AJKD

Aldosterone, Mineralocorticoid Receptor Activation, and CKD

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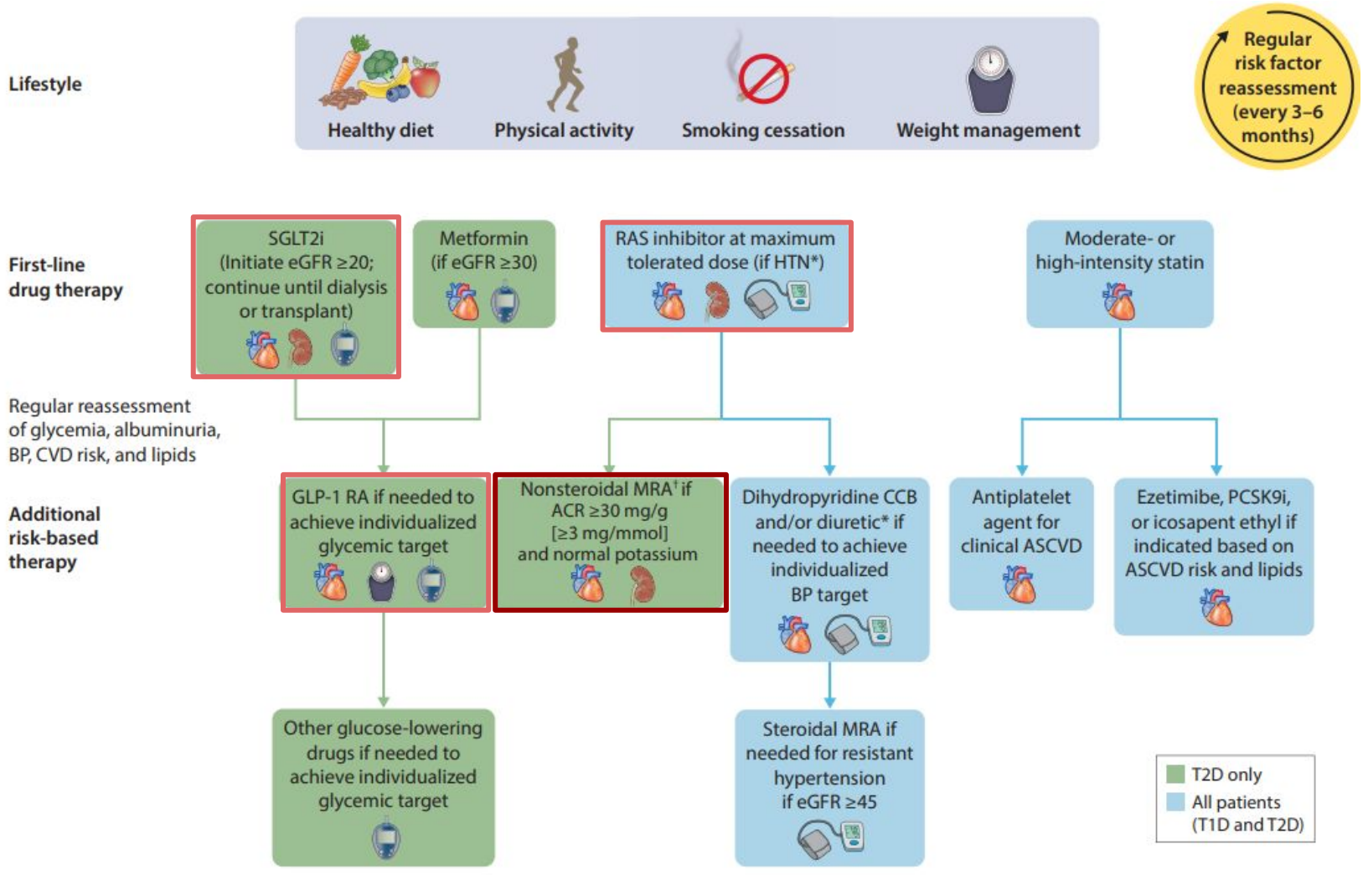

Lifestyle
Healthy diet
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
First-line drug therapy
SGLT2i (Initiate eGFR ≥20; continue until dialysis or transplant)
Metformin (if eGFR ≥30)
RAS inhibitor at maximum tolerated dose (if HTN*)
Moderate- or high-intensity statin
Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids
Additional risk-based therapy
GLP-1 RA if needed to achieve individualized glycemic target
Nonsteroidal MRA† if ACR ≥30 mg/g [≥3 mg/mmol] and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target
Antiplatelet agent for clinical ASCVD
Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids
Other glucose-lowering drugs if needed to achieve individualized glycemic target
Steroidal MRA if needed for resistant hypertension if eGFR ≥45
T2D only
All patients (T1D and T2D)

MR Activation in Kidney Pathophysiology

Evolving Understanding of the **Role of Aldosterone** in Kidney Physiology
The Role of **Nonepithelial MR Activation** in CKD Progression
The Interrelationship of **Fibroblast Growth Factor 23** and **Aldosterone**

Evolving Understanding of the Role of Aldosterone in Kidney Physiology

The **steroid aldosterone** is the **primary mineralocorticoid hormone**; its **synthesis** is prompted by **hyperkalemia** or **sodium and volume depletion** as the end result of RAS activation.

