Core curriculum Nephrology

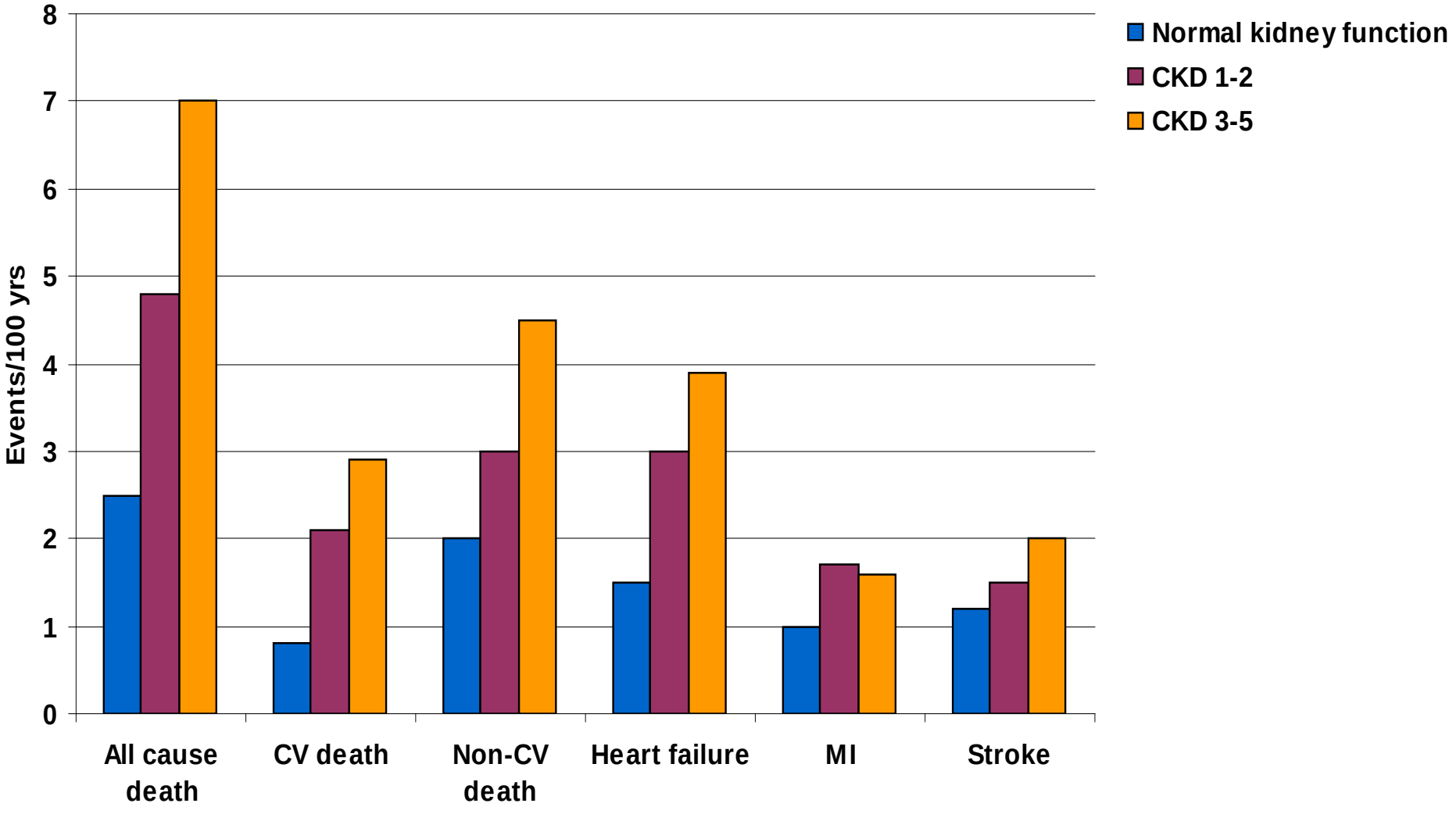
CKD Part 2

JM Krzesinski

Complications of CKD

- Mortality
- AKI
- HTA and CV disease
- CKD metabolic bone disease
- Anemia
- Metabolic acidosis
- Hyperkalemia
- Infection, toxicity of renally excreted drug
- Late complications: pericarditis, polyneuropathy, encephalopathy, skin and sexual disorders, bleeding, GI troubles, denutrition, water intoxication

Causes of death in CKD



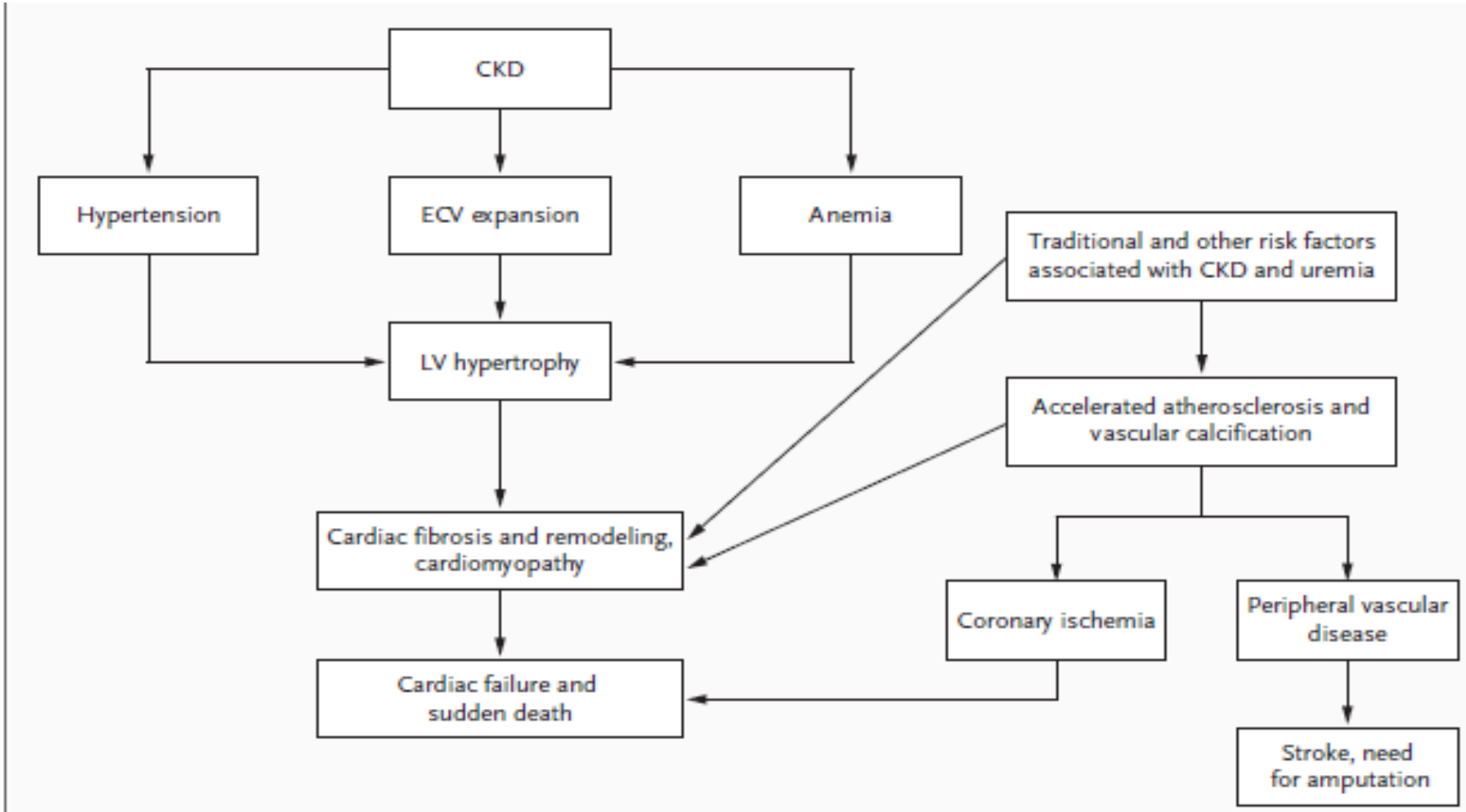


Figure 1. Cardiovascular Disease in Patients with Chronic Kidney Disease.

Cardiovascular disease in patients with advanced chronic kidney disease (CKD) is characterized by left ventricular (LV) hypertrophy, which occurs in large part as a result of hypertension, expansion of extracellular volume (ECV), and anemia. The left ventricular hypertrophy may be accompanied by left ventricular remodeling and fibrosis, and these changes, with or without coronary artery disease, may lead to cardiac failure, myocardial infarction, or sudden death.

