REVIEW ARTICLES

Angiotensin Converting Enzyme (ACE) inhibitors and Anogiotensin II Receptor Blockers (ARBs) in renal disease

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Summary:

Chronic Kidney disease is emerging as a new health problem. Therapy with angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) have shown improvement in patients with hypertension, proteinuria and chronic renal failure. This improvement in GFR, fall in plasma renin activity (PRA) is due to improved sympathetic activity, improved endothelial function, reduced inflammation or combination of these factors. Several large scale, prospective randomized studies with clinical end point have strongly suggested that both ACEI or ARBs can slow progression of chronic glomerulonephritis alone. However, beneficial effect are much pronounced in combined group. Both ACEI & ARBs can prevent the progression from microalbuminuria to overt albuminuria in both type I and type II diabetes. When progression of renal disease is used as end point, protection has been demonstrated with ACEI for type I, but not type II diabetes. In type II only ARB have shown to slow progression to ESRD. Combination of ACEI and ARB is superior than maximum ACEI dose in type I diabetes. Whereas calcium channel blocker (CCB) and ARB combination is better option for type II diabetes. Patients treated with ACEI or ARBs should be monitored for hypertension, decrease GFR and hyperkalaemia. These two drugs should not be used in pregnancy for risk of foetal abnormality.

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Introduction:

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) are currently recommended for management and prevention of renal disease. In 1898, Tiegerstedt and Berg man found that crude saline extracts of kidney contained a pressor substance which is termed renin[1]. Renin exists in both inactive (prorenin) and active renin form. Active renin is a product primarily if not exclusively of the kidneys. Active renin is formed in the secretary granules of the juxtaglomerular cells and renin has a half life of 80 minutes or less in the circulation. Renin acts on the basic substrate angiotensinogen, circulating (a_2 globulin synthesized in liver to form the decapeptide angiotensin I. Angitensin I is then transformed to the octapeptide angiotensin II by angiotensin coverting enzyme (ACE). Angiotensin II cause deleterious effect such as vasoconstriction, salt retenion, inflammation, fibrosis and increased oxidative stress. Most of the converting enzyme that form angiotensin II in circulation is located in the endothelial cells particularly the pulmonary vascular endothelium. This angiotensin II was synthesined by Schwyer and Bumpus in 1957. Later, ACEI and ARB were developed in the year 1982 & 1988 respectively[2,3].

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Factors leading to progressive renal insufficiency

Patients with almost any form of renal disease are at risk of progressive decline renal functions over variable period of time. Risk factors are -

1) Persistent immune insult to glomerulus or disease gene abnormality
2) Coexisting modifiers of risks like infection, obstruction & drugs to the kidney
3) Systemic hypertension and glomerular capillary hypertension and hyperperfusion leading to enhanced internal traffic of protein & structural injury.
4) Proteinuria.
5) Low number of nephrons caused by congenital or acquired nephropathy,
6) Hyperlipidemia,
7) Metabolic factors like phosphate, calcium & urate depositon[4].

Systemic Hypertension

The mechanism by which systemic hypertension play role in progression of renal disease include injury to preglomerular arteries, leading to glomerular ischaemia with progressive luminal narrowing and hence fall in glomerular blood flow. Renal vessels and glomeruli appear susceptible to adverse effect of systemic hypertension when proteinuria or when there is glomerular inflammation and vascular damage. One of the cellular mechanisms of hypertensive renal injury is mediated by elevated angiotensin II[5].

Angiotensin II mediated renal injury

Angitensin II can be viewed as central molecule in several of the processes involved in chronic renal injury. When the number of nephrons is reduced to critical extent there is compensatory increase in renal plasma flow and increase in amount of filtrate in each remaining nephrons. Increase flow rates result from dilatation of afferent arteriole to a greater extent than efferent arteriole which is under the influence of angiotensin II. These changes increase glomerular capillary pressure with subsequent increase in single nephron glomerular filtration rate (GFR). This adaptive response to maintain GFR in the failing kidney may be maladaptive response in long term, cause renal functional and structural damage.