Aldosterone is an important contributor to both **blood pressure** control and — by provoking renal sodium reabsorption and **potassium excretion**.

Angiotensin is **not the main trigger** for aldosterone secretion.

MR is stimulated by several ligands (**aldosterone**, **cortisol**) and undergoes **nonligand activation** (via the regulatory protein Rac family small guanosine triphosphatase 1 [**Rac1**], elevated **glucose**, and **high salt levels**).

Leptin affects **aldosterone synthesis**, acting directly on adrenal glomerulosa cells to upregulate the expression of aldosterone synthase (encoded by CYP11B2) and increase the production of aldosterone via calcium-dependent mechanisms.

The Role of Nonepithelial MR Activation in CKD Progression

The best-known function of aldosterone is its contribution to the control of electrolyte and fluid balance by interaction with **MR expressed in aldosterone-sensitive kidney epithelial cells** in the **distal nephron**.

What is not as widely appreciated is that **nonepithelial tissues** also express MR, including the **heart**, adipocytes, **podocytes**, inflammatory cells, endothelial cells and **vascular smooth muscle cells** (VSMCs)

The **MR in nonepithelial cells** offers an attractive target for **protecting against inflammation** and **fibrosis** in both the kidneys and the cardiovascular system.

Box 1. MR Activation in Nonepithelial Cells

Podocytes

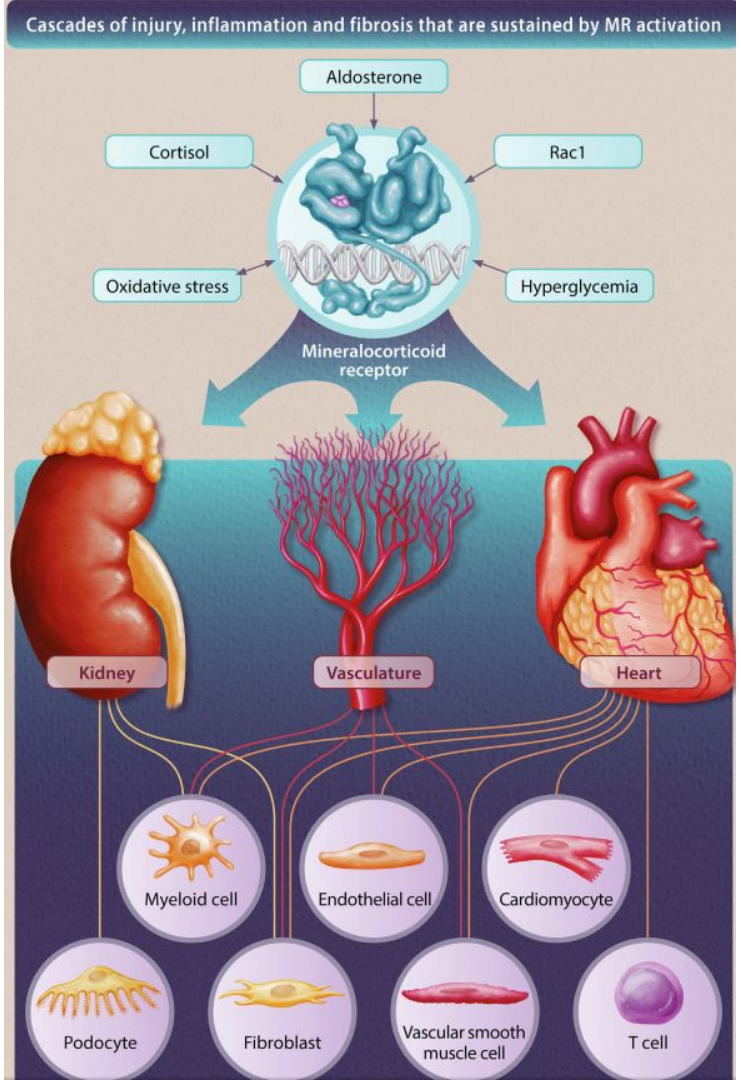
- MR activation increases autophagy of podocytes in vivo and restores autophagy in podocytes under mechanical stress.
- Addition of aldosterone to podocytes in vitro induces the downregulation of nephrin, podocin, podoplanin, and podocalyxin.

Fibroblasts

- MR activation in renal fibroblasts may contribute to kidney remodeling during CKD.
- Aldosterone stimulates fibronectin synthesis in isolated renal fibroblasts.
- Conversely, incubation of fibroblasts with MRAs reduces extracellular matrix component production induced by either platelet-derived growth factor or connective tissue growth factor.

