Angiotensin II Receptor Blockers: Current Perspective

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A cceptance of the notion that physiologically specific interruption of renin-angiotensin system (RAS) has considerable influence in the treatment of various conditions like hypertension and congestive heart failure has paved the way for search and conscious development of novel pharmacological inhibitors of this system. Angiotensin converting enzyme (ACE) inhibitors have been proven beyond doubt to be effective in treatment of these conditions. However a new class of drug - Angiotensin II Receptor Blockers (ARBs) has emerged in the recent past, which dwindles between rejection and acceptance. Nevertheless strong evidence-based opinions are slowly emerging with the arrival of results of recent trials. This review attempts to provide a comprehensive overview of these drugs and their current clinical status.

RENIN-ANGIOTENSIN-SYSTEM (RAS)

Renin is secreted from juxta - glomerular cells of the kidneys as prorenin, a precursor molecule. Renin metabolises angiotensinogen to the inactive decapeptide angiotensin I (Ang I), a rate limiting enzymatic step.¹ Ang I is metabolised to angiotensin II (Ang II) by angiotensin converting enzyme (ACE), which is found in plasma as well as on plasma membrane of endothelial cells and a number of other cell types. ACE is a non-specific metalloprotease that also comprises of the activity of kininase II that is responsible for the metabolism of bradykinin. Hence, inhibition of ACE leads to an increase in the levels of bradykinin, which is also responsible for the side effects of ACE inhibitors like cough and angioedema.^{2, 3}

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Circulating RAS		Tissue-based RAS	
1.	Peripheral vasoconstriction	1.	Hypertrophy
2.	Aldosterone release	2.	Hyperplasia
3.	Arginine vasopressin release	3.	Remodeling
4.	Stimulate thirst and sodium appetite	4.	Cytokine activation
5.	Renal sodium and water reabsorption	5.	Collagen deposition (fibrosis)

In recent years, the application and development of cellular

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706

and molecular biology techniques have revealed another aspect of Ang II as a tissue hormone or autocoid with paracrine, autocrine and intracrine actions.^{4,5} The renal renin and circulating components of RAS are produced in amounts greater by several orders of magnitude than the amounts produced by extra-renal tissues and are mainly or solely responsible for the systemic hormonal and hemodynamic effects Ang II. On the other hand, the minute amounts of Ang II produced locally may be responsible for its direct effects that persists even an renoprival state.⁶ The systemic and tissue effects of Ang II are well documented (Table 1). In addition to Ang II, the truncated Ang III, Ang IV and Ang-(1-7) are also bioactive but their role in normal physiology and in disease is unclear. In addition to renin, other enzymes like cathepsin D, pepsin, renin-like enzyme etc. also release Ang I from angiotensinogen. Moreover serine proteases including tonin, cathepsin G, trypsin and kallikrein can release Ang II directly from angiotensinogen. Furthermore enzymes other than ACE may convert Ang I to Ang II (Fig. 1). The importance of bioactive enzymes other than Ang II lies in part in the effects on their levels by ACE inhibition and AT1 receptor antagonism. ACE inhibition increases the levels of Ang -(1-7) heptapeptide in part because of the increase in levels of Ang I while ARBs increase the levels of all angiotensin peptides. AT1 receptor antagonism blocks the effect of Ang II on AT I receptors but leaves other receptors exposed to increased levels of angiotensin peptides.⁷

ANGIOTENSIN RECEPTORS

AT1 receptors are GTP - binding protein - linked integral membrane proteins with seven transmembrane spanning domains that bind the diphenylimidazole derivative-Losartan. AT-1 receptor subtypes are highly homologous and are linked to the activation of phospholipase - C and release of inositol triphosphate (IP3) and diacylglycerol (DAG), which increase intracellular calcium.8,9 AT1 receptors are predominantly found on vascular endothelium and are linked to all the known physiological and pharmacologic actions of Ang II. Stimulation of ATI receptors by angiotensin-II induces vasoconstriction, renal tubular sodium reabsorption, aldosterone release, vascular smooth muscle remodelling and stimulation of central and peripheral sympathetic activity, thus leading to increases in blood volume and blood pressure. Almost all the known clinical effects of Ang II are mediated by AT1 receptor.10



