Mineralocorticoid receptor antagonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease.

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Abstract

Diabetic kidney disease develops in about 40% of patients with diabetes and is the commonest cause of chronic kidney disease worldwide. Patients with chronic kidney disease, especially those with diabetes mellitus, are at high risk of both developing kidney failure and cardiovascular death. The use of renin-angiotensin system blockers to reduce the incidence of kidney failure in patients with diabetic kidney disease dates back to studies that are now 20 or more years old. During the last few years sodium-glucose co-transporter-2 inhibitors have shown beneficial renal effects in randomized trials. However, even in response to combined treatment with renin-angiotensin system blockers and sodium-glucose co-transporter-2 inhibitors, the renal residual risk remains high with kidney failure only deferred, but not avoided. The risk of cardiovascular death also remains high even with optimal current treatment. Steroidal mineralocorticoid receptor antagonists reduce albuminuria and surrogate markers of cardiovascular disease in patients already on optimal therapy. However, their use has been curtailed by the significant risk of hyperkalaemia. In The FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) study comparing the actions of the non-steroidal mineralocorticoid receptor antagonist finerenone with placebo, finerenone reduced the progression of diabetic kidney disease and the incidence of cardiovascular events with a relatively safe adverse event profile. This document presents in detail the available evidence on the cardioprotective and nephroprotective effects of mineralocorticoid receptor antagonists, analyses the potential mechanisms involved and discusses their potential future place in the treatment of patients with diabetic chronic kidney disease.

Epidemiology and outcomes of diabetic kidney disease in 2020

Around 850 million persons in the world have chronic kidney disease (CKD), with 3.9 million receiving kidney replacement therapy [1]. Diabetic kidney disease (DKD) develops in about 40% of patients with diabetes and is the leading cause of CKD worldwide [2]. The use of renin-angiotensin system (RAS) blockers in patients with type 2 diabetes mellitus (T2DM) with CKD mainly originates from the Reduction of Endpoints with the Angiotensin II Antagonist Losartan (RENAAL) [3] and Irbesartan in Diabetic Nephropathy Trial (IDNT) [4] studies published twenty years ago. Within the last 5 years, sodium-glucose co-transporter-2 inhibitors (SGLT2i) have shown beneficial renal and cardiovascular (CV) effects in randomized trials [5]. However, even in response to combined treatment with renin-angiotensin system blockers and sodium-glucose co-transporter-2 inhibitors, the renal residual risk remains high with kidney failure only deferred, but not avoided [2, 5, 6]. Furthermore, for patients with CKD stage 3 (estimated glomerular filtration rate (eGFR) 30-59 ml/min/1.73m^2) the risk of CV death is at least ten-times higher than the risk of developing kidney failure [7]. Classical steroidal mineralocorticoid receptor antagonists (MRA) reduce albuminuria and blood pressure, and thus are potentially useful for nephroprotection and cardioprotection, but their use may be limited by the risk of hyperkalaemia, especially in patients with both CKD and diabetes mellitus [8-10]. Non-steroidal MRA, with a potentially more favourable side-effect profile are currently at different stages of development. Of these finerenone is currently the most studied. The recent publication of the The FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) [11] results comparing the actions finerenone with placebo provides shows that the deterioration in renal function can be slowed in patents with DKD. This document presents current evidence on the cardioprotective and nephroprotective effects of MRA, analyzes potential mechanisms involved in these beneficial

actions and discusses their potential future place in the treatment of patients with DKD following the recent publication of the FIDELIO-DKD trial.

Current status of nephroprotection and cardioprotection in diabetic kidney disease

Before SGLT2-inhibitors

Intensified multifactorial intervention in T2DM patients delays renal and CV complications of diabetes [12, 13]. This intervention focuses mainly on lowering body weight, hyperlipidaemia and albuminuria and keeping glycosylated haemoglobin (HbA1c) levels in 6.5-8% range and systolic and diastolic blood pressure below 130 and 80 mmHg [14-17].

RAS blockade with either angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) is first line therapy in DM patients with hypertension and albuminuria [14, 15]. From landmark trials like the Captopril Study in Type 1 DM (T1DM) [18], to RENAAL [3] and IDNT [4] in T2DM, to relevant meta-analyses [19, 20], data confirm that RAS blockade reduces the risk of the hard renal outcomes such as doubling of serum creatinine, end-stage kidney disease (ESKD) or death by 15-20%, and decreases proteinuria by about 30% compared to placebo. Combination therapy of ACEi and ARB, or aliskiren, a renin inhibitor, with ACEi or ARB, may intensify the anti-proteinuric actions but hyperkalaemia and acute kidney injury are serious side effects that counterbalance the possible benefits. In this regard, the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) [21] and the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) [22] trials, with hard renal outcomes were prematurely terminated due to an unfavourable risk/benefit ratio. New anti-diabetic drugs like Glucagon-like peptide-1 receptor agonists decrease major adverse cardiovascular events by 12% and reduce albuminuria, although whether or not they preserve

renal function is presently unknown [23]. However, all relevant studies were designed with a CV primary end point and trials with strict kidney outcomes are still missing [5].

Despite the solid evidence and guidelines existing for many years, in the real world, many patients with DKD are deprived from the benefits of single RAS blockade, mainly due to drug intolerance and suboptimal medication doses prescribed mainly to avoid the common side-effects of hyperkalaemia and acute kidney injury [24, 25]. Moreover, even in the strict environment of clinical trials, a high residual risk for CV death and CKD progression still remains in patients with DKD [2, 6].