In kidney, local generation of anginotensin II is formed in excessive amount during haemodynamic injury to the endothelium and physical stretching of tuft. Angiotension II induced increased glomerular capillary pressure impairs the parmeselective selective function of glomerular filtration barriers leading to proteinuria and chronic parenchymal injury. Elevation in glomerular capillary pressure do enlarge the; c radius of the pores in glomerular membrane. Excessive angiotensin II formation or action may promote functional & structural injury. Other mechanism of injury include increase influx of macromolecule into mesangium, thereby inciting cytokines release, glomerular cell proliferation and macrophage influx and mesangial matrix formation. Angitensin II may directly induce expression of transforming growth factors B (TGF-B) responsible for extracellular matrix overproduction. Glomerular hypertensin is associated with change of endothelial cell function & structure which is potential cellular source of TGF-B and growth factor (platelet derived growth factor, PDGF) and basic roblast growth factor (BFGF).[6] Thus breach of the glomerular barrier to protein is perhaps most threatening consequences of increased glomerular capillary pressure. Glomerular hypertrophy which develops during adaptive response of the kidney to nephron loss precedes and may predispose to glomerular scarring. Therefore, angiotensin II is responsible for chronic renal injury by several mechanims. Angiotensin II is rapidly metabolized by various peptidases and half life is 1-2 minutes. Through several mechanisms, angiotensin II alter peripheral resistance, renal function and finally cardiovascular structure.

Physiology in RAS.

Juxtraglomerular apparatus (JGA) is located in vascular pole of glomerulus where distal tubule comes in contact with parent glomerulus. It has two components namely vascular & tubular component. Vascular component consists of terminal portion of afferent arteriole, initial portion of efferent arteriole and extraglomerular mesangial region. Tubular component consists of cells of distal tubule in contact with afferent arteriole, which become tall & columnar termed macula densa. Extraglomerular portion contain lucis cells bounded by macula densa, specialized region of afferent & efferent arteriole & intraglomerular mesangial cells. Myoepithelial cells or granular cells of afferent arteriole known as juxtraglomerular cells (JG cells) produce renin. The lucis cells, the JG cells and macula densa constitute JGA[7].

Control of Renin secretion

Renin secretion is regulated by two local pathway in the kidney and third one acts through central nervous system (CNS). First pathway of renin secretion is intrarenal mechanism by macula densa. Increased Nacl flux in macula densa inhibit and decrease Nacl flux which stimulate renin secretion. Second pathway for renin secretion is intrarenal baroreceptor pathway in which decreased tension in afferent arteriolar wall increase and increased tension decrease renin secretion.

Negative feedback of renin secretion

Increase renin secretion enhance the formation of angiotensin II and angiotensin II stimulates

angiotensin subtype I (AT I) receptors to juxtra glomerular cells to inhibit renin release. This mechanism has been termed short loop negative feedback mechanism. Agiotensin II induced increase blood pressure inhibit renin release by: a) activation of high pressure baroreceptor thereby reducing renal sympathetic tone b) Increased pressure in preglomerular vessel (c) reducing Nacl absorption in proximal tubule (pressure natriuresis) which increase tubular delivery of NaCl at macula densa. This is long loop negative feedback mechanism of renin secretion. Angiotensinogen is primarily synthesised in liver. Synthesis is stimulated by inflammation, estrogen, glucocorticoid, thyroid hormone, insulin, angiotensin II and in pregnancy. During pregnancy plasma level of angiotensinogen increase several fold due to estrogen[8].

Angiotensin converting enzyme (ACE):
This octoenzyme is located in endothelial cells, much abundant in lung and also in all other tissues[9]. ACE is identical to kinase which inactivate bradykinin and other potent vasodilators peptide.

Alternative pathway for angiotensin pathways
Some tissues contain nonrenin angiotensin processing enzymes that convert angiotensinogen to angiotensin I or directly to angiotensin II. Chymase possibly mast cell derived contributes to local tissue conversion of angiotensin I to angiotensin II particularly in heart and kidneys[10].

