Role of Primary Care Providers in Effective Management of Chronic Kidney Disease-2008

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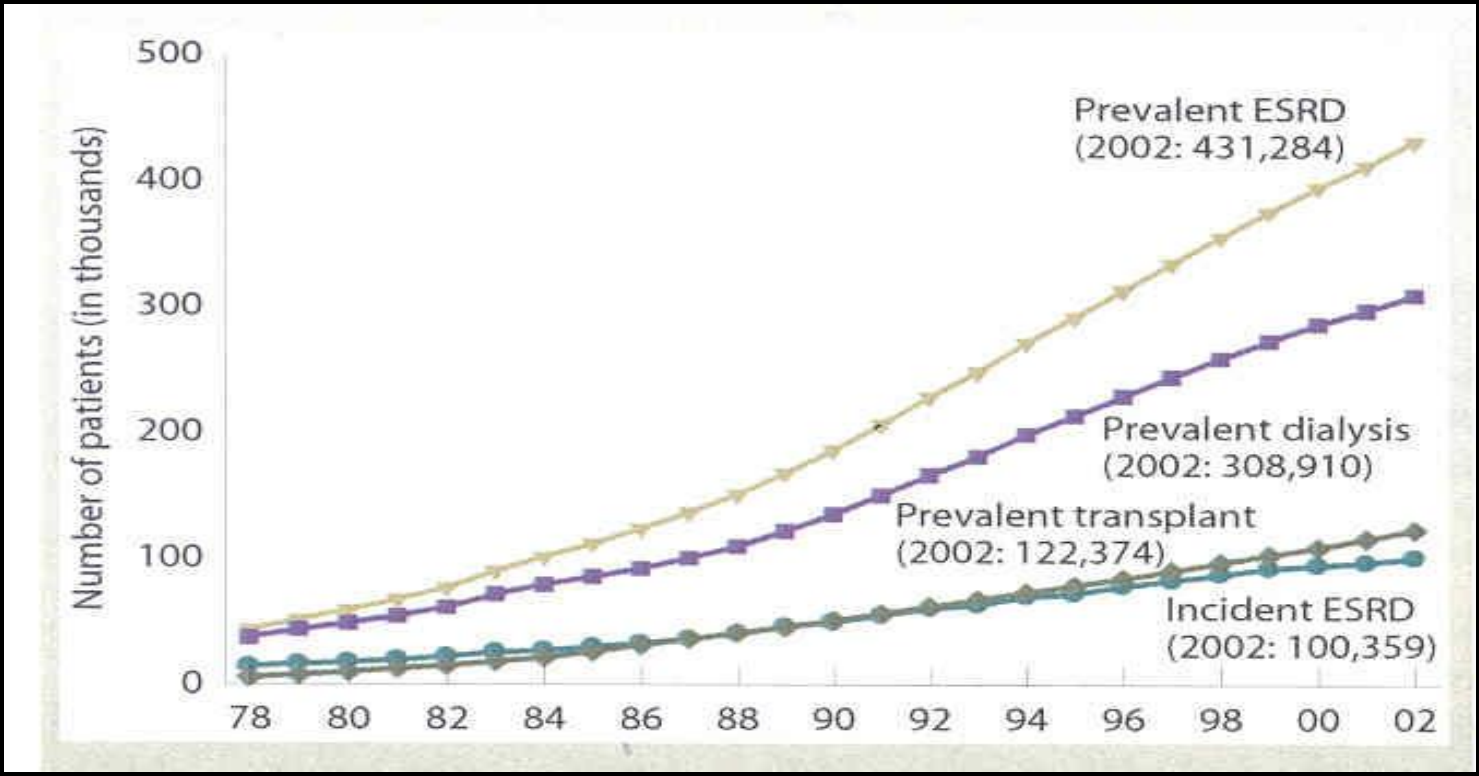
Aims of Talk

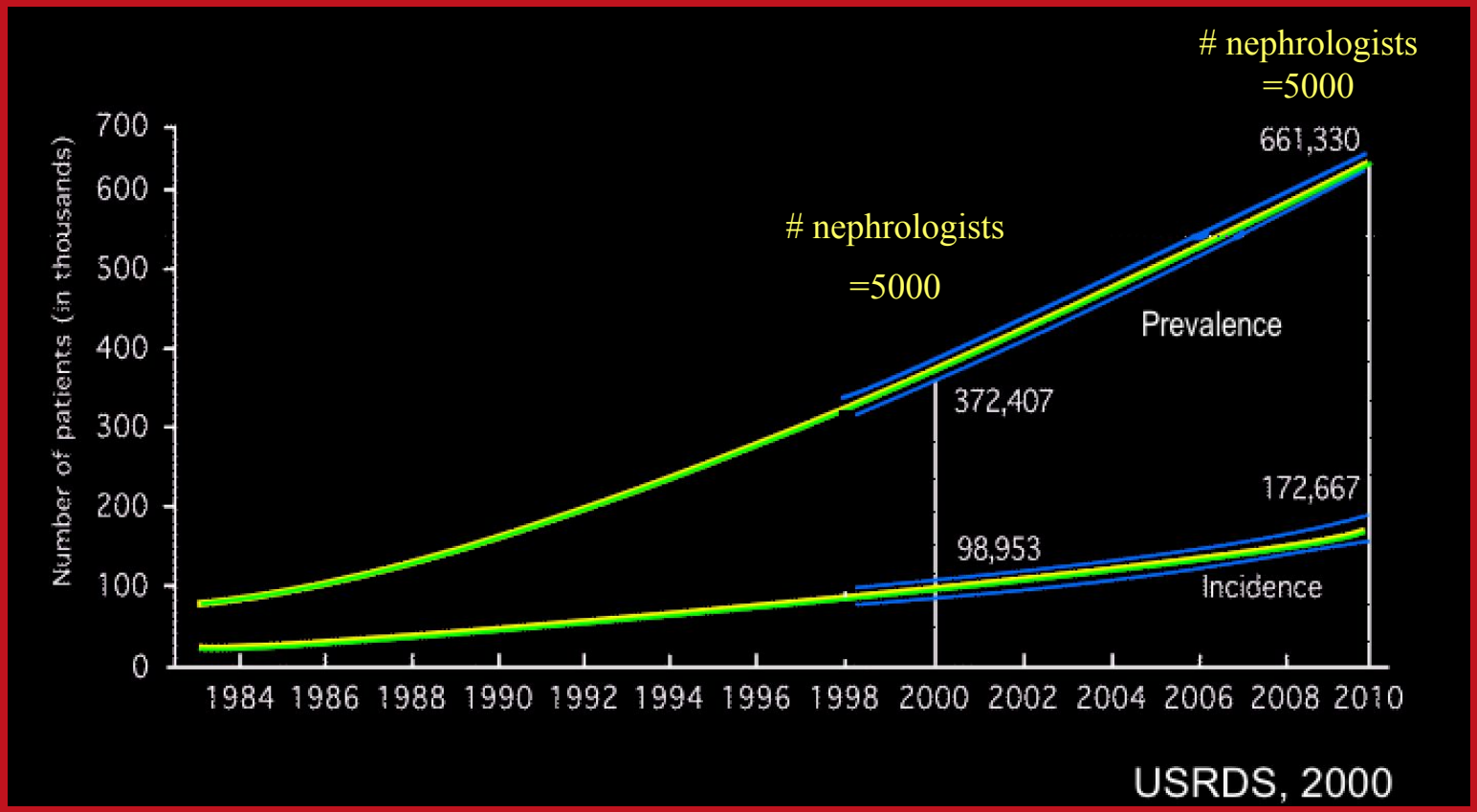
- CKD is a growing problem in MS and the US
- The progression to ESRD can be slowed
- Creatinine (or even eGFR) is not an absolute indicator of kidney function!
- Early referral to a Nephrologist may help your patient's QOL and longevity:
  - Hypertension, proteinuria and volume control
  - Electrolyte problems
  - Anemia and renal bone disease
  - Nutrition and chronic inflammation
  - Access placement
  - Incident (first year) mortality on dialysis: nutrition, catheters

