Can we postpone CKD progression - where do we stand today?

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Presentation outline

- **CKD definition & detection - diagnosis**

  Rationale for screening – progression

  - Risk for progression to ESRD
  - Death

- **Early detection**

  (Stage & albuminuria, Biomarkers, Proteomics)

- **Intervention for delaying the progression**

  - Standard of care
  - Adjuvant therapies
  - SGLT2 inhibitors
  - ns MRA antagonists

Early CKD: diagnosis, risk for ESRD progression or death - rationale

- Distinction between early CKD and normal age-related decline in renal function
- Most of CKD patients do not progress to ESRD - stages 1–3 CKD - unlikely to advance (unselected treatment - clinically & economically inappropriate)
- Rational screening - high-risk groups (DM & HTA with proteinuria, obesity)
- Asymptomatic & insidious onset of CKD – new biomarkers and prognostic techniques required

Wouters et al, Nat Rev Nephrol. 2015; 11(8): 491–502

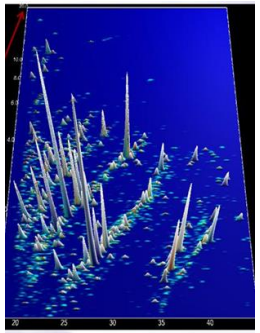
Staging of patients who meet the definition of CKD

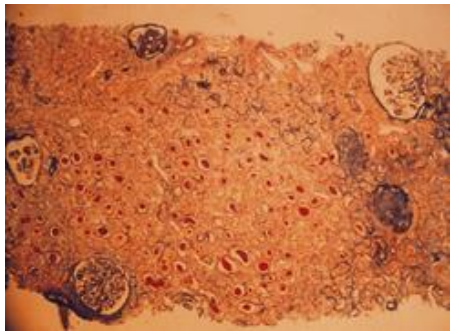
GFR categories (mL/min/1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60-89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria - reflect the risk of progression and associated mortality by intensity of coloring (green, yellow, orange, red, deep red) - times/year FU

Kidney Int Suppl (2011). 2013; 3(1):19-62

Biomarkers





Healthy

Molecular alterations

Minor structural changes

Advanced organ damage

ESRD

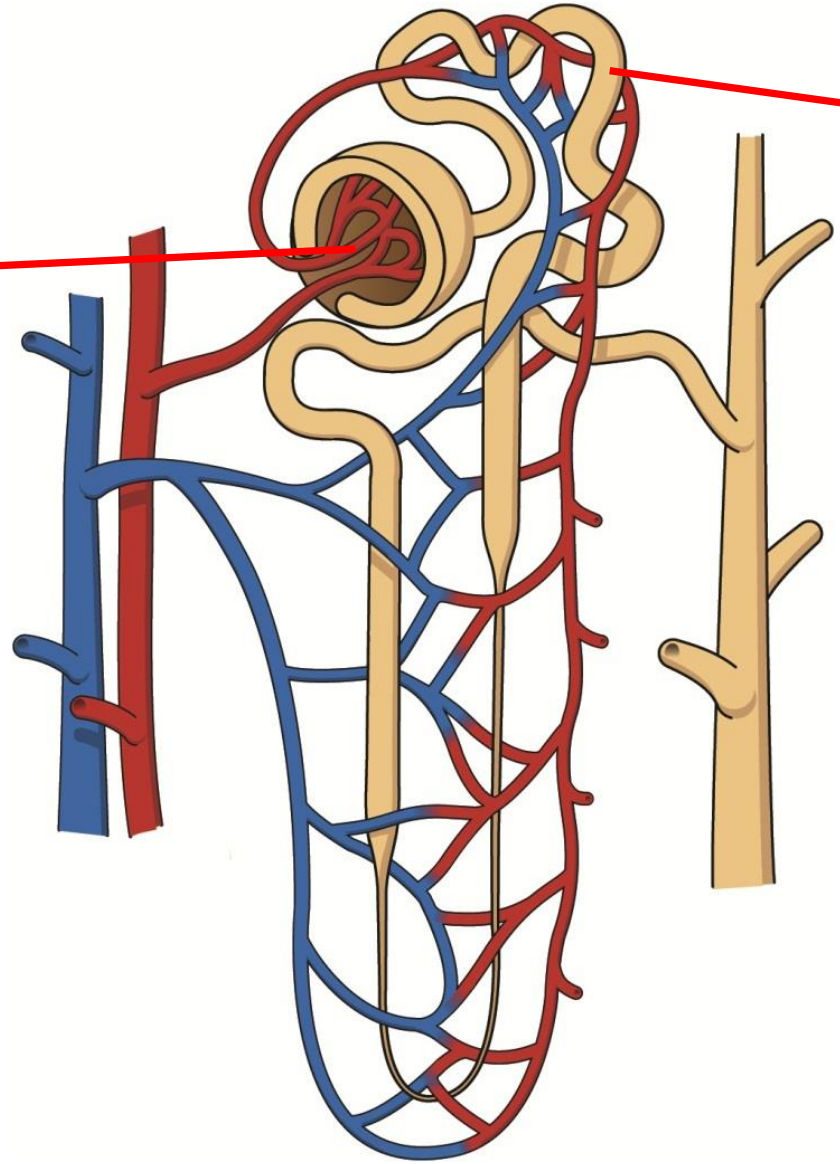
Biomarkers of Onset and Progression of CKD

Glomerular Markers

Transferrin
Type IV collagen
Ceruloplasmin
Podocytes and related proteins

Markers of oxidative stress/inflammation

8-OHdG
Pentosidine
AGA
TNF-α
STNFR 1 / 2
IL-6
MCP-1



Tubular Markers

NGAL
KIM-1
NAG
L-FABP
β2-microglobulin
α1-microglobulin
RBP
GGT
UMOD

Currie G & Delles C. World J Diabetes 2014

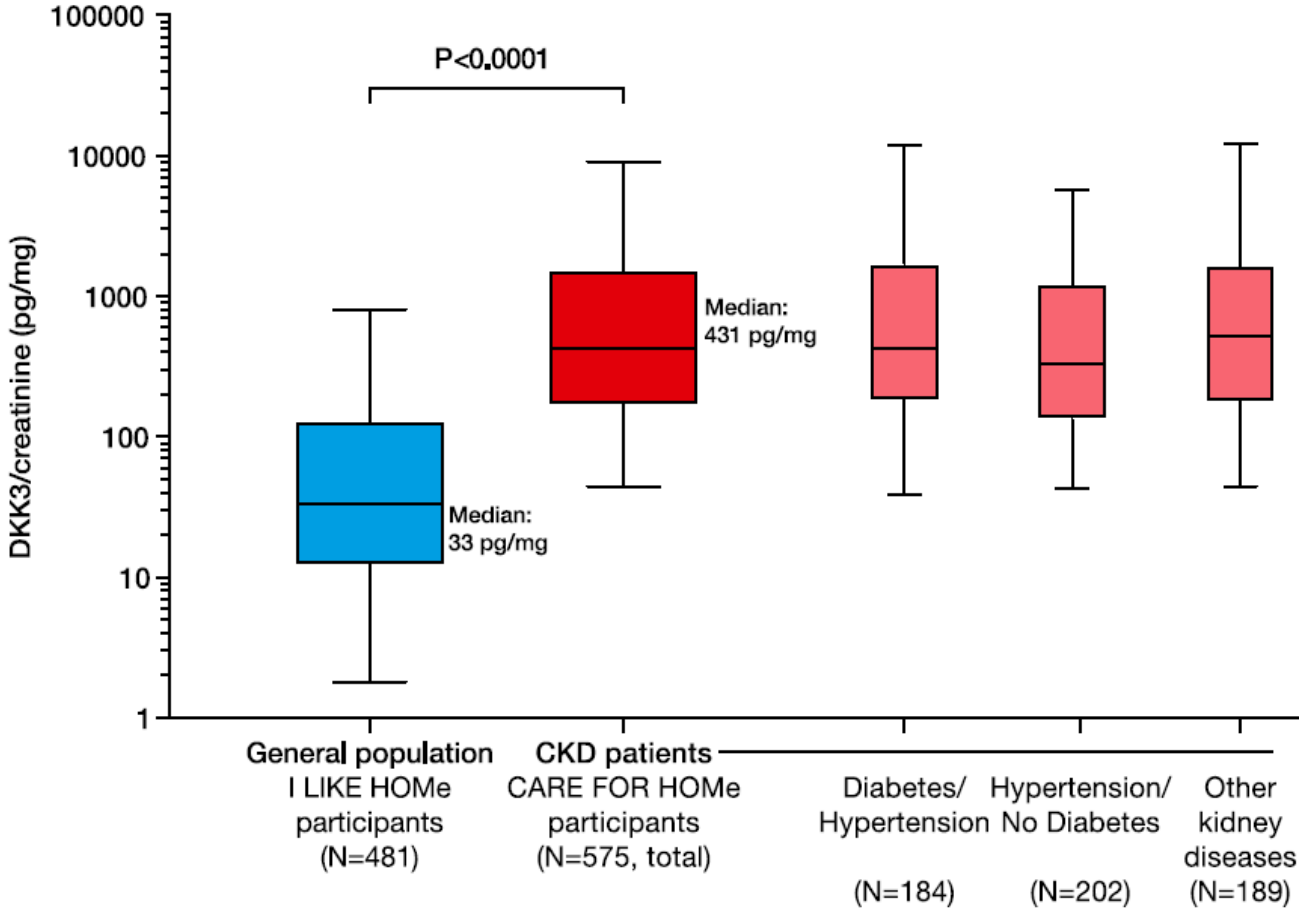
Use of biomarkers in the progression of CKD

CLINICAL EPIDEMIOLOGY www.jasn.org

J Am Soc Nephrol 29: 2722–2733, 2018.

Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-Term Risk of eGFR Loss

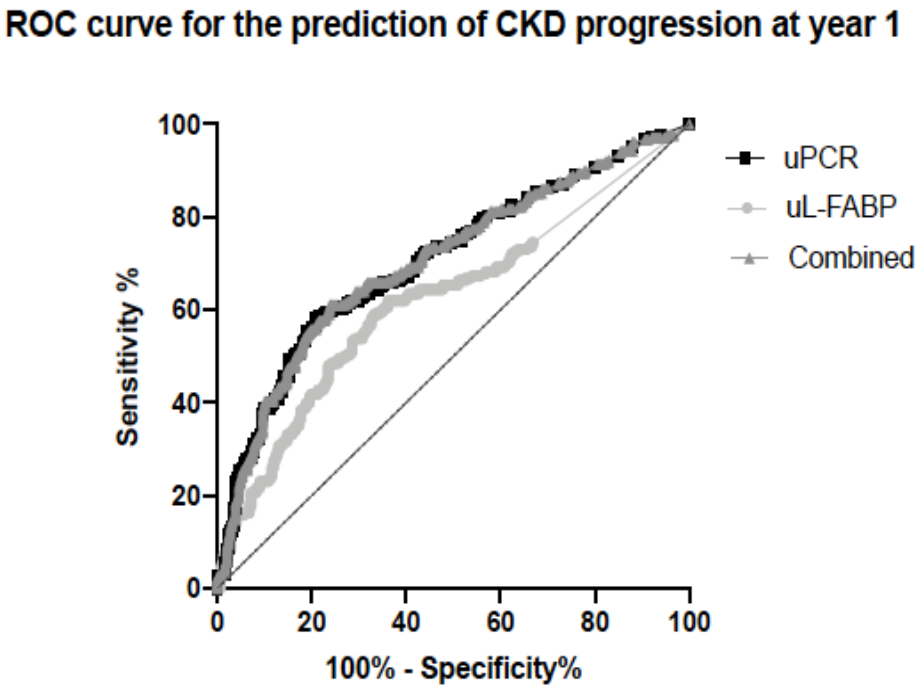
Stephen Zewinger,[1] Thomas Rauen,[2] Michael Rudnicki,[3] Giuseppina Federico,[4] Martina Wagner,[1] Sarah Triem,[1] Stefan J. Schunk,[1] Ioannis Petrakis,[1] David Schmit,[1] Stefan Wagenpfeil,[5] Gunnar H. Heine,[1] Gert Mayer,[3] Jürgen Floege,[2] Danilo Fliser Hermann-Josef Gröne,[4] and Thimoteus Speer[1]



Conclusions

Urinary DKK3 levels identify patients at high risk for eGFR decline over the next 12 months regardless of the cause of kidney injury and beyond established biomarkers, potentially providing a tool to monitor CKD progression and assess effects of interventions.

a.



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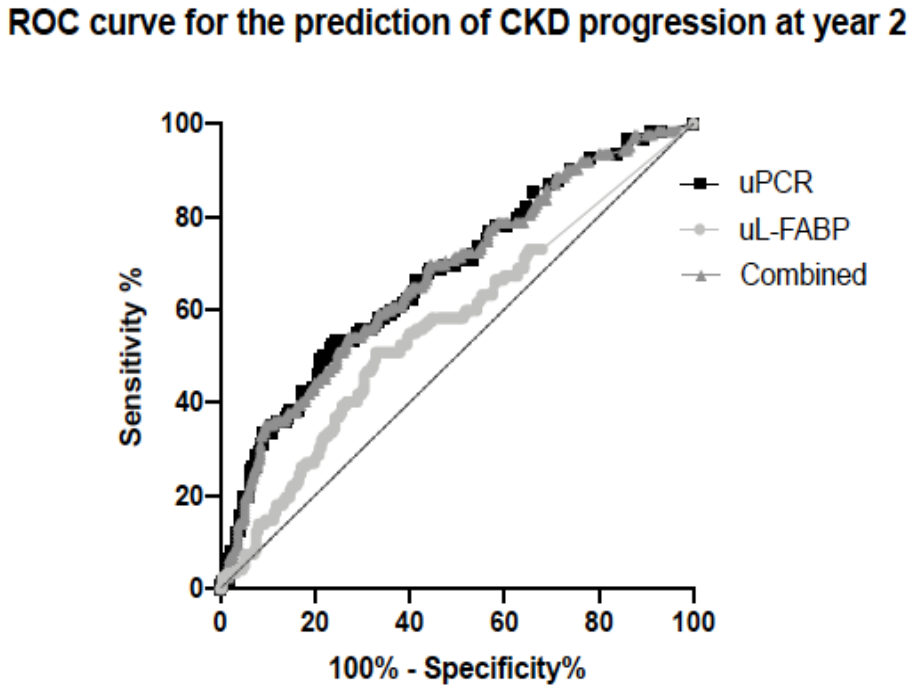


Figure. a, 4b. ROC curve analysis of the sensitivity and specificity of urinary L-FABP, PCR and the combined effect of the 2 biomarkers in predicting CKD progression at years 1 and 2.

Conclusions

UL-FABP appears to be a highly sensitive and specific biomarker of CKD progression that predict an increase in serum creatinine in **the absence of significant proteinuria**

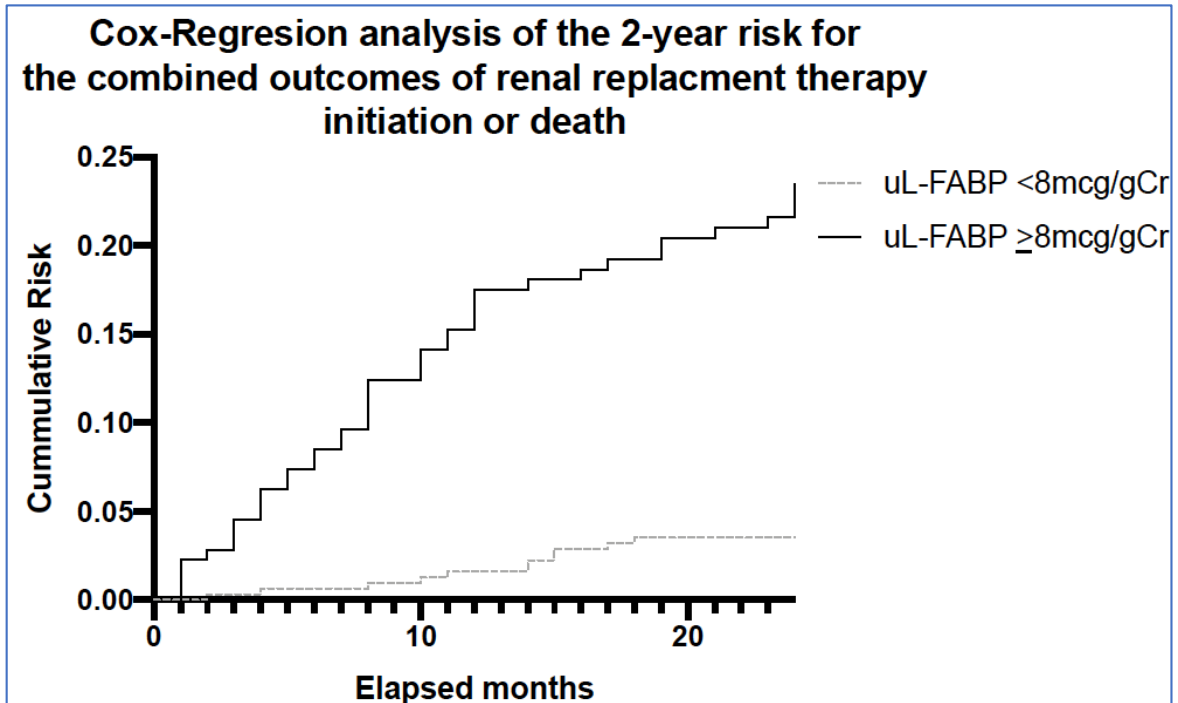


Figure. Analysis for the combined outcome of RRT initiation or death over the 2-year follow-up period stratified by participants uL-FABP levels at baseline.

Use of biomarkers in the progression of CKD - Omics

"The goal of proteomics is a comprehensive, quantitative description of protein expression and its changes under the influence of biological perturbations such as disease or drug treatment."

