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MICROVASCULAR COMPLICATIONS—NEPHROPATHY (M AFKARIAN AND B ROSHANRAVAN, SECTION EDITORS)

Mineralocorticoid Antagonism and Diabetic Kidney Disease

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Abstract

Purpose of Review Type 2 diabetes (T2D) is associated with an increased risk of diabetic kidney disease (DKD), cardiovascular disease, and heart failure, in part through activation of the renin-angiotensin-aldosterone system (RAAS). Although recent cardiovascular outcome trials have identified newer therapeutic agents such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1)-receptor agonists that reduce the risk of these complications, patients still exhibit residual cardiorenal morbidity and mortality. Accordingly, the identification of pharmacological agents that attenuate micro- and macrovascular complications related to T2D is a major priority. Our aim was to review evidence for the role of novel mineralocorticoid receptor antagonists (MRAs) that are being developed as adjunctive therapies to reduce the risk of DKD and cardiovascular disease in the setting of T2D.

Recent Findings Dual RAAS blockade with angiotensin-converting enzyme (ACE) inhibitor plus angiotensin receptor blockade (ARB) or ARB plus renin inhibition increases serious adverse events such as acute kidney injury and stroke. Due to the potential for these serious side effects, more recent interest has focused on newer, more selective non-steroidal MRAs such as finerenone as cardiorenal protective therapies. Finerenone reduces albuminuria in the setting of DKD in patients with T2D and has a lower risk of hyperkalemia compared to currently available MRAs.

Summary Novel MRAs such as finerenone have the potential to reduce the risk of DKD progression in patients with T2D. The impact of finerenone on hard, long-term cardiorenal endpoints is being examined in the FIGARO and FIDELIO trials in patients with DKD.

Keywords Mineralocorticoid receptor antagonist · Diabetes · Diabetic kidney disease

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Introduction

In the USA, > 20 million adults are diagnosed with type 2 diabetes (T2D) [1], and the prevalence of this condition is increasing annually [2]. Unfortunately, 20 to 40% of patients with T2D ultimately develop diabetic kidney disease (DKD), which is the leading cause of end-stage kidney disease [3]. The development of kidney disease in patients with diabetes is also associated with a greater risk of cardiovascular disease (CVD). Control of hyperglycemia and blood pressure, along with the blockade of the renin-angiotensin-aldosterone system (RAAS) are key elements for the prevention and treatment of DKD [4, 5]. However, even when followed judiciously, those strategies slow, but do not prevent DKD progression in many patients, highlighting the critical need for newer renal protective therapies [6]. Moreover, traditional inhibitors of the RAAS have significant side effects including hyperkalemia, which limits their use in a significant proportion of patients with T2D. In this review, we will discuss the main clinical and physiological aspects of RAAS inhibition and review the rationale for the development and use of mineralocorticoid receptor antagonists (MRAs) as cardiorenal protective strategies in patients with T2D and DKD, as well as ongoing trials using these agents (Table 1).

Renin-Angiotensin-Aldosterone System Inhibition and DKD

In addition to glucose and blood pressure control, the inhibition of the RAAS using traditional angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) plays an important role in the slowing DKD progression [7]. For primary prevention, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) randomized 1204 T2D patients with hypertension and normal urinary albumin excretion into four groups: monotherapy with an ACE inhibitor (trandolapril), monotherapy with a calcium channel blocker (verapamil), combination of trandolapril and verapamil, or placebo [8]. After a mean follow-up of 3.6 years, the combined therapy of trandolapril plus verapamil and the monotherapy with trandolapril (but not with verapamil) delayed the onset of albuminuria. The positive impact of trandolapril (but not verapamil) on albuminuria was independent of the reduction in blood pressure [9]. Similarly, in the intensive blood pressure arm of the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial, perindopril plus indapamide reduced the risk of moderately increased albuminuria when compared to placebo in T2D patients, albeit in the context of anticipated anti-hypertensive effects [10]. For trials with ARBs in T2D patients, the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial demonstrated a significant reduction in microalbuminuria risk [11], while the Diabetic Retinopathy Candesartan Trials (DIRECT) showed neutral effects with another ARB, candesartan [12].

The results of secondary prevention studies with ARBs have been even more consistent in favor of RAAS inhibitor use. For example, in the Effect of Irbesartan in the Development of Diabetic Nephropathy in Patients with T2DM (IRMA-2) trial, irbesartan reduced the progression of albuminuria in 590 hypertensive T2D patients with moderately increased albuminuria [13]. Similarly, in the Irbesartan Diabetic Nephropathy Trial (IDNT) involving 1715 hypertensive T2D patients with DKD (proteinuria > 900 mg/24 h, with serum creatinine between 1 and 3 mg/dL), irbesartan [14] reduced the risk of doubling the baseline serum creatinine concentration, development of end-stage kidney disease, and all-cause death after treatment for 2.6 years vs. placebo or amlodipine comparators. The Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the

