# From Filtration to Precision: Evolving CKD Therapies

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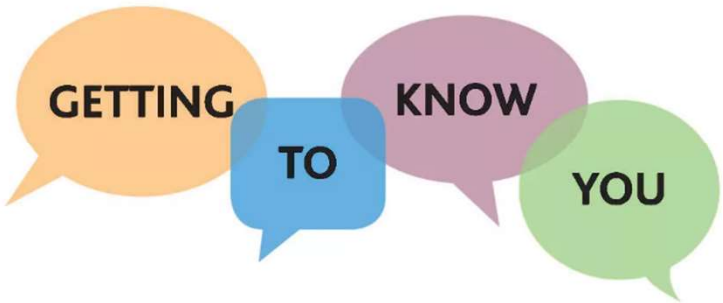


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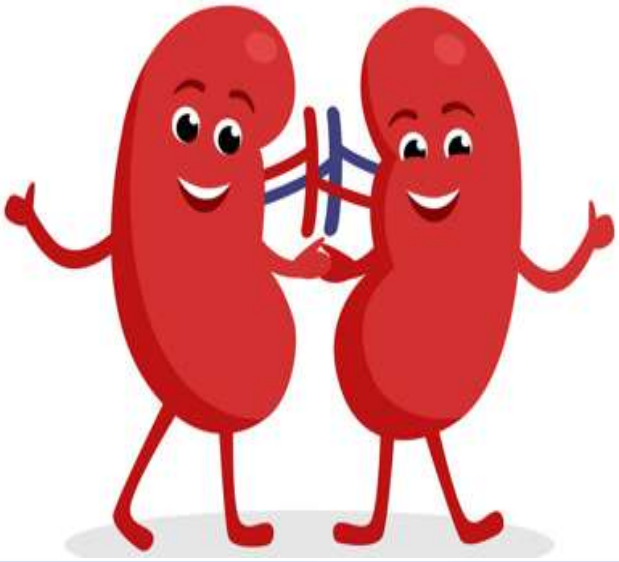
## Pharmacists' Learning Objectives

- Interpret laboratory values indicative of chronic kidney disease (CKD)
- Develop prevention and treatment plans for patients with CKD and metabolic disorders
- Discuss medications that may cause CKD and/or require renal dose adjustments



https://www.vectorstock.com/royalty-free-vector/strong-healthy-kidneys-cartoon-characters-isolated-vector-20632113

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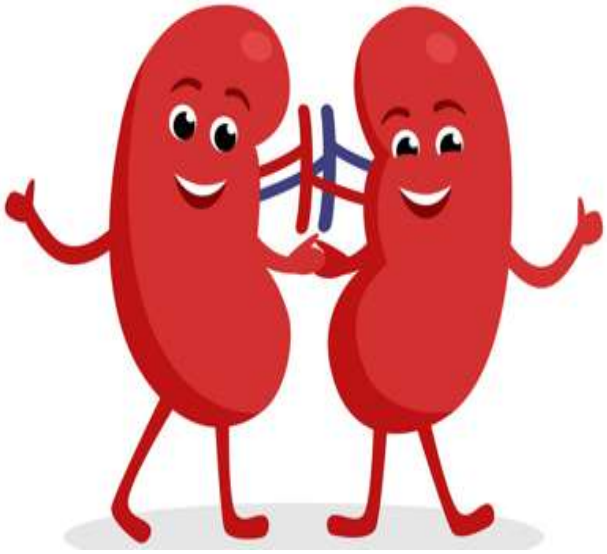
## Technicians' Learning Objectives

- Identify laboratory values indicative of chronic kidney disease (CKD)
- Review treatment plans for patients with CKD, and metabolic disorders
- List medications that may cause CKD and/or require renal dose adjustments



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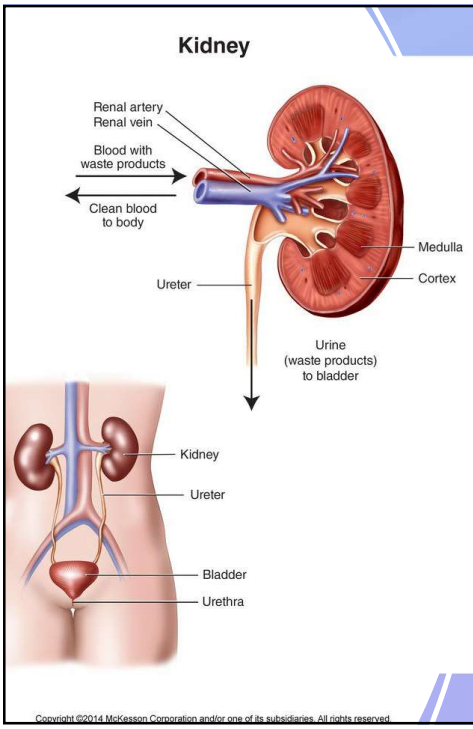



# Functions of the Kidneys

- Waste excretion
- Fluid and electrolyte regulation
- Maintenance of acid-base homeostasis
- Secretion of hormones and prostaglandins
  - Calcium homeostasis
  - RBC production

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# Background

- Chronic kidney disease (CKD): abnormalities of kidney structure of function present > 3 months, with implications for health
  - Characterized by progressive deterioration in kidney function and irreversible structural damage to nephrons
- CKD classification based on:
  - Cause
  - GFR category (G1-G5)
  - Albuminuria category (A1-A3)

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# Criteria for CKD

**Table 1 | Criteria for chronic kidney disease (either of the following present for a minimum of 3 months)**

| | |
|---|---|
| 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) |

ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate.

KDIGO 2024 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International.* 2024; 105(4S).

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# Staging in CKD: GFR

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.

Inker LA, Astor BC, Fox CH, et al. KDOQI US Commentary on the 2012 KDIGO Clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* 2014;63(5):713-735.

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# Staging in CKD: Albuminuria

Albuminuria categories in CKD

| Category | AER (mg/24 hours) | ACR (approximate equivalent) (mg/mmol) | (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]).

Inker LA, Astor BC, Fox CH, et al. KDOQI US Commentary on the 2012 KDIGO Clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* 2014;63(5):713-735.

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Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

| GFR categories (ml/min/1.73 m²), description and range | | | | Persistent albuminuria categories, description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 | A2 | A3 |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g <3 mg/mmol | 30–300 mg/g 3–30 mg/mmol | >300 mg/g >30 mg/mmol |
| | G1 | Normal or high | ≥90 | | | |
| | G2 | Mildly decreased | 60–89 | | | |
| | G3a | Mildly to moderately decreased | 45–59 | | | |
| | G3b | Moderately to severely decreased | 30–44 | | | |
| | G4 | Severely decreased | 15–29 | | | |
| | G5 | Kidney failure | <15 | | | |

green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

Inker LA, Astor BC, Fox CH, et al. KDOQI US Commentary on the 2012 KDIGO Clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* 2014;63(5):713-735.

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## Creatinine-based eGFR(eGFRcr) versus Creatinine and cystatin C-based eGFRcr-cys)

- Creatinine may be misleading
  - Extreme body habitus or specific conditions
- Cystatin C is impacted by several variables
- Combined calculation provides more accurate estimates of GFR when combined

$$\text{eGFR cr-cys} = 135 \times \min(SCr/\kappa,1)^{\alpha} \times \max(SCr/\kappa,1)^{-0.544} \times \min(Scys/0.8,1)^{-0.323} \times \max(Scys/0.8,1)^{-0.778} \times 0.9961^{Age} \times 0.963 \text{ [if female]}$$

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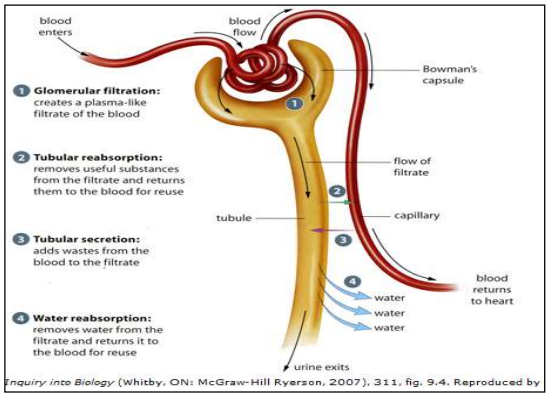
## Pathophysiology

