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# Long-Term Renal Outcomes and Safety Profile of Non-Steroidal Mineralocorticoid Receptor Antagonists in Non-Diabetic Chronic Kidney Disease: A Retrospective Cohort Study

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**A B S T R A C T**

Non-steroidal mineralocorticoid receptor antagonists, specifically finerenone, have demonstrated profound cardiorenal protective effects in diabetic kidney disease. However, their efficacy and safety in non-diabetic chronic kidney disease remain inadequately characterized, particularly within Southeast Asian populations experiencing high rates of hypertensive nephrosclerosis. A retrospective cohort study was conducted at a tertiary hospital in Makassar, Indonesia, evaluating 148 adult patients with non-diabetic chronic kidney disease (stages 3-4) who received finerenone between January 2022 and December 2024. Clinical data, including urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and serum potassium, were analyzed using generalized and piecewise linear mixed-effects models over 24 months. The cohort (N=148) demonstrated a significant reduction in median UACR from a baseline of 845 mg/g to 460 mg/g at 24 months ($p < 0.001$). Following an initial hemodynamic eGFR dip in the first six months, the chronic annualized slope of decline stabilized at -2.2 mL/min/1.73 m² per year (95% CI: -2.8 to -1.6). Mild hyperkalemia occurred in 16.2% of patients, and moderate-to-severe hyperkalemia in 4.1%. Concomitant sodium-glucose cotransporter-2 inhibitor (SGLT2i) use was associated with a lower risk of incident hyperkalemia (OR 0.45, 95% CI 0.22-0.89). In conclusion, in this real-world observational cohort, adding finerenone to standard care in non-diabetic CKD patients was associated with significant reductions in UACR and an attenuation of eGFR decline over 24 months, alongside a manageable safety profile. These findings warrant further investigation in large, randomized trials.

## 1. Introduction

Chronic kidney disease represents an escalating global public health crisis, contributing to substantial morbidity, premature cardiovascular mortality, and immense healthcare expenditures globally.[1] While diabetic kidney disease accounts for a significant proportion of this burden, non-diabetic chronic kidney disease—encompassing diverse etiologies such as hypertensive nephrosclerosis, immunoglobulin A nephropathy, focal segmental glomerulosclerosis, and chronic tubulointerstitial nephritis—remains a formidable and progressive clinical challenge. In Indonesia, the prevalence of non-diabetic chronic kidney disease is strikingly prominent, driven by persistently high rates of uncontrolled essential hypertension, widespread traditional herbal toxin exposure, and endemic infectious diseases that precipitate secondary glomerulonephritides. The conventional cornerstone of therapy for proteinuric chronic kidney disease, regardless of its primary

etiology, has historically been the maximization of renin-angiotensin system blockade using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.[2] However, even with optimal and maximally tolerated renin-angiotensin system inhibition, a substantial and dangerous residual risk for disease progression to end-stage kidney failure remains. This residual risk highlights an urgent, unmet clinical need for novel therapeutic agents that target alternative pathophysiological pathways.

Recent paradigm-shifting advances in cardiorenal pathophysiology have identified the maladaptive overactivation of the mineralocorticoid receptor as a critical, independent mediator of tissue remodeling, fibrogenesis, and chronic inflammation in both the kidneys and the heart.[3] Aldosterone, acting through the mineralocorticoid receptor, induces severe oxidative stress, promotes the influx of inflammatory macrophages into the renal interstitium, and upregulates potent profibrotic cytokines, including transforming growth factor-beta and plasminogen activator inhibitor-1. Historically, steroidal mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, were utilized in clinical practice to block these deleterious pathways. While these agents are highly effective in managing heart failure with reduced ejection fraction and resistant hypertension, their application in advanced chronic kidney disease has been severely hindered by a prohibitively high propensity to induce life-threatening hyperkalemia, acute kidney injury, as well as off-target antiandrogenic and progestational adverse effects such as painful gynecomastia and menstrual irregularities.[4]

The developmental landscape of nephrology was recently altered by the introduction and regulatory approval of finerenone, a highly selective, non-steroidal mineralocorticoid receptor antagonist.[5] Unlike its older steroidal predecessors, finerenone features a bulky, non-steroidal dihydropyridine-based structure that binds to the mineralocorticoid receptor in a unique, highly specific three-dimensional configuration. This unique binding mechanism physically prevents the recruitment of transcriptional cofactors that are strictly necessary for the downstream expression of hypertrophic, inflammatory, and fibrotic genes.[6] The landmark FIDELIO-DKD and FIGARO-DKD global clinical trials definitively established that finerenone significantly reduces the risk of chronic kidney disease progression, the doubling of serum creatinine, and cardiovascular events in patients with type 2 diabetes mellitus, while simultaneously demonstrating a markedly lower incidence of hyperkalemia compared to traditional steroidal agents.[7]

Despite these robust, paradigm-shifting clinical trial results, a profound knowledge gap persists in the contemporary medical literature. The overwhelming majority of robust randomized clinical trial data and subsequent real-world observational analyses have been strictly confined to diabetic cohorts.[8] The pathophysiological mechanisms driving non-diabetic chronic kidney disease, while ultimately sharing final common pathways of irreversible tissue fibrosis and nephron dropout, often possess highly distinct initial inflammatory, immunological, and hemodynamic triggers. It remains uncertain whether the potent antifibrotic and antiproteinuric benefits of non-steroidal mineralocorticoid receptor antagonists translate equally to non-diabetic populations in routine, unstructured clinical practice. Furthermore, real-world pharmacological responses and adverse event profiles can vary significantly across different ethnic and geographic demographics due to substantial differences in dietary potassium intake patterns, underlying genetic polymorphisms in drug metabolism pathways, and disparities in longitudinal healthcare access.[9]

