Boca Raton Hospital Annual Conference

Nephroprotection Strategies 2024

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Disclosures

Warren Kupin, M.D., faculty for this educational activity, has no relevant financial relationships with ineligible companies to disclose, and has indicated that the presentation or discussion will not include off-label or unapproved product usage.

The Battle for Nephroprotection / Nephropreservation

Opportunities for Nephroprotection

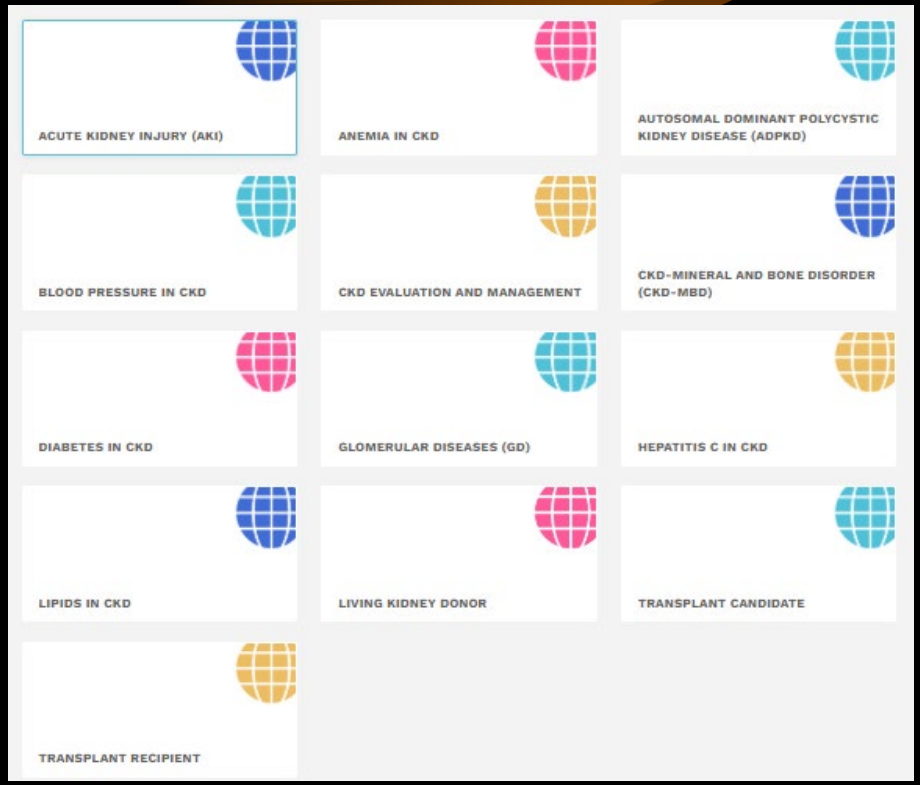
CKD — Preserve the long term function of the remaining nephrons

AKI — Protect the nephrons from hemodynamic / toxic injury

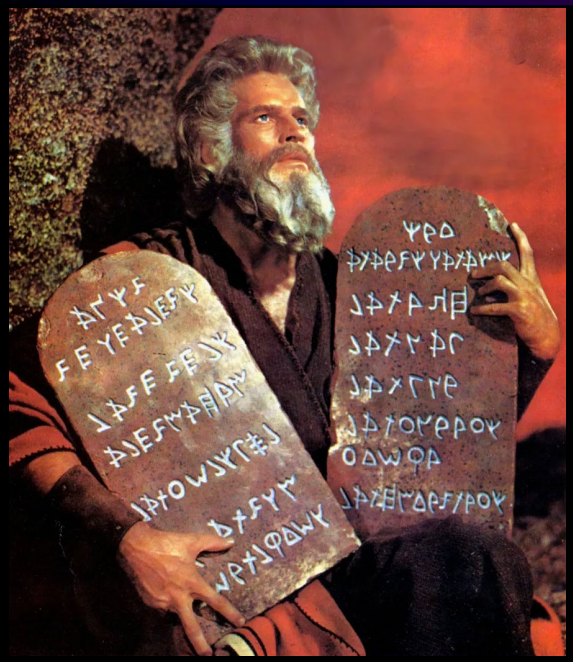
KT — Protect the nephrons from preservation injury and preserve long term nephron function

Kidney Disease: Improving Global Outcomes (KDIGO)

- Originally established in 2003 by the National Kidney Foundation
- KDIGO is a global organization developing and implementing evidence-based clinical practice guidelines in kidney disease
- It is now an independent, volunteer-led, self-managed foundation incorporated in Belgium



Behold !!! The Guidelines are Here !!!
The Commandments of Treating CKD and Preserving the Nephrons!!!



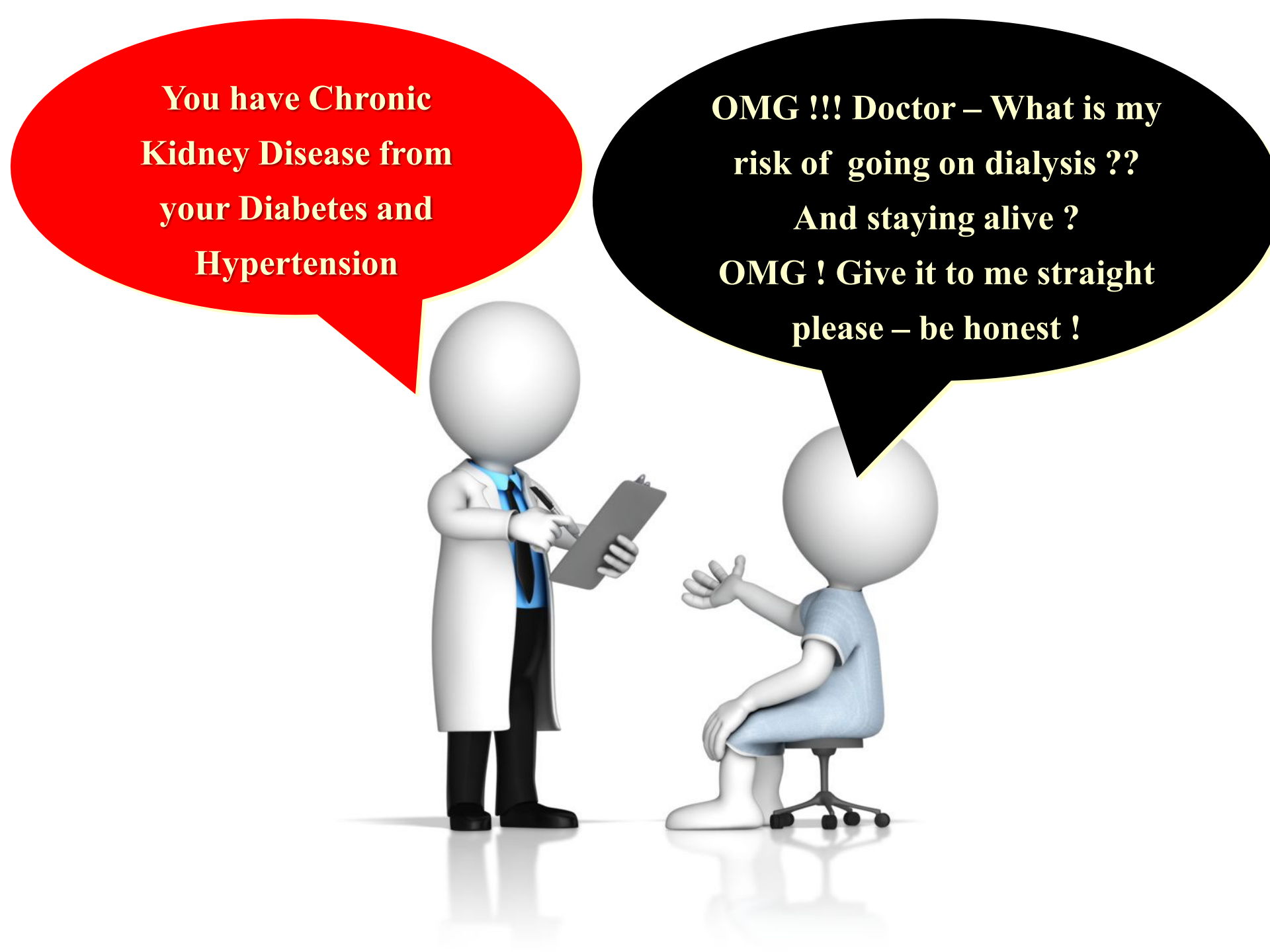
KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES

KDIGO

KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

1) 2 Tablets - 10 commandments
2) Published 2500 yrs ago
3) Revisions – none
4) Peer reviewed – no
5) Public commentary – none
6) References – 0

1) 269 pages
2) Published 2024
3) Revisions – 2002, 2012
4) Peer reviewed – yes
5) Public commentary – yes
6) References – 782


You have Chronic Kidney Disease from your Diabetes and Hypertension
OMG !!! Doctor – What is my risk of going on dialysis ?? And staying alive ?
OMG ! Give it to me straight please – be honest !

