Diabetic Kidney Disease: Improving Outcomes and Reducing Costs

Joseph A. Vassalotti, MD
Chief Medical Officer, National Kidney Foundation
Clinical Professor of Medicine, Icahn School of Medicine at Mount Sinai
@Joe_Vassalotti

National Kidney Foundation

Icahn School of Medicine at Mount Sinai

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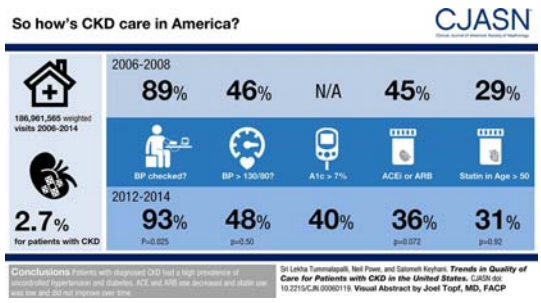


1

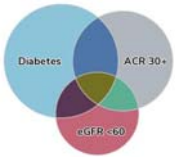
Learning Objectives

- Define applications of eGFR and urine albumin-creatinine ration (uACR) tests in individuals with T2DM for detection and risk stratification of CKD as defined by the kidney health evaluation for patients with diabetes Healthcare Effectiveness Data and Information Set (HEDIS) measure
- Describe how CKD risk stratification informs interventions to reduce kidney failure, decrease cardiovascular risk and limit hospitalizations
- Cite recent studies of the kidney and cardiovascular protective effects of specific treatment regimens, and their indications for management in individuals with T2DM and CKD
- Examine interventions to decrease the risks for cardiovascular disease and dialysis in individuals with T2DM and CKD, based on an understanding of the pathophysiology of progression to these disorders

2

CKD Definition and Risk Stratification

C G A Classification: Cause - GFR - Albuminuria



NHANES 2013-2018
13.1% of adults had Diabetes
27.5% of those with Diabetes had uACR > 30
17.3% of those with Diabetes had eGFR < 60

Diabetes Management in Chronic Kidney Disease: Synopsis of the 2020 KDIGO Clinical Practice Guideline. Ann Intern Med. [Epub ahead of print 10 November 2020]. doi: 10.7326/M20-5938

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 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–300 mg/g 3–30 mg/mmol	A3 Severely increased >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.

3

Different Categories for Albuminuria

Albuminuria+ Terminology	Dipstick Proteinuria	Albumin+ Excretion mg/day	uACR+ mg/g	uPCR* mg/g
Normal – mildly increased (A1)	negative	< 30	< 30	< 142
Moderately increased (A2)	+1	30 to 300	30 to 300	142 to 660
Severely Increased (A3)	+2 or greater	> 300	> 300	> 660

Required for KED Measure

These categories incorporate approximations and inaccuracies depending on gender, age and other factors, but is useful as a pragmatic approach when ACR is not available.

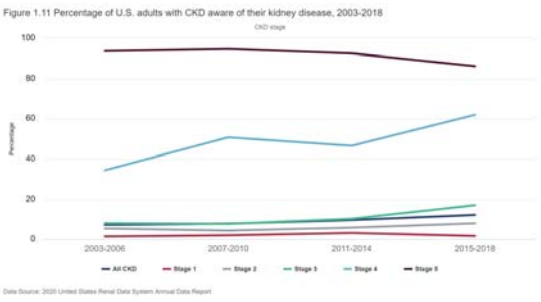
These categories are adapted from KDIGO; Kidney Disease Improving Global Outcomes.+

These categories are from a meta-analysis of uPCR to uACR conversion.

Ann Intern Med. 2020;173(6):426-435

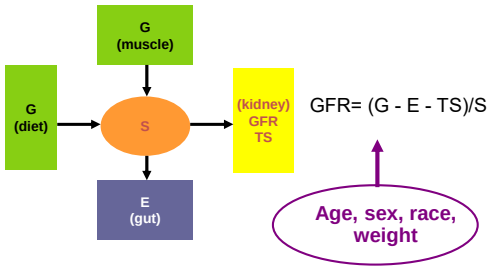
4

Low CKD Awareness by NHANES



5

Creatinine Physiology



Slide courtesy of Lesley A. Inker, MD, MS

6

Serum Creatinine

Age	Gender	Race	SCr (mg/dL)	Estimated GFR* (mL/min/1.73 m²)
20	M	B	1.30	91
20	M	W	1.30	79
20	F	B	1.30	69
55	M	W	1.30	61
55	F	B	1.30	54
55	F	W	1.30	46

