Aldosterone, Mineralocorticoid Receptor Activation, and CKD: A Review of Evolving Treatment Paradigms

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Mineralocorticoid receptor (MR) activation is involved in propagating kidney injury, inflammation, and fibrosis and in the progression of chronic kidney disease (CKD). Multiple clinical studies have defined the efficacy of MR antagonism in attenuating progressive kidney disease, and the US Food and Drug Administration recently approved the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone for this indication. In this review, we consider the basic science and clinical applicability of MR antagonism. Because hyperkalemia constitutes a constraint to implementing evidence-based MR blockade, we review MRA-associated hyperkalemia in the context of finerenone and discuss evolving mitigation strategies to enhance the safety and efficacy of this treatment. Although the FIDELIO-DKD and FIGARO-DKD clinical trials focused solely on patients with type 2 diabetes mellitus, we propose that MR activation and the resulting inflammation and fibrosis act as a substantive pathogenetic mediator not only in people with diabetic CKD but also in those with CKD without diabetes. We close by briefly discussing both recently initiated and future clinical trials that focus on extending the attributes of MR antagonism to a wider array of nondiabetic kidney disorders, such as patients with nonalbuminuric CKD.

The past 8 decades have provided a wonderful backdrop for appreciating the extraordinary trajectory in elucidating the pathogenetic role of aldosterone and mineralocorticoid receptor (MR) activation as determinants of chronic kidney disease (CKD) progression independent of the renin-angiotensin system (RAS). Strong evidence has now accumulated to show that MR activation leads to many “off-target” effects on the heart, the vasculature, and the kidney.1-3

In this review, we summarize our growing understanding of role of MR activation in propagating kidney injury, inflammation, and fibrosis and the consequent progression of CKD. We review the recent clinical studies that investigated and defined the efficacy of MR antagonism in attenuating progressive kidney disease4,5 and that culminated in an MR antagonist (MRA) becoming an approved treatment for retarding CKD progression.6 We also critically consider both the efficacy and safety of a newly approved novel nonsteroidal mineralocorticoid MRA, finerenone, and evolving mitigation strategies for MRA-associated hyperkalemia to enhance the safety and efficacy of new and emerging treatment paradigms.

MR Activation in Kidney Pathophysiology

Evolving Understanding of the Role of Aldosterone in Kidney Physiology

The steroid aldosterone is the primary mineralocorticoid hormone; its synthesis is prompted by hyperkalemia or sodium and volume depletion as the end result of RAS activation.6-10 Among other tissues, the kidney, colon, heart, central nervous system, brown adipose tissue, and sweat glands all express MR and thus are responsive to aldosterone signaling.1,9,11 Aldosterone is an important contributor to both blood pressure control and—by provoking renal sodium reabsorption and potassium excretion—maintenance of extracellular volume homeostasis.1,12-14

Our understanding of the role of aldosterone is markedly evolving. It is now accepted that

- Angiotensin is not the main trigger for aldosterone secretion.1
- MR is stimulated by several ligands (aldosterone, cortisol) and undergoes nonligand activation (via the regulatory protein Rac family small guanosine triphosphatase 1 [Rac1], elevated glucose, and high salt levels).1,9,14,15
- Leptin affects aldosterone synthesis, acting directly on adrenal glomerulosa cells to upregulate the expression of aldosterone synthase (encoded by CYP11B2) and increase the production of aldosterone via calcium-dependent mechanisms.16

Over the past decade emerging data have implicated aldosterone and MR activation in many aspects of renal and cardiovascular injury, including progression of CKD and cardiovascular disease as well as heart failure with reduced ejection fraction (HFrEF), arterial stiffness, and the metabolic syndrome.3,9,11,15,16

