Updates in Chronic Kidney Disease

Heather Henderson, DO FACP FASN
Program Director Nephrology Fellowship
Henry Ford St. John
Detroit, Michigan

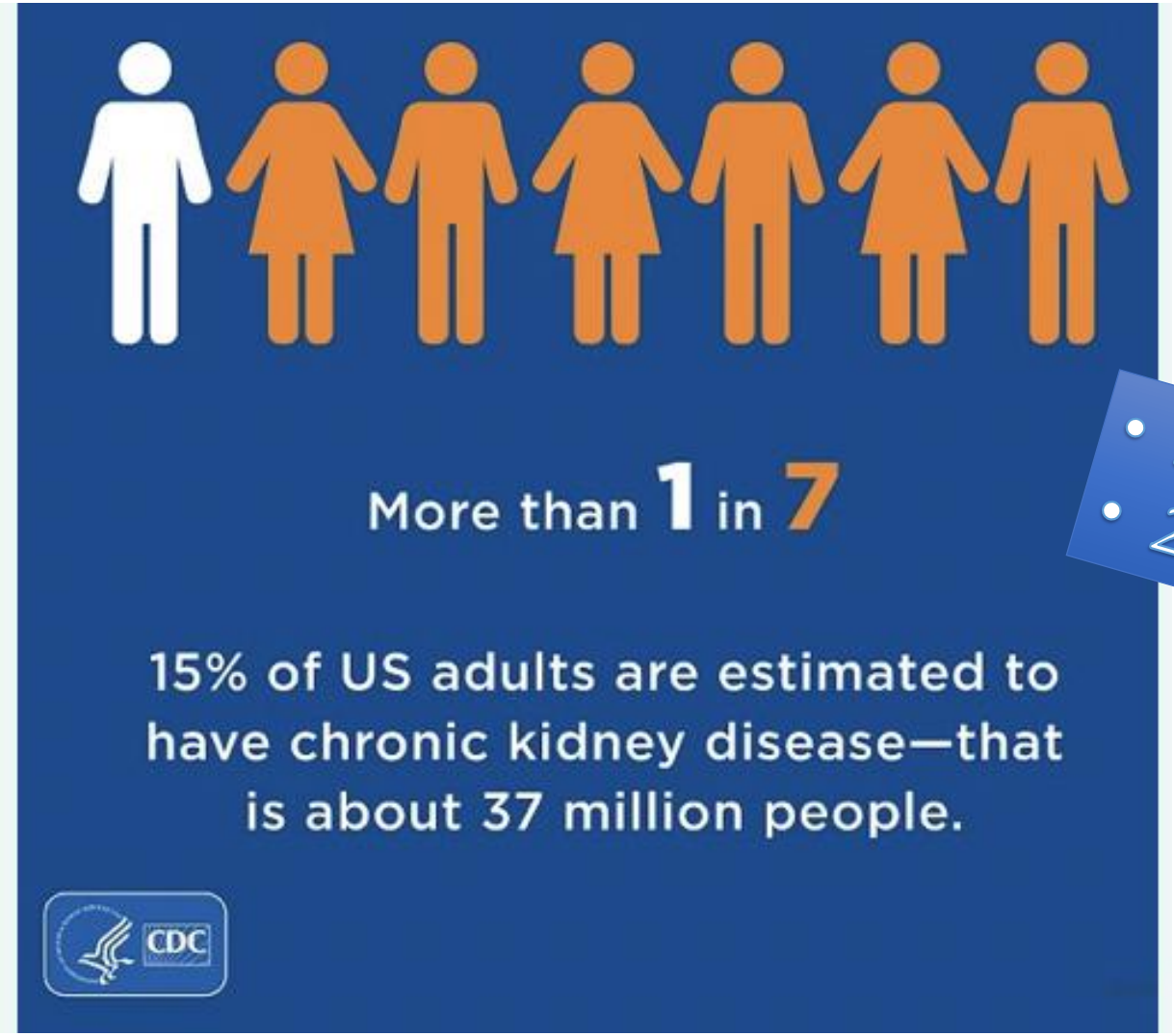
Affiliations/Conflicts of Interest

- Program Director Nephrology Fellowship Henry Ford St. John Hospital
- Partner, St. Clair Nephrology
- Medical Director and Joint Venture Partner Davita Dialysis
- Chair, Scientific Advisory Board National Kidney Foundation of Michigan

- No conflict of interest for this talk.

42 year old obese female with hypertension and DMII. Her creatinine is 0.98 mg/dl and ACR=535 mg/g.


CHECKLIST
Incidence of CKD in the United States
GFR calculation and staging
New Guidelines
New Treatments
When to refer to Nephrology

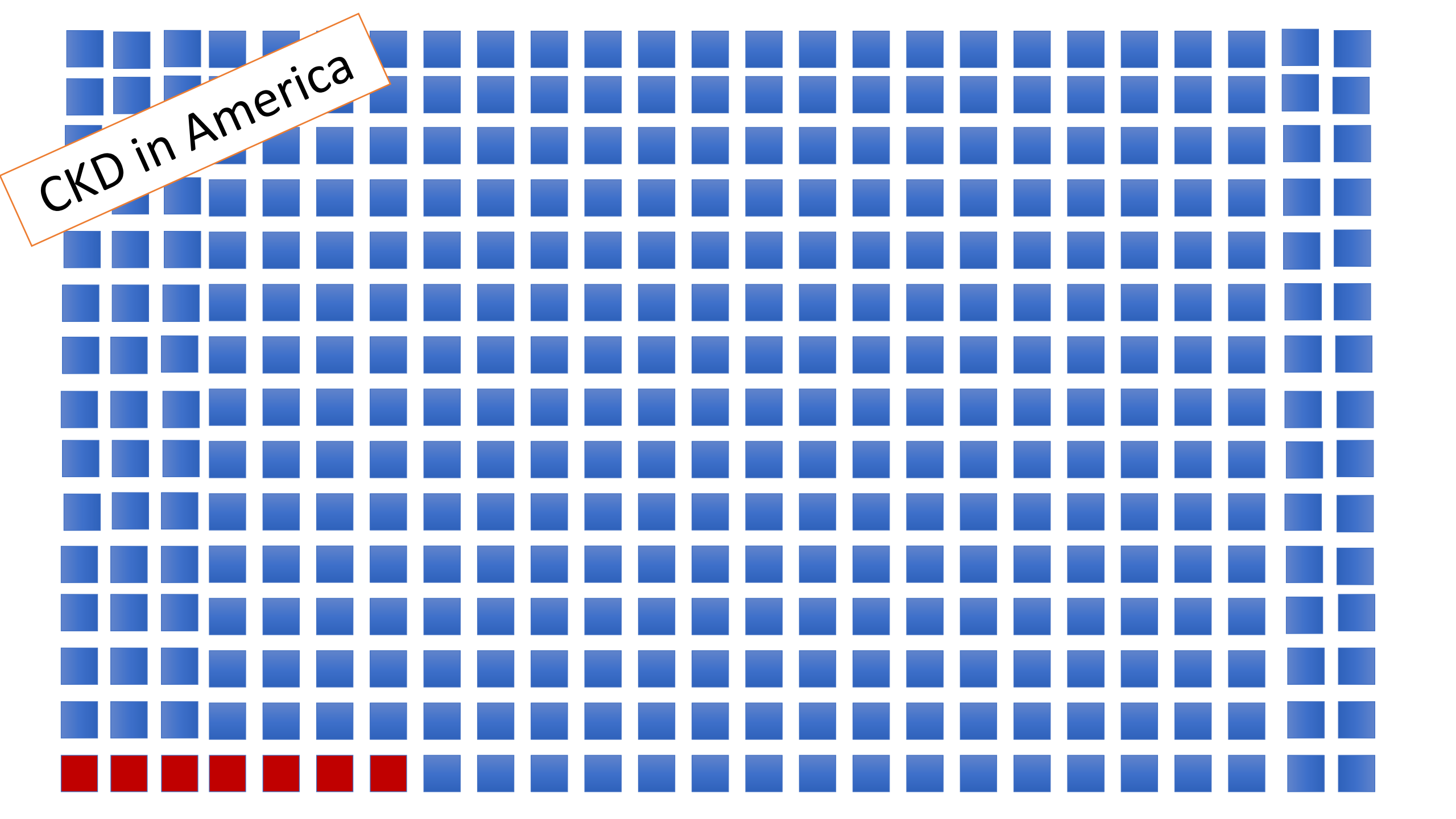


- 9 in 10 adults with CKD don't know
- 2 in 5 adults with severe CKD don't know

CDC.gov


= 100,000 people

CKD in America


CKD in America

Definition of CKD

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			

KDIGO.org

Race and GFR

BUN	H 32 mg/dL	H
Creatinine	H 3.18 mg/dL	H
GFRA	* L 23	
GFRC	L 20	
BUN/CREAT Ratio	L 10.1	L
Sodium Level	141 mmol/L	1
Potassium Level	4.7 mmol/L	3
Chloride	H 112 mmol/L	1
CO2	L 20 mmol/L	L
AGAP	9 mmol/L	1
Calcium	9.4 mg/dL, 9.4	9
Phosphorus	3.2 mg/dL	

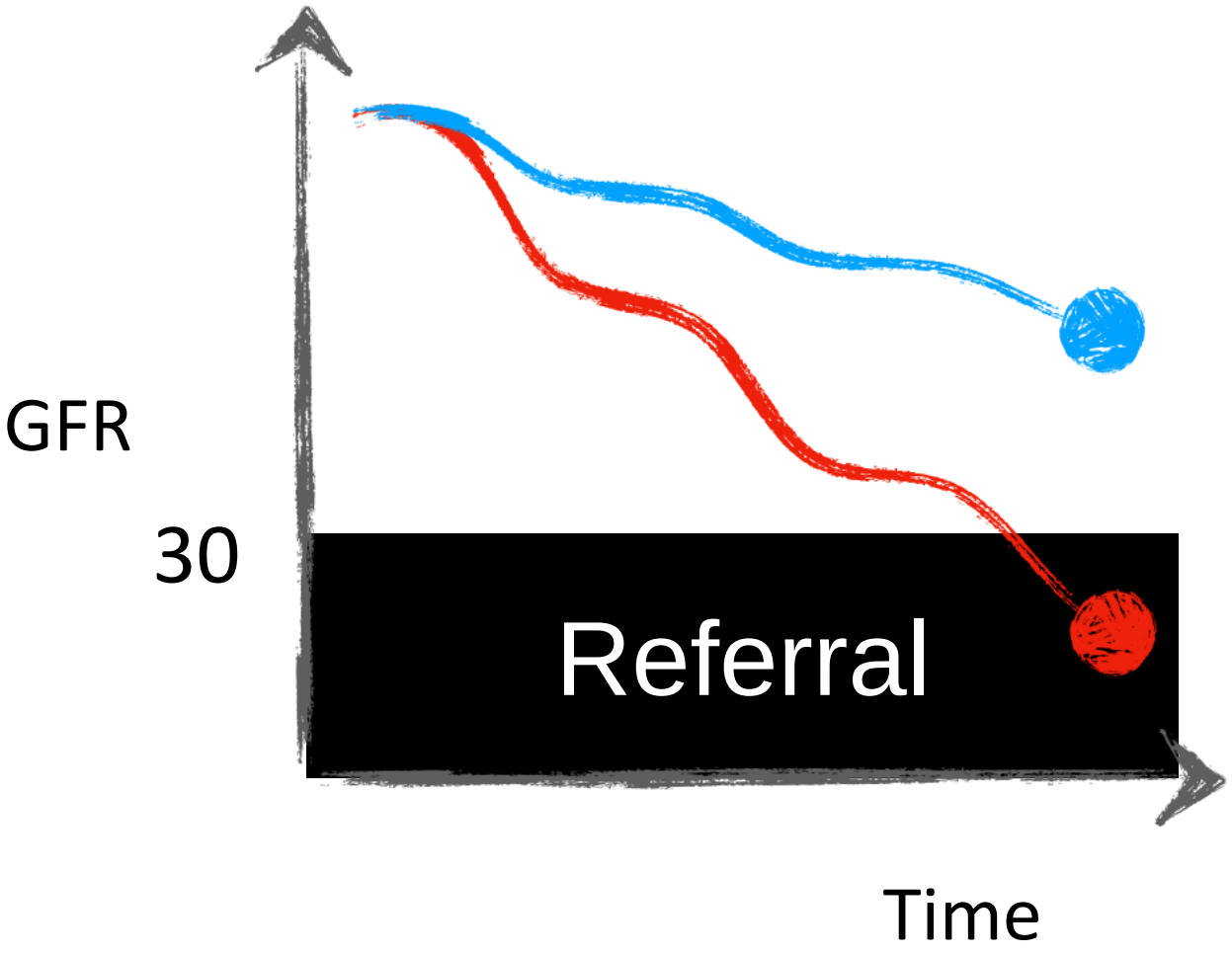
People have different definitions of race depending on where they live, "A person who could be categorized as black in the United States might be considered white in Brazil or colored in South Africa" Racial identity can shift with experience and time.

Onwuachi-Willig, A. (2016). Race and racial identity are social constructs. *The New York Times*, 6.

"Race and ethnicity are social and not biologic constructs"

JASN 32:1305-1317, 2021


Not Black
Black
Dichotomization

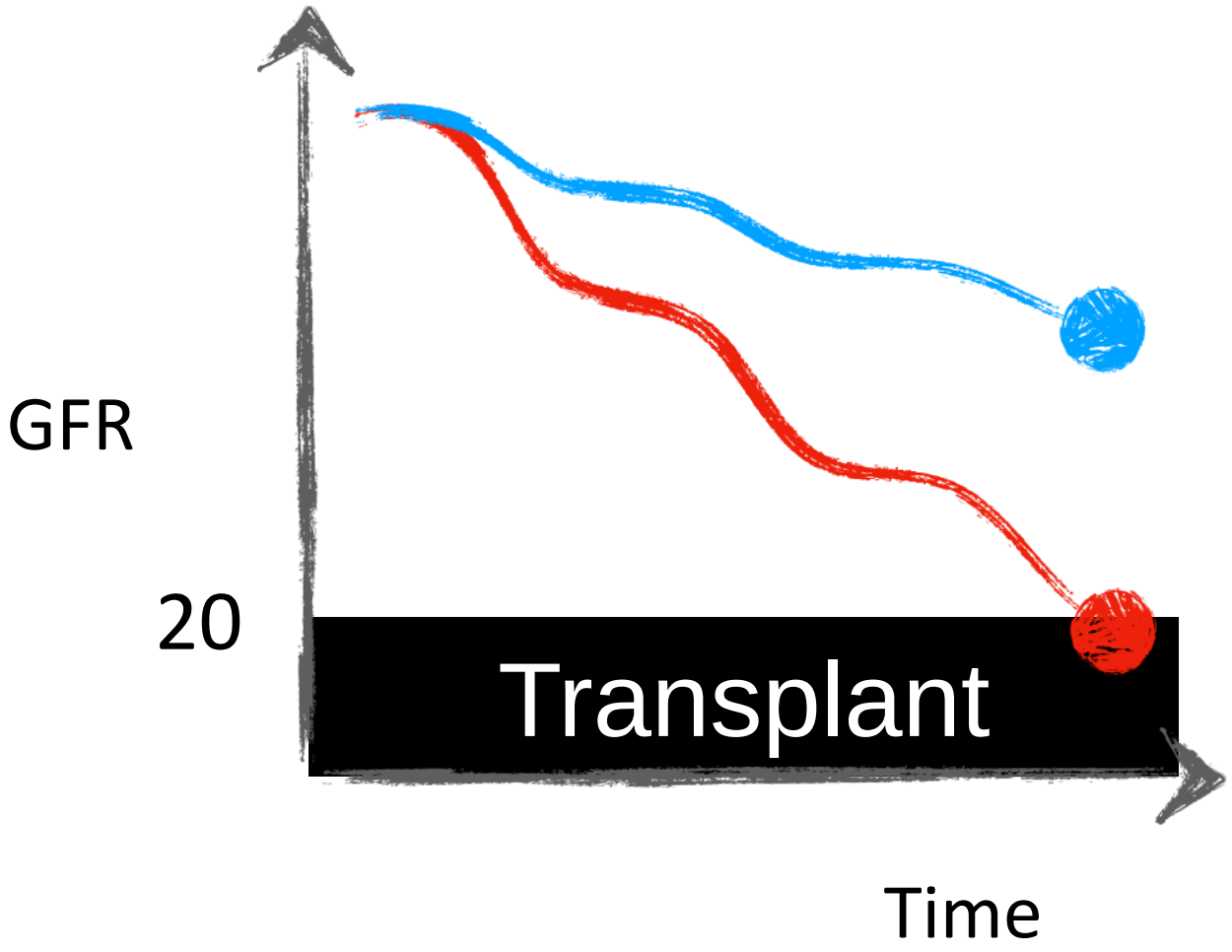


Creatinine 2.1

50 year old female

Black	**32**
Not Black	**26**

Andrew Levey 4-variable MDRD Formula 1999 21% higher for black people



Creatinine 3.0

50 year old female

Black	**21**
Not Black	**18**

Andrew Levey 4-variable MDRD Formula 1999 21% higher for black people

Sept 23, 2021

How to remove race?

