Classification of CKD by Diagnosis

- **Diabetic Kidney Disease**
- **Glomerular diseases** (autoimmune diseases, systemic infections, drugs, neoplasia)
- **Vascular diseases** (renal artery disease, hypertension, microangiopathy)
- **Tubulointerstitial diseases** (urinary tract infection, stones, obstruction, drug toxicity)
- **Cystic diseases** (polycystic kidney disease)
- **Diseases in the transplant** (Allograft nephropathy, drug toxicity, recurrent diseases, transplant glomerulopathy)

How Do We Define and Stage CKD?

- Chronic kidney disease (CKD)
  - Kidney damage with normal glomerular filtration rate (GFR) or GFR <60 mL/min/1.73 m^2 for ≥3 months with or without kidney damage
- Kidney damage
  - Pathologic abnormalities or markers of damage including abnormality in blood or urine tests or imaging studies

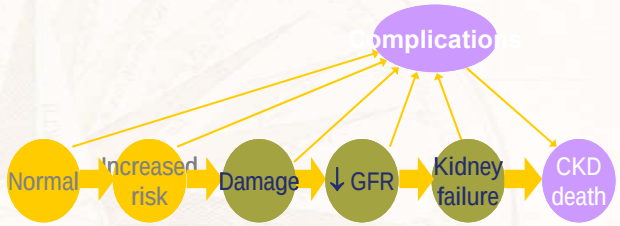
Coresh J, et al. *Am J Kidney Dis.* 2003;41:1-12.
NKF. *Am J Kidney Dis.* 2002;39(2 suppl 1):S1-S266.

Staging CKD

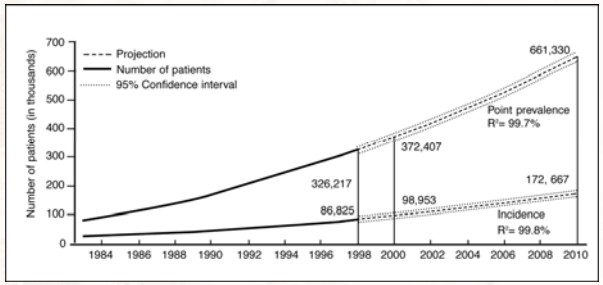
Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 or RRT

RRT = renal replacement therapy.
Levey AS, et al. *Ann Intern Med.* 2003;139:137-147.

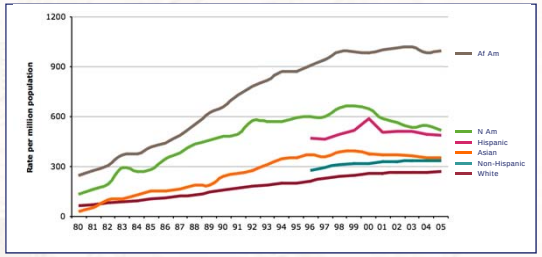
Stages in Progression of Chronic Kidney Disease and Therapeutic Strategies



Incidence and Prevalence of End-Stage Renal Disease in the US



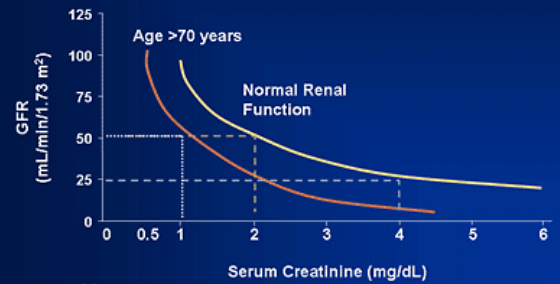
Incidence varies widely by race and ethnicity



Incident ESRD patients; rates adjusted for age & gender.

Relationship Between SCr and GFR

- Serum creatinine is a poor predictor of GFR



SCr = serum creatinine.

Eranten AJ, et al. *Nephrol Dial Transplant.* 2005;20:707-711.

The perils of using serum creatinine to "guess" level of renal function

	24-yo Black Man	63-yo White Man	59-yo White Woman
SCr	1.3 mg/dL	1.3 mg/dL	1.3 mg/dL
GFR as estimated by MDRD Study equation	≥60 mL/min/1.73 m^2	59 mL/min/1.73 m^2	45 mL/min/1.73 m^2

Estimating GFR: MDRD and Cockcroft-Gault

- **Abbreviated MDRD Equation**

$$GFR\ (mL/min/1.73\ m^2) = 186 \times (SCr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

- **Cockcroft-Gault Equation**

$$C_{Cr}\ (mL/min) = \frac{(140 - age\ [y] \times weight\ [kg])}{72 \times SCr\ (mg/dL)} \times 0.85 \text{ if patient is female}$$

C_{Cr} = creatinine clearance; MDRD = Modification of Diet in Renal Disease.

Levey AS, et al. *Ann Intern Med*. 2003;139:137-147.

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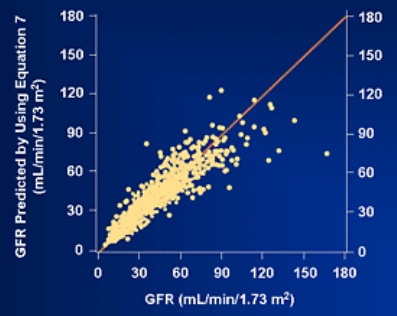
GFR Prediction by MDRD Formula



Levey AS, et al. *Ann Intern Med*. 1999;130:461-470.