The Role of Nonepithelial MR Activation in CKD Progression

The best-known function of aldosterone is its contribution to the control of electrolyte and fluid balance by interaction with MR expressed in aldosterone-sensitive kidney epithelial cells in the distal nephron. What is not as widely appreciated is that nonepithelial tissues also express MR, including the heart, adipocytes, podocytes, inflammatory cells, endothelial cells and vascular smooth muscle cells (VSMCs) (summarized in Fig 1 and Box 1). Several lines of evidence suggest that the MR in nonepithelial cells offers an attractive target for protecting against inflammation and
fibrosis in both the kidneys and the cardiovascular system. The development of cell-specific MR knockout mouse model facilitates our ability to understand exactly how MR in podocytes, vascular cells (endothelial cells and VSMCs), inflammatory cells, and fibroblasts relates to MR overactivation–associated kidney injury. These cascades of injury have recently been reviewed in Kintscher et al. and are summarized in Box 1 and Figure 1.
Box 1. MR Activation in Nonepithelial Cells

**Podocytes**

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

**Fibroblasts**

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

**Endothelial cells**

- Aldosterone increases ICAM-1, VCAM-1, E-selectin, and MCP-1 expression.
- Aldosterone promotes oxidative injury through increasing the expression of the NADPH oxidase subunits Nox2, p47phox, p22phox and by stimulating Rac1 activation.
- Aldosterone impairs endothelial function through a reduction in eNOS phosphorylation.

Representative examples compiled from Jaisser et al,2 Kintscher et al,3 Buonafine et al,9 Fuller et al,9 and Barrera-Chimal et al.10 Abbreviations: CKD, chronic kidney disease; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule 1; MCP-1, monocyte chemoattractant protein 1; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NADPH, reduced nicotinamide adenine dinucleotide phosphate; Nox2, NADPH oxidase 2; Rac1, Rac family small guanosine triphosphatase 1; VCAM-1, vascular cell adhesion molecule 1.

The Interrelationship of Fibroblast Growth Factor 23 and Aldosterone

As we detailed in a recent review,18 fibroblast growth factor 23 (FGF-23) and membrane αKlotho (hereafter called Klotho) intersect with the renin-angiotensin-aldosterone system (RAAS). Of interest, FGF-23 is involved in local RAAS activation, including aldosterone, in the heart.18,19 Aldosterone and angiotensin II increase FGF-23 expression in bone and boost levels of FGF-23 in the circulation.18,19 Taken together, these findings imply that aldosterone may play an important role in increased FGF-23 secretion in patients with CKD.

Levels of circulating FGF-23 and aldosterone have been observed to move in tandem in patients with CKD across glomerular rate filtration (GFR) categories 1-5 (CKD G1-G5).20,21 Also, after the administration of the MRA canrenone, an active metabolite of spironolactone, uremic mice with elevated aldosterone levels were shown to have a significant decrease in previously elevated concentrations of circulating FGF-23; this provides evidence that aldosterone may directly influence FGF-23 secretion by the bone.20

Concomitantly, once Klotho in the kidney is released from its membrane-bound form into the circulation, it demonstrates an array of cardio-renal protective properties.18,22,23 In experimental CKD, Klotho lessens tissue injury and fibrosis and improves hypertension by downregulating RAAS activity.18 As we have recently proposed,17 the many examples of the links between these seemingly disparate relationships detailed previously may provide new therapeutic avenues to block the vicious cycle of aldosteron/MR overactivation and FGF-23 secretion with concomitant Klotho insufficiency, which often exists in patients with CKD. Whether therapeutic MR antagonism in the setting of preserved soluble Klotho concentrations is able to retard the progression of kidney and cardiac injury in CKD is a hypothesis to be tested.