ORIGINAL ARTICLE

New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

L.A. Inker, N.D. Eneanya, J. Coresh, H. Tighiouart, D. Wang, Y. Sang, D.C. Crews, A. Doria, M.M. Estrella, M. Froissart, M.E. Grams, T. Greene, A. Grubb, V. Gudnason, O.M. Gutiérrez, R. Kalil, A.B. Karger, M. Mauer, G. Navis, R.G. Nelson, E.D. Poggio, R. Rodby, P. Rossing, A.D. Rule, E. Selvin, J.C. Seegmiller, M.G. Shlipak, V.E. Torres, W. Yang, S.H. Ballew, S.J. Couture, N.R. Powe, and A.S. Levey, for the Chronic Kidney Disease Epidemiology Collaboration*

ABSTRACT

BACKGROUND
Current equations for estimated glomerular filtration rate (eGFR) that use serum creatinine or cystatin C incorporate age, sex, and race to estimate measured GFR. However, race in eGFR equations is a social and not a biologic construct.

METHODS
We developed new eGFR equations without race using data from two development data sets: 10 studies (8254 participants, 31.5% Black) for serum creatinine and 13 studies (5352 participants, 39.7% Black) for both serum creatinine and cystatin C. In a validation data set of 12 studies (4050 participants, 14.3% Black), we compared the accuracy of new eGFR equations to measured GFR. We projected the prevalence of chronic kidney disease (CKD) and GFR stages in a sample of U.S. adults, using current and new equations.

RESULTS
In the validation data set, the current creatinine equation that uses age, sex, and race overestimated measured GFR in Blacks (median, 3.7 ml per minute per 1.73 m^2 of body-surface area; 95% confidence interval [CI], 1.8 to 5.4) and to a lesser degree in non-Blacks (median, 0.5 ml per minute per 1.73 m^2; 95% CI, 0.0 to 0.9). When the adjustment for Black race was omitted from the current eGFR equation, measured GFR in Blacks was underestimated (median, 7.1 ml per minute per 1.73 m^2; 95% CI, 5.9 to 8.8). A new equation using age and sex and omitting race underestimated measured GFR in Blacks (median, 3.6 ml per minute per 1.73 m^2; 95% CI, 1.8 to 5.5) and overestimated measured GFR in non-Blacks (median, 3.9 ml per minute per 1.73 m^2; 95% CI, 3.4 to 4.4). For all equations, 85% or more of the eGFRs for Blacks and non-Blacks were within 30% of measured GFR. New creatinine–cystatin C equations without race were more accurate than new creatinine equations, with smaller differences between race groups. As compared with the current creatinine equation, the new creatinine equations, but not the new creatinine–cystatin C equations, increased population estimates of CKD prevalence among Blacks and yielded similar or lower prevalence among non-Blacks.

CONCLUSIONS
New eGFR equations that incorporate creatinine and cystatin C but omit race are more accurate and led to smaller differences between Black participants and non-Black participants than new equations without race with either creatinine or cystatin C alone. (Funded by the National Institute of Diabetes and Digestive and Kidn

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Inker at the Division of Nephrology, Tufts Medical Center, 800 Washington St., Box 391, Boston, MA 02111, or at linker@tuftsmedicalcenter.org.

*The members of the Chronic Kidn Disease Epidemiology Collaboration listed in the Supplementary Appe available at NEJM.org.

This article was published on Septe 2021, and updated on September at NEJM.org.

DOI: 10.1056/NEJMoa2102953

SPECIAL ARTICLE www.jasn.org

A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease

Cynthia Delgado,[1] Mukta Baweja,[2] Deidra C. Crews,[3] Nwamaka D. Eneanya,[4] Crystal A. Gadegbek..,[5] Lesley A. Inker,[6] Mallika L. Mendu,[7] W. Greg Miller,[8] Marva M. Moxey-Mims,[9] Glenda V. Rob..,[10] Wendy L. St. Peter,[11] Curtis Warfield,[12] and Neil R. Powe[13]

Due to the number of contributing authors, the affiliations are listed at the end

ABSTRACT

Background In response to a natio cal algorithms, the National Kidney Nephrology (ASN) established a Tas mation of GFR in the United States ment of patients with, or at risk for, kid

Process & Deliberations The Task Forc to (1) clarify the problem and evidence (described previously in an interim report), to address use of race in GFR estimation, a 26 approaches for the estimation of GFR th our focus, by consensus, to five of those approach considering six attributes: assay ava population diversity in equation developme GFR, consequences to clinical care, populatio teredness. To arrive at a unifying approach to and evidence from many sources in assessing s each approach, recognizing the number of Black

Recommendations (1) For US adults (>85% of recommend immediate implementation of the CK the race variable in all laboratories in the United S in the calculation and reporting, included diversity available to all laboratories in the United States, an acteristics and potential consequences that do no group of individuals. (2) We recommend national effo and timely use of cystatin C, especially to confirm eG have CKD, because combining filtration markers (creat rate and would support better clinical decisions than ei dence supports acceptable performance, the CKD-EPI eGFR creatinine–cystatin C (eGFRcr-cys_R) refit withou adopted to provide another first-line test, in addition Research on GFR estimation with new endogenous filtra tions to eliminate race and ethnic disparities should be investment in science is needed for newer approaches that and precise GFR measurement and estimation without the promote health equity and do not generate disparate care.

Implementation This unified approach, without specific adopted across the United States. High-priority and multis implement this solution.

JASN 32: •••–•••, 2021. doi: https://doi.org/10.1681/ASN.2021070988

Español

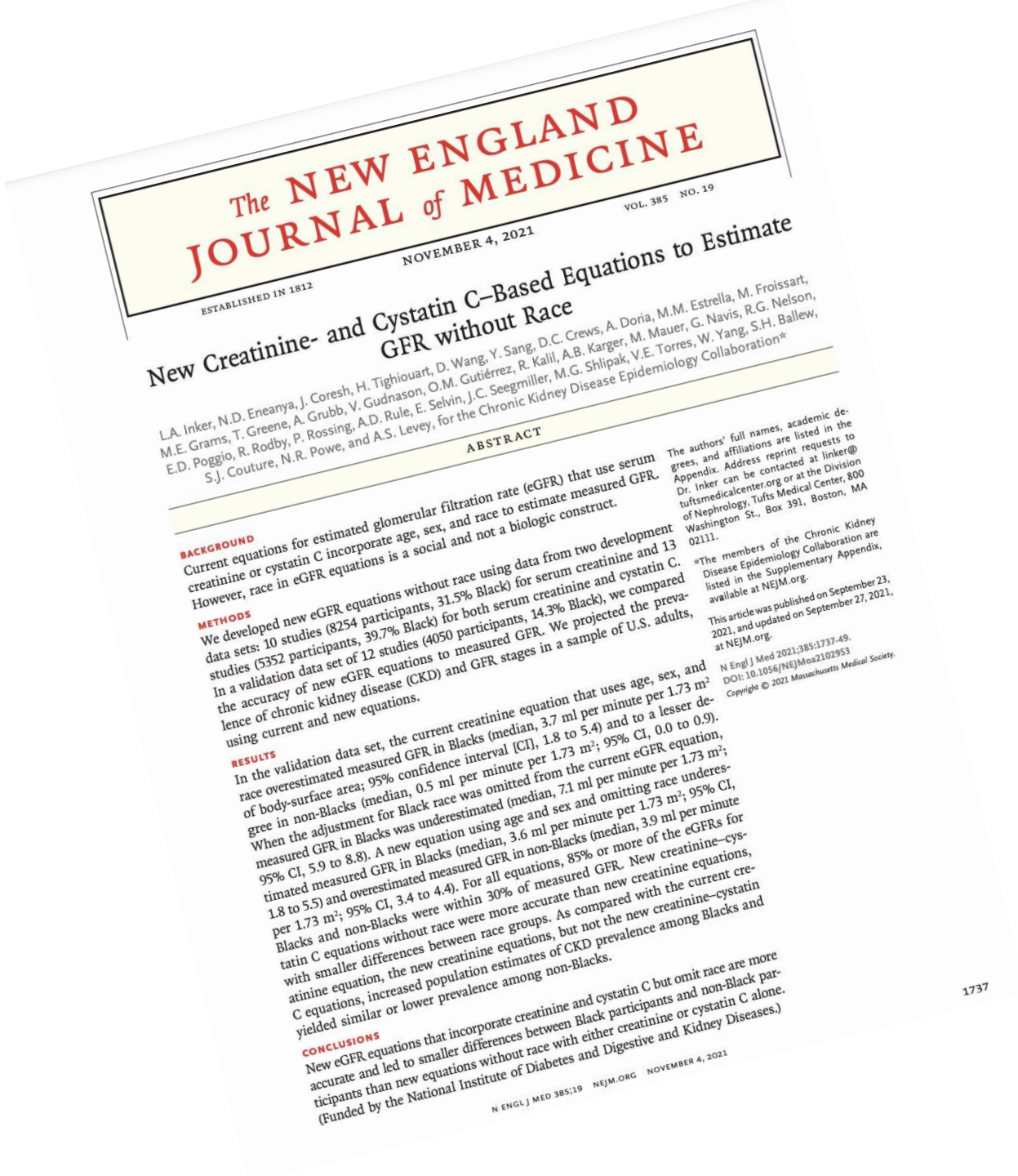
NATIONAL KIDNEY FOUNDATION®

Donate

NKF and ASN Release New Way to Diagnose Kidney Diseases

Both Organizations Recommend Race-Free Approach to Estimate GFR

Sept. 23, 2021, New York, NY – Today, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases has released its final report, which outlines a new race-free approach to diagnose kidney disease. In the report, the NKF-ASN Task Force recommends the adoption of the new **eGFR 2021 CKD EPI creatinine equation that estimates kidney function without a race variable. The task force also recommended increased use of cystatin C combined with serum (blood) creatinine, as a confirmatory assessment of GFR or kidney function.** The final report, published today online in the *American Journal of Kidney Diseases (AJKD)* and the *Journal of the American Society of Nephrology (JASN)*, was drafted with considerable input from hundreds of patients and family members, medical students and other trainees, clinicians, scientists, health professionals, and other stakeholders to achieve consensus for an unbiased and most reasonably accurate



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 4, 2021 VOL. 385 NO. 19

New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

L.A. Inker, N.D. Eneanya, J. Coresh, H. Tighiouart, D. Wang, Y. Sang, D.C. Crews, A. Doria, M.M. Estrella, M. Froissart, M.E. Grams, T. Greene, A. Grubb, V. Gudnason, O.M. Gutiérrez, R. Kalil, A.B. Karger, M. Mauer, G. Navis, R.G. Nelson, E.D. Poggio, R. Rodby, P. Rossing, A.D. Rule, E. Selvin, J.C. Seegmiller, M.G. Shlipak, V.E. Torres, W. Yang, S.H. Ballew, S.J. Couture, N.R. Powe, and A.S. Levey, for the Chronic Kidney Disease Epidemiology Collaboration*

ABSTRACT

BACKGROUND
Current equations for estimated glomerular filtration rate (eGFR) that use serum creatinine or cystatin C incorporate age, sex, and race to estimate measured GFR. However, race in eGFR equations is a social and not a biologic construct.

METHODS
We developed new eGFR equations without race using data from two development data sets: 10 studies (8254 participants, 31.5% Black) for serum creatinine and 13 studies (5352 participants, 39.7% Black) for both serum creatinine and cystatin C. In a validation data set of 12 studies (4050 participants, 14.3% Black), we compared the accuracy of new eGFR equations to measured GFR. We projected the prevalence of chronic kidney disease (CKD) and GFR stages in a sample of U.S. adults, using current and new equations.

RESULTS
In the validation data set, the current creatinine equation that uses age, sex, and race overestimated measured GFR in Blacks (median, 3.7 ml per minute per 1.73 m^2 of body-surface area; 95% confidence interval [CI], 1.8 to 5.4) and to a lesser degree in non-Blacks (median, 0.5 ml per minute per 1.73 m^2; 95% CI, 0.0 to 0.9). When the adjustment for Black race was omitted from the current eGFR equation, measured GFR in Blacks was underestimated (median, 7.1 ml per minute per 1.73 m^2; 95% CI, 5.9 to 8.8). A new equation using age and sex and omitting race underestimated measured GFR in Blacks (median, 3.6 ml per minute per 1.73 m^2; 95% CI, 1.8 to 5.5) and overestimated measured GFR in non-Blacks (median, 3.9 ml per minute per 1.73 m^2; 95% CI, 3.4 to 4.4). For all equations, 85% or more of the eGFRs for Blacks and non-Blacks were within 30% of measured GFR. New creatinine–cystatin C equations without race were more accurate than new creatinine equations, with smaller differences between race groups. As compared with the current creatinine equation, the new creatinine equations, but not the new creatinine–cystatin C equations, increased population estimates of CKD prevalence among Blacks and yielded similar or lower prevalence among non-Blacks.

CONCLUSIONS
New eGFR equations that incorporate creatinine and cystatin C but omit race are more accurate and led to smaller differences between Black participants and non-Black participants than new equations without race with either creatinine or cystatin C alone. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Inker can be contacted at linker@tuftsmedicalcenter.org or at the Division of Nephrology, Tufts Medical Center, 800 Washington St., Box 391, Boston, MA 02111.

*The members of the Chronic Kidney Disease Epidemiology Collaboration are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on September 23, 2021, and updated on September 27, 2021, at NEJM.org.

N Engl J Med 2021;385:1737-49.
DOI: 10.1056/NEJMoa2102953

- *Current race eGFR overestimated Black GFR*
- *Race free creatinine based equations under estimate Black GFR*
- *Combined Creatinine with Cystatin C race free equations are most accurate in black and non-black patients*

NEJM 385; 19:1737-1749; 2021

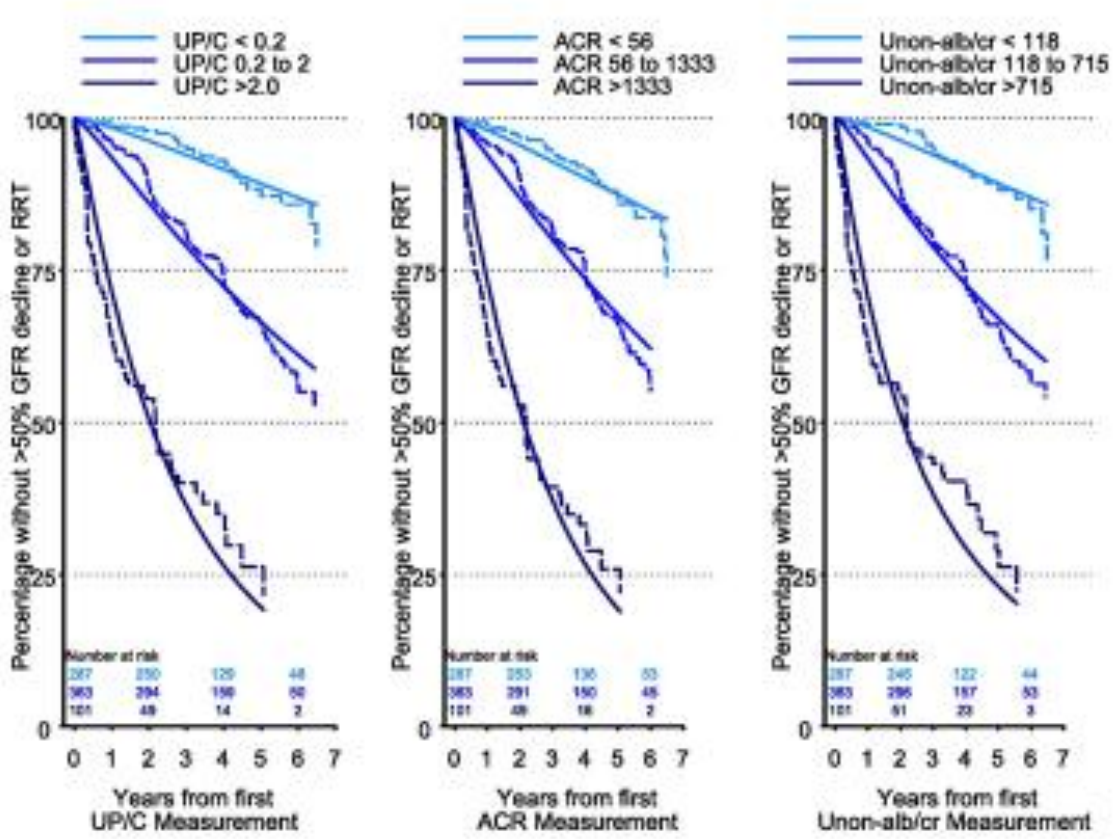
Go beyond GFR and look at other axis of kidney health…albuminuria…volume control…blood pressure

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m^2), 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			

