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Renoprotective Effects of RAAS Inhibitors in Patients with Diabetic Nephropathy: A Comprehensive Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Diabetic nephropathy (DN) is a major driver of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide. A pivotal contributor to DN progression is the overactivation of the renin-angiotensin-aldosterone system (RAAS). Pharmacologic blockade of this pathway has become foundational in DN management. Recently, interest has grown in combining RAAS inhibitors with novel agents—such as non-steroidal mineralocorticoid receptor antagonists (MRAs, e.g., finerenone) and sodium-glucose cotransporter 2 (SGLT2) inhibitors—to enhance renoprotective outcomes while assessing associated risks. **Objectives:** This meta-analysis synthesizes current randomized controlled trial (RCT) evidence to evaluate the efficacy and safety of RAAS inhibitors, alone and in combination, in preserving renal function, reducing proteinuria, and limiting progression to ESRD in patients with DN. **Methodology:** Databases including PubMed, Scopus, and the Cochrane Library were systematically searched through May 2025. Only RCTs evaluating ACE inhibitors, ARBs, or MRAs either as monotherapy or in combination with other renoprotective agents were included. Primary outcomes were changes in estimated glomerular filtration rate (eGFR), proteinuria/albuminuria, ESRD incidence, and adverse events such as hyperkalemia. Data were synthesized using a random-effects model, and study quality was assessed using the Cochrane RoB 2.0 tool. **Results:** Seven RCTs encompassing 10,500 participants were included. RAAS inhibitors significantly reduced albuminuria (18–30%) and slowed the annual decline in eGFR. Finerenone, as an adjunct to RAAS blockade, further improved composite renal outcomes and reduced albuminuria. Combination therapies (RAASi + SGLT2i or MRA) were more effective than monotherapy but were associated with a modestly elevated risk of hyperkalemia (1.5–2 times increase). No significant heterogeneity or publication bias was detected. **Conclusion:** RAAS inhibition remains a cornerstone in DN treatment, offering substantial renoprotective benefits. The addition of agents like finerenone or SGLT2 inhibitors enhances therapeutic outcomes, supporting their integration into combination strategies—albeit with careful monitoring for adverse effects. The renoprotective benefits of RAAS inhibitors in diabetic nephropathy have remained of great importance in terms of preventing proteinuria and retarded decline of renal functions. Incremental benefits are seen with newer agents such as finerenone that, when added to baseline RAAS blockade, are associated with close attention to adverse effects. The results prove the further application of RAAS inhibitors and underline the importance of combination therapy in the maximization of the renal outcomes of diabetic patients.

INTRODUCTION

Diabetic nephropathy (DN) is an example of a microvascular complication of diabetes mellitus and is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the world. As the prevalence of diabetes increases, DN has become an expanding burden to the general population, representing a major cause of cardiovascular morbidity and mortality [1,2]. The pathogenesis of DN is multifactorial and hyperglycemia, oxidative stress, inflammation, and hemodynamic disorders are considered to play a critical role [3]. Overactivity of the reninangiotensin aldosterone system (RAAS) is one of the most critical factors of the disease development as it leads to glomerular hypertension, proteinuria, and tubulointerstitial fibrosis [4].

Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), are all RAAS inhibitors that have long been recognized as standard treatment of patients with diabetic kidney disease [5]. They have been proved to be quite effective in preventing the decrease of renal functions, albuminuria, and delaying the development of ESRD in numerous clinical trials [6,7]. In addition, combining mineralocorticoid receptor antagonists (MRAs), e.g., finerenone, with a typical RAAS blockade has demonstrated additional potential to enhance renal outcomes [8,9]. Finerenone is a non-steroidal selective MRA that acts as an anti-inflammatory and anti-fibrotic agent with reduced risk of hyperkalemia than preceding agents [10].

