

Chapter 36

Drugs Affecting Renin-Angiotensin System

RENIN-ANGIOTENSIN SYSTEM

Angiotensin-II (Ang II) is an octapeptide generated in the plasma from a precursor plasma α_2 globulin called *angiotensinogen*, and is involved in electrolyte, blood volume and pressure homeostasis. Pressor action of kidney extracts was known since the turn of the 19th century. The active material was termed '*Renin*'. In the 1940s renin was shown to be a protease enzyme which acted indirectly by producing a pressor principle from plasma protein. Subsequently, it became clear that the product of renin action was an inactive decapeptide *angiotensin-I* (Ang I) which was converted to the active octapeptide Ang II by an *angiotensin converting enzyme* (ACE). The renin-angiotensin system (RAS) has attracted considerable attention over the past 30 years, particularly after the development of ACE inhibitor *captopril*.

Circulating renin-angiotensin system The generation and metabolism of Ang II in circulation is depicted in Fig. 36.1. Normally, the amount of renin in plasma secreted by the juxtaglomerular cells in the kidney acts as the limiting factor for Ang II generation. The plasma $t_{1/2}$ of renin is 15 min. The biological potency of Ang I is only 1/100 that of Ang II, but it is rapidly converted into the latter by ACE which is a *dipeptidyl carboxypeptidase*, an ectoenzyme located primarily on the luminal surface of vascular endothelial cells (especially in lungs). Circulating Ang II also has a very short $t_{1/2}$

(1 min). The first degradation product produced by the action of an aminopeptidase is the heptapeptide termed *Angiotensin-III* (Ang III). It is 2–10 times less potent than Ang II, except in stimulating aldosterone secretion, in which it is equipotent. Ang III is again attacked by another aminopeptidase, and the resulting hexapeptide (3-8) is called Ang IV which has very different central (and some peripheral) actions elicited through a specific AT_4 receptor. Both Ang III and Ang IV are broken into inactive fragments by nonspecific peptidases termed *angiotensinases*.

Tissue (local) renin-angiotensin systems

Extrinsic local RAS Apart from Ang II generated in circulation as described above, blood vessels capture circulating angiotensinogen and renin to produce Ang II at the surface of their intima. This Ang II diffuses to act locally on the angiotensin receptors producing localized responses.

Intrinsic local RAS Many tissues, especially heart, blood vessels, brain, kidneys, adrenals possess the capacity to synthesize all components of RAS within their cells. They generate Ang II and III intracellularly as per physiological need and pathological status. These signal molecules are instrumental in regulating organ function, cell growth (hypertrophy), cell death (apoptosis), remodeling and fibrosis.

The local RAS operate in several organs in addition to the liver and kidney dependent circulating RAS.

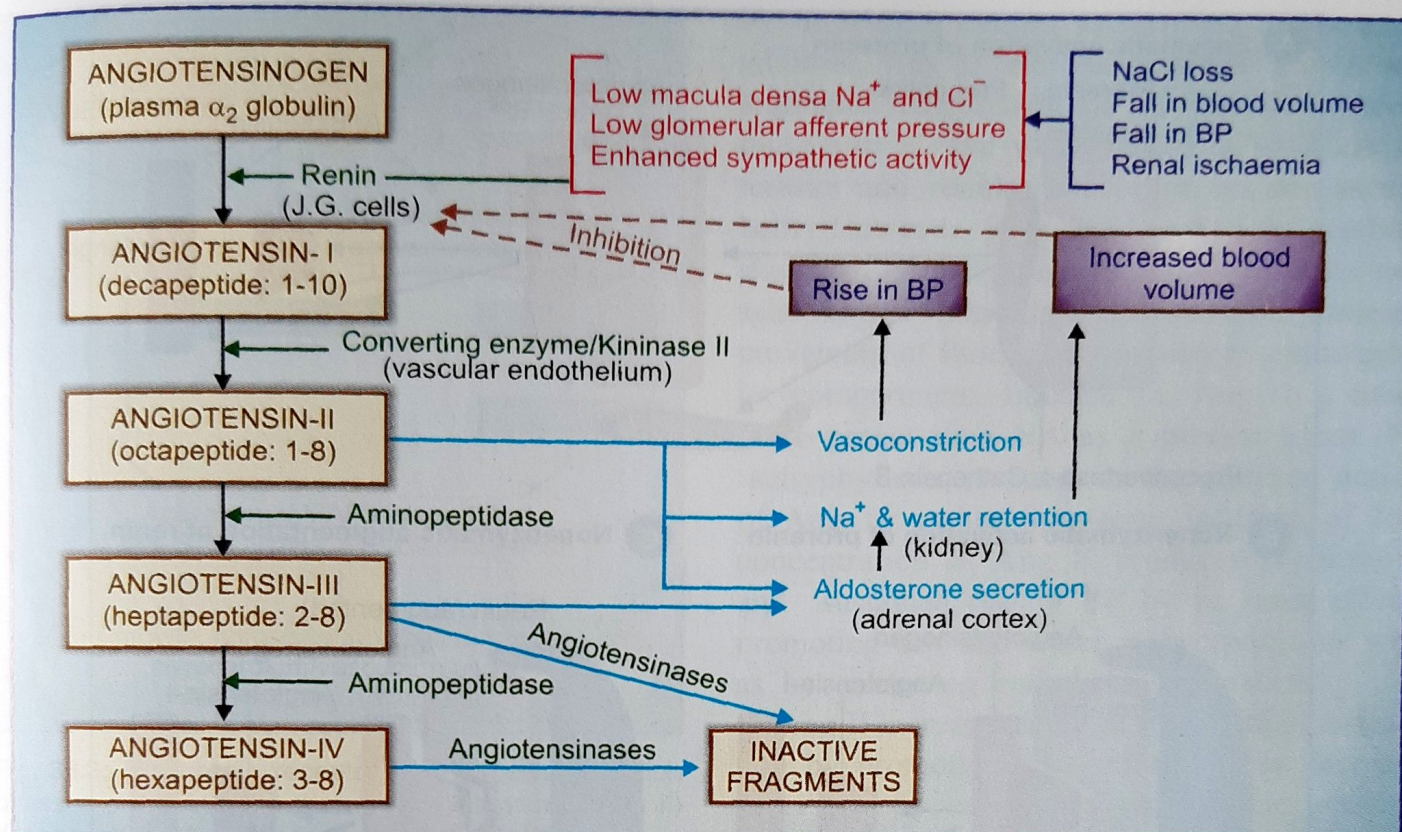


Fig. 36.1: Physiological regulation of electrolyte balance, plasma volume and blood pressure by the renin-angiotensin system
J.G. cells—Juxtaglomerular cells

Prorenin and (Pro) renin receptor (PRR)

Renin is synthesized in the juxtaglomerular (JG) cells of kidney and in tissues expressing local RAS as a larger peptide *pre-prorenin*. In response to appropriate stimuli both prorenin and renin are secreted; the former in much larger quantities. The concentration of prorenin in circulation is 5–10 fold higher than that of renin. Till recently, prorenin was considered to be only the inactive precursor of renin, but now it is recognized to be active in its own right.