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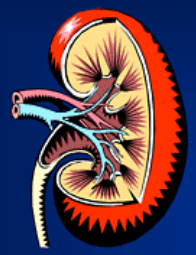
Why Does Identifying Early and Progressive CKD Matter?



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The people to test are those at greatest risk

- Diabetes mellitus
- Hypertension
- Cardiovascular disease
- Family members of patients with ESRD

Note on pediatric patients:

- CKD may start with childhood obesity
- No recommendations for routine testing

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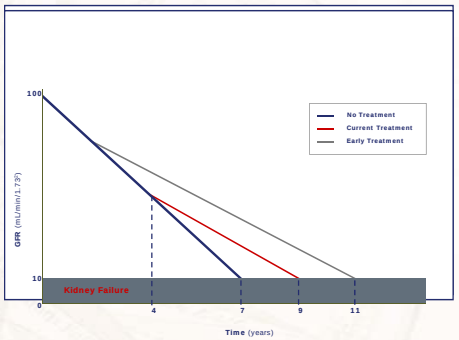
Early treatment can make a difference



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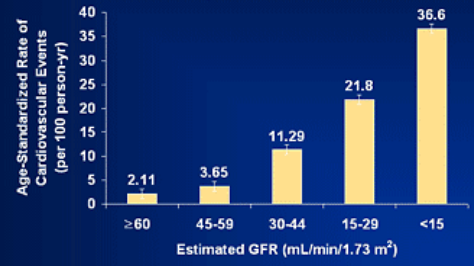
Even Early-Stage CKD Increases Risk of Cardiovascular Events

The risk of cardiovascular disease began to rise once the GFR dropped below 60 mL/min/1.73 m^2 of body surface area.



No. of events:	73,108	34,690	18,580	8809	3824

Go AS, et al. *N Engl J Med*. 2004;351:1296-1305.

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Epidemiology of CKD

- From NHANES III using estimated GFR
  - Prevalence of CKD Stages 3 and 4 in US adults was 4.5% (8 million people)
- Epidemiology of early-stage CKD not the same as end-stage renal disease (ESRD)
- No higher prevalence of CKD in African Americans despite much higher prevalence of ESRD

NHANES III = Third National Health and Nutrition Examination Survey.

Coresh J, et al. *Am J Kidney Dis*. 2003;41:1-12.

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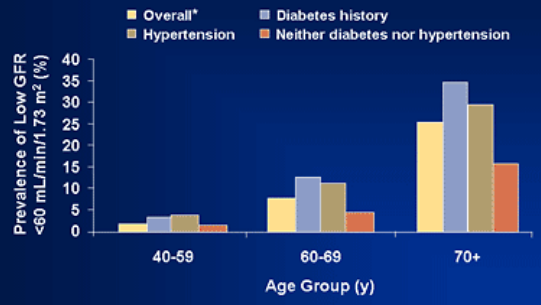
How Big Is the Problem?



*Overall noninstitutionalized US population according to NHANES III, 1988-1994.

Coresh J, et al. *Am J Kidney Dis*. 2003;41:1-12.

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Percent of patients with CKD, by demographic characteristics, comorbidity, & dataset, 2011

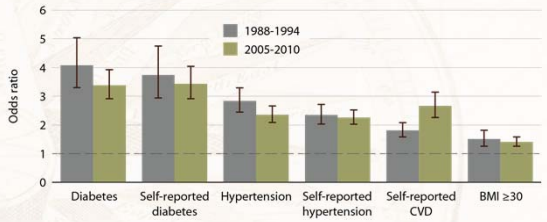
Table 2.d (Volume 1)

	NHANES	Medicare (65+)			Truven Health MarketScan (50–64)		
	Any CKD	DM (no HTN)	HTN (no DM)	CVD	DM (no HTN)	HTN (no DM)	CVD
All	14.0	10.8	16.8	24.5	6.2	5.6	10.4
20-49	6.5						
50-54	8.4				5.1	4.5	8.1
55-59	13.3				5.9	5.3	9.8
60-64	17.2				7.1	6.6	12.0
65-74	29.1	8.8	11.8	20.3			
75-79	49.5	11.3	17.0	24.6			
80+	65.5	15.2	22.9	28.7			
Male	12.1	11.8	19.2	25.7	6.7	6.3	11.0
Female	15.8	9.7	15.3	23.4	5.6	4.8	9.5
White	14.3	10.8	16.6	23.6			
Black/Af Am	16.0	11.5	20.6	33.7			
Native American		9.2	15.4	26.1			
Asian		11.1	14.9	27.2			
Other/unk.	11.9	10.3	15.2	26.0			

Medicare patients age 65 & older & Truven Health MarketScan patients age 50–64, alive & eligible for all of 2011. CKD claims as well as other diseases identified in 2011. NHANES 2005–2010 participants, age 20 & older; eGFR estimated by CKD-EPI equation.

