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The Role of Renin Angiotensin System Inhibitors in Renal Protection: Lessons from Clinical Trials

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1. Introduction

The prevalence of chronic kidney disease (CKD) is on the rise, and it is estimated that more than 26 million Americans suffer from CKD[1]. The leading risk factors in the development of CKD are hypertension (HTN), diabetes mellitus (DM) and obesity. Because of the increasing prevalence of these risk factors as well as their frequent coexistence in the same patient, prevention strategies that would be able to decrease the progression of CKD to end stage renal disease (ESRD) are of paramount importance.

There is a growing body of evidence showing that the activation of the renin angiotensin aldosterone system (RAAS) plays an important role in the development of cardiovascular and renal disorders[2,3]. RAAS is one of the key players in human physiology, and under normal physiological conditions it regulates blood pressure homeostasis, water balance, renal function and cellular growth. RAAS consists of a cascade of peptide hormones, with the enzyme renin catalyzing the first step in a cascade leading to the production of angiotensin I (AngI) from a precursor angiotensinogen (Figure 1). The cleavage of angiotensinogen, catalyzed by renin, is the rate-limiting step in RAAS activation. AngI does not possess vasoconstricting abilities, and it is cleaved by angiotensin-converting enzyme (ACE) into active angiotensin II (AngII). AngII binds to angiotensin receptors and exerts powerful vasoconstricting abilities. AngII also activates aldosterone production, and regulates sodium and water reapsorption (Figure 1). The kidneys are one of the major targets for RAAS as evidenced by the robust expression of RAAS components and receptors in the kidney[4]. Renal effects of AngII include regulation of renal blood flow, glomerular filtration rate (GFR) and sodium and water balance[5]. Upregulation of renal RAAS has been linked to the development of CKD in both HTN and DM[4].

Hence, therapies that modulate RAAS have emerged as essential tools in decreasing the progression of CKD. Pharmacological inhibition of RAAS can be obtained via three different mechanisms: 1. Inhibition of conversion of AngI to active AngII via angiotensin I converting enzyme inhibitors (ACEI); 2. Selective inhibition of angiotensin receptor 1 (AR-1) via angiotensin receptor blockers (ARB); 3. Direct inhibition of AngI production via direct rennin inhibitors (DRI).
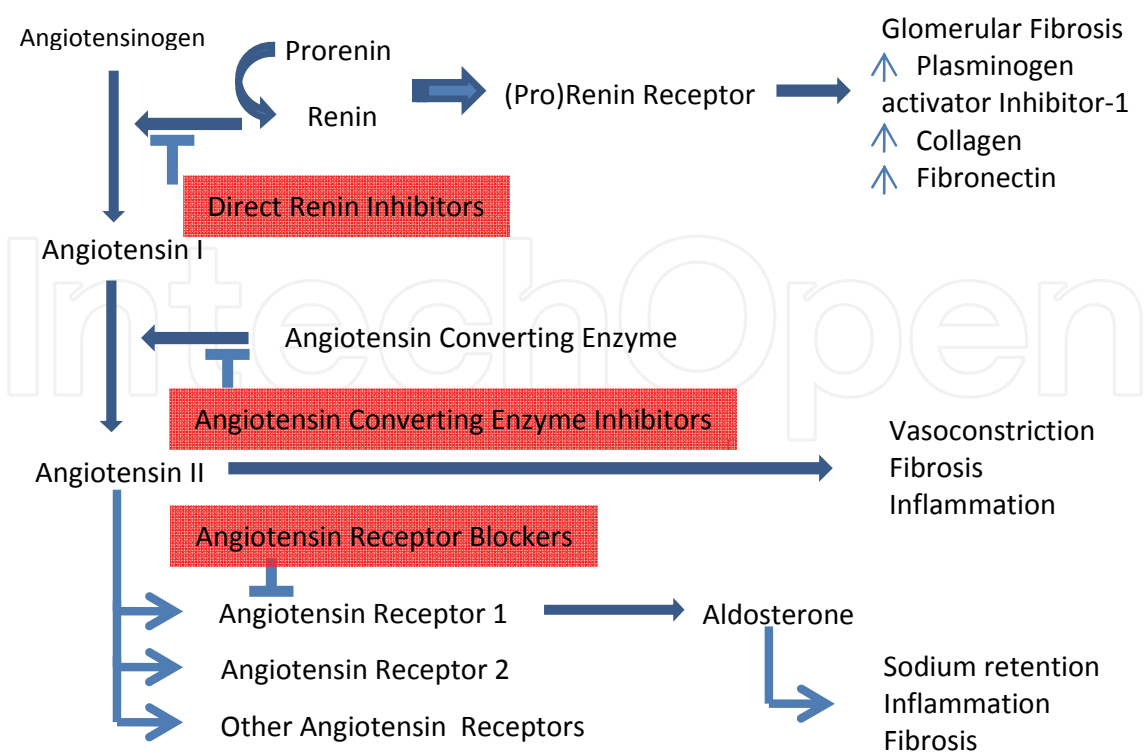
Fig. 1. Renin Angiotensin System Activation Cascade and its Effects on Target Tissues

