MAYO CLINIC

Evolution of Mineralocorticoid Receptor Antagonists in the Treatment of Chronic Kidney Disease Associated with Type 2 Diabetes Mellitus

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Abstract

Chronic kidney disease (CKD) is one of the most frequent complications associated with type 2 diabetes mellitus (T2DM) and is also an independent risk factor for cardiovascular disease. The mineralocorticoid receptor (MR) is a nuclear receptor expressed in many tissue types, including kidney and heart. Aberrant and long-term activation of MR by aldosterone in patients with T2DM triggers detrimental effects (eg, inflammation and fibrosis) in these tissues. The suppression of aldosterone at the early stage of T2DM has been a therapeutic strategy for patients with T2DM-associated CKD. Although patients have been treated with renin–angiotensin system (RAS) blockers for decades, RAS blockers alone are not sufficient to prevent CKD progression. Steroidal MR antagonists (MRAs) have been used in combination with RAS blockers; however, undesired adverse effects have restricted their usage, prompting the development of nonsteroidal MRAs with better target specificity and safety profiles. Recently conducted studies, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD), have reported that finerenone, a nonsteroidal MRA, improves both renal and cardiovascular outcomes compared with placebo. In this article, we review the history of MRA development and discuss the possibility of its combination with other treatment options, such as sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide–1 receptor agonists, and potassium binders for patients with T2DM-associated CKD.

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DIABETES, HEART FAILURE, AND CHRONIC KIDNEY DISEASE

Diabetes mellitus (DM) is a major global health concern. It is estimated that 463 million people worldwide had DM in 2019, with that number projected to reach 700 million by 2045.[1] Chronic hyperglycemia stimulates inflammatory cytokines, growth factors, and the renin–angiotensin system (RAS).[2,3] Resultant oxidative stress is linked to the formation of advanced glycation end products as well as activation of protein kinase C and polyol and hexosamine metabolic pathways.[2,3] Up-regulation of profibrotic growth factors, such as transforming growth factor beta, results in mature collagen deposition, which is one of the characteristic features of diabetic nephropathy (DN).[4]

Diabetic nephropathy is the leading cause of chronic kidney disease (CKD), defined as persistently (>3 months) elevated urine albumin excretion level (≥30 mg/g creatinine) and/or reduced estimated glomerular filtration rate (eGFR; <60 mL/min per 1.73 m^2).[5,6] Although considerable progress has been made in treatments aimed at modifying the course of disease in DN, progression to kidney failure and end-stage kidney disease (ESKD) remains a major concern.[1] Globally, >80% of ESKD is caused by DM and/or hypertension, and the prevalence of ESKD is up to 10 times higher in patients with DM than those

without DM.[1] According to the Centers for Disease Control and Prevention, 1 of every 3 adults with DM in the United States may have kidney disease.[7] Diseases of the kidney are the ninth leading cause of death in the United States.[7,8] In 2019, the Advancing American Kidney Health initiative was launched with the following 3 major goals: (1) reduce the risk of kidney failure; (2) improve access to and quality of person-centered treatment options; and (3) increase access to kidney transplants.[8]

Type 2 DM (T2DM) and heart failure (HF) often coexist, with DM occurring in up to 24% of patients with chronic HF and in up to 40% of those hospitalized with acute HF.[9,10] Up to 50% of patients with HF also present with CKD, which significantly increases the mortality risk.[11,12] The United States Renal Data System 2020 Annual Data Report suggests that the 24-month survival probability after the first diagnosis of HF in patients with stage 3 and stage 4-5 CKD declines by 7% and 23%, respectively, compared with those without CKD.[13] Kidney Disease Improving Global Outcomes (KDIGO) 2020 Clinical Practice Guideline for Diabetes Management in CKD suggests that patients with T2DM and CKD should be treated with a comprehensive approach by modifying a range of factors associated with the progression of CKD and cardiovascular disease (CVD), including glycemic and blood pressure (BP) control, lipid management, weight loss, exercise, and smoking cessation.[14] Using the KDIGO 2020 drug treatment guidelines as an example, recommendations include using the following: (1) a combination of a sodium-glucose cotransporter 2 inhibitor (SGLT-2i) and metformin for patients with eGFR $\geq$30 mL/min per 1.73 m^2; (2) glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for patients who are unable to achieve glycemic targets despite use of metformin and SGLT-2i; (3) RAS blockers, including angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs), for patients with albuminuria and hypertension; and (4) antiplatelet therapies for patients with acute coronary syndrome or percutaneous coronary intervention.[14] The KDIGO 2020 guidelines also emphasize the need for more randomized clinical studies to evaluate the following: (1) the effect of ACEis and ARBs on the outcome of albuminuria reduction and progression of DM and CKD; (2) the effect of mineralocorticoid receptor (MR) antagonists (MRAs) on the progression of CKD and CVD; (3) clinical benefits of preventing hyperkalemia (ie, with potassium binders) during RAS blockade; and (4) decision aids for hyperkalemia risk and testing during RAS blockade.[14]

In this review, we present an overview of the role of aldosterone in the pathophysiology and progression of CKD and CVD in patients with DM as well as current and future therapeutic options with a particular emphasis on the evolution of MRAs, including traditional steroidal agents and new nonsteroidal ones.

ARTICLE HIGHLIGHTS

- Chronic kidney disease (CKD) is frequently associated with type 2 diabetes mellitus (T2DM) and is also an independent risk factor for cardiovascular disease.
- Aberrant and chronic activation of the mineralocorticoid receptor by aldosterone in patients with T2DM triggers detrimental effects.
- Over the past few decades, T2DM-associated CKD has been treated with renin–angiotensin–androgen system blockers, including mineralocorticoid receptor antagonists (MRAs), but with undesirable adverse effects.
- Recent US Food and Drug Administration approval of a nonsteroidal MRA, finerenone, and a revised label for a sodium-glucose cotransporter 2 inhibitor, dapagliflozin, are expected to influence the treatment of patients with CKD.
- We hereby review the history of MRA development and discuss the possibility of combination treatment with other agents.

LITERATURE SEARCH

The searches for this narrative review were performed nonsystematically and "as needed" (when new relevant publications were available). A MEDLINE-based literature review was undertaken (limited to English language journals) using the following search terms: *diabetes*, *chronic kidney disease*, *diabetic kidney disease, mineralocorticoid receptor*, and *aldosterone*, and currently available treatments and investigational treatments for CKD and diabetes.

ALDOSTERONE AND THE MR

Aldosterone is a mineralocorticoid steroid hormone, synthesized and secreted in response to an increase in potassium levels, angiotensin II, and corticotropin and/or sodium depletion in the adrenal cortex.[15] Although mineralocorticoids are traditionally believed to be produced only in the adrenal cortex,[16] a gradient of elevating aldosterone levels from the coronary sinus to the aortic root was reported in patients with acute myocardial infarction.[17] Similarly, in patients with HF and hypertension, plasma aldosterone levels were found to be greater in the cardiac vein than in the aorta, whereas no such difference was observed in healthy persons.[18,19] These results suggest de novo synthesis of aldosterone in the heart under pathologic conditions, although the exact mechanism behind the local increase of aldosterone in the heart is not fully understood.[20,21]

Aldosterone functions by activating the MR, which is expressed in many tissues, such as the kidney, colon, heart, central nervous system, adipose tissue, and sweat glands.[22] The enzyme 11β-hydroxysteroid dehydrogenase II confers specificity on the renal MR by inactivating the glucocorticoid, cortisol, which it does by metabolizing cortisol to cortisone (cortisone which has no affinity for the MR), and thus keeps the MR free for aldosterone binding.[23] The aldosterone-MR system plays a major role in the following: (1) control of BP and extracellular volume homeostasis by stimulating renal sodium reabsorption; and (2) the control of serum potassium by regulating potassium excretion. The mechanism of action of aldosterone in relation to its role in regulating potassium excretion is to first, increase the intracellular potassium levels by stimulating the activity of sodium-potassium adenosine triphosphate [ATP] ases in the basolateral membrane. Second, it stimulates sodium reabsorption across the luminal membrane, thereby increasing electronegativity of the lumen, which increases the electrical gradient-favoring potassium excretion. Third, it has a direct effect on the luminal membrane, thereby increasing potassium permeability.[24] Hyperkalemia can occur in states of aldosterone deficiency or RAS blockade.[25,26] Aldosterone binds to and activates the MR, resulting in the transcriptional activation of genes involved in electrolyte homeostasis in health. When abnormally elevated over a long-term, the aldosterone-MR complex also activates proinflammatory and profibrotic genes through hormone response elements in their promoters.[27] In epithelial tissues, including the kidney, MR activates the expression of ionic transporters in the cellular membrane that controls salt and water homeostasis. In nonepithelial tissues, including the heart, the aldosterone-MR complex up-regulates genes involved in cell proliferation, fibrosis, vascular injury, and tissue inflammation.[28] In addition to these genomic MR effects, its expression in immune cells appears to contribute to the inflammation process through DNA binding—independent signaling in macrophages as well as T-cell activation, as summarized in a recent review by Barrera-Chimal et al.[29]

Early clinical results revealed that the magnitude of plasma aldosterone increase correlated with the degree of renal insufficiency,[30,31] and preclinical results suggested that administration of aldosterone resulted in renal and cardiac injury.[32,33]Administration of an MRA in rat models of CVD and kidney disease reduced proteinuria and tissue inflammation, fibrosis, and end-organ lesions.[33,34] These findings suggest that the suppression of aldosterone at an early stage in patients with DM may prevent organ damage, including CKD.

