CKD for the Non-Nephrologist

Kim Zuber, PAC
American Academy of Nephrology PAs (AANPA)
Nutrition Fellow, PA Foundation

Disclosures

I have no relevant relationships with ineligible companies to disclose within the past 24 months

I am presently running for AAPA Secretary/Treasurer

While all these stories are true and used with permission, the photos and names are intermixed

Objectives

1) Review the updated definition of CKD highlighting race and gender modifiers for staging CKD 1-5
2) Discuss both the causes and treatments of CKD
3) Demonstrate proven methods to prevent progression of CKD in patients including new dietary interventions

Kidney Disease Facts

30 million Americans have CKD

15% of the population

Most don't know it

Every 5 minutes someone's kidneys fail

Between 2000-2019, there was a 41.8% increase in ESKD cases

For the first time in the history of the ESKD program, new dialysis starts went down:

Due to Covid!

A program to increase testing/management for Am Indian population between 2000-2019, led to a less cases; saving Medicare $520 million

Kidney Disease Facts

30 million Americans have CKD

In 2019, the cost of CKD Stage 1-5 was more than $114 BILLION
Or 44% of the entire Medicare budget

This is larger than the budget of the NIH + NASA + Homeland Security all added together

And it is growing…..

- CKD is the fastest growing chronic disease
- The rate of growth is highest in the 20-54 y/o!
- The incidence of CKD grew by 89%
- Death from CKD grew by 98%
- Disability from CKD grew 62%

Analysis of the Global Burden of Disease….1990-2016, Kidney International 2018

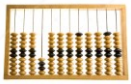
And so we are adapting…..
New in 2021

- In August 2020, the American Society of Nephrology and the NKF institute a Task Force to look into race-based issues in GFR
- Kidney Disease Improving Global Outcomes (KDIGO) announces no more updates to CKD management guidelines
- KDIGO announces specific updates for diagnoses that occur in CKD with a goal to keep the guidelines relevant
- In October 2020, ***Diabetes Management in CKD*** is published
- In February 2021, ***Hypertension Management in CKD*** is published
- In Oct 2021, NKF/ASN announce a new ***eGFR calculator***

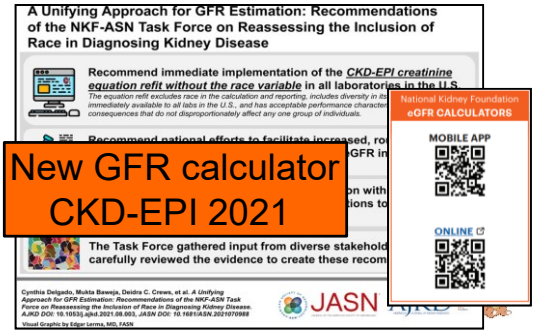
KDIGO Management of Diabetes in CKD, KDIGO Management of HTN in CKD, ASN/NKF Race Task Force

eGFR Calculators for Kidney Function

- **1976 Cockcroft-Gault formula**
  - Compared 249 White hospitalized males with inulin vs calculator
  - Requires age, gender, SCr, weight
  - 15% less in females (never confirmed)
  - Reports as CrCl, often in FDA package inserts



- **1999 Modification of Diet in Renal Disease (MDRD) formula**
  - Compared 1585 CKD patients with iothalamate vs calculator
  - Requires age, gender, SCr, BUN, Albumin, race *(Black 1.2 modifier)*
  - Adjusted to age, gender, SCr, race in 2000 *(Black 1.2 modifier)*
- **2012 CKD-EPI formula** *(on your present lab forms)*
  - Developed with input from large data bases at NIH (NHANES, AASK)
  - Contains 'correction' for race *(Black 1.16x modifier)*



New GFR calculator
CKD-EPI 2021

So….who and how do we screen?

