Clinical Pearls: Chronic Kidney Disease

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Disclosures

No conflicts of interest to disclose

Learning Objectives

- Describe the most important management principles for patients with chronic kidney disease
- Describe strategies for slowing kidney disease progression
- Describe strategies for reducing cardiovascular disease in CKD
- Recognize and implement interventions to address CKD-related complications

Outline

- Cardiovascular disease (CVD) burden in chronic kidney disease (CKD)
- Strategies for slowing kidney disease progression
- Reducing cardiovascular disease in CKD
- Treating Complications
- Vaccinations
- Referral to nephrology

Case 1

- 52 year old male with CKD stage 3B (GFR 35 ml/min) secondary to DM and HTN presents for routine follow-up. No h/o CVD, quit smoking 5 years ago. No family history of CVD.

Given this patient has CKD stage 3B he should be considered:

1. Lowest risk group for CVD irrespective of his traditional CVD risk factors

   0%

2. Moderate risk group for CVD irrespective of his traditional CVD risk factors

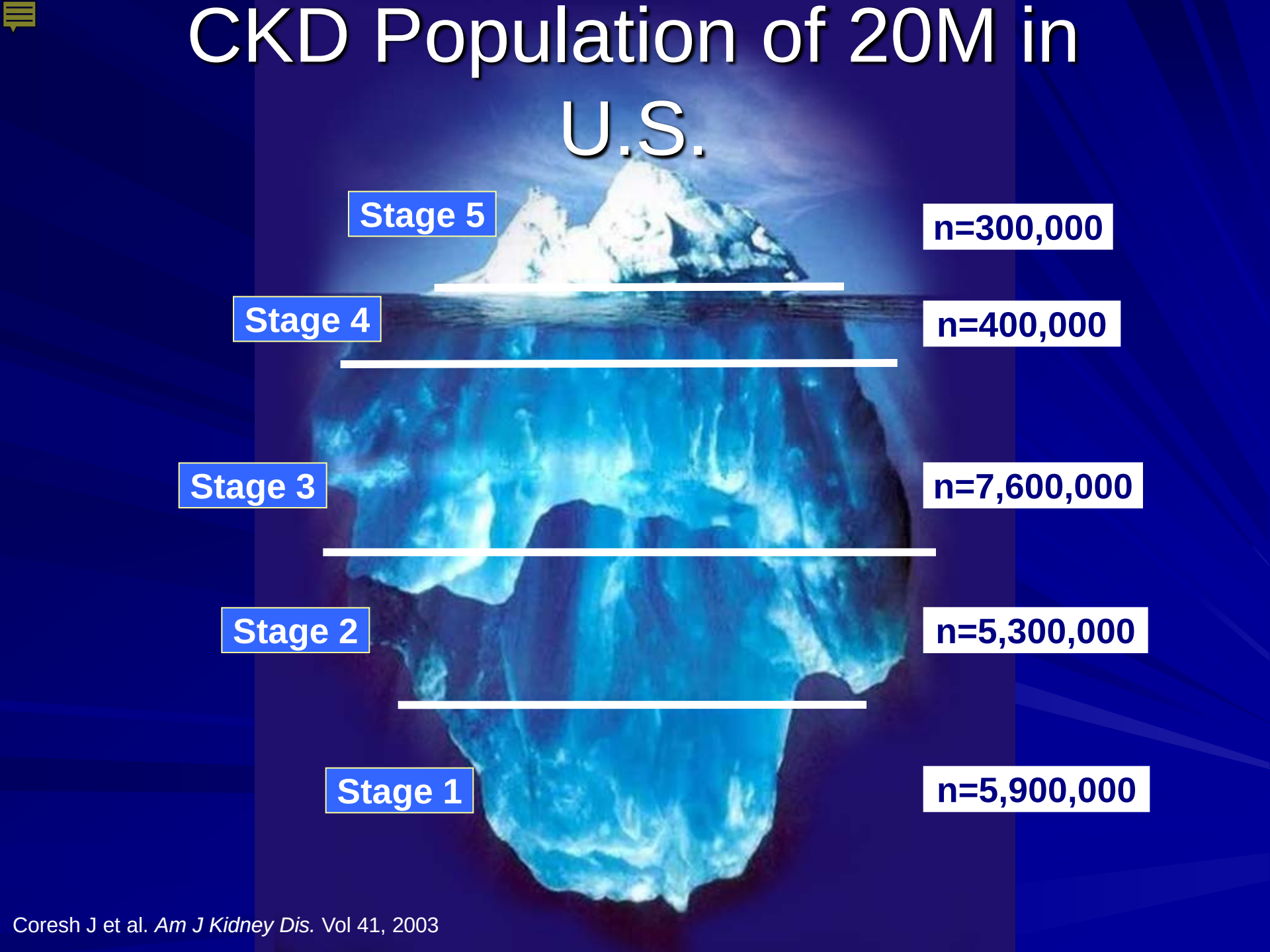
   24%

3. Highest risk group for CVD irrespective of his traditional CVD risk factors

   76%

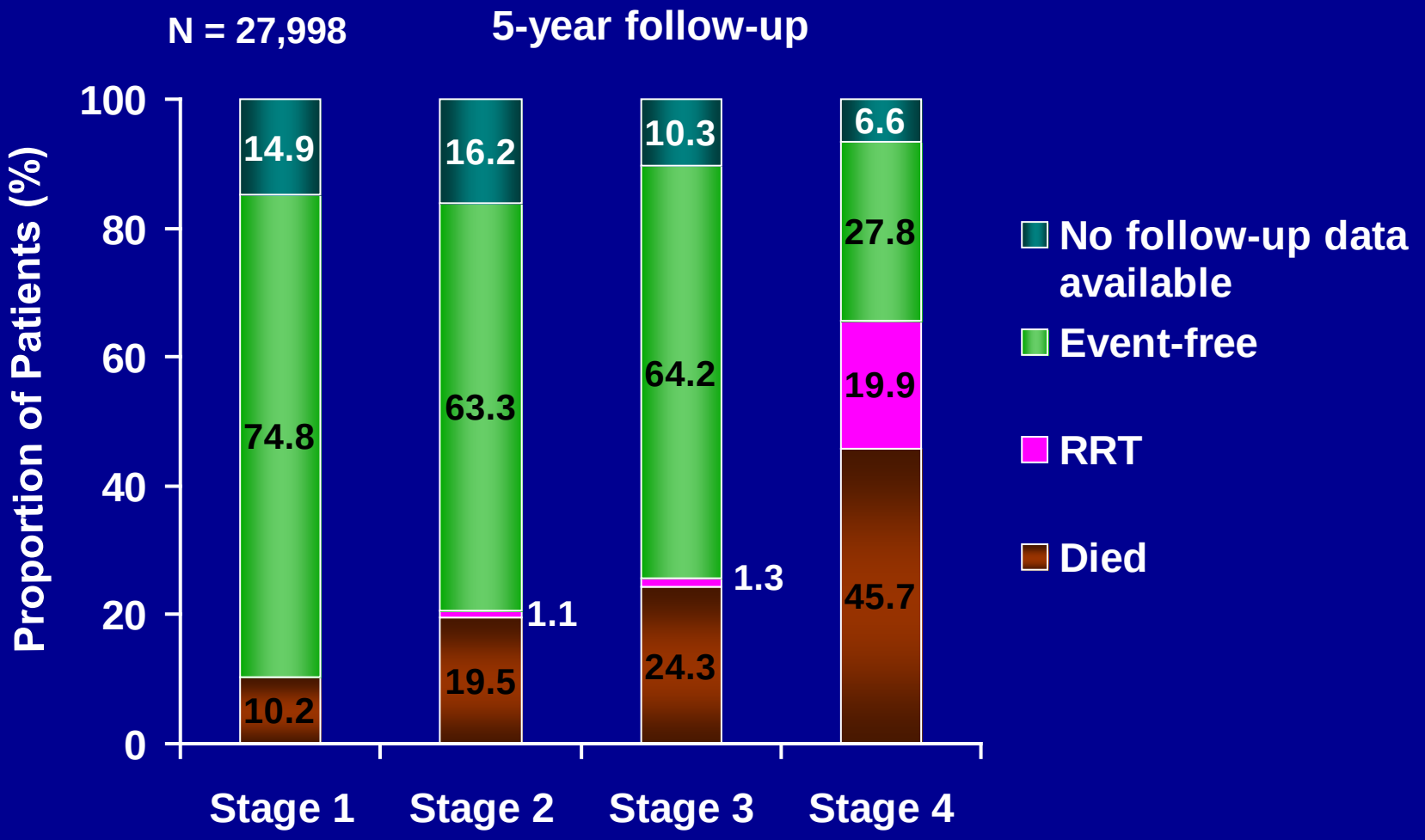
15

CKD Population of 20M in U.S.



Coresh J et al. *Am J Kidney Dis.* Vol 41, 2003

Pre-Dialysis Patients Are More Likely to Die than Progress to ESRD Dialysis Therapy

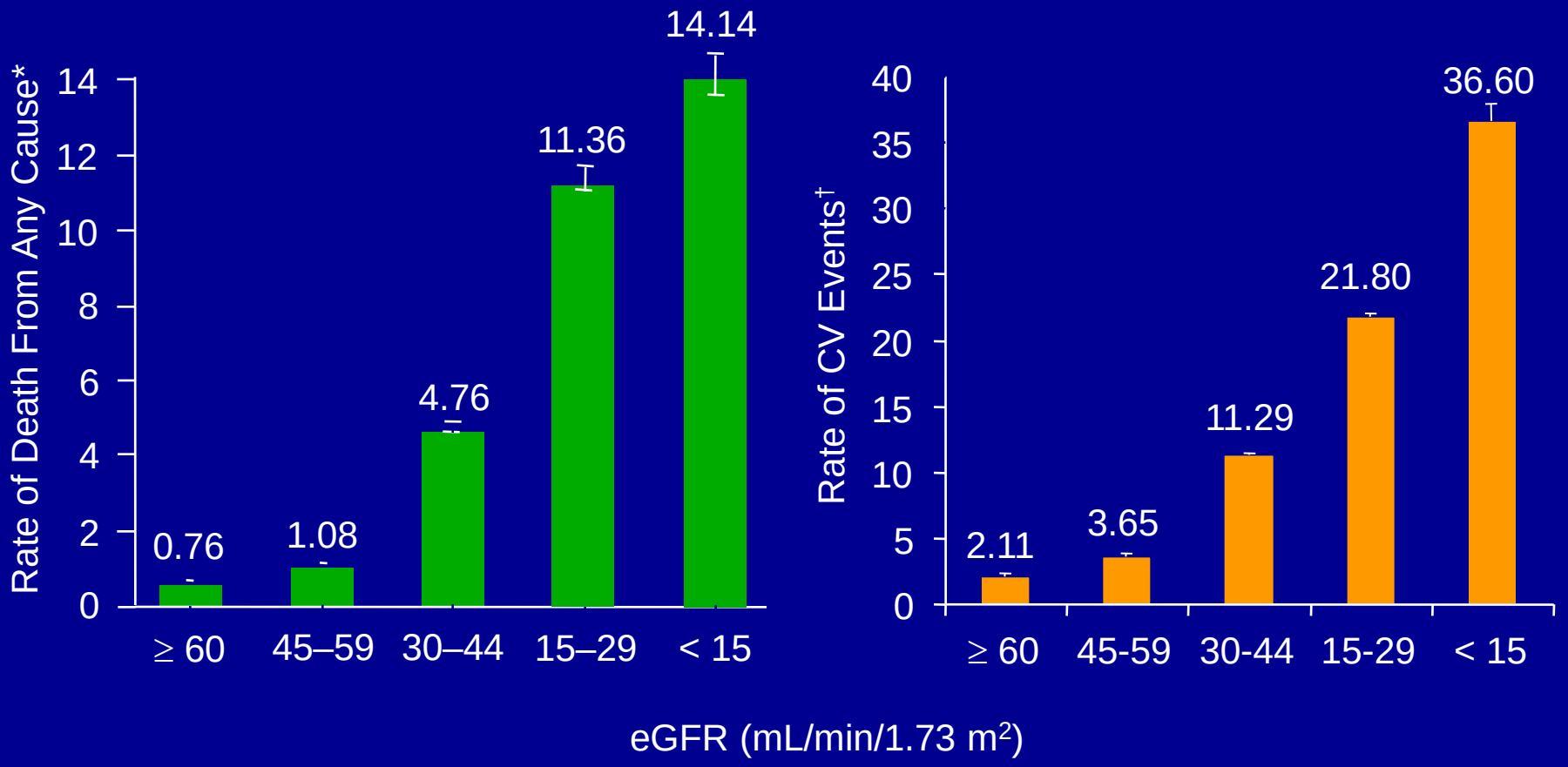


Keith D et al. *Arch Intern Med* 2004; 164: 659-663

Chronic Kidney Disease (CKD) and CVD

- Patients with CKD are at an increased risk of CVD
- CKD is an independent risk factor for CVD
  - All patients with CKD should be considered in the “highest risk” group for CVD

Rate of Death and Cardiovascular Events According to Estimated GFR



N = 1,120,295 adults.

