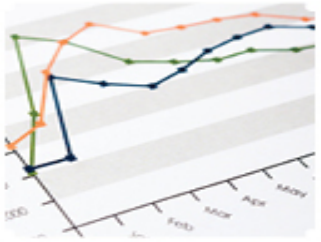
HRSA Outreach Program

Western Oklahoma Wellness

August 16, 2022



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Agenda

- Housekeeping Items
- HRSA Outreach Program – Western Oklahoma Wellness
  - Jason Felts – OFMQ
- Updates in Chronic Kidney Disease
  - Meri Hix, PharmD, BCPS
    - Associate Professor of Pharmacy Practice
    - SWOSU College of Pharmacy
- Questions & Closing

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About WOW

- Western Oklahoma Wellness is a program to advance rural healthcare through increased access to care, education, and opportunities to reduce the onset of diabetes and other chronic conditions.

- Counties We Work In:
  - Beckham, Greer, Kiowa, Washita, Roger Mills

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Funded Through HRSA

- We Work With:
  - **ONIE Project**: The Oklahoma Nutrition Information and Education (ONIE) Project promotes healthy living through innovative and creative strategies for communities, families and individuals.
  - **SWOSU Rural Health Center**: The RHC develops programs for community-based healthcare services collaborating with local pharmacies and hospitals for the advancement of the health and well-being of the medically underserved population in Oklahoma.
  - **Community Partners**: County-Specific Health Departments, State Health Department, OSU Extension, Town of Granite, Mangum Regional Hospital, Elkview General Hospital, Cordell Memorial Hospital, Roger Mills Hospital, City of Elk City
- WOW is funded through the HRSA Rural Health Care Outreach Services Program, Grant No. D04RH40277

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Meri Hix, PharmD, BCPS

Meri Hix is a 2002 graduate of Southwestern Oklahoma State University College of Pharmacy. After completing pharmacy practice and geriatric pharmacy residencies at the Central Arkansas Veterans Healthcare System in Little Rock, AR, she embarked on a career of academia and clinical pharmacy starting in 2004, taking her to Chicago, IL, Abilene, TX, and finally back to Oklahoma in 2012 where she is currently an Associate Professor of Pharmacy Practice at SWOSU COP. Over these years she has provided inpatient clinical pharmacy services in internal medicine, skilled nursing, and hospice. Her current practice is at St. Anthony Hospital in Oklahoma City with the inpatient family medicine service. Her past and current didactic teaching includes various topics in the pharmacotherapy sequence including renal, pain, thyroid, anemia, and geriatric cultural competency. She is a board-certified in pharmacotherapy specialist with interests in anticoagulation, renal disease, geriatrics, program assessment, and education and training.

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Relevant Disclosures

Under the Oklahoma State Medical Association CME guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 24 months.

Meri Hix, PharmD, BCPS has no financial relationships or affiliations to disclose.

Updates in CKD

Meri Hix, PharmD, BCPS

Associate Professor of Pharmacy Practice

SWOSU College of Pharmacy

Disclosures

- Nothing to disclose

SWOSU
Southwestern Oklahoma State University

Objectives

- Describe updates in definitions and screening for chronic kidney disease (CKD)
- Discuss prevention strategies and outcomes of CKD
- Collaborate in the management of complications after diagnosis of CKD

Guidelines & Resources

National Kidney Foundation (kidney.org)

Kidney Disease Improving Global Outcomes (KDIGO)

Kidney Disease Outcomes Quality Initiative (KDOQI)

Epidemiology

- In the US, 37 million adults with CKD while an estimated 90 percent are unaware
- Causes: HTN, DM, Glomerulonephritis, structural abnormalities, PCKD, autoimmune disorders
- Other risk factors: CAD, age, obesity, susceptible population group

National Kidney Foundation, 2021. https://www.kidney.org/atoz/content/about-chronic-kidney-disease Accessed August 1, 2022.

Defining

OR

For 3 months

- Structural or functional abnormality of the kidney
  - Albuminuria, histologic, imaging, urine sediment, electrolytes
  - + or - decline in GFR

For 3 months

- GFR < 60 ml/min/1.73m2
  - + or - kidney damage

Kidney International (2021) 99, S1–S87

Staging

KDOQI Stages	KDIGO Categories	Damage & Terminology	GFR (ml/min/1.73 m2)
Increased Risk		Risk factors	≥ 90
Stage 1	G1	Kidney damage	≥ 90
Stage 2	G2	Kidney damage, mild	60-89
Stage 3	G3a G3b	Mild to moderate decrease Moderate to severe decrease	45-59 30-44
Stage 4	G4	Severe decrease	15-29
Stage 5	G5	Kidney failure	< 15

KDIGO Category	ACR (mg/g)	Daily Excretion (mg/24h)
A1	< 30	< 30
A2	30-300	30-300
A3	> 300	> 300
A3 Nephrotic Range		> 3000

