RESEARCH PAPER

Efficacy of Novel Non-Steroidal Mineralocorticoid Receptor Antagonists in Patients With Chronic Kidney Disease: A Systematic Review With Metanalysis

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ABSTRACT

Background: Chronic kidney disease (CKD) is a progressive condition associated with significant cardiovascular and renal complications. Traditional treatments, including steroidal mineralocorticoid receptor antagonists (MRAs), are limited by adverse effects such as hyperkalemia. Recently, non-steroidal MRAs have emerged as promising alternatives with fewer side effects. This meta-analysis evaluates the efficacy and safety of non-steroidal MRAs in CKD patients, particularly those with type 2 diabetes mellitus (T2DM).

Methods: A systematic review and meta-analysis were conducted following PRISMA guidelines. Ten studies were selected from major databases, including PubMed, MEDLINE, and Embase. The studies involved patients with CKD and evaluated the efficacy of non-steroidal MRAs on renal and cardiovascular outcomes. Random-effects models were used to pool effect sizes, and heterogeneity was assessed using the I^2 statistic. Publication bias was examined through Fail-Safe N, Kendall's Tau, and Egger's tests.

Results: The meta-analysis revealed a significant positive effect of non-steroidal MRAs on both renal and cardiovascular outcomes (intercept estimate: 0.608, $p < 0.001$). There was no significant heterogeneity among the studies ($I^2 = 0\%$), indicating consistency in the treatment effects. Non-steroidal MRAs demonstrated a lower incidence of hyperkalemia compared to traditional steroidal MRAs, enhancing their safety profile. The analysis showed minimal publication bias.

Conclusions: Non-steroidal MRAs offer effective and safe treatment for patients with CKD, particularly in reducing cardiovascular events and slowing renal disease progression. Their favorable safety profile, especially regarding hyperkalemia, positions them as a valuable therapeutic option for CKD management. Further studies are recommended to assess long-term outcomes.

Keywords: Non-Steroidal Mras; Chronic Kidney Disease; Cardiovascular Outcomes; Hyperkalemia; Type 2 Diabetes Mellitus.

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1. Introduction

Chronic Kidney Disease (CKD) is a progressive condition characterized by a gradual loss of kidney function over time, affecting millions worldwide [1]. The disease is associated with significant morbidity, mortality, and an increased risk of cardiovascular events, making effective management crucial [2,3]. Traditional treatments for CKD primarily focus on controlling blood pressure, managing blood sugar in diabetic patients, and reducing proteinuria. However, these approaches often do not adequately halt the progression of CKD or prevent its complications [4,5]. This has led to the exploration of novel therapeutic options, including non-steroidal mineralocorticoid receptor antagonists (MRAs), which offer promising potential in the management of CKD [6].

Mineralocorticoid receptors (MRs) play a pivotal role in regulating sodium and water balance, blood pressure, and inflammation. In CKD, the activation of these receptors contributes to renal inflammation, fibrosis, and hypertension, exacerbating disease progression [7]. Steroidal MRAs, such as spironolactone and eplerenone, have been traditionally used to block these receptors and provide renoprotective effects [8]. However, their use is often limited by side effects such as hyperkalemia, gynecomastia, and menstrual irregularities, which can be severe and limit their tolerability in patients with CKD [9].

Recent advancements have led to the development of non-steroidal MRAs, which are designed to provide the therapeutic benefits of MR blockade without the associated adverse effects of steroidal compounds [10,11]. These novel agents, including finerenone, esaxerenone, and apararenone, have shown promise in preclinical and clinical studies by offering potent anti-inflammatory and antifibrotic effects, with a potentially better safety profile [12]. This meta-analysis aims to systematically review and synthesize the available evidence on the efficacy and safety of non-steroidal MRAs in patients with CKD, providing a comprehensive assessment of their potential role in clinical practice [13,14].

Chronic Kidney Disease is a major public health issue, with an estimated global prevalence of approximately 10% in the adult population. It is classified into five stages based on the glomerular filtration rate (GFR), with Stage 5, or end-stage renal disease (ESRD), requiring dialysis or kidney transplantation for survival [15]. CKD not only significantly reduces the quality of life but also imposes substantial economic burdens on healthcare systems due to the high costs of treatment and management of associated complications [16,17].