- Each kidney contains nephrons that maintain its own single eGFR
- With nephron loss, remaining functional nephrons increase eGFR to compensate
  - Leads to hypertrophy and irreversible loss of function from sustained increases in glomerular pressure
- Occurs over months to years
- Assessed by rate of eGFR decline



*Inquiry into Biology* (Whitby, ON: McGraw-Hill Ryerson, 2007), 311, fig. 9.4. Reproduced by

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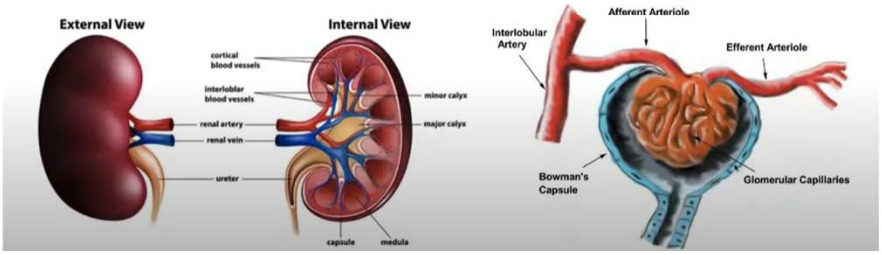
# Pathophysiology: Hypertension

Renal artery thickening ➔ reduced blood perfusion ➔ ischemia and inflammation ➔ reduced GFR




(1058) How diabetes and hypertension leads to kidney failure - YouTube

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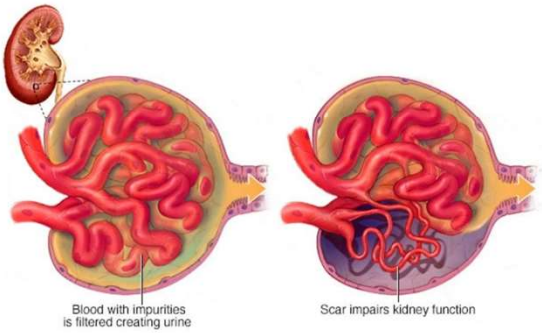
# Pathophysiology: Diabetes




Excessive glucose filtration

↓

Increase osmotic pressure

↓

Thickening of capillary basement membrane

Focal segmental glomerulosclerosis (FSGS) - Symptoms and causes - Mayo Clinic

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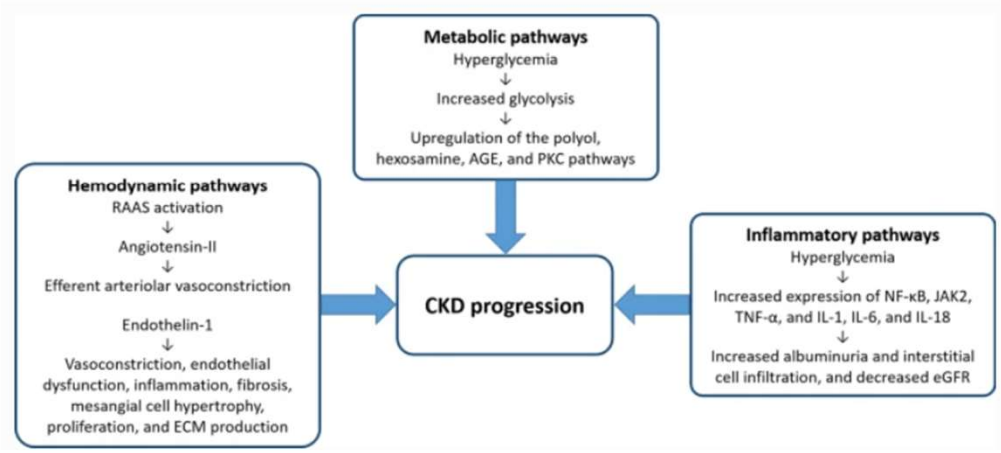
# CKD Progression




Mende, C.W. Chronic Kidney Disease and SGLT2 Inhibitors: A Review of the Evolving Treatment Landscape. *Adv Ther* **39**, 148–164 (2022).

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# Clinical Presentation

- Complications with disease progressions, most often stage 3
  - Fluid and electrolyte abnormalities
    - Uremic symptoms
  - Metabolic acidosis
  - Anemia
  - Mineral and bone disorder
  - Cardiovascular complications
  - Poor nutritional status

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## Active Learning Question #1

CKD staging is defined by:

A. Glomerular filtration rate (GFR)
B. Level of albuminuria
C. All of the above

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## Goals of Therapy

- Delay and prevent progression disease
- Minimize the development and severity of associated complications

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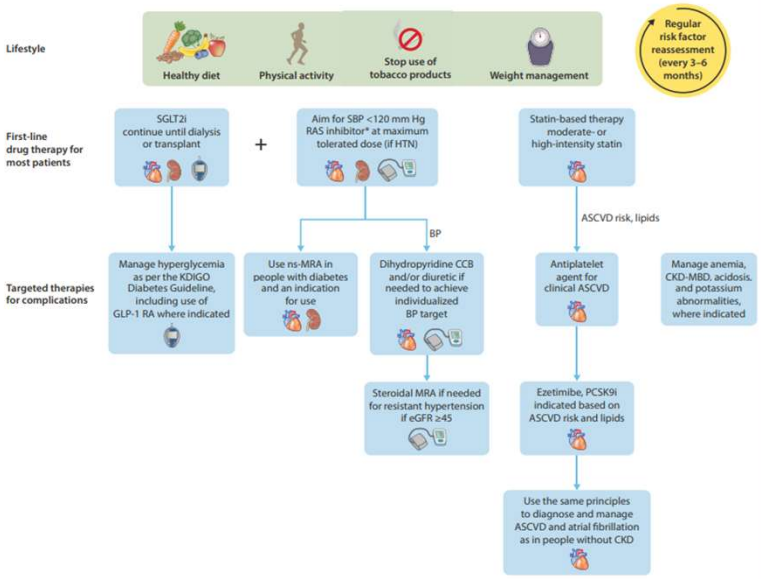
# Holistic Approach to CKD Treatment and Risk Modification




Levin A, Ahmed S. Carrero JJ. Executive summary of the KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease: Known knowns and known unknowns. *Kid Int.* 2024;105:684-701.

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# Prevention

- Control risk factors and comorbidities
  - Diabetes management
  - Dyslipidemia
  - Blood pressure management
  - Obesity
  - Smoking cessation

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# Hypertension

- BP goal
  - SBP < 120 mmHg when tolerated with standardized office BP measurement
  - Consider less intensity based on risk of hypotension/falls and limited life expectancy
- ACE or ARB at highest tolerable dose recommended first line:
  - ↑BP, CKD, albuminuria (CKD G1-G4, albuminuria category A3) without (-) diabetes
  - ↑ BP, CKD, moderate albuminuria (CKD G1-G4, albuminuria category A2) without (-) diabetes
  - ↑ BP, CKD, moderate to severe albuminuria (CKD G1-G4, albuminuria category A2-A3) with (+) diabetes
  - ↑ BP, CKD, no albuminuria ± diabetes

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# Hypertension & Dialysis

- To control blood pressure (BP) related to volume change:
  - Adjust dialysis therapy to achieve patient's *dry weight*
  - Post-dialysis weight - symptoms of hypervolemia and hypovolemia are absent

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# Hypertension

- ACEI shown to reverse left ventricular hypertrophy (LVH)
  - Start with low, renoprotective doses and titrate Q4 weeks to control proteinuria
    - Increase until proteinuria reduced by 30 – 50% or develop side effects
    - Initiation may elevate SCr ~ 25-30% within 3-7 days after initiation due to reduced intraglomerular pressure
      - If SCr rises > 30%, then reduce dose or discontinue
    - Monitor for hyperkalemia
- Gradually lower BP and avoid abrupt drops in order to maintain perfusion to kidneys

