Chronic Kidney Disease Updates

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MedNet21

Objectives

- How to diagnose Chronic Kidney Disease (CKD)
- How to assess progression in CKD
- Management of CKD
  - Target blood pressure
  - Reno-protective medications
  - Metabolic acidosis
  - Diet

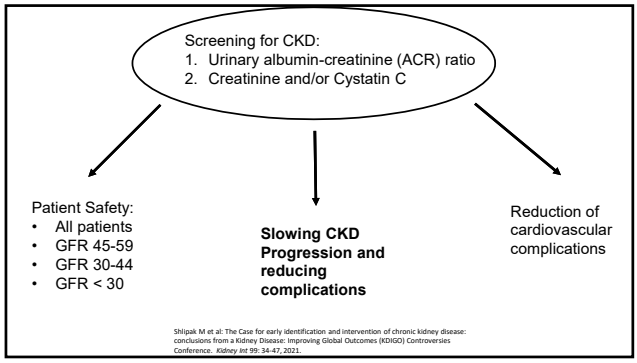
Diagnosis of CKD

"Abnormality in kidney structure or function for more than **3 months**"

- Sustained decrease in GFR < 60 ml/min per 1.73 m²
- Presence of albuminuria
- Abnormalities on urine sediment, histology, or imaging
- Electrolyte abnormalities due to tubular disorders
- Prior history of kidney transplant

Who should be screened?

- Universal screening for patients with
  - Hypertension
  - Diabetes
  - Cardiovascular disease
- Individualized approach for patients with other clinical or genetic risk factors



Shlipak M et al: The Case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 99: 34-47, 2021.

When to Refer?

- Acute Kidney Injury (AKI) for abrupt sustained drop in GFR
- GFR < 30
- Albuminuria > 300 mg/g
- Progression of CKD
- Urine red cell casts
- CKD with resistant hypertension
- Persistent electrolyte abnormalities
- Recurrent nephrolithiasis
- Hereditary kidney disease, suspected glomerular disease
- Pregnancy

Case 1

- A 72 year old female with long-standing diabetes and hypertension, coronary artery disease, right lower extremity amputation sees you for follow up. She has a serum creatinine of 1.28 mg/dl and her urinary albumin to creatinine ratio is 780 mg/g. You are considering adding a sodium/glucose cotransporter 2 inhibitor.

- What method should be used for GFR measurement?
- A. Iohexol plasma clearance
- B. 24 hour urine for creatinine clearance
- C. GFR by cystatin c
- D. GFR by creatinine
- E. Combination of creatinine and cystatin c

Assessment of kidney function

- GFR varies by time of day, diet, exercise, body size, drugs, hemodynamics

Pros	Cons
Direct measure of kidney function	Accurate measurements are difficult to perform
GFR decrease correlated with decreased endocrine/metabolic functions	Estimates can be biased and imprecise
GFR is reduced before onset of symptoms	GFR can be insensitive for early detection of kidney disease

Assessment of kidney function

- CKD-Epi 2021
- Cystatin C
- Increased research funding to optimize GFR estimation

Limitations to Creatinine and Cystatin C

Non-GFR determinant	Creatinine	Cystatin C
Body composition	Extremes of muscle mass	Obesity
Health state	Chronic severe illness/frailty	Inflammation, thyroid, smoking
Diet	High protein or creatine supplements	
Drugs	Cimetidine, trimethoprim, fenofibrate, doluegravir, tyrosine kinase inhibitors	Steroids
Increased extrarenal elimination	Antibiotics, low eGFR	
Nonsteady state	AKI, dialysis, edematous state	AKI, dialysis, edematous state

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Albuminuria

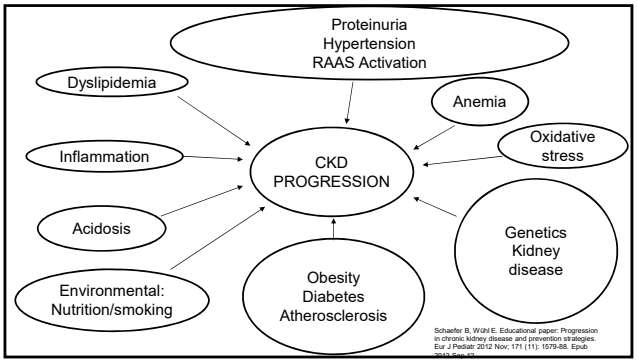
		A1	A2	A3
		< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mmol
G1	GFR ≥ 90			
G2	GFR 60-89			
G3a	GFR 45-59			
G3b	GFR 30-44			
G4	GFR 15-29			
G5	GFR < 15			

