Considerations for the future: current and future treatment paradigms with mineralocorticoid receptor antagonists—unmet needs and underserved patient cohorts

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The recent successful demonstrations that the nonsteroidal mineralocorticoid receptor (MR) antagonist finerenone provides effective kidney and cardiovascular (CV) protection in patients with chronic kidney disease (CKD) and type 2 diabetes constitutes a platform for considering and implementing an array of future clinical trials in patients with nondiabetic CKD. Activation of the MR, with consequent inflammation and fibrosis, should be operative as a pathogenetic mediator not only in patients with diabetic CKD but also in those with nondiabetic kidney disease. Consequently, it is proposed that MR antagonism therapy will be equally efficacious in patients with nondiabetic CKD. Recently, a major new clinical trial has been initiated testing finerenone in patients with nondiabetic kidney disease (FIND-CKD; NCT05047263). A second clinical development program, FIONA, is dedicated to studies of finerenone in children with glomerular and nonglomerular CKD. Finally, the interrelationship of fibroblast growth factor 23 (FGF23), membrane αKlotho (hereafter called Klotho), and aldosterone may be a propitious subject for future investigation. The interplay and intersection of these seemingly disparate yet intricate relationships may unmask novel, and indeed compelling, opportunities for therapeutic interventions that are capable of interrupting the vicious cycle of excess aldosterone/MR activation and FGF23 secretion with concomitant Klotho insufficiency characteristically present in patients with CKD.

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In addition to their demonstrating that finerenone effectively provides kidney and cardiovascular (CV) protection in patients with chronic kidney disease (CKD) and type 2 diabetes, I propose that both the FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) and the FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease (FIGARO-DKD) studies constitute a platform that should be used for implementing an array of future clinical trials. In the final section of this paper, I delineate several areas of investigative interest that beckon.

CKD of diverse etiology

The recently reported FIDELIO-DKD study demonstrated that patients with CKD and type 2 diabetes who were treated with finerenone (a novel nonsteroidal mineralocorticoid receptor [MR] antagonist [MRA]) manifested a lower risk of a primary outcome event (kidney failure, a sustained decrease of ≥40% in the estimated glomerular filtration rate (eGFR) from baseline, or death from renal causes) than patients in the comparator arm, who received placebo.[1] A complementary clinical trial, FIGARO-DKD, recently reported a lower risk of a primary outcome event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure). However, whereas FIDELIO-DKD, FIGARO-DKD, and many of the recent clinical trials on sodium–glucose co-transporter-2 inhibitors (SGLT-2i's) have focused predominantly on patients with type 2 diabetes and associated CKD and/or heart failure with reduced ejection fraction (HFrEF),[1–4] additional CKD etiologies beckon. A point that must be highlighted is that the activation of the MR, with consequent inflammation and fibrosis, should be operative as a pathogenetic mediator not only in diabetic CKD but also in the pathogenesis of nondiabetic kidney disease.

In this regard, a point that should be noted is that during the preparation of this article, 2 major new clinical trials have been initiated testing finerenone in patients with nondiabetic kidney disease. The first study (a randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 study to investigate the efficacy and safety of FInerenone, in addition to standard of care, on the progression of kidney disease in patients with Non-Diabetic Chronic Kidney Disease [FIND-CKD]; identifier: NCT05047263) is currently

enrolling patients without diabetes with CKD (urine albumin-to-creatinine ratio of ≥200–≤3500 mg/g and eGFR ≥25–<90 ml/min per 1.73 m^2). This study was started in September 2021 and is expected to be completed in November 2025.

The FInerenone for the treatment of children with chrOnic kidNey disease and proteinuriA (FIONA) trial is a 6-month randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and pharmacokinetics/pharmacodynamics of finerenone, in addition to an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, in children with glomerular and nonglomerular CKD and severely increased proteinuria (urine protein-to-creatinine ratio [UPCR] ≥0.5 g/g in children ≥2 years of age and with CKD stages 2 and 3, and UPCR ≥1 g/g in children from 6 mo to <2 years of age and in children ≥1 year of age with CKD stage 1) (EUDRACT: #2021-002071-19).

At the outset of this article, I use sickle cell disease (SCD) as an illustrative example for the possible utility of MRA therapy in a common and devastating disease. I follow up by reviewing several other clinical disorders of potential interest for future MRA therapy.

