Diabetic Nephropathy Updates

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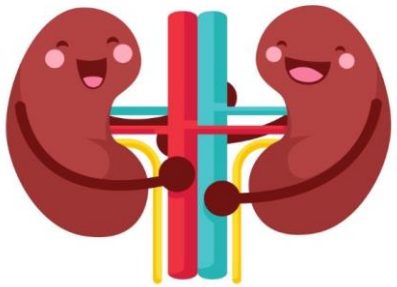
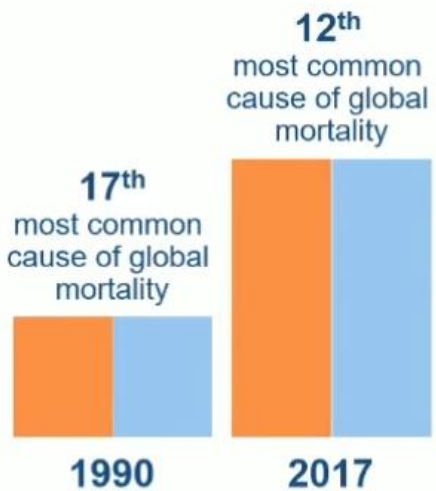


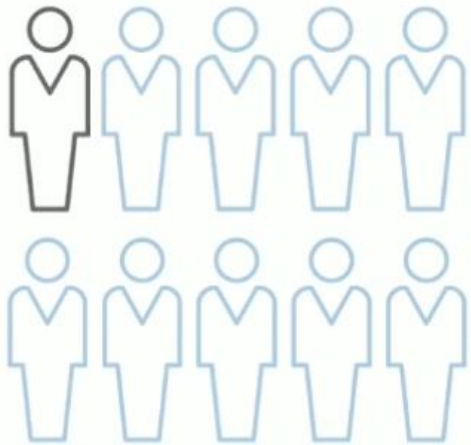
22 may 2025,Isfahan, Iran

Prevalence of chronic kidney disease

CKD rank (causes of total number of global deaths)[1]



Estimated prevalence of CKD globally: 9%[1]



Undiagnosed CKD[2]

Early-stage asymptomatic CKD

Leading causes of CKD[2]

Diabetes

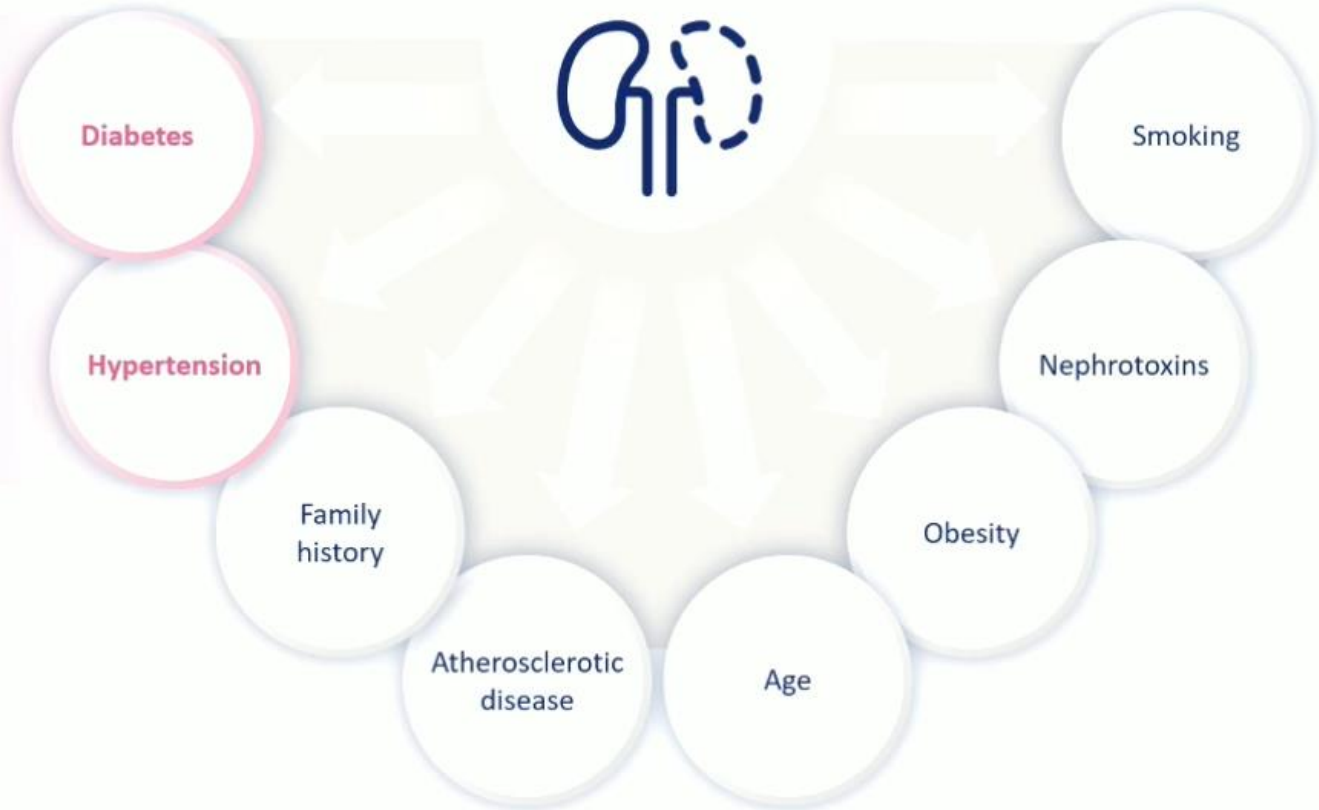
43.5% of patients with T2D in the US also have CKD[3]

Hypertension

1. GBD Chronic Kidney Disease Collaboration. Lancet. 2020; 395:709-733
2. Jha V et al. Lancet 2013; 382:260-272
3. Bailey RA, et al. BMC Res Notes 2014; 7:415

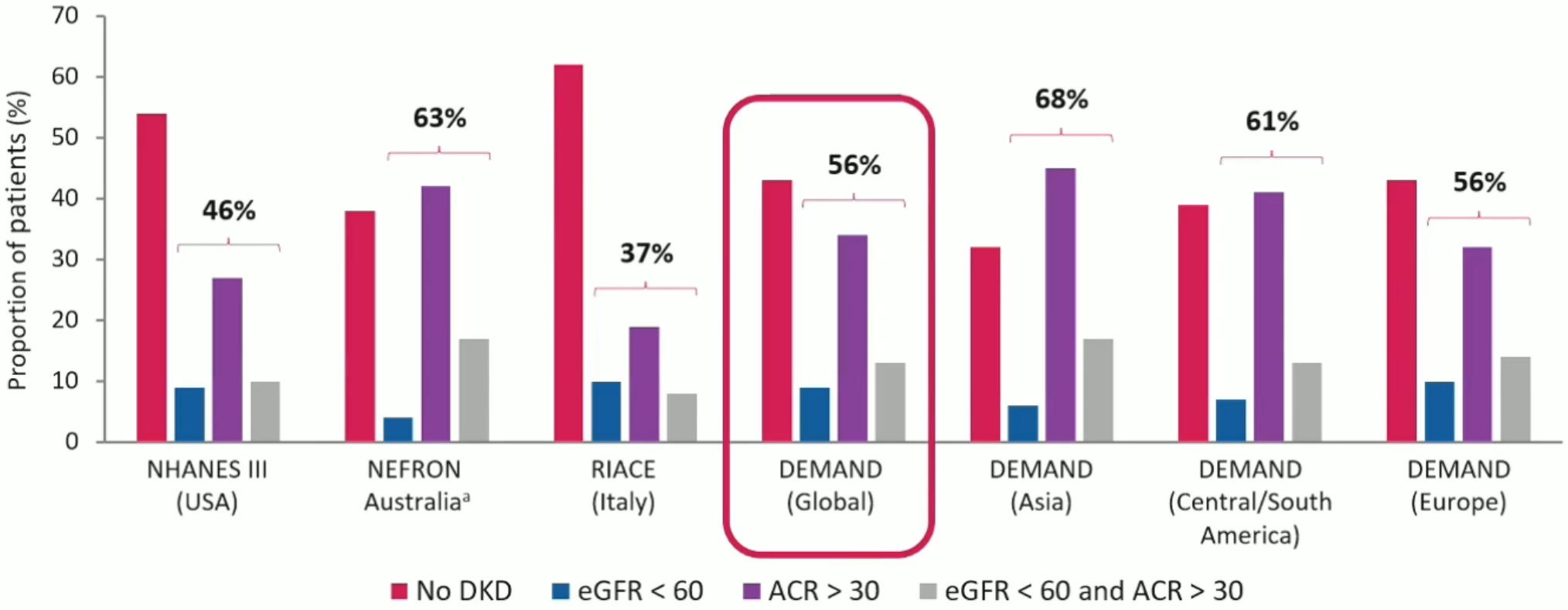
CKD has many risk factors and causes

Most common causes of CKD*



Brueck K et al. J Am Soc Nephrol. 2016 Jul; 27(7): 2135–2147; Garofalo C et al, Kidney International (2017) 91, 1224–1235

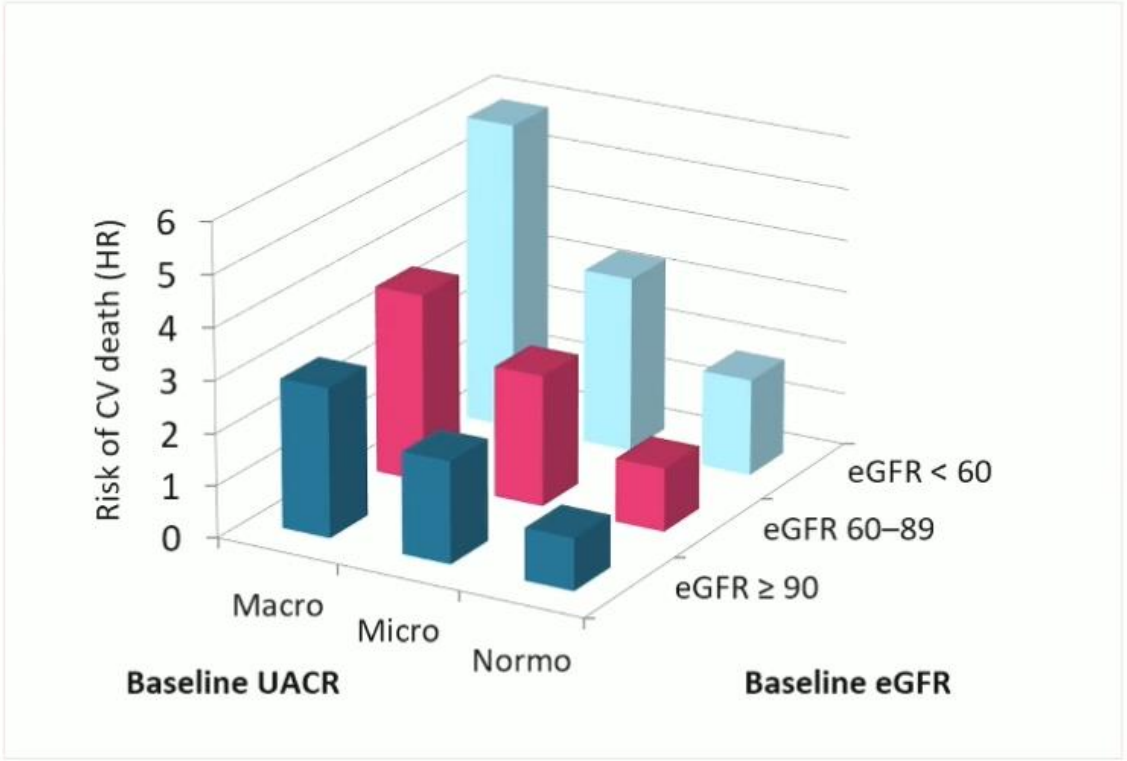
At least half of all patients with T2D worldwide also have diabetic kidney disease[1]



[a]Indiginous population
ACR measured in mg/g; eGFR measured in mL/min/1.73 m^2
ACR, albumin:creatinine ratio; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate

[1] Thomas MC et al. Nat Rev Dis Primers 2015;1:15018

Albuminuria and reduced eGFR are associated with increased risk of CV events[1]



ADVANCE

Observational analyses in patients with T2D
(N=10 640)
Median follow-up 4.3 years

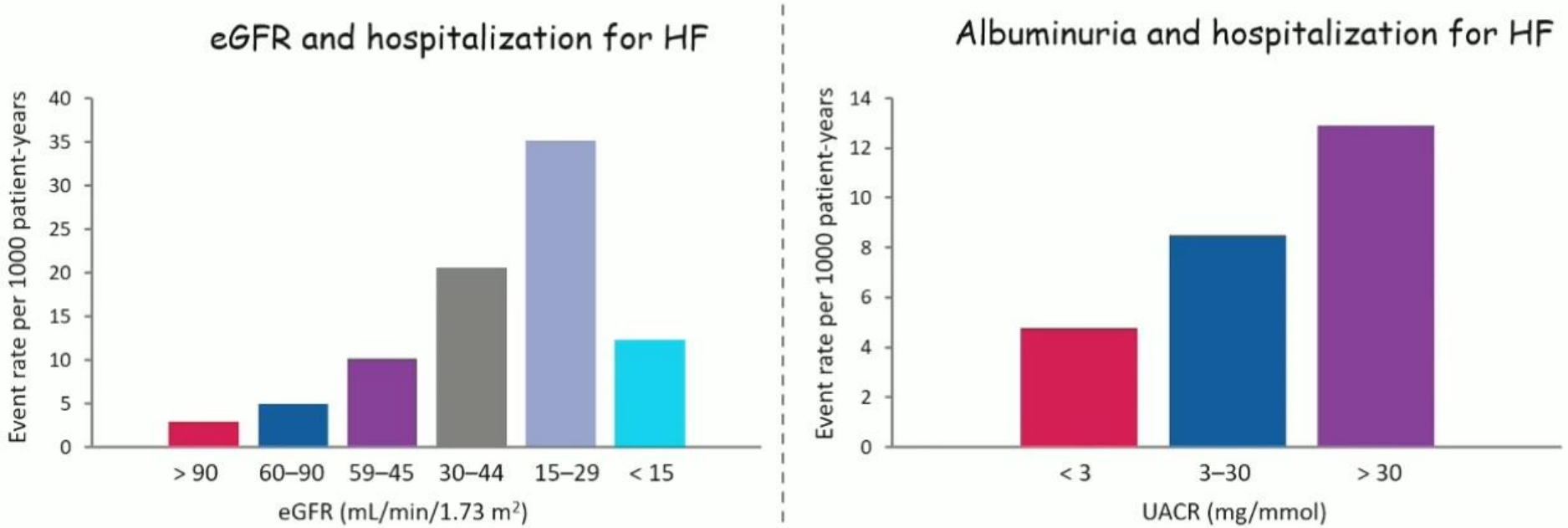
OUTCOMES

- Association between albuminuria and eGFR at baseline or during follow-up
- The risk for CV and renal events

eGFR measured in mL/min/1.73 m²
CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; UACR, urinary albumin:creatinine ratio

Ninomiya et al. J Am Soc Nephrol 2009;20:1813–21

Kidney impairment in patients with T2D increases the risk of hospitalization for heart failure



Population-matched Swedish database study; N = 266 305, median follow-up: 5.6 years

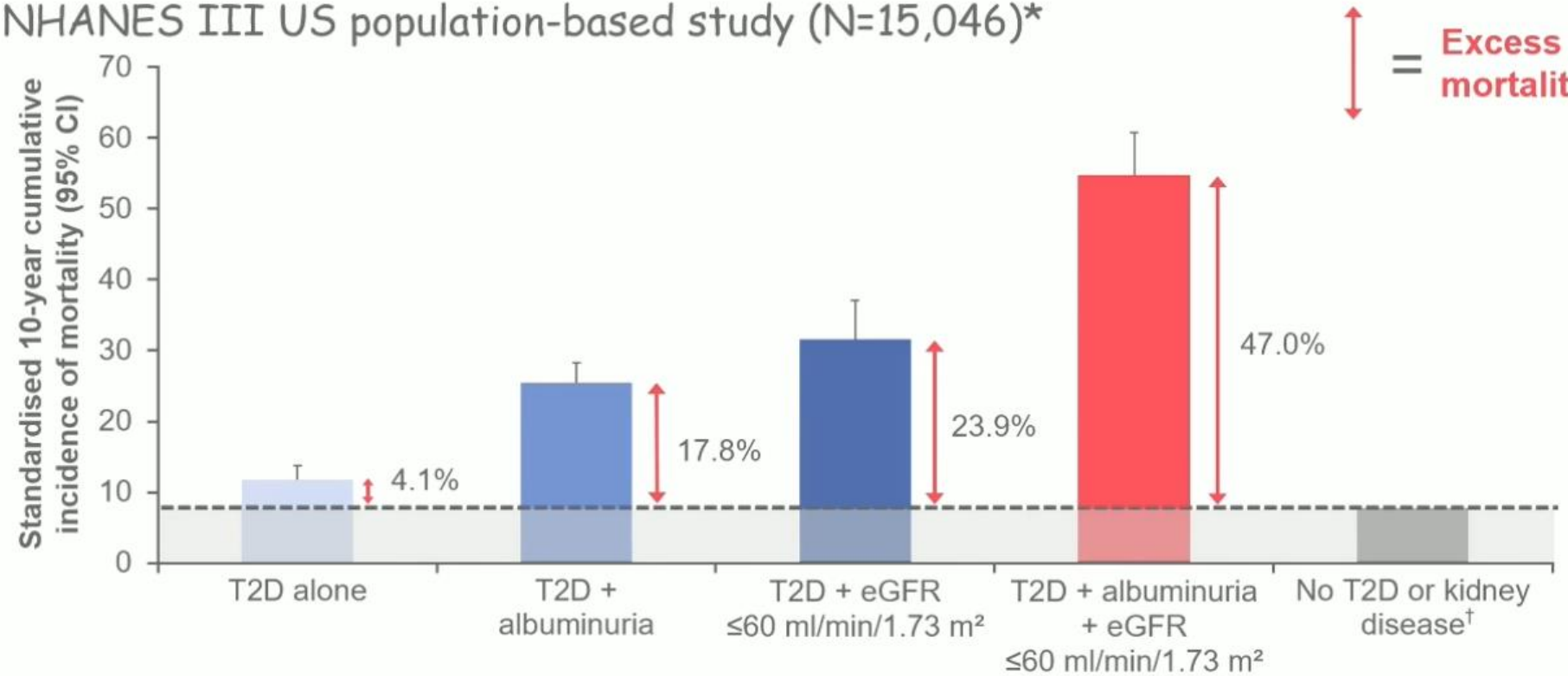
eGFR, estimated glomerular filtration rate; HF, heart failure; UACR, urine albumin:creatinine ratio

Rosengren A et al. Diabetologia 2018;61:2300–9

The presence and severity of CKD is the best and easiest marker of risk in T2D

ACROSS T2D

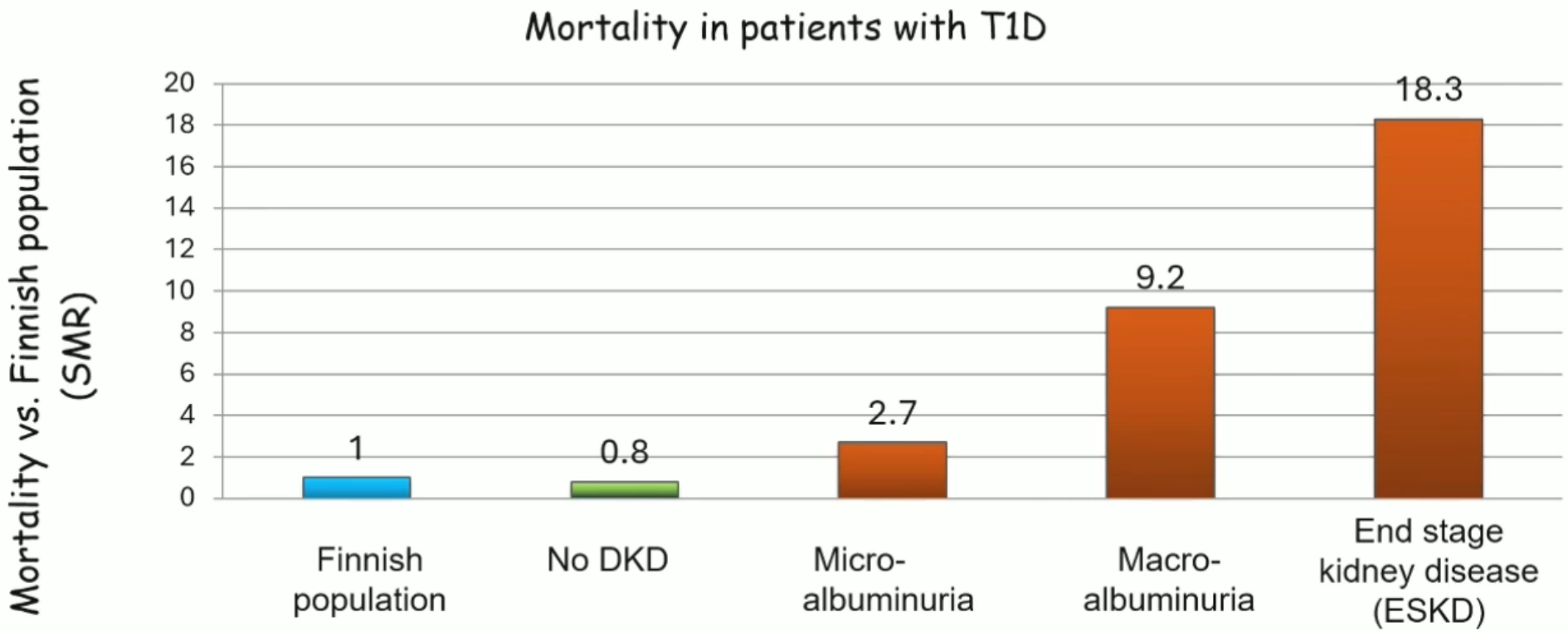
NHANES III US population-based study (N=15,046)*



Percentages indicate absolute excess mortality above the reference group (individuals with no diabetes or kidney disease)
*Adults aged ≥20 years with diabetes mellitus participating in NHANES from 1988 to 2014; †Kidney disease defined as albuminuria, impaired glomerular filtration or both
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; T2D, type 2 diabetes

Afkarian M *et al. J Am Soc Nephrol* 2013;24:302

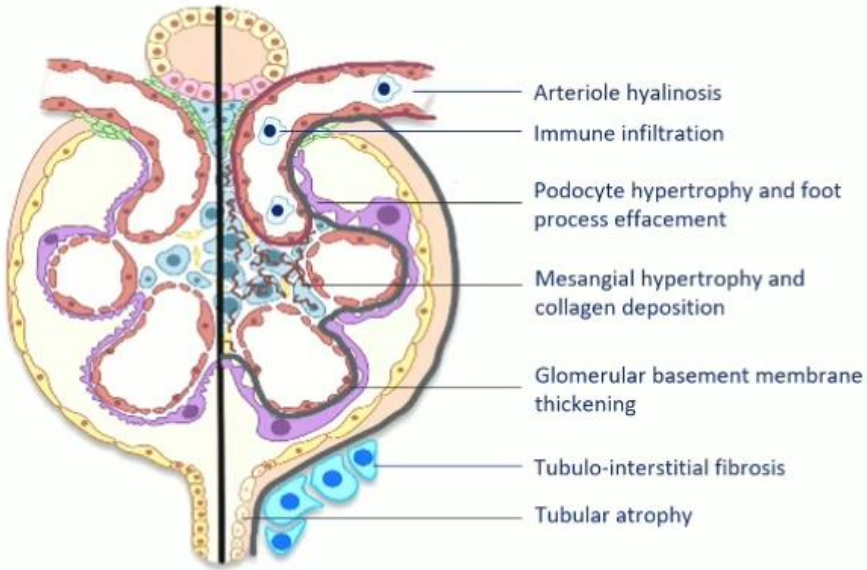
Diabetic kidney disease in type 1 diabetes is associated with high premature mortality



Groop P-H et al. Diabetes 2009

Uncontrolled T2D results in glomerulosclerosis, interstitial fibrosis and tubular atrophy[1–6]

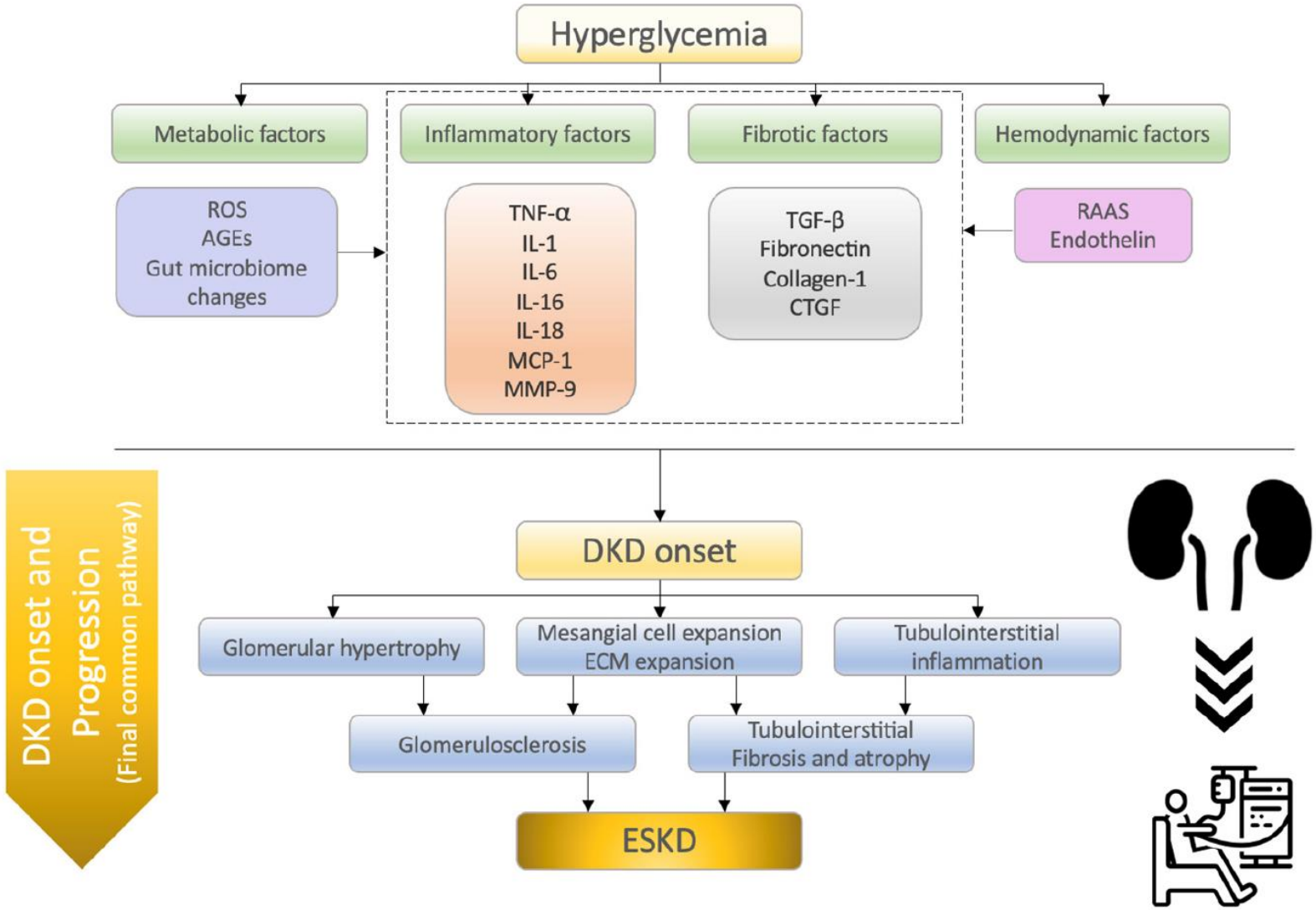
- Hyperglycaemia[1–6]
- Inflammation[1–6]
- Oxidative stress[1–6]
- RAAS activation[1–6]
- Fibrosis[1–6]