In this chapter we will summarize the role of RAAS inhibitors on renal outcomes obtained from large clinical outcome trials. Clinical outcome trials have become an essential tool in evaluating treatment strategies and are now a cornerstone of evidence-based medicine. In addition, we will outline future RAAS modulation strategies that may become an important part of the clinical armamentarium for renal protection and prevention of CKD in the future.

2. ACEI in patients with type 1 diabetes mellitus and nephropathy

Patients with DM are more prone to cardiovascular and renal complications. Diabetic nephropathy is the leading cause of ESRD in developed countries [6-8]. Even small amount of albumin in the urine (microalbuminuria) strongly predicts the development of diabetic nephropathy[9]. Since RAAS plays one of the most important roles in renal physiology, several clinical studies have been conducted to evaluate the effect of ACEI on the progression of diabetic nephropathy[10-12]. The landmark study by Lewis et al. [1993], examined the effect of ACEI captopril on the progression of diabetic nephropathy in patients with type 1 diabetes mellitus (T1DM)[13]. The primary endpoint was defined as doubling the serum creatinine to at least 2 mg/dL. Treatment with captopril was associated with a 48% risk reduction for doubling the serum creatinine as compared to the placebo. The beneficial effects of ACEI on the progression of diabetic nephropathy were subsequently confirmed by the results of two large randomized clinical trials in the patients with T1DM[11,12]. The North American Microalbuminemia Study Group evaluated whether ACEI captopril reduces the progression of microalbuminuria to overt diabetic nephropathy in 409 normotensive patients with T1DM[11]. The primary outcome was the progression of microalbuminuria (defined as albumin excretion rate of 20-200 μg/min) to clinical proteinuria (defined as albumin excretion rate of > 200 μg/min, and at least 30% above the baseline). Over a median 3 year follow-up period, patients

receiving captopril had a 67.8% risk reduction as compared to those receiving the placebo. According to the results of this clinical trial, for every 8 patients treated with captopril, the progression to proteinuria will be prevented in 1 patient in a 2-year period[11]. The EURODIAB controlled trial of lisinopril in insulin dependent diabetes (EUCLID) studied 530 normotensive T1DM patients either with little or no albuminuria (normoalbuminuria, albumin excretion rate < 20 μg/min) or with microabuminuria (albumin excretion rate > 20 μg/min)[12]. After a 2-year follow-up, the albumin excretion rate was 18.8% lower in patients who received lisinopril. When patients with normoalbuminuria and microalbuminuria were examined separately, the relative treatment difference was 49.7% in the microalbuminuric group and only 12.7% in the normoalbuminuric group. A stratified analysis of the normoalbuminuric group showed that most of the beneficial effect occurred in patients with albumin excretion rate >5 μg/min[12]. A meta-analysis of 12 clinical trials examining the effect of ACEI on T1DM confirmed the protective effect of ACEI on the progression of diabetic nephropathy in T1DM patients[14]. T1DM patients with higher urinary albumin excretion rates appear to achieve a greater benefit from RAAS blockade with ACEI[14].

