect on severity of heart failure as measured by the New York Heart Association (NYHA) classification and on symptoms of dyspnoea and fatigue. Hemodynamic effects were observed after the first dose, and appeared to be maintained in uncontrolled studies lasting as long as four months. Effects on exercise tolerance, heart size, and severity and symptoms of heart failure were observed in placebo-controlled studies lasting from eight weeks to over one year.

**Heart Failure, Mortality Trials:** In a multicenter, placebo-controlled clinical trial, 2569 patients with all degrees of symptomatic heart failure and ejection fraction ≤ 35 percent were randomized to placebo or enalapril and followed for up to 55 months (SOLVD Treatment). Use of enalapril was associated with an 11 percent reduction in all-cause mortality and a 30 percent reduction in hospitalization for heart failure. Diseases that excluded patients from enrollment in the study included severe stable angina (>2 attacks/day), hemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine >2.5 mg/dl), cerebral vascular disease (e.g., significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis and constrictive pericarditis. The mortality benefit associated with enalapril does not appear to depend upon digitalis being present.
A second multicenter trial used the SOLVD protocol for study of asymptomatic or minimally symptomatic patients. SOLVD-Prevention patients, who had left ventricular ejection fraction ≤ 35% and no history of symptomatic heart failure, were randomized to placebo (n=2117) or enalapril (n=2111) and followed for up to 5 years. The majority of patients in the SOLVD-Prevention trial had a history of ischemic heart disease. A history of myocardial infarction was present in 80 percent of patients, current angina pectoris in 34 percent, and a history of hypertension in 37 percent. No statistically significant mortality effect was demonstrated in the population. Enalapril-treated subjects had 32% fewer first hospitalizations for heart failure, and 32% fewer total heart failure hospitalizations. Compared to placebo, 32 percent fewer patients receiving enalapril developed symptoms of overt heart failure. Hospitalizations for cardiovascular reasons were also reduced. There was an insignificant reduction in hospitalizations for any cause in the enalapril treatment group (for enalapril vs. placebo, respectively, 1166 vs. 1201 first hospitalizations, 2649 vs. 2840 total hospitalizations), although the study was not powered to look for such an effect.

The SOLVD-Prevention trial was not designed to determine whether treatment of asymptomatic patients with low ejection fraction would be superior, with respect to preventing hospitalization, to closer follow-up and use of enalapril at the earliest sign of heart failure. However, under the conditions of follow-up in the SOLVD-Prevention trial (every 4 months at the study clinic; personal physician as needed), 68% of patients on placebo who were hospitalized for heart failure had no prior symptoms recorded which would have signalled initiation of treatment.

The SOLVD-Prevention trial was also not designed to show whether enalapril modified the progression of underlying heart disease.

In another multicenter, placebo-controlled trial (CONSENSUS) limited to patients with NYHA Class IV congestive heart failure and radiographic evidence of cardiomegaly, use of enalapril was associated with improved survival. The results are shown in TABLE H.
TABLE H

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>Six Months</th>
<th>One Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasotec (n = 127) (enalapril)</td>
<td>74</td>
<td>64</td>
</tr>
<tr>
<td>Placebo (n = 126)</td>
<td>56</td>
<td>48</td>
</tr>
</tbody>
</table>

In both CONSENSUS and SOLVD-Treatment trials, patients were also usually receiving digitalis, diuretics or both.

Enalapril IV results in reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients. The onset of action usually occurs within fifteen minutes of administration with the maximum effect occurring within one to four hours. The abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure.

The duration of hemodynamic effects appears to be dose-related. However, for the recommended dose, the duration of action in most patients is approximately six hours.

Following administration of enalapril, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

**INDICATIONS**

**Hypertension:** Tablets: Enalapril is indicated for the treatment of hypertension.

Enalapril is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of enalapril and thiazides are approximately additive.
Heart Failure: Enalapril is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients enalapril improves symptoms, increases survival, and decreases the frequency of hospitalization.

Asymptomatic Left Ventricular Dysfunction: In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤ 35 percent), enalapril decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure.

In using enalapril consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that enalapril does not have a similar risk.

DOSAGE AND ADMINISTRATION

Tablets

Hypertension: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of enalapril. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with enalapril to reduce the likelihood of hypotension. If the patient's blood pressure is not controlled with enalapril alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued an initial dose of 2.5mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour.

The recommended initial dose in patients not on diuretics is 5mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40mg per day administered in a single dose or two divided doses. In some patients treated once
daily, the antihypertensive effect may diminish toward the end of the
dosing interval. In such patient an increase in dosage or twice daily
administration should be considered. If blood pressure is not controlled
with enalapril alone, a diuretic may be added.

Concomitant administration of enalapril with potassium supplements,
potassium salt substitutes, or potassium-sparing diuretics may lead to
increases of serum potassium.