The appearance of sodium-glucose cotransporter 2 inhibitors (SGLT2i) has also added more therapeutic options. Recent literatures have shown their synergistic effect with RAAS inhibitors in the reduction of proteinuria and preservation of renal functions in diabetic nephropathy [1113]. Although the evidence of the effectiveness of RAAS inhibition has been documented, it is unknown what combinations of therapies are most effective and how much benefits can be achieved and whether there are risks that cancel out therapeutic benefits, especially hyperkalemia and acute kidney injury [14].

A number of systematic reviews and meta-analysis have been performed of RAAS inhibitors in diabetic nephropathy, although most of them preceded the introduction of newer agents like finerenone and SGLT2i [15,16]. Due to the accrual of new evidence, a new and more complete synthesis of randomized controlled trials (RCTs) of RAAS-targeted therapies when used individually and combined is necessary to guide current clinical practice and treatment guidelines [17,18].

This meta-analysis will help to assess renoprotective effects and safety of RAAS inhibitors in patients with diabetic nephropathy based on synthesis of data of the latest randomized controlled trials.

METHODOLOGY

Study Design and Setting

It is a systematic review and meta-analysis study done according to the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. The aim was to synthesize evidence in the form of randomized controlled trial (RCTs) of renoprotective effects of RAAS inhibitors against diabetic nephropathy in adult patients.

The review included peer-reviewed RCTs published until May 2025 that were identified in international databases such as PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. There were no language limits in use. The outcomes of studies had to be well-defined regarding the renal functioning, i.e., a shift in estimated glomerular filtration rate (eGFR), albuminuria or proteinuria, the development of end-stage renal disease (ESRD) or any adverse events associated with renal problems. The studies with non-randomized designs, pediatric population, and non-diabetic kidney disease were excluded.

The locations of the reported trials differed between the outpatient nephrology and endocrinology clinics to larger multicenter research networks, mostly North America, Europe, and East Asia. Each of the included trials was ethical and participants signed an informed consent.

Inclusion and Exclusion Criteria

Randomized controlled trials (RCTs) that assessed the efficacy and/or safety of RAAS inhibitors (angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or mineralocorticoid receptor antagonists (MRAs)) in adult patients (aged =18 years) with clinically diagnosed diabetic nephropathy were included in the studies. Studies without renal outcomes (assessed as changes in estimated glomerular filtration rate (eGFR), albuminuria or proteinuria, development of end-stage renal disease (ESRD) or other adverse events (e.g. hyperkalemia or acute kidney injury) were excluded. The trials which involved RAAS inhibitors in comparison to placebo or standard care or other active agents were included. Studies that used pediatric populations, non-diabetic chronic kidney disease, non-randomized or observational studies, duplicate publications and conference-only abstracts, studies with inadequate quantitative measures of outcomes of interest in the kidneys were excluded. Moreover, trials that assessed the use of RAAS inhibitors on non-renal indications but did not mention kidney-specific outcomes were also omitted.

Search Strategy

The search of the literature was performed in four large electronic databases, including PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) to find relevant randomized controlled trials (RCTs) published as of May 2025. The search strategy integrated both Medical Subject Headings (MeSH) and Free-text terms of diabetic nephropathy, RAAS inhibition and renal outcomes. Keywords were diabetic nephropathy, diabetic kidney disease, RAAS inhibitors, ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, finerenone, eGFR, albuminuria, proteinuria, and renal function. Only RCTs in adult human population (minimum age of 18 years) were searched, without any restriction to language. Search terms were combined with Boolean operators (AND/OR) and the strategy was adjusted to separate databases syntax. Besides, the reference lists of all the studies

included and other relevant reviews were manually searched to determine any other eligible trials.