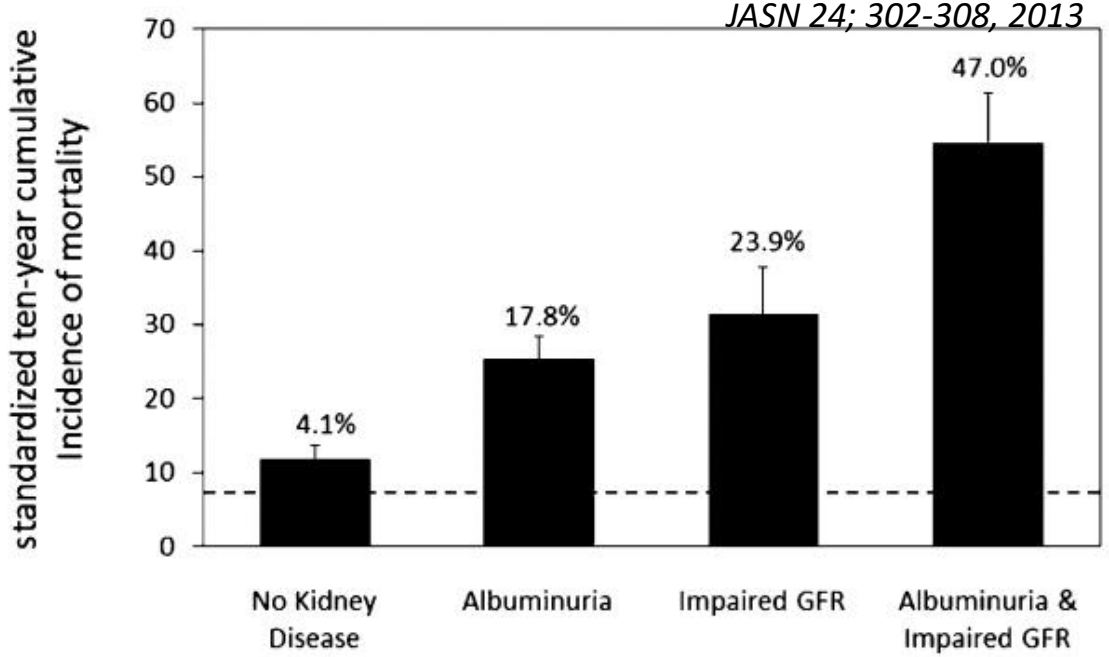
green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

Albuminuria



CJASN June 2017, 12 (6) 912-920

JASN 24; 302-308, 2013



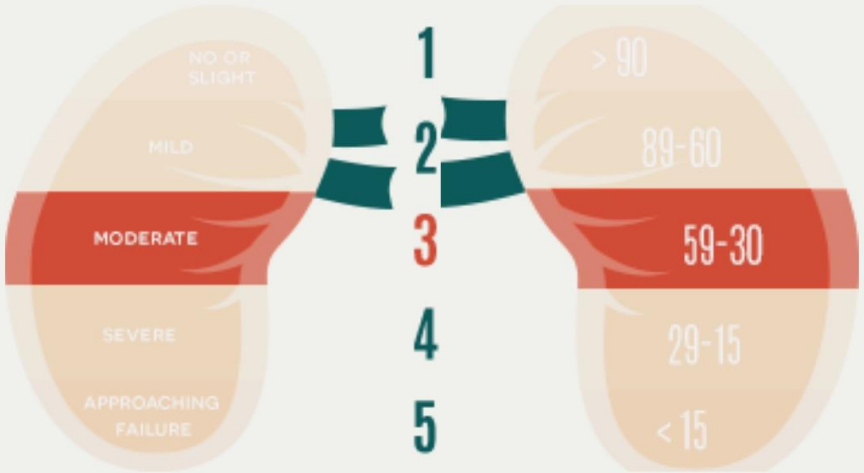
- Screen yearly in all patients with hypertension, obesity, diabetes, or chronic kidney disease
- NKF Renal Function Panel
  - eGFR and ACR

STAGE 3

MODERATE DECREASE IN FUNCTION

CKD STAGES

GLOMERULAR FILTRATION RATE



Patient risk of progression to kidney failure requiring dialysis or transplant:

AT 2 YEARS AT 5 YEARS

0.7 % 2.19 %

65 year old female

GFR=38

ACR=17 mg/g vs 5 g/g

Bicarbonate=23 mEq/l

Albumin=3.8 g/dl

Calcium=8.9 mg/dl

Phosphorus=3.2 mg/dl

JAMA 2016; 315:164-174

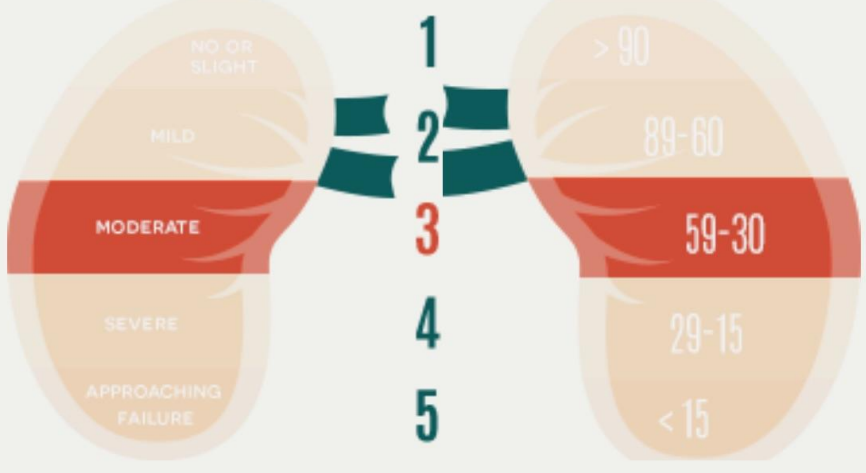
Kidneyfailurerisk.com

STAGE 3

MODERATE DECREASE IN FUNCTION

CKD STAGES

GLOMERULAR FILTRATION RATE



Patient risk of progression to kidney failure requiring dialysis or transplant:

AT 2 YEARS AT 5 YEARS

8.81 % 25.02

YOUR RESULTS

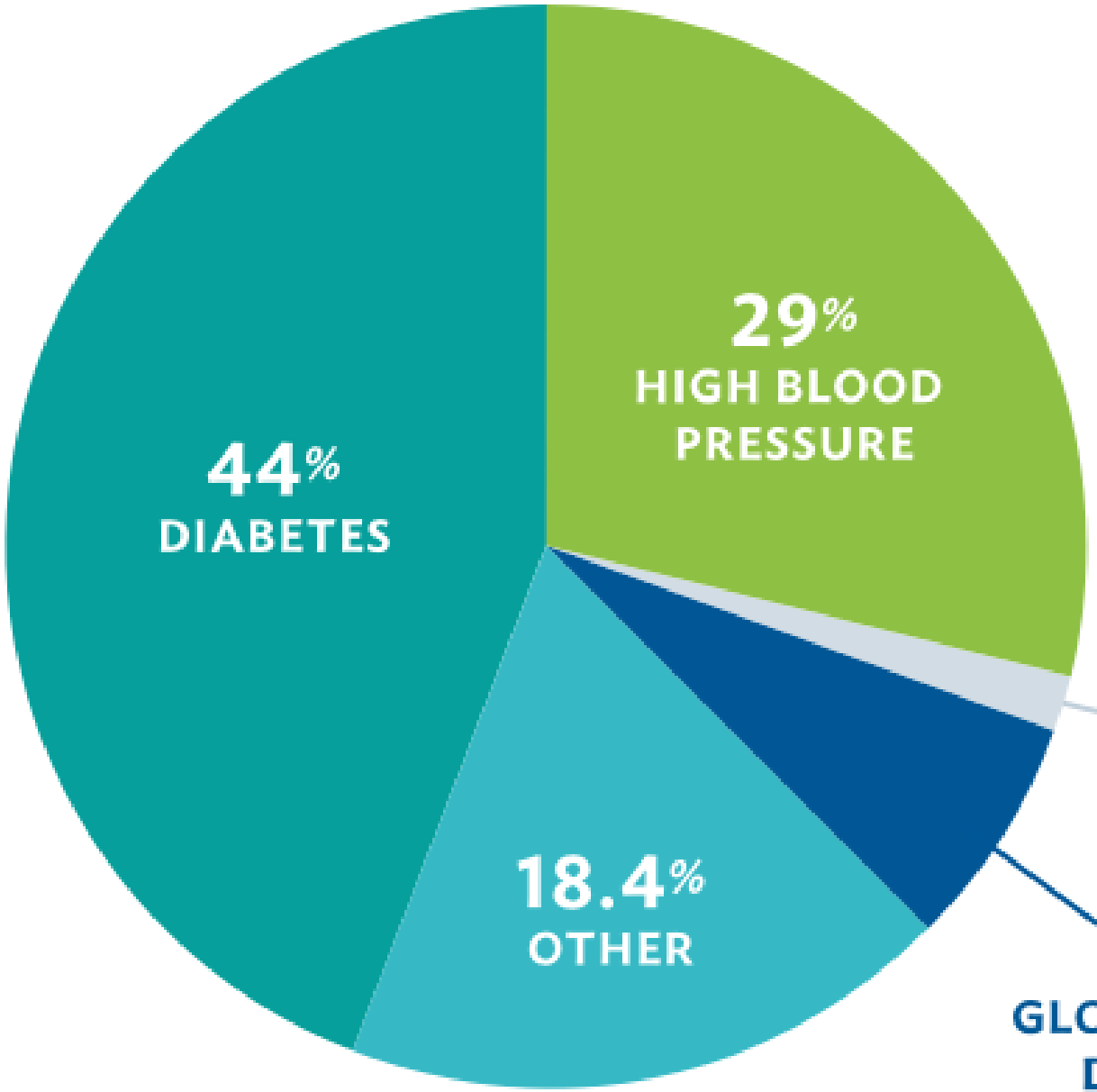
985	F	42	55
mg/g URINE ALBUMIN	SEX	AGE	mL/min/1.73 m2 GFR

AT 2 YEARS	AT 5 YEARS
1.1 %	3.39 %

Risk thresholds used in health systems include:

- 3-5 % over 5 years for referral to a kidney doctor
- 10 % over 2 years for team based care (Kidney Doctor, Nurse, Dietician, Pharmacist)
- 20-40 % over 2 years for planning a transplant or fistula

kidneyfailurerisk.com



Cost

1.5-2.5 x Greater Mortality

USRDS

90% of those with CKD don't know they have it
45% of those have Stage 4

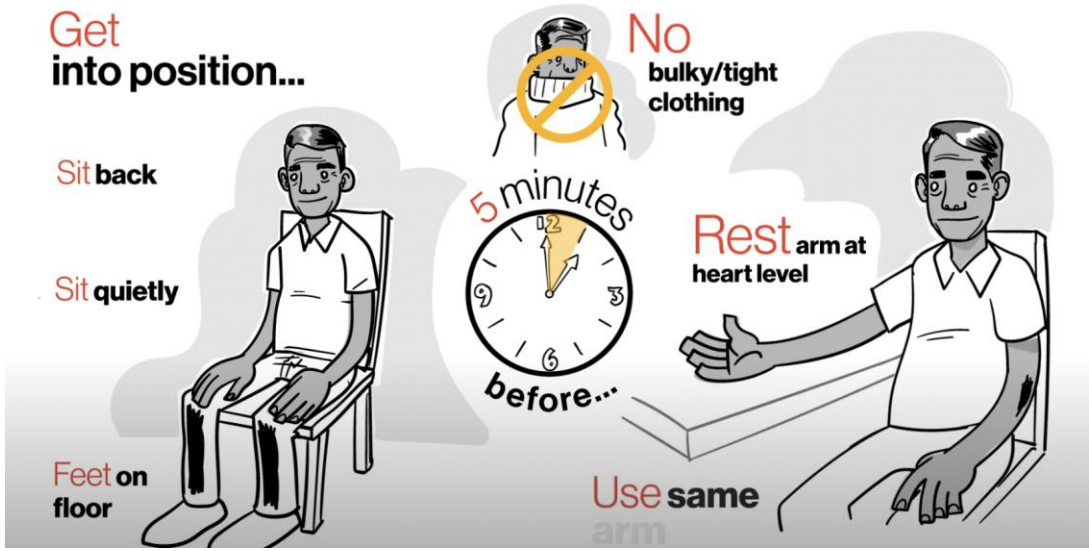
Low levels of testing in Medicare patients
-42% of DM
-6.8% of HTN

90% of DM2 with lab evidence of CKD will <u>not</u> have CKD diagnosis in their medical record

NKF and HEDIS

Blood Pressure Management in CKD

- Shoot for a target <120/80 based on *standardized in office readings*
  - Not practical in most offices
  - Most routine readings are 10-30 mmHg higher
- Based on SPRINT
  - 25% risk reduction of cardiovascular events
  - 27% reduction overall mortality
  - Cognitive benefits
  - Neutral effect kidney health
- Does not apply to transplant, dialysis or pediatric patients



NEJM 2015; 373:2103-2116

58 RCT with 300,000 participants

Outcome data type and study name	Total/No of events Intervention	Control	Effect (95% CI)	Weight (%)	Effect (95% CI)
Binary outcomes					
ACCORD 2010	1534/307	1565/329		26.99	0.94 (0.79 to 1.12)
ALTITUDE 2012	4272/123	4285/113		17.40	1.09 (0.84 to 1.42)
INFINITY 2019	99/35	100/37		4.84	0.93 (0.52 to 1.66)
NILVAD 2018	252/40	257/38		6.68	1.09 (0.67 to 1.76)
SHEP 1991	2365/303	2371/247		26.40	1.26 (1.06 to 1.51)
SPS3 2013	1519/0	1501/3		0.20	0.14 (0.01 to 2.73)
Subgroup: I^2=34.2%				82.52	1.07 (0.88 to 1.31)
with estimated prediction interval					(0.74 to 1.55)
Time to event outcomes					
SPRINT 2015	4678/105	4683/110		17.48	0.95 (0.73 to 1.23)
Heterogeneity between groups: P=0.372					
Overall: I^2=31.5%				100.00	1.05 (0.89 to 1.24)
with estimated prediction interval					(0.77 to 1.43)

0.1 1 3

Increased risk with control | Increased risk with intervention

Fig 3 | Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and falls

Outcome data type and study name	Total/No of events Intervention	Control	Effect (95% CI)	Weight (%)	Effect (95% CI)
Binary outcomes					
ACCORD 2010	2362/59	2371/58		7.62	1.02 (0.71 to 1.47)
AIRE 1993	1004/15	982/12		2.91	1.23 (0.57 to 2.63)
ALTITUDE 2012	4272/104	4285/83		9.27	1.26 (0.94 to 1.69)
EMPHASIS-HF 2011	1360/38	1369/41		6.16	0.93 (0.59 to 1.46)
EUROPA 2003	6110/20	6108/16		3.67	1.25 (0.65 to 2.42)
I-PRESERVE 2008	2067/69	2061/57		7.84	1.21 (0.85 to 1.73)
ONTARGET 2008 (combination *v* ramipril only)	4251/32	8576/48		6.14	1.35 (0.86 to 2.11)
ONTARGET 2008 (combination *v* telmisartan only)	4251/33	8542/52		6.32	1.28 (0.82 to 1.98)
ORIENT 2011	282/1	284/1		0.27	1.01 (0.06 to 16.18)
PRoFESS 2008	10146/28	10186/18		4.28	1.56 (0.86 to 2.83)
SANDS 2009	276/1	272/0		0.20	3.00 (0.12 to 74.46)
Subgroup: I^2=0%				54.69	1.20 (1.02 to 1.41)
with estimated prediction interval					(1.02 to 1.42)
Time to event outcomes					
AASK 2002	540/-	554/-		10.19	0.88 (0.68 to 1.13)
IDNT 2001 (amlodipine *v* placebo)	565/104	568/101		8.34	1.00 (0.72 to 1.40)
IDNT 2001 (irbesartan *v* placebo)	579/82	568/101		7.75	0.77 (0.54 to 1.11)
SPRINT 2015	4678/193	4683/117		9.06	1.66 (1.23 to 2.24)
VA NEPHRON-D 2013	724/130	724/80		9.97	1.70 (1.30 to 2.20)
Subgroup: I^2=82.9%				45.31	1.15 (0.73 to 1.81)
Heterogeneity between groups: P=0.812					(0.35 to 3.74)
Overall: I^2=48.1%				100.00	1.18 (1.01 to 1.39)
with estimated prediction interval					(0.76 to 1.85)

0.5 1 4

Increased risk with control | Increased risk with intervention

Fig 4 | Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and acute kidney injury

BMJ 2021; 372:n189

Potential implications of the 2021 KDIGO blood pressure guideline for adults with chronic kidney disease in the United States

2021 KDIGO Guideline

What's new for adults with CKD and high BP?