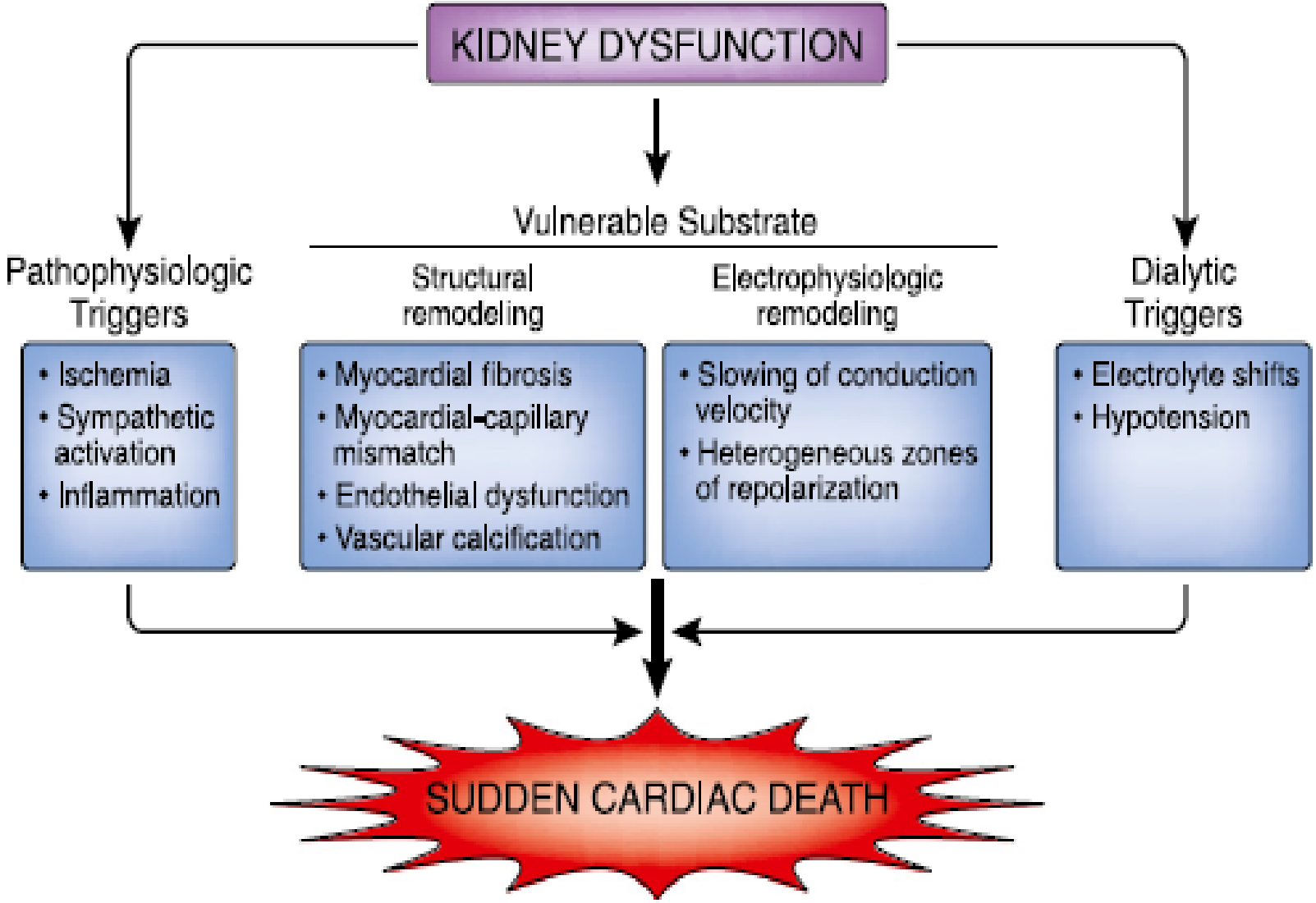


Figure 2. Overview of SCD and kidney dysfunction.

J Am Soc Nephrol **23:** 1929–1939, 2012

Atherosclerosis in CKD: differences from the general population

Drüeke, T. B. & Massy, Z. A. *Nat. Rev. Nephrol.* 6, 723–735 (2010);

Box 1 | Risk factors for atherosclerosis in CKD patients

Traditional risk factors

- Age
- Male gender
- Diabetes mellitus
- Smoking
- Hypertension
- Dyslipidemia
- Hyperhomocysteinemia
- Inflammation
- Oxidative stress

Uremia-associated risk factors

- Anemia
- Sympathetic nervous system activation
- Enhanced oxidative stress and inflammation
- Protein glycation and carbamylation
- Endothelial dysfunction
- Coagulation disorders
- Disturbances of mineral metabolism
- Uremic toxins
- Protein-energy wasting

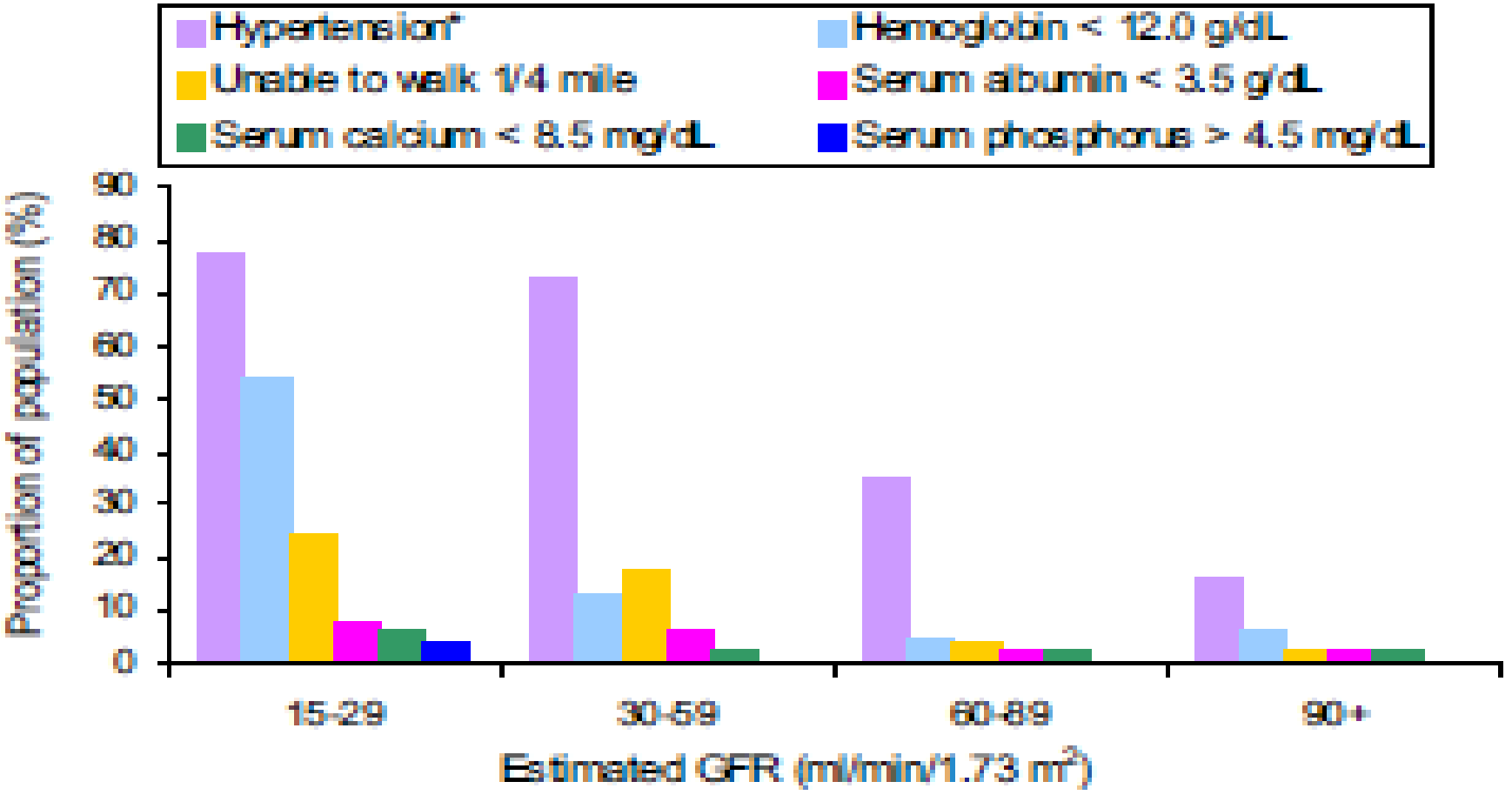
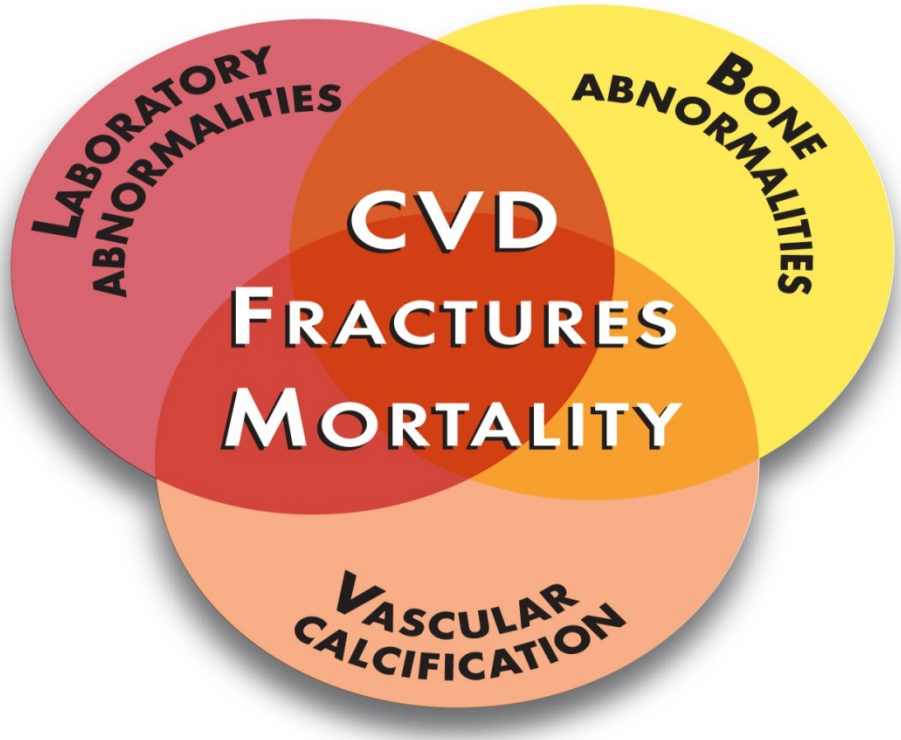


