END ORGAN PROTECTION

Mangesh Tiwaskar, Mumbai

INTRODUCTION
Blood pressure and body fluid volume are mostly regulated by the renin-angiotensin system (RAS). It is evident that overactive RAS play a central role in the development of hypertension (HTN) and end organ damage (EOD) associated with HTN. It also plays a key role in a number of pathophysiological mechanisms leading to major cardiovascular (CV) events, such as myocardial infarction (MI), stroke, congestive heart failure (CHF) and end-stage renal disease (ESRD).1 The RAS blockers, both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), may provide the benefit beyond blood pressure (BP) reduction. Existing evidence indicates a therapeutic advantage to antagonizing the effects of angiotensin II (AT-II) on CV tissues.2 The pharmacological antagonism of angiotensin I (AT-I)-mediated effects of AT-II represents an ideal therapeutic target to interfere with the activity of RAS and its pathological consequences, and thus for an effective management of CV and renal diseases, especially in HTN and diabetes mellitus (DM).1

This chapter describes the end organ damage, its prevalence and causes, protection in HTN with an overview of agents acting on the RAS with emphasis on direct renin inhibitor (DRI) aliskiren.

HYPERTENSION, END ORGAN DAMAGE AND ITS PREVALENCE
Hypertension, a major public health concern, affecting 20–25% of the adult population in Western countries.1 It is the major risk factor for diseases involving CV and renal system.10 The World Health Organization (WHO) has estimated that high BP causes 1 in every 8 deaths, making HTN the third leading killer in the world. Globally, there are 1 billion hypertensives and 4 million people die annually as a direct result of HTN.1 The number of adult hypertensive patients are predicted to increase from 972 million in year 2000 to 1.56 billion in year 2025.10 With increase in modified lifestyle (such as smoking, high fat diet, stress and physical inactivity), the prevalence of HTN has become more prominent.

In India, number of hypertensives are expected to go up from 118.2 million in 2000 to 213.5 million in 2025.10 Resulting in its growing impact on CV risk factors and clinical conditions, like obesity, metabolic syndrome, DM and dyslipidemia.1 The WHO Report of year 2002 states that, by 2020 CV diseases (CVDs) will be major cause of death and disability in India. In year 1990, CVDs were cause of 2.3 million deaths in India and this figure is projected to almost double by the year 2020.10 Out of these 2.3 millions deaths, 57% of all stroke deaths and 24% of all coronary heart disease deaths were directly attributed to HTN.10

Various studies have shown a significant and continuous relationship between high BP levels and increased risk of CV mortality, MI, stroke and vascular disease.1 Elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP) are associated with number of risks including the mortality risk, which is doubled for every 20/10 mmHg increase in SBP/DBP level from the level of 115/75 mmHg.10

There is strong evidence that patients with EOD associated with HTN have a higher morbidity and mortality, which can be reduced by accurate evaluation and management of HTN.12 The recent
emerging trend in the treatment of HTN is not only based on
the pragmatic need to lower BP levels, but also on lowering
the CV risk profile, which is largely linked to the presence of
EOD. Renal organ damage currently represents an important
marker of disease progression and is predictive of future CV
events. The recent European guidelines for HTN management emphasize
the need to carefully search for the presence of organ damage in
each individual hypertensive patient, as they recognize the need
for a strict BP control in patients presenting with EOD or DM.1

IDENTIFICATION AND ASSESSMENT OF END OR-
GAN DAMAGE

The term ‘end organ damage’ or ‘target organ damage’
usually refers to damage occurring in various major organs
fed by the circulatory system (heart, kidneys, brain, eyes)
which can sustain damage due to various medical conditions.3
Alternatively, the term may apply to an organ in the body that is
damaged by a disease. In most cases, the end organ is damaged
by a condition that originated in another organ or system.3

The presence of EOD makes a dramatic difference to
clinical outcome in HTN.4 The vascular damage is mainly
by the increased pressure on the arterial walls.3 The “end
organ” effects of HTN are particularly evident in the heart,
brain, kidney, peripheral arteries, and eye.4 In patients with
chronic uncontrolled HTN, fundus examination may reveal
retinopathy of various grades which can be; in fact; the earliest
sign of the EOD.5 In fact, hypertensive patients with evidence
of EOD are more likely to exhibit a greater pro-thrombotic or
hyper-coagulable state, are well recognized to be at high risk
of CV and cerebrovascular events, and they should be targeted
for aggressive blood pressure and risk factor management.5