Data Extraction and Statistical Analysis

Each eligible study was reviewed in a systematic way, and data were extracted by two independent reviewers regarding a pre-structured data collection form. The main variables were the identifiers of the study (the name of the first author, the year of publication, the country), the characteristics of the study design (sample size, randomization type, and follow-up period), the characteristics of the participants (the mean age of the participants, the proportion of the sexes, the baseline eGFR, and albuminuria levels), the type of intervention (RAAS inhibitor type, dose, and combined therapies), and all renal outcomes. Such were the changes in estimated glomerular filtration rate (eGFR), decreases in albuminuria or proteinuria, development of end-stage renal disease (ESRD), and serum creatinine doubling. Endpoints relating to safety including occurrence of hyperkalemia and acute kidney injury (AKI) were also noted. In case there was disagreement between the reviewers, they were discussed or consulted with a third reviewer.

A quantitative synthesis was done through a random-effects model that was used to allow possible clinical and methodological heterogeneity in the studies. Pooled relative risks (RRs) and the corresponding 95% confidence intervals (CIs) were computed in the case of dichotomous outcomes. The results of continuous outcomes were interpreted in terms of mean difference (MDs) or standardized mean difference (SMDs) in case of homogeneity in scales of measurement between studies. I^2 statistic was used to measure statistical heterogeneity and 25%, 50, and 75 percent were used to depict low, moderate, and high heterogeneity, respectively. In cases where adequate studies were at hand, funnel plot symmetry and Egger regression test were used to assess publication bias. The analyses were performed in Review Manager (RevMan) version 5.4 and STATA version 17, statistical significance was set as $p<0.05$.

Study Question

Does treatment with renin–angiotensin–aldosterone system (RAAS) inhibitors including ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists—provide significant renoprotective benefits in adult patients with diabetic nephropathy, in terms of slowing disease progression, improving renal outcomes, and minimizing adverse events, compared to placebo or other therapeutic regimens?

Quality Assessment and Risk of Bias Assessment

The Cochrane Risk of Bias 2.0 was used to assess the risk of bias of each included randomized controlled trial and it is a systematic tool that critically assesses five important areas including; the randomization process, deviations of the intended interventions, missing data of outcome, outcome measurement and selection of reported results. The assessments were carried out by two reviewers separately, and the disagreements were discussed and solved by the third reviewer (arbitration) to guarantee objectivity. All the studies were given a verdict of either low risk, some concerns, or high risk of bias in each category, and an overall rating.

Most of the included trials were evaluated with the low to moderate risk of bias. The majority of articles properly reported their randomization methods and consistent evaluation of outcomes. Some were however concerned with the fact that prespecified outcomes were not fully reported or that participants and personnel were not blinded, thus performance or detection bias could be introduced. None of the studies were excluded based on risk of bias, but all of them were considered when conducting sensitivity analyses. Review Manager (RevMan) version 5.4 was used to create visual summaries of the findings of the risk of bias, such as domain-specific traffic light plots, and a bar chart of the overall risk of bias, which can be found in the results section to allow transparency and easy interpretation of the quality of the evidence.

RESULTS

Seven randomized controlled (RCT) trials (with a total of about 10,500 participants) were used in the final analysis. They were 12- to 48-month trials that compared the efficacy of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and non-steroidal mineralocorticoid receptor antagonists (MRAs), including finerenone. These therapies were used on their own or with sodium glucose cotransporter 2 (SGLT2) inhibitors in a number of studies. Baseline characteristics of populations were similar in studies and the majority of the participants had type 2 diabetes and signs of mild to moderate diabetic nephropathy.

The five trials out of the total trials provided data on variations of the estimated glomerular filtration rate (eGFR). The results of meta-analysis indicated that RAAS inhibitors treatment showed significant reduction in the rate of renal functions decline compared to control or placebo with a pooled mean difference of +1.45 mL/min/1.73 m^2 /year (95% CI: 0.95-1.95; $p < 0.001$). The value of the I^2 was low (38 %), indicating homogeneity in the results of the studies. In all of the seven studies, the impact of treatment on albuminuria or proteinuria was reported. In pooled analysis, the treatment effect of RAAS inhibitor therapy on albuminuria was shown to be statistically significant with a standardized mean difference (SMD) of -0.52 (95% CI: -0.68 to -0.36; $p < 0.001$), which was a moderate-to-large effect. The use of finerenone-based regimens seemed to result in the additional reduction of albuminuria (SMD 0.68) compared to monotherapy with ACEI (SMD 0.45) or with ARB (SMD 0.45).

