Patient Case

Managing Diabetic Kidney Disease

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Indianapolis, IN, USA

Shirley

Shirley, a 66 y/o female presents to the office for follow-up of her previously diagnosed diabetes. She has joined a *Silver Sneakers®* exercise class and is cooking more at home. Ophthalmology reported minimal signs of cataracts

PMH: DM x 4y, hyperlipidemia x 6y, hypertension x 2y

Meds: Metformin XL 500mg bid, atorvastatin 10mg qd, lisinopril 5mg qd

Labs: A1C 7.8%, SCr 1.3mg/dL (eGFR 45ml/min *CKD-EPI 2021*), K 4.5mEq/dL, CBC WNL, LDL 96 mg/dL

PE: 132/86, lungs and chest clear, heart with RRR, abd soft, non-tender, decreased pedal pulses with normal neuro exam, 1+ bilateral edema to ankles

What is the next step in the evaluation and treatment of Shirley?

A) Increase the metformin
B) Order a urine albumin to creatinine ratio (UACR)
C) Order a lipid panel
D) Refer to cardiology

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KDIGO CKD Guidelines

A) Assessment of **both GFR and albuminuria** should be undertaken to evaluate progression with more frequent assessment required as kidney disease progresses

B) While cause of CKD is an important predictor of progression, it is the values of GFR and albuminuria that are used to assess progression

Progression of CKD is defined as either a progressive decrease in GFR or a progressive increase in albuminuria

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney inter.,* Suppl. 2013; 3: 1–150.

Staging, Monitoring and Prognosis of Chronic Kidney Disease

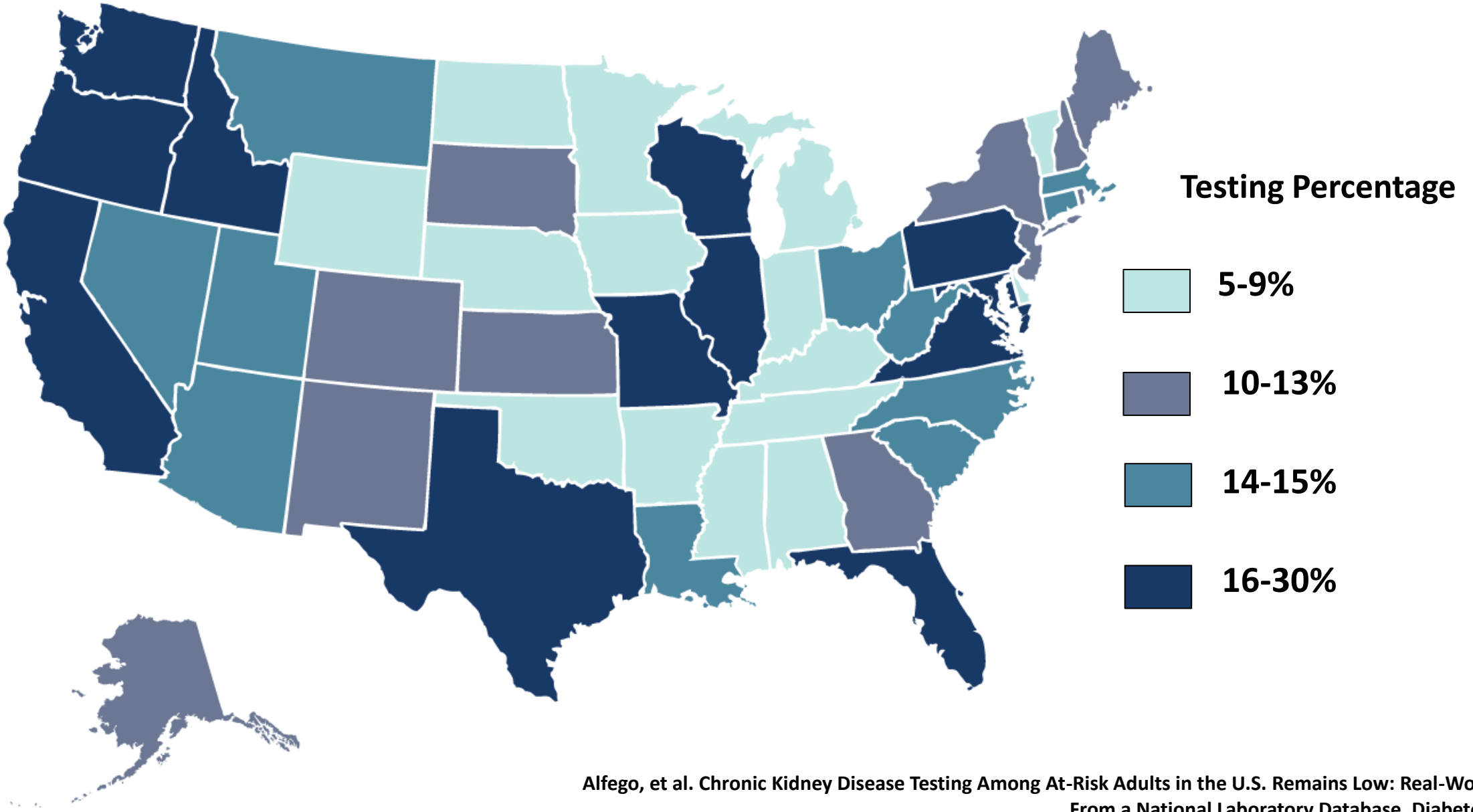
GFR categories (mL/min/1.73 m²) Description and range	Previous NKF CKD stage	Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category			Persistent albuminuria categories Description and range		
					A1	A2	A3
					Normal to mildly increased	Moderately increased	Severely increased
					<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	1	G1	Normal or high	≥90	**1 if CKD**	**1**	**2**
	2	G2	Mildly decreased	60-89	**1 if CKD**	**1**	**2**
	3	G3a	Mild to moderately decreased	45-59	**1**	**2**	**3**
		G3b	Moderately to severely decreased	30-44	**2**	**3**	**3**
	4	G4	Severely decreased	15-29	**3**	**3**	**4+**
	5	G5	Kidney failure	<15	**4+**	**4+**	**4+**

