Finerenone in the management of Diabetic Kidney Disease:

A consensus statement by the Association of British Clinical Diabetologists and UK Kidney Association

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Background

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 GFR) is an indicator of significant cardiovascular morbidity. [1]

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 GFR[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 CKD, 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.

Current management of DKD

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 (RAASi).[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 progression. However, even taking the two primary kidney studies involving SGLT2i which include CREDENCE[10] and DAPA CKD[11] where SGLT2i was added onto standard of care which included the use of RAASi, 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 or non-steroidal mineralocorticoid receptors antagonists

In 1943, the role of mineralocorticoids in relation to damage to kidney and heart tissue was demonstrated[12] and in 1999, spironolactone was shown to reduce mortality by 30% in people with heart failure.[13] This was followed by demonstration of mortality benefits post myocardial infarction and in people with mild heart failure [15 to 24%] with eplerenone in 2003 and 2011.[14,15]

Finerenone, is a selective nonsteroidal MRA which is metabolized predominantly in the liver with minimal excretion via the kidneys. At a dose of 10 mg, finerenone has been shown to be equivalent to 25 to 50 mg of spironolactone in reducing BNP and albuminuria but with less hyperkalemia [5% versus 12%] in 372 subjects of HFrEF and CKD.[16] 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%].[17]

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 GFR by 18% compared to standard of care in 5734 DKD subjects with urine ACR 30-300 mg/g and eGFR 25-60ml/min and diabetic retinopathy; or DKD with ACR 300-5000 and eGFR of 25-75 ml/Min/1.73m2.[18]

Subsequently in another large multicenter trial FIGARO, finerenone was shown to reduce the risk of MI, CVA, HF admission by 17% compared to placebo in 7437 DKD subjects with urine ACR 30-300 mg/g and eGFR 25-60ml/min and diabetic retinopathy; or DKD with ACR 300-5000 and eGFR of 25-75 ml/Min/1.73m2. Hyperkalemia with potassium >5.5 mmol/L was seen on 11% versus 5%.[19] In an analysis of the FIGARO-DKD study, finerenone reduced incident HF HR 0.68(0.50-0.93).[20]

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 SGLT 2inhibitors 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 anSGLT2i). A post-hoc analysis assessing this small subgroup suggested no difference in response to finerenone.[21] 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, HR 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 hyperfiltration while finerenone is believed to work via inhibiting the MRA pathway for inflammation and fibrosis. 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 2 combination therapy trials due to be reported in late 2023 – the MIRACLE[23] and CONFIDENCE[24] trials.

MIRACLE study will evaluate the efficacy and safety of dapagliflozin and finerenone 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/1.73 m^2[23]. **CONFIDENCE** study will demonstrate that dual initiation of finerenone and empagliflozin is superior for reducing urinary albumin to creatinine ratio compared with either empagliflozin or finerenone alone in patients with CKD and T2D[24].

Hyperkalaemia with finerenone

In the FIDELIO study over 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 hyperkalaemia

[potassium>5.5 mmol/L]; 126 of 2802 (4.5%) and 38 of 2796 (1.4%) subjects developed moderate hyperkalemia [potassium>6 mmol/L].[25]

At baseline 99% of the population was on ACEi/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/1.3m2 or 20 mg if eGFR ≥60 ml/min.1.73m2. 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 hours 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 hyperkalaemia event soon after a previous event (provided the only explanation for the recurring hyperkalaemia 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 hyperkalaemia; 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 hyperkalaemia. Risk of mild hyperkalaemia increased 1.5 and 2 times as eGFR dropped below 45 and 25 ml/min per 1.73 m2, compared with an eGFR greater than 60 ml/min per 1.73 m2.

The role of MRA in managing DKD - Current national and international guidelines

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

The **ABCD/UKKA** 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 CKD stages 1-5 and urinary ACR >30 mg/mmol. After reviewing the limited evidence available at the time for both steroidal and non-steroidal mineralocorticoid receptor antagonists (MRAs), ABCD/UKAA suggested that it may be reasonable to consider adding in an aldosterone antagonist (possibly non-steroidal), particularly for people with an eGFR of greater than 60 ml/min/1.73m2 and a serum potassium of less than 5 mmol with worsening albuminuria despite being on a maximal dose of ACEI or ARB.[26]

KDIGO Kidney (Disease Improving Global Outcomes) however are more specific and highlight that non-steroidal MRAs are most appropriate for people with T2DM who are at high risk of CKD 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/1.73m2, normal potassium concentration and albuminuria despite maximum tolerated dose of RAS inhibitor (2A).

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

With regards to managing hyperkalaemia, 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).[27]

American Diabetes Association (ADA) - Standards of Medical Care in Diabetes 2022 have updated their guidance to include evidence from trials of medication effects in people with

type 2 diabetes on heart failure, cardiovascular, and chronic kidney disease outcomes, including Empagliflozin Outcome Trial in people with Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Subjects With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF)[28], Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD), and Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD), and to remove information associated with the discontinued trial Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides In people With diabetes (PROMINENT). The SGLT2 inhibitor (dapagliflozin) in heart failure with preserved ejection fraction: a multi-centre randomized trial: 12 weeks of dapagliflozin treatment significantly improved patient-reported symptoms, physical limitations and exercise function and was well tolerated in chronic HFpEF.[28]

This update states that for people with type 2 diabetes and CKD treated with maximum tolerated doses of ACE inhibitors or ARBs, addition of non-steroidal MRA finerenone should be considered to improve CV outcomes and reduce the risk of 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 m2 or ≥ 300 mg/g, respectively (Grade A). For those who are unable to use an SGLT2 inhibitor, (finerenone) is recommended to reduce CKD progression and CV events (Grade A).[29,30]

Our recommendations:

We have used the UKKA grading system for recommendations' strength and evidence quality

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 aweaker recommendation,where the risks and benefits are more closely balanced or are more uncertain (i.e. 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 otherstudy designs with special strength. • Grade C evidence means low-quality evidence from observational studies, or from controlled trials with severalvery serious limitations. • Grade D evidence is based only on case studies or expert opinion.

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 FIDELIO-DKD, and FIGARO-DKD studies)[27]

We suggest:

- In people with T2DM and CKDwho have persistent albuminuria (ACR>30 mg/mmol) despite use of maximum tolerated dose of RASi and SGLT2i, consider addition of finerenone to reduce the risk of adverse kidney and cardiovascular outcomes. (Grade 2A or 2B)
- Fineronone can be used if eGFR is more than or equal to 25 ml/min/1.73m2 and normal potassium concentration (< 5 mmol/L). (Grade 2A)
    - Use 20mg once daily if eGFR ≥60 mL/min/1.73 m2. (Grade 2A)
    - Use 10 mg once daily if eGFR between 25 to 59 mL/min/1.73 m2. (Grade 2B)
    - 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)

Recommendation for management of Hyperkalaemia[27] (Grade 2B)

If K < 5.0 mmol/L

Initiate Finerenone

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

If K 5.0 -5.5 mmol/l

- Continue Finerenone 10 or 20 mg daily
- 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 10 mg dose when K < 5 mmol/L

Hyperkalaemia should be seen as a predictable and manageable complications 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 hyperkalaemia are described in the KDIGO guideline on the management of diabetes in CKD[27]. 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[31,32].

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