Prorenin is activated both enzymatically and non-enzymatically (Fig. 36.2). The enzymatic activation is carried out by proteases like proconvertase-1 or Cathepsin B, which cleave off the hindering 'propeptide' to produce renin with exposed catalytic domain. This activation is irreversible. Nonenzymatic and reversible activation occurs by binding of prorenin to another transmembrane protein called (Pro) renin receptor (PRR), so named because it binds renin as well. The PRR is richly

expressed in heart, blood vessels, kidney, brain, eye and liver. Binding of prorenin to PRR brings about a conformational change, the 'propeptide' segment unfolds and the catalytic domain is exposed. When renin binds to PRR, its catalytic activity is augmented several fold. However, prorenin/renin can dissociate from PRR to return to their original state, and the nonenzymatic activation/augmentation is reversible. Nonenzymatic activation of prorenin plays a major role in local RAS, where prorenin exerts effects *via* Ang II dependent and Ang II independent pathways (Fig. 36.3).

(a) *Ang II dependent pathway*: Activation of prorenin/renin generates Ang I which is converted to Ang II by ACE. Ang II acts on AT receptors on the tissue cells to produce effects on cell growth, inflammation, apoptosis, etc.

(b) *Ang II independent pathway*: Binding of prorenin/renin to PRR on cell surface directly triggers intracellular signalling *via* activation of MAP kinase, plasminogen activator-inhibitor-1

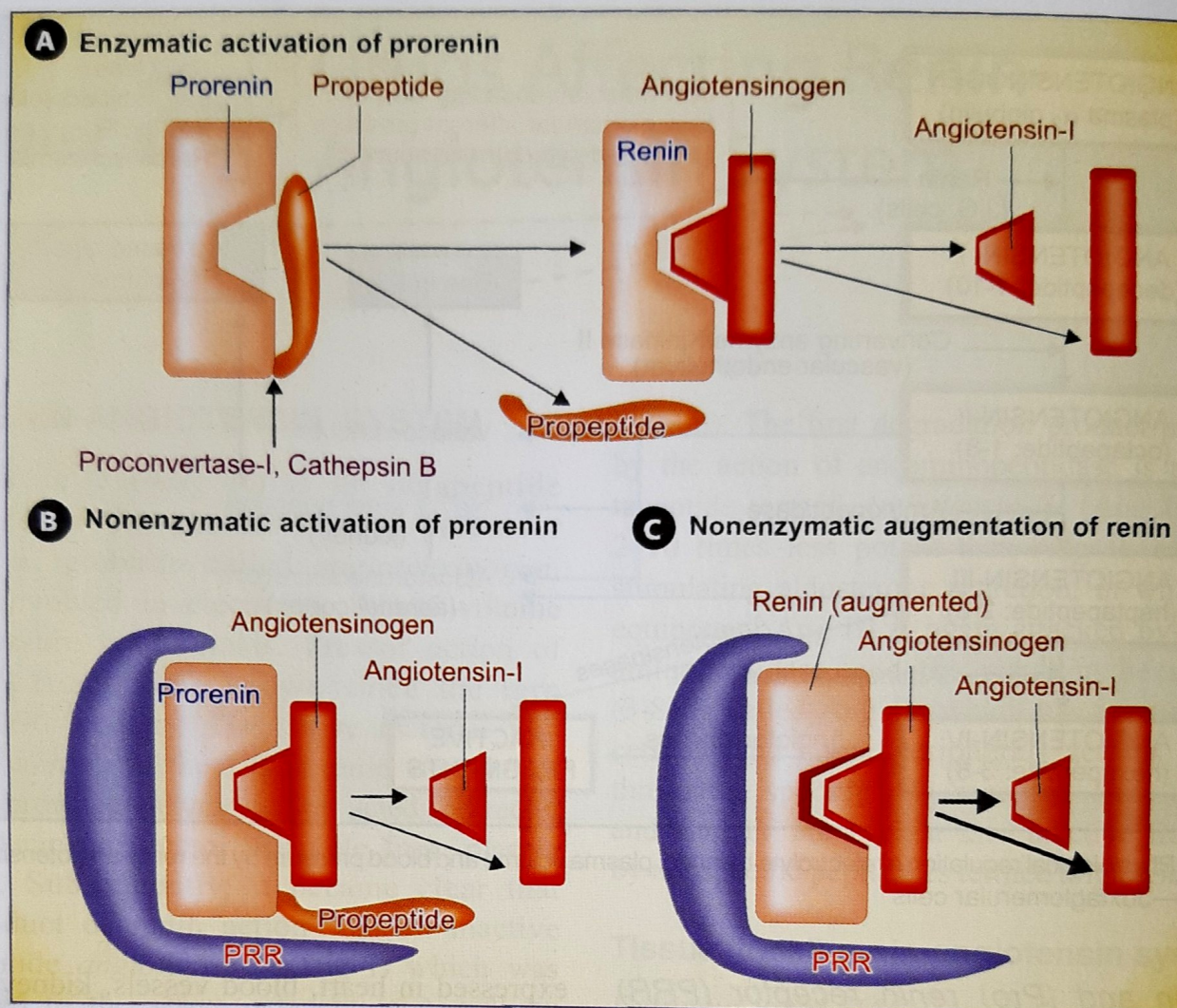


Fig. 36.2: Schematic depiction of enzymatic (A) and nonenzymatic activation of prorenin (B) and nonenzymatic augmentation of renin (C) in the tissue (local) renin-angiotensin system
 PRR—(Pro) renin receptor; Ang I—Angiotensin I.

(PAI-1), JAK-STAT pathway, transcription factors, protooncogenes, etc. to regulate cell growth, collagen deposition, fibrosis and apoptosis. Overactivity of RAS *via* such signalling abundantly contributes to pathological changes and end-organ damage in many conditions like hypertensive vascular and ventricular hypertrophy, post-infarction myocardial fibrosis and remodeling, congestive heart failure, nephropathy, retinopathy, etc. The ratio of circulating prorenin to renin is markedly elevated in diabetes, which may be causative in nephropathy and retinopathy.

Alternative (ACE-independent) pathway of Ang II production

In addition to the primary pathway described above, small quantities of Ang I and Ang II can be produced from angiotensinogen by the action of other proteases like cathepsin. Moreover, chymase can convert (although at a much slower rate) Ang I to Ang II, particularly in heart and kidney.

Other angiotensin peptides

In addition to Ang II and Ang III some other biologically active angiotensin peptides are produced in small quantities whose physio-pathological role is not well understood.

Angiotensin IV (Ang IV) It is a hexapeptide (Ang 3-8) produced by removal of arginine from aminoterminal of

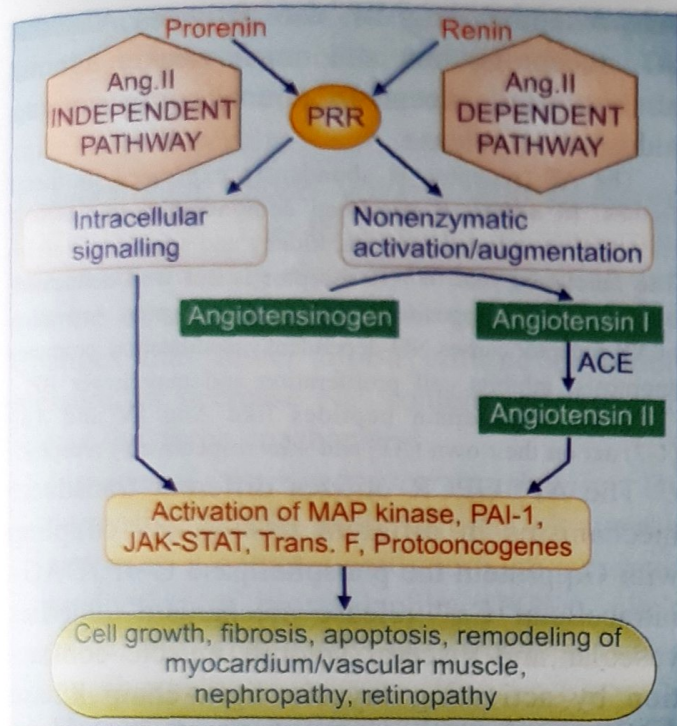


Fig. 36.3: (Pro) renin receptor (PRR) mediated action of tissue prorenin/renin through angiotensin II (Ang II) dependent and Ang II independent pathways.