Adaptation of "CKD Heat Map"

Risk Factors for CKD Progression

Sociodemographic	Behavioral	Genetic	Cardiovascular	Metabolic	Novel
Sex	**Smoking**	APOL1 gene variants	**High systolic blood pressure**	High FGF-23	NT-proBNP
Racial and ethnic	**Higher dietary animal protein intake**	RAAS pathway genetic variants	Aortic stiffness	**Low serum bicarbonate**	Urine NGAL
Environmental	**Poor self-management**		**Heart failure**	Increased urine oxalate	AKI
Nephrology care access	Fragmented and less sleep		Atrial fibrillation	Increased uric acid	Inflammation (CXCL12)

Adapted from
Anderson AH et al; CRIC Study Investigators. Novel Risk Factors for Progression of Diabetic and Nondiabetic CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2021 Jan; 77 (1): 56-73.e1.



Management of CKD

Hypertension

- Leading risk factor for progression of CKD
  - Higher prevalence in advancing stages of CKD
- Leads to development of cardiovascular disease

Case 2

- Which is true regarding reduction of blood pressure to < 120 systolic?
- A. Reduction in all-cause mortality
- B. Slows CKD progression
- C. Lower incidence of renal replacement therapy
- D. Lower incidence of kidney transplant

Case 3

- You have a 55 year old patient with CKD Stage 3aA3 due to diabetic nephropathy. Average home blood pressures are 140s/80s on Lisinopril 20 mg, Chlorthalidone 50 mg, and Amlodipine 10 mg. Her urine albumin creatinine ratio (UACR) is 800 mg/g.
- What is the appropriate next step in management?
- A. Add Losartan to her current regimen
- B. Stop Lisinopril and add Spironolactone
- C. Increase Lisinopril dose
- D. Change Chlorthalidone to Furosemide

Hypertension

- 30-60% of hypertension is heritable
- CKD patients are predisposed to salt sensitivity
- Key mechanism: inappropriate Renin-Angiotensin-Aldosterone System activation
- Environmental factors account for 40% of hypertension

Judd, H. Risk Factors, Mechanisms, and Causes of Essential Hypertension. Nephrology Self-Assessment Program Volume 21, No 4, September 2022.

Secondary Hypertension

Cause	Clinical clues	Diagnostic Testing
Primary aldosteronism	Hypokalemia, metabolic alkalosis, adrenal nodule	Aldosterone-renin ratio
Renovascular disease	Progressive CKD, asymmetric kidneys, atherosclerosis	Duplex ultrasound, CT angiography, MR angiography
Pheochromocytoma	Surges of hypertension, headaches, palpitations	Plasma free or urinary metanephrines
Kidney parenchymal disease	Known CKD	n/a
Obstructive sleep apnea	Snoring, apnea, daytime somnolence	Sleep study
Coarctation of aorta	Young patient, bp higher in upper extremities, weak femoral pulses	Transthoracic echocardiography
Cushing Syndrome	Central weight gain, round face, central obesity, abdominal striae	24-hour urinary free cortisol, late night salivary cortisol measurement

Hundemer, G. Causes, Evaluation, and Treatment of Secondary and Resistant Hypertension. Nephrology Self-Assessment Program- Volume 21, No 4, September 2022.

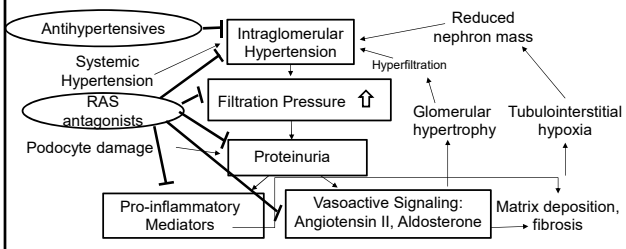
Kidney Disease Improving Global Outcomes (KDIGO) 2021 Guidelines

- 1. Target systolic blood pressure (SBP) < 120 mm Hg based on standardized office blood pressure measurements
- 2. Same SBP target regardless of albuminuria, diabetes, or older age
- 3. Kidney transplant recipients target SBP < 130 mm Hg or diastolic blood pressure (DBP) < 80 mm Hg

Implications for hypertension management

- **Per the KDIGO guideline, 69.5% of US adults with CKD are eligible for blood pressure lowering.**
- **Among patients with albuminuria, 78.2% are eligible but ONLY 39.1% take angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.**
- **THESE ARE MISSED OPPORTUNITIES TO IMPROVE BP CONTROL AND ADHERE TO GUIDELINES**

Pathophysiology of Hypertension



Wühl, E., Schaefer, F. Therapeutic strategies to slow chronic kidney disease progression. *Pediatr Nephrol* **23**, 705–716 (2008).

