Slowing the Progression of Chronic Kidney Disease

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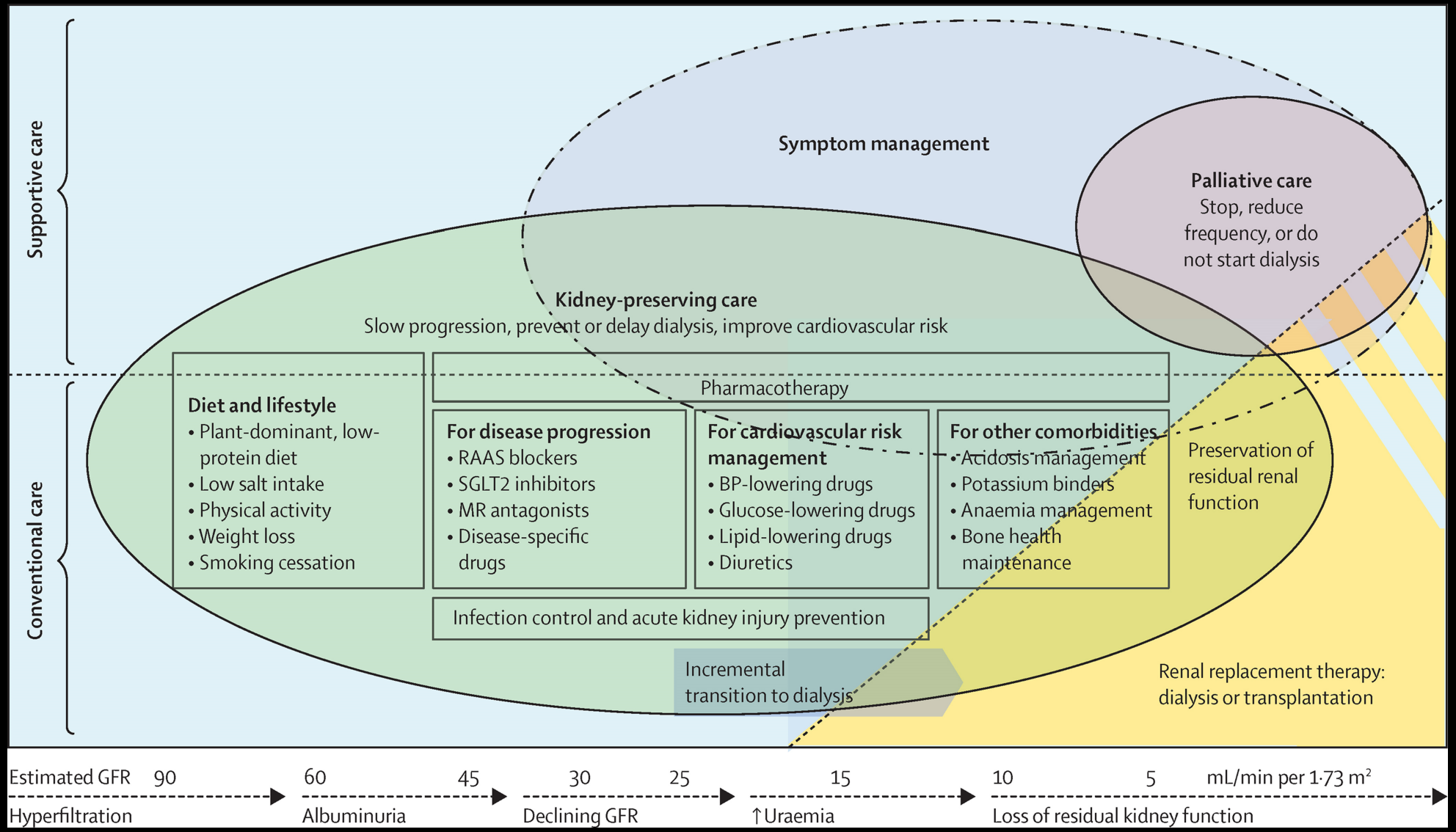
No Conflicts of Interest to Disclose.

Objectives

- Define chronic kidney disease (CKD) with a review of staging and risk factors for progression.
- Briefly review the epidemiology of CKD/ESRD
- Review the current understanding of the pathophysiology of disease progression
- Discuss current strategies that target the progression of CKD
- Discuss the future of CKD management emphasizing disease progression

The Approach



Lancet 2021; 398; 786-802

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 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			

Low risk (if no other markers of kidney disease, no CKD)	Moderately increased risk	High risk	Very high risk

KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease.

The Importance of Proteinuria

- Regardless of the underlying etiology of CKD, proteinuria is a negative prognostic factor.
- Higher degrees of urinary protein excretion are associated with a more rapid decline in GFR
- Interventions that reduce proteinuria are frequently associated with slower progression of kidney disease.

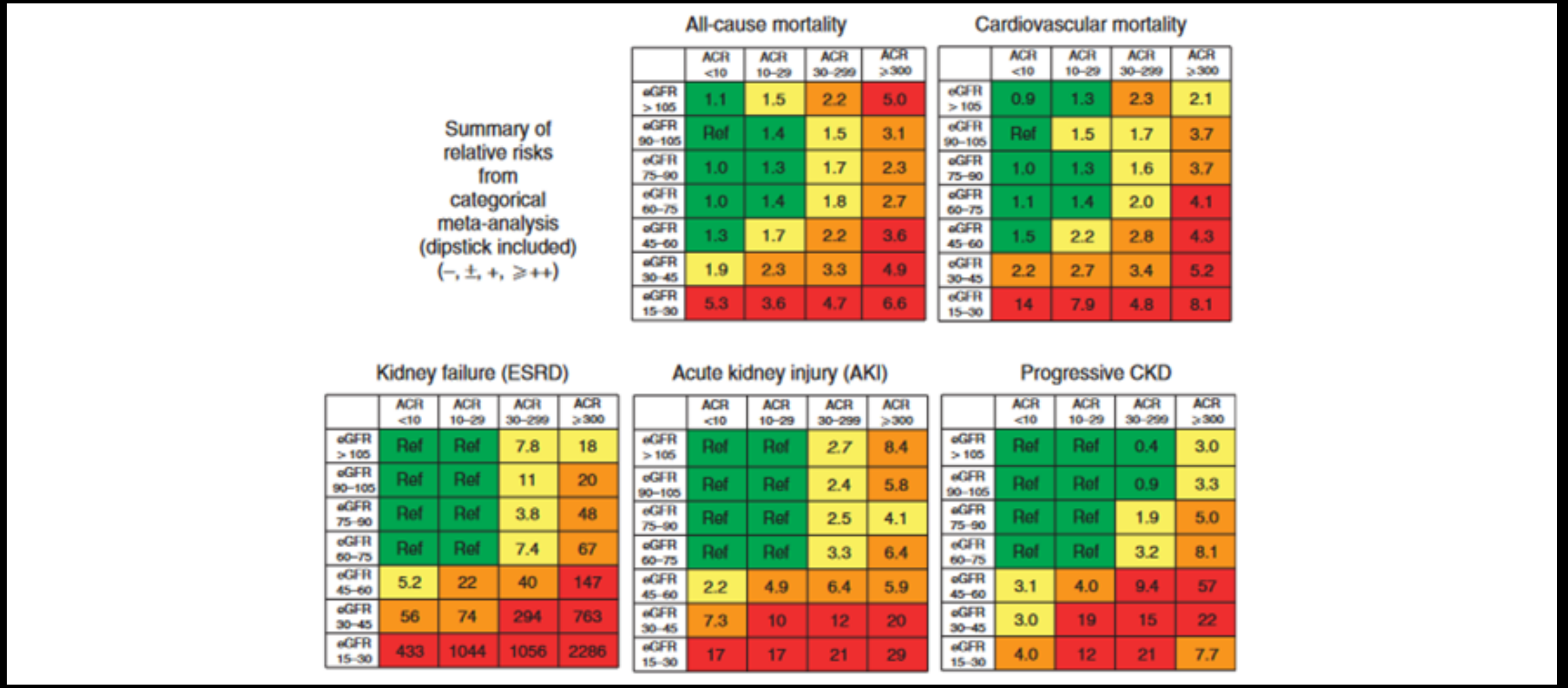


Figure 5 | Summary of categorical meta-analysis (adjusted relative risk (RR)) for general population cohorts with albumin-to-creatinine ratio (ACR).

Kidney International (2011) 80, 17–28

Fast Facts

- More than 1 in 7, that is 15% of US adults or 37 million people, are estimated to have CKD.*
- As many as 9 in 10 adults with CKD **do not know** they have CKD.
- About 2 in 5 adults with severe CKD **do not know** they have CKD.

Centers for Disease Control and Prevention. *Chronic Kidney Disease in the United States, 2021*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2021.

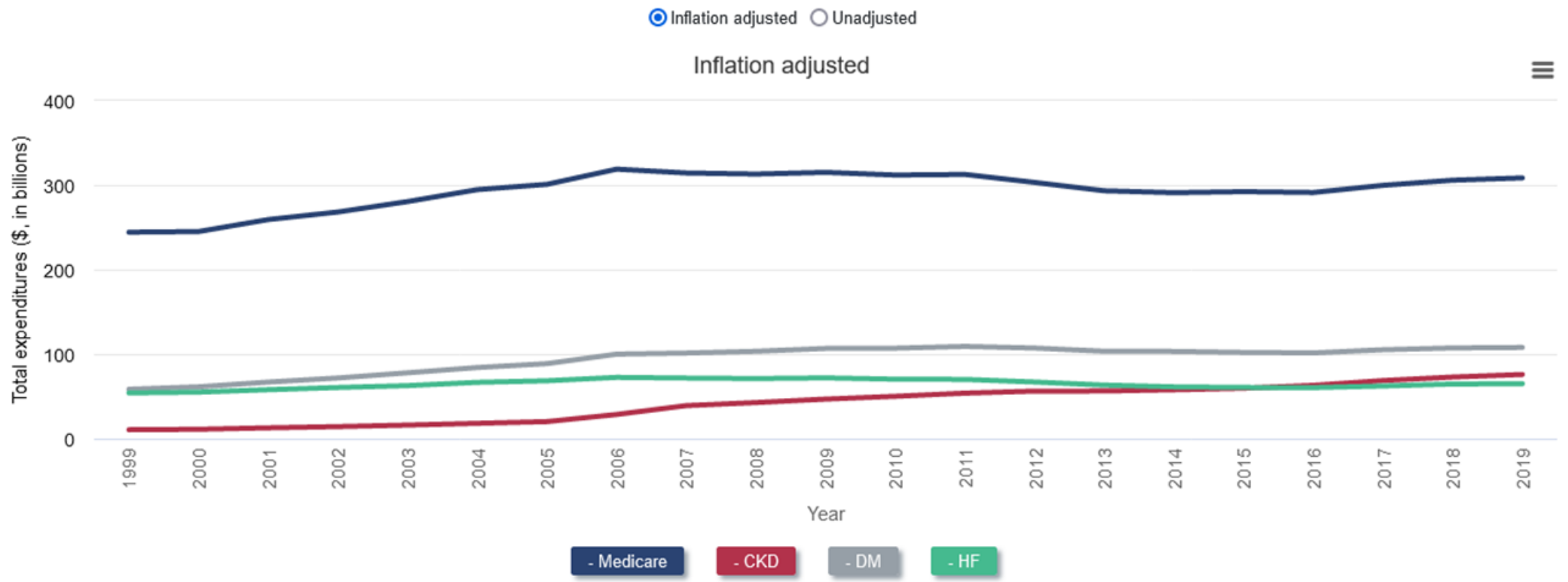
Medicare FFS | Medicare Advantage | Commercial

	All CKD	Stages 1-2	Stage 3	Stages 4-5
Patient years at risk	2,256,268	267,151	1,323,164	192,022
All patients	$26,508	$22,814	$26,020	$35,663
Age				
66-69	$25,728	$20,696	$25,947	$38,290
70-74	$25,741	$21,376	$25,690	$36,627
75-79	$26,021	$22,402	$25,429	$36,041
80-84	$26,681	$24,856	$25,603	$36,263
85+	$28,034	$25,834	$27,197	$33,359
Sex				
Female	$25,987	$22,383	$25,404	$34,422
Male	$27,127	$23,268	$26,755	$37,367
Race				
White	$26,073	$22,613	$25,609	$34,988
Black	$30,234	$25,289	$29,218	$39,953
Other	$26,721	$21,637	$27,002	$35,865
Diabetes				
No	$23,028	$19,658	$22,265	$29,750
Yes	$29,935	$26,008	$30,079	$40,347
Heart Failure				
No	$20,945	$18,341	$20,441	$26,888
Yes	$41,807	$39,284	$40,829	$49,057

Data Source: Medicare 5% FFS sample and Optum® de-identified Clinformatics® Data Mart Database (Medicare Advantage and commercial insurance). Point prevalent individuals aged ≥66 years on January 1, 2019 with CKD and Medicare Parts A, B, & D or commercial insurance coverage in 2018.

Table 6.3 presents Medicare FFS Parts A, B, and D, Medicare Advantage, and commercial insurance 2019 PPPY spending, by stage of CKD among older individuals (aged ≥66 years) with CKD. As expected, spending for individuals with advanced CKD (stages 4-5) was much higher than for those with less advanced CKD.

Figure 6.4 Inflation adjusted overall spending among older adults and for those with CKD (ESRD excluded), DM, and HF 1999-2019

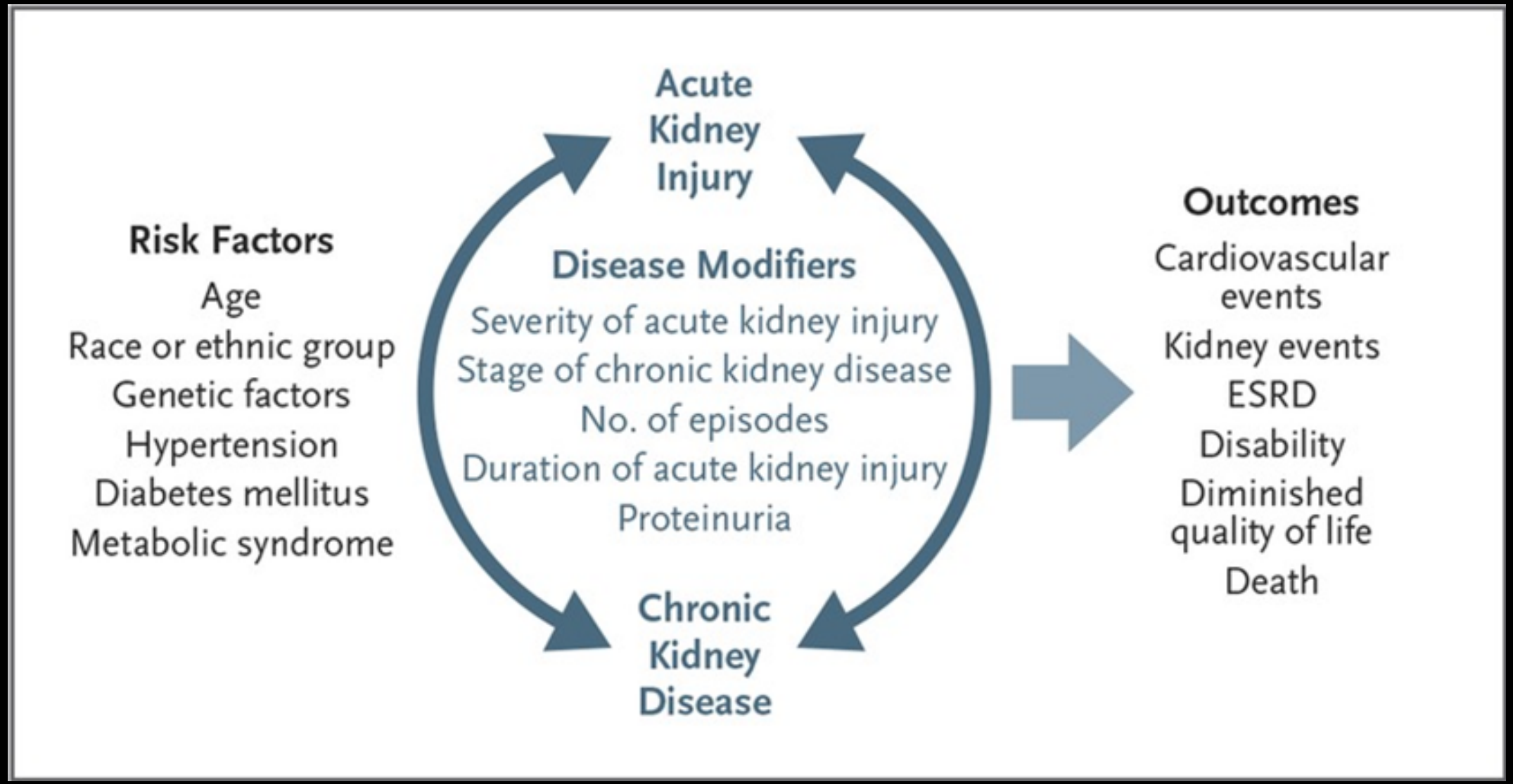


Data Source: Medicare 5% FFS sample. Point prevalent individuals aged ≥66 years on January 1, 1999-2019, with Medicare Parts A and B coverage in the prior year. Costs reported are Medicare paid costs for Parts A, B, and D (from 2006), multiplied by 20 to represent 100% Medicare FFS.

Figure 6.4 shows Medicare FFS Part A, B, and D expenditures for all beneficiaries aged ≥66 years and for those with CKD, DM, and HF. Inflation-adjusted expenditures increased only 0.9%, from $305.8B to $308.5B, between 2018 and 2019. However, expenditures for beneficiaries with CKD, which totaled $75.9B, increased far more (4.1% over one year) than for beneficiaries with DM (0.6%) or HF (0.6%). The rapid rise in costs for the CKD population reflects, in part, a rapid growth in the CKD population, which may be the result of a combination of a true increase in rates of CKD combined with an increase in recognition and coding of CKD in Medicare claims.

Pathophysiology of CKD Progression

- Activity of Underlying Disease
  - Diabetes Mellitus
  - Cardiac and Hepatic Disease
  - Obesity
  - Primary and Secondary Glomerulonephritis: Ongoing Inflammation or episodic inflammatory flares
  - Genetic Conditions: Autosomal Dominant Polycystic Kidney Disease
  - HTN
  - AKI



N Engl J Med 2014; 371:58-66 DOI: 10.1056/NEJMra1214243

Kidney Responses to Injury: How the physiology of the damaged kidney contributes to CKD progression.