Figure 2. Estimated prevalence of complications related to chronic kidney disease (CKD) according to estimated glomerular filtration rate (GFR) in the general population.

Am J Kidney Dis 53(S3):S4-S16. © 2009

Chronic Kidney Disease—Mineral and Bone Disorder



CKD-MBD

KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

VOLUME 76 | SUPPLEMENT 113 | AUGUST 2009

Supplement to Kidney International

Table 1 | KDIGO classification of CKD–MBD and renal osteodystrophy

Definition of CKD-MBD

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
- Vascular or other soft-tissue calcification.

Definition of renal osteodystrophy

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder of CKD–MBD that is quantifiable by histomorphometry of bone biopsy.

CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.
Adapted with permission from Moe *et al.*[2]

Kidney International (2009) **76** (Suppl 113), S3–S8

Osteitis fibrosa cystica, adynamic bone disease, osteomalacia, mixed uremic osteodystrophy → Bone pain, fractures most often at the dialysis stage

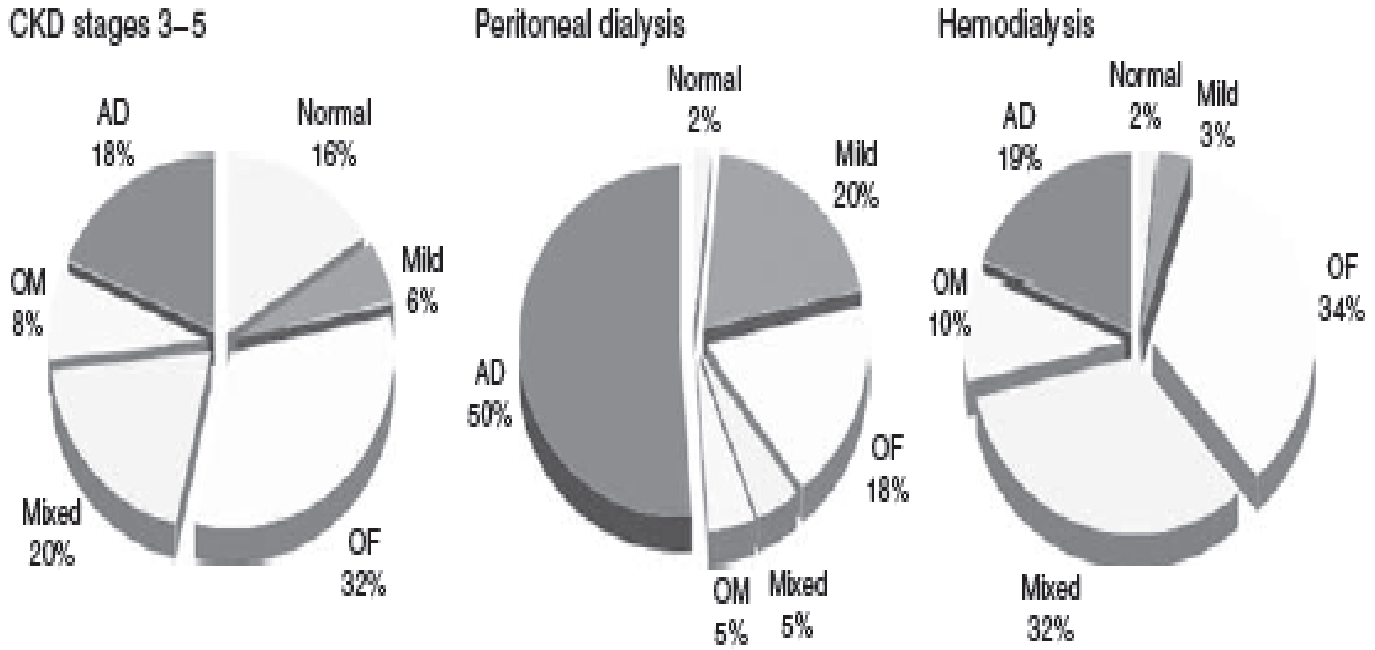
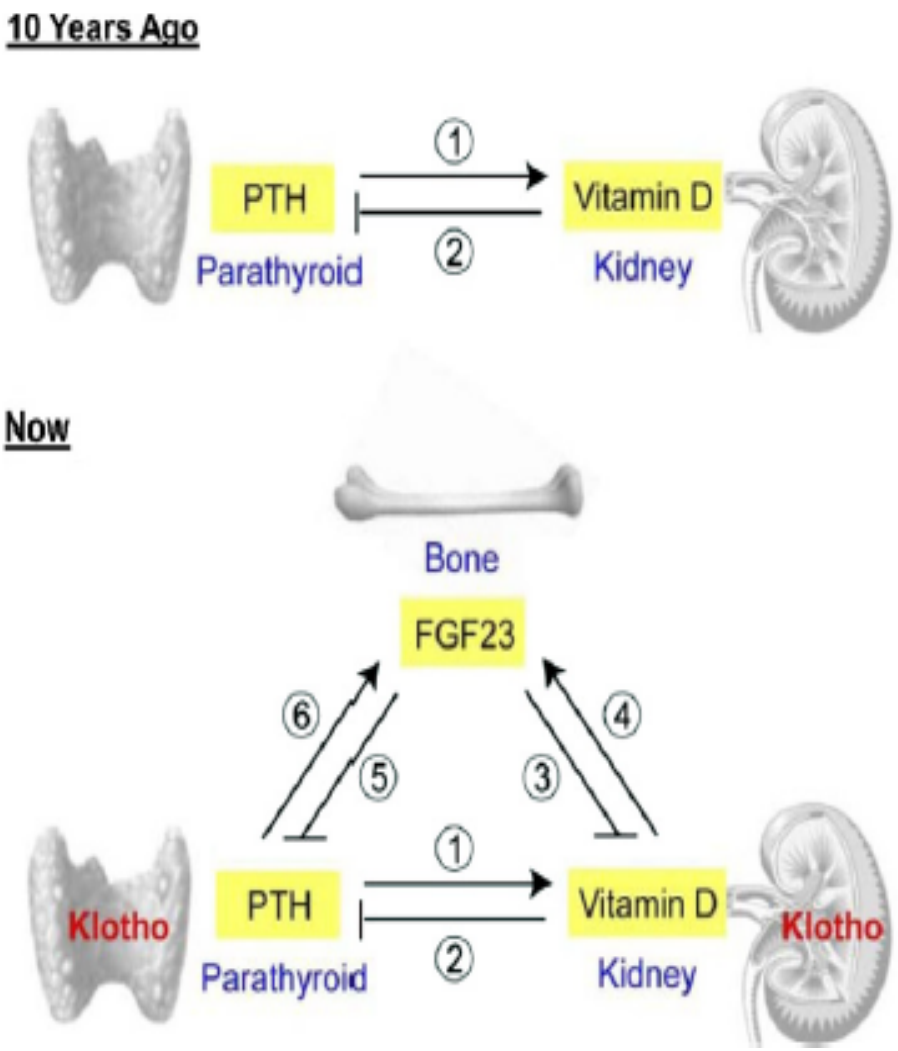


Figure 7 | Prevalence of types of bone disease as determined by bone biopsy in patients with CKD–MBD. Bone formation (turnover) is high in those with osteitis fibrosa and mild disease, and low in those with osteomalacia and adynamic bone disease. Mineralization is abnormal in those with osteomalacia and mixed disease. AD, adynamic bone; OF, osteitis fibrosa; OM, osteomalacia.

