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REVIEW

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Finerenone in the management of diabetes kidney disease

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Abstract

People with type 2 diabetes are at risk of developing progressive diabetic kidney disease (DKD) and end stage kidney failure. Hypertension is a major, reversible risk factor in people with diabetes for development of albuminuria, impaired kidney function, end-stage kidney disease and cardiovascular disease. Slowing progression of kidney disease and reducing cardiovascular events can be achieved by a number of means including the targeting of blood pressure and the use of specific classes of drugs The use of Renin Angiotensin Aldosterone System (RAAS) blockade is effective in preventing or slowing progression of DKD and reducing cardiovascular events in people with type 2 diabetes, albeit differently according to the stage of DKD. However, emerging therapy such as non-steroidal selective mineralocorticoid antagonists (finerenone) is proven to lower blood pressure and further reduce the risk of progression of DKD and cardiovascular disease in people with type 2 diabetes. This consensus reviews current evidence and make recommendations for the use of finerenone in the management of diabetes kidney disease in the UK.

Keywords Diabetes, Hypertension, Albuminuria, Diabetic kidney disease, Finerenone, ACE inhibitors, Angiotensin receptor blockers, Renin Angiotensin Aldosterone System (RAAS)

Background and challenges of diabetes kidney disease

A significant percentage of people with diabetes develop diabetic kidney disease (DKD), and as a result diabetes is also a leading cause of end-stage kidney disease (ESKD) in the UK [1]. This is exemplified by the increasing percentage of individuals with diabetes requiring ESKD treatment year on year in successive UK Renal Registry reports [2]. DKD is associated with significant morbidity and mortality, which are predominantly related to cardiovascular complications and the progression to kidney disease that requires renal replacement therapy. Indeed, the development of kidney complications (increasing albuminuria or decline in eGFR) is an indicator of significant cardiovascular morbidity [1].

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The progressive increase in people with DKD requiring ESKD treatment is likely to continue to increase and the reasons for this are multiple.

In the first instance, kidney complications and more particularly significant ESKD caused by diabetes, usually takes between 10 and 20 years from development of the diabetes. Data from Public Health England demonstrates that the number of people in the UK on the diabetes register has increased by 44% from 2,213,238 in 2008 to 3,196,124 in 2018 [3]. Whilst some of this increase is likely to represent better recognition and coding, a significant proportion of the increase is likely to represent a true increasing burden of disease. In addition to the growing denominator of individuals at risk of kidney disease due to this growth in type 2 diabetes, the longer the person lives with type 2 diabetes the lower their eGFR [4] and the younger the person is when they develop type 2 diabetes the greater likelihood there is of them reaching ESKD [5]. At present, individuals who develop DKD are more likely to die of cardiovascular disease before they reach ESKD [6]. However, over time this ratio will shift and we are likely to see many more people reaching ESKD. These epidemiological factors necessitate a strategic response to diagnose and optimise and thereby slow down or prevent progression of DKD.

Methodology

This paper is a summary of a consensus document produced by the ABCD/UKKA diabetes and kidney guideline group utilising the available evidence and publications relating to finerenone. The lead authors reviewed the relevant published randomised double blind phase 3 studies relating to finerenone and any post-hoc published analysis of those studies available at the time of constructing this consensus. Once the evidence was reviewed and recommendations graded by the lead authors, they were then consulted on by the wider membership of the ABCD/UKKA guideline committee. Comments on the proposed consensus statement were received, appropriate adjustments made and all members confirmed agreement of the final consensus statement. A further stage of consultation was undertaken before publication in which the draft consensus statement was reviewed by all members of the UKKA clinical guidelines committee and then the draft statement was placed on the website for public consultation (invitations for comments were made through the UKKA e communication channels) prior to the final version being published on both the UKKA and ABCD websites.

Current management of diabetes kidney disease

The management of DKD is underpinned by early recognition and optimisation. The factors that have proven to be central to optimisation and treatment of DKD include better glucose control, blood pressure control [7] and the use of inhibitors of the renin aldosterone angiotensin system (RAAS) [8]. In addition careful attention to lipid management is important to reduce the increased cardiovascular risk associated with DKD [9].