Proteomics

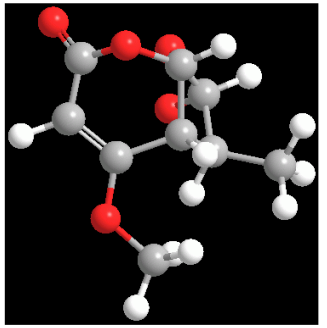
The current status

Genomics

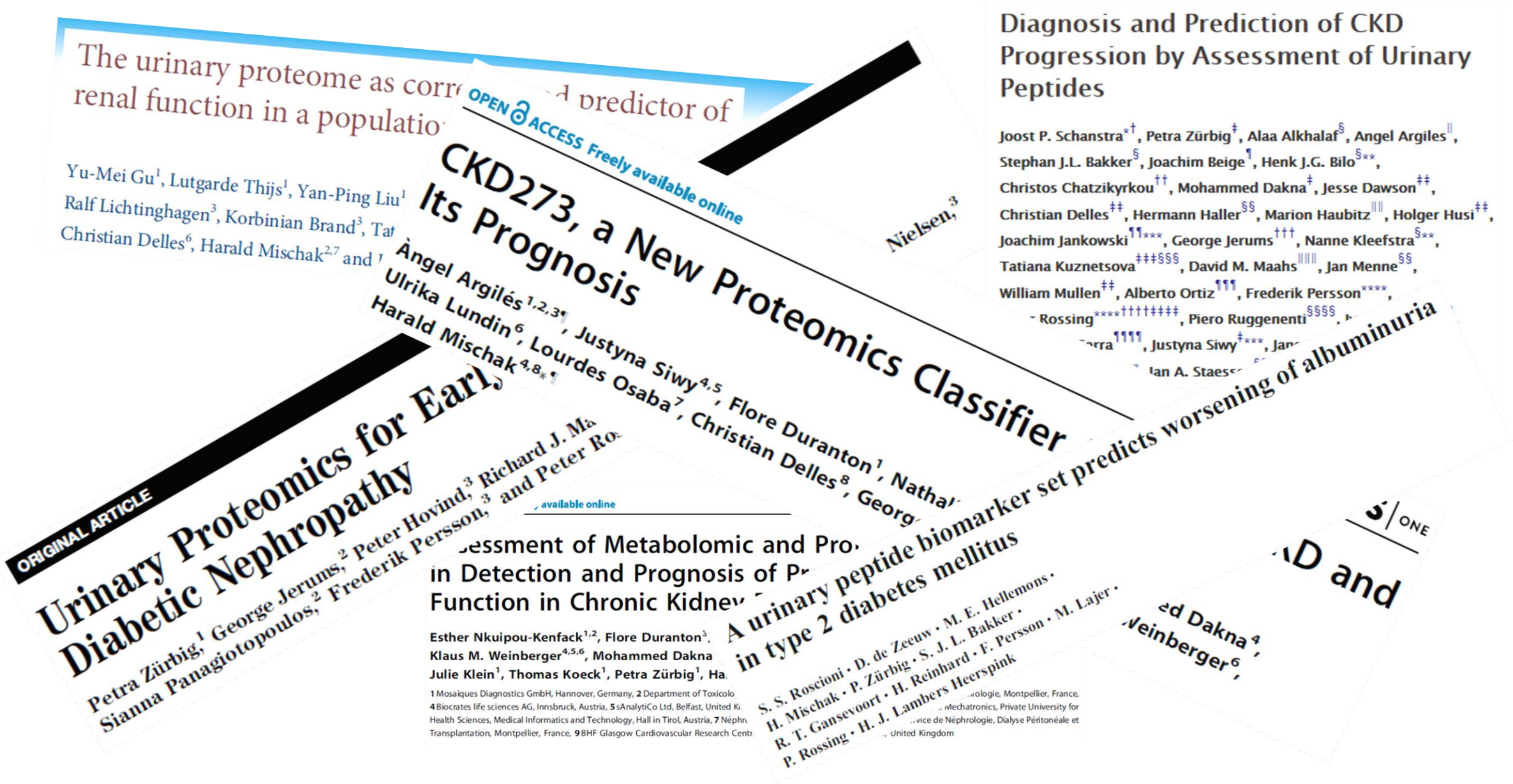
The potential

Metabolomics

The end-products



CKD273 and Renal Outcome



Diagnosis and Prediction of CKD Progression by Assessment of Urinary Peptides

- Progressive CKD is detected at a late stage by eGFR decline and/or the presence of significant albuminuria
- Urinary peptides studied in 522 pts - FU 3 years using proteomics

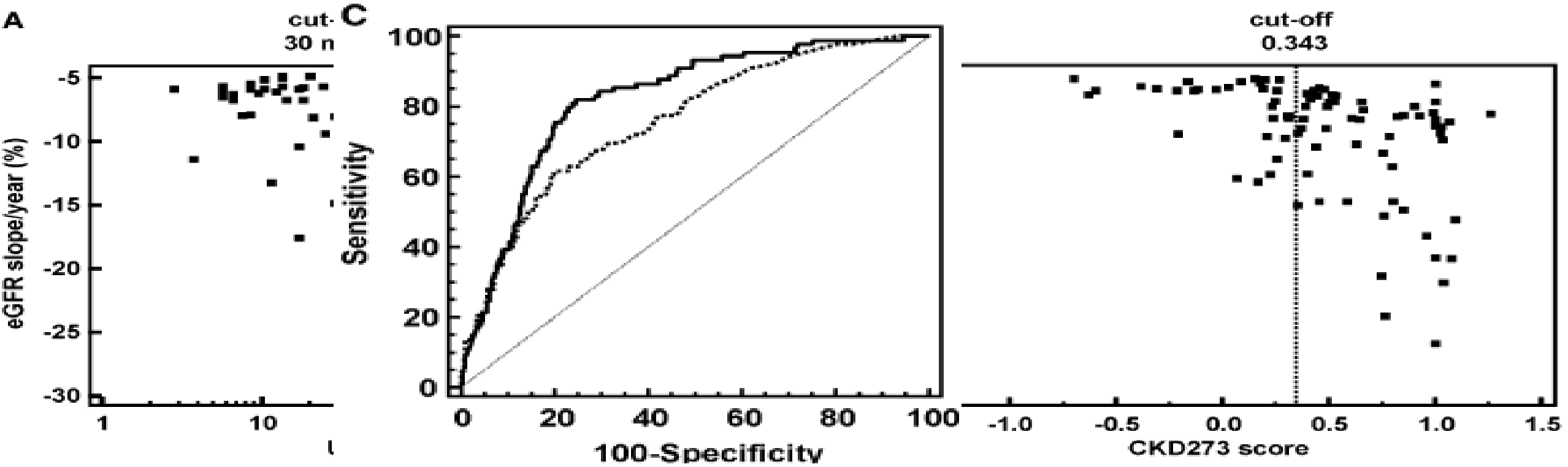
Table 2. Demographic and clinical data of the follow-up cohort

Characteristic	Follow-Up Cohort (*n*=522)	Fast Progressors (*n*=89)	Slow Progressors (*n*=433)
Sex (men/women)	298/224	51/38	247/186
Age (yr)	58±13	57±14	58±13
Urinary albumin (mg/L)	127±415	379±820	76±237
Serum creatinine (mg/dl)	1.10±0.41	1.27±0.74	1.07±0.32
Systolic BP (mmHg)	134±19	140±21	133±19
Diastolic BP (mmHg)	77±10	78±12	77±10
Baseline eGFR (ml/min per 1.73 m^2)	76±24	72±30	76±22
eGFR after 3 yr (ml/min per 1.73 m^2)	72±24	52±24	76±22
Slope of eGFR (%) per yr	−1.24±5.03	−9.29±4.48	0.42±3.21

Data are presented as the mean±SD unless otherwise indicated.

Schantra et al. JASN 2015;26(8):1999-10

Diagnosis and Prediction of CKD Progression by Assessment of Urinary Peptides

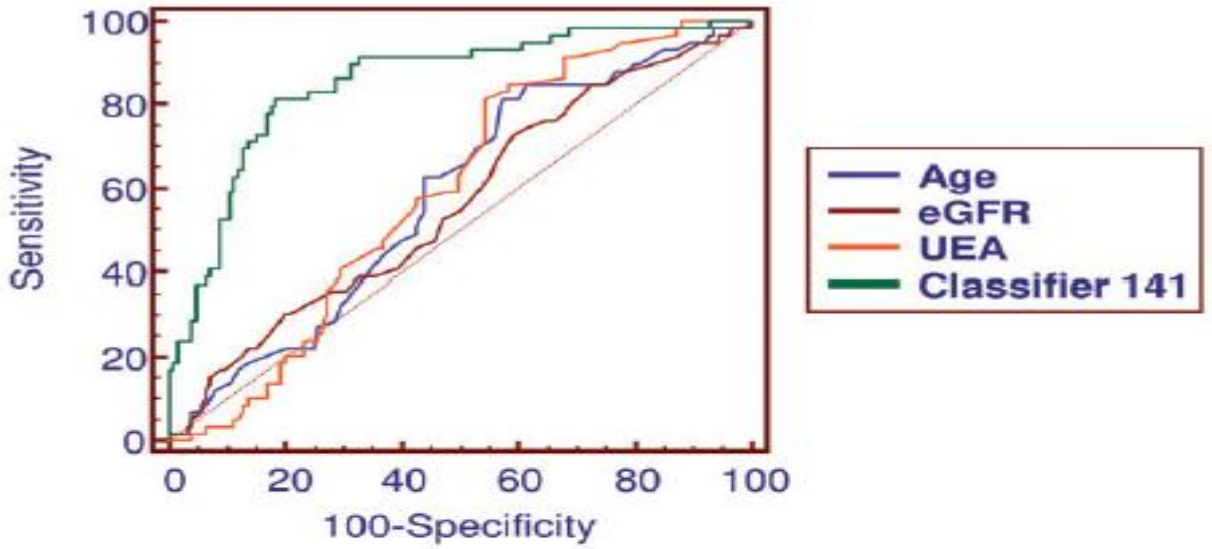


- Compared with the combination of baseline eGFR & albuminuria (AUC=0.758), CKD 273 significantly improved CKD risk prediction (AUC=0.831).
- Urinary proteome analysis might significantly improve the current state of the art of CKD detection and outcome prediction.

Schantra et al. JASN 2015;26(8):1999-10

Urinary peptide biomarker panel associated with an improvement in eGFR in CKD patients

Markoska & Spasovski. NDT 2018; 33(5):751-759



	AUC	Standard Erorr [a]	95% Confidence Interval [b]
Age	0.584	0.0436	0.509 to 0.656
eGFR	0.565	0.0452	0.490 to 0.638
UEA	0.595	0.0416	0.520 to 0.667
Classifier 141	0.854	0.0304	0.794 to 0.901

Comparison of the diagnostic performance of age, eGFR, UEA and the 141 biomarker panel to discriminate patients with an improved eGFR from those with stable eGFR over time in a validation set consisting of 59 patients with improvement and 125 stable pts.

CKD Progression

What is significant progression?

- Most patients with CKD will not progress to ESRD
  - How many patients on average have CKD?
    - 8 – 12% of the country population
  - How many start RRT each year?
    - 0.1 – 0.2% initiated on RRT

eGFR decline >5ml/min/1.73m^2/year

or >10ml/min/1.73m^2 in 5 years

How to Slow down the CKD progression

- Treatment of primary kidney disease
- Strict control of blood glucose level
- Protein restriction in diet
- Quit smoking
- Reduce weight
- Treatment of hyperlipidemia and metabolic acidosis & other CKD complications (anemia, bone disease)
- Strict control of blood pressure, blockade of RAS
- Reduce proteinuria
- New management strategies

clinical investigation www.kidney-international.org

Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury

OPEN

Yan Xie[1], Benjamin Bowe[1], Tingting Li[1,2], Hong Xian[1,3], Yan Yan[1,4] and Ziyad Al-Aly[1,2,5,6]

144,032 incident users of acid suppression therapy (125,596 PPI and 18,436 H2 blockers) consumers. Over 5 years FU in survival models, cohort participants censored at the time of AKI occurrence.