ESRD Rates Continue to Rise

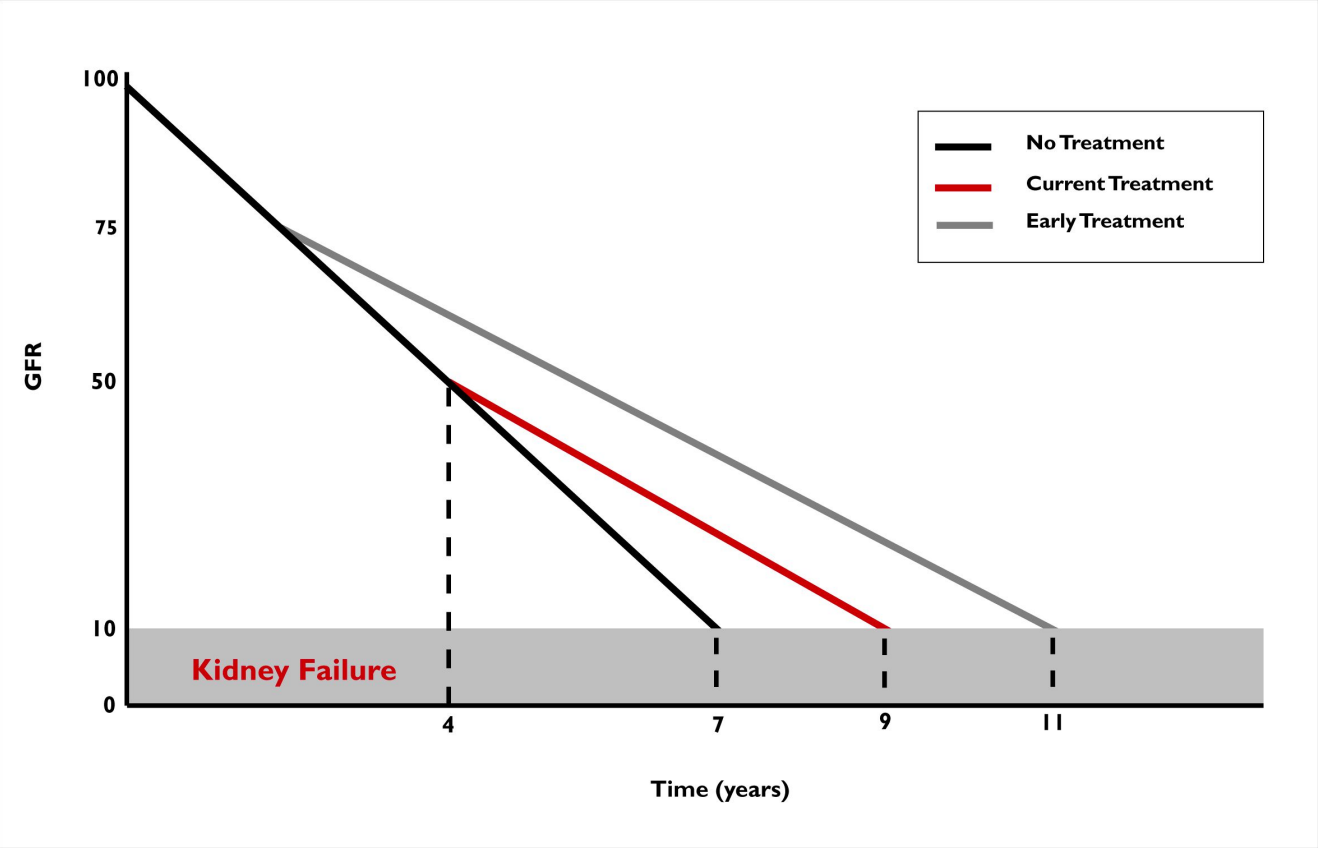


USRDS, 2004

Kidney Failure Is a Rapidly Growing Problem



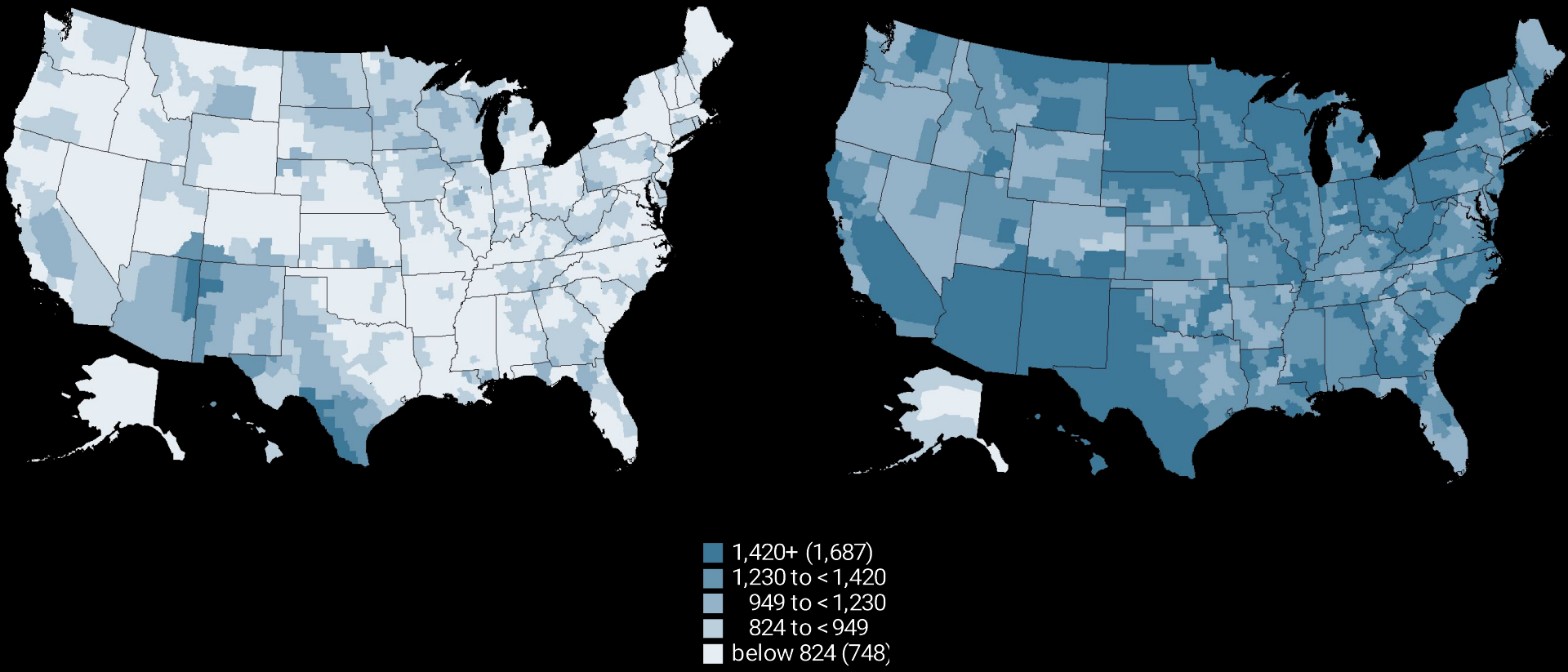
Early Treatment May Make a Difference



Brenner, et al., 2001

Prevalence of ESRD: 1991 versus 2001

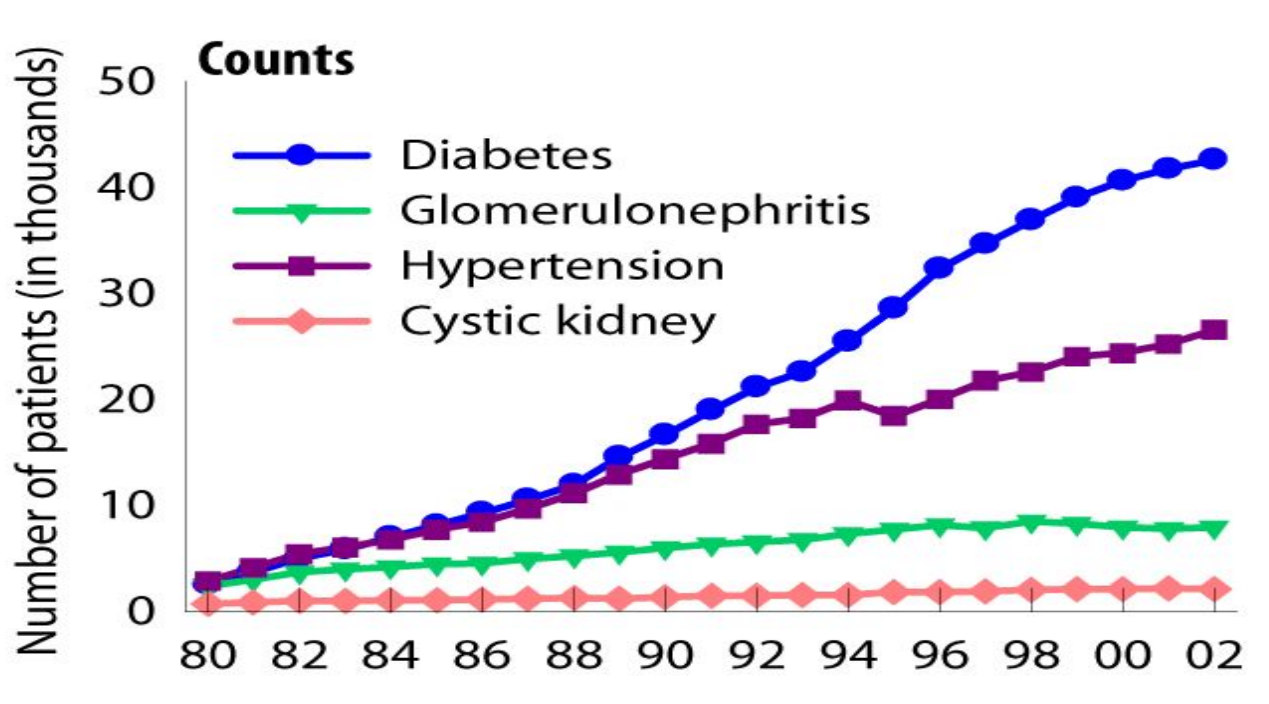
(per million population)



Incident Counts & Adjusted Rates, By Primary Diagnosis

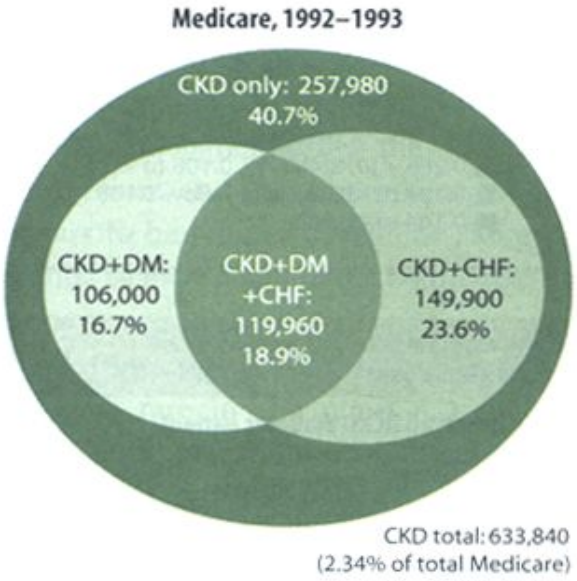
or

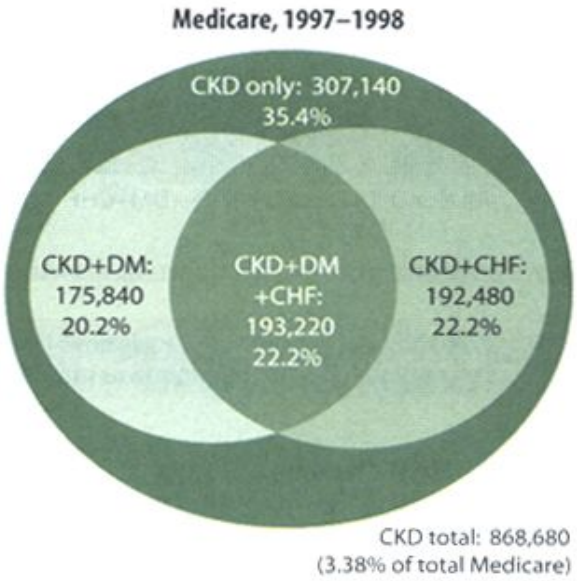
CKD as the extreme of the Metabolic Syndrome

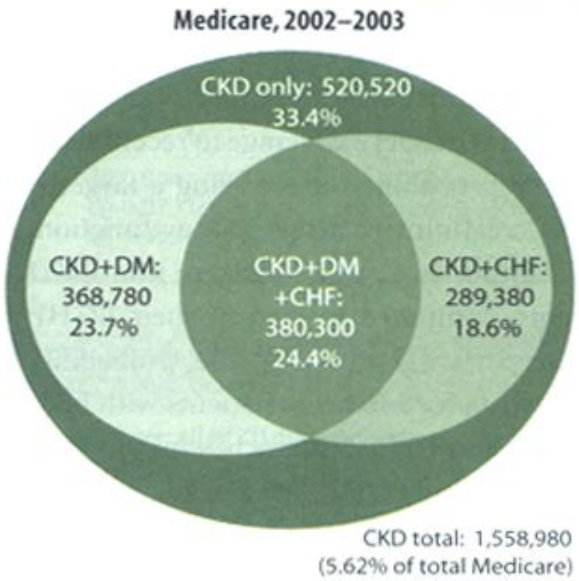


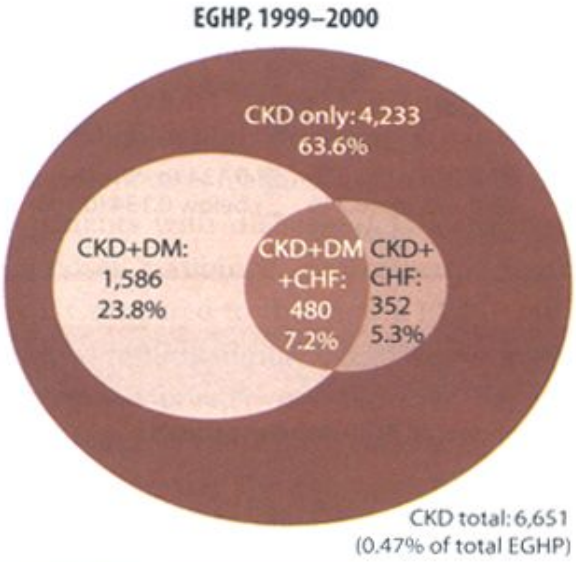
USRDS, 2004

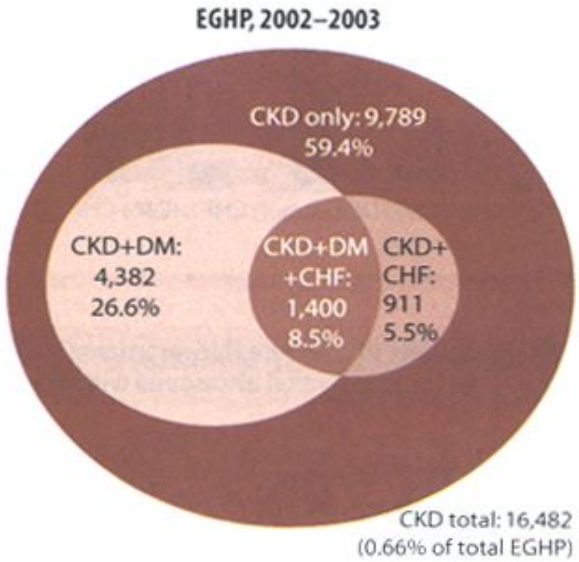
1.4 **Trends in the interactions of diabetes, congestive heart failure, & CKD** | Medicare CKD patients, & EGHP CKD patients younger than 65

