Management of Chronic Kidney Disease and Slowing Progression

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Harvard Medical School

- Honoraria for PriMed, primary care conferences
- Panel participation from Amgen on multi-disciplinary care for individuals with cystinosis

- Review screening for CKD in Diabetes mellitus
- Explore the lifestyle changes recommended for CKD (and all!) with focus on sodium and potassium intake
- Consider features of comprehensive care for CKD

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

De Boer et al KI 2022

CKD screening and diagnosis for people living with DM

Who and when to screen?

- **T1D** Yearly starting 5 years after diagnosis
- **T2D** Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

What to do with a positive result?

Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

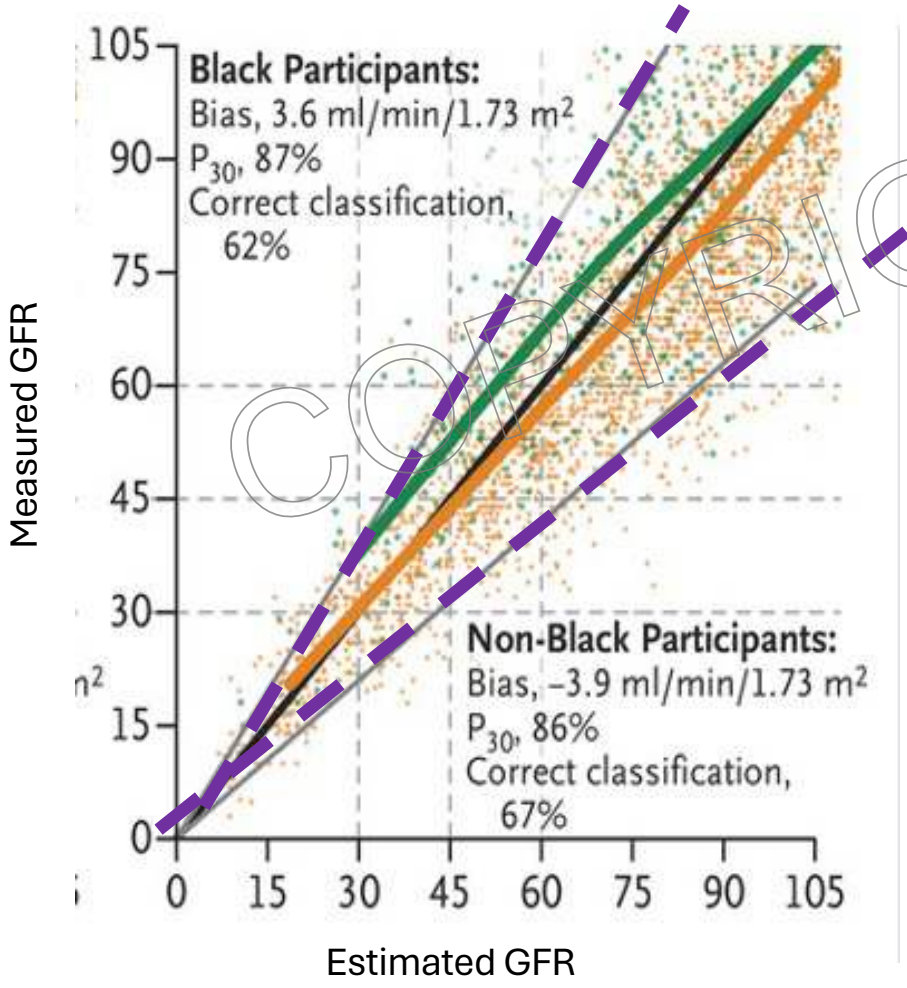
Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

De Boer et al KI 2022

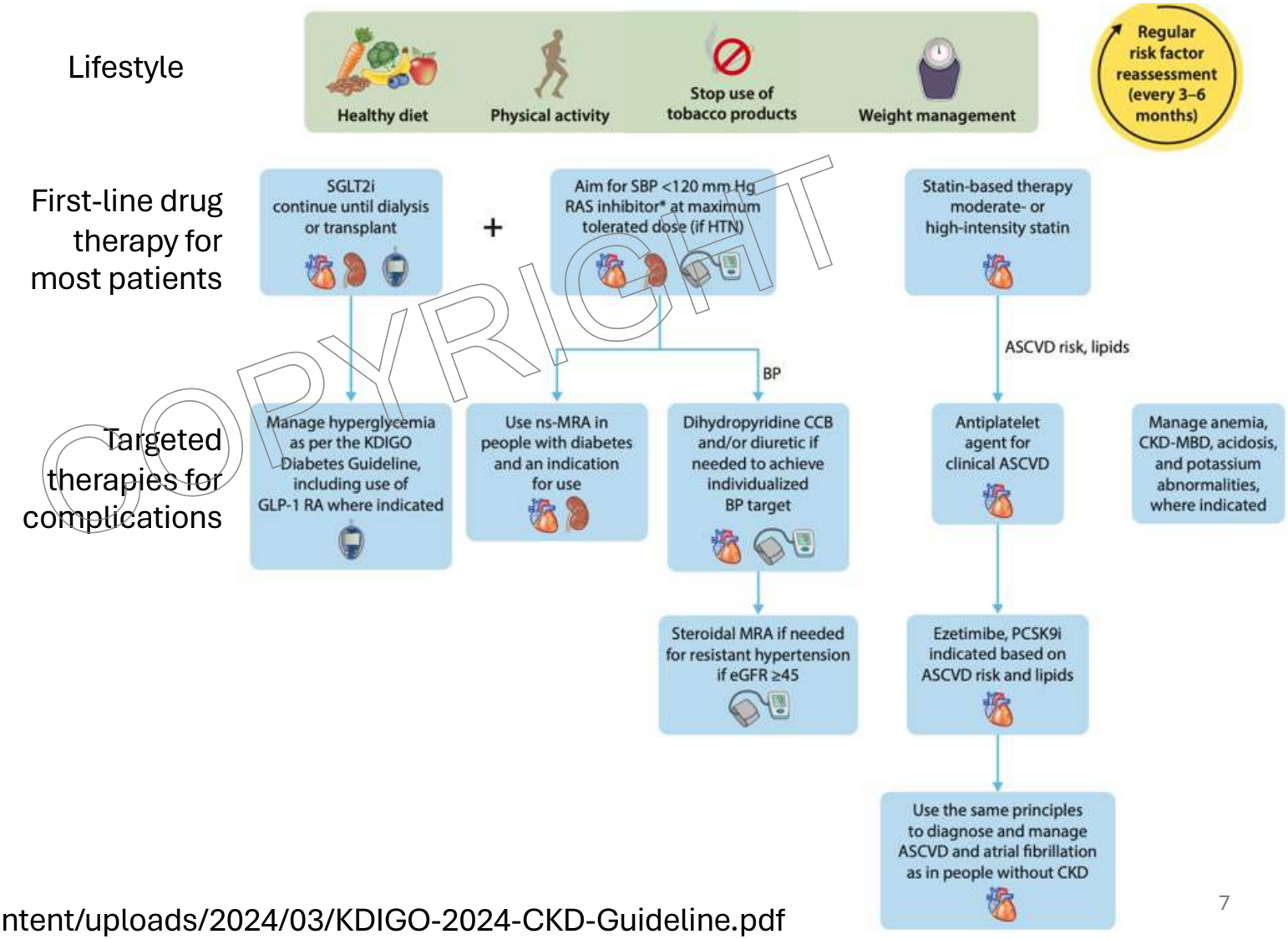
CKD is defined by the estimated GFR (not a perfect test!)



- All formulas for eGFR perform poorly when kidney function is close to normal
- All formulas are meant for the steady state, not acute kidney injury
- If concern that creatinine and eGFR are inaccurate, consider 24-hour urine collection or measure cystatin C, another filtration marker

