

CONGRESSO INTERASSOCIATIVO **SID-AMD** *Emilia Romagna*

**Prevenzione e cura:
un ponte fra presente e futuro**

Bologna, 12 Ottobre 2024

Nh Bologna De La Gare

1° Sessione **Diabete-Rene-Cuore**

*La prevenzione e la cura è un lavoro di squadra –
i diabetologi dialogano con nefrologo e cardiologo*

Moderatori: Daniela Piani (Vignola, MO),
Alessandra Sforza (Bologna)

09:30 La sindrome cardio-nefro-metabolica
Gaetano La Manna (Bologna)

09:45 La sindrome cardio-nefro-metabolica
Stefano Urbinati (Bologna)

10:00 Raccomandazioni regionali sul trattamento
integrato del diabete alla luce della nota 100
Nicola Magrini (Bologna)

10:20 Determinanti sociali della salute: il punto
di vista del paziente
Rita Lidia Stara (Cento, FE)

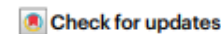
Il /la dr./sa La Manna Gaetano dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Astrazeneca
- Lilly
- Boheringer
- Bayer
- Roche
- Novo Nordisk
- Sanofi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

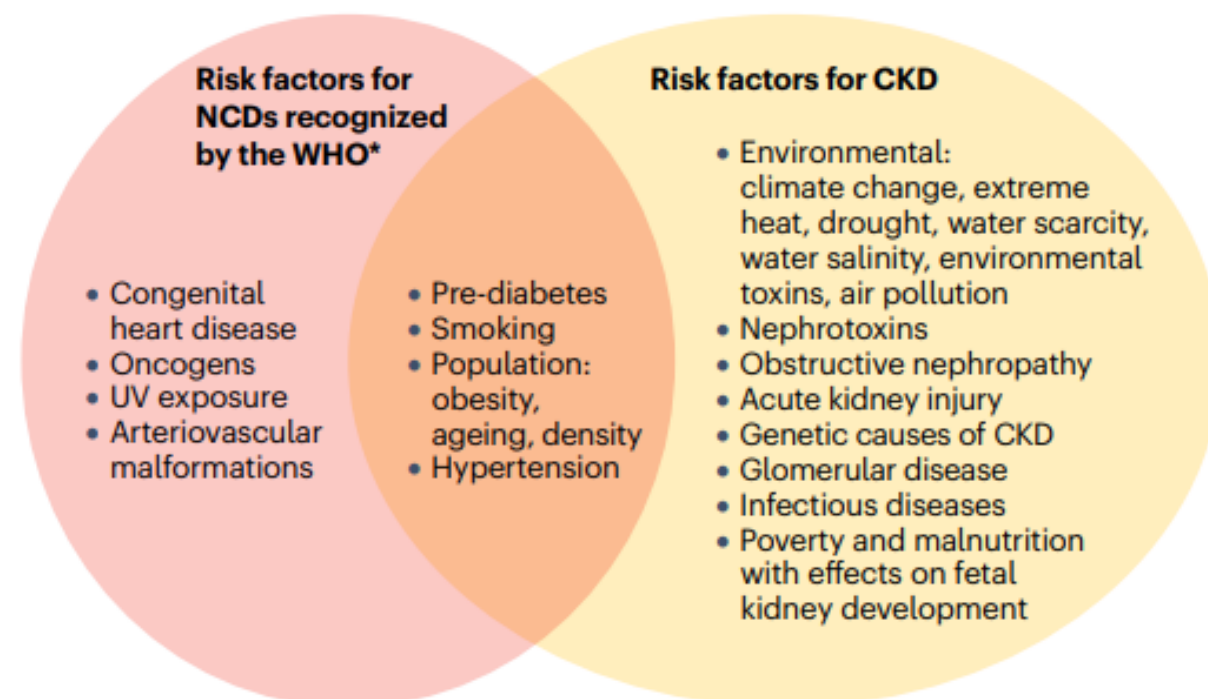
years of life lost (YLL) globally

Consensus statement



Chronic kidney disease and the global public health agenda: an international consensus

Anna Francis¹, Meera N. Harhay^{2,3}, Albert C. M. Ong⁴, Sri Lekha Tummalapalli^{5,6}, Alberto Ortiz⁷, Agnes B. Fogo⁸, Danilo Fliser⁹, Prabir Roy-Chaudhury¹⁰, Monica Fontana¹¹, Masaomi Nangaku¹², Christoph Wanner¹³, Charu Malik¹⁴, Anne Hradsky¹⁴, Dwomoa Adu¹⁵, Sunita Bavanandan¹⁶, Ana Cusumano¹⁷, Laura Sola¹⁸, Ifeoma Ulasi¹⁹, Vivekanand Jha^{20,21,22}✉, American Society of Nephrology*, European Renal Association* & International Society of Nephrology*



Box 1

The burden of kidney disease

- Premature mortality
- Disability
- Reduced quality of life
- Psychosocial harm
- High costs to governments and health care systems
- High costs to individuals and families, in part because of lost productivity

the risk of morbidity and mortality^{115,116}. In 2019, CKD in LICs led to ~600 YLL per age-standardized 100,000 population and around ~560 YLL per 100,000 in LMICs, compared with 200 YLL per 100,000 in HICs¹⁰². Increasing prevalence and the relatively young age at death mean that overall deaths and YLL due to kidney disease are predicted to escalate dramatically at a global level (Figs. 2 and 3). In 2040, kidney disease is predicted to cause 52 million YLL, moving from the 16th most common cause of YLL (in 2016) to the fifth, surpassing other major NCD drivers of early mortality listed by the WHO such as diabetes¹⁴ (Fig. 3). In 2040, CKD is expected to account for 5% of YLL^{14,18} (Fig. 4).

CKD also increases the risk of developing severe acute and chronic infections (such as COVID-19 and tuberculosis), which are major causes of death in LICs and LMICs^{117,118}. Hence, decreasing the incidence and severity of CKD will have beneficial effects on other NCDs and communicable diseases.

Secular Trend in GFR Decline in Non-Dialysis CKD Based on Observational Data From Standard of Care Arms Of Trials

Analysis



Study Design:

Systematic review and meta-analysis of the standard of care (SoC) arms of RCTs analyzed as an observational study



Selection Criteria for Studies

Phase 3 RCTs evaluating GFR decline as an outcome in SoC arms

Results



92 RCTs



32,202 adult patients

Random-effect meta-analysis showed an overall mean GFR decline of $-4.00 \text{ mL/min/1.73 m}^2 \text{ year}$ (95%CI, $-4.55, -3.44$, $P < 0.001$) in SoC arm with significant heterogeneity

Publication Decade	GFR Decline (mL/min/1.73 m ² /year)	(95% CI)
1991-2000	-5.44	(-7.15, -3.73)
2001-2010	-3.92	(-4.82, -3.02)
2011-2023	-3.20	(-3.75, -2.64)

CONCLUSION: In the last three decades, GFR decline has decreased over time in patients enrolled in RCTs receiving standard care.

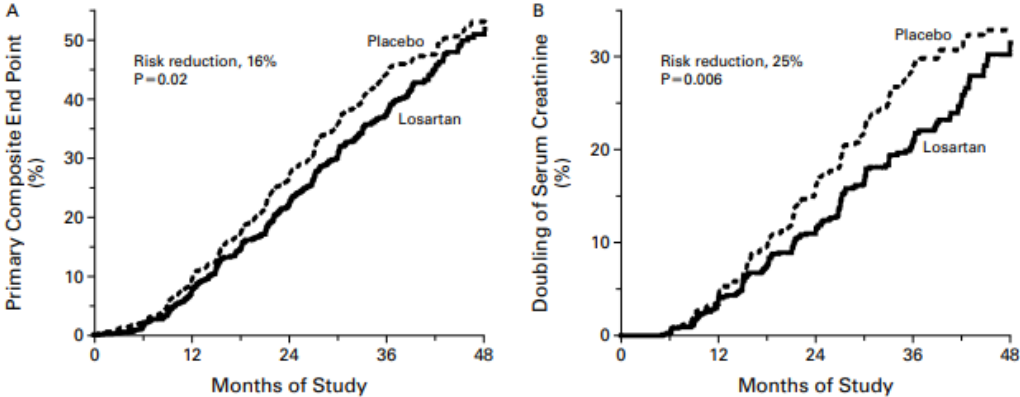
Carlo Garofalo, Silvio Borrelli, Maria Elena Liberti, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2023.09.014

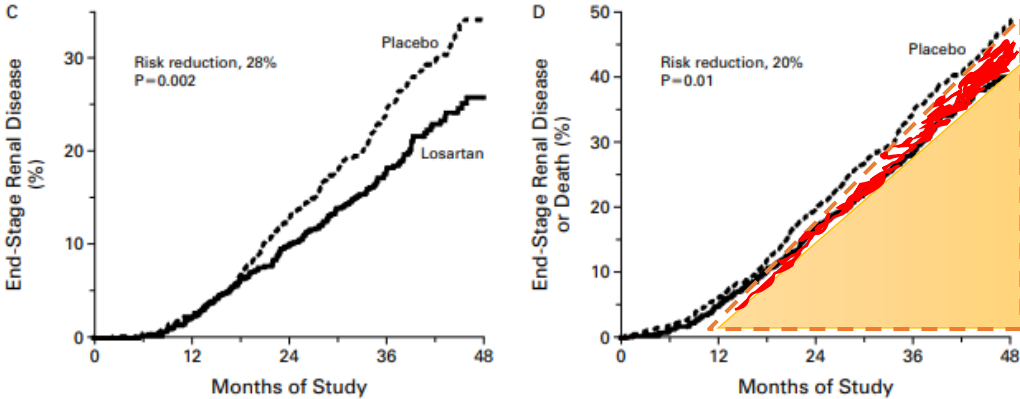
EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D., WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D., ZHONXIN ZHANG, PH.D., AND SHAHNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS*

EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES AND NEPHROPATHY



NO. AT RISK					
Placebo	762	689	554	295	36
Losartan	751	692	583	329	52

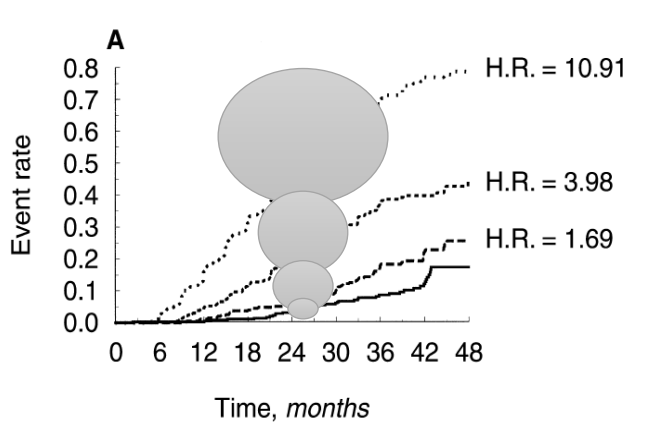


NO. AT RISK					
Placebo	762	715	610	347	42
Losartan	751	714	625	375	69

The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: The RENAAL Study

Kidney International, Vol. 63 (2003), pp. 1499–1507

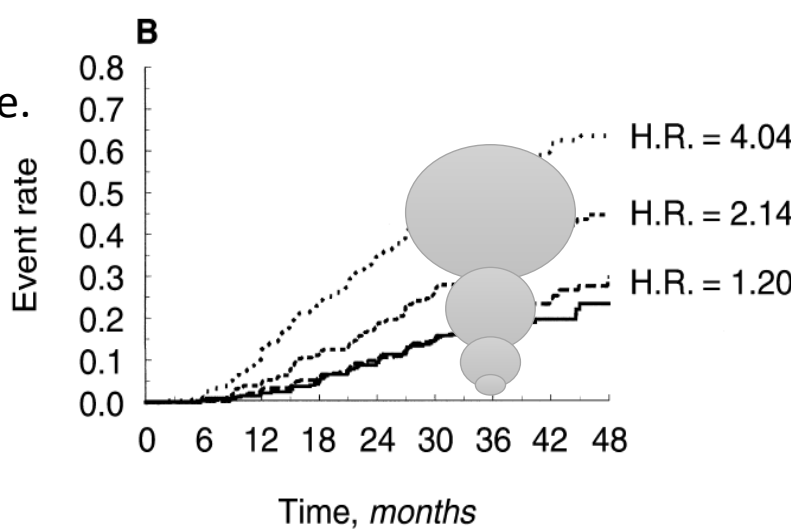
WILLIAM F. KEANE,¹ BARRY M. BRENNER,² DICK DE ZEEUW,³ JEAN-PIERRE GRUNFELD,⁴ JANET MCGILL,⁵ WILLIAM E. MITCH,⁶ ARTUR B. RIBEIRO,⁷ SHAHNAZ SHAHINFAR,⁸ ROGER L. SIMPSON,⁸ STEVEN M. SNAPINN,⁸ and ROBERT TOTO,⁹ FOR THE RENAAL STUDY INVESTIGATORS



Baseline urine albumin creatinine (Alb:Cr) ratio.

Baseline serum creatinine.

- A large number of CKD patients worsened over time
- Proteinuria and GFR were directly correlated with worse outcome



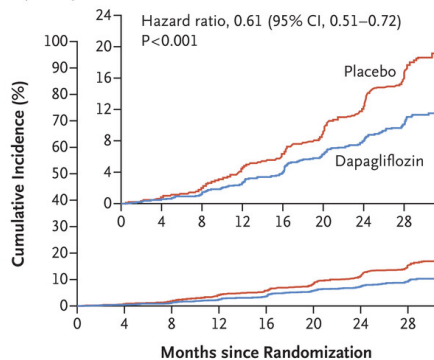
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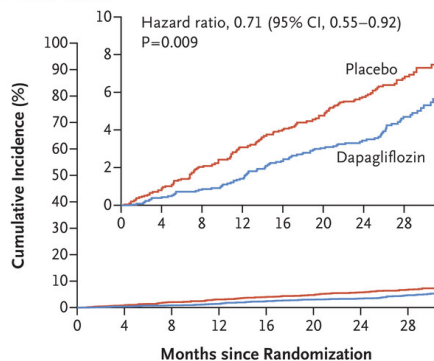
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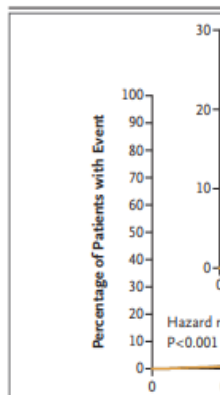
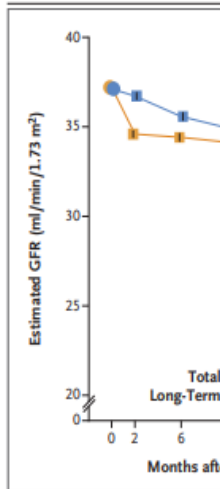
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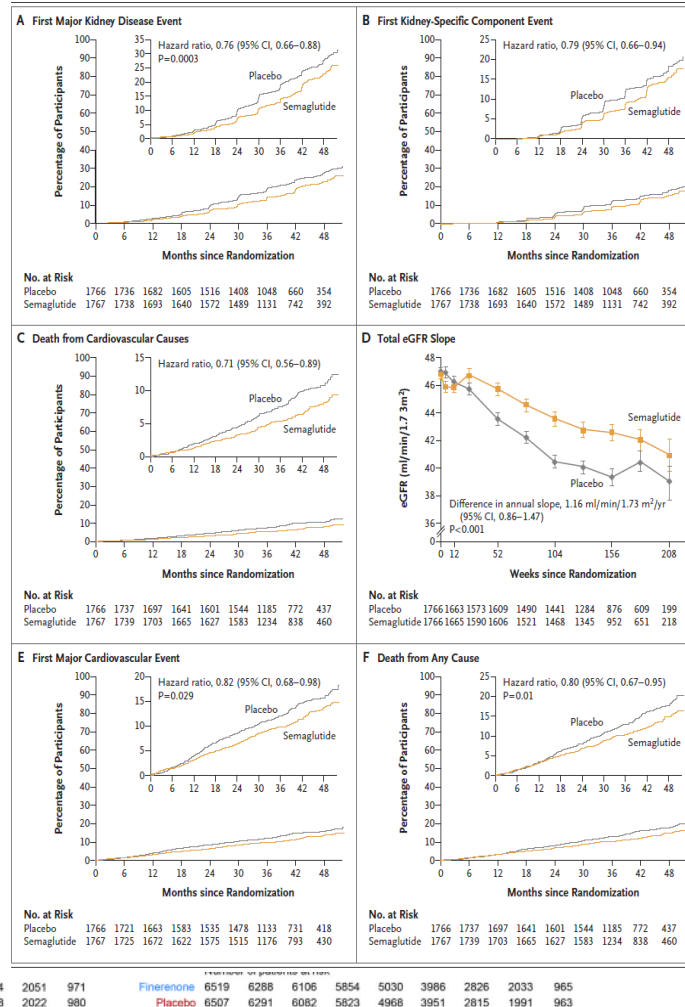
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George L. Bakris

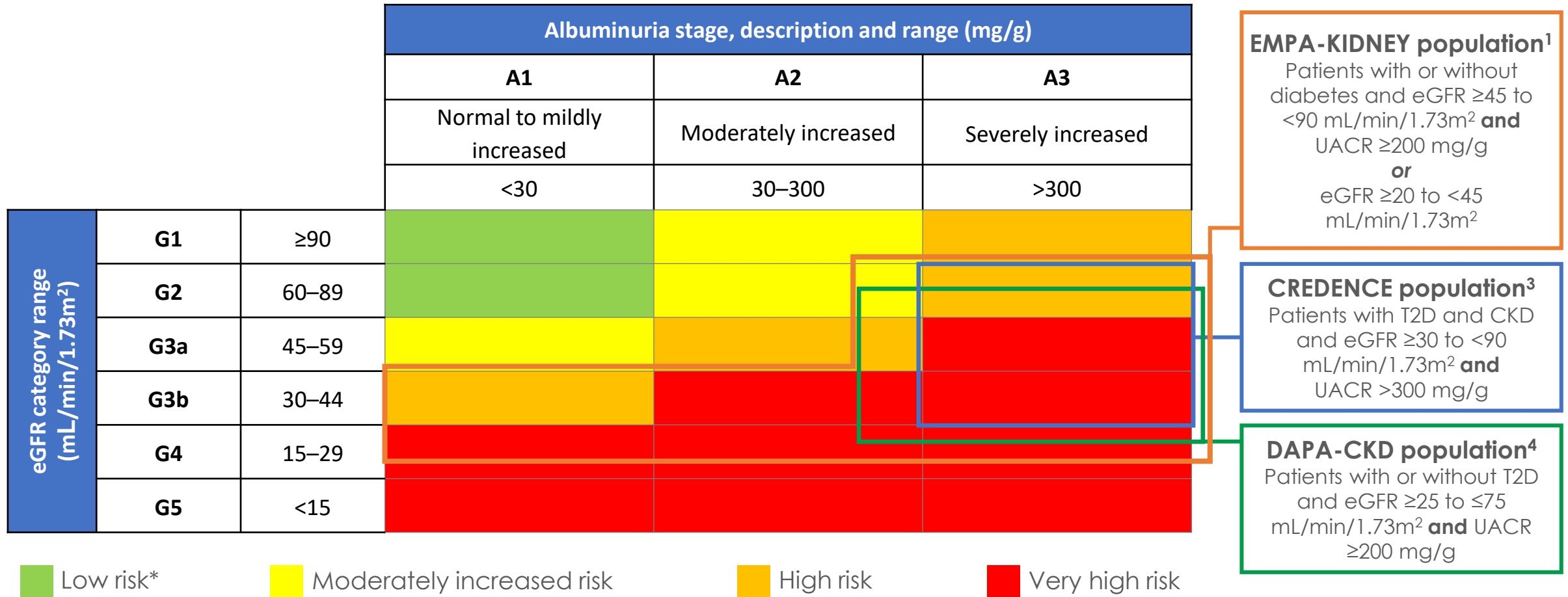
Effects of Semaglutide on Chronic Kidney Disease
in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc.,

