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CKJ Review

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CKJ REVIEW

Mineralocorticoid receptor antagonist use in chronic kidney disease with type 2 diabetes: a clinical practice document by the European Renal Best Practice (ERBP) board of the European Renal Association (ERA)

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ABSTRACT

Chronic kidney disease (CKD) in individuals with type 2 diabetes (T2D) represents a major public health issue; it develops in about 30%–40% of patients with diabetes mellitus and is the most common cause of CKD worldwide. Patients with CKD and T2D are at high risk of both developing kidney failure and of cardiovascular events. Renin–angiotensin system (RAS) blockers were considered the cornerstone of treatment of albuminuric CKD in T2D for more than 20 years. However, the residual risk of progression to more advanced CKD stages under RAS blockade remains high, while in major studies with these agents in patients with CKD and T2D no significant reductions in cardiovascular events and mortality were evident. Steroidal mineralocorticoid receptor antagonists (MRAs) are known to reduce albuminuria in individuals on RAS monotherapy, but their wide clinical use has been curtailed by the significant risk of hyperkalemia and absence of trials with hard renal outcomes. In recent years, non-steroidal MRAs have received increasing interest

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due to their better pharmacologic profile. Finerenone, the first compound of this class, was shown to effectively reduce the progression of kidney disease and of cardiovascular outcomes in participants with T2D in phase 3 trials. This clinical practice document prepared from a task force of the European Renal Best Practice board summarizes current knowledge on the role of MRAs in the treatment of CKD in T2D aiming to support clinicians in decision-making and everyday management of patients with this condition.

Keywords: chronic kidney disease, finerenone, mineralocorticoid receptor antagonists, spironolactone, type 2 diabetes

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INTRODUCTION

Recent estimates suggest that around 850 million people worldwide have chronic kidney disease (CKD), with 3.9 million receiving kidney replacement therapy [1]. Diabetes mellitus is another silent epidemic, affecting 9.3% of the adult population in 2019 and accounting for 4 million deaths in 2017 [2]. CKD develops in up to 40% of patients with diabetes mellitus. The progressive increase in the prevalence of type 2 diabetes (T2D) has led to an increase in patients diagnosed with CKD, and thus, diabetic kidney disease (DKD) is currently the leading cause of kidney failure worldwide [3]. In individuals with T2D without CKD the 10-year standardized cumulative all-cause mortality was found to be approximately 11.5%, but in those with T2D and CKD it rises to 31% [4]. Furthermore, for patients with CKD stage 3 the risk of cardiovascular death is at least 10 times higher than the risk of kidney failure [5]. Overall, CKD is projected to become the fifth global cause of death by 2040, mainly driven by CKD in T2D [6].

Following the publication of seminal clinical trials more than two decades ago [7, 8] the use of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) monotherapy has been the cornerstone of treatment for albuminuric CKD, along with lifestyle modifications, and blood pressure (BP) and glycemic control [9]. Despite the indisputable kidney protective effects of renin–angiotensin system (RAS) blockers, a high residual risk of CKD and cardiovascular disease progression remains in these patients [3, 10]. Double RAS blockade either as combination of an ACEi with an ARB or of a renin inhibitor with any of the aforementioned classes was completely abandoned, due to increased risk of hyperkalemia, acute kidney injury and cardiovascular death, in major trials in CKD in T2D [11, 12]. In contrast to this, sodium–glucose cotransporter-2 inhibitors (SGLT2i) are associated with nephro- and cardioprotection in patients with CKD with or without diabetes [13–15] and are now recommended as first-line treatment, among others, in patients with T2D and estimated glomerular filtration rate (eGFR) $\geq$20 mL/min/1.73 m^2 [9, 16, 17].

Steroidal mineralocorticoid receptor antagonists (MRAs) (Fig. 1) have been used in clinical practice for many years. The non-selective MRA spironolactone is used for the treatment of primary aldosteronism due to bilateral adrenal hyperplasia or aldosterone-producing adenomas [18] and for resistant hypertension [19], while both spironolactone and the selective MRA eplerenone reduce mortality and cardiovascular events in patients with heart failure (HF) with reduced ejection fraction [20–22], and have a Class 1A recommendation for this condition [23]. However, one population-based analysis from Canada [24] showed abrupt increases in the rate of prescriptions for spironolactone and in hyperkalemia-associated morbidity and mortality after the publication of the Randomized Aldactone Evaluation Study (RALES) trial in heart failure. Furthermore, both steroidal MRAs were shown to effectively reduce albuminuria alone or on top of a RAS blocker in patients with diabetic and non-diabetic CKD [25, 26] but their use was never expanded due to lack of randomized trials with hard kidney and cardiovascular outcomes and the potential risks of hyperkalemia. In recent years, novel non-steroidal MRAs have been developed. Among these, finerenone was recently associated in two large-scale randomized clinical trials (RCTs) with significant reductions in renal and cardiovascular outcomes in patients with T2D and moderately or severely increased albuminuria [27, 28].

This is a document prepared by a task force of the European Renal Best Practice (ERBP) board of ERA that presents in a systematic way the current evidence on the effects of MRAs on intermediate and hard kidney outcomes, summarizes the potential mechanisms involved, and discusses their place in everyday management of patients with CKD and T2D.

ALDOSTERONE-MEDIATED MINERALOCORTICOID RECEPTOR ACTIVATION IN HEALTH AND DISEASE

Aldosterone is a steroid hormone produced in the zona glomerulosa of the adrenal cortex and acts as ligand of the mineralocorticoid receptor (MR), a type of nuclear receptor, structurally similar to glucocorticoid and sex hormone receptors. MRs are expressed in epithelial and nonepithelial tissues, serving as transcription factors of target genes that regulate cellular processes [29]. In the epithelial cells of the distal nephron, aldosterone exerts its classical actions of potassium and proton secretion, and sodium retention, by regulating sodium, chloride and potassium handling, through transcription of the epithelial sodium channel (ENaC), $Cl^-/HCO3^-$ exchangers, and ROMK channels [30, 31]. In addition to the above, activation of MR in non-epithelial tissues, including cardiomyocytes, smooth muscle cells, fibroblasts, and macrophages in heart [32, 33], monocytes [34] and mesangial cells [35], induces expression of genes that are involved in tissue repair and may also promote inflammation and fibrosis [36, 37]. This is also the case for kidney epithelial cells such as glomerular podocytes [38] and kidney proximal tubular cells [39, 40].

MR has multiple ligands with high affinity, including both cortisol and aldosterone [29, 36]. Cortisol reaches up to 1000-fold higher concentrations than aldosterone in several tissues. In distal tubular epithelial cells, however, 11-beta-hydroxysteroid-dehydrogenase-2 (11βHSD2) is abundantly expressed and converts cortisol to inactive cortisone, making aldosterone the primary physiological MR ligand in these cells [37, 41]. However, the concentrations of 11βHSD2 are much less or absent in other cell

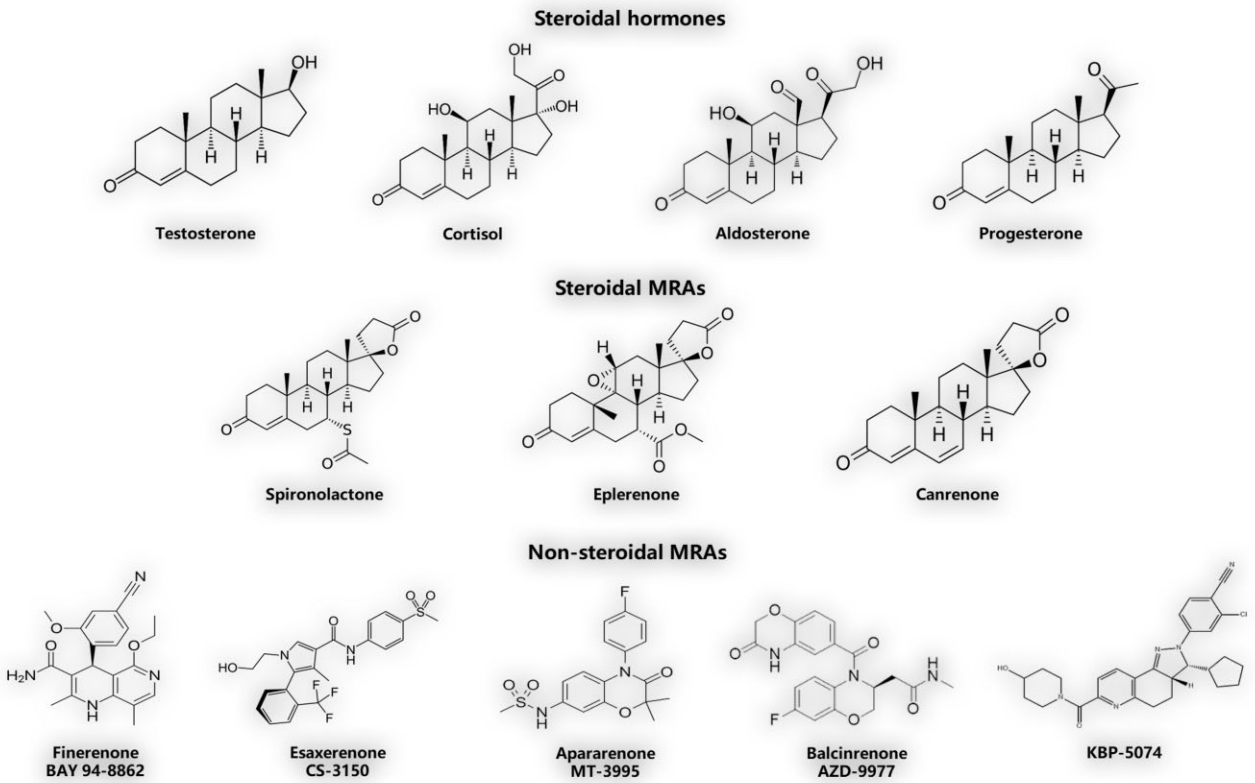


Figure 1: Chemical structure of main steroidal hormones and non-steroidal and steroidal MRAs.

types, making cortisol the primary physiological ligand of MRs in cardiomyocytes, podocytes and macrophages [37].

Aldosterone acts through genomic and nongenomic pathways. The genomic response includes all the classical steps of cell-membrane diffusion of aldosterone, binding to the MR in the cytoplasm, translocation to the nucleus of the aldosterone–MR complex and activation of gene transcription [42, 43]. This process results in an increase of ENaC concentration in epithelial cells (i.e. distal tubule, colon) within 30–60 min post–aldosterone release [44]. The nongenomic response includes rapid effects of aldosterone that cannot be explained by the traditional pathway, or be blocked by inhibitors of gene transcription such as actinomycin D or MRAs [45]. These rapid effects are considered to be also mediated by MR and associated with enhanced activity of the Na^+-K^+-$2Cl^-$ cotransporter and the Na^+-K^+-ATPase in the heart, and of the Na^+-H^+ antiporter, the ENaC and Na^+-K^+-ATPase in the kidney, and are connected to subcellular trafficking [45]. Furthermore, in recent years, an important role of cofactors that modulate the transcription factor activity of MRs to regulate gene transcription has emerged [42]. Coactivator or corepressor proteins are recruited according to distinct MR conformations induced by binding of different agonist ligands, resulting in transcription of different sets of genes [29, 42]. A few years ago, ligand-selective peptides acting as potent antagonists of MR-mediated transcription were identified [42].

Several lines of experimental evidence suggest that excess activation of MRs by aldosterone in podocytes, proximal tubular cells, monocytes and mesangial cells, induces monocyte and macrophage infiltration [46], collagen deposition, and promotion of glomerulosclerosis and interstitial fibrosis [47]. Angiotensin-II, glucose and low-density lipoprotein were shown to induce local production of aldosterone in mesangial cells, which was also proposed to participate in the pathogenesis of CKD in diabetes [48]. Additionally, Klotho deficiency, one of the earliest consequences of CKD that may be driven by albuminuria, also promotes aldosterone synthesis resulting in MR activation [49–51]. In the experimental model of streptozotocin-induced diabetes, the kidney expression of MR, NADPH oxidase and collagen I/IV mRNA results in glomerular and interstitial collagen deposition [52]. Overactivation of MR in the heart promotes, among other things, increased collagen synthesis and fibrosis along with cardiac hypertrophy and adverse remodelling [44, 53, 54]. An additional negative inotropic effect of aldosterone, counteracting the positive inotropic effect of angiotensin-II, has been also described [55].

ACEi and ARB block the RAS and decrease aldosterone synthesis [56–58]. However, the phenomenon of 'aldosterone breakthrough', which refers to the rise in plasma aldosterone levels, is documented in 10%–53% of patients within 6–12 months of ACEi/ARB treatment initiation [30, 59, 60]. Such an increase in aldosterone levels promotes the deleterious proinflammatory and profibrotic effects of aldosterone in the kidneys, heart and vessels. It is proposed that this phenomenon represents a major cause of a limited antiproteinuric response to single RAS blockade, as well as of accelerated GFR decline in patients with CKD despite RAS blocker use [37].

SYSTEMATIC SEARCH STRATEGY

A systematic literature search in PubMed/MEDLINE and Cochrane/CENTRAL up to February 2023 was performed using a

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combination of various keywords related to DKD, albuminuria and non-steroidal MRAs (including specific drug names) to identify RCTs in the field. Screening of reference lists was conducted to identify additional publications. The systematic search strategy used is presented in Supplementary data, Tables S1 and S2. The ClinicalTrials.gov database (https://clinicaltrials.gov) was also hand searched to identify ongoing or completed registered trials regarding the effect of MRAs in diabetic CKD. Eligible studies were RCTs assessing the effect of an MRA alone or on top of an ACEi, or an ARB compared with placebo or any other active treatment on renal outcomes in adults with DKD. Studies in non-adult patients or patients with CKD stage 5, as defined by the Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines, or on renal replacement therapy were excluded. Two investigators (F.I. and M.-E.A.) independently examined the records by title and abstract and then performed full text assessment to identify eligible publications. After the screening process was completed, 30 studies were found to be eligible and are reported in this review. A flow diagram of the study selection process is displayed in Supplementary data, Fig. S1. A risk of bias assessment using the revised Cochrane risk of bias tool [61] for parallel group trials and crossover trials is shown in Supplementary data, Figs S2 and S3, respectively.