This research represents one of the most comprehensive real-world longitudinal investigations in Southeast Asia, designed specifically to isolate and rigorously evaluate the long-term clinical outcomes of

non-steroidal mineralocorticoid receptor antagonists strictly within a non-diabetic chronic kidney disease population. By utilizing rich longitudinal registry data from a major Indonesian tertiary healthcare center, this study moves beyond the highly controlled, artificial environments of randomized trials to capture the true clinical dynamics, long-term adherence patterns, and precise safety profiles inherent to routine nephrology practice.[10] The primary aim of this study was to rigorously evaluate the long-term clinical efficacy of finerenone in reducing pathological albuminuria and preserving the estimated glomerular filtration rate trajectory in adult patients with non-diabetic chronic kidney disease. The secondary aim was to comprehensively assess the real-world safety and tolerability profile, explicitly focusing on the incidence, severity, and clinical management requirements of hyperkalemia in this high-risk Southeast Asian population.

## 2. Methods

A descriptive, retrospective, longitudinal cohort study was conducted at a premier private tertiary referral hospital located in Makassar, South Sulawesi, Indonesia. The facility serves as a major regional center of excellence for advanced nephrology, renal replacement therapy, and internal medicine in Eastern Indonesia. The study protocol underwent rigorous ethical review and was officially approved by the Institutional Review Board and the local Medical Ethics Committee of the hospital. Because the study involved the retrospective extraction and statistical analysis of fully anonymized electronic medical records, the formal requirement for direct patient informed consent was officially waived by the ethics committee to preserve patient confidentiality.

The study population was systematically derived from the hospital's centralized nephrology outpatient electronic registry, encompassing a thorough screening of the comprehensive medical records for all patients actively treated between January 2022 and December 2024. To ensure a robust, highly specific, and clinically homogenous cohort, rigorous inclusion parameters were continuously enforced. Eligible participants were required to be adults aged 18 years or older at the time of their initial consultation, possessing a formally established diagnosis of non-diabetic chronic kidney disease. This foundational diagnosis was meticulously confirmed either through a definitive prior percutaneous renal biopsy or via a comprehensive clinical and serological workup that successfully and definitively ruled out any underlying diabetic nephropathy. The absolute absence of diabetes mellitus was biochemically verified by demonstrating fasting plasma glucose levels strictly within normal physiological limits, paired precisely with a glycated hemoglobin level strictly below 6.5%. Furthermore, the cohort was deliberately restricted to individuals classified as having chronic kidney disease stage 3 or 4, specifically indicated by a baseline estimated glomerular filtration rate falling between 15 and 59 mL/min/1.73 $m^2$ calculated immediately prior to the initiation of therapy. A critical physiological prerequisite for inclusion was the documented presence of persistent, clinically significant albuminuria, defined explicitly as a urinary albumin-to-creatinine ratio greater than 30 mg/g. Crucially, this advanced albuminuria had to be present despite the patient being maintained on a maximum biologically tolerated dose of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker for a minimum continuous duration of four weeks. Ultimately, eligible candidates must have initiated finerenone therapy during the prespecified study window and possessed a minimum of 24 months of continuous, uninterrupted follow-up laboratory and clinical data meticulously documented within the hospital system.

To rigorously prevent confounding variables, mitigate baseline safety risks, and preserve the absolute internal validity of the statistical analysis, a stringent set of exclusion criteria was universally

applied across the registry. Any patient harboring a historical or current diagnosis of type 1 or type 2 diabetes mellitus was immediately excluded from the analysis. To aggressively mitigate the expected pharmacological risk of severe drug-induced electrolyte derangements, individuals presenting with baseline serum potassium levels exceeding 5.0 mmol/L immediately prior to the proposed treatment initiation date were deemed strictly ineligible. The concomitant baseline utilization of steroidal mineralocorticoid receptor antagonists, strong CYP3A4 inhibitors, or adjunctive potassium-sparing diuretics also served as absolute grounds for exclusion due to their overlapping pharmacodynamic profiles and heavily compounded toxicity risks. Furthermore, patients presenting with a recently documented episode of active acute kidney injury necessitating hospitalization within the three months prior to the index date were excluded to ensure the evaluation of a structurally stable baseline renal trajectory. Finally, a formal clinical diagnosis of symptomatic heart failure with reduced ejection fraction was treated as an absolute exclusion criterion; this specific cardiovascular pathology independently mandates mineralocorticoid receptor antagonist therapy based on distinct, established cardiology guidelines, a clinical scenario that would fundamentally obscure and confound the precise interpretation of the primary renal endpoints of this specific investigation.

