DIABETES AND THE KIDNEY

Update and review of the standards of care 2025

BY BEN LAWSON MD

CKD is classified based on: • **GFR (G)** • **Albuminuria (A)**				**Albuminuria categories** Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	**G1**	Normal or high	**≥90**	Screen 1	Treat 1	Treat and refer 2
	G2	Mildly decreased	**60-89**	Screen 1	Treat 1	Treat and refer 2
	G3a	Mildly to moderately decreased	**45-59**	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	**30-44**	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	**15-29**	Treat and refer 3	Treat and refer 3	**Treat and refer 4+**
	G5	Kidney failure	**<15**	**Treat and refer 4+**	**Treat and refer 4+**	**Treat and refer 4+**

Low risk (if no other markers of kidney disease, no CKD)

Moderately increased risk

High risk

Very high risk

Epidemiology of diabetes and CKD

- 20-40% of diabetics have CKD
- CKD usually develops after 10 years in type 1 diabetes
- CKD can be present at the diagnosis of type 2 diabetes
- Diabetes is the leading cause of ESRD in the USA
- CKD + Diabetes increases risk of cardiovascular disease
- Health care costs also sky rocket

Albuminuria

- Screening using spot MACR
- 24 HR urine studies: burdensome and add little to prediction or accuracy
- Normal MACR = <30mg/g
- Moderately elevated MACR 30-300mg/g
- Severely elevated MACR = >300
- Exercise, infection, fever, heart failure, hyperglycemia, menstruation, and HTN may increase MACR independent of kidney damage

eGFR

- Calculated from serum creatinine

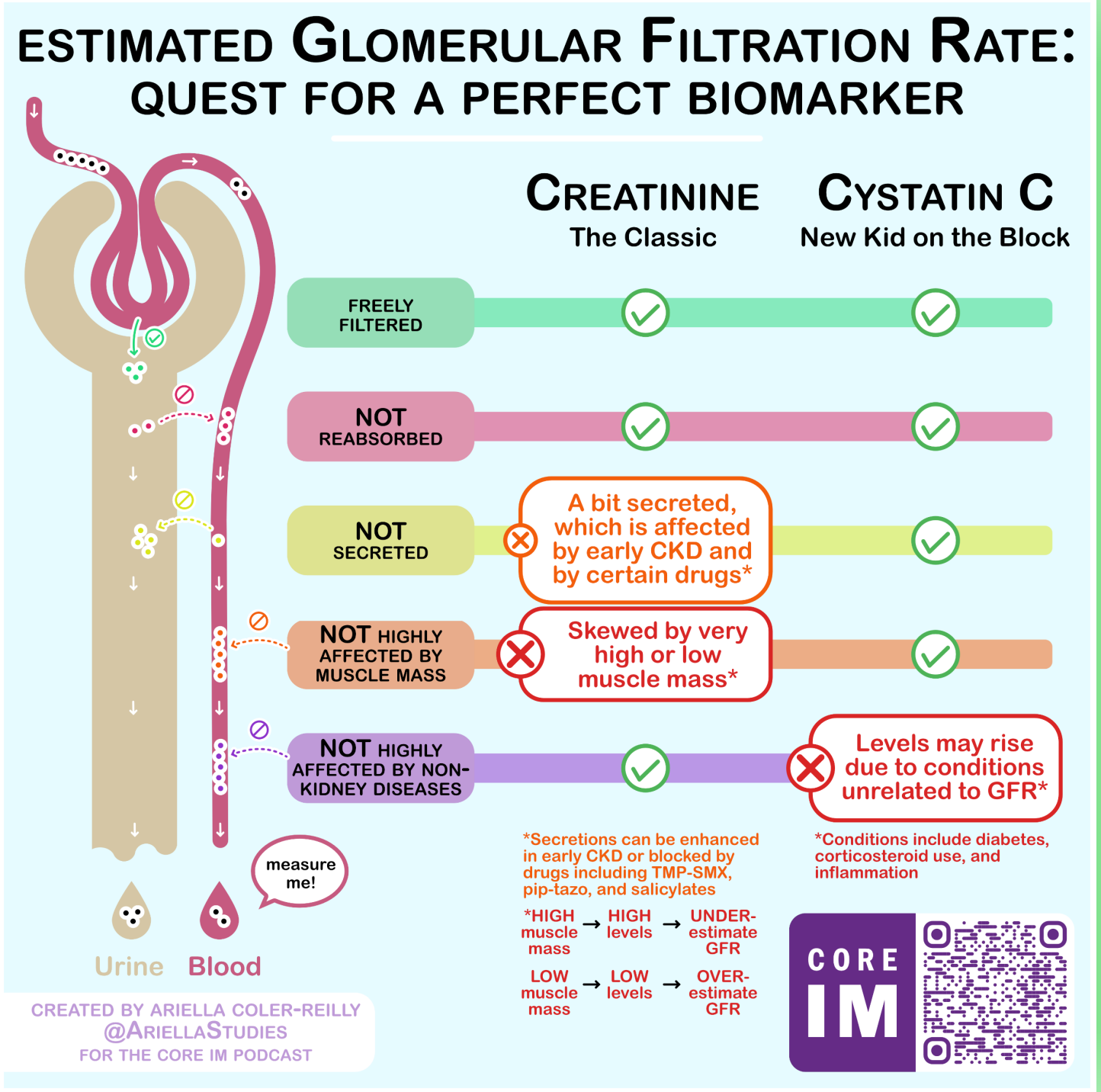
Table 3 – Formulas for estimating glomerular filtration rate*

Cockcroft-Gault[5]	$\frac{(140 - \text{age}) \times (\text{IBW})}{S_{Cr} \times 72}$
Modified MDRD[6†]	$186.3 \times S_{Cr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.210$ (if African American)

IBW, ideal body weight; S_{Cr}, serum creatinine; MDRD, Modification of Diet in Renal Disease.

*Age, years; IBW, kg; SCr, mg/dL.
†An online calculator based on the modified MDRD equation can be found at:

