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Comparative Efficacy and Safety of Finerenone, Eplerenone, and Spironolactone on Cardiorenal Outcomes in Type 2 Diabetes with Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis

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A B S T R A C T

Mineralocorticoid receptor antagonists (MRAs) are critical for managing chronic kidney disease (CKD) in type 2 diabetes (T2D), yet a "residual risk" of cardiorenal progression persists. The comparative efficacy and safety of the novel non-steroidal MRA, finerenone, versus the traditional steroidal MRAs, spironolactone and eplerenone, have not been established in a comprehensive analysis. We conducted a network meta-analysis (NMA) to create an evidence-based hierarchy for these three agents. We performed a systematic review searching MEDLINE, Embase, and Cochrane CENTRAL through March 2025 for randomized controlled trials (RCTs) in patients with CKD and albuminuria (predominantly T2D) on baseline renin-angiotensin system (RAS) blockade. We compared finerenone, spironolactone, eplerenone, and placebo. The primary efficacy outcome was the percent change in urinary albumin-to-creatinine ratio (UACR). The primary safety outcome was the relative risk (RR) of hyperkalemia (serum potassium ≥ 5.5 mmol/L). A Bayesian random-effects NMA was performed. Seven RCTs involving 15,749 patients were included. For UACR reduction, all MRAs were superior to placebo. Spironolactone (Surface Under the Cumulative Ranking [SUCRA]: 91.2%) and finerenone (SUCRA: 88.5%) were the most effective agents and were statistically indistinguishable. Both were significantly more potent than eplerenone (SUCRA: 58.1%). For hyperkalemia risk, spironolactone was definitively the least safe (SUCRA: 9.5%). Finerenone (RR vs. Spironolactone: 0.63; 95% Credible Interval [CrI]: 0.48–0.82) and eplerenone (RR vs. Spironolactone: 0.65; 95% CrI: 0.45–0.94) were significantly safer. The safety profiles of finerenone (SUCRA: 65.4%) and eplerenone (SUCRA: 62.1%) were comparable.In conclusion, finerenone and spironolactone demonstrate equivalent, superior anti-albuminuric efficacy. However, finerenone uniquely dissociates this high potency from the significant risk of hyperkalemia, offering a safety profile comparable to the less-potent eplerenone. Finerenone, therefore, represents an optimized therapeutic choice, balancing maximal renoprotective efficacy with a superior safety profile for patients with T2D and CKD.

1. Introduction

The 21st century is defined by the unabating global pandemic of type 2 diabetes (T2D), a metabolic disorder projected to affect nearly 800 million individuals by 2045.[1] This epidemic carries a devastating humanistic and economic burden, driven primarily by its microvascular and macrovascular complications. Of these, diabetic kidney disease (DKD) is arguably the most feared and resource-intensive.[2] DKD, a progressive complication characterized by persistent albuminuria and a declining estimated glomerular filtration rate (eGFR), is now the leading cause of end-stage kidney disease (ESKD) in the developed world. It is responsible for approximately 50% of all ESKD cases, condemning millions of patients to the life-altering therapies of dialysis or transplantation.[3] The economic costs are staggering, with healthcare systems allocating a disproportionate

amount of resources to the management of this single complication. The pathophysiology of DKD is a complex interplay of metabolic, hemodynamic, and inflammatory insults to the delicate microarchitecture of the kidney. Chronic hyperglycemia, the hallmark of T2D, initiates a cascade of deleterious processes. It induces glomerular hyperfiltration, a state of increased intraglomerular pressure that places immense hemodynamic stress on the glomerulus. Concurrently, hyperglycemia promotes the non-enzymatic glycosylation of proteins, leading to the accumulation of advanced glycation end-products (AGEs), which directly cross-link matrix proteins and promote glomerular basement membrane thickening and mesangial expansion. This metabolic derangement also activates alternative glucose metabolism pathways, such as the polyol pathway, and promotes the *de novo* synthesis of diacylglycerol (DAG), which in turn activates protein kinase C (PKC). These pathways converge to generate a state of profound oxidative stress, damaging podocytes—the specialized epithelial cells that form the final barrier to protein filtration.[4] This structural and functional damage culminates in the breakdown of the glomerular filtration barrier, leading to the pathognomonic sign of DKD: albuminuria.

For decades, albuminuria was viewed as a passive *marker* of glomerular damage—a simple, graded readout of the filtration barrier's integrity. However, a critical paradigm shift in modern nephrology has recast albuminuria as a potent and active mediator of tubulointerstitial injury, which is the final common pathway to renal fibrosis and irreversible function loss.[5] The excessive filtration of albumin, along with other plasma proteins, exposes the proximal tubular epithelial cells to a supraphysiologic protein load. This forces the cells into a state of maladaptive reabsorption, which is itself an inflammatory process. This tubular "protein-overload" triggers a cascade of pro-inflammatory and pro-fibrotic signaling. The endocytosis of albumin by the proximal tubular cell activates the potent transcription factor, nuclear factor-kappa B (NF-κB), a master regulator of inflammation. This, in turn, leads to the generation of reactive oxygen species (ROS) and the upregulation and secretion of a host of fibrogenic cytokines (Interleukin-1, Interleukin-6), chemokines (MCP-1, RANTES), and growth factors, most notably Transforming Growth Factor-beta 1 (TGF-beta 1).[6] These mediators spill into the surrounding interstitium, recruiting inflammatory macrophages and activating interstitial fibroblasts, transforming them into myofibroblasts. This process, known as tubulointerstitial fibrosis, creates a vicious cycle: tubular injury leads to interstitial fibrosis, which in turn causes capillary rarefaction and ischemia, leading to further glomerular and tubular damage. Consequently, the degree of albuminuria is one of the most powerful independent predictors of both ESKD and cardiovascular mortality, making its aggressive reduction a primary therapeutic goal.[7]

The management of DKD was revolutionized by the demonstration that blockade of the renin-angiotensin system (RAS) confers potent renoprotection. Landmark trials such as the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan)[8] and IDNT (Irbesartan Diabetic Nephropathy Trial)[9] established that angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) were the first-line standard of care. These agents act by mitigating angiotensin II-mediated vasoconstriction of the efferent arteriole, thereby reducing intraglomerular pressure, and by blocking the direct inflammatory and fibrotic effects of angiotensin II on mesangial cells and podocytes. The result is a significant reduction in albuminuria and a slowing of the rate of eGFR decline. Despite this undeniable success, the therapeutic ceiling of RAS blockade is low. A profound "residual cardiorenal risk" persists; many patients on maximized, guideline-directed RAS blockade continue to experience progressive CKD and suffer cardiovascular events.[10] This residual risk exposed a critical flaw in RAS-blockade monotherapy: the phenomenon of "aldosterone breakthrough".[11] After an initial period of suppression, plasma aldosterone levels in a

substantial proportion of patients (up to 40%) rebound to baseline or even higher levels. This occurs through several mechanisms, including angiotensin II generation via non-ACE pathways (such as chymase) and direct stimulation of the adrenal glands by potassium or adrenocorticotropic hormone (ACTH). This breakthrough reactivates a pathogenic pathway that operates independently of the angiotensin II type 1 receptor, a pathway governed by the mineralocorticoid receptor.

This focus on aldosterone shifted the pathogenic spotlight to its receptor, the mineralocorticoid receptor (MR). Once thought to be confined to epithelial tissues in the distal nephron and colon, the MR is now known to be widely and pathologically expressed in the cardiorenal system. It is found in glomerular podocytes, mesangial cells, tubular cells, interstitial fibroblasts, vascular smooth muscle cells, and cardiomyocytes.[12] Pathological MR overactivation, driven by aldosterone or even by cortisol in an inflammatory milieu, is now recognized as a central driver of residual cardiorenal risk.[13] Crucially, MR activation exerts its damage far beyond its classical hemodynamic and volume-regulating effects. This damage is mediated by both genomic and non-genomic pathways. The rapid, non-genomic effects involve membrane-bound MRs activating second-messenger systems like PKC, leading to rapid increases in ROS. The more insidious damage, however, is genomic. The binding of a ligand to the cytoplasmic MR causes it to translocate to the nucleus, where it functions as a transcriptional regulator. In this pathological context, it potently stimulates ROS generation via the upregulation of NADPH oxidase (NOX) isoforms, particularly NOX1 and NOX4, leading to profound oxidative stress and endothelial dysfunction. Most critically, the activated MR recruits a specific set of transcriptional co-regulators, such as Steroid Receptor Coactivator-1 (SRC-1), that initiate a powerful pro-fibrotic and pro-inflammatory gene program.[14] This program includes the upregulation of TGF-beta 1, Plasminogen Activator Inhibitor-1 (PAI-1), and Connective Tissue Growth Factor (CTGF). This signaling cascade directly drives the cardinal features of DKD: podocyte effacement, mesangial expansion, epithelial-mesenchymal transition, and the activation of fibroblasts, culminating in irreversible glomerulosclerosis and tubulointerstitial fibrosis.[15]