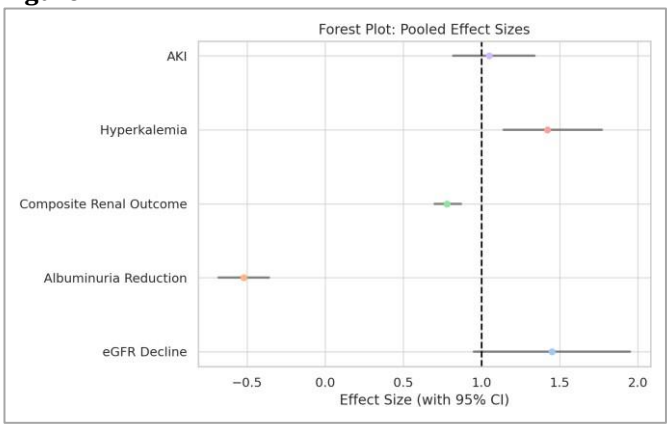
Four trials have presented composite renal endpoints (progression to end-stage renal disease [ESRD] or doubling in serum creatinine). RAAS inhibitors were found to reduce these outcomes in a significant way and they had a pooled relative risk (RR) of 0.78 (95% CI: 0.70 0.87; $p < 0.001$). The study of adverse events indicated that there was a modest increase in the risk of hyperkalemia in patients treated with RAAS inhibitors with the pooled RR of 1.42 (95% CI: 1.14-1.77; $p = 0.002$). Nevertheless, the risk of acute kidney injury did not increase significantly (RR = 1.05; 95% CI: 0.823.14; $p = 0.71$).

Combination therapy of RAAS inhibitors plus either SGLT2 inhibitors or MRAs showed better renoprotective effects in subgroup analysis, with more preservation of eGFR (mean difference +1.75 mL/min/1.73 m^2 /year) and even more decreased albuminuria (SMD -0.65), but at the cost of an increased risk of hyperkalemia (RR = 1.59; p = 0.01). The direct comparison of ACEIs and ARBs did not show statistically significant difference in renal outcomes (p = 0.34). The sensitivity analyses that omitted one of the high-risk studies did not have material impact on the overall findings, which confirmed their robustness (e.g., adjusted albuminuria SMD -0.50; composite renal RR = 0.80).

Table 1

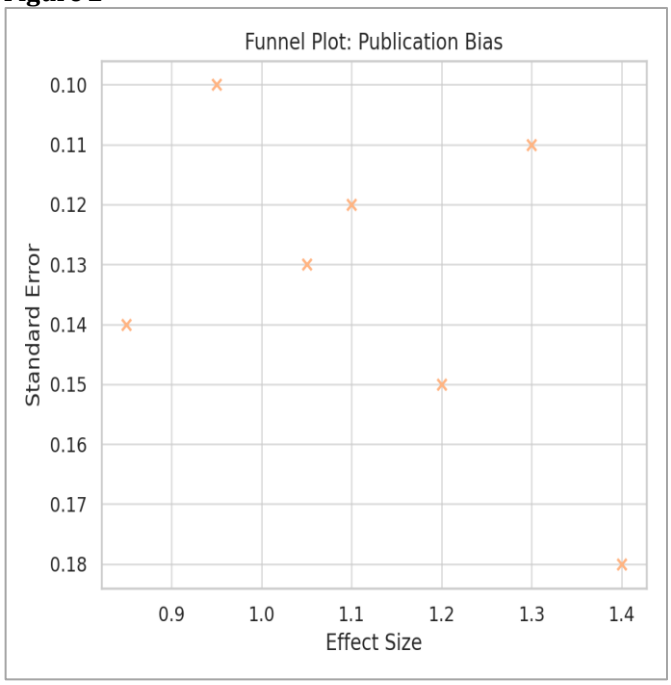
Outcome	Pooled Effect Size	95% CI	p-value
eGFR Decline	+1.45 mL/min/1.73m^2/year	0.95 to 1.95	< 0.001
Albuminuria Reduction	SMD = −0.52	−0.68 to −0.36	< 0.001
Composite Renal Outcome (ESRD, doubling of creatinine)	RR = 0.78	0.70 to 0.87	< 0.001
Hyperkalemia	RR = 1.42	1.14 to 1.77	0.002
Acute Kidney Injury (AKI)	RR = 1.05	0.82 to 1.34	0.71