Table 1 Summary of ongoing studies examining the use of MRAs in DKD

Study	Intervention	Cohort	Primary outcome	Expected study completion
FIDELIO-DKD (NCT02540993)	Finerenone (10 mg or 20 mg) vs. placebo in addition to standard of care (ACEi or ARB), 48 months	T2D with CKD $n = 4800$	Time to first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of estimated glomerular filtration rate (eGFR) ≥ 40% from the baseline over at least 4 weeks and renal death	October 2019
FIGARO-DKD (NCT02545049)	Finerenone (10 mg or 20 mg) vs. placebo in addition to standard of care (ACEi or ARB), 53 months	T2D with CK $n = 6400$	Time to the first occurrence of the composite endpoint of cardiovascular death and non-fatal cardiovascular events (myocardial infarction, stroke, or hospitalization for heart failure)	February 2020

Angiotensin II Antagonist Losartan (RENAAL) trial also examined the impact of an ARB (losartan, 50 or 100 mg daily) in 1513 patients with DKD, as defined by proteinuria > 500 mg/24 h and serum creatinine between 1.3 and 3.0 mg/dL [15]. After a 3.4-year follow-up, losartan reduced the DKD composite primary outcome (same outcome used in IDNT) by 16% and decreased the risk of end-stage kidney disease by 28%, without affecting mortality [15]. Patients received conventional anti-hypertensive therapy as needed throughout the follow-up, and losartan benefits were significantly independent of blood pressure control. Despite these salutary effects of ACE inhibitor or ARB therapies on DKD risk, T2D patients remain at increased risk for the development of DKD. In the RENAAL trial, for example, patients in the losartan arm experienced a 43.5% rate of combined renal outcomes, and 21% of these patients died during the follow-up [15].

In an attempt to reduce residual renal and cardiovascular risks in patients taking RAAS inhibitor monotherapy, subsequent studies focused on the role of dual RAAS inhibition to achieve more complete physiological inhibition of the RAAS, thereby preventing chronic kidney disease (CKD) progression [16]. Accordingly, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) enrolled 25,560 patients with vascular disease or diabetes with end-organ damage (38% of all patients). Patients were randomized to ramipril (10 mg/day), telmisartan (80 mg/day), or both and followed for a median of 56 months [17]. Although dual therapy did reduce proteinuria more than either monotherapy, there was no cardiovascular benefit, and dual RAAS-inhibition patients developed hypotensive symptoms, syncope, diarrhea, hyperkalemia, and renal impairment, leading to higher rates of treatment discontinuation. In addition, dual therapy was associated with a greater risk of the composite endpoint of dialysis, doubling of serum creatinine, and death (HR 1.09; CI 1.01 to 1.18; $p = 0.037$) [18]. Similar to ONTARGET, the Veterans Affairs Nephropathy in Diabetes (VA-NEPHRON-D) trial assigned 1448 patients with T2D and nephropathy (albumin-to-creatinine ratio ≥ 300 mg/g and estimated glomerular filtration rate of 30.0 to 89.9 ml/min/1.73 m^2) to receive losartan 100 mg daily or combination therapy with losartan and lisinopril (10 to 40 mg/day) [19]. The study was stopped early, after 2.2 years, due to safety concerns with dual therapy including hyperkalemia and acute kidney injury. Finally, the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) examined the effect of dual RAAS inhibition with a direct renin inhibitor (DRI), aliskiren, with an ARB or with an ACE inhibitor [20]. This study was also stopped prematurely, due to an increase in hypotension and hyperkalemia in the aliskiren combination arm, without any signal of benefit. Considering the results of these trials, dual RAAS blockade with ACE inhibitors and/or ARB and/or aliskiren is not recommended for the treatment of DKD [7, 21, 22], and similarly increases risk in patients with heart failure [23].

Based on deleterious effects of RAAS inhibition using more than one agent in the ACE inhibitor/ARB/DRI families, attention has shifted to the identification of alternative DKD therapies, including MRAs, to improve clinical outcomes in patients with DKD, while at the same time minimize risks such as kidney injury and hyperkalemia.

Aldosterone Physiology and DKD

RAAS activation is central to the pathogenesis of diabetes-related complications. Acting in part through angiotensin II (Ang II), the RAAS pathway mediates increases in the synthesis of aldosterone, a mineralocorticoid hormone that plays a critical role in physiologic regulation of the salt and water balance and blood pressure (Fig. 1). In addition to Ang II regulation, aldosterone synthesis is increased in zona glomerulosa of the adrenal cortex by hyperkalemia, sodium deficiency, and corticotropin [24]. Aldosterone exerts most of its effects by binding to an intracellular nuclear receptor type, the mineralocorticoid receptor (MR), found mainly in epithelial cells of the kidney, the gastrointestinal mucosa, salivary glands, sweat glands as well as in non-classical, non-epithelial target tissues of the hippocampus, arterial smooth muscle cells, mammary gland, and leukocytes [25]. In addition to the effects observed in normal physiology, activation of MR mediates many of the deleterious renal, cardiovascular, and central nervous system effects of diabetes (Fig. 1). By targeting apical epithelial sodium channel and the basolateral Na^+, K^+-ATPase at the distal tubules and cortical collecting ducts of the kidney, aldosterone stimulates increased sodium reabsorption, potassium excretion, and water retention, effects that may lead to hypertension. In non-epithelial tissues including the myocardium, aldosterone stimulates inflammation, cardiac fibrosis, and hypertrophy independently from its effects on blood pressure, reflecting direct effects of aldosterone on the heart [26, 27]. Similar aldosterone-mediated inflammatory and profibrotic effects are also observed in the kidney; the resulting glomerular podocyte injury and mesangial cell proliferation may manifest as glomerular injury, renal vasoconstriction, and proteinuria [28–30]. Therefore, aldosterone-mediated non-epithelial effects play an important role in vascular inflammation and injury, endothelial dysfunction, end-organ fibrosis, and apoptosis culminating in vasoconstrictive and hypertensive effects, as well as direct cardiac and renal injury [30, 31]. Moreover, some animal studies suggest that aldosterone may also elevate blood pressure by stimulation of the MR in the circumventricular region of the brain, thereby compounding deleterious effects of aldosterone in the heart and kidney [32].