Endothelial cells

- Aldosterone increases ICAM-1, VCAM-1, E-selectin, and MCP-1 expression.
- Aldosterone promotes oxidative injury through increasing the expression of the NADPH oxidase subunits Nox2, p47*phox*, p22*phox* and by stimulating Rac1 activation.
- Aldosterone impairs endothelial function through a reduction in eNOS phosphorylation.


Cascades of injury, inflammation and fibrosis that are sustained by MR activation
Aldosterone
Cortisol
Rac1
Oxidative stress
Hyperglycemia
Mineralocorticoid receptor
Kidney
Vasculature
Heart
Myeloid cell
Endothelial cell
Cardiomyocyte
Podocyte
Fibroblast
Vascular smooth muscle cell
T cell

The Interrelationship of Fibroblast Growth Factor 23 and Aldosterone

Aldosterone and **angiotensin II** increase **FGF-23 expression in bone** and boost levels of FGF-23 in the circulation.

Aldosterone may play an important role in **increased FGF-23 secretion** in patients with CKD.

After the administration of the **MRA canrenone**, an **active metabolite of spironolactone**, uremic mice with **elevated aldosterone levels** were shown to have a **significant decrease** in previously elevated concentrations of circulating **FGF-23**.

In experimental CKD, **Klotho lessens tissue injury and fibrosis** and **improves hypertension** by **downregulating RAAS activity**.

New therapeutic avenues to block the vicious cycle of aldosterone/MR overactivation and FGF-23 secretion with concomitant Klotho insufficiency, which often exists in patients with CKD.

MR Antagonism as a Therapeutic Strategy

Steroidal MRAs
Novel Nonsteroidal MRAs

Steroidal MRAs

In **2006** came the **first** assessment of the **albuminuria-lowering effects of eplerenone** in **patients with type 2 diabetes mellitus** (T2DM). Adding eplerenone, in doses of **50** or **100 mg**, to enalapril resulted in a substantive and statistically **significant reduction in albuminuria** in patients with T2DM.

Novel Nonsteroidal MRAs

In response to concerns about the benefit-safety profile of steroidal MRAs, several new **selective nonsteroidal MRA**s were developed with the dual goal of **improving efficacy** and **reducing unwanted side effects**, primarily **hyperkalemia**.

	Steroidal MRAs		Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
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	+++	++	+

Figure 2. Schematic of spironolactone, eplerenone, and finerenone binding with proposed/hypothesized conformational change of helix 12 and summary of respective key pharmacodynamic and pharmacokinetic characteristics. Abbreviations: BP, blood pressure; CNS, central nervous system; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist. Reproduced from Kintscher[3] under the terms of the Creative Commons Attribution License (CC BY 4.0).

Finerenone

The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (**FIDELIO-DKD**) and Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (**FIGARO-DKD**)

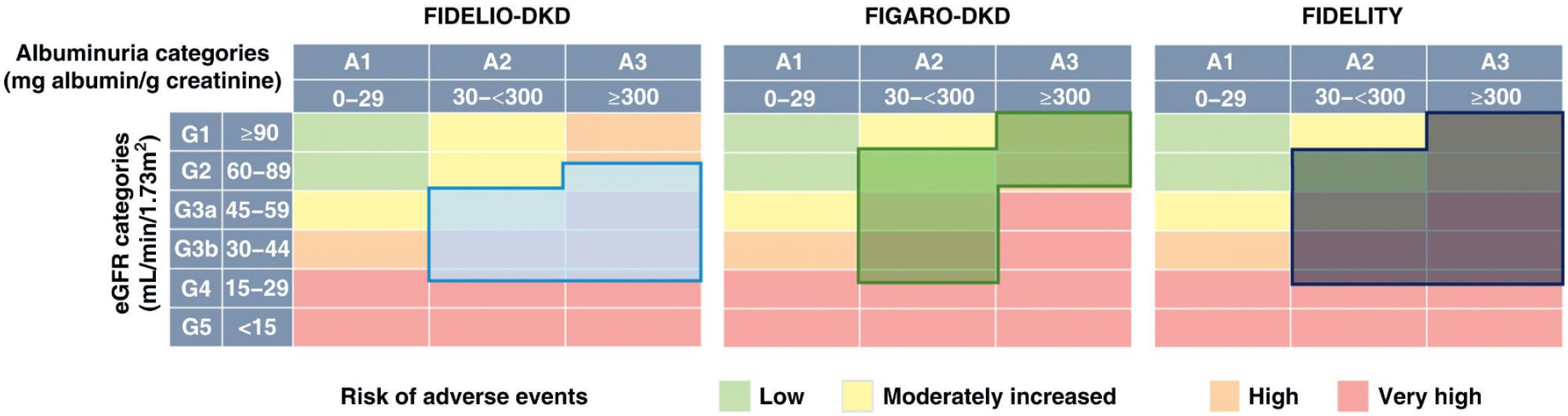


Figure 1. FIDELIO-DKD

Does finerenone improve outcomes in CKD with type 2 diabetes?