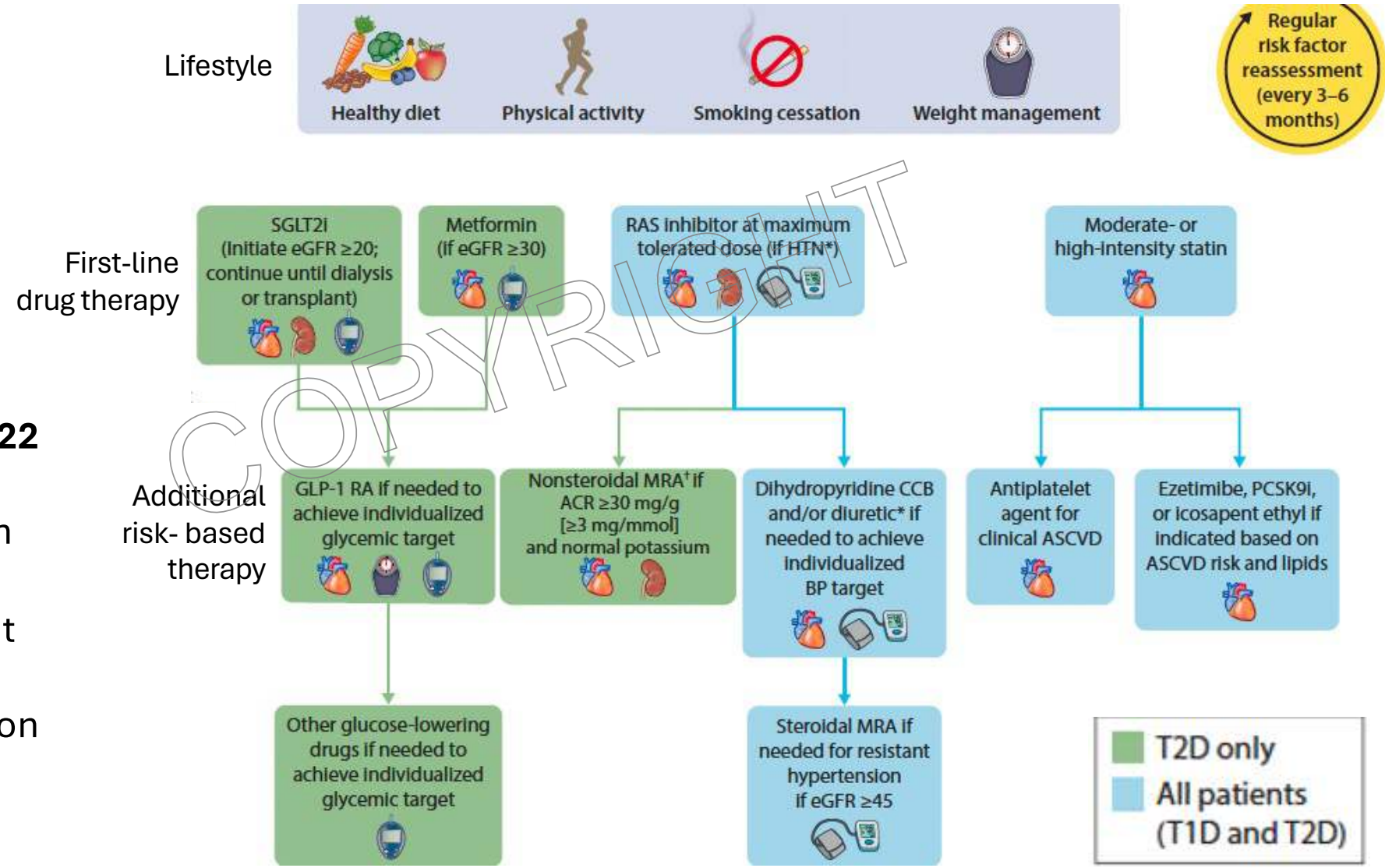
Inker et al. NEJM 2021

KDIGO 2024
Holistic approach to CKD treatment and risk modification



https://kdigo.org/wp-content/uploads/2024/03/KDIGO-2024-CKD-Guideline.pdf

KDIGO 2022
Holistic approach to DKD treatment and risk modification

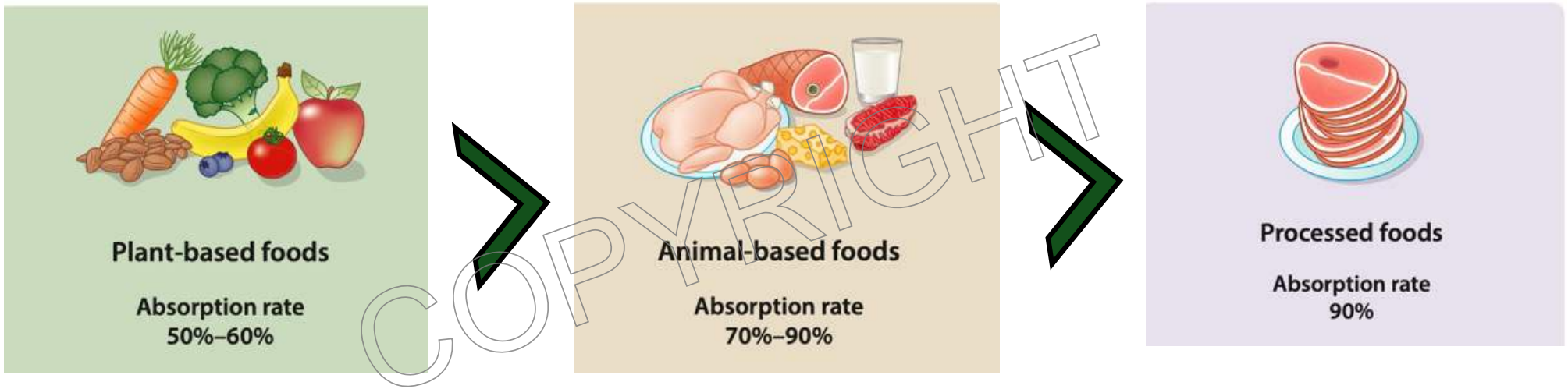


Lifestyle in DM

Regular risk factor reassessment (every 3–6 months)

Manage anemia, CKD-MBD, acidosis, and potassium abnormalities, where indicated

https://kdigo.org/wp-content/uploads/2024/03/KDIGO-2024-CKD-Guideline.pdf



The Kidney Diet is a Healthy Diet

From KDIGO CKD 2024

- Sodium
- Potassium
- Phosphate
- Protein

World Health Organization
Africa

INTERSECTORAL CASE STUDY
SUCCESSFUL SODIUM REGULATION IN SOUTH AFRICA

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WHAT YOU NEED TO KNOW ABOUT THE SODIUM REGULATIONS

6 September 2021. By FACTS in Regulatory & Nutrition

In 2013, the Minister of Health signed legislation to make sodium reduction in the food industry mandatory, to help achieve the government's target of reducing salt intake to less than 5g a day by 2020. This makes South Africa the first country in the world to legislate salt levels to help

Need help with yo
food & allergen te

TABLE 2: MAXIMUM LIMITS OF SODIUM CONTENT IN TARGETED FOOD PRODUCTS BY RESPECTIVE DEADLINES *(25)*

Foodstuff category	2010 Baseline	30 June 2016	30 June 2019
Bread	528 mg	400 mg	380 mg
Breakfast cereals and porridges	638 mg	500 mg	400 mg
Butter and spreads such as margarine	867 mg	550 mg	450 mg
Savoury snacks (excluding salt and vinegar flavour)	1000 mg	800 mg	700 mg
Flavoured potato crisps (excluding salt and vinegar flavour)	1067 mg	650 mg	550 mg
Salt and vinegar flavoured savoury snacks and potato crisps	1730 mg	1 000 mg	850 mg
Cured processed meat	1596 mg	950 mg	850 mg
Raw processed meat sausages and similar products	1061 mg	800 mg	600 mg

Why does the government want to control sodium consumption in South Africa?

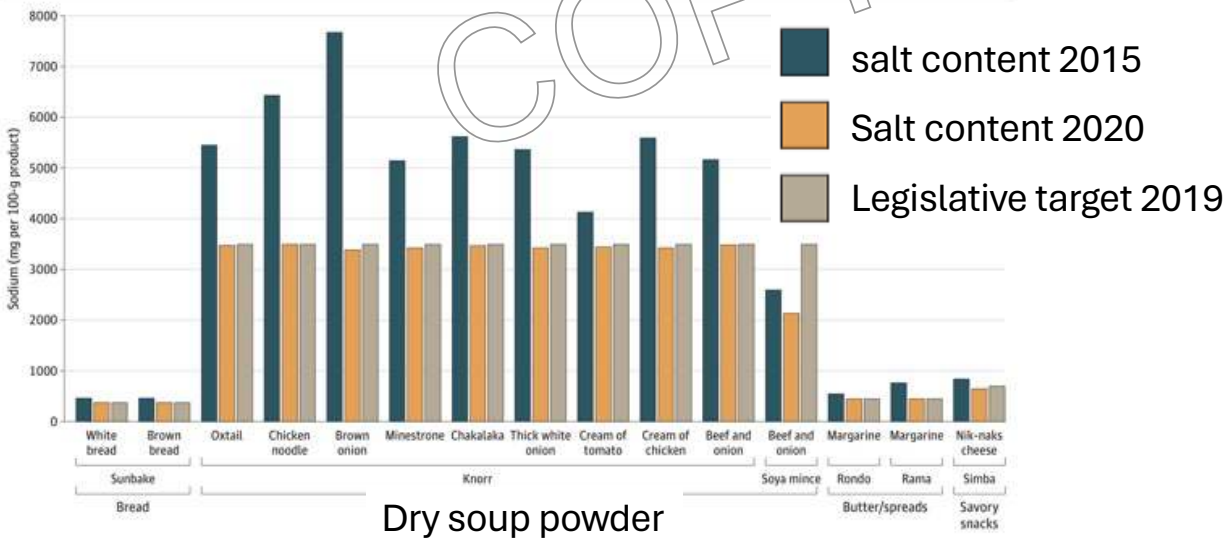
South Africa has one of the highest rates of hypertension worldwide. It is estimated that up to 1 in 3 adults have raised blood-pressure levels. High blood pressure is a key risk factor for heart disease, and the most important risk factor for stroke. Furthermore, high salt intake is an established risk factor for increased blood pressure. South Africans consume too much salt – 6 to 11 grams per day, which is more than double the recommended amount.

JAMA Cardiology | Original Investigation 2025

Sodium Reduction Legislation and Urinary Sodium and Blood Pressure in South Africa

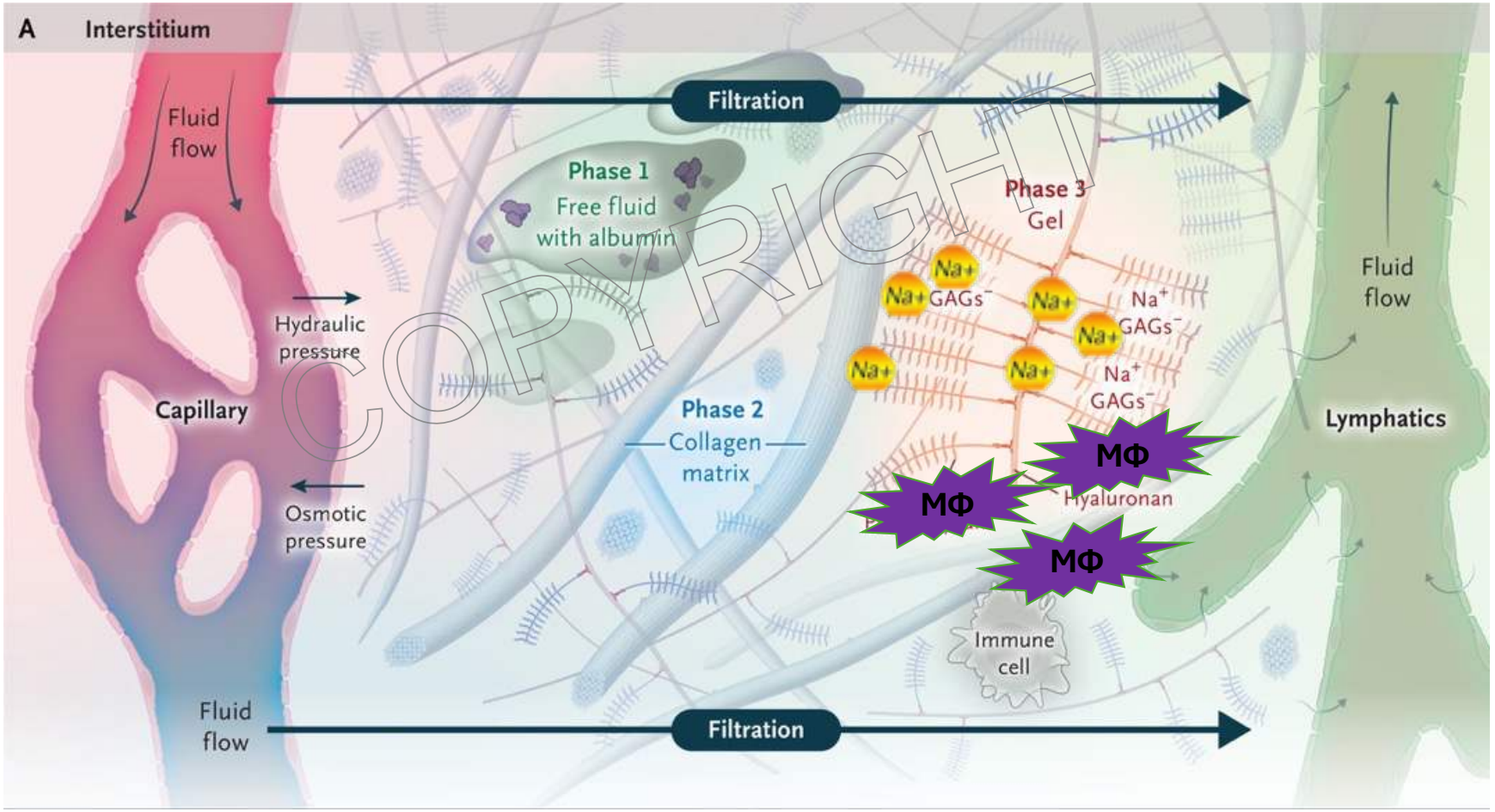
Thomas Gaziano, MD; David Kapaon, MA, MS; Jacques D. du Toit, MBBCh, MSc; Nigel J. Crowther, PhD; Alisha N. Wade, MBBS, DPhil; June Fabian, MD, PhD; Carlos Riumallo-Herl, PhD; F. Carla Roberts-Toler, MSc; Xavier Gómez-Olivé, MD, PhD; Stephen Tollman, MMed, PhD

Figure 2. Sodium Content on Packaging in a Basket of Food Products in the Agincourt-Bushbuckridge by Wave and Legislative Target

