Optum Health Education™

Pillars of kidney and cardiovascular protective interventions in Chronic Kidney Disease

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19 July 2023

Disclosures

- Personal fees and non-financial support received from:
  - Renalytix, plc.
  - AstraZeneca, inc.

Objectives

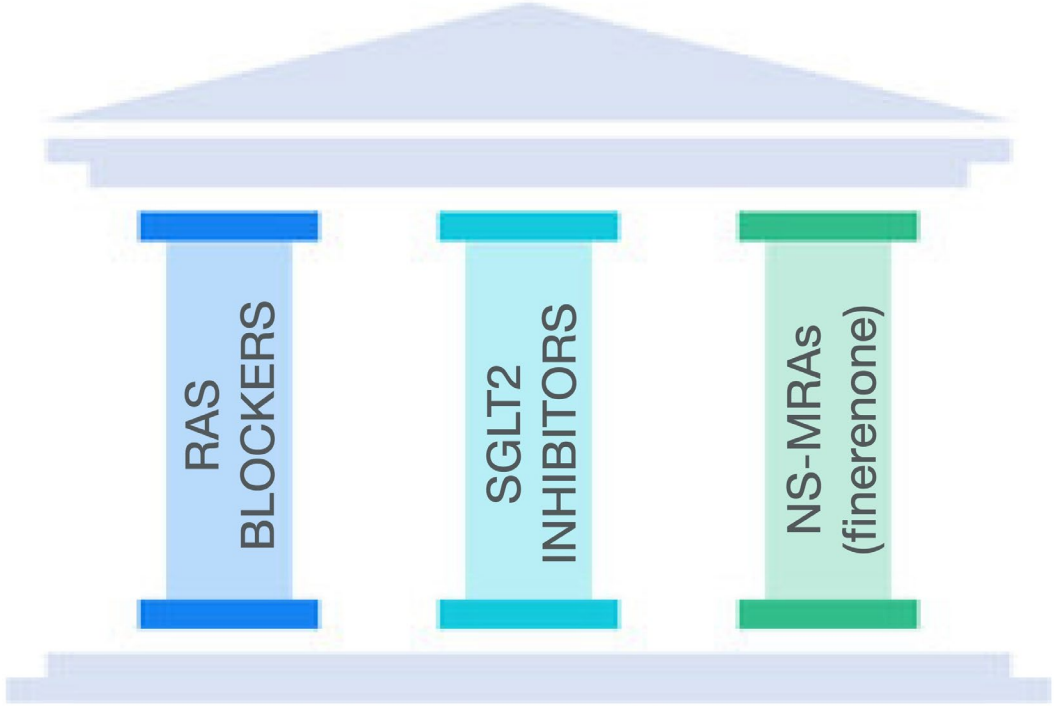
- Identify how kidney- and cardiovascular-protective interventions in CKD are based on risk stratification or heat map using eGFR and uACR
- Discuss SGLT-2 inhibitor-class medications for CKD, including considerations such as eGFR, uACR, heart-failure status, and risk of adverse effects
- Describe approaches to interdisciplinary care coordination for CKD that may include dietitians, pharmacists, nephrologists, and other health care professionals

Case Presentation

- 65-year-old man
- Type-2 diabetes since 2005, dyslipidemia and hypertension complicated by HFpEF and CAD s/p MI and LAD ICS.
- Diabetic retinopathy
- Medications: lisinopril 20 mg daily, metoprolol succinate 100 mg daily, clopidogrel 75 mg daily, aspirin 81 mg daily, atorvastatin 40 mg daily, & insulin lispro and glargine.
- BP 142/78 P 72

- How would you test for CKD and evaluate risk?

Kidney and Cardiovascular Protection



Pillars Needed to Maximally Slow Diabetic Kidney Disease Progression and Reduce Heart Failure Risk

Lifestyle

Healthy diet

Physical activity

Smoking cessation

Weight management

Regular risk factor reassessment (every 3–6 months)

Foundation

- Cessation of tobacco smoking
- Glycemic control, the level of which is individualized.
- Treated blood pressure to a target range of systolic 110 – 130 mm Hg
- Management of dyslipidemia centered on statin-based therapy
- Healthy diet with a low glycemic index and restricted in sodium
- Maintenance of a healthy weight
- Optimizing physical activity

Nephrology Dialysis Transplantation 2023;38:253-257

Assessment of both albuminuria and eGFR is required for early CKD diagnosis[1–4]

CKD is defined as abnormalities in kidney structure or function, present for >3 months, which have implications for health[1]

Early detection of kidney dysfunction or impairment facilitates the appropriate diagnosis and treatment of CKD[2]

The clinical diagnosis of CKD in a person with diabetes is based on:[1–4]

The presence of albuminuria*
uACR >30 mg/g (>3 mg/mmol)

and/or

Reduced kidney function
(eGFR <60 ml/min/1.73 m^2)

in the absence of signs or symptoms of other primary causes of kidney damage

*Elevated UACR should be confirmed in the absence of urinary tract infection with two additional early-morning urine samples collected over the next 2 months

1. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int Suppl* 2013;3:1–163; 2. Levey AS, *et al. JAMA* 2015;313:837–846;
3. National Kidney Foundation. *Am J Kidney Dis* 2007;49(Suppl 2):S1–S180; 4. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184

What is new with GFR estimation based on creatinine?

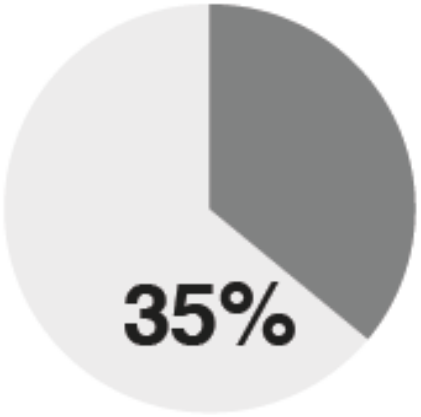
Use of race in clinical algorithms is problematic.

- Race is a social, not a biological construct ≠ genetic ancestry.
- Genetic ancestry variation within racial groups is substantial and genetic admixture across groups is common.
- Increasing biracial and multiracial individuals in the U.S. make racial categorization impractical.
- When assigning race in clinical algorithms, we risk accepting health inequities as immutable facts rather than injustices.

N Engl J Med 2021; 384:474-480.
N Engl J Med 2020; 383:874-882

Kidney Disease in the U.S. Today

% Black
U.S. population



% Black
U.S. on dialysis

- **Kidney health inequity** includes disproportionate prevalence of diabetes, hypertension, CKD and dialysis treatment for Blacks or African Americans and other races.

- **Kidney health inequity** includes lower access to nephrology care, home dialysis and kidney transplant for Blacks or African Americans and other races.

United States Renal Data System www.usrds.org

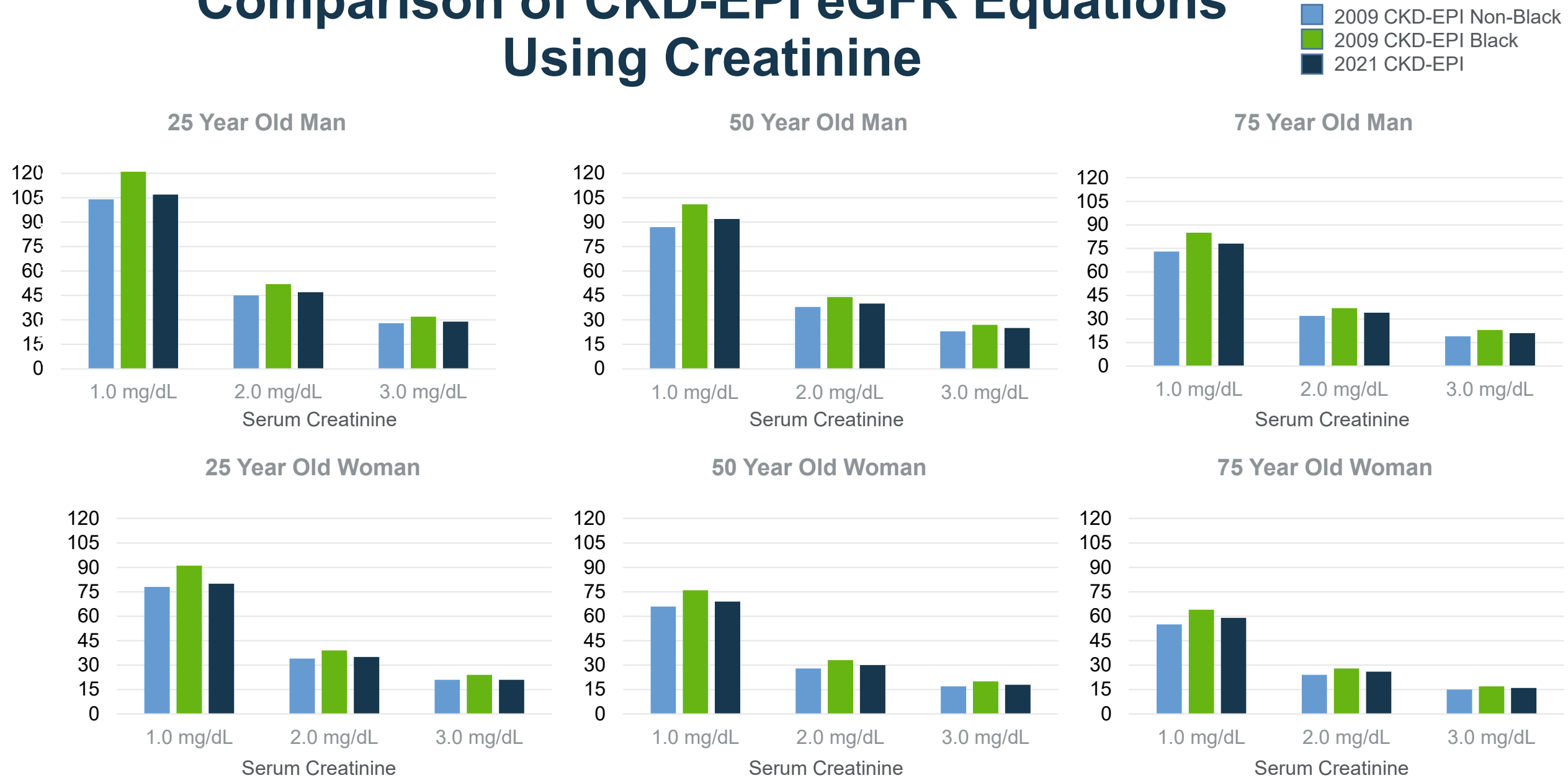
CDC CKD Surveillance System https://nccd.cdc.gov/CKD

National Kidney Foundation-American Society of Nephrology Task Force Recommendations

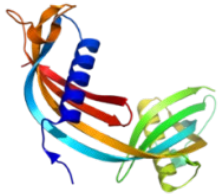
1. Immediate implementation of 2021 CKD-EPI eGFRcr equation refit without race
2. National efforts to facilitate increased, routine, and timely use of cystatin C
3. Research on GFR estimation with new endogenous filtration markers and on interventions to eliminate race and ethnic disparities should be encouraged and funded

Am J Kidney Dis 2021; 78(1):103-115.

Comparison of CKD-EPI eGFR Equations Using Creatinine



Serum Creatinine versus Serum Cystatin C



Creatinine

- Size ~ 1 aa
- Kidney function biomarker
- Skeletal muscle source
- Dietary source
- Tubular secretion elimination

Cystatin C

- 120 aa, 13 kDa protein
- Kidney function biomarker
- All tissues source
- Minimal muscle and diet influence
- Inflammatory marker

Adapted from W. Greg Miller, PhD

Clinical contexts in which Cystatin C may yield more accurate estimates of GFR

Serum Creatinine generation is LOW

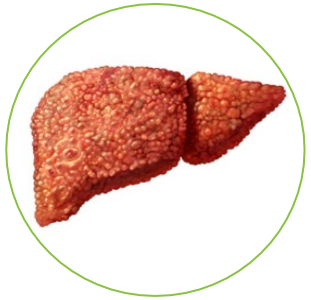
ELDERLY
FRAILTY

INACTIVITY
AMPUTATION

MALIGNANCY

VEGITARIAN DIET

HIV



CIRRHOSIS

Serum Creatinine generation is HIGH

WEIGHT-LIFTING

MEAT DIET

PROTEIN
SUPPLEMENTS

Drugs that inhibit tubular creatinine secretion

TRIMETHOPRIM
FENOFIBRATE
CIMETIDINE
DOLUTEGRAVIR/RALTEGRAVIR
COBICISTAT
RITONAVIR
RILPIVIRINE
TYROSINE KINASE INHIBITORS

Chen DC, et al. Kidney 360 2022; 3:1807-1814 (adapted)

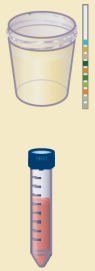
What is new with Albuminuria?

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?



Spot urine ACR

and

eGFR

What to do with a positive result?

Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

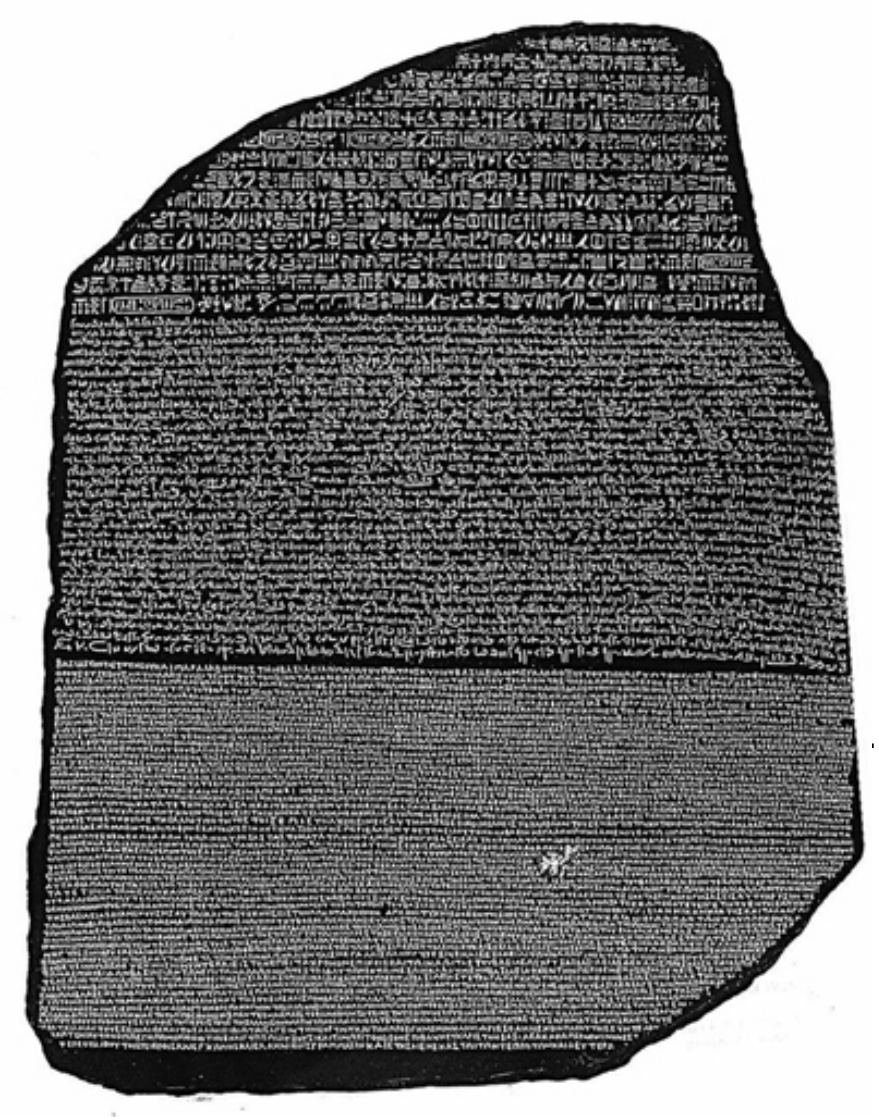
Persistent eGFR <60 mL/min/1.73 m^2

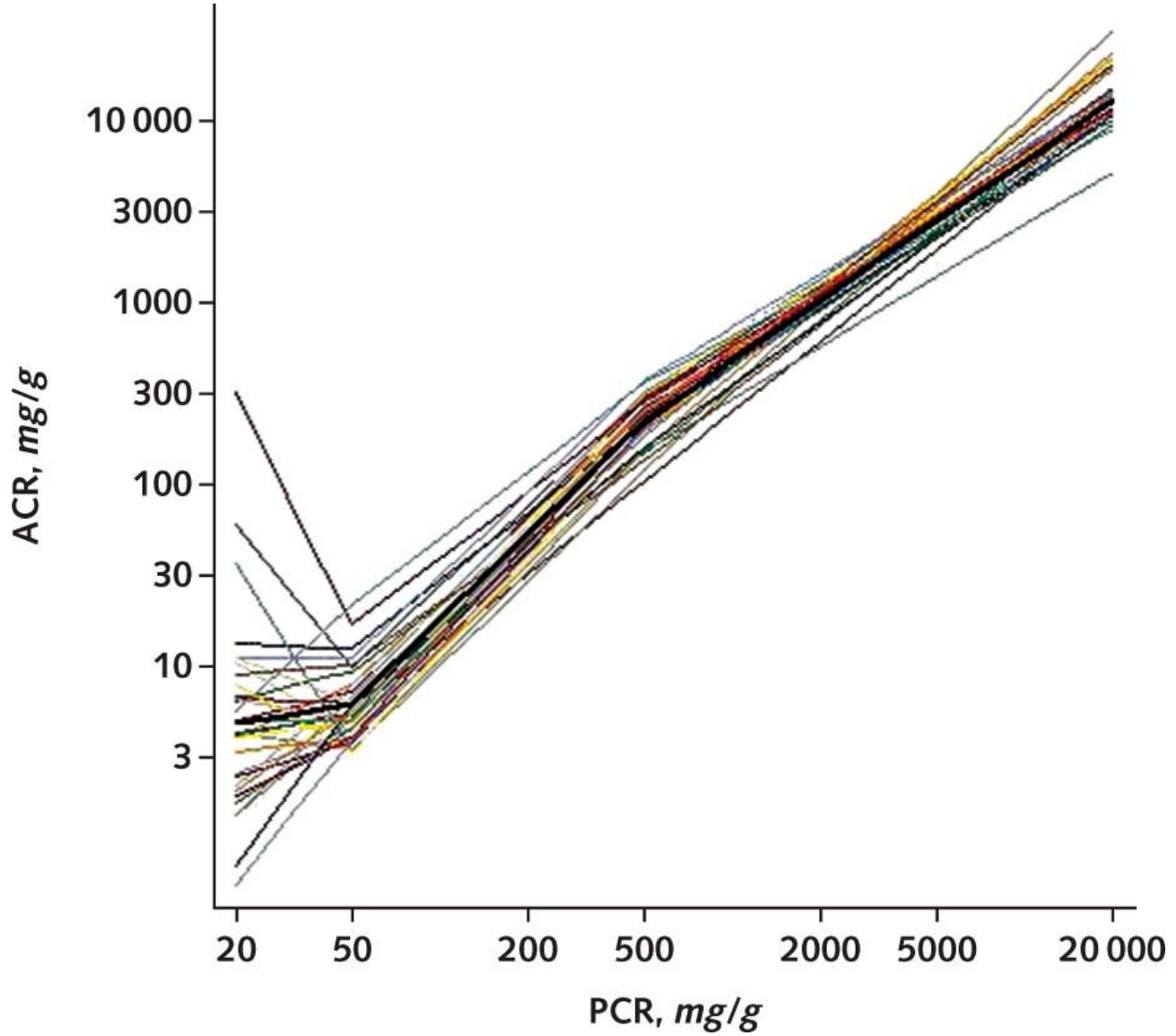
and/or

Other evidence of kidney damage

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45(12):3075-3090.

