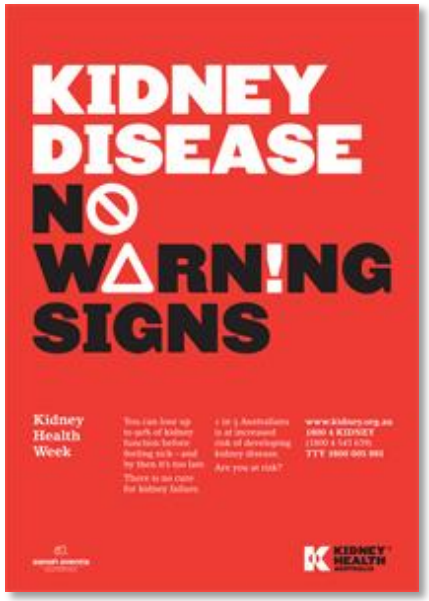
Chronic Kidney Disease

Χ. Ν. Σκαλιώτη
Επίκουρη Καθηγήτρια Νεφρολογίας - Μεταμόσχευσης Νεφρού
Κλινική Νεφρολογίας και Μεταμόσχευσης Νεφρού,
Ιατρική Σχολή ΕΚΠΑ, ΓΝΑ «Λαϊκό»

Κατ' επιλογή μάθημα «Νεφρολογία»

13/5/2025

Chronic Kidney Disease



Definition of Chronic Kidney Disease

Abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health

Markers of kidney damage (1 or more)	Albuminuria (ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Persistent hematuria Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min per 1.73 m^2 (GFR categories G3a–G5)

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease
KDIGO 2024

CKD Staging

CKD is staged based on the **C**ause (systemic disease or isolated kidney disease), **G**FR levels, and **A**lbuminuria.

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Albuminuria categories in CKD

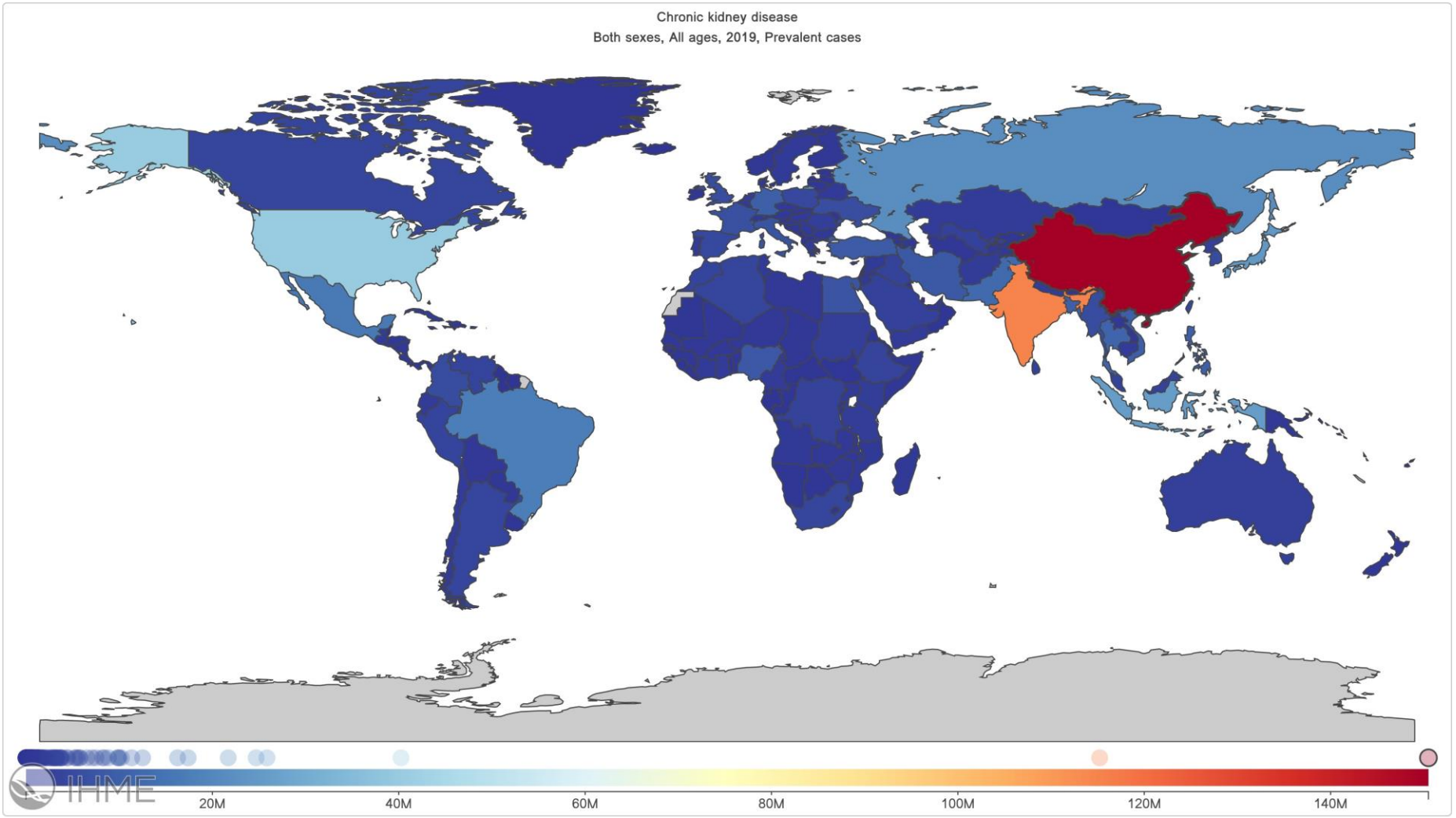
Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

Why is CKD important?

697.3 million people globally were affected by CKD in 2019



9.2% of the world's population

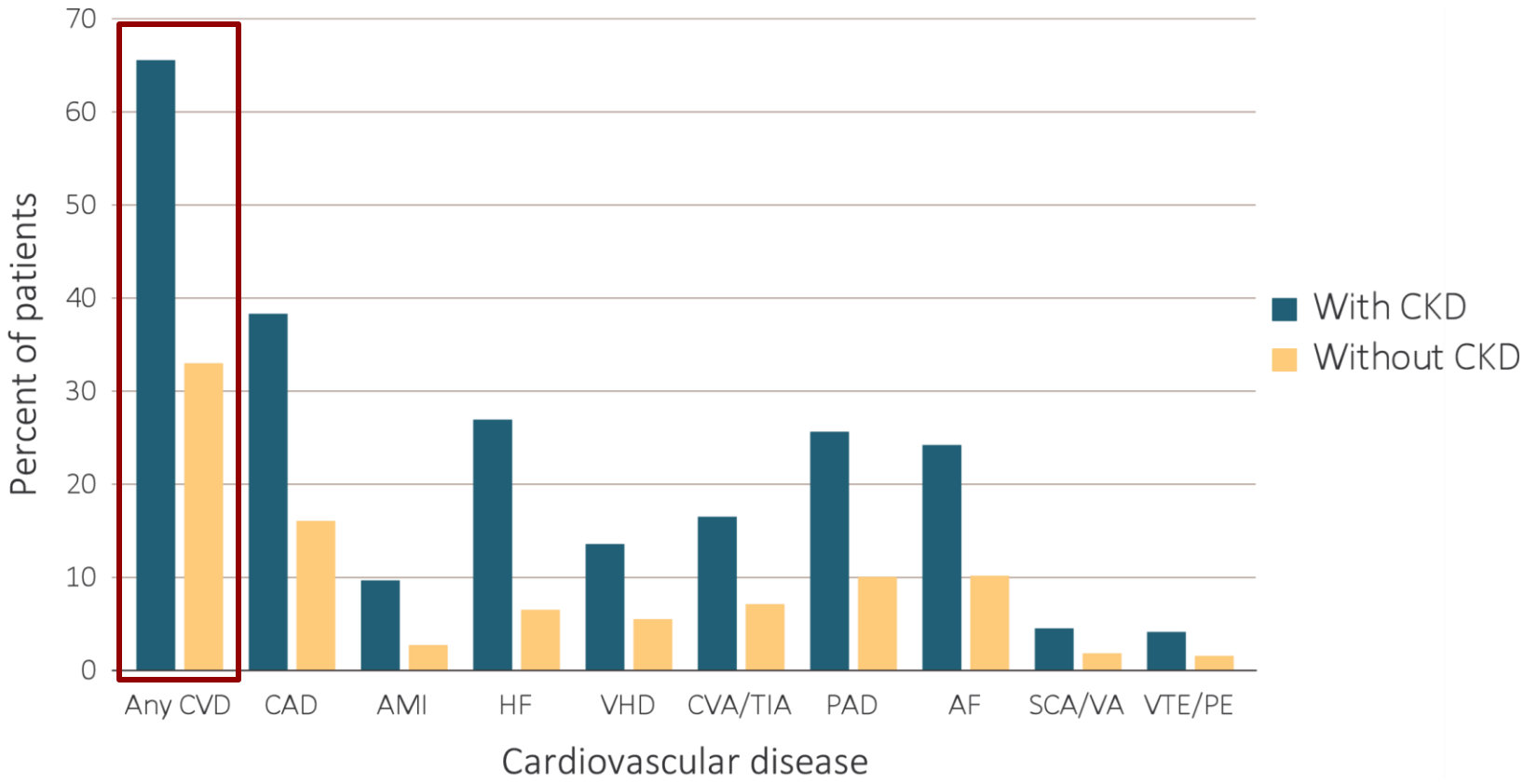
CKD Prevalence

Prevalence (thousands) 2017 counts	
Chronic kidney disease	697 509·5 (649 209·4 to 752 050·7)
Diabetes mellitus	475 995·8 (436 590·5 to 522 782·8)
Chronic obstructive pulmonary disease	299 398·2 (269 025·2 to 330 073·8)
Depressive disorders	264 455·6 (246 380·1 to 286 312·0)

CKD prevalence is higher than the preavalence of common non-communicable diseases

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, Lancet 2018

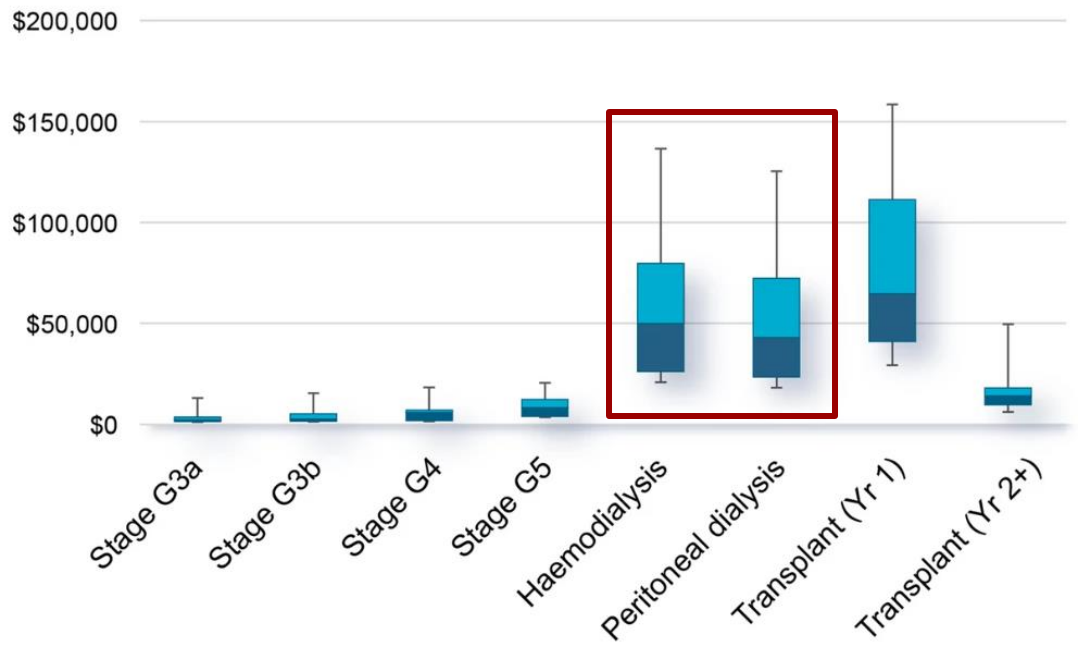
CKD and Cardiovascular Disease
USA, 2016



Data Source: Special analyses, Medicare 5% sample. Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; VHD, valvular heart disease; VTE/PE, venous thromboembolism and pulmonary embolism

United States Renal Data System, *Annual Data Report 2018*

Globally, CKD carries a **significant economic burden**,
which increases substantially with increasing disease severity.



