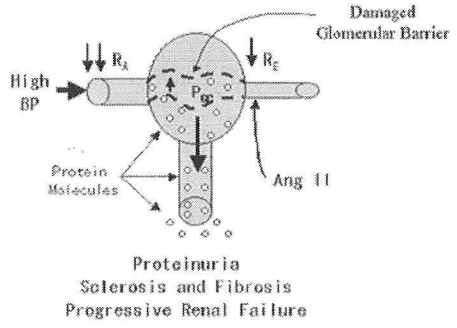
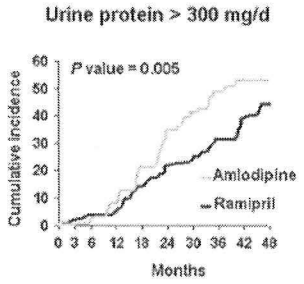
Internal Medicine Grand Rounds
August 30, 2001

Renoprotection in Common Hypertensive Renal Diseases:

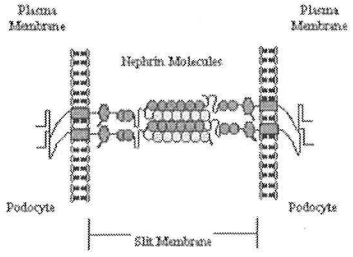
What Drugs? What Combination? and How Low Should You Go?

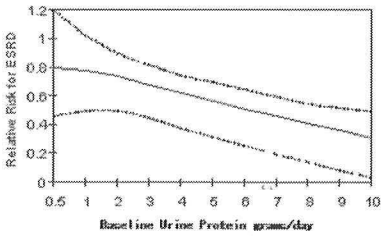
Robert D. Toto, M.D.





Basic Investigation ⟷ Clinical Trials



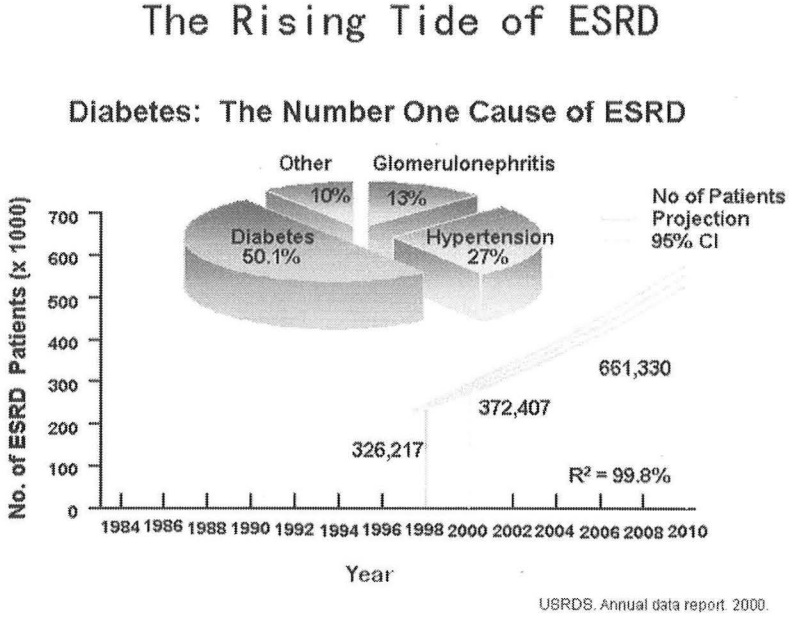


This is to acknowledge that Robert D. Toto, M.D., has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Toto will be discussing "off label" uses in his presentation.

INTRODUCTION

Approximately 360,000 persons are treated for ESRD by dialysis or kidney transplant in the United States. Moreover, the incidence of ESRD has been increasing annually since 1984 and current projections indicate that cases of ESRD will double by the end of this decade **(Figure 1)** [1]. This increase has occurred despite reductions in death due to stroke and myocardial infarction rates during the same time period. Diabetes and hypertension are highly prevalent in the United States population and together account for nearly three-fourths of all incident ESRD cases. The purpose of this Grand Rounds is to provide new insights into the pathogenesis and treatment of these common hypertensive renal diseases to clinicians who must manage the growing numbers of these (complicated) patients on a day-to-day basis. In this review I will illustrate how basic research has been translated into novel therapeutic regimens that reduce the risk for developing end-stage renal disease. In this regard, major new findings from several recently published/completed clinical trials of hypertensive renal will be discussed. Clinical investigators and their research teams at UT Southwestern Medical Center have made major contributions to this new body of evidence-based Medicine in Nephrology. The take home message from this presentation is shown in **Table 1.** I will now discuss foundations for this message.

Figure 1



Scope of the Problem

End-stage renal disease is a catastrophic illness characterized by life-threatening cardiovascular morbidity and multi-organ system dysfunction. The life-span of an average patient with ESRD treated by dialysis is approximately 7 years and the annual mortality rate of the U.S. hemodialysis

Table 1

Take Home Message: *Think Renal Protection*

- Incidence of end-stage renal disease is increasing dramatically (Type II Diabetes Mellitus)
- New clinical trials indicate that *how* you lower blood pressure (BP) makes a difference in renal outcomes
- Change your practice:
  - Achieve BP goal of $\leq$ 130/80 mmHg
  - Ace inhibitor or Angiotensin II receptor blocker first
  - Multi-drug therapy
  - Reduce proteinuria

population is about 20% per year [1]. Quality of life on dialysis is poor, characterized by high morbidity and hospitalization rates. Moreover, 60% of deaths in the hemodialysis population are attributed to cardiovascular causes. For this reason, non-renal cardiovascular diseases such as congestive heart failure, myocardial infarction, sudden death and stroke are important co-morbidities in the ESRD population. Therefore, **finding ways to prevent or stall the onset of ESRD is a high priority.**

Unfortunately, despite recent advances in our understanding of renal disease, the incidence and prevalence of ESRD are increasing in the United States driven by the epidemic of type II diabetes mellitus, the number one cause of ESRD [1]. Also certain ethnic groups including African-Americans and Mexican-Americans(MAs) have a 3-fold higher incidence of ESRD attributed to type II diabetes as compared to non-Hispanic Whites and African-Americans experience a 5-fold higher incidence of hypertensive nephrosclerosis compared to NHW and Hispanics. Compounding matters further is the fact that ESRD represents the tip of the iceberg of chronic renal disease (**Table 2**). Consequently, it is estimated that more than 7 million Americans are at risk for progressive renal disease culminating in ESRD [2]. Consistent with the statistical databases is the observations of practicing physician's offices that are filling up with hypertensive Type II diabetics with renal insufficiency. This trend will ultimately inundate ESRD care providers. As a matter of fact it is estimated that despite projected increase in ESRD **over the next 8.5 years** (to 2010), there will be **no increase in the number of nephrologists during this time period**. This means that the increasing burden of managing the patient with chronic renal disease is likely to fall on the shoulders of non-nephrologist primary care physicians, nurse practitioners and physician's assistants. To accomplish this practitioners need to understand the progressive nature of renal disease and the optimal way to manage these patients. The next section will discuss the importance of hypertension in the patient with renal disease to set the stage for key management issues that every treating physician must know.

Table 2 Estimates of Number of patients with Chronic Renal Disease in the United States

Serum Creatinine	Estimated Number in Population	Source
ESRD	350,000	USRDS
> 2.0 mg/dl	500,000	NHANES III
> 1.8 mg/dl	800,000	NHANES III
> 1.5 mg/dl	6,000,000	NHANES III

HYPERTENSION AND CHRONIC RENAL DISEASE

Hypertension is an important Risk Factor for ESRD

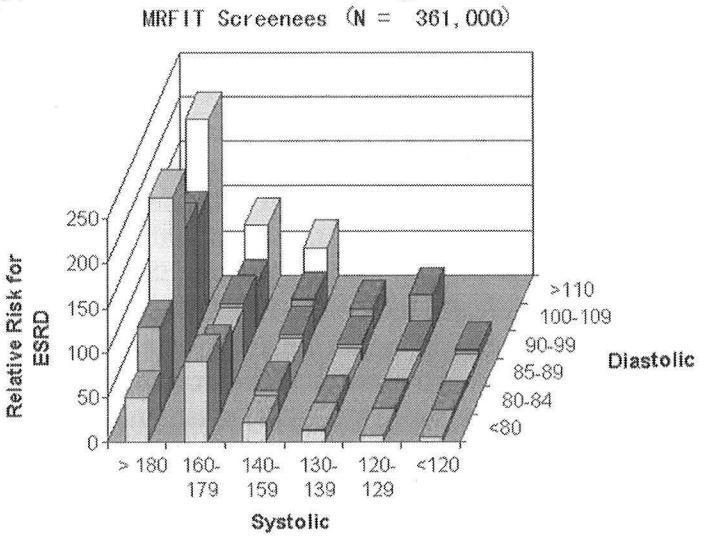
Hypertension is a major public health problem resulting highly prevalent in both diabetic and nondiabetic populations. It is estimated that between 1996 and 1998, 50 million people—or 1 in 4 adults—in the United States had hypertension defined as a systolic blood pressure (BP) $\geq$140 mm Hg or a diastolic BP $\geq$90 mm Hg [3;4]. The prevalence of hypertension varies among ethnic groups: 32.4%, non-Hispanic African Americans; 23.2%, non-Hispanic whites; and 22.6%, Mexican Americans [5]. In general, 68% of the 50 million individuals with hypertension were aware of their

diagnosis, and 53% were treated with antihypertensive agents, but only 27% were controlled with medication to a BP <140/90 mm Hg [5].