A summary of the clinical trials on RAAS inhibition in T1DM patients with nephropathy is presented in Table 1.

Study	ACEI	Number of Patients	Renal Outcome	Risk Reduction (%)	Reference
Collaborative Study Group	Captopril	207	Doubling baseline creatinine	43	13
North American Microalbuminuria Study Group	Captopril	215	Progression to clinical proteinuria (AER > 200μg/min)	67.8	11
EUCLID	Lisinopril	530	Change in AER in all patients	18.8	12
			Change in AER in normoalbuminuric patients	12.7 (NS)	
			Change in AER in microalbuminuric patients	49.7	

ACEI: Angiotensin converting enzyme inhibitor; AER: Albumin Excretion Rate; NS: not significant

Table 1. Clinical Trials in Patients with Type 1 Diabetes Mellitus and Nephropathy

3. ACEI and ARB in type 2 diabetes mellitus and nephropathy

Nephropathy secondary to type 2 diabetes mellitus (T2DM) accounts for the majority of the increase in incidence and prevalence of renal failure in the last two decades. Healthcare costs for patients with ESRD are already reaching more than $18 billion per year in the United States and are on the rise. Since ACEIs have been shown to provide renal protection in patients with T1DM and microalbuminuric nephropathy[11-13], it was of paramount interest to examine whether ACEIs have similar effect in patients with T2DM. The MICRO-HOPE substudy of the HOPE trial examined the effect of ACEI ramipril on the development of nephropathy in 3,577 patients with type 2 diabetes mellitus (T2DM)[6,15]. Over a 4.5 year follow-up period, treatment

with ramipril decreased the risk of development of overt nephropathy by 24%. However, in the follow-up analysis no change in the slope of serum creatinine rise or in the incidence of doubling serum cratinine was observed[15]. The Bergamo Nephrologic Diabetes Complication (BENEDICT) trial randomized 1,204 T2DM hypertensive patients with normal baseline renal function to receive ACEI trandolapril, calcum channel blocker verapamil or combination therapy (trandolapril plus verapamil). The primary endpoint was the development of persistent albuminuria. After a 3 year follow-up, patients who received trandolapril had a lower incidence of albuminuria, and the effect was not enhanced with the addition of verapamil[16]. The effect of verapamil alone was similar to that of the placebo[16]. Since the development of albuminuria is a major risk factor for the cardiovascular complications and death in this patient population, the authors concluded that in T2DM hypertensive patients with preserved renal function, ACEIs may be the treatment of choice[16]. In the subsequent BENEDICT-B trial they examined the effects of the addition of verapamil on trandolapril therapy in hypertensive T2DM petients with established microalbuminuria[17]. The BENEDICT-B trial showed that addition of verapamil did not improve albuminuria in T2DM patients with nephropathy. Conversely, the trandolapril treatment caused a reduction of albuminuria in 50% of the patients, and this reduction translated to a significantly lower rate of cardiovascular complications in these patients [17]. These results are in sharp contrast to the DIABHYCAR study, which failed to show the beneficial effect of ACEI ramipril on cardiovascular and renal outcomes in T2DM patients with established albuminuria[18]. The lack of an effect due to ACEIs in the DIABHCYAR study may be attributed to a mixed patient population; both normotensive and hypertensive T2DM patients with albuminuria were included in the study.