STUDIES OF STEROIDAL MRAS IN CKD WITH T2D

During the previous decades, several clinical studies investigated the effects of MRAs in patients with CKD with or without diabetes mellitus. Early works evaluated the effects of steroidal MRAs (spironolactone and eplerenone) on urinary albumin or protein excretion (UAE/UPE) (Table 1) [30, 62]. UAE is the most commonly used intermediate renal outcome, as reductions in albuminuria are strongly associated with a lower risk for renal clinical endpoints, such as kidney failure and fall of eGFR below 15 mL/min/1.73 m^2 [63, 64]. These classical steroidal MRAs antagonize aldosterone binding to the MR ligand-binding pocket, destabilizing the active conformation of the receptor [65]. In the presence of aldosterone they inhibit recruitment of some transcriptional co-activators, but in its absence they exhibit partially agonistic co-activator recruitment effects [36] (Fig. 2). They both lack tissue and ligand specificity, while spironolactone additionally lacks receptor specificity [65]. Canrenone, an active metabolite of spironolactone, was expected to present fewer side effects than spironolactone by averting the antiandrogenic and progestational actions derived from the formation of intermediate products [66]. It was approved for clinical use in Europe, but its use was restricted by hyperkalemia associated with lack of receptor-specific selectivity, similar to older MRAs [67].

Spironolactone

The first study that examined the effects of aldosterone escape and its inhibition in CKD with T2D, included 45 patients with urine albumin-to-creatinine ratio (UACR) 30–300 mg/g and creatinine clearance >60 mL/min who were followed for 40 weeks [68]. Increased aldosterone levels were detected in 40% of these patients, despite trandolapril treatment; among them, 15 patients had UACR increase from baseline, indicating a progressive weakening of the antiproteinuric effect of ACEi. Thirteen of these patients received additionally spironolactone 25 mg for 24 weeks and had significant decreases in albuminuria and left ventricular mass index. Another study [69] evaluated 41 individuals with UPE >1.5 g/day (27 with diabetes), who were randomized to ramipril/placebo/placebo, ramipril/irbesartan/placebo, ramipril/placebo/spironolactone or ramipril/irbesartan/spironolactone (Table 1). After 12 weeks of treatment, UPE reduction was 1.4%, 15.7%, 42.0% and 48.2%, respectively, in the four groups, indicating that addition of spironolactone to ramipril offered greater reduction in albuminuria and hence nephroprotection compared with addition of irbesartan, while triple therapy offered practically no advantage over dual therapy with ramipril/spironolactone. Several other clinical trials in CKD with T2D showed meaningful reductions of albuminuria (around 30%–35%), along with reductions of BP of 6–7/3–4 mmHg and small reversible early dips in eGFR at around 3 mL/min/1.73 m^2 with spironolactone 25–50 mg on top of background treatment with an ACEi or an ARB [70–73], as shown in Table 1. Another detailed study with UACR as the primary endpoint [74] randomly allocated 81 diabetic patients with UACR >300 mg/g, already under treatment with 80 mg of lisinopril, to receive placebo, losartan 100 mg daily or spironolactone 25 mg daily for 48 weeks. The study was designed to assure no differences between groups in ambulatory BP, sodium and protein intake during follow-up. A decrease in UACR by 34.0% for spironolactone and by 16.8% for losartan compared with placebo was noted, with no significant differences between the three groups in change of creatinine clearance (−13.1% for spironolactone, −16.8% for losartan and −16% for placebo, $P = .8$). Serum potassium and incidence of hyperkalemia increased with the addition of either spironolactone or losartan. Subsequent studies confirmed these observations of the significant antialbuminuric effect of spironolactone when administered in addition to an ACEi/ARB in patients with T1D or T2D and increased albuminuria [75–83] (Table 1).

The Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention Of Early Diabetic nephRopathy In TYpe 2 Diabetic Patients With Normoalbuminuria (PRIORITY) trial used the urinary peptidomics biomarker 'CKD273' to identify persons with T2D and normoalbuminuria at high risk of CKD progression [84]. The 209 participants at high risk were randomized to spironolactone or placebo on top of their baseline treatment. While CKD273 indeed identified participants at higher risk of developing moderately increased albuminuria, spironolactone did not significantly decrease the risk of developing moderately increased albuminuria [33% in the placebo group, 25% in the spironolactone group; hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.49–1.34] but increased the risk of hyperkalemia and gynecomastia.

Eplerenone

The effects of eplerenone in CKD with T2D was originally studied in a 2006 RCT that randomized 268 patients with UACR ≥50 mg/g already on enalapril to placebo, eplerenone 50 mg or eplerenone 100 mg for 12 weeks [85]. UACR reductions from baseline were 7.4%, 41.0% and 48.4%, respectively ($P < .001$ for both eplerenone groups) (Table 1). A significant decrease in systolic/diastolic BP (SBP/DBP) was evident for all three treatment groups, without significant differences in between-groups comparisons, indicating that the antialbuminuric effect of MR blockade was independent of BP reduction. There was no difference in the incidence of either sustained (>5.5 mmol/L on two consecutive measurements) or severe (≥6.0 mmol/L at any time-point) hyperkalemia among the three treatment groups. A more recent trial randomized 75 patients with T2D and UACR 30–300 mg/g in a 1:1:1 ratio to receive ramipril 10 mg, eplerenone 50 mg

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Table 1: Main characteristics of RCTs examining the effects of spironolactone, eplerenone and canrenone in albuminuria, renal and cardiovascular outcomes in patients with DKD.

Study	Study design	Patient characteristics	No. of patients	Background treatment	Active treatment	Comparator	Follow-up	Main results
Rossing *et al.* 2005 [71]	Double blind, crossover RCT	T2DM and UAE >300 mg/24 h	21	ACEi or ARB	Spironolactone	Placebo	8 weeks	↓ UAE −33% (95% CI −41%, −25%); 24-h SBP −6 mmHg (95% CI −10, −2); 24-h DBP −4 mmHg (95% CI −6, −2); eGFR −3 mL/min/1.73 m^2 (95% CI −0.3, +6.0) for spironolactone
Schjoedt *et al.* 2005 [72]	Double blind, crossover RCT	T1DM and UAE >300 mg/24 h	20	ACEi or ARB	Spironolactone	Placebo	8 weeks	↓ UAE −30% (95% CI −41%, –17%); 24-h SBP −8 mmHg (95% CI −17, +1); 24-h DBP −3 mmHg (95% CI −7, +0.2); eGFR by −3.4 mL/min/1.73 m^2 (−6.9, 0.1) for spironolactone 1 patient excluded due to hyperK in spironolactone
Chrysostomou *et al.* 2006 [69]	Double blind, parallel-group RCT	UPE >1.5 g/24h	41	Ramipril	Spironolactone	Placebo, irbesartan 150 mg	12 weeks	↓ UPE −42.0% (95% CI −60.1%, −25.5%) for ramipril/spironolactone ($P = .004$ vs ramipril) and −48.2% (95% CI −60.3%, −33.3%) for ramipril/irbesartan/spironolactone group ($P < .001$ vs ramipril)
Schjoedt *et al.* 2006 [70]	Double blind, crossover RCT	T1DM OR T2DM and UAE >2500 mg/24h	20	ACEi or ARB	Spironolactone	Placebo	8 weeks	↓ UAE −32% (95% CI −42%, −21%); 24-h SBP −6 mmHg (95% CI −10, −2); 24-h DBP −4 mmHg (95% CI −6, −2); eGFR −3 mL/min/1.73 m^2 (−6.0, +1.0) ↑ K +0.2 mmol/L (95% CI −0.004, +0.5)
van den Meiracker *et al.* 2006 [73]	Double blind, parallel-group RCT	T2DM and UAE >300 mg/24 h or UACR >20 mg/g	59	ACEi or ARB	Spironolactone	Placebo	1 year	↓ UAE −40.6% (95% CI −57.8%, −23.4%); 24-h SBP −7 mmHg (95% CI −12, −2); 24-h DBP −3 mmHg (95% CI −6, −1); eGFR −12.9 mL/min/1.73 m^2 (−16.5, −9.5) for spironolactone; −4.9 mL/min/1.73 m^2 (−8.9, −0.8) for placebo 5 patients excluded due to hyperK in spironolactone
Epstein *et al.* 2006 [85]	Double blind, parallel-group RCT	T2DM and UACR ≥50 mg/g	268	Enalapril 20 mg	Eplerenone	Placebo	12 weeks	↓ UACR −41% for eplerenone 50 mg; −48.4% for eplerenone 100 mg; −7.4% for placebo ($P < .001$ versus placebo for both) Between-group differences in sustained hyperK (>5.5 mmol/L on two consecutive measurements) $P = .29$; severe hyperK (≥6.0 mmol/L at any timepoint) $P = .38$
Saklayen *et al.* 2008 [75]	Double blind, crossover RCT	T1DM or T2DM patients with any level of proteinuria	30	ACEi or ARB	Spironolactone	Placebo	7 weeks	↓ UPCR from 1.80 ± 1.78 to 0.79 ± 0.99 for spironolactone ($P = .004$); from 1.24 ± 1.13 to 1.57 ± 2.13 for placebo ($P = .35$); eGFR from 61.91 ± 23.4 to 53.94 ± 23.58 for spironolactone ($P = .0001$)
Mehdi *et al.* 2009 [74]	Double blind parallel-group RCT	T1DM or T2DM patients and UACR >300 mg/g	81	Lisinopril 80 mg	Spironolactone	Placebo, losartan 100 mg	48 weeks	↓ UACR −34% (95% CI −51%, −11.2%) for spironolactone ($P = .007$ vs placebo); −16.8% (95% CI −37.3%, +10.5%) for losartan ($P = .2$ vs placebo); % change in creatinine clearance −13.1% (95% CI −21.3%, −3.9%) for spironolactone; −16.8% (95% CI −23.9%, −9.1%) for losartan; −16.0% (95% CI −23.3%, –7.9%) for placebo HyperK episodes (>6.0 mmol/L): 14 patients in spironolactone ($P < .001$ vs placebo); 10 in losartan ($P = .009$ vs placebo); 2 patients in placebo

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Table 1: Continued

Study	Study design	Patient characteristics	No. of patients	Background treatment	Active treatment	Comparator	Follow-up	Main results
Nielsen *et al.* 2012 [79]	Double blind, crossover RCT	T1DM and UAE >30 mg/day	21	ACEi or ARB	Spironolactone	Placebo	60 days	↓ UACR −60% (range −80% to −21%); eGFR from 78 ± 6 to 72 ± 6 mL/min/1.73 m^2 ($P = .003$) HyperK episodes (>5.7 mmol/L): 2 patients in spironolactone group
Hase *et al.* 2013 [82]	Open label, parallel-group RCT	T2DM patients and UACR >100 mg/g	36	ACEi or ARB	Spironolactone	Trichlormethiazide	24 weeks	↓ UAE −57.6 ± 21.3% ($P < .001$) for spironolactone; −48.4 ± 27.1% ($P < .001$) for trichlormethiazide
Ziaee *et al.* 2013 [76]	Parallel-group RCT	T2DM and microalbuminuria	60	Enalapril	Spironolactone	Placebo	12 weeks	↓ UACR from 126 ± 69.3 to 59.3 ± 48.1 for spironolactone ($P < .001$); eGFR from 79.8 ± 18 to 75.6 ± 16.3 mL/min/1.73 m^2 for spironolactone ($P = .6$)
Esteghamati *et al.* 2013 [80]	Open label, parallel-group RCT	T2DM and UAE ≥30 mg/day	136	Losartan	Spironolactone	Enalapril	18 months	↓ UAE −60.5 mg (95% CI −148.8, −16.4) for spironolactone; +22.0 mg (95% CI −110.3, +108.9) for placebo ($P = .017$); SBP −8.89 mmHg (95% CI −15.88, −1.89) for spirolonactone; −6.08 mmHg (−14.71, +2.57) for placebo ($P < .001$); DBP −4.44 mmHg (95% CI −8.10, −0.79) for spironolactone; −2.86 (−7.06, +1.34) for placebo ($P = .001$); eGFR −10.23 mL/min/1.73 m^2 (95% CI −16.69, −3.76) for spironolactone; −9.08 mL/min/1.73 m^2 (−16.06, −2.10) for placebo ($P = .674$)
Oxlund *et al.* 2013 [81]	Double blind, parallel-group RCT	T2DM and resistant hypertension	119	ACEi or ARB	Spironolactone	Placebo	16 weeks	↓ UACR −7.3 mg/g (95% CI −1093, +12.2) for spironolactone; +0 mg/g (95% CI +7, +146.3) for placebo ($P = .001$); placebo-corrected 24-h SBP −8.9 mmHg (95% CI −13.2, −4.6); placebo-corrected 24-h DBP −3.9 mmHg (95% CI −6.2, −1.7) ↑ K +0.26 mmol/L (95% CI +0.1, +0.4) for spironolactone; +0.02 (95% CI +0.07, +0.10) for placebo (between-group $P < .001$)
Fogari *et al.* 2014 [66]	Open label, parallel-group RCT	T2DM and UACR 60–300 mg/g	120	Valsartan	Canrenone	Hydrochlorothiazide	24 weeks	↓ UACR −45.3% for canrenone; −20.3% for hydrochlorothiazide ($P < .01$)
Momeni *et al.* 2015 [83]	Double blind parallel-group RCT	T2DM and proteinuria ≥150 mg/day	60	ACEi or ARB	Spironolactone	Placebo, hydrochlorothiazide	12 weeks	↓ Mean 24 h urine protein from 377.3 ± 250.4 to 168.2 ± 167.3 mg/24 h for spironolactone ($P < .001$); from 432.2 ± 210 to 224.6 ± 172 mg/24 h for spironolactone plus hydrochlorothiazide ($P < .001$); from 356.2 ± 210.1 to 359.4 ± 212.2 mg/24 h for hydrochlorozide alone ($P = .322$)

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Table 1: Continued

Study	Study design	Patient characteristics	No. of patients	Background treatment	Active treatment	Comparator	Follow-up	Main results
Kato *et al.* 2015 [77]	Open-label parallel-group RCT	T2DM and UACR 100–2000 mg/g	52	ACEi or ARB	Spironolactone	Placebo	8 weeks	↓ UACR −33% (95% CI −54%, −22%); eGFR −3.2 ± 9.7 mL/min/1.73 m^2 ($P = .052$)
Chen *et al.* 2018 [78]	Open-label, parallel-group RCT	T2DM and UAER 20–199 μg/min	218	Antihypertensive treatment (other than ACEi/ARB)	Spironolactone	Irbesartan 150 mg or 300 mg	72 weeks	↓ UAER −30 μg/min (95% CI −54, −15) for spironolactone/irbesartan 300 mg; −30 μg/min (95% CI −51, −12) for spironolactone/irbesartan 150 mg; −23 μg/min (95% CI −35, −12) for irbesartan 300 mg; −15 μg/min (95% CI −24, −11) for irbesartan 150 mg (between-group $P < .001$)
Derosa *et al.* 2018 [88]	Double-blind, parallel-group RCT	T2DM and hypertension	182	ARB	Canrenone	Hydrochlorothiazide	12 months	Significant ↓ K only for hydrochlorothiazide ($P < .05$); neutral effect for canrenone Significant ↓ eGFR for hydrochlorothiazide ($P < .01$) Significant ↑ eGFR for canrenone ($P < .05$)
Brandt-Jacobsen *et al.* 2021 (MIRAD trial) [87]	Double blind, parallel-group RCT	T2DM, median UACR 17 mg/g, 12% had eGFR <60 mL/min/1.73 m^2	140	Antihypertensive treatment	Eplerenone	Placebo	26 weeks	↓ UACR by −34% for eplerenone vs placebo ($P = .005$); eGFR −3.5 mL/min/1.73 m^2 for eplerenone Between-group differences in episodes of hyperkalemia (≥5.5 mmol/L) ($P = .276$) ↑ K by +0.26 mmol/L for eplerenone
Mokadem *et al.* 2020 [86]	Single-blind, parallel-group RCT	T2DM and UACR 30–300 mg/g and stage 1 hypertension	75	Antihypertensive treatment	Eplerenone	Ramipril monotherapy, eplerenone/ramipril combination	24 weeks	↓ UACR −70% for eplerenone/ramipril; −37% for ramipril; –38% for eplerenone ($P < .0001$ for combination vs both others) HyperK episodes (>5.5 mmol/L on 2 measurements): 8% for eplerenone/ramipril; 4% for ramipril; 4% for eplerenone (for eplerenone/ramipril vs others $P = 0.5$, ramipril vs eplerenone $P = .6$); for eGFR <60 mL/min/1.73 m^2: ↑ incidence of hyperK for eplerenone/ramipril vs others ($P < .05$)

hyperK, hyperkalemia; K, potassium; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UAER, urinary albumin excretion rate.