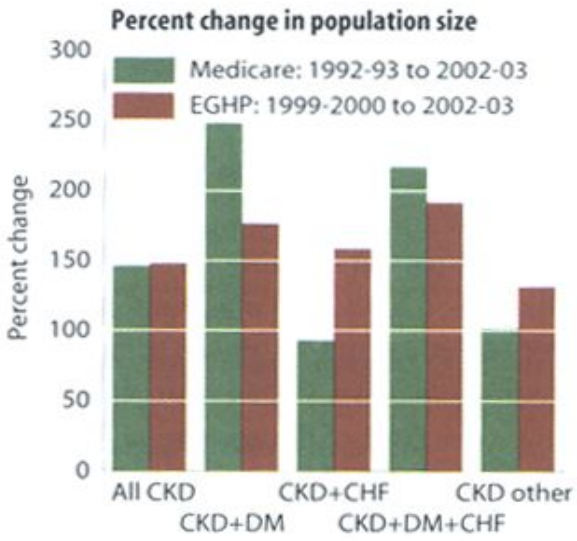






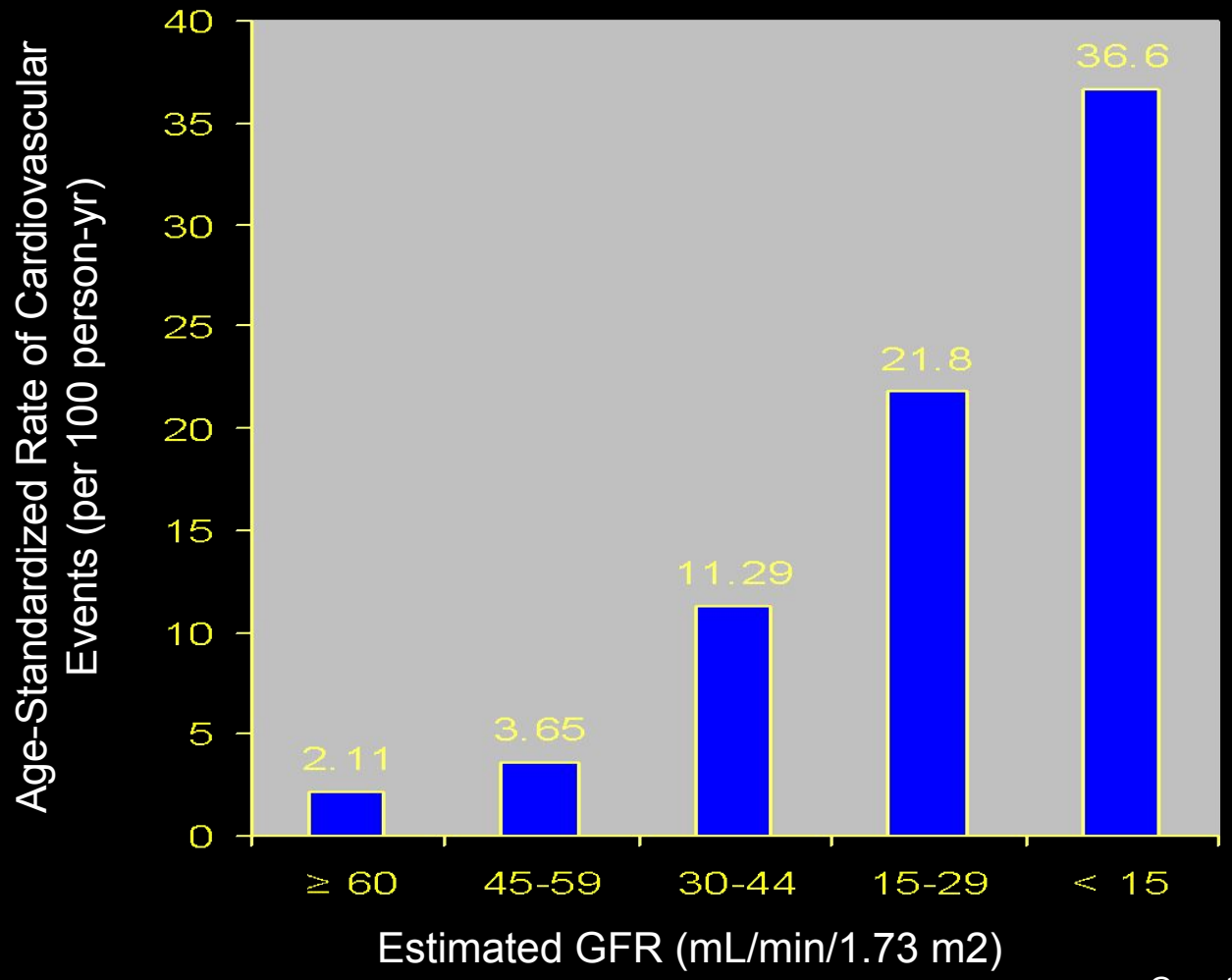




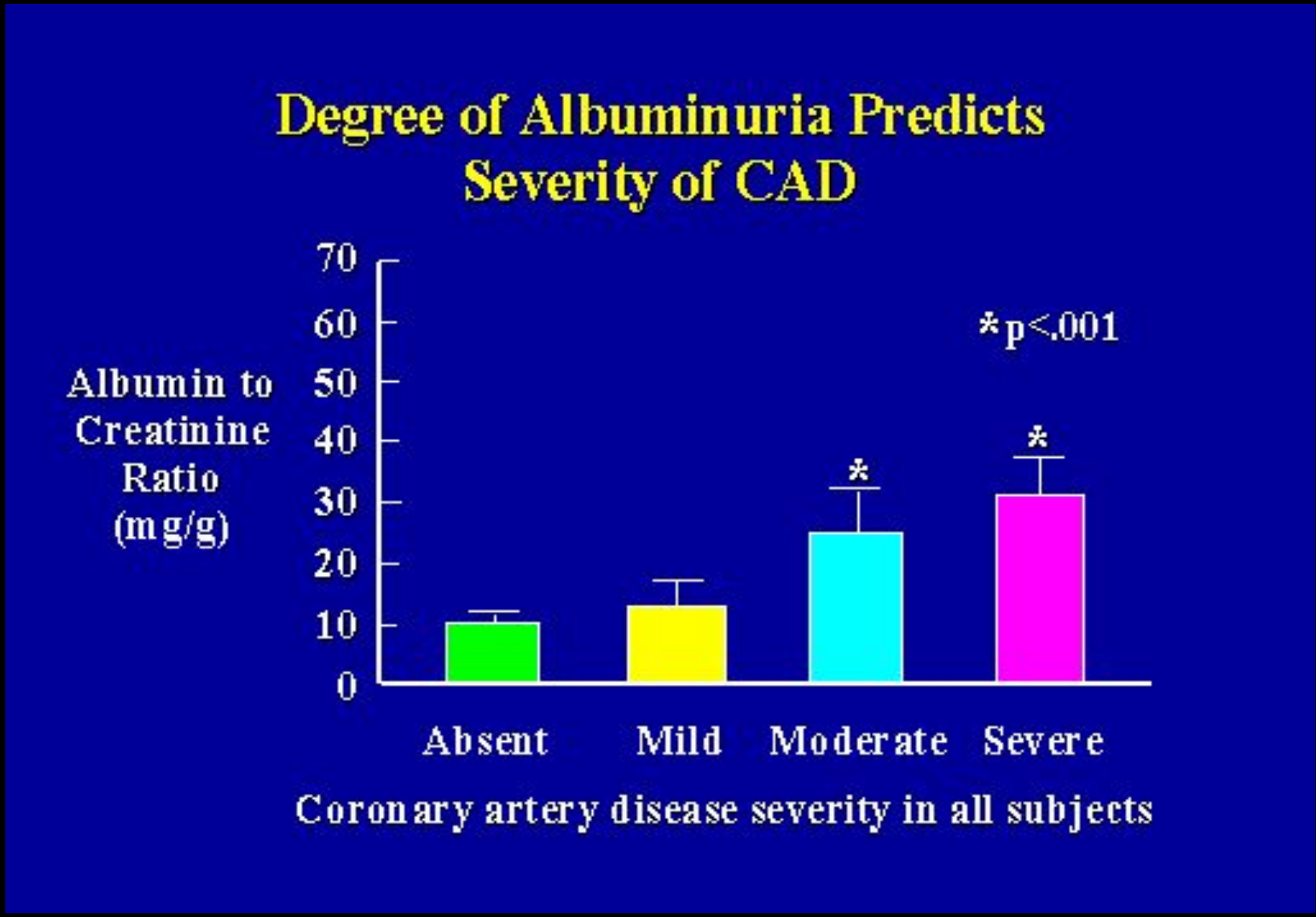


USRDS 2005 Data Report- AJKD, Jan 2006

CKD Predicts CVD



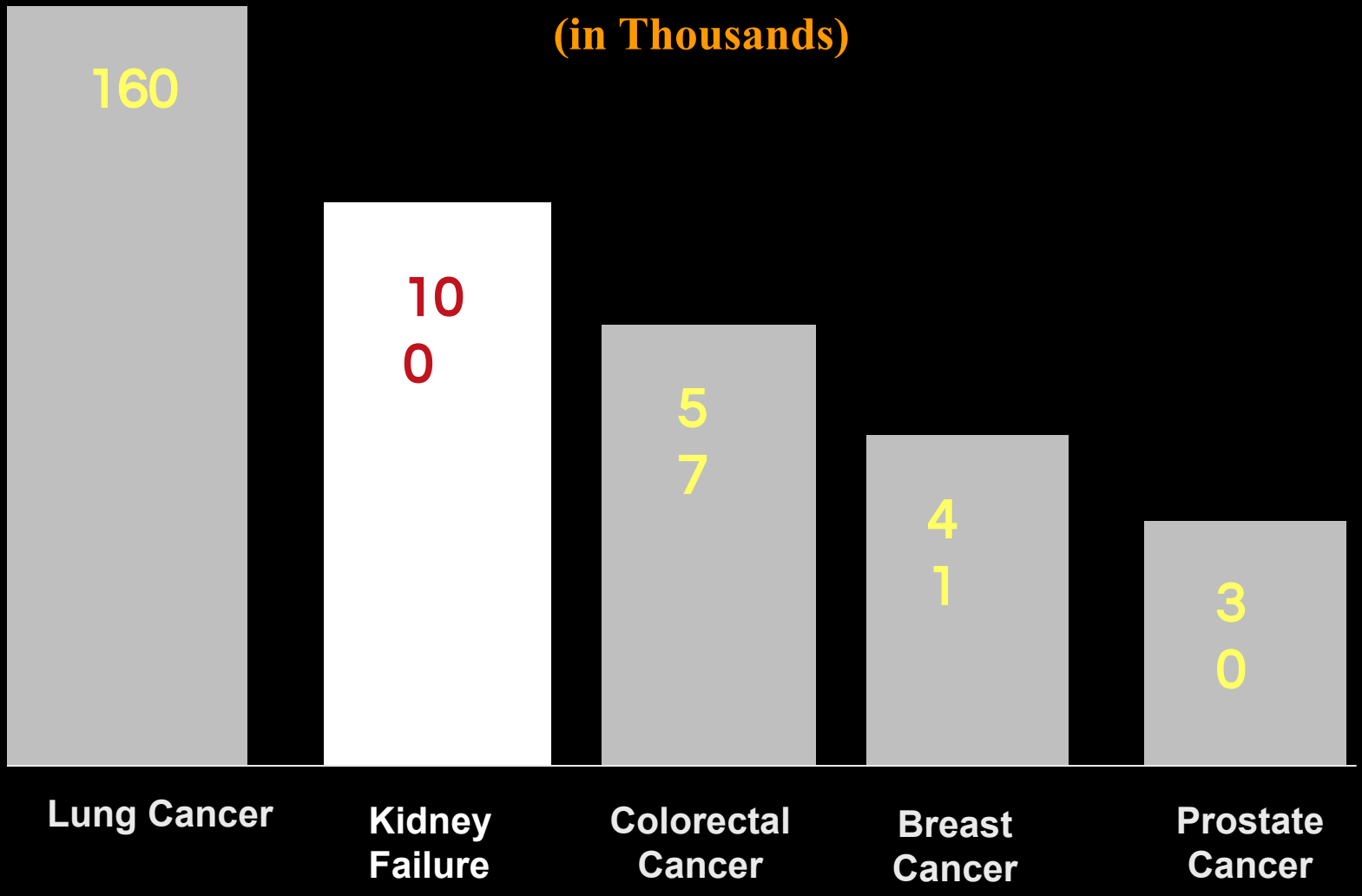
Go, et al., 2004



Chronic Kidney Disease =**GFR<60 ml/min/1.73 m2** **or persistent albuminuria**

Mortality in Kidney Failure versus Cancer Deaths in 2000

(in Thousands)



Seer, 2004

The Risk of Kidney Failure is Not Uniform

Relative risks compared to patients of European ancestry:

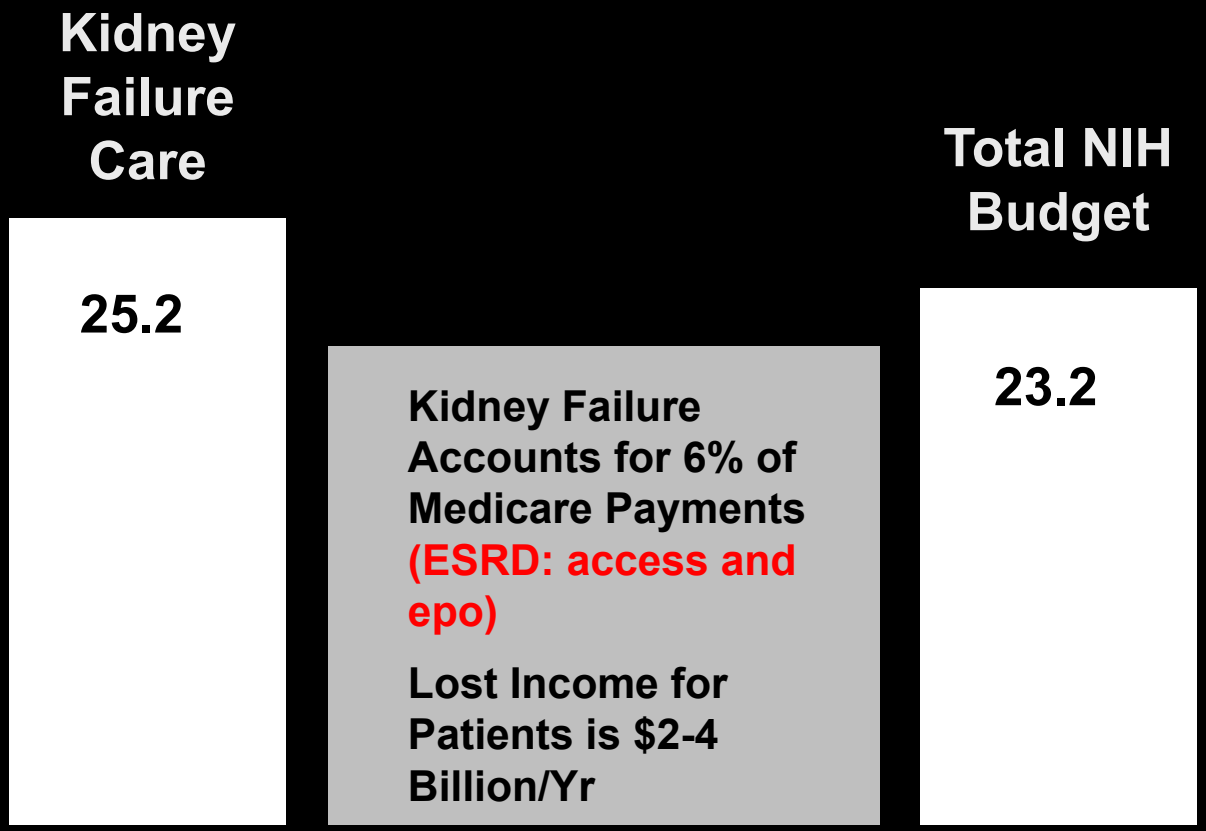
African Americans	**3.8 X**
Native Americans	**2.0 X**
Asians/Pacific Islander	**1.3 X**