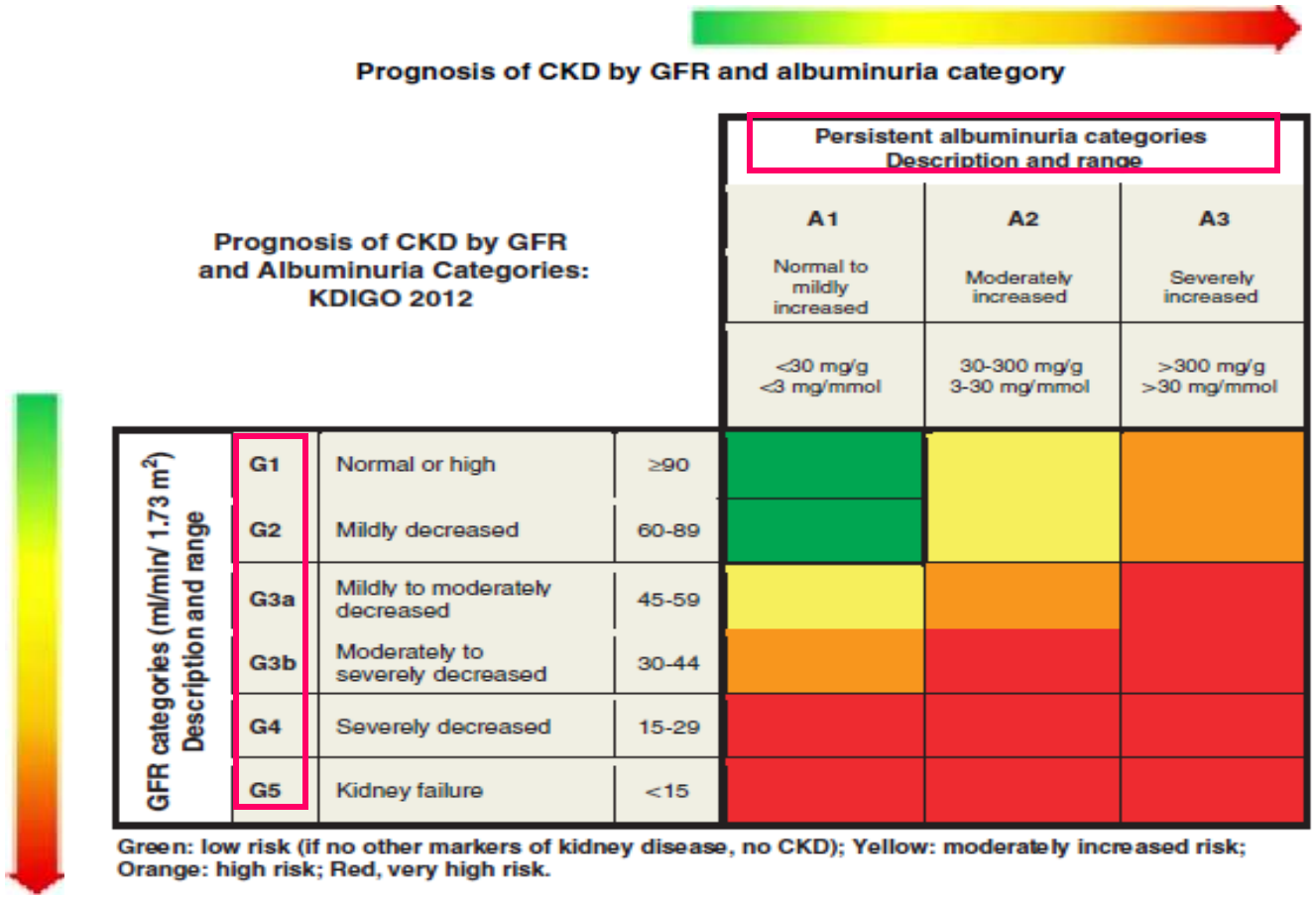
Jha V et al, Adv Ther 2023

AIM

1. **Identify** high-risk patients
2. **Assess** the degree and cause of kidney damage
3. **Prevent** progression of potentially reversible kidney damage
4. **Properly manage** the symptoms of progressive kidney function loss

Training of all healthcare professionals

Risk Stratification



Green: Low risk

Yellow: Moderately increased risk

Orange: High risk

Red: Very high risk

Case Example

- 27-year-old patient, BMI: 34
- Feb 2016: Nephrotic syndrome
- Idiopathic Membranous Glomerulopathy confirmed histologically
- Cr: 0.6 mg/dl, eGFR: 126 ml/min/m^2

CKD Stage G1, A3

High risk for progression to ESKD

estimated GFR (eGFR)

CKD-EPI Equation 2021
(Age, Sex, Creatinine)

$$eGFR = GFR = 142 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012 \text{ [if female]}$$

where,

SCr = mg/dL, K = 0.7 (females) or 0.9 (males),

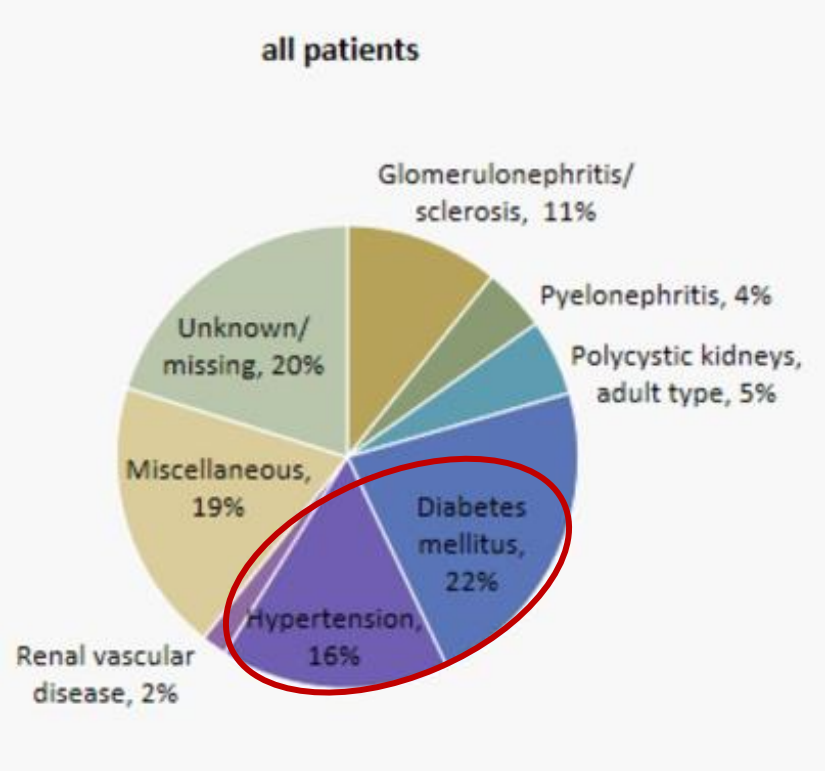
α = -0.241 (females) or -0.302 (males),

min = indicates the minimum of SCr /K or 1 and

max = indicates the maximum of SCr /K or 1

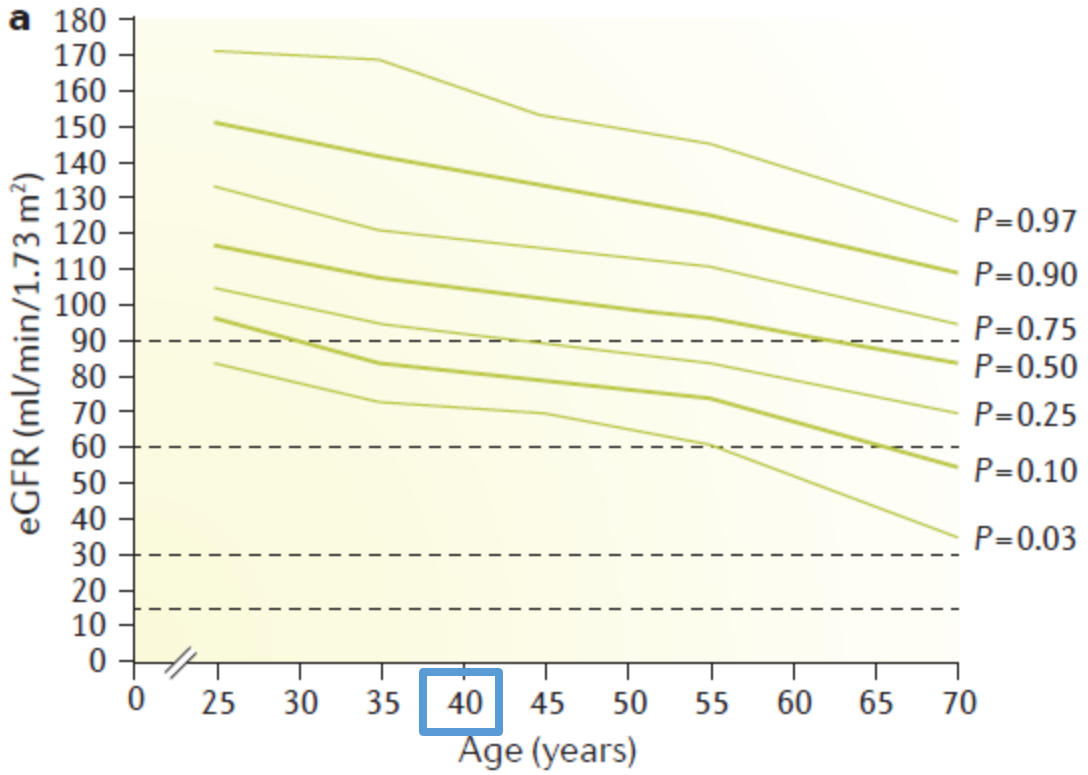
Reliable for patients with GFR >60 ml/min

Primary Causes of ESKD in Europe



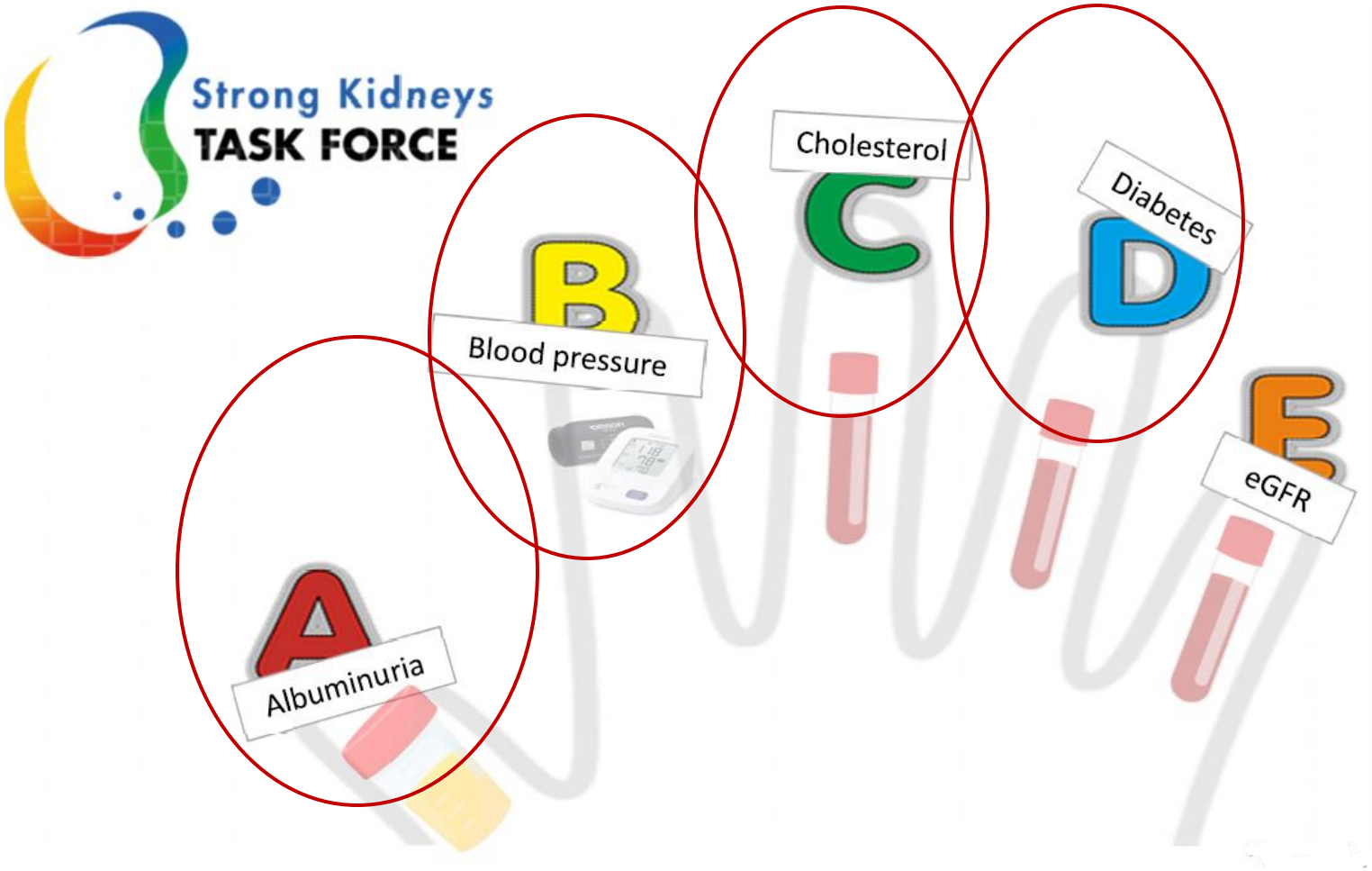
European Renal Association- European Dialysis and Transplantation Association, ERA-EDTA Registry 2019