Adjusted odds ratios of CKD in NHANES participants, by risk factor

Figure 1.4 (Volume 1)



NHANES 1988-1994 & 2005-2010 participants age 20& older; single sample estimates of eGFR and ACR. Adjusted: age, gender, race; eGFR calculated using CKD-EPI equation

Scope of the Prevalence of CKD

Stage	Description	No. of Individuals/ Prevalence (%)
1	≥90 mL/min/1.73 m^2; kidney damage with normal GFR; persistent albuminuria	5.9 million (3.3%)
2	60-89 mL/min/1.73 m^2; persistent albuminuria	5.3 million (3.0%)
3	30-59 mL/min/1.73 m^2	7.6 million (4.3%)
4	15-29 mL/min/1.73 m^2	400,000 (0.2%)
5	<15 mL/min/1.73 m^2 or dialysis; kidney failure	651,000 (0.3%)

Levey AS, et al. *Ann Intern Med* 2003;139:137-147.

What Are the Key Issues for These At-Risk Patients?

1. How can we better inform patients and physicians about the problem and the therapies of CKD?
2. What can we do to prevent progression of CKD?
3. What can we do to prevent the cardiovascular risk associated with CKD?

- An estimate based on population data--not the patient's *actual* GFR
- Not reliable when used with patients:
  - with GFR above 60 ml/ min/1.73 m^2
  - with rapidly changing creatinine levels (e.g., acute renal failure in the ICU)
  - with extremes in muscle mass, e.g. cachexia or paraplegia
  - under age 18

- Recognize and test at-risk patients
- Educate patients about CKD and treatment
- Focus on good glycemic control in people with diabetes
- For those with CKD:
  - Blood pressure below 130/80
  - Use an ACE inhibitor or ARB
  - More than one drug is usually required
  - A diuretic should be part of the regimen

Monitor eGFR and UACR

Treat cardiovascular risk, especially with smokers and hypercholesterolemia

Screen for anemia (Hgb), malnutrition (albumin), metabolic bone disease (Ca, Phos, PTH)

Refer to dietitian for nutritional guidance

Consult or team with a nephrologist

Encourage labs to report estimated eGFR and urine albumin/creatinine ratios

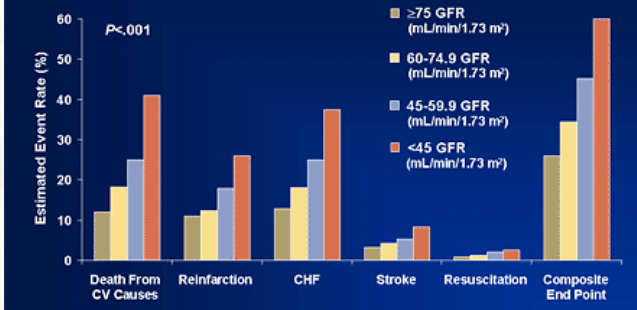
MANAGING THE COMORBIDITIES IN CKD

Percentage of 5-Year Clinical Outcomes in Patients With CKD

End point	Stage 2 eGFR 60-89* (n = 1741)	Stage 3 eGFR 30-59* (n = 11,278)	Stage 4 eGFR 15-29* (n = 777)
Progression to RRT	1.1%	1.3%	19.9%
Death	19.5%	24.3%	45.7%

*mL/min/1.73 m^2.
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy.
Keith DS, et al. *Arch Intern Med.* 2004;164:659-663.

Rates of Death at 3 Years by CV Causes*



*14,527 patients with HF or LV dysfunction post-MI.
CHF = congestive heart failure; CV = cardiovascular; HF = heart failure; LV = left ventricular; MI = myocardial infarction.
Adapted from Anavekar NS, et al. *N Engl J Med.* 2004;351:1285-1295.

Direct Relationship Between eGFR <60* and Number of Treatable CV Risk Factors

Treatable Risk Factors	Odds Ratio of eGFR <60 mL/min/1.73 m^2
0	1.25
1	4
2+	12.5

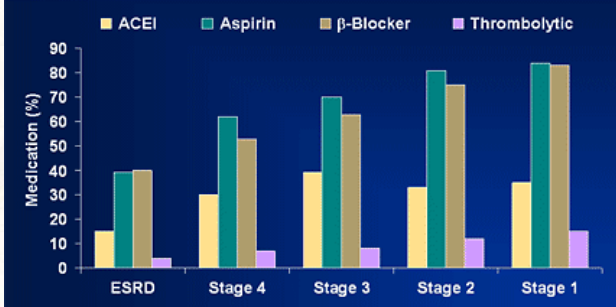
*mL/min/1.73 m^2.
Data from the Third National Health and Nutrition Examination Survey (NHANES III) (1991-1994) and NHANES 1999-2000 participants aged ≥20 years; US Renal Data System 2004 Annual Data Report. Available at: www.usrds.org. Accessed February 26, 2006.

Increased Progression of CKD: Treatable CVD Risk Factors

Treatable Risk Factors (% Patients)	Odds Ratio* (*P* value)
Anemia (84%)	3.5 (<.001)
C-Reactive Protein ≥1 mg/dL (85%)	1.7 (<.002)
Homocysteine (µmol/L) (41%)	
2.0-6.9	1.0
7.0-8.7	3.7
8.8-11.0	9.4
>11.0	40.2 (<.001)
Urinary Albumin/Creatinine (mg/g) (82%)	
<30	1.0 (<.001)
30-300	2.0
≥300	6.9 (<.001)
Number of CV Risk Factors (17%)	
0	1.0 (<.001)
1	3.9
≥2	11.9

*Adjusted odds ratio of eGFR falling <60 mL/min/1.73 m^2.
USRDS 2004 Annual Data Report. The data reported here have been supplied by the USRDS. Available at: www.usrds.org. Accessed February 24, 2006.

