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Drug and Diabetic Nephropathy

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1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defect in insulin secretion, insulin action, or both. It is the leading cause of heart disease, adult blindness, and amputation of the lower extremities¹. Diabetic patient suffer from a number of complications. Of these – hypertension, retinopathy, neuropathy, peripheral vascular disease – are most frequent ones and are responsible for considerable morbidity and mortality. Diabetic nephropathy (DN) is a chronic progressive kidney disease with high morbidity and mortality. There is a gradual loss of renal function ultimately leading to end stage renal disease (ESRD) where life is not sustainable without renal replacement therapy². The course of DN is characterized by early elevation of arterial blood pressure, increasing albuminuria with gradual decline in glomerular filtration rate (GFR) of 10-12 ml.min⁻¹.year⁻¹^{3,4,5}. The degree of albuminuria is closely related to the progression of DN⁶. Diabetic patients with nephrotic range proteinuria have the fastest decline in GFR⁷ and the shortest survival time⁸.

Proteinuria has been considered an indicator of glomerular disease severity⁹. The proposed effects of proteinuria on the kidney include increased severity of glomerulosclerosis, tubulointerstitial inflammation, and subsequent fibrosis, thereby contributing to progressive renal function loss. These facts have permitted the establishment of a “proteinuria hypothesis” that consists of three postulates: higher levels of proteinuria predict adverse clinical outcomes; reduction of proteinuria correlates with slowing of renal progression; and proteinuria is a surrogate end point and target of clinical interventions¹⁰.

Key to the development of DN is the hyperglycemic state, which has been postulated to mediate its effect in several different ways. First, glucose in sustained high concentrations may be directly toxic to cells, altering cell growth and gene and protein expression and increasing extracellular matrix and growth factor production¹¹. Second, glucose may induce its effects indirectly through the formation of metabolic derivatives such as oxidants and glycation products^{12,13}. Formation of advanced glycation end-products (AGES) may damage cells because of modifications to extracellular matrix proteins and to cellular proteins¹⁴.

The renin-angiotensin-aldosterone system (RAAS) is a coordinate cascade of proteins and peptide hormones, the principal effector of which is angiotensin II. In kidney it is regulated via a self-contained renin angiotensin system in a paracrine fashion¹⁵. Renin is an enzyme produced by the kidney in response to a number of factors including adrenergic activity (β_1 -

receptor) and sodium depletion. Renin converts circulating glycoprotein, angiotensinogen, into the biologically a high potent vasoconstrictor angiotensin II¹⁶.

Angiotensin II acts on the heart and the kidneys by binding to the G protein-coupled receptors type 1 and type 2. The angiotensin receptor type 1 mediates the more deleterious effects of angiotensin II – that is, vasoconstriction and cardiac and vessel hypertrophy¹⁷.

In diabetes mellitus, local activation of the renin angiotensin system or increased intrarenal sensitivity to angiotensin II, especially angiotensin II receptor 1 occurs. Several studies have demonstrated that, in spite of normal or suppressed plasma renin activity, the intrarenal content of renin is increased. This increase can contribute to the progression of diabetic nephropathy via several hemodynamic, tubular and growth promoting actions¹⁸.

Activation of the local renin angiotensin system also constricts the efferent more than the afferent arteriole. This glomerular hemodynamic change increases single nephron glomerular filtration rate in an attempt to maintain global glomerular filtration rate despite progressive loss of functioning nephrons in chronic kidney disease. However, if this change is sustained, it will likely result in glomerular injury and an accelerated loss of kidney function over time¹⁹.

Angiotensin II is the main effector of the RAAS and exerts its vasoconstrictor effect predominantly on the postglomerular arterioles, thereby increasing the glomerular hydraulic pressure and the ultrafiltration of plasma proteins, effects that may contribute to the onset and progression of chronic renal damage. Angiotensin II may also directly contribute to accelerate renal damage by sustaining cell growth, inflammation, and fibrosis. Interventions that inhibit the activity of the RAAS are renoprotective and may slow or even halt the progression of chronic nephropathies¹⁷.

A large number of studies established that progressive deterioration of renal function is the result of compensatory glomerular hemodynamic changes in response to nephron loss. In the widely used experimental model of renal mass reduction, the remaining nephrons undergo hypertrophy, reduced arterial resistance, and increased glomerular blood flow²⁰.

After nephron loss, the remaining nephrons develop glomerular capillary hypertension, and the single-nephron glomerular filtration rate (GFR) increase (hyperfiltration). These changes are thought to be adaptive in that they help to initially maintain the overall GFR. However, they have negative long-term effects and ultimately lead to renal insufficiency and ESRD.

Podocytes are glomerular epithelia cells for glomerular structure and function, surrounding glomerular capillaries and forming foot processes contributing to the filtration barrier and providing structural stabilization. The diabetic kidney abnormally regulates intraglomerular pressure with imbalance between afferent and efferent arteriolar vasodilatation leading to a 20 mmHg increase in glomerular pressure and allowing hypertension to be transmitted to the glomerulus²¹.

Besides these glomerular hemodynamic effects, other studies have revealed several nonhemodynamic effects of angiotensin II that may also be important in renal disease progression. These findings have suggested that angiotensin II may alter permselective properties of the glomerular capillary barrier by mediating contraction of the foot processes, ultimately changing slit-diaphragm architecture and allowing proteins to escape more easily into the urinary space²².

Nonhemodynamic effects of angiotensin II include increased production of reactive oxygen species; upregulation of cytokines, cell adhesion molecules, and profibrotic growth factors; induction of transforming growth factor- β (TGF- β) expression, increased synthesis of extracellular matrix proteins; stimulation of plasminogen activator inhibitor-1 production by endothelial and vascular smooth muscle cells; and macrophage activations and infiltrations²³.

There is increasing evidence that TGF- β is a major pro sclerotic mediator. Its production is stimulated by angiotensin II and by glucose directly. Preclinical studies have shown that TGF- β blockade prevents and also ameliorates DN^{24,25}.

In addition, to amplify some of the effects of angiotensin II, aldosterone may also directly contribute to endothelial dysfunction, aldosterone may also remodel human endothelium in vitro by increasing the size and stiffness of endothelial cells, which favors leakage through intracellular gaps²⁶.

In animal models, high intraglomerular capillary pressure impairs the size-selective function of the glomerular permeability barrier and causes protein ultrafiltration^{27, 28}. The secondary process of reabsorption of filtered proteins can contribute to renal interstitial injury by activating intracellular events. Local recruitment of macrophages by tubular cells that are loaded with ultrafiltered plasma proteins may contribute to interstitial fibrosis by engaging matrix-producing interstitial myofibroblasts. Macrophages also regulate matrix accumulation via release of growth factors, such as TGF- β and platelet derived growth factor (PDGF). TGF- β stimulates the transformation of interstitial cells into myofibroblasts. In addition proximal tubular epithelial cells communicate with interstitial fibroblasts to promote fibrogenesis via paracrine release of TGF- β . In rats with remnant kidneys at day 14, after the onset of proteinuria, TGF- β mRNA was upregulated in proximal tubular cells in parallel with early accumulation of the peritubular interstitium, suggesting that interstitial fibroblasts are the initial target of profibrogenic signals elicited by protein overreabsorption²⁹. Treatment of these rats with an angiotensin converting enzyme inhibitor (ACEI) at the same time limited excess protein overload and interstitial inflammatory cell infiltration and abrogated the abnormal TGF- β 1 gene expression in tubular cells that in all likelihood was responsible of myofibroblasts in surrounding areas. ACEI exerts beneficial effects in the glomerulus primarily by preserving the permselective barrier to proteins³⁰, thereby limiting proteinuria and filtered protein-dependent inflammatory and fibrogenic signals. The ACEI also may act locally by preventing nonhemodynamic effects of angiotensin II via apical angiotensin receptors on tubular cells, including renal cell proliferation and TGF- β 1 expression³¹.

In addition to albumin, transferrin, and Immunoglobulin, glomerular proteinuria results in ultrafiltration of high molecular weight precursor forms or complexes of growth factor proteins such as insulin like growth factor 1, hepatocyte growth factor and TGF- β 1. Inflammatory and vasoactive substances formed in excessive amounts by proximal tubuli are secreted toward the basolateral compartment of the cell and give rise to a inflammatory reaction in the interstitium that consistently precedes renal scarring. These processes can be accelerated by cytokines released by tubular epithelial cells and by inflammatory cells that accumulate in the interstitium when proteinuria is present³²⁻³⁶.

Both interstitial inflammation and progression of disease can be controlled by such drugs as ACEI, which strengthen the glomerular permeability barrier to proteins and thereby limit proteinuria and filtered protein-dependent inflammatory signals³⁷.

Lastly, the increased glomerular permeability may result in excess ultrafiltration of some complement protein fractions that may be directly toxic to proximal tubules and incite injury. In a subtotal nephrectomy model of renal insufficiency, C3 staining was associated with the appearance of interstitial infiltrate. Treatment with ACEI, which lowered proteinuria, also decreased C3 staining³⁸.

