Mineralocorticoid Receptor Antagonists in CKD: In Need of a Few Large Trials

David Collister and Michael Walsh

Only a handful of interventions are known to prevent the progression of chronic kidney disease (CKD) and the need for kidney replacement therapy. This exclusive list previously only featured angiotensin-converting enzyme inhibitors and angiotensin receptor blockers but recently was expanded to include sodium/glucose cotransporter 2 (SGLT2) inhibitors. These medications also reduce the risk of cardiovascular (CV) events in patients with kidney disease. Despite current, effective treatments, many patients will continue to face kidney failure and an excess of CV events, and the need for additional therapies remains.

Aldosterone is implicated in the pathogenesis of heart failure. Inhibiting the effects of aldosterone with mineralocorticoid receptor antagonists (MRAs) in patients with heart failure with reduced ejection fraction and after myocardial infarction (but all with largely preserved kidney function) decreases CV mortality and heart failure hospitalizations.[1] Aldosterone is also a potential mediator of kidney injury owing to its effects on endothelial activation, inflammation, and fibrosis and is an attractive therapeutic target in diabetic kidney disease. The shared relationship between mineralocorticoids, hearts, and kidneys was observed decades ago in animal experiments where salt-fed rats exposed to deoxycorticosterone developed heart failure and nephrosclerosis.[2] Later animal experiments demonstrated that blocking the effects of deoxycorticosterone with an MRA reduced adverse CV and kidney effects.[3,4]

The evidence from animal models and success in heart failure trials sparked interest in testing the efficacy and safety of MRAs to prevent kidney failure and CV events in patients with CKD, and many randomized controlled trials (RCTs) have now been performed in this population.

In a Cochrane review summary in this issue of *AJKD*, Chung et al[5] report an updated Cochrane systematic review and meta-analysis (previously published in 2014)[6] of 43 RCTs and quasi-RCTs with 5,279 patients (diabetic and nondiabetic) that compare MRAs to placebos or other antihypertensives in the setting of proteinuric CKD. Patients with estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2 or receiving dialysis were excluded. The evidence supporting an effect of MRAs on kidney failure, CV events, or mortality was inconclusive. Certainty in effects was generally downgraded, in accordance with the GRADE process, for both risk of bias (frequently owing to allocation methods) and imprecision. Of particular note, only 2 RCTs with 2 events contributed to the estimate of treatment effects on kidney failure, and only 3 RCTs with 4 events contributed to the estimate of treatment effects on mortality. To be fair, these trials were generally designed to inform the short-term effects of MRAs on laboratory parameters. It is not surprising then that the only outcomes with at least moderate certainty of an effect were for adverse effects including the increased risks of hyperkalemia, acute kidney injury, and gynecomastia. One could argue that given the large body of indirect evidence from heart failure and hypertension RCTs, these are known side effects of MRAs of which we were already highly certain. Despite the known adverse effects of MRAs, there remains hope of important kidney protective effects including attenuating loss of eGFR (mean difference, −3.00 [95% CI, −5.51 to −0.49] mL/min/1.73 m^2 at a median 3.5 months' follow-up) and reduced proteinuria (standardized mean difference, −0.51 [95% CI, −0.82 to −0.20]).[5] The authors thus conclude that the evidence supporting MRAs in proteinuric CKD is uncertain.

Their uncertainty is warranted. The importance of small, short-term changes in eGFR and proteinuria are promising but have not reliably predicted long-term treatment effects on clinically important outcomes.[7] Similarly, the clinical consequences of the increase in serum potassium caused by MRAs remain uncertain.

The review identified 2 ongoing RCTs (FIDELIO-DKD[8] [NCT02540993] and FIGARO-DKD[9] [NCT02545049]) sponsored by Bayer. Both compare finerenone, at 10-20 mg orally per day, to placebo for the prevention of kidney failure and/or CV events. FIDELIO-DKD and FIGARO-DKD are each as large as the entire systematic review's population (Table 1) and are estimated to include approximately 1,000 primary outcome events each. As a nonsteroidal MRA, finerenone may present a lower risk of gynecomastia and hyperkalemia than traditional steroidal MRAs and has already demonstrated proteinuria-reducing effects in diabetic kidney disease.[10] Importantly, FIDELIO-DKD, which focuses on reducing major adverse kidney events in patients with diabetic kidney disease, recently published their main results and demonstrated an approximate 18% relative risk reduction for the composite outcome of a ≥40% decline in eGFR, kidney failure, or renal death.[11] Additionally, finerenone resulted in an approximate 14% relative risk reduction in the main secondary outcome, a composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or heart failure hospitalization. The even larger FIGARO-DKD trial focuses on the effects of finerenone on CV morbidity and mortality in patients with CKD and type 2 diabetes at high risk of CV events.

Outside the scope of the review is the effect of MRAs in patients with kidney failure treated with dialysis. This is also important given the increasing number of patients

Table 1. Summary of FIDELIO-DKD and FIGARO-DKD

	FIDELIO	FIGARO
Sample Size	5,734	7,437
Main Eligibility Criteria	Age ≥ 18 y; T2DM; DKD, defined as UACR 30-300 & eGFR 25-60 & diabetic retinopathy *or* UACR > 300 & eGFR 25-75	Age ≥ 18 y; T2DM; DKD, defined as UACR 30-300 & eGFR 25-90 *or* UACR > 300 & eGFR ≥ 60
Enrolled Participants		
Mean eGFR	44.3	67.8
Mean UACR	851	312
Mean K^+	4.4	4.3
Concomitant SGLT2i	4.5%	8.3%
Intervention	Finerenone 10 or 20 mg once daily by mouth	Finerenone 10 or 20 mg once daily by mouth
Control	Matching placebo	Matching placebo
Main Outcomes		
Primary	Kidney failure, eGFR decline ≥ 40%, or renal death	CV death, nonfatal MI, nonfatal stroke, hospitalization for HF
Secondary	CV death, nonfatal MI, nonfatal stroke, hospitalization for HF	Kidney failure, eGFR decline ≥ 40%, or renal death