B = black; W = all ethnic groups other than black;
*CKD-EPIcreatinine Equation

7

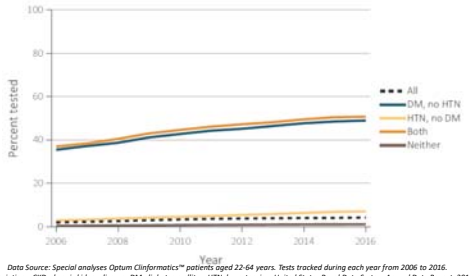
Factors Affecting Creatinine Generation*

	Factor	Affect on serum creatinine
✓	**Age**	Decrease
✓	**Female Sex**	Decrease
	Race	
✓	African American	Increase
	Hispanics	Decrease
	Asian	Decrease
	Body Habitus	
	Muscular	Increase
	Amputation	Decrease
	Obesity	No change
	Chronic Illness	
	Malnutrition, inflammation, de-conditioning	Decrease
	Neuromuscular diseases	Decrease
	Diet	
	Vegetarian Diet	Decrease
	Ingestion of Cooked Meats	Increase

*The use of race in estimating GFR is controversial but is currently being addressed by NKF and ASN Task Force

8

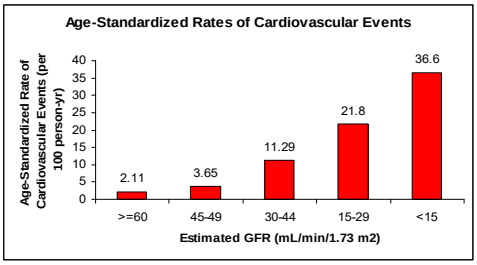
Low Albuminuria Testing in Americans With Diabetes



Data Source: Special analyses Optum Clinformatics™ patients aged 22-64 years. Tests tracked during each year from 2006 to 2016.
Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension. United States Renal Data System Annual Data Report 2018

9

CKD Severity Predicts CVD Risk: Cardiovascular events by eGFR

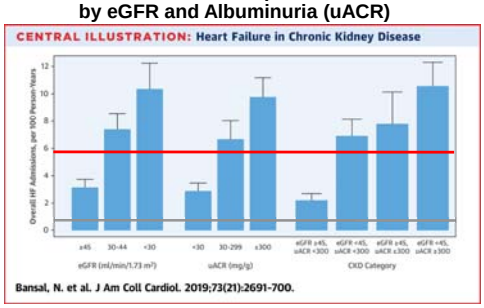


Kaiser outpatients with at least one serum creatinine - eGFR
n = 1,120,295

Go AS, et al: NEJM. 2004: 351;1296-1305

10

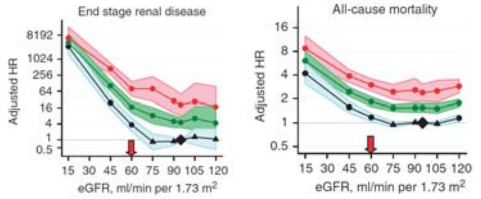
Heart Failure Hospitalization by eGFR and Albuminuria (uACR)



CRIC cohort n = 3,791, unadjusted rates shown, & Figure adapted
Crude CRIC (CKD) cohort rate 5.8
Crude general population rate 0.5

11

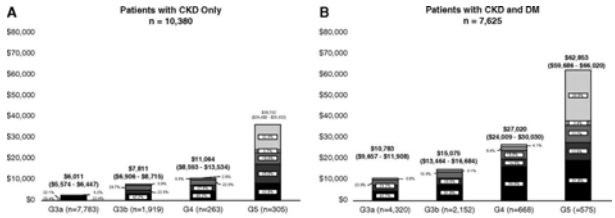
Low eGFR and Albuminuria Predict Kidney Failure and Mortality



Kidney Int. Suppl. 2013; 3: 1-150.

12

As eGFR Falls, Costs Multiply: Population Medical Costs by CKD G stage

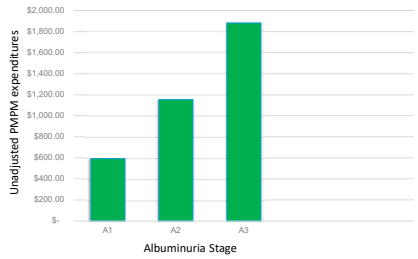


Annualized mean medical costs in total (95% CIs) and by resource adjusted for age, sex, and race/ethnicity for patients with CKD and (A) no comorbidities and (B) diabetes dramatically with declining kidney function. Similar patterns for (C) cardiovascular disease and heart failure (D) are not shown. The comorbidity groups are not mutually exclusive.