These treatments have been augmented by the recent publications that have demonstrated the significant benefit that sodium glucose co-transporter 2 inhibitors (SGLT2i) have on progression of DKD and additionally their benefits in relation to prevention of heart failure development and progression. However, even taking the two primary kidney studies involving SGLT2i which include CREDENCE [10] and DAPA CKD [11] and EMPA KIDNEY [12] where SGLT2i was added onto standard of care which included the use of RAAS inhibitors, blood pressure control and reasonable glycaemic control, there remained significant residual risk of progression of DKD.

Given the potential growth in people developing advanced kidney disease in the context of diabetes, it is only right that we continue to appraise new interventions that can provide additional benefit for those individuals at risk of progression of DKD and where these have been found to be of benefit implement their use through appropriate clinical guidelines.

Background of steroidal and non-steroidal mineralocorticoid receptors antagonists

In 1943, the role of mineralocorticoids in relation to damage to kidney and heart tissue was demonstrated [13] and in 1999, spironolactone was shown to reduce mortality by 30% in people with heart failure [14]. This was followed by demonstration of 15–24% mortality benefit post myocardial infarction in people with mild heart failure treated with eplerenone in 2003 and 2011 [15, 16].

Finerenone is a selective nonsteroidal mineralocorticoid receptor antagonist (MRA) which is metabolized predominantly in the liver with minimal excretion via the kidneys. Due to its greater mineralocorticoid receptor affinity and selectivity, finerenone is associated with less hyperkalemia and minimal gynaecomastia compared with the steroidal MRAs. At a dose of 10 mg, finerenone has been shown to be equivalent to 25 to 50 mg of spironolactone in reducing Brain Natriuretic Polypeptide (BNP) and albuminuria but with less hyperkalemia [5% versus 12%] in 372 subjects of Heart Failure with reduced Ejection Fraction (HFrEF) and CKD [17]. In 2016, finerenone 10 to 20 mg was shown to be equivalent to 50 mg of eplerenone in reducing BNP > 30% from baseline with less incidence of potassium > 5 mmol/L [3.6% versus 4.7%] [18].

Evidence for renal and cardiac protection with Finerenone

In 2020, in the FIDELIO placebo-controlled trial, finerenone was shown to reduce the risk of ESKD, death from ESKD and >40% reduction in eGFR by 18% compared to standard of care in 5734 DKD subjects with urine ACR 30–300 mg/g and eGFR 25–60 ml/min/1.73m^2 and diabetic retinopathy; or DKD with ACR 300–5000 and eGFR of 25–75 ml/min/1.73m^2 [19].

Subsequently in another large multicenter trial FIGARO, finerenone was shown to reduce the risk of Myocardial Infarction (MI), Cerebrovascular Accident (CVA) and Heart Failure (HF) admission by 17% compared to placebo in 7437 DKD subjects with urine Albumin Creatinine Ratio (ACR) 30–300 mg/g and eGFR 25–60 ml/min/1.73m^2 and diabetic retinopathy; or DKD with ACR 300–5000 and eGFR of 25–75 ml/min/1.73m^2. Hyperkalemia with potassium > 5.5 mmol/L was seen on 11% versus 5% [20]. In an analysis of the FIGARO-DKD study, finerenone reduced incident HF HR 0.68(0.50–0.93) [21].

Hence, finerenone was able to reduce renal and cardiac endpoints compared to placebo with less hyperkalemia than non-selective MRA in people with DKD and proteinuria.

Finerenone and SGLT2 inhibitors

As described SGLT2 inhibitors (SGLT2i) have now become standard of care for people with DKD. At the time of the development and recruitment into the FIDELIO-DKD trial there was not widespread use of these agents in people with DKD and particularly in those with reduced eGFR. As a result, SGLT2i use was not common in the FIDELIO trial (of the 5674 subjects included in the trial only 259 (4.6%) were on an SGLT2i). A post-hoc analysis assessing this small subgroup suggested no difference in response to finerenone [22]. However, in the pre-specified pooled analysis of the combined FIDELIO-DKD and FIGARO-DKD trials (FIDELITY), which included 877 subjects who received SGLT2i at baseline, Hazard Ratio for primary composite cardiovascular outcome was 0.63 (95% CI 0.40 to < 1.00) for baseline receipt of SGLT2i compared with HR of 0.87 (95% CI 0.79–0.96) for no baseline receipt of SGLT2i [22]. This may suggest possible additional cardiovascular benefit with combination use but more data is needed, and additional analysis of this pooled data is currently ongoing.