N ENGL J MED 391;2 NEJM.ORG JULY 11, 2024

b
HR, 0.84;
P = 0.036d
HR, 0.81;
P = 0.026Number of patient
Finerenone 6519 6291 6116 5876 5064 4012 2844 2051 971
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Finerenone 6519 6291 6116 5876 5064 4012 2844 2051 971
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Finerenone 6519 6291 6116 5876 5064 4012 2844 2051 971
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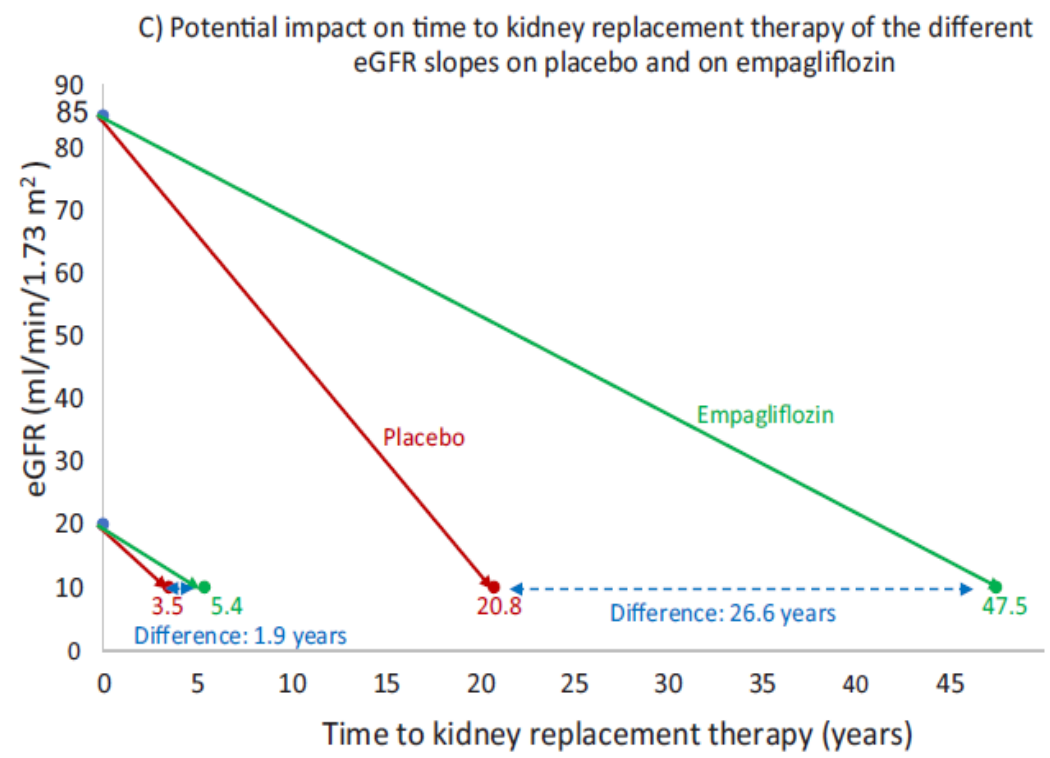
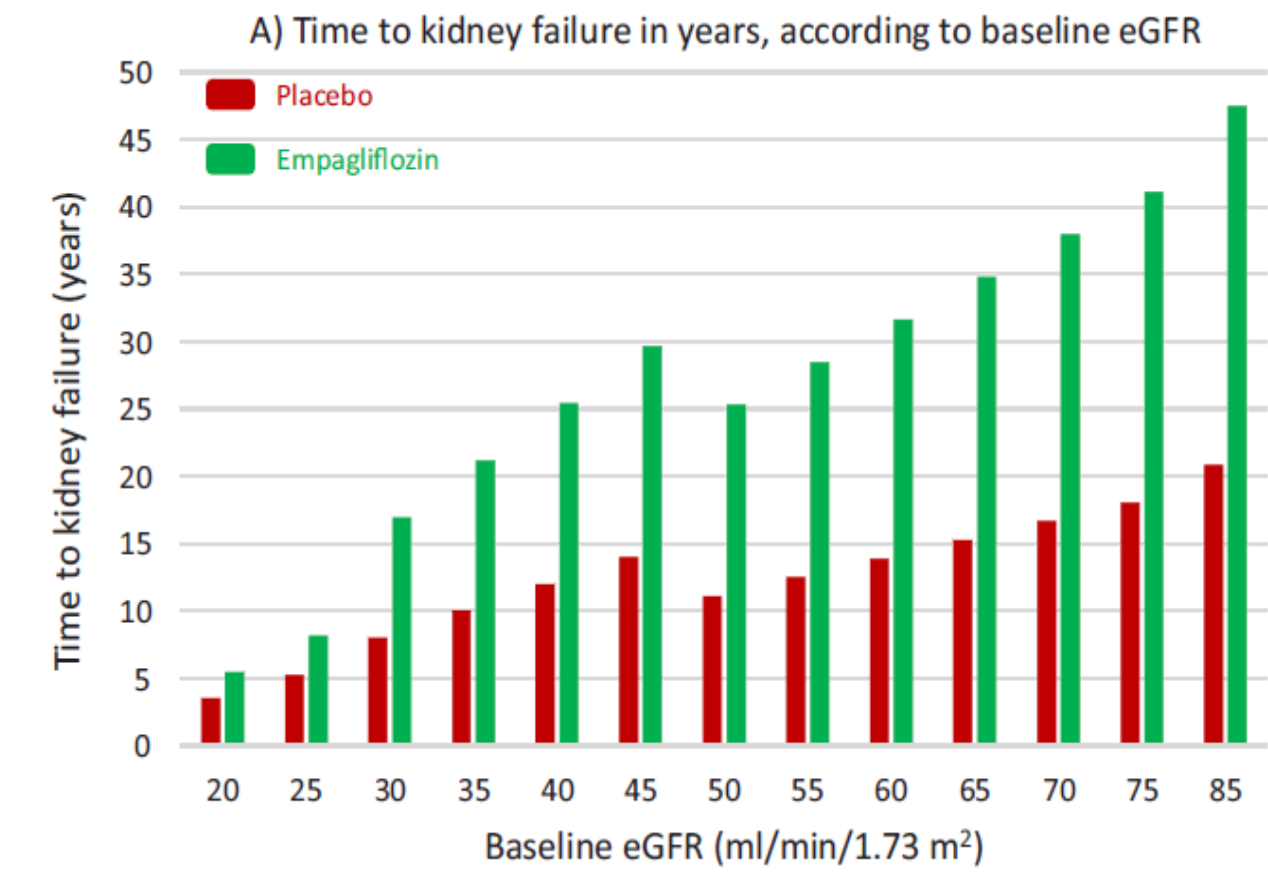
Progressive expansion of the field of therapeutic validation



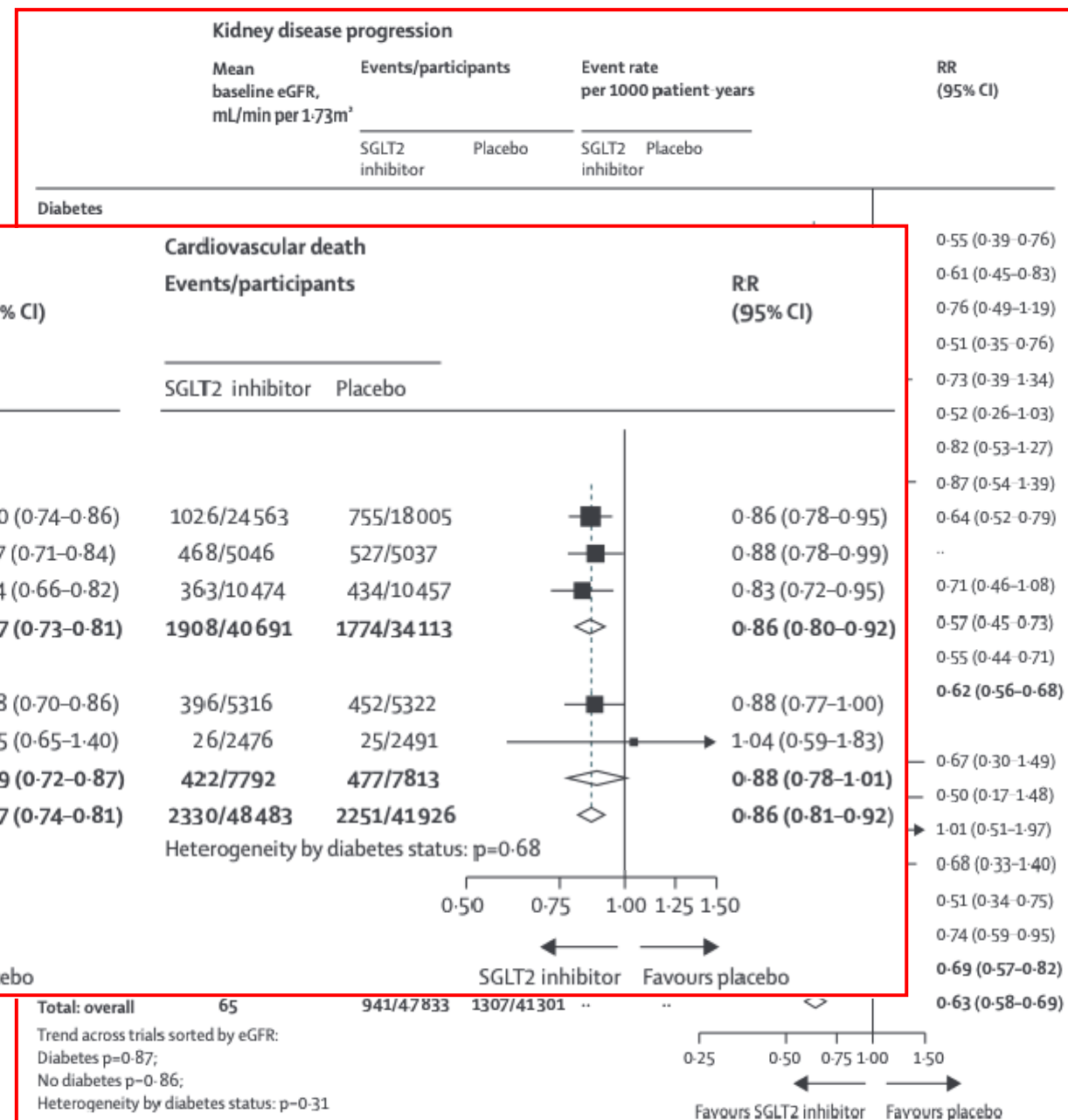
EMPA-KIDNEY: expanding the range of kidney protection by SGLT2 inhibitors