Kidney International (2021) 99, S1–S87

Determining the GFR

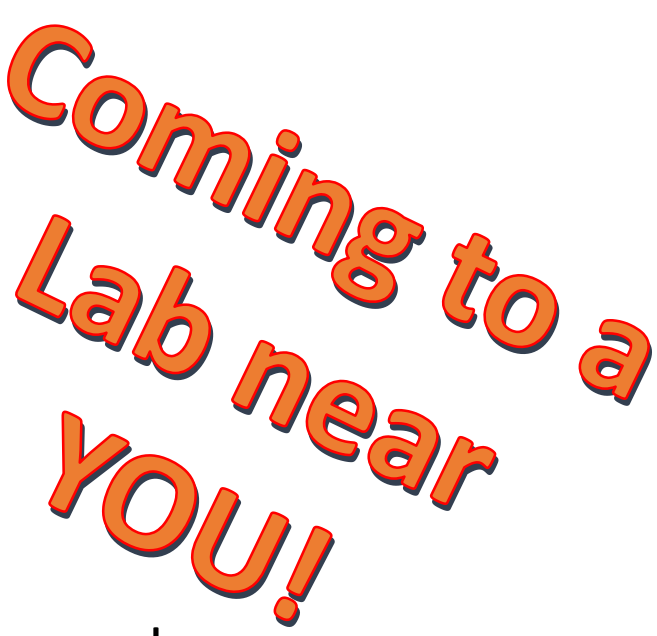
Evolution of GFR estimations

- 24-hour creatinine clearance, inulin clearance
  - Estimating equations (Cockcroft-Gault, Jelliffe, others)
    - ***Most drug-dosing***
- Estimating GFR equations
  - Modification of diet in renal disease (MDRD)
  - CKD-EPI (creatinine &/or cystatin C)
    - **Staging**

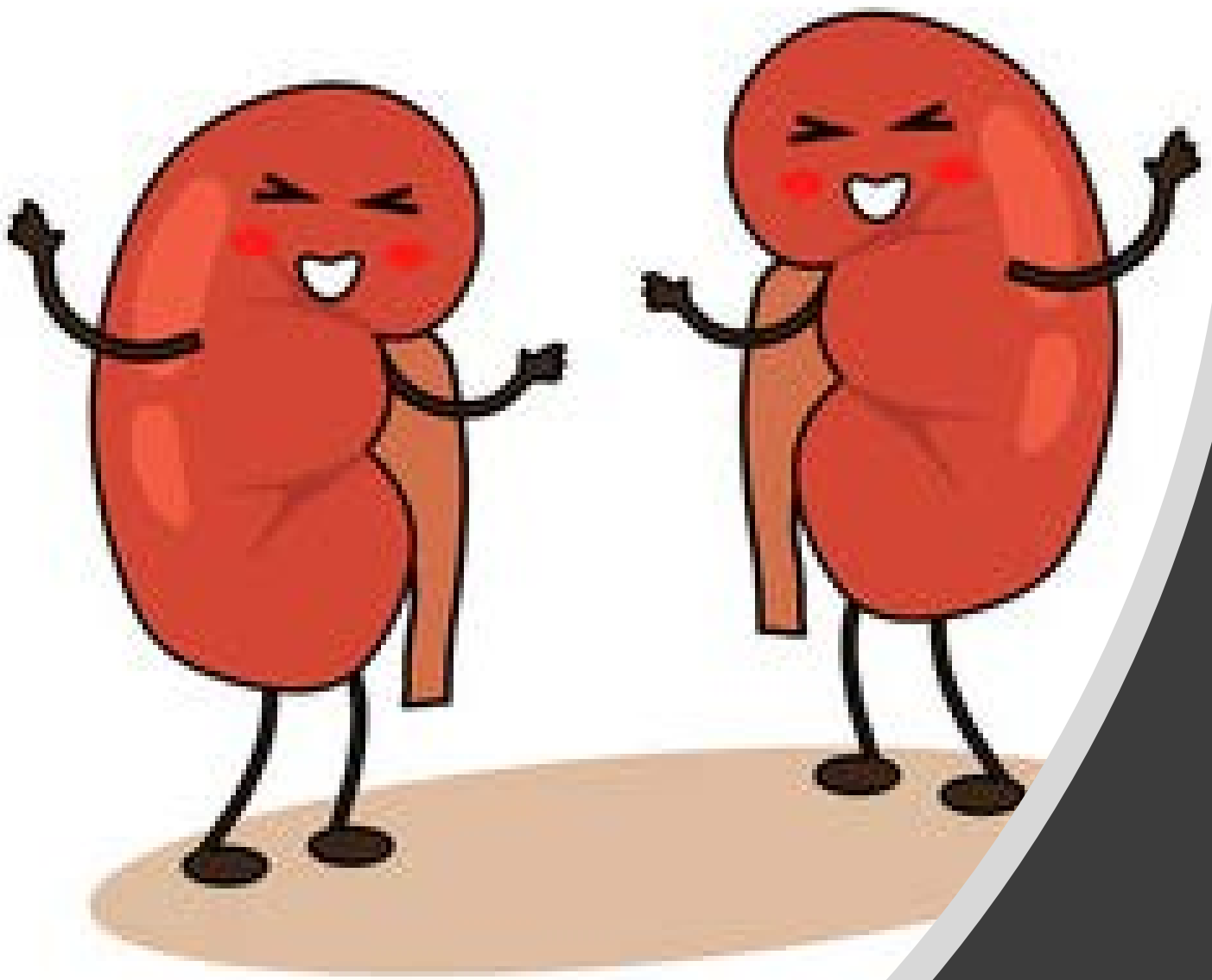
Screening

- Redefining the diagnosis in 2021, standard screening recommendations from NKF and ASN
  - CKD-EPI equation – absence of race identifier
  - Urine albumin-to-creatinine ratio (uACR)

- CKD-EPI (Epidemiology Collaboration) equation
  - Serum creatinine, cystatin, or both
  - More accurate with higher GFRs (than MDRD)
  - Cystatin-containing estimation may be more accurate with muscle mass changes
  - 80-90% of eGFRcr or eGFRcys are within 30% of measured GFR
    - Combination eGFRcr-cys is more accurate



Inker LA, Eneanya ND, MCorsh J, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. New England J Med. 2021: DOI: 10.1056/NEJMoa2102953



