# A New Approach for Evaluating Renal Function and Predicting Risk

William McClellan, MD, MPH

Emory University

Atlanta

# Goals

- Understand the limitations and uses of creatinine based measures of kidney function
- Understand the evolving role of albuminuria measurement in CKD risk stratification
- Understand the prognostic use of measures of change of GFR (slope)

# Definition of Chronic Kidney Disease (CKD)

- Etiology: primary cause of renal injury defined by history, clinical and laboratory presentation, isolated anatomic abnormalities, and radiographic evidence.
- Functional:  biomarkers to measure impaired renal function
  - Creatinine
  - Proteinuria: ACR, dipstick
- Chronicity: presence for 3 or more months
  - Persistence
  - Progression

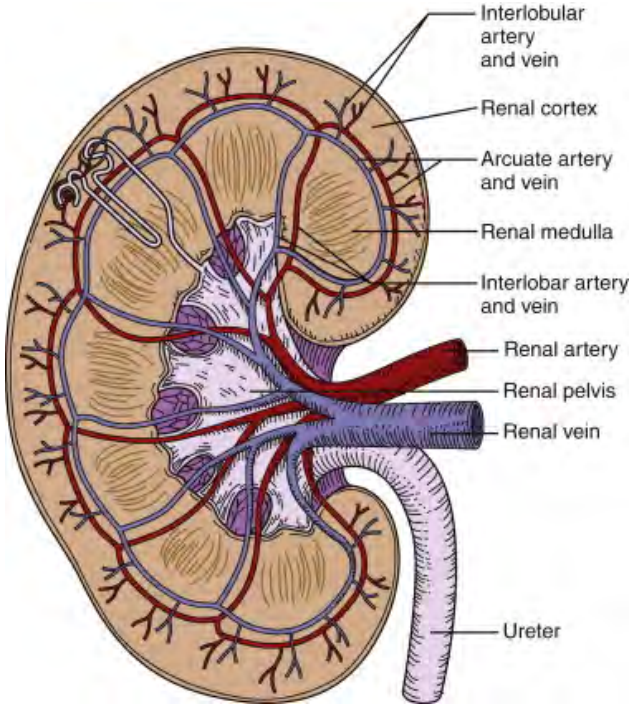
# Etiology of CKD leading to ESRD (82 categories)

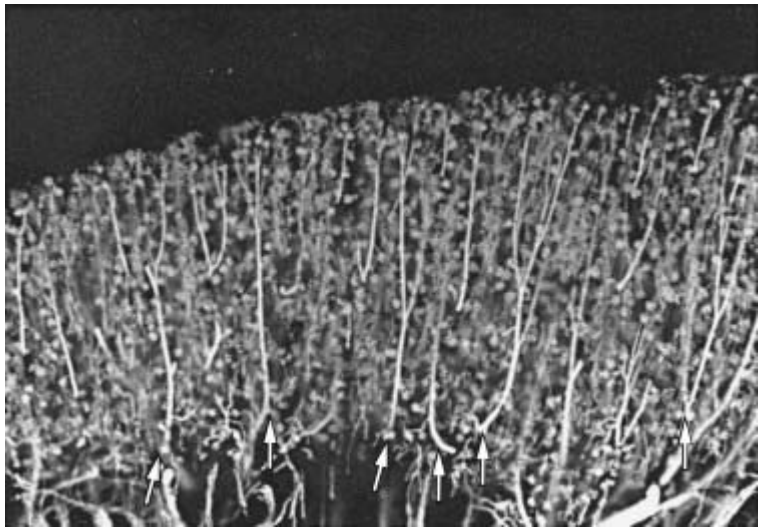
| ICD-9 | NARRATIVE |
|---|---|
| **DIABETES** | |
| 25040 | Diabetes with renal manifestations Type 2 |
| 25041 | Diabetes with renal manifestations Type 1 |
| **GLOMERULONEPHRITIS** | |
| 5829 | Glomerulonephritis (GN) (histologically not examined) |
| 5821 | Focal glomerulosclerosis, focal sclerosing GN |
| 5831 | Membranous nephropathy |
| 58321 | Membranoproliferative GN type 1, diffuse MPGN |
| 58322 | Dense deposit disease, MPGN type 2 |
| 58381 | IgA nephropathy, Berger's disease (proven by immunofluorescence) |
| 58382 | IgM nephropathy (proven by immunofluorescence) |
| 5834 | With lesion of rapidly progressive GN |
| 5800 | Post infectious GN, SBE |
| 5820 | Other proliferative GN |
| **SECONDARY GN/VASCULITIS** | |
| 7100 | Lupus erythematosus, (SLE nephritis) |
| 2870 | Henoch-Schonlein syndrome |
| 7101 | Scleroderma |
| 28311 | Hemolytic uremic syndrome |
| 4460 | Polyarteritis |
| 4464 | Wegener's granulomatosis |
| 58392 | Nephropathy due to heroin abuse and related drugs |
| 44620 | Other Vasculitis and its derivatives |
| 44621 | Goodpasture's syndrome |
| 58391 | Secondary GN, other |
| **INTERSTITIAL NEPHRITIS/PYELONEPHRITIS** | |
| 9659 | Analgesic abuse |
| 5830 | Radiation nephritis |
| 9849 | Lead nephropathy |
| 5909 | Nephropathy caused by other agents |
| 27410 | Gouty nephropathy |
| 5920 | Nephrolithiasis |
| 5996 | Acquired obstructive uropathy |
| 5900 | Chronic pyelonephritis, reflux nephropathy |
| 58389 | Chronic interstitial nephritis |
| 58089 | Acute interstitial nephritis |
| 5929 | Urolithiasis |
| 27549 | Other disorders of calcium metabolism |
| **HYPERTENSION/LARGE VESSEL DISEASE** | |
| 40391 | Unspecified with renal failure |
| 4401 | Renal artery stenosis |
| 59381 | Renal artery occlusion |
| 59383 | Cholesterol emboli, renal emboli |

