IMPROVING OUTCOMES IN DIABETIC NEPHROPATHY

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This is to acknowledge that Dr. Toto has disclosed financial interests or other relationships with commercial concerns related directly to his program. Dr. Toto will be discussing off-label uses in his presentation.

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Dr. Toto's research interests include prevention, diagnosis, and management of chronic progressive kidney diseases and their complications. His major research interest is diabetic nephropathy.

Introduction

Diabetic nephropathy is a devastating disease. It is characterized by proteinuria (> 300 mg albumin/g creatinine), elevated blood pressure, and rapidly declining renal function. Nephropathy afflicts 30-40% of diabetics, causing end-stage renal disease (ESRD) at a median age of 50 in type 1 and 65 in type 2 diabetics. Morbidity and mortality are sharply increased after onset of nephropathy, and 20% die within one year of onset of ESRD. Sadly, it is now the leading cause of ESRD not only in the United States but also around the world. Moreover, among type 2 diabetics, nephropathy disproportionately afflicts ethnic minorities, and the cost of care for ESRD alone exceeds $4 billion annually. The prevalence of ESRD in the US is projected to double over the next 10 years, and type 2 diabetes is the major reason why. The epidemic of type 2 diabetes currently affecting the US includes both young and older Americans. This in turn increases the likelihood that higher rates of ESRD attributed to type 2 diabetes will continue. Consequently, there is an urgent need to find ways to prevent development of nephropathy and identify interventions that improve outcomes.

New evidence indicates that diabetics with nephropathy are more likely to die than to develop end-stage renal disease. Myocardial infarction, heart failure, stroke and amputation, some of the devastating cardiovascular complications of diabetes so familiar to internists, can occur at higher rates in those with nephropathy. Cardiovascular outcomes are now the center of attention of most nephrologists and the focus of new clinical trials.

The purpose of this grand rounds is to discuss the latest evidence supporting use of multiple risk factor intervention in diabetics with nephropathy, not only to preserve renal function but more importantly to reduce the risk of fatal cardiovascular events. The goal is to better understand how and what interventions are appropriate now, and future directions of clinical research designed to improve outcomes in diabetic nephropathy. This discussion begins with the following case.

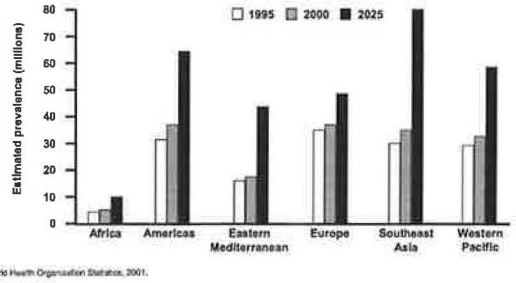
Case Presentation

History: A 55 year old black male is evaluated for lower extremity edema. He has a history of type 2 diabetes and hypertension for the past 8 years and has been taking a calcium channel blocker and a thiazide for hypertension and insulin to control his blood glucose. Past medical history is significant for non-ST myocardial infarction 2 years ago. His mother died on dialysis with ESRD attributed to diabetes and his father has hypertension and a history of stroke. He smokes 1 pack of cigarettes a day for 25 years and consumes 3 drinks per day. He is currently employed as a construction worker. Review of systems is significant for dyspnea on exertion, fatigue and nocturia. Current medications are insulin, amlodipine and traimterene/thiazide combination.

Physical examination reveals BP 150/100 mmHg, PR 86 bpm, RR 16, T 36.5 deg C. Weight 105 kg, Height 1.77 M, BMI 31.7 kg/M^2. Eye exam reveals diabetic retinopathy, S4 present, abdomen is protuberant, 2+ pretibial edema, dorsalis pedis and posterior tibial pulses 1+, decreased vibration sense below knees.

Laboratory reveals fasting glucose 201 mg/dl, A1c 8.8%, BUN 32 mg/dl, Scr 2.4 mg/dl, K 4.9 mEq/L, TCO2 18 mEq/L, Urine albumin 155 mg/dl, creatinine 100 mg/dl, Ca 8.9 mg/dl, P 4.1 mg/dl Hgb 10.5 g/dl, Hct 31, serum iron 50 ug/dl, TIBC 260 (% saturation 19.2), ferritin 150 mg/dl, normal RBC indices, albumin 3.5 g/dl, fasting triglyceride 220 mg/dl, HDL-C 33 mg/dl, LDL-C 150 mg/dl, urine albumin/creatinine ratio 1,550 mg albumin/g creatinine, urine analysis reveals 3+ protein, no RBC, no WBC, casts or crystals, EKG reveals LVH; renal sonogram reveals symmetric 10 cm kidneys with increased echogenicity.

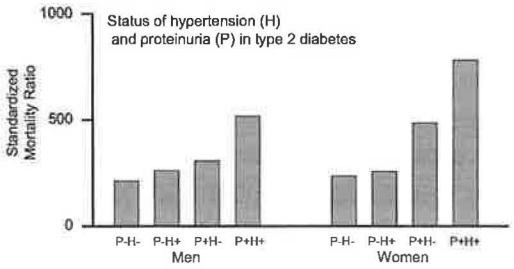
Current and Projected Prevalence Rates for Diabetes Worldwide



World Health Organization Statistics, 2001.

Figure 1

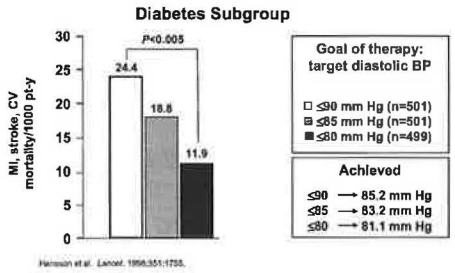
Excess Mortality With Hypertension and Proteinuria in Type 2 Diabetes



Wang SL et al. *Diabetes Care* 1996;19:305-312.

Figure 2

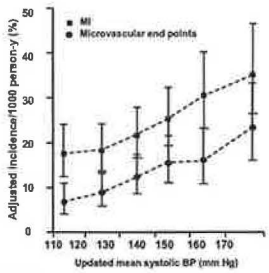
BP Control Reduces CV Events in Hypertensive Type 2 Diabetics: The HOT Trial



Hansson et al. *Lancet*. 1998;351:1755.

Figure 3a

MI and Microvascular End Points Are Lower at Lower SBP in Type 2 Diabetics: UKPDS



Adler et al. *BMJ*. 2000;321:412

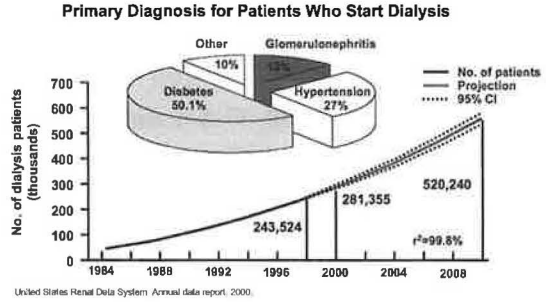
Figure 3b

Key Questions: What is the cause of his renal disease? What, if any, additional work up is needed now? What can we tell him about his renal function now and in the future? How should we manage him now?

Diabetic Nephropathy is the Number One Cause of ESRD and is Growing

Diabetes is epidemic worldwide (**Figure 1**). For example, it is estimated that in the Americas diabetes prevalence will double from 37 to about 70 million over the next 20 years. This trend is present in East Mediterranean countries, Europe, Asia, Africa and the Western Pacific. Type 2 diabetes is the major contributing factor to the skyrocketing prevalence of diabetes around the world. Moreover, mortality rates among diabetics are 2-3 times higher than non-diabetics[1]. Both hypertension and proteinuria contribute to increased mortality among male and female diabetics. The combination of hypertension and proteinuria is worse than either risk factor alone (**Figure 2**)[2]. Lowering blood pressure is associated with substantial reduction in risk for cardiovascular mortality among type 2 diabetics, and even small differences in systolic and diastolic blood pressure can translate into large reductions in cardiovascular morbidity and mortality (**Figure 3**)[3,4].

Diabetes:
The Most Common Cause of ESRD



United States Renal Data System. Annual data report. 2000.

Figure 4

Figure 4 illustrates the prevalence of treated end-stage renal disease in the United States over the past 20 years and projected forward to 2010. Accounting for the increased prevalence is an increase in both incidence rates and increased survival rates in the past 5 years. It is evident that the number of dialysis patients will nearly double from 2000-2010, and as shown in the inset, diabetes accounts for 50% of new cases of ESRD[5]. Type 2 diabetes occurs at younger ages than in the past, and diabetics are living longer; therefore, more will be at risk for kidney disease. At

this time, nearly one of every two new cases of ESRD is attributed to diabetic nephropathy. African-Americans, Hispanics, Native Americans and Asian Pacific Islanders suffer nephropathy disproportionately compared to non-Hispanic Whites. Reasons for these racial disparities are incompletely understood, but earlier onset of kidney disease and more rapid progression are possible explanations. Furthermore, 5 year survival for diabetics is about 25% compared to 55% in non-diabetics, and 2-year survival after myocardial infarction among diabetics on dialysis is 25%[6]. The increasing incidence and prevalence of diabetics with ESRD continues to be a major problem for the United States health care system, and estimated Medicare costs for ESRD alone for diabetics exceeds $4 billion (nearly 1/3 total ESRD costs). And as expected, the cost of care for a diabetic on dialysis is nearly 50% higher than a non-diabetic (USRDS). It should also be noted that NHANES III data suggest that as many as 19 million Americans may have less severe forms of chronic kidney disease. Costs of care for this group is far beyond that for the ESRD patients. Continued accession of diabetics into the end stage renal disease program will not only increase human suffering but continue to escalate the costs of lost productivity and health care. Steps must be taken to stem the tide of development and progression of diabetic nephropathy.

Summary 1

There is a global epidemic of type 2 diabetes. Hypertension and proteinuria increase risk for both progression of renal disease and cardiovascular mortality among diabetics. Nephropathy attributed to diabetes is the leading cause of ESRD in the US, it disproportionately afflicts minorities and is World. Survival on dialysis among diabetics is poor and death from cardiovascular events is common. The cost of care for ESRD alone exceeds $4 billion annually and this cost will increase in the future. Diabetic nephropathy is a major public health problem.