ALDOSTERONE BREAKTHROUGH DURING TREATMENT WITH RAS BLOCKERS

Over the past 2 decades, hypertension and albuminuria have been managed in patients with T2DM and CKD with RAS blockers, which lower plasma aldosterone levels.[14] Although clinical studies found that the use of ACEis/ARBs in patients with diabetes and CKD slows the progression of CKD, neither an ACEi nor ARB alone completely prevents CKD progression.[35] This is, in part, due to persistently elevated aldosterone levels during long-term RAS blockade with either ACEi or ARB, also known as aldosterone breakthrough.[36,37] Aldosterone breakthrough has been shown to occur in approximately 50% of patients treated with RAS blockers.[36,38]

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TABLE 1. Differences Among Spironolactone, Eplerenone, and Finerenone

	Spironolactone	Eplerenone	Finerenone
Structural aspects	Flat (steroidal)[66]		Bulky, passive antagonist (nonsteroidal)[59,66]
MRA structure	Steroidal	Steroidal	Nonsteroidal
Metabolites	Multiple, active metabolites[48]	No active metabolites[48]	No active metabolites[57]
Half-life	Spironolactone: <2 hours Active metabolites: >12-24 hours[48,50]	4 hours[55]	2-3 hours[57,58]
Tissue distribution	Heart < kidney[51]	Heart < kidney[51]	Heart ≈ kidney[61]
Affinity to MR	Finerenone > spironolactone >> eplerenone[54,56]		
Affinity to AR, GR, and PR	Spironolactone >> eplerenone ≈ finerenone[54]		
Inhibitory effect on aldosterone-dependent gene activation	Finerenone > spironolactone[60]		
Sexual side effects	Observed[51-53]	Low frequency[67]	Not observed or rare[64,65]
Effect on SBP	Spironolactone > finerenone[49] Spironolactone > eplerenone[68] Eplerenone ≈ finerenone[62]		
Effect on inflammation and fibrosis in animals	Eplerenone < finerenone[61,63]		
Risk of hyperkalemia	Eplerenone ≈ finerenone[62] Spironolactone > finerenone[49]		

AR, androgen receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; PR, progesterone receptor; SBP, systolic blood pressure.

The clinical implication of aldosterone breakthrough in kidney disease progression was examined in patients treated with an ARB, demonstrating that higher levels of aldosterone were associated with a higher rate of eGFR decline than lower aldosterone levels.[39] Although dual RAS blockade with ACEis/ARBs was examined in clinical studies, results demonstrated not only the lack of additional efficacy with respect to the progression of CKD but also an increased incidence of acute kidney injury, hypotension, and hyperkalemia.[40-42] Dual RAS blockade with an ACEi or ARB and aliskiren (a direct renin inhibitor [DRI]) did not benefit patients with DM and CVD either. Although aliskiren lowers BP, both as monotherapy and combination therapy,[43,44] and may not allow aldosterone breakthrough,[37] patients treated with aliskiren and ARB or ACEi have shown a greater risk of developing hyperkalemia and renal impairment.[45,46] Clinical guidelines from the American Diabetes Association[47] and KDIGO 2020[14] recommend the use of either an ACEi or an ARB alone, but not dual RAS blockade or the combination of ACEi or ARB with a DRI, for the treatment of hypertension. Strategies aimed at blocking the deleterious effects of aldosterone breakthrough, other than the use of combinations of ACEi/ARB and DRI, may be advantageous.

STEROIDAL MRAS: SPIRONOLACTONE AND EPLERENONE

Spironolactone was the first steroidal MRA, initially launched as a diuretic and natriuretic drug for the control of hypertension and primary aldosteronism and later for the treatment of HF.[15,48] Spironolactone can be regarded as a prodrug with a short half-life (<2 hours) that generates 3 active metabolites with longer half-lives (>12-24 hours) (Table 1).[48-68] Spironolactone may cause gynecomastia and impotence in males through its binding with the androgen receptor (AR) as an antagonist and menstrual irregularities and breast tenderness in women through its binding with the progesterone receptor (PR) as an agonist.[48,51-53,69] Research programs aimed at identifying more receptor-specific steroidal

TABLE 2. In Vitro Selectivity of MRAs in Functional Cell-Based Steroid Hormone Receptor Assays

	Spironolactone	Eplerenone	Finerenone
MR IC_{50}, nM	24.2	990	17.8
AR IC_{50}, nM	77.1	≥21,240	≥10,000
GR IC_{50}, nM	2410	≥21,980	≥10,000
PR EC_{50}, nM	740	≥31,210	≥10,000

AR, androgen receptor; EC_{50}, concentration of ligand required to achieve 50% activation of the receptor; GR, glucocorticoid receptor; IC_{50}, concentration of antagonist required to inhibit 50% activation of receptor; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; PR, progesterone receptor.

Adapted from *Eur J Heart Fail* and *J Biol Chem*.[54,71]

Higher and lower IC_{50} values are correlated with lower and higher affinities, respectively, between MRAs and steroid hormone receptors.

MRAs to decrease these side effects, led to the discovery of eplerenone. Differences in molecular structure and MRA activity underpin the distinct effects of spironolactone and eplerenone observed in preclinical and clinical studies (Table 1).[48-68]

Eplerenone is a second-generation MRA for the treatment of hypertension and HF.[22] In a steroid hormone receptor binding assay, eplerenone was found to be considerably more selective for the MR, but less potent than spironolactone (Table 2).[54,70,71] Eplerenone has no active metabolites, and its half-life of 4 hours is longer than that of spironolactone but much shorter than spironolactone's active metabolites.[48,55] The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[72] a multicenter, international, randomized, double-blind, placebo-controlled phase 3 study in patients with acute myocardial infarction complicated by left ventricular dysfunction and HF, demonstrated a significant reduction in morbidity and mortality among patients treated with eplerenone as compared with placebo, but with a significant increase in severe hyperkalemia (serum potassium concentration ≥6.0 mmol/L). Although still recommended, in particular for patients who have intolerable sex hormone—mediated side effects associated with the use of spironolactone, hyperkalemia and cost have limited the broad utilization of eplerenone in patients with HF.[73]

TREATMENT WITH STEROIDAL MRAS IN COMBINATION WITH ACEI/ARB

Several systematic reviews have suggested that the addition of a steroidal MRA to a regimen including an ACEi or ARB can improve organ protection for patients with CKD or DN but increase the risk of hyperkalemia. A Cochrane systematic review published in 2020 (44 studies with a duration of 1-36 months involving 5745 patients with CKD treated with MRAs)[74] confirmed conclusions made in 2009[75] and 2014.[76] Mineralocorticoid receptor antagonists may reduce proteinuria and systolic BP in adults who have mild-to-moderate CKD but probably increase the risk of hyperkalemia, acute kidney injury, and gynecomastia when combined with ACEi/ARB treatment.[74] Evidence for the effect of MRAs on the progression of CKD, cardiovascular (CV) events, and death is inconclusive, and data for treatment effects of nonsteroidal MRAs were not sufficient for precise estimates and meta-analysis. An increased incidence of hyperkalemia in patients receiving treatment with steroidal MRAs in addition to ACEi/ARB as compared with ACEi/ARB alone was also reported in an analyses of 8 studies involving patients with DN.[77] Similar findings were reported in a meta-analysis of 19 studies involving 1646 patients with stage 1-5 CKD, treated with MRAs (14 spironolactone and 5 eplerenone) and ACEi/ARB, in which MRAs were shown to reduce BP and albuminuria, but with a threefold higher risk of patients withdrawing from the study because of hyperkalemia than those receiving ACEi/ARB alone.[78] In another systematic review of 18 randomized, controlled studies (duration: 5 weeks-18 months), involving 1786 patients with DN treated with MRAs (15 spironolactone, 2 eplerenone, and 1 finerenone), significant reductions in urinary albumin excretion and BP and improvement in the urinary