Effects *of SGLT-2 inhibitors*

In the last five years, three major cardiovascular outcome trials with SGLT2i in patients with type 2 diabetes were published. The Empagliflozin-Cardiovascular-Outcome-Event-Trial-in-Type-2-Diabetes-Mellitus-Patients (EMPA-REG OUTCOME) showed reductions of 14% in the primary outcome (non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes), 38% in cardiovascular death, 35% in hospitalization for heart failure (HHF) and 32% in all-cause mortality compared with placebo [26]. The Canagliflozin-Cardiovascular-Assessment-Study (CANVAS) showed 14% reduction in the same primary outcome and 33% reduction in HHF, while The Multicenter-Trial-to-Evaluate-the-Effect-of-Dapagliflozin-on-the-Incidence-of-Cardiovascular-Events-Thrombolysis-In-Myocardial-Infarction 58 (DECLARE-TIMI 58) showed non-inferiority of dapagliflozin in the aforementioned primary composite outcome and a 27% reduction in HHF compared with placebo [27, 28]. A clear benefit of SGLT-2i on heart failure was recently highlighted by two randomized trials in patients with heart failure and reduced ejection fraction in persons with or without T2DM [29, 30]. Interestingly, in the EMPagliflozin outcomE tRial in Patients With

chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial over 70% of patients were on MRA, and the HR of the primary endpoint was 0.76 (0.59–0.97) in non-MRA users and 0.75 (0.63–0.88) in MRA users [30].

Most importantly, EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI showed prominent and similar effects on outcomes associated with kidney disease progression [27, 28, 31, 32]. In a meta-analysis of these trials, SGLT2i reduced the incidence of the composite renal outcome of worsening renal function (doubling of serum creatinine accompanied by an eGFR of ≤45 ml/min/1.73 m^2), ESKD or renal death by 45% (HR 0.55, 95% CI 0.48–0.64) [33]. Moreover, the CREDENCE study in 4401 patients with T2DM, CKD and albumin-to-creatinine-ratio 300-5000 mg/g was prematurely stopped because of benefit, showing reductions of 34% in the composite of ESKD, doubling of serum creatinine, or renal death and 32% in ESKD with canagliflozin compared to placebo [6]. Finally, the Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD trial) [34] confirmed the nephroprotective and cardioprotective effects of these drugs in a CKD population including patients with diabetic and non-diabetic CKD (eGFR 25-75 ml /min/1.73 m^2 and urinary albumin-to-creatinine ratio 200-5000 mg/g), with benefit observed for both diabetic and non-diabetic patient subgroups. This trial was also stopped early because of benefit and showed major benefits in the composite outcome of eGFR decline ≥ 50%, kidney failure, or death from renal causes (HR 0.56; 95% CI, 0.45-0.68), the combined outcome of death from CV causes and HHF (HR 0.71; 95% CI, 0.55 to 0.92, and all-cause mortality (HR 0.69; 95% CI, 0.53-0.88). These effects of SGLT2i are independent of age, sex, and race are equal for patients with eGFR below or above 45 ml/min/1.73 m^2.

As previously discussed in a Consensus Statement by the (EURECA-m) and Diabesity working groups of ERA-EDTA [35], an observation of major importance is that the above renoprotective effects of SGLT2i take place on top of standard treatment with an ACEi or an ARB. The main mechanism by which SGLT2i exert a renal protective effect is thought to be reduction in intraglomerular pressure and single-nephron hyperfiltration, as in the case of RAS-blockade. This is supported by a functional "dip" in eGFR during the first weeks of SGLT2i treatment [35]. Data obtained in patients with T1DM suggest that the decreased sodium reabsorption in proximal tubules resulting from the mode of action of SGLT2i increases the distal availability of sodium chloride; this is sensed by the macula densa, resulting in restoration of the tubuloglomerular feedback mechanism towards reversal of the vasodilation of afferent arterioles [36], while in T2DM, vasodilation of the efferent arteriole may also take place [37]. Other mechanisms, including tubular protection, reduced hypoxia and inflammation, and long-term effects of natriuresis have also been proposed as alternative reno-protective mechanisms [38].

Not surprisingly, in the previous Consensus Statements of ERA-EDTA, the American Diabetic Association/European Association for the Study of Diabetes [14] and the Kidney Disease Improving Global Outcomes Guidelines on DM [15] the use of SGLT2i in patients with T2DM and eGFR >30 ml/min/1.73m^2 is strongly recommended. As of this writing, there are no data on the use of SGLT2i in real world patients with CKD; based on current marketing indications, and in data from ongoing or recent trials, this percentage is anticipated to be very low. i.e. around 5% [39].

Nephroprotective properties of mineralocorticoid receptors antagonists

Evidence before FIDELIO-DKD

Following background data on a nephroprotective effect of MRA, several clinical studies evaluated the effects of spironolactone, eplerenone or finerenone on urine albumin or protein excretion (UAE/UPE), the most commonly used intermediate renal end-points [10, 40]. In a pilot study, Chrysostomou et al. [41] randomized 41 subjects with UPE >1.5 g/day previously treated with ACEi to one of four groups: (a) ramipril/placebo/placebo; (b) ramipril/irbesartan/placebo; (c) ramipril/placebo/spironolactone; or (d) ramipril/irbesartan/spironolactone. At 12 weeks, UPE reduction was 1.4%; 15.7%; 42.0%; and 48.2%, respectively, suggesting that addition of spironolactone offered significant nephroprotection, while triple therapy offered practically no advantage to dual therapy with ramipril/spironolactone. Another study randomized 81 diabetic patients with uACR >300 mg/g receiving lisinopril 80 mg to placebo, losartan 100 mg, or spironolactone 25 mg for 48 weeks [42]. Compared with placebo, uACR decreased by 34.0% (p=0.007) with spironolactone and 16.8% (p=0.20) with losartan. Clinic and ambulatory blood pressure, creatinine clearance, sodium and protein intake did not differ between groups. Serum potassium and incidence of hyperkalemia increased with the addition of either spironolactone or losartan. A recent RCT demonstrated that spironolactone did not delay or prevent development of confirmed microalbuminuria in patients with T2DM at high risk of developing microalbuminuria [43]. Hyperkalaemic episodes were reported in 9% of the 102 patients randomised to spironolactone and in 1% in the 107 patients randomised to placebo. Although possibly under-powered, this study suggests that MRA may not have a role in the prevention of DKD.