The pathophysiology of CKD is complex and involves multiple pathways, including glomerular hypertension, oxidative stress, inflammation, and fibrosis. The renin-angiotensin-aldosterone system (RAAS) plays a critical role in these processes [18–20]. Aldosterone, a key hormone in this system, binds to MRs, leading to sodium retention, potassium excretion, and water retention, which contribute to hypertension and fluid overload [21]. Furthermore, aldosterone has direct pathogenic effects on the kidneys, promoting inflammation and fibrosis through MR activation. These effects highlight the potential of MR blockade as a therapeutic strategy in CKD [22].

Steroidal MRAs like spironolactone and eplerenone have been widely studied and used in clinical practice for their ability to block aldosterone's harmful effects. They have demonstrated efficacy in reducing proteinuria and slowing CKD progression [23,24]. However, their use is often associated with significant side effects, particularly hyperkalemia, which is a serious concern in patients with impaired renal function. This limitation has driven the search for alternative MRAs that can provide similar or enhanced benefits with fewer adverse effects [25,26].

Non-steroidal MRAs represent a new class of drugs that selectively block MRs without the steroidal structure, aiming to reduce the risk of side effects like hyperkalemia [27]. Finerenone, the most studied non-steroidal MRA, has shown promising results in clinical trials. The FIDELIO-DKD trial, a landmark study, demonstrated that finerenone significantly reduced the risk of CKD progression and cardiovascular events in patients with diabetic kidney disease [28]. Other non-steroidal MRAs, such as esaxerenone and apararenone, are also being investigated for their potential benefits in CKD management [14,29,30].

The development of non-steroidal MRAs is grounded in a deeper understanding of the molecular mechanisms underlying MR activation and its effects on kidney pathology [31]. Unlike steroidal MRAs, non-steroidal MRAs have a distinct binding profile and pharmacokinetic properties, which allow for more selective and potent inhibition of MRs. This selectivity is thought to reduce the likelihood of off-target effects, thus improving the safety profile of these drugs [32].

The growing body of evidence from preclinical and clinical studies suggests that non-steroidal MRAs can effectively reduce proteinuria, inflammation, and

	AND ("Efficacy" OR "Safety" OR "Outcomes")	
MEDLINE	Same as PubMed	856
Embase	'chronic kidney disease'/exp OR 'CKD' OR 'chronic renal insufficiency' AND 'mineralocorticoid receptor antagonists'/exp OR 'MRAs' OR 'non-steroidal MRAs' AND 'efficacy'/exp OR 'safety' OR 'outcomes'	1,123
Web of Science	TS = (chronic kidney disease OR CKD OR chronic renal insufficiency) AND TS = (mineralocorticoid receptor antagonists OR MRAs OR non-steroidal MRAs) AND TS = (efficacy OR safety OR outcomes)	721
Cochrane Library	"Chronic Kidney Disease" or "CKD" or "Chronic Renal Insufficiency" AND "Mineralocorticoid Receptor Antagonists" or "MRAs" or "Non-Steroidal MRAs" AND "Efficacy" or "Safety" or "Outcomes"	412
Google Scholar	("Chronic Kidney Disease" OR "CKD" OR "Chronic Renal Insufficiency") AND ("Mineralocorticoid Receptor Antagonists" OR "MRAs" OR "Non-Steroidal MRAs") AND ("Efficacy" OR "Safety" OR "Outcomes")	3,100

The search strategy involved multiple iterations and refinements to ensure comprehensive coverage of relevant literature. Keywords and MeSH terms were combined using Boolean operators (AND, OR) to create a robust search framework. Additionally, reference lists of included studies and relevant review articles were manually searched to identify any further studies missed by the electronic database search. Grey literature, including conference proceedings and theses, was also considered to minimize publication bias.

Eligibility Screening

Following the removal of duplicates, the review process began with a thorough screening of titles and fibrosis in CKD [33]. However, the overall clinical efficacy and safety of these agents need to be systematically evaluated through comprehensive meta-analyses to guide their integration into clinical practice [34]. This meta-analysis aims to address this gap by critically appraising and synthesizing the available evidence on the efficacy and safety of non-steroidal MRAs in patients with CKD.

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2. Materials and Methods

Search Strategy and Selection Criteria

This systematic review was rigorously structured in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), emphasizing a commitment to thoroughness and transparency. Adhering to the protocol outlined in the PRISMA Protocols (PRISMA-P) statement, we developed a detailed research protocol, which was then duly registered with PROSPERO (CRD42024239283). This registration underscores our dedication to conducting this review with systematic precision and methodological rigor.