Progressive renal insufficiency leads to ESRD and 90% of patients who progress to ESRD are hypertensive during the course of renal disease [6]. Moreover, it is believed that uncontrolled hypertension accelerates the rate of progression in these individuals regardless of the cause of renal failure. Data from large clinical trials and epidemiologic studies indicate that hypertension is an important risk factor for progressive renal disease [7-10] (**Figure 2**) have demonstrated that hypertension is an important risk factor for progression of renal disease. As shown in Figure 2 the relative risk for ESRD increases with increasing systolic blood pressure independent of diastolic blood pressure. Over a 16-year period, 847 of the 361,000 men either died of or were treated for ESRD. High BP was a strong and independent risk factor for the development of ESRD, with a graded relationship between risk and BP. **Elevated systolic BP was especially predictive**, and a relatively small increase doubled the risk **of ESRD**. Mild to moderate elevations of BP correlated with renal disease, underscoring the need for control of hypertension at all levels. Moreover, in patients with type 2 diabetes mellitus, there is almost a linear relationship between increase in mean arterial BP and yearly decrease in glomerular filtration rate (GFR) [11]. These findings

Figure 2

Hypertension and End-Stage Renal Disease



Klag MJ et al. *N Engl Med* 334(1): 1996

Table 3

Blood Pressure Goals

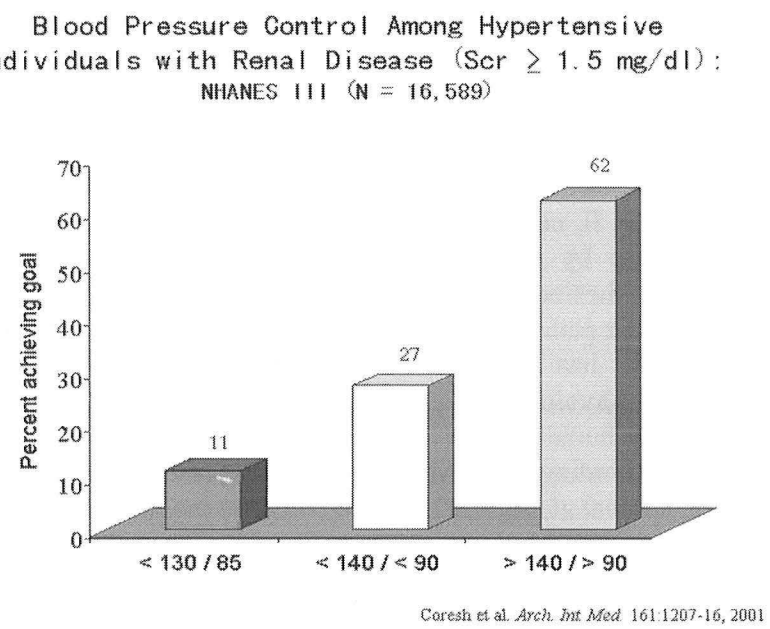
Hypertensive Category	Blood Pressure Goal
Essential	< 140 / < 90
Diabetic	130 / 80
Renal Disease	120 – 130 / 70-80* *lower BP for proteinuric

JNC VI, NKF, ADA

in part led the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) to make new recommendations for treatment goals for hypertension in general and for certain categories of hypertensives in particular **(Table 3).**

How Are We Doing in the Detection and Management of Hypertension?

Figure 3



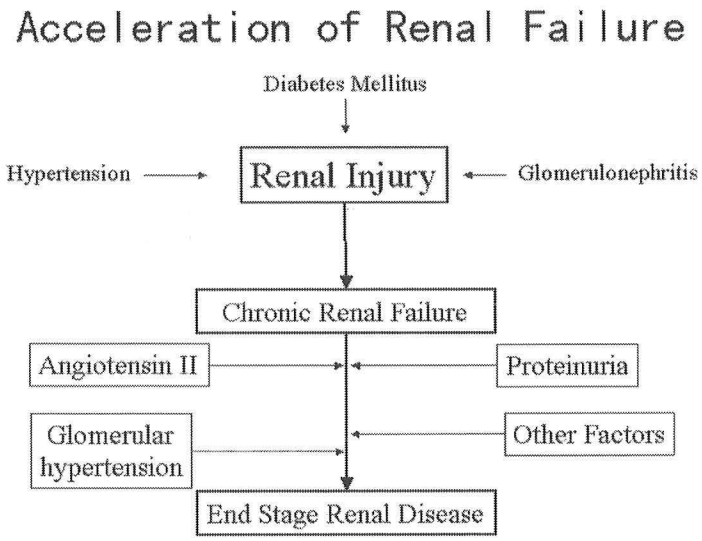
Two recently published studies using NHANES III data have evaluated blood pressure control in the overall population [12] and in those with hypercreatininemia (serum creatinine > 1.5 mg/dl) [13], a marker for chronic renal insufficiency suggest that we are not doing well. Hyman et al found that in general **older individuals with hypertension are unaware of their hypertension, are aware but not being treated and tend to have poor control rates.** These findings applied to all races evaluated and all age groups and indicated that most cases consisted of isolated systolic hypertension [12]. This is important for chronic renal disease risk because **the median age of patients entering ESRD program in the US is 64, and isolated systolic hypertension is a predictor of ESRD** (Figure 2). The NHANES III data indicate that the percentage of hypercreatininemic subjects achieving the recommended blood pressure goal is unacceptably low. That is, only 11% **(Figure 3)** of people with a serum creatinine ≥ 1.5 mg/dl have a blood pressure below 130/85, only 27% have a BP < 140/ < 90 and therefore 62% have a blood pressure > 140/ > 90 mmHg. This represents not only a huge challenge but also a major opportunity to improve the outcomes of patients with hypertensive renal disease. Given these challenges, it is important to understand the mechanisms by which renal disease may progress in the setting of poorly controlled or uncontrolled hypertension because lowering blood pressure is not the whole story.

PATHOPHYSIOLOGY

Renal Disease can be caused by many disease processes **(Figure 4).** I will concentrate on the role of angiotensin II, glomerular capillary hypertension and proteinuria which are linked in the pathogenesis and treatment of hypertensive renal disease. It should be noted that other factors not discussed are also important in renal disease progression. These other factors include non-modifiable risks such as age, gender and genetic predisposition, as well as potentially modifiable

factors such as smoking, dyslipidemia, glycemic control in diabetics and environmental and other high risk behaviors (e.g. illicit drug use). These factors have been the subject of a recent review for the eager reader [14].

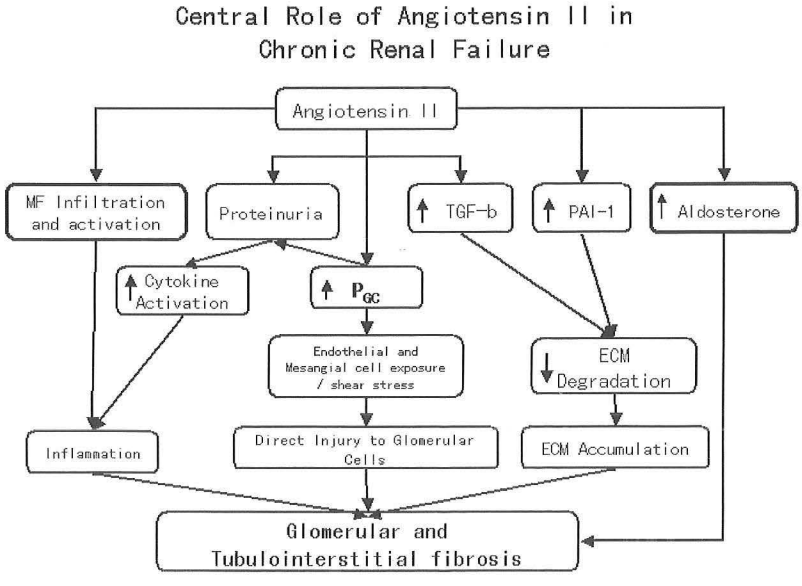
Figure 4



Role of Angiotensin II

It is well established that angiotensin II can be produced locally by many tissues and synthesized by ACE-independent pathways. Furthermore, it has been shown that physiologic effects of AII in humans are conferred by its binding to the AII subtype 1 (AT_1) receptor present in kidney, heart, brain, systemic vasculature, adrenal gland, and liver. AII binds to the AT_1 receptor on the cell surface of many cell types in these organs. resulting in tissue-specific effects of AII such as sodium reabsorption in the proximal tubule, vasoconstriction of the efferent arteriole in the kidney, aldosterone release from the adrenal gland, and increased inotropy and chronotropy in the heart as well as proliferative and hypertrophic and pro-inflammatory effects (increased tissue and plasma PAI-1 and TGF-β1 levels). The role of AII binding to the angiotensin subtype II receptor in humans remains undefined. However, studies in animal models indicate that downstream effects of AII binding to the type II receptor are opposite those of binding to the type I receptor (e.g. vasodilation, antiproliferative, apoptotic and natriuretic). These actions have been recently reviewed [15].