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

CKD = chronic kidney disease; GFR = glomerular filtration rate; NKF = National Kidney Foundation.

Vassalotti, Joseph A., et al. "*The American Journal of medicine* 2016; 129.2: 153-162.

Rates of Testing Patients with DM/HTN (CKD Risk) 2013 - 2018



Alfego, et al. Chronic Kidney Disease Testing Among At-Risk Adults in the U.S. Remains Low: Real-World Evidence From a National Laboratory Database, Diabetes Care 2021

Rates of Testing Patients with DM/HTN (CKD Risk) 2013 - 2018

Despite guideline recommendations, ordering an UACR and eGFR ranged from **5-30%** in 2018

>80% were not tested during the 6-year study period even when carrying a diagnosis of DM and/or HTN

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B) Add a 2nd diabetic medication
C) Increase the lisinopril
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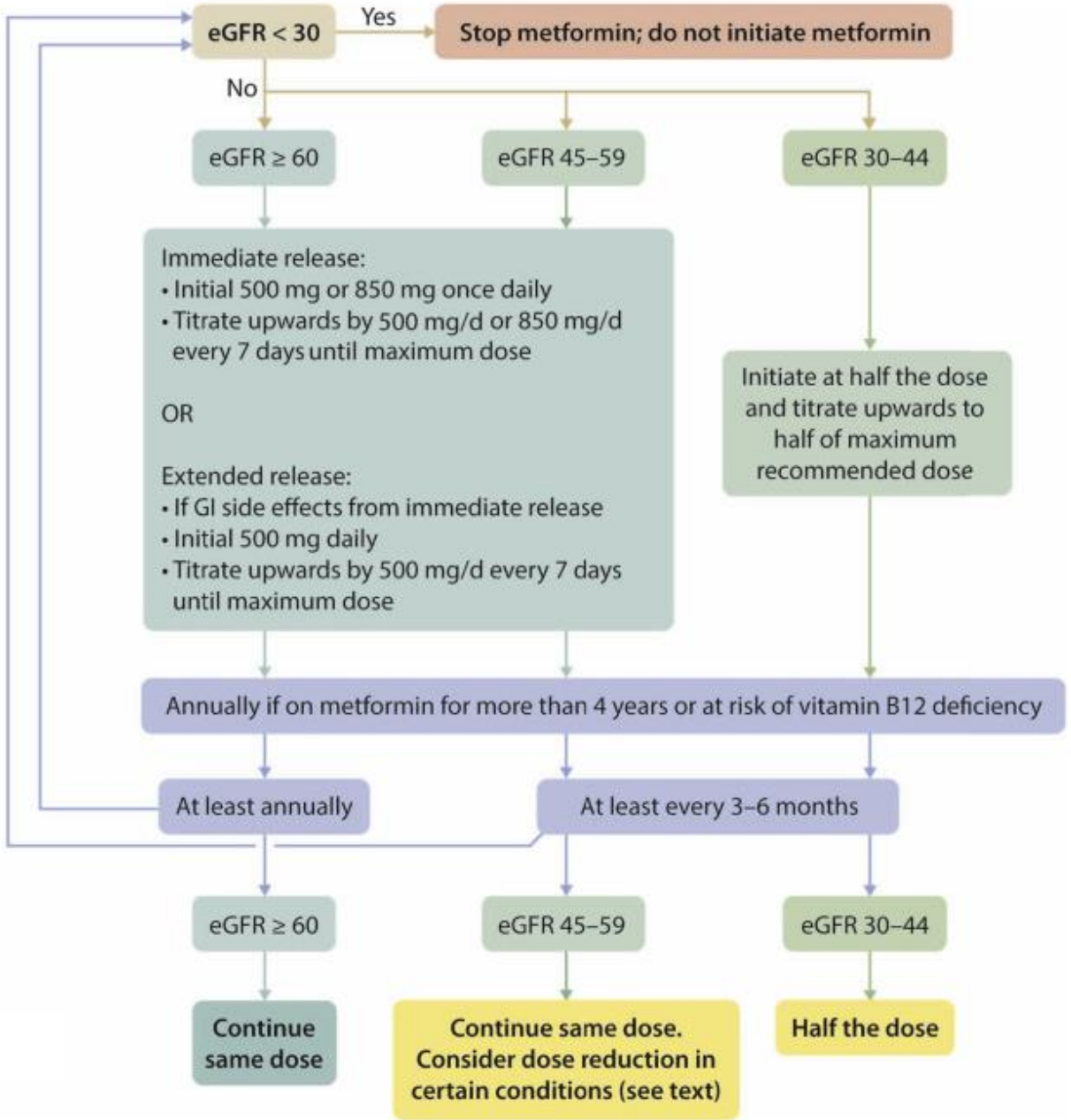
Metformin Dosing in CKD: Algorithm Format