The renal protection effect of ARB in patients with T2DM was studied extensively in the early 2000s. Two studies, the Irbesartan in Patients with Diabetes and Microalbuminuria (IRMA-2) and the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study, examined the effect of ARB in T2DM patients with microalbuminuria, but without overt diabetic nephropathy[19,20]. In patients with T2DM the presence of microalbuminuria increases the risk of development of diabetic nephropathy (defined as albumin excretion rate > 200 μg per minute) by a factor of 10 to 20. The IRMA-2 study showed that treatment with irbesartan significantly reduces the rate of progression of microalbuminuria to overt diabetic nephropathy in patients with T2DM[19]. Furthermore, the study revealed that treatment with irbesartan was associated with significantly more common restoration of normoalbuminuria as compared to standard therapy[19]. All these effects were achieved independently of the systemic blood pressure. The DETAIL study compared renoprotective effects of ACEI enalapril and ARB telmisartan[20]. In this head-to-head comparison of these two classes of RAAS inhibitors, the authors showed that both enalapril and telmisartan were equally effective in preventing the progression of renal dysfunction, measured as a decline in the GFR[20]. Two other studies, the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) examined patients with T2DM, but with a higher rate albuminuria and established renal insufficiency [10,21]. In the RENAAL study, treatment with ARB losartan was associated with a 25% reduction of risk for doubling serum creatinine level and the risk of developing ESRD was reduced by 28%[21] Again, the favorable effect seemed to be independent of blood pressure effect. The IDNT compared the effect of ARB irbesartan and calcium-channel blocker amlodipine against the progression of nephropathy[10]. The primary endpoint was a composite of doubling the serum creatinine concentration, development of ESRD, renal transplantation and death. IDNT revealed that irbesartan decreased the relative risk of

reaching the primary end point by 20% when compared to the placebo and by 23% when compared to amlodipine. IDNT data showed that the renoprotective effect of irbesartan in patients with T2DM and overt nephropathy is due to the slowing of the progression of glomerulopathy[10]. The Incipient to Overt: Angiotensin II Blocker Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study examined the effect of ARB telmisartan in 527 normotensive and hypertensive T2DM Japanese patients with microalbuminuria[22-24]. After a follow-up of 52 weeks, transition to overt nephropathy was significantly lower with telmisartan[23,24]. In a trial comparing telmisartan versus losartan in T2DM patients with overt nephropathy (AMADEO) both agents reduced blood pressure, however telmisartan was more effective in reducing albuminuria as compared to losartan[25]. In the head to head comparison of ACEI ramipril and ARB telmisartan (ONTARGET) study, an increase in urinary albumin secretion was significantly lower in the telmisartan group as compared to ramipril[26,27].

A summary of the clinical trials in patients with T2DM and nephropathy is outlined in Table 2.

Study	ACEI or ARB	Number of Patients	Renal Outcome	Risk Reduction (%)	Reference
MICRO-HOPE	Ramipril (ACEI)	3,577	Overt nephropathy	24	6, 15
BENEDICT	Trandolapril (ACEI) with or without verapamil	1,204	Development of persistent albuminuria (>200 μg/min)	Delay of onset of albuminuria by factor 2.1	16
BENEDICT-B	Trandolapril (ACEI) vs. Trandolapril/Verapamil	281	Development of persistent albuminuria (UAE >200 μg/min)	NS (between trandolapril alone vs. trandolapril/verapamil)	17
DIABHYCAR	Ramipril (ACEI)	4,912	Combined incidence of cardiovascular death, non-fatal myocardial infarction, stroke, heart failure leading to hospital admission, and end stage renal failure	0.97 (NS)	18
IRMA-2	Irbesartan (ARB)	590	Development of persistent albuminuria (UAE >200 μg/min, or ≥ 30% from baseline)	HR 0.56 (150 mg group) HR 0.32 (300 mg group)	19
DETAIL	Telmisartan (ARB) vs. enalapril (ACEI)	250	Change in GFR	ARB not inferior to ACEI	20
RENAAL	Losartan	1,513	Composite of doubling serum creatinine, ESRD or death	25	21
IDNT	Irbesartan (ARB) vs. amlodipine	1,715	Doubling baseline serum creatinine, onset of ESRD, serum creatinine of 6mg/dL and death from any cause	20 (vs. placebo 23 (vs. amlodipine)	10
INNOVATION	Telmisartan (ARB)	527	Transition rate from incipient to overt nephropathy (UACR > 300 mg/g and increase ≥ 30% from baseline)	55	23,24
AMADEO	Telmisartan (ARB) vs. Losartan (ARB)	860	Change in UPC from baseline	Telmisartan superior to losartan (29.8% vs. 21.4% reduction)	25
ONTARGET	Ramipril (ACEI), Telmisartan (ARB) or both	25,620	Composite of dialysis, doubling of serum creatinine, and death	HR 1.00 (Ramipril vs Telmisartan) HR 1.09 Combination Therapy	27