Figure 5



Angiotensin II (AII) plays a pivotal role in the development and progression renal disease in a variety of experimental animal models of chronic renal failure including renal ablation, diabetes mellitus, glomerulonephritis, and genetic models of nephrosis and hypertension [15]. In addition to the well known

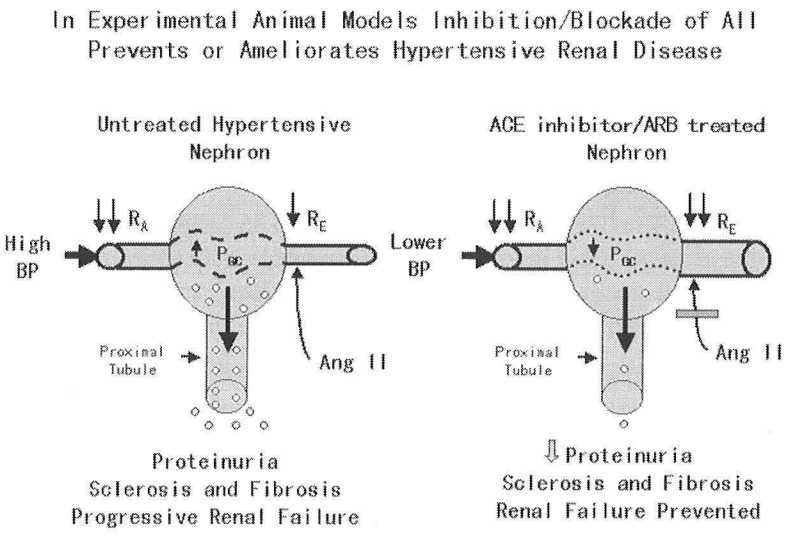
hemodynamic effects of angiotensin II including glomerular capillary hypertension due to preferential vasoconstriction of the efferent arteriole, AII has multiple non-hemodynamic effects as illustrated in **Figure 5**. on renal function in the failing kidney that can exacerbate renal disease, including systemic and glomerular hypertension, proteinuria, and glomerulosclerosis. Acute intrarenal artery injection of subpressor doses of causes proteinuria. Moreover, AII induces secretion PAI-1 and TGF-β which in turn enhance hypertrophy of glomerular and tubular cells, proteinuria, collagen formation, thrombosis, mesangial cell proliferation and extracellular matrix protein production. These effects conspire to produce sclerosis, fibrosis and chronic irreversible renal damage.

Clinical and experimental data also indicate a role for renal AII production in the development and progression of renal disease in humans. Data supporting a role for the AII in human renal disease is derived from studies in patients with renal disorders treated with agents that either inhibit AII formation or block AII receptors. These studies show equivalent reductions in BP and proteinuria when ACEIs and ARBs are compared [15] Recent evidence also indicates that intrarenal AII production is important in humans with renal disease. Moreover, dissociation between plasma angiotensin II concentration (which return to pre-ACE therapy level) and renal and cardiovascular outcomes during chronic administration of ACE inhibitors suggest that tissue angiotensin II concentration/action predominates [16].

EFFECTS OF ACEIs and ARBS in EXPERIMENTAL RENAL DISEASE

Figure 6 illustrates the typical hemodynamic picture observed during micropuncture studies of rats with renal failure caused by ablation, diabetes mellitus, glomerulonephritis [17]. As shown in the left hand panel of the figure, afferent arteriolar resistance is markedly reduced and efferent resistance is slightly reduced owing to an increase in tissue Angiotensin II. Consequently glomerular pressure (P_{GC}) is increased. In the presence of systemic hypertension glomerular hypertension is aggravated. In addition, glomerular barrier function is impaired allowing passage of protein from the capillary lumen into Bowman's space and subsequently into the urine. This picture is associated with proteinuria, glomerular and tubulointerstitial fibrosis and progressive renal disease. When these animals are treated with an ACE inhibitor or an AII receptor blocker, AII effects are blocked thus reducing efferent resistance and glomerular pressure toward normal and sharply reducing or eliminating proteinuria. Both glomerular structure and function are preserved,

Figure 6



consequently, glomerular and tubulointerstitial fibrosis are markedly reduced and renal failure is prevented [15;16]. It is important to note that when capillary pressure is lowered, glomerular filtration may also be lowered. Thus, it is quite common for clinicians to observe a small and persistent increase in serum creatinine concentration after starting a patient on an ACE inhibitor or AII receptor blocker (see below).

IMPORTANCE OF REDUCING PROTEINURIA

Detecting abnormal albumin excretion rate

Normal individuals excrete <150 mg/d of protein. Loss of protein (albumin) in the urine becomes apparent by reagent test strips when there is ≥ 300 mg/L or 300 mg albumin /g creatinine (**Table 3**). The recommended method for screening for abnormal amount of albuminuria is to first measure albumin by dipstick. If this is negative a random ("spot") urine sample should be sent to the lab to measure albumin and creatinine and the albumin/creatinine ratio is calculated. Collection of a 24 hr urine to screen for albuminuria is not recommended [18;19]. Under normal circumstances, urinary albumin measured as the ratio of albumin to creatinine on a random urine sample is <30 mg/g creatinine. Microalbuminuria is defined as an albumin excretion in the range of > 30 to < 300 mg/g creatinine and is not detected by the routine dipstick method (which by the way only detects albumin, not other proteins such as light chains). Macroalbuminuria is defined as an albumin excretion rate of ≥ 300 mg/g creatinine. Both are markers for risk for progression of nephropathy in patients with type 1 and type II diabetes and for increased risk of cardiovascular death [20-26].

Table 3

Microalbuminuria and Macroalbuminuria in Diabetes Mellitus

	Microalbuminuria	Macroalbuminuria (Overt Nephropathy)
Definition	> 30 mg < 300 mg/g Cr	≥ 300 mg / g Cr
Routine dipstick	No	Yes
Method of estimate*	Albumin / Creatinine ratio	Albumin / Creatinine ratio
Renal Significance	Marker incipient diabetic nephropathy	Marker progressive renal disease
Increased CV Risk	Yes	Yes

* Random (Spot) urine preferably A.M. sample

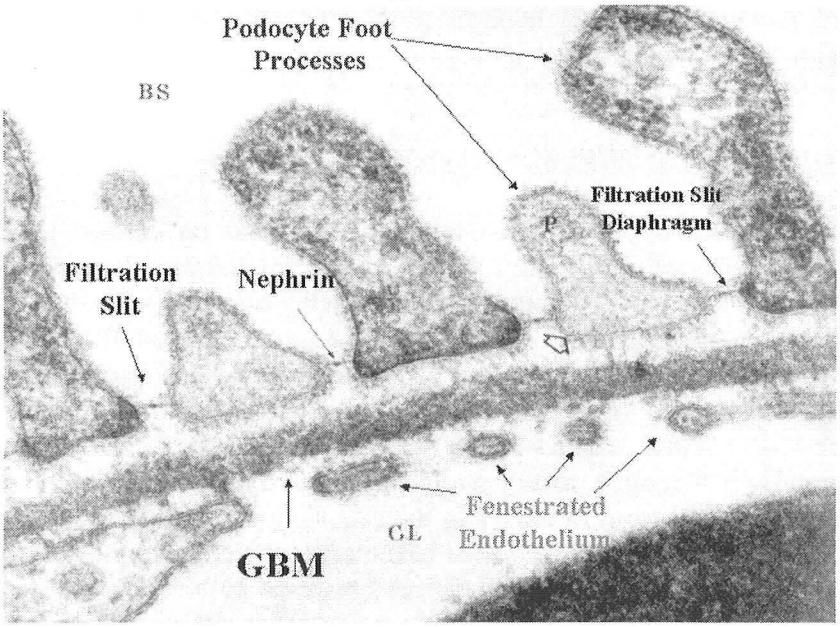
Proteinuria has been extensively studied as a marker for progression of renal disease [20;27-50]. Numerous clinical trials have shown that patients with impaired renal function and high-grade (>1 g/d) proteinuria progress at a faster rate than those with low-grade (≤1 g/d) proteinuria [51]. For example, in both diabetic and non-diabetics with proteinuric renal disease, acceleration of renal disease progression correlates with the level of baseline proteinuria. Even in patients with controlled essential hypertension and no evidence of renal disease, the onset of proteinuria may be a marker of future decline of renal function [21;22;24;52] Also, the Modification of Diet in Renal Disease (MDRD) Study, a large-scale NIH sponsored clinical trial of diet and blood pressure control in patients with established chronic renal disease, demonstrated that baseline proteinuria was an independent risk factor for progression of renal disease in nondiabetic patients, and the degree of proteinuria reduction might be a measure of the effectiveness of BP control [28-30]. In a meta-analysis described

in detail below, baseline proteinuria was a marker for progressive renal failure and those with higher grade proteinuria at baseline appear to have greater benefit when treated with an ACE inhibitor as compared to non-ACE inhibitor therapy [51].

The Molecular Basis of Proteinuria

The molecular basis of proteinuria caused by excessive leak of protein across the glomerular capillary wall (as opposed to tubular proteinuria referring to tubular diseases that can also cause loss of protein in the urine) has been extensively investigated in animals and humans [43;45;47;53-59;59-64] [23;59;62;65-73]. However, the precise mechanisms responsible for restriction of passage of protein in normal kidneys as well as the cause for abnormal permeability in disease have not been fully elucidated. Recent studies have shed new light on this issue. For example, it has recently been shown that several forms of hereditary nephroses are caused by mutations in the genes encoding structural proteins of the glomerular capillary wall. These studies provide new insights the mechanisms of massive proteinuria. A review of the normal anatomy of the glomerular capillary is helpful in understanding these new insights. As shown in **Figure 7** the glomerular capillary wall is comprised of three layers: 1) a fenestrated capillary endothelium; 2) the glomerular basement membrane and 3) the visceral epithelial cells or podocyte foot processes (pedicels). Plasma ultrafiltrate transverses the capillary wall via an extracellular route, through the fenestrae of the endothelium, the GBM and finally between the podocyte foot processes. It is known that restriction of protein from Bowman's space is in part due to a net negative charge produced by proteoglycans and other proteins on the cell surfaces and on the endothelium, GBM and podocyte [74;75]. Size selectivity is also a major component to the normal restriction (permselectivity) of the glomerular capillary wall. As shown in Figure 7, the filtration slit diaphragm is a thin membrane that is interconnected to the plasma membrane of podocytes and seated on the outer aspect of the glomerular basement membrane. Nephrin is a structural protein localized to the filtration slit diaphragm [76] and the gene for this protein has been cloned. This protein is thought to be an important component of the barrier to passage of plasma proteins as mutations in the nephrin gene result in nephrotic syndrome (see below). Mutations in human genes encoding α-actinin D, a cytoskeletal protein of the podocyte causes one form of familial focal glomerulosclerosis [77]. Also mutations in glomerular type IV collagen and podocin, a podocyte cytoskeletal protein may

