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REVIEW

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

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ABSTRACT

Diabetic kidney disease (DKD) develops in ∼40% of patients with diabetes and is the most common cause of chronic kidney disease (CKD) worldwide. Patients with CKD, especially those with diabetes mellitus, are at high risk of both developing kidney failure and cardiovascular (CV) death. The use of renin–angiotensin system (RAS) blockers to reduce the incidence of kidney failure in patients with DKD dates back to studies that are now ≥20 years old. During the last few years, sodium–glucose co-transporter-2 inhibitors (SGLT2is) have shown beneficial renal effects in randomized trials. However, even in response to combined treatment with RAS blockers and SGLT2is, the renal residual risk remains high with kidney failure only deferred, but not avoided. The risk of CV death also remains high even with optimal current treatment. Steroidal mineralocorticoid receptor antagonists (MRAs)

reduce albuminuria and surrogate markers of CV 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 DKD (FIDELIO-DKD) study comparing the actions of the non-steroidal MRA finerenone with placebo, finerenone reduced the progression of DKD and the incidence of CV events, with a relatively safe adverse event profile. This document presents in detail the available evidence on the cardioprotective and nephroprotective effects of MRAs, analyses the potential mechanisms involved and discusses their potential future place in the treatment of patients with diabetic CKD.

Keywords: cardiovascular risk, diabetic kidney disease, hyperkalaemia, mineralocorticoid antagonism, nephroprotection

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

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 ∼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 (AngII) Antagonist Losartan (RENAAL) [3] and Irbesartan in Diabetic Nephropathy Trial (IDNT) [4] studies published 20 years ago. Within the last 5 years, sodium–glucose co-transporter-2 inhibitors (SGLT2is) have shown beneficial renal and cardiovascular (CV) effects in randomized trials [5]. However, even in response to combined treatment with RAS blockers and SGLT2is, 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/1.73 m^2] the risk of CV death is at least 10 times higher than the risk of developing kidney failure [7]. Classical steroidal mineralocorticoid receptor antagonists (MRAs) reduce albuminuria and blood pressure (BP), 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 DM [8–10]. Non-steroidal MRAs, 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 FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD (FIDELIO-DKD) [11] results comparing the actions of finerenone with placebo shows that the deterioration in renal function can be slowed in patients with DKD. This document presents current evidence on the cardioprotective and nephroprotective effects of MRAs, analyses 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 DKD

Before SGLT2is

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 BP (SBP and DBP) <130 and 80 mmHg, respectively [14–17].

RAS blockade with either angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) 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 ∼30% compared with 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 CV 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 endpoint 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 of 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 SGLT2is

In the last 5 years, three major CV outcome trials with SGLT2is in patients with type 2 diabetes were published. The Empagliflozin CV Outcome Event Trial in T2DM Patients (EMPA-REG OUTCOME) showed reductions of 14% in the primary outcome (non-fatal myocardial infarction, non-fatal stroke or death from CV causes), 38% in CV death, 35% in hospitalization for heart failure (HHF) and 32% in all-cause mortality compared with placebo [26]. The Canagliflozin CV Assessment Study (CANVAS) showed 14% reduction in the same primary outcome and 33% reduction in HHF, while the

Multicentre Trial to Evaluate the Effect of Dapagliflozin on the Incidence of CV 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 SGLT2is on heart failure (HF) was recently highlighted by two randomized trials in patients with HF and reduced ejection fraction in persons with or without T2DM [29, 30]. Interestingly, in the EMPagliflozin outcomE tRial in Patients With chrOnic HF With Reduced Ejection Fraction (EMPEROR-Reduced) trial over 70% of patients were on MRAs, and the hazard ratio (HR) [95% confidence interval (CI)] 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, SGLT2is reduced the incidence of the composite renal outcome of worsening renal function (doubling of serum creatinine accompanied by an eGFR of $\leq$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 Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (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 with placebo [6]. Finally, the Dapagliflozin in Patients with CKD (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 (UACR) 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 $\geq$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 0.55–0.92) and all-cause mortality (HR 0.69; 95% CI 0.53–0.88). These effects of SGLT2is are independent of age, sex and race, and 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 European Renal and Cardiovascular Medicine (EURECA-m) and Diabesity working groups of the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) [35], an observation of major importance is that the above renoprotective effects of SGLT2is take place on top of standard treatment with an ACEi or an ARB. The main mechanism by which SGLT2is 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 SGLT2is 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 SGLT2is in patients with T2DM and eGFR >30 mL/min/1.73 m^2 is strongly recommended. As of this writing, there are no data on the use of SGLT2is 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, that is around 5% [39].