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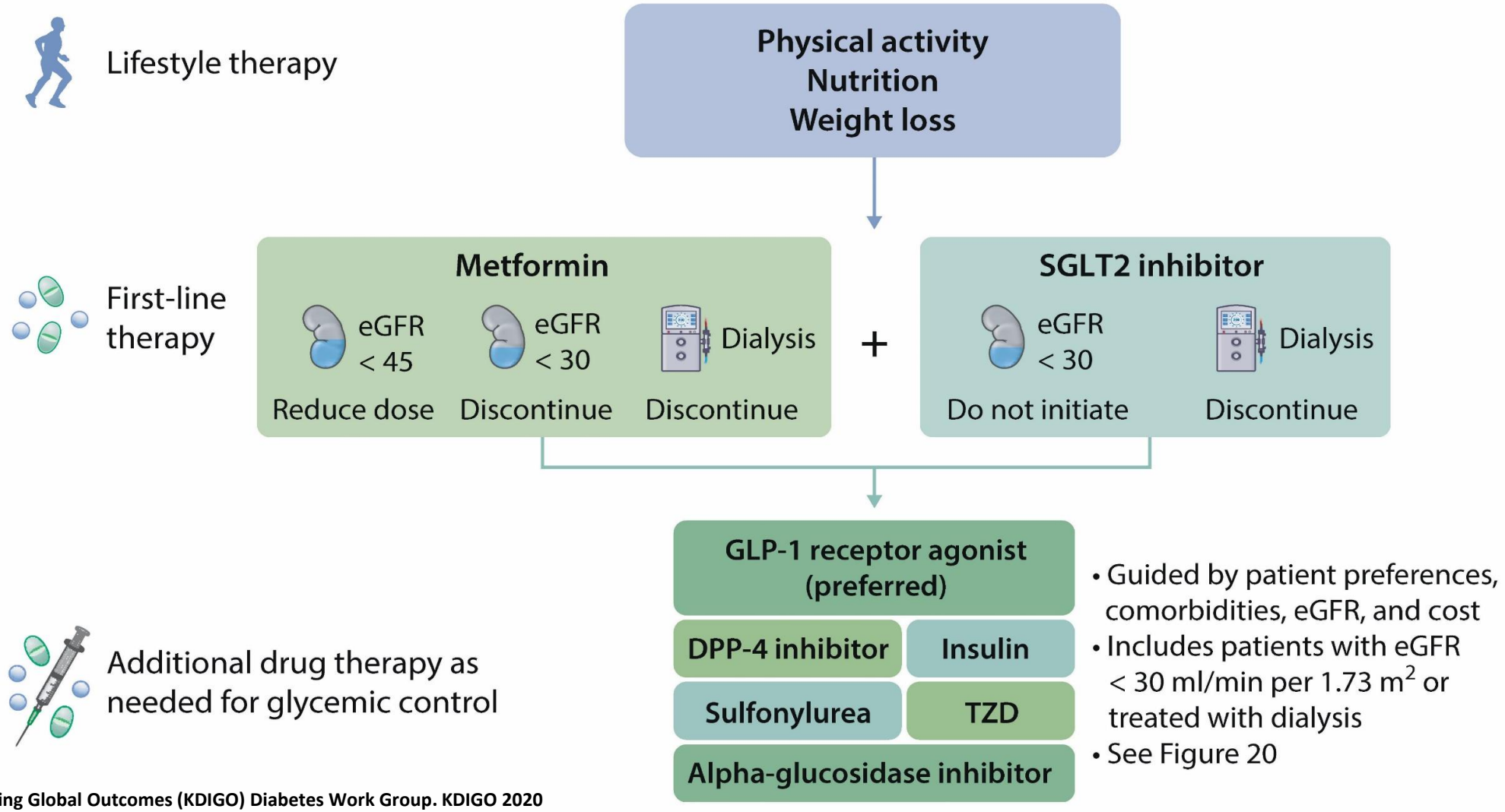
We all agree to add a 2nd diabetes medication. What would you add?