Local tissue RAS
Besides tradition circulating renin of renal origin, circulating angiotensinogen of hepatic origin, there are also extrinsic & intrinsic local renin angiotensin system found in brain, pituitary, blood vessel, heart, kidney and adrenal glands. This local production of angiotensin influences vascular, cardiac and renal function & structure[11].

Angiotensin II Receptors
The effect of angiotensins are exerted by two subtypes of receptors now designated AT, and AT_2 [12,13]. AT, receptor has high affinity for losartan and most biological effects are mediated through this receptor where as AT, has low affinity for losartan and poorly defined but may exert antiproliferative, proapoptotic and vasodilator effect.

Clinical Pharmacology of ACEI & ARBs

Currently 12 ACE inhibitors are approved for use (eleven marketed) include captropril, lisinopril, enalapril benzepril, fasinopril, moexipril, perindropril. FDA approved ARBs are candesartan cilexetil, irbesartan , lasartan, telmisartan, valsartan and eprosartan .

ACEI and ARBs in chronic kidney diseases in Adults

Chronic kidney disease (CKD) is defined as either kidney damage or GFR < 60ml/min 1.73 m^2 for ≥ 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies[14]. Adverse outcomes of chronic kidney disease can often be prevented or delayed through early detection and treatment. Earlier stages of chronic kidney disease can be detected through routine laboratory measurements. According to the K/DOQI CKD Classifications

Stages of chronic Kidney disease[14] are

Stage	Description	GFR ml/min/1.73 m^2
1	Kidney damage with normal or ?GFR	≥90
2	Kidney damage with mild ?GFR	60-89
3	Moderate ?GFR	30-59
4	Severe ?GFR	15-29
5	Kidney failure	<15 or dialysis

Mechanism of effects of ACE Inhibitors and ARBs to slow progression of CKD[15]

1. ACE inhibitors and ARBs reduce blood pressure
Hypertension accelerates the progression of kidney disease. The extent of blood pressure lowering correlates the activity of renin angiotensin system (RAS). ACEI and ARBs have greater antihypertensive effect in condition in which pressure is maintained through stimulation of RAS. By cotrast they have a lesser antihypertensive effect in condition in which pressure is maintained through ECF volume overload and concomitant suppression of RAS . CKD is associated with both stimulation of RAS and ECF volume overload. ACEI & ARBs reduce intraglomerular pressure as well as systemic blood

pressure which contributes to their beneficial effect of slowing the progression of kidney disease.

2. ACEI& ARBs reduce proteinuria:

Proteinuria is associated with faster progression of kidney disease. In controlled trial in CKD, ACE /< inhibitors & ARBs reduce proteinuria by approxiamtely 35 to 40 % which is greater than other antihypertensive agent. The nondihydropyridine agents such as verapamil and diltiazem have significant antiproteinuric effect in diabetic but not in nondiabetic kidney disease. The dihydropyridine agent such as amlodipine and nifidipine generally have no consistent effect on protein excretion. Both ACE inhibitors and ARBs reduce glomerular permeability barrier to proteins and limit proteinuria and filtered protein dependent inflammatory signals. The beneficial effects of ACE inhibitors on progression of kidney disease appears to be greater than expected due to their antiproteinuric effect.

3. ACEI & ARBs slow the progression of kidney disease by "class effect" mechanism in addition to antihypertersive and antiproteinuric effects.

The mechanism for this effects include (1) decrease glomerular intracapillary pressure (2) reduction in permselectivity (3) alteration in the function of mesangial cells (4) interfering with angiotensin mediated generation of free radical formation.

Adverse effect of ACEI & ARBs:

The incidence of adverse effects varies from 5 to 20%. Adverse effects are hypotension, worsening kidney function (acute renal failure), hyperkalaemia, cough, angioneurotic oedema, skin rash, neutropenia, agranulocytosis, fetal abnormalities.