Impact of a Decreased GFR and Albuminuria on Patient Morbidity and Mortality Compared to the General Population

CKD = 3 month persistence of either decreased GFR or albuminuria

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			

Albuminuria

GFR

Age <65	ACR, mg/g				ACR, mg/g			
eGFRcr-cys	<10	10–29	30–299	300+	<10	10–29	30–299	300+
	All-cause mortality				Myocardial infarction			
105+	0.99	1.2	1.5	2.4	0.93	1.0	1.1	2.6
90–104	ref	1.3	1.5	2.5	ref	1.2	1.3	1.9
60–89	1.2	1.6	2.0	2.9	1.3	1.4	1.6	2.1
45–59	2.1	2.7	2.9	4.5	1.8	2.6	3.1	3.5
30–44	2.7	3.8	4.2	5.6	1.9	2.3	3.0	3.9
<30	5.2	4.0	7.1	8.6	4.1	3.6	4.7	5.8
	Cardiovascular mortality				Stroke			
105+	0.95	1.4	1.7	4	0.96	1.2	1.6	2.7
90–104	ref	1.6	1.8	3.5	ref	1.2	1.5	2.2
60–89	1.3	1.7	2.3	3.9	1.2	1.4	1.7	2.6
45–59	2.5	4.0	4.6	6.0	1.9	2.0	2.5	3.8
30–44	3.1	6.6	5.3	7.1	2.6	3.7	3.5	3.5
<30	6.0	5.5	9.4	12	2.6	2.9	5.1	5.1
	Kidney failure replacement therapy				Heart failure			
105+	0.57	0.77	2.3	12	0.86	1.1	1.7	3.4
90–104	ref	1.4	3.9	11	ref	1.3	1.5	3.0
60–89	1.9	3.7	8.3	33	1.2	1.7	2.1	3.6
45–59	7.0	16	28	100	1.7	3.3	3.4	5.3
30–44	22	34	109	210	3.5	4.3	6.8	5.7
<30	335	267	419	625	7.5	6.3	9.7	8.9
	Acute kidney injury				Atrial fibrillation			
105+	0.75	1.0	1.4	3.4	0.93	1.0	1.3	1.9
90–104	ref	1.2	1.8	2.6	ref	1.2	1.4	2.3
60–89	1.6	2.7	2.9	5.8	1.1	1.3	1.5	1.8
45–59	4.2	6.0	5.6	7.6	1.5	2.0	2.1	2.6
30–44	5.7	9.4	9.8	9.4	1.8	2.4	3.0	2.8
<30	15	14	14	13	3.7	2.9	4.3	5.4
	Hospitalization				Peripheral artery disease			
105+	1.0	1.1	1.1	1.5	0.93	1.9	1.5	2.6
90–104	ref	1.1	1.2	1.3	ref	1.8	2.1	3.9
60–89	1.1	1.2	1.3	1.6	1.2	2.1	2.2	5.4
45–59	1.3	1.7	1.5	2.0	3.2	7.3	3.4	8.4
30–44	1.5	1.8	1.6	2.1	6.5	9.1	6.6	13
<30	2.1	2.4	2.4	3.5	1.4	7.6	18	16

Recommendation 2.2.1: In people with CKD G3–G5, we recommend using an externally validated risk equation to estimate the absolute risk of kidney failure *(1A)*.

Practice Point 2.2.1: A 5-year kidney failure risk of 3%–5% can be used to determine need for nephrology referral in addition to criteria based on eGFR or urine ACR, and other clinical considerations.

Practice Point 2.2.2: A 2-year kidney failure risk of >10% can be used to determine the timing of multidisciplinary care in addition to eGFR-based criteria and other clinical considerations.

Practice Point 2.2.3: A 2-year kidney failure risk threshold of >40% can be used to determine the modality education, timing of preparation for kidney replacement therapy (KRT) including vascular access planning or referral for transplantation, in addition to eGFR-based criteria and other clinical considerations.

Practice Point 2.2.4: Note that risk prediction equations developed for use in people with CKD G3–G5, may not be valid for use in those with CKD G1–G2.

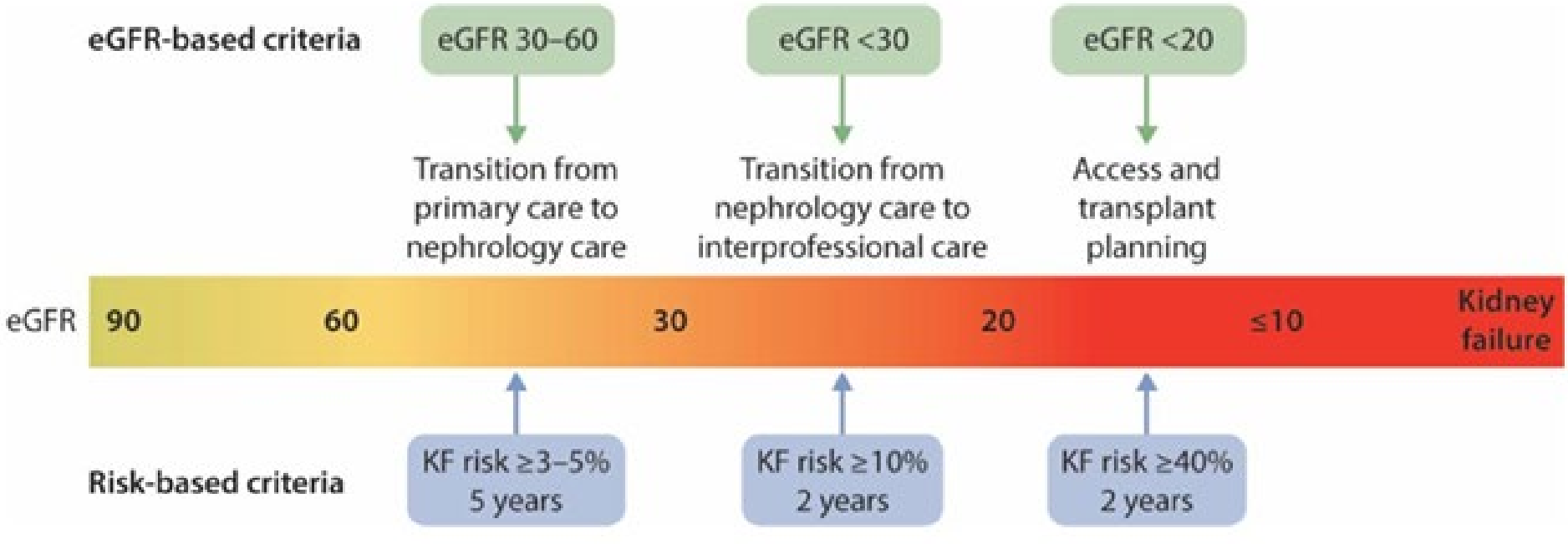
Practice Point 2.2.5: Use disease-specific, externally validated prediction equations in people with immunoglobulin A nephropathy (IgAN) and autosomal dominant polycystic kidney disease (ADPKD).

2.3 Prediction of cardiovascular risk in people with CKD

Practice Point 2.3.1: For cardiovascular risk prediction to guide preventive therapies in people with CKD, use externally validated models that are either developed within CKD populations or that incorporate eGFR and albuminuria.

Practice Point 2.3.2: For mortality risk prediction to guide discussions about goals of care, use externally validated models that predict all-cause mortality specifically developed in the CKD population.

Progression to ESRD from CKD is a Slow Process



CKD Patients have a higher risk of mortality from CVD than ending up on Dialysis

New Guideline : Perform Risk Assessment Models for ESRD and CVD in Patients with CKD

- **https://www.ckdpc.org/risk-models.html**
- **These models will provide an estimate of the risk of cardiovascular disease and risk of progressing to ESRD in patients with different degrees of CKD**
- **DO NOT USE the standard atherosclerotic risk score built into most EMR databases**
  - **Not valid in patients with CKD**
- **The SCORE2 and PCE models are recommended**

https://www.ckdpc.org/risk-models.html

Kidney Failure Risk Equation

Who is it for?
eGFR < 60 mL/min/1.73m2

What does it predict?
2- and 5-yr risk of End Stage Kidney Disease (ESKD)

Risk of 40% Decline in Kidney Function

Who is it for?
Everyone

What does it predict?
3-yr risk of 40% decline in eGFR

Advanced CKD Risk Tool

Who is it for?
eGFR < 30 mL/min/1.73m2

What does it predict?
2- and 4-yr risk of ESKD, cardiovascular disease, and death

Conversion to Urine Albumin-to-Creatinine Ratio

Who is it for?
Anyone with only a urine protein-to-creatinine ratio or urine dipstick protein level available

What does it predict?
Urine albumin-to-creatinine ratio (ACR)

SCORE2 Cardiovascular Risk with eGFR & ACR

Who is it for?
Everyone

What does it predict?
10-yr risk of myocardial infarction, stroke, and CVD mortality