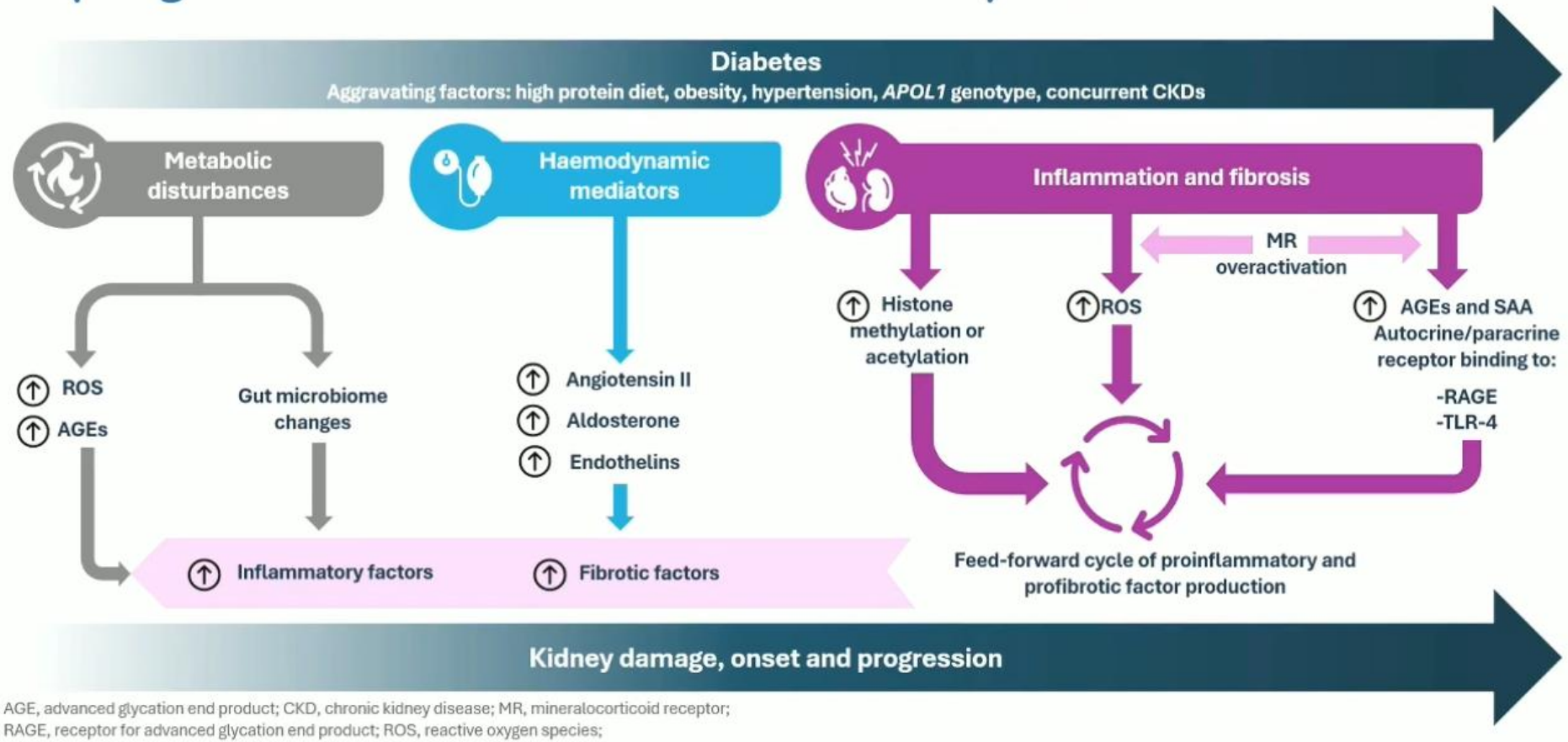
Structural and functional changes in DKD result in glomerular hyperfiltration, leading to protein leakage into the urine and disturbed fluid and solute homeostasis[1–6]

1. Jung CY, Yoo TH. Diabetes Metab J 2022;46:181–197; 2. Qazi M et al. EMJ Nephrol 2022;10:102–113; 3. Gembillo G et al. Int J Mol Sci 2021;22:4824; 4. Mora-Fernández C et al. J Physiol 2014;592:3997–4012; 5. Fu H et al. Mol Metab 2019;30:250–263; 6. Alicic RZ et al. Clin J Am Soc Nephrol 2017;12:2032–2045

Molecular mechanisms of diabetic kidney disease (DKD) onset and progression



Inflammation and fibrosis are key drivers of CKD progression which are mediated by MR overactivation



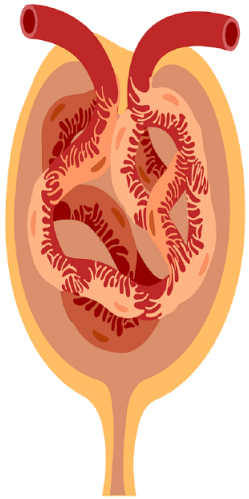
AGE, advanced glycation end product; CKD, chronic kidney disease; MR, mineralocorticoid receptor; RAGE, receptor for advanced glycation end product; ROS, reactive oxygen species; SAA, serum amyloid A; TLR-4, toll-like receptor 4.

Tuttle KR, et al. Kidney Int. 2022;102:248–260

Local mechanisms underlying glomerular hypertension

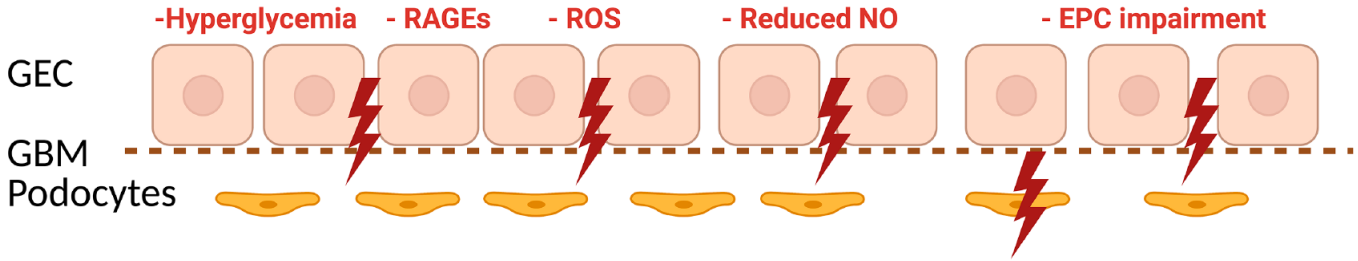
- Insulin resistance
- COX-2
- Prostanoids
- Kallikrein-kinin system

Afferent Arteriole Vasodilatation



- Angiotensin II
- Endothelin 1
- Reactive oxygen species
- Thromboxane A2

Efferent Arteriole Vasoconstriction



VEGF upregulated, increased TGF-β synthesis, podocyte death

ALBUMINURIA AND RENAL FIBROSIS

Assessment of both albuminuria and eGFR is required for early CKD diagnosis[1–4]

CKD is defined as abnormalities in kidney structure or function, present for >3 months, which have implications for health[1]

Early detection of kidney dysfunction or impairment facilitates the appropriate diagnosis and treatment of CKD[2]

The clinical diagnosis of CKD in a person with diabetes is based on:[1–4]

The presence of albuminuria*
UACR ≥30 mg/g (≥3 mg/mmol)

and/or

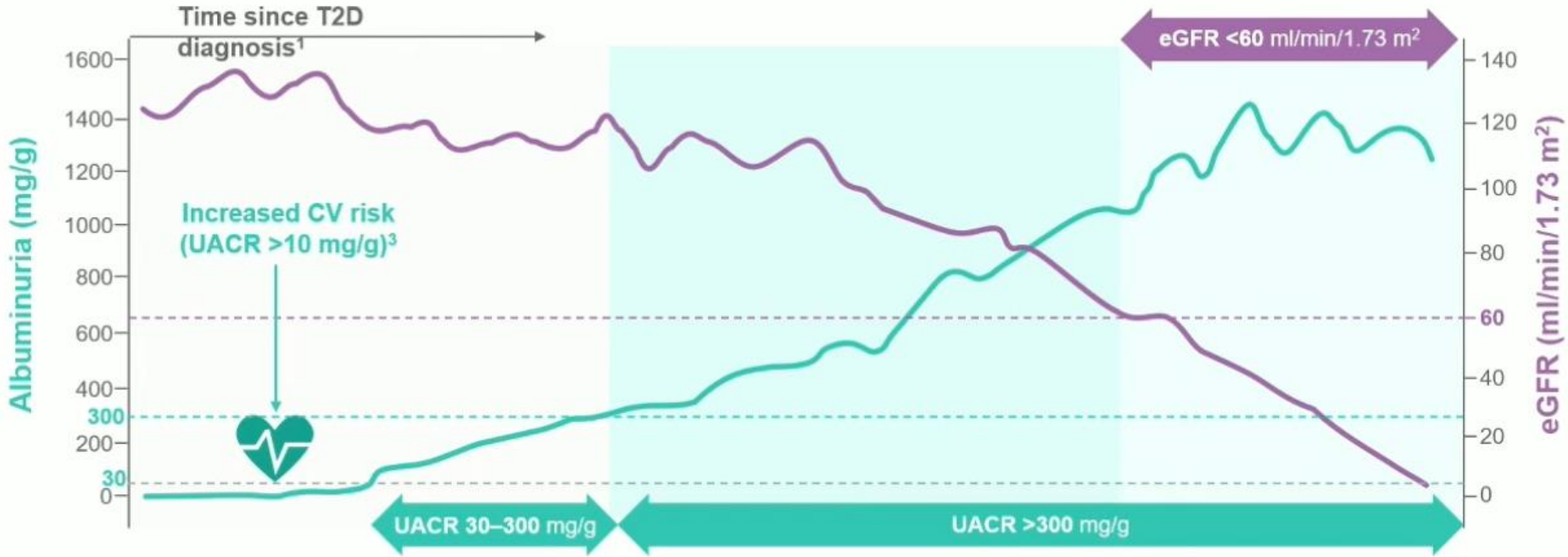
Reduced kidney function
(eGFR <60 ml/min/1.73 m^2)

in the absence of signs or symptoms of other primary causes of kidney damage

*Elevated UACR should be confirmed in the absence of urinary tract infection with two additional early-morning urine samples collected over the next 2 months

1. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int Suppl* 2013;3:1–163; 2. Levey AS, *et al. JAMA* 2015;313:837–846;
3. National Kidney Foundation. *Am J Kidney Dis* 2007;49(Suppl 2):S1–S180; 4. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184

For the early diagnosis of CKD, UACR testing is critical as increased albuminuria precedes eGFR decline[1,2]



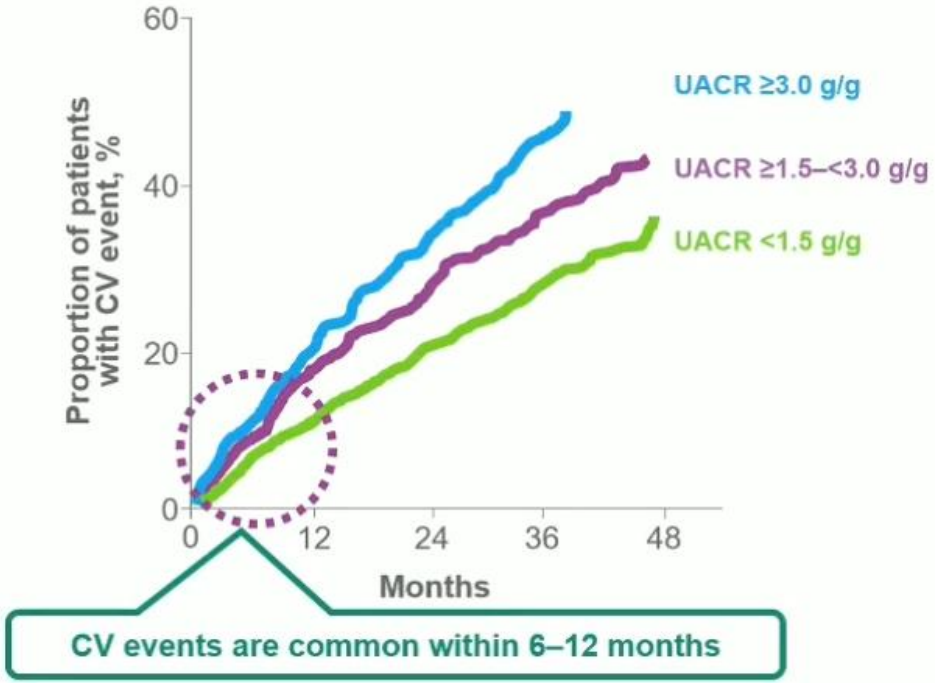
Albuminuria is often an earlier marker of CKD and increased CV risk than eGFR decline[1–3]

1. Afkarian M. *Pediatr Nephrol* 2015;30:65–74;
2. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045;
3. Fox CS, *et al. Lancet* 2012;380:1662–1673

Albuminuria is a simple yet important early predictor of heart and kidney disease outcomes[1-6]

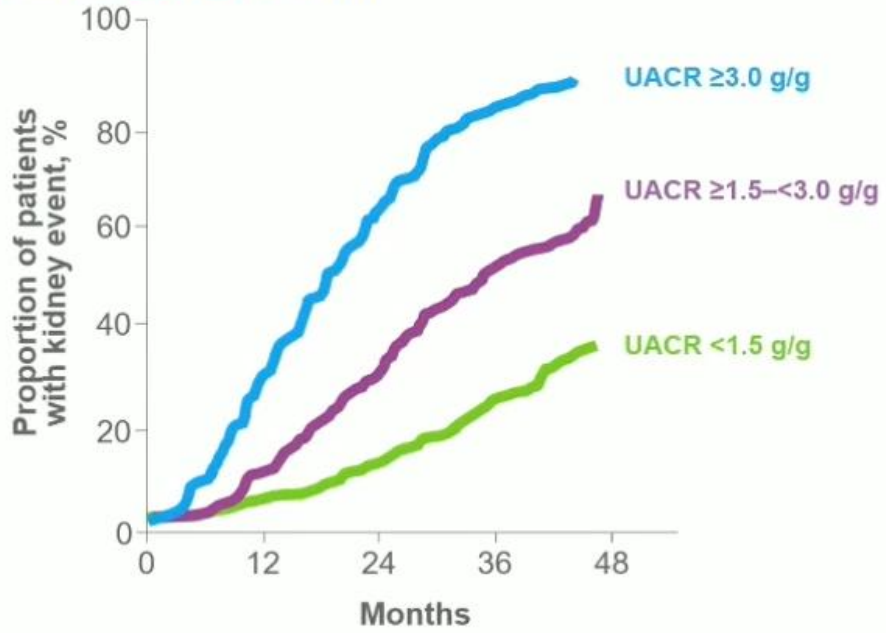
CV composite outcome[1,2]

Composite of MI, stroke, first HHF or unstable angina, coronary or peripheral revascularisation, or CV death



Kidney composite outcome[1,3]

Composite of the time to first doubling of serum creatinine, ESKD or death

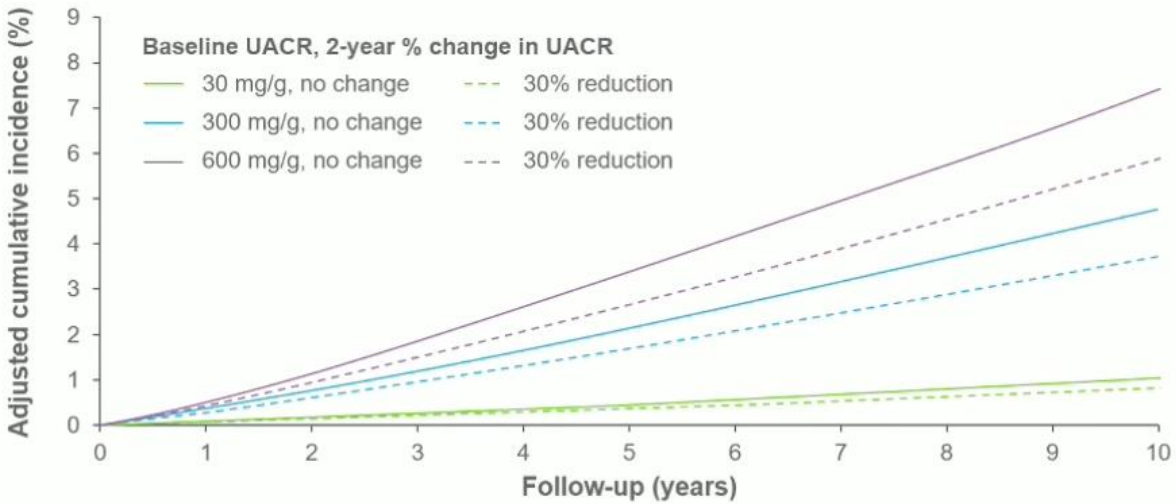


1. de Jong PE. *J Nephrol* 2007;20:375–380; 2. de Zeeuw D *et al. Circulation* 2004;110:921–927; 3. de Zeeuw D *et al Kidney Int* 2004;65:2309–2320; 4. Khan MS, *et al. JACC Rev* 2023;81:270–282; 5. American Diabetes Association Professional Practice Committee. *Diabetes Care* 2022;45:S175–S184; 6. de Jong PE & Gansevoosrt RT. *Nephron Clin Pract* 2009;111:c204–c211

A meta-analysis of cohort data has revealed a lower risk of ESKD with a 30% reduction in UACR over 2 years

Incidence of ESKD by baseline UACR – with and without a 30% reduction in UACR from baseline at 2 years

Individual-level meta-analysis of 693,816 participants from 28 observational cohorts*



A 30% reduction in UACR over 2 years reduced the risk of ESKD by 17% regardless of baseline UACR (adjusted# HR=0.83; 95% CI 0.74–0.94)

*This meta-analysis included 20 cohorts with follow-up for ESKD (only 18 of 20 cohorts were included in the adjusted cumulative incidence analysis; two cohorts were excluded because baseline risk could not be calculated) and 16 cohorts that quantified albuminuria with UACR. 80% of individuals had diabetes at baseline; #Adjusted for age, sex, race/ethnicity. (Black versus not Black), systolic blood pressure, total cholesterol, diabetes, history of CV disease, current smoking, former smoking, first eGFR and albuminuria

Coresh J, *et al. Lancet Diabetes Endocrinol* 2019;7:115–127

A meta-analysis of clinical trials suggests a 30% reduction in albuminuria reduces the risk of CKD progression

- Meta-analysis of 41 clinical trials including 29,979 participants

Primary composite kidney outcome:

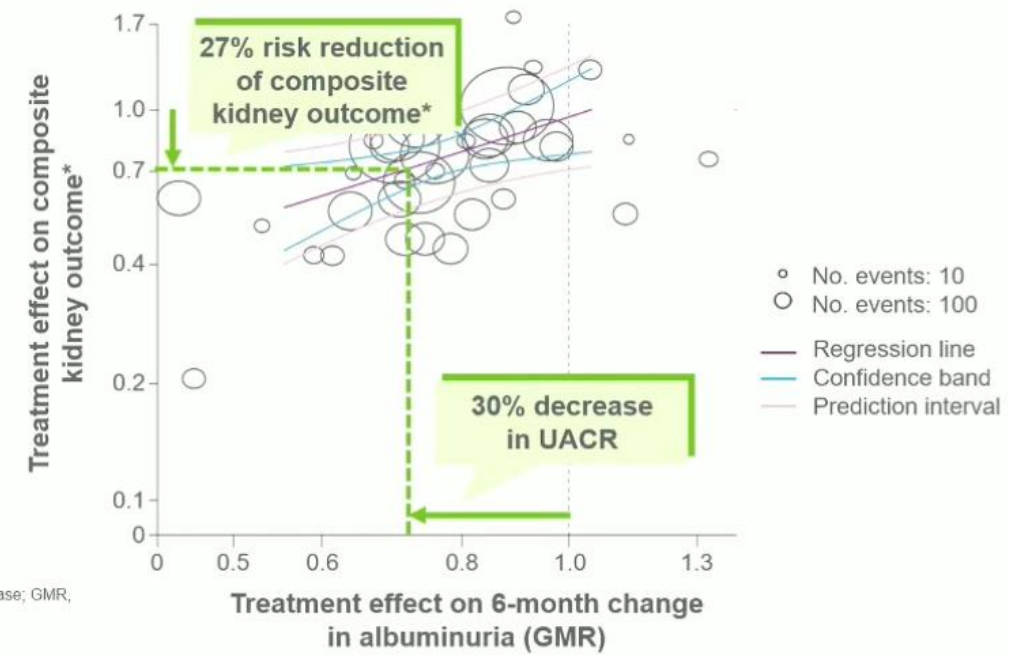
- Treated ESKD (initiation of chronic dialysis or kidney transplantation)
- eGFR <15 ml/min/1.73 m^2
- Doubling of SCr sustained at next visit

~70% of 22,544 patients with UACR ≥30 mg/g had diabetes

A 30% fall in geometric mean UACR over 6 months was associated with a 27% reduction in risk of the composite kidney outcome* in patients with baseline UACR ≥30 mg/g

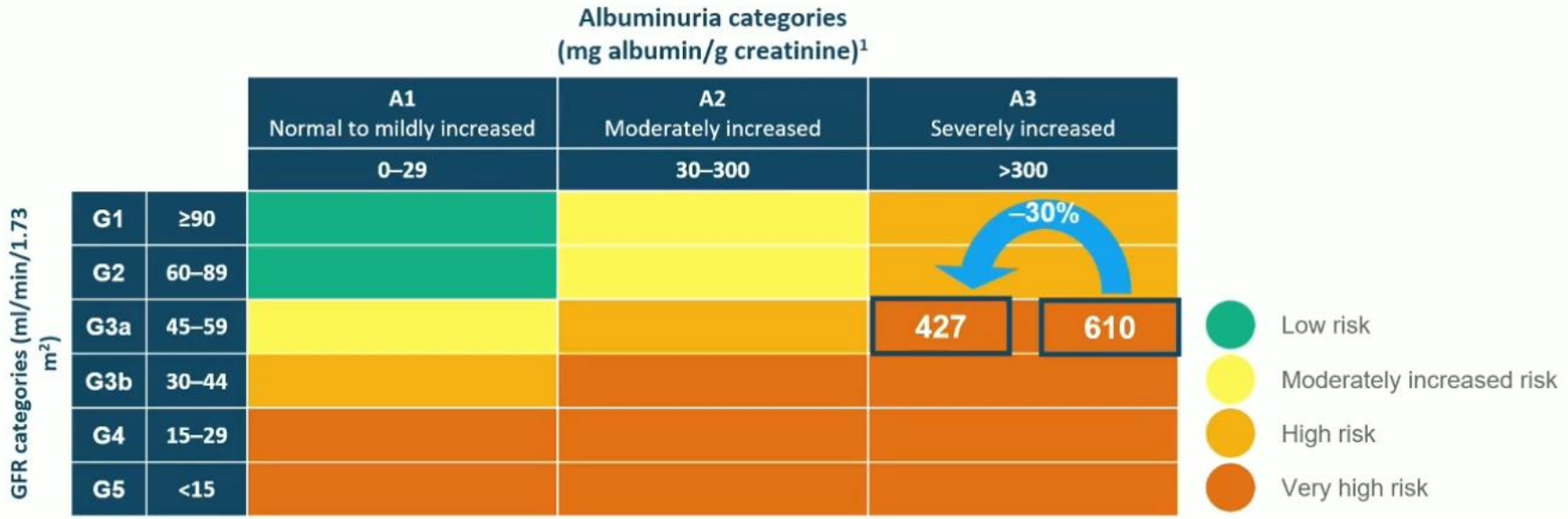
Time to treatment of ESKD (initiation of chronic treatment with dialysis or kidney transplantation), eGFR <15 mL/min/1.73 m^2, or doubling of SCr sustained at the next visit.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GMR, geometric mean ratio; SCr, serum creatinine; UACR, urine albumin-to-creatinine ratio.

Association between treatment effects on change in UACR and treatment effects on composite kidney outcome* in patients with baseline UACR ≥30 mg/g (N=22,544)



Heerspink HJL, et al. *Lancet Diabetes Endocrinol.* 2019;7:128–139

Each 30% reduction in UACR leads to kidney benefit, with the potential to reduce the risk of CKD progression from severe to moderate



A ≥30% reduction in UACR may be required for some people to reduce their risk of CKD progression from severe to moderate

ADA recommendation 11.6: In people with CKD who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow CKD progression[2]

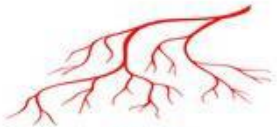
1. Kidney Disease: Improving Global Outcomes. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2022;102:S1–S127; 2. American Diabetes Association. *Diabetes Care* 2024;47(Suppl 1):S219–S230

Non-Albuminuric DKD

- (NHANES) from 1988 to 1994:
  - 20% of subjects with diabetes had advanced kidney disease (eGFR < 30 mL/min/1.72 m2) without the presence of albuminuria
  - 30% of participants 40 years and older with type 2 diabetes and low eGFR had no albuminuria or retinopathy.