The relative risk of Hispanics compared to non-Hispanics is about 1.5 X

USRDS, 2004

Costs of Kidney Failure are High

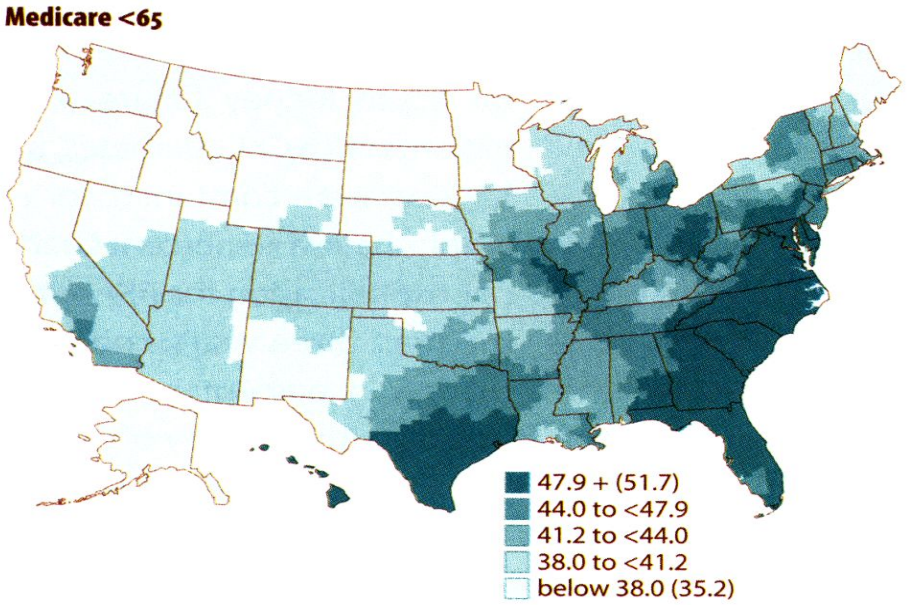
(in $billions for 2002)

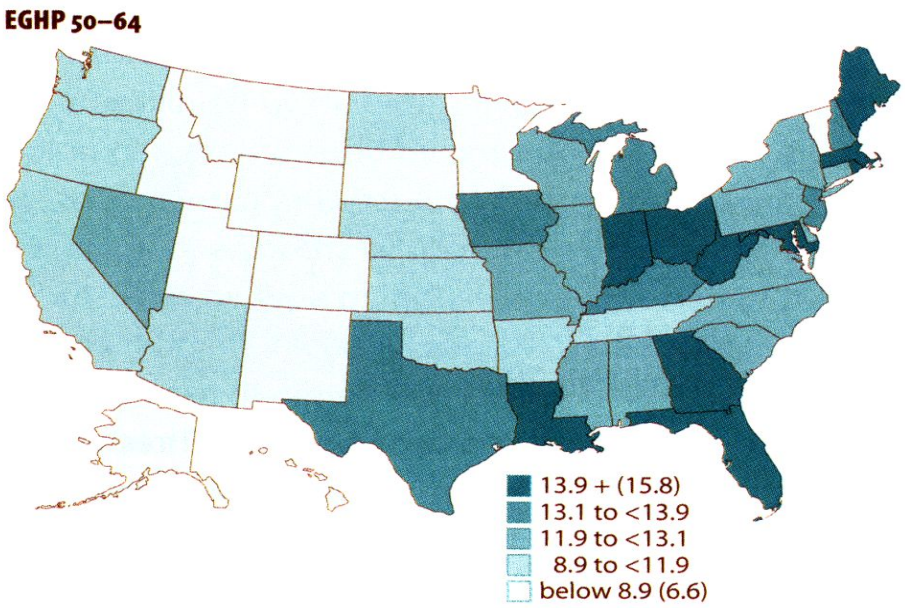


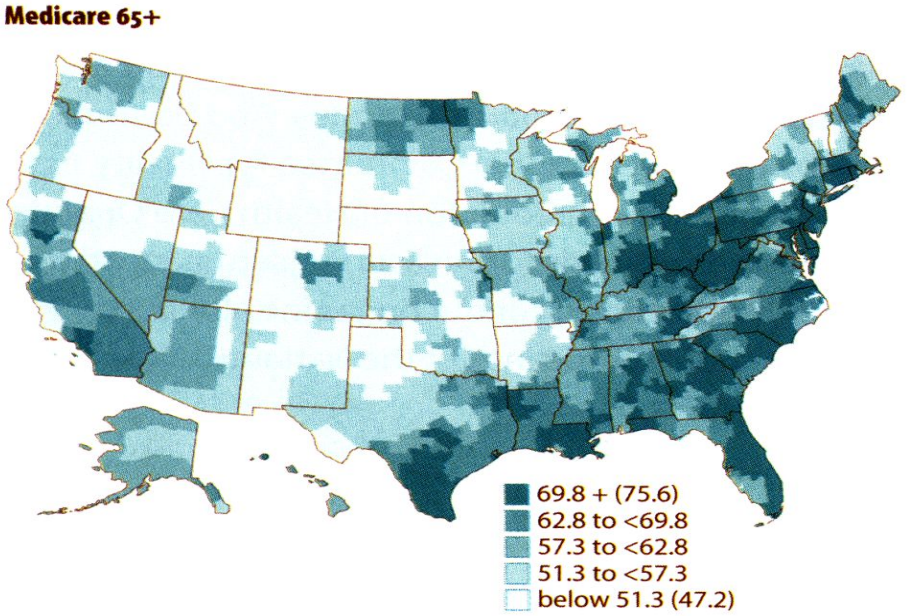
USRDS, 2004

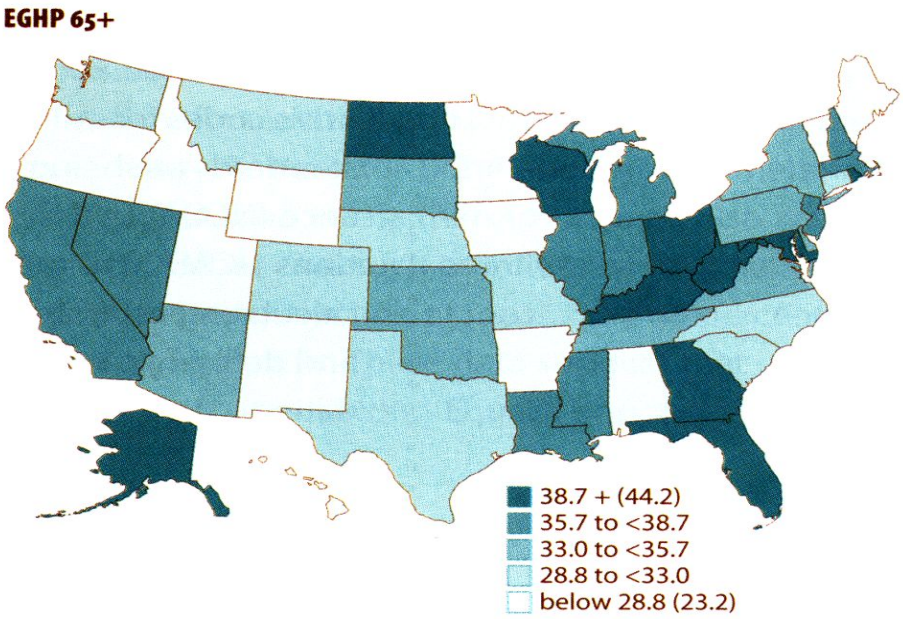
How is Mississippi doing?

