Objectives

1. Review the epidemiology of chronic kidney disease.
2. Understand the pathophysiologic concepts of each stage of chronic kidney disease.
3. Define markers of kidney damage.
4. Understand glomerular adaptations to declining kidney function.
5. Consider how glomerular adaptations may contribute to the progression of kidney disease.
6. Discuss potential therapeutic strategies to interrupt glomerular adaptations and slow the progression of chronic kidney disease.

Readings

Rose and Rennke, pages 254-275.
Rennke and Denker, pages 267-290.

I. Epidemiology of Chronic Kidney Disease

A. Model of chronic kidney disease, irrespective of cause.

[Image unavailable due to copyright restrictions.] Shaded ellipses represent stages of chronic kidney disease; unshaded ellipses represent potential antecedents or consequences of CKD. Thick arrows between ellipses represent factors associated with initiation and progression of disease that can be affected by interventions. Interventions for each stage are given beneath the stage. Complications refer to all complications of CKD and its treatment, including complications of decreased GFR and CVD.

B. Risk factors related to chronic kidney disease

Risk Factor	Definition	Examples
Susceptibility factors	Increase susceptibility to kidney damage	Older age, family history of CKD, reduction in kidney mass, low birthweight, US racial or ethnic minority status, low income or education
Initiation factors	Directly initiate kidney damage	Diabetes, high blood pressure, autoimmune disease, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity
Progression factors	Cause worsening kidney damage or faster decline in GFR	Higher level of proteinuria, higher blood pressure, poor glycemic control in diabetes, smoking
End-stage factors	Increase morbidity and mortality in kidney failure	Lower dialysis dose (Kt/V), temporary vascular access, anemia, lower serum albumin level, late referral to nephrologists

C. Definition of chronic kidney disease. Chronic kidney disease is present if any of the following criteria is present for three months or more:

1. Structural or functional abnormalities of the kidney (with or without decreased GFR). These may manifest as either:

   a. Pathologic abnormalities

   b. Markers of kidney damage

      i. Proteinuria (albumin-to-creatinine ratio >30 mg/g)

      ii. Abnormalities in the urinary sediment – cells, casts, crystals

      iii. Abnormalities on imaging studies – collecting system, cysts, stones

      iv. Tubular syndromes

   c. Kidney transplant recipients

2. GFR less than 60 ml/min/1.73 m^2, with or without kidney damage.

D. Outcomes of chronic kidney disease

1. Progressive loss of kidney function ("progression")

   a. Complications associated with decreased GFR:

      i. hypertension
      ii. anemia
      iii. malnutrition
      iv. neuropathy
      v. decreased quality of life

   b. Kidney failure

2. Cardiovascular disease (not discussed today)

   a. Shared risk factors for CKD and CVD

   b. CVD can cause CKD

      i. Atherosclerosis causes renal artery disease
      ii. Heart failure causes decreased kidney perfusion

   c. CKD is a risk factor for CVD

      i. CKD-related non-traditional risk factors
      ii. proteinuria
      iii. decreased GFR

E. Stages of CKD, Irrespective of Cause [National Kidney Foundation Kidney Disease Quality Outcomes Initiative (NKF-K/DOQI)]

Stage	Description	GFR (mL/min/1.73 m^2)	Prevalence (US Adults)* N (1000's)	%
0	At increased risk	$\geq$60 (with CKD risk factors)	>20,000	>10
1	Kidney damage with normal or ↑ GFR	$\geq$90	5,900	3.3
2	Kidney damage with mild ↓ GFR	60–89	5,300	3.0
3	Moderate ↓ GFR	30–59	7,600	4.3
4	Severe ↓ GFR	15–29	400	0.2
5	Kidney failure	<15 (or dialysis)	300	0.1

*Prevalence data for Stages 1–4 from NHANES III (1988–1994). Population of 177 million adults age ≥ 20 years. Prevalence data for Stage 5 from USRDS (1998) includes approximately 230,000 patients treated by dialysis, and assuming 70,000 additional patients not on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. For Stages 1 and 2, kidney damage estimated by spot albumin-to-creatinine ratio >17 mg/g in men or >25 mg/g in women on two measurements. Prevalence of individuals at increased risk of CKD has not been determined reliably, but is likely to be greater than the prevalence of CKD.