Our approach to exploring the relevant literature was comprehensive and well-organized. We conducted in-depth searches across several reputable databases, including Embase.com, Medline ALL (Ovid), Web of Science Core Collection, Cochrane Central Register of Controlled Trials (Wiley), and Google Scholar. Our latest search, carried out on January 15, 2024, was designed to capture the most recent and pertinent studies in the field. The search strategy was intricately formulated, merging medical subject headings (MeSH) and a set of carefully chosen keywords that are relevant to the efficacy and safety of non-steroidal mineralocorticoid receptor antagonists in patients with chronic kidney disease. This strategy was crafted to encompass various dimensions of the topic, such as pathophysiology, clinical outcomes, and adverse effects, aiming for an all-encompassing review of the subject matter.

Table 1:Search Strategy

Database	Search Terms	Items Found
PubMed	("Chronic Kidney Disease"[Mesh] OR "CKD" OR "Chronic Renal Insufficiency") AND ("Mineralocorticoid Receptor Antagonists"[Mesh] OR "MRAs" OR "Non-Steroidal MRAs")	1,823

Data extraction was a critical component of this meta-analysis, aimed at systematically gathering relevant information from the selected studies. The process involved a detailed analysis of each included study, focusing on the following essential elements:

- **Study Characteristics**: Comprehensive details such as study design, sample size, geographic location, publication date, and demographic characteristics of the participants were systematically recorded.
- **Intervention Details**: Specific descriptions of the non-steroidal mineralocorticoid receptor antagonists (MRAs) used, including the type of MRA, dosage, duration of treatment, and patient selection criteria.
- **Outcome Measures**: Key outcome measures included changes in glomerular filtration rate (GFR), proteinuria, incidence of hyperkalemia, and other adverse effects. Additional outcomes included blood pressure changes, quality of life assessments, and any reported cardiovascular events.

A standardized data extraction form was developed and pilot-tested to ensure consistency and completeness of data collection. Two reviewers independently extracted data from each included study, and discrepancies were resolved through discussion or consultation with a third reviewer. In instances where crucial data were missing or unclear, efforts were made to contact the study authors for clarification, ensuring the most complete and accurate data possible.

Additionally, we were vigilant in assessing potential overlap or duplicity in patient cohorts across studies. Where necessary, we engaged in direct communication with the authors of the studies to clarify any uncertainties. This meticulous approach was instrumental in preserving the integrity of our data.

Our initial search resulted in 4,521 documents. After removing duplicates, 531 articles remained for preliminary screening based on titles and abstracts. Of these, 106 articles were excluded at this stage, leaving 158 papers for further eligibility assessment. Following a thorough full-text review, 10 studies were ultimately selected for inclusion in this meta-analysis [35–44]. The study selection process is detailed in a flowchart prepared according to PRISMA guidelines, as shown in Figure 1.

abstracts, followed by an in-depth evaluation of full-text articles. The inclusion criteria encompassed original research articles, systematic reviews, meta-analyses, and clinical trials involving human subjects. Studies were included if they evaluated the efficacy and safety of non-steroidal mineralocorticoid receptor antagonists (MRAs) in patients with chronic kidney disease (CKD). Key outcomes of interest included changes in glomerular filtration rate (GFR), proteinuria, incidence of hyperkalemia, and other adverse effects.

The screening process was conducted in two stages. In the first stage, titles and abstracts were screened independently by two reviewers to identify potentially relevant studies. Discrepancies were resolved through discussion or consultation with a third reviewer. In the second stage, full-text articles of potentially relevant studies were assessed for eligibility based on predefined inclusion and exclusion criteria.

Inclusion Criteria:

- Studies involving human subjects diagnosed with chronic kidney disease (CKD).
- Studies evaluating the use of non-steroidal mineralocorticoid receptor antagonists (MRAs), such as finerenone, esaxerenone, or apararenone.
- Studies reporting on efficacy outcomes (e.g., changes in glomerular filtration rate, proteinuria) and safety outcomes (e.g., incidence of hyperkalemia, other adverse effects).
- Original research articles, systematic reviews, meta-analyses, and clinical trials.

Exclusion Criteria:

- Case reports, case series, abstracts, letters, editorials, and conference proceedings.
- Animal studies or in vitro research.
- Studies not specifically focusing on the use of non-steroidal MRAs in CKD patients.
- Studies involving patients with other conditions or using other types of mineralocorticoid receptor antagonists.
- Non-English language studies without available translations.