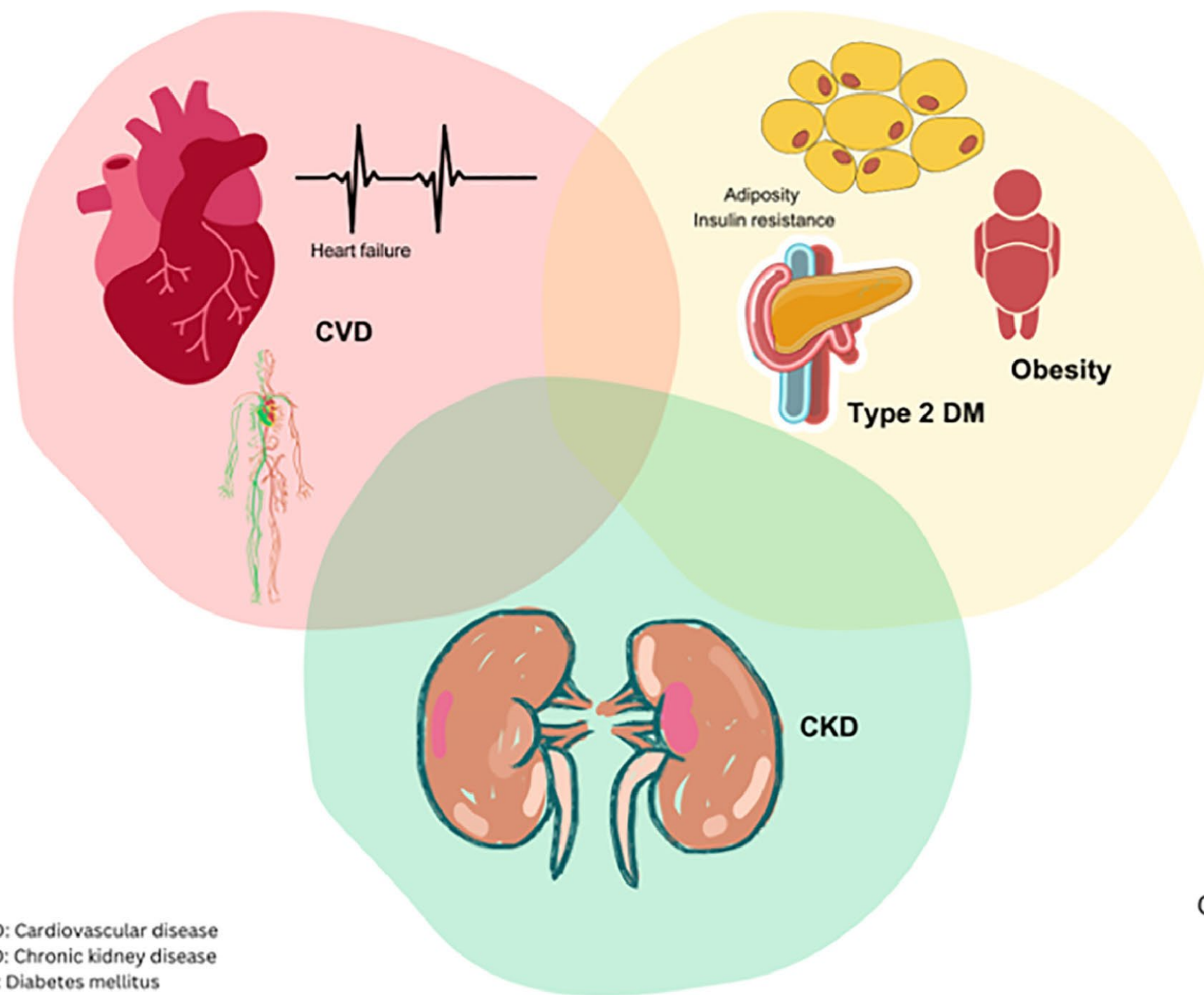
Beatriz Fernández-Fernandez^{1,2,3,4}, Pantelis Sarafidis⁵, Maria José Soler^{2,4,6} and Alberto Ortiz^{1,2,3,4}

Clinical Kidney Journal, 2023, vol. 16, no. 8, 1187–1198



The Nuffield Department of Population Health Renal Studies Group* and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium*





Excess/dysfunctional
adipose tissue

Hypertension
Dyslipidemia
Metabolic syndrome
Diabetes

Myocardial remodeling
Cardiac fibrosis

CVD

Glomerulosclerosis
Tubulointerstitial fibrosis

CKD

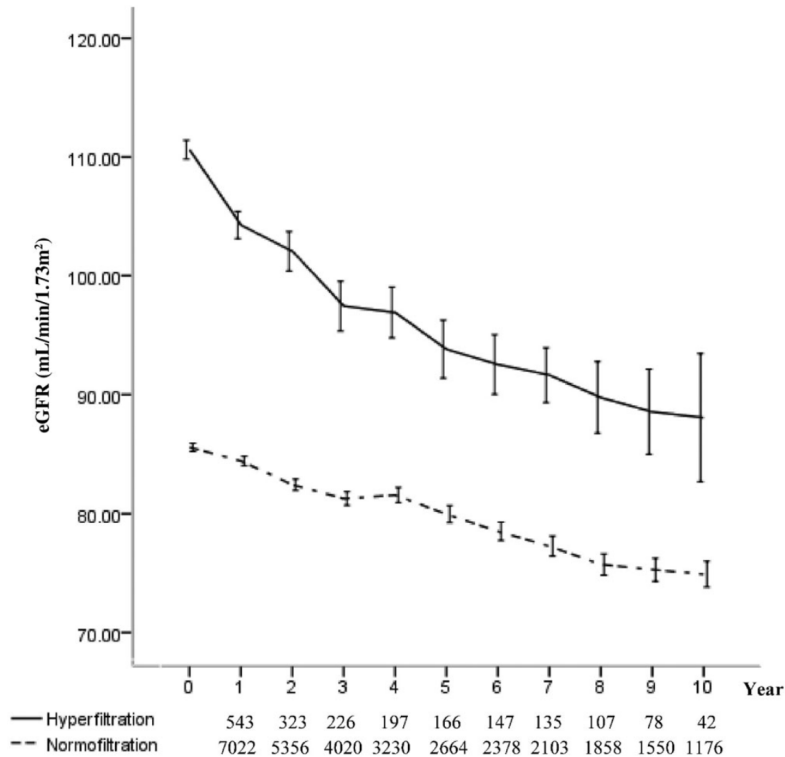
Cardiovascular-Kidney-Metabolic Syndrome

CVD: Cardiovascular disease
CKD: Chronic kidney disease
DM: Diabetes mellitus

HYPERFILTRATION

Age- and gender-adjusted estimated glomerular filtration rate definition reveals hyperfiltration as a risk factor for renal function deterioration in type 2 diabetes

Of the enrolled **7563 T2D patients**, 7.2% had hyperfiltration. Over an average follow-up period of 4.65 ± 3.86 years the hyperfiltration group had a higher prevalence of rapid progression (134/543; 24.7%) compared with the normofiltration group (1101/7020; 15.7%; $P < .001$)