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TABLE 3. Clinical Studies for Finerenone

Study	Phase	N	Patients	Study drug	Control	Duration, wk	Key findings
ARTS (NCT01345656)[49]	2	457	HFrEF with LVEF and mild[a]-to-moderate[b] CKD	Finerenone	Placebo/ spironolactone>	4	Finerenone was as effective as spironolactone in reducing hemodynamic stress and was associated with lower incidences of hyperkalemia with a smaller increase in serum potassium concentration and less worsening renal function than spironolactone. Hormone side effects were not examined because of its short duration and small number of patients.
ARTS-HF (NCT01807221)[62]	2b	1066	Worsening HFrEF with T2DM and/or CKD[c]	Finerenone	Eplerenone	12.9	The safety profile of finerenone was comparable to that of eplerenone. Death from any cause, CV hospitalization, or emergency presentation of worsening HF was lower in most of the finerenone dose groups than the eplerenone group. Whereas incidences of hyperkalemia were similar between the finerenone and eplerenone groups, mean changes from baseline in serum potassium concentration were lower in the finerenone dose groups than the eplerenone group.
ARTS-HF Japan (NCT01955694)[86]	2b	72	Worsening HFrEF with T2DM and/or CKD[c]	Finerenone	Eplerenone	12.9	Because of the small number of individuals per treatment group, no robust conclusions were drawn.
ARTS-DN (NCT01874431)[83]	2b	823	DN (T2DM)[d]	Finerenone + ACEi/ARB	Placebo + ACEi/ARB	12.9	Finerenone in combination with an ACEi/ARB showed a dose-dependent reduction in UACR compared with the placebo. No hyperkalemia leading to discontinuation was observed in the finerenone 10 mg/d group.
ARTS-DN Japan (NCT01968668)[87]	2b	96	DN (T2DM)[d]	Finerenone + ACEi/ARB	Placebo + ACEi/ARB	12.9	Finerenone reduced albuminuria without adverse effects on serum potassium levels or renal function in Japanese patients with T2DM and DN.
FIDELIO-DKD (NCT02540993)[64,84,88]	3	5734	T2DM with CKD[e]	Finerenone[f]	Placebo	135.6	Finerenone demonstrated lower risks of CKD progression and CV events than placebo. Discontinuation because of hyperkalemia was infrequent in patients who received finerenone (2.3%) and placebo (0.9%). Gynecomastia was rare and was comparable to placebo (0.2% vs 0.2%).
FIGARO-DKD (NCT02545049)[65,85,89]	3	7352	T2DM with CKD[g]	Finerenone[f]	Placebo	176.8	Finerenone improved CV outcomes compared with placebo with lower incidence of hospitalization for HR. Finerenone reduced new-onset HF and improved other HF outcomes. The incidence of hyperkalemia-related discontinuation was higher with finerenone (1.2%) than placebo (0.4%). Gynecomastia was rare and was comparable to placebo (0.1% vs 0.1%).

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARTS, minerAlocorticoid Receptor Antagonist Tolerability Study; CKD, chronic kidney disease; CV, cardiovascular; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIGARO-DKD, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-creatine ratio; wk, weeks.

[a]eGFR: 60 <90 mL/min per 1.73 m^2.

[b]eGFR: 30 <60 mL/min per 1.73 m^2.

[c]eGFR: >30 mL/min per 1.73 m^2 in patients with T2DM; 30-60 mL/min per 1.73 m^2 in patients without T2DM.

[d]UACR: ≥30 mg/g and eGFR >30 mL/min per 1.73 m^2.

[e]UACR: 30 to <300 mg/g and eGFR 25 to <60 mL/min per 1.73 m^2 or UACR ≥300 mg/g and eGFR ≥25 to <75 mL/min per 1.73 m^2.

[f]All patients were treated with either ACEi or ARB at maximum tolerated labeled dose that did not have unacceptable side effects.

[g]UACR: 30 to <300 mg/g and eGFR 25 to ≤90 mL/min per 1.73 m^2 or UACR ≥300 mg/g and eGFR ≥60 mL/min per 1.73 m^2.

albumin-creatine ratio (UACR) were observed, without a decrease in eGFR in patients treated with MRAs in combination with ACEi/ARB as compared with those receiving ACEi/ARB alone; however, the incidence of hyperkalemia was significantly higher in the former group.[79]

These analyses also noted several common limitations. First, for most of the studies, treatment duration was too short to evaluate surrogate end points (eg, proteinuria), and patient-centered outcomes (eg, death and kidney or cardiac failure) were absent or sparse. Second, patients with severe CKD were rarely included. Third, quality of reporting study methods and outcomes was inconsistent, and study design and duration were variable. Finally, data were extracted almost exclusively from studies with steroidal MRAs.

NONSTEROIDAL MRAS: APARARENONE, ESAXERENONE, AND FINERENONE

Evidence suggesting that MR blockade with steroidal MRAs combined with ACEi/ARB is associated with an increased risk of hyperkalemia prompted the development of nonsteroidal MRAs with novel physicochemical properties that may reduce electrolyte and hormonal complications.[48] Several pharmaceutical companies have identified numerous novel nonsteroidal MRA compounds, including Eli Lilly's LY2623091, Mitsubishi Tanabe Pharma Corporation's MT-3995 (apararenone), AstraZeneca's AZD 9977, Pfizer's PF-03882845, Daiichi Sankyo's CS-3150 (esaxerenone), KBP Biosciences's KBP5074, Dainippon Sumitomo Pharma's SM-368229 and DSR-71167, and Bayer's BR-4628 and BAY 94-8862 (finerenone).[27,48,80,81]

Finerenone is currently the most studied first-generation nonsteroidal MRA. Finerenone showed higher selectivity towards MR than spironolactone and a higher affinity for MR than eplerenone. Its affinity for AR, glucocorticoid receptor (GR), and PR is lower than that of spironolactone and is comparable to that of eplerenone (Table 2).[54,56,70,71] The plasma half-life is ~2 hours in healthy subjects[57] and 2-3 hours in patients with kidney failure.[58] In healthy rats, spironolactone and eplerenone accumulate more in the kidneys than in the heart, whereas, finerenone is distributed evenly between the 2 organs.[51] Finerenone acts as an MR antagonist, whereas spironolactone possesses at least partial aldosterone-like activity.[59,82]

Furthermore, RNA sequencing analyses showed that approximately 20% of transcripts induced by aldosterone were antagonized by finerenone, whereas, only 5% were antagonized by spironolactone.[60] Chromatin immunoprecipitation assays in the *SCNN1A* promoters suggest that although finerenone prevents the basal recruitment of the MR and steroid receptor coactivator 1 (SRC-1), spironolactone mildly promotes basal recruitment of these 2 regulators (aldosterone-dependent recruitment of the MR, SRC-1, and RNA polymerase II was also prevented by finerenone).[59] These results suggest that finerenone confers a more profound antagonistic effect on mineralocorticoid target genes than spironolactone.