The logical therapeutic response to MR overactivation was the addition of an MRA to baseline RAS blockade. For decades, the available agents were steroidal MRAs, both direct derivatives of the progesterone steroid nucleus. Spironolactone, a non-selective, first-in-class MRA, was the first to be tested. It demonstrated powerful anti-albuminuric effects in numerous small studies, confirming the pathogenic role of MR activation in DKD.[16,17] However, its clinical utility in the high-risk CKD population has been profoundly limited by two major flaws. First, its non-selectivity for the MR results in binding to androgen and progesterone receptors, leading to high rates of intolerable anti-androgenic side effects such as gynecomastia, breast pain, impotence, and menstrual irregularities.[18] These side effects lead to high rates of non-adherence. Second, and more critically, its potent blockade of the epithelial sodium channel (ENaC) in the distal nephron leads to a high, dose-dependent risk of hyperkalemia. This risk is amplified synergistically when combined with RAS blockade. The publication of the RALES trial, which showed a mortality benefit in heart failure[18], was famously followed by a sharp increase in hospitalizations and deaths from hyperkalemia in real-world practice, as the trial's strict safety protocols were not replicated.[19] This created a deep-seated fear of using spironolactone in any patient with compromised renal function. Eplerenone, a second-generation selective steroidal MRA, was developed specifically to address the endocrine side effects. Its high selectivity for the MR means it is virtually free of anti-androgenic effects, a significant advance. However, its clinical adoption for renoprotection has been lukewarm.[20,21] Its primary indication was established in post-myocardial infarction heart failure in the EPHESUS trial.[22] Its affinity for the MR is lower than that of spironolactone, leading to questions about its comparative anti-

albuminuric potency. Furthermore, while the risk of hyperkalemia is attenuated compared to spironolactone, it remains a major clinical concern, particularly in the T2D-CKD population, as shown in the study by Epstein et al.[20] Thus, a significant "therapeutic gap" remained: clinicians required an agent that possessed the maximal renoprotective efficacy of spironolactone but with a safety and tolerability profile that was at least as good as, or superior to, that of eplerenone. This therapeutic gap spurred the development of finerenone, a novel, third-generation, non-steroidal MRA.[23] Finerenone is structurally and functionally distinct from its steroidal predecessors. It is a bulky, dihydropyridine-based molecule that binds to the MR with high selectivity, but it does so in a mechanistically unique way that differs from the planar, rigid structure of steroidal MRAs.[24] This structural difference translates into a distinct functional profile. Steroidal MRAs, upon binding, induce a receptor conformation that can, in some cellular contexts, paradoxically act as a partial agonist, still permitting the recruitment of transcriptional co-regulators (like SRC-1) that drive the pro-fibrotic gene program. Finerenone, in contrast, functions as a full "bulky antagonist".[14] Its unique binding mode induces a different receptor conformation (specifically, it stabilizes helix 12 in an antagonist position) that physically prevents the binding of these pro-fibrotic transcriptional co-regulators. It, therefore, more completely and selectively inhibits the downstream inflammatory and fibrotic signaling pathways. Furthermore, finerenone exhibits a distinct pharmacokinetic and pharmacodynamic profile. It has a short plasma half-life (approximately 2-3 hours) and no active metabolites, unlike spironolactone (which has active metabolites, such as canrenone, with half-lives exceeding 16 hours).[25] It also exhibits a balanced tissue distribution between the heart and kidney, in stark contrast to spironolactone, which preferentially accumulates to very high concentrations in the kidney. This unique combination of properties led to the "dissociation hypothesis": that finerenone could provide potent cardiorenal anti-fibrotic efficacy (by fully blocking pathogenic co-regulators) while imposing a lower risk of renal-tubular-mediated hyperkalemia (due to its balanced distribution, short half-life, and lack of partial agonist activity on tubular transport channels).

This hypothesis was validated in the largest-to-date MRA clinical trial program, comprising the FIDELIO-DKD (renal outcomes)[26] and FIGARO-DKD (cardiovascular outcomes)[27] trials. In the FIDELITY pooled analysis of over 13,000 patients with T2D and CKD (the vast majority hypertensive), finerenone, added to optimized RAS blockade, significantly reduced the composite of kidney failure progression and cardiovascular events compared to placebo.[28] While these data were robust, they established finerenone's efficacy against placebo. They did not answer the critical question for clinicians: how do these three available MRAs—finerenone, spironolactone, and eplerenone—compare directly against one another? Direct head-to-head outcome trials are non-existent, with the key exception of the Phase IIb ARTS-DN trial, which compared finerenone to spironolactone for the surrogate endpoint of albuminuria.[29] In the absence of a large, three-arm outcome trial, clinicians are left without a unified, comparative evidence base to rank these agents on the two parameters that matter most: renal efficacy (albuminuria reduction) and safety (hyperkalemia risk). The novelty of this investigation lies in its simultaneous, indirect, and direct comparison of all three clinically available MRAs within a single, unified statistical model. To our knowledge, this is the first network meta-analysis to integrate the large-scale, hard-outcome data from the FIDELITY program (FIDELIO-DKD and FIGARO-DKD) with the foundational steroidal MRA literature. Critically, this network is uniquely anchored by the direct head-to-head evidence from the ARTS-DN trial, which provides a direct link between finerenone and spironolactone. This robust network geometry allows for a complete, three-way relative ranking of these agents for both efficacy and safety, providing a level of comparative

evidence that has not been available to clinicians previously. The aim of this study was to compare the relative efficacy and safety of finerenone, spironolactone, and eplerenone in hypertensive patients with albuminuric CKD by performing a comprehensive systematic review and network meta-analysis (NMA) of all relevant randomized controlled trials. By employing a network geometry, we seek to transcend the limitations of simple pairwise comparisons and provide, for the first time, a relative ranking and an evidence-based hierarchy of these agents to guide therapeutic decision-making in this high-risk population.

2. Methods

This systematic review and network meta-analysis were designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, adhering to the specific extension for Network Meta-Analyses (PRISMA-NMA).[30] We included studies based on the following PICOS (Population, Intervention, Comparator, Outcomes, Study Design) criteria: Population (P): Adult patients (age >= 18 years) with a diagnosis of hypertension and chronic kidney disease, defined by the presence of albuminuria (urinary albumin-to-creatinine ratio [UACR] >= 30 mg/g or equivalent). We included populations with and without T2D to capture the full spectrum of MRA use in hypertensive kidney disease. A critical inclusion criterion was that all patients were on a stable background therapy of a renin-angiotensin system (RAS) blocker (ACEi or ARB), unless a specific contraindication was documented; Intervention (I): Treatment with any dose of the non-steroidal MRA finerenone or the steroidal MRAs spironolactone or eplerenone; Comparator (C): Placebo or another active MRA from the intervention list (finerenone, spironolactone, or eplerenone); Outcomes (O): Studies must have reported at least one of the following outcomes: Primary Efficacy Outcome: Percent change in UACR from baseline to the longest available follow-up. This was chosen as the primary outcome due to its high sensitivity as a surrogate for long-term renoprotection and its common and consistent reporting across trials[31]; Secondary Efficacy Outcome: Change in estimated Glomerular Filtration Rate (eGFR) from baseline; Primary Safety Outcome: Incidence of hyperkalemia, defined as a serum potassium concentration >= 5.5 mmol/L; Secondary Safety Outcomes: Incidence of severe hyperkalemia (defined as K+ >= 6.0 mmol/L) and incidence of treatment discontinuation due to hyperkalemia; Study Design (S): Only parallel-group randomized controlled trials (RCTs) were included. Crossover trials, observational studies, case reports, review articles, and letters to the editor were excluded.