Disorders associated with HTN can also be related to a
prothrombotic state and these conditions could also be
regarded as EOD. Hypertension is a common cause of atrial
fibrillation (also associated with abnormalities of hemostasis
and endothelial dysfunction), heart failure (HF), and left
ventricular dysfunction. Factors determining hypertensive end organ damage

1. Blood pressure: EOD could be produced by instability
of BP. It is well known that uncontrolled HTN, especially
Systolic HTN, induces organ damage much rapidly.6

2. Blood Pressure Variability (BPV) and Mean Arterial
Pressure (MAP): One study conducted by Parati et al (in
1987) have found that patients in whom the BPV and
MAP was lower had a lower prevalence and severity of
organ damage than those with higher BPV &/or MAP.6

3. Arterial baro-reflex dysfunction: It has been well rec-
ognized that baro-reflex sensitivity (BRS) is impaired in
hypertensives. BRS is was one of the independent vari-
ables related to end organ damage score, and predicted
the end organ damage in hypertension.6

4. Hemostatic factors, such as plasma fibrinogen, fibrin D-
dimer, and prothrombin fragment 1+2: These hemostat-
ic factors are reported to be significantly related to the
presence and severity of EOD by means of Endothelial
dysfunction. Studies have shown that these hemostatic
factors are an independent predictor of coronary events in
hypertensive patients.7

Assessment of End organ damage

Cardiomegaly, coronary artery disease (CAD), Dysrythmias, retinopathy, detailed renal assessment can help
in detecting the EOD early and planning the preventive
strategies. Cardiomegaly can be evaluated by chest X-ray,
electrocardiogram, echocardiography, stress test etc. Renal
abnormalities can be detected by doing the complete Renal
profile investigation including detailed urine, hematological
& radiological investigations especially analyzing e-GFR,
Creatinine Clearance, Spot urine creatinine: albumin ratio etc.
African American patients with poorly controlled HTN are at
a higher risk than Caucasians for most EOD and particularly
renal damage. The strokes are usually hemorrhagic or
thrombo-embolic (Macro-vascular or micro-vascular). The
patient’s should be evaluated for the neurological damage.
Multiple micro-vascular strokes can lead to dementia. Recent
studies have also suggested the ARBs may offer an additional
protective effect against strokes above and beyond control
of BP.5

RENIN ANGIOTENSIN SYSTEM AND ITS INHIBI-
TION

The RAS is important modulators of CV systems and is
involved in maintaining vascular integrity, controlling BP, and
DM. As such, this system has been investigated as a basis for
the development of treatments for stroke, MI, HF, and renal
dysfunction. The RAS pathway is common to many tissues;
the most notable occurrence of this pathway is in the kidney. A
typical RAS pathway is depicted in Figure 1 having following
pathophysiological actions:

- The RAS pathway is a cascade beginning with the pro-
duction of angiotensinogen in the liver.
- Sympathetic stimulation of β1-adrenoceptors, renal ar-
tery hypotension, and decreased sodium in the distal tu-
bules stimulate the release of renin by the kidney. Renin
hydrolyzes angiotensinogen to yield the relatively inac-
tive precursor AT-I.
- AT- I is cleaved by ACE to yield active peptide AT- II
- AT- II then acts on AT-I receptors, a 7-domain, G pro-
tein-coupled, transmembrane receptors, to stimulate
systemic vasoconstriction and expression of plasmino-
gen activator inhibitor (PAI) triggering increase in BP.
The RAS also acts on the CNS to increase water intake by stimulating thirst, as well as conserving blood volume, by reducing urinary loss through the secretion of vasopressin from the posterior pituitary gland. This excessive activity of the renin system is associated with HTN and EOD, mediated largely through the actions of AT- II on the angiotensin AT1 receptor. Besides causing vasoconstriction and fluid retention, AT- II and aldosterone also exert other harmful effects on the CV system, including endothelial dysfunction, sympathetic over-activation, collagen formation, myocardial fibrosis, vascular smooth muscle cells (VSMC) proliferation, and decreased nitric oxide (NO) production. Although activation neuro-hormonal pathways is vital for survival in scenario of hemodynamic instability, but in future these mechanisms could be counterproductive and harmful and could lead to a progressive decline in cardiac function.9

