CAN CKD BE PREVENTED OR REVERSED ?

Christoph Wanner
Würzburg and Oxford, Germany and UK

CAN CKD BE PREVENTED OR REVERSED ?

Yes - maintaining kidney function
Yes - restoring kidney function

Todays nomenclature: conceptionally different - definition of (primary) prevention vs secondary prevention (halting progression).

The new lexicon

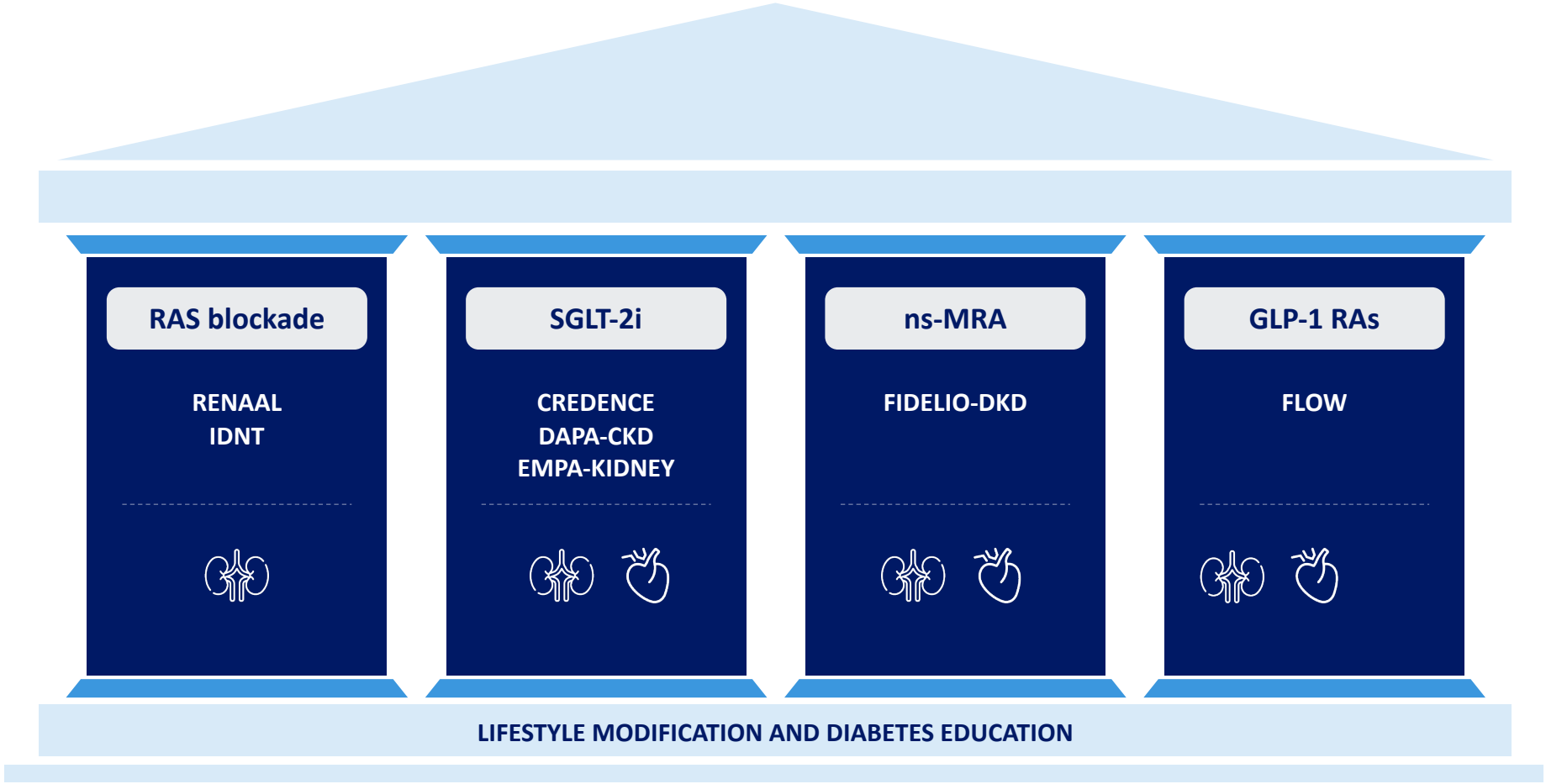
Considerations while preparing the presentation

Nephrology: The main focus today is/was retarding the progression of a diagnosed/ established disease and the treatment of kidney failure with replacement therapy

There was, so far, no focus on preservation or salvage of Kidney Health (among Nephrologists, GPs, Internists, Endocrinologists and Cardiologists). Excuse: no or little research data on early prevention is available

Guidelines (KDIGO, ADA) focus on individuals with an eGFR less than 60 ml/min/1.73m^2 or with albuminuria categories A2 or A3 (established disease, secondary prevention)

4 Foundational Therapies for Kidney Outcomes: approaches to reduce the Cardio-Renal Risk in individuals with ……



Modified figure from: 2023 ADA, Standards of Medical Care in Diabetes-2023: Diabetes Care, 2022;46:Supplement 1; Agarwal R et al, NDT 2023;38:253-257

Maintaining or **Restoring** Kidney Health

Albuminuria

KDIGO CKD-Guideline
Kidney Int Suppl.
2013;3:1-150
2024 in press

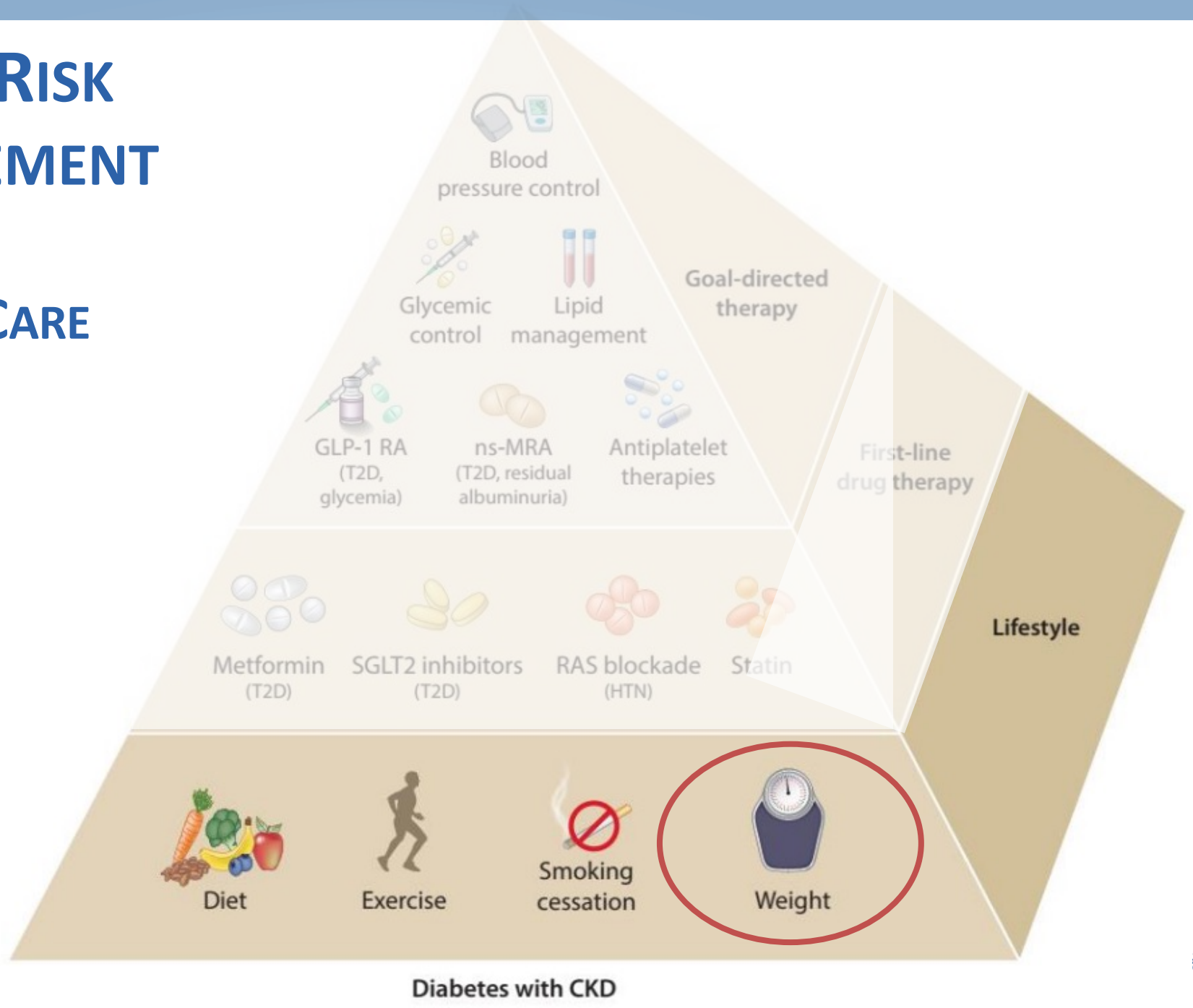
GFR categories, description and range (ml/min/1.73 m²)				Albuminuria stages, description and range (mg/g)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30	30–300	>300
	G1	Normal or high	≥90			
	G2	Mild decrease	60–89			
	G3a	Mild–moderate decrease	45–59			
	G3b	Moderate–severe decrease	30–44			
	G4	Severe decrease	15–29			
	G5	Kidney failure	<15			