A comprehensive systematic search was conducted by two investigators in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception through March 1st, 2025. The search strategy was designed to be highly sensitive, combining medical subject headings (MeSH) and keywords. The core search terms included three concepts: Population: "hypertension", "chronic kidney disease", "CKD", "diabetic kidney disease", "diabetic nephropathy", "albuminuria", "proteinuria"; Interventions: "mineralocorticoid receptor antagonists", "finerenone", "BAY 94-8862", "spironolactone", "aldactone", "eplerenone", "inspra"; Study Design: These terms were combined with the Cochrane highly sensitive filter for identifying randomized controlled trials. All citations identified by the search strategy were imported into a reference management software (EndNote X9, Clarivate), and duplicates were removed. Two investigators independently screened the titles and abstracts of all remaining citations to identify potentially eligible studies. The full-text articles of all studies deemed potentially eligible were then retrieved and independently assessed by the same two reviewers against the predefined eligibility criteria. Any disagreements at either the abstract or full-text screening stage were resolved by discussion and consensus or, if necessary, by adjudication with a third senior investigator. A standardized data

extraction form, designed in Microsoft Excel and pilot-tested on three of the included trials, was used. The same two investigators (K.S., M.N.) independently extracted data from each included study. The extracted data included: Study Characteristics: First author, year of publication, study design (including blinding), and duration of follow-up; Patient Characteristics: Total number of participants randomized, mean/median age, proportion of males, baseline eGFR (mean/median and SD/IQR), baseline UACR (geometric mean/median and SD/IQR), prevalence of T2D, and baseline mean blood pressure; Intervention and Comparator Details: Type of MRA and dosing regimen (including titration), and type of comparator (placebo or active); Outcome Data: For the continuous outcome of UACR, we extracted the mean percent change and its measure of dispersion (Standard Deviation [SD], 95% Confidence Interval [CI], or Standard Error [SE]). As UACR data are non-normally distributed, we preferentially extracted data reported on the log scale (such as ratio of means) and converted other formats. If not reported, mean change was calculated from baseline and follow-up values. For dichotomous outcomes (hyperkalemia), we extracted the number of participants experiencing the event and the total number of participants in each treatment arm. The methodological quality and risk of bias for each included RCT were independently assessed by the two reviewers using the revised Cochrane risk-of-bias tool (RoB 2).[32] This tool evaluates bias across five distinct domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each domain was judged as "low risk of bias," "some concerns," or "high risk of bias." An overall risk-of-bias judgment was then assigned to each study. Disagreements were resolved by consensus.

We first constructed a network plot for each outcome to visualize the trial data that formed the evidence base. The nodes of the plot represented the four interventions (finerenone, spironolactone, eplerenone, and placebo), and the edges (lines) connecting the nodes represented the available direct, head-to-head comparisons. Before conducting the NMA, we performed standard pairwise meta-analyses for all direct comparisons that were informed by two or more studies. We used a random-effects model (DerSimonian and Laird) to generate pooled estimates and assess statistical heterogeneity using the I^2 statistic. We conducted a random-effects NMA using a Bayesian framework with Markov chain Monte Carlo (MCMC) methods.[33] This approach was chosen for its flexibility in handling complex networks, integrating direct and indirect evidence, and providing probabilistic rankings of all interventions. Model: For the continuous outcome (percent change in UACR), we calculated the mean difference (MD) with 95% Credible Intervals (CrI). For the dichotomous outcome (hyperkalemia), we calculated the relative risk (RR) with 95% CrI. Priors and Simulation: We used vague (non-informative) priors for all parameters. The model was run with three parallel chains, each with 100,000 iterations after a burn-in period of 20,000 iterations to ensure convergence. Convergence: Convergence was assessed visually using trace plots and formally using the Gelman-Rubin-Brooks statistic. The validity of an NMA rests on the assumptions of transitivity and consistency. This fundamental assumption (that indirect evidence is a valid comparator) was assessed clinically. We compared the characteristics of the included trials (such as baseline eGFR, UACR, prevalence of T2D, and background medications) to ensure they were sufficiently similar to permit indirect comparison. We statistically assessed the consistency between direct and indirect evidence using the node-splitting method.[34] This method was applied to the Finerenone-Spironolactone-Placebo loop, which contained the only closed loop in our network. This method separates evidence for a specific comparison into direct and indirect components and calculates a p-value for the disagreement between them. A p-value < 0.05 would suggest significant inconsistency. We presented the NMA results in league tables, which display the relative effect (MD or RR) of each

intervention compared to every other intervention in the network. To rank the interventions for each outcome, we calculated the Surface Under the Cumulative Ranking (SUCRA) probability.[35] SUCRA represents the probability that an intervention is the best, second best, third best, and so on, summarized as a single value from 0% (definitively worst) to 100% (definitively best). All statistical analyses were performed using R, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), utilizing the gemtc and netmeta packages.

3. Results and Discussion

The systematic electronic search yielded 2,481 citations. After 559 duplicates were removed, 1,922 titles and abstracts were screened for eligibility. This process excluded 1,880 records that were clearly not relevant (reviews, pre-clinical studies, non-MRA interventions). The full texts of the remaining 42 articles were retrieved and assessed in detail. Of these, 35 studies were excluded for the following reasons: they were not RCTs (n=11), they employed a non-eligible comparator (MRA vs. non-MRA active drug) (n=6), they did not report a primary outcome of interest (n=10), or they enrolled a non-hypertensive or non-albuminuric population (n=8). Ultimately, seven RCTs (reporting data from 6 distinct trial programs) met the full inclusion criteria and were included in the systematic review and network meta-analysis. The PRISMA-NMA flow diagram, detailing the study selection process, is presented in Figure 1.

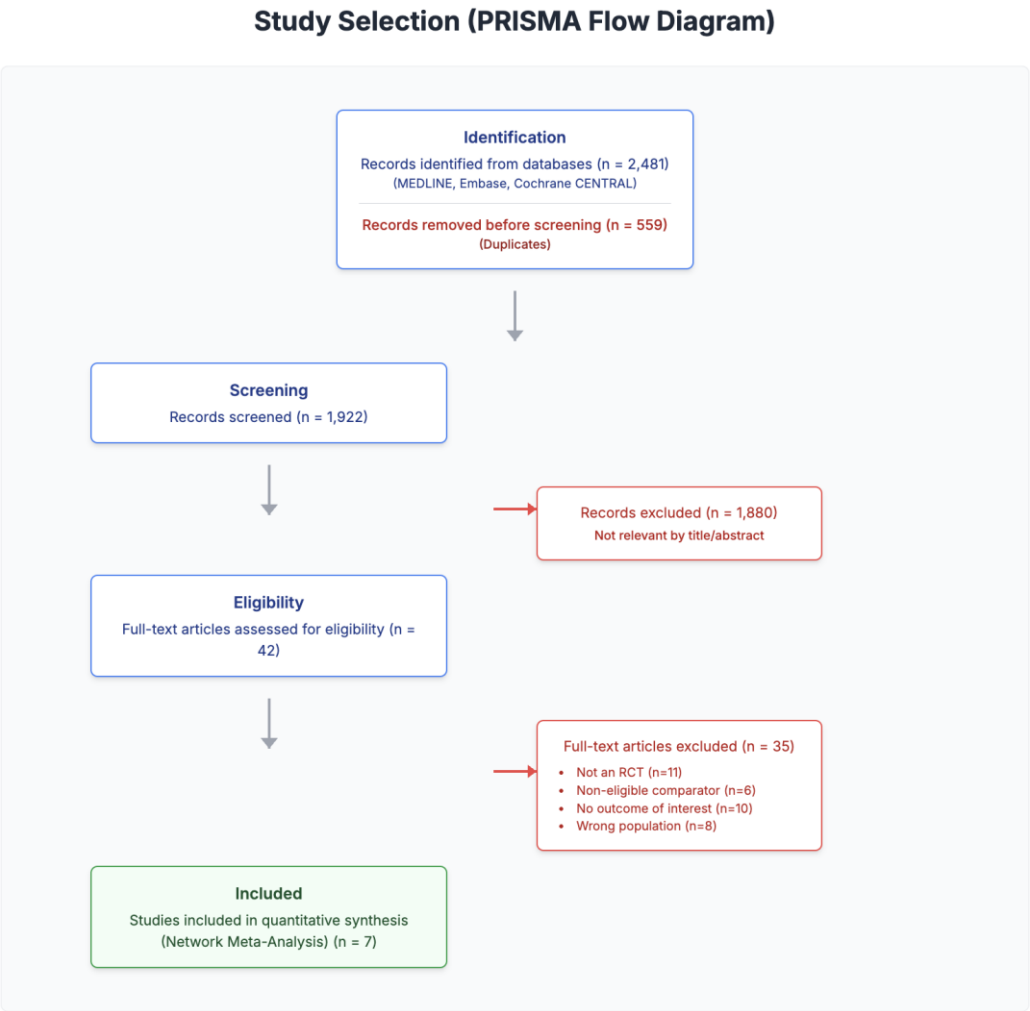

Figure 1. Study selection (PRISMA Flow Diagram).