- Compared with incident users of H2 blockers, incident users of PPIs had an increased risk of:
  - an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73m2 (hazard ratio 1.19 (19%); 95% confidence interval 1.15-1.24),
  - incident CKD (1.26; 1.20-1.33),
  - eGFR decline over 30% (1.22; 1.16-1.28), and ESRD or eGFR decline over 50% (1.30; 1.15-1.48).

Kidney Int. 2017;91(6):1482-1494

Santos dos et al. BMC Nephrology (2023) 24:285
https://doi.org/10.1186/s12882-023-03300-4

BMC Nephrology

RESEARCH Open Access

Kidney function decline associated with proton pump inhibitors: results from the ELSA-Brasil cohort

Andréza Soares dos Santos[1], Sara Teles de Menezes[2], Isabella Ribeiro Silva[1], William Neves Oliveira[1], Mariana Linhares Pereira[1], José Geraldo Mill[3], Sandhi Maria Barreto[4] and Roberta Carvalho Figueiredo[1*]

Table 2 Mean and Standard Deviation (SD) of glomerular filtration rate estimated (eGFR) and incident chronic kidney disease (CKD) (%) according to use or not of proton pump inhibitors (PPI). ELSA-Brasil. (N = 13,301)

Characteristics	Does not use PPI (N = 12,296) % or average (SD)	Use PPI (N = 1,005) % or average (SD)	Total (N = 13,301 % or average (SD)
eGFR (baseline)	87.2 (13.5)	84.9 (14.0)*	87 (13.6)
eGFR (Wave 2)	84 (13.7)	81.4 (13.9)*	83.8 (13.7)
Incident CKD (Wave 2)[a]	3.6	6.5*	3.8

a eGFR<60 ml/min/1.73 m^2

* p<0.05 in the chi-square test or t test.

Table 4 Association between time of proton pump inhibitor use and incident chronic kidney disease. ELSA-Brasil. (N = 13,004)

PPI use time	Number incident CKD events[ū]	Reference[¥]	Model 0 [π] HR (95%CI)	Model 1[†] HR (95%CI)	Model 2[‡] HR (95%CI)	Model 3[£] HR (95%CI)	Model 4[§] HR (95%CI)
Up to 6 months	5	1	0.85 (0.35–2.09)	0.75 (0.30–1.86)	0.77 (0.31–1.91)	0.74 (0.30–1.86)	0.74 (0.30–1.86)
Over 6 months	44	1	2.33 (1.69–3.22)*	1.48 (1.05–2.07)*	1.46 (1.04–2.04)*	1.42 (1.01–2.00)*	1.39 (0.99–1.96)

[ū] Number of cumulative incident CKD events during 3.9-year follow-ups

[¥] Reference: Not PPI users.

[π] Model 0: not adjusted.

[†] Model 1: adjusted for age, sex and per capita household income.

[‡] Model 2: adjusted by model 1 + excessive alcohol consumption, smoking and obesity.

[£] Model 3: adjusted by model 2 + cardiovascular disease, diabetes and hypertension.

[§] Model 4: adjusted by model 3 + use of NSAIDs, ARBs and ACEs.

*p<0.05.

Prospective study with baseline (2008–2010) and second wave (2012–2014) of the ELSA-Brasil (mean interval between visits = 3.9 years (1.7–6.0)) on the use of PPI. Renal function was assessed by CKD-EPI, <60ml/min/1.73 ml in wave 2 considered as incident CKD.

Clin Exp Nephrol (2017) 21:182–192
DOI 10.1007/s10157-016-1288-2

REVIEW ARTICLE

Time to target uric acid to retard CKD progression

Takanori Kumagai[1,2] · Tatsuru Ota[1] · Yoshifuru Tamura[1] · Wen Xiu Chang[3] · Shigeru Shibata[1] · Shunya Uchida[1]

Table 2 Randomized controlled trials using urate-lowering drugs on CKD

Author (year) [reference]	Country; at risk (*n*): follow-up, years or months	Drug, dosage per day	Finding on kidney function
Siu (2006) [69]	China; SCr 1.35–4.50 mg/dL ($n = 54$); 1 years	Allopurinol, 100–300 mg	Slowed progression of CKD
Kanbay (2007) [70]	Turkey; eGFR >60 mL/min ($n = 69$); 3 months	Allopurinol, 300 mg	Increased eGFR from 79 to 92 mL/min
Goicoechea (2010) [71]	Spain; CKD 3 ($n = 113$); 2 years	Allopurinol, 100 mg	Slowed decline in eGFR
Momeni (2010) [107]	Iran; T2DM (SCr <3.0 mg/dL) ($n = 40$); 4 months	Allopurinol, 100 mg	Reduced proteinuria
Kanbay (2011) [108]	Turkey; CKD 2 ($n = 97$); 4 months	Allopurinol, 300 mg	Increased eGFR from 86 to 90 mL/min
Pai (2013) [109]	India; CKD 3, 4 ($n = 183$); 2 years	Allopurinol, 100 mg	Reduced blood pressure and progression of CKD
Goicoechea (2015) [72]	Spain; CKD 3 ($n = 113$); 7 years	Allopurinol, 100 mg	Inhibited the incidence of renal outcome
Sircar (2015) [78]	India; CKD 3, 4 ($n = 93$); 6 months	Febuxostat, 40 mg	Slowed the decline in eGFR

SCr serum creatinine, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate

SUA is a possible mediator of the progression of kidney diseases.
The elevation of SUA may directly deteriorate the structure and function of the healthy kidney and hyperuricemia may be a target of treatments of CKD.
Promising results of delaying CKD progression to be confirmed in a larger and well-designed RCTs.

Clinical Kidney Journal, 2022, vol. 15, no. 9, 1666–1674

https://doi.org/10.1093/ckj/sfac075
Advance Access Publication Date: 12 March 2022
CKJ Review

CKJ REVIEW

Uric acid lowering for slowing the CKD-FIX trial: a solved qu

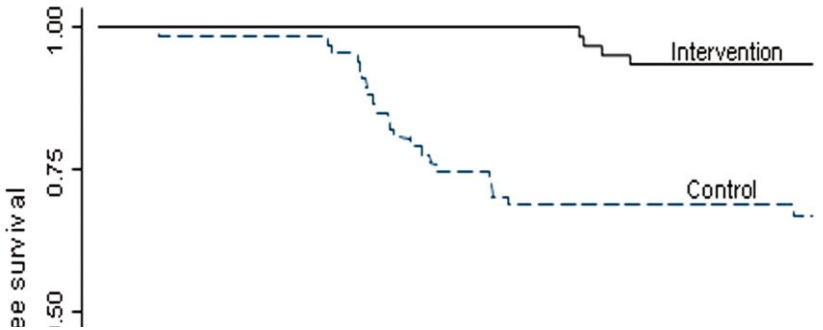
Giovanna Leoncini, Cecilia Barnini, Luc
Daniele Dotta, Martina Penso, Elisa Russo
Francesca Viazzi and Roberto Pontrem

Recent randomized controlled trials failed to demonstrate a beneficial effect of allopurinol or febuxostat on renal disease, casting doubts on the role of this therapeutical approach to improve nephroprotection.

Table 2. Major clinical trials on renal outcome with XO inhibitors at comparison

	FEATHER [41]	PERL [39]	CKD-FIX [40]
Study design	Prospective, double-blind, randomized, placebo-controlled, superiority trial	Prospective, double-blind, randomized, placebo-controlled, superiority trial	Prospective, double-blind, randomized, placebo-controlled, superiority trial
Site	Multicentre in Japan (64 sites total)	Multicentre in USA, Canada and Denmark (16 sites total)	Multicentre in Australia and New Zealand (31 sites total)
Study drug	Febuxostat *versus* placebo	Allopurinol *versus* placebo	Allopurinol *versus* placebo
Primary outcome results	eGFR slope Results: difference NS Febuxostat (0.23 ± 5.26 mL/min × 1.73 m^2 per year) and placebo (−0.47 ± 4.48 mL/min × 1.73 m^2 per year) groups [difference, 0.70 mL/min × 1.73 m^2 (95% CI −0.21 to 1.62); P = 0.1]	Change in iGFR Results: difference NS (difference between group 0.001 mL/min × 1.73 m^2 per year)	Change in eGFR Results: difference NS (difference between group 0.1 mL/min × 1.73 m^2 per year)
Secondary outcome results	Subgroup analysis of the eGFR slope showed a significant difference of 1.79 mL/min × 1.73 m^2 per year (P = 0.005) in patients without proteinuria and a significant difference of 1.76 mL/min × 1.73 m^2 per year (P = 0.009) in patients with serum creatinine < median. Differences NS in all other outcomes	Mean change in SUA: −2.2 mg/dL Differences NS in all other outcomes	Mean change in SUA : −2.7 mg/dL Differences NS in all other outcomes

Bicarbonate Supplementation Slows Progression of CKD and Improves Nutritional Status



Diagnosis and Treatment of Metabolic Acidosis in Patients with Chronic Kidney Disease – Position Statement of the Working Group of the Polish Society of Nephrology

Kidney Blood Press Res 2018;43:959-969

Marcin Adamczak[a] Anna Masajtis-Zagajewska[b] Oktawia Mazanowska[c] Katarzyna Madziarska[d] Tomasz Stompór[e] Andrzej Więcek[a]

