Julius-Maximilians-
UNIVERSITÄT
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Comprehensive Heart
Failure Center

Aldosterone antagonism and nephroprotection: from preliminary studies to FIDELIO-DKD and FIGARO-DKD

Christoph Wanner, Würzburg and Oxford, Germany and UK

honoring the late Professor George Bakris

25th Hellenic Congress of Nephrology
Symposium June 19-21, 2024

OXFORD POPULATION HEALTH
UNIVERSITY OF OXFORD

Transparency Declaration – Christoph Wanner

Honoraria: Steering Committees, AdBoards & Lecturing

Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, CSL-Vifor, FMC, GSK, Lilly, MSD, Novartis, NovoNordisk

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

N Engl J Med 2020;383:2219-29.

THE NEW ENGLAND JOURNAL OF MEDICINE July 12, 1990

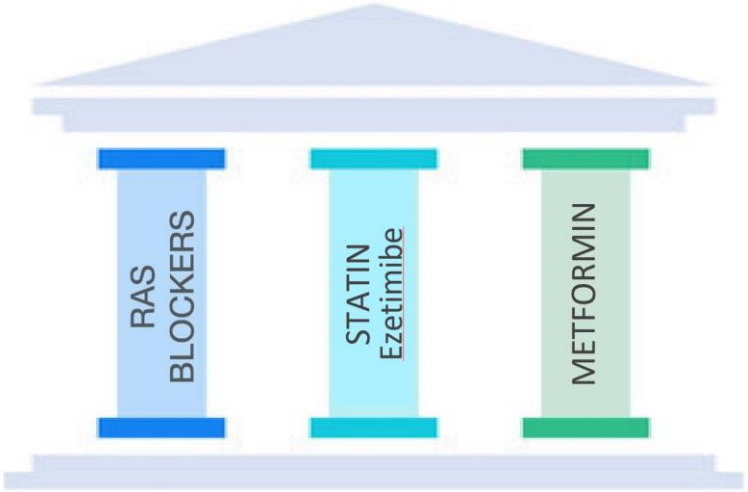
EFFECTS OF THEOPHYLLINE ON ERYTHROPOIETIN PRODUCTION IN NORMAL SUBJECTS AND IN PATIENTS WITH ERYTHROCYTOSIS AFTER RENAL TRANSPLANTATION

GEORGE L. BAKRIS, M.D., EDWARD R. SAUTER, M.D., JOHN L. HUSSEY, M.D., JAMES W. FISHER, PH.D., A. OSAMA GABER, M.D., AND REBECCA WINSETT, R.N.

1990; 323:86-90.)

Multifactorial Approach to Reduce the Cardio-Renal Risk in individuals with CKD and T2DM[2]

Basic
Standard-of-Care

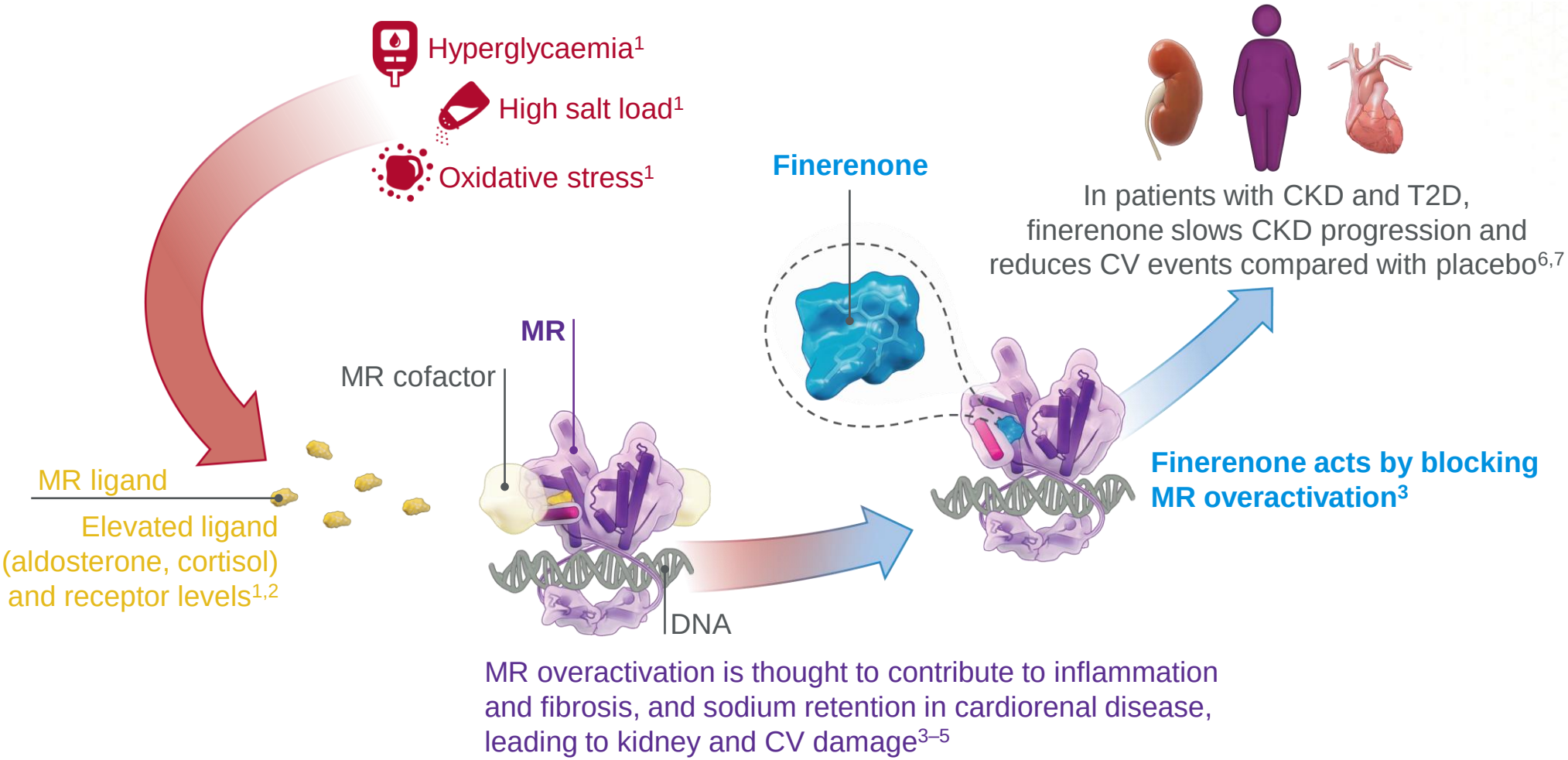


Lifestyle, Nutrition (salt), Blood pressure, Glycemic control

An ADA/KDIGO consensus report recommends a holistic approach

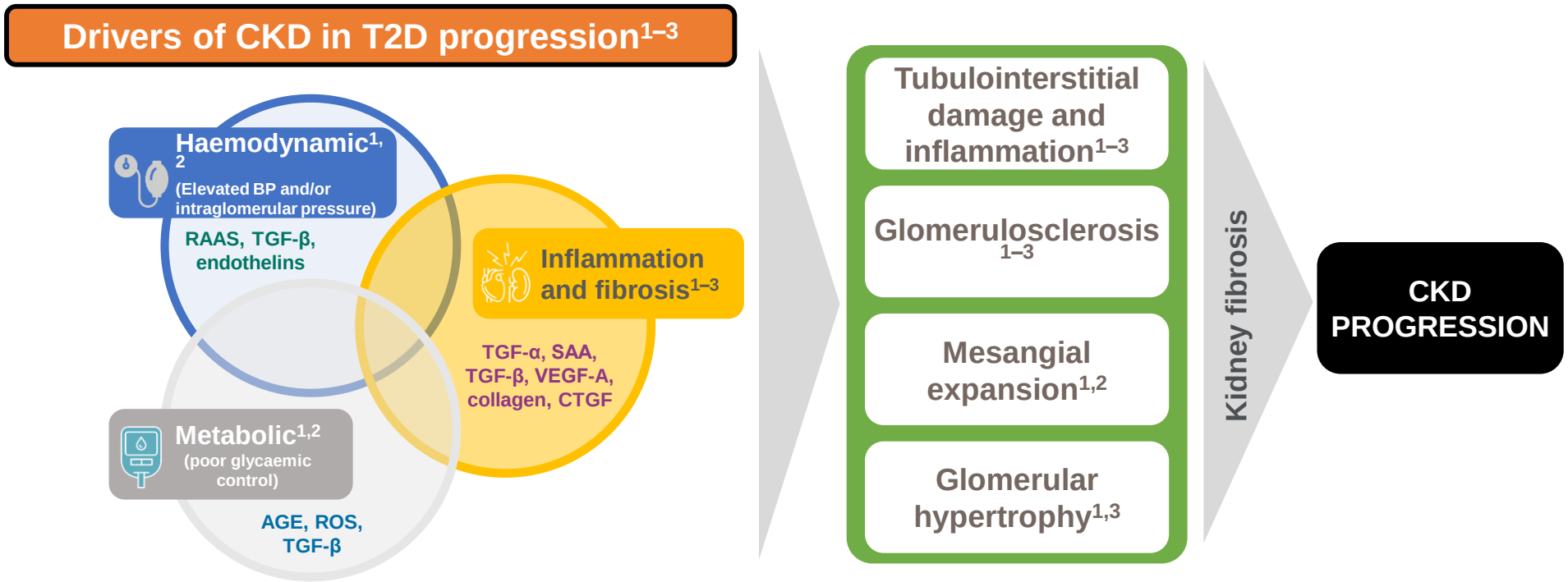
1. de Boer IH & Bakris G *et al. Diabetes Care* 2022;doi:10.2337/dci22-0027; 2. Blazek O & Bakris G. AHJO Plus: Cardiology Research and Practice 19 (2022) 100187