GFR

JAMA 2023;330: 1266-1277

KIDNEY-HEART RISK FACTOR MANAGEMENT

COMPREHENSIVE CARE



PRACTICE POINT 1.1.1.

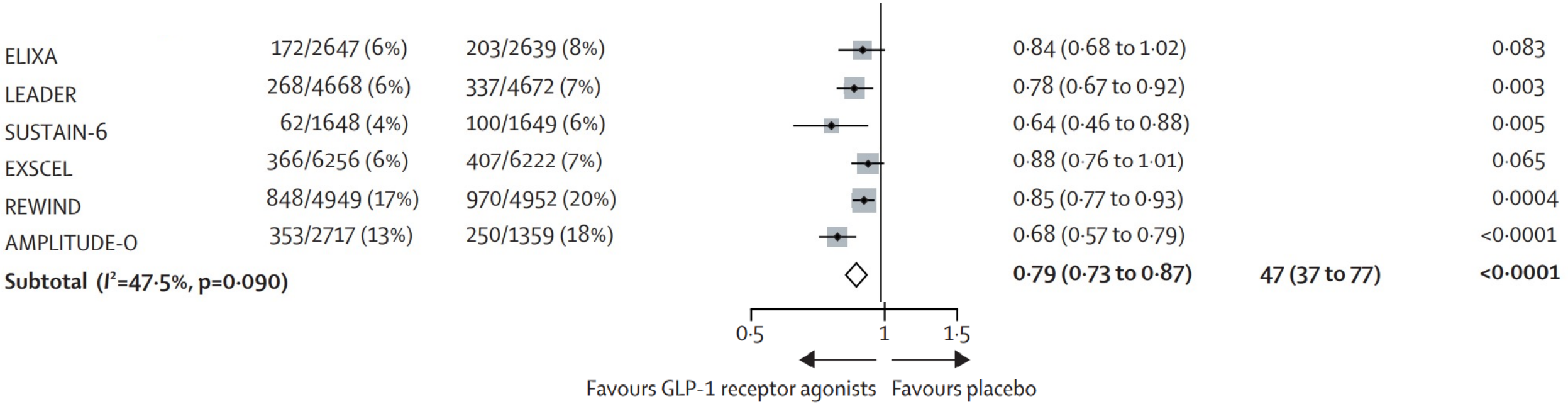
Kidney Int 2020;98:849-859

Kidney Int 2022;102:990-999

GLP-1RA have the potential to maintain Kidney Health

worsening kidney function: 40% or 57% eGFR, ESKD, renal death

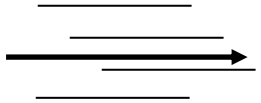
Composite including albuminuria



Sattar N et al, Lancet Diabetes Endocrinol 2021;9:653-662

Episodes 1-4, NEJM 2023