A) A DPP-4 inhibitor
B) A Sulfonylurea
C) An SGLT2i
D) A GLP1 receptor agonist

KDIGO 2020 Clinical Practice Guideline for DM Management in CKD



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Comparison of the effects of three novel classes of glucose-lowering drugs on AKI risk in patients with or without type 2 diabetes

CJASN
Clinical Journal of the American Society of Nephrology

Electronic databases
Pubmed
Embase
Cochrane CENTRAL

Up to September 2020

2 independent reviewers

Event-driven CV or kidney outcome trials

n = 18 trials
(Patients with Type 2 diabetes only)

n = 2 trials
(Patients with or without Type 2 diabetes)

18 trials

156,690
Patients with Type 2 diabetes only

2051
AKI events

Risk of AKI (vs placebo)

SGLT2 inhibitors	OR 0.76 (95% CI 0.66-0.88)
DPP-4 inhibitors	OR 1.12 (95% CI 0.93-1.35)
GLP-1R agonists	OR 0.96 (95% CI 0.83-1.11)

Risk of AKI (Comparisons between drugs)

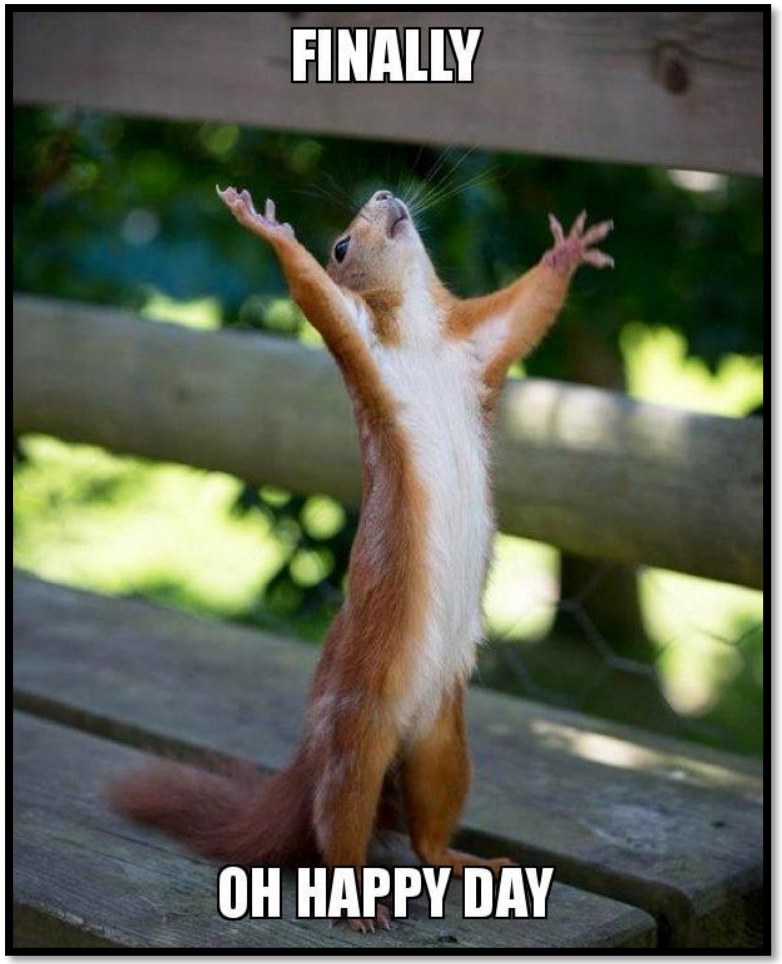
SGLT2 inhibitors vs DPP-4 inhibitors	OR 0.68 (95% CI 0.54-0.86)
SGLT2 inhibitors vs GLP1-R agonists	OR 0.79 (95% CI 0.65-0.97)

Conclusion Current evidence indicates that SGLT2 inhibitors have a lower risk of AKI than both DPP-4 inhibitors and GLP-1RAs.