Less Use of Medications to Reduce Risk of CVD as Kidney Function Decreases



ACEI = angiotensin-converting enzyme inhibitor; ESRD = end-stage renal disease.

Adapted from Abbott KC, et al. *Circulation*. 2003;108:e114-e115.

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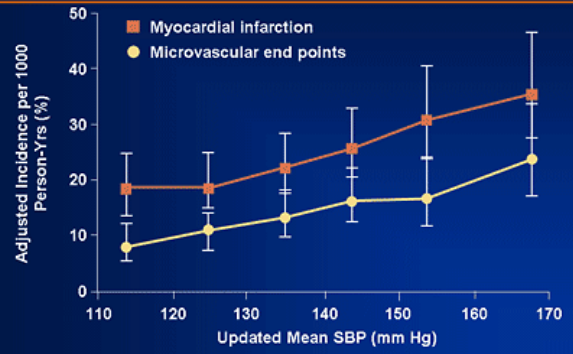
UKPDS: Rates of MI and Microvascular End Points by Category of SBP in Patients With Diabetes



SBP = systolic blood pressure; UKPDS = United Kingdom Prospective Diabetes Study.

Adapted from Adler AI, et al. *BMJ*. 2000;321:412-419.

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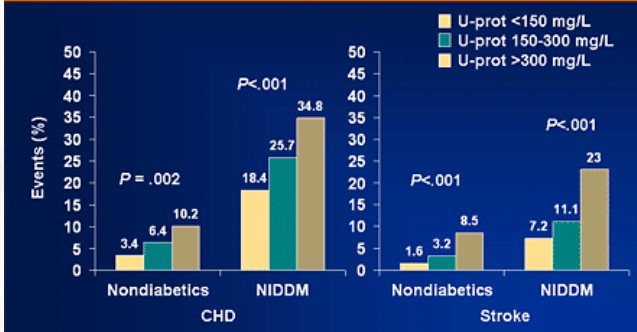
Proteinuria Predicts CHD and Stroke



CHD = coronary heart disease; NIDDM = non–insulin-dependent diabetes mellitus.

Adapted from Miettinen H, et al. *Stroke*. 1996;27:2033-2039.

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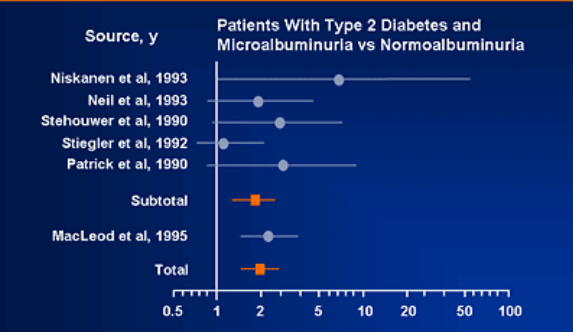
Risk of CV Morbidity and Mortality



Adapted from Dinneen SF, et al. *Arch Intern Med*. 1997;157:1413-1418.

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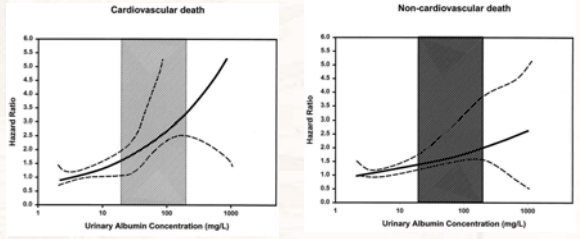
Importance of Proteinuria in CKD

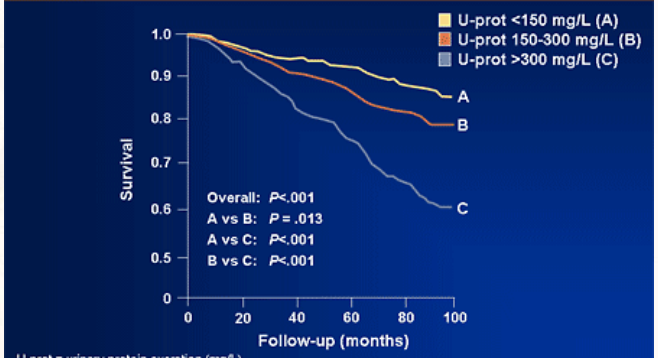
Interpretation	Explanation
Marker of kidney damage	Spot urine albumin-to-creatinine ratio >30 mg/g or spot urine total protein-to-creatinine ratio >200 mg/g for ≥3 months defines CKD
Clue to the type (diagnosis) of CKD	Spot urine total protein-to-creatinine ratio >500-1000 mg/g suggests diabetic kidney disease, glomerular diseases, or transplant glomerulopathy.
Risk factor for adverse outcomes	Higher proteinuria predicts faster progression of kidney disease and increased risk of CVD.
Effect modifier for interventions	Strict blood pressure control and ACE inhibitors are more effective in slowing kidney disease progression in patients with higher baseline proteinuria.
Hypothesized surrogate outcomes and target for interventions	If validated, then lowering proteinuria would be a goal of therapy.