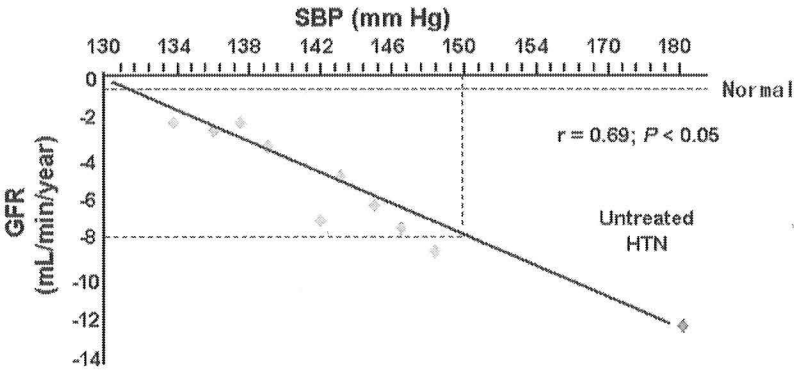
Figure 7



also cause severe proteinuria [78]. Mutations in other podocyte cytoskeletal proteins such as CD-2, an adaptor protein cause nephrotic syndrome in animal models [79]. In addition, mutations in the gene encoding **nephrin**, a structural protein localized to the filtration slit diaphragm **(Figure 7)** cause Finnish type congenital form of nephrotic syndrome [76;78]. In Finnish type congenital nephrosis and familial focal sclerosis similar electron microscopic findings include effacement of the visceral epithelial cell foot processes. How the mutations produce abnormal pathology and disease is still under investigation. In a recently published study in experimental nephrosis induced by antigen-antibody complex deposition in the kidney, investigators demonstrated downregulation of nephrin gene and protein expression in association with hypertension and severe proteinuria. Pre-treatment of rats with nephrosis using either an ACE inhibitor or an Angiotensin II receptor antagonist not only lowered blood pressure and proteinuria but also prevented downregulation of nephrin gene expression and glomerular morphologic alterations [80]. This study suggests that inhibition of synthesis or activity of AII protects glomerular structure perhaps by preservation of normal nephrin action.

Figure 8

The Impact of Blood Pressure Lowering on Progression of Renal Disease



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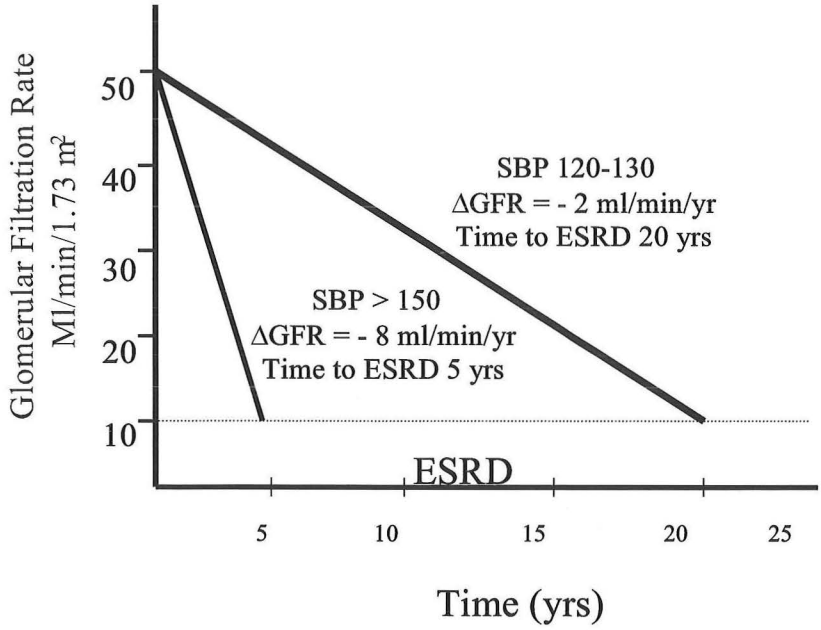
IMPORTANCE OF LOWERING BLOOD PRESSURE in RENAL DISEASE

Most large clinical trials of antihypertensive therapy have focused on cardiac and cerebrovascular endpoints. Consequently, only a few clinical trials have examined the effect of BP lowering on the progression of renal disease in both diabetic and nondiabetic patients. Early clinical trials in hypertensive patients with renal insufficiency failed to show a significant benefit of BP lowering on decline in GFR [81;82]. However, the target level of BP control in these studies was relatively high by today's standard. For example, among the small subset of patients undergoing repeated measures of GFR over a 3- to 5-year period in the VA Cooperative Trial, mean treated diastolic BP was lowered to 97 mm Hg in the active treatment arm versus 117 mm Hg in the placebo arm. At the level of 97 mm Hg, there were no differences in the rate of decline in GFR [81]. In contrast, more recent clinical trials with lower target BP levels have demonstrated lowering BP in hypertensive patients at risk for or already established renal disease preserves renal function. For example, the MDRD study which included 800 subjects with chronic renal disease of diffuse pathophysiologic origin, demonstrated that subjects with higher grade proteinuria, i.e. $\geq$ 1.0 g per day randomized to lower blood pressure goal of 125/75 had significantly slower rate of decline in

GFR as compared to those randomized to a higher BP goal of about 139/89 mmHg [83]. This is the only large-scale clinical trial of chronic renal disease in which two levels of blood pressure control were directly compared with a primary renal outcome. **Figure 8** illustrates the mean rate of decline in glomerular filtration rate plotted as a function of mean controlled systolic blood pressure in 9 clinical trials (including MDRD) of both diabetic [84-87] and non diabetics with chronic renal disease [29,47;57,60,88]. The dotted line labeled "Normal" indicates the normal rate of decline in GFR of about 0.75 ml/min/yr observed with aging alone in normal male subjects. As can be seen in the figure, lower SBP values are associated with slower rate of decline in GFR. In the only study that focused specifically on hypertensive nephrosclerosis, our group at UTSW demonstrated that lowering BP to 120–130/70–80 mm Hg in patients with established renal failure and at high risk for progression to ESRD was associated with a very slow mean decline in GFR, similar to that observed with aging (~0.8 mL/min/yr) [90]. We also found that lowering BP below the currently accepted goal to 125/75 mm Hg slows the decline in GFR particularly in patients with >1 g/d of proteinuria.[12] The clinical implications of these data for our patients is illustrated in **Figure 9**. Assuming a patient with Type II diabetic nephropathy and hypertension has a creatinine of about 2.0 mg/dl corresponding to a GFR of 50 ml/min. At a controlled systolic BP of 150 mmHg the GFR declines at a rate of about 8 ml/min/yr. At this rate the patient will be on dialysis (GFR of 10 ml/min) in 5 years (8 ml/min/year x 5 = 40). In contrast if the SBP level is controlled in the range of 130-135 mmHg GFR declines at about -2 ml/min/yr. In this case the patient would reach ESRD in 20 years.

Figure 9 Hypothetical Time to ESRD Based on Different Rates of Decline in GFR at Two Different Levels of SBP Control



How Do I Get the Blood Pressure to 130/80 mmHg in Hypertensive with Renal Disease?

Figure 10 illustrates the average number of medications required to achieve blood pressure controls in hypertension trials including patients with (denoted by asterisk) and without renal disease. As shown in the figure the average number of antihypertensive medications required to achieve the blood pressure goals cited above is 2-4 per patient. Thus, the important point is that in approach to patients with hypertensive renal diseases one must anticipate the need for multi-drug therapy. The new clinical studies presented below underscore this point.

The optimal method for achieving control has not yet been determined. However, in an effort to provide clinicians with a practical and reasonable method using evidence-based medicine, the following algorithm was developed for treatment of diabetic hypertensives including those with renal disease (**Figure 11**). The first step in this regimen is the use of an ACE inhibitor combined with a diuretic because of clinical trials indicating the use of ACE inhibition is superior to non ACE inhibition therapy. In the future this may be modified for Type II diabetics based on recent clinical trials demonstrating benefit of AII receptor antagonists on renal outcomes in Type II diabetic nephropathy (see below). Subsequent steps in the algorithm may be flexible in various patient groups. Maintaining the blood pressure within the control range is possible for prolonged periods of time but requires frequent follow-up. Achieving these goals in diabetics and nondiabetics has not been shown to increase morbidity or mortality as compared to higher BP control levels [91;92]. Home blood pressure monitoring may facilitate management and BP devices for home are now relatively inexpensive. Furthermore, most patients can be taught