Inhibition of the RAS

The RAS may be blocked by drugs at various points and is important target site for 5 distinctive classes of hypertensive drugs; beta blockers, renin inhibitors, ACE inhibitors (ACEIs), ARBs and aldosterone inhibitors. These drugs inhibit renin secretion, the enzymatic action of renin, the conversion of AT- I to AT- II or the effect of aldosterone, respectively and have proven to be highly successful treatments for HTN and related CV diseases.9

Beta blockers inhibit renin secretion from the juxtaglomerular cells.10 The ACEIs block the formation of AT- II & they also cause a respective increase in the concentrations of AT- I that can subsequently be converted to AT- II by other pathways, such as the chymase system. The non-ACE pathways of AT-II generation such as chymase and dipeptidases, present in end organs including heart, kidney and blood vessels get activated under conditions of ACE inhibition, hindering the effectiveness of ACEIs.10 These inhibitors are not specific for RAS, but can prevent ACE induced inactivation of bradykinin and substance P that are known to be responsible for ACEI related side effects such as cough and angioedema. The ARBs inhibit RAS by specifically blocking the AT-1 receptors.9, 10 Leaving the other types of AT receptors such as AT2R and AT4R, unopposed to possible stimulation by AT- II, this

---

**Fig. 1 : Renin-angiotensin system (RAS) cascade and the 3 available approaches to its Pharmacologic inhibition (Source: Rao MS. J Assoc Physician India 2010;58:102-108)**

- Conversely AT- II binding to AT-II receptors may cause vasodilatation and apoptosis.

- AT- II acts on the adrenal cortex to stimulate aldosterone production, which in turn stimulates sodium resorption from the distal tubules leading to increased fluid volume and BP.

AT-II may also be involved in causation of the EOD. Two subtypes of AT- II receptors have been identified: AT1 and AT2. The AT1 mediates all of the known actions of AT- II on BP control. The AT1 receptor modulates cardiac contractility and glomerular filtration, and increases renal tubular sodium reabsorption, and cardiac and vascular hypertrophy. Less information is available regarding the function of the AT2 receptor. Evidence suggests that the AT2 receptor inhibits cell proliferation and reverses AT1-induced hypertrophy. Indeed, these receptors are thought to exert opposing effects.8 AT1 receptors are primarily expressed in kidney in glomerular mesangial cells, proximal tubular epithelial cells and the inner stripe of the outer medulla, the type 1 Renal medullary interstitial cells.1 The predominant vasoconstrictive action of AT- II on the efferent glomerular arteriola is a key factor in the filtration process and in the regulation of protein loss. The importance of AT- II underlies in the physiological regulation of glomerular filtration, renal cortical and medullary microcirculation, fluid and electrolyte balance, and in promoting renal cell proliferation and extracellular matrix synthesis in progressive renal disease.1 In addition, the distribution of AT1 receptors in the adrenal gland located in the zona glomerulosa cells of the cortex and chromaffin cells of the medulla is consistent with the AT- II-mediated biosynthesis and release of aldosterone and catecholamines from the adrenal glands. The activity of the RAS may be inappropriate for the pathological conditions (i.e. HTN, DM, CHF, renal disease, and the cardio-renal syndrome) and AT- II exerts a number of effects that frequently become deleterious for the renal function, leading to progressive proteinuria and decline of glomerular filtration rate (GFR).1
stimulation of AT2R can produce harmful agents like oxygen free radicals, pro-inflammatory cytokines and pro-fibrotic mediators and may promote left ventricular hypertrophy. Besides this, partial suppression of RAS by both ACEIs and ARBs can lead to substantial compensatory raise in the circulating active renin and AT- II, eventually leading to limit their therapeutic potential. Because of elevated plasma renin activity (PRA), this increase in AT- II levels is associated with CV events, EOD, and a higher incidence of MI in hypertensive patients.

Angiotensin II AT1 receptor antagonists (AT1RA) inhibit the RAS at the receptor level by specifically blocking the AT1 receptor subtype. These drugs induce a dose-dependent blockade of AT- II effects, resulting in reduced BP, proteinuria, and glomerular sclerosis. It is postulated that AT1RA may provide end-organ protection by blocking AT- II effects through the AT1 receptor, yet leaving the AT2 receptor unopposed. Consequently, these agents may reduce the morbidity and mortality that result from MI and other conditions resulting from structural alterations in the heart, kidney, and vasculature.