Prevention & Management Goals

General Prevention & Management Goals

- Lifestyle interventions
- Blood pressure control
- Diabetes control
- Address proteinuria
- Anemia treatment
- Lipid management
- Avoidance of nephrotoxic agents

Lifestyle Interventions

To lower blood pressure in CKD

- Sodium restriction < 2 g/day (2C)
  - Cautious use of diets rich in potassium (K+) (e.g. DASH)
- Moderate intensity exercise (2C)

In patients with DM & CKD

- *Moderate intensity exercise (1D)*
- Smoking cessation (1D)
- Protein intake of 0.8 g/kg ABW/day (2C)

Am J Med. doi: https://doi.org/10.1016/j.amjmed.2022.06.010

Blood Pressure Control (not on dialysis)

KDIGO 2012	uACR (mg/g)	BP Goal (mmHg)	Grade
DM and non-DM	<30	≤140/90	1B
	≥30	≤130/80	2D

KDIGO 2021	Target BP (mmHg)	Grade
With high BP, + or - DM	SBP < 120, if tolerated, using standard office BP measurements	2B

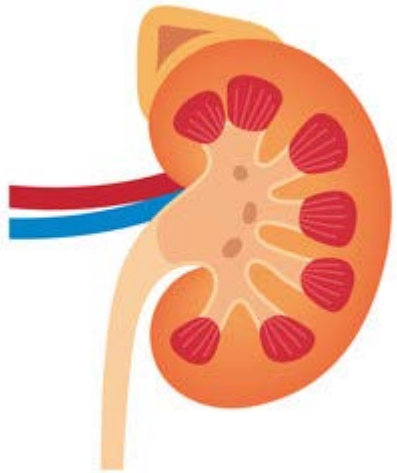
Kidney International (2021) 99, S1–S87

Glycemic Control

KDIGO 2020	eGFR (ml/min/1.73 m2)	Treatment	Grade	Target A1C
T2DM, CKD	≥ 30	Metformin* SGLT2	1B 1A	Individualized <6.5 to <8%
Hemoglobin A1C target not achieved or unable to use above agents, then				
T2DM, CKD	n/a	Long-acting GLP1 RA (or patient preference)	1B	Grade 1C
*Metformin should be discontinued when eGFR < 30 ml/min/1.73m2				

Kidney International (2020) 98, 839–848

Proteinuria Approach



KDIGO 2013 Guidelines, regardless of blood pressure

In DM + CKD with uACR 30-300 mg/g (2D)

In both DM and non-DM patients + CKD with uACR > 300 mg/g (1B)

ACEI or ARB

Kidney International Supplements (2013) 3, 5–14

Lipid Management

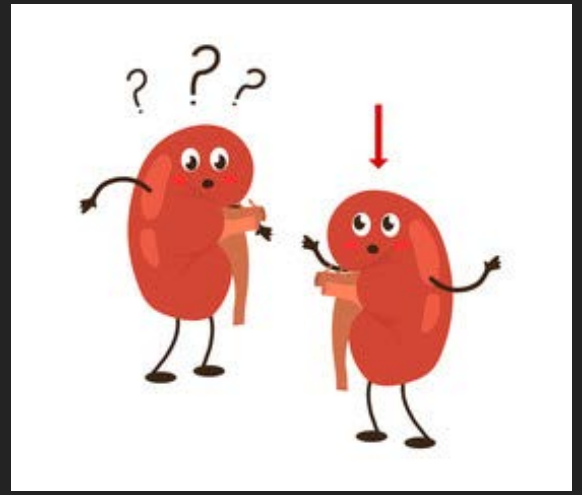
KDIGO 2013

Target group	GFR Category or function	Treatment	Grade
≥ 50 years old	G1-G2 G3a-G5, not on dialysis or transplant recipient	Statin Statin ± ezetimibe	1B 1A
Any	Dialysis-dependent	Treatment not recommended	2A
Any, already on Rx	New dialysis	Continue treatment	2C
Transplant recipient		Statin	2B
18-49 years old	Not on dialysis or transplant recipient, if • CAD • DM • Prior ischemic stroke • 10-year CV risk >10%	Statin	2A

Kidney inter., Suppl. 2013; 3: 259–305.

Nephrotoxic Agents

- Renal elimination of drugs versus nephrotoxicity
- Common agents
  - Certain antibiotics → aminoglycosides, vancomycin
  - Contrast dyes → less common
  - Drug combinations
    - vancomycin plus piperacillin/tazobactam
    - ACEIs plus sulfamethoxazole/trimethoprim
  - NSAIDs, chronic use of analgesics
  - Proton Pump Inhibitors
  - Rosuvastatin?



Rosuvastatin

Retrospective

Median 3.1 year follow-up

Prescribed rosuvastatin or atorvastatin

Results

ASCVD events
- **HR 1.02** (95% CI 0.96-1.08)

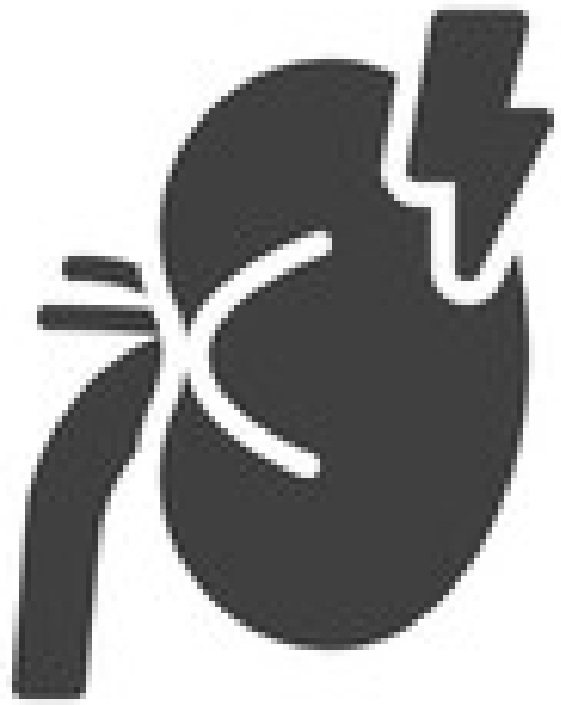
Proteinuria
- **HR 1.17** (95% CI 1.10-1.25)