**Dosage Adjustment in Hypertensive Patients with Renal
Impairment**

The usual dose of enalapril is recommended for patients with a
creatinine clearance >30 ml/min (serum creatinine of up to
approximately 3 mg/dl). For patients with creatinine clearance ≤ 30
ml/min (serum creatinine up to approximately 3 mg/dl), the first dose
is 2.5mg once daily. The dosage may be titrated upward until blood
pressure is controlled or to a maximum of 40mg daily (TABLE I).

<table>
<thead>
<tr>
<th>Renal Status</th>
<th>Creatinine Clearance ml/min</th>
<th>Initial Dose mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Renal Function</td>
<td>&gt; 80</td>
<td>5 mg</td>
</tr>
<tr>
<td>Mild Impairment</td>
<td>≤ 80 &gt;30</td>
<td>5 mg</td>
</tr>
<tr>
<td>Moderate to Severe Impairment</td>
<td>≤ 30</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Dialysis Patients*</td>
<td>--</td>
<td>2.5 mg on dialysis days†</td>
</tr>
</tbody>
</table>

† Dosage on non-dialysis days should be adjusted depending on the blood pressure response

**Heart Failure:** Enalapril is indicated for the treatment of symptomatic
heart failure, usually in combination with diuretics and digitalis. In the
placebo-controlled studies that demonstrated improved survival,
patients were titrated as tolerated up to 40mg, administered in two
divided doses.

The recommended starting dose is 2.5mg. The recommended dosing
range is 2.5 to 20mg given twice a day. Doses should be titrated
upward, as tolerated, over a period of a few days or weeks. The
maximum daily dose administered in clinical trials was 40mg in divided doses.

After the initial dose of enalapril, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilised for at least an additional hour. If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of enalapril does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

Asymptomatic Left Ventricular Dysfunction: In the trial that demonstrated efficacy, patients were started on 2.5mg twice daily and were titrated as tolerated to the targeted daily dose of 20mg (in divided doses).

After the initial dose of enalapril, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilised for at least an additional hour. If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of enalapril does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia

In patients with heart failure who have hyponatremia (serum sodium less than 130 mEq/L) or with serum creatinine greater than 1.6 mg/dl, therapy should be initiated at 2.5mg daily under close medical supervision. The dose may be increased to 2.5mg twice daily, then 5mg twice daily. And higher as needed, usually at intervals of four days or more if at the time of dosage adjustment there is not excessive...
hypotension or significant deterioration of renal function. The maximum daily dose is 40mg.

**Patients on Diuretic Therapy**

For patients on diuretic therapy the recommended starting dose for hypertension is 0.625mg administered intravenously over a five minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing, although most of the effect is usually apparent within the first hour. If after one hour there is an inadequate clinical response, the 0.625mg dose may be repeated. Additional doses of 1.25mg may be administered at six-hour intervals.

For conversion from intravenous to oral therapy, the recommended initial dose of Tablets enalapril for patients who have responded to 0.625mg of enalaprilat every six hours is 2.5mg once a day with subsequent dosage adjustment as necessary.

**Dosage Adjustment in Renal Impairment**

The usual dosage of 1.25mg of enalaprilat every six hours is recommended for patients with a creatinine clearance >30 ml/min (serum creatinine of up to approximately 3 mg/dl). For patients with creatinine clearance 30 ml/min (serum creatinine 3 mg/dl), the initial dose is 0.625mg.

If after one hour there is an inadequate clinical response, the 0.625mg dose may be repeated. Additional doses of 1.25mg may be administered at six-hour intervals.

**For dialysis patients, patients at risk of excessive hypotension**

For conversion from intravenous to oral therapy, the recommended initial dose of Tablets is 5mg once a day for patients with creatinine clearance > 30ml and 2.5mg once a day for patients with creatinine
clearance  30 ml/min. Dosage should then be adjusted according to blood pressure response.

**Patients at Risk of Excessive Hypotension**

Hypertensive patients at risk of excessive hypotension include those with the following concurrent conditions or characteristics: heart failure, hyponatremia, high doses of diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any aetiology. Single doses of enalaprilat as low as 0.2mg have produced excessive hypotension in normotensive patients with these diagnoses. Because of the potential for an extreme hypotensive response in these patients, therapy should be started under very close medical supervision. The starting dose should be no greater than 0.625mg administered intravenously over a period of no less than five minutes and preferably longer (up to one hour).

Patients should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased.

**ADVERSE REACTIONS**

Enalapril has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. Enalapril has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

For the most part, adverse experiences were mild and transient in nature. In clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 3.3 percent of patients with hypertension and in 5.7 percent of patients with heart failure. The frequency of adverse experiences was not related to total daily dosage within the usual dosage ranges. In patients with hypertension the overall percentage of patients treated with enalapril reporting adverse experiences was comparable to placebo.
Hypertension

Adverse experiences occurring in greater than one percent of patients with hypertension treated with enalapril in controlled clinical trials are fatigue, orthostatic effects, asthenia, diarrhoea, nausea, headache, dizziness, cough and rash. In patients treated with enalapril, the maximum duration of therapy was three years; in placebo treated patients the maximum duration of therapy was 12 weeks.