- Glomerular Hyperfiltration: Adaptive increase in single-nephron GFR
- Adaptation to Acidosis
- HTN
- Tubular hyper-reabsorption
- Oxidative Stress
- Proteinuria
- Fibrosis

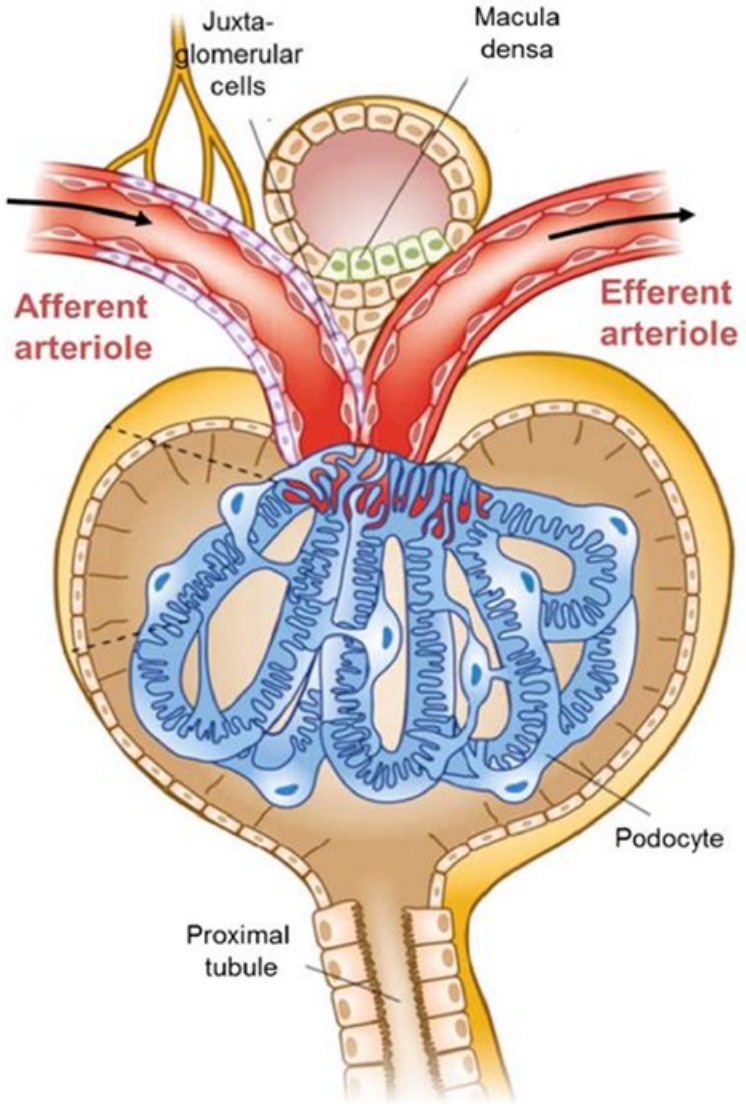
Glomerular Hyperfiltration

- Total GFR is the sum of all single nephron GFR's
- In increase in SNGFR with a normal number of nephrons with result in an absolute increase in total GFR: absolute hyperfiltration
- This can occur in healthy individuals: pregnancy, high protein intake
- It can occur in pathologic states: diabetes, obesity or polycystic kidney disease
- With a reduction of the total number of nephrons an increase in SNGFR with drive the total GFR towards normal: adaptive hyperfiltration.

Adaptive Hyperfiltration

- Determinants of SNGFR:
  - $SNGFR = k \times S \times [(P_{GC} - P_T) - (\pi_{GC} - \pi_T)]$
  - In most situations the primary determinant of SNGFR is P_{GC}
  - Variables affecting P_{GC}:
    - Systemic Blood Pressure
    - Pre-Glomerular Resistance---Afferent Arteriole vascular tone
    - Post-Glomerular Resistance----Efferent Arteriole vascular tone

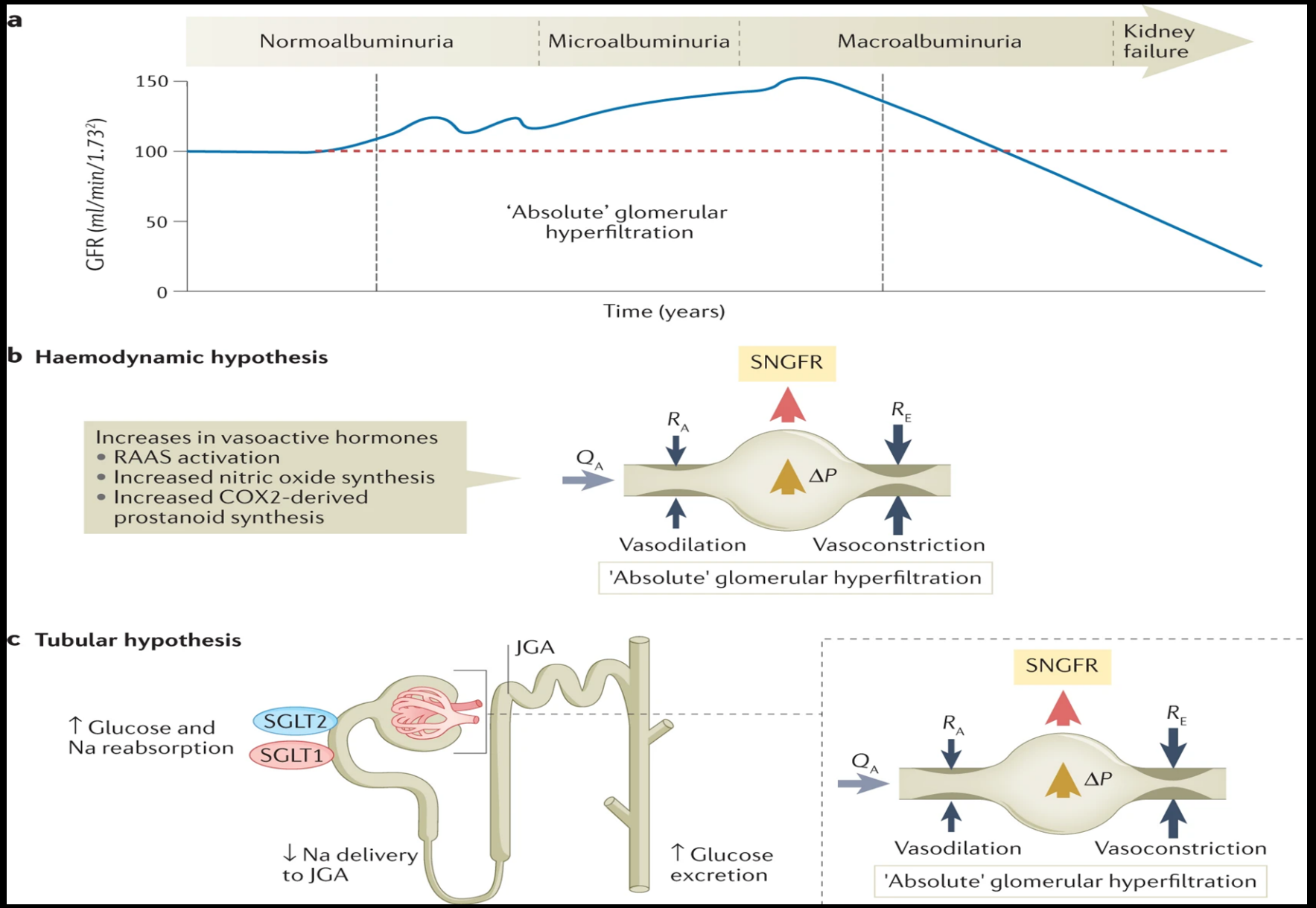
Factors causing a net reduction of afferent arteriolar resistance
Vascular factors
Nitric oxide bioavailability
COX-2 prostanoids
Kalikrein-kinins
Atrial natiuretic peptide
Angiotensin(1-7)
Hyperinsulinemia *per se*
Tubular signals
Inhibition of tubuloglomerular feedback (macula densa signals)



Factors causing a net increase of efferent arteriolar resistance
Vascular factors
Angiotensin-II
Thromboxane A2
Endothelin-1 (ETA receptor)
Reactive oxygen species

The diabetic effect…

- Diabetic nephropathy begins with a hyperfiltration phase followed by albuminuria then GFR decline.
- The RAAS, COX2 and nitric oxide systems are thought to be involved in the regulation of efferent and afferent tone in DM nephropathy---the hemodynamic hypothesis.
- Alternatively, there is the tubular hypothesis: high concentrations of glucose in the glomerular filtrate drives sodium resorption---reduced sodium chloride delivery to the macula densa leads to reduced afferent arteriolar tone and hyperfiltration.



Cortinovis, M., Perico, N., Ruggenenti, P. *et al.* Glomerular hyperfiltration. *Nat Rev Nephrol* (2022).

Ongoing Damage

- Reduction in kidney mass leads to increased SNGFR in the remaining functional nephrons.
- Increases in glomerular capillary hydraulic pressure create tensile stress and fluid low induced shear stress leading to increased GBM length and podocyte foot process length.
- Over years this leads to changes in capillary membrane permeability to water and macromolecules---podocyte injury and ultimately effacement.
- Podocytes have limited capacity for self renewal.

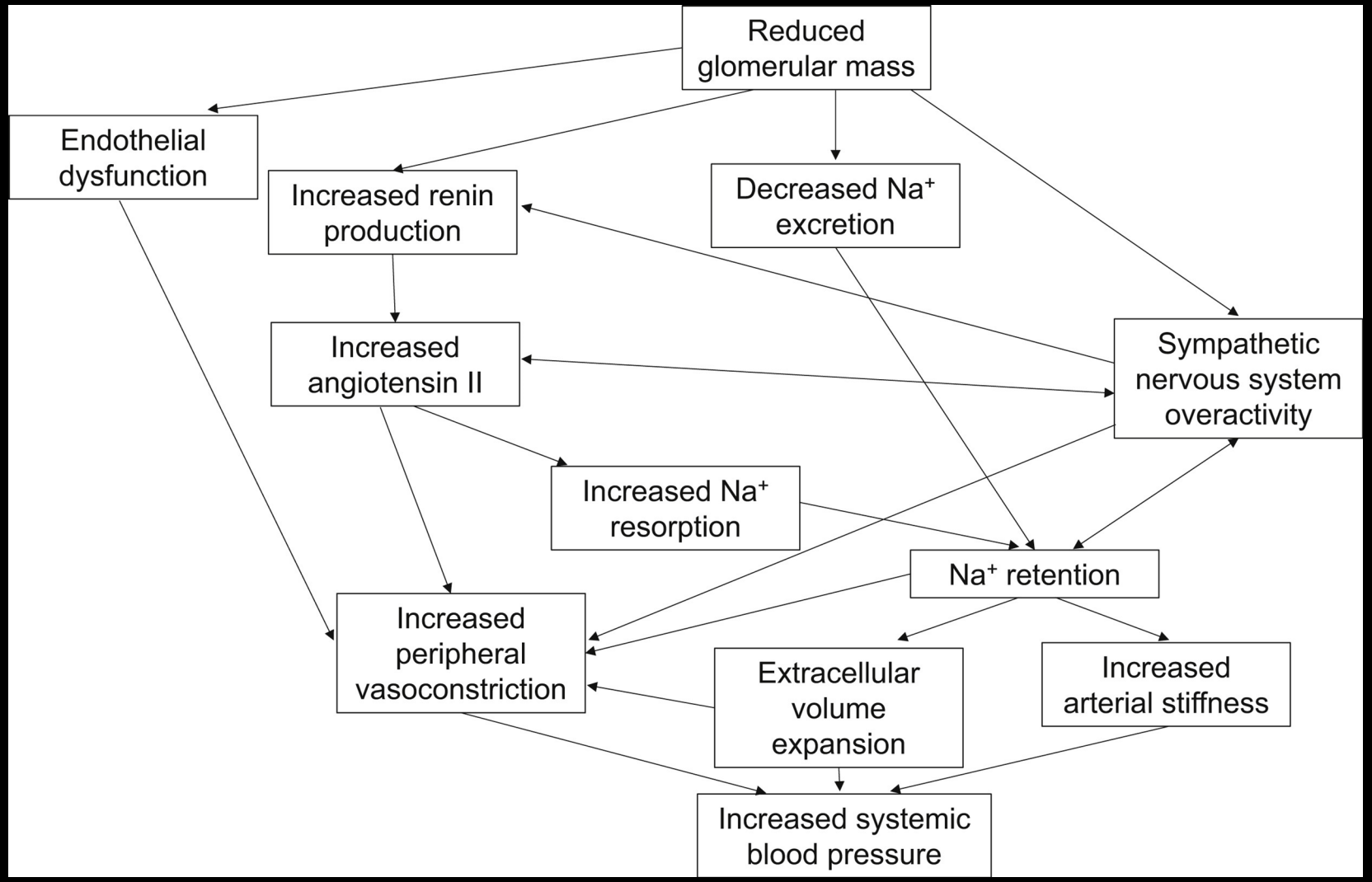
Interventions to reduce hyperfiltration (proteinuria)

- RAS Inhibition
- SLGT-2 Inhibitors
- Aldosterone Antagonists
- BP Control In General

HTN and Kidney Disease

How does kidney disease cause HTN?

- Volume Expansion: sodium retention. Particularly with glomerular disease.
  - Occurs through reduced GFR and through increased tubular resorption
    - Resistance to atrial natriuretic peptide and increased activity of Na-K ATPase in the cortical collecting duct.
- Activation of RAS
- Enhanced activation of the sympathetic nervous system
- Increased intracellular calcium (secondary hyperparathyroidism) increases vascular tone.
- Erythropoietin treatment
- Uremia impairs nitric oxide synthesis



HTN in CKD: Core Curriculum 2019. *AJKD. 3/19/2019*

How does HTN cause kidney disease?

- Chronic HTN causes remodeling of the afferent arteriole reducing its ability to constrict and dilate.
- Loss of auto regulation means increased single nephron glomerular pressure.
- Over time this leads to nephrosclerosis and progressive loss of function.

Ku, E. et al. AJKD. *Hypertension in CKD: Core Curriculum 2019*. 74:1, 7/2019, pp: 120-131.

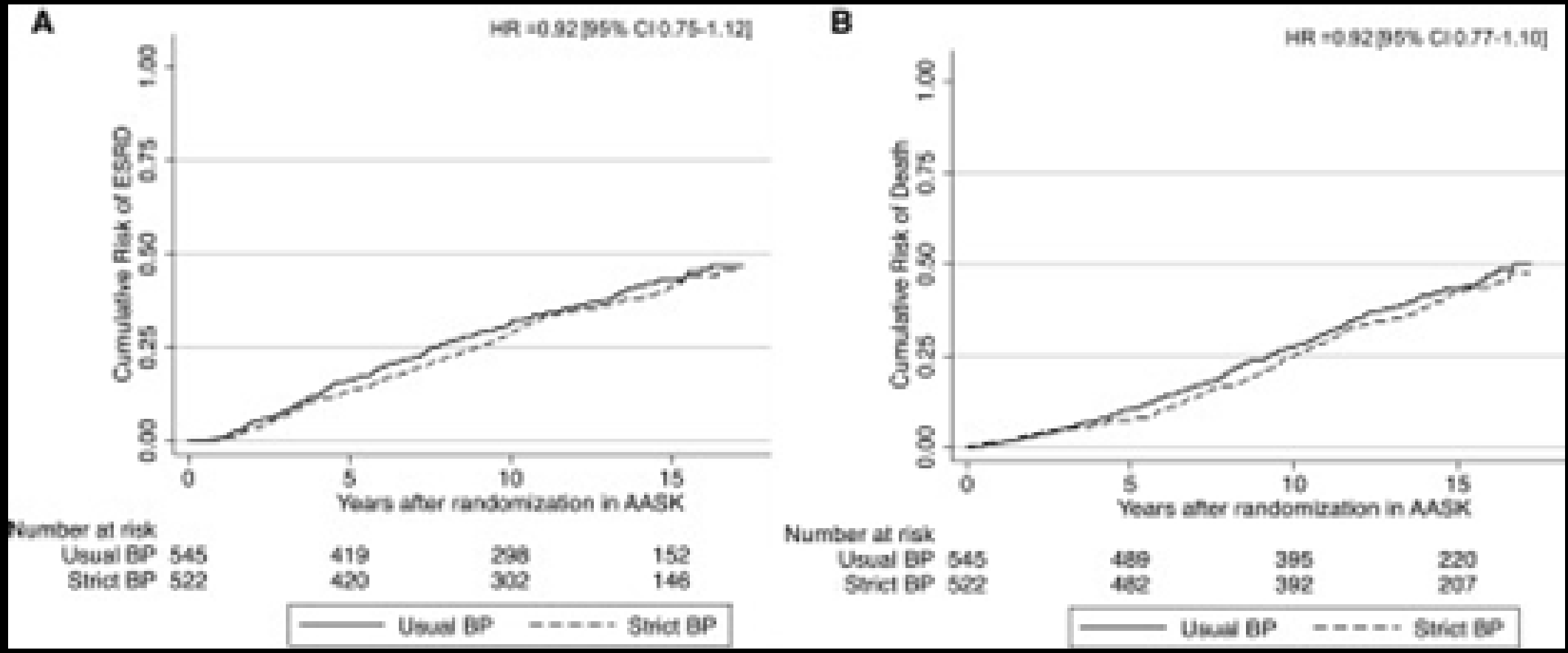
Management of HTN in non-diabetic CKD

- Proteinuric Disease
  - Lower rates of progression are associated with BP targets of < 130/80
    - RAS inhibitors are first line treatment
    - Mineralocorticoid receptor antagonists further reduce proteinuria when added to ACE or ARBs
    - Non-dihydropyridine Ca channel blockers have been shown to have anti-proteinuric effects
- In non-proteinuric CKD there is no preferential benefit of RAS inhibitors.

MDRD, AASK and REIN-2

- None of these large randomized, controlled trials testing the use of lower BP targets (goals lower than 140/90) demonstrated a reduction in the progression of CKD to ESRD.
- Each of these trials was limited in duration
  - MDRD: 2.2 years
  - AASK: 3.7 years
  - REIN-2: 1.6 years
- Observational studies with longer follow up associated lower BP with higher rates of all cause mortality.
- A meta-analysis of MDRD and AASK with extended follow up was performed.

AASK and MDRD



Usual BP: Mean ABP: 102-107 versus Strict BP: ≤ 92

- Unadjusted relative risk of ESRD was 0.88 (95% CI 0.77 to 1.10)
- Unadjusted relative risk of death was 0.87 (95% CI 0.76 to 0.99)
- For study participants who had < 1 g proteinuria RR = 1.05 (CI 0.83 to 1.32)
- For study participants who had > 1 g proteinuria RR = 0.59 (CI 0.41 to 0.85)

J Am Soc Nephrol. 2017 Feb; 28(2): 671–677.

Which agents to use?