Cystatin c

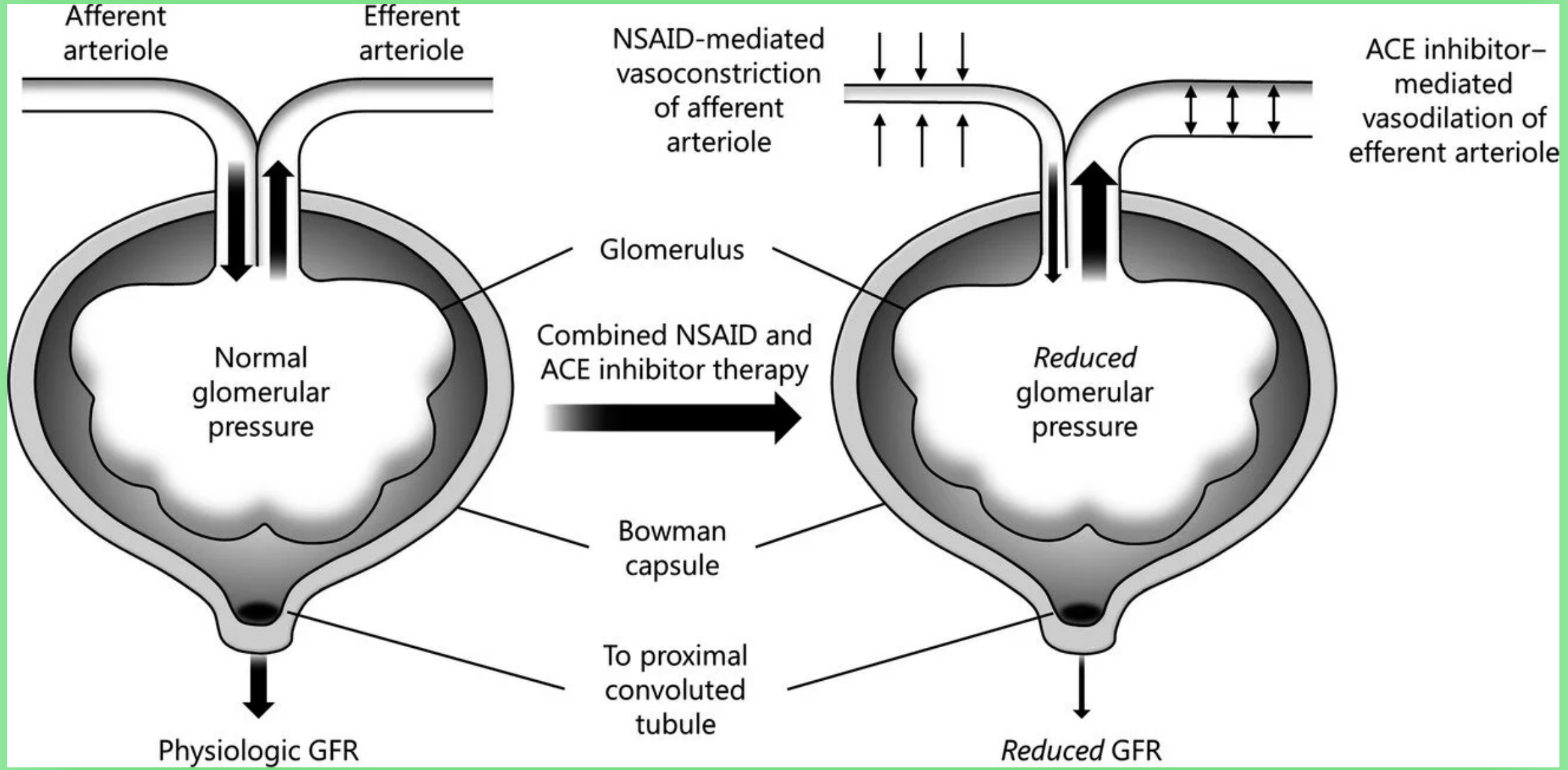

ESTIMATED GLOMERULAR FILTRATION RATE:
QUEST FOR A PERFECT BIOMARKER
CREATININE
The Classic
CYSTATIN C
New Kid on the Block
FREELY FILTERED
NOT REABSORBED
NOT SECRETED
A bit secreted, which is affected by early CKD and by certain drugs*
NOT HIGHLY AFFECTED BY MUSCLE MASS
Skewed by very high or low muscle mass*
NOT HIGHLY AFFECTED BY NON-KIDNEY DISEASES
Levels may rise due to conditions unrelated to GFR*
measure me!
Urine
Blood
*Secretions can be enhanced in early CKD or blocked by drugs including TMP-SMX, pip-tazo, and salicylates
*Conditions include diabetes, corticosteroid use, and inflammation
*HIGH muscle mass → HIGH levels → UNDER-estimate GFR
LOW muscle mass → LOW levels → OVER-estimate GFR
CREATED BY ARIELLA COLER-REILLY
@ARIELLASTUDIES
FOR THE CORE IM PODCAST
CORE IM

Diagnosis

- Clinical diagnosis
  - Based on albuminuria and reduced eGFR in absence of other causes of kidney damage
- Active urinary sediment + rapidly increasing albuminuria or total proteinuria + nephrotic syndrome + rapidly decreasing eGFR + absence of retinopathy = alternative or additional etiologies
- Rare for type 1 DM without retinopathy to develop Kidney Disease
- Renal biopsy

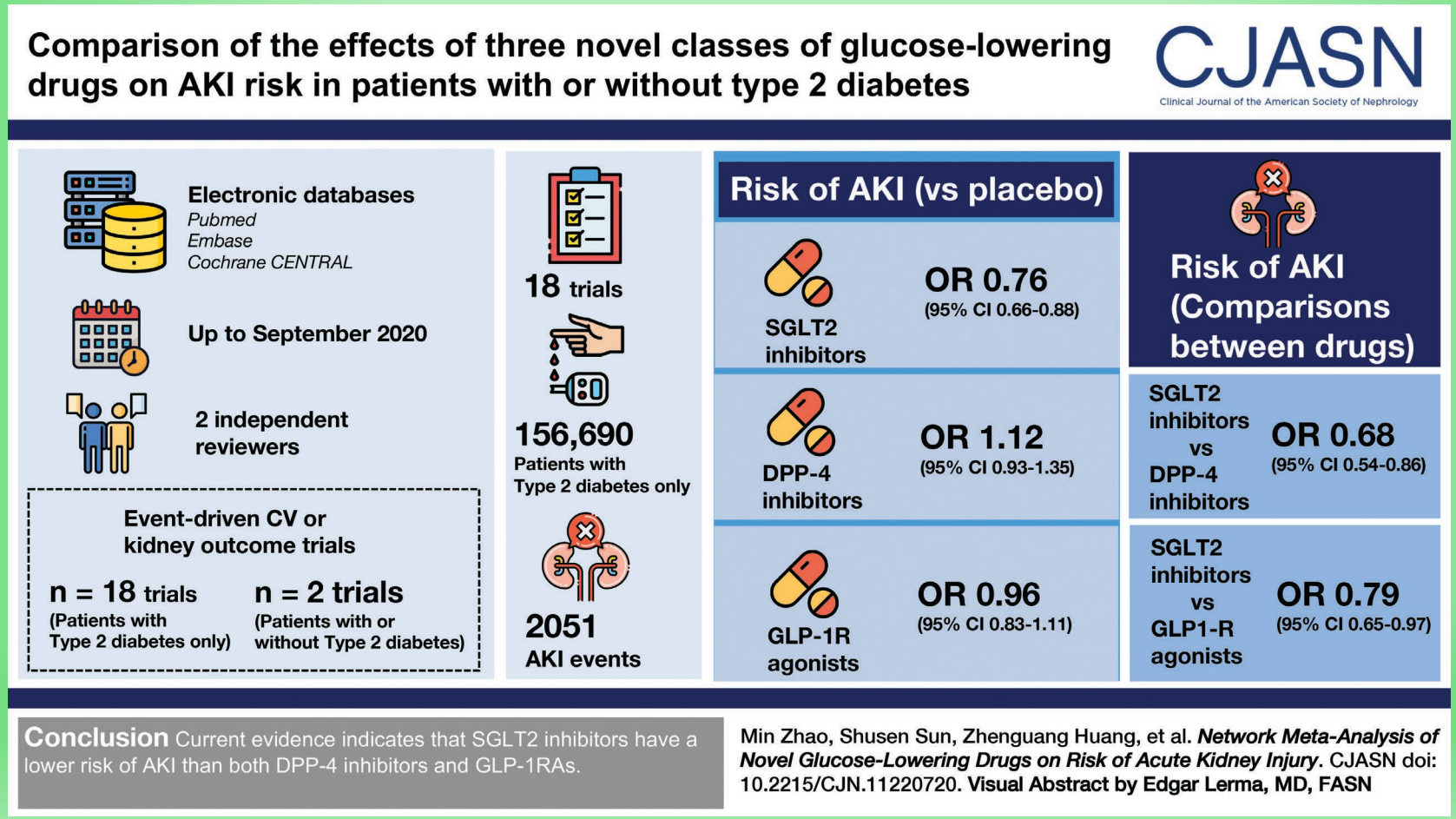
AKI

- Diagnosed by a sustained increase in serum creatinine
- Risk factors for AKI:
  - DM
  - NSAIDs
  - Iodinated radiocontrast
  - Meds that alter renal blood flow/ intrarenal hemodynamics (ACE/ARBs/ Diuretics)


Afferent arteriole
Efferent arteriole
NSAID-mediated vasoconstriction of afferent arteriole
ACE inhibitor–mediated vasodilation of efferent arteriole
Glomerulus
Normal glomerular pressure
Combined NSAID and ACE inhibitor therapy
Reduced glomerular pressure
Bowman capsule
To proximal convoluted tubule
Physiologic GFR
Reduced GFR

AKI and SGLT2 inhibitors

- Initial concern of AKI through volume depletion, especially when combined with diuretics, some studies say it does not



ACE and rise in Creatine

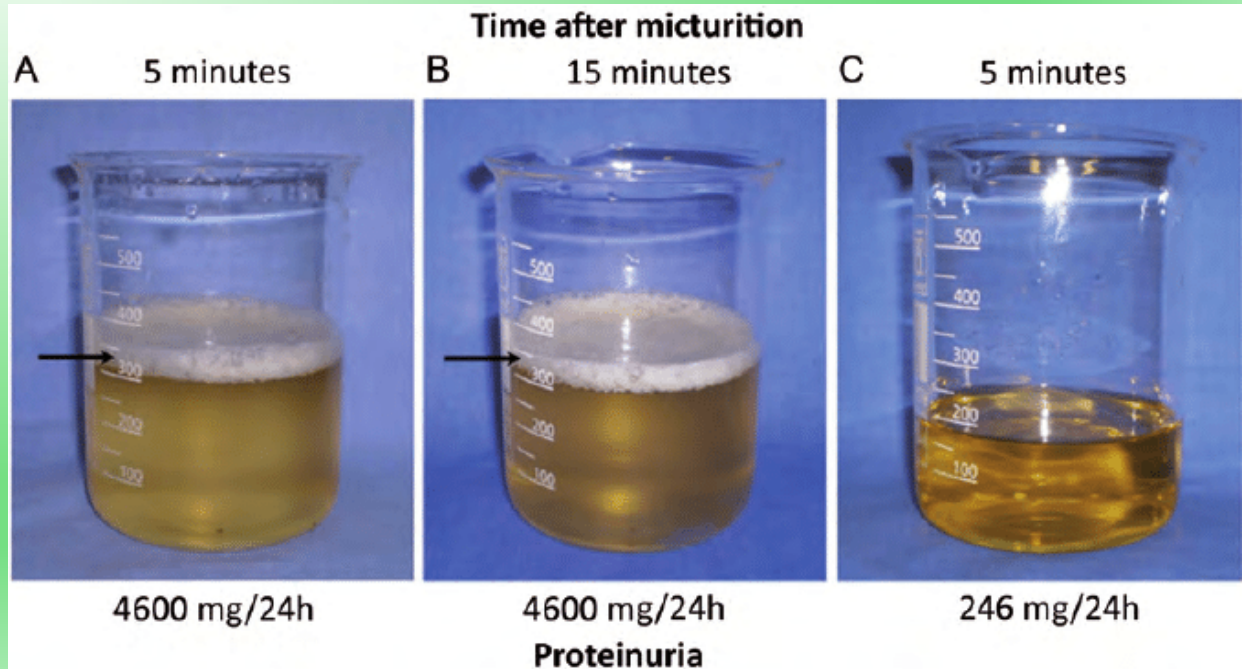
- Elevation in serum creatinine – up to 30% did not have any increase in mortality or progressive renal disease
- Therefore, ACE – and ARBs should NOT be discontinued for increases in serum creatinine < 30% in the absence of volume depletion