*Age-standardized rates per 100 person-years; †CV event defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease per 100 person-years.

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

Secondary Complications and Comorbidities of CKD

Complications

- Albuminuria
- Anemia
- Disordered Mineral Metabolism
  - Hyperphosphatemia
  - Secondary hyperparathyroidism
  - Vitamin D deficiency
  - Elevated FGF23
- Metabolic acidosis
- CVD

Comorbidities

- Diabetes mellitus
- Hypertension
- Dyslipidemia
- Obesity
- CVD

The most important management principles for CKD are…

- Delay CKD progression
- Treat complications of CKD
- Screen for and treat cardiovascular risk factors

Slowing Progression of Kidney Disease

Case 2

- 62 year old female with CKD stage 3B (GFR 32 ml/min) secondary to DM.
- PMH: DM, HTN, OSA
- Medications: lisinopril, furosemide, metoprolol, simvastatin, aspirin
- BP 145/90, pulse 72
- Proteinuria 2100 mg/day
- Serum bicarbonate 16 meq/L
- Serum phosphate 4.9 mg/dL
- Serum 25-hydroxyvitamin D 10 ng/mL
- Intact PTH 120 pg/mL
- Hemoglobin 10.3 g/dL

In additional blood pressure, diabetes and lipid control what other intervention with slow progression of her kidney disease?

1. Additional of an angiotensin receptor blocker (ARB)

64%

2. Treatment of her metabolic acidosis with sodium bicarbonate

23%

3. Treatment of her anemia to a hemoglobin > 12 g/dl

2%

4. No other intervention will slow progression of her kidney disease at this point

11%

13

Slowing Progression: Blood Pressure Control

- Over 80% of patients with CKD have HTN
- **The MOST** important factor in decreasing the progression of kidney disease
- The appropriate BP goal is unknown
  - New recommendations: <140/90 mmHg
  - Many nephrologist still do <130/80 mmHg
- BP control reduces proteinuria (another risk factor for progression of CKD)

Slowing progression: Inhibition of the Renin-Angiotensin-Aldosterone System

- RAAS has pathophysiologic role in progression of CKD
- RAAS blockade reduces proteinuria and slows progression
- Beneficial effect has been demonstrated:
  - In both diabetic and non-diabetic kidney disease
  - In advanced CKD
- Magnitude of the effect is about a 20% risk reduction
- ACEi and ARB have similar efficacy

ACE inhibitors should not be combined with ARB

- Adding ARB to ACEi is less effective than adding another agent
- Combination does not reduce cardiovascular or renal events compared to the individual agents
- Increased risk of:
  - Hyperkalemia
  - Hypotension
  - Dialysis
  - Doubling of serum creatinine
  - Death

How do we achieve BP control in CKD patients?

- Combination of 3 or more drugs are usually needed
- All diabetics with CKD should be treated with an ACEi or ARB
- All patients with proteinuria should be treated with an ACEi or ARB

Other “Traditional” Risk Factors for Kidney Disease Progression and CVD

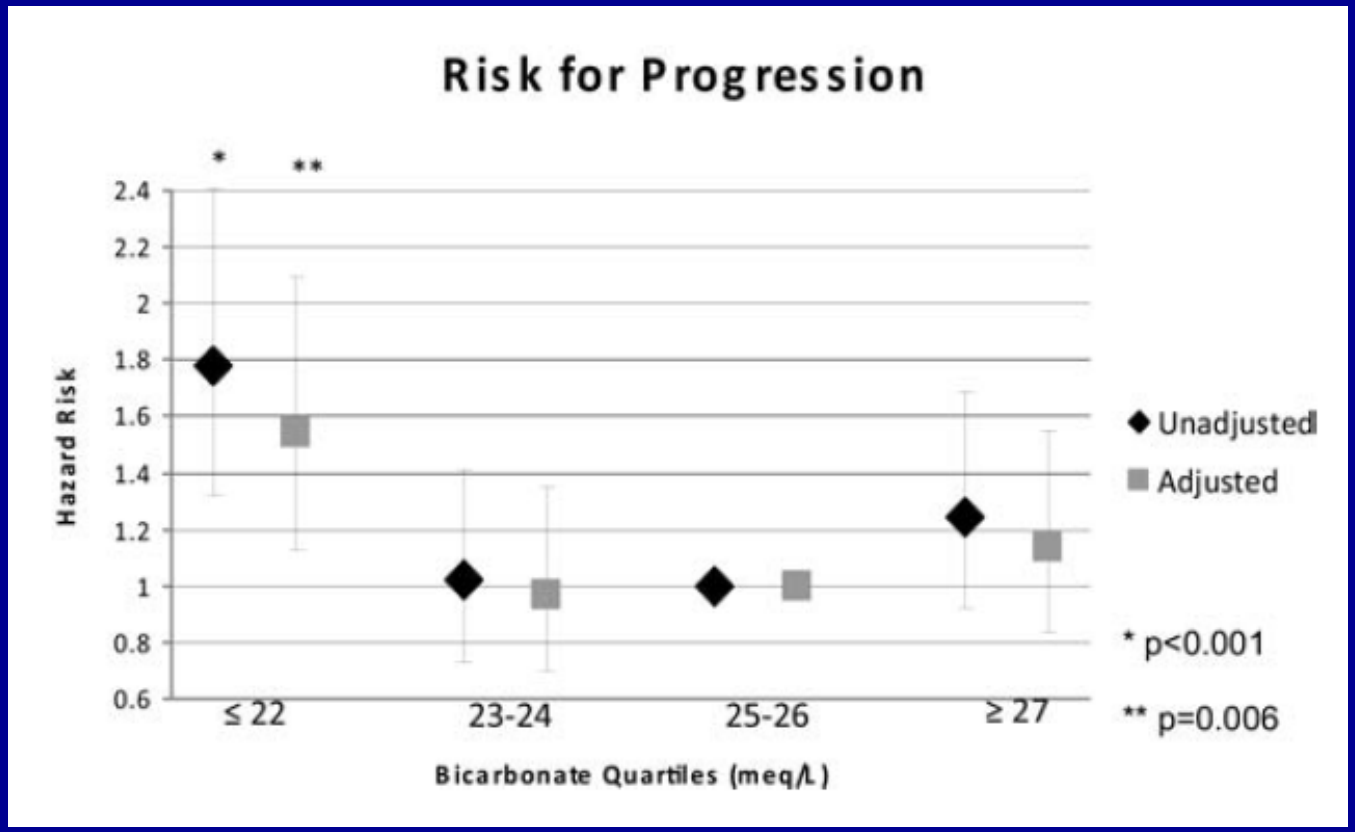
- Hyperlipidemia
- Smoking
- Obesity
- Diabetes
- Genetics
- Race and socioeconomic status

Slowing Progression: Treating Metabolic Acidosis

- Metabolic Acidosis
  - Reduction in serum HCO_3^- concentration
  - Common complication of CKD
  - Major consequences:
    - Degradation of muscle protein and muscle wasting
    - Reduced albumin synthesis
    - Production or exacerbation of bone disease
    - Impairment in glucose tolerance
  - Traditionally treatment of metabolic acidosis was for these consequences

Kraut J. Am *J Physiol Renal Physiol* 2011;300:F828-829

Metabolic Acidosis is also a Risk Factor for Kidney Disease Progression

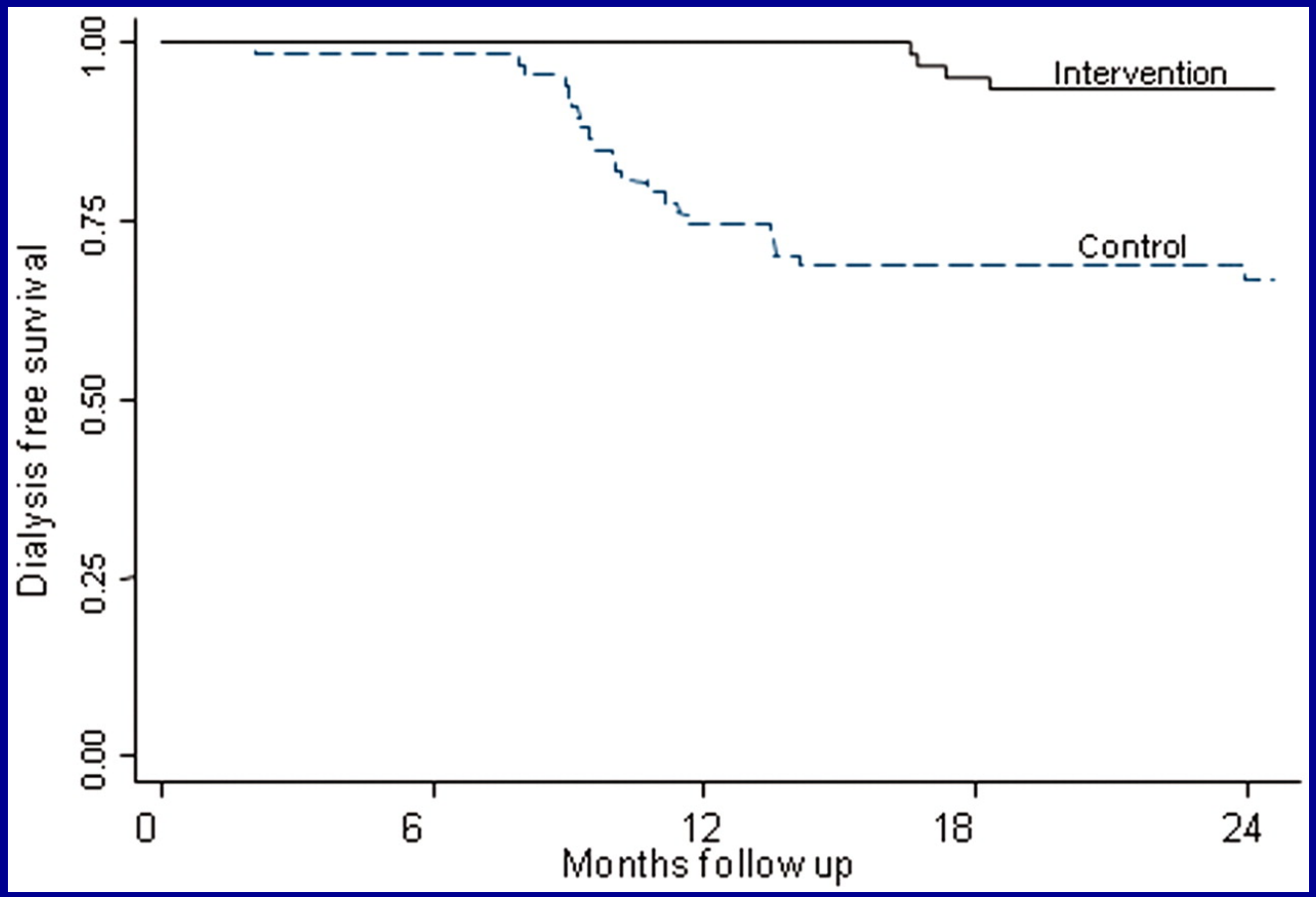


N= 5,422

Shah SN et al. *Am J Kidney Dis* 2009;54:270-277

Bicarbonate Administration Slows Progression of Kidney Disease

- 134 patients with CKD stage 4 with serum $HCO3^-$ 16-20 mmol/L
- Randomized to supplementation with sodium bicarbonate or placebo for 2 years



de Brito-Ashurst I et al. *J Am Soc Nephrol* 2009;20:2075-2084

Alkali Therapy Slows CKD Progression

- 59 CKD stage 3 patients treated with sodium citrate (1 mEq/kg/day) or standard care for 24 months
- Mean serum bicarbonate of 20 meq/L