Finerenone targets MR overactivation, which may contribute to kidney and CVD progression in patients with CKD and T2D



1. Buonafine M *et al. AJH* 2018;31:1165-74; 2. Buglioni A *et al. Hypertension* 2015;65:45-53; 3. Agarwal R *et al. NDT* 2020; doi: 10.1093/ndt/gfaa294; 4. Agarwal R *et al. EHJ* 2021;42:152-61; 5. Khan NUA & Movahed A. *Rev Cardiovasc Med* 2004;5:71-81; 6. Bakris GL, *et al. NEJM* 2020;383:2219-29; 7. Pitt B & Bakris GL *et al. NEJM* 2021; doi: 10.1056/NEJMoa2110956

The Course of Diabetic Nephropathy is determined by Hemodynamic, Inflammatory and Fibrosing Mechanisms



RBF, renal blood flow; CTGF, connective tissue growth factor; NADPH; reduced nicotinamide adenine dinucleotide phosphate; SAA, serum amyloid A; VEGF-A, vascular endothelial growth factor A. 1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263

The Trial Programme

FIDELIO-DKD[1] (n=5734) and **FIGARO-DKD**[2] (n=7437) investigated the clinical effectiveness of complementary renal and cardiovascular (CV) primary endpoints:

- Time to kidney failure*, ≥40% decline in eGFR or renal death
- Time to CV death, non-fatal MI, non-fatal stroke or HHF

- Additionally: all-cause death, all-cause hospitalisation, UACR change, kidney failure - eGFR decline - renal death

*Kidney failure: chronic dialysis ≥90 days or KTX or eGFR < 15 ml/min/1.73m^2

FIDELITY is a prespecified exploratory pooled analysis from **FIDELIO-DKD** and **FIGARO-DKD** n=13,171

- Combined CV-endpoint
- combined ≥ 57% eGFR decline endpoint

1. Bakris et al. Am J Nephrol 2019;50:333-344; 2. Ruilope et al. Am J Nephrol 2019;50_345-358

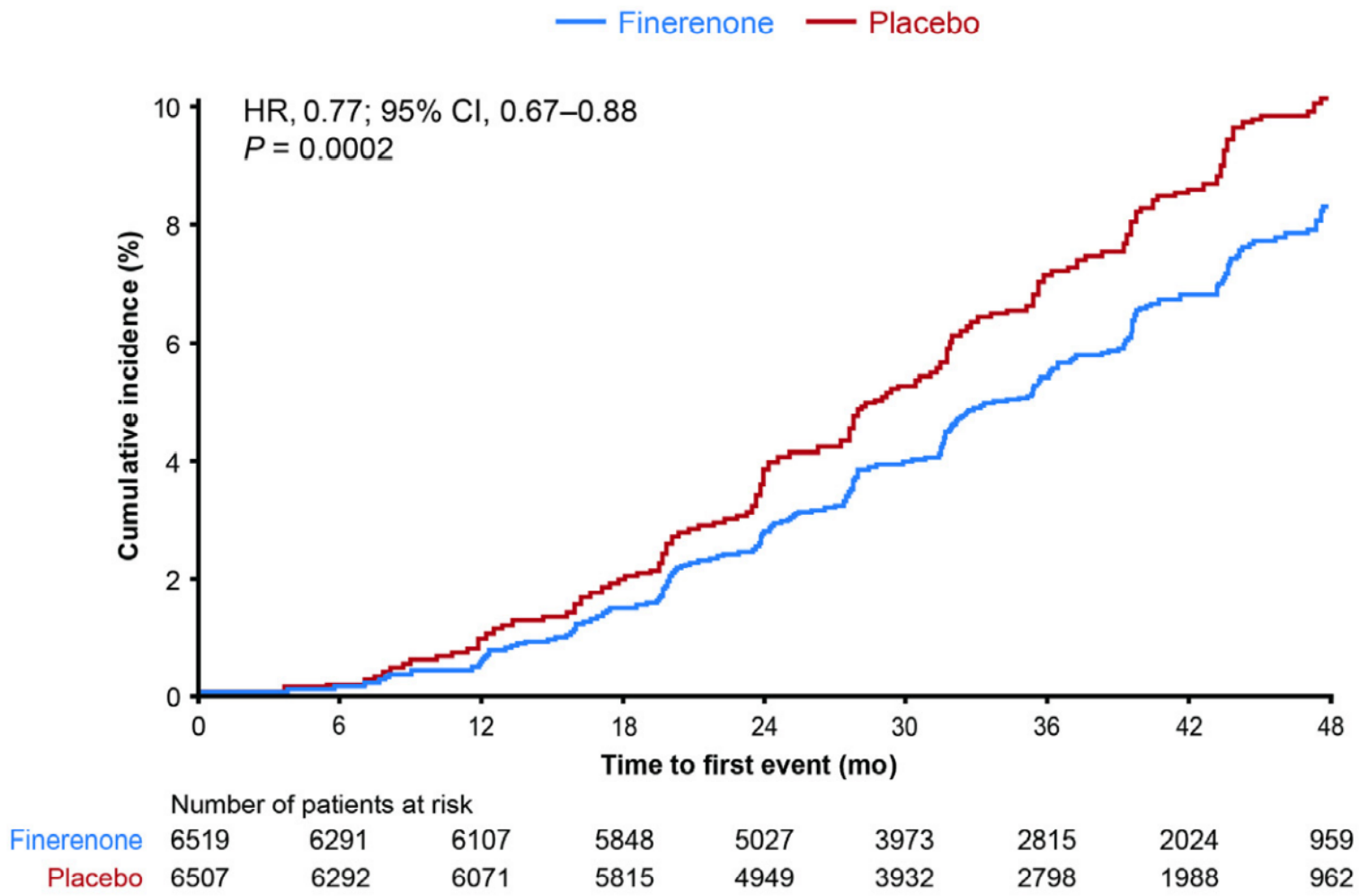
A prespecified exploratory analysis from FIDELITY examined finerenone use and kidney outcomes in patients with chronic kidney disease and type 2 diabetes

Kidney Int 2023;103:196-206

George L. Bakris[1], Luis M. Ruilope[2,3,4], Stefan D. Anker[5,6,7], Gerasimos Filippatos[8], Bertram Pitt[9], Peter Rossing[10,11], Linda Fried[12], Prabir Roy-Chaudhury[13,14], Pantelis Sarafidis[15], Christiane Ahlers[16], Meike Brinker[17], Amer Joseph[18], Robert Lawatscheck[19] and Rajiv Agarwal[20,21]; on behalf of the FIDELIO-DKD and FIGARO-DKD Investigators

Kidney Outcomes in FIDELITY (FIDELIO and FIGARO)

≥57% decline in eGFR, kidney failure (Dialyse/KTX or eGFR < 15 ml/min/1,73m²)

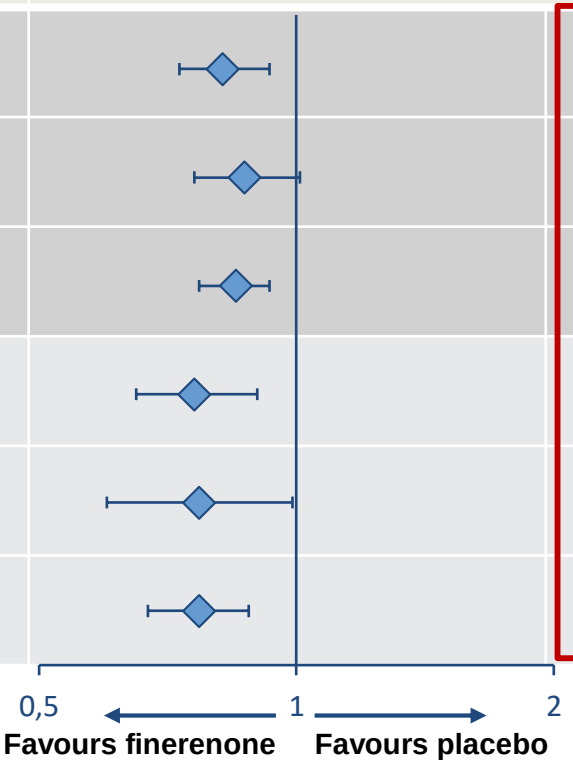


Bakris GL et al. Kidney Int 2023;103:196-206

A 23% reduction in the risk of CKD progression* was observed with finerenone vs placebo in patients with CKD and T2D