Recommends treatment to SBP <120 mmHg using standardized office BP measurement

Recommends ACEi/ARBs for adults with albuminuria and high BP (SBP ≥120 mmHg)

Current Study Goals

Determine potential implications of 2021 KDIGO guideline compared to:

2012 KDIGO guideline

2017 ACC/AHA guideline

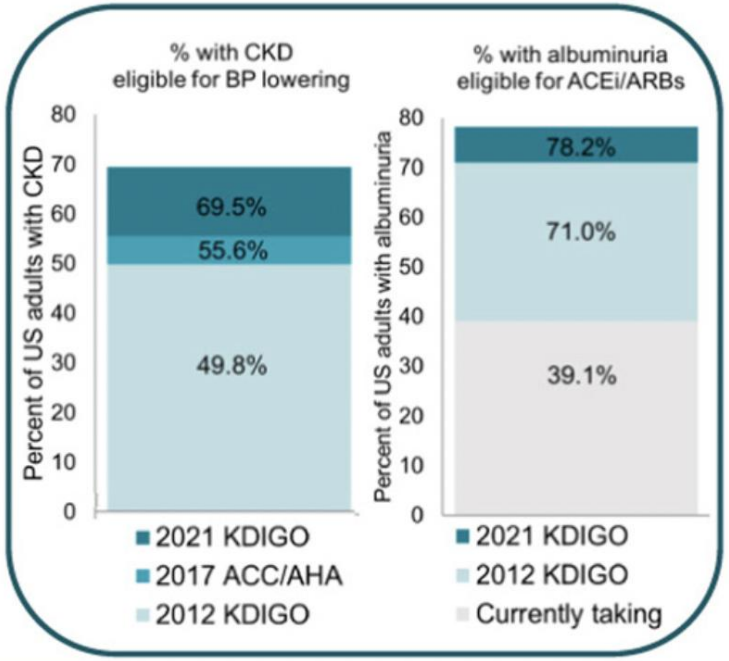
Data Source

nhanes National Health and Nutrition Examination Survey 2015-2018

N=9,419 adults aged ≥20 years with CKD

BP based on mean of up to 3 standardized measurements

Results



CONCLUSION:

Based on the 2021 KDIGO guideline, 69.5% of US adults with CKD are eligible for BP lowering. Among those with albuminuria, 78.2% are eligible but only 39.1% take ACEi/ARBs.

kidney INTERNATIONAL ISN

Foti, 2021

Hyperkalemia-Related Discontinuation of RAAS Inhibitors and Clinical Outcomes in CKD

Population

Population-based cohort study

Adults with RAASi-related hyperkalemia and CKD ($K^+ \geq 5.5$ mmol/L)

N = 7,200 in Manitoba
N = 71,290 In Ontario

Methods

RAASi continuers
vs
RAASi discontinuers

Intention-to-treat approach

Sensitivity Analysis:
Time-dependent analysis and 1:1 propensity match

Results

Reference: RAASi Continuation

	Mortality	CV Mortality	Fatal and Non-Fatal CV Events	Dialysis
	HR (95% CI)			
Manitoba	**1.32** (1.22-1.41)	**1.28** (1.13-1.44)	**1.17** (1.11-1.24)	**1.65** (1.41-1.85)
Ontario	**1.47** (1.41-1.52)	**1.32** (1.25-1.39)	**1.18** (1.15-1.22)	**1.11** (1.08-1.16)

Mortality **1.36** (1.22-1.52)

CV Mortality **1.35** (1.13-1.64)

CONCLUSION: Hyperkalemia-related RAASi discontinuation is associated with higher mortality and cardiovascular events compared with continuation in patients with CKD.

Silvia Juliana Leon, Reid Whitlock, Claudio Rigatto, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2022.01.002

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

	Sodium polystyrene sulfonate	Patiromer	Sodium zirconium cyclosilicate
Mechanism of action	Na^+-K^+ exchange resin often given with sorbitol, nonselectively binds K^+, Ca^{2+}, Mg^{2+}	Exchanges Ca^{2+} for K^+, also binds Mg^{2+}	Binds K^+ in exchange for H^+ and Na^+
Time of onset	Variable (hours to days)	7 h	1 h
Binding site	Colon	Colon	Entire intestinal tract
Commonly reported adverse reactions and precautions	Diarrhea, metabolic alkalosis, hyper-natremia, volume overload, rarely colonic necrosis, must separate dose from other oral drugs by at least 3 h	Constipation, diarrhea, flatulence, hypomagnesemia, must separate dose from other oral drugs by at least 3 h	Constipation, diarrhea, edema, can increase gastric pH potentially interfering with drugs having pH dependent solubility

	Sodium polystyrene sulfonate	Patiromer	Sodium zirconium cyclosilicate
Mechanism of action	Na^+-K^+ exchange resin of[illegible]ven wi[illegible] so[illegible]hons[illegible]vely bind[illegible]Ca[illegible]g^{2+}	Exchanges Ca^{2+} for K^+, also binds Mg^{2+}	Binds K^+ in exchange for H^+ and Na^+
Time of onset	Varia[illegible]to days)	7 h	1 h
Binding site	Colon	Colon	Entire intestinal tract
Commonly reported adverse reactions and precautions	Diarrh[illegible]olic alkal[illegible] natr[illegible]ve ove[illegible]rar[illegible]lonic ne[illegible], mus[illegible] separate dose from other oral drugs by at least 3 h	Constipation, diarrhea, flatulence, hypomagnesemia, must separate dose from other oral drugs by at least 3 h	Constipation, diarrhea, edema, can increase gastric pH potentially interfering with drugs having pH dependent solubility

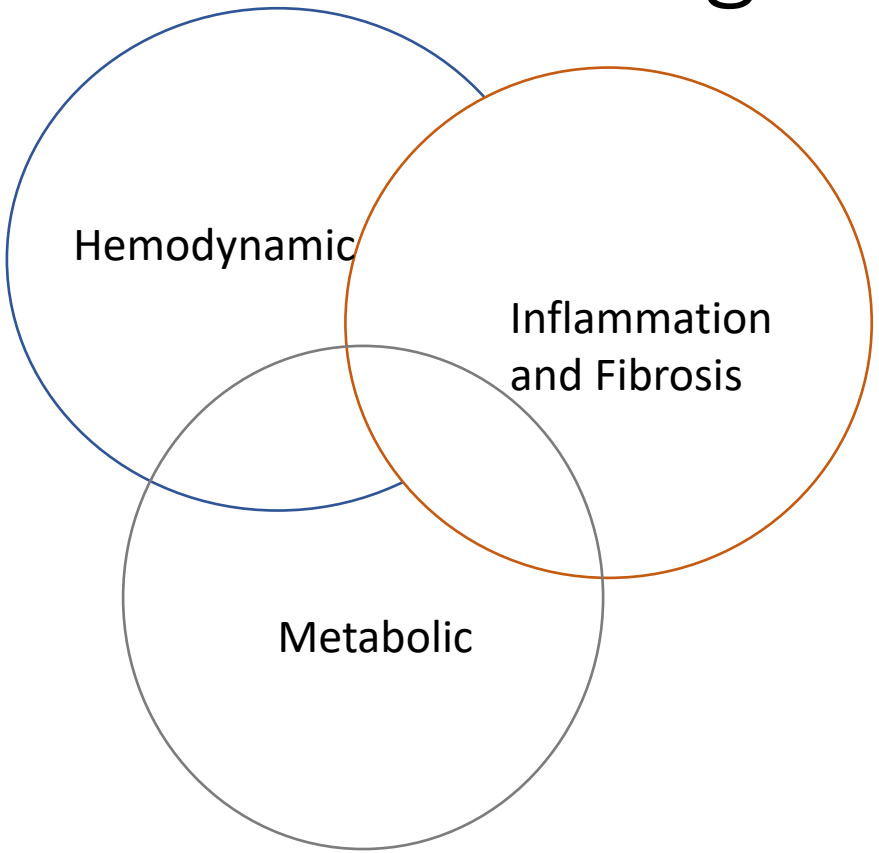
Statin- KDIGO

- “In all adults older than 50 years old with eGFR <60 neither on dialysis or kidney transplant we recommend patient be on a statin”

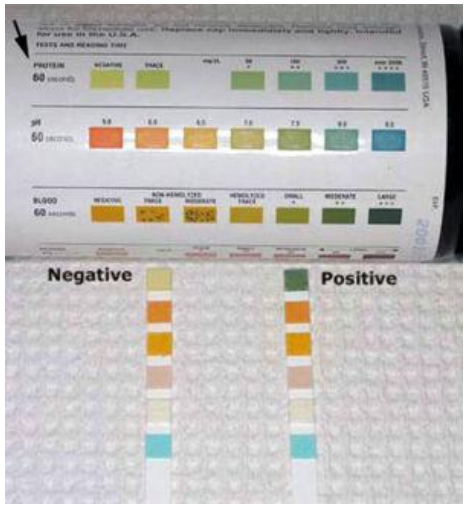
Table 4 | Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP	nd
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

CKD Progression in Type 2 Diabetes

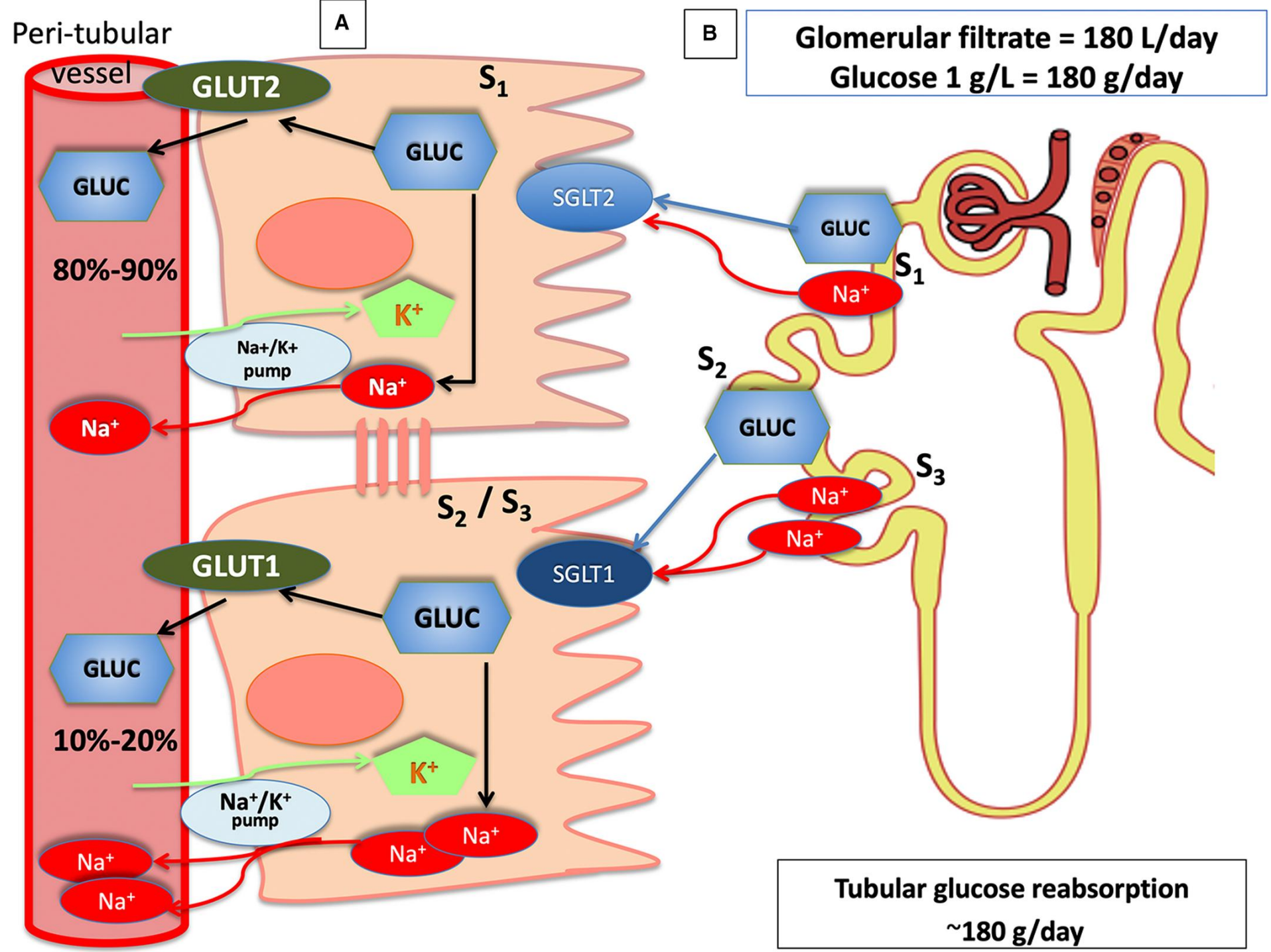


- Tubulo-interstitial damage and inflammation
- Glomerulosclerosis
- Mesangial Expansion
- Glomerular Hypertrophy
- Arteriolar hyalinosis




1998
UKPDS
Intensive glycemic control reduced micro and macroalbuminuria by 39% and 54%
2001
RENAAL
Losartan reduced risk of doubling of creatinine by 25% and ESRD by 28%. Decreased proteinuria by 35%
2001
IRMA-2
Irbesartan found to be renoprotective independent of BP lowering effect
2001
IDNT
Irbesartan associated with lower risk of creatinine doubling ESRD compared to placebo & amlodipine
2002
MARVAL
Greater decrease of micro-albuminuria with valsartan than amlodipine
2008
ACCORD
Targettng HbA1C <6% resulted in greater mortality compared to 7-7.9%
2008
ONTARGET
Combination therapy was associated with increased composite outcome of dialysis, serum creatinine doubling and death
2008
AVOID
Aliskiren/losartan combo led to reduction of UACR by 20%
2010
VITAL
Paricalcitol at 2 µg/day reduced albuminuria (20% compared with placebo). However, dose poorly tolerated
2011
ROADMAP
Olmesartan resulted in a reduction in time to micro-albuminuria onset by 23% but increased CV events
2011
BEAM
Bardoxolone resulted in a higher GFR compared with placebo at 52 weeks.
2012
ALTITUDE
Addition of aliskiren to maximal ARB - Increased risk of Hyperkalemia & hypotension.
2013
VA-NEPHRON-D
Combination therapy resulted in excessive risk of hyperkalemia & AKI
2013
BEACON
Terminated at 9 mo Bardoxolon led to a sig increase in CV morbidity
2013
CANTATA-SU
Canagliflozin initial decrease in GFR then stabilized glimepiride arm had progressive GFR decline
2015
EMPA-REG
Post hoc analyses - reduction of albuminuria, slowing down of estimated glomerular filtration rate (eGFR) decline, and a 50% reduction in risk of progressing to ESRD
2017
CANVAS
"possible benefits" of canagliflozin treatment for both progression of albuminuria & on composite renal outcome of a sustained 40% reduction in eGFR, need for RRT, or death from renal causes
2019
CREDENCE
Renal failure & CV events- lower in canagliflozin arm than placebo

@drlovygaur


A
Peri-tubular vessel
GLUT2
GLUC
GLUC
80%-90%
S_1
K+
Na+/K+ pump
Na+
Na+
S_2 / S_3
GLUT1
GLUC
GLUC
10%-20%
K+
Na+/K+ pump
Na+
Na+
Na+
Na+
B
Glomerular filtrate = 180 L/day
Glucose 1 g/L = 180 g/day
SGLT2
GLUC
Na+
S_1
S_2
GLUC
S_3
Na+
Na+
SGLT1
Tubular glucose reabsorption
~180 g/day

Does canagliflozin slow diabetic kidney disease? You bet your sweet pee it does!

#NephJC

Study Population

Randomized Control Trial (N = 4401)

63 years

HbA1c = 8.3%

Alb/Cr = 927 mg/g

eGFR = 56.2

Primary Outcome

61 per 1000 patient years

Placebo

Composite of ESRD, doubling of serum Cr, renal or CV death

HR = 0.70
(CI, 0.59 to 0.82)

Canagliflozin 43 per 1000 patient years

Renal-Specific Outcome

ESRD, 2 x serum creatinine, death from renal cause

HR = 0.66
CI 0.53 to 0.81

Cardiovascular Outcome

Cardiovascular death, myocardial infarction, or stroke

HR = 0.80
CI 0.67 to 0.95

Fractures

HR = 0.98
CI 0.70 to 1.37

Amputation

HR = 1.11
CI 0.79 to 1.56

Conclusion: In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group.

Perkovic, Vlado, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *NEJM*, 2019, doi:10.1056/nejmoa1811744.