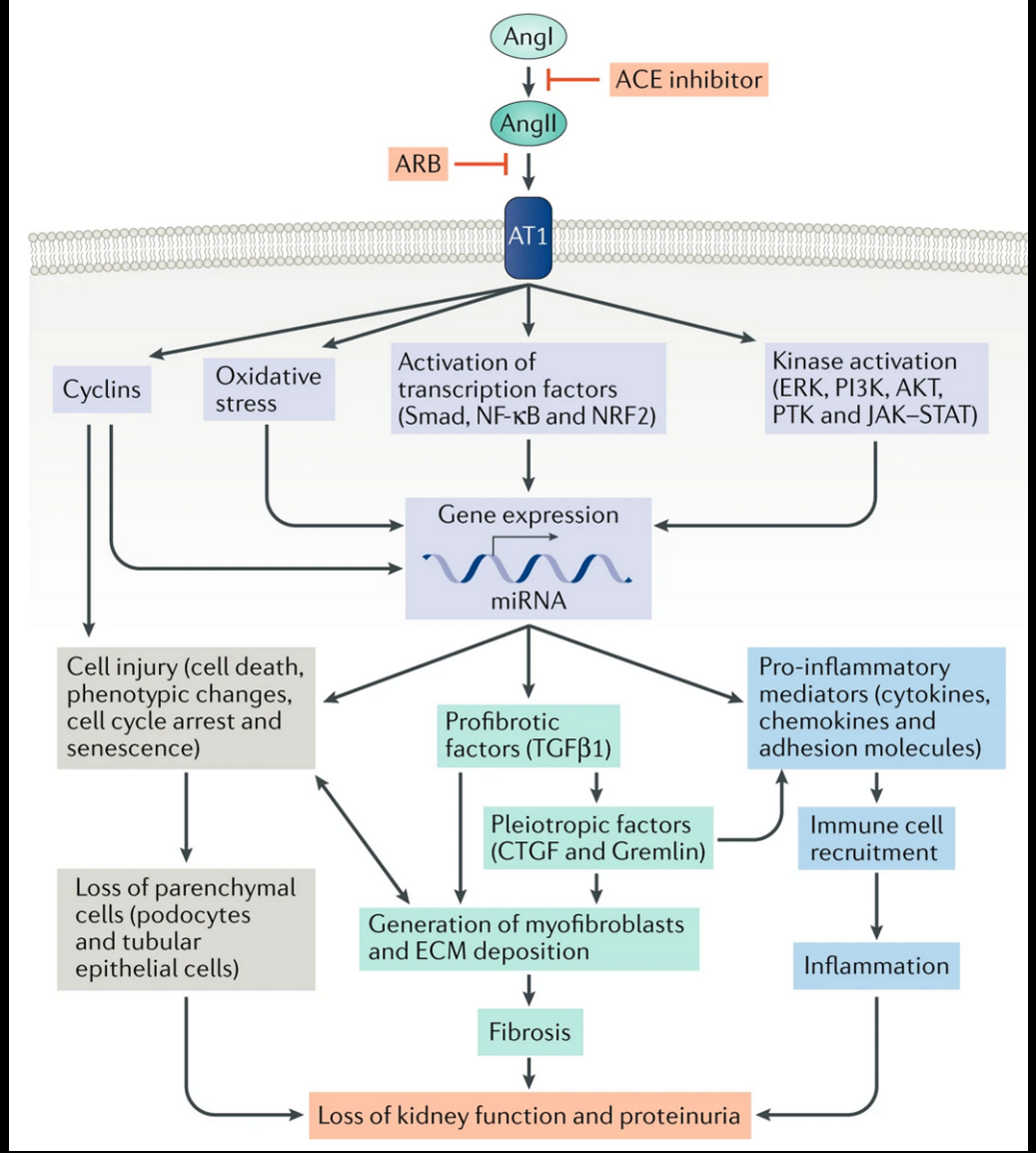
- In non-Proteinuric kidney disease, start with a diuretic if possible (2C), though it is primarily about what works.
- In Proteinuric kidney disease begin with RAS inhibition if possible (1B)

RAS Inhibition

- Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARB)
- Foundational treatment for proteinuric kidney disease.
- Dilation of both the afferent and most importantly efferent arterioles lower glomerular filtration pressure.
- There appear to be additional anti-proteinuric effects: despite the acute nature of the hemodynamic changes there is a prolonged decline in protein excretion of weeks/months.
- Likely there are direct podocyte effects from angiotensin II.
- There are also anti-fibrotic effects from RAS inhibition.

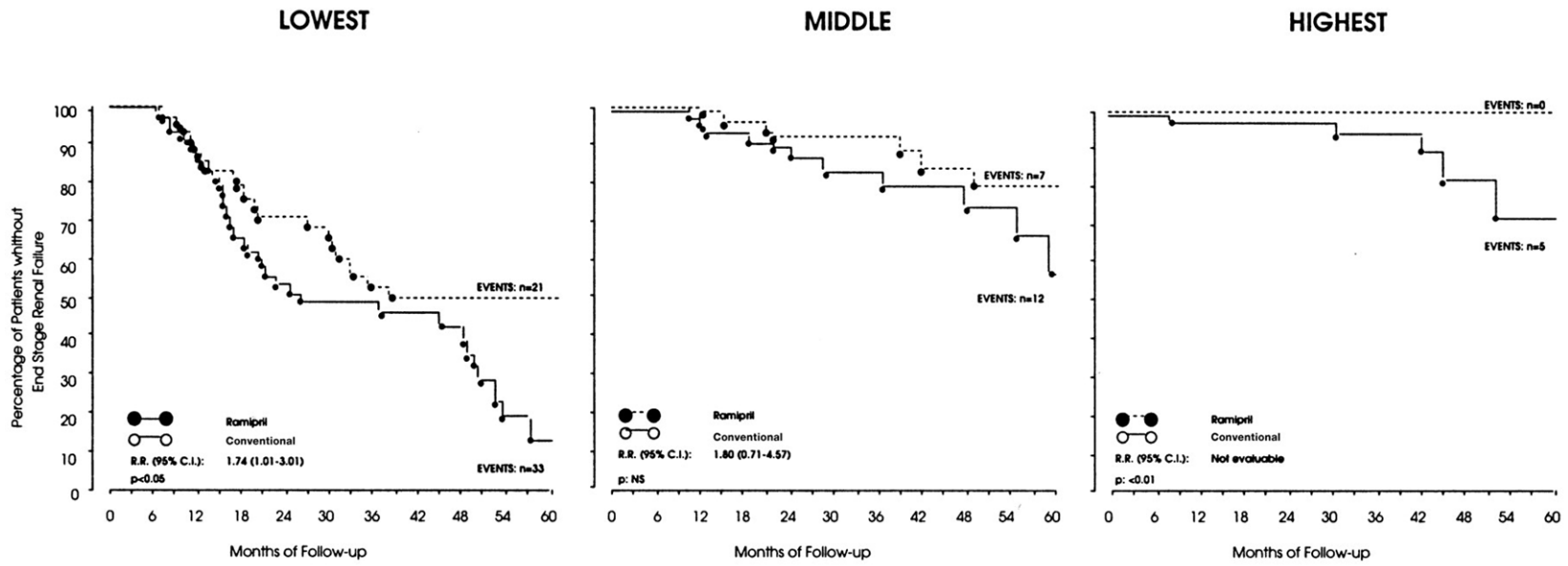
Fig. 1: Potential role of AngII in the development of kidney fibrosis.

From: Targeting the progression of chronic kidney disease



- ACEi and ARBs reduce proteinuria by about 30-35% in both nondiabetic and diabetic CKD. (multiple studies dating back to the late 1980’s)
- Reduction in proteinuria is dose related.
- RAS inhibitors reduce the progression of Proteinuric CKD.
- List of trials:
  - RENAAL
  - ROAD
  - REIN-1
  - AASK
  - IDNT
  - KVT

Figure 3. Kidney survival in 322 patients with proteinuric, chronic nephropathies according to treatment and tertiles of basal GFR.



Piero Ruggenenti et al. JASN 2001;12:2832-2837

Complications and Controversies

- Hyperkalemia: relative in the age of zirconium cyclosilicate and patiromir.
- Reduced eGFR: controversial, no specific recs on eGFR thresholds.
- KDIGO:
  - Pts at increased risk of AKI: particularly with hypotension/hyperkalemia

What about Gout? Elevated uric acid?

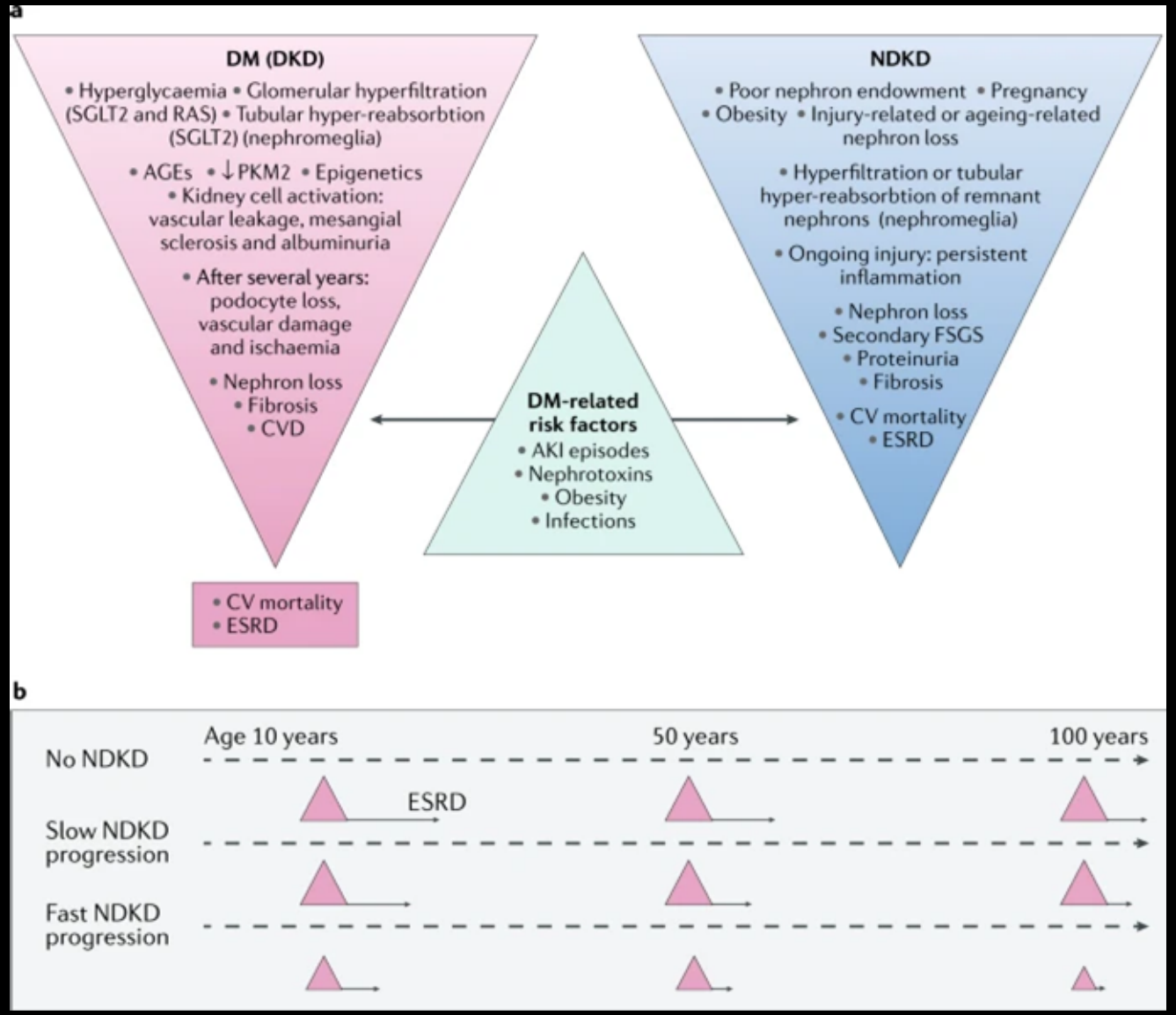
- Animal studies demonstrate a potential mechanistic role of elevated uric acid in the progression of CKD.
- Epidemiologic studies suggest an association
- KDIGO lists it as an “area of uncertainty”
- Another chicken and egg phenomenon—Which came first the hyperuricemia or the CKD?

Diabetic Kidney Disease

- A (?The) major cause of ESRD. Affects up to 50% of those diagnosed with DM.
- 44% of patients initiating dialysis in the United States carried the diagnosis of DKD.
- DKD encompasses the spectrum of people with DM who have either albuminuria or reductions in renal function.
- There is significant variation in individual rates of CKD progression and outcomes have improved over the last four decades.

Diabetes Obes Metab. 2020;22(Suppl. 1): 3-15.

- Definition: persistent albuminuria, co-existing retinopathy, no evidence of alternative kidney disease.
- Rarely presents earlier than 10 years from DM diagnosis.
- This works well for DM I, not so well for DM II.
- DKD is much more variable in DM II---consistent with the variability of the disease itself.



Anders, HJ., *et al.* CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nat Rev Nephrol* **14,** 361–377 (2018).

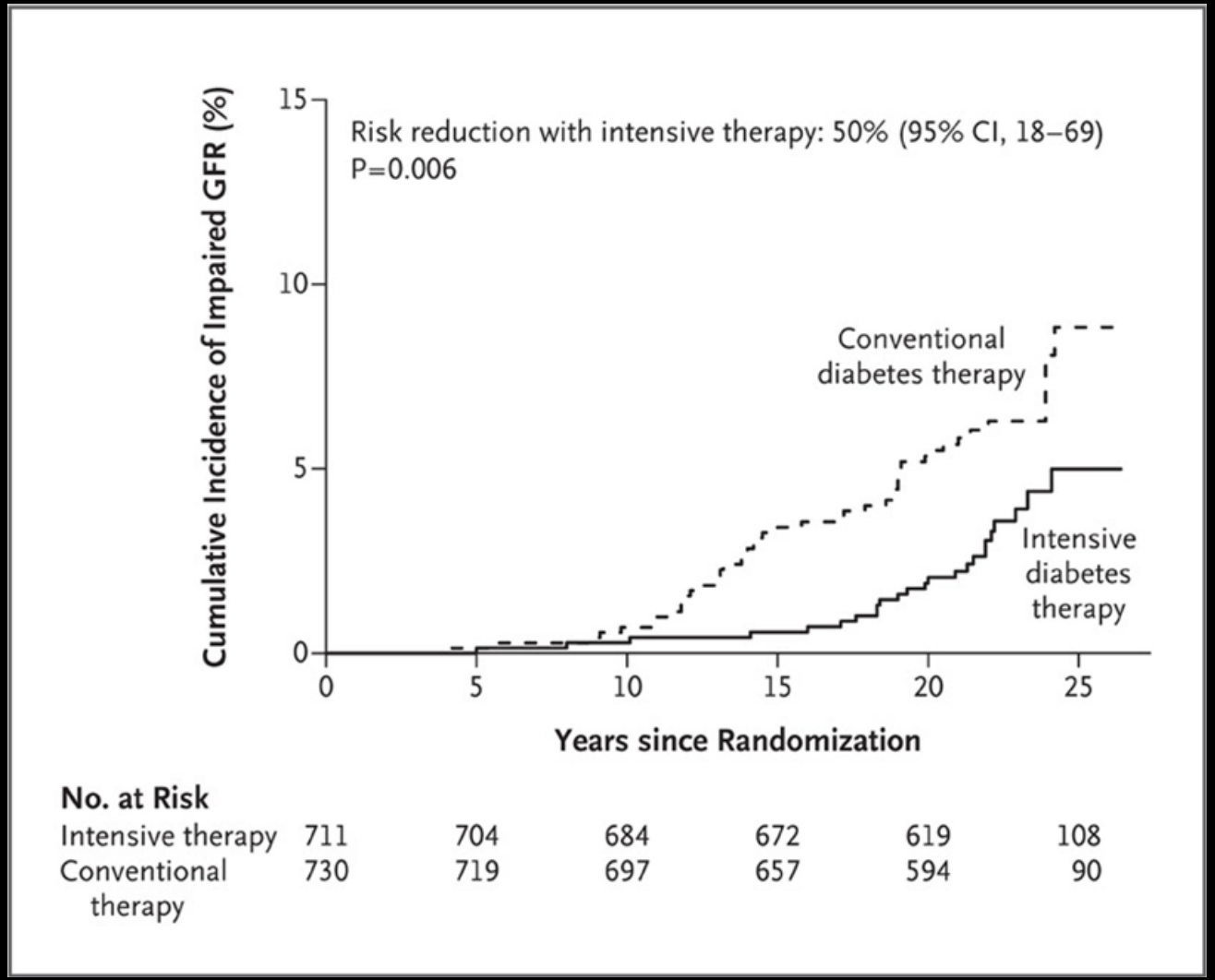
Factors affecting DM Progression

- DM I vs DM II
- Glycemic Control
- Lifestyle Factors: obesity, sodium intake, smoking
- Genetic Variability
- BP Control---RAS Inhibition
- Use of SGLT2i

Glycemic Control

Intensive (achieved A1C: 7.3%) vs. Conventional (achieved A1C: 9.1%) diabetes therapy in type I DM.

N Engl J Med 2011; 365:2366-2376
DOI: 10.1056/NEJMoa1111732



DM II is less clear

- UKPDS: 3867 participants. A1C for intensive = 7.0%, diet control = 7.9%. Differences were not observed in development of albuminuria or doubling of creatinine.
- ADVANCE: 11,140 participants. Intensive (A1C = 6.5%), Standard (A1C = 7.3%). Incidence in worsening DN was reduced (HR: 0.79): doubling of creatinine, development of A3 albuminuria. There was a trend toward reduction in need for RRT.
- ACCORD: 10,251 participants. Discontinued secondary to higher mortality in the intensive arm.