Gregory A. Nichols et al. JASN 2020;31:1594-1601

13

As Albuminuria Rises, Costs Multiply: Population Medical Costs by CKD A stage



Am J Managed Care 2019; 25(11):e326-e333

14

Kidney Health Evaluation for Patients with Diabetes (KED) HEDIS® Measure

Measure =

Patients who received a kidney profile evaluation defined by an estimated Glomerular Filtration Rate (eGFR) AND urine Albumin-Creatinine Ratio (uACR) within a 12-month period

/

Patients aged 18-85 years with a diagnosis of diabetes with at least one in person or telehealth visit within a 12-month period

Exclusions: Diagnosis of CKD stage G5 or ESRD, palliative care services and hospice enrollment

National Committee for Quality Assurance. HEDIS 2020 Technical Specifications. Vol 2; 2020. https://www.ncqa.org/hedis/

15

Glycemic Monitoring and Targets in Patients with Diabetes and CKD

Recommendation 2.2.1. We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 9) *(1C)*.

< 6.5%	HbA1c	< 8.0%
CKD G1	Severity of CKD	CKD G5
Absent/minor	Macrovascular complications	Present/severe
Few	Comorbidities	Many
Long	Life expectancy	Short
Present	Hypoglycemia awareness	Impaired
Available	Resources for hypoglycemia management	Scarce
Low	Propensity of treatment to cause hypoglycemia	High

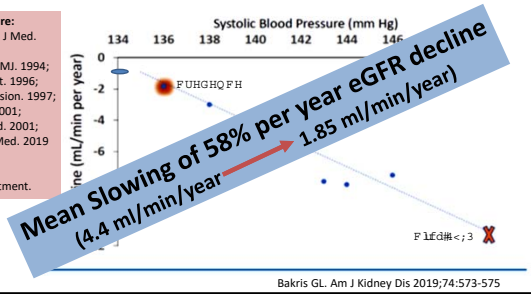
Kidney Int. 2020; 98(4S):S1-S115

16

Rate of decline in kidney function by blood pressure from clinical trials in diabetic kidney disease

Trials included in figure:
Captopril Trial, N Engl J Med. 1993;
Hannadouche et al, BMJ. 1994;
Bakris et al, Kidney Int. 1996;
Bakris et al, Hypertension. 1997;
IDNT, N Engl J Med. 2001;
RENAAL, N Engl J Med. 2001;
CREDENCE, N Engl J Med. 2019
(**orange glow**).

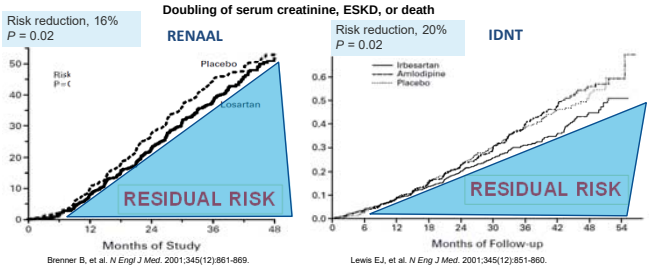
X represents -no treatment.



Bakris GL. Am J Kidney Dis 2019;74:573-575

17

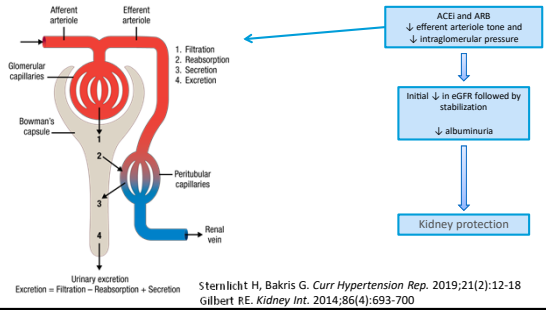
ACE inhibitors or ARBs were the only kidney protective drugs for diabetic kidney disease: RENAAL & IDNT



Brenner B, et al. *N Engl J Med.* 2001;345(12):861-869.
Lewis EJ, et al. *N Eng J Med.* 2001;345(12):851-860.

18

ACE inhibitors or Angiotensin Receptor Blockers Reduce Intraglomerular Pressure: Mechanism for Kidney Protection



Sternlicht H, Bakris G. *Curr Hypertension Rep.* 2019;21(2):12-18
Gilbert RE. *Kidney Int.* 2014;86(4):693-700

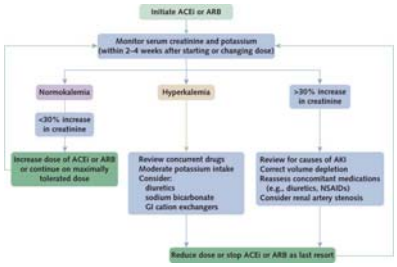
19

In my practice, I stop lisinopril 2.5 mg daily if the serum creatinine rises from 1.6 to 1.9 mg/dL?

A. Yes
B. No

20

Use of ACE inhibitors or Angiotensin Receptor Blockers in Diabetic Kidney Disease



ACEi = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug. (Reproduced from reference 4.)