Both preclinical and clinical studies have suggested that finerenone offers end-organ protection and lower or similar incidence of hyperkalemia as compared with steroidal MRAs (Tables 1 and 3).[49,62,64,83-89] In preclinical studies, finerenone provided greater reduction in proteinuria and end-organ damage than eplerenone when they were compared in equinatriuretic doses (finerenone 1 mg/kg vs eplerenone 30 mg/kg; finerenone 10 mg/kg vs 100 mg/kg), determined in rats based on the equivalent natriuretic responses achieved by both MRAs.[61] In the multicenter, randomized, double-blind, placebo-controlled, phase 2 minerAlocorticoid Receptor Antagonist Tolerability Study (ARTS, NCT01345656),[54] in HF patients with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] $\leq$40%) and mild CKD, finerenone reduced the levels of cardiac biomarkers of hemodynamic stress (B-type natriuretic peptide and N-terminal prohormone B-type natriuretic peptide) and albuminuria as effectively as spironolactone. Finerenone was associated with a lower incidence of hyperkalemia, a smaller increase in serum potassium concentration, and a lower incidence of worsening kidney function (defined as increase in serum creatinine by $\geq$0.3 mg/dL from baseline and/or decrease in eGFR by $\geq$25% from baseline) as compared with spironolactone. Hormone side effects, such as gynecomastia, were not examined because of the short duration of the study and a small number of patients.[49] Results from ARTS-HF

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(NCT01807221), a phase 2b study involving 1066 patients with HFrEF (LVEF ≤40%) and concomitant T2DM and/or CKD, showed that finerenone improved outcomes, including CV hospitalizations and death, as compared with eplerenone. Although incidence of hyperkalemia was similar between the finerenone and eplerenone groups, mean changes from baseline to day 90 in serum potassium concentration were lower in the finerenone dose groups as compared with the eplerenone group.[62] ARTS-Diabetic Nephropathy (ARTS-DN, NCT01874431),[83] a multicenter, randomized, double-blind, parallel-group, phase 2b study, compared the efficacy and safety of different once-daily oral doses of finerenone and placebo in patients with T2DM and persistent albuminuria (UACR ≥30 mg/g) who were receiving ACEi/ARB. The addition of finerenone to an ACEi or ARB resulted in a decrease in UACR in a dose-dependent manner in patients with DN.[83] Hyperkalemia developed in 8 (1.1%) of 727 patients treated with a finerenone dose used during the study (1.25-20 mg/d) and 0 of 94 treated with placebo (relative risk, 2.22; 95% CI, 0.13-38.13),[74] whereas no hyperkalemia leading to discontinuation was observed in the finerenone 10 mg/d group.[83] Unlike with steroidal MRAs,[76] only a modest reduction in BP was observed even with the highest dose of finerenone in ARTS and ARTS-DN.[49,83] The differential effect of steroidal MRAs and finerenone on BP is attributed to the fact that steroidal MRAs, unlike finerenone,[61] can cross the blood-brain barrier[73,90] and may act centrally on MRs.[91] Preclinical studies (rodents) have suggested that aldosterone is synthesized in the rodent brain, and that is critical for the regulation of BP and the development of sodium-induced hypertension even in the presence of adrenal aldosterone.[21] The mechanism of renal and CV protection with finerenone appears to be attributable to anti-inflammatory and antifibrotic effects, as suggested in preclinical studies,[61,63,92,93] rather than hemodynamic ones. Given its high potency and selectivity to MR, safety profiles with lower serum potassium concentration and/or hyperkalemia incidence than steroidal MRAs, and pharmacologic features distinctive from steroidal MRAs, finerenone emerged as a candidate for larger studies among patients with CKD and CVD associated with T2DM.

Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD, NCT02540993) is a phase 3 study investigating the efficacy of finerenone on kidney outcomes in patients with CKD and T2DM, who were treated with an ACEi/ARB at optimized doses.[64,84,88,94] Treatment with finerenone resulted in a 31% reduction in UACR from baseline to month 4 as compared with placebo, and the effect was maintained thereafter. Patients treated with finerenone showed a significant reduction in the risk of primary composite outcome, ie, kidney failure, sustained decrease of ≥40% in eGFR from baseline, and death from renal causes, as compared with those who received placebo. Patients treated with finerenone also demonstrated a significantly lower risk of achieving key secondary composite outcome, which included death from CV causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for HF, as compared with those who received placebo. Finerenone was found to be associated with a higher overall risk of hyperkalemia than placebo (15.8% vs 7.8%). However, discontinuation of finerenone because of hyperkalemia occurred in 2.3% of participants,[64] which was lower than that previously reported with dual RAS blockade with ACEi/ARB.[41,45] Gynecomastia was found to be rare and comparable with placebo (0.2% vs 0.2%).[64] For a subpopulation at high risk of kidney and CV events, the benefits of receiving finerenone were observed after 12 months for kidney outcomes and 1 month for CV outcomes, and thereafter the effect persisted throughout the study.[64]

FIDELIO-DKD is the first study demonstrating that dual-renin–angiotensin–aldosterone system (RAAS) blockade with an MRA and an ACEi/ARB is beneficial for renal and CV composite outcomes.[64,95] In another phase 3 study, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD, ClinicalTrials.gov identifier: NCT02545049),[65,85,89,94] finerenone reduced the composite risk of time to the first occurrence of CV death and nonfatal CV events in patients

with T2DM and CKD who were treated with ACEi/ARB. Hyperkalemia leading to permanent discontinuation occurred in 1.2% and 0.4% of participants in the finerenone and placebo groups, respectively. Gynecomastia was rare and was comparable to placebo (0.1% vs 0.1%). On July 9, 2021, the US Food and Drug Administration approved finerenone for the treatment of patients with T2DM-associated CKD.[82] A prespecified efficacy and safety analysis in the FIDELITY study (pooled analysis of FIDELIO-DKD and FIGARO-DKD studies) found that as compared with placebo, finerenone reduced the risk of clinically important kidney and CV outcomes in patients with T2DM and a broad spectrum of CKD stages.[96]

Esaxerenone is a highly potent and selective nonsteroidal MRA that has shown inhibition of aldosterone-dependent activation of human MR in a cell-based assay and higher potency compared with steroidal MRAs.[97,98] In a steroid hormone receptor binding assay, esaxerenone bound to MR, whereas no detectable interaction with GR, PR, and AR was observed.[80,97] Other preclinical studies using rat models demonstrated that esaxerenone reduced BP, proteinuria, and renal hypertrophy with better outcomes in cardiorenal injury than steroidal MRAs.[97,98] A randomized, double-blind, placebo-controlled, phase 2 study involving 365 Japanese patients with T2DM and microalbuminuria reported that the addition of esaxerenone to an ACEi/ARB, for 12 weeks, reduced UACR by approximately 50%, with increasing rates of UACR remission rate (defined UACR <30 mg/g creatinine at the end of treatment and ≥30% decrease from baseline), in a dose-dependent manner (JapicCTI-152774, ClinicalTrials.gov identifier: NCT02345057).[99] Incidences of hyperkalemia observed with up to 2.5 mg/d of esaxerenone were similar to placebo (up to 3% vs 1%). Although these results are promising, larger studies of longer duration evaluating the efficacy and safety of esaxerenone are needed.

Apararenone is highly selective nonsteroidal MRA; results from an in vitro study reported that apararenone has a strong affinity with human MR while having almost no binding affinity for the GR, PR, AR, and estrogen receptor.[100] A randomized, double-blind, placebo-controlled, phase 2 study involving 293 Japanese patients with T2DM and stage 2 DN demonstrated that treatment with apararenone for 24 weeks reduced UACR in a dose-dependent manner, regardless of concomitant ACEi/ARB use.[101] No cases of discontinuation because of hyperkalemia were reported over 52 weeks of treatment.

KBP-5074 is another selective nonsteroidal MRA that has shown strong MR binding affinity. A study using a steroid hormone receptor binding assay found that KBP-5074 binds to human MR, GR, and PR with half-maximal inhibitory concentration values of 2.7 nM, 2410 nM, and 122 nM, respectively, and no binding activities were observed between KBP-5074 and AR (see Table 2[54,71] and Chow et al[102] for value ranges for other MRAs). Preclinical results suggested that KBP-5074 can not only reduce BP but may also offer renoprotection.[102] BLOCK-CKD, a randomized, double-blind, placebo-controlled, phase 2b study involving 162 patients with advanced CKD, demonstrated that KBP-5074 lowered BP with a comparable incidence of hyperkalemia, thereby leading to discontinuation from the study (3.7% vs 3.5% for placebo).[81] The rate of hyperkalemia associated discontinuation (3.7%) in patients treated with KBP-5074 was comparable to those treated with finerenone (2.3%) in the FIDELIO-DKD trial[64] and was much lower than that in an HF subgroup treated with spironolactone (23%) in the AMBER trial.[103] A larger study of longer duration is ongoing (CLARION-CKD, ClinicalTrials.gov identifier: NCT04968184).