CKD-MBD

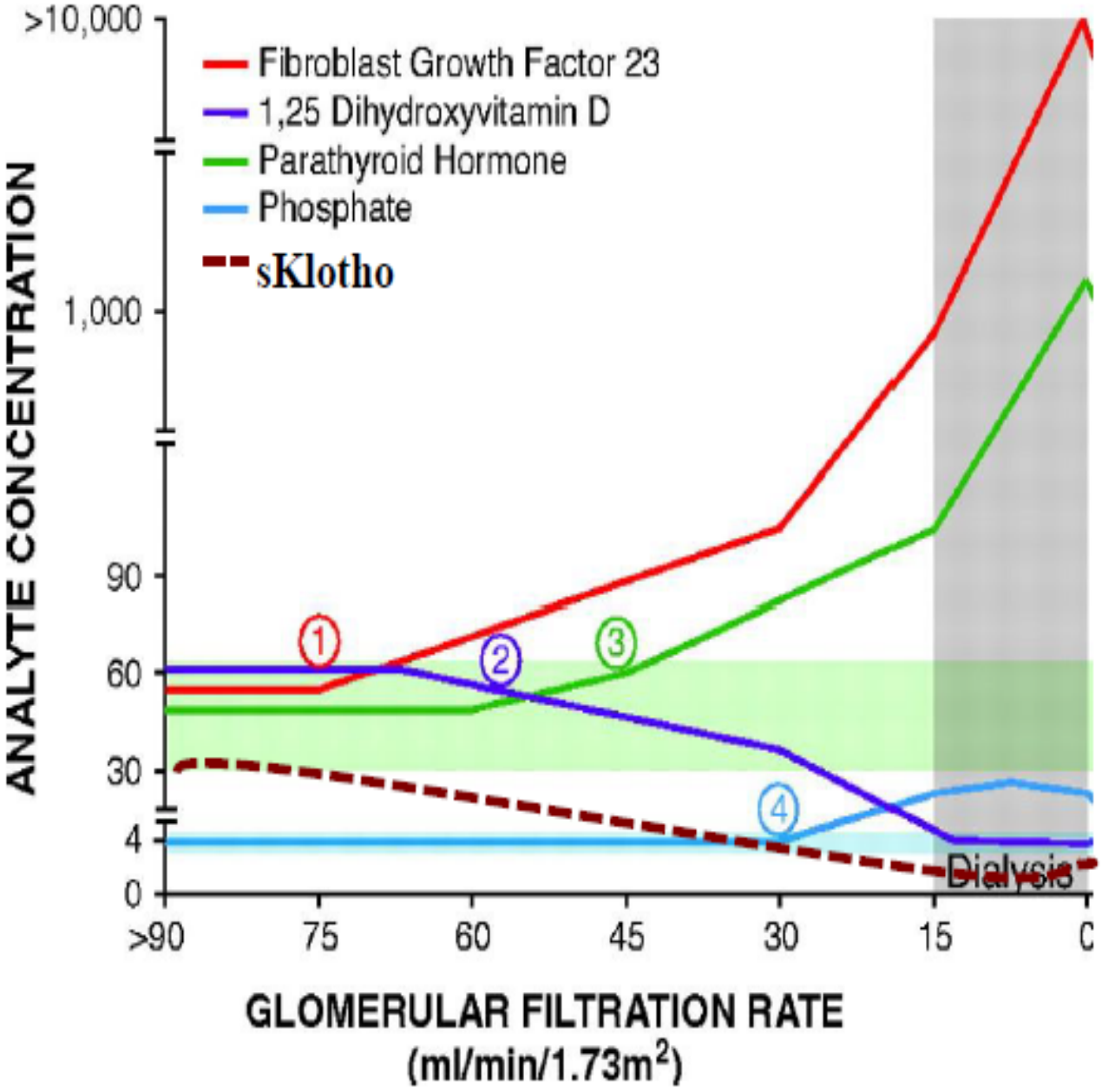
AJKD

Tangri and Levey



Am J Kidney Dis. 2012;

Relation with mortality, inflammation, LVH



sKlotho determinants:

-Gender ♀>♂

-eGFR

-Age: old < young

(not PTH, FGF23)

Adapted from Wolf M. J Am Soc Nephrol 2010;21:1427-1435

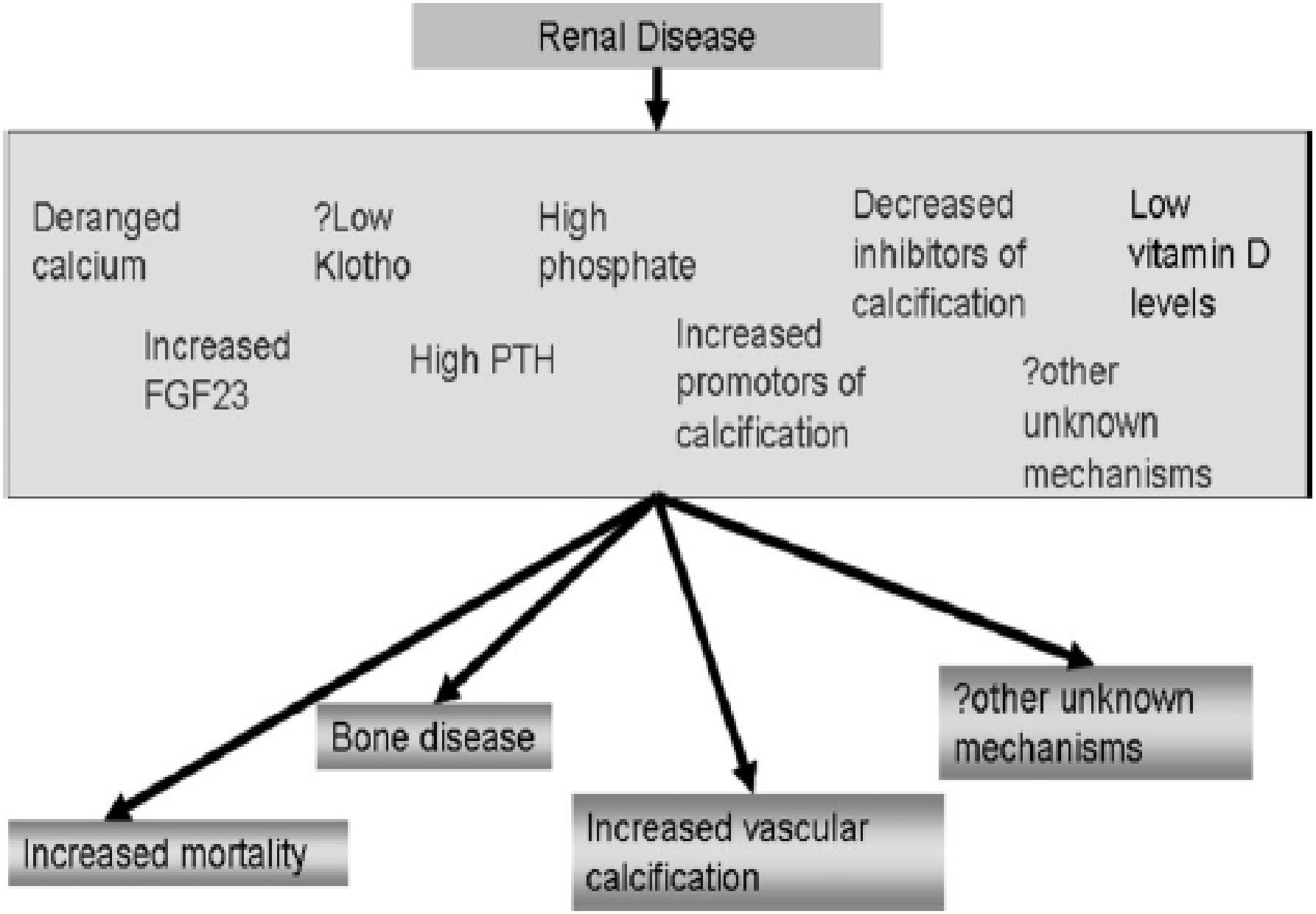


Fig. 1. Potential factors important in outcome of renal patients.