Heart Failure

Adverse experiences occurring in greater than one percent of patients with heart failure treated with enalapril are shown in TABLE 3. The incidences represent the experiences from both controlled and uncontrolled clinical trials (maximum duration of therapy was approximately one year) In the placebo treated patients, the incidences reported are from the controlled trials (maximum duration of therapy is 12 weeks). The percentage of patients with severe heart failure (NYHA Class IV) was 29 percent and 43 percent for patients treated with enalapril and placebo, respectively.

Adverse Effects:

Body as a Whole: Anaphylactoid reactions.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients; pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis (hepatocellular (proven on rechallenge) or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

Musculoskeletal: Muscle cramps.
**Nervous/Psychiatric:** Depression, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (*e.g.*, paresthesia, dysesthesia).

**Respiratory:** Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates

**Skin:** Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis, photosensitivity.

**Special Senses:** Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

**Urogenital:** Renal failure, oliguria, renal dysfunction flank pain, gynecomastia, impotence.

**Miscellaneous:** A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

**Angioedema:** Angioedema has been reported in patients receiving enalapril (0.2 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalapril should be discontinued and appropriate therapy instituted immediately.

**Hypotension:** In the hypertensive patients, hypotension occurred in 0.9 percent syncope occurred in 0.5 percent of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients. In heart failure patients, hypotension occurred in 6.7 percent and syncope occurred in 2.2 percent of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9 percent of patients with heart failure.
**Fetal/Neonatal Morbidity and Mortality: Fetal/Neonatal Morbidity and Mortality:** ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

**Cough:** Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

**Clinical Laboratory Test Findings**

**Serum Electrolytes:**

**Hyperkalemia:** Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy.

**Creatinine, Blood Urea Nitrogen (BUN):** In controlled clinical trials minor increases in BUN and serum creatinine, reversible upon discontinuation of therapy. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis.

**Hematology:** Small decreases in hemoglobin and hematocrit occur frequently in either hypertension or congestive heart failure patients treated with enalapril but are rarely of clinical importance unless another cause of anemia coexists.

**Liver Function Tests:** Elevations of liver enzymes and/or serum bilirubin may occur.

**DRUG INTERACTIONS**

**Hypotension: Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted,
may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril or enalaprilat. The possibility of hypotensive effects with enalapril or enalaprilat can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril or enalaprilat. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilised for at least an additional hour.

**Agents Causing Renin Release:** The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

**Other Cardiovascular Agents:** Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin and digoxin without evidence of clinically significant adverse interactions.

**Agents Increasing Serum Potassium:** Enalapril attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium sparing agents should generally not be used in patients with heart failure receiving enalapril.

**Lithium:** Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors.
Lisinopril

Chemical structure:

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{C} & \text{N} \text{C} \text{C} \text{N} \\
\text{H} & \text{H} \\
\text{COOH} & \text{COOH}
\end{align*}
\]

Description

Lisinopril is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril, a synthetic peptide derivative, is chemically described as \(\text{(S)-1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate.}\) Its empirical formula is \(\text{C}_{21}\text{H}_{31}\text{N}_3\text{O}_5\cdot2\text{H}_2\text{O}.\)

Clinical Pharmacology

Mechanism of Action: Lisinopril inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15% of patients had increases greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L. In the same study, patients treated with lisinopril and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum
potassium of 0.1 mEq/L; approximately 4% of patients had increases greater than 0.5 mEq/L and approximately 12% had a decrease greater than 0.5 mEq/L. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension.

**Pharmacokinetics and Metabolism:** Following oral administration of lisinopril, peak serum concentrations of lisinopril occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not appear to be bound to other serum proteins. Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large intersubject variability (6%-60%) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract. The absolute bioavailability of lisinopril is reduced to 16% in patients with stable NYHA Class II-IV congestive heart failure, and the volume of distribution appears to be slightly smaller than that in normal subjects. The oral bioavailability of lisinopril in patients with acute myocardial infarction is similar to that in healthy volunteers.
Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours. Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 mL/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and the area under the plasma concentration time curve (AUC) than younger patients. Lisinopril can be removed by hemodialysis. Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of 14C lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labelled drug to pregnant rats, but none was found in the fetuses.

Pharmacodynamics and Clinical Effects

**Hypertension:** Administration of lisinopril to patients with hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients. When given together with thiazide-type diuretics, the blood pressure lowering effects of the two drugs are approximately additive. In most patients studied, onset of antihypertensive activity was seen at one hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied,
the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing. In some patients achievement of optimal blood pressure reduction may require two to four weeks of therapy. The antihypertensive effects of lisinopril are maintained during long-term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure, or a significant increase in blood pressure compared to pretreatment levels.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of lisinopril, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large. In patients with renovascular hypertension lisinopril has been shown to be well tolerated and effective in controlling blood pressure.