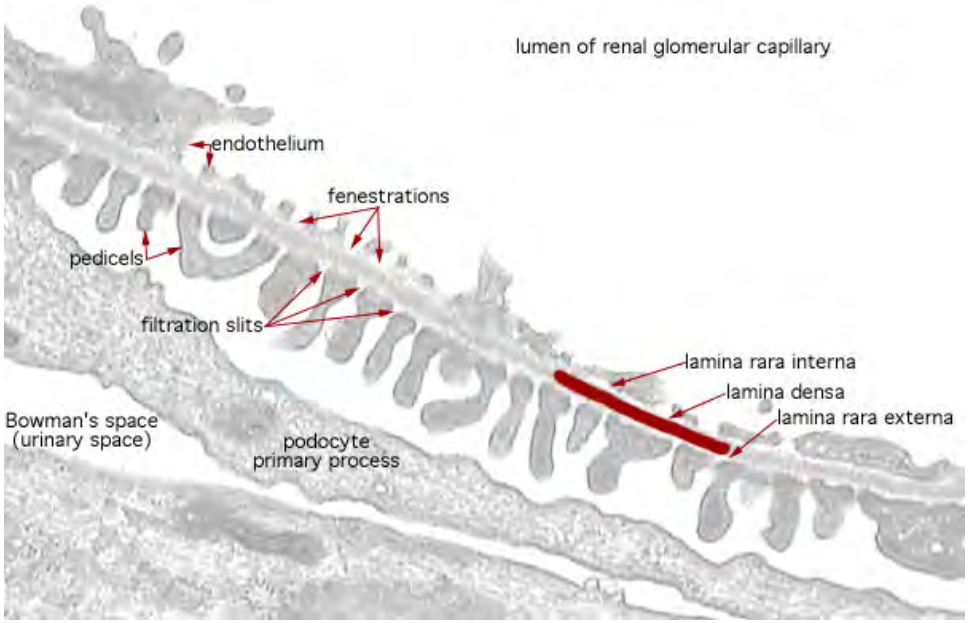
| ICD-9 | NARRATIVE |
|---|---|
| **CYSTIC/HEREDITARY/CONGENITAL DISEASES** | |
| 75313 | Polycystic kidneys, adult type (dominant) |
| 75314 | Polycystic, infantile (recessive) |
| 75316 | Medullary cystic disease, including nephronophthisis |
| 7595 | Tuberous sclerosis |
| 7598 | Hereditary nephritis, Alport's syndrome |
| 2700 | Cystinosis |
| 2718 | Primary oxalosis |
| 2727 | Fabry's disease |
| 7533 | Congenital nephrotic syndrome |
| 5839 | Drash syndrome, mesangial sclerosis |
| 75321 | Congenital obstruction of ureterpelvic junction |
| 75322 | Congenital obstruction of uretrovesical junction |
| 75329 | Other Congenital obstructive uropathy |
| 7530 | Renal hypoplasia, dysplasia, oligonephronia |
| 75671 | Prune belly syndrome |
| 75989 | Other (congenital malformation syndromes) |
| **NEOPLASMS/TUMORS** | |
| 1890 | Renal tumor (malignant) |
| 1899 | Urinary tract tumor (malignant) |
| 2230 | Renal tumor (benign) |
| 2239 | Urinary tract tumor (benign) |
| 23951 | Renal tumor (unspecified) |
| 23952 | Urinary tract tumor (unspecified) |
| 20280 | Lymphoma of kidneys |
| 20300 | Multiple myeloma |
| 20308 | Other immuno proliferative neoplasms (including light chain nephropathy) |
| 2773 | Amyloidosis |
| 99680 | Complications of transplanted organ unspecified |
| 99681 | Complications of transplanted kidney |
| 99682 | Complications of transplanted liver |
| 99683 | Complications of transplanted heart |
| 99684 | Complications of transplanted lung |
| 99685 | Complications of transplanted bone marrow |
| 99686 | Complications of transplanted pancreas |
| 99687 | Complications of transplanted intestine |
| 99689 | Complications of other specified transplanted organ |
| **MISCELLANEOUS CONDITIONS** | |
| 28260 | Sickle cell disease/anemia |
| 28269 | Sickle cell trait and other sickle cell (HbS/Hb other) |
| 64620 | Post partum renal failure |
| 042 | AIDS nephropathy |
| 8660 | Traumatic or surgical loss of kidney(s) |
| 5724 | Hepatorenal syndrome |
| 5836 | Tubular necrosis (no recovery) |
| 59389 | Other renal disorders |
| 7999 | Etiology uncertain |

FORM CMS-2728-U3 (05/04)