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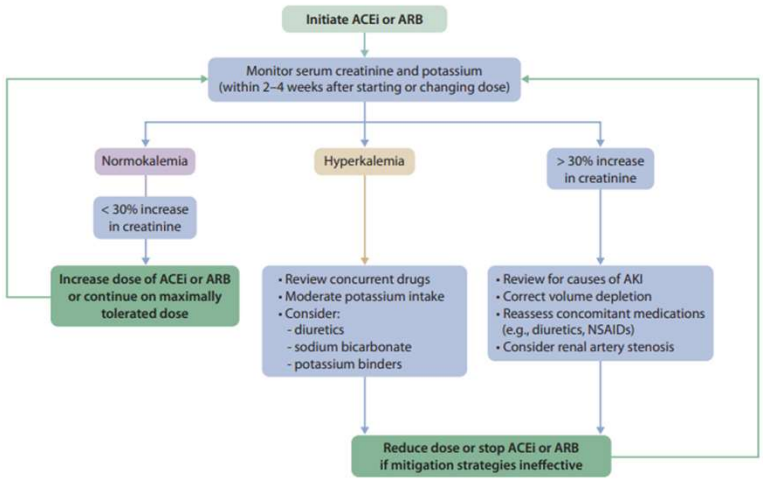
# Dose Titration for RAAS Blockade




KDIGO 2022 Clinical practice guideline for diabetes management of chronic kidney disease. *Kidney International.* 2022; 102(Suppl5S), S1-S127.

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# Hypertension

- Diuretics may be effective if adequate urinary output (UOP)
  - Thiazides generally ineffective at GFR < 30 ml/min
  - Loops – associated with resistance
  - Mineralocorticoid receptor antagonists are not recommended due to hyperkalemia
- Beta blockers
  - Counteracts the elevated sympathetic activity
  - Lowers risk of SCD, improve survival in HF
  - Dose adjustments required for less lipophilic agents (atenolol, nadolol)
- Calcium channel blockers
  - Caution in heart disease due to their negative inotropic and chronotropic effects

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# Fluids and Electrolytes

- Sodium
  - Sodium (< 2 g/day) and fluid (~ 1-2 L/day) restriction in patients with HTN and CKD
  - Dietary sodium restriction unnecessary for patients with sodium-wasting nephropathy
- Hyperkalemia:
  - Monitor serum concentration and ECG changes
  - Limit K+ intake, avoid salt substitutes rich in K+, avoid medications that may elevate levels
- Metabolic acidosis:
  - Use of preparations containing sodium bicarbonate or sodium citrate
  - Sodium bicarbonate (PO vs. IV)
    - Sodium bicarbonate 650 mg tablets contain 8 mEq sodium, 8 mEq of bicarbonate
    - May cause GI discomfort

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# Active Learning Question #2

Which of the following effects is achieved by titrating ACE inhibitors to the maximally tolerated dose?

A. Reduce blood pressure
B. Improve renal blood flow
C. Reduce proteinuria

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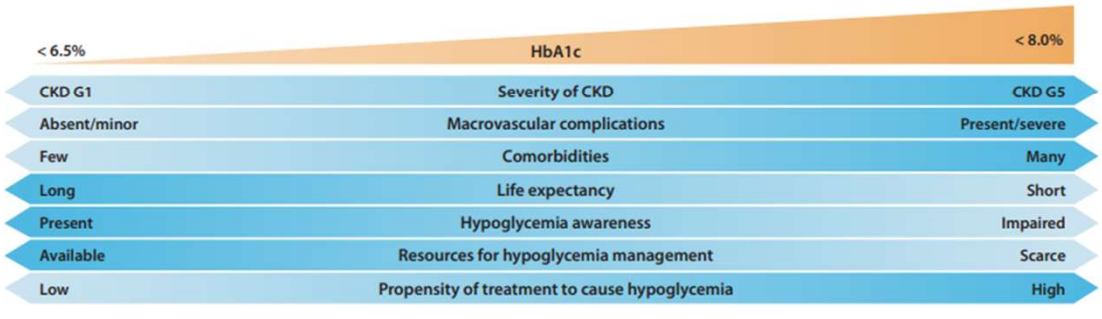
# Glycemic Targets




KDIGO 2022 Clinical practice guideline for diabetes management of chronic kidney disease. *Kidney International*. 2022; 102(Suppl5S), S1-S127.

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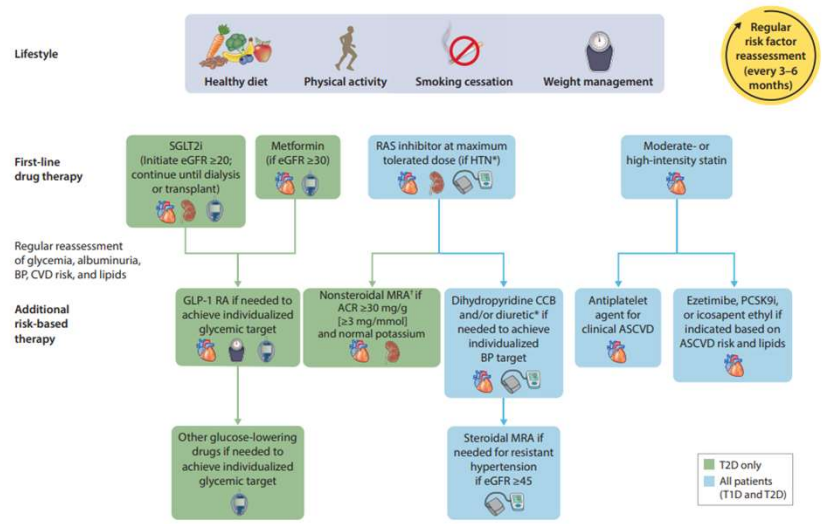
# Holistic Approach for Improving Outcomes in CKD and Diabetes




KDIGO 2022 Clinical practice guideline for diabetes management of chronic kidney disease. *Kidney International*. 2022; 102(Suppl5S), S1-S127.

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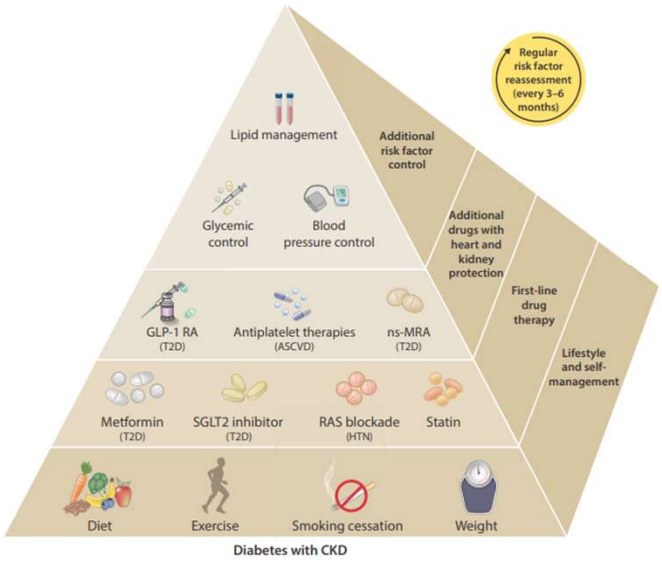
# Management of Heart & Kidney Risk Factors




KDIGO 2022 Clinical practice guideline for diabetes management of chronic kidney disease. *Kidney International*. 2022; 102(Suppl5S), S1-S127.

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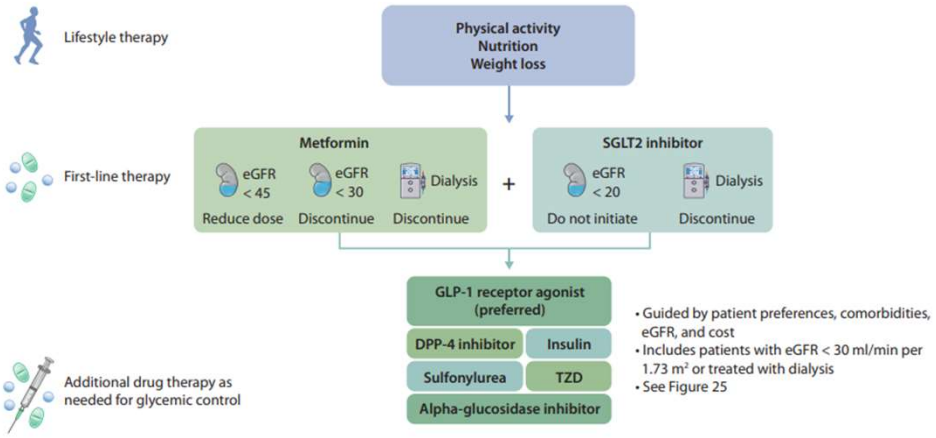
# Diabetes




KDIGO 2022 Clinical practice guideline for diabetes management of chronic kidney disease. *Kidney International*. 2022; 102(Suppl5S), S1-S127.