Sickle cell disease

Many clinical cohorts among patients with nondiabetic kidney disease are underserved. An example that I believe should be considered as a focus for increased attention and investigation is SCD-related nephropathy. SCD is one of the most common hereditary hemoglobinopathies. In the US, approximately 100,000 Americans are afflicted with SCD. Estimates suggest that approximately 300,000 infants worldwide are born every year with this condition,[5] which predominantly affects people of African descent, as well as individuals from the Middle East, India, and Mediterranean regions.[6]

A point of note that is not widely appreciated is that the natural history of SCD has changed markedly from what many of us were taught in medical school. SCD has evolved from what was once a fatal pediatric illness to a chronic adult disease characterized by progressive multi-organ failure.[5–7] Whereas the survival rate for pediatric patients continues to improve, the overall survival for adults has lagged behind. In the US, up to 100,000 people are estimated to be affected by SCD,[8] 40% of whom are children or adolescents.[9] In developed countries, more than 95% of children with SCD survive to adulthood.[10]

SCD-related nephropathy begins early in childhood, comprising failure of urinary concentrating ability (hyposthenuria), albuminuria to hyperfiltration, hematuria, and progressive decline of glomerular filtration rate eventuating to end-stage kidney disease (ESKD). Although patients are asymptomatic in the early stages of the disease, glomerular changes associated with SCD occur early in the first decade of life and are characterized by elevated renal blood flow, hyperfiltration, and hypertrophy. Urine testing can allow early diagnosis of SCD-related nephropathy; in a cross-sectional study of 410 patients with SCD aged 2–21 years (mean age: 11 years), 23% of homozygous patients manifested elevated urinary albumin excretion (≥30 mg/g).[11] The pathogenesis of SCD-related nephropathy is multifactorial, encompassing hypoxia, acidosis, hemolysis, ischemia–reperfusion injury, and, prominently, hyperfiltration.[12] Endothelial dysfunction related to chronic hemolysis and the relative kidney hypoxia caused by vaso-occluded sickle red blood cells are probably key factors for the development of kidney complications in SCD.[13]

Kidney dysfunction is more severe in homozygous individuals than in compound heterozygous patients.[13] A very recent multicenter observational study documented the progression of kidney decline in a large cohort of patients with SCD or sickle cell trait (SCT; i.e., homozygous and heterozygous patients, respectively). The study included 1251 Black adult patients with SCT, 230 with SCD, and 8729 reference patients, all with a median follow-up of 8 years. After adjustment, eGFR declined significantly faster in patients with SCT or SCD, compared with that in reference patients; adjusted eGFR decline was also faster in patients with SCD than in those with SCT.[14]

Adults with SCD are at increased risk of CKD and progression to ESKD as they age,[13] with approximately 1 in 6 patients dying of kidney disease.[15] SCD is associated with a high frequency of CKD, which is a risk factor for death in these patients. For reviews of SCD, see Audard *et al.*[7] and Willis *et al.*[16] Maigne *et al.*[17] have reported that progressive deterioration of kidney function is frequently observed in patients with SCD with glomerular disease, independent of the underlying glomerular lesions.

Treatment with inhibitors of the renin–angiotensin system (RAS)

The pivotal role for RAS inhibitors in retarding the progression of kidney disease is well established.[18] Surprisingly, in light of the predominance of hyperfiltration, very few reports have been made of studies of patients with SCD-related nephropathy who were treated with RAS inhibitors.[19,20] A 2015 Cochrane database review reported the potential for reduction in albuminuria and proteinuria with the use of captopril in patients with SCD, compared with those without the disease.[21] The paucity of clinical reports of RAS inhibition may be attributable to the failure to recognize the overriding importance of hyperfiltration in mediating the progression of SCD-related nephropathy. Possible explanations include the substantially increased risk of angiotensin-converting enzyme inhibitor-associated angioedema in African American patients compared with White subjects, and that this increased risk cannot be attributed to an effect of dose, specific angiotensin-converting enzyme inhibitor, or concurrent medications.[22–24] In summary, whereas the scant and preliminary data suggest that RAS blockade may be beneficial, we must conclude that many questions and concerns persist regarding both the benefits and risks of RAS inhibitors in SCD-related nephropathy.