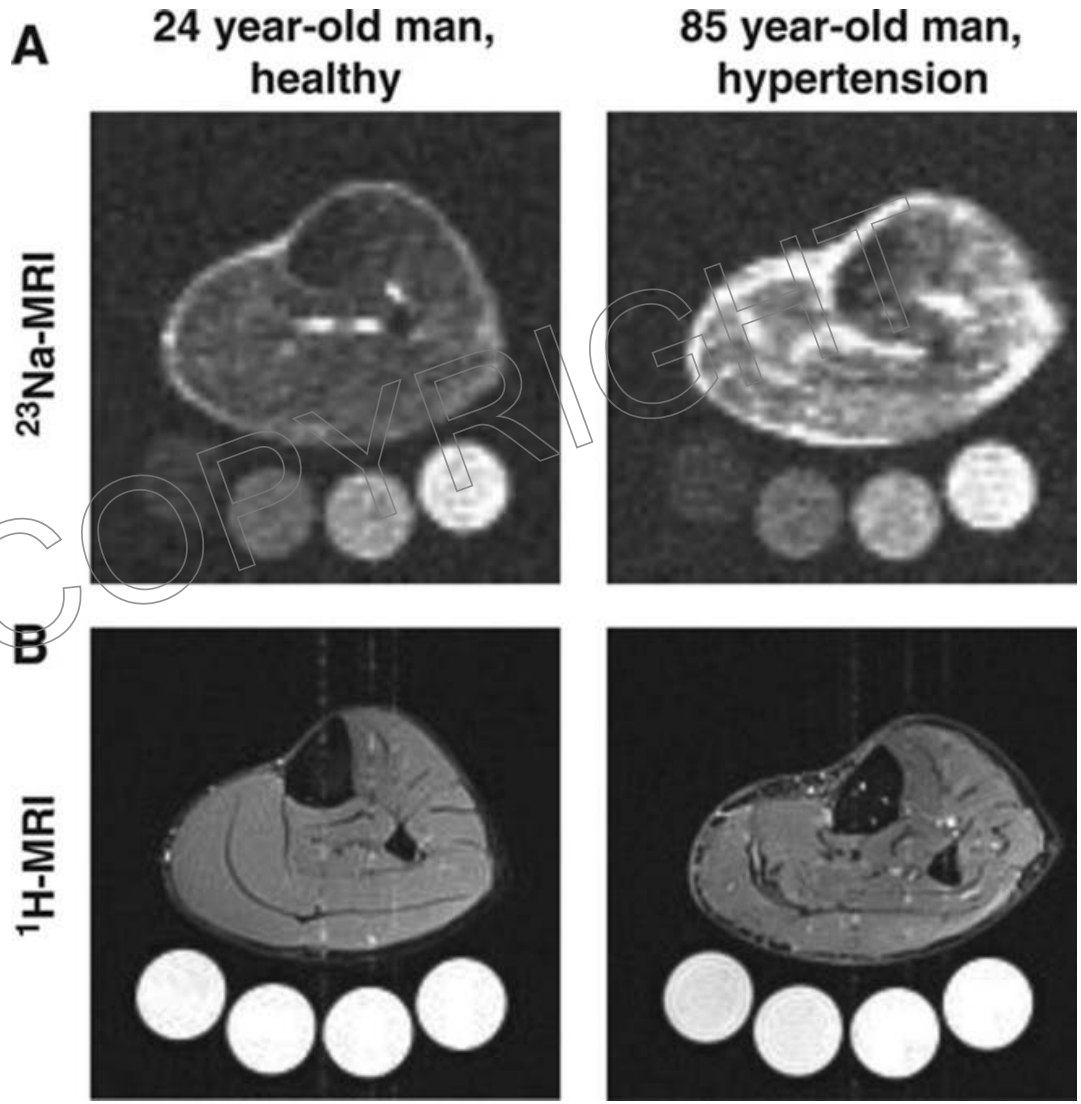


Dry soup powder

For every 1 gram/d of dietary sodium decrease (based on 24-hour urine Na), there was a 1.3 mmHg decrease in systolic BP



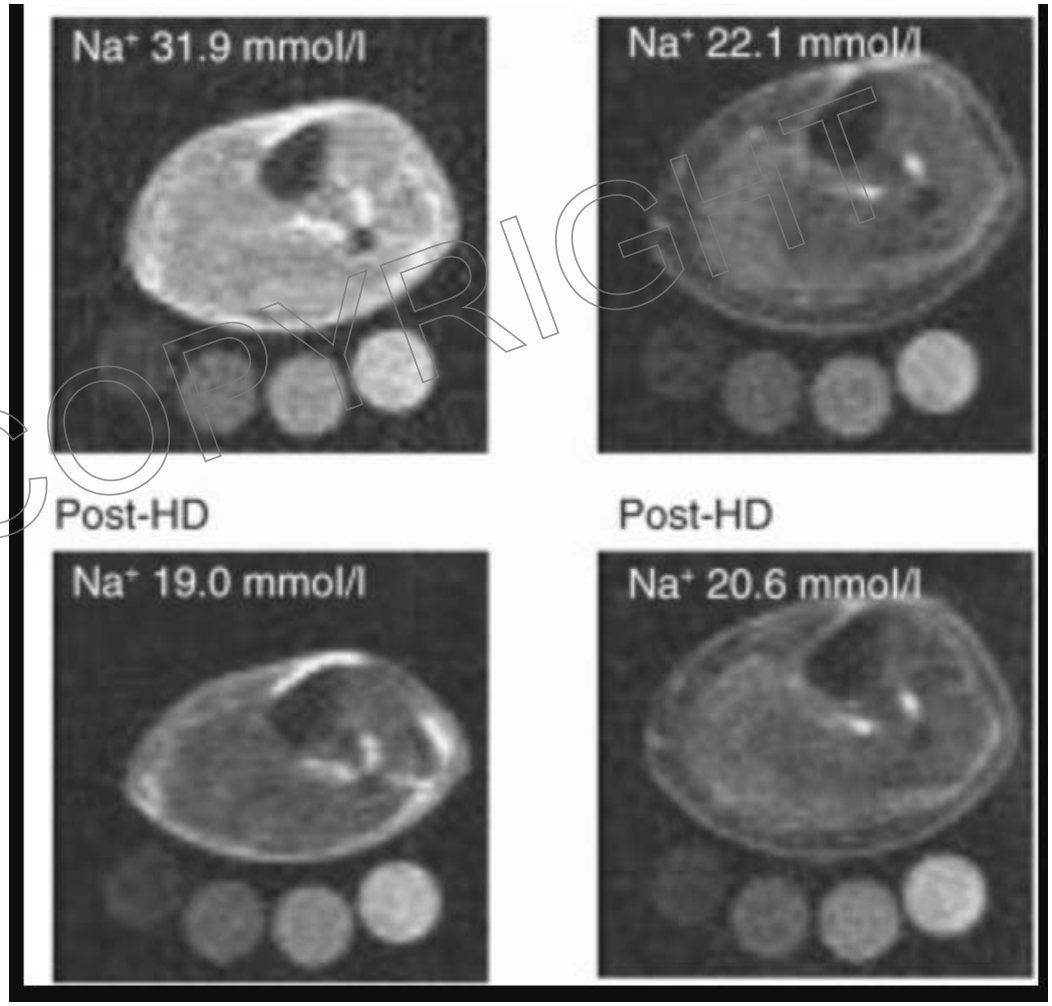
Ellison and Welling NEJM 2021


A
24 year-old man, healthy
85 year-old man, hypertension
^{23}Na-MRI
B
^{1}H-MRI

75-year-old man
High Na+ removal

77-year-old man
low Na+ removal

Pre-dialysis

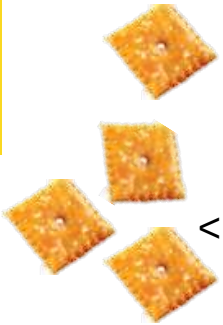


Post dialysis

K^+

Goal

3.5-5 g/day



Na^+

Goal

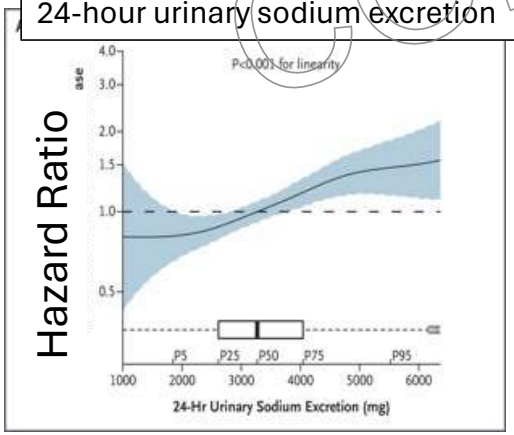
< 2 grams daily

SSASS

10,709 participants: 54% women; 571 cardiovascular events over median of 8.8 years

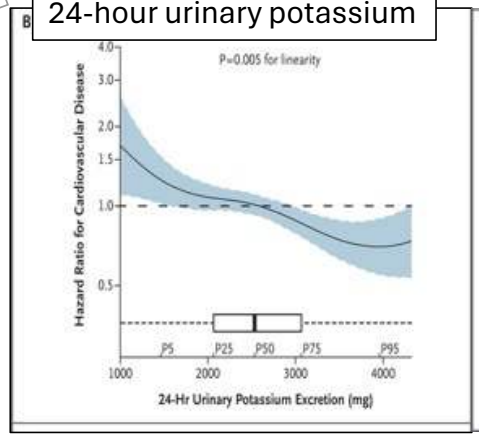
Each daily increment of 1000 mg of sodium **increased risk** by 18% AND each daily increment of 1000 mg of potassium **decreased risk** by 18%

24-hour urinary sodium excretion



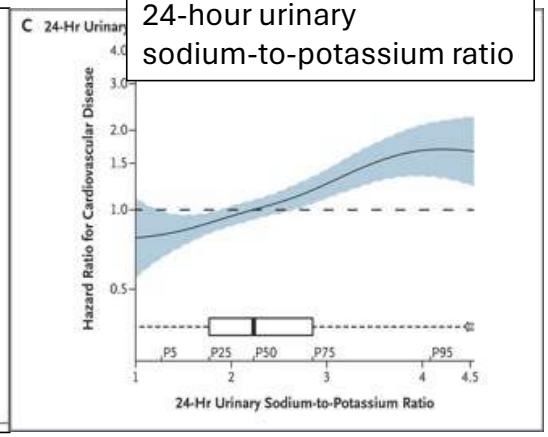
5th to 95th percentile
1846 to 5520 mg

24-hour urinary potassium



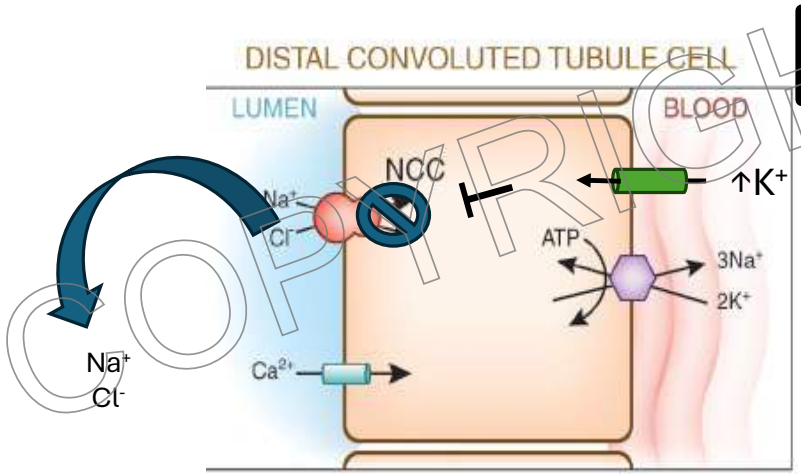
5th to 95th percentile
1462 to 3961 mg

24-hour urinary sodium-to-potassium ratio



Y Ma et al. N Engl J Med 2022;386:252-263.

