Scientific Research Publishing

Open Journal of Nephrology, 2024, 14, 216-224
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

# The Impact of Finerenone on Changes in Pulse Wave Velocity, Arterial Pressure and Heart Related Deaths in Hemodialysis Patients—Study Perspective

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**How to cite this paper:** Duric, L.F., Vujicic, B., Gulin, T. and Gulin, M. (2024) The Impact of Finerenone on Changes in Pulse Wave Velocity, Arterial Pressure and Heart Related Deaths in Hemodialysis Patients—Study Perspective. *Open Journal of Nephrology*, **14**, 216-224.
https://doi.org/10.4236/ojneph.2024.142020

**Received:** April 9, 2024
**Accepted:** May 28, 2024
**Published:** May 31, 2024



## Abstract

Cardiovascular events (CVE) pose a significant threat to individuals with end-stage renal disease (ESRD), yet these patients are often excluded from cardiovascular clinical trials, leaving prognostic factors associated with CVE in ESRD patients largely unexplored. Recent human studies have demonstrated elevated circulating aldosterone levels in ESRD patients, correlating with left ventricular hypertrophy. Additionally, animal models have shown improvements in uremic cardiomyopathy with spironolactone therapy, prompting interest in assessing the efficacy of spironolactone or eplerenone in reducing mortality and improving cardiovascular function in dialysis patients. Clinicians have historically been cautious about prescribing mineralocorticoid receptor antagonists (MRAs) to congestive heart failure patients with chronic kidney disease (CKD) due to hyperkalemia risk. However, the emergence of finerenone, a novel MR antagonist with a favorable safety profile and lower hyperkalemia risk, has renewed interest in MRA therapy in this population. Heart disease, including coronary artery disease, hypertension, and left ventricular failure, is alarmingly prevalent in dialysis patients, contributing significantly to elevated mortality rates compared to the general population. Arterial stiffness, as indicated by pulse wave velocity (PWV), progressively worsens with advancing CKD stages, peaking in severity among ESRD patients undergoing dialysis. High PWV serves as a crucial risk strati-

fication tool in ESRD. Elevated NT-proBNP and BNP levels in ESRD patients are well-documented, with significant associations observed between baseline peptide concentrations and cardiovascular morbidity and mortality. By incorporating finerenone into our study, we aim to investigate its potential benefits in reducing arterial stiffness, lowering blood pressure, and ultimately mitigating heart-related mortality among hemodialysis patients. This study holds substantial implications for hypertension and cardiovascular risk management in this vulnerable patient population. Eligible participants must have been on chronic hemodialysis for at least three months, with ACE inhibitors or angiotensin receptor blockers included in their therapy at maximum tolerable doses. Serum potassium levels ≤ 5.7 mmol/L, left ventricular ejection fraction ≤ 50%, and PWV higher than age-estimated values are also prerequisites for study entry. Randomized allocation will be conducted using a permuted block design, stratified by center, with allocation communicated via signed study forms during initial examinations. All steps of this research will be conducted in accordance with the principles of the Helsinki Declaration.

## Keywords

Cardiovascular Risk Factors, Finerenone, Arterial Stiffness, Heart Related Deaths, Hemodialysis Patients

## 1. Strengths of This Pilot Study

- One of the key strengths of this pilot study lies in the inclusion of dialysis patients, who are often an underestimated group in clinical research. This will contribute to a better understanding of cardiovascular outcomes in this specific context.
- Emphasizing the importance of simple and cost-effective measurements such as NT-pro BNP and arterial stiffness as crucial predictors of cardiovascular outcomes enhances the practicality and accessibility of these measures in clinical practice.
- This pilot study has the potential to evolve into a multicenter trial, thereby enhancing its strength and relevance across diverse clinical settings.

## 2. Limitations of This Pilot Study

- The pilot study is limited by a small sample of patients with numerous comorbidities, potentially impacting the generalizability of results to a broader population.
- The inclusion of anuric and oligoanuric patients may pose challenges, particularly in terms of an increased risk of hyperkalemia, which should be considered in interpreting the results.