21

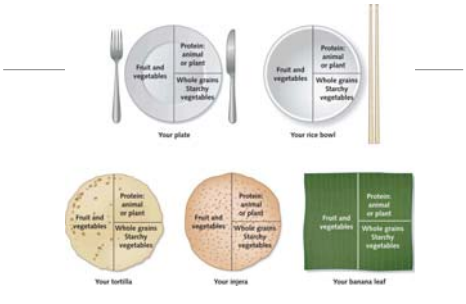
...and this dish is totally potassium-free!

Pete Quaife

22

22

Consider Medical Nutrition Therapy



Ann Intern Med. Published online: 10 November 2020doi:10.7326/M20-5938

23

Predictors of Hyperkalemia before Starting ACEi or ARB Therapy Derived from Trials[1,2]

- eGFR <45 mL/min/1.73m^2
- Serum potassium >4.5 mEq/L
- eGFR <45 mL/min/1.73m^2 + serum K >4.5 mEq/L
  (***Strongest Predictor***)

eGFR <30 mL/min/1.73m^2 obviously high risk

- **Avoid ACEi *and* ARB in combination[3-5]**
  - Risk of adverse events (hemodynamic AKI, hyperkalemia)

1. Lazich I, et al. *Semin Nephrol* 2014; 22(2):123-32
2. Khosla N, et al. *Am J Nephrol* 2009; 30(5):418-424
3. Kunz R, et al. *Ann Intern Med*. 2008;148:30-48
4. Mann J, et al. ONTARGET study. *Lancet*. 2008;372:547-553
5. Fried LF, et al. VA Nephron D Study. *N Engl J Med*. 2013;369:1892-1903

24

Agents Used for Chronic Hyperkalemia[1]

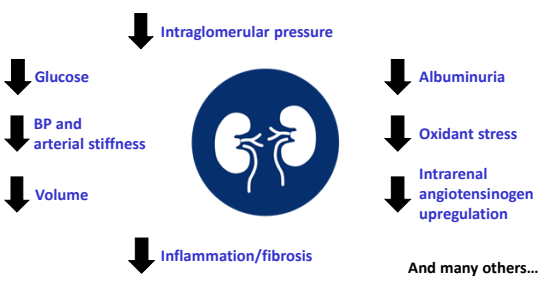
	SPS[2]	Patiromer[3]	SZC[4]
Dose	15g 1–4 times daily Maintenance: once daily	8.4–25.2g daily Titrate by 8.4 g increments	Initial (for up to 48 hours): 10g 3 times daily Maintenance: 10g once daily
Electrolyte disturbances	Hypocalcemia, Hypomagnesemia	Hypomagnesemia (5.3%)-reduction 0.15-0.2 mg	None
Drug interactions	Cation-donating antacids/laxatives, avoid sorbitol, lithium, thyroxine	Binds oral 3 medications (cipro, metformin, levothyroxine) Administer 3 hours apart	Not formally tested—label says oral meds should be spaced by 2 hours

Adverse Effects
- SPS = Sodium polystyrene sulfonate - constipation, diarrhea, nausea, intestinal necrosis (sorbitol formulation – published post-marketing reports)
- Patiromer—constipation, diarrhea, nausea, abdominal discomfort/flatulence, hypomagnesemia
- SZC= Sodium Zirconium Cyclosilicate – edema 16.1% with 10 g dosing, constipation, diarrhea, nausea

1. Initial interventions to consider are diet, diuretics, & sodium bicarbonate
2. FDA Prescribing Information; Lepage L, et al. Clin J Am Soc Nephrol. 2015;10: 2136–2142
2. Weir, MR, et al. N Engl J Med. 2015;372(3):211-21
3. Packham DK, et al. N Engl J Med. 2015; 372(3):222-231

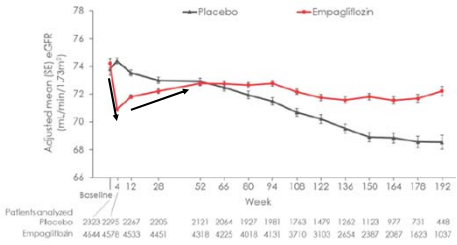
25

Many Kidney Effects of SGLT2 Inhibition



26

EMPA-REG OUTCOME Trial: Kidney Function Over Time



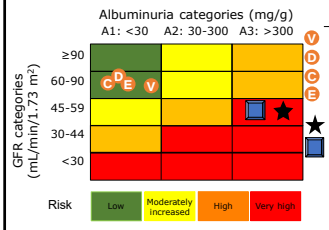
Empagliflozin 10 mg & 25 mg arms combined vs Placebo