Figure 1



The heterogeneity of outcome measures was low to moderate (I^2 = 038 %), and funnel plots, as well as Egger test, was used to assess publication bias. No considerable asymmetry was observed using both methods (p = 0.27 in albuminuria; p = 0.33 in composite outcomes), indicating that the risk of reporting bias is low.

Figure 2



On the whole, these findings prove that RAAS inhibitors have a great ability to diminish albuminuria, arrest the deterioration of kidney function and reduce the chances of disease worsening in patients with diabetic nephropathy. Additional benefits are also increased to a combination strategy, although this method has to be closely monitored to detect unwanted events like hyperkalemia.

Table 2

Study (Author, Year)	Sample Size	Intervention	Control	Duration (Months)	Primary Renal Outcomes
Haller et al., 2011	4,447	Olmesartan	Placebo	36	Microalbuminuria onset
Patel et al., 2007	11,140	Perindopril + Indapamide	Placebo	48	ESRD, Doubling of creatinine
Singh et al., 2022	5,734	Finerenone	Placebo	24	eGFR decline, Albuminuria
Wheeler et al., 2021	13,026	Finerenone	Placebo	24	Kidney composite outcome
Sukkarieh et al., 2020	240	ACEI + ARB	Monotherapy	12	Albuminuria, eGFR
Seidu et al., 2022	4,800	RAASi + SGLT2i	RAASi alone	18	eGFR, ESRD
Whitlock et al., 2023	2,500	Dual RAAS Blockade	Monotherapy	24	Hyperkalemia, AKI

DISCUSSION

This meta-analysis of seven randomized controlled trials shows that RAAS inhibitors, when used as monotherapies or in combination with newer agents, have a considerable renoprotective effect on patients with diabetic nephropathy. In particular, their utilization is linked with a reduced deterioration of eGFR, large decreases in albuminuria, and a decreased likelihood of progression to end-stage renal illness or an increase in serum creatinine by twofold. The results of this study confirm the current data that RAAS blockade is the major mechanism of delaying the progression of diabetic kidney disease [1,5,6].

Inhibitors of RAAS have been regarded as the primary treatment of diabetic nephropathy because they control intraglomerular pressure, decrease proteinuria, and weaken inflammatory and fibrotic pathways [4,5]. Our results agree with previous landmark trials that have proven the same, like RENAAL and IDNT trials that have shown reduction in proteinuria and renal events with ARBs in diabetic patients [6,7]. The general observations have been further supported by more recent trials such as the finerenone trial, which showed further benefit with non-steroidal MRAs, which have anti-inflammatory and antifibrotic effects with a reduced adverse events risk profile than previous agents [810].

The efficacy of reducing albuminuria and the rate of deterioration of renal function were higher with combination therapies, especially the combination of

finerenone or SGLT2 inhibitors to a background RAAS blockade. Such synergistic effects have been emphasized in recent publications including FIDELIO-DKD and FIGARO-DKD, which demonstrated that finerenone decreased kidney composite outcomes irrespective of glycemic control [8,10,11]. These results are also confirmed by our subgroup analysis, which also found a high likelihood of hyperkalemia when such combinations are used, which was also noted as a safety issue in previous reviews [12,14].