@MarioFunesMD

			Primary outcome		Kidney outcomes		
Drug	**Trial**	**Kidney-related eligibility criteria**	**Primary outcome**	**Effect on primary outcome**	**Effect on albuminuria or albuminuria-containing composite outcome**	**Effect on GFR loss[a]**	**Adverse effects**
SGLT2 inhibitors							
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥30 ml/min per 1.73 m^2	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥30 ml/min per 1.73 m^2	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR >300 mg/g [30 mg/mmol] and eGFR 30–90 ml/min per 1.73 m^2	Progression of CKD[b]	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥60 ml/min	Dual primary outcomes: MACE and the composite of hospitalization for heart failure or CV death[c]	↔/↓	↓	↓↓	Genital mycotic infections, DKA

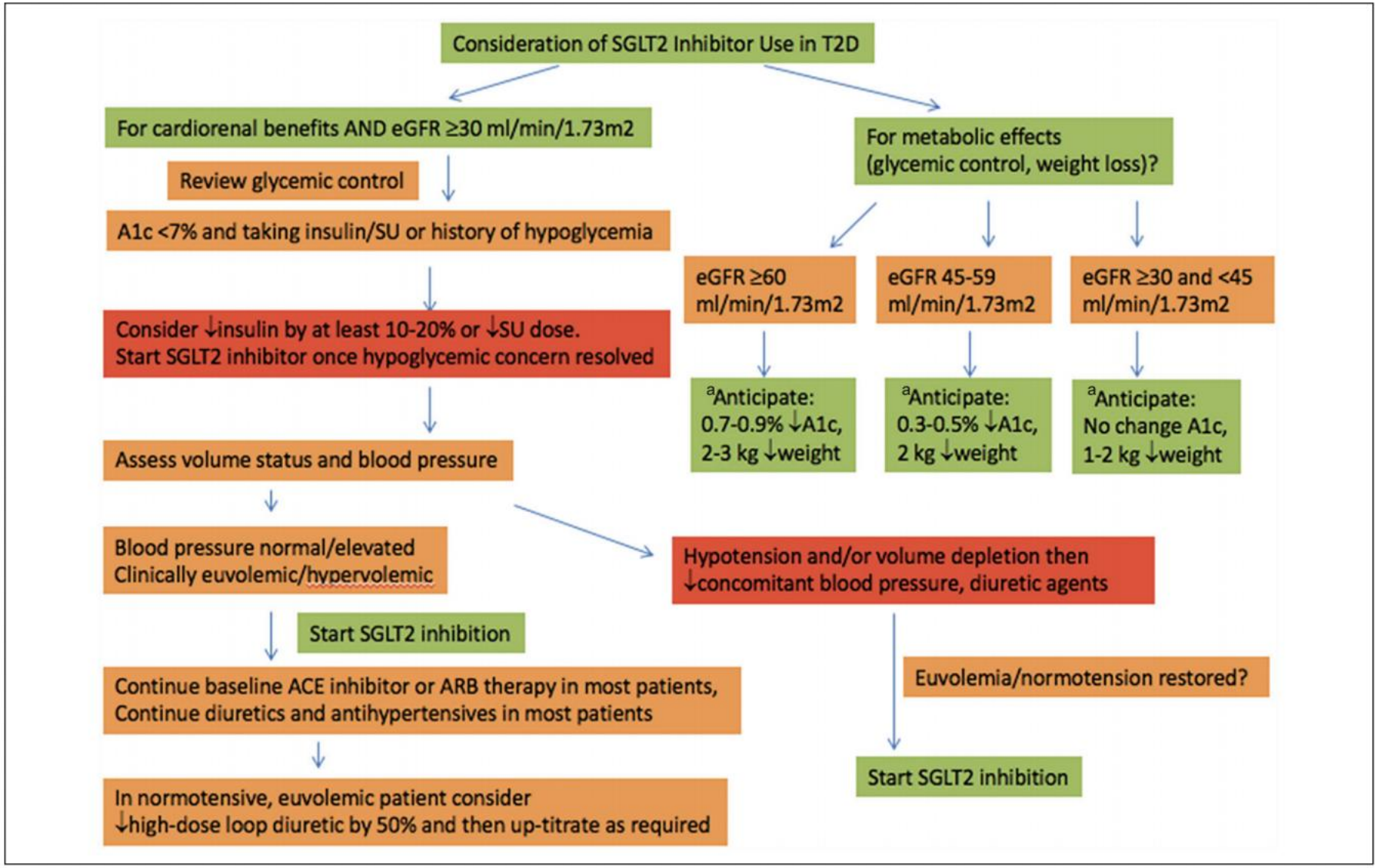


Figure 1. Proposed algorithm for SGLT2i initiation.

Note. Check electrolytes, creatinine after initiation of treatment according to local guidelines/practice. SGLT2i = sodium-glucose cotransporter-2 inhibitor; T2D = type 2 diabetes; eGFR= estimated glomerular filtration rate; SU = sulfonylurea; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

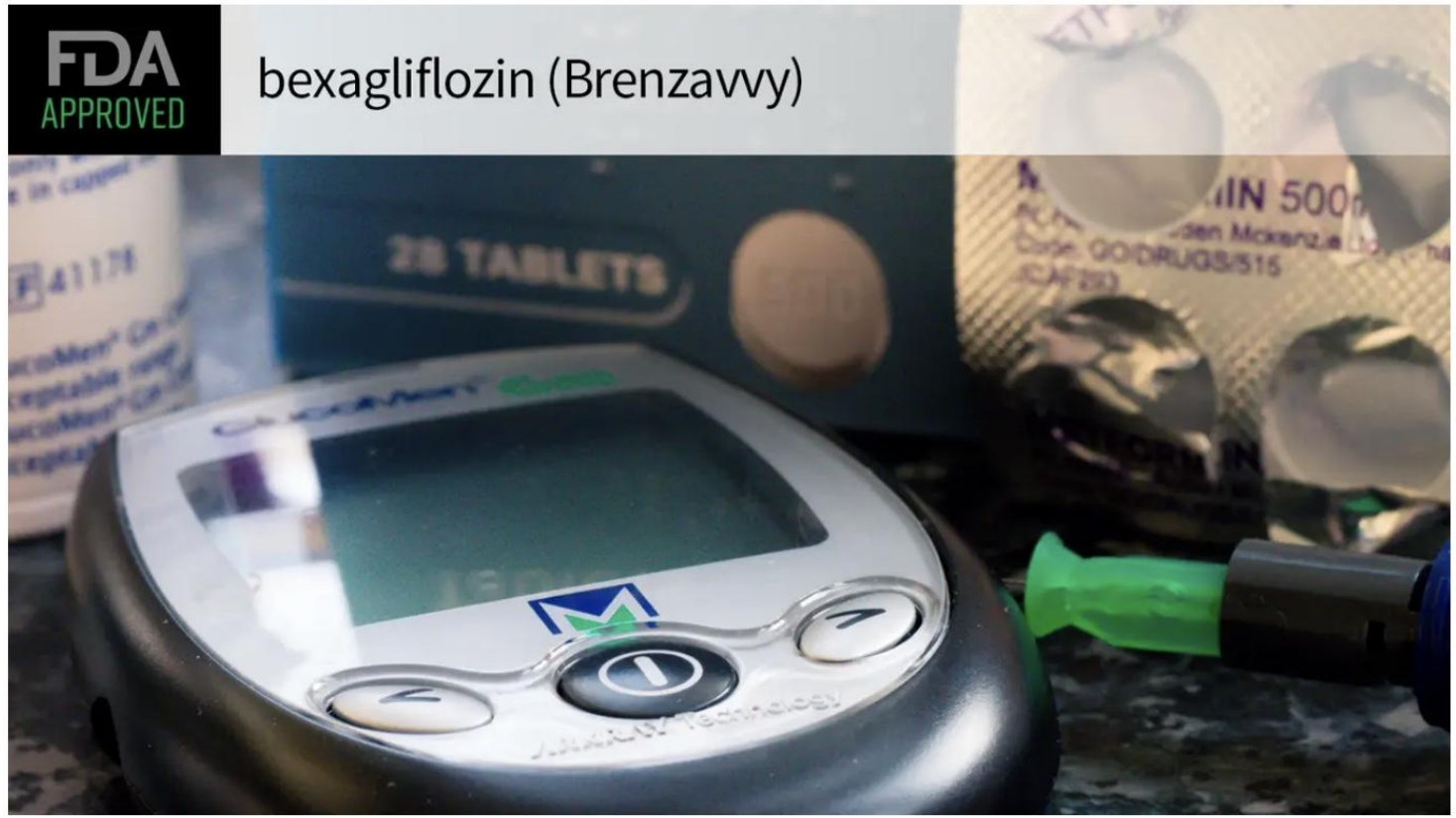
[a]Also consider following guidance around adjustment of insulin and SU therapies, diuretics, and antihypertensives prior to initiation of therapies.

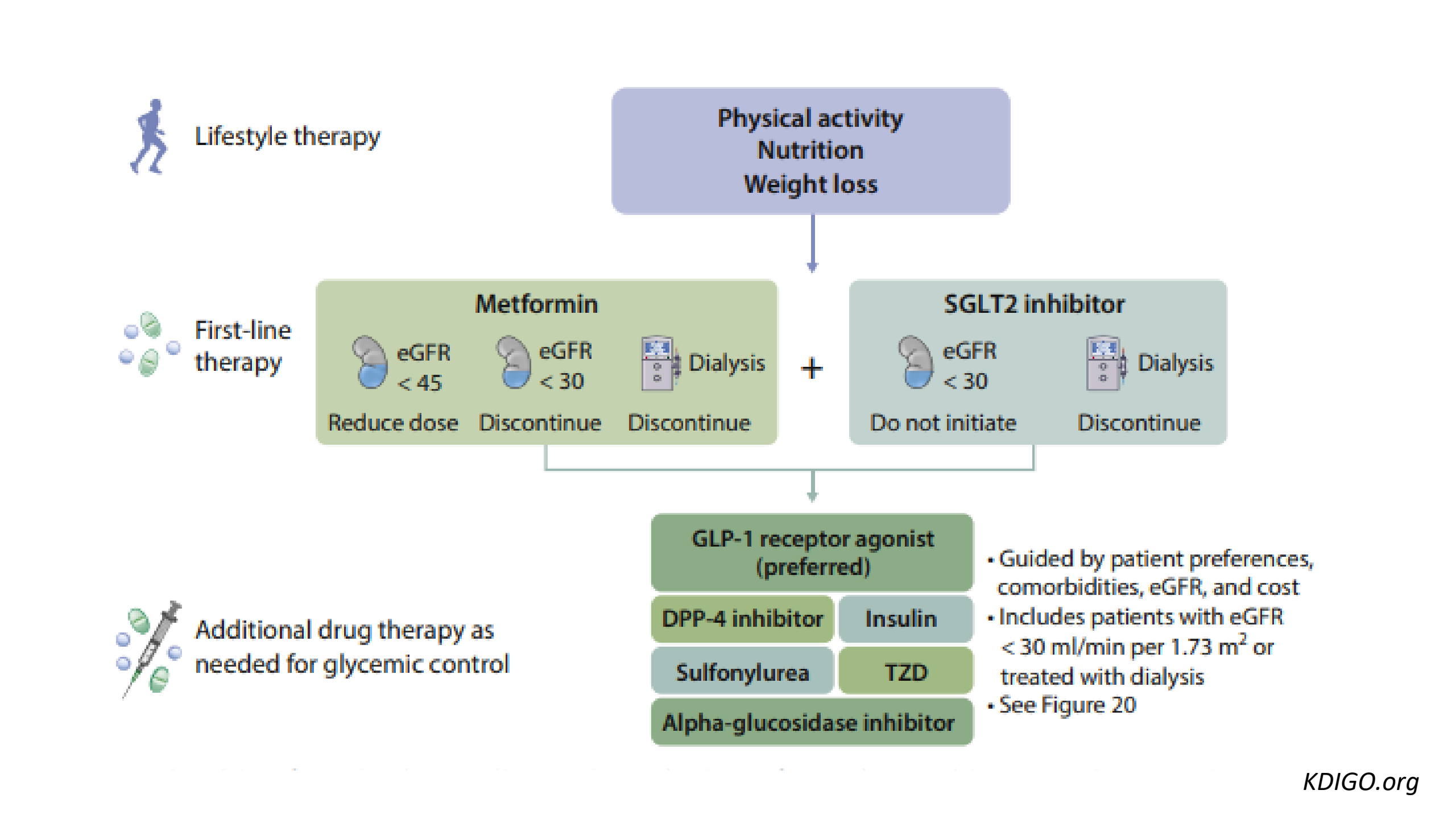
CJKHD 2020; 7:1-8

Diabetes Drug for Cats Now Approved in Humans Too

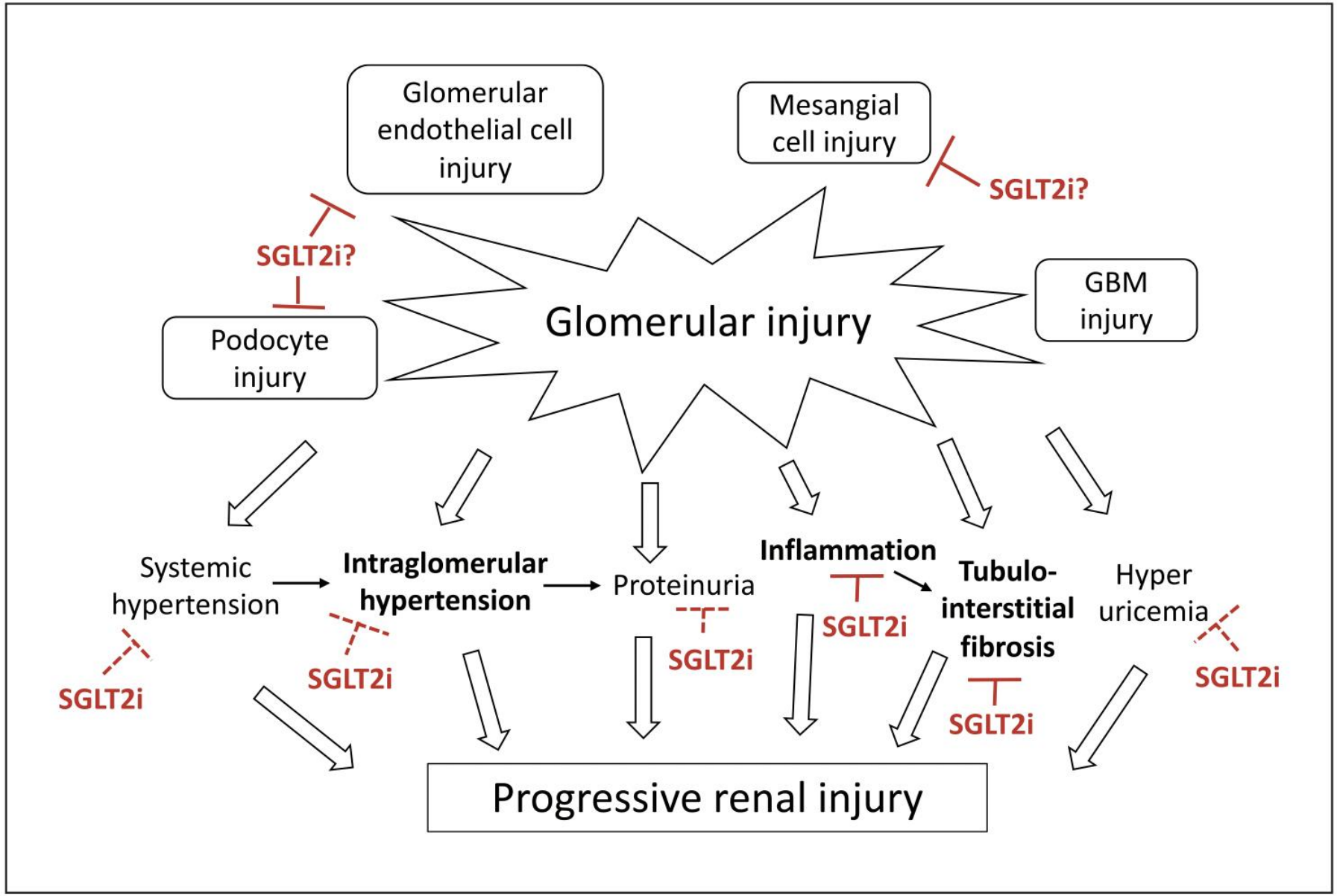
— Oral SGLT2 inhibitor bexagliflozin indicated for adults with type 2 diabetes

by Kristen Monaco, Staff Writer, MedPage Today January 23, 2023




Lifestyle therapy
Physical activity
Nutrition
Weight loss
First-line therapy
Metformin
eGFR < 45
Reduce dose
eGFR < 30
Discontinue
Dialysis
Discontinue
+
SGLT2 inhibitor
eGFR < 30
Do not initiate
Dialysis
Discontinue
Additional drug therapy as needed for glycemic control
GLP-1 receptor agonist (preferred)
DPP-4 inhibitor
Insulin
Sulfonylurea
TZD
Alpha-glucosidase inhibitor
• Guided by patient preferences, comorbidities, eGFR, and cost
• Includes patients with eGFR < 30 ml/min per 1.73 m^2 or treated with dialysis
• See Figure 20

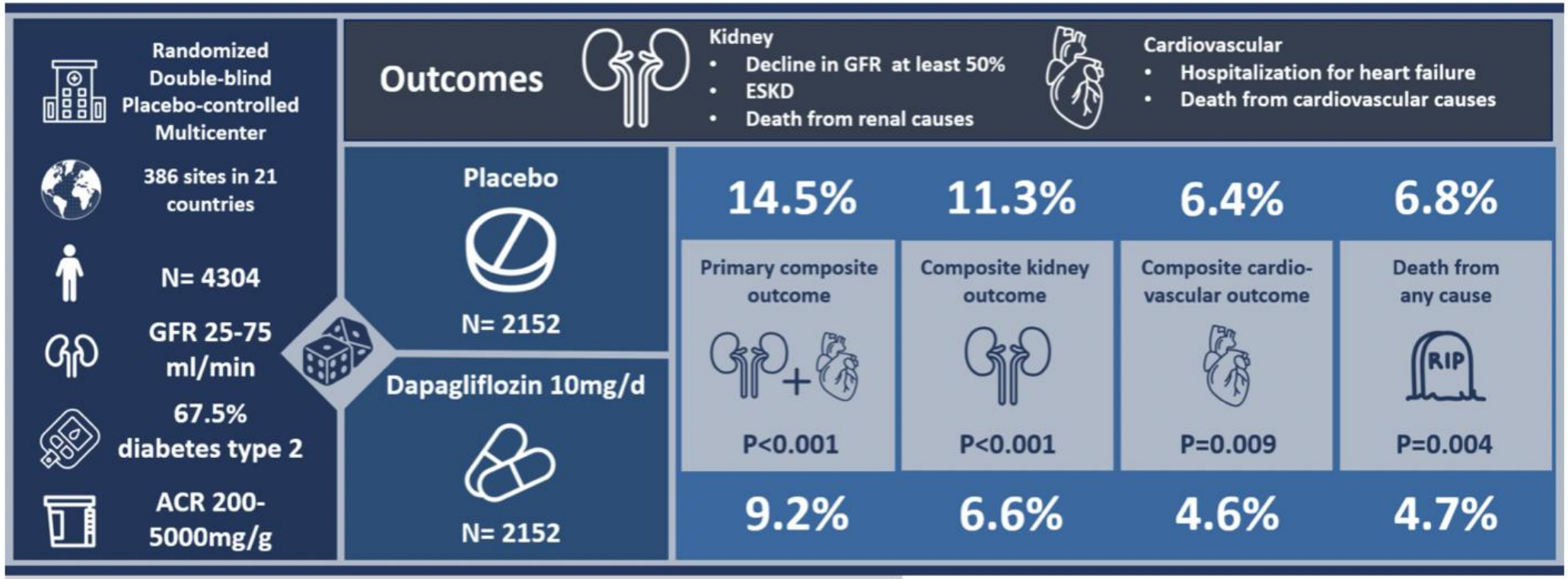
KDIGO.org



Glomerular Dis 2021; 1:21-33

Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?