MANAGEMENT OF HYPERKALEMIA

Hyperkalemia is a common complication of treatment with steroidal or nonsteroidal MRAs. In the FIDELIO-DKD and FIGARO-DKD trials, 2- to 3-fold more patients treated with finerenone demonstrated hyperkalemia-related events than those treated with placebo.[64,65] Moura-Neto and Ronco[104] have suggested that the decision to prescribe finerenone may need to be made cautiously, referring to a substantial rise in the number of hospital admissions and deaths from iatrogenic hyperkalemia associated with the significant increase in the use of spironolactone after publication of the Randomized Aldactone

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TABLE 4. Subanalyses of Phase 3 Studies Investigating CV and Renal Outcomes in Patients With T2DM and CKD Treated With Finerenone or Placebo With or Without an SGLT-2i at Baseline.

Study	N	Renal outcomes, finerenone versus placebo HR (95% CI)	CV outcomes, finerenone versus placebo HR (95% CI)
FIDELIO-DKD[118]	5674 SGLT-2i: 259 No SGLT-2i: 5415	Primary composite outcome:[a] SGLT-2i: 1.38 (0.61-3.10) No SGLT-2i: 0.82 (0.72-0.92) *P*=.21 Secondary composite outcome:[b] SGLT-2i: 0.50 (0.12-1.99) No SGLT-2i: 0.77 (0.65-0.91) *P*=.54	Composite outcome:[c] SGLT-2i: 1.12 (0.55-2.30) No SGLT-2i: 0.85 (0.74-0.98) *P*=.46
FIDELITY[96]	13,026 SGLT-2i: 877 No SGLT-2i: 12,149	NR	Composite outcome:[c] SGLT-2i: 0.63 (0.40-<1.00) No SGLT-2i: 0.87 (0.79-0.96) *P*=.41

[a]Kidney failure, a sustained decrease of ≥40% in eGFR from baseline (for ≥4 wks), or renal death.
[b]Kidney failure, a sustained decrease of ≥57% in eGFR from baseline (for ≥4 wks), or renal death.
[c]Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.
P-values for SGLT-2i use at baseline-by-treatment interaction are shown.
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; NR, not reported; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

Evaluation Study (RALES) in patients with HF.[104]

When it develops, hyperkalemia can be managed by measures, such as avoiding potassium-containing salt substitutes or food products, medications that may impair kidney excretion of potassium, initiating treatment with diuretics, and considering concomitant treatment with potassium binders (compounds that bind potassium in the gastrointestinal tract to prevent its absorption).[14,105] In patients requiring the use of RAS blockers and MRA who are considered at higher risk for developing hyperkalemia, these measures can be instituted prophylactically. Recently, 2 potassium binders, sodium zirconium cyclosilicate and patiromer, were approved for the treatment of hyperkalemia; a review published by Palmer et al[105] gives an overview of the key clinical trials involving these 2 drugs and their efficacy in terms of reducing hyperkalemia when used with RAAS inhibitors. A double-blind, randomized, phase 2 study involving patients with CKD and resistant hypertension (AMBER) demonstrated that patiromer enabled more patients to continue treatment with spironolactone, thereby pointing towards the lower incidence of hyperkalemia.[106] Notably, after the previous spironolactone dose, 75% and 36% of patients who were treated with and then discontinued spironolactone had detectable metabolites at 2 and 3 weeks, respectively.[106] Hyperkalemia may be managed more easily during treatment with finerenone than steroidal MRAs via transient treatment interruption, because of finerenone's shorter half-life and lack of active metabolites (Table 1).[27,48,49] Although studies with patiromer suggest that it might allow long-term optimization of RAAS inhibition therapy in patients at risk of hyperkalemia (eg, CKD and/or HF),[107] large, event-driven studies with it or sodium zirconium cyclosilicate are being conducted (STABILIZE-CKD, ClinicalTrials.gov identifier: NCT05056727; OPRA-HF, ClinicalTrials.gov identifier: NCT04789239).

FUTURE PERSPECTIVE: COMBINATION THERAPIES TO REDUCE THE RISK OF CKD AND/OR CVD

When associated with cardiorenal complications, treatment of DM requires a comprehensive strategy.[14] Although an ACEi/ARB has been generally recommended as standard therapy for the treatment of DM plus hypertension and/or albuminuria,[14,108] there is lesser consensus for the optimal second- or third-line agents for preventing CKD progression.[14,109-111]

SGLT-2is, glucose-lowering agents, have emerged as first-line treatment for patients with T2DM and CKD, with not only blood glucose-lowering benefits, but also reno-protective and cardio-protective effects without elevating hyperkalemia risk.[14,112-115] The American Diabetes Association guidelines recommend SGLT-2is for patients with T2DM and CKD to reduce CKD progression and CV risk. Finerenone is recommended for patients who are at increased risk of CV events or CKD progression or are unable to use an SGLT-2i.[111]

GLP-1 RAs, glucose-lowering agents, are recommended in the KDIGO 2020 guidelines for patients with CKD and T2DM who fail to achieve glycemic targets despite the use of metformin and SGLT-2is or who are unable to use either drug type.[14] GLP-1 RAs offer both CV and renal benefits, including reducing BP and albuminuria as well as slowing the rate of eGFR decline. Therefore, they are also recommended as a first-line therapy with SGLT-2is in patients with T2D and CVD[116] and as a second-line therapy in patients with T2D and CKD.[14]

Because targets of SGLT-2is and GLP-1 RAs are different from those of RAAS blockade, a combination treatment strategy using a nonsteroidal MRA and an SGLT-2i may bring an additive or synergistic effect to renal and CV outcomes. For SGLT-2is, recent data from an open-label, crossover trial in patients with CKD suggested that the combination of dapagliflozin and eplerenone robustly lowered albuminuria with a lower frequency of hyperkalemia events than eplerenone alone.[117] A subgroup analysis of FIDELIO-DKD suggested that there may be a clinically relevant improvement in albuminuria by combining finerenone with an SGLT-2i (Table 4).[96,118] Table 4 also shows the results of a prespecified subgroup analysis of CV outcomes in patients receiving SGLT-2i versus no SGLT-2i at baseline plus finerenone or placebo in the FIDELITY study (pooled analysis of FIDELIO-DKD and FIGARO-DKD).[96] In the Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure study (DAPA-HF, ClinicalTrials.gov identifier: NCT03036124), patients with HFrEF treated with an MRA and dapagliflozin had significantly reduced risk of moderate-to-severe hyperkalemia compared with an MRA alone, suggesting that SGLT-2is help with limiting hyperkalemia linked to MRA use.[119] Indeed, results from a subgroup analysis based on patients who received finerenone with an SGLT-2i at baseline, accounting for about 5% of patients in the FIDELIO-DKD study, showed a 55% lower risk of hyperkalemia vs the overall group (HR, 0.45; 95% CI, 0.27-0.75), suggesting the potential benefit of a synergistic effect and fixed-dose combination.[120] It should be noted, however, that when analyses were conducted for patients who received an SGLT-2i at any time during the trial, no significant difference in the risk of hyperkalemia was observed.[118] For GLP-1 RA, although no randomized trials have been performed in combination with nonsteroidal MRAs, results from a recent preclinical study suggest that combination treatment with potassium canrenoate, a steroidal MRA, does not demonstrate any beneficial effects in animals with HF.[121] A further subgroup analysis from FIDELIO-DKD demonstrated no additional benefit of GLP-1 RA use for the primary renal or secondary CV outcome in patients treated with finerenone.[122]

To further elucidate the additional benefits of SGLT-2is with nonsteroidal MRAs on CKD associated with T2DM, the ongoing phase 2 CONFIDENCE study (ClinicalTrials.gov identifier: NCT05254002) will investigate the efficacy and safety of finerenone plus the SGLT-2i empagliflozin, versus finerenone, or empagliflozin alone in patients with T2DM and CKD. Finerenone effect in nondiabetic CKD is also being investigated in FIND-CKD (ClinicalTrials.gov identifier: NCT05047263), an ongoing phase 3 study of finerenone efficacy and safety (vs placebo) in nondiabetic patients with CKD.

The ongoing phase 2 MIRACLE study (ClinicalTrials.gov identifier: NCT04595370) will assess the efficacy, safety, and tolerability of the selective MR modulator AZD9977 plus the SGLT-2i dapagliflozin in patients with HF (with LVEF <60%) and CKD. In addition, 2 studies are evaluating the effects of a novel nonsteroidal MRA (KBP-5074) and a novel aldosterone antagonist (CIN-107) to treat uncontrolled hypertension in patients with CKD—Clarion-CKD (ClinicalTrials.gov

identifier: NCT04968184), a phase 3 study of KBP-5074 in patients with severe/moderate CKD (vs placebo) and a phase 2 study of CIN-107 (vs placebo) (ClinicalTrials.gov identifier: NCT05432167).

