Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Deutsches Zentrum für
Herzinsuffizienz (DZHI)

Preventing CKD: today and in future

Christoph Wanner, Würzburg and Oxford, Germany and UK

UK

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

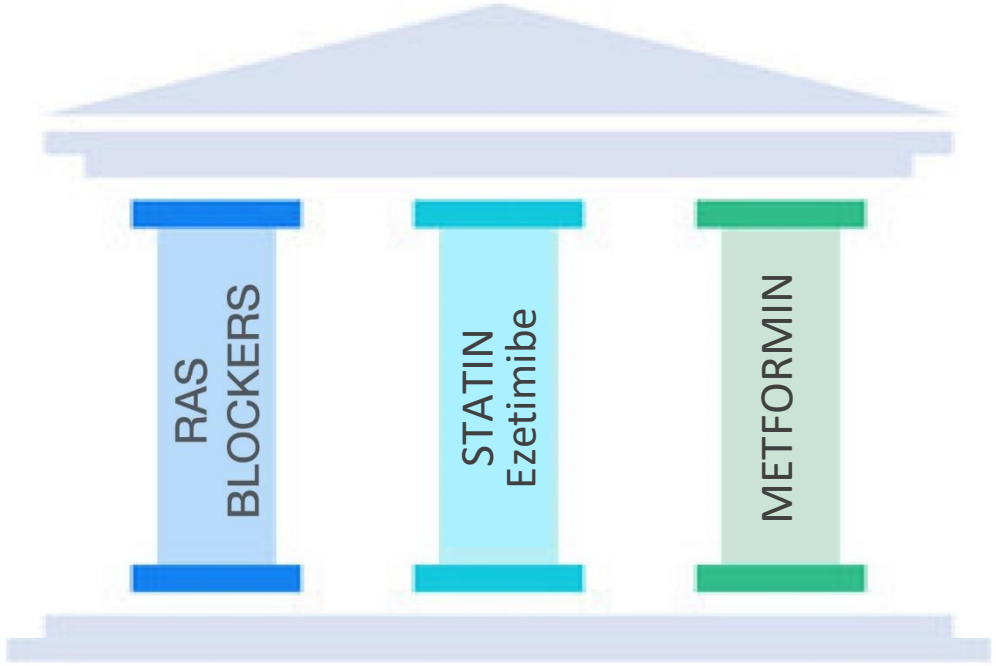
OXFORD
UNIVERSITY OF OXFORD
POPULATION
HEALTH

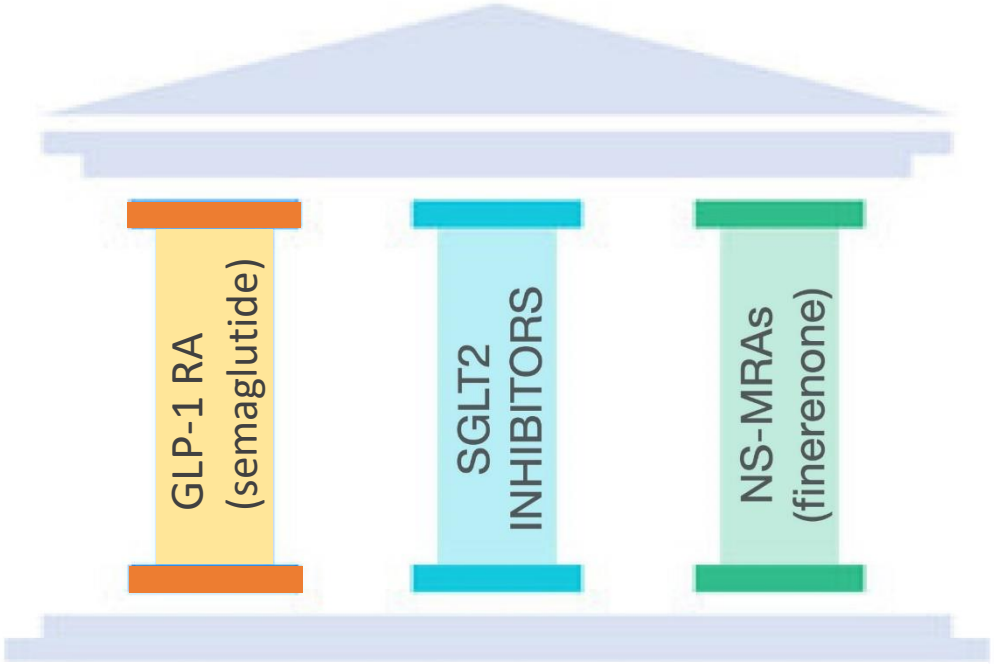
Disclosures

Honoraria: Steering Committees, AdBoards & Lecturing

Alexion, Amgen, Astellas, AZ, Bayer, BI, CSL-Vifor, FMC, GSK, Lilly, MSD, Novartis, NovoNordisk, Sanofi

A 3 Pillar Approach
- Organ Protective Therapies -





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

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

Nephropathy composite end point‡‡	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)	NA

‡‡ The nephropathy end point was a five-component composite of death from renal causes, initiation of long-term renal replacement therapy (dialysis or transplantation), onset of a persistent eGFR lower than 15 ml per minute per 1.73 m^2, persistent 50% reduction in eGFR relative to baseline, or onset of persistent macroalbuminuria (urinary albumin-to-creatine ratio, >300 mg per gram).

NEJM 2023;389:2221-2232

Global Science. Local Change.