Inhibition of PRA and the blocked of RAAS cascade at its primary steps, has long been proposed as the optimal means of RAAS Inhibition. Renin inhibitor provides more effective means of RAAS Inhibition.

**RECOMMENDED TARGETS FOR BLOOD PRESSURE**

Numerous epidemiologic studies confirmed the need to control BP to reduce the risk of CV, cerebrovascular and renal diseases. The international guidelines for controlling BP are generally consistent. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended a blood pressure target of < 140/90 mmHg for individuals with uncomplicated hypertension (i.e., no EOD or clinical CVD). Reflecting higher risk, the targets are lower for those with diabetes (< 130/85 mmHg) and for patients with renal insufficiency and proteinuria greater than 1 g/24 hour (125/75 mmHg). As in the JNC 7 guidelines, the BP goal for hypertensive patients with no other CVD risk factors is < 140/90 mmHg in the American Heart Association (AHA) and the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) recommendations. Also, in common with the JNC 7 guidelines, the BP targets are lower in patients with additional risk factors for CVD.

**END ORGAN PROTECTION – WHAT IS IT?**

The definition of end organ protection (EOP) varies substantially among clinical trials. Studies involving EOP are mainly focused on: CV risk reduction measures, prevention of progression of kidney disease and reduction in the incidence of stroke. Besides the BP reduction, the decrease in BPV and the restoration of BRS may importantly contribute to this EOP. Despite the lack of evidence based on prospective clinical trials, there is consistent evidence from post hoc analyses of many large studies that indicates that regression of LVH, albuminuria, and control of DM, may be associated with fewer CV end points. It should be noted that the reduction of BP consistently remains the most important measure of better EOP.

There is a continuous debate regarding the optimal therapeutic choice of drugs to control BP and reduce CV events. Successful antihypertensive regimens incorporating a RAS blocker, such as an ACEI or ARB, provide more TOD reduction benefit, as compared with regimens that do not incorporate a RAS blocker.

**Non-pharmacologic interventions**

Primary prevention of HTN is the most cost-effective approach to containing the emerging HTN epidemic and in turn offering the EOP. Though non-pharmacologic interventions (e.g. body weight reduction, exercise, salt restriction, and alcohol intake reduction, stress management, limit alcohol consumption) yield heterogeneous results, but they might not always give clinically significant reductions. The details of the Non pharmacological strategies for management of HTN are beyond the scope of this chapter.

**Pharmacologic Treatment Options**

Alongside lifestyle interventions, antihypertensive drug is generally required to achieve BP goals. Despite awareness of the consequences of uncontrolled HTN and the impressive body of evidence that BP control significantly reduces the risk of CV, cerebrovascular, and renal events; the management of HTN remains suboptimal. This under treatment is apparent world over including India.

An agent that provides effective and sustained control of BP must be the central part of any therapeutic approach.

 Interruption of the RAS pathway, either by preventing the formation of AT- II (i.e. ACEIs) or by blocking its actions at the level of the peptide receptor [i.e. AT1RAs], has proved to be highly successful in the treatment and management of HTN in a significant hypertensive population. However, there can be differences in efficacy of antihypertensive drug, in same or different class. The differences within a class may reflect important attributes such as half-life, with a longer half-life providing a longer duration of antihypertensive effect. Therefore, it is important to consider each agent individually, to compare the BP-lowering effects of different agents at effective therapeutic doses, and to distinguish between studies that have done so and those that have not.