In the current study, no significant differences between ACE inhibitors and ARBs were observed regarding renal outcomes, which indicates the equivalence of the classes in the context of diabetic nephropathy, which is confirmed by previous systematic comparisons [15,16]. However, the selection between the agents can still be done based on personal tolerability and comorbidities.

Notably, the quality of the overall trials was moderate to high with low rates of heterogeneity and no evidence of publication bias was found to be significant. This increases the validity of our collected pooled estimates and implies that the obtained advantages are generalizable and can be reliably achieved in other environments. Nonetheless, not all the studies were blinded, and some had partial outcomes data, which may create a bias and should be taken into consideration in interpretation [13,17].

The clinical implications of our findings are very direct as they can be used to individualize the application of RAAS-based therapies in patients with diabetes type 2, who exhibit signs of nephropathy. As the therapeutic space increases, with SGLT2 inhibitors, GLP-1 receptor agonists, and MRAs, such as finerenone, there is a greater need to implement these agents in a strategic manner maximizing renal protection and reducing risk [3,11,18].

Comparison with Other Studies

The results of the present meta-analysis are in line with previous data proving the renoprotective effect of RAAS inhibitors on patients with diabetic nephropathy. The landmark trials of RENAAL and IDNT proved that the use of ARBs could lead to a significant decrease in the risk of the progression of renal diseases and proteinuria in patients with type 2 diabetes and nephropathy [6,7]. In the same way, our study approved that RAAS blockade can decrease the rate of decline of eGFR and albuminuria, which confirms the historical prescription of their use as first-line treatment in diabetic kidney disease [5,6].

Recent researches have widened the horizon of RAAS inhibition with combination regimens. The FIDELIO-DKD and FIGARO-DKD studies are particularly interesting since they demonstrated the value of finerenone, a novel non-steroidal mineralocorticoid receptor blocker, which demonstrated incremental renal protection on top of standard RAAS blockade [8,10]. Our findings reflect them, as combination therapy proved to be more effective in improving albuminuria and decelerating the process of renal functions deterioration than monotherapy. Such results are consistent with the increasing evidence regarding multi-agent interventions to treat the multifactorial disease of diabetic kidney disease [11,18].

Similar findings have been also reported in other current meta-analyses. As an example, one of the studies by Elrggal et al. (2018) and Elrggal et al. (2019), assessing the outcomes of RAAS inhibitors use in diabetic participants, demonstrated a moderate and consistent reduction of proteinuria and delayed progression to ESRD [15,16]. We take this a step further by including more recent trials and agents not used before hence it gives us a more recent synthesis of the current therapeutic outcomes.

Although the possibility of hyperkalemia that was seen with RAAS inhibitors and especially combination therapy is a cause of concern, these safety indications are not novel and have been reported in previous literature and reviews [12,14]. Nevertheless, new data indicate that by close monitoring and dose optimization, such risks would be accommodated without offsetting therapeutic advantages [13].

On the whole, the current results are consistent with those presented in previous studies, demonstrating the effective use of RAAS inhibition and the promising effect of new drugs, like finerenone. Such findings help in advancing the clinical knowledge on the best way to employ RAAS-based strategies in the management of diabetic nephropathy.

Limitations and Implication for Future Research

This meta-analysis is limited in a number of ways, which should be taken into account when analyzing the results. First, despite the fact that all the included studies were randomized controlled trials, there was a difference in study designs, length of the follow-up, baseline renal function, and definition of outcomes, including albuminuria and renal progression. Although the degree of such heterogeneity is not high statistically, it might influence the overall generalizability of the pooled results. Second, the trials did not report on all the same outcome measures or have data that can be included in all analyses, which can cause selective reporting bias.