In principle the mechanism of action of SGLT2i and finerenone should be complimentary with the SGLT2i induced reno-protection believed to be predominantly related to reduced hyperfiltration while finerenone is believed to work via inhibiting the MRA pathway for inflammation and fibrosis. SGLT2i have also been shown to reduce the incidence of hyperkalemia associated with finerenone in the FIDELIO-DKD trial [24].

It is recognized, however, that these potential benefits are presumptive and there is no direct evidence to support it. However, we await the results of two combination therapy phase 2 trials due to be reported in the near future – MIRACLE [23] and CONFIDENCE [25] trials.

MIRACLE will evaluate the efficacy and safety of AZD9977 and dapagliflozin on urinary albumin to creatinine ratio in participants with heart failure with left ventricular ejection fraction below 60% and chronic kidney disease with estimated glomerular filtration rate between ≥ 20 and ≤ 60 mL/min/1.73m^2 [23].

CONFIDENCE trial will demonstrate the effects of dual initiation of finerenone and empagliflozin in reducing urinary albumin to creatinine ratio compared with either empagliflozin or finerenone alone in patients with chronic kidney disease and type 2 diabetes [25].

As a result of the FIDELIO-DKD trial NICE have undertaken a technology appraisal confirming their recommendation for the use of finerenone as an adjunct to standard of care with diabetic kidney disease [26].

Hyperkalemia with finerenone

In the FIDELIO study, over a 2.6-year median follow-up, 597 of 2785 (21.4%) and 256 of 2775 (9.2%) subjects on finerenone and placebo, respectively, developed mild hyperkalemia [potassium > 5.5 mmol/L]; 126 of 2802 (4.5%) and 38 of 2796 (1.4%) subjects developed moderate hyperkalemia [potassium > 6 mmol/L].[24]

At baseline 99% of the population was on Angiotensin Converting Enzyme (ACEi)/Angiotensin Receptor Blocker (ARB) and potassium was < 4.9 mmol/L. Subjects were started on finerenone or placebo at a dose of 10 mg if was eGFR < 60 ml/min/1.3m^2 or 20 mg if eGFR ≥ 60 ml/min.1.73m^2. At baseline, the mean serum potassium was 4.37 ± 0.46 mmol/L in the finerenone group and 4.38 ± 0.46 mmol/L in the placebo group. A total of 390 (6.9%) subjects had a baseline serum potassium > 5.0 mmol/L.

At regular study visits (month 1, month 4, and every 4 months thereafter), study drug dose was adjusted based on serum potassium and eGFR. If serum potassium was < 4.9 mmol/L, the dose of study drug was either up titrated from 10 mg to 20 mg od or kept at 20 mg provided eGFR decline was < 30%. If serum potassium was 4.9–<5.5 mmol/L, treatment was continued with the same dose of study drug. When serum potassium was ≥ 5.5 mmol/L, study drug was temporarily withheld and serum potassium rechecked within 72 h and if serum potassium was ≤ 5.0 mmol/L, study drug was restarted at the 10 mg daily dose; otherwise, study drug continued to be withheld until serum potassium was ≤ 5.0 mmol/L. Study drug was discontinued if a subject on the 10 mg

daily dose experienced a recurrent hyperkalemia event soon after a previous event (provided the only explanation for the recurring hyperkalemia event was the study drug), or if the investigator felt continuation of treatment was harmful.

At 1 month, 86 (3.1%) and 14 (0.5%) subjects in the finerenone group and 34 (1.2%) and four of 2749 (0.1%) subjects in the placebo group had serum potassium > 5.5 and > 6.0 mmol/L, respectively. Elevated baseline potassium was associated with an increased risk of mild hyperkalemia; the risk was increased 1.5, 2.8, and 4.2 times with serum potassium of 4.5–<4.8, 4.8–5.0, and > 5.0 mmol/L at baseline, respectively, compared with a serum potassium of 4.1–4.5 mmol/L. Lower eGFR was also an independent risk factor of hyperkalemia. Risk of mild hyperkalemia increased 1.5 and 2 times as eGFR dropped below 45 and 25 ml/min per 1.73 m [2], compared with an eGFR greater than 60 ml/min per 1.73 m [2]. Patients with an eGFR of 45 – <60 ml/min per 1.73 m [2] had a similar risk to those with an eGFR ≥ 60 ml/min per 1.73 m [2].