Speed: moderately accelerated



3 month additional loss of lifespan per 1 year due to T2DM alone

eGFR	90		60	

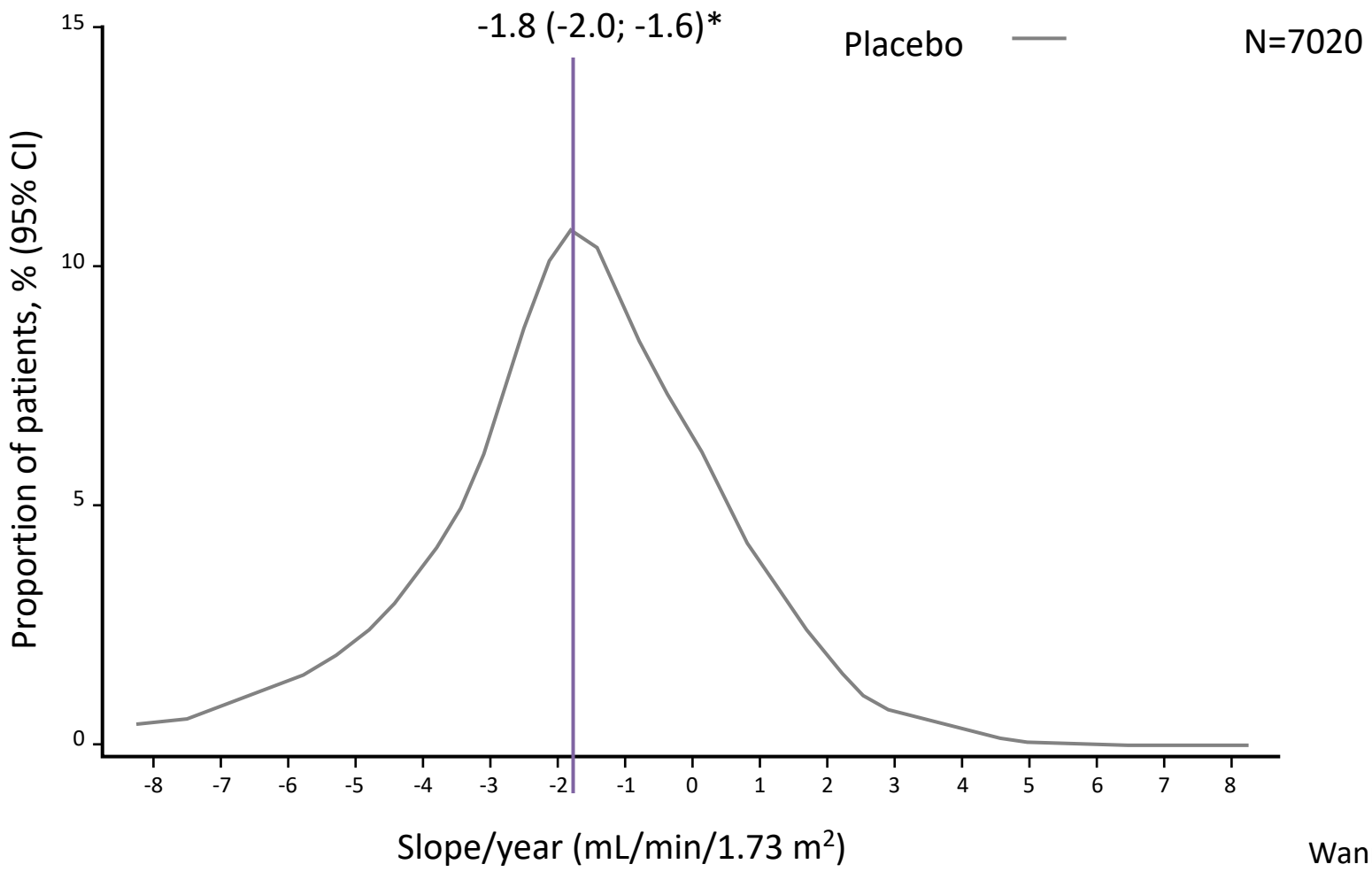
No need to have UACR measured

The Emerging Risk Factors Collaboration, JAMA 2015;314:52

Lifetime

End of life

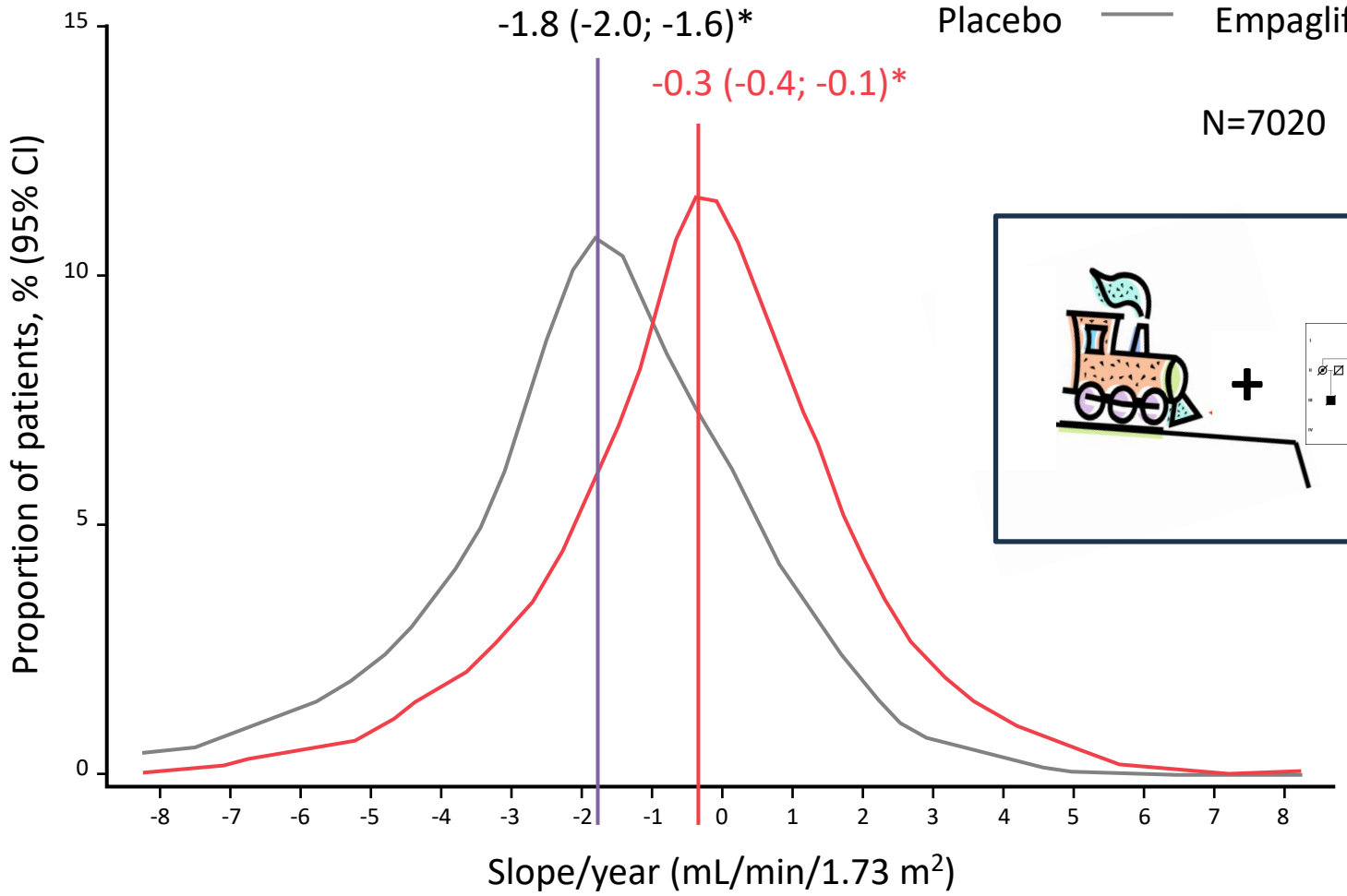
EMPAREG-OUTCOME: Distribution of individual eGFR slopes in the total cohort (baseline to follow-up)

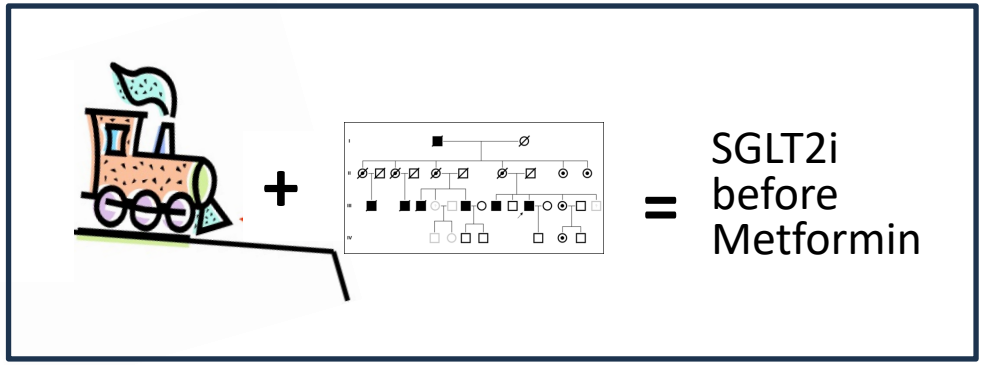


*Adjusted mean (95% CI).