Studies with eplerenone, suggested similar renoprotective properties: in a study randomizing 268 patients with diabetes and uACR ≥50 mg/g on enalapril treatment, to placebo, eplerenone 50 mg, or eplerenone 100 mg for 12 weeks, uACR reductions were 7.4%, 41%, and 48.4%, respectively (p<0.001 for both eplerenone groups) [44]. Likewise, in 821 patients with diabetes

and high or very high albuminuria on ACEi or ARB treatment, finerenone demonstrated dose-dependent reductions in uACR (placebo-corrected mean ratio of the uACR at 3 months relative to baseline at 0.79, 0.76, 0.67, and 0.62 for the finerenone 7.5, 10, 15, 20 mg/day groups respectively), with relevant incidence of hyperkalaemia leading to discontinuation at 2.1%, 0%, 3.2%, and 1.7% [45]. Other studies with MRA in patients with diabetic [46-52] or non-diabetic CKD [53-59] showed similar nephroprotection. A recent meta-analysis evaluating the nephroprotective role of MRA [60], suggested that these agents (alone or on top of RAS blockade) decreased uACR by 24.55%, and uPCR by 53.93% compared to placebo. Addition of an MRA was associated with average eGFR decrease of 2.38 ml/min/1.73m^2 (95%CI 3.51 to 1.25), rise in potassium by 0.22 mmol/l (95%CI 0.16 to 0.28) and a 2.6-fold increase in hyperkalaemia risk compared with placebo/active control. However, it should be pointed out that the study duration for the two trials with highest weight (both assessing finerenone) was 28 to 90 days, and the slight reduction in eGFR observed potentially only reflects decreased glomerular hyperfiltration [61, 62].

Renal outcomes in FIDELIO-DKD

FIDELIO-DKD was a randomized, double-blind, placebo-controlled, parallel-group, event-driven trial assessing the efficacy and safety of finerenone compared to placebo on renal and cardiovascular outcomes. The study randomly assigned 5734 patients with T2DM on maximum tolerated dose of an ACEi or an ARB that had either uACR 300-5000 mg/g and eGFR 25 to <75 ml/min/1.73 m^2 or uACR 30 to <300 mg/g and eGFR 25 to <60 ml/min/1.73 m^2 plus diabetic retinopathy [39]. All patients needed to have serum potassium ≤4.8 mmol/L at both the run-in and screening visits. Following these inclusion criteria, at baseline 12.1% of the patients had high (30 to <300 mg/g) and 87.5% very high (300-5000 mg/g) albuminuria.

The mean baseline eGFR was 44.3±12.6 ml/min/1.73m^2 with 33.5% of patients being at the 45-60 ml/min/1.73m^2 and 52.5% at the 25-45 ml/min/1.73m^2 eGFR range [11, 39].

The primary outcome was a composite of kidney failure, sustained (≥4 weeks) eGFR decrease of at least 40% from baseline, or death from renal causes. Kidney failure was defined as ESKD (dialysis for ≥90 days or kidney transplantation) or eGFR <15 ml/min/1.73m^2. During a median of 2.6 years, a primary outcome event occurred in 504/2833 patients (17.8%) in the finerenone group and 600/2841 patients (21.1%) in the placebo group (HR, 0.82; 95%CI 0.73-0.93, p=0.001). Finerenone had a rather consistent effect in the individual components of the primary outcome. Importantly, 40% of the events of the primary outcome were kidney failure events. Finerenone was associated with an even larger reduction (HR 0.76; 95%CI 0.65 to 0.90) in the main secondary renal outcome, a composite of kidney failure, sustained eGFR decrease of ≥57% (equivalent to doubling of serum creatinine), or renal death. During follow-up, the finerenone group had a 31% greater reduction in the uACR from baseline to month 4 then the placebo group. Finally, when compared to baseline, systolic blood pressure was numerically lowered at month 12 in the finerenone group (−2.1 mmHg) but not in the placebo group (+0.9 mmHg; no formal statistical analysis provided) [11].

Potential mechanisms for the nephroprotective actions of mineralocorticoid receptors antagonists

The analysis of the potential mechanisms for the nephroprotective actions of MRA and, more specifically, of finerenone, in addition to RAS blockade should answer the question of why would MRA increase nephroprotection when dual conventional RAS blockade does not [21, 22]. Two basic mechanisms for nephroprotection may be considered: a hemodynamic effect and a direct action on tissue inflammation and fibrosis (Figure 1.A). The different specificity

and impact on cofactor recruitment may account for differences between individual MRA on the adverse effect profile, including hyperkalaemia (Figure 1.B) [63-65].

Evidence supporting a haemodynamic role is that finerenone caused an early decrease in eGFR, followed by a slower slope of eGFR loss and a 40% decrease in albuminuria [11]. This pattern is consistent with the response to conventional RAS blockers and SGLT2i [66, 67] and suggests decreased intraglomerular pressure that may limit podocyte injury and albuminuria, preventing albuminuria-induced tubular cell inflammatory and profibrotic responses, thus preventing loss of Klotho, and even decreasing the metabolic load of proximal tubular cells [68-70]. Studies with SGLT2i have already demonstrated that in patients on RAS blockers there is an opportunity for further intraglomerular pressure reduction [5, 36, 37]. If this is indeed the mechanism of action of MRA, there should be some limit as to how low glomerular pressure can go, and albuminuria decreased as a direct consequence of this reduction in glomerular pressure. Interestingly, the numerical HR for the primary endpoint for the 259 patients who were treated with SGLT2i at baseline in FIDELIO-DKD was 1.38; 95% 0.61-3.1 and these patients were at very low risk of the primary endpoint on placebo [11]. No statistical interaction tests were performed while the effects of finerenone on the primary outcome were generally consistent across prespecified subgroups (i.e. HR 0.82 (0.72-0.92) in the no SGLT2i group). To clarify the mechanisms of action of MRA, it will be helpful to analyse the early impact of finerenone on eGFR and albuminuria in these patients and to also analyse the further 402 patients that started on SGLT2i during the course of the trial [11]. In prior trials of dual conventional RAS blockade that did not show nephroprotection, the initial decrease in eGFR compared to placebo was absent in the intervention arm and the difference in the decrease in albuminuria ranged from 11 to 20%, i.e., it was 2- to 4-fold lower than in FIDELIO-DKD [21, 22] (Figure 2). Thus, the different impact of dual conventional RAS blockade versus RAS

blockade and MRA on outcomes should not be used to argue against a hemodynamic effect. Rather, the question is why a hemodynamic effect, and indeed a clinical benefit, was observed with RAS blockade and MRA but not on dual conventional RAS blockade?

