

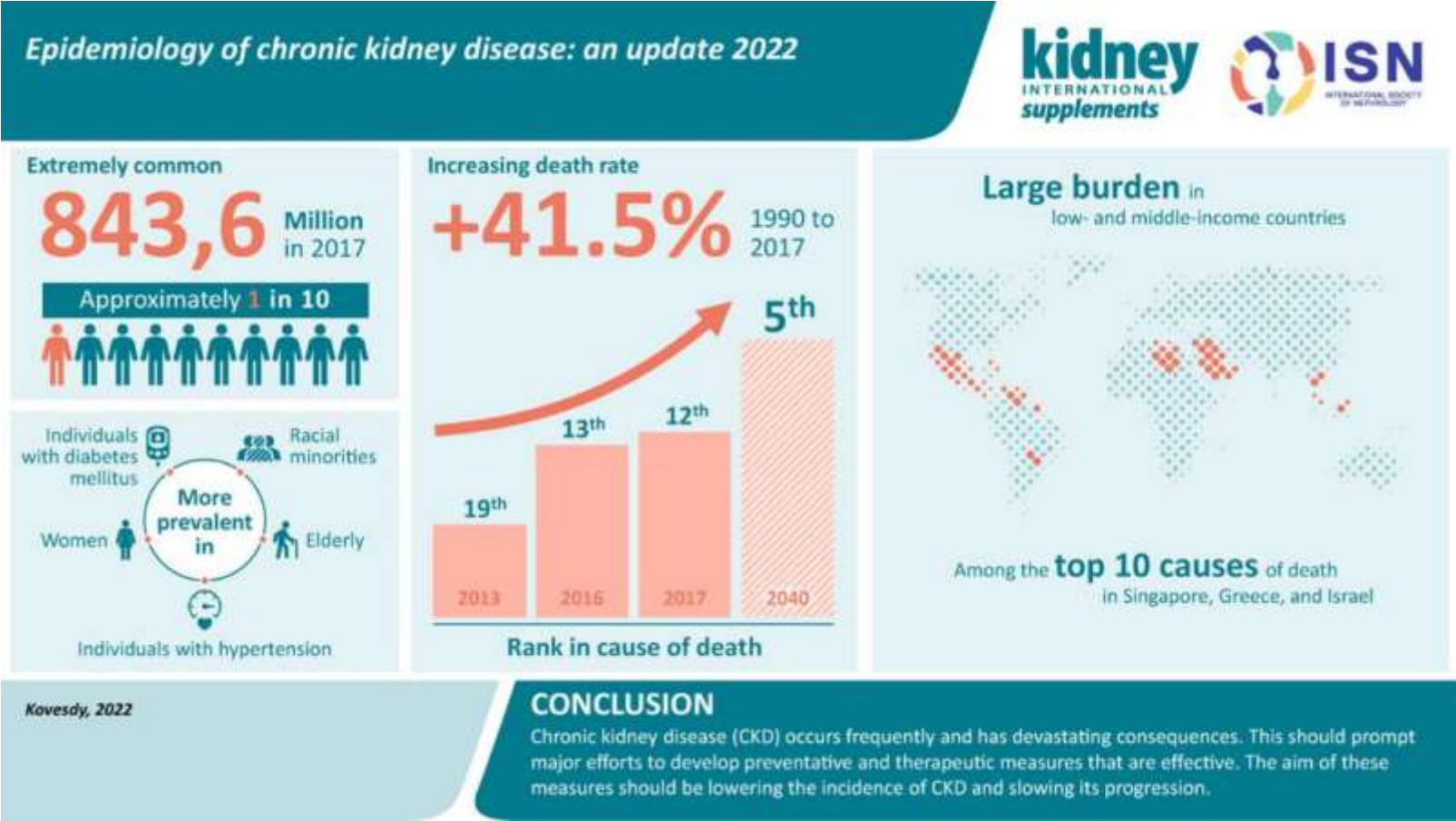
SGLT-2 inhibitoren

-Serendipiteit in het kwadraat-

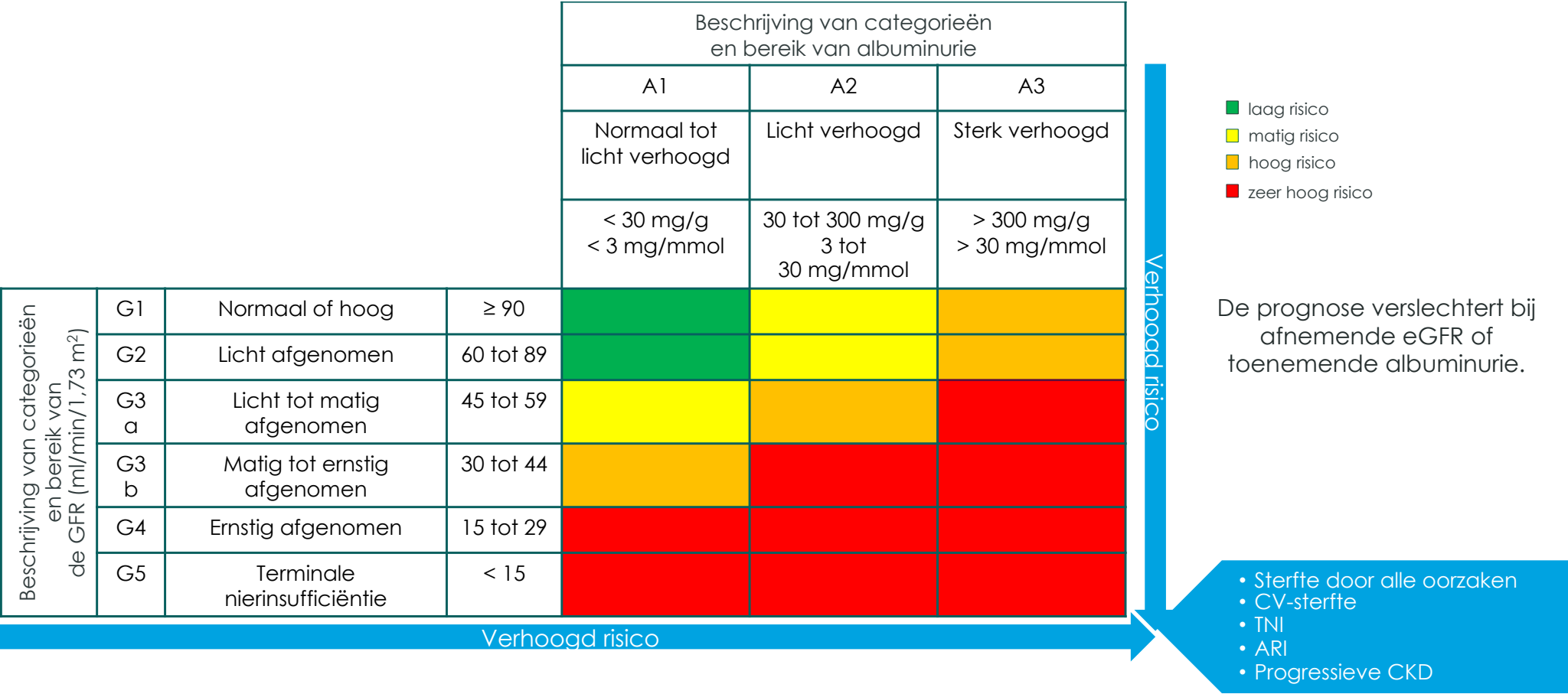


Rowena Vleut
– Internist-nefroloog –
UZA

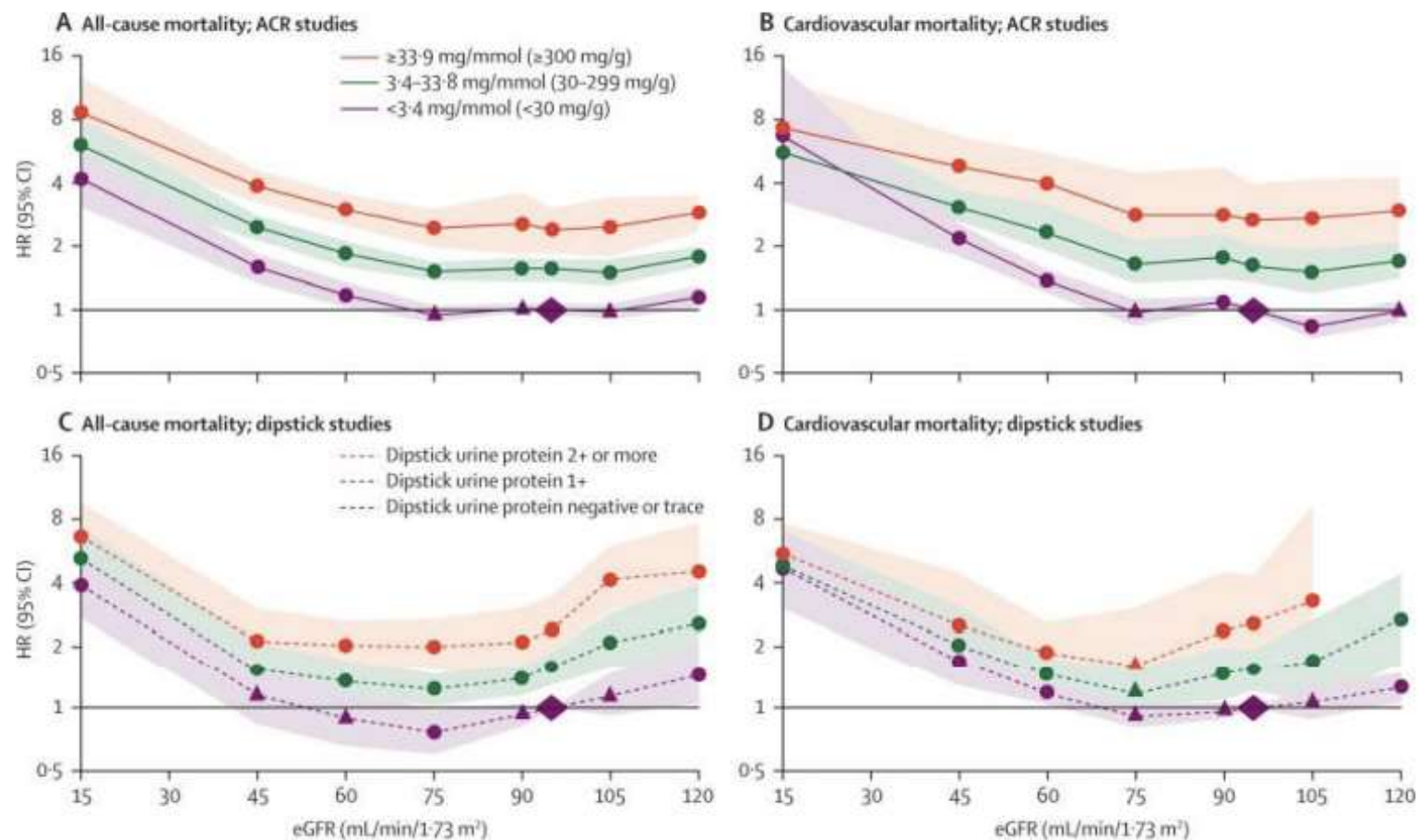
Voorspelling 2040



CKD stadia

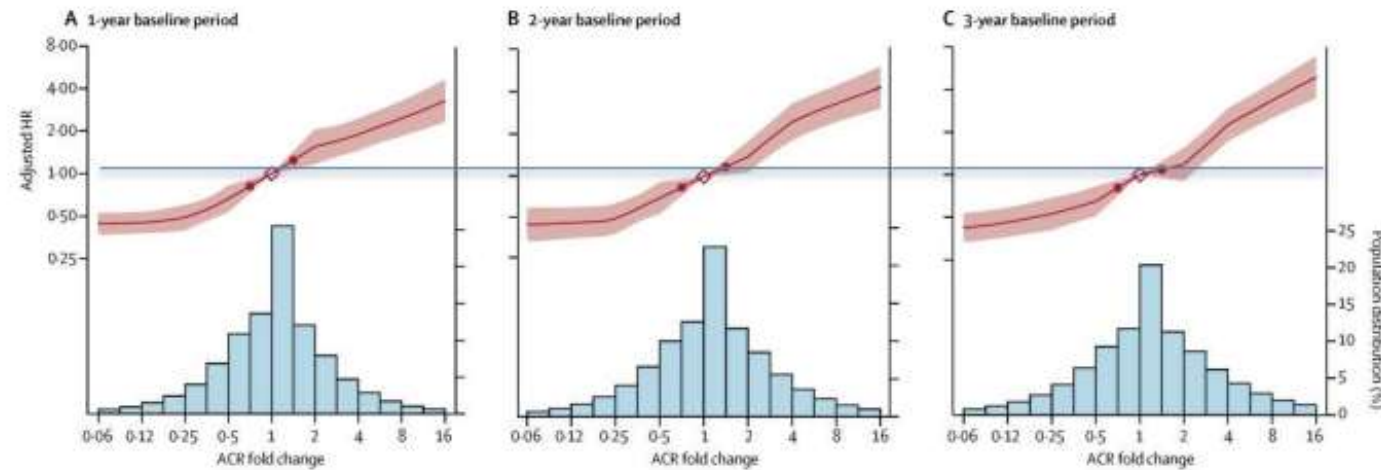


CKD prognose

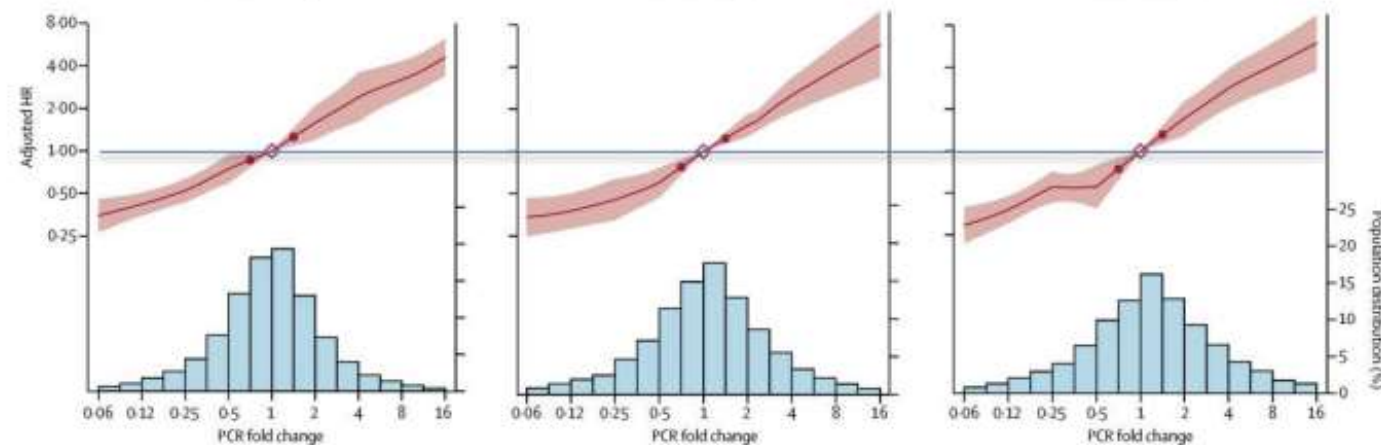


CKD prognose – Risico ESKD

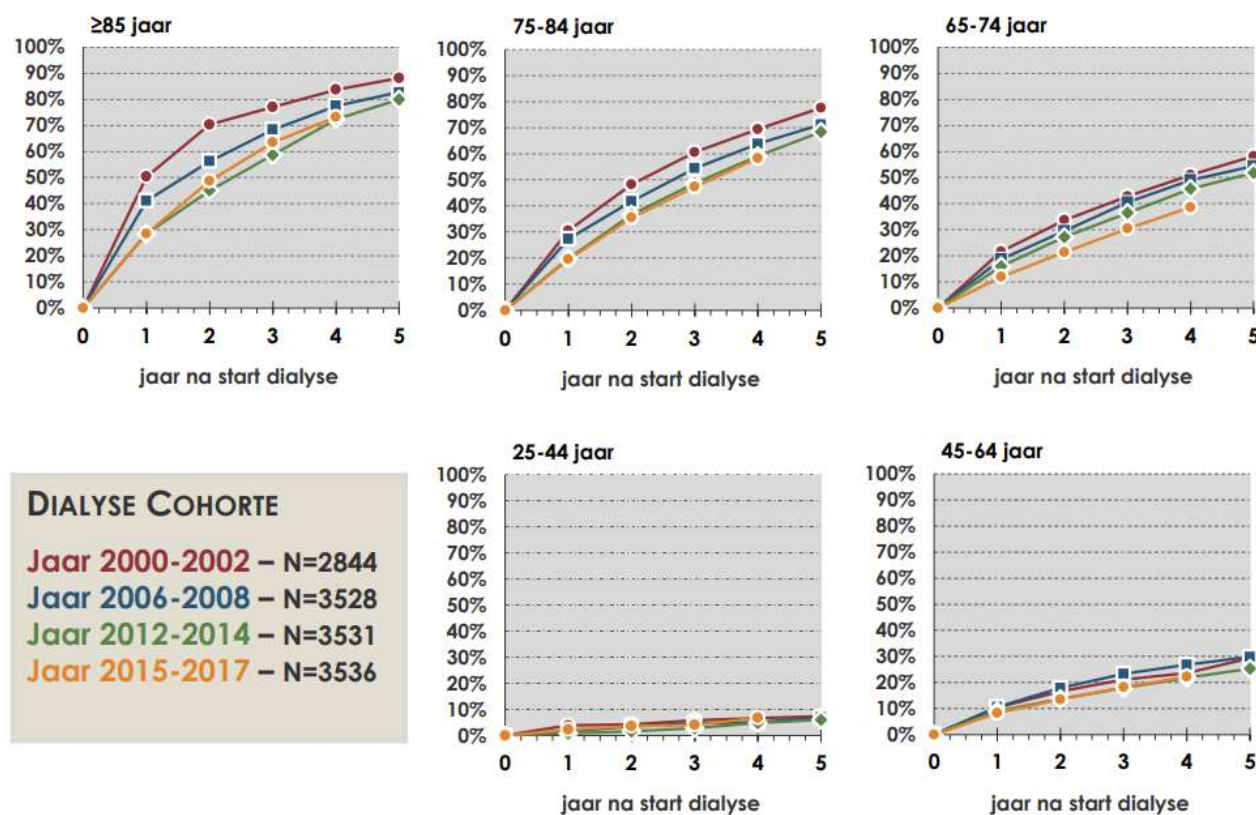
Beloop albuminurie



Beloop proteinurie



Mortaliteit dialysepatiënt



**UITKOMST
NA START DIALYSE**

Overlijden
als uitkomst na start
dialyse HD+PD
behandeling
in NBVN

Eerste registratie

Competing risks