Conversion of Urine Protein–Creatinine Ratio to Urine Albumin–Creatinine Ratio





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

Albuminuria and Proteinuria Tests Approximate Equivalents

Albuminuria Or Proteinuria Description+	Albuminuria Or Proteinuria Category	Albumin mg/24-hour urine+	uACR+ mg/g	uPCR* mg/g	Dipstick Proteinuria
Normal to mildly increased	A1	< 30	< 30	< 150*	Negative to trace
Moderately increased	A2	30 to 300	30 to 300	150 to 650*	Trace to +1
Severely Increased	A3	> 300	> 300	> 650*	+2 or greater
Nephrotic Range	A3 Nephrotic Range	>2,000*	>2,000*	>3,500+ (by definition)	+2 or greater

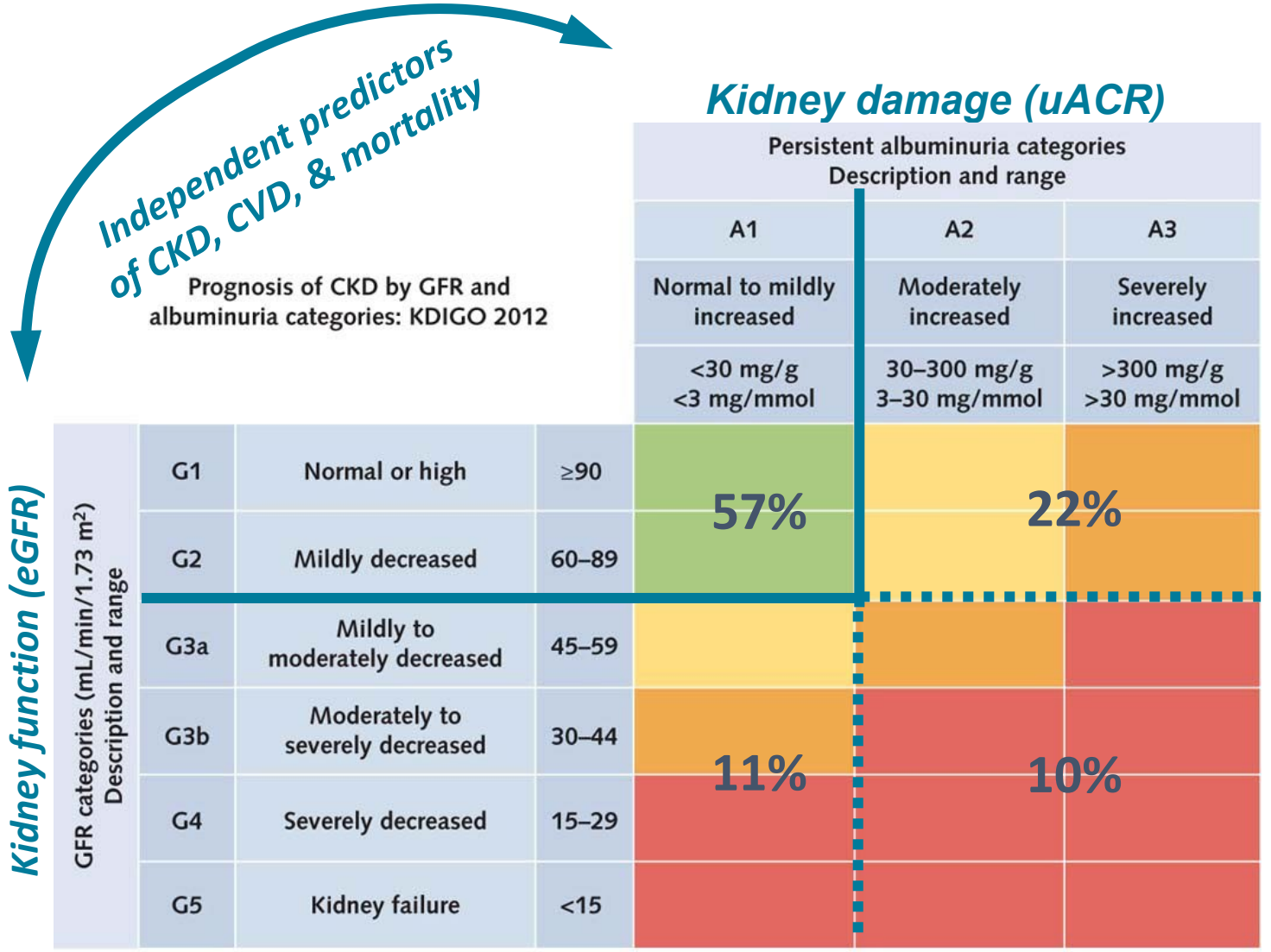
+These categories are adapted from KDIGO; Kidney Disease Improving Global Outcomes.

*These categories are from a meta-analysis of uPCR to uACR approximate conversion. Ann Intern Med 2020;173(6):426-435

This Table is in press in Clinical Chemistry 2023

Missing Albuminuria is a Missed Opportunity

- Both tests must be used
  - to identify new or undiagnosed CKD
  - to risk-stratify patients with CKD
- CKD diagnosis: decreased kidney function or increased damage for ≥ 3 months
  - eGFR < 60 ml/min/1.73m^2 **or**
  - uACR ≥ 30 mg/g
- **Half** of patients with T2D & CKD had elevated uACR *without* decreased eGFR (22% of 43%)
  - These patients would not be identified by eGFR alone.



Green, low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

BMC Res Notes. 2014 Jul 2;7:415. doi: 10.1186/1756-0500-7-415.

Kidney Health Evaluation for Patients with Diabetes HEDIS+ Measure

Measure =

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

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

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

+Healthcare Effectiveness Data and Information Set beginning measurement year 2020

https://www.ncqa.org/hedis/measures/kidney-health-evaluation-for-patients-with-diabetes/

Kidney Health Evaluation for Patients with Diabetes
Low Measure Satisfaction

Year	Commercial HMO	Commercial PPO	Medicaid HMO	Medicare HMO
2021 (%)	43.9	39.6	33.5	44.2

Missing albuminuria is a missed opportunity.

https://www.ncqa.org/hedis/measures/kidney-health-evaluation-for-patients-with-diabetes/

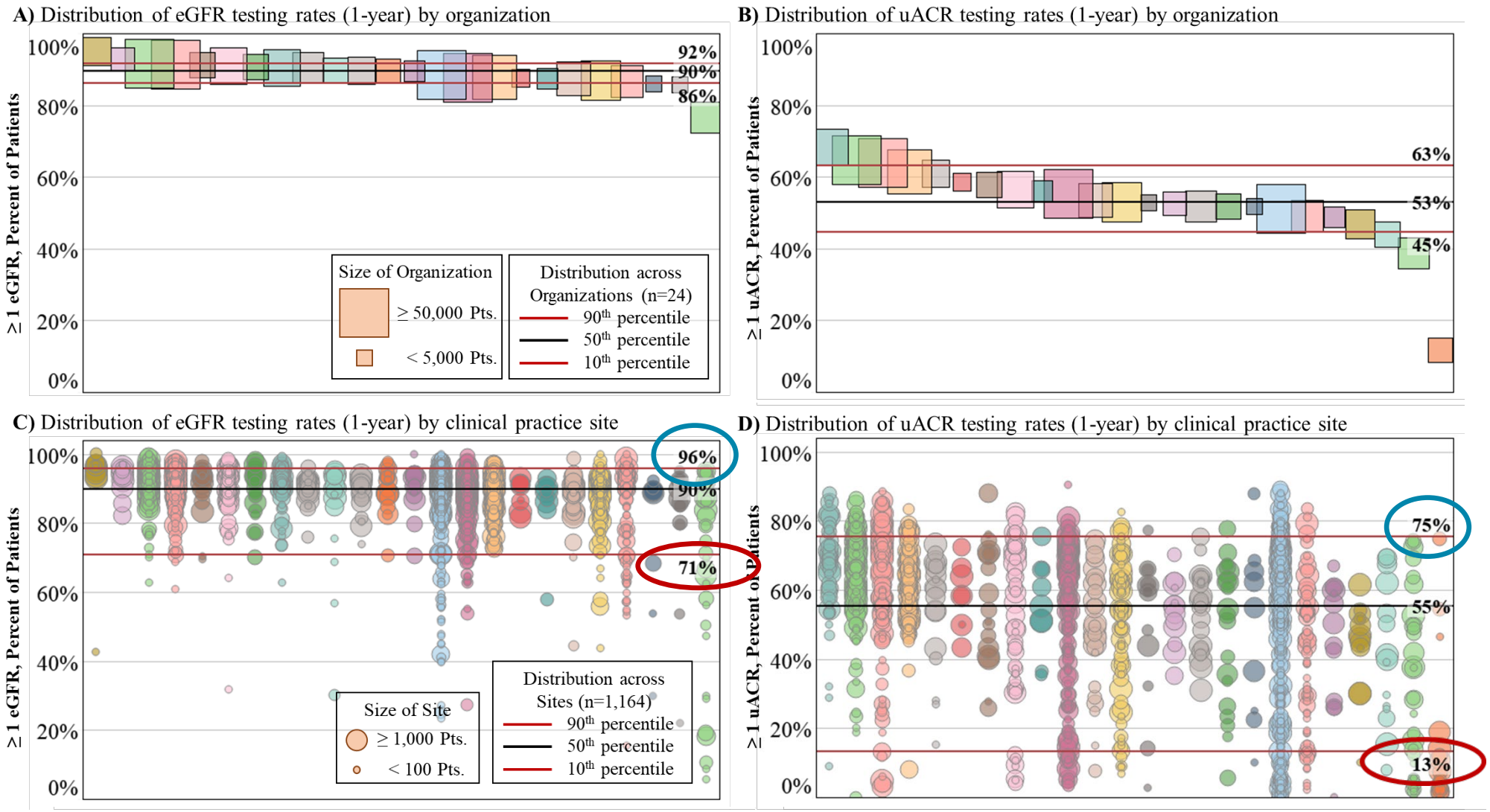
CKD Testing Among T2DM in US Healthcare Organizations

Albuminuria is most often Missing.

Many organizations have at least 1 site among the **Lowest-** & **highest-** performing sites across all organizations.

Even high testing organizations have improvement opportunities.

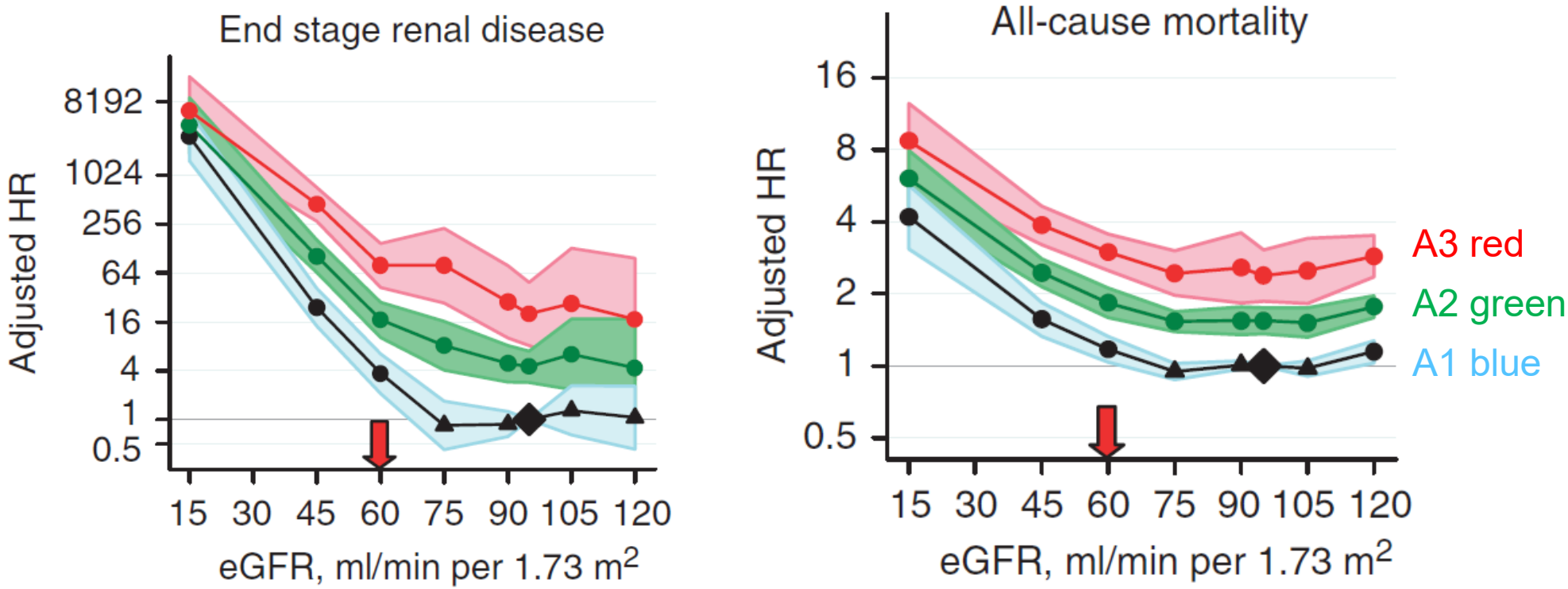
Figure 1: eGFR (panels: A, C) and uACR (panels: B, D) 1 year measurement rates by HCO (panels: A, B) and sites of care within HCOs (panels: C, D)



Each square reflects a different healthcare organization (HCO) which are ranked (horizontally) in descending order based on measurement rates. Each set of colored circles reflects the sites of care within the respective HCO with the same color above.

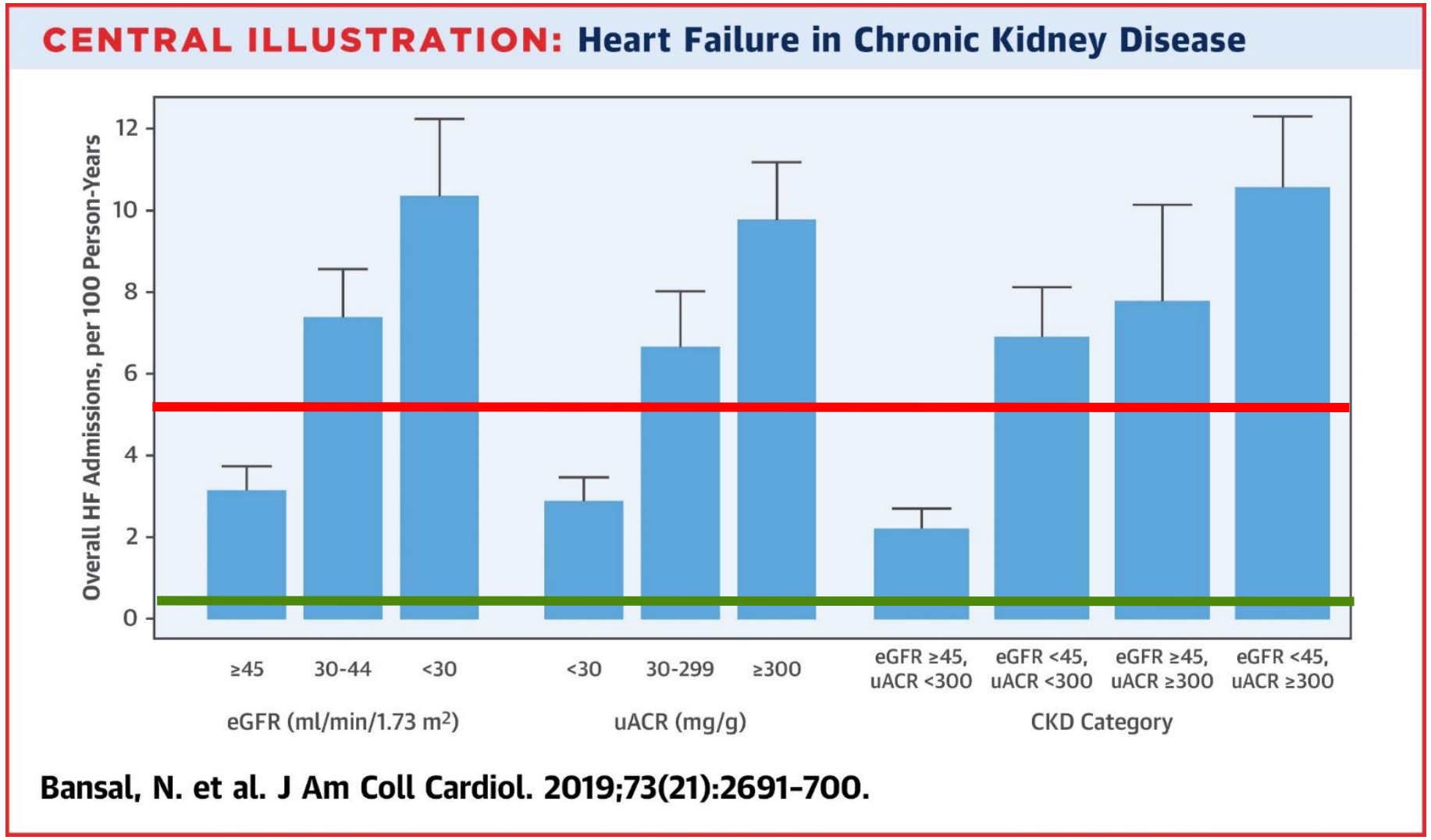
Diabetes Care 2021; 44:2000–2009

Low eGFR and Albuminuria Predict Kidney Failure and Mortality



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

Heart Failure Hospitalization by eGFR and Albuminuria (uACR)

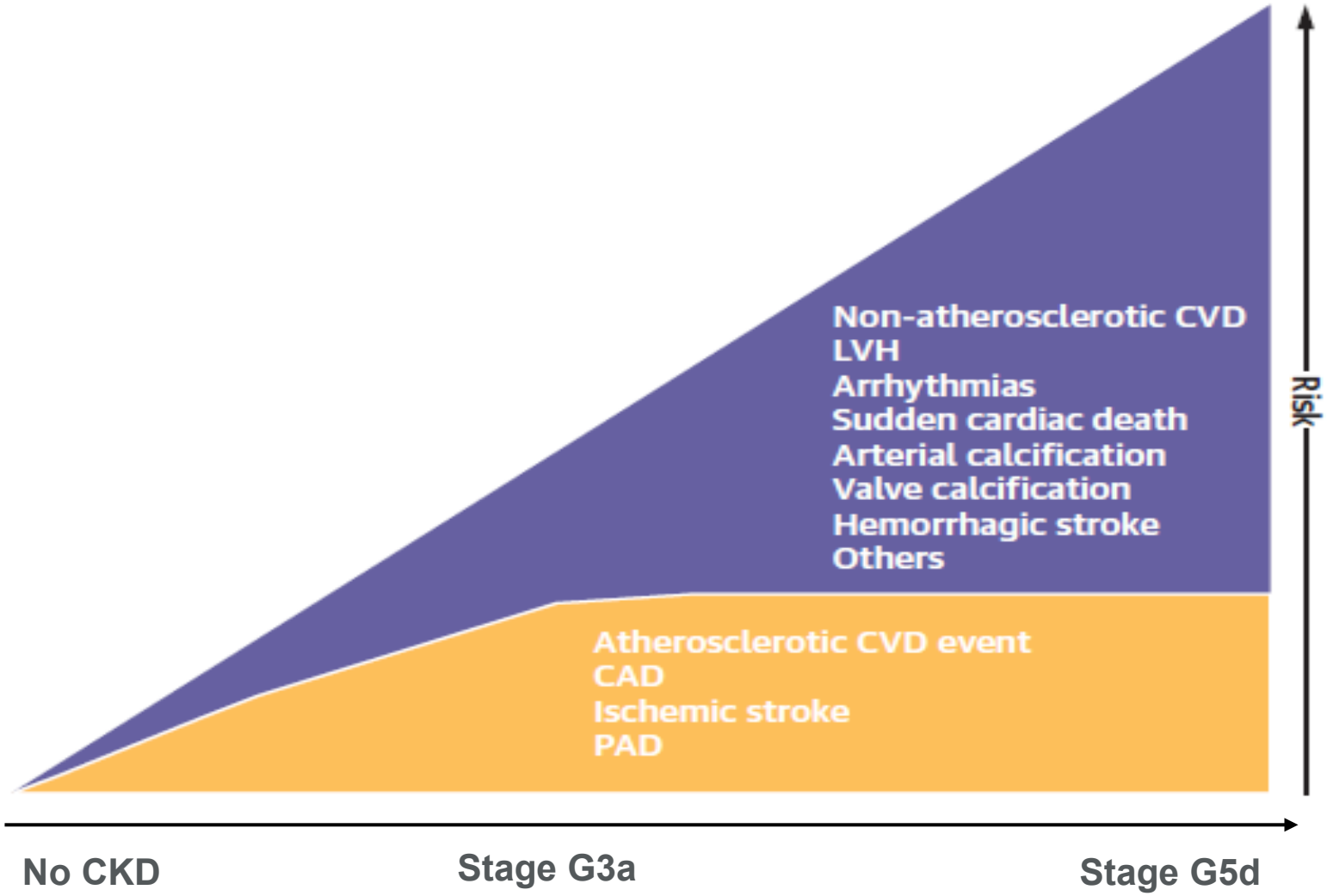


CRIC cohort n = 3,791, unadjusted rates shown, & Figure adapted

Crude CRIC (CKD) cohort rate 5.8

Crude general population rate 0.5

In CKD, the natural history of CVD is different from the General Population with more non-atherosclerotic disease



CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; PAD, peripheral artery disease

Wanner C, et al. Lancet 2016;388:276-284

Case Presentation

- 65-year-old man
- Type-2 diabetes since 2005, dyslipidemia and hypertension complicated by HFpEF and CAD s/p MI and LAD ICS.
- Diabetic retinopathy
- Medications: lisinopril 20 mg daily, metoprolol succinate 100 mg daily, clopidogrel 75 mg daily, aspirin 81 mg daily, atorvastatin 40 mg daily, & insulin lispro and glargine.
- BP 142/78 P 72

- How would you test for CKD and evaluate risk?
- Creatinine 1.40 + eGFR 46 = CKD G3a
- uACR 2200 mg/g = CKD A3 or CKD G3aA3 (chronicity defined 3 or more months)

Classification of CKD

- Cause (C)
- GFR (G)
- Albuminuria (A)

KDIGO 2012

				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
GFR Categories, Description and Range (mL/min/ 1.73 m^2)	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			

Heat Map and Frequency of Visits

KDIGO Heat Map

Guide to Frequency of Monitoring (number of times per year) + Referral decision making by GFR and Albuminuria Category

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	1 if CKD	1 Monitor	2 Refer*
	G2	Mildly decreased	60-89	1 if CKD	1 Monitor	2 Refer*
	G3a	Mildly to moderately decreased	45-59	1 Monitor	2 Monitor	3 Refer
	G3b	Moderately to severely decreased	30-44	2 Monitor	3 Monitor	3 Refer
	G4	Severely decreased	15-29	3 Refer*	3 Refer*	4+ Refer
	G5	Kidney failure	<15	4+ Refer	4+ Refer	4+ Refer

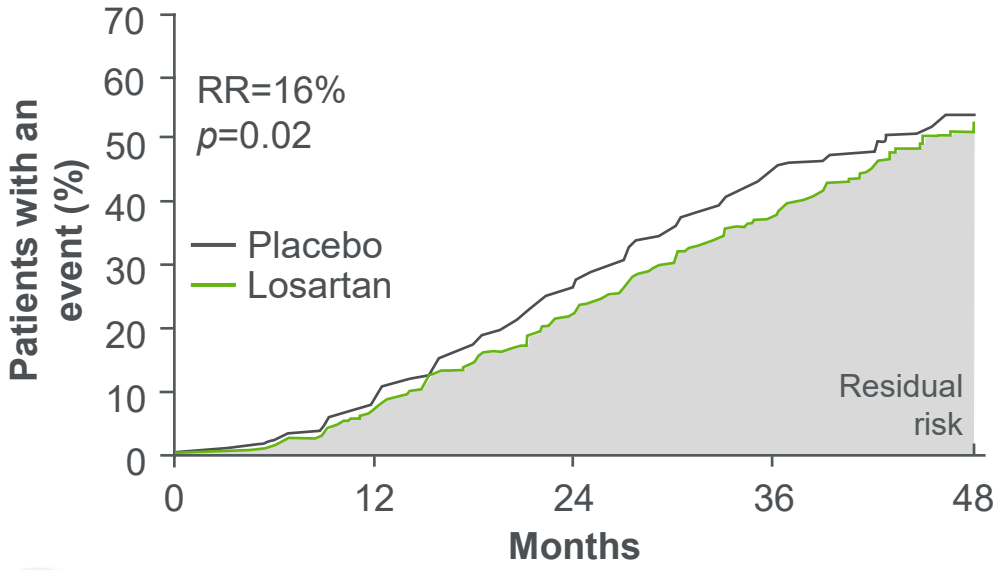
GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). The words in the boxes are a guide for referral decision making (monitor or referral to specialist kidney care services). *Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring.

KDOQI US Commentary on the 2012 KDIGO Evaluation and Management of CKD. Am J Kidney Dis 2014;63(5):713-735.

Despite RAS blockade, patients with T2DM and advanced CKD are at risk of CKD progression

RENAAL: Losartan vs placebo[1]

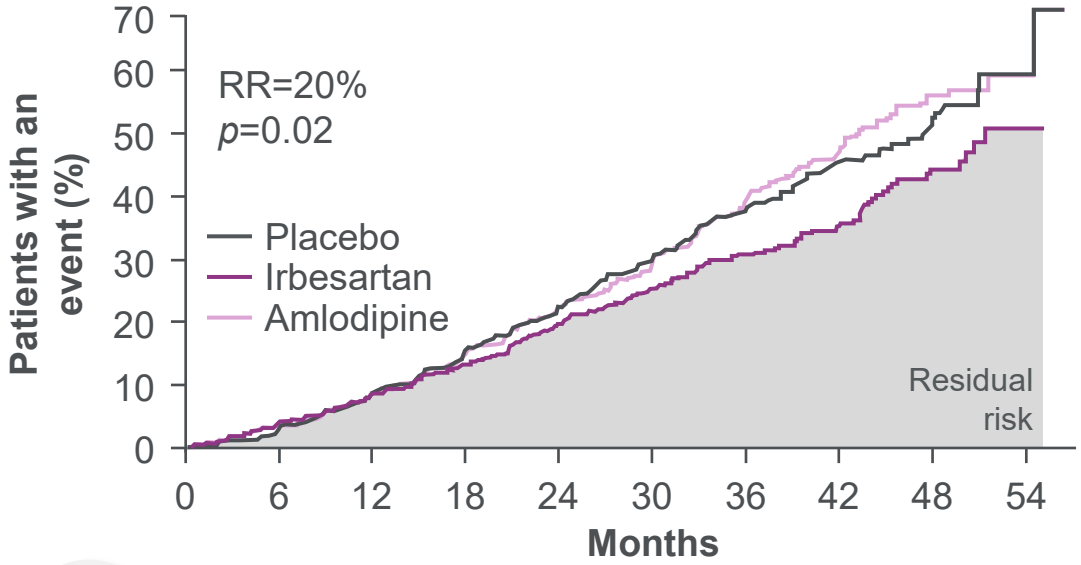
Primary composite endpoint:
Doubling of SCr, kidney failure or death



Patients with severely increased albuminuria: 100%
Median uACR: 1249 mg/g

IDNT: Irbesartan vs amlodipine vs placebo[2]

Primary composite endpoint:
Doubling of SCr, kidney failure or death



Patients with severely increased albuminuria: 100%
Median uACR: 1900 mg/g

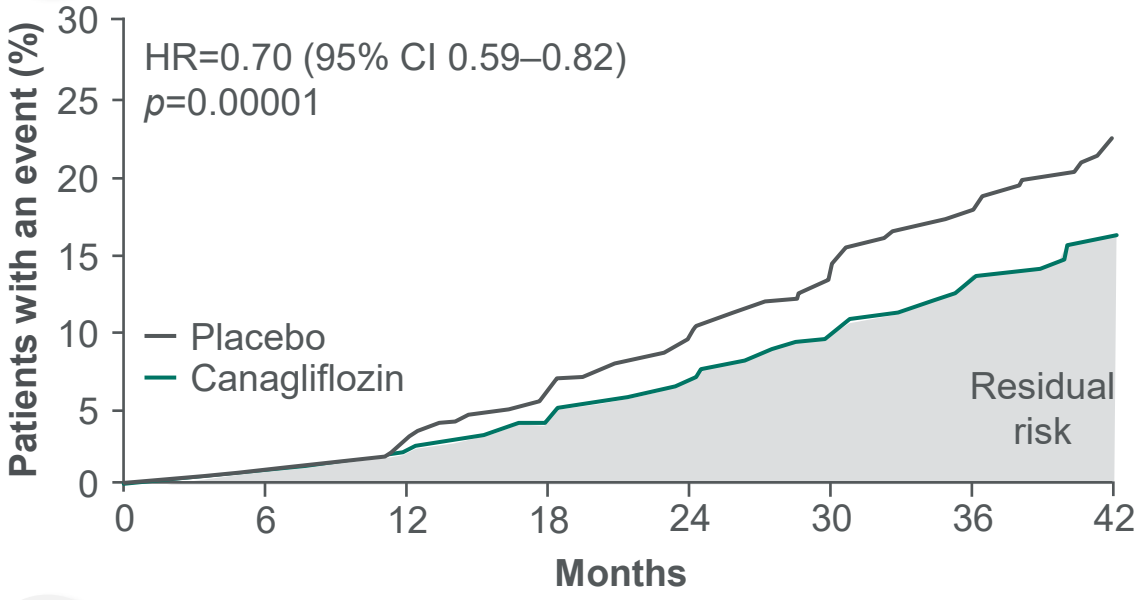
RAS, renin–angiotensin system; RR, risk reduction; SCr, serum creatinine; SOC, standard of care

1. Brenner BM, *et al. N Engl J Med* 2001;345:861–869; 2. Lewis EJ, *et al. N Engl J Med* 2001;345:851–860

Despite RAS blockade and SGLT-2 inhibition, patients with T2DM and advanced CKD are at risk of CKD progression

CREDENCE: Canagliflozin (+ ACEi/ARB) vs placebo[1]

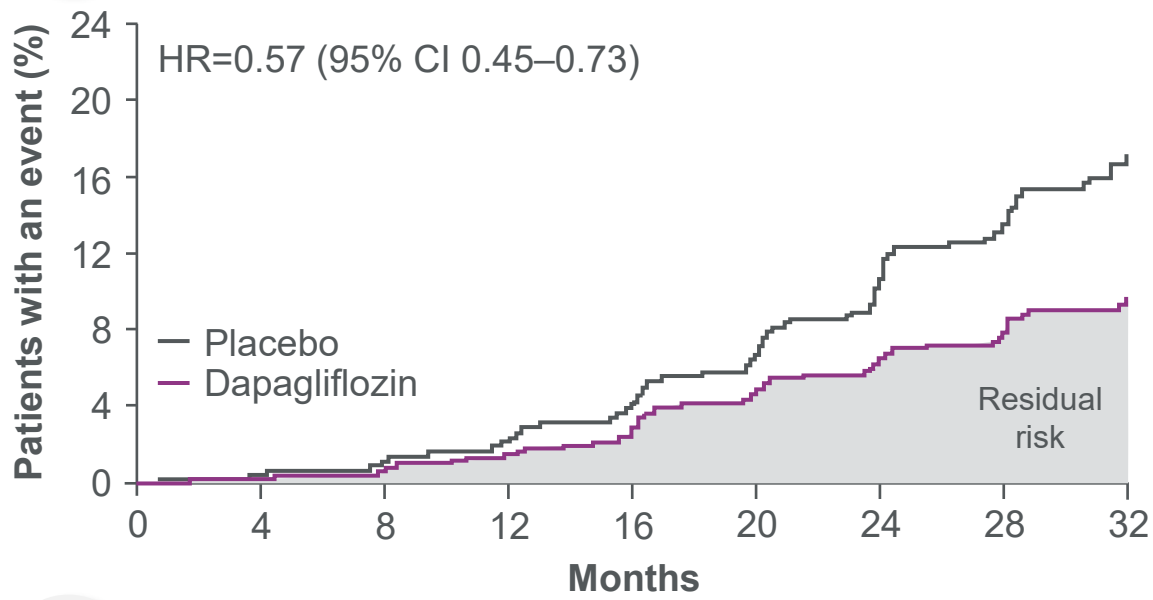
Primary composite outcome:
Kidney failure, doubling of SCr or death from kidney/CV causes



Patients with severely increased albuminuria: 88%
Median uACR: 927 mg/g

DAPA-CKD: Dapagliflozin (+ACEi/ARB) vs placebo (T2D subgroup)[2]

Secondary composite renal outcome:
Sustained ≥50% eGFR decline, ESKD or renal death

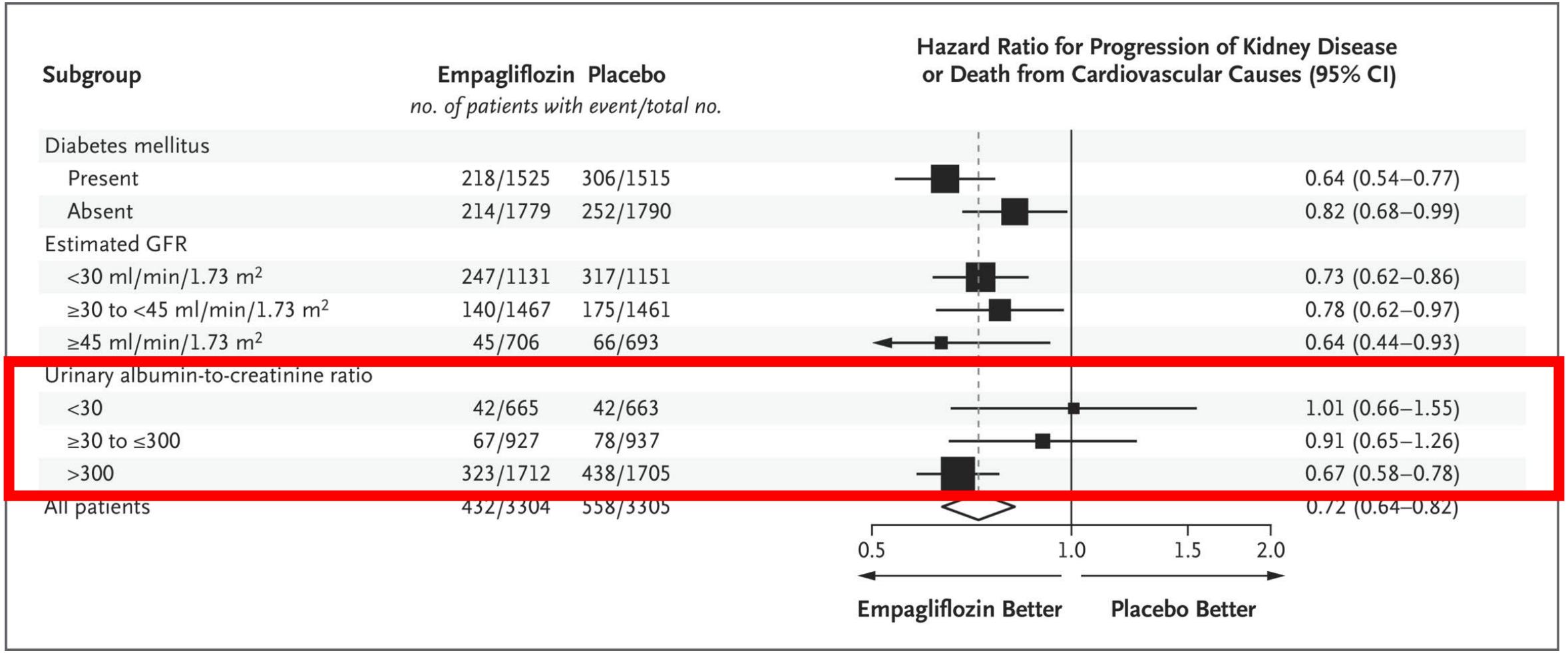


Patients with severely increased albuminuria: 89.7%
Median uACR: 949 mg/g

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; NNT, number needed to treat; SGLT-2, sodium-glucose co-transporter-2

1. Perkovic V, *et al*. *N Engl J Med* 2019;380:2295–2306; 2. Wheeler DC, *et al*. *Lancet Diabetes Endocrinol* 2021;9:22–31

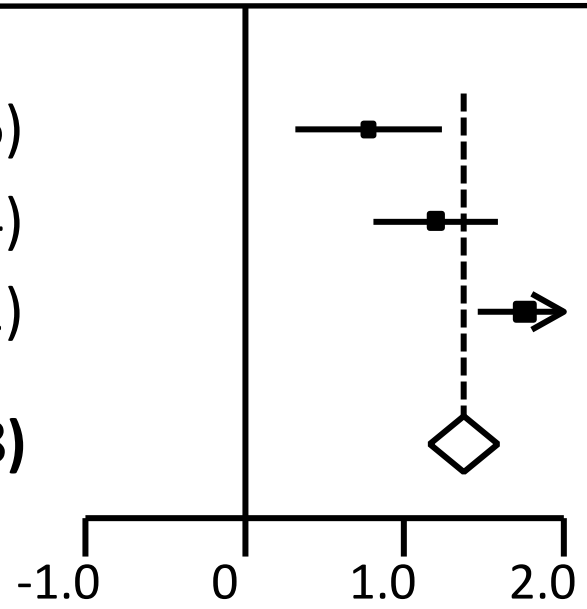
EMPA-KIDNEY Primary Outcome
Empagliflozin vs Placebo – Impact of Albuminuria



Primary Outcome = CKD progression or cardiovascular mortality
N Engl J Med 2023;388:117-127

EMPA-KIDNEY eGFR Slopes by Albuminuria: Benefit across albuminuria levels

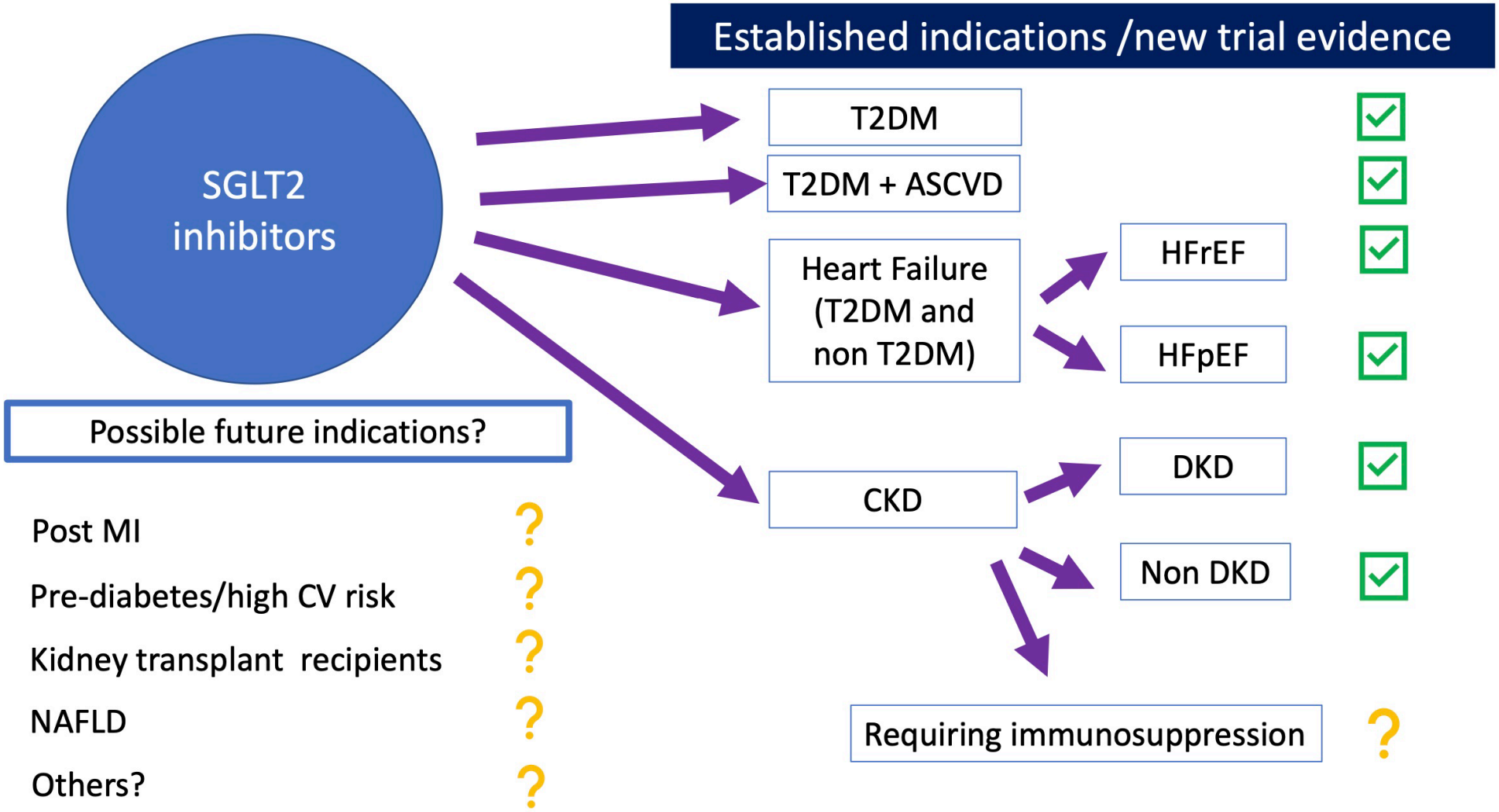
uACR (mg/g)	Mean slope (SE) mL/min/1.73m²/year Empagliflozin	Placebo	Difference between mean slopes (95% CI)	
<30	-0.11 (0.17)	-0.89 (0.16)	**0.78**	(0.32, 1.23)
≥30 <300	-0.49 (0.14)	-1.69 (0.14)	1.20	(0.81, 1.59)
≥300	-2.35 (0.11)	-4.11 (0.11)	1.76	(1.46, 2.05)
All	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37**	**(1.16, 1.59)**



Difference of at least **0.5** is considered effective

N Engl J Med 2023;388:117-127

Summary of Evidence-based SGLT-2 Inhibitor Use



Legend

Figure 1. Summary of current evidence-based indications for SGLT2 inhibition. ☑ indicates evidence-based indication for SGLT2 inhibition. ? indicates areas where more data are needed. Abbreviations: ASCVD- Atherosclerotic Cardiovascular Disease, CKD- chronic kidney disease, DKD- diabetic kidney disease, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction, MI- myocardial infarction, NAFLD- non-alcoholic fatty liver disease, T2DM- type 2 diabetes mellitus.