**MR Antagonism as a Therapeutic Strategy**

**Steroidal MRAs**

In a pioneering study 80 years ago, Hans Selye and colleagues showed that, with administration of deoxycorticosterone acetate to a rodent model with partial kidney ablation, a high salt intake (3% saline) was needed to bring about vascular inflammatory changes in the heart and the kidney.24 Subsequent studies extended Selye’s early observations and delineated a role for aldosterone, independent of the RAS, as a determinant of CKD progression.24-30

Selectively blocking aldosterone (ie, separate from renin angiotensin blockade) lowers proteinuria and nephrosclerosis in the spontaneously hypertensive stroke-prone rat model and reduces proteinuria and glomerulosclerosis in a subtotal nephrectomy rat model (ie, remnant kidney).25,26,29,31 When aldosterone is selectively reinfused, these signs of damage recur despite ongoing renin-angiotensin blockade.25 In a subsequent study in a clinical cohort, selective aldosterone blockade with eplerenone, a second-generation MRA, was found to successfully retard CKD progression.31

In 2006 came the first assessment of the albuminuria-lowering effects of eplerenone in patients with type 2 diabetes mellitus (T2DM).31 This multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in 2,686 patients compared the effect of coadministration of 2 different doses of the selective aldosterone blocker eplerenone or placebo together with an angiotensin-converting enzyme inhibitor (ACEI), enalapril, on albumin excretion in patients with T2DM and albuminuria. Adding eplerenone, in doses of 50 or 100 mg, to enalapril resulted in a substantive and statistically significant reduction in albuminuria in patients with T2DM.31

**Novel Nonsteroidal MRAs**

In response to concerns about the benefit-safety profile of steroidal MRAs, several new selective nonsteroidal MRAs were developed with the dual goal of improving efficacy and reducing unwanted side effects, primarily hyperkalemia.1,32 Figure 2 provides a direct comparison between the steroidal MRAs (spironolactone and eplerenone) and the recently approved and most widely investigated...
nonsteroidal MRA finerenone. The figure contrasts the differing binding modes of the 3 agents and summarizes key pharmacodynamic and pharmacokinetic differences.

Presently, multiple novel compounds are at different stages of development and/or approved for clinical use, including esaxerenone, AZD9977, apararenene, KBP-5074, and finerenone. We will briefly focus on esaxerenone, KBP-5074 and finerenone, which are the 3 drugs at the most advanced stage of clinical development. For a more detailed review, the reader is referred to Kintscher et al.3

**Esaxerenone**

Esaxerenone (also known as CS-3150; Daiichi Sankyo) is a nonsteroidal MRA recently approved in Japan to treat arterial hypertension. It is highly selective, with a greater than 3-fold higher preference for MR in comparison with glucocorticoid, progesterone, or androgen receptors.33 Esaxerenone’s high affinity and selectivity for MR is bolstered by both preclinical and clinical data. Moreover, the latter indicate that esaxerenone effectively lowers blood pressure in hypertensive patients34 and is safe and effective in hypertensive patients with HFrEF.35

**KBP-5074**

KBP-5074 (KBP BioSciences) is a nonsteroidal MRA with a MR binding affinity higher than for spironolactone and eplerenone (its half-maximal inhibitory concentration [IC₅₀] is 2.7 nM). In addition, it shows selectivity in binding to MR as opposed to other steroid hormone receptors.36 The first phase 2 study with KBP-5074, BLOCK-CKD, was recently published.37 This multicenter, randomized, double-blind, placebo-controlled study investigated the safety and efficacy of KBP-5074 (0.25 or 0.5 mg/d) in 162 patients with resistant or poorly controlled hypertension and advanced CKD (G3b-G4; ie, an estimated GFR between 15 and 44 mL/min/1.73 m²). Compared with placebo, the 2 doses lowered systolic blood pressure by 8 and 10 mm Hg, respectively. A phase 3 study is planned.