**Heart Failure:** During baseline-controlled clinical trials, in patients receiving digitalis and diuretics, single doses of lisinopril resulted in decreases in pulmonary capillary wedge pressure, systemic vascular resistance and blood pressure accompanied by an increase in cardiac output and no change in heart rate.

**Acute Myocardial Infarction:** The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) study was a multicenter, controlled, randomized, unblinded clinical trial conducted in 19,394 patients with acute myocardial infarction concluded the beneficial effects of lisinopril as a therapeutic agent for acute myocardial infarction.
Indications and Usage

**Hypertension:** Lisinopril is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

**Heart Failure:** Lisinopril is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis.

**Acute Myocardial Infarction:** Lisinopril is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

Contraindications

Lisinopril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

Adverse Reactions

Lisinopril has been found to be generally well tolerated in controlled clinical trials involving 1969 patients with hypertension or heart failure. For the most part, adverse experiences were mild and transient.

Hypertension

In clinical trials in patients with hypertension treated with Lisinopril, discontinuation of therapy due to clinical adverse experiences occurred in 5.7% of patients. The overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. The adverse events occurring in more than 1% of patients are:
Body as a whole: Fatigue, asthenia and orthostatic effects.

Cardiovascular: Hypotension.

Digestive: Diarrhea, nausea, vomiting and dyspepsia.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Headache, dizziness, paresthesia, decreased libido and vertigo.

Respiratory: Cough, upper respiratory infection, common cold, nasal congestion and influenza.

Skin: Rash.

Urogenital: Impotence, chest pain and back pain.

Heart Failure

In patients with heart failure treated with lisinopril for up to four years, discontinuation of therapy due to clinical adverse experiences occurred in 11.0% of patients. In controlled studies in patients with heart failure, therapy was discontinued in 8.1% of patients treated with lisinopril for 12 weeks, compared to 7.7% of patients treated with placebo for 12 weeks.

The following adverse experiences which occurred in greater than 1% of patients with heart failure treated with lisinopril or placebo for up to 12 weeks in controlled clinical trials, and more frequently on lisinopril than placebo.

Body as a whole: Chest pain and abdominal pain.

Cardiovascular: Hypotension.

Digestive: Diarrhea.

Nervous/Psychiatric: Dizziness and headache.
Respiratory: Upper respiratory infection.

Skin: Rash.

**Acute Myocardial Infarction**

In the GISSI-3 trial, in patients treated with lisinopril for six weeks following acute myocardial infarction, discontinuation of therapy occurred in 17.6% of patients. Patients treated with lisinopril had a significantly higher incidence of hypotension and renal dysfunction compared with patients not taking lisinopril.

In the GISSI-3 trial, hypotension (9.7%), renal dysfunction (2.0%), cough (0.5%), post infarction angina (0.3%), skin rash and generalized edema (0.01%), and angioedema (0.01%) resulted in withdrawal of treatment. In elderly patients treated with lisinopril, discontinuation due to renal dysfunction was 4.2%.

Other clinical adverse experiences occurring in 0.3% to 1.0% of patients with hypertension or heart failure treated with lisinopril in controlled clinical trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience are listed below, and within each category are in order of decreasing severity:

**Body as a Whole:** Anaphylactoid reactions, syncope, orthostatic effects, chest discomfort, pain, pelvic pain, flank pain, edema, facial edema, virus infection, fever, chills and malaise.

**Cardiovascular:** Cardiac arrest; myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients, pulmonary embolism and infarction, arrhythmias (including ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia and premature ventricular contractions), palpitations, transient ischemic attacks, paroxysmal nocturnal dyspnea, orthostatic hypotension, decreased blood pressure, peripheral edema, vasculitis.
**Digestive:** Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), vomiting, gastritis, dyspepsia, heartburn, gastrointestinal cramps, constipation, flatulence and dry mouth.

**Hematologic:** Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia and thrombocytopenia.

**Endocrine:** Diabetes mellitus.

**Metabolic:** Weight loss, dehydration, fluid overload, gout and weight gain.

**Musculoskeletal:** Arthritis, arthralgia, neck pain, hip pain, low back pain, joint pain, leg pain, knee pain, shoulder pain, arm pain and lumbago.

**Nervous System/Psychiatric:** Stroke, ataxia, memory impairment, tremor, peripheral neuropathy (e.g., dysesthesia), spasm, paresthesia, confusion, insomnia, somnolence, hypersomnia, irritability and nervousness.

**Respiratory System:** Malignant lung neoplasms, hemoptysis, pulmonary infiltrates, bronchospasm, asthma, pleural effusion, pneumonia, eosinophilic pneumonitis, bronchitis, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngeal pain, pharyngitis, rhinitis and rhinorrhea.