Challenges and futility of "kidney replacement therapy" in patients with CKD caused by SCD

Dialysis. Hemodialysis is reportedly the leading form of kidney replacement therapy for patients with SCD-ESKD, as well as peritoneal dialysis.[16] Patients who initiate dialysis due to SCD-associated kidney failure have a poor prognosis, with a 1.5- to 2.8-fold hazard of mortality, compared with those with other etiologies of kidney failure.[25] Mortality in patients with SCD is approximately 26% during the first year of therapy for ESKD, nearly threefold higher than that in patients with ESKD without SCD. However, patients with SCD who received predialysis nephrology care had a lower death rate than those who did not receive such care.[25] Patients with SCD often have very poor peripheral venous access, so dialysis needs to be planned carefully. Outcome data for patients with SCD on dialysis are scant. Powars *et al.*[26] reported that ESKD is associated with very poor prognosis, with a median time to death of only 4 years. Similar results have been reported in patients in Saudi Arabia.[27]

Patients with SCD suffered more infectious complications. Patients with SCD survived, on average, for only 27 months after commencing kidney replacement therapy, and they were significantly younger when they died (31 years vs. 47.8 years), compared with patients with ESKD from other causes.[27] Because of the paucity of reports, and the fact that these few reports are outdated, a constructive, potential "next step" is to encourage implementation of registries documenting outcome data in patients with SCD undergoing maintenance hemodialysis with newer dialytic modalities.

Kidney transplant. The kidney transplant operative procedure in patients with SCD-associated kidney failure is associated with multiple challenges.[28,29] This difficulty results from patients with SCD being predisposed to various immunologic, cardiorespiratory, and hematological challenges—for example, general anesthesia may worsen the hypoxic state that is often present in patients with SCD.[28] Furthermore, patients with SCD have been reported to have an impaired immune status, which could lead to increased infections and slow wound healing, thereby posing a major challenge for management, because therapeutic immunosuppression is a fundamental component of the management of kidney transplant.[28]

In a recent issue of the *Clinical Journal of the American Society of Nephrology*, Bae *et al.*[30] (2021) analyzed issues of mortality and access to kidney transplantation in patients with SCD-associated kidney failure. In their national study, they reported that kidney transplantation was associated with similar and substantial decreases in mortality in both the SCD and control groups. Nonetheless, the SCD group had worse access to transplantation, compared with the control group, even after being placed on the national kidney transplant waiting list.[30] The findings of Bae *et al.* suggest that access to transplantation in the sickle cell population constitutes a barrier to transplantation and should be improved.[30] Systematically collecting data from available dialysis and transplant registries will enable the medical community to attain a more precise understanding of the challenges and outcomes in managing SCD patients with CKD, and consequently will inform future investigations.

Implications for future research—MR antagonism in SCD. Theoretical considerations indicate that inflammation and fibrosis are mechanisms that participate in mediating SCD-related nephropathy. Preclinical investigations should be implemented in appropriate animal models, such as Berkeley sickle cell transgenic mice, to further elucidate the possible role of MR activation in promoting SCD-related nephropathy. Accruing additional preclinical data, and particularly important, a more extensive database from both dialysis and transplantation registries, may provide a platform for ascertaining whether patients with SCD-related nephropathy potentially constitute candidates for participation in clinical trials with novel nonsteroidal MRA therapy. The substantive and multifold barriers to implementation of successful dialysis and transplant programs in patients with SCD that I have enumerated in this article commend consideration of clinical trials with novel nonsteroidal MRA therapy attempting to retard the progression of eGFR decline. Several risk factors that have recently been identified should be investigated in prospective studies.[14] Collectively, the observations reviewed herein may constitute a platform for initiating clinical trials to define best practices and interventions to attenuate eGFR decline and prevent incident CKD in Black patients with both SCT and SCD.

The interrelationship of fibroblast growth factor 23 (FGF23) and aldosterone may be a propitious subject for future investigation

Patients with CKD have a high risk of CV disease, with rates several-fold higher in patients with CKD, compared with those in age-matched subjects without CKD. According to the most recent annual data report from the US Renal Data System, any CV disease was present in 37.5% of patients without CKD, compared with 63.4% of patients with stages 1–2 CKD, 66.6% of patients with stage 3 CKD, and 75.3% of patients with stages 4–5 CKD.[31]

In addition to the traditional CV risk factors, disturbances of mineral metabolism constitute specific risk factors that contribute to the excessive CV mortality in patients with CKD.[32,33] These risk factors include dysregulations of circulating factors that modulate phosphate metabolism, including FGF23 and membrane αKlotho (hereafter called Klotho). Klotho is highly expressed in the kidney and functions as a co-receptor of FGF receptors to activate a specific FGF23 signaling pathway.[33,34]