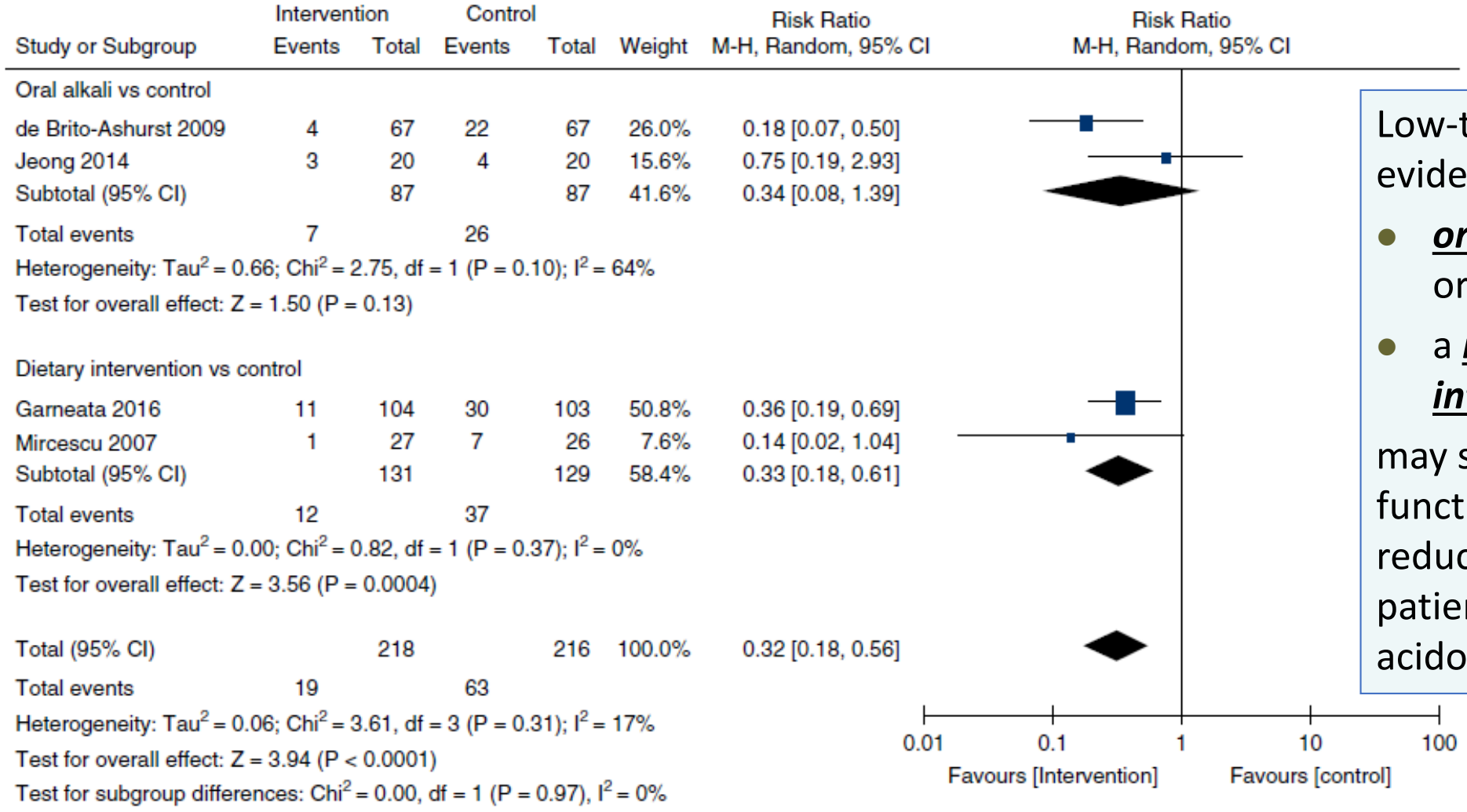
Table 1. Recommendations for the diagnosis and treatment of metabolic acidosis in patients with chronic kidney disease

Recommendation	Source of recommendation
1. Measurement of bicarbonate concentration in venous plasma or venous blood to check for metabolic acidosis should be performed in all patients with chronic kidney disease	Expert opinion
2. In patients with CKD stages 4 or 5 (not yet on renal replacement therapy), the determination of venous plasma or venous blood bicarbonate concentration should be carried out at least once a year	Expert opinion
3. Metabolic acidosis in patients with chronic kidney disease should be diagnosed when the venous plasma or venous blood bicarbonate concentration is lower than 22 mmol/l	Recommendation based on results of observational studies
4. In patients with metabolic acidosis and chronic kidney disease, oral sodium bicarbonate administration is recommended	Recommendation based on results of interventional studies
5. The goal of treatment of metabolic acidosis in patients with chronic kidney disease is to achieve a plasma or blood bicarbonate concentration equal to or	Recommendation based on results of interventional studies

Effects of Treatment of Metabolic Acidosis in CKD: A Systematic Review and Meta-Analysis.

Navaneethan SD, Shao J, Buysse J, and Bushinsky DA. Clin J Am Soc Nephrol. 2019; 14(7): 1011–1020

Pts with stage 3–5 CKD & metabolic acidosis (<22) or (22–24 mEq/L), 14 clinical trials (1394 pts), 3 months – 3 years



Low-to-moderate certainty evidence suggest that:

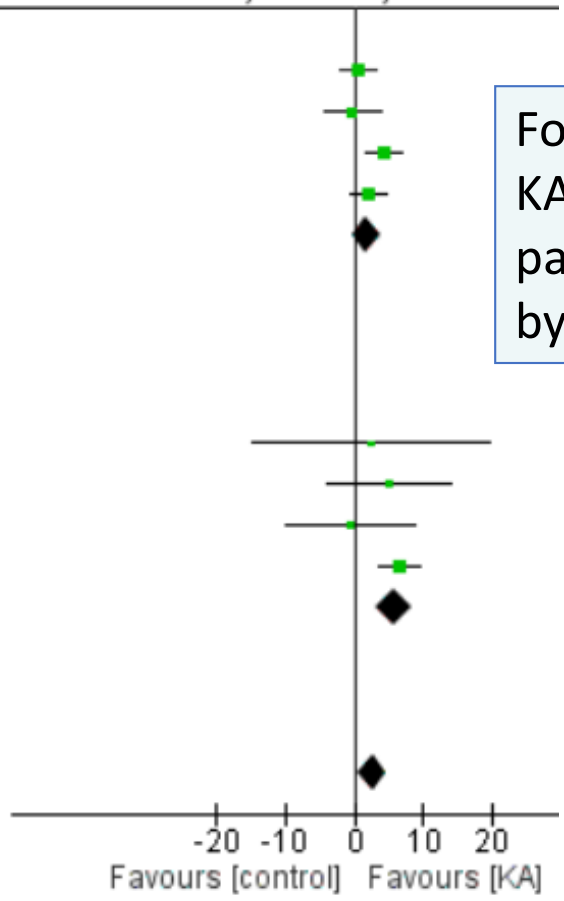
- ***oral alkali supplementation*** or
- a ***reduction in dietary acid intake***

may slow the rate of kidney function decline and potentially reduce the risk of ESKD in patients with CKD and metabolic acidosis

Figure 4. | Forest plot shows potentially reduced risk of end stage kidney disease with oral alkali supplementation or reduction of dietary acid intake. I^2 for the combined effect estimate: (95% CI, 0% to 73%). df, degrees of freedom; M-H, Mantel-Haenszel.

The Effect of Ketoanalogues on CKD Deterioration: A Meta-Analysis

Study or Subgroup	KA Mean	KA SD	KA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 eGFR < 18								
Bellizz et al. 2006 [14]	17.8	6.6	30	17.24	4.72	80	20.0%	0.56 [-2.02, 3.14]
Feiten et al. 2005 [16]	15.8	6.4	12	16.1	3.6	12	13.1%	-0.30 [-4.45, 3.85]
Garneata et al. 2016 [7]	15.1	10.93	104	10.8	8.28	103	19.7%	4.30 [1.66, 6.94]
Mircescu 2007 [21]	15.4	5	27	13.4	5.1	26	19.3%	2.00 [-0.72, 4.72]
Subtotal (95% CI)			**173**			**221**	**72.1%**	**1.87 [-0.08, 3.81]**
Heterogeneity: Tau² = 1.68; Chi² = 5.29, df = 3 (P = 0.15); I² = 43%								
Test for overall effect: Z = 1.88 (P = 0.06)								
1.3.2 eGFR > 18								
Milovanova et al. 2018 [20]	29.1	38.8	42	26.6	39.1	37	1.3%	2.50 [-14.72, 19.72]
Prakash et al. 2004 [22]	27.6	10.1	18	22.5	15.9	16	4.2%	5.10 [-3.98, 14.18]
Qiu 2012 [23]	29.19	9.13	12	29.77	13.19	11	4.0%	-0.58 [-9.93, 8.77]
Teplan 2008 [24]	29.8	8.6	66	23.2	8.4	65	18.3%	6.60 [3.69, 9.51]
Subtotal (95% CI)			**138**			**129**	**27.9%**	**5.81 [3.19, 8.44]**
Heterogeneity: Tau² = 0.00; Chi² = 2.24, df = 3 (P = 0.52); I² = 0%								
Test for overall effect: Z = 4.34 (P < 0.0001)								
Total (95% CI)			**311**			**350**	**100.0%**	**2.74 [0.73, 4.75]**
Heterogeneity: Tau² = 3.54; Chi² = 13.90, df = 7 (P = 0.05); I² = 50%								
Test for overall effect: Z = 2.67 (P = 0.008)								
Test for subgroup differences: Chi² = 5.61, df = 1 (P = 0.02), I² = 82.2%								