Kidney failure
- **HR 1.15** (95% CI 1.02-1.30)

Noted that in patients with CKD G4+

44% received higher than recommended doses

JASN July 2022, ASN.2022020135; DOI: https://doi.org/10.1681/ASN.2022020135



Treatment Effects on Chronic Kidney Disease

Treating CKD

- Renin-angiotensin-system inhibitors (RASi)
  - Angiotensin Converting Enzyme Inhibitors (ACEIs)
  - Angiotensin Receptor Blockers (ARBs)
- Sodium-glucose cotransporter 2 inhibitors (SGLT2s)
- Nonsteroidal mineralocorticoid antagonist

RASis

Titrate to highest tolerated dose

Monitor BP, K+, and Cr every 2-4 weeks after initiation or dose change

Discontinue or reduce dose if

- 30% increase in Cr after initiation or dose change
- Symptomatic hypotension or uncontrolled hyperkalemia ***despite treatment***

KDIGO 2021				
HTN	GFR	Albuminuria	Treatment	Grade
Without DM	G1-G4	A3	RASi	1B recommended
		A2	RASi	2C suggested
With DM	G1-G4	A2 and A3	RASi	1B recommended
+ or - DM	G1-G4	A1	RASi	Reasonable to start

RASi = renin-angiotensin-system inhibitors (ie, ACEIs or ARBS)

Kidney International (2021) 99, S1–S87

SGLT2 Inhibitors

- Broadly favorable effects on both major cardiovascular outcomes and kidney outcomes
- May cause transient GFR decrease
- Increased urinary output

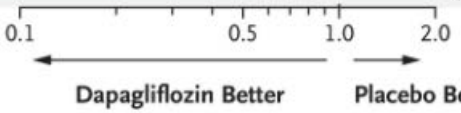
FDA Approvals	CKD	DKD
Canagliflozin	No	Yes
Dapagliflozin	Yes	Yes
Empagliflozin	No	Yes (off-label)
Ertugliflozin	No	No

SGLT2 Inhibitors

	Study Population	Pre-Randomization Characteristics	Kidney Outcomes	Results	Other findings
CREDENCE, 2019 **Canagliflozin**, CKD & T2DM	uACR 300-5000 mg/g, eGFR 30-<90, A1C 6.5-12%	RASi dose maximized & stable, excluded NYHA IV	Composite of ESKD, 2x Cr, renal or CV death	**43.2 vs 61.2 per 1000 py, HR 0.7 (0.59-0.82)**	27% drop out rate CV Secondary outcomes showed significantly reduced risk
DAPA-CKD, 2020 **Dapagliflozin**, CKD	uACR 200-5000 mg/g, eGFR 25-75	If on RASi, dose maximized & stable, Excluded T1DM, PCKD, NYHA IV + or – DM	Composite of ≥ 50% in the eGFR, ESKD, renal or CV death	**9.2 vs 14.5%, HR 0.61 (0.51-0.72)**	~13% drop out rate **Kidney outcomes without DM, HR 0.5 (0.35-0.72)**

N Engl J Med 2019; 380:2295-2306; N Engl J Med 2020; 383:1436-1446

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m^2	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)