http://www.kidney-international.org

Early chronic kidney disease–mineral bone disorder stimulates vascular calcification

Yifu Fang[1], Charles Ginsberg[1], Toshifumi Sugatani[1], Marie-Claude Monier-Faugere[2], Hartmut Malluche[2] and Keith A. Hruska[1]

Kidney International advance online publication, 24 July 2013;

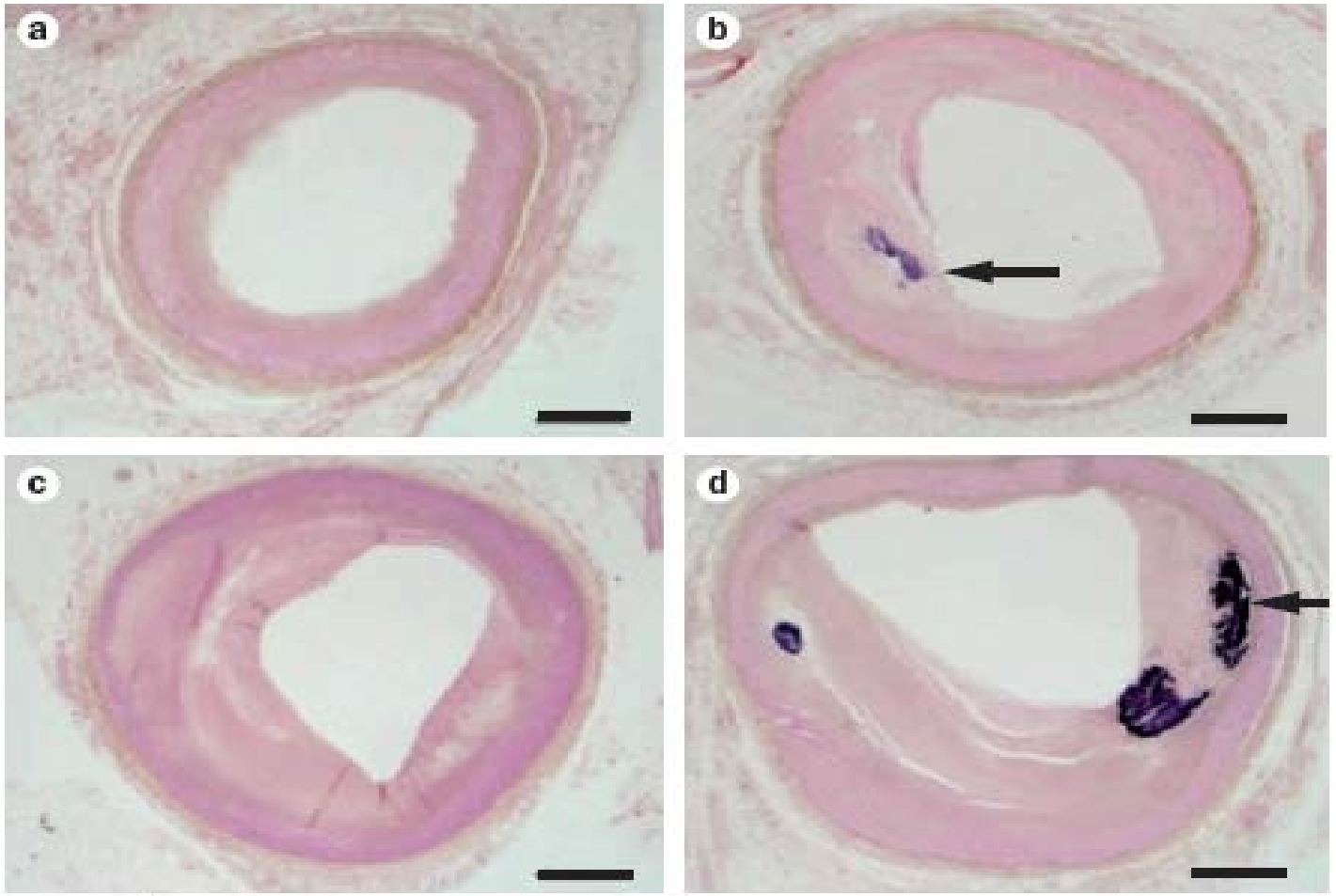


Figure 3 | Coronary atherosclerosis in patients with various degrees of chronic kidney disease (CKD). Typical light microscopy images of arteries from a postmortem study[88] of patients with CKD: **a** | stages 1–2 CKD; **b** | stage 3a CKD; **c** | stage 3b CKD; and **d** | stages 4–5 CKD. Stenosis rates of respective arteries were 36.8%, 42.3%, 54.2%, and 58.9%. The dark purple areas (indicated by arrows) in panels b and d show focal calcifications at arterial plaque sites. All sections were stained with hematoxylin and eosin. Scale bars, 1.0 mm. Permission obtained from Elsevier © Nakano, T. *et al. Am. J. Kidney Dis.* 55, 21–30 (2010).

In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).

We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD–MBD (not graded).

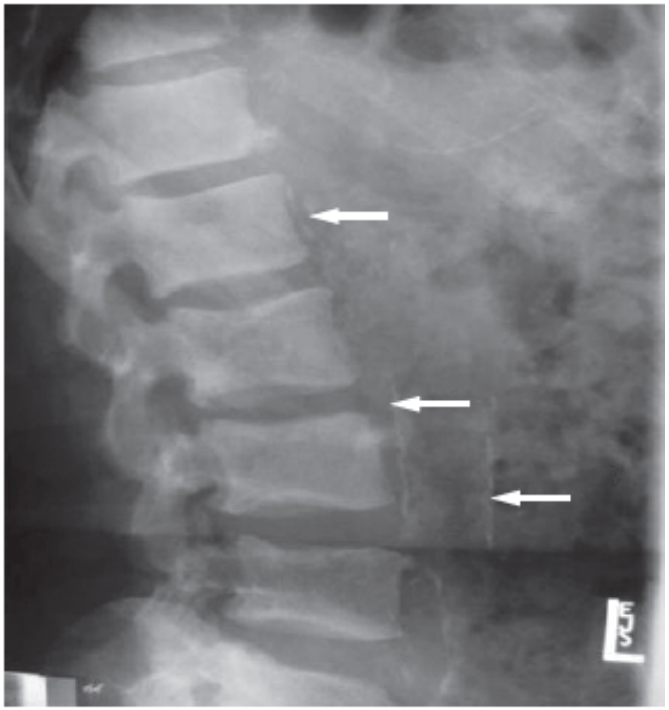
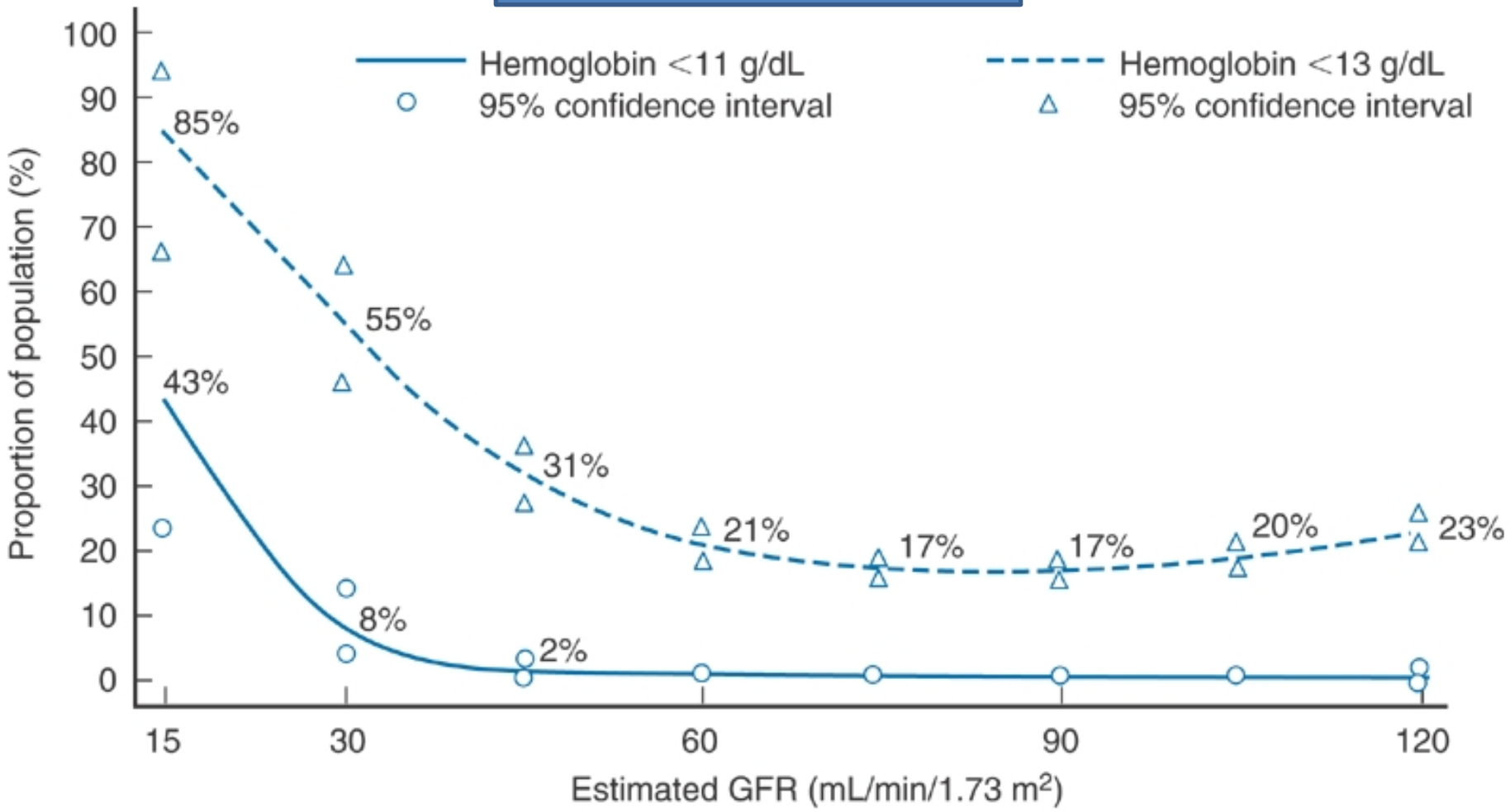