Fig. 1: Renin-Angiotensin System

AT2 receptor is also a seven - membrane spanning domain receptor with relatively low (33%) homology in its amino acid sequence with the AT-1 receptor. It was recognized later that AT 2 receptor is abundantly expressed during fetal and early postnatal life but is subsequently downregulated. AT 2 receptor is mainly found in adrenal medulla, uterus and fetal tissue but also expressed in normal human myocardium at low levels; in fact AT 2 receptor is the most abundant Ang II receptor found is adult human atrial and ventricular myocytes.^{11,12} In tissue injury states like wound healing, vascular injury, post-MI and in sodium depletion, AT2 receptors are re-expressed and upregulated.¹³⁻¹⁵ Their probable role in anti-proliferation and inhibition of cell growth, apoptosis, differentiation and vasodilatation via nitric oxide production is proposed. In vitro and in vivo studies have suggested that AT2 receptors have anti-proliferative effects on target organs. In spontaneous hypertensive rats (SHR), pretreatment with ARB allowed unopposed AT2 receptor stimulation which reduced cell proliferation.¹⁶ The antiproliferative effect on neointimal formation is blocked by an AT2 receptor antagonist.¹⁷ AT2 receptors also promote vasodilation via the sequential release of bradykinin, nitric oxide and cGMP.¹⁸ Recent data however suggests that AT2 receptor may mediate production of bradykinin and nitric oxide in the kidney.¹⁹ Thus, AT2 receptor may oppose the action of AT1 receptor.

AT3 receptor : Ang III has a role in vasopressin release and aldosterone production. It is proposed that Ang II must be converted to Ang III to exert its actions in the brain.^{20,21} Since both AT1 and AT 2 receptors recognize Ang III and because a specific AT 3 receptor has not been identified, it seems that AT1 and AT 2 receptors serve as AT 3 receptors.

AT4 receptor : discovered recently as a 186-kD integral membrane glycoprotein with a large extracellular domain but requires confirmation when the sequence identity of this receptor becomes available.

AT 1-7 receptor : though indirect evidence suggests the existence, molecular confirmation of this receptor is

controversial and needs further research.22

RATIONALE BEHIND DEVELOPING ARBS

Most ACE inhibitors do not suppress Ang II production over full 24 hours and at least partial recovery of Ang II generation occurs over a period of time (ACE- escape). Conversion of Ang I to Ang II via ACE is not the only pathway. Pathways involving cathepsin G, elastase, tPA, chymase, chymostatin -sensitive angiotensin II generating enzyme (CAGE) and tonin can produce Ang II, hence ACE inhibitors may not block Ang II formation completely. Since Ang II was the main effector molecule responsible for most ill effects (Table1), hence it made sense in trying to block it completely. Furthermore, side-effect profile including cough and angioedema are quite troublesome in some patients who are on ACE inhibitors, which were proposed to be less likely with ARBs due to their lack of effect on bradykinin system.

ANGIOTENSIN II RECEPTOR BLOCKERS: PHARMACOLOGY

Saralasin was the first ARB synthesized in 1971and it heralded a new world of angiotensin II receptor blockade. Its efficacy as an antihypertensive therapy as well as utility in congestive heart failure was recognized. However, saralasin had a few drawbacks, being an intravenous preparation with short duration of action with poor bioavailability and induced hypertension in low renin states. The first orally bioavailable, long acting non-peptide ARB was losartan. Most of the currently available ARBs are AT1 receptor blockers with very high affinity for this receptor and almost none for AT2 receptors. All these agents display high protein binding capacity. These are competitive antagonists with very low dissociation from the receptor and block the pressor response in the dose-dependent manner. These AT 1 receptor antagonists induce to a variable degree, an "insurmountable blockade".^{23,24} Currently available ARBs include losartan, valsartan, irbesartan, candesartan, telmesartan and eprosartan.25

- Losartan : The first orally active AT 1 receptor blocker available in the market. It has an active metabolite EXP 3174 which is responsible for most of Losartan's effects. Administered intravenously, EXP3174 is 10-20 times more potent than Losartan and has a longer duration of action. Losartan binds competitively to AT 1 receptors and hence has a shorter duration of action. It is also the only ARB with a uricosuric action. Losartan and its metabolite are excreted by the kidney and in the bile. Neither compound is dialyzable. Clinically significant interactions with rifampicin and fluconazole lead to its reduced levels. Dose ranges from 25-100mg daily with recommended initial dose of 50mg once daily.
- Valsartan : It has only one inactive metabolite. Food decreases its absorption by 40%. It is excreted by the bile (70%) and the kidneys (30%) both. Dose ranges from 80-320 mg daily with initial recommended dose of 80 mg once daily.