ACEI: Angiotensin converting enzyme inhibitor; AER: Albumin Excretion Rate; GFR: Glomerular Filtration Rate; UACR: Urinary albumin-to-Creatinine ratio; UPC: Urinary Protein-to-Creatinine; HR: Hazard Ratio; NS: not significant

Table 2. Clinical Trials in Patients with Type 2 Diabetes and Nephropathy

As a result of the renoprotective effect of RAAS blockade in T1DM and T2DM patients with established albuminuria, the American Diabetes Asociation (ADA) recommends using ACEI and ARBs in diabetic patients with nephopathy[28]. Specifically, the ADA recommends ACEI in hypertensive T1DM patients with albuminuria and ACEI or ARB in hypertensive T2DM patients with albuminuria. In hypertensive T2DM patients with already established renal insufficiency, ARBs are recommended as a first line of treatment[28].

Even though ACEIs and ARBs have become a cornerstone of treatment of diabetic patients with established nephropathy (secondary prevention), it is still unclear whether RAAS blockade may be beneficial in preventing renal damage in diabetic patients without proteinuria. More recent clinical trials focused on the effect of ACEIs and ARBs on normotensive diabetic patients with normal renal function in order to examine whether early RAAS inhibition could prevent the development of renal disease in this patient population. It is estimated that about 20-30% of T1DM and T2DM patients develop nephropathy over the course of their illness[28]. The DIRECT program was established to investigate the effect of ARB candersartan in the development of diabetic retinopathy, and as a secondary outcome it addressed the effect of candersartan in the primary prevention of diabetic nephropathy (DIRECT-Renal)[29]. They included 3,326 T1DM and 1,905 T2DM patients, and after a follow up of 4.7 years, candersartan did not prevent microalbuminuria in normotensive patients with either T1DM or T2DM[29]. The Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) examined the effect of ARB telmisartan on cardiovascular outcomes in ACEI intolerant patients[26,30]. In this multicenter multinational study they included 5,926 diabetic patients with known cardiovascular disease, but without microalbuminuria. After 56 months follow-up, no important difference was found in the composite renal outcome (dialysis, doubling serum creatinine, changes in albuminuria and GFR) between patients treated with telmisartan versus placebo[30]. In the Renin – Angiotensin System Study (RASS), the authors examined whether a blockade of RAAS with either ACEI enalapril or ARB losartan prevents the development of structural glomerular changes consistent with the nephropathy in renal biopsy specimens of 285 normotensive T1DM patients with preserved GFR[31]. The results showed no significant difference in the progression of glomerular structural changes among the treatment groups[31].

Taken together, the present evidence does not support the use of ACEI or ARB in the primary prevention of diabetic nephropathy in patients with T1DM or T2DM.

A summary of the clinical trials in patients with DM and without HTN and nephropathy is presented in Table 3.

4. Direct renin inhibitor aliskiren and renal protection

The recent discovery of (pro)rennin receptor has added a new perspective to the RAAS physiology, and has opened new avenues for drug development and RAAS targeting[32]. It has became clear that both prorenin and renin can bind to (pro)renin receptors and activate intracellular signal transduction pathway, independent of angiotensin receptor activation[33,34]. Activation of the (pro)rennin receptor-mediated pathway results in glomerular fibrosis, due to upregulation of transforming growth factor β (TGF β) and increased synthesis of plasminogen activator inhibitor-1 and fibrotic glomerular matrix components, fibronectin and collagen I (Figure 1)[35].