Albuminuria as a Risk Factor for CVD in PREVEND



Hillege HL et al. Circulation 2002: 106: 1777-1782

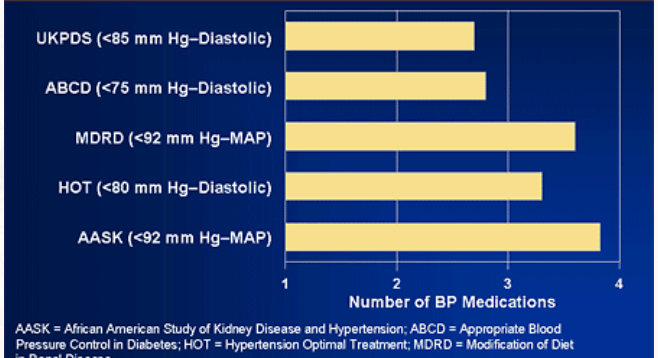
Survival Curves for CVD Mortality by Urinary Protein Concentration



U-prot = urinary protein excretion (mg/L).

Adapted from Miettinen H, et al. *Stroke*. 1996;27:2033-2039.

Blood Pressure Control Requires Multiple Medications



AASK = African American Study of Kidney Disease and Hypertension; ABCD = Appropriate Blood Pressure Control in Diabetes; HOT = Hypertension Optimal Treatment; MDRD = Modification of Diet in Renal Disease.

Adapted from Bakris GL, et al. *Am J Kidney Dis*. 2000;36:646-661.

Clinical Practice Guidelines for Management of Hypertension in CKD

Type of Kidney Disease	Blood Pressure Target (mm Hg)	Preferred Agents for CKD, with or without Hypertension	Other Agents to Reduce CVD Risk and Reach Blood Pressure Target
Diabetic Kidney Disease	<130/80	ACE inhibitor or ARB	Diuretic preferred, then BB or CCB
Nondiabetic Kidney Disease with Urine Total Protein-to-Creatinine Ratio ≥200 mg/g			
Nondiabetic Kidney Disease with Spot Urine Total Protein-to-Creatinine ratio <200 mg/g		None preferred	Diuretic preferred, then ACE inhibitor, ARB, BB or CCB
Kidney Disease in Kidney Transplant Recipient			CCB, diuretic, BB, ACE inhibitor, ARB

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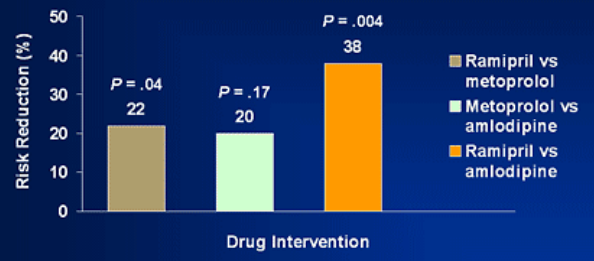
Risk Reduction of GFR Event,* ESRD, or Death



*Reduction in GFR by ≥50% (or ≥25 mL/min/1.73 m²).
Wright JT Jr, et al, for the AASK Study Group. *JAMA*. 2002;288:2421-2431.

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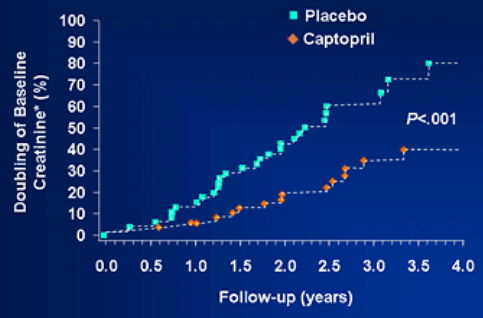
Renoprotection of ACEIs in Patients With Type 1 Diabetes



*Baseline creatinine ≥1.5 mg/dL.
SCr = serum creatinine.
Lewis EJ, et al, for the Collaborative Study Group. *N Engl J Med*. 1993;329:1456-1462.

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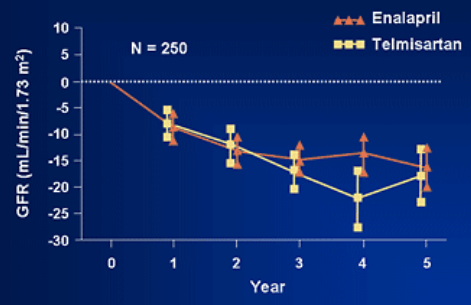
Renoprotection of Telmisartan and Enalapril in Patients With Type 2 Diabetes



Changes from baseline GFR, based on 5-year data according to treatment group of enalapril or telmisartan in patients with type 2 diabetes and nephropathy.
Adapted from Barnett AH, et al. *N Engl J Med*. 2004;351:1952-1961.

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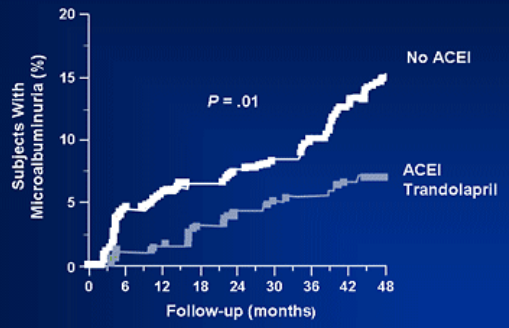
ACEIs Prevent Microalbuminuria in Patients With Type 2 Diabetes



N = 1204 subjects with hypertension, type 2 diabetes, and normal urinary albumin excretion.