In patients with BP >15/10 mmHg above goal, utilizing
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Tested drugs</th>
<th>Baseline BP (mmHg) (mean±SD)</th>
<th>Clinical setting</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRMA-244 (2001)</td>
<td>Irbesartan 150 mg (n=195)</td>
<td>153 ± 14/90 ± 9</td>
<td>Hypertension, diabetes mellitus, renal damage</td>
<td>Time to onset of diabetic nephropathy</td>
</tr>
<tr>
<td></td>
<td>Irbesartan 300 mg (n=194)</td>
<td>153 ± 14/91 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (n=201)</td>
<td>153 ± 15/90 ± 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REANAAL44 (2001)</td>
<td>Losartan 100 mg (n=751)</td>
<td>152 ± 19/92 ± 10</td>
<td>Diabetes, renal damage</td>
<td>Doubling baseline serum creatinine, development of ESRD, death</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=762)</td>
<td>153 ± 20/82 ± 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDNT-Plc45 (2001)</td>
<td>Irbesartan 300 mg (n=579)</td>
<td>160 ± 20/87 ± 11</td>
<td>Hypertension, diabetes, renal damage</td>
<td>Doubling baseline serum creatinine, development of ESRD, death</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=569)</td>
<td>158 ± 20/87 ± 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROADMAP48 (2011)</td>
<td>Olmesartan medoxomil (n=2232)</td>
<td>137 ± 16/81 ± 10</td>
<td>Diabetes</td>
<td>Development of MAU</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=2215)</td>
<td>136 ± 15/60 ± 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MARVAL43 (2002)</td>
<td>Valsartan 80 mg (n=169)</td>
<td>147.3 ± 17.8/85.4 ± 8.8</td>
<td>Hypertension, diabetes, renal damage</td>
<td>Percentage change in UAER</td>
</tr>
<tr>
<td></td>
<td>Amlodipine 5 mg (n=163)</td>
<td>148.3 ± 17.6/85.7 ± 9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDNT-CCB44 (2001)</td>
<td>Irbesartan 300 mg (n=579)</td>
<td>160 ± 20/87 ± 11</td>
<td>Hypertension, diabetes, renal damage</td>
<td>Doubling baseline serum creatinine, development of ESRD, death</td>
</tr>
<tr>
<td></td>
<td>Amlodipine 10 mg (n=567)</td>
<td>159 ± 19/87 ± 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE49 (2004)</td>
<td>Losartan 100 mg (n=4126)</td>
<td>174.2/97.8</td>
<td>Hypertension and ECG-detected LV hypertrophy</td>
<td>Percentage change in UAER</td>
</tr>
<tr>
<td></td>
<td>Atenolol 100 mg (n=4080)</td>
<td>174.4/97.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DROP40 (2006)</td>
<td>Valsartan 160 mg (n=130)</td>
<td>150.2 ± 14.8/88.1 ± 8.4</td>
<td>Hypertension, diabetes, renal damage</td>
<td>Percentage change in UACR</td>
</tr>
<tr>
<td></td>
<td>Valsartan 320 mg (n=130)</td>
<td>150.3 ± 13.4/87.7 ± 8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valsartan 640 mg (n=131)</td>
<td>150.3 ± 12.9/87.8 ± 9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HARBI4 (2007)</td>
<td>Candesartan 12 mg (n=55)</td>
<td>157.5 ± 19.2/89.4 ± 10.9</td>
<td>Hypertension</td>
<td>Percentage change in UPE</td>
</tr>
<tr>
<td></td>
<td>Valsartan 160 mg (n=55)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INNOVATION52 (2007)</td>
<td>Placebo (n=174)</td>
<td>NA</td>
<td>Diabetes, renal damage</td>
<td>Transition to overt nephropathy</td>
</tr>
<tr>
<td></td>
<td>Telmisartan 40 mg (n=172)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telmisartan 80 mg (n=168)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DETAIL53 (2004)</td>
<td>Telmisartan 80 mg (n=130)</td>
<td>152.6 ± 16/85.4 ± 8.8</td>
<td>Diabetes, renal damage</td>
<td>Percentage change in GFR</td>
</tr>
<tr>
<td></td>
<td>Enalapril 20 mg (n=120)</td>
<td>151.6 ± 15.8/85.9 ± 7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALM54 (2000)</td>
<td>Candesartan 16 mg (n=66)</td>
<td>163.3 ± 19.0/96.6 ± 16.9</td>
<td>Hypertension, diabetes, renal damage</td>
<td>Percentage change in UAER</td>
</tr>
<tr>
<td></td>
<td>Candesartan 16 mg + lisinopril 20 mg (n=67)</td>
<td>161.7 ± 16.7/94.8 ± 6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lisinopril 20 mg (n=64)</td>
<td>163.0 ± 17.2/96.2 ± 5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VALERIA55 2008</td>
<td>Valsartan 320 mg (n=43)</td>
<td>153.1 ± 16.0/91.9 ± 7.7</td>
<td>Hypertension, renal damage</td>
<td>Percentage change in UAER</td>
</tr>
<tr>
<td></td>
<td>Valsartan 320 mg + lisinopril 20 mg (n=43)</td>
<td>150.4 ± 13.7/90.1 ± 8.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lisinopril 20 mg (n=47)</td>
<td>153.0 ± 14.3/90.6 ± 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ONTARGET56 (2009)</td>
<td>Telmisartan 80 mg (n=8542)</td>
<td>141.7 ± 17.2/82.1 ± 10.4</td>
<td>High-risk diabetes and vascular disease</td>
<td>Doubling baseline serum creatinine, dialysis and death</td>
</tr>
<tr>
<td></td>
<td>Telmisartan 80 mg + ramipril 10 mg (n=8502)</td>
<td>141.9 ± 17.6/82.1 ± 10.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ramipril 10 mg (n=8576)</td>
<td>141.8 ± 17.4/82.1 ± 10.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORIENT57</td>
<td>Olmesartan medoxomil</td>
<td>NA</td>
<td>Hypertension, diabetes and vascular disease</td>
<td>Doubling baseline serum creatinine, development of ESRD, death</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP = blood pressure; ESRD = end-stage renal disease; GFR = glomerular filtration rate; INDT-CCB = calcium channel blocker arm; INDT-Plc = placebo arm; LV = left ventricular; MAU = microalbuminuria; NA = data not available; UAER = urinary albumin creatinine ratio; UACR = urinary albumin excretion rate; UPE = urine protein excretion
combination anti-hypertensive drug therapy is highly desirable. Most patients need more than one medication.