PCE ASCVD Risk with GFR + ACR

Who is it for?
Everyone

What does it predict?
10-yr risk of atherosclerotic cardiovascular disease

YOUR RESULTS

250 mg/g
URINE ALBUMIN

M
SEX

65
AGE

55 mL/min/1.73 m2
GFR

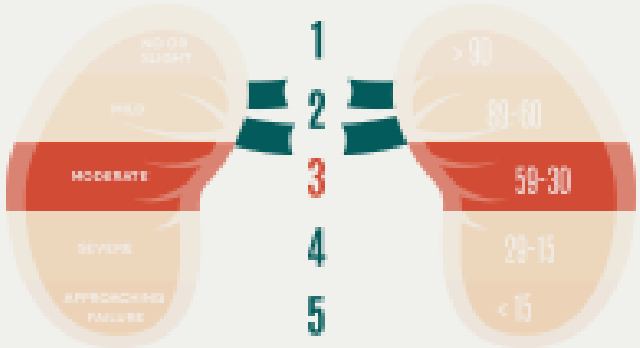
ASSESSMENT

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
0.45 %	1.42 %

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

YOUR RESULTS

250 mg/g
URINE ALBUMIN

M
SEX

30
AGE

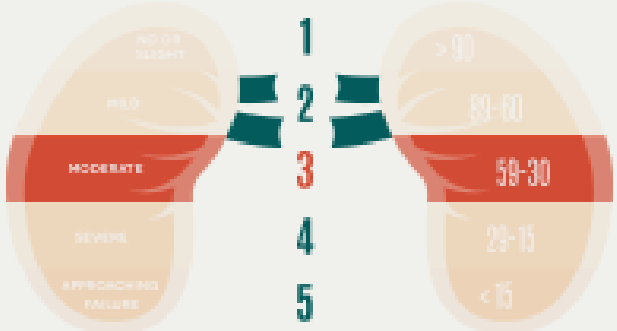
55 mL/min/1.73 m2
GFR

ASSESSMENT

STAGE 3

MODERATE DECREASE IN FUNCTION

CKD STAGES



GLOMERULAR FILTRATION RATE

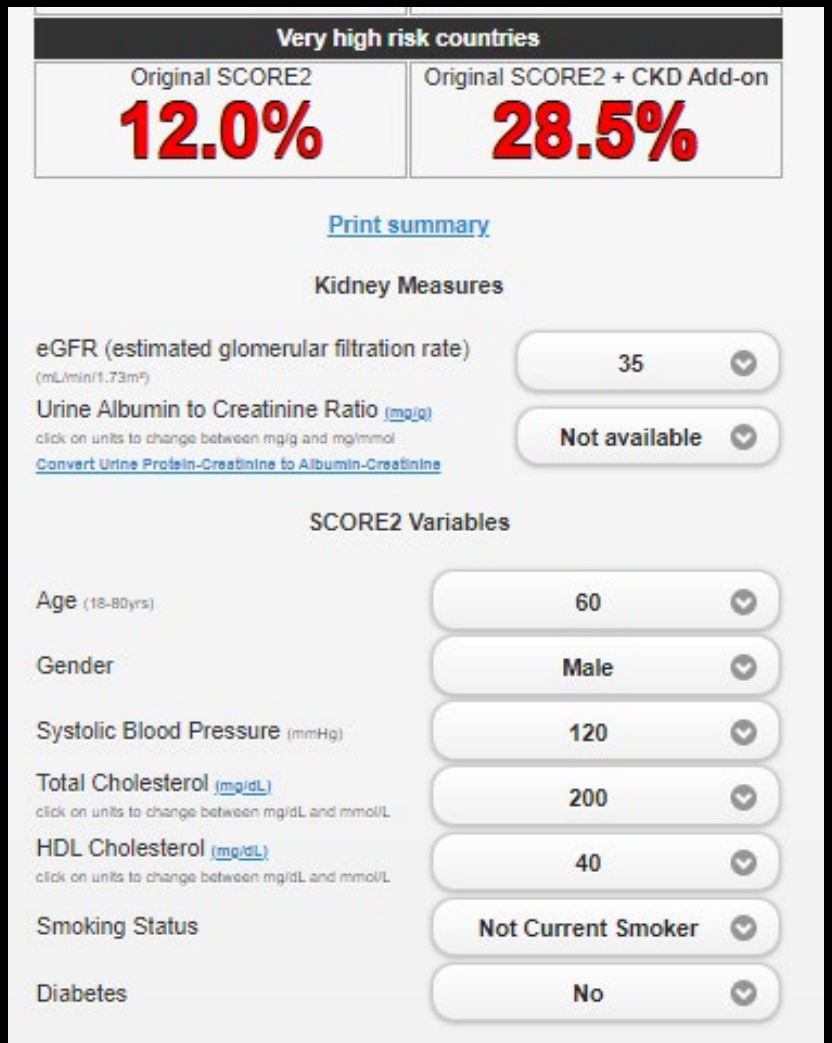
Patient risk of progression to kidney failure requiring dialysis or transplant:

AT 2 YEARS	AT 5 YEARS
0.99 %	3.05 %

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

GFR is a Major Influence on the Risk of Developing CVD



Take home message

CKD guidelines are now requesting physicians be familiar and perform CVD risk assessment profiles in their patients and follow this longitudinally

Nephroprotection in CKD

Dietary and Medical management to control Blood Sugar as needed

Dietary and Medical management to control Blood Pressure 130/80

Kidney International (2024) 105 (Suppl 4S), S117–S314

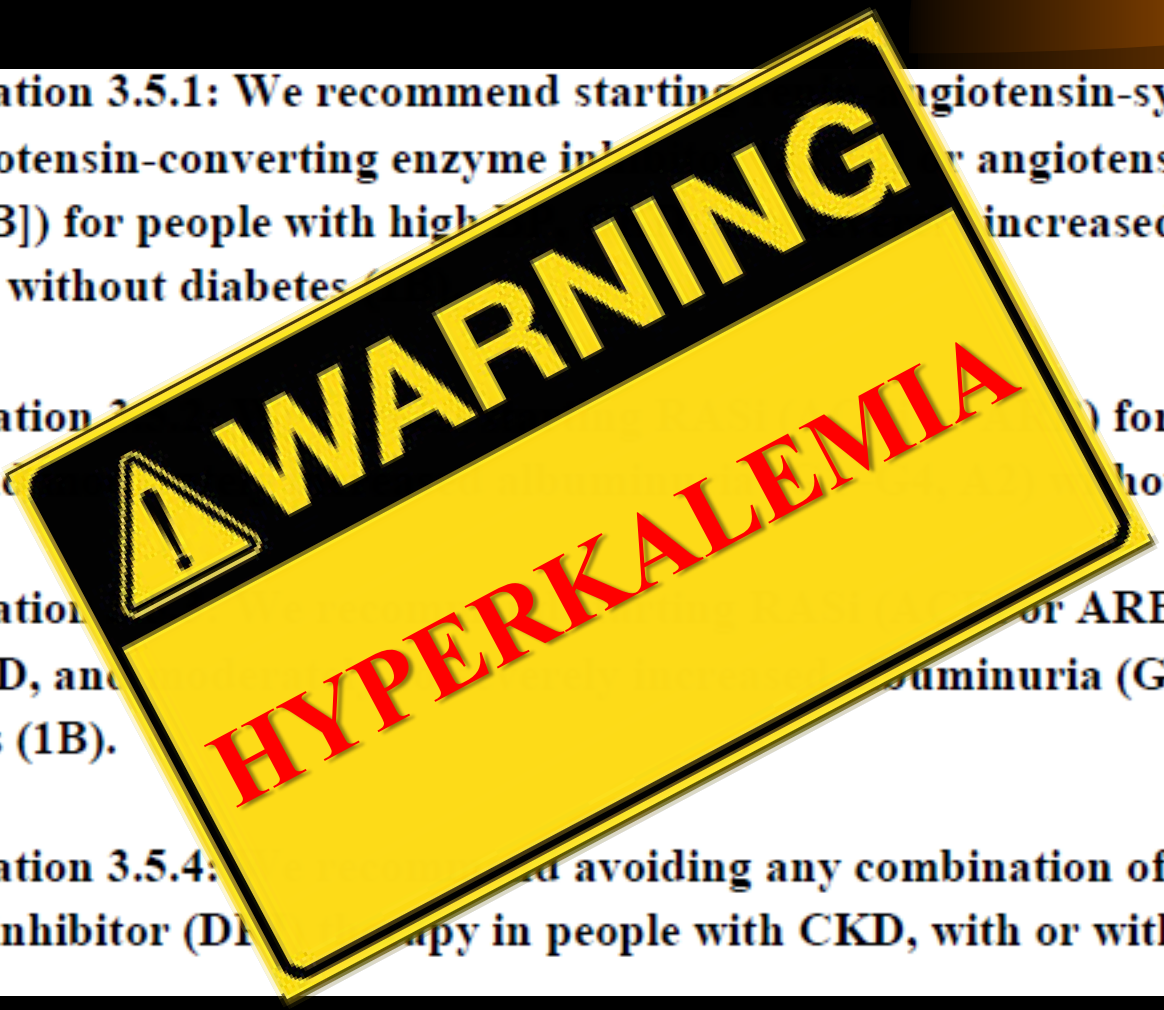
Nephroprotection
Maximal RAAS Inhibition Required !!

Recommendation 3.5.1: We recommend starting **giotensin-system inhibitors (RASi) (angiotensin-converting enzyme in** **angiotensin II receptor blocker [ARB]) for people with high** **increased albuminuria (G1–G4, A3) without diabetes**

Recommendation **) for people with high BP, CKD, an** **hout diabetes (2C).**

Recommendation **or ARB) for people with high BP, CKD, an** **buminuria (G1–G4, A2 and A3) with diabetes (1B).**

Recommendation 3.5.4: **d avoiding any combination of ACEi, ARB, and direct renin inhibitor (DI** **apy in people with CKD, with or without diabetes (1B).**



Nephroprotection
Maximal RAAS Inhibition Required !!

Veltassa (Patiromer)
Ca-K exchange

Lokelma (sodium zirconium cyclosilicate)
Na-K exchange

K binding exchange resins can prevent the risk of Hyperkalemia and allow for maximum titration of RAAS inhibition

Nephroprotection
Maximal RAAS Inhibition Required !!

Practice Point 3.5.4: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose.

Consider reducing diuretic dose if this occurs and recheck

Every effort should be made

<u>not to reduce RAAS inhibition</u>

We Discussed this Last Year !

Keep RAAS Inhibition even at Stage 4 CKD

Does the discontinuation of RAS inhibitors improve eGFR in patients with advanced CKD?

#NephJC

- Open-Label Randomized Control Trial
- 39 Centers United Kingdom
- 411 Adults Stage 4 or 5 CKD (eGFR < 30 mL/min/1.73m²)
- > 2 mL/min/1.73m² per year eGFR decline over 2 year
- RAS inhibitor > 6 months (ACEi or ARB)

	1° Outcome eGFR (by MDRD*)	2° Outcome (ESKD or RRT)	MACE
✓ Continue RAS inhibitor n=205	13.3±0.6 mL/min/1.73m²	56% (115/205)	43% (88/205)
3 years	P = 0.42 (-2.5 to 1.0)	HR =1.28 (0.99 to 1.65)	Similar
✗ Discontinue RAS inhibitor n=206	12.6±0.7 mL/min/1.73m²	62% (128/206)	52% (108/206)

Conclusion: Among patients with advanced and progressive chronic kidney disease, the discontinuation of RAS inhibitors was not associated with a significant between-group difference in the long-term rate of eGFR decline.

*Modification of Diet in Renal Disease

Reference: STOP ACEi trial investigators, Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease.

Visual Abstract by: Dana Larsen, MD @dana_m_larsen

Nephroprotection in CKD

Dietary and Medical management to control Blood Sugar as needed

Dietary and Medical management to control Blood Pressure 130/80

Are you Flozinators ?