analyse
tot minstens 4 jaar
na start dialyse

per leeftijdsklasse
en
per instroom cohorte

5 jaar overleving dialysepatiënt

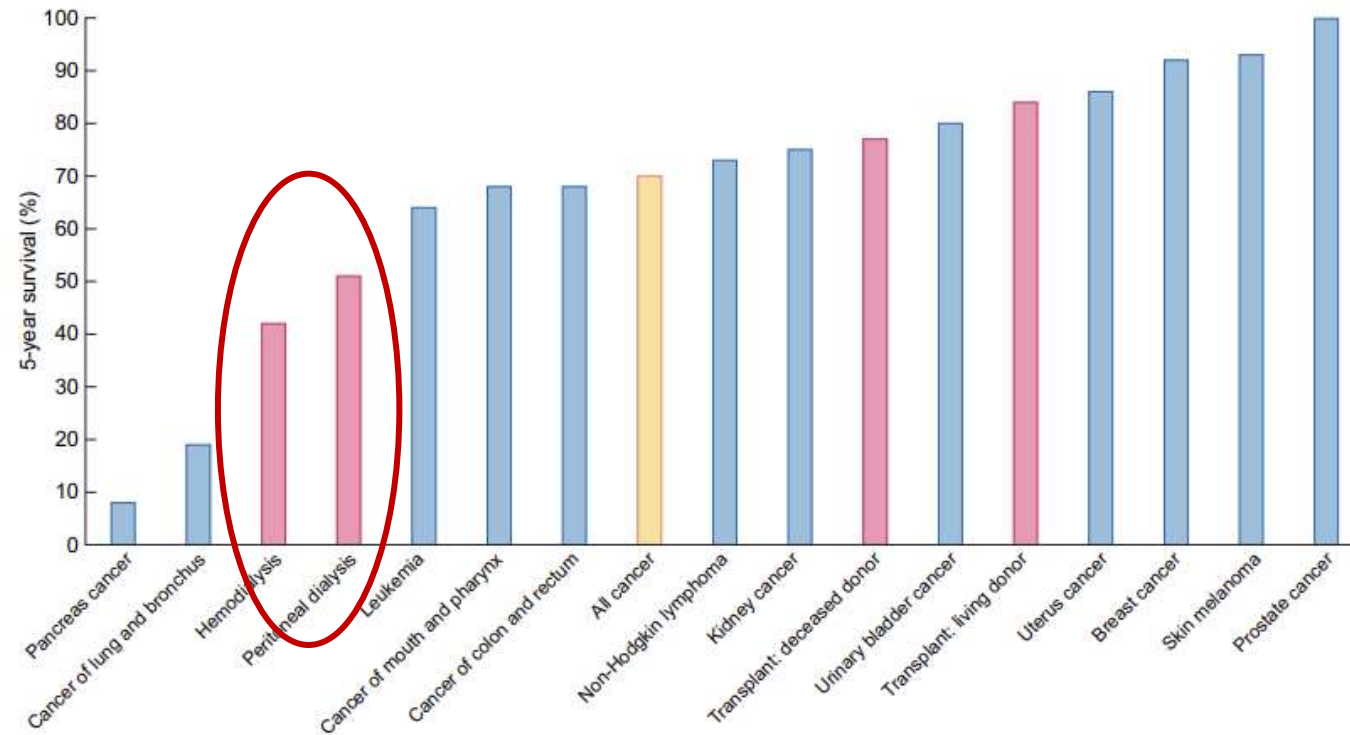
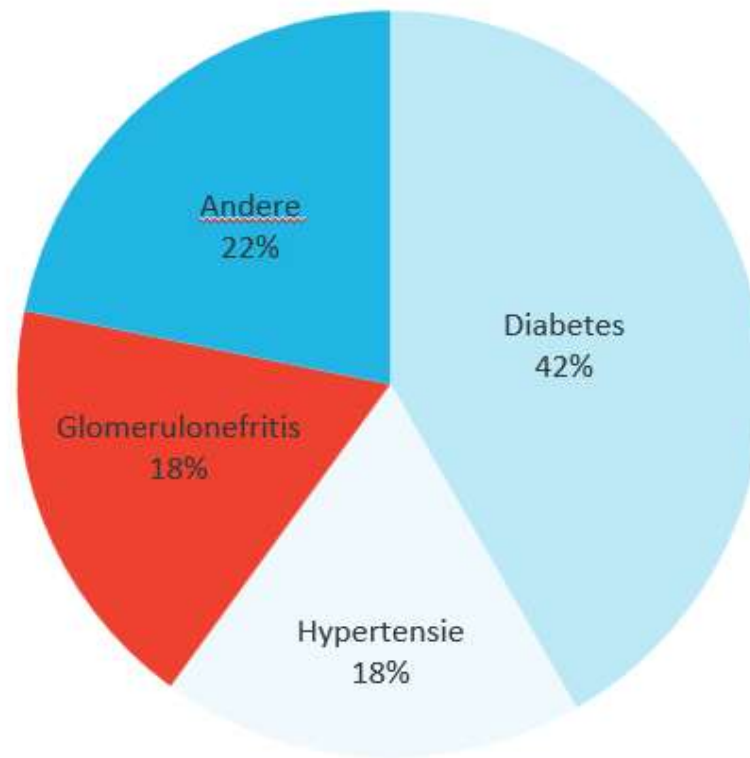


FIGURE 2: Percent 5-year survival of kidney replacement treatment modalities (red bars) (HD, PD, transplantation after deceased donation and transplantation after living donation) or 5 years after the diagnosis of cancer (blue bars). Only malignancies with an incidence >3% of all cancers are illustrated. Orange bar: all cancers aggregated. Based on 2016 data [40, 41].

Oorzaken CKD