Table 2 | SBP, Pcr, and eGFR before (0 months) and after 24 months of No-NaCit vs NaCit

	No-NaCit (n=29)			NaCit (n=30)			P-value, NaCit vs No-NaCit	
	Month 6	Month 30	P-value, 30 vs 6 months	Month 6	Month 30	P-value, 30 vs 6 months	Month 6	Month 30
SBP	132.1 ± 6.3	131.9 ± 3.8	0.870	132.4 ± 6.2	132.7 ± 5.7	0.761	0.839	0.490
Pcr (mg/dl)	3.30 ± 0.91	4.24 ± 1.55	< 0.0001	3.31 ± 0.69	3.61 ± 0.78	< 0.0001	0.954	0.057
eGFRcr (ml/min)	32.5 ± 8.3	24.9 ± 9.7	< 0.0001	32.7 ± 8.2	29.5 ± 8.8	< 0.0001	0.945	0.066
Pcys (mg/l)	3.94 ± 1.10	5.24 ± 1.41	< 0.0001	3.93 ± 0.80	4.33 ± 0.89	< 0.0001	0.952	0.005
eGFRcys (ml/min)	31.7 ± 7.9	23.0 ± 6.05	< 0.0001	31.4 ± 8.2	27.8 ± 7.4	< 0.0001	0.885	0.008

Abbreviations: eGFR, estimated glomerular filtration rate; Pcr, plasma creatinine; Pcys, plasma cystatin; SBP, systolic blood pressure.

Phisitkul S et al. *Kidney Int* 2010;77:617-623

Bicarbonate Therapy is Safe

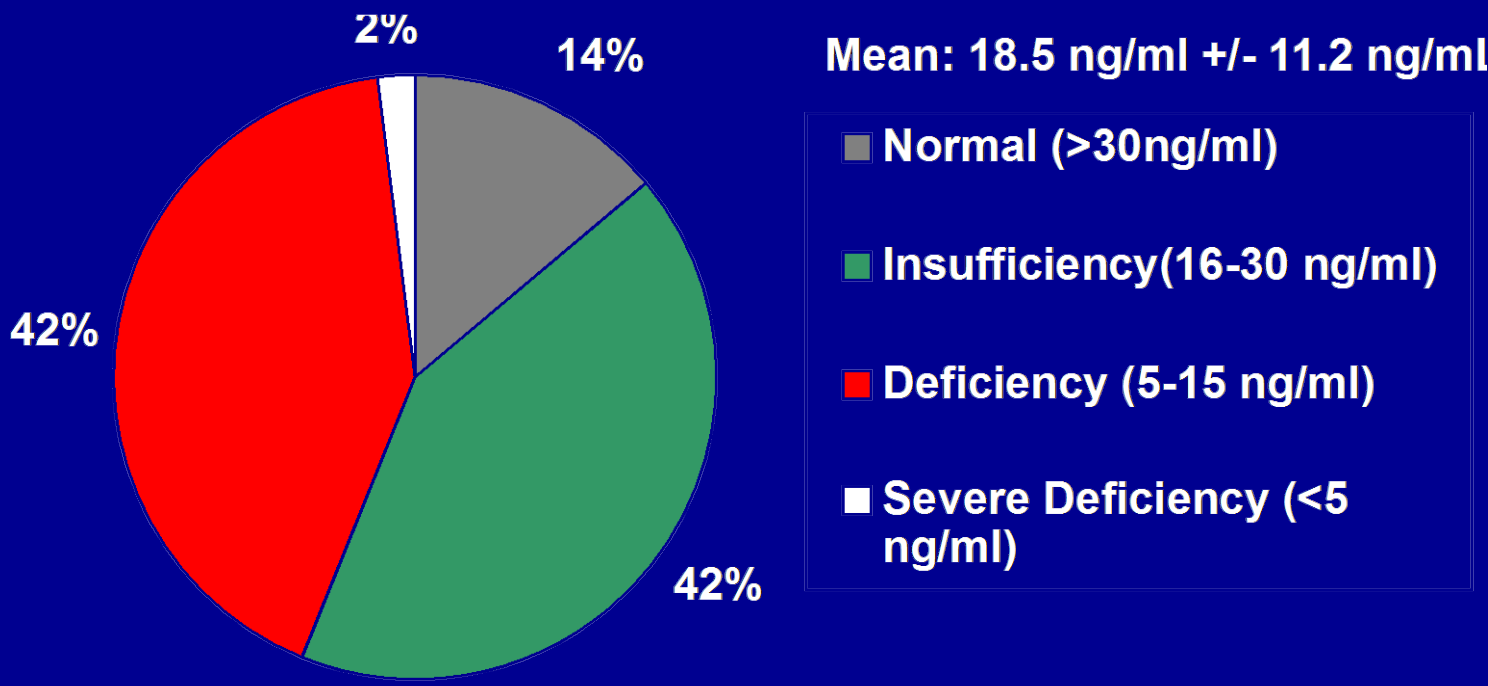
- Sodium bicarbonate therapy is not associated with a higher likelihood of increasing or starting antihypertensive therapies
  - No detrimental effect as far as hypertension from the sodium load

Recommendations for Bicarbonate Therapy

- Bicarbonate therapy appears to slow the rate of progression in patients with moderate to severe CKD with acidosis
- Bicarbonate therapy should be started in patients with serum bicarbonate levels < 22 meq/L
- Target bicarbonate level is > 22 meq/L
- At this time, unclear if we should be treating earlier CKD patients with serum HCO_3 > 23 meq/L

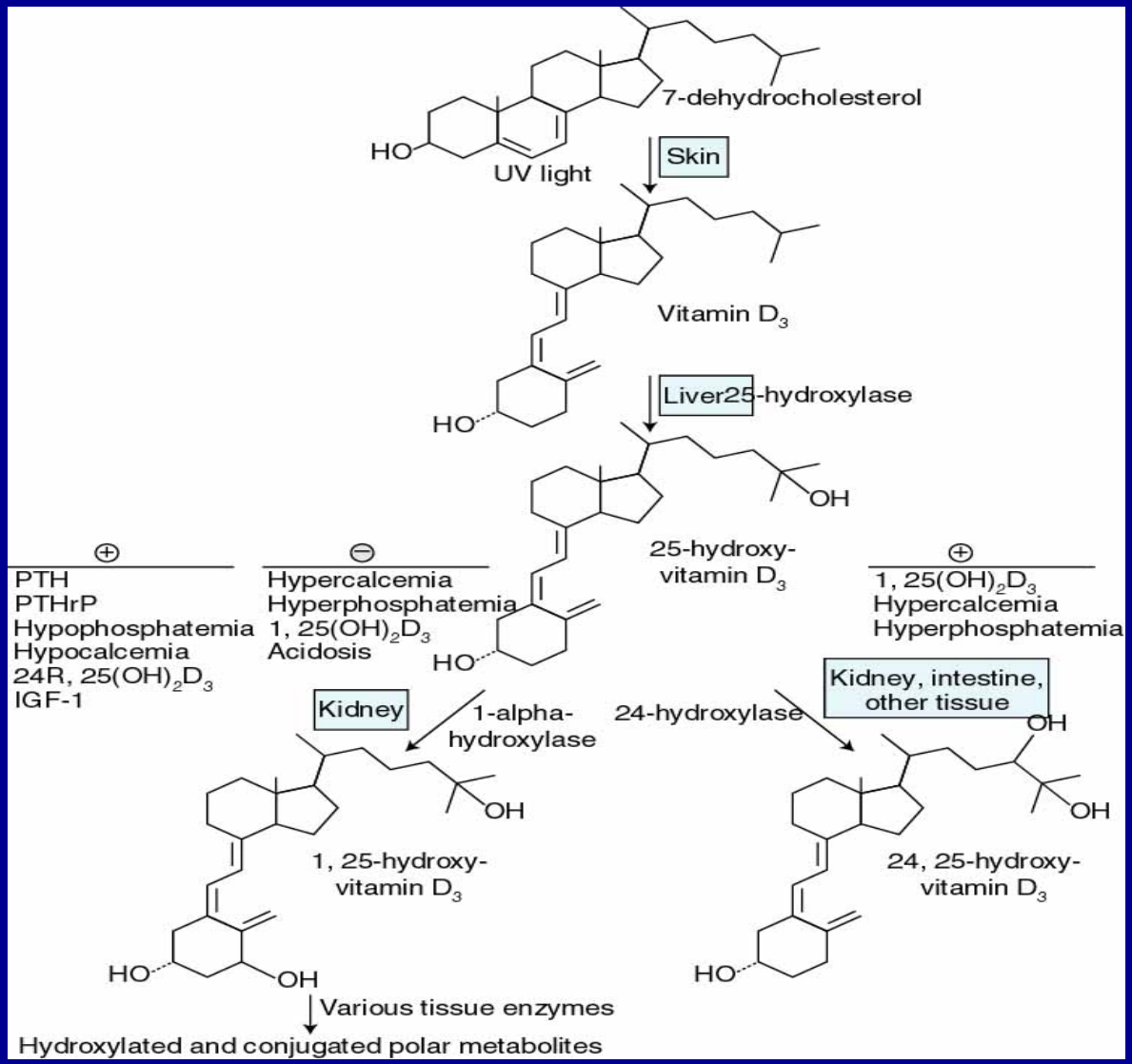
Slowing Progression: Treating Vitamin D Deficiency