F. Causes of chronic kidney disease

Disease	Major Types (Examples)*	Approximate Prevalence Among Patients with Kidney Failure**
Diabetic kidney disease	*Type 1 and type 2 diabetes mellitus*	33%
Non-diabetic kidney diseases	*Glomerular diseases (autoimmune diseases, systemic infections, drugs, neoplasia)*	19%
	Vascular diseases (hypertension, renal artery disease, microangiopathy)	21%
	Tubulointerstitial diseases (urinary tract infection, stones, obstruction, drug toxicity)	4%
	Cystic diseases (polycystic kidney disease)	6%
Diseases in the kidney transplant	Allograft nephropathy (chronic rejection)	NA
	Drug toxicity (cyclosporine or tacrolimus)	
	Recurrent diseases (glomerular diseases)	
	Transplant glomerulopathy	

*Examples of some causes for specific pathologic types. Italics indicate types of kidney disease that may be associated with large amounts of proteinuria (for example, spot urine total protein-to-creatinine ratio >500-1000 mg/g).
** Prevalence varies with age. Based on USRDS Annual Data Report 2002.

G. Pathophysiology of stages of CKD

1. At Increased Risk

   a. Susceptibility to kidney damage. Sociodemographic factors: older age, US ethnic minority status (African American, Native American, Hispanic, Asian American

   b. Exposure to initiation factors. Clinical factors: hypertension, diabetes, family history of chronic kidney disease, autoimmune diseases, systemic infections, urinary tract disorders (infection, obstruction, stones, vesicoureteral reflux), neoplasia, exposure to drugs with kidney toxicity, recovery from acute renal failure.

2. Kidney damage (Stages 1 and 2)

   a. GFR may be normal or mildly decreased. In diabetes, GFR is increased.

   b. Initiated by a variety of factors:

      immunologic (most causes of glomerulonephritis)
      hemodynamic (hypertensive nephrosclerosis)
      ischemic (cortical necrosis)
      coagulation (hemolytic-uremic syndrome)
      metabolic (diabetes, stones)
      genetic (polycystic kidney disease)
      other factors

   c. Pathological features of kidney damage are usually widespread.

   d. Markers reflect site of damage.

   e. Common pathogenesis for worsening kidney damage and declining GFR. If initial damage is severe and bilateral, kidney damage worsens and GFR declines, even if the initial injury resolves.

3. Decreased GFR (Stages 3-4, also called "Renal Insufficiency"): Functional and pathological features of the kidney disease are similar, irrespective of the inciting event. Pathological changes are a heterogeneous process: focal glomerular sclerosis progressing to global sclerosis, tubular atrophy and interstitial fibrosis are observed, glomerular and tubular hypertrophy develop, and hypertension and tubular adaptations occur. Tubular adaptations and adaptations in other organs maintain solute levels despite decreased GFR. The number and severity of clinical complications varies inversely with the level of GFR. High risk of CVD.

4. Kidney Failure (Stage 5, also called "End-Stage Renal Disease"): Uniform pathologic appearance, irrespective of the cause, with diffuse glomerular sclerosis, tubular atrophy, interstitial fibrosis, and arterial sclerosis. GFR falls to less than 15 ml/min/1.73 m^2, and signs and symptoms of uremia appear. High risk of CVD.

H. Puzzles in the Pathophysiology of Chronic Kidney Disease

1. No apparent regulation of levels of nitrogenous wastes; levels rise reciprocally with decline in GFR.

2. Uniform appearance of "end-stage kidney" irrespective of pathologic process.

3. Progression of kidney disease despite resolution of initial injury (two cases).

BB: 23 female	NC: 29 male
1973 – RPGN Serum creatinine rose to 15 mg/dl, then fell to 1.3 mg/dl Urine protein excretion remained elevated at 1 g/d	**1975 - Unilateral nephrectomy for kidney donation** Serum creatinine rose from 0.9 to 1.3 mg/dl, Urine protein excretion remained normal.
1974-1983 progressive rise in serum creatinine	**1975 – present** good general health normal serum creatinine normal urine protein
1984 dialysis begun	