Clinical Studies:

Meta analysis of randomised clinical trials suggest ACEI have substantial beneficial effect in delaying progression of renal disease and ACEIs are more effective than other antihypertensive agents. ACEI reduce urinary total protein and favourable impact on long term renal functions[16,17]. ARBs are alternative drugs inhibiting renin angiotensin system and has renoprotective activity. Observation of one study, use of ACEI and ARBs alone or in combination showed combination of drugs cause significantly a greater antiproteinuric effect. In this study losartan 25 mg and enalapril 10 mg was used alone and in combination on 17 patients in each group for 3 months with chronic glomerulonephritis (Ccr 36-93 ml/min). Reduction of proteinuria in losartan group is 25.35%, in enalapril group is 45.07% and enalapril + losartan group is 65.96% (P=0.0/09, combined group vs. losartan group). Treatment with losartan is associated with less fall in GFR. Decreased blood pressure was pronounced in combined group[18]. Observation from another study described fasinopril 20 mg/day, lrbesartan 150 mg /day and, combination of these two drugs in 3 groups of patients with chronic glomerulonephritis (Ccr 40-106 ml/min) was used. Preliminary results from after 6 weeks showed reduction of proteinuria is much greater in combined group[19]. Similar result was shown by another study that co-administration of losartan and enalapril exerts additive antiproteinuric effect in (IgA) nephropathy. Enalapril and losartan administration alone reduced proteinuria by same extent, but no further reduction when doses were doubled[20].

Chronic kidney disease (CKD) is emerging as a new health pandemic. Underlying the global rise in CKD is an increase in diabetic nephropathy which is the leading cause of end stage renal disease (ESRD). In terms of renal protection, there are ample data to support a role for both ACEI and ARBs to prevent the progression from microalbuminuria to overt albuminuria in both type I and type II diabetes. However, when progression of renal disease is used as an end point, protection has been demonstrated with ACEI only in type I but not for type II diabetes. In the later group, only ARB have been shown to slow progression of ESRD[21]. Cardiovascular protection effect of ACEI in high risk population is widely appreciated. Most head to head comparisons between ACEI and ARB have yeilded comparable cardiovascular protective effect with ARBs being associated fewer side effects [21].

Losartan (angiotensin II antagonist) has an antihypertensive effect equivalent to ACE inhibitors, however its role in microvascular complication is not yet known. However, in one study showed losartan remarkably improves albuminuria, benefit in autonomic or peripheral neuropathy in normotensive type II diabetes seen over 12 weeks[22]. Several clinical trials have established the benefits of ACEI & ARBs

in patients with diabetes. ACEI have shown to delay renal decline in patients with type I diabetes, whereas protective effect with type II diabetes is less clear. The ARBs have shown to provide significant benefits with type II diabetes, both early (microalbuminuria) and late (proteinuria) stages of renal decline. In the Irbesartan Diabetic Nephropathy Trial (IDNT) and the reduction of end points in NIDDM with the angiotensin II antagonist losartan(RENNAL) study, ARB therapy significantly reduced the progression of overt nephropathy (composite of doubling of serum creatinine, ESRD and death) benefit that has not been shown for ACE inhibitor.

Addition of ARB with maximized ACE inhibitor

Prolonged angiotensin coverting enzyme ACE inhibitors therapy lead to angiotensin I accumulation which may escape ACE inhibition generate angiotensin II, stimulate angiotensin II subtype AT, receptor and exerts deleterious renal effects in patient with chronic renal disease like vasoconstriction, salt retension, inflammation and fibrosis and enhance the activity of central & peripheral sympathetic activity. Furthermore, pathway other than ACE may be responsible for angiotensin II generation particularly in tissues of blood vessels. ARBs can overcome these shortcomings of ACEI by antagonizing the AT1 receptors.

In addition, because AT2 receptor mediate the beneficial effects of angiotensin II, by blocking ATI receptors with ARBs, angiotensin II would be available to stimulate the AT2 receptors[24].