CONCLUSION

In 2017, Kolkhof and Bärfacker[48] summarized 60 years of MRA research with 3 major waves: (1) identification, shortly after the isolation of aldosterone, of spironolactone as the first MRA in the 1950s; (2) identification of receptor-specific steroidal MRAs like eplerenone in the late 1980s; and (3) identification of novel nonsteroidal MRAs with safety and efficacy for a broader spectrum of diseases than steroidal MRAs since 2010. Over the past 10 years, remarkable progress has been made in the preclinical and clinical characterization of nonsteroidal MRAs, including finerenone, which demonstrated clinical benefits for patients with T2DM, CKD, and CV risk in FIDELIO-DKD and FIGARO-DKD. Although more studies are necessary, other nonsteroidal MRAs, including KBP5074, apararenone, and esaxerenone, may also be beneficial for patients with CKD. Further clinical studies will help determine the efficacy of nonsteroidal MRAs in combination with SGLT-2is, GLP-1 RAs, and/or potassium binders in patients with T2DM and CKD. The application of nonsteroidal MRAs to other diseases, including nondiabetic CKD and HF, also awaits evidence.

POTENTIAL COMPETING INTERESTS

Dr Wish has served on advisory boards for AstraZeneca, Akebia, CSL Behring, Rockwell Medical, Otsuka, and Vifor Pharma; has been a consultant for FibroGen; has been on the speakers bureau for AstraZeneca and Akebia; and has received registration fee for 2021 European Renal Association Meeting supported by AstraZeneca. Dr Pergola has received research support and consulting fees from Akebia, Ardelyx, AstraZeneca, Bayer, Corvidia Therapeutics, FibroGen, Gilead Sciences, Otsuka, Reata Pharmaceuticals, Tricida, and Unicycive Therapeutics; reports ownership interest with Unicycive Therapeutics and has received research funding as principal investigator or sub-investigator on multiple clinical trials with his practice; has acted as scientific advisor or has membership with Ardelyx and Unicycive Therapeutics; and is on the speakers bureau for AstraZeneca.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACEi**, angiotensin-converting enzyme inhibitor; **ADA**, American Diabetes Association; **AR**, androgen receptor; **ARB**, angiotensin II receptor blocker; **ARTS**, minerAlocorticoid Receptor Antagonist Tolerability Study; **BP**, blood pressure; **CKD**, chronic kidney disease; **CV**, cardiovascular; **CVD**, cardiovascular disease; **DM**, diabetes mellitus; **DN**, diabetic nephropathy; **eGFR**, estimated glomerular filtration rate; **ESKD**, end-stage kidney disease; **FIDELIO-DKD**, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; **FIGARO-DKD**, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; **GLP-1 RA**, glucagon-like peptide 1 receptor agonists; **GR**, glucocorticoid receptor; **HF**, heart failure; **HFrEF**, heart failure with reduced ejection fraction; **KDIGO**, Kidney Disease Improving Global Outcomes; **MR**, mineralocorticoid receptor; **MRA**, mineralocorticoid receptor antagonist **PR**, progesterone receptor; **RAAS**, renin—angiotensin—aldosterone system; **RAS**, renin—angiotensin system; **SGLT-2i**, sodium-glucose cotransporter 2 inhibitor; **T2DM**, type 2 diabetes mellitus; **UACR**, urinary albumin-creatine ratio

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REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. 9th ed. International Diabetes Federation; 2019.
2. Amorim RG, Guedes GDS, Vasconcelos SML, Santos JCF. Kidney disease in diabetes mellitus: cross-linking between hyperglycemia, redox imbalance and inflammation. *Arq Bras Cardiol*. 2019;112(5):577-587. Published correction appears in 2019;113(1):182.

3. Elmarakby AA, Abdelsayed R, Yao Liu J, Mozaffari MS. Inflammatory cytokines as predictive markers for early detection and progression of diabetic nephropathy. *EPMA J*. 2010;1(1):117-129.
4. Yokoyama H, Deckert T. Central role of TGF-beta in the pathogenesis of diabetic nephropathy and macrovascular complications: a hypothesis. *Diabet Med*. 1996;13(4):313-320.
5. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *Am J Kidney Dis*. 2012;60(5):850-886.
6. Thomas RL, Halim S, Gurudas S, Sivaprasad S, Owens DR. IDF Diabetes Atlas: a review of studies utilising retinal photography on the global prevalence of diabetes related retinopathy between 2015 and 2018. *Diabetes Res Clin Pract*. 2019;157:107840.
7. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States. Updated. 2021: https://www.cdc.gov/kidneydisease/publications-resources/CKD-national-facts.html. Accessed October 6, 2022.
8. US Department of Health and Human Services. Advancing American Kidney Health. Updated. 2019: https://aspe.hhs.gov/sites/default/files/private/pdf/262046/AdvancingAmericanKidneyHealth.pdf. Accessed October 6, 2022.
9. Dei Cas A, Khan SS, Butler J, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail*. 2015;3(2):136-145.
10. Fonarow GC, Abraham WT, Albert NM, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med*. 2008;168(8):847-854.
11. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;35(7):455-469.
12. Löfman I, Szummer K, Hagerman I, Dahlström U, Lund LH, Jernberg T. Prevalence and prognostic impact of kidney disease on heart failure patients. *Open Heart*. 2016;3(1):e000324.
13. United States Renal Data System. USRDS Annual Data Report: Epidemiology of kidney disease in the United States. *2020*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020. https://adr.usrds.org/2020/. Accessed October 6, 2022.
14. Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2020;98(4S). S1-S115.
15. Kolkhof P, Joseph A, Kintscher U. Nonsteroidal mineralocorticoid receptor antagonism for cardiovascular and renal disorders - new perspectives for combination therapy. *Pharmacol Res*. 2021;172:105859.
16. Rossier BC, Baker ME, Studer RA. Epithelial sodium transport and its control by aldosterone: the story of our internal environment revisited. *Physiol Rev*. 2015;95(1):297-340.
17. Hayashi M, Tsutamoto T, Wada A, et al. Relationship between transcardiac extraction of aldosterone and left ventricular remodeling in patients with first acute myocardial infarction: extracting aldosterone through the heart promotes ventricular remodeling after acute myocardial infarction. *J Am Coll Cardiol*. 2001;38(5):1375-1382.
18. Mizuno Y, Yoshimura M, Yasue H, et al. Aldosterone production is activated in failing ventricle in humans. *Circulation*. 2001;103(1):72-77.
19. Yamamoto N, Yasue H, Mizuno Y, et al. Aldosterone is produced from ventricles in patients with essential hypertension. *Hypertension*. 2002;39(5):958-962.
20. He BJ, Anderson ME. Aldosterone and cardiovascular disease: the heart of the matter. *Trends Endocrinol Metab*. 2013;24(1):21-30.
21. Taves MD, Gomez-Sanchez CE, Soma KK. Extra-adrenal glucocorticoids and mineralocorticoids: evidence for local synthesis, regulation, and function. *Am J Physiol Endocrinol Metab*. 2011;301(1):E11-E24.
22. Jaisser F, Farman N. Emerging roles of the mineralocorticoid receptor in pathology: Toward new paradigms in clinical pharmacology. *Pharmacol Rev*. 2016;68(1):49-75.
23. Palmer BF. Regulation of potassium homeostasis. *Clin J Am Soc Nephrol*. 2015;10(6):1050-1060.
24. Palmer BF, Clegg DJ. Extrarenal effects of aldosterone on potassium homeostasis. *Kidney360*. 2022;3(3):561-568.
25. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. *J Am Heart Assoc*. 2017;6(7):e005428.
26. DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int*. 1980;17(1):118-134.
27. Agarwal R, Kolkhof P, Bakris G, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J*. 2021;42(2):152-161.
28. Viengchareun S, Le Menuet D, Martinerie L, Munier M, Pascual-Le Tallec L, Lombès M. The mineralocorticoid receptor: insights into its molecular and (patho)physiological biology. *Nucl Recept Signal*. 2007;5:e012.
29. Barrera-Chimal J, Lima-Posada I, Bakris GL, Jaisser F. Mineralocorticoid receptor antagonists in diabetic kidney disease—mechanistic and therapeutic effects. *Nat Rev Nephrol*. 2022;18(1):56-70.
30. Berl T, Katz FH, Henrich WL, de Torrente A, Schrier RW. Role of aldosterone in the control of sodium excretion in patients with advanced chronic renal failure. *Kidney Int*. 1978;14(3):228-235.
31. Hené RJ, Boer P, Koomans HA, Mees EJ. Plasma aldosterone concentrations in chronic renal disease. *Kidney Int*. 1982;21(1):98-101.
32. 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):232-237.
33. Rocha R, Stier CT Jr, Kifor I, et al. Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. *Endocrinology*. 2000;141(10):3871-3878.
34. Bauersachs J, Jaisser F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. *Hypertension*. 2015;65(2):257-263.
35. Zheng CM, Wang JY, Chen TT, et al. Angiotensin-converting enzyme inhibitors or angiotensin receptor blocker monotherapy retard deterioration of renal function in Taiwanese chronic kidney disease population. *Sci Rep*. 2019;9(1):2694. Published correction appears in *Sci Rep*. 2020;10(1):6631. Pubmed Partial Author articletitle
36. Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. *Nat Clin Pract Nephrol*. 2007;3(9):486-492.
37. Schrier RW. Aldosterone 'escape' vs 'breakthrough. *Nat Rev Nephrol*. 2010;6(2):61.
38. Sato A, Fukuda S. Effect of aldosterone breakthrough on albuminuria during treatment with a direct renin inhibitor and combined effect with a mineralocorticoid receptor antagonist. *Hypertens Res*. 2013;36(10):879-884.
39. Schjoedt KJ. The renin-angiotensin-aldosterone system and its blockade in diabetic nephropathy: main focus on the role of aldosterone. *Dan Med Bull*. 2011;58(4):B4265.
40. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892-1903. Published correction appears in *N Engl J Med*. 2014;158:A7255.
41. Imai E, Chan JC, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. *Diabetologia*. 2011;54(12):2978-2986.
42. Yusuf S, Teo KK, Pogue J, et al. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559.
43. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in