- 3) Irbesartan : is longer acting ARB with very high affinity for AT 1 receptors. In contrast to losartan, irbesartan has no active metabolite. It is cleared predominantly by bile (80%) and partly by the kidney (20%). Dose range: 75-30 mg daily, with initial recommended dosage of 150 mg once daily.
- 4) Candesartan cilexetil : It is also a long acting ARB 2 with a long half-life. It is administered as a prodrug to overcome its otherwise poor bioavailability. Candesartan's AT 1 binding affinity is 80 times greater than that of losartan and 10 times greater than EXP 3174. It is eliminated principally by the kidneys (60%) and bile (40%). Dose range: 8-32 mg daily with recommended initial dose of 16 mg once daily.
- 5) Telmisartan : Longest acting ARB available in the market. It undergoes minimal transformation and is excreted almost completely by the faeces (98%). Telmisartan has been shown to raise digoxin levels. Dose range 40-160 mg daily with recommended initial dose 40 mg once daily.
- 6) *Eprosartan* : Latest angistensin II receptor antagonist with shortest half-life of 5-7 hours. Food decreases the absorption of eprosartan by 25%. It is excreted mostly by biliary (90%) but also by renal (10%) routes. Dose range: 400-800mg daily.

ARBS IN HYPERTENSION

ARBs have emerged as an effective class of drugs for treatment of hypertension.

A meta-analysis of 43 randomised clinical trials in 11281 patients comparing ARBs with other ARBs, with placebo and with other anti-hypertensive drug classes. It showed comparable anti-hypertensive effects for losartan, valsartan, irbesartan, candesartan and telmisartan as monotherapy. Out of these, 25 trials also showed equivalent anti-hypertensive actions of ARBs and other classes including ACE inhibitors, calcium channel blockers, beta-blockers and diuretics. Enhanced response is seen with addition of low dose hydrochlorthiazide.²⁶ Cough occurred significantly less with ARBs. Some recent landmark trials are being discussed below.

LIFE (Losartan in Hypertension For Endpoint reduction)²⁷

The LIFE study is a double blind, randomised trial conducted in 9193 patients with essential hypertension of moderate to severe grade (aged 55-80 years, sitting blood pressure 160-200/95-115 mmHg), aimed at analysing whether ARBs reduce left ventricular hypertrophy (LVH) and cardiovascular mortality beyond blood pressure reduction with atenolol. Atenolol was given in a dose of 50mg same as that of losartan. The results obtained after an average of 4.8 years of follow up showed similar reductions in blood pressure in the losartan and atenolol group. The primary composite end-point of death, myocardial infarction and stroke occurred much less in losartan group (P=0.021) and was mainly due to 25% reduced rate of stroke (P=0.001). There were no significant difference in total mortality, need for

revascularization, hospital admissions or resuscitated cardiac arrests. There was significant reduction of LVH in losartan group (p<0.001) and losartan was better tolerated (p=0.001) than atenolol. New onset diabetes was also less in losartan group (p=0.001) by about 25% probably because of a beneficial effect on insulin resistance. Thus, losartan proved to be an effective antihypertensive agent, reduced stroke risk, new onset diabetes and LVH to greater degree and was better tolerated.

SCOPE (Study on Cognition and Prognosis in Elderly)²⁸

It is a multi-center, prospective, randomized, double blind study of 4,964 patients from 15 different countries. Soon after the study started, the SYST-EUR²⁹ results were announced, and it was agreed that all patients should be offered some sort of antihypertensive treatment. The placebo group was therefore offered treatment with a diuretic, calcium blocker, or beta-blocker, so the trial became a comparison of two treatment strategies. The primary end-point of SCOPE was a composite of death/MI/stroke. This was not significantly different between the two groups, but a trend was seen toward benefit in the candesartan group (11% relative reduction, p=0.19). Candesartan was associated with a significant 28% relative reduction in nonfatal stroke (p=0.041). This was despite only a small difference in blood pressure reduction between the two groups (3.2 mm Hg systolic and 1.6 mm Hg diastolic) in favour of candesartan. The SCOPE trial also looked at dementia and cognitive decline but found no significant difference in these outcomes between the two groups

VALUE (Valsartan Antihypertensive Long-term Use Evaluation)³⁰

A prospective, multicentric, double blind, randomized control ongoing trial in 31 countries, in 15,314 previously treated (92%) or untreated patients. The projected duration is 4 years after randomization or until 14,400 events have accumulated. Patients receive losartan 80 mg or amlodipine 5 mg once daily, titrated after 4 weeks according to blood pressure response to 160 mg or 10 mg, respectively, with subsequent add-on hydrochlorthiazide 12.5 and 25 mg/day, followed by other antihypertensive agents as needed (but excluding ACE inhibitors, calcium channel blockers, ARBs, or other diuretics).