II. CKD Stage 1: Markers of Kidney Damage

A. Clinical and pathological classification reflect the site of damage.

1. Proteinuria is the most common marker of kidney damage, indicating glomerular damage.

2. Abnormalities of the urine sediment, indicating glomerular, tubular or interstitial damage.

3. Abnormal imaging studies, indicating vascular, ureteral, cystic lesions, or diffuse parenchymal damage.

4. Tubular syndromes

B. Proteinuria.

1. Types of urine protein: Urinary protein is a mixture of plasma proteins that cross the filtration barrier and non-plasma proteins that originate in the tubules and lower urinary tract. Of the total, albumin constitutes 30-40%, IgG 5-10%, light chains 5%, IgA 3%, and Tamm Horsfall tubular protein about 50%.

   a. Filtered serum proteins: The glomerulus is permeable to small molecules (MW <10,000 daltons). Filtered proteins are reabsorbed by specific tubular transport pathways and degraded within tubular cells. Normal urine proteins filtered from plasma include albumin and low molecular weight globulins.

Macromolecule	Molecular Weight (daltons)	Approximate Molecular Radius (nm)	Ratio of Glomerular Filtrate to Plasma
Inulin	5,200	1.4	1.0
Insulin	6,000	1.6	0.9
Lysosyzme	14,608	1.9	0.75
Myoglobin	16,900	1.9	0.75
Parathyroid hormone (cow)	9,000	2.1	0.65
Growth hormone (rat)	20,000	2.1	0.6-0.7
Immunoglobulin light chains	44,000	2.8	0.09
Amylase	48,000	2.9	0.02
Albumin	69,000	3.6	0.02
Immunoglobulins	168,000	5.5	0.0
Ferritin	480,000	6.1	0.02

   b. Proteins secreted by tubular epithelial cells: IgA, urokinase, and Tamm-Horsfall protein are secreted by cells lining the distal tubule.

2. Measurement of urine protein

   a. Total urine protein is measured by turbidity after precipitation of proteins with acid. Normal mean value for total urine protein in adults is approximately 50 mg/d.

   b. Albumin and other specific proteins can be measured by specific immunoassays. Normal mean value for urine albumin in adults is 10 mg/d.

   c. Other types of proteins are detected and characterized by electrophoresis or immuno-electrophoresis.

3. Pathophysiology of proteinuria

   a. Altered glomerular permeability: Increased permeability allows filtration and excretion of larger molecules, such as albumin. **Albuminuria is a sign of glomerular damage. The predominant urine protein in most chronic kidney diseases in adults is albumin, reflecting glomerular damage as either the primary site of injury, or as a secondary effect.**

   b. Altered tubular reabsorption: Low molecular weight globulins are filtered and reabsorbed. Tubular damage allows excretion of smaller molecules. Some chronic kidney diseases are characterized by "tubular proteinuria" in the absence of albuminuria.

   c. Overload proteinuria: Overproduction of low molecular weight proteins, such as immunoglobulin light chains, occurs in some B-cell proliferative disorders. The amount of proteinuria correlates with tumor burden. Light chains may cause kidney damage.

Definitions of Proteinuria and Albuminuria

	Urine Collection Method	Normal	Micro-albuminuria	Albuminuria or Clinical Proteinuria
Total Protein	24-Hour Excretion (varies with method)	<300 mg/day	NA	>300 mg/day
	Spot Urine Dipstick	<30 mg/dL	NA	>30 mg/dL
	Spot Urine Protein-to-Creatinine Ratio (varies with method)	<200 mg/g	NA	>200 mg/g
Albumin	24-Hour Excretion	<30 mg/day	30–300 mg/day	>300 mg/day
	Spot Urine Albumin-Specific Dipstick	<3 mg/dL	>3 mg/dL	NA
	Spot Urine Albumin-to-Creatinine Ratio (varies by gender)	<17 mg/g (men) <25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	>250 mg/g (men) >355 mg/g (women)