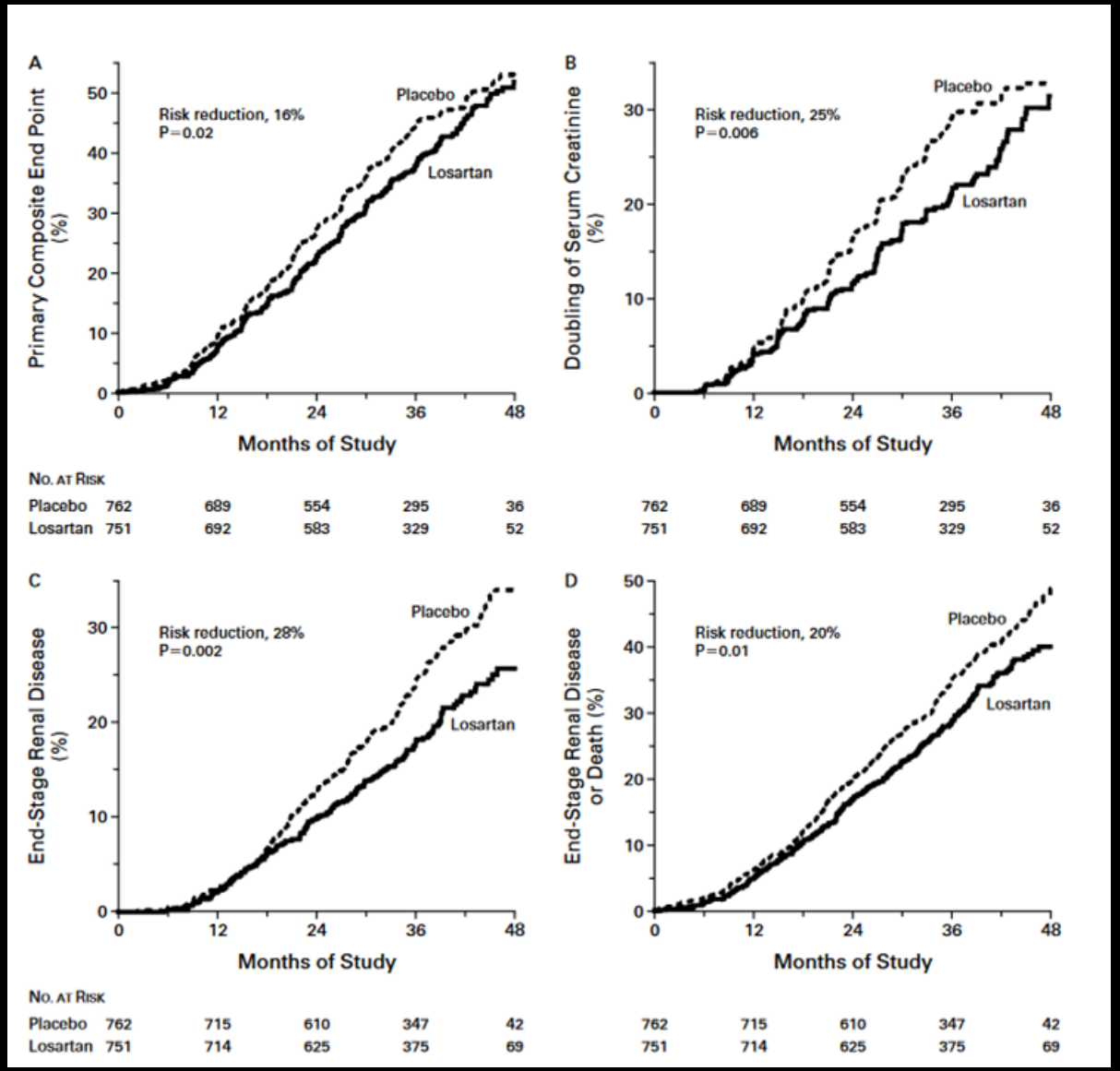
Summary

- Intensive control can reduce the risk of DN and DN progression but increases risk of hypoglycemic events.
- The evidence is clearer for type I DM.
- Intensive control does not eliminate the risk of DN.

RAS Inhibition

- RAS inhibition is foundational to the management of DN.
- In DM I: Captopril reduced the risk of doubling in serum creatinine by about 50%. It definitively reduced proteinuria. (N Engl J Med. 1993: 329(20): 1456-1462)
- In DM II:
  - IDNT: 1715 participants: irbesartan resulted in 20% risk reduction in doubling of serum creatinine, ESKD or death vs. amlodipine or placebo.
  - RENAAL : 1513 participants: losartan resulted in 16% risk reduction in doubling of serum creatinine, ESKD or death

RENAAL

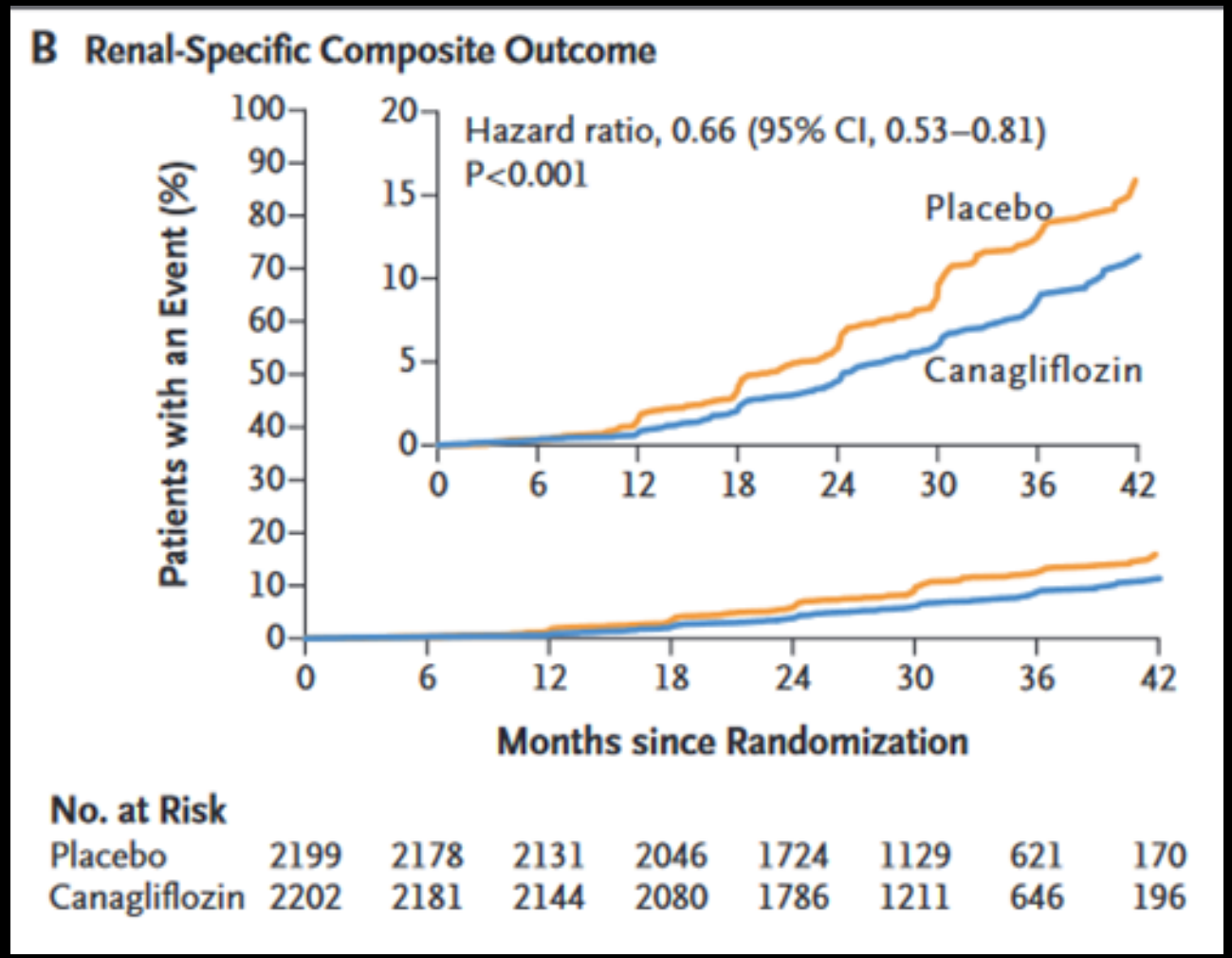


N Engl J Med 2001; 345:861-869

SGLT 2 Inhibition

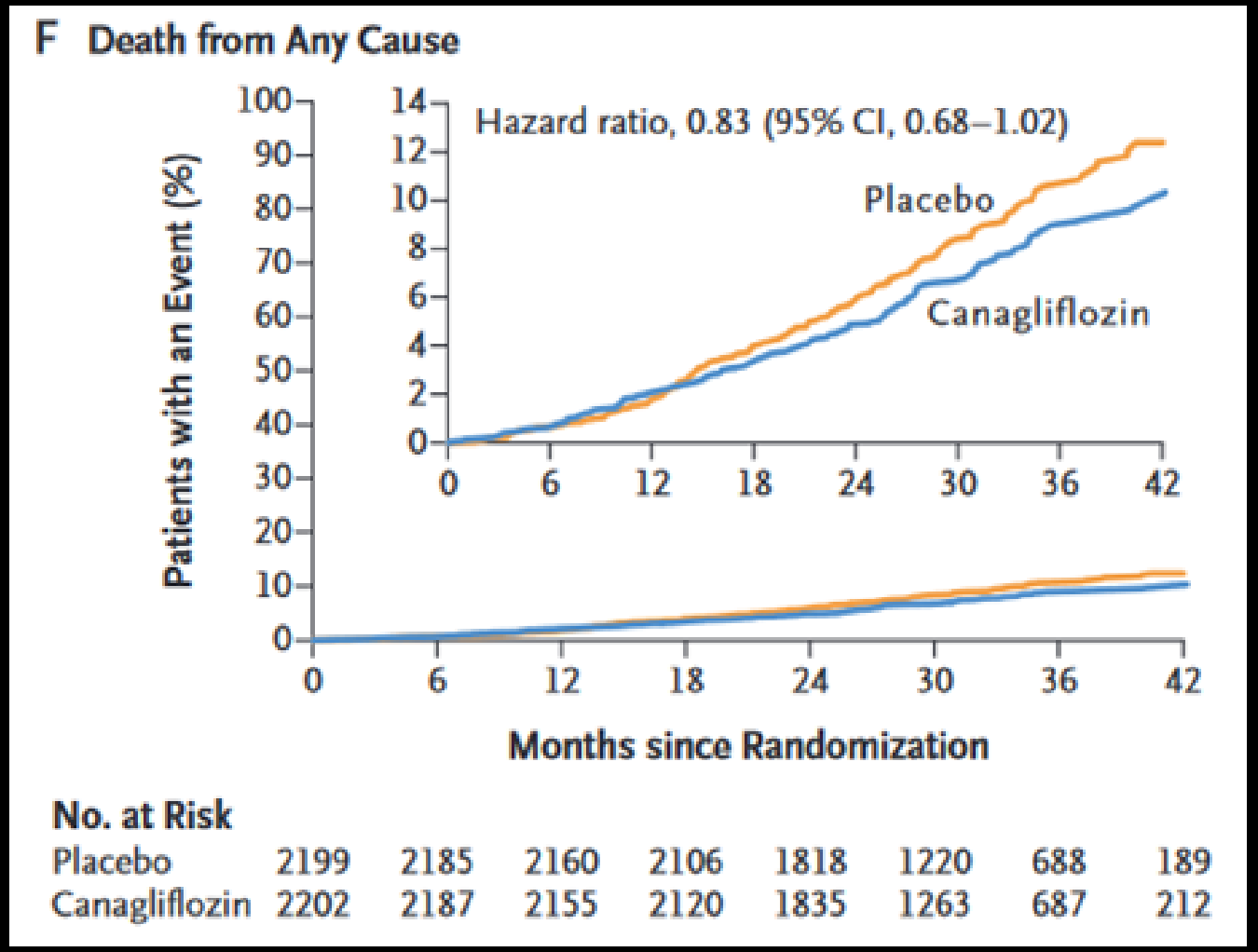
- These agents reduce serum glucose by inhibiting glucose resorption in the proximal tubule
- This results in decreased single nephron filtration through increased sodium at the macula densa and has been shown to reduce the progression of DN.
- CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. Doubling of creatinine, ESRD, death from renal cause was reduced by 34% in the canagliflozin group. (N Engl J Med 2019; 380:2295-2306 DOI: 10.1056/NEJMoa1811744)
- DAPA-CKD: Hazard ratio for 50% decline in eGFR, ESKD, death from renal cause was 0.56 in the dapagliflozin group. This study included both diabetic and non-diabetic CKD patients.

CREDENCE

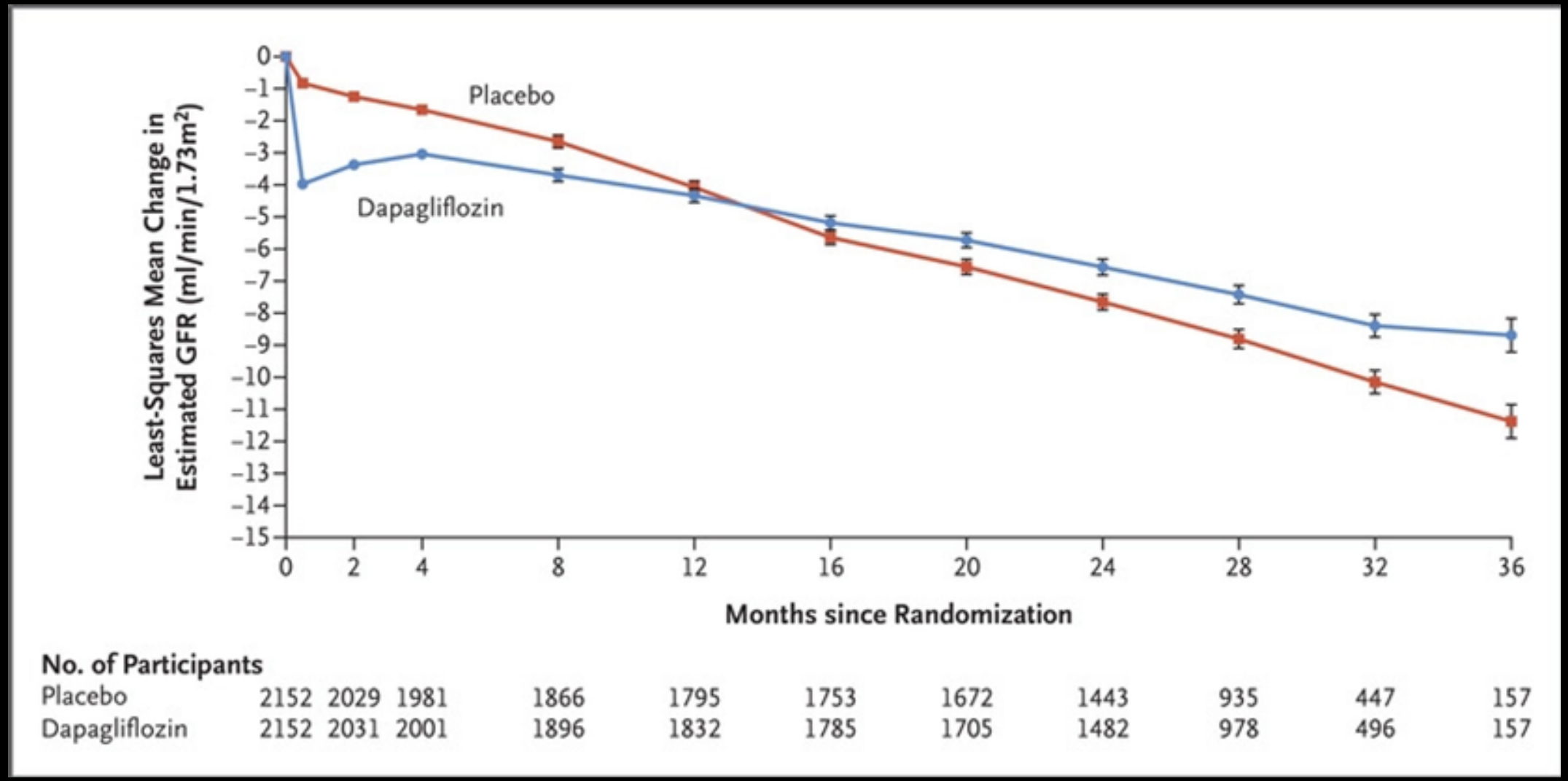


Renal-Specific Composite Outcome: ESKD, Doubling of serum creatinine, renal death.