patients with hypertension: a randomised, double-blind trial. *Lancet*. 2007;370(9583):221-229. Published correction appears in *Lancet*. 2007;370(9598):1542.
44. Villamil A, Chrysant SG, Calhoun D, et al. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens*. 2007; 25(1):217-226.
45. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204-2213.
46. Zheng SL, Roddick AJ, Ayis S. Effects of aliskiren on mortality, cardiovascular outcomes and adverse events in patients with diabetes and cardiovascular disease or risk: a systematic review and meta-analysis of 13,395 patients. *Diab Vasc Dis Res*. 2017; 14(5):400-406.
47. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: Standards of medical care in diabetes-2022. *Diabetes Care*. 2022; 45(suppl 1):S144-S174. Published correction appears in *Diabetes Care*. 2022;45(5):1296.
48. Kolkhof P, Bärfacker L. 30 years of the mineralocorticoid receptor: mineralocorticoid receptor antagonists: 60 years of research and development. *J Endocrinol*. 2017;234(1):T125-T140.
49. Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J*. 2013;34(31):2453-2463.
50. ALDACTONE (spironolactone). Prescribing Information. Pfizer. 2021: https://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=520. Accessed October 6, 2022.
51. Kolkhof P, Borden SA. Molecular pharmacology of the mineralocorticoid receptor: prospects for novel therapeutics. *Mol Cell Endocrinol*. 2012;350(2):310-317.
52. Mann NM. Gynecomastia during therapy with spironolactone. *JAMA*. 1963;184(10):778-780.
53. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol*. 1988;118(5):687-691.
54. Pitt B, Filippatos G, Gheorghiade M, 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):668-675.
55. Cook CS, Berry LM, Bible RH, Hribar JD, Hajdu E, Liu NW. Pharmacokinetics and metabolism of [14C]eplerenone after oral administration to humans. *Drug Metab Dispos*. 2003; 31(11):1448-1455.
56. Bärfacker L, Kuhl A, Hillisch A, et al. Discovery of BAY 94-8862: a nonsteroidal antagonist of the mineralocorticoid receptor for the treatment of cardiorenal diseases. *ChemMedChem*. 2012;7(8):1385-1403.
57. Gerisch M, Heinig R, Engelen A, et al. Biotransformation of finerenone, a novel nonsteroidal mineralocorticoid receptor antagonist, in dogs, rats, and humans, in vivo and in vitro. *Drug Metab Dispos*. 2018;46(11):1546-1555.
58. Heinig R, Kimmeskamp-Kirschbaum N, Halabi A, Lentini S. Pharmacokinetics of the novel nonsteroidal mineralocorticoid receptor antagonist finerenone (BAY 94-8862) in individuals with renal impairment. *Clin Pharmacol Drug Dev*. 2016;5(6): 488-501.
59. Amazit L, Le Billan F, Kolkhof P, et al. Finerenone impedes aldosterone-dependent nuclear import of the mineralocorticoid receptor and prevents genomic recruitment of steroid receptor coactivator-1. *J Biol Chem*. 2015;290(36):21876-21889.
60. Le Billan F, Perrot J, Carceller E, et al. Antagonistic effects of finerenone and spironolactone on the aldosterone-regulated transcriptome of human kidney cells. *FASEB J*. 2021;35(2):e21314.
61. Kolkhof P, Delbeck M, Kretschmer A, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol*. 2014;64(1):69-78.
62. Filippatos G, Anker SD, Böhm M, 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*. 2016;37(27): 2105-2114.
63. Grune J, Beyhoff N, Smeir E, et al. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. *Hypertension*. 2018;71(4):599-608.
64. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383(23):2219-2229.
65. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med*. 2021;385(24):2252-2263.
66. Kintscher U, Bakris GL, Kolkhof P. Novel non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease. *Br J Pharmacol*. 2022;179(13):3220-3234.
67. Craft J. Eplerenone (Inspra), a new aldosterone antagonist for the treatment of systemic hypertension and heart failure. *Proc (Bayl Univ Med Cent)*. 2004;17(2):217-220.
68. Weinberger MH, Roniker B, Krause SL, Weiss RJ. Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. *Am J Hypertens*. 2002;15(8):709-716.
69. Corvol P, Michaud A, Menard J, Freifeld M, Mahoudeau J. Antiandrogenic effect of spirolactones: mechanism of action. *Endocrinology*. 1975;97(1):52-58.
70. 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. Published correction appears in *Eur J Heart Fail*. 2017;19(6):811.
71. Fagart J, Hillisch A, Huyet J, et al. A new mode of mineralocorticoid receptor antagonism by a potent and selective nonsteroidal molecule. *J Biol Chem*. 2010;285(39):29932-29940.
72. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14): 1309-1321. Published correction appears in *N Engl J Med*. 2003;348(22):2271.
73. Pitt B, Pedro Ferreira J, Zannad F. Mineralocorticoid receptor antagonists in patients with heart failure: current experience and future perspectives. *Eur Heart J Cardiovasc Pharmacother*. 2017;3(1):48-57.
74. Chung EY, Ruospo M, Natale P, et al. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2020;10(10):CD007004.
75. Navaneethan SD, Nigwekar SU, Sehgal AR, Strippoli GFM. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2009;3: CD007004.
76. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GFM. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2014;4: CD007004.
77. Mavrakanas TA, Gariani K, Martin PY. Mineralocorticoid receptor blockade in addition to angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment: an emerging paradigm in diabetic nephropathy: a systematic review. *Eur J Intern Med*. 2014;25(2):173-176.
78. Currie G, Taylor AH, Fujita T, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol*. 2016;17(1):127.
79. 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):609-618.