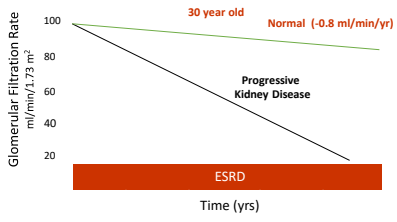
How do I find CKD?

- **Go for the obvious!**
  - Elderly (60!!!!)
  - Minority
  - Hypertension/CVD
  - Diabetes
  - Family history
  - Female
    - *Although less likely to go to ESRD!*
  - On their medical history!

Go for the less obvious!

Previous AKI
Lupus, sarcoid, amyloid, gout, auto-immune…
Previous donor/Previous transplant
History of stones
History of cancer
History of oophorectomy
History of gout
Smoker (any type)
Soda drinkers
Moms who drank with pregnancy
NACL bingers
Almost any medical condition

Normal Age Progression of Kidney Function



Stages of CKD

Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009)

GFR stages, description and range (ml/min per 1.73 m²)				Albuminuria stages, description and range (mg/g) A1 Optimal and high-normal <10	A1 Optimal and high-normal 10–29	A2 High 30–299	A3 Very high and nephrotic 300–1999	A3 Very high and nephrotic ≥2000
	G1	High and optimal	>105					
			90–104					
	G2	Mild	75–89					
			60–74					
	G3a	Mild-moderate	45–59					
	G3b	Moderate-severe	30–44					
	G4	Severe	15–29					
	G5	Kidney failure	<15					

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD, *Kidney International*, Jan 2013, Vol 3, Issue 1

Sadie

She reports she is 85 y/o, female, and she has diabetes

Labs: eGFR 45ml/min

If you lose 1%/yr above the age of 30,
85-30 means 55 years of GFR loss
Or
100 (*average perfect kidney function*)-55 (*years*)
or expected eGFR is **45ml/min**
She is age appropriate….will she progress?

Albuminuria As Risk Factor

The relationship between magnitude of proteinuria reduction and the risk of ESRD: Results of the AASK study of kidney disease and hypertension Ach Intern Med 2001

JAMA ARCHIVES OF INTERNAL MEDICINE

The Progression of CKD: A 10-year population-based study of the effects of gender and age. KI 2006

kidney

JASN

Combining GFR and albuminuria to classify CKD improves prediction of ESRD, JASN 2009

Changes in Albuminuria and the Risk of Major Clinical Outcomes in Diabetes: Results From ADVANCE-ON

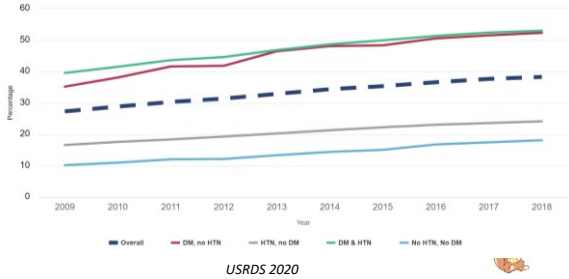
AJKD AMERICAN JOURNAL OF KIDNEY DISEASES

American Diabetes Association. Diabetes Care

Changes in Albuminuria and subsequent risk of incident kidney disease, JASN 2017

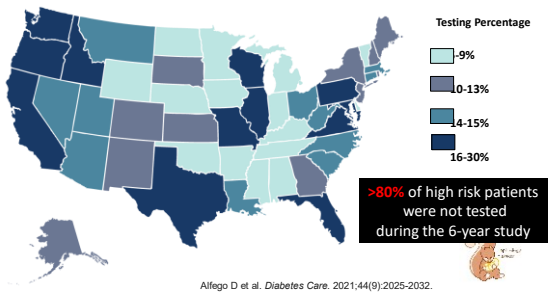
Alberta Kidney Disease Network: Relation between kidney function, proteinuria, and adverse outcomes, JAMA 2010

Probability of urine albumin testing in at-risk Medicare patients



USRDS 2020

Testing Rates of Patients at Risk for CKD Across U.S. From 2013 to 2018



>80% of high risk patients were not tested during the 6-year study

Alfego D et al. *Diabetes Care.* 2021;44(9):2025-2032.