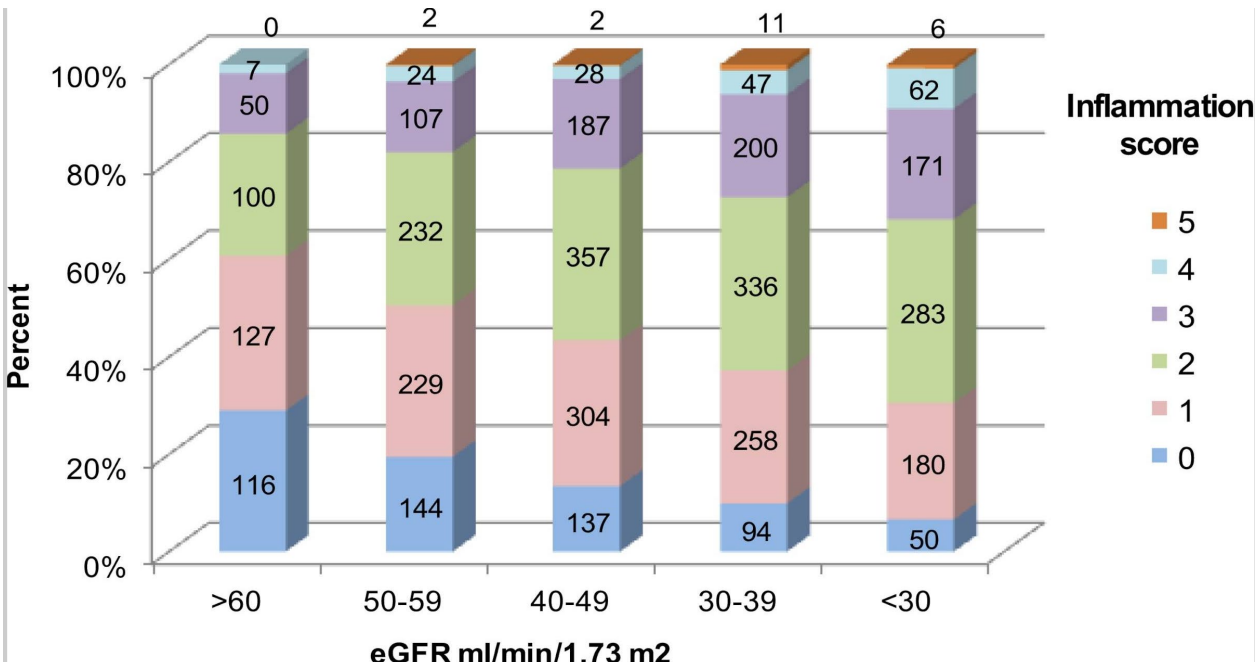
	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (y)	0.98 (0.98-0.99)	< .001	1.02 (1.01-1.02)	< .001
Female gender	0.77 (0.71-0.84)	< .001		
Disease duration	1.002 (1.002-1.003)	< .001	1.001 (1.000-1.002)	.020
Smoking (yes)	6.01 (5.69-6.34)	< .001	1.92 (1.72-2.15)	< .001
CVD (yes)	4.91 (4.67-5.16)	< .001		
BMI (kg/m ²)	1.043 (1.042-1.043)	< .001	1.018 (1.015-1.022)	< .001
sBP (10 mmHg)	1.20 (1.19-1.20)	< .001	1.09 (1.08-1.10)	< .001
dBP (10 mmHg)	1.21 (1.21-1.22)	< .001	1.10 (1.08-1.12)	< .001
TG (50 mg/dL)	1.08 (1.07-1.08)	< .001	1.04 (1.02-1.05)	< .001
HDL-C (mg/dL)	0.99 (0.99-1.00)	< .001		
LDL-C (mg/dL)	1.016 (1.016-1.017)	< .001	1.008 (1.006-1.009)	< .001
HbA1c (%)	1.104 (1.101-1.107)	< .001	1.04 (1.04-1.05)	< .001
	A1 (ACR < 30 mg/g)	A2 (ACR 30 ~ 300 mg/g)	A3 (ACR > 300 mg/g)	
Hyperfiltration	1.76 (1.43-2.16)*	2.56 (1.94-3.39)*	3.11 (1.71-5.65)*	
Normofiltration	Reference	1.56 (1.40-1.74)*	2.70 (2.31-3.14)*	

INFLAMMATION

Association between Albuminuria, Kidney Function, and Inflammatory Biomarker Profile in CKD in CRIC

Jayanta Gupta,* Nandita Mitra,* Peter A. Kanetsky,* Joe Devaney,† Maria R. Wing,† Muredach Reilly,* Vallabh O. Shah,‡
Vaidyanathapura S. Balakrishnan,§ Nicolas J. Guzman,† Matthias Girndt,|| Brian G. Periera,§ Harold I. Feldman,*
John W. Kusek,¶ Marshall M. Joffe,* Dominic S. Raj,¶† and for the CRIC Study Investigators

The CRIC study is a prospective observational cohort study of 3939 participants with established CKD. The organization, design, and methods of the CRIC study have been previously reported (15).



“An inverse association between the **inflammation score** and **eGFR** was seen ($P<0.001$). Biomarkers of inflammation were inversely associated with measures of kidney function and positively with albuminuria”

This study measured the plasma levels of IL-1 β , IL-1 receptor antagonist (IL-1RA), IL-6, TNF- α , TGF- β , high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and serum albumin in 3939 participants enrolled in the Chronic Renal Insufficiency Cohort study between June 2003 and September 2008.

Molecular mechanisms and therapeutic targets for diabetic kidney disease

Kidney International (2022) 102, 248–260; <https://doi.org/10.1016/j.kint.2022.05.012>

Katherine R. Tuttle^{1,2}, Rajiv Agarwal^{3,4}, Charles E. Alpers⁵, George L. Bakris⁶, Frank C. Brosius^{7,8,9}, Peter Kolkhof¹⁰ and Jaime Uribarri¹¹

Table 1 | Targeted interventions for inflammation and fibrosis to treat diabetic kidney disease

Intervention	Diabetic populations	Therapeutic targets	Proposed mechanisms	Clinical outcomes
Therapies with regulatory approval				
SGLT2 inhibition ^{11-13,15-17,30,31,81-84} <i>Canagliflozin</i> <i>Dapagliflozin</i> <i>Empagliflozin</i>	DKD or CVD	Block reabsorption of glucose in the proximal tubule	- Restore tubuloglomerular feedback and reduce <u>glomerular hyperfiltration</u> <u>Decrease oxidative stress</u> and AGE formation in proximal tubular cells <u>Natriuresis</u> <u>Decrease blood levels of IL-6, CRP, TNFR1, MMP7, and fibronectin-1</u>	- Reduce risks of substantial eGFR decline, kidney failure, heart failure as well as death from kidney and CV causes - Glycemic efficacy lost at low eGFR
Nonsteroidal mineralocorticoid receptor antagonists ^{85,86,97} <i>Finerenone</i>	DKD	- Downregulate proinflammatory and profibrotic pathways in non-epithelial cells - Downregulate ion channels for sodium and potassium in kidney tubular epithelial cells	<u>Decrease kidney inflammation and fibrosis</u> - Decrease in the number of <u>macrophages with proinflammatory phenotype in the kidney</u>	Reduce risks of substantial eGFR decline, kidney failure, heart failure, atherosclerotic CV events as well as death from kidney and CV causes
GLP-1R agonists ^{32,87-89} <i>Liraglutide</i> <i>Semaglutide</i> <i>Dulaglutide</i> <i>Efpeglenatide</i>	DKD or high CV risk	Downregulate proinflammatory pathways	<u>Decrease kidney expression of TGF-β1, ICAM-1, TNF-α, and IL-1β</u> <u>Decrease macrophage infiltration of the kidney</u> - Increase cellular cAMP and inhibit NADPH oxidase	- Reduce risks of atherosclerotic CV events and deaths, albuminuria, rate of eGFR decline - Glycemic efficacy preserved at low eGFR - Weight loss

Association of Albuminuria With Chronic Kidney Disease Progression in Persons With Chronic Kidney Disease and Normoalbuminuria

A Cohort Study

Ashish Verma, MB, BS; Insa M. Schmidt, MD, MPH; Sophie Claudel, MD; Ragnar Palsson, MD; Sushrut S. Waikar, MD, MPH; and Anand Srivastava, MD, MPH

Study Population

The CRIC study is a multicenter, prospective, observational cohort study designed to investigate the risk factors for death, cardiovascular disease, and CKD progression in persons with mild to severe CKD (20). The CRIC study enrolled 3939 men and women aged 21 to 74 years between June 2003 and September 2008 across 7 clinical centers in the United States. Persons were included if they met age-defined criteria for eGFR of 20 to 70 mL/min/1.73 m² (21, 22). Exclusion

Table. Baseline Characteristics of CRIC Study Participants, by Categories of UACR

Characteristic	Overall	Category 1: UACR 0 to <5 mg/g	Category 2: UACR 5 to 15 mg/g	Category 3: UACR ≥15 mg/g
Participants, n	1629	570	677	382
Median UACR (IQR), mg/g	6.9 (4.0-14.2)	3.4 (2.7-4.1)	7.9 (6.3-10.8)	20.3 (17.3-24.6)
Mean age (SD), y	60.2 (9.6)	58.8 (10.1)	60.9 (9.3)	61.2 (9.4)
Female, n (%)	847 (52.0)	269 (47.2)	397 (58.6)	181 (47.4)
Race, n (%)				
White	884 (54.3)	324 (56.8)	372 (54.9)	188 (49.2)
Black	619 (38.0)	211 (37.0)	246 (36.3)	162 (42.4)
Other	126 (7.7)	35 (6.1)	59 (8.7)	32 (8.4)
Current smoker, n (%)	166 (10.2)	50 (8.8)	68 (10.0)	48 (12.6)
Mean BMI (SD), kg/m ²	32.0 (7.8)	32.2 (7.6)	31.5 (7.7)	32.5 (8.3)
Cardiovascular disease, n (%)	460 (28.2)	139 (24.4)	193 (28.5)	128 (33.5)
Diabetes, %	568 (34.9)	162 (28.4)	232 (34.3)	174 (45.5)
ACEi/ARB, %	1030 (63.5)	344 (60.8)	416 (61.6)	270 (70.9)
Hypertension, %	1310 (80.4)	430 (75.4)	537 (79.3)	343 (89.8)
Mean systolic blood pressure (SD), mm Hg	120.7 (18.1)	118.2 (16.1)	120.4 (18.8)	124.9 (18.9)
Peripheral vascular disease, n (%)	61 (3.7)	14 (2.5)	22 (3.2)	25 (6.5)
Mean eGFR (SD), mL/min/1.73 m ²	49.6 (14.7)	52.3 (14.5)	49.7 (14.6)	45.4 (14.2)
Mean serum albumin (SD), g/L	40 (3)	41.2 (4)	40.9 (4)	40.6 (4)
Mean hemoglobin A _{1c} (SD), %	6.2 (1.1)	6.1 (1.1)	6.2 (1.2)	6.4 (1.2)
Mean hemoglobin (SD), g/L	129 (16)	132 (16)	129 (16)	126 (17)
Median high-sensitivity C-reactive protein (IQR), %, mg/L	2.3 (1.0-5.9)	2.0 (0.9-5.9)	2.4 (1.0-5.8)	2.5 (1.1-6.4)
Aldosterone antagonist, n (%)	86 (5.3)	36 (6.4)	33 (4.9)	17 (4.5)