KDIGO Controversies Conference on Maintaining Kidney Health and Preventing CKD

November 30 – December 3, 2023

Rome, Italy

Maintaining or **Restoring** Kidney Health

Albuminuria

GFR

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

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			

JAMA 2023;330:
1266-1277

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

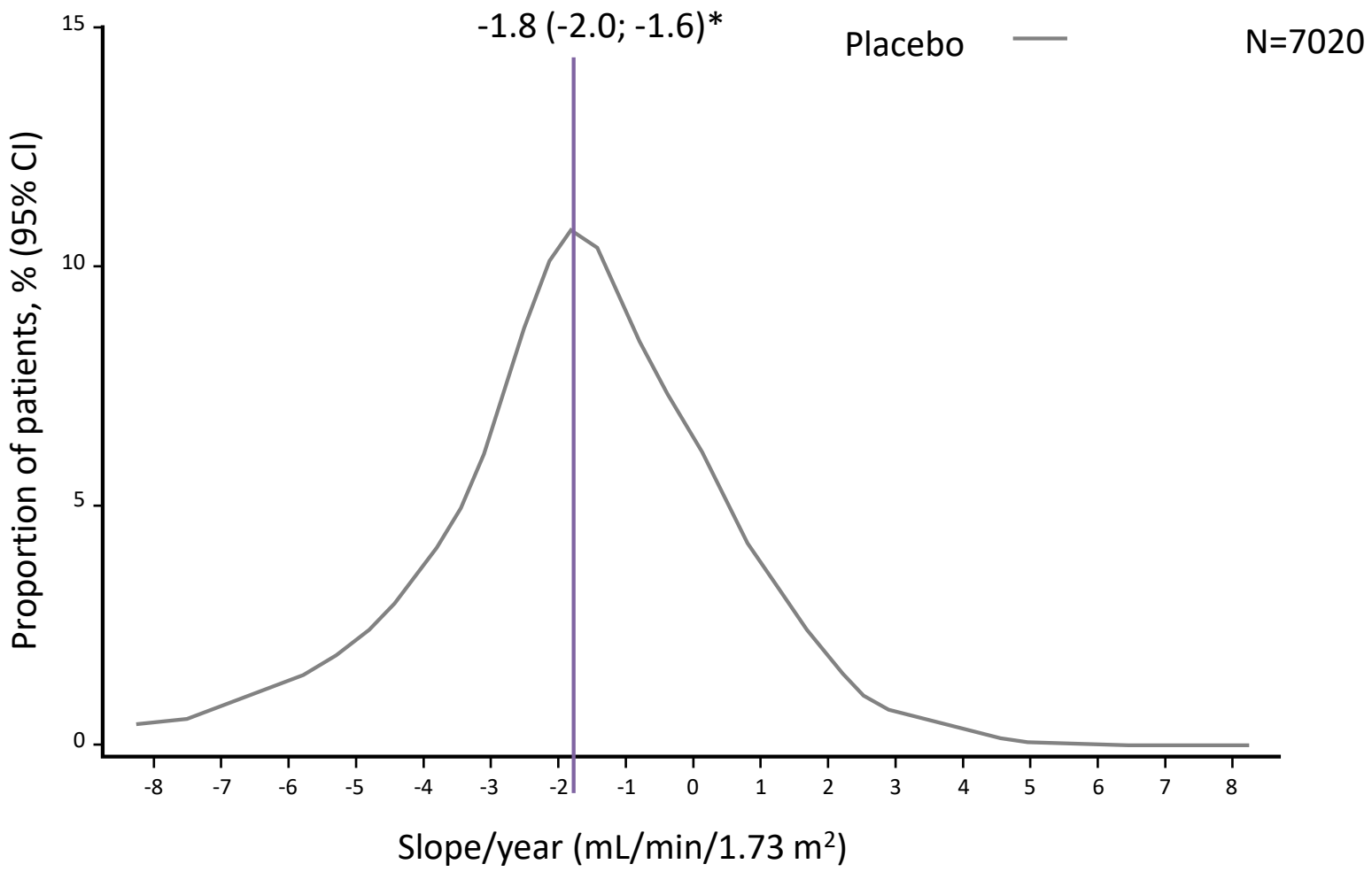
C) Environmental

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

Discussed by

In a controversy conference on early prevention, Rome, Dec 3-5, 2023

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

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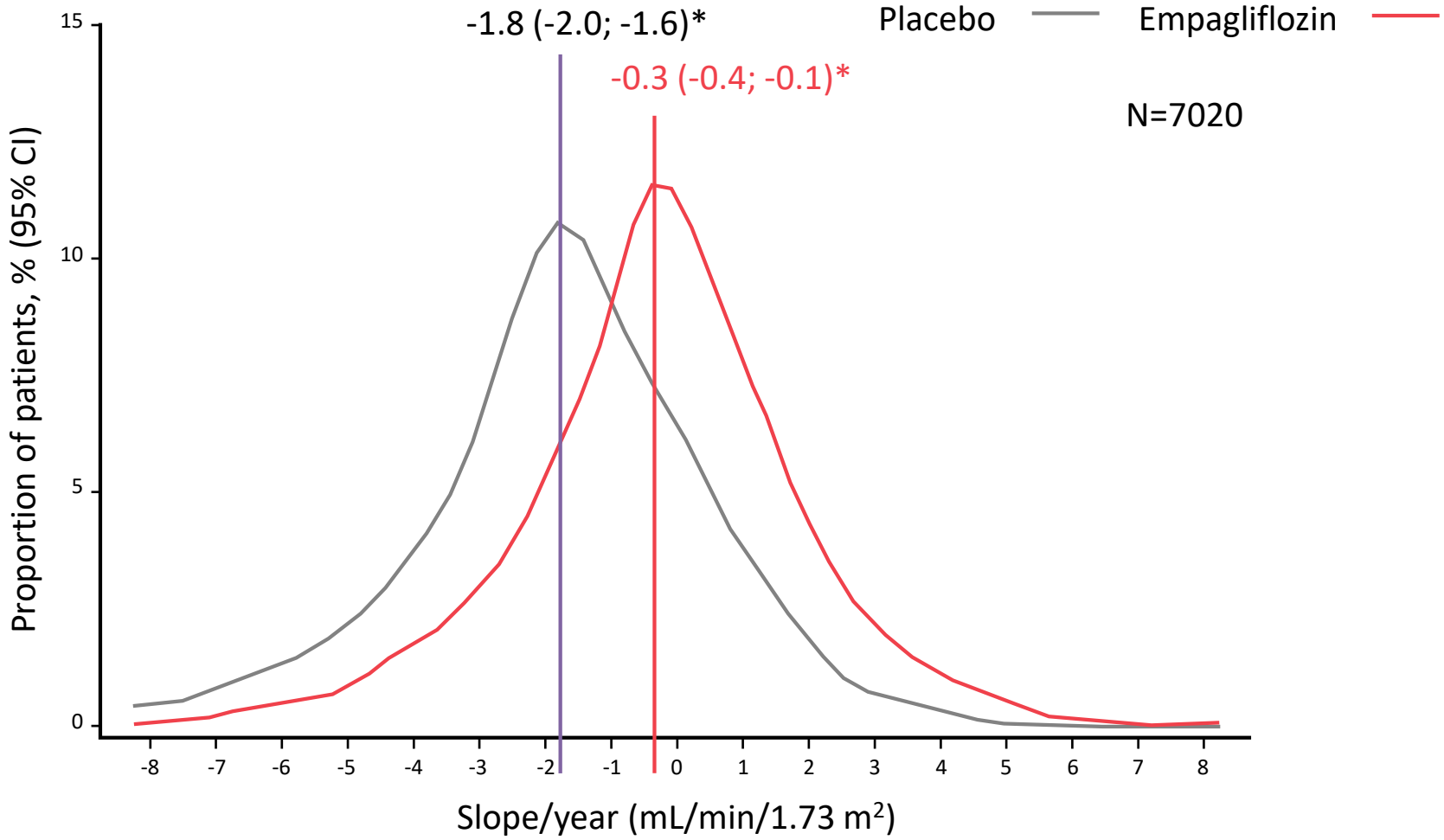