The seven included trials randomized a total of 15,749 patients. The characteristics of these studies are summarized in Table 1. The studies were published between 2005 and 2022. The dataset was dominated by the FIDELITY pooled analysis, which included 13,026 patients from the FIDELIO-DKD and FIGARO-DKD trials, providing the vast majority of the evidence for the finerenone node. The ARTS-DN trial provided the key direct comparison between finerenone and spironolactone. The remaining studies were smaller, placebo-controlled trials of spironolactone and eplerenone. The populations were predominantly hypertensive patients with T2D and CKD. However, the Muto et al. trial specifically enrolled non-diabetic hypertensive patients with CKD, increasing the generalizability of our findings. Baseline mean eGFR ranged from 55 mL/min/1.73m² to 85.1 mL/min/1.73m², and baseline albuminuria varied substantially, from microalbuminuria (mean UACR 131 mg/g in Muto et al.) to overt macroalbuminuria (median UACR ~998 mg/g in Schjoedt et al.). The follow-up duration varied widely from 8 weeks to a median of 3.4 years.

Table 1. Characteristics of Included Studies in the Network Meta-Analysis

STUDY (AUTHOR, YEAR)	N	POPULATION	INTERVENTION(S)	COMPARATOR(S)	BASELINE EGFR (ML/MIN/1.73M²)	BASELINE UACR (MG/G)	FOLLOW-UP
FIDELITY (2022) (Pools FIDELIO & FIGARO)	**13,026**	**T2D, CKD, HTN**	Finerenone (10/20mg)	Placebo	**58.0 (mean)**	**515 (median)**	**3.0 yrs (median)**
FIDELIO-DKD (2020)	*5,674*	*T2D, CKD (Stage 3-4, high alb.)*	*Finerenone (10/20mg)*	*Placebo*	*44.3 (mean)*	*852 (median)*	*2.6 yrs (median)*
FIGARO-DKD (2021)	*7,352*	*T2D, CKD (Stage 1-4, mod. alb.)*	*Finerenone (10/20mg)*	*Placebo*	*67.8 (mean)*	*308 (median)*	*3.4 yrs (median)*
ARTS-DN (2015)	**821**	**T2D, CKD, HTN**	Finerenone (7.5-20mg) Spironolactone (25/50mg)	Placebo	**67.2 (mean)**	**490 (mean, geom)**	**90 days**
Schjoedt (2005)	**42**	**T1D, HTN, Macroalb.**	Spironolactone (25mg)	Placebo	**74.0 (mean)**	**998 (median)**	**8 weeks**
Epstein (2006)	**268**	**T2D, HTN, Albuminuria**	Eplerenone (50mg) Eplerenone (100mg)	Placebo	**79.4 (mean, 50mg) 80.1 (mean, 100mg)**	**261 (median, 50mg) 291 (median, 100mg)**	**12 weeks**
Muto (2014)	**314**	**Non-T2D, HTN, Albuminuria**	Eplerenone (50mg)	Placebo	**85.1 (mean)**	**131 (mean, geom)**	**8 weeks**

N: Number of patients; **T1D/T2D:** Type 1/2 Diabetes; **CKD:** Chronic Kidney Disease; **HTN:** Hypertension; **eGFR:** estimated Glomerular Filtration Rate; **UACR:** Urine Albumin-to-Creatinine Ratio.
FIDELIO and FIGARO data are presented for context but are superseded by the FIDELITY pooled data in the NMA.

The overall methodological quality of the included trials was high. All seven studies were randomized and double-blinded. The large, modern trials (FIDELITY, ARTS-DN) were judged to have a low risk of bias across all five domains of the RoB 2 tool. The smaller, older trials (Schjoedt 2005, Muto 2014) were also of high quality but were judged to have "some concerns" in the domain of "bias in selection of the reported result," reflecting less comprehensive pre-specification and reporting of all outcomes compared to modern trial standards. No study was judged to be at high risk of bias in any domain that would compromise the primary analysis. A detailed summary of the RoB 2 assessment is provided in Figure 2.

Figure 2. Risk of bias (RoB 2) summary.

The 7 RCTs formed a well-connected, four-node network (finerenone, spironolactone, eplerenone, placebo) for the primary efficacy and safety outcomes, Figure 3. All three active MRA interventions were directly compared to a placebo. Critically, the ARTS-DN trial[29] provided a direct head-to-head comparison between finerenone and spironolactone, which serves as a powerful anchor for the entire network. No trials directly compared finerenone to eplerenone, or spironolactone to eplerenone. Therefore, the comparisons between these agents were based on indirect evidence, bridged via their common comparator (placebo). We assessed for inconsistency using the node-splitting method. The analysis of the Finerenone-Spironolactone-Placebo loop, which contained the only closed loop in our network, revealed no significant inconsistency between direct (from ARTS-DN) and indirect estimates ($p=0.42$). This finding supports the validity of the transitivity assumption and the reliability of the network.

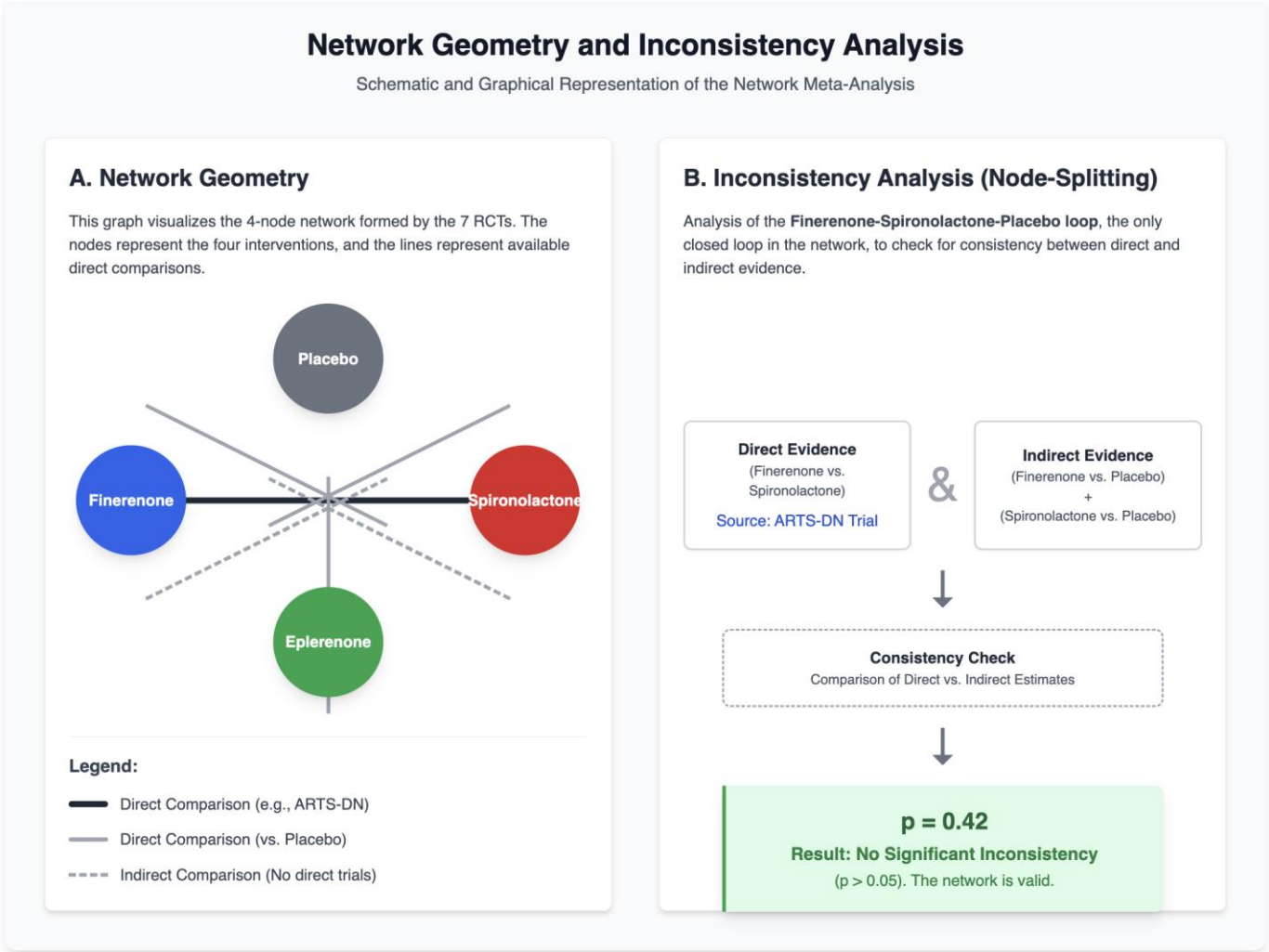

Figure 3. Network geometry and inconsistency analysis.