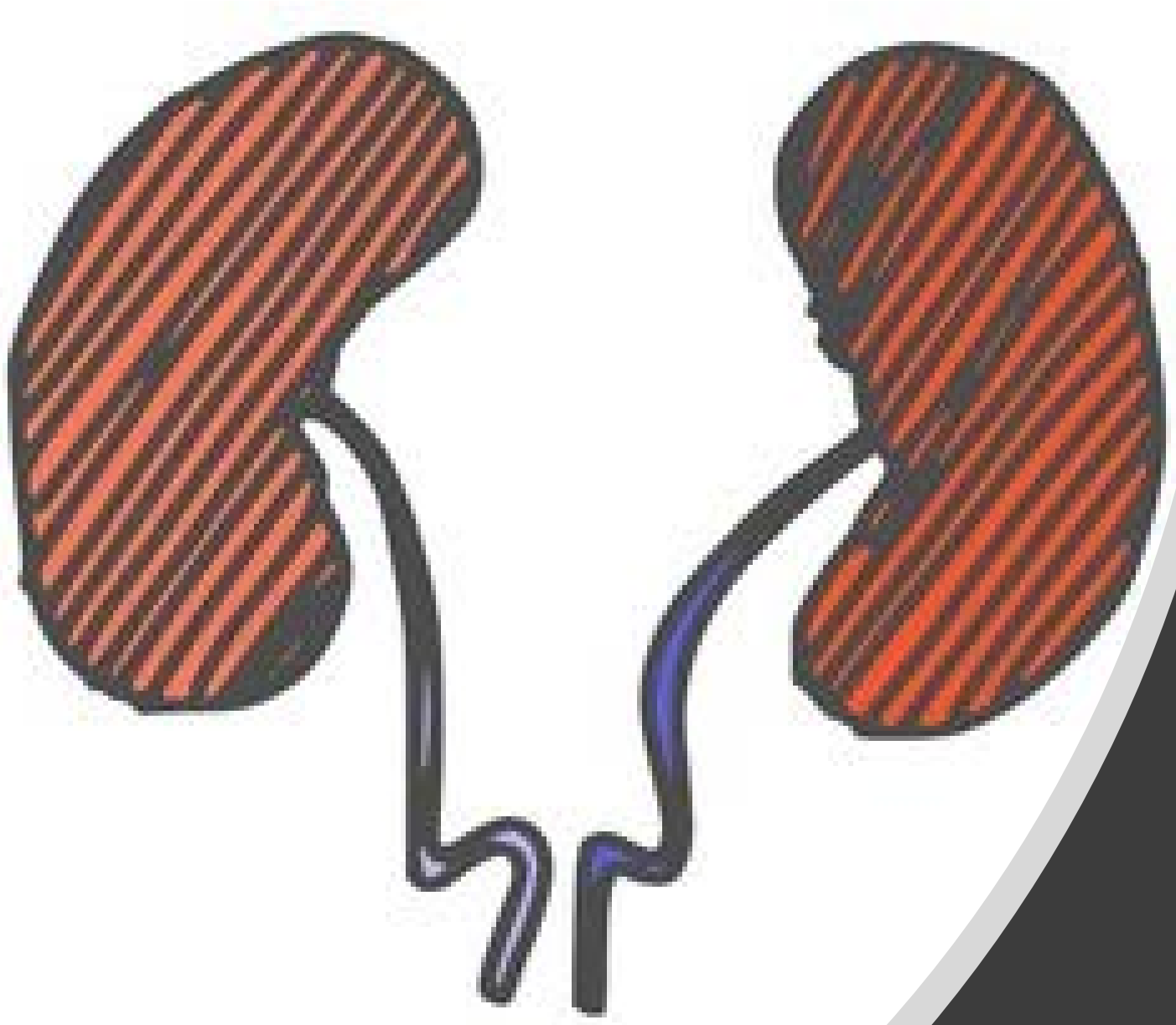
Finerenone

- Kerendia®
- Nonsteroidal mineralocorticoid antagonist
- Contraindicated with strong CYP3A4 inhibitors and adrenal insufficiency
- Dose adjustments based on eGFR and serum K+
- Use in HTN with non-diabetic CKD not established

Finerenone

	Study Population	Pre-Randomization Characteristics	Kidney Outcomes	Results	Other Outcomes	Results
FIDELIO-DKD, 2020 (CKD and T2DM)	uACR 30-<300 mg/g, eGFR 25-<60, retinopathy OR uACR 300-5000 mg/g, eGFR 25-<75	RASi dose maximized Excluded symptomatic HFrEF	Composite of kidney failure, decrease of ≥ 40% in the eGFR, or death from renal causes	**17.8 vs 21.1%, HR 0.82 (0.73-0.93)**	Composite of CV death, nonfatal MI, nonfatal stroke, or HF hospitalization	**13 vs 14.8%, HR 0.86 (0.75-0.99)**
FIGARO-DKD, 2021 (CKD and T2DM)	uACR 30-<300 mg/g + eGFR 25-90 OR uACR 300-5000 mg/g + eGFR ≥ 60	RASi dose maximized Excluded symptomatic HFrEF Metformin use not reported	Composite of kidney failure, decrease of ≥ 40% in the eGFR, or death from renal causes	**9.5 vs 10.8%, HR 0.87 (0.76-1.01)**	Composite of CV death, nonfatal MI, nonfatal stroke, or HF hospitalization	**12.4 vs 14.2%, HR 0.87 (0.76 to 0.98)**

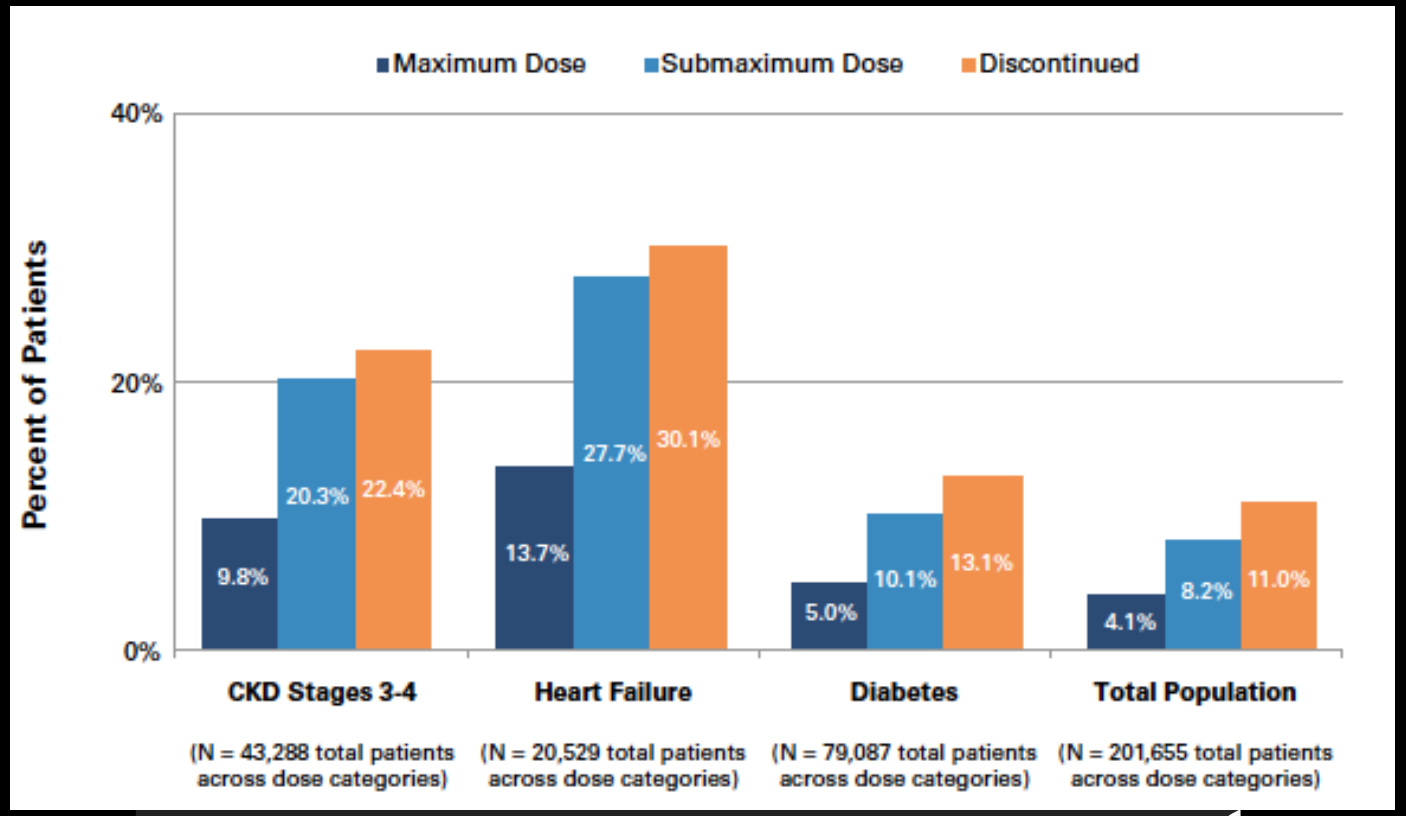
N Engl J Med 2020; 383:2219-2229, N Engl J Med 2021; 385:2252-2263