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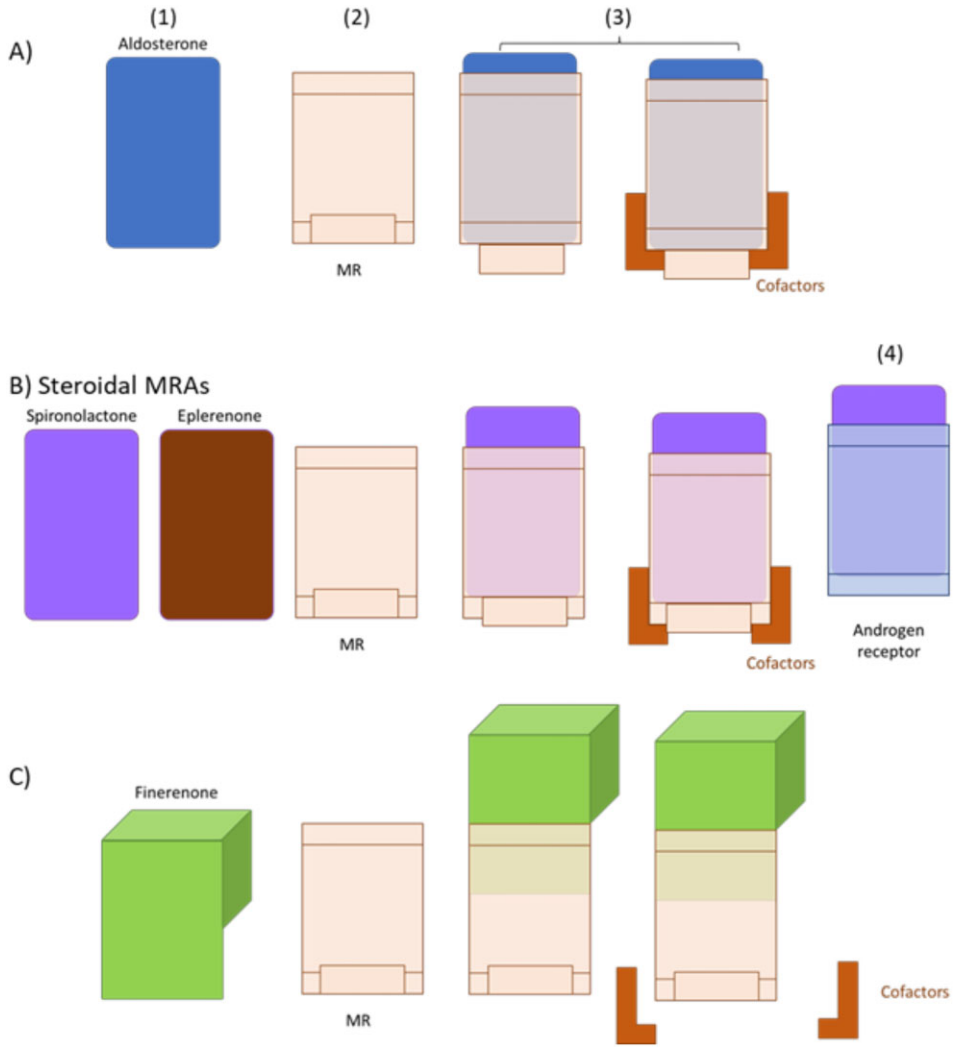


Figure 2: Conceptual representation of MRA structure and impact on MR activation and recruitment of cofactors. (**A**) Aldosterone is an almost planar steroidal molecule that upon binding to the MR promotes its nuclear migration and recruitment of coactivators such as steroid receptor coactivator-1 (SRC-1). (**B**) Spironolactone and eplerenone are quasi-planar MRAs that still retain the capacity to activate the MR and recruit cofactors such as SRC-1, although to a lower extent than aldosterone, hence their inhibition of aldosterone binding and action. Spironolactone can additionally bind to sex hormone receptors. (**C**) Finerenone is a non-steroidal bulky MRA that cannot activate the MR or induce conformational changes required to allow the recruitment of cofactors such as SRC-1. Each panel presents the ligand (1), the MR (2) and the interaction between ligand and MR (3). Panel (C) also shows the interaction between spironolactone and sex hormone receptors (4).

or combination therapy of eplerenone/ramipril 50/10 mg for 24 weeks [86]. A significantly greater reduction in UACR by 70% was observed in the combination group compared with ramipril (37%) or eplerenone (38%) monotherapy groups ($P < .001$ for combination group compared with both monotherapy groups). Overall, no significant differences were noted in the incidence of sustained hyperkalemia (>5.5 mmol/L on two consecutive occasions) between the three treatment groups. However, patients with eGFR <60 mL/min/1.73 m^2 showed a higher incidence of sustained hyperkalemia in the eplerenone/ramipril combination group. A pre-specified analysis of the Mineralocorticoid Receptor Antagonist in Type 2 Diabetes (MIRAD) trial [87] examined effects of either a high dose of eplerenone (100–200 mg) or placebo on top of background antihypertensive treatment for 26 weeks on UACR and changes in 24-h ambulatory BP from baseline in 140 patients with T2D with established or at high risk of cardiovascular disease. A decrease of UACR by 34% was observed for eplerenone compared with placebo ($P = .005$), an effect that was consistent across several subgroups after *post hoc* analysis. The incidence of mild hyperkalemia (≥5.5 mmol/L) did not differ between the two groups ($P = .276$); however, eplerenone was associated with an increase in serum potassium by 0.26 mmol/L and a decrease in eGFR of 3.5 mL/min/1.73 m^2 compared with placebo.

Canrenone

The effects of canrenone on albuminuria, BP levels and kidney-related outcomes were examined in 120 patients with T2D, uncontrolled BP and UACR 60–300 mg/g [66]. After a 2-week placebo period and a 4-week period of combination therapy with valsartan 160 mg plus amlodipine 5 mg, patients were randomized to canrenone or hydrochlorothiazide for a total of 24 weeks. A similar decrease in 24-h SBP/DBP was observed in the two groups, while UAE decreased by 45.3% from baseline in the canrenone group and by 20.3% in the hydrochlorothiazide group ($P < .01$). No significant changes in serum levels of creatinine and potassium were noted. In another study from the same group in

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182 patients with T2D and hypertension [88], a slight decrease in eGFR was observed with hydrochlorothiazide but not with canrenone, and canrenone had a neutral effect on serum potassium levels.

STUDIES OF NOVEL MRAS IN CKD WITH T2D

Finerenone is a third-generation, non-steroidal MRA with tissue and ligand specificity, and equal distribution between heart and kidneys. It inhibits binding of coregulatory molecules to the MR independently of the presence or absence of aldosterone *in vitro* [30]. Finerenone displays distinct effects from steroidal MRAs on cofactor recruitment following MR binding, a fact that was proposed to result in the more potent inhibition of inflammatory and fibrotic pathways, with less potent disruption of the genomic MR effects, resulting in milder BP reduction and potassium retention [36]. Esaxerenone and apararenone are other highly selective non-steroidal MRAs [89, 90]. Finerenone is licensed in Europe, the USA and other countries for nephroprotection and cardioprotection in CKD with T2D, following results of phase 3 RCTs discussed below. Esaxerenone is licensed for hypertension treatment in Japan, following evidence of a dose-dependent BP reduction that is at least equivalent to eplerenone [91]. Both esaxerenone and apararenone have been tested in phase 2 RCTs on CKD with T2D.

Finerenone

The first randomized, double-blind, placebo-controlled study that tested the safety and efficacy of finerenone was the Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study (Table 2) [92]. In this, 821 patients with T2D and moderately or severely increased albuminuria on ACEi or ARB treatment were randomized to placebo and different finerenone doses. Finerenone displayed dose-dependent reductions in placebo-corrected mean ratio of UACR at 3 months relative to baseline (0.79, 0.76, 0.67 and 0.62 for the finerenone 7.5, 10, 15 and 20 mg/day dose groups, respectively); the incidence of hyperkalemia leading to study discontinuation was 2.1%, 0%, 3.2% and 1.7%, respectively. ARTS-DN Japan [93] included 96 patients with T2D and albuminuria and had similar results.

Two large, phase 3 RCTs, Finerenone in reducing kidney failure and disease progression in DKD (FIDELIO-DKD) [27] and Finerenone in reducing cardiovascular mortality and morbidity in DKD (FIGARO-DKD) [28] examined the effects of finerenone on hard renal and cardiovascular outcomes in CKD with T2D. FIDELIO-DKD included 5734 patients with T2D treated with maximum tolerated doses of an ACEi or ARB with either 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 [27]. All patients were required to have serum potassium ≤4.8 mmol/L at screening. Participants were randomized to finerenone 10–20 mg or placebo. At baseline, 12.1% of the participants had moderately (KDIGO A2 albuminuria) and 87.5% severely increased albuminuria (KDIGO A3 albuminuria), while the mean eGFR was 44.3 ± 12.6 mL/min/1.73 m^2. During a median of 2.6 years follow-up finerenone significantly reduced the primary outcome [kidney failure, i.e. dialysis for ≥90 days or kidney transplantation or eGFR <15 mL/min/1.73 m^2, sustained (≥4 weeks) decrease in the eGFR ≥40% from baseline or death from renal causes] compared with placebo (HR 0.82, 95% CI 0.73–0.93). This was also the case for the main secondary renal outcome (kidney failure, sustained eGFR decrease of ≥57% from baseline or renal death; HR 0.76, 95% CI 0.65–0.90) and the secondary cardiovascular outcome [time to first occurrence of cardiovascular death, nonfatal myocardial infraction (MI), nonfatal stroke or hospitalization for heart failure (HHF); HR 0.86, 95% CI 0.75–0.99]. Patients in the finerenone group had a higher mean serum potassium level (maximal difference 0.23 mmol/L) than those on placebo. Hyperkalemia episodes leading to drug discontinuation were more frequent with finerenone compared with placebo but were uncommon (2.3% vs 0.9%).

In the FIGARO-DKD study, 7437 patients with T2D and either 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, who had serum potassium ≤4.8 mmol/L at screening, were randomized to receive finerenone 10–20 mg or placebo on top of a maximum tolerated RAS blocker monotherapy [28]. During a median follow-up of 3.4 years, the primary outcome (cardiovascular death, nonfatal MI, nonfatal stroke or HHF) was reduced with finerenone (HR 0.87, 95% CI 0.76–0.98). The greatest benefit was observed in reduction of risk for HHF (HR 0.71, 95% CI 0.56–0.90). Finerenone was also associated with a marginally significant lower risk for the key secondary renal outcome (kidney failure, sustained decrease in the eGFR ≥40% from baseline, or renal death; HR 0.87, 95% CI 0.76–1.01) and a significant reduction in incidence of end-stage kidney disease (HR 0.64, 95% CI 0.41–0.995). Hyperkalemia leading to drug discontinuation was less common than in the FIDELIO-DKD study (1.2% vs 0.4%, respectively).

It is worth noting that these reductions in the risk of hard renal outcomes with finerenone were originally seen as numerically smaller than those observed with SGLT2i in relevant major trials [13–15]. However, this appears to be largely related to the actual population under study, as exemplified by a *post hoc* analysis of the FIDELIO-DKD [94] including only patients who met the CKD inclusion criteria of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study (UACR >300–5000 mg/g and eGFR 30–<90 mL/min/1.73 m^2) and showing reductions of similar magnitude in cardiorenal endpoints examined.

The FIDELITY analysis was a pre-specified pooled analysis of both FIDELIO-DKD and FIGARO-DKD [95] including a total of 13 171 patients, with mean eGFR 57.6 mL/min/1.73 m^2 and median UACR 515 mg/g. Patients receiving finerenone had lower risk for the composite cardiovascular outcome of time to cardiovascular death, nonfatal MI, nonfatal stroke or HHF (HR 0.86, 95% CI 0.78–0.95) and the composite kidney outcome of time to first onset of kidney failure, sustained eGFR decrease ≥57% or renal death (HR 0.77, 95% CI 0.67–0.88). Among the components of the renal outcome, a 20% reduction in the risk for end-stage kidney disease (HR 0.80, 95% CI 0.64–0.99) was noted. Higher rates of hyperkalemia leading to drug discontinuation were reported with finerenone (1.7%) compared with placebo (0.6%) but no hyperkalemia-related deaths occurred. In a more recent FIDELITY on-treatment analysis [96], finerenone was shown to reduce the incidence of all-cause (HR 0.82, 95% CI 0.70–0.96) and cardiovascular mortality (HR 0.82, 95% CI 0.67–0.99) compared with placebo.