GFR decreases by 0.8-1 ml/min/year after the age of 40



Benghanem G et al, *Kidn Int 2016*

Risk Factors for CKD



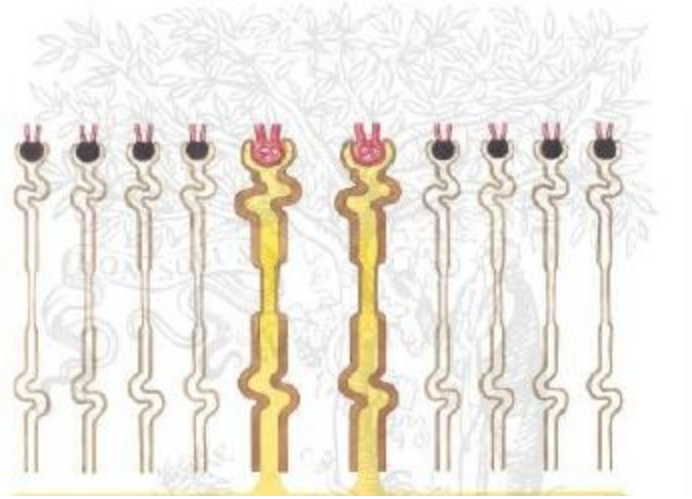
- **A**lbuminouria
- **B**lood pressure
- **C**holesterol
- **D**iabetes Mellitus
- Medications, Episodes of AKI
- Socioeconimic parameters

Ferro CJ et al, Strong Kidneys Taskforce, Nephrol Dial Transplantation 2025

Chronic Kidney Disease
Pathophysiological mechanism

Bricker NS, 1960 -1970

"The intact nephron hypothesis"

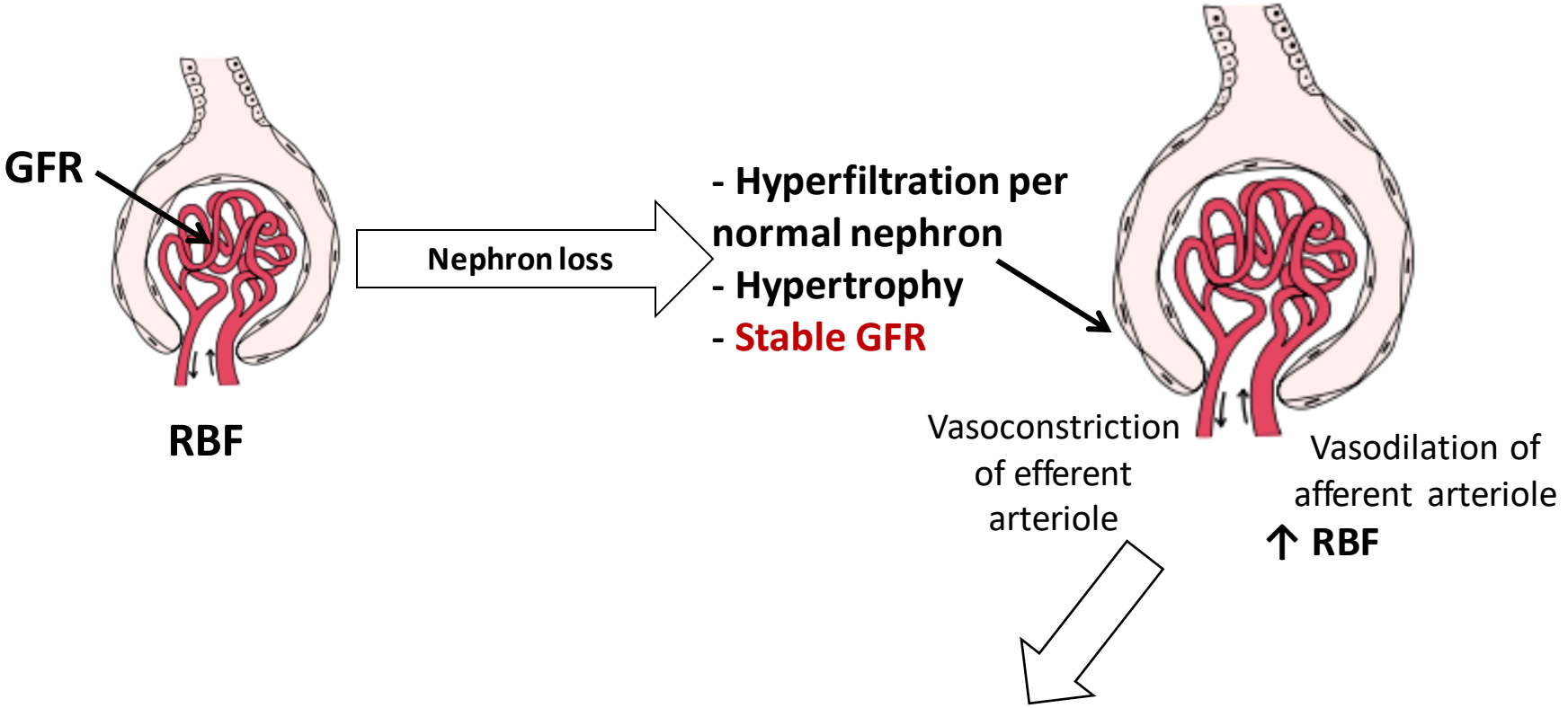


...As the number of functioning nephrons decreases each remaining nephron must perform a greater fraction of total renal excretion. The functional capacity of the nephron in the affected kidney is largely independent of the specific form of kidney disease.

The reduction in the number of nephrons is clearly responsible for many of the abnormalities that develop in the patient.

The remaining nephrons allow the patient to survive...

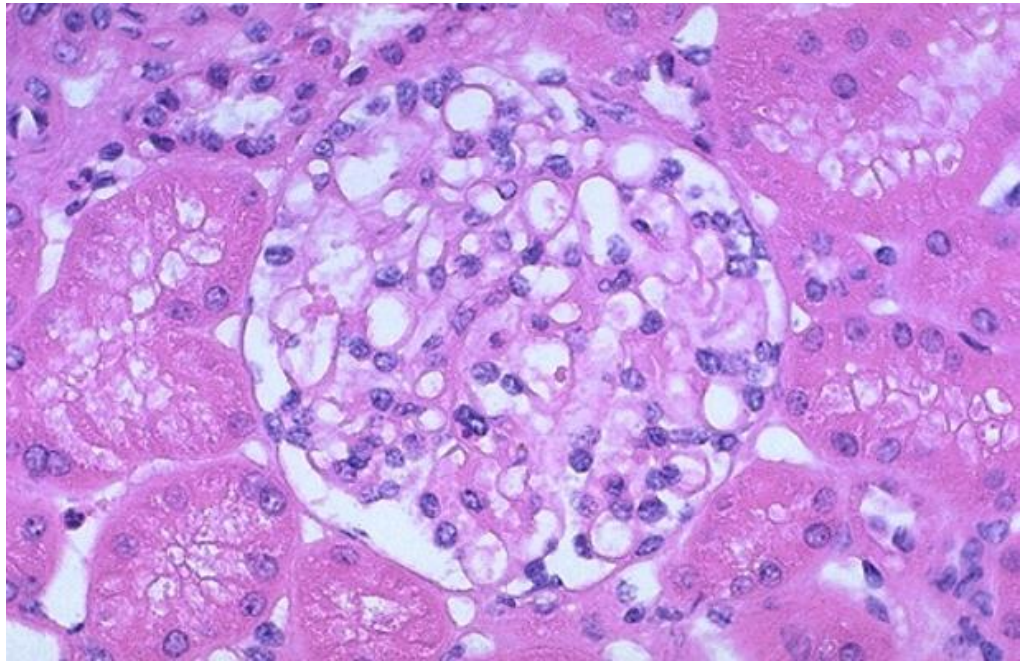
Pathophysiology of CKD



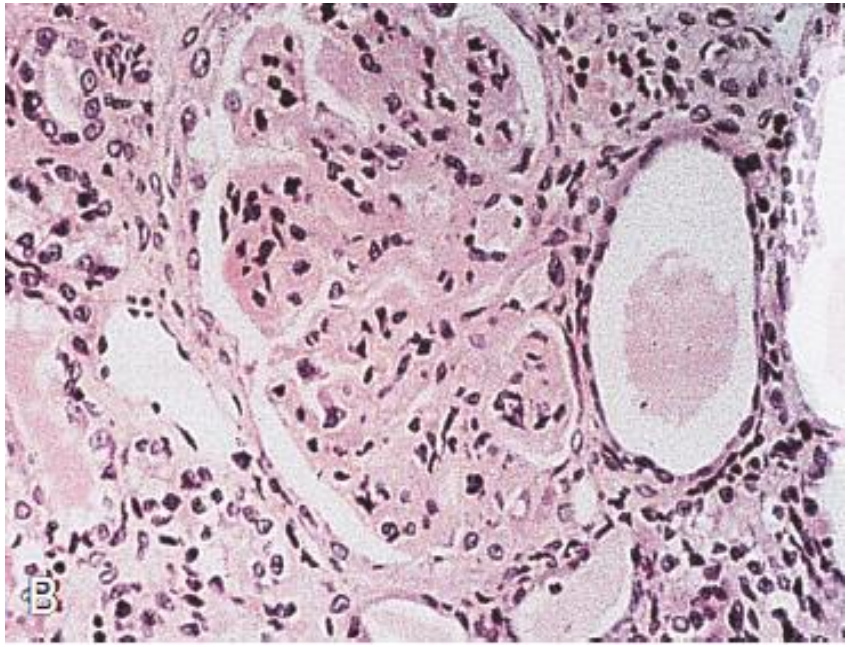
Intraglomerular hypertension

Initially, it is useful, but in the long term, it causes damage to all glomeruli.

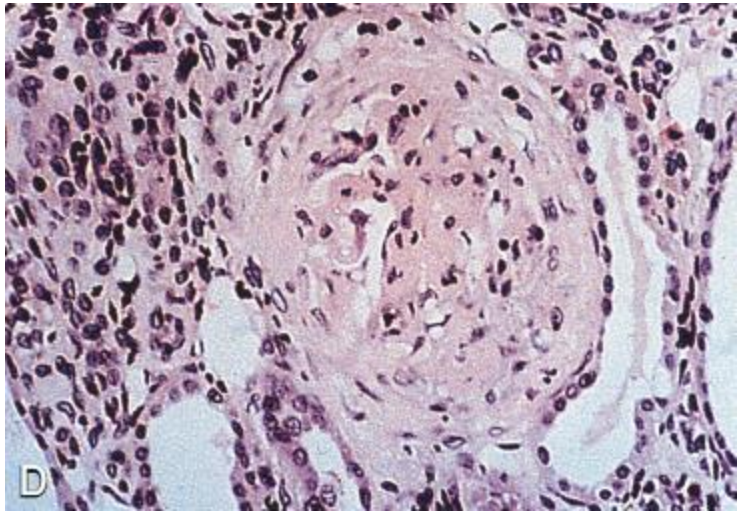
RBF: Renal Blood Flow



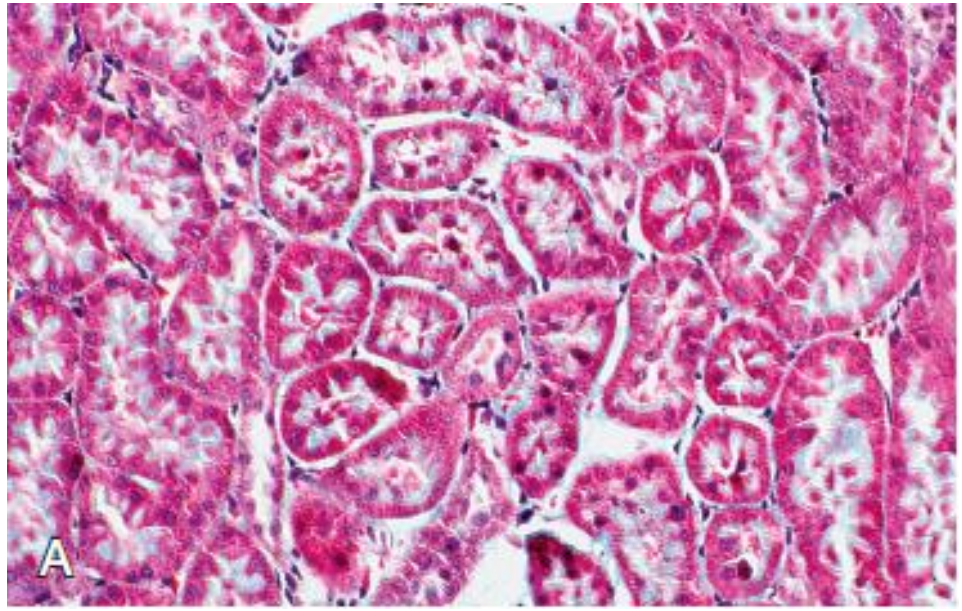
Normal glomerulus



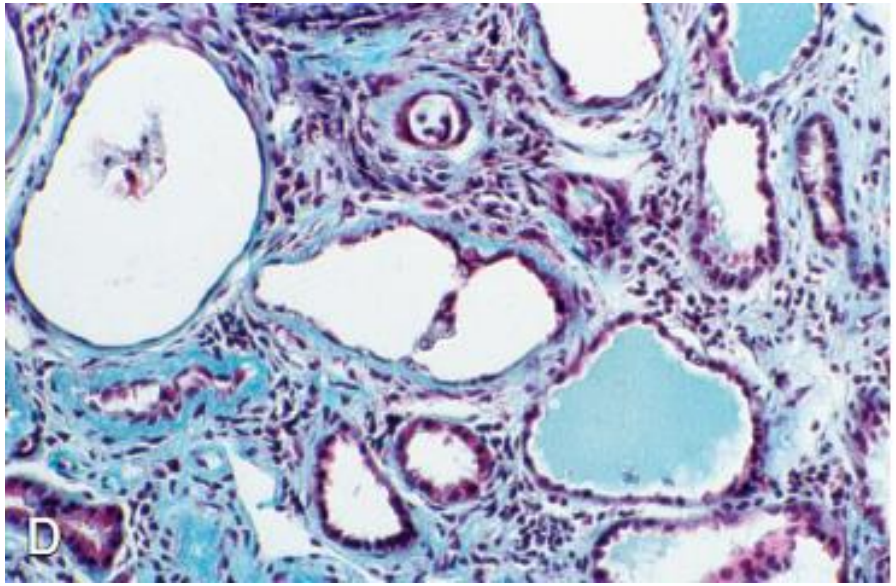
Glomerular hypertrophy
Mesangial proliferation