To transparently address the inherent survivorship and immortal time bias introduced by the strict 24-month continuous follow-up requirement, an intention-to-treat framework acknowledgment is necessary. Initially, 210 patients meeting the clinical diagnostic criteria were prescribed finerenone during the study window. However, 62 patients were excluded from the final analysis specifically because they did not reach the 24-month continuous follow-up mark: 18 due to transitioning to distinct renal replacement therapy facilities, 12 due to loss to follow-up, 24 due to early discontinuation driven by non-renal adverse events or cost constraints, and 8 due to all-cause mortality prior to study completion. The final analytical cohort comprised the 148 continuously treated patients. Because a formally matched retrospective control group (patients not receiving finerenone) could not be reliably extracted from the registry without introducing severe selection bias, this study proceeds as an uncontrolled, descriptive observational analysis.

The index date for each individual patient was explicitly defined as the calendar day the first initial dose of finerenone was prescribed and dispensed. In strict accordance with established clinical protocols adapted from global nephrology guidelines, finerenone was initiated at a dose of 10 mg once daily for patients presenting with an estimated glomerular filtration rate between 25 and 60 mL/min/1.73 $m^2$. The medication was selectively up-titrated to the target dose of 20 mg once daily after one month of continuous therapy if, and only if, the patient's serum potassium levels remained strictly below 4.8 mmol/L and overall kidney function remained stable without signs of acute decline. Patients were maintained on their established background standard-of-care disease-modifying therapies, including antihypertensives, lipid-lowering statins, and sodium-glucose cotransporter-2 inhibitors, which were meticulously recorded as baseline covariates.

To guarantee maximum data integrity throughout the investigation, all clinical information was independently extracted by two board-certified internal medicine physicians utilizing a rigorously standardized electronic case report form. The initial data collection captured essential baseline demographic and physiological variables, specifically encompassing the patient's age, sex, body mass index, the primary documented etiology underlying their non-diabetic chronic kidney disease, and baseline hemodynamic parameters including both systolic and diastolic blood pressure measurements. In assessing therapeutic efficacy, the primary clinical endpoints

focused on comprehensive longitudinal renal tracking. This involved measuring the absolute and relative percentage changes in the urinary albumin-to-creatinine ratio from the established baseline to prespecified analytical intervals at 6, 12, and 24 months. Additionally, the investigators meticulously mapped the exact longitudinal trajectory and calculated the annualized slope of the estimated glomerular filtration rate, strictly applying the Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine-based equation to accurately reflect renal function preservation.

Concurrently, the safety analysis was heavily weighted toward monitoring potential electrolyte derangements and maintaining hemodynamic stability within this vulnerable cohort. The primary safety endpoints were specifically defined to capture the exact incidence rate of mild hyperkalemia, classified as a serum potassium level precisely between greater than 5.0 and 5.5 mmol/L, as well as the incidence of moderate to severe hyperkalemia, defined as serum potassium levels strictly exceeding 5.5 mmol/L. Finally, to fully characterize the real-world tolerability of the intervention, the researchers tracked the absolute rate of any required clinical modifications, thoroughly documenting all finerenone dose reductions, temporary therapeutic suspensions, and permanent treatment discontinuations that were directly attributed to adverse pharmacological events.

Continuous variables were rigorously tested for normal distribution utilizing the Shapiro-Wilk test. Normally distributed parametric data were expressed as means accompanied by standard deviations, while non-normally distributed non-parametric data were reported as medians accompanied by interquartile ranges. Categorical variables were expressed as absolute frequencies and corresponding percentages. To appropriately handle the longitudinal and highly skewed nature of the urinary albumin-to-creatinine ratio data without inflating Type I error rates via multiple testing, the continuous effect of the drug on albuminuria was modeled utilizing a Generalized Linear Mixed Model (GLMM) on log-transformed data.

The complex longitudinal trajectory of the estimated glomerular filtration rate over the entire 24-month period was modeled utilizing a piecewise linear mixed-effects model (spline model) incorporating random intercepts and slopes to rigorously account for intra-patient correlation over continuous time points. A knot was placed precisely at Month 6. This sophisticated modeling allowed the calculation of two distinct, highly informative slopes: an acute slope (Baseline to Month 6) representing the initial, purely hemodynamic effect of the drug, and a chronic slope (Month 6 to Month 24) representing the true long-term antifibrotic structural preservation. The fixed effects of the linear mixed-effects model were rigorously adjusted for critical baseline covariates, specifically baseline proteinuria, underlying hypertension status, and background SGLT2 inhibitor usage. Finally, a multivariable logistic regression analysis model was constructed to identify specific independent baseline clinical predictors associated with the development of incident hyperkalemia. The model's discriminative ability was assessed via the C-statistic (Area Under the Receiver Operating Characteristic Curve - AUROC), and calibration was confirmed using the Hosmer-Lemeshow goodness-of-fit test. A two-sided p-value of less than 0.05 was considered statistically significant for all analyses. All advanced statistical computations were performed utilizing standard biomedical statistical software platforms.

## 3. Results and Discussion

A total of 148 continuously monitored patients successfully met all strict inclusion and exclusion criteria and formed the final analytical cohort. The baseline demographic and comprehensive clinical parameters of the cohort are detailed in Table 1. The cohort demonstrated a slight male predominance. The most common underlying etiologies for non-diabetic chronic kidney disease within this specific hospital

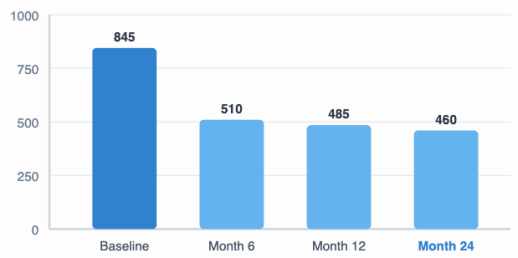
population were primary hypertensive nephrosclerosis and primary immunoglobulin A nephropathy. Background utilization of organ-protective medical therapies was remarkably high, reflecting the specialized, advanced nature of the tertiary referral center. A full 100% of the cohort was maintained on optimal ACE inhibitor or ARB therapy, and 68.9% were concurrently prescribed an SGLT2 inhibitor.

**Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (N = 148)**

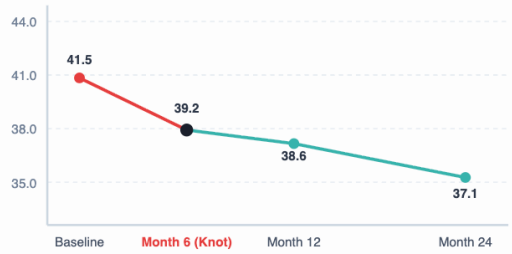
| Demographic Characteristics | Value |
|---|---|
| Age (years), Mean (SD) | 52.4 (11.8) |
| Sex, n (%) | |
| Male | 82 (55.4%) |
| Female | 66 (44.6%) |
| Body Mass Index (kg/m²), Mean (SD) | 26.3 (4.1) |
| **Primary Etiology of CKD, n (%)** | |
| Hypertensive Nephrosclerosis | 64 (43.2%) |
| IgA Nephropathy | 41 (27.7%) |
| Focal Segmental Glomerulosclerosis | 18 (12.2%) |
| Chronic Tubulointerstitial Nephritis | 15 (10.1%) |
| Undetermined / Other | 10 (6.8%) |
| **Baseline Hemodynamics, Mean (SD)** | |
| Systolic Blood Pressure (mmHg) | 138 (14) |
| Diastolic Blood Pressure (mmHg) | 82 (9) |
| **Baseline Laboratory Parameters** | |
| eGFR (mL/min/1.73 m²), Mean (SD) | 41.5 (12.3) |
| UACR (mg/g), Median (IQR) | 845 (410 - 1520) |
| Serum Potassium (mmol/L), Mean (SD) | 4.4 (0.3) |
| **Background Medications, n (%)** | |
| ACE Inhibitor or ARB | 148 (100%) |
| SGLT2 Inhibitor | 102 (68.9%) |
| Statins | 115 (77.7%) |
| Calcium Channel Blockers | 88 (59.5%) |

The continuous administration of finerenone was associated with an early, profound, and highly sustained reduction in pathological albuminuria across the observed cohort. Modeled utilizing the generalized linear mixed model, the median urinary albumin-to-creatinine ratio decreased significantly from a baseline of 845 mg/g to 510 mg/g by month 6. This represents a robust initial therapeutic response that continued to improve and was strictly maintained through the terminal month 24 observation point, reaching a final median of 460 mg/g, representing a 45.5% relative reduction. Regarding overall renal function, the piecewise linear mixed-effects model precisely captured an initial, purely hemodynamically driven dip in the estimated glomerular filtration rate within the first six months of active therapy. Following this acute phase, the subsequent longitudinal annualized slope of decline stabilized remarkably, adjusting for baseline covariates. The acute annualized slope (Month 0 to Month 6) was calculated at -4.6 mL/min/1.73 m² per year (95% CI: -5.3 to -3.9), reflecting the initial hemodynamic pressure relief. Crucially, the chronic structural annualized slope (Month 6 to Month 24) stabilized substantially to -2.2 mL/min/1.73 m² per year (95% CI: -2.8 to -1.6), detailed in Figure 1.

**Longitudinal UACR Reduction (mg/g)**




**Piecewise eGFR Trajectory (mL/min/1.73 m²)**




**Absolute and Percentage Reduction in UACR**

| Parameter | Baseline | Month 6 | Month 12 | Month 24 |
|---|---|---|---|---|
| UACR (mg/g), Median (IQR) | 845 (410 - 1520) | 510 (245 - 980) | 485 (210 - 920) | 460 (195 - 890) |
| Absolute UACR Reduction | 0 | -335 | -360 | -385 |
| UACR Reduction Percentage (%) | 0.0% | 39.6% | 42.6% | 45.5% |

**eGFR Trajectories (Adjusted Piecewise LMM)**

| Parameter | Baseline | Month 6 | Month 12 | Month 24 |
|---|---|---|---|---|
| eGFR (mL/min/1.73 m²), Mean (SD) | 41.5 (12.3) | 39.2 (11.8) | 38.6 (12.0) | 37.1 (12.5) |
| Acute Annualized Slope (Month 0-6) | — | -4.6 mL/min/yr | — | — |
| Chronic Annualized Slope (Month 6-24) | — | — | -2.2 mL/min/yr (95% CI: -2.8 to -1.6) | |

*Figure 1. Primary Clinical Outcomes: Proteinuria Reduction and Estimated Glomerular Filtration Rate Preservation Over 24 Months, modeled via generalized and piecewise linear mixed-effects analysis.*

The safety analysis demonstrated a mild, predictable elevation in mean serum potassium levels across the cohort, which stabilized early in the treatment course. The mean serum potassium rose from a baseline of 4.4 mmol/L to 4.6 mmol/L by month 6, remaining stable thereafter through month 24 ($p = 0.045$). The therapy was well tolerated; while mild hyperkalemia occurred in 16.2% of the population, moderate to severe hyperkalemia (> 5.5 mmol/L) occurred in only 4.1%. There were zero hospitalizations strictly due to hyperkalemia and zero reported incidents of drug-induced gynecomastia. Clinical interventions primarily involved temporary dietary potassium restriction or brief dose suspensions, with only 2.0% of the cohort requiring permanent cessation of the medication, detailed in Figure 2.