Although aldosterone is not directly targeted by ACE inhibitor/ARB/DRI therapies, these agents can reduce

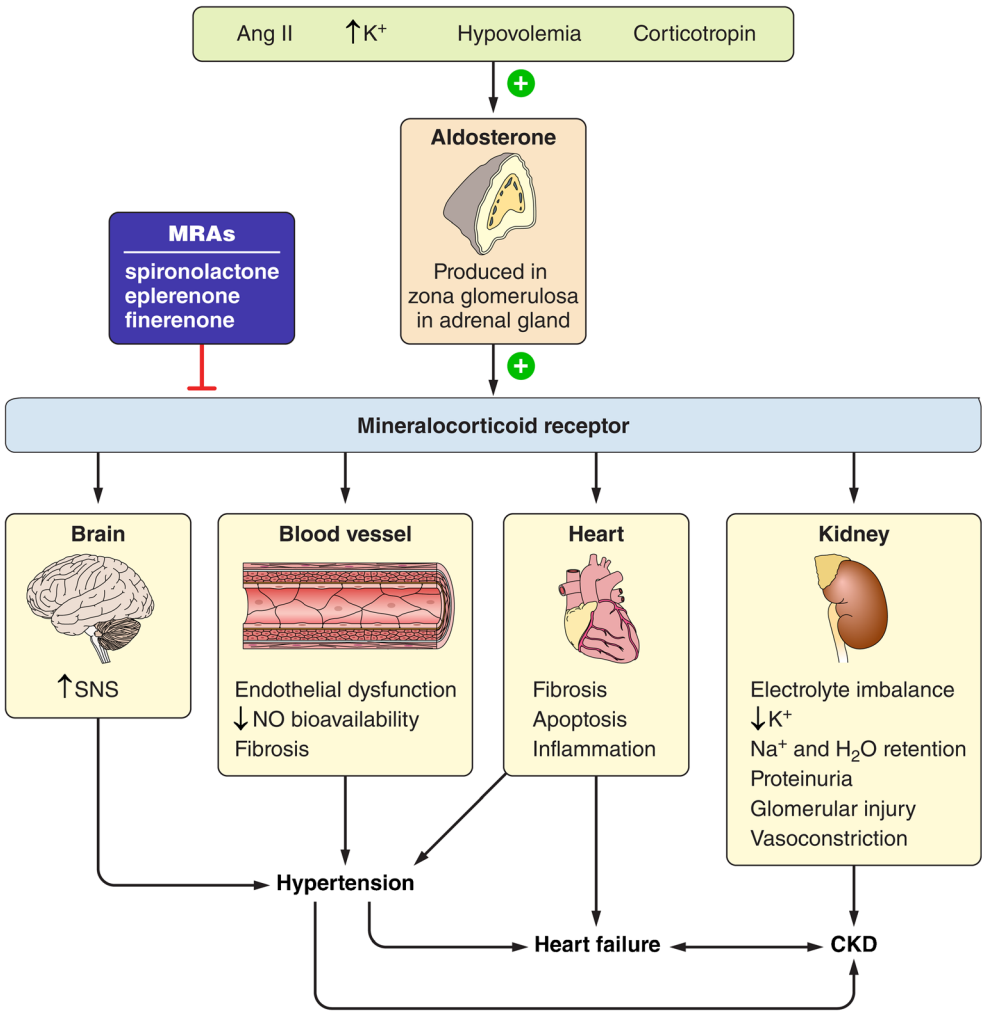

Fig. 1 Mechanisms of MRA-mediated cardiovascular and renal protection

circulating aldosterone levels in a proportion of patients. Unfortunately, aldosterone levels can rebound after long-term ACE inhibitor/ARB/DRI therapies in a subset of patients, a phenomenon called "aldosterone escape" [33]. This phenomenon may have deleterious effects on blood pressure, left ventricular hypertrophy, and urinary albumin excretion [34] and has been demonstrated in patients with hypertension [34–36], heart failure [37, 38], acute myocardial infarction [39], and diabetes [40, 41]. Aldosterone escape is observed in 40% of patients with diabetes and is associated with estimated glomerular filtration rate (eGFR) decline [40, 41]. Although the mechanisms of the aldosterone escape phenomenon are not clear, targeting aldosterone with MRAs may offer additional cardiovascular and renal benefit when added to ACE inhibitors or ARBs by attenuating aldosterone escape and through direct inhibition of aldosterone bioactivity.