Of interest, FGF23 may also constitute a modulator of the renin–angiotensin–aldosterone system. FGF23 has been shown to be involved in the activation of the local renin–angiotensin–aldosterone system, including aldosterone in the heart promoting cardiac fibrosis and hypertrophy.[35] FGF23 is induced by an activated profibrotic crosstalk between cardiac myocytes and fibroblasts.[35] FGF23 may also downregulate the cardiac vasoprotective angiotensin-converting enzyme 2/

angiotensin–(1-7) pathway,[36] thereby contributing to cardiac remodeling and hypertrophy. At the same time, aldosterone and angiotensin II upregulate bone FGF23 expression and increase circulating FGF23 levels.[33,35] In concert, these observations suggest that aldosterone may be a key driver of enhanced FGF23 secretion in patients with CKD. Positive correlations between circulating FGF23 and aldosterone have been observed in patients with CKD across stages 1–5.[37,38] Following the administration of the MRA canrenone, uremic mice with elevated aldosterone levels experienced a significant drop in the elevated circulating FGF23 concentrations, suggesting that aldosterone plays a direct role in FGF23 secretion by the bone.[37]

Klotho acts as a co-receptor for FGF23-mediated FGF receptor activation in the kidney.[33] Once this membrane-bound Klotho is cleaved and released from the kidney into the circulation as Klotho, it has demonstrated cardiorenal protective properties, including attenuation of hypertension, oxidative stress, progression of CKD, cardiac fibrosis and myocardial hypertrophy, and vascular calcification.[34,39–41]

Klotho is downregulated by angiotensin II, and the absence of Klotho upregulates cytochrome P450 (CYP) 11B2 , which is responsible for aldosterone synthesis.[33,34] Conversely, Klotho downregulates renin–angiotensin–aldosterone system activity, and thus attenuates tissue injury and fibrosis and improves hypertension in experimental CKD.[34]

A tempting proposal is that an in-depth consideration of the interplay and intersection of these seemingly disparate yet intricate relationships may disclose and unmask novel opportunities for therapeutic interventions that are capable of interrupting the vicious cycle of excess aldosterone/MR activation and FGF23 secretion with concomitant Klotho insufficiency characteristically present in patients with CKD.[33] Collectively, the studies cited above suggest opportunities for implementing clinical studies to evaluate the potential beneficial effects of both MR antagonism and the following:

(i) maintaining appropriate soluble Klotho levels in the prevention, or possibly attenuation, of endothelial dysfunction and vascular stiffness in patients with CKD; and
(ii) interventions with MR antagonism and concomitant maintenance of soluble Klotho levels, to interrogate the intricate intersections and interrelationships between an activated RAS (including aldosterone), excess FGF23, and insufficient Klotho to abrogate and retard the initiation and progression of kidney and cardiac injury in CKD (Figure 1).

Combination therapy with an SGLT-2i and an MRA

Combination therapy with an SGLT-2i and an MRA has been advocated recently as the "next step" for treating HFrEF and CKD progression. To provide context, the potential advantages of fixed-dose combination medications have been reviewed extensively.[42] SGLT-2i's and MRAs may have complementary mechanisms of action and may constitute an attractive combination for the treatment of both HFrEF and CKD.[43] Recent preclinical studies by Kolkhof *et al.*[44] in a nondiabetic cardiorenal rat model have demonstrated that treatment with the combination of the novel nonsteroidal MRA finerenone and the SGLT-2i empagliflozin conferred kidney protection, as assessed by an efficacious reduction in proteinuria, kidney lesions, and mortality. Low-dose combination, but not the respective low-dose monotherapies, significantly reduced plasma creatinine and plasma uric acid concentrations after 6 weeks. Dose-dependent protection from cardiac and kidney fibrosis was found, as well as vasculopathy with both agents, and low-dose combination therapy was more efficient than the respective monotherapy dosages with regard to most cardiorenal histology parameters.[44]