- 25(OH)D status throughout the spectrum of CKD

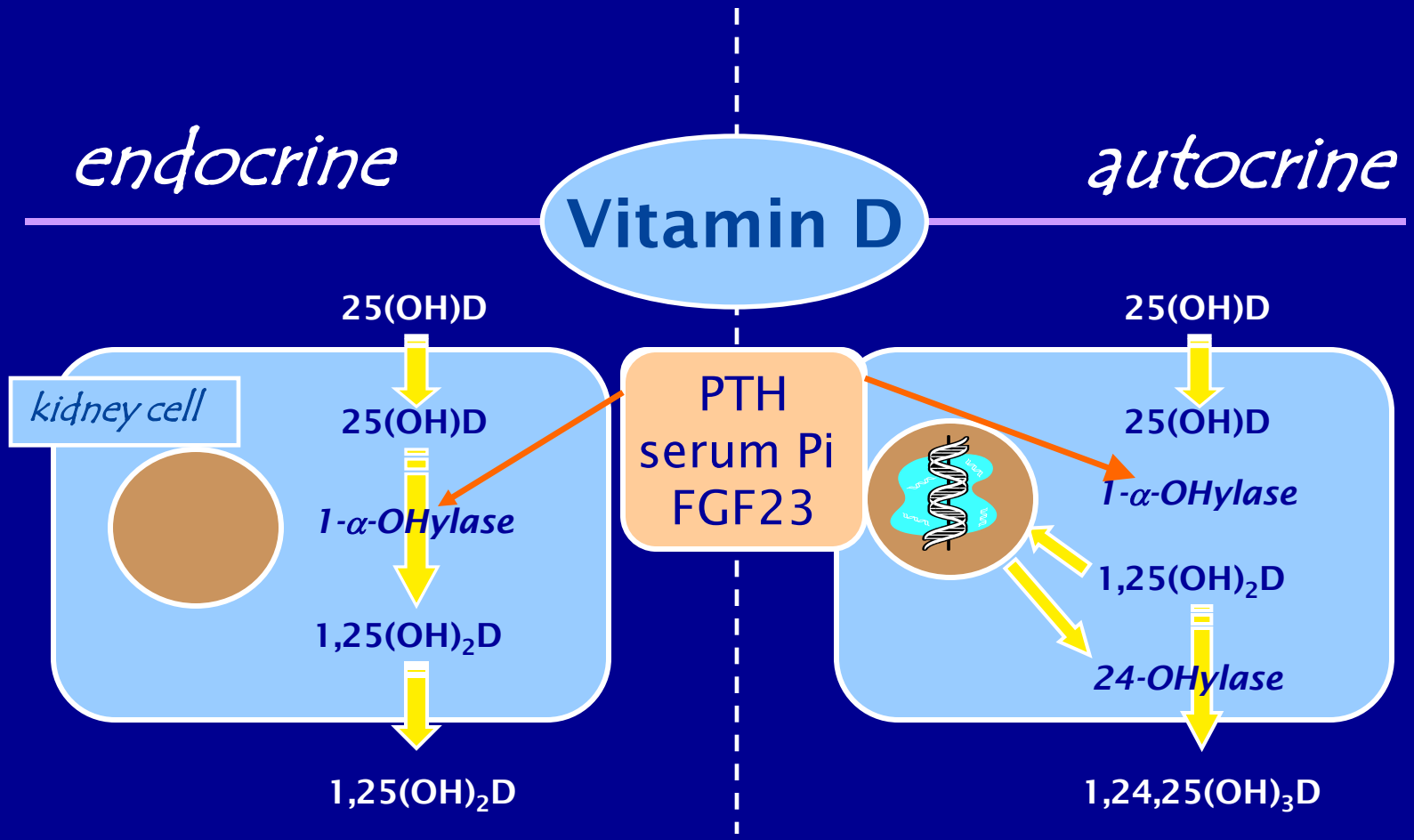


Gonzalez et al. *Am J Nephrol* 2004;24:503-510

Vitamin D Metabolism



Holik MF. *Seminars in Dialysis* 2005; 18:266-275



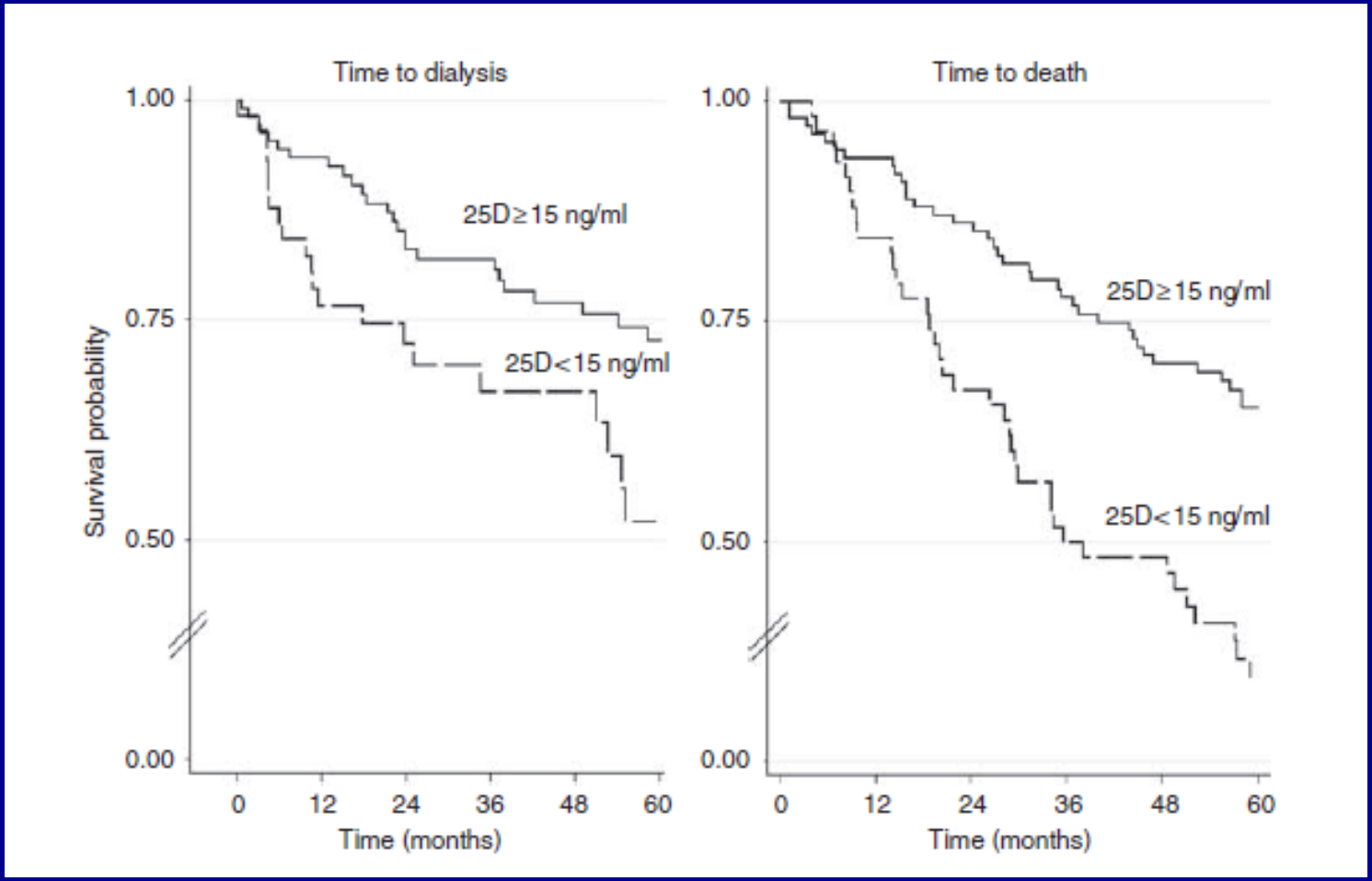
Calcemic Effects

Non-Calcemic Effects

Non-Calcemic Effects of Vitamin D

- Inhibition of the renin angiotensin aldosterone system
- Anti-inflammatory properties
- Reduces podocyte injury
- Results in cardiomyocyte remodeling

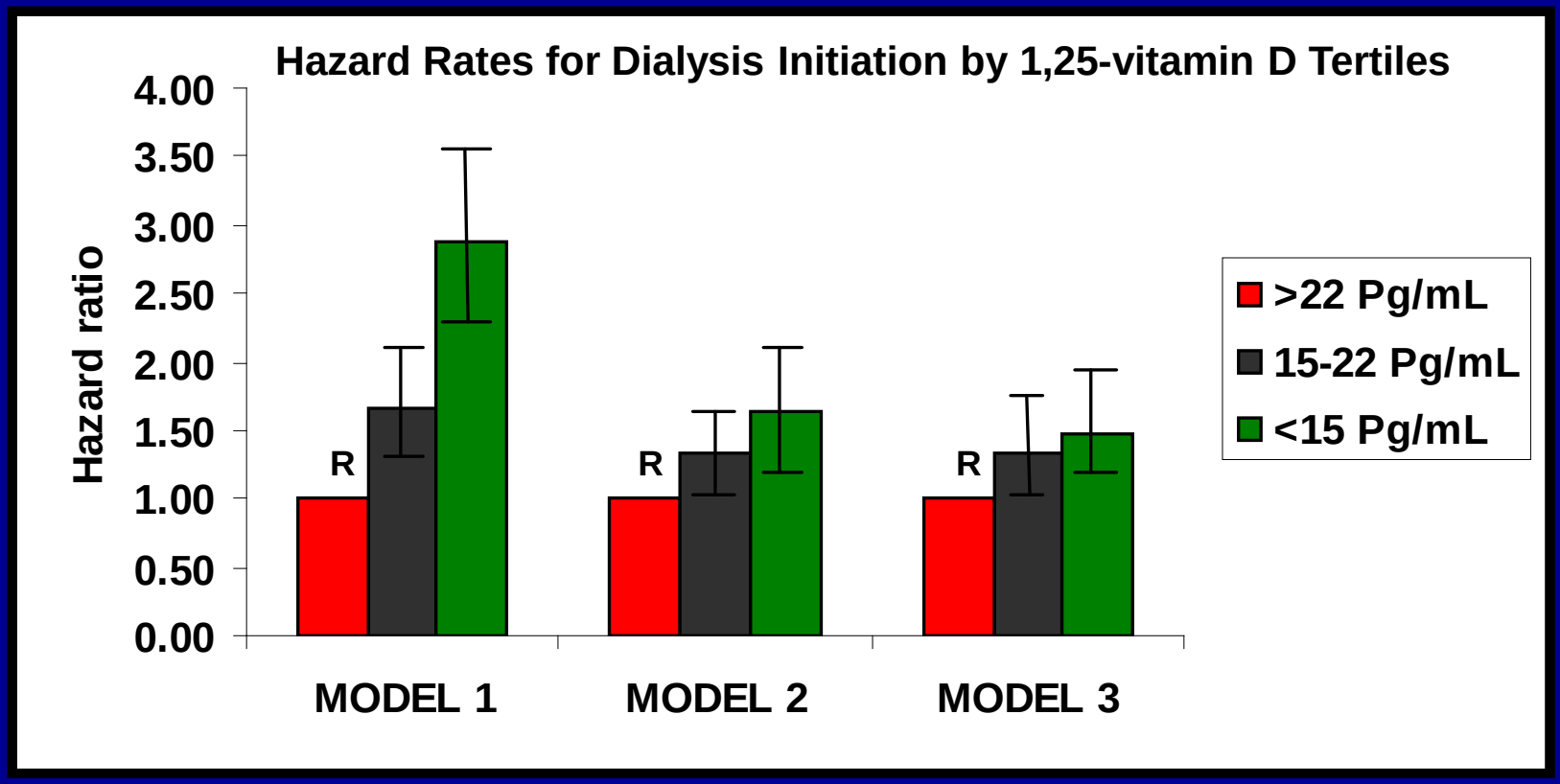
Low 25-vitamin D Levels are a Risk Factor for Kidney Disease Progression