C. Urine Sediment Abnormalities

Predominant Urinalysis Abnormality									
RBC	**RBC Casts ***	**WBC**	**WBC Casts**	**Tubular Cells**	**Cellular Casts**	**Granular Casts**	**Fat ****	**Total Protein-to-Creatinine Ratio (mg/g) †**	**Associated Kidney Disease**
+	+								Proliferative glomerulonephritis or hereditary nephritis
+	–			+		+			Hereditary nephritis, or disease of small vessels (microangiopathy)
+	–			–		–			Cystic kidney disease, kidney neoplasms or urinary tract lesions other than kidney disease
±	–	+	+					200-1,000	Tubulointerstitial nephritis
		+	–					<200	Urinary tract lesions other than kidney disease
				+	+	+			May be present in all types of kidney disease, but most abundant in acute tubular necrosis (the most common kidney disease causing acute kidney failure)
–	–						+	>1,000	Diabetic kidney disease and non-inflammatory glomerular diseases
–	–	–	–	–	–	–	–	200–1,000	Non-inflammatory glomerular disease, non-inflammatory tubulointerstitial disease, or diseases affecting medium-sized arteries

* Detection of red blood cell casts requires careful preparation and thorough and repeated examination of sediment from freshly obtained urine specimens. Even under ideal conditions, red blood cell casts may not always be detected in patients with proliferative glomerulonephritis.

** Oval fat bodies, fatty casts, free fat

† Cut-off values are not precise.

Abbreviations and symbols: RBC, red blood cells; WBC, white blood cells; +, abnormality present; –, abnormality not present; ±, abnormality may or may not be present

D. Abnormalities on Imaging Studies as Markers of Kidney Damage

Imaging Modality/Feature	Associated Kidney Disease
Ultrasonography	
General appearance	May show nephrocalcinosis, discrete stones, hydronephrosis, cysts or masses.
Increased echogenicity	May indicate cystic disease or "medical renal disease."
Small, "hyperechoic" kidneys	Generally indicate chronic kidney disease.
Large kidneys	Generally indicate tumors, infiltrating diseases or diseases causing nephrotic syndrome.
Size disparities and scarring	Suggest vascular, urologic or tubulointerstitial diseases due to stones or infection.
Doppler interrogation	May be useful in investigation of venous thrombosis, less so in arterial stenosis.
Intravenous pyelography (IVP) [a]	May reveal asymmetry of kidney size or function, presence of obstructing stones, tumors, scars, or dilated collecting ducts in medullary sponge kidney.
Computed tomography (CT) [b]	May show obstruction, tumors (e.g. angiomyolipoma), cysts or ureteral calculi. Helical CT with contrast may show sites of anatomic renal artery stenosis.
Magnetic resonance imaging (MRI)	May show mass lesions, renal vein thrombosis, cysts, etc. MR angiography using gadolinium may be useful in patients with decreased kidney function.
Nuclear scans [c]	May reveal asymmetry of kidney size or function, functional evidence of renal artery stenosis, acute pyelonephritis, or scars.

[a] This modality has been largely supplanted by computed tomography, although it remains useful to describe fine detail in the collecting system.
[b] With or without contrast
[c] Captopril renography, mercaptoacetyltriglycine (MAG3), dimercaptrosuccinic acid (DMSA)

E. Tubular Syndromes (examples)

Renal tubular acidosis
Nephrogenic diabetes insipidus
Barrter's syndrome and Gittleman's syndrome
Kidney potassium wasting
Kidney phosphate wasting
Kidney glycosuria
Fanconi's syndrome

III. Stage 2 CKD: Progression of Kidney Disease

A. Glomerular Adaptations to Declining Glomerular Function

Why does the GFR decline in chronic kidney disease? In principle,

$$GFR = N * SNGFR$$

where N is the number of nephrons and SNGFR is the single-nephron GFR.

$$SNGFR = K_f * P_{UF}$$

where K_f is the ultrafiltration coefficient and P_{UF} is the filtration pressure. Then:

$$SNGFR = S * k * (\Delta P - \Delta \Pi)$$

where S is the glomerular capillary surface area, k is the hydrostatic permeability coefficient of the glomerular capillary membrane, ΔP is the transcapillary hydrostatic pressure and $\Delta \Pi$ is the transcapillary oncotic pressure.

B. Neither the number of nephrons nor the determinants of SNGFR can be measured in humans. However, they have been determined in animals with experimental kidney disease. These experiments take advantage of the kidney morphology of Munich-Wistar rats, in which the glomeruli lie just below the surface of the kidney and are accessible to micropuncture in vivo.

