Finerenone is a novel non-steroidal selective mineralocorticoid receptor antagonist (MRA) with quite different pharmacokinetics and clinical effects to the steroid MRAs spironolactone and eplerenone. It exhibits milder antihypertensive effects, lower rates of hyperkalemia and fewer steroid-induced adverse effects. The drug has been evaluated in complementary studies 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) which investigated kidney and cardiovascular outcomes in patients with type 2 diabetes (T2DM) and CKD. The FIDELIO-DKD trial primarily focused on the treatment effect of finerenone on kidney endpoints, whereas the FIGARO-DKD trial aimed to detect its impact on cardiovascular endpoints. Together, they form the largest cardiorenal outcomes programme type 2 diabetes-related CKD to date. Recently, the combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis (FIDELITY) pooled these complementary studies to conduct an individual patient-level analysis across a broad range of CKD and offer reassurance regarding outcomes, safety and efficacy of finerenone in comparison to placebo.

The primary endpoints in the FIDELITY pooled analysis were time to kidney failure, sustained 57% or more decrease in estimated glomerular filtration rate (eGFR) from baseline or kidney death. Among 13,026 patients with a median follow-up of three years, finerenone significantly reduced the hazard of a kidney composite outcome by 23% versus placebo, including a reduction in the risk of dialysis by 20%. The study also indicated a consistent and significant cardiovascular benefit with an observed risk reduction of 14% regarding hospitalization for heart failure. The positive outcomes were predominantly noted in terms of heart failure, with encouraging decreasing rates of both cardiovascular death and non-fatal myocardial infarction. All-cause and cardiovascular mortality were decreased in patients who remained on treatment, thus emphasizing the need of following the prescribed treatment regimen.

Finerenone and atherosclerosis

Similar to finerenone, the sodium-glucose transport protein 2 (SGLT2) inhibitors also exhibited major benefits in reducing new-onset heart failure and cardiovascular death. These results raise the question of whether the evolving concept of cardiovascular disease poses a new standpoint for treatment or whether the limit of what can be accomplished with statins has already been reached. The evidence suggests that statins have made significant advances in reducing atherosclerotic damage, emphasizing the strategies for improving other aspects of cardiovascular health. However, recent experimental data imply that the combination of SGLT2 inhibitors and finerenone can reduce atherosclerotic disease even further. Moreover, the progress made.
with atherosclerotic disease in recent years due to interventions such as statins, anti-hypertensive therapy, and smoking cessation has led to increased longevity, which, in turn, resulted in an increased incidence of heart and kidney failure. Therefore, the availability of multiple treatment options for these conditions is important.

Finerenone across the spectrum of glycemic control and with or without the use of antidiabetic agents

The FIDELITY trial offered a unique opportunity to explore the efficacy of finerenone across a range of subgroups within a large patient population. Nephrologists and endocrinologists now have access to several compelling therapeutic options, including renin-angiotensin system (RAS) blockade, SGLT2 inhibitors, and finerenone, with glucagon-like peptide receptor agonists (GLP1-RA) potentially joining their ranks in the near future. A sub-analysis revealed that finerenone’s beneficial effects on cardiovascular and kidney outcomes were consistent across patients with varying levels of haemoglobin A1C at baseline. Given that finerenone is not a glucose-lowering drug, this suggests that it may be effective in diabetic patients regardless of glycaemic control.

SGLT2 inhibitors have recently been included in the guidelines for CKD management in patients with diabetes. For this reason, the FIDELITY analysis was extended to include individuals treated with an SGLT2 inhibitor at baseline and, according to the results, finerenone reduced the risk of cardiovascular and kidney composite outcomes irrespective of SGLT2 inhibitor use. These findings suggest that there may be additional benefits to using finerenone without the simultaneous use of SGLT2i, but there are wide confidence intervals. Only a small proportion of patients were treated with an SGLT2i at baseline, but benefits were still observed. For instance, finerenone had the same effect on albuminuria regardless of whether patients were on GLP-1RA or SGLT2i at baseline, and the use of SGLT2i throughout the trial did not significantly interact with the effects of finerenone. An ongoing trial is currently investigating the effects of SGLT2i, finerenone, and their combination, and the results are expected soon. An additional analysis was conducted to assess results from individuals who received treatment with a GLP-1RA at baseline. Although only 8% of patients used GLP-1RA, this subgroup still consisted of more than 900 individuals due to the size of the FIDELITY analysis. Results showed a similar beneficial effect of finerenone regardless of GLP-1RA use, with no significant interaction observed for either cardiovascular or kidney composite outcomes. Therefore, it is possible that patients on a GLP-1RA treatment would still receive the added benefit of finerenone. Additionally, finerenone reduced the risk of cardiovascular and kidney composite outcomes compared to placebo regardless of GLP-1RA use at any time during the study.