NEPHROPROTECTIVE PROPERTIES OF MRAs

Evidence before FIDELIO-DKD

Following background data on a nephroprotective effect of MRAs, several clinical studies evaluated the effects of spironolactone, eplerenone or finerenone on urine albumin or protein excretion (UPE), the most commonly used intermediate renal endpoints [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: (i) ramipril/placebo/placebo; (ii) ramipril/irbesartan/placebo; (iii) ramipril/placebo/spironolactone; or (iv) 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 BP, creatinine clearance, sodium and protein intake did not differ between groups. Serum potassium and incidence of hyperkalaemia increased with the addition of either spironolactone or losartan. A recent randomized controlled trial (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 randomized to spironolactone and in 1% of the 107 patients randomized to placebo. Although possibly under-powered, this study suggests that MRAs 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 $\geq$50 mg/g on enalapril treatment, to placebo, eplerenone 50 mg or eplerenone 100 mg for 12 weeks, UACR reductions were 7.4%, 41% and 48.4%, respectively ($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 and 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 MRAs in patients with diabetic [46–52] or non-diabetic CKD [53–59] showed similar nephroprotection. A recent meta-analysis evaluating the nephroprotective role of MRAs [60] suggested that these agents (alone or on top of RAS blockade) decreased UACR by 24.55%, and uPCR by 53.93% compared with placebo. Addition of an MRA was associated with average eGFR decrease of 2.38 mL/min/1.73 m^2 (95% CI 3.51–1.25), rise in potassium by 0.22 mmol/L (95% CI 0.16–0.28) 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 28–90 days, and the slight reduction in eGFR observed potentially only reflects decreased glomerular hyperfiltration [45, 61].

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 with placebo on renal and CV outcomes. The study randomly assigned 5734 patients with T2DM on maximum tolerated dose of an ACEi or an ARB who had either UACR 300–5000 mg/g or 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/1.73 m^2, with 33.5% of patients being at the 45–60 mL/min/1.73 m^2 and 52.5% at the 25–45 mL/min/1.73 m^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/1.73 m^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 on 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 0.65–0.90) 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 than the placebo group. Finally, when compared with baseline, SBP 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 MRAs

The analysis of the potential mechanisms for the nephroprotective actions of MRAs and, more specifically, of finerenone, in addition to RAS blockade should answer the question of why would MRAs increase nephroprotection when dual conventional RAS blockade does not [21, 22]. Two basic mechanisms for nephroprotection may be considered: a haemodynamic effect and a direct action on tissue inflammation and fibrosis (Figure 1A). The different specificity and impact on cofactor recruitment may account for differences between individual MRA on the adverse effect profile, including hyperkalaemia (Figure 1B) [62–64].

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 SGLT2is [65, 66] 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 [67–69]. Studies with SGLT2is 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 SGLT2is at baseline in FIDELIO-DKD was 1.38 (95% CI 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 pre-specified subgroups [i.e. HR 0.82 (95% CI 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 an 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 with placebo was absent in the intervention arm and the difference in the decrease in albuminuria ranged from 11% to 20%, that is 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 haemodynamic effect. Rather, the question is why a haemodynamic effect, and indeed a clinical benefit, was observed with RAS blockade and MRA but not on dual conventional RAS blockade?

A second hypothesis, which is neither supported nor discarded by the available FIDELIO-DKD data, relates to inhibition of proinflammatory and profibrotic effects recruited by