Dietary potassium influences the thiazide sensitive cells



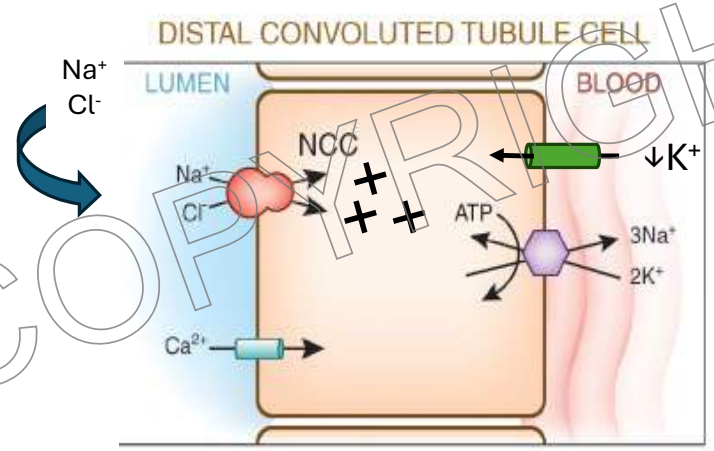
K⁺ sensor

High K⁺ diet

High K⁺ diet leads to
- ↑ K⁺ excretion
- Mild naturiesis

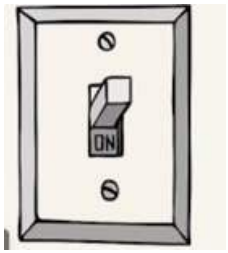
Hoenig

Dietary potassium influences the thiazide sensitive cells



LOW K^+ diet

The K^+ "switch"



Low K+ diet leads to
- ↑ Na^+ reabsorption
- ↓ K^+ excretion

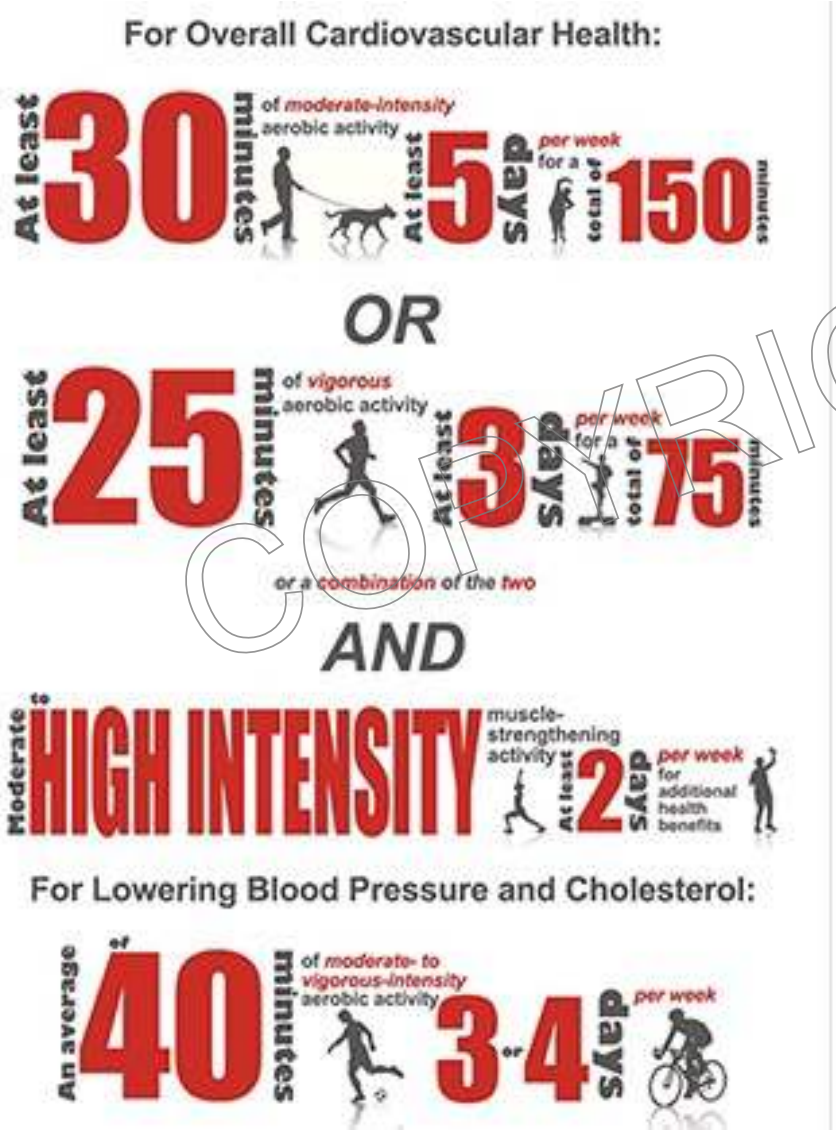
Hoenig

Lifestyle in DM

Regular risk factor reassessment (every 3–6 months)

Manage anemia, CKD-MBD, acidosis, and potassium abnormalities, where indicated

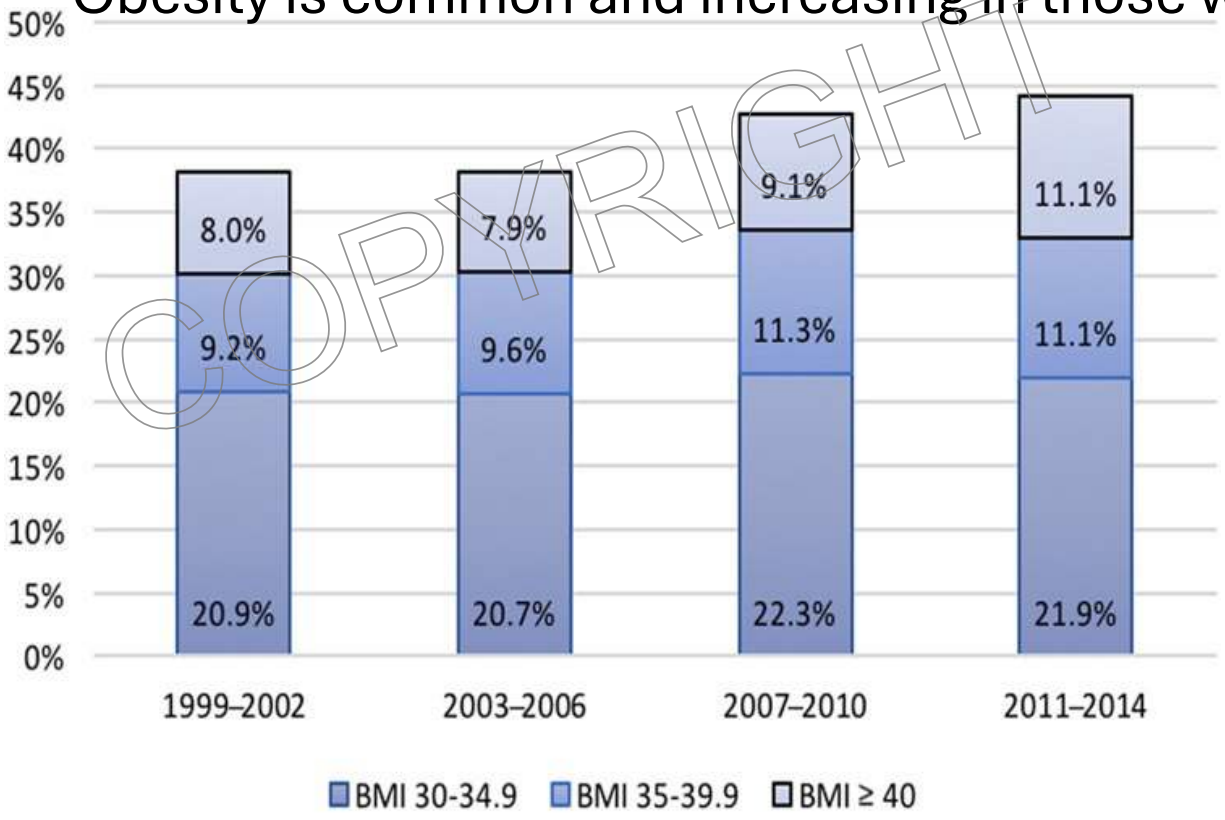
https://kdigo.org/wp-content/uploads/2024/03/KDIGO-2024-CKD-Guideline.pdf



American Heart Association Recommendations for Physical Activity for Adults

Weight management

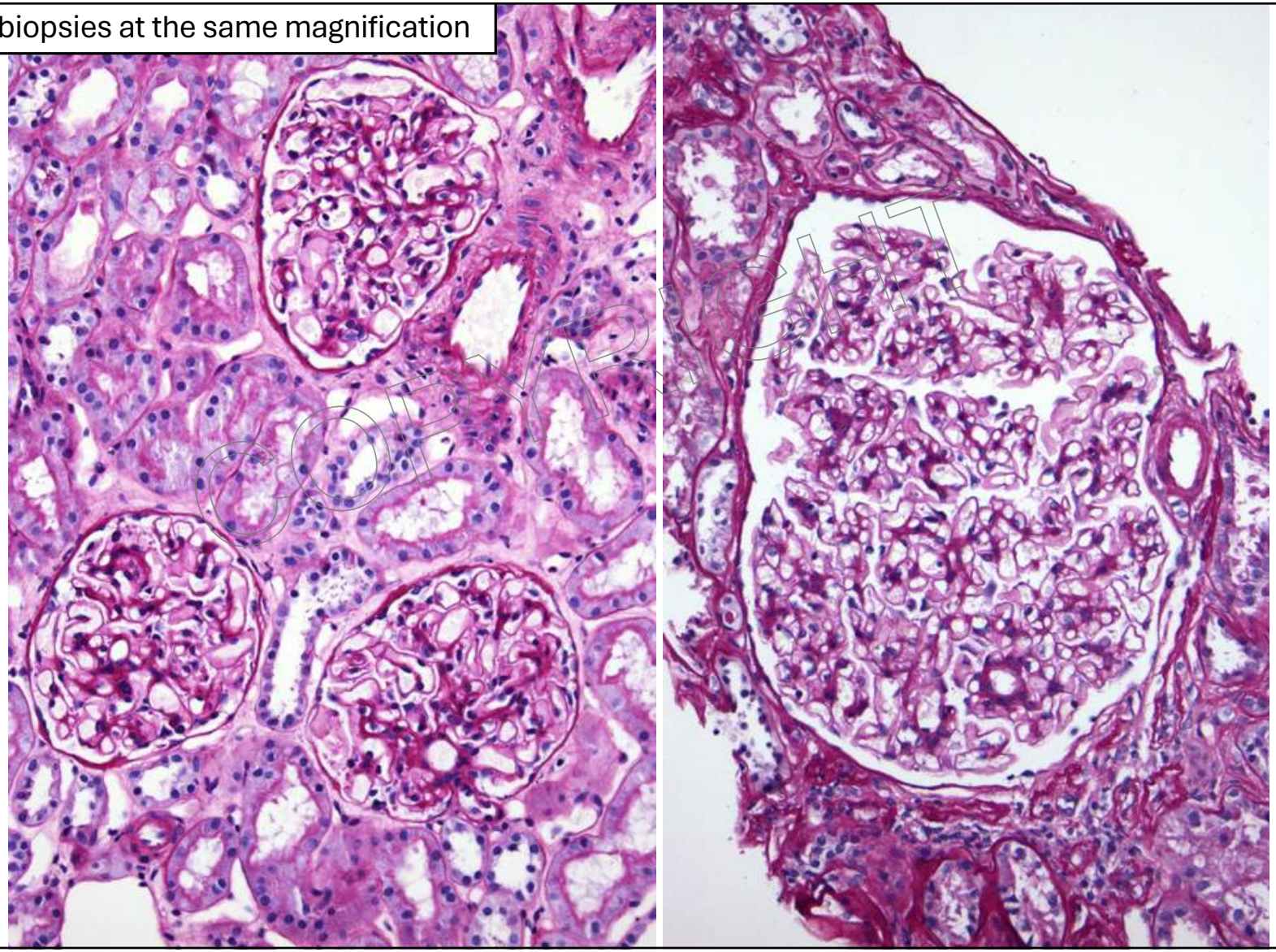
Obesity is common and increasing in those with CKD