Recent studies utilizing transgenic rats with overexpression of the angiotensin II type 1 receptor in podocytes revealed that increased angiotensin receptor type 1 signaling in podocytes leads to structural podocyte damage and protein leakage³⁹. To support this finding from a therapeutic point of view, recent studies showed that ACEI and angiotensin receptor blocker (ARB) induce redistribution of the molecules in the slit diaphragm, which determine leakage of protein through glomerular filtration barrier⁴⁰⁻⁴².

There are some data showing that some of the beneficial effects of the RAAS blockade may be related to anti-inflammatory properties of ACEI and ARB⁴³. In a clinical study, Stevinkel et al found low plasma levels of tumor necrosis factor- α and C-reactive protein (CRP) in ESRD patients treated with ACEI⁴⁴. The benefit seen with these drugs is beyond that which would be expected from their antihypertensive effects.

The disassociation between doses needed to inhibit local tissue actions of angiotensin II and circulatory concentrations directly involved in blood pressure regulation may be due to reduced tissue penetration or higher tissue concentration of angiotensin II or its receptor⁴⁵. Increased RAAS activity and augmented angiotensin II receptor density in the diseased renal tissue together with reduced penetration of the drug may explain that higher doses are needed for complete RAAS blockade in the tissue responsible for antiproteinuric effects as compared to circulatory levels regulating systemic blood pressure⁴⁶.

Several underlying mechanisms may explain the blood pressure independent antiproteinuric effects of agents blocking the RAAS⁴⁷⁻⁵⁰. These include reduced intraglomerular hydraulic pressure independent of systemic blood pressure by vasodilatation preferentially of the post glomerular arterioles⁵¹ and improved permselective properties of the glomerular membrane⁵². In addition, ARBs may prevent the occurrence of proteinuria by reducing the loss of glomerular nephrin⁵³ and by reducing renal levels of proinflammatory cytokines such as TGF- β and CTGF⁵⁴.

Doses of ACEI that exceed their maximal antihypertensive dose have not been examined adequately, because, ultrahigh doses of ACEI (doses above those approved for antihypertensive treatment according to the FDA and the European agency for the evaluation of medicinal products) was thought to be associated with serious side effects⁵⁵⁻⁵⁷. In contrast, ARB has tested over a wide range of doses, without showing an increase of side effects with ultrahigh doses. Various clinical studies support the notion that the dose of ARB is inversely related to proteinuria, independent of blood-pressure control⁵⁸⁻⁶¹.

2. Rationale for higher dose

ACEI and ARB have been shown to reduce proteinuria, blood pressure and thereby retarded deteriorating kidney function in diabetic subjects. Doses of ACEI and ARB currently employed in clinical practice and even in experimental protocols are based essentially on the observation of the maximal effects of these drugs on blood pressure.

“Conventional” doses of these drugs may be insufficient to completely neutralize the anomalous activation of the RAAS, thus helping to explain their failure to achieve complete renal protection⁶².

So far reno protective therapy has been administered in doses extrapolated from the treatment of essential hypertension, with doses that may be suboptimal for reno protection. Studies of dose-related efficacy of ACEI or ARBs with dose titration based upon achieving the maximum antiproteinuric effect for reno protection have not been adequately performed⁶³.

The full reno- and cardiovascular protective potential of agents blocking the RAAS may not be reached in patients with diabetic renal disease when recommended doses of these agents are extrapolated from their blood pressure-lowering properties, which is currently the case for all ACEI and ARBs used for renoprotection. By exceeding currently recommended maximal dose, it has been demonstrated that within the recommended dose interval higher doses provide greater antiproteinuric effects than lower doses⁶⁴.

Recent trials investigating the ability of these agents to protect patients against target organ damage have now repeatedly shown that the higher doses were most effective, thus recommending more aggressive treatment in future⁶⁵.

The study of the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA-2) investigated the reversibility of kidney function changes after withdrawal of 2 years’ antihypertensive treatment. They included 133 hypertensive type 2 diabetic patients with persistent microalbuminuria, randomized to double-masked treatment with either placebo, irbesartan 150 mg, or irbesartan 300 mg once daily for 2 years. Arterial blood pressure, overnight urinary albumin excretion rate, and glomerular filtration rate (GFR) were determined repeatedly. In IRMA-2 trial the benefit of protein reduction was maintained only in the group that was treated with the higher dose of Irbesartan 300mg/day⁶⁶.

A double-masked randomized crossover trial included 52 (41 males) hypertensive type 2 diabetic patients with microalbuminuria on ongoing antihypertensive medication. Following 2 months wash-out (baseline), patients were treated randomly with irbesartan 300, 600, and 900 mg once daily, each dose for 2 months. This study by Rossing et al., revealed that ultrahigh dosing of irbesartan [900mg O.D (3 times higher maximal recommended dose)] was generally safe and offers additional nephroprotection independent of changes in systemic blood pressure and glomerular filtration rate in comparison to the currently recommended dose of 300mg⁴⁶. In another study conducted by Andrei Forclaz et al., assessed the blockade of the rennin-angiotensin system (RAS) achieved with 2 angiotensin antagonists given either alone at different doses or with an ACE inhibitor. First, 20 normotensive subjects were randomly assigned to 100 mg Losartan once daily or 80 mg Telmisartan once daily for 1 week; during another week, the same dose of losartan and telmisartan were combined with 20 mg Lisinopril once daily. Then, 10 subjects were randomly assigned to 200 mg losartan once daily and 160 mg of Telmisartan once daily for 1 week and 100 mg losartan twice daily and 80 mg telmisartan twice daily during the second week. This study stated that the blockade of the renin angiotensin system (RAS) being only partial with 100mg Losartan and 80mg Telmisartan⁶⁷. Previous studies with ACEI and angiotensin II receptor antagonists have shown that increasing the dose once

daily has little effect on the peak inhibition but tends to prolong the duration of the inhibition. In accordance with this observation increasing the dose of Losartan to 200mg (2 times higher than maximal recommended dose) once daily and that of Telmisartan to 160mg once daily significantly improved the trough blockade^{68,69,70}. Another study with a total of 23 hypertensive patients with type 2 diabetes and nephropathy was carried out with four treatment periods, each lasting 2 months. This study stated that, albuminuria was reduced significantly more by Candesartan 16 and 32mg (recommended maximal dose) as compared with 8mg daily, without differences between the two highest doses⁴⁵. Study with 64mg (2 times maximal recommended dose) was more effective in reducing proteinuria in patients with chronic kidney disease than 16 and 32mg/day Candesartan⁷¹. Data from another study of 10 older patients with heavy proteinuria (>1.5 g/day) of different etiology have suggested that additional reduction in proteinuria can be obtained by increasing the dose of Candesartan from 32 to 96mg (3 times maximal recommended dose) daily⁷². A recent short-term safety study of 12 patients with various forms of chronic renal diseases with severe proteinuria also demonstrated good tolerability of the ARB Candesartan in doses 5 times higher than currently approved maximum dose⁵⁸.

Vogt et al., conducted study with Lisinopril 10, 20, 30 and 40mg/day (2 times higher the usual dose) in 12 (8 of whom were finally selected for the study) nondiabetic proteinuric patients. The eligible patients entered the run-in phase in which previous medication was replaced for the highest recommended daily dose irbesartan 300 mg combined with the diuretic hydrochlorothiazide 12.5 mg once daily. Then, patients with proteinuria >1 g/d and serum potassium concentration <5.5 mmol/L entered the phase of dose titration. In this phase, lisinopril was added in increasing daily doses to a maximum of 40 mg. All periods of treatment (run-in and up-titration) lasted at least 6 weeks. Their study concluded that, dose titration induced further reduction of residual proteinuria⁷³. Fujihara et al., concluded that the renal protection afforded by ARB in renal ablation was dose dependent and maximal protection may require doses several fold higher than those currently employed. In rat model, treatment with Losartan at a dose 10 fold higher than dose 50mg/kg/day and 50 fold higher than those usually employed in experimental studies, arrested the progression of both glomerulosclerosis and interstitial expansion. This dose dependence of Losartan is likely to be observed in human as well, since clinical studies showed that the human responses can be predicted with reasonable accuracy from animal experiments⁶². The effects of different dosage of ramipril, from a minimum of 5mg/day to a maximum of 20 mg/day (4 times the recommended maximum dosage) were evaluated on the level of proteinuria. Although the higher dosage had no additional effect on blood pressure, urinary protein excretion rates were further reduced³⁷.

In a study by Ruggenenti P, uptitration of lisinopril from 10 to 40 mg was done in 28 patients with nondiabetic chronic nephropathies. These patients entered 4-week lisinopril uptitration periods (from 10, to 20, 30, and 40 mg/d), followed by a 6-week backtitration period to lisinopril 10 mg/d and 4-week recovery period (lisinopril withdrawal). Maximum lisinopril doses significantly and safely reduced proteinuria, serum total, LDL cholesterol, and triglycerides without substantially affecting serum HDL and renal hemodynamics⁷⁴. More recently in a preliminary report, Schjoedt et al.⁷⁵ studied 56 patients with type 1 diabetes and nephropathy, who in a double masked crossover trial received 20, 40 or 60 mg/day of lisinopril. The 40 mg/day dose provided a great antiproteinuric effect than 20 mg/day but 60 mg/day did not afford further renoprotection.