Diabetic Nephropathy is a Clinical Diagnosis That Carries an Increased Risk for Morbidity and Mortality

Clinical and Pathologic Features of Diabetic Nephropathy

Clinical	Pathological
• Albuminuria (> 300 mg/g)	• Glomerulosclerosis
• Elevated blood pressure	• Tubulointerstitial fibrosis
• Rapidly declining function	• Vascular disease

Table 1

Definition: Diabetic nephropathy is characterized by proteinuria, elevated blood pressure, relentless decline in renal function and very high cardiovascular morbidity and mortality. Biopsy, surgical or autopsy specimens of kidneys from patients with these characteristics typically reveal glomerular, vascular and tubulointerstitial abnormalities (**Table 1**). Typical lesions include thickening of the glomerular basement membrane, diffuse and nodular glomerulosclerosis (Kimmelstiel-Wilson lesion), arteriolar sclerosis, arteriolar hyalinosis, chronic tubulointerstitial nephritis and fibrosis[7-15]. Importantly, there is a strong correlation glomerulosclerosis and loss of glomerular filtration. Filtration function also correlates with flattening of podocyte foot processes and the presence of these epithelial cells in the urine of diabetics with nephropathy. Advanced sclerosis of the juxtaglomerular apparatus is common in type 1 and 2 diabetics and is in part responsible for the development of hyporeninemia and hypoaldosteronism commonly observed in these patients. However, seldom is a kidney biopsy performed to diagnose diabetic nephropathy. Indeed there are a number of non-typical or alternative lesions that may be seen in type 2 diabetics when biopsied to evaluate hematuria or proteinuria[16,17]. Therefore, it is likely that many patients diagnosed with diabetic nephropathy are misclassified. In the future, changing the standard of care to include a renal biopsy or identifying better noninvasive markers (e.g. genetic, other) will resolve this problem. Therefore, in

Proteinuria in Diabetes Mellitus

	Microalbuminuria	Macroalbuminuria (Overt Nephropathy)
Routine dipstick	No	Yes
Urine Albumin / Cr	30 - 300 mg Alb / g Cr	≥ 300 mg Alb / g Cr
Renal Significance	Marker incipient diabetic nephropathy	Marker progressive renal disease
CV significant	↑ CV death	↑ CV death

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

Table 2

most cases such as our patient, diabetic nephropathy is a clinical diagnosis that does not require a biopsy by today's standard of care.

Table 2 illustrates the definition of abnormal albumin excretion rate currently adopted and promulgated by the American Diabetes Association (ADA) and the National Kidney Foundation (NKF) for the clinical diagnosis of diabetic nephropathy[18]. Importantly, abnormal albumin excretion rate is not only associated with progressive renal disease (macroalbuminuria) but also with increased risk for cardiovascular death (micro and macroalbuminuria). The importance of measuring albuminuria as sign for vascular and kidney disease has been underscored by the NIH special panel on markers of renal function[19]. Currently most authorities accept microalbuminuria as a marker of vascular endothelial dysfunction that carries with it increased risk for cardiovascular and all cause mortality. For the purposes of this discussion the term diabetic nephropathy refers to those patients with albuminuria in the range ≥ 300 mg albumin/g creatinine. Some have termed this condition "overt nephropathy".

Proteinuria, Glycemia, Activation of Renin-Angiotensin-Aldosterone System (RAAS), Hypertension, Dyslipidemia and Anemia are Important Risk Factors Among Diabetics with Nephropathy

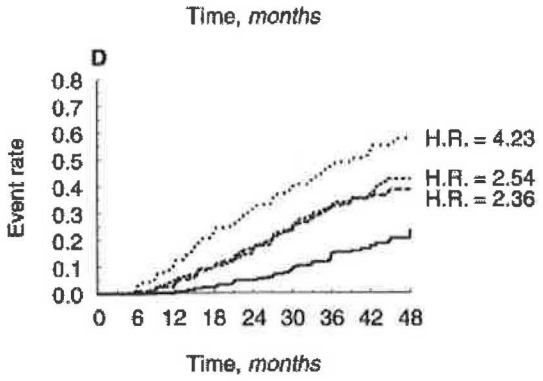


Figure 5: Keane et al, *Kidney Int*, 63:1499-1507, 2003

Shown on the Y-axis is the event rate for the composite endpoint of doubling serum creatinine and ESRD. Curves represent baseline urine protein quartiles for participants with type 2 diabetes and nephropathy. As shown in the figure those with the highest baseline quartile have a 4 fold higher event rate than those in the lowest quartile (quartile ranges are 1 < 0.5; 0.6-1, 1.-3 and ≤ g albumin/g creatinine.

Traditional cardiovascular risk factors, including hypertension, dyslipidemia and impaired glucose tolerance, are common in diabetic nephropathy. In addition, proteinuria, anemia and activation of the RAAS are non-traditional risk factors ever present in such patients. Both traditional and non-traditional risk factors are potentially modifiable and doing so may improve outcomes in diabetic with nephropathy.

Proteinuria is the strongest and most consistent predictor of improved long-term renal survival in diabetic nephropathy[13,20-34]. Furthermore, it has been hypothesized but not proven that excessive protein filtration causes further renal injury in diabetic (and non-diabetic) nephropathy[35-38]. Therefore, treatment strategies that maximally reduce proteinuria in diabetic nephropathy would be predicted to improve outcome. Intensive BP lowering is one such therapy. Intensive lowering of BP combined with ACEi therapy in heavily proteinuric (up to 20%)[39] type 1 diabetics dramatically attenuates proteinuria and stabilizes renal function[39-41]. For these reasons, the National Kidney Foundation has recommended BP lowering combined with an ACE inhibitor as first-line

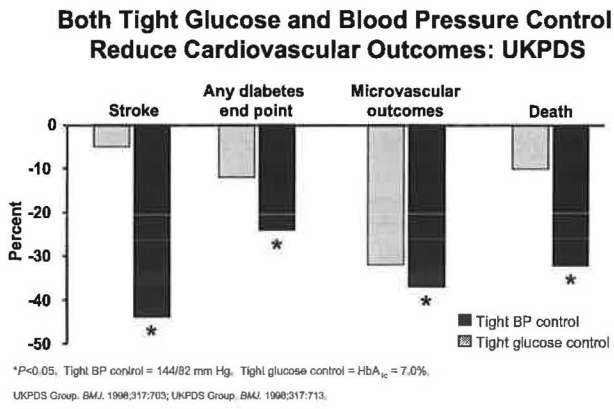


Figure 6

therapy for hypertensive diabetics with nephropathy[42]. However, BP lowering in large clinical trials of diabetic nephropathy is suboptimal[22,43,44], and those with greatest renal benefit have lower average clinic BP[40].

Analysis of outcomes from the Reduction in Endpoints in NIDDM with the Angiotensin Antagonist Losartan (RENAAL) trial demonstrated that proteinuria at baseline predicted subsequent development of doubling of serum creatinine and end-stage renal disease (**Figure 5**).

Glycemic Control is an important factor in the development and progression of nephropathy. Tighter glucose control is associated with decreased risk for development and progression of both type 1 and type 2 diabetics with nephropathy [45-49] (**Figure 6**).

Activation of the RAAS is a prominent feature of diabetics with nephropathy. The RAAS plays a major role in the onset and progression of diabetic nephropathy, and abundant evidence indicates that intrarenal angiotensin II production and/or (sensitivity to) action are increased in diabetic nephropathy. AII binding to type 1 (AT_1) receptors causes glomerular hypertension, renal hypertrophy, sclerosis, proteinuria and accelerated decline in renal function by hemodynamic and non-hemodynamic mechanisms. These effects are mediated through multiple cascading pathways, including growth-promoting factors, pro-fibrotic factors, prothrombotic cytokines such as PAI-1, and increased oxidative state, which conspire to cause progressive renal disease. Chronic inhibition of AII production by ACEi or selective AT_1 receptor blockade by ARBs dramatically attenuates glomerular and tubular damage, proteinuria, and renal failure in animal models and slows progression of renal disease in humans with diabetic nephropathy (**Figure 7**)[50].

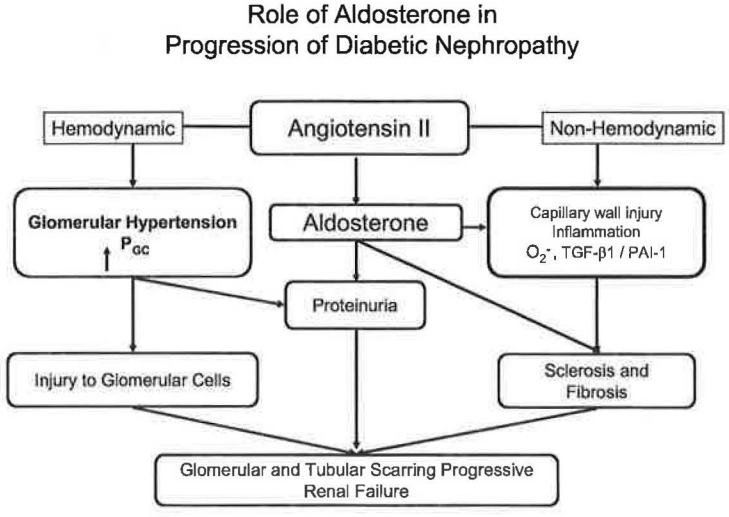


Figure 7

New information indicates that aldosterone may play an independent role in causing general vascular toxicity as well as direct renal injury. Experimental animal studies suggest that aldosterone acts independent of AII to cause proteinuria and renal fibrosis, and reducing aldosterone level or blocking its receptor are renoprotective. Plasma aldosterone is increased in some patients with diabetic nephropathy, and plasma angiotensin II level is elevated in some patients with type 2 diabetes and early nephropathy, and chronic ACEi treatment in hypertensive patients may increase plasma aldosterone levels despite persistent hypotensive effect of ACEi. Several lines of evidence indicate that aldosterone may produce vascular toxicity, and this may be mediated through increased sodium channel activity in endothelial cells of the

vasculature[51-59]. However, no study has correlated plasma aldosterone, AII or PRA with progression of renal disease, and there are no well controlled trials of the effect of MRAs on proteinuria in diabetic nephropathy. In patients with congestive heart failure and post-myocardial infarction, long-term MRA treatment provides additive survival benefit to ACEi-based regimens[60,61].