Prevalence of CKD per 1000 – USRDS 2007



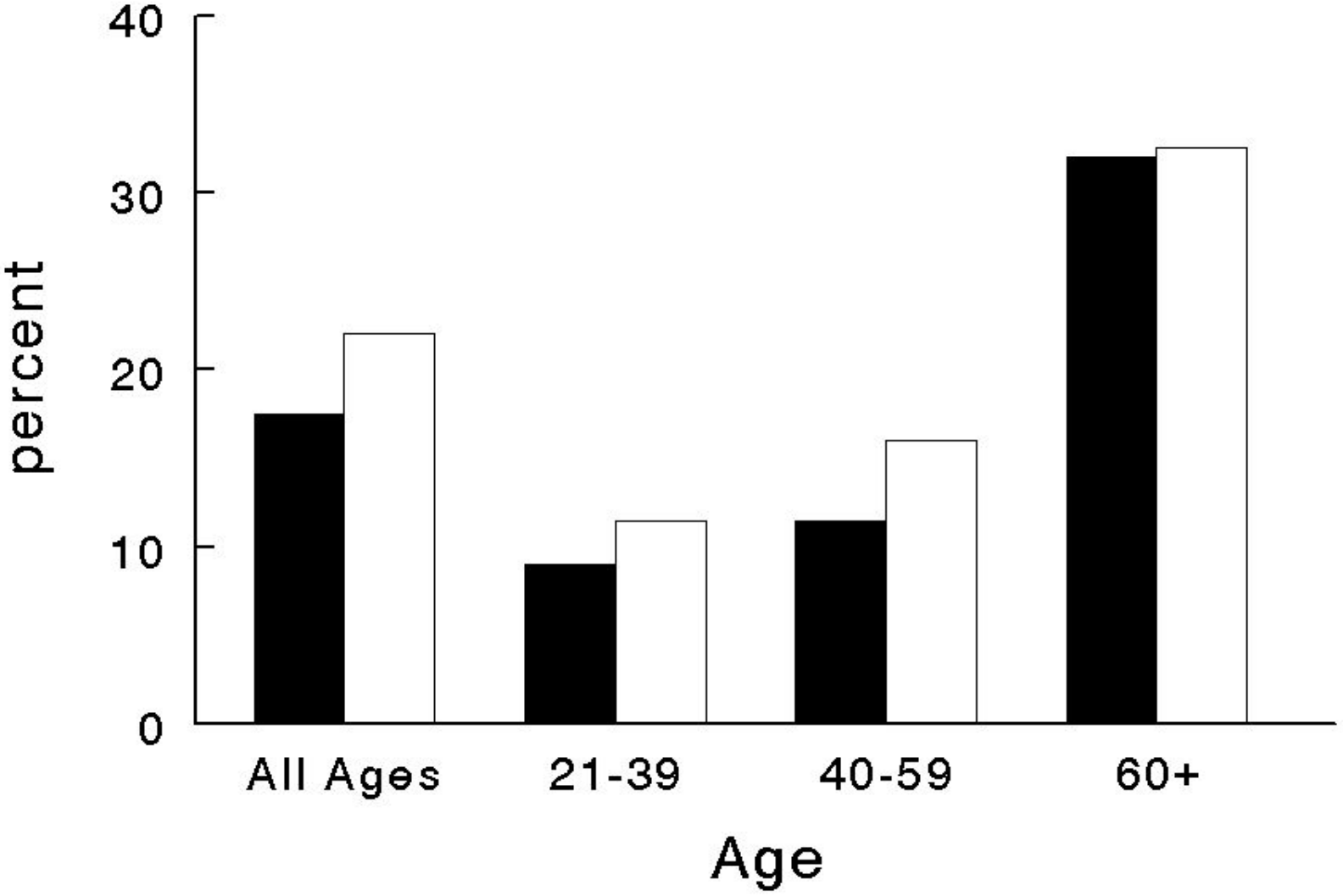






Prevalence of CKD in JHS

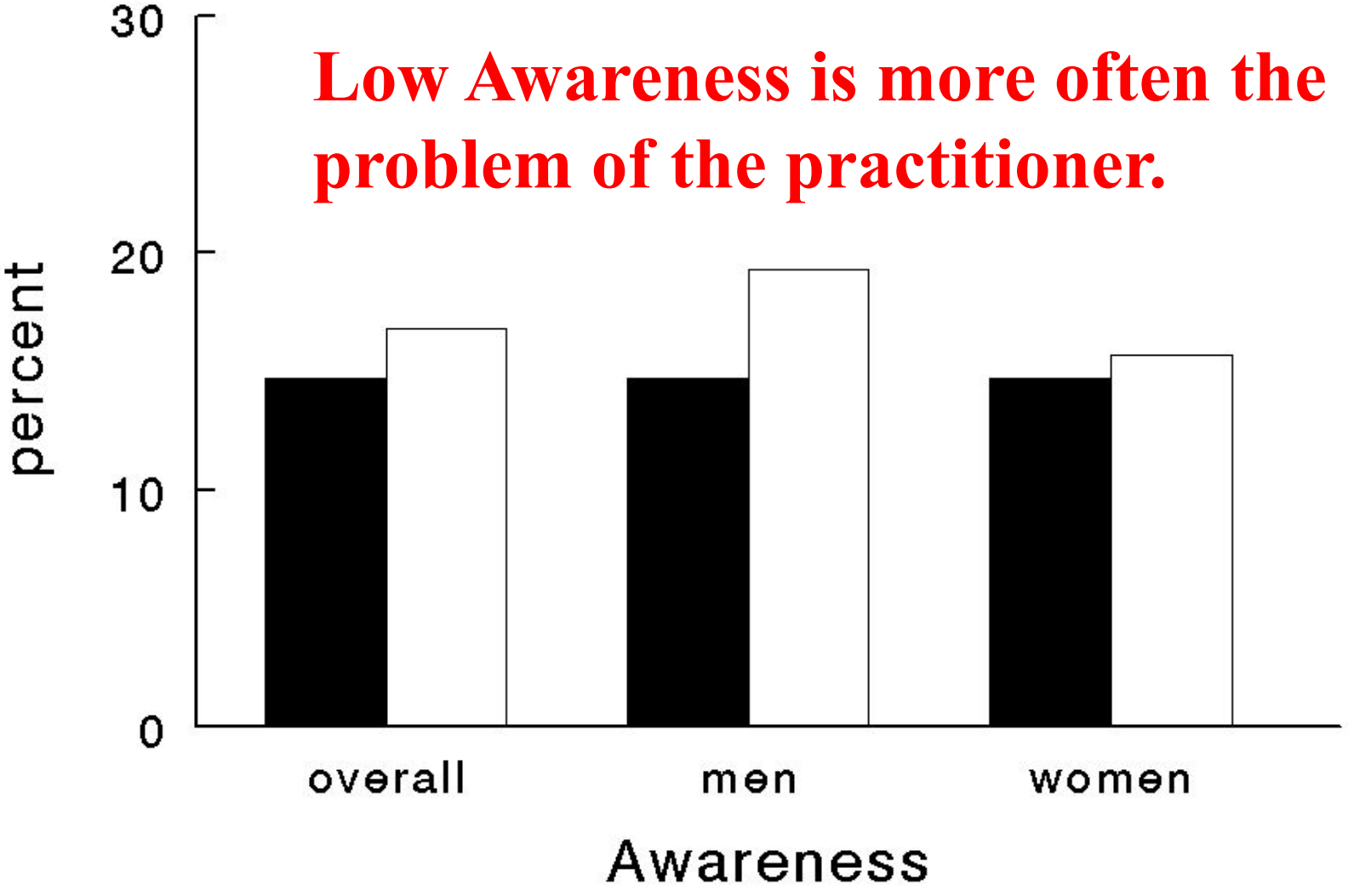
men = solid bars; women = open bars



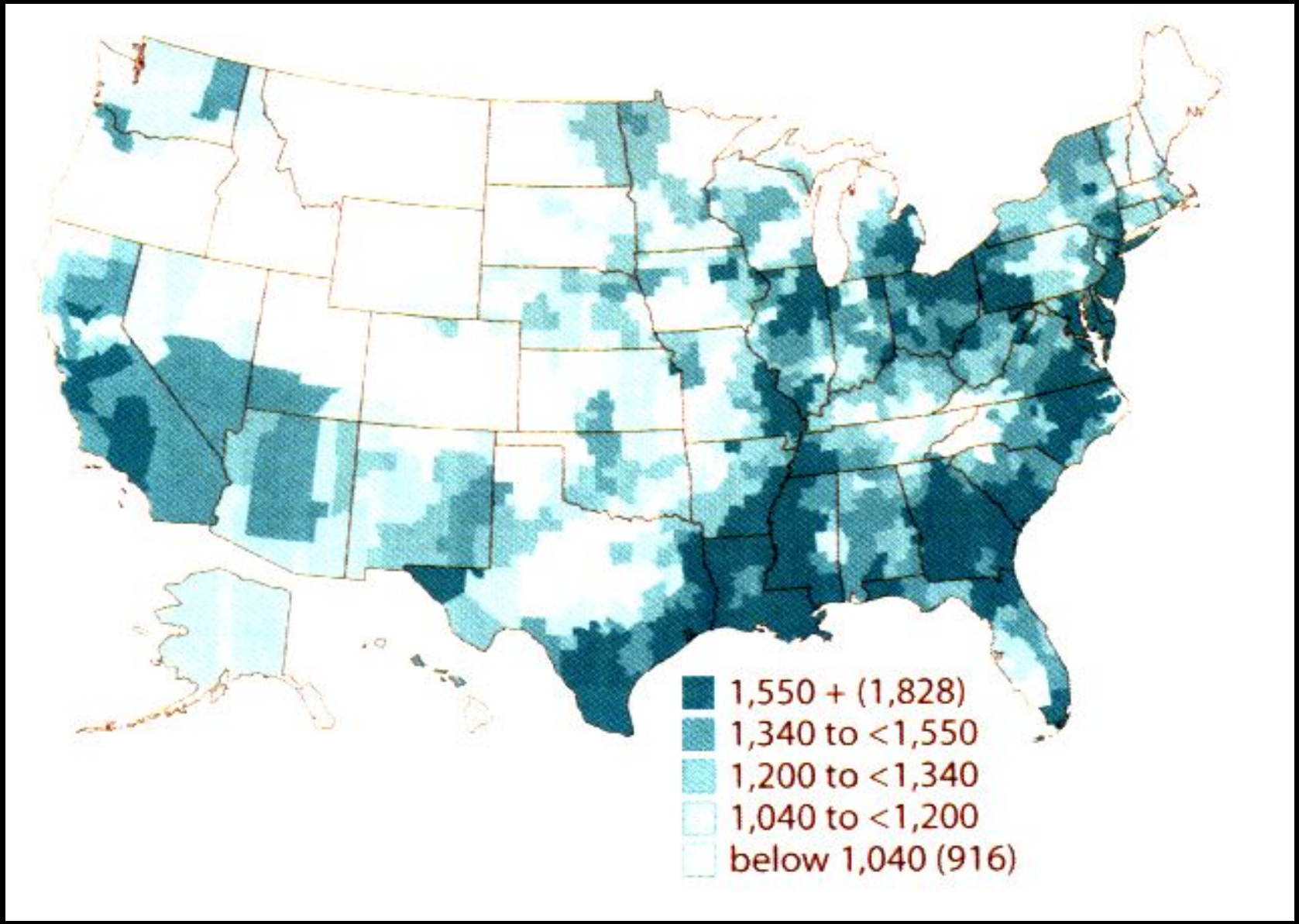
Awareness of CKD

JHS = solid bars; NHANES = open bars

Low Awareness is more often the problem of the practitioner.



Incidence of ESRD per million



USRDS 2007

Summary of the Problem

- Incidence and Prevalence of CKD and ESRD are increasing in the setting of poorly-controlled obesity-induced diabetes, HTN, and CVD.
- African Americans have a 4-fold higher incidence of End Stage Renal Disease than patients of European ancestry in the US. Hispanics have even greater risk. **Most are unaware of their disease.**
- Mississippi needs to address the growing population with obesity, diabetes, and CKD.

Outline

- Prevalence and Incidence of CVD and CKD
- **Timeline of CRI: Progressive Changes in Physiology and Metabolism**
- Specific Problems:
- - slowing the progression
- - hypertension/cardiovascular disease
- - anemia
- - metabolic acidosis
- - secondary hyperparathyroidism
- - potassium/sodium balance/nutrition
- Role of the Primary Care MD: when to refer

CHRONIC RENAL INSUFFICIENCY: GFR TIMELINE

NKF Stage	DESCRIPTION	GFR ml/min/ 1.73 m^2	COMPLICATION	PREVALENCE (adults> 20yrs)
↑ risk	At risk: DM, HTN AfrAm; Native Am	≥ 90	Microproteinuria; HTN; hyperfiltration	>20 million (> 12%)
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5	ESRD	< 15	Metabolic acidosis; anemia; hyperparathyroidism; fluid balance; potassium + Uremia	0.4 million (0.1%) Many have already died

Renal insufficiency: Outdated definition:

Men: Serum creatinine > 1.5 mg/dL

Women: Serum creatinine > 1.2 mg/dL

Outdated Criteria for referral:

Serum creatinine; ~7-10 (BAD)

Serum Creatinine ~ 2-3 was OK

Louisiana experience with "healthy donors"

Determine an Estimate of GFR to estimate the degree of renal insufficiency

- Glomerular filtration rate (GFR) measures kidney function but is difficult to determine accurately in a clinical setting: inulin, iothalamate, iohexol, creatinine
- Creatinine excretion is affected by collection compliance, variable tubular secretion, ingestion of boiled or broiled (but not raw or fried) beef.
- **Recommendation**: Several formulas are available to estimate GFR from SCr levels in combination with other factors, such as age, body weight and gender.

Bolton WK et al. *Am J Kidney Dis.* 2000;36(suppl 3):S4-S12; 2.

Estimating the Glomerular Filtration Rate with the MDRD equation (recommended by the NIH):

GFR (ml/min/1.73 m^2)

$= 186 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times$

(0.742 if female) x (1.21 if AfAm)

Caveat: ONLY VALIDATED IN PATIENTS ALREADY DIAGNOSED WITH CKD (may be misleading in healthy people) SO ADDRESS RISK FACTORS (DM,HTN, PROTEINURIA, FAMILY HISTORY)

COCKCROFT-GAULT Equation vs MDRD Equation

$$GFR = \frac{(140\text{-age})(\text{weight in kg})}{72 \times \text{Screatinine in mg/dL}} \quad (\times 0.85 \text{ for women})$$

3 patients with SCr levels of 1.5 mg/dL

Young Man	Young Woman	Older Woman
Age = 25 years	**Age = 25 years**	Age = 75 years
Weight = 100 kg	**Weight = 50 kg**	Weight = 45 kg
Cockcroft-Gault:		
Estimated GFR = 106 mL/min	Estimated GFR = 45 mL/min	Estimated GFR = 23 mL/min
MDRD: 94	**43**	**26**

Serum creatinine is not an absolute indicator of renal function but must be modified by age, weight, muscle mass, gender, and state of health.

Cockgroft, Gault Nephron 16:31, 1976.

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Risk Factors for CKD

- Diabetes (type 1 and type 2)
- Hypertension
- Advancing age
- Proteinuria
- Family history of kidney disease
- Environmental nephrotoxins (NSAIDs)
- Race

Healthy People 2010; Nelson NA et al, *Am J Nephrol, 1999;* US Renal Data System. *2001 Atlas of ESRD in the United States.*

Courtesy of Jack Reed MD

Diabetic Nephropathy

- 20% to 30% of patients with type 1 or type 2 diabetes will develop nephropathy[1]
- Intensive glycemic control significantly reduces the risk of development of nephropathy in diabetic patients[2]
- Hypertension accelerates progression of diabetic nephropathy
  - **In hypertensive patients with microalbuminuria or clinical albuminuria, treatment including ACE inhibitors[3] and ARBs[4] has been shown to delay the progression of kidney disease**

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker

1. ADA. *Diabetes Care*. 2001;24(suppl 1):S69-S72; 2. DCCT. *N Engl J Med*. 1993;329:977-986; 3. Chan JC et al. *Kidney Int*. 2000;57:590-600; 4. Brenner BM et al. *N Engl J Med*. 2001;345:861-869.

Microalbuminuria: A Risk Factor for Morbidity and Mortality in Diabetic Patients

- Microalbuminuria =**Albumin excretion of 30 – 299 mg/24 h[1] –methodical, no threshold**
- Predicts proteinuria in diabetics[2]
- Increases risk for cardiovascular disease[1,2]
- Increases risk for peripheral vascular disease[1,2]

1. ADA. *Diabetes Care.* 2001;24(suppl 1):S69-S72; 2. Laragh JH et al. In: *Brenner & Rector's The Kidney,* 2000:1967-2006.

Hypertension

- CKD may exacerbate hypertension by multiple pathways[1-3]
  - **Volume overload, chronic inflammation**
  - **Renin-angiotensin-aldosterone system stimulation with increased sympathetic activity**
  - **Vascular calcification with accelerated atherosclerosis**
- Hypertension increases the risks of cardiac disease[4] and further decreases renal function, particularly in diabetic patients [5]
- **HTN control including ACE inhibitors and ARBs can slow deterioration of renal function in diabetic and non-diabetic patients**[6-8]

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1. Anderson S et al. In: *Brenner & Rector's The Kidney*, 2000; 2. Laragh JH et al. In: *Brenner & Rector's The Kidney*, 2000; 3. Mailloux LU et al. *Am J Kidney Dis*. 1998;32(suppl 3):S120-S141; 4. Parfrey PS et al. *J Am Soc Nephrol.* 1999;10:1606-1615; 5. ADA. *Diabetes Care*. 2001;24(suppl 1):S69-72; 6. Lewis EJ et al. *N Engl J Med.* 1993;329:1456-1462; 7. Jafar TH et al. *Ann Intern Med.* 2001;135:73-87; 8. Brenner BM et al. *N Engl J Med*. 2001;345:861-869.