Common Complications & Management Options

Common Complications

- Hyperkalemia
- Hypocalcemia & hyperphosphatemia
- Hyperparathyroidism
- Anemia



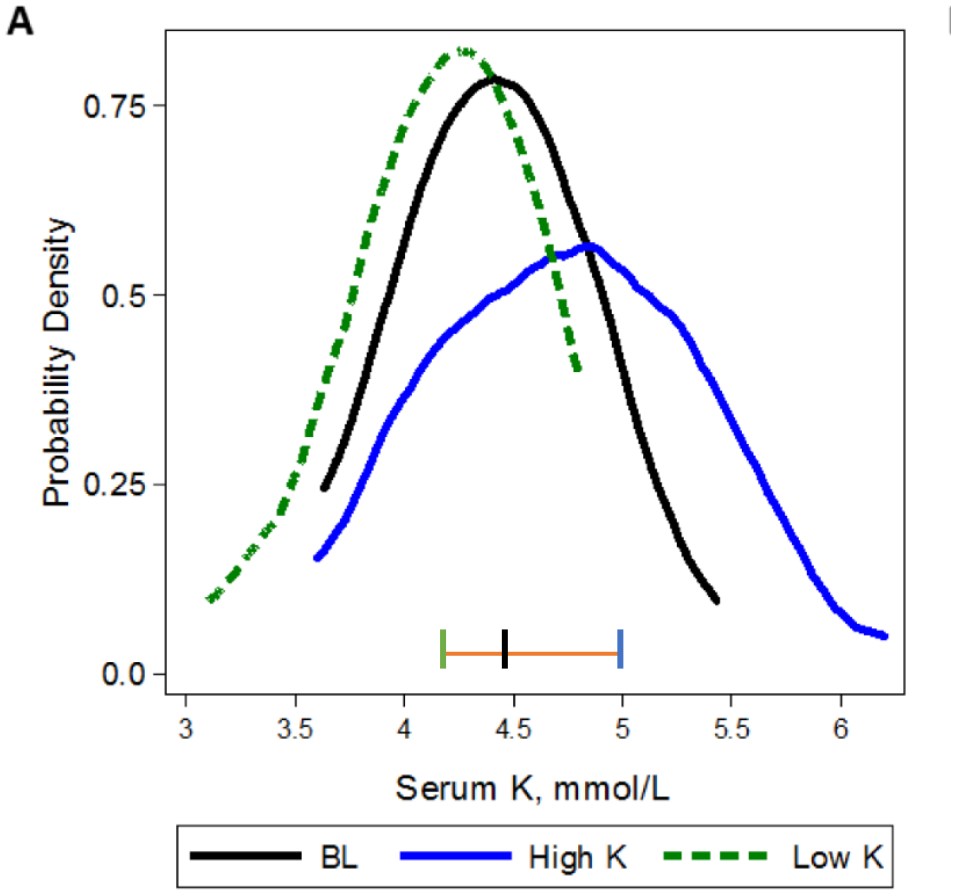
Hyperkalemia: RASi Dose and Mortality

- Guideline directed medical therapy recommend “Maximally tolerated doses”
- Mortality endpoints in CKD & HF studies reported at higher doses than often achieved in the “real world”
- Mortality at sub-maximum doses increases across disease states