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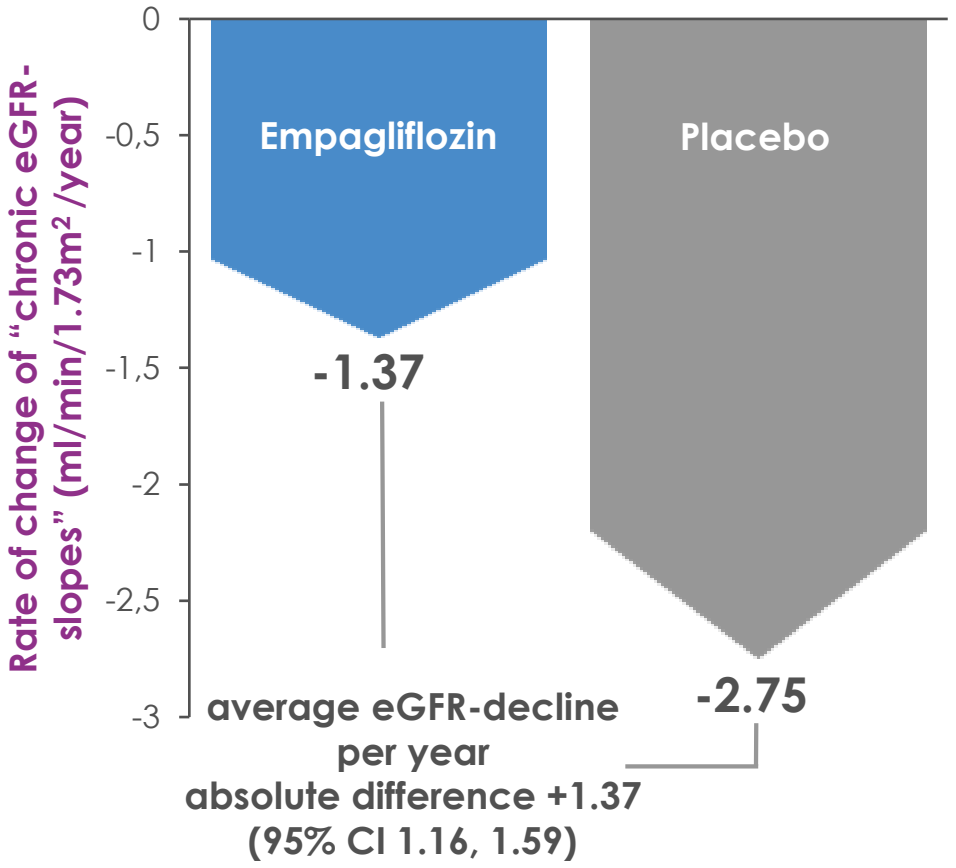
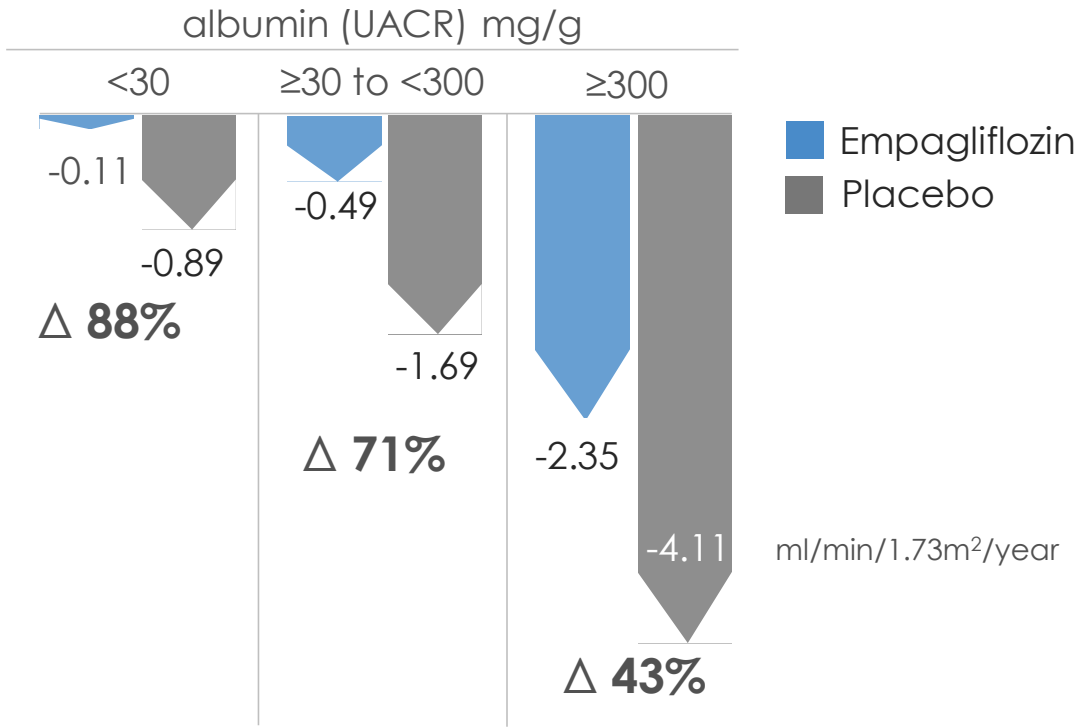
Wanner et al JASN 2018;29:2755-2769

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



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

Do we need an implementation trial ?

Science is global - Implementation is local

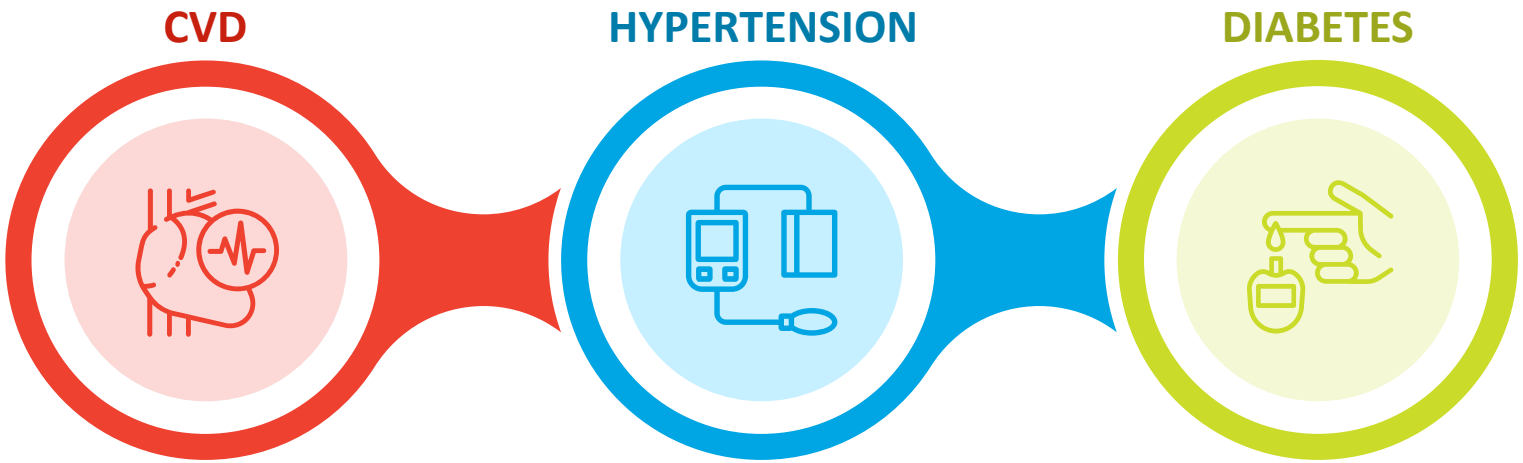
We need more trials ?