Study	ARB	Number of Patients	Renal Outcome	Risk Reduction (%)	Reference
DIRECT-Renal	Candesartan (ARB)	3,326 T1DM 1,905 T2DM	Primary Prevention of Diabetic Nephropathy (secondary outcome)	NS over placebo	29
TRANSCEND	Telmisartan (ARB)	5,926	Composite renal outcome (Dialysis, doubling serum creatinine, changes in albuminuria and GFR)	NS over placebo	30

ARB: Angiotensin Receptor Blocker; GFR: Glomerular Filtration Rate; NS: not significant

Table 3. Clinical Trials in Patients with Diabetes Mellitus without Hypertension and Proteinuria (Primary Prevention)

DRI aliskiren is the newest addition to RAAS blocking agents[36]. Preclinical studies offered very attractive effect of aliskiren in renal protection in diabetic and non-diabetic models of CKD. Aliskiren has been shown to have antihypertensive and a renoprotective effect in diabetic experimental nephropathy[37]. The profound effect of aliskiren on renal RAAS was due to selective renal accumulation (aliskiren renal/plasma concentration ratio of 60)[37]. The promising preclinical renoprotective effect of aliskiren was then tested in clinical trials in patients with diabetic nephropathy. In the largest to date Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study, 599 patients with T2DM, hypertension and nephropathy were enrolled[38]. The addition of aliskiren to the maximum renoprotective dose of ARB losartan further reduced albuminuria by 20%[38]. The reduction of albuminuria was achieved despite a non-significant decrease in blood pressure, suggesting that the renoprotective effect of aliskiren was independent of the blood pressure control[38,39]. In the subsequent AVOID subanalysis, aliskiren was found to decrease urinary aldosterone level, which may be partially responsible for the additional renoprotective effect of aliskiren seen in the AVOID study[40]. The ongoing Aliskiren Trial in Type 2 Diabetic Nephropathy (ALTITUDE) study will give further insights into whether a dual RAAS blockade with either ACEIs or ARBs in combination with DRI aliskiren is beneficial in preventing progression of nephropathy in T2DM[41].

5. Controversies of dual RAAS blockade

5.1 Rationale for dual ACEI and ARB therapy
Despite proven efficacy of ACEIs and ARBs in decreasing the progression of renal decline and cardiovascular complications in patients with DM and nephropathy, residual cardiovascular and renal complications are still high[42]. Dual RAAS inhibition has a theoretical advantage over single therapy, since all classes of drugs that target RAAS have

been proven to possess renal and cardiovascular protective effects. The rationale of dual blockade lies in the fact that inhibition of AngII production by ACEIs cause an increase in AngI levels, and increased levels of AngI lead to additional production of AngII via ACE-independent pathways (ACE escape). Blockade of AT1 receptors by ARBs leads to a compensatory increase of AngII[43], which may partly offset AT1 blockade by ARB (AngII escape). Dual blockade with ACEIs and ARBs has a theoretical advantage over monotherapy, since it may offer a more effective overall inhibition of RAAS. However, results from large clinical trials have been inconsistent. The results from the Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE) trial, which was the only large clinical trial so far showing improved renal outcomes with combination ACEI/ARB therapy, were recently retracted due to inconsistencies in the data[44,45]. In the OTNTARGET study, dual blockade with ACEI ramipril and ARB telmisartan was associated with worse renal outcomes and an increased risk of acute renal failure[27]. Subgroup analysis of the ONTARGET data showed that a dual blockade was harmful primarily in patients with a low renal risk, which does not exclude the potential benefit of a dual ACEI/ARB blockade in patients with high renal risk (i.e. patients with DM and nephropathy).

Ongoing studies on dual ACEI/ARB blockade in patients with DM and nephropathy: Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)[46] and the Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO)[47] are designed specifically to assess ACEI/ARB combination therapy in high risk patients. The VA-NEPHRON-D will assess combination of ACEI lisinopril and ARB losartan on the progression of kidney disease in patients with DM and nephropathy[46]. The LIRICO trial will evaluate the cardiovascular and renal effects of ACEI/ARB combination therapy in patients with preexisting albuminuria and at least one more cardiovascular risk factor (cigarette smoking, DM, HTN, visceral obesity, dyslipidemia, or family history of cardiovascular diseases)[47]. Results of these studies should provide more information on the usefulness of dual ACEI/ARB therapy in high risk patients.