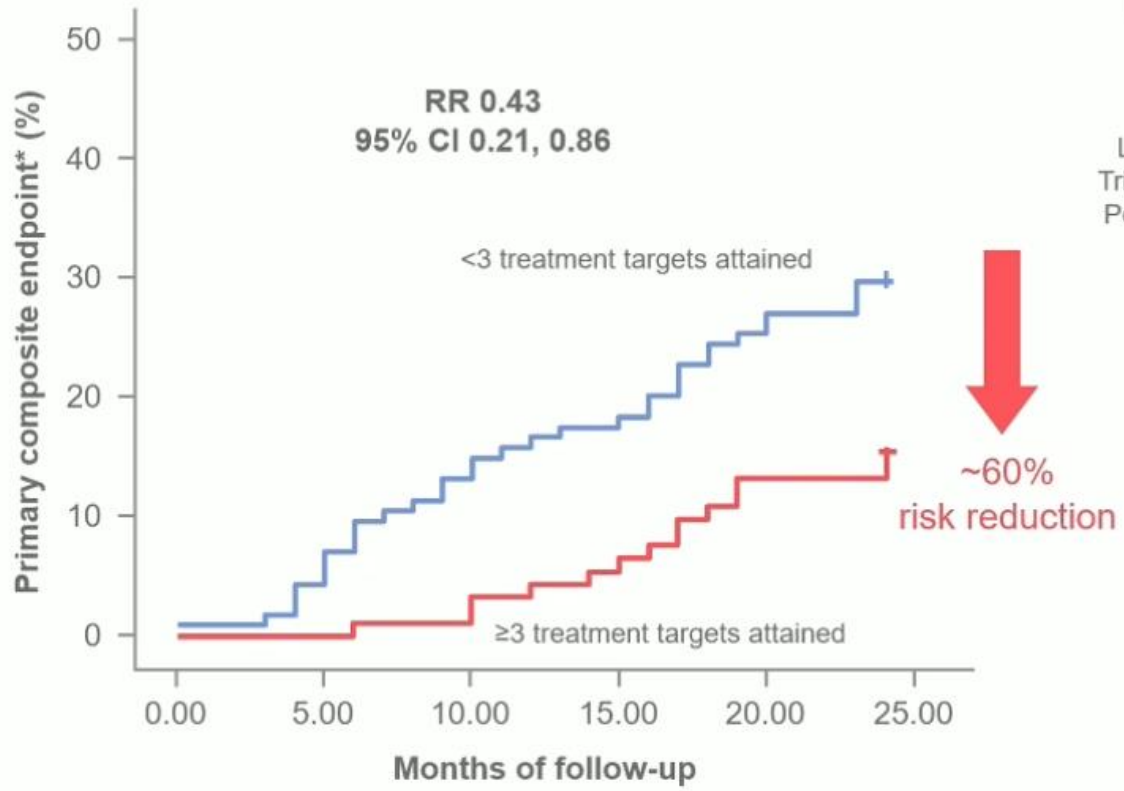
- (NEFRON) survey of primary care patients with type 2 diabetes:
  - 55% of those with low eGFR were persistently non-albuminuric

Non-albuminuric DKD phenotype: a breakthrough in DKD classic conception

Albuminuric DKD		Non-albuminuric DKD
UACR > 30 mg/g	 	eGFR < 60 ml/min/1.73m^2 and UACR < 30 mg/g
Microangiopathy	 	Macroangiopathy
Correlation with retinopathy	 	No correlation with retinopathy
Glomerulosclerosis	 	Tubular and vascolar damage
Male sex	 	Female sex
Correlation with Hb1Ac	 	No correlation with Hb1Ac

Differences between albuminuric and non-albuminuric phenotypes: diagnosis, clinical presentation, risk factors , and pathogenesis

Attaining multiple treatment targets is associated with lower risk of ESKD and related death in T2D



Predefined protocol and targets

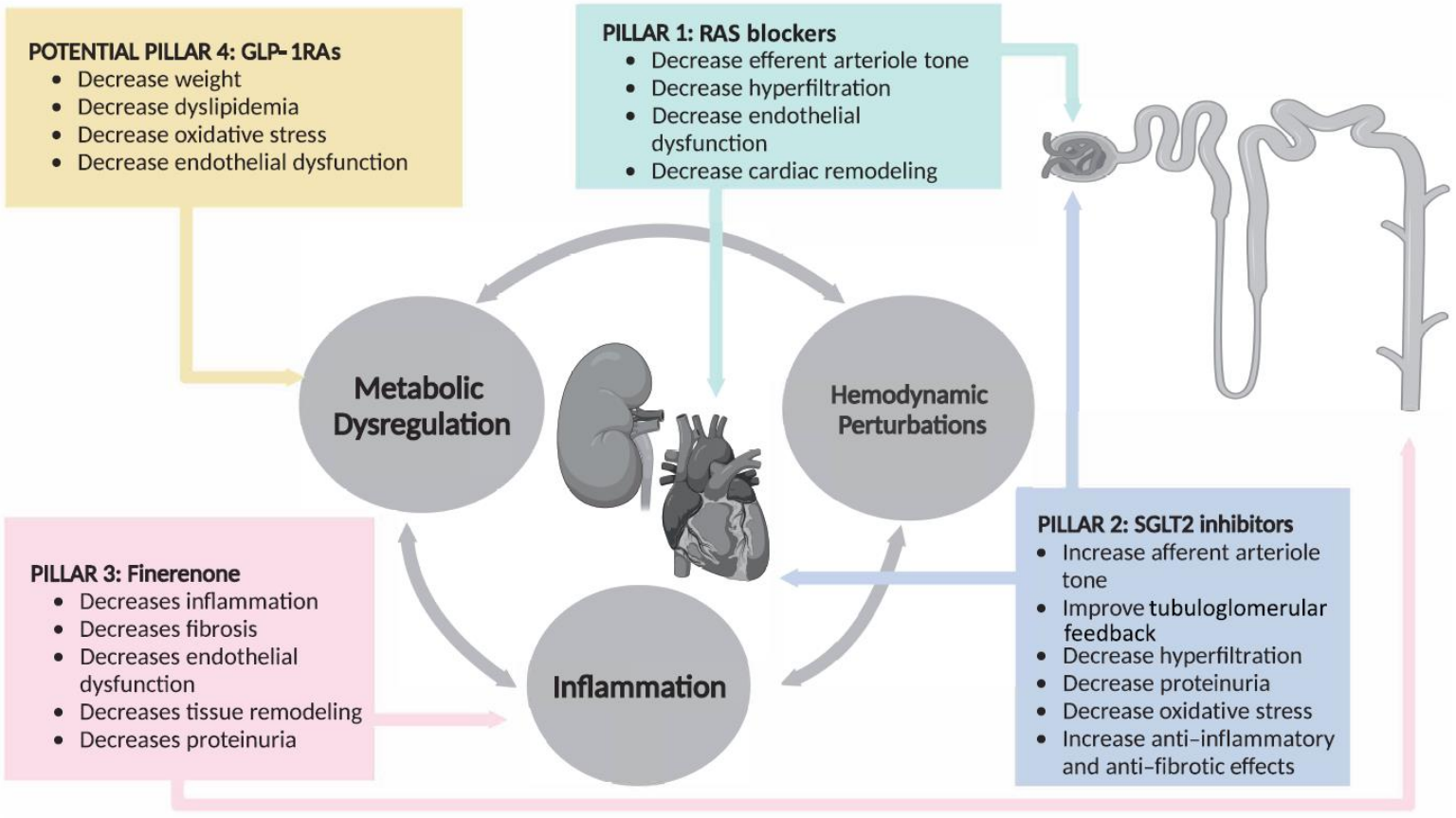
HbA1c <7%
BP <130/80mmHg
LDL-C <2.6 mM (100 mg/dl)
Triglyceride <2 mM (177 mg/dl)
Persistence with RAS inhibitor
Stop smoking
"Five-finger rule"

*Death and/or ESRD, defined as the need for dialysis, or plasma creatinine level 500 µmol/l
BP, blood pressure; ESRD, end-stage renal disease; HbA1c, glycated haemoglobin; LDL-C, Low-density lipoprotein cholesterol; RAS, renin-angiotensin system; RR, risk ratio

Chan JC et al Diabetes Care 2009;32:977

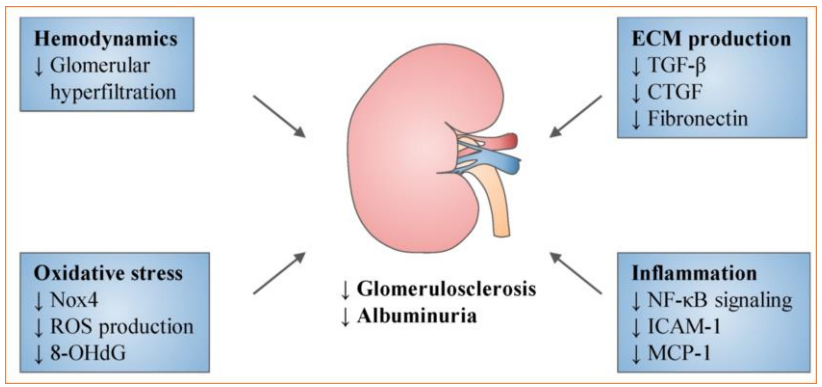
Diabetic Nephropathy: Update on Pillars of Therapy Slowing Progression

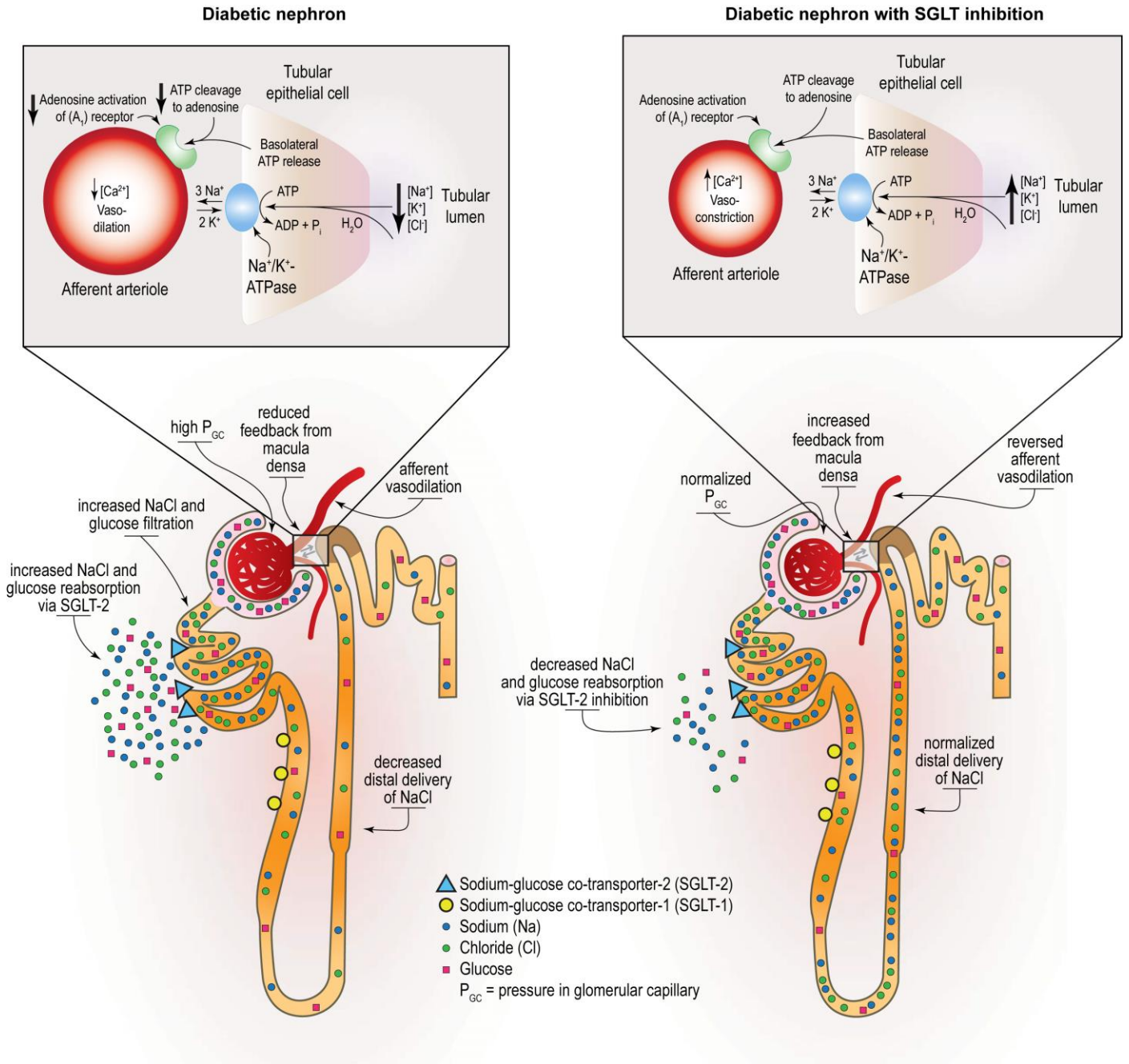
Sandra C. Naaman and George L. Bakris



Novel medications

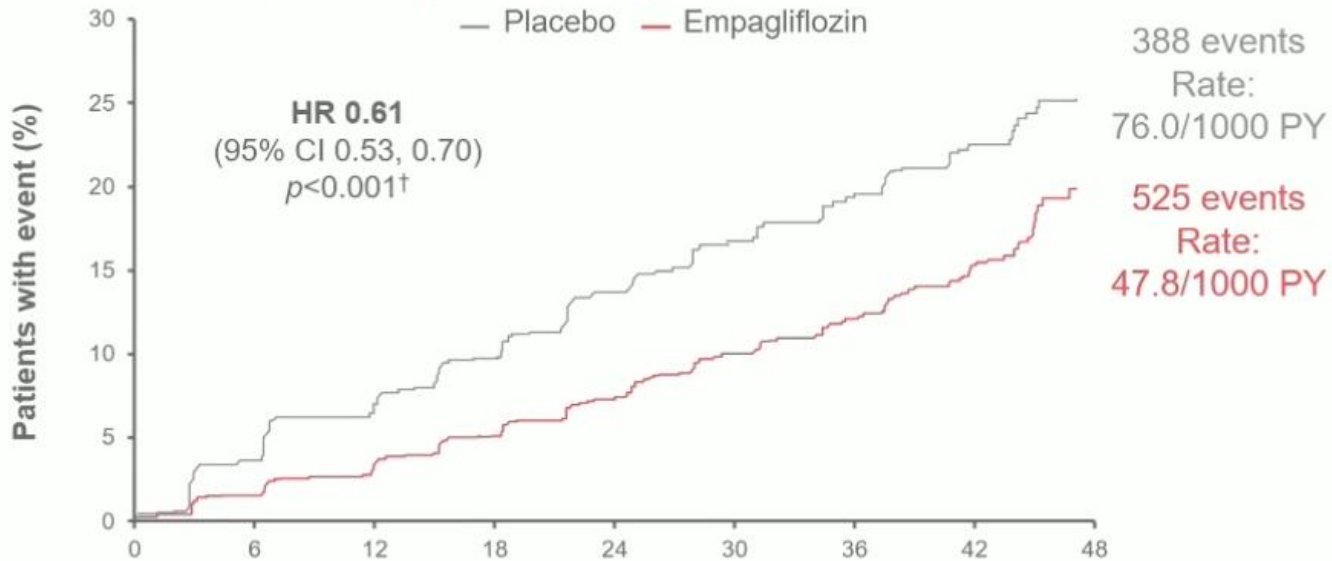
SGLT2-inhibitors


Hemodynamics
↓ Glomerular hyperfiltration
ECM production
↓ TGF-β
↓ CTGF
↓ Fibronectin
Oxidative stress
↓ Nox4
↓ ROS production
↓ 8-OHdG
Inflammation
↓ NF-κB signaling
↓ ICAM-1
↓ MCP-1
↓ Glomerulosclerosis
↓ Albuminuria


Diabetic nephron
Diabetic nephron with SGLT inhibition
Tubular epithelial cell
Adenosine activation of (A1) receptor
ATP cleavage to adenosine
Basolateral ATP release
[Ca2+] Vaso-dilation
3 Na+
2 K+
ATP
ADP + Pi
H2O
[Na+] [K+] [Cl-]
Tubular lumen
Na+/K+-ATPase
Afferent arteriole
[Ca2+] Vaso-constriction
high PGC
reduced feedback from macula densa
afferent vasodilation
increased NaCl and glucose filtration
increased NaCl and glucose reabsorption via SGLT-2
decreased distal delivery of NaCl
normalized PGC
increased feedback from macula densa
reversed afferent vasodilation
decreased NaCl and glucose reabsorption via SGLT-2 inhibition
normalized distal delivery of NaCl
Sodium-glucose co-transporter-2 (SGLT-2)
Sodium-glucose co-transporter-1 (SGLT-1)
Sodium (Na)
Chloride (Cl)
Glucose
PGC = pressure in glomerular capillary

EMPA REG OUTCOME: 39% risk reduction in kidney outcomes with empagliflozin compared to placebo

Kidney outcomes* occurred in 525 (12.7%) patients in the empagliflozin group and in 388 (18.8%) patients in the placebo group, a significant relative risk reduction of 39%



No. at risk									
Placebo	2061	1946	1836	1703	1433	1016	833	521	106
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290

Cox regression analysis in patients treated with ≥1 dose of study drug.

*Incident or worsening nephropathy, defined as progression to macroalbuminuria (UACR >300 mg/g), doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73 m²), initiation of RRT or death from kidney disease; †Nominal *p*-value. Analysis of incident or worsening nephropathy was a prespecified secondary outcome (see Slide 6). MDRD, Modification of Diet in Renal Disease; PY, patient-years; RRT, renal replacement therapy

Wanner C *et al. N Engl J Med* 2016;375:323

SGLT2 Inhibitors and Renal Outcomes : A comparison of RCTs

Infographic by-: Priti Meena, M.D @Priti899

CREDENCE

Double-blind, Placebo-controlled,
Multicentric RCT
(N=4401)

Inclusion:
Type 2 DM
eGFR: ≥30-90
and UACR: >300-≤5000 mg/g

Canagliflozin VS placebo

2019

Median follow-up: 2.62 yrs

Renal-specific composite of ESKD, 2* S. Cr or death from renal causes:
HR 0.66; (0.53 to 0.81)

CV death, MI, or stroke:
HR 0.80 (0.67 -0.95)
Hospitalization for heart failure:
HR 0.61; (0.47 to 0.80)

DAPA-CKD

Double-blind, Placebo-controlled,
Multicentric RCT
(N=4304)

Inclusion:
eGFR: ≥25-75 and
UACR: ≥200-≤5000 mg/g

With or without DM

Dapagliflozin VS placebo

2020

Median follow up : 2.4 yrs

Composite of sustained decline in eGFR of at least 50%, ESKD, or death from renal causes:
HR 0.56; (0.45 to 0.68)

Composite of death from CV causes or hospitalization for heart failure:
HR 0.71; (0.55 to 0.92)

EMPA-KIDNEY

Double-blind, Placebo-controlled,
Multicentric parallel group RCT
(N=6609)

Inclusion:
eGFR: ≥20-45 or
eGFR ≥45 to <90 with UACR ≥200 mg/g

With or without DM

Empagliflozin VS placebo

2022

Median follow-up: 2 yrs

Progression of kidney disease or death from CV causes:
HR 0.72; (0.64 to 0.82)

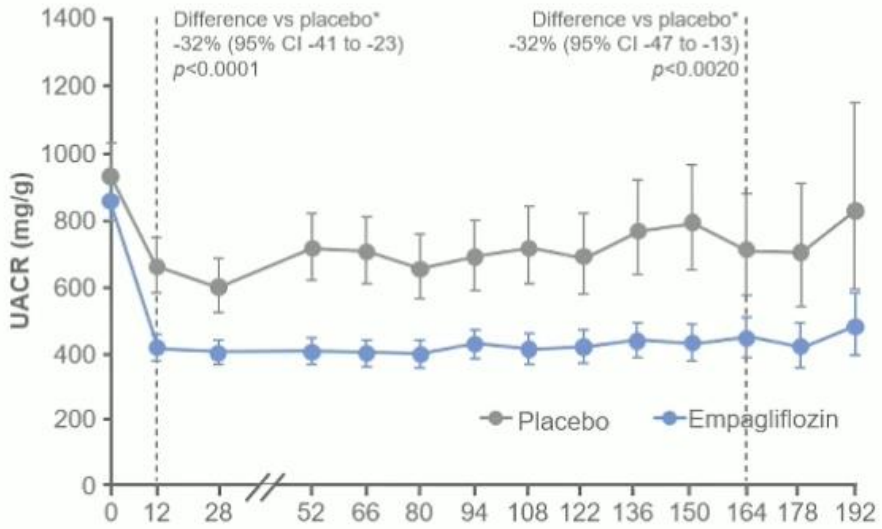
Rate of hospitalization from any cause:
HR 0.86; (0.78 to 0.95)

CV: cardiovascular, ESKD: End-stage kidney diseases, eGFR: estimated glomerular filtration rate in ml per minute per 1.73 m^2 HR: Hazard ratio, MI: Myocardial infarction, RCT: Randomized Controlled Trials, S.Cr: Serum creatinine, SGLT2: Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors, UACR: urinary albumin-to-creatinine ratio

Effect of SGLT2 inhibitors on albuminuria (UACR) slope

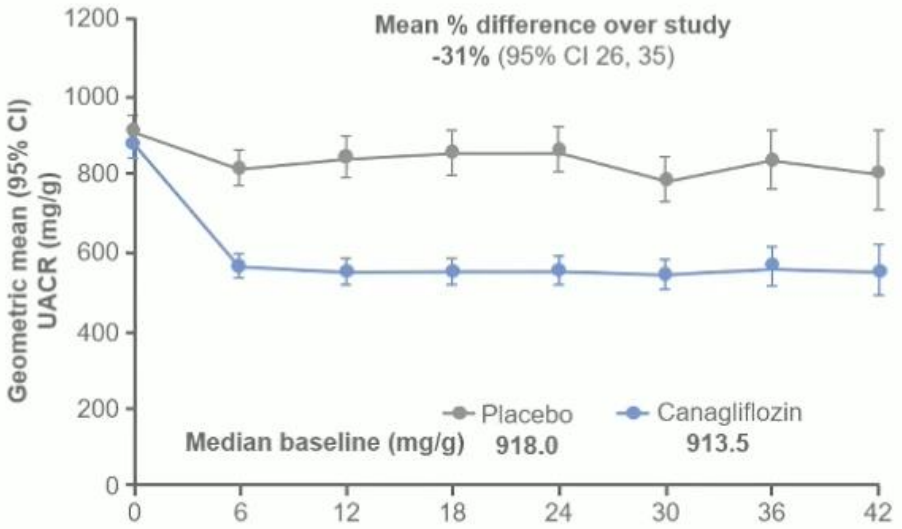
In patients with macroalbuminuria, SGLT2 inhibitor treatment led to a significant reduction in UACR compared to placebo; this difference remained significant throughout the trials

EMPA-REG OUTCOME



Number of patients														
Placebo	257	249	233	220	206	193	195	168	137	109	100	86	56	31
Empagliflozin	498	480	477	452	435	404	425	377	324	265	241	206	157	96

CREDENCE



Number of participants								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	270

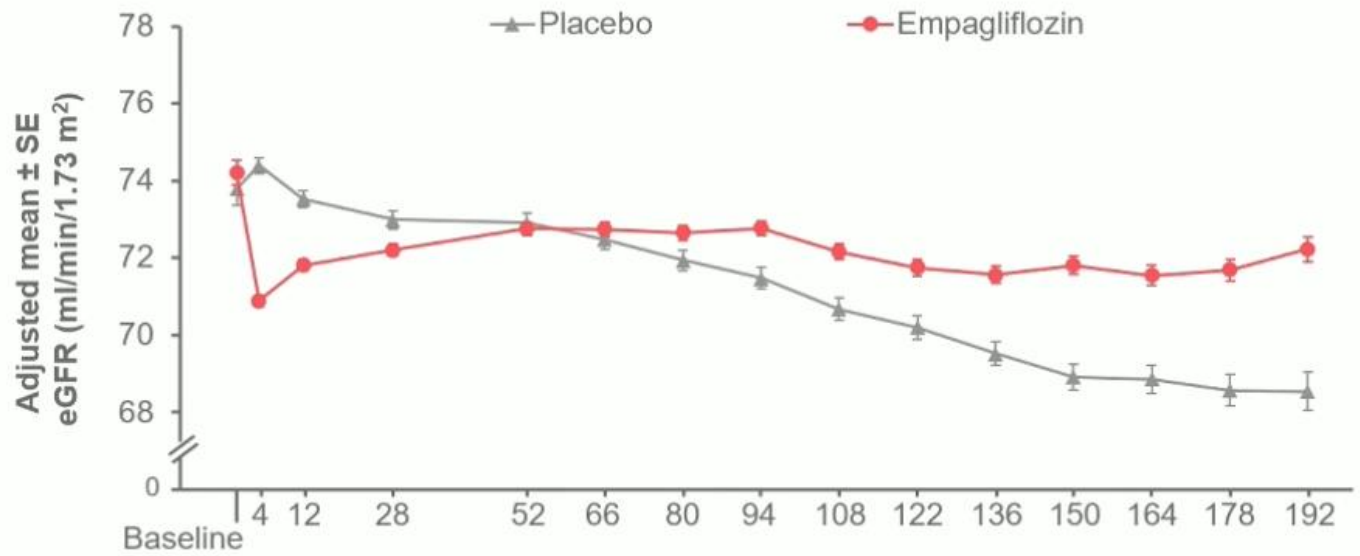
CI, confidence interval; SGLT2, sodium-glucose cotransporter-2; UACR, urine albumin-to-creatinine ratio
*Placebo-corrected adjusted geometric mean ratio (95% CI) of relative change from baseline with empagliflozin.