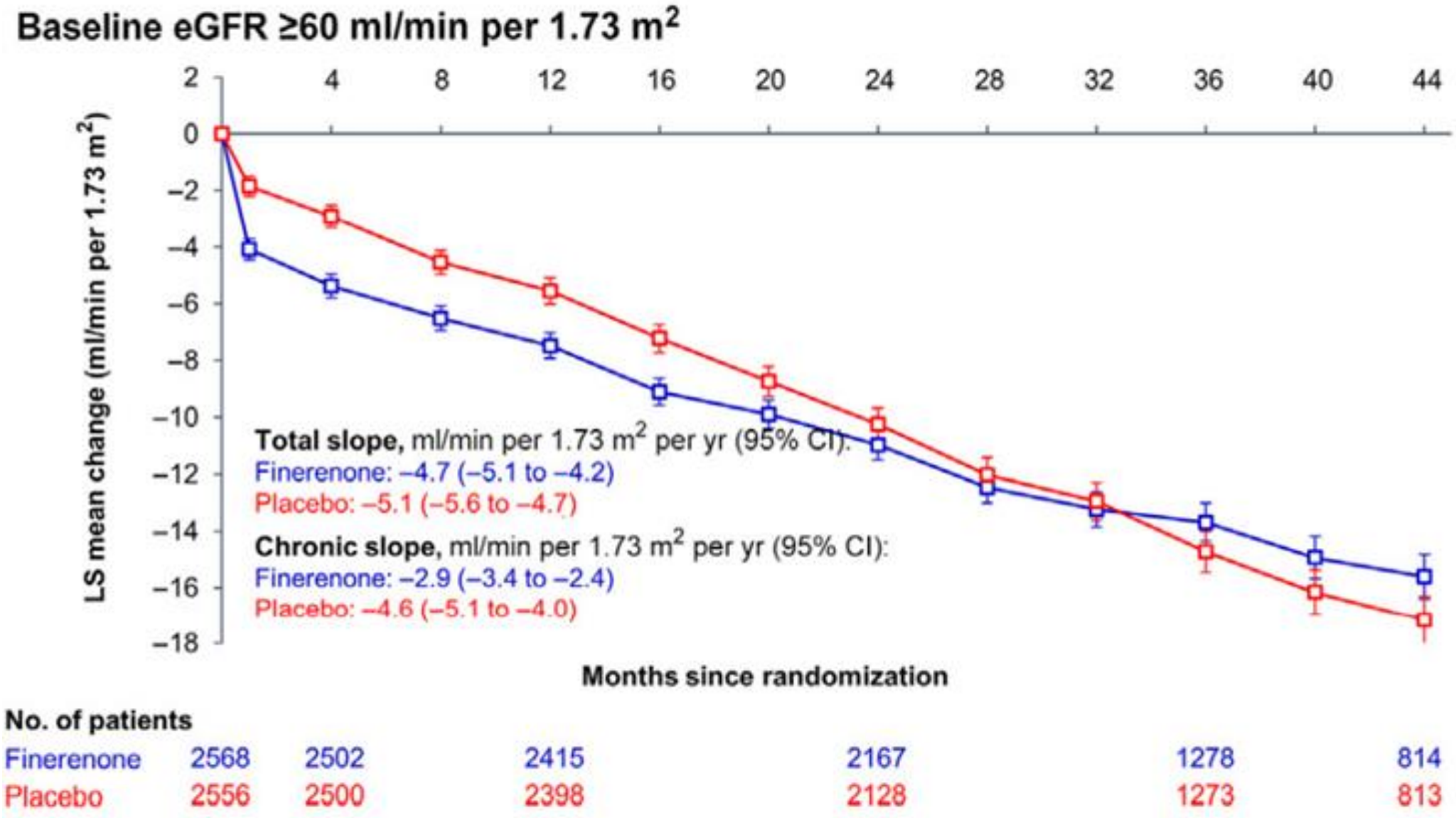
Kidney outcomes in FIDELIO-DKD, FIGARO-DKD and FIDELITY[1–3]

Kidney composite outcome	Trial and population (n finerenone/n placebo)	Finerenone n/100 PY	Placebo n/100 PY	HR (95% CI)	*p*-value
Kidney composite outcome with ≥40% eGFR decline#	FIDELIO-DKD (n=2833/n=2841)[1]	7.59	9.08	0.82 (0.73–0.93)	0.001
	FIGARO-DKD (n=3686/n=3666)[2]	3.15	3.58	0.87 (0.76–1.01)	–
	FIDELITY (n=6519/n=6507)[3]	4.81	5.64	0.85 (0.77–0.93)	0.0004
Kidney composite outcome with ≥57% eGFR decline*	FIDELIO-DKD (n=2833/n=2841)[1]	3.64	4.74	0.76 (0.65–0.90)	–
	FIGARO-DKD (n=3686/n=3666)[2]	0.95	1.23	0.77 (0.60–0.99)	–
	FIDELITY (n=6519/n=6507)[3]	1.96	2.55	0.77 (0.67–0.88)	0.0002



*Time to kidney failure, sustained ≥57% eGFR decline decrease or renal death; #Time to kidney failure, sustained ≥40% eGFR decline or renal death;

1. Bakris et al. NEJM 2020;383:2219-29; 2. Pitt et al. NEJM 2021;385:2252-63; 3. Agarwal et al. EHJ 2021; doi:10.1093/eurheartj/ehab777.



Bakris GL et al. Kidney Int 2023;103:196-206

Safety parameter were overall consistent – for patients with or without SGLT-2i treatment at baseline

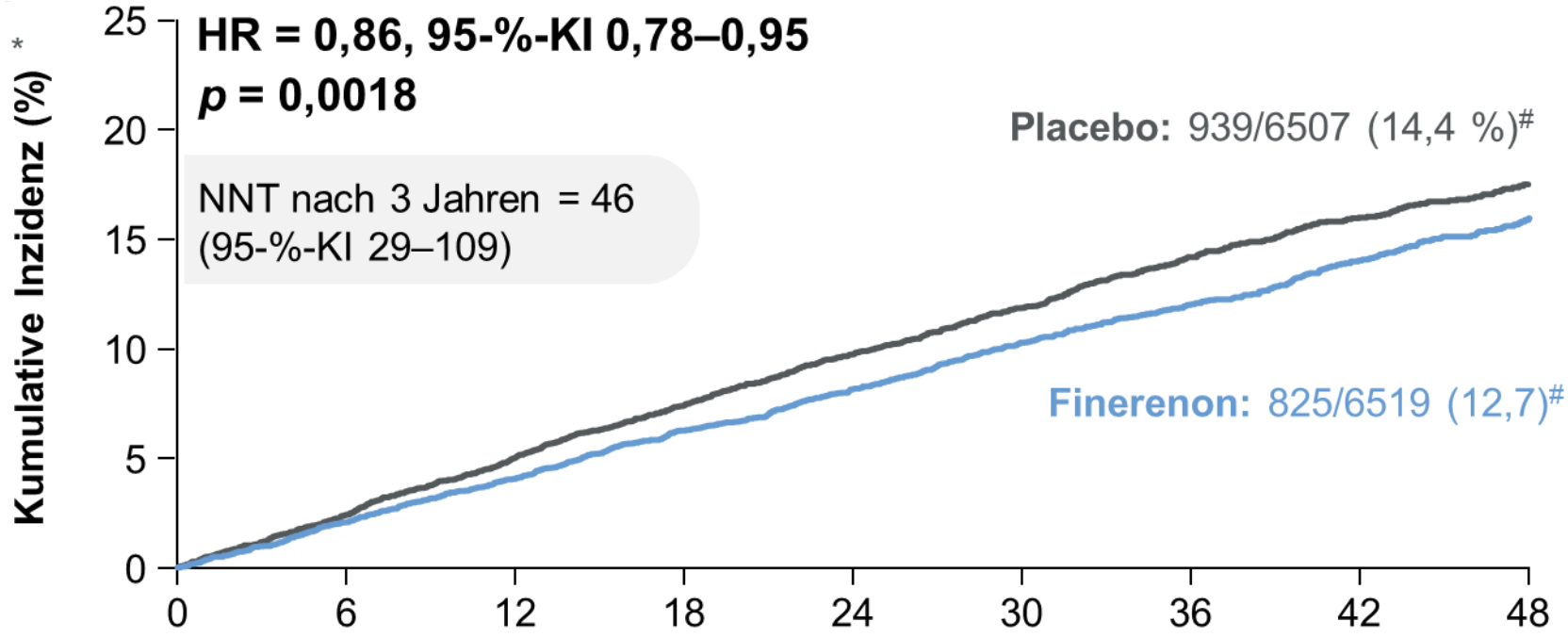
Treatment emergent UE, n (%)	No SGLT-2i		SGLT-2i	
	Finerenone (n = 6072)	Placebo (n = 6050)	Finerenone (n = 438)	Placebo (n = 439)
All AE	5204 (85,7)	5223 (86,3)	398 (90,9)	384 (87,5)
Treatment interruption	396 (6,5)	328 (5,4)	18 (4,1)	23 (5,2)
All SAE	1914 (31,5)	2045 (33,8)	146 (33,3)	141 (32,1)
Treatment interruption	138 (2,3)	146 (2,4)	7 (1,6)	8 (1,8)
AE assocated with death	108 (1,8)	142 (2,3)	2 (0,5)	9 (2,1)
Hyperkalemia, n (%)				
All AE	867 (14,3)	436 (7,2)	45 (10,3)	12 (2,7)
Treatment interruption	105 (1,7)	35 (0,6)	5 (1,1)	3 (0,7)

Rossing P, *et al. Diabetes Care. 2022 Aug 15;dc220294. doi: 10.2337/dc22-0294. Online ahead of print.*

FIDELITY

On top of optimized RAS-Blockade Finerenon significantly lowered the Risk for a composite CV-Endpoint by 14%

Time to CV-death, non fatal MI, non fatal stroke or hospitalisation for heart failure

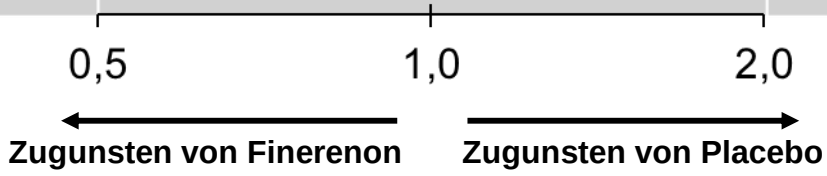


Risikopopulation									
Finerenon	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

The statistical analyses are explorative. Only confirmatoriy hypothesis generating tests were done. *Cumulative Inzidenz calculated using the Aalen-Johansen-estimator and using death rates due to other causes as competing risk, #number of patients with an event during a median observation time of 3 years

Fidelity: the CV benefit of Finerenone was mainly based on a reduction of HHF and CV-Mortality*

Endpunkt	Finerenon (n = 6519) n (%)	Placebo (n = 6507) n (%)	HR (95-%-KI)	*p*-Wert
kombinierter CV-Endpunkt	825 (12,7)	939 (14,4)	0,86 (0,76–0,95)	0,0018
HHF	256 (3,9)	325 (5,0)	0,78 (0,66–0,92)	0,0030
CV-Tod	322 (4,9)	364 (5,6)	0,88 (0,76–1,02)	0,092
Nicht tödlicher MI	173 (2,7)	189 (2,8)	0,91 (0,74–1,12)	0,36
Nicht tödlicher Schlaganfall	198 (3,0)	198 (3,0)	0,99 (0,82–1,21)	0,95



Die statistischen Analysen sind explorativ. Es wurden keine konfirmatorischen Hypothesentests durchgeführt. Falls statistische Tests durchgeführt wurden, sind die p-Werte explorativ. *Prüfpräparat und Placebo wurden zusätzlich zu der gemäß den jeweiligen Leitlinien empfohlenen medikamentösen Standardtherapie (optimierte RASi) verabreicht. Filipatos G. Abstract 7161 presented at the ESC 2021)

www.KDIGO.org

Global Action. Local Change.

KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANGEMENT IN CHRONIC KIDNEY DISEASE

Kidney Int 2022;102:990-999

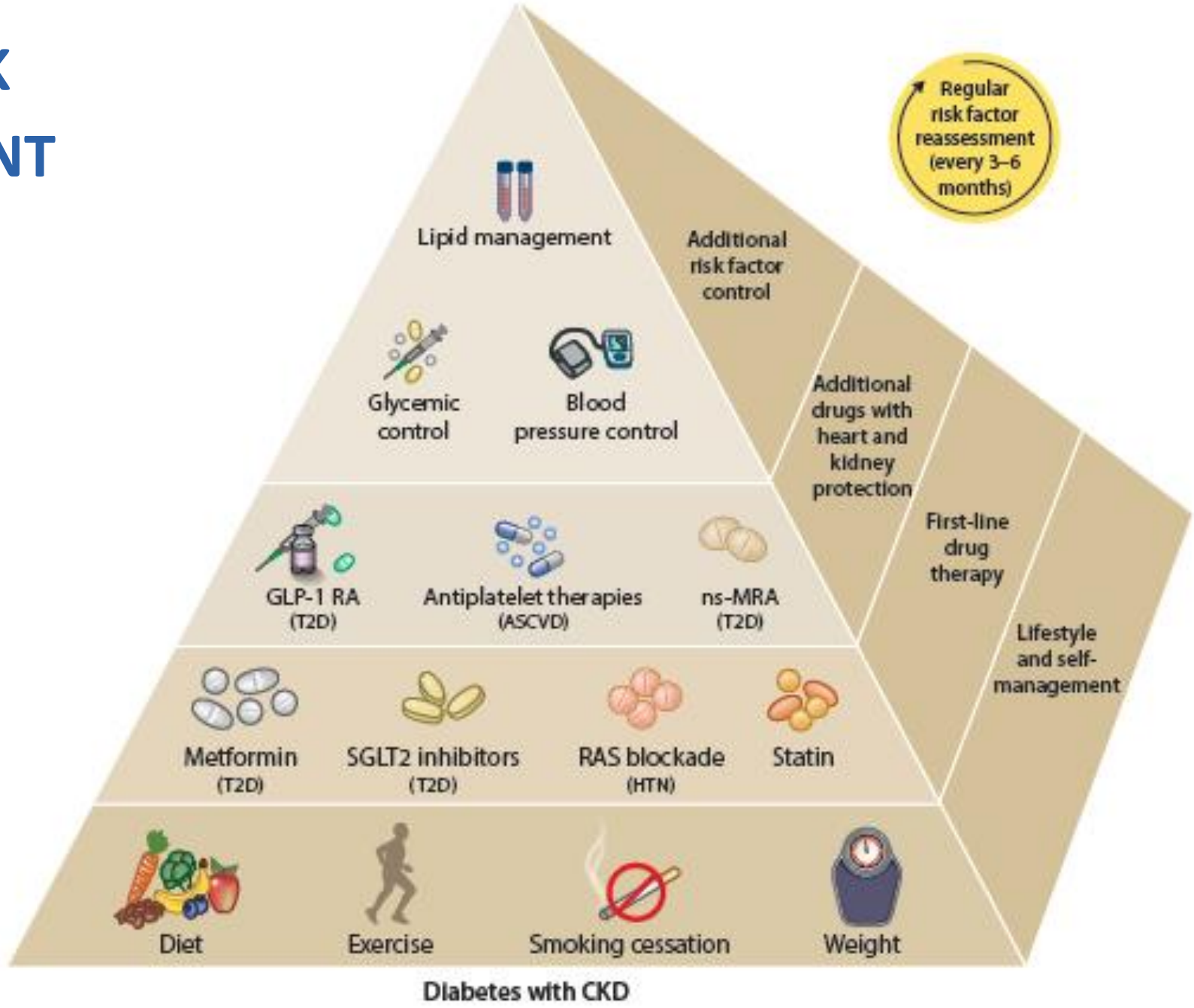
Diabetes Care

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

https://doi.org/10.2337/dci22-0027

Kidney-Heart Risk Factor Management

Comprehensive Care



Kidney Int 2022;102:990-999

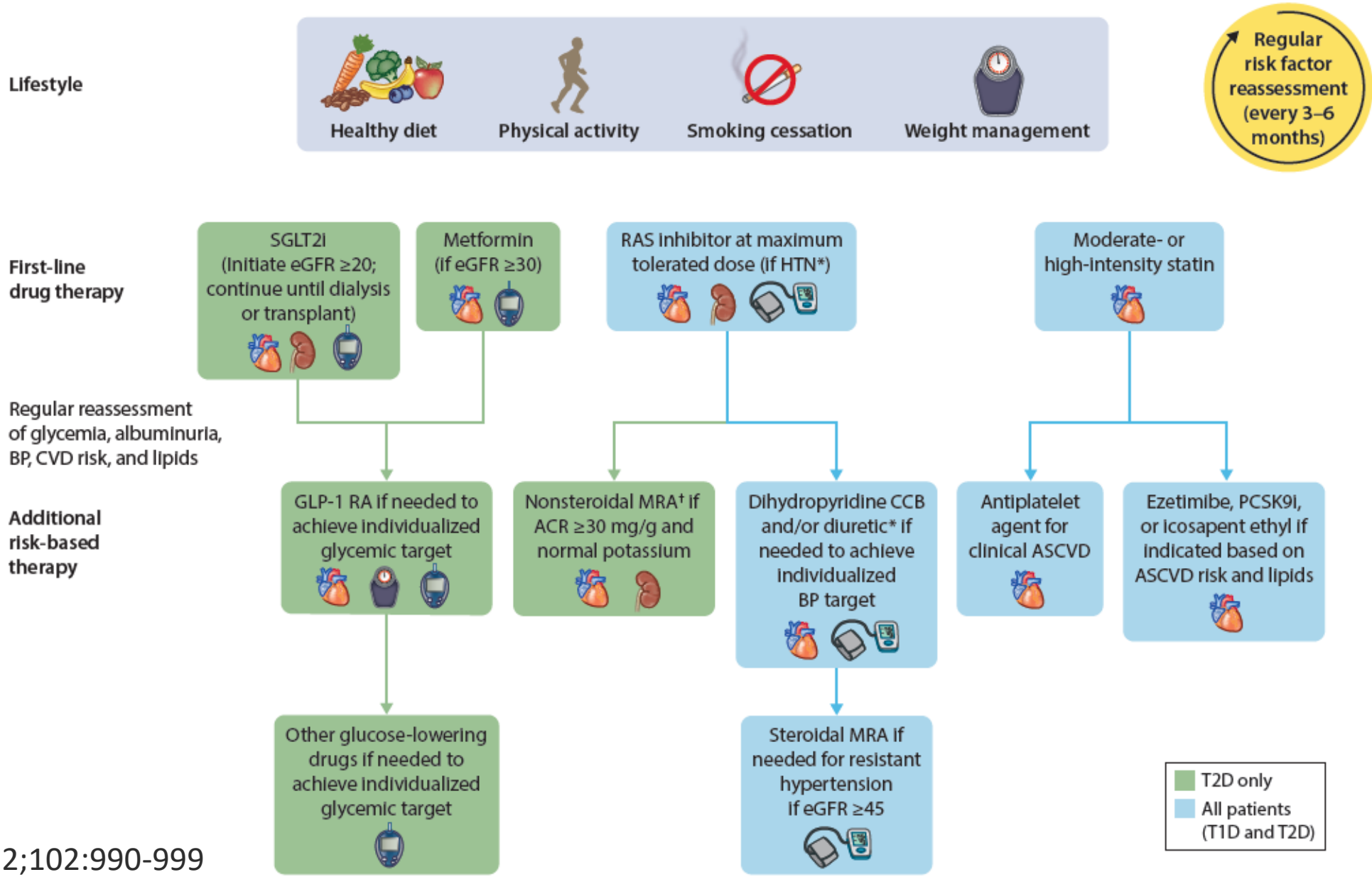
KDIGO Guideline update 2022

1.4 Mineralocorticoid receptor antagonists (MRA)

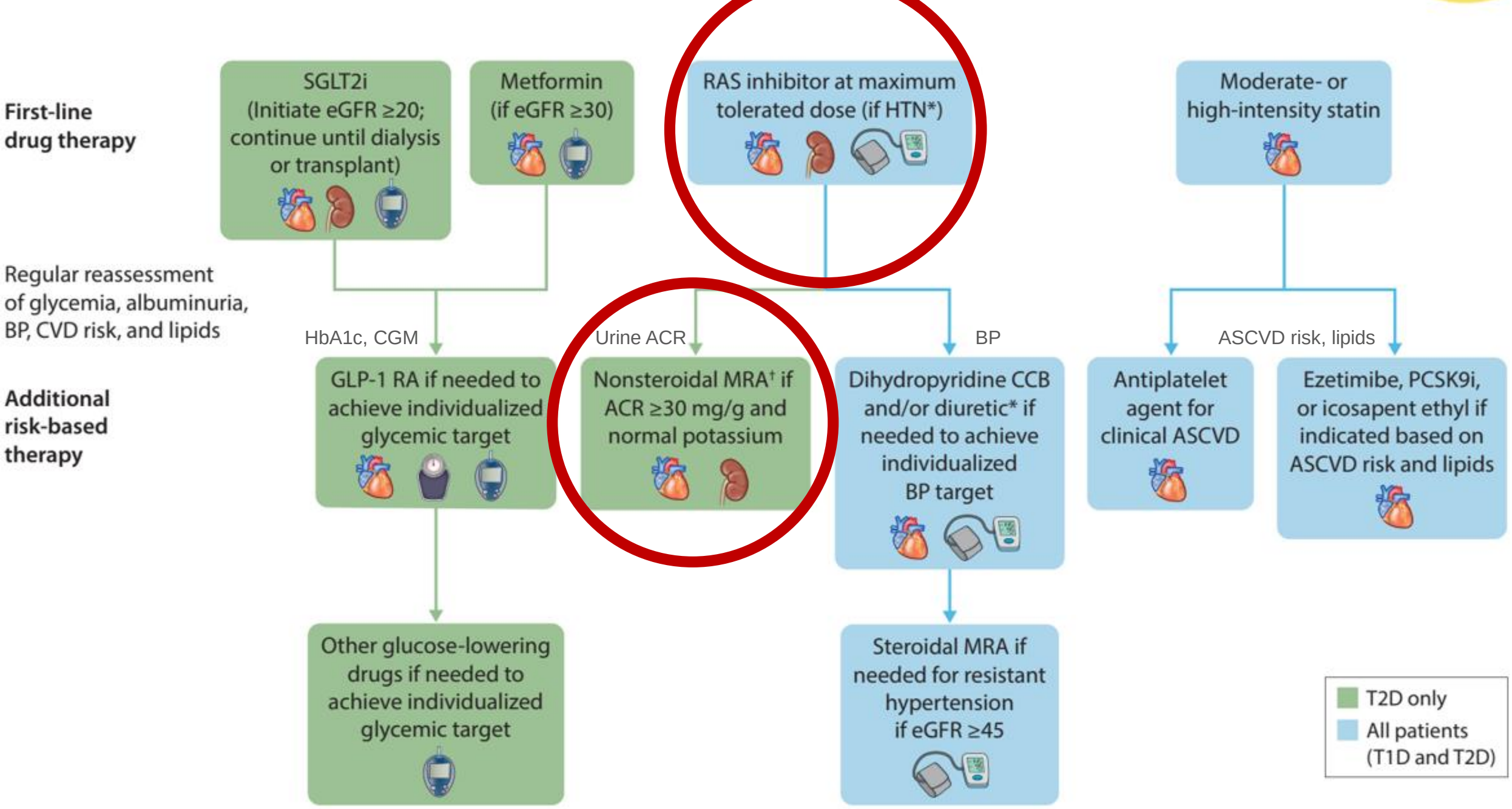
Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min/1.73 m^2, normal serum potassium concentration, and albuminuria (≥30 mg/g [3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi). *(2A)*

Kidney Int 2022;102:S1-S127

Holistic approach for improving outcomes in patients with Diabetes and CKD



Kidney Int 2022;102:990-999



Kidney Int 2022;102:990-999

ESC European Society of Cardiology

European Heart Journal (2023) 00, 1–98
https://doi.org/10.1093/eurheartj/ehad192

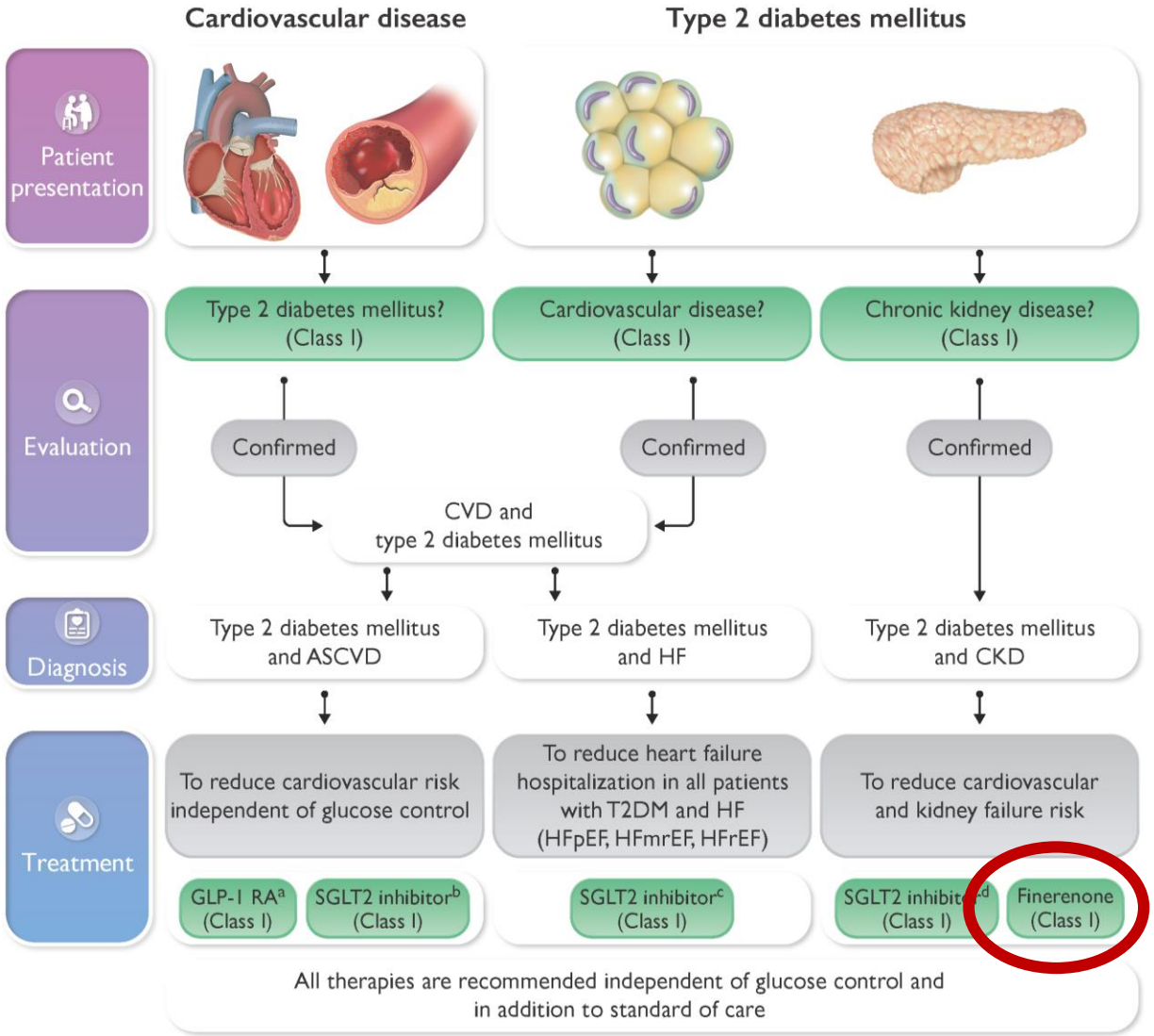
ESC GUIDELINES

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

Authors/Task Force Members: Nikolaus Marx *†, (Chairperson) (Germany), Massimo Federici *†, (Chairperson) (Italy), Katharina Schütt ‡, (Task Force Co-ordinator) (Germany), Dirk Müller-Wieland ‡, (Task Force Co-ordinator) (Germany), Ramzi A. Ajjan (United Kingdom), Manuel J. Antunes (Portugal), Ruxandra M. Christodorescu (Romania), Carolyn Crawford (United Kingdom), Emanuele Di Angelantonio (United Kingdom/Italy), Björn Eliasson (Sweden), Christine Espinola-Klein (Germany), Laurent Fauchier (France), Martin Halle (Germany), William G. Herrington (United Kingdom), Alexandra Kautzky-Willer (Austria), Ekaterini Lambrinou (Cyprus), Maciej Lesiak (Poland), Maddalena Lettino (Italy), Darren K. McGuire (United States of America), Wilfried Mullens (Belgium), Bianca Rocca (Italy), Naveed Sattar (United Kingdom), and ESC Scientific Document Group

Central figure - Management of cardiovascular disease in patients with type 2 diabetes: clinical approach and key recommendations