PAI-1—Plasminogen activator inhibitor-1;

Trans. F—Transcription factors

Ang III by an aminopeptidase. Ang IV inhibits an insulin regulated aminopeptidase (IRAP) which is considered to be its specific receptor and is labelled AT_4 receptor. Binding of Ang IV to IRAP prevents degradation of neuropeptides involved in cognitive function and memory in animals. Thus Ang IV improves memory. Some vascular, renal and other peripheral effects of Ang IV have also been described.

Angiotensin (1-7) This heptapeptide can be produced from Ang I or Ang II by the action of another carboxypeptidase labelled ACE 2. In animals, Ang (1-7) produces effects which are in general opposite to those of Ang II, including vasodilatation (NO dependent), antithrombotic, anti-ischaemic and antiproliferative effects by binding to a protooncogene receptor. The clinically used ACE inhibitors do not inhibit ACE 2. Rather, when these drugs are given levels of Ang (1-7) are increased due to diversion of Ang I from ACE and inhibition of degradation of Ang (1-7).

Attempts are being made to therapeutically exploit the Ang II related peptides.

ACTIONS

1. CVS The most prominent action of Ang II is vasoconstriction, which is produced directly as well as by enhancing Adr/NA release from adrenal medulla/adrenergic nerve endings and

by increasing central sympathetic outflow. In addition, Ang II inhibits reuptake of NA and augments responsiveness of vascular smooth muscle to it. The vasoconstriction involves arterioles and venules and occurs in all vascular beds. However, it is less marked in cerebral, skeletal muscle, pulmonary and coronary vessels. Ang II induced vasoconstriction promotes movement of fluid from vascular to extravascular compartment. Injected i.v. Ang II is much more potent than NA as a pressor agent. No tachyphylaxis is seen in the pressor action of Ang II; rather long-term infusion of low concentration of Ang II produces progressive and sustained rise in BP by its renal effects promoting salt and water reabsorption, as well as by enhancing endothelin generation.

Ang II increases force of myocardial contraction by promoting Ca^{2+} influx. It can increase heart rate by enhancing sympathetic activity, but this is opposed by the reflex effect of rise in BP. Cardiac output is often reduced and cardiac work is increased (due to rise in peripheral resistance). In contrast to NA, Ang II does not activate latent pacemakers. As such, it has little arrhythmogenic propensity.

Ang II acting on a chronic basis induces hypertrophy, hyperplasia and increased intercellular matrix production in the myocardium as well as vascular smooth muscle by direct cellular effects involving expression of protooncogenes and transcription of several growth factors. Indirectly, volume overload and increased t.p.r. caused by Ang II contributes to the hypertrophy and remodeling (abnormal redistribution of muscle mass) in heart and blood vessels. Long standing hypertension increases vessel wall as well as intimal thickness and causes ventricular hypertrophy. Fibrosis and dilatation of infarcted area with hypertrophy of the noninfarcted ventricular wall is seen after myocardial infarction. Progressive cardiac myocyte death and fibrotic transformation occurs in CHF. These changes are important risk factors for cardiovascular morbidity and mortality. ACE inhibitor therapy retards/reverses many

of these changes imparting a pivotal role to Ang II in vascular and ventricular hypertrophy, apoptosis and remodeling. As described above, the local RAS and prorenin-PRR systems are crucial in these responses.

2. Adrenal cortex Ang II and Ang III are trophic to the zona glomerulosa of adrenal cortex. They enhance synthesis and release of aldosterone which acts on distal tubule in kidney to promote Na^+ reabsorption and K^+/H^+ excretion. These effects are exerted at concentrations lower than those required to cause vasoconstriction.

3. Kidney In addition to exerting indirect effect on kidney through aldosterone, Ang II promotes Na^+/H^+ exchange in proximal tubule $\rightarrow$ increased Na^+ , Cl^- and HCO_3^- reabsorption. Further, Ang II reduces renal blood flow and GFR, and produces intrarenal haemodynamic effects which normally result in Na^+ and water retention. However, an opposite effect has been observed in cirrhotics and renovascular disease patients in whom Ang II increases GFR by strongly constricting glomerular efferent vessels.

4. CNS It has been noted that systemically administered Ang II can gain access to certain periventricular areas of the brain to induce drinking behaviour and ADH release—both of which would be conducive to plasma volume expansion. Ang II also increases central sympathetic outflow, which contributes to the pressor response.

5. Peripheral sympathetic structures Ang II enhances sympathetic activity by peripheral action as well. It releases Adr from adrenal medulla, stimulates autonomic ganglia and increases the output of NA from adrenergic nerve endings.

Angiotensin receptors and transducer mechanisms Specific Ang II receptors are expressed on the surface of target cells. Two subtypes (AT_1 and AT_2) have been differentiated pharmacologically: *Losartan* is a selective AT_1 antagonist, while PD 123177 is a selective AT_2 antagonist. Both subtypes are GPCRs. However, all major effects of Ang II are mediated by

AT_1 receptor. Ang III also activates AT_1 and AT_2 receptors, but is a much weaker agonist at most sites, except on adrenal cortex causing aldosterone release.

The AT_2 receptor is abundantly expressed in foetal tissues. In adults, it has been demonstrated in vascular endothelium, adrenal medulla, kidney and some brain areas. The functional role of AT_2 receptor is not well delineated, but is generally opposite to that of AT_1 receptor. Activation of AT_2 receptor causes NO-dependent vasodilatation, promotes apoptosis, inhibits cell proliferation and may lower BP.

Other angiotensin peptides like Ang IV and Ang (1-7) act on their own (AT_4 and *Mas* respectively) receptors.

The AT_1 GPCR utilizes different transducer mechanisms in different tissues. By coupling with Gq protein the phospholipase C- IP_3 /DAG-intracellular Ca^{2+} release mechanism underlies vascular and visceral smooth muscle contraction by activating myosin light chain kinase (MLCK). In addition, membrane Ca^{2+} channels are activated. Enhanced Ca^{2+} movement also induces aldosterone synthesis/release, cardiac inotropy, depolarization of adrenal medullary and autonomic ganglionic cells, resulting in CA release or sympathetic discharge. DAG activates protein kinase C (PKC) which phosphorylates several intracellular proteins and augments the above responses as well as participates in promotion of cell growth. In liver and kidney, Ang II inhibits adenylyl cyclase by AT_1 receptor coupled to Gi protein. The intrarenal homeostatic action involves phospholipase A_2 activation and PG/LT production.

In many tissues, especially myocardium, vascular smooth muscle and fibroblasts, AT_1 receptor also mediates long-term effects of Ang II on cell growth. Ang II activates MAP kinase, TAK2 tyrosine protein kinase, PKC and utilizes the JAK-STAT pathway which together enhance expression of proto-oncogenes, transcription factors and growth factors. As a result, cell growth is promoted and more intercellular matrix is synthesized.

PATHOPHYSIOLOGICAL ROLES

1. Mineralocorticoid secretion There is no doubt that Ang II (also Ang III) is the physiological stimulus for aldosterone secretion from

adrenal cortex. It also exerts trophic influence on the glomerulosa cells so that effects are augmented under conditions which persistently raise Ang II levels.