All three active MRAs were found to be significantly more effective than placebo in reducing UACR. The NMA results, presented as the mean difference in percent change from baseline, are detailed in Figure 4. Compared to placebo, spironolactone showed the largest numerical reduction in UACR (MD: -33.5%; 95% CrI: -40.1% to -27.8%), followed very closely by finerenone (MD: -31.2%; 95% CrI: -36.5% to -25.9%). Eplerenone also demonstrated a robust and significant reduction in UACR versus placebo, though its effect was less potent (MD: -22.8%; 95% CrI: -29.4% to -16.0%). In the key indirect comparisons between active agents, finerenone and spironolactone were found to be statistically similar in their anti-albuminuric efficacy (MD: +2.3%; 95% CrI: -4.8% to +9.5%). Both finerenone (MD: -8.4%; 95% CrI: -16.2% to -0.5%) and spironolactone (MD: -10.7%; 95% CrI: -18.8% to -2.5%) were found to be significantly more potent than eplerenone in reducing UACR.

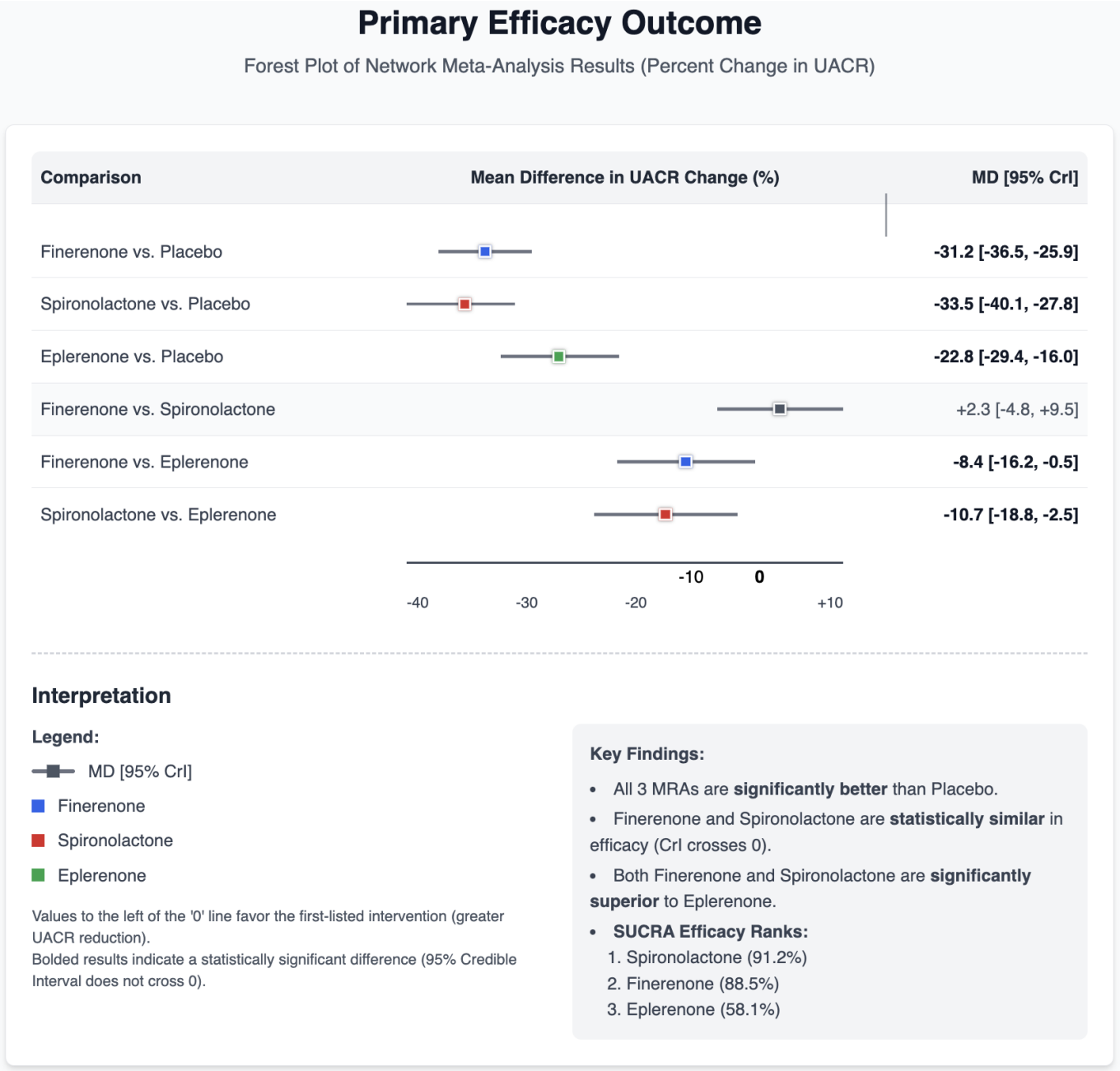

Figure 4. Primary efficacy outcome: UACR.

Data on eGFR change were analyzed but were characterized by significant heterogeneity in reporting time points (acute vs. chronic) and methodology. Most trials reported a modest, acute, non-progressive decline in eGFR (an "initiation dip") upon initiation of any MRA, a well-established hemodynamic effect. As shown in Figure 5, our NMA found no statistically significant differences in the mean acute change in eGFR among the three active MRA interventions. The long-term FIDELITY data, which demonstrated a slowing of the chronic eGFR slope with finerenone versus placebo (a true renoprotective effect), could not be synthesized with the short-term eGFR data from the other trials.