ACCESS : Acute Candesartan Cilexetil Evaluation in Stroke Survivors study³¹

A Double-blind, randomized, multicenter trial with a planned enrollment of 500 patients, was prematurely halted and 342 patients were randomized from 53 centers.

Trial was aimed at evaluating the effectiveness of an early, moderate BP reduction in patients with acute cerebral ischemia in comparison to restrictive antihypertensive therapy. Inclusion criteria was an initial BP \geq 200/110, acute cerebral ischemia and motor paresis. Patients were randomized to receive candesartan cilexitil or placebo for 7 days. The placebo group was treated with candesartan if they were hypertensive after 7 days. Normotensive patients were followed up but not treated. Combined endpoint of total mortality, cerebral complications and cardiovascular complications, was reduced by 47.5 percent for patients treated with candesartan (4-16 mg) initiated within 72 hrs post-stroke.

Status in hypertension : In general, the blood pressurelowering effects of ARBs are similar to those of ACE inhibitors, dihydropyridine calcium channel blockers, and ß1selective antagonists. ARBs are particularly recommended in diabetic hypertensive population where they also reduce microalbuminuria. At present according to the sixth report of Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC VI), ARBs are indicated in patients who are intolerant to ACE inhibitors. Ongoing clinical trials will help in deciding their place among the already established world of anti-hypertensives.

USE OF ARBS IN HEART FAILURE

During the last several years, ACE inhibitors have been proven beneficial beyond doubt and are current standard therapy in heart failure. Improvements in left ventricular mass, ejection fraction and neurohumoral activity and survival benefits are well documented with ACE inhibitors. Despite this, the mortality and morbidity in CHF remains high. The proposed reasons for this are "ACE-escape" and underutilization of optimum dose of ACE inhibitors as suggested in ATLAS trial.³² Also addition of aldosterone antagonist spironolactone as in RALES study³³ to existing ACE inhibitor therapy contributed to additional mortality benefits justifying the use of ARBs in CHF. Some landmark trials with ARBs in CHF are discussed.

ELITE (Evaluation of Losartan in The Elderly study)³⁴

A double blind, randomized, placebo controlled trial in elderly patients to determine the safety and efficacy of losartan compared to captopril in patients with heart failure. Seven hundred and twenty two patients, age 65 years or older with symptomatic heart failure (NYHA Class II-IV), with an ejection fraction (EF) of 40% or less and no prior history of ACE inhibitor therapy were enrolled. Patients received either captopril 6.25mg TID titrated to 60mg TID plus placebo, or losartan 12.5mg once daily titrated to 50mg once daily plus placebo. The primary endpoint was renal dysfunction, defined as an increase in serum creatinine by 0.3mg/dL or more from baseline confirmed by a repeat measurement 5-14 days later. Hospital admission for death and/or worsening heart failure occurred in 13.2% of patients receiving captopril and 9.4% of those taking losartan (p=0.075). This risk reduction was primarily due to a decrease in all-cause mortality, 8.7% versus 4.8% for captopril and losartan, respectively, (p = 0.035). However, when all-cause mortality and hospital admission rates are viewed separately, losartan was superior to captopril (p=0.035 and 0.014, respectively). Losartan was better tolerated than captopril in regards to adverse effects and discontinuation rates, although there was no difference between either drug's effects on renal function. This study also found a lower mortality rate in the group receiving losartan than captopril.