- **Double-blinded**
- **Type 2 diabetes**
- **2.6 years**
  Median follow-up
- **RAAS blockade**
  Maximum tolerable dose

Stratification

- **eGFR 25 to <75** (mL/min/1.73 m²)
- **uACR 300 to 5000** (mg/g)

- **eGFR 25 to <60** (mL/min/1.73 m²)
- **uACR 30 to <300** (mg/g)
- **Diabetic retinopathy**

	1 Primary composite outcome	2 Key secondary composite outcome	Safety
	Kidney failure Sustained decrease of ≥40% in eGFR Death from renal causes	Cardiovascular death Nonfatal MI and stroke Hospitalization for heart failure	Discontinuation of trial regimen due to hyperkalemia
Placebo n = 2841	**REFERENCE**	**REFERENCE**	**0.9%**
Finerenone n = 2833	**HR 0.82** (0.73 to 0.93)	**HR 0.86** (0.75 to 0.99)	**2.3%**

Conclusion In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo.

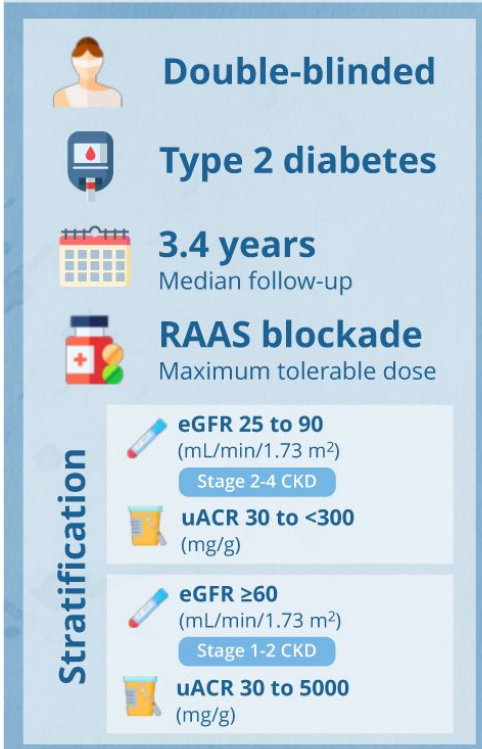
RAAS, renin–angiotensin–aldosterone system; uACR, urine albumin-creatinine ratio; HR, hazard ratio

Bakris GL, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020; 383:2219–2229. doi: 10.1056/NEJMoa2025845

Visual abstract by Michelle Lim, MBChB, MRCP

Figure 2. FIGARO-DKD

Does finerenone improve cardiovascular outcomes in type 2 diabetes and CKD?