**Skin:** Urticaria, alopecia, herpes zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema, flushing, diaphoresis. Other severe skin reactions have been reported rarely, including toxic epidermal necrolysis and Stevens-Johnson syndrome; causal relationship has not been established.

**Special Senses:** Visual loss, diplopia, blurred vision, tinnitus, photophobia and taste alteration.
**Urogenital System:** Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction, pyelonephritis, dysuria, urinary tract infection and breast pain.

**Miscellaneous:** A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

**ANGIOEDEMA:** Angioedema has been reported in patients receiving lisinopril (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with lisinopril should be discontinued and appropriate therapy instituted immediately. In very rare cases, intestinal angioedema has been reported in post marketing experience.

**HYPOTENSION:** In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. In patients with heart failure, hypotension occurred in 5.3% and syncope occurred in 1.8% of patients. These adverse experiences were possibly dose-related (see above data from ATLAS Trial) and caused discontinuation of therapy in 1.8% of these patients in the symptomatic trials. In patients treated with lisinopril for six weeks after acute myocardial infarction, hypotension (systolic blood pressure <100 mmHg) resulted in discontinuation of therapy in 9.7% of the patients.

**Clinical Laboratory Test Findings**

**Serum electrolytes:** Hyperkalemia and hyponatremia.

**Serum creatinine and Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon
discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with lisinopril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 11.6% of patients with heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

**Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with lisinopril but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

**Liver Function Tests:** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. In hypertensive patients, 2.0% discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%) and serum potassium (0.4%). In the heart failure trials, 3.4% of patients discontinued therapy due to laboratory adverse experiences; 1.8% due to elevations in blood urea nitrogen and/or creatinine and 0.6% due to elevations in serum potassium. In the myocardial infarction trial, 2.0% of patients receiving lisinopril discontinued therapy due to renal dysfunction (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration); less than 1.0% of patients discontinued therapy due to other laboratory adverse experiences: 0.1% with hyperkalemia and less than 0.1% with hepatic enzyme alterations.
Dosage and Administration

Hypertension

Initial Therapy: In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with lisinopril alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of lisinopril.

Diuretic Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of lisinopril. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with lisinopril to reduce the likelihood of hypotension. The dosage of lisinopril should be adjusted according to blood pressure response. If the patient’s blood pressure is not controlled with lisinopril alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. Concomitant administration of lisinopril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium.
**Dosage Adjustment in Renal Impairment:** The usual dose of lisinopril (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance > 10 mL/min < 30 mL/min (serum creatinine > 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

**Heart Failure**

Lisinopril is indicated as adjunctive therapy with diuretics and (usually) digitalis. The recommended starting dose is 5 mg once a day. When initiating treatment with lisinopril in patients with heart failure, the initial dose should be administered under medical observation, especially in those patients with low blood pressure (systolic blood pressure below 100 mmHg). The mean peak blood pressure lowering occurs six to eight hours after dosing. Observation should continue until blood pressure is stable. The concomitant diuretic dose should be reduced, if possible, to help minimize hypovolemia which may contribute to hypotension. The appearance of hypotension after the initial dose of lisinopril does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual effective dosage range is 5 to 40 mg per day administered as a single daily dose. The dose of lisinopril can be increased by increments of no greater than 10 mg, at intervals of no less than 2 weeks to the highest tolerated dose, up to a maximum of 40 mg daily. Dose adjustment should be based on the clinical response of individual patients.

**Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia:** In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min or serum
creatinine > 3 mg/dL), therapy with lisinopril should be initiated at a
dose of 2.5 mg once a day under close medical supervision.

**Acute Myocardial Infarction**

In hemodynamically stable patients within 24 hours of the onset of
symptoms of acute myocardial infarction, the first dose of lisinopril is 5
mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours
and then 10 mg of lisinopril once daily. Dosing should continue for six
weeks. Patients should receive, as appropriate, the standard
recommended treatments such as thrombolytics, aspirin, and beta-
blockers. Patients with a low systolic blood pressure (£ 120 mmHg)
when treatment is started or during the first 3 days after the infarct
should be given a lower 2.5 mg oral dose of lisinopril. If hypotension
occurs (systolic blood pressure < 100 mmHg) a daily maintenance dose
of 5 mg may be given with temporary reductions to 2.5 mg if needed. If
prolonged hypotension occurs (systolic blood pressure < 90 mmHg for
more than 1 hour) lisinopril should be withdrawn.

**Dosage Adjustment in Patients with Myocardial Infarction with
Renal Impairment:** In acute myocardial infarction, treatment with
lisinopril should be initiated with caution in patients with evidence of
renal dysfunction, defined as serum creatinine concentration exceeding
2 mg/dL. No evaluation of dosing adjustments in myocardial infarction
patients with severe renal impairment has been performed.