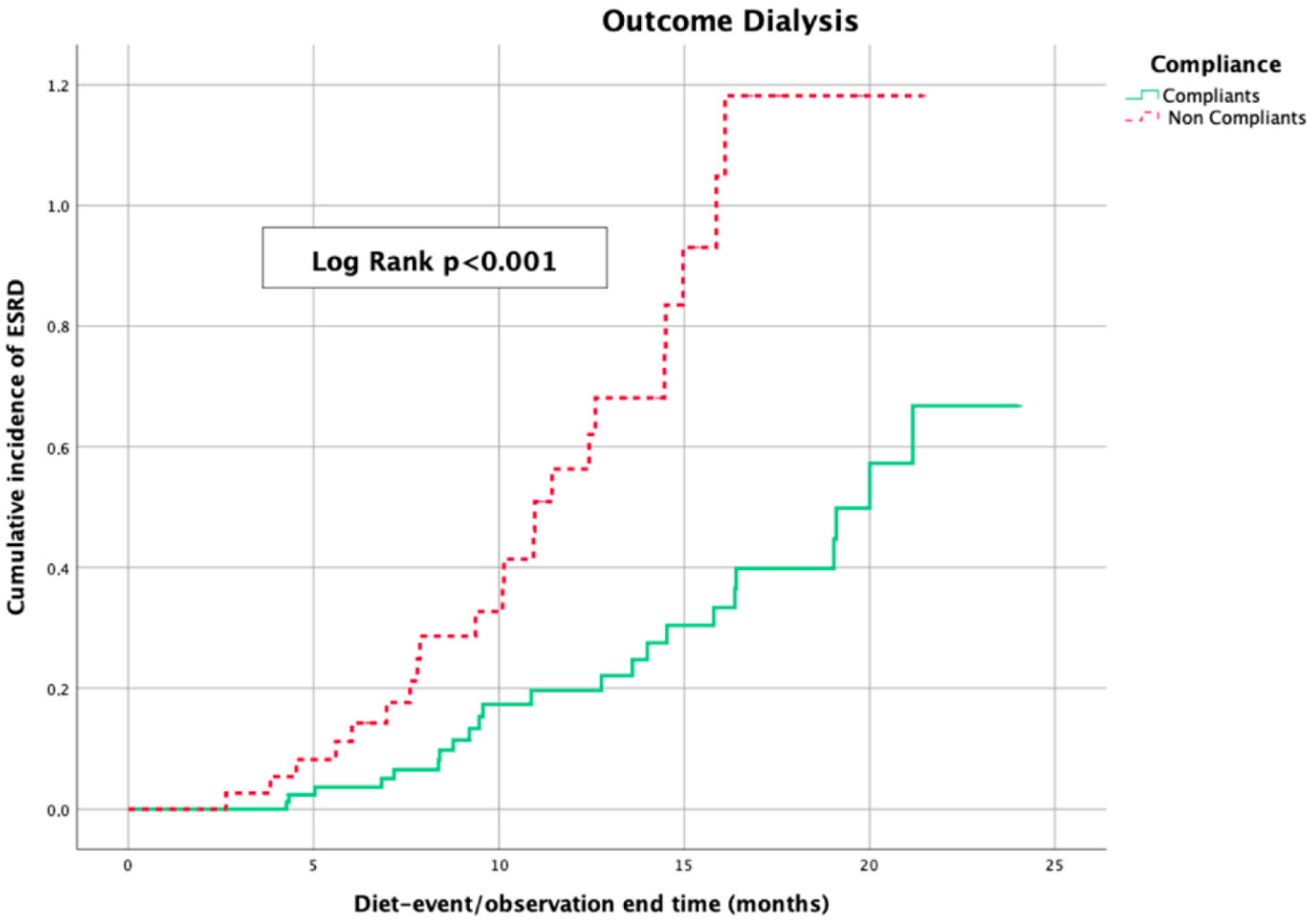


Forest plot of effects of KA on eGFR in CKD patients sub-grouped by eGFR.

Heterogenous studies from 3 months - 4 years on low & very low restriction of proteins and ketoanalogues treatment: A restricted protein diet supplemented with ketoanalogues (RPKA) was found to significantly delay the progression of CKD (p = 0.008), particularly in patients with an estimated glomerular filtration rate (eGFR) > 18 mL/min/1.73 m2 (p < 0.0001) without causing malnutrition and reverse CKD-MBD in patients with eGFR < 18 mL/min/1.73 m2.

Li at al. Nutrients 2019; 11(5): 957

Supplemented Very Low Protein Diet (sVLPD) in Patients with Advanced Chronic Renal Failure: Clinical and Economic Benefits



sVLPD (0.3 g/kg/prot/day) supplemented with only essential amino acids (EAA) without ketoanalogues in stage 5 pts.

Over the 24 months period of observation the progression of CKD slowed down (mean eGFR 11.6 ± 3.3 vs. 9.3 ± 2.7 mL/min/1.73 m^2, $p < 0.001$) and the start of the dialysis treatment (adjusted HR = 0.361, CI 0.200–0.650, $p = 0.001$) was delayed without evidence of malnutrition, in compliant vs. non-compliant patients leading to a substantial cost reduction for the National Health System.

Thus, VLPD supplemented with EAA could be extensively used to reduce the incidence of dialysis treatments, with a favorable economic impact on the NHS.

Cecchi et al. Nutrients 2023; 15(16): 3568

toxins. 2021;13(5):334.

Article

An Innovative Synbiotic Formulation Decreases Free Serum Indoxyl Sulfate, Small Intestine Permeability and Ameliorates Gastrointestinal Symptoms in a Randomized Pilot Trial in Stage IIIb-IV CKD Patients

Carmela Cosola [1,†], Maria Teresa Rocchetti [2,†], Ighli di Bari [1], Paola Maria Acquaviva [1], Valentina Maranzano [1], Simone Corciulo [1], Agostino Di Ciaula [3], Domenica Maria Di Palo [3], Flavia Maria La Forgia [4], Sergio Fontana [4], Maria De Angelis [5], Piero Portincasa [3] and Loreto Gesualdo [1,*]

Proteolytic dysbiosis of the gut microbiota with UTs like IS and PCS - risk factor for CKD progression.

Synbiotic formulation NATUREN G® in 2 months decrease free IS, compared with the controls only in the CKD group.

nutrients 2022;14(4):805.

Article

The Effect of ß-Glucan Prebiotic on Kidney Function, Uremic Toxins and Gut Microbiome in Stage 3 to 5 Chronic Kidney Disease (CKD) Predialysis Participants: A Randomized Controlled Trial

Zarina Ebrahim [1,*,†], Sebastian Proost [2,3,*,†], Raul Yhossef Tito [2,3], Jeroen Raes [2,3], Griet Glorieux [4], Mohammed Rafique Moosa [5] and Renée Blaauw [1]

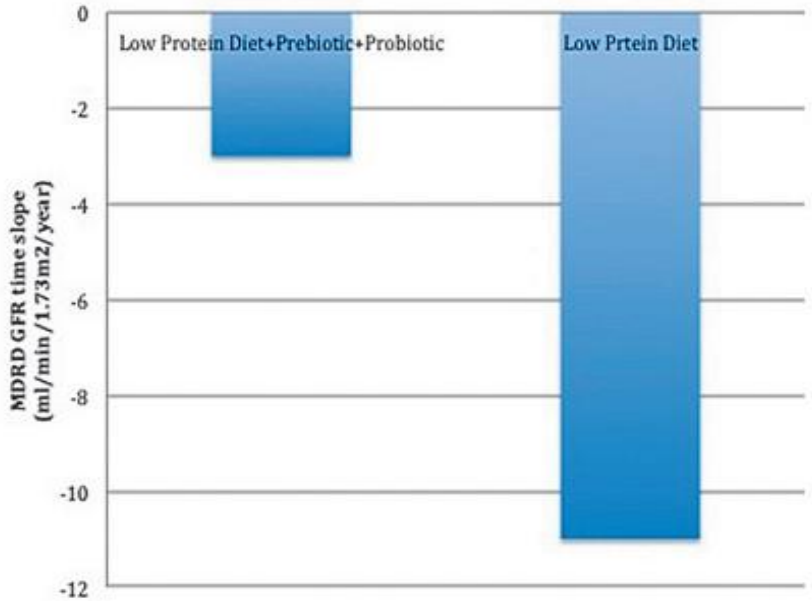
The effect of a ß-glucan prebiotic on kidney function, uremic toxins and the gut microbiome in CKD stage 3 to 5. There was a significant reduction in IS at 8 and 14 weeks, pCS The ß-glucan prebiotic favorably affected the gut microbiome.

Influence of prebiotic and probiotic supplementation on the progression of chronic kidney disease

TABLE III.—*Comparison of variables between the low protein diet + prebiotic + probiotic supplementation and low protein diet alone.*

	Low protein diet + Prebiotic + Probiotic (N.=12)	Low protein diet (N.=12)	P value
Serum creatinine (mg/dL)	4.45±0.30	4.3±0.31	NS
eGFR (mL/min per 1.73 m²)	14.5±11.7	14.9±10.1	NS
SBP, mm Hg	146.6±7.2	144.7±14.7	NS
DBP, mm Hg	92.0±7.2	90.4±6.8	NS
Hb	9.8±1.3	10.2±1.4	NS
Calcium (mg/dL)	8.74±1.62	8.80±1.84	NS
Phosphorus	4.52±3.18	4.42±4.24	NS
Albumin (g/dL)	3.4±0.1	3.6±0.8	NS
Antihypertensive medications (number)	3	3	NS

SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; NS: not significant.



Whether prebiotic and probiotic suppl. along with low protein diet retards the progression of CKD vs VLPD only.