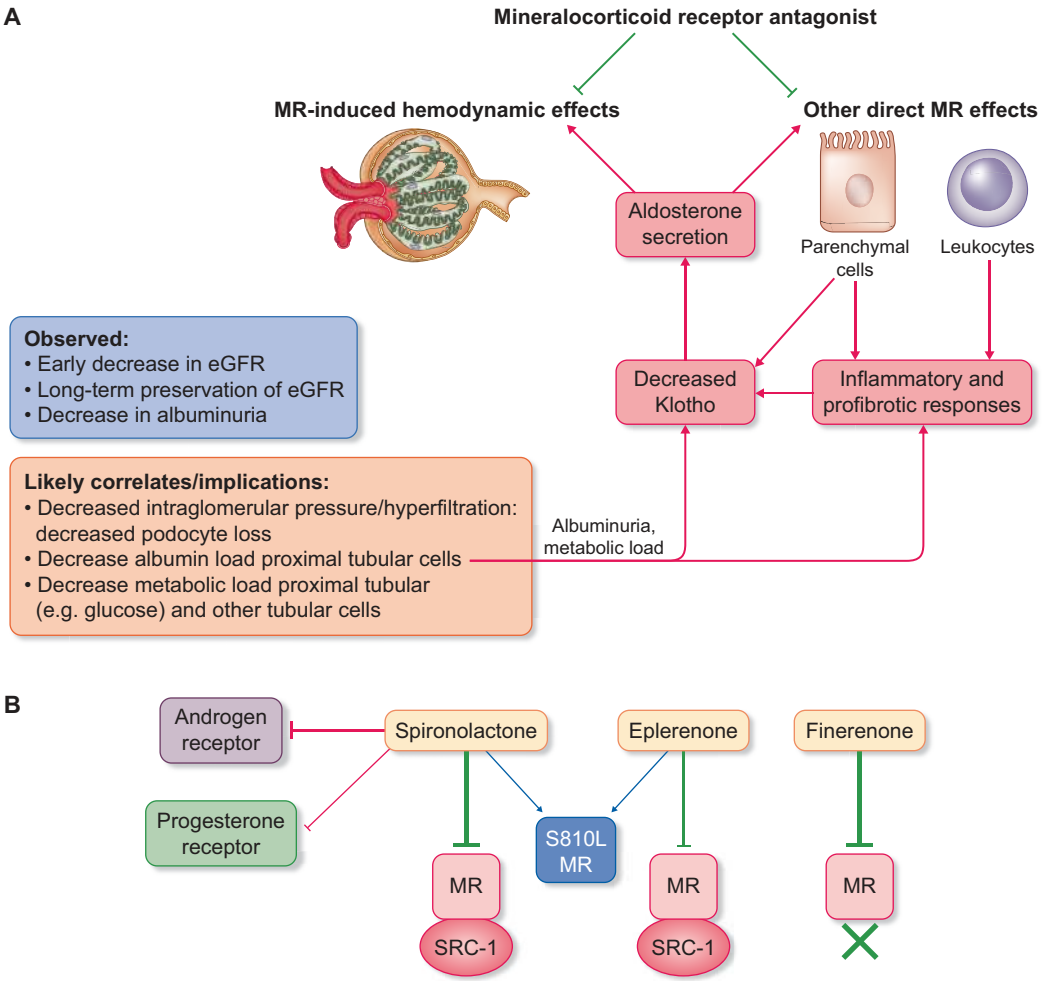

FIGURE 1: Potential mechanisms of action of MRAs on DKD and key differences between MRAs. (**A**) MRAs may be nephroprotective through haemodynamic actions, decreasing intraglomerular pressure, glomerular filtration and albuminuria and thus decreasing workload for tubular cells and the resulting adverse 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 haemodynamic effect. Additionally, MRAs 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 MRAs in pre-clinical studies. Sources for images: Wikipedia, smart.servier. (**B**) Spironolactone and eplerenone are steroid MRAs 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 gynaecomastia. The selectivity of eplerenone is higher, but the affinity for MR is lower than that of spironolactone and finerenone. There are further differences [62–64]. 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 [64]. 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 [63, 64].

the transcription factor induction via MR. In common with the activation of the AngII/angiotensin receptor axis [70, 71], MR activation leads also to non-haemodynamic actions [72, 73]. Specifically, direct proinflammatory and profibrotic effects on a variety of cell types and organs have been well characterized in pre-clinical studies [72, 74]. 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 [75]. In this regard, multiple human kidney parenchymal cell types express the *NR3C2* gene encoding the MR (Figure 3A–C) [76]. Indeed, MR expression is increased in kidney leukocytes in DKD, potentially sensitizing them to MR activation (Figure 3D) [77].