Primary Outcome (not shown) 14% ↓3 Point MACE (13% ↓MI, 24% ↓CVA, 36% ↓CV Death)

Wanner C, et al. JASN 2018;29:2755

27

Kidney Risk in Cohorts Studied with SGLT2 inhibitors



Trial	Mean eGFR (mL/min/1.73 m²)	Median uACR (mg/g)
V VERTIS	76	X
D DECLARE	85	13
C CANVAS Program	76	12
E EMPA-REG OUTCOME	74	18
CREDENCE	**56**	**927**
DAPA-CKD	**43**	**965**

Sustained RRT Events

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11
CREDENCE	**176**
DAPA-CKD	**178**

X 1.31 mg/mmol mean

Perkovic V, et al. NEJM 2019; 380:2295-2306
Heerspink HJL, et al. NEJM 2020; 383:1436-1446

28

CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

The George Institute for Global Health

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

eGFR 57

UACR 927 mg/g

Intervention

Stable on maximum dose tolerated ACEi or ARB for 4 weeks

Canagliflozin Placebo

Outcomes

Primary outcome (Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)

HR 0.70 (95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68 (95% CI 0.54-0.86)

NNT 42

No increased risk of:

Amputations HR 1.10 (95% CI 0.79-1.56)

Fractures HR 0.98 (95% CI 0.70-1.37)

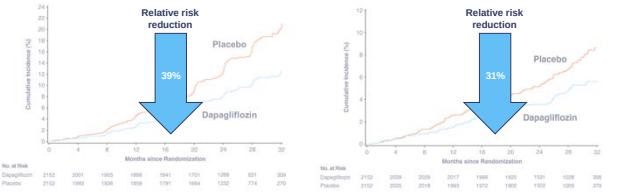
Conclusion

In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

29

DAPA-CKD
Kidney and Cardioprotective Effects

Primary outcome:
Sustained ≥50% eGFR decline, end-stage kidney disease, kidney or cardiovascular death



Secondary outcome:
All-cause mortality

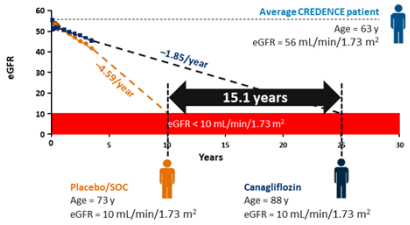
32.5% CKD without type 2 diabetes
14.5% eGFR below 30 ml per minute per 1.73 m²

ESC Congress 2020
The Digital Experience

Heerspink HJ, et al. N Engl J Med 2020;383:1436-46

30

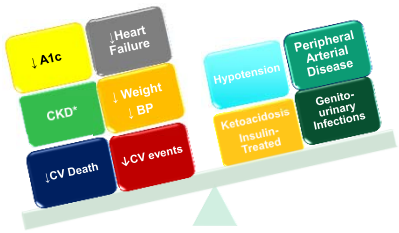
Projected Effects of Canagliflozin on eGFR



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

31

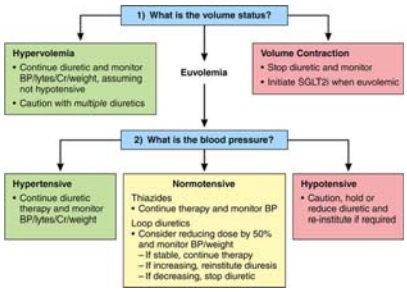
Get with the Flozins by Balancing Benefits and Risks: Practical use of SGLT2-Inhibitors



Adapted: Curr Opin Cardiol 2018; 33:676–682
*FDA approval only if eGFR ≥ 30 ml/min/1.73m²

32

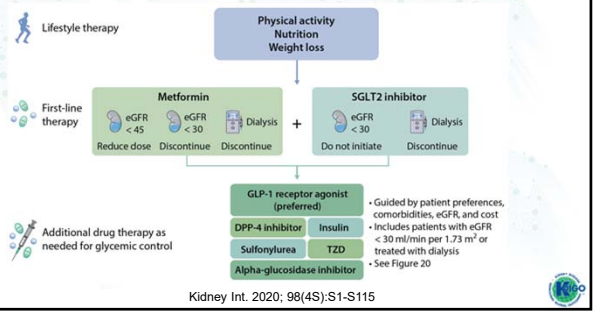
An Approach to Diuretic Use With SGLT-2i



Use of SGLT-2i in the Hands of Cardiologists.
Circulation 2016; 134(24):915-1917

33

TREATMENT ALGORITHM FOR SELECTING ANTIHYPERGLYCEMIC DRUGS FOR PATIENTS WITH T2D AND CKD



Kidney Int. 2020; 98(4S):S1-S115

34

In my practice, I use a conceptual list of indications for nephrology consultation?

