

# The Impact of Mineralocorticoid Receptor Blockers on Changes in Pulse Wave Velocity, Arterial Pressure and Heart Related Deaths in Hemodialysis Patients

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**Abstract:** *The unique electrolytic and pathophysiological environment of hemodialysis patients, along with their increased cardiovascular risk and vulnerability, requires dedicated exploration of the therapeutic potentials of mineralocorticoid receptor agonists (MRAs). The presence of chronic kidney disease (CKD) often influences the decision to start, uptitrate, or discontinue possible life-saving therapies, especially when it comes to patients with reduced left ventricular ejection fraction (HFrEF), the treatment approach needs to be carefully considered. Our goal is to outline the design and rationale of our pilot study, which investigates the impact of mineralocorticoid receptor blockers (MRAs), more precisely finerenone on changes in pulse wave velocity (PWV), arterial pressure, and heart-related deaths in patient undergoing hemodialysis. To be eligible for study enrollment patients must be at least three months on a chronic hemodialysis program, ACE inhibitors or angiotensin receptor blockers must be included in the therapy at maximum tolerable doses from the beginning, serum potassium level between two dialysis needs to be  $\leq$  mmol/L, left ventricular ejection fraction needs to be  $\leq$  50%, pulse wave velocity higher than estimated for the age. Patients who meet the criteria will be randomized into two groups in a 1: 1 ratio. Randomized allocation was assigned by a permuted block design, stratified by center. The allocation notification to the group was conveyed through a study form signed by the patient during the initial examination. Group A = RAAS blockers and finerenone 10 mg. Group B: RAAS blockers with other conventional therapy and placebo. This pilot study addresses responses to whether changes in pulse wave and arterial pressure, through MRAs therapy, can reduce the number of heart-related deaths in dialysis patients. The findings aim to shed light on the potential impact of MRAs on cardiovascular outcomes in this population. The pilot study will be completed 12 months after the last enrolment.*

**Keywords:** arterial hypertension, arterial stiffness, heart related deaths, hemodialysis patients

## 1. Strengths of the Study

- 1) One of the key strengths of this 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.
- 2) 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.
- 3) This study has the potential to evolve into a multicenter trial, thereby enhancing its strength and relevance across diverse clinical settings

## 2. Limitations of the Study

- 1) The study is limited by a small sample of patients with numerous comorbidities, potentially impacting the generalizability of results to a broader population.
- 2) 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

Chronic kidney disease (CKD) as identified by a reduced

estimated glomerular filtration rate (eGFR) is a common comorbidity in patients with heart failure with reduced ejection fraction (HFrEF) (1). Several studies have demonstrated that patients with chronic kidney disease (CKD) have elevated levels of aldosterone (2, 3).

Aldosterone is thought to play a role in the development of hypertension, vascular structure alteration, vascular smooth muscle hypertrophy, endothelial dysfunction, renal injury, proteinuria, left ventricular remodelling, collagen synthesis, and myocardial fibrosis. With excess aldosterone, both renal and extrarenal mineralocorticoid receptors are activated further exacerbating the effect of angiotensin II and other products of the renin-angiotensin-aldosterone system (RAAS) (4, 5).

Excessive activation of RAAS contributes to the development of cardiac hypertrophy and myocardial fibrosis (6) and leads to complex pathophysiological effects that may result in hypertension, heart failure, and other cardiovascular disorders.

Randomized controlled trials (7, 8, 9, 10) have demonstrated efficacy of MRA in heart failure with reduced ejection fraction (HFrEF), both in patients with NYHA functional classes III and IV and in asymptomatic and mildly symptomatic patients (NYHA classes I and II) (9, 10). The RALES (Randomized Aldactone Evaluation Study) (7) trial was the first to demonstrate the efficacy of an MRA

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(spironolactone) in the treatment of patients with severe chronic HFrEF. In the RALES study, the risk of mortality and hospitalization due to HF in patients treated with spironolactone was similar for those with reduced eGFR and those with normal eGFR (7, 11)

EPHESUS clearly demonstrated a benefit in terms of improved survival and reduced hospitalisation with the addition of eplerenone to the usual treatment regimen of ACE inhibitors, diuretics and beta - blockers in patients with post - MI heart failure (11) Recent data in patients with heart failure with preserved ejection fraction are encouraging that MRAs may also be applicable to HD patients (12).

The results from FIGARO - DKD and Fidelity study demonstrate that finerenone has favourable effects on cardiovascular and renal outcomes in patients with T2DM and CKD who were receiving maximum renin - angiotensin - aldosterone system blockade therapy (13, 14). Chronic kidney disease (CKD) presents a complex clinical scenario, particularly for HFrEF patients. The significance of understanding and addressing cardiovascular outcomes in the specific population of hemodialysis patients stems from the intersecting challenges posed by CKD and heart failure.

Heart disease is extremely recurrent in dialysis patients and coronary artery disease, hypertension and left ventricular failure account for the majority of cases in this subgroup of patients (15 - 19).

Patients with end - stage renal failure (ESRF) and on hemodialysis often die of heart disease at a much higher rate (20 to 40 times) compared to general population (20, 21, 22).