Figure 10

Average Number of Antihypertensive Agents Required to Achieve BP Goals

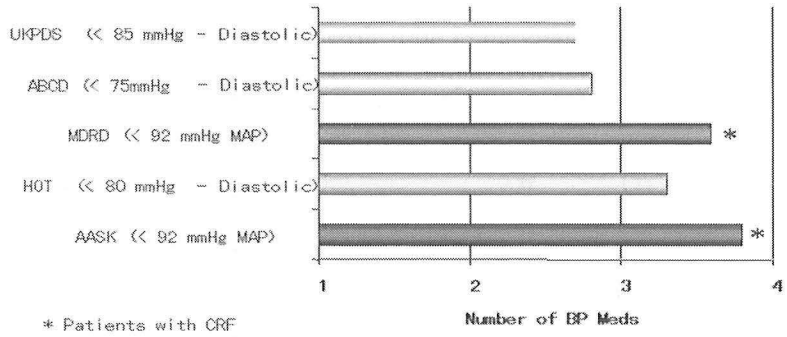
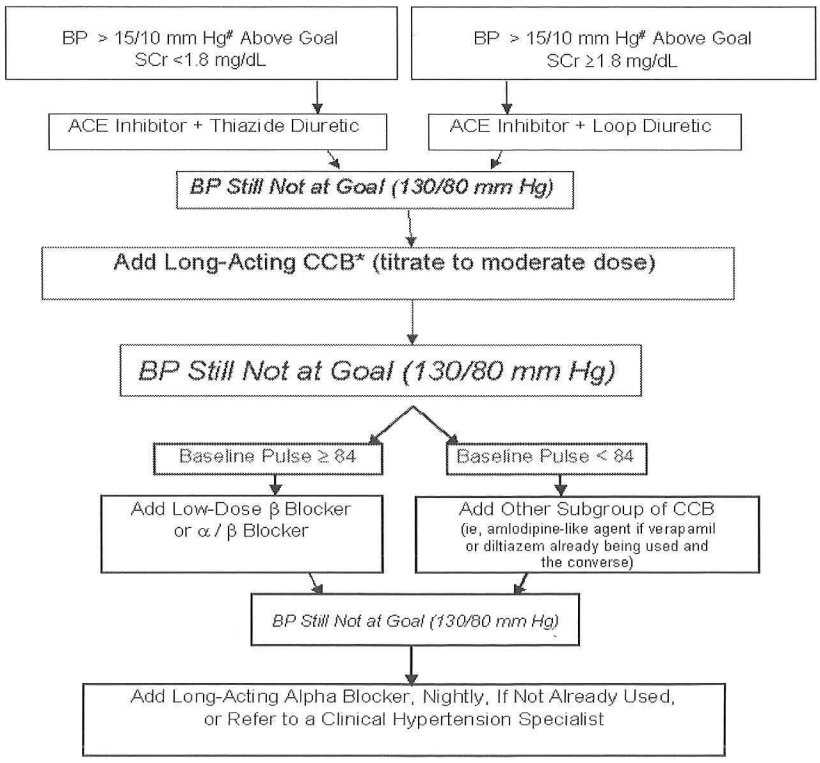


Figure 11

Algorithm for BP Control in Hypertensive Renal Diseases



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how to use BP devices to their advantage in long-term treatment. I encourage all of my patients with hypertensive renal disease to purchase a BP device and record their blood pressure daily and use it as guide to keep their pressure under control.

MEASURING OUTCOMES IN PATIENTS WITH CHRONIC RENAL DISEASE

To introduce this topic it is important to review methods used in renal trials to measure outcomes. Clinical trials of patients with renal disease generally use two types of endpoints for measuring outcomes. The first method is the ***rate of decline in glomerular filtration rate*** either by direct measurement or estimate based on measured creatinine clearance. This approach although scientifically correct is not a practical method. The second method is *combined endpoints* in which estimating renal outcomes based on time to event of ***doubling of serum creatinine, time to end-stage renal disease and/or death***. Some trials and meta-analysis of trials utilize both types of endpoints. The latter method is considered by most authorities to be more clinically relevant and is less expensive than measuring GFR repeatedly. The studies described below have been published or completed and presented at National meetings within the past 3 months. Two major trials recently completed but not yet published were performed in Type II diabetes, a common problem in an Internist's office today.

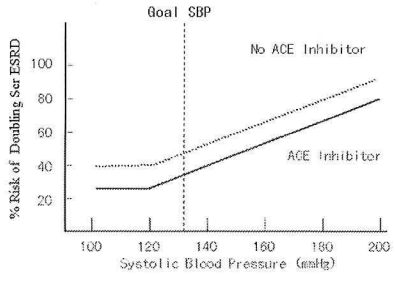
CLINICAL TRIALS OF TREATMENT OF HYPERTENSIVE RENAL DISEASE: The Importance of Lowering Blood Pressure and Proteinuria with Drugs that Inhibit the Renin-Angiotensin System

META-ANALYSIS OF NON-DIABETIC CHRONIC RENAL DISEASE

A meta-analysis of individual patient data from 11 randomized, controlled clinical trials in non-diabetic patients with chronic renal disease assessing the effects of ACE inhibitors on renal disease progression was reported by a group of investigators including myself in the ***Annals of Internal Medicine*** **on July 17, 2001** [51]. All patients in these trials had documentation of doubling of serum creatinine and ESRD and 8 trials used repeated measurements of GFR to monitor renal function. In this analysis the authors reported on the risk of: 1) developing doubling of serum creatinine and 2) ESRD amongst this sample of 1,860 patients. Hypertension or decreased renal

Figure 12

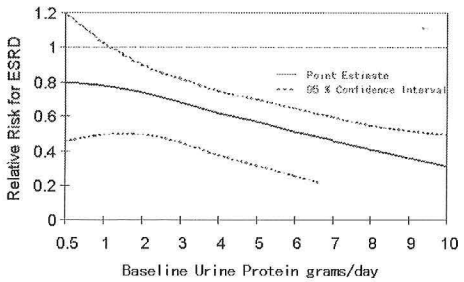
Lowering Systolic Blood Pressure Reduces the Risk for ESRD in *Non*-Diabetic Nephropathy: (N = 1860)



Jaffar et al. *Ann. Int. Med.* 2001

Figure 13

Patients With Greater Urinary Protein Excretion at Baseline Benefited More from ACE inhibitor Therapy



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function was required for entry and patients were excluded if they had acute renal failure, immunosuppressive medications, congestive heart failure, urinary obstruction, renal artery stenosis, systemic disease, renal transplant, pregnancy or allergy to ACE inhibitors. Control groups received placebo in 5 studies, a specified medication in 5 studies and no specified medication in 1 study. Other antihypertensive medications were used to achieve goal BP of < 140/90 mmHg. We found that for **any level of systolic blood pressure the risk for development of ESRD was lower in the ACE inhibitor treated as compared to the non-ACE inhibitor treated patients**. Notice that the reduction in risk for lowering blood pressure begins to plateau but does not increase as SBP approaches 120 mmHg, consistent with the recommendation for achieving a goal systolic blood pressure of 120-130 mmHg. An additional important finding in this analysis is shown in **Figure 13**. This figure illustrates the point estimates for the relative reduction in risk reduction for ESRD (solid line) the 95% confidence interval for these estimates (dotted line). **The beneficial effect of ACE inhibition to reduce the risk for ESRD was greatest in subjects who had the highest baseline proteinuria**. This is compatible with the MDRD study and studies in diabetics with nephropathy [30;60;93;94]. However, **one limitation of these data** is noteworthy. As can be seen in the figure the upper 95% CI crosses the 1.0 level just under 1.0 grams per day of proteinuria. This means that **for subjects with ≤ 1.0 grams per day of proteinuria in this analysis, one cannot be certain that the superior effect of the ACE inhibitor persists below this level.** The effect of ACE inhibitors in this study was further analyzed after adjusting for baseline proteinuria, baseline systolic blood pressure and follow up proteinuria and systolic blood pressure. **Table 4** shows the relative risk reduction for developing ESRD during treatment with an ACE inhibitor after controlling for these variables in a multivariate analysis. As shown in the table **the effect of ACE inhibition on reduction in risk for ESRD was robust**. After controlling for effects of lowering blood pressure and proteinuria, the renoprotective effect of ACE inhibition persisted. From this analysis we concluded that: 1) Antihypertensive regimens including ACE inhibitors are more effective than regimens not including an ACE inhibitor; 2) beneficial effects of ACE inhibition go beyond BP and proteinuria lowering and 3) ACE inhibitors are indicated in the treatment of nondiabetic patients with chronic renal disease and proteinuria and perhaps for those with less than 1 gram per day of proteinuria as well. **The main message is: Use an ACE inhibitor as part of the anithypertensive regimen for treating hypertension in non-diabetic chronic renal disease.**

Table 4

	Relative Risk ACEI vs no ACEI	(95% C.I.)
Unadjusted	0.63	(0.51 - 0.85)
Adjusted for Baseline SBP	0.66	(0.48 - 0.89)
Adjusted for Baseline proteinuria	0.66	(0.49 - 0.91)
Adjusted for Follow-up SBP and Proteinuria	0.69	(0.51 - 0.94)

THE AFRICAN AMERICAN STUDY of KIDNEY DISEASE AND HYPERTENSION (AASK) TRIAL

End-stage renal disease attributed to hypertension occurs at rates 5- fold higher in African-Americans compared to NHW and Hispanics. The rate of increase in ESRD attributed to