1. Cherney DZI *et al. Lancet Diabetes Endocrinol* 2017;5:610; 2. Perkovic V *et al. N Engl J Med* 2019;380:2295

EMPA REG OUTCOME: Empagliflozin slowed eGFR decline over time

Mean adjusted eGFR over time

Wanner C *et al. J Am Soc Nephrol* 2018;29:2755

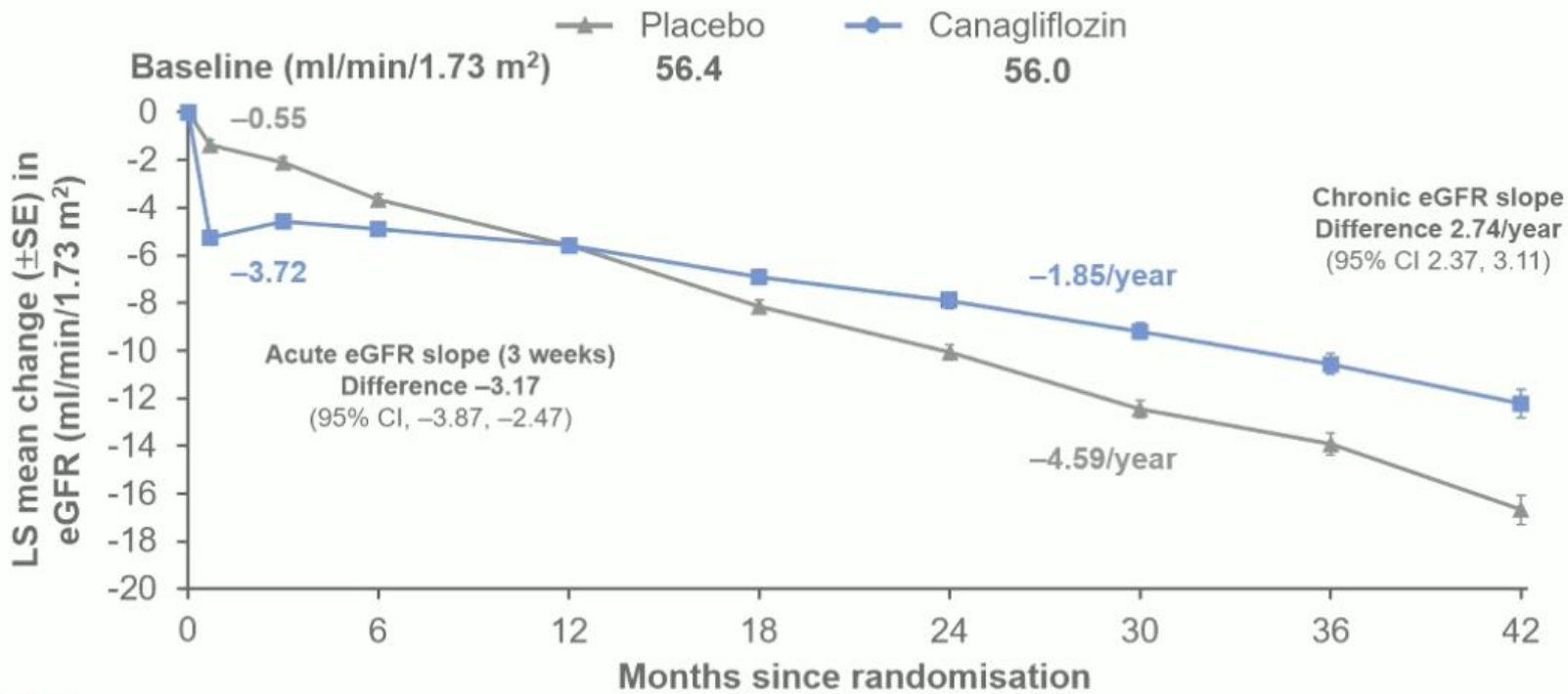


No. of patients															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin	4644	4578	4533	4451	4318	4225	4018	4131	3710	3103	2654	2387	2087	1623	1037

Prespecified mixed model repeated measures analysis in patients treated with ≥1 dose of study drug who had a baseline and post-baseline measurement

Wanner C *et al. J Am Soc Nephrol* 2018;29:2755

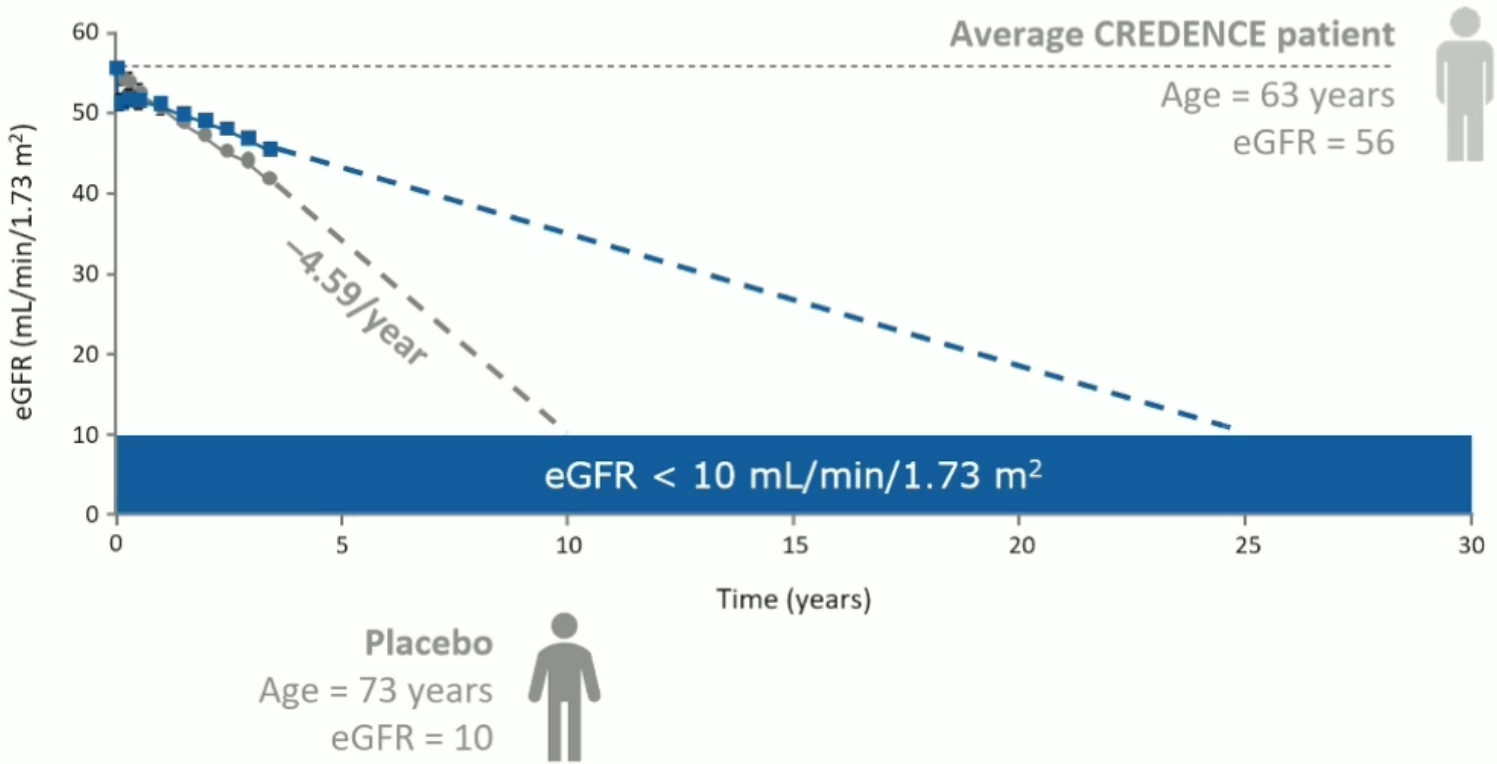
CREDENCE: Effect on the eGFR slope



No. of patients								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

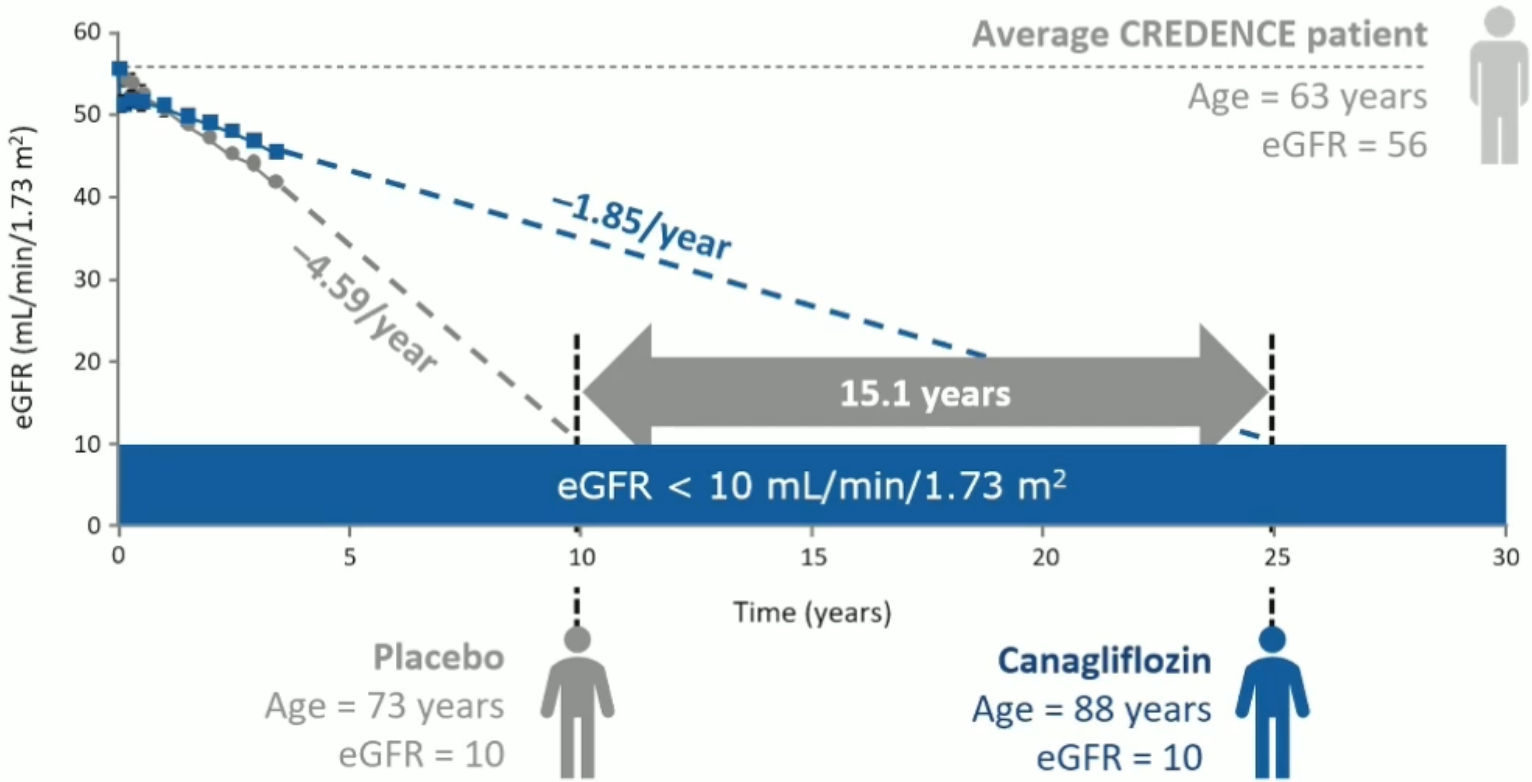
Perkovic V *et al. N Engl J Med* 2019; doi: 10.1056/NEJMoa1811744

Projected effects on the eGFR slope based on the CREDENCE data[1]



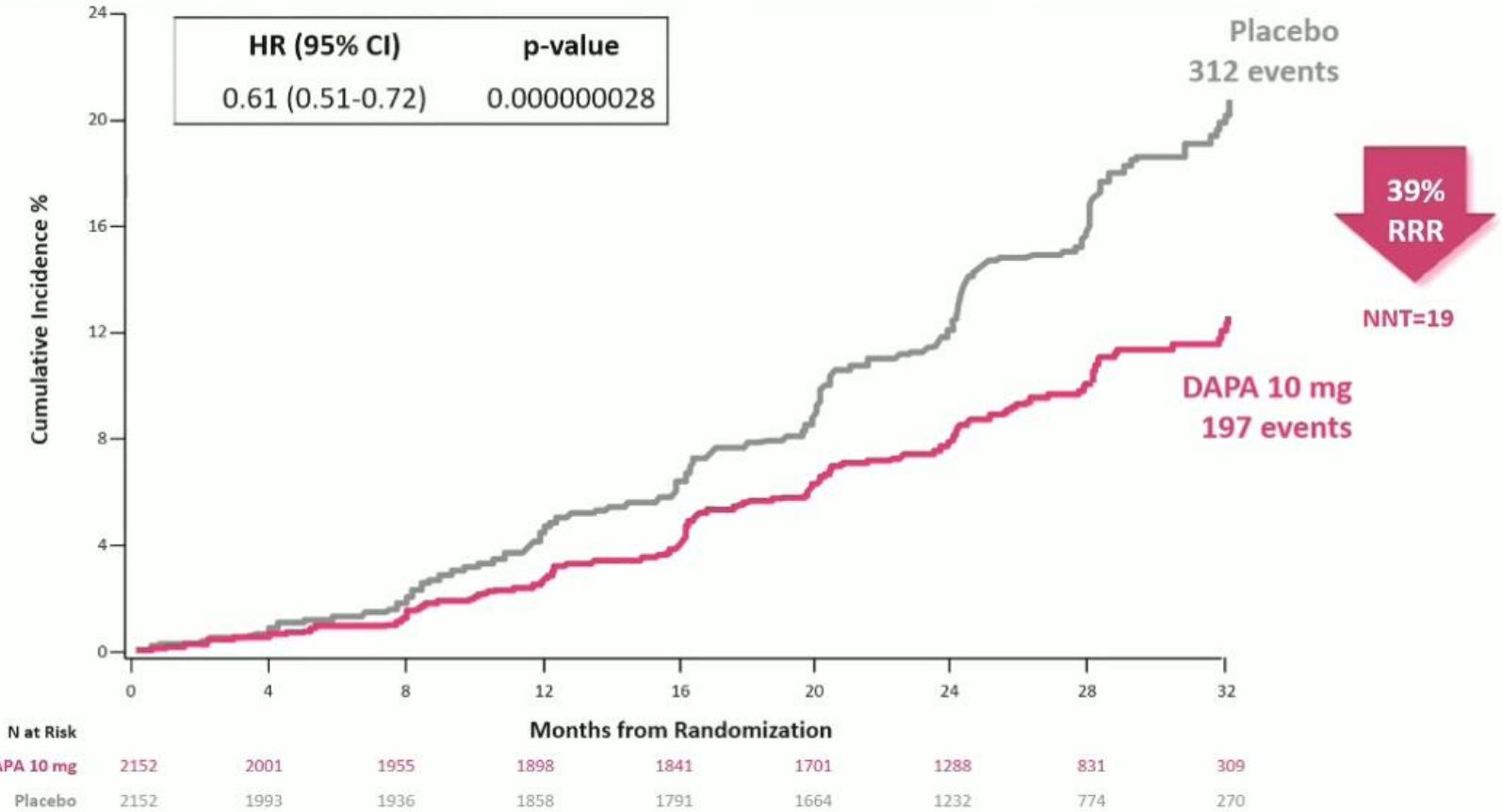
1. Perkovic V *et al. N Engl J Med* 2019; 380: 2295–2306

Projected effects on the eGFR slope based on the CREDENCE data[1]



1. Perkovic V *et al. N Engl J Med* 2019; 380: 2295–2306

DAPA-CKD: Primary Composite Outcome Composite of sustained ≥50% eGFR decline, ESKD, renal or CV death[a]



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15 mL/min/1.73 m² for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason

1. Heerspink HJL et al. N Engl J Med 2020;383:1436–46; 2. Heerspink HJL et al. Nephrol Dial Transplant 2020;35:274–82

EMPA-KIDNEY included people with T2D as well as no diabetes with established kidney disease

Aimed to be more reflective of patients seen in clinical practice, including primary care

eGFR category range (ml/min/1.73 m²)			Albuminuria stage, description and range (mg/g)		
			A1	A2	A3
			Normal-to-mildly increased	Moderately increased	Severely increased
			<30	30–300	>300
	G1	≥90			
	G2	60–89			
	G3a	45–59			
	G3b	30–44			
	G4	15–29			
	G5	<15			

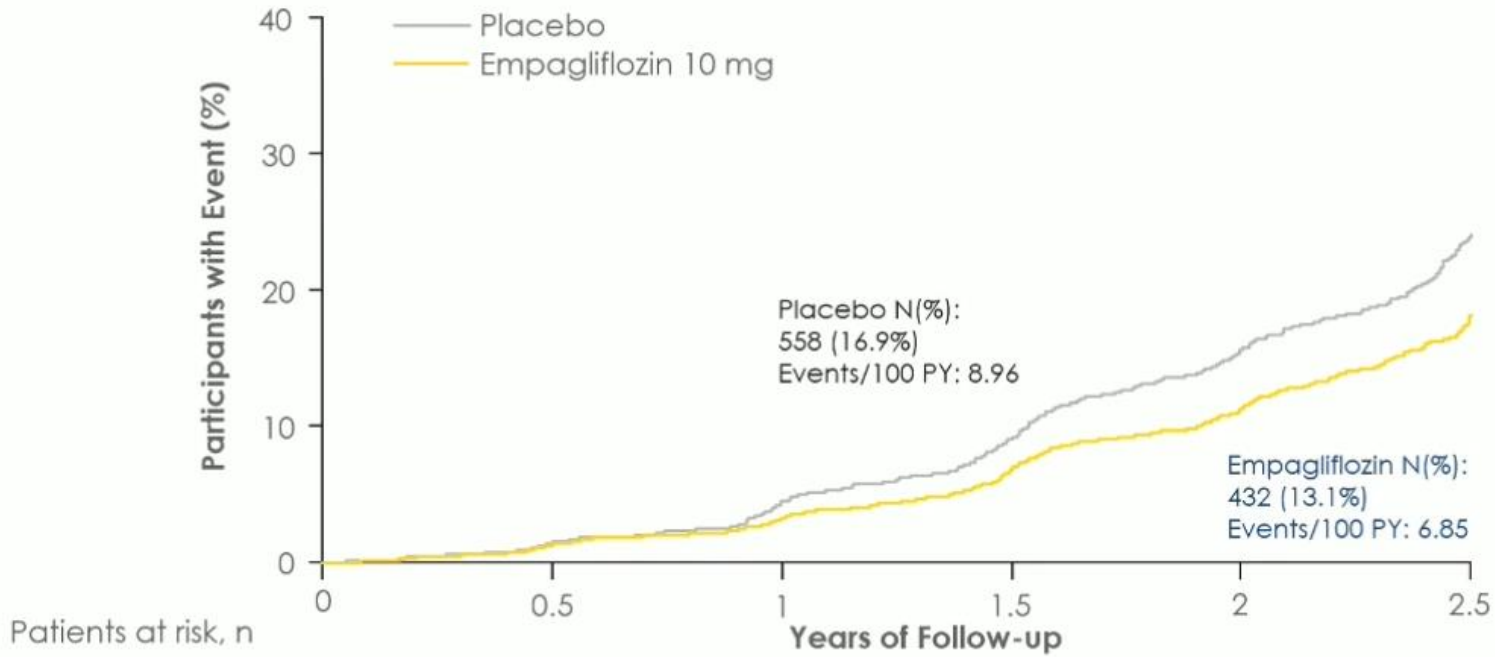
Low risk* Moderately increased risk High risk Very high risk

EMPA-KIDNEY population[1]
eGFR ≥45 to <90 ml/min/1.73 m² **and** UACR ≥200 mg/g
or
eGFR ≥20 to <45 ml/min/1.73 m²

*If no other markers of kidney disease, no CKD. eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

The EMPA-KIDNEY Collaborative Group. N Engl J Med 2022; DOI: 10.1056/NEJMoa2204233;
Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney Int Suppl 2013;3:1.

EMPA KIDNEY: Kidney disease progression or CV death
Primary composite outcome



Patients at risk, n

Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

HR 0.72
(95% CI 0.64, 0.82)
P < 0.001

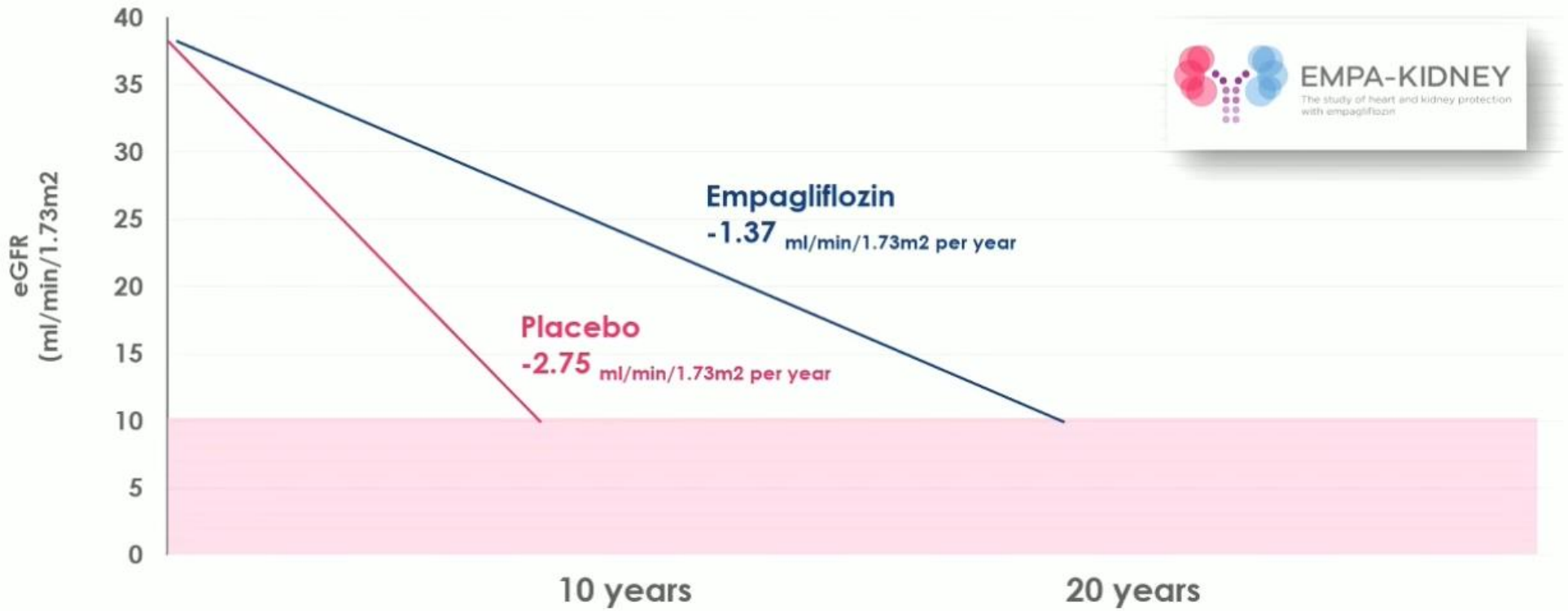
RRR 28%

NNT=28*

ARR: 3.6%† *NNT: 28 (95% CI 19, 53) per 2 years at risk[2]; †ARR for the primary composite outcome of kidney disease progression or CV death is 3.6% per patient year at risk. Figure adapted from Figure 1 of reference.
Kidney disease progression defined as end-stage kidney disease, a sustained decline in eGFR to <10 ml/min/1.73 m², renal death, or a sustained decline of ≥40% in eGFR from randomization
ARR, absolute risk reduction; CV, cardiovascular, eGFR, estimated glomerular filtration rate; NNT, number needed to treat; PY, patient years; RRR, relative risk reduction; UACR, urine albumin-to-creatinine ratio

The EMPA-KIDNEY Collaborative Group. N Engl J Med 2022. DOI: 10.1056/NEJMoa2204233

EMPA-KIDNEY: How long does take for eGFR to fall below 10 ml/min/1.73m^2?

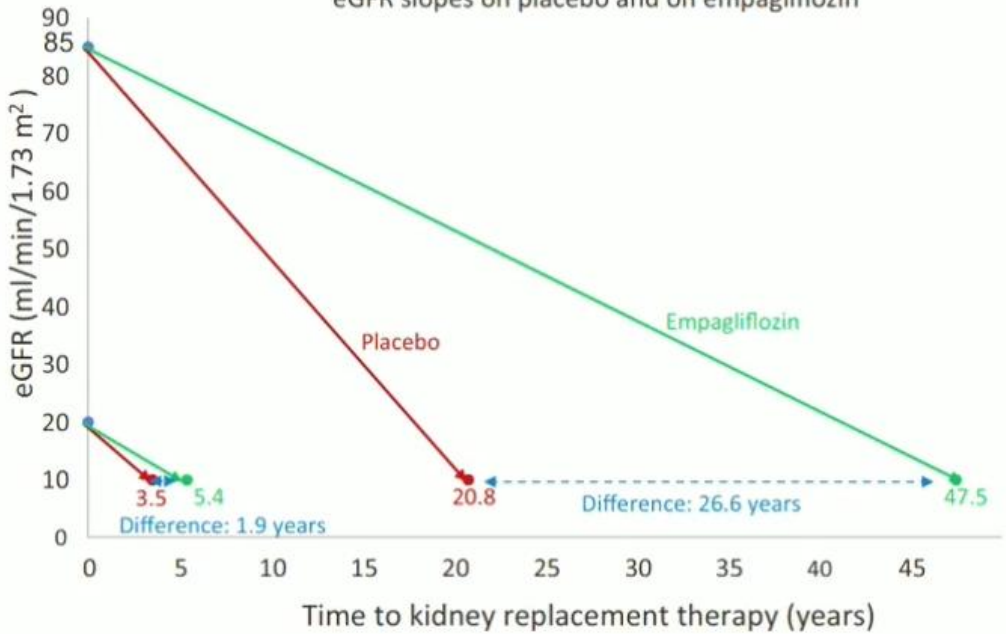


The EMPA-KIDNEY Collaborative Group. N Engl J Med 2022; DOI: 10.1056/NEJMoa2204233

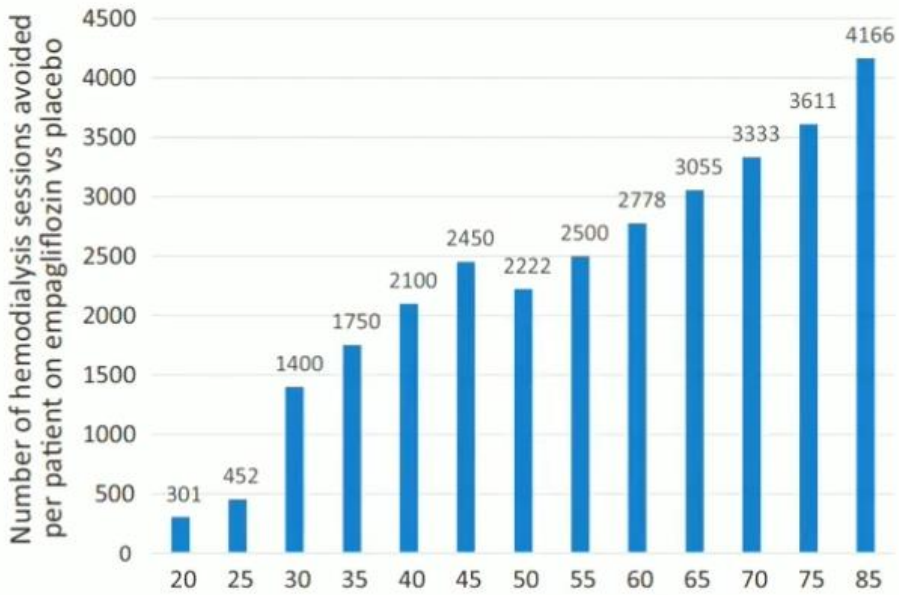
Early initiation of empagliflozin when eGFR is 85mL/min/1.73m² may delay KRT 26.6 years and avoid > 4000 HD sessions

Hypothetical transformation of chronic eGFR slopes into time to kidney failure, defined as eGFR 10 mL/min/1.73 m², in the EMPA-KIDNEY trial.

C) Potential impact on time to kidney replacement therapy of the different eGFR slopes on placebo and on empagliflozin



D) Number of hemodialysis sessions potentially avoided by delaying the need for kidney replacement therapy



C) Graphical presentation of representative chronic eGFR slopes from baseline to kidney failure, i.e. to the need for kidney replacement therapy. Hypothetical lines have been traced starting from extremes of the baseline eGFR inclusion criteria values (20 and 85 mL/min/1.73 m2) to eGFR 10 mL/min/1.73 m2, corresponding to chronic eGFR slopes of participants on placebo and on empagliflozin within each baseline eGFR subgroup, as per EMPA-KIDNEY main publication. (D) Number of hemodialysis sessions potentially avoided by delaying the need for kidney replacement therapy by prescribing empagliflozin instead of placebo at each baseline eGFR value. The model assumes that patients will live up to the point where they need kidney replacement therapy and that they would continue hemodialysis throughout. While this is not expected to occur in every patient, it is a real possibility for some of them.

Fernández-Fernandez B, et al. EMPA-KIDNEY: expanding the range of kidney protection by SGLT2 inhibitors. Clin Kidney J. 2023 Jun 16;16(8):1187-1198. doi: 10.1093/ckj/sfad082.