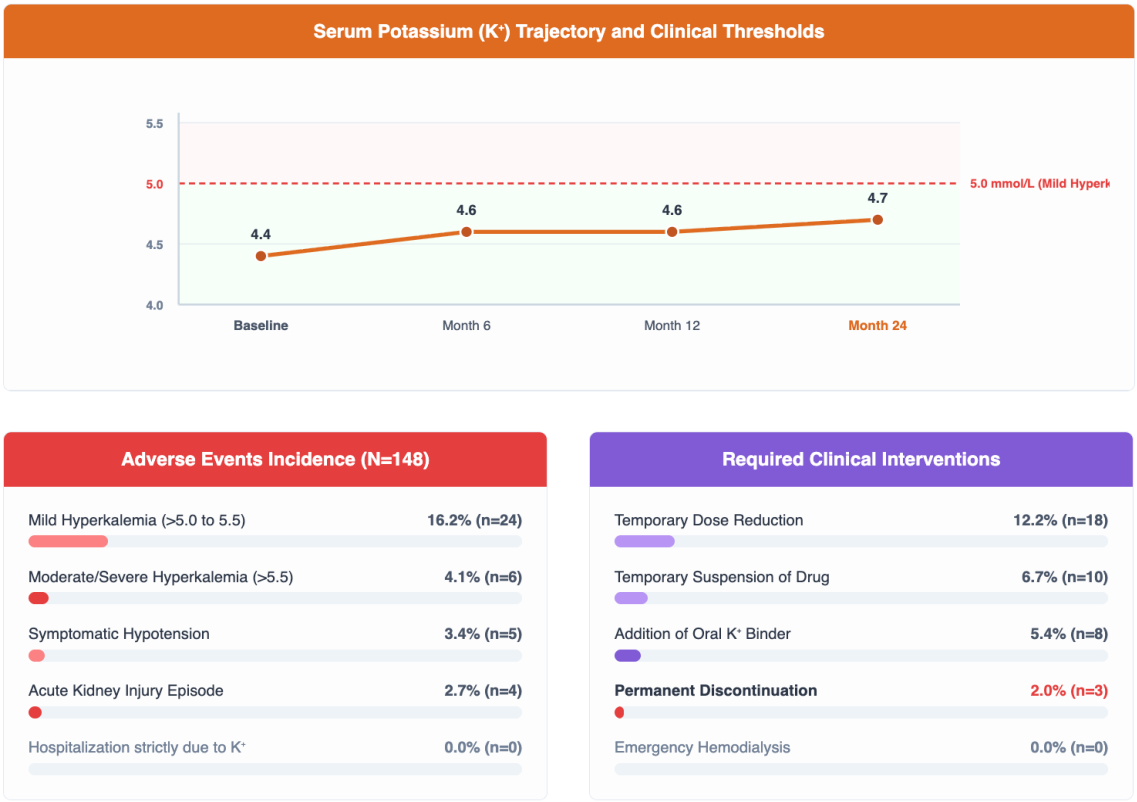
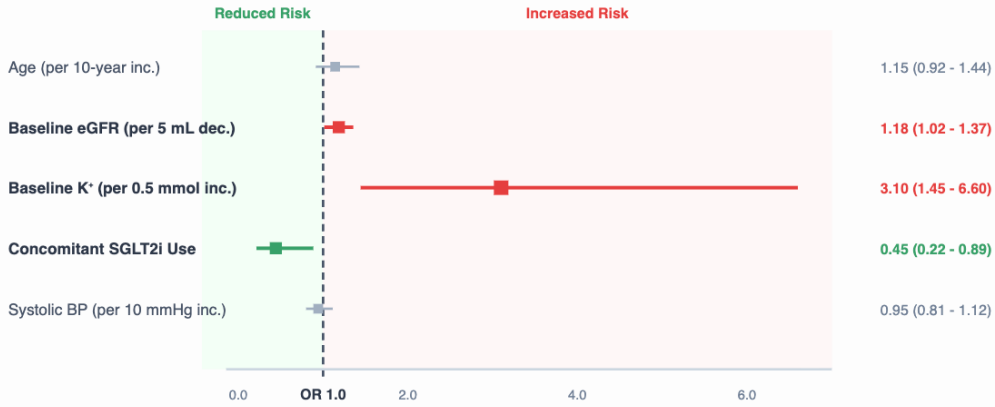



*Figure 2. Safety Profile: Serum Potassium (K⁺) Dynamics, Adverse Events Incidence, and Required Clinical Interventions Over 24 Months.*

To guide clinical practice, a multivariable logistic regression model was deployed to identify independent predictors for the development of any incident hyperkalemia (> 5.0 mmol/L) during the observation period. The model demonstrated excellent discriminative ability (AUROC = 0.79) and appropriate calibration (Hosmer-Lemeshow $p = 0.42$). As detailed in Figure 3, elevated baseline serum potassium levels drastically increased the risk of incident hyperkalemia (OR 3.10 for every 0.5 mmol/L increase, $p = 0.012$). Conversely, the concomitant background use of an SGLT2 inhibitor was highly protective, independently reducing the odds of developing hyperkalemia by 55% (OR 0.45, 95% CI 0.22 - 0.89, $p = 0.021$).