C. Experimental kidney disease (Brenner, Hostetter, Anderson and colleagues)

	GFR ml/min	SNGFR nl/min	SBP mmHg	P_{GC} mmHg	RPF nl/min	R_A	R_E
Ablation							
Control	0.72	28	112	49	74	3.5	2.2
5/6 Nephrectomy	0.21	63	128	63	187	1.4	1.1
% Δ	↓71%	↑125%	↑14%	↑29%	↑153%	↓60%	↓50%
Diabetes							
Control	1.10	48.9	103	48	142	3.0	2.1
Moderate Hyper-glycemia	1.47	69.0	114	56	240	1.9	1.6
% Δ	↑34%	↑41%	↑11%	↑17%	↑69%	↓36%	↓24%
Note: No important changes in P_T, Π_{GC}, or Π_T in these models.							

GFR	Glomerular filtration rate (whole kidney), ml/min
SNGFR	Single nephron GFR, nl/min
SBP	Mean femoral arterial pressure, mm Hg
P_{GC}	Glomerular capillary pressure, mm Hg
RPF	Plasma volume flow rate, nl/min
R	Resistance to blood flow, 10^{10} dyn·s·cm^{-5} (subscripts: A, afferent; E, efferent)

1. Experimental kidney disease due to reduced nephron number: The classic model is **ablation** of kidney mass due to unilateral nephrectomy and infarction of approximately 2/3 of the remaining kidney by ligation of renal artery branches. The reduction in GFR is due to reduction in the number of nephrons to 1/6.

   a. Surprisingly, SNGFR is increased, due to increased ΔP arising from increased P_{GC}. The increased P_{GC} is due to several factors: systemic hypertension (increased AP), vasodilation (reduced R_T), and a greater percent reduction in afferent arteriolar resistance (R_A 60%) than in efferent arteriolar resistance (R_E 50%). Glomerular and tubular hypertrophy are observed. Hypertension, vasodilation, increased P_{GC}, and glomerular hypertrophy can be viewed as "adaptive" because they maintain GFR at a higher level than would be expected based solely on the reduction in nephron number.

   b. A progressive kidney disease evolves, manifested by glomerular and tubular hypertrophy, and subsequent focal glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Proteinuria, decline in GFR, and hypertension occur. Eventually, kidney failure ensues, with death from uremia.

2. Experimental kidney disease due to induction of insulin-dependent diabetes mellitus: Diabetes mellitus is induced by chemical ablation of pancreatic islets by alloxan or streptozotocin. In the absence of insulin, there is severe hyperglycemia (blood glucose 500-600 mg/dl) due to an inability to use glucose in muscle and adipose tissue, and increased glucose production in liver from catabolism of protein and fat. The increase in protein catabolism also leads to an increased excretion of nitrogenous wastes by the kidney. Insulin is administered to partially restrain catabolism and maintain moderate hyperglycemia (blood glucose 300-400 mg/dl). The initial finding is an increase in GFR and enlargement of the kidneys.

   a. As expected, since there is no reduction in nephron number, SNGFR is increased. In this model, the increase is due to increased ΔP arising from increased P_{GC}; AP is not increased. The increased P_{GC} is due to vasodilation (reduced R_T) and a greater percent reduction in R_A (36%) than in R_E (24%). In addition, there is glomerular and tubular hypertrophy. In this model, the vasodilatation, increase in P_{GC}, and hypertrophy may be an "adaptation" to the higher protein catabolism due to inadequate insulin replacement.

   b. Again, a progressive kidney disease evolves with pathological and functional features similar to the ablation model, culminating in kidney failure.

   c. With severe hyperglycemia, (blood glucose 500-600 mg/dl), ΔP and P_{GC} are not increased. Instead, vasoconstriction is observed (increased R_T) due to volume depletion as a result of osmotic diuresis from extreme glycosuria (data not shown).

D. Hypothesis: The Progression of Kidney Disease is Due to Glomerular Adaptations (Glomerular Adaptations Are "Maladaptive")

In both models, adaptation is an increased work per nephron, manifest as increased SNGFR. The increase in SNGFR is adaptive, but the mechanism of adaptation is ultimately "maladaptive," because it leads to further nephron injury. Many theories have been advanced. Only a few are mentioned here.