Wereldwijd naar leeftijd gestandaardiseerd prevalentiecijfer van CKD in 2016, volgens oorzaak, per 100.000 personen¹



1. Jager KJ et al. Nephrol Dial Transplant. 2019;34:1803-1805; 2. World Health Organisation 2016; 3. Ravera M et al. Am J Kidney Dis. 2011;57(1):71-77. 4. GBD Chronic Kidney Disease Collaboration. Lancet. 2020;395(10225):709-733. 5. Ryan TP et al. Am J Med. 2007;120(11):981-986. 6.

https://organesdeconcertation.sante.belgique.be/sites/default/files/documents/2020_-_rapport_national_-_college_de_medecins_nephrologie_0.pdf

Pathofysiologie progressieve nefropathie

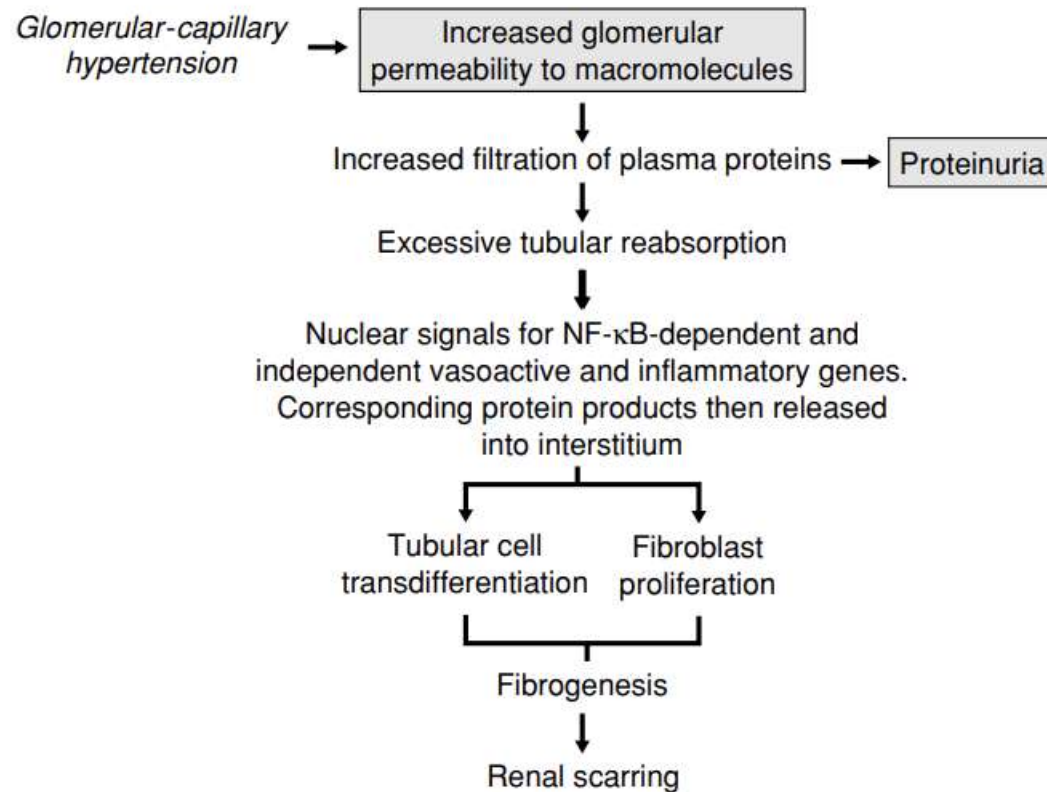
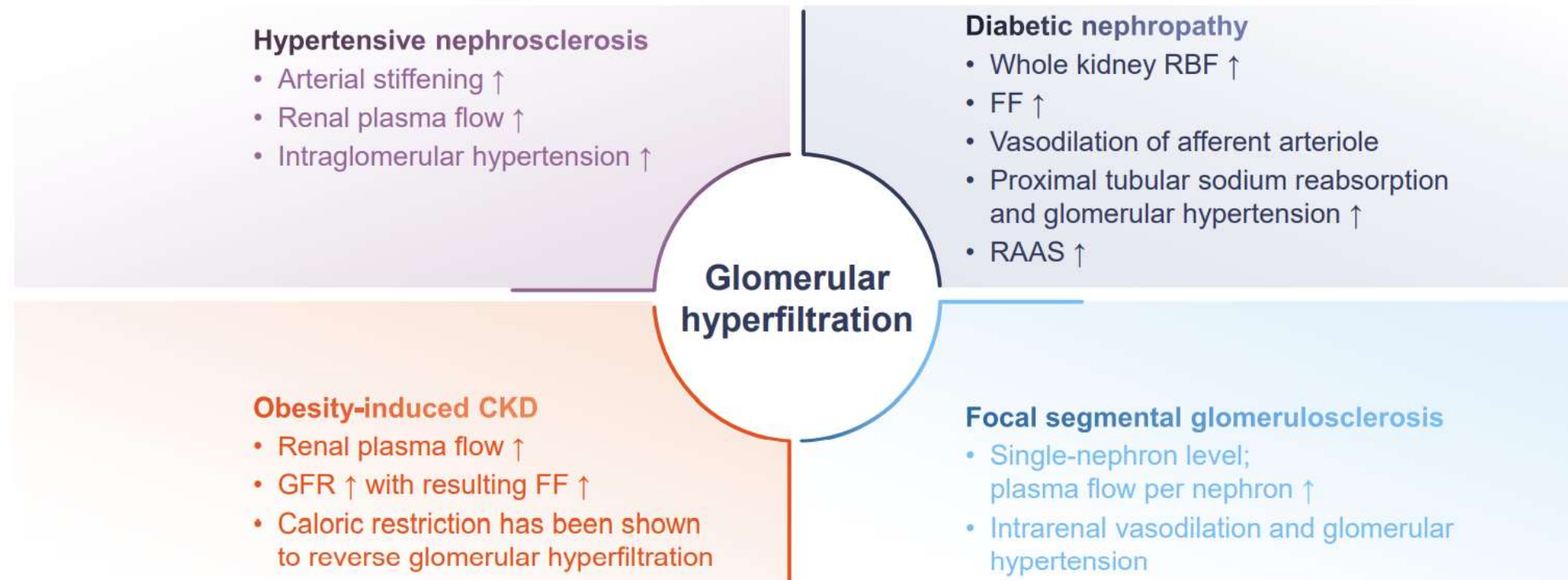