The lack of diagnosis (missing screenings)

„Before the treatment there is a diagnosis“

Adherence - Compliance

Even in these patients, rates of undiagnosed CKD are as high as 95% [3–5,b]



Prevalence of CKD[1,2,a]

KDIGO defines patients at high risk for CKD as those with:

SCREENING IS RECOMMENDED IN THESE PATIENTS[1]

[a]Based on data from USA 2015-2018; [b]Based on CKD Stage 3 diagnosis rate data from German, France, Japan and US cohorts included in REVEAL-CKD study. 1. ISN. CKD Early Identification & Intervention Toolkit. Available at: https://www.theisn.org/wp-content/uploads/2021/10/ISN_KDIGO_EarlyScreeningBooklet_WEB_updatedOct11.pdf (Accessed April 2023); 2. USRDS. 2021 Annual Data Report. Available at: https://usrds-adr.niddk.nih.gov/2021 (Accessed April 2023); 3. Schneider MP, et al. Presented at WCN, March 24–27, 2022. Virtual and Kuala Lumpur, Malaysia; 4. Sultan AA, et al. Presented at ADA, June 25–29, 2021. Virtual ; 5. Virgitti JB, et al. Presented at ASN, November 4–7, 2021. Virtual

Why A and E

KDIGO CKD-Guideline; 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)		
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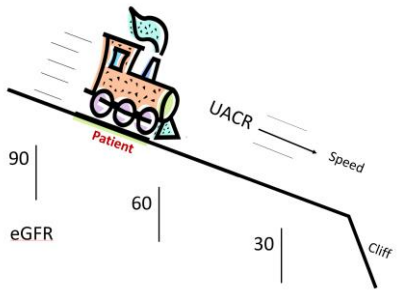
General Practicioners do not measure UACR

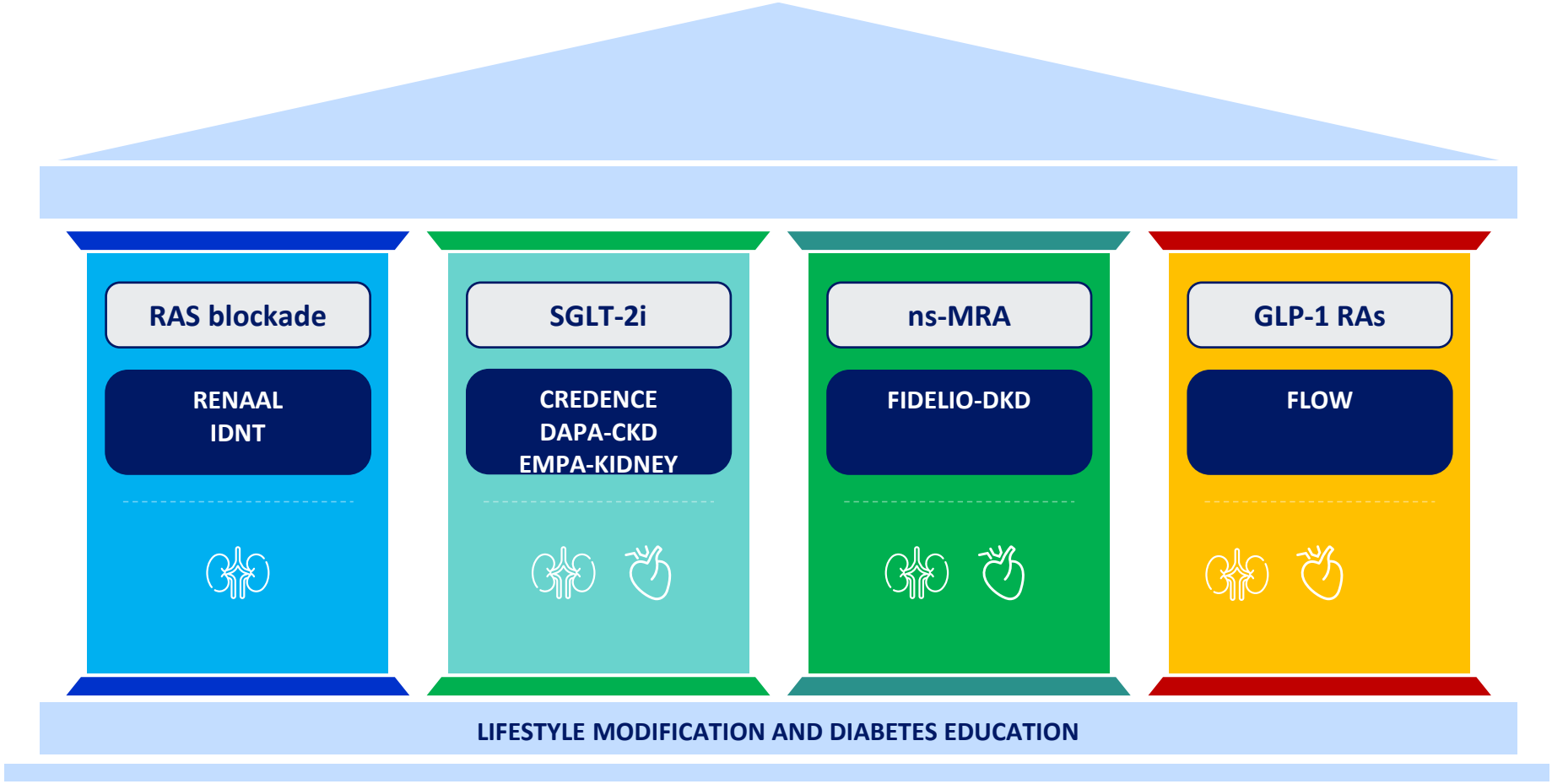
A task for specialists to collaborate with GPs?

Please answer the following W‘s for UACR

When	do I sample ?	Morning spot urine
Where	to send and how ?	Central lab, together with blood
What	does it cost ?	3 Euro 40 Cent (Germany)
Who	is paying ?	Insurance (different among countries)
What	does it mean (mg/g) ?	



The 4 Foundational Therapies – The 4 Pillar Approach



Modified figure from: 2023 ADA, Standards of Medical Care in Diabetes - 2023: Diabetes Care, December 2022, 46, Supplement 1; Agarwal R et al, Nephrology Dialysis Transplantation (2023) 38: 253–257

How to optimally implement ….. ?

