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INVITED EDITORIAL

Mineralocorticoid receptor antagonist use in renal dialysis: will evidence from prospective randomized trials confirm the results from 'real-world' evidence?

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This article refers to 'The effects of mineralocorticoid receptor antagonists on cardiovascular outcomes in patients with end-stage renal disease and heart failure' by D.S. Lin *et al.*, published in Eur J Heart Fail 2023;25: 98–107.

In patients with end-stage renal disease (ESRD) on chronic renal dialysis the cardiovascular (CV) mortality rate is 10 to 20 times higher than in the general population and among adults younger than 45 years of age the mortality rate is approximately 100 times higher than that in the general population. Hence, treatments to improve survival, more specifically CV outcomes, in this population are urgently needed.[1,2]

Activation of mineralocorticoid receptors (MR) in patients with chronic kidney disease (CKD) leads to adverse outcomes, especially hospitalization for heart failure (HF), ventricular arrhythmias, sudden cardiac death as well as progression of CKD to ESRD[2,3] through several mechanisms, including inflammation, oxidative stress, endothelial dysfunction, vascular fibrosis, stiffening and calcification,[3–5] all of which are relevant in patients undergoing renal dialysis.[2] MR antagonists (MRAs) are currently approved and/or are recommended in European and international guidelines in patients with resistant hypertension, diabetic nephropathy and in HF with a reduced ejection fraction (HFrEF), where they are one of the 'four pillars' along with angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), sacubitril/valsartan, beta-blockers, and sodium–glucose cotransporter 2 inhibitors. MRAs are therefore prime candidates to be assessed in prospective randomized clinical trials in patients undergoing renal dialysis. However, in view of the risk of developing hyperkalaemia, especially in those on an ACEI or ARB, there has been a reluctance to initiate therapy with a MRA in patients with ESRD undergoing renal dialysis. The concomitant use of one of the new potassium binders, such as patiromer, as demonstrated in clinical trials[6,7] along with a MRA may help to reduce the risk of hyperkalaemia but does not eliminate it. Despite the lack of evidence regarding the effectiveness and safety of MRAs in patients undergoing renal dialysis and the fact that they are currently contraindicated, some clinicians have initiated their off-label use.

In a previous issue of the Journal, Lin *et al.*[8] evaluated the effectiveness and safety of MRAs on CV outcomes in patients with HF undergoing maintenance renal dialysis in a real-world setting followed for slightly over 2 years. They performed a retrospective analysis within the Taiwan National Health Insurance Research Database (NHIRD), using propensity score matching during the years 2001 to 2013. They concluded that in patients undergoing renal dialysis who are diagnosed with HF the use of MRAs was associated with a lower risk of all-cause mortality (hazard ratio (HR) 0.88, 95% confidence interval [CI] 0.83–0.94) and CV death (HR 0.88, 95% CI 0.80–0.95) but not hospitalizations for HF, myocardial infarction or stroke in comparison to those not on a MRA. The benefits of MRA administration appeared to be greater in those patients undergoing haemodialysis as compared to those undergoing peritoneal dialysis. However, the number of patients undergoing peritoneal dialysis was rather small and therefore it is difficult to reach any definitive conclusion as to the relative efficacy of MRAs in patients undergoing haemodialysis versus peritoneal dialysis. The benefits of MRAs in these patients with ESRD undergoing renal dialysis was attributed to their effect on reducing ventricular arrhythmias and sudden

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cardiac death. However, while the use of MRAs was shown to be beneficial in these high-risk patients, the risk of new-onset hyperkalaemia, defined as a serum potassium >6 mEq/L, was significantly higher in the MRA group (HR 1.34, 95% CI 1.17–1.54) compared to those not on a MRA, which could limit the clinical application of MRAs in patients with ESRD.