Articles

Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials

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

Lancet 2022; 400: 1788–801

Summary

Background Large trials have shown that sodium glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of adverse

SMART-C

OXFORD POPULATION HEALTH CTSU

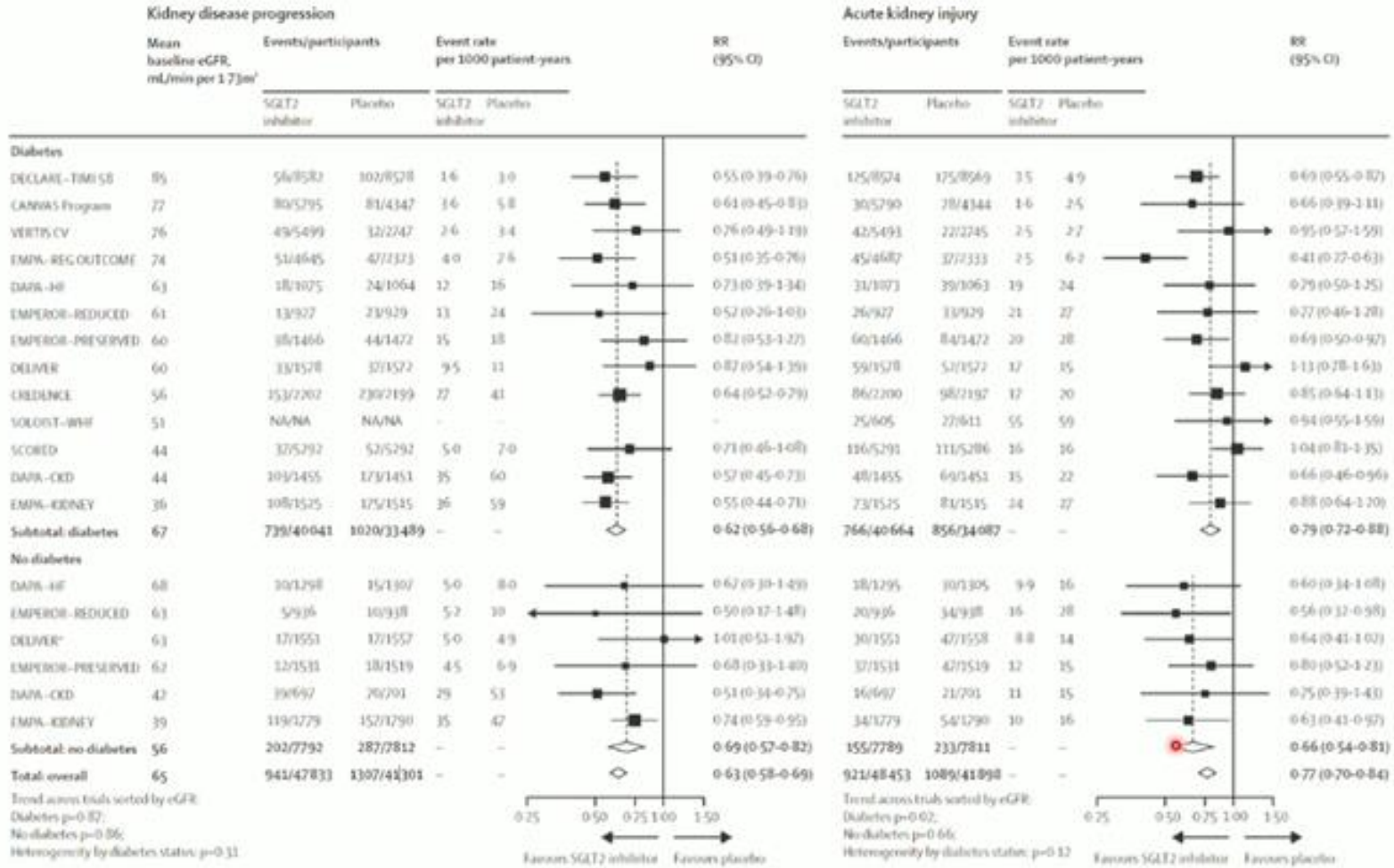
MRC Population Health Research Unit

OXFORD

Sodium Glucose Cotransporter-2 (SGLT2) Inhibitors Among Patients With and Without Diabetes:

Collaborative Meta-Analysis of Large Placebo-Controlled Trials

Effect of SGLT2 i on kidney disease outcomes by diabetes status



KDIGO 2024- SGLT2i

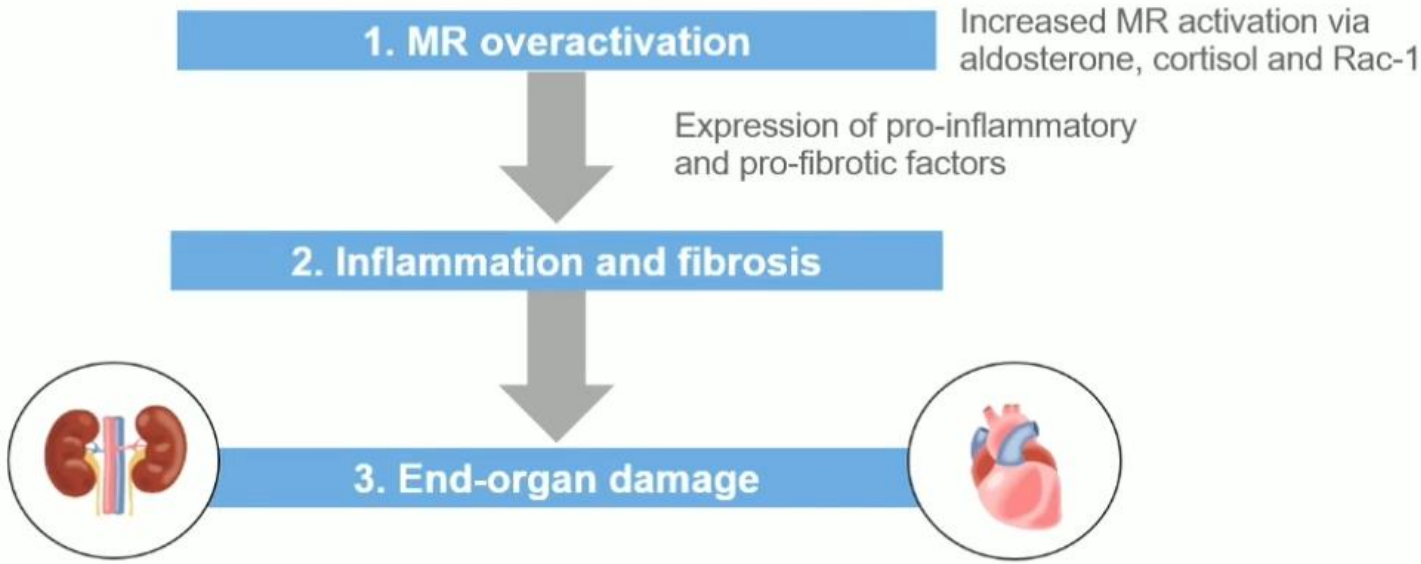
- SGLT2i in all
- Strongest recommendation for:
  - CKD (eGFR>20) and T2D (1A)
  - CKD (eGFR>20) and ACR>20mg/mmol (1A)
  - CKD (eGFR>20) and HF(regardless of UACR) (1A)

- Still recommended for:
  - CKD (eGFR 20-45) and UACR<20mg/mmol (2B)

Novel medications

nsMRA finerenone

MR overactivation, which contributes to inflammation and fibrosis, is a treatment target

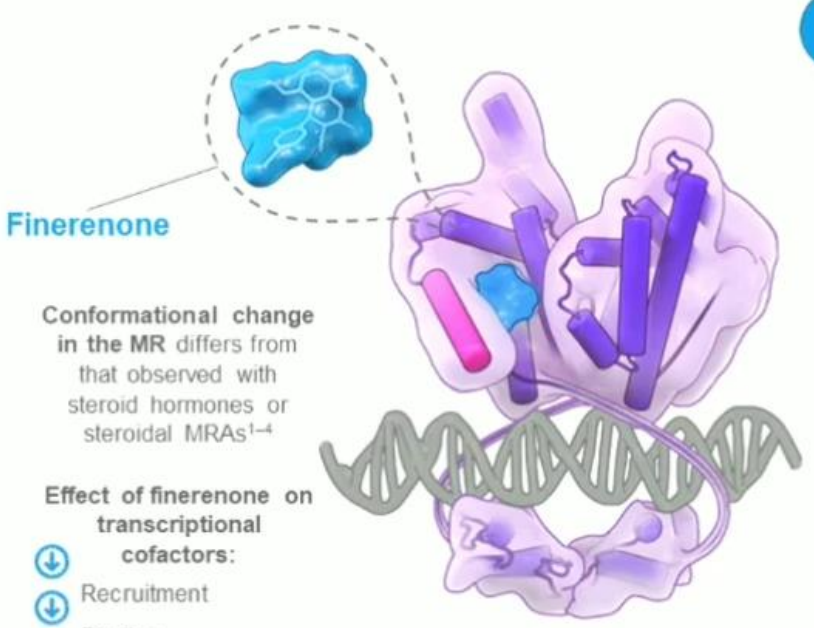


Blocking MR overactivation may prevent adverse renal and cardiovascular outcomes mediated through inflammatory and fibrotic pathways[1–7]

MR, mineralocorticoid receptor; Rac-1, ras-related C3 botulinum toxin substrate 1

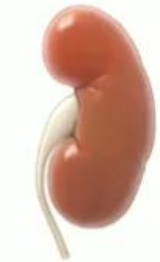
1. Cannavo A, et al. Oxid Med Cell Longev 2018;2018:1204598; 2. Kolkhof P, et al. J Cardiovasc Pharm 2014;64:69-78; 3. Bertocchio JP, et al. Kidney Int 2011;79:1051-1060; 4. Belden Z, et al. Am J Nephrol 2017;46:298-314; 5. Ong GS, et al. J Med Endocrinol 2017;58:R33-R57; 6. Bauersachs J, et al. Hypertension 2015;65:257-263; 7. Grune J, et al. Hypertension 2018;71:599-608

Finerenone, a selective, non-steroidal MRA, blocks MR overactivation, slowing kidney and CV disease progression[1–3]

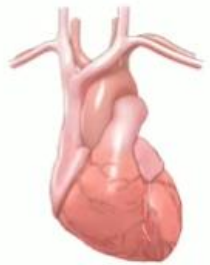


Slowed CKD and HF progression[1-3]

- Haemodynamic factors
- Inflammation and fibrosis
- Albuminuria



Kidney and heart protection



CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist.

1. Kintscher U, et al. Br J Pharmacol. 2022;179:3220–3234; 2. Agarwal R, et al. Eur Heart J. 2022;43:474–484; 3. Agarwal R, et al. Nephrol Dial Transplant. 2022;37:1014–1023; 4. Amazit L, et al. J Biol Chem. 2015;290:21876–21889.

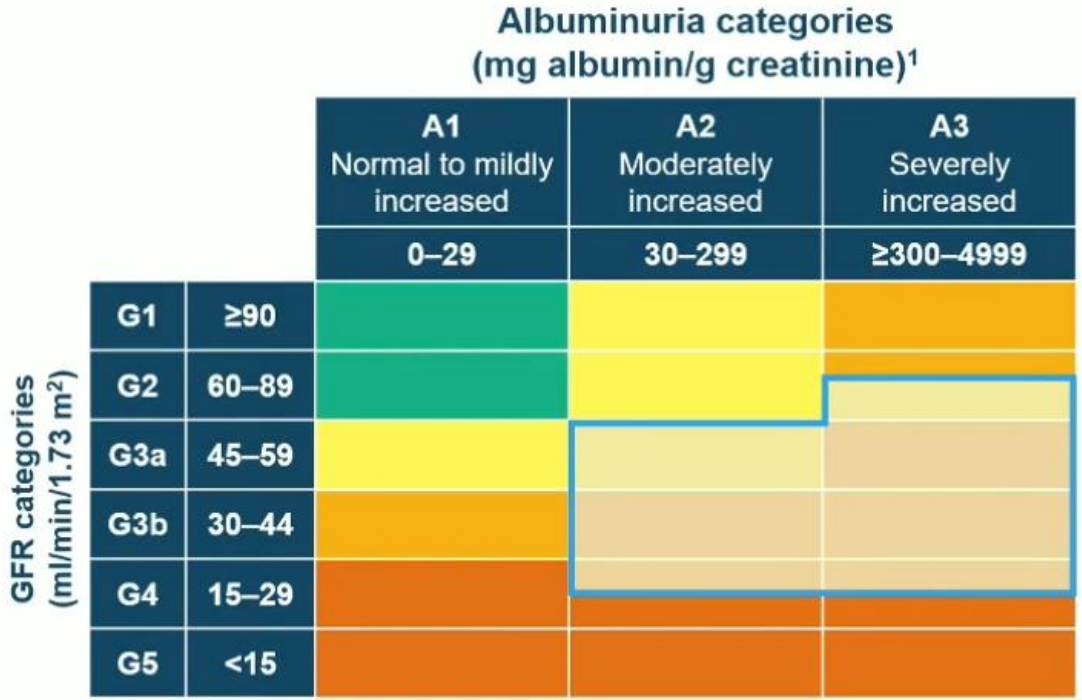
Finerenone and steroidal MRAs have key pharmacodynamic and pharmacokinetic differences[1-3]

	Aldosterone antagonists		Finerenone
			
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency against MR	+++	+	+++
Selectivity for MR	+	++	+++
CNS penetration	+	+	–
Sexual side effects	++	(+)	–
Half-life	>20 hours*	4–6 hours*	2–3 hours#
Active metabolites	++	–	–
Effect on BP	+++	++	+
Indication	**Congestive HF[4]**	**HF and LVEF ≤40% or ≤30%[5]**	**CKD (with albuminuria) associated with T2D[6]**

* In patients with HF
# In healthy volunteers
CNS, central nervous system; LVEF, left ventricular ejection fraction

1. Kintscher U, et al. Br J Pharmacol 2021; doi: 10.1111/bph.15747; 2. Schwabe JW, et al. Cell 1993;75:567–578; 3. Tanenbaum DM, et al. Proc Natl Acad Sci USA 1998;95:5998–6003; 4. Pfizer Ltd. Aldactone (spironolactone) Summary of Product Characteristics. 2019. https://www.medicines.org.uk/emc/product/2899/smpc [accessed 28 Mar 2022]; 5. Zentiva Pharma UK Limited. Eplerenone Summary of Product Characteristics. 2021. https://www.medicines.org.uk/emc/product/3665/smpc#INDICATIONS [accessed 28 Mar 2022]; 6. Kerendia Hong Kong Prescribing Information.

The finerenone phase III programme included patients across the spectrum of CKD severity



FIDELIO-DKD (N=5734)[2]

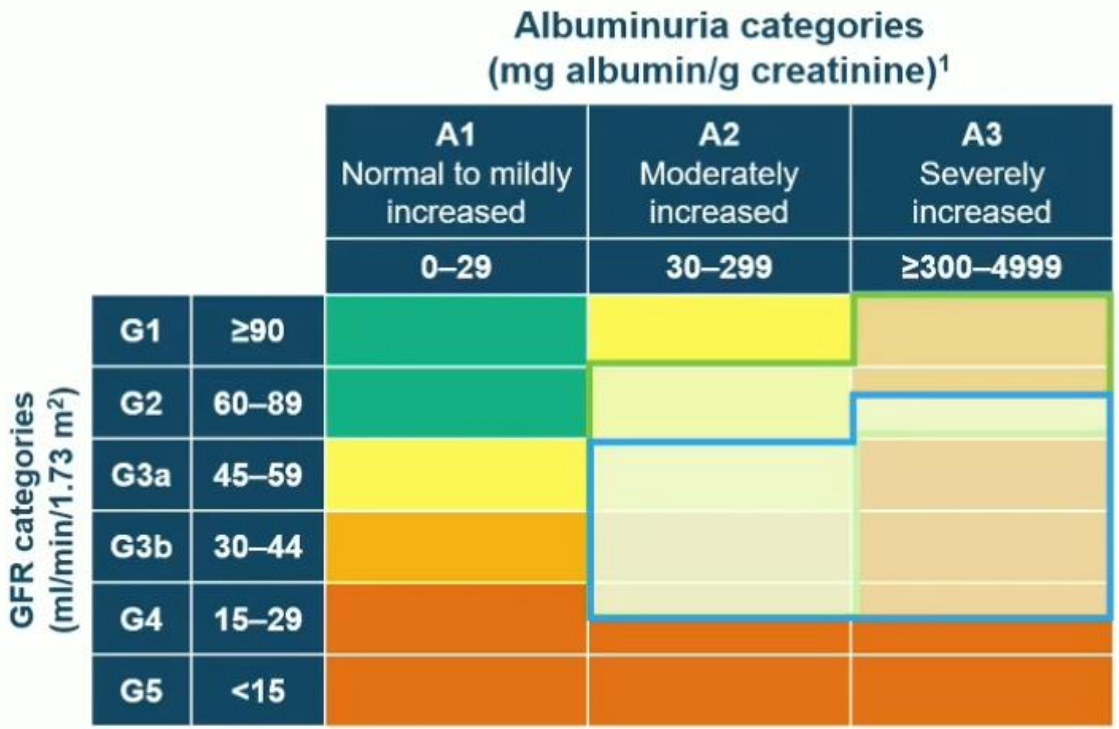
Representative of late-stage CKD

- UACR 30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m² and a history of diabetic retinopathy
- Or UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m²

GFR, glomerular filtration rate; UACR, urine albumin-to-creatinine ratio

1. Kidney Disease: Improving Global Outcomes. *Kidney Int* 2020;98:S1–S115; 2. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 3. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356;
4. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

The finerenone phase III programme included patients across the spectrum of CKD severity



FIGARO-DKD (N=7437)[3]
Representative of early-stage CKD

- UACR 30–<300 mg/g and eGFR 25–≤90 ml/min/1.73 m²
- **Or** UACR ≥300–≤5000 mg/g and eGFR ≥60 ml/min/1.73 m²

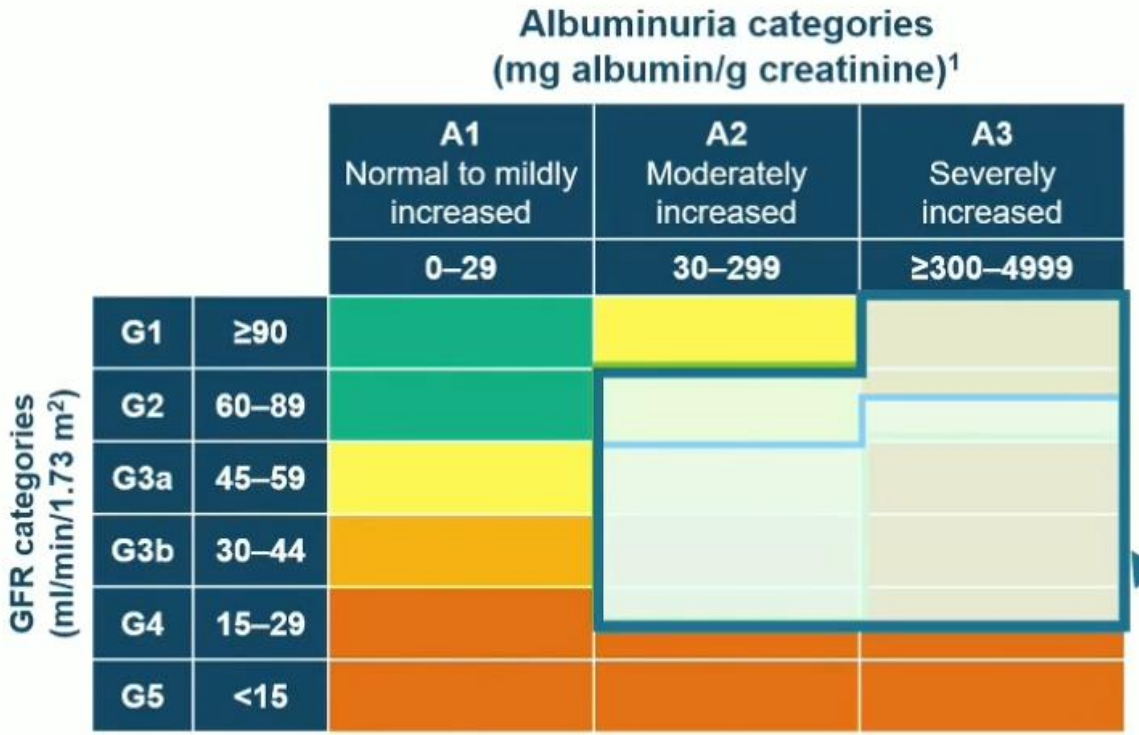
FIDELIO-DKD (N=5734)[2]
Representative of late-stage CKD

- UACR 30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m² and a history of diabetic retinopathy
- Or UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m²

GFR, glomerular filtration rate; UACR, urine albumin-to-creatinine ratio

1. Kidney Disease: Improving Global Outcomes. *Kidney Int* 2020;98:S1–S115; 2. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 3. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356;
4. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

The finerenone phase III programme included patients across the spectrum of CKD severity



FIGARO-DKD (N=7437)[3]
Representative of early-stage CKD

- UACR 30–<300 mg/g and eGFR 25–≤90 ml/min/1.73 m²
- **Or** UACR ≥300–≤5000 mg/g and eGFR ≥60 ml/min/1.73 m²

FIDELIO-DKD (N=5734)[2]
Representative of late-stage CKD

- UACR 30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m² and a history of diabetic retinopathy
- Or UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m²

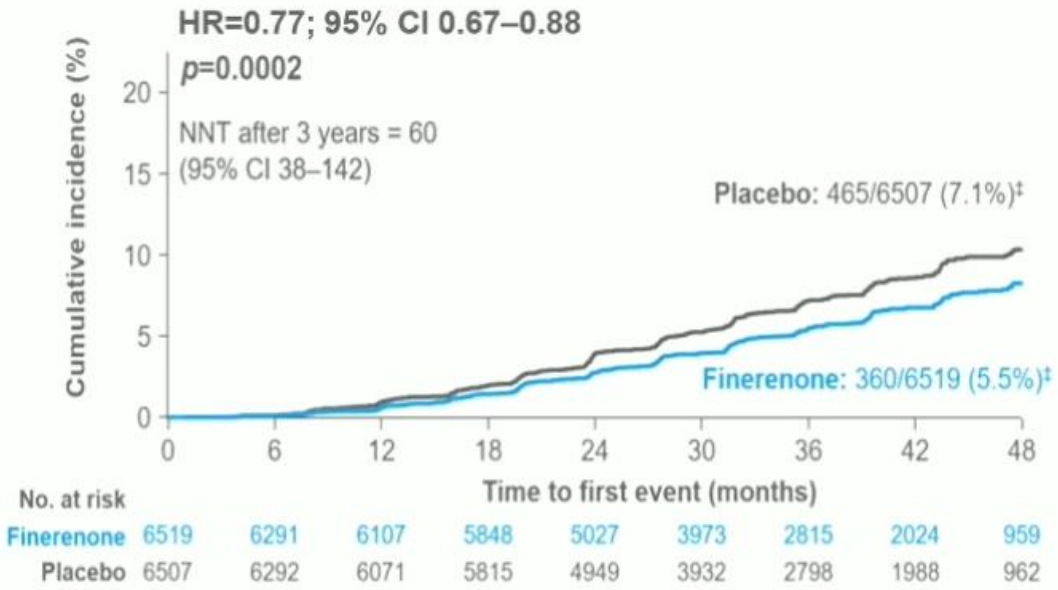
FIDELITY (N=13,171)[4]
Prespecified pooled analysis
CKD stage 1-4

GFR, glomerular filtration rate; UACR, urine albumin-to-creatinine ratio

1. Kidney Disease: Improving Global Outcomes. *Kidney Int* 2020;98:S1–S115; 2. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 3. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356;
4. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

In FIDELITY, finerenone reduced the risk of kidney composite outcome by 23%

Time to kidney failure,* sustained ≥57% decrease in eGFR from baseline, or renal death#

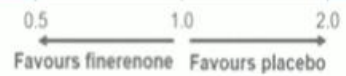


*ESKD or an eGFR <15 ml/min/1.73 m²; #events were classified as renal death if: (1) the patient died; (2) kidney replacement therapy had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; ‡cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk; ¶number of patients with an event over a median of 3.0 years of follow-up

Finerenone reduced the risk of ESKD* by 20% vs placebo

Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	p-value
eGFR 57% composite kidney outcome	360 (5.5)	465 (7.1)	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	297 (4.6)	0.84 (0.71–0.99)	0.039
ESKD#	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040‡
eGFR <15 ml/min/1.73 m²¶	195 (3.0)	237 (3.6)	0.81 (0.67–0.98)	0.026‡
≥57% decrease in eGFR from baseline¶	257 (3.9)	361 (5.5)	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	4 (<0.1)	0.53 (0.10–2.91)	–

≥57% decrease in eGFR is equivalent to doubling of serum creatinine



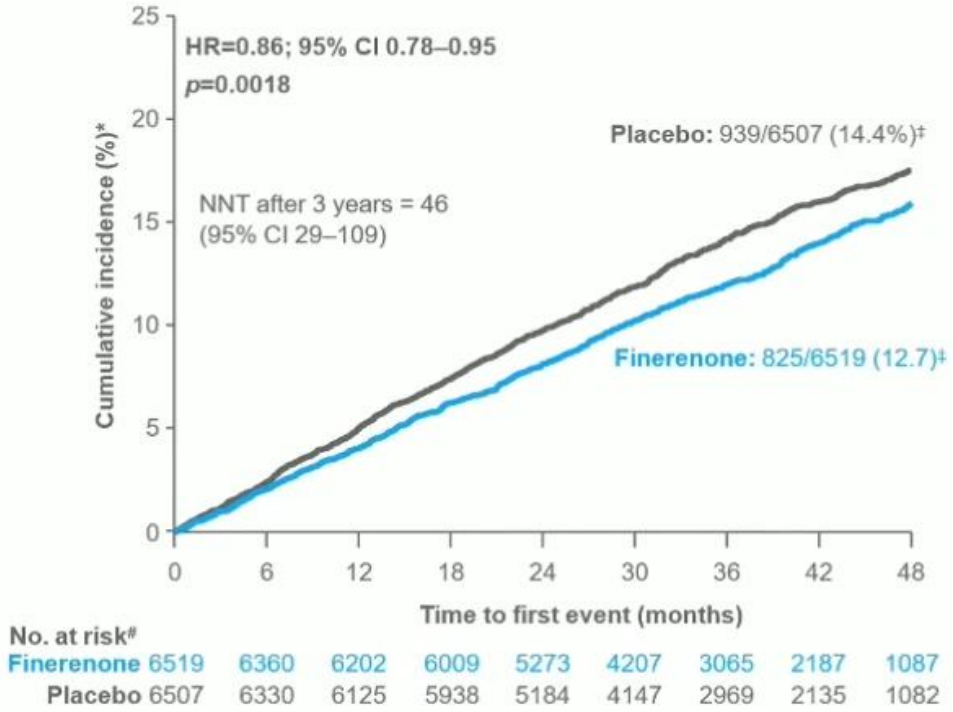
*Only 6 patients experienced renal death; #initiation of chronic dialysis for ≥90 days or kidney transplant; ‡analysis for *p*-values not prespecified; ¶confirmed by two eGFR measurements ≥4 weeks apart

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

FIDELITY

Finerenone reduced the risk of the CV morbidity & mortality by 14% compared with placebo

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



Finerenone reduced the risk of HHF by 22% vs placebo

Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	p-value
Composite CV outcome§	**825 (12.7)**	**939 (14.4)**	**0.86 (0.78–0.95)**	**0.0018**
CV death	322 (4.9)	364 (5.6)	0.88 (0.76–1.02)	0.092
Non-fatal MI	173 (2.7)	189 (2.9)	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	198 (3.0)	0.99 (0.82–1.21)	0.95
Hospitalisation for HF	256 (3.9)	325 (5.0)	0.78 (0.66–0.92)	0.0030

*Cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk; #at-risk subjects were calculated at start of time point; ‡number of patients with an event over a median of 3.0 years of follow-up; §composite of time to first onset of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF CI, confidence interval; HR, hazard ratio; NNT, number needed to treat.