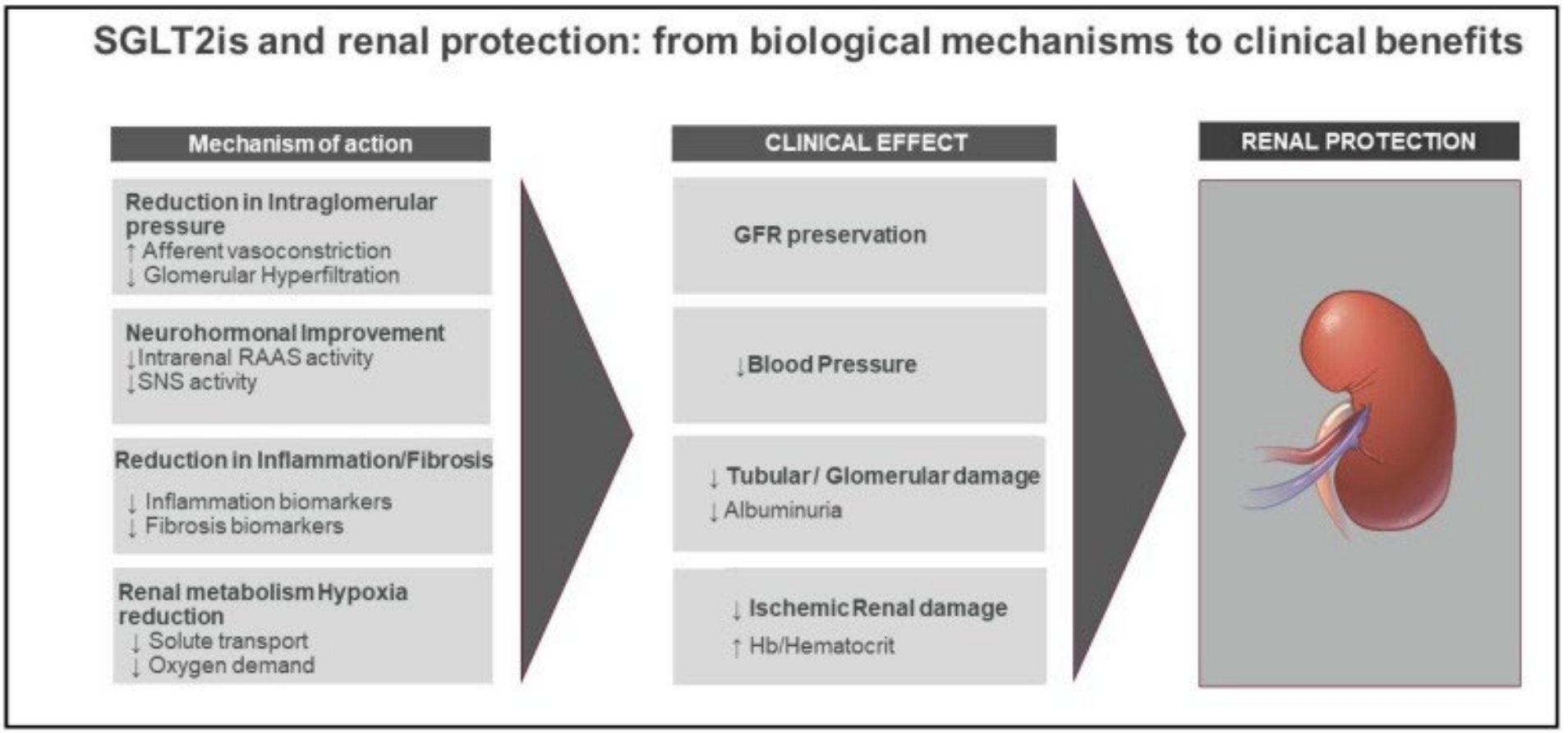
SGLT-2 Inhibitors Recommended in Diabetic and Non- Diabetic CKD

Recommendation 3.6.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i (1A).

Practice Point 3.6.1: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or KRT is initiated.

Practice Point 3.6.2: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when people may be at greater risk for ketosis).

Recommendation 3.6.3: We suggest treating adults with eGFR ≥20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g with an SGLT2i (2B).



- **The Nephroprotective effects of SGLT2 inhibitors represent a class effect**
- **Multiple mechanisms are involved both renal and extrarenal**

Leoncini G.Int J Mol Sci. 2021 May; 22(9): 4441

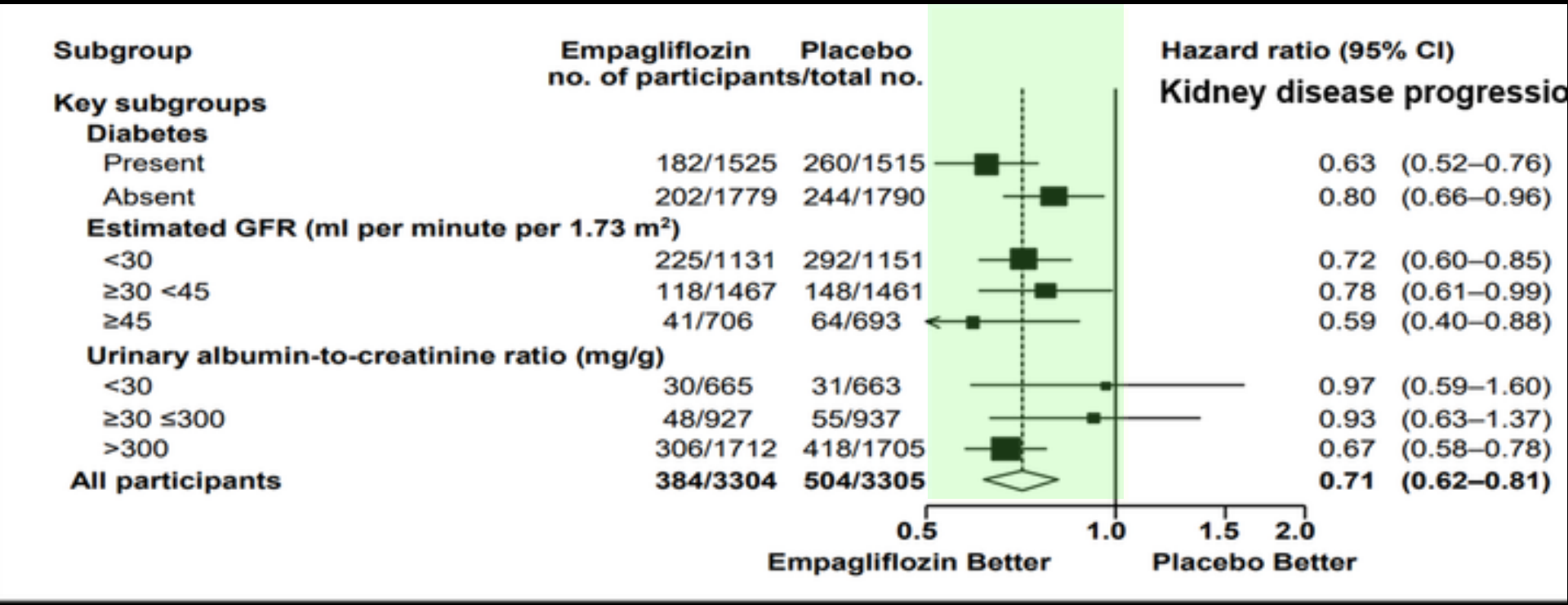
The Flozin Winning Streak in CKD/DM/CHF
Every Study ….. A Success !!!

EMPA-REG	**CANVAS**	**SCORED**
VERTIS CV	**DECLARE-TIMI**	**CREDENCE**
DAPA-CKD	**DAPA-HF**	**DELIVER**

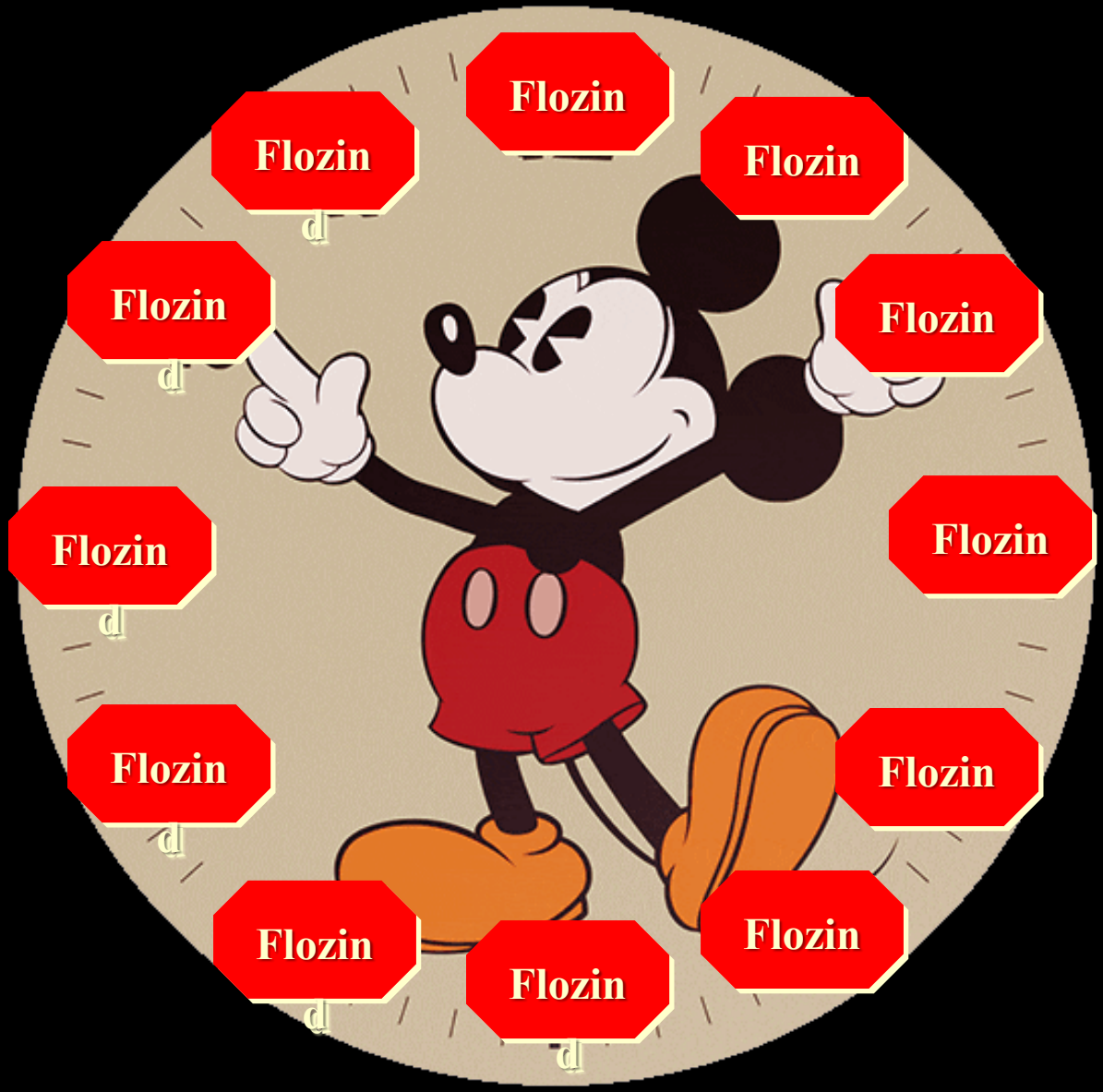
EMPA-KIDNEY Collaborative Group. N Engl J Med. 2022 Nov 4

EMPA Outcome : CKD and CVD

Benefit Across all subgroups with Empagliflozin



SGLT-2 Inhibitors – Where Dreams Come True !
It's Always Flozin Time !