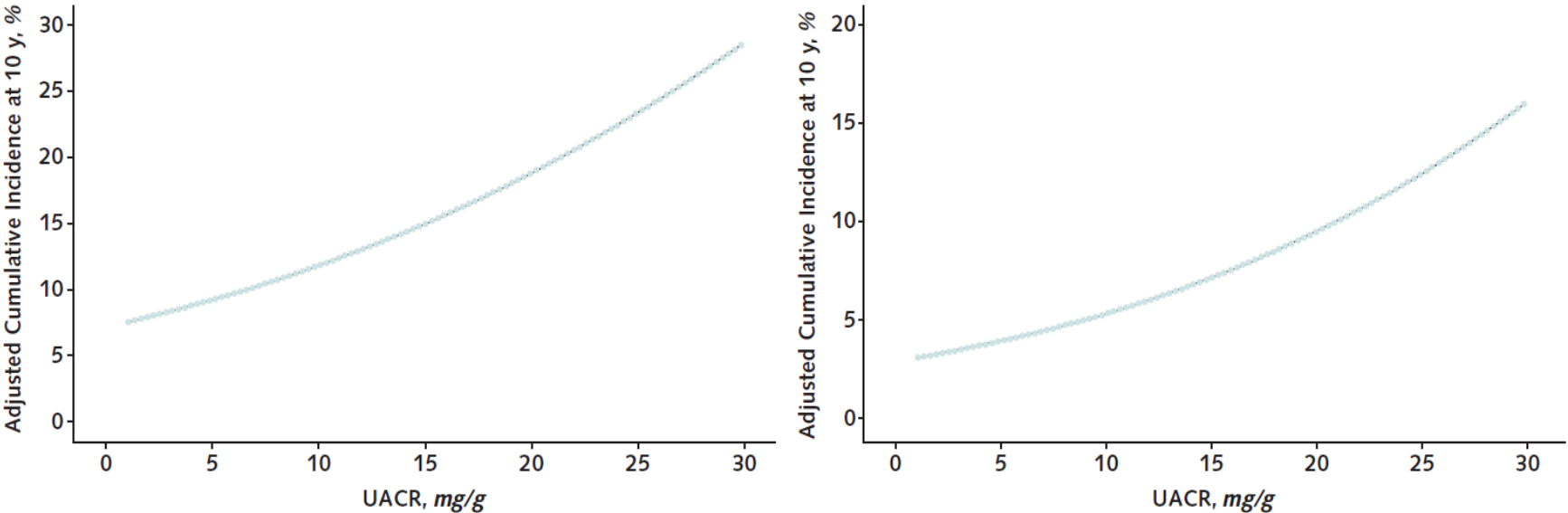
Figure 2. The 10-year adjusted cumulative incidence for CKD progression (left) and kidney failure (right), by baseline levels of UACR.

UACR

0 to <5 mg/g

5 to <15 mg/g

15 to <30 mg/g

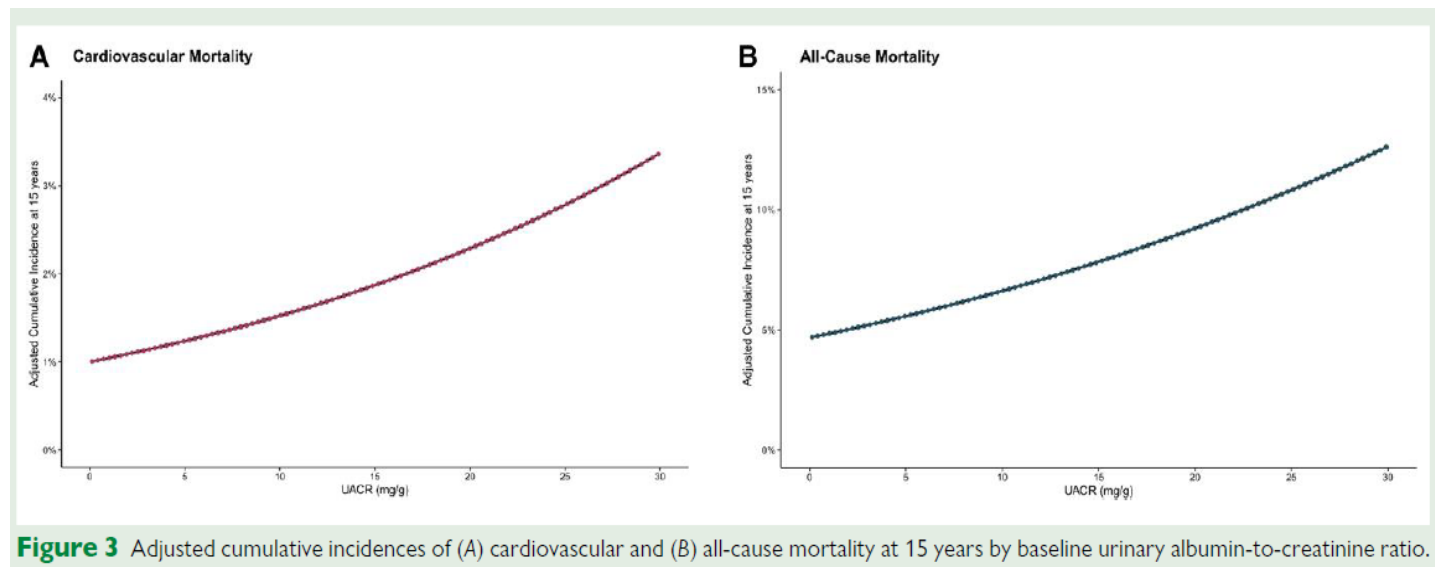
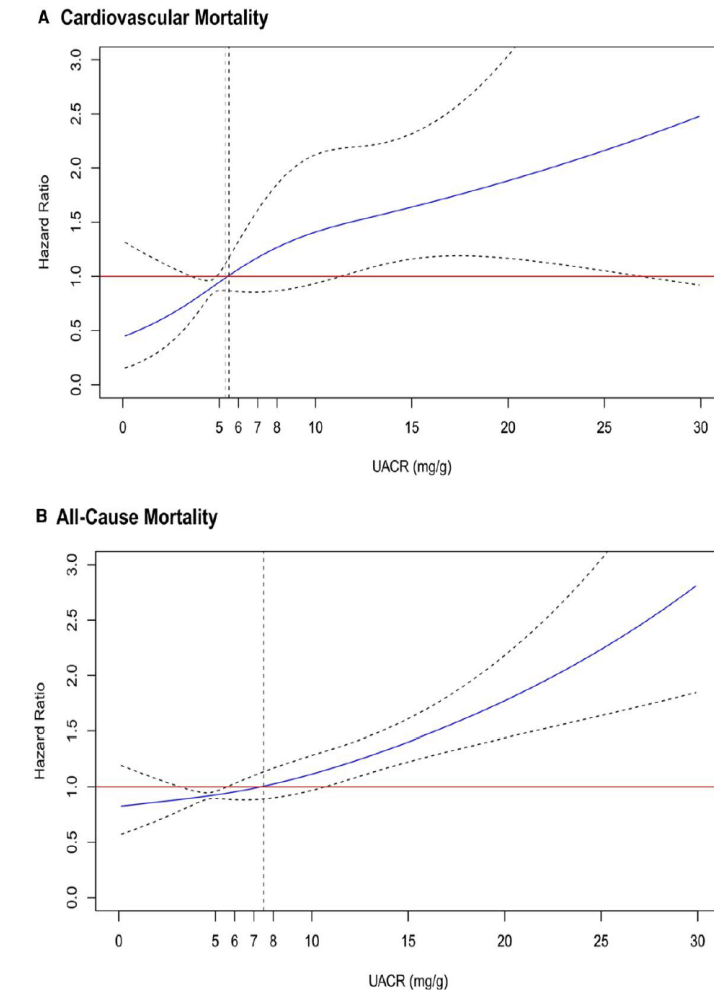


The relationship between low levels of albuminuria and mortality among adults without major cardiovascular risk factors

European Journal of Preventive Cardiology (2024) **00**, 1–10
<https://doi.org/10.1093/eurjpc/zwae189>

Sophie E. Claudel ^{1,2}, Sushrut S. Waikar ^{2,3}, Insa M. Schmidt ^{3,4},
Ramachandran S. Vasan ^{2,5}, and Ashish Verma ^{2,3*}

The association between UACR and cardiovascular mortality was investigated among 12 835 participants in the 1999–2014 National Health and Nutrition Examination Survey using Cox proportional hazard models and confounder-adjusted survival curves. We excluded participants with baseline cardiovascular disease, hypertension, diabetes, pre-diabetes, an estimated glomerular filtration rate <60 mL/min/1.73 m², currently pregnant, and those who received dialysis last year. Over a median