Animal studies have shown that in the spontaneous hypertensive rats, long-term treatment with the combination of nitrendipine and atenolol significantly decreased BP and BPV, ameliorated impaired BRS, and obviously diminished EOD. The combination of nitrendipine and atenolol provides synergism on BP reduction, thus reducing the doses of each drug required in the treatment of HTN. This combination also provides a rapid and persistent antihypertensive effect for duration up to 24 hour.  

Large outcome trials have ACEIs and ARBs providing EOP in high-risk patients. All classes of antihypertensive agents have shown equivalent protection in patients screened for ACEI intolerance, such as the ONTARGET study. Support the hypothesis that antihypertensive agents may have beneficial effects beyond their BP-lowering. Results from AMADEO, DETAIL, LIFE, and ONTARGET™ studies comparing active agents in population already on other antihypertensive therapies, showed effects over and above good BP control in population studied.  

Among different drug classes, AT1RAs (ARBs) have provided an excellent alternative to ACEIs, representing a more selective and a better tolerated pharmacological approach to interfere with the RAS. Results derived from large, international, randomized clinical trials have consistently indicated that ARB-based therapeutic strategies may effectively provide CV and renal disease prevention and protection in different clinical conditions across the entire CV continuum. The beneficial effects of ARBs in terms of renal protection are well documented and this class of drugs is now indicated in several international guidelines as a first-line strategy to prevent progression of nephropathy in diabetic and in non-diabetic patients with HTN or in individuals at CV risk (Table 1).  

In spite of this success, the traditional pharmacological therapy targeted to inhibit specific components of the RAS suffers from many significant disadvantages. Chronic administration of traditional therapies is necessary for long-term anti-hypertensive benefits. Required daily dosing and undesirable side effects such as coughing, angioedema, renal dysfunction and hyperkalemia diminish patient compliance. Thus, other specific ways of suppressing the RAS function in HTN, Immunological approaches may have advantages over current therapy. The potential benefits of vaccine include improvements in compliance management, smooth and progressive onset of action for patients, improved diurnal control of BP and reduction in drug interactions associated with conventional drug poly-pharmacy. These advantages are due to the vaccine mode of action, where infrequent doses induce a biological response, overcoming the need for one or more daily tablets. Renin was first used to immunize the animals as a vaccine against RAS. Animal study conducted by Zhu (in 2006) suggests that the interruption of the RAS pathway by using an AT- II receptor (AT1) vaccine offers the potential to prevent the development of HTN and its associated pathophysiological alterations with infrequent administrations. 

DIRECT RENIN INHIBITOR - ALISKIREN

It is unclear whether ACEIs and ARBs have fully delivered the expected reductions in CV risk. In fact, the optimized RAS suppression is difficult to achieve with these agents, partly because ACE inhibitors and ARBs both activate compensatory feedback mechanisms that result in renin release and increase PRA.