Taken together, these findings suggest that combining a MRA with an ACEi could provide additive beneficial effects in patients with diabetic nephropathy. Two studies have suggested that eplerenone alone or in combination with an ACEi can reduce proteinuria in diabetics; however, hyperkalemia may be problematic at high doses[62-64]. There are no studies yet in patients with diabetic nephropathy that have systematically examined renal benefit of MRAs (see below).

Hypertension increases the likelihood of renal disease progression among diabetics. Lowering blood pressure has been demonstrated to slow the decline in renal function in both hypertensive type 1 and type 2 diabetics with nephropathy[40,42,65-69]. Systolic blood pressure is the strongest predictor of renal outcome in diabetics with nephropathy. **Figure 8a** illustrates the relationship between mean systolic blood pressure (X-axis) and rate of decline in glomerular filtration rate over time (Y-axis) in clinical trials of diabetic and non-diabetic nephropathies. The largest trials represented are in type 1 and type 2 diabetics. The figure indicates that lower blood pressure is associated with slower rate of decline in GFR in diabetics with nephropathy. Reduction in systolic blood pressure below 140 mmHg is associated with reduced risk for doubling serum creatinine and end-stage renal disease (**Figure 8b**)[66]. However, it is important to note that the rate of decline in GFR does not return to normal (about 1 ml/min/year after age 45) at systolic blood pressure of 130-134 mmHg. In addition, strict blood pressure reduction among *normotensive* type 2 diabetics can significantly reduce albuminuria (**Table 3**). However, aggressive control of BP lowering in these normotensive patients populations did not slow decline in GFR or save lives.

Dyslipidemia is common among diabetics. Atherogenic dyslipidemia consisting of elevated triglyceride level, low HDL-cholesterol, and increased

Lowering Blood Pressure Retards Progression of Chronic Kidney Disease

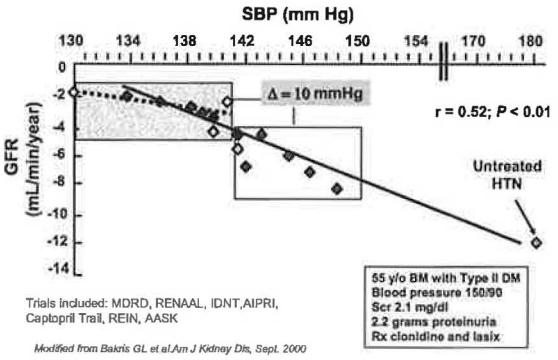


Figure 8a

Event Rate for the Primary Composite Endpoint and ESRD alone by Systolic Blood Pressure Level

Bakris GL, et al Arch Intern Med 2003;162:1555-1565

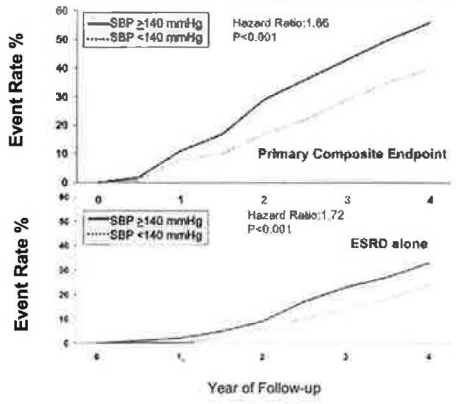


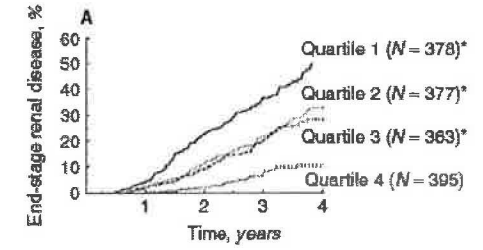
Figure 8b

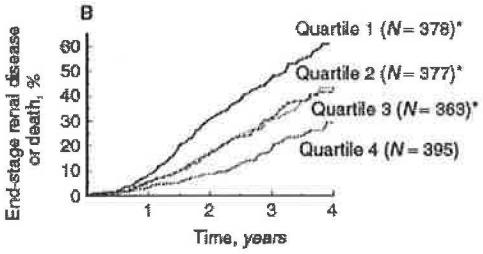
Intensive BP Lowering in Normotensive Type 2 Diabetics Slows Albuminuria Progression: ABCD Trial

Group	Baseline BT mmHg	Follow-up BP mmHg	Change Ccr ml/min	Albuminuria
Intensive	136/84	125/78	-4	Stable
Moderate	137/84	137/81	-4	Increase
Difference	None	Significant	None	Significant

Shriner et al., *Kidney Int* 61:1086-1097, 2002

Table 3





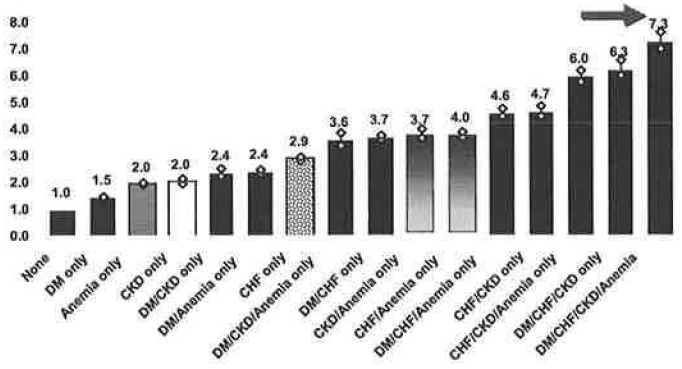
No. at risk					
Quartile 1	378	346	262	125	17
Quartile 2	377	357	311	166	30
Quartile 3	363	343	301	184	22
Quartile 4	395	383	361	247	42
Total	1513	1430	1237	725	115

Figure 9

small LDL subfractions are highly characteristic of diabetics and those with metabolic syndrome. Dyslipidemia is associated with onset and progression of kidney disease and for development of cardiovascular complications, including heart attack and stroke[70-74]. Whether plasma lipids deposit in the kidney causing renal damage has not yet been established. However, lipid lowering drugs can slow decline in renal function in dyslipidemic diabetics with renal disease[71] Lower plasma lipid levels predict sustained regression of microalbuminuria among type 1 diabetics followed for long periods of time at the Joslin clinic[75].

Anemia is common in patients with diabetic nephropathy. Several lines of evidence suggest that anemia may play a role in decline in renal function and cardiovascular disease in type 2 diabetics with nephropathy. Anemia is associated with development of congestive heart failure, left ventricular hypertrophy and renal disease progression in clinical trials and observational studies.[76-90]. Our group recently demonstrated that anemia is an independent risk factor for developing ESRD. After controlling for risk factors known to be associated with renal disease progression, participants enrolled in the RENAAL trial with a baseline Hb $\leq$ 11.3 g/dl were nearly twice as likely to develop ESRD as those with a Hb $\geq$13.8 g/dl [91] (**Figure 9**). Moreover, as shown in **Figure 10**, anemia is a risk multiplier for mortality among the elderly. For example, diabetics with chronic kidney disease, diabetes and anemia are about 1.5 times more likely to die than diabetics with CKD and no anemia.

RR for Death in CKD (pre-ESRD) Augmented by Anemia, CHF and DM



Source: Medicare sample (5%), followup from 1996 to 1997 of enrollees aged $\geq$ 65 y.o., adjusted for age, gender and race.

Figure 10

Summary 2:

Diabetic nephropathy is a clinical phenotype consisting of diabetes, elevated blood pressure and proteinuria. Most patients do not undergo biopsy. Nephropathy carries an increased risk for morbidity and mortality. Potentially modifiable risk factors including proteinuria, glycemia, activated renin-angiotensin aldosterone system, hypertension, dyslipidemia and anemia are important and may be altered to improve renal and cardiovascular outcomes.

Outcomes in Diabetic Nephropathy: Patients are More Likely to Die Than Develop ESRD

Outcomes in Diabetic Nephropathy

RENAL	CARDIOVASCULAR
• Surrogate	• Cardiac
– Doubling serum creatinine	– Coronary artery disease
– Increasing albuminuria	– Congestive heart failure
• Hard	• Cerebrovascular
– End-Stage Renal disease	– Stroke
	• Peripheral
	– Amputation

Table 4

Outcomes in patients with diabetic nephropathy can be divided into renal and cardiovascular (**Table 4**). The importance of both factors will be discussed with an emphasis on cardiovascular death.

Renal outcomes

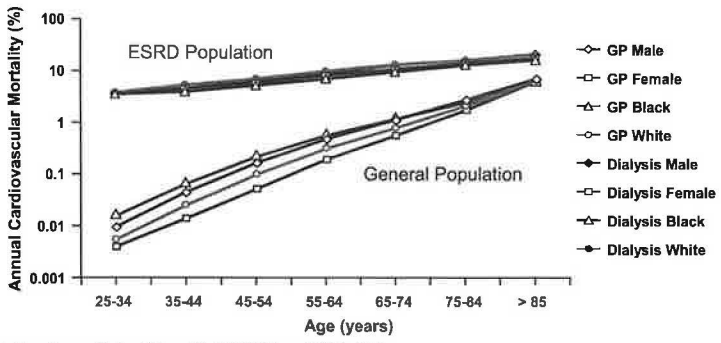
Renal outcomes include measures of declining GFR, worsening proteinuria, and end-stage renal disease. In fact, most clinical trials of renal disease have used surrogate markers to measure renal outcomes, although recently more emphasis on end-stage renal disease as an outcome has been popular. Primary endpoints utilizing proteinuria include 1) development of macroalbuminuria in microalbuminuric patients; 2) reversion of microalbumnuria to normoalbuminuria; and 3) significant reduction in albuminuria or proteinuria. Although proteinuria endpoints are well accepted in the literature, they are not established as surrogates for ESRD by the Food and Drug Administration (FDA). Still, clinical trials utilize proteinuria as a marker for kidney disease based on the strong association with progression and the fact the reduction in proteinuria reduces likelihood of kidney disease progression[92].