1. Hemodynamic hypothesis: Reduction in nephron number or increased protein catabolism leads to vasodilatation and **increased P_{GC}**. Increased P_{GC} causes hemodynamic injury to the glomerular capillary wall, resulting in glomerular sclerosis, reduction in nephron number, and further stimulus to increased SNGFR.

2. Growth factor hypothesis: Reduction in nephron number or increased protein catabolism leads to stimulation of a variety of growth factors, reflected in glomerular and tubular hypertrophy. Growth factors also stimulate **fibrosis**, resulting in glomerular sclerosis, reduction in nephron number, and further stimulus to growth factor elaboration.

3. Consequences of abnormal permeability to macromolecules: Either mechanism described above leads to **proteinuria**, which has two harmful consequences: an increase in macromolecules in the mesangium which stimulates fibrosis, and an increase in serum level of LDL with consequent glomerular toxicity. Both pathways lead to glomerular sclerosis, reduction in nephron number, and further proteinuria.

IV. Strategies to Interrupt Glomerular Adaptations

A. Rationale for experimental maneuvers

1. Blood pressure control: Antihypertensive agents can lower P_{GC}. Review of determinants of glomerular capillary pressure.

   a. Kidney perfusion pressure: Elevated systemic blood pressure, in association with normal or decreased glomerular arteriolar resistances, increases P_{GC}. Reducing systemic blood pressure without a change in arteriolar resistance decreases P_{GC}.

   b. Afferent (pre-capillary) arteriolar resistance: Antihypertensive drugs that primarily dilate this vessel may not lower P_{GC}.

   c. Efferent (post-capillary) arteriolar resistance: Antihypertensive drugs that primarily dilate this vessel will lower P_{GC}.

2. Interruption of the renin-angiotensin system: Angiotensin II (AII) causes constriction of the efferent arteriole, increasing P_{GC}. In addition, AII is a growth factor in the

glomerulus. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB) might lower P_{GC} and reduce the stimulus for hypertrophy.

3. Dietary protein restriction: Short-term dietary protein load causes kidney vasodilation, increased glomerular capillary blood flow, and increased SNGFR. Prolonged dietary protein feeding causes glomerular hypertrophy. Restriction of dietary protein might prevent vasodilation and thus lower P_{GC}, thereby preventing hypertrophy.

4. Blood glucose control (in diabetes): Inadequate insulin replacement is associated with increased protein catabolism and widespread arteriolar vasodilatation. More intensive insulin therapy would improve glucose control and might lower P_{GC} and prevent hypertrophy.

B. Experiments in the Ablation Model

C. Experiments in the Diabetic Model

V. Results of Clinical Trials

A. Diabetic kidney disease: Diabetes is the most frequent cause of new onset kidney failure in the U.S. and Europe.

1. Natural history: Stages of disease are classified by extent of urinary albumin excretion (UAE).

a. Preclinical Phase (0 to 15 years)

i. Normal UAE (CKD Stage 0, at increased risk): Increased GFR and kidney size, improved but not to normal by improved metabolic control. Increased UAE may occur at times of poor metabolic control.

ii. "Microalbuminuria" (CKD Stage 1): UAE 30-300 mg/day (albumin-to-creatinine ratio 30-300 mg/g), and increased GFR. Requires special tests to detect urine albumin at low end of the range. Blood pressure rises during this stage, and hypertension may occur.

b. Clinical Phase (>15 years)

i. "Clinical proteinuria" (CKD Stage 2): UAE >300 mg/day (albumin-to-creatinine ratio >300 mg/g, detected by "dipstick") and GFR begins to decline. Hypertension is usual.

ii. ↓ GFR (CKD Stages 3-4): Retinopathy, hypertension, nephrotic syndrome, and progressive decline in GFR.

iii. Kidney failure (CKD Stage 5): Uremia, cardiovascular disease.