Another FIDELITY analysis, examined the influence of concomitant SGLT2i use on the study outcomes [97]. About 6.7% of patients were on SGLT2i at baseline and 8.5% initiated one during the trials. The HRs with finerenone versus placebo for the kidney composite outcome were 0.80 (95% CI 0.69–0.92) without and 0.42 (95% CI 0.16–1.08) with SGLT2i. For the cardiovascular composite, the HRs were 0.87 (95% CI 0.79–0.96) without and

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Table 2: Main characteristics of RCTs examining the effects of finerenone in albuminuria, renal and cardiovascular outcomes in patients with DKD.

Study	Study design	Patient characteristics	No. of patients	Background treatment	Comparator	Follow-up	Main results
Bakris *et al.* 2015 (ARTS-DN) [92]	Double blind, parallel-group RCT	T2DM and UACR 30–<300 mg/g or >300 mg/g (stratified randomization)	821 (4 different finerenone dose groups)	ACEi or ARB	Placebo	90 days	↓ Placebo-corrected mean ratio of UACR at Day 90 relative to baseline: finerenone 7.5 mg 0.79 ($P = .004$); finerenone 10 mg 0.76 ($P = .001$); finerenone 15 mg 0.67 ($P < .001$); finerenone 20 mg 0.62 ($P < .001$) Significantly ↑ incidence of hyperK episodes leading to study discontinuation: finerenone 7.5 mg 2.1%, finerenone 15 mg 3.2% and finerenone 20 mg 1.7% No significant ↑ in the risk of hyperK for placebo and finerenone 10 mg
Katayama *et al.* 2017 [93]	Double blind, parallel-group RCT	T2DM and UACR 30 to <300 mg/g or >300 mg/g (stratified randomization)	96 (4 different finerenone dose groups)	ACEi or ARB	Placebo	90 days	↓ LS mean ratio of finerenone to baseline (0.712); LS mean ratio of finerenone to placebo (0.670) for finerenone 20 mg ($P = .0240$) ↑ K for finerenone (+0.025, +0.167 mmol/L) vs placebo (−0.075 mmol/L)
Bakris *et al.* 2020 (FIDELIO-DKD) [27]	Double blind, parallel-group RCT	T2DM and: (a) UACR 300–5000 mg/g and eGFR 25–75 mL/min/1.73 m^2 or (b) UACR 30–300 mg/g, eGFR 25–60 mL/min/1.73 m^2, diabetic retinopathy	5734	ACEi or ARB	Placebo	2.6 years	Primary composite endpoint of kidney failure (ESKD or eGFR <15 mL/min/1.73 m^2), eGFR decrease of ≥40%, renal death: HR 0.82, 95% CI 0.73–0.93 Secondary: kidney failure HR 0.87, 95% CI 0.72–1.05; eGFR decrease of ≥40% HR 0.81, 95% CI 0.72–0.92 Secondary composite endpoint of kidney failure (ESKD or eGFR <15 mL/min/1.73 m^2), eGFR decrease of ≥57%, renal death: HR 0.76, 95% CI 0.65–0.90 Secondary composite endpoint of CV death, nonfatal MI/stroke, HHF: HR 0.86, 95% CI 0.75–0.99 Secondary: CV death: HR 0.86, 95% 0.68–1.08; nonfatal MI: HR 0.80, 95% CI 0.58–1.09; nonfatal stroke: HR 1.03, 95% CI 0.76–1.38; HHF: HR 0.86, 95% CI 0.68–1.08 HyperK leading to drug discontinuation: 2.3% for finerenone; 0.9% for placebo
Pitt *et al.* 2021 (FIGARO-DKD) [28]	Double blind, parallel-group RCT	T2DM and: (a) UACR 30–300 mg/g, eGFR ≥25–90 mL/min/1.73 m^2 or (b) UACR 300–5000 mg/g, eGFR ≥60 mL/min/1.73 m^2	7437	ACEi or ARB	Placebo	3.4 years	Primary composite endpoint of CV death, nonfatal MI/stroke, HHF: HR 0.87, 95% CI 0.76–0.98 Secondary: HHF HR 0.71, 95% CI 0.56–0.90 Secondary composite endpoint of kidney failure (ESKD or eGFR <15 mL/min/1.73 m^2), eGFR decrease of ≥40%, renal death: HR 0.87, 95% CI 0.76–1.01 Secondary: ESKD HR 0.64, 95% CI 0.41–0.995 HyperK leading to drug discontinuation: 1.2% finerenone; 0.4% placebo

CV, cardiovascular; ESKD, end-stage kidney disease; hyperK, hyperkalemia; K, potassium; LS, least-squares; T2DM, type 2 diabetes mellitus.

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0.67 (95% CI 0.42–1.07) with SGLT2i. As such, baseline SGLT2i use or SGLT2i at any time did not affect risk reduction with finerenone for the main outcomes. Patients receiving an SGLT2i at baseline had lower incidence of hyperkalemia in both the placebo and finerenone groups. These findings may suggest that MRA and SGLT2i may be complementary to each other in improving efficacy, as assessed by the reduction in the risk of kidney events and cardiovascular events while improving safety by reducing the risk of hyperkalemia [98].

Esaxerenone

Three studies evaluated the effects of esaxerenone on albuminuria in patients with CKD with T2D (Table 3). In a phase 2b trial, 365 patients with T2D, UACR ≥45–<300 mg/g and eGFR ≥30 mL/min/1.73 m^2 treated with a RAS blocker were randomly assigned to receive 0.625, 1.25, 2.5 or 5 mg/day of esaxerenone or placebo for 12 weeks [99]. A dose-dependent reduction of albuminuria was evident with esaxerenone (21% for 0.625 mg, 38% for 1.25 mg, 50% for 2.5 mg and 56% for 5 mg/day) versus placebo that was significantly different from placebo for all esaxerenone dose groups except for the lowest one. In the phase 3 Esaxerenone in Patients with Type 2 Diabetes and Microalbuminuria (ESAX-DN) study, 455 patients with T2D and UACR ≥45–<300 mg/g were randomized to receive esaxerenone 1.25 mg/day, up-titrated to 2.5 mg/day based on serum potassium levels, or placebo on top of a RAS blocker for 52 weeks [100]. Esaxerenone-treated patients had a mean reduction of UACR by 58% versus an 8% increase for placebo-treated patients ($P < .001$), while remission of albuminuria occurred in 22% versus 4% of participants ($P < .001$) in the two groups. More patients in the esaxerenone group had a serum potassium of ≥6.0 or ≥5.5 mmol/L on two consecutive occasions (9% versus 2%, $P = .002$), and 4% versus 1% of patients, in exaserenone and placebo groups, respectively, discontinued treatment due to hyperkalemia. A significantly higher eGFR decline at study-end with esaxerenone (11% vs 1%, respectively) was noted. Finally, in a single-arm, open-label phase 3 study including 56 patients with T2D, UACR ≥300 mg/g and eGFR ≥30 mL/min/1.73 m^2, administration of esaxerenone on top of RAS blockade was associated with UACR reduction by 54.6% and eGFR decline by 8.3 mL/min/1.73 m^2 compared with baseline [101]. Serum potassium levels ≥6.0 mmol/L or ≥5.5 mmol/L on two consecutive occasions occurred in 5.4% of participants.

Apararenone

A phase 2 RCT randomized 293 Japanese patients with T2D and UACR 50–300 mg/g to apararenone 2.5, 5 or 10 mg or placebo [90]. Only around 64% of study patients were treated with a RAS blocker at randomization. After 24 weeks of treatment, a significantly higher dose-dependent UACR decrease by 46.5%–62.9% was observed with apararenone compared with placebo ($P < .001$ for all comparisons). Apararenone was associated with higher rates of UACR remission to <30 mg/g and a decrease in UACR of ≥30% from baseline (7.8%, 29.0% and 28.1%) for the three apararenone doses, respectively. These results were consistent during an open-label extension up to 52 weeks. A dose-dependent increase in serum potassium between 0.14–0.25 mmol/L was observed with apararenone.

POTENTIAL MECHANISMS FOR THE NEPHROPROTECTIVE ACTIONS OF MRAS

As discussed above, previous trials in CKD with T2D investigating dual RAS blockade [i.e. the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) and Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trials] [11, 12] were prematurely terminated due to increased risk for adverse effects, without strong signals of efficacy. Exploring the potential kidney protective mechanisms of action of MRAs and, more specifically, of finerenone, on top of RAS monotherapy should answer the question of why this combination could increase kidney protection when dual conventional RAS blockade does not.

Two main mechanisms have been proposed for the kidney protective effects of MRAs: a haemodynamic impact and a direct action on tissue inflammation and fibrosis. In the FIDELIO-CKD study, finerenone led to an early reduction in UACR by 40% which persisted over time, along with an early eGFR decline, followed by a lower rate of eGFR loss [27], thus supporting that a beneficial act may be driven by a haemodynamic effect. This pattern suggests a decreased intraglomerular pressure which limits podocyte injury and albuminuria, a response similar to conventional RAS blockers and SGLT2i [102, 103]. Albuminuria reduction averts activation of inflammatory and fibrogenic mediators, which contribute to renal scarring, prevents loss of Klotho and even decreases the metabolic load of proximal tubular cells [49, 104, 105]. Studies with SGLT2i have already demonstrated that in patients receiving RAS blockers further reduction of intraglomerular pressure may be of benefit [16, 106, 107]. In previous trials evaluating dual conventional RAS blockade that did not show kidney protection, there was an overlap in the eGFR values early post-initiation of the intervention or placebo, as compared with a clear early dip in eGFR in the finerenone arm of FIDELIO-DKD (Fig. 3). Furthermore, in dual RAS blockade trials the difference in the decrease in albuminuria between the intervention and placebo groups ranged from 11% to 20%, i.e. it was 2- to 4-fold lower than the difference observed in FIDELIO-DKD [11, 12] (Fig. 3). These data are compatible with a contribution of a mild early hemodynamic effect of combining RAS blockade and MRA which was not as evident in dual conventional RAS blockade and which might contribute to finerenone-associated nephroprotection.

The decrease in renal hyperfiltration cannot be the only mechanism of action of MRAs, as there is a limit on the benefits of glomerular pressure reduction and the associated albuminuria decrease. This is partly supported by the analyses of patients who were receiving or started an SGLT2i during the trial, suggesting similar benefits of finerenone in those with or without SGLT2i treatment [97]. As such, a second mechanism related to the nephroprotective action of MRAs has been suggested, involving inhibition of proinflammatory and profibrotic effects originated by transcription factor activity of MR on proinflammatory and profibrotic genes [36, 37]. In previous studies in animal models of diabetes, spironolactone or eplerenone were shown to block MR overexpression [52], reduce collagen deposition [108] and macrophage infiltration [39], prevent podocyte injury [109], and ameliorate glomerulosclerosis. Other benefits of MR antagonism may include preserving Klotho expression and limiting the aldosterone-dependent but RAS-independent adverse effects of Klotho deficiency on cardiorenal injury [51, 110].

Finerenone delays aldosterone-induced nuclear accumulation of MR more efficiently than spironolactone. In contrast

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Table 3: Main studies examining the effects of esaxerenone and apararenone in albuminuria, renal and cardiovascular outcomes in patients with DKD.

Study	Study design	Patient characteristics	No. of patients	Background treatment	Active treatment	Comparator	Follow-up	Main results
Ito *et al.* 2019 [99]	Double-blind, parallel-group RCT	T2DM, UACR 45–300 mg/g, eGFR ≥30 mL/min/1.73 m^2	365	ACEi or ARB	Esaxerenone	Placebo	12 weeks	↓ UACR −38% for esaxerenone 1.25 mg; –50% for esaxerenone 2.5 mg; −56% for esaxerenone 5 mg; −7% for placebo ($P < .001$) Remission of albuminuria: 21% for esaxerenone groups 2.5 and 5 mg; 3% for placebo ($P < .05$ for both comparisons) HyperK leading to drug discontinuation: 3% for esaxerenone 1.25 and 2.5 mg; 10% esaxerenone 10 mg; 1% for placebo
Ito *et al.* 2020 (ESAX-DN) [100]	Double-blind, parallel-group RCT	T2DM, UACR 45–300 mg/g, eGFR ≥30 mL/min/1.73 m^2	455	ACEi or ARB	Esaxerenone	Placebo	52 weeks	↓ UACR −58% for esaxerenone; +8% for placebo ($P < .001$); eGFR −11% for esaxerenone; −1% for placebo Remission of albuminuria: 22% in esaxerenone; 4% in placebo ($P < .001$) Time to 1st transition to overt proteinuria: HR 0.23, 95% CI 0.11–0.48 for esaxerenone HyperK episodes (>6.0 mmol/L or ≥5.5 mmol/L at two consecutive occasions): 9% esaxerenone; 2% placebo ($P = .002$) HyperK leading to drug discontinuation: 4% for esaxerenone; 1% for placebo
Ito *et al.* 2021 [101]	Open label, single-arm study	T2DM, UACR ≥300 mg/g, eGFR ≥30 mL/min/1.73 m^2	56	ACEi or ARB	Esaxerenone		28 weeks	↓ UACR −54.6% ($P < 0.001$); eGFR −8.3 mL/min/1.73 m^2 for esaxerenone HyperK episodes (>6.0 mmol/L or ≥ 5.5 mmol/L at two consecutive occasions): 5.4% for esaxerenone
Wada *et al.* 2021 [90]	Double-blind, parallel-group RCT with open-label extension	T2DM, UACR 50–300 mg/g	293	ACEi or ARB	Apararenone	Placebo	24 and 28 weeks	↓ UACR at 23 weeks −62.9% apararenone 2.5 mg; −50.8% apararenone 5 mg; −46.5% apararenone 10 mg; +113.7% placebo ($P < .001$ versus placebo for all comparisons) % change in eGFR at 52 weeks: −5.3% (−22.0, +10.5) apararenone 2.5 mg; −10.2% (−34.5, +14.6) apararenone 5 mg; −10.80% (− 36.8, +19.1) apararenone 10 mg ↑ K at 52 weeks: +0.14 mmol/L (0.006–0.22) apararenone 2.5 mg; +0.18 mmol/L (0.1–0.26) apararenone 5 mg; +0.25 mmol/L (0.16–0.33) apararenone 10 mg

hyperK, hyperkalemia; K, potassium; T2DM, type 2 diabetes mellitus.