Spironolactone was the first MRA to be approved and was viewed as a potassium-sparing diuretic for use in conjunction with thiazide diuretics in patients with hypertension. Spironolactone was subsequently shown to reduce urinary albumin excretion, proteinuria, and left ventricular mass index with modest or neutral effects on blood pressure in short-term studies in patients with DKD taking ACE inhibitor or ARB therapy [40, 42]. The effect of spironolactone on albuminuria is, however, variable with 15–60% declines in albuminuria in studies that varied between 4 and 52 weeks in duration [42–49]. Longer-term studies over 25 months involving 87 patients with proteinuria despite treatment with ACE inhibitor or ARBs demonstrated better long-term renal function preservation measured by eGFR slope [50]. Spironolactone, however, is not selective for MR and is, therefore, significantly limited by dose-dependent sexual side effects, including gynecomastia, impotence, breast tenderness, and menstrual irregularities (Table 2). Unlike spironolactone, eplerenone is a more selective MRA, with minimal affinity for progesterone and androgen receptors, reducing adverse effects related to the gonadal axis. Studies with eplerenone demonstrated dose-dependent decreases in blood pressure that were similar to enalapril when administered alone, and additive blood

Table 2 Summary of adverse effects and associated mechanisms of the first-, second-, and third-generation MRAs

	1st-generation spironolactone	2nd-generation eplerenone	3rd-generation finerenone
Selectivity for MR	+	++	+++
Affinity for progesterone and androgen receptors	+++	++	+[a]
Gonadal axis–related side effects: gynecomastia, impotence, breast tenderness, menstrual irregularities	+++	++	+[a]
Hyperkalemia side effects	+++	++	+

[a] Confirmation required from future clinical trials of longer duration

pressure–lowering effects with side effects of hyperkalemia when administered in conjunction with ACE inhibition or ARB therapies.

To further understand the impact of MRAs on renal parameters, a large meta-analysis examining 27 studies with a total of 1549 patients with proteinuric CKD revealed that compared to ACE inhibitor or ARB (or both), adding MRA treatment significantly reduced 24-h protein excretion, systolic and diastolic blood pressure, although it induced a twofold risk of hyperkalemia and an increased risk of gynecomastia, while data on eGFR change over time were inconclusive [43, 47, 51, 52]. Such observations were also reported in a smaller meta-analysis that included patients with DKD and non-diabetic CKD [53]. A more recent meta-analysis of 18 trials in patients with DKD compared co-administration of MRA with ACE inhibitor/ARB to ACE inhibitor/ARB alone and showed a decrease in albuminuria, but no difference in eGFR change over time [54]. Prior to the completion of dual RAAS blockade trials such as ONTARGET, VA-Nephron-D, and ALTITUDE, several smaller studies were undertaken to determine the impact of triple therapy with ACE inhibitor plus ARB plus MRA on albuminuria and blood pressure and did demonstrate additional improvements in urinary albumin excretion [43, 48, 55, 56]. In light of the publication of modern dual RAAS inhibition studies, however, this strategy is known to be associated with an increase in the risk of adverse events as described above, so this line of investigation has been largely abandoned.

Beyond these surrogate clinical markers, MRAs (including finerenone, as discussed below) also suppress measures of oxidative stress, inflammation, and fibrosis in the kidney and heart, leading to additional cardiovascular and renal protective effects over time that may not be adequately captured in small, short-term studies using relatively blunt endpoints such as albuminuria or eGFR decline [33, 53, 57, 58]. Fortunately, larger outcome trials with MRAs have been performed, but have been limited to the examination of hard clinical endpoints in patients with heart failure, where adding either eplerenone or spironolactone to standard ACE inhibitor therapy reduced mortality to a greater extent in the Randomized Aldactone [spironolactone] Evaluation Study (RALES) for congestive heart failure and Eplerenone Neurohormonal Efficacy and Survival Studies (EPHESUS) [37, 59]. In contrast, clinical trials assessing (surrogate) renal endpoints are generally limited to small, short-term studies in patients with DKD who experienced a high rate of side effects such as hyperkalemia, gynecomastia, and other sex hormone–related side effects, as described above. The risk of hyperkalemia restricts the use of these medications to conditions and other concomitant medications that do not predispose to hyperkalemia. Moreover, eplerenone is metabolized via the cytochrome P450 3A4 system and cannot be used with medications that alter the activity of this metabolizing enzyme.

New-Generation Mineralocorticoid Receptor Antagonists

Given the side effects of the currently available, non-selective MRAs, strategies have been pursued to design more selective MRAs, with the aim to improve the ratio between efficacy and side effects, as reviewed elsewhere [60, 61]. Some newer-generation MRAs are non-steroidal by structure and have mostly been based on a dihydropyridine backbone, although they lack L-type calcium channel activity which is characteristic of calcium receptor antagonists [62]. Of these drugs in development, finerenone (BAY-94-8862) is being evaluated in the largest clinical development program, and other agents are at various phases of pharmaceutical development [63, 64]. Finerenone is a third-generation non-steroid dihydropyridine derivative with potent binding to the MR (Table 2). Importantly, it exhibits more affinity for the MR than for other steroid receptors including the glucocorticoid, androgen, and progesterone receptors, particularly when compared to steroid MRAs such as spironolactone and eplerenone. This specificity reduces the risk of side effects including gynecomastia and impotence associated with the latter drugs. In addition, due to different tissue distributions, finerenone has greater cardiac and vascular bioactivities compared to the kidneys, which may contribute to the reduced incidence and/or severity of MRA-associated hyperkalemia [65].