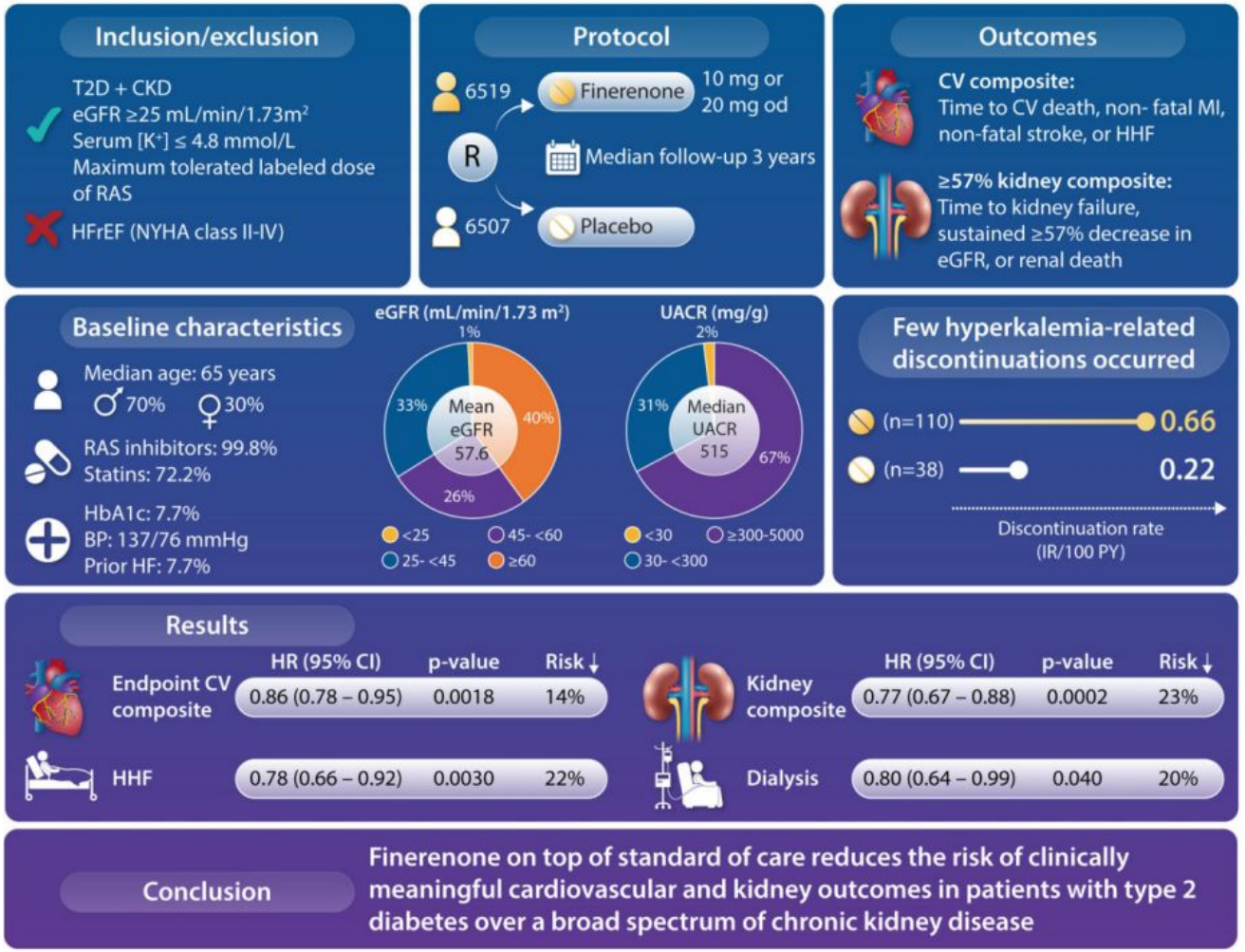


Conclusion Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared

Pitt B, et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* [published online ahead of print August 28, 2021]. doi: 10.1056/NEJMoa2110956

Visual abstract by Michelle Lim, MBChB, MRCP

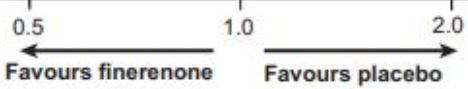
FIDELITY
pooled
analysis



European Heart Journal (2022) 43, 474–484

Study name	FIDELIO-DKD[7]	FIGARO-DKD[10]
Publication year	2020	2021
Study design	Phase III, randomized, double-blind, placebo-controlled, multicentre clinical trial	Phase III, randomized, double-blind, placebo-controlled, multicentre clinical trial
Sample size[a]	5734	7437
Inclusion criteria	• Age ≥18 years • T2D and CKD defined as UACR 30–<300 mg/g, eGFR 25–<60 mL/min/1.73 m^2, and diabetic retinopathy, *or* UACR 300–5000 mg/g and eGFR 25–<75 mL/min/1.73 m^2 • Maximum tolerated dose of an RAS inhibitor • Serum potassium ≤4.8 mmol/L	• Age ≥18 years • T2D and CKD defined as UACR 30–<300 mg/g and eGFR 25–90 mL/min/1.73 m^2, *or* UACR 300–5000 mg/g and eGFR ≥60 mL/min/1.73 m^2 • Maximum tolerated dose of an RAS inhibitor • Serum potassium ≤4.8 mmol/L
Exclusion criteria	• Non-diabetic kidney disease • Uncontrolled hypertension[b] • HbA1c >12% • SBP <90 mmHg • Chronic symptomatic HFrEF[c] • Recent CV event • Dialysis for acute kidney failure • Kidney transplant	• Non-diabetic kidney disease • Uncontrolled hypertension[b] • HbA1c >12% • SBP <90 mmHg • Chronic symptomatic HFrEF[c] • Recent CV event • Dialysis for acute kidney failure • Kidney transplant
Follow-up period, median	2.6 years	3.4 years
Primary outcome	Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death	Time to CV death, non-fatal MI , non-fatal stroke, or HHF
Secondary outcome	Time to CV death, non-fatal MI , non-fatal stroke, or HHF	Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death

Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
Composite cardiovascular outcome[b]	825 (12.7)	4.34	939 (14.4)	5.01	0.86 (0.78–0.95)	0.0018
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)	0.95
Hospitalization for heart failure	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)	0.0030
eGFR ≥57% composite kidney outcome[c]	360 (5.5)	1.96	465 (7.1)	2.55	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease[d]	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040[e]
Sustained decrease in eGFR to <15 mL/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026[e]
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	< 0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.46[e]
eGFR ≥40% composite kidney outcome[f]	854 (13.1)	4.81	995 (15.3)	5.64	0.85 (0.77–0.93)	0.0004
Sustained ≥40% decrease in eGFR from baseline	817 (12.5)	4.60	962 (14.8)	5.45	0.84 (0.76–0.92)	0.0002
Death from any cause	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–>1.00[g])	0.051[e]
Hospitalization for any cause	2836 (43.5)	19.04	2926 (45.0)	19.91	0.96 (0.91–1.01)	0.087[e]



FIDELITY pooled analysis

The **main time-to-event efficacy outcomes** were a **composite cardiovascular outcome** (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or HHF) and a **composite kidney outcome** (kidney failure, a sustained ≥57% decrease in estimated GFR from baseline over ≥4 weeks, or death from kidney causes).