While this provocative study is supported by robust statistical methodology, there are however inherent limitations to such retrospective analyses, even with propensity matching. As pointed out by the authors, unmeasured confounders could have a profound effect on the physicians' choice to administer a MRA. Therefore, as acknowledged by the authors, further prospective randomized evidence is warranted in patients with ESRD, both with and without concomitant HF, before we can confidently recommend the use of MRAs in patients undergoing renal dialysis. Interestingly, a prior meta-analysis[9] gathering data from 14 randomized trials with steroidal MRAs in 1309 patients with ESRD also revealed a significant reduction in both CV mortality (relative risk [RR] 0.41, 95% CI 0.24–0.70; $p = 0.001$; $n = 975$) and all-cause mortality (RR 0.44, 95% CI 0.30–0.66; $p < 0.001$; $n = 1246$) in patients receiving MRAs compared to the control group. Similar to the analysis by Lin *et al.* there was no evidence of a reduction in stroke or non-fatal CV events. However, in contrast to the analysis by Lin *et al.*,[8] the use of a MRA was not associated with an increased risk of hyperkalaemia (RR 1.12, 95% CI 0.91–1.36; $p = 0.29$), Moreover, no obvious subgroup difference was observed ($I^2 = 0\%$; $p = 0.48$). In the discussion, the authors point out that their results were heavily influenced by just two studies of modest size and therefore they point out the need for further evidence regarding the effectiveness of MRAs in patients with ESRD. The authors of this meta-analysis also acknowledge that their result on hyperkalaemia 'contradicts that of a previous meta-analysis[10] that described a significantly higher risk of hyperkalaemia in MRA-treated dialysis patients. However, after incorporating more recent trials, the risk of hyperkalaemia was negated'. These two trials (Spin-D and MiREnDa trials) were actually phase 2 trials.[2] Importantly, the largest trial considered in the meta-analysis (Matsumoto *et al.*[11]) was an open label Japanese only trial of 309 patients (corresponding to half of the initial recruitment target).[12] Thus, despite the retrospective evidence presented by Lin *et al.*[8] and the meta-analysis of randomized trials by Chen *et al.*[9] more evidence based on large prospective international double-blind placebo controlled CV outcome trials is warranted. Thus, we must await the results of prospective randomized trials of the steroidal MRA spironolactone in patients with ESRD undergoing renal dialysis. The ALCHEMIST trial (NCT01848639) which randomized patients to spironolactone up to 25 mg/day or placebo was completed at the end of 2022 and enrolled its scheduled 825 high risk CV haemodialysis patients. In the ALCHEMIST trial, hyperkalaemia, defined by a serum potassium >5.5 mmol/L within 2 weeks, is an exclusion criteria. The ACHIEVE trial (NCT03020303) plans to randomize 2750 patients, likely lower CV risk patients on haemo -or peritoneal dialysis to 25 mg/day of spironolactone or placebo and excludes patients with hyperkalaemia, defined as a serum potassium >5.8 mmol/L within 6 weeks, is scheduled for completion of recruitment in December 2024 (according to ClinicalTrials.gov, last accessed 14 January 2023). It should however be emphasized that these two trials are randomizing patients with a demonstrated tolerance to spironolactone (25 mg every other day in ALCHEMIST: drop out if hyperkalaemia ≥5.5 mmol/L twice) or (25 mg/day in ACHIEVE: randomization if no hyperkalaemia >6 mmol/L and 80% adherence) in terms of hyperkalaemia during a run-in phase of 4 and 8 weeks, respectively. Therefore, a number of patients intolerant to a steroidal MRA due to hyperkalaemia will be excluded from these trials. Furthermore, should the incidence of hyperkalaemia be increased in patients randomized to spironolactone in these trials, this could limit its long-term use despite a significant reduction in CV mortality or morbidity, since hyperkalaemia is highly prevalent in patients undergoing chronic haemodialysis[13] and clinicians may be reluctant to initiate spironolactone, serially monitor serum potassium and adjust its dose accordingly. Therefore, the combined use of potassium mitigating strategies, with either potassium binders (used by 9.5% of the patients included in the analysis by Lin *et al.* in Taiwan[8]) or low dialysis potassium concentrations might need to be considered.[13] Alternatively, selective non-steroidal MRAs, such as finerenone (REF 14) or KB-P5074,[15] or an aldosterone synthase inhibitor (ASI) such as baxdrostat,[16] which appear to be less prone to induce hyperkalaemia than spironolactone, might provide greater safety with similar or possibly even greater efficacy than spironolactone. Further data will however be required before considering larger scale phase 3 registration trials to assess the safety, tolerability, and to provide evidence of efficacy of these new non-steroidal MRAs and ASIs in patients with ESRD undergoing renal dialysis. For example, the FIDELIO-DKD and FIGARO-DKD phase 3 trials of finerenone[15] in patients with diabetic nephropathy and an estimated glomerular filtration rate >25 ml/min/1.73 m^2 demonstrated nephroprotection along with CV prevention, with a relatively low incidence and easily manageable burden of hyperkalaemia. The efficacy and safety of finerenone however has not as yet been evaluated in patients with ESRD undergoing renal dialysis.

In conclusion, real-world evidence from the off-label use of MRAs in patients with HF undergoing renal dialysis in Taiwan[8] and a meta-analysis of relatively small randomized trials[9] provide reassuring but still preliminary evidence regarding the benefits and safety of MRAs in patients undergoing renal dialysis. Before widespread clinical application of MRAs to patients with ESRD undergoing renal dialysis we should await the results of the recently completed ALCHEMIST and still ongoing ACHIEVE trials. Should the results of these trials show that spironolactone is effective and safe in patients undergoing renal dialysis, they could result in a major change in clinical practice. Spironolactone is universally available, generic and therefore relatively inexpensive. Therefore, proof of its efficacy and safety in high-risk patients with ESRD undergoing renal dialysis could have a profound effect on CV morbidity, mortality, quality of life and health care costs. Let us stay tuned!

Conflict of interest: P.R. reports consulting for Idorsia, G3P, honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Cincor, CVRx, Fresenius, KBP BioSciences, Novartis, NovoNordisk, Relypsa, Servier, and Vifor Fresenius Medical Care Renal Pharma; and travel grants from AstraZeneca, Bayer, CVRx, Novartis, and Vifor Fresenius Medical Care Renal Pharma;

cofounder: CardioRenal. B.P. consultant: Bayer, AstraZeneca, Boehringer Ingelheim, Merck, Lexicon, KBP BioSciences (stock options), Vifor (stock options), Sarfez (stock options), scPharmaceuticals (stock options), SQ Innovation (stock options), G3pharkaceuticsls, ProtonIntel (stock options), Cereno Scientific (stock options), Brainstorm Medical (stock options). US patent 9931422 - site specific delivery of eplerenone to the myocardium. US patent pending63/045783 Histone acetylation modulating agents for the protection and treatment of organ damage.

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