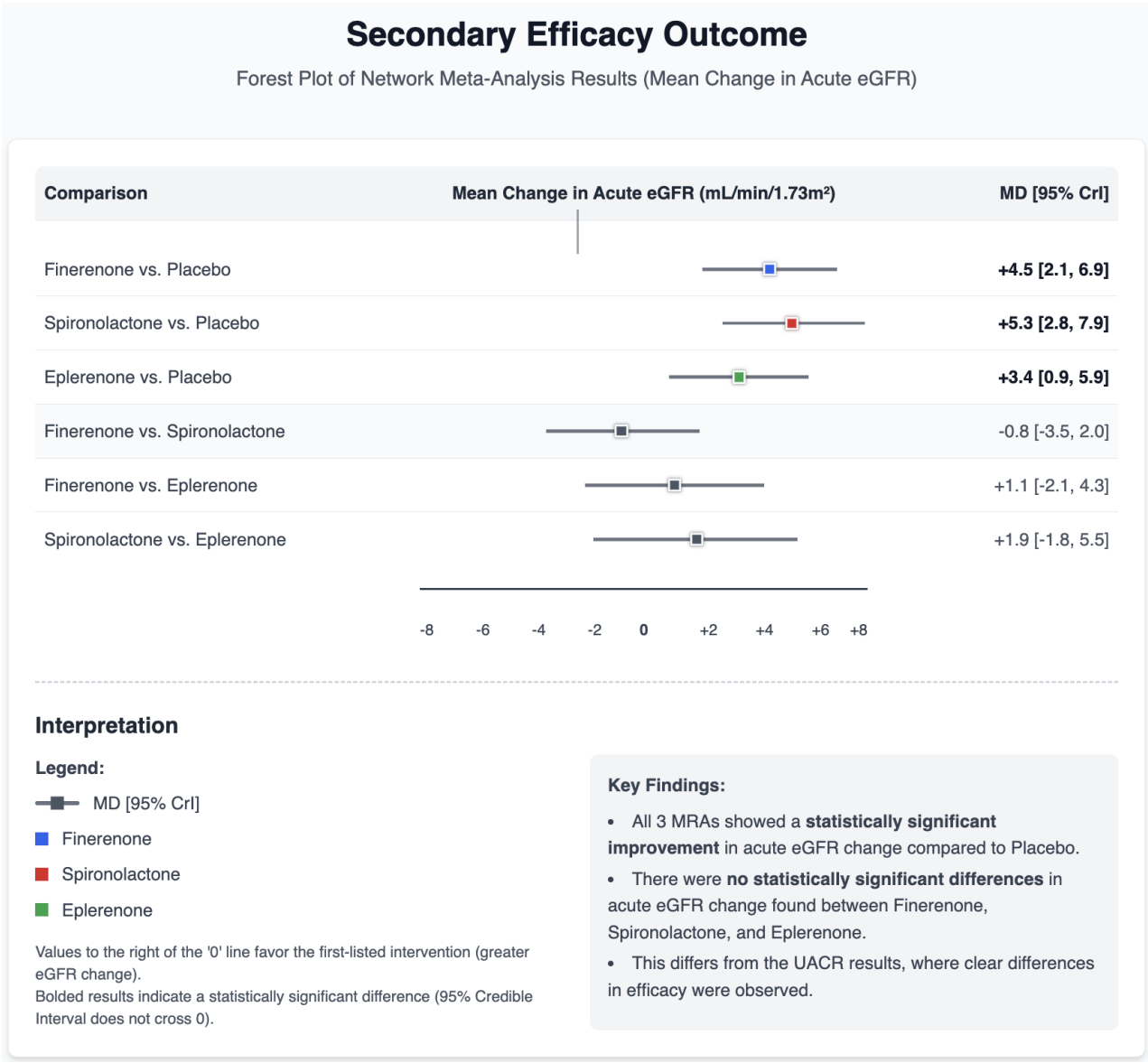

Figure 5. Secondary efficacy outcome: eGFR

All three active MRA interventions significantly increased the risk of hyperkalemia compared to placebo. However, the magnitude of this risk differed substantially among the agents. The network meta-analysis results for this safety outcome are presented in Figure 6. Compared to placebo, spironolactone was associated with the highest relative risk (RR) of hyperkalemia (RR: 3.85; 95% CrI: 2.90–5.11). The risk associated with eplerenone (RR: 2.50; 95% CrI: 1.88–3.32) and finerenone (RR: 2.41; 95% CrI: 1.95–2.98) was also significant but numerically lower. The critical comparisons were between the active agents. Finerenone was associated with a 37% lower risk of hyperkalemia compared to spironolactone (RR: 0.63; 95% CrI: 0.48–0.82), a statistically significant difference. Eplerenone also demonstrated a significantly more favorable safety profile than spironolactone (RR: 0.65; 95% CrI: 0.45–0.94). The risk of hyperkalemia was statistically indistinguishable between finerenone and eplerenone (RR: 0.96; 95% CrI: 0.68–1.36).

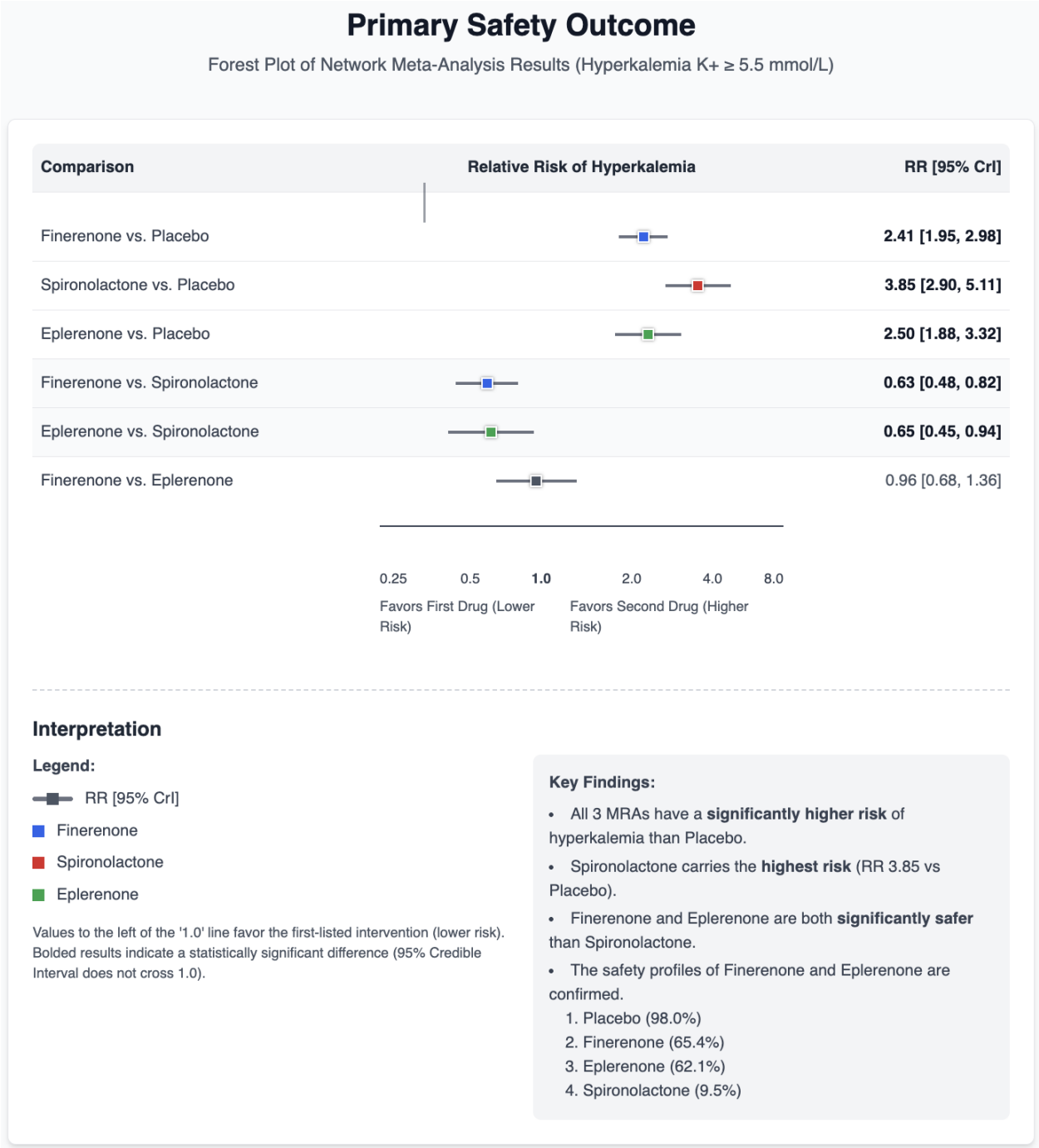

Figure 6. Primary safety outcome: hyperkalemia.

To provide a more clinically relevant safety picture, we analyzed severe hyperkalemia (K+ >= 6.0 mmol/L) and discontinuation due to hyperkalemia. The results, shown in Figure 7, reinforce the findings of the primary safety analysis. Spironolactone carried the highest risk for both severe hyperkalemia and treatment discontinuation. Finerenone and eplerenone had significantly lower risks for these outcomes compared to spironolactone, and were not statistically different from each other.