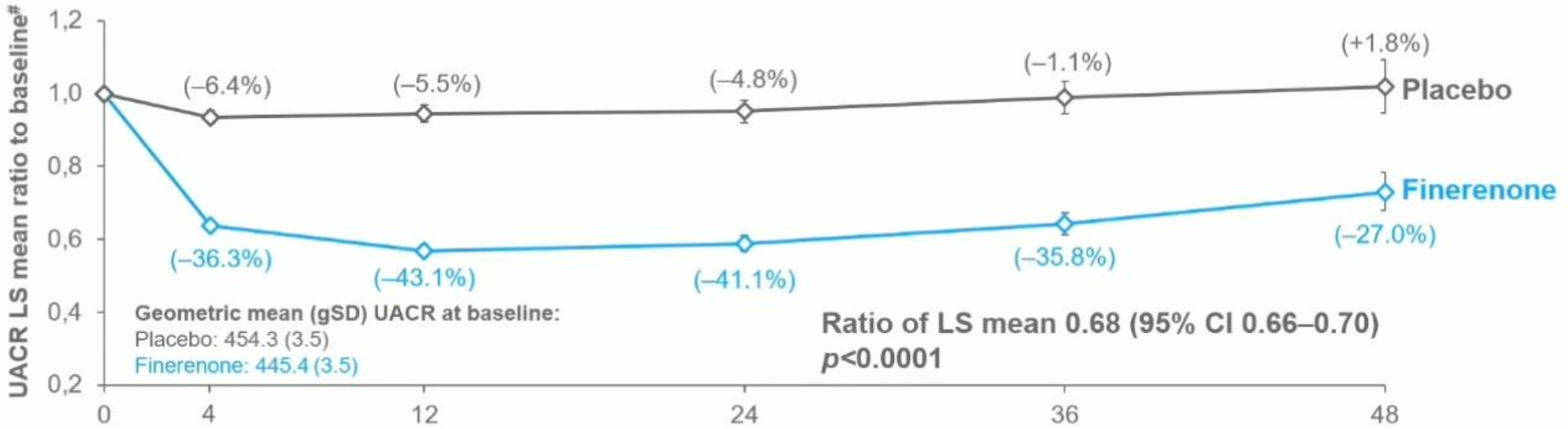
FIDELITY

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

Finerenone reduced UACR by 32% between baseline and month 4 vs placebo*

FIDELITY

A lower mean UACR with finerenone vs placebo was maintained throughout the study



No. of patients						
Finerenone	6519	6273	5988	4867	2745	899
Placebo	6507	6239	5973	4829	2706	872

*Full analysis set. Mixed model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history, time, treatment*time, study, study*treatment, log-transformed baseline value nested within type of albuminuria at screening and log-transformed baseline value*time as covariate. Separate unstructured covariance patterns are estimated for each treatment group; #data are LS mean/95% CI

Data in parentheses are mean change from baseline
CI, confidence interval; eGFR, estimated glomerular filtration rate; gSD, geometric standard deviation; LS, least-squares; UACR, urine albumin-to-creatinine ratio

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

Finerenone demonstrated significant risk reductions in CV and kidney outcomes in two phase III clinical trials

FIDELITY

Prespecified pooled analysis of data from the **FIDELIO-DKD and FIGARO-DKD** trials

>13,000 patients **across the disease continuum of CKD and T2D** (CKD stage 1–4) with moderate-to-severely elevated albuminuria (UACR ≥30 mg/g)

14% reduced **risk of CV morbidity and mortality** versus placebo (HR=0.86; 95% CI 0.78–0.95; *p*=0.002)[1] [ARR=1.7%]

22% reduced **risk of first HHF*** versus placebo (HR=0.78; 95% CI 0.66–0.92; *p*=0.003)[1] [ARR=1.1%]

23% reduced **risk of CKD progression**† versus placebo (HR=0.77; 95% CI 0.67–0.88; *p*=0.0002)[1] [ARR=1.6%]

20% reduced **risk of ESKD** versus placebo (HR=0.80; 95% CI 0.64–0.99; *p*=0.040)[1,‡] [ARR=0.6%]

32% reduction in **UACR** (ratio of LS mean change from baseline 0.68; 95% CI 0.66–0.70)[1]

Finerenone is indicated for the treatment of CKD (with albuminuria) associated with T2D in adults[2]

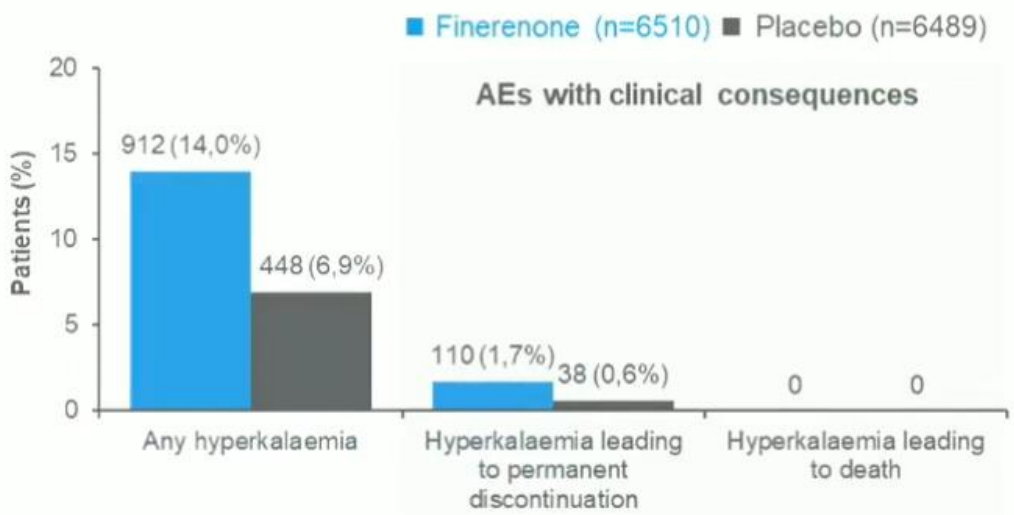
*First HHF defined as first event after randomisation; †ESKD or an eGFR <15 mL/min/1.73 m2, events were classified as renal death if: (1) The patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death;3 ‡Analysis for p-value not prespecified.

1. Agarwal R, et al. Eur Heart J. 2022;43:474–484; 2. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2024. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed Jan 2025]. 3. Agarwal R, et al. Eur Heart J. 2022;43:474–484 (supplement).

Finerenone had a similar AE profile to placebo and an increased incidence of hyperkalaemia, but the clinical impact was minimal[1]

Incidence of AEs and changes in vital signs were similar between finerenone and placebo[1]

- **Any AE: 86.1% vs 86.4%**
- **AKI: 3.4% vs 3.6%**
- **Gynaecomastia: 0.1% vs 0.2%**
- **No change in HbA1c**



Maximum difference in mean serum [K^+] between finerenone and placebo[1]

0.19 mmol/l at month 4

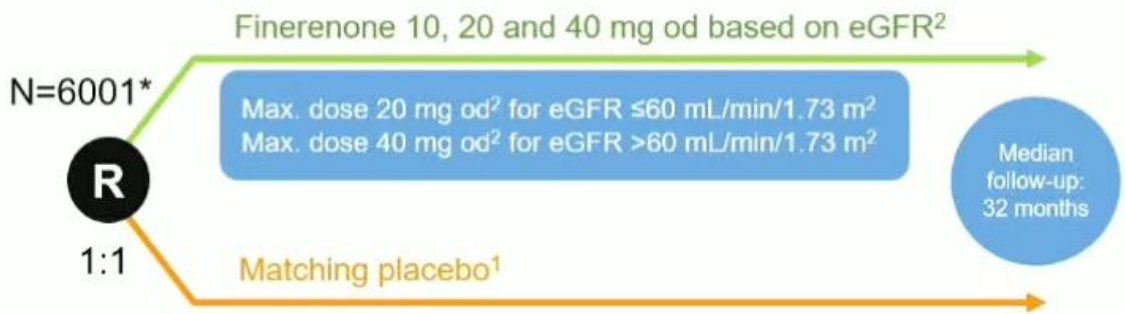
Hyperkalaemia risk factors[2]:
High baseline [K^+], lower eGFR, higher UACR, beta blocker use

FIDELITY

In FIDELITY, the total number of patients with an event in the finerenone group was n=6510, and n=6489 in the placebo group.
AE, adverse event; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; K, potassium; UACR, urine albumin-to-creatinine ratio.
1. Agarwal R, et al. Eur Heart J. 2022;43:474–484; 2. Agarwal R, et al. J Am Soc Nephrol. 2022;33:225–237.

FINEARTS-HF evaluated the efficacy and safety of finerenone in patients with HF LVEF ≥40%[1]

FINEARTS-HF



Primary endpoint[1]

Number of **CV deaths** and **total HF events†** (first and recurrent)

Secondary endpoints[1]

- **Total HF events†** (first and recurrent)
- Change from baseline to Months 6, 9, and 12 in **KCCQ-TSS**
- Improvement in **NYHA Class** from baseline to Month 12
- **Composite renal endpoint** (sustained decrease in eGFR ≥50%; sustained eGFR decline <15 mL/min/1.73 m²; initiation of dialysis or kidney transplantation)
- **All-cause mortality**

✓ Key inclusion criteria:[2]

- Aged ≥40 years
- HF diagnosis; NYHA Class II–IV (ambulatory or hospitalized primarily for HF)
- LVEF ≥40% measured within last 12 months
- Structural heart abnormalities within last 12 months
- Diuretics in 30 days prior to randomization
- NT-proBNP ≥300 pg/mL or BNP ≥100 pg/mL (sinus rhythm); NT-proBNP ≥900 pg/mL or BNP ≥300 pg/mL (atrial fibrillation)

✗ Key exclusion criteria:[2]

- eGFR <25 mL/min/1.73 m²
- Serum plasma potassium >5.0 mmol/L
- MI or any event that could have reduced the EF
- Acute inflammatory heart disease, CABG, stroke or TIA within last 90 days or PCI in the last 30 days
- Alternative causes of HF symptoms
- SBP ≥160 mmHg‡

Finerenone is indicated for the treatment of chronic kidney disease (with albuminuria) associated with T2D in adults.[3] For prescribing information, please refer to the SmPC of the product applicable in your country. Finerenone is not indicated for the treatment of HF. 40 mg od is not a licensed dosage of finerenone.

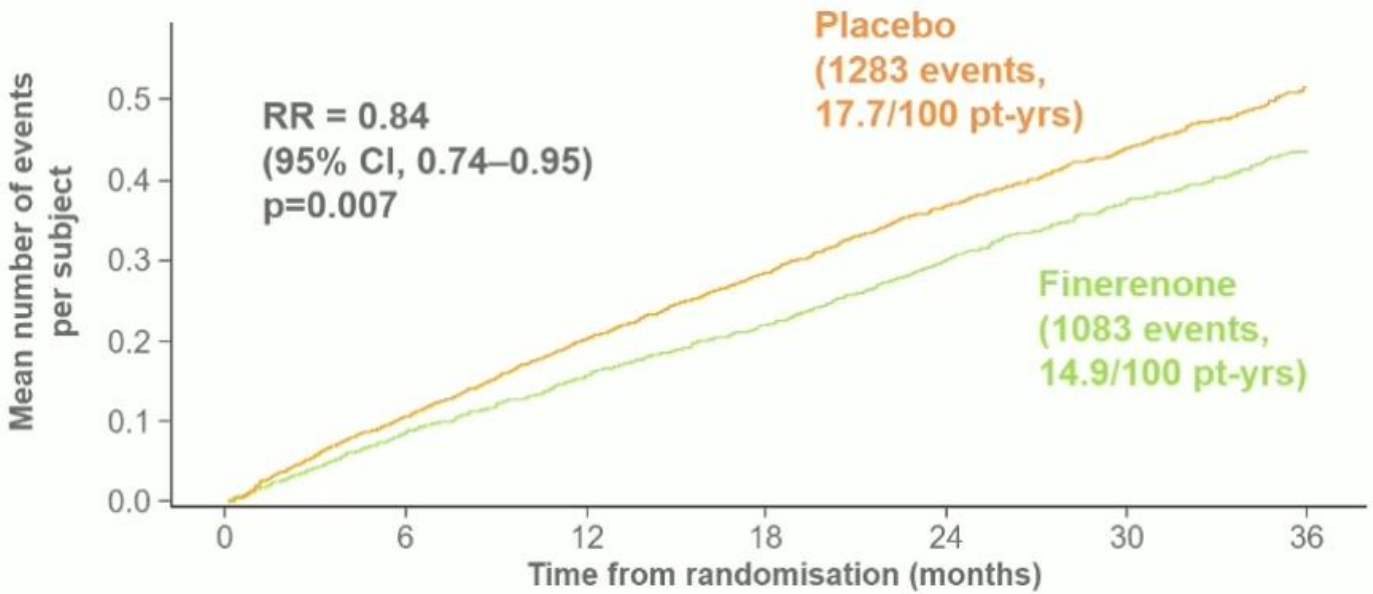
*6016 randomized, 6001 included in efficacy analysis[1]; †HF events defined as either an unplanned HHF or an urgent HF visit; ‡If not on treatment with ≥3 blood-pressure-lowering medications or ≥180 mmHg irrespective of treatments.
BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; od, once daily; PCI, percutaneous coronary intervention; R, randomization; SBP, systolic blood pressure; TIA, transient ischemic attack; T2D, type 2 diabetes.

1. Solomon SD, et al. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2407107; 2. Bayer AG. https://clinicaltrials.gov/ct2/show/NCT04435626 [accessed September 2024]; 3. Bayer AG. KERENDIA®(finerenone) Summary of Product Characteristics. 2024. https://www.ema.europa.eu/en/documents/product-information/kerendia-epar-product-information_en.pdf [accessed September 2024]

Finerenone demonstrated a clinically meaningful 16% relative risk reduction in the composite of CV deaths and total HF events

FINEARTS-HF

Primary endpoint: Number of CV deaths and total HF events



Differences in treatment effect on the composite CV outcome were observed early and remained consistent throughout FINEARTS-HF

Figure adapted from Solomon S, et al. *N Engl J Med* 2024;391(16):1475–1485.

CI, confidence interval; CV, cardiovascular; HF, heart failure; PY, patient-years; RR, rate ratio.
Solomon SD, et al. *N Engl J Med.* 2024;391:1475–1485.

Finerenone is recommended to reduce CV and kidney failure risk and for the prevention of HF in patients with CKD and T2D

ESC

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes[1]

To reduce CV risk

- Statin-based regimen — Class IA
- ACEi or ARB — Class IA

To reduce kidney failure risk

To reduce CV and kidney failure risk

- Finerenone — Class IA
- SGLT-2i — Class IA
- BP control — Class IA

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[2]

Prevention of HF in CKD and T2D

- **Finerenone***
  – in patients with CKD and T2D recommended to reduce the risk of HHF
  Class IA
- **SGLT-2is#**
  – in patients with CKD and T2D recommended to reduce the risk of HHF or CV death
  Class IA

*For finerenone, CKD was defined as an eGFR of 25–60 ml/min/1.73 m2, UACR of 30–300 mg/g, and diabetic retinopathy, or an eGFR 25–75 ml/min/1.73 m2 and UACR of 300–5000 mg/g in FIDELIO-DKD; an eGFR 25–90 ml/min/1.73 m2 and UACR of 30 to <300 mg/g or an eGFR >60 ml/min/1.73 m2 and UACR of 300–5000 mg/g in FIGARO-DKD; #for SGLT-2is, CKD was defined as an eGFR of 25–75 ml/min/1.73 m2 and UACR of ≥200–5000 mg/g in DAPA-CKD; an eGFR of 20–45 ml/min/1.73 m2 or an eGFR of 45–90 ml/min/1.73 m2 with UACR of ≥200 mg/g in EMPA-KIDNEY.

1. Marx N, et al. Eur Heart J. 2023;00:1–98; 2. McDonagh TA, et al. Eur Heart J. 2023;44:3627–3639.

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Rationale and design of a randomised phase III registration trial investigating finerenone in participants with type 1 diabetes and chronic kidney disease: The FINE-ONE trial

Hiddo J.L. Heerspink [a,*], Andreas L. Birkenfeld [b,c,d], David Z.I. Cherney [e], Helen M. Colhoun [f], Linong Ji [g], Chantal Mathieu [h], Per-Henrik Groop [i], Richard E. Pratley [j], Sylvia E. Rosas [k], Peter Rossing [l,m], Jay S. Skyler [n], Katherine R. Tuttle [o], Robert Lawatscheck [p], Charlie Scott [q], Robert Edfors [r], Markus F. Scheerer [s], Peter Kolkhof [t], Janet B. McGill [u]

FINE-ONE is a global, randomized, phase III clinical trial designed to expand the kidney protective indication of finerenone to adults with T1D and CKD[1,2]

FINE-ONE

To understand if finerenone, in addition to SoC, has superior efficacy to placebo (by reducing UACR) and a tolerable safety profile in adult patients with CKD and T1D over 6 months

Study design

87 centers across 9 countries

Key dates

Actual study start:
February 2024

Estimated study completion:
October 2025

Finerenone is indicated in the EU for the treatment of CKD (with albuminuria) associated with T2D in adults. CV prevention is not an approved indication for finerenone in the EU.

*For participants with an eGFR ≥25–<60 mL/min/1.73 m², starting dose is 10 mg od. For participants with an eGFR ≥60 mL/min/1.73 m², starting dose is 20 mg od. Up-titration and down-titration of study intervention will be based on local serum [K⁺] and kidney function (eGFR) values.

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; [K⁺], potassium concentration; SoC, standard of care; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

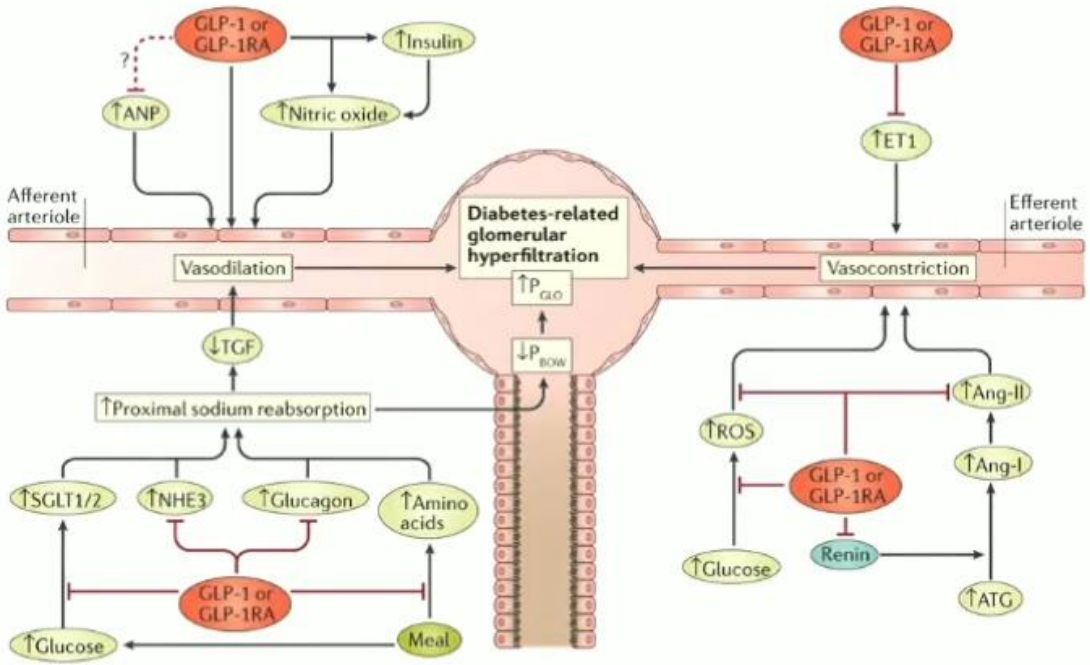
1. Bayer. https://clinicaltrials.gov/study/NCT05901831 [accessed 18 Feb 2025]; 2. Heerspink HJL, et al. *Diabetes Res Clin Pract.* 2023;204:110908.

Novel medications

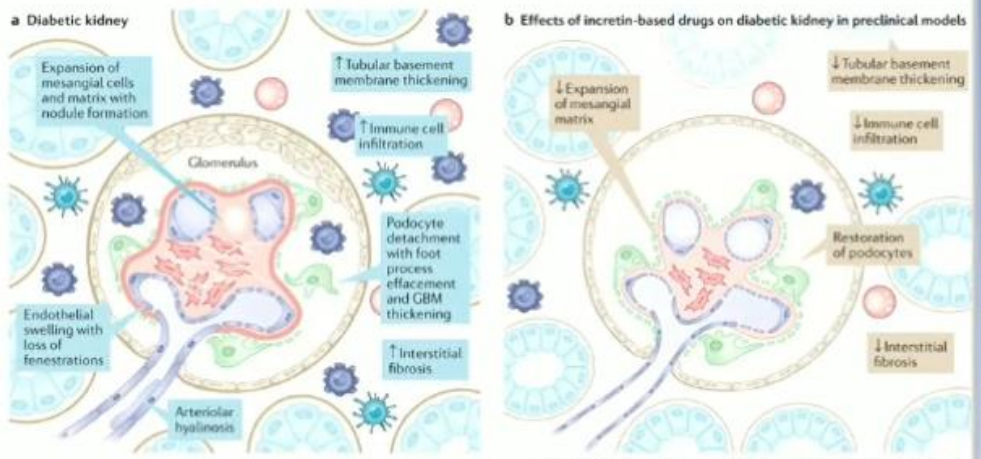
GLP-1 agonists

Potential kidney protective mechanisms of the GLP1-RA

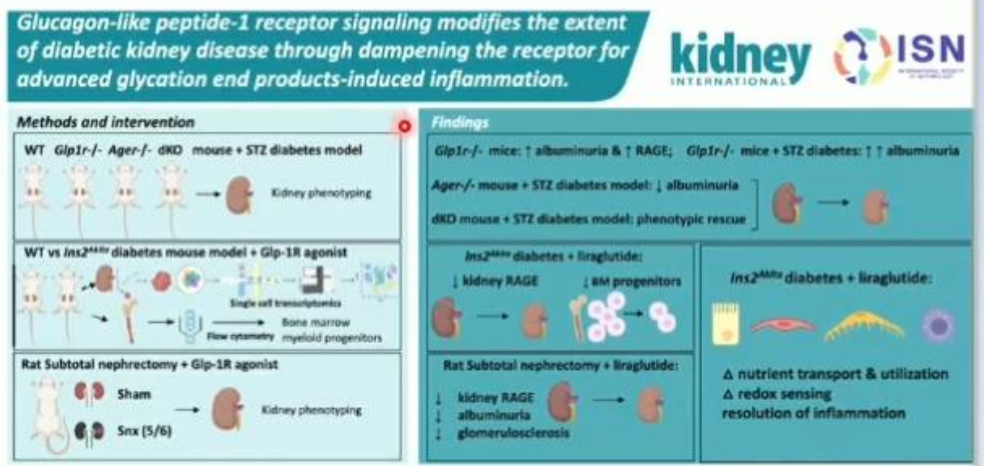
direct vasodilative actions and inhibition of pathways of glomerular hyperfiltration



Muskeit RA, et al. Nat Rev Nephrol 2017

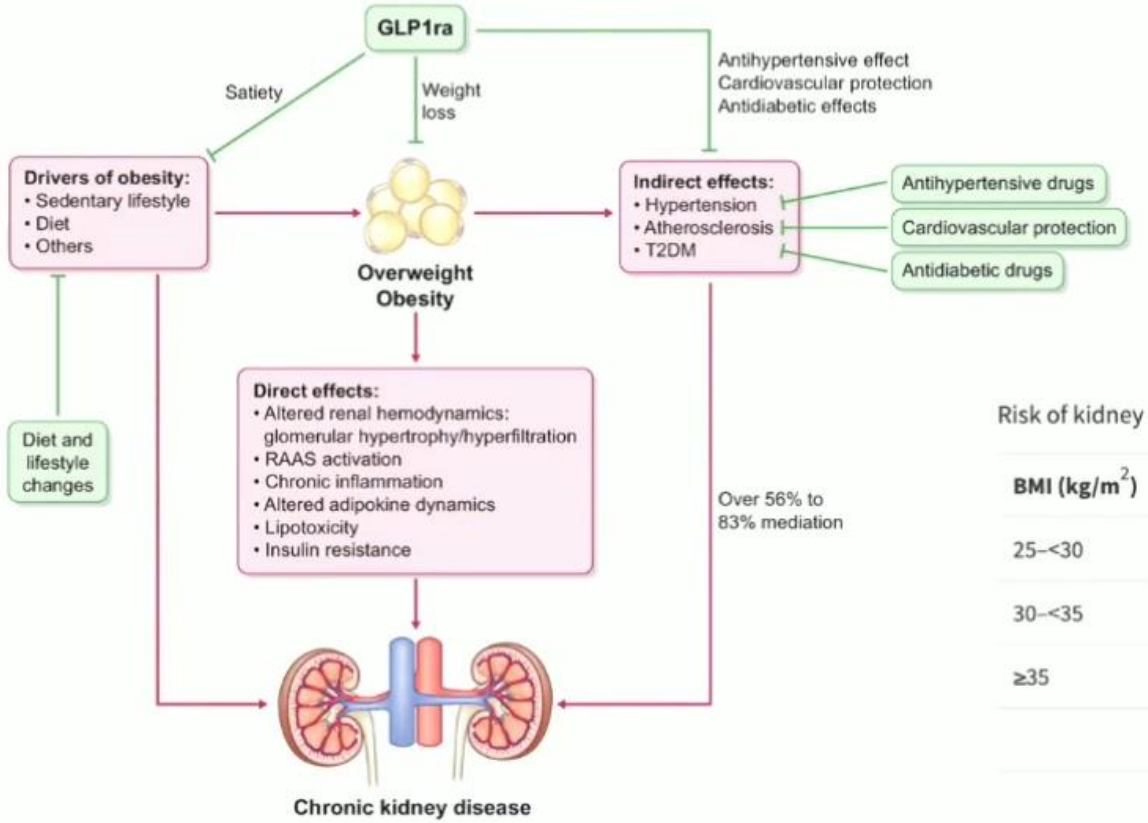


Alicic RZ, et al. Nat Rev Nephrol 2017



Sourris KC, et al 2024

Obesity is an independent risk factor for CKD

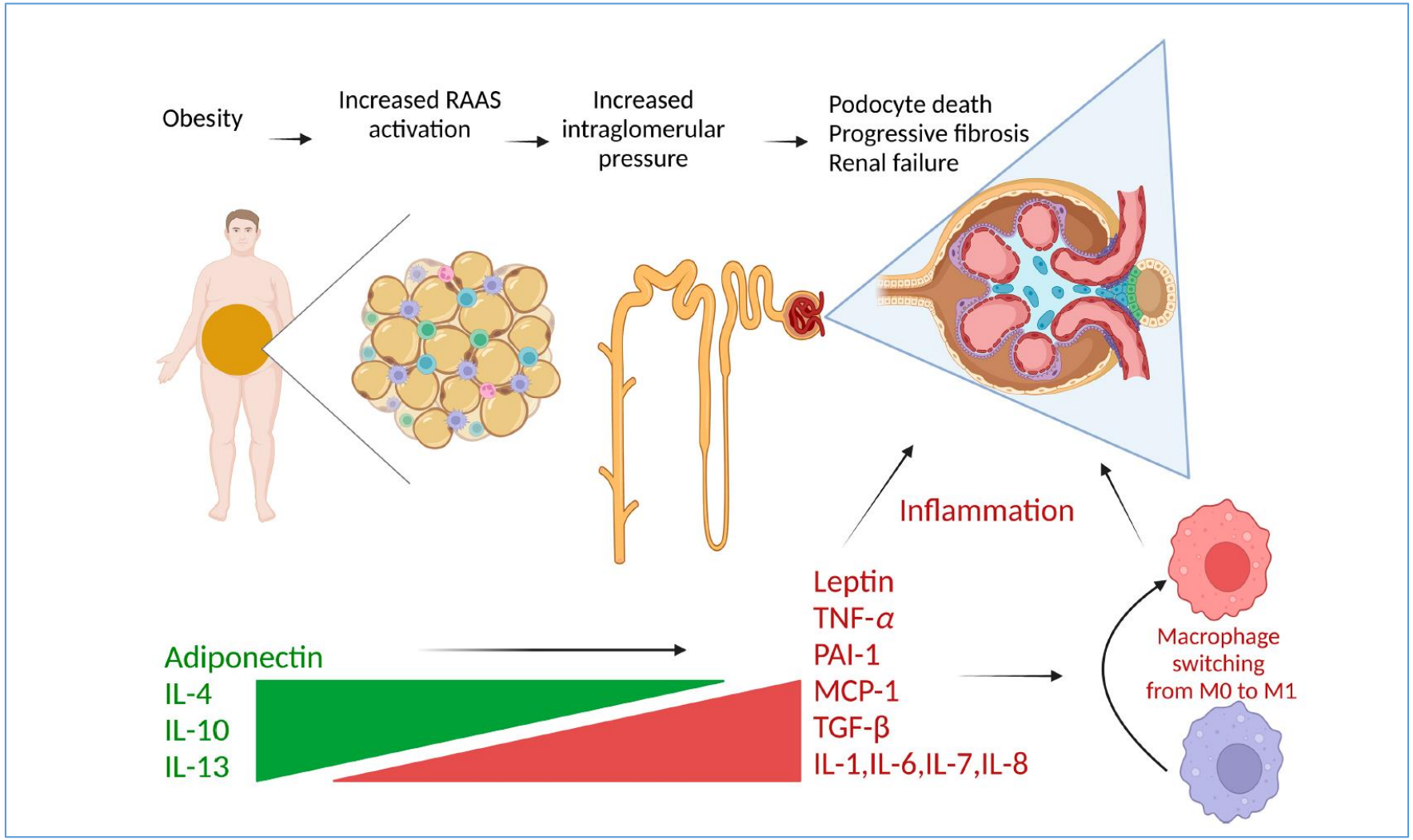


Risk of kidney disease in persons with overweight/obesity [5, 23].