The role of mineralocorticoid receptor antagonist(MRA) in managing diabetes kidney disease: current national and international guidelines

National and international guidelines have varied consensus on the use of finerenone in people with T2DM and DKD although this is influenced by their year of publication.

The **ABCD/UKKA** [27] Hypertension in diabetes guidelines suggest strict BP control (target < 130/80mmHg) and use of an ACEI (ARB if not tolerated) as first choice antihypertensive agents in those with DKD stages 1–5 and urinary ACR > 30 mg/mmol. After reviewing the limited evidence available at the time for both steroidal and non-steroidal MRAs, ABCD/UKKA suggested that it may be reasonable to consider adding in an aldosterone antagonist (possibly non-steroidal), particularly for people with an eGFR > 60 ml/min/1.73m^2 and a serum potassium of < 5 mmol with worsening albuminuria despite being on a maximal dose of ACEI or ARB.

KDIGO (Kidney Disease Improving Global Outcomes) [28] however are more specific and highlight that non-steroidal MRAs are most appropriate for people with T2DM who are at high risk of DKD progression and cardiovascular events as demonstrated by persistent albuminuria despite other standard of care therapies (ACE/ARB) based on high-quality evidence from FIDELIO- DKD and FIGARO – DKD studies. They suggest nonsteroidal MRA fineronone (with proven kidney or cardiovascular benefits) for people with T2DM, an eGFR more than or equal to 25 ml/min/1.73m^2, normal potassium concentration and albuminuria despite maximum tolerated dose of RAASi (2A).

They state that for people with T2D and DKD, both a RAASi and an SGLT2i should generally be prescribed prior to initiating a non-steroidal MRA. However, finerenone may be added to a RAASi alone for people who do not tolerate or are not candidates for an SGLT2i.

With regards to managing hyperkalemia, they suggest selecting people with consistently normal serum potassium concentration (< 5 mmol) and to monitor serum potassium regularly after initiation of a non-steroidal MRA (1 month initially and every 4 monthly thereafter) [28].

American Diabetes Association (ADA) [29, 31] - Standards of Medical Care in Diabetes 2024 recommend an evidence-based approach to reduce risks of microvascular outcomes, including kidney, retinopathy, neurologic, and cardiovascular complications. They have updated their guidance to include evidence from trials in people with type 2 diabetes on heart failure, cardiovascular, and chronic kidney disease outcomes. These include Empagliflozin Outcome Trial in people with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) [30], Symptoms and Functional Status in Subjects With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF) [32] and the FIDELIO-DKD and FIGARO-DKD studies [24].

This update states that for people with type 2 diabetes and CKD treated with maximum tolerated doses of ACEi or ARBs, addition of non-steroidal MRA finerenone should be considered to improve Cardiovascular (CV) outcomes and reduce the risk of Chronic Kidney Disease (CKD) progression, with potassium monitoring (Grade A). They also mention considering use of SGLT2 inhibitors additionally for CV risk reduction when eGFR and urinary albumin creatinine are ≥ 25 mL/min/1.73 m [2] or ≥ 300 mg/g, respectively (Grade A). For those who are unable to use an SGLT2 inhibitor, finerenone is recommended to reduce DKD progression and CV events (Grade A).

They recommend the use of a non-steroidal MRA to reduce cardiovascular events and CKD progression (if eGFR is ≥ 25 mL/min/1.73 m [2]) with potassium monitoring in people with CKD and albuminuria, given the increased risk for cardiovascular events and CKD progression.

We have used the UKKA grading system which is defined in the national guideline manual and is consistent with the KDIGO approach to assessing the strength of evidence and the quality of evidence (Table 1).

Based on the significant on-going residual renal and cardiovascular risk in people with T2DM and DKD with persistent albuminuria, and the strong evidence of protection offered by the addition of finerenone (from the

Table 1 UKKA grading system for strength of evidence and evidence quality (https://www.ukkidney.org/health-professionals/guidelines/guidelines-commentaries)

Level of evidence	Evidence quality
• Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients (i.e. recommendations) • Grade 2 recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain (suggestions)	• Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomized controlled trials, or overwhelming evidence of some other sort. • Grade B evidence means moderate-quality evidence from randomized trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength. • Grade C evidence means low-quality evidence from observational studies, or from controlled trials with several very serious limitations. • Grade D evidence is based only on case studies or expert opinion.