N Engl J Med 2019;380:2295-306



N Engl J Med 2019;380:2295-306



N Engl J Med 2020; 383:1436-1446 DOI: 10.1056/NEJMoa2024816

Cautions with SGLT2 Inhibitors

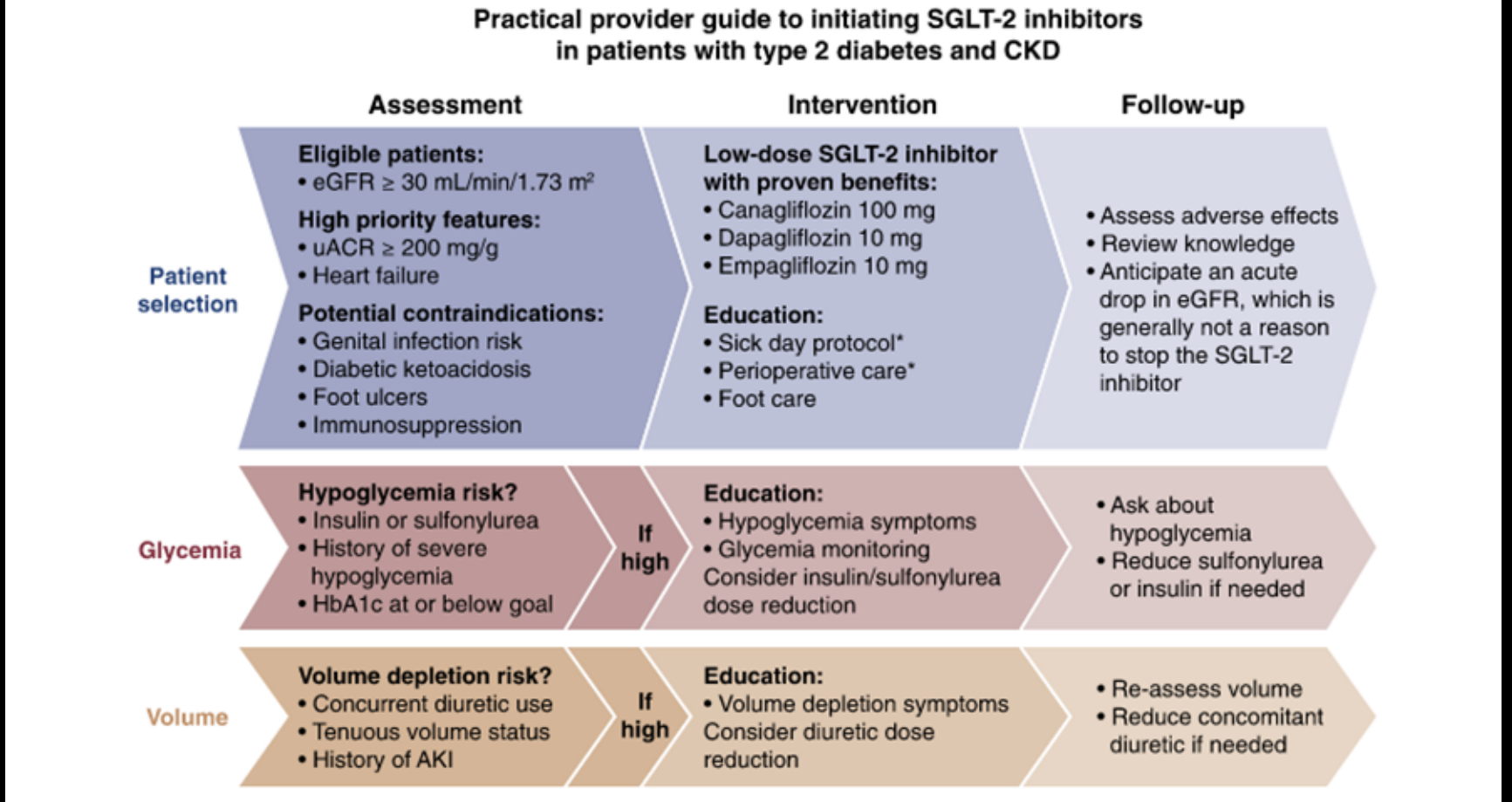
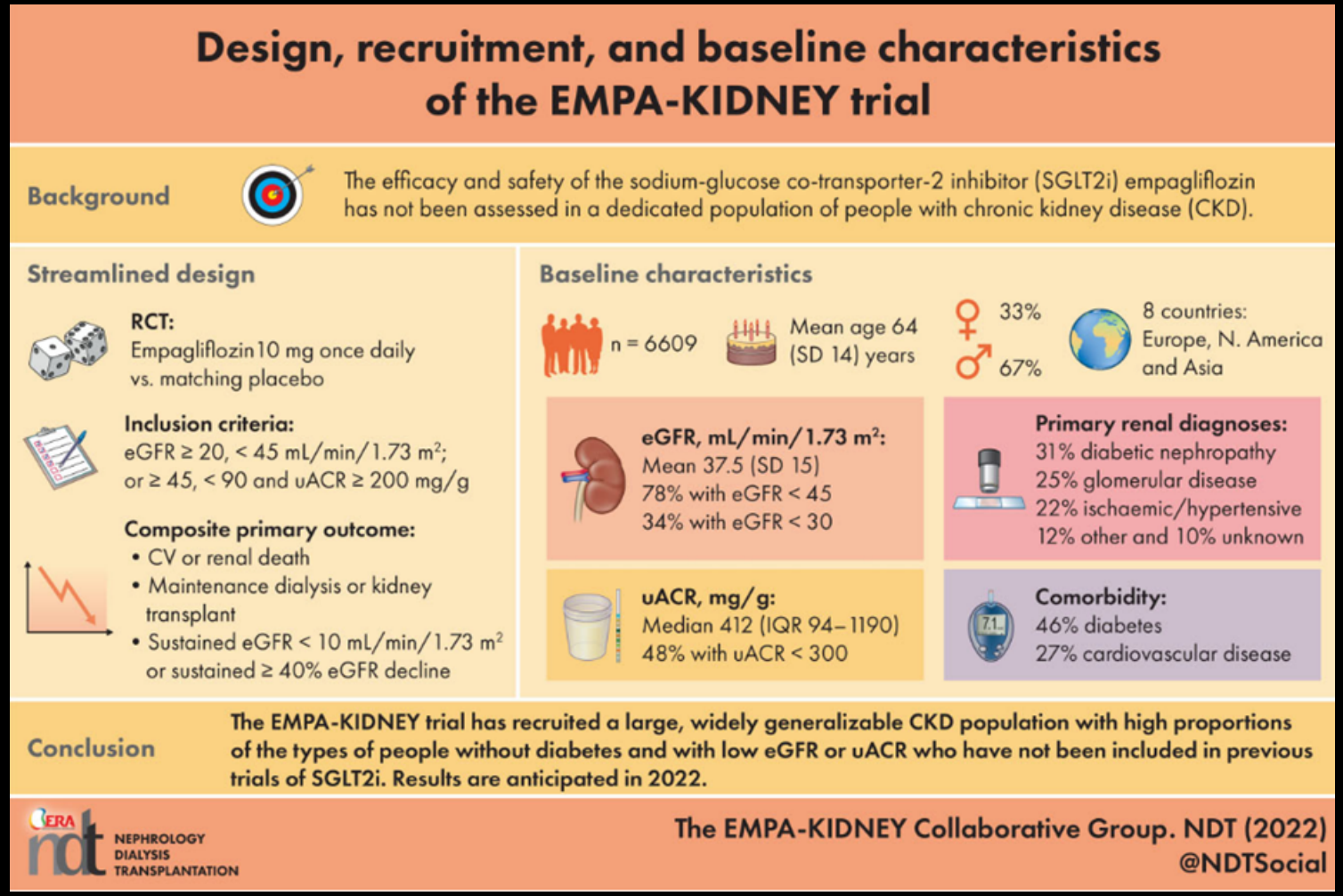


Figure 1. | Practical approach to initiating sodium-glucose transport protein 2 (SGLT2) inhibitors in patients with type 2 diabetes and CKD.

CJASN 16: ccc–ccc, 2021. doi: https://doi.org/10.2215/CJN.18881220

EMPA-Kidney Trial



54% of recruited patients had no prior history of DM.

Lower eGFR's, down to 20 ml/min were included.

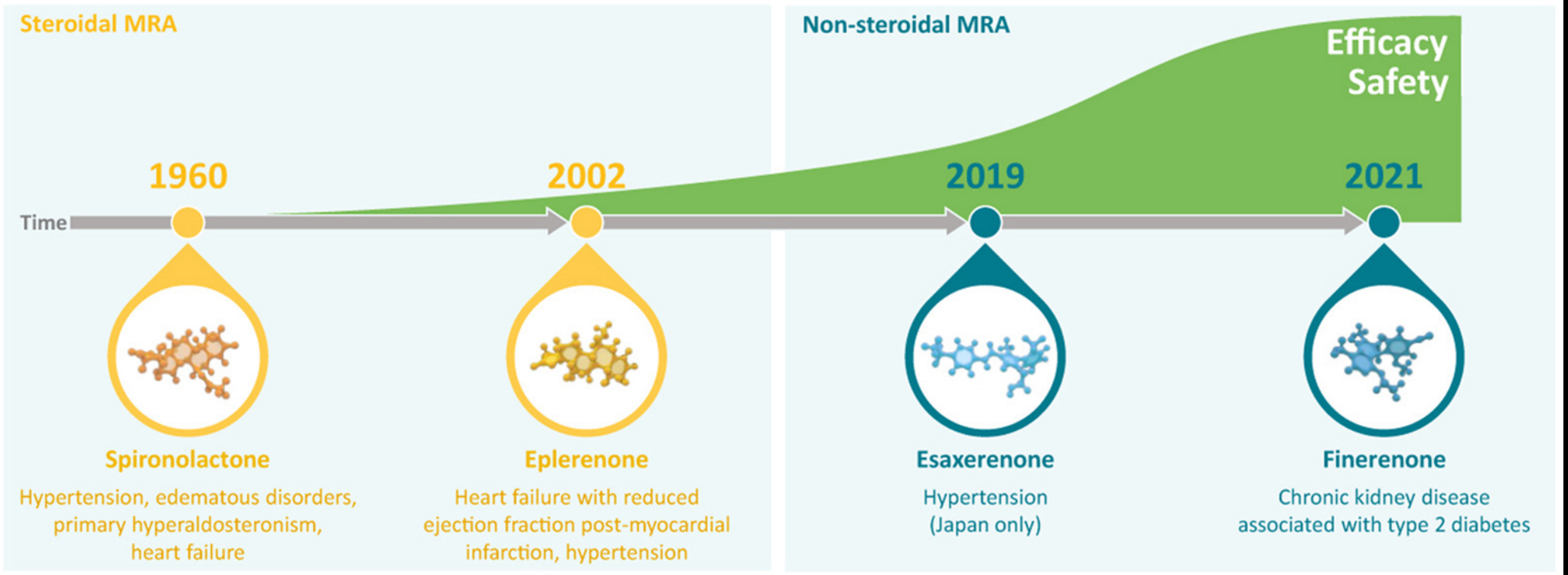
Trial ended early—final f/u completed 7/2022

Results release anticipated later this year.

Clinical perspective—evolving evidence of mineralocorticoid receptor antagonists in patients with chronic kidney disease and type 2 diabetes

kidney INTERNATIONAL supplements

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY



Rossing, 2022

CONCLUSION

In the past, the cardiorenal-protective effect of aldosterone blockade was difficult to study.
Now, recent evidence from the FIDELIO-DKD and FIGARO-DKD trials demonstrates a beneficial role for the nonsteroidal, selective mineralocorticoid receptor antagonist (MRA) finerenone.

Mineralocorticoid Receptor Antagonists (MRAs)

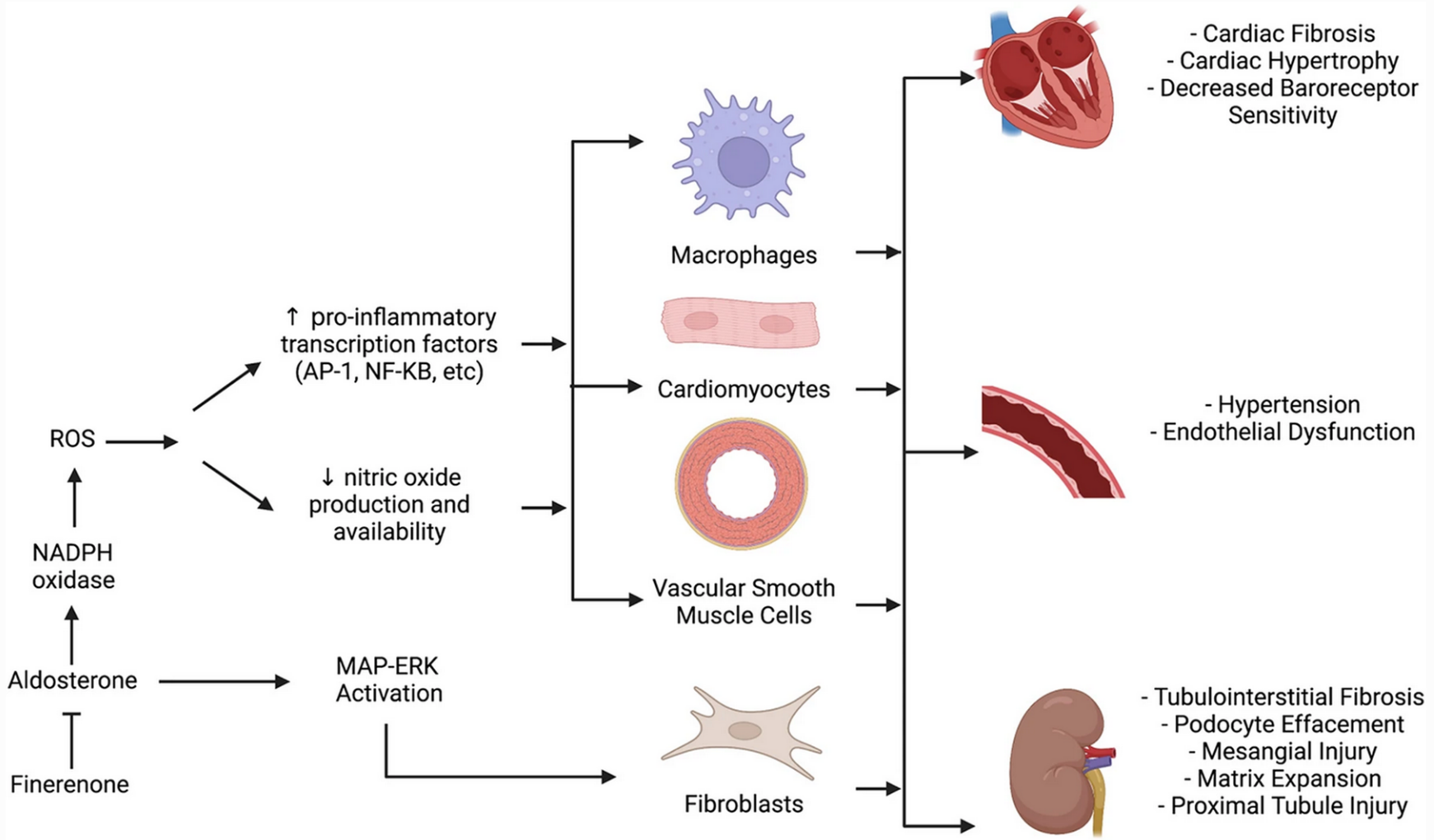
- Adding the MRAs spironolactone and eplerenone to RAS inhibition has been shown to reduce albuminuria by 25-30% but with an increased risk of hyperkalemia and no significant change in CKD progression (as measured by GFR)
- Finerenone is a nonsteroidal MRA with greater receptor selectivity---FIDELIO-DKD: Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease
- 5734 patients with DM II and CKD (eGFR 25 – 74), UACR of 300-5000 mg/g. Finerenone vs placebo.

- Primary composite endpoint: ESKD, sustained decrease in eGFR > 40% or death from a kidney cause.
- 18% lower incidence of the primary endpoint
- Higher incidence of hyperkalemia in the finerenone group which lead to a higher discontinuation rate c/w placebo.
- Only 4.6% of participants were treated with SGLT-2 inhibitor, 6.9% with a GLP-1 receptor agonist.

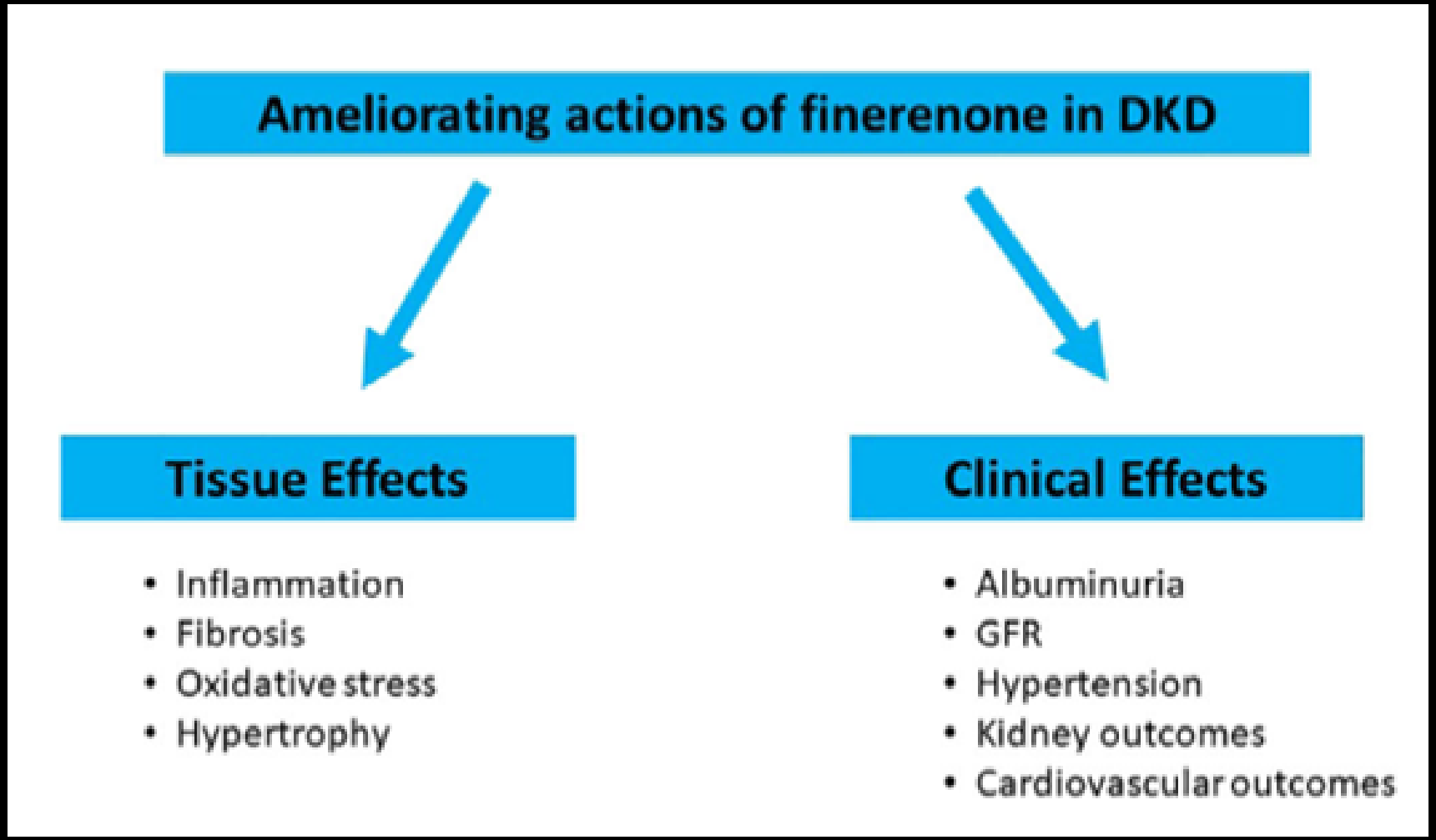
Bakris GL et al, Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *NEJM 2020;383:2219=29.*

Fig. 1

From: Cardiovascular and Renal Outcomes with Finerenone, a Selective Mineralocorticoid Receptor Antagonist



Pathologic mechanisms of aldosterone on the cardiac, vascular, and renal systems. *ROS* reactive oxygen species, *AP-1* activator protein 1, *NF-KB* nuclear factor kappa B. Created with BioRender.com



Diabetes Obes Metab.2022;24:1197–1205

FIGARO and FIDELITY Trials

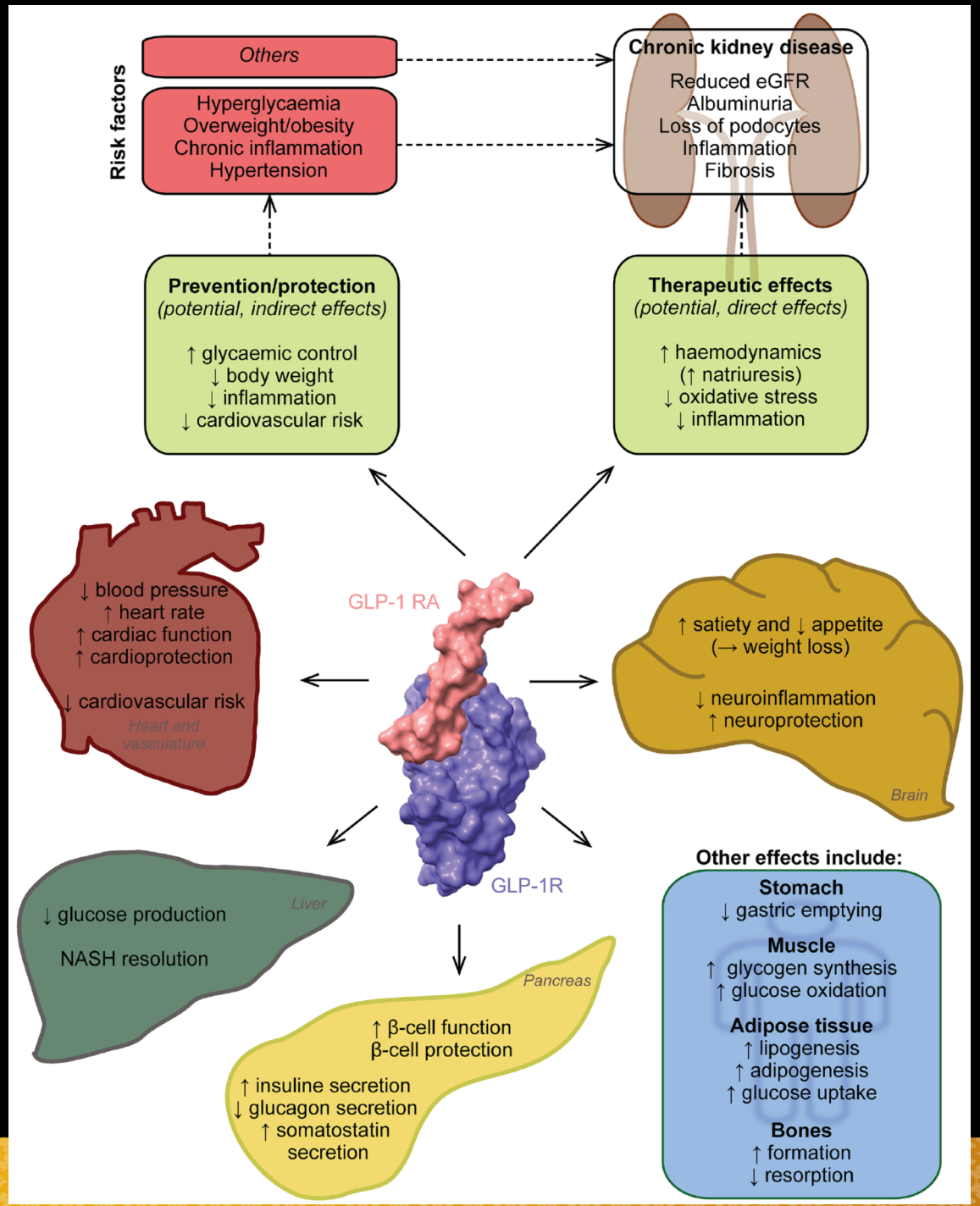
- Similar to FIDELIO-DKD trial but the primary endpoints were cardiovascular, secondary endpoints were renal: sustained eGFR decrease ≥ 40%, kidney failure, death from renal causes.
- Renal outcomes were reduced by 13% in the finerenone group over a mean f/u of 3.4 years.
- Both FIDELIO and FIGARO were done with maximized RAS blockade.
- FIDELITY: time to event outcome. Kidney outcomes: kidney failure, a sustained ≥ 57% decrease in eGFR from baseline over ≥ 4 weeks, or renal death.
- 23% risk reduction in eGFR decrease, 20% risk reduction in progression to ESKD.