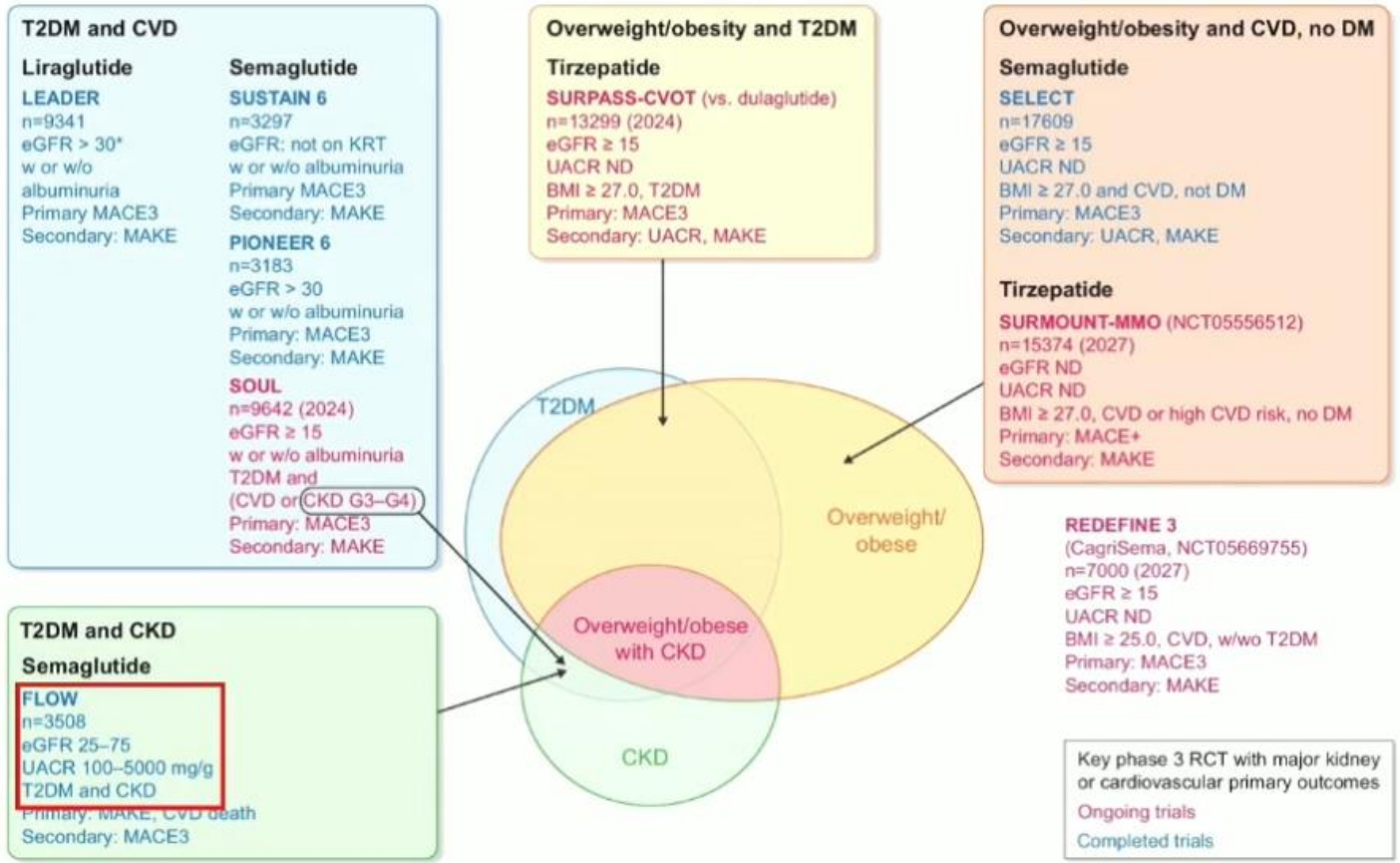
BMI (kg/m^2)	CKD G4–G5, HR (95% CI)	BMI (kg/m^2)	Kidney failure, HR (95% CI)
25–<30	1.34 (1.30–1.38)	25–<30	1.87 (1.64–2.14)
30–<35	1.94, 1.87–2.01	30–<35	3.57 (3.05–4.18)
≥35	3.10, 2.95–3.25	35–<40	6.12 (4.97–7.54
	≥40	7.07 (5.37–9.31	

Abasheva D, Ortiz A, Fernandez-Fernandez B. Clin Kidney J. 2024

Obesity reduces the production of adiponectin in favor of leptin. Gene transcription of inflammatory mediators such as IL-1, IL-6, IL-7, I-8, and TNF-a is increased, which creates a proinflammatory state and oxidative stress



Key phase 3RCTs with kidney or CV primary outcomes



Abasheva D, Ortiz A, Fernandez-Fernandez B. Clin Kidney J. 2024

FLOW semaglutide | renal outcomes trial

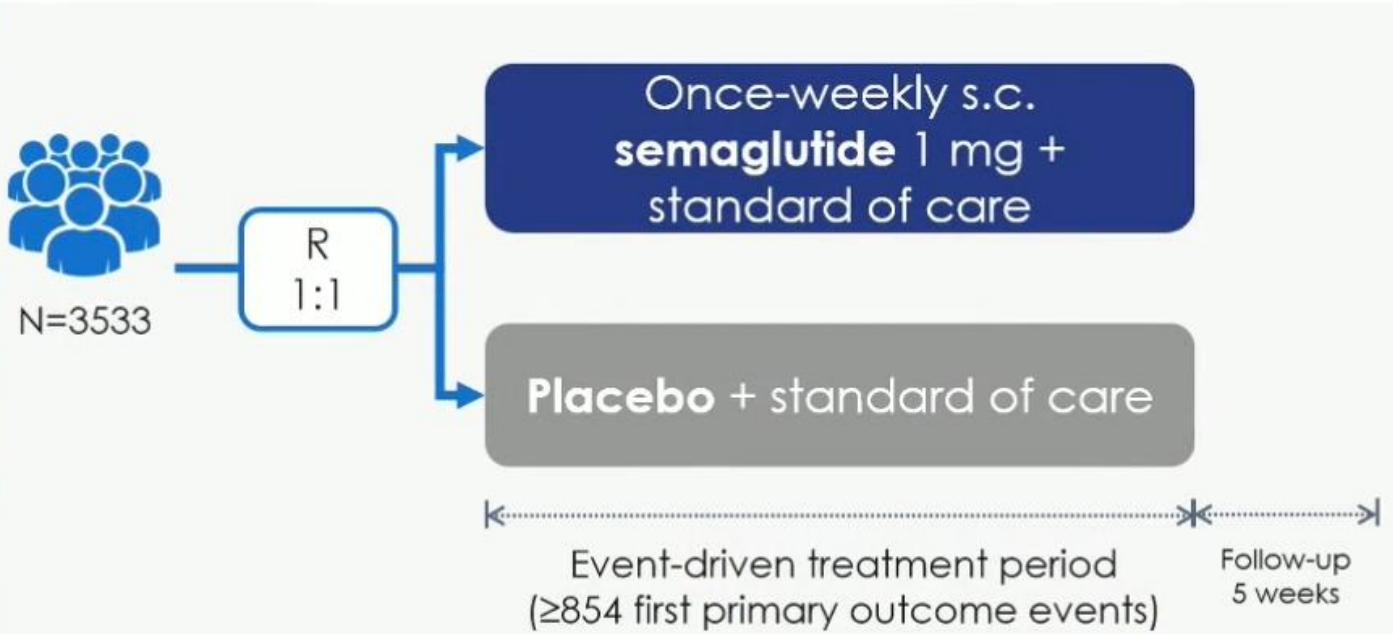
61 ERA CONGRESS STOCKHOLM & VIRTUAL MAY 23-26, 2024

Trial design

A multinational, randomised controlled clinical trial

Key eligibility criteria

- Adults with T2D, HbA_{1c} ≤10%
- RAAS blocker
- eGFR ≥50 and ≤75 mL/min/1.73 m^2 and UACR >300 and <5000 mg/g
  OR
  eGFR ≥25 and <50 mL/min/1.73 m^2 and UACR >100 and <5000 mg/g



eGFR was calculated using the CKD-EPI formula.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; R, randomisation; RAAS, renin–angiotensin–aldosterone system; s.c., subcutaneous; T2D, type 2 diabetes; UACR, urinary albumin:creatinine ratio.

ERA

More than two-thirds of the FLOW trial population were at very high risk of CKD progression at baseline

According to KDIGO guideline categorisation, 68.2% were at very high risk for CKD progression

KDIGO risk categories among FLOW participants, n (%)

eGFR categories (mL/min/1.73 m²)	UACR categories (mg/g)		
	<30	≥30–<300	≥300
≥90	1 (<0.1)	7 (0.2)	23 (0.6)
≥60–<90	24 (0.7)	173 (4.9)	491 (13.9)
≥45–<60	37 (1.0)	324 (9.2)	694 (19.6)
≥30–<45	40 (1.1)	414 (11.7)	906 (25.6)
≥15–<30	7 (0.2)	87 (2.5)	306 (8.6)
<15	NA	NA	NA

FLOW population

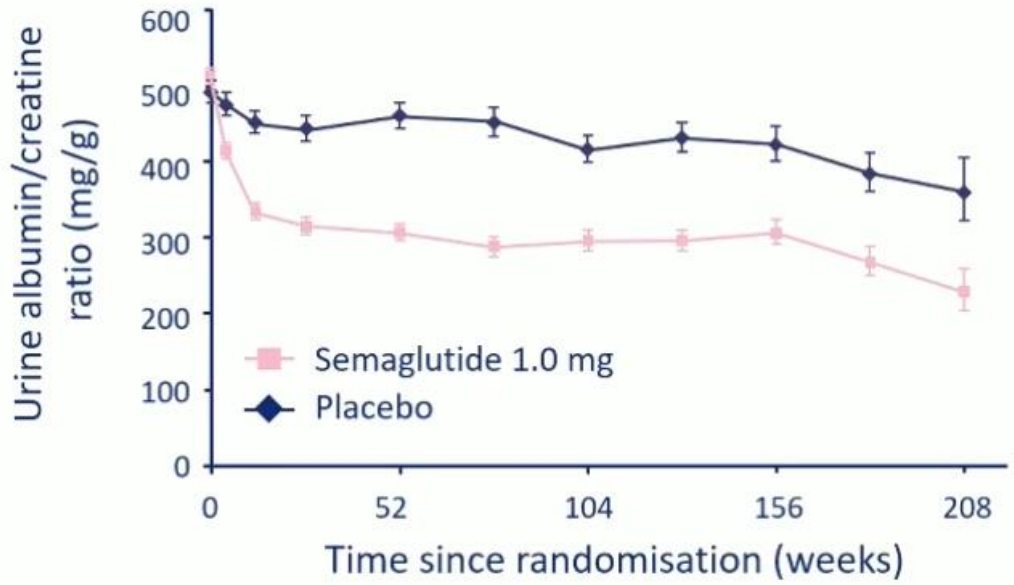
Low risk n=25 (0.7%) | Moderate risk n=217 (6.1%) | High risk n=878 (24.8%) | Very high risk n=2,413 (68.2%)

Adapted from KDIGO Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease; Kidney International (2022) 102 (Suppl 5S), S1–S127.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-creatinine ratio. Rossing P et al. Nephrol Dial Transplant 2023;38:2041–2051; Perkovic V et al. N Engl J Med. 2024; DOI: 10.1056/NEJMoa2403347

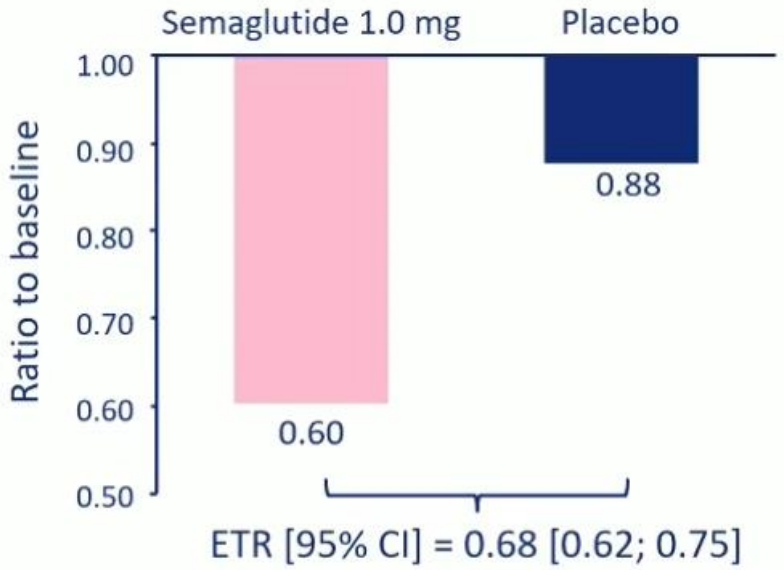
FLOW: UACR was significantly reduced and maintained throughout time with semaglutide 1.0 mg

In-trial full analysis set

Observed geometric mean by week



Ratio to baseline at week 104



Mean estimates are from an ANCOVA with treatment and use of SGLT-2 inhibitor (yes/no) at baseline as fixed factors and baseline value as covariate. The imputation model (linear regression) was done separately for each treatment arm and includes baseline value as a covariate and use of SGLT-2 inhibitor (yes/no) at baseline as a fixed factor and was fitted to all subjects with a measurement regardless of treatment status at week 104. The ratio to baseline and the corresponding baseline value were log-transformed prior to analysis The complete datasets were analysed and the results combined using Rubin's rule. Mean estimates were adjusted according to observed baseline distribution. Error bars are +/- standard error of the mean. CI, confidence interval; ETR, estimated treatment ratio; UACR, urine albumin-creatinine ratio.

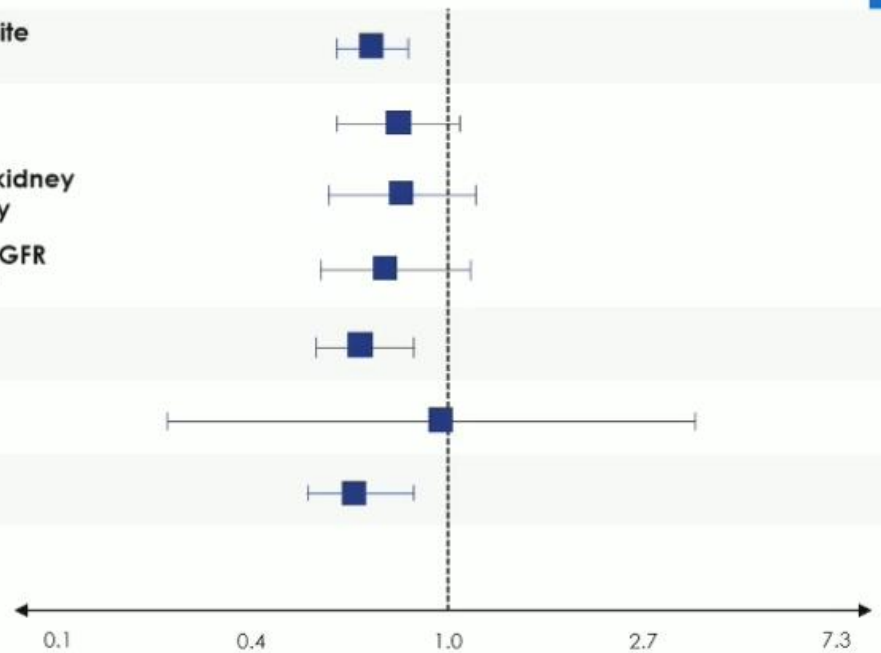
Perkovic V et al. N Engl J Med. 2024; DOI: 10.1056/NEJMoa2403347

Composite kidney outcome

FLOW semaglutide | renal outcomes trial

61 ERA CONGRESS STOCKHOLM & VIRTUAL MAY 23-26, 2024

	HR (95% CI)	Semaglutide (n/N)	Placebo (n/N)
Primary outcome: Composite kidney outcome	**0.76** (0.66, 0.88)	331/1767	410/1766
Kidney failure†	**0.83** (0.66, 1.03)	142/1767	165/1766
Initiation of chronic kidney replacement therapy	**0.84** (0.63, 1.12)	87/1767	100/1766
Onset of persistent eGFR <15 mL/min/1.73 m²	**0.80** (0.61, 1.06)	92/1767	110/1766
Onset of persistent ≥50% reduction in eGFR	**0.73** (0.59, 0.89)	165/1767	213/1766
Kidney death	**0.97** (0.27, 3.49)	5/1767	5/1766
CV death	**0.71** (0.56, 0.89)	123/1767	169/1766



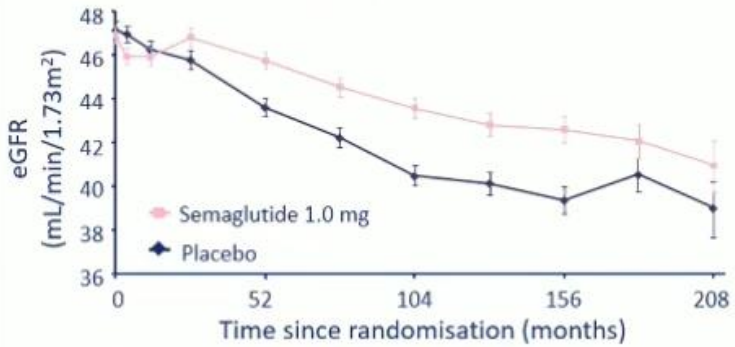
Full analysis set. Data from the in-trial period. CV death includes undetermined cause of death.
†Data on file. Kidney failure was a three-component composite outcome consisting of initiation of chronic replacement therapy (dialysis or kidney transplantation), onset of persistent eGFR <15 mL/min/1.73 m² and kidney death.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

ERA

FLOW: Semaglutide 1.0 mg showed significant improvement in secondary outcomes

Confirmatory secondary outcomes: in-trial full analysis set

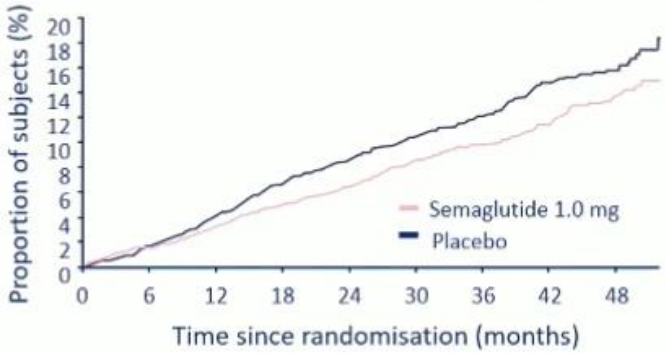
eGFR slope (observed mean by week)



ETD: 1.16 mL/min/1.73m²/year; 95% CI [0.86; 1.47]

P-value: <0.001#

First EAC-confirmed MACE



HR: 0.82; 95% CI: [0.68; 0.98]

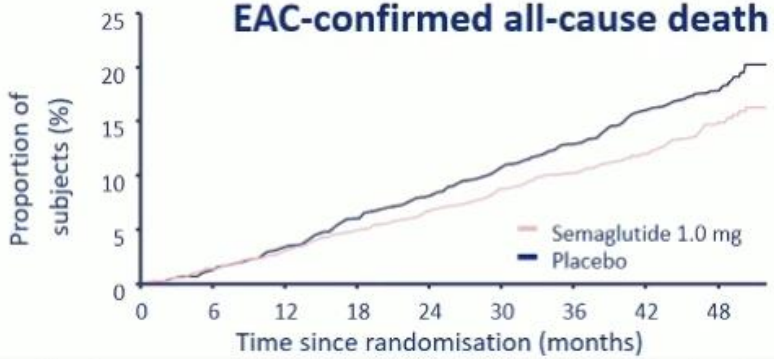
P-value: 0.029#

Events:

Semaglutide 1.0 mg: 212

Placebo: 254

EAC-confirmed all-cause death



HR: 0.80; 95% CI: [0.67; 0.95]

P-value: 0.01#

Events:

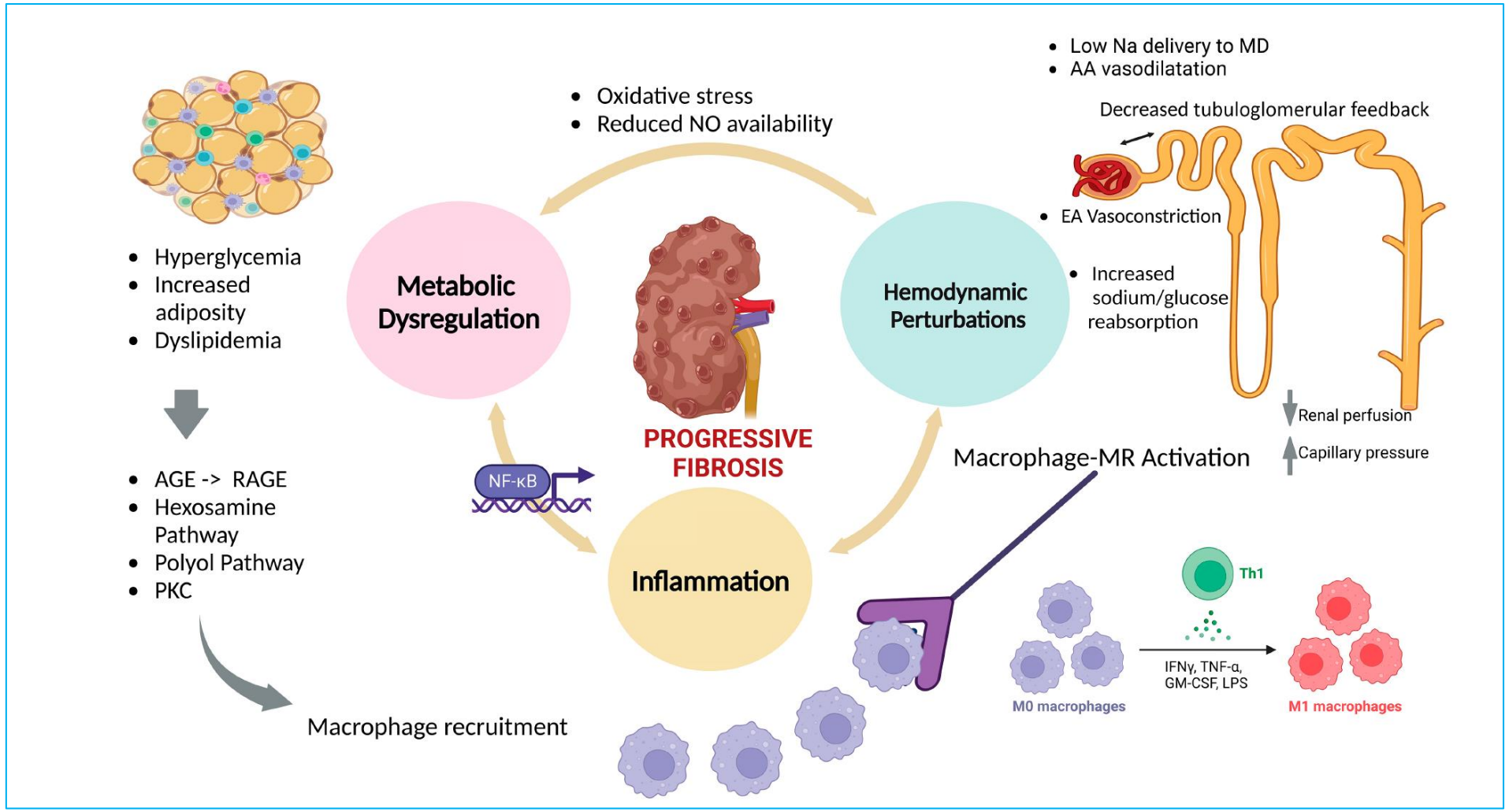
Semaglutide 1.0 mg: 227

Placebo: 279

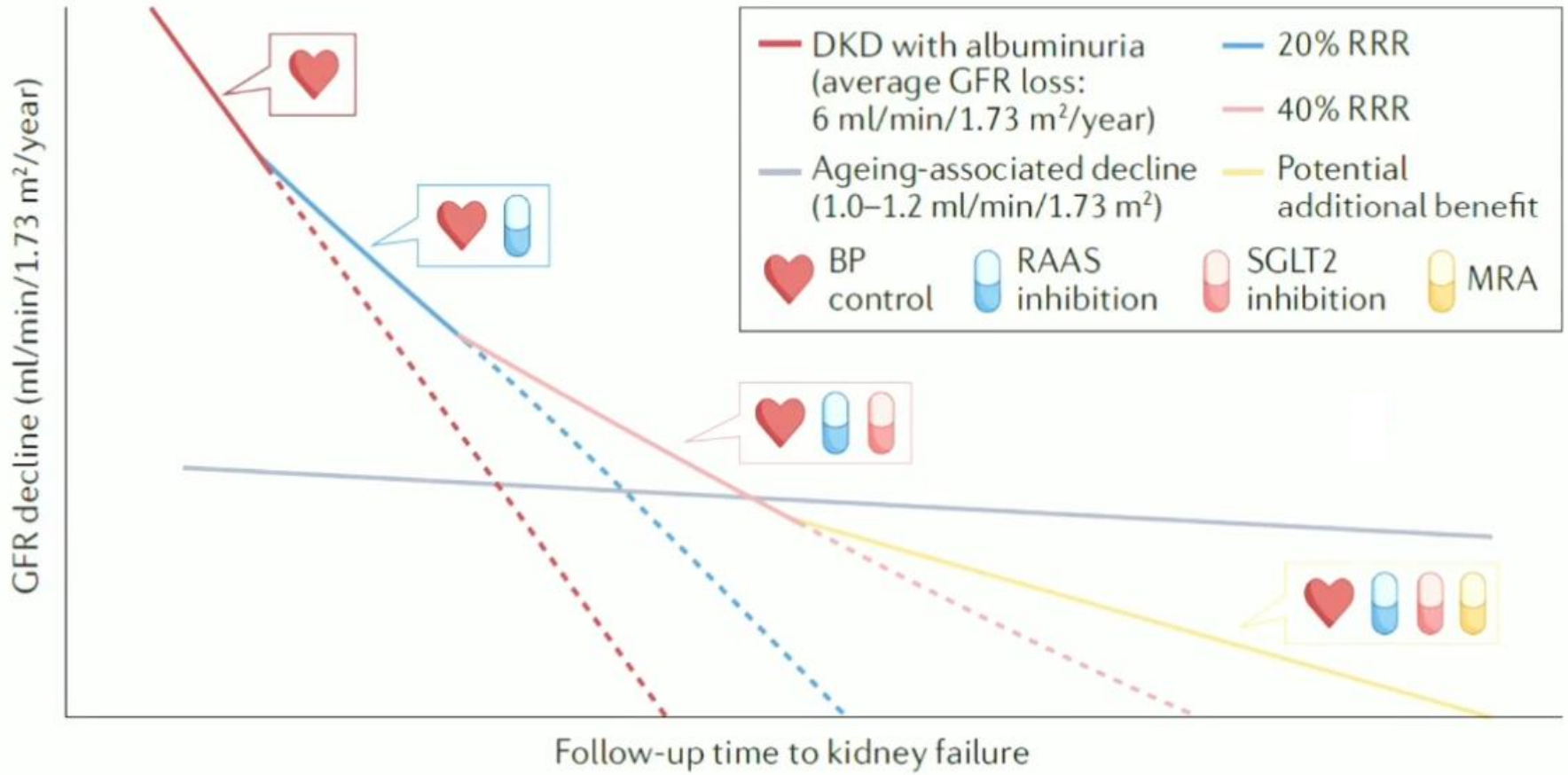
Annual rate of change in eGFR was analysed using a linear random effects model with treatment, use of SGLT-2 inhibitors (yes/no) at baseline. eGFR was calculated using the CKD-EPI formula. Time from randomisation to first EAC-confirmed MACE and EAC-confirmed all-cause death was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by use of SGLT-2 inhibitor (yes/no) at baseline. # Superiority if p value <<0.0322. CI, confidence interval; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; HR, hazard ratio.