Gold Standard:
Urine albumin to creatinine ratio (UACR)

Urinary protein

Urine protein to creatinine ratio

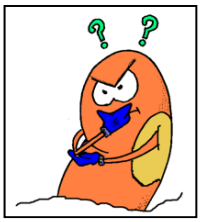
Special Thanks to Scott and White of Temple TX for use of their kidney comic

Urine Pearls

- Some labs (Quest, LabCorp) refer to a UACR as 'microalbuminuria'
- NKF has joined with Quest (*Code: 39165, CPT: 82043; 82565; 82570*) and LabCorp (*Code: 140301, CPT: 82043; 82565; 82570*) to roll out a 'Kidney Profile' that incorporates both the SCr + the UACR

- **Order a UACR at least 1x/yr to monitor kidney function**
  - **For all patients with hypertension**
  - **For all patients with diabetes**
  - **For all patients with risk factors**
  - **Age >60 y/o is a risk factor**

So we know who has CKD And we tested their urine



Now…how do we manage CKD in 2022?

The Big 5

1) **Hypertension (NEW IN 2021)**
2) **Diabetes (NEW IN 2021)**
3) Obesity
4) Cardiovascular Disease
5) This and That (kind of defies categorization)

Hypertension (New in 2021)

The most common comorbidity in CKD is HTN

If HTN doesn't cause your CKD, your CKD will cause HTN

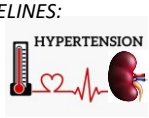
So what is the GOAL?

KDIGO 2021 HTN Management in CKD GUIDELINES:

Target SBP 120mm Hg

Use an automatic office cuff measurement

No DBP goal



Effectiveness of Lifestyle Changes

Modification	Example	Approx Reduction
Physical activity	Aerobic (brisk walking?) >30/day, most days	**4-9mmHg**
DASH eating plan	Low fat diet rich in fruits, vegetables	**8-14mmHg**
NACL restriction	Decrease to 2.4gm/day	**2-8mm Hg**
Moderate ETOH	1 drink/women, 2 drinks/men	**2-4mmHg**
Weight loss	BMI 18.5-25	**5-20mmHg/10kg weight loss**
Stress reduction	Practice modality	**5mmHg**
Quit smoking	Any which way	**2-4mmgHg after 1 week**

NACL Restriction

Stage of Kidney Disease
= NACL clearance

Most effective in
patients of color

Tricks:

Pork holidays

No cooking w/NACL

'B' cooking

First Choice: ACEi/ARB

ACEi OR ARB:

First choice in Diabetes and/or CKD
Even in the AA population
Will decrease albuminuria….
Use it even if there is no albuminuria
It doesn't matter ACEi vs ARB

Only 1 or the other due to:

- inc risk of hyperkalemia
- Hypotension
- AKI/failure
- no decrease in mortality

One or the other
NOT BOTH!

Rose

74 y/o routine visit
PMH: PVD, HL, HTN
Meds: metoprolol, HCTZ, amlodipine, ASA, atorvastatin
PE: 168/98, home 150-160s
Labs: SCr 1.2mg/dL, UACR 30mg/dL, eGFR 56mm/min
Add lisinopril for BP/UACR control

F/U labs 2 weeks later, SCr 1.5mg/dL with K 5.2mEq/L

What is an acceptable rise in SCr starting an ACEi/ARB?

Acceptable rise in SCr is 20-30%

When do I stop an ACEi/ARB?

- If hyperkalemia cannot be **controlled**
  - Diet, education, medication
  - What is hyperkalemia?
    - Lab dependent
    - >5.5mEq/L in CKD 4
    - >6mEq/L in CKD 5
    - >We'll tell you in CKD 5D!!!