#NephJC



Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.

Reference: Heerspink HJL *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Sep 24. DOI: 10.1056/NEJMoa2024816.

Visual abstract: Denisse Arellano, MD @deniise_am

NEPHROLOGY SOCIAL MEDIA COLLECTIVE EST 2015

	Mean baseline eGFR, mL/min per 1·73m²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2inhibitor	Placebo	
Diabetic kidney disease or nephropathy*						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA–CKD	43	93/1271	157/1239	36	64	0·55 (0·43–0·71)
EMPA–KIDNEY	36	85/1032	133/1025	42	67	0·56 (0·43–0·74)
Subtotal	**46**	**368/9797**	**572/9755**	..	..	**0·60 (0·53–0·69)**
Ischaemic and hypertensive kidney disease						
DAPA–CKD	43	18/324	26/363	28	37	0·74 (0·40–1·36)
EMPA–KIDNEY	35	37/706	52/739	27	37	0·69 (0·45–1·05)
Subtotal	**38**	**55/1030**	**78/1102**	..	..	**0·70 (0·50–1·00)**
Glomerular disease						
DAPA–CKD	43	21/343	46/352	33	70	0·43 (0·26–0·72)
EMPA–KIDNEY	42	69/853	95/816	44	64	0·68 (0·50–0·93)
Subtotal	**42**	**90/1196**	**141/1168**	..	..	**0·60 (0·46–0·78)**
Other kidney disease or unknown						
DAPA–CKD	43	10/214	14/198	25	37	0·81 (0·35–1·83)
EMPA–KIDNEY	36	36/713	52/725	26	36	0·72 (0·47–1·10)
Subtotal	**38**	**46/927**	**66/923**	..	..	**0·74 (0·51–1·08)**
Any diagnosis						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA–CKD	43	142/2152	243/2152	33	58	0·56 (0·45–0·68)
EMPA–KIDNEY	37	227/3304	332/3305	36	52	0·64 (0·54–0·76)
Total	**44**	**559/12 950**	**857/12 948**	..	..	**0·62 (0·56–0·69)**

Heterogeneity across groups of primary kidney disease: p=0·67
Trend across trials sorted by eGFR for any diagnosis: p=0·88

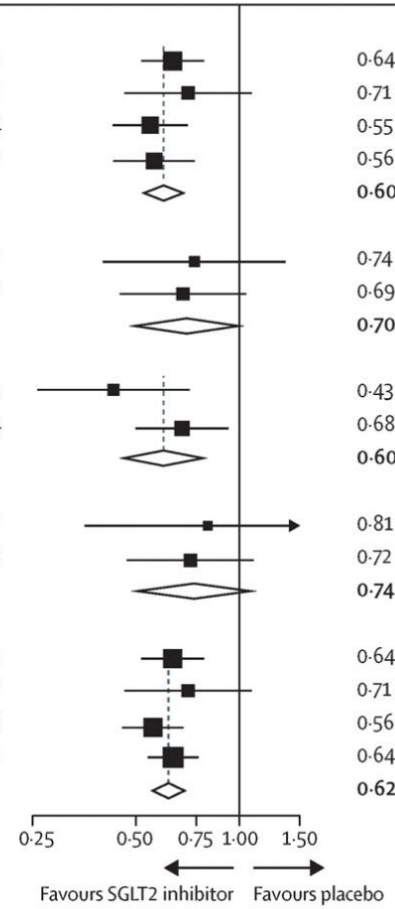
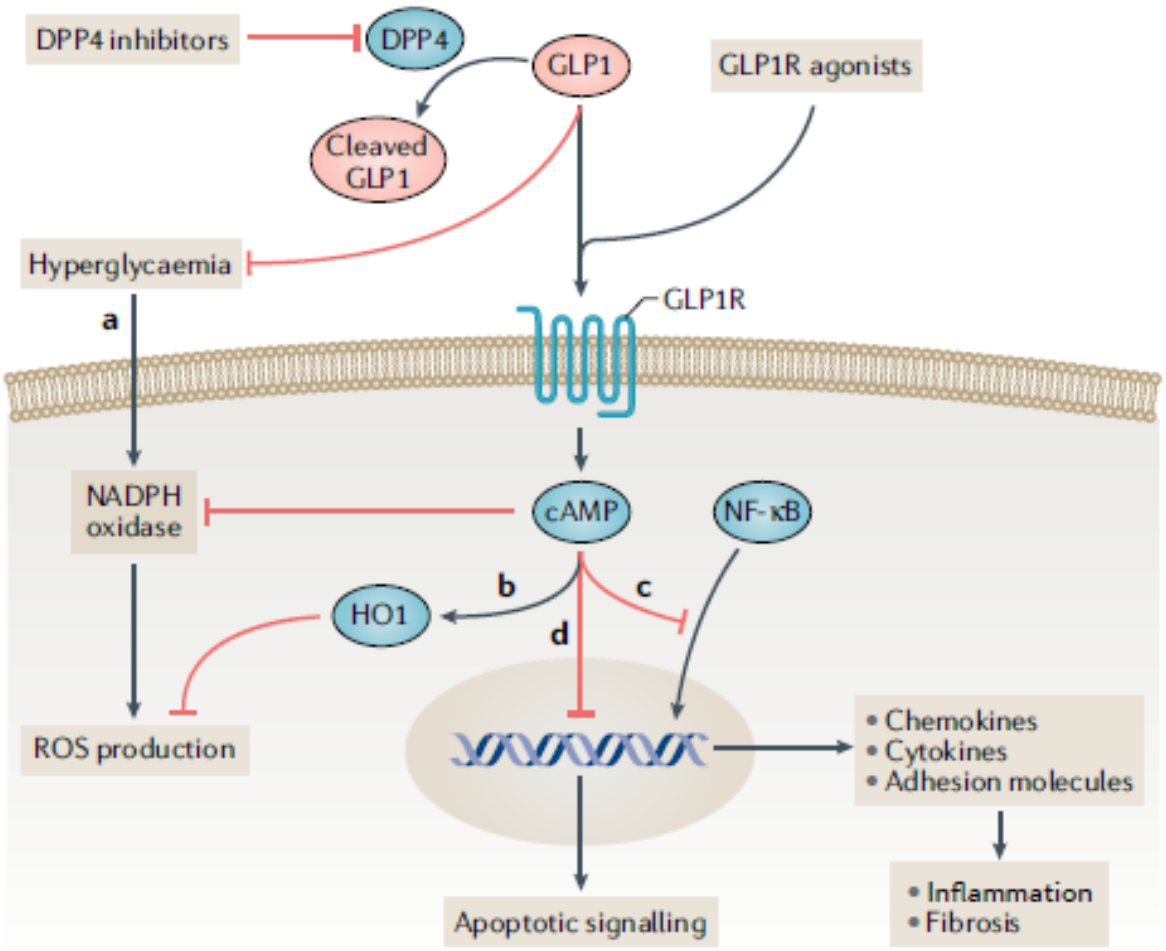
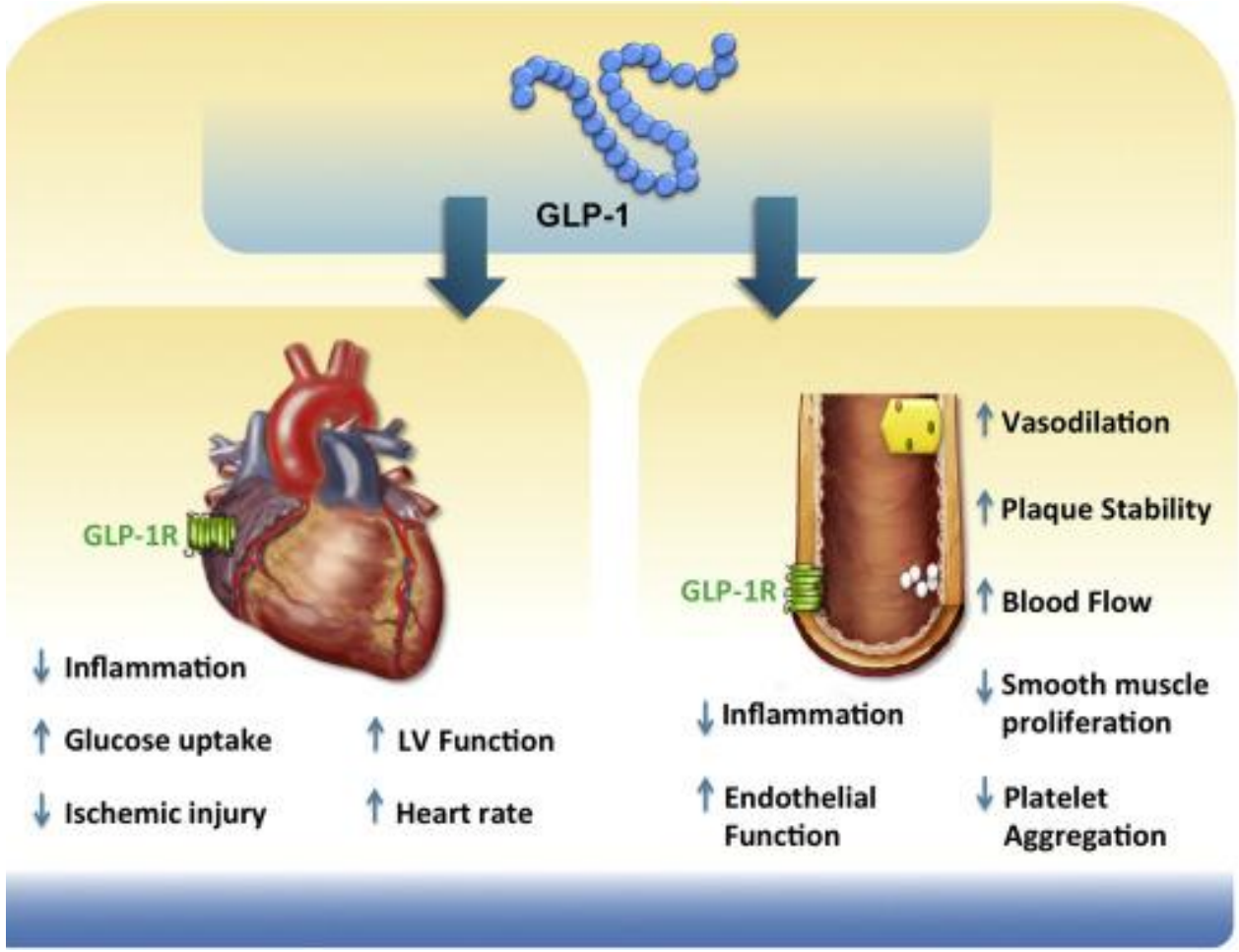
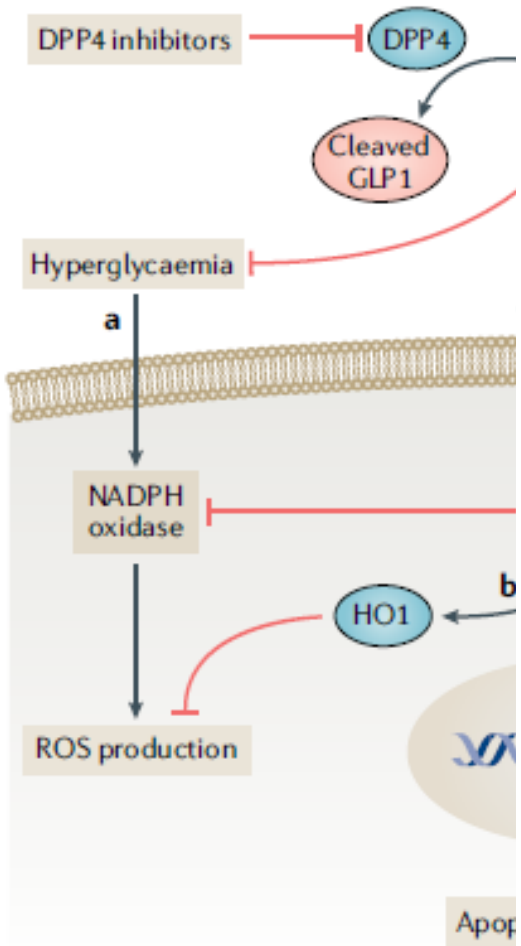


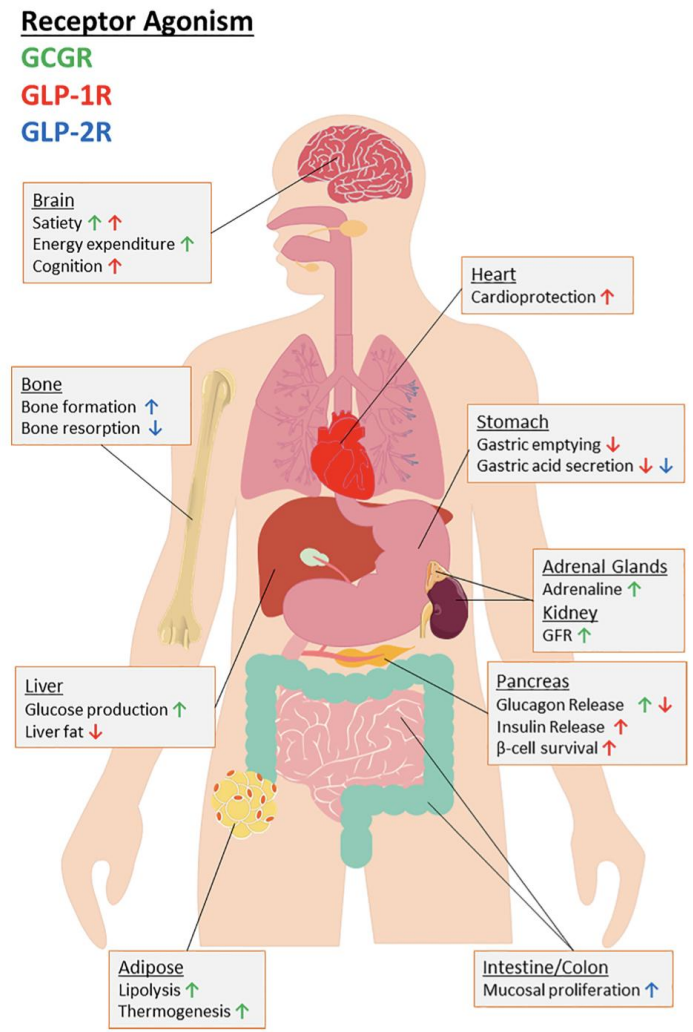
Figure 1. Effect of SGLT2 inhibitors versus placebo on kidney disease progression, stratified by underlying cause of kidney disease. Reprinted from ref. 18, with permission. RR, relative risk.