Ravani P et al. *Kidney Int* 2009;75:88-95

N=168

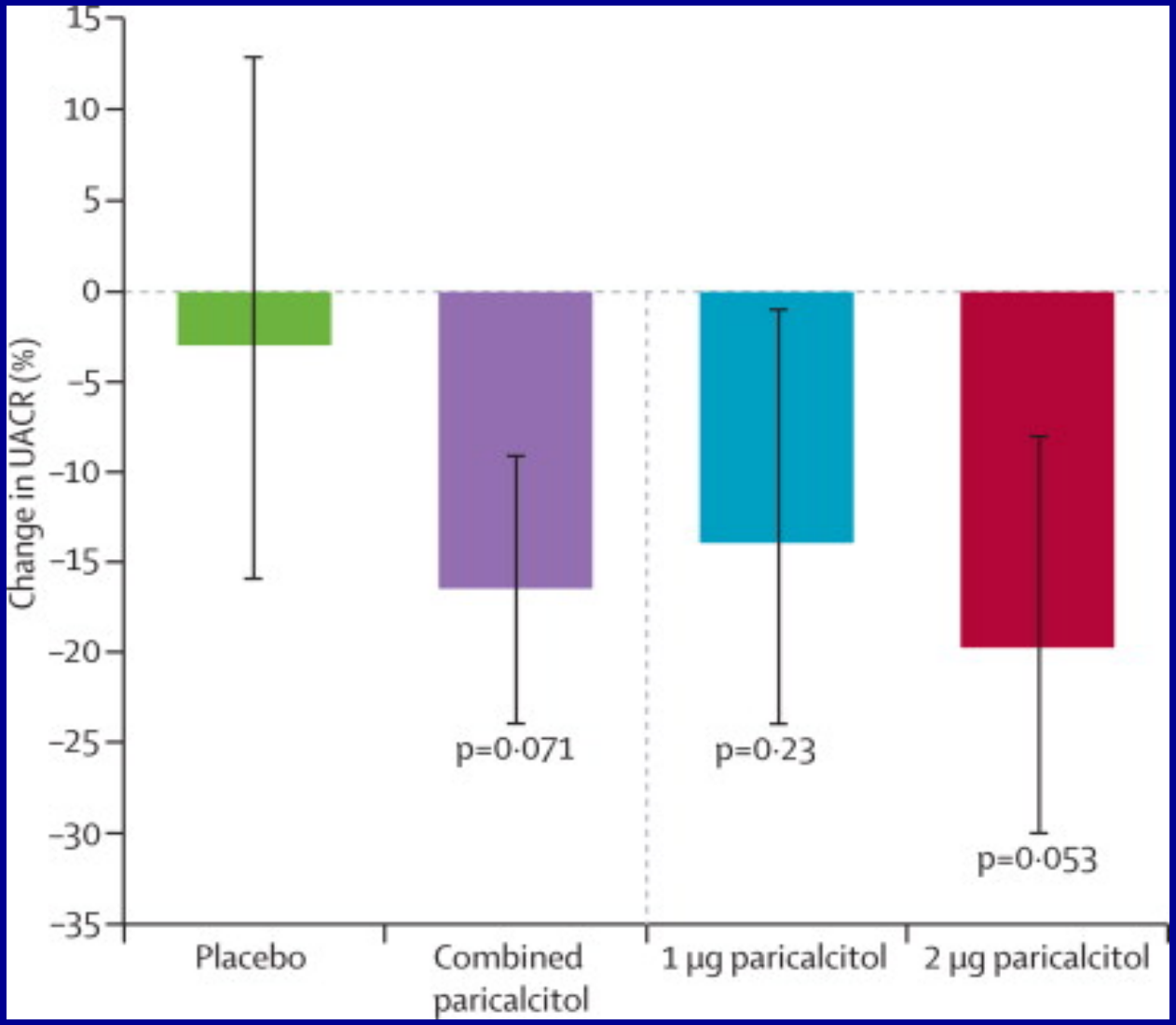
Low 1,25-vitamin D (calcitriol) Levels are a Risk Factor for CKD Progression



N=1,099

Kendrick J et al. *Am J Kidney Dis* 2012; epub ahead of print

Treatment with Active Vitamin D (Calcitriol) Reduces Proteinuria



N=281

De Zeeuw D et al. *Lancet* 2010;376:1543-1551

Recommendations for Vitamin D Replacement

- No randomized trials showing vitamin D slows progression
- All CKD patients with 25-vitamin D levels < 30 ng/mL should receive repletion with nutritional vitamin D
- The use of active vitamin D analogues (e.g. calcitriol) in CKD patients not yet on dialysis is controversial

Reducing Cardiovascular Risk Factors in CKD

“Traditional” Risk Factors for CVD in CKD

- Hypertension
- Hyperlipidemia
- Smoking
- Obesity
- Diabetes
- Genetics
- Race and socioeconomic status

Case 3

- 60 year old male with CKD stage 4 (GFR 25 ml/min) secondary to DM and HTN.
- PMH: DM, HTN, gout
- SH: non-smoker
- BP 135/80, pulse 65
- A1C 7.2%, LDL 80 mg/dL
- Proteinuria 1200 mg/day
- Serum phosphate 5.1 mg/dL
- Serum 25-hydroxyvitamin D 15 ng/mL
- Intact PTH 130 pg/mL
- Hemoglobin 9.2 g/dL

In addition to his traditional CVD risk factors what kidney disease-related (nontraditional) CVD risk factors does this patient have?

1. Vitamin D deficiency
   - **3%**
2. Hyperphosphatemia
   - **3%**
3. Secondary hyperparathyroidism
   - **3%**
4. Proteinuria
   - **5%**
5. All of the above
   - **88%**

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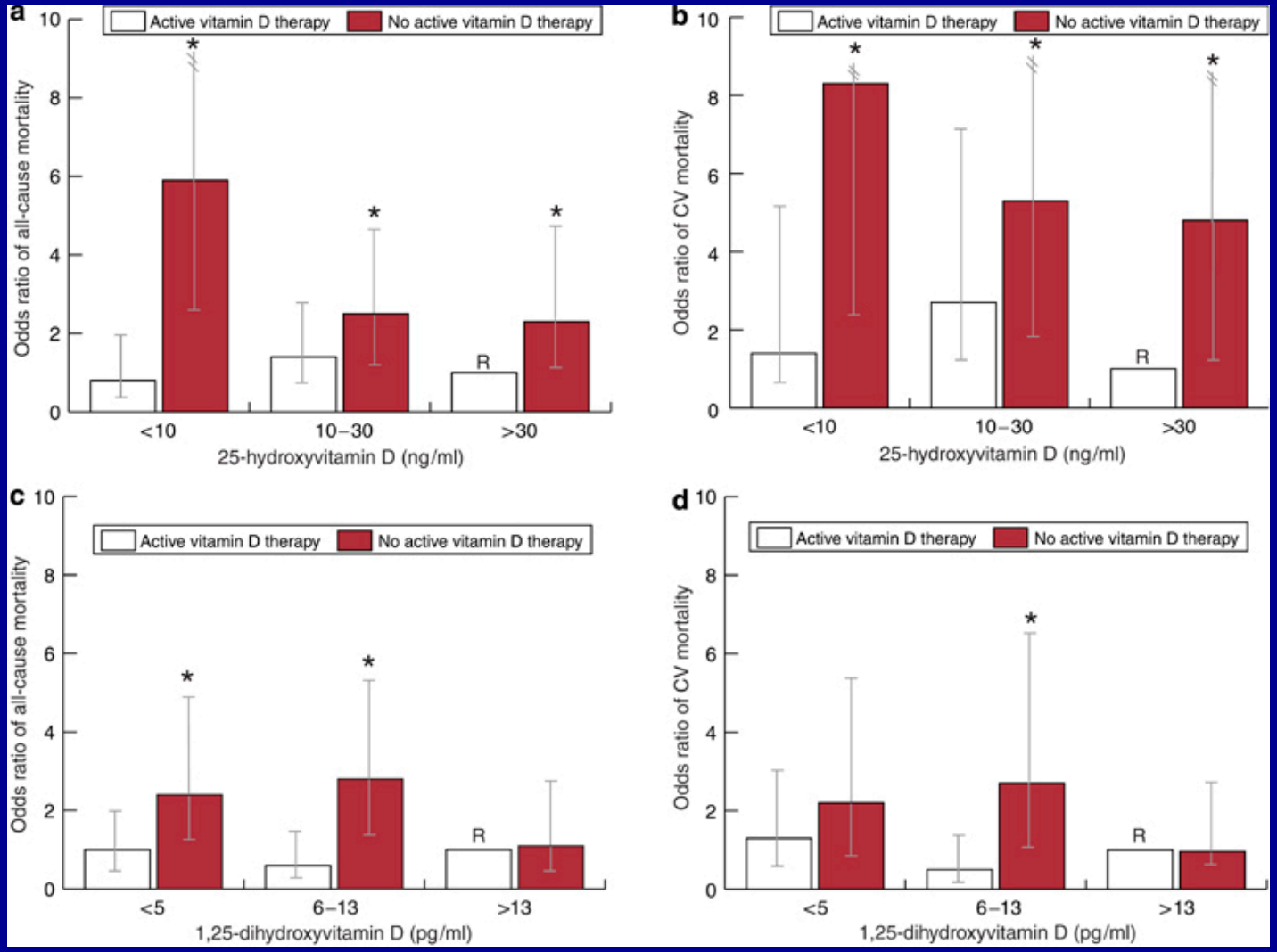
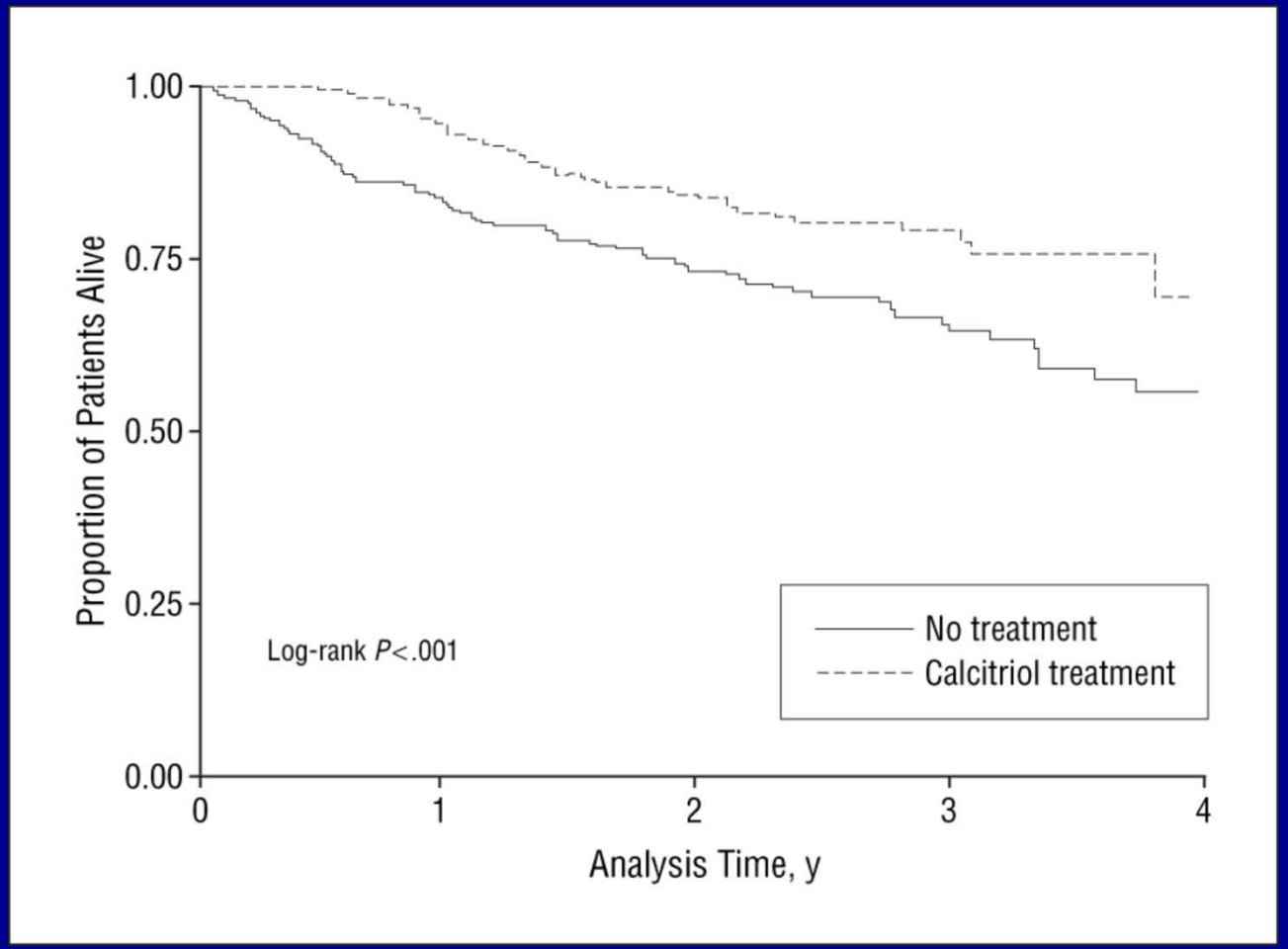
Nontraditional Risk Factors: Vitamin D Deficiency