Adapted from Ruggenenti P, et al, for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. *N Engl J Med.* 2004;351:1941-1951.

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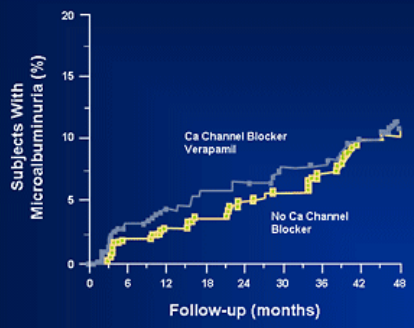
Ca Channel Blockers in Patients With Type 2 Diabetes



N = 1204 subjects with hypertension, type 2 diabetes, and normal urinary albumin excretion.

Adapted from Ruggenenti P, et al, for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. *N Engl J Med.* 2004;351:1941-1951.

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Therapy for Management of BP and RAS in Patients With CKD

Patient Population	Goal BP (mm Hg)	First-Line Therapy	Adjunctive Therapy
Diabetes	<130/80	ACEI or ARB	Diuretics then BB or CCB
Proteinuria without diabetes	<130/80	ACEI or ARB	Diuretics then BB or CCB
No diabetes or proteinuria	<130/80	No preference*	No preference*

*Diuretics then ACEI, ARB, BB, or CCB.

BB = β-blocker; CCB = calcium channel blocker; RAS = renin-angiotensin system.

ADA. *Diabetes Care.* 2004;27(suppl 1):S15-S35; Chobanian AV, et al, and the National High Blood Pressure Education Program Coordinating Committee. *JAMA.* 2003;289:2560-2572; NKF. *Am J Kidney Dis.* 2004;43(5 suppl 1):S1-S290.

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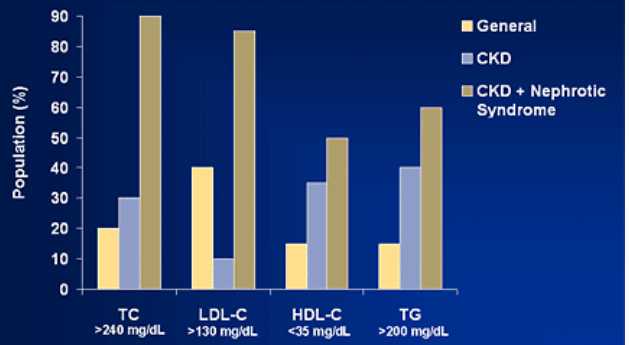
Prevalence of Dyslipidemia in Patients With CKD



HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Adapted from Kasiske BL. *Am J Kidney Dis.* 1998;32(5 suppl 3):S142-S156.

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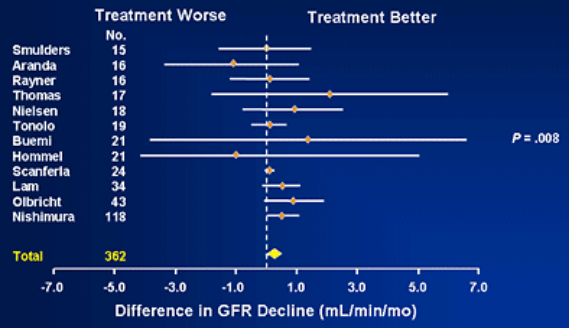
Meta-Analysis: Lipid Reduction on Progression of Renal Disease



Adapted from Fried LF, et al, for the Lipids and Renal Disease Progression Meta-Analysis Study Group. *Kidney Int*. 2001;59:260-269.

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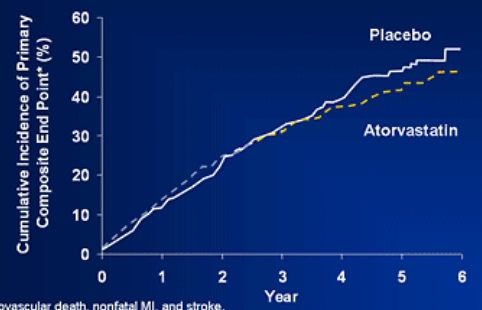
4D Study: Treatment Has No Effect on Composite Primary End Point



*Cardiovascular death, nonfatal MI, and stroke.
4D Study = randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis.
Adapted from Wanner C, et al, for the German Diabetes and Dialysis Study Investigators. *N Engl J Med*. 2005;353:238-248.

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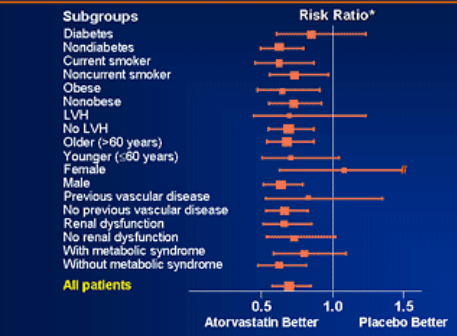
ASCOT: Reduction in CV Events With Statin Treatment



*Area of squares is proportional to the amount of statistical information.
ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial.
Adapted from Sever PS, et al, for the ASCOT Investigators. *Lancet*. 2003;361:1149-1158.