Combination treatment with ACEI & ARBs safely retards progression of non diabetic renal disease compared with monotherapy of each drug at its maximum dose[25]. The benefit of combination therapy of its antiproteinuric effect was different between 1gA and diabetic nephropathy over the 12 weeks trial. 24 hours urinary total protein excretion rate was significantly reduced by combination therapy in patients with IgA nephropathy but no reduction with diabetic nephropathy with combination therapy[26] however, one study showed dual blockade of renin angiotensin system is superior to maximal recommended dose of ACE inhibitions with regard to lowering of albuminuria and blood pressure in type I patients with diabetic nephropathy. Another study suggests that combined antihypertensive therapy with either a calcium channel blocker (CCB) plus an ARB or an ACEI plus ARB exerts an antiproteinuric effect in patients with type II diabetic nephropathy with mild renal impairment. ACEI and ARB combination had more profound effect, but it was associated with increase in serum potassium concentration and worsening of renal anaemia. Thus, combination of CCB and ARB should be first line for antihypertensive therapy in those overt type 2 diabetic nephropathy[28]. To sumerise the combination therapy ACEI & ARBs showed benefical effect in both non diabetic and type I diabetic nephropathy patients. In type II diabetic nephropathy ARB plus CCB combination is better option of combination treatment.

Patient treated with ACE inhibitor & ARBs

Patient treated with ACEI & ARBs should be monitored for hypertension, decrease GFR and hyperkalaemia[15]. At initiation and increase in dose of ACE inhibition or ARB, the level of blood pressure, GFR and serum potassium should be measured to establish a "baseline" or "new baseline". Transient abrupt decrease in blood pressure occur in about 2.5% of patients. Clinician should be cautious to lower systolic blood pressure below 110 mm Hg. Causes of hypotension in CKD are excessive dose of antihypertensive agents, extracellular fluid depletion (diuretics), cardiovascular diseases (myocardial infarction, heart failure, arrhythmia, valvular disease, pericarditis), neurological diseases, liver disease, haemorrhage & sepsis[15].

An early decrease in GFR is defined as a decrease in GFR by more than 15% from baseline within 4 weeks after initiation of ACEI or ARB. The reported incidence varies from 4% to 17% and most common causes are ECF volume depletion, excessive dose of ACEIs or ARBs and concomitant use of diuretics or NSAIDs[15]. If GFR decreases by more than 30% over base line, the dose of ACEI or ARB may be reduced and GFR reassessed. If GFR does not return to baseline within appropriate interval ACEI or ARBs should be discontinued with alternative antihypertensive agents. Hyperkalaemia is defined when single measurement of serum potassium > 5 mEq/1, > 6 mEq/L, or persistant or single increase of

0.5 mEq/1 above baseline. Reported incidence of hyperkalemia ranges from 1% to 62.5% of patients. Causes of hyperkalaemia in CKD are food, acidosis, hyperglycaemia, hyperproteinemic hyperaldosteronism, oliguria and drugs[15].

Conclusion

Chronic kidney disease is emerging as new health pandemic. Emerging evidences strongly suggest that inhibition of renin-angiotensin-aldosterone system confers significant renal and cardioprotection for patient with CKD. Several large scale, prospective randomized studies with clinical end point have been performed with ACEI or ARBs alone or in combination both in non diabetic and diabetic renal disease.

Both ACEls or ARBs can slow progression of chronic glomerulonephritis alone. However, recent studies suggest beneficial effect are much pronounced in combined group. Both ACEI & ARB can prevent the progression from microalbuminuria to overt albuminuria in both type I and type II diabetes. However when progression of renal disease is used as an end point, protection has been demonstrated with ACEI for Type 1 not Type II diabetes. In type II only ARB have been shown to slow progression to ESRD. Combination of ACEI and ARB is superior than maximum ACEI dose in Type I diabetes. Whereas calcium channel blocker (CCB) and ARB combination is better option for Type II diabetes. Patients treated with ACEI or ARB should be monitored for hypertension, decreased GFR and hyperkalaemia. These two drugs should not be used in pregnancy for risk of foetal abnormality.

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