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EDITORIAL

Finerenone: Do We Really Need an Additional Therapy in Type 2 Diabetes Mellitus and Kidney Disease?

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Abstract

Patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM) face considerable cardiorenal morbidity and mortality despite existing therapies. Recent clinical trials demonstrate the efficacy of finerenone, a novel non-steroidal mineralocorticoid receptor antagonist, in reducing adverse renal and cardiovascular outcomes. This editorial briefly reviews the evidence and its implications for clinical practice, advocating the use of finerenone in these high-risk patients in combination with currently established treatment agents.

Key words: chronic kidney disease; type 2 diabetes; diabetic nephropathy

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Introduction

Diabetes mellitus (DM) is a disease of increasing global prevalence and poses a major public health concern with type 2 diabetes mellitus (T2DM) accounting for greater than 90% of the total cases. The International Diabetes Federation (2021) estimates that over 780 million people worldwide will be affected by DM in the next 20 years, causing a global healthcare expenditure of more than 1 trillion USD. These surging numbers have a direct multi-fold effect on major health complications of DM, particularly chronic kidney disease (CKD), with DM contributing up to 40–50% of all CKD cases (International Diabetes Federation, 2023). The risks of multiple adverse outcomes including cardiovascular (CV) events, acute kidney injury (AKI), end stage renal disease (ESRD), and death escalate with the severity and stage of CKD, defined by the decline in estimated glomerular filtration rate (eGFR) and/or increase in albuminuria, both of which can be prominent findings of diabetic kidney disease (DKD) (Alicic et al, 2017; Writing Group for the CKD Prognosis Consortium, 2023). This prompts the need for better treatment of diabetes-related CKD in its early stages (International Diabetes Federation, 2023).

For several years, focus on good glycaemic, lipid, and blood pressure control, and blockade of the renin-angiotensin system (RAS) have been the main proven cardiorenal protective management of CKD in T2DM (Kidney Disease: Improving Global Outcomes CKD Work Group, 2013; Kidney Disease: Improving Global Outcomes Diabetes Work Group, 2022; Solis-Herrera and Triplitt, 2024; Zhang

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et al, 2023). In recent years, there has been an increased move towards the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA) as additional therapies, retarding progression of CKD, whilst abrogating CV events (American Diabetes Association Professional Practice Committee, 2022; Cosentino et al, 2020; Kidney Disease: Improving Global Outcomes Diabetes Work Group, 2022; Zhang et al, 2023).

What is Finerenone and the Clinical Evidence for Its Use in Patients with T2DM and CKD?

The overactivation of the mineralocorticoid receptor (MR) is implicated in driving inflammation and fibrosis in the heart, kidneys, and vasculature, with a direct role in sodium retention, vasoconstriction, and cardiomyocyte electrical remodelling, all of which can exacerbate CKD and CV disease progression (Agarwal et al, 2020; Agarwal et al, 2021; Solis-Herrera and Triplitt, 2024). Finerenone, a novel, selective, "nonsteroidal" MR antagonist (nsMRA), blocks MR-mediated overactivation and is the first approved nsMRA for patients with T2DM and CKD.

Despite existing steroidal MRAs (sMRAs) such as spironolactone and eplerenone, finerenone is known to have a significantly higher affinity for the MR with much more potent anti-inflammatory and antifibrotic effects, but lesser risk of hyperkalaemia and AKI when used in concordance with angiotensin-converting enzyme inhibitors (ACEi) or angiotension receptor blockers (ARBs) for the management of T2DM with albuminuria and CKD (Agarwal et al, 2020; Agarwal et al, 2021; Bakris et al, 2015; Solis-Herrera and Triplitt, 2024; Whitlock et al, 2023). In addition, finerenone accumulates in the kidney and heart tissue in a unified manner, a contrasting find to steroidal MRAs (sMRAs) which preferentially saturate the kidneys explaining more cardioprotection and less hyperkalaemia (Agarwal et al, 2020; Agarwal et al, 2021; Solis-Herrera and Triplitt, 2024). The phase II Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) study involving over 800 patients with T2DM and albuminuria demonstrated this; whilst showing a dose-dependent reduction in urinary albumin-creatinine ratio (uACR) in the finerenone arm. Minimal adverse effect on eGFR, potassium levels, and blood pressure were noted despite patients already established on an ACEi or ARB (Bakris et al, 2015).