2. Electrolyte, blood volume and pressure homeostasis The RAS plays an important role in maintaining electrolyte composition and volume of extracellular fluid (see Fig. 36.1). Changes that lower blood volume or blood pressure, or decrease Na^+ content induce renin release by three mechanisms.

- **Intrarenal baroreceptor pathway:** By decreasing tension in the afferent glomerular arterioles, it operates partly through increased production of prostaglandins (PGE_2), nitric oxide, etc, and partly *via* stretch sensitive ion channels.
- **Macula densa pathway:** Low Na^+ and Cl^- concentration in the tubular fluid sensed by macula densa cells triggers this pathway. It has been found that COX-2 and neuronal nitric oxide synthase (nNOS) are induced in macula densa cells by Na^+ depletion $\rightarrow$ release of PGE_2 and PGI_2 is enhanced both due to increased amount of COX-2 as well as its activation by NO. The locally released PGs act on juxtaglomerular cells to promote renin secretion.
- **β adrenoceptor pathway:** Baroreceptor and other reflexes which increase sympathetic impulses to JG cells activate β_1 adrenoceptors expressed on their surface $\rightarrow$ increased intracellular cAMP triggers renin release.

Increased renin is translated into increased plasma Ang II which produces acute rise in BP by vasoconstriction, and more long-lasting effects by directly as well as indirectly increasing Na^+ and water reabsorption in the kidney. Rise in BP in turn inhibits renin release : the *long-loop negative feedback mechanism*. It has been shown that Ang II can be formed within the kidney and exerts important local regulatory effects. A *short-loop negative feedback mechanism* operates within the kidney : activation of AT_1 receptors on JG cells inhibits renin release directly. Long-term stabilization of BP despite

varying salt and water intake appears to be achieved through these mechanisms.

The mechanisms of regulation of renin release have important pharmacological implications:

- ACE inhibitors and AT_1 antagonists enhance renin release by interfering with both the short-loop and long-loop negative feedback mechanisms.
- Vasodilators and diuretics stimulate renin release by lowering BP.
- Loop diuretics increase renin production by reducing entry of Na^+ and Cl^- into macula densa cells.
- Central sympatholytics and β blockers decrease renin release by interfering with the β adrenoceptor pathway.
- NSAIDs, including selective COX-2 inhibitors, and nNOS inhibitors decrease renin release by inhibiting PG production $\rightarrow$ cause Na^+ and water retention.

3. Development of hypertension The RAS is directly involved in renovascular hypertension: plasma renin activity (PRA) is raised in most patients. In essential hypertension also it appears to have a permissive role, though PRA may be either raised or low. Since ACE inhibitors consistently lower BP in hypertensives, the involvement of this system appears to be more widespread. A positive correlation between circulating angiotensinogen levels and essential hypertension has also been found. Several evidences point to causation of pregnancy-induced hypertension (preeclampsia) by production of autoantibodies which activate AT_1 receptor. The role of Ang II in hypertrophy/remodeling of heart and blood vessels is now well recognized (see above).

4. Secondary hyperaldosteronism The RAS is instrumental in the development of secondary hyperaldosteronism.

5. CNS Ang II can be formed locally in the brain and may function as transmitter or modulator. Regulation of thirst, hormone release and sympathetic outflow may be the responses mediated.

Ang II is not available commercially, and not used clinically.

Inhibition of renin-angiotensin system

This can be achieved by:

1. Sympathetic blockers (β blockers, adrenergic neurone blockers, central sympatholytics)—decrease renin release.
2. Direct renin inhibitors (DRIs, e.g. aliskiren): block renin action—interfere with generation of Ang I from angiotensinogen (rate limiting step).
3. Angiotensin converting enzyme (ACE) inhibitors (e.g. captopril)—prevent generation of the active principle Ang II.
4. Angiotensin receptor blockers (ARBs, e.g. losartan)—antagonise the action of Ang II on target cells.
5. Aldosterone antagonists (e.g. spironolactone)—block mineralocorticoid receptors.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Captopril, a dipeptide analogue, is the first orally active ACE inhibitor which was introduced in 1977 and quickly gained wide usage. A multitude of other ACE inhibitors have since been added, of which—*enalapril*, *lisinopril*, *benazepril*, *ramipril*, *fosinopril*, *quinapril*, *trandolapril*, *imidapril* and *perindopril* are available in India. Many others are marketed elsewhere. The pharmacology of captopril is described as prototype, since most of its effects are class effects common to all ACE inhibitors.

Captopril

It is a sulfhydryl containing dipeptide surrogate of proline which abolishes the pressor action of Ang I but not that of Ang II: It does not block AT_1 or AT_2 receptors.

ACE is a relatively nonspecific enzyme; splits off a dipeptidyl segment from several peptides including bradykinin, substance P, a natural stem cell regulating peptide, enkephalins, etc. in addition to Ang I. As such, captopril increases plasma kinin levels and potentiates the hypotensive action of exogenously administered bradykinin. Pretreatment with B_2 kinin receptor antagonist has shown that

kinins do contribute to the acute vasodepressor action of ACE inhibitors, but they appear to have little role in the long-term hypotensive effect, probably because, firstly kinins play only a minor role, if at all, in BP regulation, and, secondly another enzyme 'Kininase I' (which also degrades bradykinin) is not inhibited by captopril. Nevertheless, elevated kinins (and PGs whose synthesis is enhanced by kinins) may be responsible for cough and angioedema induced by ACE inhibitors in susceptible individuals. ACE inhibitors interfere with degradation of substance P also. Rise in the level of stem cell regulator peptide caused by ACE inhibitors could, in part, be responsible for their cardioprotective effect in CHF.

Captopril lowers BP, but in the short-term, magnitude of response is dependent on the Na^+ status and the level of RAS activity. In normotensive Na^+ replete individuals, the fall in BP attending initial few doses of ACE inhibitors is modest. Fall in BP is more marked when Na^+ has been depleted by dietary restriction or diuretics, because renin level is high. In CHF also, the renin level is raised and anti-hypertensive doses of captopril initially cause marked fall in BP. ACE inhibitor therapy in these situations has to be initiated at much lower doses. A greater fall in BP also occurs in renovascular, accelerated and malignant hypertension. In essential hypertension it has been found that RAS is overactive in 20%, normal in 60% and hypoactive in the rest. Thus, this system contributes to maintenance of vascular tone in over 80% cases and its inhibition results in lowering of BP. Treatment with ACE inhibitors causes feedback increase in renin release resulting in overproduction of Ang I. Since its conversion to Ang II is blocked, Ang I is diverted to produce more Ang (1-7) which has vasodilator property, and could contribute to the BP lowering action of ACE inhibitors. In the long-term however, no correlation has been observed between plasma renin activity (PRA) and magnitude of fall in BP due to captopril.

Captopril induced hypotension is a result of decrease in total peripheral resistance. The arterioles dilate and compliance of larger arteries is increased. Both systolic and diastolic BP fall. Cardiac output is not affected. Cardiovascular reflexes are not interfered with and there is little dilatation of capacitance vessels. As such, postural hypotension is not a problem. Reflex sympathetic stimulation does not occur despite vasodilatation, and ACE inhibitors can be safely used in patients with ischaemic heart disease. The renal blood flow is not compromised even when BP falls substantially. This is due to greater dilatation of renal vessels (Ang II markedly constricts them). Cerebral and coronary blood flow are also not compromised.

