Finerenone in chronic kidney disease and type 2 diabetes: the known and the unknown

Fu, E.L.; Kutz, A.; Desai, R.J.

nephron endowment, and estimation not just of baseline estimated glomerular filtration rate but also of the presence of hyperfiltration and the level of renal functional reserve (see Figure 1 for factors that contribute to the outcome). Recent work indicates that kidney growth is useful as a measure, and that metric has been helpful in the assessment of risk in other conditions such as polycystic kidney disease and renal hypodysplasia. Renal endowment—that is, nephron number, has proven difficult to measure noninvasively, but there are promising new techniques under development.[9] In addition, as a field, we would do well to assess renal functional reserve prospectively, using standardized protein loads or amino acid infusion, or as-yet undeveloped methodology.[10] Only if we obtain better prospective data will we know which children and adolescents with an SFK to watch closely. Doing so would have a good chance of decreasing the prevalence of advanced CKD, which would go a long way to preventing the need for dialysis and transplantation.

DISCLOSURE
The author declared no competing interests.

REFERENCES

1. Doroshow LW, Abeshouse BS. Congenital unilateral solitary kidney: report of 37 cases and a review of the literature. *Urol Surv*. 1961;11:219–229.
2. Sammon JD, Zhue G, Sood A, et al. Pediatric nephrectomy: incidence, indications and use of minimally invasive techniques. *J Urol*. 2014;191:764–770.
3. Westland R, Schreuder MF, Bökenkamp A, et al. Renal injury in children with a solitary functioning kidney—the KIMONO study. *Nephrol Dial Transplant*. 2011;26:1533–1541.
4. Groen in 't Woud S, Roeleveld N, Westland R, et al. Uncovering risk factors for kidney injury in children with a solitary functioning kidney. *Kidney Int*. 2023;103:156–165.
5. Van Rooij IALM, van der Zanden LFM, Bongers EMHF, et al. AGORA, a data- and biobank for birth defects and childhood cancer. *Birth Defects Res A Clin Mol Teratol*. 2016;106:675–684.
6. Groen In 't Woud S, Westland R, Feitz WFJ, et al. Clinical management of children with a congenital solitary functioning kidney: overview and recommendations. *Eur Urol Open Sci*. 2021;25:11–20.
7. Groen In 't Woud S, Gobino A, Roeleveld N, et al. Kidney injury rates after unilateral nephrectomy in childhood—a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2022;37:2457–2473.
8. Cochat P, Febvey O, Bacchetta J, et al. Towards adulthood with a solitary kidney. *Pediatr Nephrol*. 2019;34:2311–2323.
9. Bennett KM, Baldelomar EJ, Morozov D, et al. New imaging tolls to measure nephron number *in vivo*: opportunities for developmental nephrology. *J Dev Orig Health Dis*. 2021;12:179–183.
10. Jufar AH, Lankadeva YR, May CN, et al. Renal functional reserve: from physiological phenomenon to clinical biomarker and beyond. *Am J Physiol Regul Integr Comp Physiol*. 2020;319:R690–R702.

Finerenone in chronic kidney disease and type 2 diabetes: the known and the unknown

Edouard L. Fu[1], Alexander Kutz[1] and Rishi J. Desai[1]

The novel nonsteroidal mineralocorticoid receptor antagonist finerenone has been shown to reduce the risk of kidney and cardiovascular outcomes in patients with type 2 diabetes and chronic kidney disease. In this issue of *Kidney International*, Bakris *et al.* present new data on the kidney efficacy of finerenone across subgroups of estimated glomerular filtration rate and urinary albumin–to–creatinine ratio, as well as safety data. We attempt to place these results in context by discussing the benefits and risks of finerenone, as well as the generalizability of the study findings to routine care settings.