Perkovic V et al. N Engl J Med. 2024; DOI: 10.1056/NEJMoa2403347

Metabolic, hemodynamic, and inflammatory pathways implicated in the underlying pathophysiology of DKD, underscoring the need for multitargeted therapies to halt disease progression



The potential incremental benefit of multifactorial intervention on GFR decline in DKD



Fioretto, P., Pontremoli, R. *Nat Rev Nephrol* **18**, 78–79 (2022)

Estimated treatment effects on CKD progression and all-cause mortality with SGLT2i, GLP-1 RA, nsMRA added to RAS-blockade

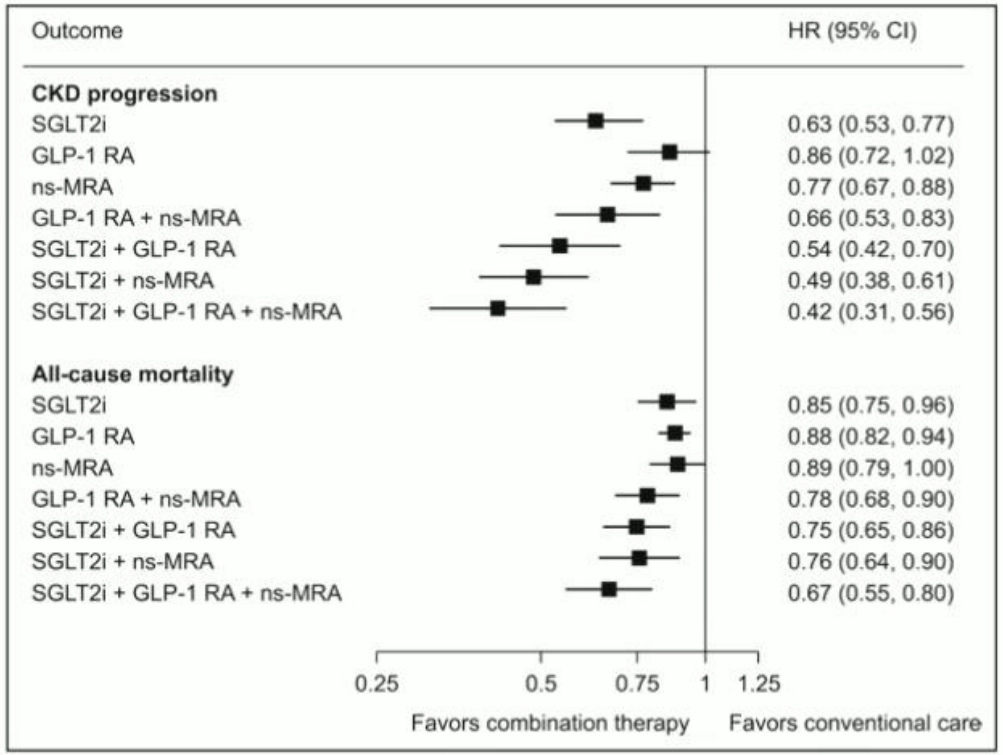


Figure 2. Estimated treatment effects on CKD progression and all-cause mortality with SGLT2i, GLP-1 RA, and ns-MRA, alone and in combination, when added to renin-angiotensin system blockade in patients with type 2 diabetes.
CKD progression defined as doubling of serum creatinine, kidney failure, or death resulting from kidney failure, apart from with GLP-1 RAs, for which it was defined as sustained reduction in kidney function, kidney failure, or death resulting from kidney failure. CKD indicates chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; and SGLT2i, sodium glucose cotransporter-2 inhibitor.

Neuen et al. Circulation 2024, 149: 450-462

Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study

Nikita Simms-Williams,[1] Nir Treves,[2] Hui Yin,[1] Sally Lu,[3] Oriana Yu,[3,4] Richeek Pradhan,[5] Christel Renoux,[3,6,7] Samy Suissa,[3,6] Laurent Azoulay[3,6,8]

BMJ: first published as 10

Exposure	No of patients	Events	Person years	Incidence rate (95% CI)*	Hazard ratio (95% CI)†
Primary outcomes					
MACE:					
GLP-1 RAs	6696	113	10971	10.3 (8.5 to 12.4)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	45	6417	7.0 (5.1 to 9.4)	0.70 (0.49 to 0.99)
Serious renal events:					
GLP-1 RAs	6696	51	10992	4.6 (3.5 to 6.1)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	13	6453	2.0 (1.1 to 3.4)	0.43 (0.23 to 0.80)

Exposure	No of patients	Events	Person years	Incidence rate (95% CI)*	Hazard ratio (95% CI)†
Primary outcomes					
MACE:					
SGLT-2 inhibitor	8942	141	13160	10.7 (9.0 to 12.6)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	55	7250	7.6 (5.7 to 9.9)	0.71 (0.52 to 0.98)
Serious renal events:					
SGLT-2 inhibitor	8942	26	13243	2.0 (1.3 to 2.9)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	10	7278	1.4 (0.7 to 2.5)	0.67 (0.32 to 1.41)

Clinical guidelines for management of CKD in T2D recommend a combination of drug therapies to optimally reduce risks[1–3] with finerenone proposed as a core treatment pillar[4]

ESC European Society of Cardiology

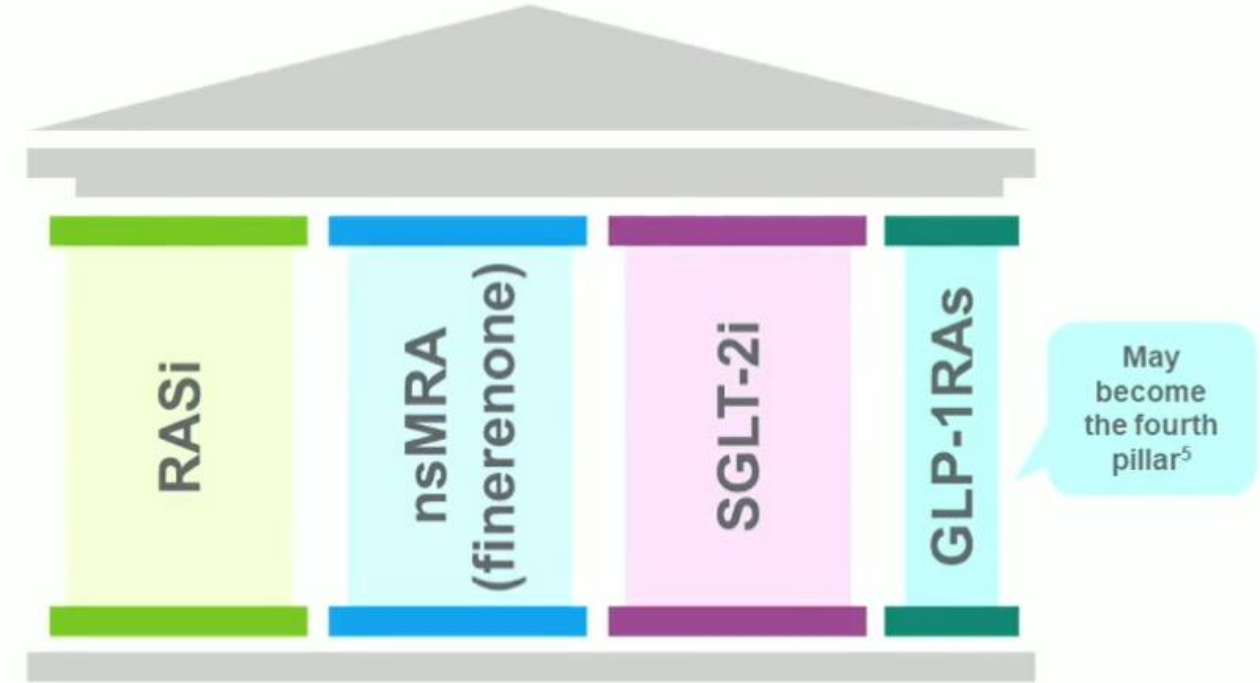
European Society of Hypertension

ADA KDIGO Consensus 2022

ERA ERBP European Renal Best Practice

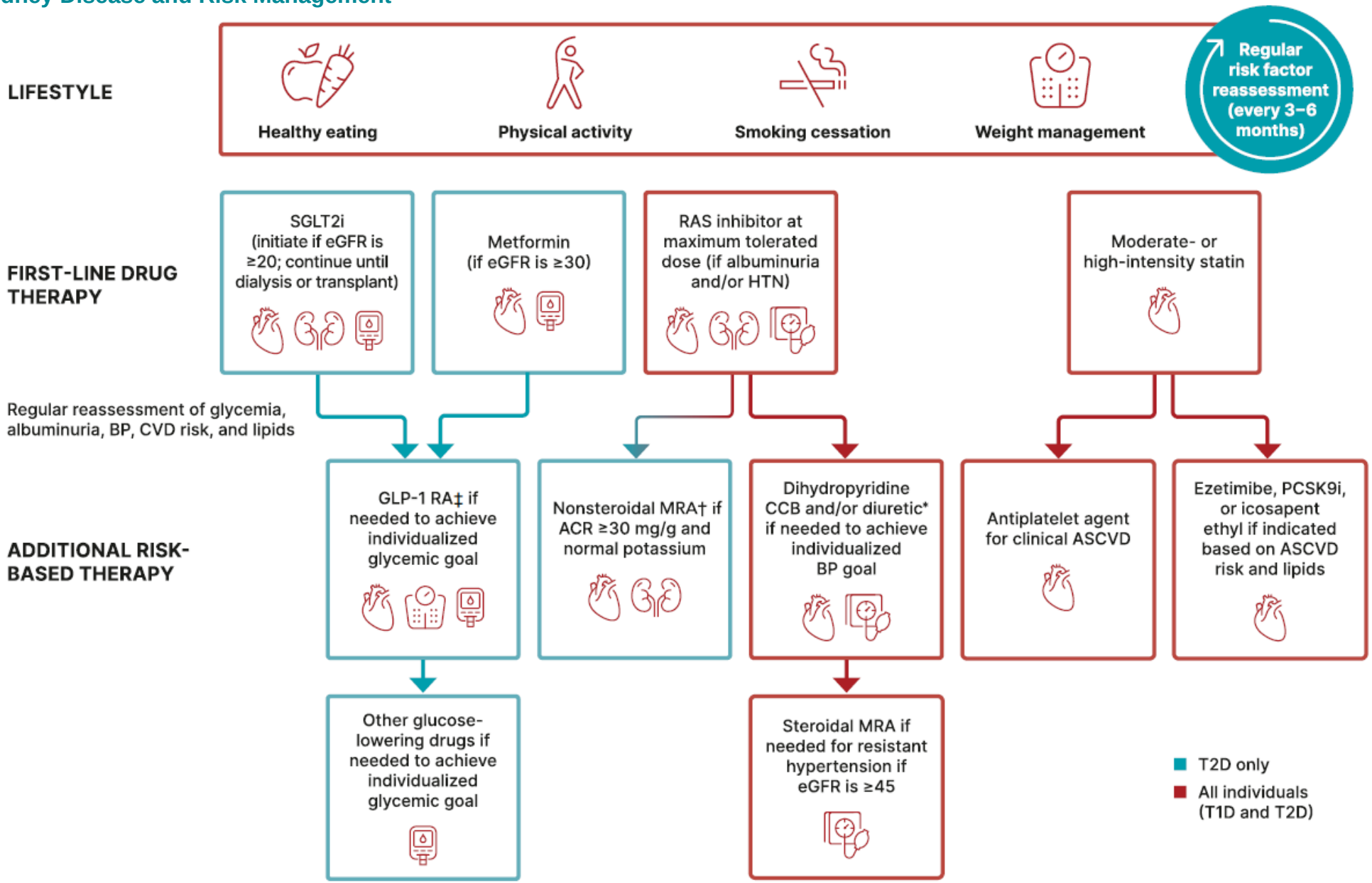
KDIGO Kidney Disease: Improving Global Outcomes

American Diabetes Association



ADA, American Diabetes Association; CKD, chronic kidney disease; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ERA, European Renal Association; ERBP, European Renal Best Practice; GLP-1RA, glucagon-like peptide-1 receptor agonist; KDIGO, Kidney Disease: Improving Global Outcomes; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.

1. KDIGO Diabetes Work Group. Kidney Int. 2022;102:S1–S127; 2. American Diabetes Association. Diabetes Care. 2024;47(Suppl 1):S179; 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. Perkovic V, et al. N Engl J Med. 2024;391:109–121.



Chronic Kidney Disease and Risk Management:
Standards of Care in Diabetes - 2025 Diabetes Care 2025;48(Suppl. 1):S238-S251

Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial

Endothelin-1 (ET-1) is a potent vasoconstrictor and profibrotic peptide elevated in DN.

Selective endothelin-A (ET_A) receptor blockade has been tested (atrasentan) in DN.

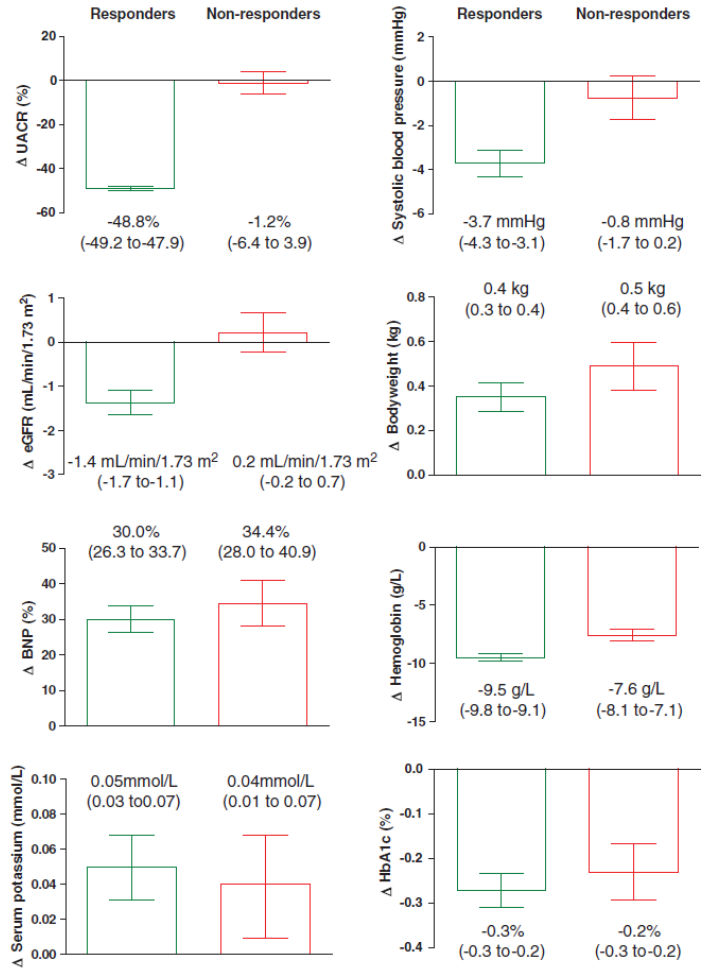
SONAR trial: diabetic CKD patients (eGFR 25–75, albuminuria ≥300) underwent an enrichment period to exclude fluid-sensitive patients, then were randomized to atrasentan 0.75 mg vs placebo.

Among responders, atrasentan significantly reduced the primary renal outcome (HR ≈0.65) and slowed eGFR loss by ~0.7 mL/min/year (vs placebo).

SONAR noted more fluid retention (38% vs 33%) and a non-significant trend toward higher heart failure hospitalizations with atrasentan.

Earlier trials with a dual ET_A/ET_B antagonist (avosentan) were halted due to excess heart failure.

Newer trials are exploring highly selective ET_A agents (e.g. zibotentan) and combination with SGLT2i to mitigate fluid overload.

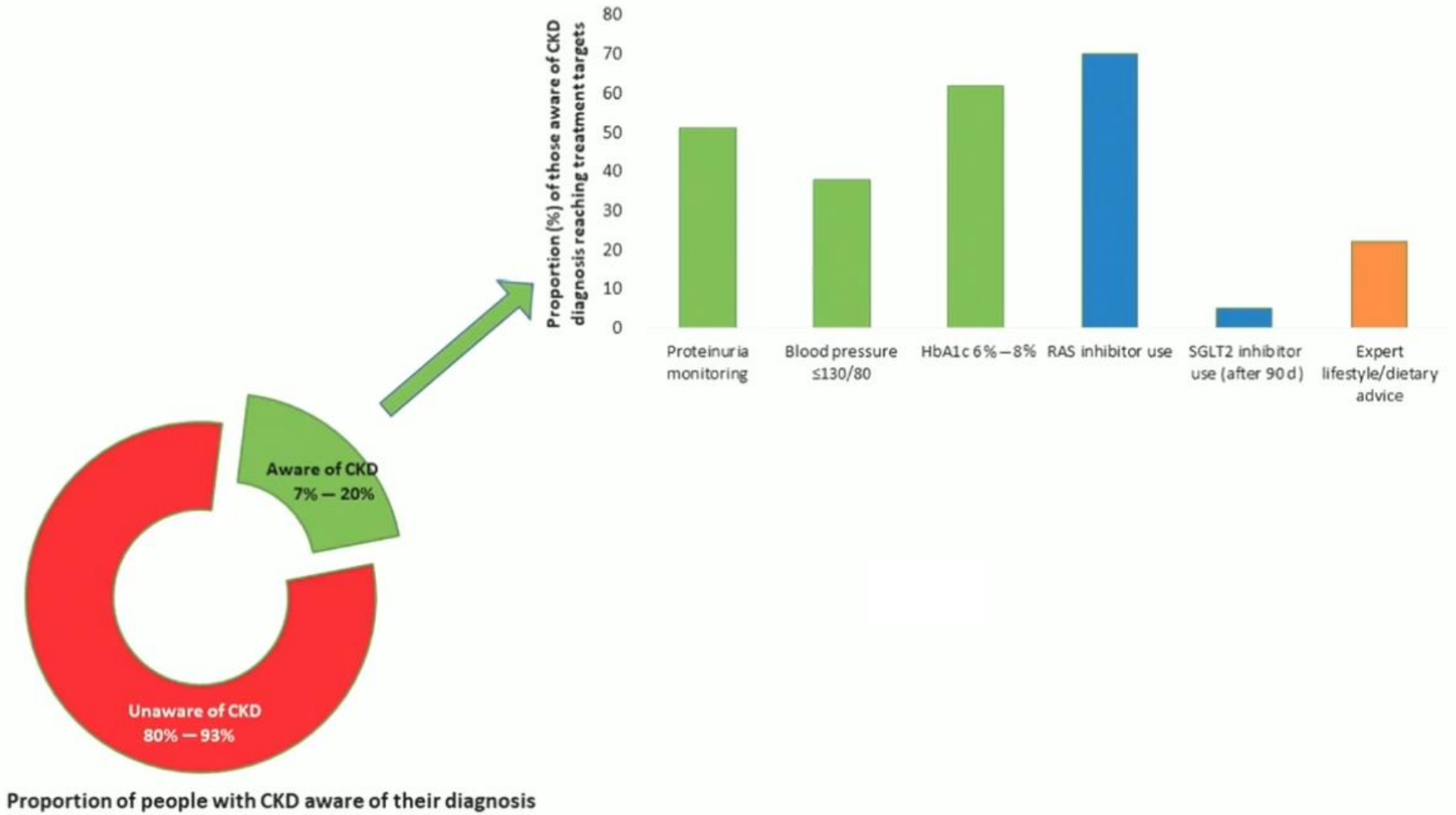


Anti-inflammatory and Antifibrotic Agents

- Baricitinib (a JAK1/2 inhibitor) showed in Phase 2 trials a significant reduction in proteinuria and plasma TNF-α in DN patients.
- Pentoxifylline, an anti-TNF drug, modestly lowers albuminuria in small studies.
- Pirfenidone (an oral TGF-β antagonist) (Targeting fibrosis) improved GFR in a small trial, though results on hard outcomes are pending.
- Selonsertib (ASK1 inhibitor) slowed eGFR decline by ~18% in a Phase 2 trial.
- Bardoxolone, anti-oxidative agents, have been tested but faced safety issues.

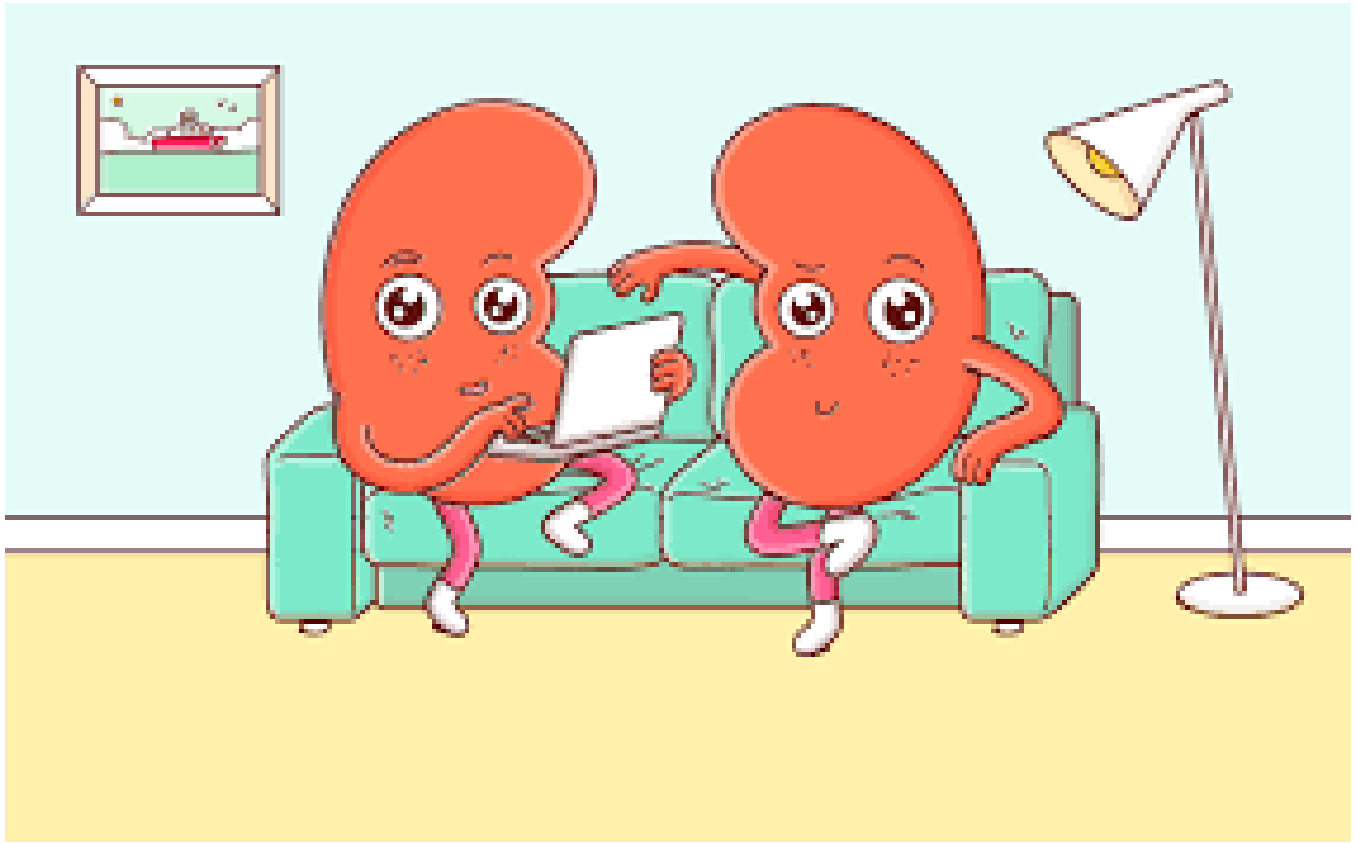
Cellular and Gene-based Therapies

- Mesenchymal stem cell (MSC) therapy has shown anti-inflammatory and reparative effects in animal models of DN.
  - A recent review notes that systemic MSC infusion may positively impact DKD progression in preclinical studies, but clinical trials are few and small.
  - Biomarkers (e.g. KIM-1, NAG) are being used to gauge tubular injury improvement in these studies.
- Gene therapies (e.g. siRNA, CRISPR) or microRNA modulators are being explored in labs; for instance, modulating miR-21 or miR-192 has shown to affect fibrosis in models.
  - These remain investigational, with potential high promise but requiring proof of safety and efficacy in humans.



American Journal of Hypertension, 2024, **37**, 640–649

- CKD in individuals with T2D is common…..
- …… and have grim consequences
- An individual with T2D with early signs of CKD may have up to 9 years shorter life expectancy
- Novel medications such as SGLT2-inhibitors, nsMRA finerenone and GLP-1 RA have been shown to dramatically improve cardiovascular and kidney health in individuals with T2D
- Early signs of CKD are "a call for action"



Thank you for your attention