Nephroprotection in CKD

Dietary and Medical management to control Blood Sugar as needed

Dietary and Medical management to control Blood Pressure 130/80

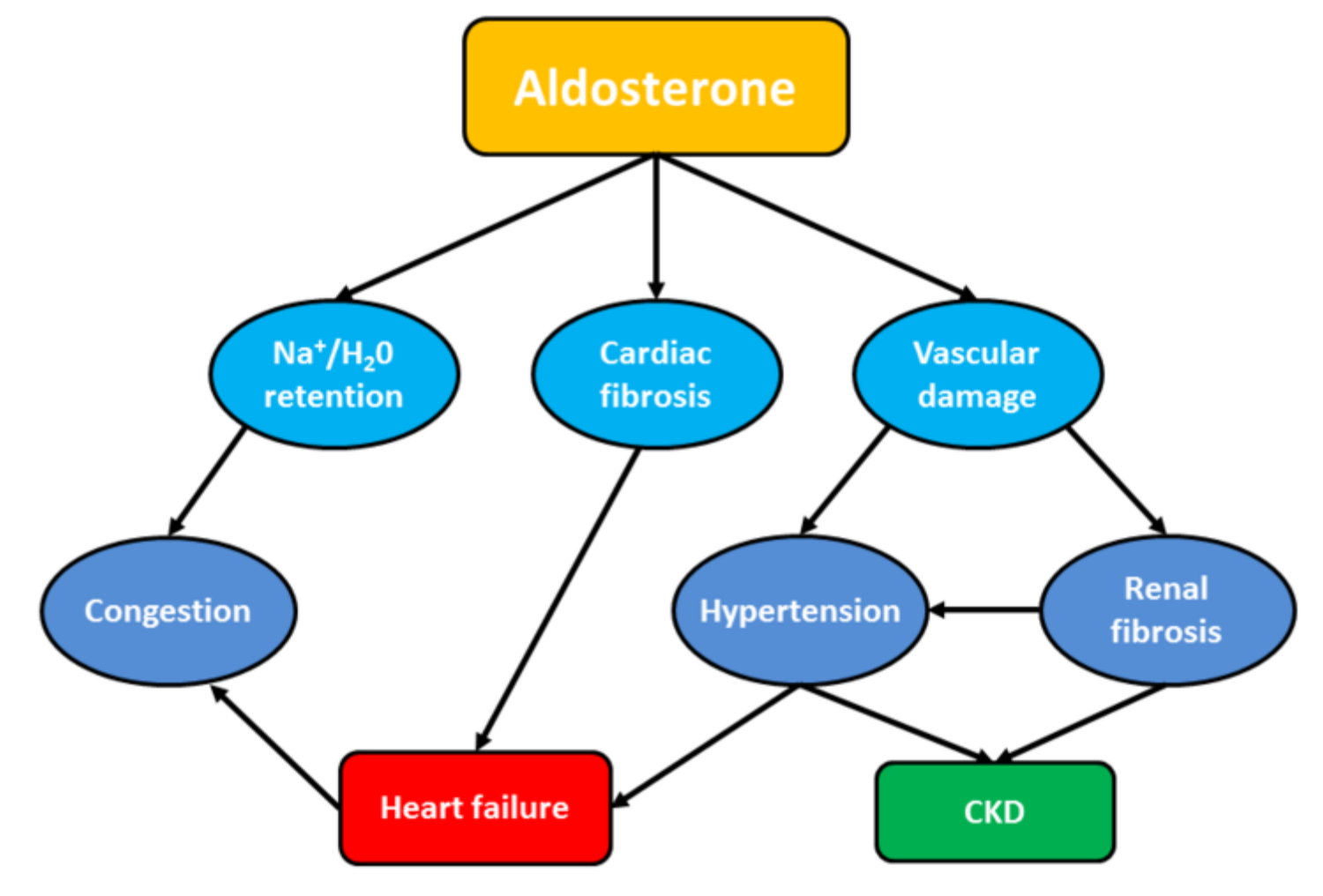
Mineralocorticoid Inhibitors as Add on Therapy for Nephroprotection

Recommendation 3.7.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an eGFR >25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) (2A).

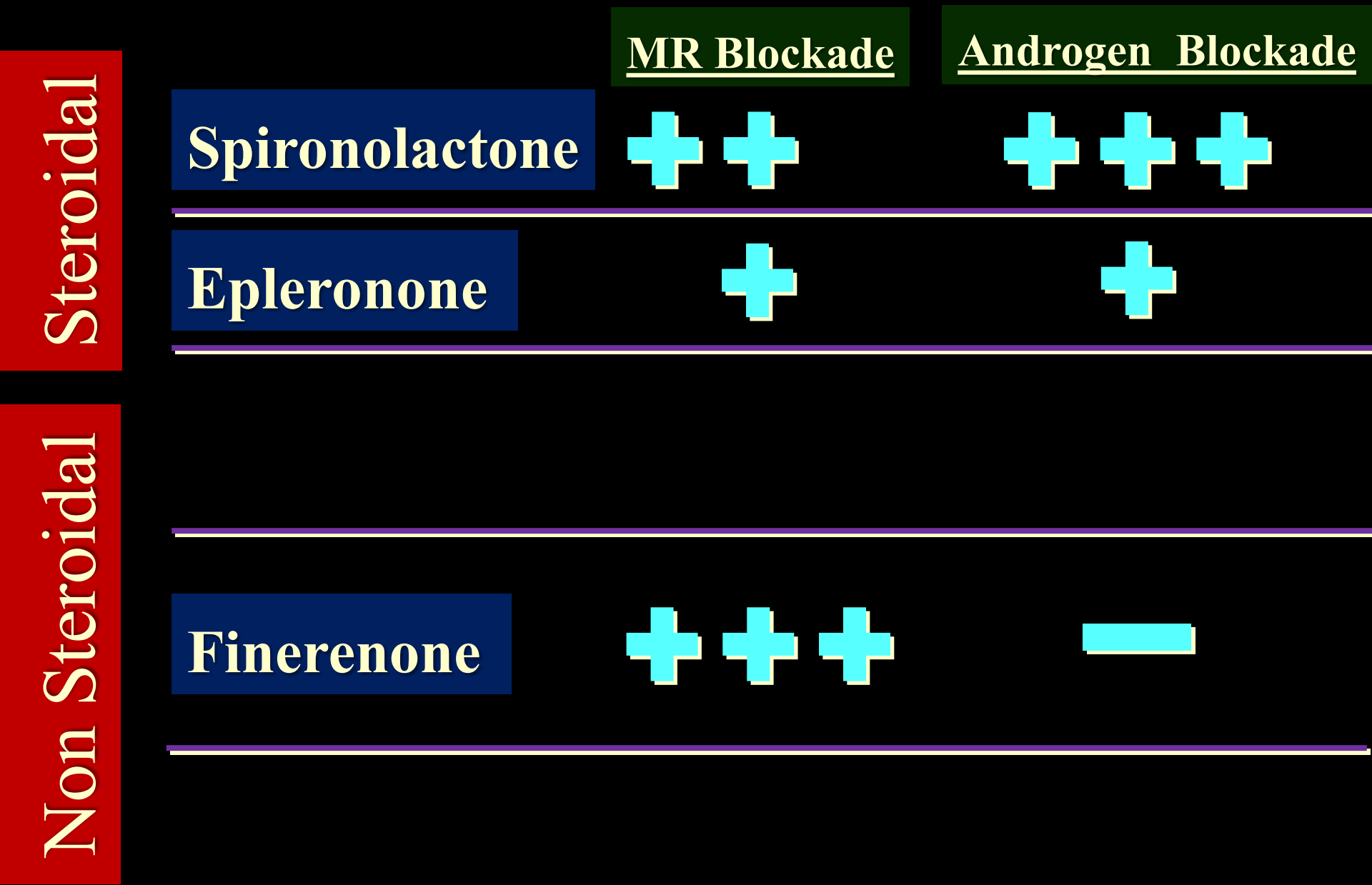
Practice Point 3.7.1: Nonsteroidal MRA are most appropriate for adults with T2D who are at high risk of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard-of-care therapies.

Practice Point 3.7.2: A nonsteroidal MRA may be added to a RASi and an SGLT2i for treatment of T2D and CKD in adults.

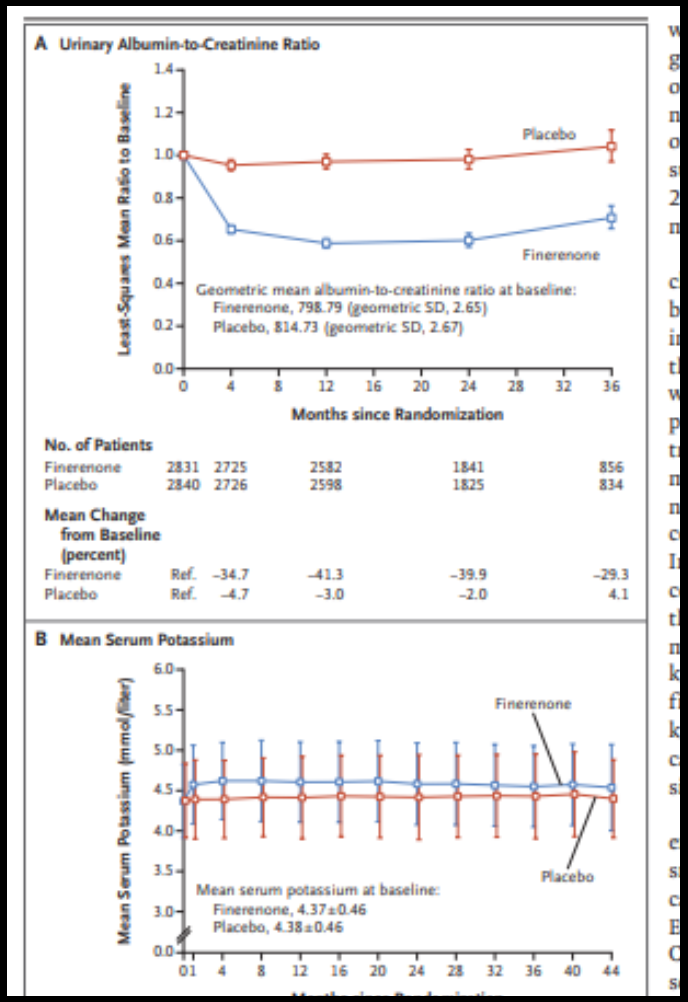
Adverse Consequences of Chronic Elevation of Angiotensin II / Aldosterone