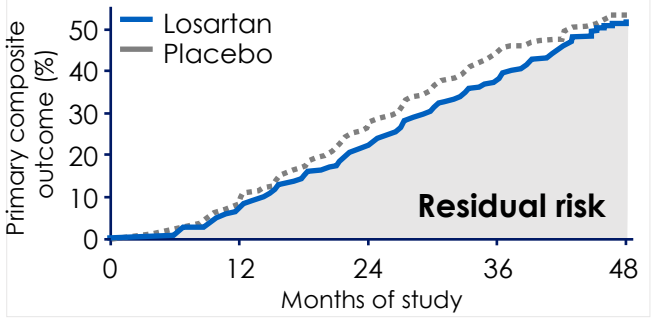
- **Why do we need** all 4 treatments ?
- **A good sequence**: RASi - SGLT2i - nsMRA ?
- **Add** GLP1-RA **at any time** – preference by specialists, by ‚consensus' !
- **All-in -** in 3 months – Do we hesitate because we think we may cause harm ?
- **Adherence/Compliance**: the polypill for baseline therapy – standard of care
  (RASi, CCBs, statin – or RASi, HCTZ, CCBs)

To overcome barriers to combine all current kidney protective therapies

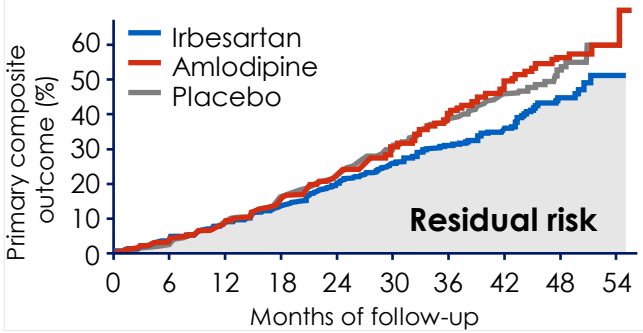
Residual risk despite available treatment options

RAAS blockers

RENAAL[1]

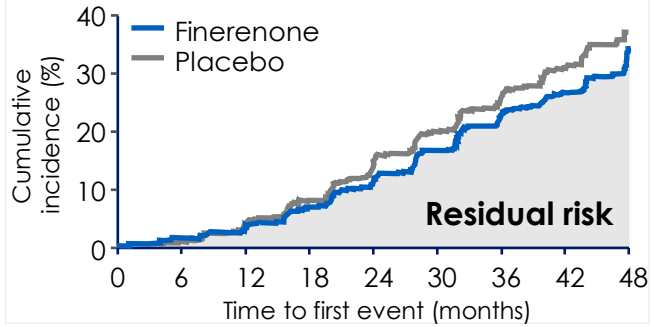


IDNT[2]



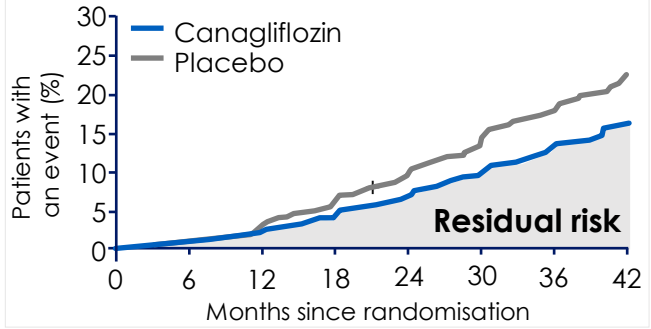
Non-steroidal MRAs

FIDELIO-DKD[3]

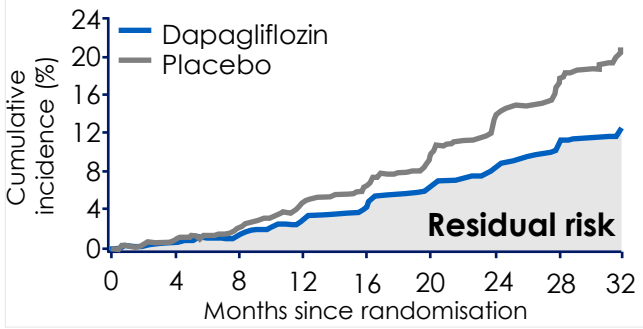


SGLT2 inhibitors

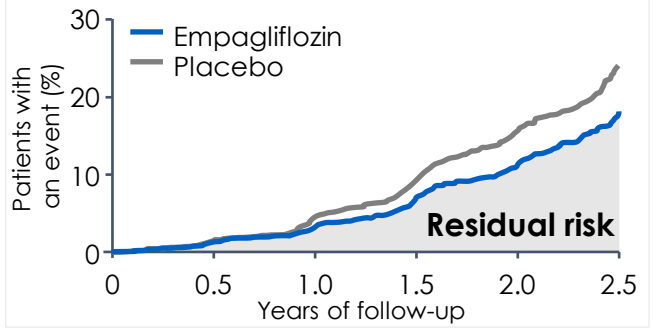
CREDENCE[4]



DAPA-CKD[5]



EMPA-KIDNEY[6]



1. Brenner BM et al. *NEJM* 2001;345:861-69; 2. Lewis EJ et al. *NEJM* 2001;345:851-60; 3. Bakris GL et al. *NEJM* 2020;383:2219-29; 4. Perkovic V et al. *NEJM* 2019;380:2295-306; 5. Heerspink HJL et al. *NEJM* 2020;383:1436.46; 6. The EMPA-KIDNEY Collaborative Group. *NEJM* 2023;388:117-27