80. Sueta D, Yamamoto E, Tsujita K. Mineralocorticoid receptor blockers: novel selective nonsteroidal mineralocorticoid receptor antagonists. *Curr Hypertens Rep*. 2020;22(3):21.
81. Bakris G, Pergola PE, Delgado B, et al. Effect of KBP-5074 on blood pressure in advanced chronic kidney disease: results of the BLOCK-CKD study. *Hypertension*. 2021;78(1):74-81.
82. Finerenone (Kerenida). *Prescribing Information*. Bayer HealthCare Pharmaceuticals Inc; 2021.
83. Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA*. 2015;314(9):884-894.
84. Filippatos G, Anker SD, Agarwal R, et al. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. *Circulation*. 2021;143(6):540-552.
85. Ruilope LM, Agarwal R, Anker SD, et al. Design and baseline characteristics of the finerenone in reducing cardiovascular mortality and morbidity in diabetic kidney disease trial. *Am J Nephrol*. 2019;50(5):345-356.
86. Sato N, Ajioka M, Yamada T, et al. A randomized controlled study of finerenone vs. eplerenone in Japanese patients with worsening chronic heart failure and diabetes and/or chronic kidney disease. *Circ J*. 2016;80(5):1113-1122.
87. Katayama S, Yamada D, Nakayama M, et al. A randomized controlled study of finerenone versus placebo in Japanese patients with type 2 diabetes mellitus and diabetic nephropathy. *J Diabetes Complications*. 2017;31(4):758-765.
88. Filippatos G, Bakris GL, Pitt B, et al. Finerenone reduces new-onset atrial fibrillation in patients with chronic kidney disease and type 2 diabetes. *J Am Coll Cardiol*. 2021;78(2):142-152.
89. Filippatos G, Anker SD, Agarwal R, et al. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. *Circulation*. 2022;145(6):437-447.
90. Schmiedek P, Sadée W, Baethmann A. Cerebral uptake of a 3 H-labelled spirolactone compound in the dog. *Eur J Pharmacol*. 1973;21(2):238-241.
91. Gomez-Sanchez EP, Gomez-Sanchez CE. Central regulation of blood pressure by the mineralocorticoid receptor. *Mol Cell Endocrinol*. 2012;350(2):289-298.
92. Lattenist L, Lechner SM, Messaoudi S, et al. Nonsteroidal mineralocorticoid receptor antagonist finerenone protects against acute kidney injury-mediated chronic kidney disease: role of oxidative stress. *Hypertension*. 2017;69(5):870-878.
93. Barrera-Chimal J, Estrela GR, Lechner SM, et al. The myeloid mineralocorticoid receptor controls inflammatory and fibrotic responses after renal injury via macrophage interleukin-4 receptor signaling. *Kidney Int*. 2018;93(6):1344-1355.
94. Agarwal R, Anker SD, Bakris G, et al. Investigating new treatment opportunities for patients with chronic kidney disease in type 2 diabetes: the role of finerenone. *Nephrol Dial Transplant*. 2022;37(6):1014-1023.
95. Sridhar VS, Liu H, Cherney DZI. Finerenone-A new frontier in renin-angiotensin-aldosterone system inhibition in diabetic kidney disease. *Am J Kidney Dis*. 2021;78(2):309-311.
96. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J*. 2022;43(6):474-484. Published correction appears in *Eur Heart J*. 2022;43(20):1989.
97. Arai K, Homma T, Morikawa Y, et al. Pharmacological profile of CS-3150, a novel, highly potent and selective non-steroidal mineralocorticoid receptor antagonist. *Eur J Pharmacol*. 2015;761:226-234.
98. Arai K, Tsuruoka H, Homma T. CS-3150, a novel non-steroidal mineralocorticoid receptor antagonist, prevents hypertension and cardiorenal injury in Dahl salt-sensitive hypertensive rats. *Eur J Pharmacol*. 2015;769:266-273.
99. Ito S, Shikata K, Nangaku M, Okuda Y, Sawanobori T. Efficacy and safety of esaxerenone (CS-3150) for the treatment of type 2 diabetes with microalbuminuria: a randomized, double-blind, placebo-controlled, phase II trial. *Clin J Am Soc Nephrol*. 2019;14(8):1161-1172.
100. Kikkawa K, Shirata N, Takakuwa M, et al. MT-3995, a novel non-steroidal mineralocorticoid receptor antagonist, has pharmacological profiles differentiated from eplerenone and spironolactone. Presented at: ASN Kidney Week; October 31-Nov 5, 2017; New Orleans, LA.
101. Wada T, Inagaki M, Yoshinari T, et al. Apararenone in patients with diabetic nephropathy: results of a randomized, double-blind, placebo-controlled phase 2 dose-response study and open-label extension study. *Clin Exp Nephrol*. 2021;25(2):120-130.
102. Chow CP, Liu JR, Tan XJ, Huang ZH. Pharmacological profile of KBP-5074, a novel nonsteroidal mineralocorticoid receptor antagonist for the treatment of cardiorenal diseases. *J Drug Res Dev*. 2017;3(2):1-9.
103. Rossignol P, Williams B, Mayo MR, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): results in the pre-specified subgroup with heart failure. *Eur J Heart Fail*. 2020;22(8):1462-1471.
104. Moura-Neto JA, Ronco C. The RALES legacy and finerenone use on CKD patients. *Clin J Am Soc Nephrol*. 2021;16(9):1432-1434.
105. Palmer BF. Potassium binders for hyperkalemia in chronic kidney disease-diet, renin-angiotensin-aldosterone system inhibitor therapy, and hemodialysis. *Mayo Clin Proc*. 2020;95(2):339-354.
106. Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet*. 2019;394(10208):1540-1550.
107. Palmer BF, Carrero JJ, Clegg DJ, et al. Clinical management of hyperkalemia. *Mayo Clin Proc*. 2021;96(3):744-762.
108. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127-e248. Published correction appears in *J Am Coll Cardiol*. 2018;71(19):2275-2279.
109. Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: core curriculum 2019. *Am J Kidney Dis*. 2019;74(1):120-131.
110. Bashier A, Bin Hussain A, Abdelgadir E, Alawadi F, Sabbour H, Chilton R. Consensus recommendations for management of patients with type 2 diabetes mellitus and cardiovascular diseases. *Diabetol Metab Syndr*. 2019;11:80.
111. Draznin B, Aroda VR, Bakris G, et al. American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(suppl. 1):S175-S184.
112. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. *Cardiovasc Diabetol*. 2020;19(1):98.
113. Pirklbauer M. Anti-inflammatory potential of empagliflozin. *Inflammopharmacology*. 2021;29(2):573-576.
114. Yavin Y, Mansfield TA, Ptaszynska A, Johnsson K, Parikh S, Johnsson E. Effect of the SGLT2 inhibitor dapagliflozin on potassium levels in patients with type 2 diabetes mellitus: a pooled analysis. *Diabetes Ther*. 2016;7(1):125-137.
115. Butler J, Usman MS, Khan MS, et al. Efficacy and safety of SGLT2 inhibitors in heart failure: systematic review and meta-analysis. *ESC Heart Fail*. 2020;7(6):3298-3309. Published correction appears in *ESC Heart Fail*. 2021;8(3):2362.
116. Grant PJ, Cosentino F. The 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: new features and the 'Ten Commandments' of the 2019 Guidelines are discussed by Professor Peter J. Grant and Professor Francesco Cosentino, the Task Force chairmen. *Eur Heart J*. 2019;40(39):3215-3217.

117. Provenzano M, Puchades MJ, Garofalo C, et al. Albuminuria-lowering effect of dapagliflozin, eplerenone, and their combination in patients with chronic kidney disease: a randomized crossover clinical trial. *J Am Soc Nephrol*. 2022;33(8):1569-1580.

118. Rossing P, Filippatos G, Agarwal R, et al. Finerenone in predominantly advanced CKD and type 2 diabetes with or without sodium-glucose cotransporter-2 inhibitor therapy. *Kidney Int Rep*. 2021;7(1):36-45.

119. Kristensen SL, Docherty KF, Jhund PS, et al. Dapagliflozin reduces the risk of hyperkalaemia in patients with heart failure and reduced ejection fraction: a secondary analysis DAPA-HF. *Eur Heart J*. 2020;41(suppl 2):ehaa946.0939.

120. Agarwal R, Wilson D, Joseph A, et al. Incidence and predictors of hyperkalemia in patients with CKD and T2D in the FIDELIO-DKD trial. Presented at: ISN World Congress of Nephrology; April 15-19, 2021: Virtual.

121. Demkes EJ, Wenker S, Silvis MJM, et al. Neutral effects of combined treatment with GLP-1R agonist exenatide and MR antagonist potassium canrenoate on cardiac function in porcine and murine chronic heart failure models. *Front Pharmacol*. 2021;12:702326.

122. Rossing P, Agarwal R, Anker SD, et al. Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP-1RA treatment: a subgroup analysis from the FIDELIO-DKD trial. *Diabetes Obes Metab*. 2022;24(1):125-134.