A second hypothesis, that is neither supported not discarded by the available FIDELIO-DKD data, relates to inhibition of proinflammatory and profibrotic effects recruited by the transcription factor induction via MR. In common with the activation of the angiotensin II/angiotensin receptor axis [71, 72], MR activation leads also to non-hemodynamic actions [73, 74]. Specifically, direct proinflammatory and profibrotic effects on a variety of cell types and organs have been well characterized in preclinical studies [73, 75]. Furthermore, MR activation is a key mediator of kidney damage induced by Klotho deficiency and results from the loss of direct actions of Klotho on adrenal cells, independently from the RAS [76]. In this regard, multiple human kidney parenchymal cell types express the *NR3C2* gene encoding the MR (Figure 3A-C) [77]. Indeed, MR expression is increased in kidney leukocytes in diabetic kidney disease, potentially sensitizing them to MR activation (Figure 3.D) [78].

Cardioprotective properties of mineralocorticoid receptors antagonists

Evidence before FIDELIO-DKD

The concept that aldosterone promotes cardiovascular damage is well established. Epidemiological evidence from the Framingham study demonstrated that higher concentrations of aldosterone are associated with left ventricular hypertrophy (LVH), which in turn is associated with the syndrome of heart failure with preserved ejection fraction (HFpEF) [79, 80]. LVH becomes increasingly prevalent in CKD as eGFR falls [81] and it is plausible that aldosterone excess is a major pathological mechanism underpinning HFpEF in patients with CKD. In this regard, aldosterone excess was associated with myocardial fibrosis both in

experimental and human studies [82, 83]. It is now well established that inhibition of the RAS with ACEi or ARB alone does not fully suppress aldosterone production and aldosterone is only transiently suppressed by RAS blockers [84]. These data provide the rationale for addition of MRA to conventional RAS inhibition for cardiovascular protection [74].

The greatest magnitude of benefit of MRA on cardiovascular outcomes was generally observed in patients with heart failure, and particularly in those with heart failure and reduced left ventricular ejection fraction (LVEF), HFrEF. In the Randomised Aldactone Evaluation Study (RALES) trial of 1,663 people with LVEF <35%, allocation of spironolactone led to a 30% reduction in CV mortality (RR 0.69 95%CI 0.58 to 0.82) [85]. Two subsequent large RCTs of eplerenone in patients with heart failure following myocardial infarction or patients with left ventricular systolic dysfunction but less severe symptoms showed similar benefits [86, 87]. Such consistent results led to MRA receiving a Level 1A grading for use in heart failure and reduced ejection fraction across international guidelines [88].

To date, no therapy has been demonstrated to alter outcomes in HFpEF- the dominant form of heart failure in patients with CKD. Spironolactone reduced left ventricular mass and vascular stiffness in patients with stage 2-3 CKD in a placebo controlled RCT and therefore it is plausible that MRA would improve outcomes in HFpEF [89]. In the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial in 3445 patients (median eGFR 65 [54–79] ml/min/1.73 m^2, 39% had CKD), spironolactone was associated with fewer episodes of hospitalization compared to placebo (206 patients [12.0%] vs. 245 patients [14.2%]; HR 0.83 95%CI, 0.69 to 0.99), but there was no statistically significant impact on the primary composite end point of the trial of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure [90]. However, a *post hoc* analysis

revealed regional differences in patient characteristics, study drug adherence, and responses to spironolactone, with notably profound different event rates for patients in the United States, Canada, Brazil and Argentina compared to those from Russia and Georgia [91]. A separate analysis of patients from the Americas suggested that spironolactone may indeed improve clinical outcomes in HFpEF [91] and led to a class IIb level B-R grading by US guidelines [88]. Spironolactone for HFpEF is being retested in two separate trials; the Spironolactone Initiation Registry Randomized Interventional Trial (SPIRRIT; NCT02901184) and the SPIRolactone In the Treatment of Heart failure (SPIRITHF; EudraCT 2017-000697-11]) [88].

In all the cardiovascular outcomes trials in heart failure, the incidence of hyperkalaemia and serum potassium was higher in the MRA group compared to placebo [85-87, 90] but hyperkalemia occurrence did not hinder the clinical benefit of MRA [92] [93] even in high-risk subgroups (CKD, diabetes, elderly patients) [94, 95].

Cardiovascular Outcomes of the FIDELIO-DKD study

In the FIDELIO-DKD trial, the key composite secondary outcome consisted of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke and hospitalization for heart failure [39]. Patients treated with finerenone had a lower incidence of this secondary outcome compared with placebo (13.0 vs 14.8%; HR 0.86 95%CI 0.75 to 0.99: p=0.03) [11]. The CV benefit was seen within a month and continued to be observed thereafter. Interestingly, although the individual components of the key composite secondary outcome tended to improve with finerenone treatment, the incidence of stroke did not (HR 1.03 95%CI 0.76 to 1.38). This is consistent with the important role of BP for stroke risk and the very little difference in BP between the groups [17, 96]. The improvement in the key secondary CV outcome was independent of having had a history of previous CV disease [97]. Indeed,

FIDELIO-DKD is the first study in patients with CKD showing a reduction in CV events in a population in which symptomatic heart failure or reduced left ventricular ejection fraction were excluded [97].

Potential mechanisms for the cardioprotective actions of mineralocorticoid receptors antagonists

Apart from its obvious cardioprotective impact by reducing sodium retention and, therefore volume expansion, MRA elicit direct effects in different cell types of the cardiovascular system. Furthermore, a post-hoc analysis of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) trial in heart failure post myocardial infraction suggested that an early (one-month) rise in serum potassium as a potassium -sparing effect, and an early diuretic effect may contribute to the beneficial effects of eplerenone [98]. In FIDELIO-DKD, the early CV benefit is compatible with a haemodynamically mediated mechanism via natriuresis, although other actions cannot be excluded and were not explored, such as improvement in endothelial dysfunction and possibly an improvement in vascular stiffness and myocardial remodelling in the longer term [99-101].