What do the present studies say? *All observational trials*

Continued use of ACEi/ARB with a GFR<30mm/min protected the heart \ increase in ESRD*

Stopping ACEi/ARB increased mortality and MACE endpoints by 11.9-13.6% with a <8% increase in ESRD in Stage 5 patients**

Inc death rate due to CVD in those who had ACE/ARB stopped for hyperkalemia***

*Association Between Renin-Angiotensin System Blockade Discontinuation and All-Cause Mortality Among Persons With Low Estimated Glomerular Filtration Rate, *JAMA Intern Med.* March 9, 2020
**Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcomes: A Nationwide Study, JASN Feb 2021
***Hyperkalemia-Related Discontinuation of Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in CKD: A Population-Based Cohort Study, AJKD 2022

When do I stop an ACEi/ARB?

The STOP-ACEi trial

Multicenter UK randomized controlled trial of ACEi/ARB withdrawal in advanced kidney disease

Enrollment completed June 2018

Trial time line 3 years

Cardiac vs ESRD…

Or

Do the patients have more cardiac events or more GFR loss??

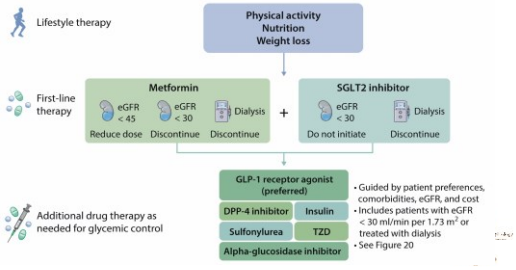
Results to be determined

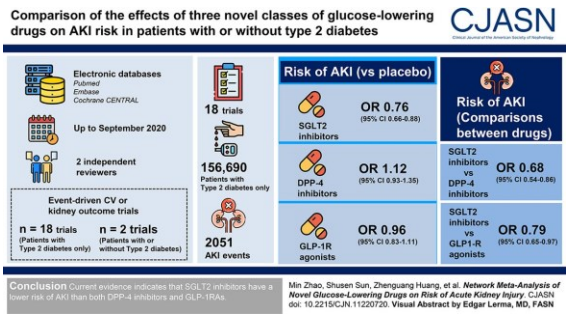
Note: Trial data collection in the UK has slowed due to Covid…

Hypertension Pearls

- NACL restriction is just as effective as medications
- Always tell a patient that it will take 3-4 meds for control;
  If it takes fewer, they think you are brilliant
- Start with ACEi/ARB, then diuretic (if possible)
- Consider an SGLT2i early in the process; It is a diuretic
- Calcium channel blockers work **VERY** well in the AA population
- With cardiovascular disease…ACE/CCB>ACE/diuretic
- Thiazide diuretics do **NOT** work if the GFR<30ml/min
- **NOTHING works if you cannot afford it**

KDIGO: Update for Diabetes Treatment in CKD



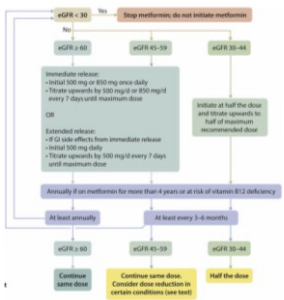


Kidney Specific Family Details: Metformin

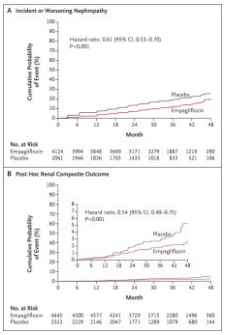
- This should be the first medication for any DM patient
- Metformin is underutilized in DKD
- It is an older medications and therefore cheap
- **No renal dosing needed**
- Dosing is dependent of side effects (usually GI)
- Decreases CV risks which cause 70% of all CKD deaths
- Often will decrease cholesterol, triglycerides and weight