**Finnenone**

The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD)4 and Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD)5 studies have advanced our understanding of the clinical utility of MRA blockade on clinical outcomes. In the first, patients with CKD and T2DM who received finerenone were observed to have a lower risk of a primary outcome event (defined as kidney failure, or a sustained decrease of ≥40% in the estimated GFR from baseline, or death from kidney causes) than the comparator placebo arm (17.8% vs 21.1%; hazard ratio, 0.82 [95% CI, 0.73-0.93]; P = 0.001). Patients in the intervention group also showed a lower risk of key secondary outcome events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (HHF).4 The renop- and cardioprotective effects of finerenone were confirmed in the FIGARO-DKD study.5

After the publication of FIDELIO and FIGARO trials, a prespecified pooled analysis (FIDELITY) of these 2

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

Figure 2. Schematic of spironolactone, eplerenone, and finerenone binding with proposed/hypothesized conformational change of helix 12 and summary of respective key pharmacodynamic and pharmacokinetic characteristics. Abbreviations: BP, blood pressure; CNS, central nervous system; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist. Reproduced from Kintscher3 under the terms of the Creative Commons Attribution License (CC BY 4.0).
complementary trials was performed, comprising 13,026 patients with a median follow-up period of 3.0 years. The main time-to-event efficacy outcomes were a composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or HHF) and a composite kidney outcome (kidney failure, a sustained ≥57% decrease in estimated GFR from baseline over ≥4 weeks, or death from kidney causes). The combined analysis showed consistency across all kidney end points, which is reassuring and corroborates the individual FIDELIO and FIGARO results.

We wish to emphasize 2 important points derived from the FIDELITY analysis. First, it provides the best evidence to date that finerenone prevents HHF in a high-risk population. Second, the reduction in HHF was the primary contributor to finerenone’s cardiovascular benefit, with a relative risk reduction of 22% compared with placebo (P = 0.003) in a study population in which patients with chronic symptomatic HFrEF at the run-in visit were excluded. This is an important and highly relevant finding for nephrologists because heart failure is a key contributor to morbidity and health care costs among patients with CKD and T2DM. An important limitation of FIDELITY is that it did not include patients with nonalbuminuric CKD, highlighting the importance of conducting similar finerenone studies in a nonalbuminuric CKD cohort.

The results of FIDELIO-DKD and FIGARO-DKD (and the pooled analysis in FIDELITY) imply that finerenone is an effective treatment for kidney and cardiovascular protection in patients with CKD and T2DM. It is noteworthy the benefits of finerenone were seen early—as soon as 1 month after drug initiation for the cardiovascular outcome and just after 12 months for the kidney outcome—and persisted for the 3-year duration of the trials. Based on these 2 studies, finerenone was recently approved by the US Food and Drug Administration (FDA). Furthermore, the recently published, much-anticipated annual American Diabetes Association Standards of Medical Care in Diabetes guidelines recommend using finerenone to reduce CKD progression and cardiovascular events (recommendation 11.3c).

### Barriers to Implementing Guideline-Recommended MR Blockade

#### Hyperkalemia

Despite strong recommendations for treatment with RAS inhibitors and MRA by numerous guidelines, implementation in real-world practice remains suboptimal, with hyperkalemia constituting one, if not the major, cause. The groundbreaking RALES trial reported that spironolactone reduced all-cause mortality by 30% in patients with reduced ejection fraction who were on RAS inhibitors and had levels of potassium ≤5.0 mEq/L and creatinine ≤2.5 mg/dL at baseline. Subsequently, a population-based study assessing the postpublication impact of the RALES trial found higher spironolactone prescriptions in patients with heart failure on RAS inhibitors and, concerning higher hyperkalemia-induced hospitalization and death. Regrettfully, no information on the indications for spironolactone use were available in this study; further, potassium monitoring and appropriateness of prescription in terms of whether patients met the ejection fraction and baseline potassium and creatinine criteria were unknown. Nevertheless, this publication has resulted in a lingering cloud of concern regarding the dangers of MRA-induced hyperkalemia and may have been the major driver limiting their use.