Tang et al., in their study on 75 patients with chronic heart failure with low Enalapril (5 mg) dose and high dose (40 mg) over six months and found that there was not any significant reduction in systolic and diastolic blood pressure between the two dose groups. They also measured serum aldosterone and angiotensin II levels in their study and they observed that these renin system hormones weren't adequately suppressed even with the higher dose⁷⁶.

Most studies that showed effective reduction of blood pressure and proteinuria included mostly normotensive and/ or microalbuminuric group of patients. In the study conducted by Adrienne et al.,⁷⁷ the antiproteinuric effects of losartan in 147 normotensive patients with type 2 diabetes and microalbuminuria was assessed. The losartan dose was 50 mg during the first 5 weeks and 100 mg during the subsequent 5 weeks. A significant 25% relative reduction in the albumin excretion rate occurred after 5 weeks of the 50 mg losartan dose, with further improvement over the subsequent 5 weeks with the 100 mg dose. Losartan was safe and well tolerated in these normotensive patients.

Lacouriciere et al.,⁷⁸ in their studies after using Losartan and Enalapril found significantly decreased blood pressure in hypertensive type 2 diabetics with early nephropathy. The study was a one-year prospective, double blind trial with losartan and enalapril administered alone or in combination with hydrochlorothiazide and other antihypertensive agents. Arterial Blood Pressure and renal and biochemical parameters were measured at baseline and after 12, 28, and 52 weeks of active treatment. 92 hypertensive type 2 diabetics with early nephropathy completed the study.

It may be possible that advanced renal failure patients with proteinuria may not respond to increasing doses of Enalapril. Similar findings were also seen by Jensen et al.,⁷⁹. They conducted study with normal to high Enalapril dose (5 to 40 mg) including macroproteinuric patients with advanced renal insufficiency of variable etiologies. They found that at study end blood pressure and proteinuria didn't change significantly in both dose groups.

Anderson et al.,⁶³ in their study with 50 consecutive hypertensive type 1 diabetic patients with diabetic nephropathy received increasing doses of losartan 50, 100, and 150 mg once daily in three periods each lasting 2 months. Using Losartan from 50 to 150 mg among macroproteinuric patients with normal renal function found that maximum antiproteinuric effect was at 100 mg dose without any adverse effect at 150 mg. No significant benefit of increasing dose from 100 to 150 mg was observed in their study groups.

Huo et al.,⁸⁰ undertook a study with Losartan starting with 50 mg and then increasing to 200 mg in a total 360 proteinuric nephropathy patients for a period of 3 years and found significant reduction in blood pressure and proteinuria. But in their study, to control blood pressure, concomitant antihypertensive drugs were used in their patients. It may be possible that antihypertensive drugs in Hou's study reduced blood pressure significantly which influenced the proteinuria reduction to a significant level unlike ours.

Woo et al.,⁸¹ carried out a study in nondiabetic proteinuric subjects with renal dysfunction using 10 mg Enalapril and 100 mg Losartan. 41 patients with biopsy-proven IgAN entered a control trial, with 21 in the treatment group and 20 in the control group. Patients in the treatment group received ACEI/ATRA or both with 3 monthly increases in dosage. They found that blood pressure or proteinuria was reduced only in 30% to 50 % patients. The non responder patients were those who had heavy proteinuria (>2 g/day) and more

advanced renal dysfunction (serum creatinine > 2.5 mg/dl). Study results indicate that combination of heavy proteinuria with advanced renal impairment may be less or non responsive to angiotensin converting enzyme inhibitors or angiotensin receptor blocker even at higher doses.

Rocca et al.,⁸² in 45 chronic heart failure patients showed increasing dose of Enalapril from 5 to 40 mg reduced blood pressure more and cough was more common on highest than lowest dose. The dosage was changed three times to treat all patients with lower, higher, and finally, the initial dosage for 4 weeks each. Within patient comparison revealed that serum potassium and creatinine were higher on the highest than the lowest dose. The patient's included in that trial were suffering from chronic heart failure and were primarily non diabetic and non proteinuric patients. It is possible that these patients are more susceptible to adverse effect with increasing doses of angiotensin converting enzyme inhibitor.

Brenner et al.,⁸³ conducted a study with a total 1513 patients having hypertension, type 2 DM and nephropathy (S. cr 1.3-3 mg/dl) for a mean of 3.4 years. A total of 327 patients in the losartan group reached the primary end point, as compared with 359 in the placebo group. Their study established that losartan, along with conventional antihypertensive treatment as needed, conferred strong renal protection in these patients. The risk of the primary end point a composite of doubling of the S. creatinine concentration, ESRD was reduced by 25% & 28% respectively with losartan but had no effect on the rate of death. The level of proteinuria declined by 35% with losartan.

3. Safety monitoring

Enalapril was well tolerated even at 40mg (maximal recommended dose) once daily dose, as compared with 5mg once daily dose. In fact, there were more reported adverse events and death (requiring withdrawal from the trial) in the low-dose group than in the high-dose group. As seen in previous studies, a large proportion of patients with advanced chronic heart failure could receive up to very high doses of Lisinopril (medium-dose 12.5 or 15.0 mg once daily for 2 to 4 weeks and then randomized to high 35.0 or 32.5 mg once daily or low-dose 5.0 or 2.5 mg once daily) and Enalapril without significantly more adverse effects^{84,85}. Losartan could be administered at an extremely high dose without any perceptible toxic effect. In rat model, treated with 500mg/kg/day, had no hypotension and plasma K⁺ concentration was not higher⁶³. In the trial with lisinopril (where a total of 3164 patients were assigned randomly with either low dose of 2.5 to 5.0 mg daily lisinopril in 1596 patients or high doses of 32.5 to 35 mg daily lisinopril to 1568 patients for 39 to 58 months), increase in serum creatinine in the high-dose group (35mg/day) was slightly greater than in the low-dose group (5mg/day), but the number of patients with major increase in serum creatinine (>1mg/dl) was not different⁸⁶. There was a therapy with Candesartan 8, 16, 32mg (maximal recommended dose) in a total of 23 hypertensive patients with type 2 diabetes and nephropathy with four treatment periods, each lasting for 2 months. The therapy was well tolerated without associated adverse events. A slight increase in serum K⁺ was found, but no incidence of hyperkalemia and hypotension was observed in these patients⁴⁵. No serious adverse event was reported in relation to the ultrahigh dose (64mg i.e. 2 times maximal recommended dose) of candesartan. This confirmed previous studies observing no dose-response curves of serious adverse effect of increasing dose of ARB⁷⁰.

In a pilot study, 12 patients (10 males; age = 57 ± 14 years) with a history of diabetic or non-diabetic chronic kidney disease received candesartan in an 8-week open-label trial in which drug was titrated to a targeted dosage of 160 mg/day (5 times above the currently approved maximum dose) and remained at that dosage for the subsequent 4 weeks. Candesartan was well tolerated with no serious drug-related adverse events reported. Serum creatinine concentrations throughout the study were not different from baseline levels. Plasma potassium concentrations at 160 mg/day candesartan were similar to those at baseline. The results of this pilot study suggest that supramaximal doses of ARBs are safe and well tolerated in patients with chronic kidney disease, while reducing both blood pressure and proteinuria⁵⁸.

In Irbesartan Diabetic Nephropathy Trial (IDNT), Irbesartan (titrated to 300mg/day i.e. maximal recommended dose) slowed the deterioration of renal function by decreasing risk of doubling of serum creatinine, development of end stage renal disease, or death by 20%. Fewer patients receiving Irbesartan had a doubling of their serum creatinine concentration than placebo⁸⁷.

Treatment with Irbesartan was carried out in 52 (41 males) hypertensive type 2 diabetic patients with microalbuminuria. Following 2 months of wash-out (baseline), patients were treated randomly with irbesartan 300, 600, and 900mg/day (3 times higher maximal recommended dose), each dose for 2 months. The therapy induced an increase in plasma K^+ and these changes were only marginally greater when exceeding the currently recommended dose of Irbesartan. None of the patients developed hyperkalemia⁴⁶.

In RENAAL (Reduction of Endpoints in NIDDM with the AngiotensinII II Antagonist Losartan) study, 50 consecutive hypertensive type 1 diabetic patients with diabetic nephropathy received increasing dose of losartan, 50, 100, and 150 mg once daily in three periods each lasting 2 months. Losartan 50mg to 100mg reduced the primary end point (doubling of baseline serum creatinine, end stage renal disease, or death). Potassium, sodium, and cholesterol, including HDL-cholesterol, remained unchanged at 50, 100 and 150mg/day with Losartan. Levels of uric acid in serum did not exceed the upper normal range in this study⁶³.