**Forest Plot: Multivariable Logistic Regression (Odds Ratios)**




| Predictor Variable | Odds Ratio (OR) | 95% Confidence Interval | p-value |
|---|---|---|---|
| Age (per 10-year increase) | 1.15 | 0.92 – 1.44 | 0.21 |
| Baseline eGFR (per 5 mL/min decrease) | **1.18** | **1.02 – 1.37** | **0.031*** |
| Baseline Serum K⁺ (per 0.5 mmol/L increase) | **3.10** | **1.45 – 6.60** | **0.012*** |
| Concomitant SGLT2 Inhibitor Use | **0.45** | **0.22 – 0.89** | **0.021*** |
| Systolic Blood Pressure (per 10 mmHg increase) | 0.95 | 0.81 – 1.12 | 0.48 |
| **Model Discriminative Ability (AUROC): 0.79** | | **Hosmer-Lemeshow Goodness-of-Fit: p = 0.42** | |

*Figure 3. Forest plot and data table demonstrating multivariable logistic regression analysis of independent baseline clinical predictors for the development of incident hyperkalemia (> 5.0 mmol/L). Variables with confidence intervals that do not cross the 1.0 odds ratio threshold (*) are statistically significant.*

This descriptive retrospective cohort study provides compelling real-world evidence exploring the clinical association between finerenone, a highly selective novel non-steroidal mineralocorticoid receptor antagonist, and longitudinal outcomes strictly within a non-diabetic chronic kidney disease population. The comprehensive findings systematically demonstrate that the intervention is associated with a continuous, sustained reduction in pathological albuminuria, coupled with an apparent stabilization of the chronic glomerular filtration rate trajectory over a 24-month longitudinal observation period. Furthermore, the safety profile regarding the expected risk of hyperkalemia was highly manageable within a routine outpatient setting in Indonesia. This observational data addresses and assuages the primary clinical barrier that has historically precluded the routine use of older steroidal agents in populations with advanced, progressive renal impairment.[11]