Min Zhao, Shusen Sun, Zhenguang Huang, et al. ***Network Meta-Analysis of Novel Glucose-Lowering Drugs on Risk of Acute Kidney Injury***. CJASN doi: 10.2215/CJN.11220720. **Visual Abstract by Edgar Lerma, MD, FASN**

Benefits of SGLT2i

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



Kristensen KB, et al. Diabetilogia 2021

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90 day repeat labs: A1C of 7.5%, SCr 1.3mg/dL, UACR of 427 mg/g, BP 124/74

PE: 128/78, lungs and chest clear, heart with RRR, abd soft, non-tender, decreased pedal pulses with normal neuro exam, 1+ bilateral edema to ankles

What is the next step for Shirley?

A) Wait and repeat labs in another 90 days
B) Add a GLP1 receptor agonist
C) Add finerenone
D) Add a TZD

Very High Risk ASCVD Conditions
CKD (eGFR 15-59ml/min) + A2 albuminuria
Persistently elevated LDL-C (LDL-C>100mg/dL) on medication
History of heart failure
Age > 65y
Heterozygous familial hypercholesteremia
History of previous CABG or coronary intervention
Diabetes mellitus
HTN
Current Smoker

Grundy SM, et al. *Circulation.* 2019; 139:e1082–e1143

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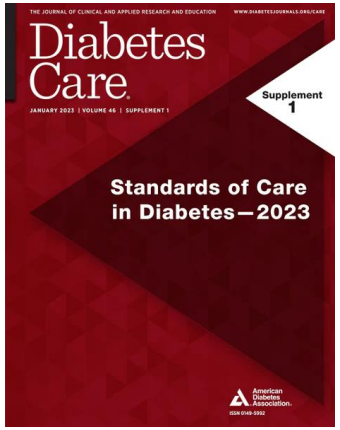
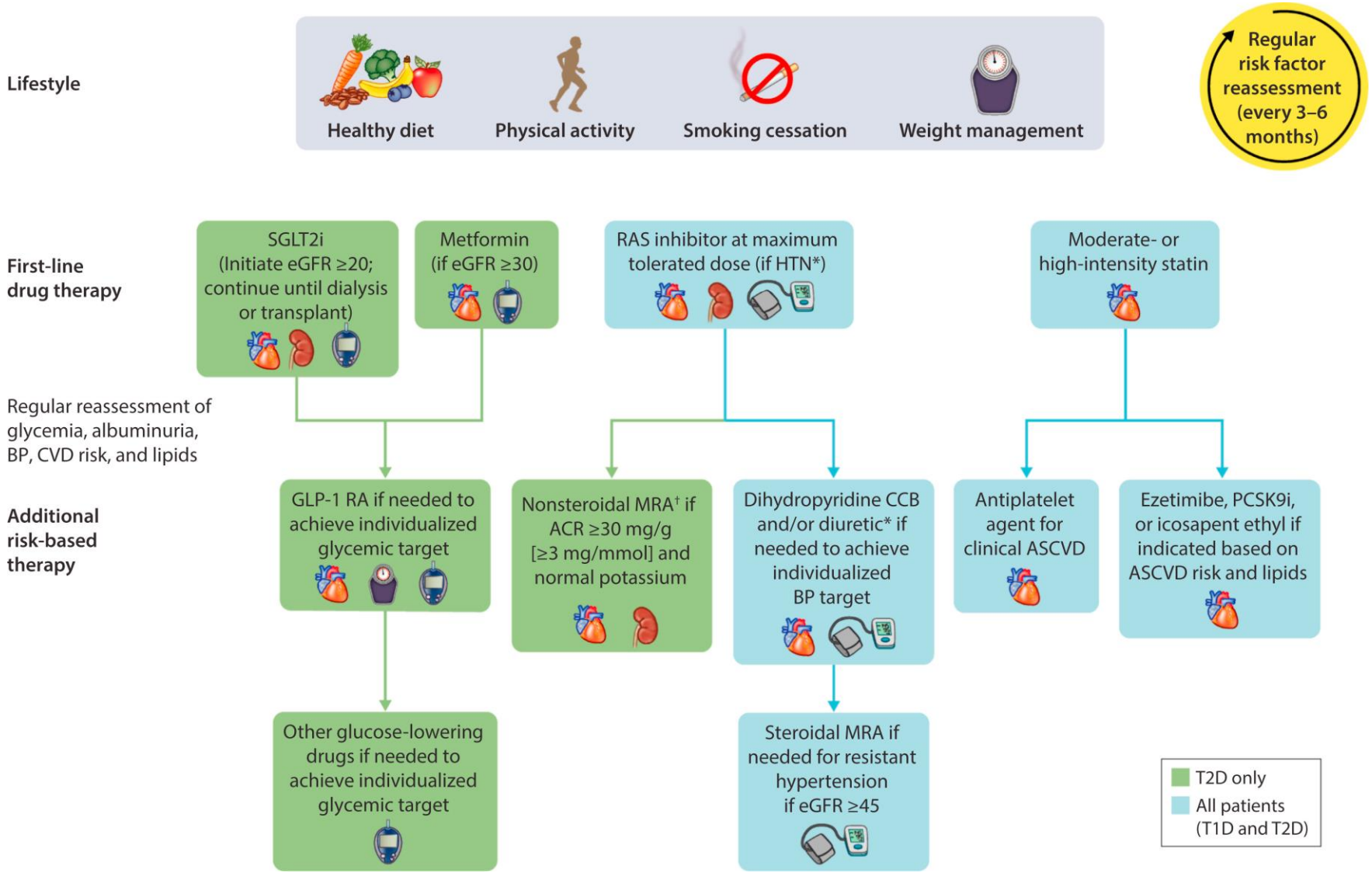
2023 ADA Standards of Care