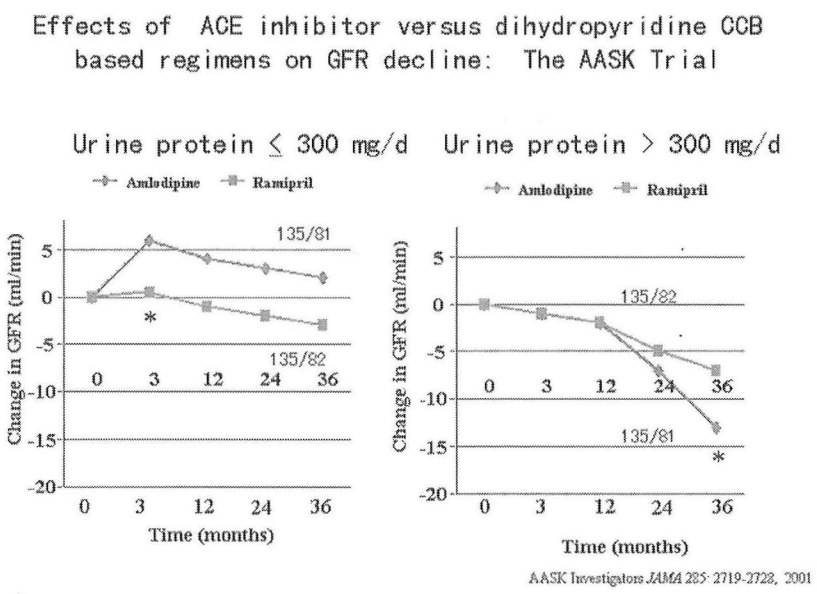
hypertension has been rising and it is the second leading cause of ESRD accounting for about one-fourth of all new cases of ESRD. In 1994 we became a leading clinical center for the African-American Study of Kidney Disease and Hypertension and our center played a major role in the design and conduct of the full-scale trial in which still ongoing. The full-scale trial is an NIH sponsored large-scale multicenter (20 centers) long-term randomized, double-blind study in African-Americans with hypertensive nephrosclerosis designed to determine whether strict blood pressure control and/or specific antihypertensives are superior for slowing progression of renal disease in African-Americans with hypertensive nerphrosclerosis. Participants are African-American aged 18-70 years, with GFR between 20-65 ml/min/1.73 m^2 and no other identified causes of renal disease. Exclusions are DBP < 95 mmHg, history of DM, urine protein/creatinine ratio > 2.5, accelerated hypertension within 6 months, secondary hypertension and clinical congestive heart failure. The study uses a 3 X 2 factorial design to evaluate two different levels of blood pressure control-MAP < 92 mmHg and MAP 120-107 mmHg and three primary (administered in a double-blind fashion) antihypertensive classes including an ACE inhibitor (ramipril), a dihydropyridine calcium channel blocker (DHP CCB) (amlodipine) and a β-blocker (Metoprolol XL) in hypertensive African-Americans with established chronic renal insufficiency. Doses of these blinded antihypertensive medications were 50-200 mg/day, 2.5-10 mg/day, and 5-10 mg/day, respectively. If the BP goal was not achieved on the study drug, additional unmasked drugs were added in the following recommended order: furosemide, doxazosin, clonidine, hydralazine, and minoxidil. The dosage of each drug was increased to the maximum tolerated dose before the addition of a subsequent agent. Study drug assignment but not BP goal was double-blinded. During the six-month period following randomization, antihypertensive drugs were adjusted at monthly visits to achieve the BP goal. Subsequent protocol visits occurred at two-month intervals. GFR was assessed by ^{125}iothalamate clearance at baseline twice, then at 3, 6 and every six months thereafter.

The primary analysis of renal function is based on the rate of change in GFR (GFR slope). GFR slope was determined separately over the first three months after randomization (acute phase) and during the remainder of follow-up (chronic phase), because previous studies indicated that drug interventions could result in acute changes in GFR that differ from long-term effects on renal disease progression[5;21-25].

A secondary clinical-outcome analysis was based on the time from randomization to any of the following endpoints: i) a confirmed reduction in GFR by 50% or by 25 ml/min/1.73m^2 from the mean of the two baseline GFR measurements, ii) ESRD, defined as need for renal replacement therapy, or iii) death. The clinical endpoint analysis was identified as the principal assessment of patient benefit. In contrast to the analysis of GFR slope, which addresses the mean drug effect on renal function in all patients including those with little or no GFR decline, the clinical endpoint analysis is based on events of clinical impact, either large declines in renal function or death. During interim analyses, a significant interaction between the ACEI vs. DHP-CCB comparison and baseline proteinuria for the acute and total mean GFR slopes was identified. Therefore, subgroup analyses were performed in participants with baseline UP/Cr above and below 0.22 (a value corresponding approximately to 300 mg/day, which indicates the presence of microalbuminuria). The baseline UP/Cr > 0.22 subgroup includes one-third of the study participants, with the remaining two-thirds belonging to the baseline UP/Cr ≤ 0.22 subgroup. The UP/Cr cutpoint of 0.22 was post-hoc but was selected independently of the AASK data. The amlodipine arm of the study was subsequently discontinued and the results comparing amlodipine to ramipril were published in the ***JAMA* June 6, 2001** [(95)]. The blood pressure control arms, and β–blocker versus ramipril data end in October 2001.

During the chronic phase, mean GFR declined 1.16 ml/ min/1.73m^2/yr (95% confidence interval, 0.42 to 1.90) faster in the amlodipine than the ramipril group (p = 0.002). However, during the acute phase, GFR increased 4.19 ml/min/1.73m^2/yr (95% confidence interval, 2.64 to 5.74) more in the amlodipine than ramipril group (p < 0.001); consequently the mean total slope (including acute and chronic phases) did not differ significantly (p = 0.38) between the treatment groups. As described below, the different results for chronic and total slopes are clarified by taking into account the level of baseline proteinuria.

Figure 14



The acute rise in GFR produced by amlodipine was confined to the patients with baseline protein excretion of <300 mg/day (i.e. urine protein to creatinine ratio of ≤ 0.22). As a consequence there were highly significant interactions of the treatment regimen with baseline proteinuria for both the acute GFR slope (p=0.001) and the total mean slope (p < 0.001). As shown in **Figure 14**, left panel, the mean ± SE total decline in GFR to three years was 1.22 ± 0.44 ml/min/1.73m^2/yr faster in the ramipril group than in the amlodipine group among participants with baseline UP/Cr ≤ 0.22 (~300 mg/day)(p = 0.006), but was 2.02 ± 0.74 slower in the ramipril group than in the amlodipine group among the patients with baseline proteinuria of > 0.22 (p=0.006), (**Figure 14**, right panel).

During the chronic phase, mean GFR declined at a substantially faster rate in patients with higher baseline proteinuria (UP/Cr >0.22) than in patients without proteinuria ≤ 0.22 (p < 0.001). The rate of GFR decline during the chronic phase was 2.37 ± 0.80 ml/min/1.73m^2/yr less in the ramipril group than in the amlodipine group in participants with baseline UP/Cr > 0.22 (p = 0.003). Among participants with baseline UP/Cr ≤ 0.22, the difference in mean chronic GFR slope between ramipril and amlodipine groups was somewhat smaller (0.80 ± 0.43, p = 0.07).

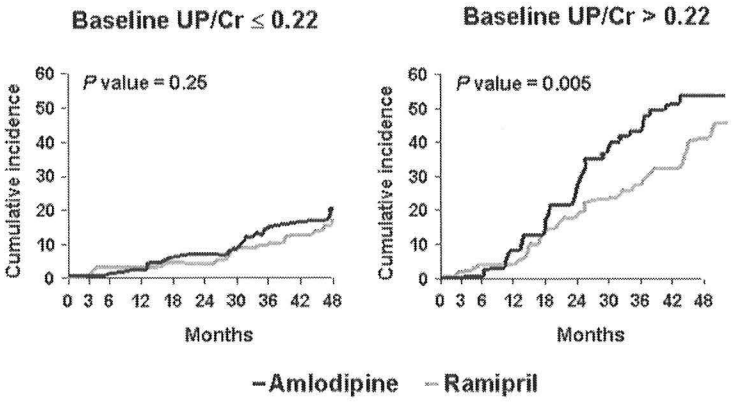
Clinical endpoint analysis

The results of the analysis of clinical endpoints are presented in **Figure 15**. Without covariate adjustment, the risk reduction for the ramipril vs. amlodipine groups for the clinical composite outcome including all three endpoints was 26% (95% confidence interval, -4% to 47%), p = 0.085. After adjustment for the prespecified covariates as required by the study's analysis plan, the risk reduction for the ramipril vs. amlodipine groups in the clinical composite outcome was 38%, (95% confidence interval, 13% to 56%, p = 0.005), for the combined hard endpoints of ESRD or death (excluding GFR events) it was 41%, (95% confidence interval,14% to 60%, p = 0.007), and for the two renal endpoints, major declines in GFR or dialysis, censoring death, it was 38%, (95%

confidence interval, 10% to 58%, p = 0.01). The risk reduction in the clinical endpoints for the ramipril group was not significantly related to baseline proteinuria (p = 0.25), but was strongly influenced by the subgroup with baseline proteinuria UP/Cr> 0.22 (~300 mg/day) since 90 of these 143 events (62.9%) occurred in this group.