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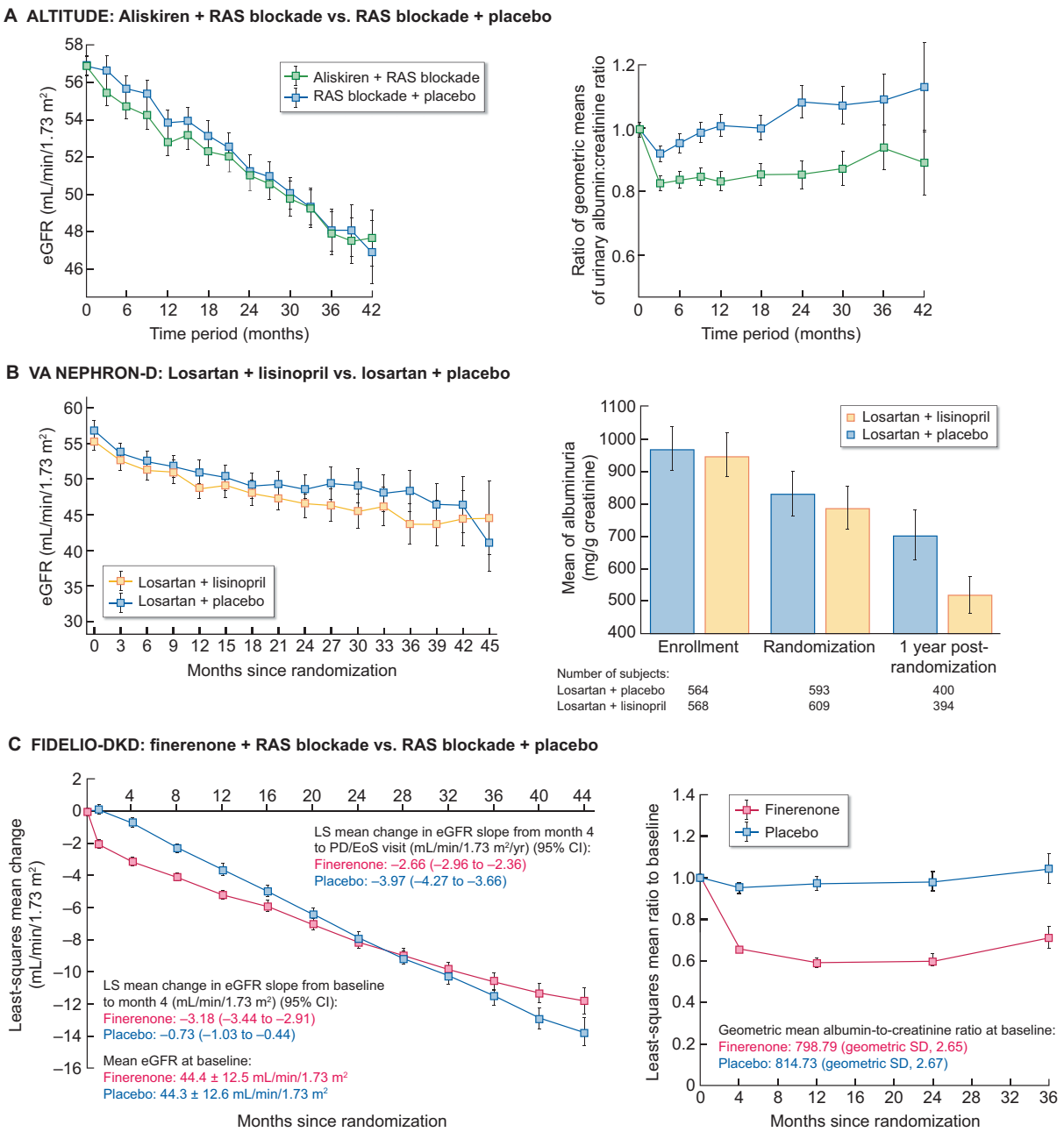


Figure 3: Haemodynamic impact of dual conventional RAS blockade vs MRA plus RAS blockade according to selected large outcomes clinical trials. (**A**) ALTITUDE. Aliskiren + RAS blockade vs placebo + RAS blockade [11]. Note the overlapping SE bars for early eGFR changes and milder early impact on albuminuria than in FIDELIO-DKD. (**B**) VA NEPHRON-D. Losartan + lisinopril vs losartan + placebo [12]. Note overlapping 95% CI bars for early eGFR changes and milder early impact on albuminuria than in FIDELIO-DKD. (**C**) FIDELIO-DKD. Note the non-overlapping 95% CI for the early decrease in eGFR as well as the large decrease in albuminuria. Finerenone + RAS blockade vs RAS blockade + placebo [27]. Note different scales for different graphs (reproduced with permission from Ortiz *et al.* [151]).

to spironolactone, finerenone inhibits MR, steroid receptor coactivator-1 and RNA polymerase II recruitment to MR target genes, thus differentially regulating gene expression [111]. Moreover, both eplerenone and spironolactone behave as activators of the S810L mutant MR responsible for a severe form of early onset hypertension, while finerenone is an antagonist. Finerenone demonstrated stronger anti-inflammatory and anti-fibrotic properties compared with natriuretic-related equivalent doses of eplerenone [112]. Preclinical studies support a benefit of non-steroidal MR antagonism in acute kidney injury (AKI) induced by ischaemia/reperfusion, related to reduced oxidative stress in smooth muscle cells, thus leading to inefficient endothelin-B receptor signalling and defective endothelial nitric oxide synthase (eNOS) activation [113]. In addition, MR antagonism prevented the AKI-to-CKD transition, decreasing pro-inflammatory macrophage infiltration and promoting macrophage polarization to an M2-repair phenotype (over inflammatory M1 macrophage) in the acute phase after the ischaemic injury, through an increased macrophage interleukin-4 receptor expression and activation [114].

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KEY ONGOING STUDIES WITH MRAS OF NEPHROLOGICAL INTEREST

The recently completed Aldosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST) [115] and the ongoing Aldosterone bloCkade for Health Improvement Evaluation in End-stage Renal Disease (ACHIEVE; NCT03020303) are two trials aiming to examine the effect of spironolactone on cardiovascular outcomes and mortality in the dialysis population [116]. Spironolactone is also being retested in patients with heart failure with preserved ejection fraction in the Spironolactone Initiation Registry Randomized Interventional Trial (SPIRRIT; NCT02901184) and the SPIRolactone In the Treatment of Heart Failure (SPIRIT-HF; EudraCT 2017-000697-11).

The phase 3 Trial to Learn How Well Finerenone Works and How Safe it is in Adult Participants With Non diabetic Chronic Kidney Disease (FIND-CKD; NCT05047263) is examining the effect of finerenone versus placebo on top of a RAS blocker in 1580 patients with non-diabetic albuminuric CKD (Table 4). The primary endpoint is mean rate of change in eGFR and the estimated completion date is February 2026. The combination of finerenone and empagliflozin compared with monotherapy with either drug is tested in the phase 2 Study to Learn How Well the Treatment Combination of Finerenone and Empagliflozin Works and How Safe it is Compared to Each Treatment Alone in Adult Participants With Long term Kidney Disease and Type 2 Diabetes (CONFIDENCE; NCT05254002) [117]; the primary endpoint is the relative change from baseline in UACR at 180 days in the combination therapy group versus the empagliflozin monotherapy or the finerenone monotherapy groups. The FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure (FINEARTS-HF; NCT04435626) is evaluating the effects of finerenone on patients with heart failure [New York Heart Association (NYHA) 2–4] and left ventricular ejection fraction (LVEF) ≥40% with a primary endpoint of cardiovascular mortality and HHF. A composite renal endpoint is being tested among the secondary outcomes.

Among other novel non-steroidal MRAs, balcinrenone (AZD-9977) recently completed phase 1 studies in healthy volunteers [118] and patients with heart failure with preserved or mid-range LVEF in comparison with spironolactone [119], while another study has enrolled patients with various degrees of renal impairment (NCT04469907). A phase 2 study (NCT04595370) is comparing the antiproteinuric effect of balcinrenone at ascending doses in combination with dapagliflozin versus dapagliflozin alone in patients with heart failure (NYHA 2–3) with an LVEF <60%, CKD stage 3 and albuminuria. BI690517 completed a phase 1 study in patients with diabetic nephropathy (NCT03165240) and will be evaluated in a phase 2 study (NCT05182840) for its antialbuminuric impact compared with either placebo or empagliflozin monotherapy or combination therapy. KBP-5074 has been tested for BP lowering in a phase 2 trial in patients with uncontrolled hypertension and CKD stage 3b–4 [mean eGFR of 34 mL/min/1.73 m^2 (NCT03574363)] [120], showing placebo-subtracted SBP changes of −7.0 mmHg and −10.2 mmHg with KBP-5074 0.25 and 0.5 mg respectively, and no hyperkalemia-related serious adverse events or hospitalizations. A phase 3 study is currently recruiting patients to assess changes in SBP/DBP, and UACR compared with placebo (NCT04968184). Among other non-steroidal MRAs, LY2623091 [121] was examined in a phase 2 trial including 42 patients with CKD compared with eplerenone (NCT01427972) and PF03882845 [122, 123] in phase 1 studies, but clinical development has been discontinued for both.

MRAS VERSUS ALDOSTERONE SYNTHASE INHIBITORS

Aldosterone synthase (CYP11B2) inhibitors are also being tested in clinical trials [124, 125]. Aldosterone synthase inhibitors may decrease all genomic and non-genomic actions of aldosterone, including non-genomic actions not mediated by the MR [126]. To what extent they may have advantages and improve outcomes over available MRAs remains unclear [127]. In the phase 2 BrigHTN trial, 248 participants with treatment-resistant hypertension (BP ≥130/80 mmHg and receiving a diuretic and at least two other antihypertensive drugs) were randomized to the aldosterone synthase inhibitor baxdrostat (0.5–2.0 mg/day) or placebo. After 12 weeks, systolic BP was reduced by 12.1–20.3 mmHg with baxdrostat and 9.4 mmHg with placebo [128]. A phase 2 RCT is testing different doses of the aldosterone synthase inhibitor BI690517 alone or in combination with empagliflozin to improve kidney function in people with CKD (NCT05182840).

SAFETY OF MRAS IN CKD WITH T2D

Spironolactone and eplerenone have class 1A recommendation for patients with HF with reduced ejection fraction (HFrEF) [23], approximately 30% of whom will also have CKD [129, 130]. According to registry data, however, only 70% of eligible patients are treated with these agents and 70% of these are underdosed [131, 132]. A main reason for physician inertia in this area is the fear of hyperkalemia and impaired kidney function. Spironolactone also induces breast pain and gynecomastia, erectile dysfunction in men, and menstrual irregularities in premenopausal women [130]. Despite not being life-threatening, these adverse effects often influence treatment adherence. These hormonal-type side effects are much less common with eplerenone and no different with finerenone than with placebo in recent trials [27, 28], due to the high selectivity of these drugs. Furthermore, in FIDELIO-DKD and FIGARO-DKD, the incidence of AKI and related discontinuation of drug treatment was low and similar between groups.

The issue of hyperkalemia with MRAs in CKD with T2D should be discussed within the broad concept of hyperkalemia in CKD. Low renal function *per se* is a factor associated with increased serum potassium [133], but development of hyperkalemia in these patients is most commonly multifactorial [134, 135]. Use of ACEi or ARB monotherapy is a usual cause of hyperkalemia and, on the other hand, hyperkalemia is the most common reason for reducing the dose or stopping these agents in the real-word setting [134, 136, 137]. Among patients with CKD, hyperkalemia is more common in those with diabetes mellitus [138]. In the RENAAL trial, an episode of serum potassium ≥5 mmol/L was noted in 22.8% and 38.4% of placebo- and losartan-treated patients, and of ≥5.5 mmol/L in 5.1% and 10.8%, respectively [7, 139]. In ALTITUDE, serum potassium ≥5.5 and <6 mmol/L was noted in 16.9% and 21.2% in RAS monotherapy and combination groups, and >6 mmol/L in 7.2% and 11.2% of participants, respectively (Fig. 3) [11]. Finally, in the NEPHRON-D trial, hyperkalemia defined as potassium >6.0 mmol/L or emergency visit, hospitalization or dialysis was noted in 4.4% and 9.9% of participants on ACEi monotherapy or the ACEi/ARB combination, respectively [12].

Combining a RAS blocker with an MRA is expected to result in even higher rates of hyperkalemia than dual RAS blockade. Indeed, in a meta-analysis of studies evaluating MRAs for albuminuria, addition of an MRA to placebo/active drug was

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Table 4: Key ongoing RCTs or RCTs with pending publications with MRAs and primary kidney outcomes.

Study	Drug	Comparator	Phase	*N*	Population	CKD Exclusion	Primary end point	Status	Estimated completion
NCT05047263 FIND-CKD	Finerenone (BAY94-8862)	Placebo	3	1580	Non-diabetic CKD, UACR ≥200 and ≤3500 mg/g and eGFR ≥25 and <90 mL/min	eGFR <25 mL/min/ 1.73 m²	Mean rate of change in eGFR	Recruiting	February 2026
NCT05254002, CONFIDENCE	Finerenone (BAY94-8862) Empagliflozin	Empagliflozin or placebo	2	807	T2DM and CKD, UACR ≥300 and <5000 mg/g and: in part A eGFR 40–90 mL/min, in part B eGFR 30–90 mL/min	eGFR <30 mL/min/ 1.73 m²	(i) Relative change in UACR at 180 days in finerenone/empagliflozin vs empagliflozin group (ii) Relative change in UACR at 180 days in finerenone/empagliflozin vs finerenone group	Recruiting	June 2024
NCT04595370, MIRACLE	Balcinrenone AZD-9977	Dapagliflozin 10 mg	2	500	HF with LEVF <60%, eGFR ≥30 and ≤60 mL/min and UACR ≥30 and <3000 mg/g	eGFR <30 mL/min/ 1.73 m²	Percent change from baseline in UACR at 12 weeks	Recruiting	December 2023
NCT03165240	BI 690 517	Eplerenone or placebo	1	62	DKD, ≥200 and <3500 mg/g and eGFR ≥20 and <75 mL/min	eGFR <20 mL/min/ 1.73 m²	Percentage of patients with drug-related AEs	Completed	May 2020
NCT05182840	BI 690 517	Empagliflozin or placebo	2	714	CKD, UACR ≥200 and <5000 mg/g and eGFR ≥30 and <90 mL/min	eGFR <30 mL/min/ 1.73 m²	Change from baseline in log transformed UACR up to 14 weeks	Active, not recruiting	July 2023
NCT04968184	KBP-5074	Placebo	3	600	Uncontrolled hypertension CKD Stage 3B/4	eGFR <15 mL/min/ 1.73 m²	Change in SBP	Recruting	Jnuary 2025

AE, adverse events; T2DM, type 2 diabetes mellitus.