Wanner et al
JASN 2018;29:2755-2769
NEJM 2016;375:323-334

EMPAREG-OUTCOME: Distribution of individual eGFR slopes in the total cohort (baseline to follow-up)





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J Diabetes Complications 2023 Nov;37(11):108628. doi: 10.1016

Contents lists available at ScienceDirect

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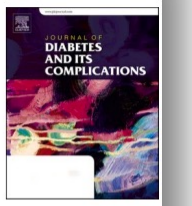
journal homepage: www.elsevier.com/locate/jdiacomp



Check for updates

Shifts in KDIGO CKD risk groups with empagliflozin: Kidney-protection from SGLT2 inhibition across the spectrum of risk

Robert Weingold [a], Bernard Zinman [b], Michaela Mattheus [c], Anne Pernille Ofstad [d,e], Dominik Steubl [c,f], Christoph Wanner [g], Silvio E. Inzucchi [a,*]

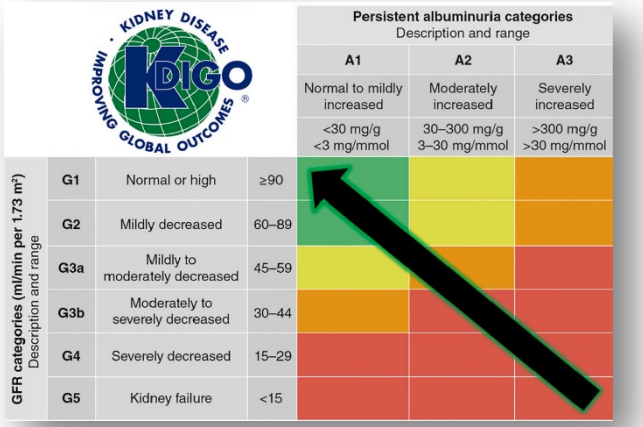


Table 1

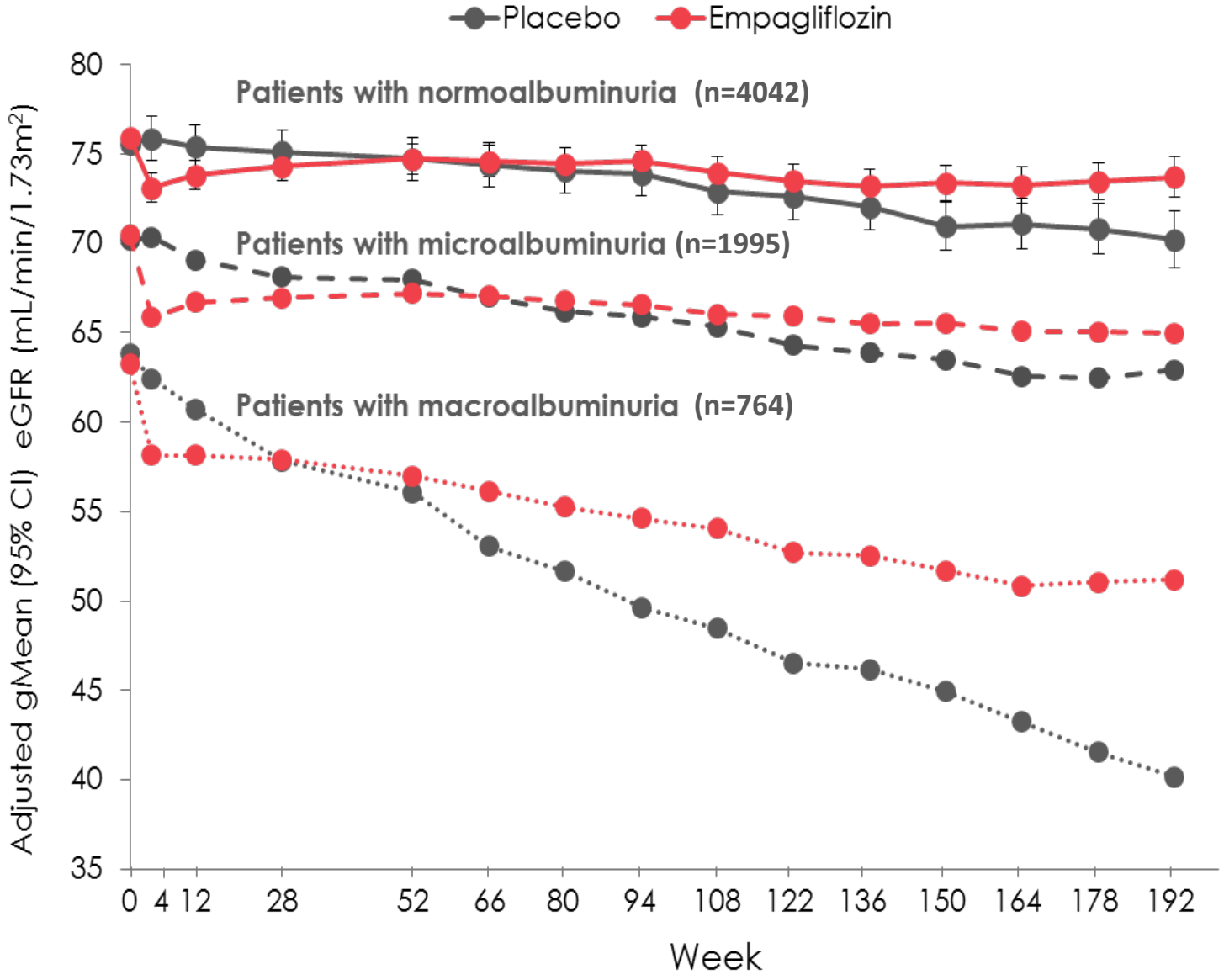
Proportions of patients who experienced change in UACR and/or eGFR category among all patients who experienced the corresponding change (i.e., worsening or improvement) in KDIGO risk category.

	Reason for risk change		
Worsening in KDIGO risk category	↑UACR	↓eGFR	↑UACR + ↓eGFR
Placebo (N = 661)	47.5 %	39.6 %	12.9 %
Empagliflozin (N = 1017)	44.2 %	42.0 %	13.8 %
Improvement in KDIGO risk category	↓UACR	↑eGFR	↓UACR + ↑eGFR
Placebo (N = 208)	58.2 %	33.2 %	8.7 %
Empagliflozin (N = 576)	63.7 %	29.9 %	6.4 %