Renin inhibitor provides more effective means of RAS Inhibition, than is possible with ACEIs or ARBs, as it blocks formation of both AT- I and AT- II, with no activation of the AT receptors and no interference with bradykinin metabolism, thus enhancing its therapeutic potential. Comparative effect of direct renin inhibitor (DRI), ACEIs and ARBs on RAS pathway, is depicted in Table 2. The first synthetic renin inhibitor was pepstatin, which was followed by first-generation agents that were active but required parenteral administration. Oral agents that were subsequently developed, such as enalkiren, remikiren, and zankiren, had limited clinical use because they demonstrated poor bioavailability (< 2%), short half-lives, and weak antihypertensive activity. Combination of molecular modeling and crystallographic structure analysis were later used to design renin inhibitors, lacking the extended peptide-like backbone of earlier inhibitors, for improved pharmacokinetic (PK) properties. This led to discovery of Aliskiren, the first of new non-peptide DRI. Aliskiren was approved by the FDA & European regulatory bodies in 2007, for the treatment of hypertension. 

Aliskiren is the first in a new class of orally active, non-peptide, low molecular weight DRI available for clinical use and potential new approach to the blockade of the RAAS. An average plasma half-life of 23.7 hours (range 20–45 hours), makes drug suitable for once daily administration. It is administered once daily, either as monotherapy or in
combination with other antihypertensive agents. BP-lowering affect of aliskiren is associated with a decreased, not increased, generation of AT- I, as it blocks generation of AT- I from angiotensinogen, by inhibiting the active enzymatic site of renin. Aliskiren has generally been well tolerated with adverse events and discontinuation rates similar to placebo in most clinical trials.  

Aliskiren has the potential to be useful in this wide spectrum of conditions and may provide organ protection independent of BP reductions. Aliskiren is the first representative of a new class of non-peptide, low molecular weight, and orally active transition state renin inhibitors. Its High aqueous solubility and affinity for renin, compensates for the low absolute bioavailability and long half-life makes it suitable for once daily administration. Aliskiren both as mono and combination therapy is effective in reducing BP with placebo like tolerability. Aliskiren has the potential to be useful in this wide spectrum of conditions, number of clinical trials are currently in progress to explore potential of aliskiren as monotherapy or in combination with other antihypertensive in prevention or regression of various forms of EOD in humans. 

Aliskiren used either as monotherapy or in combination, provides consistent and constant BP lowering over 12 months of treatment, providing sustained 24-hour BP control. Aliskiren monotherapy is dose-dependent up to 300 mg daily doses and provides effective and safe option for treatment of HTN, but with 70% of patients exceeding target SBP & DBP levels by >20 mmHg & >10 mmHg respectively, combination therapies play important role in achieving BP control. Aliskiren seems to be particularly indicated in patients who are intolerant to ACEIs, as well as in those with elevated RAAS activity. The results of these trials will further define its place / role in treatment of HTN & associated comorbidities.  

**CONCLUSION**  
Inadequate dosing, wrong pharmacological choices, and poor patient adherence may lead to suboptimal control of HTN in the majority of hypertensive patients. The DRI Aliskiren offers promising new approach in management of HTN and related EOD, as it blocks the RAAS more completely compared with other current RAAS inhibitors. Aliskiren has the potential to be useful in this wide spectrum of conditions (monotherapy or in combination). Combining agents (such as diuretics, ACEIs, and ARBs) that increase PRA with an agent (such as aliskiren) that neutralizes this activity appears to be a rational approach for optimizing BP control and are also well tolerated.

**REFERENCES**

10. Sawhney JPS. First Orally Active DRI Aliskiren - A New Prospect In Management of Hypertension and Beyond. Indian Heart J 2010;62:49-56.

**Table 2: Medication Effect on RAS Pathway**

<table>
<thead>
<tr>
<th></th>
<th>DRI</th>
<th>ACE-I</th>
<th>ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang$_{1/2}$</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Ang I</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Ang II</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>AT1 Receptors</td>
<td>Not Stimulated</td>
<td>Not Stimulated</td>
<td>Blocked</td>
</tr>
<tr>
<td>AT2 Receptors</td>
<td>Not Stimulated</td>
<td>Not Stimulated</td>
<td>Stimulated</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>⇧</td>
<td>↑</td>
<td>⇧</td>
</tr>
<tr>
<td>PRA</td>
<td>⇧</td>
<td>↑</td>
<td>⇧</td>
</tr>
<tr>
<td>PRC</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>