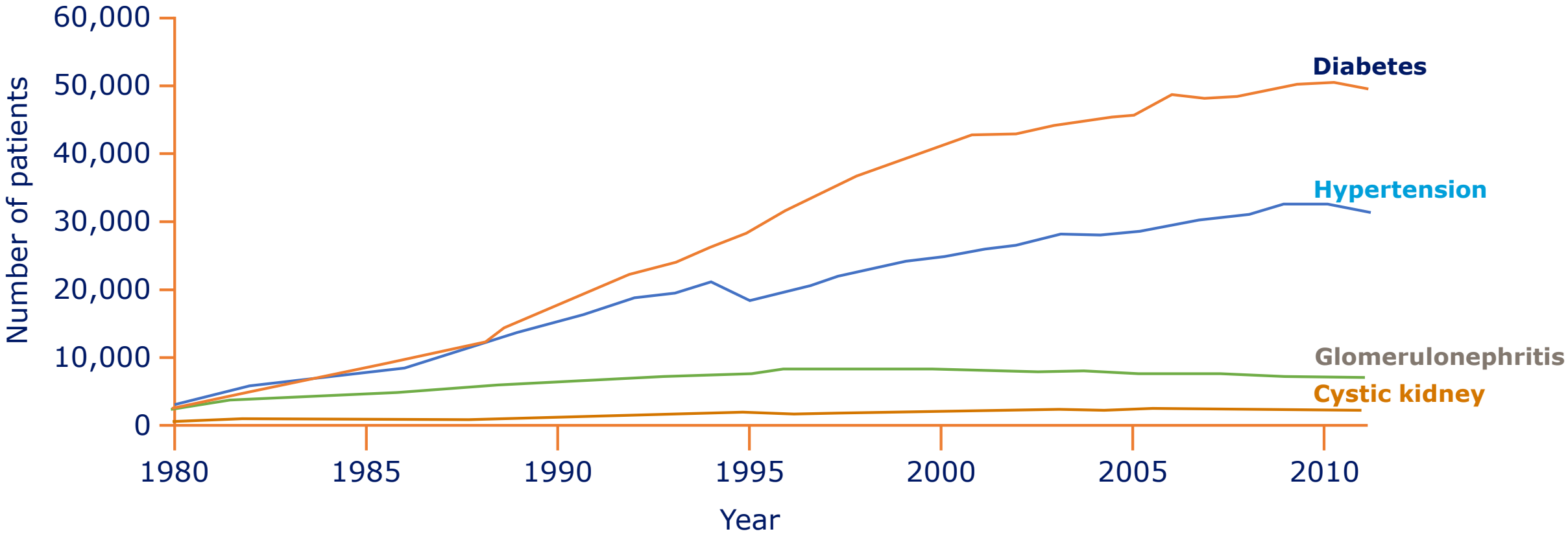
In a **1-year** prospective observation study with a randomized control and open-label design, **24 stable CKD stage III to V patients** [low protein diet + prebiotic + probiotic supplementation (n=12), and the control group receiving low protein diet only (n=12)].

The **declining GFR during prebiotic and probiotic supplementation were significantly lower** (-11.6±8.6 vs. -3.4±4.6 mL/min per 1.73 m2 per year, 95% CI -6.45 - -9.86, P<0.001) than those with low protein diet alone.

Prebiotic and probiotic supplementation along with low protein diet delayed the progression of CKD.

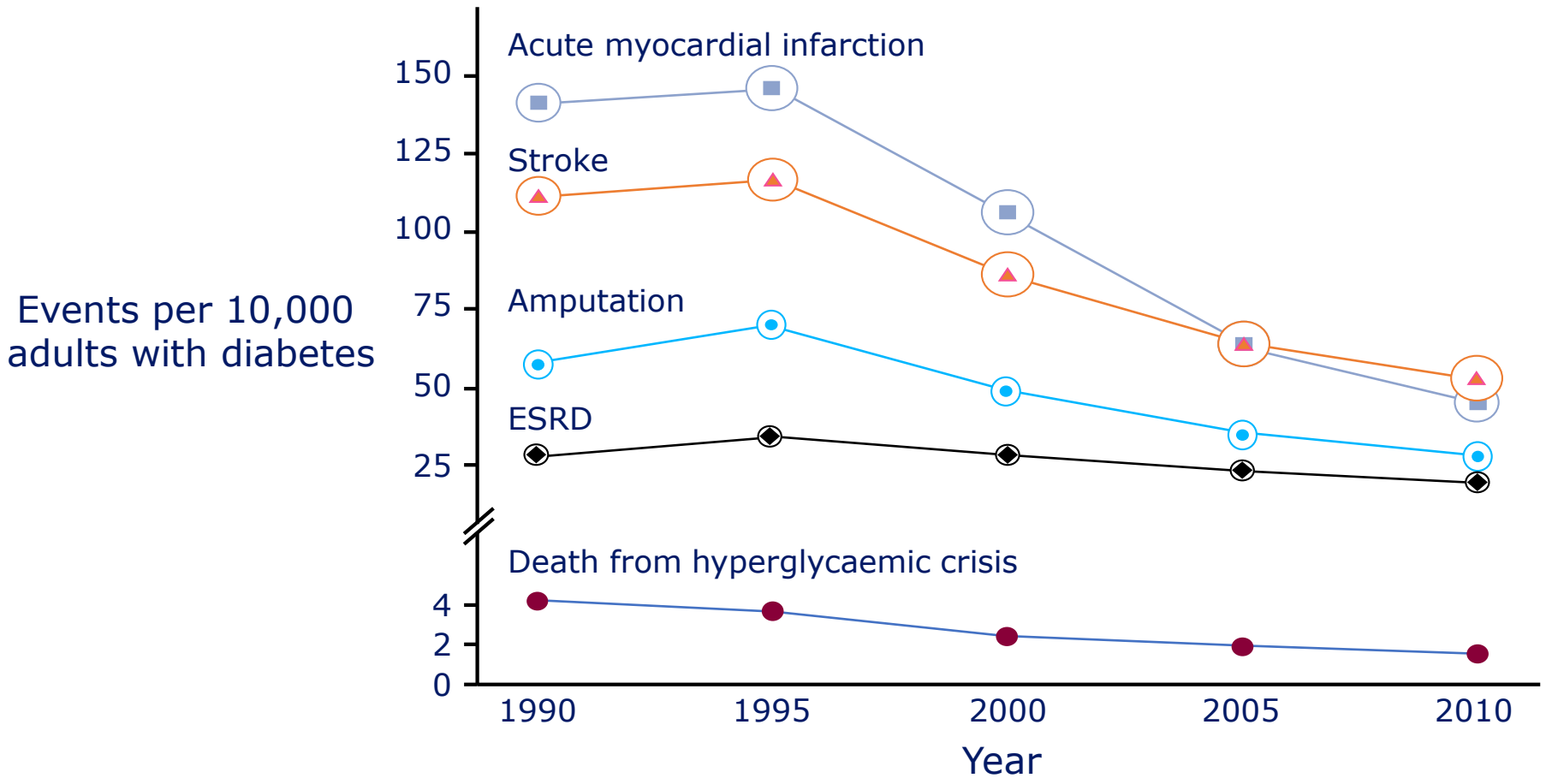
Pavan M. Minerva Urol Nefrol 2016;68(2):222-6.

Diabetes is the leading cause of kidney failure



- United States Renal Data System. 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.

Only minor improvement in risk for ESKD



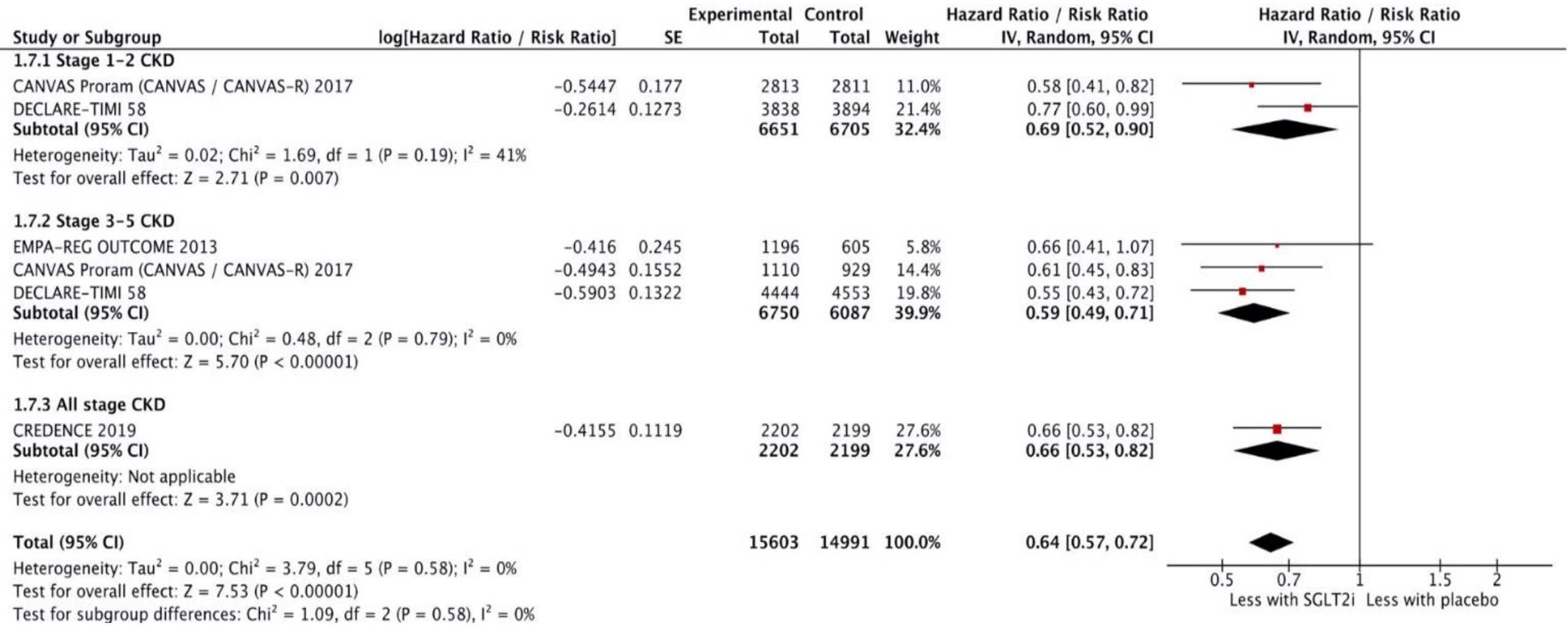
- Largest relative declines (%) in acute myocardial infarction (**–67.8%**)
- Smallest decline was in end-stage renal disease (**–28.3%**)

- Gregg EW et al. *N Engl J Med* 2014;370:1514–23.

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis.

Neuen B et al The Lancet D&E 2019; 7(11):845-854

SGLT2 INHIBITORS AND CKD PROGRESSION



Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial

Background

The efficacy and safety of the sodium-glucose co-transporter-2 inhibitor (SGLT2i) empagliflozin has not been assessed in a dedicated population of people with chronic kidney disease (CKD).