Mineralocorticoid Receptor (MR) Antagonists



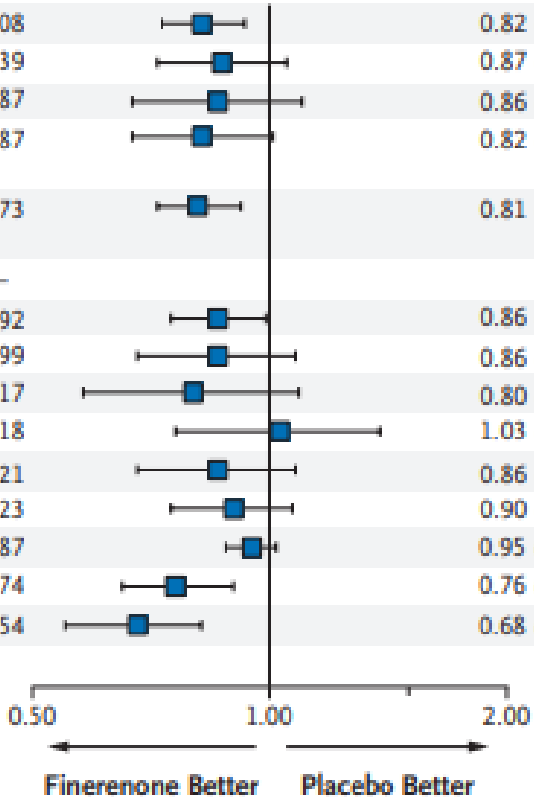
The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD)



- **Significant reduction in albuminuria without a major risk of Hyperkalemia**

The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD)

Outcome	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2833)	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m^2	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—



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News Release

Not intended for U.S. and UK Media

U.S. FDA approves finerenone for the treatment of patients with chronic kidney disease associated with type 2 diabetes

- Finerenone is the first non-steroidal, selective mineralocorticoid receptor (MR) antagonist to demonstrate positive kidney and cardiovascular outcomes in patients with chronic kidney disease associated with type 2 diabetes
- Despite guideline-directed therapies, many patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D) still progress to loss of kidney function and are at high risk for cardiovascular events
- By blocking MR overactivation, a key driver of CKD progression, finerenone works on a pathway largely unaddressed by existing treatments for CKD in T2D

Berlin, July 9th, 2021 – Bayer announced today that the U.S. Food and Drug Administration (FDA) has approved finerenone, the first non-steroidal, selective mineralocorticoid receptor (MR) antagonist, under the brand name Kerendia®. Finerenone 10 mg or 20 mg is indicated to reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).

The approval of finerenone by the FDA is based on the positive results of the pivotal Phase III FIDELIO-DKD study, presented at the American Society of Nephrology's (ASN) Kidney Week Reimagined 2020 and simultaneously published in the *New England Journal of Medicine* in October 2020, and follows Priority Review designation granted by the FDA in January 2021.

Treatment of Diabetic Kidney Disease

1) ACEI / ARB
2) SGLT2 inhibitors
3) Finerenone

Insurance Coverage for Nonsteroidal Mineralocorticoid Inhibitors ?

But …….. It is worth an effort as this drug class is significantly superior to steroidal MRA with proven benefit

Nephroprotection in CKD

Dietary and Medical management to control Blood Sugar as needed

Dietary and Medical management to control Blood Pressure 130/80

We Already Know this about GLP-1 Agonists …..

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

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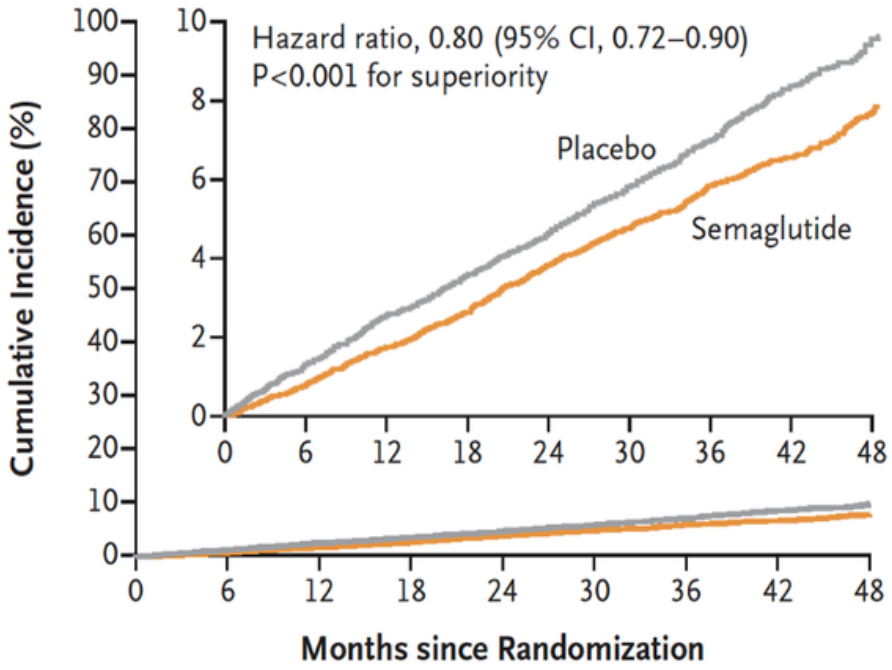
November 11, 2023
DOI: 10.1056/NEJMoa2307563

Primary Cardiovascular Composite End Point



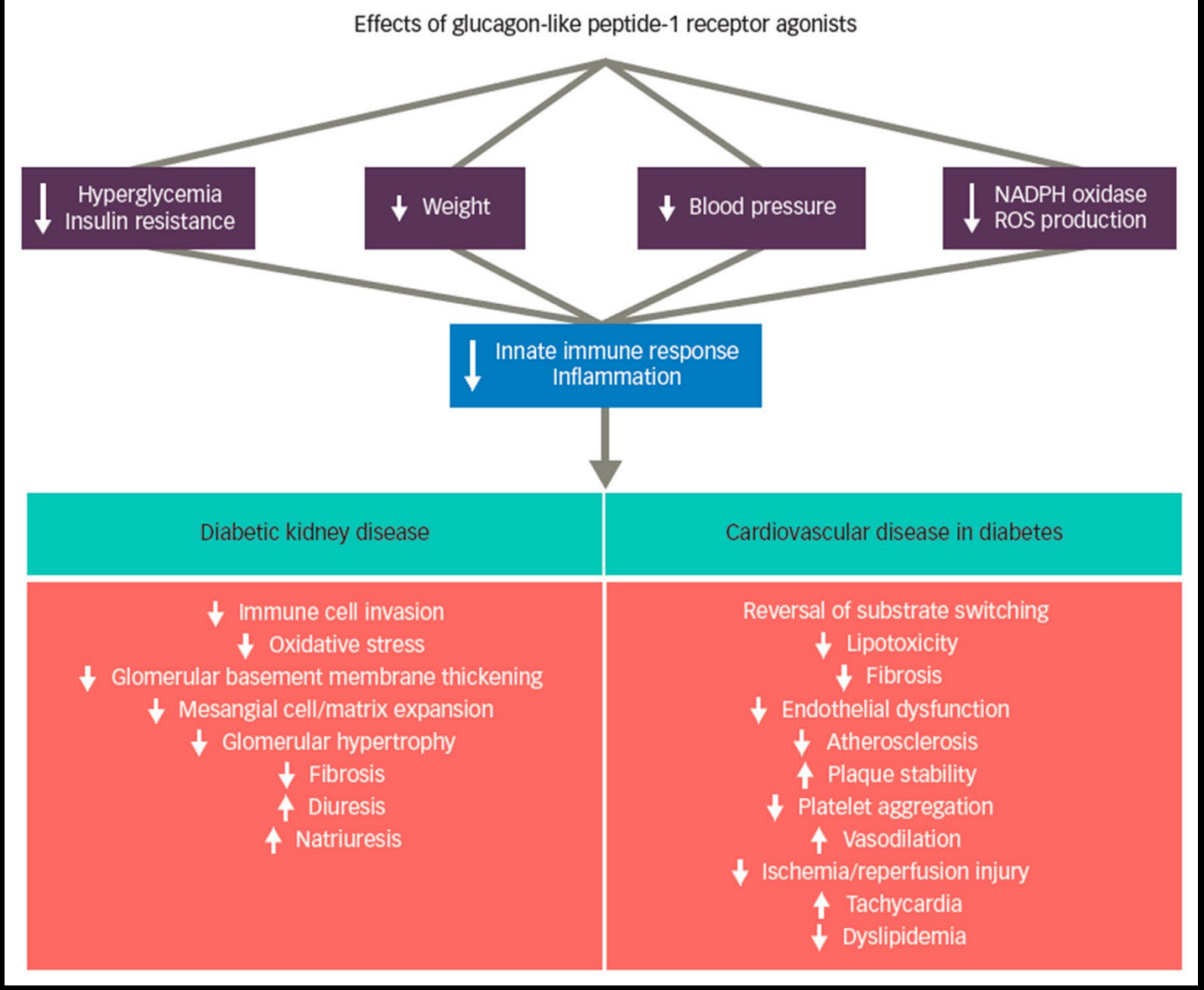
No. at Risk

Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

But …. What about This ?
Brand NEW !!!

Recommendation 3.8.1: In adults with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2 inhibitor treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B).