New vs. Old

- Finerenone has higher selectivity than spironolactone
- Finerenone has higher MR affinity than eplerenone.
- Finerenone had reduced rates of hyperkalemia and kidney dysfunction than spironolactone.
- Smaller effect on blood pressure.
- Unlike steroidal MRA’s, finerenone has been shown to reduce the decline in eGFR in DKD.

Guidelines….

- KDIGO has yet to comment on finerenone.
- US Food and Drug Administration and the European Medicines Agency have approved its use for CKD in patients with type II DM.
- American Diabetes Association recommends finerenone to reduce progression of CKD in high risk patients who cannot tolerate SGLT-2 I’s.

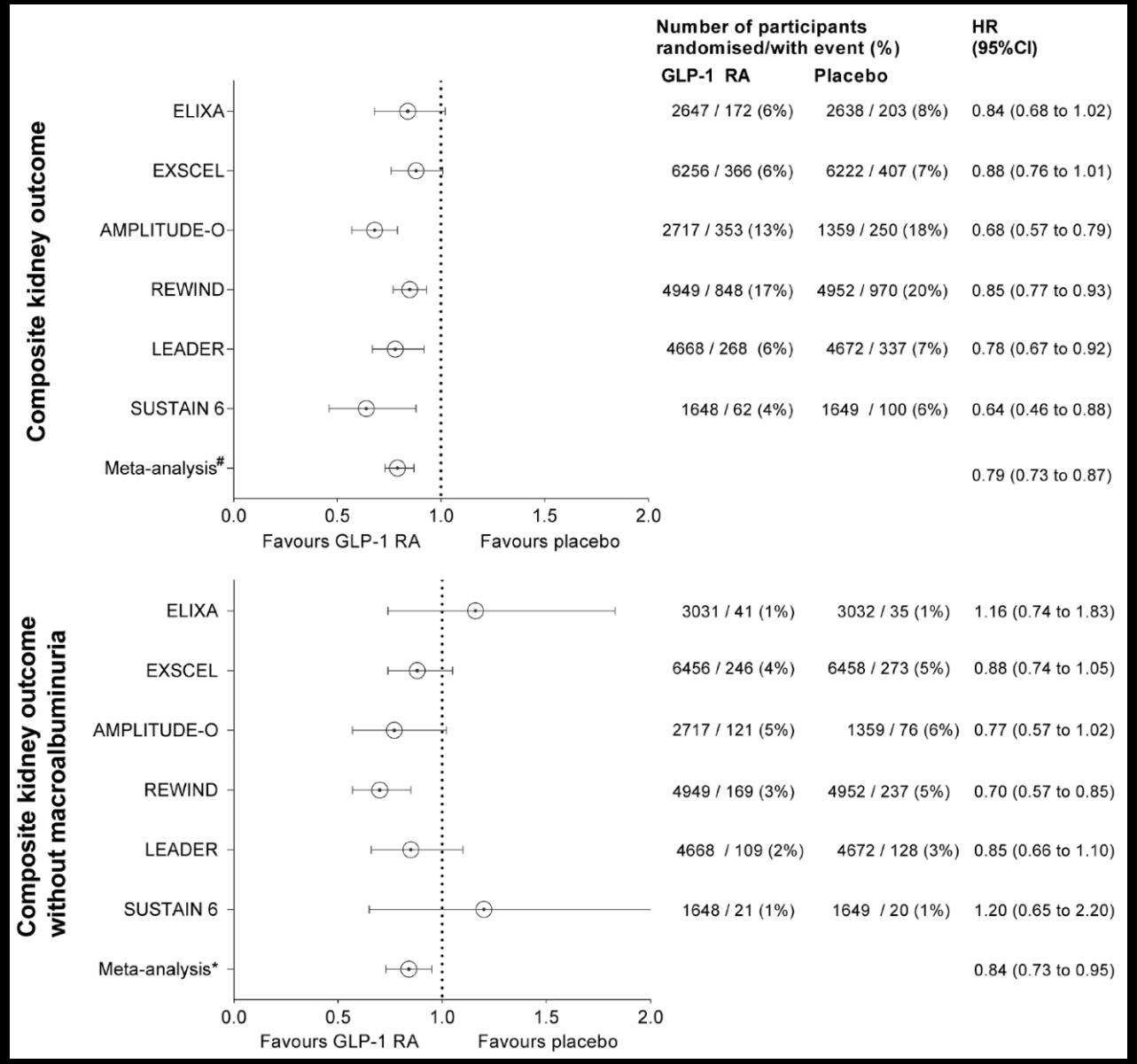


Ther Adv Endocrinol Metab.
2022, Vol. 13: 1–14

Glucagon-like Peptide-1 Receptor Agonists: GLP-1 RA

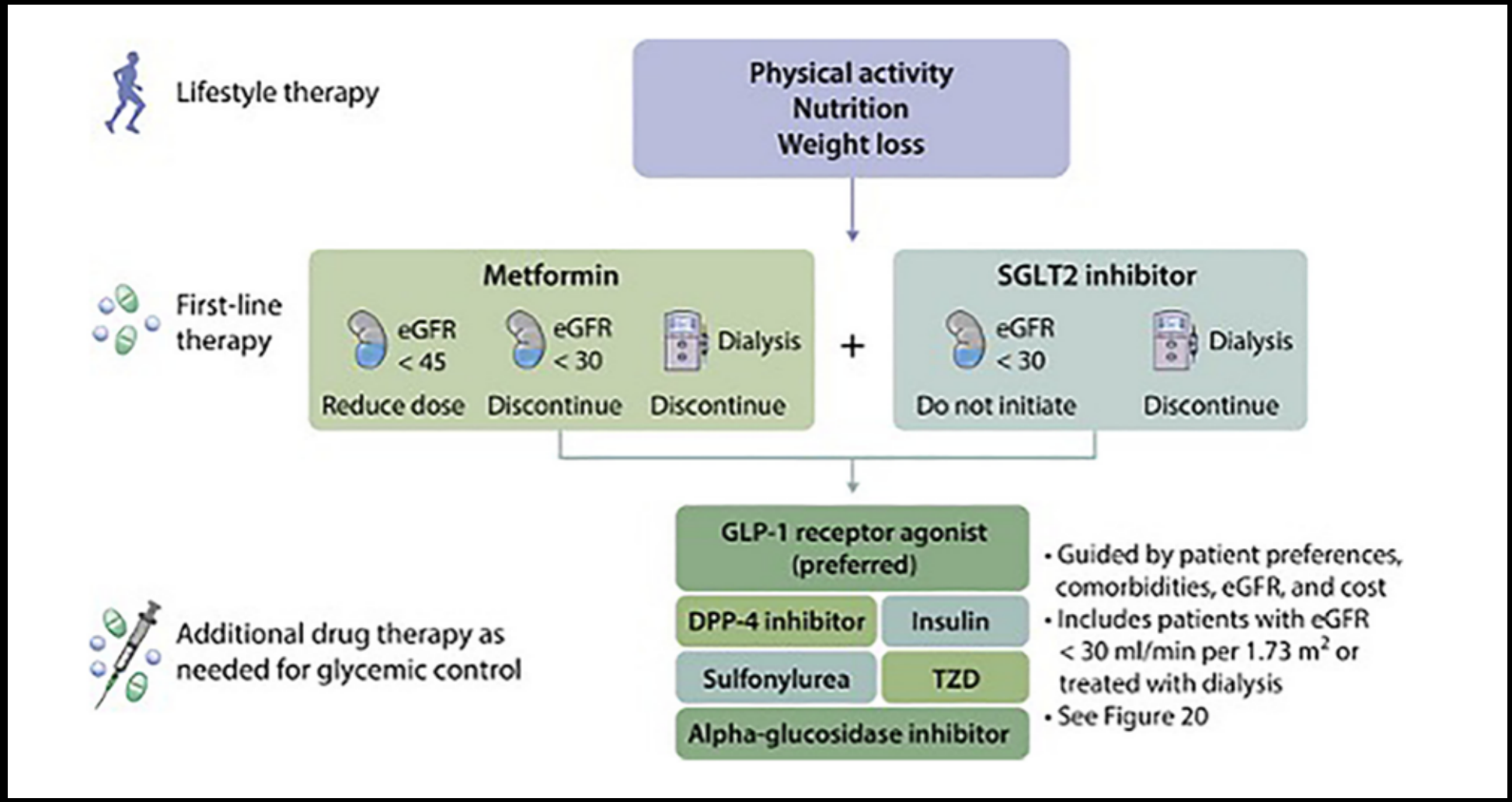
- Shown to reduce risk of cardiovascular events in patients with DM II
- Glucagon like peptide-1 receptor agonists have shown potential efficacy decreasing renal outcomes in cardiovascular studies
- LEADER Trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) evaluated microvascular, retinal and kidney composite outcome.
- For kidneys: new-onset UACR > 300, doubling of creatinine, eGFR <45, ESKD or death from renal cause.
- Kidney events were reduced: HR = 0.78, p = 0.003)

- SUSTAIN-6: Semaglutide and Cardiovascular Outcomes in Patients with Type 2 DM.
- Semaglutide group vs placebo: reduction in nephropathy, HR: 0.64, p = 0.005.
- Outcome was primarily driven by a reduction in the incidence of UACR > 300
- REWIND: Dulaglutide and CV Outcomes in Type 2 Diabetes also showed a decrease in kidney outcomes
- In a 2019 meta-analysis, GLP-1 receptor agonists reduced renal outcomes by 17%.
- The FLOW and REMODAL trails (specifically focusing on kidney outcomes and renal protective mechanisms) are ongoing.


Number of participants randomised/with event (%)
GLP-1 RA
Placebo
HR (95%CI)
Composite kidney outcome
ELIXA
2647 / 172 (6%)
2638 / 203 (8%)
0.84 (0.68 to 1.02)
EXSCEL
6256 / 366 (6%)
6222 / 407 (7%)
0.88 (0.76 to 1.01)
AMPLITUDE-O
2717 / 353 (13%)
1359 / 250 (18%)
0.68 (0.57 to 0.79)
REWIND
4949 / 848 (17%)
4952 / 970 (20%)
0.85 (0.77 to 0.93)
LEADER
4668 / 268 (6%)
4672 / 337 (7%)
0.78 (0.67 to 0.92)
SUSTAIN 6
1648 / 62 (4%)
1649 / 100 (6%)
0.64 (0.46 to 0.88)
Meta-analysis#
0.79 (0.73 to 0.87)
0.0
0.5
1.0
1.5
2.0
Favours GLP-1 RA
Favours placebo
Composite kidney outcome without macroalbuminuria
ELIXA
3031 / 41 (1%)
3032 / 35 (1%)
1.16 (0.74 to 1.83)
EXSCEL
6456 / 246 (4%)
6458 / 273 (5%)
0.88 (0.74 to 1.05)
AMPLITUDE-O
2717 / 121 (5%)
1359 / 76 (6%)
0.77 (0.57 to 1.02)
REWIND
4949 / 169 (3%)
4952 / 237 (5%)
0.70 (0.57 to 0.85)
LEADER
4668 / 109 (2%)
4672 / 128 (3%)
0.85 (0.66 to 1.10)
SUSTAIN 6
1648 / 21 (1%)
1649 / 20 (1%)
1.20 (0.65 to 2.20)
Meta-analysis*
0.84 (0.73 to 0.95)
0.0
0.5
1.0
1.5
2.0
Favours GLP-1 RA
Favours placebo

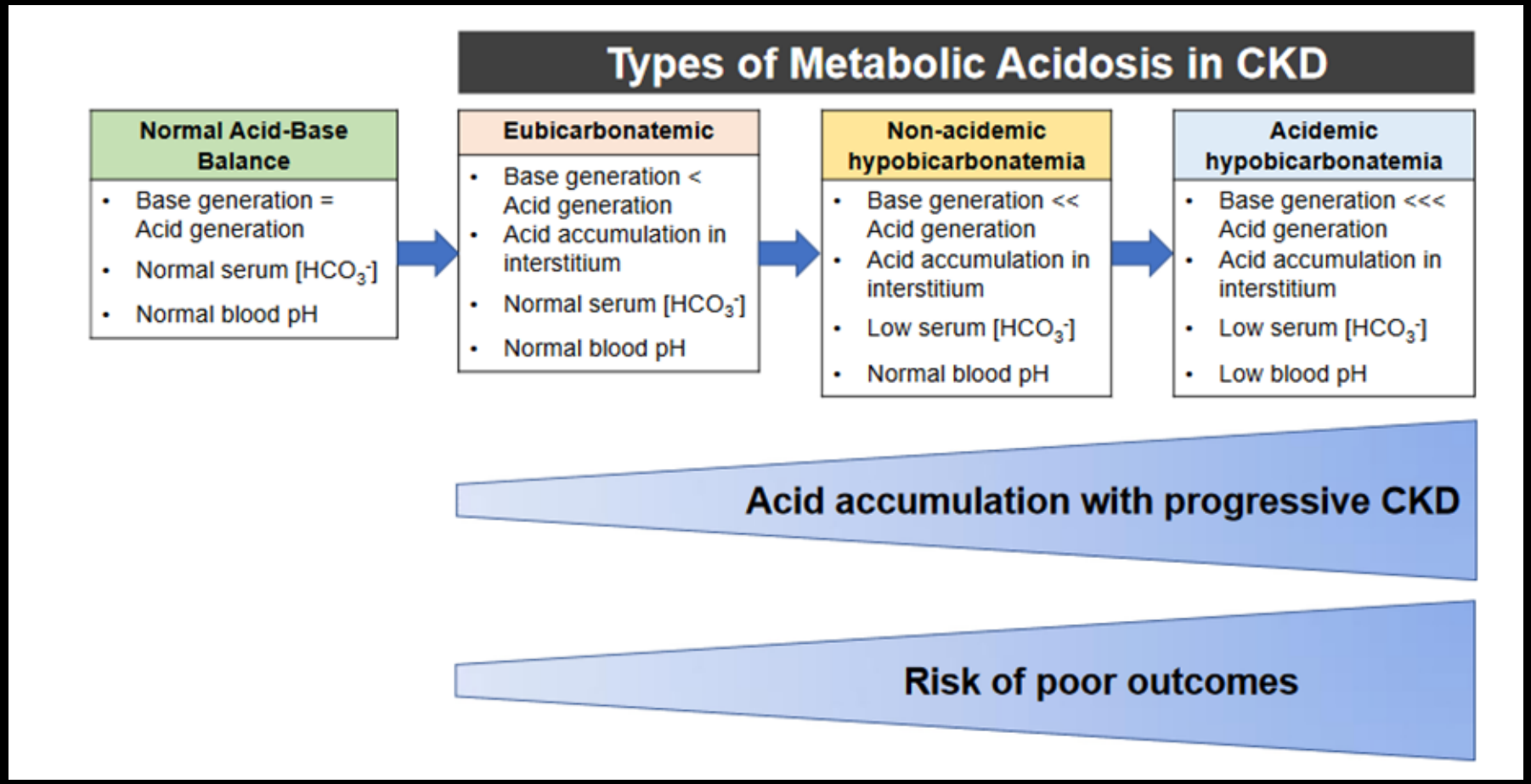
Dual GIP/GLP-1 Receptor Agonist: Tirzepatide

- SURPASS showed profound glycemic and weight reducing benefits which may translate to kidney protection.
- Analysis of SURPASS-4 by Heerspink, et al showed a HR of 0.59 for new onset macroalbuminuria and eGFR decline.
- Like GLP-1 receptor agonists, kidney specific outcomes studies are needed.