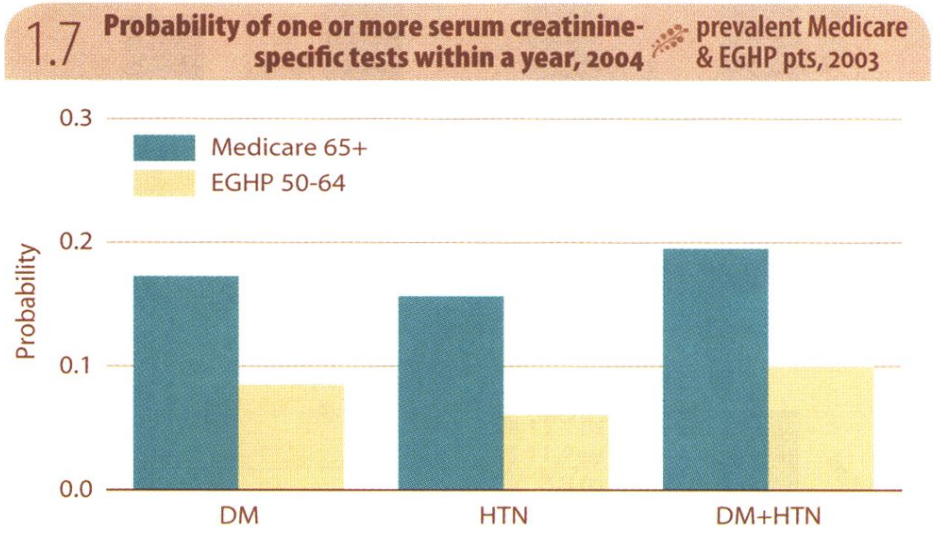
Dyslipidemia

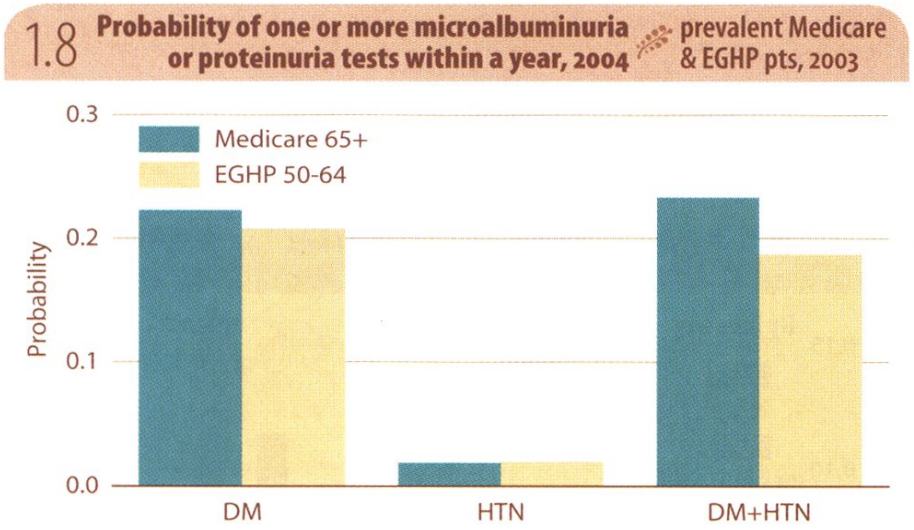
- Abnormalities include[1,2]
  - **Hypercholesterolemia**
  - **Hypertriglyceridemia, low HDL**
  - **Increases in LDL and VLDL cholesterol**
- Contributes to[1,2]
  - **Coronary atherosclerosis**
  - **Increased incidence of myocardial infarction**
- Is associated with more rapid decline of kidney function[2,3]

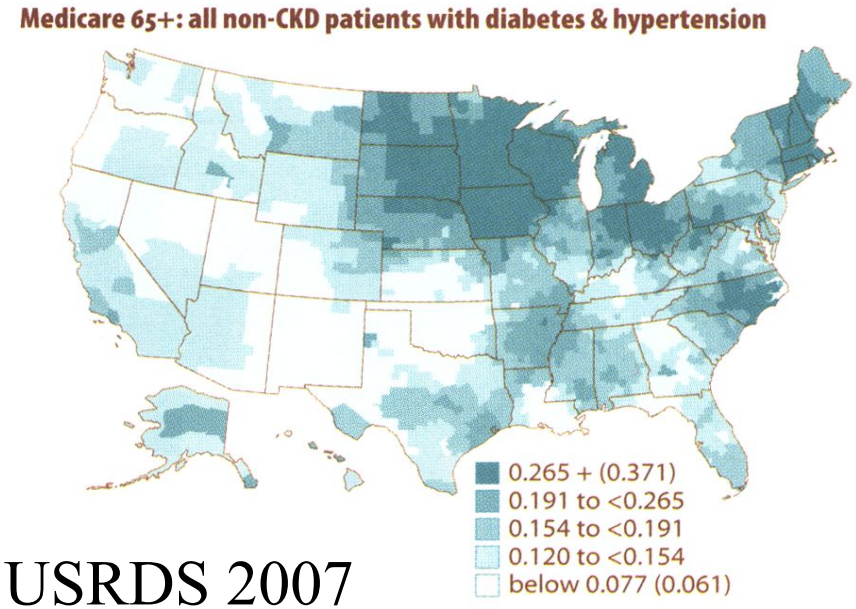
LDL = low-density lipoprotein; VLDL = very low-density lipoprotein

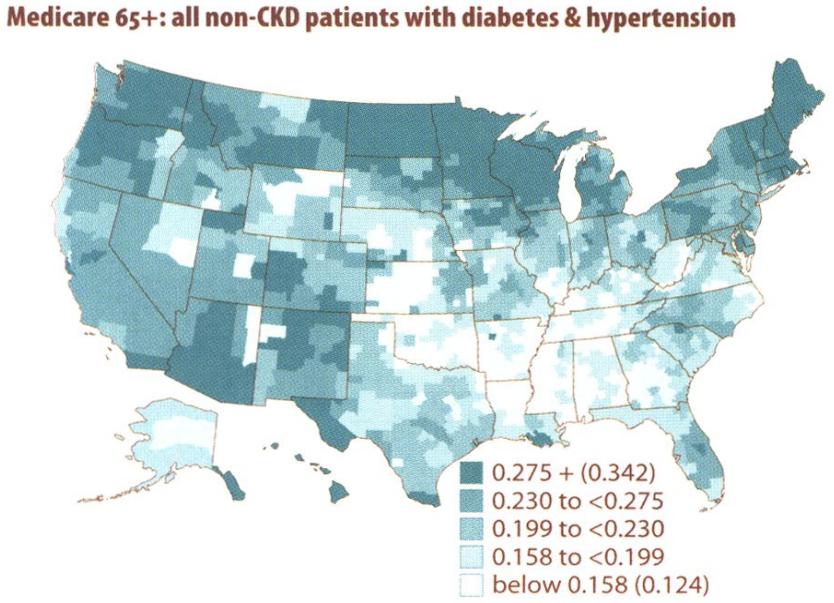
1. Zabetakis PM et al. *Am J Kidney Dis*. 2000;36(suppl 3):S31-S38; 2. Falk RJ et al. In: *Brenner & Rector's The Kidney,* 2000; 3. Mackenzie HS et al. In: *Brenner & Rector's The Kidney,* 2000.

How well do we follow these guidelines?









USRDS 2007

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Care of patients with GFR > 90

- Renal ultrasound: size, shape, echogenicity; r/o hydronephrosis
- Metabolic screens: HbA1C, fasting lipids, protein quantitation serum electrolytes
- Stop NSAIDS
- **Refer to nephrologist for evaluation**

Interventions for At-Risk Patients

- Control BP: ACEI, ARB, β- and Ca Channel Blockers, etc
- Control Na intake
- Control BGs: DCCT KI 1995; 47:1703.
- Control Lipids: Statins (may decrease chronic inflammation)!
- Nutrition: lower protein intake: MDRD NEJM 1994; 330:877.
- Avoid toxic drugs: NSAIDS (includes Cox-2 I)
- Stop smoking
- Weight reduction, exercise!
- Check for proteinuria rise in serum creatinine
- For diabetic patients: follow the urine albumin to creatinine ratio (initial screening) or protein/creatinine if proteinuria already present (>200 mg/day)

Interventions for Mild CKD

- Treat HTN, volume, proteinuria, BS control, lipids
- Lifestyle modification (salt, protein intake, weight loss, exercise, stop smoking)
- Follow blood chemistries regularly
- Iderntify and stop nephrotoxins

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COCKCROFT-GAULT EQUATION

$$SCr = \frac{(140\text{-age})(\text{weight in kg})}{72 \times GFR\ (ml/min)} \quad (\times 0.85 \text{ for women})$$

3 patients with GFR 30-59 ml/min/1.73 m^2

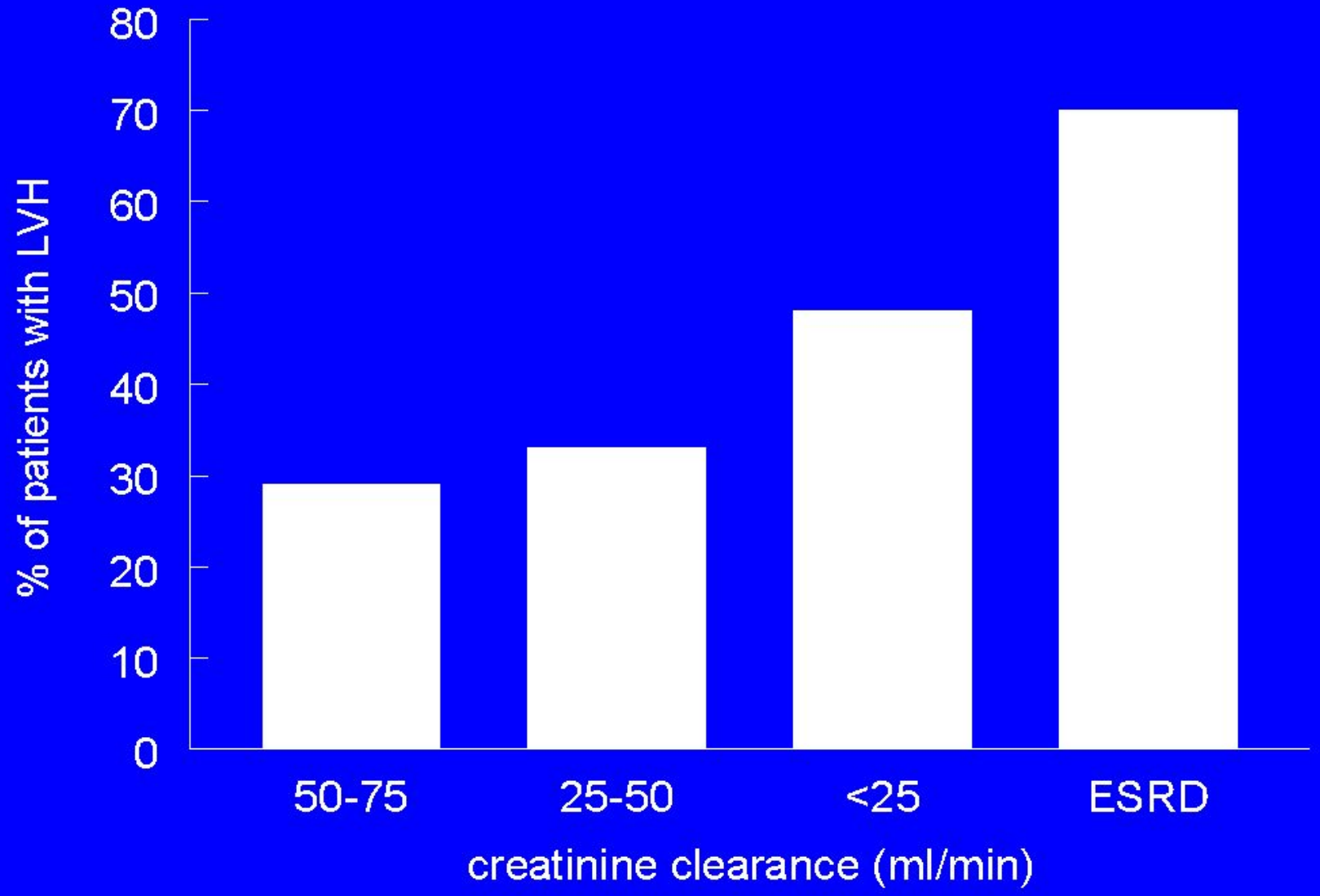
Young Man	Young Woman	Older Woman
Age = 25 years	**Age = 25 years**	Age = 75 years
Weight = 100 kg	**Weight = 50 kg**	Weight = 45 kg
Estimated Cr = 5.3 – 2.7	Estimated Cr = 2.3 - 1.1	Estimated Cr > 1.1
MDRD: 4.2-2.2	1.8-1.1	1.4-1.1