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# SGLT2I Recommendations in CKD

- Recommend treating patients with type 2 diabetes, CKD, and eGFR ≥ 20 ml//min/1.73m$^2$ with an SGLT2I
- Recommend treating adults with CKD with an SGLT2I for the following:
  - eGFR ≥ 20 ml//min/1.73m$^2$ with urine ACR ≥ 200 mg/g or
  - Heart failure, irrespective of level of albuminuria
- Suggest treating adults with eGFR 20-45 ml//min/1.73m$^2$ with urine ACR < 200 mg/g with an SGLT2I

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# SGLT2 Inhibitors (SGLT2Is)

- SGLT2 inhibitors
  - Mechanism: reduce intraglomerular pressure by increasing afferent arteriolar vasoconstriction
    - Expected initial decrease in eGFR by ~4-5 ml/min/1.73 $m^2$ within first 2-3 weeks
  - Benefits:
    - Slow progression to ESRD
    - Reduce risk of CV death and hospitalization for HF (HHF)
  - Adverse effects: UTIs, genital mycotic infections
  - Not recommended for CKD treatment in patients with:
    - Polycystic kidney disease
    - Recent immunosuppressive therapy for kidney disease

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# SGLT2 Inhibitors (SGLT2Is)

- Canagliflozin (Invokana®) – treatment of CKD in patients with T2DM and diabetic nephropathy with albuminuria > 300 mg/day and eGFR ≥ 30 ml/min /1.73 $m^2$
- Dapagliflozin (Farxiga®) – treatment of CKD with eGFR ≥ 25 ml/min/1.73 $m^2$ (regardless of T2DM diagnosis)
  - Additionally reduces CV death and HHF in HFrEF
- Empagliflozin (Jardiance®) – treatment of CKD with eGFR ≥ 30 ml/min/1.73 $m^2$ (regardless of T2DM diagnosis)

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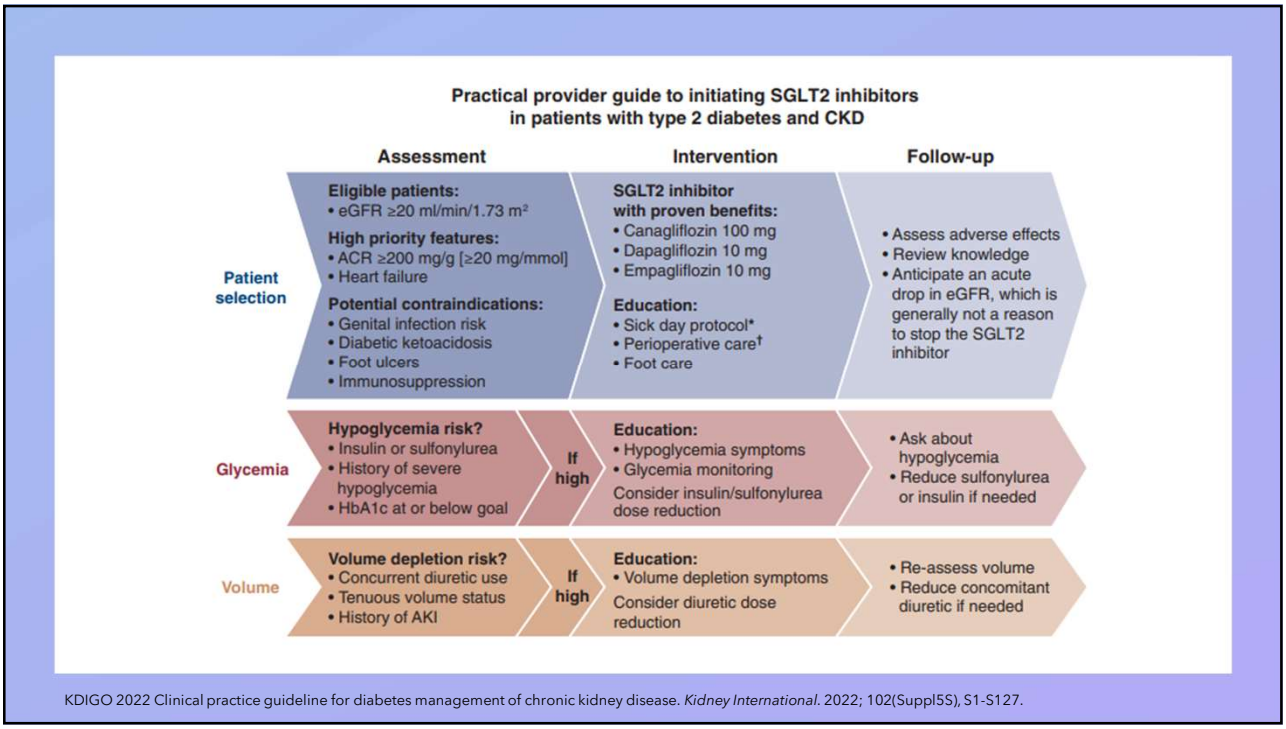


KDIGO 2022 Clinical practice guideline for diabetes management of chronic kidney disease. *Kidney International*. 2022; 102(Suppl5S), S1-S127.

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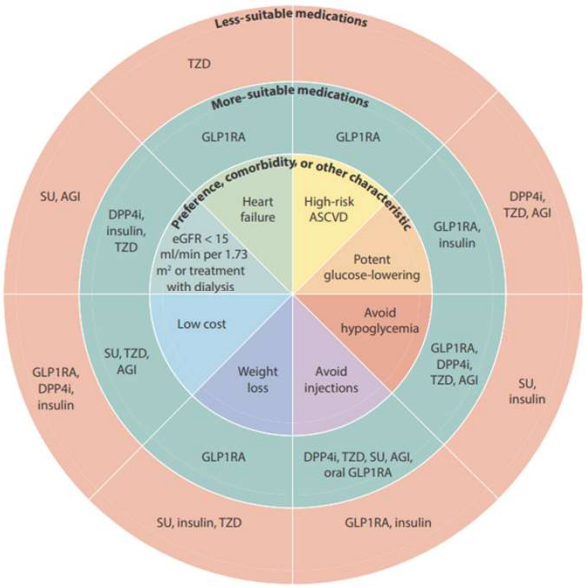
# Additional Glucose Lowering Options




KDIGO 2022 Clinical practice guideline for diabetes management of chronic kidney disease. *Kidney International*. 2022; 102(Suppl5S), S1-S127.