Reflex (postural) changes in plasma aldosterone are abolished and basal levels are somewhat decreased as a consequence of loss of its regulation by Ang II. However, physiologically sufficient mineralocorticoid is still secreted under the influence of ACTH and plasma K^+ . Levels of plasma renin and Ang I are increased as a compensatory measure, but the physiological significance of this appears to be minor (most actions are exerted through generation of Ang II).

Pharmacokinetics About 70% of orally administered captopril is absorbed. Presence of food in stomach reduces its bioavailability. Penetration in brain is poor. It is partly metabolized and partly excreted unchanged in urine. The plasma $t_{1/2}$ is ~2 hours, but actions last for 6–12 hours.

Adverse effects The adverse effect profile of all ACE inhibitors is similar. Captopril is well tolerated by most patients, especially if daily dose is kept below 150 mg.

- *Hypotension*: An initial sharp fall in BP occurs especially in diuretic treated and CHF patients; persistent hypotension may be troublesome in MI patients.
- *Hyperkalaemia*: This is likely in patients with impaired renal function and in those taking

K^+ sparing diuretics, NSAIDs or β blockers. In others significant rise in plasma K^+ is rare.

- *Cough*: A persistent brassy cough occurs in 10–16% patients within 1–8 weeks, often requires discontinuation of the drug—subsides 4–6 days thereafter. It is not dose related and appears to be caused by inhibition of bradykinin/substance P breakdown in the lungs of susceptible individuals.
- *Rashes, urticaria*: Occur in 1–4% recipients; but do not usually warrant drug discontinuation. *Angioedema* is rare.
- *Dysgeusia*: Reversible loss or alteration of taste sensation due to captopril occurs in few patients, rarely with other ACE inhibitors.
- *Foetopathic*: Foetal growth retardation, hypoplasia of organs and foetal death may occur if ACE inhibitors are given during later half of pregnancy. A recent report indicates 2.7-fold higher malformation rate in foetuses exposed to ACE inhibitors in the first trimester. ACE inhibitors must be stopped when the woman conceives.
- *Headache, dizziness, nausea and bowel upset*: Each of these is reported in 1–4% patients.
- *Granulocytopenia and proteinuria*: These are rare, but warrant withdrawal. Renal disease predisposes to these adverse effects. However, ACE inhibitors retard diabetic nephropathy, reduce attendant proteinuria, and are renoprotective.
- *Acute renal failure*: It may be precipitated by ACE inhibitors in patients with bilateral renal artery stenosis due to fall in glomerular filtration pressure.

Interactions

- Diuretics synergise with the hypotensive action of ACE inhibitors by depleting Na^+ and raising renin levels. In diuretic treated patients, the starting dose of ACE inhibitors should be low.
- Indomethacin (and other NSAIDs) attenuate the hypotensive action by retaining salt and water. Incidents of renal failure have been reported when a NSAID was given to

patients (especially elderly) receiving ACE inhibitor + diuretic.

- Hyperkalaemia can occur if K^+ supplements/ K^+ sparing diuretics are given with any ACE inhibitor.
- Antacids reduce bioavailability of captopril.
- ACE inhibitors reduce Li^+ clearance and predispose to its toxicity.

Dose: 25 mg BD, increased gradually upto 50 mg TDS according to response. In patients on diuretics and in CHF patients it is wise to start with 6.25 mg BD to avoid marked fall in BP initially. Tablets should be taken 1 hr before or 2 hr after a meal.

Captopril has become less popular due to need for twice/thrice daily dosing and possibly higher incidence of side effects compared to other ACE inhibitors.

ANGIOPRIL 25 mg tab, ACETEN 12.5, 25 mg tab.

OTHER ACE INHIBITORS

All ACE inhibitors have the same pharmacological actions, therapeutic uses and spectrum of adverse effects, drug interactions and contraindications. Differences among them are primarily pharmacokinetic, reflected in time course of action. Their important features are compared in Table 36.1. No single drug is superior to others.

Enalapril This is the second ACE inhibitor to be introduced. It is a prodrug, deesterified in the liver to *enalaprilat* (a tripeptide analogue), which is not used as such orally because of poor absorption, but is marketed as injectable

preparation in some countries. Enalapril may offer certain advantages over captopril:

1. More potent, effective dose 5–20 mg OD or BD.
2. Its absorption is not affected by food.
3. Onset of action is slower (due to need for conversion to active metabolite), less liable to cause abrupt first dose hypotension.
4. Has a longer duration of action: most hypertensives can be treated with single daily dose.
5. Rashes and loss of taste are probably less frequent.

ENAPRIL, ENVAS, ENAM 2.5, 5, 10, 20 mg tab.

Lisinopril It is the lysine derivative of enalaprilat; does not require hydrolysis to become active ACE inhibitor. Its oral absorption is slow (making first dose hypotension less likely) and incomplete, but unaffected by food. The duration of action is considerably longer, permitting single daily dose and ensuring uniform hypotensive action round the clock.

LINVAS, LISTRIL, LIPRIL 2.5, 5, 10 mg tab, LISORIL 2.5, 5, 10, 20 mg tab.

Perindopril Another long-acting ACE inhibitor with a slow onset of action: less chance of first dose hypotension. Though 66–95% of orally administered perindopril is absorbed, only about 20% is converted to the active metabolite *perindoprilat*. Extensive metabolism

Table 36.1: Comparative features of some ACE inhibitors

	Captopril	Enalapril	Lisinopril	Fosinopril	Perindopril	Ramipril
1. Chemical nature	Sulphydryl	Carboxyl	Carboxyl	Phosphinate	Carboxyl	Carboxyl
2. Activity status	Active	Prodrug	Active	Prodrug	Prodrug	Prodrug
3. Bioavailability (as active form)	70%	50%	25%	30%	30–50%	60%
4. Time to peak action	1 hr	4–6 hr	6–8 hr	3–5 hr	6 hr	3–6 hr
5. Elimination $t_{1/2}^*$	2 hr	11 hr	12 hr	12 hr	25–30 hr	8–18 hr
6. Mode of excretion	Renal	Renal	Renal	Renal/hepatic	Renal	Renal
7. Duration of action	6–12 hr	24 hr	≥ 24 hr	24 hr	> 24 hr	> 24 hr
8. Daily dose (mg)	25–150	2.5–40	5–40	10–40	2–8	1.25–10

* $t_{1/2}$ including that of active metabolite

to other inactive products occurs. Efficacy and tolerance of perindopril are similar to other ACE inhibitors.

COVERSYL 2, 4 mg tab.

Fosinopril This ACE inhibitor is unique in being a phosphinate compound that is glucuronide conjugated and eliminated both by liver and kidney. The $t_{1/2}$ is not altered by renal impairment and the dose remains the same. However, like most others, it is a prodrug suitable for once daily administration. First dose hypotension is more likely.

Dose: Initially 10 mg (elderly 5 mg) OD; maximum 40 mg/day.

FOSINACE, FOVAS 10, 20 mg tabs.

Ramipril The distinctive feature of this long-acting ACE inhibitor is its extensive tissue distribution. Greater inhibition of local RAS has been claimed. However, whether this confers any therapeutic advantage is not known. The plasma $t_{1/2}$ of its active metabolite ramiprilat is 8–18 hours, but terminal $t_{1/2}$ is longer due to slow release of tissue bound drug.

CARDACE, RAMIRIL, CORPRIL, R.PRIL 1.25, 2.5, 5 mg caps.