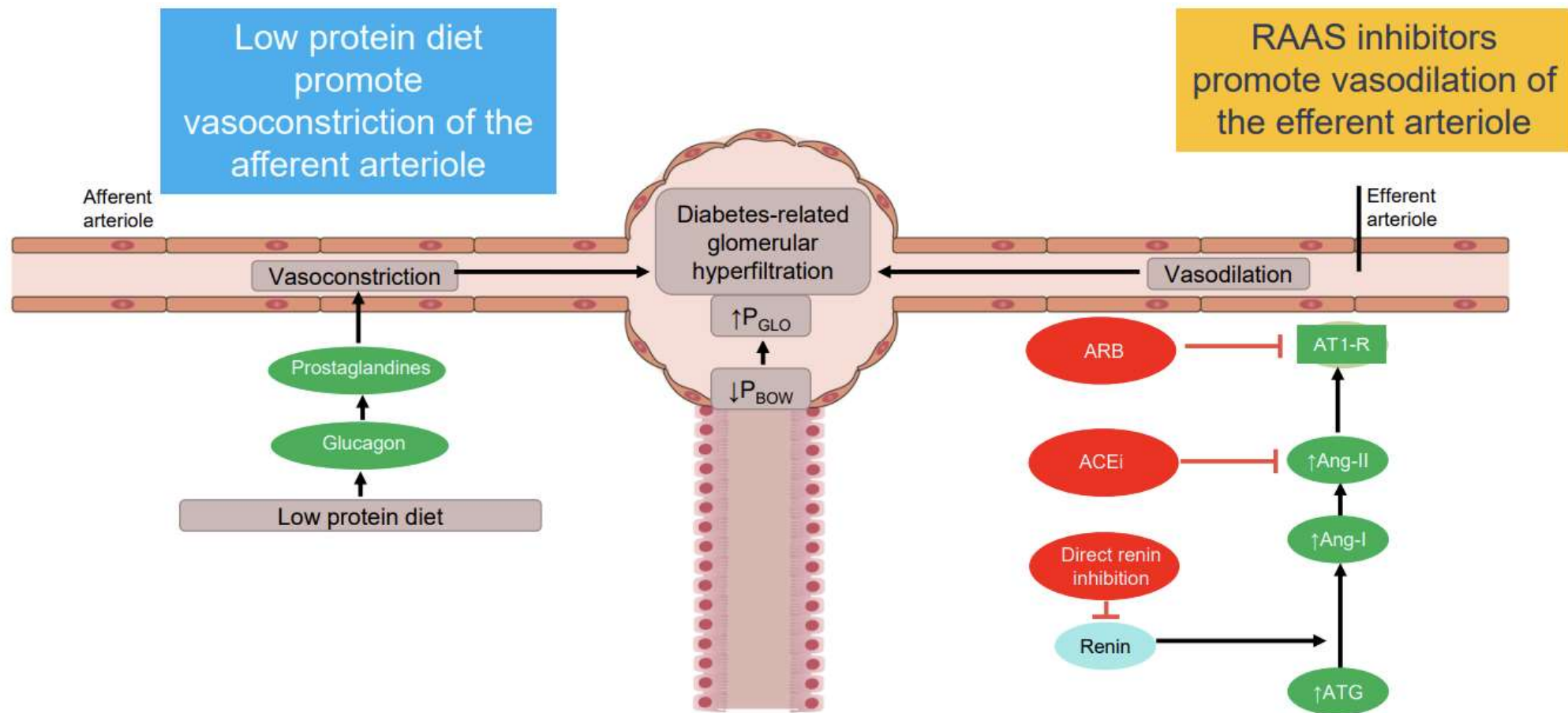
Fig. 2. Pathophysiology of progressive nephropathies.

Glomerulaire hyperfiltratie



CKD, chronic kidney disease; FF, filtration fraction; GFR, glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system; RBF, renal blood flow

Nefroprotectie



SGLT-2 inhibatoren



Diabetocardiorenal syndroom



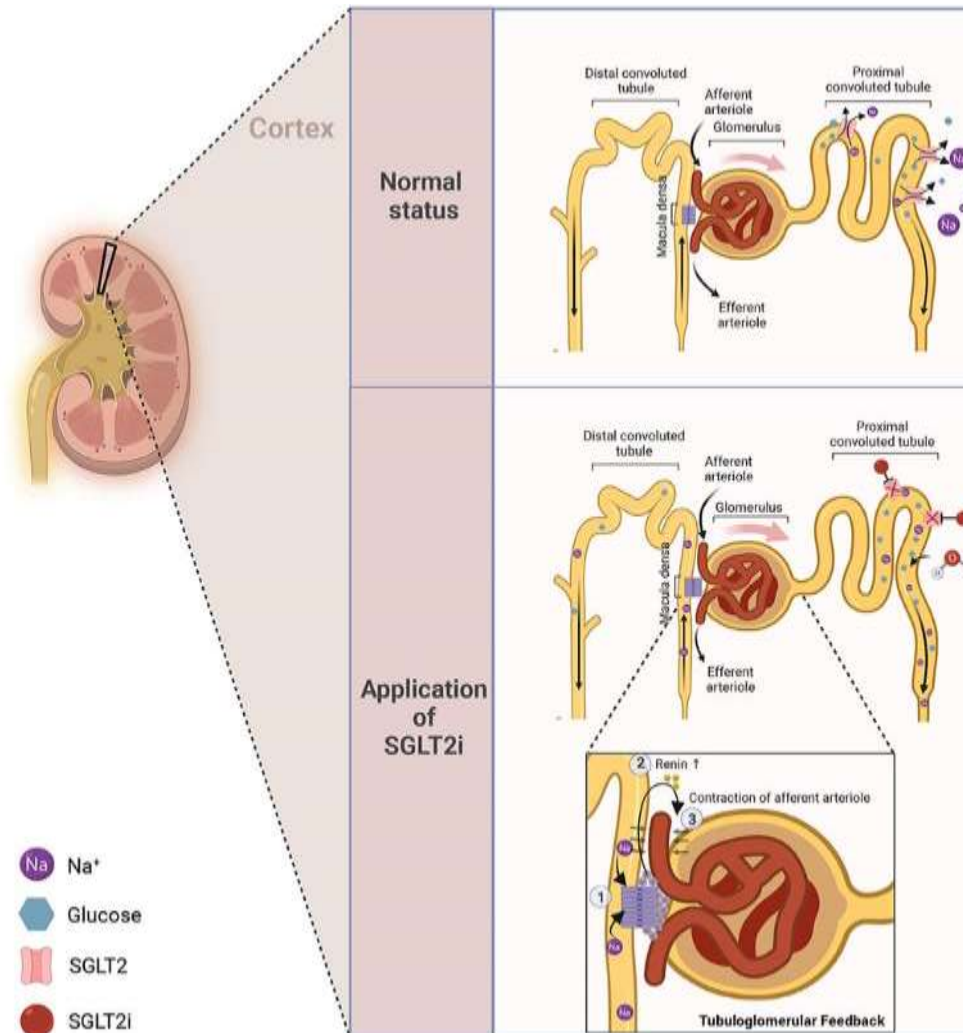
CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Lancet. 2018;392:1789-1858; 2. Parving HH et al. Kidney Int. 2006;

3. Birkeland KI et al. Diabetes Obes Metab. 2020; 4. Ronco C et al. J Am Coll Cardiol. 2008.

Hoe werken SGLT-2 inhibitoren?

- Glucosurie
- Natriurese
- Osmotische diurese



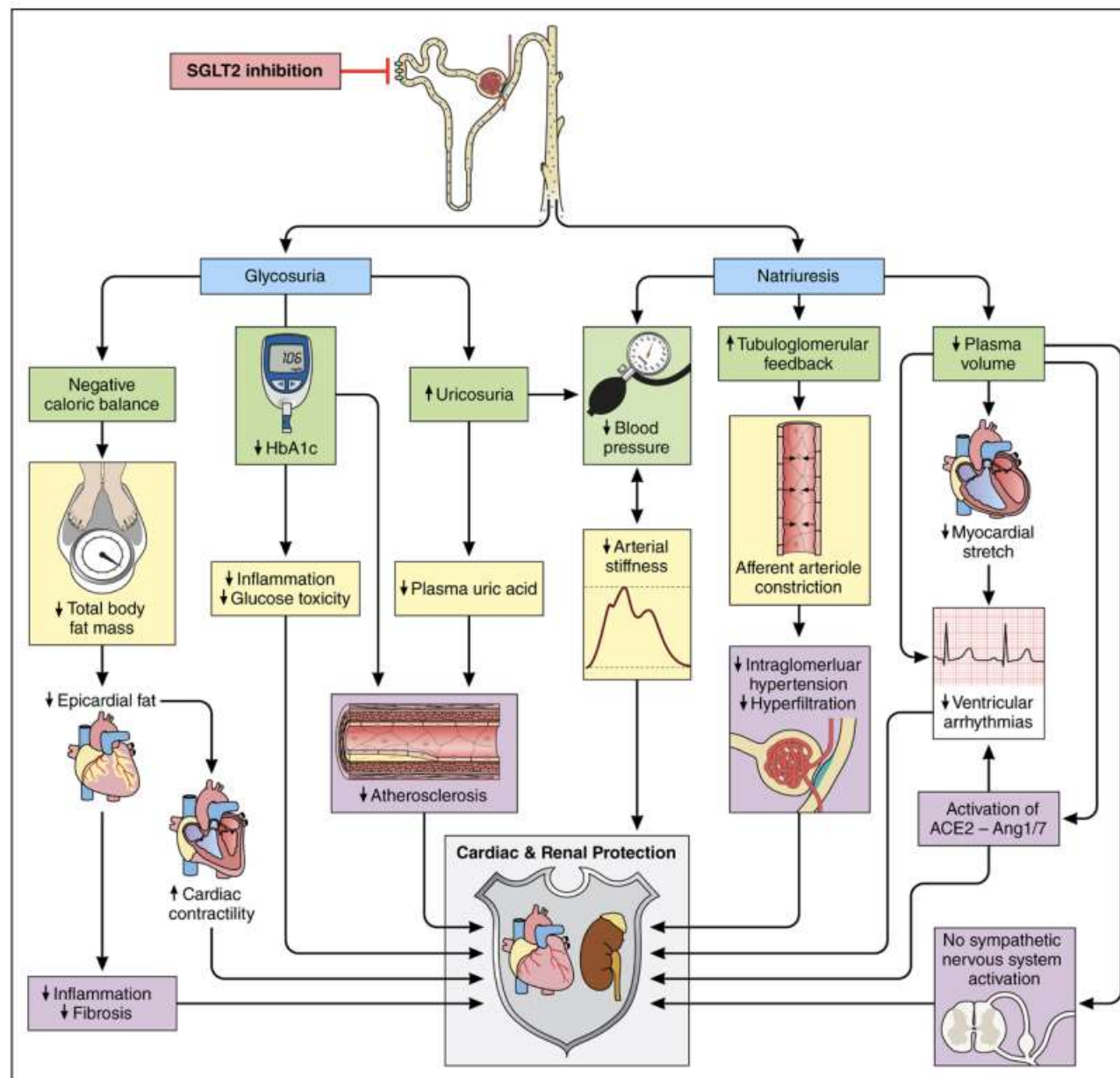


Figure 2. Physiologic mechanisms implicated in the cardiovascular and renal protection with SGLT2 inhibition. HbA1c indicates hemoglobin A1c; and SGLT2, sodium-glucose cotransporter-2.