Therapeutic Considerations for Antihyperglycemic Agents in DKD CJASN May 2017

Metformin Dosing in CKD: Algorithm Format



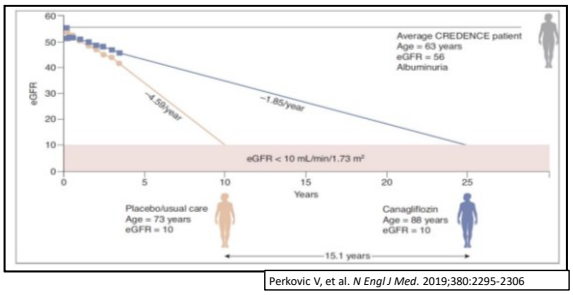
EMPA-REG (Secondary Outcome) *Protected against Nephropathy* By lowering albuminuria, slowing GFR loss, lowering kidney/CV death



44% DECREASE for kidney endpoint
Hazard ratio, 0.61 (95% CI, 0.53–0.70)
***P* <0.001**

Wanner C, for the EMPA-REG Trial Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med.* 2019;380:2295-2306

CREDENCE: Using Canagliflozin postpones Dialysis



Perkovic V, et al. *N Engl J Med.* 2019;380:2295-2306

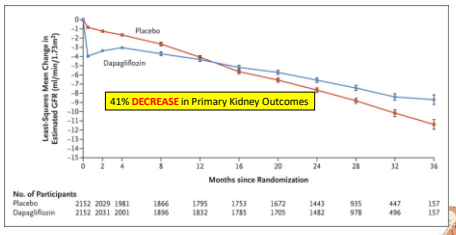
Dapagliflozin: DAPA-CKD Trial

If an SGLT2i is renoprotective AND the A1C does not go down, Is an SGLT2i renoprotective for CKD WITHOUT Diabetes?

- 4425 patients, 30% without diabetes
  - eGFR: 25 to 75 mL/min/1.73 m²
  - UACR: 200 to 5000 mg/g
  - Stabilized on ACEI or ARB therapy
- Random assignment (1:1)
- Stratified by eGFR
- Blinded
- Dapagliflozin 10mg/d vs Placebo
- Follow-up 2.4y, stopped early by safety committee

Heerspink HJL, et al. *N Engl J Med.* 2020;383(15):1436-1446.

Dapagliflozin: DAPA-CKD Trial



Heerspink HJL, et al. *N Engl J Med*. 2020;383(15):1436-1446.

Using SGLT2 inhibitors

- Initially treat with maximum dose of ACE/ARB before adding SGLT2i
  SGLT2i can be used up to Stage 3a or Stage 3b for canagliflozin
- If patient on loop diuretic, ½ the dose….
  (was researcher choice: ½ number of daily doses or ½ each dose)
- Tell patient to increase fluid *(water)*
- Monitor blood pressure; all SGLT2i are diuretics too!
- There will be a drop in eGFR (inc in SCr) but take a deep breath, step away from EHR and ignore
- The A1C may not decline by much as CKD progresses, however, reno/cardio protection occurs
- SCr bump from RAAS is 4-6w but from SGLT2i is 4-6mo
  Even those with a bump in GFR had better kidney outcomes

Benefits of SGLT2i

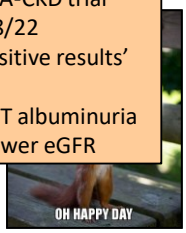
- **Slows progression of CKD**
  - CREDENCE: if eGFR 56ml/min, UACR 927mg/dL-slow progression by 2.74ml/min/year
  - DAPA-CKD: if eGFR 44ml/min, UACR 930mg/dL-slow progression by 1.8ml/min/year
- **Reduces albuminuria**
  - 30-40% and this is on top of ACE/ARB
- **SBP reduction**
  - 4mm Hg
- **Weight reduction**
  - 5-6lb (if eGFR>45ml/min)
- **Reduce A1C**
  - 0.5-0.8% (if eGFR>45ml/min)
- **Lower uric acid by 10%**
  - A 50% lower risk of nephrolithiasis