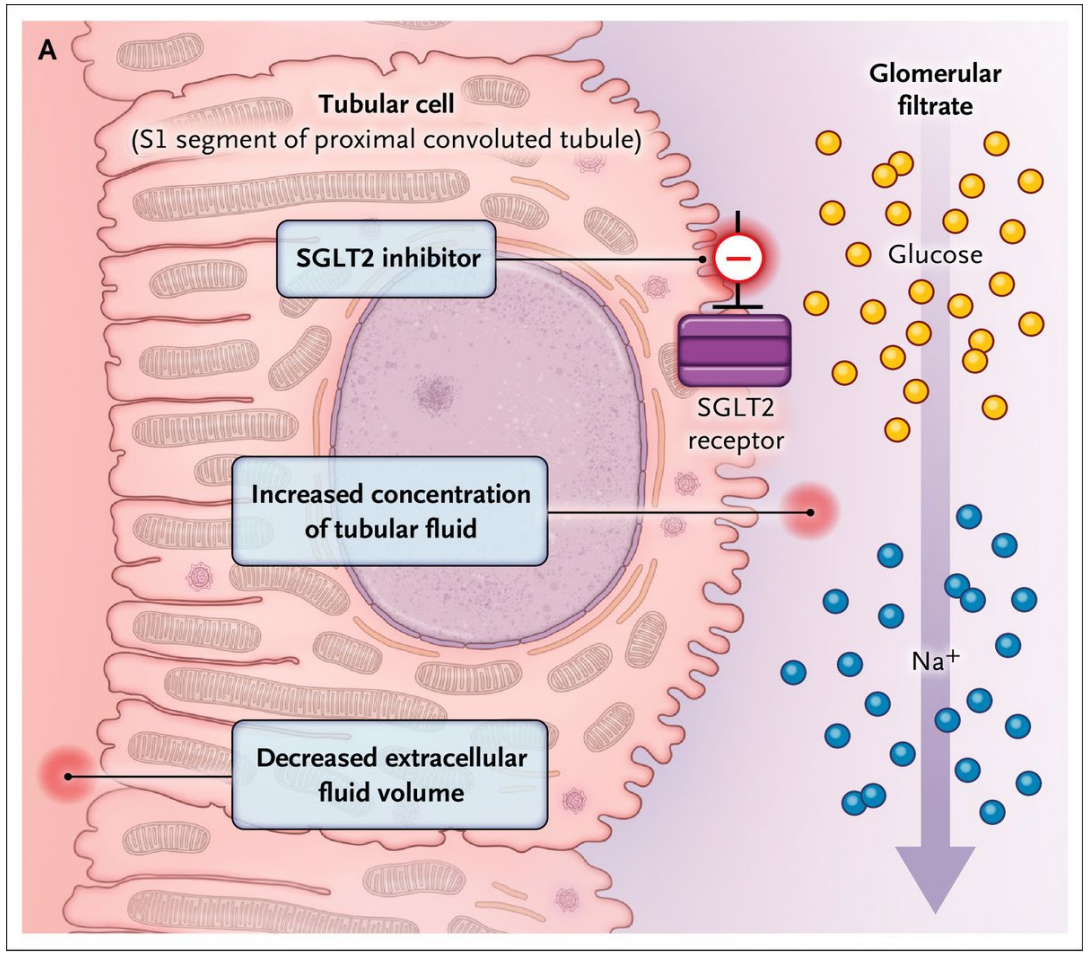
Lancet 2022:400(10365): 1745-1747

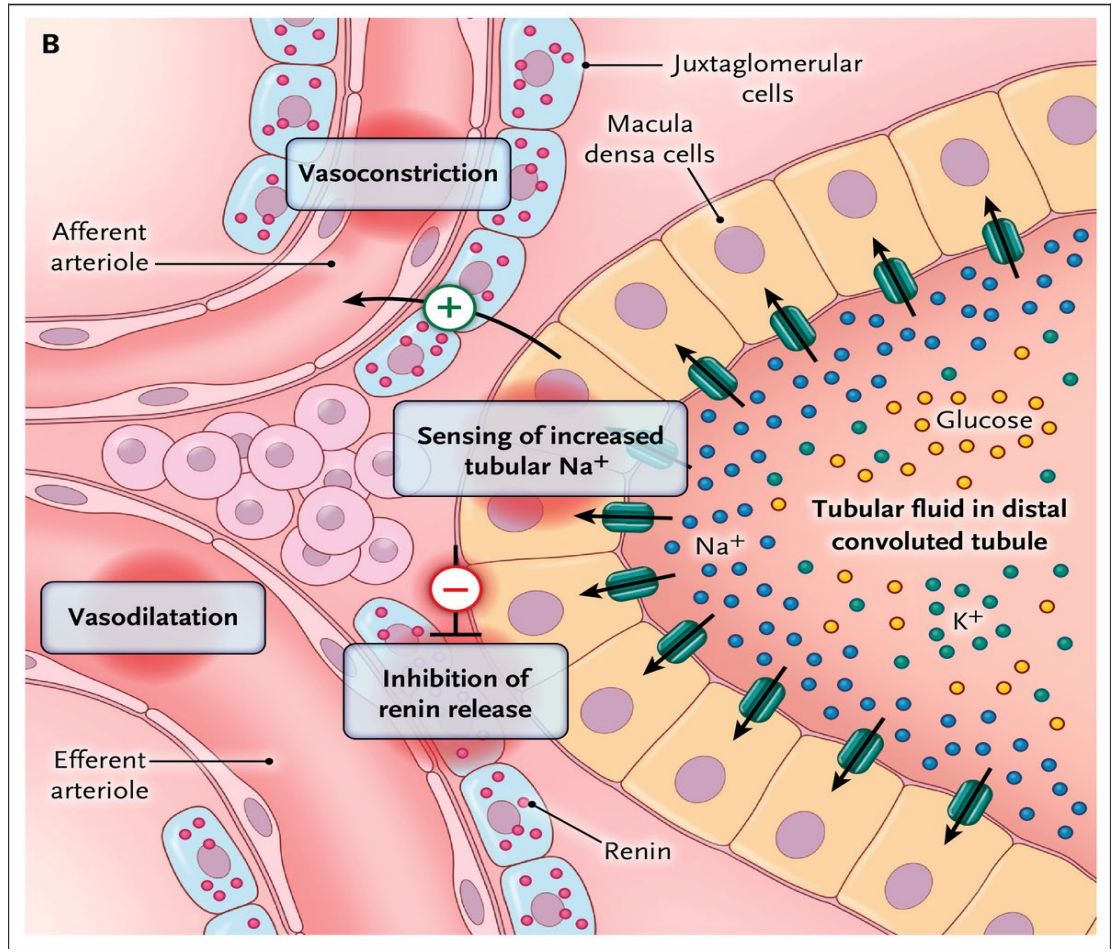
What do the clnical practice guidelines say about SGLT-2 inhibitors in CKD?

In summary, most current guidelines agree with the recommendation to use SGLT2i in CKD (grade 1A where reported) with minor differences in eGFR thresholds, but with substantial variation regarding albuminuria levels (if any). Most guidelines also mention that SGLT2i can be continued up to the initiation of renal replacement therapy or kidney transplantation. From a glycemic therapy, SGLT2i have evolved into organ-protective therapy with several indications and a solid evidence base.

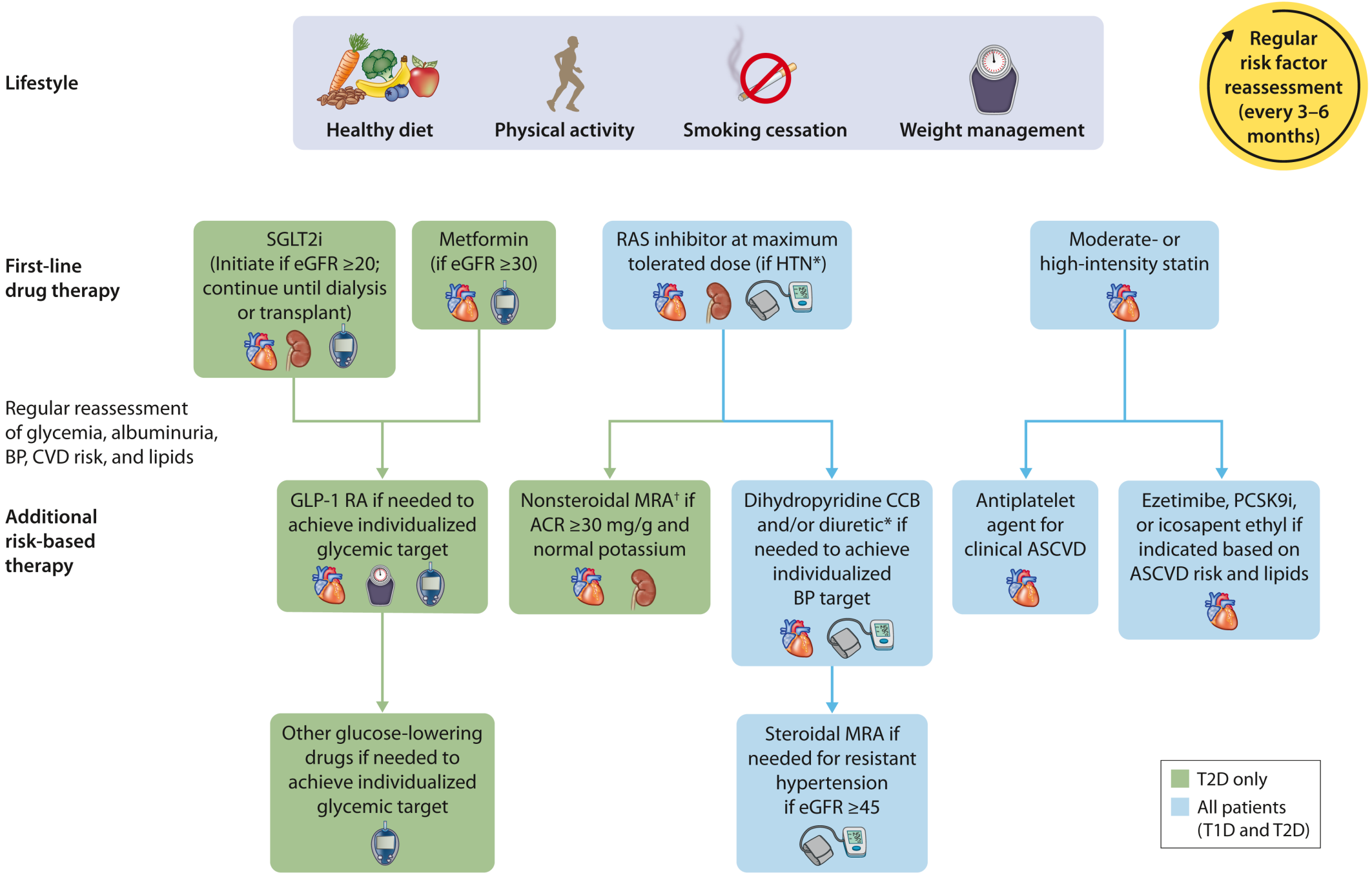
Zhang, RM, Persson, F, McGill, JB, Rossing P. NDT 2023; 38:542-550.

Effects of SGLT-2 Inhibition





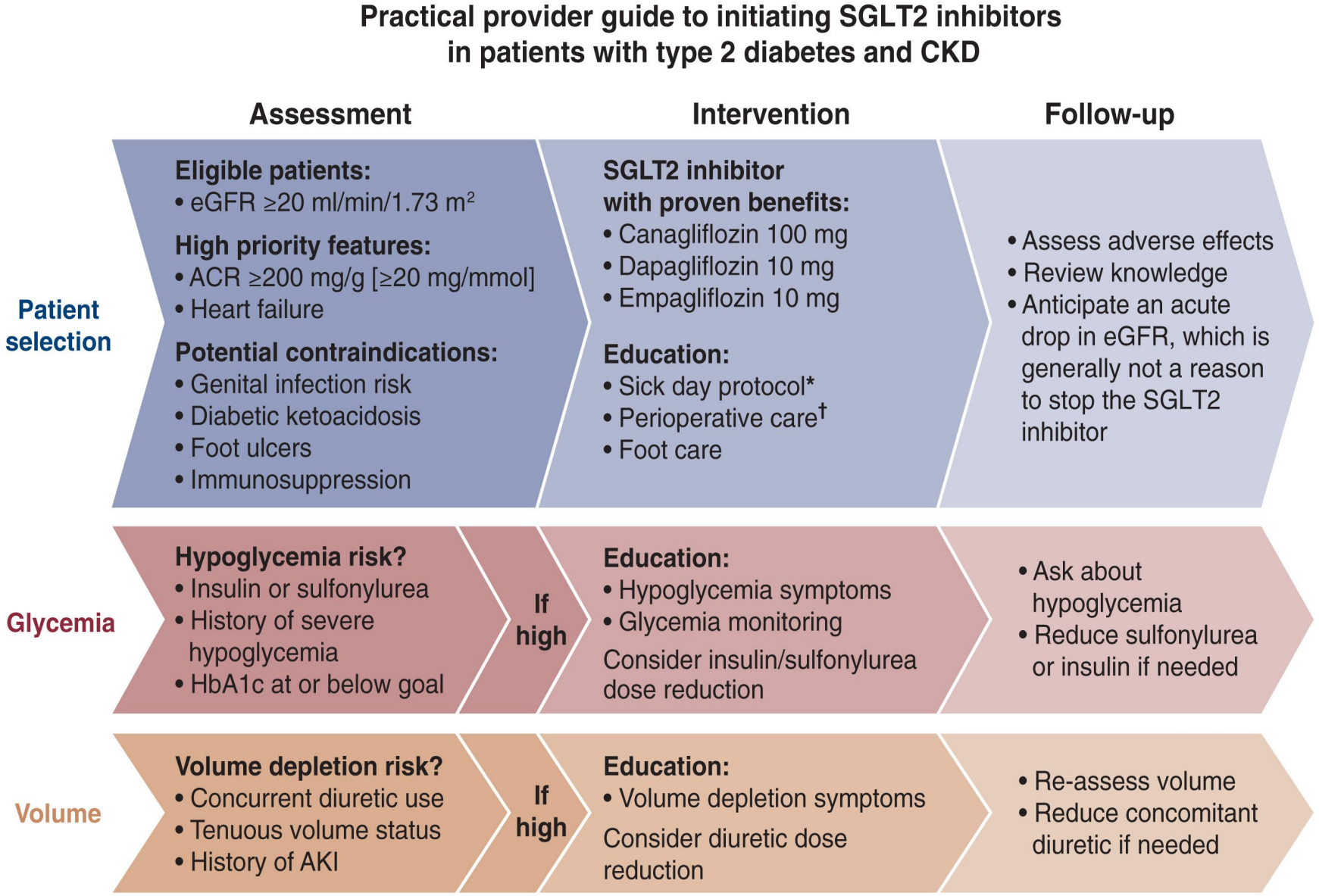
Brunwald E. N Engl J Med 2022; 386: 2024-2034



KDIGO Diabetes in CKD
Kidney Int 2022;102
(Suppl S5):S1-S127

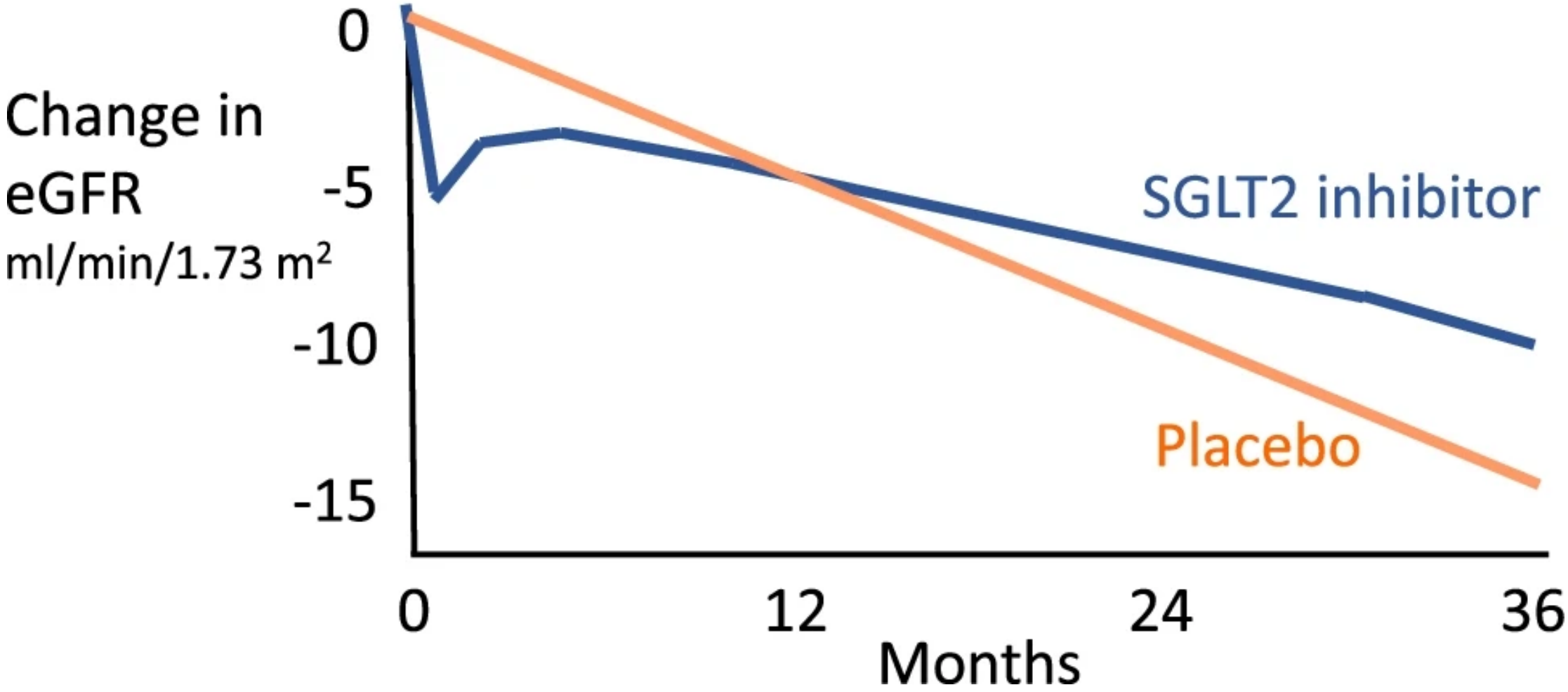
Patient Selection, Intervention and Follow-up for SGLT-2 inhibitor Use in CKD with T2D

Recommendation 1.3.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.