- CKD broken out to its own section
- Cardiovascular disease (CVD) is more likely to kill your DKD patient (60-70%)
- Use an SGLT-2i with an eGFR ≥20 mL/min and UACR ≥200 mg/g (reduces CKD progression and CV events)
- SGLT2i for CV risk reduction with an eGFR or UACR ≥20 mL/min/1.73 m^2 or from normal - 200 mg/g, respectively
- Consider a glucagon-like peptide agonist, or the non-steroidal MRA finerenone (if eGFR ≥25 mL/min/1.73 $m^{2)}$ additionally for cardiovascular risk reduction
- In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events

ADA, 11. Chronic kidney disease and risk management: Standards of medical care in diabetes—2023. Diabetes Care. 2023;46(1):S191-S202

2022 KDIGO Guidelines for Diabetes Management in CKD



Executive Summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging evidence. ***Kidney Int.*** **2022;102.5: 990-999.**

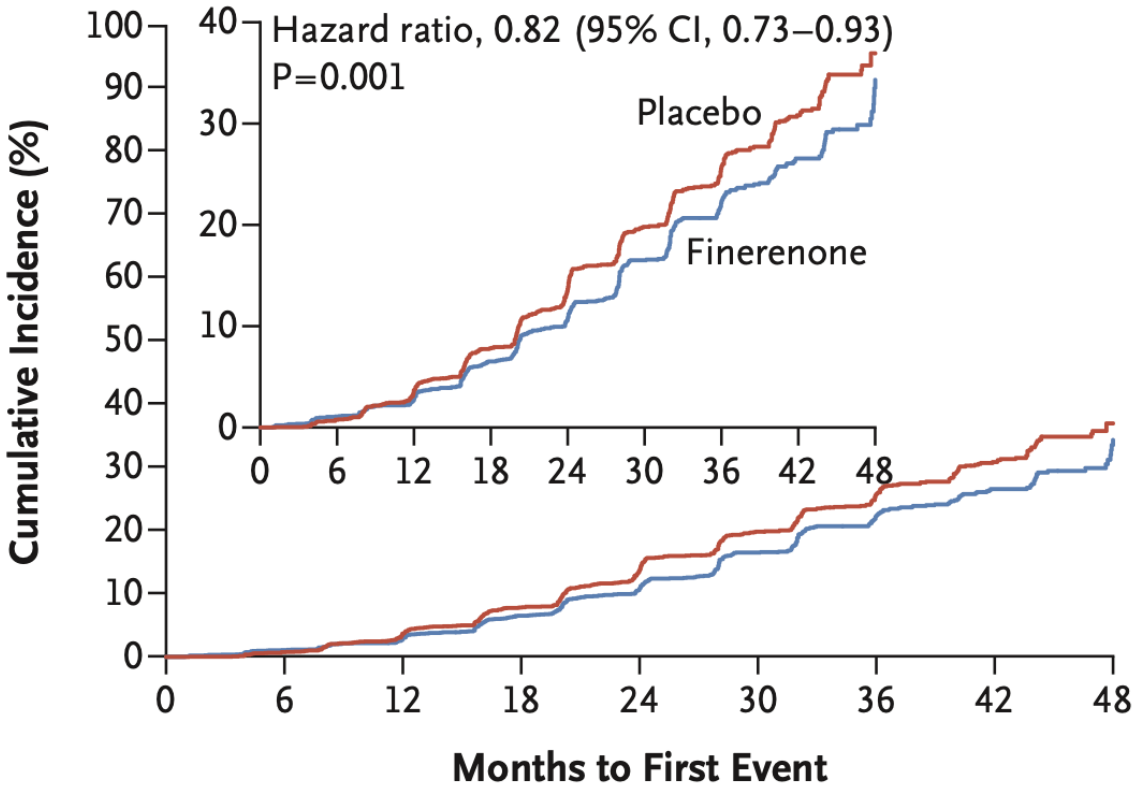
Mineralocorticoid Receptor Antagonist (MRA)