Kristensen KB, et al. Diabetiologia 2021

Benefits of SGLT2i

- **Slows progression of CKD**
- **R**
- **S**
- **V**
- **R**
- **Lower uric acid by 10%**
  - A 50% lower risk of nephrolithiasis

Preliminary data from the EMPA-CKD trial
Presented at NKF on 4/8/22
Trial stopped 2 weeks ago for 'positive results'
Analysis underway
Many were CKD patients WITHOUT albuminuria
Only with CKD identified by lower eGFR



Kristensen KB, et al. Diabetiologia 2021

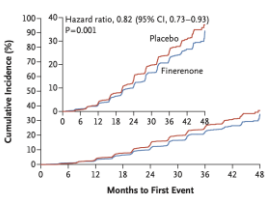
SGLT2 inhibitors in 2021/2022

- SGLT2i are reno-protective in diabetes
- SGLT2i are cardio-protective in diabetes
- SGLT2i are reno-protective in CKD
- SGLT2i are cardio-protective in CKD
- There may not be a lowering of the A1C with an SGLT2i in CKD with diabetes but it still is reno-protective
- SCr bump from RAAS is 4-6w but from SGLT2i is 4-6mo

Dapagliflozin is now FDA approved for use in CKD WITHOUT DIABETES

New Kid on the Block- Non-steroidal MRA Finerenone (Kerendia®)

Primary Composite Outcome



Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229

Mechanism of Action
Induces conformational change within the mineralocorticoid receptor
Works to decrease inflammation?

FDA 7/9/21:
1) Reduce the risk of loss of kidney function
2) Reduce incidence of kidney failure
3) Reduce cardiovascular death
4) Reduce non-fatal heart attacks
5) Reduce hospitalization for heart failure in adults with CKD and T2DM

MRA-Mineralocorticoid Receptor Antagonists

Bariatric Surgery

Dec 4th, 2016

Estimated GFR before and after Bariatric surgery in CKD

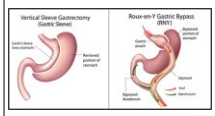
Imam, et al

Large Kaiser group (714) over 3 years
44% minority, 58±8 (SD) y/o, 77% female
66% w/DM, 91% w/HTN

Surgical patients had nearly 10mL/min better eGFRs at 3 years than non-surgical

RYGB had 6.6mL/min better eGFR @ 3y than **sleeve gastrectomy**

AJKD AMERICAN JOURNAL OF KIDNEY DISEASES



Diabetes and Obesity Pearls

- Losing weight saves your kidneys
  - Studies show >7 year protection after bypass surgery *(JASN 2018, 2144 patients)*
- CKD diagnosis helps for Medicare coverage for Bariatric Surgery
- Some diabetic medications promote weight loss…Use them!
- If you actually followed the diabetic, kidney, hypertensive, cardiovascular diet, you would only be allowed to eat cardboard
- Mediterranean diet is best, plant protein>animal protein
- High fruit and vegetables can cause hyperkalemia
  - Monitor K with any new diet changes ***(and in Jan)***
- **NACL holidays help with HTN and weight loss**

Cardiovascular Disease (CVD)

- More than 70% of kidney patients die of CVD
- Statins are underutilized in CKD
- CKD patients are **2-3X** more likely to have atrial fibrillation
  - Take the time to listen with that stethoscope
  - Warfarin vs DOACs is still debated but KDIGO states to use NOACs
- Smoking is an issue
  - Including vaping, marijuana and cigarette
  - Oral marijuana is safe in CKD
  - No studies on chewing tobacco