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# Mineralocorticoid Receptor Antagonists (MRAs)

- Suggested for adults with T2DM, eGFR ≥ 25 ml/min /1.73 $m^{2,}$ normal potassium and albuminuria > 30 mg/day despite maximally tolerated dose of RAS inhibitor
  - High risk of CKD progression and CV events
- Mechanism:
  - Blocks mineralocorticoid receptor overactivation in the kidneys, heart, and blood vessels
  - Blocks mineralocorticoid receptor-mediated sodium reabsorption
  - MRA overactivation in the kidneys, heart, and blood vessels to reduce long term inflammation and fibrosis

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# Mineralocorticoid Receptor Antagonists (MRAs)

- Finerenone (Kerendia®) – reduce risk of sustained eGFR decline, ESRD, CV death, non-fatal MI, and hospitalization for HF patients with CKD and T2DM
  - Dose: 10-20 mg once daily based on eGFR and K levels; titrate to max dose in 4 weeks
- Mechanism:
  - Blocks mineralocorticoid receptor overactivation in the kidneys, heart, and blood vessels
  - Blocks mineralocorticoid receptor-mediated sodium reabsorption
  - MRA overactivation in the kidneys, heart, and blood vessels to reduce long term inflammation and fibrosis

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# Mineralocorticoid Receptor Antagonists (MRAs)

- Effect of Finerenone on CKD Outcomes in T2DM (FIDELIO-DKD Trial)

**5674 adults** with CKD associated with T2D randomized 1:1 to receive KERENDIA or placebo
- Double-blind, placebo-controlled, multicenter, phase 3 study with a median follow-up duration of 2.6 years

4- to 16-week run-in period to adjust **ACEi or ARB to the maximum tolerated labeled dose**

**Primary composite endpoint consisted of:**
- Kidney failure*
- Sustained decline of ≥40% in eGFR
- Renal death

**Key secondary composite endpoint consisted of:**
- CV death
- Non-fatal MI
- Non-fatal stroke
- Heart failure hospitalization

Clinical trial results for KERENDIA® (finerenone) tablets (kerendiahcp.com)

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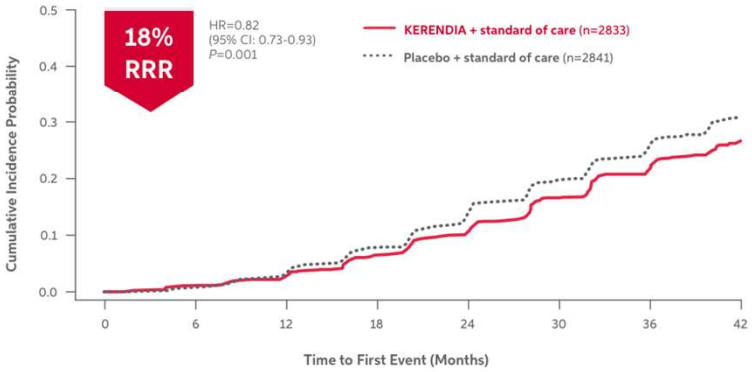
# Effect of Finerenone on CKD Outcomes in T2DM (FIDELIO-DKD Trial)




- Primary composite endpoint: kidney failure, sustained decline ≥ 40% in eGFR, or renal death
- Treatment effect: reduction in a sustained decline in eGFR ≥ 40% and progression to kidney failure

Clinical trial results for KERENDIA® (finerenone) tablets (kerendiahcp.com)

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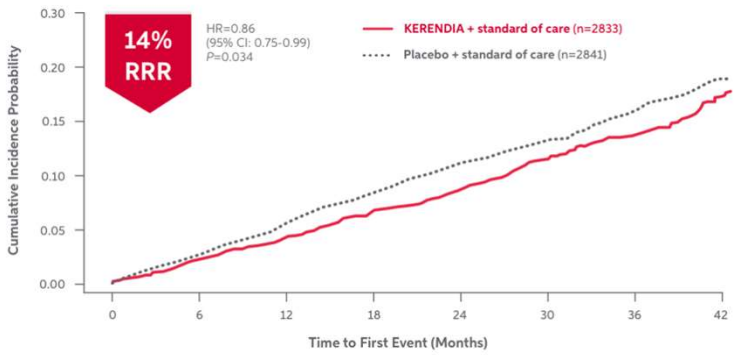
# Effect of Finerenone on CKD Outcomes in T2DM (FIDELIO-DKD Trial)




- Secondary composite endpoint: CV death, non-fatal MI, hospitalization for HF
- Treatment effect: reduction in CV death, non-fatal MI, hospitalization for HF
- Long-term effects on kidney and CV outcomes remain unknown

Clinical trial results for KERENDIA® (finerenone) tablets (kerendiahcp.com)

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# Active Learning Question #3

Which SGLT2Is are indicated for CKD regardless of T2DM diagnosis?

A. canagliflozin
B. dapagliflozin
C. empagliflozin

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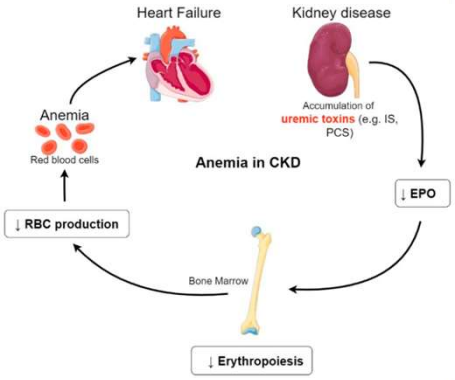
# Anemia

- Appears as early as stage 3 CKD
- Commonly normochromic and normocytic
  - Unless a concomitant iron, folate, or vitamin B12 deficiency exists
- Complete workup recommended for GFR < 60 and done regularly which includes:
  - Monitoring Hgb and Hct
  - Assessment of iron indices
  - Evaluation for sources of blood loss




Cells | Free Full-Text | Uremic Toxins Affect Erythropoiesis during the Course of Chronic Kidney Disease: A Review | HTML (mdpi.com)

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# Causes of Iron Deficiency in CKD

Increased iron loss

- Hemodialysis
- Upper GI inflammation and peptic ulceration
- Drugs (heparin, warfarin, aspirin)

Reduced iron intake

- Inflammatory state (hepcidin)
- Poor appetite
- Drugs (PPI, phosphate binders)

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# Iron Restricted Erythropoiesis

Absolute iron deficiency

- Depleted iron stores
- Environmental
  - Diet, malnutrition
- Physiologic
  - Menstrual blood loss, pregnancy
- Pathologic
  - Chronic blood loss, malabsorption

Functional iron deficiency

- Normal/elevated iron stores
- Impaired delivery of iron to erythroid precursors
  - Anemia of chronic disease
    - Inflammation → iron sequestration

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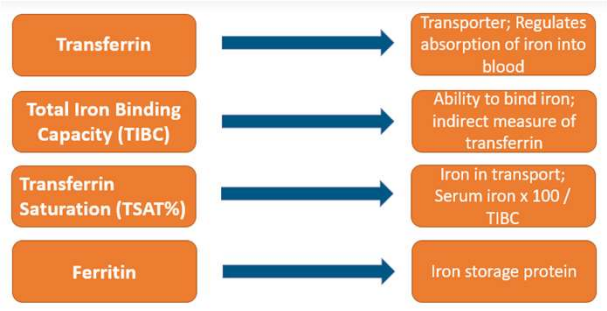
# Anemia




- TSAT% - iron available for RBC production
  - [Serum iron (mcg/dL) / TIBC] x 100
- Ferritin – acute phase reactant indicative of iron reserve
  - Insufficient marker of erythropoiesis
  - 1mcg/L = 8-10 mg iron
  - General recommendation: 500-800 ng/mL
  - Severe iron deficiency: ≤ 30 ng/ml

Fawaz S. Who's Fit for the Iron Throne? Iron Deficiency Associated with CKD and the Role of Iron Supplementation. 2019

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# Iron Supplementation

Iron deficiency is primary cause of erythropoiesis stimulating agent (ESA) hyporesponsiveness.

Assessment and correction should occur **prior** to ESA initiation.

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# Iron Supplementation

- When to initiate iron:
  - KDIGO
    - Warrant an increase of Hgb concentration and/or decrease in ESA dose AND
    - TSAT ≤ 30% and ferritin < 500 ng/mL
  - NKF-KDOQI
    - Therapeutic trial of IV iron (on ND-CKD, a trial of PO iron in ND-CKD) could be considered when TSAT ≤ 30%, even if ferritin is ≥500 ng/mL
  - Evaluate TSAT and ferritin Q3 months during ESA therapy

HD-CKD= Hemodialysis-dependent CKD
ND-CKD= Non-dialysis-dependent CKD
PD-CKD= Peritoneal dialysis-dependent CKD

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# Iron Supplementation

- Goals of therapy (NKF-KDOQI):
  - TSAT > 20%
  - Serum ferritin:
    - > 100 ng/mL for ND-CKD and PD
    - > 200 for stage HD-CKD
  - Hgb 11-12 g/dL
    - ≥ 13 g/dL – increased risk of cerebrovascular or cardiovascular events and mortality

HD-CKD= Hemodialysis-dependent CKD
ND-CKD= Non-dialysis-dependent CKD
PD-CKD= Peritoneal dialysis-dependent CKD

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# Oral Iron Supplements

- Iron supplementation – 200 mg/d elemental iron
- Administration
  - Take on empty stomach
  - Acid environment needed for adequate absorption
- GI side effects – constipation, nausea, abdominal pain, dark stools
  - (all ↑ with ↑ dose, except for last one)
- Drug interactions: antacids, fluoroquinolone antibiotics

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# Oral Iron Preparations

| Preparation | Common Brand Names | Prescribed Unit (Elemental Iron in mg) |
|---|---|---|
| Ferrous sulfate | Slow FE®, Feri-In-Sol® | 325 (65) |
| Ferrous gluconate | Feratab® | 325 (36) |
| Ferrous fumarate | Femiron®, Feostat® | 200 (66) |
| Iron polysaccharide | Niferex®, Nu-Iron® | 150 (150 |
| Heme iron polypeptide | Proferrin-ES®, Proferrin-Forte® | 12 (12) |

Mason DL, Assimon MM. Chronic Kidney Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BP. *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs.* 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins. 2013: 764 – 796.