We wish to emphasize 2 important points derived from the FIDELITY analysis.
First, it provides the best evidence to date that **finerenone prevents HHF in a high-risk population**. Second, the **reduction in HHF was the primary contributor to finerenone's cardiovascular benefit**, with a **relative risk reduction of 22%** compared with placebo (P =0.003) in a study population in which patients with chronic symptomatic HFrEF at the run-in visit were excluded. This is an important and highly relevant finding for nephrologists because **heart failure is a key contributor to morbidity** and health care costs among **patients with CKD and T2DM**.

An important limitation of **FIDELITY** is that it **did not** include **patients with nonalbuminuric CKD**, highlighting the importance of conducting similar finerenone studies in a nonalbuminuric CKD cohort.

It is noteworthy the benefits of finerenone were seen early — **as soon as 1 month** after drug initiation for the **cardiovascular outcome** and just **after 12 months** for the **kidney outcome** — and **persisted for the 3-year duration of the trials**. Based on these 2 studies, finerenone was recently approved by the US Food and Drug Administration (FDA).

Barriers to Implementing Guideline-Recommended MR Blockade

Hyperkalemia

Hyperkalemia

The groundbreaking **RALES trial** reported that **spironolactone reduced all-cause mortality** by **30%** in patients with **reduced ejection fraction** who were on RAS inhibitors and had levels of potassium ≤5.0 mEq/L and creatinine ≤2.5 mg/dL at baseline.

A population-based study assessing the postpublication impact of the RALES trial found **higher spironolactone prescriptions** in patients with **heart failure on RAS inhibitors** and, concerningly, **higher hyperkalemia-induced hospitalization** and **death**.

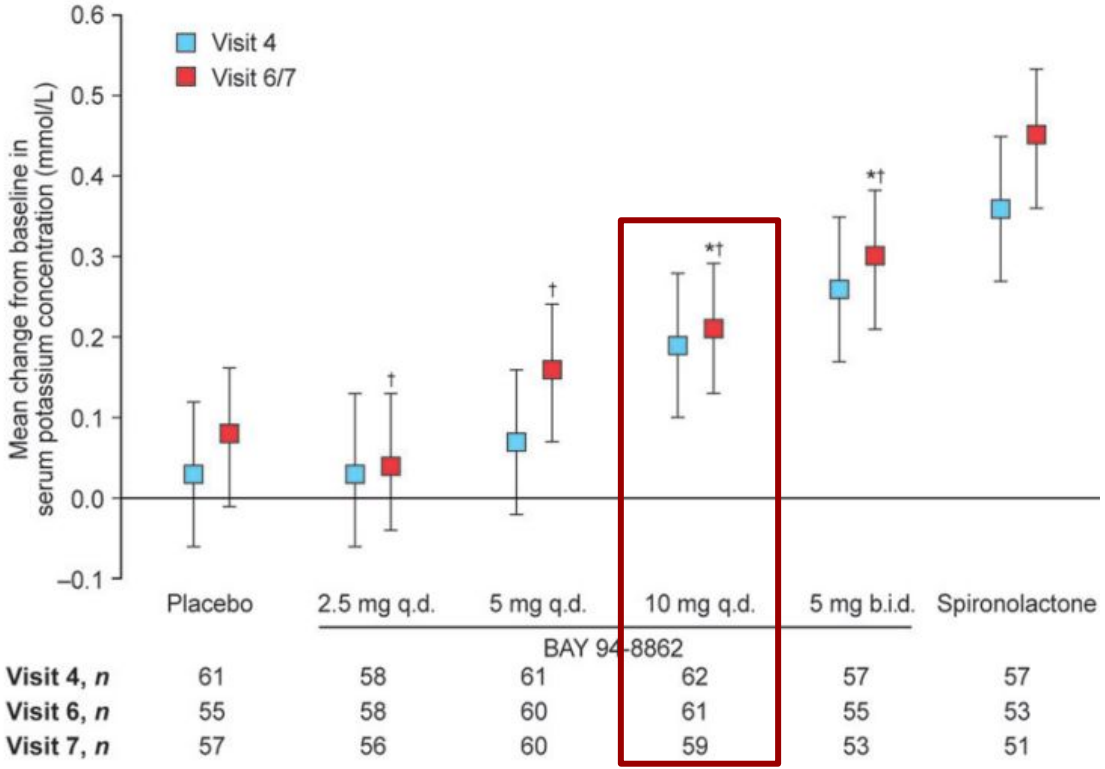
Contemporary data from a **Swedish general population cohort** indicated that a plasma **potassium level of > 5.0mEq/L** occurred in **19%** of individuals **newly started on an MRA**

Although patients who **stopped MRA** treatment after a hyperkalemia episode experienced **fewer subsequent hyperkalemia** events compared with those who continued the MRA despite hyperkalemia, importantly they also had a **higher risk of cardiovascular events**.