Kidney International (2023) **103,** 30–33; https://doi.org/10.1016/j.kint.2022.09.012

see clinical trial on page 196

Diabetes is the leading cause of end-stage kidney disease worldwide.[1] Identifying therapies that slow the progression of diabetic kidney disease is therefore of paramount importance. The 2020 Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Management in Chronic Kidney Disease (CKD) Guideline recommends the use of renin-angiotensin system inhibitors in patients with diabetes, hypertension, and albuminuria (i.e., persistent urinary albumin–to–creatinine ratio [UACR] ≥3 mg/mmol) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in patients with diabetes, CKD, and estimated glomerular filtration rate (eGFR) ≥30 ml/min per 1.73 m^2, to reduce the risk of CKD progression.[1]

Recently, 2 randomized trials have shown that the novel nonsteroidal mineralocorticoid receptor antagonist finerenone reduces the risk of kidney and cardiovascular outcomes in patients with type 2 diabetes and CKD: FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease).[2] FIDELIO-DKD enrolled 5674 patients with type 2 diabetes who had either (i) UACR ≥30–<300 mg/g, eGFR ≥25–<60 ml/min per

[1]*Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA*

Correspondence: *Edouard L. Fu, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont Street, Suite 3030, Boston, Massachusetts 02120, USA. E-mail: edfu@bwh.harvard.edu*

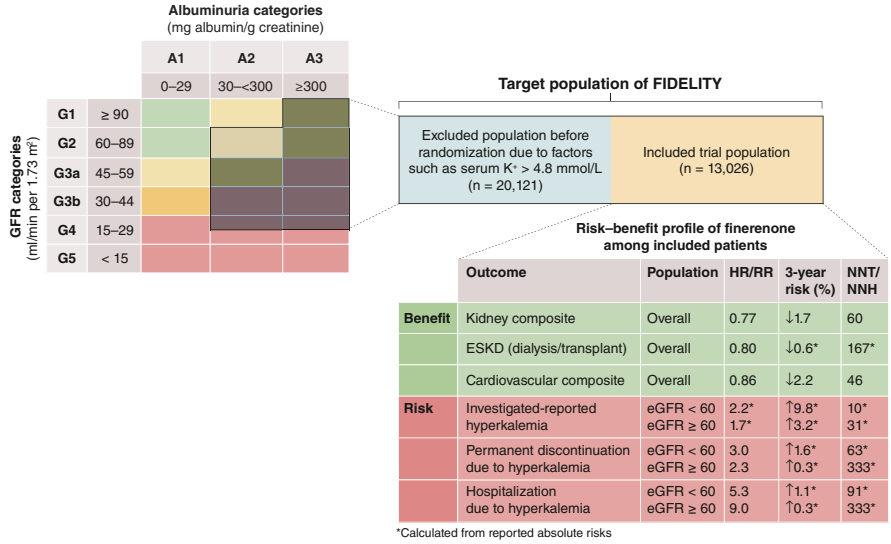

Figure 1 | Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis (FIDELITY)results in context. eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HR, hazard ratio; NNH, number needed to harm; NNT, number needed to treat; RR, risk ratio.

1.73 m^2, and diabetic nephropathy; or (ii) UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min per 1.73 m^2, and showed a reduction in the primary end point of kidney outcomes. FIGARO-DKD included 7352 patients with either (i) UACR ≥30–<300 mg/g and eGFR ≥25–<90 ml/min per 1.73 m^2; or (ii) UACR ≥300–≤5000 mg/g and eGFR ≥60 ml/min per 1.73 m^2, and showed a reduction in the primary cardiovascular outcome.

The participants from both trials were pooled and analyzed in FIDELITY (Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis). The population included in FIDELITY is shown in Figure 1. The aim of this prespecified individual participant analysis of 13,026 patients was to provide more precise estimates of the efficacy and safety of finerenone across the spectrum of patients with CKD and type 2 diabetes. In a recent publication of FIDELITY,[2] finerenone reduced the composite cardiovascular outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure during a median follow-up of 3.0 years, with a hazard ratio (HR) of 0.86 (95% confidence interval [CI], 0.78–0.95). This was primarily driven by a reduction in hospitalization for heart failure (HR, 0.78; 95% CI, 0.66–0.92). The absolute risk of the cardiovascular composite after 3 years was 2.2% lower for finerenone, translating to a number needed to treat of 46 patients for 3 years to prevent 1 composite cardiovascular outcome event.