## 3. Introduction

Aldosterone is often associated with the development of hypertension, changes

in vascular structure, vascular smooth muscle hypertrophy, endothelial dysfunction, kidney damage, proteinuria, left ventricular remodeling, collagen synthesis, and myocardial fibrosis [1]. Patients with chronic kidney disease (CKD) have a high prevalence of left ventricular (LV) abnormalities and high cardiovascular mortality [2]. Previous studies have demonstrated the cardioprotective effect of mineralocorticoid receptor antagonists (MRAs) and their positive effect on reducing intima-media thickness, left ventricular mass, fibrosis, blood pressure, and pulse wave velocity [3] [4] [5]. Preliminary observations suggest that MRAs may improve survival in patients with end-stage renal disease (ESRD), although their widespread use is limited due to the risk of hyperkalemia [6]. This creates a particular dilemma, as sudden cardiac arrest is the predominant cause of death in patients with advanced CKD [7]. Patients with ESRD on hemodialysis often die from heart disease at a much higher rate than the general population [8]. The results of several studies with MR antagonists promise to reduce cardiovascular events and heart-related deaths in these high-risk patients with ESRD on hemodialysis [9], and studies have also shown the safety of MR antagonist use in patients undergoing hemodialysis, especially regarding hyperkalemia [10] [11].

In the RALES study, spironolactone demonstrated the effectiveness of MRAs in treating patients with severe chronic heart failure with reduced ejection fraction (HFrEF) [12]. The EPHESUS study clearly demonstrated the benefits of improved survival and reduced hospitalizations by adding eplerenone to standard therapy with ACE inhibitors, diuretics, and beta-blockers in patients with post-myocardial infarction heart failure [13]. The results of the FIGARO-DKD and FIDELITY studies show that finerenone has favorable effects on cardiovascular and renal outcomes in patients with type 2 diabetes mellitus (T2DM) and CKD who are receiving maximal renin-angiotensin-aldosterone system blockade [14] [15] [16]. By focusing on a high-risk patient group, our study aims to fill gaps in research and offer specialized insights into the potential benefits associated with finerenone in patients on hemodialysis, such as reducing vascular stiffness and decreasing NT-proBNP levels as independent cardiovascular risk factors [17]. In summary, the selection of hemodialysis patients for this pilot study is driven by the need to contribute to knowledge in an area where there are controversies and a lack of information due to the limitations imposed by the risk of hyperkalemia [18]. The goal is to improve existing treatment modalities, enhance quality of life, and reduce unwanted cardiac deaths in these patients.

## 4. Patients and Methods

Inclusion criteria:

- Age between 18 and 80 years.
- Undergoing hemodialysis for more than 3 months, three times a week.
- No history of hemodynamic instability during hemodialysis.
- Serum potassium levels within specified ranges (≤ 5.7 mmol/L).
- Signed informed consent.

Exclusion criteria:

- Hyperkalemia (serum potassium ≥ 5.7 mmol/L).

### 4.1. Baseline Characteristics

In this study perspective 80 patients treated by chronic haemodialysis (>3 months) aged 20 - 80 for more than 3 months, will be enrolled. Randomized allocation will be assigned by a permuted block design, stratified by center. The allocation notification to the group will be conveyed through a study form signed by the patient during the initial examination. The patients who meet the criteria will be randomized into two groups: the Control Group receiving RAAS blockers and placebo, and the Mobilization Group receiving the same treatment protocol with the addition of finerenone (10 mg). All patients must receive, in addition to conventional therapy, an ACE inhibitor or angiotensin receptor blocker (sartan) at the maximum tolerable dose.

All patients are on renal replacement therapy with dialysis three times a week, and they do not have an incidence of hemodynamic instability events occurring during hemodialysis. This study's perspective will be conducted by the principles outlined in the Declaration of Helsinki.

### 4.2. Methods

#### 4.2.1. Clinical and Biochemical Assessments

Demographic information such as age, sex, medical history (hypertension, DM, and the use of antihypertensive drugs), blood tests (serum hemoglobin, albumin, blood urea nitrogen, creatinine, calcium, phosphorous, potassium, intact parathyroid hormone, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides), and NT-proBNP will be obtained from the EMR system at the time of enrolment, after 3, 6 month and at the end of the follow-up period.