ELITE II³⁵

ELITE II Losartan Heart Failure Survival Study was undertaken to confirm the findings of ELITE. It was a double blind, randomized, controlled trial of 3152 patients aged 60 years or older with New York Heart Association class II-IV heart failure and ejection fraction of 40% or less. Patients, stratified for beta-blocker use, were randomly assigned losartan (n=1578) titrated to 50 mg once daily or captopril (n=1574) titrated to 50 mg three times daily. Median follow-up was 555 days. There were no significant differences in allcause mortality (11.7 vs. 10.4%) or sudden death or resuscitated arrests (9.0 vs 7.3%) between the two treatment groups. However, the difference in the combined risk of sudden cardiac death and resuscitated cardiac arrest approached significance (p=0.08), with a trend favoring captopril. Losartan was not superior to captopril in improving survival in elderly heart-failure patients, but was significantly better tolerated. ELITE II failed to confirm the findings of ELITE.

RESOLVD Pilot Study

The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot Study³⁶ was a randomized double blind trial. In phase I of the RESOLVD study, 768 patients with NYHA class II-IV heart failure were randomized to receive either monotherapy with candesartan or combination therapy for 43 weeks. The primary end-point was exercise tolerance. The results showed candesartan as monotherapy and combination therapy to be less efficacious than enalapril in improving exercise tolerance. There were no differences among the groups in NYHA functional class, quality of life indices, or 6-minute walk distance, symptoms, exercise capacity, or ventricular function. However, there was a trend towards increased ejection fraction in the candesartan plus enalapril group, as compared to either therapy alone. There also was a significant benefit with combination therapy in blood pressure control and less of an increase in enddiastolic volume and end-systolic volume in the combination group. The investigators concluded that most patients tolerated combination therapy with ACE inhibitors and ARBs, and that combined therapy is theoretically appealing and was shown in this study to be more beneficial than either treatment alone in improving the neurohormonal balance and left ventricular remodeling. This study raised more questions than it answered which made the results of further trials even more important.

Val-HeFT (Valsartan Heart Failure Trial)

Valsartan heart failure trial³⁷ was a randomized, placebo controlled, double blind multicentric trial involving 5010 patients in an age group of \geq 18 years with NYHA class II-IV congestive heart failure for at least 3 months with ejection fraction (EF<40%). The study was armed at evaluating valsartan in a dose of 160 mg twice daily versus placebo as an add-on therapy to standard therapy for heart failure. At two years, there was insignificant effect on mortality (19.4% placebo versus 19.7% valsartan) but a significant effect on combined endpoint of all cause mortality and morbidity (p=0.009), largely due to a 24% reduction in hospitalizations in valsartan group. There was also significant improvement in NYHA class, ejection fraction, signs, and symptoms of heart failure and quality of life. At the time of randomisation, 93% patients were taking beta-blockers. Patients receiving valsartan alone (without addition of beta-blockers or ACE inhibitor) faired better than when valsartan was added to ACE inhibitors and beta-blockers. The worst outcome was seen in patients receiving all the three. Valsartan was well tolerated. Addition of Valsartan to a patient already receiving ACE inhibitors and Beta-blockers was found to increase mortality, which is indeed a cause of concern as most patients with CHF are likely to be on them. However, Valsartan as monotherapy was beneficial and attenuation of the benefit was seen if ACEI or beta-blocker was added.

CHARM

(Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity).³⁸ This ongoing multicentric, randomized, placebo-controlled trial has enrolled 7572 patients with NYHA class II-IV heart failure, and includes patients with ejection fractions both greater and less than 40%. The less than 40% ejection fraction group is divided into ACE inhibitor (combination)-treated and ACE inhibitorintolerant groups, and each of these groups has been randomized to either candesartan or placebo. All patients will be followed for 42 months, and the primary overall endpoint is all-cause mortality. The trial is scheduled to finish in 2003.

ARBs in CHF : Where Do We Stand?

In a direct comparison trial (ELITE-II), ARBs were found to have no benefit over ACE inhibitor therapy. Thus, ACE inhibitors should remain first-line treatment for heart failure. For patients intolerant to ACE inhibitors, ARB therapy is recommended and provides excellent tolerability. In patients already on ACE inhibitor therapy, the addition of an ARB reduced the number of heart failure hospitalizations (Val-HeFT). Therefore, ARBs can safely be added to ACE inhibitor therapy in patients who remain symptomatic. The caveat is that patients on both ACE inhibitors and beta-blockers did not appear to benefit from the ARB. For patients on ACE inhibitors and not beta blockers, the addition of a beta blocker is preferred over an ARB, since multiple studies have shown a mortality benefit in heart failure patients taking beta blockers. The CHARM study should help to define the use of ARBs as either ACE inhibitor add-on or substitute therapy in patients with heart failure.