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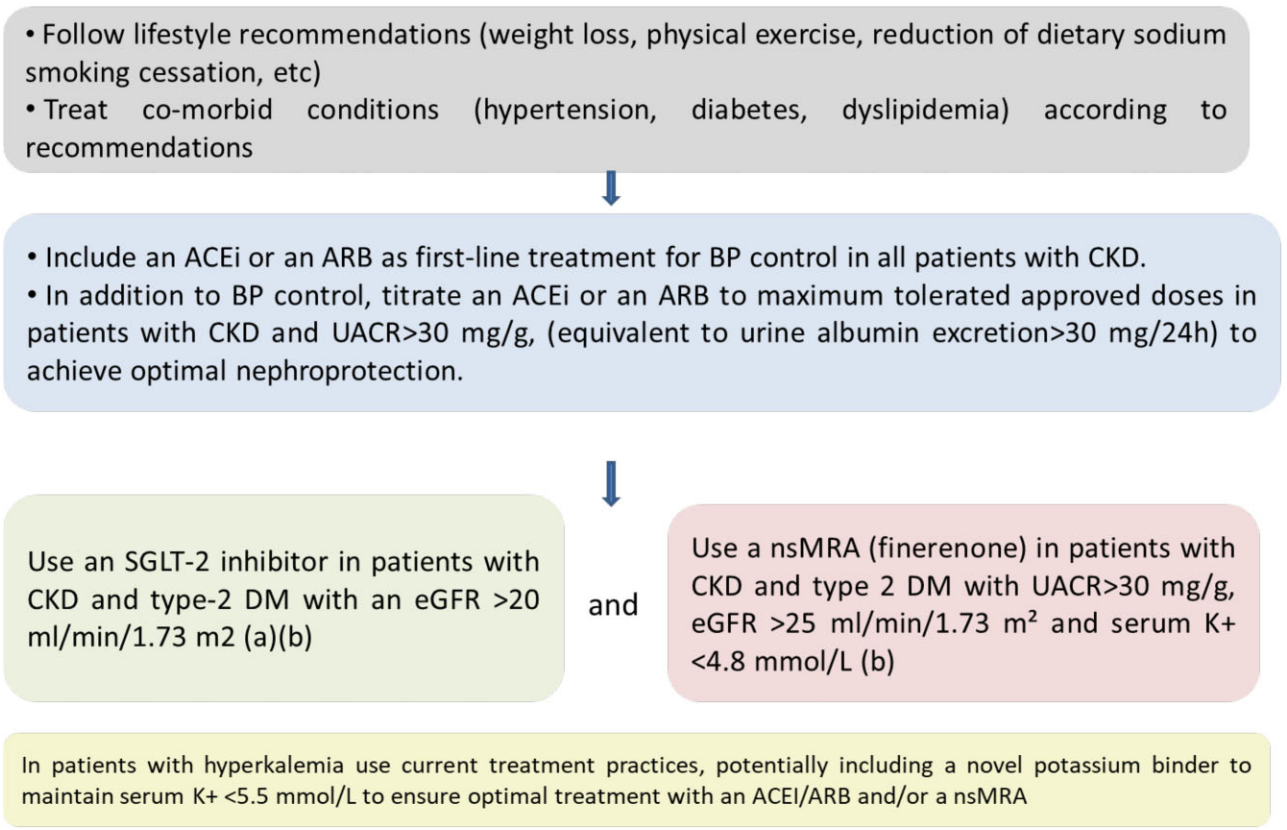


Figure 4: Clinical practice algorithm for treatment of DKD.

associated with 2.6-fold higher hyperkalemia risk. This rose to 4.4-fold if only studies using MRA on top of RAS blockers were considered [26]. The Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease (AMBER) phase 2 trial randomized 295 patients with resistant hypertension and advanced CKD [i.e. eGFR 25–45 mL/min/1.73 m^2 (mean 36 mL/min/1.73 m^2)] to the potassium binder patiromer or placebo to evaluate the rate of hyperkalemia. Two-thirds of patients in the placebo group developed hyperkalemia over the 12-week follow-up, and this risk was halved in the patiromer group [140]. This renin–angiotensin–aldosterone system inhibitor enabling effect of patiromer was also demonstrated in studies in CKD (57% with T2D) [141] and in HFrEF [142, 143].

In the FIDELIO-DKD trial, requiring a serum potassium ≤4.8 mmol/L at study entry, mean serum potassium was about 0.23 mmol/L higher with finerenone than placebo and around 4.6 mmol/L throughout the trial. Incidences of hyperkalemia, defined as serum potassium >5.5 mmol/L occurred in 4.5% and 21.7% of participants and >6.0 mmol/L in 1.4% and 9.8% of participants on placebo and finerenone, respectively [27]. However, the rates of hyperkalemia leading to discontinuation of the trial regimen were rather acceptable (2.3% vs 0.9%), while no fatal hyperkalemia adverse events were reported. Although no head-to-head comparisons in phase 3 trials are available, a previous phase 2 trial directly comparing finerenone with spironolactone in HFrEF [144] and an indirect comparison using AMBER and FIDELITY data in patients with CKD and resistant hypertension [145] support that the rates of hyperkalemia are considerably lower with finerenone than with other steroidal MRAs. As these rates are non-negligible, however, it is strongly recommended to follow the summaries of product characteristics (SPC) recommendations on the use of finerenone, as well as to institute available treatment practices to reduce hyperkalemia risk, potentially including the use of new potassium-binding agents to enable maintenance of RAS blockers and/or non-steroidal MRA, as described in detail elsewhere [135, 146].

CONCLUSIONS ON MRAS USE IN CKD WITH T2D

A multifactorial intervention in patients with T2D, including proper glycaemic and BP control, treatment with an ACEi or ARB, using statins, and implementing lifestyle interventions such as weight loss and physical exercise slows CKD progression and lowers cardiovascular risk. However, such multifactorial interventions have been recommended for decades with implementation rates that are not optimal, while several disappointing RCTs have been performed in patients with CKD and T2D, with agents such as bardoxolone [147], aliskiren [11, 148] and darbepoetin [149]. In the last few years, major trials in patients with T2D, as well as in patients with diabetic and non-diabetic CKD have provided undisputable evidence on the beneficial effects of SGLT2i on renal and cardiovascular outcomes, changing the landscape of the treatment of CKD [13–16]. As such, current recommendations advocate the preferred use of SGLT2i in patients with CKD and T2D on top of single RAS blockade, within their licensed indications [17, 150].

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Following the results from the FIDELIO-DKD [27] and FIGARO-DKD [28] trials, finerenone is currently licensed in several countries for prevention of both kidney and cardiovascular events in patients with CKD and T2D (Fig. 4). A key point is the relative position of SGLT2i and finerenone or other novel MRAs in kidney and cardiovascular protection in CKD with T2D. In this regard, as previously pointed out, SGLT2i were allowed in FIDELIO-DKD and FIGARO-DKD [27, 28], whereas patients treated with MRAs were either excluded or very uncommon in the major SGLT2i trials [13–15]. Preclinical evidence and subgroup analyses of clinical trials currently suggest that the actions of these drug classes may be complementary, but details on whether combination of both would offer additional protection are expected from ongoing RCTs, as discussed above. In addition, the residual risk in these patients is considerable even after SGLT2i use and further justify an SGLT2i and finerenone combination strategy. Similarly, whether finerenone would offer benefits in non-diabetic CKD is expected to be known when the results of the FIND-CKD study are available.

Until further evidence is available, finerenone should be used for nephroprotection and cardioprotection on top of an ACEi or an ARB in maximum tolerated doses and independently of the use of an SGLT2i in patients with CKD with T2D with eGFR >25 mL/min/1.73 m^2, moderately or severely increased albuminuria and serum potassium ≤4.8 mmol/L. As such, treatment for such individuals should be based on three pillars: ACE or ARB, SGLT2i and finerenone. Whether an SGLT2i and finerenone should be started simultaneously or not, or which one should be used first is not known from RCTs currently available, but a personalized approach and regular clinical judgment would rather enable the use of both agents in most patients with a relevant indication, perhaps with a few (i.e. 4–6) weeks interval between the initiation of each of them to allow for repeat checking of BP, eGFR and serum potassium. It should be emphasized that, although currently available steroidal MRAs (i.e. spironolactone and eplerenone) have shown similar benefits in the intermediate outcomes of albuminuria and proteinuria in CKD, none of them has been tested on hard outcomes in CKD. Therefore, the results of FIDELIO-DKD and FIGARO-DKD, in terms of both efficacy on hard kidney and cardiovascular outcomes and safety, cannot be extended to them due to the lack of relevant evidence. The results of currently ongoing and future trials with finerenone and other non-steroidal MRAs and aldosterone synthase inhibitors in CKD with or without T2D are awaited to shed more light on this field.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

REFERENCES

1. Jager KJ, Kovesdy C, Langham R *et al*. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Nephrol Dial Transplant* 2019;**34**:1803–5. https://doi.org/10.1093/ndt/gfz174.
2. Saeedi P, Petersohn I, Salpea P *et al*. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2019;**157**:107843. https://doi.org/10.1016/j.diabres.2019.107843.
3. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol* 2017;**12**:2032–45. https://doi.org/10.2215/CJN.11491116.
4. Afkarian M, Sachs MC, Kestenbaum B *et al*. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013;**24**:302–8. https://doi.org/10.1681/ASN.2012070718.
5. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006;**69**:375–82. https://doi.org/10.1038/sj.ki.5000058.
6. Ortiz A; Asociación Información Enfermedades Renales Genéticas (AIRG-E), European Kidney Patients' Federation (EKPF), Federación Nacional de Asociaciones para la Lucha

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7. Brenner BM, Cooper ME, de Zeeuw D *et al*. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–9. https://doi.org/10.1056/NEJMoa011161.
8. Lewis EJ, Hunsicker LG, Clarke WR *et al*. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–60. https://doi.org/10.1056/NEJMoa011303.
9. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020;**98**:S1–115.
10. Sarafidis P, Papadopoulos CE, Kamperidis V *et al*. Cardiovascular protection with sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists in chronic kidney disease: a milestone achieved. *Hypertension* 2021;**77**:1442–55. https://doi.org/10.1161/HYPERTENSIONAHA.121.17005.
11. Parving HH, Brenner BM, McMurray JJ *et al*. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;**367**:2204–13. https://doi.org/10.1056/NEJMoa1208799.
12. Fried LF, Emanuele N, Zhang JH *et al*. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892–903. https://doi.org/10.1056/NEJMoa1303154.
13. Perkovic V, Jardine MJ, Neal B *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–306. https://doi.org/10.1056/NEJMoa1811744.
14. Heerspink HJL, Stefánsson BV, Correa-Rotter R *et al*. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–46. https://doi.org/10.1056/NEJMoa2024816.
15. The EMPA-KIDNEY Collaborative Group;Herrington WG, Staplin N, Wanner C *et al*. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023;**388**:117–27.
16. Sarafidis P, Ferro CJ, Morales E *et al*. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrol Dial Transplant* 2019;**34**:208–30. https://doi.org/10.1093/ndt/gfy407.
17. de Boer IH, Khunti K, Sadusky T *et al*. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* 2022;**45**:3075–90. https://doi.org/10.2337/dci22-0027.
18. Lim PO, Young WF, MacDonald TM. A review of the medical treatment of primary aldosteronism. *J Hypertens* 2001;**19**:353–61. https://doi.org/10.1097/00004872-200103000-00001.
19. Williams B, MacDonald TM, Morant S *et al*. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;**386**:2059–68. https://doi.org/10.1016/S0140-6736(15)00257-3.
20. Pitt B, Zannad F, Remme WJ *et al*. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study investigators. *N Engl J Med* 1999;**341**:709–17. https://doi.org/10.1056/NEJM199909023411001.
21. Pitt B, Remme W, Zannad F *et al*. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–21. https://doi.org/10.1056/NEJMoa030207.
22. Zannad F, McMurray JJV, Krum H *et al*. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21. https://doi.org/10.1056/NEJMoa1009492.
23. Ponikowski P, Voors AA, Anker SD *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
24. Juurlink DN, Mamdani MM, Lee DS *et al*. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;**351**:543–51. https://doi.org/10.1056/NEJMoa040135.
25. Mullens W, Damman K, Testani JM *et al*. Evaluation of kidney function throughout the heart failure trajectory - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:584–603. https://doi.org/10.1002/ejhf.1697.
26. Alexandrou M-E, Papagianni A, Tsapas A *et al*. Effects of mineralocorticoid receptor antagonists in proteinuric kidney disease: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens* 2019;**37**:2307–24. https://doi.org/10.1097/HJH.0000000000002187.
27. Bakris GL, Agarwal R, Anker SD *et al*. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:2219–29. https://doi.org/10.1056/NEJMoa2025845.
28. Pitt B, Filippatos G, Agarwal R *et al*. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;**385**:2252–63. https://doi.org/10.1056/NEJMoa2110956.
29. Gomez-Sanchez E, Gomez-Sanchez CE. The multifaceted mineralocorticoid receptor. *Compr Physiol* 2014;**4**:965–94. https://doi.org/10.1002/cphy.c130044.
30. Sarafidis PA, Memmos E, Alexandrou M-E *et al*. Mineralocorticoid receptor antagonists for nephroprotection: current evidence and future perspectives. *Curr Pharm Des* 2018;**24**:5528–36. https://doi.org/10.2174/1381612825666190306162658.
31. Shibata S, Rinehart J, Zhang J *et al*. Mineralocorticoid receptor phosphorylation regulates ligand binding and renal response to volume depletion and hyperkalemia. *Cell Metab* 2013;**18**:660–71. https://doi.org/10.1016/j.cmet.2013.10.005.
32. Brown NJ. Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nat Rev Nephrol* 2013;**9**:459–69. https://doi.org/10.1038/nrneph.2013.110.
33. Lavall D, Selzer C, Schuster P *et al*. The mineralocorticoid receptor promotes fibrotic remodeling in atrial fibrillation. *J Biol Chem* 2014;**289**:6656–68. https://doi.org/10.1074/jbc.M113.519256.