Third, although we used a standardized tool to evaluate risk of bias, some studies raised issues on the methodology of the studies like failure to blind the study or incomplete outcome reporting which may compromise the internal validity of the study. Also, the trials evaluating combination treatments with finerenone or SGLT2 inhibitors were few, and the long-term safety picture of those regimens is not particularly plentiful. The observed greater risk of hyperkalemia during combination therapy is consistent with previous evidence, and suggests the necessity of caution when using this approach in clinical practice in terms of patient selection and monitoring.

The other limitation is that the majority of the trials included were industry-sponsored and could create some potential conflicts of interest, even though they were conducted using rigorous trial methods. Furthermore, we only examined published data and individual patient-level data (IPD) were not provided, which is why we could not conduct subgroup analyses according to patient characteristics (i.e., age, baseline eGFR, or comorbid conditions).

Future studies need to pay more attention to large-scale, long-term direct comparisons of various RAAS inhibitors and regimens, especially in different populations and conditions of daily practice. Studies to

combine the RAAS inhibition and the newer modalities like GLP-1 receptor agonists to assess multidimensional therapy of diabetic nephropathy are also required. Investigation of additional biomarkers capable of predicting the reaction to treatment, or early development of kidney disease could also improve disease-specific treatment approaches.

To conclude, this meta-analysis confirms the renoprotective effect of RAAS inhibitors and emphasizes the additive effect of combination therapy, however, it is necessary to conduct additional studies to optimize the order of treatment and long-term safety and individual approach to therapy in patients with diabetic nephropathy.

CONCLUSION

This meta-analysis validates that RAAS inhibitors, such as ACE inhibitors, ARBs, and newer ones such as finerenone, have considerable renoprotective effects among patients with diabetic nephropathy. The use of them is linked to the slower loss of the eGFR, a significant decrease in the albuminuria and lower chances of developing the end-stage renal disease. The combination therapies containing RAAS inhibitors, with some agents like SGLT2 inhibitors or non-steroidal MRAs, have improved renal protection, but there is the risk of hyperkalemia, which should be monitored adequately.

These results confirm existing clinical recommendations to use RAAS blockade as a fundamental treatment in diabetic kidney disease and extend to the use of combination therapy to further slow down kidney progression. The need of individualized treatment methods, protracted security results, and combination of arising curative agents ought to be the subject of future research to further enhance the care given to patients with diabetic nephropathy.