Nephrologists, including basic and clinical researchers as well as clinicians, have focused on investigations and strategies to slow progression of kidney disease and preserve renal function, and appropriately so. However, given the increasing prevalence of chronic kidney disease and the discovery that more patients with diabetic nephropathy die before progressing to end-stage renal disease, it is now paramount that cardiovascular disease complications and death be considered a major aspect for disease prevention and management. Here is why.

Cardiovascular Outcomes-Death

First of all it is important to appreciate that the cardiovascular morbidity and mortality rates among patients with chronic kidney disease and diabetes are much higher than patients without chronic kidney disease[29,93-101]. **Figure 11** illustrates the relationship between cardiovascular mortality and age among dialysis patients and the general population. At any age, ESRD is associated with a relative mortality 5-500 times higher than the corresponding age category. Conclusion, patients with ESRD are at extreme high risk for cardiovascular mortality. But, this is the extreme case of ESRD. What about lesser degree of nephropathy?

CVD is the Major Cause of Mortality in ESRD



Samak MJ and Levey AS. *Am J Kidney Dis.* 2000;35(4)(suppl1):S117-S131.
Foley RN. *Am J Kidney Dis.* 1998;32(S3):S112-119.

Figure 11

Death is a competing risk in any clinical trial or clinical intervention. A meaningful conclusion from a clinical trial can be deduced when competing endpoints such as ESRD and death are employed, as they are both clinically relevant and both the patient and physician understand these endpoints. Composite clinical endpoints in clinical trials of patients with nephropathy incorporate doubling of serum creatinine, end-stage renal disease, and death. In contrast, surrogate markers such as blood pressure, glycemia, proteinuria or a designated decline in GFR are more difficult to interpret in terms of long-term outcomes such as ESRD or death.

It is important to note that no one has yet been able to determine whether nephropathy is a manifestation of more severe vascular disease associated with diabetes as opposed to an independent risk factor. After all, a major sign of disease in the kidney is damage to the vasculature, including the microvasculature (glomerulus) and the arteries and arterioles. Moreover, common to diabetics with and without renal disease is the presence of endothelial dysfunction. In fact, most authorities believe that microalbuminuria is an index of endothelial dysfunction associated with widespread vascular disease and inflammation and increased cardiovascular death rather than a specific sign of nephropathy[99,102-105].

Taken together these data indicate that cardiovascular death risk in diabetics with nephropathy is very high; therefore, cardiovascular risk factor management is critical to survival in this patient population. Competing risks for ESRD and mortality are observed in clinical trials of patients with nephropathy[106]. Finally, the emerging data concerning death vs development of ESRD in diabetics with nephropathy beg the question: If my patient reaches ESRD is this a success?

Kidney Disease Outcomes Quality Initiative: Chronic Kidney Disease

- Kidney damage (≥ 3 months) defined by structural or functional abnormalities of the kidney, with or without decreased GFR manifest by

EITHER

- pathological abnormalities; or markers of kidney damage including abnormalities in composition of blood or urine, or imaging tests

OR

- GFR ≤ 60 ml/min/1.73 m^2

NKF Am. J. Kid. Dis. 39 (2) Suppl. Feb 2002

Table 5

Summary 3:

Diabetics with nephropathy are at high cardiovascular risk for death. The risk of death is a competing outcome for end-stage renal disease and death is more common than development of ESRD. Improving outcomes should include reducing not only progression of kidney disease but also cardiovascular events, the main cause of death in this population.

Evaluation of the Patient with Diabetic Nephropathy

Chronic kidney disease is defined as shown in **Table 5.** The term chronic kidney disease replaces all previous terminology such as chronic renal insufficiency, renal dysfunction, renal impairment, etc. The term chronic kidney disease is preferred and should be used instead of other outdated terminology. Evaluation of the patient with diabetic nephropathy should include routine history and physical examination with particular attention to blood pressure and signs of cardiovascular disease/comorbidities. Routine laboratory measurements should include serum electrolytes, albumin, BUN, creatinine, hemoglobin, serum iron, total iron binding capacity, ferritin, stool guaiac, A1c, lipid panel including triglyceride, HDL- and LDL-cholesterol levels, urine analysis, urine albumin to creatinine ratio and estimation of glomerular filtration rate.

Estimating risk for progression of nephropathy

A recent analysis of data from the RENAAL trial identified four independent risk factors for progression of diabetic nephropathy to end-stage: 1) proteinuria; 2) level of kidney function 3) serum

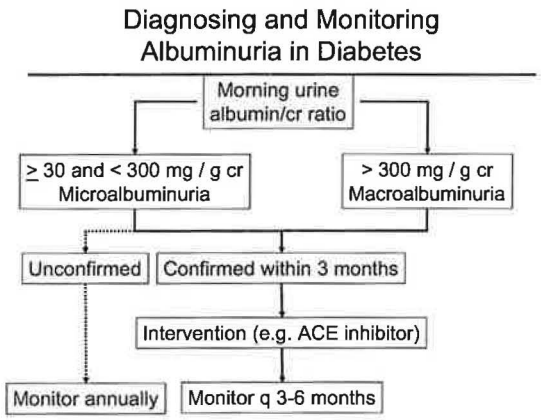


Figure 14

Kidney Disease Outcomes Quality Initiative: Chronic Kidney Disease

Stage	CV Risk	GFR (ml/min/1.73 m²)	Action
	At increased risk	≥ 90 with CKD risk factors	Screening,CKD risk reduction
1	Kidney Damage with Normal or Inc. GFR	≥ 90	Dx and Rx. Treat comoridities, slow progression, CVD RR
2	Mild	60-89	Estimating progression
3	Moderate	30-59	Evaluating and treating complications
4	Severe	15-29	Preparation for RRT*
5	ESRD	< 15	RRT

* RRT = renal replacement therapy

NKF Am. J. Kid. Dis. Feb 2002

Table 6

albumin and 4) hemoglobin. Patients with higher protein excretion rates, lower level of kidney function and serum albumin and lower hemoglobin are at highest risk for progression to ESRD. The presence of baseline urine protein excretion exceeding 2000 mg albumin per day is associated with a cumulative event rate of doubling serum creatinine or ESRD of 80% over 4 years[107].

Estimating albuminuria: Documenting persistence of abnormally increased urine albumin/creatinine ratio (**Table 2, Figure 14**) is recommended in order to establish cardiovascular and renal risk, diagnose nephropathy, and institute treatment. *Estimation of GFR* is performed *to stage chronic kidney disease*[108] (**Table 6**). Staging chronic kidney disease has implications for approach to management and specific intervention priorities. For example, in addition to managing risk factors in patients with stage 4 or 5 CKD, considerations for dietary restrictions, placement of vascular access and preparation for dialysis are important. In contrast for those with stage 1 and 2 kidney disease, management of risk factors concentrating on slowing progression of kidney disease and prevention of cardiovascular complications are of the highest priority. The NKF guidelines recommend estimation of the urine albumin creatinine ratio on spontaneously voided urine, not a 24-hour urine. The use of 24 hour urine measurement is no longer recommended. This measurement is useful for monitoring dietary sodium and potassium intake but is not necessary to diagnose, monitor or manage patients with nephropathy.

How to estimate GFR: To calculate the estimated GFR linear regression, equations using serum creatinine demographic and anthropometric markers are preferred to use of serum creatinine alone. **Table 7** shows the steps required to estimate GFR using linear regression equation derived from patient with chronic kidney disease. This calculation requires age, serum creatinine, gender and ethnicity (African-American or non-African-American). These four variables are entered into fields on the website (www.hdcn.com or www.nkf.org), and the estimated GFR is calculated and displayed instantly. Estimation of GFR with this technique is currently under investigation by large national laboratory chains and is anticipated to become routine in the future. An alternative is to use the Cockcroft-Gault equation [(140-age)*(Body weight in kg)/(Scr)(72)]*0.85 (for women), which estimates creatinine clearance. Returning to our patient, using the GFR equation, based on his age, serum creatinine, gender and race, we calculate an estimated GFR of 36 ml/min. His urine albumin creatinine ratio is 1550. This combination indicates that he

How do I estimate GFR in the Clinic?

- Go to computer and log on internet
- Type in www.HDCN.COM or www.NKF.ORG
- Register as limited user
- Click on the Calculator button
- Enter the age, gender, serum creatinine and race (black or not black)
- Write it on the chart
- Include the Stage in your note

Table 7

Diagnosis of Anemia in CKD
DOQI Guidelines

- Diagnosis:
  - Hb < 11 g/dl in premenopausal women and prepubertal patients and
  - Hb < 12 in men and postmenopausal women
- Evaluation (before beginning Epo therapy)
  - Hb, RBC indices, Reticulocyte Count
  - Iron, TIBC, % Sat, Stool Occult Blood
- Target: Hb 11-12 g/dl
  - Hb < 11 g/dl is below normal range for premenopausal women
  - Hb < 10 g/dl increases mortality in ESRD, LVH, and poor quality of life

DOQI *Am. J. Kid. Dis.* 37(1): S184, 2001

Table 8

has diabetic nephropathy with stage 3 chronic kidney disease.

Identifying comorbidities

Identification of comorbid conditions, including prior cardiovascular events such as stroke, myocardial infarction and heart failure, is an important component. For example, heart failure can exacerbate kidney disease and is associated with increased mortality risk.

Assessment of Anemia

Anemia is an emerging risk factor for heart failure, kidney disease and cardiovascular death risk. The NKF recommendations for anemia diagnosis, work up and rationale for treatment are illustrated in **Table 8**.

Assessment of dyslipidemia

The ADA and NKF guidelines recommend measurement of LDL-cholesterol, triglycerides and HDL-cholesterol. In addition non-HDL cholesterol (Total cholesterol-HDL) is included in the NCEPATP III guidelines as a target for lipid lowering treatment.