Glomerulosclerosis



Normal glomeruli - Interstitial space



Diffuse tubular atrophy,
Interstitial fibrosis

Clinical Manifestations per CKD Stage

Stage	Description	GFR (ml/min/1.73m²)	Clinical Features
1	**Normal/high GFR**	≥90	Albuminuria, proteinuria, hematuria, imaging or histological lesions
2	**Mild GFR reduction**	60-89	
3a	**Mild to moderate**	45-59	Hypertension, edema, anemia
3b	**Moderate to severe**	30-44	
4	**Severe GFR reduction**	15-29	Electrolyte disturbances, metabolic acidosis
5	**Kidney failure**	<15	Uremic syndrome

Clinical manifestations - Complications of CKD

- **Disorders of water/electrolytes (sodium-potassium)**

  Edema, hypertension, hyperkalemia

- **Disorders of acid-base balance**

  Metabolic acidosis

- **Disorders of erythropoiesis**

  Anemia of CKD

- **Disorders of bone and mineral metabolism**

  Hyperphosphatemia

  Secondary hyperparathyroidism

- **Arterial hypertension - Cardiovascular disease**

- **UREMIA**

Sodium balance in CKD

- Increased filtered sodium amount (hyperfiltration) and fractional excretion per healthy nephron
- Reduction in sodium reabsorption

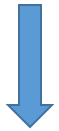
↓

Maintenance of satisfactory sodium balance up to stage 5

In end-stage CKD, retention of sodium and water, edema, and hypertension

Potassium balance in CKD

- Increased filtered amount of potassium (hyperfiltration) and fractional excretion per healthy nephron
- Satisfactory function of the distal tubule
- Normal secretion of aldosterone & response to its action
- Increased excretion from the intestine

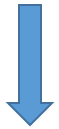


Maintenance of satisfactory potassium balance in advanced stages

In the end stage, hyperkalemia

Acid-base balance in CKD

- Excretion of H+ with NH_3 and PO_4
- Neutralization of H+ by calcium carbonate of bones
- Increased reabsorption of bicarbonates



Maintenance of satisfactory
blood pH until CKD stage 4

Anemia in CKD

Insufficient production of erythropoietin (EPO)

In kidney

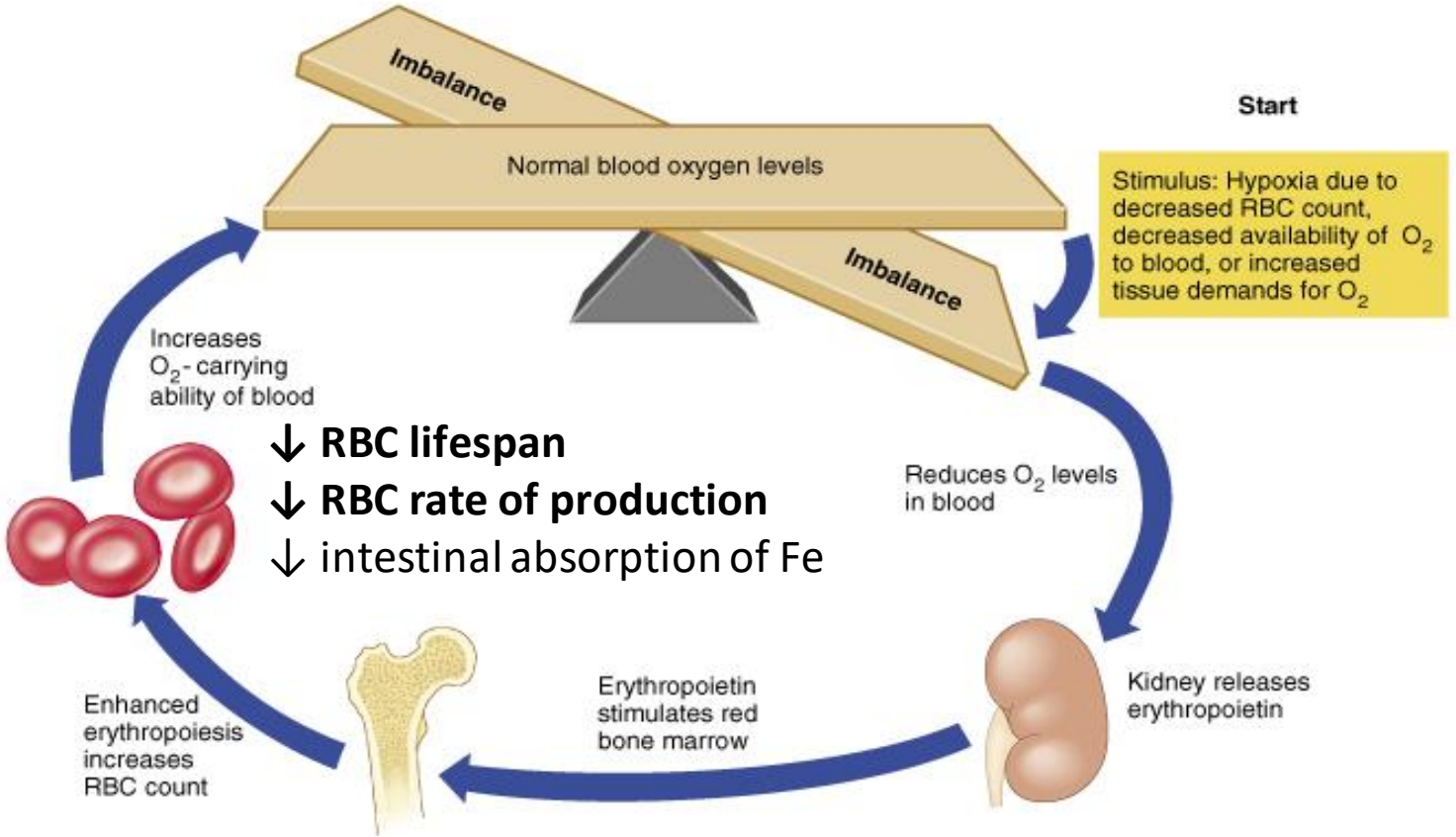
- Normally: EPO synthesis in kidney (only 10% in liver)

from a population of fibroblasts in the interstitial tissue

- **Anemia: normochromic, normocytic**

- It develops at **GFR < 50 ml/min**

Anemia in CKD
Pathogenesis



↓ RBC lifespan
↓ RBC rate of production
↓ intestinal absorption of Fe

↑ PTH
Kidney bone disease

Progressive decline in kidney function → **↓EPO**

Benjamin Cummings 2001

Anemia in CKD

Management

- **Erythropoietin peros (sbc, IV)**

  Epoetin alpha, 3/week

  Epoetin beta, 3 /week

  Darbopoietin /1-4 weeks

  Methoxy polyethylene glycol-epoetin beta /4 weeks

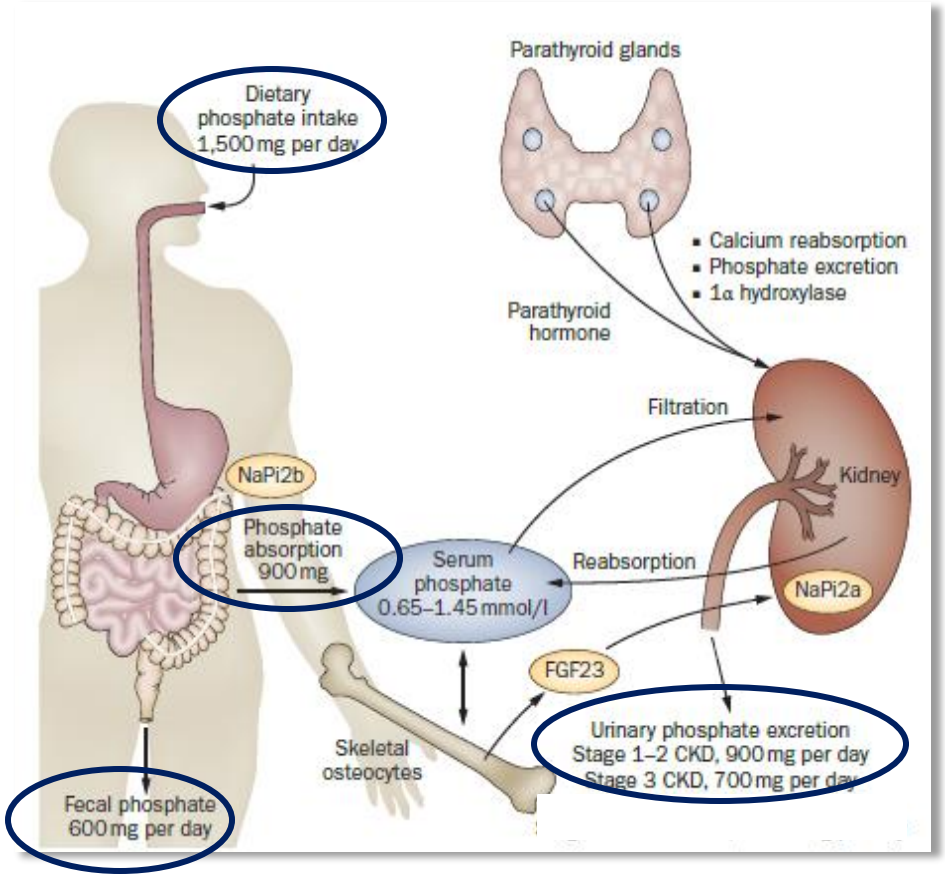
- **Iron supplementation, transfusions when necessary**

Targets: Hemoglobin 10-11.5 g/dl, Ferritin 100-500 µg/l, TSAT 20-30%

KDIGO 2025

Disturbed phosphate balance in CKD

Progressive decline in GFR → Reduced phoshpate excretion



- ↑ FGF-23

  ↓ tubular phosphate reabsorption , **Phosphaturia**

- ↓ Calcitriol, Hypocalcemia

- **↑ PTH**

  ↓ tubular phosphate reabsorption , **Phosphaturia**

GFR > 30 ml/min/1,73 m² (XNN I-III)

Plasma phosphate does not increase significantly

Hutchinson JA et al, Nat Rev Nephrol 2011

Disturbed phosphate balance in CKD

GFR ≤ 30 ml/min/1,73 m^2 (XNN IV-V)

- **Φορτίο προσλαμβανόμενου φωσφόρου > Απεκκρινόμενου φωσφόρου**
- Phosporus excretion in CKD IV: 600mg/24h

  XNN V: 0 - 500mg /24h
- Anuric patient under dialysis – Phosphorus balance

Dialysis session: removal of 800-1000 mg P

Hyperphosphatemia

What are the implications of hyperphosphatemia in patients with CKD?

- **Chronic Kidney Disease Mineral and Bone Disorder (CKD-BMD),**

  Vascular Calcifications – Cardiovasular Disease

- **Deterioration of kidney function ?**

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

Systemic disorder of bone, calcium, and phosphorus metabolism

Manifested by one or more of the following:

- Abnormalities of calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume linear growth, or strength
- **Extraskeletal calcification**