2:1

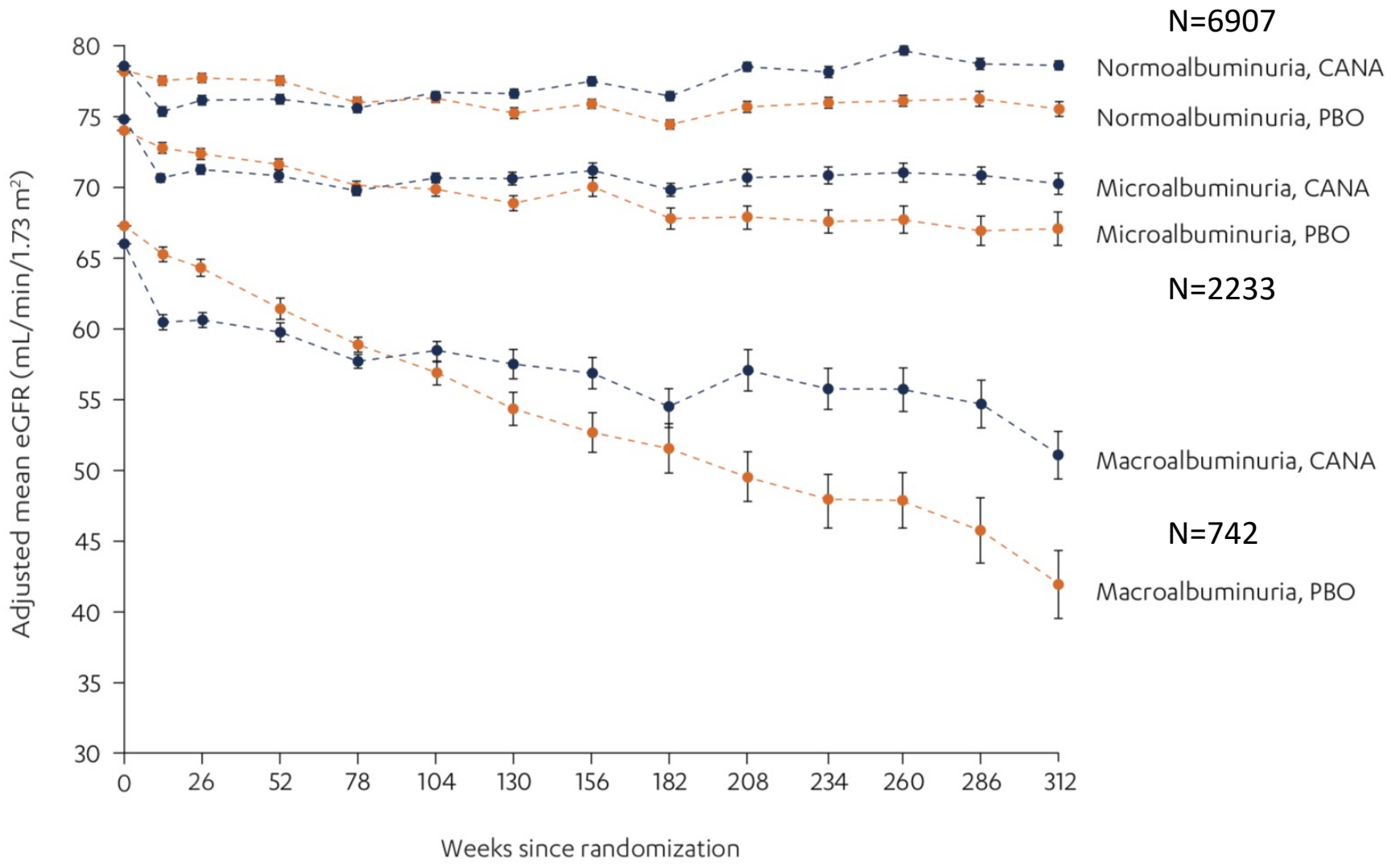
EMPAREG-OUTCOME

N=7020



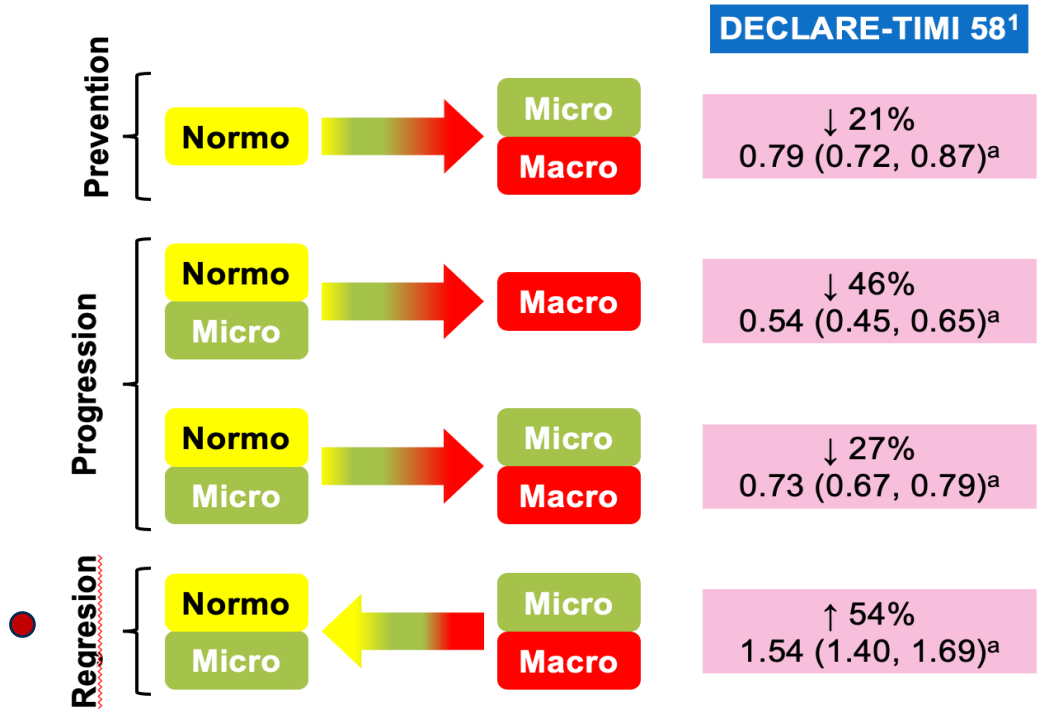
Lancet Diabetes Endocrinol 2017;5:610-621; NEJM 2016;375:323-334