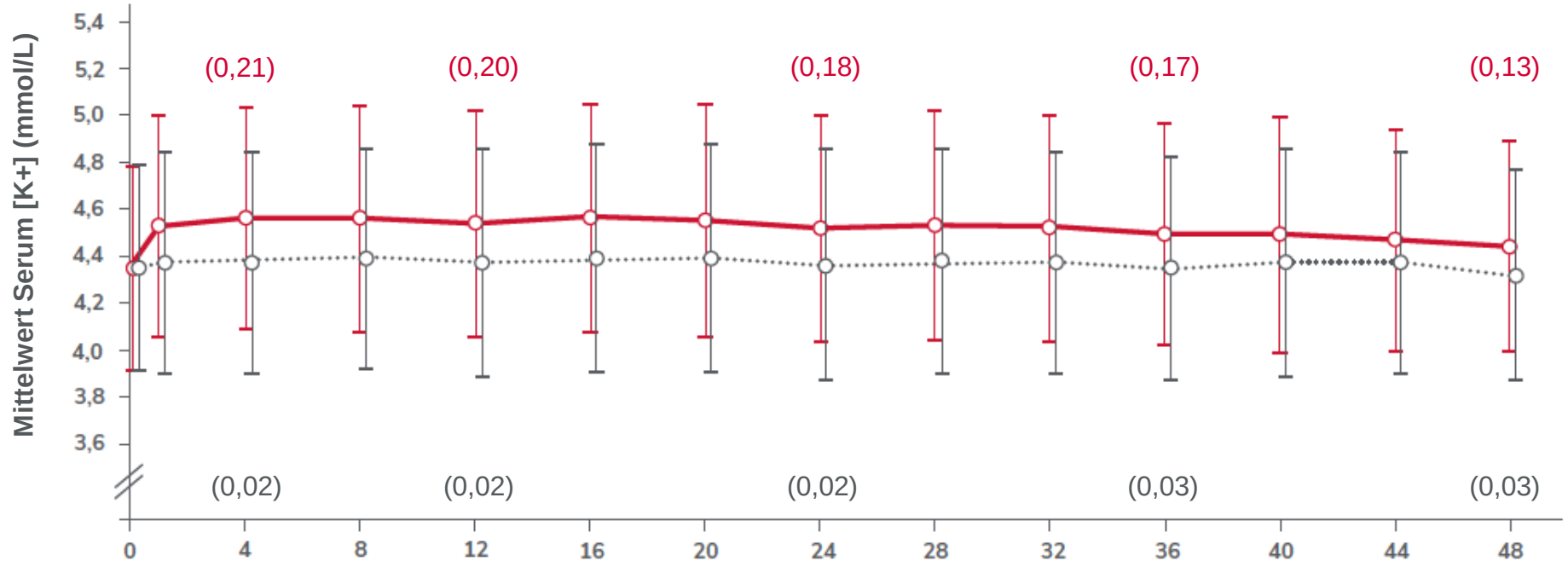


2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
Marx N, Federici M, et al. European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192

Finerenon shows a predictible effect on Serumkalio

The max Difference of mean Serum [K+] between groups was 0,19 mmol/l at month 4*

Mean Baseline Serum [K⁺]
Finerenon: 4,35± 0,44
Placebo: 4,35±0,44

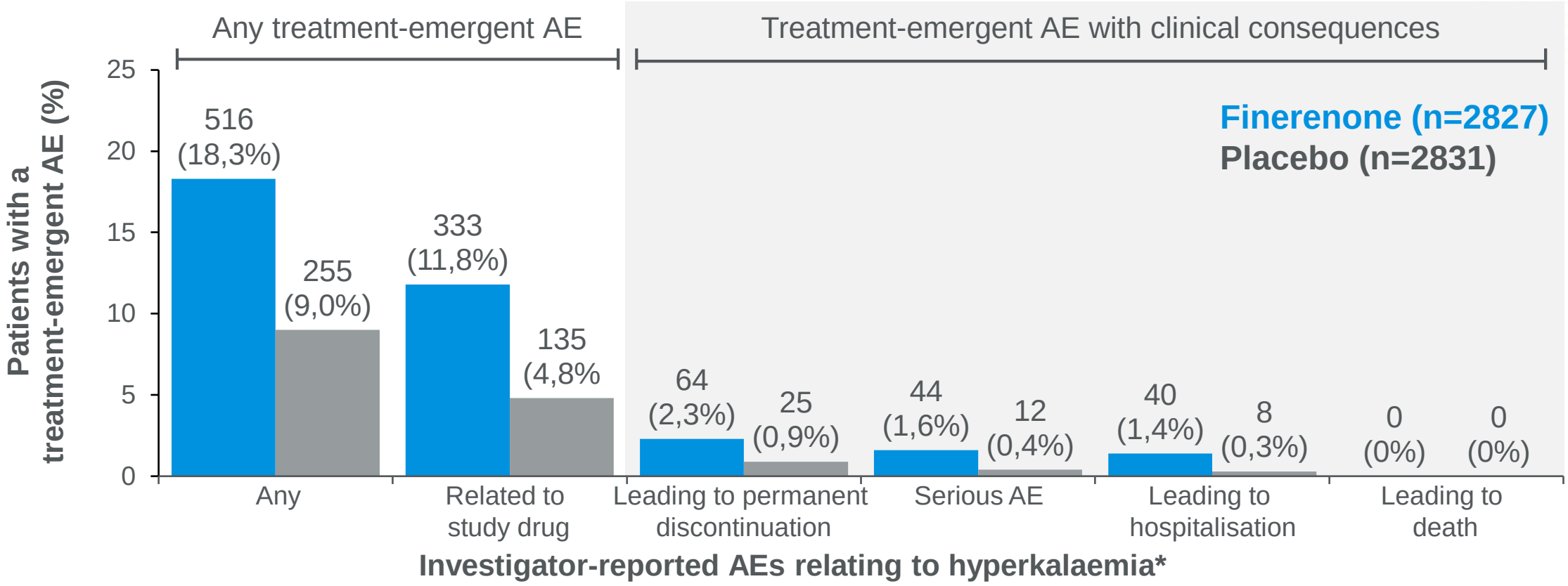


N						
Finerenon	6.510	6.234	5.990	4.916	2.781	912
Placebo	6.487	6.229	5.965	4.878	2.759	887

Agarwal R, et al. Eur Heart J 2022;43:474-484

FIDELITY

Although investigator-reported hyperkalaemia was increased, the clinical impact was minimal



There were no deaths due to hyperkalaemia, and the incidences of treatment discontinuation or hospitalisation due to hyperkalaemia were low

*Investigator-reported AEs using the MedDRA preferred terms 'hyperkalemia' and 'blood potassium increased'. AE, adverse event; SAE, serious adverse event

Bakris GL, *et al.* *NEJM* 2020

KDIGO Recommendations: Measuring Kalio in serum with Finerenon Therapy

$K^+ \leq 4.8$ mmol/l

- Initiate finerenone
  - 10 mg daily if eGFR 25–59 ml/min/1.73 m^2
  - 20 mg daily if eGFR ≥60 ml/min/1.73 m^2
- Monitor K^+ at 1 month after initiation and then every 4 months
- Increase dose to 20 mg daily, if on 10 mg daily
- Restart 10 mg daily if previously held for hyperkalemia and K^+ now ≤5.0 mmol/l

Kidney Int 2022;102:990-999

The challenge: before the treatment of kidney disease we need a diagnosis !

