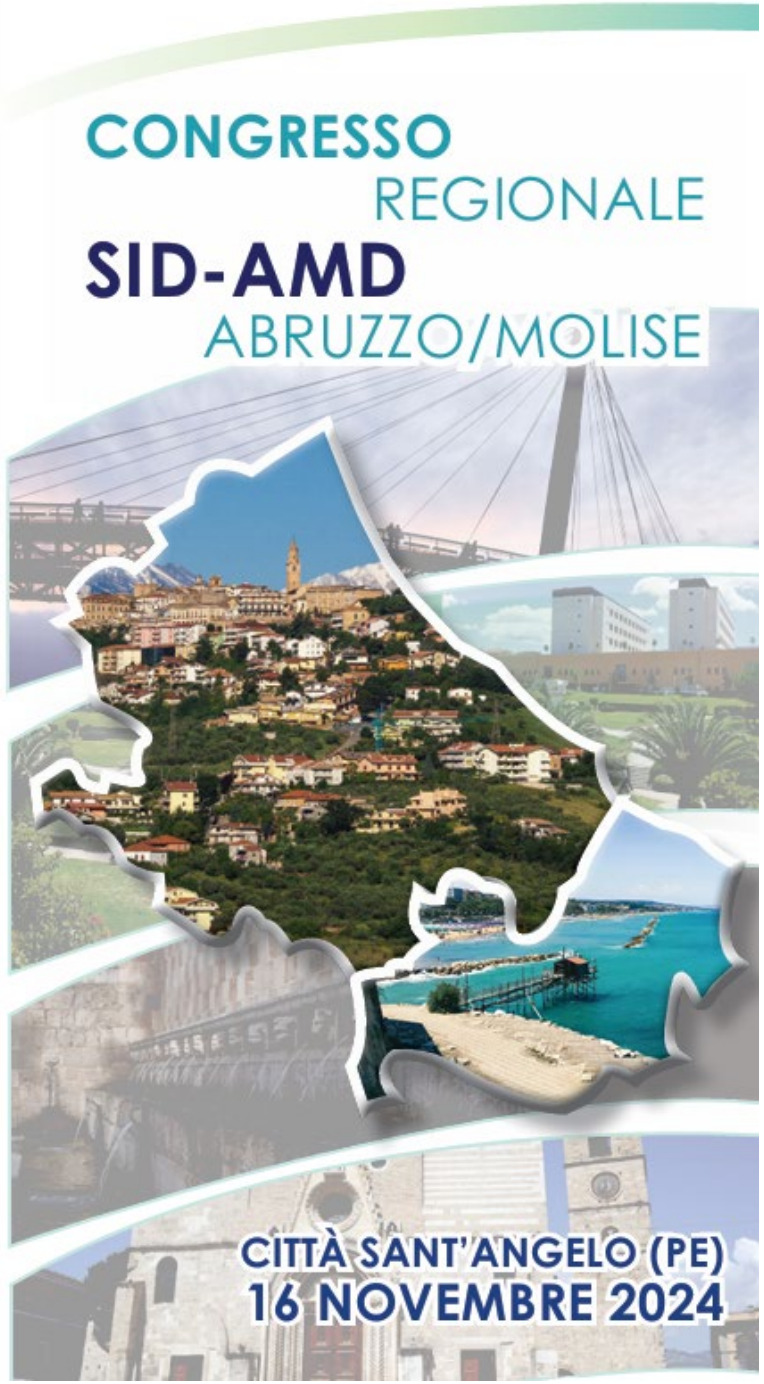


La gestione olistica della persona con diabete: confronto tra gli algoritmi proposti dalle linee guida

PROTEZIONE RENALE

Livia Santarelli

Sulmona e Castel di Sangro

Conflitti di interesse

La Dott.ssa Livia Santarelli dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:
- Novonordisk
- Beringher

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

Diagnosi di Malattia Renale Cronica (MRC)

La diagnosi clinica di malattia renale cronica in un paziente con diabete si basa sulla presenza, per almeno 3 mesi, di:

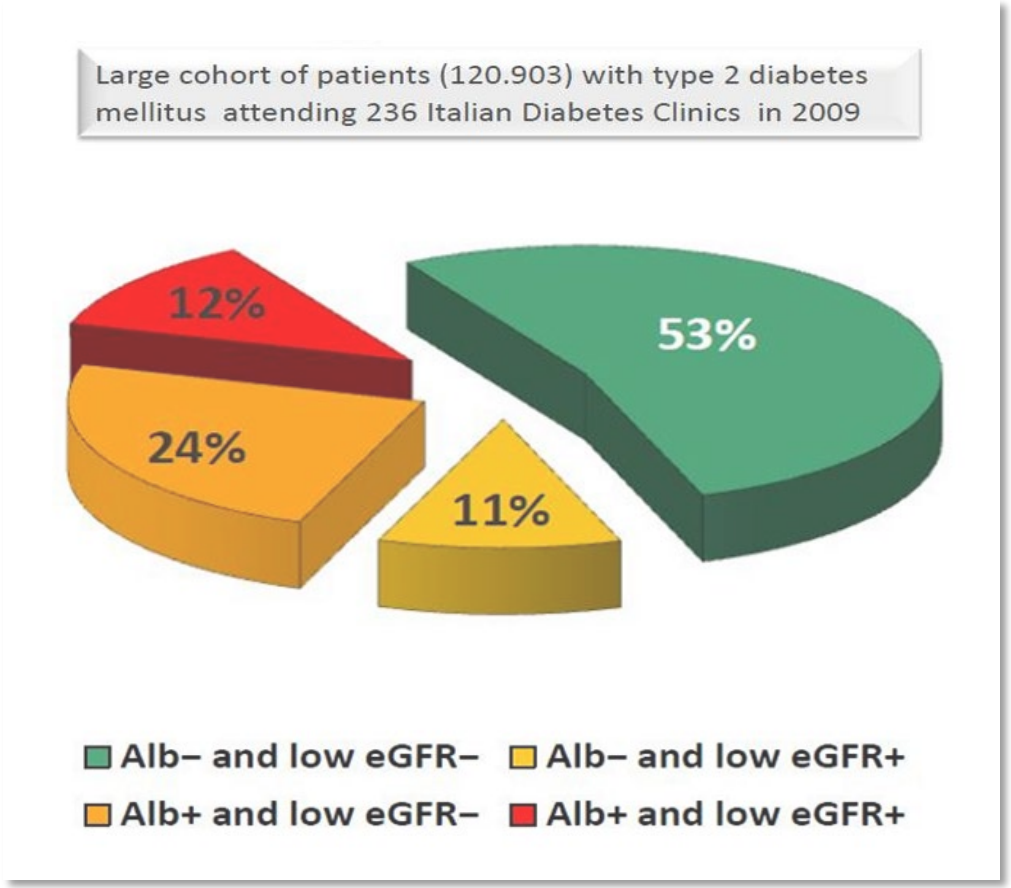
ALBUMINURIA
ACR ≥ 30 mg/g
(albumin to creatinine ratio)

e/o

RIDOTTA FUNZIONE RENALE
eGFR 60 < mL/min/1.73 m2
(estimated glomerular filtration rate)

in assenza di segni o sintomi di altre cause primarie di danno renale

Fenotipi di MRC nel diabete mellito tipo 2



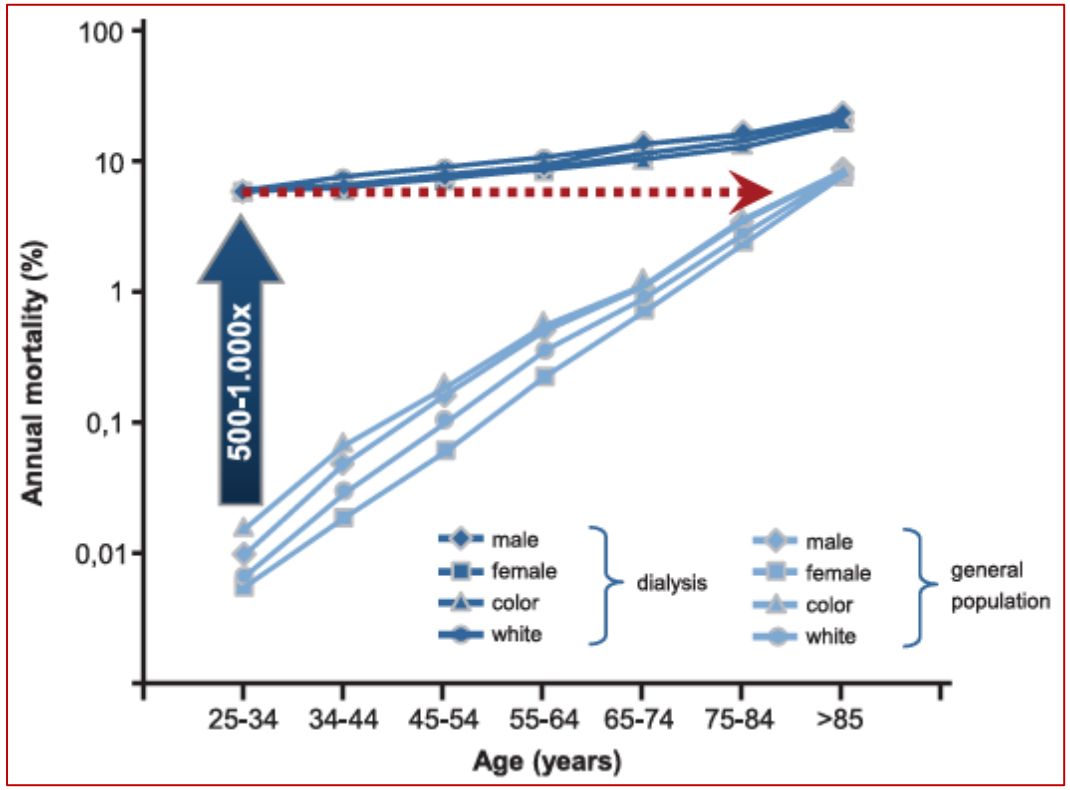
De Cosmo S et al. *for AMD-Annals Study Group.* NDT 2014

Evoluzione clinica della malattia renale cronica

La malattia renale cronica (*chronic kidney disease, CKD*) è una condizione classicamente silente, almeno fino alle fasi avanzate, quando iniziano a manifestarsi sintomi e segni riferibili alla perdita delle principali funzioni dei reni (stimolazione dell'eritropoiesi, mantenimento dell'equilibrio idro-elettrolitico e del ricambio minerale).

Il diabete mellito è la principale causa di insufficienza renale terminale (*end stage kidney disease, ESKD*) nel mondo.

Cardiovascular mortality in the general population and in patients with end-stage kidney disease.



Jankowsk J et al. *Circulation*. 2021;143:1157-1172.

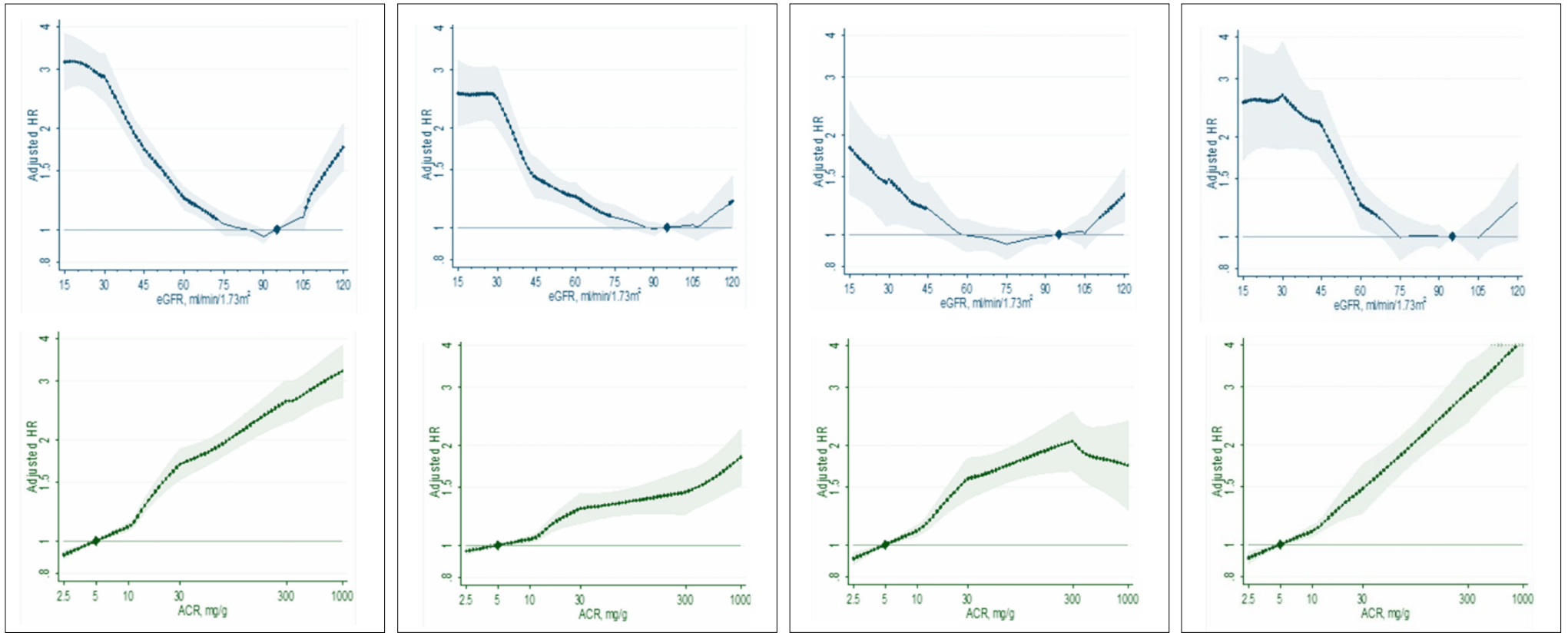
Relationship of albuminuria and eGFR with cardiovascular mortality and morbidity

Collaborative meta-analysis from 24 cohorts

637 315 individuals without a history of cardiovascular disease from the Chronic Kidney Disease Prognosis Consortium

eGFR

ACR

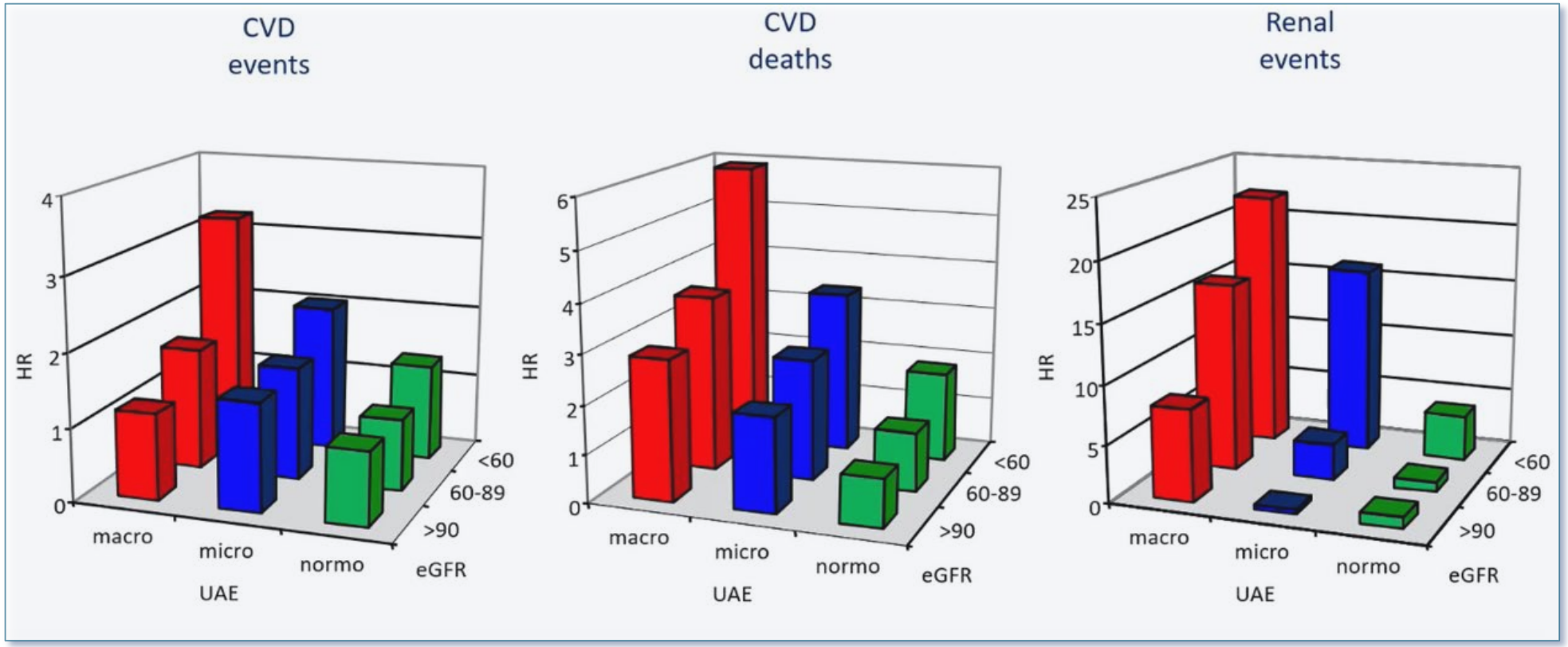


CARDIOVASCULAR MORTALITY | **CORONARY HEART DISEASE** | **STROKE** | **HEART FAILURE**

Modificato da Matsushita K ed al. *Lancet Diabetes Endocrinol.* 2015;3:514-25

Relationship of albuminuria and eGFR with cardiovascular and renal outcomes

The Action in Diabetes and Vascular disease: preterAx and diamicronN-MR Controlled Evaluation (ADVANCE) study



10,640 patients with type 2 diabetes

Ninomiya T et al. *J AM Soc Nephrol.* 2009;20:1813-21

Stadiazione della malattia renale cronica nel diabete

Categorie KDIGO				Categorie albuminuria persistente (mg/24 o mg/g creatinina)		
				A1	A2	A3
				Normale o lievemente aumentata (Normo)	Moderatamente aumentata (Micro)	Severamente aumentata (Macro)
				<30	30-299	≥300
Categorie eGFR (ml/min/1.73 m²)	G1	Normale-alto	≥90			
	G2	Lievemente ridotto	60-89			
	G3a	Lievemente-moderatamente ridotto	45-59			
	G3b	Moderatamente-severamente ridotto	30-44			
	G4	Severamente ridotto	15-29			
	G5	Insufficienza renale terminale	<15			

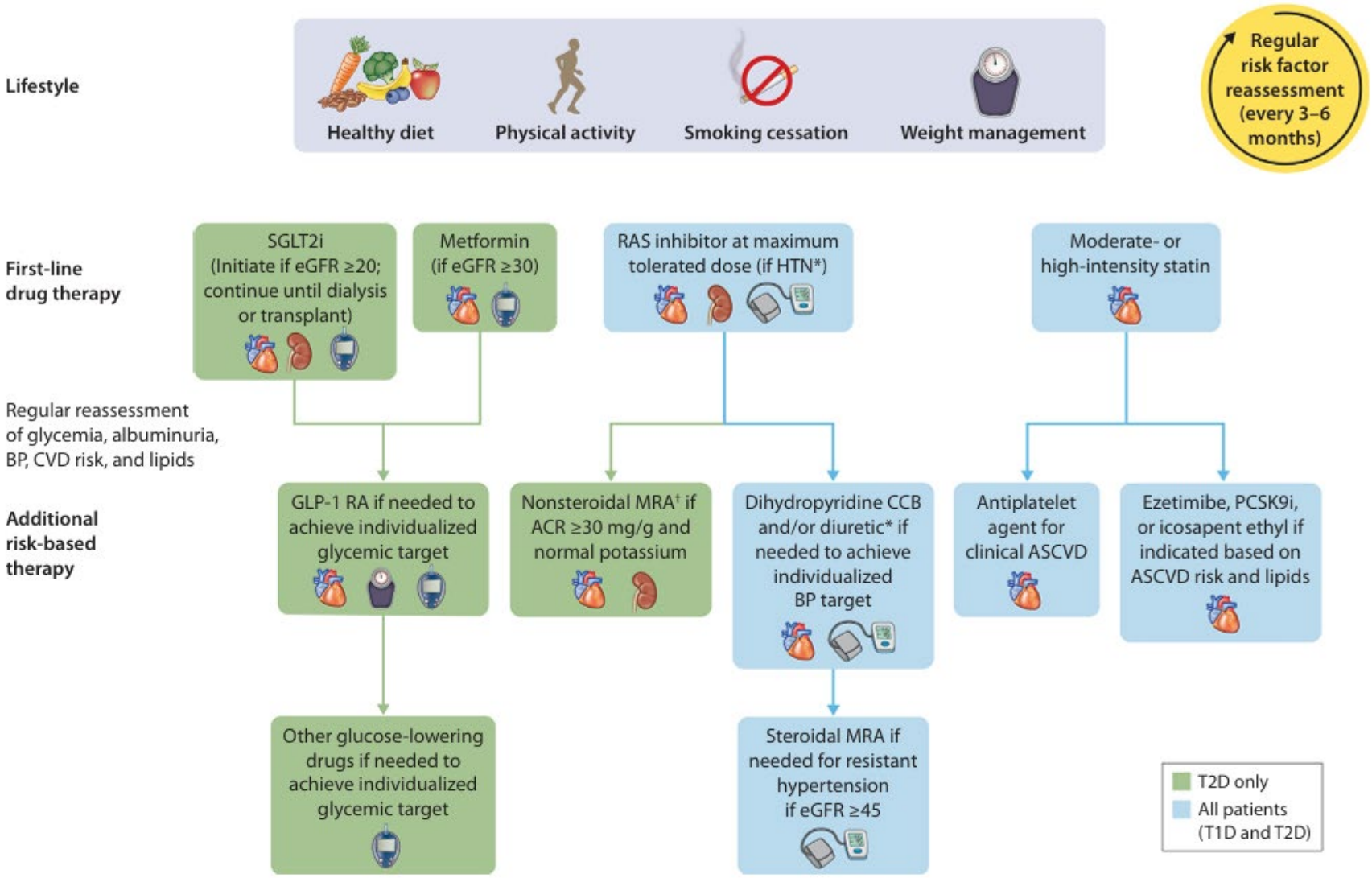
Verde = rischio basso (se non altri marcatori di danno renale, no CKD);
giallo = rischio moderato; arancio = rischio alto; rosso = rischio molto alto

Provenzano M e Pugliese G. *Vademecum per la gestione della malattia renale cronica nella persona con diabete.* 2024

OBIETTIVI della protezione renale

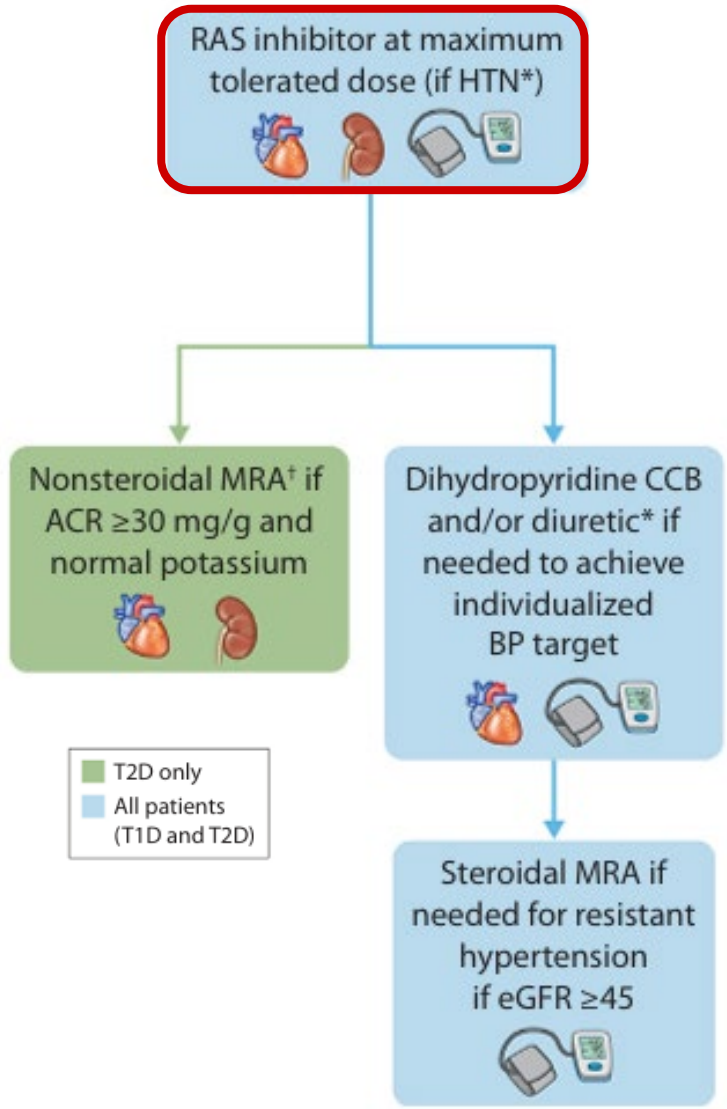
- Ridurre la progressione verso l'insufficienza renale terminale
- Diminuire gli eventi cardiovascolari
- Ridurre la mortalità prematura

Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease (CKD)



IH de Boer et al.: *Diabetes management in CKD: consensus report by ADA and KDIGO. 2022*

Blood pressure management



An ACE inhibitor (ACEi) or angiotensin II receptor blocker (ARB) is recommended for patients with T1D or T2D who have hypertension and albuminuria, titrated to the maximum antihypertensive or highest tolerated dose.

Consensus ADA-KDIGO 2022

11.3 Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD and reduce cardiovascular risk. **A**

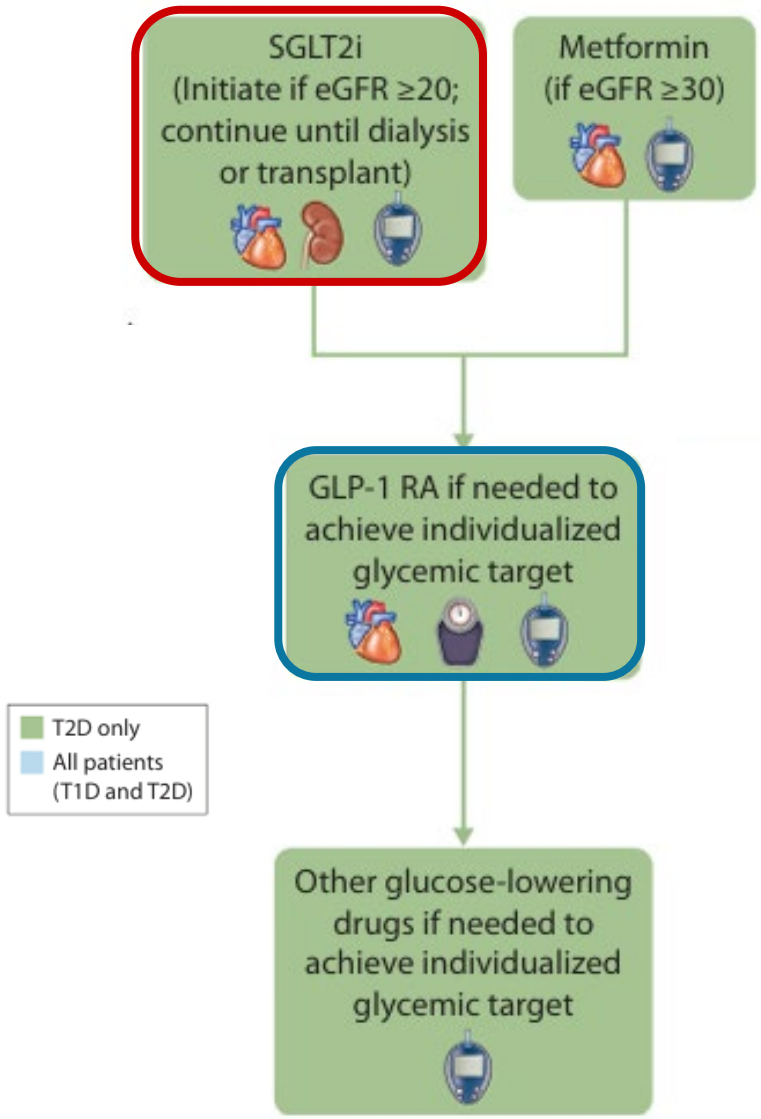
11.4a In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended for those with moderately increased albuminuria (UACR 30–299 mg/g creatinine) **B** and is strongly recommended for those with severely increased albuminuria (UACR ≥300 mg/g creatinine) and/or eGFR <60 mL/min/1.73 m^2 to prevent the progression of kidney disease and reduce cardiovascular events. **A**

Standard of Care in Diabetes - 2024

American Diabetes Association®

KDIGO® Kidney Disease: Improving Global Outcomes

Glycemic control



A sodium–glucose cotransporter-2 inhibitor (SGLT2i) with proven kidney or cardiovascular benefit is recommended for patients with T2D, CKD, and eGFR ≥20 ml/min/1.73 m^2. Once initiated, the SGLT2i can be continued at lower levels of eGFR.

A glucagon-like peptide 1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended for patients with T2D and CKD who do not meet their individualized glycemic target with metformin and/or an SGLT2i or who are unable to use these drugs.

Consensus ADA-KDIGO 2022

11.5a For people with type 2 diabetes and CKD, use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine. **A**

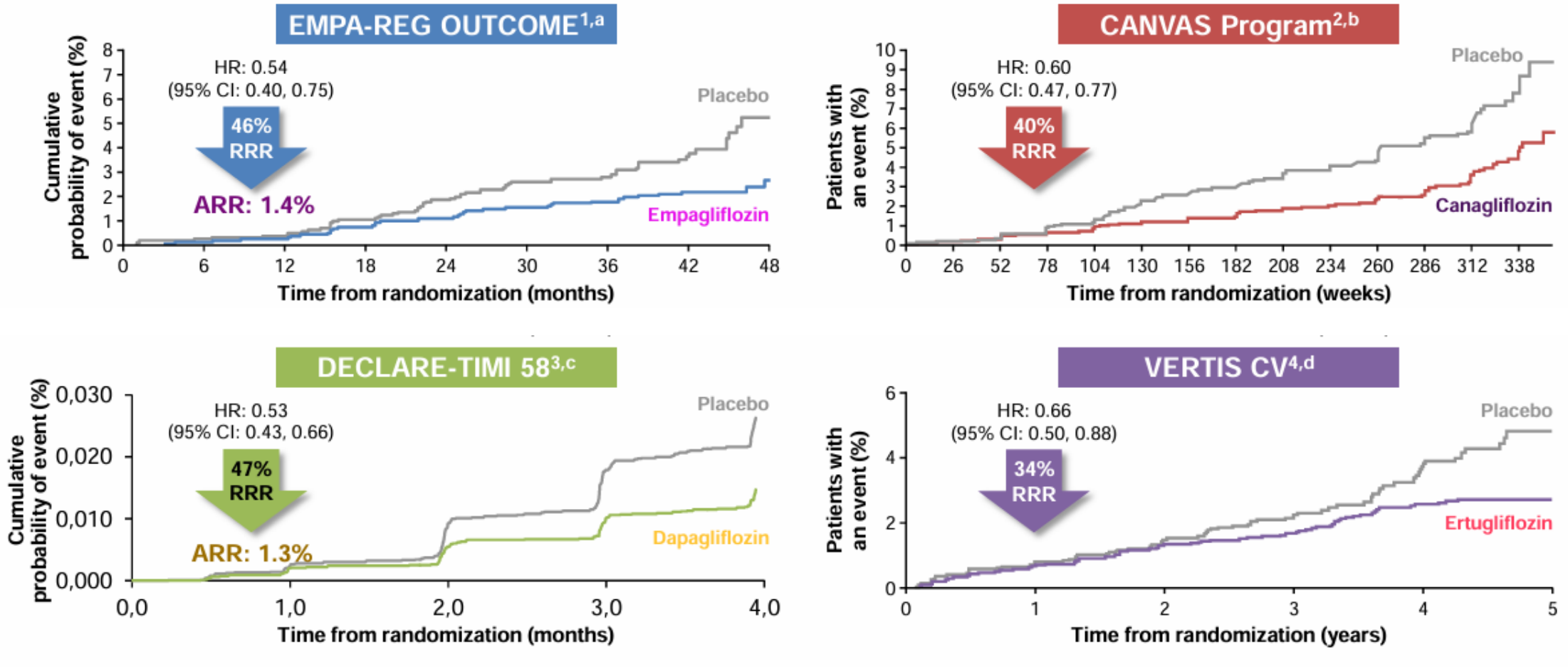
11.5b For people with type 2 diabetes and CKD, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. **B**

Standard of Care in Diabetes - 2024

American Diabetes Association.

KDIGO Kidney Disease: Improving Global Outcomes

SGLT2 inhibitors in CVOTs consistently reduced the risk of kidney composite endpoints (sustained ≥ 40% decline in eGFR, ESKD or renal death) compared with placebo



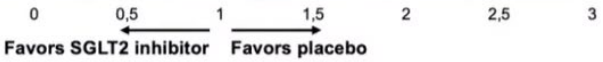
1. Wanner C, et al. *N Engl J Med* 2016;375:323–334; 2. Neal B, et al. *N Engl J Med* 2017;377:644–657; 3. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 4. Cherney DZI, et al. *Diabetologia* 2021;64:1256–1267

The kidney benefit of SGLT2 inhibitors were consistent over a wide range of eGFR as well ad over a range of UACR

The kidney benefit Effect of SGLT2 inhibitors on composite kidney enpoints, stratified by:

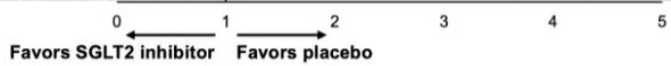
eGFR

	Events	Patients	RR (95% CI)
eGFR ≥90 mL/min/1.73 m²			
EMPA-REG OUTCOME	22	1529	0.21 (0.09, 0.53)
CANVAS Program	17	2476	0.32 (0.12, 0.88)
DECLARE-TIMI 58	120	8162	0.50 (0.34, 0.73)
VERTIS CV[a]	61	2048	0.89 (0.53, 1.49)
eGFR 60–<90 mL/min/1.73 m²			
EMPA-REG OUTCOME	61	3638	0.61 (0.37, 1.02)
CANVAS Program	30	5625	0.48 (0.23, 0.98)
DECLARE-TIMI 58	186	7732	0.54 (0.40, 0.73)
VERTIS CV[a]	86	4390	0.47 (0.31, 0.72)
eGFR 45–<60 mL/min/1.73 m²			
EMPA-REG OUTCOME	39	1238	0.68 (0.36, 1.28)
CANVAS Program	16	1485	0.74 (0.28, 2.01)
VERTIS CV[a]	51	1807	0.86 (0.49, 1.52)
eGFR <45 mL/min/1.73 m²			
EMPA-REG OUTCOME	30	563	0.63 (0.30, 1.29)
CANVAS Program	10	554	0.79 (0.21, 2.94)



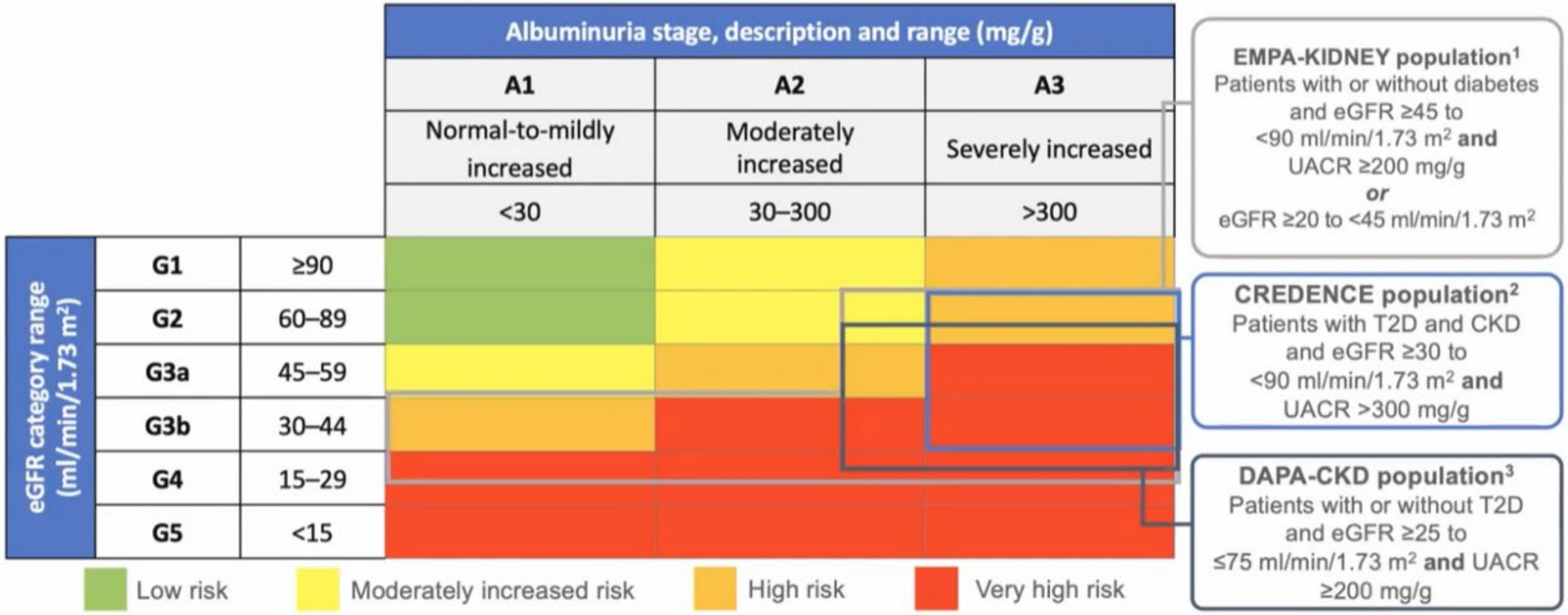
UACR

	Events	Patients	RR (95% CI)
UACR <30 mg/g			
EMPA-REG OUTCOME	48	4142	0.41 (0.23, 0.72)
CANVAS Program	15	7007	0.22 (0.07, 0.69)
DECLARE-TIMI 58	145	11644	0.52 (0.37, 0.74)
VERTIS CV	66	4783	0.47 (0.29, 0.77)
UACR 30–300 mg/g			
EMPA-REG OUTCOME	40	1996	0.67 (0.36, 1.26)
CANVAS Program	19	2266	1.42 (0.51, 3.95)
DECLARE-TIMI 58	105	4030	0.59 (0.39, 0.87)
VERTIS CV	60	2492	0.93 (0.55, 1.59)
UACR >300 mg/g			
EMPA-REG OUTCOME	61	764	0.51 (0.31, 0.85)
CANVAS Program	39	760	0.45 (0.24, 0.86)
DECLARE-TIMI 58	106	1169	0.38 (0.25, 0.58)
VERTIS CV	66	755	0.56 (0.35, 0.91)



1. Neuen BL, et al. Lancet Diabetes Endocrinol 2019; 2. Cherney DZI, et al. Diabetologia 2021

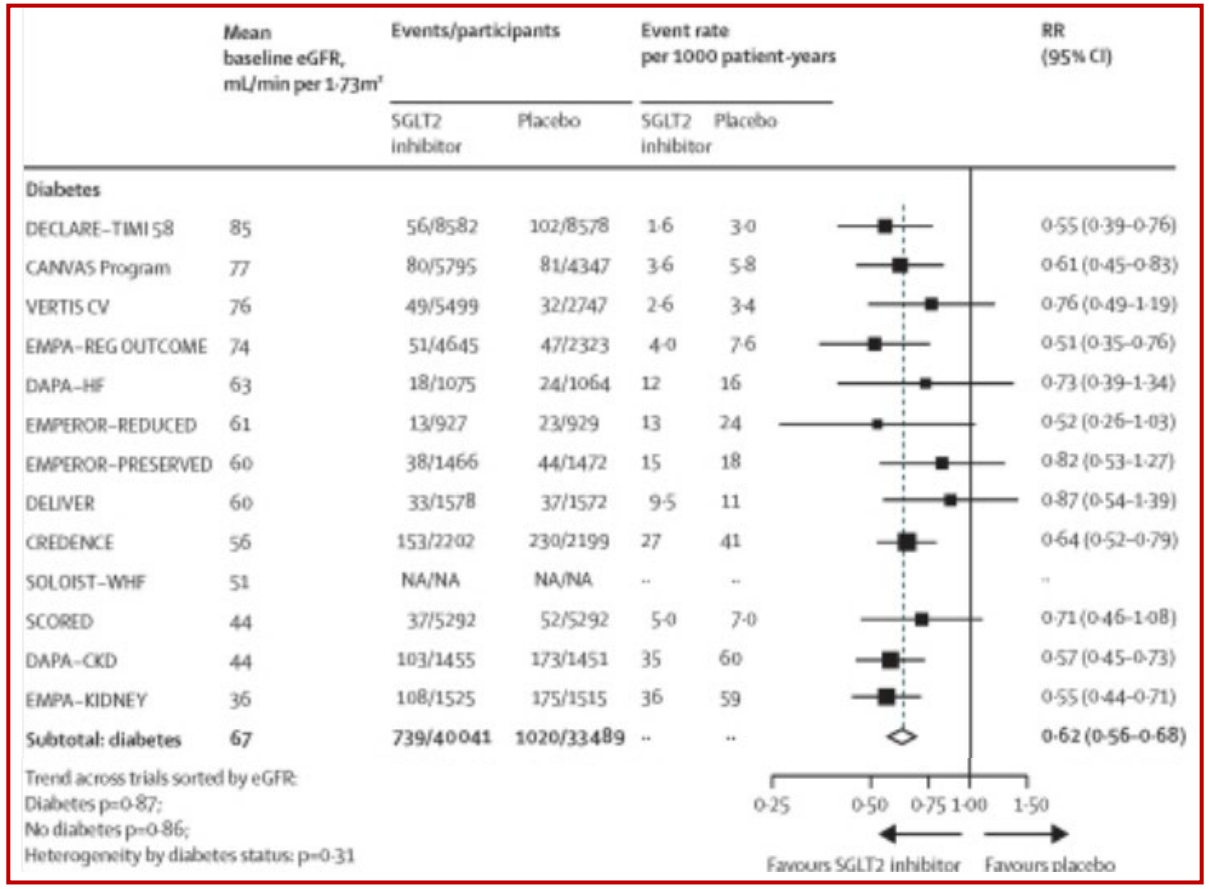
CKD population within kidney outcome trials



1. The EMPA-KIDNEY Collaborative Group. N Engl J Med 2023;388:117; 2. Perkovic V et al. N Engl J Med 2019;380:2295; 3. Wheeler DC et al. Nephrol Dial Transplant 2020;35:1700

Effect of SGLT2 inhibitors on kidney disease progression

Kidney disease progression was defined as a sustained decrease in eGFR (≥50%) from randomisation, a sustained low eGFR, end-stage kidney disease, or death from kidney failure in all presented trials



	Mean baseline eGFR, mL/min per 1·73m²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	
Diabetes						
DECLARE–TIMI 58	85	56/8582	102/8578	1·6	3·0	0·55 (0·39–0·76)
CANVAS Program	77	80/5795	81/4347	3·6	5·8	0·61 (0·45–0·83)
VERTIS CV	76	49/5499	32/2747	2·6	3·4	0·76 (0·49–1·19)
EMPA–REG OUTCOME	74	51/4645	47/2323	4·0	7·6	0·51 (0·35–0·76)
DAPA–HF	63	18/1075	24/1064	12	16	0·73 (0·39–1·34)
EMPEROR–REDUCED	61	13/927	23/929	13	24	0·52 (0·26–1·03)
EMPEROR–PRESERVED	60	38/1466	44/1472	15	18	0·82 (0·53–1·27)
DELIVER	60	33/1578	37/1572	9·5	11	0·87 (0·54–1·39)
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SOLOIST–WHF	51	NA/NA	NA/NA	..	..	..
SCORED	44	37/5292	52/5292	5·0	7·0	0·71 (0·46–1·08)
DAPA–CKD	44	103/1455	173/1451	35	60	0·57 (0·45–0·73)
EMPA–KIDNEY	36	108/1525	175/1515	36	59	0·55 (0·44–0·71)
Subtotal: diabetes	**67**	**739/40041**	**1020/33489**	..	..	**0·62 (0·56–0·68)**

Trend across trials sorted by eGFR:
Diabetes p=0·87;
No diabetes p=0·86;
Heterogeneity by diabetes status: p=0·31

-38%

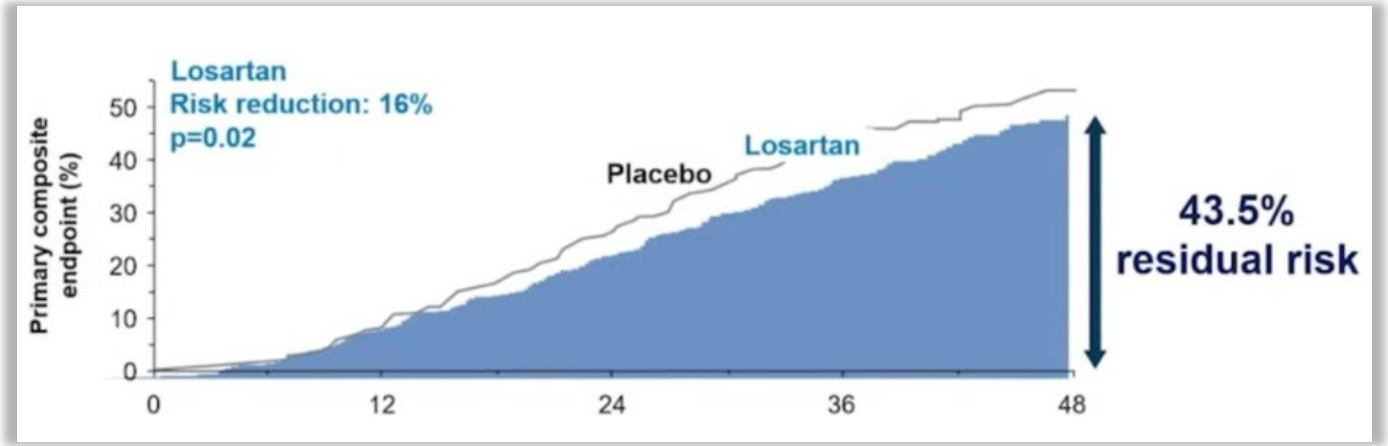
The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. *Lancet* 2022;400:1788

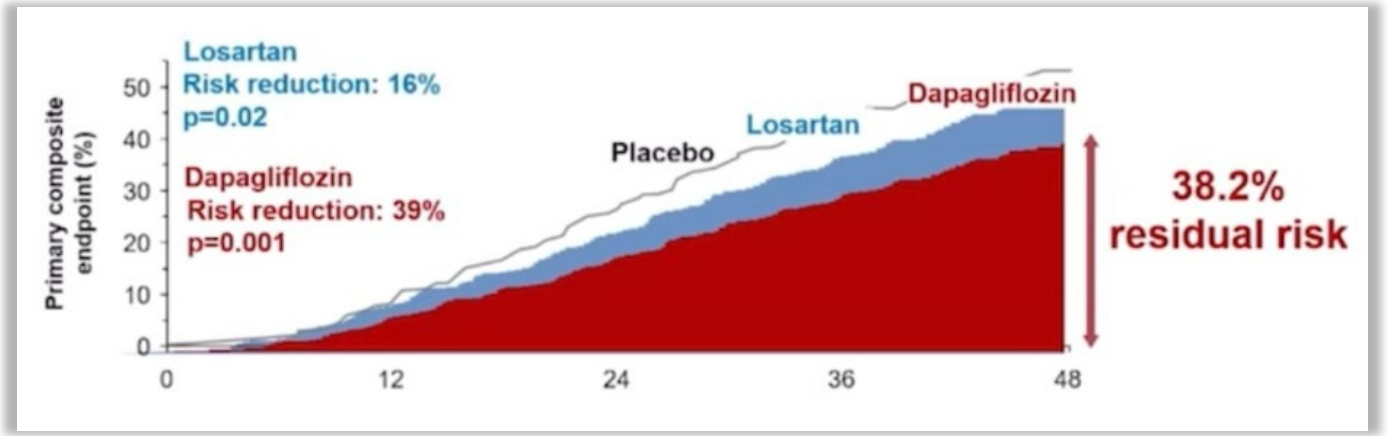
Residual renal risk with RASi and SGLT2i

RENAAL and DAPA-CKD

Risk of 2xsCr, ESKD or death

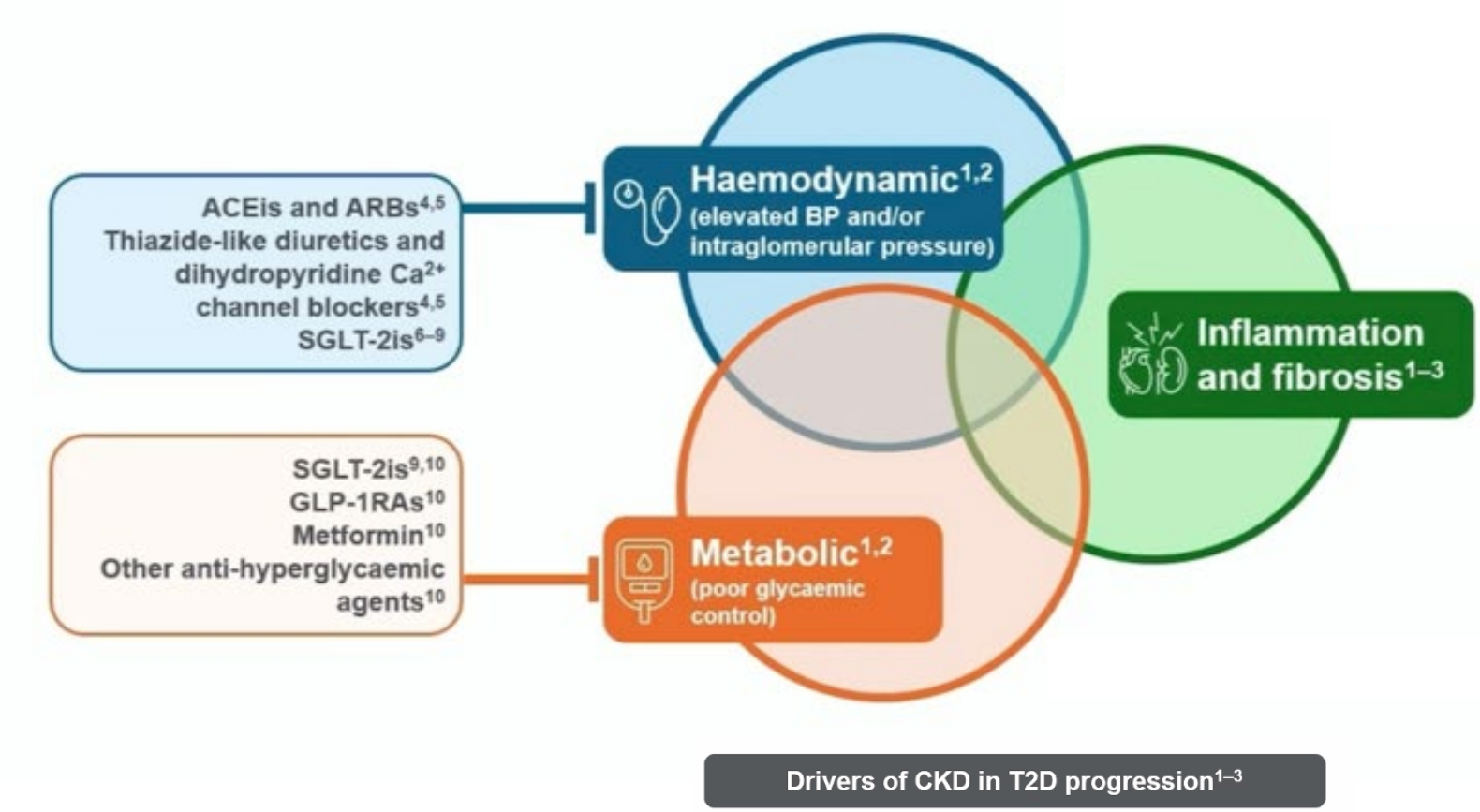
In pazients with T2D and overt nephropathy





Brenner BM, et al. *N Engl J Med*. 2001. Heerspink HJL, et al. *N Engl J Med*. 2020.

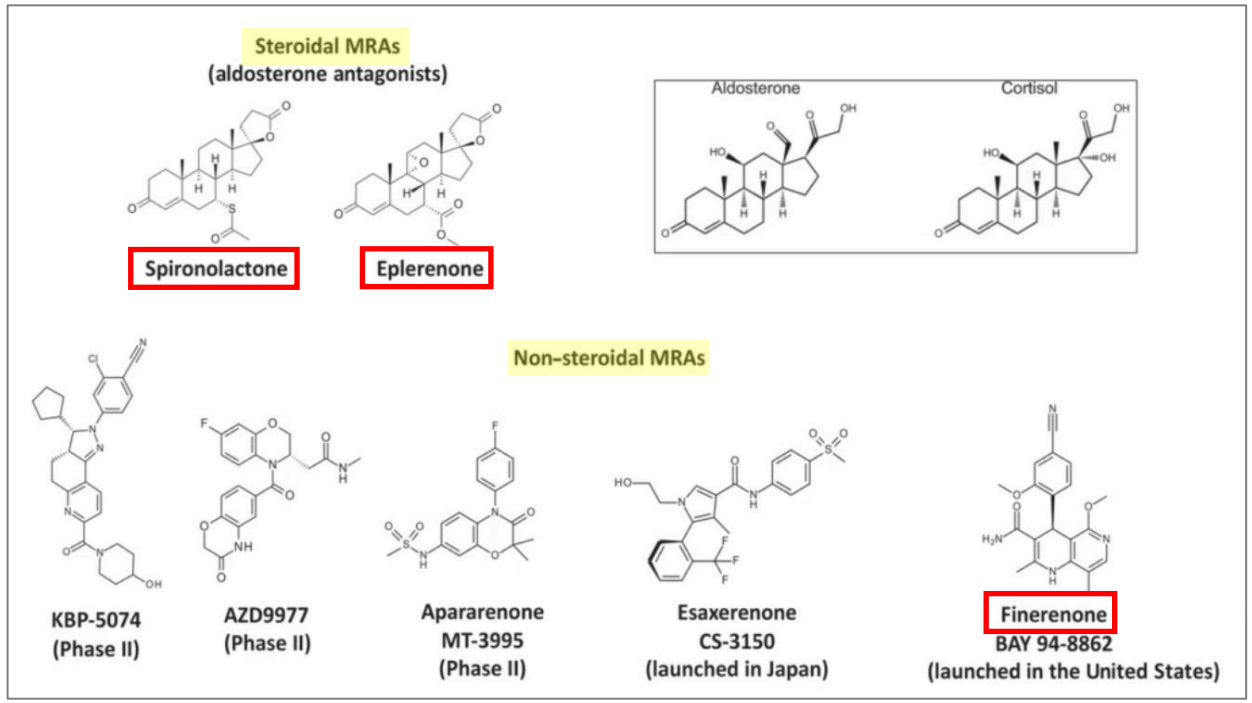
CKD in T2D progression is driven by the combined effects of metabolic, haemodynamic, inflammatory and fibrotic factors



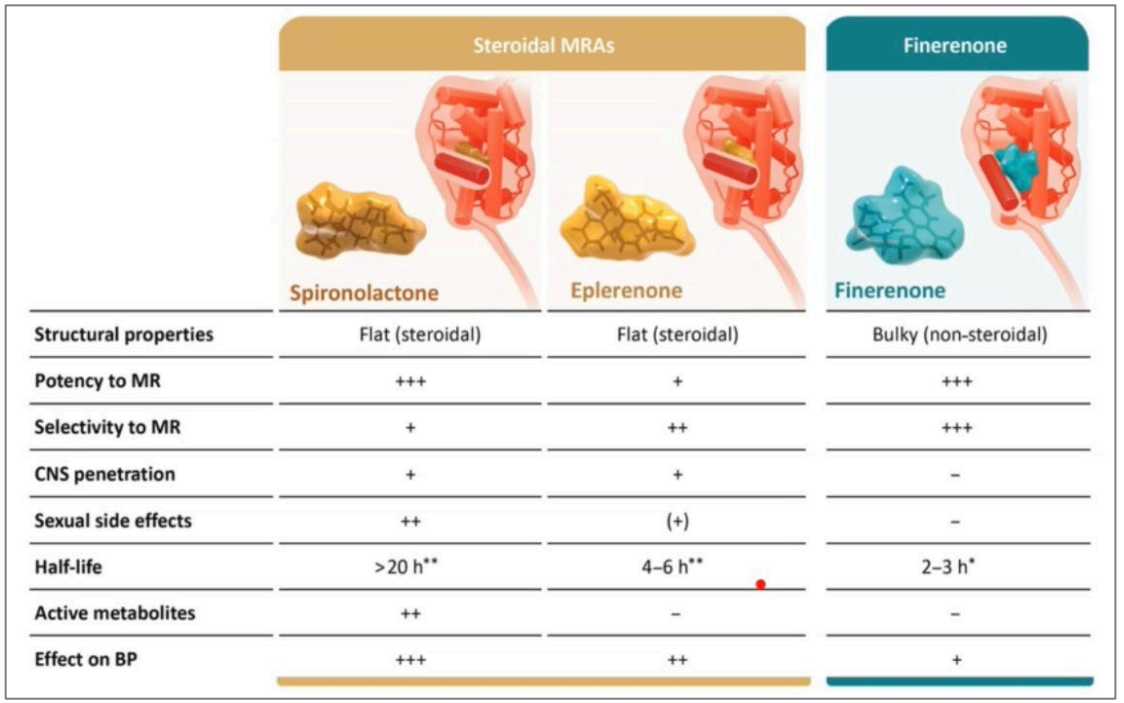
1. Alicic RZ et al, *Clin J Am Soc Nephrol* 2017;12:2032-2045. 2. Mora-Fernanández C et al, *J Physiol* 2014;18:3997. 3. Bauersachs J et al, *Hypertension* 2015;65:257-263. 4. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175-S184. 5. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S144-S174. 6. Kidokoro K et al, *Circulation* 2019;140:303-315. 7. Zelniker TA and Braunwald E, *J Am Coll Cardiol* 2018;72(15):1845-1855. 8.Heerspink HJ et al, *Circulation* 2016;134:752-772. 9. Zelniker TA and Braunwald E, *J Am Coll Cardiol* 2020;75:422-434. 10. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S125-S143. 11. Agarwal R et al, *Eur Heart J* 2021;42:152-162. 12. Agarwal R et al, *Nephrol Dial Transplant* 2022;37:1014-1023.

Mineralcorticoid receptor antagonists (MRAs)

Chemical structures



Pharmacokinetc and pharmacodynamic characteristics



	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	–
Sexual side effects	++	(+)	–
Half-life	>20 h**	4–6 h**	2–3 h*
Active metabolites	++	–	–
Effect on BP	+++	++	+

Kintscher U, et al. *Br J Pharmacol* 2022;179(13):3220-3234.

FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease

Double-blind, randomized, placebo-controlled trial
- 5734 patients randomized
- 2,6 years median follow-up

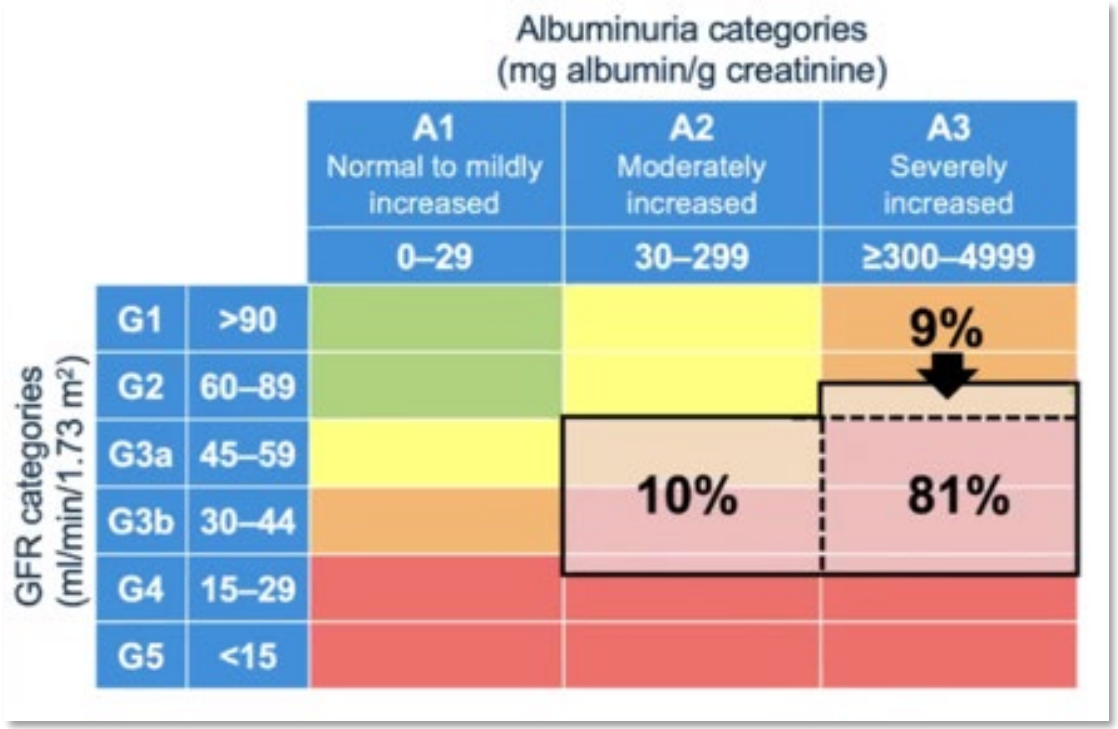
Finerenone	eGFR<60 ml/min71.73m^2 → 10 mg od
	eGFR≥60 ml/min71.73m^2 → 20 mg od

✓ Inclusion criteria[1,2]

- T2D and CKD, defined as **either:**
  - UACR 30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m^2 *# **or**
  - UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m^2 *
- Treated with either an ACEi or an ARB at maximal tolerated dose
- [K$^+$] ≤4.8 mmol/l

✗ Key exclusion criteria[1,2]

- HFrEF with NYHA class II–IV
- Other kidney disease‡
- Uncontrolled arterial hypertension§
- Dialysis for acute kidney failure or kidney transplant



1. Bakris GL, et al. *Am J Nephrol* 2019;50:333-344.
2. Bakris GL, et al. *N Engl J Med* 2020;383:2219-2229

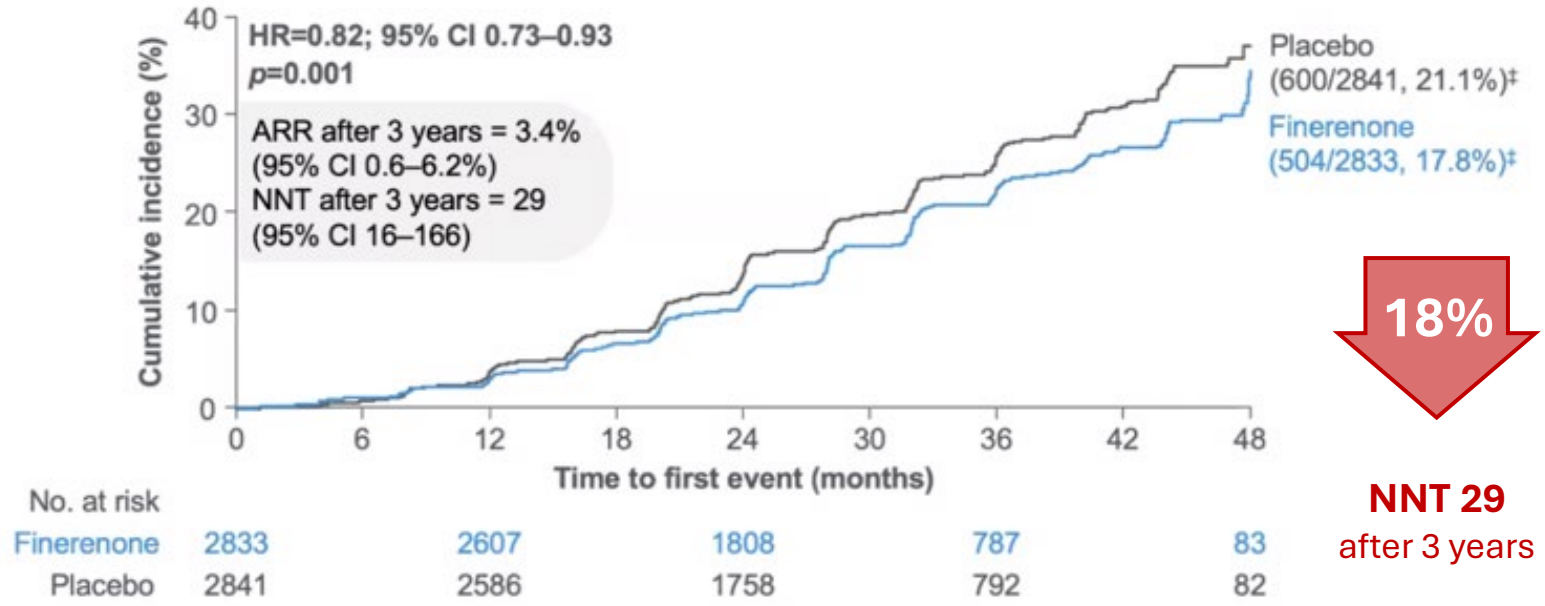
Risk of the primary composite kidney endpoint vs placebo

PRIMARY ENDPOINT

Kidney composite

Time to kidney failure°, sustained ≥40% decrease in eGFR from baseline*, or renal death

°ESKD or an eGFR <15 mL/min/1,73 m2
*sustained over ≥4 week



18%

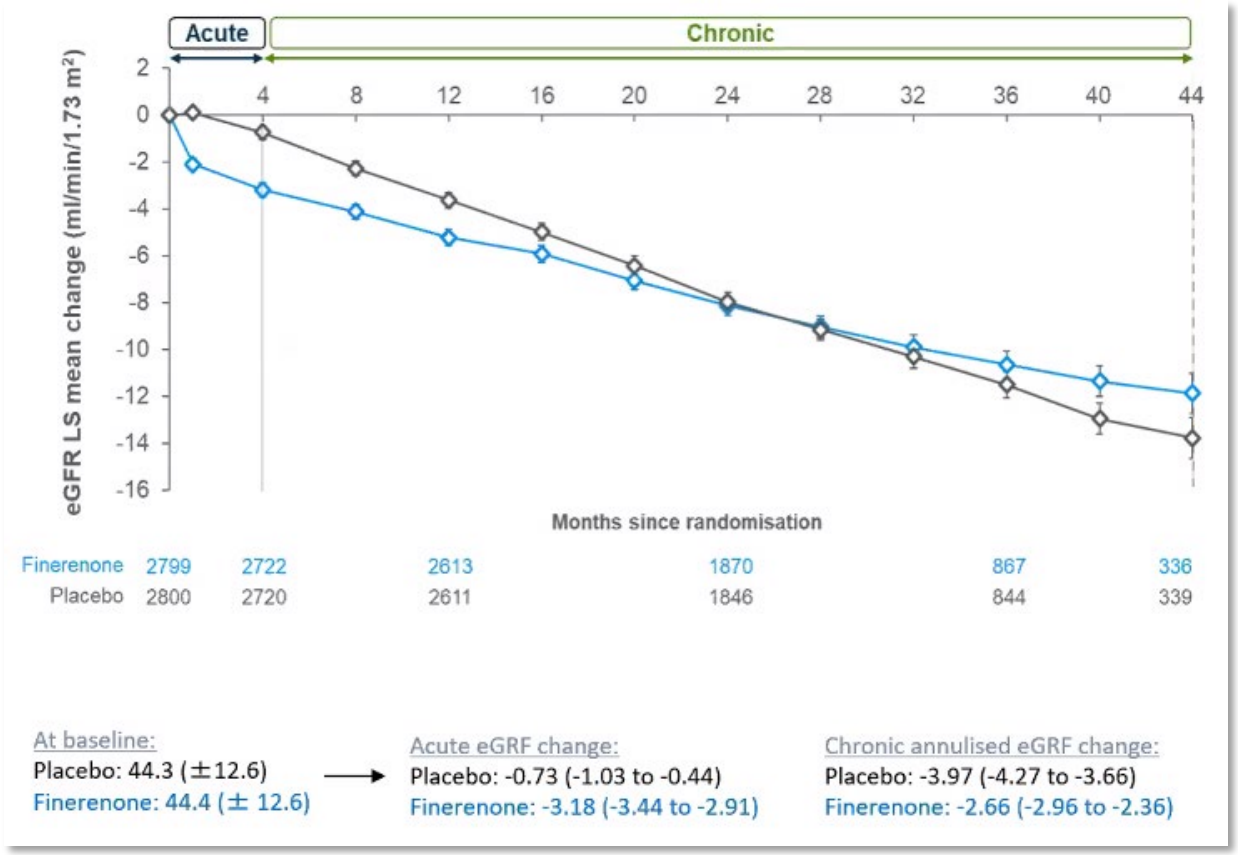
NNT 29
after 3 years

Endpoint	Finerenone (n=2833) n (%)	Finerenone (n=2833) n per 100 PY	Placebo (n=2841) n (%)	Placebo (n=2841) n per 100 PY	Hazard ratio (95% CI)	p-value
Primary composite kidney endpoint	504 (17.8)	7.59	600 (21.1)	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	2.99	235 (8.3)	3.39	0.87 (0.72–1.05)	–
End-stage kidney disease	119 (4.2)	1.60	139 (4.9)	1.87	0.86 (0.67–1.10)	–
Sustained* decrease in eGFR to <15 ml/min/1.73 m²	167 (5.9)	2.40	199 (7.0)	2.87	0.82 (0.67–1.01)	–
Sustained* ≥40% decrease in eGFR from baseline	479 (16.9)	7.21	577 (20.3)	8.73	0.81 (0.72–0.92)	–
Renal death	2 (<0.1)	–	2 (<0.1)	–	–	–

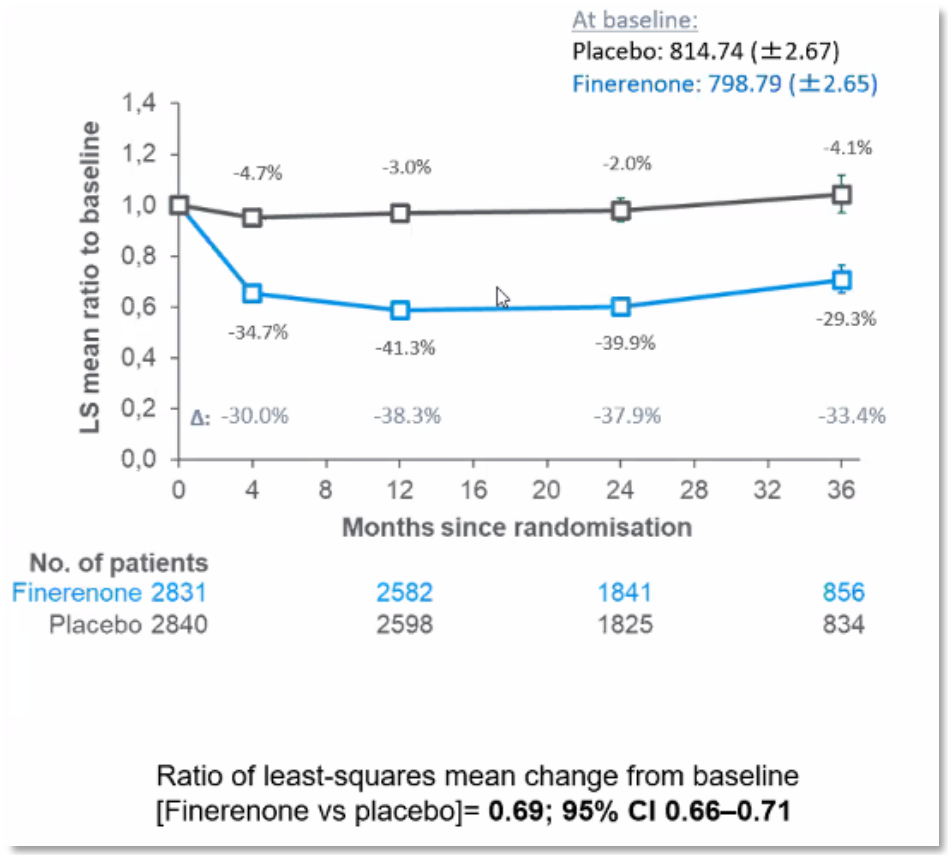
Bakris GL, et al. *N Engl J Med* 2020;383:2219-2229

Finerenone reduces worsening of eGFR overtime and UACR starting from 4th months

eGFR



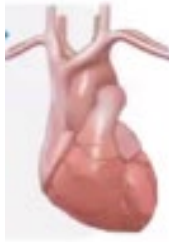
UACR



Bakris GL, et al. *N Engl J Med* 2020;383:2219-2229

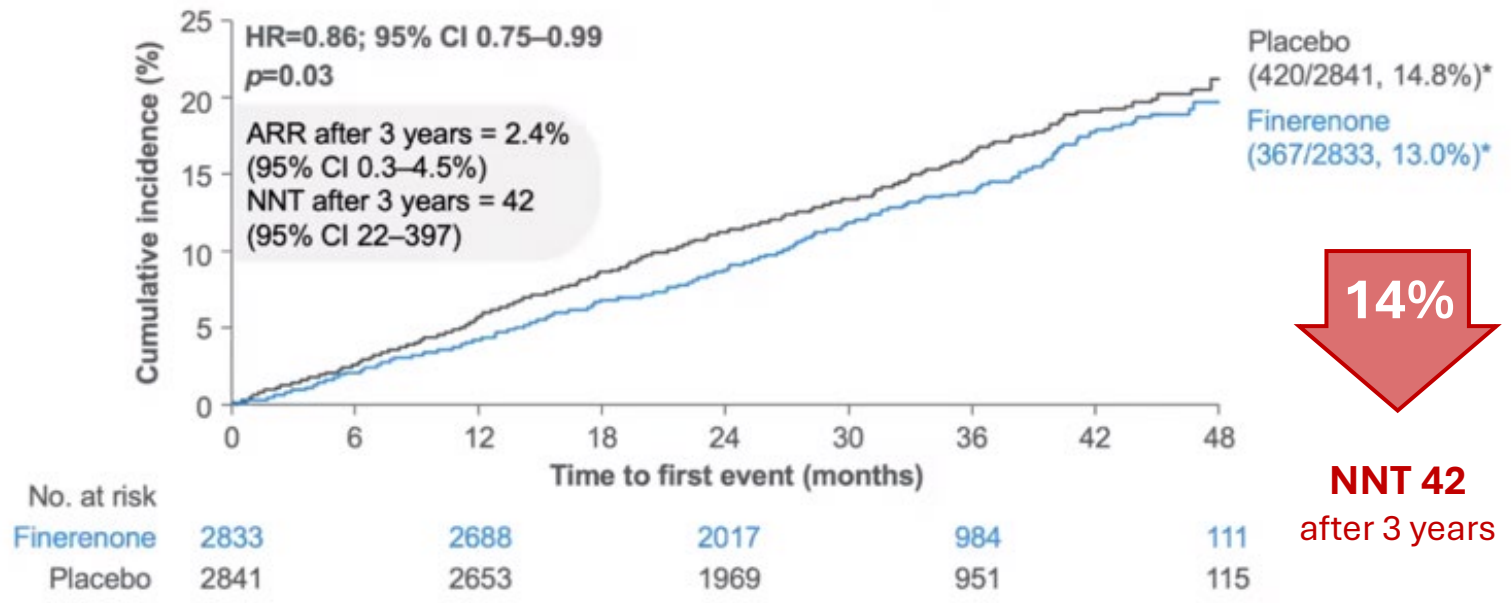
Risk of the key secondary CV endpoint vs placebo

SECONDARY ENDPOINT



CV composite

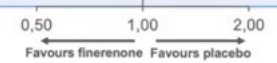
Time to CV death, non fatal MI, non fatal stroke or hospitalisation for HF



14%

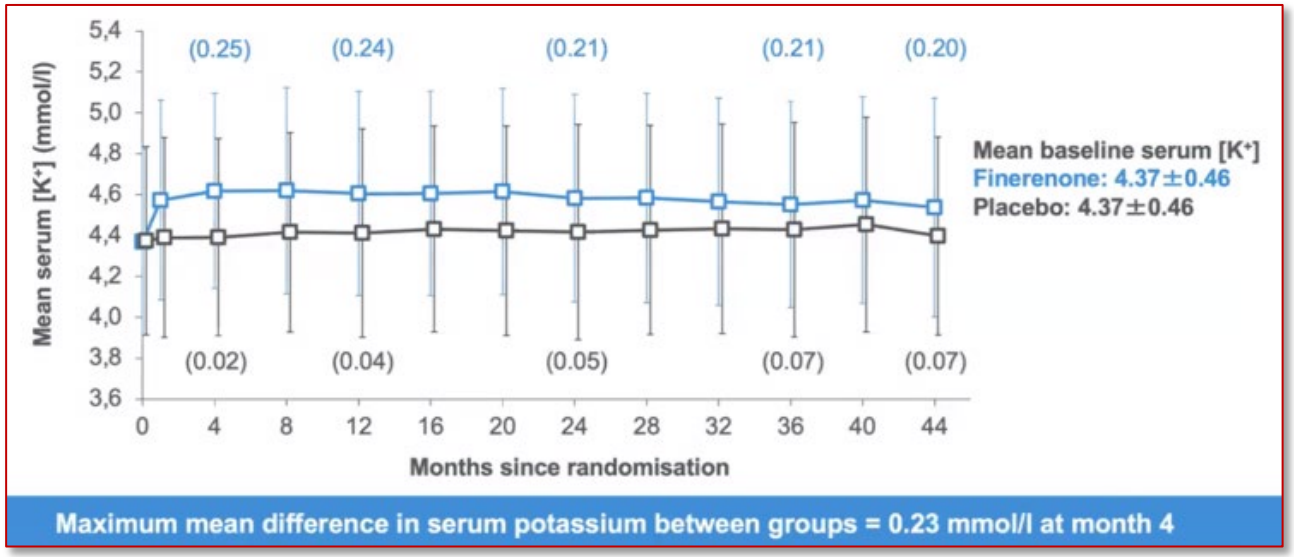
NNT 42
after 3 years

Endpoint	Finerenone (n=2833) n (%)	Finerenone (n=2833) n per 100 PY	Placebo (n=2841) n (%)	Placebo (n=2841) n per 100 PY	Hazard ratio (95% CI)	p-value
Key secondary cardiovascular composite endpoint	367 (13.0)	5.11	420 (14.8)	5.92	0.86 (0.75–0.99)	0.03
Cardiovascular death	128 (4.5)	1.69	150 (5.3)	1.99	0.86 (0.68–1.08)	–
Non-fatal MI	70 (2.5)	0.94	87 (3.1)	1.17	0.80 (0.58–1.09)	–
Non-fatal stroke	90 (3.2)	1.21	87 (3.1)	1.18	1.03 (0.76–1.38)	–
Hospitalisation for HF	139 (4.9)	1.89	162 (5.7)	2.21	0.86 (0.68–1.08)	–

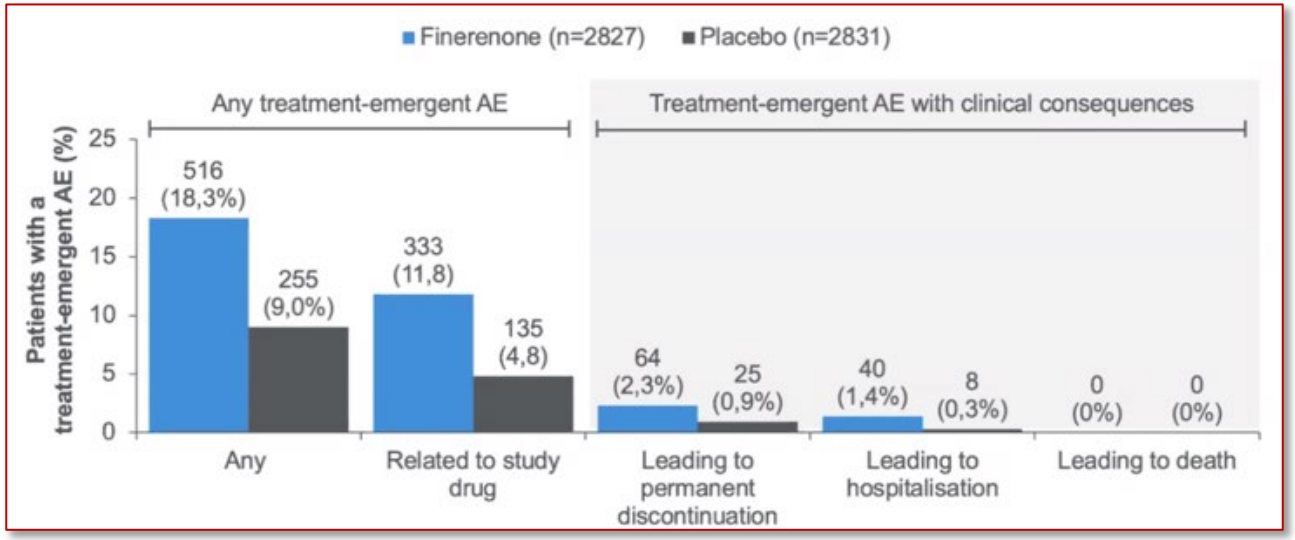


Bakris GL, et al. *N Engl J Med* 2020;383:2219-2229

Finerenone and potassium



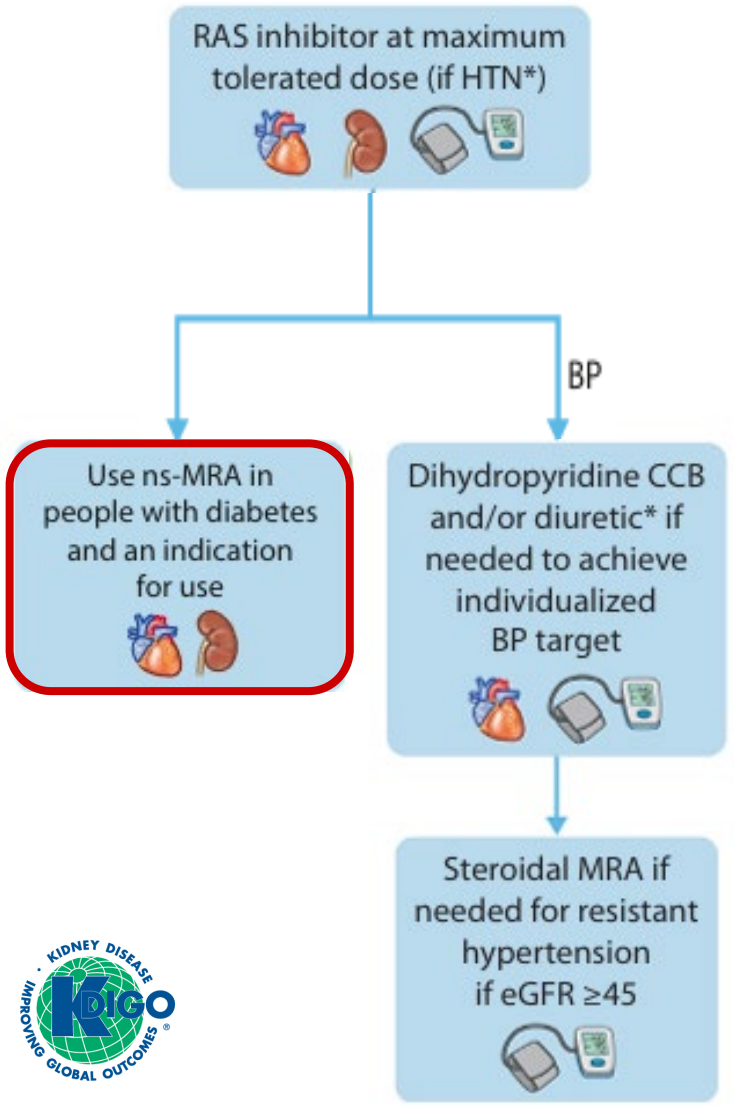
Mean serum potassium (mmol/L)



Patients with treatment-emergent hypercalaemia AE (%)

Bakris GL, et al. *N Engl J Med* 2020;383:2219-2229

Clinical guidelines for the management of CKD in T2D recommended finerenone as a core treatment pillar



Recommendation 3.8.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an eGFR >25 ml/min per 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)*.

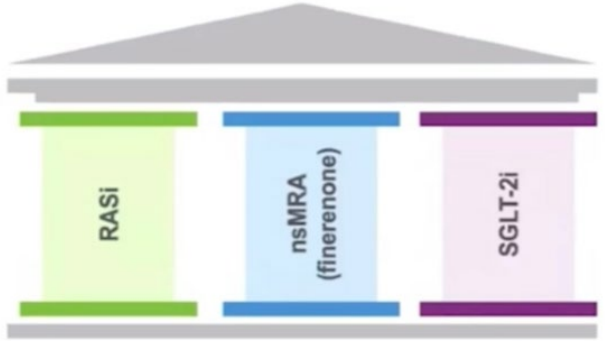
Practice Point 3.8.1: Nonsteroidal MRA are most appropriate for adults with T2D who are at high risk of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard-of-care therapies.

Practice Point 3.8.2: A nonsteroidal MRA may be added to a RASi and an SGLT2i for treatment of T2D and CKD in adults.

Practice Point 3.8.3: To mitigate risk of hyperkalemia, select people with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA (Figure 26).

Practice Point 3.8.4: The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

KDIGO Clinical Practice Guidelines -2024



European Society of Hypertension

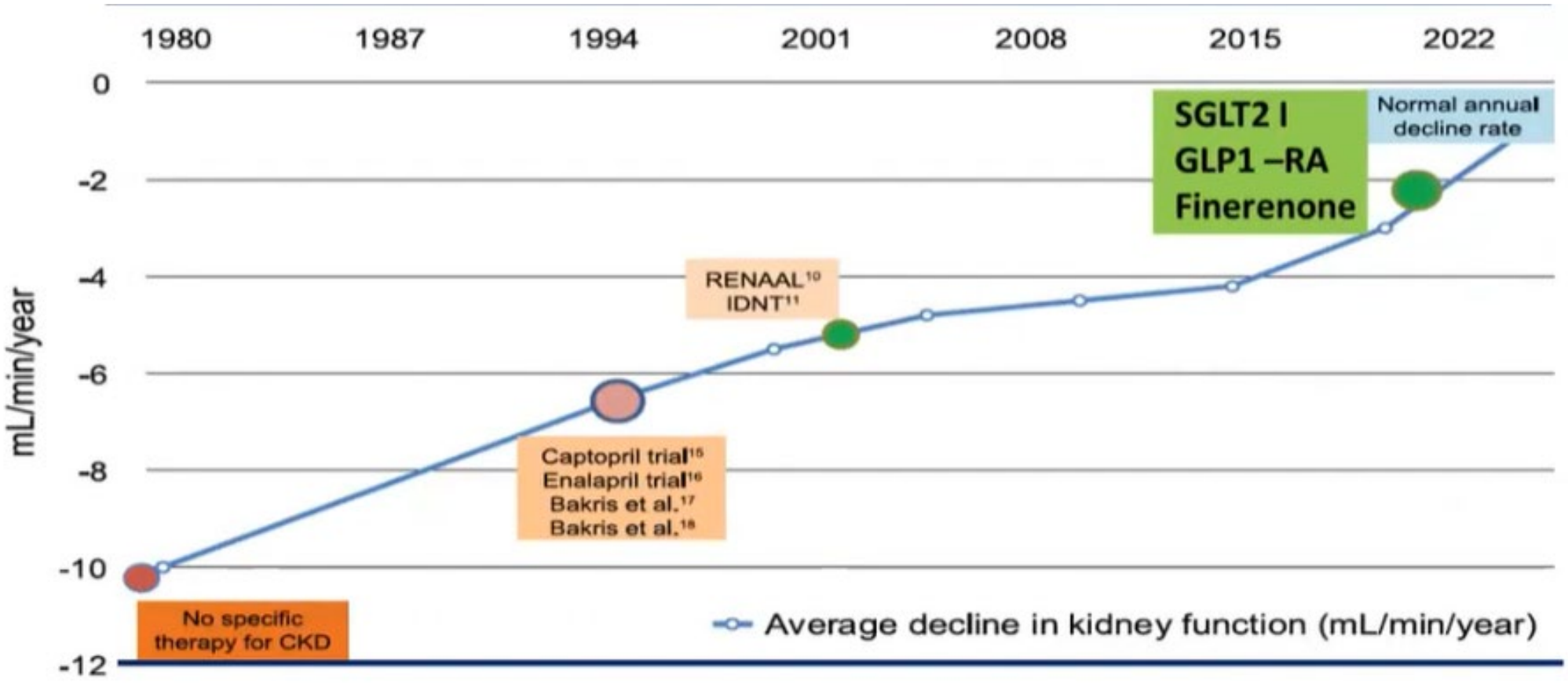
ESC European Society of Cardiology

AACE American Association of Clinical Endocrinology

11.5d As people with CKD and albuminuria are at increased risk for cardiovascular events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist that has been shown to be effective in clinical trials is recommended to reduce cardiovascular events and CKD progression (if eGFR is ≥25 mL/min/1.73 m^2).

Standard of Care in Diabetes - 2024

Historical perspective on slowing CKD progression associated with T2D



Naaman SC and Bakris GL, *American Diabetes Association* 2021.

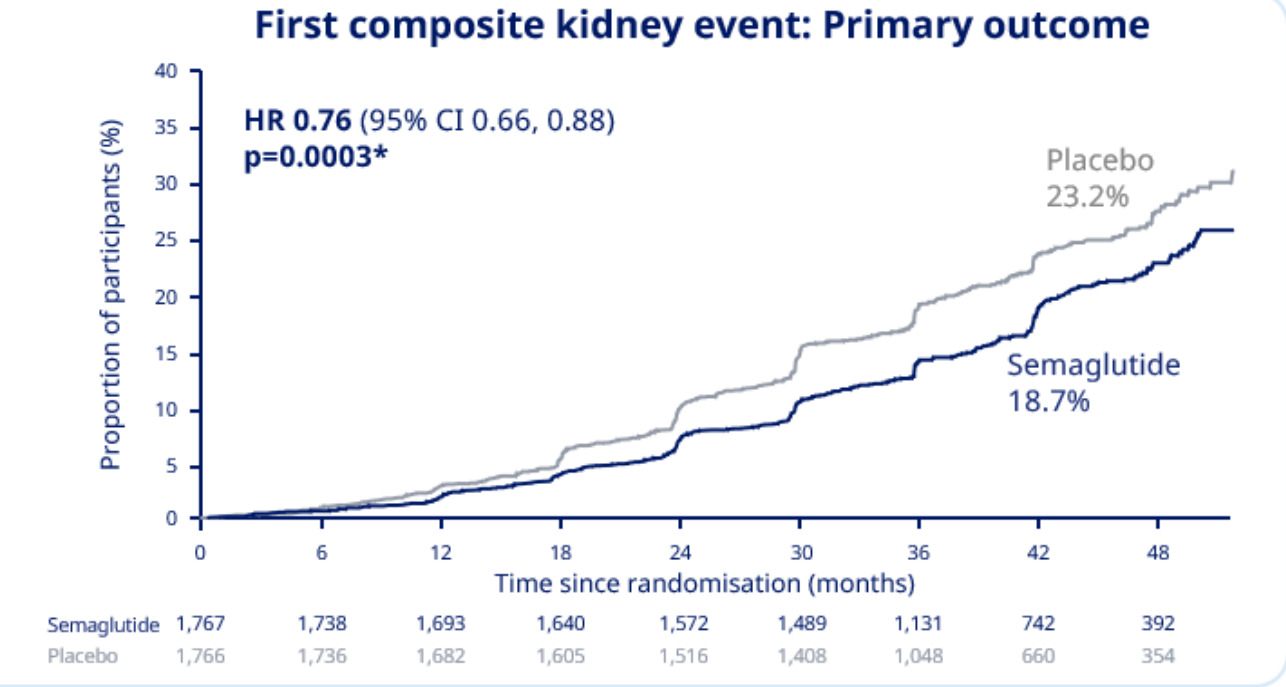
OW semaglutide s.c. 1.0 mg showed a 24% risk reduction of a composite outcome, incl. kidney disease progression, CV and Kidney death in people with CKD and T2D

Primary kidney endpoint

FLOW

Time to first occurrence of a composite endpoint consisting of:

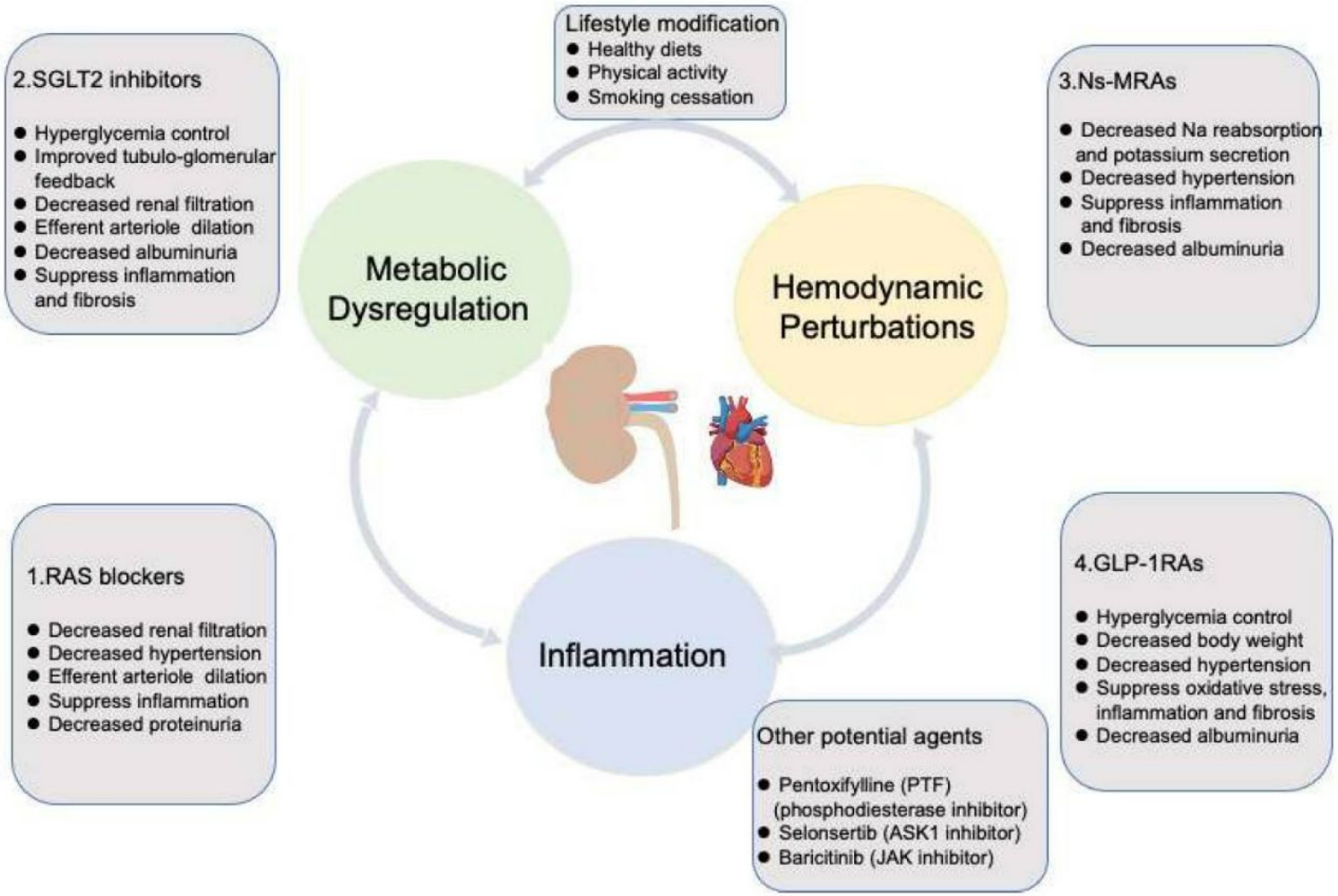
- Onset of persistent ≥50% reduction in eGFR compared with baseline
- Onset of persistent eGFR <15 mL/min/1.73 m^2
- Initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- Renal death
- CV death



*Full analysis set. Data from the in-trial period. * Superiority if p value <0.0322*
Numbers shown in the lower panels represent the number of participants at risk. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio. Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347

Perkovic V, et al. *N Engl J Med* 2024391(2):109-121.

Recent Advances in the Management of Diabetic Kidney Disease: Slowing Progression



Wang NA and Zhang C. *Int J Mol Sci* 2024;25(6):3086.

Grazie