Surveillance

- Albuminuria and eGFR should be monitored at least annually to
  - enable timely diagnosis of CKD
  - Monitor progression of CKD
  - Detect superimposed kidney diseases including AKI
  - Assess risk of CKD complications
  - Dose medications
  - Determine nephrology referral
- EGFR less than 60 with ACE/ ARB or MRAs – monitor serum potassium

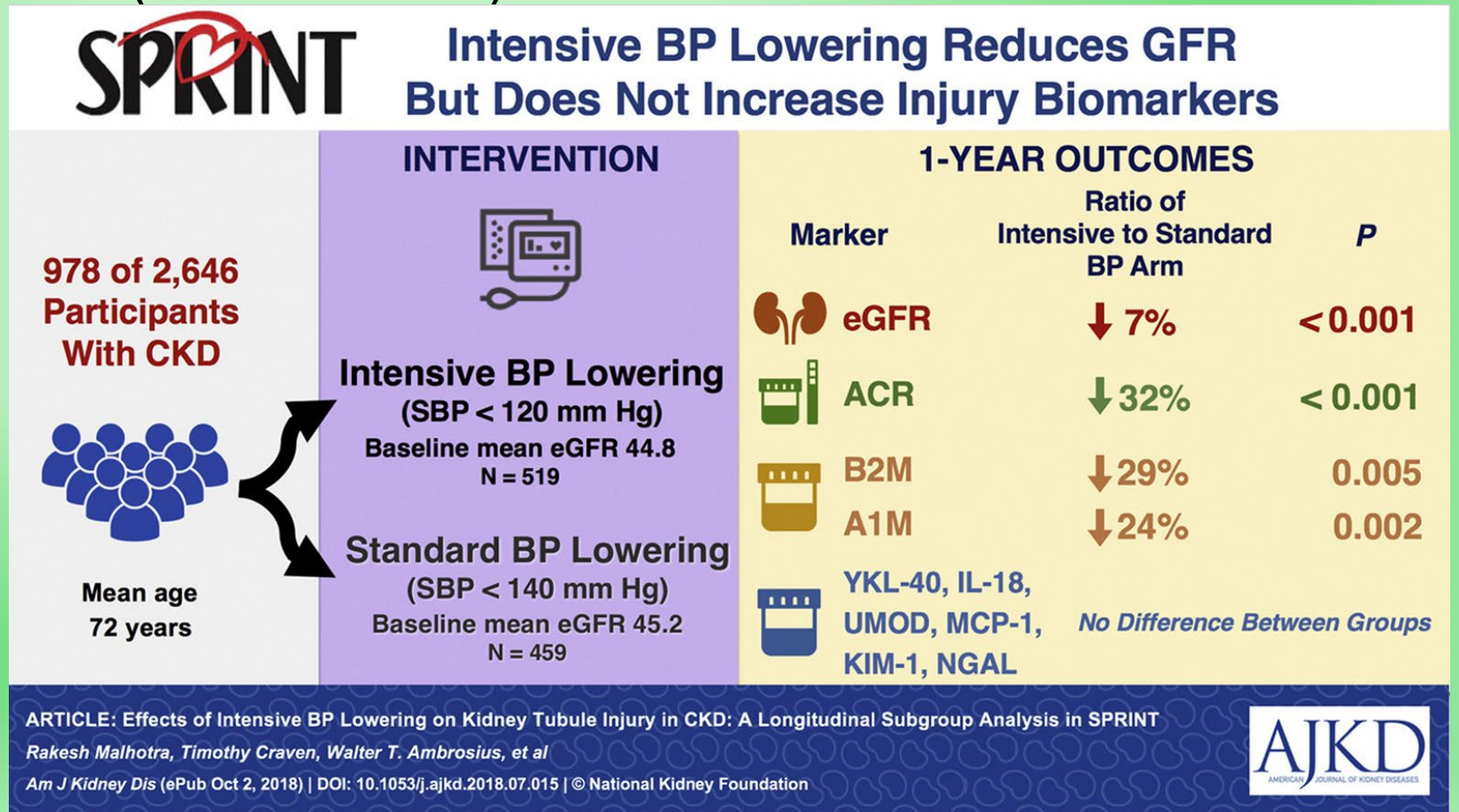
Ultimate goal – decrease proteinuria

- Interventions that lower albuminuria:
  - Blood glucose management
  - Blood pressure management
  - Treatment with ACE or ARB
  - Smoking cessation
  - Weight loss
  - Decrease salt in take
  - SGLT2 inhibitors, MRAs, GLP-1 RAs



Prevention

- Only proven primary prevention interventions for CKD in people with diabetes are blood glucose (A1C less than 7%) and blood pressure management (SPRINT Trial)

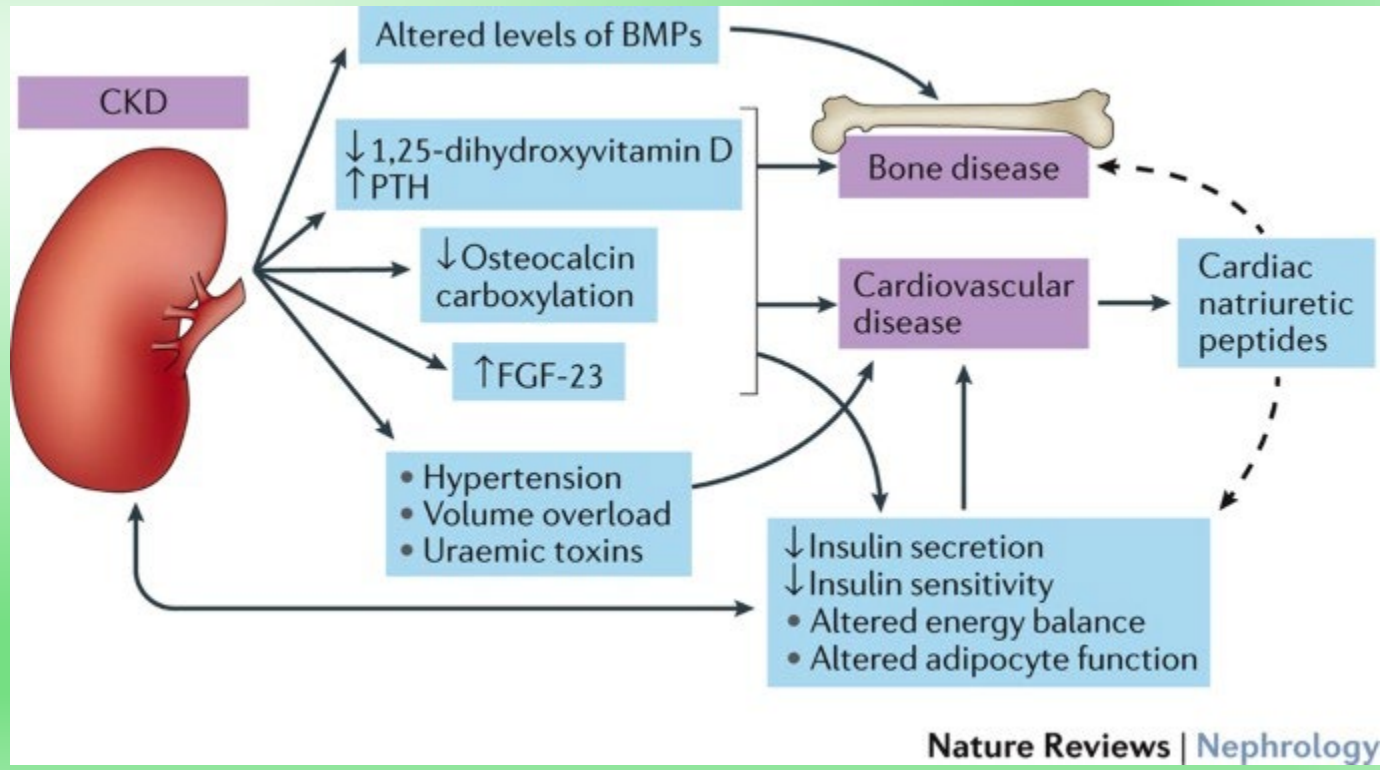


Interventions

- Nutrition:
  - CKD Stages 3-5 (non dialysis): protein intake should be about 0.8g/kg body weight per day
  - Higher levels of dietary protein intake (>1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality
  - Reducing protein intake to less than 0.8g/kg/day is not recommended
    - Does not alter glucose, CVD, or GFR decline
  - Restriction of dietary sodium (less than 2,300mg/day)