Of note, a recent secondary analysis of the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced; NCT03057977) trial did not align with this formulation. Ferreira *et al.*[45] examined the influence of steroidal MRA use at baseline on the efficacy and safety of empagliflozin, and whether empagliflozin influenced the prescribing of MRAs following randomization. They concluded that the use of MRAs did not influence the effect of empagliflozin in reducing adverse heart failure and kidney outcomes. Finally, a recent publication reviews the potential attributes of combination therapy with a nonsteroidal MRA and an SGLT-2i.[43] In summary, some, but not all, findings support a potential role for combined clinical use in cardiorenal patient cohorts. The newly registered Efficacy, Safety and Tolerability of AZD9977 and Dapagliflozin in Participants With Heart Failure and Chronic Kidney Disease (MIRACLE; NCT04595370) trial will investigate potential benefits of combining SGLT-2i and MRA treatments in patients with HFrEF and CKD.[46]

Leptin-mediated aldosterone production and the "metabolic syndrome"

CV diseases constitute the leading cause of death worldwide. Overweight and obesity are strongly associated with comorbidities, including hypertension, arterial stiffness, and insulin resistance, which collectively contribute to the development of CV diseases and resultant morbidity and mortality. In the US, 42% of adults are obese, and a total of 1.9 billion adults worldwide are overweight or obese.[47] Consequently, the nexus of obesity and MR activation is of interest.

As detailed by Epstein in the introductory article of this supplement,[48] recent studies have demonstrated that leptin is a regulator of aldosterone synthesis that acts directly on adrenal glomerulosa cells to increase CYP11B2 expression and enhance aldosterone production via calcium-dependent mechanisms. Consequently, leptin-mediated aldosterone production constitutes a novel candidate mechanism underlying obesity-associated hypertension, particularly in female patients.[49]

Increasing evidence suggests that overactivation of the MR plays a role in the pathophysiology of the diverse components of metabolic syndrome in addition to hypertension,