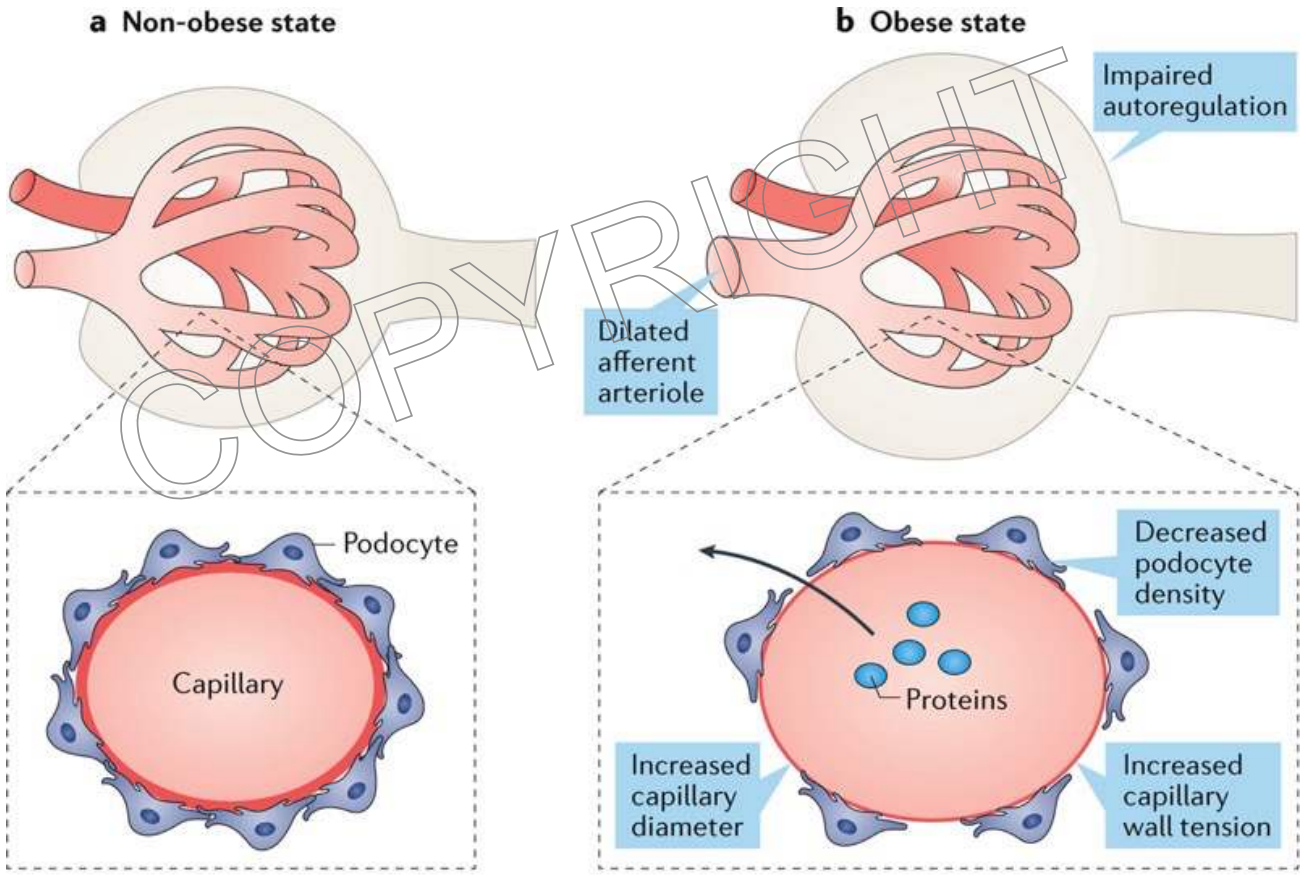
Trends in obesity in US adults with CKD (NHANES data)

Chang et al KI reports 2017

Two kidney biopsies at the same magnification



One of several mechanisms of glomerular injury in obesity



Nature Reviews | Nephrology

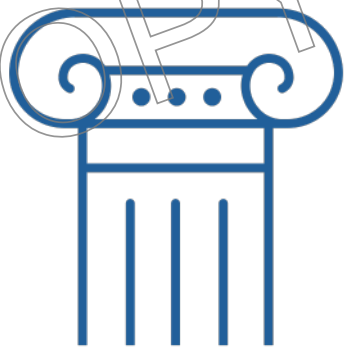
Câmara, N. O. S. *et al.* (2017) *Nat. Rev. Nephrol.*

4 “Pillars” of therapy for Diabetic (proteinuric) Kidney disease

RASi (ACEi/ARB)

✓ Proteinuria

SGLT2i



✓ Proteinuria
With or
without T2DM

GLP1Ra

✓ Proteinuria
With Obesity
And/or T2DM

MRA

✓ Proteinuria
(finerenone for
T2DM in US)

Lifestyle in DM

Regular risk factor reassessment (every 3–6 months)

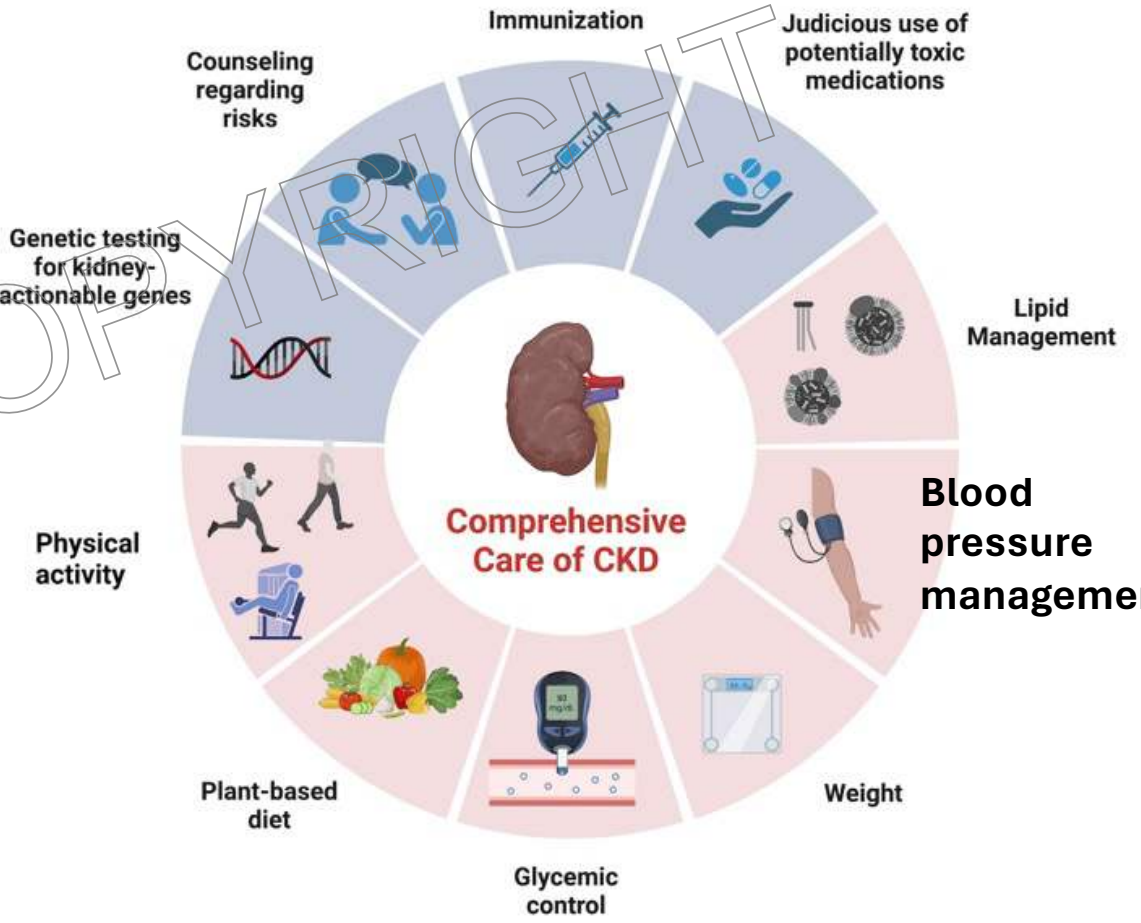
Manage anemia, CKD-MBD, acidosis, and potassium abnormalities, where indicated

https://kdigo.org/wp-content/uploads/2024/03/KDIGO-2024-CKD-Guideline.pdf

Care should be comprehensive

Specific CKD complications

- Anemia
- Hyperkalemia
- Acidosis
- Bone mineral disorders
- Gout



Adapted from Chen, Hoenig, Nitsch, Grams. Nat Rev Nephrol 2023

Management of those with CKD may begin with management of blood pressure

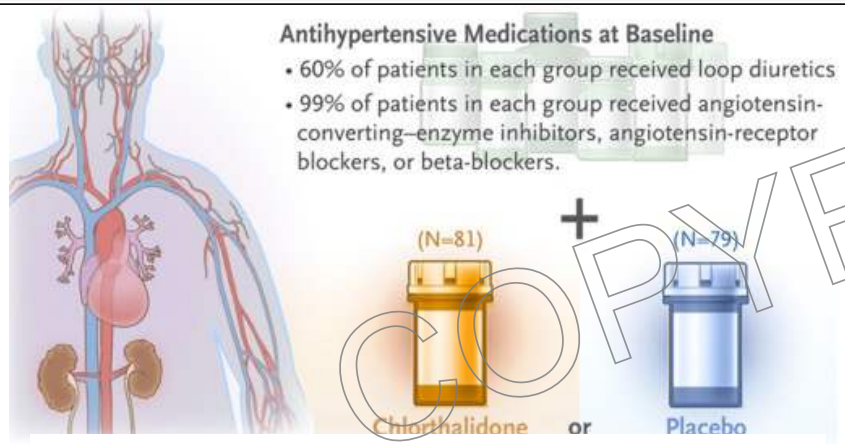
Target <120/80 mmHg

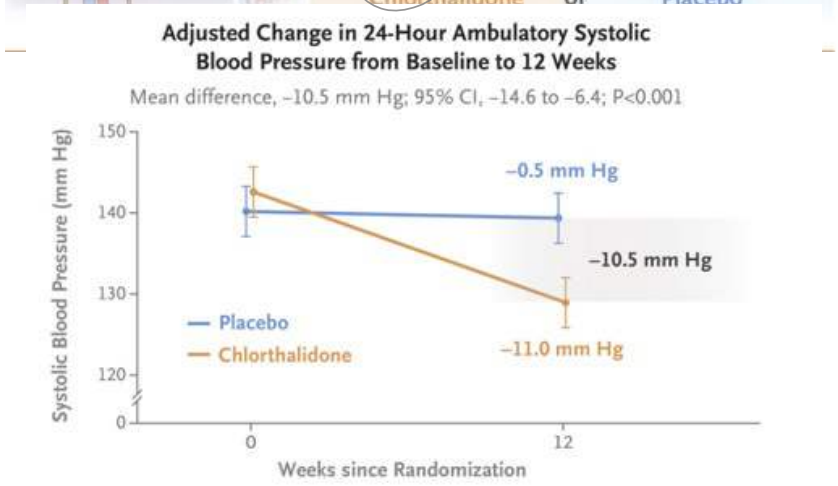
Adapted from Chen, Hoenig, Nitsch, Grams BMJ 2023

ORIGINAL ARTICLE

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Rajiv Agarwal, M.D., Arjun D. Sinha, M.D., Andrew E. Cramer, B.S., Mary Balmes-Fenwick, M.S., Jazmyn H. Dickinson, B.S., Fangqian Ouyang, M.S., and Wanzhu Tu, Ph.D.