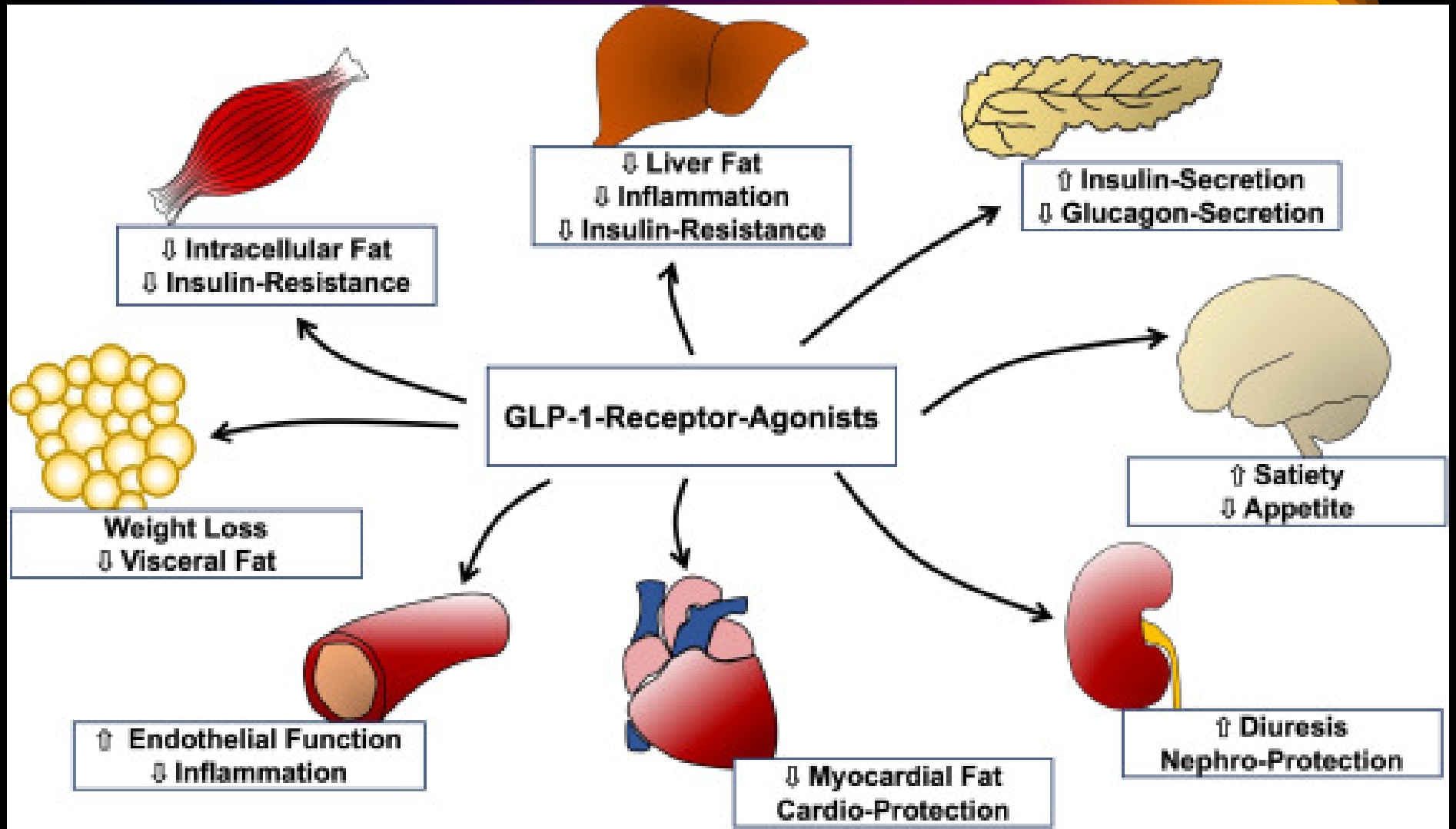
Practice Point 3.8.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.



Cox, E.J.;. *US Endocrinol.* 2020: *16*, 80–87.

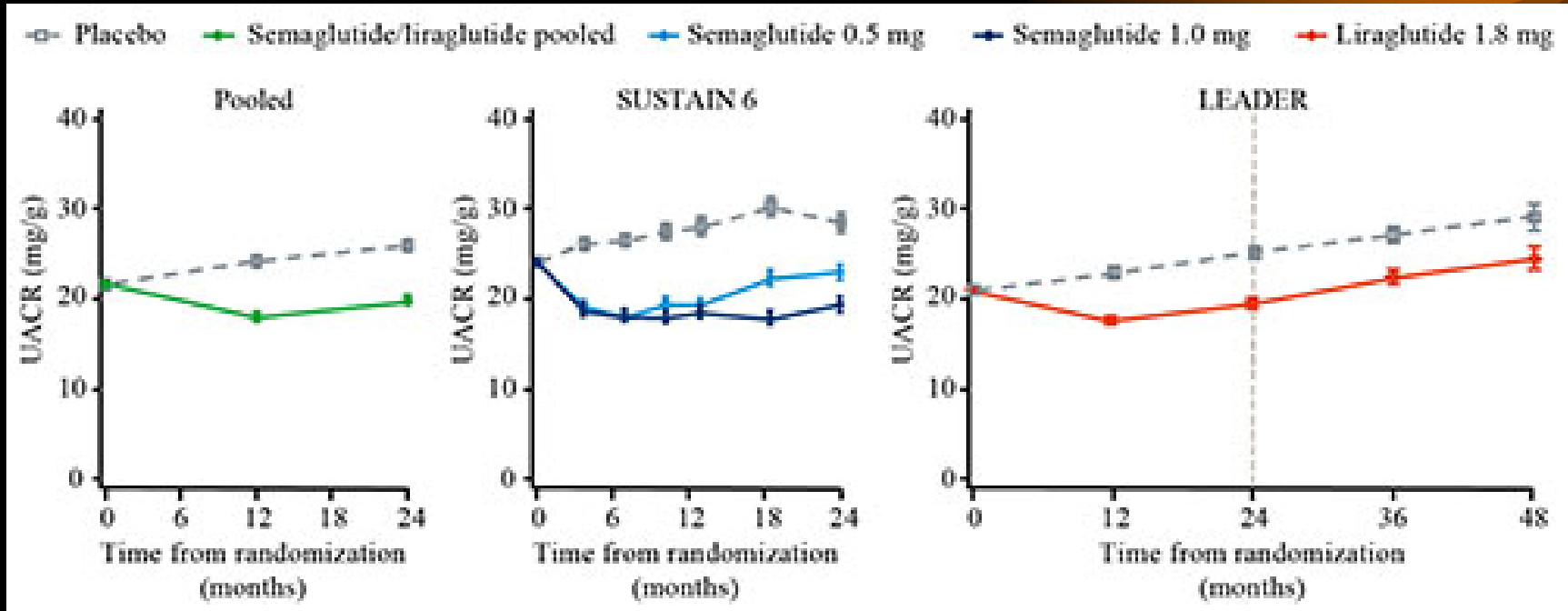
Janina Senn, Stefan Fischli, in Visceral and Ectopic Fat, 2023

Multi-Organ Effects of GLP-1 Activation



Shaman A. et al. Circulation. 2022;145:575–585

GLP-1 Agonists Reduce Proteinuria Indepedant of other Therapy



Estimated treatment ratio at 2 years (treatment vs placebo) [95% CI]; *p* value*			
Overall pooled trial population	SUSTAIN 6		LEADER
	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Liraglutide 1.8 mg
0.76 [0.73, 0.80]; $p<0.001$	0.80 [0.72, 0.90]; $p<0.001$	0.67 [0.60, 0.76]; $p<0.001$	0.77 [0.73, 0.82]; $p<0.001$
Estimated treatment ratio at 2 years (by-treatment comparisons) [95% CI]; *p* value			
Liraglutide 1.8 mg vs semaglutide 0.5 mg	0.96 [0.85, 1.09]; $p=0.53$	Liraglutide 1.8 mg vs semaglutide 1.0 mg	1.15 [1.02, 1.31]; $p=0.024$

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GLP-1 Agonists Reduce Decline in GFR

Subgroup/outcome	Events/N_{Active}	Events/$N_{Placebo}$	HR [95% CI]	*p* value	*p* value for interaction
Pooled population					
30% eGFR reduction	791/6316 (12.5%)	848/6321 (13.4%)	0.92 [0.84, 1.02]	0.10	
40% eGFR reduction	378/6316 (6.0%)	432/6321 (6.8%)	0.86 [0.75, 0.99]	0.039	
50% eGFR reduction	185/6316 (2.9%)	229/6321 (3.6%)	0.80 [0.66, 0.97]	0.023	
57% eGFR reduction	121/6316 (1.9%)	135/6321 (2.1%)	0.89 [0.69, 1.13]	0.34	
eGFR ≥90 mL/min/1.73m²					
30% eGFR reduction	255/2112 (12.1%)	246/2156 (11.4%)	1.05 [0.88, 1.25]	0.61	0.017
40% eGFR reduction	110/2112 (5.2%)	116/2156 (5.4%)	0.95 [0.73, 1.23]	0.71	0.16
50% eGFR reduction	45/2112 (2.1%)	48/2156 (2.2%)	0.94 [0.63, 1.41]	0.77	0.11
57% eGFR reduction	26/2112 (1.2%)	23/2156 (1.1%)	1.14 [0.65, 1.99]	0.66	0.035
eGFR >60—<90 mL/min/1.73m²					
30% eGFR reduction	279/2633 (10.6%)	290/2673 (10.8%)	0.98 [0.83, 1.16]	0.82	0.017
40% eGFR reduction	117/2633 (4.4%)	132/2673 (4.9%)	0.90 [0.70, 1.16]	0.42	0.16
50% eGFR reduction	52/2633 (2.0%)	60/2673 (2.2%)	0.88 [0.61, 1.28]	0.51	0.11
57% eGFR reduction	31/2633 (1.2%)	32/2673 (1.2%)	0.99 [0.60, 1.62]	0.97	0.035
eGFR 30—<60 mL/min/1.73m²					
30% eGFR reduction	202/1400 (14.4%)	256/1333 (19.2%)	0.71 [0.59, 0.85]	0.0003	0.017
40% eGFR reduction	108/1400 (7.7%)	146/1333 (11.0%)	0.67 [0.52, 0.86]	0.002	0.16
50% eGFR reduction	56/1400 (4.0%)	91/1333 (6.8%)	0.56 [0.40, 0.78]	0.001	0.11
57% eGFR reduction	36/1400 (2.6%)	61/1333 (4.6%)	0.54 [0.36, 0.81]	0.003	0.035
eGFR <30 mL/min/1.73m²					
30% eGFR reduction	55/171 (32.2%)	56/159 (35.2%)	0.86 [0.60, 1.25]	0.44	0.017
40% eGFR reduction	43/171 (25.1%)	38/159 (23.9%)	1.04 [0.67, 1.61]	0.86	0.16
50% eGFR reduction	32/171 (18.7%)	30/159 (18.9%)	0.99 [0.60, 1.62]	0.96	0.11
57% eGFR reduction	28/171 (16.4%)	19/159 (11.9%)	1.36 [0.76, 2.44]	0.30	0.035