**Use in Elderly:** In general, blood pressure response and adverse
experiences were similar in younger and older patients given similar
doses of lisinopril. Pharmacokinetic studies, however, indicate that
maximum blood levels and area under the plasma concentration time
curve (AUC) are doubled in older patients, so that dosage adjustments
should be made with particular caution.
Overdosage

Following a single oral dose of 20 g/kg no lethality occurred in rats, and death occurred in one of 20 mice receiving the same dose. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril can be removed by hemodialysis.

Drug Interactions

**Hypotension - Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with lisinopril. The possibility of hypotensive effects with lisinopril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with lisinopril. If it is necessary to continue the diuretic, initiate therapy with lisinopril at a dose of 5 mg daily, and provide close medical supervision after the initial dose until blood pressure has stabilized. When a diuretic is added to the therapy of a patient receiving lisinopril, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic.

**Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of lisinopril alone were compared to lisinopril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

**Other Agents:** Lisinopril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. This included post myocardial infarction patients who were receiving intravenous or transdermal nitroglycerin. No clinically important pharmacokinetic interactions occurred when lisinopril was
used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of lisinopril.

**Agents Increasing Serum Potassium:** Lisinopril attenuates potassium loss caused by thiazide-type diuretics. Use of lisinopril with potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium sparing agents should generally not be used in patients with heart failure who are receiving lisinopril.

**Lithium:** Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended that serum lithium levels be monitored frequently if lisinopril is administered concomitantly with lithium.

**Use in Pregnancy**

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, lisinopril should be discontinued as soon as possible.
3.6.2 NSAID Used in the Present Study

Diclofenac Sodium

Chemical structure:

Diclofenac, as the sodium salt, is a benzeneacetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid monosodium salt. Molecular weight of the diclofenac sodium is 318.14.

Pharmacodynamics

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain related to inflammation and primary dysmenorrhea. With regard to its analgesic effect, diclofenac is not a narcotic.

Pharmacokinetics

Absorption

Under fasting condition, diclofenac is completely absorbed from the gastrointestinal tract. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. In some fasting volunteers, measurable plasma levels are observed within 10 minutes of dosing with diclofenac. Peak plasma levels are achieved in
approximately 1 hour in fasting normal volunteers, with a range from 0.33 to 2 hours.

The extent of diclofenac absorption is not significantly affected when it is taken with food. However, the rate of absorption is reduced by food, as indicated by a delay in $T_{\text{max}}$ and decrease in $C_{\text{max}}$ values by approximately 30%. After repeated oral administration of 50mg tablets t.i.d. no accumulation of diclofenac in plasma occurred.

**Distribution**

Plasma concentrations of diclofenac decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac is reversibly bound to human plasma albumin.

As with other NSAIDs, diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

**Metabolism and Elimination**

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulphate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Conjugates of unchanged diclofenac account for 5%-10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged un conjugated drug is excreted. Conjugates of the principal metabolite account for 20%-30% of the dose excreted in the urine and for 10%-20% of the dose excreted in the bile. Conjugates of three other metabolites together account for 10%-20% of the dose.
excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

Special Populations

*Patients with Renal and/or Hepatic Impairment:* To date, no differences in the pharmacokinetics of diclofenac have been detected in studies of patients with renal (50mg intravenously) or hepatic impairment (100mg oral solution). In patients with renal impairment (N=5, creatinine clearance 3 to 42 mL/min), AUC values and elimination rates were comparable to those in healthy subjects. In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubin, N=10), diclofenac concentrations and urinary elimination values were comparable to those in healthy subjects.

Clinical Studies

The analgesic efficacy of diclofenac was demonstrated in trials of patients with postoperative pain (following gynecologic, oral, and orthopedic surgery), osteoarthritis of the knee, and primary dysmenorrhea. The effectiveness of diclofenac in studies of pain or primary dysmenorrhea showed that onset of analgesia began, in some patients, as soon as 30 minutes, and relief of pain lasted as long as 8 hours, following single 50mg or 100mg doses. Duration of pain relief was judged by the time at which approximately half of the patients needed remedication. The onset and duration of pain relief for either the 50mg or 100mg dose was essentially the same, whether patients had moderate or severe pain at baseline.

Diclofenac was studied in single-dose and multiple-dose pain trials. The pain models in single-dose studies were post-dental extraction and
post-gynecologic surgery: the efficacy of the 50mg dose (N=258) and the 100mg dose (N=225) was comparable to aspirin 650mg in onset of pain relief, but generally provided a longer duration of analgesia than aspirin. The pain models for multiple-dose trials were post-orthopedic surgery pain as well as pain associated with primary dysmenorrhea: the efficacy of the 50mg dose (N=101) and the 100mg dose (N=442) followed by 50mg every 8 hours, was comparable to naproxen sodium 550mg followed by 275mg every 8 hours. In one study of chronic pain, in patients with osteoarthritis (N=196), diclofenac 50mg t.i.d. was comparable in efficacy to ibuprofen 800 mg t.i.d.