A. Yes
B. No

35

Indications for Nephrology Referral for People with CKD

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		Monitor	Refer*
	G2	Mildly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

KDOQI US Commentary on the 2012 KDIGO Evaluation and Management of CKD.

36

Why Refer to Nephrology

- Identify Cause – Kidney biopsy in selected cases
- Slow Progression of CKD
- CKD Complications management
  - CKD Anemia
  - CKD Hyperkalemia
  - CKD Mineral and Bone Disease
  - CKD Metabolic Acidosis
  - CKD Malnutrition
- Medication management
- Kidney Replacement Therapy (KRT) decision making and planning

37

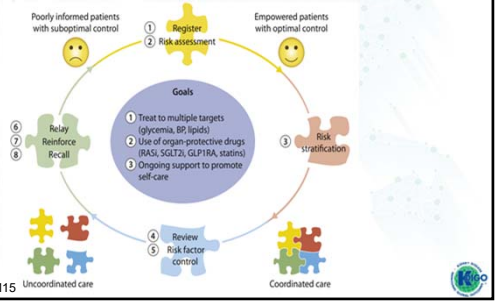
Observational Studies of Early versus Late Nephrology Consultation

Variable	Early referral Mean (SD)	Late referral mean (SD)	P value
Overal mortality %	11 (3)	23 (4)	<0.0001
1-year motality %	13 (4)	29 (5)	0.028
Hospital stay, days	13.5 (2.2)	25.3 (3.8)	0.0007
KRT serum albumin (mg/dL)	3.62 (0.05)	3.40 (0.03)	0.001
KRT hematocrit %	30.54 (0.18)	29.71 (0.10)	0.013

Chan M, et al. *Am J Med*. 2007;120:1063-1070.
KDIGO CKD Work Group. *Kidney Int Suppls*. 2013;3:1-150.

38

Approaches to Management of Patients with Diabetes and CKD: Interdisciplinary Care



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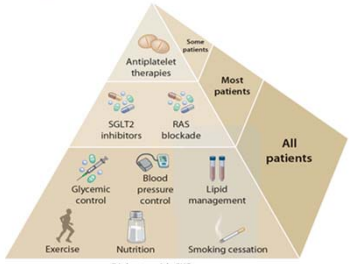
39

Comprehensive Care in Patients with Diabetes and CKD

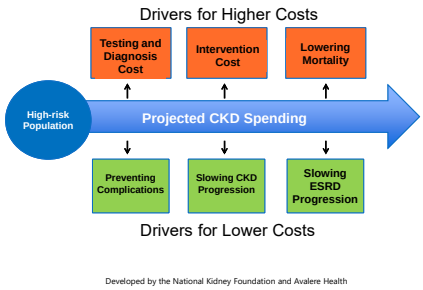
Patients with diabetes and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease.



Kidney Int. 2020; 98(4S):S1-S115

40

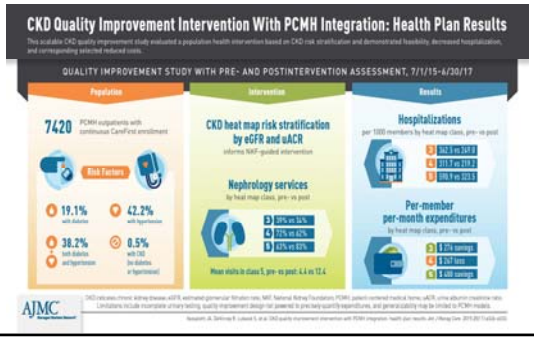
Population Health Potential for CKD



Developed by the National Kidney Foundation and Avalere Health

41

CKD Population Health Impact: Reduce Hospitalizations and Costs



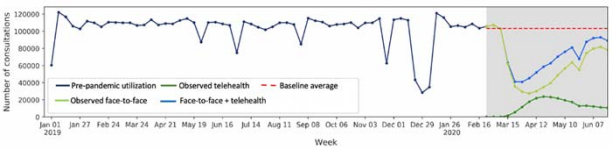
42

The Impact of the COVID-19 Pandemic on Outpatient Visits: Think about how to engage your missing patients.

Source: Ateev Mehrotra et al. The Impact of the COVID-19 Pandemic on Outpatient Visits: Changing Patterns of Care in the Newest COVID-19 Hot Spots (Commonwealth Fund, Aug.13, 2020). https://doi.org/10.26099/vaqe-q550

43

Who are your Missing Patients?
Telehealth use only partially compensated for missing clinician visits



> 10 million healthcare encounters from the UHG Medicare Advantage population
CKD Stages G3-4 in 2018. Care during the pre-pandemic period (Jan 1, 2019 to Feb 29, 2020) was used to predict visits for the pandemic period (March 1 to June 30, 2020).