Interventions

- Glycemic control:
  - Achieving near-normoglycemia has been shown in large, randomized studies to delay the onset and progression of albuminuria and reduce GFR in people with DM1 and 2

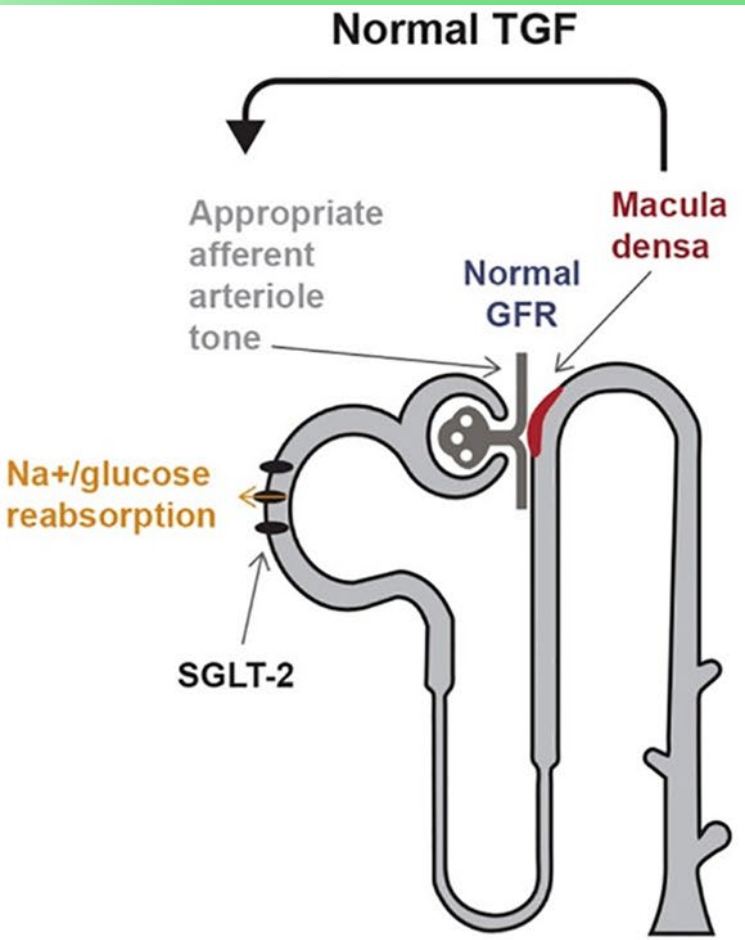


Interventions

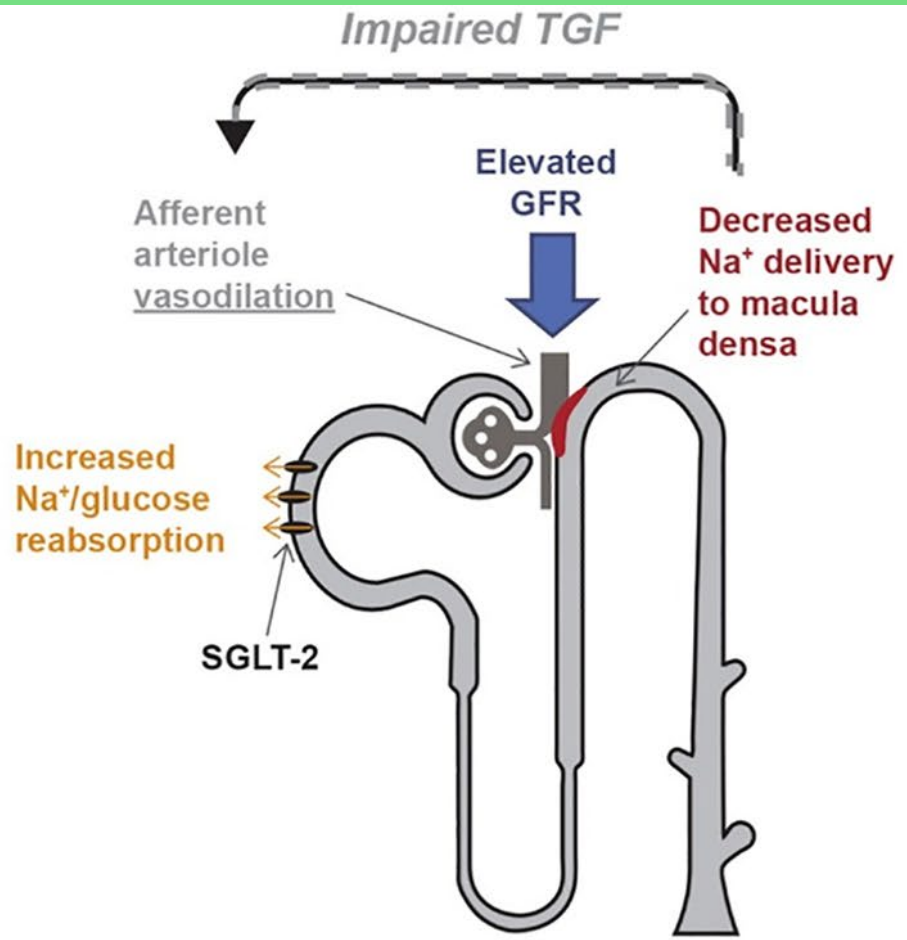
- BP control
  - Use of ACE – and ARBs remain mainstay of management with CKD and albuminuria for treatment of HTN in DM
  - HTN strong risk factor for progression of CKD
  - BP less than 130/80mmHg is recommended to reduce CVD mortality and slow CKD progression among those with DM
  - When increase in serum creatine reach 30% without associated hyperkalemia, RAS blockade should be continued ***
  - Avoid combination of ACE- and ARB – no benefit

Interventions

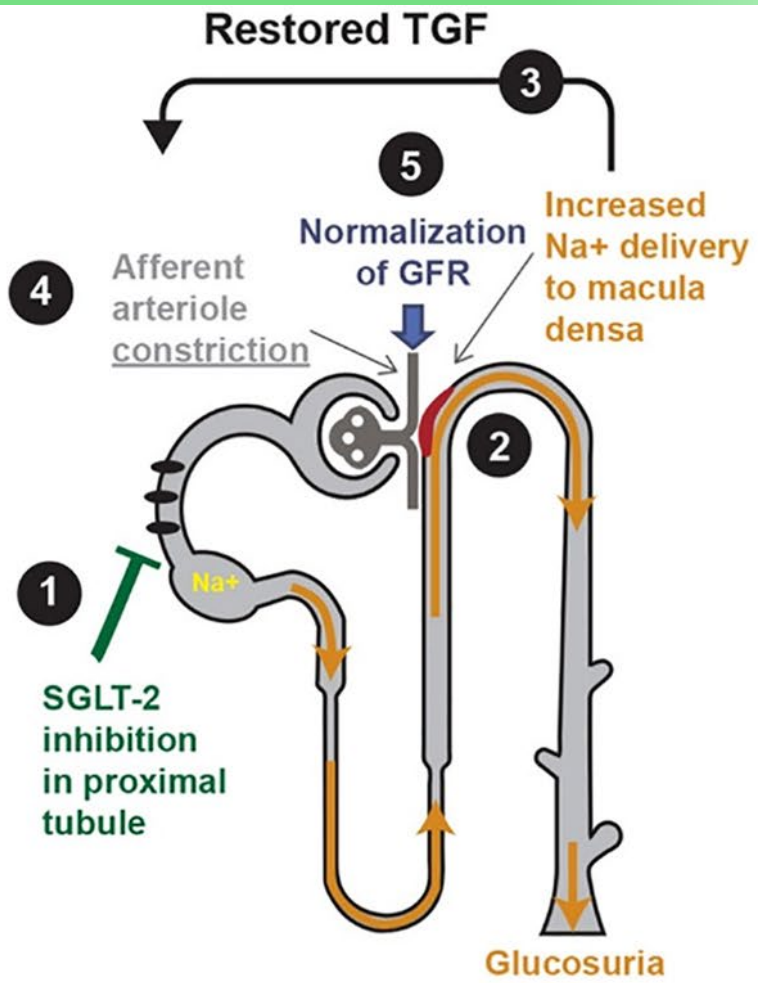
- Glucose lowering medications:
  - SGLT2 inhibitors:
    - reduce renal tubular glucose reabsorption, weight, systemic BP, intraglomerular pressure, and albuminuria and slow GFR loss
    - Reduce oxidative tress in the kidney by >50%
    - Reduce NLRP3 inflammasome activity
    - Recommend when GFR is equal or greater than 20!
  - GLP1 receptor agonist (Ozempic/ Mounjaro) – also improve outcomes