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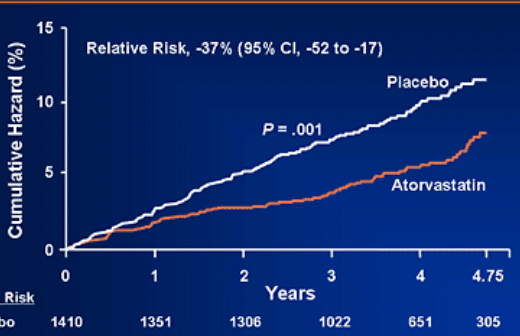
CARDS: Prevention of CVD With Atorvastatin in Type 2 Diabetes



No. at Risk						
Placebo	1410	1351	1306	1022	651	305
Atorvastatin	1428	1392	1361	1074	694	328

Adapted from Colhoun HM, et al, on behalf of the CARDS Investigators. *Lancet*. 2004;364:685-696.

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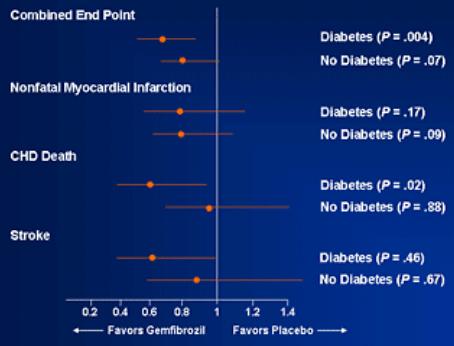
VA-HIT: Treatment With Gemfibrozil Reduces CVD Risk in Patients With Diabetes



VA-HIT = Department of Veterans Affairs HDL Intervention Trial.
Adapted from Rubins HB, et al, for the VA-HIT Study Group. *Arch Intern Med*. 2002;162:2597-2604.

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NKF Guidelines: Management of Dyslipidemias in Adults With CKD

Dyslipidemia	Goal	Initiate	Increase	Alternative
TG ≥500 mg/dL	TG <500 mg/dL	TLC	TLC + fibrate or niacin	Fibrate or niacin
LDL-C 100-129 mg/dL	LDL-C <100 mg/dL	TLC	TLC + low-dose statin	Bile acid sequestrant or niacin
LDL-C ≥130 mg/dL	LDL-C <100 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Bile acid sequestrant or niacin
TG ≥200 mg/dL and non–HDL-C ≥130 mg/dL	Non–HDL-C <130 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Fibrate or niacin

TLC = therapeutic lifestyle changes.
Adapted from NKF. *Am J Kidney Dis*. 2003;41(4 suppl 3):I-IV, S1-S91.

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Summary: Reducing Cardiorenal Risk in Patients With CKD

- Major cause of death for patients with CKD is CVD
- Risk reduction treatment paradigms include
  - Control of BP to <130/80 mm Hg
  - Multidrug regimens with ACEI or ARB
  - RAS blockade
  - Control of lipids to LDL-C <100 mg/dL, TG <150 mg/dL, HDL-C >40 mg/dL in men, and >50 mg/dL in women
- There is great need for more studies that focus specifically on patients with CKD

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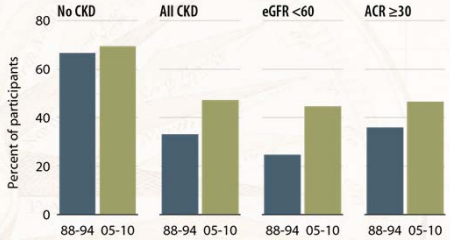
NHANES participants at target blood pressure

Figure 1.12 (Volume 1)



NHANES 1988–1994 & 2005–2010 participants age 20 & older; single sample estimates of eGFR & ACR; dialysis patients excluded from NHANES 2005–2010. eGFR calculated using the CKD-EPI equation. This figure cannot be directly compared to values in Table 1.b. The table represents NHANES participants who are classified as hypertensive (measured/treated) but some of those are at target blood pressure. Represents all hypertensives plus those hypertensives who are at target blood pressure probably due to medication.

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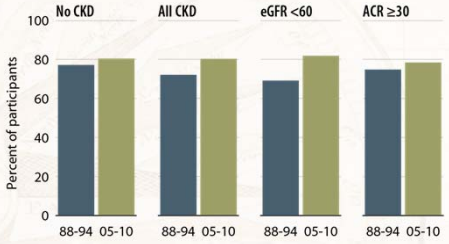
NHANES participants within HDL cholesterol target range

Figure 1.14 (Volume 1)



NHANES 1988–1994 & 2005–2010 participants age 20 & older; single sample estimates of eGFR & ACR; dialysis patients excluded from NHANES 2005–2010. eGFR calculated using the CKD-EPI equation.

Clinical Practice Guidelines for the Detection, Evaluation and Management of CKD

Stage	Description	GFR	Evaluation	Management
	At increased risk		Test for CKD	Risk factor management
1	Kidney damage with normal or ↑ GFR	>90	Diagnosis Comorbid conditions CVD and CVD risk factors	Specific therapy, based on diagnosis Management of comorbid conditions Treatment of CVD and CVD risk factors
2	Kidney damage with mild ↓ GFR	60-89	Rate of progression	Slowing rate of loss of kidney function [1]
3	Moderate ↓ GFR	30-59	Complications	Prevention and treatment of complications
4	Severe ↓ GFR	15-29		Preparation for kidney replacement therapy Referral to Nephrologist
5	Kidney Failure	<15		Kidney replacement therapy

[1]Target blood pressure less than 130/80 mm Hg. Angiotension converting enzyme inhibitors (ACEI) or angiotension receptor blocker (ARB) for diabetic or non-diabetic kidney disease with spot urine total protein-to-creatinine ratio of greater than 200 mg/g.