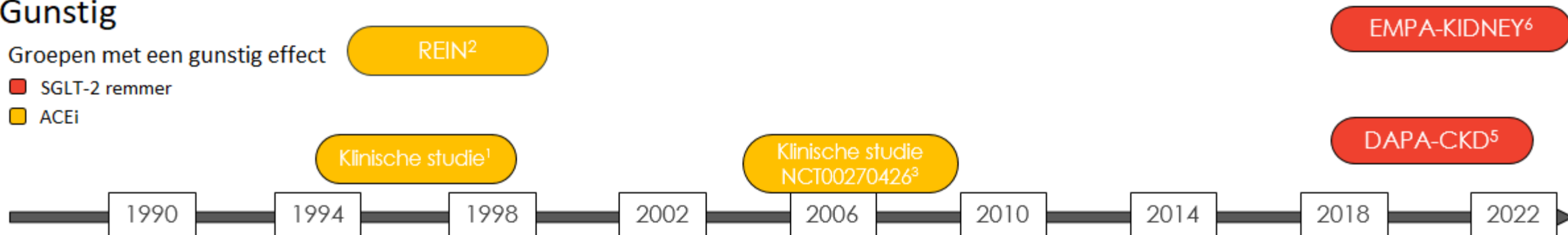
Klinische studies ND nefropathie

Gunstig

Groepen met een gunstig effect

■ SGLT-2 remmer

■ ACEi



Neutraal of schadelijk

Groepen met neutrale of schadelijke effecten

■ AST-120

EPPIC-1 and
EPPIC-2⁴

DAPA-CKD

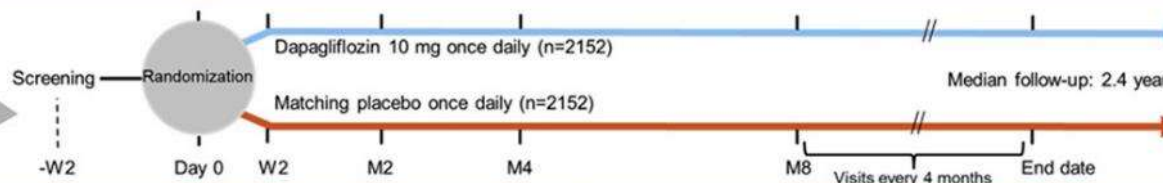
A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function.

kidney
INTERNATIONAL



Study design

- eGFR 25–75 mL/min/1.73m²
- UACR 200–5000 mg/g
- With/without type 2 diabetes
- Stable, maximally-tolerated ACEi/ARB dose

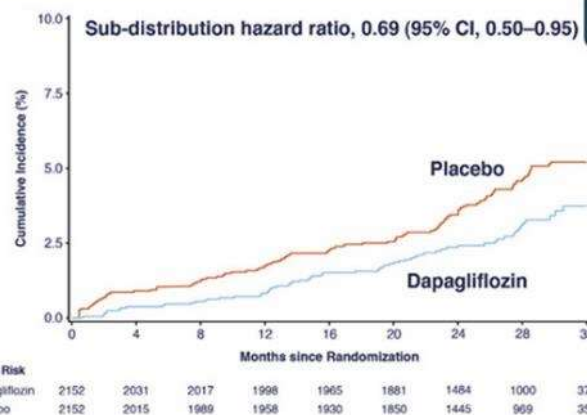


Outcomes

- Abrupt declines in kidney function, defined as a doubling of serum creatinine between two subsequent visits (median time-interval, 100 days)
- Investigator-reported SAEs of acute kidney injury (pre-defined list)

Sub-distribution hazard ratio, 0.69 (95% CI, 0.50–0.95)

Results



- Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease with increased albuminuria (Figure)
- No heterogeneity in effect of dapagliflozin versus placebo across baseline subgroups
- SAEs of acute kidney injury occurred less frequently with dapagliflozin versus placebo

Heerspink et al, 2021

eGFR=estimated glomerular filtration rate; SAE=serious adverse event; UACR=urinary albumin-to-creatinine ratio

CONCLUSION: Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease and substantial albuminuria, with and without type 2 diabetes

DAPA-CKD

Prognosis of CKD by GFR and Albuminuria Categories

				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30-299 mg/g 3-29 mg/mmol	Severely increased ≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60-90	Green	Yellow	Orange
	G3a	Mildly to moderately decreased	45-59	Yellow	Orange	Red
	G3b	Moderately to severely decreased	30-44	Orange	Red	Red
	G4	Severely decreased	15-29	Red	Red	Red
	G5	Kidney failure	<15	Red	Red	Red

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

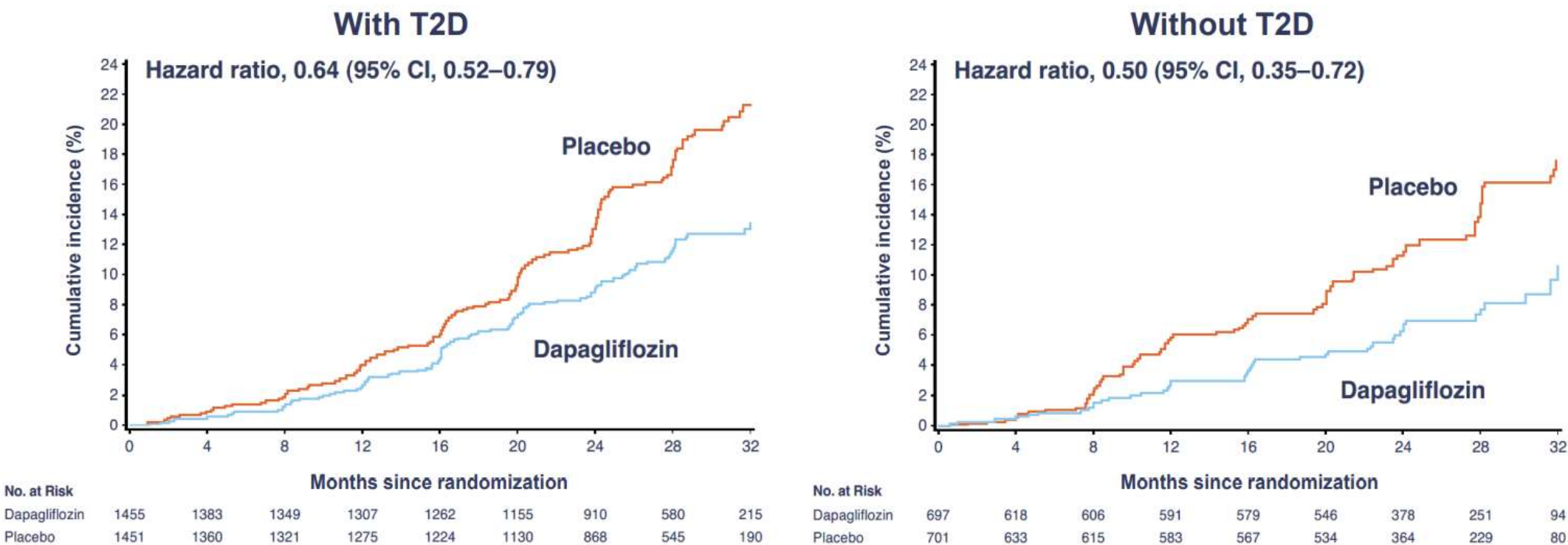
Inclusie-criterium

Gerecruteerd:

- eGFR: mean ±SD
- Albuminuria: Median ± IQR

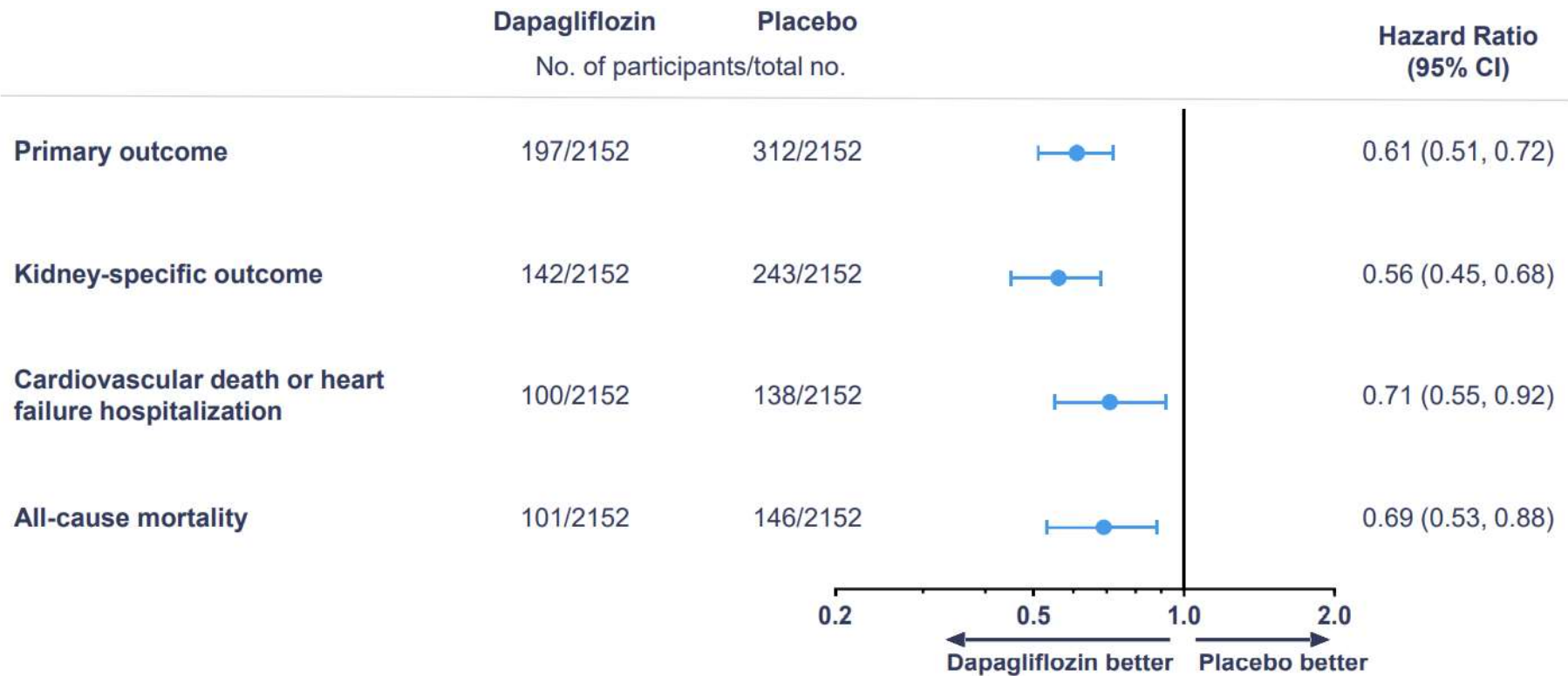
DAPA-CKD

Composite of sustained decline in eGFR of at least 50%,
ESKD, or kidney-related or cardiovascular death