Lancet 400: 1788–1801, 2022


DPP4 inhibitors
DPP4
GLP1
GLP1R agonists
Cleaved GLP1
Hyperglycaemia
a
GLP1R
NADPH oxidase
cAMP
NF-κB
b
c
d
HO1
ROS production
• Chemokines
• Cytokines
• Adhesion molecules
• Inflammation
• Fibrosis
Apoptotic signalling


GLP-1
GLP-1R
↓ Inflammation
↑ Glucose uptake
↓ Ischemic injury
↑ LV Function
↑ Heart rate
GLP-1R
↓ Inflammation
↑ Endothelial Function
↑ Vasodilation
↑ Plaque Stability
↑ Blood Flow
↓ Smooth muscle proliferation
↓ Platelet Aggregation





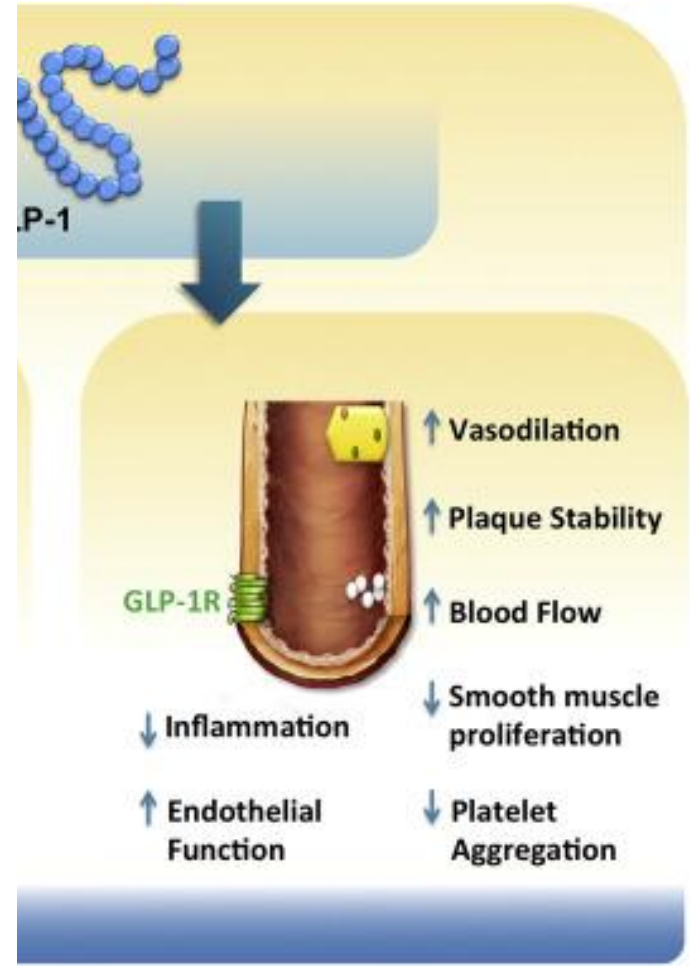
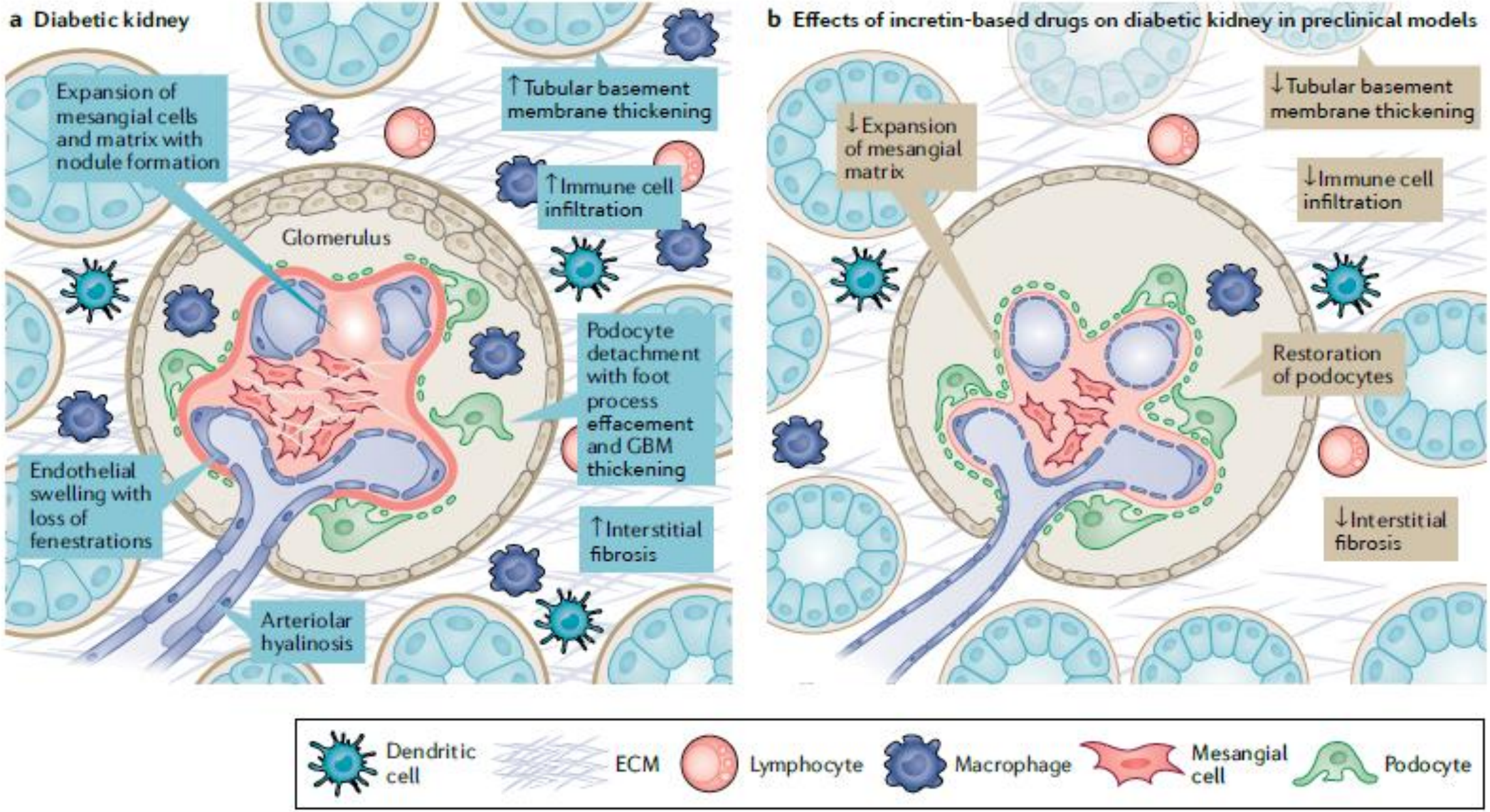
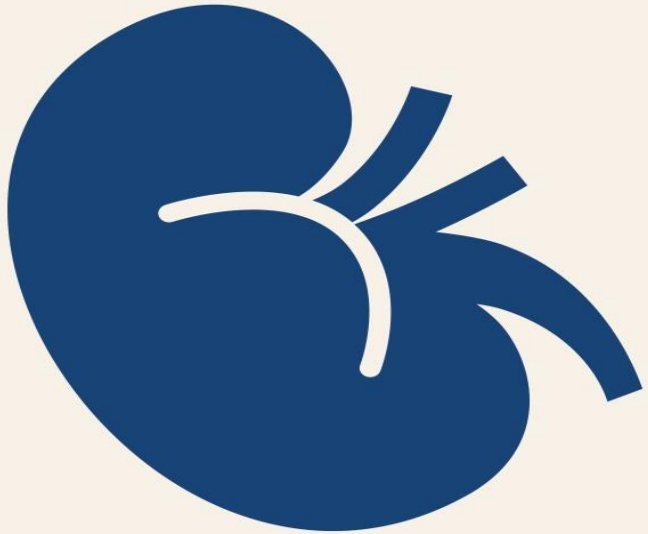


FIGURE 3 | An overview of the biological consequences for agonism of target receptors of major PGDP's, namely glucagon receptor (GCGR) and glucagon-like peptide-1 and -2 receptors (GLP-1R, GLP-2R). Organ-specific actions are provided with arrows indicating up or downregulation of specific effects to highlight the therapeutic potential for multiagonism in relation to PGDP's. As indicated by the key, the colour of arrow indicates the receptor interactions responsible. "GFR" indicates glomerular filtration rate.



Nature Reviews Nephrology 2021



2024

FLOW TRIAL

Effects of Semaglutide on Chronic Kidney Disease (CKD) in Patients with Type 2 Diabetes

A randomized, placebo controlled trial

Objective: To evaluate the safety and efficacy of semaglutide in slowing kidney function decline and reducing major adverse kidney events in patients with type 2 diabetes.

3533 Patients

Inclusion criteria: Age 18 years or older; diabetic, HbA1c ≤ 10%, renal impairment and undergoing treatment with maximum labelled or tolerated dose of ACE inhibitor or an ARB. **Exclusion criteria:** Congenital or autoimmune kidney disease, recent GLP-1 receptor agonist use or cardiovascular events, severe heart failure.

Semaglutide group (n = 1767)	vs.	Placebo group (n = 1766)

Primary Outcome

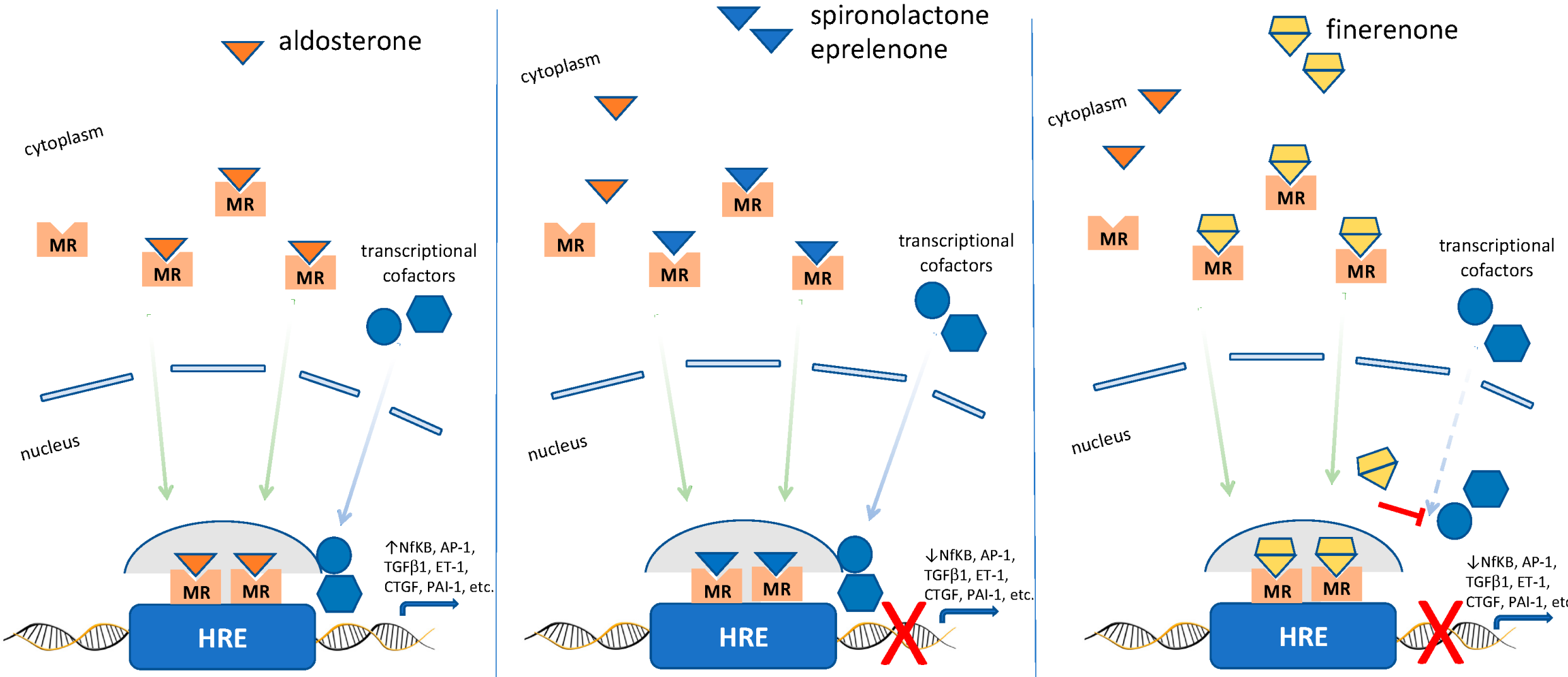
Semaglutide group (n = 1767)		Placebo group (n = 1766)
331	Major kidney disease events (N) HR, 0.76; 95% CI, 0.66 to 0.88 (P = 0.0003)	410

Secondary Outcomes

Semaglutide group (n = 1767)		Placebo group (n = 1766)
Slow	Decline in mean annual eGFR (By 1.16 ml per minute per 1.73 m2) (P < 0.001)	Fast
49.6	Serious adverse events (%)	53.8

Conclusion: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

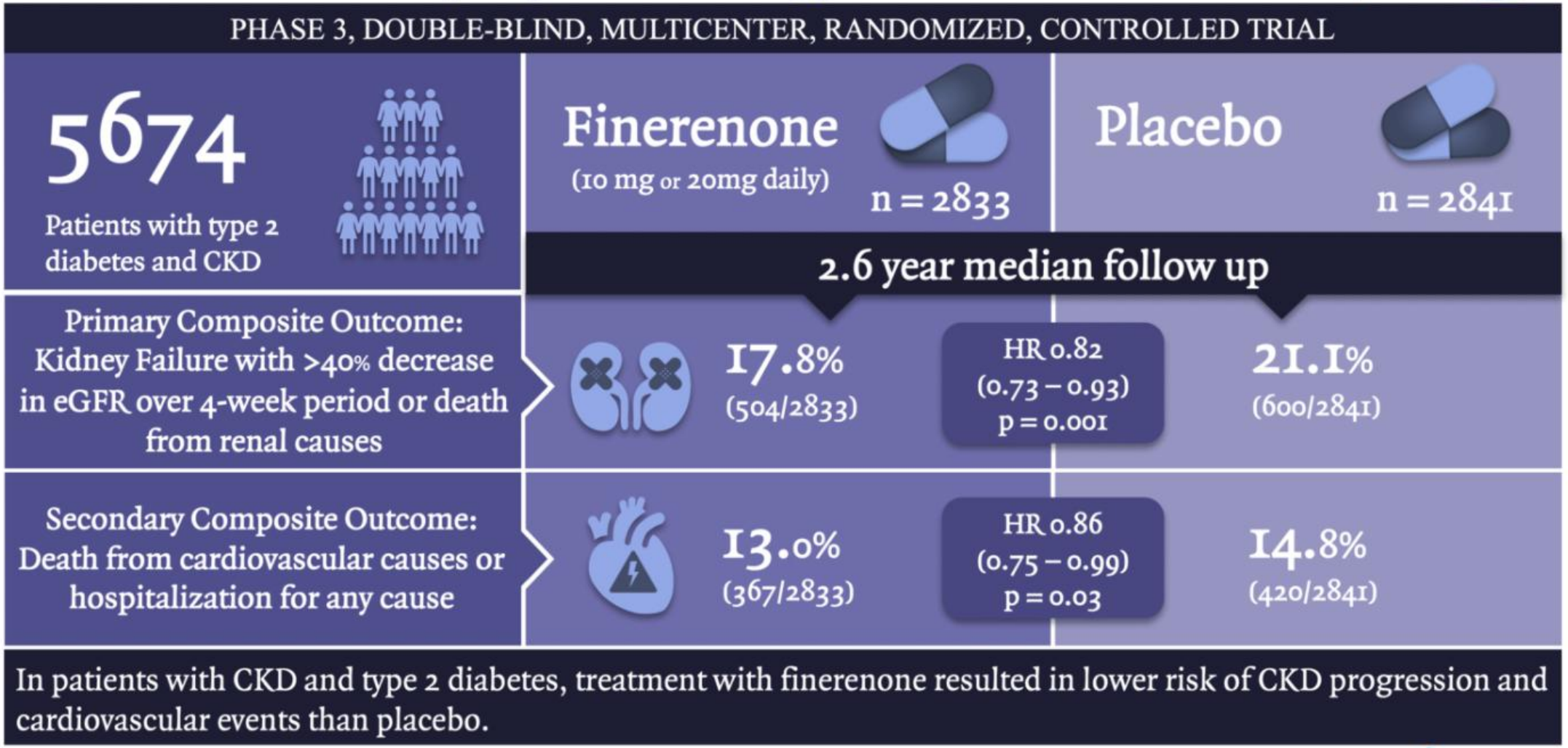
Perkovic V et al. NEJM 2024;DOI:10.1056/NEJMoa2403347



Pharmaceutics **2023**, *15*(5), 1343

Does finerenone slow progression of CKD and reduce cardiovascular mortality in patients with type 2 diabetes?