Normal physiology



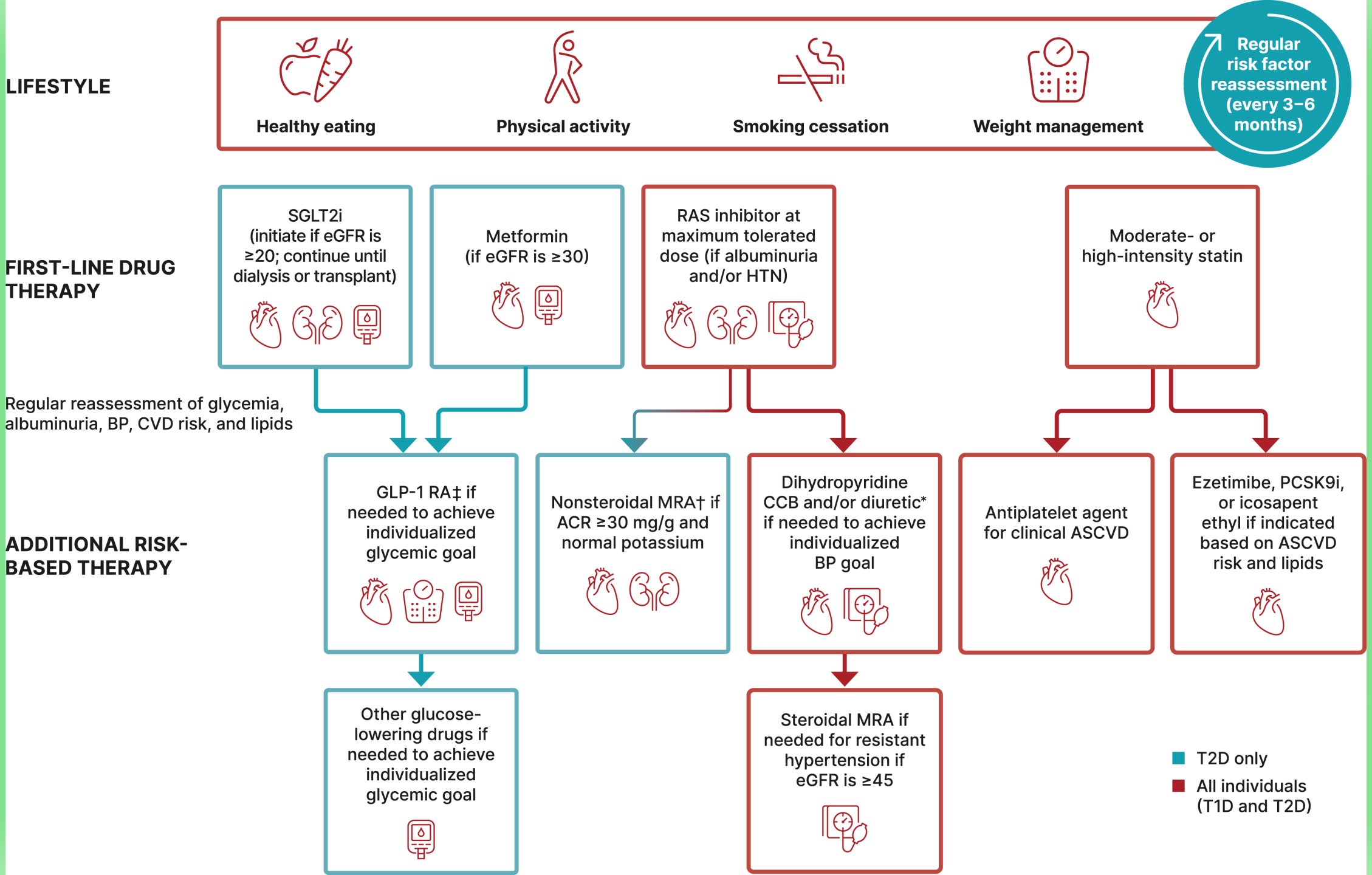
Hyperfiltration in early stages of diabetic nephropathy



SGLT-2 inhibition reduces hyperfiltration via TGF

Interventions

- Selection of Glucose lowering medications for people with CKD
  - Metformin:
    - contraindicated with GFR less than 30.
    - do not initiate if GFR less than 45
    - DC at the time or before iodinated contrast imaging procedures with GFR 30-60


LIFESTYLE
Healthy eating
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
FIRST-LINE DRUG THERAPY
SGLT2i (initiate if eGFR is ≥20; continue until dialysis or transplant)
Metformin (if eGFR is ≥30)
RAS inhibitor at maximum tolerated dose (if albuminuria and/or HTN)
Moderate- or high-intensity statin
Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids
ADDITIONAL RISK-BASED THERAPY
GLP-1 RA‡ if needed to achieve individualized glycemic goal
Nonsteroidal MRA† if ACR ≥30 mg/g and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP goal
Antiplatelet agent for clinical ASCVD
Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids
Other glucose-lowering drugs if needed to achieve individualized glycemic goal
Steroidal MRA if needed for resistant hypertension if eGFR is ≥45
T2D only
All individuals (T1D and T2D)

Trials to know

- EMPA-REG: empagliflozin reduced risk of incident or worsening nephropathy by 39% and risk of doubling of serum Cr accompanied by eGFR less or equal to 45 by 44%
- CANVAS: canagliflozin reduced risk of progression of albuminuria by 27% and risk of reduction in eGFR, ESKD, or death from ESKD by 40%
- LEADER: liraglutide reduced risk of new or worsening nephropathy by 22%
- SUSTAIN-6: semaglutide reduced risk of new or worsening nephropathy by 36%

CREDENCE

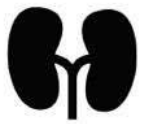
CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

The George Institute for Global Health

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

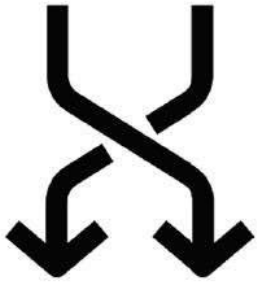


eGFR 57

UACR 927 mg/g

Intervention

Stable on maximum dose tolerated ACEi or ARB for 4 weeks

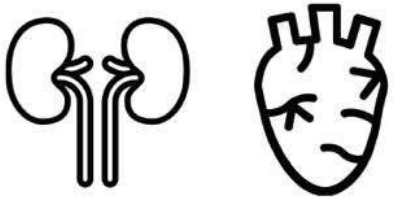


Canagliflozin **Placebo**

Outcomes

Primary outcome

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



HR 0.70
(95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68
(95% CI 0.54-0.86)

NNT 42

No increased risk of:

Amputations

HR 1.10
(95% CI 0.79-1.56)

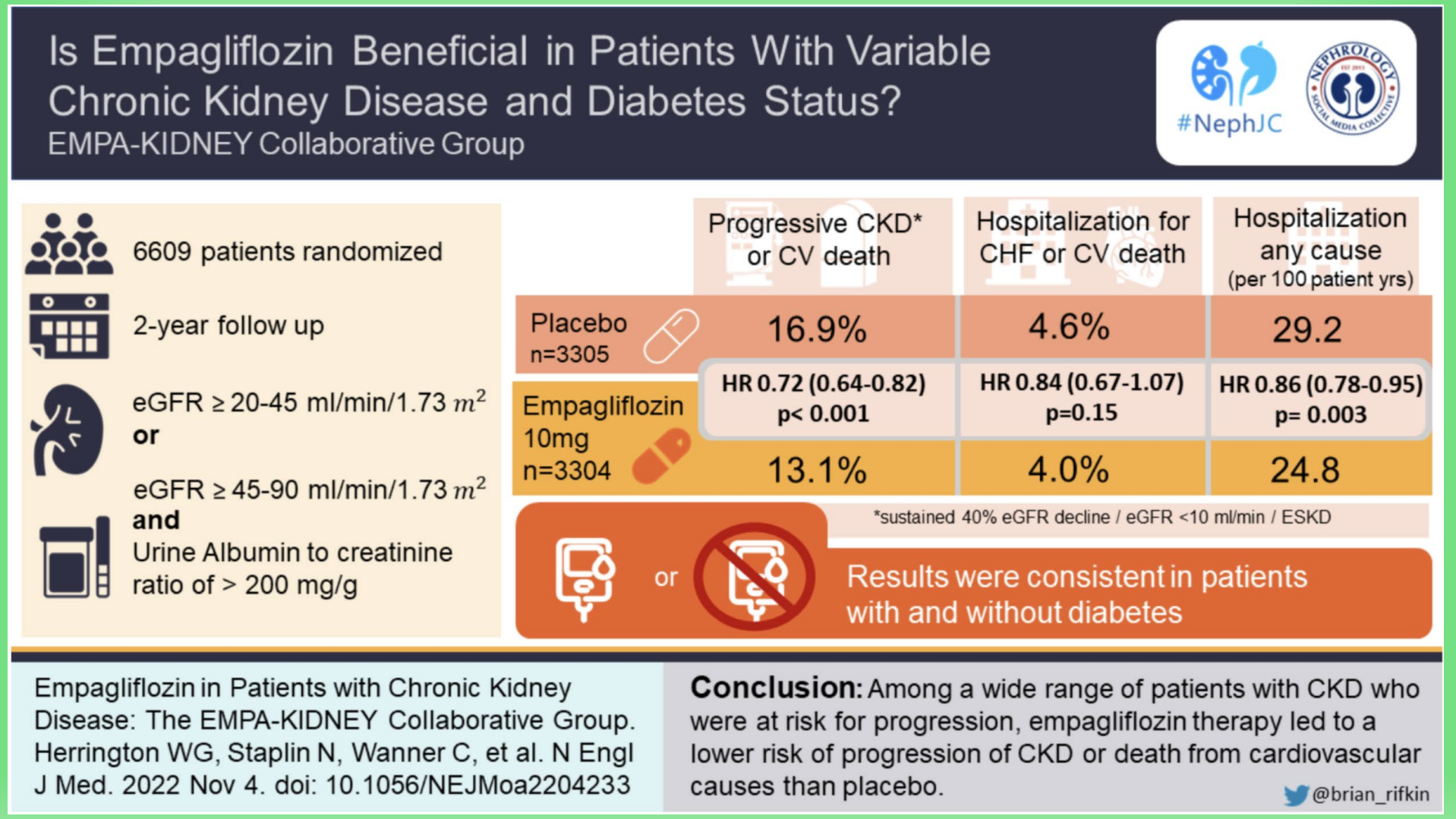
Fractures

HR 0.98
(95% CI 0.70-1.37)