- Spironolactone introduced in 1987
- Originally developed as inhibitors of aldosterone activity and cortisol in order to decrease cardiac hypertrophy
- Used by cardiology to treat heart failure by inhibiting aldosterone at the mineralocorticoid receptor
- *Potential adverse effects*
  - *Gynecomastia (10% incidence)*
  - *Hyperkalemia (incidence depends of baseline K, eGFR)*
- Next generation introduced in 2021, a non-steroidal MRA, finerenone

Kolkhof P, Bärfacker L. *J Endocrinol*. 2017;234(1):T125-T140

Why Was Finerenone Added to the ADA Guidelines?

Primary Composite Outcome



Mechanism of Action

Induces conformational change within the mineralocorticoid receptor

Works to decrease inflammation

FDA 7/9/21:

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

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

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Shirley is at high risk for a cardiac event

She is showing persistent <u>hypertension and albuminuria</u>

2023 ADA guidelines state to add finerenone to treat both of these issues

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Which of the following need to be done prior to initiation of finerenone?

A) Cardiac cath
B) K levels
C) Serum calcium/phos level
D) Renal ultrasound

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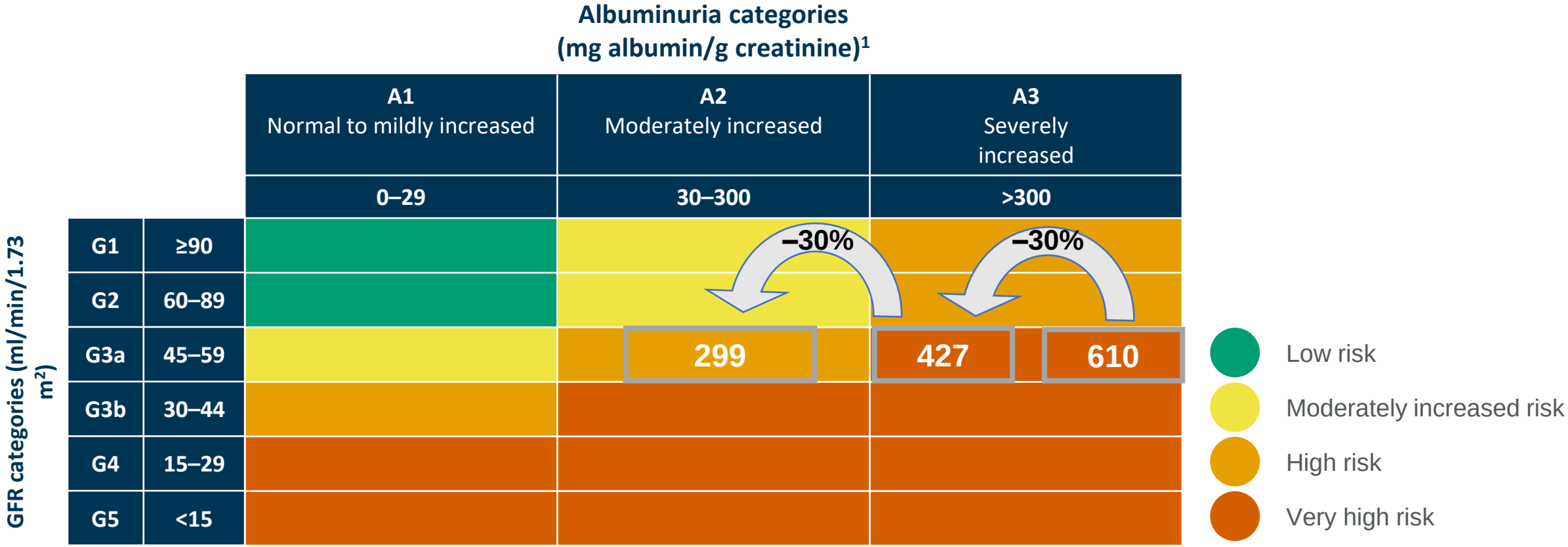
Each 30% reduction in UACR leads to kidney benefit, with the potential to reduce the risk of CKD progression from severe to moderate