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# IV Iron Preparations

- IV iron:
  - Reserved for patients that have failed PO
  - Infusion related AE
    - Hypotension, myalgia, arthralgias, dizziness, HA
  - Dextran product – FDA mandated boxed warning requiring test dose before administration due to anaphylaxis reaction

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# IV Iron Preparations

| Preparation | Common Brand Names | FDA-Approved Dosing |
|---|---|---|
| Iron dextran | INFeD®, DexFerrum® | Dose (mL) = 0.0442 (desired hemoglobin - observed hemoglobin) x LBW + (0.26 x LBW)<br>Desired hemoglobin: Usually 14.8 g/dL<br>LBW = Lean body weight in kg |
| Sodium ferric gluconate | Ferrlecit® | 125 mg elemental iron per dialysis session |
| Iron sucrose | Venofer® | HD-CKD: 100 mg elemental iron per dialysis session<br>ND-CKD: 200 mg elemental iron administered on 5 different occasions within 14 days |
| Ferumoxytol | Feraheme® | Two doses of 510 mg elemental iron dosed 3 to 8 days apart |

Mason DL, Assimon MM. Chronic Kidney Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BP. *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins. 2013: 764 – 796.

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# Newer Iron Supplements

- Sucroferric oxyhydroxide (Velphoro®)
  - Chewable tablets
  - Initial dose: 500 mg iron TID with meals; titrate weekly in increments of 500 mg iron/day (maintenance 1.5 grams iron daily)
  - Adverse effects: diarrhea, dark stool, nausea
  - Drug-drug interactions: levothyroxine, tetracycline derivatives
- Ferric pyrophosphate (Triferic®)
  - Intradialytic with each dialysis session
- Ferric carboxymaltose (Injectafer®) – iron deficiency anemia in adults with ND-CKD

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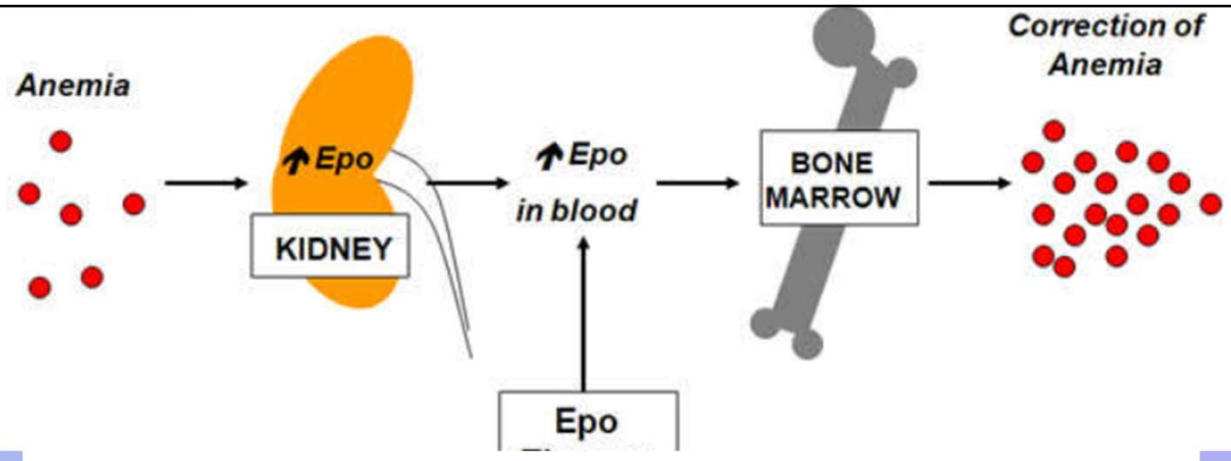


**Erythropoiesis Stimulating Agents (ESAs)**

Stimulate the proliferation and differentiation of erythroid progenitor cells, increase hemoglobin synthesis, and accelerate the release of reticulocytes from the bone marrow

The Story of Erythropoietin - Hematology.org

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# Erythropoiesis Stimulating Agents (ESAs)

- When to initiate ESAs:
  - KDIGO
    - ND-CKD with Hgb < 10 g/dL
      - Assess: rate of Hgb decline, symptoms of anemia, response to iron therapy, risk of requiring blood transfusions, risks associated with ESA therapy
    - HD-CKD – with Hgb 9-10 ng/dL to avoid dropping < 9 ng/dL
    - Not to maintain Hgb > 11.5 g/dL in CKD
  - NKF-KDOQI
    - Should not be used to maintain Hgb > 11 ng/dL
  - Hgb target not to exceed 13 g/dL

HD-CKD= Hemodialysis-dependent CKD
ND-CKD= Non-dialysis-dependent CKD
PD-CKD= Peritoneal dialysis-dependent CKD

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# Erythropoiesis Stimulating Agents (ESAs)

| Preparation | Dose |
|---|---|
| Epoetin alfa (Epogen®/Procrit®) | HD-CKD: 50-100 units/kg SQ TIW<br>ND-CKD: 50-100 units/kg once weekly |
| Darbepoetin (Aranesp®) | HD-CKD: Starting dose: 0.45 mcg/kg weekly OR 0.75 mcg/kg QOW<br>ND-CKD: 0.45 mcg/kg SQ monthly |

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# Erythropoiesis Stimulating Agents (ESAs)

- Epoetin alfa (Epogen®, Procrit®)
  - SC (lower doses administered less frequently) vs. IV
- Darbepoetin alfa (Aranesp®)
  - 3x longer half-life → less frequent dosing
- Most common adverse effect: hypertension
- Boxed warning: monitor Hgb and adjust dose to maintain lowest dose needed to avoid transfusions
- Hgb Monitor:
  - Every 1 – 2 weeks after initiation and dose adjustment
  - Every 2 – 4 weeks once stable

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# Erythropoiesis Stimulating Agents (ESAs)

- Dose adjustments
  - Every 4 – 6 weeks due to time for response
  - If rapid response is observed ( > 1 g/dL in 2 weeks) or target Hgb is exceeded, then reduce dose by 25%
  - If response is inadequate (Hgb increase < 1 g/dL in 4 weeks), then dose increase dose by 25%
- Once stable, monitor Hgb every 2 - 4 weeks

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# ESA Boxed Warnings

- Cardiovascular events: Increased risk death, MI, stroke, VTE
- CKD: Greater risk of CV events when target Hb > 11 g/dL
- Cancer: Shortened overall survival/increased tumor progression
- *Peri-surgery: Increased risk DVT, DVT ppx warranted

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# Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHI)

- Daprodustat – once-daily oral HIF-stabilizing agent
- Mechanism:
  - Low nanomolar HIF-PHI prevents degradation of HIF → production of increased levels of erythropoietin (EPO) production → induction of erythropoiesis
- Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis (Singh et al.)
  - Randomized, open-label phase 3 non-inferiority trial of oral daprodustat v. injectable ESA in HD-CKD
  - Primary endpoints
    - Efficacy: Hgb level changes
    - Safety: first occurrence to MACE (death from any cause, nonfatal MI, nonfatal stroke)
  - Conclusion: daprodustat non-inferior in both endpoints

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# Active Learning Question #4

Which Hgb level is associated with greater risk of cardio- or cerebrovascular events and mortality?