N=825

Wolf M et al. *Kidney Int* 2007;72:1004-1013

Treatment with Active Vitamin D is Associated with a Lower Risk of Death in CKD Patients



N=520

Kovesdy et al. *Arch Intern Med* 2008;168:397-403

Treatment with paricalcitol does not improve LVMI in patients with CKD

- 220 patients with CKD stage 3-4
- Randomized to treatment with paricalcitol or placebo for 48 weeks

Table 3. Repeated-Measures Analysis of Change in Cardiovascular Magnetic Resonance Imaging Measures From Baseline to 24 and 48 Weeks (Intention-to-Treat Population)[a]

	24 Weeks			48 Weeks			
Measures	Paricalcitol (n = 104)	Placebo (n = 98)	*P* Value[b]	Paricalcitol (n = 88)	Placebo (n = 91)	*P* Value[b]	Overall *P* Value[c]
Left ventricular mass index, g/m$^{2.7}$	0.27 (–0.15 to 0.68)	–0.15 (–0.57 to 0.27)	.05	0.34 (–0.14 to 0.83)	–0.07 (–0.55 to 0.42)	.15	.06

- Number of CVD hospitalizations was lower in paricalcitol group

Thadhani et al. *JAMA* 2012;307:674-684

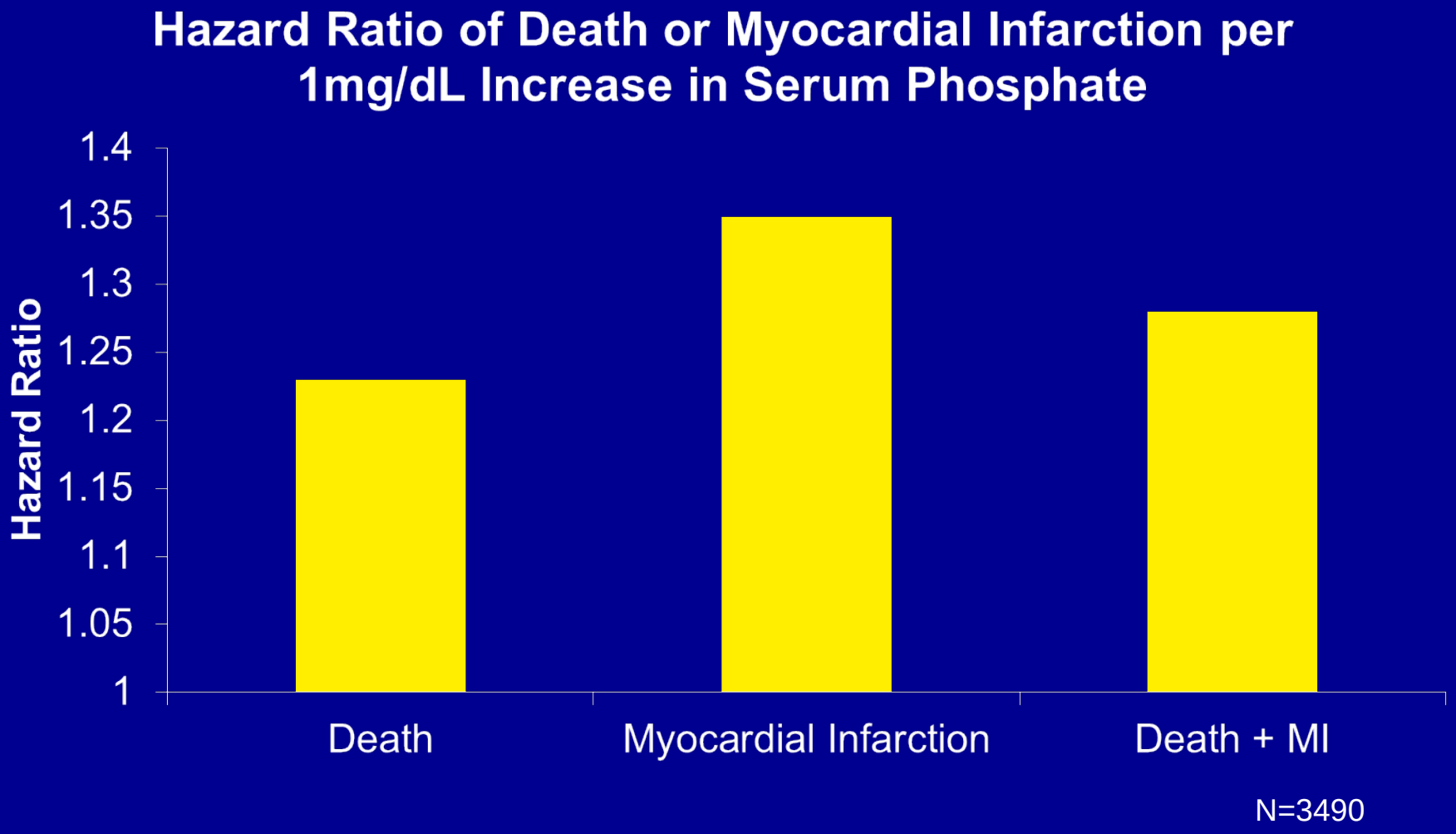
Recommendations for Vitamin D Replacement in CKD

- All CKD patients with 25-vitamin D levels < 30 ng/mL should receive repletion with nutritional vitamin D
- The use of active vitamin D analogues (e.g. calcitriol) in CKD patients not yet on dialysis is controversial
  - Currently only recommended for treating secondary hyperparathyroidism

Nontraditional Risk Factors for CVD: Serum Phosphate

- As GFR declines, serum phosphate levels increase
- Overt hyperphosphatemia is rare until the GFR is less than 20 ml/min
- Phosphate is associated with all-cause and cardiovascular mortality in patients with CKD
- Even serum phosphate within normal range is associated with adverse events in CKD

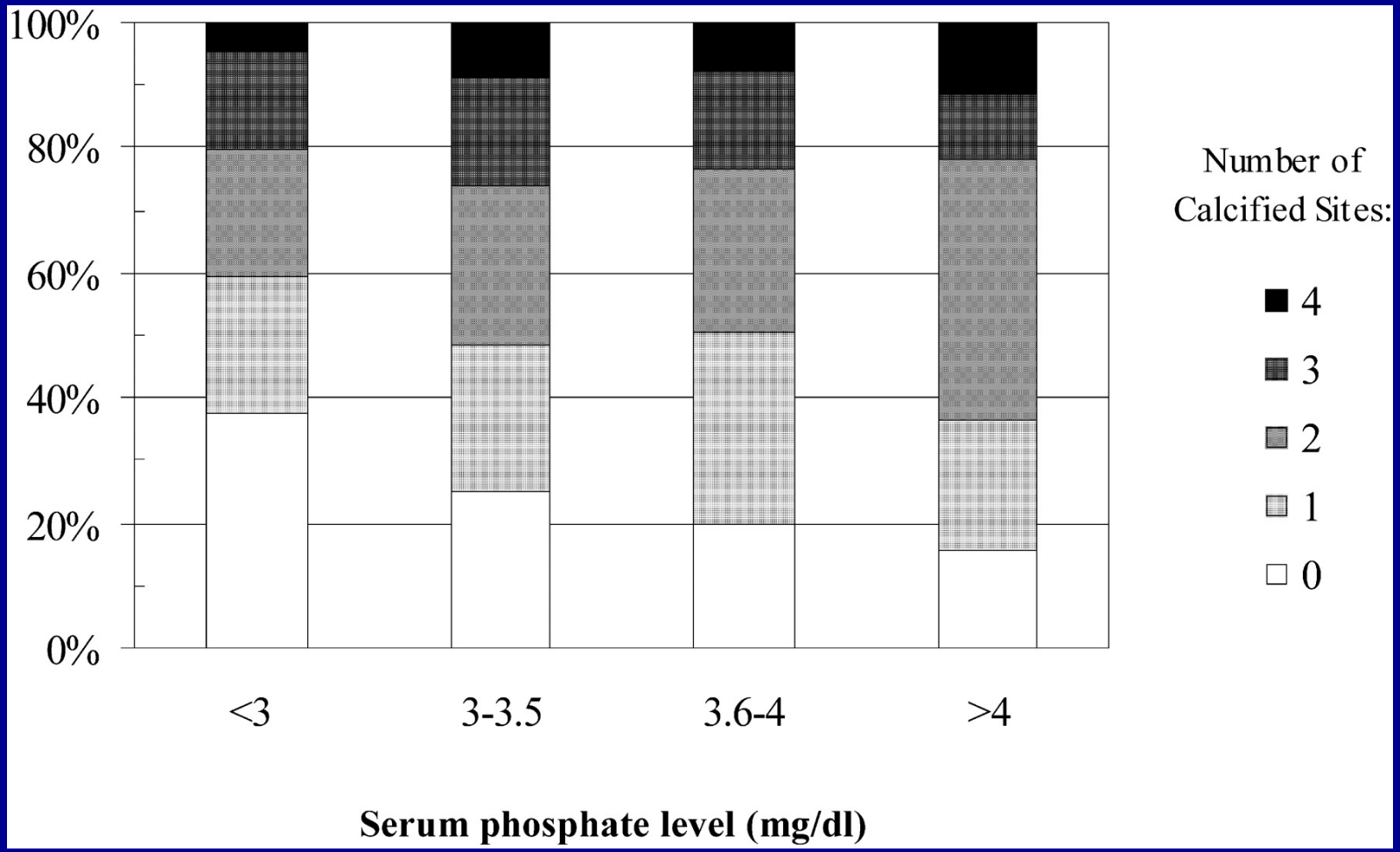
Serum Phosphate is Associated with an Increased Risk of Death and Myocardial Infarction in Patients with CKD



Kestenbaum B et al. *J Am Soc Nephrol* 2005;16:520-528

Higher Serum Phosphate is Associated with Vascular and Cardiac Valve Calcification in CKD

Proportion of calcified sites by serum phosphate group.