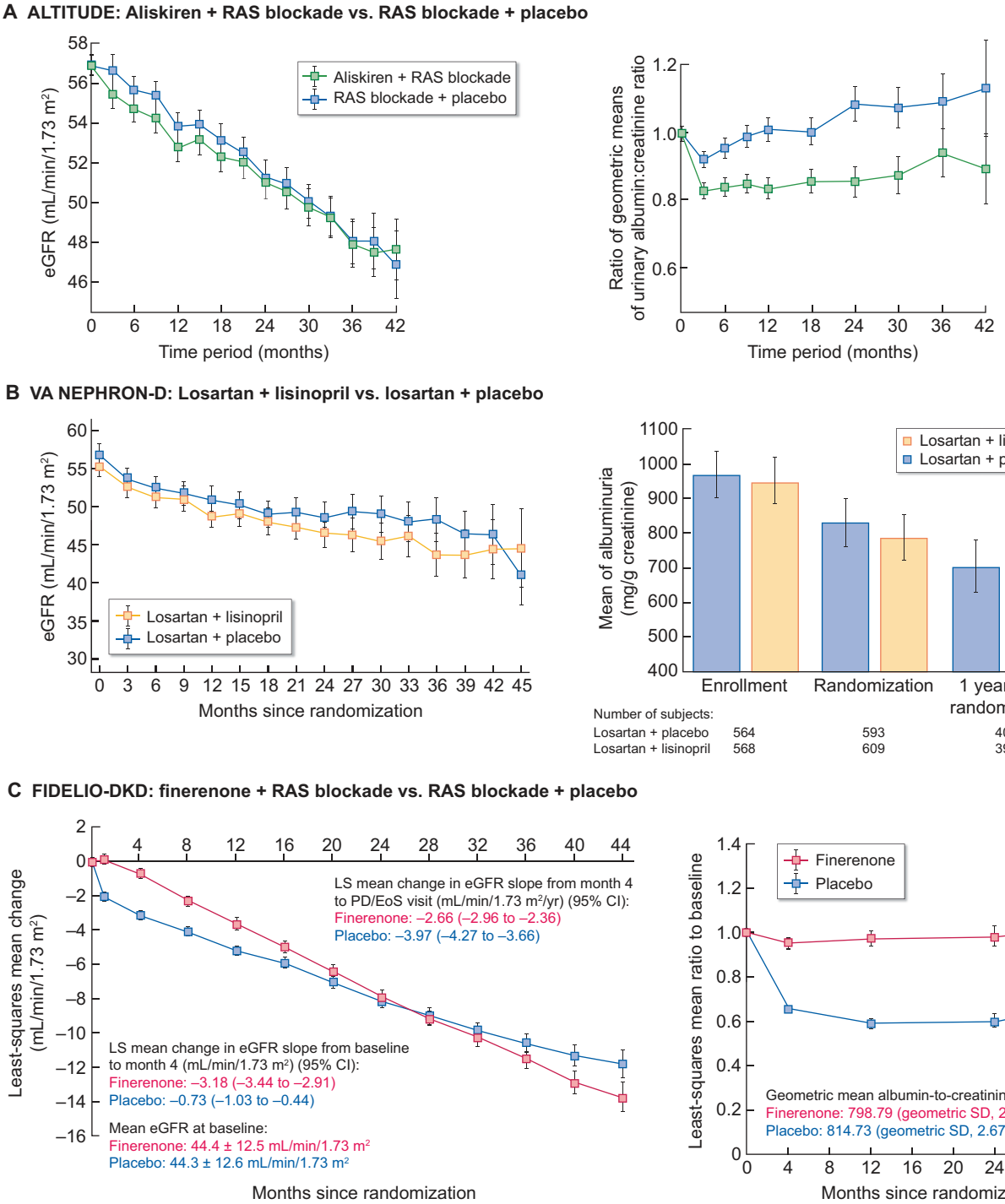

FIGURE 2: Haemodynamic impact of dual conventional RAS blockade versus MRA plus RAS blockade according to selected large outcomes clinical trials. (**A**) ALTITUDE. Aliskiren + RAS blockade versus RAS blockade + placebo [21]. Note the overlapping SE bars for early eGFR changes and milder early impact on albuminuria than in FIDELIO-DKD. (**B**) VA NEPHRON-D. losartan + lisinopril versus 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 versus RAS blockade + placebo [11]. Note different scales for different graphs.

CARDIOPROTECTIVE PROPERTIES OF MRAs

Evidence before FIDELIO-DKD

The concept that aldosterone promotes CV 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 HF with preserved ejection fraction (HFpEF) [78, 79]. LVH becomes increasingly prevalent in CKD as eGFR falls [80]