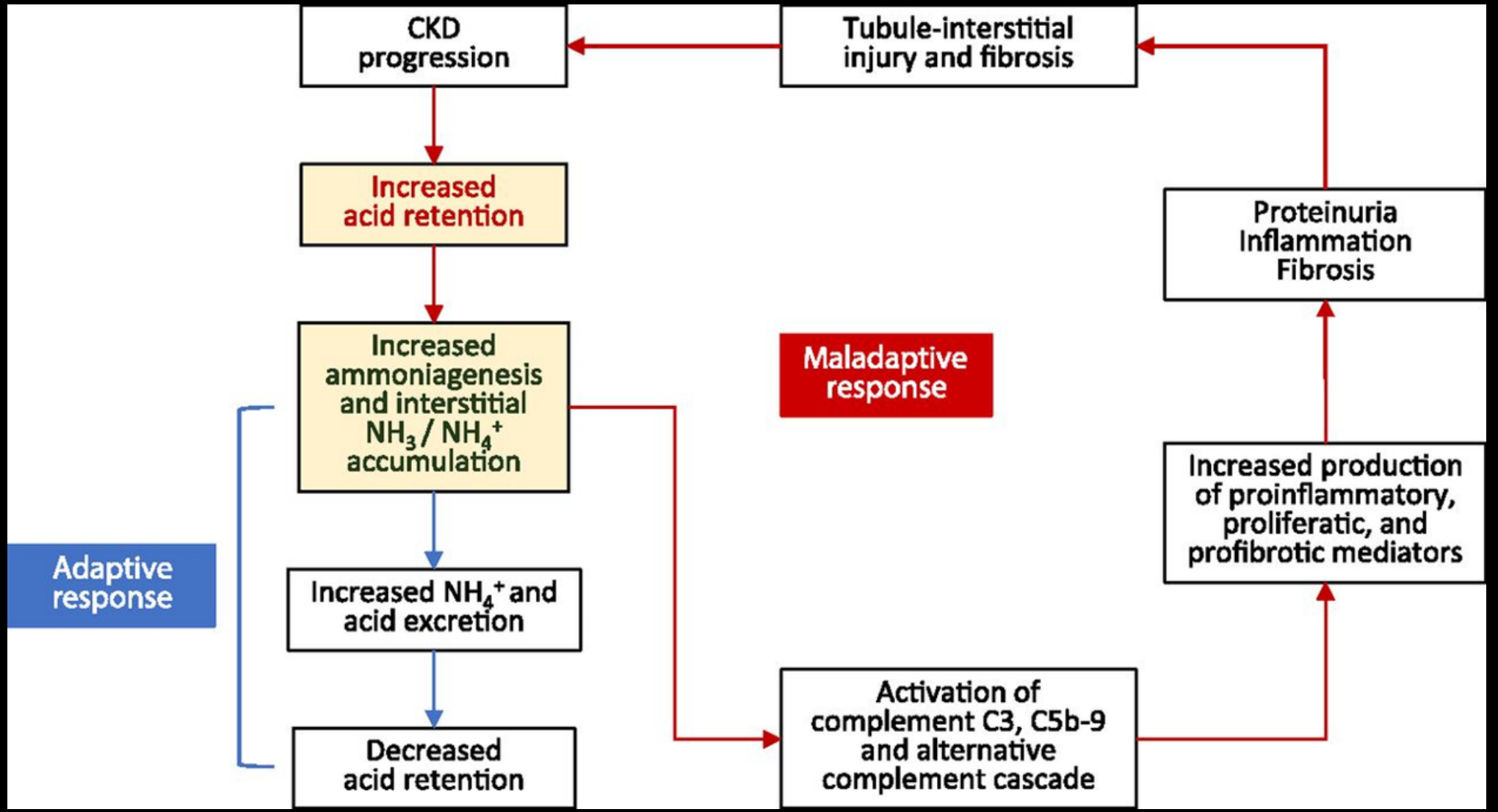


J Osteopath Med 2022; 122(1): 55-63

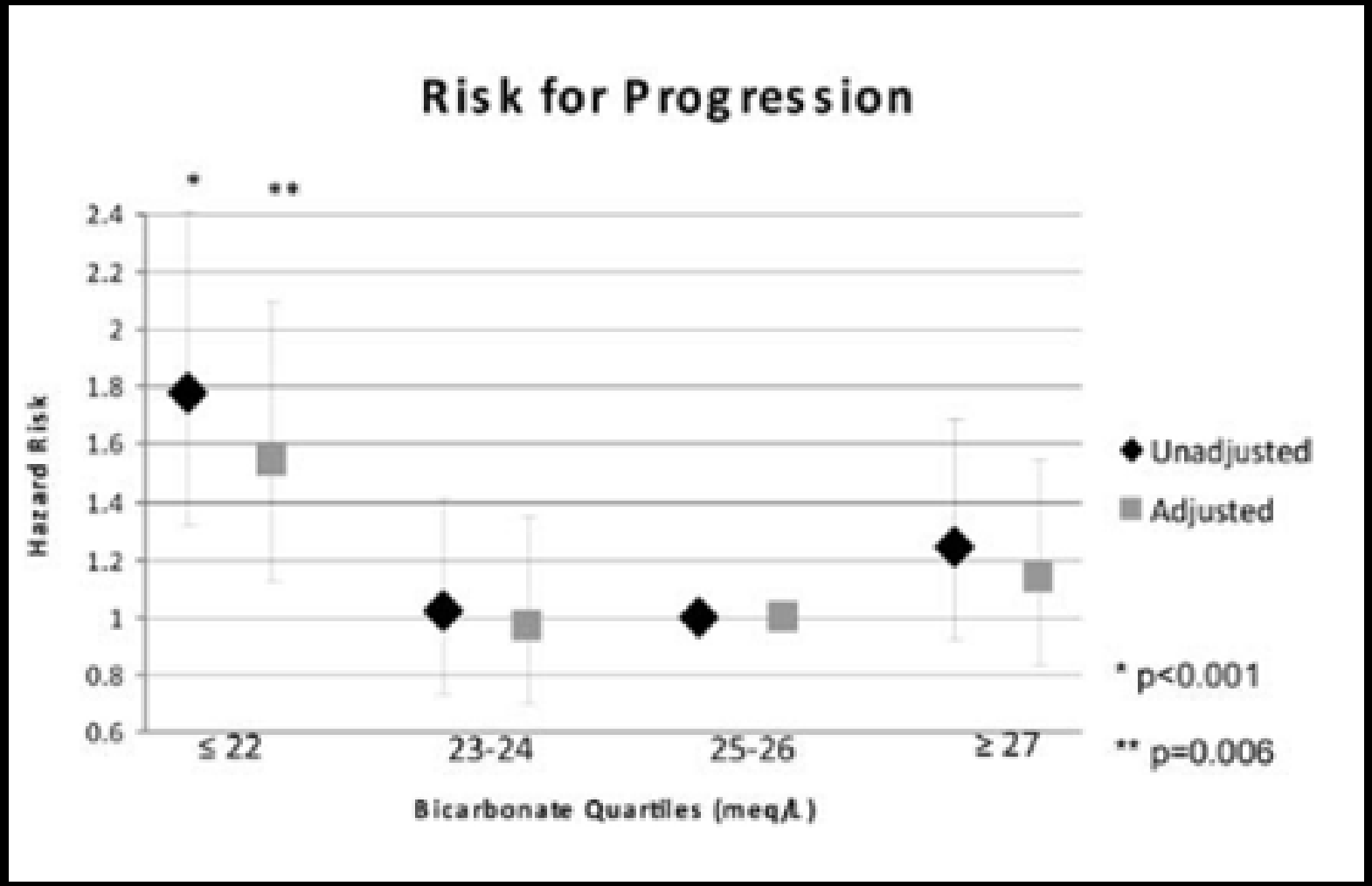
Acidosis is not good for kidneys



Kidney Med Vol 3 | Iss 2 | March/April 2021



JASN March 2020, 31 (3) 469-482; DOI: https://doi.org/10.1681/ASN.2019070677



Am J Kidney Dis 54:270-277. © 2009 by the National Kidney Foundation, Inc.

Table 1. Summary of Recent Interventional Trials

Trial	Population	Serum Bicarbonate, mEq/L	Total Sample Size	Duration	Intervention	Major Findings
UBI[8]	CKD stage 3, 4, or 5	>18 but <24	795	36 mo	$NaHCO_3$ to target bicarbonate 24-28 mEq/L	• Lower risk for serum creatinine doubling, RRT, and death
BiCARB[9]	Age > 60 y, eGFR < 30 mL/min/1.73 m^2	<22	300	24 mo	$NaHCO_3$ up to 3,000 mg/d	• No significant effect on Short Physical Performance Battery after 12 mo • Shorter 6-min walk distance and reduction in hand-grip strength in treatment group • More adverse events with treatment
Alkali Therapy in CKD[10]	CKD stage 3 or 4	20-26	149	24 mo	$NaHCO_3$, 0.4 mEq/kg of body weight/d	• No significant effect on bone mineral density, sit-to-stand time, other physical function assessments, or eGFR
VA BiCARB[11]	Diabetes CKD 2, 3, or 4 ACR > 30 mg/g	22-28	74	6 mo	0.5 mEq/kg of lean body weight/d	• No statistically significant effect on urinary markers of kidney injury
BASE Pilot Trial[12]	CKD stage 3b or 4 or CKD 3a with ACR ≥ 50 mg/g	20-28	192	28 wk	0.5 or 0.8 mEq/kg lean body weight/d	• No significant effect on blood pressure or weight • Dose-dependent increase in serum bicarbonate • Dose-dependent increase in urinary ACR
Veverimer (40-wk extension study)[13]	eGFR 20-40 mL/min/1.73 m^2	12-20	196	52 wk	Veverimer 6 g/d then titrated to target bicarbonate 22-29 mEq/L	• 3% in veverimer vs 10% in placebo discontinued treatment • Treatment with veverimer improved physical function • Fewer treated with veverimer died or progressed to ESKD

Abbreviations: ACR, albumin-creatinine ratio; BASE, Bicarbonate Administration to Stabilize eGFR; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; RRT, renal replacement therapy; UBI, Use of Bicarbonate in CKD.

The effect of oral alkali supplementation or dietary acid reduction on decline in GFR.

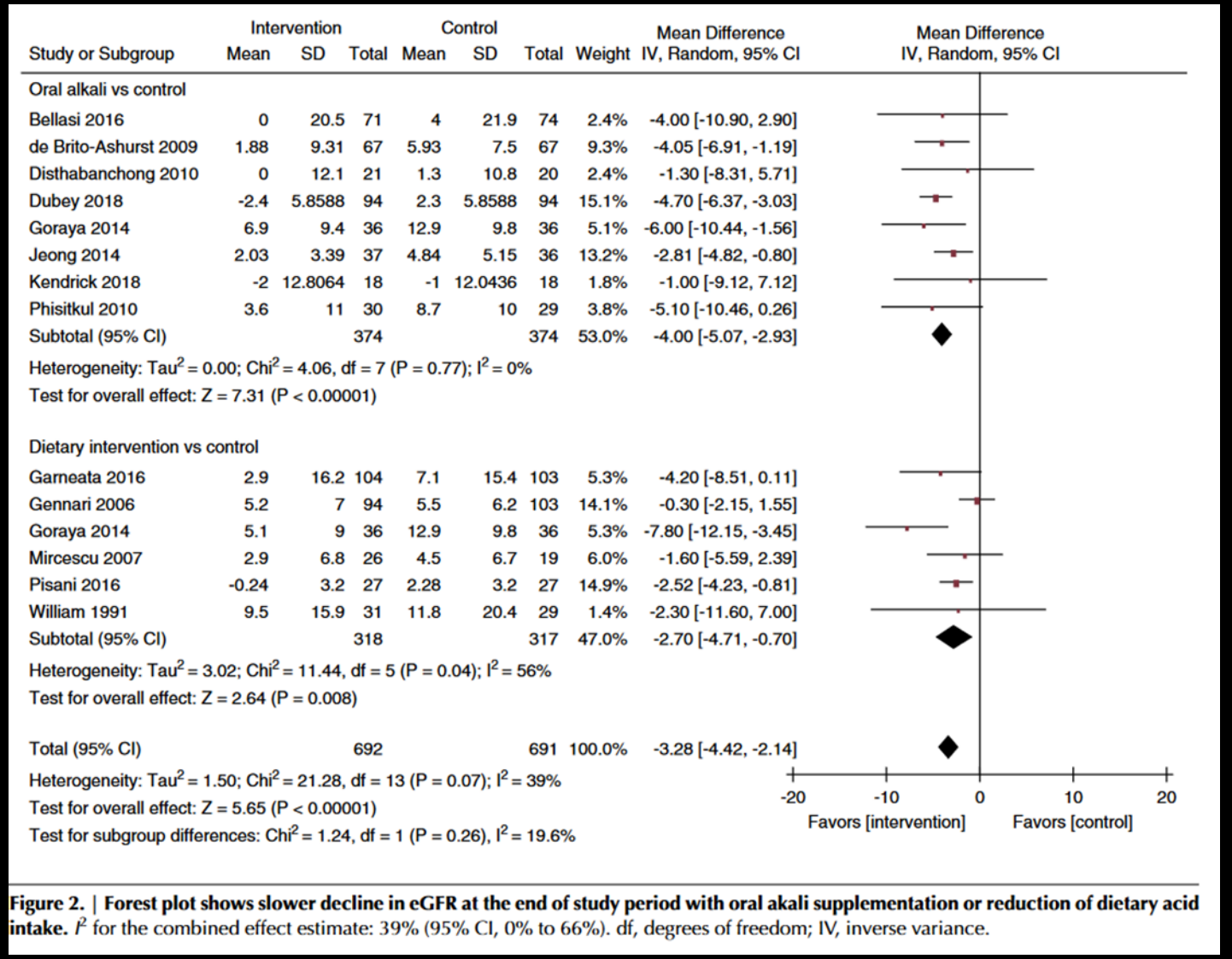


Figure 2. | Forest plot shows slower decline in eGFR at the end of study period with oral akali supplementation or reduction of dietary acid intake. I^2 for the combined effect estimate: 39% (95% CI, 0% to 66%). df, degrees of freedom; IV, inverse variance.

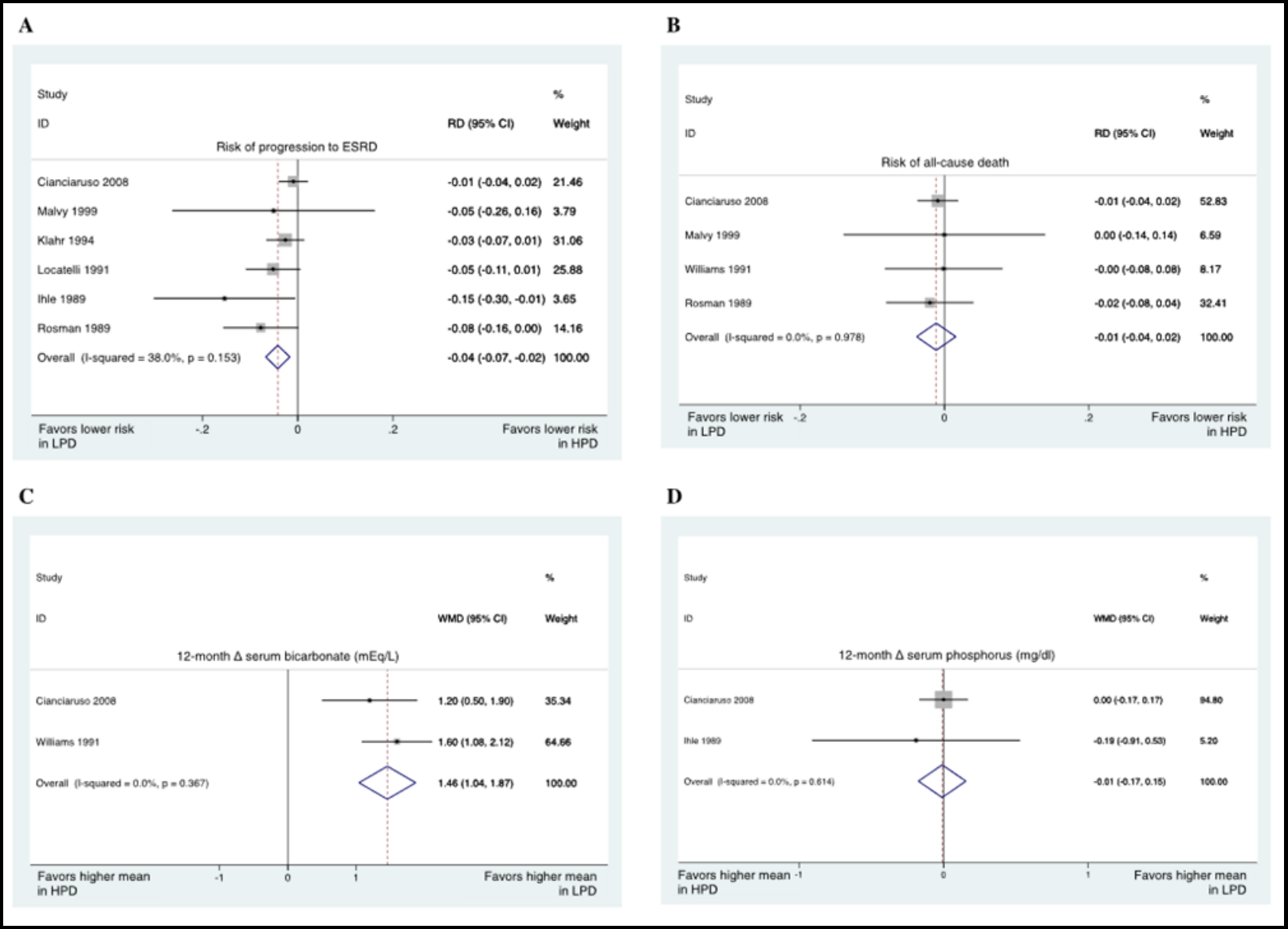
www.cjasn.org Vol
14 July, 2019

High Protein Intake

- An animal protein-rich meal leads to an acute decline in renal vascular resistance accompanied by increased renal plasma flow and GFR.
- It appears that this effect occurs because of a complex interplay of hormonal responses: glucacon, RAAS, nitric oxide, prostaglandins.
- Proteins derived from meat can lead to a 15-25% increase in GFR.
- Vegetable proteins have a much more limited effect.
- The popularity of high protein, low carbohydrate diets have stimulated an interest in the role of this protein effect in CKD.
- Animal models (rodent, pigs) have demonstrated hyperfiltration, proteinuria, and a greater prevalence of kidney histological damage compared with normal diet controls.

- There have been mixed results in human studies.
- Limited by design, accuracy of measuring protein consumption, lack of a uniform definition of high protein intake.
- But there does seem to be a difference in progression of disease.
- How practical are these protein restrictions in our patient population?