Serum K^+ and serum creatinine were slightly, higher at high [40mg/day (4 times the recommended dose)] than at low (10mg/day) enalapril levels. Most patients show an only mild increase in serum creatinine, and ACEI therapy did not have to be discontinued in these patients. An increase in enalapril dose did not lead to hyperkalemia. Serious adverse events (i.e. worsening of chronic heart failure, anuria and serious arrhythmia) tended to be more common after downward than after upward titration of enalapril⁸². In the ValHeft (Valsartan in Heart Failure) trial, patients received 160mg valsartan twice daily without any serious adverse effect⁸⁸. In a study by Hou et al. , the incidence of cough was significantly higher in the benazepril arm as compared to losartan arm, but it did not seem to be dosage related. Hyperkalemia occurred in eight (4.4%) patients in the benazepril arm and eight (4.4%) patients in the losartan arm. Of these 16 patients, six were successfully treated with dietary modification, concomitant diuretic therapy, and optimized acid-base balance. The remaining 10 patients withdrew from the study⁸⁰. In the study with ultrahigh dose of Irbesartan (900 mg) total 58 patients having hypertension, type 2 diabetes mellitus with microalbuminuria (persistent Urinary Albumin Excretion between 30 & 300 mg/24hours) on ongoing antihypertensive (wash out done) were included. 4 patients were excluded due to

adverse clinical events, which were not considered related to the study medication. 1 patient discontinued the study after 2 weeks on Irbesartan 900 mg before any clinical examination was performed due to complaints of dizziness & general discomfort. Among 52 patients completing the study, 7 patients complained of mild & transient dizziness, 1 patient during 300 mg, 3 patients during 600 mg & 3 during 900 mg. There was a significant increase in plasma K^+ of 0.3 mmol/L during treatment with irbesartan 300 & 600 mg & by 0.4 mmol/L during treatment with 900 mg. However, none of the patients included in the study developed hyperkalemia (plasma $K^+ > 5.5$ mmol/L). Plasma hemoglobin decreased significantly from 8.7 mmol/L at baseline to 8.2 mmol/L during treatment with 300 & 600 mg & to 8.1 mmol/L during irbesartan 900 mg⁴⁶.

4. Dual blockage of RAAS with ACEIs and ARBs

An insufficient response to ACE inhibition might be explained by the incomplete blockade of the RAS obtained with ACE inhibitors, which are unable to block completely the formation of angiotensin II (Ang II), because some generation of Ang II is produced via other non-ACE pathways⁸⁹. Furthermore, Ang II levels return to normal values after chronic therapy with ACE inhibition, the so-called “ACE escape phenomenon”⁹⁰.

The demonstration of local angiotensin II (Ang II) synthesis in numerous tissues and organs has led to the concept of local or tissue-based RAASs that are independent of but can interact with the traditional circulating RAAS⁹¹. These local RAASs appear to act in a paracrine/autocrine manner to regulate organ function and are involved in pathologic events associated with end-organ damage. The kidney contains all the elements of the RAAS, and intrarenal formation of Ang II independent of the circulating RAAS was first demonstrated more than 30 years ago⁹².

Local AngII in the kidney has multiple roles contributing in hypertension and kidney damage. It enhances capillary filtration pressure, directly by efferent arterial vasoconstriction and indirectly through TGF- β 1 (transforming growth factor beta1) mediated impaired afferent arteriole autoregulation⁹³. AngII decreases the synthesis of negatively charged proteoglycans and suppresses nephrin transcription^{94, 95}, which results in podocyte apoptosis. Through VEGF (vascular endothelial growth factor) and TGF- β 1, induces synthesis of the α 3 chain of collagen type IV, the principal ingredient of the glomerular basement membrane⁹⁶, stimulates upregulation of adhesion molecules such as vascular cellular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and integrins, allowing circulating immune cells to adhere on capillaries. Ang II induces nuclear factor $K\beta$ (NF- κ B) -mediated transcription of chemokines, including monocyte chemoattractant protein-1 (MCP-1), RANTES, and others, resulting in renal tissue infiltration with leukocytes and also induces plasminogen activator inhibitor-1 (PAI-1) and tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) which inhibits metalloproteinases resulting in accumulation of extracellular matrix. Through all these mechanisms, AngII induces proteinuria, inflammation, growth effects, apoptosis and fibrosis⁹⁷.

Chymase-dependent Ang II formation may be at least partly responsible for ‘ACE escape’. This term refers to the observation that, in a high proportion of patients chronically treated with ACE inhibitors, Ang II levels gradually return to baseline after an initial decline. This increase in Ang II formation in the presence of ACE inhibitors is likely due to a compensatory increase in plasma renin activity (PRA) caused by disruption of the feedback loop by which

AngII normally inhibits renin release⁹⁸. Under these circumstances, Ang II can be formed from Ang I by alternative, ACE-independent pathways, such as chymase, which has been shown to be upregulated in diabetic and hypertension-related nephropathies⁹⁹.

ACE-I inhibits the angiotensin-converting enzyme (ACE), thereby reducing the synthesis of Ag II. In addition, it inhibits the degradation of bradykinin, a vasodilator that stimulates nitric oxide, prostaglandin E2, prostacyclin and cyclic guanosine monophosphate production. This might confer additional renal protection, beyond that achieved by the inhibition of Ag II. However, with prolonged ACE-I therapy, the Ag II level can increase through an escape mechanism via peripheral chymase action^{89,99}. ARB, on the other hand, acts directly on the Ag II type 1 receptor (AT 1) and thus blocks all the known actions of Ag II. In addition, by blocking AT 1, it provides unopposed stimulation of the Ag II type 2 receptor (AT 2) in the kidney. Stimulation of the AT 2 receptor has been associated with increased nitric oxide production, increased natriuresis as well as growth inhibitory effects¹⁰⁰. In order to take advantage of the distinct properties of both these medications, a number of studies have explored the possibility of dual blockade of the RAAS with ACE-I and ARB.

In the search of new alternatives that could improve the antiproteinuric and nephroprotective effects of RAS blockers, we believe that the association of ACE inhibitors and ARB might prove useful. ARB produces a complete blockade of the RAS and stimulates the vasodilating and non-proliferative actions of Ang II via the AT2 receptor¹⁰¹. Furthermore, ACE inhibitors, but not ARB, inhibit the metabolism of kinins, which increases the levels of bradykinin, also a potent vasodilator¹⁰².

Recently, some authors have reported a superior effect of the combination of ACE inhibition and ARB on microalbuminuria and on clinical proteinuria in patients with primary nephropathies¹⁰³⁻¹⁰⁵, and in type 1 and type 2 diabetic patients^{106, 107}.

The rationale for combined therapy with ACE inhibitors and ARB is based on the different mechanism of these two drugs in the RAS blockade. Both drugs inhibit the action of Ang II. It is known that Ang II plays a pivotal role in the pathophysiological course of renal disease progression. ACE inhibition could not completely inhibit the generation of Ang II, which may be produced via other non-ACE pathways⁸⁹. In contrast, ARB completely abolishes the action of Ang II through blockading the AT1 receptor, producing an accumulation of Ang II that stimulates the vasodilatory and antiproliferative actions of Ang II mediated through the AT2 receptor¹⁰¹. On the other hand, ACE inhibitors but not ARB, decreases degradation of bradykinin, which is a potent vasodilator¹⁰².

A recent meta-analysis by Jennings et al reported a greater reduction in proteinuria with combination therapy when compared with ACE-I alone¹⁰⁸. The response to treatment with ACE-I and ARB may differ among different races¹⁰⁹.

Mogensen et al studied 197 hypertensive patients with type 2 DM and microproteinuria, and found that combination therapy with once daily candesartan 16 mg and lisinopril 20 mg was more effective in reducing BP and albuminuria than monotherapy with either drug alone¹⁰⁶.

Cetinkaya et al found that a combination of enalapril 10 mg daily and losartan 50 mg daily decreased both the proteinuria and MAP by a greater extent when compared with the administration of either drug alone¹¹⁰.

In two separate randomised double-blind crossover studies, Rossing et al found a further reduction in albuminuria when candesartan 16 mg was added to the pre-existing ACE-I therapy in hypertensive type 2 diabetic patients. In the first study involving 18 type 2 diabetic patients who were taking the recommended doses of ACE-I, corresponding to 20 mg of enalapril/lisinopril once daily or 100 mg of captopril daily, the administration of candesartan 16 mg daily for two months induced a 25% reduction in albuminuria, together with a 10 mmHg reduction in 24-hour systolic BP¹¹¹. In the second study involving 20 type 2 diabetic patients on a maximal recommended dose of ACE-I (enalapril/lisinopril 40 mg daily or captopril 150 mg daily), there was a further 28% significant reduction in albuminuria, and a modest but non-significant reduction in BP after two months of being administered candesartan at 16 mg daily¹¹². On the other hand, the addition of Losartan 50 mg daily for one month did not improve proteinuria in 16 obese, hypertensive patients (12 with diabetic nephropathy) with moderately advanced renal failure and heavy proteinuria (mean urinary protein 3.8 g/day)¹¹³. A Korean group also reported no beneficial effect on proteinuria when candesartan was added to ramipril therapy in type 2 diabetic patients with nephropathy despite the positive anti-proteinuric effect seen in patients with IgA nephropathy following the same regimen^{114, 115}.