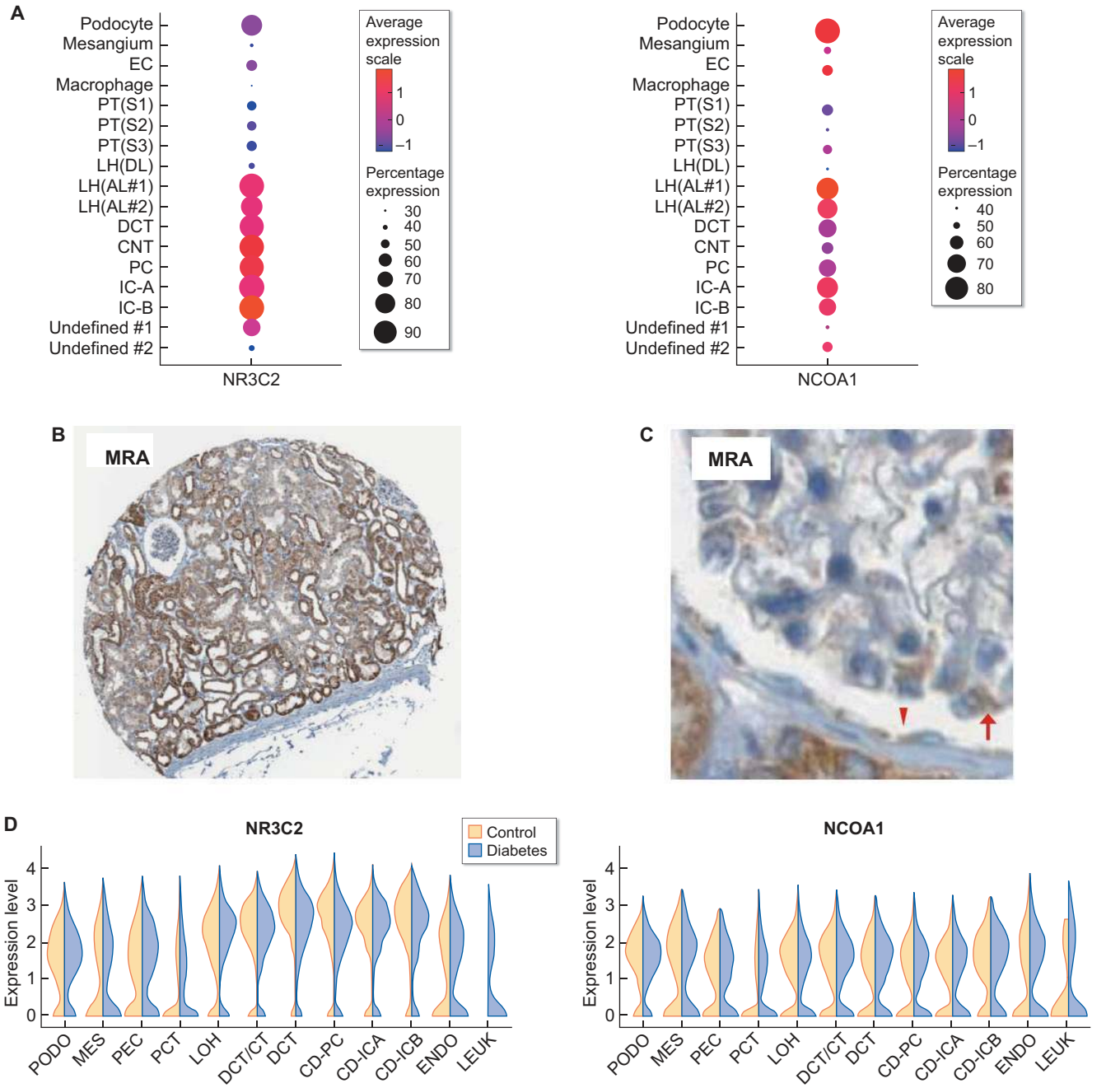

FIGURE 3: Kidney expression of key genes involved in MR signalling. (**A**) Multiple human cell types, including ECs, podocytes, mesangial cells, proximal and distal tubular epithelial cells, expressed *NR3C2* encoding the MR as well as *NCOA1* encoding its key cofactor steroid receptor coactivator-1 (SRC-1) [76]. 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* were increased in human DKD, 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 [77]. (Images from http://humphreyslab.com/SingleCell/ and https://www.proteinatlas.org/ENSG00000151623-NR3C2/tissue/kidney#img; accessed 24 October 2020.)

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 [81, 82]. 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 [83]. These data provide the rationale for

addition of MRAs to conventional RAS inhibition for CV protection [73].

The greatest magnitude of benefit of MRAs on CV outcomes was generally observed in patients with HF, and particularly in those with HF and reduced left ventricular ejection fraction (LVEF), heart failure with reduced ejection fraction (HFrEF). In the Randomized Aldactone Evaluation Study trial of 1663 people with LVEF <35%, allocation of spironolactone led to a 30% reduction in CV mortality [relative risk (RR) 0.69; 95% CI 0.58–0.82] [84]. Two subsequent large RCTs of eplerenone in patients with HF following myocardial infarction or patients with left ventricular systolic dysfunction but less severe symptoms showed similar benefits [85, 86]. Such consistent results led to MRAs receiving a Level 1A grading for use in HFrEF across international guidelines [87].

To date, no therapy has been demonstrated to alter outcomes in HFpEF—the dominant form of HF in patients with CKD. Spironolactone reduced left ventricular mass and vascular stiffness in patients with Stages 2–3 CKD in a placebo-controlled RCT and therefore it is plausible that MRAs would improve outcomes in HFpEF [88]. In the Treatment of Preserved Cardiac Function HF 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 with placebo [206 patients (12.0%) versus 245 patients (14.2%); HR 0.83; 95% CI 0.69–0.99], but there was no statistically significant impact on the primary composite endpoint of the trial of death from CV causes, aborted cardiac arrest or hospitalization for the management of HF [89]. 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 USA, Canada, Brazil and Argentina compared with those from Russia and Georgia [90]. A separate analysis of patients from the Americas suggested that spironolactone may indeed improve clinical outcomes in HFpEF [90] and led to a Class IIb level B-R grading by US guidelines [87]. 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 HF (EudraCT 2017-000697-11) [87].