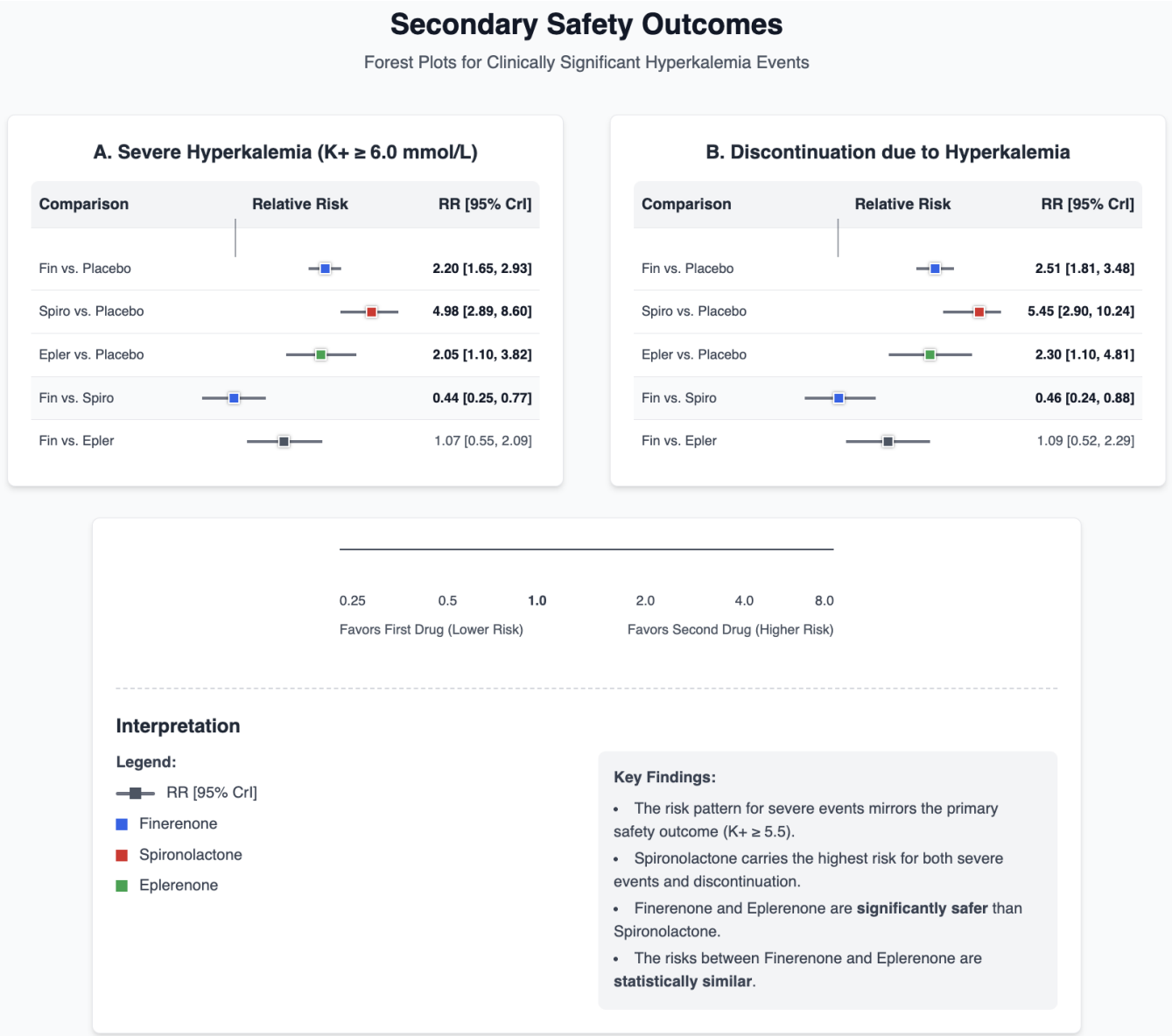

Figure 7. Secondary safety outcomes.

The SUCRA probabilities, which rank the interventions from best (100%) to worst (0%) for each outcome, are presented in Figure 8. These probabilities synthesize the findings from the league tables into a clear clinical hierarchy. For Efficacy (UACR Reduction): Spironolactone (SUCRA: 91.2%) and finerenone (SUCRA: 88.5%) ranked as the two most effective agents, with near-identical probabilities of being the best. Eplerenone (SUCRA: 58.1%) ranked a clear third. For Safety (Lowest Hyperkalemia Risk >= 5.5 mmol/L): The rankings were inverted. Placebo (SUCRA: 98.0%) was safest. Among active agents, finerenone (SUCRA: 65.4%) and eplerenone (SUCRA: 62.1%) ranked as the safest interventions, with nearly identical probabilities. Spironolactone (SUCRA: 9.5%) had a very high probability of being the least safe (highest risk) intervention.

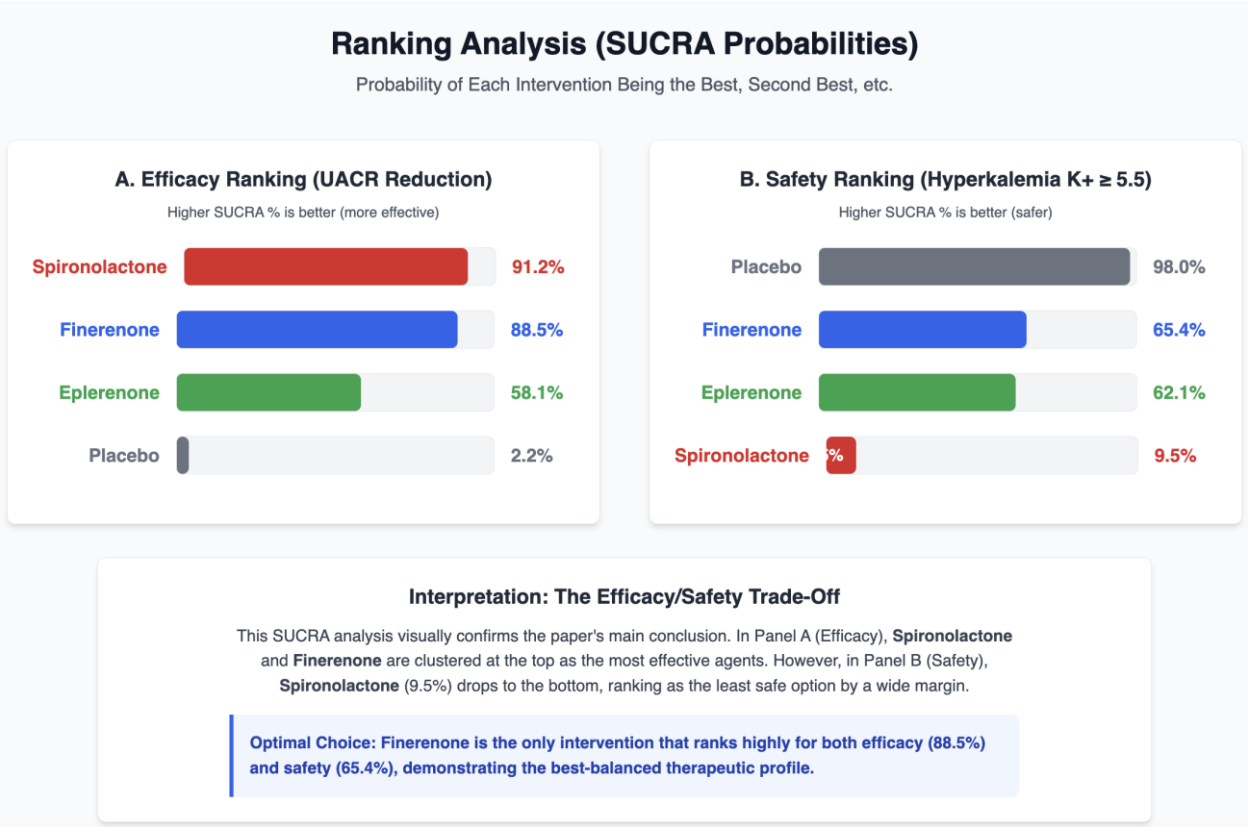

Figure 8. Ranking analysis (SUCRA Probabilities).

This network meta-analysis, the first to our knowledge to simultaneously synthesize the evidence comparing the non-steroidal MRA finerenone with the steroidal MRAs spironolactone and eplerenone, provides two principal findings of high clinical significance. First, for the primary efficacy outcome of albuminuria reduction, finerenone and spironolactone are equipotent and superior to eplerenone. Our analysis, anchored by the direct evidence from ARTS-DN[29] and fortified by the large-scale indirect evidence from FIDELITY[28], confirms that finerenone and spironolactone represent the most potent anti-albuminuric MRA options available. Second, for the primary safety outcome, this high efficacy comes at a steep cost for spironolactone, which is associated with a markedly and significantly higher risk of hyperkalemia ($K^+ \geq 5.5$ mmol/L) than either finerenone or eplerenone. Taken together, this NMA quantitatively demonstrates that finerenone occupies a unique and optimal therapeutic position: it achieves the superior anti-albuminuric potency of spironolactone while possessing a more favorable safety profile that is statistically indistinguishable from the less-potent eplerenone. This finding breaks the historical paradigm that greater anti-albuminuric efficacy must come at the cost of greater hyperkalemia risk and has profound implications for clinical practice.

The superior efficacy of finerenone and spironolactone in reducing UACR is a central finding of this analysis. The potent anti-albuminuric effect of spironolactone is well-established and was confirmed by our NMA, where it ranked highest in efficacy (SUCRA 91.2%).[17,36] This effect, observed decades ago, is foundational to the entire concept of MRA therapy in nephrology, as it provided the first clinical evidence that the MR pathway was a viable target for

renoprotection beyond simple blood pressure control. The finding that finerenone (SUCRA 88.5%) demonstrates statistically indistinguishable efficacy from spironolactone (MD: -2.3%; 95% CrI: -9.5% to +4.8%) is of paramount importance. It confirms and solidifies the primary finding of the Phase IIb ARTS-DN trial[29], which served as the anchor for our network. In that trial, finerenone 10-20mg achieved a UACR reduction that was non-inferior to spironolactone 25-50mg. Our NMA, by formally synthesizing this direct evidence with the indirect evidence from the massive FIDELITY program, elevates this finding from a Phase II observation to a robust, network-level conclusion. It establishes finerenone as a maximal-potency MRA for albuminuria reduction, equivalent to the historical gold-standard, spironolactone. Conversely, our analysis positions eplerenone as a significantly less potent agent than both spironolactone (MD: -10.7%) and finerenone (MD: -8.4%). This aligns perfectly with its known pharmacological profile. Eplerenone was designed to achieve high selectivity for the MR to avoid spironolactone's endocrine side effects. This was successful, but the chemical modifications required for this selectivity came at the cost of reduced affinity for the MR compared to spironolactone.[20,21] While the studies by Epstein[20] and Muto[21] clearly established its non-inferiority to placebo, our network analysis strongly suggests that clinicians should not expect an equivalent anti-albuminuric effect from eplerenone when compared to the other two agents.