Dual blockade of RAAS at different steps with ACEI and ARB would be an attractive alternative.

In meta-analysis, Doultou et al demonstrated that combination therapy provided a further 30%- 39% drop in proteinuria compared to monotherapy¹¹⁶ and in MacKinnon et al resulted in a significant decline in proteinuria both in diabetic and nondiabetic patients with a slight but significant increase in potassium, and an insignificant drop in GFR¹¹⁷.

The IMPROVE (Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events) study has shown no further benefit on albuminuria reduction in patients treated with combination therapy despite the fact that BP reduction was slightly better in the combination group. Subgroup analyses showed the largest reduction in albuminuria occurred in patients with overt nephropathy but it did not reach statistical significance¹¹⁸.

In contrast to these studies, the VALERIA (Valsartan in Combination With Lisinopril Versus the Respective High Dose Monotherapies in Hypertensive Patients With Microalbuminuria) trial demonstrated that combination therapy was more effective in reducing microalbuminuria despite the fact that patients received the maximal recommended doses of lisinopril or valsartan as monotherapy¹¹⁹.

5. Direct renin inhibition

Aliskiren is the first orally active Direct Renin Inhibitor (DRI) to receive regulatory approval for hypertension. By inhibiting the enzymatic conversion by renin of Angiotensinogen to Angiotensin I, DRIs inhibit the initial and rate-limiting step in the RAAS cascade, thus reducing the production of all downstream products derived from Angiotensin^{120, 121}. Furthermore, in both clinical studies¹²² and in experimental animals¹²³, aliskiren reduces plasma and/or urinary excretion of aldosterone. The role of aldosterone in endothelial dysfunction, inflammation, proteinuria and fibrosis is well known⁹⁷.

Fig. 1. Effect of increased glomerular permeability to proteins on progressive renal injury

The mechanisms by which aliskiren may impart renoprotection are still under investigation. However, a number of possible mechanisms can be envisioned. First, aliskiren not only inhibits renin but also inhibits the activity of prorenin¹²⁴ following its non-proteolytic activation upon binding to the (pro)renin receptor¹²⁵. This may be of particular importance in diabetes in which prorenin levels are elevated and may contribute to local Ang II formation¹²⁶. Second, aliskiren blocks the circulating RAAS and lowers blood pressure¹²⁷. Hypertension is one of the most common comorbidities in CKD and its control is essential in reducing further renal damage and cardiovascular risk in CKD patients¹²⁸. Third, aliskiren blocks the intrarenal RAAS and lowers renal Ang I and Ang II levels¹²⁹, thus reducing the deleterious renal effects of Ang II⁹⁷ (fig. 1). Finally, aliskiren has been shown to reduce the renal expression of the (pro)renin receptor in an animal model of diabetes¹²⁴. If the (pro)renin receptor plays a role in CKD, downregulation of this receptor may reduce the Ang II-independent effects of (pro)renin receptor activation on renal fibrotic pathways¹³⁰ (Fig. 3).

Fig. 2. Final common pathway for progression of chronic renal disease

Fig. 3. Multiple role of the Renin angiotensin aldosterone system in the pathogenesis of chronic kidney disease

In patients who have vascular disease or high risk diabetes without heart failure, angiotensin-converting-enzyme inhibitors reduce mortality and morbidity from cardiovascular causes, but the role of angiotensin-receptor blockers in such patients is unknown. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) was carried out for the comparative study between ramipril, telmisartan and the combination of both in patients with vascular disease or high risk diabetes. After a 3 week, single-blind run-in period, patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg telmisartan per day, and 8502 assigned to receive both drugs (combination therapy). Telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit¹³¹.

Fig. 4. Mechanism of proteinuria in diabetic nephropathy

Stage	Glomerular Filtration Rate	Urinary albumin excretion (mg/ d)	Blood pressure	Years after diagnosis
i. Hyperfiltration	Supernormal	<30	Normal	0
ii. Microalbuminuria	High normal To normal	30-300	Rising	5-15
iii. Proteinuria	Normal To decreasing	>300	Elevated	10-20
iv. Progressive nephropathy	Decreasing	Increasing	Elevated	15-20
v. End stage renal disease	<15ml/ min	Nephrotic	Elevated	20-30

Table 1. Stages of Diabetic Nephropathy

Fig. 5. Pathogenesis of Diabetic nephropathy

6. Conclusion

ACE inhibitors and ARBs, as monotherapy or in combination, have evolved as accepted first-line agents for delaying the progression of diabetic nephropathy. Currently, recommendations favor ACE inhibitors for type 1 and ARBs or ACE inhibitors for type 2 diabetes as a result of large, controlled clinical trials. Therapeutic goals should be addressed not only for BP reduction, but in diminishing albuminuria as well. In subjects with microalbuminuria, the dose of ARBs or ACE inhibitors should be titrated by the clinician until normoalbuminuria is induced, even if supramaximal doses or a combination of ARBs and ACE inhibitors are necessary. There is evidence that achieving reduction in both microalbuminuria and in heavy proteinuria at greater doses than those used to control BP may be required using monotherapy or a combination of these RAS blockers¹³².

Different studies showed that higher doses of angiotensin converting enzyme inhibitors and angiotensin receptor blocker are safer and beneficial. Rationale to use higher doses of angiotensin converting enzyme inhibitors or angiotensin receptor blocker is not only to reduce proteinuria and or to control blood pressure. Additional beneficial effects are

observed at higher doses other than renal systems. Losartan showed cardio protection by cardiac remodeling, vascular remodeling, atherosclerosis, endothelial function, inhibition of thrombus formation and platelet aggregation, reduction of risk factor for stroke in addition to renal effects¹³³.

Higher drug doses can reduce nephrotoxic components like TGF β ¹³⁴, connective tissue growth factor¹³⁵, inflammatory mediators like cytokines⁶³ etc. It is evident that, these drugs, even when do not reduce proteinuria or blood pressure significantly, may provide the additional renoprotection with higher doses.

Dual blockade of the RAS provides superior short-term renoprotection independent of systemic blood pressure changes in comparison with maximally recommended doses of ACEI in patients with type 2 diabetes as well as nephropathy.

The ability of these two therapeutic agents to synergistically antagonize the RAAS can also be explained by their complimentary mechanisms of action. For example, ACE inhibition leads to a prolonged half-life of bradykinin, a potent vasodilator believed to be renoprotective. ARBs do not increase the half-life of bradykinin. They can further ablate the damaging effects resulting from the production of angiotensin II by non-ACE pathways, which is not completely blocked by an ACEI. Thus, it seems plausible that combining these two agents could more effectively oppose the RAAS than either agent alone¹³⁶.

7. References

- [1] Anderson RN. Deaths: Leading causes for 1999. Natl Vital Stat Rep. 2001; 49: 1-87.
- [2] Turnar R, Holman R, Stratton I, Cull C, Frighi V, Manley S, Matthews D, Neil A, McElroy H, Kohner E, Fox C, Hadden D, Wright D. Tight blood pressure control and risk of macrovascular and microvascular complications type 2 diabetes. BMJ. 1998; 317: 703-13.
- [3] Rahman M, Roy AC, Chowdhury D, Hossain M. Clinicopathological spectrum of renal diseases in IPGMR. An analysis of 2000 cases in 11 years. Journal of BCPS 1985; 11: 3-11.
- [4] Mogensen CE. Progression of nephropathy in long-term diabetics with proteinuria and effect of initial antihypertensive treatment. Scand J Clin Lab Invest 1976; 36: 383-88.
- [5] Parving HH, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in Diabetic Nephropathy. Lancet 1 1983: 1175-79.
- [6] Wilmer WA, Hebert LA, Lewis EJ, Rohd RD, Whittier F, Cattran D, Levey AS, Lewis JB, Spitalowitz S, Blumenthal S, Bain RP. Remission of nephritic syndrome in type 1 diabetes: long term follow of patients in the captopril study. Am J Kidney Dis. 1999; 34: 308-14
- [7] Lewis E, Hunsicker L, Bain R, Rhode R. The effect of angiotensin converting enzyme inhibition on Diabetic nephropathy. N Engle J Med. 1993; 329: 1456-62.
- [8] Björck S, Mulec H, Johnsen SA, Norden G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. BMJ 1992; 304: 339-43.
- [9] Campese Vm, Bianchi S, Bigazzi R. Is microalbuminuria a predictor of cardiovascular and renal disease in patients with essential hypertension? Curr Opin Nephron Hypertens. 2000; 9: 143-47.