Am J Manag Care. 2015;21:S212-S220

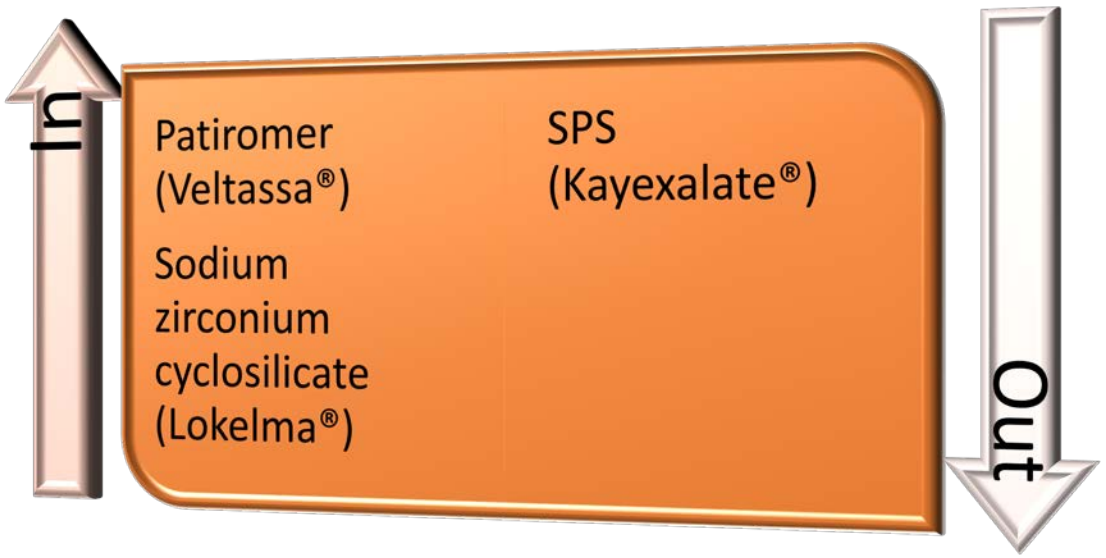
Hyperkalemia & Dietary Intake

- As GFR decreases, higher portion of K+ elimination shifts to GI
- n= 29
- Crossover, CKD Stage 3
- 1 week after consuming high vs low K+ diets



Turban et al. Nutrients 2021

Potassium Exchange Resins



	K+ decrease (mEq/L)	Dose
OPAL-HK (Pat) – 4 wk	1.01 (95%, 1.07-0.95)	12.8-21.4 g/day, average
AMETHYST-DN (Pat) – 1 year	0.51 (95%, 0.38-0.64)	8.4 g twice daily, initial dose
HARMONIZE (SZC) – 28 days	0.6 (95%, 0.5-0.6)	10g, initial

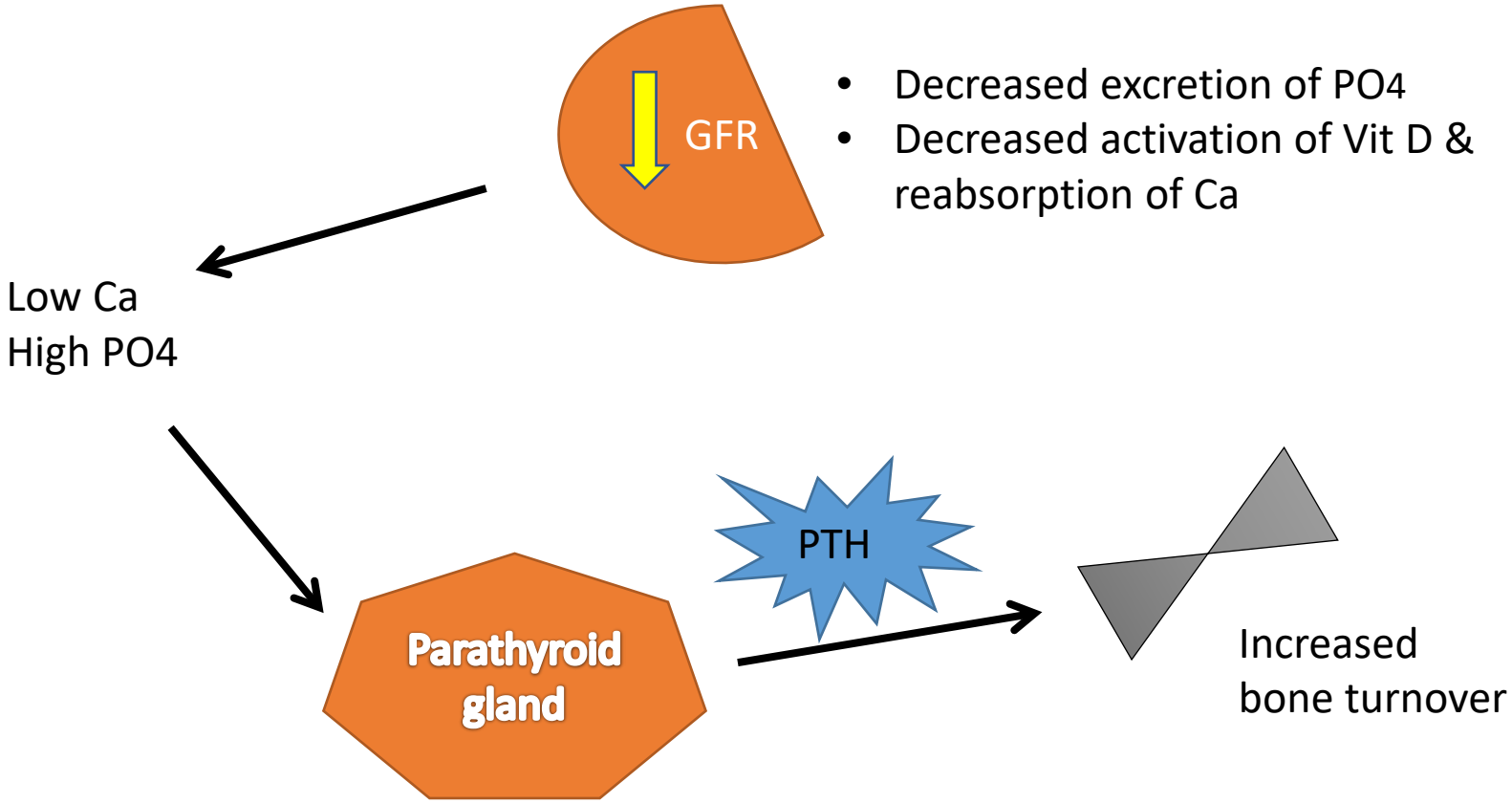
Kosiborod et al. JAMA. 2014;312(21):2223-2233; Bakris et al. JAMA. 2015;314(2):151-161; Weir et al. N Engl J Med 2015; 372:211-221