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

High bone turnover

- **Secondary hyperparathyroidism**

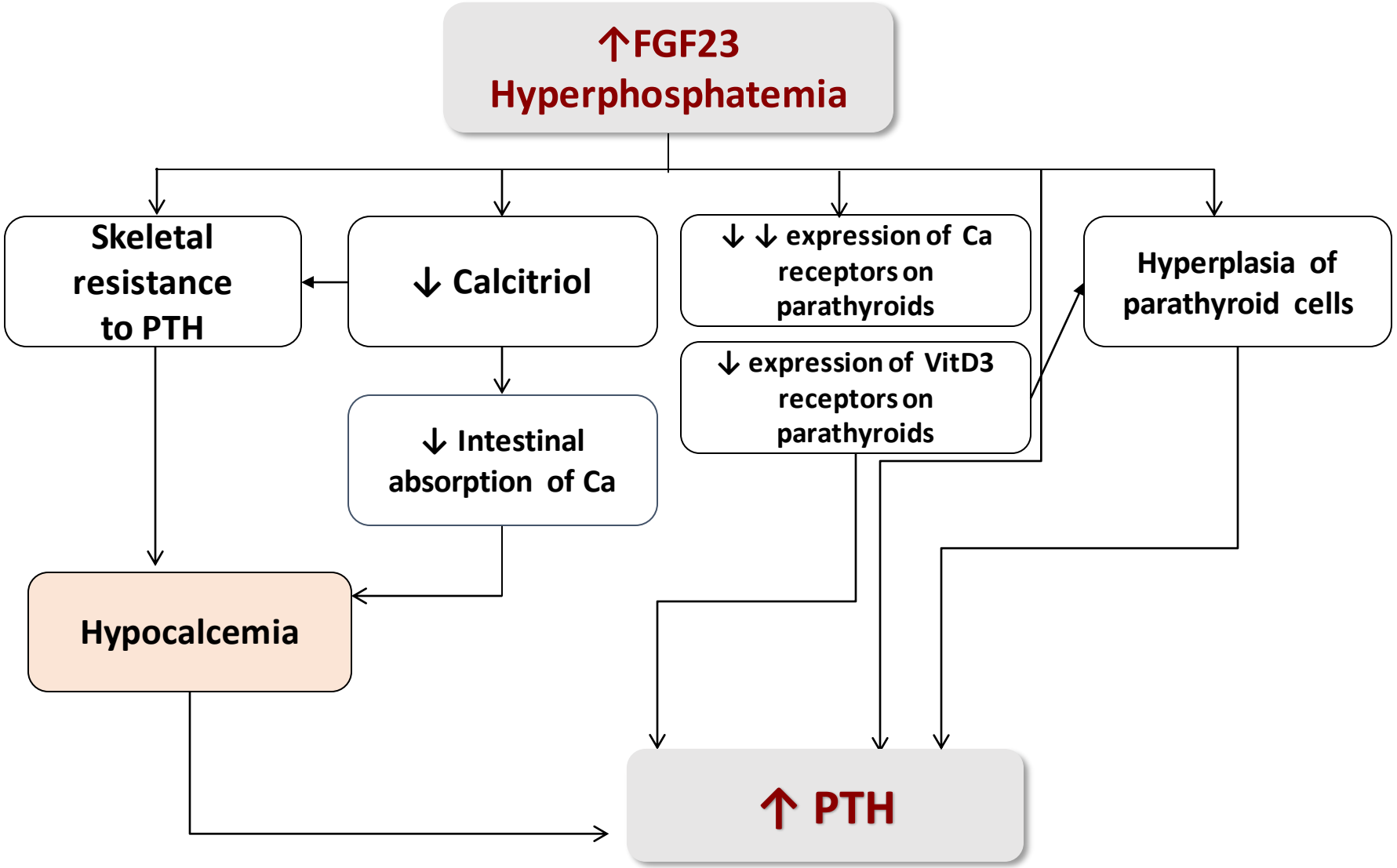
Low bone turnover

- Adynamic bone disease
- Osteomalacia

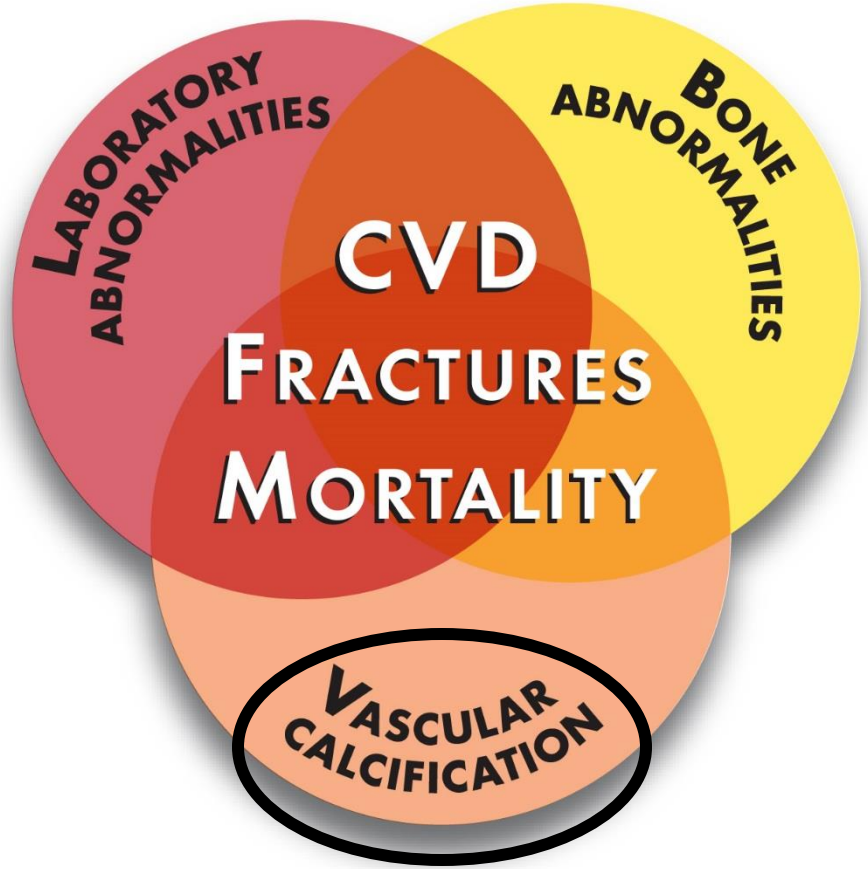
Mixed uremic osteodystrophy

KDIGO 2017

Secondary Hyperparathyroidism



Chronic Kidney Disease–Mineral and Bone Disorder



CKD-MBD

Risk of potentially fatal complications

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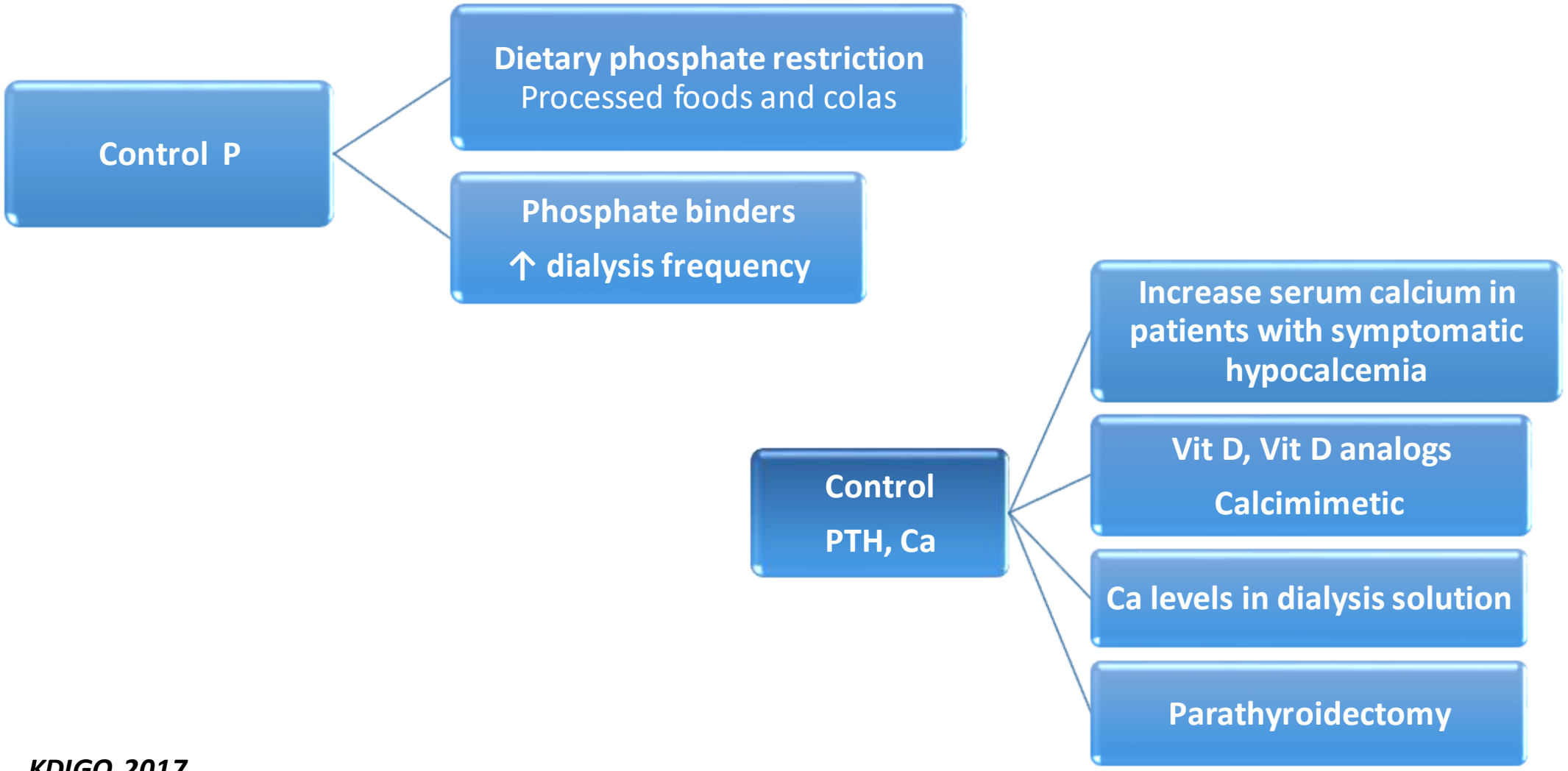
Vascular calcifications

Soft tissue calcifications


R

Hyperphosphatemia management

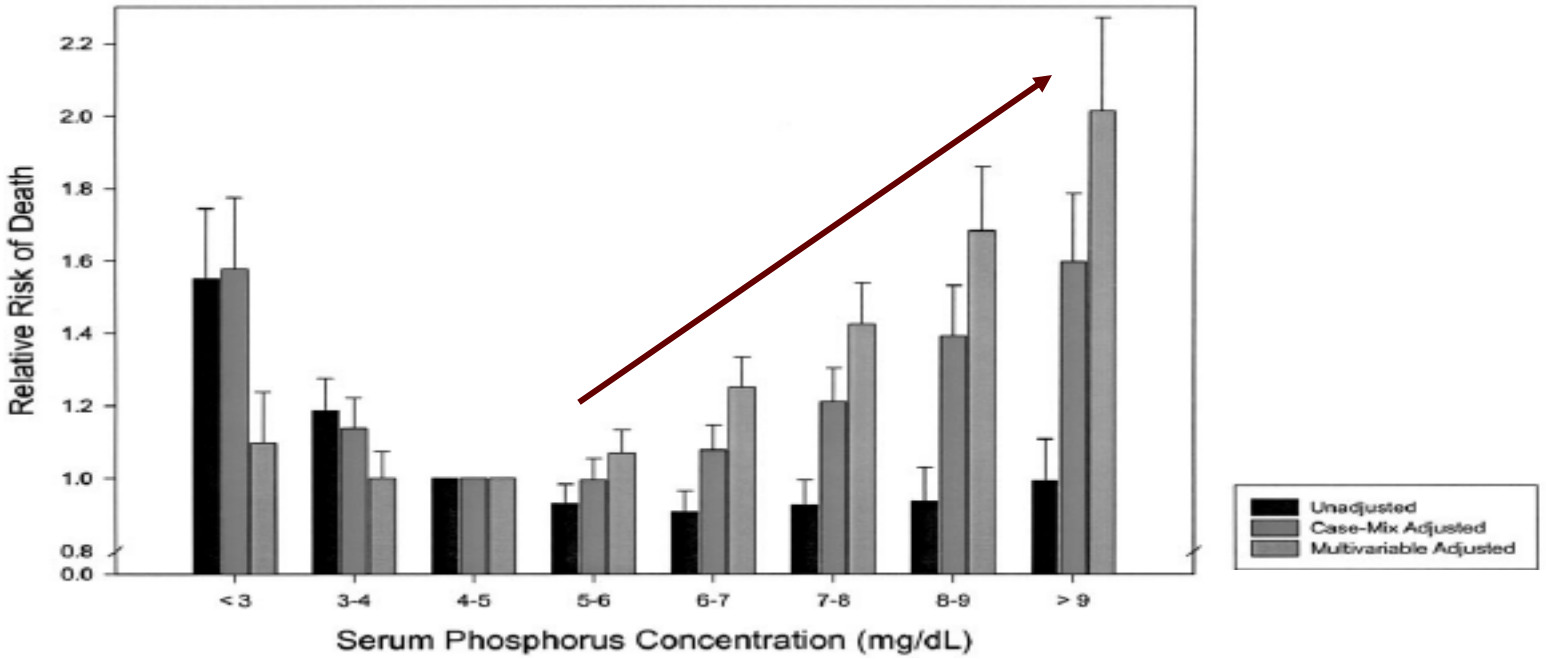


KDIGO 2017

Vascular Calcifications – Cardiovascular Disease

Hemodialysis patients (n: 40.000)

Hyperphosphatemia and risk of death



Block GA et al, J Am Soc Nephrol 2004

Arterial Hypertension
Cardiovascular Disease in CKD

- **High prevalence of hypertension (50-85% in CKD stages 3-5)**
- **Common conditions**