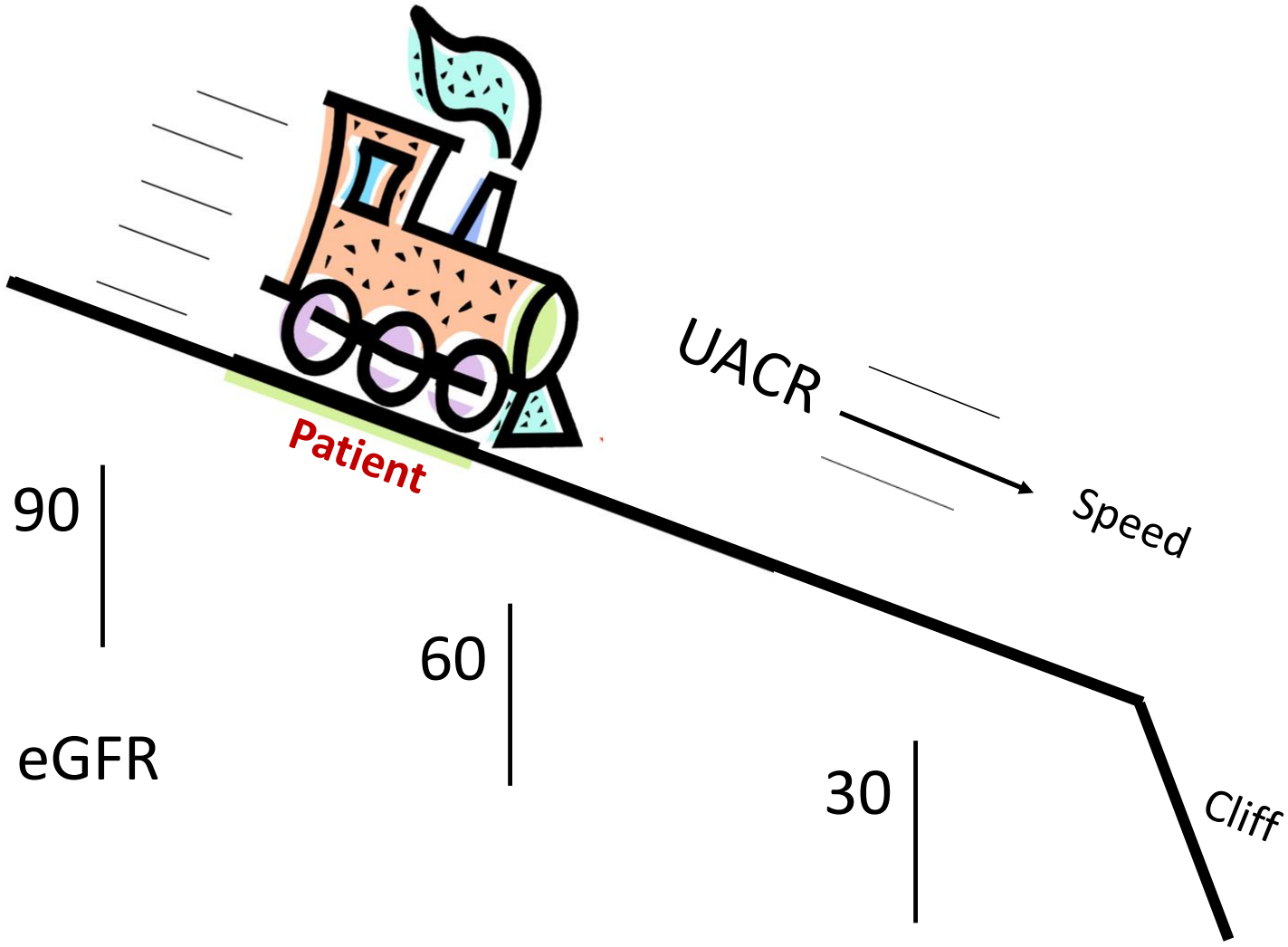
CKD-Definition

KDIGO CKD-Leitlinie; Kidney Int Suppl. 2013;3:1-150

Albuminuria

eGFR

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			


Patient
UACR
Speed
90
60
30
eGFR
Cliff

In Summary: my personal experience

- I dont see potassium raising (all my patients: on top of SGLT2i)
- I see a challenge to interrupt Finerenone treatment due to potassium > 5.5 mmol/L
- My patients do not always come back after 1 month
- My colleagues say *“Dapagliflozin or Empagliflozin are more potent than Finerenone (38% versus 23% RRR)”*. This may not be true because they do not distinguish hemodynamic (rapid) effects versus antifibrotic (long-term) protection
- There is a discussion ongoing whether Finerenone works on top of SGLT2i or viceversa
- What does the A grading (2A vs 1A) – ADA, KDIGO, ESC mean?
- Hot-topic: the “All-in within 6 months” concept. Still a sequential therapy concept in kidney care !?
- The communication with general practitioners about albuminuria. The 5 Ws

Recent clinical guidelines for the management of CKD in patients with T2D recommend a combination of drug therapies to optimally reduce risks,[1–3] with finerenone recommended as a core treatment pillar[4,5]

ERBP European Renal Best Practice

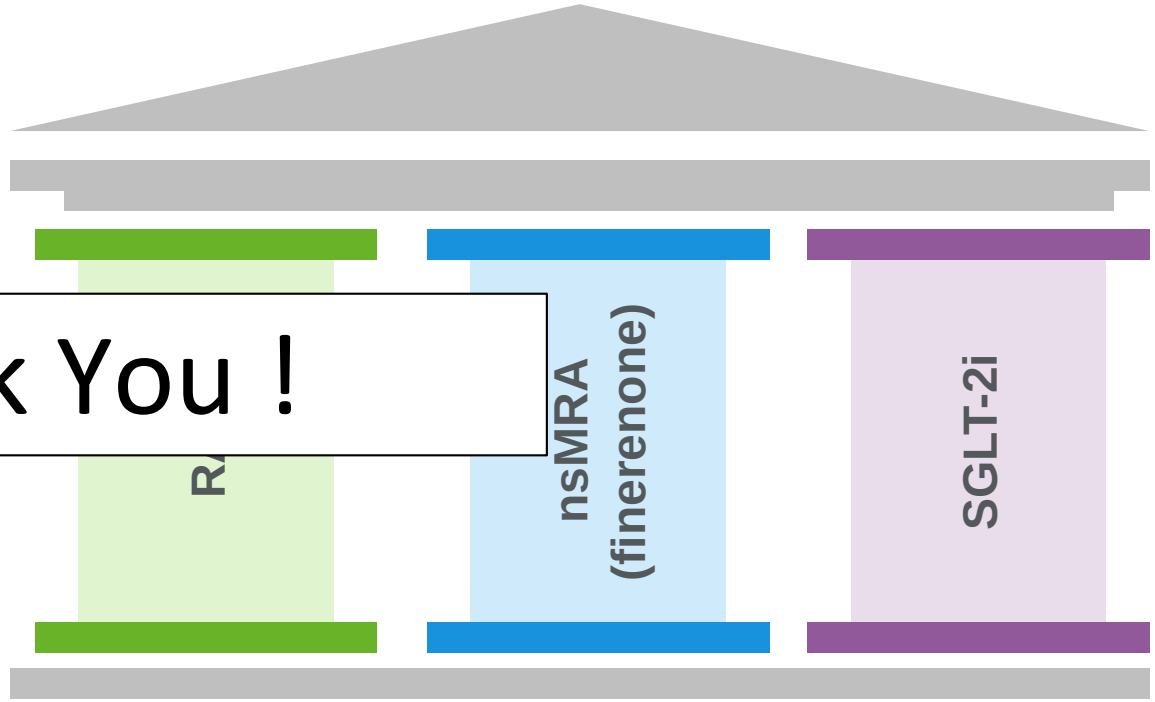
KDIGO Kidney Disease Improving Global Outcomes

ESC European Society

American Diabetes Association

ADA KDIGO Consensus 2022

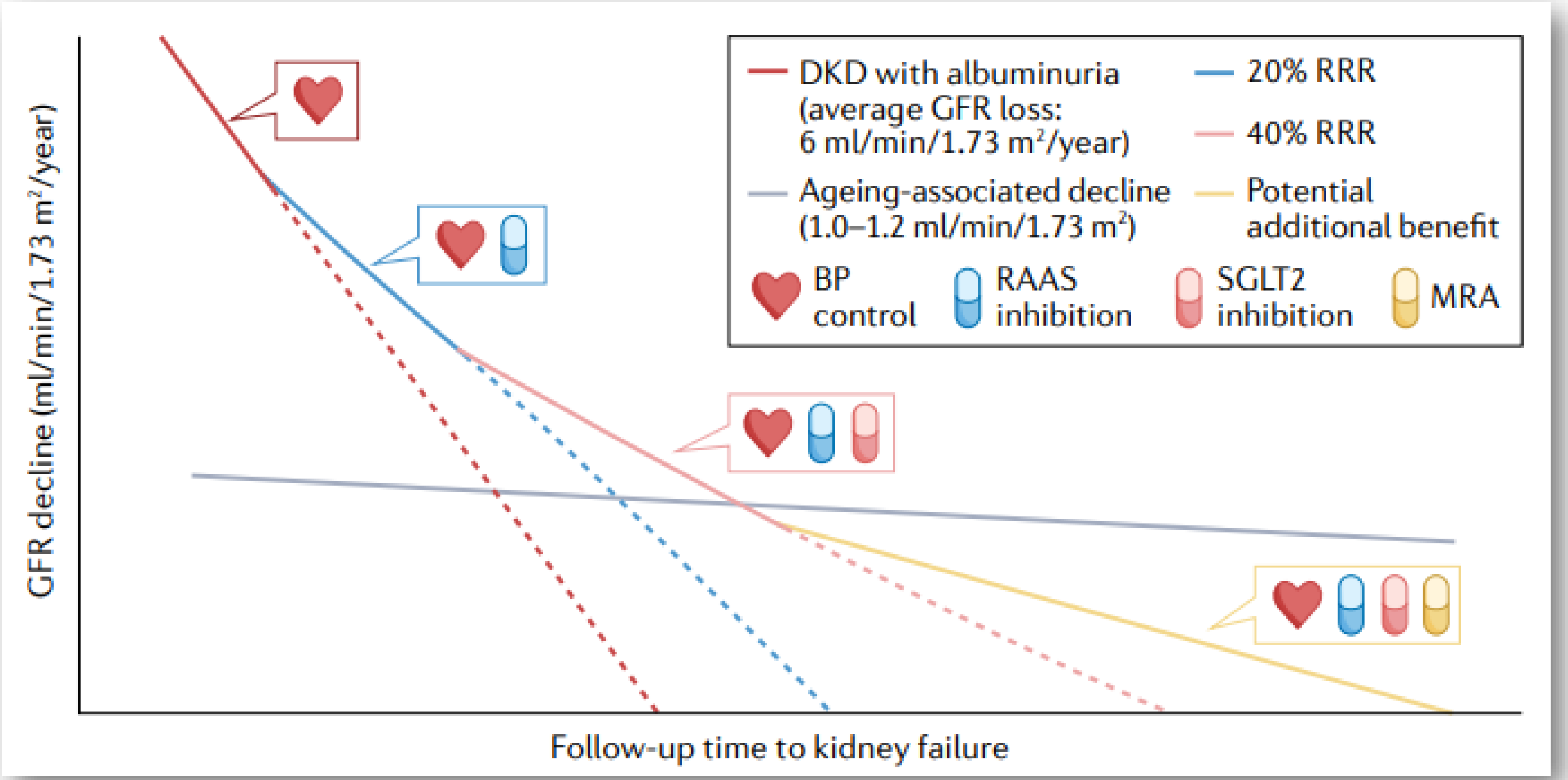
Thank You !



To optimise risk reduction, the three-pillar drug therapy should be combined with glycaemic control, blood pressure control, lipid control, smoking cessation, proper nutrition and regular exercise[4]

ADA, American Diabetes Association; ERBP, European Renal Best Practice; ESC, European Society of Cardiology; KDIGO, Kidney Disease Improving Global Outcomes; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.