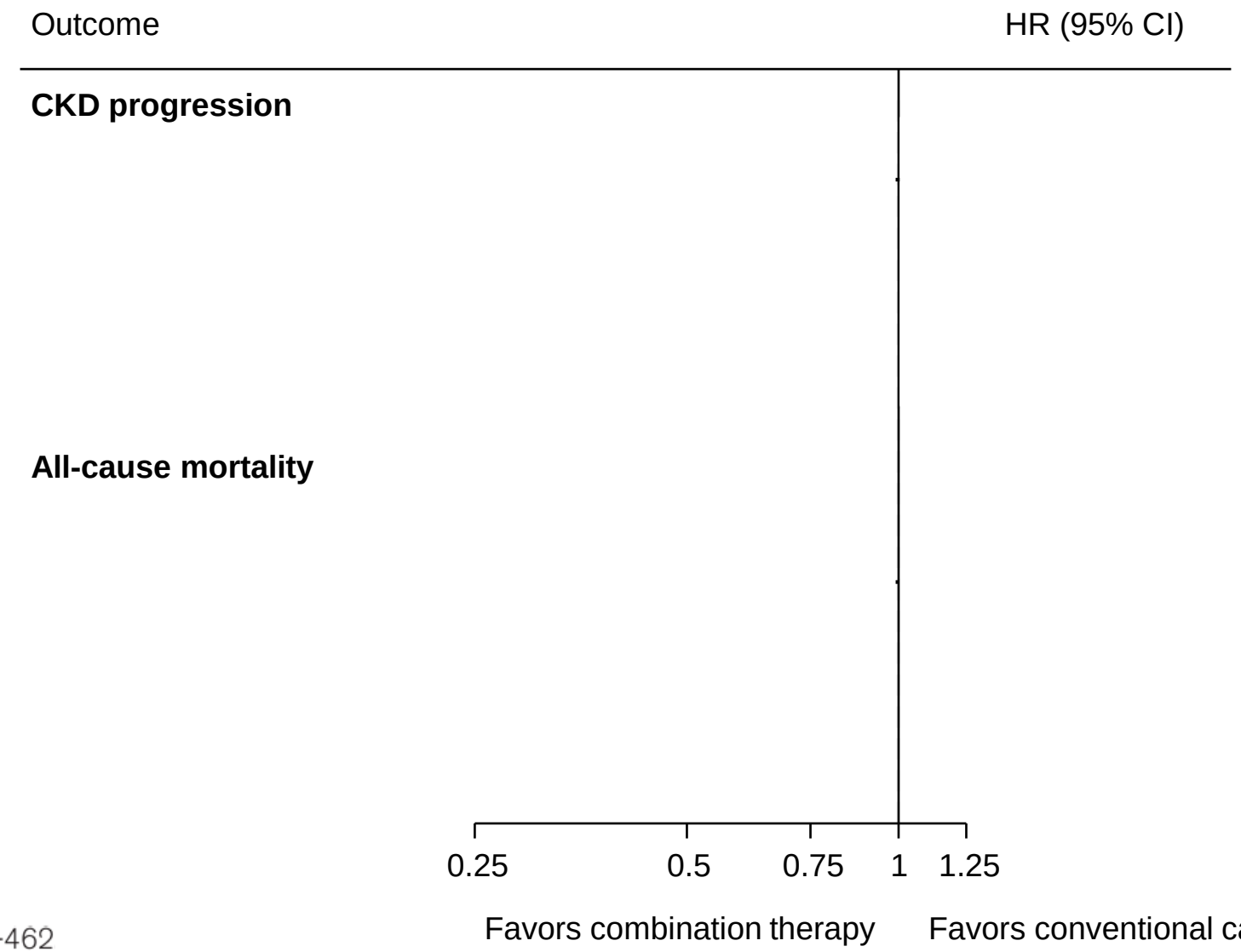
ORIGINAL RESEARCH ARTICLE

Estimated Lifetime Cardiovascular, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria

Brendon L. Neuen, MBBS, MSc, PhD; Hiddo J.L. Heerspink, PhD; Priya Vart, PhD; Brian L. Claggett, PhD; Robert A. Fletcher, MSc; Clare Arnott, MBBS, PhD; Julianna de Oliveira Costa, PhD; Michael O. Falster, PhD; Sallie-Anne Pearson, PhD; Kenneth W. Mahaffey, MD; Bruce Neal, MB ChB, PhD; Rajiv Agarwal, MD; George Bakris, MD; Vlado Perkovic, MBBS, PhD; Scott D. Solomon, MD; Muthiah Vaduganathan, MD, MPH