- [10] Williams ME. Diabetic nephropathy: The proteinuria hypothesis. *Am J Nephrol*. 2005; 25: 77-94.
- [11] Raptis AE, Viberti G. Pathogenesis of diabetic nephropathy. *Exp Clin Endocrinol Diabetes*. 2001; 109 (Suppl 2): S424-S437.
- [12] Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA*. 2002; 288 (20): 2579-88.
- [13] Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001; 414: 813-20.
- [14] Vlassara H, Palace MR. Diabetes and advanced glycation end products. *J Intern Med*. 2002; 251 (2): 87-101.
- [15] Carey RM and Siragy HM. The intrarenal renin angiotensin system and diabetic nephropathy. *TRENDS in Endocrin and Met*. 2003; 14: 274-81.
- [16] Bennett PN and Brown MJ. Arterial hypertension, angina pectoris, myocardial infarction. In: *Clinical Pharmacology*; Ninth edition. New York: Churchill Livingstone; 2003: pp 467.
- [17] Remuzzi G, Perico N, Macia M, Ruggenenti P. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. *Kidney Int*. 2005; 68, Supplement 99: S57-S65.
- [18] Andersen S, Jung FF, Ingelfinger JR. Renal renin-angiotensin system in diabetes. Functional, immunohistochemical and molecular biological correlations. *AM J Physiol*. 1993; 265: F477-F86.
- [19] Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int*. 1996; 49: 1774-77.
- [20] Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest*. 1986; 77 (6): 1993-2000.
- [21] Zachary T, Bloomgarden MD. Diabetic nephropathy. *Diabetes care*. 2005; 28: 745-75.
- [22] Shake JG, Brandt RC, Daniels BS. Angiotensin II induces actin polymerization within the glomerular filtration barrier: Possible role in the local regulation of ultrafiltration. *J Am Soc Nephrol*. 1992; 3: 568A.
- [23] Ruiz-Ortega M, Lorenzo O, Suzuki Y, Rupérez M, Egido J. Pro-inflammatory actions of angiotensins. *Curr Opin Nephrol Hypertens*. 2001; 10: 321-29.
- [24] Choles HR, Kasinath BS, Gorin Y, Abboud He. Angiotensin II and growth factors in the pathogenesis of diabetic nephropathy. *Kidney Int Suppl*. 2002; 82: 8-11.
- [25] Brenner BM. Remission of renal disease: Recounting the challenge, acquiring the goal. *J Clin Invest*. 2002; 110: 1753-58.
- [26] Oberleithner H. Aldosterone makes human endothelium stiff and vulnerable. *Kidney Int*. 2005; 67: 1680-82.
- [27] Yoshioka T, Mitarai T, Kon V, Deen WM, Rennke HG, Ichikawa I. Role for angiotensin II in an overt functional proteinuria. *Kidney Int*. 1986; 30: 538-45.
- [28] Yoshioka T, Rennke HG, Salant DJ, Deen WM, Ichikawa I. Role of abnormally high transmural pressure in the permselectivity defect of glomerular capillary wall: a study in early passive Heymann nephritis. *Circ Res*. 1987; 61: 531-38.
- [29] Abbate M, Zoja C, Rottoli D, Corna D, Tomasoni S, Remuzzi G. Proximal tubular cells promote fibrogenesis by TGF β 1 mediated induction of peritubular myofibroblasts. *Kidney Int*. 2002; 61: 2066-77.

- [30] Abbate M, Zoja C, Morigi M, Rottoli D, Angioletti S, Tomasoni S, Zanchi C, Longheretti L, Donadelli R, Remuzzi G. Transforming growth factor beta 1 is upregulated by podocytes in response to excess intraglomerular passage of proteins. *Am J Pathol.* 2002; 161: 2179-93.
- [31] Cao Z, Cooper ME. Role of angiotensin II in tubule interstitial injury. *Semin Nephrol.* 2001; 21: 554-62.
- [32] Eddy AA. Molecular insights into renal interstitial fibrosis [Editorial]. *J Am Soc Nephrol.* 1996; 7: 2495-508.
- [33] Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. *N Engl J Med.* 1994; 331: 1286-92.
- [34] Postlethwaite AE, Holness MA, Katali H, Raghow R. Human fibroblasts synthesize elevated levels of extracellular matrix proteins in response to interleukin 4. *J Clin Invest.* 1992; 90: 1479-85.
- [35] Jarma K, Ziyadeh FN. The transforming growth factor-beta system and the kidney. *Semin Nephrol.* 1993; 13: 116-28.
- [36] AC, Jowett TP, Firth JD, Burton S, Kitamura M, Fine LG. A new paracrine loop implicated in human tubulo-interstitial fibrosis: tubular derived endothelins modulate renal interstitial fibroblast function [Abstract]. *J Am Soc Nephrol.* 1993, 4: 473.
- [37] Remuzzi G MD, Ruggenenti P. Chronic renal disease: Renoprotective benefits of renin angiotensin system inhibition. *Ann Intern Med.* 2002; 136: 604-15.
- [38] Abbate M, Zoja C, Rottoli D, Corna D, Perico N, Bertani T, Remuzzi G. Antiproteinuric therapy while preventing the abnormal protein tubule abrogates protein and complement dependent interstitial inflammation in experimental renal disease. *J Am Soc Nephrol.* 1999; 10: 804-13
- [39] Hoffmann S, Podlich D, Hahnel B, Kriz W, Gretz N. Angiotensin II type 1 receptor overexpression in podocytes induces glomerulosclerosis in transgenic rats. *J Am Soc Nephrol.* 2004; 15: 1475-87.
- [40] Macconi D, Ghilardi M, Bonassi ME, Mohamed EI, Abbate M, Colombi F, Remuzzi G, Remuzzi A. Effect of Angiotensin-Converting Enzyme Inhibition on Glomerular Basement Membrane Permeability and Distribution of Zonula Occludens-1 in MWF Rats. *J Am Soc Nephrol.* 2000; 11: 477-89.
- [41] Benigni A, Tomasoni S, Gagliardini E, Zoja C, James A, Grunkemeyer, Kalluri R, Remuzzi G. Blocking angiotensin II synthesis/activity preserves glomerular nephrin in rats with severe nephrosis. *J Am Soc Nephrol.* 2001; 12: 941-48.
- [42] Bonnet F, Cooper ME, Kawachi H, Allen TJ, Boner G, Cao Z. Irbesartan normalizes the deficiency in glomerular nephrin expression in a model of diabetes and hypertension. *Diabetologia.* 2001; 44: 874-77.
- [43] Stevinkel P, Ketteles M, Johnson R, Lindholm B, Pecotis-Filho R, Riella M, Heimbürger O, Cederholm T, Girndt M. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia- The good, the bad, and the ugly. *Kidney Int.* 2005;67: 1216-33.
- [44] Stevinkel P, Anderson A, Wang T, Lindholm B, Bergstrom J, Palmblad J, , Heimbürger O, Cederholm T. Do ACE-inhibitors suppress tumor necrosis factor alpha production in advanced chronic renal failure? *J Int Med.* 1999; 246 (5): 503-7.
- [45] Rossing K, Christensen PK, Hansen BV, Carstensen B, Parving HH. Optimal dose of candesartan for renoprotection in type 2 diabetic patients with nephropathy. *Diabetes care.* 2003; 26: 150-55.

- [46] Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving HH. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. *Kidney Int.* 2005; 68: 1190-98.
- [47] Parving HH, Lehnert H, Jens B, Mortensen C, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2001; 345: 870-78.
- [48] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn V, Zhang Z, Shahnaz. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes mellitus and nephropathy. *N Engl J Med.* 2001; 345: 861-69.
- [49] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Itamar Raz. Reno protective effects of the angiotensin receptor antagonists irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001; 345: 851-60.
- [50] Viberti G and Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus- A blood pressure independent effect. *Circulation.* 2002; 106: 672-78.
- [51] Imanishi M, Yoshika K, Konish Y. Glomerular hypertension as one of albuminuria in type 2 diabetic patients. *Diabetologia.* 1999; 42: 999-1005.
- [52] Andersen S, Blouch K, Bialek J, Deckert M, Parving HH, Myers BD. Glomerular permselectivity in early stages of overt diabetic nephropathy. *Kidney Int.* 2000; 58: 2129-37.
- [53] Bennet P, Cooper ME, Kawachi H, Allen TJ, Boner G, Cao Z. Irbesartan normalizes the deficiency in glomerular nephrin expression in a model of diabetes and hypertension. *Diabetologia.* 2001; 44: 874-77.
- [54] Maciasaac RJ, Jerums G, Cooper ME. New insights into the significance of microalbuminuria. *Curr Opin Nephrol Hypertens.* 2004; 13: 83-91.
- [55] Sturgill BC and Shearlock KT. Membranous glomerulopathy and nephrotic syndrome after captopril therapy. *JAMA.* 1983; 250: 2343-45.
- [56] Textor SC, Gephardt GN, Bravo EL, Tarazi RC, Fouad FM, Tubbs R, McMahon JT. Membranous glomerulopathy associated with captopril therapy. *Am J Med.* 1983; 74: 705-12.
- [57] Hoorntje SJ, Kallenberg CG, Weening JJ, Donkar AJ, The TH, Hoedemaeker PJ. Immune-complex glomerulopathy in patients treated with captopril. *Lancet.* 1980; 1: 1212-15.
- [58] Weinberg AJ, Zappe DH, Ashton M, Weinberg MS. Safety and tolerability of high dose angiotensin blocker therapy in patients with chronic kidney disease: A pilot study. *Am J Nephrol.* 2004; 24: 340-45.
- [59] Schmieder RE. Talmesartan/hydrochlorothiazide combination therapy in the treatment of essential hypertension. *Expert Opin Pharmacother.* 2004; 5: 2303-10.
- [60] Benigni A and Remuzzi G. How renal cytokines and growth factors contribute to renal disease progression. *Am J Kidney Dis.* 2001; 37[Suppl 2]: S21-S24.
- [61] Donadelli R, Zanchi C, Morigi M, Buelli S, Batani C, Tomasoni S, Corna D, Rottoli D, Benigni A, Abbate M, Remuzzi G, Zoja C. Protein overload induces fractalkine upregulation in proximal tubular cells through nuclear factor kappaB- and p38 mitogen activated protein kinase dependent pathways. *J Am Soc Nephrol.* 2003; 14: 2436-46.