Streamlined design

RCT:
Empagliflozin 10 mg once daily
vs. matching placebo

Inclusion criteria:
eGFR ≥ 20, < 45 mL/min/1.73 m²;
or ≥ 45, < 90 and uACR ≥ 200 mg/g

Composite primary outcome:
- CV or renal death
- Maintenance dialysis or kidney transplant
- Sustained eGFR < 10 mL/min/1.73 m² or sustained ≥ 40% eGFR decline

Baseline characteristics

n = 6609

Mean age 64 (SD 14) years

♀ 33%
♂ 67%

8 countries: Europe, N. America and Asia

eGFR, mL/min/1.73 m²:
Mean 37.5 (SD 15)
78% with eGFR < 45
34% with eGFR < 30

uACR, mg/g:
Median 412 (IQR 94–1190)
48% with uACR < 300

Primary renal diagnoses:
31% diabetic nephropathy
25% glomerular disease
22% ischaemic/hypertensive
12% other and 10% unknown

Comorbidity:
46% diabetes
27% cardiovascular disease

Conclusion

The EMPA-KIDNEY trial has recruited a large, widely generalizable CKD population with high proportions of the types of people without diabetes and with low eGFR or uACR who have not been included in previous trials of SGLT2i. Results are anticipated in 2022.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

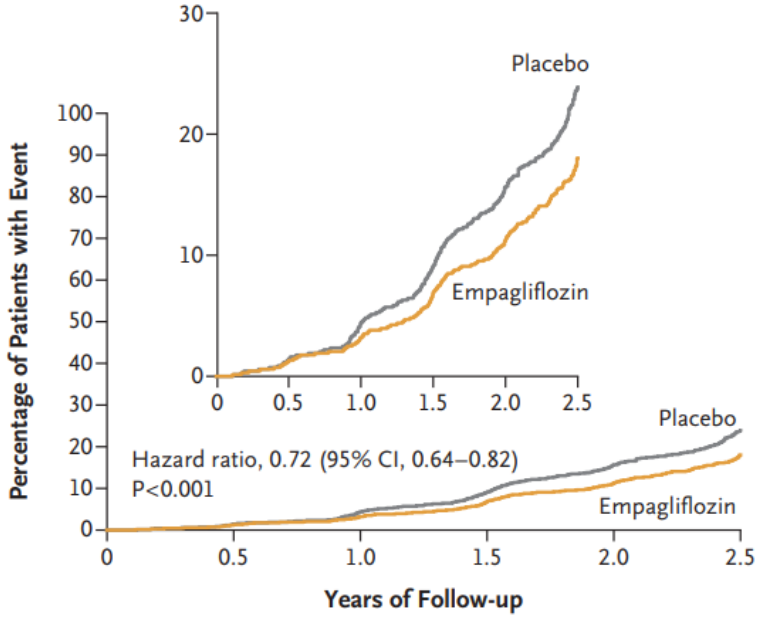
The EMPA-KIDNEY Collaborative Group. NDT (2022)
@NDTSocial

November 4, 2022, at NEJM.org.

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*



No. at Risk						
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.

Shown are the results of the primary composite outcome of progression of kidney disease or death from cardiovascular causes. Over a median of 2 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 patients (13.1%) in the empagliflozin group and in 558 patients (16.9%) in the placebo group, representing 42 fewer primary-outcome events per 1000 patients in the empagliflozin group than in the placebo group over 2 years. The inset shows the same data on an enlarged y axis.

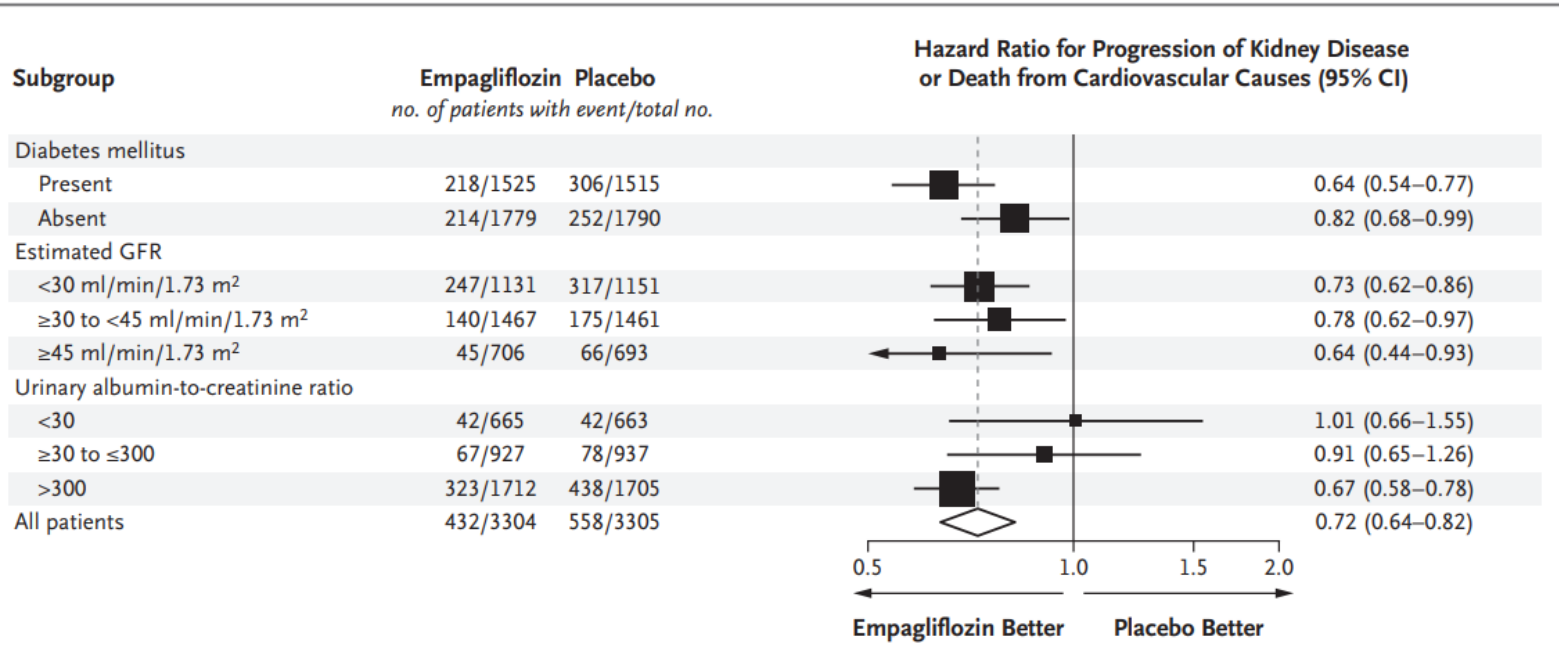


Figure 2. Primary Outcome in Key Prespecified Subgroups.

Shown are the hazard ratios for the primary outcome in key prespecified subgroups defined according to baseline characteristics. Hazard ratios and confidence intervals were estimated with the use of Cox proportional-hazards regression models, with adjustment for age, sex, history of diabetes, estimated glomerular filtration rate (GFR), urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams), and geographic region. The area of each box is proportional to the inverse of the variance of the log hazard ratios. The arrow indicates that the boundary of the 95% confidence interval is outside the graphed area. The diamond represents the result of the primary analysis, with the width of the diamond indicating the 95% confidence interval. The dashed line indicates the hazard ratio in the overall population.

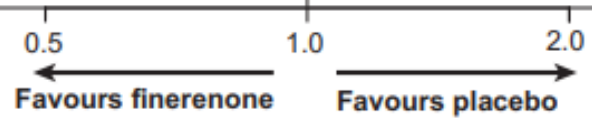
CONCLUSIONS

Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.)

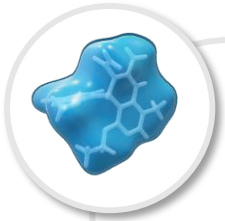
Cardiovascular and kidney outcomes with Finerenone in patients with T2D diabetes and CKD: the FIDELITY pooled analysis

Agarwal R et al. European Heart Journal (2022) 43, 474–484

Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
Composite cardiovascular outcome[b]	825 (12.7)	4.34	939 (14.4)	5.01	0.86 (0.78–0.95)	0.0018
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)	0.95
Hospitalization for heart failure	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)	0.0030
eGFR ≥57% composite kidney outcome[c]	360 (5.5)	1.96	465 (7.1)	2.55	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease[d]	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040[e]
Sustained decrease in eGFR to <15 mL/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026[e]
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	< 0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.46[e]
eGFR ≥40% composite kidney outcome[f]	854 (13.1)	4.81	995 (15.3)	5.64	0.85 (0.77–0.93)	0.0004
Sustained ≥40% decrease in eGFR from baseline	817 (12.5)	4.60	962 (14.8)	5.45	0.84 (0.76–0.92)	0.0002
Death from any cause	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–>1.00[g])	0.051[e]
Hospitalization for any cause	2836 (43.5)	19.04	2926 (45.0)	19.91	0.96 (0.91–1.01)	0.087[e]



Recommendations for finerenone use in the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD[1]



Finerenone is recommended by KDIGO for patients with CKD and T2D[1]

Inclusion in the guideline came within 2 years of the publication of the FIDELIO-DKD and FIGARO-DKD phase III clinical trials[2,3]

Recommendation 1.4.1:
'We suggest a nonsteroidal MRA with proven kidney or CV benefit for patients with T2D, eGFR ≥25 ml/min/1.73 m^2, normal serum [K^+] and albuminuria (≥30 mg/g) despite maximum tolerated dose of RASi.' **(2A)**

[K^+] , potassium concentration

1. Kidney Disease: Improving Global Outcomes. *Kidney Int* 2022;102:S1–S128; 2. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 3. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263

Conclusion: treatment of CKD progression

- **Comprehensive treatment including life-style measures & diet**
- **Evidence for PPI temporary use, bicarbonate use, KA or EAA, pre-probiotic use**
- **SGLT2 inhibitors in use for CKD indication**
- **NS MRA (finerenone) used on top of the standard care improves kidney outcome in patients with CKD**
- **Follow the guidelines**

Thank you!

How to Slow down the CKD progression

- Treatment of primary kidney disease
- Strict control of blood glucose level
- Protein restriction in diet
- Quit smoking
- Reduce weight
- Treatment of hyperlipidemia and metabolic acidosis & other CKD complications (anemia, bone disease)
- Strict control of blood pressure, blockade of RAS
- Reduce proteinuria
- New management strategies