A. >11 mg/dL
B. >12 mg/dL
C. >13 mg/dL

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# Mineral and Bone Disorders of CKD

- Secondary hyperparathyroidism and renal osteodystrophy
- CKD-MBD
  - Mineral (phosphorus, calcium, parathyroid hormone)
  - Bone (osteodystrophy)
  - Soft-tissue calcification
- Clinical presentation:
  - Bone pain, myopathy, vascular calcification, valvular calcification, fractures

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# Mineral and Bone Disorders of CKD

- Pathophysiology: calcium and phosphorus homeostasis by four hormones:
  - Parathyroid hormone (PTH)
  - Precursor of vitamin D (25-hydroxyvitamin D = 25-OHD)
  - Active vitamin D (calcitriol or 1,25-dihydroxyvitamin D)
  - Fibroblast growth factors-23 (FGF-23)
- Complications:
  - Hyperphosphatemia
  - Hypocalcemia
  - Hyperparathyroidism
  - Decreased production of active vitamin D
  - Resistance to vitamin D

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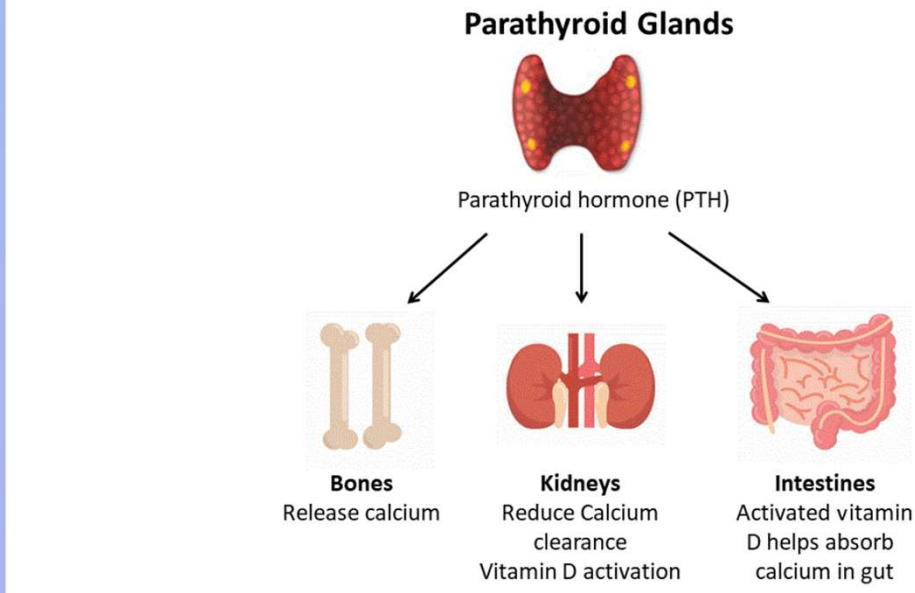


PTH-hormones.gif (758 × 676) (hormones-australia.org.au)

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# Mineral and Bone Disorders of CKD

- Goals of therapy:
  - Manage serum calcium and phosphorus
  - Prevent/manage secondary hyperparathyroidism
  - Restore normal skeletal development

| Parameter | Stage 3 | Stage 4 | Stage 5 |
|---|---|---|---|
| Corrected calcium (mg/dL) | Normal | Normal | 8.4 – 9.5 |
| Phosphorus (mg/dL) | 2.7 – 4.6 | 2.7 – 4.6 | 3.5 – 5.5 |
| Ca x P | < 55 | < 55 | < 55 |
| Intact PTH (pg/mL) | 35 – 70 | 70 – 110 | 150 - 300 |

Mason DL, Assimon MM. Chronic Kidney Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BP. *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins. 2013: 764 – 796.

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# Corrected Calcium Equation

- Corrected Ca = measured Ca + 0.8 (4 - serum albumin)
- 4 = average albumin level

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# Monitoring

- Begin monitoring serum calcium, phosphate, and PTH in stage CKD G3a with frequency based on magnitude and rate of progression.

| CKD Stage | Ca and Phos | PTH | Alkaline Phosphatase |
|---|---|---|---|
| G3a-G3b | 6-12 months | Baseline level and CKD progression | Baseline level and CKD progression |
| G4 | 3-6 months | 6-12 months | 6-12 months |
| G5 | 1-3 months | 3-6 months | 3-6 months |
| G4-G5 | | | 12 months |

- Routine BMD testing to assess fracture risk

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# Management of Phosphorus & Calcium

Treatment of Abnormal Phosphorus and Calcium

- In CKD G3a-G5, treatment of CKD-MBD based on assessment of phosphate, calcium, and PTH levels together
  - Lower phosphate levels towards normal range
  - Avoid hypercalcemia
- Treatment in CKD G3a-G5
  - Phosphate lowering treatment:
    - Limit dietary phosphate intake
    - Restrict the dose of calcium-based phosphate binders
    - Avoid long-term use of aluminum-containing phosphate binder

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# Management of PTH Levels

Treatment of Abnormal PTH Levels

- In CKD G3a-G5 not on dialysis, optimal PTH levels unknown
  - Address modifiable risk factors: hyperphosphatemia, hypocalcemia, phosphate intake, vitamin D deficiency
  - Avoid hypercalcemia
- Treatment in CKD G3a-G5 not on dialysis
  - Reserve calcitriol and vitamin D analogs for patients with CKD G4-G5
- Treatment in CKD G5
  - Goal intact PTH levels ~2-9x ULN
  - Recommend calcimimetics, calcitriol, or vit D analogs

OR

combination of calcimimetics + vitamin D analogs

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# Phosphate-Binding Agents

- Phosphorus restriction: 800 – 1,000 mg/day
- Phosphate binders limit phosphorus absorption from GI tract – administered with meals
- Calcium-containing preparations:
  - Calcium carbonate, calcium acetate
  - SE: Nausea, diarrhea, constipation, hypercalcemia
  - Concerns with DDI – fluoroquinolone antibiotics and iron at least 1 – 2 h before meal

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# Calcium-Containing Preparations

| Product | Trade Name | Content (mg) | Starting Dose | Titration |
|---|---|---|---|---|
| Calcium carbonate (40% elemental calcium) | Tums® | 500 | 0.5 – 1 g (elemental Ca) with meals | Increase or decrease by 500 mg per meal |
| | Os-Cal 500® | 1250 | | |
| | Caltrate 600® | 1500 | | |
| Calcium acetate (25% elemental calcium) | Phos-Lo® | 667 | 1334 mg with each meal | Increase or decrease by 667 mg per meal |

Mason DL, Assimon MM. Chronic Kidney Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BP. *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins. 2013: 764 – 796.

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# Sevelamer

Formulations:

- Sevelamer hydrochloride (Renagel®)
- Sevelamer carbonate (Renvela®) – avoids metabolic acidosis

Clinical Pearls:

- Adverse effects: fecal impaction, ileus, intestinal obstruction, perforation
- Also lowers LDL and serum cholesterol
- DDI: avoid by administering 1 hour before or 3 hour(s) after drugs with narrow therapeutic indices
- 800 mg sevelamer = 667 mg calcium acetate

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# Sevelamer

| Product | Trade Name | Content (mg) | Starting Dose | Titration |
|---|---|---|---|---|
| Sevelamer hydrochloride | Renagel® | 400<br>800 | Based on baseline phos level:<br><br>1 tablet with meals (if serum phos < 7.5) = 800 mg<br><br>2 tablets with meals (if serum phos > 7.5) = 1600 mg | Increase or decrease by 800 mg per meal<br><br>Adjustments at 2 week intervals based on phosphorus levels |
| Sevelamer carbonate | Renvela® | 800<br>0.8 g (powder) | | |

Mason DL, Assimon MM. Chronic Kidney Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BP. *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins. 2013: 764 – 796.