160 individuals with stage IV CKD randomized, double-blind, placebo controlled

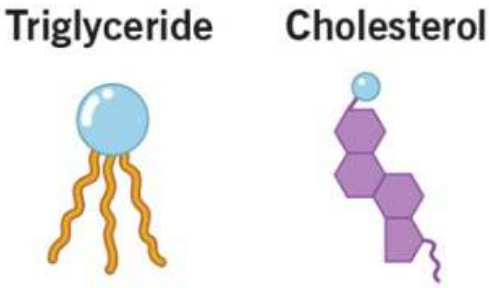
To 12.5 chlorthalidone or placebo, dose titrated to 50 mg as needed

Adverse Events during the Treatment Period

no. with event/total no. (%)	Chlorthalidone	Placebo
Increase in serum creatinine level (>25% from baseline)	33/74 (45)	10/77 (13)
Hypokalemia	8/81 (10)	0
Hypomagnesemia	19/81 (23)	13/79 (16)
Hyponatremia	9/81 (11)	6/79 (8)
Hyperglycemia	13/81 (16)	4/79 (5)
Hyperuricemia	16/81 (20)	7/79 (9)
Dizziness	20/81 (25)	13/79 (16)

Agarwal R NEJM 2021

Medications for lipid disorders in CKD



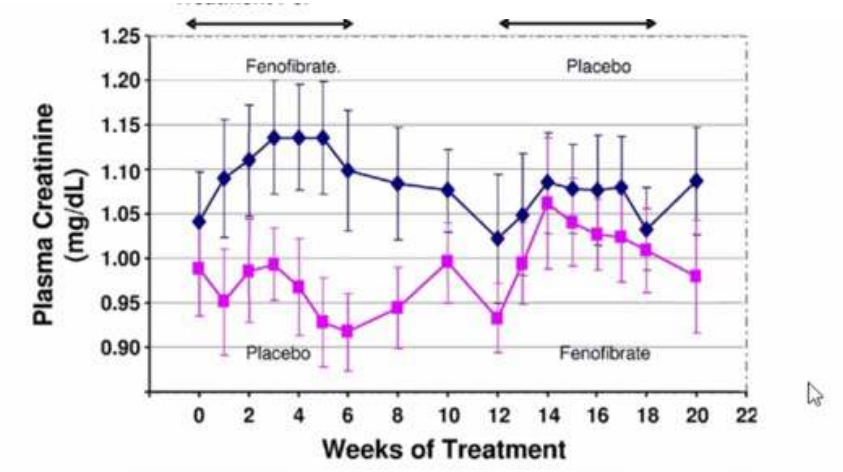
Statins

- Despite concerns regarding AKI, proteinuria, large scale studies and metanalyses have not shown consistent negative effect
- In high dose, may block tubular albumin reabsorption without causing kidney disease
- **Recommended for individuals over 50 years with CKD stage 3a-5 and suggested for those with stage 1,2)**

Fenofibrate

- May cause reversible increase in creatinine
- Mechanism unclear

Randomized controlled crossover-trial

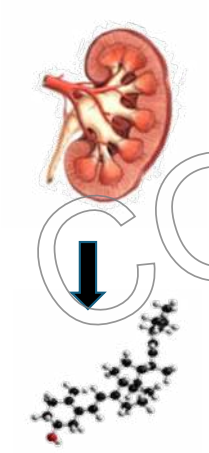


See KDGIDO CKD and lipid guidelines

Ansquer J et al AJKD 2008

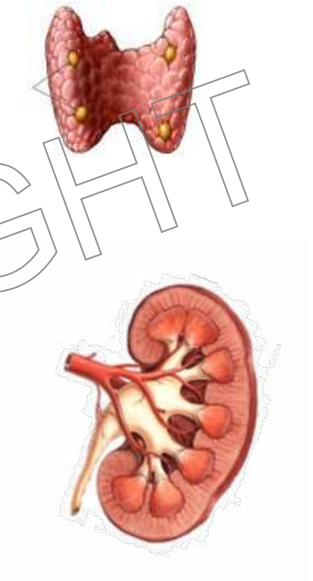
Bone-Mineral Metabolism

Parathyroid glands are stimulated by low Ca^{++} or high PO_4



The kidney makes active 1,25 vit D

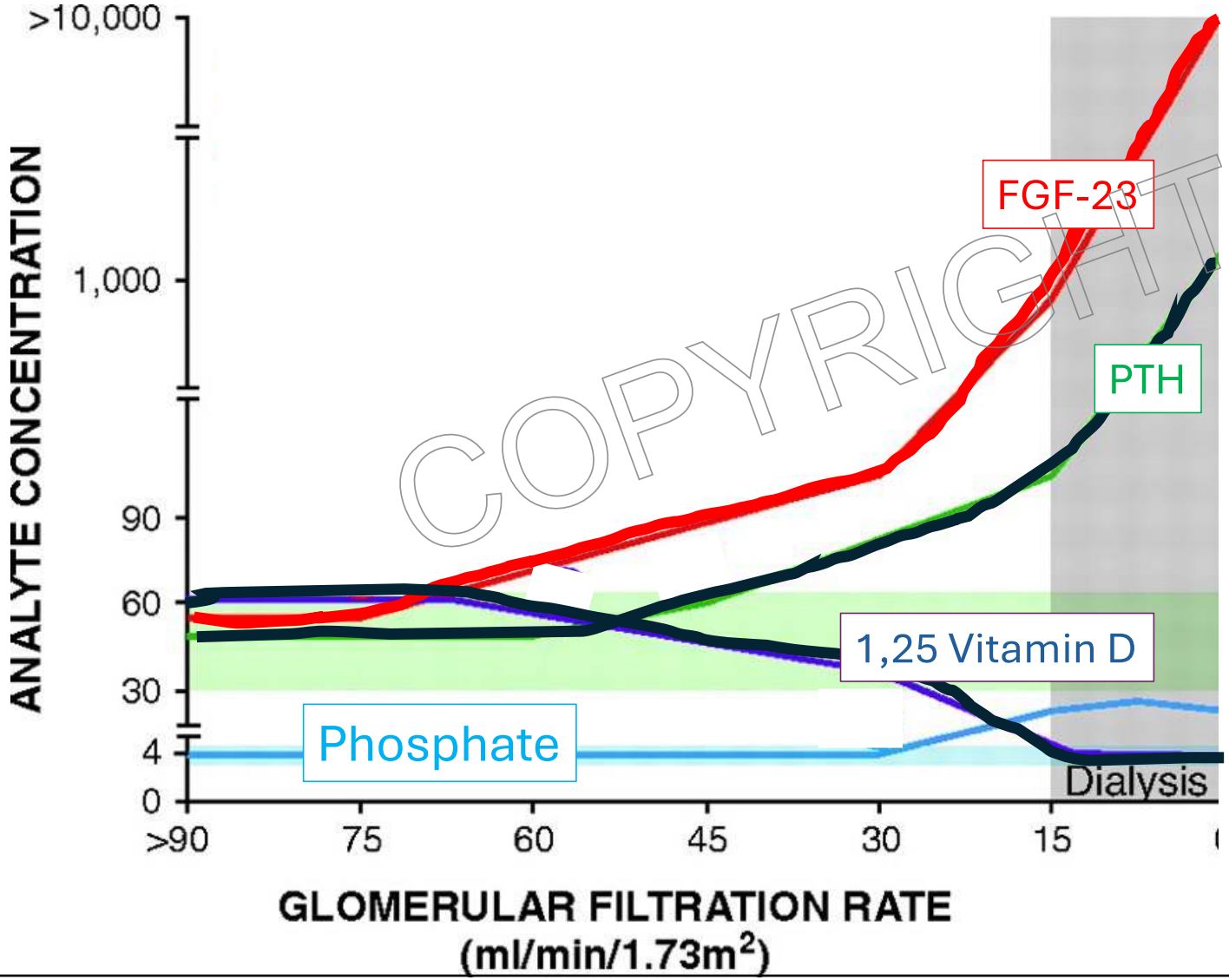
1,25 vit D increases calcium reabsorption from enterocytes



The kidney excretes excess phosphate

If PO_4 cannot be excreted, this stimulates PTH to increase urinary excretion (but releases more Ca^{++} and PO_4 from bone)

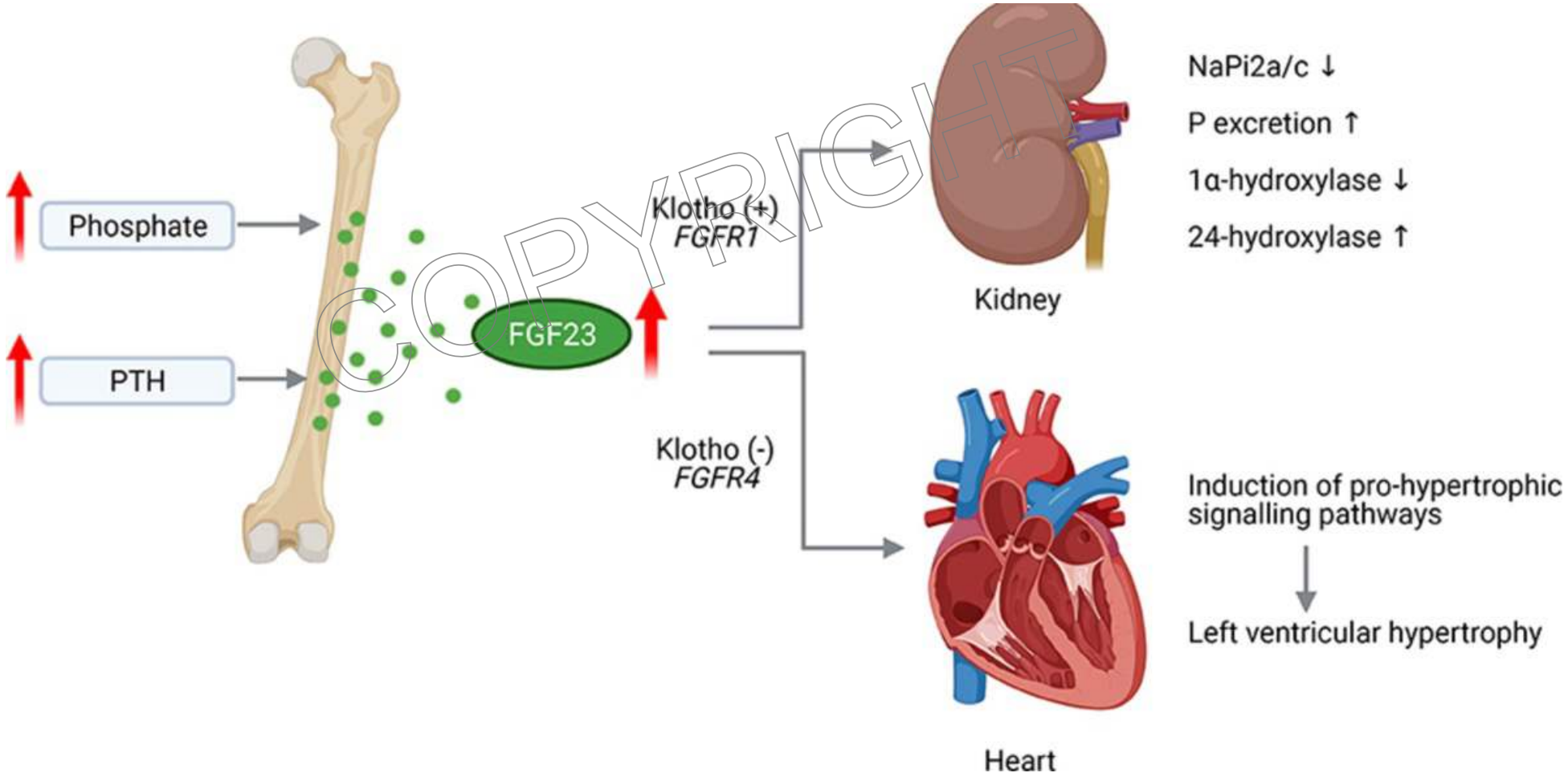
Without 1,25 vitamin D (and dietary Ca^{++}), PTH increases to release Ca^{++} from bone



1. FGF-23 increases phosphate excretion and rises before PTH in progressive CKD
2. The phosphate looks normal with significant hormonal changes behind the scenes

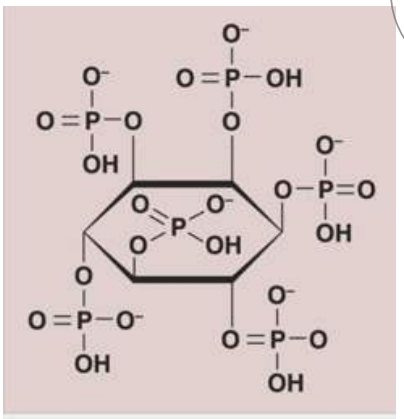
Myles Wolf JASN 2010;21:1427-1435

In addition to its phosphaturic effect, FGF-23 has an “off-target effect” on cardiac muscle and leads to hypertrophy and stiffening.