Novelty and implications of this FIDELITY analysis

In this issue of *Kidney International*, Bakris *et al.* present additional detailed analyses of FIDELITY of great interest to the medical community.[3] The article provides important efficacy data of finerenone on kidney outcomes, as well as safety data on hyperkalemia. Results are presented for the overall population as well as relevant subgroups, including eGFR and UACR strata. In the overall population, finerenone reduced the kidney composite outcome, composed of kidney failure (i.e., dialysis, transplantation, or sustained decrease in eGFR to <15 ml/min per 1.73 m^2), sustained ≥57% eGFR decline, and kidney death, with an HR of 0.77 (95% CI, 0.67–0.88). Furthermore, all the individual components of the kidney composite end point were reduced, including end-stage kidney disease (HR, 0.80; 95% CI, 0.64–0.99; absolute risk, 0.6% lower), except for kidney death, which only occurred in 6 patients. The absolute risk for the kidney composite end point at 3 years was 1.7% lower for finerenone, translating to a number needed to treat of 60 patients for 3 years to prevent 1 kidney composite outcome event (Figure 1).

Prespecified subgroup analyses across strata of eGFR (≥60, 45–<60, and 25–<45 ml/min per 1.73 m^2) and baseline UACR (30–300 and ≥300 mg/g) did not show statistically significant heterogeneity in kidney benefits of finerenone. However, as appropriately stated by the authors, the effect had a high degree of uncertainty among those with UACR 30 to 300 mg/g, with an HR of 0.94 (95% CI, 0.60–1.47) for the composite kidney end point. Notably, whether the benefits extend to patients with UACR <30 mg/g or those with eGFR <25 ml/min per 1.73 m^2 remain unclear as these patients were underrepresented in FIDELITY because of prespecified exclusion criteria.

Of special relevance in this FIDELITY analysis are the safety results for the subgroup with eGFR <60 ml/min per 1.73 m^2, as previous observational studies have shown that low eGFR is a strong independent risk factor for developing hyperkalemia.[4] Among trial participants with eGFR <60 ml/min per 1.73 m^2, the

absolute risk for investigator-reported hyperkalemia was 18.3% in the finerenone arm versus 8.5% in the placebo arm, corresponding to a nearly 10% higher absolute risk for finerenone (Figure 1). The risk of permanent discontinuation due to hyperkalemia was 2.4% for finerenone versus 0.8% for placebo (risk ratio, 3.0; 95% CI, 2.0–4.5; absolute risk difference, 1.6%). Hyperkalemia leading to hospitalization was also higher for finerenone than for placebo (1.4% vs. 0.3%), with a risk ratio of 5.3 (95% CI, 2.7–10.4). Although absolute risks for hyperkalemia were lower for those with eGFR ≥60 ml/min per 1.73 m^2, relative risks were consistently higher for finerenone.

Given the clear signal for this important adverse event of hyperkalemia observed in FIDELITY, a nuanced discussion regarding the risk-benefit profile of finerenone is warranted. It is plausible to hypothesize that the substantial risk of hyperkalemia observed with finerenone in FIDELITY may in fact be an underestimation due to a key design feature that mandated exclusion of patients with serum potassium >4.8 mmol/L during either the run-in or screening visit. After up titrating to maximum tolerated labeled dose of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers during the run-in period, 6090 individuals of 29,604 (20.6%) with available potassium measurements were excluded during the run-in visit, and another 2527 (15.3%) of 18,075 potassium measurements were excluded at the screening visit.[3] As a result of this design decision, the randomized population in FIDELITY likely excluded patients more susceptible to hyperkalemia with finerenone. Among the included patients, the potassium management strategy in FIDELIO-DKD has previously been published, and potassium was measured at all scheduled study visits (month 1, month 4, and every 4 months thereafter), as well as after any treatment interruption or uptitration.[5] As highlighted in that previous publication, routine potassium monitoring, with temporary treatment interruption and dose reduction in the event of hyperkalemia, was necessary for the safe use of finerenone.[5] In routine care, such careful monitoring of potassium may not be practiced.[6] Taken together, these observations indicate that the hyperkalemia risk for finerenone is likely going to be a greater concern in the "real world" than in monitored trial settings. Observational studies of finerenone will need to further clarify the safety of finerenone in diverse populations under routine care, and the ongoing observational study FINE-REAL (a study called FINE-REAL to learn more about the use of the drug finerenone in a routine medical care setting) (NCT05348733) may partly fill this knowledge gap.