#NephJC



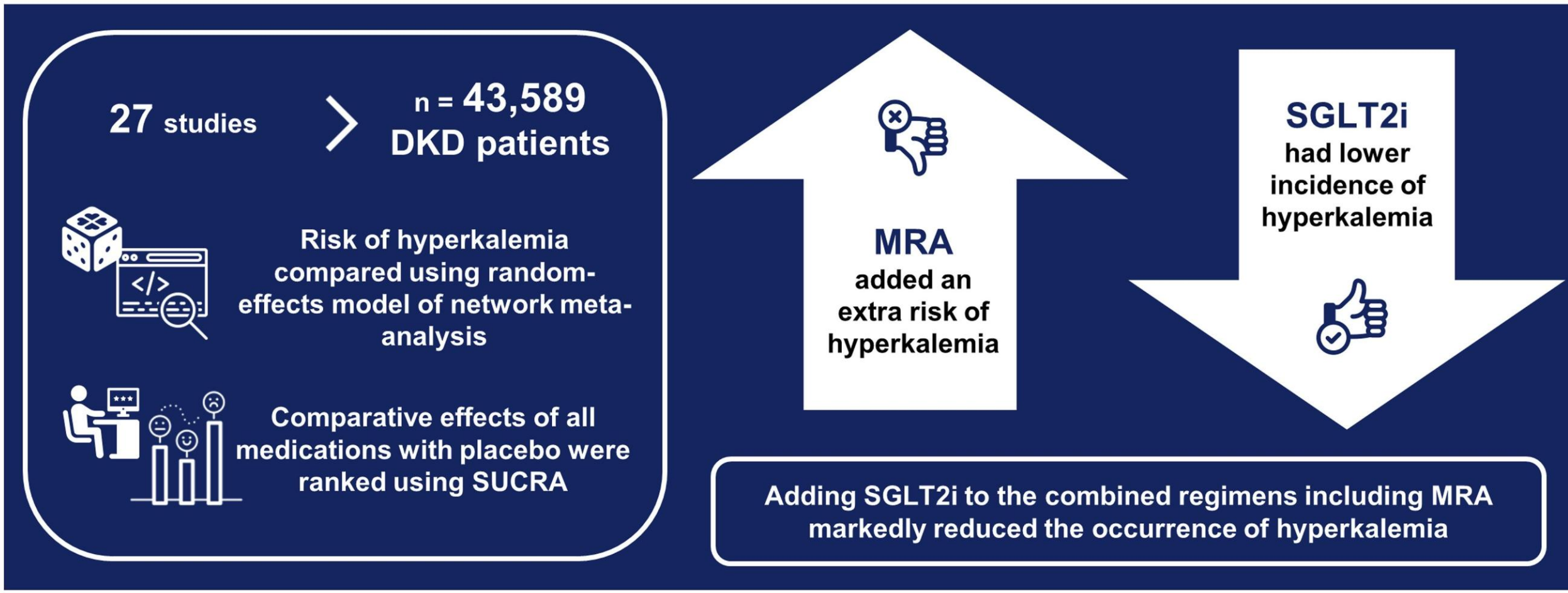
Reference: Bakris GL, Agarwal R, Anker S, Pitt B, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. NEJM

VA by Dhwanil Patel @iheartkidneys

NEJM Dec 2020

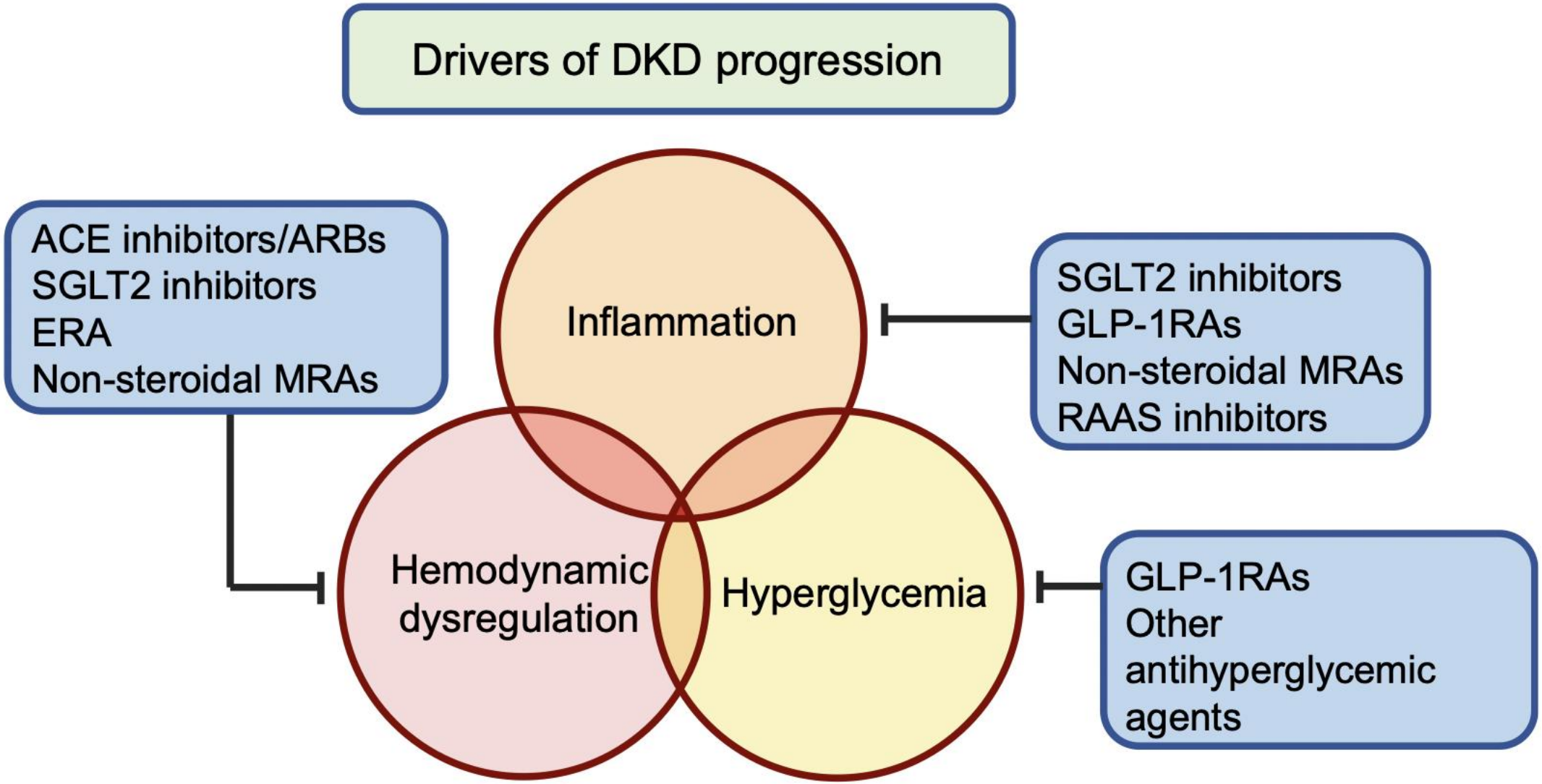
Influence of SGLT2i and RAASi and their combination on risk of hyperkalemia in DKD: A network meta-analysis

CJASN
Clinical Journal of the American Society of Nephrology



Conclusions: MRA added extra risk of hyperkalemia, while SGLT2i had the opposite effect, even in presence of MRA.

Xiaoling Luo, Jing Xu, Shoulian Zhou, et al. ***Influence of SGLT2i and RAASi and Their Combination on Risk of Hyperkalemia in DKD***. CJASN doi: 10.2215/CJN.0000000000000205. **Visual Abstract by José A. Moura-Neto, MD, FASN, FRCP**



AJKD 2021; 78:309-311

JS

42 year old obese female

Hypertension and DMII.

Creatinine=0.98 mg/dl

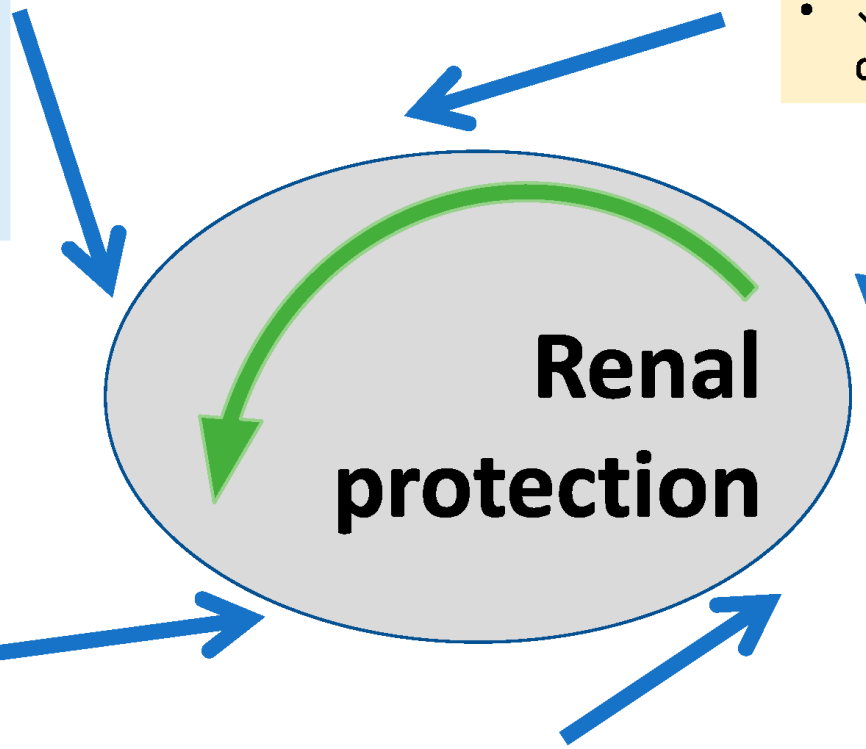
ACR=535 mg/g.

SGLT2 inhibitors

- ↓ glomerular hypertension
- ↑ HIF-2α (improved kidney tissue hypoxia)
- ↓ inflammation and fibrosis
- ↓ circulating volume
- ↑ natriuresis with ↑RAAS ⇢ ↑Angiotensin 1-7 → MAS receptor activation (potentiated by use of ACEis or ARBs)

Non-steroidal mineralocorticoid antagonists

- ↓ inflammation and fibrosis
- ↓ hyperkalaemia with double RAAS inhibition



RAAS inhibitors

- ↓ glomerular hypertension
- ↓ inflammation and fibrosis

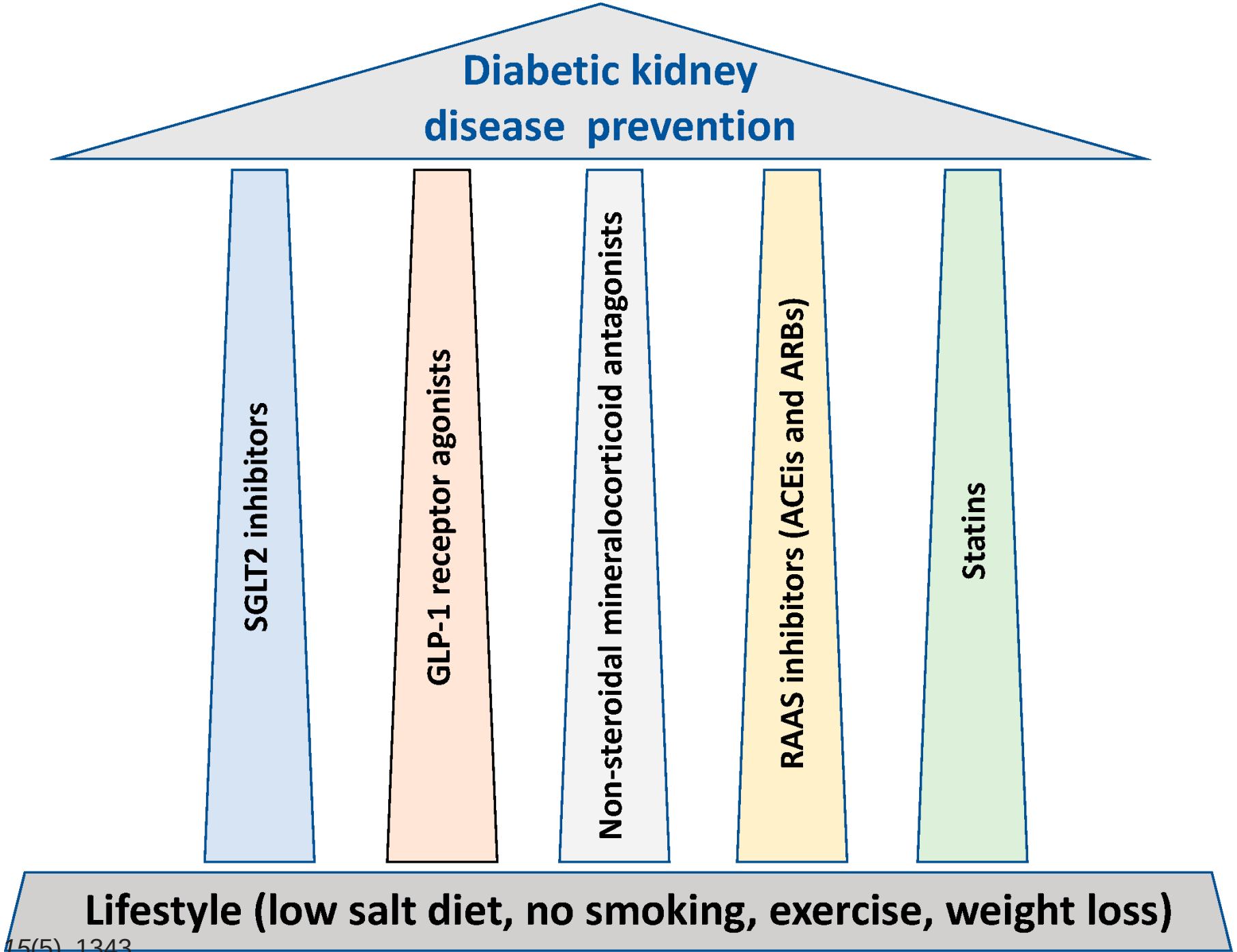
Statins

- ↓ lipids
- ↑ cardiovascular protective effects (pleiotropic)

GLP1 receptor agonist

- ↓ angiotensin-2
- ↑Natriuresis

Pharmaceutics **2023**, *15*(5), 1343

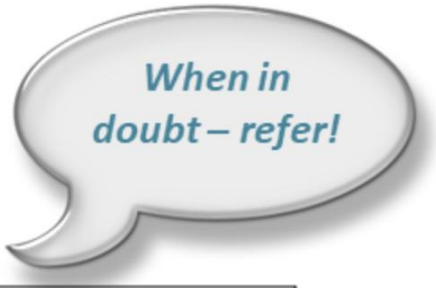


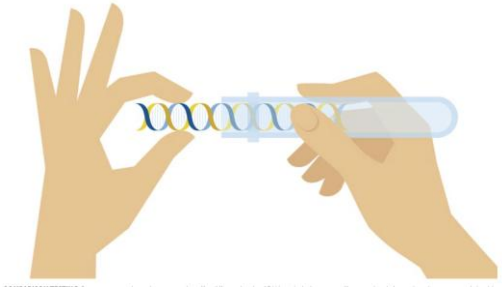
Pharmaceutics **2023**, *15*(5), 1343

- Healthy diet is imperative for prevention of CKD and its progression
- Focus on diets higher in fruits, vegetables, nuts, seeds, and whole grains and lower in meat, milk, and processed foods
- Need to have thoughtful consideration to the “Renal Diet”
- When need to recommend low potassium diet consider reducing animal foods not plant based potassium sources
  - In plant-based foods, potassium is only 50%–60% bioavailable for digestion and absorption

When to Refer to a Nephrologist

- ✓ Acute change or sustained decline in kidney function
- ✓ Albuminuria greater than 300 mg/g or proteinuria/albuminuria of unknown cause
- ✓ Hematuria associated with proteinuria
  (for isolated microhematuria evaluate for urologic causes first)
- ✓ Difficult to control high blood pressure
- ✓ Significant abnormalities of serum electrolytes
- ✓ Recurrent or extensive nephrolithiasis
- ✓ Hereditary kidney disease





Persistent albuminura categories Description and range			GFR categories (ml/min/ 1.73 m²) Description and range					
			G1	G2	G3a	G3b	G4	G5
			Normal or High	Mildly decreased	Mildly to moderately decreased	Moderately to severely decreased	severely decreased	Kidney Failure
			≥90	60-89	45-59	30-44	15-29	<15
	A1	Normal to mildly increased	<30 mg/g <3 mg/mmol			Monitor	Refer	Refer	Refer	Refer
	A2	Moderately increased	30-300 mg/g 3-30 mg/mmol	Monitor	Monitor	Refer	Refer	Refer	Refer
	A3	Severely increased	>300 mg/g >30 mg/mmol	Refer	Refer	Refer	Refer	Refer	Refer

Late nephrology referrals before the onset of chronic kidney failure remain too common. U.S. Renal Data Systems data indicates that **42% of new dialysis patients had no prior nephrology care**[1].

[1]U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States refers to Chapter 1, Volume 2, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013

Summary

- CKD population is rising in the United States
- Screening for albuminuria is an important part of management
- Goal BP <120/80 for most CKD patients
- SGLT2 inhibitors should be considered in management of all CKD patients
- Early referral and multidisciplinary care of CKD patients is important to improve care and reduce cost