Figure 3 | Lateral lumbar X-ray from a patient undergoing hemodialysis. Linear calcifications (arrows) delineate the wall of the abdominal aorta in front of lumbar vertebrae 1–4.

Kidney International (2009) **76** (Suppl 113), S3–S8

ANEMIA



(Adapted from National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 39(2)[suppl 1]:1-246, 2002.)

ANEMIA

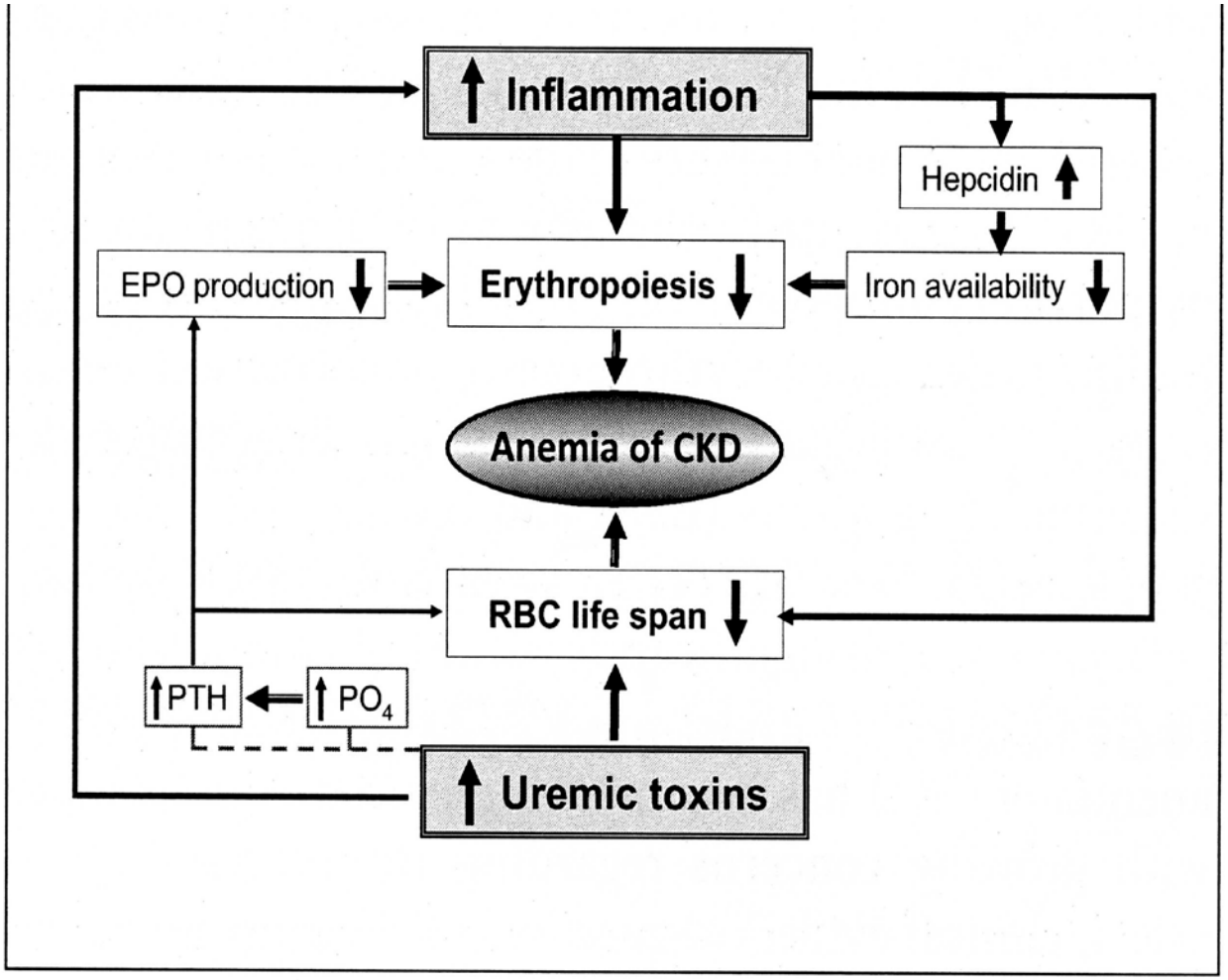


Fig. 1. Uremic toxicity and inflammation both exacerbate anemia of CKD, affecting bone marrow erythropoiesis and erythrocyte survival. Dialysis therapies that curb the effects of both uremic toxins and inflammatory mediators enable anemia correction.

Bowry S. and Gatti E., *Blood Purification*, 2011, **32**, 210-219.

Table 1. Detrimental effects of anemia in patients with chronic kidney disease

Decreased	Increased
Exercise capacity	Depression
Skeletal muscle oxidative capacity	Sleep/awake pattern
Coagulation	Cardiac output
Immune response	Angina
Cognitive function	Left ventricular hypertrophy
Sexual function	Cardiac failure
Appetite/nutrition	Myopathy
Quality of life	Morbidity
Growth in children	Mortality

J Lopez Gomez et al., *Kidney Int*, 2002, **61**, suppl 80, S39-S43.