Circulation. 2024;149:450–462

Effects of combination therapy on CKD progression and all-cause mortality



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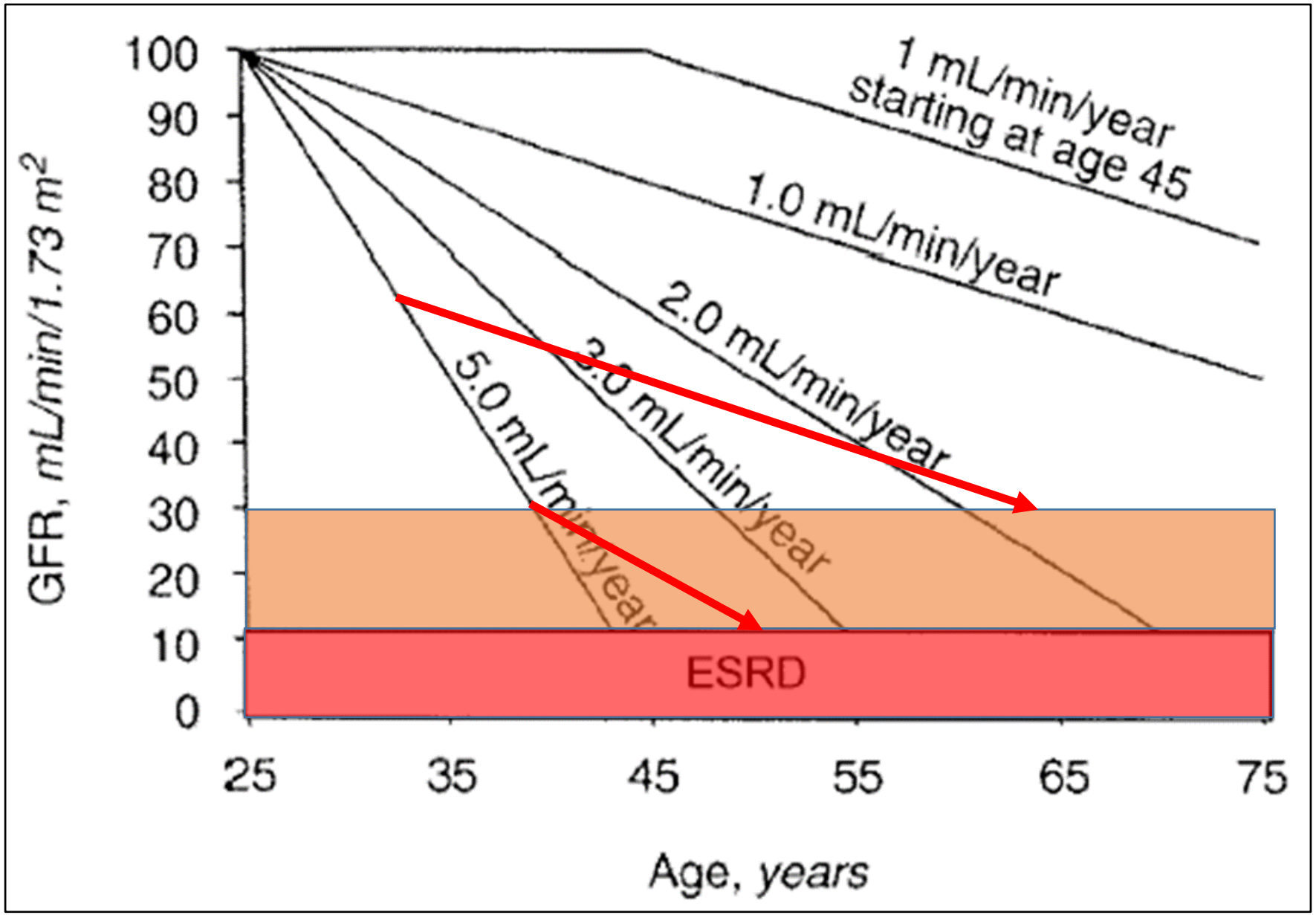
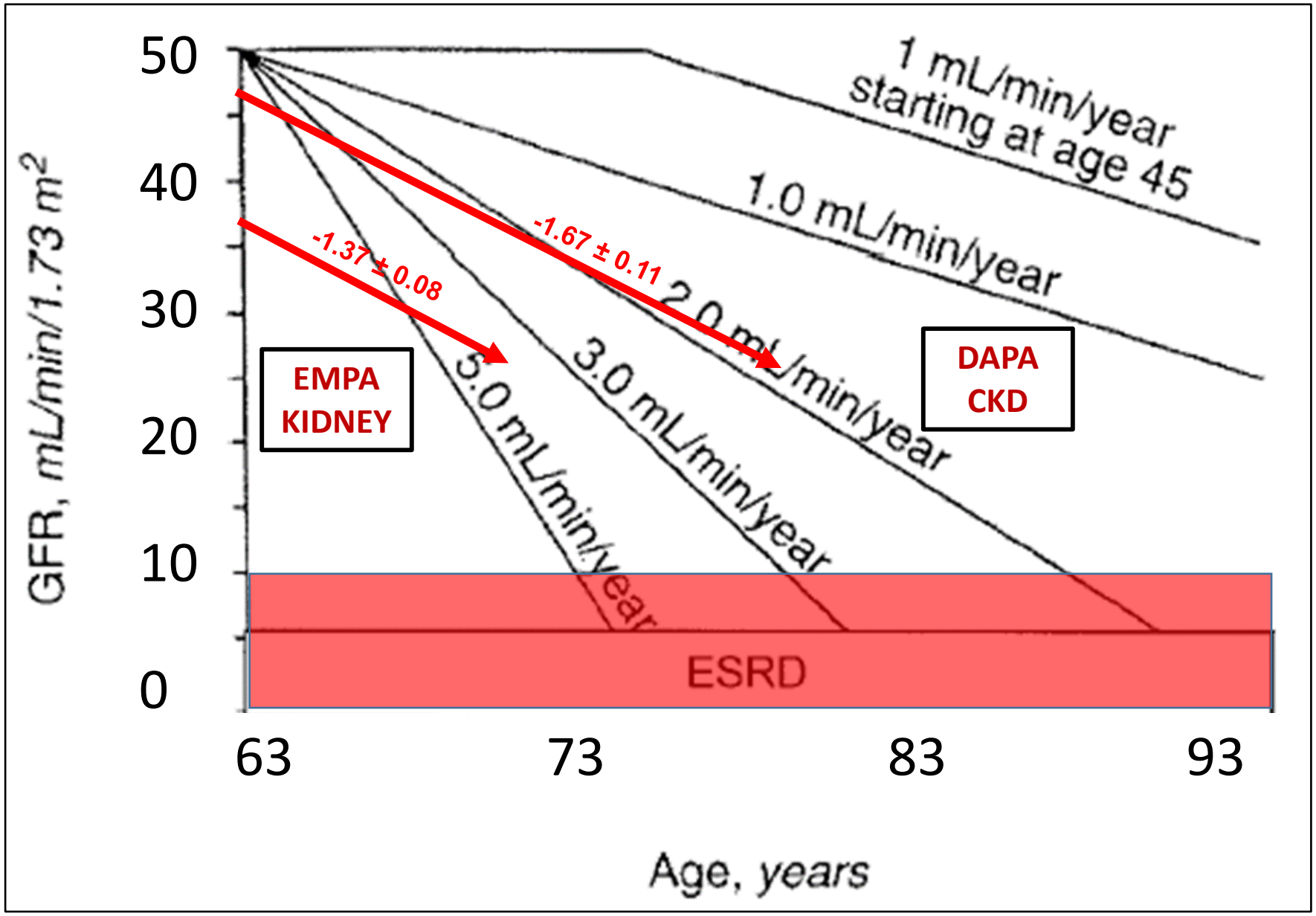


Willmer et al. J Am Soc Nephrol. 2003;14:3217-3232.



Wilmer et al. J Am Soc Nephrol. 2003;14:3217-3232.

Intermediate summary: to overcome barriers to combine all kidney protective therapies

- **We need** all 4 treatments
- **Any sequence** is good, as long as implemented. Dont lose time
- **Add** GLP1-RA **at any time**
- **All-in** appears to be a good concept
- **Ask the GP** and the patient may never need a nephrologist

Do we need more trials ?

Dissemination is easy

Do we need an implementation trial ?

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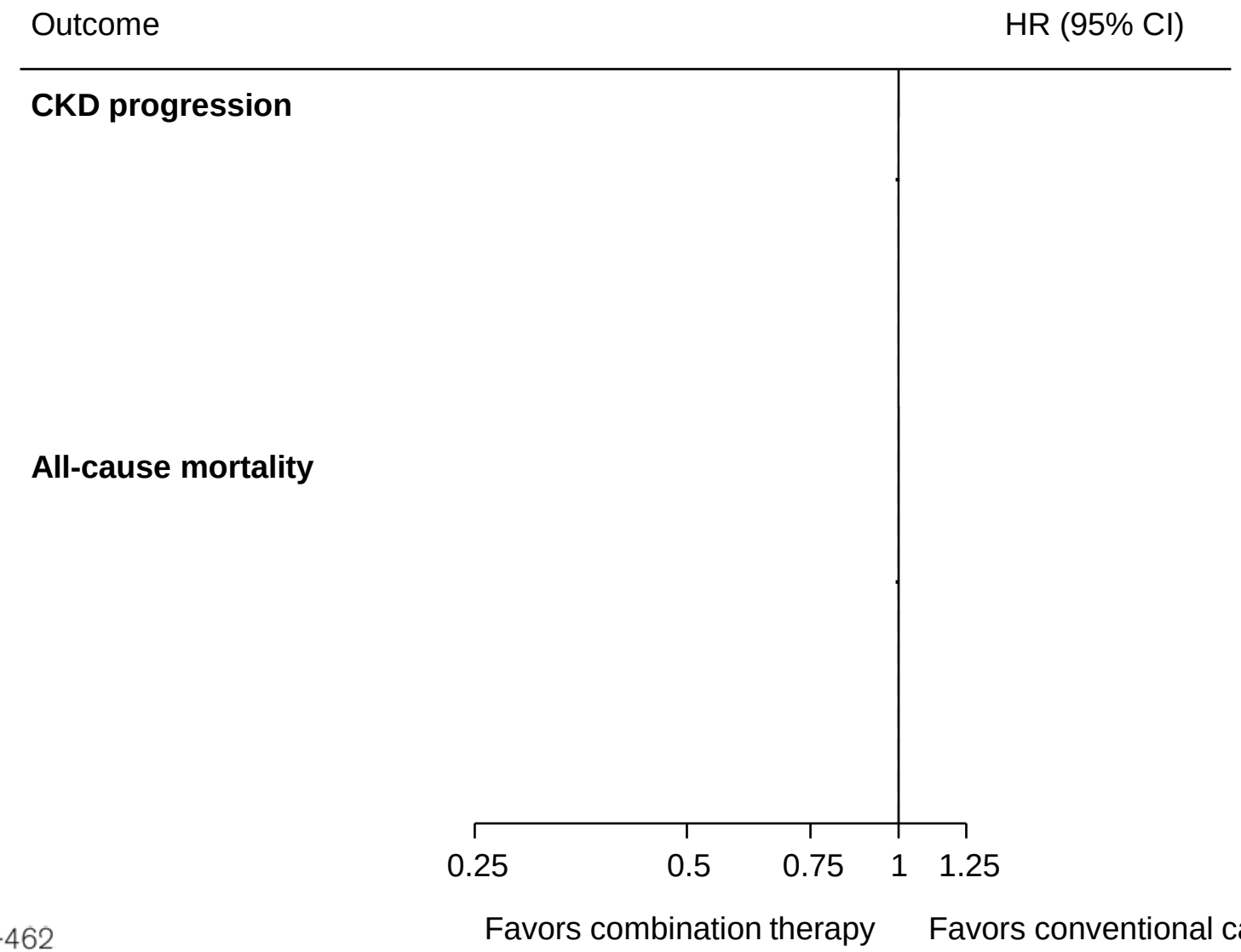