Most clinicians are hesitant to prescribe MRAs to patients with congestive heart failure, especially those with CKD, due to the risk of hyperkalemia. Currently, MRAs are contraindicated for patients with an eGFR <30 ml/min/1.73 m<sup>2</sup>, including those on HD.

Recent clinical studies have demonstrated the safety of MRAs in HD patients, particularly in regards to hyperkalemia. Studies have also suggested a CV protective effect of MRAs on intima - media thickness, left ventricular mass, fibrosis, and pulse wave velocity (PWV) (23 - 30).

The results of several ongoing studies offer the promise of reducing CV events and heart related deaths in these high - risk patients with ESRD on hemodialysis (31, 32).

Patients with CKD have a high prevalence of left ventricular (LV) abnormalities and high cardiovascular mortality (33). Because B - type natriuretic peptide (BNP) is released by the left ventricle in response to LV end - diastolic wall stress (34), this biomarker has been studied as a predictor of patient outcome. Changes in NT - proBNP levels over time vary according to the stage of CKD, with the greatest change observed in hemodialysis patient (35).

Randomized controlled trials in patients with heart failure have demonstrated a reduced mortality when interventions are applied in a BNP - driven management strategy (36); in

patients undergoing dialysis, appropriate interventions remain to be identified. A BNP - guided management strategy might include improving volume control with dialysis or titrating medications with prognostic benefit in cardiovascular studies, such as  $\beta$  - blocker therapy, which has been demonstrated to decrease BNP in dialysis patients (37, 38). or maybe MRAs therapy.

The rationale for selecting hemodialysis patients as the focus of this study is multifaceted. Firstly, this population is often underrepresented in clinical research, leading to a gap in our understanding of therapeutic interventions, efficacy and safety specifically tailored to their needs. Secondly, the intricate interplay between CKD and HFrEF poses unique challenges in the selection and optimization of life - saving therapies. As these patients are at an increased risk of cardiovascular events, exploring novel interventions, such as MRAs, becomes imperative.

Patients undergoing chronic hemodialysis face a heightened cardiovascular risk due to factors such as fluid and electrolyte imbalances, chronic inflammation, and accelerated vascular calcification. This vulnerable patient population is frequently excluded from traditional heart failure trials, leading to limited evidence - based guidance for therapeutic decision - making. By focusing on this particular group, our study aims to fill this research gap and offer specialized insights into the potential benefits and challenges linked to MRAs in hemodialysis patients.

Furthermore, investigating the impact of MRAs on pulse wave velocity, arterial pressure, and heart - related deaths in this context becomes crucial. The outcomes of this study aim to contribute not only to the scientific community's understanding of CKD and HFrEF intersections but also to inform clinical practice by providing evidence for personalized and effective treatment strategies in this underrepresented patient population.

In summary, the selection of hemodialysis patients for this pilot study is driven by the need to address the specific challenges they face and to contribute to the knowledge in an area where controversies and a lack of information exist due to limitations within this specific cohort. The goal is to enhance existing treatment modalities and contribute to improving the quality of life and reducing unwanted cardiac deaths in these patients.

#### 4. Methods

This study is a pre - post, prospective, superiority, randomized clinical trial. We plan to examine 80 patients undergoing haemodialysis (>3 months) aged 20 - 80. All patients are on renal replacement therapy with dialysis three times a week, and they must sign an informed consent before investigation. No incidence of hemodynamic instability event can occur during haemodialysis. The participants (n = 80) will be randomly distributed into two groups. The control group will receive RAAS blockers and placebo, the mobilization group will receive the same protocolled treatment and finerenone 10 mg.

IEM Mobil - O - Graph with software for measuring central

blood pressure and pulse wave velocity and appropriate arm cuff will be applied on a non - access upper arm after the HD session ended. In every patient a routine daily activities will be noticed during the measurement, which were carried out 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:** Minimum 70 % of successful readings, minimum 14 daytime and 7 night time measurements. Our analysed group contained 80 patients.

Echocardiography was performed using an ultrasound machine LOGIC Q9 from company General Electrics, USA. All patients underwent examination always during an interdialytic day according to the standard protocol and recommendations of ASE (American Society of Echocardiography) (39).

Basic laboratory parameters will be examined and used for analysis during routine monthly blood test control in which 24 - h ABPM was provided. The serum potassium level will be assessed after the initiation of mineralocorticoid receptor blockers twice a week for the first month, and subsequently, at least once a week, in patients on finerenone until the end of the follow - up period. The serum NT - proBNP levels will be determined for all patients. initially and at the end of the follow - up period. All patients must receive, in addition to conventional therapy, an ACE inhibitor or angiotensin receptor blocker (sartan) at the maximum tolerable dose.

The measurements will be performed at baseline, after 6 months, and at the end of the 12 - month follow - up period.

## Design and Methods

### Study design

This pilot study randomized hemodialysis patients into a group receiving finerenone and a group receiving a placebo. Randomization will be conducted using a random block method with stratification based on the center. The responsible individual for the randomization process will be a nephrologist and the head of the dialysis center at UHC Zagreb. This team has prior experience in executing similar randomized clinical trials.