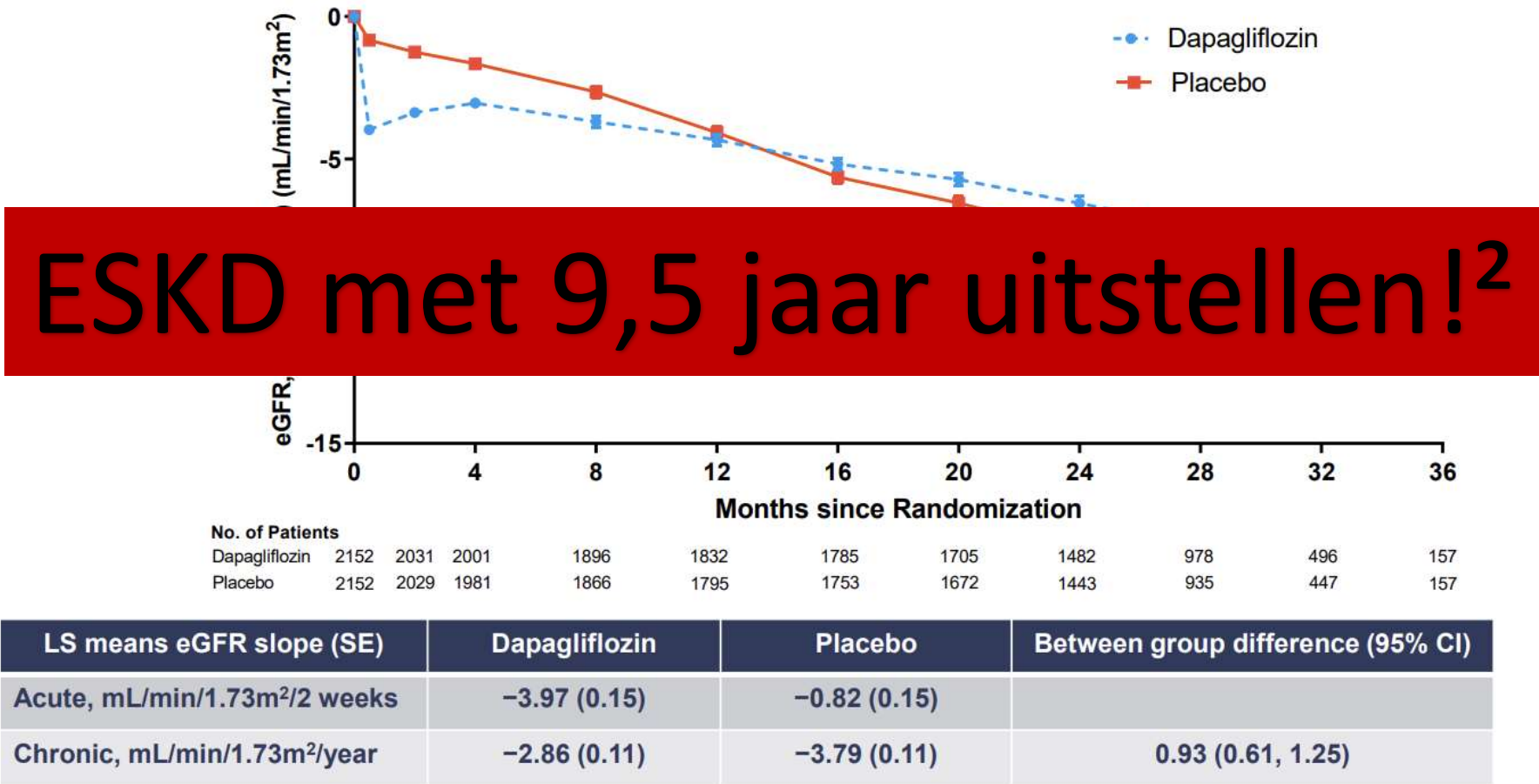
CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; T2D, Type 2 diabetes
Wheeler DC, et al. *Lancet Diabetes Endocrinol* 2021;9:22–31

DAPA-CKD



Primary outcome: sustained $\geq 50\%$ eGFR decline, ESKD, renal or cardiovascular death; kidney-specific outcome: sustained $\geq 50\%$ eGFR decline, ESKD, renal death
eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease
Heerspink HJL. et al. *N Engl J Med* 2020;383:1436-1446.

eGFR afname tijdens studie

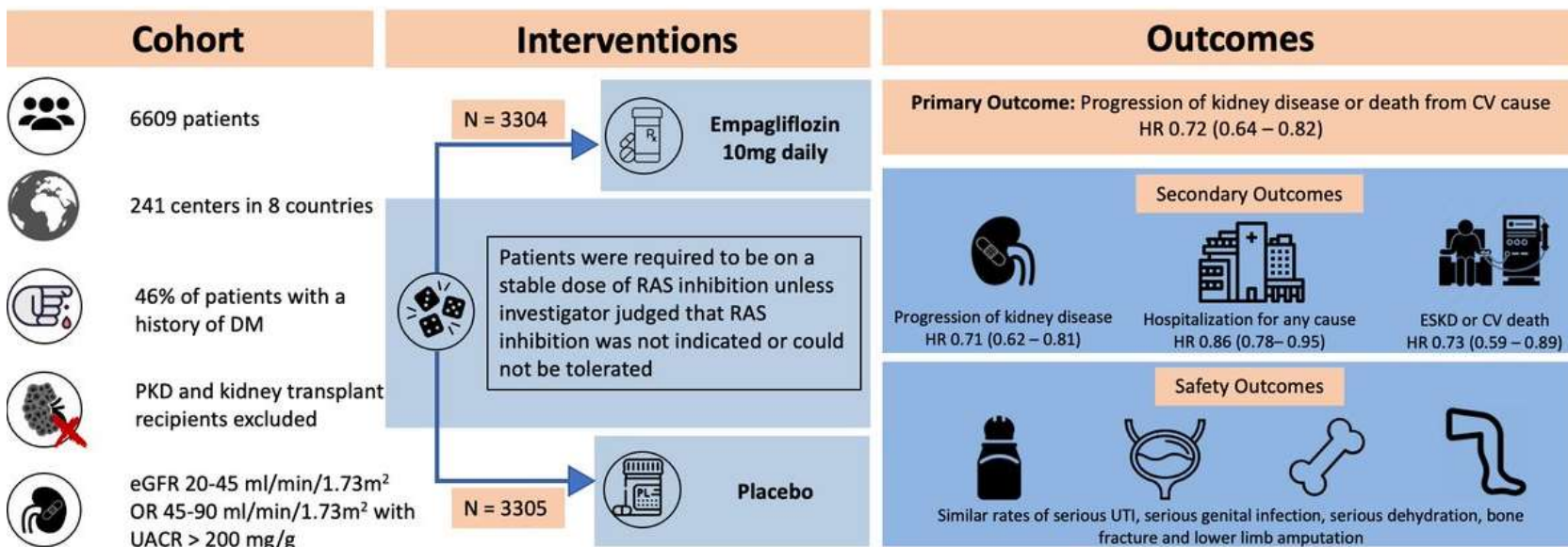


CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares; SE, standard error.
 Heerspink HJL. et al. *N Engl J Med* 2020;383:1436-1446.

EMPA-Kidney

EMPA-KIDNEY

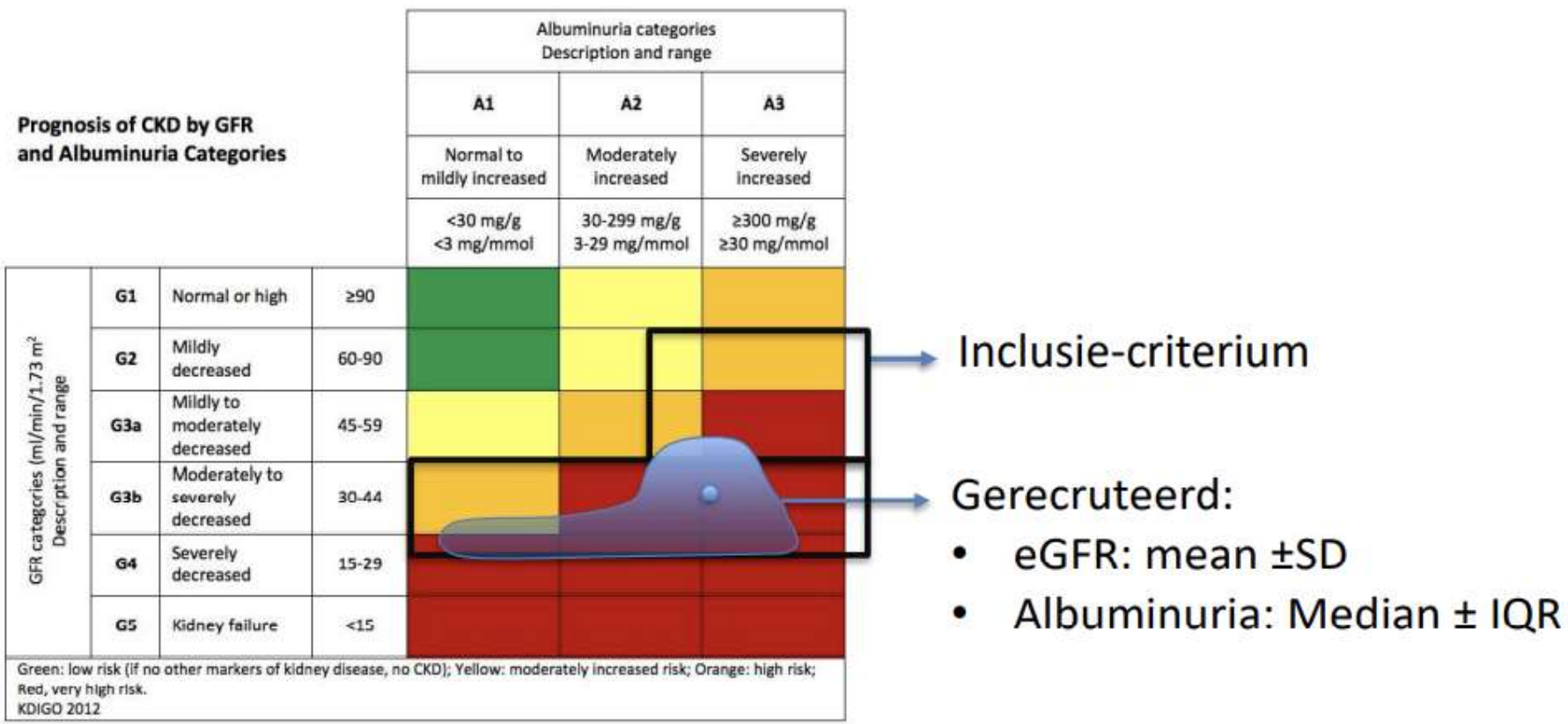
Empagliflozin in Patients with Chronic Kidney Disease