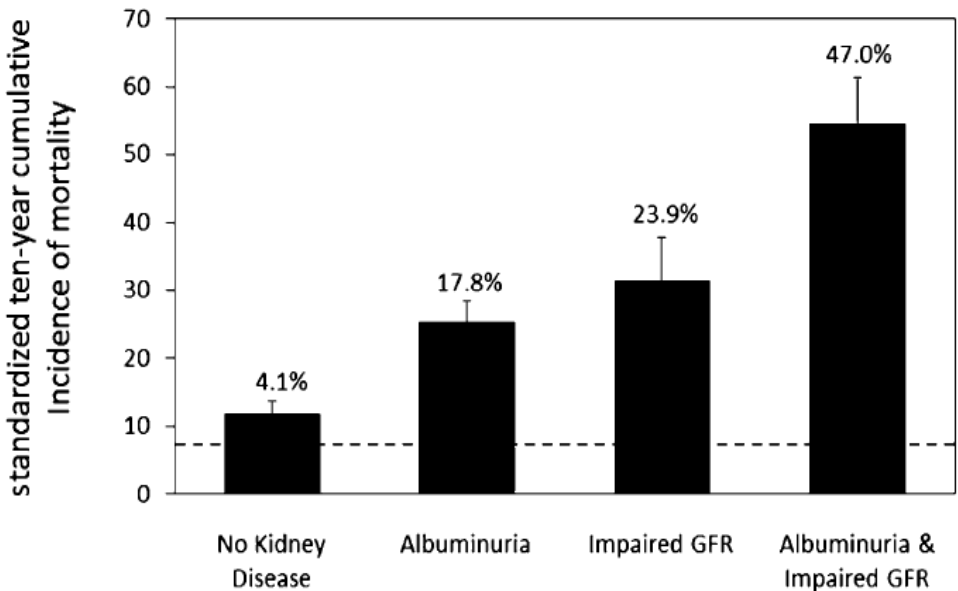
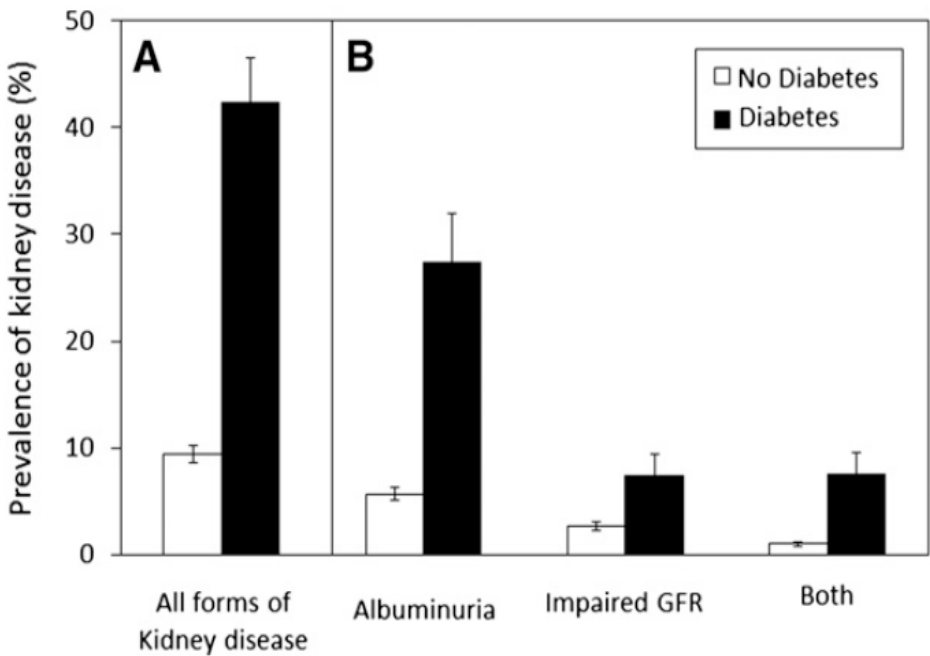
Adults with elevated levels of albuminuria within the low range (UACR <30 mg/g) and no major cardiovascular risk factors had elevated risks of cardiovascular and all-cause mortality. The risk increased linearly with higher albuminuria levels. This emphasizes a risk gradient across all albuminuria levels, even within the supposedly normal range, adding to the existing evidence.

Kidney Disease and Increased Mortality Risk in Type 2 Diabetes

Maryam Afkarian,* Michael C. Sachs,* Bryan Kestenbaum,* Irl B. Hirsch,[†] Katherine R. Tuttle,*[‡] Jonathan Himmelfarb,* and Ian H. de Boer*

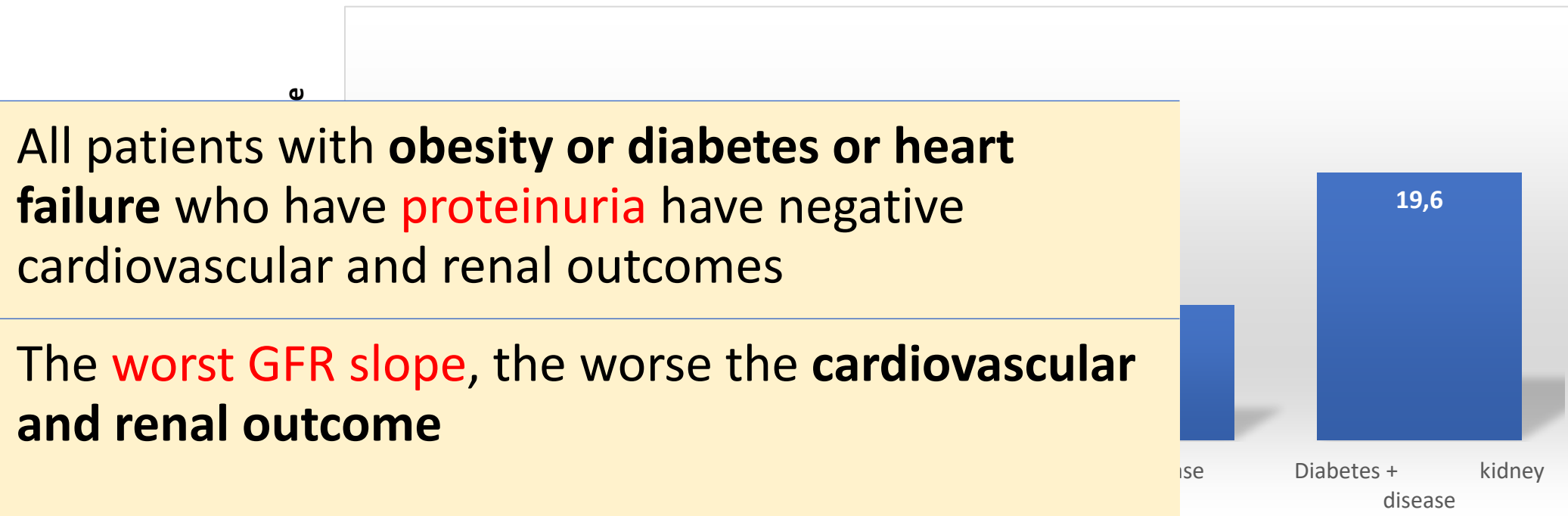
Table 1. Baseline characteristics of participants

Variable	No Diabetes				Diabetes			
	No Kidney Disease		Kidney Disease		No Kidney Disease		Kidney Disease	
	n	Weighted Proportion or Mean (SEM)	n	Weighted Proportion or Mean (SEM)	n	Weighted Proportion or Mean (SEM)	n	Weighted Proportion or Mean (SEM)
Age (yr)	11,742 ^a	90.6(0.4)	1874	9.4 (0.4)	772	57.7 (2.1)	658	42.3 (2.1)
Female	6203	42 (15.0)	1026	57 (20)	365	56 (13.4)	370	62 (14.0)
Race								
White, not Hispanic	5081	51.5 (0.5)	664	59.9 (2.5)	280	41.2 (2.6)	198	57.4 (3.5)
Black, not Hispanic	3191	77 (1.3)	419	72.7 (1.9)	278	66.4 (3.2)	174	69.1 (3.1)
Mexican American	3401	10 (0.6)	300	14.4 (1.2)	259	17.8 (1.7)	191	16.9 (2.1)
Current smoker	3262	5.3 (0.4)	386	4.5 (0.5)	155	7.2 (0.9)	107	6.8 (0.8)
Body mass index (kg/m ²)		29.9 (0.9)		23.8 (1.9)		20 (2.1)		20.6 (3.2)
eGFR (ml/min per 1.73 m ²) ^b		26.2 (5.4)		26.9 (5.8)		30.5 (6.7)		31.1 (6.5)
Albumin/creatinine ratio (mg/g)		102.1 (17.7)		78.5 (28.5)		92.9 (17.8)		75.6 (26.7)
Lipids		7 (5.2)		128 (369.5)		10 (7.4)		317 (873.0)
Non-HDL cholesterol (mg/dl)		150 (42.8)		164.8 (47.2)		170.4 (45.6)		186.4 (52.9)
Lipid-lowering agents (%) ^c	169	1.6 (0.2)	72	4.8 (1)	40	9.3 (1.7)	34	8.4 (1.8)
BP (mmHg)								
Systolic		120 (15.4)		135 (23.1)		132 (16.8)		140 (20.8)
Diastolic		74 (9.66)		77 (11.97)		76 (9.78)		77 (10.56)
Antihypertensive agents (%) ^c	1442	10.3 (0.5)	818	38.5 (1.6)	265	34.7 (3)	397	59.2 (3.9)
HbA1C (%)						7.9 (1.7)		8.3 (2.1)
Glucose-lowering agents (%) ^c								
None					396	47.9 (2.8)	253	38.7 (3)
Oral agents only					266	34.1 (2.4)	226	37 (2.9)
Insulin ± oral agents					110	18 (2.8)	179	24.3 (2.8)
Duration of diabetes (yr) ^d								
Previously undiagnosed					313	37.1 (2.4)	173	30.9 (3.1)
0–4.9					180	27.4 (3)	134	26.4 (2.9)
5–9.9					99	16.8 (2.9)	86	13.6 (2.2)
10–19.9					112	13.4 (1.8)	140	17.7 (2.6)
≥20					51	5.3 (1.1)	108	11.4 (1.8)