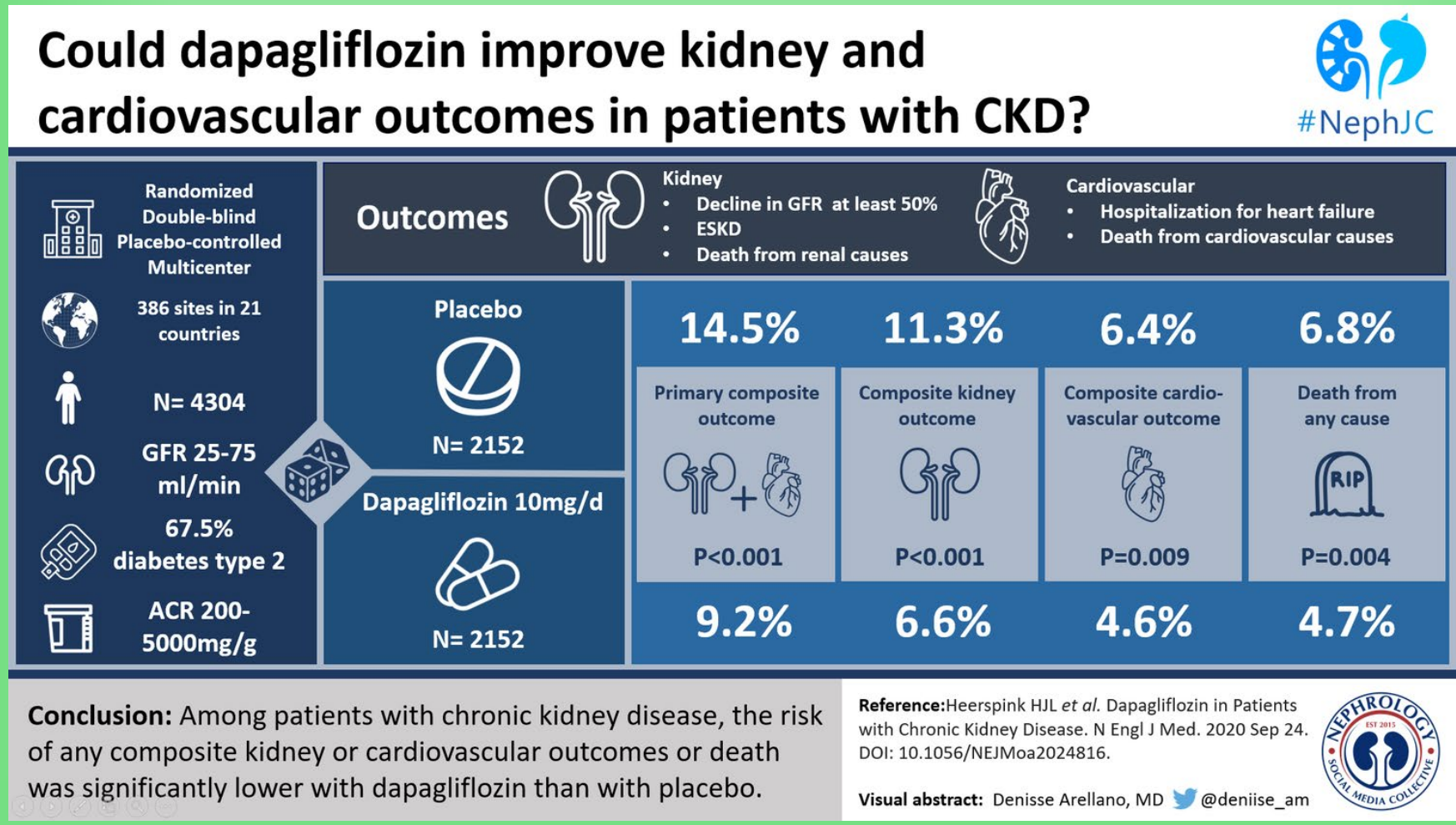
Conclusion

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

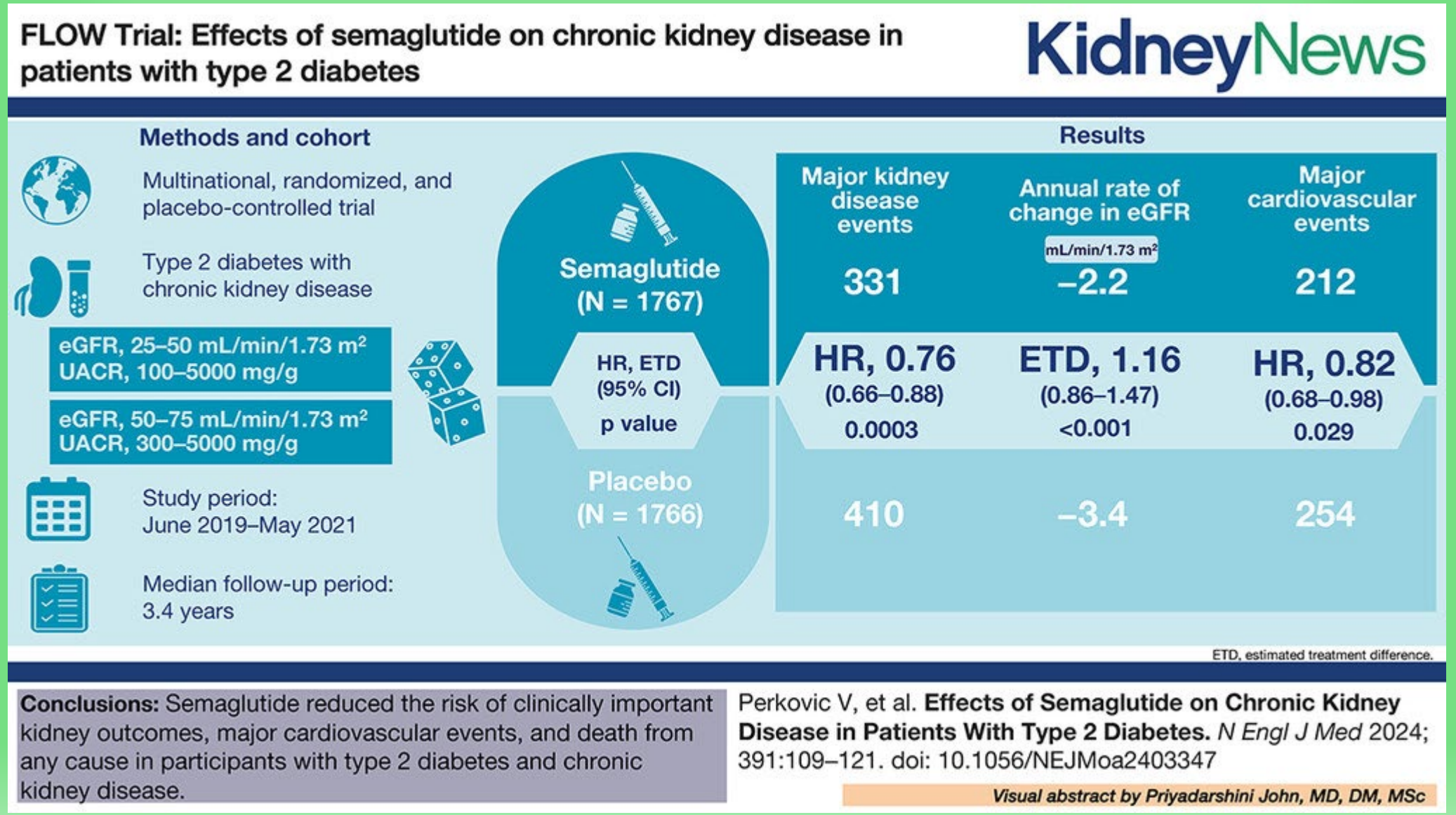
EMPA-KIDNEY


Is Empagliflozin Beneficial in Patients With Variable Chronic Kidney Disease and Diabetes Status?
EMPA-KIDNEY Collaborative Group
#NephJC
6609 patients randomized
2-year follow up
eGFR ≥ 20-45 ml/min/1.73 m^2
or
eGFR ≥ 45-90 ml/min/1.73 m^2
and
Urine Albumin to creatinine ratio of > 200 mg/g
Progressive CKD* or CV death
Hospitalization for CHF or CV death
Hospitalization any cause
(per 100 patient yrs)
Placebo
n=3305
16.9%
4.6%
29.2
HR 0.72 (0.64-0.82)
p< 0.001
HR 0.84 (0.67-1.07)
p=0.15
HR 0.86 (0.78-0.95)
p= 0.003
Empagliflozin
10mg
n=3304
13.1%
4.0%
24.8
*sustained 40% eGFR decline / eGFR <10 ml/min / ESKD
or
Results were consistent in patients with and without diabetes
Empagliflozin in Patients with Chronic Kidney Disease: The EMPA-KIDNEY Collaborative Group. Herrington WG, Staplin N, Wanner C, et al. N Engl J Med. 2022 Nov 4. doi: 10.1056/NEJMoa2204233
Conclusion: Among a wide range of patients with CKD who were at risk for progression, empagliflozin therapy led to a lower risk of progression of CKD or death from cardiovascular causes than placebo.
@brian_rifkin