Mineralocorticoid Receptor Antagonists and the Vasculature

The MR is a functional transcription factor in vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) [102]. The VSMC-MR directly contributes to blood pressure control and vascular tone by regulating L-type calcium channel expression and function [103], mediating angiotensin II (AngII) signalling [104] and regulating the phosphorylation of contractile regulatory proteins [105]. The VSMC-MR also contributes to vascular remodelling by regulating genes involved in vascular fibrosis, inflammation, and calcification [106, 107]. Thus, VSMC-MR knockout mice exhibit less aging-associated vascular stiffness [108]. A

direct role for VSMC-MR in vascular remodelling after injury from mechanical damage has been also demonstrated [109].

The EC-MR does not appear to play a major role in either basal vasomotor function or blood pressure control [110]. However, EC-MR contributes to endothelial dysfunction and vascular damage when cardiovascular risk factors are present, through mechanisms involving oxidative stress, inflammation, and vessel stiffening [111, 112]. Overexpression of human MR in EC increased blood pressure [113]. However, EC-specific MR deletion did not alter basal blood pressure [110], although it protected against AngII-induced hypertension [114] and DOCA/salt hypertension-mediated vascular inflammation and fibrosis [110]. Furthermore, global MR blockade increases nitric oxide bioavailability by reducing endothelial nitric oxide synthase uncoupling and increasing vascular superoxide dismutase and catalase expression [115]. Aldosterone may also favour inflammation by promoting intercellular adhesion molecule-1 expression [116], thereby promoting leukocyte adhesion to EC [111]. Furthermore, aldosterone is implicated in vascular remodelling in the context of abnormal sodium handling (which may be comparatively more important in patients with CKD where sodium excess is common) by promoting sodium entry into fibrocytes which stimulates collagen synthesis [117].

Mineralocorticoid Receptor Antagonists and the Heart

The MR is also expressed in cardiomyocytes and myofibroblasts [118]. Aldosterone directly induces cardiac hypertrophy, ventricular remodelling, arrhythmia and ischaemia, independently of its hemodynamic effects [119] and it appears that progression from LVH to cardiac failure is mediated by aldosterone through the MR [120]. Moreover, MR activation stimulates apoptosis and induces coronary vasoconstriction in animal hearts [121] and MR overexpression in the mouse heart results in severe ventricular arrhythmias [122]. By contrast,

MR deletion in cardiomyocytes in mice had no adverse consequences [123], prevented left ventricular dilatation and dysfunction after chronic pressure overload [124] and improved infarct healing and prevented progressive adverse cardiac remodelling, cardiac hypertrophy and contractile dysfunction in ischemic heart failure [125], mainly through decreased apoptosis [126]. In addition, some cardiac protective effects of MRA *in vivo* can be partially mediated by macrophages, in which MR deletion elicited effects similar to those of MRA [127, 128]. MRA limit also infarct size after reperfusion in mice through nongenomic intracellular signalling including adenosine receptor stimulation, and activation of the Reperfusion Injury Salvage Kinase (RISK) pathway [129] [130]. Indeed, MRA have consistently shown beneficial effects on left ventricular dilation, cardiac function, fibrosis or collagen content in preclinical studies [131-133]. Furthermore, aldosterone may stimulate proliferation of myofibroblasts [134], an important cell type in scar formation.

Safety of mineralocorticoid receptors antagonists in diabetic kidney disease

Despite the class 1A recommendation of using MRA in patients with HFrEF, approximately 30% of whom will also have CKD [135, 136], the use of the two approved steroidal MRA (i.e. spironolactone and eplerenone) is limited by the fear of hyperkalemia and impaired kidney function. According to registry data, only 70% of eligible patients are treated and 70% of these are underdosed [137, 138]. Spironolactone is also prone to induce breast pain and gynecomastia, erectile dysfunction in men, and menstrual irregularities in premenopausal women [136]. Despite not being life-threatening, these adverse effects may compromise treatment adherence and persistence.

As discussed above, in a meta-analysis of studies evaluating the effect of MRA on albuminuria or proteinuria, most of which included patients with CKD, the addition of an MRA to

placebo/active drug was associated with an overall 2.6-fold increase in hyperkalemia risk (RR 2.63 95%CI 1.69 to 4.08) [60]. However, this meta-analysis also found that the RR of hyperkalaemia was 4.44 (95%CI 1.99 to 9.93) for MRA compared to placebo in patients already on a single RAS blocker as were those that participated in the FIDELIO-DKD trial.

A number of approaches have been proposed to reduce the risk of hyperkalemia associated with the use of the steroidal MRA such as the concomitant use of potassium binders [139] and the development of non-steroidal MRA, such as finerenone [136]. In the AMBER phase II trial, 295 patients with resistant hypertension and an eGFR between 25 and 45 mL/min/1.73m^2 (mean 36 mL/min/1.73m^2), the potassium binder patiromer, compared to placebo, enabled a more persistent use and a higher dose of spironolactone. Two-thirds of patients in the placebo group developed hyperkalemia over the twelve-week follow-up, and this risk was halved in the patiromer group ($p<0.0001$) [139].

In the FIDELIO-DKD trial, the incidence of all and serious adverse events during the treatment period was similar in the finerenone and placebo groups. Mean serum potassium was about 0.23 mmol/L higher with finerenone, remaining around 4.6 mmol/L. Incidences of hyperkalemia, defined as serum potassium >5.5 mmol/l and > 6.0 mmol/l were 21.7% and 4.5%, respectively, in the finerenone group and 9.8% and 1.4%, respectively, in the placebo group [11]. Investigator reported hyperkalemia (18.3% vs 9.0%) and hyperkalemia leading to discontinuation of the trial regimen (2.3% vs 0.9%) were higher with finerenone, while no fatal hyperkalemia adverse events were reported. The above rates of discontinuation due to hyperkalemia are rather low, when compared to the relevant rates with dual RAS blockade with ACEi/ARB and the direct renin inhibitor aliskiren (4.8%) in the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) [21] and combined losartan and lisinopril

treatment (9.9%) in the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial [22] over similar follow-up periods. Therefore, the burden of hyperkalemia associated with steroidal MRA use in patients treated with single, conventional RAS blockade could be alleviated by the use of finerenone or of other non-steroidal MRA under development [140, 141]. Furthermore, in FIDELIO-DKD, the incidence of acute kidney injury and related discontinuation of drug treatment was low and similar between groups.