Table 1 | Potentially correctable versus non-correctable factors involved in the anemia of CKD, in addition to erythropoietin deficiency (reproduced from KDIGO Guideline for Anemia, *KI Suppl* 2012)

Easily correctable	Potentially correctable	Impossible to correct
Absolute iron deficiency	Infection/ inflammation	Hemoglobinopathies
Vitamin B_{12}/folate deficiency	Underdialysis	Bone marrow disorders
Hypothyroidism	Hemolysis	
ACEi	Bleeding	
Non-adherence	Hyperparathyroidism	
	PRCA	
	Malignancy	
	Malnutrition	

Investigation of anemia

1.3: In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (*Not Graded*):

- Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count
- Absolute reticulocyte count
- Serum ferritin level
- Serum transferrin saturation (TSAT)
- Serum vitamin B12 and folate levels

Kidney International (2012) **82**, 952–960

Hydro-ionic abnormalities

- Hyperkalemia
- Metabolic acidosis

Table 2. Potential Adverse Effects of Metabolic Acidosis in Patients With CKD

Effect	Comments
Muscle wasting	Seen with even mild metabolic acidosis; important factor in causing muscle wasting in patients with CKD
Reduced albumin synthesis	Acidosis is one of many factors contributing to hypoalbuminemia in patients with CKD
Bone disease	Acidosis contributes to the genesis of bone disease by diverse mechanisms; contributory rather than primary mechanism in producing bone disease
Impaired insulin sensitivity	Effect unclear given the impact of changes in insulin metabolism with renal failure; could induce metabolic changes similar to those seen in syndrome X*
β_2-Microglobulin accumulation	Found with studies of acetate *v* bicarbonate dialysis in dialysis patients; no studies of patients with CKD not on dialysis therapy
Exacerbation of renal failure	Data for and against role of acidosis in progression of renal failure
Impaired thyroid metabolism	May contribute to abnormalities in basal metabolic rate
Stunted growth in children	Reversed in part by correction of acidosis
Cardiac disease	Role in the development of cardiac disease is theoretical, not proven
Increased inflammation	Conflicting evidence for and against the role of acidosis in dialysis patients

NOTE. Potential adverse effects of metabolic acidosis from studies of healthy individuals and patients with CKD.

*Syndrome X is characterized by dyslipidemia, hyperinsulinemia, hypertension, abdominal obesity, glucose intolerance, and insulin resistance.

TABLE 131-5 -- UREMIA RESULTS FROM THE DYSFUNCTION OF MANY ORGANS SUGGESTING GENERALIZED TOXICITY

Affected System	Cause or Mechanism	Clinical Syndrome
Systemic symptoms	Anemia, inflammation	Fatigue, lassitude
Skin	Hyperparathyroidism, calcium-phosphate deposition	Rash, pruritus, metastatic calcification
Cardiovascular disease	Hypertension, anemia, homocysteinemia, vascular calcification	Atherosclerosis, heart failure, stroke
Serositis	Unknown	Pericardial or pleural pain and fluid, peritoneal fluid
Gastrointestinal	Unknown	Anorexia, nausea, vomiting, diarrhea, gastrointestinal tract bleeding
Immune system	Leukocyte dysfunction, depressed cellular immunity	Infections
Endocrine	Hypothalamic-pituitary axis dysfunction	Amenorrhea, menorrhagia, impotence, oligospermia, hyperprolactinemia
Neurologic	Unknown	Neuromuscular excitability, cognitive dysfunction progressing to coma, peripheral neuropathy (restless leg syndrome or sensory deficits)

Vascular Risk Factors and Cognitive Impairment in Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort (CRIC) Study

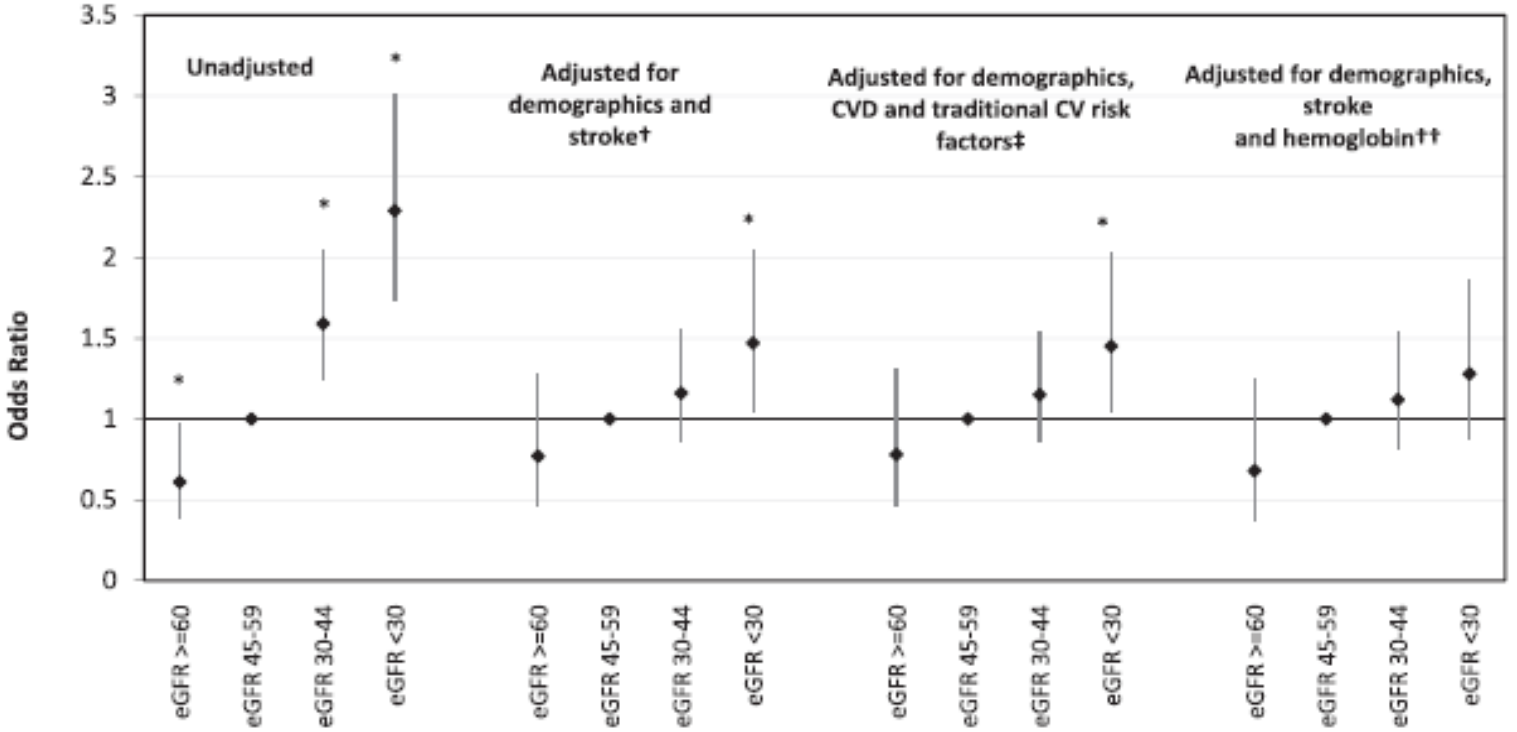
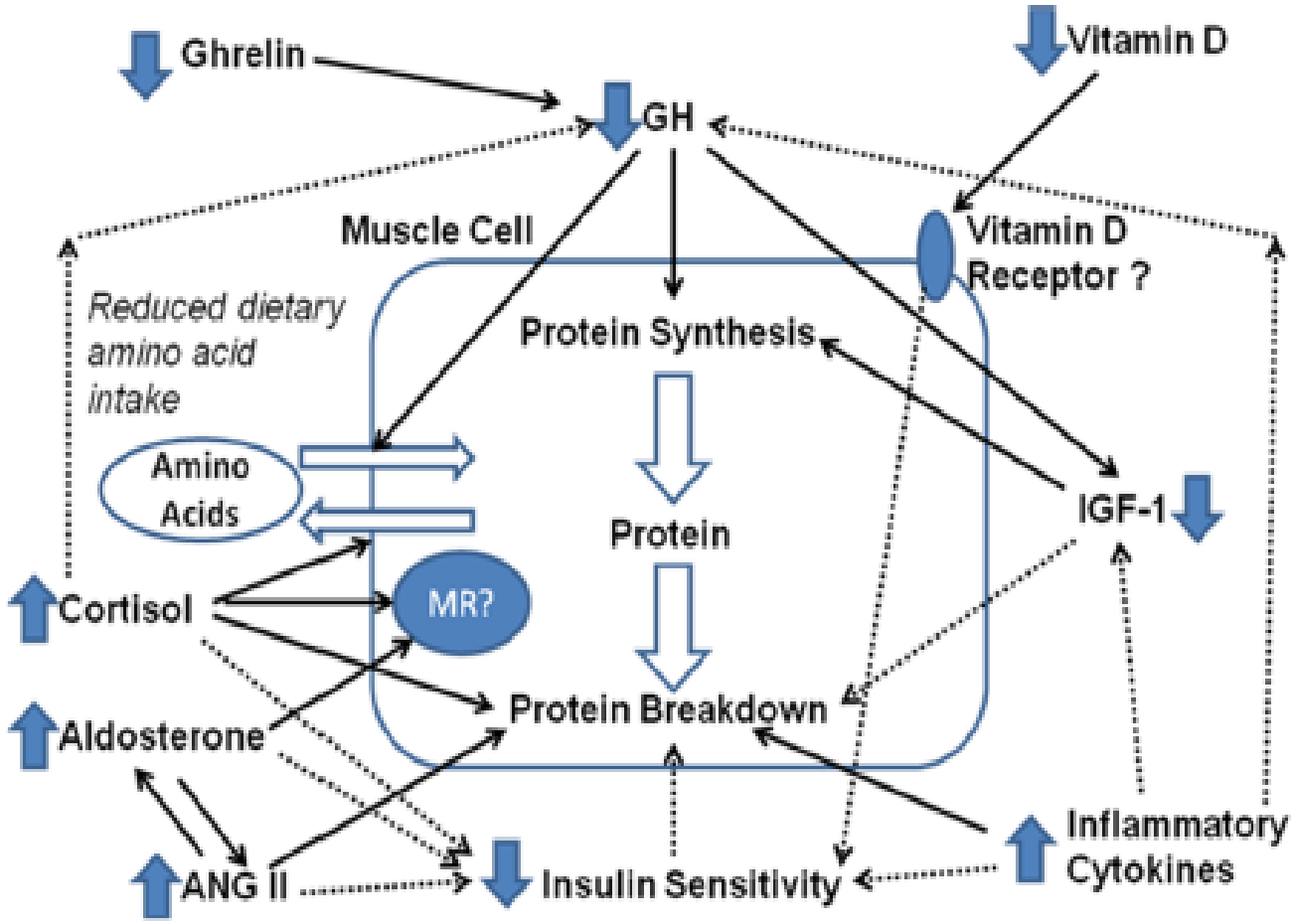