Contemporary data from a Swedish general population cohort indicated that a plasma potassium level of >5.0 mEq/L occurred in ~19% of individuals newly started on an MRA; of these, only a fraction restarted the MRA during subsequent follow-up. Although patients who stopped MRA treatment after a hyperkalemia episode experienced fewer subsequent hyperkalemia events compared with those who continued the MRA despite hyperkalemia, importantly they also had a higher risk of cardiovascular events. Notwithstanding the possibility that MRA therapy could be beneficial despite inducing hyperkalemia, the (real or perceived) short-term risks of hyperkalemia may prompt health care providers to discontinue and subsequently not restart the MRA. It is unfortunate and indeed ironic that the precise populations that could benefit most from MRA therapy are those who are at increased risk for hyperkalemia.

The development of a novel class of nonsteroidal MRAs (including finerenone, aparenone, and esaxerenone, as discussed previously) generates excitement due to the promise of provoking less hyperkalemia than steroidal MRAs (spironolactone and eplerenone), owing to differences in their chemical structure and an altered mechanism of action. To date, only 1 head-to-head comparison of finerenone with spironolactone exists: a randomized controlled trial of patients with HFrEF and mild CKD wherein serum potassium rose by end of study (3-4 weeks) in all groups. The increase was 0.21 mmol/L in patients receiving finerenone at 10 mg daily, 0.30 mmol/L in patients receiving finerenone at 5 mg twice daily, and 0.45 mmol/L in patients receiving spironolactone (mean dose of 37 mg). Interpretation is challenging because all 3 agents were administered at different (nonequivalent) doses. It is important to recognize, therefore, that even the newer nonsteroidal MRAs are expected to raise potassium levels compared with placebo. Furthermore, it should be emphasized that the observed potassium levels were incurred in the context of treatment on top of maximally tolerated RAS inhibitor therapy and there were relatively small absolute between-group differences in FIDELIO and FIGARO (of 0.23 and 0.16 mmol/L, respectively).

Notwithstanding the reality of the risks posed by hyperkalemia, it is our belief that we should approach this question with respect but not fear. This requires a nuanced
approach that allows the application of an effective therapy while mitigating its potential risks. First, it is important to accurately understand the magnitude of the risk of hyperkalemia. In FIDELITY, the total incidence of hyperkalemia-related adverse events was 14.0% for finerenone compared with 6.9% for placebo; meanwhile, the number of hospitalizations due to hyperkalemia was 0.9% versus 0.2%, and the number of permanent discontinuations due to hyperkalemia was 1.7% versus 0.6%. Four months after treatment start, the mean increase in serum potassium was 0.21 mEq/L with finerenone and 0.02 mEq/L with placebo. Most importantly, in patients receiving finerenone there were no deaths attributable to hyperkalemia.

The low incidence of permanent discontinuation of finerenone and the absence of deaths attributable to hyperkalemia were in large part due to a proactive approach aimed at minimizing the occurrence of hyperkalemia (Box 2). The FDA specifies a similar monitoring and mitigation strategy in its finerenone label: limiting the prescribing of the drug to patients with prespecified characteristics, including GFR ≥25 ml/min/1.73 m², and systematically applying careful monitoring and mitigation strategies. This should enable the safe and continued use of finerenone (and potentially other new MRAs) in patients with CKD who meet the trial’s inclusion criteria.

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

Cost

Because cost is often cited as a barrier to use, it is appropriate to compare the relative costs of recently available drugs that can be prescribed for diabetic kidney disease (DKD) patients. The wholesale cost for finerenone oral tablet, 10 mg, is around US$604 for a supply of 30 tablets. For comparison, dapagliflozin costs US$579 per month. Monthly costs for popular glucagon-like peptide 1 receptor agonists (GLP-1RAs) include US$826 for exenatide, US$913 ( dulaglutide), and US$1,385 (lisubclass glutide). However, it is important to note that this comparison is imperfect owing to the rebates and confidential discounts offered on some drugs to patients who are commercially insured.