Quinapril A prodrug carboxyl ACE inhibitor that is rapidly and completely converted in the liver to the active form Quinaprilat. Like ramiprilat, it is highly bound to the tissue ACE and exhibits a biphasic plasma $t_{1/2}$ of 2 hours and 24 hours. Elimination occurs in urine and bile in a ratio of 2:1.

Dose: 10–40 mg/day

ACCUPRIL-H: Quinapril 20 mg + hydrochlorothiazide 12.5 mg tab.

Trandolapril It is a carboxyl prodrug that is 40–60% bioavailable in the active form. Absorption is delayed but not decreased by food. The peak effect occurs at 4–6 hours. It is partly metabolized and eliminated both in urine and faeces. The plasma $t_{1/2}$ of active metabolite is biphasic 10–24 hours, suitable for once daily dosing.

Dose: 2–4 mg (max 8 mg) OD; ZETPRIL 1, 2 mg tabs.

Imidapril The oral bioavailability of this long-acting prodrug ACE inhibitor is 40%, which is reduced by taking the drug with meals. The

peak effect occurs at 6–8 hours and plasma $t_{1/2}$ is >24 hours.

Dose: Initially 5 mg OD taken 1 hour before food; usual maintenance dose 10 mg OD.

TANATRIL 5, 10 mg tabs.

Benazepril Another nonsulfhydryl prodrug ACE inhibitor; has a bioavailability of 37% and is excreted by kidney with a $t_{1/2}$ of 10–12 hr.

Dose: 10 mg initially, max 20–40 mg/day;

BENACE 5, 10, 20 mg tab.

USES

1. Hypertension The ACE inhibitors are first line drugs in all grades of hypertension, but the angiotensin receptor blockers (ARBs) have now surpassed them in popularity. About 50% patients of essential hypertension respond to monotherapy with ACE inhibitors and many of the rest to their combination with diuretics or β blockers. The antihypertensive effect of lower doses develops gradually over 2–3 weeks. They offer the following advantages:

- Free of postural hypotension, electrolyte disturbances, feeling of weakness and CNS effects.
- Can be used in asthmatics, diabetics and peripheral vascular disease patients.
- Long-term ACE inhibitor therapy has the potential to reduce incidence of type 2 diabetes in high risk subjects.
- Secondary hyperaldosteronism and K^+ loss due to diuretics is prevented.
- Renal blood flow is well maintained.
- Left ventricular hypertrophy and increased wall-to-lumen ratio of blood vessels that occurs in hypertensive patients is reversed.
- No hyperuricaemia, no deleterious effect on plasma lipid profile.
- No rebound hypertension on withdrawal.
- Minimum worsening of quality of life parameters like general wellbeing, work performance, sleep, sexual performance, etc.

Large multicentric trials have confirmed that ACE inhibitors reduce cardiovascular morbidity and increase life expectancy of hypertensive

patients. It appears that by their specific effect on myocardial and vascular cell growth/remodeling, they have greater protective potential than other classes of antihypertensive drugs.

ACE inhibitors are effective and first choice drugs in renovascular and resistant hypertension. They are particularly suitable for diabetic hypertensives in whom they reduce cardiovascular complications more than other antihypertensive drugs, probably by improving endothelial function.

2. CHF ACE inhibitors cause both arteriolar and venodilatation in CHF patients; reduce afterload as well as preload on heart and improve all haemodynamic parameters. Though they have no direct action on myocardium, stroke volume and cardiac output are increased, while heart rate is reduced. Diuresis occurs initially and the accumulated salt and water are lost due to improved renal perfusion and abolition of mineralocorticoid mediated Na^+ retention. Cardiac work as measured by heart rate $\times$ pressure product is reduced; thereby, exercise capacity of CHF patients is enhanced. Beneficial effects are well sustained with chronic therapy and the NYHA functional class of most patients is improved.

Robust multicentric trials have shown that ACE inhibitors retard the progression of left ventricular systolic dysfunction and prolong survival of CHF patients of all grades (I to IV). Mortality is reduced by $\sim 20\%$ in symptomatic CHF patients. Unless contraindicated, ACE inhibitors are now advocated by several professional bodies, including American Heart Association and American College of Cardiology, as first line drugs in all patients with symptomatic as well as asymptomatic left ventricular inadequacy because even in asymptomatic cases, they prevent progression to overt heart failure. A diuretic, β blocker with or without digitalis may be added according to need. ACE inhibitors reduce episodes of decompensation, myocardial infarction and sudden death. In addition to improved haemodynamics, long-term benefits of ACE inhibitors accrue from

withdrawal of Ang II mediated ventricular hypertrophy, remodeling, accelerated myocyte apoptosis and fibrosis. Indirect benefits occur due to reduction in sympathetic activation and aldosterone levels.

The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial on 3164 heart failure patients (NYHA class II to IV) has shown that high dose lisinopril (32.5–35 mg/day) given for 39–58 months was more effective in reducing all cause mortality, hospitalization for heart failure and risk of MI than lower dose (2.5–5 mg/day). To afford maximum protection against progression of heart failure, the dose of ACE inhibitors needs to be titrated to nearly the upper limit of recommended dose range, as shown in other mega trials like GISSI-3, SOLVD, AIRE, etc. as well. ACE inhibitors are effective in reducing development of ventricular dysfunction, heart failure and related mortality in post-MI patients also (SAVE, TRACE, AIRE trials).

3. Myocardial infarction (MI) Several mega-trials have established that oral ACE inhibitors administered while MI is evolving (within 24 hr of an attack) and continued for 6 weeks reduce early as well as long-term mortality, irrespective of presence or absence of systolic dysfunction, provided hypotension is avoided. In high risk patients and those with latent or overt ventricular dysfunction (CHF) extension of therapy continues to afford survival benefit over years. In unstable angina/non-ST segment elevation MI (NSTEMI), long-term ACE inhibitor therapy reduces recurrent MI and need for coronary angioplasty (SAVE and SOLVD trials), though no benefit was apparent in the short-term (ISIS-4 study). Current evidence shows that if there are no contraindications, all MI patients stand to gain from ACE inhibitor therapy, though magnitude of benefit is greatest in those having associated hypertension and/or diabetes.

4. Prophylaxis in high cardiovascular risk subjects The results of Heart Outcomes Prevention Evaluation (HOPE) study in 9297 post-MI and other high risk subjects, but having no left ventricular dysfunction or heart failure have shown that ramipril reduced cardiac death and MI or stroke by 22% over a period of 4.5 years. Risk of developing heart failure or diabetes was also reduced. These results were

confirmed by the EUROPA trial and appear to hold true even for patients who have undergone coronary revascularization (APRES trial). Thus, ACE inhibitors are protective in high cardiovascular risk subjects even when there is no associated hypertension or left ventricular dysfunction. Protective effect is exerted both on myocardium as well as vasculature; may involve improved endothelial function, and is independent of hypotensive action.

5. Diabetic nephropathy Prolonged ACE inhibitor therapy has been found to prevent or delay end-stage renal disease in type I as well as type II diabetics. Albuminuria (an index of glomerulopathy) remains stable in those treated with ACE inhibitor, but aggravates in untreated diabetics. Treated patients have higher creatinine clearance, require less dialysis and have longer life expectancy. Benefits appear to be due to haemodynamic (systemic and intrarenal) as well as abnormal mesangial cell growth attenuating effects of ACE inhibitors. They reduce intraglomerular pressure and hyperfiltration. ACE inhibitors arrest/partly reverse any degree of albuminuria, but benefits in type 2 diabetics are rather limited once macroalbuminuria has set in. The RAS seems to accentuate micro- and macrovascular complications in diabetics, and ACE inhibitors have specific organ protective effect by attenuating the same. All patients with diabetic nephropathy, whether hypertensive or normotensive, deserve ACE inhibitor therapy. Deterioration of retinopathy in diabetics also appears to be retarded by ACE inhibitors.