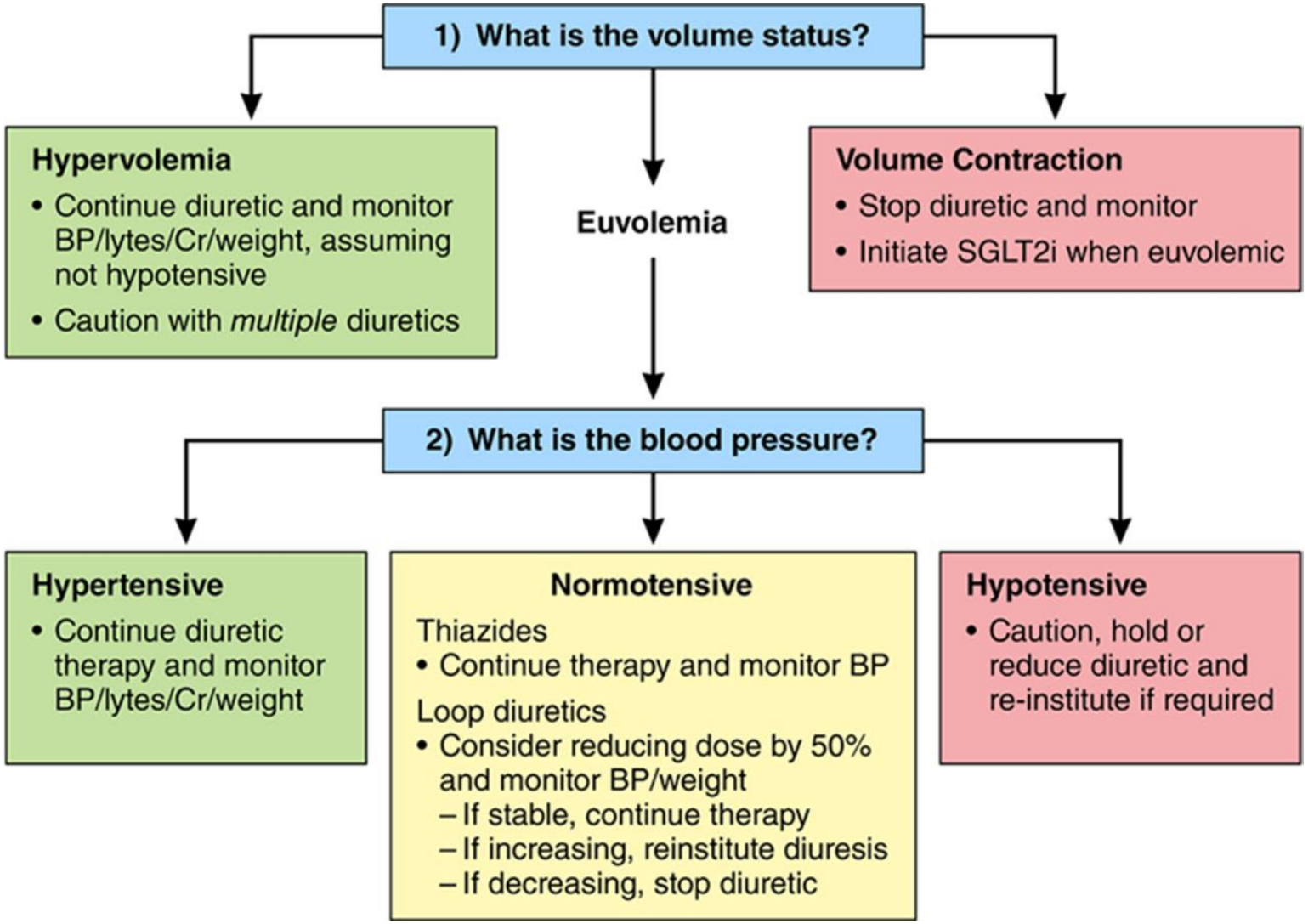
Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int 2022;102(5S):S1–S127.

Expect Hemodynamic Loss of eGFR in the First 4 Weeks After Starting an SGLT-2 Inhibitor



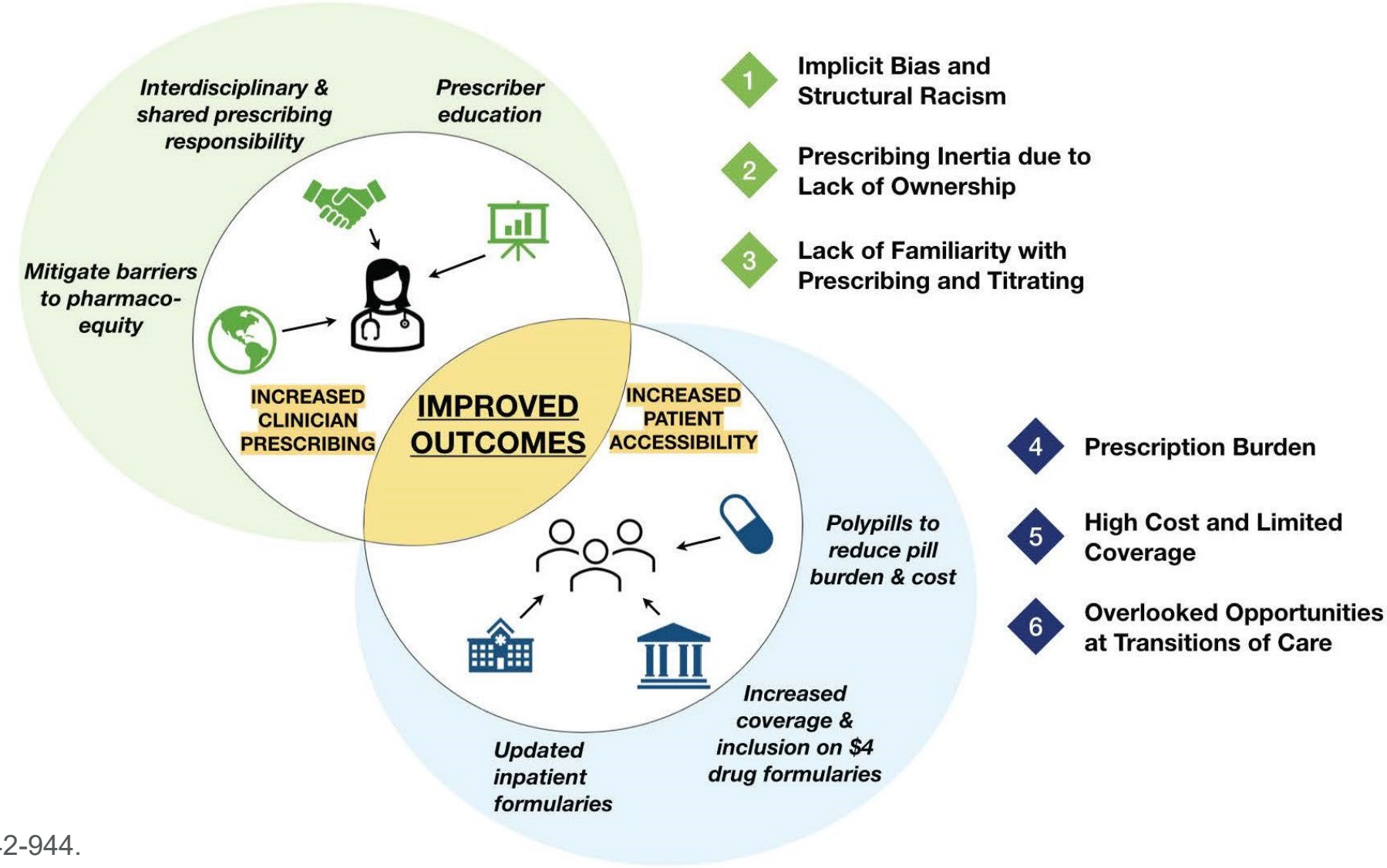
Curr Diab Rep 2022;22(1):39-52. Concept slide loosely based on EMPA-REG, CREDENCE and DAPA-CKD trials

An Approach to Diuretic Use With SGLT-2 inhibitors



Circulation 2016; 134(24):915-1917

Achieving Equitable Access to SGLT-2 inhibitors and Finerenone

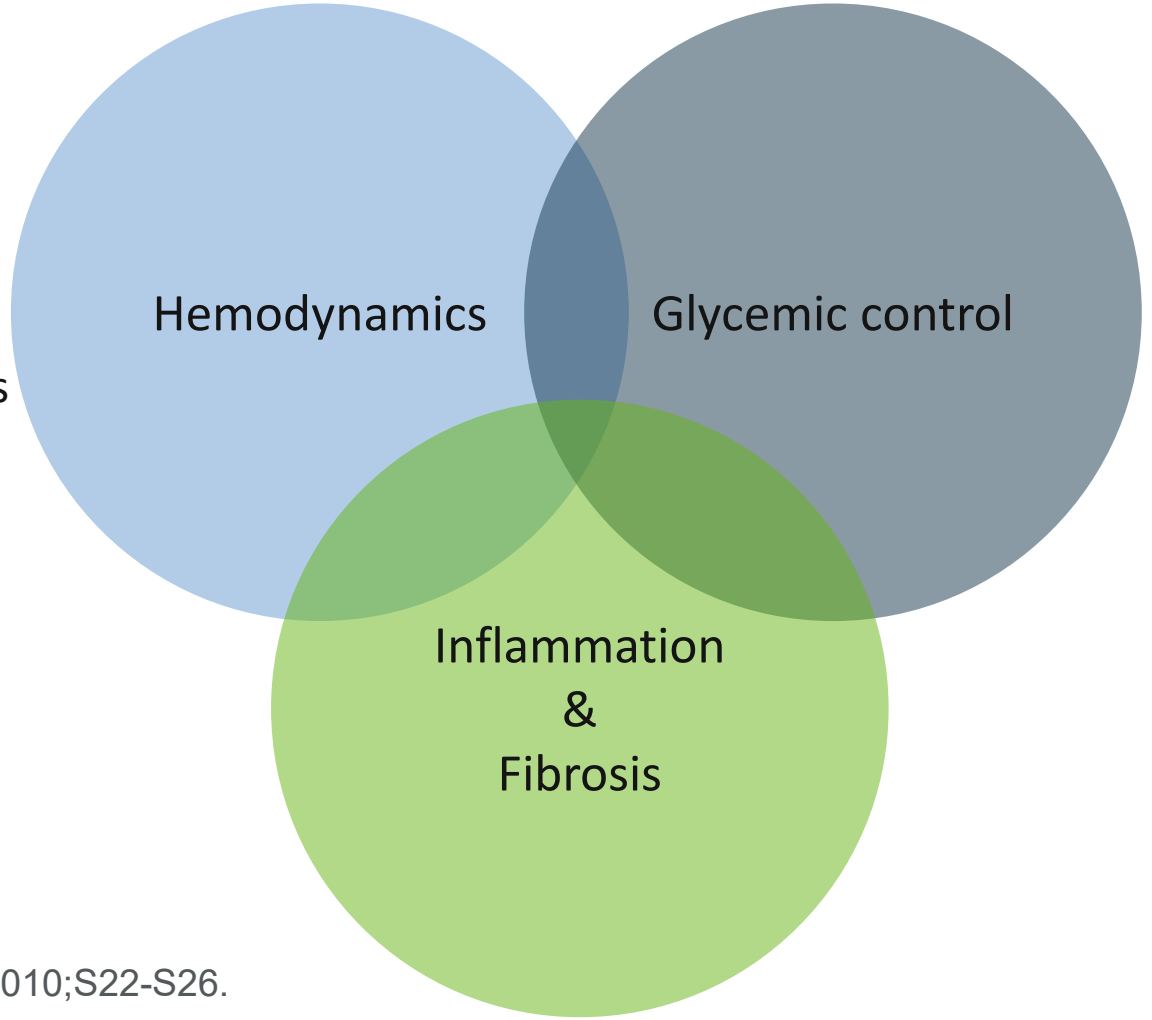


Kidney360. 2022;3(5)942-944.

Annals Int Med 2023;176(3):417-418.

Strategies to Slow Progression of Chronic Kidney Disease

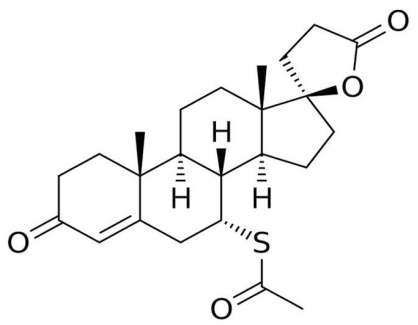
ACE inhibitors
ARBs
SGLT-2 inhibitors

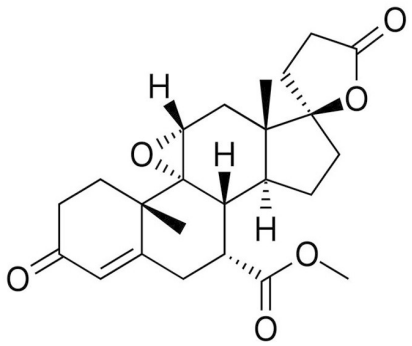


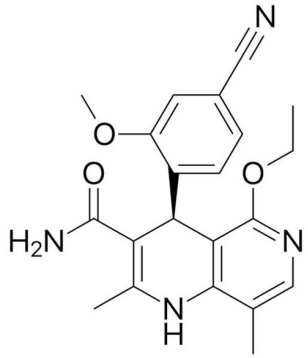
Metformin,
SGLT-2 inhibitors
(several mechanisms may be independent of glucose–lowering)

Lee SB, et al. *Kidney Int Suppl*. 2010;S22-S26.

Mineralocorticoid Receptor Antagonists







	Spironolactone	Eplerenone	Finerenone
Structure	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
Tissue distribution	Kidney > heart	Kidney > heart	Balanced kidney-heart
Active metabolites	+++	-	-
Half-life	Long*	4-6 hours	2-3 hours
Sexual side-effects	++	+	-

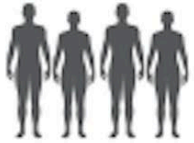
Am J Hypertens. *2023:* 36(3):135-143.https://doi.org/10.1093/ajh/hpac124

Spironolactone versus Finerenone: Comparative Post Hoc Analysis

Methods

FIDELITY-TRH

AMBER



CKD + T2D + TRH

Indirect comparison of a subgroup from the FIDELITY trial, matched to the AMBER trial eligibility criteria

Outcomes:

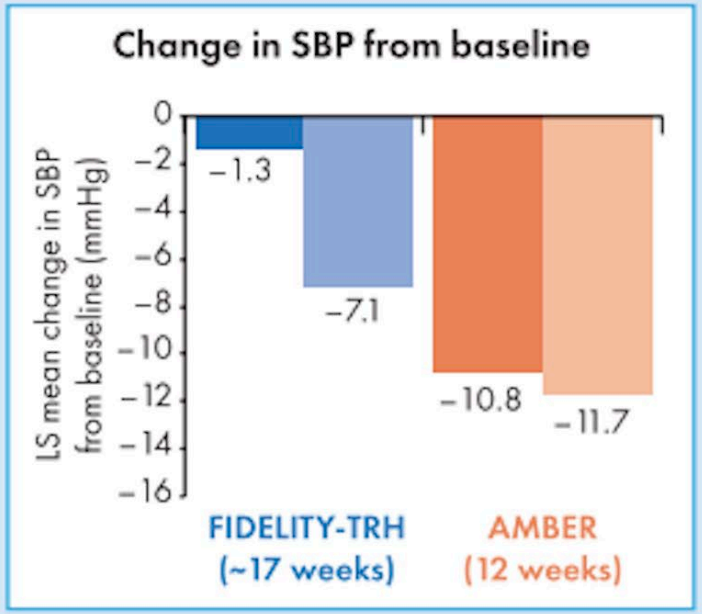
FIDELITY-TRH
At 4 months (~17 weeks)

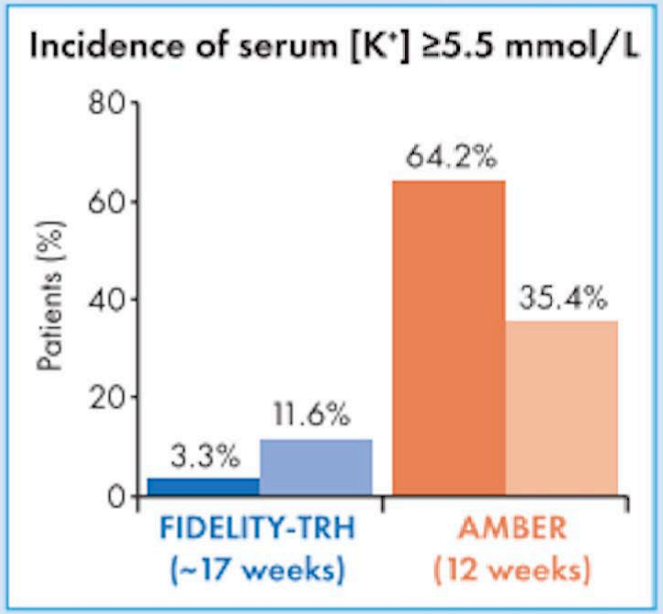
AMBER
At 12 weeks

- Change from baseline in **SBP**
- **Serum [K+]** ≥ 5.5 mmol/L
- **Hyperkalemia** leading to treatment discontinuation

Results

Finerenone reduced **SBP**, although to a lesser extent than **spironolactone** with/without a K^+-binding agent, and resulted in fewer instances of **hyperkalemia** (serum $[K^+] \geq 5.5$ mmol/L).





Placebo | Finerenone | Spironolactone + placebo | Spironolactone + patiromer

Clin Kidney J 2022;16(2):293-302.


Wolfgang Amadeus Mozart
Le Nozze di Figaro
The Metropolitan Opera

Phase III Clinical Trials of Finerenone in T2DM with CKD

FIDELIO-DKD

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven phase III study to investigate the safety and efficacy of finerenone, in addition to standard of care, on the progression of kidney disease in subjects the clinical diagnosis of chronic kidney disease in T2D.[1]

FIGARO-DKD

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven phase III study to investigate the safety and efficacy of finerenone, in addition to standard of care, on the reduction of cardiovascular morbidity and mortality in subjects with the clinical diagnosis of chronic kidney disease in T2D.[2]

1. Bakris GL, et al. *Am J Nephrol*. 2019;50:333-344; 2. Ruilope LM, et al. *Am J Nephrol*. 2019;50:345-356.

Key question posed by the phase 3 finerenone program: FIDELITY analysis

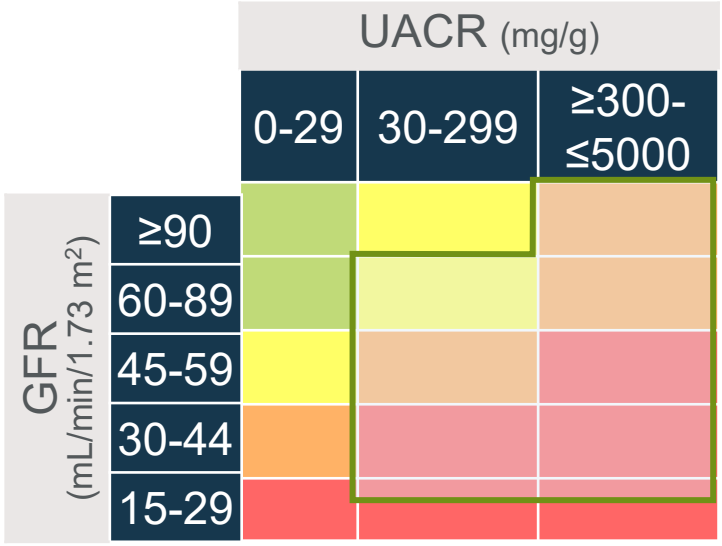
- Does finerenone, a non-steroidal mineralocorticoid receptor antagonist, added to maximized RAS inhibition reduce cardiovascular disease and kidney disease progression over a broad range of chronic kidney disease in people with type 2 diabetes?