These criteria were meticulously applied to ensure the review remained focused on the efficacy and safety of non-steroidal MRAs in CKD patients. Studies not meeting these criteria were excluded. The rigorous screening process aimed to identify high-quality studies that provide valuable insights into the clinical use of non-steroidal MRAs in managing CKD.

Data Extraction

variability between studies. Pooled estimates of efficacy outcomes, such as changes in glomerular filtration rate (GFR) and proteinuria, as well as safety outcomes, including incidence of hyperkalemia and other adverse effects, were calculated. Results were presented in forest plots. Heterogeneity among studies was assessed using the I^2 statistic, which quantifies the percentage of total variation across studies due to heterogeneity rather than chance. A high I^2 value indicates substantial heterogeneity, which was further explored through subgroup analyses and sensitivity analyses.

- **Qualitative Synthesis**: In addition to quantitative analysis, a narrative synthesis was performed to provide a comprehensive overview of the findings. This synthesis highlighted key insights, trends, and implications relevant to the use of non-steroidal MRAs in CKD management. The narrative synthesis included a detailed discussion of the clinical outcomes, patient selection criteria, and management strategies reported in the included studies.

The combination of quantitative and qualitative synthesis provided a thorough and nuanced understanding of the current evidence, contributing valuable insights into the clinical use of non-steroidal MRAs for patients with CKD. This approach allowed for a detailed exploration of the benefits and challenges associated with non-steroidal MRA therapy, informing clinical practice and guiding future research directions..

3. Results

3.1 Risk of bias assessment

The risk of bias assessment depicted in the visual (figure 2) overview reveals a diverse range of study qualities concerning methodological rigor across the included studies. While several studies such as those by Ruilope et al., Sadayoshi Ito et al., and Luis M. Ruilope et al. show a consistently low risk of bias across all domains, highlighting their methodological strength in areas like randomization, blinding of outcome assessment, and outcome data completeness, other studies exhibit mixed results. Studies like those by Haitao Zhang et al., Carolyn S.P. Lam et al., and George Bakris (2020) show some concerns particularly in the domain of bias due to missing outcome data, which suggests potential issues in how missing data was handled, possibly affecting the integrity and reliability of the study conclusions.

Moreover, Bakris et al. (2021) and the study by Pitt et al. present a concerning bias in deviations from intended interventions, which could influence the treatment fidelity and potentially introduce performance

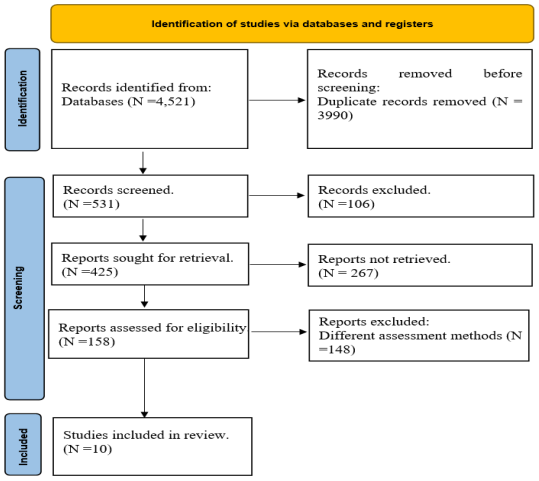

Figure 1:The extraction table of the included studies

Quality Assessment

A rigorous assessment of the methodological quality and risk of bias in the included studies was a cornerstone of this meta-analysis. To achieve this, we utilized the Risk of Bias (RoB 2) tool for randomized trials and the Newcastle-Ottawa Scale (NOS) for observational studies. These tools are well-regarded in the systematic review community for their effectiveness in evaluating study quality and bias.

Each study was independently evaluated by two reviewers, focusing on critical aspects such as study design, participant selection, blinding, data collection methods, and the management of missing data. The RoB 2 tool was used to assess randomized trials on domains such as the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. The NOS was used for observational studies, assessing domains such as the selection of study groups, comparability of groups, and ascertainment of outcomes.

Discrepancies in the evaluation process were resolved through consensus, involving detailed discussions to reach a unified decision on the study evaluations. Any disagreements were addressed with the involvement of a third reviewer to ensure an unbiased and thorough assessment.