Abbreviations: CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); HF, heart failure; K^+, potassium concentration (in mmol/L); MI, myocardial infarction; SGLT2i, sodium/glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-creatinine ratio (in mg/g).

being treated with dialysis globally and the very high rate of CV morbidity and mortality they experience.[12] The effects of aldosterone on CV dysfunction may be even more important in kidney failure owing to the more disordered potassium and volume homeostasis and frequently elevated aldosterone concentrations. Recent RCTs and systematic reviews suggest promising treatment effects but, like the Cochrane Review for the effects of MRAs in proteinuric CKD, the certainty of beneficial effects is low owing to high risk of bias (unclear allocation, high losses to follow-up) and imprecision (few outcome events).[13] Like FIDELIO-DKD and FIGARO-DKD in proteinuric CKD, 2 larger RCTs are ongoing in patients receiving dialysis, ALCHEMIST (NCT01848639) and ACHIEVE (NCT03020303), with target sample sizes of 825 and at least 2,750 participants, respectively. Both are investigator-initiated, placebo-controlled international trials focusing on the effects of spironolactone on composite CV outcomes.

The medical community is anxiously awaiting the results of these RCTs, which will be relevant to nephrologists, cardiologists, endocrinologists, and primary care providers. Despite the size of these trials, there will almost certainly be some questions that remain unanswered owing to the rapidly evolving evidence in this area. Will the effects of finerenone exist above and beyond the use of SGLT2 inhibitors? Will finerenone be effective in nondiabetic kidney disease including transplantation? To what degree will the effects observed in FIDELIO-DKD and FIGARO-DKD be relevant to patients with eGFR < 25 mL/min/1.73 m^2, including those treated with dialysis? Will finerenone be safe in patients with a serum potassium > 4.8 mmol/L? To what extent are the results achieved with finerenone generalizable to other MRAs and vice versa? The last of these questions is particularly applicable to the Cochrane Review, where the majority of evidence will now come from a new drug with unique properties compared to prior MRAs. Regardless of the remaining questions, FIDELIO-DKD and FIGARO-DKD serve to remind the nephrology community that we should participate in and support the generation of high-quality evidence from such large trials so that we need not resign ourselves to decision making on the basis of low-certainty evidence.

Article Information

Authors' Full Names and Academic Degrees: David Collister, MD, and Michael Walsh, MD, PhD.

Authors' Affiliations: Section of Nephrology, Department of Medicine, University of Manitoba, Winnipeg, Canada (DC), Chronic Disease Innovation Center, Winnipeg, Canada (DC), Department of Medicine, McMaster University, Hamilton, Canada (MW), Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada (MW), and Population Health Research Institute, Hamilton Health Sciences / McMaster University, Hamilton, Canada (MW).

Address for Correspondence: Michael Walsh, St. Joseph's Hospital, 50 Charlton Ave, Hamilton, Ontario, Canada L8N 4A6. Email: lastwalsh1975@gmail.com

Support: Dr Walsh is supported by a Clive Kearon Mid-Career Investigator Award from McMaster University.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Other Disclosures: MW and DC are the principal investigator and scientific officer, respectively, of the ACHIEVE trial.

Peer Review: Received October 15, 2020 in response to an invitation from the journal. Direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form November 17, 2020.

 Published online January 5, 2021 with doi 10.1053/j.ajkd.2020.11.020

References

1. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J*. 2009;30(4):469-477.
2. Selye H, Hall CE, Rowley EM. Malignant hypertension produced by treatment with desoxycorticosterone acetate and sodium chloride. *Can Med Assoc J*. 1943;49(2):88-92.
3. Kolkhof P, Delbeck M, Kretschmer A, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist

protects from rat cardiorenal injury. *J Cardiovasc Pharmacol*. 2014;64(1):69-78.
4. Blasi ER, Rocha R, Rudolph AE, Blomme EA, Polly ML, McMahon EG. Aldosterone/salt induces renal inflammation and fibrosis in hypertensive rats. *Kidney Int*. 2003;63(5):1791-1800.
5. Chung EY, Strippoli GF. Aldosterone antagonists in addition to renin agniotensin system antagonists for preventing the progression of CKD: editorial summary of a Cochrane review. *Am J Kidney Dis*. 2021;77(5):810-812.
6. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2014;4:CD007004.
7. Pyne L, Guyatt GH, Walsh M. Change in albuminuria as a surrogate endpoint in chronic kidney disease. *Lancet Diabetes Endocrinol*. 2019;7(5):335.
8. Bakris GL, Agarwal R, Anker SD, et al. Design and baseline characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial. *Am J Nephrol*. 2019;50(5):333-344.
9. Ruilope LM, Agarwal R, Anker SD, et al. Design and baseline characteristics of the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease Trial. *Am J Nephrol*. 2019;50(5):345-356.
10. Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA*. 2015;314(9):884-894.
11. Bakris GL, Agarwal R, Anker SD, et al; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383(23):2219-2229.
12. McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD incidence and prevalence in the United States through 2030. *J Am Soc Nephrol*. 2019;30(1):127-135.
13. Quach K, Lvtvyn L, Baigent C, et al. The safety and efficacy of mineralocorticoid receptor antagonists in patients who require dialysis: a systematic review and meta-analysis. *Am J Kidney Dis*. 2016;68(4):591-598.