Sources and “bioavailability of dietary phosphate

Source	Bioavailability
Plant	20-40%
Dairy	30-60%
Meat	Up to 80%
Inorganic phosphate additives	90-100%



Reduced intestinal absorption of phosphate in plant foods is attributed to phylate

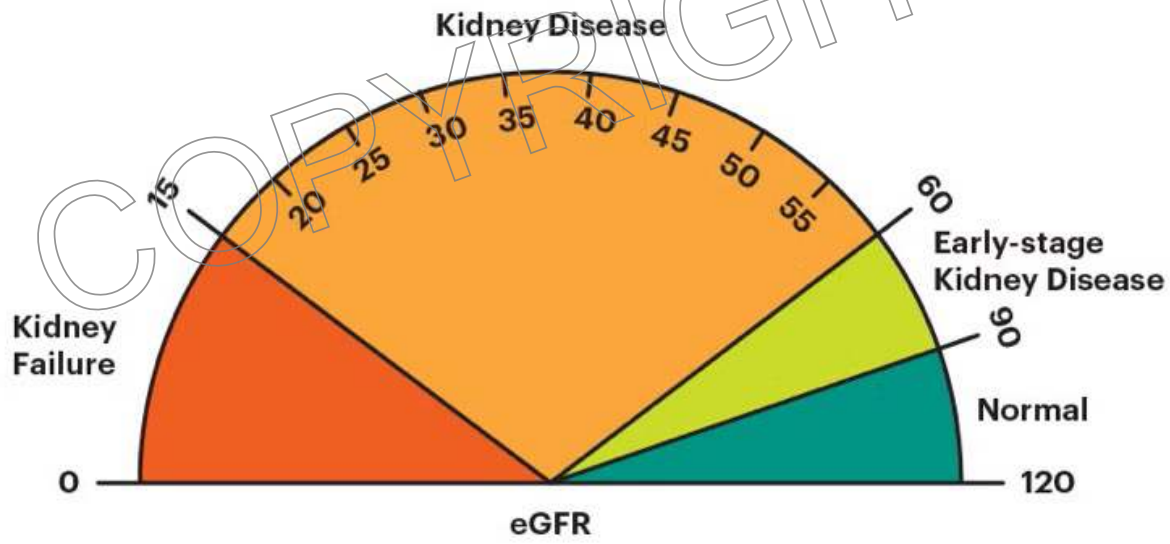
Adapted from Rose and Strombom 2019; Ekramzedah M et al. CJASN 2024

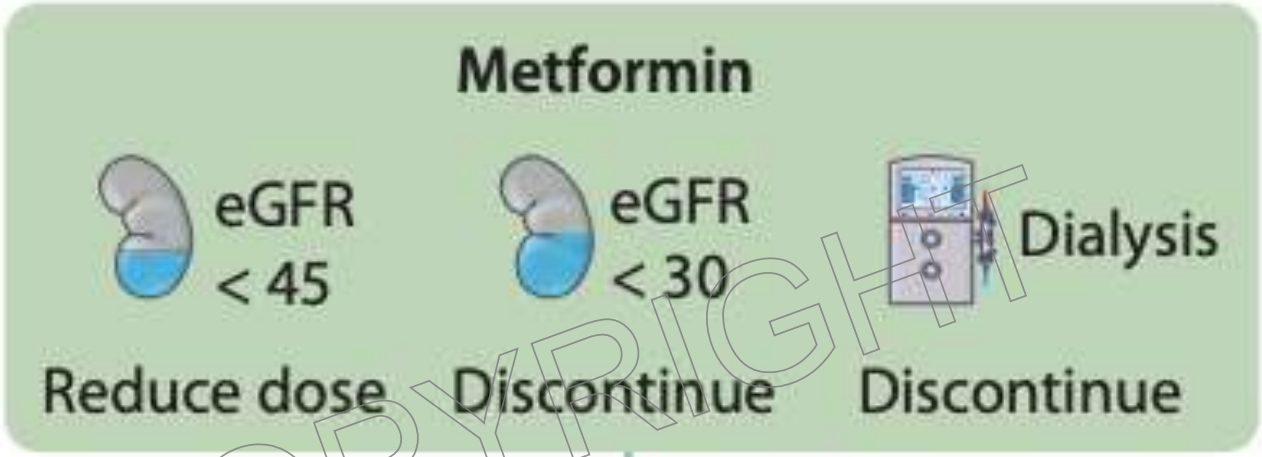
https://healthymissiondietitian.com/do-i-need-to-avoid-foods-high-in-phosphorus/

Treating 2° hyperparathyroidism

- Target normal phosphate and treat vitamin D deficiency
- **Limit ultra-processed foods high in bioavailable phosphates
- Replete vitamin D with 50,000 IU ergocalciferol weekly X 12 weeks (or more)
- Rx*- Hyperphosphatemia-mg per mg, binders are roughly equivalent
  - Ca carbonate, Ca acetate, sevelamer , lanthanum
- Active vitamin D and vitamin D analogues are used to replete 1,25 vitamin D and suppress PTH- “target PTH” increases with worsening GFR

Medication concerns and dosing in CKD





- Begin at 500 mg once daily increase as needed/tolerated to 2,000 mg/day in divided doses (max 2500)
- Not nephrotoxic but cleared by kidneys
- Hold metformin with clinical conditions when kidney function may decline suddenly
- Metformin-associated lactic acidosis is rare but has a high mortality

From KDIGO CKD DM guidelines 2022

Short-term NSAID use (<5 days) is often reasonable in CKD

Potential for adverse effects:

- Acute kidney injury
- Hypervolemia and sodium avidity
  - edema, CHF, diuretic resistance
- Interstitial Nephritis (rare)
- Nephrotic syndrome (rare)
  - membranous and minimal change
- Papillary Necrosis (rare)

❖ **eGFR 30-45 (CKD 3b)**

- Use for specific acute indication
- Limit chronic use
- Use short acting formulations

(such as ibuprofen and diclofenac)

❖ **eGFR <30 (CKD 4 and 5)**

Avoid oral or IV

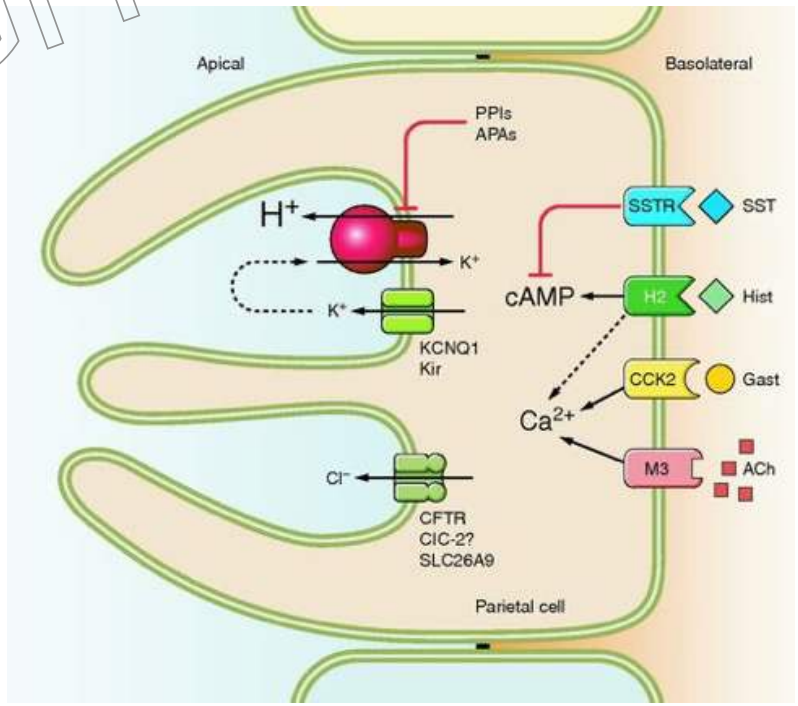
Topical NSAIDs likely safe at any GFR

Baker M and Perazella MA AJKD 2020

Image- https://www.the-rheumatologist.org/article/fda-issues-stronger-nonsteroidal-anti-inflammatory-drugs-nsaids-warning/

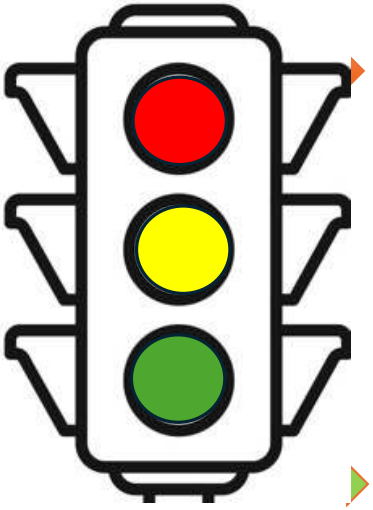
Proton Pump Inhibitors

- Can cause acute and chronic interstitial nephritis
- Associated with CKD
- Prescribe PPI at lowest dose and shortest duration for the indication
- Discontinue PPI in patients without clear indication (Taper dose to avoid rebound hypersecretion from long term use)



Kopik and Geibel 2013

When to stop RASi (ACEi and ARB)?