1. KDIGO Diabetes Work Group. *Kidney Int* 2022;102:S1–S127; 2. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202; 3. de Boer IH, *et al. Diabetes Care* 2022;45:3075–3090; 4. Blazek O & Bakris GL. *Am Heart J Plus* 2022;19:100187; 5. Marx N, *et al*. *Eur Heart J* 2023: doi:10.1093/eurheartj/ehad192



Fioretto & Pontremoli, Nat Rev Nephrol 2022;18:78-79

My patient in 2020

67y, male, IgAN (biopsy 8y ago)
T2DM (diagnosed 4 years ago)
eGFR 52 ml/min/1.73m^2, UACR 1.2 g/g
sBP 145/87 mmHg
BMI 32 kg/m^2
LDL-C 98 mg/dl
HbA1c 7.6 %
Hb 11.8 g/dl

On treatment with

ramipril 5 mg/d
amlodipine 5 mg/d
simvastatin 20 mg/d
~~aspirin 100 mg/d~~
metformin 2 g/d
DPP-4i
+SGLT2i

Nonsmoker, struggles with lifestyle,
experienced dyspnoea while walking stairs, reports to take 7 pills per day

A different view on the patient: What is important ?

Versus to complete Standard-of-Care

To proceed with organprotective therapy at first place or improve the metabolic and hemodynamic profile ?

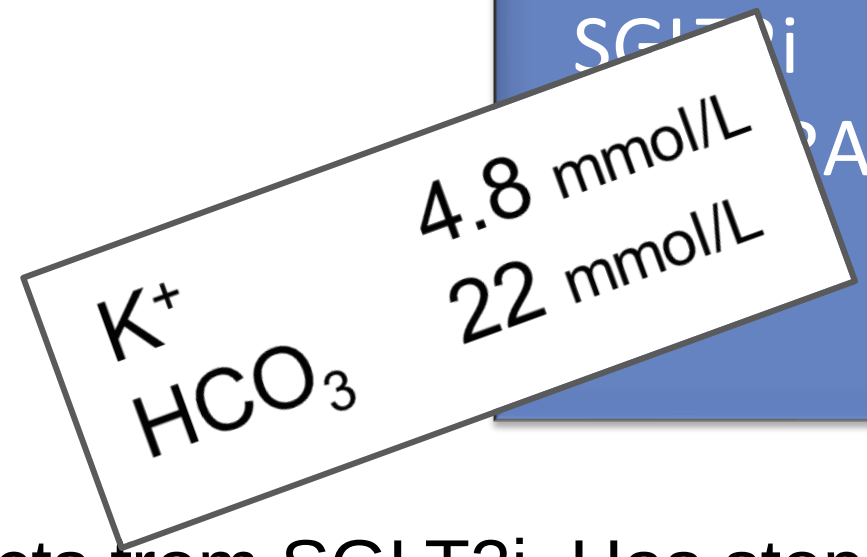
Dietary intervention	- Salt
Diabetes consulting	- HbA1c
Cardiologist	- Stressecho?
Eye Clinic	*- Retinopathy-Lasertherapy*
Podologist	*- Foot care*
Kidney focus	- Compliance! Should Nephrology introduce the beneficial model of involving heart failure nurses?

Patient should come back in 3 months

Did not come after 3 months
but 6 months later *with concerns*

sBP	☺	132/78 mmHg
eGFR	☹	42 ml/min/1.73m²
UACR	☺	0.4 g/g
BMI	☺	minus 8 kg
LDL-C	☺	72 mg/dl
HbA1c	☺	6.5 %
Hb	⬆	13.2 g/dl

PolyPill	ACE-I/CaA/Statin (10/10/40)
Indapamide	1x1,5 mg/d
Metformin	2x500 mg/d
SGLT2i	1x1
GLP1-RA	1xWeek sc



Real patients, few changes

Did not report side effects from SGLT2i. Has stopped aspirin.
Diabetologist: switched DPP4i to GLP1-RA
Qualified for Finerenone treatment

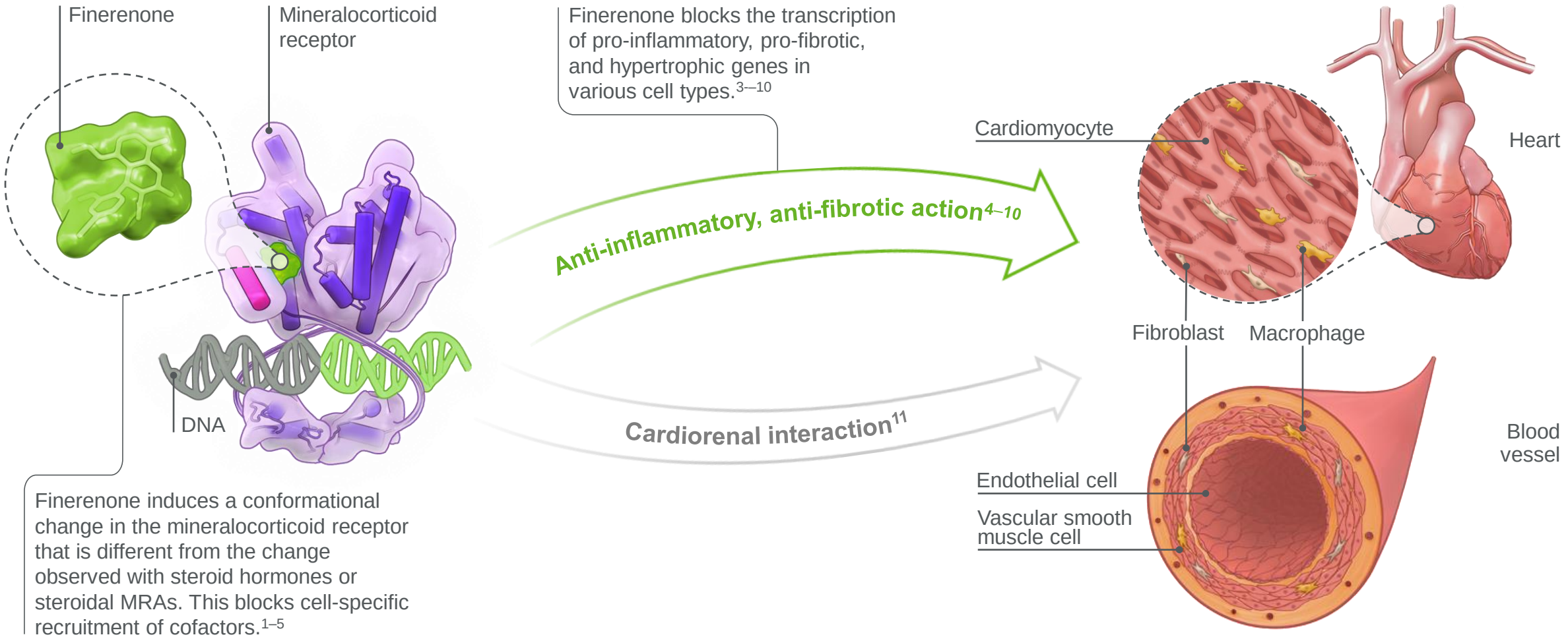
2021-2023

sBP	130/75 mmHg
eGFR	40 ml/min/1.73m^2
UACR	175 mg/g
BMI	gained 2 kg
LDL-C	65 mg/dl
HbA1c	7.1 %
K^+	4.8 mmol/L
HCO_3	22 mmol/L

PolyPill	ACE-I/CaA/Statin (10/10/40)
Indapamide	2.5 mg/d
Metformin	2x500 mg/d
SGLT2i	10 mg/d
Finerenone	10 mg/d

Stopped GLP1-RA because of recurrent nausea

The proposed mode of action of finerenone in the heart and blood vessels



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CardioRenal Initiative

Albuminuria

FIDELIO and FIGARO: Finerenone for the treatment of CKD (with albuminuria) in adults with T2DM and CKD

GFR

GFR-Kategorien (ml/min/ 1,73 m²) Beschreibung und Bereich				Persistente Albuminurie-Kategorien Beschreibung und Bereich		
				A1	A2	A3
				Normal bis leicht erhöht	Moderat erhöht	Stark erhöht
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal oder hoch	≥90			
	G2	Leicht verringert	60-89			
	G3a	Leicht bis moderat verringert	45-59			
	G3b	Moderat bis stark verringert	30-44			
	G4	Stark verringert	15-29			
	G5	Nierenversagen	<15			

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

META-ANALYSIS | OCTOBER 04 2023

Effects of Mineralocorticoid Receptor Antagonists for Chronic Kidney Disease: A Systemic Review and Meta-Analysis

Subject Area: Nephrology

Chen-Yi Yuan; Yuan-Cheng Gao; Yi Lin; Lin Liu; Xiao-Gang Shen; Wen-Li Zou; Min-Min Wang; Quan-Quan Shen; Li-Na Shao; Yue-Ming Liu; Jia-Wei Zhang; Zhi-Hui Pan; Yan Zhu; Jing-Ting Yu; Xu-Guang Yu; Bin Zhu

Am J Nephrol (2024) 55 (1): 1–17.

53 trials, 6 different MRAs, 22,792 participants

UACR (weighted mean difference [WMD],	−91 mg/g	(95% CI −140,−42 mg/g)
24-h urinary protein excretion	−0.2 g	(95% CI, −0.28, −0.12 g),
eGFR	−1.99 mL/min/1.73 m2	(95% CI, −3.28, −0.70)
chronic renal failure events	RR, 0.86	(95% CI, 0.79–0.93)
cardiovascular events	RR, 0.84	(95% CI, 0.77–0.92)
Hyperkalemia	RR, 2.04	(95% CI, 1.73–2.40)
Hypotension	RR, 1.80	(95% CI, 1.41–2.31).

Increased the risk of breast disorders