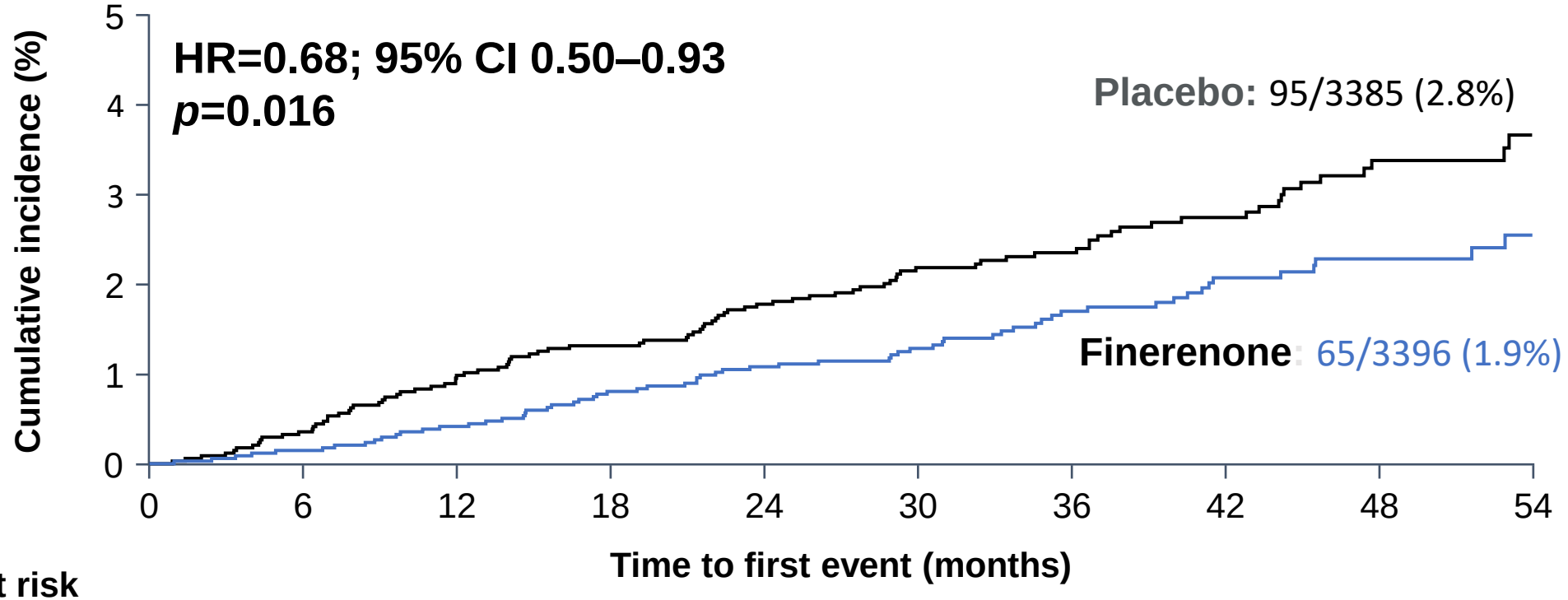


A >30% reduction in UACR may be required for some people to reduce their risk of CKD progression from severe to moderate

Kidney Disease: Improving Global Outcomes. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int 2022;102:S1–S127

On top of optimised RAS blockade, finerenone significantly reduced the risk of new-onset HF by 32%

Finerenone reduced new-onset HF in patients without a history of HF at baseline by 32%



No. at risk										
Finerenone	3396	3367	3323	3274	3195	2710	2168	1705	1091	608
Placebo	3385	3351	3294	3236	3154	2694	2131	1674	1091	606

FIGARO-DKD

Circulation. 2021;143:540–552.

Pearls for Management of DKD

- Over 40% of patients with diabetes will develop CKD;
  It is important to be aggressive with these patients
- You MUST have both an eGFR and UACR to stage and follow the DKD patient
- Start with metformin and an SGLT2i
- If persistent albuminuria or progressive loss of eGFR, add finerenone
- Your DKD patient is more likely to die of CVD than kidney failure