FIDELIO-DKD, and FIGARO-DKD studies) [24], **our recommendations are**:

- In people with T2DM and DKD who have persistent albuminuria (ACR > 30 mg/mmol) despite use of maximum tolerated dose of RAASi and SGLT2i, consider addition of finerenone to reduce the risk of adverse kidney and cardiovascular outcomes [33] (Grade 1 A).
- Fineronone can be used if eGFR is more than or equal to 25 ml/min/1.73m^2 and the potassium concentration is < 5 mmol/L. (Grade 2A)
- Finerenone can be used either as a second line drug in addition to ACEi or ARB (if SGLT2i not tolerated or contraindicated) or as part of third line therapy in addition to ACEi/ARB + SGLT2i. (Grade 2D)
- There is currently no evidence to support use of finerenone in people without proteinuria (Grade 2 A).

Dose

- Initiate finerenone 20 mg once daily if eGFR ≥ 60 mL/min/1.73 m2. (Grade 2 A)
- Initiate finerenone 10 mg once daily if eGFR between 25 and 59 mL/min/1.73 m2. (Grade 2B)

Recommendation for management of hyperkalemia [29](Grade 2B)

Initiate finerenone

If K < 4.8 mmol/L.

- 10 mg daily if eGFR < 60 ml/min/1.73 m2.
- 20 mg daily if eGFR > 60 ml/min/1.73 m2.
- Monitor K at 1 month after starting treatment and every 4 months thereafter.
- Restart 10 mg daily if previously held for hyperkalemia and potassium now < 5.0 mmol/L.

Monitoring finerenone

If K 4.9–5.5 mmol/l.

- Continue finerenone 10 or 20 mg daily as per eGFR.
- Monitor K every 4 months.

If K > 5.5 mmol/L.

- Discontinue finerenone.
- Consider adjustment to diet or concomitant medications.
- Recheck K in 3 days' time.

Consider reinitiating on 10 mg/day dose when K < 5 mmol/L.

Hyperkalemia should be seen as a predictable and manageable complication of the use of these agents as it is in the use of inhibitors of the renin angiotensin system. Good practice in relation to reducing the risks of hyperkalemia are described in the KDIGO guideline on the management of diabetes in CKD [29]. In particular, we suggest that non dietary causes of hyperkalemia such as constipation, acidosis and poorly controlled diabetes should be addressed. Adjustment to diet should be advised in the least restrictive way and not at the expense of a healthy balanced diet. Diets rich in fruits and vegetables are associated with a reduced risk of CKD and better survival in those with CKD [34–36]. Furthermore, it is highlighted that NICE have now approved the use of new potassium binders where hyperkalaemia impairs the ability of clinicians to maximise therapy with inhibitors of the renin angiotensin system [37, 38].

Conclusion

Despite currently available interventions and advances in treatment, people with type 2 diabetes continue to have unmet needs and remain at risk of diabetic kidney disease and adverse cardiovascular outcomes. In patients with T2DM, the unique non-steroidal MRA finerenone is a welcome addition and has shown significant effects on reducing the risk of progression of kidney disease as well as cardiovascular events. The FIDELIO-DKD and FIGARO-DKD trials have clearly demonstrated the renal and cardiovascular benefits of finerenone on background RAAS blockade therapy. The associated risk of hyperkalemia is much lower compared with conventional steroidal MRA. Current evidence suggests that finerenone either as second line or third line post RAAS blockade and or SGLT2i use could be beneficial in delaying

the progression of DKD through an additive beneficial action.

Most specialist societies have incorporated a strategy for use of finerenone in their guidelines and we have produced a consensus statement on behalf of ABCD-UKKA to guide practicing clinicians on their evidence base and usability. This rapid emergence and evidence base of a new therapeutic option in the armamentarium for DKD management is exciting, and now more than ever, clinicians have the opportunity to tailor therapy to the individual needs of their DKD patients.

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Not applicable.

Consent for publication
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Competing interests
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AF has attended drug advisory boards of Boehringer Ingleheim, AstraZeneca, NAPP, Novo Nordisk, MSD, VP UK.
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