KDIGO Guidelines for dosing in A Fib

CrCl (ml/min)	Apixaban* (Eliquis®)	Dabigatran (Pradaxa®)	Edoxaban** (Savaysa®, Lixiana®)	Rivaroxaban (Xarelto®)
>95	5mg bid	150mg bid	60mg qd^^	20mg qd
51-95	5mg bid	150mg bid	60mg qd	20mg qd
31-50	5mg bid (CrCl cut off 25ml/min)	150mg bid or 110mg bid^	30mg qd	15mg qd
15-30	2.5mg bid	Unknown	30mg qd could be considered	15mg qd could be considered
<15 not on dialysis	Unknown	Not recommended	Not recommended	Unknown
<15 on dialysis	Unknown	Not recommended	Not recommended	Unknown

Decrease Smoking Rates

PEDIATRICS

Kidney function and tobacco smoke exposure in US adolescents
Pediatrics May 2013

For current black smokers there is an 83%↓kidney function
19 cig/day =↓75% kidney function
>20 cig/day= ↓97% kidney function
…worse with menthol cigarettes!
J Am Heart Association, May 2016

SMOKING or VAPING KILLS NEPHRONS
Marijuana is safe in CKD (effective??)
As long as it is not smoked or vaped

Hyperlipidemia

CKD = Heart Disease

SHARP Trial: Statins or statins + ezetimibe
Fibrates are not recommended in CKD by KDIGO
Debatable is effective in Stage 5/5D CKD

Uremia affects LDL levels making them unreliable
When you put a CKD patent on a Statin
FIRE AND FORGET
http://kdigo.org/home/guidelines/lipids/

SHARP: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with CKD (Study of Heart and Renal Protection): a randomised placebo-controlled trial, Lancet 2011

Hyperlipidemia: KDIGO Guidelines

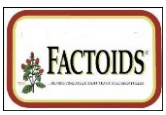
Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP (General public)	nd (not determined)
Fluvastatin	GP	80[1]
Atorvastatin	GP	20[2]
Rosuvastatin	GP	10[3]
Simvastatin/Ezetmibe	GP	20/10[4]
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

CVD Pearls

- A CKD patient is more likely to die of CVD than via kidney failure
- All CKD and DM patients should be on a statin
  - Add Vit D if leg cramps
  - **REAL** rhabdo from statins is <5%
- CKD patients are 2X more likely to have cardiac arrythmias
  - Mainly a fib
- **All patients with CKD have heart disease**

This and That



- Drinking soda after exercise hurts the kidney
- Sleep (7h/night) is reno-protective
- Bilateral oophorectomy increases CKD risk
  - Increase 7.5% if premenopausal
- Increasing H2O does not help the kidneys
- Marijuana (oral) does not hurt the kidney and may be helpful in pain
- ETOH is reno-protective
- PPIs **do** cause CKD but very small risk
- As you lose kidney function, you are more likely to have a serious fall
- Untreated Hepatitis C will cause loss of GFR
- Gut and Dental disease are predictive of CKD

Optimal Follow-up Guidelines for CKD Office visit + Labs

CKD Stage	Length	of time	for next	appointment
3A	6 months			
3B		3.2 months		
4			2 months	
5				1.2 months

The Magic Referral

I always hear that your nephrology consultants complain about referrals…
We *are* overwhelmed but…
Start your referral with:

'Per KDIGO Guidelines,
I am referring this patient due to…'

1) Uncontrolled HTN
2) Stage 4 CKD
3) eGFR dropped 25% in 6 months *or*
4) SCr increased 25% in 6 months
5) Patient request

Thank you for helping us care for our CKD Patients!

Kim Zuber, PAC aanpa1@yahoo.com

References

1) Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4S):S1–S115.

2) Centers for Disease Control and Prevention, Chronic Kidney Disease (CKD) Surveillance System 2021, https://www.cdc.gov/kidneydisease/pdf/Chronic-Kidney-Disease-in-the-US-2021-h.pdf

3) Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021;99(3S):S1–S87.

4) United States Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020.

5) Center for Disease Control and Prevention, Chronic Kidney Disease in the United States 2021, https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html