In all the CV outcome trials in HF, the incidence of hyperkalaemia and serum potassium was higher in the MRA group compared with placebo [84–86, 89] but hyperkalaemia occurrence did not hinder the clinical benefit of MRAs [91, 92] even in high-risk subgroups (CKD, diabetes and elderly patients) [93, 94].

CV outcomes of the FIDELIO-DKD study

In the FIDELIO-DKD trial, the key composite secondary outcome consisted of death from CV causes, non-fatal myocardial infarction, non-fatal stroke and HHF [39]. Patients treated with finerenone had a lower incidence of this secondary outcome compared with placebo (13.0% versus 14.8%; HR 0.86; 95% CI 0.75–0.99; 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 0.76–1.38). This is consistent with the important role of BP for stroke risk and the very little difference in BP between the groups [17, 95]. The improvement in the key secondary CV outcome was independent of having had a history of previous CV disease [96]. Indeed, FIDELIO-DKD is the first study in patients with CKD showing a reduction in CV events in a population in which symptomatic HF or reduced LVEF were excluded [96].

POTENTIAL MECHANISMS FOR THE CARDIOPROTECTIVE ACTIONS OF MRAs

Apart from its obvious cardioprotective impact by reducing sodium retention and, therefore volume expansion, MRAs elicit direct effects in different cell types of the CV system. Furthermore, a *post hoc* analysis of the Eplerenone Post-Acute Myocardial Infarction HF Efficacy and Survival trial (EPHESUS) in HF post-myocardial infraction suggested that an early (1 month) rise in serum potassium as a potassium-sparing effect, and an early diuretic effect may contribute to the beneficial effects of eplerenone [97]. 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 [98–100].

MRAs and the vasculature

The MR is a functional transcription factor in vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) [101]. The VSMC-MR directly contributes to BP control and vascular tone by regulating L-type calcium channel expression and function [102], mediating AngII signalling [103] and regulating the phosphorylation of contractile regulatory proteins [104]. The VSMC-MR also contributes to vascular remodelling by regulating genes involved in vascular fibrosis, inflammation and calcification [105, 106]. Thus, VSMC-MR knockout mice exhibit less aging-associated vascular stiffness [107]. A direct role for VSMC-MR in vascular remodelling after injury from mechanical damage has been also demonstrated [108].

The EC-MR does not appear to play a major role in either basal vasomotor function or BP control [109]. However, the EC-MR contributes to endothelial dysfunction and vascular damage when CV risk factors are present, through mechanisms involving oxidative stress, inflammation and vessel stiffening [110, 111]. Overexpression of human MR in EC increased BP [112]. However, EC-specific MR deletion did not alter basal BP [109], although it protected against AngII-induced hypertension [113] and DOCA/salt hypertension-mediated vascular inflammation and fibrosis [109]. Furthermore, global MR blockade increases nitric oxide bioavailability by reducing endothelial nitric oxide synthase uncoupling and increasing vascular superoxide dismutase and catalase expression [114]. Aldosterone may also favour inflammation by

promoting intercellular adhesion molecule-1 expression [115], thereby promoting leukocyte adhesion to EC [110]. 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 [116].

MRAs and the heart

The MR is also expressed in cardiomyocytes and myofibroblasts [117]. Aldosterone directly induces cardiac hypertrophy, ventricular remodelling, arrhythmia and ischaemia, independently of its haemodynamic effects [118], and it appears that progression from LVH to cardiac failure is mediated by aldosterone through the MR [119]. Moreover, MR activation stimulates apoptosis and induces coronary vasoconstriction in animal hearts [120] and MR overexpression in the mouse heart results in severe ventricular arrhythmias [121]. By contrast, MR deletion in cardiomyocytes in mice had no adverse consequences [122], prevented left ventricular dilatation and dysfunction after chronic pressure overload [123], and improved infarct healing and prevented progressive adverse cardiac remodelling, cardiac hypertrophy and contractile dysfunction in ischaemic HF [124], mainly through decreased apoptosis [125]. In addition, some cardiac protective effects of MRAs *in vivo* can be partially mediated by macrophages, in which MR deletion elicited effects similar to those of MRAs [126, 127].

MRAs limit also infarct size after reperfusion in mice through non-genomic intracellular signalling including adenosine receptor stimulation, and activation of the Reperfusion Injury Salvage Kinase pathway [128, 129]. Indeed, MRAs have consistently shown beneficial effects on left ventricular dilation, cardiac function, fibrosis or collagen content in pre-clinical studies [130–132]. Furthermore, aldosterone may stimulate proliferation of myofibroblasts [133], an important cell type in scar formation.