The FInerenone in reducing kiDnEy faiLure and disease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) and FInerenone in reducing cArdiovascular mortality and mOrbidity in Diabetic Kidney Disease (FIGARO-DKD) were multinational, randomised, placebo-controlled phase III trials jointly representing the largest (n = 5674 and n = 7354, respectively) cardiorenal outcomes program in CKD and T2DM to date. These trials assessed the efficacy and safety of finerenone when added to maximal tolerated RAS inhibitors (RASi) and showed a marked reduction in CKD progression and CV events in patients with diverse CKD and albuminuric T2DM (Bakris et al, 2020; Pitt et al, 2021). Although conducted independently, the complimentary nature of these two studies meant that the composite primary endpoints of one study was the key secondary endpoints of the other,

collectively creating a large dataset particularly comprising of a high albuminuria population (an independent risk factor of CV and all-cause mortality). Together, they provided robust evidence supporting finerenone's efficacy in reducing clinically significant outcomes in a high-risk population which was highlighted by the FIDELITY Pooled Analysis (n = 13,036) (Agarwal et al, 2022). Both FIDELIO-DKD and FIGARO-DKD demonstrated that finerenone reduced kidney failure, defined as a ≥40% decrease in eGFR from baseline, and renal death (significant relative risk reduction [RRR] of 23% as per FIDELITY). More importantly, there was significantly lower CV adverse outcomes, including CV-related death, non-fatal myocardial infarction (MI)/stroke, and hospitalisation for heart failure (HF) with finerenone versus placebo (14% in the composite cardiovascular endpoints and 22% RRR in HF-related hospitalization as per FIDELITY). Finerenone was well tolerated with low rates of kidney-related and serious AEs (adverse events) occurring similarly between the treatment and placebo groups. Expectantly hyperkalaemia was higher with finerenone although discontinuation rates were low (Agarwal et al, 2022; Bakris et al, 2020; Pitt et al, 2021).

A recent press release from the European Society of Cardiology showcased the pooled FINE-HEART analysis including data from FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF, focusing on patients with CKD and T2DM as well as HF. The analysis included 18,991 participants, revealing lower CV death in the finerenone group compared to placebo with a reduced all-cause mortality and hospitalisations for HF. This analysis highlighted a potential role for finerenone in the broader cardio-kidney-metabolic spectrum (Vaduganathan et al, 2024).

Using Finerenone in Clinical Practice—The Need to Promote Combination Therapy

Whilst current evidence supports finerenone's benefits in CKD and T2DM, questions remain regarding the potential additive effects of combining finerenone with the already established use of SGLT2i, because the rates of use in FIDELIO and FIDELITY. The ongoing CONFIDENCE (COmbinatioN effect of FInerenone anD EmpaglifloziN) trial aims to assess whether dual therapy with finerenone and empagliflozin is superior in reducing uACR compared to either agent alone (Green et al, 2023). This may establish a foundation for simultaneous therapies that could further slow kidney disease progression and enhance long-term outcomes in patients with CKD and type 2 diabetes (Georgianos et al, 2023).

Nevertheless, many national and international guidelines have already incorporated finerenone in the treatment algorithm for patients with T2DM and CKD ideally already established on RASi and SGLT2i (de Boer et al, 2022; Kidney Disease: Improving Global Outcomes Diabetes Work Group, 2022). Kidney Disease: Improving Global Outcomes Diabetes Work Group (2022) recommends finerenone if eGFR >25 mL/min/1.73 m^2, serum potassium is normal, and albuminuria (3 mg/mmol) remains present, despite maximal RASi with frequent serum potassium monitoring and dose adjustments. The Association of British Clinical Diabetologists and UK Kidney Association (ABCD-UKKA) consensus statement, further

supports the use of finerenone, highlighting its lower incidence of hyperkalaemia compared to sMRAs (Khine et al, 2024). The UK's National Institute for Clinical Excellence (NICE) guidance (TA877) recommends finerenone as an add-on therapy for adults with stage 3 and 4 CKD and albuminuria, only when combined with optimised standard care (National Institute for Health and Care Excellence, 2023). These recommendations align with the authors' opinion on stepwise approach to the management of patients with DKD (Fig. 1, https://medscape-uk.co/Hack-CKD, authors own work, reference for this infographic).