- [62] Fujihara C K, Velho M, Malheiros DMAC, Zatz R. An extremely high dose of losartan affords superior renoprotection in the remnant model. *Kidney Int.* 2005; 67: 1913-1924.
- [63] Anderson S, Rossing P, Juhl TR, Deinum J, Parving HH. Optimal dose of losartan for renoprotection in diabetic nephropathy. *Nephrol Dial Transplant* 2002; 17: 1413-18.
- [64] Laverman GD, Navis G, Henning RH, De Jong PE, de Zeeuw D. Dual renin-angiotensin system blockade at optimal doses for proteinuria. *Kidney Int* 2002; 62: 1020-25.
- [65] Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet.* 2002; 359: 995-1003.
- [66] Andersen S, Brochuer – Mortensen J, Parving HH. For the Irbesartan in patients with type 2 Diabetes & Microalbuminuria. Study Group: Kidney function during & after withdrawal of long-term irbesartan treatment in patients with type 2 diabetes and microalbuminuria. *Diabetes Care.* 2003; 26: 3296-3302.
- [67] Forclaz A, Maillard M, Nussberger J, Brunner H R, Burnier M. Angiotensin II Receptor Blockade. Is There a Benefit of Adding an ACE Inhibitor? *Hypertension.* 2003; 41: 31-36.
- [68] Maillard MP, Wurzner G, Nussberger J, Centeno C, Burnier M, Brunner HR. Comparative angiotensin II Receptor blockade in healthy volunteers: the importance of dosing. *Clinical Pharmacol Ther.* 2002; 71: 68-76.
- [69] Maillard MP, Mazzolai L, Daven V, Centeno C, Nussberger J, Brunner HR, Burnier M. Assessment of angiotensin II receptor blockade in humans using a standardized angiotensin II receptor-binding assay. *Am J Hypertens.* 1999; 12:1201-1208.
- [70] Ferguson RK, Turini GA, Brunner HR, Gavras H, McKinstry DN. A specific orally active inhibitor of angiotensin-converting enzyme in man. *Lancet.* 1977; 309:775-778.
- [71] Schmieder RE, Klingbeil AU, Fleischgmann EH, Veelken R, Delles C. Additional antiproteinuric effect of ultra high dose candesartan: A double-blind, randomized, prospective study. *J Am Soc Nephrol* 2005; 16: 3038-45.
- [72] Weinberg MS, Weinberg AJ, Cor R, Zapper DH. The effect of high-dose angiotensin II receptor blockade beyond maximal recommended doses in reducing urinary protein excretion. *J Renin Angiotensin Aldosterone Syst.* 2001; 2: S 196 –S 198.
- [73] Vogt L, Navis G, de Zeeuw D. Individual titration for maximal blockade of renin-angiotensin system in proteinuric patients: A feasible strategy? *J Am Soc Nephrol* 2005; 16: S53-S57.
- [74] Ruggenti P, Mise N, Pisoni R, Arnoldi F, Pezzotta A, Perna A, Cattaneo D, Remuzzi G. Diverse effects of increasing lisinopril doses on lipid abnormalities in chronic nephropathies. *Circulation* 2003; 107: 586 – 592.
- [75] Schjoedt KJ, Astrup A, Persson F et al. Optimal dose of lisinopril for renoprotection in type 1 diabetic patients with diabetic nephropathy. *Proceeding from the European Association for the Study of Diabetes (EASD),* 2007.
- [76] Tang WHW, Vagelos RH, Yee YG, Benedict CR, Willson KRN, Liss CL, LaBella P, Fowler MB, Neurohormonal and clinical response to high versus low-dose Enalapril therapy in chronic heart failure. *J Am Coll Cardiol.* 2002; 39: 70-78.
- [77] Adrienne AM, Zandbergen, Marinus GA, Baggen, Lamberts SWJ, Bootsma A H, de Zeeuw D, Ouwendijk RJT. Effect of Losartan on Microalbuminuria in Normotensive Patients with Type 2 Diabetes Mellitus. *Ann intern Med.* 2003; 139: 90-96.

- [78] Lacourciere Y, Belanger A, Godin C, Halle JP, Ross S, Wright N, Marion J. Long-term comparison of losartan and enalapril on the kidney function in hypertensive type 2 diabetics with early nephropathy. *Kidney Int.* 2000; 58: 762-769.
- [79] Jensen TE, Heusterberg J, Sonne J, Strndgaard S, Kamper AL. Enalapril dosage in progressive chronic nephropathy: a randomised, controlled trial. *Eur J Clin Pharmacol.* 2005; 61: 87-96.
- [80] Hou FF, Xie D, Zhang X, Chen PY, Zhang WR, Liang M, Guo ZJ, Jiang JP. Renoprotection of optimal antiproteinuric dose (ROAD) study: A randomized controlled study of Benajepiril and Losartan in chronic renal insufficiency. *J Am Soc Nephrol.* 2007; 18: 1889-98.
- [81] Woo KT, Lau YK, Wong KSGSC. ACEI/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis. *Kidney Int.* 2000; 58: 2485-91.
- [82] Rocca HPBLA, Weilenmann D, Kiowski W, Friedrich E, Maly, Follath F. Plasma level of Enalaprilat in chronic therapy of heart failure: Relationship to adverse events. *J Pharmacol and Exp Ther.* 1999; 289: 565-571.
- [83] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn V, Zhang Z, Shahnaz. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes mellitus and nephropathy. *N. Engl. J. Med.* 2001; 345: 861-869.
- [84] Massie BM, Armstrong PW, Cleland JGF. Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure. *Arch Intern Med.* 2001; 161:165-71.
- [85] Kostis JB, Shelton BJ, Yusuf S. Tolerability of enalapril initiation by patients with left ventricular dysfunction: results of the medication of challenge phase of the Studies of Left Ventricular Dysfunction. *Am Heart J.* 1994; 128: 358-64.
- [86] Packer M, Wilson P A P, Armstrong P W, Cleland JGE, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure. *Circulation* 1999; 100: 2312-2318.
- [87] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins R C, Rohde R, Itamar Raz. Reno protective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N. Engl. J. Med.* 2001; 345: 851-860.
- [88] Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Eng J Med* 2001; 345: 1667-75.
- [89] Hollenberg NK, Fisher NDL, Price DA: Pathways for angiotensin II generation in intact human tissue-evidence from comparative pharmacological interruption of the renin system. *Hypertension* 1998; 32:387-392.
- [90] Nussberger J, Brunner DB, Waeber B, Brunner HR: Plasma angiotensins under sustained converting enzyme inhibition with enalapril in normal humans. *J Hypertens* 1985; 3(Suppl 3):S269-S270.
- [91] Kobori H, Nangaku M, Navar LG, Nishiyama A: The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. *Pharmacol Rev* 2007; 59: 251-87.
- [92] Kimbrough HM Jr, Vaughan ED Jr, Carey RM, Ayers CR: Effect of intrarenal angiotensin II blockade on renal function in conscious dogs. *Circ Res* 1977; 40: 174-78.