ARBS IN MYOCARDIAL INFARCTION

Role of ARBs in post - myocardial infarction state is controversial. Some recent trials are mentioned below which would provide the answers.

OPTIMAL

(Optimal Trial In Myocardial Infarction with Angiotensin II Antagonist Losartan) : A multicentric, randomized trial in 5004 patients to test the hypothesis that losartan would be

superior or non-inferior to captopril in decreasing all-cause mortality in high-risk patients following acute myocardial infarction with left ventricular dysfunction. Patients were assigned to a target dose of losartan 50 mg/day and captopril 50 mg t.i.d., as tolerated. The primary end-point was all-cause mortality and there were insignificant difference of 18% versus 16% deaths in the losartan and captopril group, respectively (p=0.07). However, there were significantly more cardiovascular deaths with losartan (15%) than with captopril (13%; p=0.03). Losartan was better tolerated than captopril with fewer patients discontinuing medication (17% versus 23% for losartan and captopril, respectively). In conclusion, if tolerated, captopril and other ACE inhibitors should remain the preferred treatment for patients after complicated acute myocardial infarction.

VALIANT (Valsartan in Acute Myocardial Infarction Trial)

VALIANT⁴⁰ is a 14,500 patient, international, double blind, randomized, active controlled study comparing long term treatment with valsartan, captopril and their combination in high risk patients after acute myocardial infarction. Main inclusion criteria were recent myocardial infarction (within 12 hours to 10 days), clinical signs and symptoms of heart failure and/or evidence of left ventricular systolic dysfunction. The study will continue until 2,700 patients have reached the primary endpoint, death. The results are expected by the end of 2003.

Conclusion

At present ARBs are not recommended in post-myocardial infarction patients ahead or instead of ACE inhibitors. VALIANT is likely to throw more light on the subject in near future.

ARBS IN DIABETIC NEPHROPATHY

In both type 1 and type 2 diabetes, microalbuminuria is a predictor of persistent proteinuria and early death from cardiovascular disease. The renin-angiotensin system (RAS) is considered to be a paracrine regulator of renal function and blood flow, thus playing an important role in the progression of chronic renal disease, as seen in diabetic nephropathy. The effects of blocking the RAS with ACE inhibitors on delay or prevention of incipient to overt nephropathy and renal failure are widely recognized. Recent trials with ARBs are proving to be equally effective.

RENAAL (Reduction of Endpoints in NIDDM with Ang II Antagonist Losartan)⁴¹

Enrolled 1,513 patients with a mean age of 60 years for nearly 4 years, was a multinational, prospective, randomized, double-blinded trial in subjects with type 2 diabetes mellitus and evidence for renal disease. The primary end-point of this study was a composite of the time to first event of doubling of serum creatinine, end-stage renal disease (ESRD) or death. Estimation of urinary albumin excretion at baseline was the most powerful predictor of the composite end-point as well as individually the renal or all-cause mortality end-points. Results showed a significant decrease in risk of progression to end-stage renal disease (28%), hospitalization for heart failure by 32% and proteinuria by 35% with losartan.

CALM (Candesartan And Lisinopril Microalbumiuria)42

Candesartan (16 mg) once daily is as effective as lisinopril (20 mg) once daily each in reducing blood pressure and microalbuminuria in hypertensive patients with type 2 diabetes mellitus. Combination treatment was well tolerated and more effective in reducing blood pressure.

IDNT and IRMA43,44

In the Irbesartan Diabetic Nephropathy Trial (IDNT), irbesartan was effective in protecting against the progression of nephropathy due to type 2 diabetes, lowering both the risk of doubling the serum creatinine concentration and the relative risk of end-stage renal disease. In the IRbesartan microalbuminuric type 2 diabetes in hypertensive patients (IRMA II) study, irbesartan was protective against the onset of persistent albuminuria in hypertensive patients with type 2 diabetes and microalbuminuria.

MARVAL⁴⁵

Microalbuminuria Reduction with Valsartan trial, enrolled 332 patients with type 2 diabetes and microalbuminuria, both with and without hypertension, who were randomized to either 80-mg/day valsartan or 5-mg/day amlodipine for 24 weeks; the urinary albumin excretion (UAER) was 56% in valsartan group as compared to 92% in patients randomized to the amlodipine arm (p<0.001). The UAER reduction in the valsartan patients was similar in both the hypertensive and non-hypertensive patients. Overall blood pressure reduction was no different between the valsartan and amlodipine groups.