**Future Treatment Paradigms With Nonsteroidal MRAs**

**Nondiabetic Kidney Disease**

To date, the finerenone clinical development program has concentrated on showing the efficacy of finerenone in kidney and cardiovascular protection in patients with CKD and T2DM. Although FIDELIO-DKD and FIGARO-DKD, as well as many of the recent clinical SGLT2 inhibitor clinical trials, have primarily involved albuminuric patients with T2DM, we suggest that MR activation and the associated inflammation and fibrosis may be relevant not just in patients with diabetes and CKD but also in the pathogenesis of nondiabetic kidney disease. Accordingly, it is reasonable to argue that MR antagonism may be an effective therapeutic in nondiabetic CKD. Therefore, we propose that FIDELIO-DKD and FIGARO-DKD should constitute a platform for implementing a constellation of future clinical trials beyond the narrow focus of people with type 2 diabetes. In this final section of this review, we briefly discuss recently initiated and future clinical trials that are planned to extend and leverage the attributes of MR antagonism to a wide array of kidney disorders.

A recently initiated major clinical trial will examine finerenone in nondiabetic kidney disease. FIND-CKD (Clinicaltrials.gov identifier NCT05047263) is currently enrolling patients to examine the effects of finerenone plus guideline-directed therapy on CKD progression, with expected completion in November 2025. Box 3 summarizes the primary and secondary end points as well as the exclusion and inclusion criteria of this trial.

FIONA is 6-month multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy,
safety, pharmacokinetics, and pharmacodynamics of an age- and body-weight-adjusted oral finerenone regimen in addition to an ACEI or angiotensin receptor blocker for the treatment of children with CKD and proteinuria. It includes participants aged 6 months to younger than 18 years of age with glomerular and nonglomerular CKD (EudraCT number 2021-002071-19). The first patient was enrolled in March 2022.

### Combination Therapy

The potential value of a combination therapy with the nonsteroidal MR antagonist finerenone and SGLT2 inhibitors remains unestablished. Kolkhof et al. recently investigated cardiorenal protection afforded by both monotherapy and combination therapy of these 2 drug classes in a preclinical model of hypertension-induced end-organ damage. In this animal model of nondiabetic cardiorenal disease, Kolkhof et al. demonstrated that a combination of finerenone with the SGLT2 inhibitor empagliflozin, administered at low dosages, led to improvements in an array of relevant outcomes such as proteinuria, blood pressure, plasma creatinine, plasma uric acid, and mortality. Co-administration of low dosages of finerenone and empagliflozin led to a stronger survival benefit than equivalent or higher doses given individually. CONFIDENCE is a planned phase 2 clinical trial that will leverage the preclinical studies and examine the effects of finerenone and empagliflozin alone and in combination versus placebo on reduction of albuminuria in patients with CKD and T2DM (ClinicalTrials.gov identifier NCT05254002). Although we are unaware of any preclinical or clinical data to suggest how MRAs, SGLT2 inhibitors, and GLP-1RAs should be used sequentially, such investigations should be initiated.

### Conclusion

With the recent publication of FIDELIO-DKD and FIGARO-DKD, and with several other novel nonsteroidal MRAs under robust development, treatment paradigms encompassing nonsteroidal MRAs will gain in importance in the clinical practice of nephrology. We have reviewed the key differences between steroidal and nonsteroidal MRAs in terms of clinical efficacy and serious adverse events. An important and overriding challenge is the hyperkalemia evoked by treatment with MRAs. We encourage systematic application of careful monitoring and an array of mitigation strategies that should enable sustained therapy with finerenone (and potentially other new MRAs) in most patients with CKD while obviating the need to permanently discontinue MRAs due to hyperkalemia.

We propose that activation of MR, along with the associated inflammation and fibrosis, is relevant to the pathogenesis of CKD whether or not there is co-occurring diabetes. We conclude on a propitious note by briefly discussing recently initiated or planned clinical trials (CKD-FIND, FIONA, CONFIDENCE) that are investigating either the efficacy of finerenone in retarding and abrogating progression in patients with nondiabetic CKD, or finerenone in combination with SGLT2 inhibitors. We are not aware of any new evidence on the efficacy of MRAs for patients without albuminuria or any planned studies in this area.
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