Moderate CKD

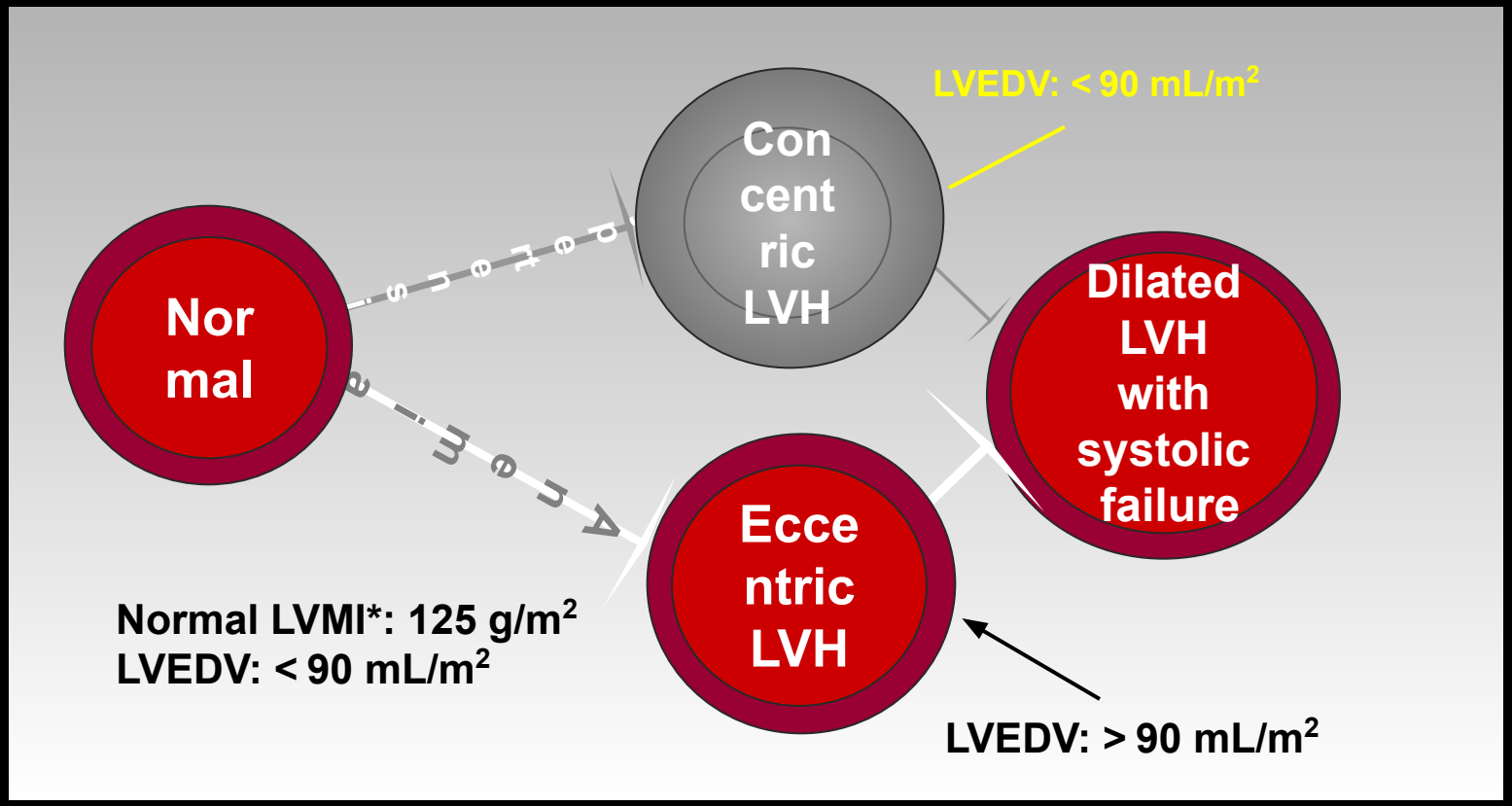
- Anemia: variable production of erythropoietin; iron deficiency almost universal; anemia is often associated with nephrotic syndrome, slow GI bleed
- Metabolic acidosis: as the kidney fails to recover sufficient HCO_3^-, bone is used as a buffer -diet, diuretics
- Hyperphosphatemia: develops as phosphate cannot be sufficiently cleared. Hypocalcemia follows due to lack of 1-25 OH-Vitamin D_3 production by kidney and to "salting out". Secondary hyperparathyroidism is one of the complications from this process.
- Incipient nutritional deficiencies develop with the protein malnutrition/chronic inflammation syndrome
- Variations in drug metabolism and excretion (insulin, antibiotics).

Prevalence of LVH during CRI

Levin. AJKD 1999; 34:125.



Consequences of Hypertension and Anemia: Cardiac Remodeling

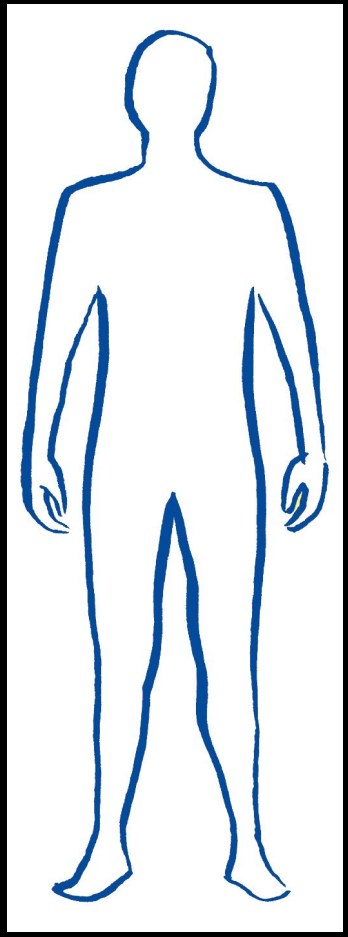


LVH = left ventricular hypertrophy; LVM = LV mass; LVEDV = LV end-diastolic volume.

Lopez-Gomez JM et al. *Kidney Int.* 1998;54:S92-S98; London GM et al. *Adv Ren Replace Ther.* 1997;4:194-211; *Casale et al. *Ann Intern Med* 1986;10:173-178.

Anemia of CKD Has Many Consequences

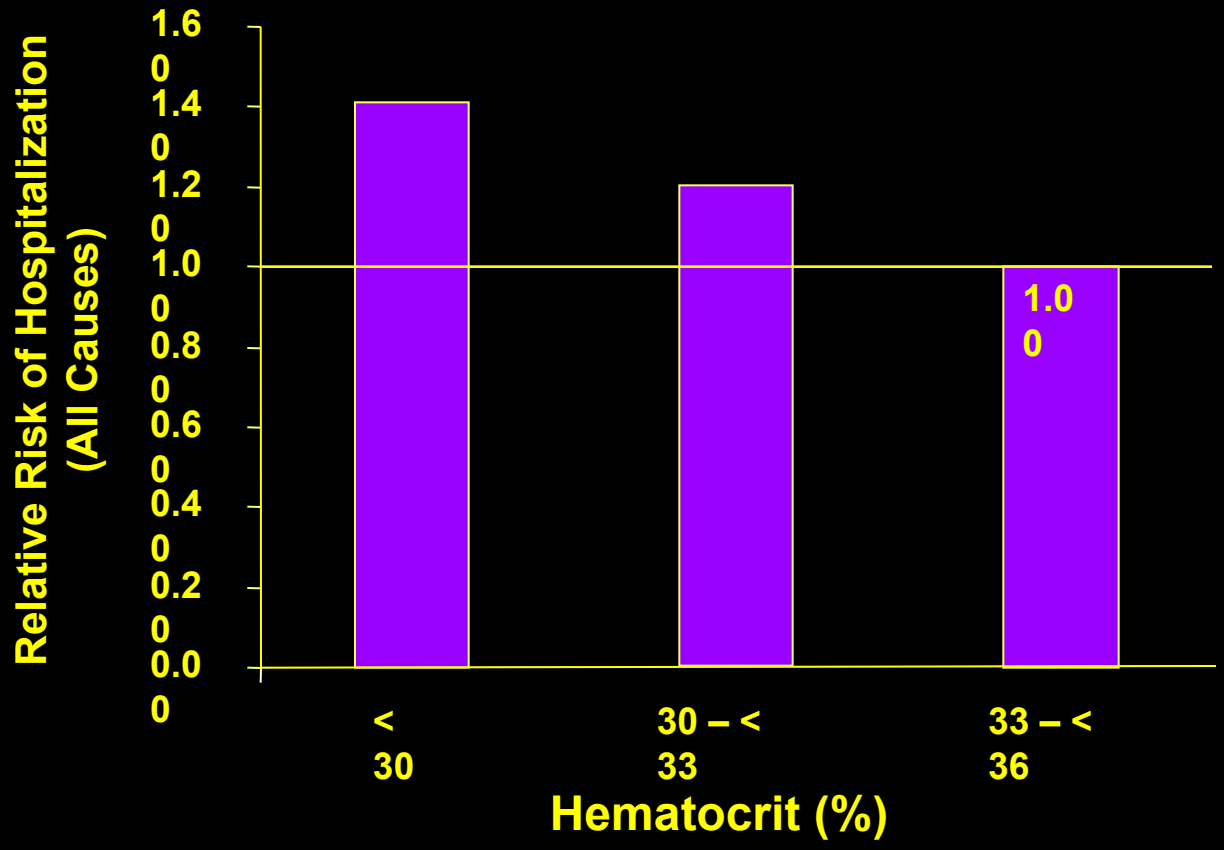
- Lethargy[1]
- Confusion[1]
- Cardiac enlargement[2,3]
- Angina[1,5]
- Impaired cognition[4]
- Impaired immune system[4]
- Tinnitus[4,5]
- Reduced exercise capacity[4]



- Weakness[1,4] ,nausea
- Shortness of breath[1,4,5]
- Palpitations[4,5]
- Impaired libido/impotence[4]
- Headache[4,5]
- Pallor[4,5]
- Edema[4,5]
- Paresthesia in fingers and toes[5]

1. Hoffbrand AV et al. *Essential Hematology,*1993; 2. Levin A et al. *Am J Kidney Dis.* 1999;34:125-134; 3. Foley RN et al. *Am J Kidney Dis.* 1998;28:53-61; 4. Ludwig H et al. *Semin Oncol.* 2001;28(suppl 8):7-14; 5. Mackie MJ et al. In: Edwards CRW et al, eds. *Davidson's Principles and Practice of Medicine*, 1995.

Higher Hematocrit Is Associated With a Lower Risk of Hospitalization (ESRD)



Collins A et al. ASN Annual Meeting, 2000. Abstract.

Hyperphosphatemia in CKD

- Results from PO_4^{-2} retention by failing kidney
- Forms precipitates at Ca x P product of > 70
- Results in soft tissue calcifications, vascular calcifications, and calciphylaxis
- Increases morbidity and mortality

Slatopolsky et al AJKD 2001; 37(suppl 2): S54.

Cardiac Calcification Predicts Ischemic CVD

- 205 hemodialysis patients studied w electron-beam tomography
- coronary artery calcification = independent predictor of CVD
- increased in older age, white males w DM, HD, high Ca x P.

Raggi. J Am Col Cardiology 2002; 39:695.

Treatment of Hyperphosphatemia and Secondary Hyperparathyroidism

- **Limit Ca x P as close to normal as possible by decreasing PO_4 intake + use binders**
- **iPTH: try to maintain slightly above upper limit of normal (vitamin D analogs)**

Monitoring CKD and Related Complications: Laboratory and Clinical Checklist

Laboratory Test	Normal Values	Recommended Targets
BP (mm Hg)	< 120/80	< 130/80
Hb (g/dL)	13.5 – 17.5	11 to 12
TSAT	20 – 50%	> 20%
HbA_{1c} (%)	4.55 – 5.55	< 7
Phosphorus	<4	< 5.5

Levey AS et al. *Am J Kidney Dis.*1998;32:853-906; NKF-K/DOQI. *Am J Kidney Dis*. 2001;37:S182-S238; Burtis CA et al. *Tietz Textbook of Clinical Chemistry*, 1998. ADA, 2001 (modified).

CHRONIC RENAL INSUFFICIENCY: GFR TIMELINE

NKF Stage	DESCRIPTION	GFR ml/min/ 1.73 m^2	COMPLICATION	PREVALENCE (adults> 20yrs)
↑ risk	At risk: DM, HTN AfrAm; Native Am	≥ 90	Microproteinuria; HTN; hyperglycemia	>20 million (> 12%)
1	Early renal damage	≥ 90	proteinuria, hematuria HTN; progression	>5.9 million (3.3%)
2	Mild renal insufficiency	60-89	Proteinuria/hematuria; HTN; progression	>5.3 million (3%)
3	Moderate renal insufficiency	30-59	Metabolic acidosis; anemia; hyperparathyroidism	>7.7 million (4.3%)
4	**Severe renal insufficiency**	15-29	anemia; hyperparathyroidism; fluid balance; malnutrition	0.4 million (0.2%)
5	ESRD	< 15	Metabolic acidosis; anemia; hyperparathyroidism; fluid balance; potassium + Uremia	0.4 million (0.1%)

COCKCROFT-GAULT EQUATION

$$SCr = \frac{(140\text{-age})(\text{weight in kg})}{72 \times GFR\ (ml/min)} \quad (\times 0.85 \text{ for women})$$

3 patients with GFR 15-29 ml/min/1.73 m^2

Young Man	Young Woman	Older Woman
Age = 25 years	**Age = 25 years**	Age = 75 years
Weight = 100 kg	**Weight = 50 kg**	Weight = 45 kg
Estimated Cr = 10.6-5.3	Estimated Cr = 4.6-2.3	Estimated Cr = 2.1-1.1
MDRD: 7.4-4.2	3.5-1.8	2.4-1.4

Patient #1: 85 yo, sedentary female, 42 kg, lives with her extended family. Her family has noted over the last 6 months, that her appetite has decreased and that she seems to nap a lot during the day. Her BP is normal and she is not diabetic, but she has not seen a doctor since her children were born. Blood chemistries reveal:

BUN = 10; Cr = 2.5; PO_4 = 3.0; HCO_3 = 20; HCT = 30; Ca = 8.2; Alb = 3.0

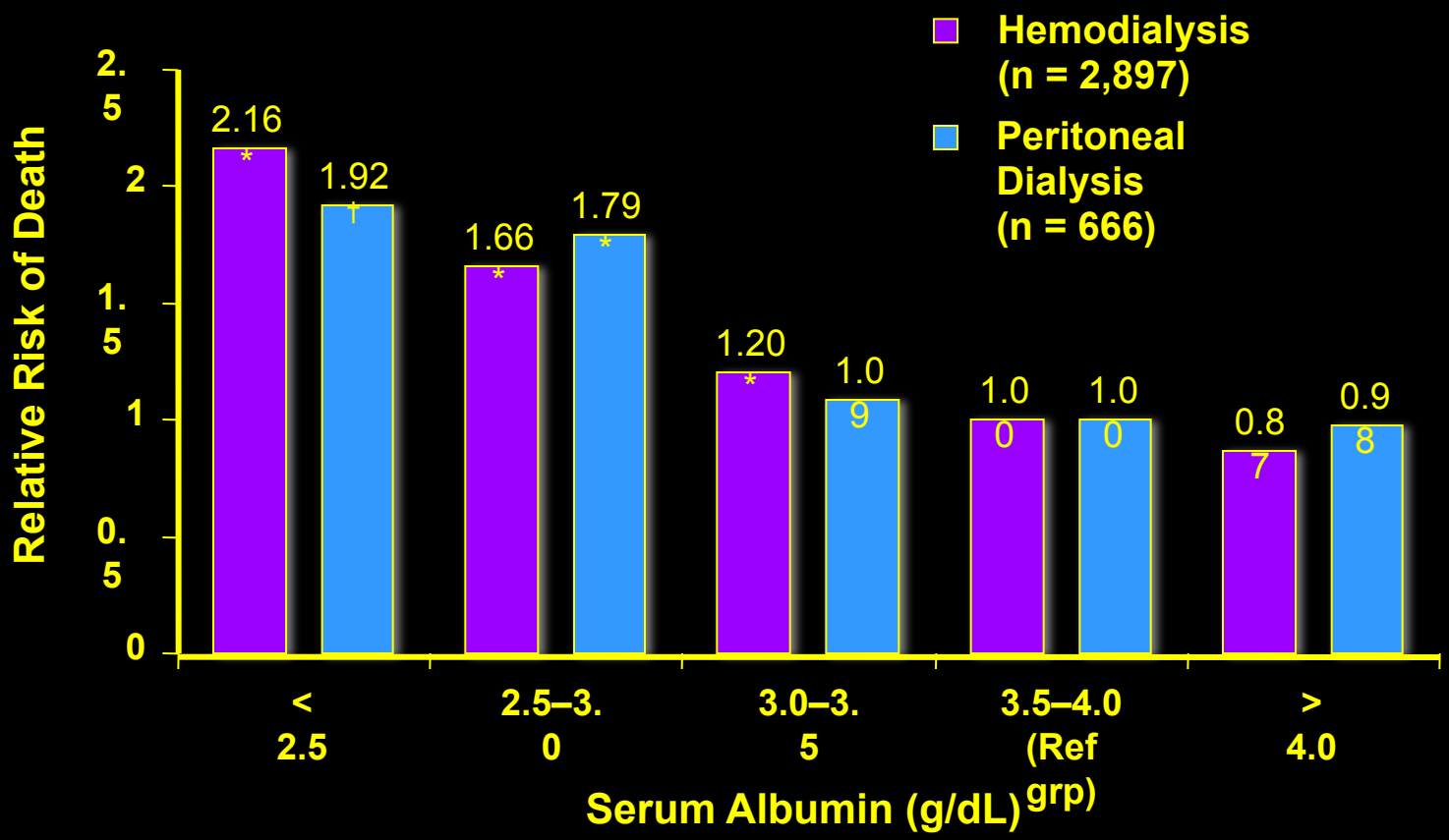
Patient #2: 38 yo male, 110 kg, works construction and says he "hasn't felt right for weeks". BP = 190/115; Blood chemistries: Cr = 10.0; BUN = 110; PO_4 = 8.0; HCO_3 = 18; HCT = 30; Ca = 8.0; Alb = 4.1.

Who is more uremic and closer to ESRD?

Nutritional Challenges in CKD

- As the kidney fails, protein intake should be maintained at 1 g/kg/day (early on this is a reduction later on it may be an increase) and caloric intake at 25-35 kcal/kg/day. These goals, if not approached carefully with a disciplined diet, often result in:
  - hyperphosphatemia
  - hyperkalemia
  - uremia
  - hypoalbuminemia ± elevated CRP
  - metabolic acidosis
  - iron deficiency

Hypoalbuminemia at Dialysis Initiation: Mortality Association



*P<0.01 compared to ref group

†P=0.02 compared to ref group

Port FK. *Kidney Int.* 1994;46:1728-1737.

CHRONIC RENAL INSUFFICIENCY: GFR TIMELINE

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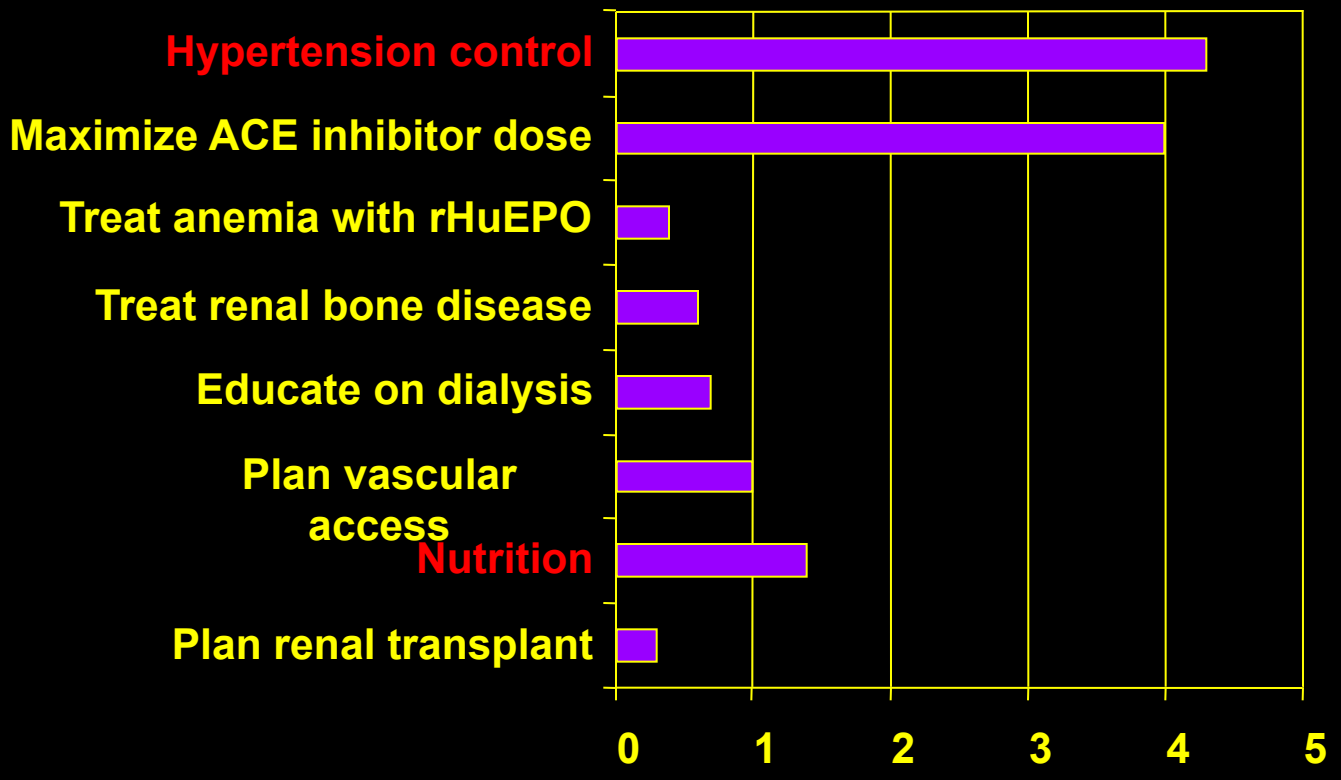
If referred at this stage…..

- Hypervolemia, CHF, uncontrolled BP
- Malnutrition, chronic inflammation: increased cardiac and infectious morbidity
- Untreated anemia, renal bone disease
- Delays in modality teaching and transplant workup and referral (pre-emptive transplant….)
- Access problems (temporary access: increased mortality)
- Etiology for enormous incident mortality (first year) on hemodialysis

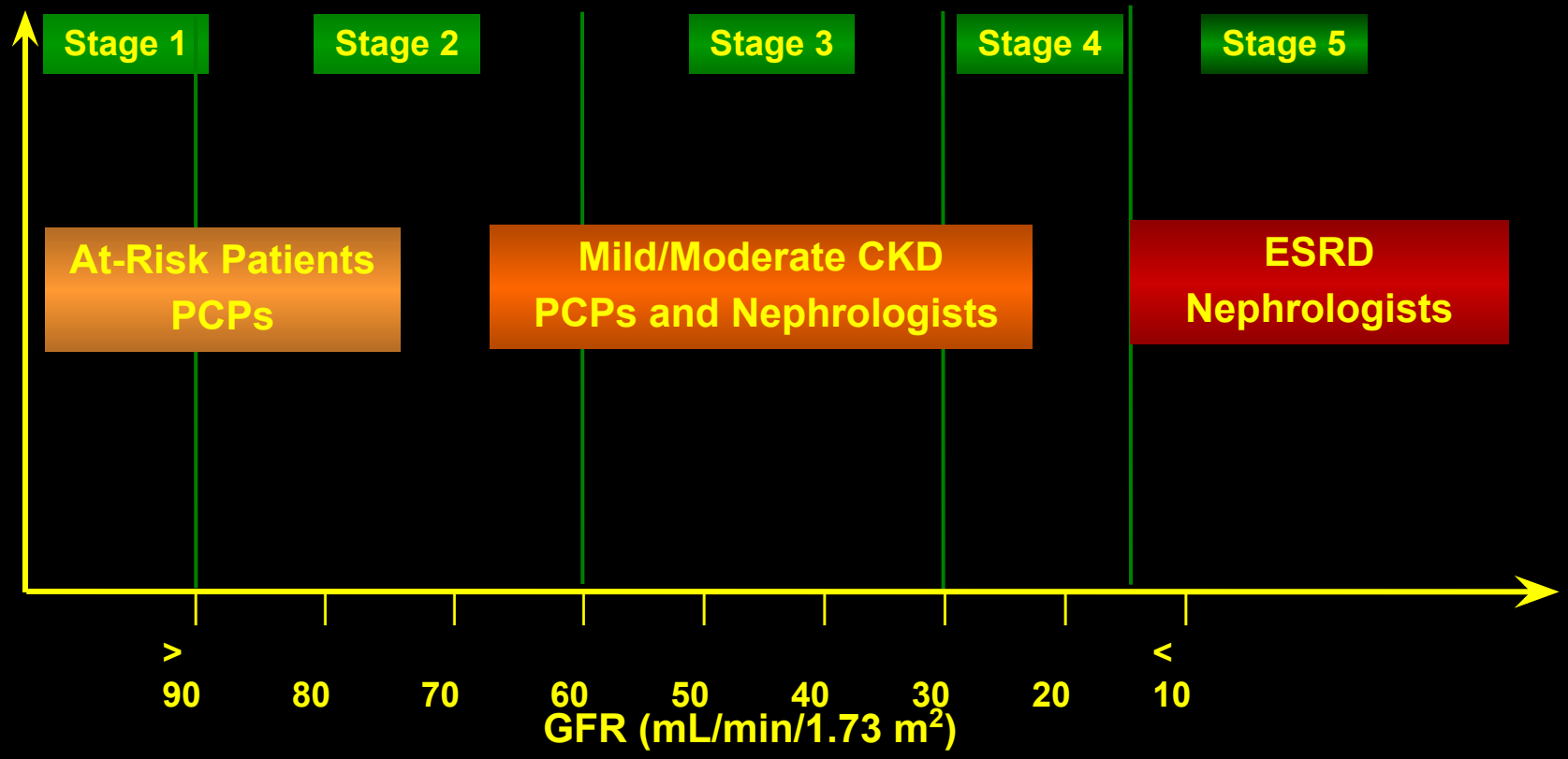
Primary Care Survey: Comfort With CKD Treatment



Ratings of comfort with each area of CKD treatment on a scale of 0 (low) to 5 (high) by 105 primary care physicians from Long Island, NY.

Fishbane S. *Intern Med News*. 2001; suppl:14-15.

Proposed Collaborative Relationships in Treating CKD



Adapted from Obrador GT et al. *Am J Kidney Dis*. 1998;31:398-417.

Summary

Consequences of CKD if left untreated:

- **↑ Progression to ESRD**
- **↓ QOL**
- **↑ LVH**
- **↑ Malnutrition**
- **↑ Hospitalization**
- **↑ Mortality**

Conclusions

- CKD is a growing problem in MS and the US
- The progression to ESRD can be slowed sometime stopped by controlling blood pressure and diabetes, proteinuria and with lifestyle modifications.
- Creatinine is not an absolute indicator of kidney function- we use global multidisciplinary clinical assessment plus estimated GFR.
- Early referral to a Nephrologist may help your patient's QOL and longevity