CANVAS



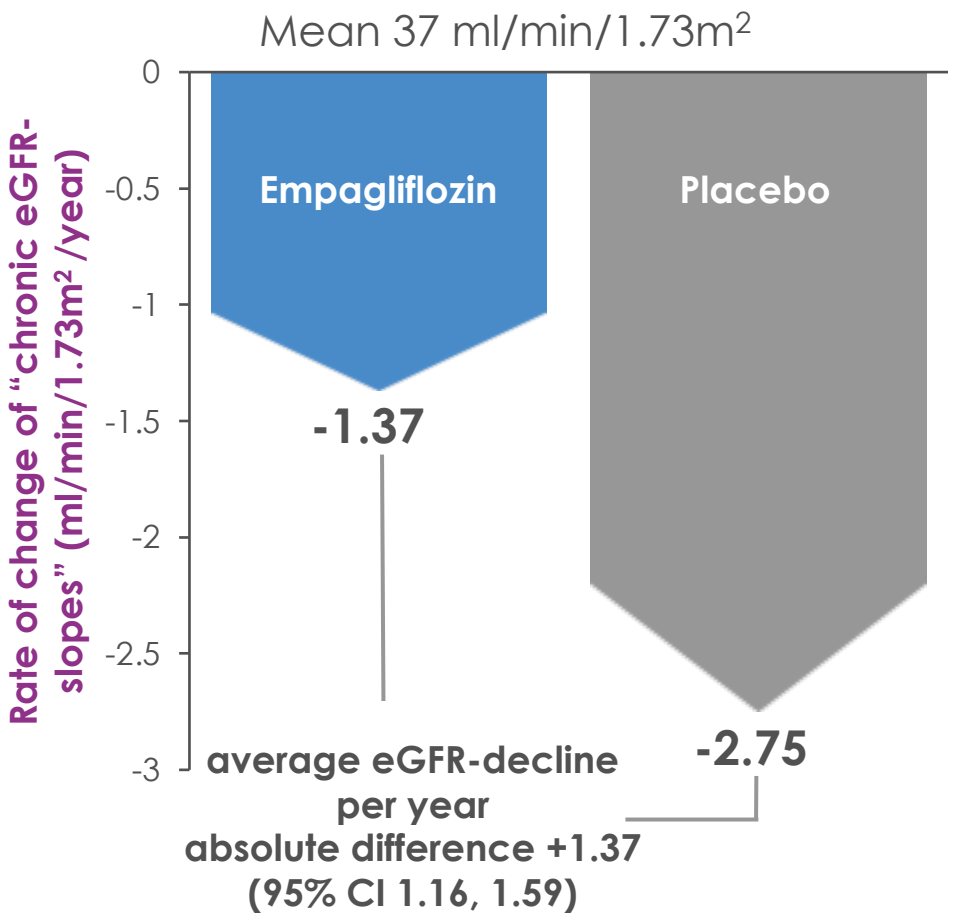
Neuen BL et al JASN 2019;30:2229-2242

DECLARE included substantial numbers of participants with normal kidney function



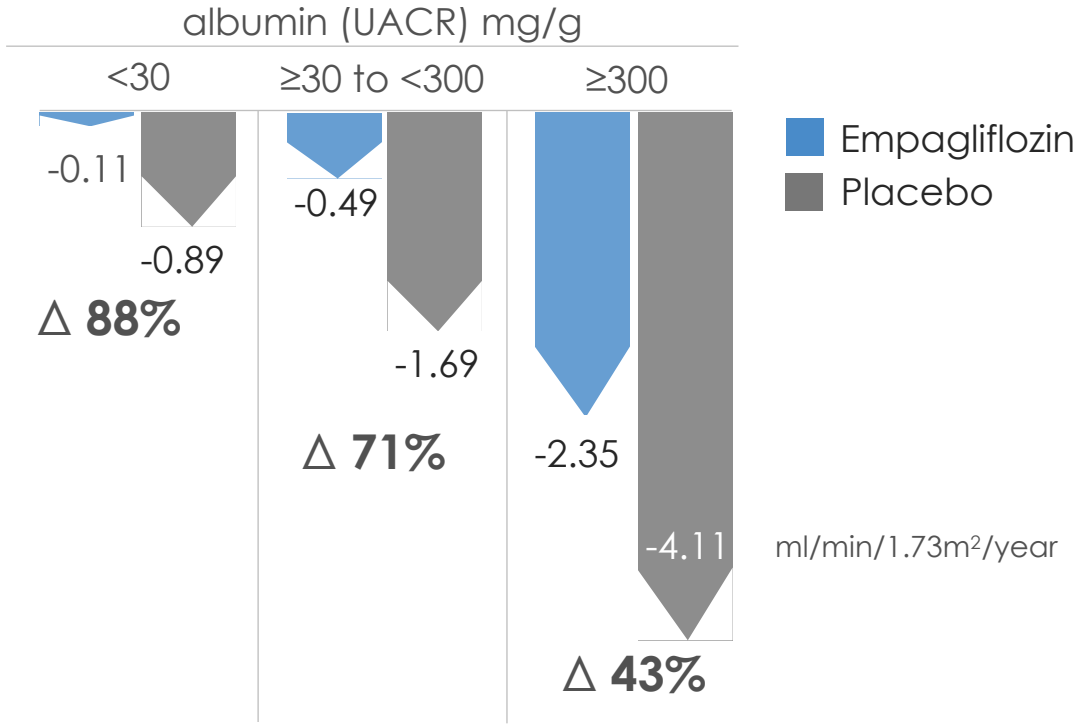
Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; Raz I, et al. : 79th ADA; June 7th-11th, 2019; San Francisco, CA, USA; 244-OR

EMPA-KIDNEY: loss of kidney function in relation to albuminuria[1]

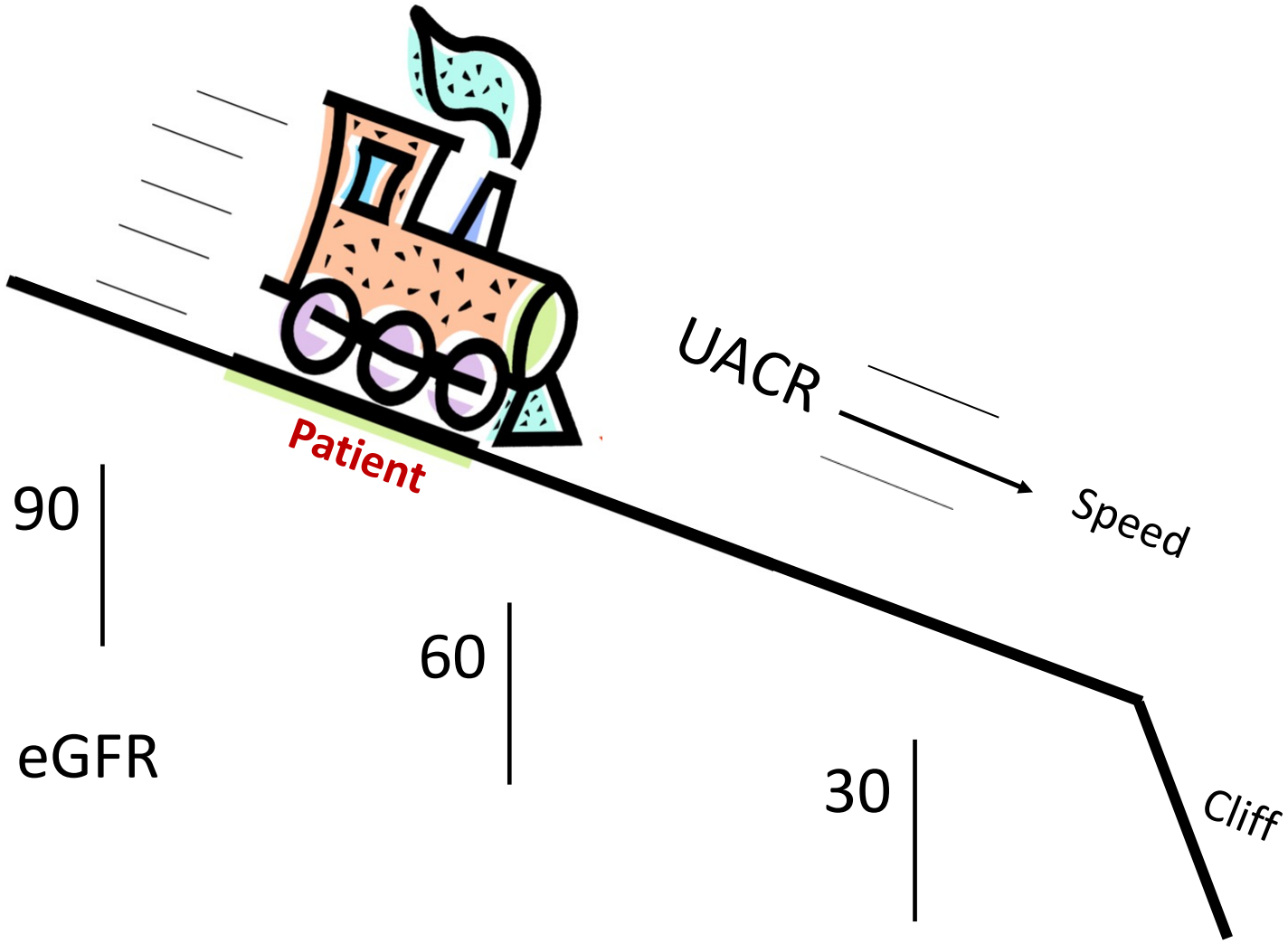


Compared to Placebo Empagliflozin reduces the decline in eGFR (ml per year)

with and without albuminuria+



The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117


Patient
UACR
Speed
90
60
30
eGFR
Cliff

Analyses show that patients at lower risk - many of whom in their lifetime would otherwise develop kidney failure - could benefit in terms of preservation of kidney function.
If widely implemented, use of SGLT2i could therefore have a substantial impact on the public health impacts of CKD.

Maintaining Kidney Health: How to identify ?

Should we* go for population based screening to detect people at risk (the Thomas Study) ?

Participation rate and yield of two home-based screening methods to detect increased albuminuria in the general population in the Netherlands (THOMAS): a prospective, randomised, open-label implementation study

Dominique van Mil, Lyanne M Kieneker, Birgitte Evers-Roeten, Marc H M Thelen, Hanne de Vries, Marc H Hemmelder, Annemiek Dorgelo, Ronald W van Etten, Hiddo J L Heerspink, Ron T Gansevoort

www.thelancet.com **Published online August 16, 2023** **https://doi.org/10.1016/S0140-6736(23)01140-6**

Should we* not better define individuals at risk to screen and treat early ?