Figure 15

AASK: Incidence of Declining GFR Events, Dialysis, or Death



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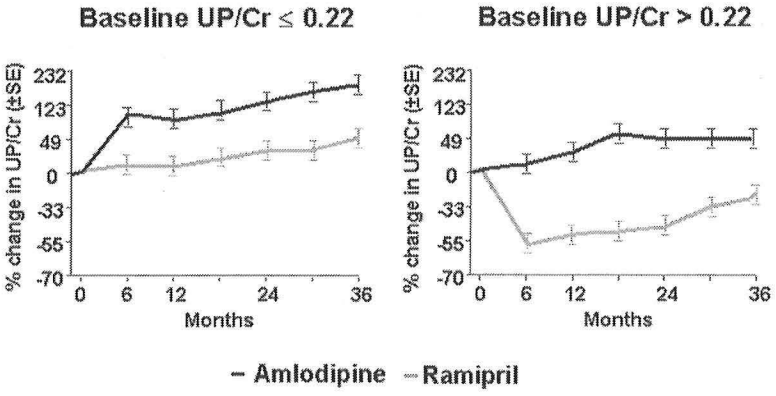
Proteinuria

Proteinuria (geometric mean UP/Cr) **increased by 57.9% in participants in the amlodipine group and declined by 20.2% in the ramipril group during the first 6 months of the study.** This difference between treatment groups was highly significant (P<0.001) and persisted throughout the follow-up period, with moderate increases in proteinuria in both groups. The percentage increase in proteinuria was significantly greater with amlodipine than ramipril in both baseline proteinuria strata (**Figure 16**). However, the magnitude of the difference between the ACEI and DHP-CCB groups in the median change in UP/Cr was larger for the baseline UP/Cr > 0.22 strata (0.35 gm protein/gm creatinine) than for the baseline UP/Cr < 0.22 strata (0.02 gm protein/gm creatinine). Nonetheless, the length of time until UP/Cr first reached 0.22 (~300 mg/day) for those participants with baseline UP/Cr £ 0.22 was substantially shorter for the amlodipine than the ramipril group (p = 0.002, data not shown). From this component of the AASK study we concluded that: 1) initial antihypertensive therapy with an ACE inhibitor offers greater benefit in slowing deterioration of renal function than DHP-CCB in patients with mild to moderate chronic renal

Figure 16

AASK: % Change in Proteinuria From Baseline



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insufficiency associated with hypertensive nephrosclerosis; 2) ACE inhibitors are useful in lowering blood pressure and proteinuria in hypertensive African-Americans with renal disease and 3) ACE inhibitors are renoprotective particularly in patients with urine protein/creatinine ratio > 300 mg/g creatinine or a value of > 0.22 but also mitigate proteinuria as compared to DHP-CCB in patients with urine protein < 300 mg or a urine protein creatinine ratio of ≤ 0.22. **The main message is: Use an ACE inhibitor as part of the anithypertensive regimen for treating hypertension in patients with hypertensive nephrosclerosis, especially African-Americans.**

ANGIOTENSIN II RECEPTOR ANTAGONISTS IN NEPHROPATHY CAUSED BY TYPE II DIABETES MELLITUS

ACE Inhibitors in Type II Diabetic Nephropathy

Diabetic Nephropathy is the leading cause of ESRD and is driving the rising tide of ESRD. Moreover, type II diabetes accounts for the majority of cases of diabetic ESRD and this trend is expected to increase in the future. However, in contrast to type I diabetes there are no large scale trials using ACE inhibitors to prevent renal failure. Several small clinical trials in patients with microalbuminuria and overt nephropathy in the setting of type II diabetes mellitus demonstrated reduction in proteinuria and/or slowing of glomerular filtration rate decline; however until now there have been no randomized controlled trials examining outcomes such as doubling serum creatinine, ESRD and death in type II diabetes [11]. Despite this revelation, ACE inhibitors have been applied to the type II diabetes population with established or suspected diabetic nephropathy through extrapolation from studies performed in type I diabetics with nephropathy [93]. In the Type I collaborative group trial, patients with overt nephropathy were found to benefit from captopril as compared to non-ACE inhibitor therapy. Two important findings in this trial deserve emphasis: 1) the benefit of captopril as compared to placebo control was observed only in patients with an elevated serum creatinine at baseline (> 1.5 mg/dl) and 2) captopril but not placebo significantly lowered urine protein excretion despite the fact that mean reduction in blood pressure was similar among treatment groups and did not explain the difference in outcome. In this section I will discuss two recently completed, but **unpublished clinical trials of nephropathy in patients with type II diabetes mellitus using angiotensin II receptor antagonists.** The first trial is the Renal Endpoints in NIDDM with the Angiotensin II Antagonist Losartan, or RENAAL trial.

The RENAAL Trial

On the basis of the lack of evidence of studies with ACE inhibition in Type II diabetics with nephropathy and with the advent of the angiotensin II antagonists, this trial was designed and conducted. The study design has been published [96]. Briefly, RENAAL is a multinational, double-blind randomized placebo-controlled trial evaluating the renal protective effects of losartan in 1,513 patients with Type II diabetes and nephropathy at 250 centers in 29 countries around the globe. The study was initiated in 1996 and enrollment was completed in 1998 and the study was closed out in March of 2001 with an average of 3.4 years of follow-up. Participants were included if they had type 2 diabetes defined as age > 30 years at diagnosis, insulin not required within six months , no DKA currently treated with diet, oral hypoglycemics, or insulin, urine protein albumin to creatinine ratio of > 300 mg/g, serum creatinine ≥ 1.5 mg/dl (1.3 mg/dl in women) to 3.0 mg/dl, HgbA1c < 12 mg%, and age 31-70. Patients were excluded if they had type 1 diabetes, history of nondiabetic renal disease, history of MI, CABG within past month, CVA, PTCA within 6 months, or TIA within 12

months, history of heart failure or known renal artery stenosis, primary aldosteronism or pheochromocytoma. After completing a baseline evaluation, participants were maintained on conventional therapy at baseline then randomized to either placebo or losartan 50 mg administered once daily. The dose of losartan was titrated to 100 mg/day and other conventional, non-ACE inhibitor (or other AII receptor antagonist) therapy to achieve a target BP goal of < 140/90 mmHg (remember this was designed in 1996 when BP goal for renal disease was not yet defined as stringently as today). The primary composite endpoint of the trial was time to first event of doubling serum creatinine, end-stage renal disease or death. Secondary endpoints were the time to first cardiovascular event including myocardial infarction, congestive heart failure, unstable angina, CVA, reduction in proteinuria and decrease in the rate of decline in GFR estimated by 1/Scr versus time. The results showed that losartan treatment reduced the risk of the primary composite outcome by 16% (P = 0.024). The risk reduction for doubling serum creatinine was 25% (p=0.006) and ESRD was 28% (P = 0.002), and the risk reduction for the combination of ESRD or death was 20% (P=0.10). This is the **first and only clinical trial in any form of renal disease ever to demonstrate a significant risk reduction for an *end-stage renal disease* endpoint.** There was no significant difference in all-cause mortality in losartan treated patients. In the secondary outcomes analysis, the losartan-treated group had a 32% risk reduction for first hospitalization for heart failure. Furthermore, median proteinuria decreased by 35% in the losartan as compared to a slight increase in the placebo group (P = 0.0001). The rate of decline in GFR was also significantly attenuated with losartan as compared to placebo (P = 0.01)slower in the Importantly, there was no difference in blood pressure level between groups: 140/74 mmHg for losartan and 142/74 mmHg for placebo (P = NS). An additional important finding a 32% risk reduction in subsequent development of ESRD in those patients who experienced a doubling of serum creatinine (endpoint) but continued on blinded study medication. This finding indicates that continuing the administration of losartan despite renal disease progression continues to provide renal protection by prolonging the time to ESRD and thus renal replacement therapy (dialysis or transplantation). The reported incidence of clinical and laboratory adverse events was similar between losartan and placebo.

In summary, the RENAAL trial demonstrated that treatment of type II diabetic nephropathy with losartan (alone or in combination with conventional antihypertensive therapy) delays the progression to ESRD, reduces proteinuria and reduces the incidence of hospitalization for heart failure. Moreover, these benefits are largely independent of achieved blood pressure. Because there was no head-to-head comparison with ACE inhibitors it is not known whether similar results would be obtained with this group of agents. How the RENAAL data will affect clinical practice remains to be determined and should await publication with subsequent debate and discussion within the medical community. Nevertheless, **the main message from this trial is that the AII receptor antagonist losartan in conjunction with conventional antihypertensive therapy is preferable to conventional antihypertensive therapy alone because of its superior renoprotective effect in Type II diabetic nephropathy.**

<u>Irbesartan Diabetic Nephropathy Trial</u>

The Irbesartan in Diabetic Nephropathy Trial has been completed and the primary results presented. UT Southwestern investigators in the Nephrology Division also participated in the design and conduct of this trial. But like the RENAAL trial, the IDNT is yet to be published. This study was performed contemporaneously with the RENAAL trial in a nearly identical patient population with the same primary composite endpoint as RENAAL. The study design and baseline patient

characteristics have been published [97]. However, the IDNT is unique in that it studied 1,715 patients randomized in double-blind fashion to one of three (about 550 patients per group) groups: 1) irbesartan; 2) amlodipine; and 3) conventional antihypertensive therapy excluding ACE inhibitors, all types of calcium channel blockers and other angiotensin II receptor blockers. Conventional therapy was also employed in the irbesartan and amlodipine groups to achieve a goal blood pressure of < 135/<85 mmHg. The average follow up was about 3 years. The results indicated that irbesartan compared to amlodipine and conventional groups reduced the risk for the primary composite endpoint of doubling serum creatinine, ESRD or death by 20% and relative risk for doubling of serum creatinine was reduced by 39%. There was also a reduction in proteinuria in the irbesartan but not the other control groups. Blood pressure control was similar among groups indicating that the beneficial effects of irbesartan on renal outcomes were independent of the blood pressure lowering effects. **The main message from this trial is that the AII receptor antagonist irbesartan is preferable to amlodipine or conventional antihypertensive therapy alone or because of its superior renoprotective effect in Type II diabetic nephropathy.**

In summary, we now have two completed large multicenter clinical trials in Type II diabetics involving more than 3,000 Type II diabetics with nephropathy that both demonstrate risk reduction for progression of renal disease. These two trials represent advances in the management of Type II diabetic nephropathy and will have to be reckoned with. It is noteworthy that neither study was sufficiently powered to detect differences in death among treated groups. This is an important point in view of the results from the HOPE trial in which the ACE inhibitor ramipril was shown to lower mortality in the 3,000 patient cohort with Type II diabetes. However, it is important to point out that the diabetic population included in the HOPE study was dramatically different from the populations studied in RENAAL and IDNT. There are several reasons that come to mind. First, the HOPE trial was not designed to study patients with renal disease or to evaluate renal outcomes. Thus only 275 diabetic patients in the HOPE study had microalbuminuria whereas all 3,230 of the RENAAL and IDNT patients had overt proteinuria. Second, few HOPE study patients had advanced renal disease and only 956 of the total HOPE trial cohort had a serum creatinine above 1.4 mg/dl. Third, the diabetic patients were not severely hypertensive and had few CV complications prior to onset of the trial.