Long-Term Efficacy & Safety

- Open-Label extension of HARMONIZE study with SZC + RASi (n=83)
- Dose maintained in most patients: 10 g/day
- Adverse events reported: 67% of patients
  - GI: 18.7%
  - HTN: 12.2%
  - UTI: 8.9%
  - Edema: 8.1%
- Mean serum K+ ≤5.1 mEq/L maintained in 76.6–87.5% of patients
- Maintained or increased RASi dose: 86%

Am J Nephrol. 2019;50(6):473-480. doi:10.1159/000504078

Mineral & Bone Disorders



As GFR decreases…

Less sensitivity to PTH-mediated effects on Ca^{2+} and PO_4 reabsorption	Renal activation of Vitamin D	Approach to treatment	Targets
• PTH normally enhances reabsorption of Ca^{2+} and decreases reabsorption of PO_4	• Declines	• Evaluate and treat modifiable causes (diet, Ca, PO_4, Vitamin D) • Re-evaluate PTH for worsening/persistence	• CKD 3a-5: optimal levels of iPTH unknown • Dialysis: iPTH 2 to 9x normal levels

Frequency of Monitoring

KDIGO 2017				
CKD Category	Calcium & Phosphate	PTH	Alkaline Phosphatase	Vitamin D 25(OH)D
G3a-b	Q6-12 months	Based on progression		Initial and based on GFR progression & interventions
G4	Q3-6 months	Q6-12 months	Q12 months	
G5 & G5D	Q1-3 months	Q3-6 months	Q12 months	

- Monitor serum Ca, PO4, PTH, and alkaline phosphatase activity beginning in CKD G3a (1C)

Kidney International Supplements (2017) 7, 1–59

Calcium Supplementation

When to treat hypocalcemia?

- Symptomatic
- High PO4
- Vitamin D deficiency-related hypocalcemia

Avoid hypercalcemia

Treat with calcium products and Vitamin D as with general population

- Inactive Vitamin D products (ergocalciferol, cholecalciferol)

Phosphate Binders

Target of therapy

- Initiate treatment when persistently high
- Phosphate levels *toward* normal range

Regimen considerations

- Administered with meals & snacks
- Empiric dosing
- Titrate based on PO4 levels
- May use combination of calcium-based and non-calcium based binders

Calcium-based

Calcium acetate (PhosLo) > Calcium carbonate

Non-calcium based

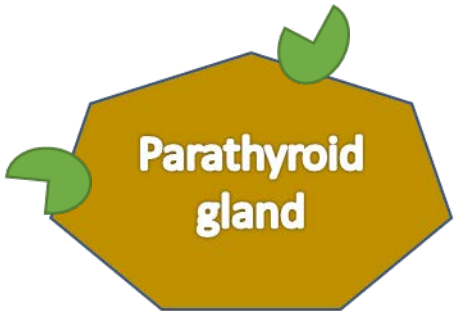
- Sevelamer (Renvela®)
- Lanthanum (Fosrenol®)
- Ferric citrate (Auryxia®)
- Sucroferric oxyhydroxide (Velphoro®)

Hyperparathyroidism

- Optimal levels of PTH for non-dialysis patients not established
- Calcitriol and vitamin D analogs
  - Reserved for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (Not Graded)
- Discontinue if hypercalcemia or hyperphosphatemia develops

Calcimimetics

- Cinacalcet (Sensipar®) and Etelcalcetide (Parsabiv®)
  - Sensitize the calcium-sensing receptors on parathyroid gland
- Reserved for CKD 5D, secondary hyperparathyroidism
- Standard initial dosing, titrate based on PTH response
- May use in combination with Vitamin D, PO4 binders
- Do not use in hypocalcemia
- Nausea



Anemia of CKD

Anemia monitoring in non-dialysis patients

- Without anemia, G3-G5: 1-2x/year
- With anemia, G3-G5: q 3 months

Anemia screening includes

- CBC with differential
- Retic counts
- Ferritin
- TSAT%
- B12 and Folate

Epo & Iron Administration

Iron replacement when TSAT% ≤30%, ferritin≤ 500 mcg/L

- Check iron status every 3 months
- Trial IV iron regardless of dialysis status
- May try oral iron for 1-3 months

Erythropoietin stimulating agents

- EPO, Darbepoetin
- In CKD 5D patients, initiate when Hgb between 9-10 g/dL
- Hyporesponsiveness if Hgb does not increase after 1 month
- Target Hgb not more than 11.5 g/dL

Thank you

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Questions?

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Upcoming Events

- WOW Consortium Meeting
  - Tuesday, September 20th (2-3pm)
  - Microsoft Teams

- *Webinar Series*: Inpatient Glycemic Control
  - Mary Shreffler, OU Health
  - Tuesday, September 27th (12-1pm)

- *Webinar Series*: Food Insecurity in Rural Communities
  - Hunger Free Oklahoma
  - Wednesday, October 12th (TBD)

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For more information on WOW and to join our consortium:

Email jnoble@ofmq.com

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