Summary: Among patients with CKD, empagliflozin led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. This is consistent among patients with or without diabetes. Risk reduction seems to be larger among patients with higher urinary albumin-to-creatinine ration (UACR)

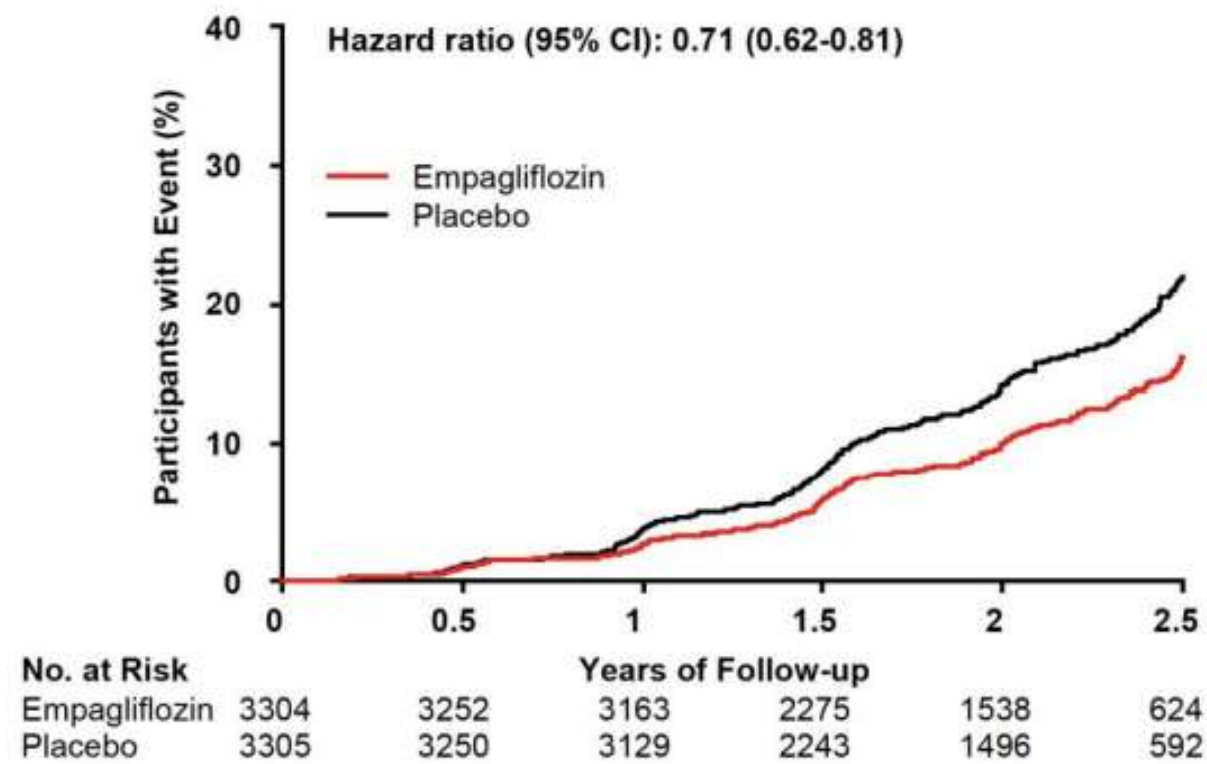
Reference: EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2022 Nov 4.

EMPA-Kidney



EMPA-Kidney

Figure S2a. Kidney Disease Progression



Bijwerkingen

- Euglycemische (diabetische) keto-acidose
 - 016-0,76/1000 patiënt jaar
 - Risicofactoren: infectie, malnutritie, braken
- Genitale schimmelinfectie
- Urineweginfectie



Medicines to stop on sick days

- ☐ ACE inhibitors: medicine names ending in "pril"
- ☐ ARBs: medicine names ending in "sartan"
- ☐ Diuretics: eg, furosemide, bendroflumethiazide
- ☐ Metformin: a medicine for diabetes
- ☐ NSAIDs: eg, ibuprofen, diclofenac, naproxen

Other medicines to stop taking

- ☐ _____
- ☐ _____
- ☐ _____
- ☐ _____

Minder hyperkaliëmie

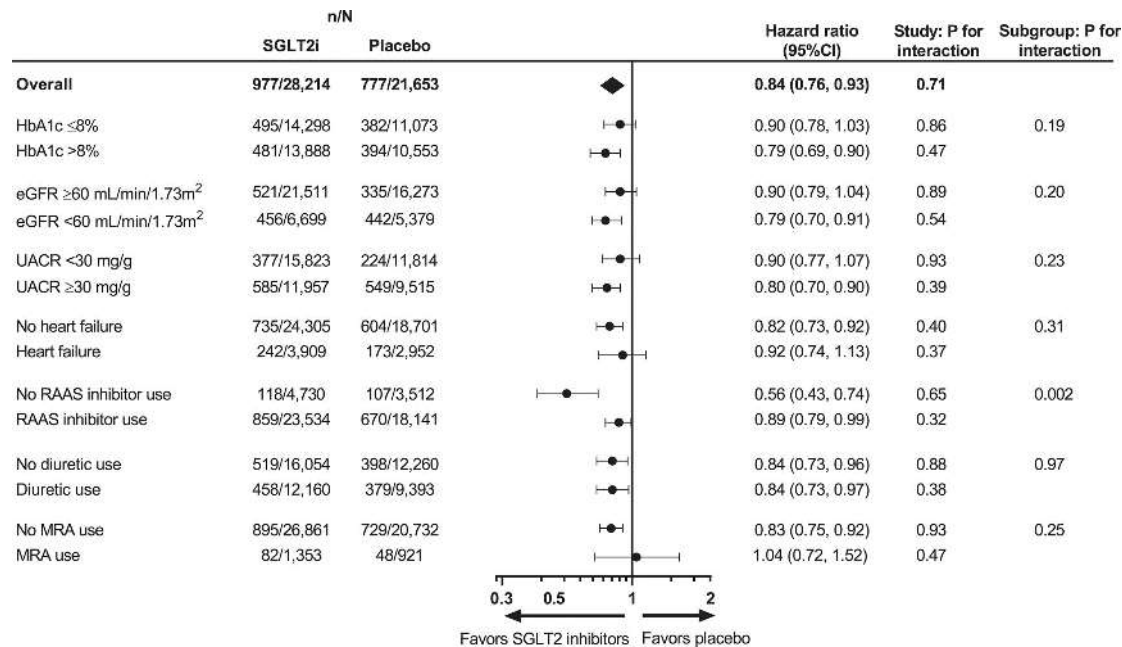


Figure 3. Effect of SGLT2 inhibitors on serious hyperkalemia (central laboratory–determined serum potassium ≥6.0 mmol/L) according to baseline participant characteristics. eGFR indicates estimated glomerular filtration rate; HbA1c, glycohemoglobin; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose cotransporter 2 inhibitor; and UACR, urinary albumin-to-creatinine ratio;