Systolic Blood Pressure Intervention Trial (SPRINT)

- A study of 9361 patients > 50 years old
- Patients were assigned to SBP < 130 mm Hg versus < 140 mm Hg
- Lower blood pressure group had lower risk for cardiovascular events and all-cause mortality
- NO difference in CKD progression

Lewis C, et al. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2021; 384:1921-30.

Approach to the Management of Hypertension

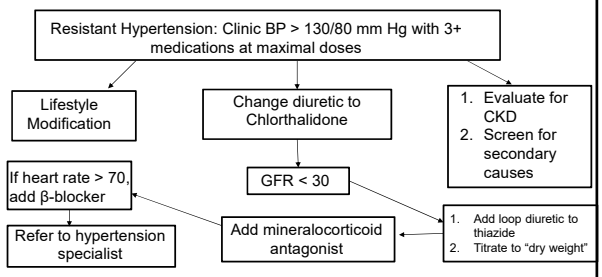
- KDIGO 2021
  - Albuminuria without diabetes: start RASi for systolic blood pressure > 120 mm Hg
  - Albuminuria with diabetes: start RASi
- ACC/AHA 2017
  - Treatment with RASi is reasonable for patients with hypertension and GFR < 60 ml/min/1.73 m² or GFR ≥ 60 ml/min/1.73 m² with UACR ≥ 300 mg/g

Renin-Angiotensin System Inhibitors (RASi) in advanced CKD

- Current recommendation: Continue RASi if creatinine change is < 30% within the first month after initiation of therapy
- Continuation of RASi is associated with lower risk of major adverse cardiac events and overall mortality
- Risk of progression to end stage renal disease is unclear

Goraya N. Management of CKD. Nephrology Self Assessment Program Volume 21: Issue 2. Jun 2022.

Resistant Hypertension Algorithm



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Nonsteroidal Mineralocorticoid Receptor Antagonists (MRA)

- Nonsteroidal MRAs are more selective for the mineralocorticoid receptor, so they have less antiandrogenic and progestagenic side effects
- Lower risk of hyperkalemia
- Finerenone was approved 7/2021
  - Suppresses expression of proinflammatory and profibrotic genes in the presence or absence of aldosterone

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Case 4

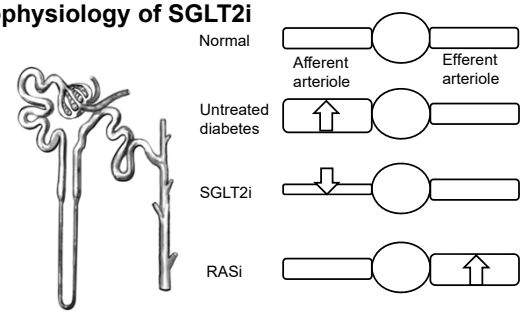
- You have a 48 year old male patient with DM2 with CKD Stage 3aA2 with retinopathy and hypertension. His medications include Losartan 100 mg, Metoprolol 75 mg BID, Metformin 500 mg BID. His blood pressure is under acceptable control, but you note that his albuminuria has been steadily worsening to 1000 mg/g in the past year.
- What is the next best step?
- A. Start SGLT2i to reduce albuminuria
- B. Start SGLT2i to reach A1c < 7.0%
- C. Add Finerenone
- D. Stop the Metformin

Sodium-Glucose Cotransporter Inhibitors

- Inhibits the primary glucose transporter in the proximal tubule and inhibits proximal tubule sodium reabsorption
- Reduce intraglomerular pressure by restoring tubuloglomerular feedback
- Increased distal sodium delivery leading to natriuresis
  - Decrease circulating volume and improved blood pressure, improved cardiac preload
- Anti-inflammatory effects

Goraya N. Management of CKD. Nephrology Self Assessment Program Volume 21: Issue 2. Jun 2022.

Pathophysiology of SGLT2i



Palmer B et al. Kidney-Protective Effects of SLGT2 Inhibitors. CJASN 18:279-289, 2023.