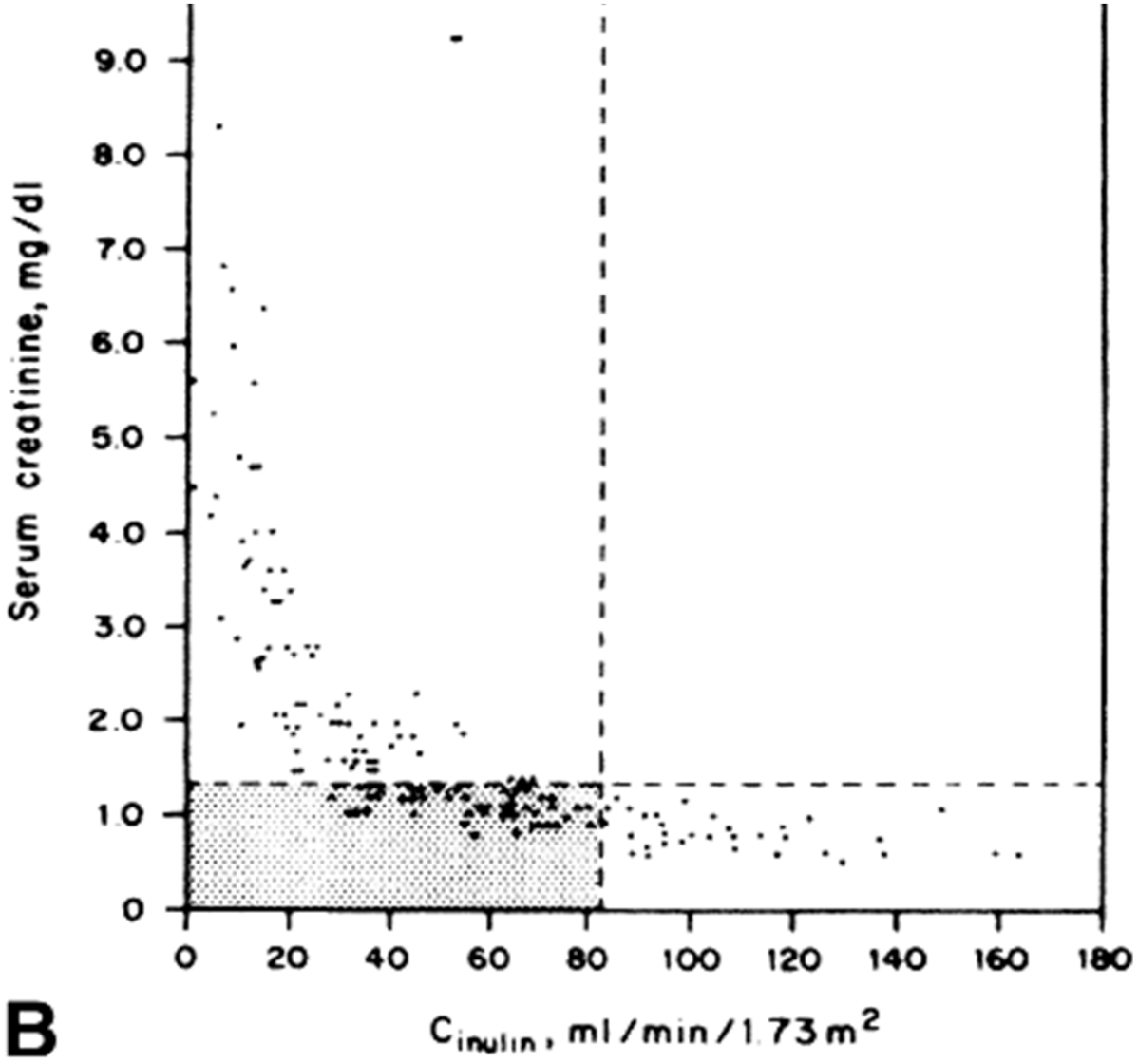
# Assessment of Kidney Function





# Functional evaluation: Serum creatinine misleading with respect to GFR




http://www.kidney.org

# The Perils of Using Serum Creatinine Only to “Guess” level of Renal Function

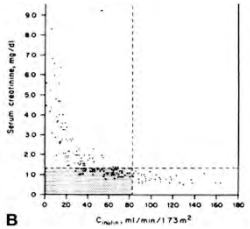
| Scr | Age | Sex | Ethnicity | Estimated GFR |
|---|---|---|---|---|
| 1.4 | 45 | M | White | 71 |
| 1.4 | 45 | F | Black | 52 |
| 1.4 | 70 | M | Black | 63 |
| 1.4 | 70 | F | White | 41 |

Creatinine

$$C_{CR} = \frac{U_{CR} \times V}{P_{CR}}$$

# MDRD equation: better estimation of GFR

- GFR mL/min/1.73 $m^2$ = 186 x (Scr)*-1.154 x (Age)*-0.203 x (0.742 if female) x (1.210 if black)



- PDA calculator: http://www.kidney.org/professionals/kdoqi/
- Online GFR calculator
- Clinical Laboratory Guidelines http://www.nkdep.nih.gov/healthprofessionals/

http://www.nkdep.nih.gov/healthprofessionals/tools/gfr_adults.htm

# Limitations to creatinine measurement

(1) Modified creatinine production
- a) Muscle mass
  - Increased (black race, male)
  - Decreased (amputation, cachexia, age, female)
- b) Diet: ingested cooked meat and protein restriction

(2) Creatinine secretion
- a) Modified by cimetidine, trimethoprim

(3) Creatinine assay standardization and calibration (traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure)

1.4.3: Evaluation of GFR: KIDNEY DISEASE | IMPROVING GLOBAL OUTCOMES (KDIGO) 2012 Guidelines

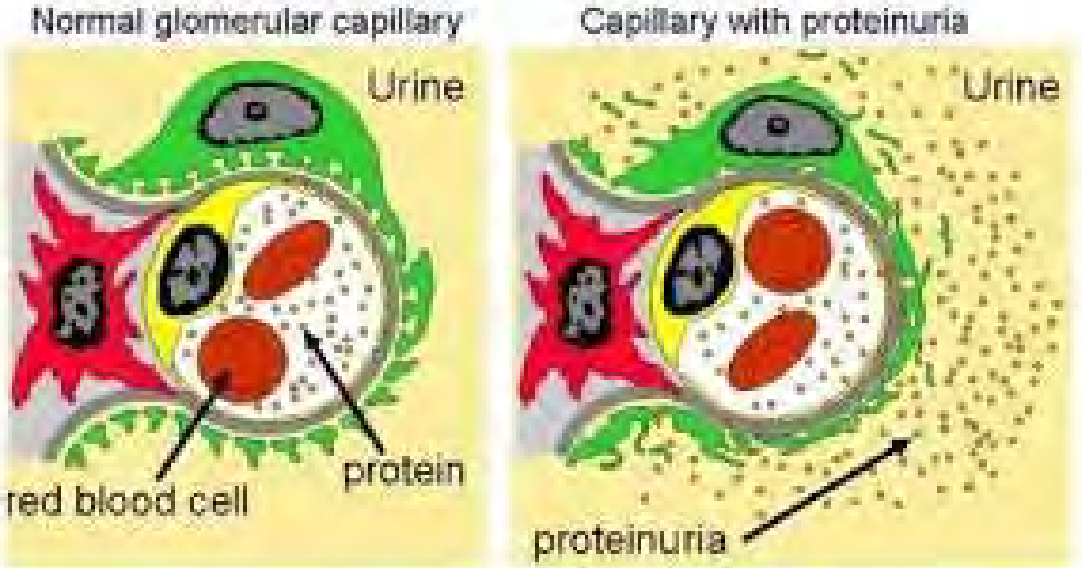
1.4.3.1: Use serum creatinine and a GFR estimating equation for initial assessment. (1A)

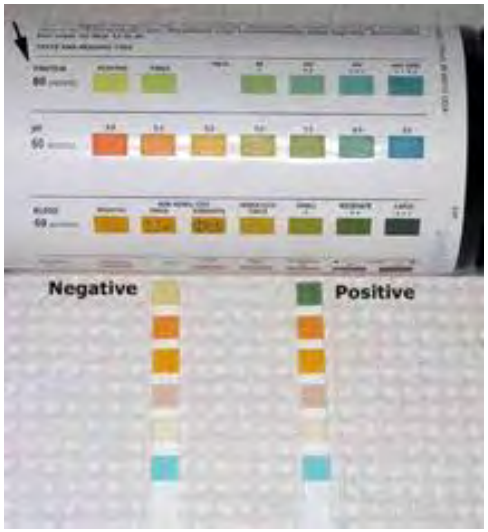
1.4.3.2: Use additional tests (cystatin C or creatinine clearance) in specific circumstances when eGFR based on serum creatinine is less accurate. (2B)

1.4.3.3: We recommend that clinicians (1B): use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone and understand clinical settings in which eGFRcreat is less accurate.