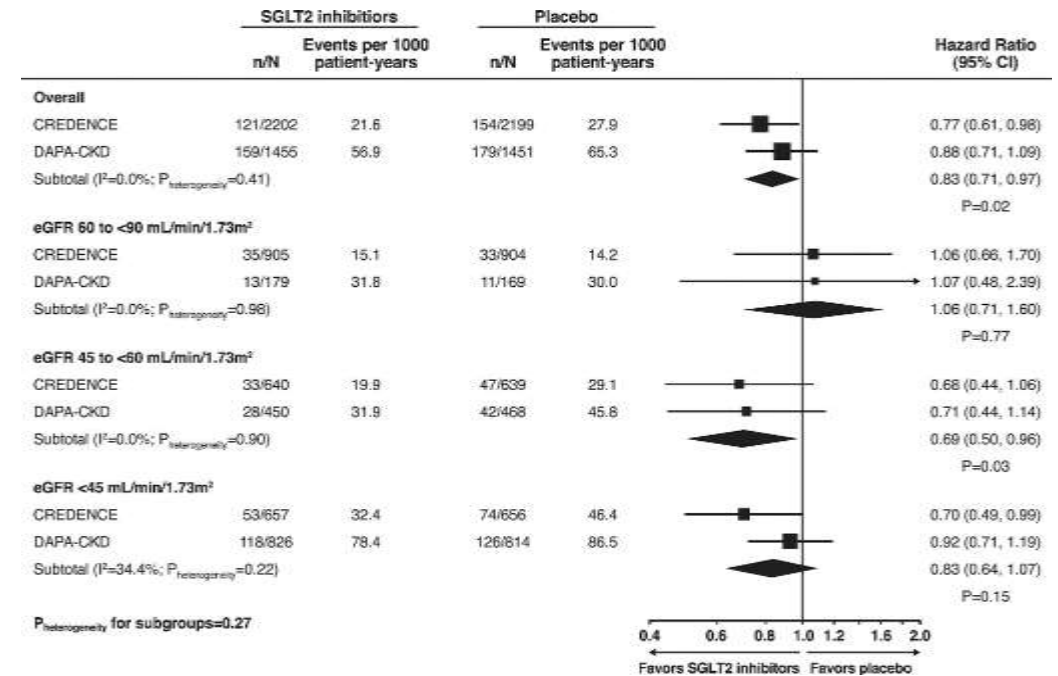
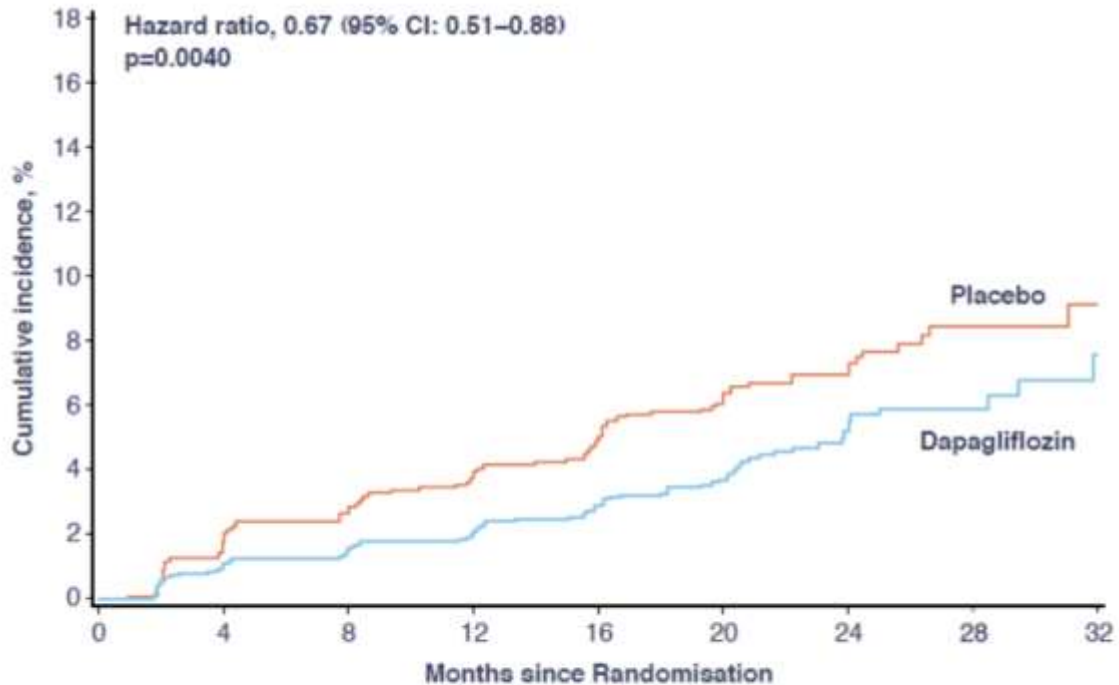


Figure 4. Effect of SGLT2 inhibitors on serious hyperkalemia (central laboratory–determined serum potassium ≥6.0 mmol/L) across the spectrum of kidney function in CREDENCE and DAPA-CKD. CREDENCE indicates Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR: estimated glomerular filtration rate; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

Minder kans op de novo diabetes

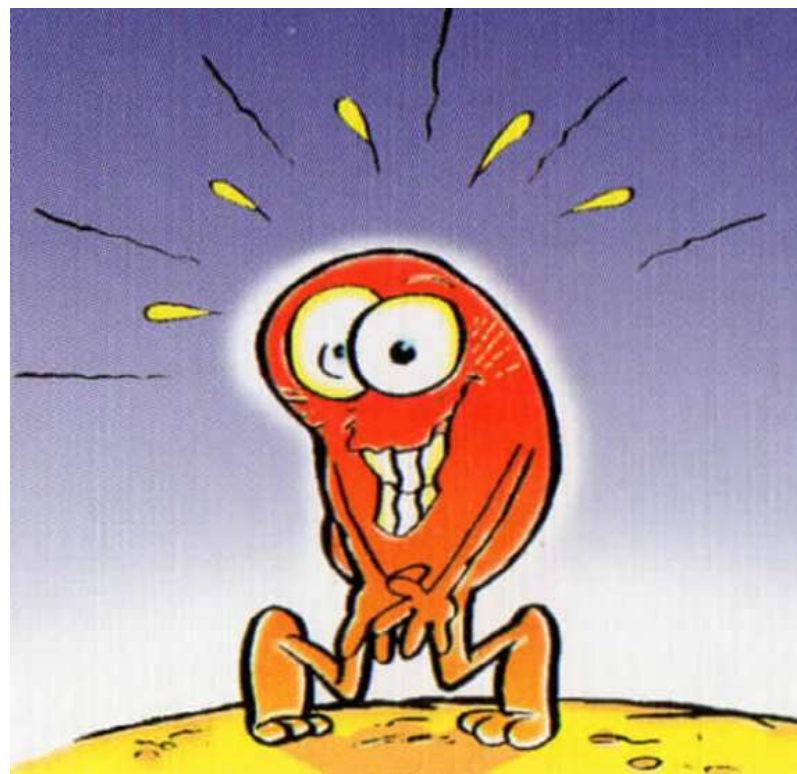
DAPA-CKD + DAPA-HF



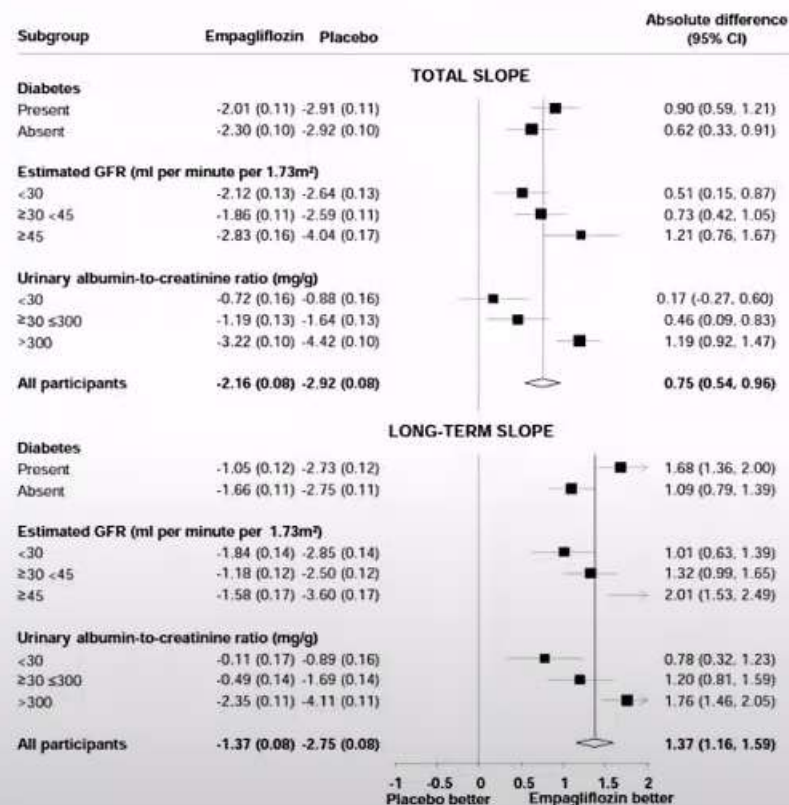
RRR 33%

No. at Risk									
Dapagliflozin	1995	1889	1846	1743	1432	1067	556	285	108
Placebo	2008	1891	1840	1743	1404	1037	536	271	102

Bedankt voor jullie aandacht

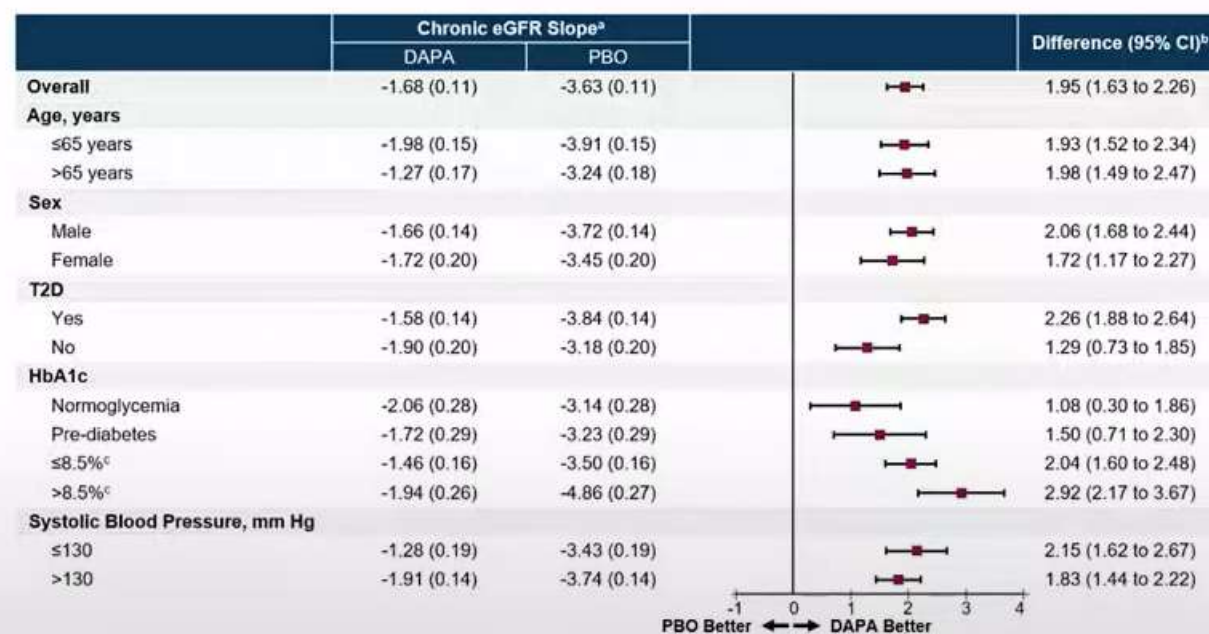


Mean annual rate of change in estimated GFR
(ml per minute per 1.73m² per year)



EMPA KIDNEY 2022, NEJM

Chronic eGFR Slope (Week 2 to End of Treatment) by Baseline Subgroups DAPA-CKD



Heerspink HJL et al. *Lancet Diabetes Endocrinol.* 2021