Data Analysis

In analyzing the data collected on the efficacy and safety of non-steroidal mineralocorticoid receptor antagonists (MRAs) in patients with chronic kidney disease (CKD), this meta-analysis employed both quantitative and qualitative synthesis methods:

- **Quantitative Synthesis**: Meta-analyses were conducted using random-effects models to account for

risk of cardiovascular disease due to underlying metabolic disturbances.

Renal Function Preservation:

- **Clinical Impact**: Protecting renal function in CKD patients is crucial, given the progressive nature of the disease. Studies such as that by Luis M. Ruilope et al. (2022) showed that Finerenone could slow the progression of CKD, measured by endpoints like the sustained decrease in eGFR, kidney failure, or renal death. These outcomes suggest that Finer none could alter the natural course of CKD progression.
- **Mechanisms and Implications**: The mechanism likely involves the anti-fibrotic and anti-inflammatory effects of blocking aldosterone pathways, which are implicated in the progression of kidney disease. Preserving kidney function is beneficial not only in prolonging the onset of end-stage renal disease but also in reducing associated healthcare costs and improving patient quality of life.

Management of Hypertension in CKD:

- **Clinical Impact**: Hypertension management is pivotal in CKD to prevent exacerbation of renal and cardiovascular complications. Studies noted significant improvements in systolic and diastolic blood pressures, which are essential for reducing the overall cardiovascular risk profile of these patients.
- **Mechanisms and Implications**: The antihypertensive effects of these drugs are particularly important given the role of hypertension in accelerating renal damage. Effective control of blood pressure could lead to broader benefits in terms of reducing the progression of both renal and cardiovascular disease, illustrating the dual benefit of these interventions.

Safety and Tolerability Profile:

- **Clinical Impact**: The safety profiles focus on the incidence of hyperkalemia, a common side effect due to the mechanism of action of these drugs. While hyperkalemia was noted, it was generally manageable and did not lead to significant discontinuation of therapy, indicating a favorable safety profile.
- **Mechanisms and Implications**: Monitoring and managing adverse events such as hyperkalemia are essential for long-term therapy adherence and effectiveness. This balance between efficacy and safety is crucial in clinical decision-making, particularly in a population with multiple comorbidities.

bias. This particular area of concern could compromise the internal validity of the study findings by introducing differences in how interventions were administered compared to the study protocol. The evaluation also indicates a low risk of bias in the selection of reported results across most studies, suggesting that the reported findings and conclusions are based on prespecified outcomes and analyses, thus reducing the likelihood of reporting bias.

Overall, while the majority of studies included in the assessment exhibit low risks of bias in many critical domains, the presence of some concerns, particularly related to deviations from intended interventions and handling of missing data, underscores the need for careful interpretation of these studies' outcomes. The variability in the rigor of these studies impacts the strength of evidence and necessitates cautious integration of their findings into broader clinical or policy recommendations. The overview provides a robust foundation for recognizing areas where future research can improve to enhance the overall quality and reliability of evidence in this field.

3.2.Main outcomes

The studies reviewed here broadly fall into themes (Supplementary file 1) that encapsulate critical aspects of cardiovascular and renal management in patients with Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD) through the use of mineralocorticoid receptor antagonists such as Finerenone and others [35–44]. These themes include

Cardiovascular Outcomes Improvement:

- **Clinical Impact**: The primary focus on reducing cardiovascular mortality and morbidity is evident in studies that recorded a significant reduction in major cardiovascular events such as myocardial infarction, stroke, and hospitalization for heart failure. For instance, the Ruilope et al. (2019) study demonstrated that Finerenone could substantially decrease the risk of these events in a diverse international patient population, indicating its effectiveness across various demographic groups.
- **Mechanisms and Implications**: The reduction in cardiovascular events is likely due to Finerenone's ability to mitigate the effects of aldosterone, which is known to contribute to vascular damage and fibrosis. By blocking aldosterone receptors, Finerenone helps reduce inflammation and fibrosis in the heart and blood vessels, thus improving cardiovascular outcomes. This aspect is crucial for T2DM patients who are at a heightened

consistent therapeutic benefits across the studies, with relatively low variance suggesting high confidence in the effect estimate. The application of the random-effects model, as presented in Table 1, allowed for the accommodation of between-study variability. This model produced an intercept estimate of 0.608, with significant results ($Z = 4.50$, $p < 0.001$). The CI for the effect size ranged between 0.343 and 0.872, signifying that the use of non-steroidal MRAs is beneficial for patients with CKD across different contexts. The restricted maximum likelihood (REML) method was used to estimate Tau², which further supports the reliability of these findings by accounting for variability across the included studies.