  Arrythmias

  Cardiorenal syndrome

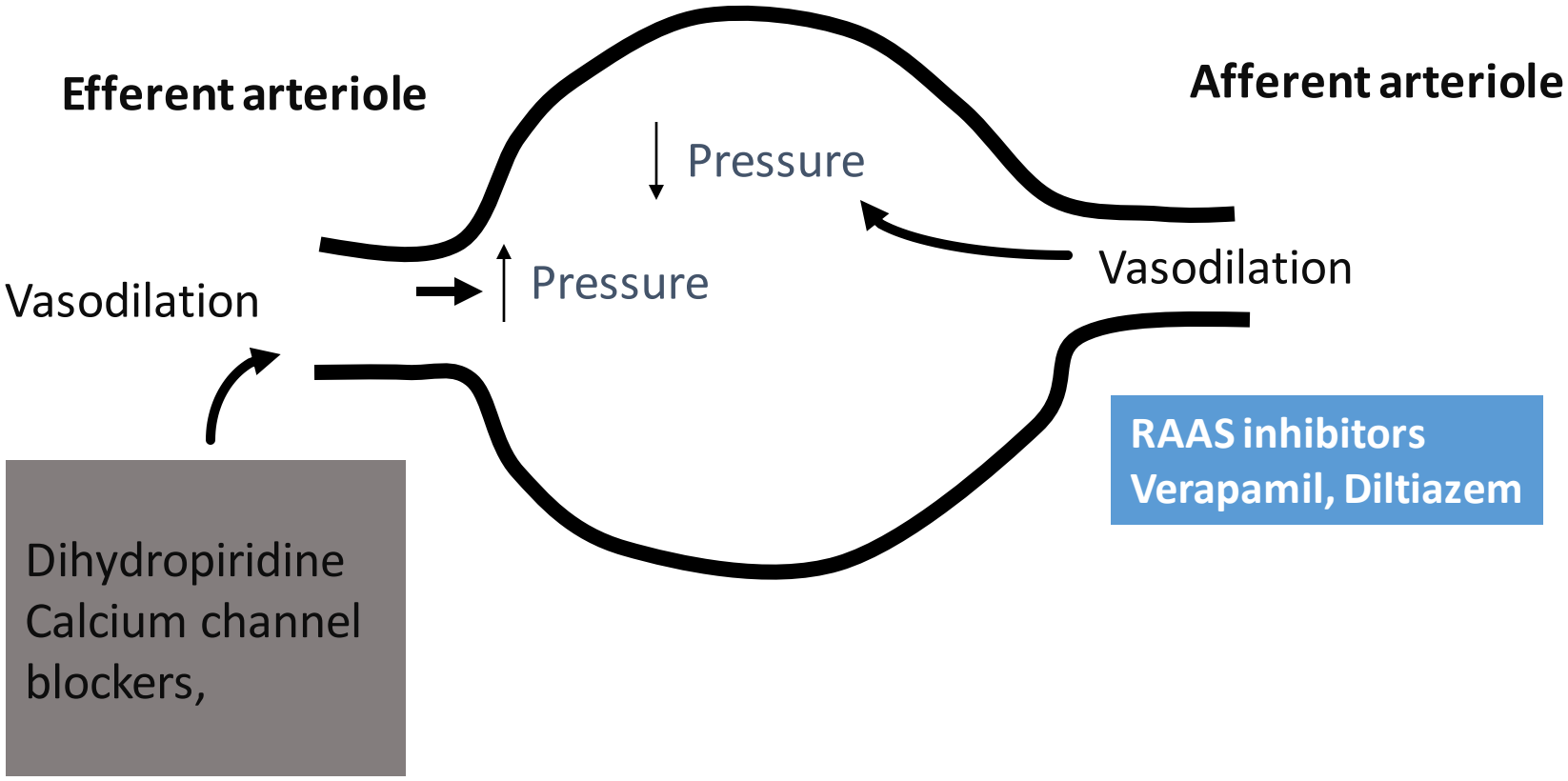
  Pericarditis

  Periphelar arterial disease, Coronary artery disease, Cerebrovacular disease

  Heart failure

Arterial Hypertension in CKD

Antihypertensives and intraglomerular pressure



Antihypertensive Therapy Recommendations

- **Target BP < 120 mmHg when tolerated**

  Less intensive BP-lowering therapy in people with frailty, high risk of falls and fractures, very limited life expectancy, or symptomatic postural hypotension

- **Salt restriction (2g/24h)**
- Use of agents according to age, coexistent CVD, and other comorbidities; risk of progression of CKD; and tolerance to treatments
- **First-line: RAAS inhibitors (ACEi/ARB), that decrease intraglomerular pressure**
- **Hypervolemia**

  Loop diuretics, especially when eGFR< 30 ml/min

KDIGO 2024

Antihypertensive Therapy Recommendations

RAAS Inhibitors (ACEi or ARB)

First-line medications

- Anti-proteinuric action
  - ↓ Intraglomerular pressure
  - Effect on glomerular filtration barrier permeability
- Anti-fibrotic action
  - ↓ Ang-II & TGF-β
- ACEi: ↓ proteinuria by 30-35% in both diabetic & non-diabetic CKD
- Slowing CKD progression even when eGFR <30 ml/min
- Changes in BP, **serum creatinine, and serum potassium** should be checked **within 2–4 weeks** of initiation or increase in the dose of a RASi

KDIGO Blood Pressure Work Group, Kidney Int Suppl 2012
KDOQI Commentary on KDIGO Blood Pressure Guidelines, Am J Kidney Dis. 2013

Antihypertensive Therapy Recommendations

Mineralocorticoid Receptor Antagonists (MRA)

Finerenone

Patients with DM 2 under treatment with RAASi

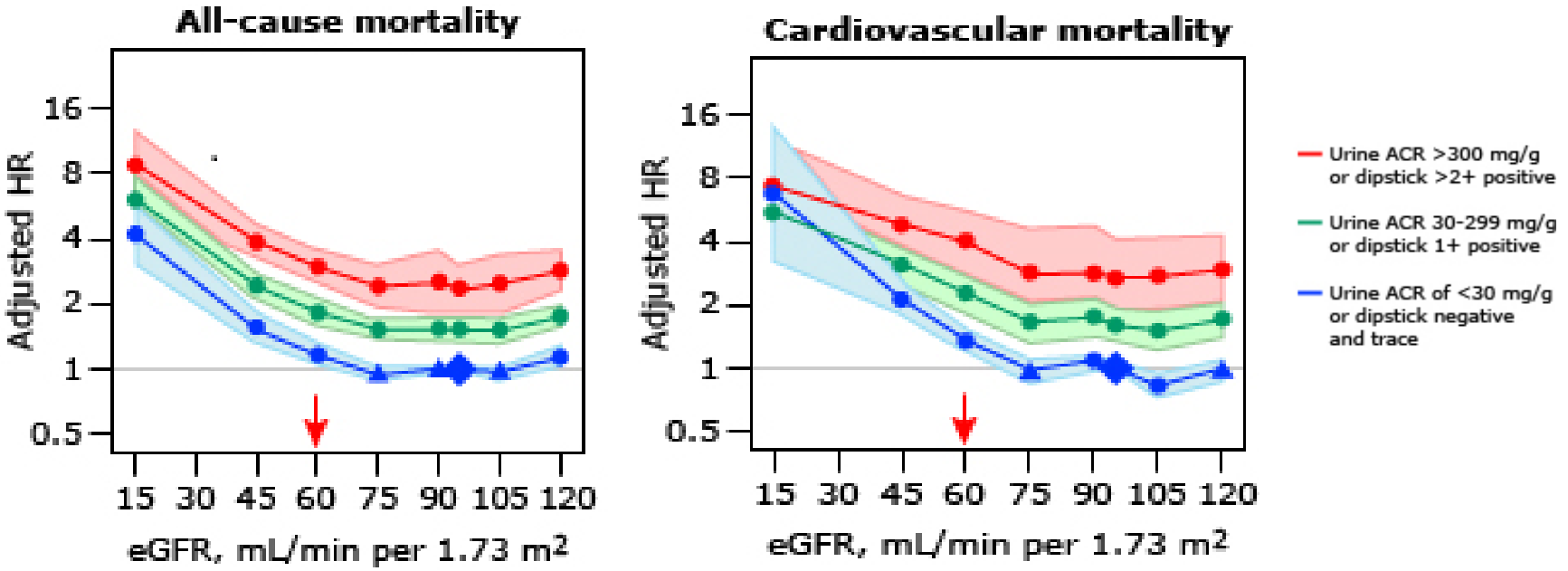
- **Dose-dependent ↓ albuminuria**
- **Delay in the progression of kidney disease**
- **↓ incidence of hyperkalemia**

Bakris GL et al, JAMA 2015

CKD & Factors associated to Cardiovascular Disease Pathogenesis

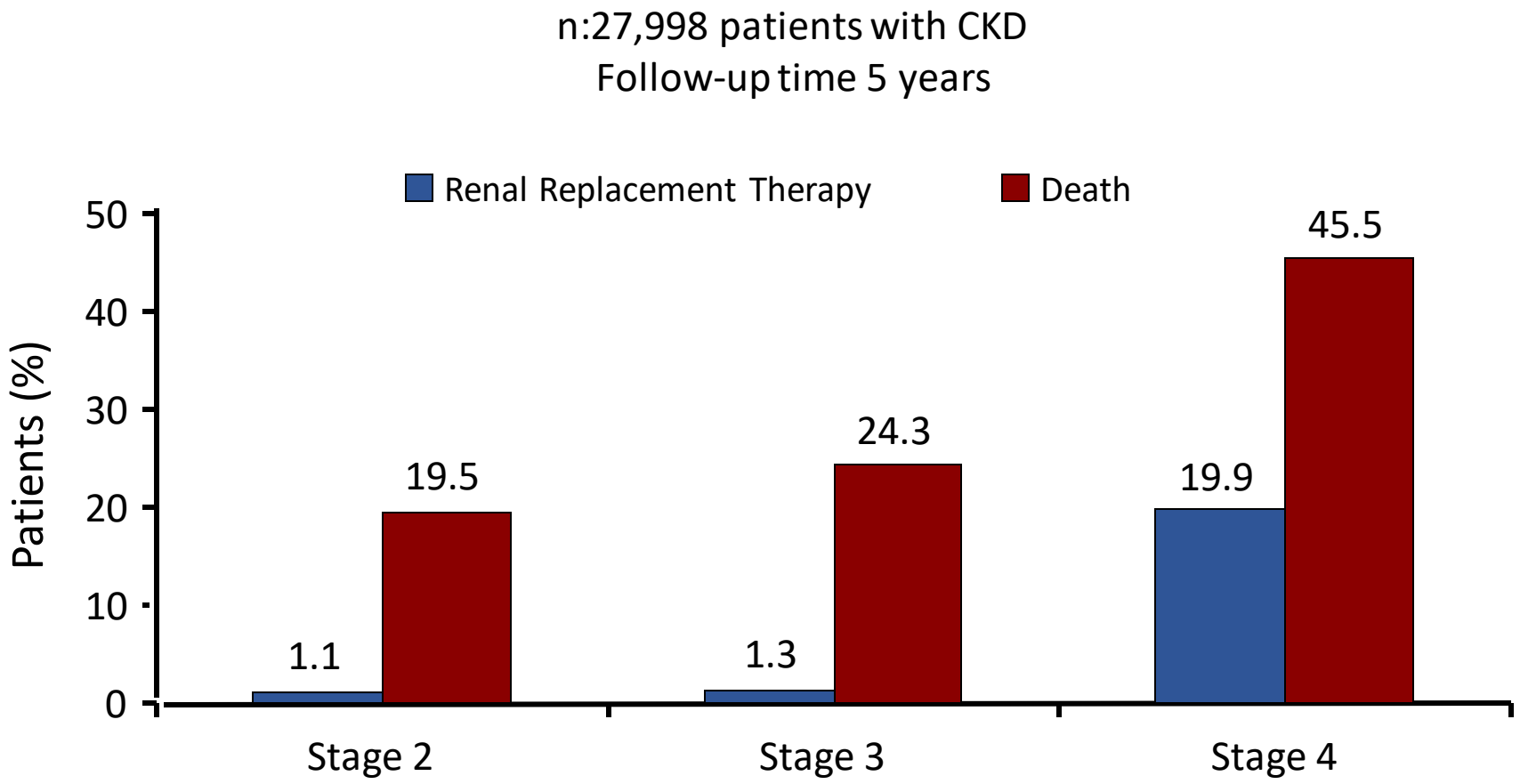
Classic factors	Factors associated with CKD
Age	**Chronic inflammation**
Smoking	**Albuminuria**
History of cardiovascular disease	**Oxidative stress - Endothelial dysfunction**
Diabetes mellitus	**Anemia**
Arterial hypertension	**Disorders of bone and mineral metabolism**
Dyslipidemia	**Na& H_2O retention**
Insulin resistance	**Uremic toxins - Malnutrition**

CKD, Albuminuria & Mortality Risk



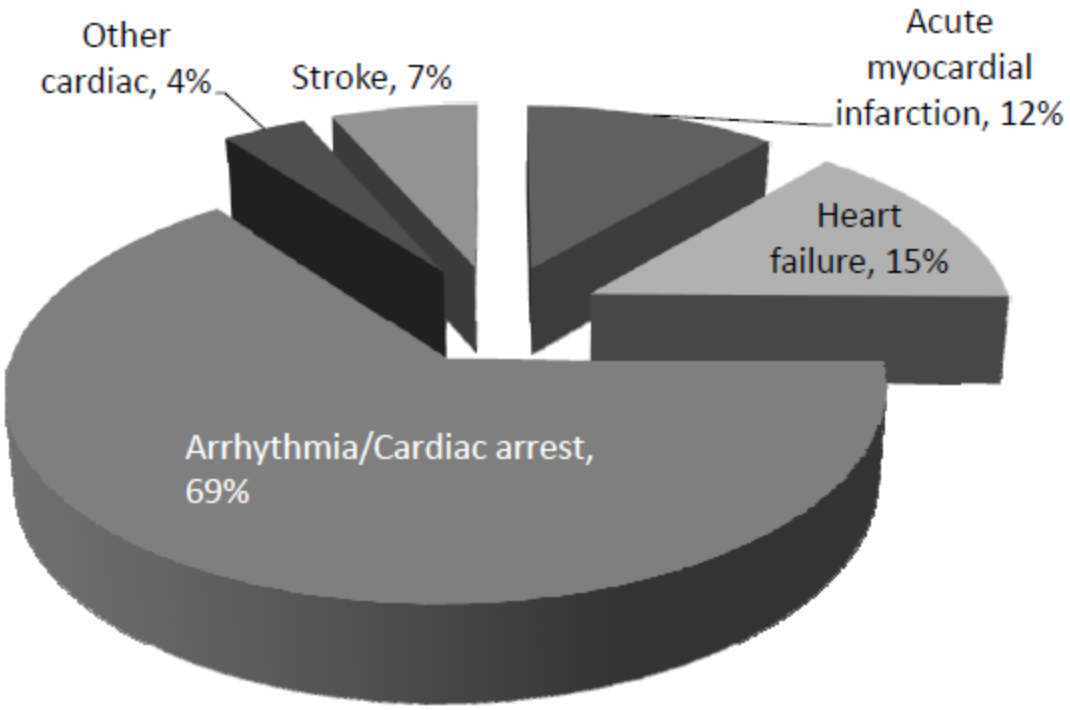
Levey AS et al, *Kidn Int 2011*; 80(1): 17
Matsushita K et al, *Lancet 2010*; 375:2073-2081

Individuals with CKD often die before reaching dialysis



Keith DS et al, Arch Intern Med 2004

Cardiovascular Morbidity in CKD
Causes of Death



Cai Q et al, Curr Cardiol Rev 2013

Cardiovascular Mortality in ESKD

- 50% of patients with ESKD die from a **cardiovascular event**
- The overall cardiovascular mortality of patients aged 25-34 with ESRD is 500-1000 times higher compared to the general population of similar risk without CKD.
- The average survival of a 60-64-year-old patient on hemodialysis is about 4.5 years, whereas in the general population it is 17-22 years.