In addition to reducing side effects, based on preclinical studies, finerenone may also have greater renal protective potential compared to steroidal MRAs. For example, equivalent natriuretic doses of finerenone (1–10 mg/kg) reduced

proteinuria and glomerular and tubular injury more than eplerenone (30–100 mg/kg) in a rodent model of hyperaldosteronism-induced (deoxycorticosterone acetate (DOCA)/salt) renal insufficiency [65]. This was confirmed in a study in hypertensive rats [62], where finerenone, but not eplerenone or spironolactone, reduced urinary protein excretion and structural kidney damage. Finerenone has also been studied in non-diabetic subtotal nephrectomy models of CKD [66]. While there was no difference in measures of kidney function or fibrosis in finerenone- vs. placebo-treated animals in this study, the development of cardiac diastolic dysfunction, which is common in the setting of CKD, was attenuated in MRA-treated animals.

After completing phase 1 studies in healthy individuals where safety endpoints were met, the phase-2 minerAlocorticoid Receptor Antagonist Tolerability Study (ARTS) was conducted [67••, 68–71]. The ARTS trial consisted of two separate placebo-controlled, randomized studies. In study A, 65 patients with heart failure with reduced ejection fraction (< 40%; HFrEF) and mild renal impairment (eGFR 60–90 ml/min/1.73m^2) were randomized 1:1:1:1 to receive finerenone 2.5, 5, or 10 mg once daily, or placebo for a treatment duration of 4 weeks. After several safety aspects including hyperkalemia were met in ARTS-A, study B was conducted in HFrEF patients with moderate renal impairment (eGFR 30–60 ml/min/1.73m^2). In this trial, patients were randomized 1:1:1:1:1:1 to receive finerenone 2.5, 5, or 10 mg once daily, or 5 mg twice daily, placebo or open-label spironolactone up-titrated to 50 mg for a duration of 1 month. Finerenone induced a dose-dependent increase in serum potassium levels that was significant vs. placebo in the 10-mg dosages. The increment in serum potassium was, however, significantly less than the spironolactone group for all finerenone doses examined. Blood pressure was reduced by spironolactone only (~ 6 mmHg, placebo-adjusted). On the other hand, eGFR was decreased in all active-treatment groups, but this was most pronounced for spironolactone. Finally, in this non-DKD cohort that would not necessarily have albuminuria, urine albumin-to-creatinine ratio (UACR) decreased non-significantly by 20–30% for all treatment groups vs. placebo. Adverse events in the studies were mild, and serious adverse events were equally divided across treatment groups (5.5%).

The results of these studies have paved the way for the ARTS-Diabetic Nephropathy (DN) trial [72••]. ARTS-DN was a multi-center, randomized, double-blind, placebo-controlled phase 2B study that assessed the effects of 90-day finerenone treatment, added to standard of care including treatment with a RAAS inhibitor, in T2D patients with albuminuria (UACR > 30 mg/g) and eGFR > 30 ml/min/1.73m^2. Importantly, potassium concentrations at screening had to be lower than 4.8 mmol/L. Initially, finerenone dosages of 1.25, 2.5, 5, 7.5, and 10 mg once daily were studied, but based on the recommendation of an independent data monitoring committee after review of safety data, treatment groups of 15 mg and 20 mg once daily were added. Out of 823 randomized patients, 764 patients finished treatment (93%). Finerenone induced a dose-dependent reduction in UACR, with the largest reduction (− 48%) in the group receiving 20 mg. Finerenone dosages resulted in small declines in eGFR (~ 2–4 ml/min/1.73m^2) and blood pressure (~ 3–5 mmHg). Significant hyperkalemia was reported in 1.5% of patients ($n = 12$), as defined by a potassium concentration > 5.6 mmol/L. Finerenone doses showed a similar incidence of adverse events and serious adverse events compared to the placebo group.

Based on these data, compared to previous MRAs, finerenone appears to have the benefit of less hyperkalemia risk compared to steroidal MRAs. Although the length of the studies was sufficient to assess effects on potassium levels, the duration may not have been sufficient to fully capture other side effects associated with steroidal MRAs such as gynecomastia. In addition, the mechanism(s) for the albuminuria reduction with finerenone is not yet fully understood, since reductions in blood pressure and eGFR did not explain reductions in UACR in ARTS-DN, and mechanistic studies in humans for this compound are lacking [72••].

To better understand the impact of finerenone on the renal and cardiovascular systems, two large-sized long-term phase-3 outcome trials are currently underway (Table 1). In the FIDELIO-DKD trial (a randomized, double-blind, placebo-controlled, multi-center, event-driven study), the effects of finerenone (10 or 20 mg) in addition to standard of care on the progression of kidney disease in DKD patients are studied. The primary outcome is time to the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥ 40% from the baseline over at least 4 weeks, and renal death. Secondary outcomes include several other renal and cardiovascular outcomes including 3-point MACE and hospitalization for heart failure (NCT02540993). Study completion is expected in October 2019.