SAFETY OF MRAs IN DKD

Despite the Class 1A recommendation of using MRAs in patients with HFrEF, ∼30% of whom will also have CKD [134, 135], the use of the two approved steroidal MRAs (i.e. spironolactone and eplerenone) is limited by the fear of hyperkalaemia and impaired kidney function. According to registry data, only 70% of eligible patients are treated and 70% of these are underdosed [136, 137]. Spironolactone is also prone to induce breast pain and gynaecomastia, erectile dysfunction in men and menstrual irregularities in pre-menopausal women [135]. 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 MRAs 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 hyperkalaemia risk (RR 2.63; 95% CI 1.69–4.08) [60]. However, this meta-analysis also found that the RR of hyperkalaemia was 4.44 (95% CI 1.99–9.93) for MRAs compared with 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 hyperkalaemia associated with the use of the steroidal MRAs such as the concomitant use of potassium binders [138] and the development of non-steroidal MRA, such as finerenone [135]. In the AMBER Phase II trial, 295 patients with resistant hypertension and an eGFR between 25 and 45 mL/min/1.73 m^2 (mean 36 mL/min/1.73 m^2), the potassium binder patiromer, compared with placebo, enabled a more persistent use and a higher dose of spironolactone. Two-thirds of patients in the placebo group developed hyperkalaemia over the 12-week follow-up, and this risk was halved in the patiromer group ($P < 0.0001$) [138].

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 ∼0.23 mmol/L higher with finerenone, remaining around 4.6 mmol/L. Incidences of hyperkalaemia, 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 hyperkalaemia (18.3% versus 9.0%) and hyperkalaemia leading to discontinuation of the trial regimen (2.3% versus 0.9%) were higher with finerenone, while no fatal hyperkalaemia adverse events were reported. The above rates of discontinuation due to hyperkalaemia are rather low, when compared with the relevant rates with dual RAS blockade with ACEi/ARB and the direct renin inhibitor aliskiren (4.8%) in the ALTITUDE [21] and combined losartan and lisinopril treatment (9.9%) in the VA NEPHRON-D trial [22] over similar follow-up periods. Therefore, the burden of hyperkalaemia 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 MRAs under development [139, 140]. 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 DKD (FIGARO-DKD; NCT02545049) study [141] will compare finerenone versus placebo on CV and renal outcomes and has randomized 7437 patients with T2DM. The study design of FIDELIO-DKD and FIGARO-DKD is quite similar, apart from that the primary outcome of FIGARO-DKD is CV and not renal and there are slightly different inclusion/exclusion criteria. Indeed, patients were permitted to switch between the two studies before randomization. Both studies excluded patients with an eGFR <25 mL/min/1.73 m^2, with FIGARO-DKD also including patients with better-preserved kidney function (maximum allowed eGFR of 90 mL/min/1.73 m^2 compared with 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 an

SGLT2i at baseline was higher at 613 (8.3%), and this may be increased by patients starting an 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, non-fatal myocardial infarction, non-fatal stroke or HHF; this is 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 programme designed to investigate the occurrence of fatal and non-fatal CV events and progression of kidney disease in <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/1.73 m^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/1.73 m^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 MRAs OF NEPHROLOGICAL INTEREST

There are further ongoing clinical trials testing MRAs of nephrological interest. The ALdosterone antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST) [142] and the Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease (ACHIEVE; ClinicalTrials.gov identifier: NCT03020303) are two ongoing CV 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 sAfety superioR to placebo in paTientS with HF (FINEARTS-HF; ClinicalTrials.gov identifier: NCT04435626). This trial will randomize subjects with HF [New York Heart Association (NYHA) 2–4] and LVEF ≥40% to either finerenone or placebo. The study is primarily aimed at testing CV and heart-related endpoints, with a composite renal endpoint among the secondary outcomes.

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

Esaxerenone (CS-3150) is being developed for the treatment of essential hypertension and DKD [143, 144]. It was approved for the treatment of essential hypertension in Japan in 2019 [143, 144]. 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 with 3% in those taking placebo [145]. In a further Phase III study, 455 patients with DKD and UACR 45 to <300 mg/g

Table 1. Ongoing studies with non-steroidal MRAs

Study	Drug	Comparator	Phase	*N*	Population	CKD exclusion	Primary endpoint	Status	Estimated completion
NCT02545049 FIGARO-DKD	Finerenone (BAY94-8862)	Placebo	III	7437	DKD with albuminuria (UACR ≥30 to ≤5000 mg/g)	eGFR <25 mL/min/1.73 m^2	Composite of CV death and non-fatal CV events (myocardial infarction, stroke or hospitalization for HF)	Enrolment complete	February 2021
NCT04435626 FINEARTS-HF	Finerenone (BAY94-8862)	Placebo	III	5500	HF (NYHA 2–4), LVEF ≥40%	eGFR <25 mL/min/1.73 m^2	CV deaths and HF events	Recruiting	2024
NCT04469907	AZD-9977	NA	I	32	Healthy subjects or GFR 15–89 mL/min/1.73 m^2	eGFR <15 mL/min/1.73 m^2	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 m^2	Percentage 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 m^2	Change in SBP	Enrollment complete	November 2020

already on RAS inhibitors were randomized to either esaxerenone or placebo [146]. The proportion of patients with UACR remission was higher in the esaxerenone group (22%) compared with the placebo group (4%; $P < 0.001$) at the end of 52 weeks of treatment.