- [93] Sharma K, Cook A, Smith M, Valancius C, Inscho EW: TGF-beta impairs renal autoregulation via generation of ROS. *Am J Physiol Renal Physiol* 2005; 288: F1069-F1077.
- [94] Wolf G, Butzmann U, Wenzel UO: The renin-angiotensin system and progression or renal disease: From hemodynamics to cell biology. *Nephron Physiol* 2003; 93: 3 -13.
- [95] Chen S, Lee JS, Iglesias-de la Cruz MC, Kasama Y, Izquier-do-Lahuerta A, Wolf G, Ziyadeh FN: Angiotensin II stimulates alpha3(IV) collagen production in mouse podocytes via TGF-beta and VEGF signaling: Implications for diabetic nephropathy. *Nephrol Dial Transplant* 2005; 20: 1320-28.
- [96] Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2003; 108: 2154-2169.
- [97] Ruster C, Wolf G. Renin-Angiotensin-Aldosterone System and Progression of Renal Disease. *J Am Soc Nephrol* 2006; 17:2985-91.
- [98] Atlas SA: The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm* 2007; 13: 9-20.
- [99] Huang XR, Chen WY, Truong LD, Lan HY: Chymase is upregulated in diabetic nephropathy: implications for an alternative pathway of angiotensin II-mediated diabetic renal and vascular disease. *J Am Soc Nephrol* 2003; 14: 1738-47.
- [100] Burns KD. Angiotensin II and its receptors in the diabetic kidney. *Am J Kidney Dis* 2000; 36:449-67.
- [101] Siragy HM: The role of the AT2 receptor in hypertension. *Am J Hypertens* 2000; 3 Suppl(5 Pt 2):62S-67S.
- [102] Allen TJ, Cao Z, Youssef S, et al: The role of angiotensin II and bradykinin in experimental diabetic nephropathy: Functional and structural studies. *Diabetes* 1997; 46:1612-1618.
- [103] Russo D, Pisano A, Balletta MM, et al: Additive antiproteinuric effects of converting enzyme inhibitor and losartan in normotensive patients with IgA nephropathy. *Am J Kidney Dis* 1999; 33:851-856.
- [104] Ruilope LM, Aldigier JC, Ponticelli C, et al: Safety of the combination of valsartan and benazepril in patients with chronic renal disease. European Group for the Investigation of Valsartan in Chronic Renal Disease. *J Hypertens* 2000; 18:89-95.
- [105] Ferrari P, Marti HP, Pfister M, Frey JF: Additive antiproteinuric effect of combined ACE inhibition and angiotensin II receptor blockade. *J Hypertens* 2002; 20:125-130.
- [106] Mogensen CE, Neldam S, Tikkanen I, et al: Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: The candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000; 321:1440-1444.
- [107] Jacobsen P, Andersen S, Rossing K, et al: Dual blockade of the renin angiotensin system in type 1 patients with diabetic nephropathy. *Nephrol Dial Transplant* 2002; 17:1019-1024.
- [108] Jennings DL, Kalus JS, Coleman CI, Manierski C, Yee J. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. *Diabet Med*. 2007; 24:486-93.

- [109] Hostetter TH. Prevention of end-stage renal disease due to type 2 diabetes. *N Engl J Med* 2001; 345:910-2.
- [110] Cetinkaya R, Odabas AR, Selcuk Y. Anti-proteinuric effects of combination therapy with enalapril and losartan in patients with nephropathy due to type 2 diabetes. *Int J Clin Pract* 2004; 58:432-5.
- [111] Rossing K, Christensen PK, Jensen BR, Parving HH. Dual blockade of the renin-angiotensin system in diabetic nephropathy: a randomized double-blind crossover study. *Diabetes Care* 2002; 25:95-100.
- [112] Rossing K, Jacobsen P, Pietraszek L, Parving HH. Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy: a randomized double-blind crossover trial. *Diabetes Care* 2003; 26:2268-74.
- [113] Agarwal R. Add-on angiotensin receptor blockade with maximized ACE inhibition. *Kidney Int* 2001; 59:2282-9.
- [114] Song JH, Lee SW, Suh JH, et al. The effects of dual blockade of the renin-angiotensin system on urinary protein and transforming growth factor-beta excretion in 2 groups of patients with IgA and diabetic nephropathy. *Clin Nephrol* 2003; 60:318-26.
- [115] Kim MJ, Song JH, Suh JH, Lee SW, Kim GA. Additive antiproteinuric effect of combination therapy with ACE inhibitor and angiotensin II receptor antagonist: differential short-term response between IgA nephropathy and diabetic nephropathy. *Yonsei Med J* 2003; 44:463-72.
- [116] Douulton TW, He FJ, MacGregor GA. Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 2005; 45: 880-86.
- [117] MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD: Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006; 48: 8-20.
- [118] Bakris GL, Ruilope L, Locatelli F, et al: Treatment of microalbuminuria in hypertensive subjects with elevated cardiovascular risk: results of the IMPROVE trial. *Kidney Int* 2007; 72: 879-85.
- [119] Menne J, Farsang C, Deak L, Klebs S, Meier M, Handrock R, et al: Valsartan in combination with lisinopril versus the respective high dose monotherapies in hypertensive patients with microalbuminuria: the VALERIA trial. *J Hypertens* 2008; 26: 1860-67.
- [120] Persson F, Rossing P, Schjoedt KJ, Juhl T, Tarnow L, Stehouwer CD, Schalkwijk C, Boomsma F, Frandsen E, Parving HH: Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. *Kidney Int* 2008; 73: 1419-25.
- [121] Persson F, Rossing P, Reinhard H, Juhl T, Stehouwer CD, Schalkwijk C, Danser AH, Boomsma F, Frandsen E, Parving HH: Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. *Diabetes Care* 2009; 32: 1873-79.
- [122] Yarows SA: Aliskiren/valsartan combination for the treatment of cardiovascular and renal diseases. *Expert Rev Cardiovasc Ther* 2010; 8: 19-33.
- [123] Feldman DL: New insights into the renoprotective actions of the renin inhibitor aliskiren in experimental renal disease. *Hypertens Res* 2010; 33: 279-287.

- [124] Feldman DL, Jin L, Xuan H, Contrepas A, Zhou Y, Webb RL, Mueller DN, Feldt S, Cumin F, Maniara W, Persohn E, Schuetz H, Jan Danser AH, Nguyen G: Effects of aliskiren on blood pressure, albuminuria, and (pro)renin receptor expression in diabetic TG(mRen-2)27 rats. *Hypertension* 2008; 52: 130–136.
- [125] Danser AH: The increase in renin during renin inhibition: does it result in harmful effects by the (pro)renin receptor? *Hypertens Res* 2010; 33:4–10.
- [126] Feldman DL: New insights into the renoprotective actions of the renin inhibitor aliskiren in experimental renal disease. *Hypertens Res* 2010; 33: 279–287.
- [127] Pimenta E, Oparil S: Role of aliskiren in cardiorenal protection and use in hypertensives with multiple risk factors. *Ther Clin Risk Manag* 2009; 5: 459–464.
- [128] KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis* 2007; 49:S12–S154.
- [129] Pilz B, Shagdarsuren E, Wellner M, Fiebeler A, Dechend R, Gratzke P, Meiners S, Feldman DL, Webb RL, Garrelds IM, Jan Danser AH, Luft FC, Muller DN: Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. *Hypertension* 2005; 46: 569–576.
- [130] Huang Y, Wongamorntham S, Kasting J, Mc-Quillan D, Owens RT, Yu L, Noble NA, Border W: Renin increases mesangial cell transforming growth factor- β_1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. *Kidney Int* 2006; 69: 105–113.
- [131] Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Hamilton ON, Schumacher H, Ingelheim B, Dagenais G, Sleight P, Anderson C. Telmisartan, Ramipril, or Both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547–59.
- [132] Marc S. Weinberg, MD, Nicholas Kaperonis, MD, and George L. Bakris, MD. How High Should an ACE Inhibitor or Angiotensin Receptor Blocker Be Dosed in Patients with Diabetic Nephropathy? *Current Hypertension Reports* 2003; 5:418–425.
- [133] Dahlöf B, Devereux R, de Faire U. The Losartan Intervention For Endpoint reduction (LIFE) in Hypertension study: rationale, design, and methods. The LIFE Study Group. *Am J Hypertens*. 1997; 10: 705–713.
- [134] Anderson S, Rossing P, Juhl TR, Deinum J, Parving HH. Optimal dose of losartan for renoprotection in diabetic nephropathy. *Nephrol Dial Transplant* 2002; 17: 1413–18.
- [135] Andersen S, Frans A, Nieuwenhoven V, Tarnow L, Rossing P, Rossing K, Wieten L, Goldschmeding R, Parving HH. Reduction of urinary connective tissue growth factor by Losartan in type 1 patients with diabetic nephropathy. *Kidney Int*. 2005; 67: 2325–29.
- [136] Imig JD. ACE inhibition and bradykinin-mediated renal vascular responses. *Hypertension* 2004; 43: 533.

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Internationally renowned experts have provided data on their own studies, and discuss the relative usefulness of their work in relation to diabetic nephropathy. The first section describes the novel role of intrarenal renin-angiotensin-aldosterone system (RAAS) and oxidative stress in the development of diabetic nephropathy and discusses the current and novel pharmacological interventions in the treatment of diabetic nephropathy. The second section discusses other important contributors outside of the RAAS in the pathogenesis of diabetic nephropathy including AGE/RAGE, epithelial-mesenchymal-transition (EMT) and immune cytokines. Features: Provides novel information on various pathophysiological determinants in the development of diabetic nephropathy Provides novel information on various pharmacological interventions of diabetic nephropathy

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