Outlook

If the risk of hyperkalemia in routine clinical care turns out to be substantial with finerenone, explicit strategies to mitigate this risk may be needed to optimize the risk-benefit tradeoff. In FIDELITY, 1.4% of patients (in both the finerenone and placebo groups) were receiving potassium binders at baseline; following study initiation, 7.3% of patients in the finerenone group and 4.4% of patients in the placebo group received potassium binders. In the recent Patiromer for the Management of Hyperkalemia in Participants Receiving RAASi Medications for the Treatment of Heart Failure (DIAMOND) trial, the potassium binder patiromer reduced mineralocorticoid receptor antagonist discontinuation or dose reduction, as well as the number of hyperkalemia events.[7] The strategy of prescribing medications to mitigate adverse effects of another drug may be questionable in routine clinical care as this further increases the prevalence of polypharmacy in this setting of mostly multimorbid patients, and may compromise adherence to other prescribed treatments.

The combination treatment of finerenone and SGLT-2i is also of special interest. The 2020 KDIGO Diabetes Management in CKD Guideline give SGLT-2i a class IA recommendation in the population included in the finerenone trials. Besides reducing cardiovascular and kidney outcomes, SGLT-2i have also been shown to lower potassium and reduce the risk of hyperkalemia.[8] Furthermore, among patients receiving SGLT-2i at baseline (n = 877; 6.7%), finerenone seemed to lower the cardiovascular composite (HR, 0.67; 95% CI, 0.42–1.07) and kidney composite (HR, 0.42; 95% CI, 0.16–1.08), albeit with broad CIs. Future studies should confirm these findings.

Conclusion

The current study by Bakris *et al.*,[3] published in this issue of *Kidney International*, provides useful and timely data on the kidney effectiveness and safety of finerenone, including risk of hyperkalemia. However, several knowledge gaps remain to be addressed, including the effectiveness and safety of finerenone among patients who were excluded from the trial, such as those with UACR <30 mg/g or those with higher propensity of developing hyperkalemia. Use of finerenone in patients with diabetes and CKD in routine care would require a careful balancing act between cardiorenal efficacy and safety, most notably hyperkalemia risk. Additional research providing insights into these gaps, including data from routine clinical practice, is keenly awaited.

DISCLOSURE

RJD reports serving as principal investigator on research grants to Brigham and Women's Hospital from Vertex, Novartis, and Bayer. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

ELF is supported by a Rubicon grant from the Netherlands Organization of Scientific Research (NWO). AK is supported by a Postdoc Mobility grant (P400PM 194479/1) from the Swiss National Science Foundation and by an educational grant from Novo Nordisk.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2020;98(4S):S1–S115.
2. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY

pooled analysis. *Eur Heart J*. 2022;43:474–484.
3. Bakris GL, Ruilope LM, Anker SD, et al. A prespecified exploratory analysis from FIDELITY examined finerenone use and kidney outcomes in patients with chronic kidney disease and type 2 diabetes. *Kidney Int*. 2023;103:196–206.
4. Nilsson E, Gasparini A, Arnlov J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol*. 2017;245:277–284.
5. Agarwal R, Joseph A, Anker SD, et al. Hyperkalemia risk with finerenone: results from the FIDELIO-DKD trial. *J Am Soc Nephrol*. 2022;33:225–237.
6. Shah KB, Rao K, Sawyer R, Gottlieb SS. The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. *J Am Coll Cardiol*. 2005;46:845–849.
7. Butler J, Anker SD, Lund LH, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. *Eur Heart J*. 2022;43:4362–4373.
8. Neuen BL, Oshima M, Agarwal R, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. *Circulation*. 2022;145:1460–1470.