Nondiabetic nephropathy There is evidence now that chronic renal failure due to nondiabetic causes may also be improved by ACE inhibitors. These drugs reduce proteinuria by decreasing the pressure gradient across glomerular capillaries as well as by altering membrane permeability. This retards disease progression. Among hypertensive nephropathy patients the incidence of doubling of serum creatinine or end stage renal failure is significantly lower in those treated with ACE inhibitors than those treated with other antihypertensive drugs.

6. Scleroderma crisis The marked rise in BP and deterioration of renal function in scleroderma crisis is mediated by Ang II. ACE inhibitors produce dramatic improvement and are life saving in this condition.

Captopril test This test has been devised to obviate the need for renal angiography for diagnosis of renovascular hypertension. The basis of the test is—acute blockade of Ang II formation by captopril results in a reactive increase in PRA which is much higher in renovascular compared to essential hypertension. However, this test is only of adjunctive value.

ANGIOTENSIN ANTAGONISTS (Angiotensin receptor blockers or ARBs)

Over the past 25 years, several nonpeptide orally active AT_1 receptor blockers (ARBs) have been developed as alternatives to ACE inhibitors. These include *losartan*, *candesartan*, *valsartan*, *telmisartan*, *olmesartan* and *irbesartan*. Selective antagonists of AT_2 receptors as well as combined $AT_1 + AT_2$ antagonists have also been produced, but are not used clinically.

Losartan It is a competitive antagonist and inverse agonist, 10,000 times more selective for AT_1 than for AT_2 receptor; does not block any other receptor or ion channel, except thromboxane A_2 receptor (has some platelet antiaggregatory property). All overt actions of Ang II, viz. vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and ADR from adrenals, renal actions promoting salt and water reabsorption, central actions like thirst, vasopressin release and growth-promoting actions on heart and blood vessels are blocked. No inhibition of ACE has been noted.

Pharmacologically, ARBs differ from ACE inhibitors in the following ways:

- They do not interfere with degradation of bradykinin and other ACE substrates: no rise in level or potentiation of bradykinin, substance P occurs. Consequently, ACE inhibitor related cough is rare.
- They result in more complete inhibition of AT_1 receptor activation, because responses to Ang II generated *via* alternative pathways

and consequent AT_1 receptor activation (which remain intact with ACE inhibitors) are also blocked.

- They result in indirect AT_2 receptor activation. Due to blockade of AT_1 receptor mediated feedback inhibition—more Ang II is produced which acts on AT_2 receptors that remain unblocked.
- ARBs cause little increase in the level of Ang (1-7) which is raised by ACE inhibitors, since Ang (1-7) is also partly degraded by ACE.

The impact of these differences on clinical efficacy and therapeutic value of the two classes of RAS inhibitors is not known.

Losartan causes fall in BP in hypertensive patients which lasts for 24 hours, while HR remains unchanged and cardiovascular reflexes are not interfered. No significant effect on plasma lipid profile, carbohydrate tolerance or insulin sensitivity has been noted. A mild probenecid-like uricosuric action is produced.

Pharmacokinetics Oral absorption of losartan is not affected by food, but bioavailability is only 33% due to first pass metabolism. It is partially carboxylated in liver to an active metabolite (E3174) which is a 10–30 times more potent noncompetitive AT_1 receptor antagonist. After oral ingestion peak plasma levels are attained at 1 hr for losartan and at 3–4 hours for E3174. Both compounds are 98% plasma protein bound, do not enter brain and are excreted by the kidney. The plasma $t_{1/2}$ of losartan is 2 hr, but that of E3174 is 6–9 hr. No dose adjustment is required in renal insufficiency, but dose should be reduced in presence of hepatic dysfunction.

Adverse effects Losartan is well tolerated; has side effect profile similar to placebo. Like ACE inhibitors it can cause hypotension and hyperkalemia, but first dose hypotension is uncommon. Though, a few reports of dry cough have appeared, losartan is considered to be free of cough and dysgeusia inducing potential. Patients with a history of ACE inhibitor related cough have taken losartan without recurrence. Angioedema is reported in fewer

cases. Headache, dizziness, weakness and upper g.i. side effects are mild and occasional. However, losartan has fetopathic potential like ACE inhibitors; it should not be administered during pregnancy.

Dose: 50 mg OD, rarely BD; in liver disease or volume depleted patients 25 mg OD; addition of hydrochlorothiazide 12.5–25 mg enhances its effectiveness.

LOSACAR, LOSAR, TOZAAR, ALSARTAN 25, 50 mg tabs.

Candesartan It has the highest affinity for the AT_1 receptor and produces largely unsurmountable antagonism, probably due to slow dissociation from the receptors or receptor desensitization. Elimination occurs by both hepatic metabolism and renal excretion with a $t_{1/2}$ of 8–12 hours: action lasts 24 hours.

Dose: 8 mg OD (max 8 mg BD), liver/kidney impairment 4 mg OD.

CANDESAR 4, 8, 10 mg tab., CANDILONG, CANDES-TAN 4, 8 mg tabs.

Irbesartan The oral bioavailability of this ARB is relatively high. It is partly metabolized and excreted mainly in bile. The $t_{1/2}$ is ~12 hours.

Dose: 150–300 mg OD.

IROVEL, IRBEST 150, 300 mg tabs.

Valsartan The AT_1 receptor affinity of valsartan is similar to that of losartan. Its oral bioavailability averages 23% and food interferes with its absorption. Elimination occurs mainly by the liver in unchanged form with a $t_{1/2}$ of 6–9 hours; action lasts 24 hours.

Dose: 80–160 mg OD 1 hour before meal (initial dose in liver disease 40 mg).

DIOVAN, STARVAL, VALZAAR 40, 80, 160 mg tabs.

Olmesartan Another potent ARB with high affinity for AT_1 receptor. It is available as an ester prodrug which is completely hydrolysed during absorption from the gut. It is eliminated in urine as well as in bile with a $t_{1/2}$ of ~12 hours. No dose adjustment is needed in liver or kidney disease, unless it is severe. Abdominal pain and sprue-like symptoms have been reported in few recipients.

Dose: 20–40 mg OD; **OLMAT, OLSAR 20, 40 mg tabs.**

Telmisartan The AT_1 receptor blocking action of telmisartan is similar to losartan, but it does not produce any active metabolite. After an oral dose, peak action occurs in 3 hours and

action lasts > 24 hours. It is largely excreted unchanged in bile; dose reduction is needed in liver disease.

Dose: 20–80 mg OD.

TELMA, TELSAR, TELVAS 20, 40, 80 mg tabs.

Eprosartan It is a newer AT₁ receptor antagonist which is believed to lower BP by blocking vasoconstrictor AT₁ receptors as well as by reducing NA release. Though, blockade of prejunctional AT₁ receptors on sympathetic neurones and resultant decrease in sympathetic outflow is a class effect of ARBs, this action is claimed to be more prominent in eprosartan, so as to be clinically meaningful. Oral bioavailability of eprosartan is low (~13%) and it is mainly excreted unchanged in faeces. Renal excretion is about 10% and the terminal elimination t_{1/2} is 20 hours.

Dose: 600 mg OD (range 400–800 mg OD).

TEVETEN, EPROZAR 600 mg tab.