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34. Calò LA, Zaghetto F, Pagnin E *et al*. Effect of aldosterone and glycyrrhetinic acid on the protein expression of PAI-1 and p22(phox) in human mononuclear leukocytes. *J Clin Endocrinol Metab* 2004;**89**:1973–6. https://doi.org/10.1210/jc.2003-031545.
35. Terada Y, Kobayashi T, Kuwana H *et al*. Aldosterone stimulates proliferation of mesangial cells by activating mitogen-activated protein kinase 1/2, cyclin D1, and cyclin A. *J Am Soc Nephrol* 2005;**16**:2296–305. https://doi.org/10.1681/ASN.2005020129.
36. Agarwal R, Kolkhof P, Bakris G *et al*. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J* 2021;**42**:152–61. https://doi.org/10.1093/eurheartj/ehaa736.
37. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis. *Kidney Int* 2019;**96**:302–19. https://doi.org/10.1016/j.kint.2019.02.030.
38. Shibata S, Nagase M, Yoshida S *et al*. Podocyte as the target for aldosterone: roles of oxidative stress and Sgk1. *Hypertension* 2007;**49**:355–64. https://doi.org/10.1161/01.HYP.0000255636.11931.a2.
39. Han S-Y, Kim C-H, Kim H-S *et al*. Spironolactone prevents diabetic nephropathy through an anti-inflammatory mechanism in type 2 diabetic rats. *J Am Soc Nephrol* 2006;**17**:1362–72. https://doi.org/10.1681/ASN.2005111196.
40. Patni H, Mathew JT, Luan L *et al*. Aldosterone promotes proximal tubular cell apoptosis: role of oxidative stress. *Am J Physiol Renal Physiol* 2007;**293**:F1065–71. https://doi.org/10.1152/ajprenal.00147.2007.
41. Seckl JR, Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1- a tissue-specific amplifier of glucocorticoid action. *Endocrinology* 2001;**142**:1371–6. https://doi.org/10.1210/endo.142.4.8114.
42. Yang J, Chang C, Safi R *et al*. Identification of ligand-selective peptide antagonists of the mineralocorticoid receptor using phage display. *Mol Endocrinol* 2011;**25**:32–43. https://doi.org/10.1210/me.2010-0193.
43. Viengchareun S, Le Menuet D, Martinerie L *et al*. The mineralocorticoid receptor: insights into its molecular and (patho)physiological biology. *Nucl Recept Signal* 2007;**5**:e012. https://doi.org/10.1621/nrs.05012.
44. Hermidorff MM, de Assis LVM, Isoldi MC. Genomic and rapid effects of aldosterone: what we know and do not know thus far. *Heart Fail Rev* 2017;**22**:65–89. https://doi.org/10.1007/s10741-016-9591-2.
45. Ruhs S, Nolze A, Hübschmann R *et al*. 30 years of the mineralocorticoid receptor: nongenomic effects via the mineralocorticoid receptor. *J Endocrinol* 2017;**234**:T107–24. https://doi.org/10.1530/JOE-16-0659.
46. Rocha R, Rudolph AE, Frierdich GE *et al*. Aldosterone induces a vascular inflammatory phenotype in the rat heart. *Am J Physiol Heart Circ Physiol* 2002;**283**:H1802–10. https://doi.org/10.1152/ajpheart.01096.2001.
47. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest* 1996;**98**:1063–8. https://doi.org/10.1172/JCI118867.
48. Nishikawa T, Matsuzawa Y, Suematsu S *et al*. Effect of atorvastatin on aldosterone production induced by glucose, LDL or angiotensin II in human renal mesangial cells. *Arzneimittelforschung* 2010;**60**:445–51.
49. Fernandez-Fernandez B, Izquierdo MC, Valiño-Rivas L *et al*. Albumin downregulates Klotho in tubular cells. *Nephrol Dial Transplant* 2018;**33**:1712–22. https://doi.org/10.1093/ndt/gfx376.
50. Voelkl J, Alesutan I, Leibrock CB *et al*. Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho-hypomorphic mice. *J Clin Invest* 2013;**123**:812–22.
51. Zhou X, Chen K, Wang Y *et al*. Antiaging gene klotho regulates adrenal CYP11B2 expression and aldosterone synthesis. *J Am Soc Nephrol* 2016;**27**:1765–76. https://doi.org/10.1681/ASN.2015010093.
52. Taira M, Toba H, Murakami M *et al*. Spironolactone exhibits direct renoprotective effects and inhibits renal renin-angiotensin-aldosterone system in diabetic rats. *Eur J Pharmacol* 2008;**589**:264–71. https://doi.org/10.1016/j.ejphar.2008.06.019.
53. Nagase M, Ayuzawa N, Kawarazaki W *et al*. Oxidative stress causes mineralocorticoid receptor activation in rat cardiomyocytes: role of small gtpase Rac1. *Hypertension* 2012;**59**:500–6. https://doi.org/10.1161/HYPERTENSIONAHA.111.185520.
54. Köhler E, Bertschin S, Woodtli T *et al*. Does aldosterone-induced cardiac fibrosis involve direct effects on cardiac fibroblasts? *J Vasc Res* 1996;**33**:315–26.
55. Chai W, Garrelds IM, de Vries R *et al*. Nongenomic effects of aldosterone in the human heart: interaction with angiotensin II. *Hypertension* 2005;**46**:701–6. https://doi.org/10.1161/01.HYP.0000182661.98259.4f.
56. Atlas SA, Case DB, Sealey JE *et al*. Interruption of the renin-angiotensin system in hypertensive patients by captopril induces sustained reduction in aldosterone secretion, potassium retention and natruiresis. *Hypertension* 1979;**1**:274–80. https://doi.org/10.1161/01.HYP.1.3.274.
57. Atlas SA, Niarchos AP, Case DB. Inhibitors of the renin-angiotensin system. Effects on blood pressure, aldosterone secretion and renal function. *Am J Nephrol* 1983;**3**:118–27. https://doi.org/10.1159/000166701.
58. Sánchez RA, Marcó E, Gilbert HB *et al*. Natriuretic effect and changes in renal haemodynamics induced by enalapril in essential hypertension. *Drugs* 1985;**30 Suppl 1**:49–58. https://doi.org/10.2165/00003495-198500301-00008.
59. Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. *Nat Clin Pract Nephrol* 2007;**3**:486–92. https://doi.org/10.1038/ncpneph0575.
60. Sarafidis PA, Ruilope LM. Cardiorenal disease development under chronic renin-angiotensin-aldosterone system suppression. *J Renin Angiotensin Aldosterone Syst* 2012;**13**:217–9. https://doi.org/10.1177/1470320312439140.
61. Sterne JAC, Savović J, Page MJ *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. https://doi.org/10.1136/bmj.l4898.
62. Sarafidis PA, Ruilope LM. Aggressive blood pressure reduction and renin-angiotensin system blockade in chronic kidney disease: time for re-evaluation? *Kidney Int* 2014;**85**:536–46. https://doi.org/10.1038/ki.2013.355.
63. Carrero JJ, Grams ME, Sang Y *et al*. Albuminuria changes are associated with subsequent risk of end-stage renal disease and mortality. *Kidney Int* 2017;**91**:244–51. https://doi.org/10.1016/j.kint.2016.09.037.
64. Heerspink HJL, Greene T, Tighiouart H *et al*. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. *Lancet Diabetes Endocrinol* 2019;**7**:128–39. https://doi.org/10.1016/S2213-8587(18)30314-0.

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65. Rogerson FM, Yao Y, Smith BJ *et al*. Differences in the determinants of eplerenone, spironolactone and aldosterone binding to the mineralocorticoid receptor. *Clin Exp Pharmacol Physiol* 2004;**31**:704–9. https://doi.org/10.1111/j.1440-1681.2004.04079.x.
66. Fogari R, Derosa G, Zoppi A *et al*. Comparative effect of canrenone or hydrochlorothiazide addition to valsartan/amlodipine combination on urinary albumin excretion in well-controlled type 2 diabetic hypertensive patients with microalbuminuria. *Expert Opin Pharmacother* 2014;**15**:453–9. https://doi.org/10.1517/14656566.2014.874415.
67. Gomez-Sanchez EP. Third-generation mineralocorticoid receptor antagonists: why do we need a fourth? *J Cardiovasc Pharmacol* 2016;**67**:26–38. https://doi.org/10.1097/FJC.0000000000000329.
68. Sato A, Hayashi K, Naruse M *et al*. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. *Hypertension* 2003;**41**:64–8. https://doi.org/10.1161/01.HYP.0000044937.95080.E9.
69. Chrysostomou A, Pedagogos E, MacGregor L *et al*. Double-blind, placebo-controlled study on the effect of the aldosterone receptor antagonist spironolactone in patients who have persistent proteinuria and are on long-term angiotensin-converting enzyme inhibitor therapy, with or without an angiotensin II receptor blocker. *Clin J Am Soc Nephrol* 2006;**1**:256–62.
70. Schjoedt KJ, Rossing K, Juhl TR *et al*. Beneficial impact of spironolactone on nephrotic range albuminuria in diabetic nephropathy. *Kidney Int* 2006;**70**:536–42. https://doi.org/10.1038/sj.ki.5001580.
71. Rossing K, Schjoedt KJ, Smidt UM *et al*. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. *Diabetes Care* 2005;**28**:2106–12. https://doi.org/10.2337/diacare.28.9.2106.
72. Schjoedt KJ, Rossing K, Juhl TR *et al*. Beneficial impact of spironolactone in diabetic nephropathy. *Kidney Int* 2005;**68**:2829–36. https://doi.org/10.1111/j.1523-1755.2005.00756.x.
73. van den Meiracker AH, Baggen RG, Pauli S *et al*. Spironolactone in type 2 diabetic nephropathy: effects on proteinuria, blood pressure and renal function. *J Hypertens* 2006;**24**:2285–92. https://doi.org/10.1097/01.hjh.0000249708.44016.5c.
74. Mehdi UF, Adams-Huet B, Raskin P *et al*. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol* 2009;**20**:2641–50. https://doi.org/10.1681/ASN.2009070737.
75. Saklayen MG, Gyebi LK, Tasosa J *et al*. Effects of additive therapy with spironolactone on proteinuria in diabetic patients already on ACE inhibitor or ARB therapy: results of a randomized, placebo-controlled, double-blind, crossover trial. *J Investig Med* 2008;**56**:714–9. https://doi.org/10.2310/JIM.0b013e31816d78e9.
76. Ziaee A, Abbas Vaezi A, Oveisi S *et al*. Effects of additive therapy with spironolactone on albuminuria in diabetes mellitus: a pilot randomized clinical trial. *Caspian J Intern Med* 2013;**4**:648–53.
77. Kato S, Maruyama S, Makino H *et al*. Anti-albuminuric effects of spironolactone in patients with type 2 diabetic nephropathy: a multicenter, randomized clinical trial. *Clin Exp Nephrol* 2015;**19**:1098–106. https://doi.org/10.1007/s10157-015-1106-2.
78. Chen Y, Liu P, Chen X *et al*. Effects of different doses of irbesartan combined with spironolactone on urinary albumin excretion rate in elderly patients with early type 2 diabetic nephropathy. *Am J Med Sci* 2018;**355**:418–24. https://doi.org/10.1016/j.amjms.2018.01.017.
79. Nielsen SE, Persson F, Frandsen E *et al*. Spironolactone diminishes urinary albumin excretion in patients with type 1 diabetes and microalbuminuria: a randomized placebo-controlled crossover study. *Diabet Med* 2012;**29**:e184–90. https://doi.org/10.1111/j.1464-5491.2012.03585.x.
80. Esteghamati A, Noshad S, Jarrah S *et al*. Long-term effects of addition of mineralocorticoid receptor antagonist to angiotensin II receptor blocker in patients with diabetic nephropathy: a randomized clinical trial. *Nephrol Dial Transplant* 2013;**28**:2823–33. https://doi.org/10.1093/ndt/gft281.
81. Oxlund CS, Henriksen JE, Tarnow L *et al*. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. *J Hypertens* 2013;**31**:2094–102. https://doi.org/10.1097/HJH.0b013e3283638b1a.
82. Hase M, Babazono T, Ujihara N *et al*. Comparison of spironolactone and trichlormethiazide as add-on therapy to renin-angiotensin blockade for reduction of albuminuria in diabetic patients. *J Diabetes Investig* 2013;**4**:316–9. https://doi.org/10.1111/jdi.12029.
83. Momeni A, Behradmanesh MS, Kheiri S *et al*. Evaluation of spironolactone plus hydrochlorothiazide in reducing proteinuria in type 2 diabetic nephropathy. *J Renin Angiotensin Aldosterone Syst* 2015;**16**:113–8. https://doi.org/10.1177/1470320313481485.
84. Tofte N, Lindhardt M, Adamova K *et al*. Early detection of diabetic kidney disease by urinary proteomics and subsequent intervention with spironolactone to delay progression (PRIORITY): a prospective observational study and embedded randomised placebo-controlled trial. *Lancet Diabetes Endocrinol* 2020;**8**:301–12. https://doi.org/10.1016/S2213-8587(20)30026-7.
85. Epstein M, Williams GH, Weinberger M *et al*. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2006;**1**:940–51. https://doi.org/10.2215/CJN.00240106.
86. El Mokadem M, Abd El Hady Y, Aziz A. A prospective single-blind randomized trial of ramipril, eplerenone and their combination in type 2 diabetic nephropathy. *Cardiorenal Med* 2020;**10**:392–401. https://doi.org/10.1159/000508670.
87. Brandt-Jacobsen NH, Johansen ML, Rasmussen J *et al*. Effect of high-dose mineralocorticoid receptor antagonist eplerenone on urinary albumin excretion in patients with type 2 diabetes and high cardiovascular risk: data from the MIRAD trial. *Diabetes Metab* 2021;**47**:101190. https://doi.org/10.1016/j.diabet.2020.08.005.
88. Derosa G, Gaudio G, Pasini G *et al*. A randomized, double-blind clinical trial of canrenone vs hydrochlorothiazide in addition to angiotensin II receptor blockers in hypertensive type 2 diabetic patients. *Drug Des Devel Ther* 2018;**12**:2611–6. https://doi.org/10.2147/DDDT.S151449.
89. Takahashi M, Ubukata O, Homma T *et al*. Crystal structure of the mineralocorticoid receptor ligand-binding domain in complex with a potent and selective nonsteroidal blocker, esaxerenone (CS-3150). *FEBS Lett* 2020;**594**:1615–23. https://doi.org/10.1002/1873-3468.13746.