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# Lanthanum Carbonate (Fosrenol®)

Dosing:

- Chewable tablets: 250, 500, 750, 1000 mg
- Initiation: 750 – 1500 mg with meals
- Max dose: 3,000 mg

Clinical pearls:

- Adverse effects: nausea and vomiting
- DDI: reduced bioavailability of ciprofloxacin and levothyroxine

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# Other Phosphate Lowering Agents

- Aluminum preparation
  - Concerns with aluminum accumulation and toxicities
  - Need deferoxamine to treat (chelator)
  - Example: AlternaGel® suspension
- Magnesium preparation
  - Limited use due to high doses required for effect
  - AE: Diarrhea, hypermagnesemia
  - Example: Milk of magnesium suspension or tablet

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# Vitamin D Supplementation

| Generic | Brand | Dose Range | Form | Frequency |
|---|---|---|---|---|
| Ergocalciferol | Vitamin D2 | 400 – 50,000 IU | PO | Daily<br>Weekly or monthly |
| Cholecalciferol | Vitamin D3 | 400 – 50,000 IU | PO | Daily<br>Weekly or monthly |
| Calcitriol | Calcijex®<br>Rocaltrol® | 0.5 – 2 mcg<br>0.2 – 0.5 mcg | IV<br>PO | TIW<br>Daily, QOD, TIW |
| Paricalcitol | Zemplar® | 1 – 2 mcg<br>0.04 – 0.1 mcg/kg | PO<br>IV | Daily or TIW<br>TIW |
| Doxercalciferol | Hectoral® | 10 mcg<br>1 – 6 mcg | PO<br>IV | Daily or TIW<br>TIW |

Mason DL, Assimon MM. Chronic Kidney Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BP. *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins. 2013: 764 – 796.

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# Calcimimetics

- Cinacalcet (Sensipar®)
  - Mechanism: acts on the calcium-sensing receptors on the surface of the chief cells of the parathyroid glands to mimic the effect if extracellular ionized calcium, increases sensitivity of receptor to reduce PTH secretion
  - Dosage: initiation: 30 mg daily, titrate dose every 2 – 4 weeks, max dose: 180 mg/day
  - Monitoring:
    - Serum calcium and phosphorus within 1 week of initiation or dose adjustment
    - PTH levels should be drawn 4 week(s) of initiation or dose adjustment
  - Adverse effects: Nausea and vomiting
  - DDIs: Inhibitor of CYP 2D6 and substrate of CYP 3A4

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# Calcimimetics

- Etelcalcetide (Parsabiv®)
  - Starting dose: IV: 5 mg bolus 3x/week at the end of HD
    - Titrate dose in 2.5 – 5 mg increments not more frequently than every 4 weeks
    - Conversion from cinacalcet: discontinue cinacalcet for at least 7 days prior to initiation
    - Missed dose: if HD is missed, do not administer. Resume etelcalcetide upon completion of next HD session. If doses are missed for > 2 doses, re-initiate with 5 mg (or 2.5 mg if this was last dose) TIW.
    - Max dose: 15 mg TIW
  - Monitoring:
    - Corrected serum calcium levels: prior to initiation and 1 week after dose initiation or adjustment, then every 4 weeks after maintenance dose established
    - PTH levels: prior to initiation and 4 weeks after dose initiation or adjustment
  - Adverse effects: diarrhea, nausea, headache, and vomiting

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# Active Learning Question #5

Calcimimetics and vitamin D analogs are recommended for treatment of hyperparathyroidism in which stage(s) of CKD?

A. CKD G3
B. CKD G4
C. CKD G5

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# References


- Bakris GL, Agrawal R, Anker SD, et al. Effect of finerenone on chronic kidney disease in type 2 diabetes. *NEJM*. 2020; 383:2219-2229.
- Burton ME, Shaw LM, Schentag JJ, and WE Evans. Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring. Maryland: Lippincott, Williams, & Wilkins. 2006.
- Darbepoetin Alfa [package insert]. Amgen Inc: Thousand Oaks, CA; 2011.
- Epoetin Alfa [package insert]. Amgen Inc: Thousand Oaks, CA; 2008.
- Hamza E, Metzinger L, Metzinger-Le Meuth. Uremic toxins affect erythropoiesis during the course of chronic kidney disease: A review. *Cells*. 2020;9(9);2039.
- Heerspink HJ, Stefansson BV, Correa-Rotter R. Dapagliflozin in patients with chronic kidney desease. *N Engl J Med*. 2020 Oct 8;383(15):1436-1446.
- Hudson JQ, Wazny LD. *Chronic Kidney Disease*. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. *Pharmacotherapy: A Pathophysiologic Approach*. 10th ed. New York, NY: McGraw-Hill. 2017.
- Inker LA, Astor BC, Fox CH, et al. KDOQI US Commentary on the 2012 KDIGO Clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63(5):713-735.
- Isakova T, Nickolas TL, Denburg M. KDOQI US Commentary on the 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention, ad treatment of chronic kidney disease – mineral and bone disorders (CKD-DMB). *Kidney International*. 2017; 70(6).
- Johnson HN, Prasad Reddy L. Updates in Chronic Kidney Disease. *J Pharm Pract*. Published online June 14, 2024. doi:10.1177/08971900241262381KDIGO 2020 Clinical practice guideline for diabetes management in chronic kidney disease. *Kidney International*. 2020; 98:S1-S115.
- KDIGO 2024 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International*. 2024; 105(4S).
- KDIGO 2022 Clinical practice guideline for diabetes management of chronic kidney disease. *Kidney International*. 2022; 102(Suppl5S), S1-S127.
- KDIGO 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention, ad treatment of chronic kidney disease – mineral and bone disorders (CKD-DMB). *Kidney International*. 2017; 7(1).
- KDIGO Clinical practice guideline for anemia in chronic kidney disease. *KDIGO*. 2012; 2(4).


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# References


- Kerendia. < Clinical trial results for KERENDIA® (finerenone) tablets (kerendiahcp.com)> Accessed online: September 21, 2022.
- Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: What's changed and KDIGO 2012 Clinical practice guideline for the evaluation and why it matters. management of chronic kidney disease. *Kidney International*. 2017; 92:26-36.
- Ketteler M, Block GA, Evenepoel P, et al. Diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder: synopsis of the Kidney Disease: Improving global outcomes 2017 clinical practice guideline update. *Ann Intern Med*. 2018; 168(6):422-460.
- Kliger AS, Foley RN, Goldfarb DS. KDOQI US Commentary on the 2012 KDIGO Clinical practice guideline anemia in CKD. *Am J Kidney Dis*. 2013;62(5):849-859.
- Kovesy CP, Ureche V, Lu JL, Kalantar-Zadeh K. Outcome predictability of serum alkaline phosphatase in men with pre-dialysis CKD. *Nephrol Dial Transplant*. 2010; 25:3003-3011.
- Kumar V, Abbas A, Aster J. *Kidney and It's Collecting System*. In: *Robbins Basic Pathophysiology*. 10th ed. Philadelphia, PA: Elsevier. 2018.
- Levin A, Ahmed S. Carrero JJ. Executive summary of the KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease: Known knowns and known unknowns. *Kid Int*. 2024;105:684-701.
- Macdougall, I.C. Iron supplementation in nephrology and oncology: What do we have in common? *Oncologist* 2011;16(suppl 3):25-34.
- Mason DL, Assimon MM. Chronic Kidney Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BP. *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins. 2013: 764 – 796.
- Mende, CW. Chronic kidney disease and SGLT2 inhibitors: A review of the evolving treatment landscape. *Adv Ther*. 2022;39:148–164.
- Singh AK, Carroll K, McMurray JV, et al. Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis. *N Engl J Med*. 2021;385(25):2313-2324.
- Taylor SJ, Agarwal R, Bakris GL, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. *Am J Kidney Dis*. 2013;62(2):201-213.
- Tomson CR, Cheung AK, Mann JF. Management of blood pressure in patients with chronic kidney disease not receiving dialysis: Synopsis of the 2021 KDIGO clinical practice guideline. *Ann Intern Med*. 2021; Jun 2022 [epub ahead of print].
- Winter M E. Basic Clinical Pharmacokinetics. 5th ed. Maryland: Lippincott, Williams, & Wilkins. 2010.


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Questions?

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# From Filtration to Precision: Evolving CKD Therapies

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