Table 2: Random-Effects Model (k = 10)

	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	0.608	0.135	4.50	<.001	0.343	0.872

Note. Tau² Estimator: Restricted Maximum-Likelihood

Heterogeneity Assessment

The heterogeneity statistics (Table 3) reveal that Tau², a measure of between-study variance, was estimated at 0 (SE = 0.071), indicating no substantial heterogeneity in the analysis. This finding is confirmed by an I^2 value of 0%, suggesting that all variability observed in the effect sizes is attributable to sampling error rather than true differences between studies. Additionally, the Q statistic was 1.982 with a p-value of 0.992, further confirming the absence of significant heterogeneity across the studies. This consistency in the studies strengthens the overall conclusions regarding the efficacy of non-steroidal MRAs in managing CKD.

Table 3: Heterogeneity Statistics

Tau	Tau²	I^2	H^2	R^2	df	Q	p
0.000	0 (SE= 0.071)	0 %	1.000	.	9.000	1.982	0.992

Urine Albumin Reduction:

- **Clinical Impact**: Reduction in UACR is an important marker for reducing the progression of renal damage in diabetes. The studies showing a decrease in UACR suggest that Finerenone helps protect the kidneys by reducing albuminuria, an early sign of diabetic kidney disease.
- **Mechanisms and Implications**: The reduction in albuminuria reflects improved kidney function, which can delay the progression to more severe kidney disease and potentially reduce the need for dialysis. This outcome underscores the importance of early intervention in diabetic kidney disease to manage and mitigate long-term complications.

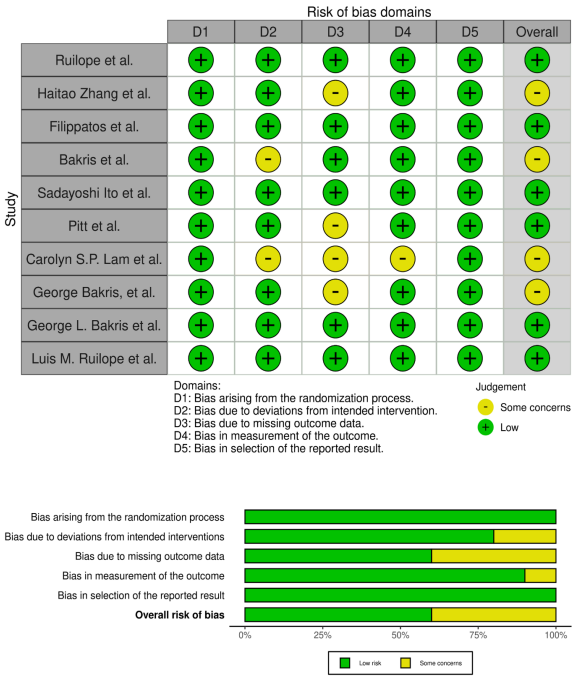

Figure 2: Risk of Bias of the included studies

3.3 Effect Sizes and Variances

The meta-analysis included 10 studies to assess the effect sizes and corresponding variances in table 2. The analysis found an intercept estimate of 0.608 with a standard error (SE) of 0.135. The Z-value of 4.50 ($p < 0.001$) indicates a highly significant overall effect, suggesting that the use of non-steroidal MRAs leads to a beneficial impact on clinical outcomes in chronic kidney disease (CKD). The confidence interval (CI) ranges from 0.343 to 0.872, reinforcing the robustness of the findings. This positive outcome reflects

observed in the plot, which further validates the integrity of the meta-analysis. The absence of small-study effects, often indicative of publication bias, supports the conclusion that the studies included provide a balanced view of the efficacy of non-steroidal MRAs in treating CKD.