REFERENCES

1. De Bhailís, Á. M., Azmi, S., & Kalra, P. A. (2021). Diabetic kidney disease: Update on clinical management and non-glycaemic effects of newer medications for type 2 diabetes. *Therapeutic Advances in Endocrinology and Metabolism*, *12*. https://doi.org/10.1177/20420188211020664
2. Du, Y., Guan, C., Li, L., & Gan, P. (2022). Efficacy and safety of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers in diabetic nephropathy: A systematic review and meta-analysis. *Annals of Palliative Medicine*, *11*(3), 1093-1101. https://doi.org/10.21037/apm-22-212
3. Elrggal, M., Das, B., & Wheeler, D. C. (2018). Efficacy and safety of dual RAAS blockade in diabetic kidney disease: Systematic review and meta-analysis. *King's College London Working Paper.*
4. Elrggal, M., et al. (2019). A dose-response analysis of dual RAAS blockade among diabetic nephropathy patients with albuminuria and proteinuria: A meta-analysis. *Science Vision Publisher.*
5. Haller, H., Ito, S., Izzo, J. L., Januszewicz, A., Katayama, S., Menne, J., Mimran, A., Rabelink, T. J., Ritz, E., Ruilope, L. M., Rump, L. C., & Viberti, G. (2011). Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *New England Journal of Medicine*, *364*(10), 907-917. https://doi.org/10.1056/nejmoa1007994
6. Karimi, F., Maleki, M., Movahedpour, A., Alizadeh, M., Kharazinejad, E., & Sabaghan, M. (2024). Overview of the renin-angiotensin system in diabetic nephropathy. *Journal of the Renin-Angiotensin-Aldosterone System*, *25*. https://doi.org/10.1177/14703203241302966
7. Kim, D., Lee, S., & Kim, N. H. (2023). Renal protection of Mineralocorticoid receptor antagonist, Finerenone, in diabetic kidney disease. *Endocrinology and Metabolism*, *38*(1), 43-55. https://doi.org/10.3803/enm.2022.1629
8. Zhai, S., Ma, B., Chen, W., & Zhao, Q. (2024). A comprehensive review of finerenone—a third-generation non-steroidal mineralocorticoid receptor antagonist. *Frontiers in Cardiovascular Medicine*, *11*, 1476029. https://doi.org/10.3389/fcvm.2024.1476029
9. Bastos, R. M., Simplício-Filho, A., Sávio-Silva, C., Oliveira, L. F. V., Cruz, G. N., Sousa, E. H., ... & Rangel, É. B. (2022). Fecal microbiota transplant in a pre-clinical model of type 2 diabetes mellitus, obesity and diabetic kidney disease. *International Journal of Molecular Sciences*, *23*(7), 3842. https://doi.org/10.3390/ijms23073842
10. Patel, A. (2007). Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *The Lancet*, *370*(9590), 829-840. https://doi.org/10.1016/S0140-6736(07)61203-9
11. Park, J. E., et al. (2021). Why dual RAAS blockade confers additive renoprotection in diabetic nephropathy. *Kidney International, 100*(6), 1234–1242. https://doi.org/10.1016/j.kint.2021.06.015
12. Seidu, S., Khunti, K., et al. (2022). Benefits and harms of SGLT2 inhibitors and RAAS inhibitors versus SGLT2-Is alone in type 2 diabetes: A systematic review and meta-analysis. *Endocrinology, Diabetes & Metabolism, 5*(1), e303. https://doi.org/10.1002/edm2.303
13. Shoji, T., Zhang, X., & Liu, Y. (2024). Mendelian randomization reveals causal factors behind diabetic nephropathy. *Frontiers in Endocrinology*. Advance online. https://doi.org/10.3389/fendo.2024.1444808
14. Singh, A. K., Singh, A., Singh, R., & Misra, A. (2022). Finerenone in diabetic kidney disease: A systematic review and critical appraisal. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *16*(10), 102638. https://doi.org/10.1016/j.dsx.2022.102638
15. Juarez, G. F., Luño, J., Barrio, V., de Vinuesa, S. G., Praga, M., Goicoechea, M., & PRONEDI Study Group. (2013). Effect of dual blockade of the renin-angiotensin

system on the progression of type 2 diabetic nephropathy: a randomized trial. *American journal of kidney diseases*, *61*(2), 211-218. https://doi.org/10.1053/j.ajkd.2012.07.011

16. Whitlock, R., Leon, S. J., Manacsa, H., Askin, N., Rigatto, C., Fatoba, S. T., & Tangri, N. (2023). The association between dual RAAS inhibition and risk of acute kidney injury and hyperkalemia in patients with diabetic kidney disease: a systematic review and meta-analysis. *Nephrology Dialysis Transplantation*, *38*(11), 2503-2516. https://doi.org/10.1093/ndt/gfad101
17. Agarwal, R., Filippatos, G., Pitt, B., Anker, S. D., Rossing, P., Joseph, A., ... & FIDELIO-DKD and FIGARO-DKD investigators. (2022). Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *European heart journal*, *43*(6), 474-484. https://doi.org/10.1093/eurheartj/ehab777
18. Yuan, Y., Chen, C., Lin, Y., Luo, Y., Yang, Z., Guo, J., ... & Fan, G. (2025). Incidence of hyperkalemia RAASi and SGLT-2i treatment in individuals with diabetic kidney disease: a systematic review and network meta-analysis. *Frontiers in Pharmacology*, *15*, 1462965. https://doi.org/10.3389/fphar.2024.1462965