In the FIGARO-DKD study (a randomized, double-blind, placebo-controlled, multi-center, event-driven study), the effects of finerenone (10 or 20 mg) in addition to standard of care on cardiovascular outcome in DKD patients are studied. The primary outcome is time to the first occurrence of the composite endpoint of cardiovascular death and non-fatal cardiovascular events (myocardial infarction, stroke, or hospitalization for heart failure). Secondary outcomes include analysis for renal outcomes similarly defined as in FIDELIO-DKD (NCT02545049). Study completion is expected in February 2020.

Methods to Mitigate The Risk of Hyperkalemia Associated with MRA

Hyperkalemia is a major concern when treating patients with RAAS inhibitors, especially in patients with DKD

[54]. Importantly, hyperkalemia is associated with an increase in cardiovascular risk [73]. The current approach for treating hyperkalemia in non-dialysis patients usually includes therapies of variable efficacy, which can also have serious side effects (e.g., the use of diuretics, bicarbonate, sodium polystyrene sulfonate, and dietary modification) and discontinuation of relevant agents, including RAAS inhibitors. Unfortunately, hyperkalemia requiring discontinuation of RAAS inhibition may have a negative impact on prognosis in patients with DKD or heart failure. More recently, novel potassium-lowering gastrointestinal cation exchange agents were developed to both minimize hyperkalemia, improve palatability, and mitigate the risks of serious adverse effects associated with older potassium-binding agents, such as intestinal necrosis [74].

Patiromer is a non-absorbable organic polymer, which exchanges potassium for calcium in the colon. In the Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia (OPAL-HK) trial, 237 patients with CKD, receiving RAAS inhibitor therapy and with hyperkalemia (serum K^+ between 5.1 and 6.5 mmol/L) were treated with patiromer for 4 weeks. After that, patients that successfully presented a reduction in the K^+ levels below 5.1 mmol/L (76% of the original cohort) were randomized to either patiromer or placebo. The patiromer group presented a smaller increase in serum K^+ and less episodes of hyperkalemia recurrences. The main adverse effect was constipation (11% of the patients in the patiromer group) [75]. The recommended initial dose of patiromer is 8.4 g once daily and the maximum dose is 25.2 g/day [76].

Sodium zirconium cyclosilicate (SZC) is a non-absorbable inorganic compound that shifts both sodium and hydrogen ions for potassium in the intestine. This drug was evaluated in a double-blinded trial that randomized 753 patients with hyperkalemia to receive either SZC or placebo. After the first 48 h of treatment, patients in the SZC group experienced a significant reduction in the K^+ levels, when compared to placebo, and this reduction was maintained during the next 12 days [77]. The main observed side effect was diarrhea. Another phase-3 trial with SZC showed similar results [78]. The recommended dose of SZC is 10 g three times per day for up to 48 h and then 10 g daily (maximum, 15 g/daily) as maintenance therapy [79]. Based on the relatively small, yet significant risk of hyperkalemia, novel potassium-binding agents may become more popular to be taken in combination with both existing RAAS inhibitors and MRAs if and when they become available for clinical use.

Conclusion

The treatment of DKD has evolved over the last 2–3 years with the demonstration that several newer antihyperglycemic therapies—sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists—reduce proteinuria and the risk of hard renal endpoints [80–82]. The DKD treatment paradigm may be poised to shift again with the development of selective MRAs, which reduce albuminuria and blood pressure when added to standard of care RAAS inhibitors and have an overall lower risk of side effects vs. older MRAs. Based on the available evidence, newer MRAs have the potential to fill an important unmet need in patients with DKD who are still at high risk of disease progression. The results of cardiorenal outcome trials with newer MRAs will help to establish their role in the clinical management of patients with diabetes.

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Compliance with Ethical Standards

Conflict of Interest Yuliya Lytvyn, Lucas C. Godoy, and Rosalie A. Scholtes declare that they have no conflict of interest.