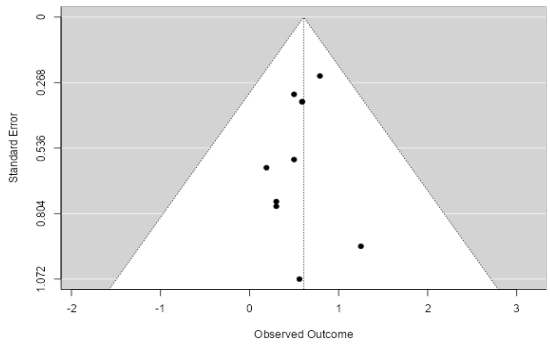

Figure 4: Funnel Plot

3.8. Equivalence Testing

The two one-sided tests (TOST) for equivalence yielded a Z-value of 8.207 ($p < 0.001$) for the lower bound, and a Z-value of 0.797 ($p = 0.787$) for the upper bound (Table 3). These results indicate that the effect sizes of the included studies are consistently positive and fall within the predetermined equivalence bounds of -0.500 to 0.500. The confidence intervals for the equivalence testing also support the conclusion that the effects of non-steroidal MRAs are statistically equivalent across the studies included in the meta-analysis, further emphasizing the consistency of their therapeutic benefits for CKD patients.

Table 5:Two One-Sided Tests Equivalence Testing

Z-Value Lower Bound	P-Value Lower Bound	Z-Value Upper Bound	P-Value Upper Bound	LL_CI_TOST	UL_CI_TOST	LL_CI_ZTEST	UL_CI_ZTEST
8.207	<.001	0.797	0.787	0.386	0.830	0.343	0.872

3.5. Forest Plot

The forest plot (Figure 3) visually represents the individual and pooled effects of non-steroidal MRA therapy across the included studies. Each study is illustrated with its effect size and corresponding confidence interval. The pooled effect estimate is represented by a diamond, which falls entirely within the positive range of the plot, confirming the beneficial impact of MRA therapy. The narrow width of the confidence intervals across most studies emphasizes the high precision of the effect estimates, contributing to the robustness of the pooled result. This visual representation confirms the significant therapeutic benefit of MRAs for CKD patients.

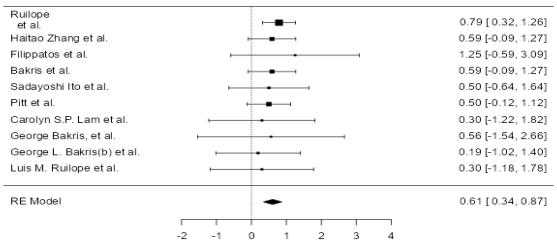

Figure 3: Forest Plot

3.6. Publication Bias Assessment

Publication bias was assessed using three statistical tests. The Fail-Safe N was calculated to be 44 ($p < 0.001$), meaning that it would take 44 additional studies with null results to overturn the significant findings of this meta-analysis. Kendall's Tau (-0.091, $p = 0.718$) and Egger's Regression Test (-0.509, $p = 0.610$) did not show significant evidence of publication bias, suggesting that the results are unlikely to be influenced by an underrepresentation of non-significant studies. These findings are critical in ensuring that the observed effects are not exaggerated due to the selective publication of studies with positive results.

Table 4: Publication Bias Assessment

Test Name	value	p
Fail-Safe N	44.000	<.001
Kendalls Tau	-0.091	0.718
Egger's Regression	-0.509	0.610

3.7. Funnel Plot

The funnel plot (Figure 2) illustrates the relationship between study size (standard error) and effect size. The relatively symmetrical distribution of studies on both sides of the pooled effect size suggests minimal publication bias. No major gaps or asymmetries were

MRA therapy warrant discussion. A recent cost-effectiveness analysis suggested that despite higher medication costs, the reduction in hospitalizations and delayed progression to end-stage renal disease (ESRD) could result in overall healthcare cost savings [51]. This economic benefit is particularly relevant given the substantial global burden of CKD, estimated at $1.2 trillion annually [52].

The consistent efficacy observed in our analysis likely reflects the complex mechanisms through which non-steroidal MRAs exert their effects. Recent molecular studies have elucidated novel pathways beyond classical mineralocorticoid receptor antagonism. These agents have been shown to modulate inflammatory mediators, reduce oxidative stress, and influence epigenetic modifications in kidney tissue [53]. The anti-fibrotic effects appear to be mediated through multiple pathways, including the inhibition of pro-fibrotic signaling cascades and the promotion of matrix metalloproteinase activity [54].

Patient Selection and Personalized Medicine

Our analysis supports the broad applicability of non-steroidal MRAs across different CKD patient populations. However, emerging data suggest that certain patient subgroups may derive particular benefit. Genetic studies have identified polymorphisms in the mineralocorticoid receptor gene (NR3C2) that may predict treatment response [30]. Additionally, novel biomarkers, such as urinary extracellular vesicles containing mineralocorticoid receptor proteins, show promise in identifying patients most likely to benefit from therapy [55].