Figure 2. | Association of estimated GFR with cognitive impairment in unadjusted and adjusted models among 3591 CRIC

Conclusions The prevalence of cognitive impairment was higher among those with lower eGFR, independent of traditional vascular risk factors. This association may be explained in part by anemia.

Clin J Am Soc Nephrol 6: 248–256, 2011. doi: 10.2215/CJN.02660310



Key: ⬆ Arrows indicate relative levels and activities in human CKD; ⟶ arrows indicate stimulatory effects; ⇢ dashed arrows indicate inhibitory effects in normal state. ANG II, angiotensin-II; GH, growth hormone; IGF-1, insulin-like growth factor-I; MR, mineralcorticoid receptor.

Figure 2 Depiction of some of the different pathways that may potentially interact in muscle tissue in CKD affecting protein turnover.

Follow up of the patients

Guide to Frequency of Monitoring (in months) by GFR and Albuminuria Category

GFR Categories (mL/min/ 1.73m²)				Albuminuria Categories (mg/g or mg/mmol)		
				A1	A2	A3
				Normal to increased	Moderately increased	Severely increased
				10-29 mg/g (<3 mg/mmol)	30-299 mg/g (3-29 mg/mmol)	>300 mg/g (>30 mg/mmol)
	G1	high and optimal	≥90	12 if CKD	12	6
	G2	Mild	60-89	12 if CKD	12	6
	G3a	mild-moderate	45-59	12	6	4
	G3b	moderate-severe	30-44	6	4	4
	G4	Severe	15-29	4	4	≤3
	G5	kidney failure	<15	≤3	≤3	≤3

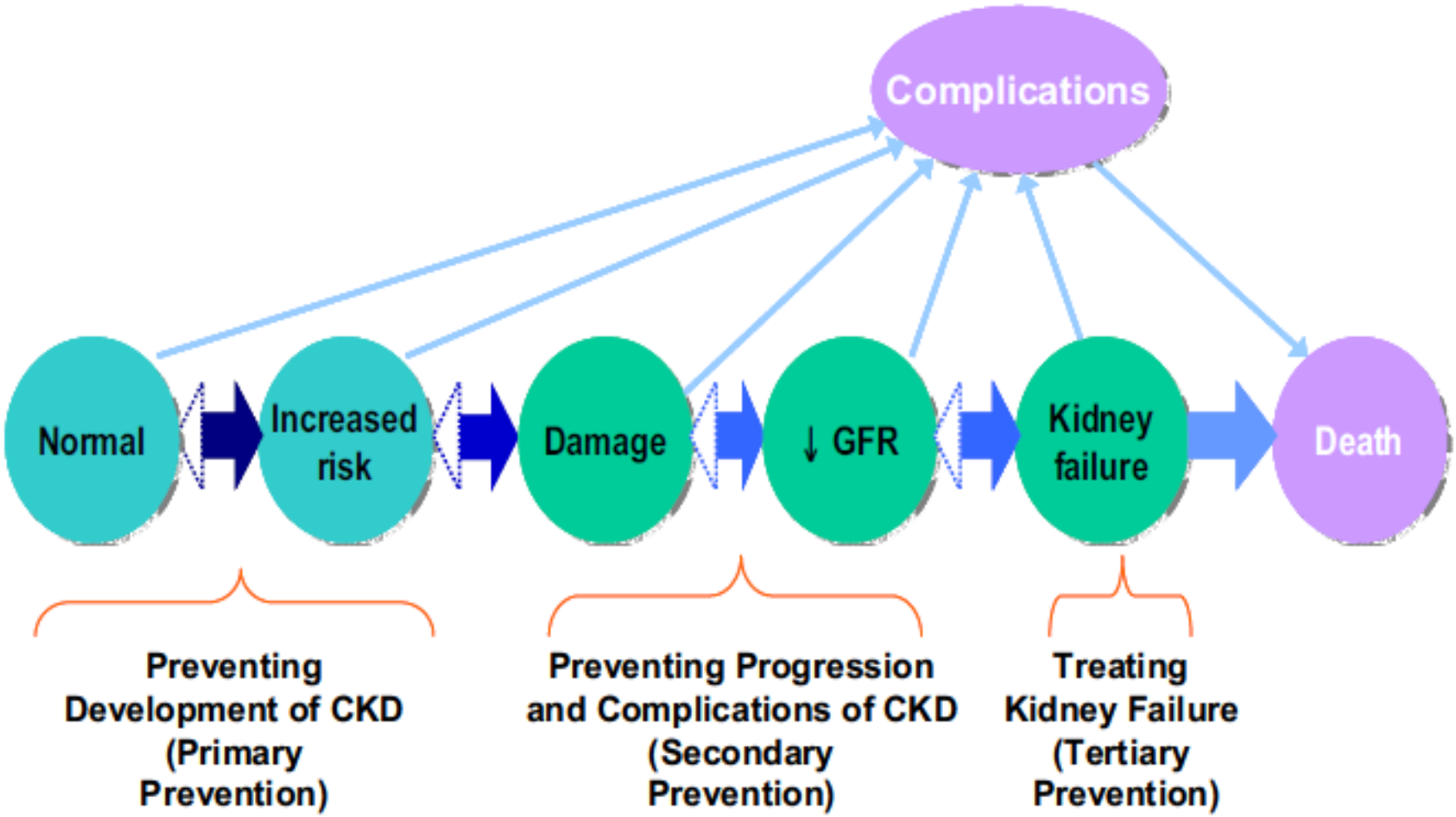


Figure 1. Conceptual model of chronic kidney disease (CKD). Overall, this diagram presents the continuum of the development, progression, and complications of CKD. Green circles, stages of CKD; aqua circles, potential antecedents of CKD; lavender circles, consequences of CKD; thick arrows between ellipses, risk factors associated with the development and progression and remission of CKD. "Complications" refers to all complications of CKD and its treatment, including complications of decreased glomerular filtration rate (GFR) and cardiovascular disease. Stages of prevention are shown along the continuum. Modified and reprinted with permission from the National Kidney Foundation.[1]

Am J Kidney Dis 53(S3):S4-S16. © *2009*

Take home messages

Levin, A. & Stevens, P. E. *Nat. Rev. Nephrol.* 7, 446–457 (2011):

- Chronic kidney disease (CKD) is prevalent worldwide and occurs in conjunction with cardiovascular disease and diabetes
- CKD should be defined in terms of both estimated glomerular filtration rates and albuminuria, as each is an independent predictor of prognosis with respect to renal and cardiovascular outcomes
- Early detection of CKD allows implementation of treatments and strategies that can influence both progression of kidney disease and cardiovascular health
- Detection and identification of CKD facilitates avoidance of drugs and situations that may cause worsening of kidney function and acute kidney injury
- CKD is recognized to have widely varying outcomes, which makes predicting the prognosis of individual patients difficult
- Improved prediction of renal and other risks in patients with CKD is a focus for research