What to expect from FIGARO-DKD

In addition to FIDELIO-DKD, the Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD, NCT02545049) study [142] will compare finerenone to placebo on CV and renal outcomes and has randomised 7,437 patients with T2DM. The study design of FIDELIO-DKD and FIGARO-DKD is quite similar, apart that the primary outcome of FIGARO-DKD is cardiovascular and not renal and there are slightly different inclusion/exclusion criteria. Indeed, patients were permitted to switch between the two studies before randomisation. Both studies excluded patients with an eGFR <25 ml/min/1.73m^2, with FIGARO-DKD also including patients with better preserved kidney function (maximum allowed eGFR of 90 mL/min/1.73 m^2 compared to 75 mL/min/1.73 m^2 in FIDELIO-DKD). Different parameters were also given for high- and very-high albuminuria, and for the coexistence of diabetic retinopathy (not necessary for inclusion in FIGARO-DKD). Additionally, the number of patients on SGLT2i at baseline was higher: 613 (8.3%) and this may be increased by patients starting SGLT2i during the trial, potentially allowing a better assessment of the impact of finerenone/SGLT2i combination therapy, especially if analysed together with FIDELIO-DKD data. The FIGARO-DKD study has at least 90% power to detect a 20% reduction in the primary outcome, a composite of time to first occurrence of CV death,

nonfatal myocardial infarction, nonfatal stroke, or HHF; the same as for the CV outcomes in FIDELIO-DKD. Data presentation is expected in 2021.

Combined, FIDELIO-DKD and FIGARO-DKD will constitute the largest cardiorenal outcome program designed to investigate the occurrence of fatal and nonfatal CV events and progression of kidney disease in more than 13,000 patients with T2DM. In addition, unlike previous studies, recruited patients will not only have high levels of albuminuria and CKD stages 3-4 (eGFR 15-59 ml/min/1.73m^2) but will also include patients with CKD stages 3-4 with low levels of albuminuria (uACR ≥30 mg/g but <300 mg/g) as well as patients with CKD stages 1-2 (eGFR ≥60 ml/min/1.73m^2) and high levels of albuminuria (uACR>300 mg/g). Therefore, taken together, the results of the FIDELIO-DKD and FIGARO-DKD studies should provide the strongest level of evidence as to whether optimally treated patients with T2DM and CKD at high risk of CV events and renal progression of CKD will have improved cardiorenal outcomes with the addition of a non-steroidal MRA to their treatment regimen.

Other ongoing studies with mineralocorticoid receptor antagonists of nephrological interest

There are further ongoing clinical trials testing MRA of nephrological interest. The ALdosterone Antagonist Chronic Hemodialysis Interventional Trial (ALCHEMIST) [143] and the Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease (ACHIEVE; NCT03020303) are two ongoing cardiovascular outcome trials using spironolactone in dialysis patients. Beyond the previously quoted SPIRIT and SPIRRIT trials with spironolactone in HFpEF, another ongoing trial with finerenone, expected to be completed in May 2024, is the FINerenone trial to investigate Efficacy and sAfetysuperioR to placebo in paTientS with Heart Failure. (FINEARTS-HF. ClinicalTrials.gov identifier: NCT04435626).

This trial will randomize subjects with heart failure (NYHA 2-4) and LVEF≥ 40% to either finerenone or placebo. The study is primarily aimed at testing cardiovascular and heart-related endpoints, with a composite renal endpoint among the secondary outcomes.

Other non-steroidal MRA are undergoing clinical development in patients with DKD, hypertension and heart failure (Table 1).

Esaxerenone (CS-3150) is being developed for the treatment of essential hypertension and DKD [144, 145]. It was approved for the treatment of essential hypertension in Japan in 2019 [144, 145]. In patients with T2DM, esaxerenone induces uACR remission (defined as uACR<30 mg/g at the end of treatment and ≥30% decrease from baseline) in 21% of participants compared to 3% in those taking placebo[146]. In a further phase 3 study, 455 patients with DKD and uACR 45 to <300 mg/g already on RAS inhibitors were randomised to either esaxerenone or placebo [147]. The proportion of patients with uACR remission was higher in the esaxerenone group (22%) compared to the placebo group (4%; P<0.001) at the end of 52 weeks treatment.

Apararenone (MT-3995) is being developed for the treatment of diabetic nephropathy [148, 149]. In a phase-II clinical trial in patients with diabetic nephropathy, 24 weeks of apararenone decreased uACR by 54% and induced uACR remission in 28% of participants taking the higher dose of 10 mg daily [150].

AZD-9977 recently completed phase I studies in healthy volunteers [151] and ongoing phase I studies are enrolling patients with various degree of renal impairment (ClinicalTrials.gov identifier: NCT04469907) and heart failure with preserved or mid-range LVEF in comparison

to spironolactone (ClinicalTrials.gov identifier: NCT03682497). A large, randomized, phase-II study (ClinicalTrials.gov identifier: NCT04595370) has just started to compare the antiproteinuric effect of AZD-9977 at ascending dose in combination with dapagliflozin to either dapagliflozin alone or placebo. As a secondary outcome, the trial will also test the change of eGFR during a three-month follow-up period. The study population will be made of patients with stable symptomatic heart failure (NYHA 2-3) with a LVEF<55%, CKD stage 3 and micro-macroalbuminuria. The direct comparison or combination with SGLT2i makes this a significant trial.

KBP-5074 is under development for the treatment of cardiorenal diseases. It has finished recruiting into phase-II trial in patients with uncontrolled hypertension and CKD stage 3b-4 (ClinicalTrials.gov identifier: NCT03574363) [141, 152].