Diamantidis C, Cook D, Westman J et al.
Missing Care: The Impact of the COVID-19 Pandemic on CKD Care Delivery.
National Kidney Foundation. Abstract Spring Clinical Meeting 2021 (in press).

44

CKD Population Health Impact: Summary for Comments and Questions

- Kidney Health Evaluation for Patients with Diabetes (KED)
- Testing with kidney function (eGFR) and albuminuria (uACR)

- Diagnosis
- Risk stratification or heat map
- Interventions
- Patient engagement
- Interdisciplinary care
- Reduce transitions between stages and prevent or delay kidney failure
- Reduce cardiovascular complications
- Contain costs
- Repeat testing at least annually

45

45

Extra Slides for Questions

46

46

eGFR Estimating Equations and Race Coefficients

- MDRD Equation

  $eGFR = 175 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \times 0.742[\text{if female}] \times 1.212[\text{if black}]$

- CKD-EPI Creatinine Equation (2009)

  $eGFR = 141 \times \min(S_{Cr}/\kappa,1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$

  κ=0.7 (if female) or 0.9 (if male); α=-0.329(if female) or -0.411(if male)

- CKD-EPI Creatinine-Cystatin Equation (2012)

  $eGFR = 135 \times \min(S_{Cr}/\kappa,1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-0.601} \times \min(S_{cys}/0.8,1)^{-0.375} \times \max(S_{cys}/0.8,1)^{-0.711} \times 0.993^{Age} \times 0.969[\text{if female}] \times 1.08[\text{if black}]$

  κ=0.7 (if female) or 0.9 (if male); α=-0.248(if female) or -0.207(if male)

- CKD-EPI Cystatin C Equation (2012)

  $eGFR = 133 \times \min(S_{cys}/0.8,1)^{-0.499} \times \max(S_{cys}/0.8,1)^{-1.328} \times 0.996^{Age} \times 0.932[\text{if female}]$

47

Implications of Removing Race from eGFR Equations

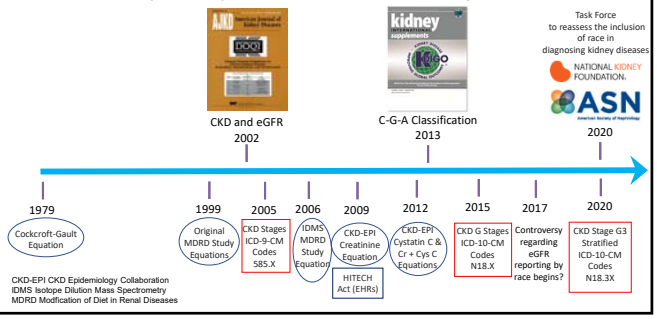
Table. Potential Implications for Black Adults in the US Following Removal of Race From eGFRcr[a]

Implication[b]	eGFR range, mL/min/1.73 m²	No. in NHANES (weighted %)		Absolute change, weighted % (95% CI)
		Including race	Removing race	
CKD diagnosis	<60	1646 (14.9)	2051 (18.4)	3.5 (3.2-3.9)
Ineligible to donate kidney	<60	3848 (38.5)	4088 (40.6)	2.1 (1.8-2.4)
Reclassification: CKD stage 3b or higher and related drug recommendations[c]	<45	282 (2.3)	439 (3.5)	1.2 (1.0-1.5)
Medical nutrition therapy covered	13-50	724 (5.0)	789 (5.5)	0.47 (0.37-0.60)
Reclassification: CKD stage 4 or higher and related drug recommendations[d]	<30	120 (1.0)	155 (1.3)	0.29 (0.18-0.43)
Referral to nephrologist	<30	357 (3.2)	384 (3.4)	0.22 (0.13-0.35)
Kidney disease education covered	15-29	33 (0.22)	52 (0.36)	0.14 (0.07-0.25)
Eligible for kidney transplant waiting list	<20	74 (0.66)	82 (0.71)	0.051 (0.02-0.10)

Diao JA, et al. JAMA 2021; 325: 184-186

48

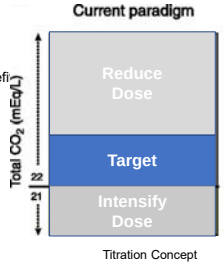
Timeline of Influencers: clinical practice guidelines, GFR equation publications, EHRs and diagnosis codes



49

CKD Metabolic Acidosis: Alkali Therapy Implementation

- Patient engagement
  - Protect kidney function
  - Promote bone and muscle health
  - Dietary fruits and vegetables benefi
  - Understand the target
- Titrate to target tCO2 22-24 mEq/L
- Sodium load consider initiating or adjusting diuretics