Metformin Use

- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m² and shouldn't be initiated in eGFRs of 30–45 mL/minute/1.73 m². For patients whose eGFR declines into the 30–45 mL range while on treatment, clinicians should assess risks and benefits before continuing.

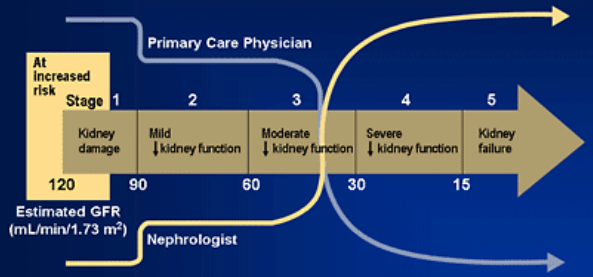
Metformin should be stopped at or before an iodinated contrast imaging procedure in patients whose eGFR is 30–60 mL/minute/1.73 m²; in those with a history of liver disease, alcoholism, or heart failure; or in those who will be given intra-arterial iodinated contrast.

Care Is Fragmented

Who is currently caring for patients with CKD?

CKD = chronic kidney disease.

Continuum of CKD Care: Interaction of PCP and Nephrologist



GFR = glomerular filtration rate; PCP = primary care physician.

Eknoyan G, et al. *Postgrad Med J*. 2001;110:23-29.

Team Approach: Roles of PCP and Nephrologist in CKD

PCP

- Screen and identify risk factors of CKD, including:
  - Diabetes
  - CVD
  - Anemia
- Provide ongoing management for patients with CKD
- Provide role-specific patient education

Nephrologist

- Assist in development of care strategy
- Aid recommendation and implementation of patient care
- Provide role-specific patient education

CVD = cardiovascular disease.

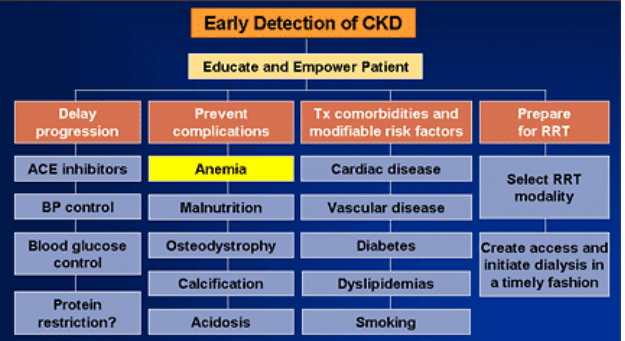
Delayed Detection of CKD Leads to Underuse of Interventions

- Lack of rHuEPO use
- Lack of interventions to treat hypertension, CVD, diabetes, and malnutrition
- Underuse and delayed consultations with nephrologists, cardiovascular specialists, or dieticians
- Lack of patient education
- Lack of a permanent vascular access at initiation of hemodialysis

rHuEPO = recombinant human erythropoietin.

Obrador GT, et al. *J Am Soc Nephrol*. 1999;10:1793-1800.
Pereira BJ. *Kidney Int*. 2000;57:351-365.
Zabetakis PM, et al. *Am J Kidney Dis*. 2000;36(6 suppl 3):S31-S38.

Components of a Comprehensive CKD Care Plan



ACE = angiotensin-converting enzyme; BP = blood pressure.

Adapted from Pereira BJ. *Kidney Int*. 2000;57:351-365.

Primary care professionals can play a significant role in early diagnosis, treatment, and patient education

Therapeutic interventions for diabetic CKD are similar to those required for optimal diabetes care
Control of glucose, blood pressure, and lipids

A greater emphasis on detecting CKD, and managing it prior to referral, can improve patient outcomes

CKD is Part of Primary Care

Scope of the Prevalence of CKD

Stage	Description	No. of Individuals/ Prevalence (%)
1	≥90 mL/min/1.73 m^2; kidney damage with normal GFR; persistent albuminuria	5.9 million (3.3%)
2	60-89 mL/min/1.73 m^2; persistent albuminuria	5.3 million (3.0%)
3	30-59 mL/min/1.73 m^2	7.6 million (4.3%)
4	15-29 mL/min/1.73 m^2	400,000 (0.2%)
5	<15 mL/min/1.73 m^2 or dialysis; kidney failure	651,000 (0.3%)

Levey AS, et al. *Ann Intern Med*. 2003;139:137-147.

Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *New England Journal of Medicine*. 2004 Sep 23;351(13):1285-95.

Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *Journal of the American Medical Association*. 2007 Nov 7;298(17):2038-47.

Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. *Annals of Internal Medicine*. 1997 Sep 1;127(5):337-45.

Go AS, Chertow GM, Fan D, McCulloch CE, Chi-Yuan H. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *New England Journal of Medicine*. 2004 Sep 23;351(13):1296-1305.

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National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *American Journal of Kidney Diseases*. 2002 Feb;39(2 Suppl 1):S1-266.