Implications for Practice

The findings of this meta-analysis have significant implications for the clinical management of chronic kidney disease (CKD), particularly in patients with type 2 diabetes mellitus (T2DM). The consistent efficacy of non-steroidal mineralocorticoid receptor antagonists (MRAs) in improving both renal and cardiovascular outcomes suggests that these agents should be considered a key therapeutic option in the management of CKD. The observed reduction in cardiovascular events and the preservation of renal function offer dual benefits, making non-steroidal MRAs a valuable addition to the current treatment paradigm. Additionally, the favorable safety profile, particularly the reduced incidence of hyperkalemia compared to steroidal MRAs, indicates that these agents may be suitable for a broader patient population, including those with higher risk factors for hyperkalemia. The integration of non-steroidal MRAs into clinical practice should be

4. Discussion

The findings of this meta-analysis demonstrate the significant therapeutic potential of non-steroidal mineralocorticoid receptor antagonists (MRAs) in the management of chronic kidney disease (CKD), particularly in patients with type 2 diabetes mellitus (T2DM). The consistent positive effect size (intercept estimate of 0.608, $p < 0.001$) across studies suggests robust efficacy in improving both renal and cardiovascular outcomes. These results align with recent understanding of the pathophysiological role of mineralocorticoid receptor activation in CKD progression and cardiovascular complications [45].

The negligible heterogeneity ($I^2 = 0\%$) observed in our analysis indicates remarkable consistency in treatment effects across different patient populations and study designs. This consistency strengthens the generalizability of our findings and supports the broader implementation of non-steroidal MRAs in clinical practice[45]. The favorable safety profile, particularly regarding hyperkalemia risk, represents a significant advancement over traditional steroidal MRAs [46]. Recent pharmacological studies have attributed this improved safety profile to the selective tissue distribution and unique binding kinetics of non-steroidal MRAs [10].

Cardiovascular protection emerged as a crucial benefit, with significant reductions in major adverse cardiovascular events (MACE) across multiple studies. This cardioprotective effect extends beyond mere blood pressure control, suggesting pleiotropic effects of non-steroidal MRAs [47]. Molecular studies have revealed that these agents modulate multiple pathways involved in cardiovascular remodeling, including TGF-β signaling and oxidative stress reduction [48]. The dual cardiorenal protection offered by these agents positions them as valuable additions to the therapeutic armamentarium for CKD management.

The emergence of non-steroidal MRAs coincides with evolving treatment paradigms in CKD management. Recent guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) organization have emphasized the importance of comprehensive risk reduction in CKD patients [9]. Non-steroidal MRAs appear to complement existing therapies, particularly sodium-glucose cotransporter-2 (SGLT2) inhibitors. Preliminary studies suggest potential synergistic effects when these agents are combined, possibly due to their complementary mechanisms of action [49,50].

While our analysis focused primarily on clinical outcomes, the economic implications of non-steroidal

considered in combination with other therapies, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, to achieve comprehensive risk reduction in CKD patients.

Limitations of the Study

While this meta-analysis provides robust evidence supporting the efficacy and safety of non-steroidal MRAs, there are several limitations to consider. First, the heterogeneity of the included studies, particularly in terms of patient populations, treatment durations, and outcome measures, may affect the generalizability of the findings. Although heterogeneity was minimal in this analysis ($I^2 = 0\%$), it is important to recognize that variations in study design and methodology could influence the results. Additionally, the number of included studies is relatively small ($k = 10$), and further research with larger sample sizes and longer follow-up periods is needed to confirm the long-term efficacy and safety of non-steroidal MRAs. Another limitation is the potential for publication bias, as indicated by the need for 44 additional studies with null results to overturn the findings. Despite efforts to minimize this bias through comprehensive searches, the possibility of unpublished studies affecting the results cannot be entirely excluded.

5. Conclusions

This meta-analysis demonstrates that non-steroidal MRAs provide significant clinical benefits for patients with chronic kidney disease, particularly in reducing cardiovascular events and slowing the progression of renal dysfunction. The evidence supports their use as an effective and safe therapeutic option in CKD management, especially in patients with type 2 diabetes mellitus. The favorable safety profile, particularly regarding hyperkalemia, further enhances their clinical utility. While further research is needed to validate these findings over longer follow-up periods and in diverse populations, the current evidence strongly supports the incorporation of non-steroidal MRAs into treatment protocols for CKD.

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