Ann Intern Med. 2013;158:825-30.

# Measuring albumin excretion



# CKD Prognosis Consortium

| | Region | Number of participants | Age, mean (years) | Male (%) | Black (%) |
|---|---|---|---|---|---|
| **Studies with ACR measurements** | | | | | |
| ARIC[20] | USA | 11408 | 63 | 44% | 22% |
| AusDiab*[21] | Australia | 11244 | 52 | 45% | 0 |
| Beijing[22] | China | 1563 | 60 | 50% | 0 |
| CHS[23] | USA | 3230 | 78 | 40% | 16% |
| COBRA[24] | Pakistan | 2872 | 52 | 48% | 0 |
| Framingham[25] | USA | 2956 | 59 | 47% | 0 |
| Gubbio[26] | Italy | 1684 | 55 | 45% | 0 |
| HUNT[5] | Norway | 9525 | 62 | 45% | 0 |
| MESA[27] | USA | 6705 | 62 | 47% | 28% |
| NHANES III[15] | USA | 15853 | 47 | 47% | 27% |
| PREVEND[28] | Netherlands | 8370 | 49 | 50% | 1% |
| Rancho Bernardo[29] | USA | 1759 | 71 | 39% | 0 |
| REGARDS[30] | USA | 27583 | 65 | 45% | 42% |
| ULSAM[31] | Sweden | 1120 | 71 | 100% | 0 |
| **Studies with dipstick measurements** | | | | | |
| AKDN[16] | Canada | 690680 | 47 | 45% | NA |
| Beaver Dam[32] | USA | 4926 | 62 | 44% | 0 |
| ESTHER[33] | Germany | 9350 | 62 | 45% | 0 |
| MRC Older People[34] | UK | 12158 | 81 | 39% | 0 |
| Ohasama[35] | Japan | 1466 | 63 | 34% | 0 |
| Severance[36] | South Korea | 42637 | 46 | 51% | 0 |
| Taiwan[3] | Taiwan | 367093 | 42 | 50% | 0 |

Lancet. 2010; 375:2073-81

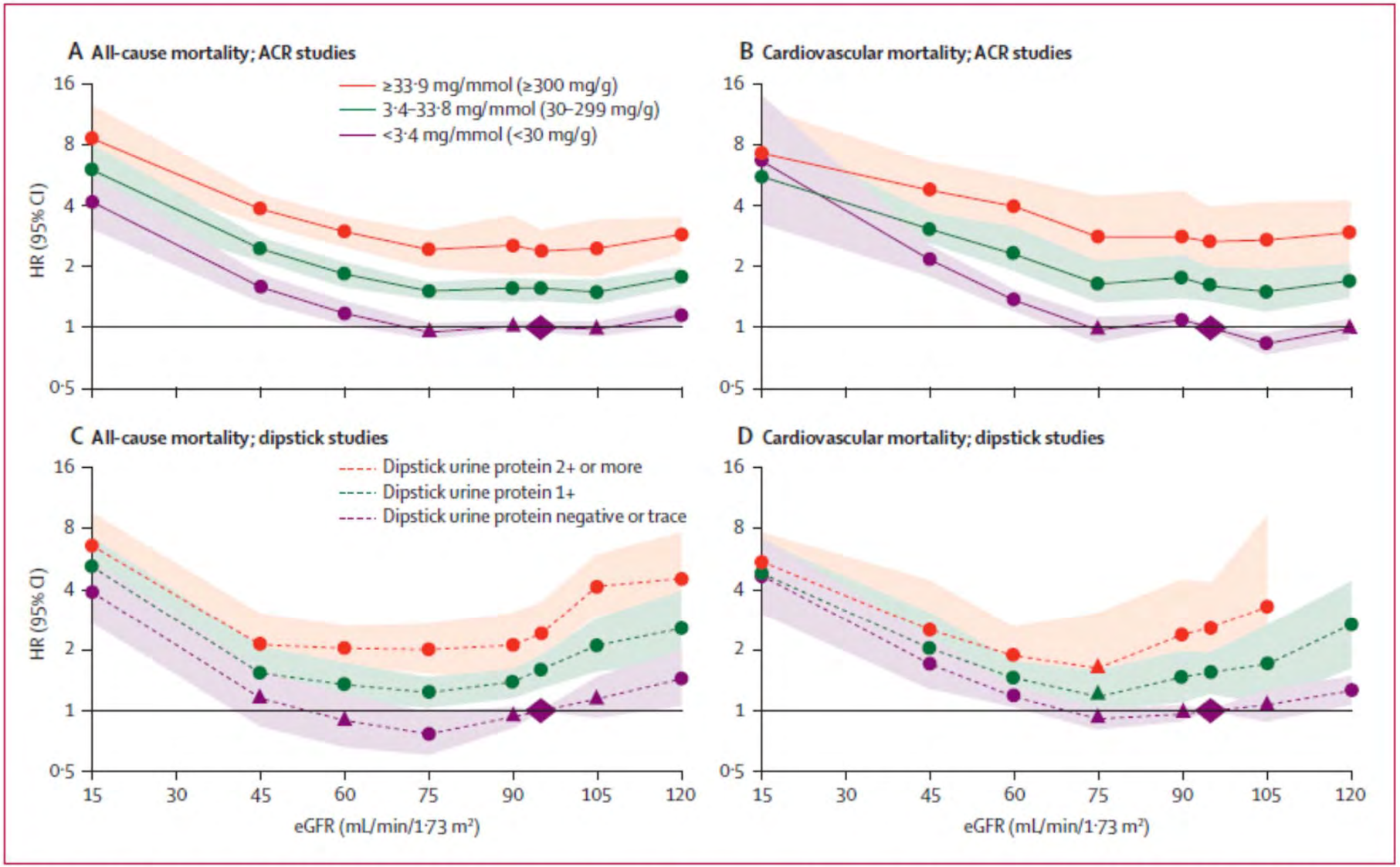



*Figure* 3: Hazard ratios and 95% CIs for all-cause and cardiovascular mortality according to spline estimated glomerular filtration rate (eGFR) and categorical albuminuria