5.2 Rationale for ACEI/ARB and DRI combination therapy

Both ACEI and ARB therapy cause a compensatory increase of plasma rennin activity (PRA) up to 15-fold[48,49]. High PRA has been shown to increase the risk of myocardial infarction in patients with HTN[50], and is associated with increased mortality in patients with heart failure[51]. DRI aliskiren inhibits ~75% of PRA, and selectively accumulates in the kidney[52]. Thus, combination therapy of aliskiren and either ACEIs or ARBs may provide an additional benefit especially in patients with preexisting renal impairment and high PRA. As previously mentioned, the AVOID study offered promising results of ARB and DRI combination therapy in T2DM patients with nephropathy[39,40]. The ongoing ALTITUDE study will assess combination therapy with either ACEI or ARB and DRI aliskiren in 8,600 T2DM patients with nephropathy and/or cardiovascular disease. The primary endpoint is the time to first event for the composite endpoint of cardiovascular death, resuscitated death, myocardial infarction, stroke, unplanned hospitalization for heart failure, onset of ESRD or doubling of baseline serum creatinine concentration[41].

A summary of the clinical trials evaluating combination RAAS therapy is presented in Table 4.

Study	Combination Therapy	Number of Patients	Renal Outcome	Risk Reduction (%)	Reference
COOPERATE	ACEI/ARB		RETRACTED (Inconsistency of data)		44,45
ONTARGET	Ramipril (ACEI), Telmisartan (ARB) or both	25,620	Composite of dialysis, doubling of serum creatinine, and death (primary endpoint) Dialysis, doubling serum creatinine (secondary endpoints)	HR 1.09 for primary outcome HR 1.24 for secondary outcome Worse renal outcome and increased risk of ARF in combination group	27
VA NEPHRON-D	Combination Lisinopril (ACEI) and Losartan (ARB)		Time to reduction in eGFR >50%, ESRD and death	Ongoing	46
LIRICO	Combination of ACEI and ARB	2,100	ESRD and Renal function (secondary outcome)	Ongoing	47
AVOID	Combination of losartan (ARB) and aliskiren (DRI)	599	Changes in UACR and eGFR (*post hoc* analysis)	Significant difference in number of patients with a >50% reduction in UACR from Baseline Reduction in eGFR decline only in group with HTN >140/90 mmHg at baseline	39, 40
ALTITUDE	Combination of aliskiren (DRI) with either ACEI or ARB	8,600	Time to first event for the composite endpoint of cardiovascular death, resuscitated death, myocardial infarction, stroke, unplanned hospitalization for heart failure, onset of ESRD or doubling of baseline serum creatinine concentration	Ongoing	41

ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; DRI: Direct Renin Inhibitor; AER: Albumin Excretion Rate; HR: hazard ratio; ARF: Acute Renal Failure; ESRD: End Stage Renal Disease; eGFR: estimated Glomerular Filtration Rate; UACR: Urinary Albumin Creatinine Ratio; NS: not significant

Table 4. Clinical Trials with Dual Renin Angiotensin System Blockade

Ongoing and future studies should answer questions regarding safety and efficacy of RAAS combination therapy, as well as to to assess specific patient populations that may benefit from a more intense RAAS blockade.

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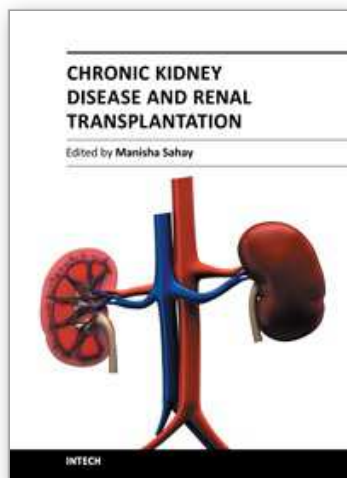
Chronic Kidney Disease and Renal Transplantation

Edited by Prof. Manisha Sahay

This valuable resource covers inpatient and outpatient approaches to chronic renal disease and renal transplant with clinical practicality. This first section of the book discusses chronic disease under distinct topics, each providing the readers with state-of-the-art information about the disease and its management. It discusses the fresh perspectives on the current state of chronic kidney disease. The text highlights not just the medical aspects but also the psychosocial issues associated with chronic kidney disease. The latest approaches are reviewed through line diagrams that clearly depict recent advances. The second section of the book deals with issues related to transplant. It provides effective and up-to-date insight into caring for your transplant patients.

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