Lowering Blood Pressure and Blocking the RAAS is Good for the Kidneys, the Heart and the Brain

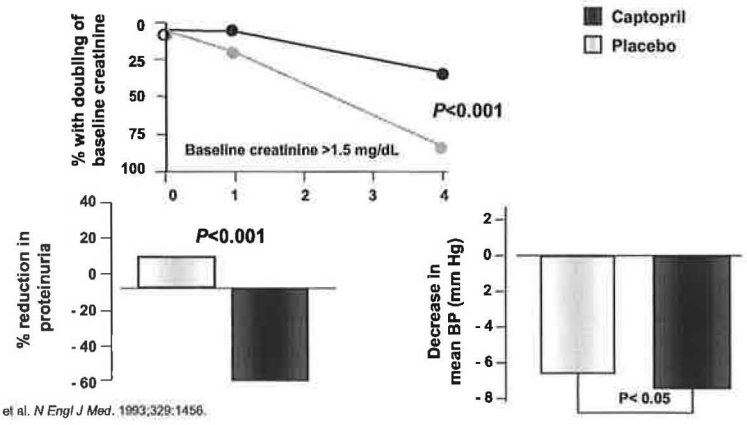
THE KIDNEY

In this section, I will review some key studies on outcomes in diabetics with nephropathy, including renal and cardiovascular. In addition I will highlight cardiovascular outcomes that apply to diabetics at risk for development of nephropathy and its subsequent complications.

Type 1 Diabetes

Many studies have shown that ACE inhibitors as compared to non-ACEi therapies improve outcomes in type 1 diabetics with nephropathy[40,109-111]. These studies demonstrated that ACE inhibitors consistently reduced proteinuria to a greater extent as compared to comparator drugs and blood pressure control was similar between treatment arms. The key study in type 1 diabetics involved 409 patients with microalbuminuria. Captopril 25 mg three times daily as compared to placebo reduced the risk of doubling of baseline serum creatinine and the combined endpoints of ESRD + death by 50% (**Figure 15**). Two key findings deserve emphasis: 1) the benefit of captopril was observed in patients with an elevated serum creatinine at

Captopril Is Renoprotective in Type 1 Diabetics with Nephropathy



Lewis et al. *N Engl J Med.* 1993;329:1456.

Figure 15

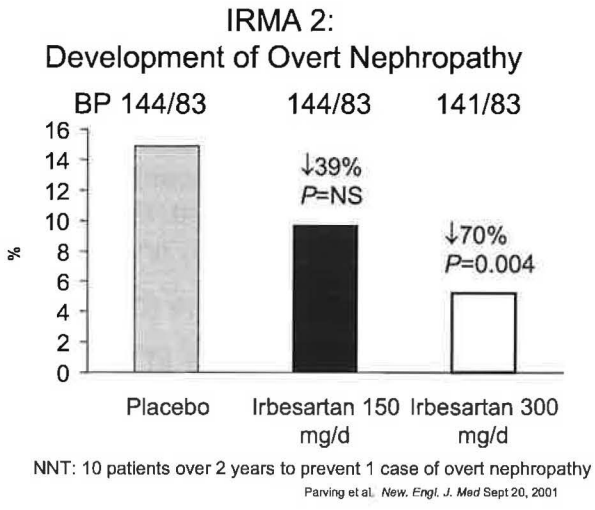


Figure 16

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 (albeit slightly lower in captopril-treated group). Therefore an elevated creatinine alone is not a reason to withhold ACEi therapy in a type 1 diabetic.

Type 2 diabetes

Microalbuinuria: The Irbesartan in Type 2 diabetics with MicroAlbuminuria (IRMA 2) trial

IRMA 2 trial was a multicenter, randomized, double-blind, placebo-controlled trial comparing irbesartan at a dose of either 150 mg or 300 mg once daily with other proven antihypertensive medications (excluding ACEIs, ARBs, and dihydropyridine calcium channel blockers)[112] in 590 hypertensive type 2 diabetes with microalbuminuria. Primary outcome was development of macroalbuminuria defined as ≥ 300 mg/24 hours and at least a 30% decrease from baseline. The study found that 5% of the 194 patients in the 300-mg irbesartan group and 9.7% of 195 patients in the 150 mg irbesartan group reached the primary end point, as compared with 14.9% of the 201 patients in the placebo group (**Figure 16**). There was a 70% risk reduction for the primary endpoint in the 300 mg once daily dose of irbesartan as compared with placebo. Average blood pressure during the study was 144/83 mmHg in the placebo group, 143/83 mmHg in the 150-mg group, and 141/83 mmHg in the 300-mg group. The authors concluded that irbesartan is renoprotective independently of its blood pressure lowering effect in patients with type 2 diabetes and microalbuminuria. **Table 9** compares results from clinical trials of microalbuminuric type 2 diabetics in which the outcome was development of overt nephropathy. Three ACE inhibitor trials are compared to the IRMA 2 trial to put this study in perspective. As shown in **Table 9**, the magnitude of reduction in risk of onset of overt nephropathy was greatest in the IRMA 2 trial. IRMA 2 and Ravid trials were designed and powered for renal outcomes, whereas the UKPDS and HOPE trials were designed and powered for all cause mortality and cardiovascular outcomes. Development of macroalbuminuria was a secondary outcome observed in participants who had baseline microalbuminuria. It is also important to note that there are no head-to-head comparisons of ACEi and ARB in any of these studies.

Development of Overt Nephropathy in Type 2 diabetics with Microalbuminuria: ACEi and ARB studies

Study	N	ACEi / ARB	Dose mg/day	Risk Reduction	P value
IRMA 2	590	Irbesartan	150	39 %	< 0.05
		vs placebo	300	71%	< 0.001
MicroHOPE	1,140	Ramipril	10	24%	= 0.027*
		vs placebo		22%	= 0.07**
UKPDS	299	Captopril vs Atenolol	50 -100	- 20%	= 0.09
Ravid	104	Enalapril vs placebo	10	30%	< 0.001

*Macroalbuminuria defined as Spot Urine ACR > 36 mg/mmol
**Macroalbuminuria defined as 24 hour urine albumin ≥ 300 mg per day

Table 9

Overt Nephropathy: The Reduction in endpoints in NIDDM with the angiotensin II receptor antagonist losartan (RENAAL) Trial

RENAAL was 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. Participants were included if they had type 2 diabetes, 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.

Losartan Increased the Time to ESRD

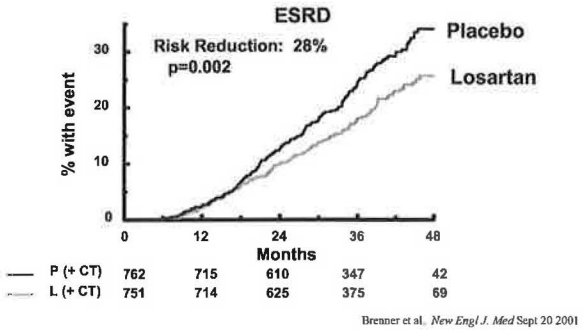


Figure 17a

RENAAL:
Change From Baseline in Proteinuria

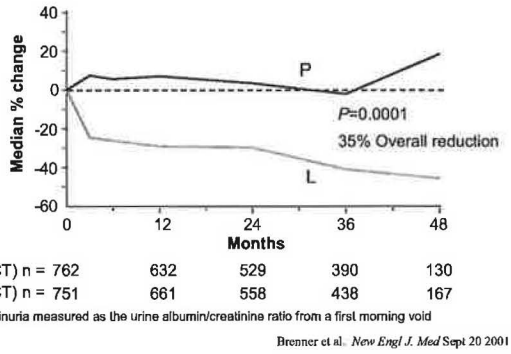


Figure 17b

Losartan Reduced the Rate of
First Hospitalization for Heart Failure

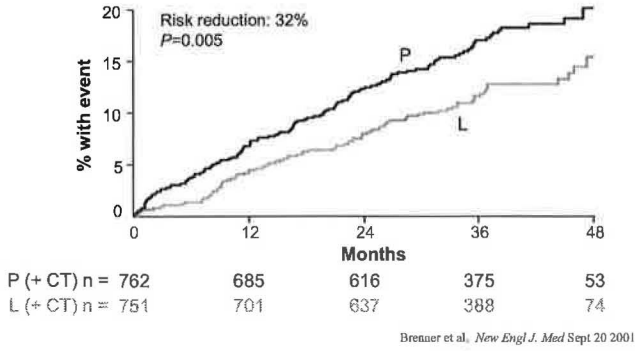


Figure 17c

They were excluded if they had a history of myocardial infarction, coronary artery bypass graft within past month, cerebrovascular accident, percutaneous coronary angioplasty within 6 months, or transient ischemic attack within 12 months and history of heart failure. The dose of losartan was titrated to 100 mg/day and conventional, non-ACE inhibitor (or other AII receptor antagonist) therapy was added as needed to achieve a target BP goal of < 140/<90 mmHg. The outcome was a composite endpoint of time to first event of doubling serum creatinine, end-stage renal disease or death. Secondary endpoints included myocardial infarction and congestive heart failure. **Figure 17** illustrates that losartan was superior to placebo for reducing risk for ESRD and hospitalization for heart failure in association with a significant reduction in proteinuria. 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.