**Individualization of Dosage**

Diclofenac, like other NSAIDs, shows inter-individual differences in both pharmacokinetics and clinical response (pharmacodynamics). Consequently, the recommended strategy for initiating therapy is to use a starting dose likely to be effective for the majority of patients and to adjust dosage thereafter based on observation of diclofenac's beneficial and adverse effects.

In patients weighing less than 60kg (132lb), or where the severity of the disease, concomitant medication, or other diseases warrant, the maximum recommended total daily dose of diclofenac should be reduced. Experience with other NSAIDs has shown that starting therapy with maximum doses in patients at increased risk due to renal or hepatic disease, low body weight (< 60kg), advanced age, a known ulcer diathesis, or known sensitivity to NSAID effects, is likely to increase frequency of adverse reactions and is not recommended.

**Osteoarthritis / Rheumatoid Arthritis / Ankylosing Spondylitis:**
The usual starting dose of diclofenac immediate-release tablets for patients with osteoarthritis, is 100 to 150 mg/day, using a b.i.d. or t.i.d. dosing regimen. For patients with osteoarthritis, the usual starting dose of diclofenac is 100mg q.d.
For most patients with rheumatoid arthritis, the usual starting dose of diclofenac is 150 mg/day, using a b.i.d. or t.i.d. dosing regimen. The usual starting dose of diclofenac is 100mg q.d. Patients requiring more relief of pain and inflammation may increase the dose to 200 mg/day.

The recommended dose of diclofenac for patients with ankylosing spondylitis is 100 to 125 mg/day, using a q.i.d. dosing regimen.

**Analgesia / Primary Dysmenorrhea:** Because of earlier absorption of diclofenac from immediate-release tablets, it is the formulation indicated for management of pain and primary dysmenorrhea when prompt onset of pain relief is desired. The results of clinical trials suggest an initial diclofenac dose of 50mg for pain or for primary dysmenorrhea, followed by doses of 50mg every 8 hours, as needed. With experience, some patients with recurring pain, such as dysmenorrhea, may find that an initial dose of 100mg of diclofenac, followed by 50mg doses, will provide better relief. After the first day, when the maximum recommended dose may be 200mg, the total daily dose should generally not exceed 150mg.

**Indications**

Diclofenac is indicated for the acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis.Diclofenac extended-release tablets are indicated for chronic therapy of osteoarthritis and rheumatoid arthritis. In addition, diclofenac is indicated for the treatment of ankylosing spondylitis. Only diclofenac immediate-release tablet is indicated for the management of pain and primary dysmenorrhea, when prompt pain relief is desired, because it is formulated to provide earlier plasma concentrations of diclofenac.

**Dosage and Administration**

Diclofenac may be administered as 50mg immediate-release tablets, as 25mg, 50mg, and 75mg delayed-release tablets, or as 100mg extended-release tablets. Diclofenac immediate-release tablets is the formulation
indicated for management of acute pain and primary dysmenorrhea when prompt onset of pain relief is desired because of earlier absorption of diclofenac. For the same reason, diclofenac extended-release tablets are not indicated for the management of acute painful conditions and should be used as chronic therapy in patients with osteoarthritis and rheumatoid arthritis.

The dosage of diclofenac should be individualized to the lowest effective dose to minimize adverse effects.

**Osteoarthritis:** The recommended dosage is 100 to 150 mg/day: Diclofenac immediate-release or delayed-release 50mg b.i.d. or t.i.d.; or delayed-release 75mg b.i.d.. The recommended dosage for chronic therapy with delayed-release tablets is 100 mg q.d.. Dosages of diclofenac extended-release tablets of 200mg daily are not recommended for patients with osteoarthritis. Dosages above 200 mg/day have not been studied in patients with osteoarthritis.

**Rheumatoid Arthritis:** The recommended dosage is 100 to 200 mg/day. Diclofenac immediate-release or delayed-release 50mg t.i.d. or q.i.d.; or delayed-release 75mg b.i.d.. The recommended dosage for chronic therapy with diclofenac extended-release is 100mg q.d.. In the rare patient where diclofenac extended-release 100 mg/day is unsatisfactory, the dose may be increased to 100mg b.i.d. if the benefits outweigh the clinical risks. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis.

**Ankylosing Spondylitis:** The recommended dosage is 100 to 125 mg/day. Diclofenac 25mg q.i.d. with an extra 25mg dose at bedtime if necessary. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

**Analgesia and Primary Dysmenorrhea:** The recommended starting dose of diclofenac immediate-release tablets is 50mg t.i.d.. With experience, physicians may find that in some patients an initial dose of 100mg of diclofenac, followed by 50mg doses, will provide better relief.
After the first day, when the maximum recommended dose may be 200mg, the total daily dose should generally not exceed 150mg.

The drug is not recommended for children, nursing mothers, or pregnant women.

**Adverse Reactions**

Adverse reaction information is derived from blinded, controlled, and open-label clinical trials, as well as world-wide marketing experience. In the description below, rates of more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally not possible.