Agarwal R, *et al. Eur Heart J* 2021; 42(2):152-161

FIDELITY ANALYSIS: Inclusion & Exclusion criteria

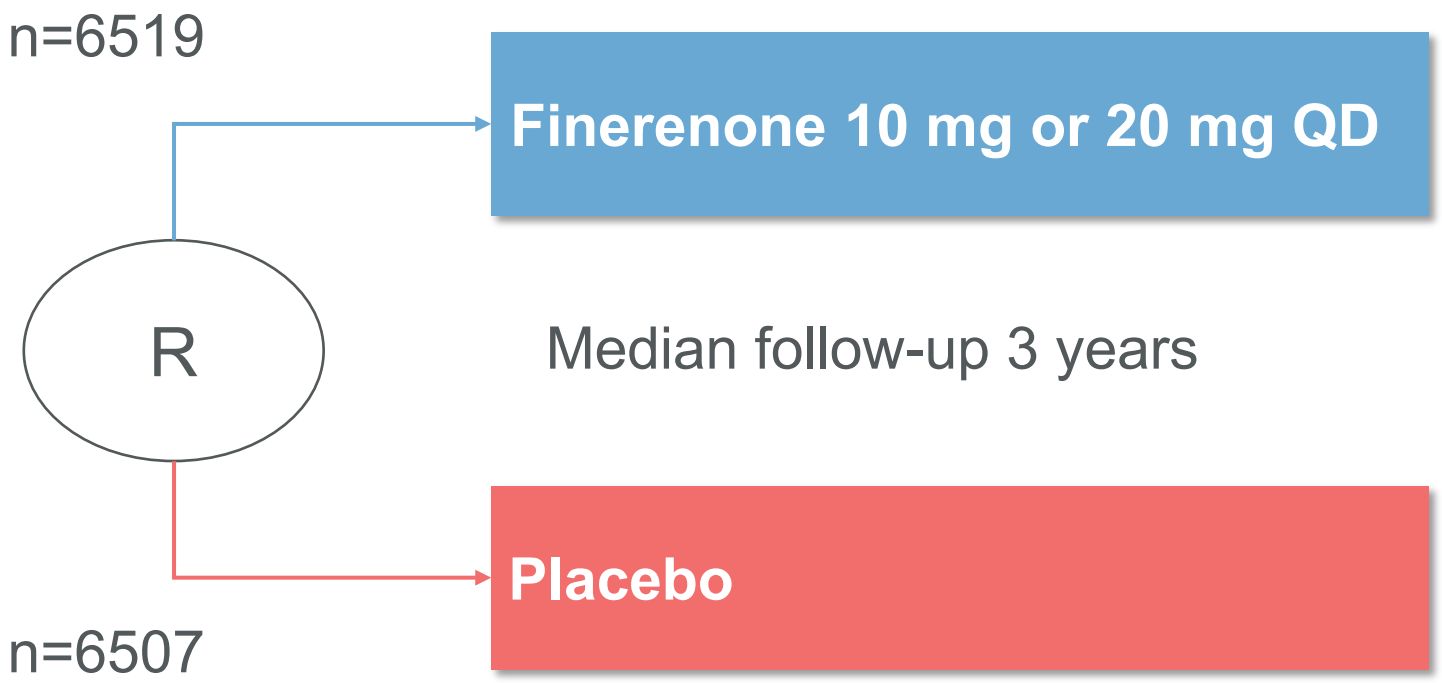
T2D + CKD
eGFR ≥25 mL/min/1.73 m^2
UACR 30-5000 mg/g
Serum [K^+] ≤ 4.8 mmol/L
Maximum tolerated labeled dose of RAS

Symptomatic HFrEF



Agarwal R, *et al. Eur Heart J* 2021; 42(2):152-161

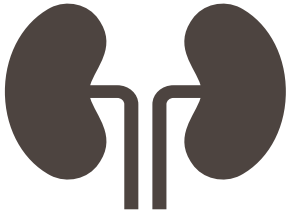
FIDELITY Protocol



Agarwal R, *et al. Eur Heart J* 2021; 42(2):152-161

FIDELITY Outcomes

CV composite:
Time to CV death, non-fatal MI, non-fatal stroke, or HHF



≥57% kidney composite: Time to kidney failure, sustained ≥57% decrease in eGFR, or renal death

Agarwal R, *et al. Eur Heart J* 2021; 42(2):152-161

At baseline, patients had well-controlled blood pressure and HbA1c, and CV medications were used by most patients

Characteristic	Total (n=13,026)
Age, years	65
Male, %	70
Duration of T2D, years	15.4
HbA1c, %	7.7
SBP/DBP, mmHg	**137/76**
History of CV disease, n (%)	**5935 (46)**
History of HF, %	**1007 (7.7)**
Serum [K^+], mmol/l	4.4

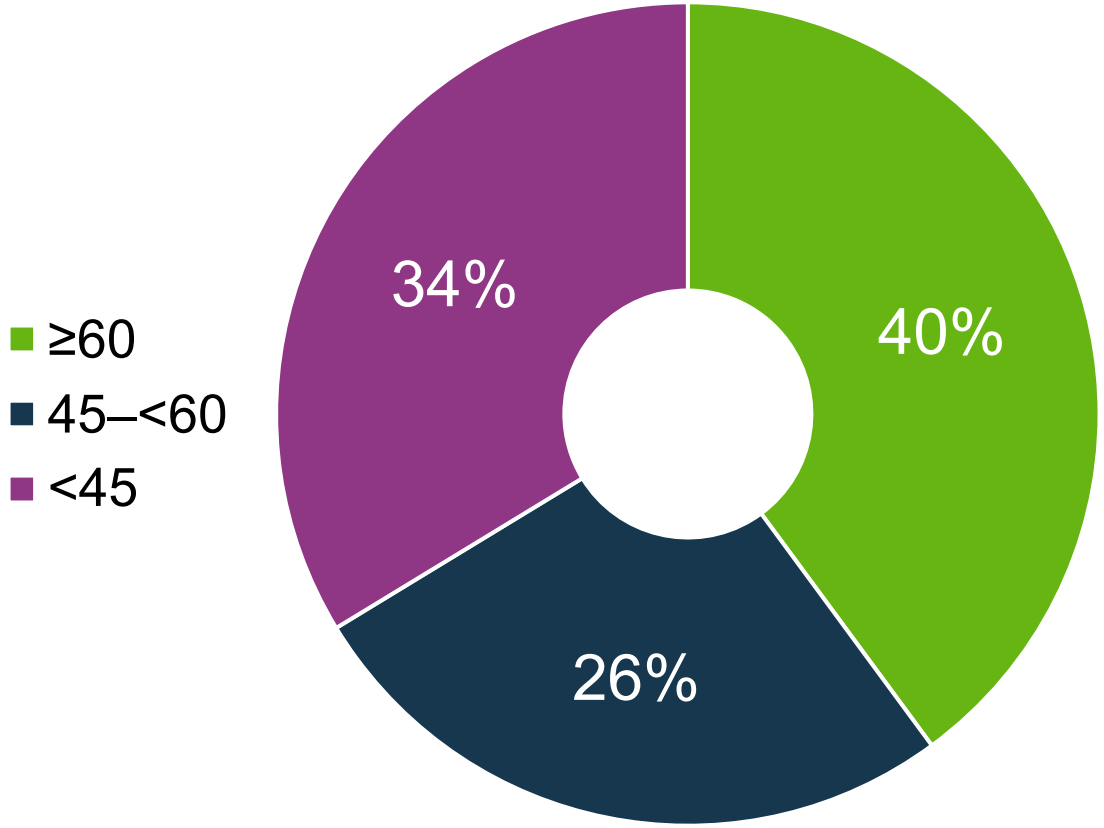
Medications, n (%)	Total (n=13,026)
CV medications	
RASi	**13,003 (100)**
Statins	**9399 (72)**
Beta-blocker	6504 (50)
Calcium antagonist	7358 (57)
Diuretic	**6710 (52)**
Glucose-lowering therapy	12,720 (98)
Metformin	7557 (58)
Insulin	7630 (59)
GLP-1RA	944 (7.2)
SGLT-2i	877 (6.7)

CV, cardiovascular; DBP, diastolic blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure; SGLT-2, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes

1. Agarwal R, *et al. Eur Heart J* 2021; doi: 10.1093/eurheartj/ehab777

In FIDELITY, 40% patients had CKD with an eGFR ≥60 ml/min/1.73 m²

Baseline eGFR (ml/min/1.73 m²)*



A high proportion of patients had albuminuric CKD with preserved kidney function (eGFR ≥60 ml/min/1.73 m²)

- This highlights the importance of uACR assessment to detect patients at risk

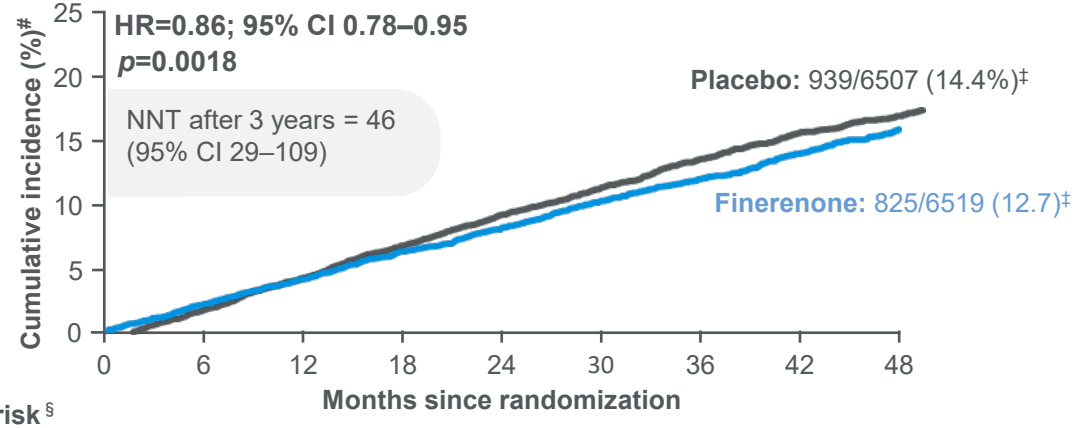
*Data were missing for 3 patients

Filippatos G, *et al*. *ESC* 2021; oral presentation

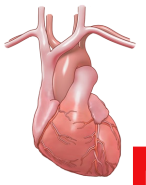
The FIDELITY primary analysis showed significant risk reductions in CV and kidney outcomes

CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF



No. at risk §									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

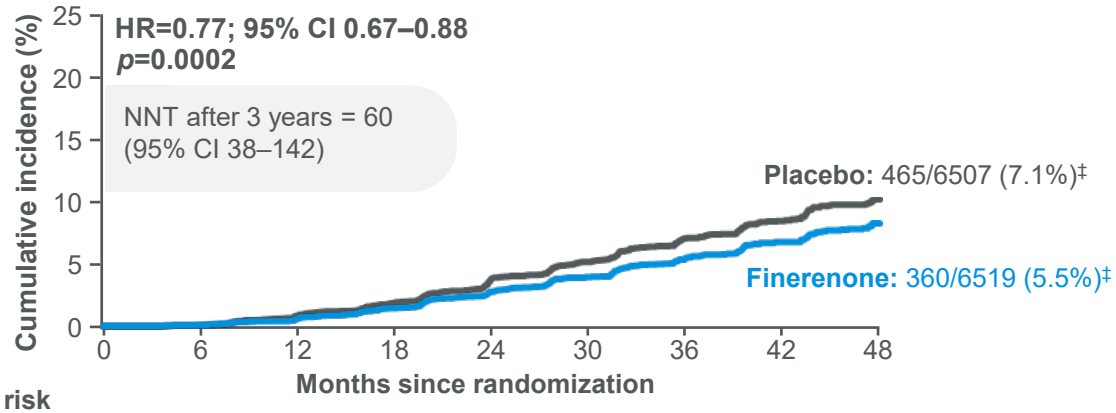


14% reduced **risk of CV morbidity and mortality** vs placebo

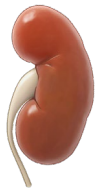
NNT 46 (HR=0.86; 95% CI 0.78–0.95)[1]

Kidney composite

Time to kidney failure*, sustained ≥57% decrease in eGFR from baseline, or kidney-related death



No. at risk									
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962



23% reduced **risk of CKD progression*** vs placebo

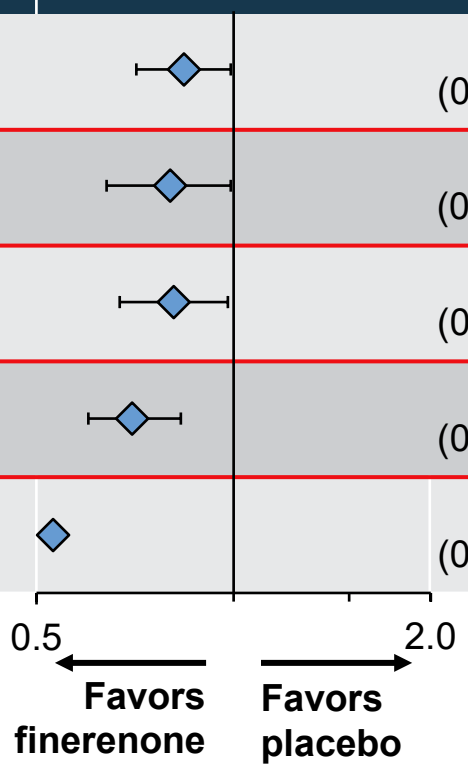
NNT 60 (HR=0.77; 95% CI 0.67–0.88)[1]

*ESKD or an eGFR <15 mL/min/1.73 m^2; events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; #Cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk; ‡number of patients with an event over a median of 3.0 years of follow-up; § at-risk subjects were calculated at start of time point; CI, confidence interval; ESKD, end-stage kidney disease; HR hazard ratio; KRT, kidney replacement therapy; NNT, number needed to treat

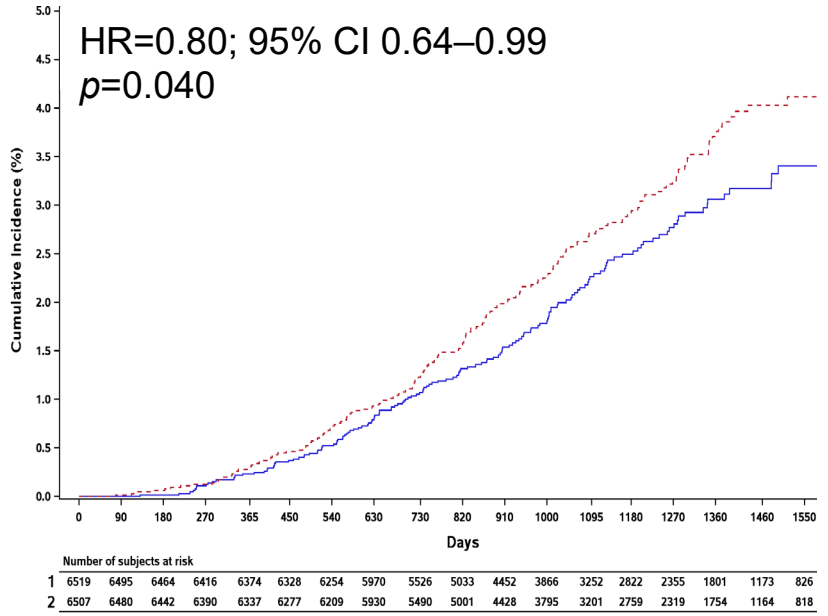
1. Agarwal R, *et al. Eur Heart J* 2021; doi: 10.1093/eurheartj/ehab777

Finerenone significantly reduced the risk of all non-fatal components of the ≥57% eGFR kidney composite outcome[1]

Component of ≥57% eGFR kidney composite	Finerenone (n=6519) n (n/100 PY)	Placebo (n=6507) n (n/100 PY)	HR (95% CI)	*p*-value
Kidney failure	254 (1.38)	297 (1.62)	0.84 (0.71–0.99)	0.039
ESKD*	151 (0.76)	188 (0.96)	0.80 (0.64–0.99)	0.040#
eGFR <15 ml/min/1.73 m^2‡	195 (1.06)	237 (1.29)	0.81 (0.67–0.98)	0.026#
≥57% decrease in eGFR‡¶	257 (1.40)	361 (1.98)	0.70 (0.60–0.83)	<0.0001
Renal death	2 (0.01)	4 (0.02)	0.53 (0.10–2.91)	–



Finerenone reduced the risk of ESKD* by 20% vs placebo

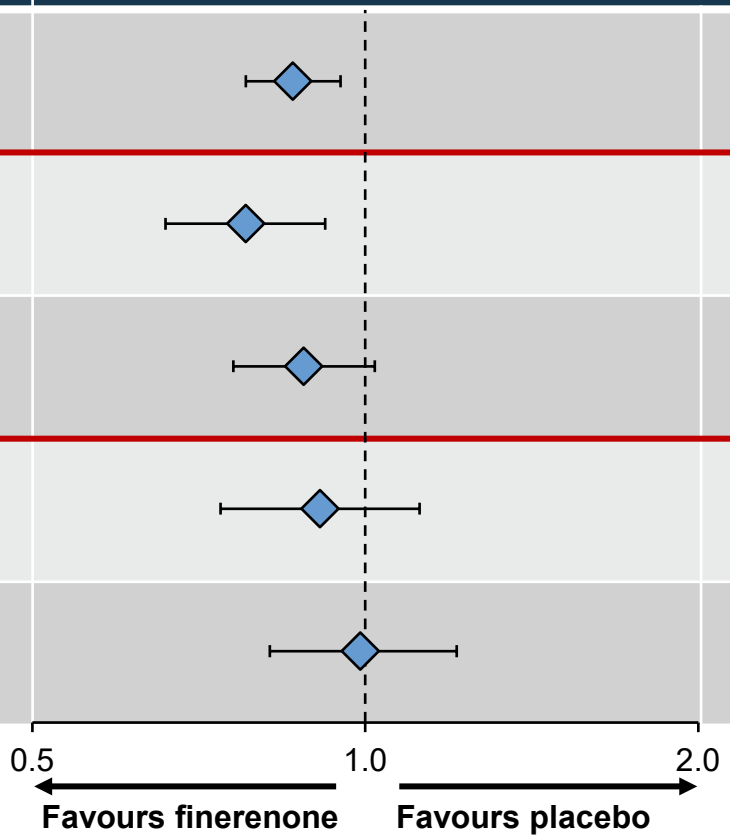


*Initiation of chronic dialysis for ≥90 days or kidney transplant; #analysis for *p*-values not prespecified; ‡confirmed by two eGFR measurements ≥4 weeks apart; ¶from baseline
PY, patient-years

1. Agarwal R, *et al. Eur Heart J* 2021; doi: 10.1093/eurheartj/ehab777

The CV benefits of finerenone were primarily driven by reduction in HHF, and also CV death

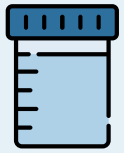
Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	*p*-value
Composite CV outcome	825 (12.7)	939 (14.4)	0.86 (0.78–0.95)	0.0018
HHF	256 (3.9)	325 (5.0)	0.78 (0.66–0.92)	0.0030
CV death	322 (4.9)	364 (5.6)	0.88 (0.76–1.02)	0.092
Non-fatal MI	173 (2.7)	189 (2.8)	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	198 (3.0)	0.99 (0.82–1.21)	0.95



CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction

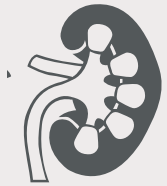
1. Agarwal R, *et al. Eur Heart J* 2021; doi: 10.1093/eurheartj/ehab777

Practical considerations for finerenone use



Measure uACR

To identify patients at highest risk of CKD progression and CV events[1] and who stand to benefit from finerenone treatment[2,3]



Measure eGFR[2,3]

Starting dose of finerenone depends on a patient's eGFR*

Measure serum [K+] regularly to minimize risk of hyperkalemia[2–4]

During treatment, the dose of finerenone depends on a patient's serum [K+]#

Temporarily withhold finerenone if serum [K+] >5.5 mmol/l‡

Continue standard of care therapy, including RASi and blood glucose lowering drugs[5]

*10 mg od for patients with an eGFR <60 ml/min/1.73 m^2, 20 mg od for patients with an eGFR ≥ 60 ml/min/1.73 m^2; #serum [K+] ≤4.8 mmol/l, 20 mg od; serum [K+] >4.8–≤5.0 mmol/l, maintain dose (10 mg od or 20 mg od); ‡restart treatment at 10 mg od when serum [K+] <5.0 mmol/l

1. Kidney Disease Improving Global Outcomes. *Kidney Int* 2013;3:1–150; 2. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 3. Pitt B, *et al. N Engl J Med* 2021; doi: 10.1056/NEJMoa2110956;
4. Agarwal R. *WCN* 2021; abstract WCN21-0607; 5. American Diabetes Association. *Diabetes Care* 2021;44:S151–S167

Five facts of Finerenone for use in CKD in T2DM

- start if K < 5
- keep going till K at most 5.5.
- use if eGFR > 25 (5 x 5).
- expect a 5th reduction in dialysis
- and more than a 5th reduction in Heart Failure Hospitalization.