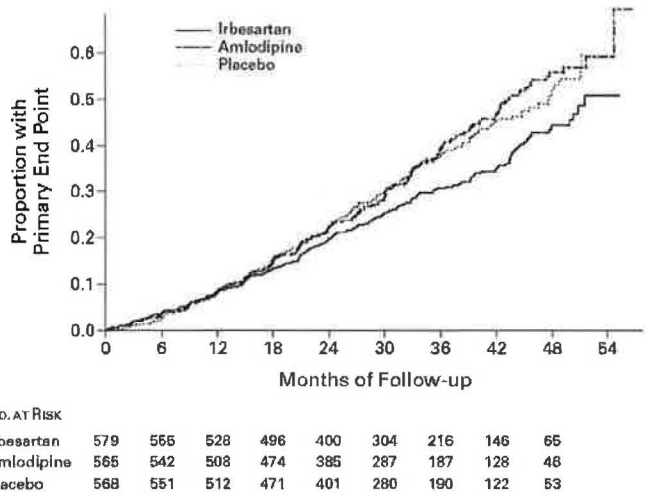


Figure 18: Berl, T et al. *Ann Int Med* 138:542-549, 2003

Irbesartan Diabetic Nephropathy Trial (IDNT)

The Irbesartan in Diabetic Nephropathy Trial evaluated the effect of irbesartan in comparison to placebo and amlodipine groups on the background of conventional (non-ACEi) therapy in a 1,715 type 2 diabetics with similar characteristics of the RENAAL participants. Average follow up was 2.6 years. Irbesartan treatment resulted in a risk reduction of 20% ($p < 0.02$) compared to placebo and 23% ($p < 0.006$). The risk of a doubling of the serum creatinine concentration was 33 percent lower in the irbesartan group than in the placebo group (P=0.003) and 37 percent lower in the irbesartan group than in the amlodipine group (P<0.001). The relative risk reduction for development of ESRD was 23% lower than both other groups (p=0.07) (**Figure 18)** Like RENAAL, the differences in outcome could not be explained by differences in achieved blood pressure. No differences in cardiovascular composite end point were observed between groups. Interestingly, myocardial infarction was significantly less common in those treated with amlodipine[113]

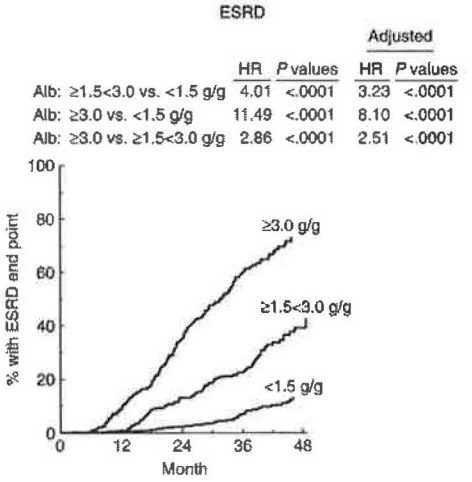


Figure 19a

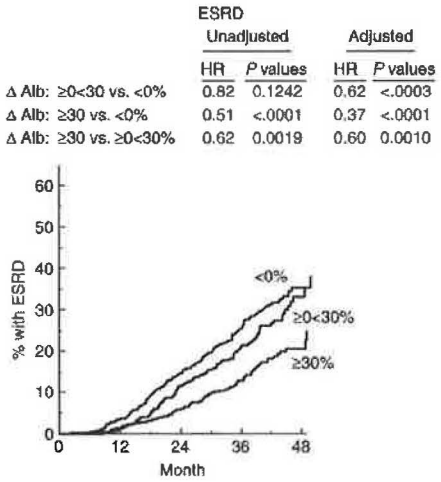


Figure 19b

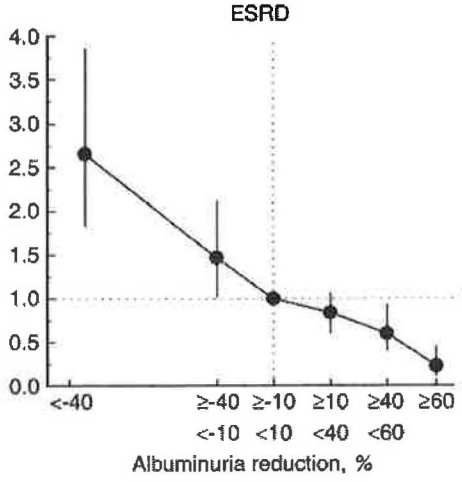


Figure 19c

The Importance of Reducing Proteinuria and Outcomes in Diabetic Nephropathy

As already stated, proteinuria is the strongest known risk factor for progression of diabetic nephropathy to ESRD. All three of the above trials demonstrated significant reductions in proteinuria in the RAAS blocking arms as compared to placebo (and amlodipine in case of IDNT) groups. More recent analyses from The RENAAL trial indicate that the antiproteinuric response to losartan predicts outcome and should be a target for treatment. As shown in **Figure 19**, baseline urine protein excretion rate was strongly related to doubling of serum creatinine and ESRD or ESRD alone. Moreover, as compared to no change in urine protein excretion from baseline, a 0-30% or $\geq$ 30% decrease in proteinuria was associated with a significant reduction in ESRD events. Finally, increases

in proteinuria after treatment increased the risk and decreases in proteinuria decreased the risk for development of ESRD. The findings suggest that reduction in proteinuria should be considered a target for treatment of patients with diabetic nephropathy. However, it is not known what the optimal target is. Ideally, return of protein excretion to normal range would be optimal but is difficult to achieve even with combination drug therapies (see below).

THE HEART

Data on cardiovascular outcomes in major trials of diabetic nephropathy have been reviewed above. In this section cardiovascular outcomes trials in diabetics with or without albuminuria will be discussed.

The MicroHOPE (Heart Outcomes Protection Evaluation) study evaluated outcomes in the subgroup (about 3300) of type 2 diabetics with at least one other cardiovascular risk enrolled in the HOPE trial. In MicroHOPE, ramipril (10 mg/d) reduced the risk for cardiovascular death, myocardial infarction and stroke by about 25% as compared to placebo (**Figure 20**). Those with microalbuminuria (about 1100) also demonstrated improved outcomes when treated with ramipril. There were too few cases of overt nephropathy to discern whether the effect is beneficial in such cases, but presumably patients living longer would continue to be at risk for nephropathy in the future albeit at a later date[114].

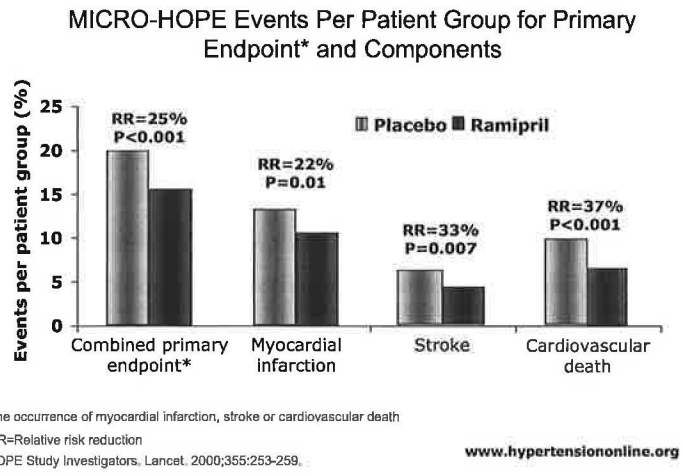


Figure 20

The Losartan Intervention For Endpoints (LIFE) trial included 9,193 hypertensive patients with ECG-documented LVH and was double-blind study controlled trial comparing once-daily losartan 50-100 mg vs atenolol 50-100 mg. The study lasted 4.8 years and the primary outcome was the composite of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. Approximately 1100 participants were type 2 diabetics mostly without nephropathy. As shown in **Figure 21**, losartan treatment significantly reduced risk for this endpoint by about 25% as compared to placebo. The benefit was largely due to a reduction in cardiovascular mortality.

THE BRAIN

Stroke risk was significantly reduced by 33% among type 2 diabetics treated with ramipril as compared to placebo in HOPE (**Figure 21**). In addition, administration of losartan to the overall LIFE study population was associated with a 25% risk reduction for stroke and a strong trend (though not significant) for the same in the diabetic subgroup[115].

Extrapolation from the HOPE and RENAAL trials suggests that blockade of the rennin-angiotensin-aldosterone system is good for the brain and heart in patients with kidney disease as well. However, there are still no trials focused on the diabetic nephropathy population examining whether any intervention reduces cardiovascular mortality that is saves lives.

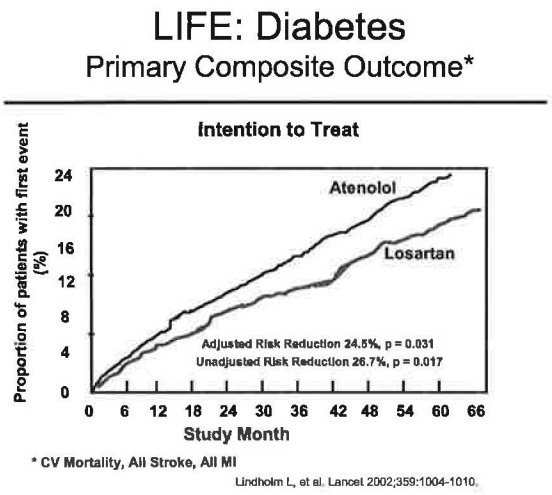


Figure 21a

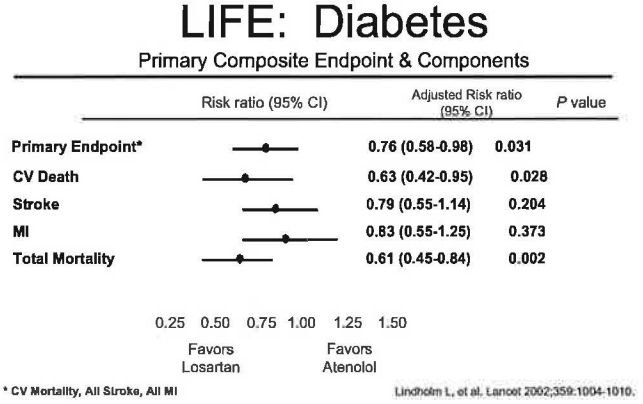


Figure 21b

Advances and Shortcomings of Outcomes Trials in Diabetic Nephropathy

Blockade of the RAAS by ACEi in type 1 diabetes and ARBs in type 2 diabetes improves renal outcomes. Heart failure is reduced by ARB treatment (RENAAL trial) in type 2 diabetics, and the estimated rate of decline in GFR is slower with RAAS blockade. However, the rate of decline in GFR (estimated from creatinine clearance) among patients in the ACEi and ARB arms is still far above normal (range of 4-6 ml/min/year) and the maximum delay in ESRD is about 12 months. Moreover, none of these trials showed a difference in mortality between treatment arms (due to low power to detect such difference). In other words, current intervention trials of established nephropathy in type 2 diabetes have not identified a cure for ESRD; rather, they delay its onset. Moreover, they have taught us that competing outcomes, including cardiovascular mortality, are in fact a critical outcome not addressed in this patient population. Therefore, earlier intervention and/or new treatment regimens and risk factor interventions are needed to further improve the outcomes of such patients. The following sections will discuss such studies.