Kidney disease approximately triples the risk of CV mortality in patients with CKD and T2D compared to patients with CKD alone

10-year standardised CV mortality (%)



All patients with **obesity or diabetes or heart failure** who have **proteinuria** have negative cardiovascular and renal outcomes

The **worst GFR slope**, the worse the **cardiovascular and renal outcome**

The association of **reduced GFR and albuminuria** represents the **most negative sign** in obese, diabetic, heart failure and renal failure patients

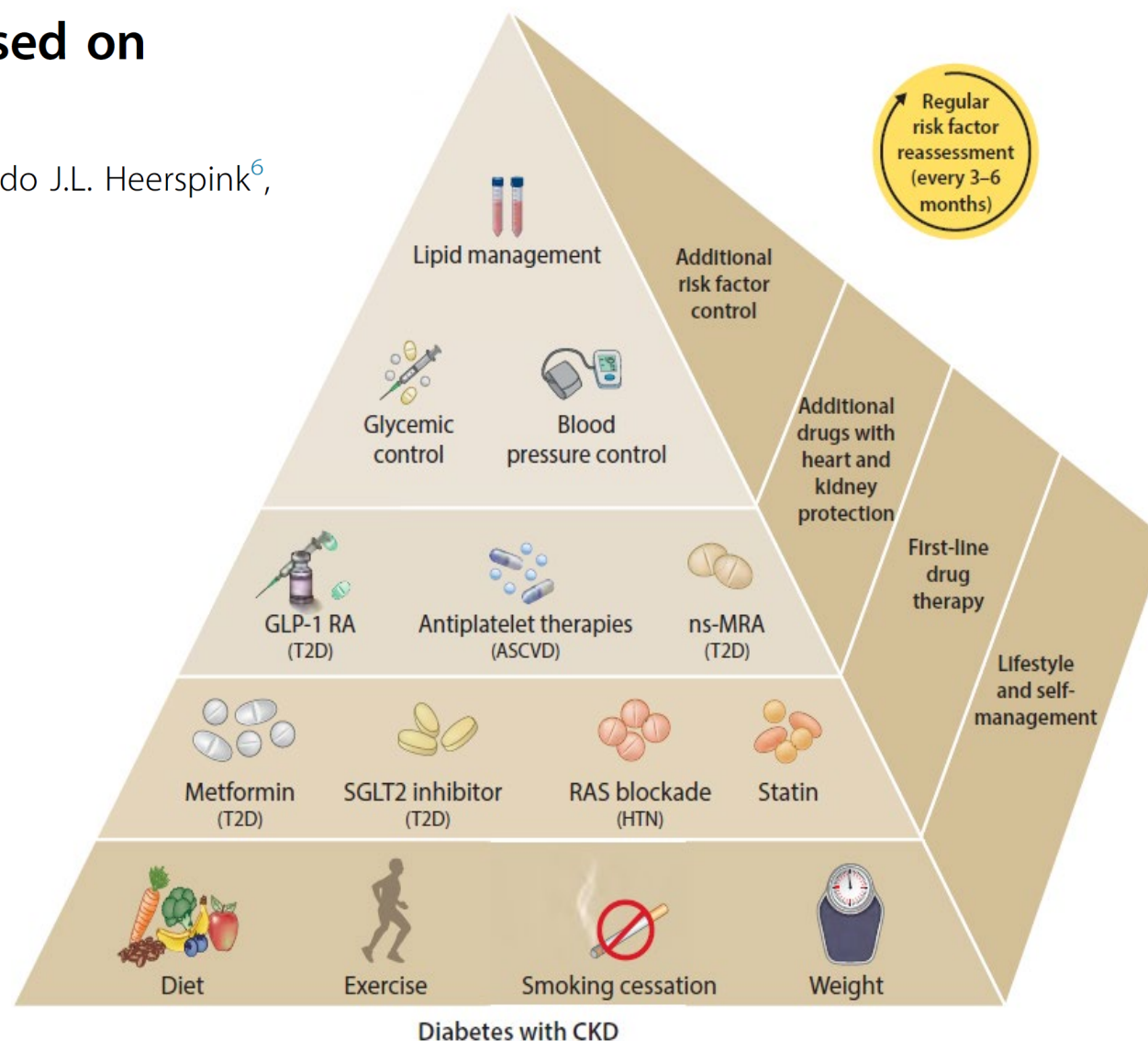
CVD among patients with diabetes (albuminuria, impaired eGFR, or both).¹

Health and
disease;
eGFR,

Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence

Peter Rossing^{1,2}, M. Luiza Caramori³, Juliana C.N. Chan^{4,5}, Hiddo J.L. Heerspink⁶,

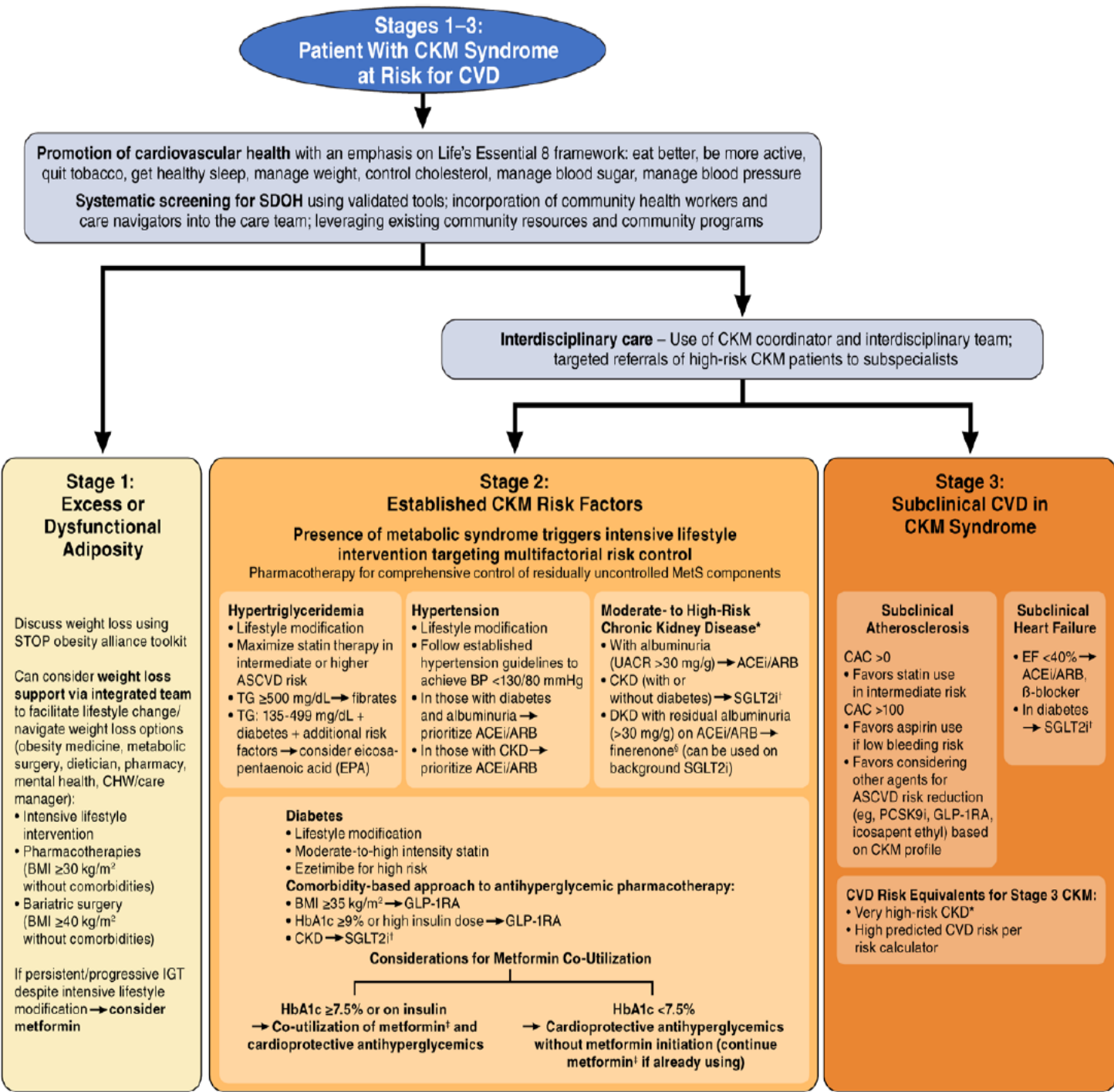
Kidney International (2022) **102**, 990–999



Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association

Circulation. 2023;148:1606–1635. DOI: 10.1161/CIR.0000000000001184

This presidential advisory provides guidance on the **definition, staging, prediction paradigms, and holistic approaches to care for patients with cardiovascular-kidney-metabolic syndrome** and details a multicomponent vision for effectively and equitably enhancing cardiovascular-kidney-metabolic health in the population.



Current Perspectives in Kidney Disease

Editors

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