Finerenone and diabetic eye disease

Besides CKD, diabetic retinopathy is also a major form of microvascular complication in patients with diabetes. The recently published ReFineDR study suggested the potential benefits of finerenone in the delay of progression of non-proliferative diabetic retinopathy and prevention of required ocular interventions. These results corroborate the findings from the sub-analysis of the FIDELITY trial. Nevertheless, these findings do not suggest that finerenone could be used as a treatment option for diabetic retinopathy, but advocate that further analysis or studies may be warranted.

Jerome et al. used a murine model to evaluate the effects of finerenone on vascular pathology and inflammation in diabetic and neovascular retinopathy by administering finerenone or the angiotensin-converting enzyme (ACE) inhibitor perindopril to diabetic and hypertensive transgenic rats overexpressing the RAS activity for 12 weeks. Among diabetic rats, both treatments reduced systolic blood pressure (SBP), but only finerenone lowered vascular endothelial growth factor, intercellular adhesion molecule, and interleukin-1β. Finerenone also reduced neovascularization, vascular leakage, and microglial density, and increased regulatory T cells in the blood, spleen, and retina. In the context of the FIDELIO-DKD and FIGARO-DKD these findings indicate the potential of finerenone as an effective oral treatment for diabetic retinopathy.

Figure 2.
Finerenone reduces the risk of cardiovascular and renal outcomes regardless of SGLT2i

Figure 3.
ReFine DR study: time to vision-threatening complications in patients with diabetes treated with finerenone or placebo
Finerenone across the spectrum of BP control

The FIDELIO-DKD trial also considered the relationship between office SBP and cardiorenal outcomes in patients with type 2 diabetes and CKD treated with finerenone on top of optimized RAS blockade. Apparently, finerenone reduced office SBP across the baseline quartiles and patients with lower baseline office SBP and greater SBP decline from baseline exhibited better cardiorenal outcomes. Based on these results, finerenone should be considered in patients with diabetic kidney disease, irrespective of their baseline office SBP levels, due to its beneficial renal and cardiovascular effects.

Another study indirectly compared the effect of finerenone vs spironolactone on SBP and serum potassium in a population with treatment-resistant hypertension and moderate to advanced CKD. A sub-group from the FIDELITY trial was matched to the AMBER trial eligibility criteria. Results showed that finerenone reduced sPB, albeit to a lesser extent than spironolactone, and resulted in fewer episodes of hyperkalaemia.

The Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) trial assessed the effects of finerenone on 24-h ambulatory BP in patients with CKD and type 2 diabetes. In this study, finerenone reduced 24-hour, daytime, and night-time SBP compared with a placebo. Changes in BP were persistent over 24 hours with a single morning drug dose, suggesting that finerenone has hemodynamic effects in patients with CKD and type 2 diabetes that are unlikely to be attributable to its pharmacokinetic properties. These hemodynamic effects provide a biological basis for a greater incidence of hypotension, a lower incidence of hypertension, and an early separation in curves of the time to the first cardiovascular event seen with finerenone.

**KEY POINTS**

1. The FIDELIO-DKD and FIGARO-DKD trials showed a clear reduction in both primary renal and co-primary cardiovascular endpoints with finerenone.

2. The FIDELITY trial demonstrated consistent benefits of finerenone across patients with varying levels of glycemic control.

3. The combination of SGLT2 inhibitors and finerenone appears to produce even more favourable outcomes.

4. The decrease of vascular pathology and inflammation in diabetic and neovascular retinopathy with finerenone treatment identifies a pathway worth exploring.

5. The FIDELITY trial demonstrated consistent benefits of finerenone across patients with varying levels of BP control.

Figure 4.
Finerenone effects on blood pressure – FIDELITY-TRH and AMBER studies

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Further readings