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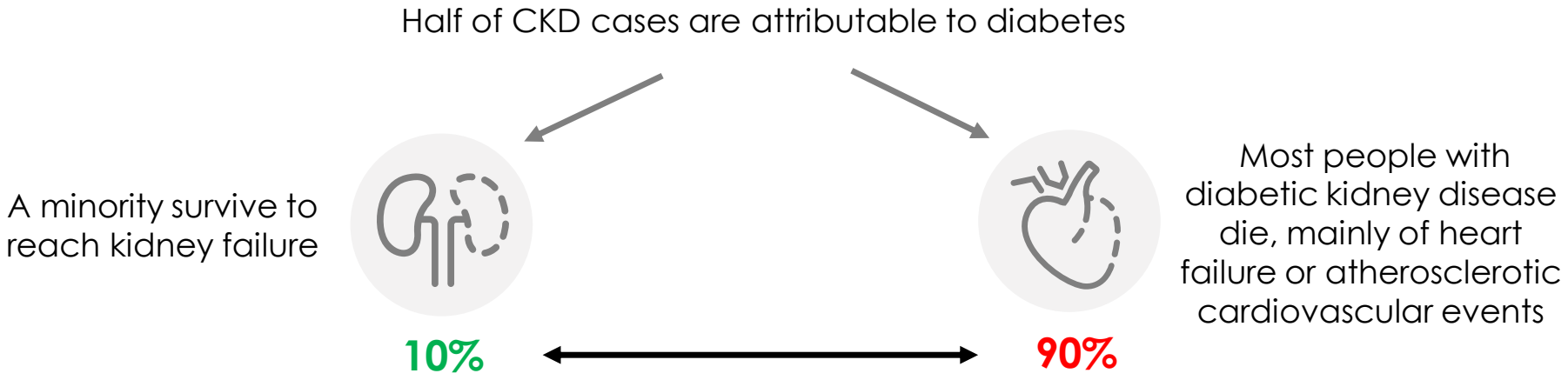
To overcome barriers on

optimally combine all current renoprotective treatments?

What problem are we trying to solve?

FLOW
semaglutide | renal outcomes trial



FLOW Authors: "Clinicians and patients will need to consider the order and priority of use for semaglutide" …. "the benefits for these outcomes shown in the FLOW trial provide a rationale to consider the use of semaglutide as part of initial therapeutic options in this patient population"

Prioritization-Opinion: SLT2i for kidney outcomes and HF, Finerenone for both, kidney and CV outcomes, Semaglutide for CV outcomes **?**

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Tuttle KR et al. *Clin J Am Soc Nephrol* 2022;17:1092–1103, Perkovic V et al. NEJM 2024, May 24. doi: 10.1056/NEJMoa2403347. Online ahead of print
.

Death from any Cause: Event rates in Placebo treated patients in Landmark trials

		no. of patients with event per 1000 patient-yr	Age yr
EMPA-REG OUTCOME	(2015)	28.6	63.2
CREDENCE	(2019)	35.0	62.2
DAPA-CKD	(2020)	31.0	61.9
FIDELIO-DKD	(2021)	32.3	65.7
EMPA KIDNEY	(2023)	25.8	63.8
FLOW	(2024)	48.4	66.6

>95% ACEi/ARB
>80% 'statin'
>15% SGLT2i

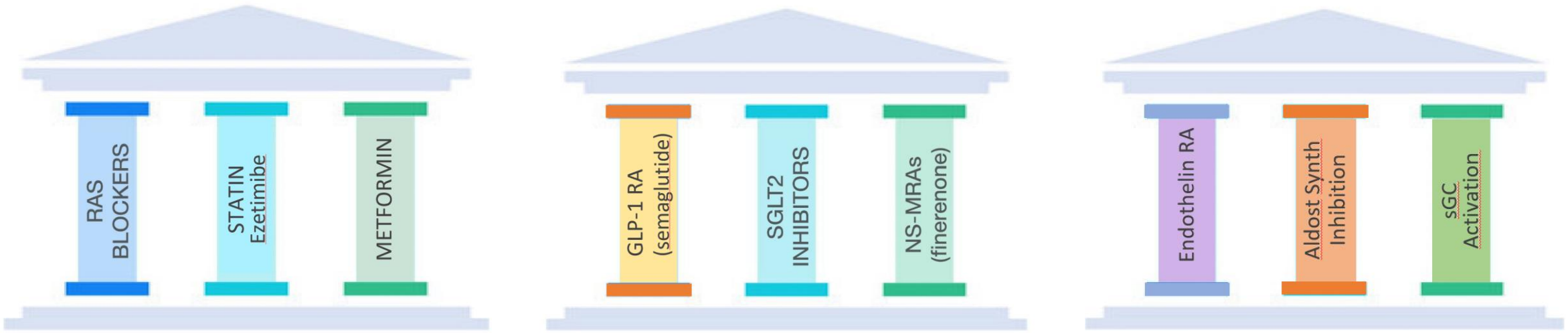
Semaglutide reduced mortality in the FLOW trial

Current and future treatment with an one size fits all approach

Basic Standard-of-Care

Current Organ Protective Treatments

Future Potential Additions



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

EASi-KIDNEY
Aldosterone Synthase inhibition & Empagliflozin in CKD

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


GINGLE BELLS

EASi-KIDNEY
Aldosterone Synthase inhibition & Empagliflozin in CKD

Thank You!