Titration Concept

Adapted: Am J Med. 2016 Feb;129(2):153-162

50

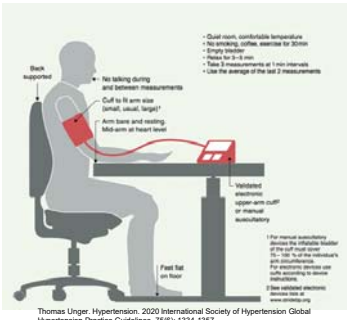
Metformin-containing Medicines FDA Labeling Revisions: Risk of Lactic Acidosis, 4/08/16

Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2.
Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf

51

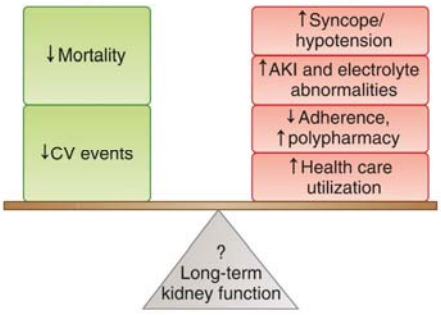
How to Measure Blood Pressure



Thomas Unger. Hypertension. 2020 International Society of Hypertension Global Hypertension Practice Guidelines, 75(6): 1334-1357

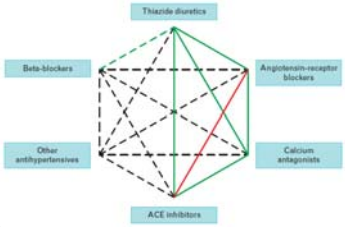
52

Pros **< 130/80 mm Hg?** **Cons**



53

BP Medication Combinations: Conceptual Diagram



Abbreviations:

Green lines = preferred
Green dashes = useful
Black dashes = possible
Red line = not recommended

2013 ESH/ESC Guidelines
J Hypertens 2013

54

Prescribing Steps in CKD: One Approach[1]

1. ACEi or ARB if albuminuria or proteinuria
2. Diuretic or CCB
3. CCB or Diuretic
4. Mineralocorticoid Receptor Blocker (MRB)*

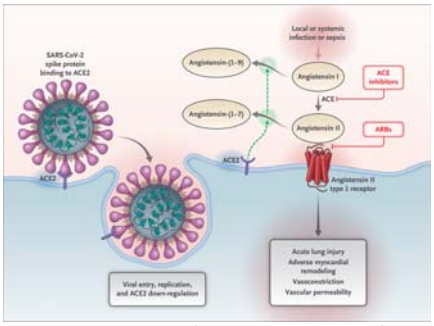
*MRB effective in Resistant HTN based the PATHWAY-2 trial that excluded eGFR <45
AMBER trial[2] RCT spironolactone vs spironolactone vs patiromer with eGFR 25-45

ACEi = Angiotensin Converting Enzyme Inhibitor
ARB = Angiotensin II Receptor Blocker
CCB = Calcium Channel Blocker

1. Sinha AD, Agarwal R. C. JASN 2019;14(5):757-764
2. Agarwal R, et al. Lancet 2019 394(10208):1540-1550

55

ACEi or ARB and SARS-CoV-2



NEJM 2020 Mar 30. doi: 10.1056/NEJMsr2005760. [Epub ahead of print]

56

ACE inhibitors or ARBs do not increase SARS-CoV-2 Risk: Observational Data*

Over 12 thousand NYC patients with SARS-CoV-2 testing
59.1% + test and 24.6% severe illness

No significant difference in SARS-CoV-2 positive testing
No significant difference in severe illness (data not shown)

Blood Pressure (BP) Medication	Matched Patients Treated with BP Medication +SARS-CoV-2/Total	Matched Patients not Treated with BP Medication +SARS-CoV-2/Total	% Median Difference (95% Confidence Interval)
ACE inhibitor	627/1044 (60.1%)	653/1044 (62.5%)	-2.5 (-6.7 to 1.6)
ARB	664/1137 (58.4%)	639/1137 (56.2%)	2.2 (-1.9 to 6.3)
ACE inhibitor or ARB	1110/1909 (58.1%)	1101/1909 (57.7%)	0.5 (-2.6 to 3.6)
Beta-blocker	912/1686 (54.1%)	976/1686 (57.9%)	-3.8 (-7.2 to -0.4)
Calcium-channel blocker	992/1672 (59.3%)	976/1672 (58.4%)	0.9 (-2.3 to 4.3)
Thiazide diuretic	549/986 (55.7%)	590/986 (59.8%)	-4.2 (-8.5 to 0.2)

*Reynolds HR et al. N Engl J Med 2020;382:2441-2448
BRACE Corona Trial presented at European Society of Cardiology 9/01/20 (unpublished data not shown)

57