Conclusion

Three large, randomized trials IDNT, RENAAL, and the IRMA-2 demonstrated very impressive renoprotective effects of ARBs in hypertensive patients with type 2 diabetes. The renoprotective effect of ARBs in these trials was largely independent of blood pressure lowering. Trends towards fewer composite cardiovascular events were observed in the ARB groups in these studies, and in RENAAL there were trends towards fewer myocardial infarctions in the losartan group. American Diabetes Association currently recommends ARBs as the first drug in patients with this disease.

OTHER TRIALS TO WATCH OUT FOR!

ONTARGET⁴⁶

The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial will enroll approximately 23,000 patients 55 years or older with history of CAD, stroke, or peripheral arterial disease, but without heart failure or known low LVEF. It will compare major cardiovascular events in those treated with ARBs, ACE inhibitors, or combined therapy (telmisartan, 80 mg/d versus ramipril, 10 mg/d versus combined telmisartan plus ramipril).

TRANSCEND⁴⁶

The Telmisartan Randomized Assessment Study in ACEiNhibitor intolerant patients with Cardiovascular Disease trial will compare telmisartan to placebo in 5000 similar patients, who cannot tolerate ACE inhibitors. The ONTARGET and TRANSCEND trials are designed to test the hypothesis that ARBs and/or combined ARB/ACE inhibitor treatment reduces atherosclerotic events.

SAFETY AND TOLERABILITY PROFILE

The overall incidence of adverse effects as evident from various clinical studies is 15.3% in patients treated with losartan as compared with 15.5% in patients receiving placebo. Similar results have been obtained with other ARBs. Headache was the commonest drug-related side effect. Other were dizziness, fatigue and asthenia. Cough which is the most common side- effect observed with ACE inhibitors (10% approx) and more commonly seen in Blacks and Asian patients was much less with losartan. Pylypchuk⁴⁷ compared the tolerability of ACE inhibitors with that of ARBs and the frequency of associated cough and angioedema through a review of published data and found the frequency of dry cough to be similar to that of placebo(1.5 - 3.0%). Angioedema was not reported in this series. Available data does not firmly rule out the occurrence of angioedema in patients receiving ARBs as several cases of angioedema with losartan have been reported but not proven beyond doubt to be exclusively due to ARB use. Rare side effects like ageusia (reversible), migraine, reversible psychosis and impotence have been reported. Serum potassium levels are increased slightly by ARBs due to transient decrease in plasma aldosterone levels. In hypertensives with normal renal functions, the changes in serum potassium were negligible with valsartan, candesartan, and irbesartan. With losartan, the incidence of hyperkalemia was 1.5% as compared to 1.3% with ACE inhibitors and placebo. As with ACE inhibitors the risk of hyperkalemia was more in diabetics, renal insufficiency or with concurrent potassium-sparing diuretic use or potassium supplement. Eprosartan causes relatively lesser increase in potassium levels. Acute renal failure may be precipitated in patients with bilateral renal artery stenosis or diffuse intrarenal vascular sclerosis, similar to ACE inhibitors. In mild to moderate renal failure the ARBs do not affect the GFR adversely. First dose hypotension commonly seen with the use of ACE inhibitors in salt-depleted or hypovolemic hypertensive patients is not seen with ARBs. No rebound hypertension is observed with these drugs and are well tolerated in all age groups. During pregnancy losartan has been shown in animal study to cause serious fetal toxicity in second trimester. Thus, like ACE inhibitors, which cause severe hypotension and renal failure in the newborn, ARBs are also contraindicated in pregnancy. Animal study also indicate that losartan is secreted in milk and this drug should be used with caution in breast-feeding mothers.

CURRENT STATUS OF ARBS : SUMMARY

- 1. ARBs offer an equally efficacious alternative to ACE inhibitors in management of hypertension especially in ACE inhibitor intolerant patients.
- 2. ACE inhibitors remain the drugs of choice for patients with congestive heart failure and left ventricular dysfunction after myocardial infarction.
- 3. ARBs offer an alternative in these patients when ACE inhibitors are not tolerated.
- 4. ARBs have proved to be equally efficacious as ACE inhibitors in preventing progression of diabetic nephropathy.

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