### Participants

Inclusion criteria will be:

- age between 18 and 80 years;
- on renal replacement therapy with dialysis >3 months and three times a week
- no incidence of hemodynamic instability event can occur during haemodialysis
- Serum potassium  $\leq 5.8$  mmol/L in the 6 weeks prior to enrollment or Serum potassium  $\leq 6.0$  mmol/L during active run - in
- signed written informed consent prior to participating in the study

### Exclusion criteria:

Hyperkalemia

Serum potassium  $> 5.8$  mmol/L in the 6 weeks prior to enrollment or Serum potassium  $> 6.0$  mmol/L during active

run - in

The study aims to enroll 80 (n=80) oligoanuric patients who have been on chronic renal replacement therapy through dialysis for a minimum of three months. This cohort will consist of 48 women and 32 men, providing a gender - stratified representation. Inclusion criteria also require participants to have a left ventricular ejection fraction (LVEF) of 50% or less, a pulse wave velocity higher than age - estimated values, and serum potassium levels of 5.7 mmol/L or lower.

Additionally, participants must be at least 18 years old and no older than 80, emphasizing the inclusion of a broad age range to enhance the generalizability of study findings. To ensure stability during hemodialysis sessions, participants should not have experienced hemodynamic instability events during previous treatments.

Upon meeting the inclusion criteria, the 80 eligible participants will be randomly assigned to one of two groups in a 1: 1 ratio. Group allocation will be achieved through a permuted block design, stratified by center.

- 1) Group A (Intervention Group): Participants in this group will receive angiotensin - converting enzyme inhibitors (ACEi) or sartans as part of their therapy, alongside other conventional treatments. Additionally, they will be administered finerenone.
- 2) Group B (Control Group): Participants in this group will receive angiotensin - converting enzyme inhibitors (ACEi) or sartans as part of their therapy, along with other conventional treatments. However, instead of finerenone, they will be administered a placebo.

This allocation strategy aims to compare the effectiveness of adding finerenone to the existing treatment regimen in Group A against the conventional therapy without finerenone in Group B. Randomization and blinding procedures will be diligently implemented to ensure unbiased evaluation of the intervention's impact on the specified cardiovascular outcomes

Furthermore, the study prioritizes diversity in comorbidities to reflect the real - world complexity of the target population. Participants may have various underlying health conditions commonly observed in hemodialysis patients, such as diabetes mellitus, hypertension, or cardiovascular diseases.

The inclusion of these diverse characteristics aims to capture the heterogeneity within the hemodialysis patient population, making the study results more applicable to a broader range of individuals managing chronic kidney disease and heart failure.

### Data collection

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

### 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 incidence of heart failure and heart - related deaths in dialysis patients.

### Statistical analysis

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

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

For the 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 enable us to precisely assess the influence of therapy on these key cardiovascular outcome indicators.

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

The comparison of median values between patients receiving MRAs 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.

The investigation of the association between clinical features and the occurrence of the shift from MRAs to placebo administration will be conducted using binary logistic regression, and the results will be 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, the investigators plan to provide feedback to surgeons regarding functional outcomes in patients undergoing hemodialysis with either MRAs or a placebo.

## 5. Discussion

In contemplating the potential clinical implications of our study's results, several key considerations arise, 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 Management:** 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.

Furthermore, investigating the impact of MRAs on pulse wave velocity, arterial pressure, and heart - related deaths in this context becomes crucial. The outcomes of this study aim to contribute not only to the scientific community's understanding of CKD and HFrEF intersections but also to inform clinical practice by providing evidence for personalized and effective treatment strategies in this underrepresented patient population.

The selection of hemodialysis patients for this study is driven by the need to address the specific challenges they face and to fill the existing void in evidence - based interventions. This research endeavor strives to unravel the complexities of CKD and HFrEF synergy, providing a

foundation for tailored therapeutic approaches that can significantly impact the cardiovascular outcomes of hemodialysis patients.

Our study's potential clinical implications extend beyond the immediate findings, offering a pathway to more personalized, effective, and guideline - informed care for hemodialysis patients with reduced left ventricular ejection fraction. The anticipated positive impact includes enhanced risk management, well - informed therapeutic decisions, and the potential to shape broader clinical practices by integrating innovative therapies into established guidelines.

In conclusion, our study's potential clinical implications extend beyond the immediate findings, offering a pathway to more personalized, effective, and guideline - informed care for hemodialysis patients with reduced left ventricular ejection fraction. The envisioned ripple effect encompasses improved risk management, informed therapeutic decisions, and the possibility of influencing broader clinical practices through the integration of novel therapies into established guidelines.

We believe that whether controlled administration of finerenone, along with other RAAS system blockers, in HD patients would reduce their overall cardiovascular risk. This aims to provide an answer by positively impacting blood pressure, pulse wave velocity, left ventricular mass, and help determines if finerenone (10mg/day, compared to placebo) reduces heart failure and heart related deaths in dialysis patients. There are currently only a limited number of studies on this, emphasizing the need for further research to definitively respond to this inquiry.

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