Adeney KL et al. *J Am Soc Nephrol* 2009;20:381-387

N=439

Treatment of Serum Phosphate and Outcomes

- Currently there is no evidence from randomized trials that lowering serum phosphate within a target range improves clinical outcomes
- All recommendations are based on observational data
- Randomized trials have been done in CKD patients but they have only compared two different binders
  - Data is conflicting
  - No placebo controlled trials

Recommendations for Treatment of Serum Phosphate in CKD

- Current recommendations are to initiate treatment once serum phosphate levels exceed normal range
- Goal is to keep serum phosphate within the normal laboratory range
  - Limit amount of dietary phosphate in diet
  - Use of phosphate binders
- Insufficient evidence to recommend one phosphate binder over another

Treating Complications of CKD

Case 4

- 47 yo female with CKD stage 4, eGFR 20 ml/min.
- Hb 9.8 g/dL
- Ferritin 50 ng/mL
- Tsat 15%

How should her anemia be treated?

1. An erythropoetin stimulating agent (ESA) should be stated

12%

2. Iron supplementation should be started

12%

3. ESA + iron supplementation should be started

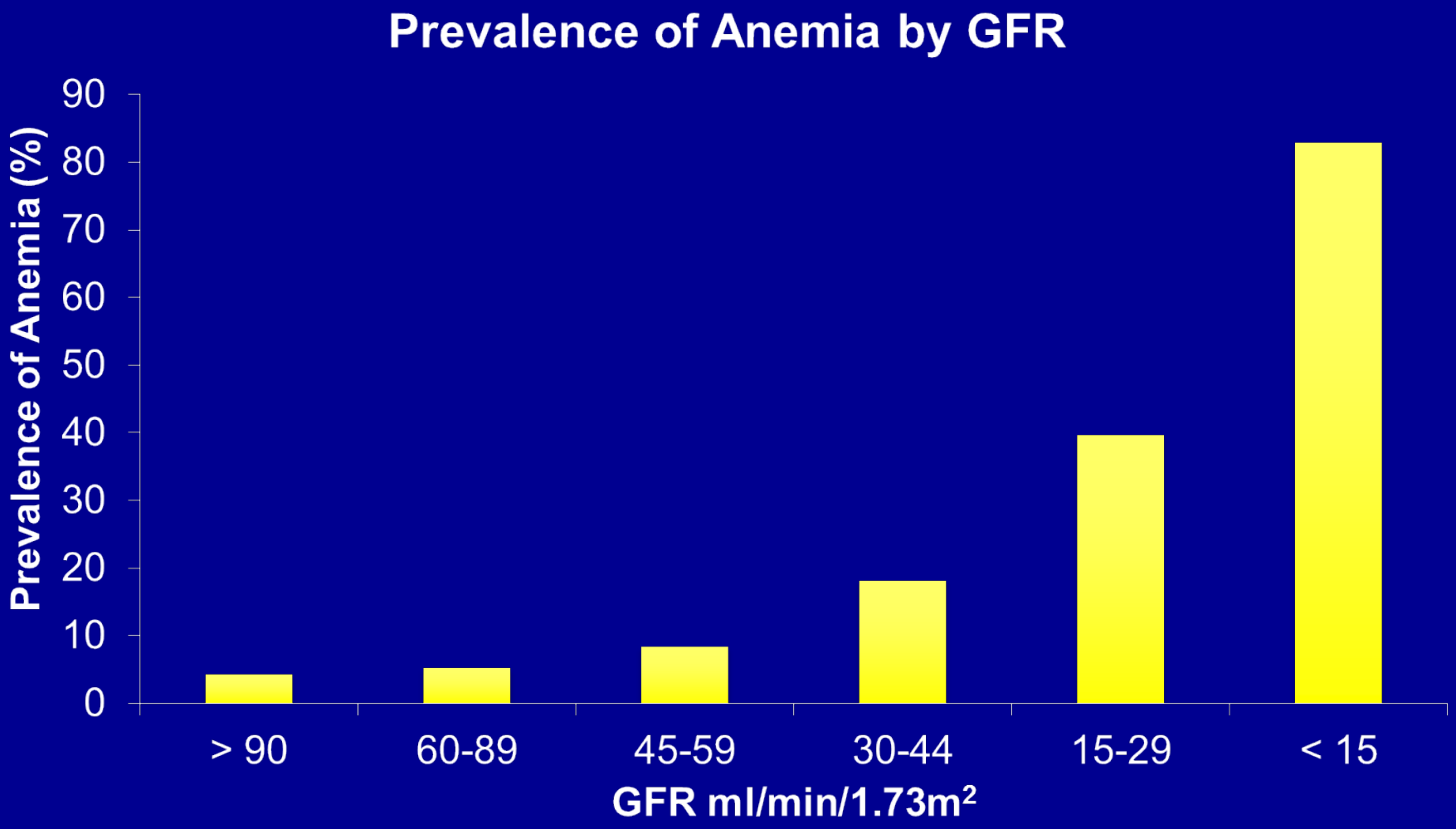
49%

4. No treatment is required

27%

11

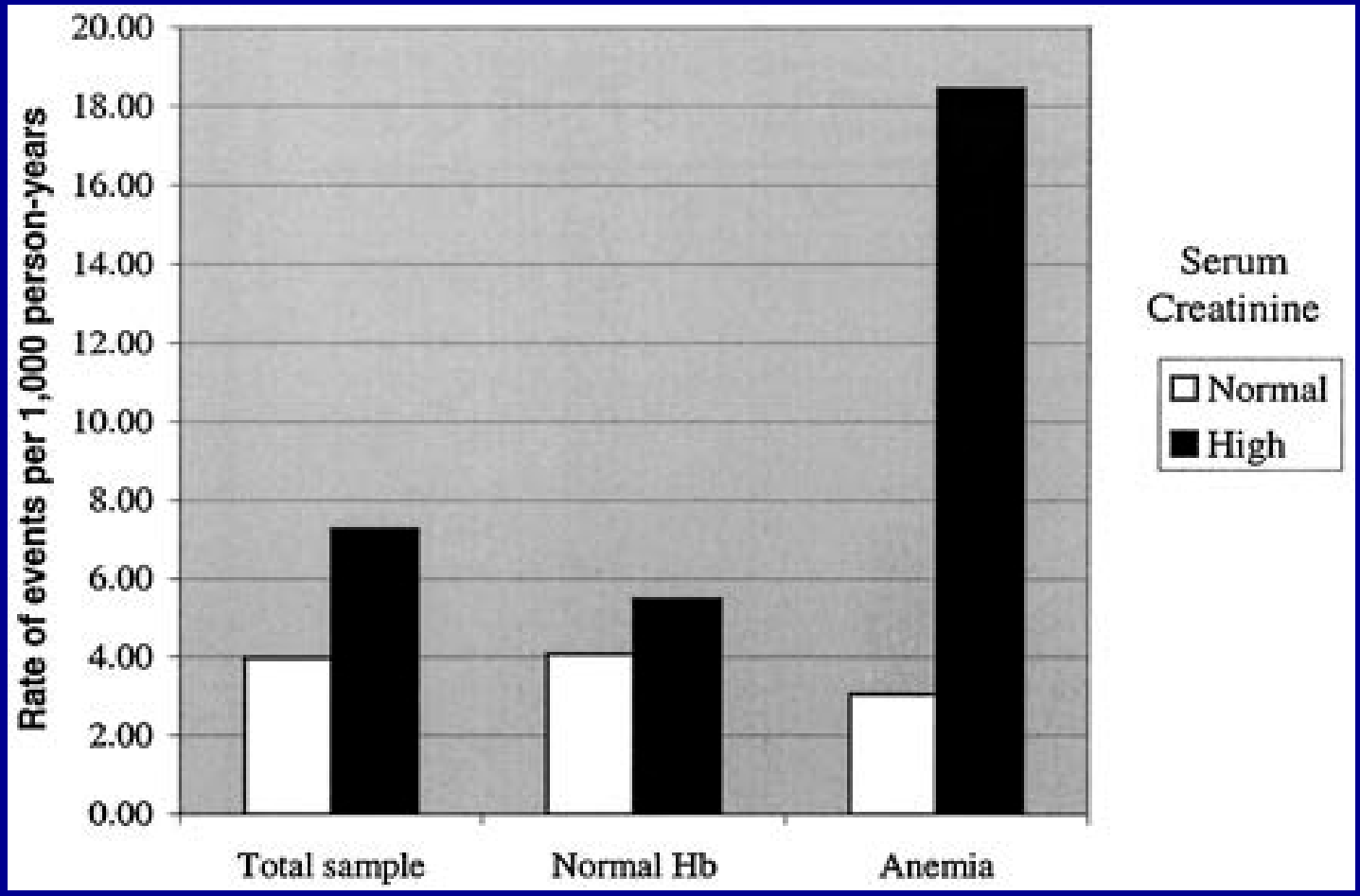
Anemia



N=94,000

Kohagura K et al. *Clin Exp Nephrol* 2009;13:614-620

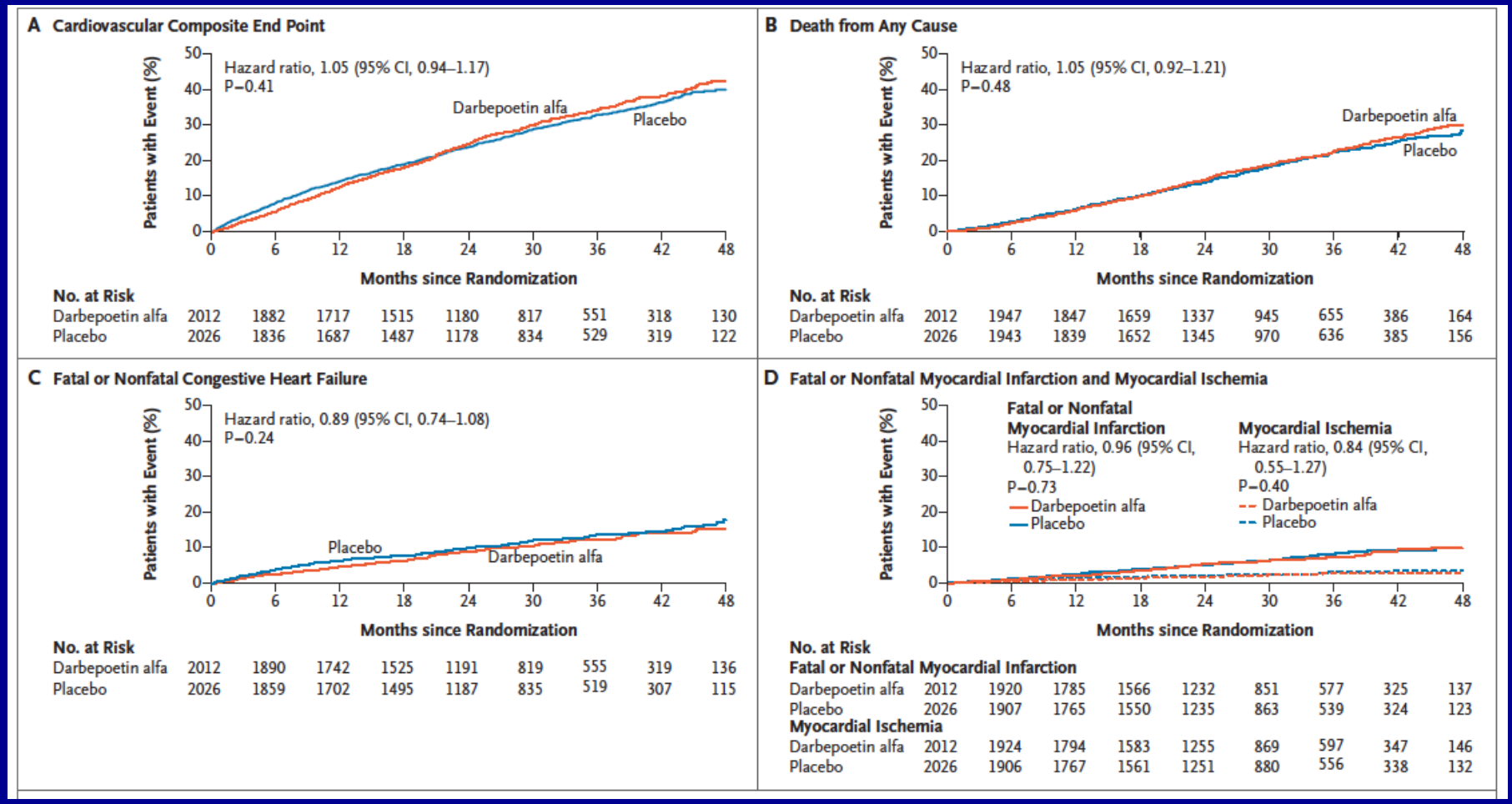
Presence of Anemia in CKD Portends a Worse Prognosis