* We = General Practitioners ?

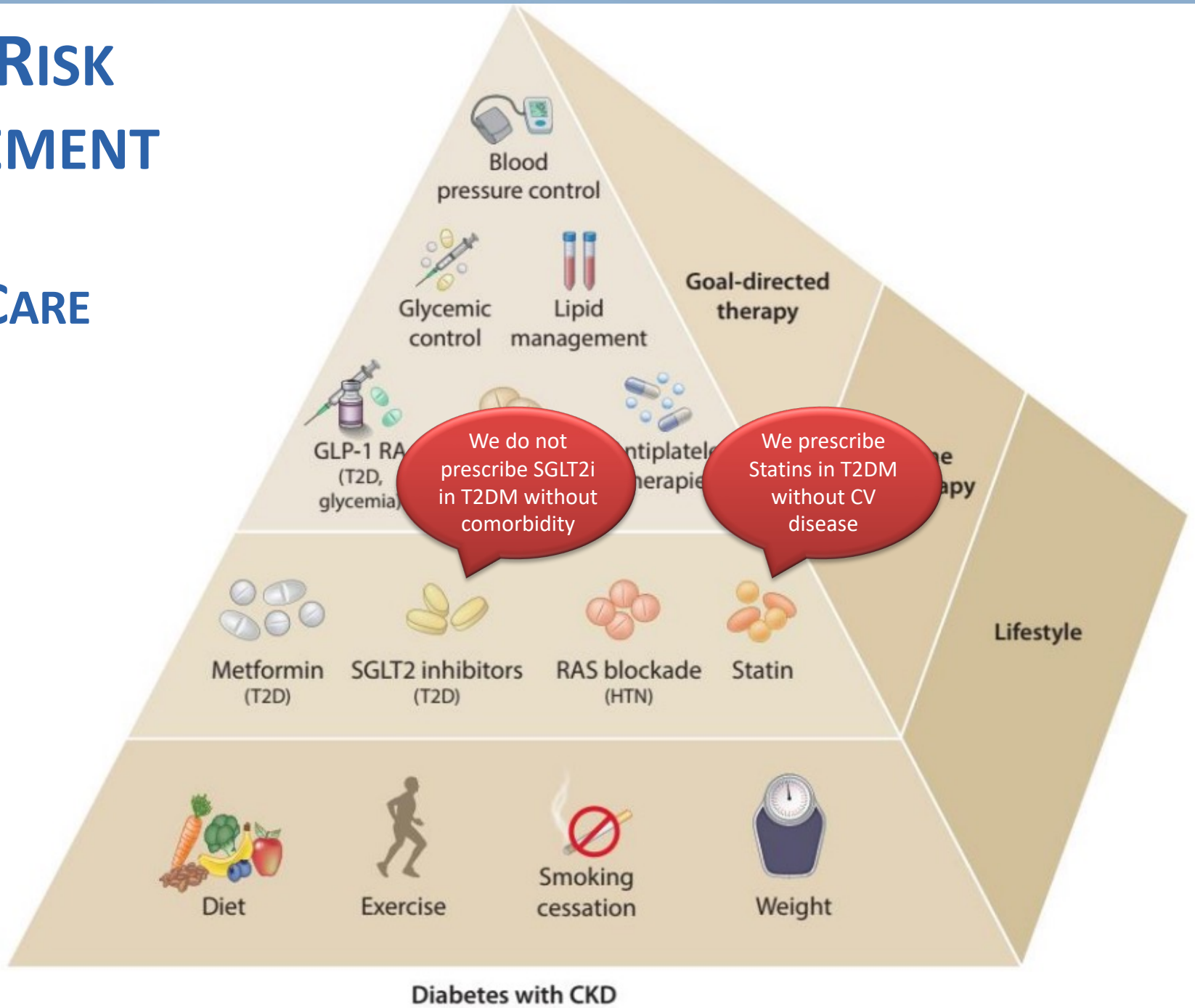
TOP 11 factors that define early risk for CKD and potential treatment target populations

1. T1D/T2D (steatotic liver disease), morbid obesity (in aging and aged societies)
2. Pre stational diabetes
3. Adve uterine child conditions (metabolic imprinting, epigenetic factors)
4. CKD in families (a high genetic risk score), ethnic minorities
5. Gestational age - preterm - low birth weight
6. High BP, preeclampsia
7. toxins (environmental, air pollution), NSAIDs
8. AKI, the risk at the ICU
9. Young rural males in central America
10. Gout arthritis, chemotherapy
11. CAKUT, unilateral nephrectomy and albuminuria

Fabry disease: We prescribe ERT to prevent onset

Kidney-Heart Risk Factor Management

Comprehensive Care



Practice point 1.1.1.

Kidney Int 2020;98:849-859

Kidney Int 2022;102:990-999

TOP 11 factors that define early risk for CKD and potential treatment target populations

1. T1D/T2D, SLD (steatotic liver disease), morbid obesity (in aging and aged societies)
2. Prediabetes, gestational diabetes
3. Adverse intrauterine child conditions (metabolic imprinting, epigenetic factors)
4. CKD in families (a high genetic risk score), ethnic minorities
5. Gestational age - preterm - low birth weight
6. High BP, preeclampsia
7. toxins (environmental, air pollution), NSAIDs
8. AKI, the risk at the ICU
9. Young rural males in central America
10. Gout arthritis, chemotherapy
11. CAKUT, unilateral nephrectomy and albuminuria

3 categories that define early risk for CKD

A) Metabolic diseases

1. T1D/T2D, SLD (steatotic liver disease), morbid obesity (in aging and aged societies)
2. Prediabetes, gestational diabetes
3. Adverse intrauterine child conditions (metabolic imprinting, epigenetic factors)
4. Gout & arthritis