Summary 4

Renal outcomes trials designed to examine renal endpoints have shown that agents that block RAAS are preferable to other classes as first-line agents for diabetics with microalbuminuria and established nephropathy. Cardiovascular outcome trials including diabetics have generally not included those with nephropathy. However, these trials by and large have shown benefit from RAAS blockade as well. There are still no outcomes trials examining CV events in diabetics with nephropathy.

Does Multi-risk Factor Intervention Improve Outcomes in Diabetics without overt Nephropathy?

This question has not been answered yet. However, Gaede et al. have provided some of the best evidence yet that aggressive targeted multi-risk intervention does save lives in type 2 diabetics with microalbuminuria. In this study, long-term intensified management of blood pressure, A1c, cholesterol and triglycerides combined with aspirin treatment was utilized to test the hypothesis that aggressive multi-risk factor intervention could improve survival in type 2 diabetics. 160 microalbuminuric type 2

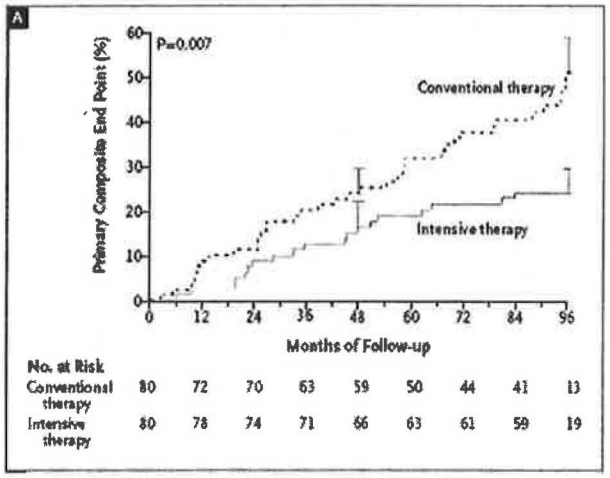


Figure 22

diabetics were randomized to aggressive versus standard care and followed for up to 8 years. The primary composite outcome was death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization and amputation. Goals for intervention included A1c < 6.5%, total cholesterol < 175 mg/dl, triglycerides < 150 mg/dl, systolic BP < 130 mmHg and diastolic BP < 80 mmHg. The study combined exercise, good eating habits, blood pressure lowering with ACE inhibition or ARB treatment, lipid lowering strategies and aspirin as part of the treatment plan. Note that *ACE inhibitors were administered to all study participants unless contraindicated, in which case an ARB was prescribed regardless of blood pressure level.* **Figure 22** illustrates the results from the study, indicating that intensive multi-risk factor intervention significantly reduced the composite endpoint by 53%. In addition risk reductions of 61% for nephropathy, 58% for retinopathy and 63% for autonomic neuropathy were observed. This is a relatively small study but proves the point that intensive intervention in type 2 diabetics can save lives.

What are The Next Steps To Further Improve Outcomes in Diabetic Nephropathy?

Renal Outcomes: Combining agents that block the RAAS

Trial comparing ARB, MRA and Placebo

Recently, the combination of the angiotensin converting enzyme inhibitor (ACEi) trandolapril + the angiotensin II receptor blocker (ARB) losartan was reported to be more renoprotective than either agent alone in *non-diabetics* with nephropathy[116], despite similar blood pressure control. However, there are no comparable studies in diabetics with nephropathy, a population that is known to benefit from either ACEi or ARB treatment. Furthermore, there are no studies comparing the effects of combing an ACEi + an ARB to an ACEi + a mineralocorticoid antagonist (MRA). The rationale for combining these agents is based on several lines of evidence. For example, ACE inhibition does not completely inhibit angiotensin II production and plasma levels may return to normal[21,22,117-119]. Moreover, diabetics with nephropathy appear to have increased renal expression of chymase, a non ACEi sensitive pathway for producing angiotensin II[50,116]. Also, ARBs do not block receptor continuously so that AII may still find access to the type 1 receptor[21,117]. Furthermore, aldosterone has been shown to induce renal injury independent of angiotensin II, perhaps by activating vascular receptors in the kidney and systemic vasculature as well as the renal tubules[22]. Large-scale clinical trials in humans with chronic heart disease have demonstrated that MRAs improve survival[120,120]. In addition, several studies have demonstrated that MRAs, alone or in combination with an ACE inhibitor, lower blood pressure, regress left ventricular hypertrophy and reduce albuminuria in patients with diabetes[121,122]. Taken together, the available evidence suggests that combination therapies that inhibit the RAAS at multiple sites are beneficial in patients with chronic heart disease and non-diabetic kidney disease (**Figure 23**).

Based on this evidence my colleagues (Dr. Ronald Victor, Dr. Philip Raskin and Dr. Gloria Vega) designed a study to test the hypothesis that blockade of the renin-angiotensin system beyond ACE

Multiple Sites of Blockade of the Renin-Angiotensin-Aldosterone System

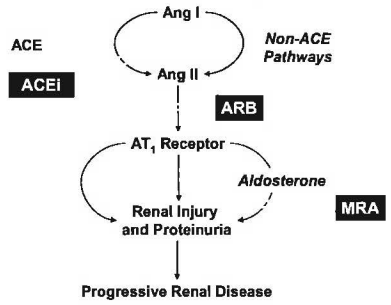


Figure 23

inhibition decreases proteinuria and slows progression of renal disease in diabetics with overt nephropathy by suppressing aldosterone synthesis or blocking the aldosterone receptor.

To accomplish this we goal we are recruiting a multiethnic cohort of 72 young adults (ages 20-50) with type 1 (n=36) or type 2 (n=36) diabetes and overt nephropathy (defined as a urine albumin/creatinine ratio > 300 mg albumin/g creatinine) and randomizing them in a double blind fashion to a control group consisting of ACEI-based therapy alone (lisinopril 80 mg once daily) or one of two experimental groups: 1) ACEI + ARB (lisinopril 80 mg once daily plus losartan 100 mg once daily) or 2) ACEI + mineralocorticoid receptor antagonist (lisinopril 80 mg once daily plus spironolactone 25 mg once daily). The study is a 12 month prospective study to determine if proteinuria is reduced to a greater extent when either the ARB or MRA is added to ACEi-based therapy. The study has 90% power to detect a 30% greater reduction in urine albumin/creatinine excretion ratio in either experimental group versus control with 24 patients per group. Secondary endpoints to be examined include: (a) serum potassium and creatinine to assess safety, (b) TGF-β, the latter as a surrogate marker for ongoing renal injury, (c) plasma renin activity, angiotensin II and aldosterone levels and (d) plasma lipids and lipoprotein composition (**Figure 24**). In addition, we are performing repeated ambulatory blood pressure monitoring to examine the renoprotective effects of the three different regimens at comparable goal 24-hour blood pressure level of ≤ 125/75 mmHg. This study is a feasibility study that will answer several important questions concerning the efficacy and safety of combining these agents in diabetics. Hyperkalemia is an important potentially limiting factor and has not been adequately explored in this patient population. This clinical trial is unique and is supported by an R01 grant from the National Institute of Diabetes Digestive and Kidney Diseases. The trial is in the recruitment phase. More information is available on our website at www.utsouthwestern.edu/diabetic-outcomes.

Combined Inhibition of the RAAS Pathway: ACEi + ARB vs ACEi + MRA in Diabetic Nephropathy

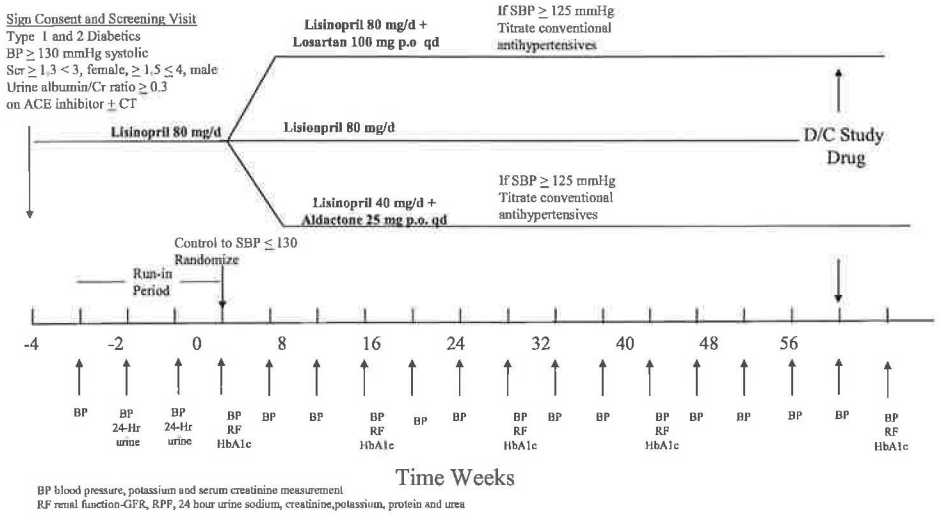


Figure 24

Inhibition of Protein Kinase C-β1: Ruboxistaurin in clinical trials

Hyperglycemia is known to cause cellular proliferation, including in the kidney. This is mediated in part by an increase in cytosolic concentration of diacylgycerol, which in turn activates the β-1 isoform of protein kinase C (PKC-β1). PKC-β1activation affects kidneys, blood vessels, heart and retina. Inhibition of PKC-β1 is associated with reduction in transforming growth factor β-1, normalization of renal hemodynamics, and decreased mesangial matrix expression and proteinuria in experimental animal models of diabetic nephropathy. Thus on a molecular level PKC activation is thought to play a key role in cellular pathophysiology of diabetic nephropathy and other microvascular complications. On the basis of experimental animal studies and phase 3 clinical trials for prevention of diabetic retinopathy, trials with the novel orally active PKC-β1 inhibitor ruboxistaurin are underway to determine if this agent can reduce proteinuria in type 2 diabetics with nephropathy despite ACE inhibitor treatment.