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90. Wada T, Inagaki M, Yoshinari T *et al*. Apararenone in patients with diabetic nephropathy: results of a randomized, double-blind, placebo-controlled phase 2 dose-response study and open-label extension study. *Clin Exp Nephrol* 2021;**25**:120–30. https://doi.org/10.1007/s10157-020-01963-z.
91. Ito S, Itoh H, Rakugi H *et al*. Double-blind randomized phase 3 study comparing esaxerenone (CS-3150) and eplerenone in patients with essential hypertension (ESAX-HTN Study). *Hypertension* 2020;**75**:51–8. https://doi.org/10.1161/HYPERTENSIONAHA.119.13569.
92. Bakris GL, Agarwal R, Chan JC *et al*. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* 2015;**314**:884–94. https://doi.org/10.1001/jama.2015.10081.
93. Katayama S, Yamada D, Nakayama M *et al*. A randomized controlled study of finerenone versus placebo in Japanese patients with type 2 diabetes mellitus and diabetic nephropathy. *J Diabetes Complications* 2017;**31**:758–65. https://doi.org/10.1016/j.jdiacomp.2016.11.021.
94. Agarwal R, Anker SD, Filippatos G *et al*. Effects of canagliflozin versus finerenone on cardiorenal outcomes: exploratory post hoc analyses from FIDELIO-DKD compared to reported CREDENCE results. *Nephrol Dial Transplant* 2022;**37**:1261–9. https://doi.org/10.1093/ndt/gfab336.
95. Agarwal R, Filippatos G, Pitt B *et al*. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;**43**:474–84. https://doi.org/10.1093/eurheartj/ehab777.
96. Filippatos G, Anker SD, August P *et al*. Finerenone and effects on mortality in chronic kidney disease and type 2 diabetes: a FIDELITY analysis. *Eur Heart J Cardiovasc Pharmacother* 2023;**9**:183–91. https://doi.org/10.1093/ehjcvp/pvad001.
97. 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. *Diabetes Care* 2022;**45**:2991–8. https://doi.org/10.2337/dc22-0294.
98. Ortiz A, Sarafidis P, Ferro CJ. Cardiovascular events with finerenone in CKD and diabetes. *N Engl J Med* 2022;**386**:e43.
99. Ito S, Shikata K, Nangaku M *et al*. Efficacy and safety of esaxerenone (CS-3150) for the treatment of type 2 diabetes with microalbuminuria: a randomized, double-blind, placebo-controlled, phase II trial. *Clin J Am Soc Nephrol* 2019;**14**:1161–72. https://doi.org/10.2215/CJN.14751218.
100. Ito S, Kashihara N, Shikata K *et al*. Esaxerenone (CS-3150) in patients with type 2 diabetes and microalbuminuria (ESAX-DN): phase 3 randomized controlled clinical trial. *Clin J Am Soc Nephrol* 2020;**15**:1715–27. https://doi.org/10.2215/CJN.06870520.
101. Ito S, Kashihara N, Shikata K *et al*. Efficacy and safety of esaxerenone (CS-3150) in Japanese patients with type 2 diabetes and macroalbuminuria: a multicenter, single-arm, open-label phase III study. *Clin Exp Nephrol* 2021;**25**:1070–8. https://doi.org/10.1007/s10157-021-02075-y.
102. Fernandez-Fernandez B, Fernandez-Prado R, Górriz JL *et al*. Canagliflozin and renal events in diabetes with established nephropathy clinical evaluation and study of diabetic nephropathy with atrasentan: what was learned about the treatment of diabetic kidney disease with canagliflozin and atrasentan? *Clin Kidney J* 2019;**12**:313–21. https://doi.org/10.1093/ckj/sfz070.
103. Fernandez-Fernandez B, Sarafidis P, Kanbay M *et al*. SGLT2 inhibitors for non-diabetic kidney disease: drugs to treat CKD that also improve glycaemia. *Clin Kidney J* 2020;**13**:728–33. https://doi.org/10.1093/ckj/sfaa198.
104. Zoja C, Benigni A, Remuzzi G. Cellular responses to protein overload: key event in renal disease progression. *Curr Opin Nephrol Hypertens* 2004;**13**:31–7. https://doi.org/10.1097/00041552-200401000-00005.
105. Fernández-Fernández B, Valiño-Rivas L, Sánchez-Niño MD *et al*. Albuminuria downregulation of the anti-aging factor Klotho: the missing link potentially explaining the association of pathological albuminuria with premature death. *Adv Ther* 2020;**37**:62–72. https://doi.org/10.1007/s12325-019-01180-5.
106. Cherney DZI, Perkins BA, Soleymanlou N *et al*. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;**129**:587–97. https://doi.org/10.1161/CIRCULATIONAHA.113.005081.
107. van Bommel EJM, Muskiet MHA, van Baar MJB *et al*. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. *Kidney Int* 2020;**97**:202–12. https://doi.org/10.1016/j.kint.2019.09.013.
108. Fujisawa G, Okada K, Muto S *et al*. Spironolactone prevents early renal injury in streptozotocin-induced diabetic rats. *Kidney Int* 2004;**66**:1493–502. https://doi.org/10.1111/j.1523-1755.2004.00913.x.
109. Kang YS, Ko GJ, Lee MH *et al*. Effect of eplerenone, enalapril and their combination treatment on diabetic nephropathy in type II diabetic rats. *Nephrol Dial Transplant* 2009;**24**:73–84. https://doi.org/10.1093/ndt/gfn448.
110. Kanbay M, Demiray A, Afsar B *et al*. Role of Klotho in the development of essential hypertension. *Hypertension* 2021;**77**:740–50. https://doi.org/10.1161/HYPERTENSIONAHA.120.16635.
111. Amazit L, Le Billan F, Kolkhof P *et al*. Finerenone impedes aldosterone-dependent nuclear import of the mineralocorticoid receptor and prevents genomic recruitment of steroid receptor coactivator-1. *J Biol Chem* 2015;**290**:21876–89. https://doi.org/10.1074/jbc.M115.657957.
112. Kolkhof P, Delbeck M, Kretschmer A *et al*. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol* 2014;**64**:69–78. https://doi.org/10.1097/FJC.0000000000000091.
113. Fiorentino M, Grandaliano G, Gesualdo L *et al*. Acute kidney injury to chronic kidney disease transition. *Contrib Nephrol* 2018;**193**:45–54. https://doi.org/10.1159/000484962.
114. Barrera-Chimal J, Rocha L, Amador-Martínez I *et al*. Delayed spironolactone administration prevents the transition from acute kidney injury to chronic kidney disease through improving renal inflammation. *Nephrol Dial Transplant* 2019;**34**:794–801. https://doi.org/10.1093/ndt/gfy246.
115. Rossignol P, Frimat L, Zannad F. The safety of mineralocorticoid antagonists in maintenance hemodialysis patients: two steps forward. *Kidney Int* 2019;**95**:747–9. https://doi.org/10.1016/j.kint.2018.12.006.
116. Rossignol P, Pitt B. Mineralocorticoid receptor antagonist use in renal dialysis: will evidence from prospective randomized trials confirm the results from "real-world"

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evidence? *Eur J Heart Fail* 2023;**25**:361–3. https://doi.org/10.1002/ejhf.2804.
117. Green JB, Mottl AK, Bakris G *et al*. Design of the COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using an UACR Endpoint study (CONFIDENCE). *Nephrol Dial Transplant* 2023;**38**:894–903. https://doi.org/10.1093/ndt/gfac198.
118. Whittaker A, Kragh AM, Åm K *et al*. Safety, tolerability, and pharmacokinetics of the mineralocorticoid receptor modulator AZD9977 in healthy men: a phase I multiple ascending dose study. *Clin Transl Sci* 2020;**13**:275–83. https://doi.org/10.1111/cts.12705.
119. Squire IB, Gabrielsen A, Greasley PJ *et al*. Effect of AZD9977 and spironolactone on serum potassium in heart failure with preserved or mildly reduced ejection fraction, and renal impairment: a randomized trial. *Clin Transl Sci* 2022;**15**:2493–504. https://doi.org/10.1111/cts.13377.
120. Bakris G, Pergola PE, Delgado B *et al*. Effect of KBP-5074 on blood pressure in advanced chronic kidney disease: results of the BLOCK-CKD study. *Hypertension* 2021;**78**:74–81. https://doi.org/10.1161/HYPERTENSIONAHA.121.17073.
121. Wang EB, Chaudhary A, Waterhouse TH *et al*. Population pharmacokinetics of LY2623091 in patients with hypertension and chronic kidney disease. *J Clin Pharmacol* 2017;**57**:739–46. https://doi.org/10.1002/jcph.865.
122. Orena S, Maurer TS, She L *et al*. PF-03882845, a non-steroidal mineralocorticoid receptor antagonist, prevents renal injury with reduced risk of hyperkalemia in an animal model of nephropathy. *Front Pharmacol* 2013;**4**:115. https://doi.org/10.3389/fphar.2013.00115.
123. Sueta D, Yamamoto E, Tsujita K. Mineralocorticoid receptor blockers: novel selective nonsteroidal Mineralocorticoid receptor antagonists. *Curr Hypertens Rep* 2020;**22**:21. https://doi.org/10.1007/s11906-020-1023-y.
124. Sloan-Lancaster J, Raddad E, Flynt A *et al*. LY3045697: results from two randomized clinical trials of a novel inhibitor of aldosterone synthase. *J Renin Angiotensin Aldosterone Syst* 2017;**18**:1470320317717883. https://doi.org/10.1177/1470320317717883.
125. Forzano I, Mone P, Varzideh F *et al*. The selective aldosterone synthase inhibitor baxdrostat significantly lowers blood pressure in patients with resistant hypertension. *Front Endocrinol (Lausanne)* 2022;**13**:1097968. https://doi.org/10.3389/fendo.2022.1097968.
126. Azizi M, Amar L, Menard J. Aldosterone synthase inhibition in humans. *Nephrol Dial Transplant* 2013;**28**:36–43. https://doi.org/10.1093/ndt/gfs388.
127. Ando H. Inhibition of aldosterone synthase: does this offer advantages compared with the blockade of mineralocorticoid receptors? *Hypertens Res* 2023;**46**:1056–7. https://doi.org/10.1038/s41440-023-01188-z.
128. Freeman MW, Halvorsen Y-D, Marshall W *et al*. Phase 2 trial of baxdrostat for treatment-resistant hypertension. *N Engl J Med* 2023;**388**:395–405. https://doi.org/10.1056/NEJMoa2213169.
129. Zannad F, Rossignol P. Cardiorenal syndrome revisited. *Circulation* 2018;**138**:929–44. https://doi.org/10.1161/CIRCULATIONAHA.117.028814.
130. Pitt B, Rossignol P. The safety of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure. *Expert Opin Drug Saf* 2016;**15**:659–65. https://doi.org/10.1517/14740338.2016.1163335.
131. Maggioni AP, Anker SD, Dahlström U *et al*. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013;**15**:1173–84. https://doi.org/10.1093/eurjhf/hft134.
132. Rossignol P, Lainscak M, Crespo-Leiro MG *et al*. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail* 2020;**22**:1378–89. https://doi.org/10.1002/ejhf.1793.
133. Sarafidis PA, Blacklock R, Wood E *et al*. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin J Am Soc Nephrol* 2012;**7**:1234–41. https://doi.org/10.2215/CJN.01150112.
134. Sarafidis PA, Georgianos PI, Bakris GL. Advances in treatment of hyperkalemia in chronic kidney disease. *Expert Opin Pharmacother* 2015;**16**:2205–15. https://doi.org/10.1517/14656566.2015.1083977.
135. Valdivielso JM, Balafa O, Ekart R *et al*. Hyperkalemia in chronic kidney disease in the new era of kidney protection therapies. *Drugs* 2021;**81**:1467–89. https://doi.org/10.1007/s40265-021-01555-5.
136. Einhorn LM, Zhan M, Hsu VD *et al*. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;**169**:1156–62. https://doi.org/10.1001/archinternmed.2009.132.
137. Epstein M, Reaven NL, Funk SE *et al*. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015;**21**:S212–20.
138. Loutradis C, Tolika P, Skodra A *et al*. Prevalence of hyperkalemia in diabetic and non-diabetic patients with chronic kidney disease: a nested case-control study. *Am J Nephrol* 2015;**42**:351–60. https://doi.org/10.1159/000442393.
139. Miao Y, Dobre D, Heerspink HJL *et al*. Increased serum potassium affects renal outcomes: a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. *Diabetologia* 2011;**54**:44–50. https://doi.org/10.1007/s00125-010-1922-6.
140. Agarwal R, Rossignol P, Romero A *et al*. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2019;**394**:1540–50. https://doi.org/10.1016/S0140-6736(19)32135-X.
141. Weir MR, Bakris GL, Bushinsky DA *et al*. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015;**372**:211–21. https://doi.org/10.1056/NEJMoa1410853.
142. Pitt B, Anker SD, Bushinsky DA *et al*. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011;**32**:820–8. https://doi.org/10.1093/eurheartj/ehq502.
143. Butler J, Anker SD, Lund LH *et al*. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. *Eur Heart J* 2022;**43**:4362–73. https://doi.org/10.1093/eurheartj/ehac401.
144. Pitt B, Kober L, Ponikowski P *et al*. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J* 2013;**34**:2453–63. https://doi.org/10.1093/eurheartj/eht187.

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145. Agarwal R, Pitt B, Palmer BF *et al*. A comparative post hoc analysis of finerenone and spironolactone in resistant hypertension in moderate-to-advanced chronic kidney disease. *Clin Kidney J* 2023;**16**:293–302. https://doi.org/10.1093/ckj/sfac234.
146. Rossignol P, Silva-Cardoso J, Kosiborod MN *et al*. Pragmatic diagnostic and therapeutic algorithms to optimize new potassium binder use in cardiorenal disease. *Pharmacol Res* 2022;**182**:106277. https://doi.org/10.1016/j.phrs.2022.106277.
147. de Zeeuw D, Akizawa T, Audhya P *et al*. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med* 2013;**369**:2492–503. https://doi.org/10.1056/NEJMoa1306033.
148. Tang SCW, Chan KW, Ip DKM *et al*. Direct renin inhibition in non-diabetic chronic kidney disease (DRINK): a prospective randomized trial. *Nephrol Dial Transplant* 2021;**36**:1648–56. https://doi.org/10.1093/ndt/gfaa085.
149. Pfeffer MA, Burdmann EA, Chen C-Y *et al*. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**:2019–32. https://doi.org/10.1056/NEJMoa0907845.
150. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2022;**102**:S1–127. https://doi.org/10.1016/j.kint.2022.06.008.
151. Ortiz A, Ferro CJ, Balafa O *et al*. Mineralocorticoid receptor antagonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. *Nephrol Dial Transplant* 2023;**38**:10–25. https://doi.org/10.1093/ndt/gfab167.

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