It is unfortunate and indeed ironic that the precise **populations that could benefit most from MRA** therapy are those who are **at increased risk for hyperkalemia**.

The development of a novel class of **nonsteroidal MRAs** (including finerenone, aparenone, and esaxerenone, as discussed previously) generates excitement due to the promise of provoking **less hyperkalemia** than steroidal MRAs (spironolactone and eplerenone).

eGFR (mL/min/1.73m²)	Starting Dose
⩾ 60	20 mg once daily
⩾ 25 to < 60	10 mg once daily
< 25	Not Recommended



	Placebo	2.5 mg q.d.	5 mg q.d.	10 mg q.d.	5 mg b.i.d.	Spironolactone
Visit 4, *n*	61	58	61	62	57	57
Visit 6, *n*	55	58	60	61	55	53
Visit 7, *n*	57	56	60	59	53	51

The increase was **0.21 mmol/L** in patients receiving **finerenone at 10 mg daily**, **0.30 mmol/L** in patients receiving **finerenone at 5 mg twice daily**, and **0.45 mmol/L** in patients receiving **spironolactone** (mean dose of **37 mg**). Interpretation is challenging because all 3 agents were administered at different (nonequivalent) doses.

European Heart Journal (2013) 34, 2453–2463

Strategies used to mitigate hyperkalemia

Box 2. Strategies Used to Mitigate Hyperkalemia in Patients Treated With Finerenone

- Requirement for pretreatment serum potassium of ≤4.8 mEq/L[a]
- Serum potassium monitoring: 1 month after start and every 4 months afterward; also after each dose change
- Dose adjustment strategy
  - ◇ First measurement after start:
    - Serum potassium ≤ 4.8 mEq/L: if on 10 mg daily, increase dose to 20 mg daily; if on 20 mg daily, continue same dose
    - Serum potassium 4.9–5.5 mEq/L: continue on same dose
    - Serum potassium > 5.5 mEq/L: withhold drug and recheck potassium within 72 hours
  - ◇ Subsequent measurements:
    - Serum potassium ≤ 5.0 mEq/L: restart study drug at 10 mg daily dose
    - Serum potassium > 5.0 mEq/L: continue to withhold drug and monitor serum potassium; only restart finerenone (at the 10 mg daily dose) once serum potassium ≤ 5.0 mEq/L
- Permanent discontinuation: if hyperkalemia was recurrent soon after a previous event despite discontinuation of drug without alternative explanation for the hyperkalemia
- Diet: no restrictions on potassium intake
- Potassium binders: permitted, discontinuation encouraged once serum potassium returned to normal

Based on use of finerenone in the FIDELIO-DKD and FIGARO-DKD clinical trial protocol.[4,5]

It is important to accurately understand the magnitude of the risk of hyperkalemia. In **FIDELITY**, the total incidence of **hyperkalemia-related adverse events** was **14.0%** for finerenone compared with **6.9%** for **placebo**; meanwhile, the number of **hospitalizations due to hyperkalemia** was **0.9%** versus **0.2%**, and the number of **permanent discontinuations due to hyperkalemia** was **1.7%** versus **0.6%**.

Four months after treatment start, the mean increase in serum potassium was 0.21 mEq/L with finerenone and 0.02 mEq/L with placebo. Most importantly, in patients receiving finerenone there were **no deaths attributable to hyperkalemia**.

The **low incidence** of **permanent discontinuation of finerenone** and the **absence of deaths** attributable to **hyperkalemia** were in large part due to a **proactive approach** aimed at **minimizing the occurrence of hyperkalemia**.

Importantly both **newer potassium binders** and **sodium/glucose cotransporter 2 (SGLT2) inhibitors** provide additional mitigation possibilities to reduce the risk of hyperkalemia.

Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: The CREDENCE trial

European Heart Journal (2021) 42, 4891–4901

European Heart Journal

METHODS

4401 patients with type 2 diabetes and CKD randomized to:

Canagliflozin Placebo

99.9% maximum labelled or tolerated RAS blockade

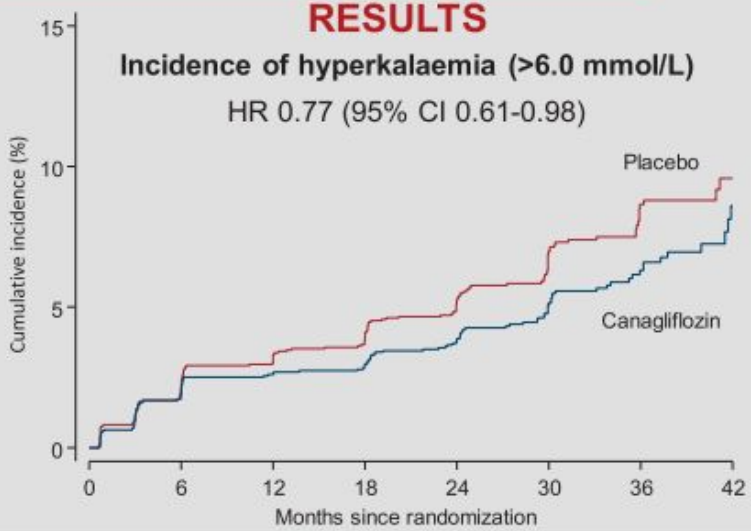
eGFR 56 mL/min/1.73m²

Serum potassium 4.5 mmol/L

RESULTS

Incidence of hyperkalaemia (>6.0 mmol/L)

HR 0.77 (95% CI 0.61-0.98)



CONCLUSION Among patients treated with RAS blockade, canagliflozin reduces the risk of hyperkalaemia in people with T2DM and CKD without increasing the risk of hypokalaemia. The lower risk of hyperkalaemia with SGLT2 inhibition may enable greater use of RAS blockade and mineralocorticoid receptor antagonists in CKD and/or heart failure.

Post hoc analysis of the CREDENCE trial demonstrated that **canagliflozin reduced the risk of investigator-reported hyperkalemia** or **initiation of potassium binders** compared with placebo

Future Treatment Paradigms With Nonsteroidal MRAs

Nondiabetic Kidney Disease
Combination Therapy

Nondiabetic Kidney Disease

FIND-CKD(Clinicaltrials.gov identifier NCT05047263) is currently enrolling patients to examine the effects of **finerenone plus guideline-directed therapy** on **CKD progression**, with expected completion in November 2025

Combination Therapy

Coadministration of **low dosages** of **finerenone** and **empagliflozin** led to a **stronger survival benefit** than equivalent or higher doses given individually.

CONFIDENCE is a planned phase 2 clinical trial that will leverage the preclinical studies and examine the effects of **finerenone** and **empagliflozin alone** and i**n combination** versus placebo on reduction of albuminuria in patients with CKD and T2DM (Clinicaltrials.gov identifier NCT05254002).

Although we are unaware of any preclinical or clinical data to suggest **how MRAs, SGLT2 inhibitors, and GLP-1RAs** should be **used sequentially**, such investigations should be initiated.

Albuminuria Lowering Effect of Dapagliflozin, Eplerenone and Their Combination in Patients with Chronic Kidney Disease: A Randomized Cross-Over Clinical Trial

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

46 patients

- Age ≥18 years
- UACR 100-3500 mg/24-hour
- eGFR >30 - <90 mL/min/1.73m²
- Stable (>4 weeks) dose of ACEi **or** ARB

Dapagliflozin 10 mg → **Eplerenone** 50 mg → **Eplerenone** 50 mg **Dapagliflozin** 10 mg

4-weeks treatment in random order with 4-weeks wash-out in between

OUTCOMES

UACR change (%) from baseline

combination vs. dapa: p<0.001

combination vs. eple: p=0.0127

Change from baseline in serum K (mmol/L)

combination vs. dapa: p<0.0018

combination vs. eple: p=0.0296

Conclusion

Dapagliflzoin in combination with eplerenone reduced albuminuria to a greater extent than either drug alone. Compared to eplerenone, dapagliflozin-eplerenone combined decreased serum potassium.

doi: 10.1681/ASN.2022020207

Conclusion

Recent publication of **FIDELIO-DKD** and **FIGARO-DKD**

Key differences between steroidal and nonsteroidal MRAs in terms of **clinical efficacy** and **serious adverse events**

Overriding challenge is the **hyperkalemia** evoked by treatment with MRAs

Systematic application of **careful monitoring** and an array of **mitigation strategies** that should enable sustained therapy with finerenone

We propose that activation of MR, along with the associated inflammation and fibrosis, is relevant to the pathogenesis of CKD whether or not there is co-occurring diabetes.

Recently initiated or planned clinical trials (**CKD-FIND**, **CONFIDENCE**) that are investigating either the efficacy of finerenone in retarding and abrogating progression in patients with **nondiabetic CKD**, or **finerenone in combination with SGLT2 inhibitors**

We are **not aware** of any new **evidence** on the **efficacy of MRAs** for patients **without albuminuria** or any planned studies in this area.