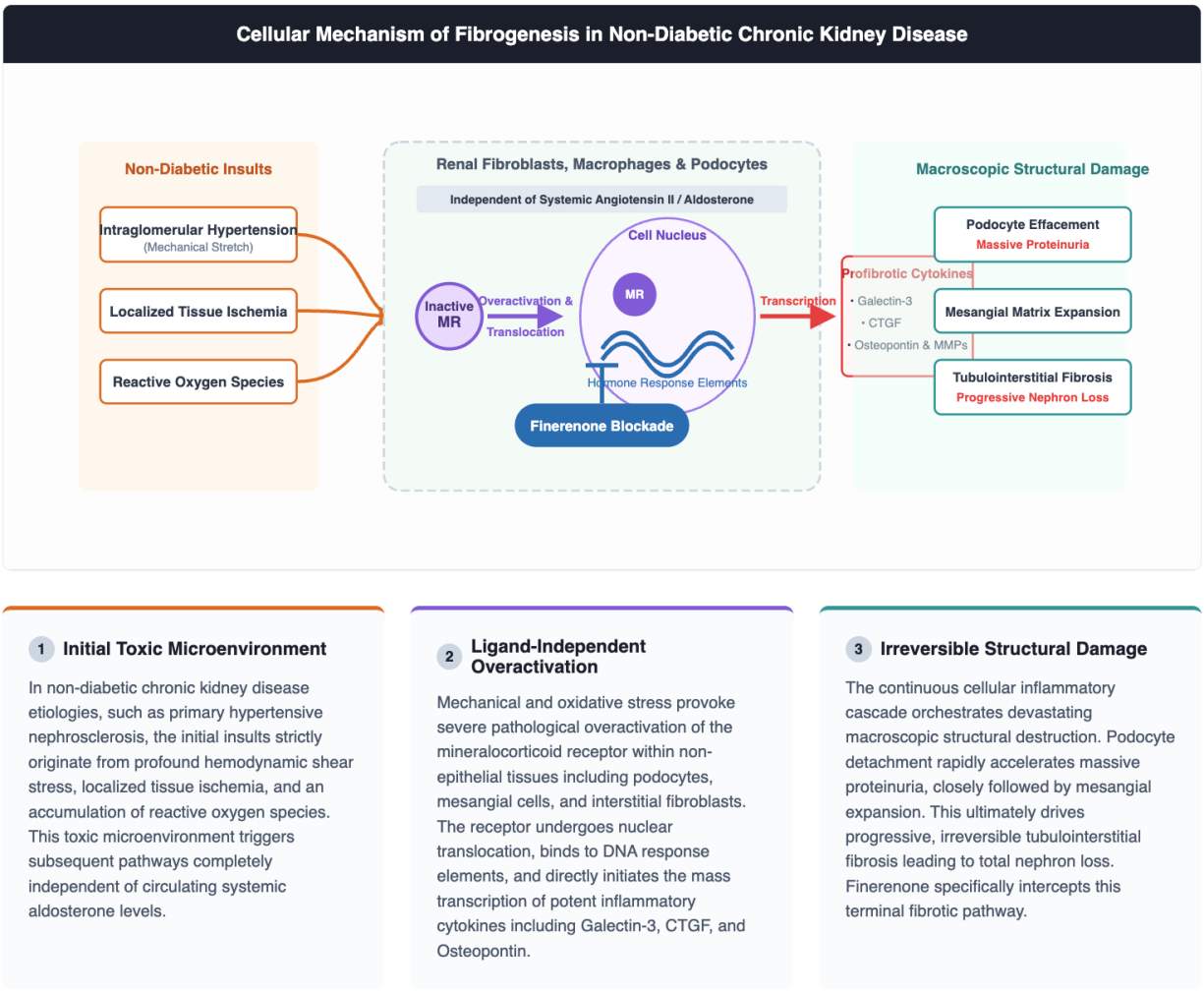



*Figure 4. Schematic representation detailing the precise cellular pathophysiology of ligand-independent mineralocorticoid receptor overactivation in non-diabetic chronic kidney disease. The diagram illustrates the continuous molecular cascade from initial mechanical and oxidative insults to terminal fibrogenesis, highlighting the exact pharmacological interception point of finerenone.*

To properly contextualize the magnitude of these clinical findings, it is essential to delve deeply into the underlying cellular and molecular pathophysiology of the mineralocorticoid receptor within the renal parenchyma.[12] Historically, the medical and scientific community viewed aldosterone almost exclusively as a systemic endocrine hormone responsible for sodium homeostasis, intravascular volume regulation, and blood pressure control via its action on the epithelial cells of the distal convoluted tubule and the cortical collecting duct. However, contemporary advances in molecular biology and transcriptomics have definitively elucidated that the mineralocorticoid receptor is ubiquitously expressed in non-epithelial tissues throughout the entire kidney. This includes dense receptor populations within glomerular podocytes, mesangial cells, vascular endothelial cells, smooth muscle cells, and tubulointerstitial fibroblasts.[13] In the highly toxic microenvironment of chronic kidney disease, severe mechanical stretch originating from intraglomerular hypertension, localized tissue ischemia, and chronically elevated

levels of reactive oxygen species provoke the severe pathological overactivation of the mineralocorticoid receptor. Critically, this receptor overactivation occurs entirely independent of systemic angiotensin II levels or circulating systemic aldosterone levels. This ligand-independent activation perfectly explains why maximal therapeutic doses of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers uniformly fail to halt the long-term progression of renal disease—a well-documented phenomenon clinically referred to as aldosterone breakthrough. Once pathologically activated in renal fibroblasts and infiltrating macrophages, the mineralocorticoid receptor rapidly undergoes nuclear translocation and directly binds to specific hormone response elements on the host DNA. This exact binding event directly and forcefully initiates the mass transcription of extremely potent profibrotic and proinflammatory cytokines. The downstream targets heavily include galectin-3, connective tissue growth factor, osteopontin, and various matrix metalloproteinases. Over continuous months and years, this microscopic, relentless inflammatory cascade orchestrates devastating macroscopic structural damage. The clinical manifestations begin with podocyte effacement and detachment, leading directly to the massive proteinuria observed in the study's baseline data. This is rapidly followed by mesangial matrix expansion, widespread focal segmental glomerulosclerosis, and ultimately, progressive, irreversible tubulointerstitial fibrosis leading to complete nephron loss and end-stage renal disease.[14] In specific non-diabetic etiologies such as primary hypertensive nephrosclerosis or primary immunoglobulin A nephropathy, the initial acute insult is strictly hemodynamic sheer stress or aberrant immune complex deposition in the mesangium, respectively. Yet, the final common pathway driving the chronicity and irreversibility of the disease state is the continuous, maladaptive fibrotic tissue remodeling mediated heavily by the unchecked mineralocorticoid receptor. By strategically deploying a non-steroidal antagonist, this exact specific final common pathway of fibrosis is therapeutically intercepted and blocked, theoretically independent of the original disease trigger, detailed in Figure 4.

The profound clinical results documented in the present study, specifically showcasing a 45.5% relative median reduction in the urinary albumin-to-creatinine ratio without a corresponding massive, dangerous spike in severe hyperkalemia, perfectly highlight the critical structural and pharmacological differences between finerenone and traditional steroidal agents like spironolactone or eplerenone. Steroidal mineralocorticoid receptor antagonists are fundamentally flat, planar steroid molecules. They bind to the mineralocorticoid receptor and act purely as passive, bulky antagonists, occupying the receptor site but allowing the receptor to maintain a somewhat active molecular conformation. Furthermore, steroidal agents accumulate extensively in the renal tissue at concentrations vastly higher than in the myocardium, leading to pronounced, localized electrogenic shifts in the distal nephron. This massive localized accumulation severely impairs essential potassium excretion mechanisms, leading to the notoriously high rates of hyperkalemia that limit their clinical utility.[15]