Low-protein diet for conservative management of chronic kidney disease: a systematic review andmeta-analysis of controlled trials



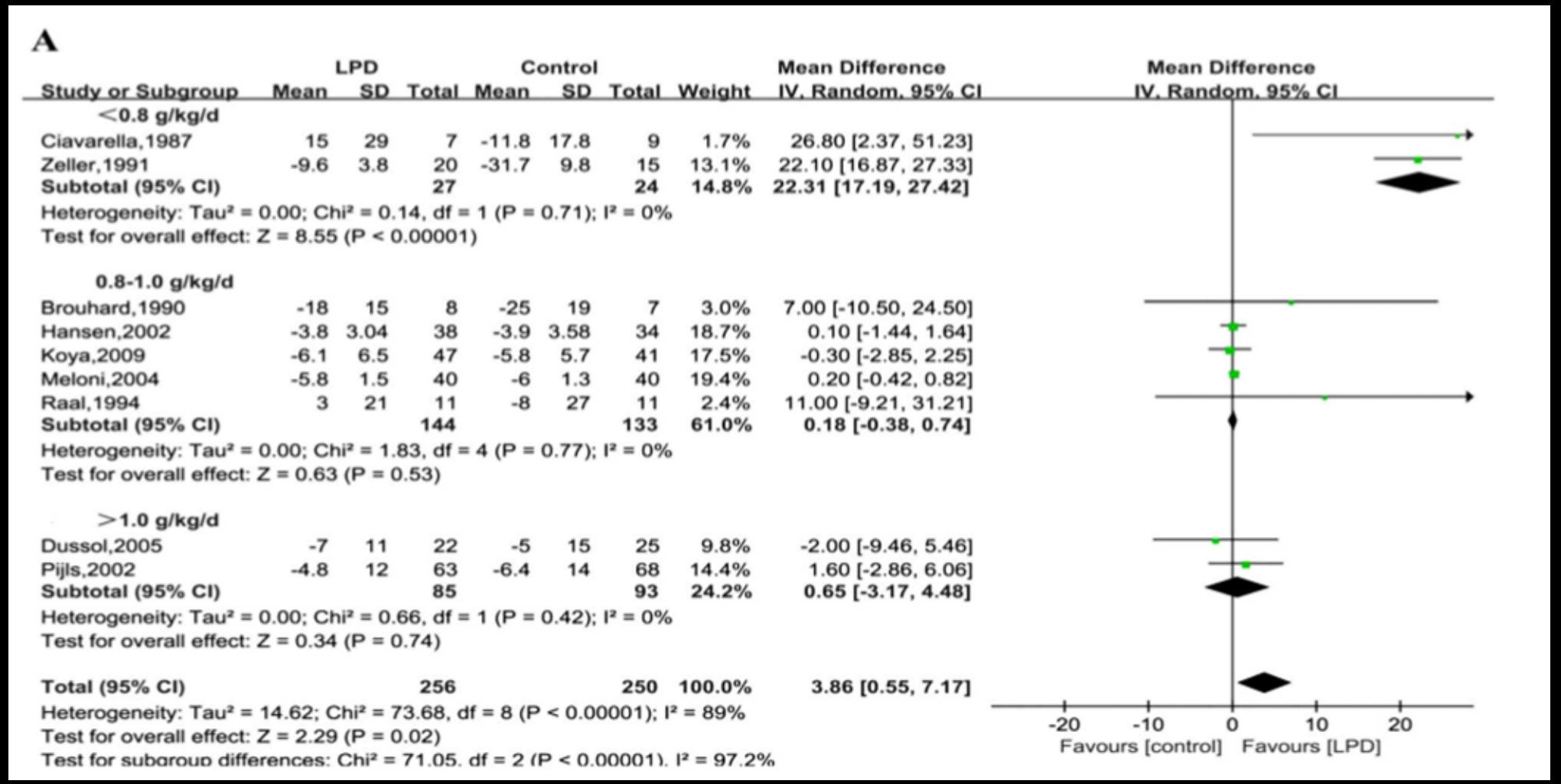
A. 4% risk reduction in progression to ESRD
B. Trend toward reduced risk of all cause death
C. Higher Bicarb with LPD
D. No difference in phosphorus with LPD

Journal of Cachexia, Sarcopenia and Muscle: 2018;9: 235–245

What to do?

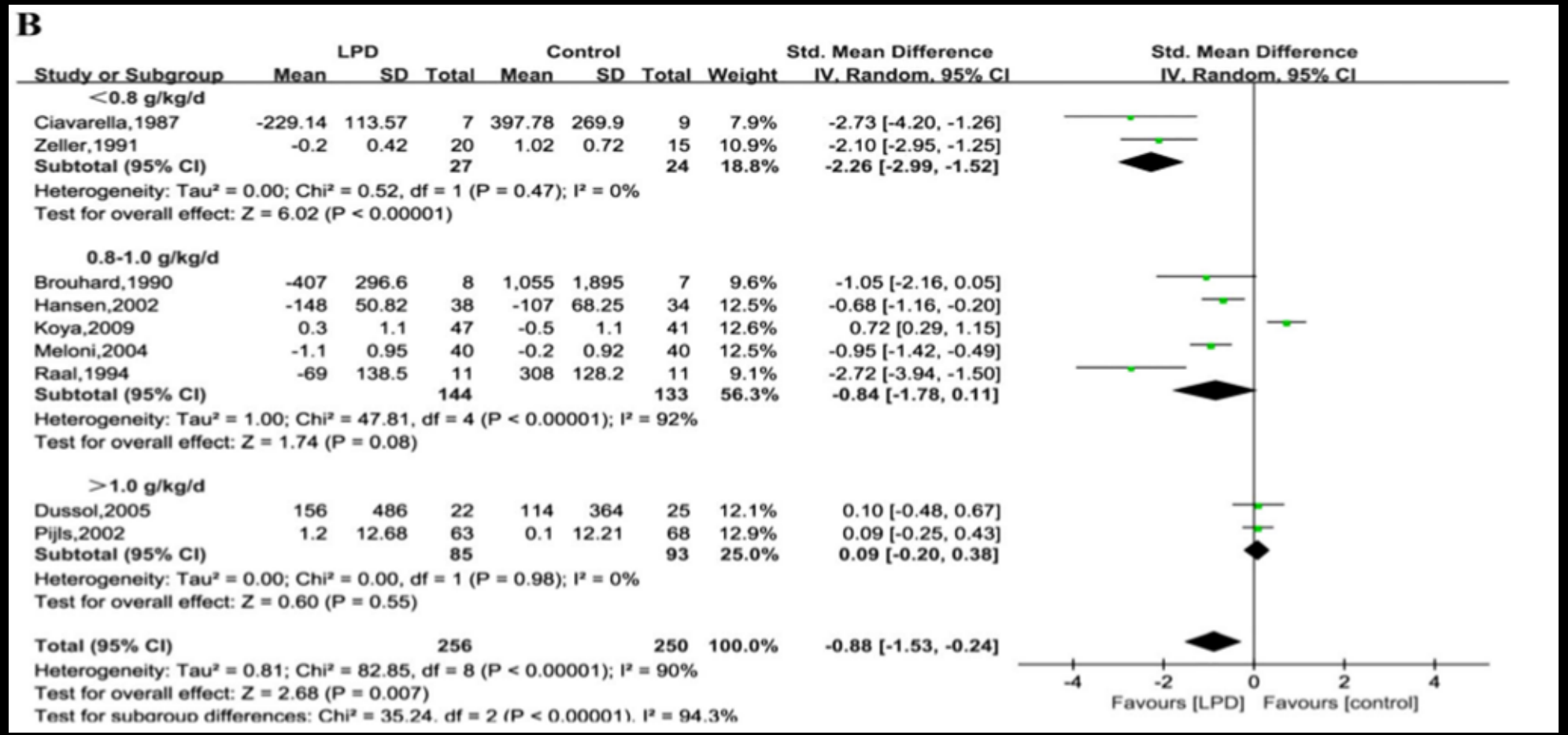
- Daily protein consumption in adults in the US (2001 – 2014, NHANES): 1.1 to 1.5 g/kg/day. Varies with age and sex.
- In adults without CKD minimal protein intake to avoid negative nitrogen balance is approximately 0.8g/kg/day.
- 2020 KDOQI update recommends 0.55 to 0.6 g/kg/day for CKD III to V. Lower with AA supplementation. Diabetics: 0.8 g/kg/day. Illness: 1.0 g/kg/day. Strength of recommendation: 2C---weak recommendation: closely balanced risks and benefits.
- The committee's justification for the committee's revised goals are based on glomerular hyperfiltration observed with higher protein diets, theoretically reduced uremic toxins and phosphorus.
- KDIGO 2012 recommendations: 0.8 g/kg/day for eGFR <30, avoid high protein intake (> 1.3 g/kg/day). Guideline update launched in 1/2022.

Effect of low protein diet (0.6 to 0.8 g/kg/day) on eGFR in diabetic pts with CKD I to III



Diabetes Ther (2021) 12:21–36

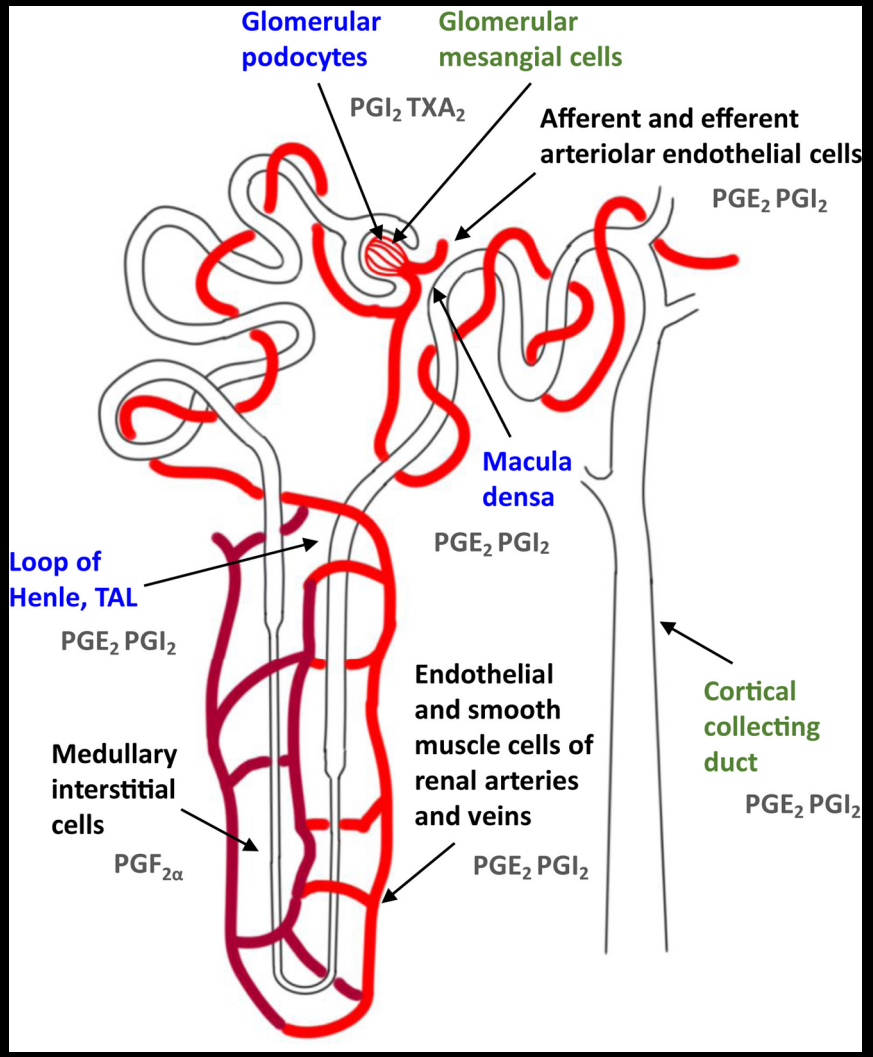
Effect of low protein (0.6 to 0.8g/kg/day) diet on proteinuria



Diabetes Ther (2021) 12:21–36

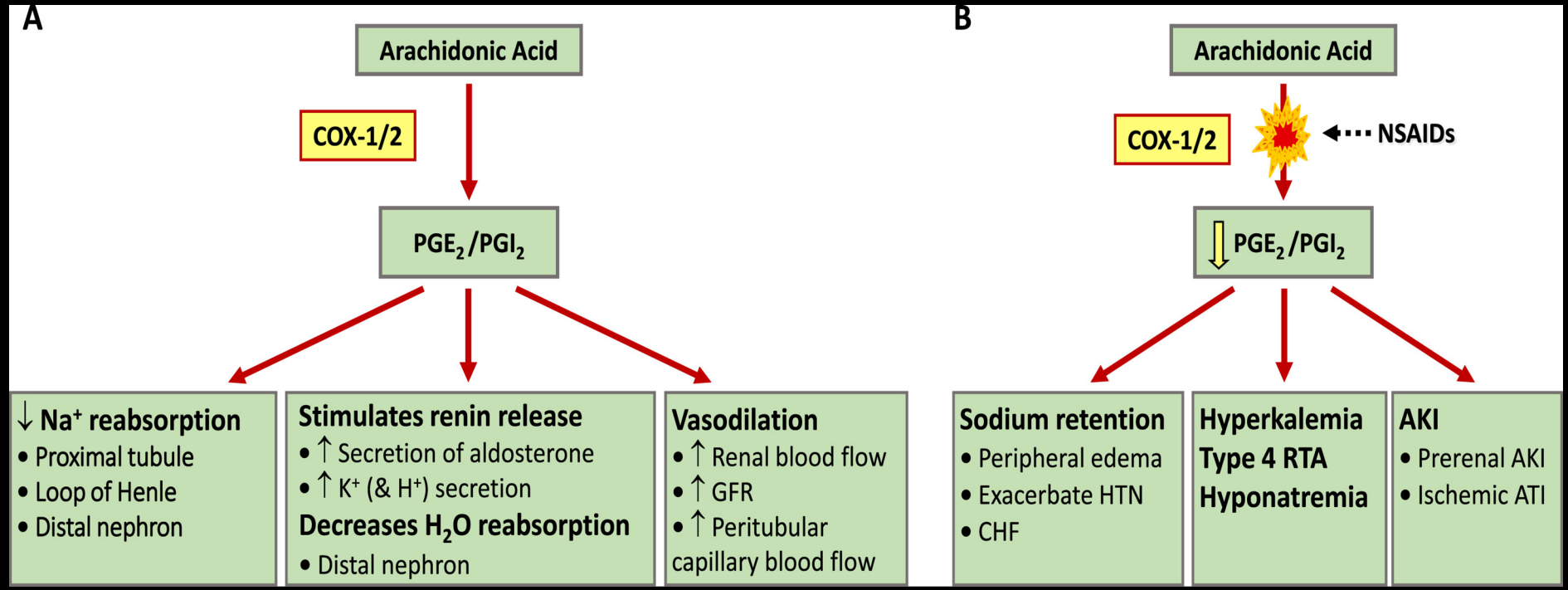
“Avoid Nephrotoxins….”

Prostaglandins and the nephron



American Journal of Kidney Diseases 2020 76546-557DOI: (10.1053/j.ajkd.2020.03.023)

NSAIDS provide their analgesic/anti-inflammatory and antipyretic effects through inhibition of cyclooxygenase (COX) enzymes.



American Journal of Kidney Diseases 2020 76546-557DOI: (10.1053/j.ajkd.2020.03.023)

Box 1. Adverse Effects of NSAIDs on the Kidney

- Acute kidney injury
  - ◇ Hemodynamic and acute tubular injury
- Hyperkalemia ± metabolic acidosis
- Hyponatremia
- Hypervolemia and sodium avidity
  - ◇ Edema, congestive heart failure
  - ◇ Diuretic resistance
- Exacerbation of hypertension
- Acute interstitial nephritis
- Nephrotic syndrome
  - ◇ Membranous nephropathy
  - ◇ Minimal change disease
- Acute or chronic papillary necrosis
- Progression of chronic kidney disease

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

It’s not just about the lower GFR…

Box 2. Risk Factors for NSAID Nephrotoxicity

Acute Kidney Injury

- True circulating volume depletion
  - ◇ Exercise-induced, diarrhea, vomiting, excessive diuresis poor oral intake
- Effective circulating volume depletion
  - ◇ Nephrotic syndrome, cirrhosis, CHF, hypoalbuminemia
- High cumulative dose exposure
- Concurrent calcineurin inhibitors and other vasoconstrictor
- Concurrent therapy with RAAS inhibitors, diuretics, or both

Hyperkalemia

- Concurrent use of medications promoting hyperkalemia
  - ◇ RAAS inhibitors, trimethoprim, heparin, other drugs
- Exposure to radiocontrast with concomitant RAAS inhibitor
- Age > 65 y
- Hyporeninemic hypoaldosteronism
- Type 4 RTA

Hyponatremia

- True or effective circulating volume depletion (outlined above
- Conditions associated with SIADH
- Increased free water intake ± increased sodium losses (eg with extreme exercise)
- Thiazide use in elderly patients

Hypervolemia

- Underlying comorbid conditions promoting sodium avidity including CHF, cirrhosis, and nephrotic syndrome

Worsened hypertension

- Underlying hypertension, including on effective treatment
- Hyporeninemic states, as seen in elderly and diabetes mellitus

Progression of CKD

- Age > 65 y
- High cumulative dose exposure
- Coronary artery disease
- Combination analgesics (banned)

*Nephrotoxicity**	Stage 1-2 CKD	Stage 3 CKD	Stage 4 CKD	Stage 5 CKD, No KRT
AKI	Low risk, similar to general population†.	Low risk, similar to non-elderly general population†, mildly increased in elderly.	At least moderately increased risk compared with general population.	High risk compared with general population.
	Risk posed by concurrent RAASi and/or diuretic use greater than in general population.			
Hyperkalemia	Low risk, similar to general population†.	Low risk, similar to general population†.	Moderately increased risk compared with general population.	High risk compared with general population.
Hyponatremia	Low risk, similar to general population†. Risk may be increased with DM.	Low risk, similar to general population†. Risk may be increased with DM.	Risk may be elevated compared with general population, but data lacking.	Risk may be elevated compared with general population, but data lacking.
Hypervolemia	Risk similar to general population†.	Risk similar to general population†.	Increased risk due to risk for Na^+ and water retention and reduced GFR.	High risk due to risk for Na+ and water retention and reduced GFR.
Hypertension	Likely increased risk compared with general population based on level of underlying hyporeninemia.	Mildly increased risk compared with general population based on level of underlying hyporeninemia.	Increased risk due to risk for precipitating hypervolemia and systemic vasoconstriction.	High risk due to risk for precipitating hypervolemia and systemic vasoconstriction.
Progression of CKD	No increased risk with NSAID use†.	No increased risk with NSAID use†.	Likely moderate increased risk.	Moderate to high increased risk.

What to do? Can't use opiods, acetaminophen doesn't work, nephrologist says no NSAIDS…

	Stage 1-2 CKD	Stage 3 CKD	Stage 4 CKD	Stage 5 CKD, No KRT
Data Strength	Strong-moderate	Moderate	Weak	Weak
Recommen-dations	Short-term use for ≤5 days acceptable**. Long-term use also acceptable on case-by-case basis**, with close monitoring for nephrotoxicity and for development of risk factors for nephrotoxicity as in Table 3.		Consider short-term, low-dose NSAID use on a case-by-case basis with close monitoring**. In patients with underlying hyperkalemia, should consider NSAIDs contraindicated.	Would consider NSAIDs as absolutely contraindicated except under circumstances of palliative care.

Conclusions

- There has been an encouraging expansion of options to slow down the progression of CKD.
- Life style modification that may make a difference: reasonable protein reduction/plant based diet, smoking cessation, exercise, wgt loss.
- All pts with proteinuric CKD should be on RAS inhibition unless there is a contra-indication.
- In DM Nephropathy SGLT-2 Inhibitors, and GLP-1 Agonists should be strongly considered in addition to RAS inhibition for appropriate patients.
- Finerenone should be considered in patients with DKD
- Metabolic Acidosis in patients with CKD should be treated.