N=13,329

Jurkovitz CT et al. *J Am Soc Nephrol* 2003; 14:2919-2925

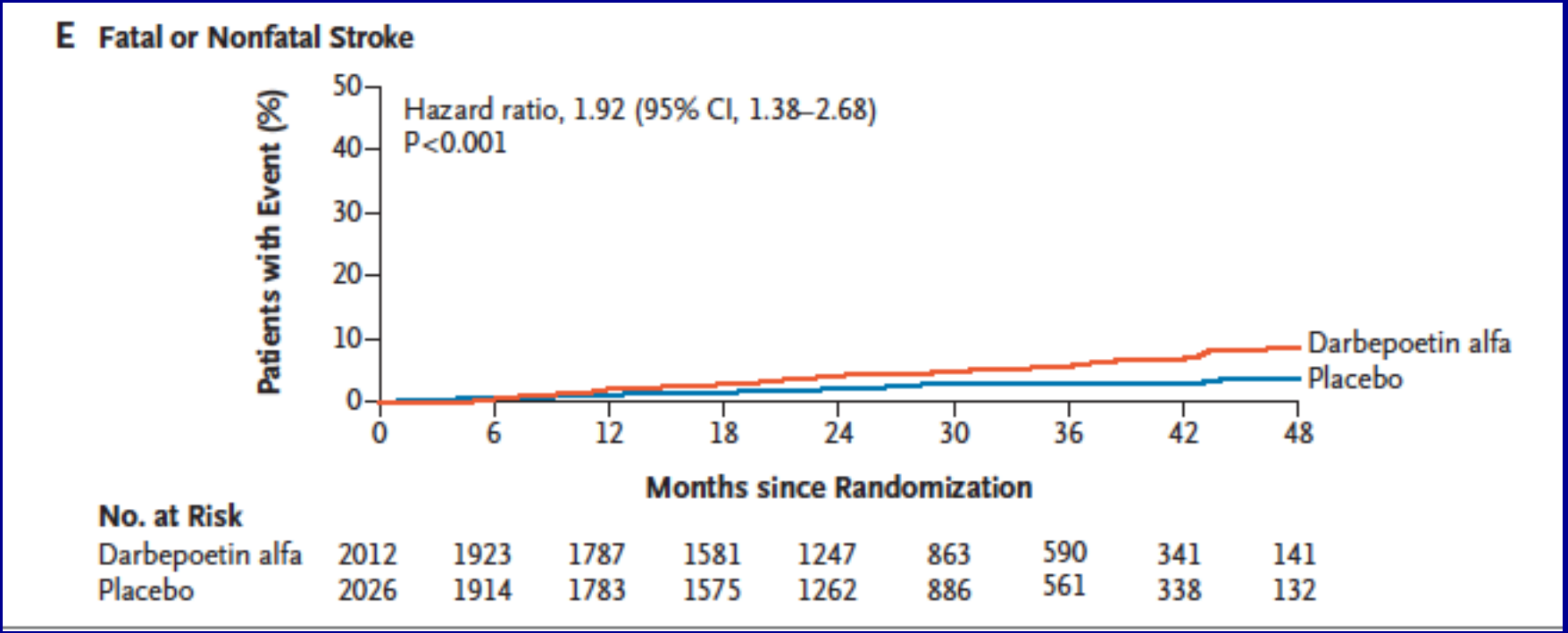
Treatment of Anemia with ESAs does not Improve Outcomes



N=4038

Pfeffer MA et al. *N Engl J Med* 2009; 361:2019-2032

Treatment of Anemia with ESAs Resulted in an Increased Risk of Stroke

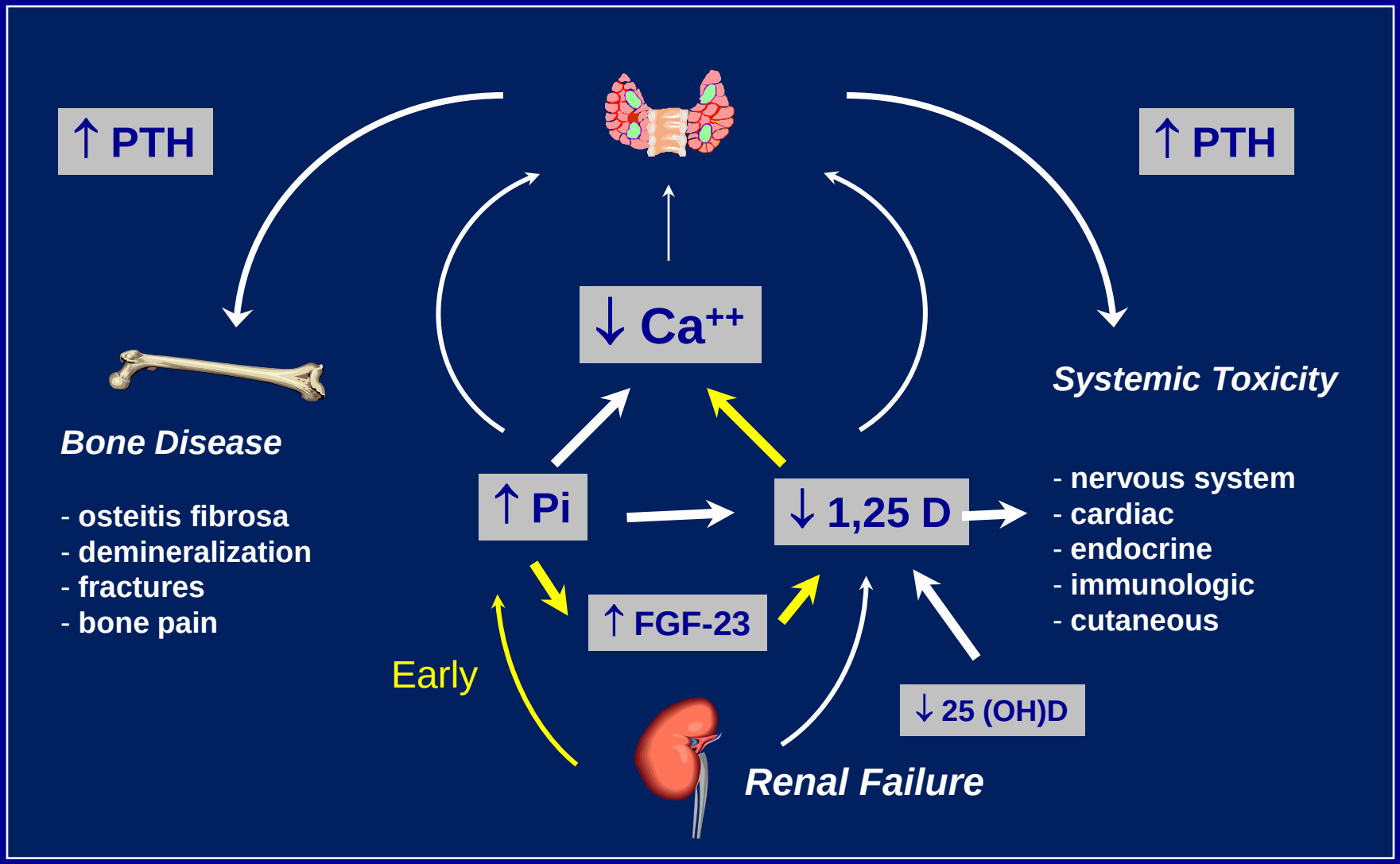


Pfeffer MA et al. *N Engl J Med* 2009; 361:2019-2032

Recommendations for Treatment of Anemia in CKD

- Goal Hemoglobin is 10-11 g/dL
- Use of ESAs is not recommended unless used as rescue therapy for Hemoglobin < 9 g/dL
- All CKD patients with anemia should be screened for iron deficiency anemia
- Check CBC and iron studies at least once a year
- Targets for iron therapy in CKD
  - Transferrin saturation > 20%
  - Serum Ferritin > 100 ng/mL

Secondary Hyperparathyroidism



Treatment of Secondary Hyperparathyroidism

- The optimal PTH levels for patients not on dialysis is not known
- Correct serum calcium, phosphorus and 25-vitamin D levels first
- If PTH remains elevated then treat with active vitamin D (e.g. calcitriol)
  - Active vitamin D can result in hyperphosphatemia and hypercalcemia
- Very reasonable to refer to nephrology for treatment of elevated PTH

Recommended Monitoring Intervals

	GFR 30-60 ml/min/1.73m^2	GFR < 30 ml/min/1.73m^2
25-hydroxyvitamin D	Q 6 months	Q 6 months
Parathyroid Hormone	Q 6 months	Q 3 months
Phosphorus	Q 6 months	Q 3 months
Calcium	Q 6 months	Q 3 months
Bicarbonate Level	Q 6 months	Q 3 months
CBC	Yearly	Q 6 months
Iron studies	Yearly	Yearly

Immunizations

- Rates of infection are 3 to 4 times that of general population
- Second leading cause of death in patients with CKD
- Most common infections are: UTI, pneumonia and sepsis
- Vaccines are underused in CKD population

Vaccine Recommendations in CKD

- Influenza for all adults unless contraindicated
- Pneumococcal vaccine (unless contraindicated in):
  - All adults with eGFR < 30 ml/min
  - Those at high risk of infection (nephrotic syndrome, diabetes, immunosuppression)
- Hepatitis B immunization:
  - All adults with eGFR <30 ml/min
  - Adults with rapid progression of CKD

Referral to Nephrology

- 1/3 of patients with CKD do not see a nephrologist before initiation of RRT
- >80% of patients who do not see a nephrologist before RRT start dialysis with a catheter
- Only 13% of patients see a dietician before initiation of RRT

Refer to Nephrology When:

- GFR < 30 ml/min/1.73m^2
- GFR decrease >30% in 4 months without explanation
- Resistant hypertension
- Persistent hyperkalemia
- Persistent proteinuria despite ACEi/ARB use
- Unclear etiology of CKD

What will the nephrologist do?

- Delay progression
- Treat complications of CKD
- Educate patients early and frequently about CKD
- Dialysis and transplant education
- Referral for permanent vascular access
- Referral for transplantation early
- Dietary education

Conclusions

- Patients with CKD have an increased risk of CVD
- Management of CKD must focus on all risk factors for CVD and kidney disease progression
- Continue ACEi/ARB as long as possible
- Treat complications of CKD
- Early referral to nephrology
- Multidisciplinary approach to management is needed