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

SGLT2i Trials

Drug	Trial	Kidney-Related Eligibility Criteria	Primary Outcome	Effect on Primary Outcome	Effect on albuminuria	Effect on GFR loss
Empagliflozin	EMPA-REG OUTCOME CANVAS	GFR ≥ 30	Major Adverse Cardiac Events (MACE)	↓	↓↓	↓↓
Canafliglozin	CREDENCE	GFR ≥ 30	Progression of CKD	↓↓	↓↓	↓↓
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥ 60 ml/min	MACE, hospitalization for HF or CV death	⟺ ↓	↓	↓↓

DAPA-CKD

- Evaluated effect of Dapagliflozin in patients with CKD due to DM, IgA, FSGS, etc
- Patients with GFR 25-75 mg/min per 1.73 m² and UACR 200-5000 mg/g
- Randomized to Dapagliflozin vs Placebo
- **Overwhelming efficacy!**

1. Reduced the primary outcome of sustained decline in GFR > 50%
2. Decreased risk of death from renal or CV event by 50%
3. Benefits consistent across all stages of CKD, degrees of albuminuria, presence or absence of DM

Empagliflozin EMPA-KIDNEY

- A study of 6609 patients with GFR of at least 20 but < 45 ml/min/1.73 m with UACR of at least 200 mg/g
- Primary outcome: progression of kidney disease or death from cardiovascular causes
- Across a wide range of GFRs and levels of albuminuria and causes of CKD, there was 28% less risk for progression of kidney disease of death from CV cause on Empagliflozin

The EMPA-KIDNEY Collaborative Group; Herrington WG et al. "Empagliflozin in Patients with Chronic Kidney Disease." N Engl J Med 2023; 388: 117-27.

Summary of SGLT2i

- Reduced renal events by 34-47%
- Reduction in risk of cardiovascular events 7-14%
- Decreased risk of hospitalization for heart failure by 3

Goraya N. Management of CKD. Nephrology Self Assessment Program Volume 21: Issue 2. Jun 2022.

Initiating SGLT2i in DM2 and CKD

- GFR ≥ 30 ml/min/1.73 m²
- UACR ≥ 200 mg/g
- Heart failure
- Consider contraindications

⇨

Low-dose SGLT2i:
- Canafliglozin 100 mg
- Dapagliflozin 10 mg
- Empagliflozin 10 mg

⇨

Follow Up:
- Assess for any adverse effects
- Anticipate acute decline in GFR

Case 4

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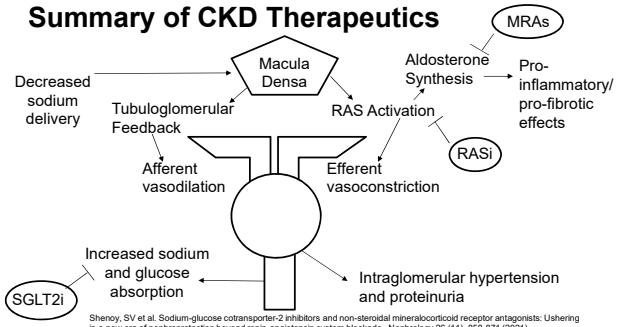
Summary of CKD Therapeutics



Shenoy, SV et al. Sodium-glucose cotransporter-2 inhibitors and non-steroidal mineralocorticoid receptor antagonists: Ushering in a new era of nephroprotection beyond renin-angiotensin system blockade. Nephrology 26 (11), 858-871 (2021).

Lifestyle Modification in CKD

- A recent meta-analysis showed diet consisting of fruits, vegetables, whole grains, and fiber plus a lower intake of sodium, red meat, and sugar was associated with a 30% reduced odds of kidney damage
- Exercise/weight loss
- Smoking cessation
  - Smoking was associated with higher prevalence of coronary artery calcification in CKD

Bach KE, Kelly JT, Palmer SC, Khalesi S, Strippoli GFM, Campbell KL: Healthy dietary patterns and incidence of CKD: A meta-analysis of cohort studies. *Clin J Am Soc Nephrol* 14: 1441–1449, 2019

Metabolic Acidosis

- Western diets (high protein) cause higher acid load
- CKD lead to decreased acid excretion; unable to synthesize ammonia and excrete hydrogen (H+) ions
- Metabolic acidosis can cause bone disease, increased risk of cardiovascular disease, and decline in GFR
- Ways to treat
  - Sodium bicarbonate
  - Sodium citrate
  - Diet high in fruits and vegetables
- Goal is to raise serum bicarbonate to > 22 mM/l

Key Points: Diabetic Kidney Disease

- Treat patients with DM2 and CKD with GFR ≥ 20 ml/min/1.73 m² with SGLT2i (1A)
- Add nonsteroidal MRA with DM2 and GFR ≥ 25 ml/min/1.73 m² if normal serum creatinine and albuminuria ≥ 30 mg/g despite max RASi therapy (2A)
- Target A1c ranging from < 6.5% to < 8.0% in patients with diabetes and CKD not yet on dialysis (1C)

KDIGO Guideline 2022