#### 4.2.2. Measurement of ABP

OBP will be measured by medical staff using a mercury sphygmomanometer with an appropriately sized cuff. All patients rested for 5 minutes before BP measurement and were prohibited from smoking and ingesting caffeine for 30 minutes before the measurements. Three measurements were performed at 1-minute intervals, and the average of the last two measurements was taken as the OBP. The 24-hour ABPM will be performed using the Mobile-O-Graph (I.E.M. GmbH, Stolberg, Germany) between two dialysis sessions. Daytime was defined as 8 AM to 10 PM and nighttime as 10 PM to 8 AM. More than 16 acceptable daytime readings and 12 acceptable nighttime readings were obtained. The time interval between BP measurements was 30 minutes. BP groups were divided according to the 2017 ACC/AHA guidelines. Extreme dippers were defined as patients with a nighttime-daytime systolic BP ratio of ≤0.8; dippers, 0.8 to 0.9; non-dippers, 0.9 to 1.0; and reverse dippers, >1.0.

#### 4.2.3. Measurement of PWV

An IEM Mobil-O-Graph with software for measuring central blood pressure and pulse wave velocity, along with an appropriate arm cuff, will be applied to a non-access upper arm after the hemodialysis session has ended. During each measurement, routine daily activities will be noted in all patients, with measurements taken every 20 minutes during the daytime (6 a.m. - 10 p.m.) and every 40 minutes during the nighttime (10 p.m. - 6 a.m.). Inclusion criteria require a minimum of 70% successful readings, with a minimum of 14 daytime and 7 nighttime measurements. Our analyzed group consists of 80 patients.

#### 4.2.4. Echocardiography Parameters

Echocardiography will be performed using an ultrasound machine LOGIC Q9 from General Electric, USA. All patients will undergo examination on an interdialytic day according to the standard protocol and recommendations of the American Society of Echocardiography (ASE) [19]. From M mode in projection on the long parasternal axis, interventricular septum end-diastolic thickness (IVSd), posterior wall thickness (PWd), and left ventricular end-diastolic diameter (LVEDD) will be measured. Left atrial diameter (LA) will be measured in the same projection at the end of diastole. Left ventricular ejection fraction (EF) will be obtained according to Simpson in the 4-chamber apical projection. Left ventricular mass (LVM) will be calculated according to ASE: LVM (g) = 0.8. 1.04. [(IVSd + LVEDD + PWd) 3 − LVEDD3] + 0.6 g (values IVSd, LVEDD, PWd in mm). Left ventricular mass index (LVMI) will be derived from the formula: LVM/body surface area (BSA). LVMI ≤125 g/m$^2$ and in women ≤110 g/m$^2$ will be considered as evidence of normal findings. Left ventricular relative wall thickness (RT) will be defined as: (IVSd + PWd/LVEDD). RT values ≤0.44 in both genders will be considered normal.

Parameters of left ventricular diastolic function will be measured in 80 patients with sinus rhythm according to transmitral flow: peak velocity of early diastolic filling (E), peak velocity of late diastolic filling (A), ratio of peak early to late diastolic filling velocity (E/A), deceleration time (DCT), and isovolumic relaxation time (IVRT). The relevance of echocardiographic parameters and NT-proBNP values will be compared.

## 5. Data Collection

All data is collected through an on-line electronic data capture system. Secure access to this online platform is restricted to each center investigator and designed collaborators and ensured by individual passwords.

## 6. Study Endpoints

The primary outcome is to evaluate the impact of MRAs on changes in pulse wave velocity, NT-proBNP, and ejection fraction as independent predictors of cardiovascular outcomes.

The secondary outcome is to examine how MRA therapy influences the inci-

dence of heart failure and heart-related deaths in dialysis patients.

## 7. Statistical Analysis

All analyses of outcomes will be conducted using an intention-to-treat approach, accommodating missing data through multiple imputation techniques. In cases of missing data points, established statistical methods, such as multiple imputations, will be employed to impute missing values. The imputation model will include relevant covariates to ensure robust estimation of missing data. Sensitivity analyses will assess the impact of missing data on study results, enhancing the reliability and generalizability of findings.