B) Familial, in-extrinsic, multifactorial

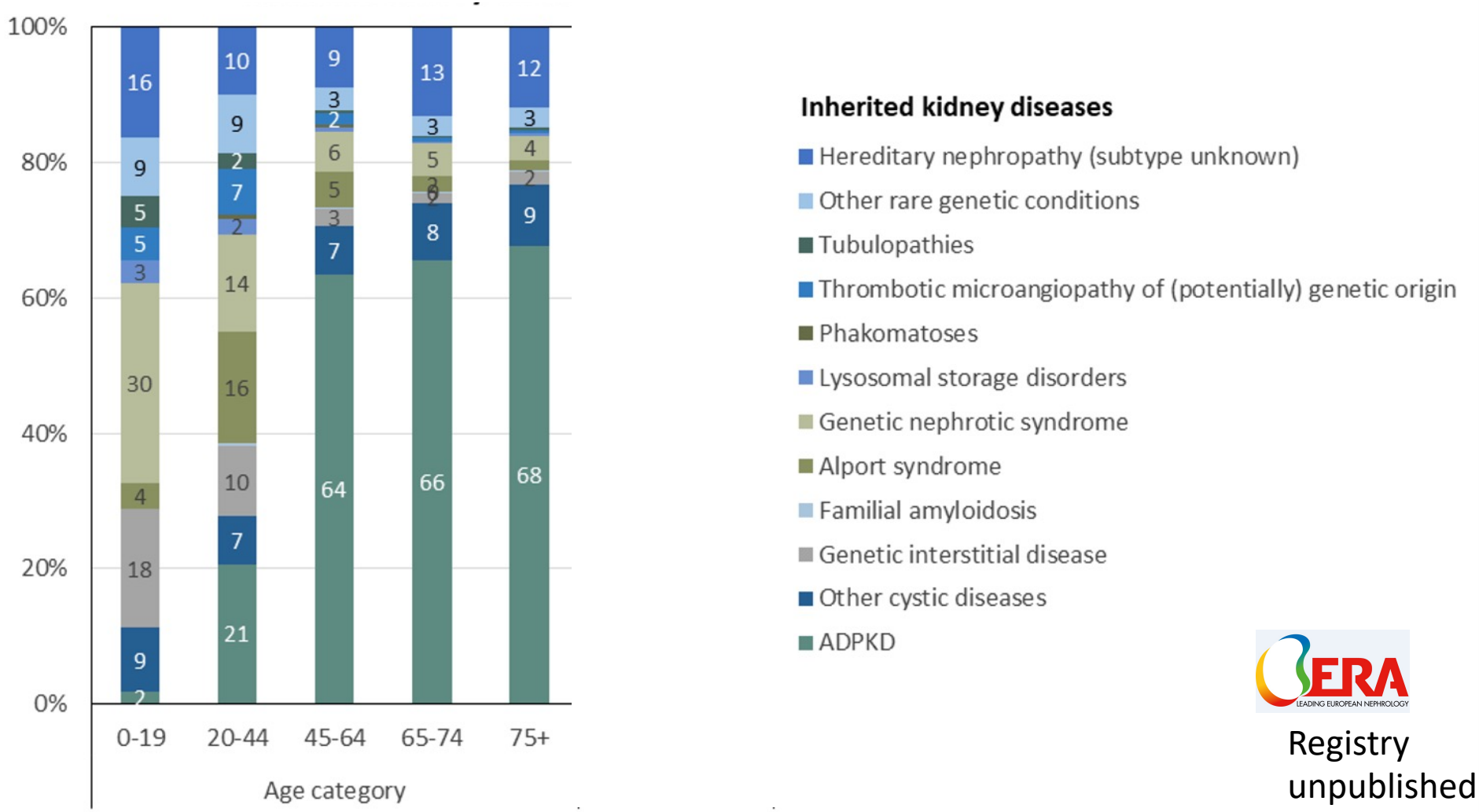
1. CKD in families (a high genetic risk score), Gestational age - preterm - low birth weight
2. High BP, preeclampsia, CAKUT, unilateral nephrectomy and albuminuria
3. Ethnic minorities

C) Environmental

1. Toxins (air pollution), NSAIDs, chemotherapy
2. ICU risks, AKI
3. Young rural males in central America

Monogenic risk justifying early adjunctive treatment ?

Diagnosis of prevalent KRT patients 2019
on the basis of genetic nephropathies



Registry unpublished

What is missing:

- Mechanisms of preventing CKD (tubular stress, address biomarkers, consumption of kidney functional reserve)
- More focus on nonCKD trials with SGLT2i, Inkretines and anti-inflammatory therapies to identify more subgroups who carry a risk for CKD development
- The healing process: personalized medicine in specific forms of kidney disease (IgAN, MN, Lupus Nephritis, FSGS etc) targetting causal pathomechanisms to stabilize nephron loss or kidney volume

The predictable Future

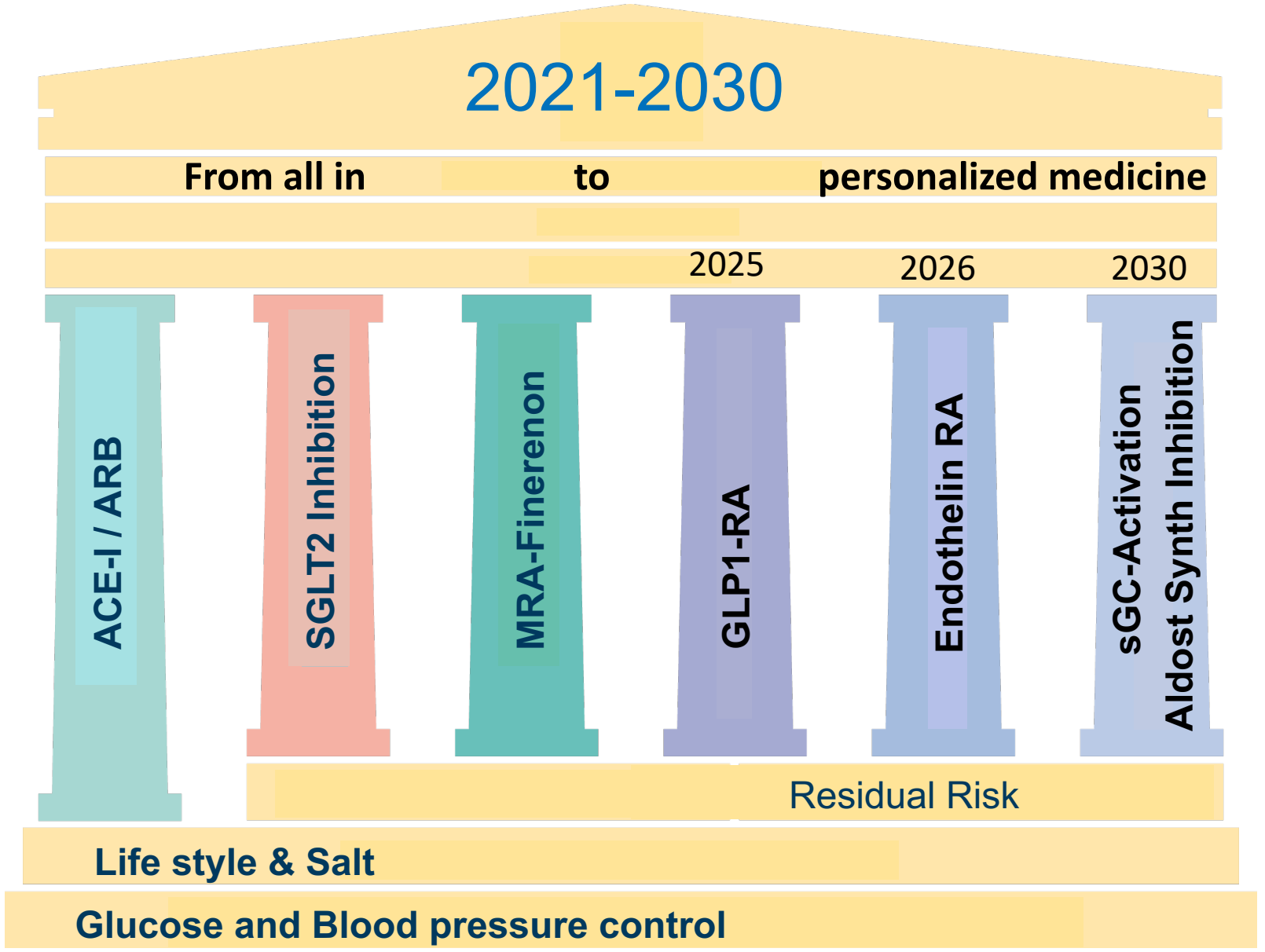
New approaches/studies are being developed to retard the progression of kidney disease in a broad population with established disease

Subgroup analysis of such trials may also provide relevant data

The unpredictable future

- Demographie (Langlebigkeit)
- Klima, Hitze
- Umweltbelastung (Toxizität), Luftqualität

Therapy of CKD ± T2D



Die vorhersagbare Zukunft

Neue Ansätze/Studien zur Progressionsverzögerung einer etablierten Erkrankung.
Aus Subgruppenanalysen dieser Studien werden neue Erkenntnisse erwartet

The unpredictable future

- Demography (longevity)
- Change in climate, heat waves (special populations)
- Environment (toxicity), pollution (air)