Foley RN et al, Am J Kidney Dis 1998

Uremic Syndrome in ESKD

- The deterioration of multiple biochemical and physiological functions in parallel with progressive kidney dysfunction, resulting in complex but variable symptomatology
- **Accumulation of solutes / uremic toxins in the blood & tissues**
  - Small, water-soluble compounds with no or minimal protein binding, such as urea
  - Small, lipid-soluble compounds with substantial protein binding, such as the phenols
  - Larger, so-called middle molecules, such as beta2-microglobulin (beta2-m)
- **Factors affecting uremic retention solutes**
  - Dietary protein breakdown
  - Changes in the composition of the intestinal microbiome
  - Medications

Clinical manifestations of uremia

Early	Late
Nutritional Disorders	Metabolic acidosis
Hypervolemia	Hyperkalemia
Hypertension	Pericarditis
Anemia	Peripheral neuropathy
Secondary hyperparathyroidism	Encephalopathy
Growth retardation	Gastrointestinal bleeding
Reduced fertility	
Menstrual disorders	

Management of a patient with ESRD

Methods of renal replacement therapy

Haemodialysis
- In-center
- At home

Peritoneal dialysis
- Continuous Ambulatory Peritoneal Dialysis (CAPD)
- Continuous Cyclic Peritoneal Dialysis (CCPD)

Transplantation

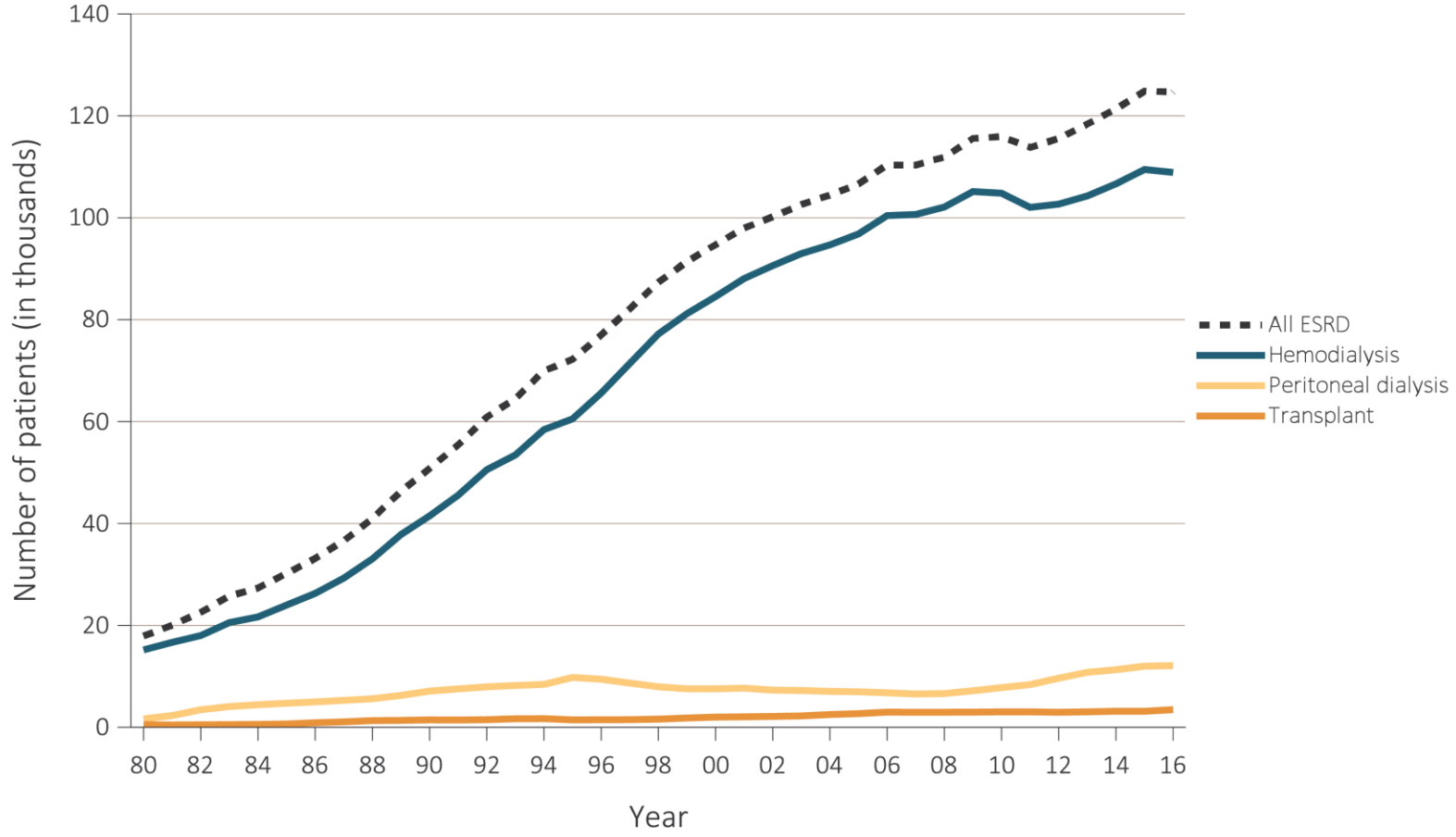
From a deceased donor

From a living donor

- Related
- Unrelated

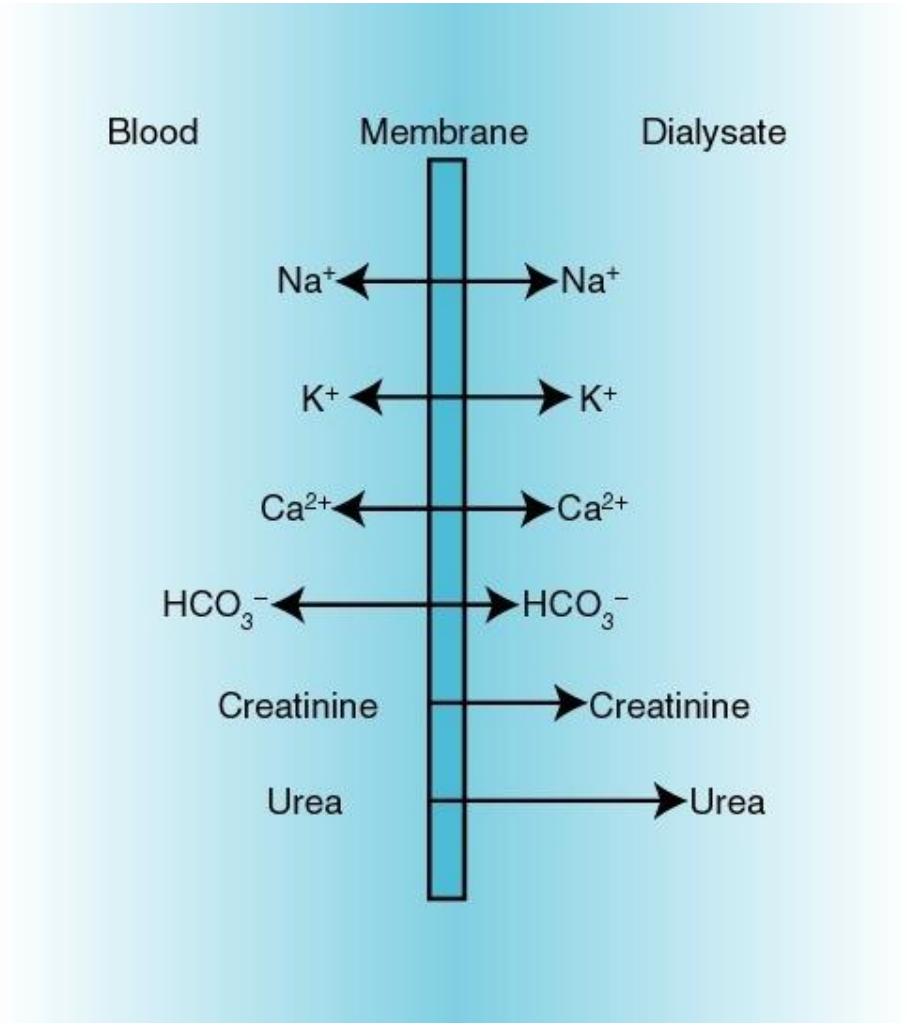
ESRD Incidence in the USA (1980-2016)

By Modality



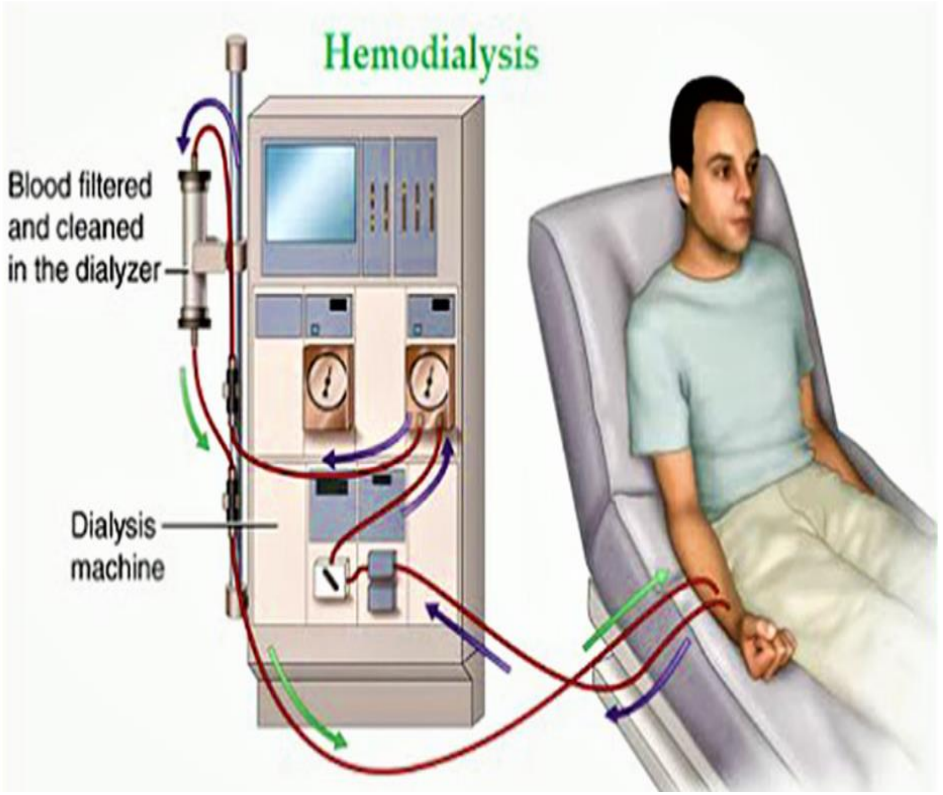
United States Renal Data System, USRDS 2018