Lancet. 2010 Jun 12;375:2073-81

# Risk stratification: Combining information about eGFR and ACR

**Prognosis of CKD by GFR and albuminuria category**

**Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012**

| GFR categories (ml/min/ 1.73 m$^2$) Description and range | | | | Persistent albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 Normal to mildly increased | A2 Moderately increased | A3 Severely increased |
| | | | | <30 mg/g <3 mg/mmol | 30-300 mg/g 3-30 mg/mmol | >300 mg/g >30 mg/mmol |
| | G1 | Normal or high | ≥90 | | | |
| | G2 | Mildly decreased | 60-89 | | | |
| | G3a | Mildly to moderately decreased | 45-59 | | | |
| | G3b | Moderately to severely decreased | 30-44 | | | |
| | G4 | Severely decreased | 15-29 | | | |
| | G5 | Kidney failure | <15 | | | |

**Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.**

Am J Kidney Dis. 2014; 63:713-35

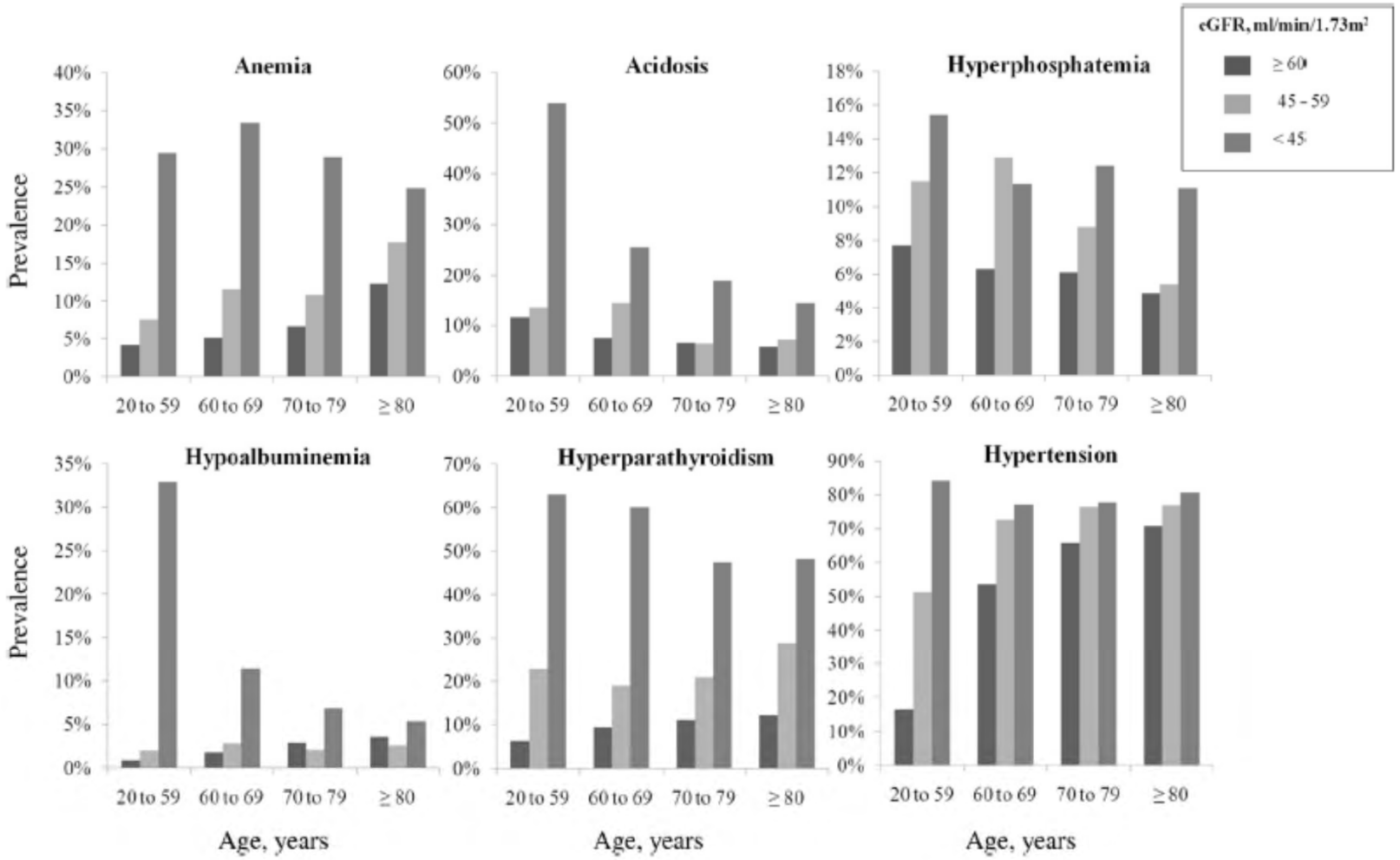
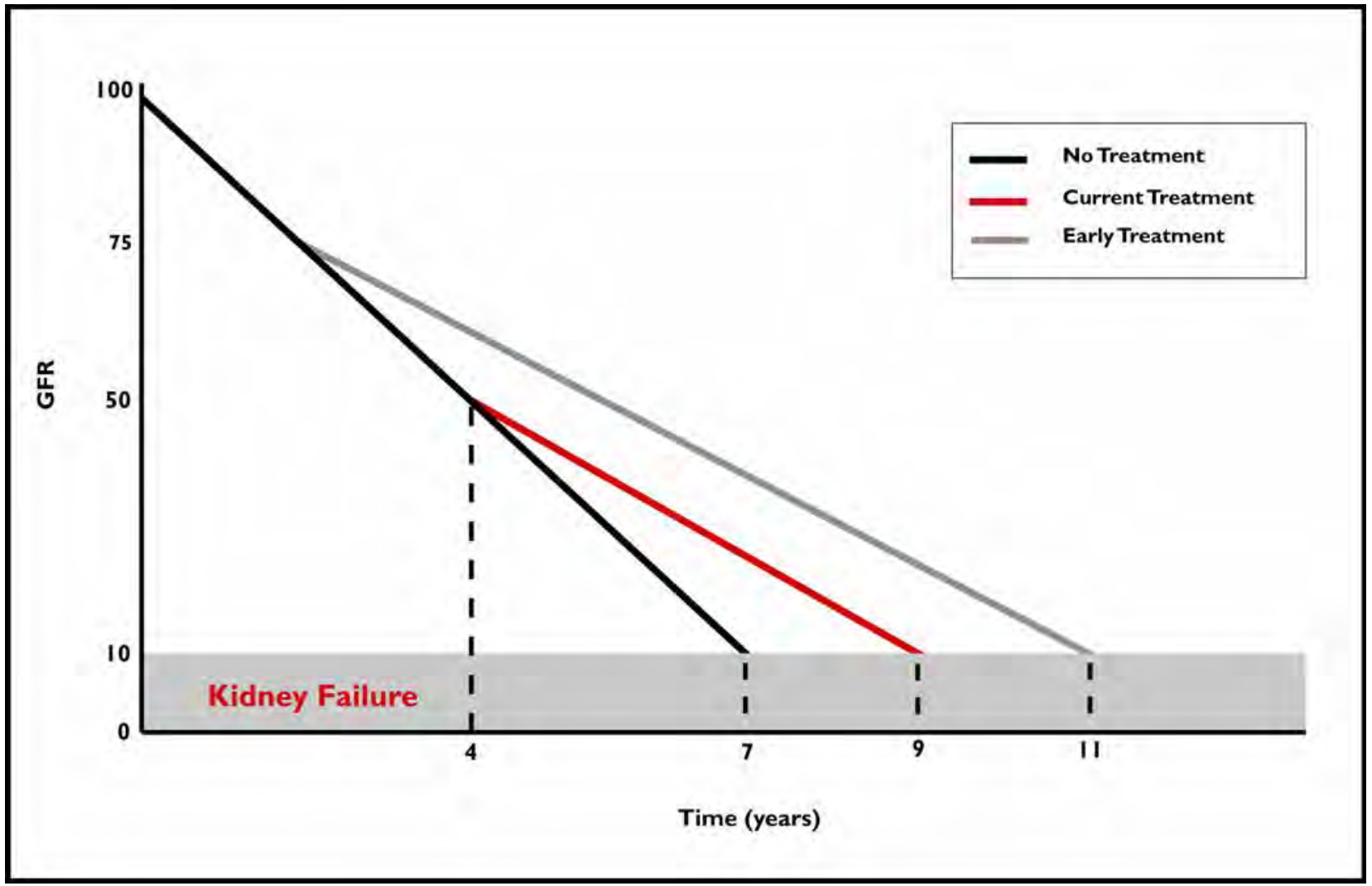