In 718 patients treated for shorter periods, i.e., 2 weeks or less, with diclofenac immediate-release tablets, adverse reactions were reported one-half to one-tenth as frequently as by patients treated for longer periods. In a 6-month, double-blind trial comparing diclofenac immediate-release tablets (N=196) versus diclofenac delayed-release tablets (N=197) versus ibuprofen (N=197), adverse reactions were similar in nature and frequency. In controlled clinical trials, the incidence of adverse reactions for diclofenac delayed-release tablets and diclofenac extended-release tablets at comparable doses were similar.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1,543 patients treated up to 13 weeks with diclofenac delayed-release tablets. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3%, of patients. Peptic ulcer or G.I. bleeding occurred in clinical trials in 0.6% (95% confidence interval: 0.2% to 1%) of approximately 1,800 patients during their first 3 months of diclofenac treatment and in 1.6% (95% confidence interval: 0.8% to 2.4%) of approximately 800 patients followed for 1 year.
Gastrointestinal symptoms were followed in frequency by central nervous system side effects such as headache (7%) and dizziness (3%).

Meaningful (exceeding 3 times the Upper Limit of Normal) elevations of ALT (SGPT) or AST (SGOT) occurred at an overall rate of approximately 2% during the first 2 months of diclofenac treatment. Unlike aspirin-related elevations, which occur more frequently in patients with rheumatoid arthritis, these elevations were more frequently observed in patients with osteoarthritis (2.6%) than in patients with rheumatoid arthritis (0.7%). Marked elevations (exceeding 8 times the ULN) were seen in 1% of patients treated for 2-6 months.

The following adverse reactions were reported in patients treated with diclofenac:

**Body as a Whole:** Abdominal pain or cramps, headache, fluid retention, abdominal distention, malaise, swelling of lips and tongue, photosensitivity, anaphylaxis and anaphylactoid reactions.

**Cardiovascular:** Hypertension, congestive heart failure.

**Digestive:** Diarrhea, indigestion, nausea, constipation, flatulence, liver test abnormalities, peptic ulcer with or without bleeding and/or perforation, or bleeding without ulcer, vomiting, jaundice, melena, esophageal lesions, stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, hepatic necrosis, cirrhosis, hepatorenal syndrome, appetite change, pancreatitis with or without concomitant hepatitis and colitis.

**Nervous System:** Dizziness, insomnia, drowsiness, depression, diplopia, anxiety, irritability, aseptic meningitis and convulsions.

**Skin and Appendages:** Rash, pruritus, alopecia, urticaria, eczema, dermatitis, bullous eruption, erythema multiforme major, exfoliative dermatitis, angioedema and *Stevens-Johnson syndrome*. 
**Special Senses:** Tinnitus, blurred vision, taste disorder, reversible and irreversible hearing loss and scotoma.

**Hemic and Lymphatic:** Hemoglobin decrease, leukopenia, thrombocytopenia, eosinophilia, hemolytic anemia, aplastic anemia, agranulocytosis, purpura and allergic purpura.

**Metabolic and Nutritional Disorders:** Azotemia.

**Respiratory:** Epistaxis, asthma and laryngeal edema.

**Urogenital:** Nephrotic syndrome, proteinuria, oliguria, interstitial nephritis, papillary necrosis and acute renal failure.

**Drug Interactions**

**Aspirin:** Concomitant administration of diclofenac and aspirin is not recommended because diclofenac is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations, peak plasma levels, and AUC values.

**Anticoagulants:** While studies have not shown diclofenac to interact with anticoagulants of the warfarin type, caution should be exercised, nonetheless, since interactions have been seen with other NSAIDs. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including diclofenac, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

**Digoxin, Methotrexate, Cyclosporine:** Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of diclofenac may increase serum concentrations of digoxin and methotrexate and increase cyclosporine's nephrotoxicity. Patients who begin taking diclofenac or who increase their diclofenac dose or any other NSAID while taking digoxin, methotrexate, or cyclosporine may develop toxicity characteristics for these drugs. They
should be observed closely, particularly if renal function is impaired. In the case of digoxin, serum levels should be monitored.

**Lithium:** Diclofenac decreases lithium renal clearance and increases lithium plasma levels. In patients taking diclofenac and lithium concomitantly, lithium toxicity may develop.

**Oral Hypoglycemics:** Diclofenac does not alter glucose metabolism in normal subjects nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experiences, of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac that necessitated changes in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

**Diuretics:** Diclofenac and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

**Other Drugs:** In small groups of patients (7-10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline, or digitoxin did not significantly affect the peak levels and AUC values of diclofenac. Phenobarbital toxicity has been reported to have occurred in a patient on chronic phenobarbital treatment following the initiation of diclofenac therapy.

**Drug/Laboratory Test Interactions**

**Effect on Blood Coagulation:** Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are
unlikely to be clinically important. Diclofenac is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed.