Non-steroidal mineralocorticoid receptor antagonists (ns MRA): a new therapeutic pillar for cardiorenal protection in patients with CKD and T2D

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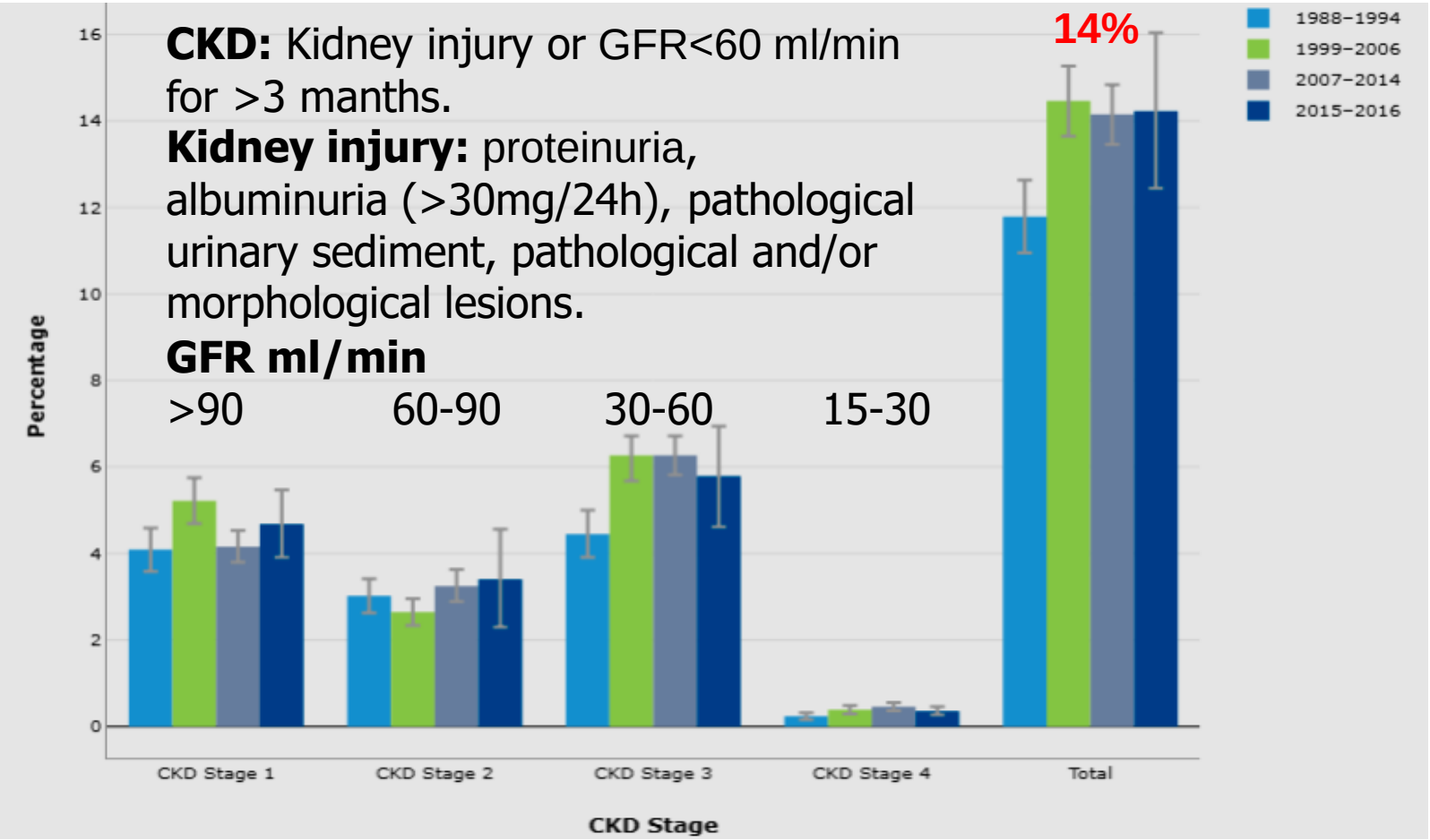
Conflict of interest

- Honorary payment by Bayer

Non-steroidal MRA in DKD

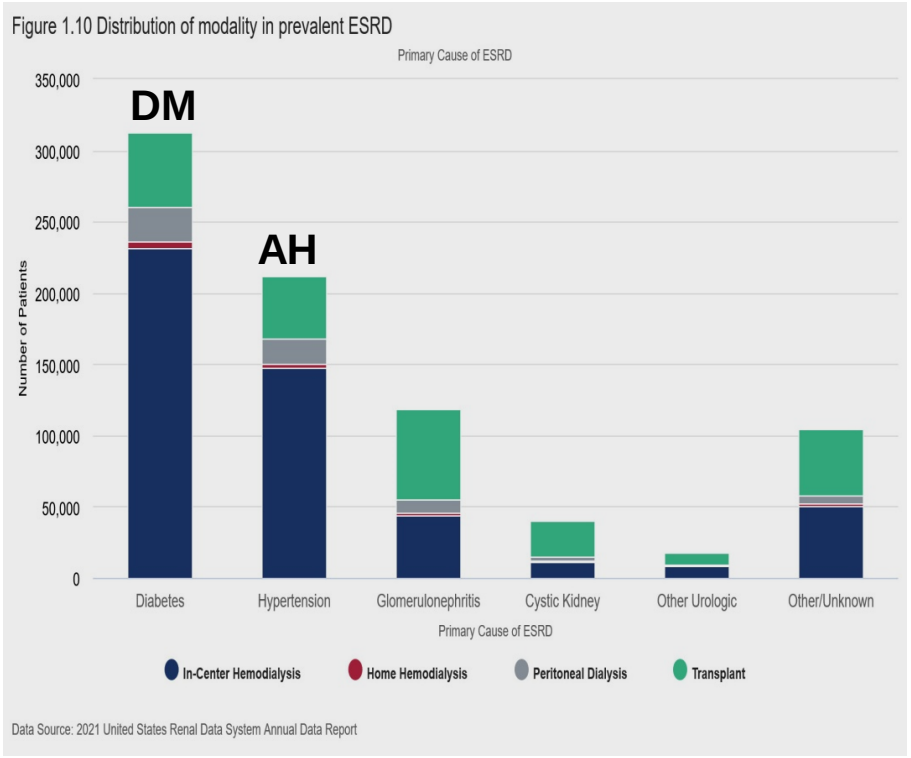
- Epidemiology
- Diagnosis
- Mechanisms of action (finerenone)
- Clinical trials, Clinical Guidelines
- Special issues, short case analysis

Chronic Kidney Disease (CKD)



Collins et al. Am J Kidney Dis. 2014;63(1)(suppl 1):e1-e420.

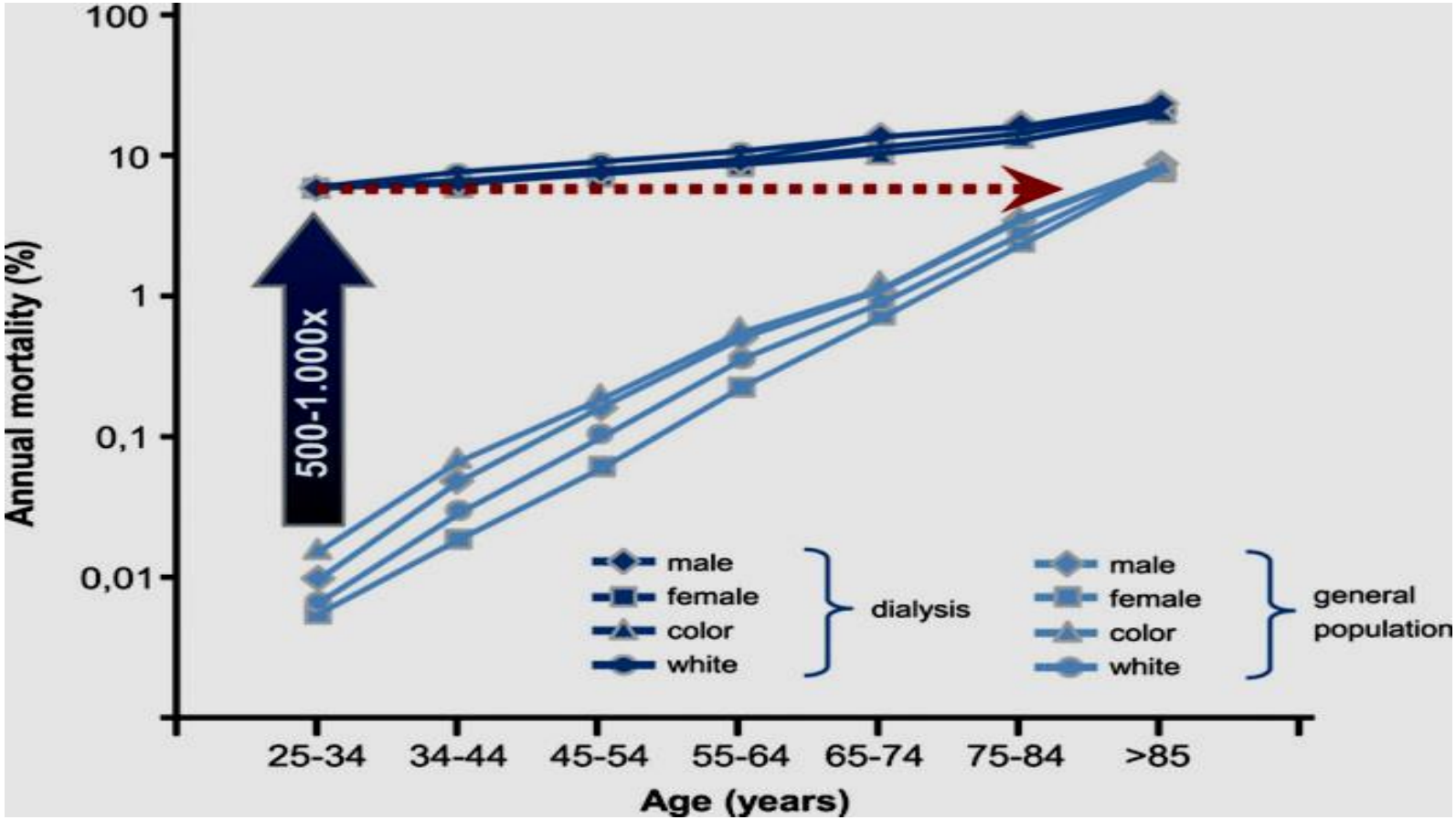
Epidemiology – etiology CKD



- Diabetes mellitus
- Arterial hypertension
- Cardiovascular diseases
- Age (>60 years)
- Family history of end-stage CKD

Prevalent ESRD rates, by primary diagnosis, adjusted for age, gender, & race.
USRDS Annual Data Report, 2021

Cardiovascular mortality in hemodialysis



Levey AS et al. *Am J Kidney Dis* 1998; 32: 853-906.

Cardiovascular mortality in CKD

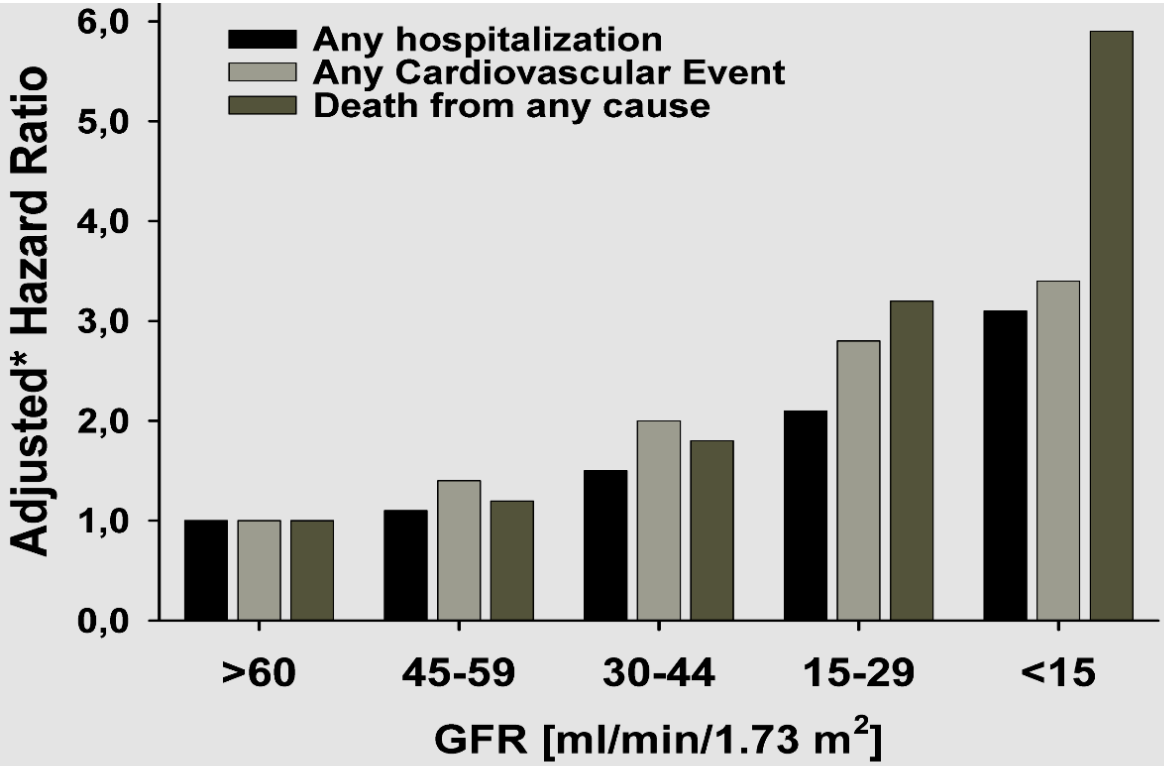
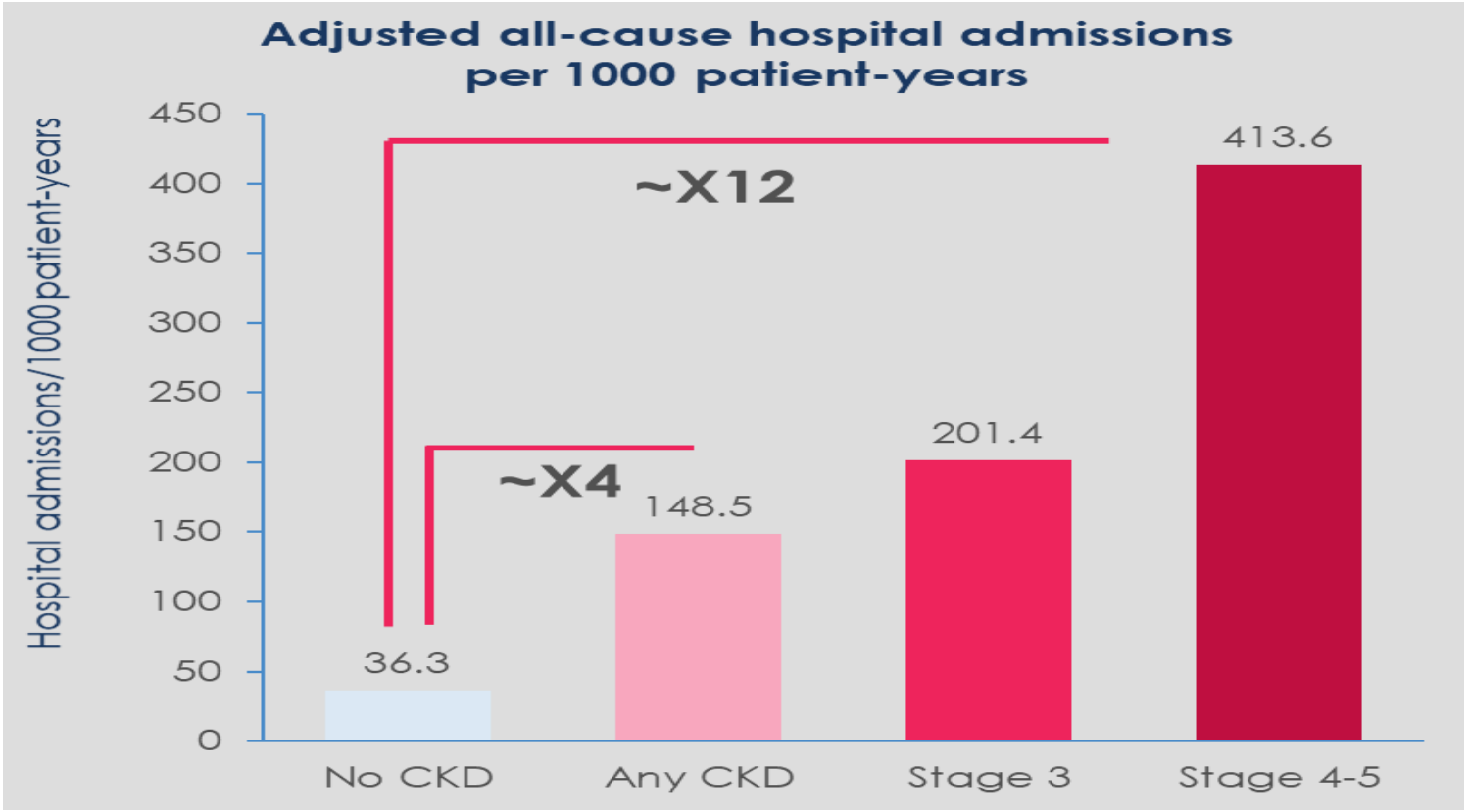


Figure. Adjusted hazard ratio among 1,120,295 ambulatory adults, according to the estimated GFR (eGFR).

*Adjustment for age, gender and age.

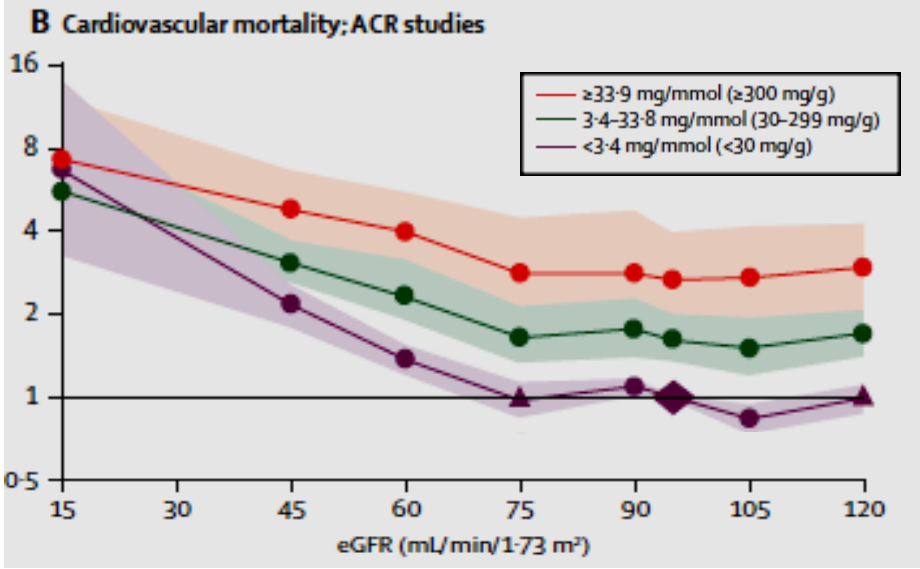
Go et al. N Engl J Med 2004;351:1296-1305.

Cardiovascular mortality in CKD



United States Renal Data System. 2021 USRDS Annual Data Report. 2021. https://adr.usrds.org/2021

CKD as cardiovascular risk factor



Matsushita K et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010.

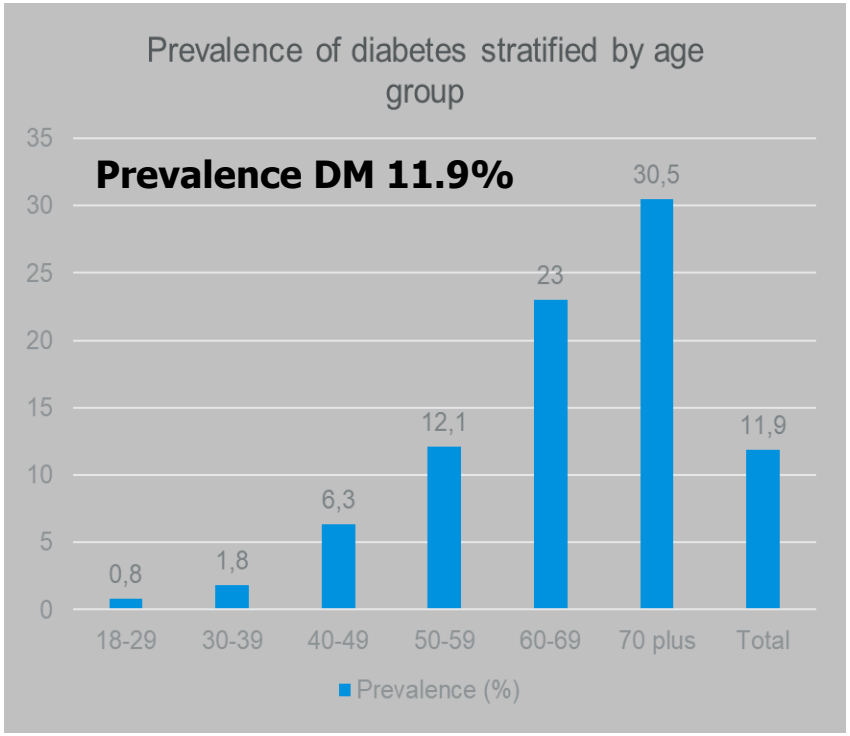
Gansevoort RT et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet.2013

Progression of CKD by GFR and Albuminuria Categories				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m²) Description and range	G1	Normal to high	≥90			
	G2	Mildly decreased	60–90			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	15			

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Chapter 1: definition and classification of CKD. Kidney Int Suppl (2011). 2013;3:19-62.

Diabetes epidemiology in Greece

- Results of the first national Health Examination Survey (HES) on the prevalence of diabetes, its pharmacologic treatment and level of control, as well as prediabetes in Greece.
- Data were derived from the National Survey of Morbidity and Risk Factors (EMENO), in a randomly selected, representative sample of the adult Greek population.
- Total diabetes prevalence was 11.9% (95% CI: 10.9–12.9), known diabetes 10.4% (9.5–11.4), and unknown 1.5% (1.1–1.9), with considerable increase in older age groups.



Makrilakis K, Kalpourtzi N, Ioannidis I, et al. Prevalence of diabetes and pre-diabetes in Greece. Results of the First National Survey of Morbidity and Risk Factors (EMENO) study. Diabetes Res Clin Pract. 2021;172:108646. https://doi.org/10.1016/j.diabres.2020.108646

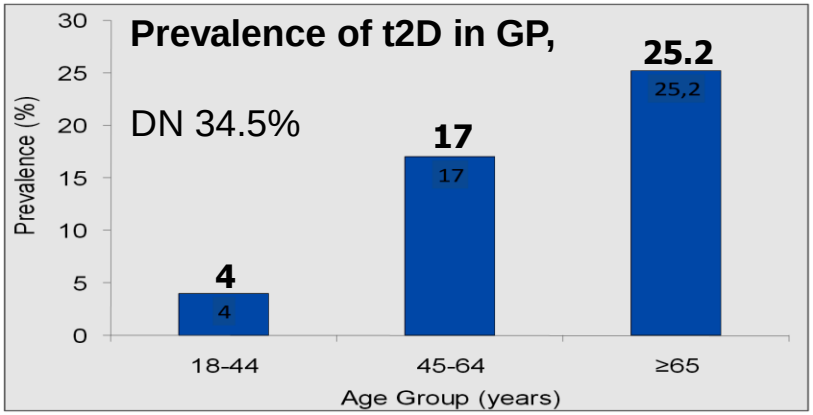
Hellenic Diabetic Nephropathy Study (HDNS) Group: REDIT-2 DIAG study

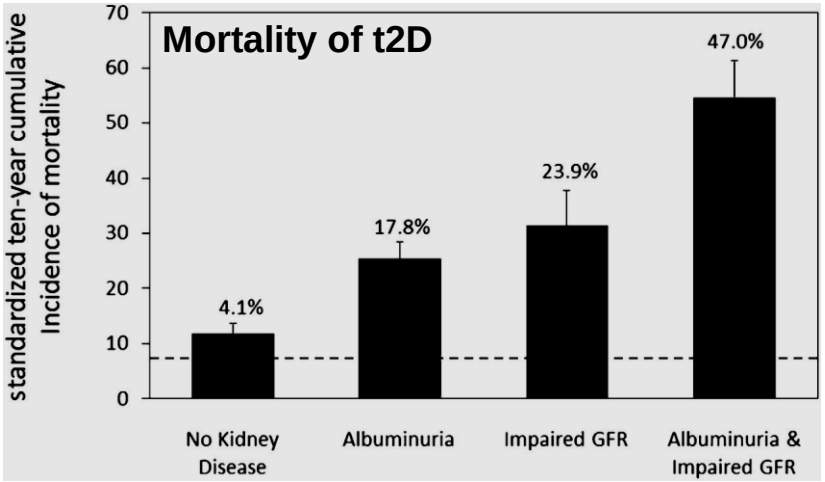
Among the entire population (n = 1759), the overall prevalence of DCKD was 43% including mild, moderate and severe CKD.

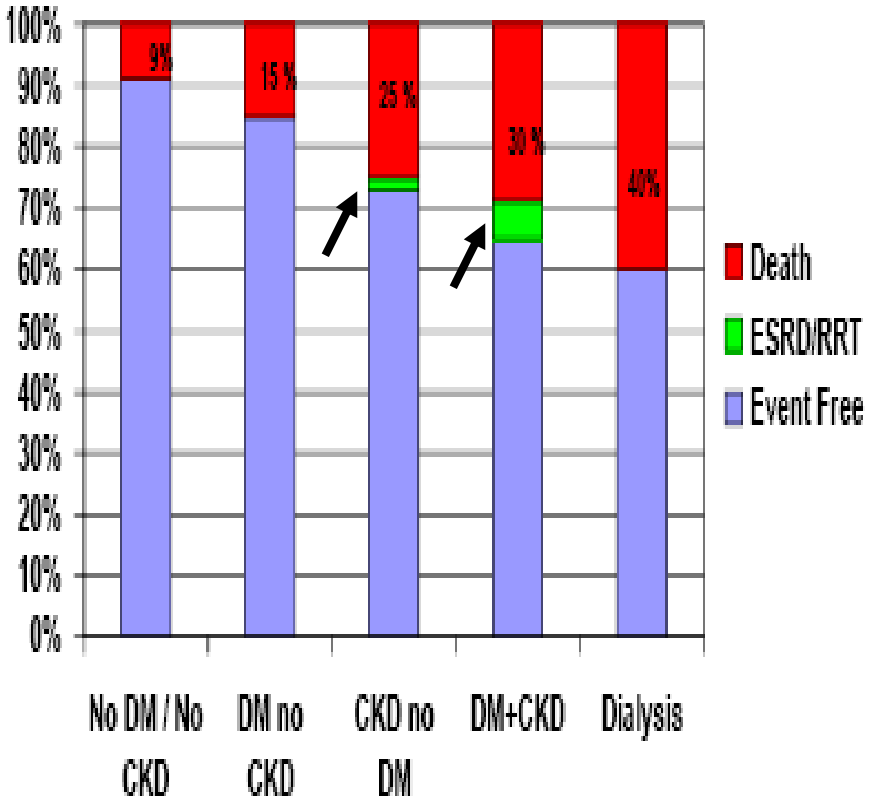
GFR categories description and range (ml/min/1.73 m2)				Albuminuria categories Description and range (mg albumin/g creatinine)		
				A1	A2	A3
				0–29	30-299	>300
	G1	High and optimal	>90	24	10	1
	G2	Mild	60-89	33	14	2
	G3a	Mild–moderate	45-59	5	5	1
	G3b	Moderate–severe	30-44	2	2	1
	G4	Severe	15-29	0,3	0,6	1
	G5	Kidney failure	<15	0,2	0,1	4

Migdalis IN, Papanas N, Raptis AE, et al. The prevalence of diabetic chronic kidney disease in adult Greek subjects with type 2 diabetes mellitus: A series from hospital-based diabetes clinics. Diabetes Res Clin Pract. 2020;166:108243. https://doi.org/10.1016/j.diabres.2020.108243

DM and CKD

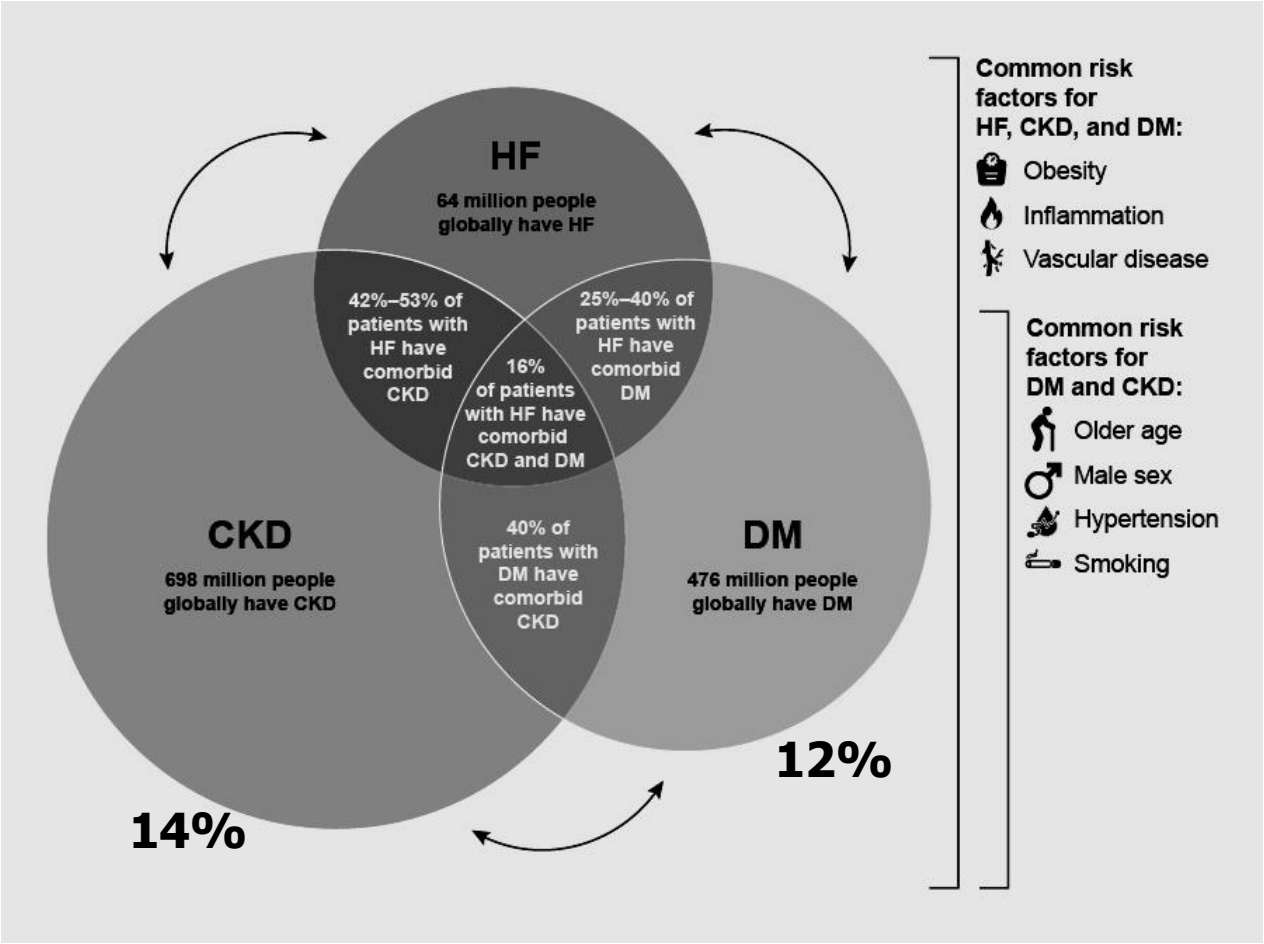






CDC National Diabetes Statistics Report, 2017
De Boer et al. JAMA 2011; 305:2532–2539
Afkarian et al. *J Am Soc Nephrol 2013.* 24:302–308

Interrelationship of DM CKD and HF, common risk factors



Vijay et al. Heart Failure in Patients with Diabetes and Chronic Kidney Disease: Challenges and Opportunities. Cardiorenal Med. 2022;12:1-10.

Key points 1

- The prevalence of CKD in the general population is 14% and T2DM 12%.
- DM followed by hypertension are the most common causes of CKD and ESRD. DCKD is found in 40% of DM patients.
- Mortality and morbidity of CKD are many times higher than in the general population. They even higher when T2D and CKD coexist.
- A prerequisite for reducing DKD mortality is the timely intervention, with an efficient screening program and implementation of evidence-based (EB) and guidelines directed medical treatment (GDMT).

Albuminuria

- Albuminuria is measured in 24h urine (UA mg/d) or as a ratio of urinary creatinine in a random (morning) urine sample (UACR mg/g).
- The concentration of albumin and creatinine in the urine sample is measured and calculated:

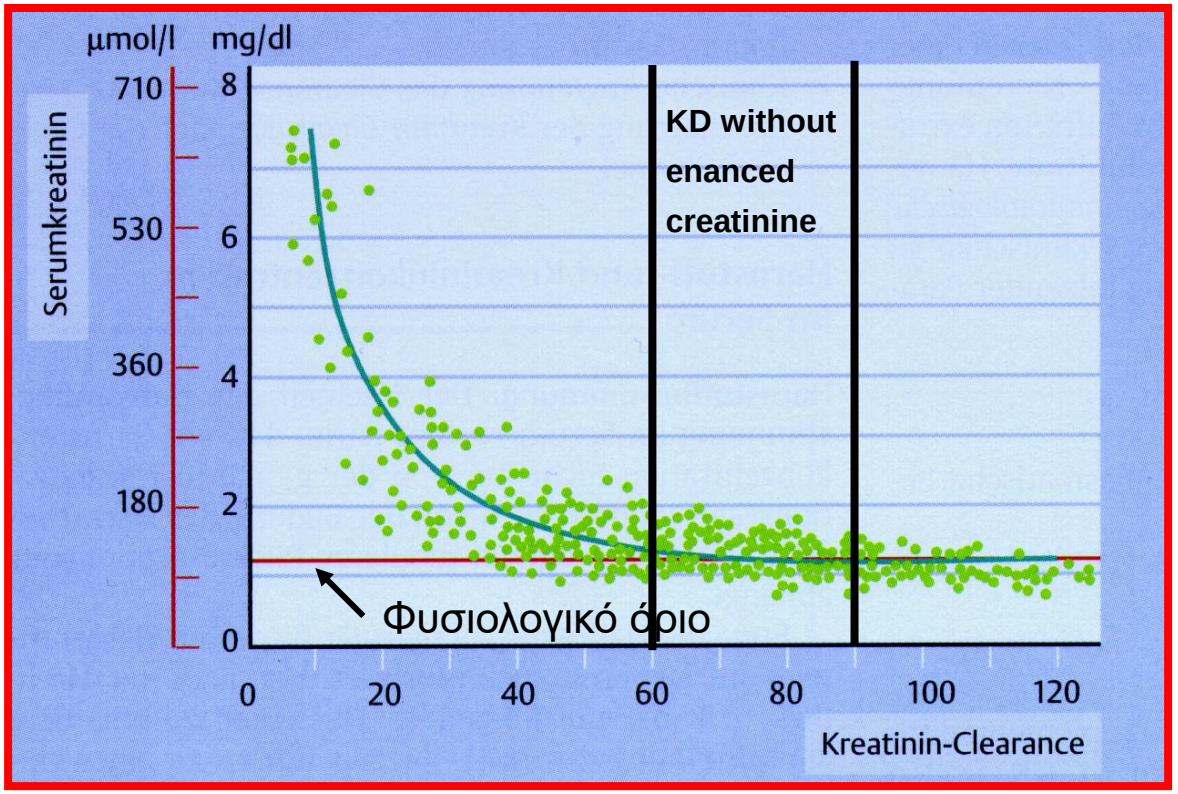
$$\frac{\text{Urine albumin (mg/dL)}}{\text{Urine creatinine (g/dL)}} = \text{UACR (mg/g)} \cong \text{Albumin excretion in mg/day}$$

- The limit is 30mg/g for moderate and 300mg/g for severe albuminuria.

https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-education-outreach/quick-reference-uacr-gfr

Determination of GFR

- **Serum creatinine**
- Cystatin C
- Creatinine clearance
- eGFR by CKD-EPI (or MDRD)



Hoek et al. Nephrol. Dial. Transplant. 2003;18:2024-2031

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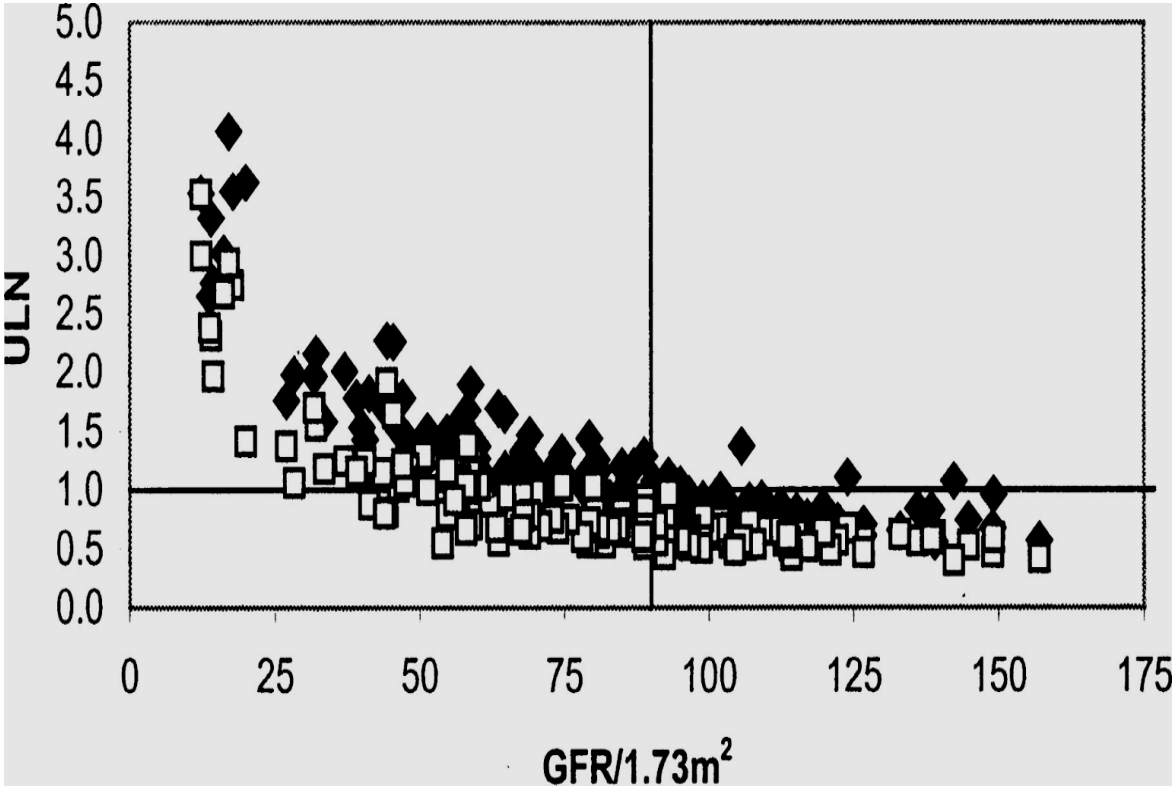


Hoek et al. Nephrol. Dial. Transplant. 2003;18:2024-2031

Determination of GFR

- Serum creatinine
- Cystatin C
- Creatinine clearance
- **eGFR by CKD-EPI (or MDRD)**

CKD EPI & MDRD GFR Calculator - (With SI Units)

4 variable MDRD CKD EPI Equation (with SI Units)
using standardized serum creatinine, age, race, gender

by Stephen Z. Fadem, M.D., FACP, FASN
and Brian Rosenthal

Serum creatinine 1.3
◉ mg/dL ○ µmol/L

NOTE: CKD EPI GFR is only valid with creatinine methods are traceable to IDMS

Age 55 years

Race ○ African American ◉ All other races*

Gender ◉ Male ○ Female

TRACEABLE TO IDMS (What is this?) ○ No ◉ Yes

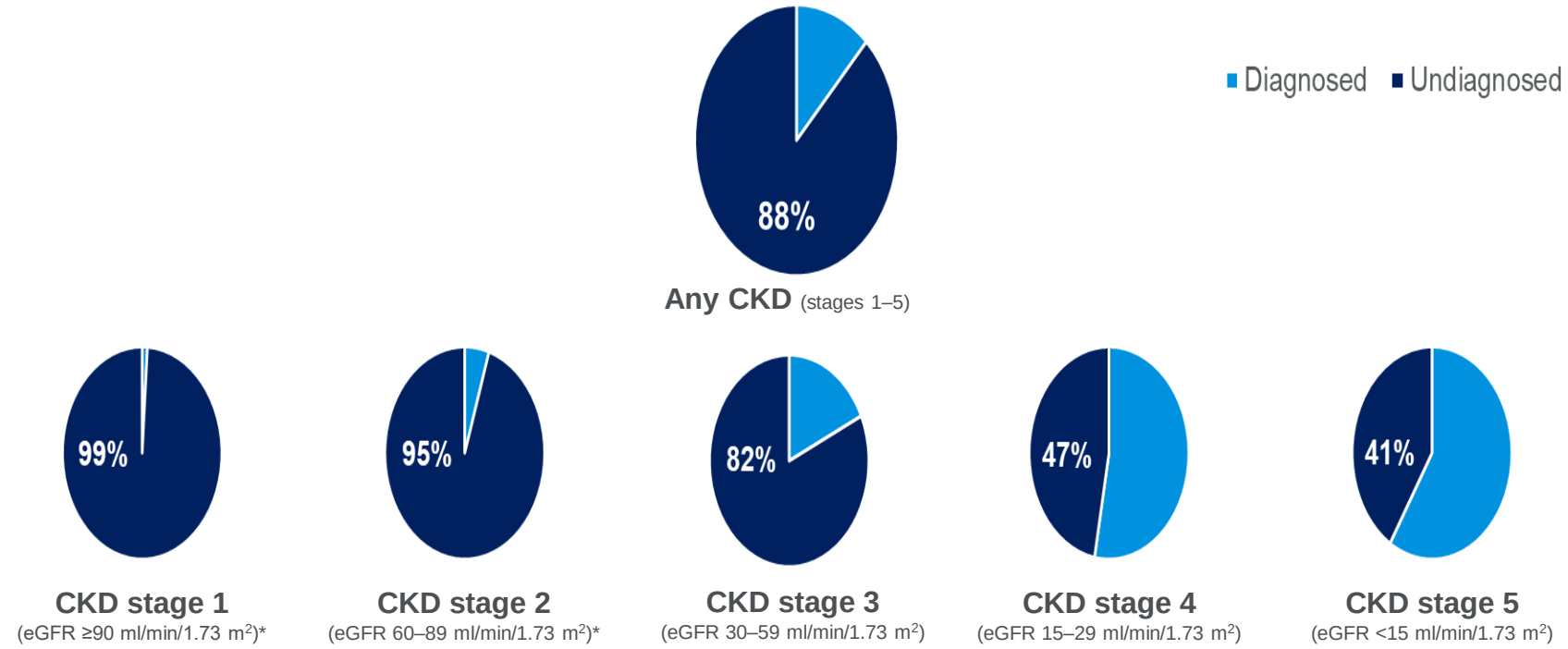
CKD EPI Value: **61** mL/min/1.73 m^2 in a 55 year old non African American male.

MDRD GFR: **57** mL/min/1.73 m^2 in a 55 year old non African American male.

GFR calculators: http://www.kidney.org/professionals/KLS/gfr_calculator.cfm

DKD is under-diagnosed in T2D

5036 patients with T2D and CKD: The ADD-CKD study



85% of patients had eGFR assessed during the 15 months prior to study participation, but only 47% had UACR assessment

***+UACR ≥30 mg/g or positive protein in urine**

ADD-CKD, Awareness, Detection and Drug Therapy in Type 2 Diabetes and Chronic Kidney Disease

Szczech LA, *et al. PLoS One* 2014;9:e110535

Screening for DKD (DN) – ADA, KDIGO

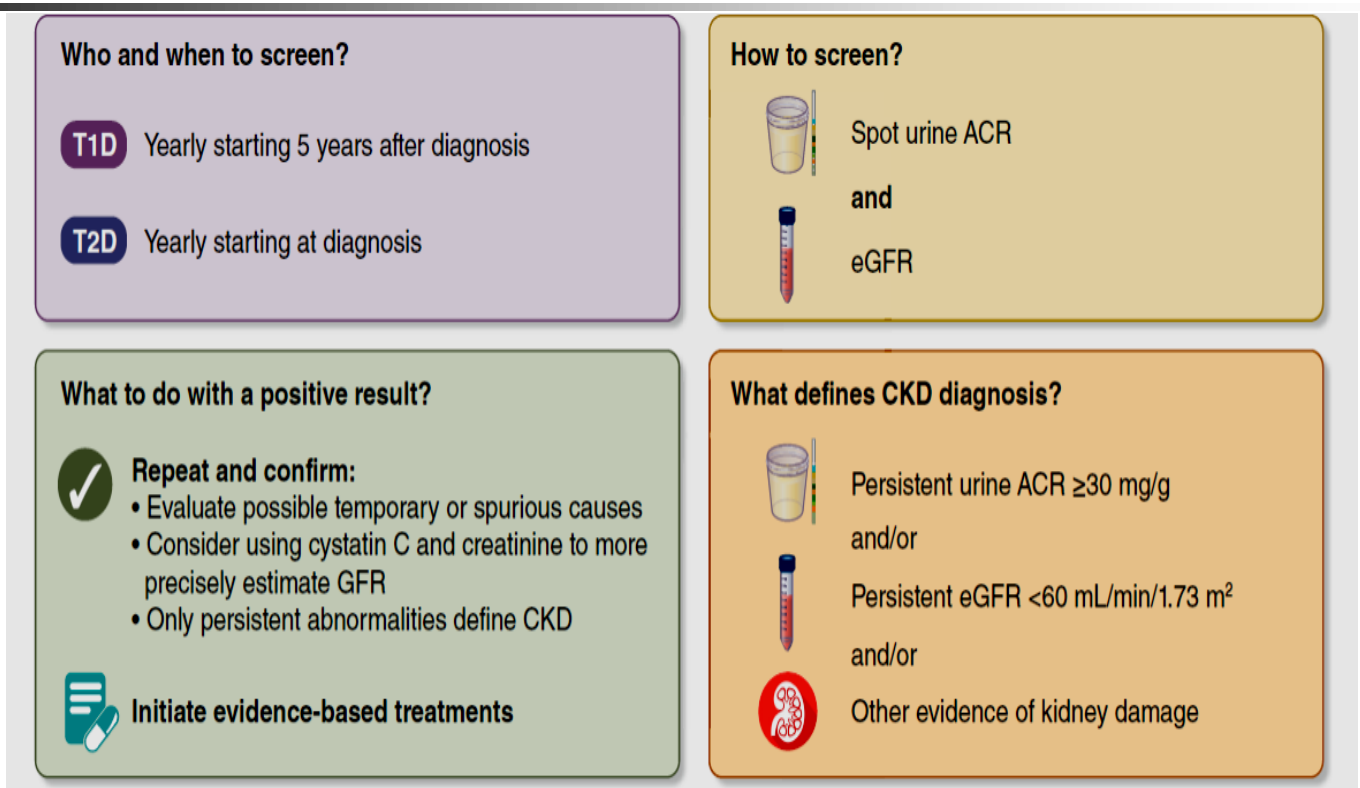


Figure 1—CKD screening and diagnosis for people living with diabetes. Screening includes measurement of both urine albumin and eGFR. Abnormalities should be confirmed. Persistent abnormalities in either urine ACR or eGFR (or both) diagnose CKD and should lead to immediate initiation of evidence-based treatments. ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T1D, type 1

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

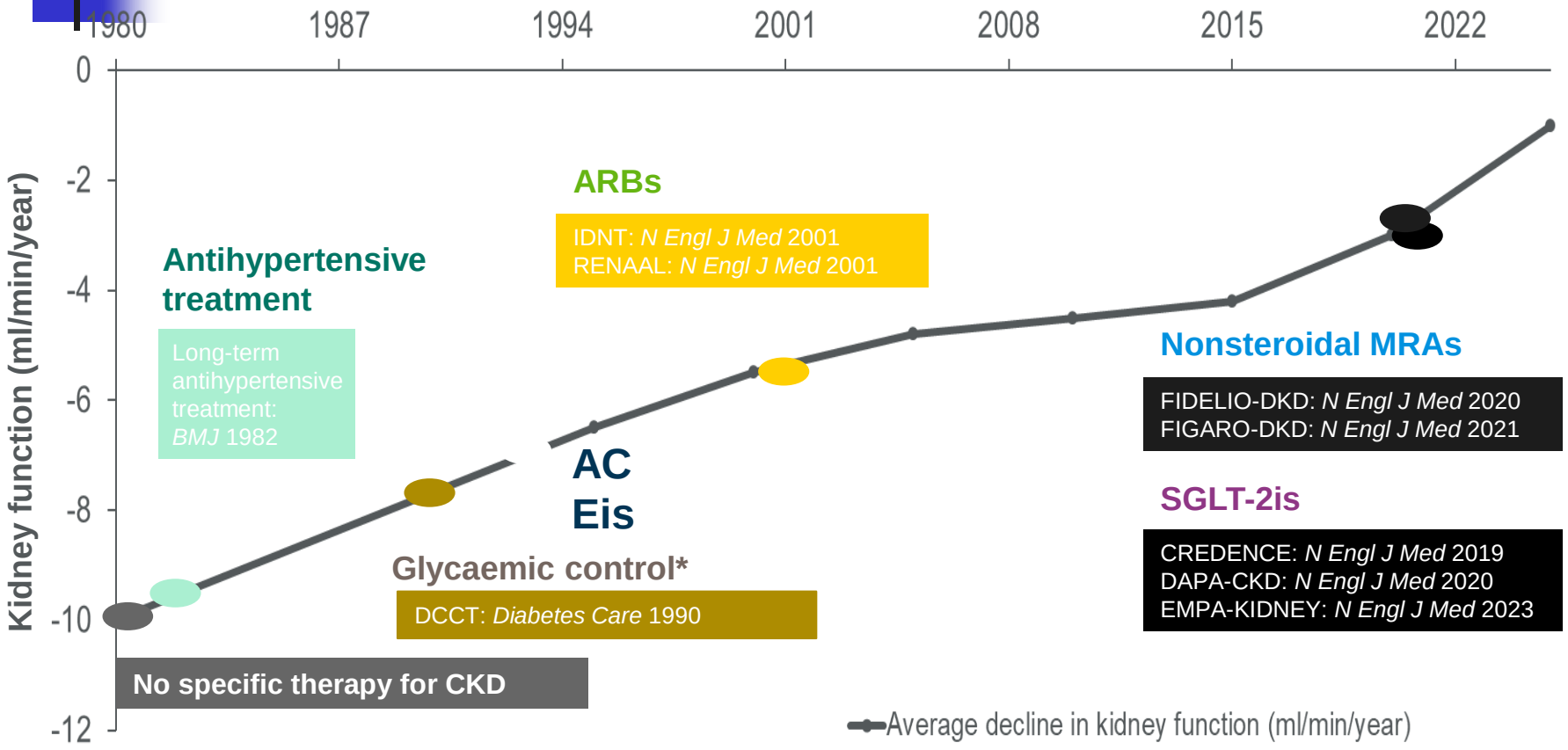
de Boer et al. Kidney Int. 2022;102:974-989. https://doi.org/10.2337/dci22-0027

Key points 2

- Diagnosis of CKD (and DN): Urine albumin measurement (preferably UACR in a random sample). Calculation of eGFR (CKD-EPI Equation).
- In DM DKD is largely under-diagnosed. The frequency of measuring UACR and eGFR (only in 47 and 88 % respectively) is unsatisfactory.
- Nephrologists have a key role in establishing UACR measurement and a timely screening.

ADD-CKD, Awareness, Detection and Drug Therapy in Type 2 Diabetes and Chronic Kidney Disease
Szczech LA, et al. PLoS One 2014;9:e110535

Prevention of CVD and DKD in T2D during the last 40-years

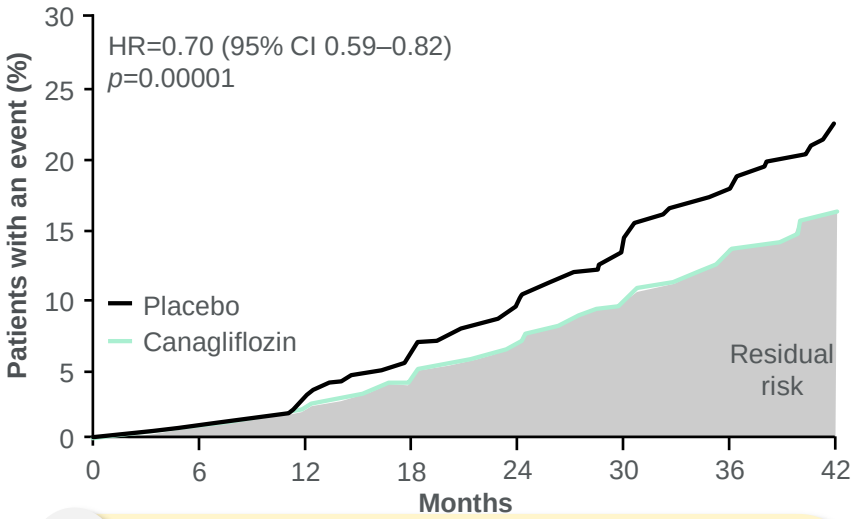


Recent findings on the cardiorenal benefits of finerenone and SGLT-2is have changed the therapeutic landscape for CKD and T2D

*Microvascular complications.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.
Adapted from Naaman SC & Bakris GL. In: Chronic Kidney Disease and Type 2 Diabetes. Arlington: American Diabetes Association; 2021. p28–32.

In DKD risk remains still very high

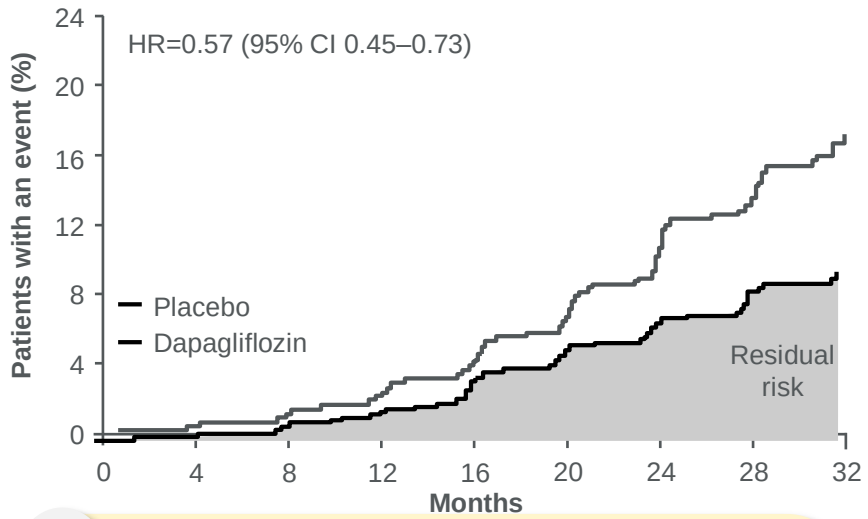
CREDENCE: Canagliflozin (+ ACEi/ARB) vs placebo[1]



Patients with DN eGFR 30-90 and UACR 300
Patients with severely increased albuminuria: 88%
Median UACR: 927 mg/g

Primary composite outcome:
Kidney failure, doubling of SCr or death from kidney/CV causes

DAPA-CKD: Dapagliflozin (+ACEi/ARB) vs placebo (T2D subgroup)[2]



Patients with DN eGFR 25-75 UACR >200
Severely increased albuminuria: 89.7%
Median UACR: 949 mg/g

Secondary composite renal outcome:
Sustained ≥50% eGFR decline, ESKD or renal death

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; UACR, urine albumin-to-creatinine ratio; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine

1. Perkovic V, *et al*. *N Engl J Med* 2019;380:2295–2306; 2. Wheeler DC, *et al*. *Lancet Diabetes Endocrinol* 2021;9:22–31

Pathogenesis and treatment of DKD[1-3]

ACEis and ARBs[4,5]
Thiazide-like diuretics and dihydropyridine Ca^{2+} channel blockers[4,5]
SGLT-2is[6–9]

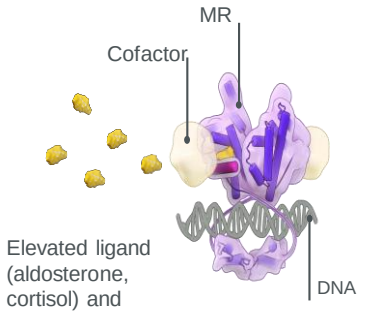
Haemodynamic[1,2] (elevated BP and/or intraglomerular pressure)

Current therapies for patients with CKD and T2D primarily target haemodynamic and metabolic factors

SGLT-2is[9,10]
GLP-1RAs[10]
Metformin[10]
Other anti-hyperglycaemic agents[10]

Metabolic[1,2] (poor glycaemic control)

MR *overactivation*

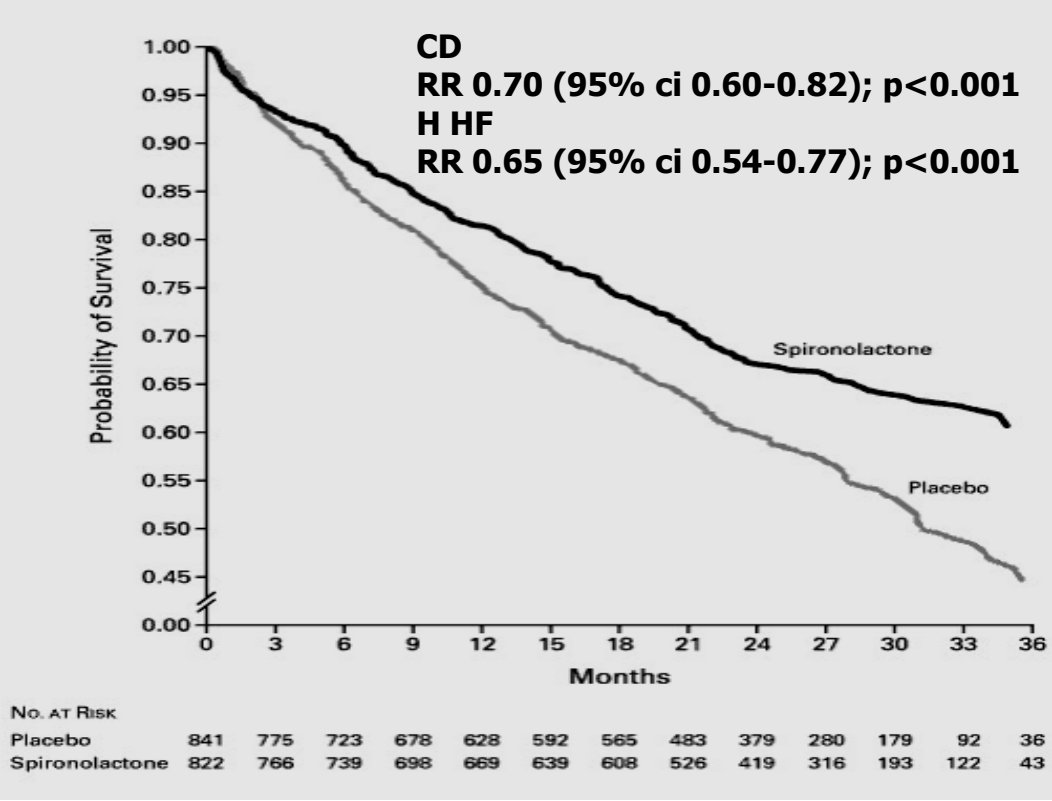


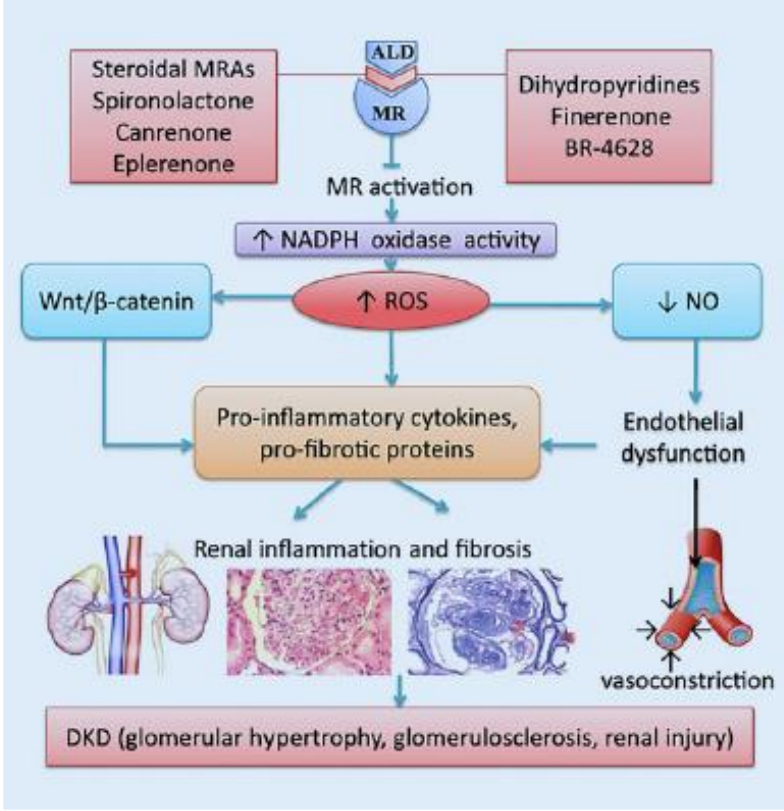
In T2D, MR overactivation may contribute to CKD progression[11,12]

BP, blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; MoA, mechanism of action

1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263; 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 & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 8. Heerspink HJ, *et al. Circulation* 2016;134:752–772; 9. Zelniker TA & 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

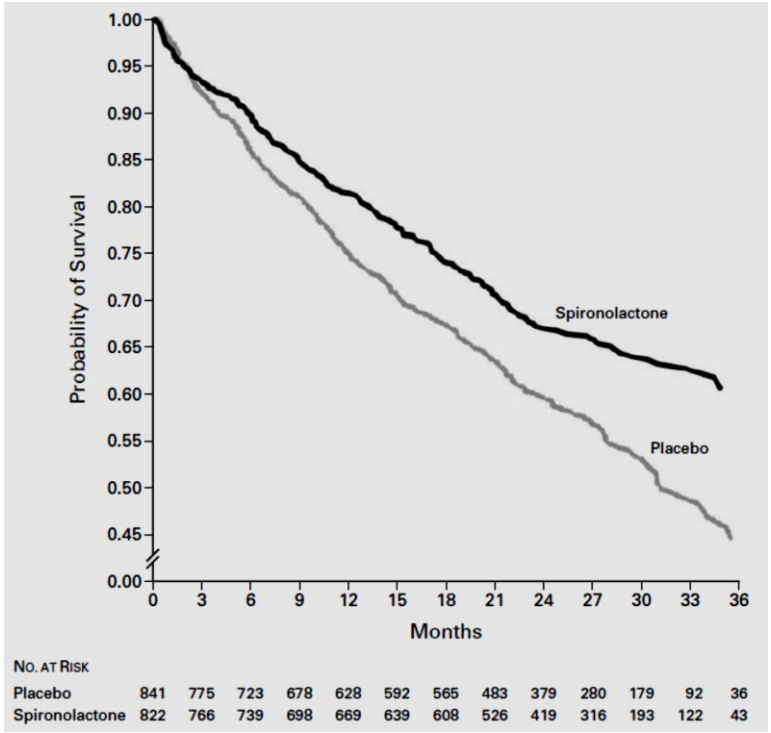
Aldosterone (steroidal AMR)

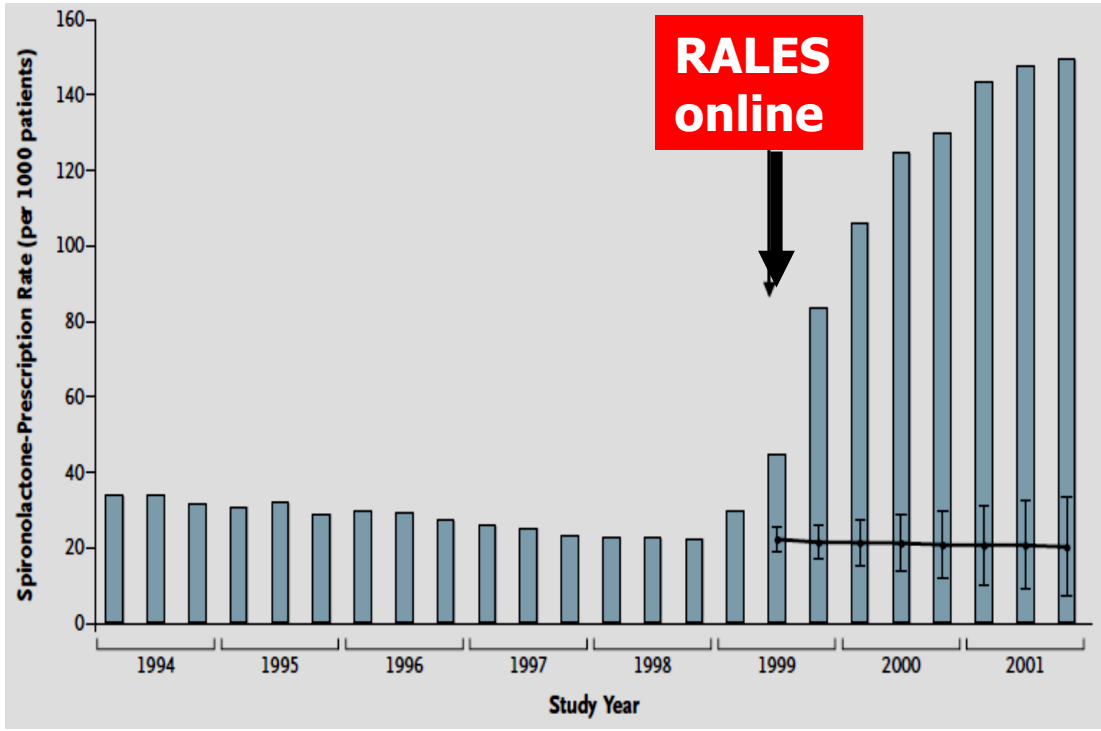




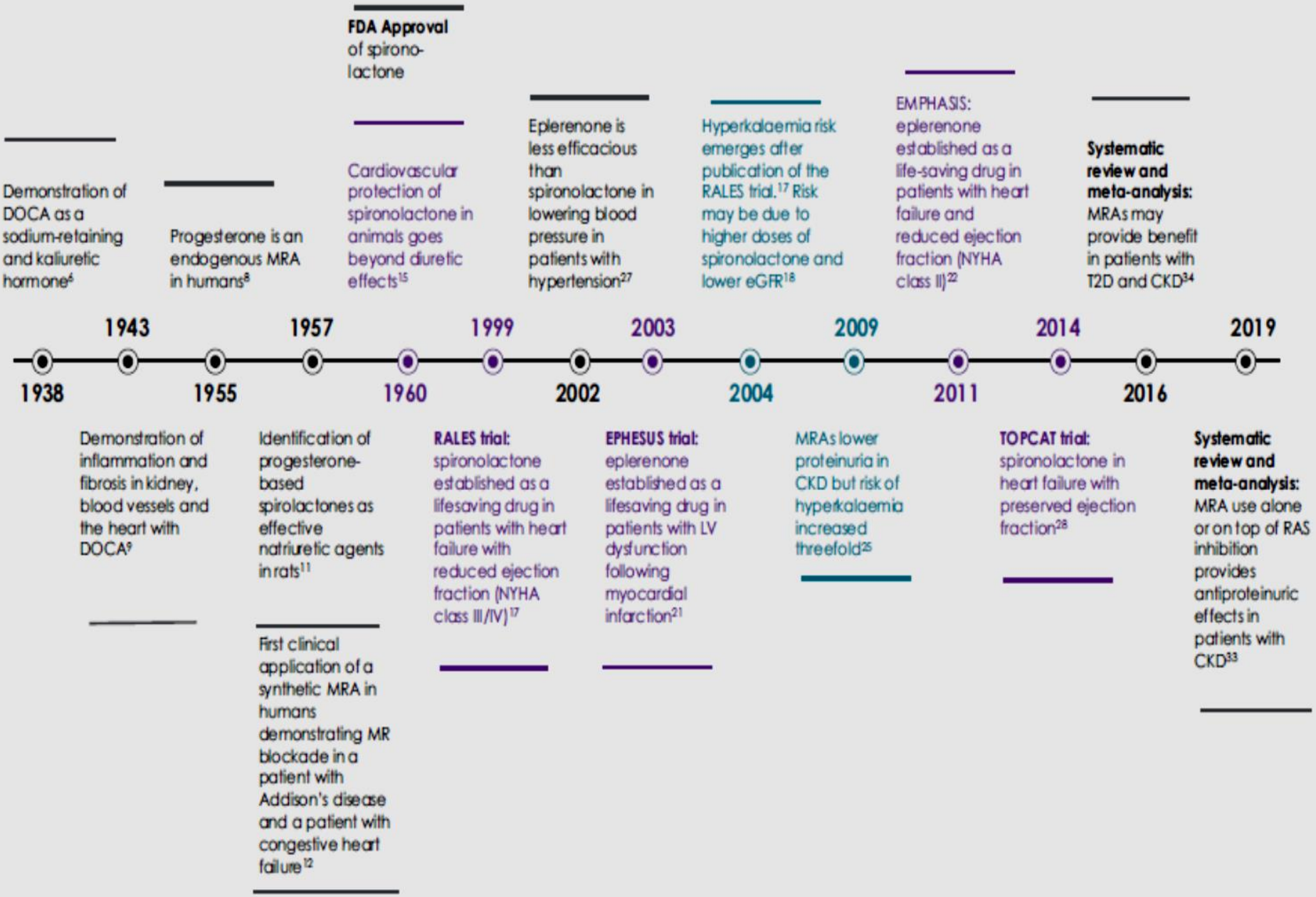
Pitt et al. Randomized Aldactone Evaluation Study. N Engl J Med. 1999;341:709-17.
Haller H. Herz. 2022;47:401-409.

RALES and hospitalization due to hyperkalemia





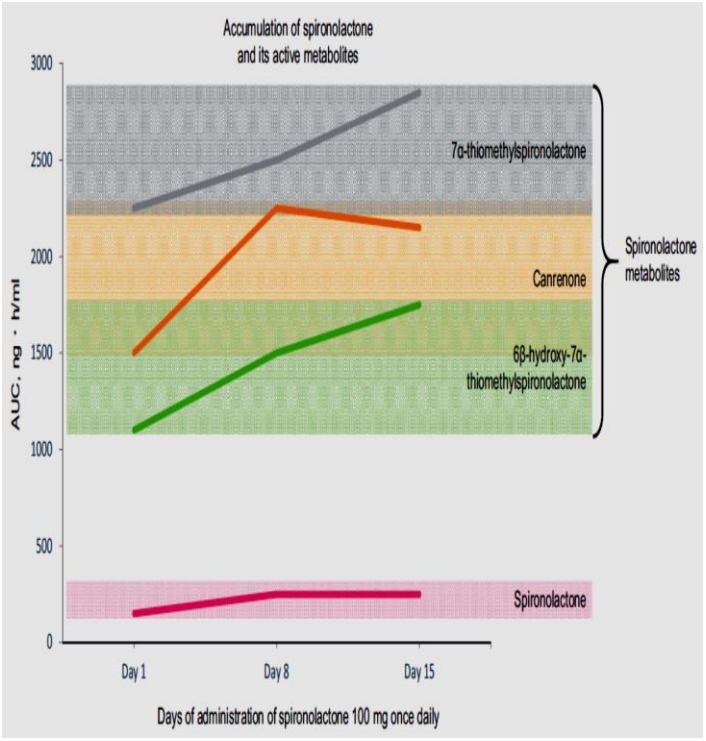
Pitt B, et al; for Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-717.
Juurlink DN, et al. N Engl J Med. 2004;351(6):543-551.



Agarwal et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J. 2021;42:152-161.

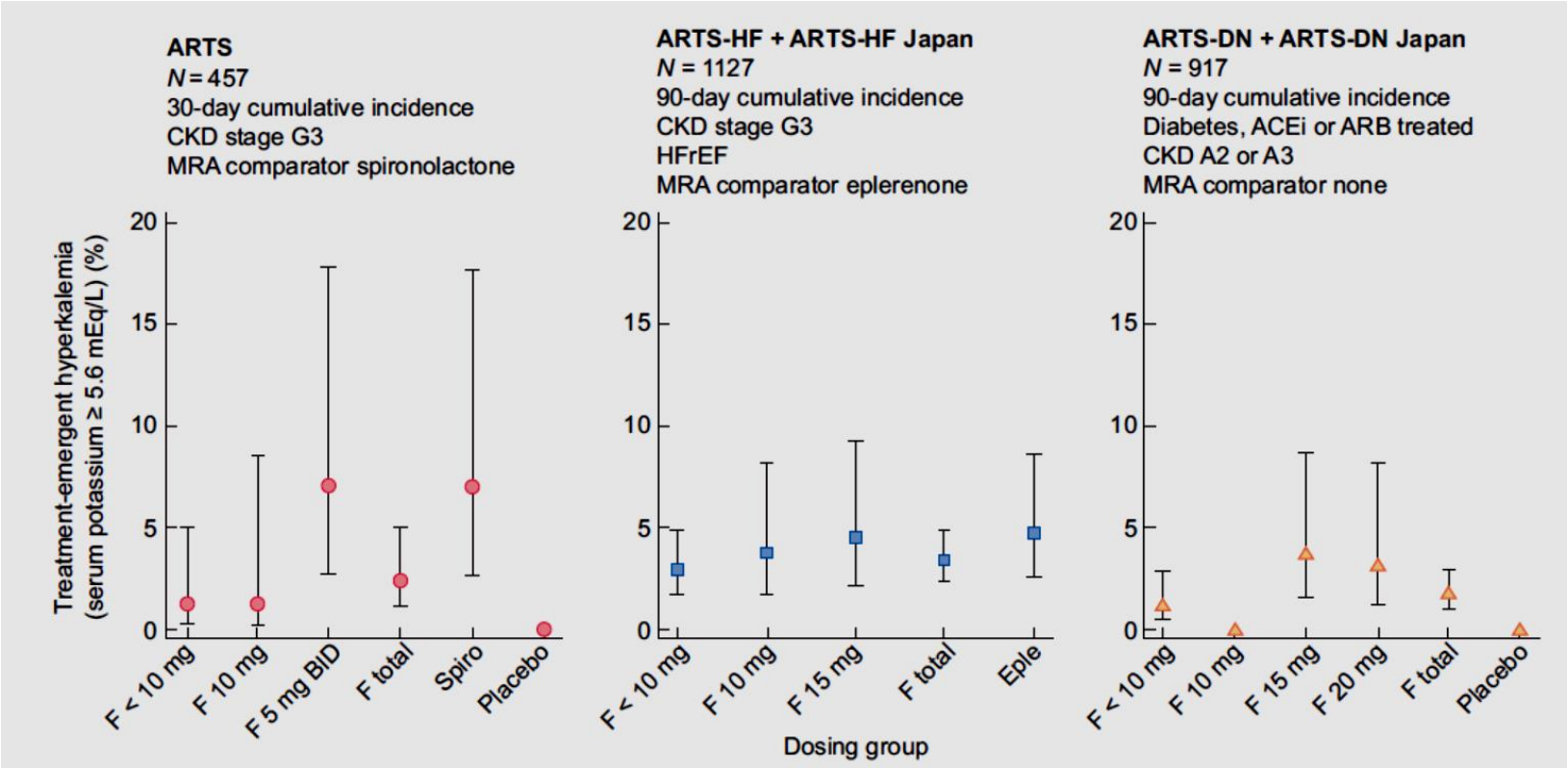
Finerenone vs. Non-steroidal MRA

	Steroidal MRA		Non-steroidal MRA
	Spironolactone	Eplerenone	Finerenone
Active metabolites	Yes	No	No
Half-life	≥24 h	4-6 h	2.8 h
Distribution (kidney-heart)	>6:1	≈3:1	1:1
Antagonism over MR			
Power	High	Low	High
Selectivity	Low	Medium	High (Bulky [large] and passive)
Effect on recruitment of cofactors (without aldosterone)	Partial agonist	Partial agonist	Inverse agonist
Effect on recruitment of cofactors (with aldosterone)	Inhibition	Inhibition	Blocking
Effect on inflammation and fibrosis	Moderate	Moderate	High
Blood pressure reduction	Marked	Marked	Moderate (greater at high doses)
Effect on proteinuria and kidney damage	Moderate	Moderate	Powerful
Hyperkalemia risk	High	High	Moderate
Other adverse effects	Gynecomastia		



González-Juanatey et al. Cardiorenal benefits of finerenone: protecting kidney and heart. Ann Med. 2023;55:502-513.
Agarwal et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J. 2021;42:152-161.

Hyperkalemia moderate



Agarwal et al. Nephrol Dial Transplant. 2022;37:1014-1023.

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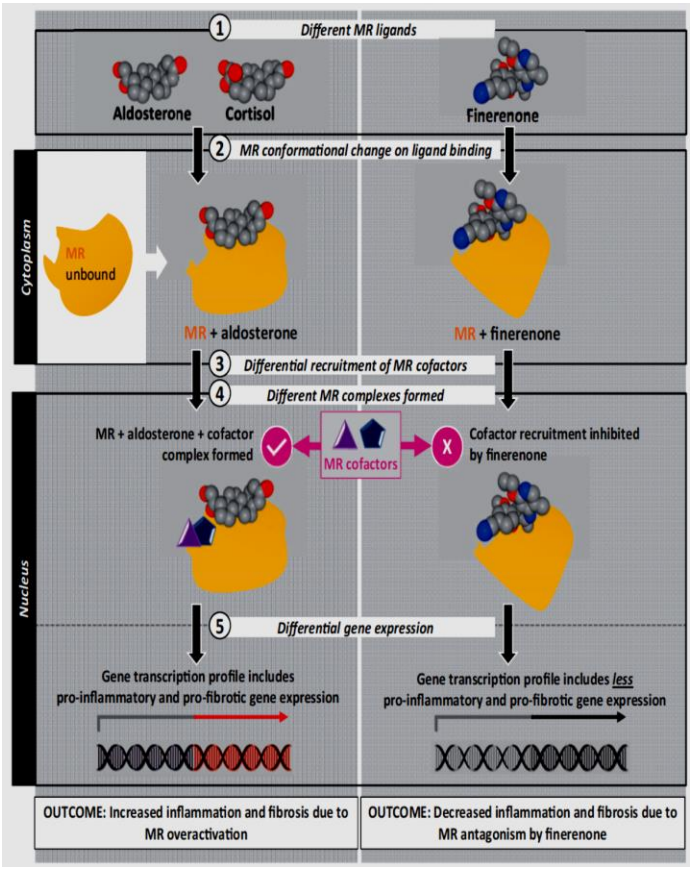

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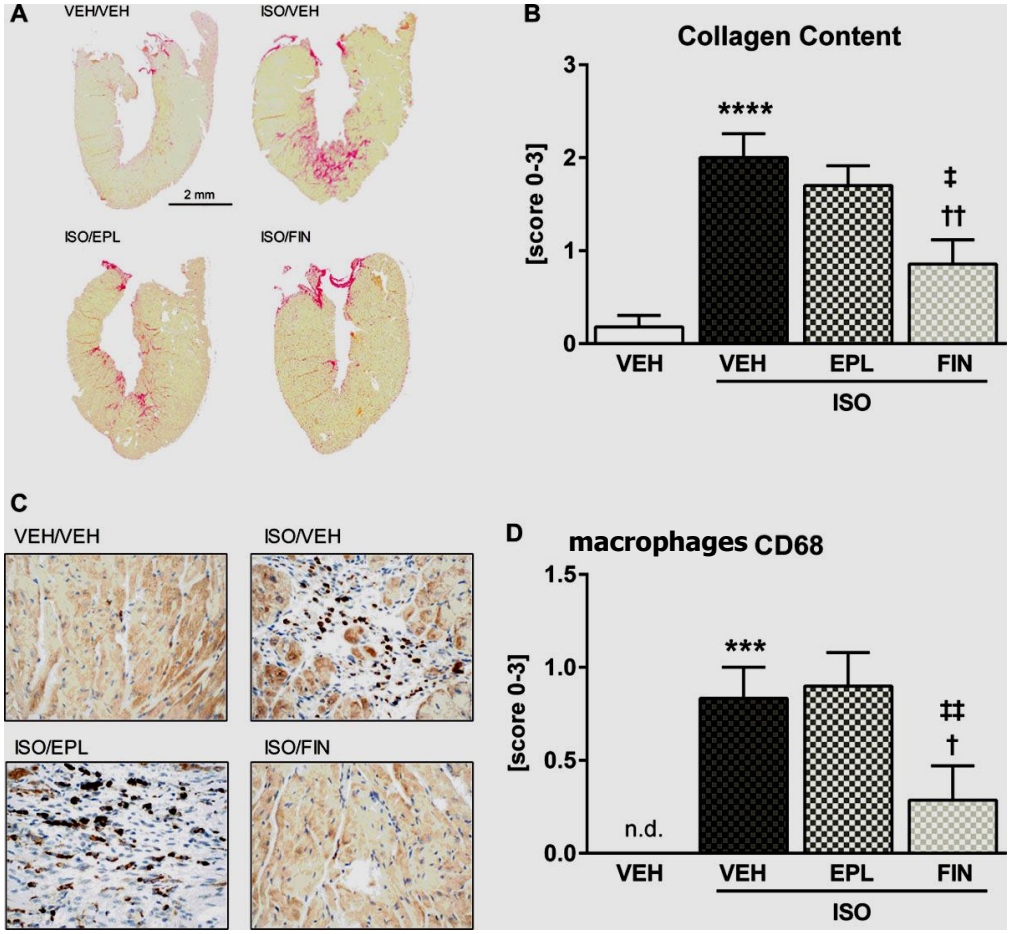
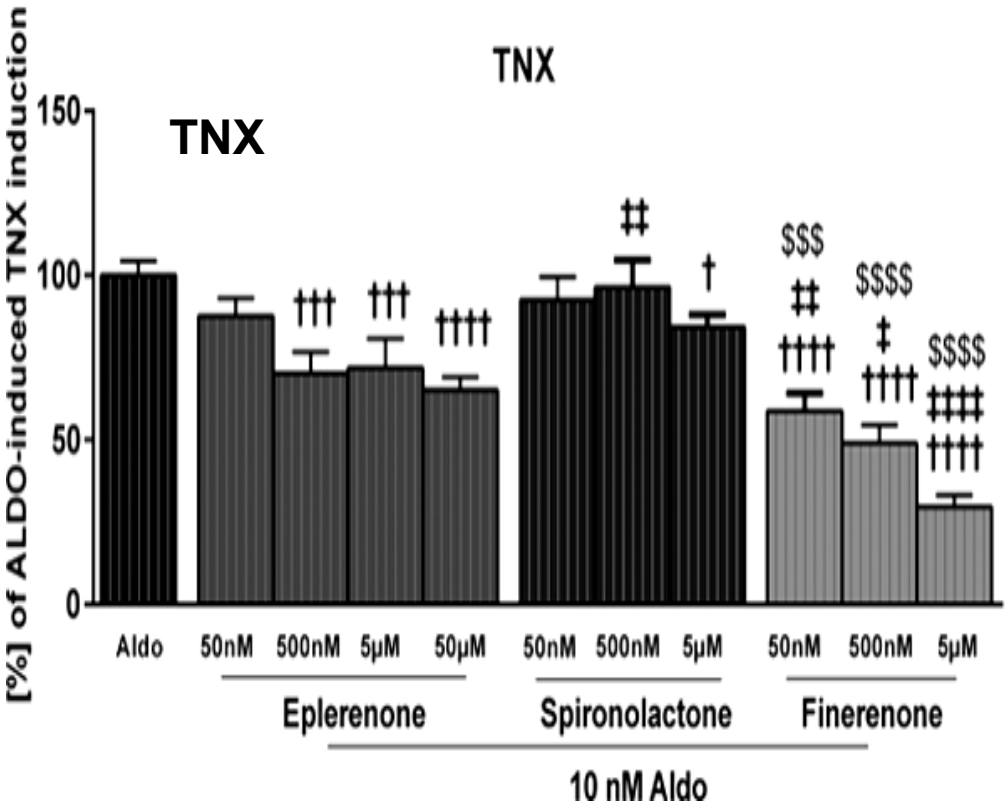
Selective Mineralocorticoid Receptor Cofactor Modulation – Molecular Basis for Antifibrotic Activity of Finerenone



- Isoproterenol-infused mice an experimental model of cardiac fibrosis and hypertrophy.
- Fibrosis and heart collagen content is inhibited by finerenone, not eplerenone. The same effect is seen on macrophage content.

Grune et al. Hypertension. 2018;71:599-608.

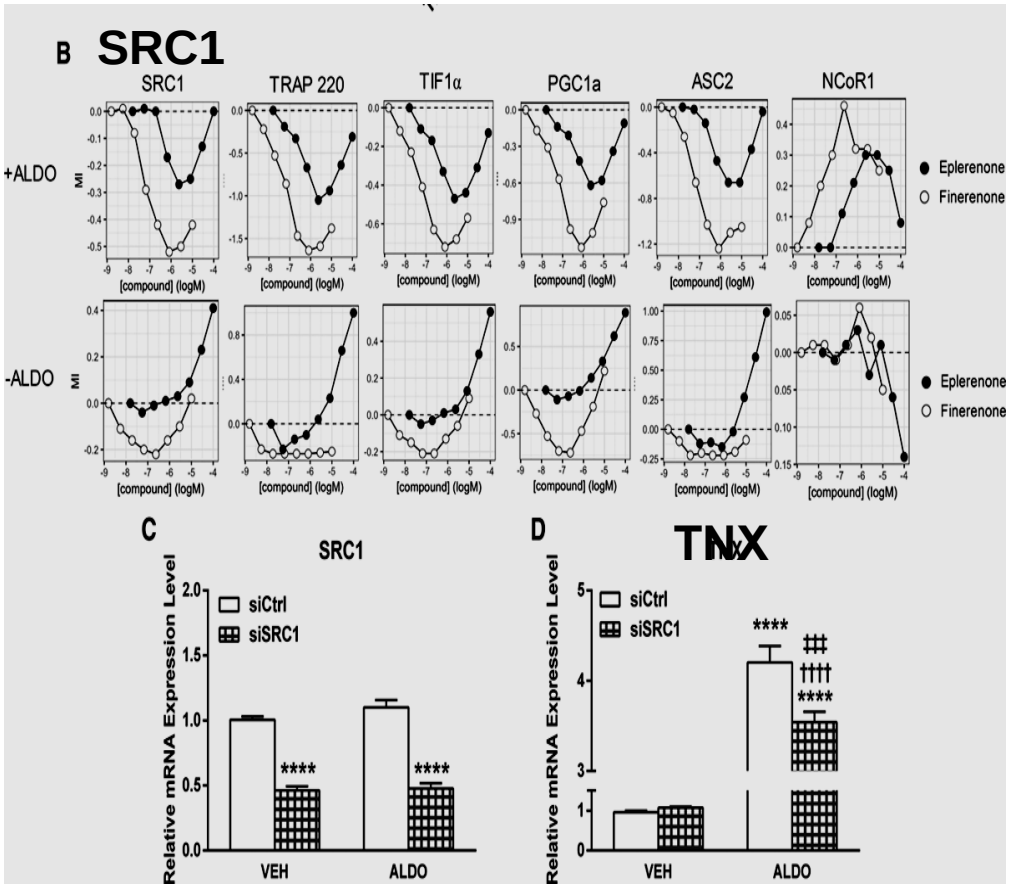
Selective Mineralocorticoid Receptor Cofactor Modulation – Molecular Basis for Antifibrotic Activity of Finerenone



- In culture of cardiac cells the same effect. TNX a fibrosis inducing factor in cellular level is significantly reduced by finerenone.
- Finerenone has higher MR activity and inverse agonist activity. It inhibits and practically blocks binding of MRA cofactors.
- The inhibition of fibrosis is attributed to the latter effect of finerenone on MR binding of cofactors.

Grune et al. Hypertension. 2018;71:599-608.

Selective Mineralocorticoid Receptor Cofactor Modulation – Molecular Basis for Antifibrotic Activity of Finerenone



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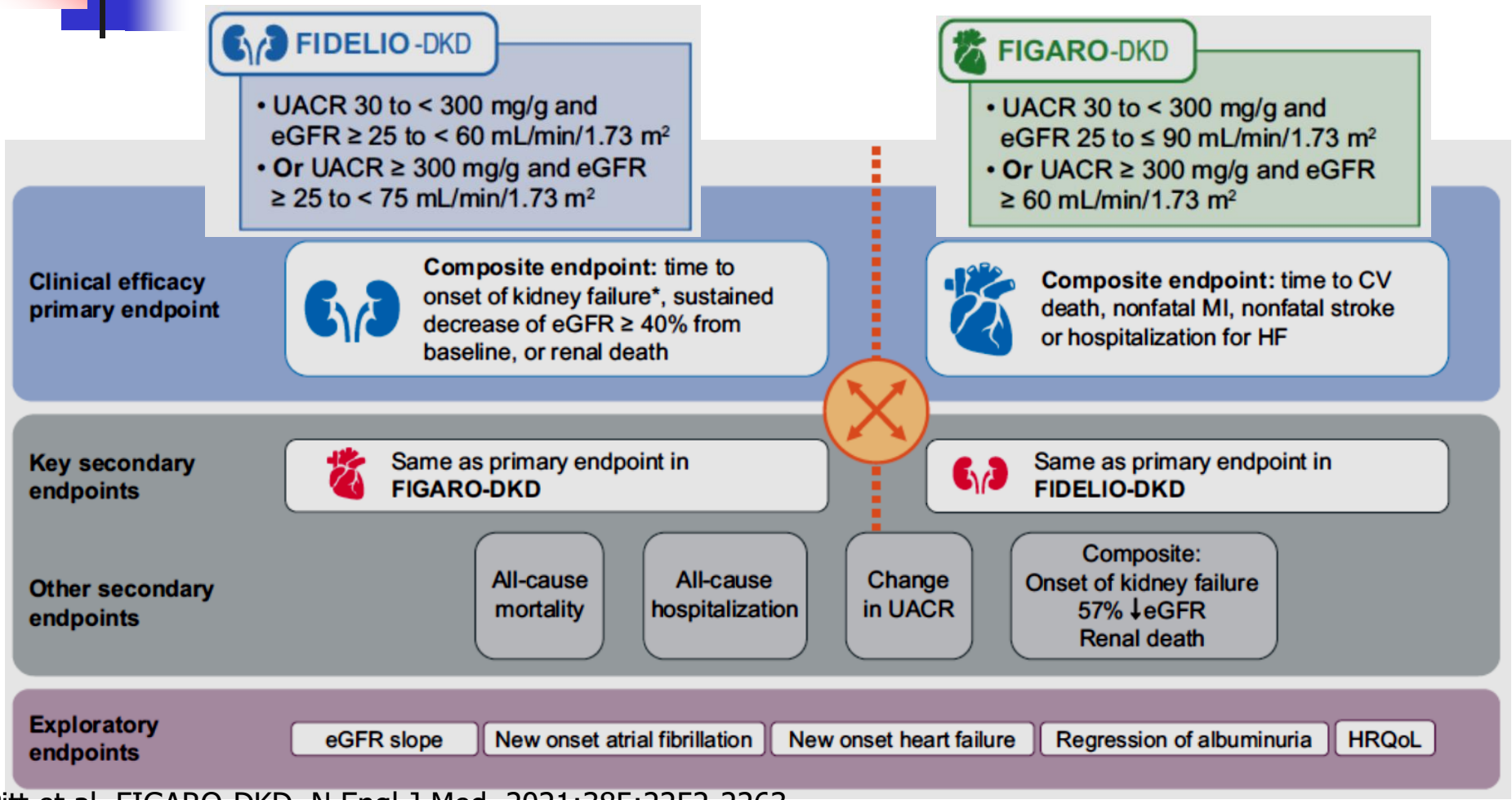
- The inhibition of fibrosis is attributed to the latter effect of finerenone on MR binding of cofactors.

Grune et al. Hypertension. 2018;71:599-608.

Key points 3

- Finerenone is a non-steroidal powerful and selective MRA.
- It is characterized by a short half life (2.8h), low concentration in the kidneys vs. the heart.
- In Finerenone MRA-induced hyperkalemia is moderate.
- Finerenone acts as an inverse agonist blocking binding of active cofactors on MR.
- Inhibits more powerfully tissue fibrosis and inflammation.

Finerenone Phase 3 trials DKD: FIGARO, FIDELIO



Pitt et al. FIGARO-DKD. N Engl J Med. 2021;385:2252-2263.
Bakris et al. FIDELIO-DKD. N Engl J Med. 2020;383:2219-2229.

Finerenone (non-steroidal AMR)

RESEARCH SUMMARY

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

Pitt B et al. DOI: 10.1056/NEJMoa2110956

Clinical Problem

Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, improves cardiorenal outcomes in patients with stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. Whether finerenone is beneficial in patients with diabetes and less-advanced CKD is unclear.

Clinical Trial

Design: A phase 3, multicenter, randomized, placebo-controlled trial examined the efficacy and safety of finerenone in adults with type 2 diabetes and a range of CKD stages.

Intervention: 7437 patients with diabetes and CKD treated with a maximum-dose renin–angiotensin system inhibitor were assigned to receive oral finerenone or placebo. Eligible patients had persistent, moderately elevated albuminuria plus an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m^2 (stage 2 to 4 CKD) or persistent, severely elevated albuminuria plus an eGFR of at least 60 ml per minute per 1.73 m^2 (stage 1 or 2 CKD). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

Results

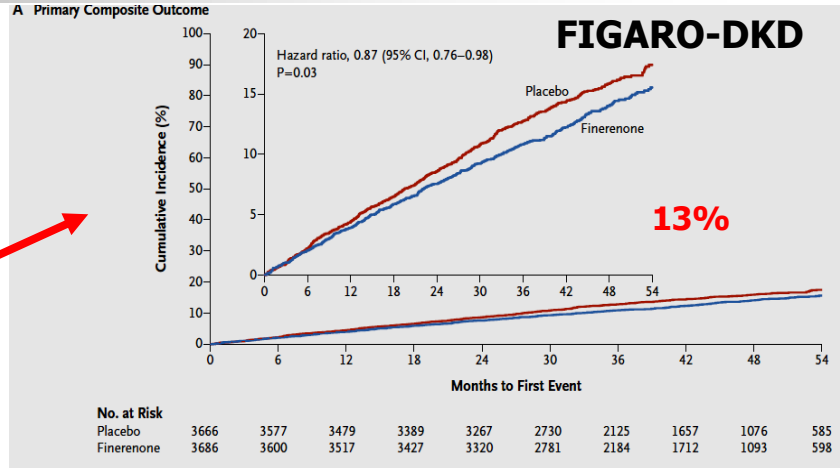
Efficacy: During a median 3.4 years of follow-up, the incidence of primary outcome events was lower with finerenone than with placebo, a difference driven mainly by a lower incidence of hospitalization with finerenone.

Safety: The incidence of serious adverse events was similar in the two groups. Hyperkalemia occurred more often with finerenone but did not result in any deaths and rarely resulted in treatment discontinuation.

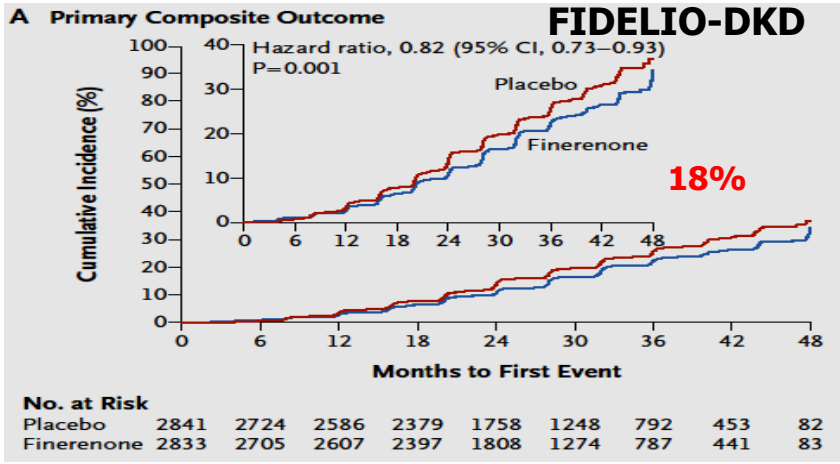
Limitations and Remaining Questions

- Few Black patients were included. Patients with symptomatic heart failure with a reduced ejection fraction were excluded.
- Current clinical guidance recommends sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes and CKD. Whether using finerenone with these agents offers additive cardiorenal benefits is unclear.

Links: Full Article | NEJM Quick Take



N=7352, Median follow up **3.4 years**



N=5674, Median follow up **2.6 years**

Pitt et al. FIGARO-DKD. N Engl J Med. 2021;385:2252-2263.
Bakris et al. FIDELIO-DKD. N Engl J Med. 2020;383:2219-2229.

Finerenone – FIDELITY

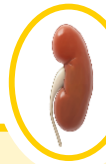
FIDELITY

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** (HR=0.86; 95% CI 0.78–0.95; *p*=0.002)[1]

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



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

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

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

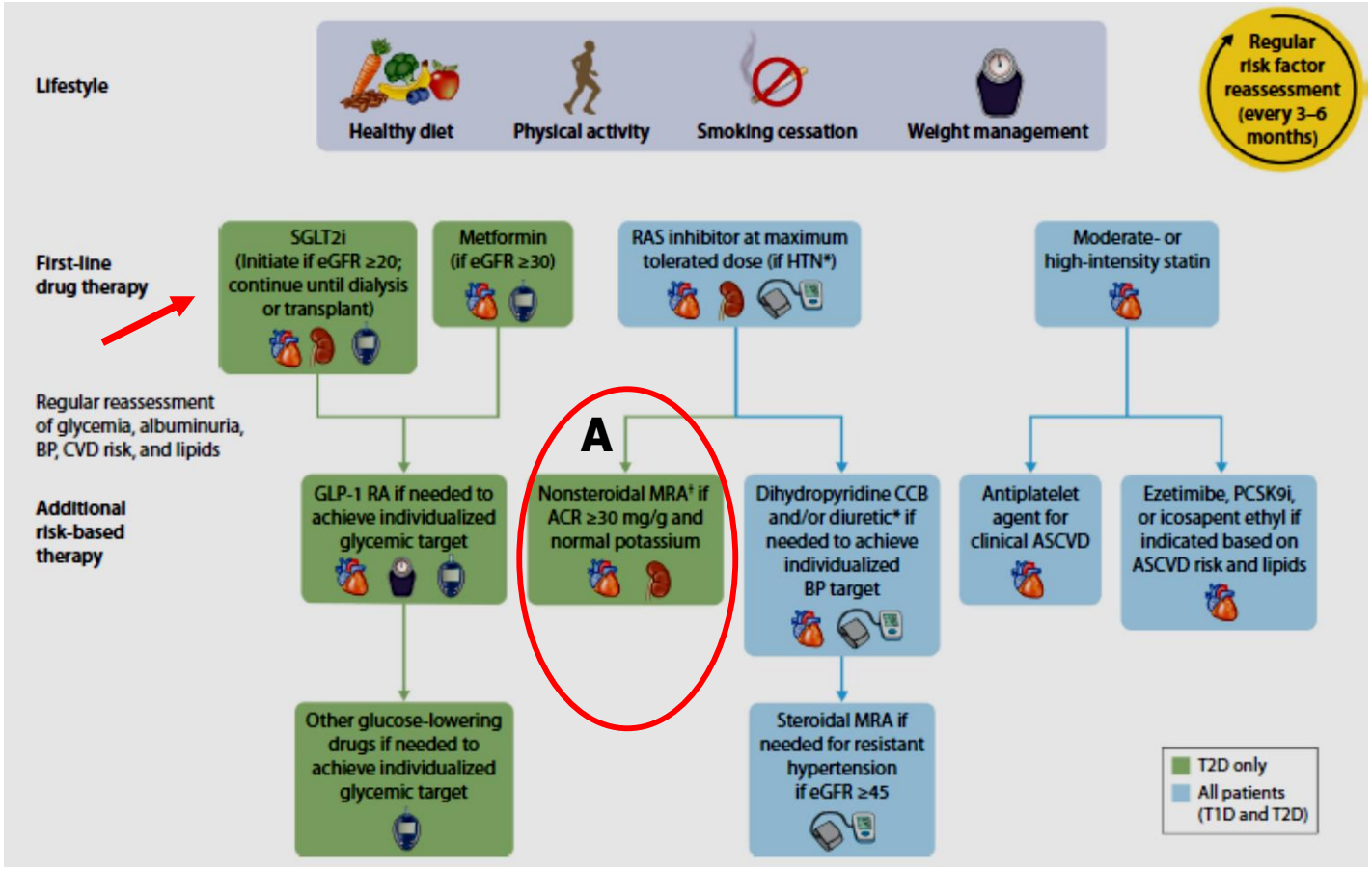
Finerenone is indicated for the treatment of CKD (with albuminuria) associated with T2D in adults[2]

*First HHF defined as first event after randomisation; [#]ESKD or an eGFR <15 ml/min/1.73 m^2; 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; [‡]analysis for *p*-value not prespecified.

HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure; KRT, kidney replacement therapy; LS, least-squares

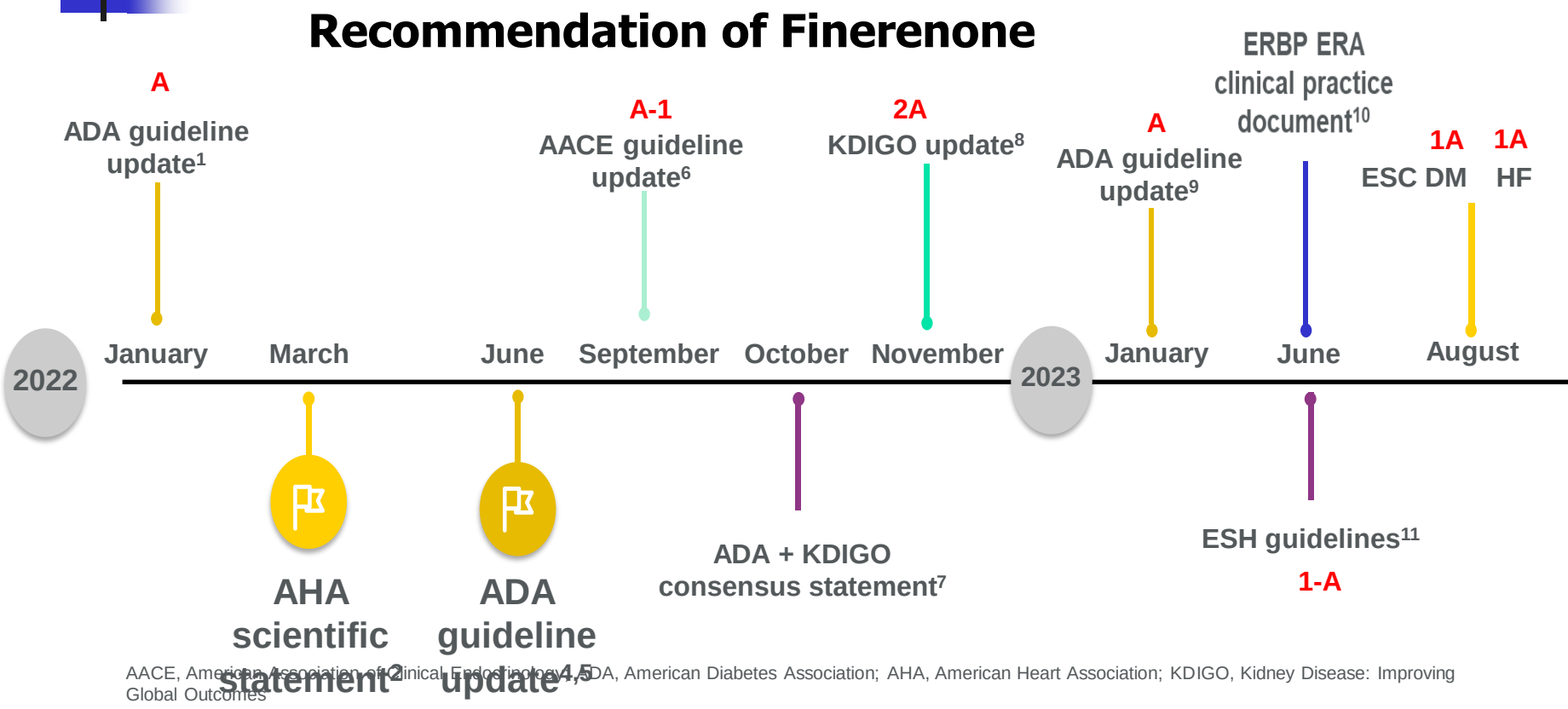
1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 2. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 23 Mar 2023]

Consensus ADA, KDIGO



de Boer et al. Kidney Int. 2022;102:974-989.

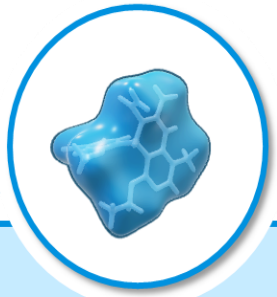
Update of guidelines



AACE, American Association of Clinical Endocrinology; ADA, American Diabetes Association; AHA, American Heart Association; KDIGO, Kidney Disease: Improving Global Outcomes

1. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1); 2. Joseph JJ, *et al. Circulation* 2022;145:e722–e759; 3. Kidney Disease: Improving Global Outcome (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease – Public Review Draft; March 2022; 4. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S144–S174 (Addendum) 5. American Diabetes Association. Diabetes Care 2022;45(Suppl 1);S175–S184 (addendum); 6. Blonde L *et al. Endo Practice* 2022;28:923–1049; 7. de Boer IH, *et al. Diabetes Care* 2022;45:3075–3090; 8. Kidney Disease: Improving Global Outcomes. *Kidney Int* 2022;102:S1–S128; 9. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202; 10. Sarafidis PA et al. Clin Kidney J 2023; doi:10.1093/ckj/sfad139; 11. Mancia G et al. J Hypertens 2023; doi:10.1097/HJH.0000000000003480

Key points 4



Finerenone is a selective nonsteroidal MRA that has been shown to provide **CV and kidney benefits** in **patients with CKD and T2D**[1,2]

Finerenone slows CKD progression and reduces CV risk in a broad range of patients with **CKD and T2D**[1]

Finerenone reduces UACR by >30% and has cardiorenal benefits in patients across the spectrum of CKD severity[4–6]

Major clinical guidelines recommend finerenone as a therapeutic option **to reduce CKD progression and CV events** in people with CKD and T2D[3,4]

1. Fox CS, *et al. Lancet* 2013;381:532–533; 2. Matsushita K, *et al. Lancet* 2013;375:2073–2081; 3. Mernagh P, *et al. ERA* 2022; abstract MO375;
4. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 5. Ruilope LM, *et al. Nephrol Dial Transplant* 2023;38:372–383; 6. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263

Case with T2D and CKD

Maria*

- 67-year-old female
- T2D for 6 years
- Newly diagnosed CKD

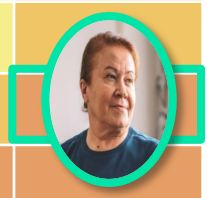
- HbA1c 7.8%
- Blood pressure 137/84 mmHg

- eGFR 54 ml/min/1.73 m^2
- UACR 380 mg/g
- Serum [K^+] 4.3 mmol/l

- Glycaemic control including SGLT-2i
- Anti-hypertensive treatment including maximum tolerated dose of RASi

Albuminuria categories (mg albumin/g creatinine)[1]

GFR categories (ml/min/1.73 m^2)	A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
	<30 mg/g <3 mg/mmol	30–300 mg/g (3–30 mg/mmol)	>300 mg/g (>30 mg/mmol)

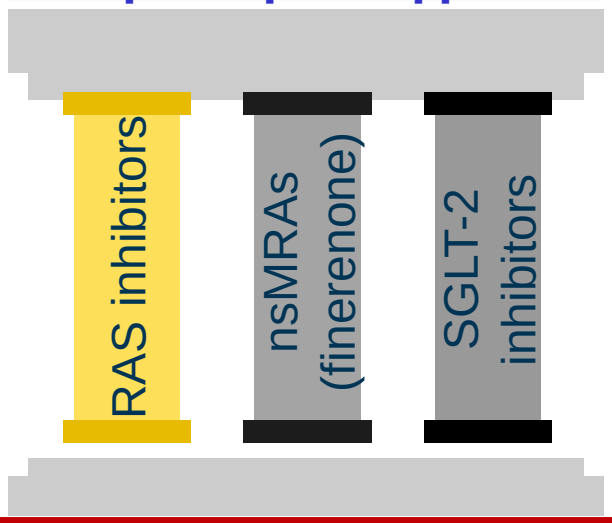


What would be the expected benefits of adding finerenone to Maria's treatment regimen?

*Fictitious patient case
GFR, glomerular filtration rate
1. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2022;102:S1–S128

Three pilars of EBT and GDMT

Proposed pillar approach[1]



Maximum tolerated doses of RASi with an SGLT-2i and finerenone should provide maximal benefit to slow CKD progression and reduce CV outcomes#

- eGFR 54 ml/min/1.73 m^2
- UACR 380 mg/g

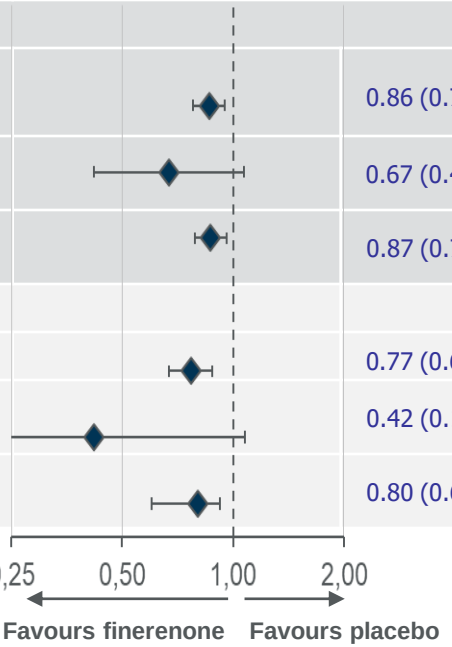
- RASi
- Finerenone
- SGLT-2i

*Patients with diagnosed HFrEF and NYHA II-IV were excluded from the finerenone phase III clinical studies (see section 5.1 of Kerendia (finerenone) SmPC);[2] #the CV outcomes referred to pertain to HHF risk in particular NYHA, New York Heart Association

1. Blazek O & Bakris GL *Am Heart J Plus* 2022;19:100187; 2. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 23 March 2023]

Finerenone and SGLT2i – FIDELITY

Endpoint	n/N (%)		n events per 100 PY		Hazard ratio (95% CI)	$p_{interaction}$
	Finerenone	Placebo	Finerenone	Placebo		
Composite CV outcome						
Overall	825/6519 (12.7)	939/6507 (14.4)	4.34	5.01	0.86 (0.78–0.95)	0.46
SGLT-2i at baseline	39/438 (8·9)	52/439 (11·8)	2·95	4·08	0.67 (0.42–1·07)	
No SGLT-2i at baseline	786/6081 (12·9)	887/6068 (14·6)	4·44	5·08	0.87 (0.79–0.96)	
Kidney composite outcome						
Overall	360/6519 (5.5)	465/6507 (7.1)	1.96	2.55	0.77 (0.67–0.88)	0.29
SGLT-2i at baseline	9/438 (2·1)	17/439 (3·9)	0·7	1·37	0.42 (0.16–1.08)	
No SGLT-2i at baseline	351/6081 (5·8)	448/6068 (7·4)	2·06	2·64	0.80 (0.69–0.92)	

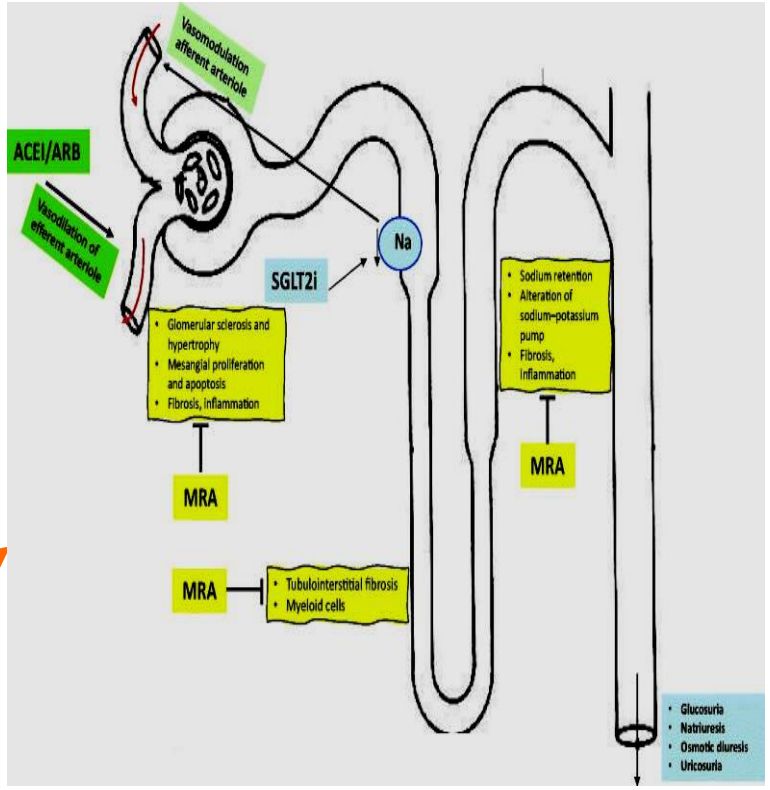


CI, confidence interval; CKD, chronic kidney disease; PY, patient year; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatine ratio

Rossing P, Anker SD, Filippatos G, et al. Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Sodium-Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis [published online ahead of print, 2022 Aug 15]. Diabetes Care. 2022;dc220294. https://doi.org/10.2337/dc22-0294

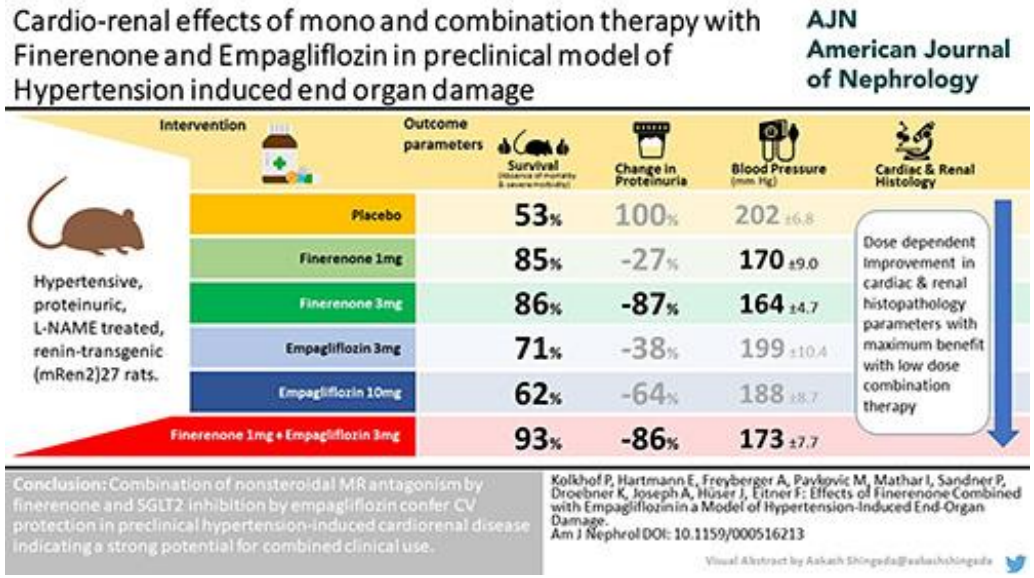
Finerenone and SGLT2i – FIDELITY

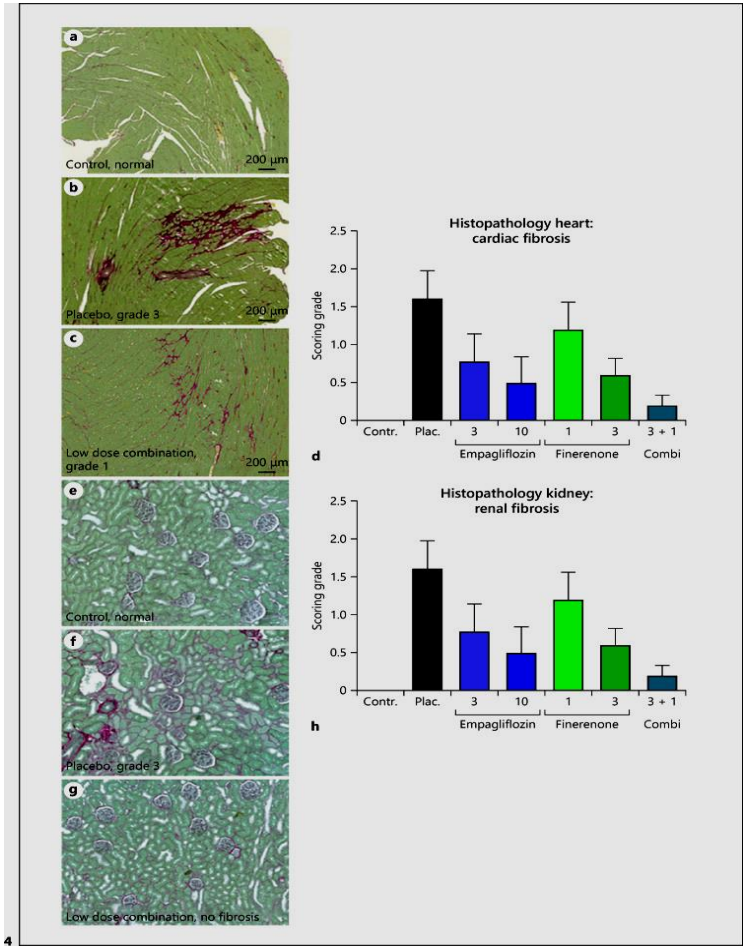
- FIDELITY among 13,026 patients with CKD in type 2 diabetes, 877 (6.7%) received SGLT2i at baseline and 1,113 (8.5%) received it during the study.
- Finerenone reduced the risk of cardiovascular and renal outcomes compared with placebo, and concomitant treatment with an SGLT2i at baseline or any time point of study did not modify observed results.
- The largely independent and complementary mechanisms of action of finerenone and SGLT2i are the basis for their effective and safe combined use.



Rossing P, Anker SD, Filippatos G, et al. Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Sodium-Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis [published online ahead of print, 2022 Aug 15]. Diabetes Care. 2022;dc220294. https://doi.org/10.2337/dc22-0294
González-Juanatey et al. Ann Med. 2023 Dec;55(1):502-513. doi: 10.1080/07853890.2023.2171110.

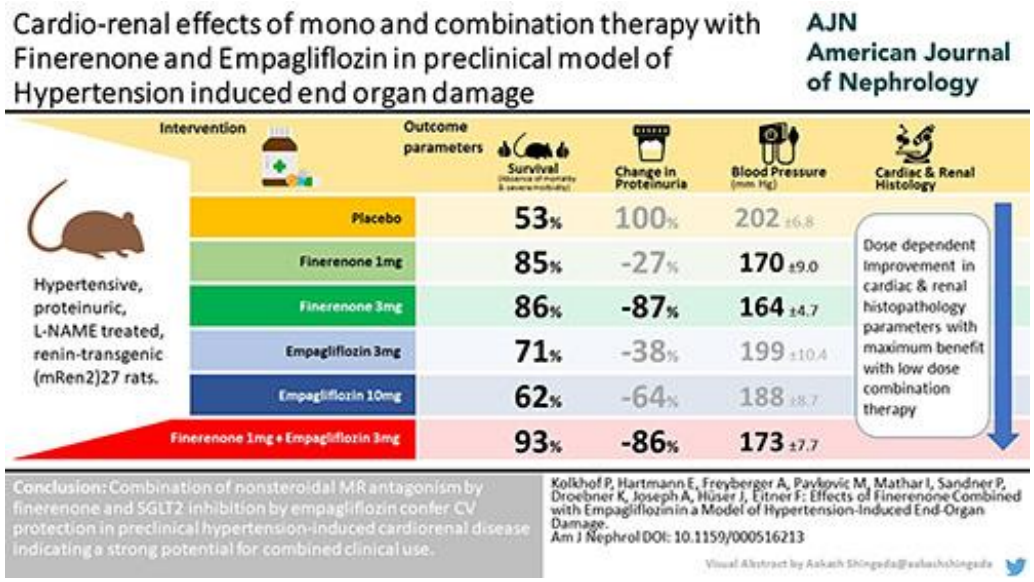
SGLT-2i and finerenone in a mouse hypertension model (end organ damage)

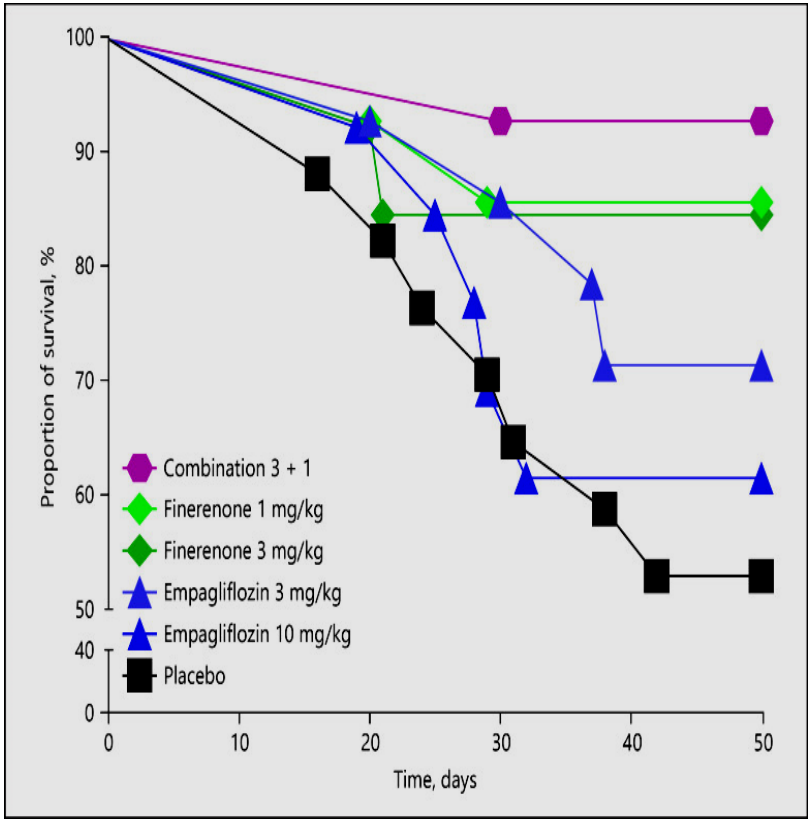




Kolkhof P, et al. Am J Nephrol 2021;52:642–652

SGLT-2i και φινερενόνη σε υπερτασικό μοντελο αρουραίου



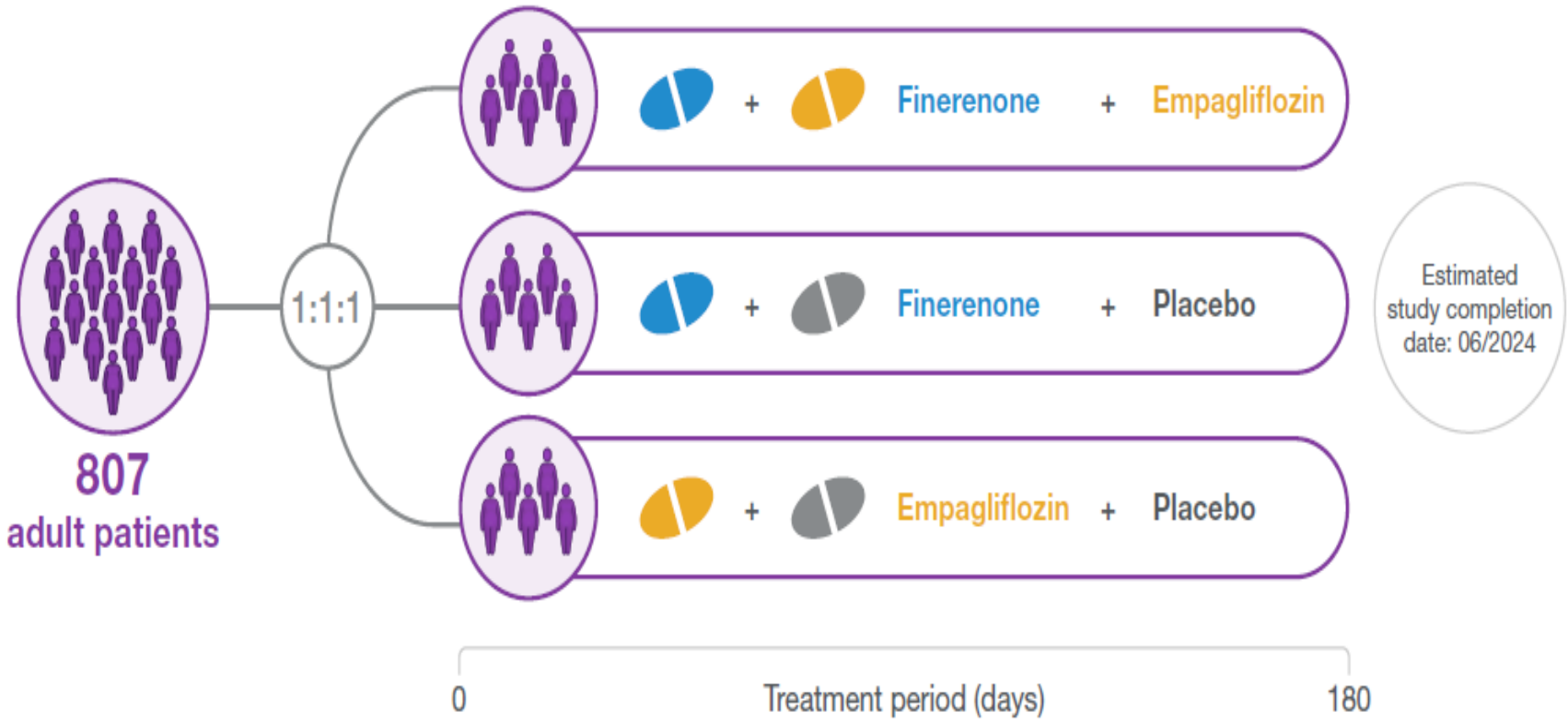


Kolkhof P, et al. Am J Nephrol 2021;52:642–652

CONFIDENCE

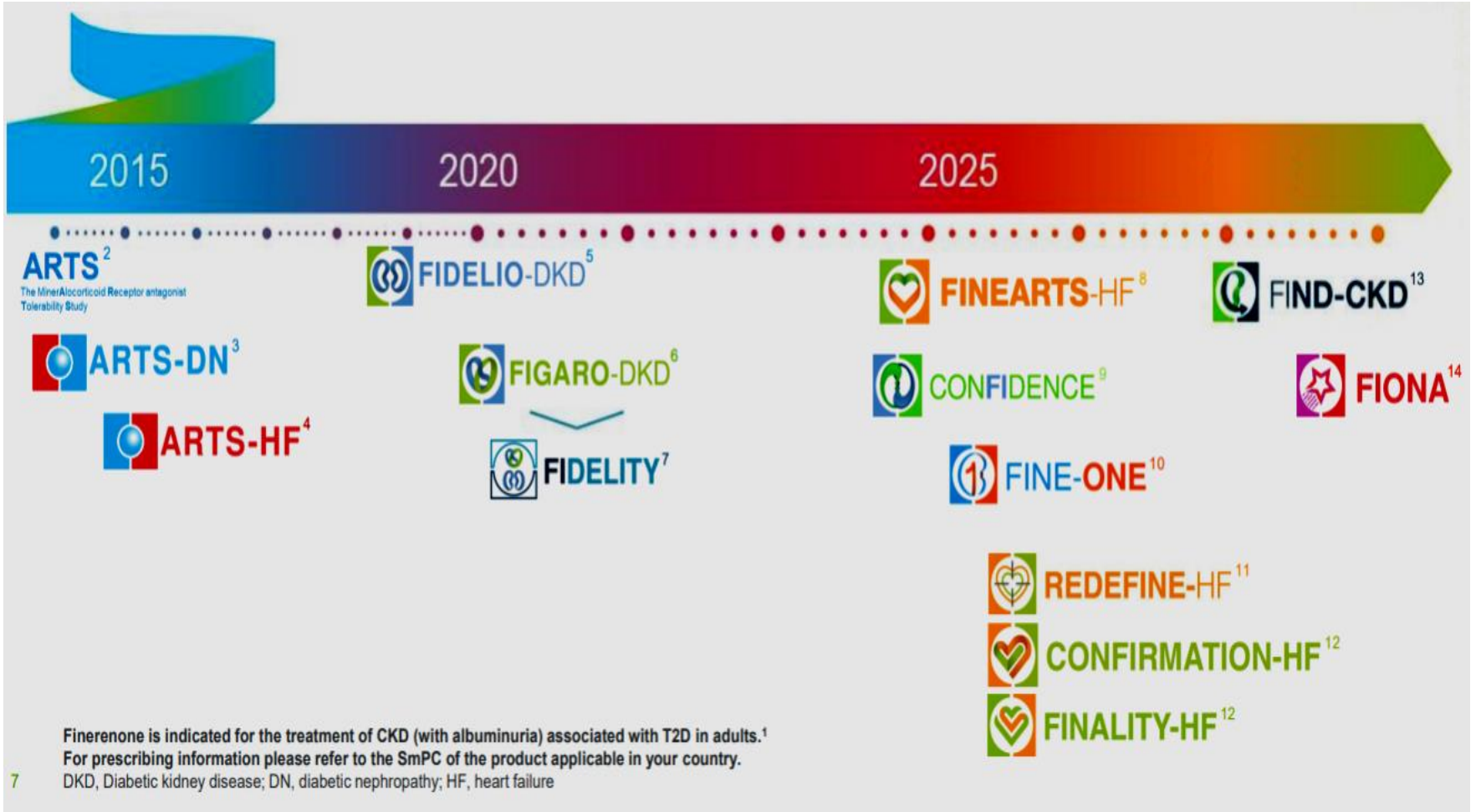
CKD and T2D
807 adult patients

Randomization and treatment



CKD, chronic kidney disease; T2D, type 2 diabetes

Studies on CV and renal outcomes are under way



Prerequisite for Finerenone treatment are serum K+ και eGFR

If serum [K^+] ≤4.8 mmol/l*

Maria's serum [K^+]: 4.3 mmol/l

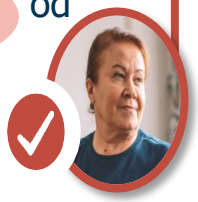
If eGFR ≥25 ml/min/1.73 m^2

Maria's eGFR: 54 ml/min/1.73 m^2

Maria can initiate treatment with finerenone

Starting dose: 10 mg od

(if eGFR is <60 ml/min/1.73 m^2)



Target and maximum recommended dose: 20 mg od

(and starting dose if eGFR ≥60 ml/min/1.73 m^2)

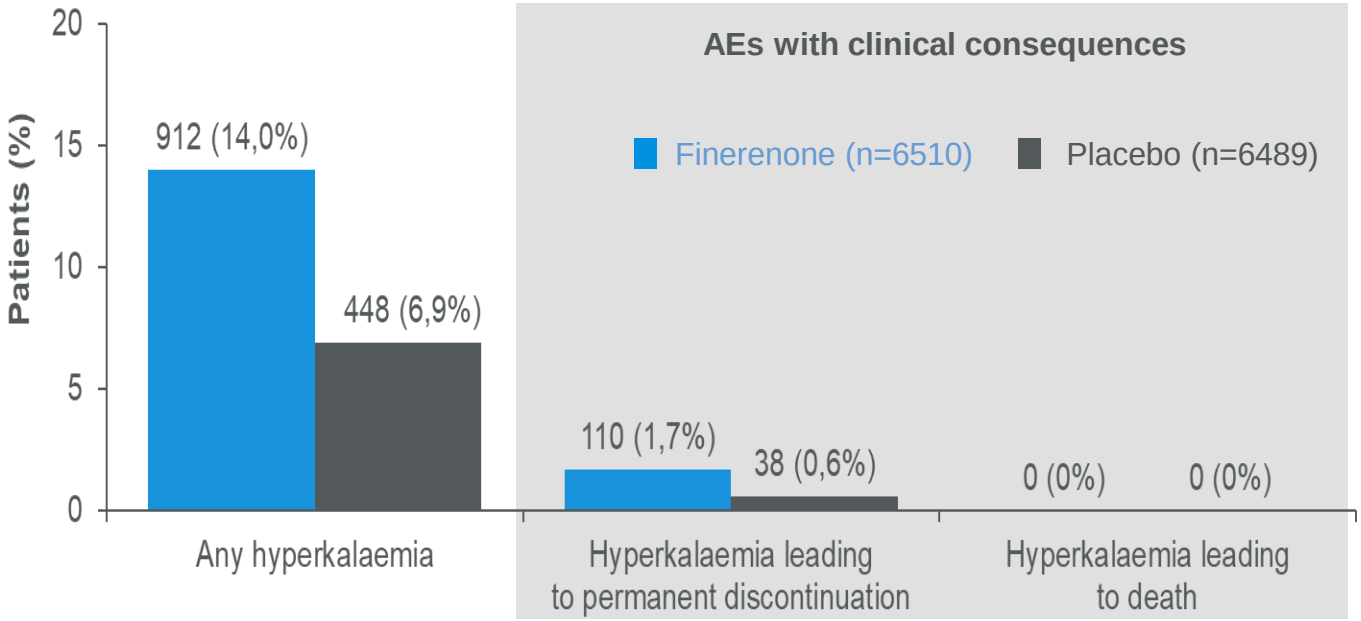
Treatment can be **maintained** in patients with an **eGFR ≥15 ml/min/1.73 $m^{2\#}$**

*If serum [K^+] is >4.8–5.0, initiation of finerenone may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum [K^+]; #if eGFR falls below 15 ml/min/1.73 m^2, treatment should be discontinued

Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 1 Mar 2023]

Hyperkalemia – FIDELITY

Investigator-reported hyperkalaemia adverse events[1]*



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

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

*Investigator-reported AEs using the MedDRA preferred terms 'hyperkalaemia' and 'blood potassium increased'
AE, adverse events; MedDRA, Medical Dictionary for Regulatory Activities

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;
3. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; Supplementary appendix

FIDELITY

K+ Finerenone + SGLT2i – FIDELITY

Table 2—Overall safety and selected treatment-emergent AEs of interest in patients receiving or not receiving an SGLT2i at baseline

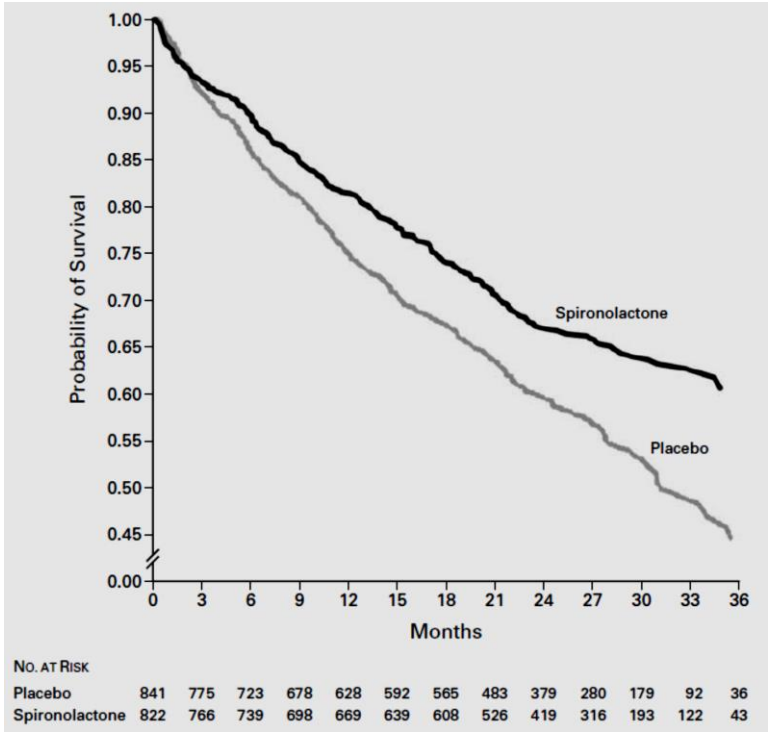
	SGLT2i at baseline		No SGLT2i at baseline	
Investigator-reported, treatment-emergent AE	Finerenone (*n* = 438)	Placebo (*n* = 439)	Finerenone (*n* = 6,072)	Placebo (*n* = 6,050)
Any AE	398 (90.9)	384 (87.5)	5,204 (85.7)	5,223 (86.3)
Leading to discontinuation	18 (4.1)	23 (5.2)	396 (6.5)	328 (5.4)
Any serious AE	146 (33.3)	141 (32.1)	1,914 (31.5)	2,045 (33.8)
Leading to discontinuation	7 (1.6)	8 (1.8)	138 (2.3)	146 (2.4)
Any AE resulting in death	2 (0.5)	9 (2.1)	108 (1.8)	142 (2.3)
Hyperkalemia-related AEs				
Any AE	45 (10.3)	12 (2.7)	867 (14.3)	436 (7.2)
Leading to discontinuation	5 (1.1)	3 (0.7)	105 (1.7)	35 (0.6)
Leading to hospitalization	1 (0.8)	0	39 (1.4)	8 (0.3)
Renal AEs				
Acute kidney injury	5 (1.1)	15 (3.4)	215 (3.5)	219 (3.6)
Worsening renal function leading to discontinuation	2 (0.5)	2 (0.5)	50 (0.8)	40 (0.7)
Hypertension	15 (3.4)	30 (6.8)	404 (6.7)	551 (9.1)
Hypotension	21 (4.8)	14 (3.2)	261 (4.3)	163 (2.7)
Hypoglycemia	17 (3.9)	19 (4.3)	323 (5.3)	356 (5.9)
Central laboratory assessments				
Serum potassium >5.5 mmol/L	34 (7.9)	13 (3.0)	1,041 (17.4)	457 (7.7)
Serum potassium >6.0 mmol/L	4 (0.9)	3 (0.7)	207 (3.4)	77 (1.3)

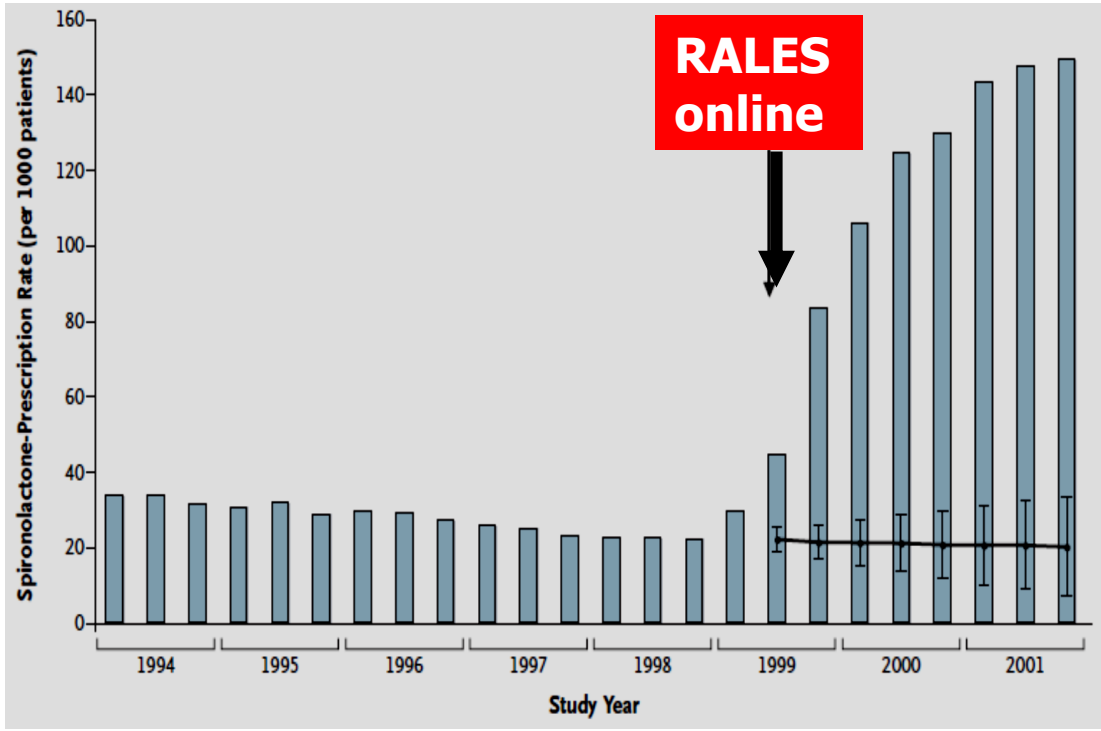
Data are *n* (%). AE, adverse event; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Rossing et al. Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Sodium-Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis. Diabetes Care. 2022;45:2991-2998.

FIDELITY

RALES and hospitalization due to hyperkalemia





Pitt B, et al; for Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-717.
Juurlink DN, et al. N Engl J Med. 2004;351(6):543-551.

First control examination

eGFR	Serum [K⁺]	Finerenone dose adjustment
eGFR decline <30%	☑ ≤4.8	10 → 20 → 20 — Increase to* or maintain **20 mg od**
	☑ >4.8–5.5	**Maintain current dose**
	☒ >5.5	**Withhold treatment** Restart at 10 mg od when serum [K⁺] is ≤5.0 mmol/l

If at 1 month, Maria's serum [K⁺] remains below 4.8 mmol/l and her eGFR has not declined by >30%, her dose of finerenone can be increased to 20 mg od

If Maria's serum [K⁺] increases to 5.0 mmol/l, her dose of finerenone should be maintained at 20 mg od

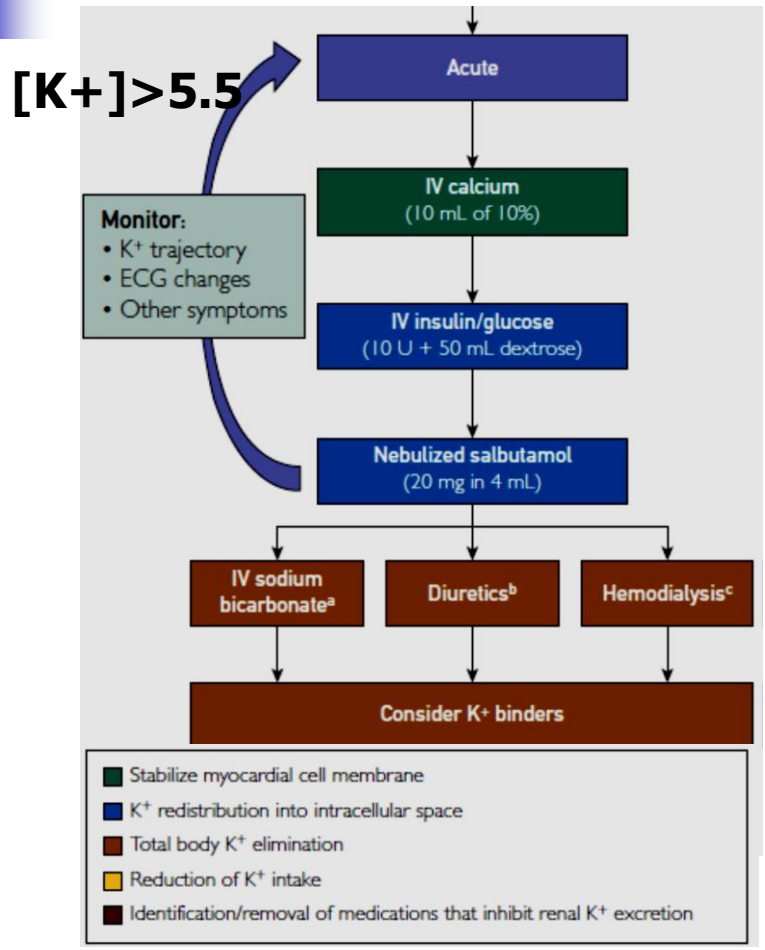
At follow-up, if Maria's serum [K⁺] has increased to 5.6 mmol/l, treatment with finerenone should be withheld

Serum [K⁺] and eGFR should be remeasured 4 weeks after initiation or after restarting finerenone treatment, or after an increase in dose#

periodically and as needed based on patient characteristics and serum [K⁺]

Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf
[accessed 1 Mar 2023]

Management of hyperkalemia



- **[K+]>5.0** Review diet (and kidney function)
- We treat, if needed, with
  - Loop diuretics, thiazides,
  - Bicarbonate
- Avoidance of drugs that reduce potassium excretion (eg NSAIDs, amiloride)
- Decrease (or probably stop) RAASi in mild hyperkalemia [K+]>5.0mEq/L and stop at [K+]>5.5mEq/L.
- Administration of K+ ion exchangers per os. Target [K+]<5.0mEq/L and
- restart treatment with RAASi.

Murphy D, Banerjee D. Hyperkalaemia in Heart Failure: Consequences for Outcome and Sequencing of Therapy. Curr Heart Fail Rep. 2022;19:191-199.

Guidelines KDIGO

K^+ ≤4.8 mmol/l	K^+ 4.9–5.5 mmol/l	K^+ >5.5 mmol/l
• Initiate finerenone - 10 mg daily if eGFR 25–59 ml/min per 1.73 m^2 - 20 mg daily if eGFR ≥60 ml/min per 1.73 m^2 • Monitor K^+ at 1 month after initiation and then every 4 months • Increase dose to 20 mg daily, if on 10 mg daily • Restart 10 mg daily if previously held for hyperkalemia and K^+ now ≤5.0 mmol/l	• Continue finerenone 10 mg or 20 mg • Monitor K^+ every 4 months	• Hold finerenone • Consider adjustments to diet or concomitant medications to mitigate hyperkalemia • Recheck K^+ • Consider reinitiation if/when K^+ ≤5.0 mmol/l

Rossing et al. Executive summary of the KDIGO 2022 Kidney Int. 2022;102:990-999.

Bowel K+ exchangers

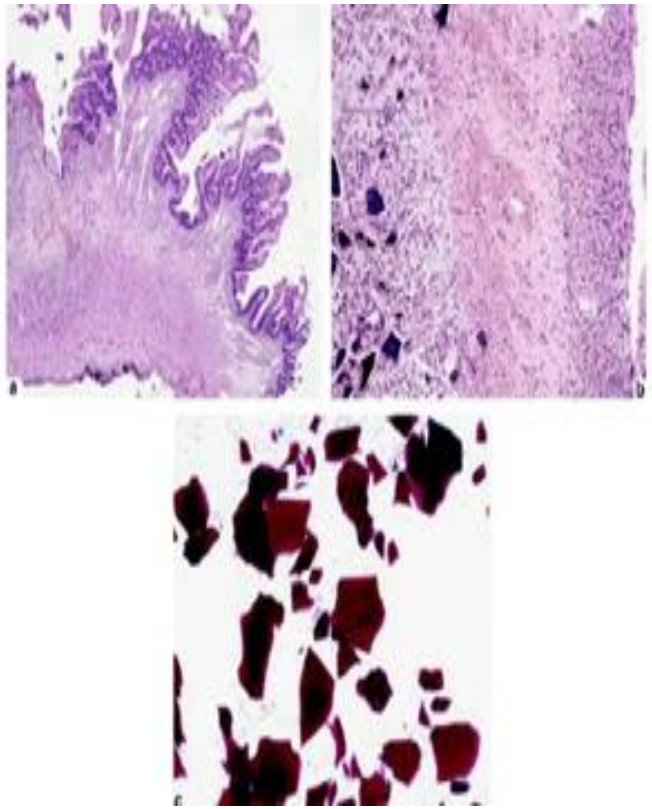
- SPS
- Patiromer
- SZC

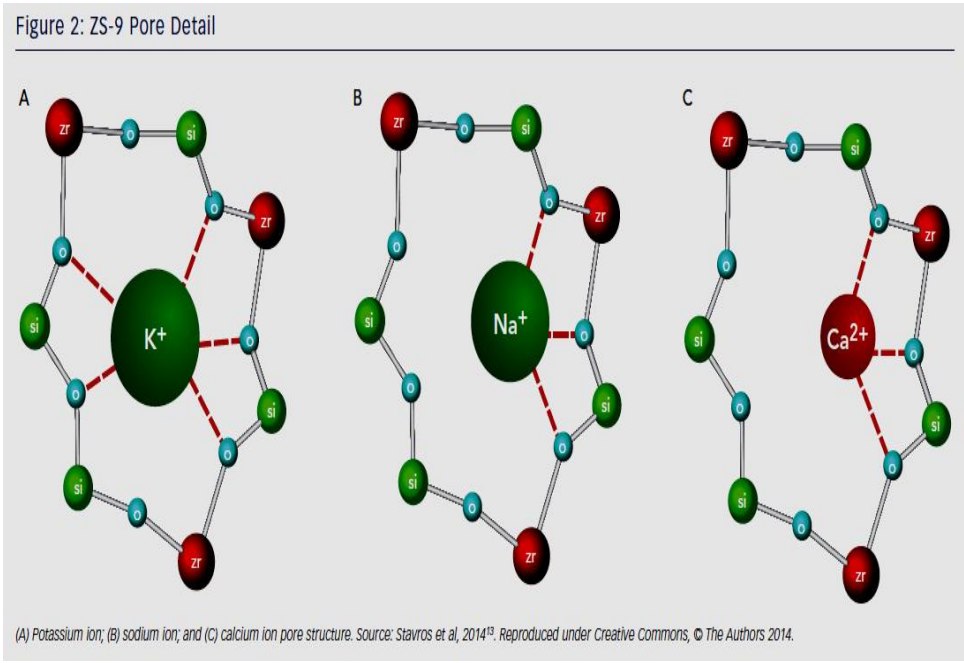
Table 2: Comparison of Therapies for Intermittent Hyperkalaemia

Property	Sodium polystyrene sulfonate	Patiromer	ZS-9
Chemical properties	Cation-exchange polymer resin	Non-absorbed organic resin and sorbitol complex; preferentially binds K+ in the colon	Inorganic crystalline polymer; enables cation exchange
Sorbitol content	20 g in each 15 g	2 g in each 4.2 g	None
Site of action	Colon	Colon	Entire gastrointestinal tract
Means of administration	Daily; oral suspension or enema	Twice daily; oral suspension in water with meals	Three times daily (acute); daily (long-term); oral suspension or tablet
Time to onset of action	12 h	7 h	1 h

Palmer et al. Clinical Management of Hyperkalemia. Mayo Clin Proc. 2021;96:744-762.

Bowel K+ exchangers

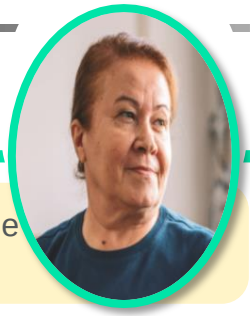




Palmer et al. Clinical Management of Hyperkalemia. Mayo Clin Proc. 2021;96:744-762.

4 months later

Maria*



- 67-year-old female
- T2D and CKD

- RASi
- Finerenone#
- SGLT-2i#

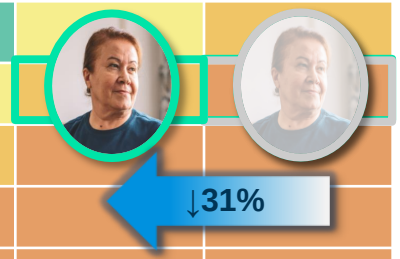
- HbA1c 7.8%
- Blood pressure 135/83 mmHg

- eGFR 53 ml/min/1.73 m^2
- **UACR 262 mg/g**
  - Reduced from 380 mg/g at the start of treatment

Albuminuria categories (mg albumin/g creatinine)[1]

A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
<30 mg/g <3 mg/mmol	**30–300 mg/g** (3–30 mg/mmol)	**>300 mg/g** (>30 mg/mmol)

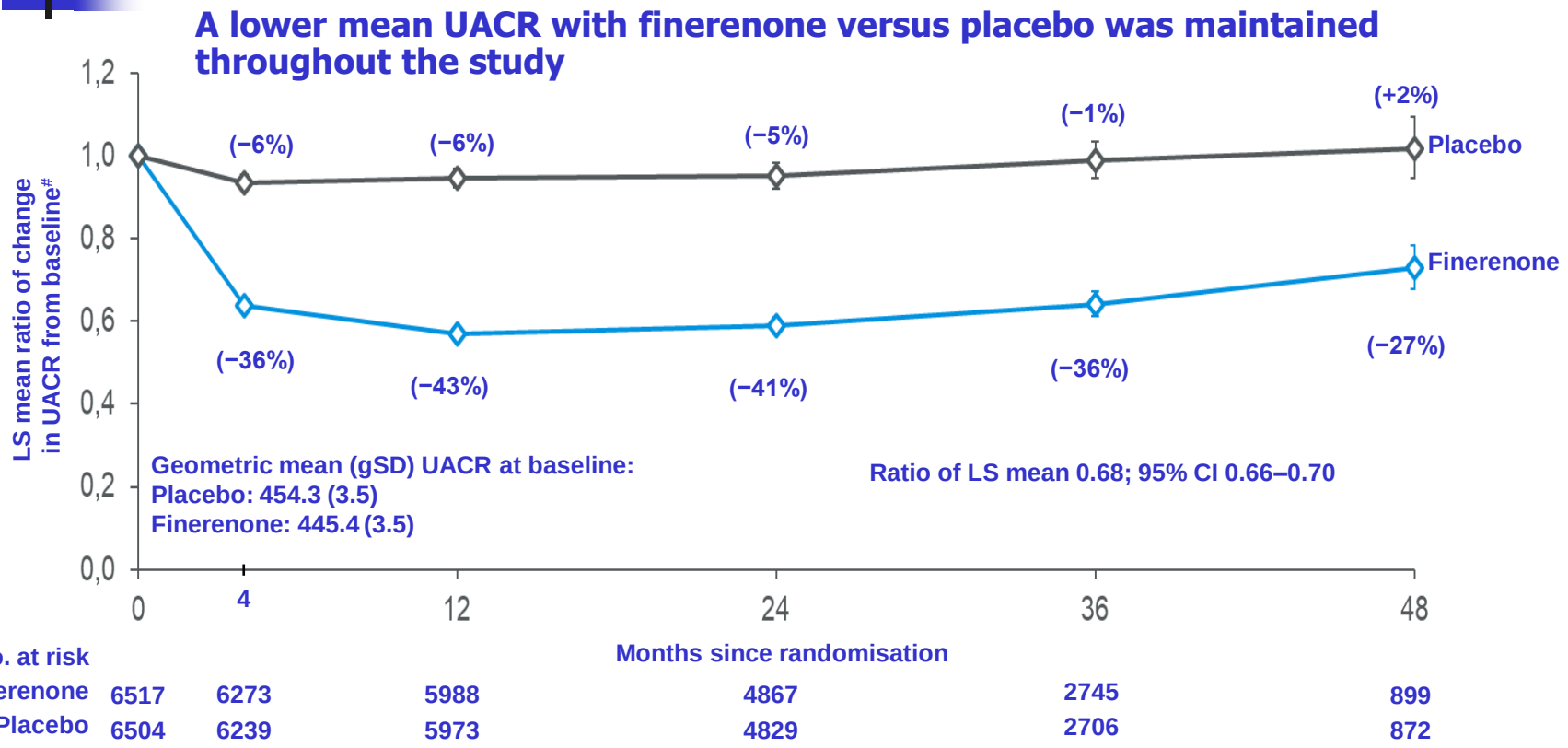
GFR categories (ml/min/1.73 m^2)



What does this mean for Maria's prognosis?

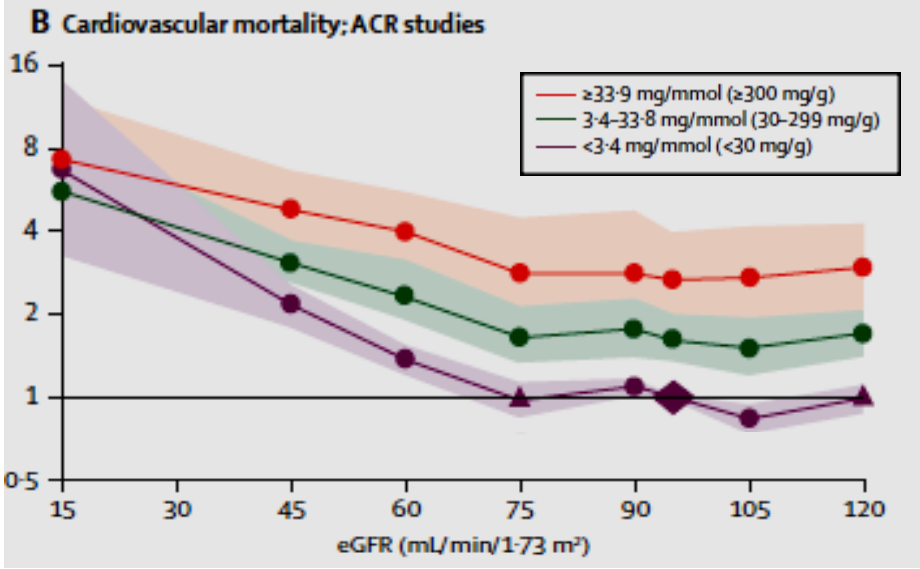
*Fictitious patient case; #on top of a maximum tolerated dose of RASi

Influence of Finerenone on albuminuria



Data in parentheses are mean changes from baseline. *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 ± SD
gSD, geometric standard deviation
Agarwal R, *et al*. *Eur Heart J* 2022;43:474–484

CKD as cardiovascular risk factor



Matsushita K et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010.

Gansevoort RT et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet.2013

Progression of CKD by GFR and Albuminuria Categories				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m²) Description and range	G1	Normal to high	≥90			
	G2	Mildly decreased	60–90			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	15			

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Chapter 1: definition and classification of CKD. Kidney Int Suppl (2011). 2013;3:19-62.

Key points 5

- Guidelines-recommended treatment with finerenone for patients with T2D and DKD is independent from the use of SGLT2i.
- Recommended target dosis 20mg od.
- Finerenone-induced hyperkaliemia is moderate and not so frequent as in steroidal MRA.
- A rigorous K+ control according to guidelines is essential and effektive to prevent complicated hyperkalemia.
- Chronic treatment with bowel potassium binders may be needed for a really GDMT.

Conclusion

UACR is an important **marker of kidney damage**; in patients with CKD, **increasing UACR** is **associated with** an **increased risk** of CV and kidney outcomes[1,2]

Early detection and treatment of CKD **improve outcomes** for patients and **reduce healthcare costs**[3]

Nephrologists play a key role in advocating for **early UACR screening**!

Finerenone reduces UACR by >30% and has cardiorenal benefits in patients across the spectrum of CKD severity[4–6]

Its positive effects for DKD are independent from other treatments

1. Fox CS, *et al. Lancet* 2013;381:532–533; 2. Matsushita K, *et al. Lancet* 2013;375:2073–2081; 3. Mernagh P, *et al*. *ERA* 2022; abstract MO375;
4. Agarwal R, *et al*. *Eur Heart J* 2022;43:474–484; 5. Ruilope LM, *et al. Nephrol Dial Transplant* 2023;38:372–383; 6. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263

Ευχαριστούμε για την συμμετοχή σας !

Σκανάρετε εδώ για να αξιολογήσετε την εκδήλωση :

Ευχαριστώ!

- Superior doctors prevent disease
- Mediocre doctors treat disease before it's evident
- Inferior doctors treat full blown disease
- Huang Dee Nai-Chan (2600 BC), first Chinese medical text