**Figure 1. | Unadjusted age-specific prevalence of concurrent complications of chronic kidney disease by estimated GFR (eGFR, ml/min per 1.73 m²).**

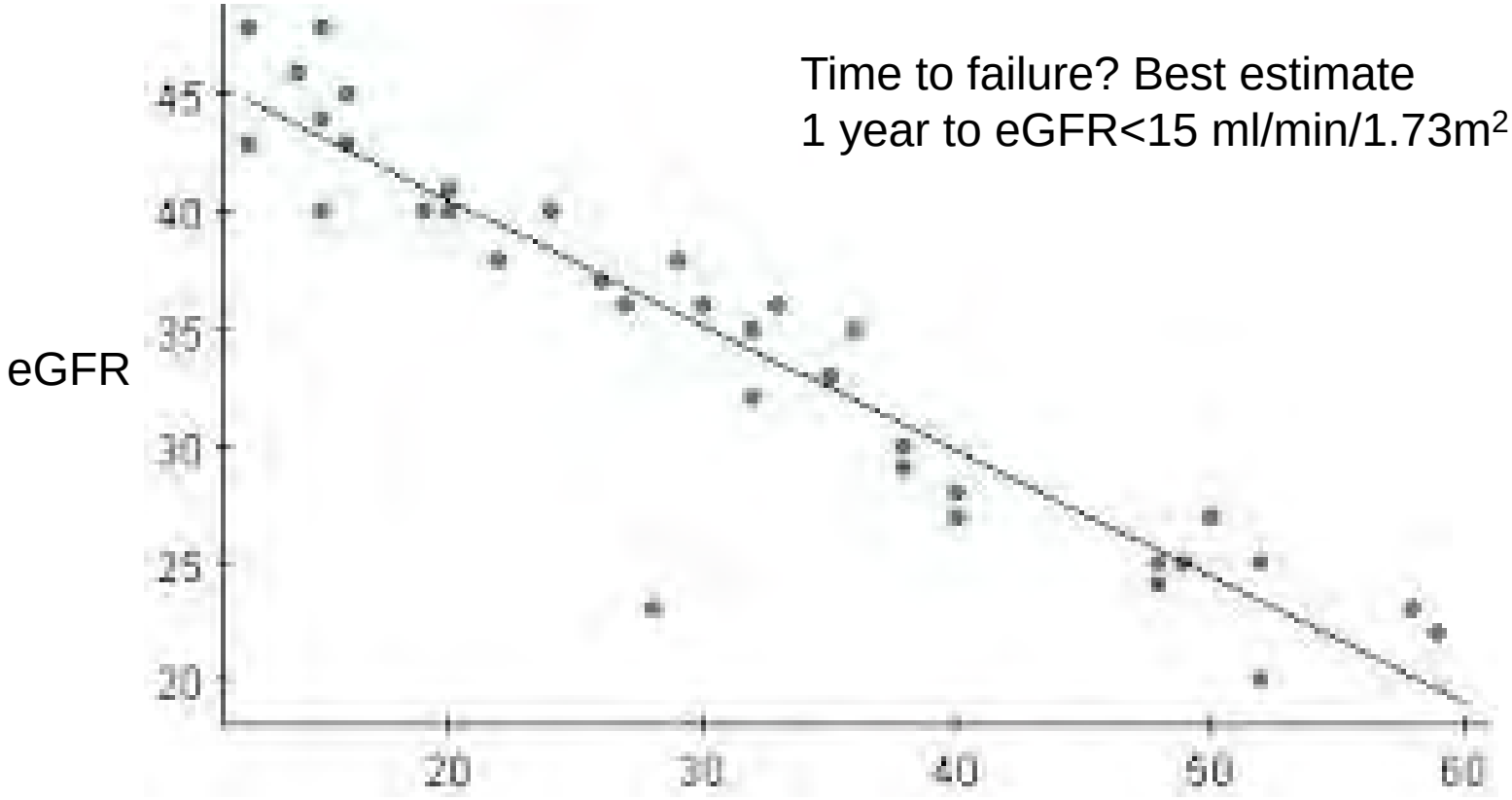
Clin J Am Soc Nephrol. 2011;6:2822-8.

# GFR over time (Slope): Early Intervention important to preserve kidney function

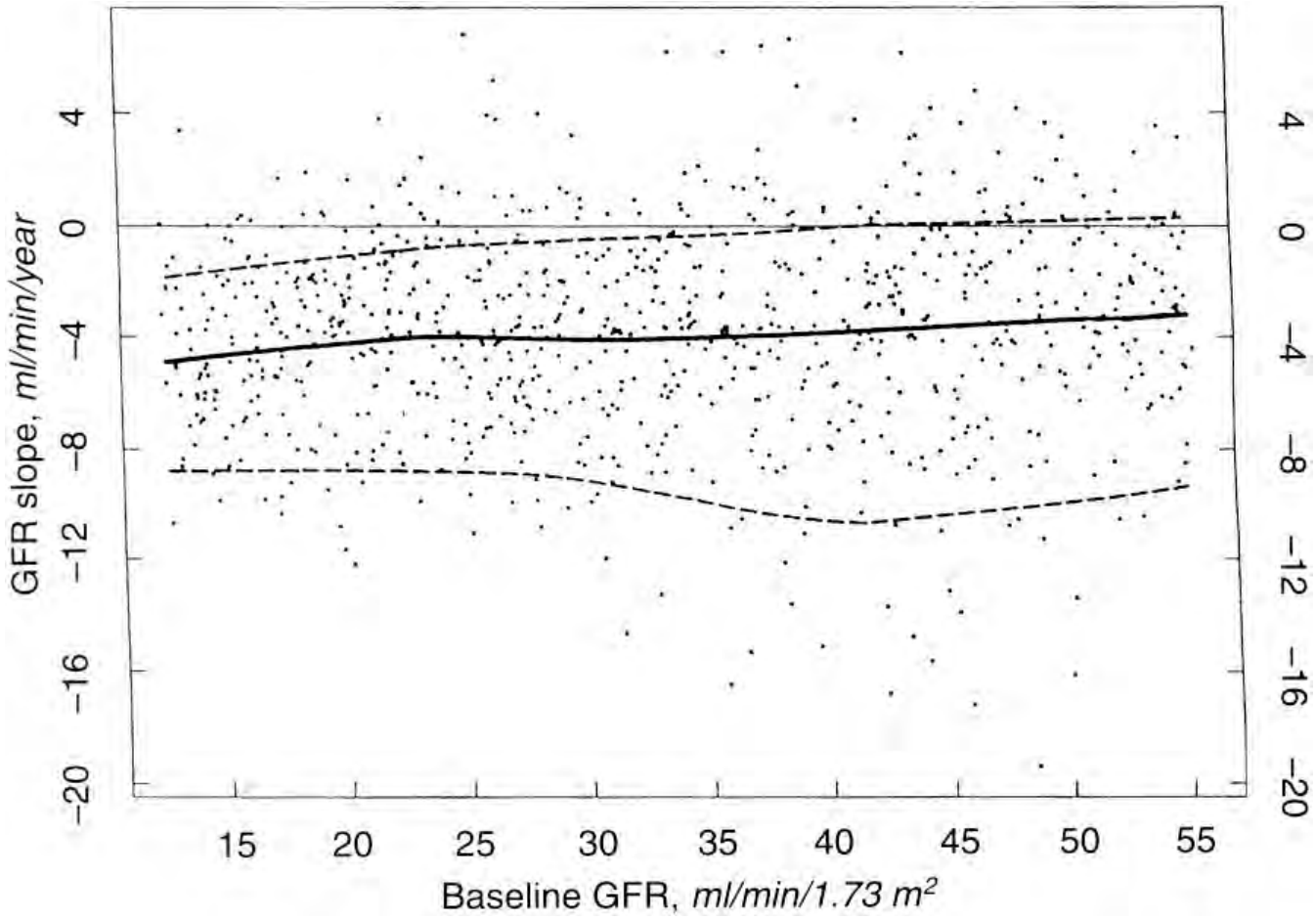


(45-20)ml/min/1.73m2/(60-10) months= 25/50 = 0.5ml/min/1.73m$^2$/mo or 6ml/min/1.73m$^2$/yr. This is a 27% reduction in GFR over 2yrs.

Time to failure? Best estimate
1 year to eGFR<15 ml/min/1.73m$^2$



# Slopes are variable in patients with CKD




Mean three-year two-slope mixed-effects GFR slopes for participants in the MDRD study A or overall GFR slope for participants in Study B by baseline GFR. Kidney Int. 1997; 51:1908-19.