2. Clinical trials: Example: ACE inhibition in type 1 diabetic nephropathy

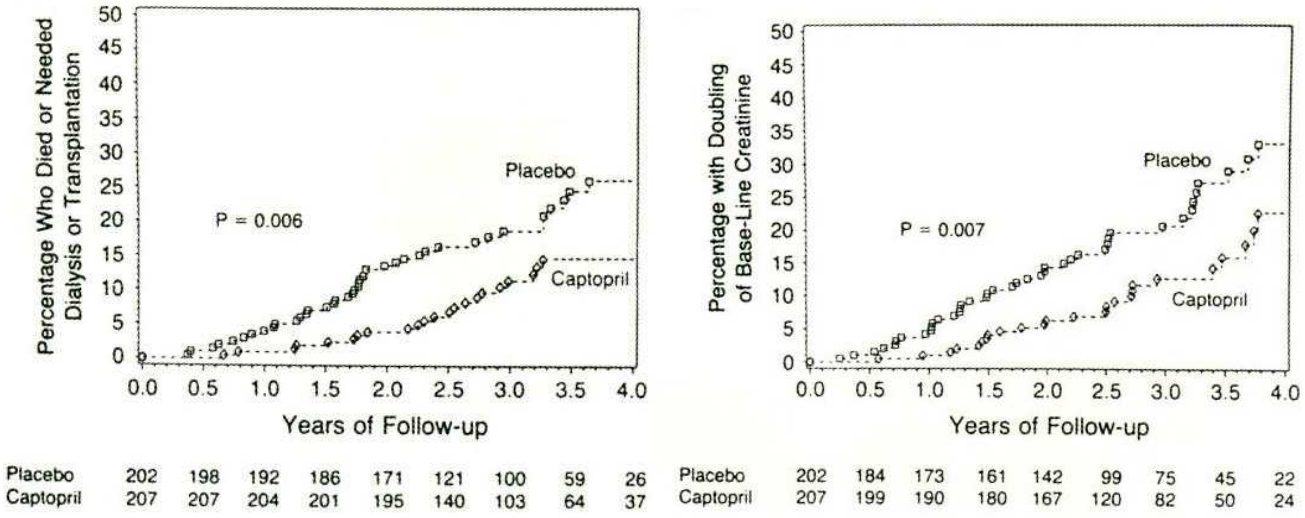

Figure 1: Diabetic Kidney Disease, Collaborative Study Group. Source: *NEJM* 1993; 329: 1456-1462

B. Non-Diabetic Kidney Disease: Because of their lower prevalence, many diseases are grouped together in clinical studies.

1. Natural history is variable, because of the variety of diseases grouped together. The only feature many have in common is the progressive decline in GFR. The rate of GFR decline is slower on average than in diabetic nephropathy. The greater variability and slower rate of progression make it more difficult to observe the beneficial effect of treatment in clinical trials, if such an effect exists . Multicenter trials with a long duration of follow-up are required.

2. Clinical trials. Example: Meta-analysis of patient level data from clinical trials of ACE inhibition in non-diabetic kidney.

Comparisons of Randomized Groups Adjusted for Baseline and Follow-Up Factors

Analysis	ESRD (RR, CI)	Cr Doubling (RR, CI)
Unadjusted	0.63 (0.47-0.85)	0.63 (0.51-0.80)
Adjusted for Baseline	0.62 (0.45-0.84)	0.58 (0.46-0.73)
Adjusted for Baseline, ΔSBP and ΔUP	0.69 (0.51-0.94)	0.69 (0.55-0.87)

C. Summary of ACE Inhibitor Trials

1. Effects in CKD

   a. Lower blood pressure
   b. Lower urine protein
   c. Slow the decline in GFR (rise in serum creatinine)

2. Mechanisms to slow GFR decline

   a. Lowering blood pressure
   b. Lowering urine protein
   c. Additional mechanisms

3. Effect modification (interactions)

   Greater beneficial effect in patients with proteinuria

D. Therapies That Slow the Progression of Chronic Kidney Disease

	Diabetic	Non-Diabetic
ACE Inhibition	Yes	Yes (more in patients with proteinuria)
Strict BP Control	Probably	Yes (more in patients with proteinuria)
Protein Restriction	Uncertain	Uncertain
Glucose Control	Yes	--

VI. Summary

1. Adaptations to chronic kidney disease results in increased work per nephron and nephron hypertrophy, with gradual fibrosis and progression of kidney disease.

2. Therapies that interfere with adaptation can slow the progression of kidney disease.

3. Proteinuria both reflects kidney damage and may further injury the kidney.

4. Modifiable risk factors for progression of kidney disease include hypertension, proteinuria, and glycemic control.

VII. References

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