MRA BI690517 recently (May 2020) completed a phase-II study in patients with diabetic nephropathy (ClinicalTrials.gov identifier: NCT03165240). Other non-steroidal MRA, LY2623091[153] and PF03882845[154] are not being developed further[155].

Conclusions on Mineralocorticoid Receptor Antagonists use for Diabetic Kidney Disease and Current Research Needs

A multifactorial intervention in patients with T2DM, including improving glycaemic control, treating hypertension with ACEi/ARB, using statins and implementing lifestyle interventions slows CKD progression and lower cardiovascular risk [5, 156]. However, such multifactorial interventions have been used for decades with very little progress, while several disappointing RCTs have been performed in DKD patients, with agents such as bardoxolone [157], aliskiren [158, 159] and darbepoetin [160]. However, published RCT in the last few years, have provided important evidence on the effects of SGLT2i on renal and cardiovascular outcomes, changing

the landscape in treatment of T2DM [5]. Reports advocate the preferred use of these agents in patients with T2DM and CKD, within their licensed indications [5]. To add to these promising developments comes the results from the FIDELIO-DKD trial [11]. In this RCT, finerenone, a nonsteroidal MRA, lowered the risk of progression of kidney disease and cardiovascular events with a low risk of side-effects, especially of hyperkalaemia.

On the basis of FIDELIO-DKD, applications to licence finerenone in the European Union and United States were filed on November 9, 2020. Once licensed and reimbursed, it will become a valuable addition to the available treatment options for patients with T2DM and CKD. Based on the evidence presented herein (prone to slight changes pending license indications and available doses), finerenone is likely to be efficacious for cardioprotection and nephroprotection when used on top of an ACEi or an ARB in maximum tolerated doses and independently of the use of an SGLT2i in patients with T2DM and CKD with: eGFR 25 to 75 ml/min/1.73 m^2, moderately or severely increased albuminuria and serum potassium ≤4.8 mmol/L (Box 1, Box 2). Although currently direct evidence that finerenone provides additional cardioprotection and nephroprotection in patients treated with RAS blockers and SGLT2i is not available, the residual risk in these patients still remains high and would potentially justify this approach. It should be remembered that, although other currently available steroidal MRA spironolactone and eplerenone have shown similar benefits in the intermediate outcomes of albuminuria and proteinuria in CKD, the results of FIDELIO-DKD, in terms of both efficacy on hard renal outcomes and safety, cannot be extended to them due to the lack of relevant evidence. The results of currently ongoing and future trials with finerenone and other nonsteroidal MRA are awaited to shed more light on this field.

A key point that requires further evidence development is the relative position of SGLT2i and finerenone or other MRA in kidney and cardiovascular protection in DKD. In this regard, as previously pointed out, SGLT2i were allowed in FIDELIO-DKD, whereas patients treated with MRA were excluded from the CREDENCE and DAPA-CKD trials. Although preclinical evidence suggests that the mechanisms of kidney and cardiovascular protection by MRA and by SGLT2i may be complementary, whether the combination of both agents offers additional protection should be ideally tested in randomized clinical trials. Meanwhile, insights into potentially additive benefit may be derived from subgroup analysis of trials that allowed the combined use of MRA and SGLT2i in DKD patients on RAS blockers, although data obtained with other MRA may not necessarily reflect the behaviour of finerenone. In a recent randomised trial testing sotagliflozin in DKD patients (most on RAS blockade) with a primary kidney endpoint, 15% of patients were on MRA and subgroup analyses of those with HF-related criteria was consistent with additional benefit on those already on an MRA for the primary end point of the composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure [161]. Further information will likely be available in the near future. FIGARO-DKD includes a higher percentage of patients on SGLT2i at baseline than FIDELIO-DKD, leading to an overall number of 872 patients in both trials, which may allow a combined analysis. Additionally, trials specifically addressing this question are ongoing for AZD-9977.

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Box 1. Patients that are likely to benefit from treatment with finerenone*

Type 2 diabetes mellitus	As defined by the American Diabetes Association[12]
Diagnosis of diabetic kidney disease	Persistent high albuminuria (30-299 mg/g) and presence of diabetic retinopathy and eGFR ≥25 but < ml/min/1.73m2 OR Persistent very high albuminuria (≥300 mg/g) and eGFR ≥ 25 but < 75 ml/min/1.73m2
Serum potassium	<4.8 (mmol/L)
Treatment with maximum labelled and tolerated dose of ACE inhibitor or ARB therapy for at least 4 weeks	
Blood pressure	SBP≤160 mmHg and DBP≤100 mmHg
Absence of clinical diagnosis of heart failure with reduced ejection fraction	
HBA1c	<12%
Absence of significant non-diabetic renal disease, including clinically relevant renal artery stenosis	
No recent (within 12 weeks) episode of acute kidney injury requiring dialysis	

*based on the inclusion and exclusion criteria for the FIDELIO-DKD trial.

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP. Systolic blood pressure.

Box 2. Potential use of mineralocorticoid receptor antagonist finerenone for diabetic kidney disease patients who are already on renin-angiotensin system blockers with or without sodium-glucose co-transporter-2 inhibitors

1. Finerenone was safe and showed efficacy in improving kidney and cardiovascular outcomes in patients with diabetic kidney disease (DKD) who are already on renin-angiotensin system (RAS) blockers
2. Thus, when approved by health authorities, finerenone may represent an alternative to sodium-glucose co-transporter-2 inhibitors (SGLT2i) to provide kidney and cardiovascular protection in patients with DKD (eGFR 25-75 ml/min/1.73m^2) who are already on RAS blockers
3. In this regard, finerenone may be a kidney and cardiovascular protective agent for patients with DKD who are already on RAS blockers and cannot tolerate SGLT2i or in whom these are contraindicated
4. At present, it is not clear whether the use of finerenone for kidney and cardiovascular protection provides additional benefit in patients with DKD who are already on RAS blockers and SGLT2i.
5. Since the mechanism of action of finerenone does not depend on the underlying metabolic defect of type 2 diabetes mellitus, the available data supports the hypothesis that the kidney and cardiovascular protection exhibited by finerenone might also be observed in non-diabetic kidney chronic kidney disease patients on RAS blockade. However, this needs to be shown in future studies.