# Change in GFR in Cohort of > 2300 CKD Patients: the CRIOS Study

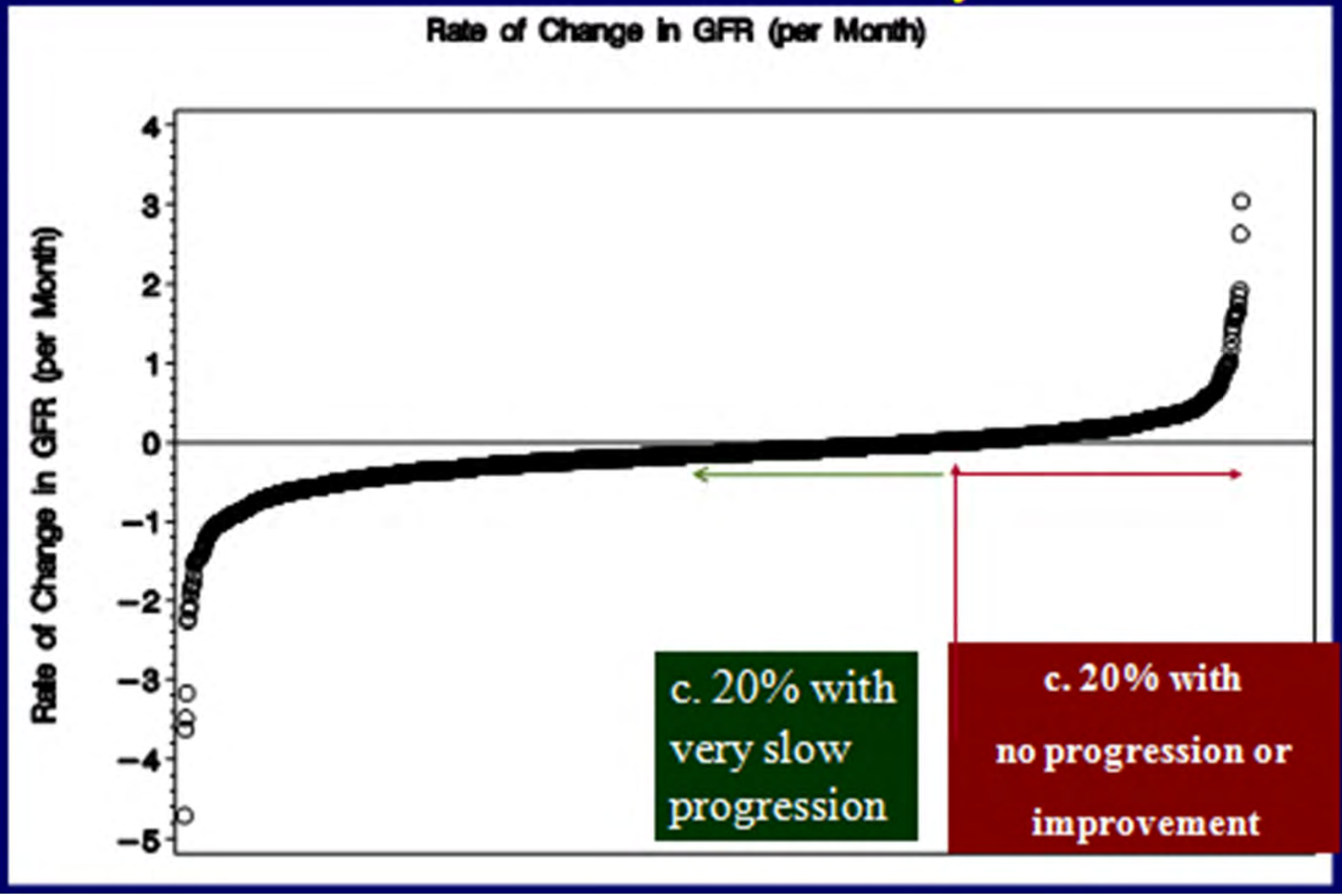
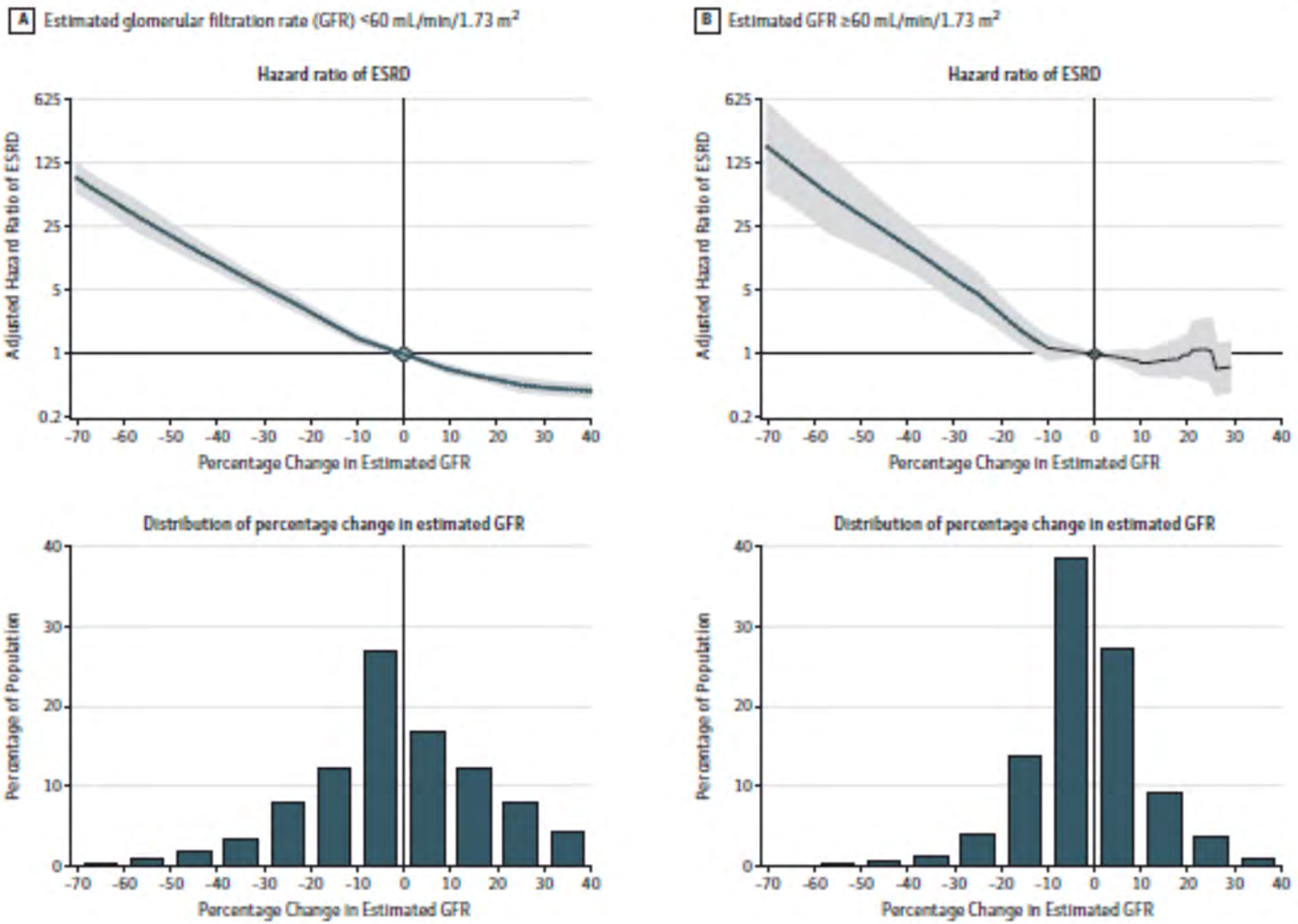


Figure 1. End-Stage Renal Disease (ESRD) Associated With Percentage Change in Estimated GFR During a 2-Year Baseline Period




JAMA. 2014;311(24):2518-2531.

# A CKD Clinical Action Plan

| CKD Management | Stages 1-2 | Stage 3 | Stage 4 | Stage 5 |
|---|---|---|---|---|
| **GFR mL/min/1.73 $m^2$** | **>60** | **30-59** | **15-29** | **<15** |
| BP<130/80 mm Hg | | | | |
| ACEI/ARB | | | | |
| Lipids/smoking | | | | |
| NSAIDs/contrast | | | | |
| Anemia | | | | |
| Nutrition | | | | |
| Vascular access | | | | |

http://www.nkdep.nih.gov/healthprofessionals/tools/template.asp. Accessed 3/24/05.

# Check list for contemporary evaluation of renal function and risk in patients with CKD

- Clinical lab: IDMS calibrated assay?
- Electronic medical record: Reports eGFR and creatinine?
- Both eGFR and ACR assessed in CKD?
  - Combined to a KDIGO risk stratification?
- eGFR slope periodically assessed?
- Clinical decision making reflects KDIGO stage and eGFR slope?