DAPA-CKD


Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?
#NephJC
Randomized
Double-blind
Placebo-controlled
Multicenter
386 sites in 21 countries
N= 4304
GFR 25-75 ml/min
67.5% diabetes type 2
ACR 200-5000mg/g
Outcomes
Kidney
• Decline in GFR at least 50%
• ESKD
• Death from renal causes
Cardiovascular
• Hospitalization for heart failure
• Death from cardiovascular causes
Placebo
N= 2152
Dapagliflozin 10mg/d
N= 2152
14.5%
11.3%
6.4%
6.8%
Primary composite outcome
Composite kidney outcome
Composite cardio-vascular outcome
Death from any cause
RIP
P<0.001
P<0.001
P=0.009
P=0.004
9.2%
6.6%
4.6%
4.7%
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

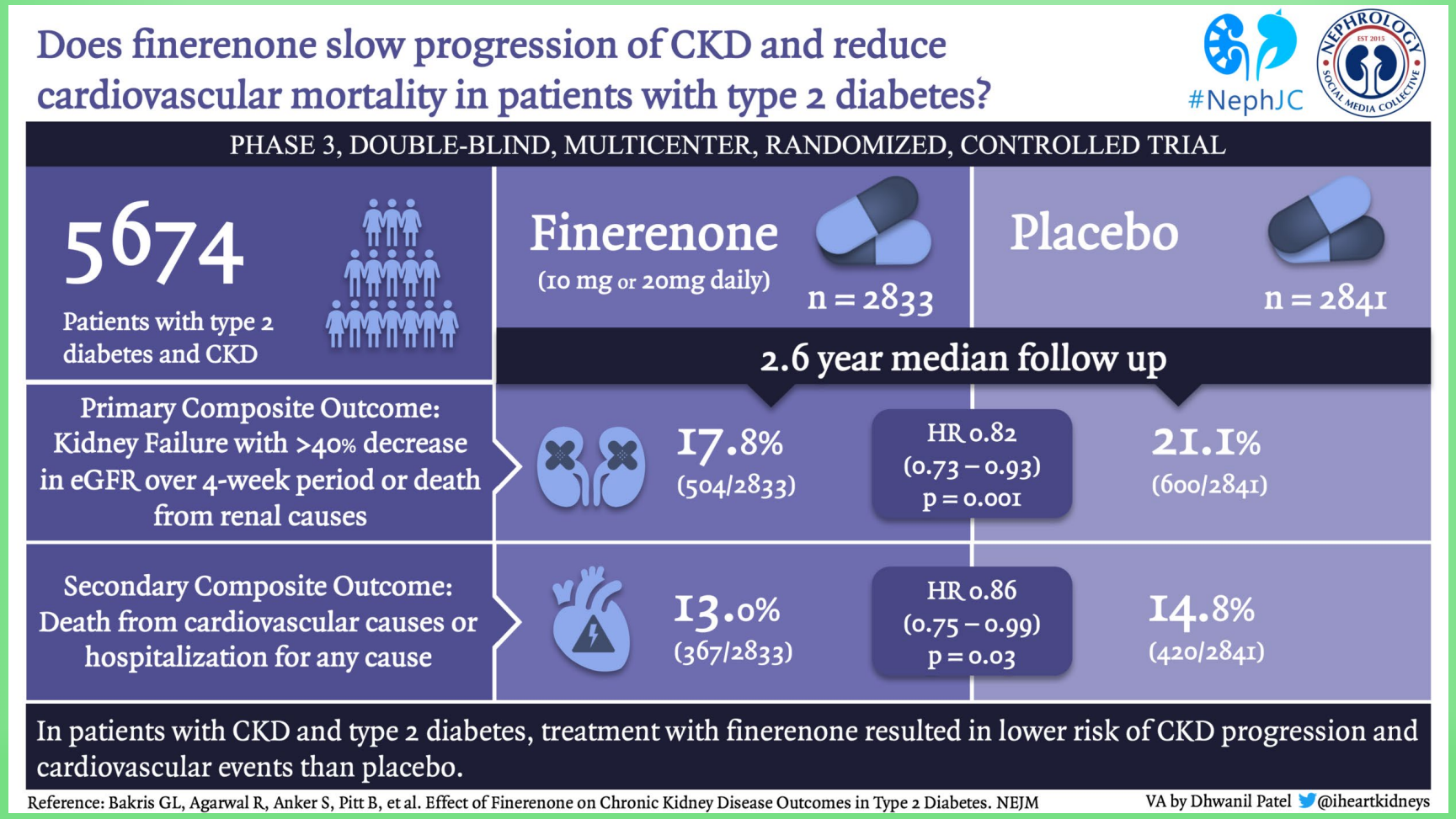
FLOW STUDY


FLOW Trial: Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes
KidneyNews
Methods and cohort
Multinational, randomized, and placebo-controlled trial
Type 2 diabetes with chronic kidney disease
eGFR, 25–50 mL/min/1.73 m²
UACR, 100–5000 mg/g
eGFR, 50–75 mL/min/1.73 m²
UACR, 300–5000 mg/g
Study period:
June 2019–May 2021
Median follow-up period:
3.4 years
Semaglutide
(N = 1767)
HR, ETD
(95% CI)
p value
Placebo
(N = 1766)
Results
Major kidney disease events
Annual rate of change in eGFR
mL/min/1.73 m²
Major cardiovascular events
331
−2.2
212
HR, 0.76
(0.66–0.88)
0.0003
ETD, 1.16
(0.86–1.47)
<0.001
HR, 0.82
(0.68–0.98)
0.029
410
−3.4
254
ETD, estimated treatment difference.
Conclusions: Semaglutide reduced the risk of clinically important kidney outcomes, major cardiovascular events, and death from any cause in participants with type 2 diabetes and chronic kidney disease.
Perkovic V, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients With Type 2 Diabetes. N Engl J Med 2024; 391:109–121. doi: 10.1056/NEJMoa2403347
Visual abstract by Priyadarshini John, MD, DM, MSc