Adapted from Rajiv Agarwal

What do the guidelines say about GLP1RAs in CKD?

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have benefits in improving CV outcomes in RCTs. The KDIGO 2020 guidelines recommend a long-acting GLP-1 RA for patients with T2D and CKD unable to reach glycemic targets with or unable to tolerate metformin and a SGLT2i [17]. In the ADA 2022 guidelines, patients with T2D and at risk for or with atherosclerotic cardiovascular disease (ASCVD), heart failure or CKD should receive a GLP-1 RA or SGLT2i with CV benefit for glycemic control and CV risk reduction regardless of HbA_{1c} [31]. For nonalbuminuric CKD, a GLP-1 RA with proven CV benefit can be used to reduce CV risk. Further, for CKD subjects with albuminuria $\geq$200 mg/g, the ADA guidelines recommend GLP-1 RA if SGLT2i is unable to be used [31]. Finally, the ESC 2019 guidelines recommends the use of liraglutide and semaglutide for T2D when eGFR >30 mL/min/1.73 m^2 due to the association with a "lower risk of renal endpoints" [21]. In summary, GLP-1 RA are an important adjunctive therapy for patients with T2D and CKD in all guidelines, though dedicated renal outcome trials have not been completed.

Zhang, RM, Persson, F, McGill, JB, Rossing P. NDT 38: 542-550, 2023

Interdisciplinary Kidney Health Care

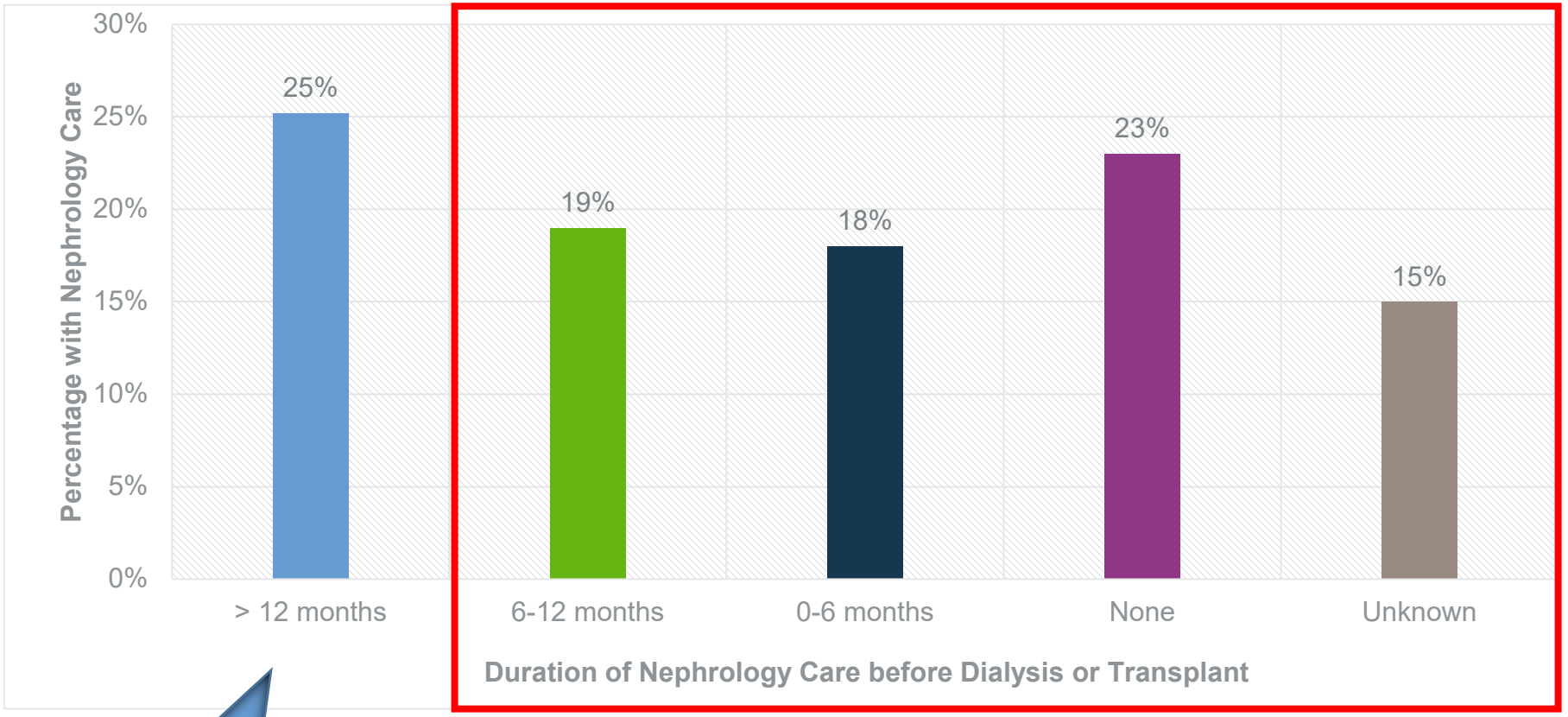
- Internist
- Pharmacist
- Dietitian or Diabetes Educator
- Endocrinologist
- Cardiologist
- Nephrologist

Case Presentation

- 65-year-old man
- Type-2 diabetes since 2005, dyslipidemia and hypertension complicated by HFpEF and CAD s/p MI and LAD ICS.
- Diabetic retinopathy
- Medications: lisinopril 20 mg daily, metoprolol succinate 100 mg daily, clopidogrel 75 mg daily, aspirin 81 mg daily, atorvastatin 40 mg daily, & insulin lispro and glargine.
- BP 142/78 P 72

- How would you test for CKD and evaluate risk?
- Creatinine 1.40 + eGFR 46 = CKD G3a
- uACR 2200 mg/g = CKD A3 or CKD G3aA3 (chronicity defined 3 or more months)

Late Nephrology Referral is Common



Only 1/4rd have more than 1 year of Nephrology Care

United States Renal Data System. 2022 *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, 2022.

Indications for Nephrology Referral for People with CKD

KDIGO Heat Map

Guide to Frequency of Monitoring (number of times per year) + Referral decision making by GFR and Albuminuria Category

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	1 if CKD	1 Monitor	2 Refer*
	G2	Mildly decreased	60-89	1 if CKD	1 Monitor	2 Refer*
	G3a	Mildly to moderately decreased	45-59	1 Monitor	2 Monitor	3 Refer
	G3b	Moderately to severely decreased	30-44	2 Monitor	3 Monitor	3 Refer
	G4	Severely decreased	15-29	3 Refer*	3 Refer*	4+ Refer
	G5	Kidney failure	<15	4+ Refer	4+ Refer	4+ Refer

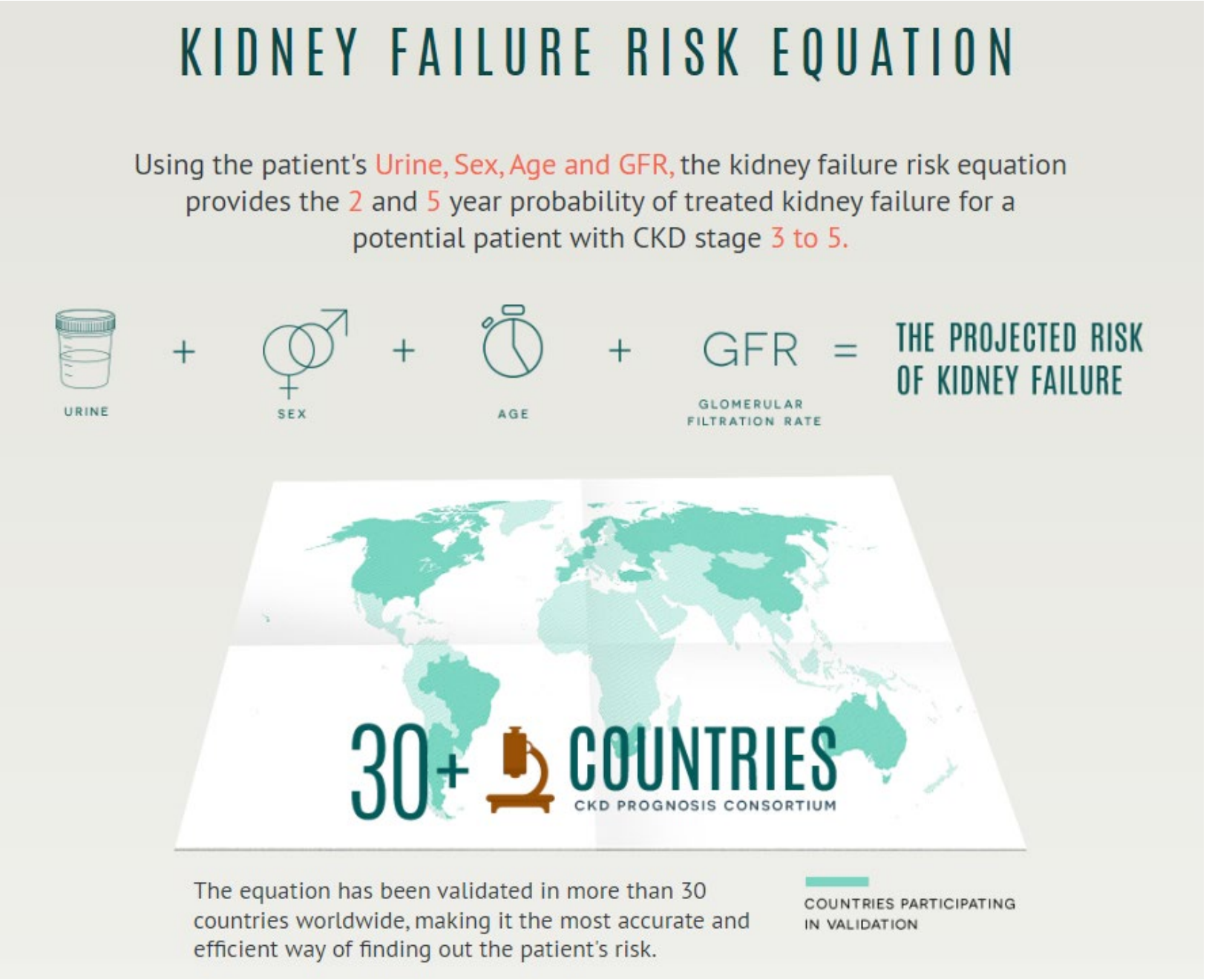
GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). The words in the boxes are a guide for referral decision making (monitor or referral to specialist kidney care services). *Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring.

KDOQI US Commentary on the 2012 KDIGO Evaluation and Management of CKD. Am J Kidney Dis 2014;63(5):713-735.

KidneyFailureRisk.com

Alternative risk prediction model to inform indications for nephrology consultation

JAMA 2016;315(2):1-11



Patient risk of progression to kidney failure requiring dialysis or transplant

AT 2 YEARS	AT 5 YEARS
~1%	~3%

Risk thresholds used in health systems include:

- 3-5% at 5 years for referral to nephrologist

- 10% at 2 years for team-based care

  (Nephrologist, Nurse, Dietitian, Pharmacist)

JAMA 2016;315(2):1-11
https://kidneyfailurerisk.com

Early vs. Late Nephrology Referral: Benefits and Improved Outcomes

Consequences of late referral	Benefits of early referral
Anemia and bone disease	Delay need to initiate RRT
Severe hypertension and fluid overload	Increased proportion with permanent access
Low prevalence of permanent access	Greater choice of treatment options
Delayed referral for transplant	Reduced need for urgent dialysis
Higher initial hospitalization rate	Reduced hospital length of stay and costs
Higher 1-year mortality rate	Improved nutritional status
Less patient choice of RRT modality	Better management of CVD and comorbid conditions
Worse psychosocial adjustment	Improved patient survival

Abbreviations: CVD, cardiovascular disease; RRT, renal replacement therapy.

Variable	Early referral mean (SD)	Late referral mean (SD)	P value
Overall mortality, %	11 (3)	23 (4)	<0.0001
1-year mortality, %	13 (4)	29 (5)	0.028
Hospital length of stay, days	13.5 (2.2)	25.3 (3.8)	0.0007
Serum albumin at RRT start, g/dl [g/l]	3.62 (0.05) [36.2 (0.5)]	3.40 (0.03) [34.0 (0.3)]	0.001
Hematocrit at RRT start, %	30.54 (0.18)	29.71 (0.10)	0.013

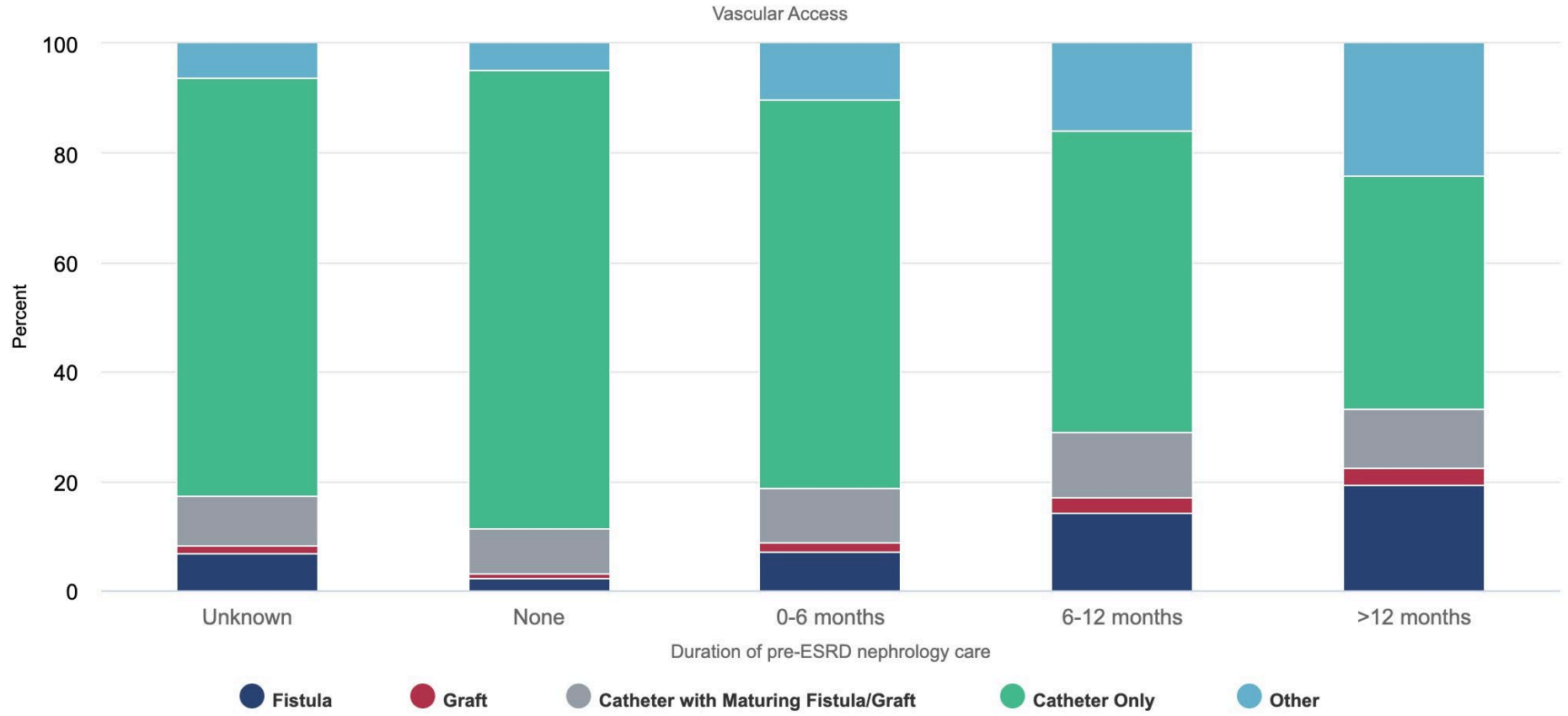
Abbreviation: RRT, renal replacement therapy.

Adapted from Am J Med, Chan MR, Dall AT, Fletcher KE, *et al.*[673] Outcomes in patients with chronic kidney disease referred late to nephrologists: a meta-analysis. 120: 1063-1070, 2007, with permission from Elsevier; accessed http://download.journals.elsevierhealth.com/pdfs/journals/0002-9343/PIIS000293430700664X.pdf

Kidney Int Suppl. 2013;3: 1–150

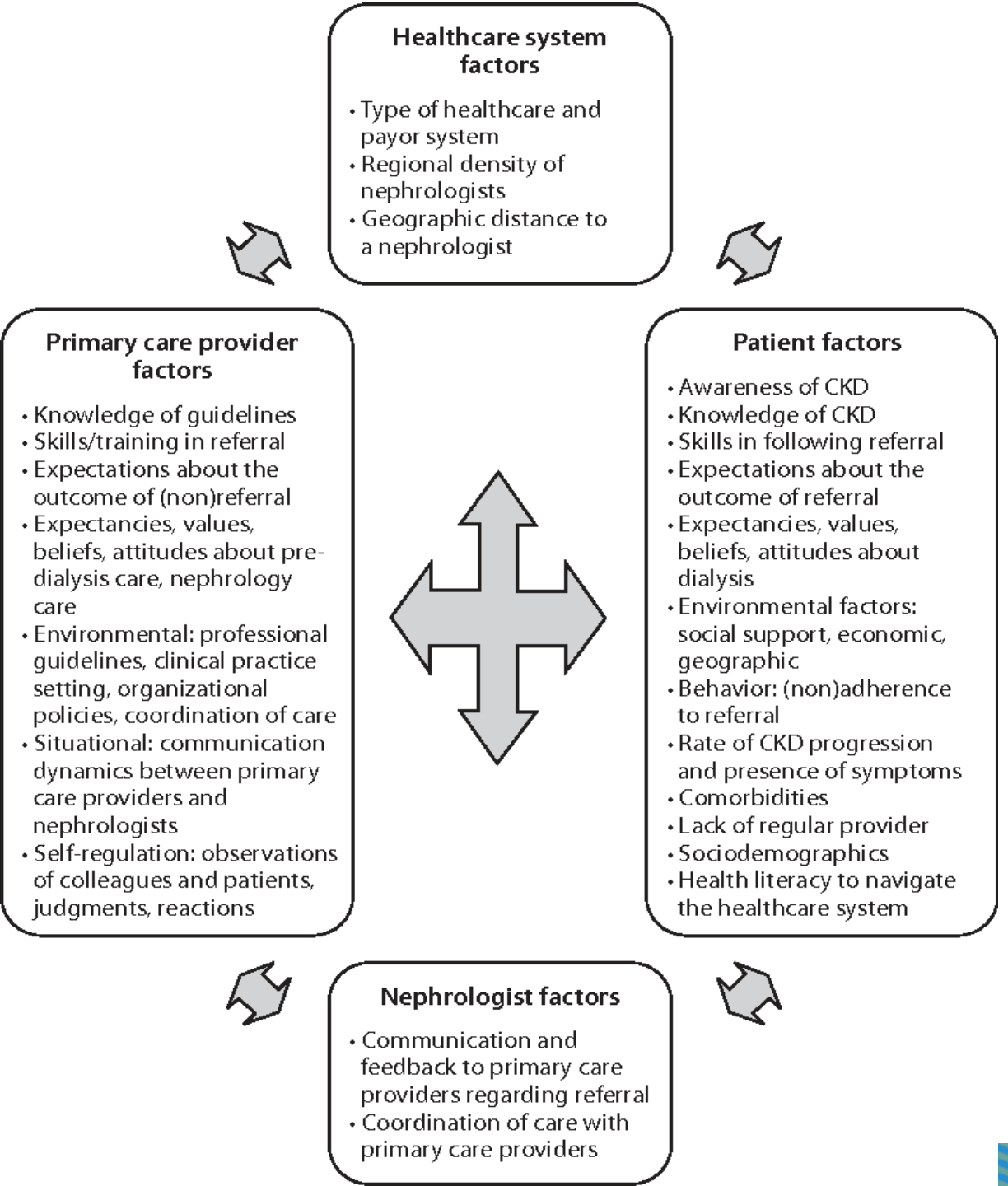
Early Nephrology Referral: Less Hemodialysis Catheter Use