Lessons from the Meta-analysis, AASK, RENAAL and IDNT

It is important to note several common themes in these trials. First, in all of these trials drugs that inhibit the renin-angiotensin system were found to be superior to those that do not. Second, multiple drug therapy was required to reach the target BP goals in patients with renal disease. Third, after controlling for blood pressure reduction, the most striking (renal) benefits were observed in patients with abnormally elevated baseline serum creatinine and protein excretion rates. Moreover, these beneficial effects were accompanied not only by a reduction in blood pressure but also by a reduction in proteinuria. This means that the an elevated serum creatinine concentration per Se is not a contraindication to the use of an ACE inhibitor or AII receptor antagonists. Quite the contrary. All of the evidence indicates that is precisely the patients with an elevated baseline serum creatinine who actually benefit in clinical trials. The reasons not to use these agents is in the case of 1) hyperkalemia; 2) known allergy (e.g. rash, angioedema, cough, etc.); 3) known or suspected critical bilateral renal artery stenosis. The observation that serum creatinine often increases after administration of an ACE inhibitor or AII receptor antagonist in patients with nephropathy is common and as alluded to earlier is expected based on the known intrarenal hemodynamic effects of inhibition of AII production or action.

Figures 17 and 18, illustrate the results of short-term and long-term impact of inhibition of renal angiotensin II with an ACE inhibitor or an AII receptor blocker (ARB) in a patient with chronic renal disease with a baseline GFR of 50 ml/min and a serum creatinine of 2.0 mg/dl. The resulting stable increase in serum creatinine from 2.0 to 2.5 mg/dl shown in Figure 16 is associated with delayed onset of ESRD as shown in Figure 17. Under these circumstances the patient should

Figure 17

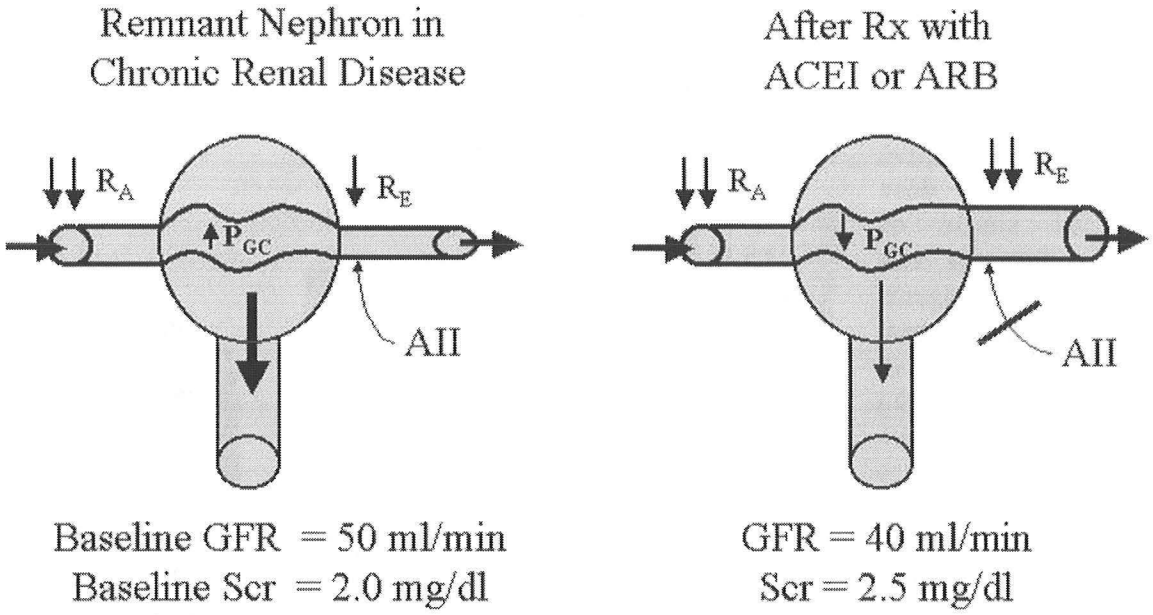
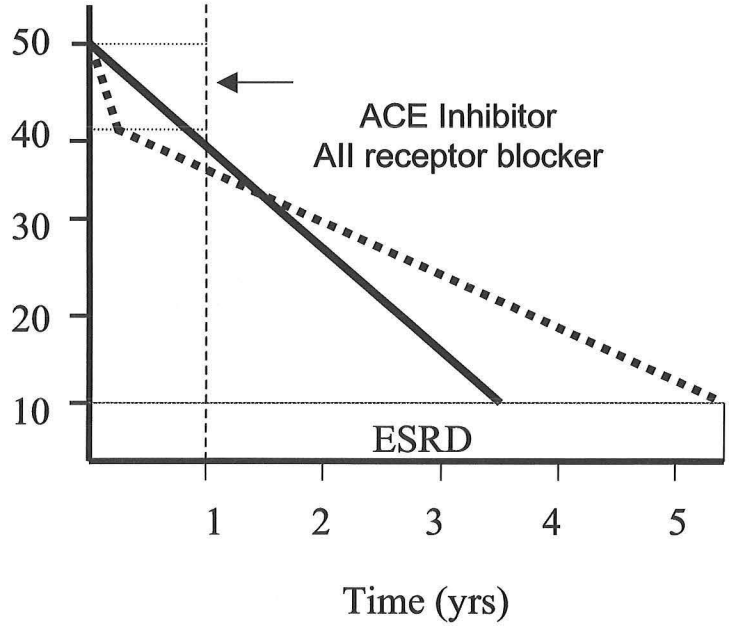


Figure 18 Short-term and Long-Term Impact of ACE Inhibitor or AII receptor blocker in Chronic Renal Disease



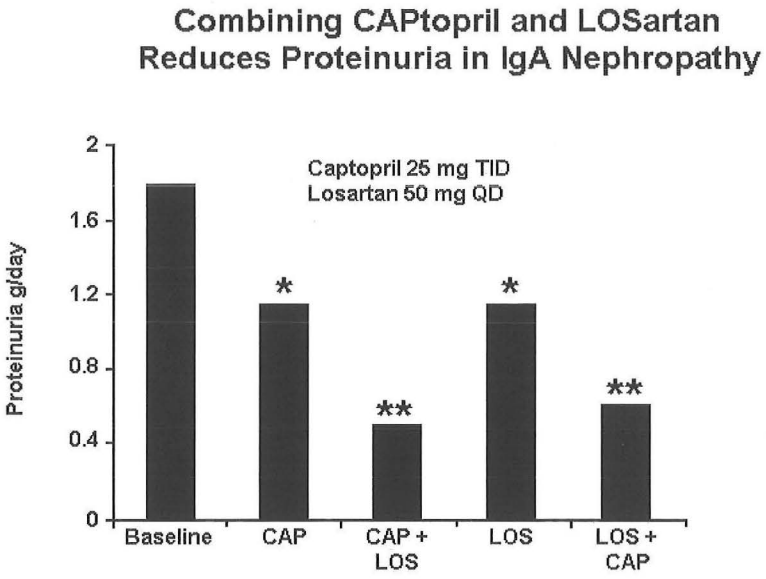
not be taken off the ACE inhibitor or AII antagonist. However, if serum creatinine is rising abruptly or inexorably, the drug should be stopped and a search for hemodynamic or other causes of acute renal insufficiency should be undertaken. In most instances low blood pressure, volume depletion (e.g. overdiuresis) or decompensated heart failure is the cause and these drugs can be restarted once the creatinine returns to baseline. And as shown in the RENAAL trial continuing losartan in patients with gradually rising serum creatinine is still preferable to discontinuation (i.e. time to ESRD is prolonged by continued use of losartan compared to continued use of placebo). **The main message is that optimal care of the patient with progressive renal**

disease due to diabetic and non-diabetic nephropathies should include ACE inhibitors or angiotensin II receptor antagonists (Type II diabetic with nephropathy).

When Should I Use an ACE inhibitor in combination with an AII receptor antagonist?

This is a frequently asked and important clinical question. Unfortunately, there are few studies examining this issue in patients with renal disease. There are no prospective studies examining dose titration of single or combination therapies with these two classes of agents in patients with renal disease. In a small clinical trial (**Figure 19**) demonstrated that the combination of captopril 25 mg po tid to losartan 50 mg po qd significantly reduced proteinuria to a greater extent than either drug alone in patients with IgA nephropathy [98]. Theoretically, this combination would be beneficial in patients with persistent severe proteinuria who are at the blood pressure goal of $\leq$ 130/90 mmHg. Further research in this area is needed.

Figure 19



Conclusion

In conclusion, the following points should be emphasized. End-stage renal disease incidence and prevalence are increasing and Type II diabetes mellitus has emerged as the major cause of ESRD. Lowering blood pressure preserves renal function in patients with common hypertensive renal diseases including hypertensive nephrosclerosis and diabetes. The clinician should focus on achieving a goal blood pressure of 120-130 systolic and 70-80 diastolic with the emphasis on BP "goal" rather than "control". Optimal management of hypertension in this setting should include either an ACE inhibitor or Angiotensin II receptor antagonist as part of the antihypertensive regimen (in Type II diabetes mellitus). Furthermore, reduction of both blood pressure and proteinuria should be achieved. reduced along with blood pressure in order to maximize renal protection. Using this approach we may be able to stem the ever rising tide of ESRD.

ACKNOWLEDGEMENTS

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