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References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Benjamin EJ, Virani SS, Callaway CW, Chang AR, Cheng S, Chiuve SE, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. 2018.
2. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet (London, England). 2016;387(10027):1513–30.
3. de Boer IH, Afkarian M, Rue TC, Cleary PA, Lachin JM, Molitch ME, et al. Renal outcomes in patients with type 1 diabetes and macroalbuminuria. J Am Soc Nephrol. 2014;25(10):2342–50.
4. Wong MG, Perkovic V, Chalmers J, Woodward M, Li Q, Cooper ME, et al. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. Diabetes Care. 2016;39(5):694–700.
5. The BErgamo NEphrologic DIabetes Complications Trial (BENEDICT): design and baseline characteristics. Controlled clinical trials. 2003;24(4):442–61.
6. Lytvyn Y, Bjornstad P, Pun N, Cherney DZ. New and old agents in the management of diabetic nephropathy. Curr Opin Nephrol Hypertens. 2016;25(3):232–9.
7. McFarlane P, Cherney D, Gilbert RE, Senior P. Chronic kidney disease in diabetes. Can J Diabetes. 2018;42(Suppl 1):S201–s9.
8. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med. 2004;351(19):1941–51.
9. Ruggenenti P, Perna A, Ganeva M, Ene-Iordache B, Remuzzi G. Impact of blood pressure control and angiotensin-converting enzyme inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: a post hoc analysis of the BENEDICT trial. J Am Soc Nephrol: JASN. 2006;17(12):3472–81.
10. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet (London, England). 2007;370(9590):829–40.
11. Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011;364(10):907–17.
12. Magee GM, Bilous RW, Cardwell CR, Hunter SJ, Kee F, Fogarty DG. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. Diabetologia. 2009;52(4):691–7.
13. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345(12):870–8.
14. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, 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(12):851–60.
15. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–9.
16. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med. 2008;148(1):30–48.
17. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547–59.
18. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet (London, England). 2008;372(9638):547–53.
19. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369(20):1892–903.
20. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367(23):2204–13.
21. Microvascular Complications and Foot Care: Standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S105-s18.
22. KDOQI clinical practice guideline for diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012;60(5):850–86.
23. Danser AH, van den Meiracker AH. Heart failure: new data do not SUPPORT triple RAAS blockade. Nat Rev Nephrol. 2015;11(5):260–2.
24. Magni P, Motta M. Aldosterone receptor antagonists: biology and novel therapeutic applications. Curr Hypertens Rep. 2005;7(3):206–11.
25. Lombes M, Farman N, Bonvalet JP, Zennaro MC. Identification and role of aldosterone receptors in the cardiovascular system. Ann Endocrinol (Paris). 2000;61(1):41–6.
26. Fullerton MJ, Funder JW. Aldosterone and cardiac fibrosis: in vitro studies. Cardiovasc Res. 1994;28(12):1863–7.
27. Rocha R, Stier CT Jr, Kifor I, Ochoa-Maya MR, Rennke HG, Williams GH, et al. Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. Endocrinology. 2000;141(10):3871–8.
28. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. J Clin Invest. 1996;98(4):1063–8.
29. Rocha R, Chander PN, Zuckerman A, Stier CT Jr. Role of aldosterone in renal vascular injury in stroke-prone hypertensive rats. Hypertension. 1999;33(1 Pt 2):232–7.
30. Hollenberg NK. Aldosterone in the development and progression of renal injury. Kidney Int. 2004;66(1):1–9.
31. Romagni P, Rossi F, Guerrini L, Quirini C, Santiemma V. Aldosterone induces contraction of the resistance arteries in man. Atherosclerosis. 2003;166(2):345–9.
32. Huang BS, White RA, Jeng AY, Leenen FH. Role of central nervous system aldosterone synthase and mineralocorticoid receptors in salt-induced hypertension in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol. 2009;296(4):R994–R1000.
33. Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. Nat Clin Pract Nephrol. 2007;3(9):486–92.
34. Sato A, Saruta T. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in essential hypertensive patients with left ventricular hypertrophy. J Int Med Res. 2001;29(1):13–21.
35. Lijnen P, Staessen J, Fagard R, Amery A. Increase in plasma aldosterone during prolonged captopril treatment. Am J Cardiol. 1982;49(6):1561–3.
36. Staessen J, Lijnen P, Fagard R, Verschueren LJ, Amery A. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. J Endocrinol. 1981;91(3):457–65.
37. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, 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(10):709–17.

38. Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. J Card Fail. 1996;2(1):47–54.
39. Borghi C, Boschi S, Ambrosioni E, Melandri G, Branzi A, Magnani B. Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. J Clin Pharmacol. 1993;33(1):40–5.
40. Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. Hypertension. 2003;41(1):64–8.
41. Schjoedt KJ, Andersen S, Rossing P, Tarnow L, Parving HH. Aldosterone escape during blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy is associated with enhanced decline in glomerular filtration rate. Diabetologia. 2004;47(11):1936–9.
42. Saklayen MG, Gyebi LK, Tasosa J, Yap J. 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(4):714–9.
43. Chrysostomou A, Pedagogos E, MacGregor L, Becker GJ. 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: CJASN. 2006;1(2):256–62.
44. Rossing K, Schjoedt KJ, Smidt UM, Boomsma F, Parving HH. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. Diabetes Care. 2005;28(9):2106–12.
45. Schjoedt KJ, Rossing K, Juhl TR, Boomsma F, Rossing P, Tarnow L, et al. Beneficial impact of spironolactone in diabetic nephropathy. Kidney Int. 2005;68(6):2829–36.
46. Schjoedt KJ, Rossing K, Juhl TR, Boomsma F, Tarnow L, Rossing P, et al. Beneficial impact of spironolactone on nephrotic range albuminuria in diabetic nephropathy. Kidney Int. 2006;70(3):536–42.
47. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int. 2006;70(12):2116–23.
48. Furumatsu Y, Nagasawa Y, Tomida K, Mikami S, Kaneko T, Okada N, et al. Effect of renin-angiotensin-aldosterone system triple blockade on non-diabetic renal disease: addition of an aldosterone blocker, spironolactone, to combination treatment with an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. Hypertens Res. 2008;31(1):59–67.
49. Guney I, Selcuk NY, Altintepe L, Atalay H, Basarali MK, Buyukbas S. Antifibrotic effects of aldosterone receptor blocker (spironolactone) in patients with chronic kidney disease. Ren Fail. 2009;31(9):779–84.
50. Morales E, Millet VG, Rojas-Rivera J, Huerta A, Gutierrez E, Gutierrez-Solis E, et al. Renoprotective effects of mineralocorticoid receptor blockers in patients with proteinuric kidney diseases. Nephrol Dial Transplant. 2013;28(2):405–12.
51. Epstein M, Williams GH, Weinberger M, Lewin A, Krause S, Mukherjee R, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol: CJASN. 2006;1(5):940–51.
52. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2014;4:CD007004.
53. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis. 2008;51(2):199–211.
54. Sun LJ, Sun YN, Shan JP, Jiang GR. Effects of mineralocorticoid receptor antagonists on the progression of diabetic nephropathy. J Diabetes Investig. 2017;8(4):609–18.
55. Tylicki L, Rutkowski P, Renke M, Larczynski W, Aleksandrowicz E, Lysiak-Szydlowska W, et al. Triple pharmacological blockade of the renin-angiotensin-aldosterone system in nondiabetic CKD: an open-label crossover randomized controlled trial. Am J Kidney Dis. 2008;52(3):486–93.
56. Tylicki L, Rutkowski P, Renke M, Rutkowski B. Addition of aldosterone receptor blocker to dual renin-angiotensin-aldosterone blockade leads to limitation of tubulointerstitial injury of kidney. Kidney Int. 2007;72(9):1164–5.
57. Lattenist L, Lechner SM, Messaoudi S, Le Mercier A, El Moghrabi S, Prince S, et al. Nonsteroidal mineralocorticoid receptor antagonist finerenone protects against acute kidney injury-mediated chronic kidney disease: role of oxidative stress. Hypertension. 69(5):870–8.
58. Barrera-Chimal J, Andre-Gregoire G, Nguyen Dinh Cat A, Lechner SM, Cau J, Prince S, et al. Benefit of mineralocorticoid receptor antagonism in AKI: role of vascular smooth muscle Rac1. J Am Soc Nephrol. 28(4):1216–26.
59. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309–21.
60. Kolkhof P, Nowack C, Eitner F. Nonsteroidal antagonists of the mineralocorticoid receptor. Curr Opin Nephrol Hypertens. 2015;24(5):417–24.
61. Wang EB, Chaudhary A, Waterhouse TH, Dickinson GL. Population pharmacokinetics of LY2623091 in patients with hypertension and chronic kidney disease. J Clin Pharmacol. 2017;57(6):739–46.
62. Bramlage P, Swift SL, Thoenes M, Minguet J, Ferrero C, Schmieder RE. Non-steroidal mineralocorticoid receptor antagonism for the treatment of cardiovascular and renal disease. Eur J Heart Fail. 2016;18(1):28–37.
63. Bisping E, Wakula P, Poteser M, Heinzel FR. Targeting cardiac hypertrophy: toward a causal heart failure therapy. J Cardiovasc Pharmacol. 2014;64(4):293–305.
64. Orena S, Maurer TS, She L, Eudy R, Bernardo V, Dash D, 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.
65. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Barfacker L, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. J Cardiovasc Pharmacol. 2014;64(1):69–78.
66. Bonnard B, Pieronne-Deperrois M, Djerada Z, Elmoghrabi S, Kolkhof P, Ouvrard-Pascaud A, et al. Mineralocorticoid receptor antagonism improves diastolic dysfunction in chronic kidney disease in mice. J Mol Cell Cardiol. 121:124–33.
67.•• Filippatos G, Anker SD, Bohm M, Gheorghiade M, Kober L, Krum H, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J. 37(27):2105–14. **Results of the phase-2 minerAlocorticoid Receptor Antagonist Tolerability Study (ARTS) in patients with heart failure showed a decreased risk of side effect and potential for albuminuria reduction with novel MRA agent, finerenone when compared to spironolactone.**
68. Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B. Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: comparison at bench and bedside. Handb Exp Pharmacol. 2017;243:271–305.
69. Pitt B, Anker SD, Bohm M, Gheorghiade M, Kober L, Krum H, et al. Rationale and design of MinerAlocorticoid Receptor

antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. Eur J Heart Fail. 2015;17(2):224–32.

70. Pitt B, Filippatos G, Gheorghiade M, Kober L, Krum H, Ponikowski P, et al. Rationale and design of ARTS: a randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. Eur J Heart Fail. 2012;14(6):668–75.
71. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, 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(31):2453–63.
72.•• Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA. 2015;314(9):884–94. **This study provides evidence that treating T2D patients with albuminuria and eGFR >30 ml/min/1.73m^2 with finerenone for 90 days reduces albuminuria without side effects associated with older MRA agents.**
73. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol. 2017;46(3):213–21.
74. Goutorbe P, Montcriol A, Lacroix G, Bordes J, Meaudre E, Souraud JB. Intestinal necrosis associated with orally administered calcium polystyrene sulfonate without sorbitol. Ann Pharmacother. 2011;45(2):e13.
75. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211–21.
76. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol. 2001;21(12):2046–50.
77. Thadhani R, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA. 2012;307(7):674–84.
78. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA. 2014;312(21):2223–33.
79. Miller J, Tobe S, Skorecki K. Control of extracellular fluid volume and the pathophysiology of edema formation. In: Brenner B, editor. Brenner and Rector's the kidney. I. 5th ed. Philadelphia: WB Saunders; 1996. p. 817–72.
80. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323–34.
81. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.
82. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2018. https://doi.org/10.1056/NEJMoa1812389.