In stark pharmacological contrast, finerenone is a non-steroidal, highly bulky, three-dimensional dihydropyridine-derivative molecule.[16] Upon binding to the mineralocorticoid receptor, finerenone forces the receptor to undergo a highly specific, restrictive structural conformational change. This altered three-dimensional shape physically and completely prevents the receptor from recruiting the essential transcriptional coregulators strictly required to express the downstream fibrotic and inflammatory genes. Consequently, finerenone acts as a highly potent, active inverse agonist for inflammation and fibrosis, actively shutting down the disease process rather than passively blocking a binding site. Crucially regarding safety, finerenone exhibits a perfectly equal

tissue distribution ratio between the heart and the kidney. Furthermore, it possesses a remarkably short plasma half-life of roughly two to three hours and produces zero active metabolites. This balanced tissue distribution and complete lack of prolonged, localized tissue accumulation perfectly explain the highly muted effect on distal tubule potassium transport. This specific pharmacokinetic profile is the primary mechanistic reason for the highly favorable, manageable safety profile observed in this cohort, where a mere 2.0% of patients required permanent discontinuation due to hyperkalemia, despite the presence of advanced stage 3 and 4 chronic kidney disease.[17]

The data regarding the trajectory of the estimated glomerular filtration rate perfectly align with the expected hemodynamic physiological response to potent intrarenal blockade. Internal medicine practitioners are often concerned when initiating a nephroprotective agent results in an acute rise in serum creatinine.[18] However, the initial reduction in estimated glomerular filtration rate observed during the first six months of therapy (represented by the acute piecewise slope of -4.6 mL/min/yr) is absolutely not indicative of structural acute kidney injury or nephrotoxicity. Rather, it strictly represents a benign, reversible hemodynamic phenomenon. By blocking the mineralocorticoid receptor, finerenone reduces localized intraglomerular pressure, slightly lowering the filtration rate initially, which simultaneously rapidly diminishes the mechanical stretch on podocytes, immediately reducing proteinuria. Following this initial protective hemodynamic reset, the pure antifibrotic mechanisms dominate the long-term clinical picture, successfully blunting the long-term, irreversible structural decline of the nephron mass as evidenced by the stabilization of the chronic slope to -2.2 mL/min/yr.

Furthermore, the baseline data reveal that 68.9% of the cohort was concomitantly utilizing sodium-glucose cotransporter-2 inhibitors. Recent theoretical physiological models and emerging data suggest a profoundly synergistic physiological relationship between these two distinct drug classes. Sodium-glucose cotransporter-2 inhibitors fundamentally alter tubuloglomerular feedback and vastly increase distal tubular sodium delivery. This enhanced distal sodium delivery directly promotes necessary potassium excretion via the sodium-potassium exchange channels, thereby powerfully mitigating the mild potassium-retaining effects of the mineralocorticoid receptor antagonist. This theoretical mechanism is beautifully validated by our multivariable regression analysis, which proved that concomitant SGLT2 inhibitor use was an independent, powerful predictor of lower hyperkalemia risk. The dual, simultaneous targeting of glomerular hemodynamics via the sodium-glucose cotransporter-2 inhibitor and direct interstitial fibrosis via finerenone almost certainly contributed directly to the robust, combined stabilization of the estimated glomerular filtration rate observed longitudinally in this specific cohort.[19]

The baseline demographic data meticulously reflect a highly typical Southeast Asian non-diabetic chronic kidney disease cohort, characterized heavily by a high prevalence of hypertensive nephrosclerosis. Traditional Indonesian diets are frequently extremely rich in dietary potassium, heavily derived from tropical fruits, raw coconut water, and specific regional root vegetables. This distinct cultural and dietary pattern inherently and substantially elevates the baseline population risk of hyperkalemia, particularly in patients with already compromised renal clearance capabilities.[20] The critical finding that hyperkalemia was seamlessly managed—frequently requiring only minor, temporary dietary counseling interventions or brief, temporary dose adjustments rather than catastrophic hospital admissions—is a profoundly important, practice-changing validation for regional practicing nephrologists and general internists. It demonstrates that the theoretical risks of advanced therapy can be safely mitigated with standard clinical

vigilance, even in potassium-rich environments.

This study contains highly significant inherent limitations typical of retrospective observational study designs. The most severe limitation is the strict lack of a randomized, double-blinded, active-comparator placebo control group. Without a matched comparator, it is mathematically impossible to definitively prove causality; the findings must be interpreted strictly as associative. The stabilization of the estimated glomerular filtration rate observed could partially represent the natural, heterogeneous trajectory of patients aggressively managed at a premier private tertiary referral center, subject to regression to the mean. Furthermore, the inclusion criteria mandating a minimum of 24 months of continuous, uninterrupted follow-up inherently introduce severe survivorship and immortal time bias into the analysis. As noted in the methods, 62 patients were excluded, some due to early discontinuation or death. This systematically guarantees that the final reported cohort (N=148) represents the most compliant fraction of the actual treated population who biologically tolerated the drug, inherently and artificially inflating both the safety and long-term efficacy profiles presented. Finally, the potential for unmeasured confounding factors remains high, and these data should not be used as a standalone justification for universal treatment protocols outside of clinical trial settings.

## 4. Conclusion

In this real-world, single-center observational cohort, the addition of finerenone to standard care in advanced non-diabetic chronic kidney disease patients was associated with significant reductions in pathological albuminuria and a substantial attenuation of estimated glomerular filtration rate decline over a 24-month period. The therapy exhibited a highly favorable, manageable safety profile, circumventing the severe hyperkalemia historically associated with older steroidal agents, largely facilitated by synergistic co-administration with SGLT2 inhibitors. While these findings suggest significant potential clinical utility in blocking intrarenal fibrogenesis, large, randomized, placebo-controlled clinical trials are strictly required to definitively establish therapeutic efficacy within broad non-diabetic populations.

## 5. References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