Figure 1.13 Clinical characteristics and care of incident ESRD patients by duration of pre-ESRD nephrology care, 2020



Data Source: 2022 United States Renal Data System Annual Data Report

United States Renal Data System. 2022 *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, 2022



Interventions to Improve Early Nephrology Referral

- Health System
- Patient
- Primary Care
- Nephrologist

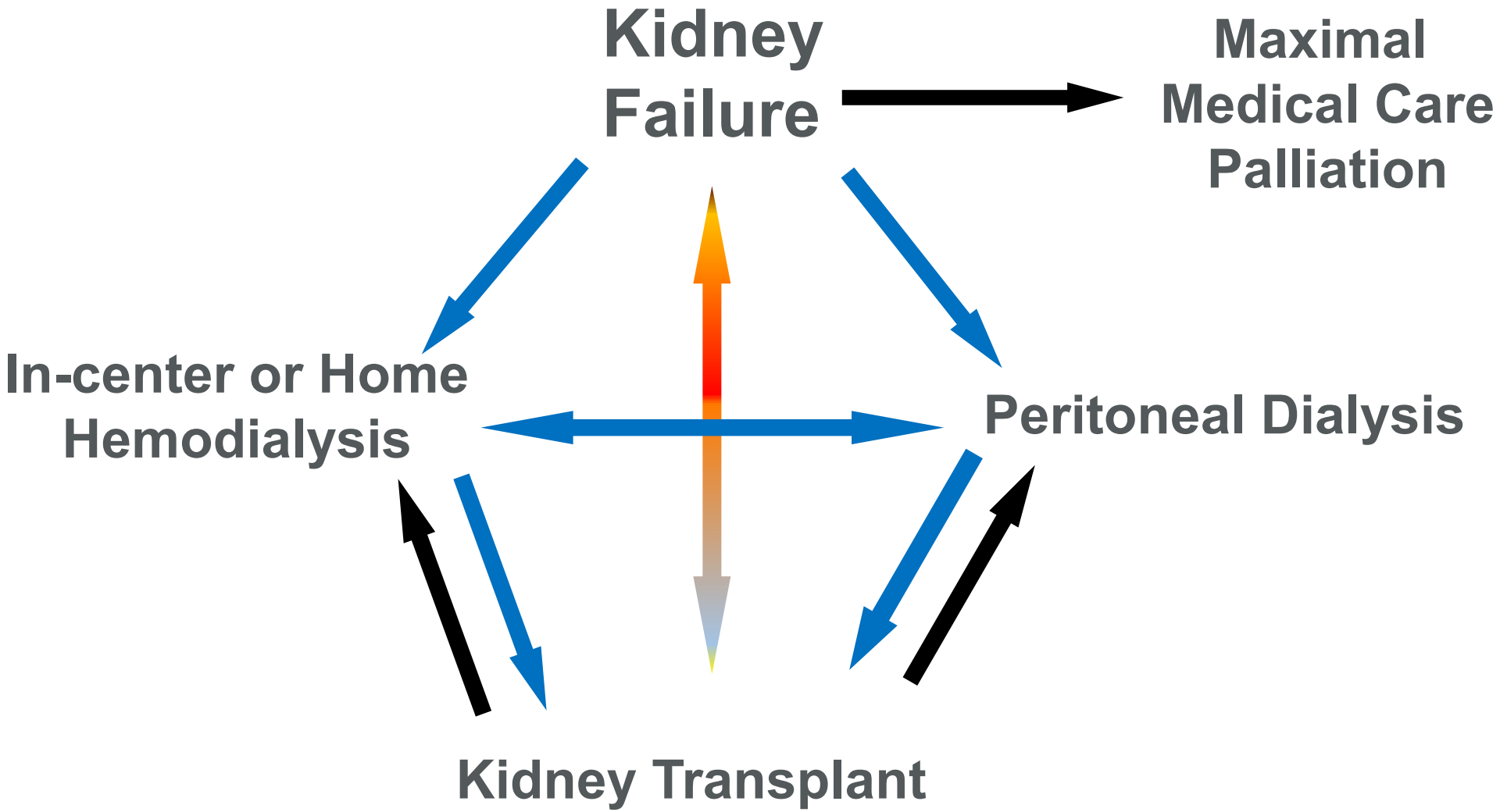
Am J Nephrol 2011;33:60–69

Nephrology Consultant Selection
Suggestions based on opinion and data

- Uses the same electronic health record[1]
- Communicates effectively[1]
- Offers e-consultations[2]
- Offers the full spectrum of kidney failure replacement therapies
- Is your peer or your co-trainee?[3]

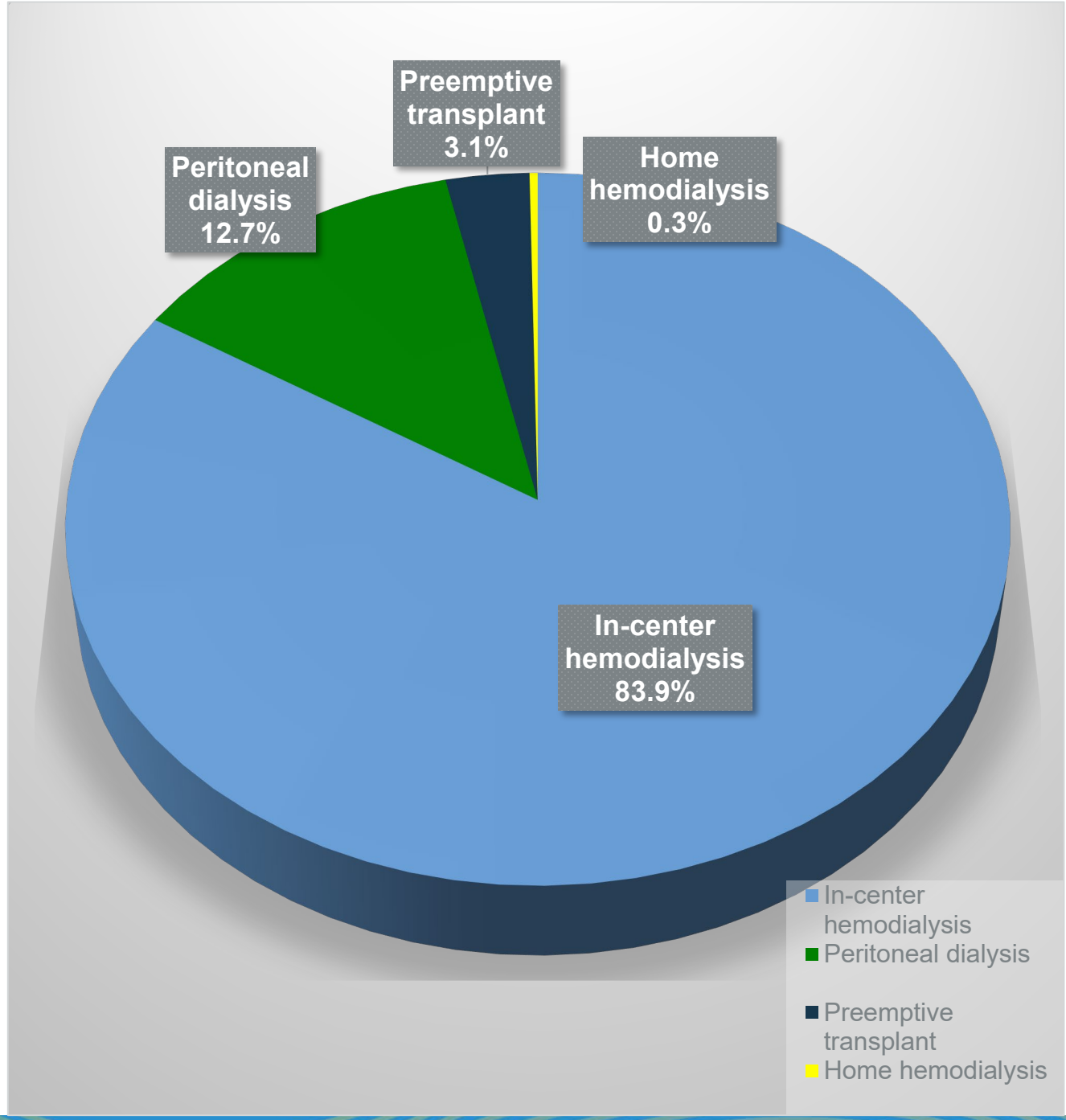
1. J Gen Intern Med 2019;34:1228-1235
2. Am J Kidney Dis 2017;70:122-131
3. JAMA Intern Med 2023; Jan 3 doi:10.1001/aja,momterm,ed.2022.6007. online ahead of print

Kidney Failure Replacement Therapy



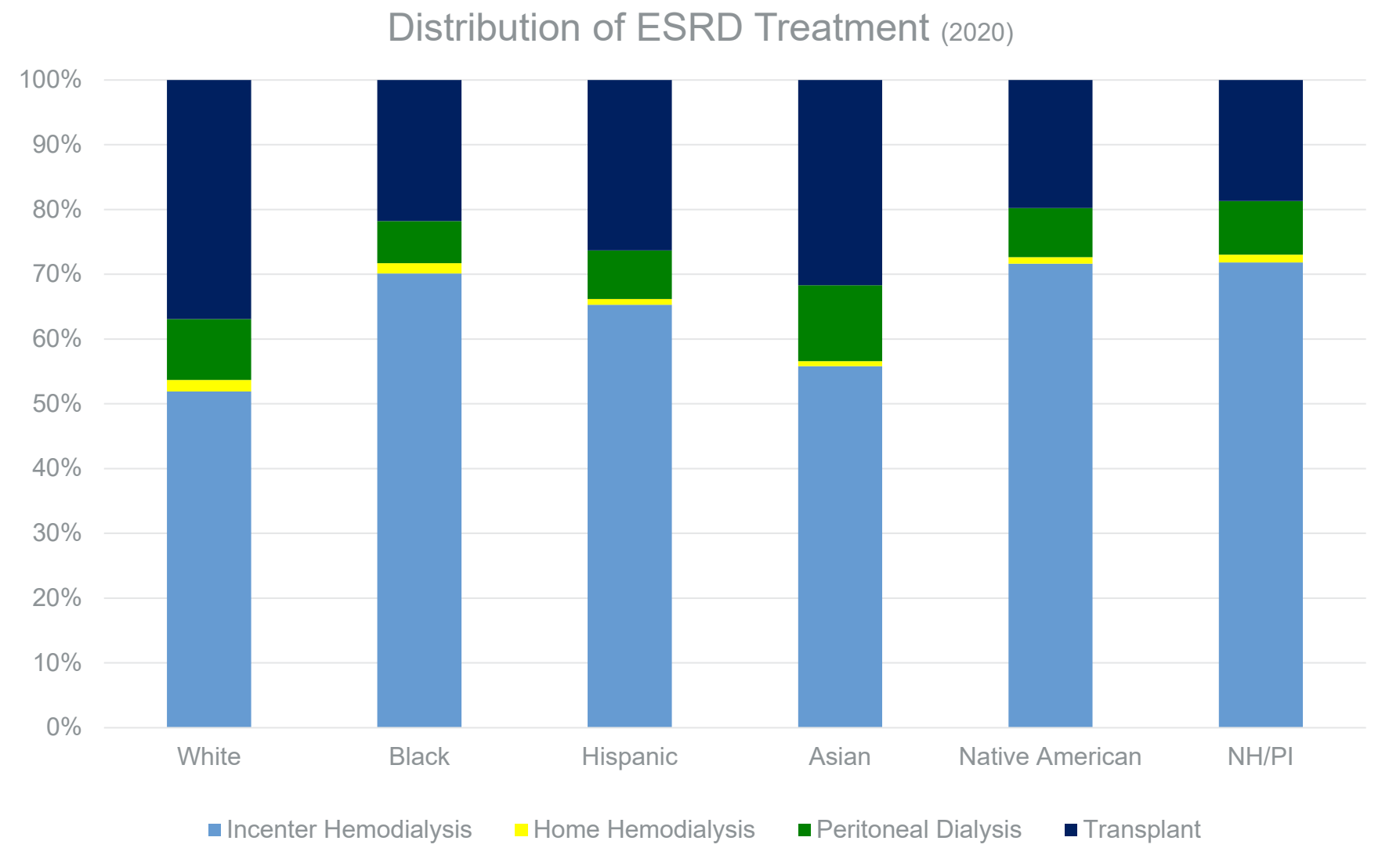
Treatment for New Kidney Failure

- Goal of the AAKHI is 80% of new or incident patients treated with home dialysis or preemptive transplant by 2025 vs current 16.1%.
- Health disparities exist in access to these patient centric therapies.
- Early nephrology referral improves access to home therapies and kidney transplantation.



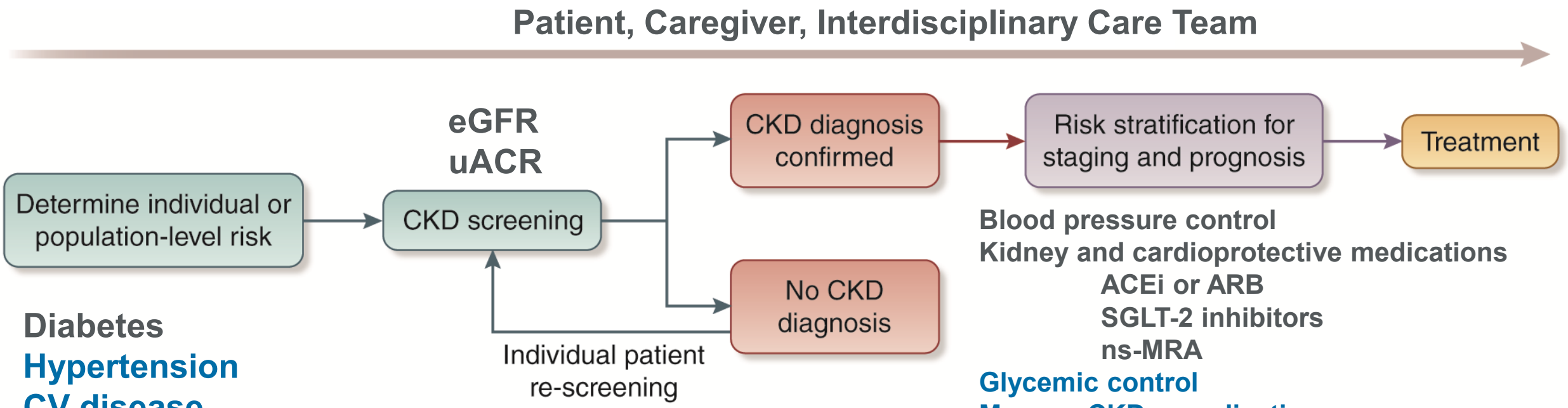
United States Renal Data System. 2022 *USRDS Annual Data Report: Epidemiology of kidney disease in the United States.* National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022

Access to Kidney Transplant is Unequal



USRDS, 2020 https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities

Match CKD Risk Stratification to Interventions

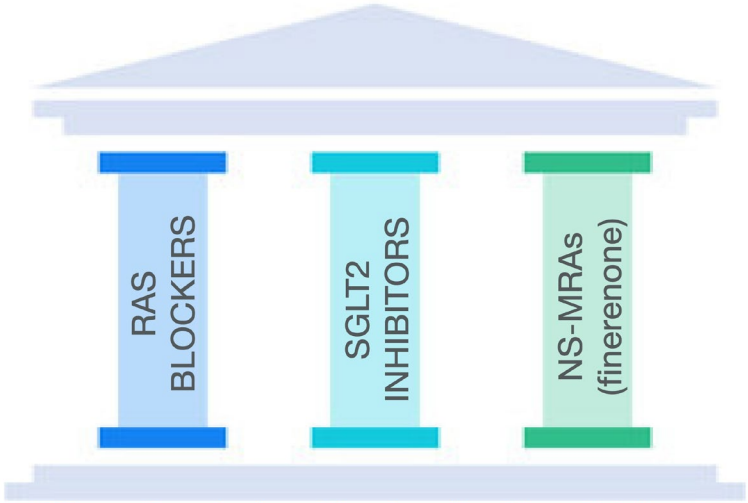


Kidney Int 2021;99:34-47;
Kidney Int Rep 2022;7:389-96.

Integrating CKD Management in Internal Medicine Practice

- Major risk conditions for CKD are DM, HTN & cardiovascular disease.
- Identify CKD early
- Universal implementation of uACR screening in those at risk will maximize the opportunity to modify kidney & cardiovascular risk; albuminuria is no longer an academic exercise
- Foundations of therapy in include tobacco cessation, life-style modifications, BP control, glycemic control, and lipid management.

Therapies to Slow CKD Progression and Reduce Heart Failure Risk



Pillars Needed to Maximally Slow Diabetic Kidney Disease Progression and Reduce Heart Failure Risk

	ACE inihibitors and ARBs		SGLT2 inhibitors		Non-steroidal MRAs*
Effects on CKD progression	RENAAL	IDNT	CREDENCE	DAPA-CKD	FIDELIO/FIGARO
	↓ 21%	↓ 20%	↓ 30%	↓ 39%	↓ 23%
	RENAAL & IDNT RR: 0.79 (95% CI: 0.66-0.95) RR: 0.80, *P*=0.02		CREDENCE & DAPA-CKD HR: 0.70 (95% CI: 0.59-0.82) HR: 0.61 (95% CI: 0.51-0.72)		FIDELIO/FIGARO HR: 0.77 (95% CI: 0.67-0.88)
Effects on heart failure hospitalization	RENAAL	IDNT	CREDENCE	DAPA-CKD	FIDELIO/FIGARO
	↓ 32%	↓ 23%	↓ 39%	↓ 49%	↓ 22%
	RENAAL RR: 0.68, *P*=0.005		CREDENCE & DAPA-CKD HR: 0.61 (95% CI: 0.47-0.80) HR: 0.51 (95% CI: 0.34-0.76)		FIDELIO/FIGARO HR: 0.78 (95% CI: 0.66-0.92)

* In diabetes and CKD. † Responders and non-responders

J Am Coll Cardiol HF. 2022;10 (7) 508–511

Integrating CKD Management in Internal Medicine Practice

- The pharmacological pillars for kidney and cardiovascular health are:
  - ACEi or ARBs
  - SGLT-2 inhibitors
  - MRA

- Who should implement the guidelines?
  - Internist, endocrinologist, nephrologist, cardiologist, or interdisciplinary team?
  - This should be everyone’s responsibility

Upcoming Investigation

- SGLT-2 inhibitor + Finerenone
  - FLAMINgO observational study of any SGLT-2 inhibitor + finerenone in T2DM and CKD[1]
  - CONFIDENCE prospective trial of empagliflozin alone vs finerenone alone vs combination empagliflozin + finerenone in T2DM and CKD[1]

- Finerenone
  - FINE-1 prospective trial of finerenone vs placebo in T1DM and CKD
  - FIND-CKD prospective trial of finerenone vs placebo in non-DM CKD

- GLP-1 RA
  - FLOW prospective trial of semaglutide vs placebo in T2DM and CKD[2]

1. www.clinicaltrials.gov
2. Nephrol Dial Transplant. 2023 Jan 18 doi: 10.1093/ndt/gfad009. Online ahead of print.