Uses of ARBs

The ARBs have the same overall range of clinical utility as ACE inhibitors, but the suitability and efficacy of one over the other is not clearly defined; may depend on the condition being treated and/or specific features of the patient.

Hypertension Losartan and other ARBs are now first line drugs, comparable in efficacy and desirable features to ACE inhibitors, with the advantage of not inducing cough and a lower incidence of angioedema, rashes and dysgeusia. As such, they are more commonly prescribed now than ACE inhibitors, though superiority of one over the other is not established. Like ACE inhibitors, the maximum antihypertensive effect is reached in 2–4 weeks and ventricular/vascular hypertrophy/remodeling is arrested/reversed similarly. No additional benefit has been obtained by combining an ACE inhibitor with an ARB in the treatment of hypertension.

The Losartan intervention for endpoint reduction in hypertension (LIFE, 2002) study has found losartan to be more effective than β -blockers in reducing stroke among > 9000 hypertensive patients with left ventricular hypertrophy, and is approved for stroke prevention. In cirrhotics, losartan has been found to control portal hypertension.

CHF The ARBs afford clear-cut symptomatic relief as well as survival benefit in CHF. However, their relative value compared to ACE inhibitors, especially in long-term morbidity and mortality reduction, is still uncertain.

A number of large randomized endpoint trials like Evaluation of losartan in the elderly (ELITE, 1997), ELITE-II (2000), OPTIMAAL (2002), Valsartan in acute MI (VALIANT, 2003) have produced inconsistent results. This may be due to within group differences among specific ARBs. Valsartan and candesartan have produced superior benefits than losartan and irbesartan. Thus, for CHF, it may be prudent to use ACE inhibitors as the first choice drugs and to reserve specific ARBs for those who fail to respond well or who develop cough/angioedema/other intolerance to ACE inhibitors.

Myocardial infarction The evidence so far indicates that utility of ARBs in MI, including long-term survival, is comparable to ACE inhibitors. However, the latter are generally used first, since there is greater experience with them.

Diabetic nephropathy Several studies have confirmed that ARBs are renoprotective in type 2 diabetes mellitus, independent of BP lowering. The magnitude of benefit is comparable to ACE inhibitors, but because of better tolerability profile, many consider ARBs to be the first choice now.

Combination of ACE inhibitors with ARBs There are theoretical reasons to combine an ACE inhibitor with an ARB to obtain more complete suppression of RAS and achieve added cardioprotection in CHF or renoprotection in diabetic nephropathy. These are:

- Ang II is generated in several tissues (especially heart and kidney) by non-ACE mechanisms, whose effect can be blocked by ARBs.
- ACE inhibitors produce bradykinin and Ang (1-7) related vasodilatation and other effects that are not produced by ARBs.
- ARBs cause compensatory increase in Ang II production that can be checked by ACE inhibitors.

Additional haemodynamic and symptomatic improvement over short-term has been obtained in CHF with addition of an ARB to existing ACE inhibitor therapy. However, risk of hyperkalemia, hypotension and renal impairment is also increased. Several large randomized trials

including Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD, 1999), Valsartan heart failure trial (VAL-He FT, 2001), CHARM-additive trial (2003), VALIANT (2003) trial, Ongoing Telmisartan alone and in combination with ramipril global endpoint trial (ON TARGET, 2008) of combinations of ARBs and ACE inhibitors *vs* their monotherapy in affording mortality and other endpoint benefits in CHF have yielded discordant results. Thus, it is not certain that long-term use of ARB + ACE inhibitor combination is uniformly beneficial. However, selected cases, not optimally benefited by monotherapy, may be offered combined therapy, especially by including candesartan or valsartan as the ARB.

In non-diabetic renal disease, the Combination treatment of ARB and ACE inhibitor randomized trial (COOPERATE, 2003) has concluded that ARB + ACE inhibitor combination therapy retards progression of non-diabetic renal disease to a greater extent compared with their monotherapy.

DIRECT RENIN INHIBITOR

Aliskiren

Direct renin inhibitors (DRIs) are the latest class of RAS inhibitory drugs, of which only one member *Aliskiren* has become available for the treatment of cardiovascular and renal diseases in which ACE inhibitors and ARBs are currently used. Aliskiren is a nonpeptide which binds selectively to the catalytic site of renin and competitively blocks the access of angiotensinogen to this site. As a result Ang I is not produced and the effector chain of RAS is interrupted. While the concentration of renin in plasma is increased by feed back, the plasma renin activity (PRA) is decreased. Ang I and Ang II levels fall in a dose-dependent manner.

Aliskiren causes dose related fall in BP which is more marked in the Na⁺ depleted subjects with high basal PRA. Similar to ACE inhibitors, plasma aldosterone levels are

lowered accompanied by mild natriuresis and a tendency to K⁺ retention. The antihypertensive efficacy of aliskiren is nearly equivalent to that of ACE inhibitors or ARBs. Combination of these drugs with aliskiren produces greater fall in BP, at least in the short term. This is due to blockade of rise in PRA caused by ACE inhibitors/ARBs. The pattern of haemodynamic effect of aliskiren resembles ACE inhibitors; postural hypotension is not a problem.

Trials so far have shown that aliskiren reduces hypertensive left ventricular hypertrophy and benefits CHF patients, but its value compared to ACE inhibitors/ARBs as monotherapy and as additional drug remains to be established on the basis of outcome data. Aliskiren reduces albuminuria and has renoprotective effect in hypertension and diabetes mellitus.

At present, aliskiren is recommended as an alternative antihypertensive drug (for those who do not respond or do not tolerate 1st line drugs) and in combination with ACE inhibitor/ARB to achieve more complete RAS blockade and greater BP lowering/cardioprotection. However, addition of aliskiren to ACE inhibitor/ARB in type 2 diabetics has not produced any beneficial effect; may even worsen outcome and is not advised.

Pharmacokinetics Aliskiren is administered orally, but bioavailability is very low due to active extrusion of the absorbed drug by P-glycoprotein. The drug is mainly eliminated in faeces; small amount in urine. The plasma $t_{1/2}$ is > 24 hours, and its BP lowering effect persists for days after regular intake.

Adverse effects Aliskiren produces few and mild side effects—mainly dyspepsia, abdominal pain, loose motions, headache and dizziness. Acute hypotension, hyperkalemia, cough, angioedema and rashes are less frequent than with ACE inhibitors. Aliskiren is contraindicated during pregnancy.

Dose: 150–300 mg OD; **RASILEZ 150 mg tab;**
RASILEZ-HC: along with hydrochlorothiazide.

PROBLEM DIRECTED STUDY

36.1 A 65-year-male was diagnosed to be suffering from congestive heart failure (CHF). He had pitting edema of feet, dyspnoea and cough on mild exertion, fatigue, engorged neck veins, soft enlargement of liver, pulmonary congestion and mild cardiac dilatation. The pulse was 100/min, respiration 20/min and BP 130/86 mm of Hg. He was prescribed—
Tab furosemide 40 mg once daily in the morning.

Tab captopril 25 mg twice daily, morning and evening.

After 2 hours of taking the medicines, he started passing increased quantity of urine and in the next few hours he gradually started feeling weakness, nausea, sweating and fainted while walking to the toilet. The pulse was recorded as 110/min and BP 80/40 mm Hg.

(a) What could be the cause of sudden onset symptoms and the marked fall in BP?

(b) Is the choice of drugs incorrect?

(c) How could such adverse event be prevented?

(d) What immediate management is required?

(see Appendix-1 for solution)