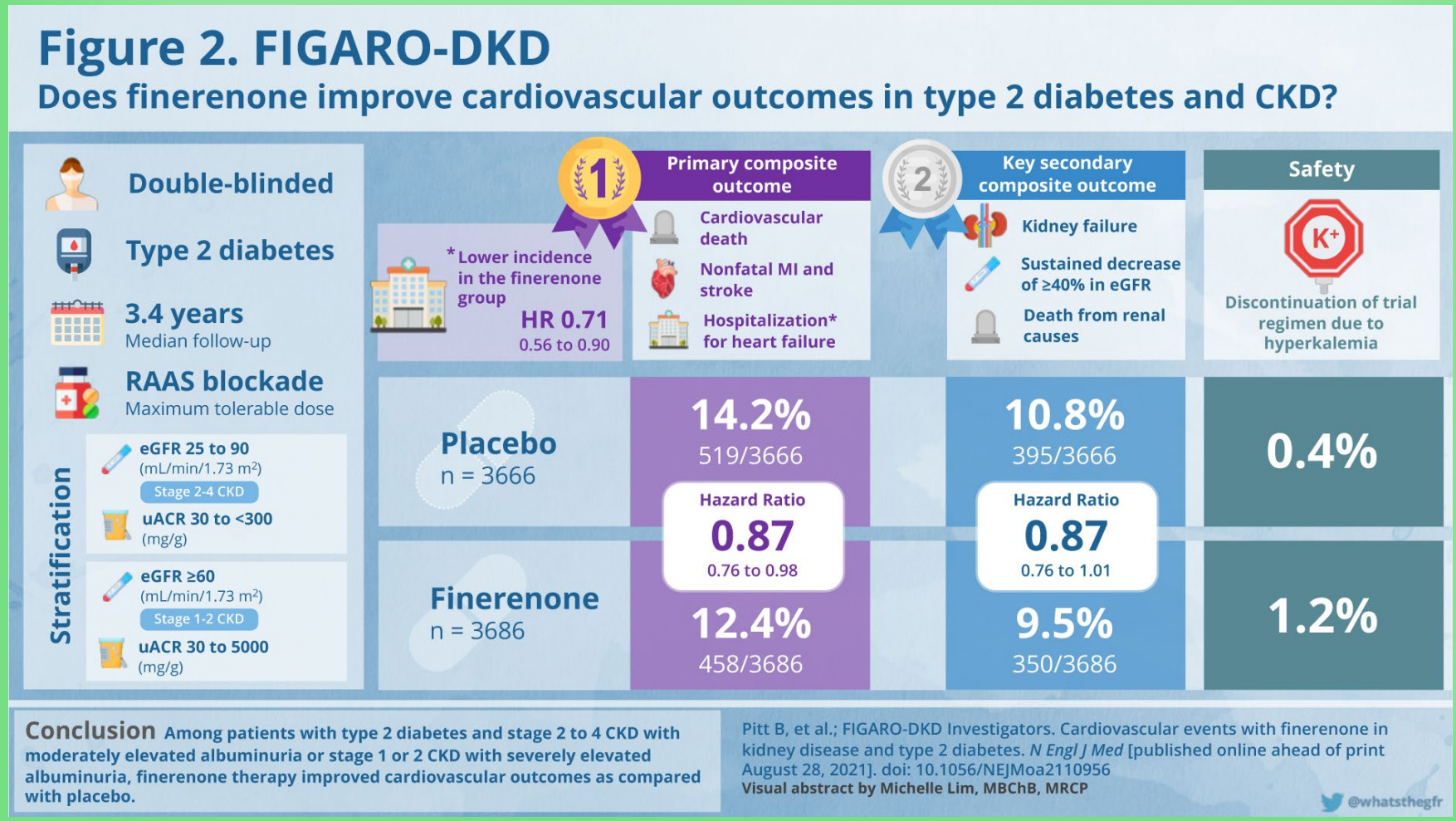
MRAs and CKD

- MRAs have not been well studied in DM and CKD 2/2 to risk of hyperkalemia
- Data that do exist suggest sustained benefit on albuminuria reduction

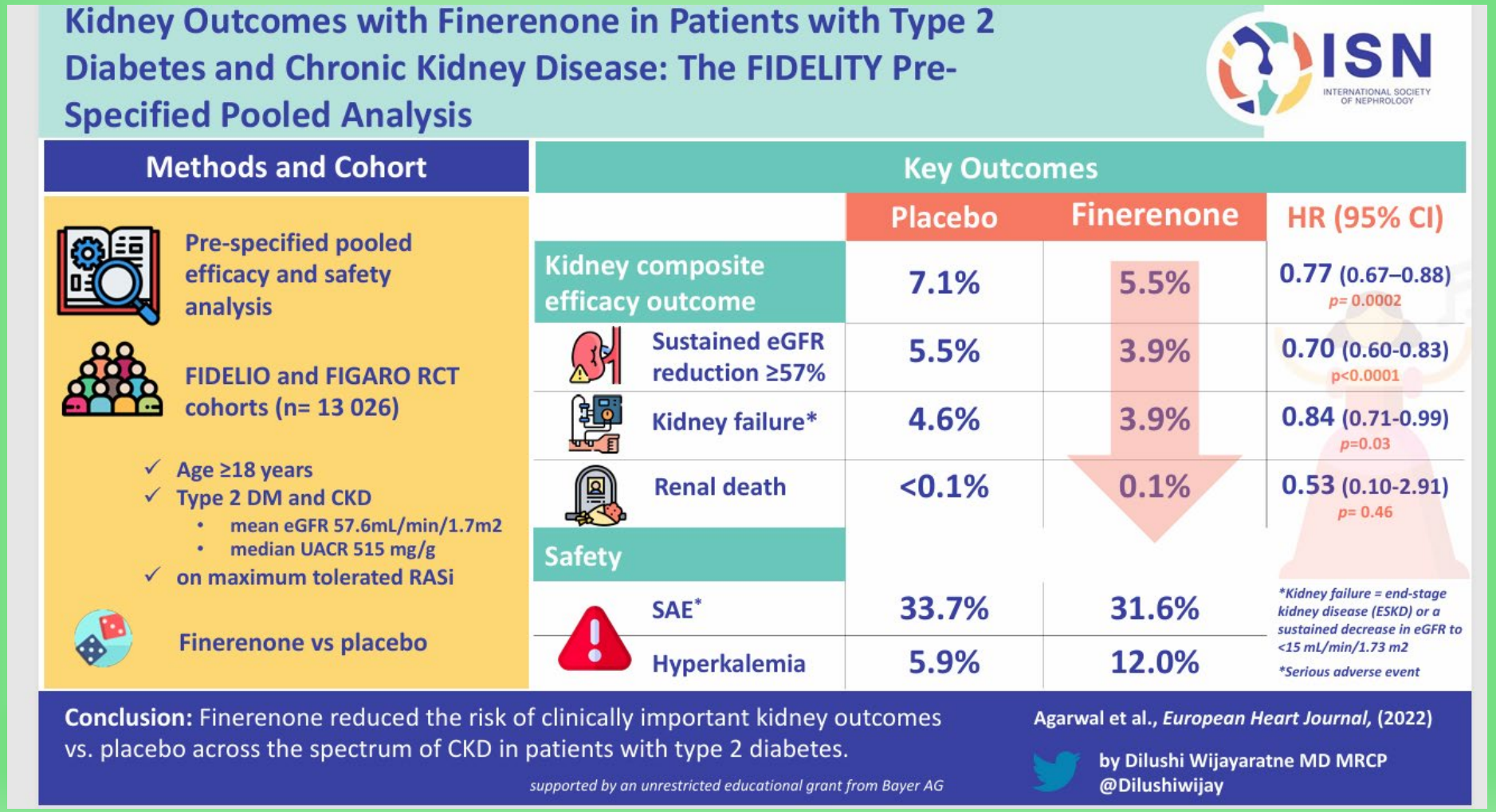
FIDELIO-DKD Tril



FIGARO-DKD Trial



FIDELITY Trial



MRA vs SGLT2 inhibitors

- No direct comparison exists currently
- Also, no studies directly comparing MRAs, SGLT2 inhibitors and GLR-1RAs

Referral to a Nephrologist

- Continuous rising UACR levels
- Continuous declining GFR levels
- Uncertainty of etiology
- Advanced CKD
- Early referral can reduce morbidity and mortality, cost. Also improve quality of care and delay dialysis

Cheng et al. BMC Nephrology (2025) 26:25
https://doi.org/10.1186/s12882-025-03944-4

BMC Nephrology

RESEARCH Open Access

Early versus late nephrology referral and patient outcomes in chronic kidney disease: an updated systematic review and meta-analysis

Linan Cheng[1,2,3,4,5], Nan Hu[1,2,3,4,5], Di Song[1,2,3,4,5], Li Liu[1,2,3,4,5] and Yuqing Chen[1,2,3,4,5*]

Abstract

Background Nephrology referral has been recognized as a modifiable factor influencing patient outcomes. The study aimed to compare clinical outcomes among patients referred early versus late to nephrologists.

Methods We searched online database from inception to June 1, 2022, to obtain all eligible literature reporting outcomes of patients referred early versus late to nephrologists. The early and late referral was defined by the time at which patients were referred to nephrologists before dialysis onset.

Results Seventy-two studies with over 630,000 patients met the inclusion criteria. A lower likelihood of all-cause mortality (HR = 0.67, 95% CI: 0.62–0.72) was achieved among patients referred early to nephrologists. The survival advantage of early referral was apparent in the first 6 months and extended to the 5th year after dialysis onset (6 months: HR = 0.52, 95% CI: 0.40–0.68; 5 years: HR = 0.67, 95% CI: 0.60–0.74). The early referral was associated with shorter durations of initial hospitalization, a higher rate of kidney transplantation (RR = 1.41, 95% CI: 1.12–1.78), a lower likelihood of emergency start (RR = 0.39, 95% CI: 0.28–0.54), a higher likelihood of permanent access creation (RR = 3.34, 95% CI: 2.43–4.59), increased initial use of permanent access (RR = 2.60, 95% CI: 2.18–3.11), and reduced initial catheter use (RR = 0.43, 95% CI: 0.32–0.58).

Conclusions Our study showed a lower risk of mortality, shorter lengths of initial hospitalization, and better preparations for renal replacement therapy among patients referred early to nephrologists. Early nephrology care should be promoted to improve the management of advanced chronic kidney disease.

Keywords Chronic renal insufficiency, Referral, Meta-analysis, Mortality

CKD is classified based on: • **GFR (G)** • **Albuminuria (A)**				**Albuminuria categories** Description and range		
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				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	**G1**	Normal or high	**≥90**	Screen 1	Treat 1	Treat and refer 2
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	G4	Severely decreased	**15-29**	Treat and refer 3	Treat and refer 3	**Treat and refer 4+**
	G5	Kidney failure	**<15**	**Treat and refer 4+**	**Treat and refer 4+**	**Treat and refer 4+**

Low risk (if no other markers of kidney disease, no CKD)

Moderately increased risk

High risk

Very high risk

- Accepting new patients!
- Montanakidney.com
- Office phone: 406-213-8939
- Office fax: 406-224-6127

References

- "11. Chronic kidney disease and risk management: Standards of Care in Diabetes—2025." *Diabetes Care* 48, no. Supplement_1 (2025): S239-S251.