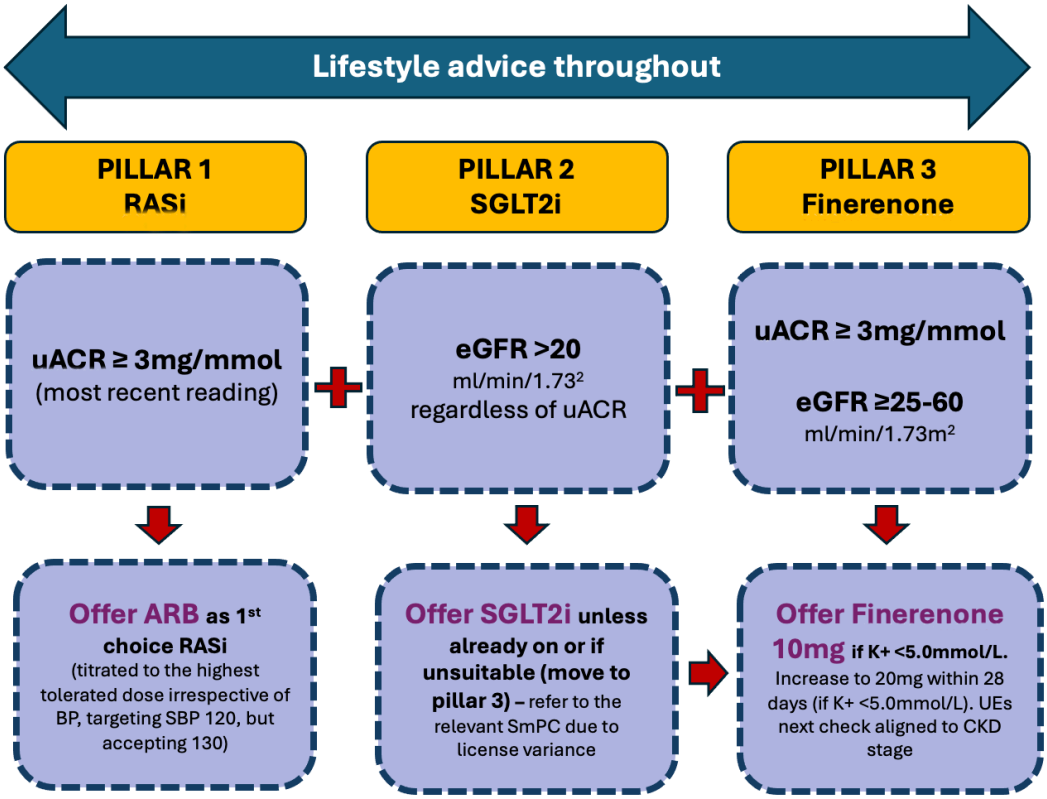

Fig. 1. A three pillars approach treating CKD & T2DM. ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RASi, Renin Angiotensin System inhibition; SBP, systolic blood pressure; SmPC, summary of product characteristics; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus; uACR, urine albumin-creatinine ratio; UE, urea and electrolytes.

In summary, treatment with the addition of nsMRA finerenone after maximal RAS blockade and SGLT2i introduction has the potential of significantly reducing cardiorenal events and improving overall survival in type 2 diabetics with CKD. Combination therapies with nsMRA, SGLT2i, and GLP-1 RA with the foundation therapy of RASi can now be deemed the key "pillars" of therapy for CKD and T2DM.

Key Points

- Finerenone significantly reduces the risk of CKD progression and cardiovascular events in patients with T2DM and CKD, as evidenced by FIDELIO-DKD and FIGARO-DKD trials.
- The FIDELITY and FINE-HEART integrated pooled analysis confirms the consistent efficacy of finerenone across a broad spectrum of CKD patients.
- The CONFIDENCE trial may elucidate the benefits of combining finerenone with SGLT2 inhibitors for enhanced renal and cardiovascular protection.
- The American Diabetes Association (ADA), Kidney Disease: Improving Global Outcomes (KDIGO), UKKA and NICE TA877, recommend finerenone as an add-on therapy to optimize standard care.
- Adding Finerenone, with attendant monitoring of potassium and remembering the role of potassium binders to help avoid hyperkalaemia and to keep patients on proven therapy for longer.

Availability of Data and Materials

Not applicable.

Author Contributions

DM, NG and WH contributed to the conception, drafting, and important revision of the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

DM and NG declared no conflicts of interest. WH accepted sponsorship to attend European Renal Congress from Bayer (Finerenone distributors), instead of us-

ing NHS funding and was compliant with the ABPI code of conduct and is deemed non-personal interest. Like all experts, he has also received speaker fees and provided consultancy for other pharmaceutical companies.

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