RASi has the potential to worsen kidney function (by decreasing glomerular pressure)

- Acute kidney injury (AKI)
- Refractory hyperkalemia
- Bilateral renal artery stenosis

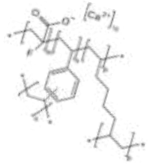
RASi has the potential to protect kidney function (by decreasing glomerular pressure)

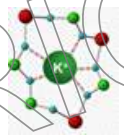
- Have a “sick day” plan
- Low risk pre-operative setting
- Chronic dialysis (still an excellent option for BP and heart failure)

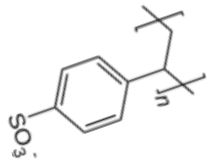
Stop-no-Stop Trial found no difference in post-op complications for major noncardiac surgery (Legrand JAMA 2024)

Tailored options for hyperkalemia

1.Ensure adequate fluid intake
2.Moderate the potassium in diet
3.Medication changes
4. K-wasting diuretics (loop and thiazide) plus SGLT2i!
5.resins-polystyrene and newer agents







Patiromer
(marketed as Veltassa)
FDA-approved for CHRONIC not acute HYPERKALEMIA
Exchanges Ca^{++} for K^{+}
hypomagnesemia and constipation

Sodium zirconium cyclosilicate (Zs9)
(marketed as Lokelma)
FDA approved for CHRONIC not acute HYPERKALEMIA
traps K^{+}
but not Mg^{++} or Ca^{++}

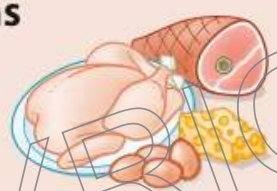
Sodium Polystyrene sulfonate (SPS)
(Kayexalate)
Exchanges Na^{+} for K^{+}
Efficacy never rigorously studied
Warning! Risk for colonic necrosis

Marketed to maintain RASi

Recommendations regarding treatment of metabolic acidosis are in flux and now "suggested" rather than recommended by KDIGO. Many are emphasizing limiting animal protein in favor of plant-based protein

Bicarbonate supplements Vs.

Animal proteins



Meat, poultry, fish, seafood, eggs:
28 g (1 oz) = 6–8 g protein
1 egg = 6–8 g protein

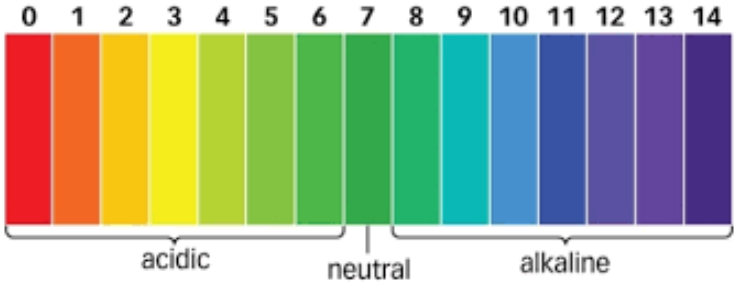
Dairy, milk, yogurt, cheese: 250 ml (8 oz) = 8–10 g protein
28 g (1 oz) cheese = 6–8 g protein

Plant proteins

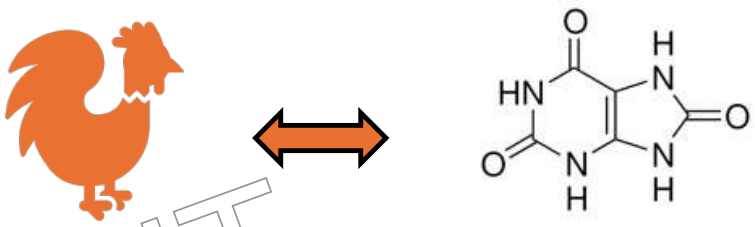
Legumes, dried beans, nuts, seeds:
100 g (0.5 cup) cooked = 7–10 g protein

Whole grains, cereals:
100 g (0.5 cup) cooked = 3–6 g protein

Starchy vegetables, breads:
2–4 g protein

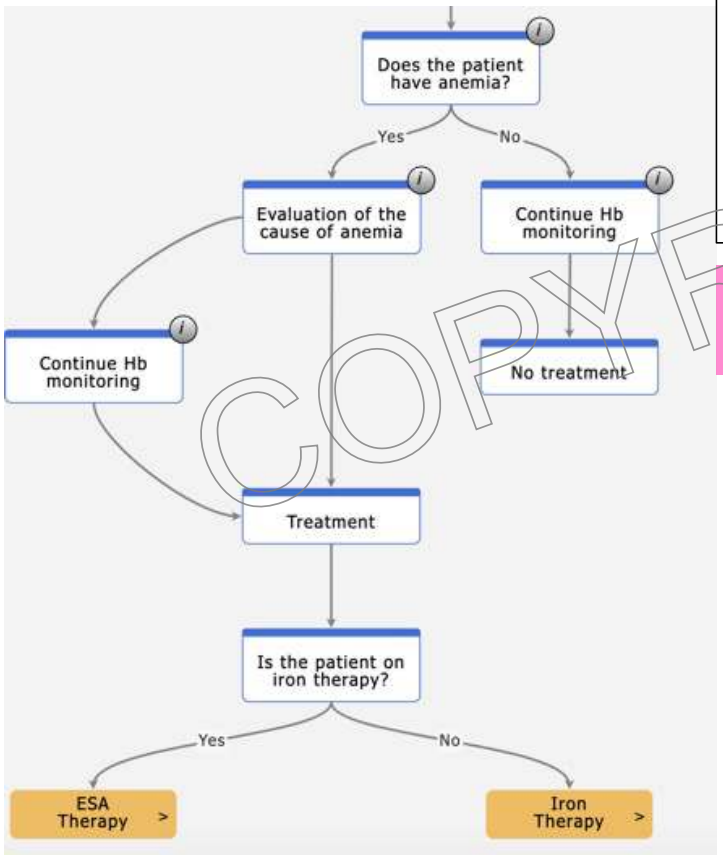


Hyperuricemia



- ↓ kidney function is associated with ↑ serum uric acid levels
- Hyperuricemia is also associated with development and progression of CKD
- ACR recommends **urate lowering therapy (ULT)** with 1st episode of gout in a patient with CKD
- Conservative measures: decrease in purine rich foods, fructose rich beverages and EtOH
- Pharmacologic therapy to target a serum level <6 (<5 with tophi)
- Use prophylactic anti-inflammatory agent with initiation of ULT

Anemia in CKD



Suggested interval for measurement of hemoglobin

- CKD 3: annually
- CKD 4: q 6 months
- CKD 5: q6 months
- On dialysis – per nephrology (at least q 3 months)

Evaluation of anemia
KDIGO guideline 1.3 –not graded

Investigations should include:

- CBC
- Absolute reticulocyte count
- Ferritin
- TSAT (iron ÷ TIBC)
- Vitamin B12 (in some cases)
- Folic acid (in some cases)

Address all correctable causes before initiation of Erythropoiesis stimulating therapy (ESA)

With ESA, target Hgb is 10-11 g/dl

KDIGO Anemia update 2022

Iron Before ESA

- Trial of oral iron first
- Target iron saturation (Fe/TIBC)>20 or 30 % and
  ferritin >200-500 ng/mL
- Many cannot tolerate oral iron or it cannot be replenished effectively/sufficiently
- IV iron is safe
  - –Multiple products
  - –Differential cost

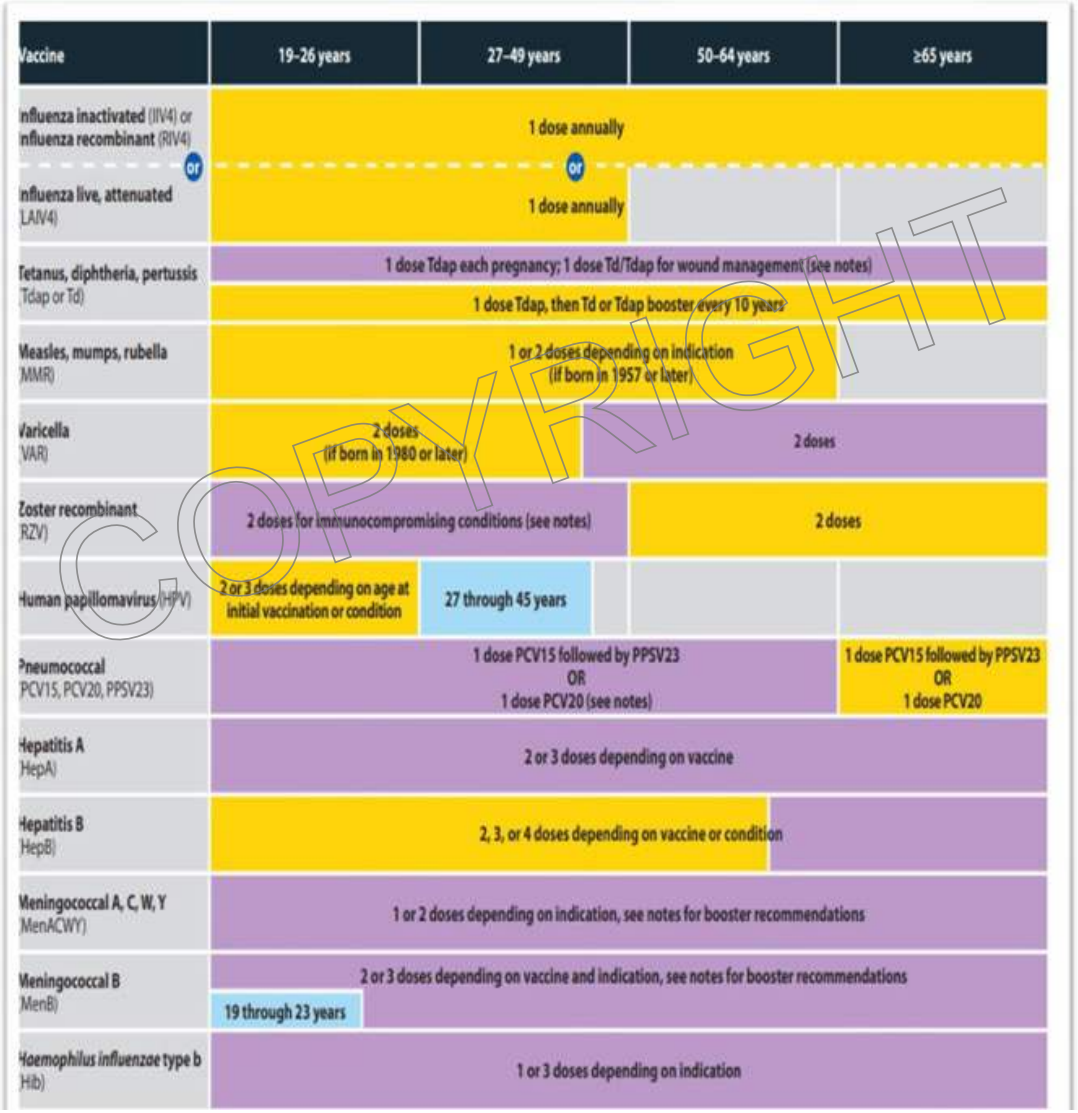
$ Slow IV infusion
Test dose

Fastest $$$$$$

Generally, drink to thirst (more if kidney stones, less if hyponatremia

Age-appropriate vaccinations

Note some kidney disorders can “flair” with vaccinations Especially IgA nephropathy



Recommended for adults who meet age requirement without evidence of vaccination or past infection

Recommended if additional risk factor

Recommended based on shared decision making

Hoenig

Thompson D J Nat Med Assoc 2022

Targeted therapies for kidney disorders are coming! Here's a sampling!

Disorder	FDA approved treatment
PCKD	Tolvaptan to slow cyst growth (more drugs in pipeline)
IgA nephropathy	Budesonide (synthetic corticosteroid) Sparsentan (dual endothelin-angiotensin receptor antagonist--conditional approval for rapidly declining kidney function) (more in pipeline)
ANCA associated glomerulonephritis	C5A receptor inhibitor (as an add-on to current standard therapy)
Genetic FSGS associated with ApoL1	*Not approved but exciting! –inoxaplin – small molecule inhibitor of ApoL1 channel function (successful phase 2a study-- Egbuna NEJM 2023)*

Consult nephrology:

- eGFR <<<60 ml/min/1.73m^2 (or ≤45, if >60 years)
- Rising albuminuria
  - Assistance in diagnosis
  - Assistance in optimal management
  - Difficult to control hypertension
  - Rapidly worsening kidney function
  - Unexplained urinalysis findings
  - Assistance with managing electrolytes
  - Early preparation for ESKD

Thank you!

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