Figure legends

Figure 1. Potential mechanisms of action of mineralocorticoid receptor antagonists on diabetic kidney disease and key differences between mineralocorticoid receptor antagonists. **A)** MRA may be nephroprotective through hemodynamic actions, decreasing intraglomerular pressure, glomerular filtration and albuminuria and thus decreasing workload for tubular cells and the resulting adverse effects of albuminuria on inflammation, fibrosis and Klotho expression. FIDELIO-DKD observed an early decrease in GFR, followed by a slower loss of eGFR thereafter as well as a large decrease in albuminuria, consistent with a hemodynamic effect. Additionally, MRA may have direct effects on leukocytes and kidney cells, decreasing the proinflammatory and profibrotic actions of MR activation and preserving Klotho expression. Decreased Klotho, in turn, results in aldosterone secretion. Klotho is an anti-aging protein expressed mainly by kidney cells that has among others anti-inflammatory and antifibrotic properties. In blue, FIDELIO-DKD observations, in brown, likely pathophysiological correlates; in red, injury pathways shown to be responsive to MRA in preclinical studies. Sources for images: Wikipedia, smart.servier, **B)** Spironolactone and eplerenone are steroid MRA while finerenone is a non-steroidal MRA. Spironolactone may antagonize additional receptors for steroid hormones, including the androgen and progesterone receptors. This may explain adverse effects such as gynecomastia. The selectivity of eplerenone is higher, but the affinity for MR is lower than that of spironolactone and finerenone. There are further differences [63-65]. Additionally, the impact on the recruitment of cofactors required for gene transcription may differ. As an example, while eplerenone has intrinsic activity recruiting cofactors to the MR, finerenone actually decreased the baseline interaction between MR and its cofactors and this may result in additional antifibrotic activity [65]. Specifically, only finerenone prevented the interaction of the MR with its key cofactor

steroid receptor coactivator-1 (SRC-1). These and other differences in cofactor recruitment may explain the milder impact of finerenone on serum potassium while preserving nephroprotective characteristics [64, 65].

Figure 2. Hemodynamic impact of dual conventional RAS blockade vs MRA plus RAS blockade according to selected large outcomes clinical trials. A) ALTITUDE. Aliskiren+RAS blockade vs RAS blockade+placebo [21]. Note the overlapping SE bars for early eGFR changes and milder early impact on albuminuria than in FIDELIO-DKD. **B)** VA NEPHRON-D: Losartan+Lisinopril vs losartan+placebo [22]. Note overlapping 95% CI bars for early eGFR changes and milder early impact on albuminuria than in FIDELIO-DKD. **C)** FIDELIO-DKD. Note the non-overlapping 95% CI for the early decrease in eGFR as well as the large decrease in albuminuria. Finerenone+RAS blockade vs RAS blockade+placebo [11]. Note different scales for different graphs.

Figure 3. Kidney expression of key genes involved in mineralocorticoid receptor (MR) signaling. A) Multiple human cell types, including endothelial cells (EC), podocytes, mesangial cells, proximal and distal tubular epithelial cells expressed *NR3C2* encoding the MR as well as *NCOA1* encoding its key cofactor steroid receptor coactivator-1 (SRC-1)[77]. However, macrophage expression of both *NR3C2* and *NCOA1* was very low, questioning a role of MR activation in kidney macrophages in healthy kidneys. **B)** Protein Atlas confirmed the wide expression of MR in different types of tubular cells; **C)** as well as in podocytes and parietal epithelial cells (Inset, arrow and arrowhead, respectively). **D)** Both proximal tubular cell and leukocyte expression of both *NR3C2* and *NCOA1* was increased in human diabetic kidney disease, suggesting a potential impact of inhibition of MR activation in additional tubular cells and inflammatory cells in the mechanism of action of MR antagonists in DKD

[78] (Images from http://humphreyslab.com/SingleCell/ and https://www.proteinatlas.org/ENSG00000151623-NR3C2/tissue/kidney#img; accessed October 24, 2020).

Table 1 Ongoing Studies with Non-Steroidal Mineralocorticoid Receptor Antagonists

Study	Drug	Comparator	Phase	N	Population	CKD Exclusion	Primary end point	Status	Estimated completion
NCT02545049 FIGARO-DKD	Finerenone (BAY94-8862)	Placebo	III	7437	DKD with albuminuria (UACR ≥30 to ≤5,000 mg/g)	eGFR <25 mL/min/1.73 m²	Composite of CV death and non-fatal CV events (myocardial infarction, stroke, or hospitalization for HF)	Enrollment complete	February 2021
NCT04435626 FINEARTS-HF	Finerenone (BAY94-8862)	Placebo	III	5500	HF (NYHA II-IV, LVEF ≥40%	eGFR <25 mL/min/1.73 m²	CV deaths and HF events	Recruiting	2024
NCT04469907	AZD-9977	NA	I	32	Healthy subjects or GFR 15-89 ml/min/1.73 m²	eGFR <15 mL/min/1.73 m²	Pharmacokinetics	Recruiting	March 2021
NCT04595370 MIRACLE	AZD-9977	Dapagliflozin 10 mg or Placebo	II	540	HF with LEVF <55% eGFR ≥30 and ≤60 mL/min and UACR >30 and <3000 mg/g	eGFR <25 mL/min/1.73 m²	Percent change from baseline in UACR at 12 weeks	Not yet recruiting	March 2022
NCT03574363	KBP-5074	Placebo	II	165	– Uncontrolled Hypertension – CKD Stage 3B/4	eGFR <15 mL/min/1.73 m²	Change in SBP	Enrollment complete	November 2020

DKD, diabetic kidney disease; UACR, urinary albumin to creatinine ratio; CV, cardiovascular; eGFR estimated glomerular filtration rate; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; ABPM, ambulatory blood pressure monitoring.

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