Cardiovascular Outcomes

Anemia

Anemia is common in chronic kidney disease and is associated with significant morbidity and mortality. As noted above, prospective observational studies in CKD patients indicate a strong association between anemia and increased risk for cardiac dilatation, cardiac failure, left ventricular hypertrophy and cardiovascular death[82,85,86,89,123,124]. Also, anemia is associated with increased risk for death and hospitalization in elderly patients with CHF and treatment of anemia improves functional capacity and left ventricular function in patients with CHF with or without CKD[125,126]. Congestive heart failure is a common finding in patients with CKD, and anemia is known to cause heart failure. Treatment of anemia with erythropoietin in CKD patients with clinical congestive heart failure is associated with improvement in cardiac and renal function as well as exercise capacity and improved quality of life[89,127-130]. Recent studies indicate that LVH is common in CKD patients even in early stages of the disease. In prospective studies, worsening anemia is an independent predictor of new onset LVH and carries the same relative risk as increasing systolic blood pressure.[131,132] Importantly, anemia and hemoglobin were shown to confer similar risk increase for LVH. Specifically, for each 0.5 g/dl decline in hemoglobin there was a 32% increase in risk for LVH, whereas for every 15 mmHg increase in systolic blood pressure there as a 36% increase in risk for LVH during the 12 month follow-up interval. In addition, retrospective analyses indicate that left ventricular mass regression is associated with increased survival on dialysis, but this has not been shown in a prospective study[133-135]. The high prevalence of anemia in CKD patients in association with a high rate of cardiovascular disease and mortality suggests that a low hemoglobin level may link the two. Anemia prevalence is up to 10-fold higher in those with CKD + CHF + diabetes mellitus as compared to those with CKD alone or diabetes alone. This finding suggests that anemia is a major modifiable risk factor for CHF. Observational data also point to anemia as a death risk multiplier among older individuals with CKD and CHF[136]. However, studies thus far do not prove that anemia treatment to any level improves survival in CKD patients. Future studies of anemia in chronic kidney disease are needed to further elaborate the mechanisms of anemia, to determine cause and effect of anemia and cardiovascular and renal outcomes, novel methods to measure erythropoiesis and novel cardioprotective and neuroprotective effects of erythropoietin independent of its hematopoietic effect, and whether anemia is directly causing cardiac or progression of renal disease in those with chronic kidney disease. In addition, anemia may be a factor contributing to progression of CKD as already mentioned (see above). Correction of anemia does improve quality of life in CKD patients[90]; however, there are no randomized controlled clinical trials that have documented reductions in morbidity and mortality

during treatment of anemia in CKD patients. Two ongoing clinical trials are designed to address this issue.

The first trial is the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), a randomized open label trial that is ongoing. The primary hypothesis of this study is that anemia correction with once weekly dosing of erythropoietin in subjects with chronic kidney disease will decrease all-cause mortality, cardiovascular morbidity, and progression to ESRD compared to subjects with lower correction of anemia. Enrollment of approximately 1500 participants in this study has been completed. The primary outcome is the composite of CV hospitalization (including stoke), death, myocardial infarction and renal replacement therapy. The study is a randomized comparison of complete (Hb > 13 g/dl) versus partial (Hb 11-12 g/dl) correction of anemia with erythropoietin alfa. Participants will be followed for up to 3 years.

The second and more recent trial is the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial, a prospective randomized placebo controlled study that will enroll type 2 diabetics with nephropathy and anemia and evaluate the impact of anemia treatment with darbepoietin alfa (Aranesp) on the composite endpoint, comprising time to all-cause mortality and cardiovascular morbidity, including myocardial infarction, acute myocardial ischemia, congestive heart failure and stroke. This is a global multicenter trial that will enroll 4,000 participants and follow them for up to 4 years. The TREAT is event-driven and will include type 2 diabetics with an eGFR of 20 to 60 mL/min/1.73 m^2 and hemoglobin $\leq$ 11 g/dL. The participants will be randomized to receive darbepoetin alfa to achieve and maintain target hemoglobin of 13 g/dL, or to placebo. Placebo treated participants who experience hemoglobin < 9 g/dL will receive rescue therapy with darbepoetin alfa until hemoglobin is $\geq$ 9 g/dL.

Dyslipidemia

The role of dyslipidemia as a contributing factor to renal and cardiovascular outcomes has been discussed. In patients with CHD but without evidence of CKD, statins have been shown to reduce risk of coronary events by about 25% and of ischaemic stroke by a similar amount. However, these trials generally excluded CKD patients. In the Cholesterol And Recurrent Events (CARE) study, pravastatin 40 mg daily was beneficial for reducing recurrent events in participants with stage 2 CKD, all of whom had CHD[137]. Also, in the Heart Protection Study (HPS), simvastatin 40 mg daily was beneficial among patients with increase in serum creatinine (1.5-2.0 mg/dl range)[73]. There are currently no outcomes studies in patients with CKD evaluating the impact of cholesterol lowering. The Study of Heart Protection in Renal Patients (SHARP) is a multicenter, multinational clinical trial designed to determine whether lowering cholesterol with the combination of a statin and a inhibitor of intestinal cholesterol absorption can reduce cardiovascular morbidity and mortality in patients with stages 3-5 chronic kidney disease[138]. This study is currently in the recruitment phase and UT Southwestern Medical Center is a participating center.

How Do I Manage My Patient today? (Table 10)

Our patient is at high risk for progression of nephropathy based on his proteinuria, low GFR, reduced serum albumin and anemia[107]. His risk for progression to ESRD within the next 2 years is greater than 50%. In addition, his history of an MI increases dramatically the likelihood that he will experience another coronary event in the next few years. Intensive multi-risk factor intervention is appropriate in this setting.

Diabetic Nephropathy Management

Parameter	Target
• Lower BP	• < 130/80 mm/Hg
• Block RAAS	• ACEi or ARB to max tolerated
• Improve glycemia	• A1c < 6.5% (Insulin/TZD other)
• Lower LDL cholesterol	• < 70 mg/dl w statin (± other)
• Anemia management	• Hb 11-12 g/dl (Epo + iron)
• Endothelial protection	• Aspirin daily

Table 10

Lower the blood pressure

First and foremost is to treat blood pressure to goal of < 130/<80 mmHg. This should include non-pharmacologic and pharmacologic therapies. Weight loss, physical exercise, modest alcohol intake, and dietary sodium intake of 2 grams per day are important in this patient. For pharmacologic therapy use an ACE inhibitor or an angiotensin receptor antagonist combined with a diuretic. In this case, the estimated GFR of near 30 ml/min indicates the need for a loop diuretic dosed at least twice daily is appropriate. My next choice of agent to add on if the above does not achieve SBP goal of < 130 is a long-acting once daily calcium channel blocker, followed by a beta blockers and then an alpha blocker. In most patients either CCB or B-blocker can be used, but both can also be administered. Non-dihydropyridine CCBs have higher likelihood of reducing proteinuria, but either class is acceptable as add-on drug[139,140]. Finally, adding on an ARB or a mineralocorticoid antagonist (MRA) such as spironolactone or eplerenone may be helpful, particularly if the patient has heart failure or is post-MI[60,141]. However, combining these agents must be done with extreme caution because of the risk for significant hyperkalemia, particularly in elderly patients[142].

Block the Renin-Angiotensin-Aldosterone System

Blocking the RAAS with an ACEi or ARB is recommended by the American Diabetes Association and the National Kidney Foundation. This maneuver is designed to lower blood pressure and to reduce proteinuria and to block many downstream pathways responsible for renal disease progression as well as for cardiovascular protection.

Improve Glycemic Control

Lowering his A1c to a level < 7% is associated with improved microvascular outcomes[143-145] and is the recommended goal by the ADA[18]. It should be noted that the DCCT trial data suggest that an A1c level of 7% represents a mean plasma glucose of about 170 mg/dl. Tighter glycemic control to 6.5% was used in the Gaede study (see above) and is recommended by some diabetologists. This is achievable with appropriate diet, weight loss and combination of insulin with non-insulin therapies such as thiazolidinediones. In this patient metformin is contraindicated because of his chronic kidney disease stage (serum creatinine > 1.4 mg/dl is cutoff recommended by manufacturer).

Lower LDL cholesterol with a statin

Lowering LDL cholesterol starting with a statin is the best approach for this patient's dyslipidemia. Targeting an LDL cholesterol of <70 mg/dl in this patient is consistent with new ATPIII guideline published in 2004 by Dr. Scott Grundy and the NCEP expert panel[146]. Statins, in addition to lowering cholesterol, have other effects such as anti-inflammatory and antioxidative properties that may be beneficial. Cardiovascular protection, although not proven in advanced renal disease, is prudent in this patient who is already in the category of secondary prevention. This drug class is well tolerated by diabetics with nephropathy, and there is a very small risk for myositis or rhabdomyolysis in patients even with doses of 20-40 mg per day. Additional lipid lowering agents such as ezetimibe, niacin or cholestyramine can be added on to statins. However both niacin and cholestyramine carry a significant risk of untoward side effects.

Treat anemia

Before treating anemia with erythropoietin and iron, the NKF recommends initial work up to include history, physical examination, stool guaiac, CBC with RBC indices, and iron studies (serum iron, TIBC, ferritin). Additional testing for vitamin deficiencies, hemolytic or other causes of anemia should also be undertaken based on the findings and results of recommended work up. Blood erythropoietin levels are not recommended for diagnosis of management of anemia attributed to CKD.

Treatment of anemia with erythropoietin and iron is recommended by the NKF for CKD patients with a Hb level < 11.0 g/dl according to current guidelines. The rationale for this is based on observational data in ESRD patients and quality of life studies and in short-term regression of left ventricular hypertrophy. However, it should be noted that there are no outcome studies proving benefit of treatment of anemia for reducing CV events or slowing progression of kidney disease.

Use aspirin

Daily dose of aspirin (75-325 mg) in this patient as an endothelial protective agent may help to reduce the risk for recurrent coronary event and stroke. This is a prudent and cost effective maneuver and the ADA recommends aspirin for cardiovascular protection for all adult diabetics with macrovascular disease.

Smoking cessation

Smoking, in addition to its linkage to macrovascular disease, has been shown to accelerate decline in kidney function in some studies[147-150]. All patients who smoke should be provided with every opportunity and aids to stop.

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