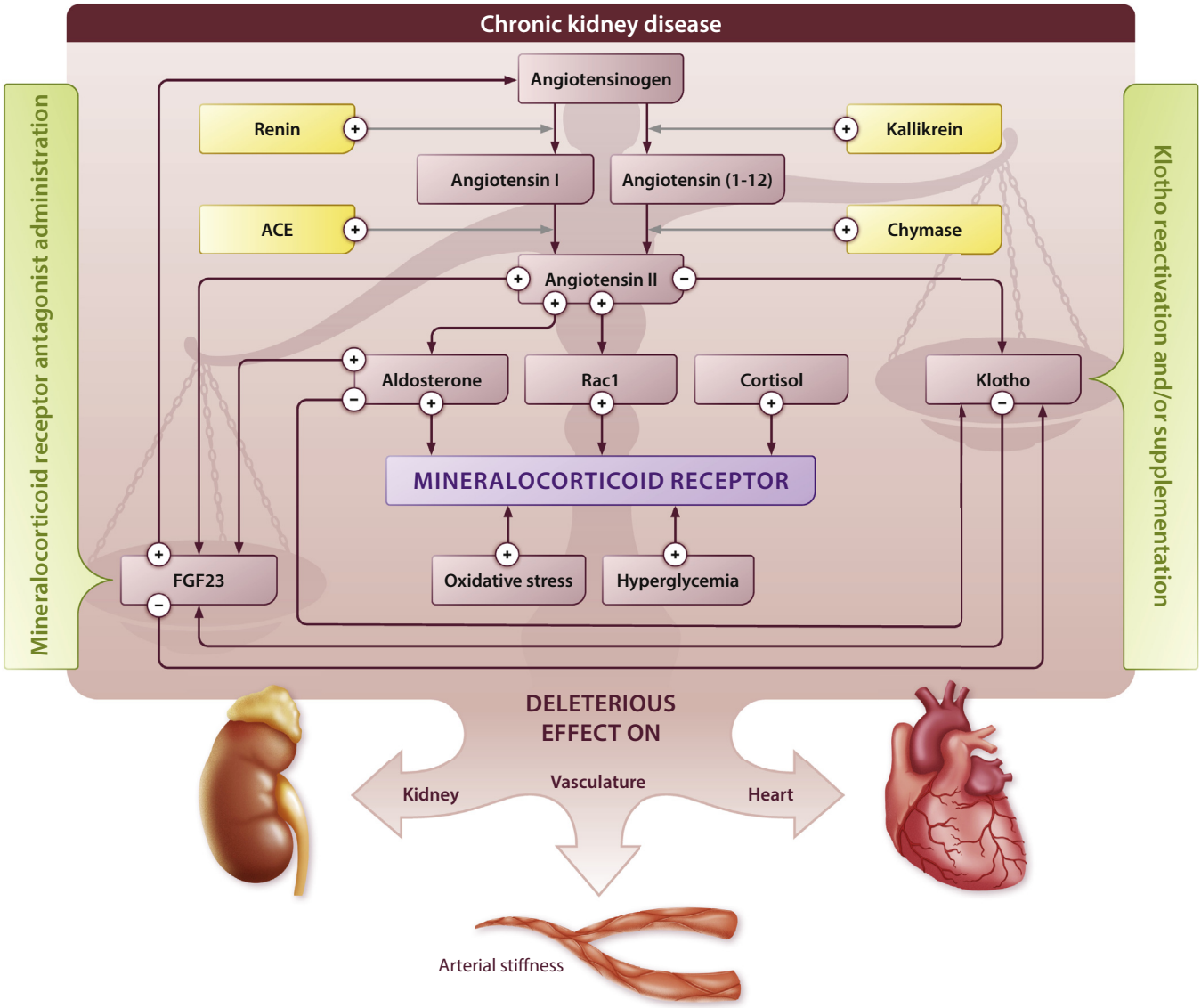

Figure 1 | Complementary interplay of "cascades of injury." Fibroblast growth factor (FGF)23/Klotho–renin–angiotensin–aldosterone system–mineralocorticoid receptor and their interrelationships. Both angiotensin II and aldosterone directly stimulate FGF23 secretion. In chronic kidney disease, (*right*) Klotho insufficiency and (*middle*) mineralocorticoid receptor activation act on different cell types and through multipronged and complementary systemic and local molecular and signaling mechanisms to promote cardiorenal injury. As detailed in the text, both (*broad green vertical band on the right*) Klotho reactivation and/or Klotho supplementation and (*broad green vertical band on the left*) mineralocorticoid receptor antagonist administration may potentially prevent and attenuate these numerous cardiorenal injury–promoting cascades. For additional information, see a very recent review by the author that details in depth the expansive array of intersections and interplays of the 3 cascades of injury.[33] ACE, angiotensin-converting enzyme.

promoting adiposity, inflammation, and glucose intolerance, and that MRAs may confer beneficial effects on energy and substrate homeostasis and cardiometabolic diseases.[50,51] The implications of the leptin–aldosterone interplay are profound. As an example, in the US, two-thirds of adults are overweight or obese, and 34.2 million people have diabetes (10.5% of the US population).[52] Consequently, the hypothesis that aldosterone and MR signaling represents an ideal candidate pathway linking early promoters of diabetes, especially overnutrition and obesity, to vascular insulin resistance, dysfunction, and disease provides a template for developing future treatment paradigms that may be widely beneficial. I suggest that a priority should be to implement clinical trials with novel nonsteroidal MRAs, to elucidate the potential beneficial effects of MR antagonism in tamping down the diverse components of the current epidemic of metabolic syndrome, thereby reducing the associated components of adiposity, inflammation, and glucose intolerance.

Conclusions

Recent studies have demonstrated a wider and expanded role for aldosterone in nonepithelial activity, thereby influencing

inflammation, collagen formation, fibrosis, and necrosis. Increasing evidence has accrued that clearly implicates pathophysiological overactivation of the MR as a major determinant of progression of CKD and its associated morbidity and mortality. In accordance with this formulation, MR antagonism is currently being investigated as a novel treatment regimen to retard the progression of CKD. Based on the success of both the FIDELIO-DKD and FIGARO-DKD studies,[1,4] future studies should be implemented testing the hypothesis that a wide array of nondiabetic CKD clinical cohorts, many of which are unappreciated and underserved, are also modulated by overactivation of the MR. Consequently, these nondiabetic CKD cohorts may be amenable to treatment with novel nonsteroidal MRAs such as finerenone.

The rationale is also strong for investigating the interrelationship of FGF receptor 2 and aldosterone in nondiabetic patients with CKD. As well as MR activation and elevated aldosterone levels, excess FGF23 and Klotho insufficiency have emerged as important mediators of kidney and CV injury, and they consequently constitute major catalysts for accelerating both CKD progression and cardiac fibrosis and hypertrophy. Data also support the hypothesis that FGF receptor 2 levels are driven by aldosterone in CKD, and a positive correlation between the 2 is found across CKD stages.

Finally, implementing combination therapy approaches with SGLT-2i's and MRAs, such as finerenone, offers a promising research avenue for treating HFrEF and CKD progression, based on their complementary modes of action and preclinical data supporting the efficacy of the approach in animal models; the MIRACLE trial is underway in this setting.[46]

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