Apararenone (MT-3995) is being developed for the treatment of diabetic nephropathy [147, 148]. In 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 [149].

AZD-9977 recently completed Phase I studies in healthy volunteers [150] and ongoing Phase I studies are enrolling patients with various degree of renal impairment (ClinicalTrials.gov identifier: NCT04469907) and HF with preserved or mid-range LVEF in comparison with 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 3-month follow-up period. The study population will be made of patients with stable symptomatic HF (NYHA 2–3) with an LVEF <55%, CKD Stage 3 and micro-macroalbuminuria. The direct comparison or combination with SGLT2is 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 Stages 3b–4 (ClinicalTrials.gov identifier: NCT03574363) [140, 151].

MRA BI690517 recently (May 2020) completed a Phase II study in patients with diabetic nephropathy (ClinicalTrials.gov identifier: NCT03165240). Other non-steroidal MRA, LY2623091 [152] and PF03882845 [153] are not being developed further [154].

CONCLUSIONS ON MRAs USE FOR DKD 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 lowers CV risk [5, 155]. 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 [156], aliskiren [21, 157] and darbepoetin [158]. However, published RCTs in the last few years have provided important evidence on the effects of SGLT2is on renal and CV 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 non-steroidal MRA, lowered the risk of progression of kidney disease and CV 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 USA were filed on 9 November 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

Box 1. Patients who are likely to benefit from treatment with finerenone[a]

T2DM	As defined by the American Diabetes Association [12]
Diagnosis of DKD	Persistent high albuminuria (30–299 mg/g) and presence of diabetic retinopathy and eGFR ≥25 but <60 mL/min/1.73 m^2 or Persistent very high albuminuria (≥300 mg/g) and eGFR ≥25 but <75 mL/min/1.73 m^2
Serum potassium	<4.8 mmol/L
Treatment with maximum labelled and tolerated dose of ACEi or ARB therapy for at least 4 weeks	
BP	SBP ≤160 mmHg and DBP ≤100 mmHg
Absence of clinical diagnosis of HF 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	–

[a]Based on the inclusion and exclusion criteria for the FIDELIO-DKD trial.

Box 2. Potential use of the MRA finerenone for DKD patients who are already on RAS blockers with or without SGLT2i

1. Finerenone was safe and showed efficacy in improving kidney and CV outcomes in patients with DKD who are already on RAS blockers.
2. Thus, when approved by health authorities, finerenone may represent an alternative to SGLT2i to provide kidney and CV protection in patients with DKD (eGFR 25–75 mL/min/1.73 m^2) who are already on RAS blockers.
3. In this regard, finerenone may be a kidney and CV 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 CV 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 T2DM, the available data support the hypothesis that the kidney and CV protection exhibited by finerenone might also be observed in non-diabetic kidney CKD patients on RAS blockade. However, this needs to be shown in future studies.

or an ARB in maximum tolerated doses and independently of the use of an SGLT2is in patients with T2DM and CKD with: eGFR 25–75 mL/min/1.73 m^2, moderately or severely increased albuminuria and serum potassium $\leq$4.8 mmol/L (Boxes 1 and 2). Although currently direct evidence that finerenone provides additional cardioprotection and nephroprotection in patients treated with RAS blockers and SGLT2is 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 MRAs 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 non-steroidal MRAs are awaited to shed more light on this field.

A key point that requires further evidence development is the relative position of SGLT2is and finerenone or other MRAs in kidney and CV protection in DKD. In this regard, as previously pointed out, SGLT2is were allowed in FIDELIO-DKD, whereas patients treated with MRAs were excluded from the CREDENCE and DAPA-CKD trials. Although pre-clinical evidence suggests that the mechanisms of kidney and CV protection by MRAs and by SGLT2is 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 MRAs and SGLT2is in DKD patients on RAS blockers, although data obtained with other MRAs may not necessarily reflect the behaviour of finerenone. In a recent randomized trial testing sotagliflozin in DKD patients (most on RAS blockade) with a primary kidney endpoint, 15% of patients were on MRAs and subgroup analyses of those with HF-related criteria was consistent with additional benefit on those already on an MRA for the primary endpoint of the composite of the total number of deaths from CV causes, hospitalizations for HF and urgent visits for HF [159]. Further information will likely be available in the near future. FIGARO-DKD includes a higher percentage of patients on SGLT2is 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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