Haemodialysis: Convection



Dialysis Machine

Haemodialysis



3 sessions per week in a chronic hemodialysis unit

Session duration: 4 hours

Fluid loss: 1-3 liters per session

Fluid intake: Depends on urine output

Anuric patients: 500 ml of fluids per 24 hours

https://healthjade.com/hemodialysis/

Vascular Access for Haemodialysis

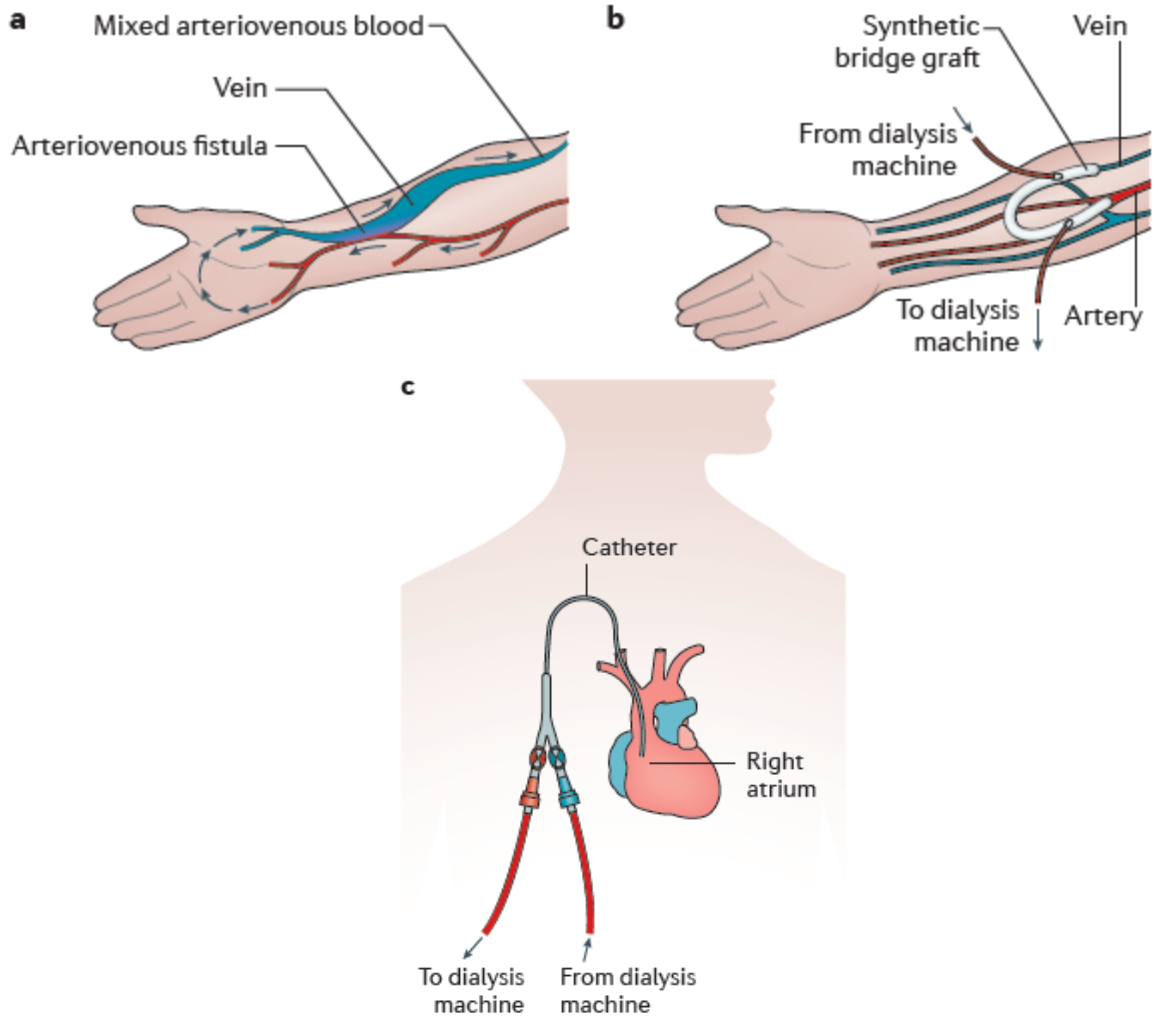
- **Arteriovenous fistula /graft**

  Lower rate of infections

  Long time of maturation

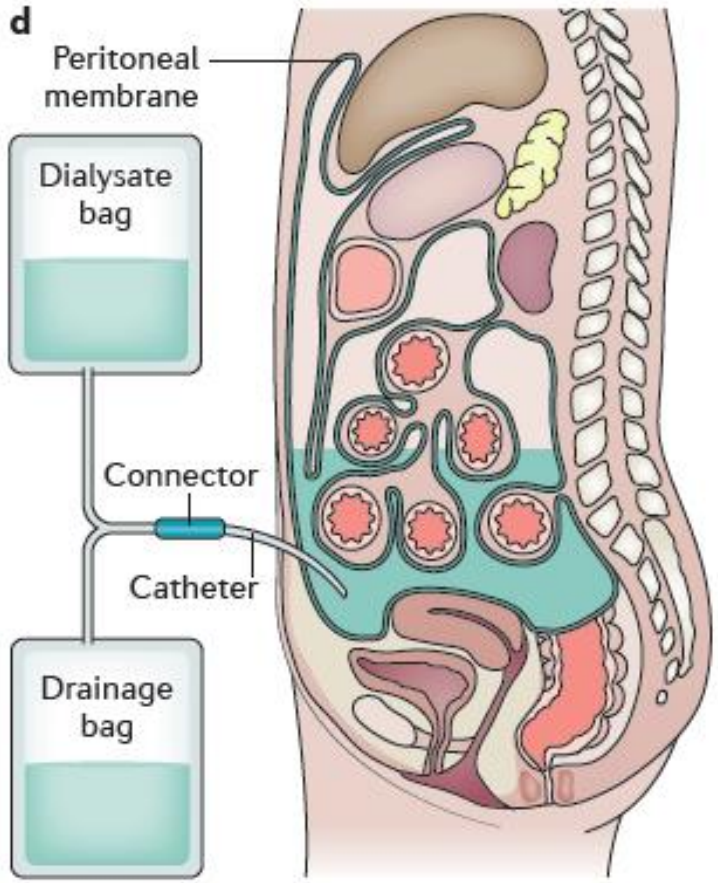
- **Central Venous Catheter**

  Internal jugular vein



Rpmagnani P et al, Nat Rev Primer Diseases 2017

Peritoneal Dialysis



- **Peritoneal catheter**
- Continuous Ambulatory, CAPD: Exchanges during 24h
- Automated: Multiple overnight exchanges using a cycler
- **Daily dialysis modality**

  Haemodynamic stability
- **Fluid intake:** Depends on urine output

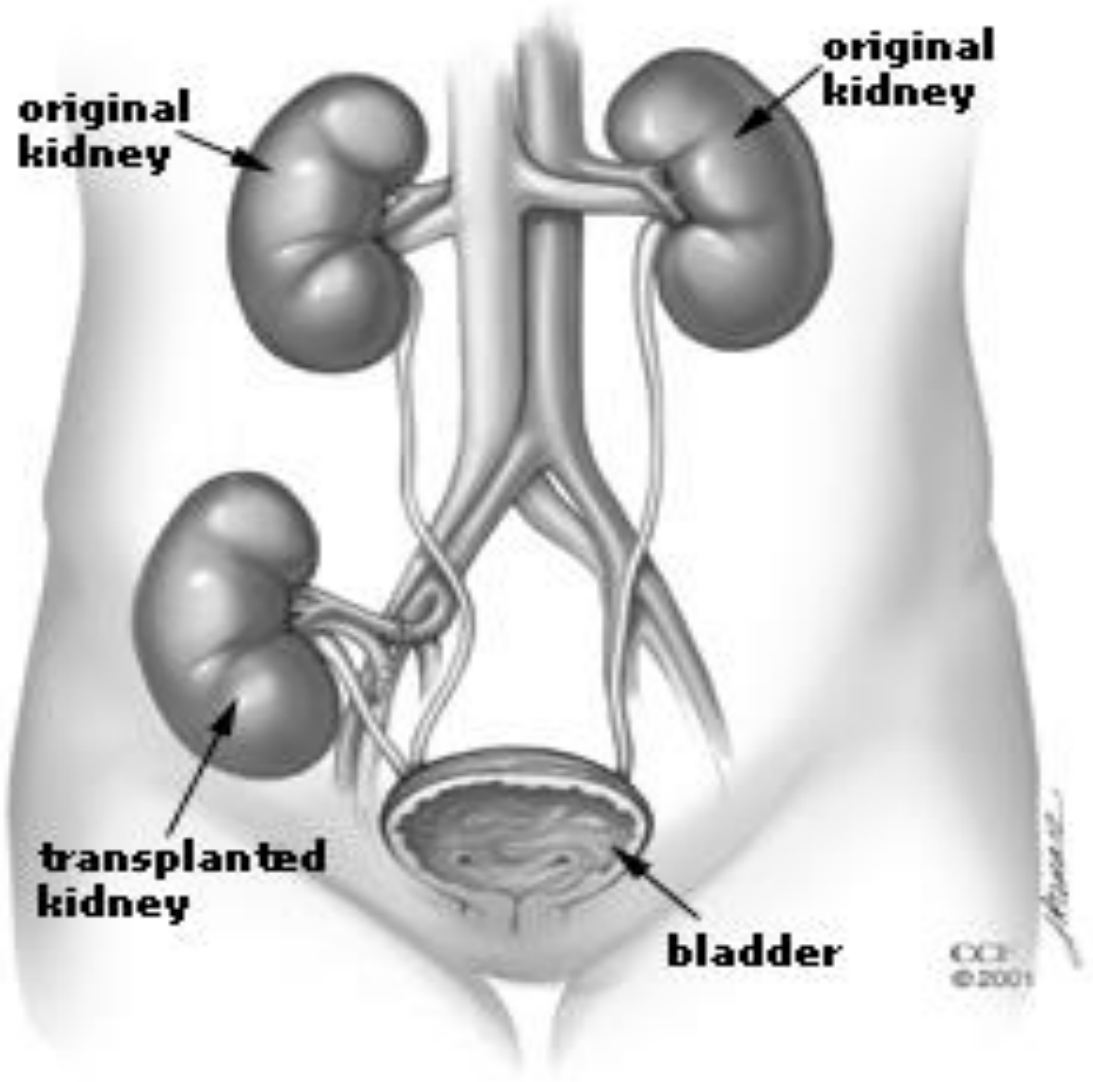
  Anuric patients: 500 ml of fluids per 24 hours
- **Medical consultation/2 months**
- Increased risk of peritonitis

Rpmagnani P et al, Nat Rev Primer Diseases 2017

Peritoneal Dialysis

- Peritoneal dialysis can work well as a long-term therapy for almost any patient and should be included in most options discussions
- **Absolute contraindication**: lack of a functional peritoneal membrane
- **Relative contraindication**
    - Peritoneal scarring
    - Physical, cognitive, or psychological impairment
    - Lack of appropriate environment
    - Active inflammatory process or cancer
    - Surgical ostomies
    - Large abdominal wall hernia
    - Ventriculoperitoneal shunts

Kidney Transplantation



CKD Management by GFR Stage

Stage	Description	GFR ($ml/min/1.73m^2$)	Ενέργεια
1	Normal/high GFR	≥90	**Diagnose & treat primary disease, Manage comorbidities Control risk of cardiovascular morbidity**
2	Mild GFR reduction	60-89	**Assess progression**
3a	Mild to moderate	30-59	**Evaluate and treat clinical manifestations/complications**
3b	Moderate to severe	15-29	Prepare for Transplantation/ Kidney Replacement Therapy, KRT
4	Severe GFR reduction	<15	Renal Transplantation KRT

Primary CKD Prevention

Early & effective management

of CKD risk factors

Secondary CKD Prevention

Early CKD Diagnosis (CKD 1-2, GFR≥60 ml/min/1.73 m^2)

- **Proper assessment of kidney function in all patients: eGFR**

  CKD-EPI formula

- **Regular monitoring of high-risk patients**

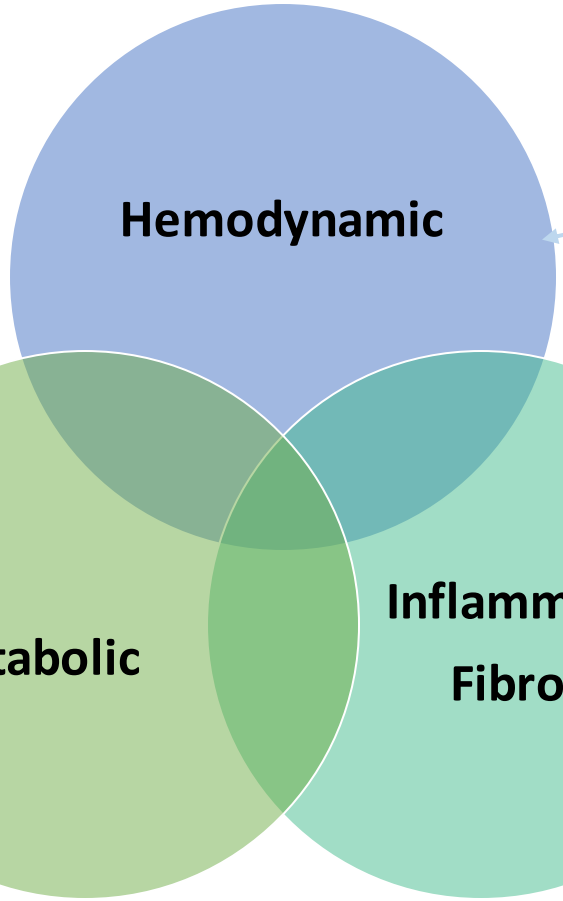
  GFR, Albuminuria, Urinalysis, Urine sediment

  Ultrasound examination (kidney size, cortical thickness)

Education & collaboration among healthcare professionals

Delaying CKD progression
Targeted drug therapy

Progression of CKD is driven by three inter-related pathophysiological processes



RAS inhibitors
SGLT2 inhibitors
↑ Efferent arteriole tone
↓ Intraglomerular hypertension
↓ Arterial Hypertension

SGLT2 inhibitors
GLP-1 RA
↓ Glucose & HbA1c

Non-steroidal Mineralocorticoid Receptor Antagonists
GLP-1 RA

Early diagnosis & management delays progression to ESRD