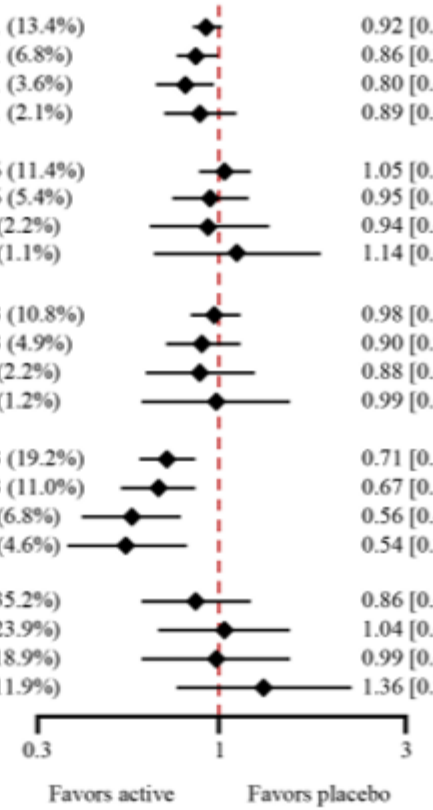


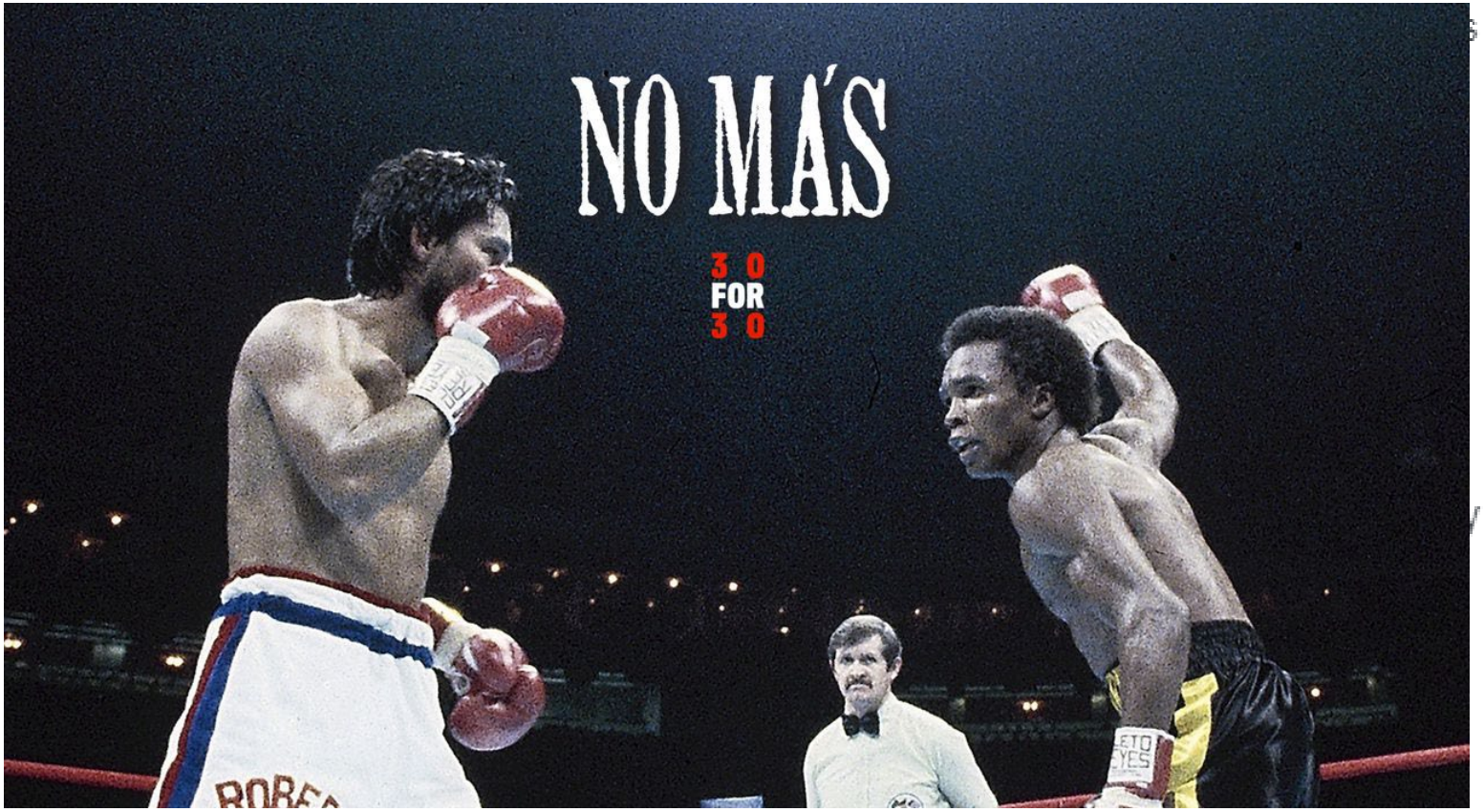
Figure 3. Effects of semaglutide and liraglutide versus placebo on time to the first persistent reduction in eGFR in the pooled population and subgroups according to eGFR at baseline.

FLOW TRIAL

- **Randomized, double-blind, parallel-group, placebo-controlled, superiority trial comparing injectable semaglutide 1.0 mg against placebo therapy as an adjunct to standard of care on kidney outcomes in DM and CKD**
  - **Onset of persistent ≥ 50% reduction in eGFR according to the CKD-EPI2 equation compared with baseline**
  - **Onset of persistent eGFR (CKD-EPI2) < 15 mL/min/1.73 m2,**
  - **Initiation of chronic kidney replacement therapy**
  - **Death from kidney disease or death from CVD**
  - **Annual rate of decline of GFR**

BioSpace

Novo Ends Semaglutide Kidney Study Early Due to Strong Efficacy Signals



Semaglutide WINS !!!

24% Reduction in CKD Progression


Nephroprotection in CKD
RAAS Inhibition
SGLT2 Inhibitors
Aldosterone Inhibitors
GLP-1 Agonists
Protein Restriction
Dietary and Medical management to control Blood Sugar as needed
Dietary and Medical management to control Blood Pressure 130/80

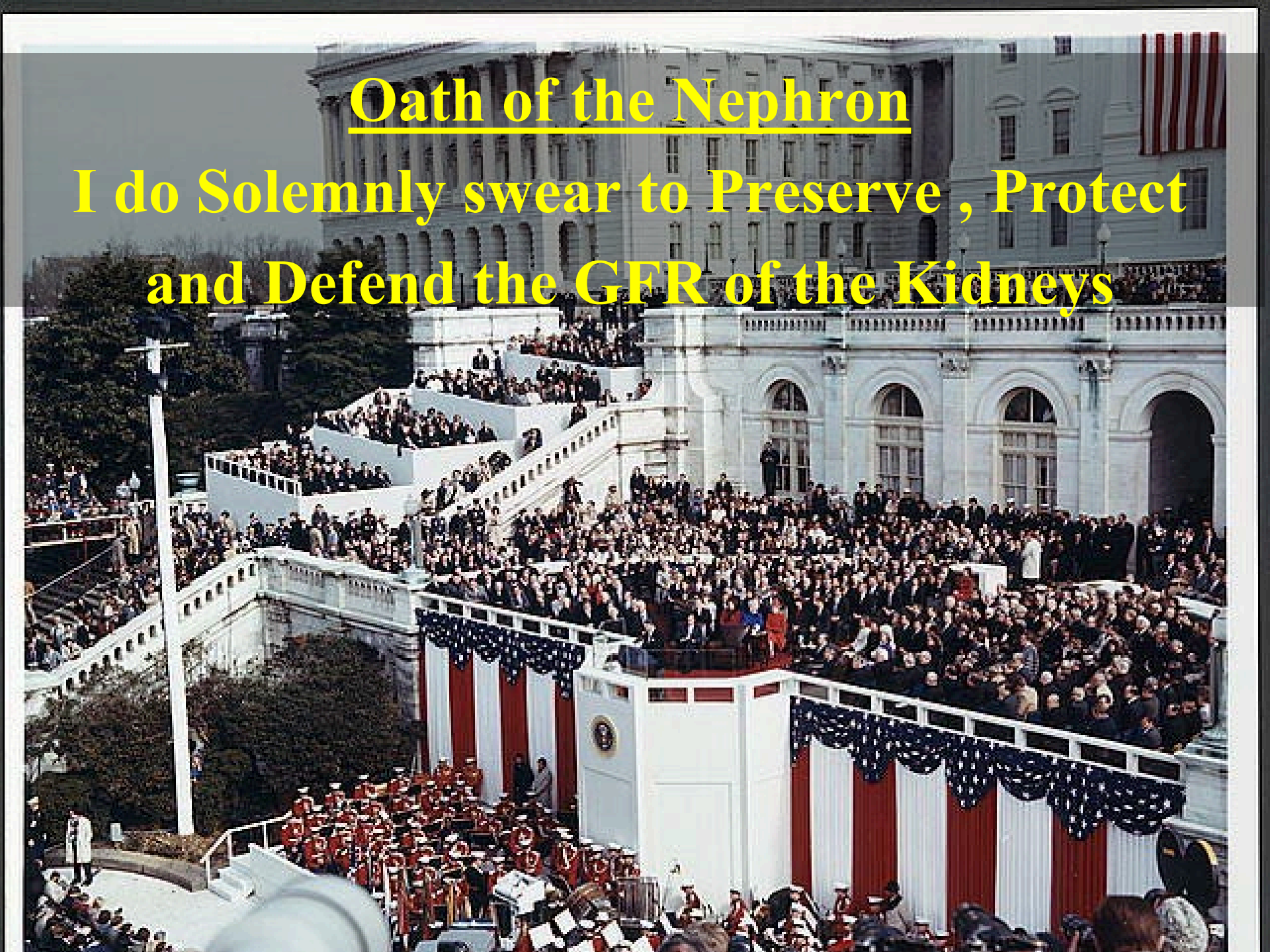
Nephroprotection : Decreased Emphasis on Protein Restriction

- **Early studies demonstrated a slower rate of decline of GFR in patients on low protein diets (<0.8 gm/kg/day)**
- **These results have not been substantiated in followup studies**
  - **Increase risk of malnutrition**
  - **Difficult to tolerate**
- **High protein diets have been shown in increase GFR and increase decline in GFR**

3.3.1. Protein intake
Recommendation 3.3.1.1: We suggest maintaining a protein intake of 0.8 g/kg/day in adults with CKD G3–G5 (2C).

Practice Point 3.3.1.2: Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression.

Interventions that Improve Morbidity and Mortality but Are Not Associated with Nephroprotection


Oath of the Nephron
I do Solemnly swear to Preserve , Protect
and Defend the GFR of the Kidneys

References

- KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International (2024) 105 (Suppl 4S), S117–S314
- Cox, E.J. (2020). US Endocrinology, 16, 80–87.
- Shaman, A., et al. (2022). Circulation, 145, 575–585.
- Schaefer, L., & Pierre, S. V. (2023). Cell and Molecular Physiology Section of the American Physiological Society in connection with American Journal of Physiology-Cell Physiology. American Journal of Physiology-Cell Physiology, 325(1), C362-C363.