Categorical variables will be summarized as absolute and relative frequencies, while numerical variables will be presented as means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate.

For primary objectives, including the impact of MRAs on changes in pulse wave velocity, NT-proBNP, and ejection fraction values, analysis of variance (ANCOVA) will be utilized to compare mean values across different treatment groups. These methods will precisely assess therapy's influence on key cardiovascular outcome indicators.

For secondary objectives, encompassing therapy's impact on the frequency of cardiac decompensation and death in the dialysis patient population, survival analysis will be employed. Kaplan-Meier curves will depict time to events, while the log-rank test or Cox regression will allow comparisons between treatment groups, providing a deeper understanding of therapy's impact on long-term cardiovascular outcomes.

Comparison of median values between patients receiving finerenone and the placebo group will be performed using the non-parametric Mann-Whitney test for independent samples. Complication rates will be compared using Fisher's exact test.

Hazard ratios (HRs) for clinical outcomes associated with different NT-proBNP and BNP ranges will be categorized into common thresholds and pooled using random-effects meta-analysis.

The association between clinical features and the occurrence of the shift from finerenone to placebo administration will be investigated using binary logistic regression, with results quantified by odds ratio (OR). All analyses will be conducted as two-sided tests.

The study results will be presented through various analyses, including "intention to treat", "per protocol", and "effective treatment" approaches. Additionally, feedback on functional outcomes in patients undergoing hemodialysis with either finerenone or placebo will be provided to the medical team involved in patient care.

## 8. Discussion

Considering the potential clinical implications of our study's results, several key

considerations emerge, shedding light on the broader context and applicability of our findings.

1) Personalized Treatment Approaches: The study's exploration of mineralocorticoid receptor blockers (MRAs), particularly finerenone, within the hemodialysis patient population provides a foundation for personalized treatment approaches. If our results demonstrate a significant reduction in heart-related deaths and improvements in pulse wave velocity and arterial pressure, clinicians may consider tailoring therapy based on individual patient profiles.

2) Enhanced Cardiovascular Risk Control: Identifying the impact of MRAs on cardiovascular outcomes in hemodialysis patients can contribute to enhanced risk management strategies. The study's focus on pulse wave velocity, arterial pressure, and heart-related deaths addresses critical aspects of cardiovascular health, offering insights that may aid in refining guidelines for managing cardiovascular risk in this vulnerable population.

3) Optimizing Therapeutic Decision-Making: By including patients undergoing chronic hemodialysis and assessing the effects of finerenone alongside standard treatments, our study aims to optimize therapeutic decision-making. The results may guide clinicians in navigating the delicate balance between the benefits and potential risks of MRAs in patients with reduced left ventricular ejection fraction (HFrEF) on dialysis, paving the way for more informed and tailored treatment choices.

4) Potential for Multicenter Trials: The strength and relevance of our findings may open avenues for future multicenter trials. If our study demonstrates promising outcomes, it could serve as a catalyst for larger-scale investigations involving multiple dialysis centers. This collaborative approach would further validate the generalizability and robustness of our initial findings.

5) Integration into Guidelines and Protocols: Successful results from our study may prompt the integration of MRAs, especially finerenone, into existing clinical guidelines and protocols for managing cardiovascular risk in hemodialysis patients. This would mark a significant step toward improving the standard of care and outcomes for this often overlooked patient population.

Arterial stiffness, expressed as pulse wave velocity, becomes an important characteristic in the effectiveness of therapeutic strategies [20]. Changes in NT-proBNP levels over time vary according to the stage of CKD, with the greatest changes observed in patients undergoing hemodialysis. Patients undergoing hemodialysis have the ability to monitor serum potassium levels every other day during dialysis, so we consider the use of finerenone justified and safe in this population

In further research, we aim to definitively respond to this question.

## Conflict of Interest

All authors of this pilot study declare that they have no conflicts of interest that could influence the results or interpretation of this work.

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