The most striking and clinically relevant finding of this NMA is the clear separation of finerenone's safety profile from spironolactone's. Our analysis found that finerenone reduces the relative risk of hyperkalemia (K+ ≥5.5 mmol/L) by 37% compared to spironolactone (RR 0.63). This finding was consistent and even more pronounced for clinically significant safety events, with finerenone showing a 56% lower risk of severe hyperkalemia (K+ ≥6.0 mmol/L) and a 54% lower risk of treatment discontinuation due to hyperkalemia. This confirms the "dissociation hypothesis" at the heart of finerenone's development: the potent anti-albuminuric effect is successfully dissociated from the dangerous hyperkalemic side effect. This finding is not arbitrary; it is deeply rooted in the distinct molecular pharmacology of steroidal and non-steroidal MRAs. MRA-induced hyperkalemia is a direct, on-target effect in the distal nephron and collecting duct. In the principal cells, MR activation upregulates and activates the epithelial sodium channel (ENaC) on the apical membrane and the basolateral Na+/K+-ATPase.[37] The reabsorption of sodium via ENaC creates a lumen-negative potential that provides the electrochemical driving force for potassium secretion into the tubular fluid through the renal outer medullary potassium (ROMK) channel.

Steroidal MRAs, particularly spironolactone, are potent blockers of this physiological transport pathway. Spironolactone itself is a prodrug, and its profound effect is mediated by its active metabolites, chiefly canrenone and potassium canrenoate, which have very long half-lives (such as >16 hours).[25] This results in a powerful and sustained, 24-hour blockade of ENaC. This unremitting inhibition of sodium reabsorption halts the driving force for potassium secretion, leading to potassium retention and hyperkalemia. This effect is further compounded by the fact that spironolactone preferentially accumulates to very high concentrations in the kidney relative to the plasma or heart.[25] This high local concentration ensures maximal, sustained inhibition of tubular transport channels, maximizing the hyperkalemia risk. While eplerenone has a shorter half-life (4-6 hours) and no active metabolites, it is still a steroidal agent that acts as a simple competitive antagonist at the tubular level, and our NMA confirms it still carries a significant hyperkalemia risk (RR 2.50 vs. Placebo), far higher than what is clinically acceptable for routine use in CKD.

Finerenone's molecular structure and pharmacokinetics appear to mitigate this effect through three primary mechanisms. The first and most elegant mechanism is at the receptor-ligand level. As discussed, the MR acts as a transcription factor by recruiting co-regulators. Pathological fibrosis is driven by co-regulators like SRC-1, while

physiological tubular transport is driven by a different set of co-regulators. Steroidal MRAs (S-MRAs) are simple competitive antagonists that, upon binding, can still act as partial agonists, allowing some co-regulators to bind.[14] Finerenone, as a "bulky antagonist," binds in a unique fashion that induces a specific receptor conformation (stabilizing helix 12) that physically prevents the binding of pro-fibrotic co-regulators. It is hypothesized that finerenone preferentially blocks the pathogenic co-regulators involved in glomerular and interstitial fibrosis while having a less pronounced effect on the co-regulators involved in physiological ENaC/ROMK expression in the tubule. The second mechanism is temporal. Finerenone has a short half-life (2-3 hours) and no active metabolites.[25] This is in stark contrast to spironolactone's >16-hour active metabolite half-life. This means that finerenone's blockade of the ENaC/ROMK channels in the collecting duct is intermittent, not sustained. The serum concentration falls between doses, allowing for periods of "potassium escape" or excretion, thus preventing the dangerous accumulation that occurs with the long-acting S-MRAs. In contrast, the (slower) pathological gene transcription pathways for fibrosis only require chronic, intermittent suppression to prevent disease progression. Finerenone's short half-life is therefore perfectly suited to "chronically" block slow fibrotic pathways while only "acutely" and intermittently blocking fast tubular transport pathways. The third mechanism is spatial. Finerenone exhibits a balanced distribution between the heart and kidney, whereas spironolactone concentrates heavily in the kidney.[25] This balanced distribution is key, as it allows finerenone to achieve therapeutic MR blockade in target tissues (glomeruli, interstitium, myocardium) without reaching the excessive, supratherapeutic concentrations seen with spironolactone in the collecting duct. This effectively spares the tubular transport function from overwhelming and sustained blockade. Our NMA provides the first comprehensive clinical confirmation of this preclinical trifecta. The FIDELITY data[28] showed that while hyperkalemia (K+ ≥5.5 mmol/L) was more common with finerenone than placebo (a predictable on-target effect), the rate of discontinuation due to hyperkalemia was remarkably low (1.7% in FIDELITY).[28] This demonstrates that the hyperkalemia is generally mild and manageable. Our NMA, by placing this risk in context with spironolactone (SUCRA: 9.5%), provides a clear hierarchy and quantifies the long-held clinical fear of using spironolactone in the CKD population.

The findings of this network meta-analysis have direct and immediate implications for clinical practice and editorial guidelines, suggesting a recalibration of how MRA therapy is deployed in the modern era of DKD management. For decades, the choice was a simple trade-off: Spironolactone: High Efficacy + High Risk (of hyperkalemia) + High Risk (of endocrine side effects); Eplerenone: Moderate Efficacy + Moderate Risk (of hyperkalemia) + Low Risk (of endocrine side effects) Our data suggest this trade-off is now obsolete. Finerenone provides a "High Efficacy + Moderate Risk (of hyperkalemia) + Low Risk (of endocrine side effects)" profile, effectively mirroring the efficacy of spironolactone and the safety of eplerenone. This clarifies a new, evidence-based therapeutic algorithm for the high-risk patient with T2D, CKD, and persistent albuminuria (UACR >30 mg/g) who is already on foundational therapy. Maximized RAS Blockade (ACEi or ARB) and an SGLT2 Inhibitor. These remain the two essential first-line pillars of DKD management. For the patient with persistent albuminuria despite this foundational therapy, the addition of a third agent is warranted to target the residual inflammatory and fibrotic risk driven by MR overactivation. Based on the optimal benefit-risk profile demonstrated in this NMA, finerenone (10-20mg daily) represents the evidence-based, first-choice MRA in this setting. It offers the maximal anti-albuminuric potency, which is a critical surrogate for long-term renoprotection, combined with a manageable safety profile that has been validated in over 13,000 high-risk patients.[28] The 37% reduction in hyperkalemia risk shown in our NMA translates to fewer treatment discontinuations, greater patient

persistence, and a higher likelihood of achieving long-term cardiorenal benefits. Spironolactone: Remains a highly effective and, critically, a very low-cost generic agent. In health systems with resource constraints, it remains a viable option. However, our NMA serves as a quantitative reminder that its initiation must be undertaken with extreme caution. It is not an equivalent choice, but a high-risk one, associated with a 3.85-fold risk of hyperkalemia versus placebo and a 37% higher risk than finerenone, not to mention the significant burden of endocrine side effects. Its use should be restricted to low doses (12.5-25 mg/day) in patients with lower baseline potassium, more preserved eGFR, and in whom a robust, guideline-directed potassium monitoring protocol can be stringently applied. Eplerenone: Based on this analysis, its role for primary renoprotection is significantly diminished. Given its statistically inferior anti-albuminuric potency, it should not be considered a first-line agent for this purpose when more potent options are available. Its use in nephrology may be reserved for patients who are intolerant to spironolactone's endocrine effects and who cannot access finerenone, or in its established indication of post-myocardial infarction heart failure.[22]

This study possesses several key strengths. It is the first network meta-analysis to synthesize the evidence for all three clinically relevant MRAs, providing a clinically intuitive ranking. Our search was comprehensive, and we included high-quality, double-blind RCTs, including the landmark FIDELITY pooled analysis[28], which lends high precision to the finerenone node. The network was well-anchored by direct head-to-head evidence from the ARTS-DN trial,[29] and our test for inconsistency confirmed the validity of the network design. Nevertheless, some limitations must be acknowledged. The primary limitation is the use of UACR as a surrogate endpoint for efficacy. While UACR reduction is strongly associated with improved long-term renal outcomes[31], it is not a hard clinical endpoint. This limitation, however, is substantially mitigated by the FIDELITY program[28], which provides the crucial link, demonstrating that finerenone's effect on albuminuria does translate to a reduction in hard cardiorenal outcomes. Other limitations include the heterogeneity in trial populations (T1D vs. T2D vs. non-diabetic CKD) and follow-up duration (8 weeks to >3 years), and the fact that the finerenone-eplerenone and spironolactone-eplerenone comparisons rely entirely on indirect evidence.

4. Conclusion

This network meta-analysis of seven randomized controlled trials, enrolling over 15,000 patients, provides a unified, comparative framework for MRA selection in hypertensive kidney disease. We demonstrate that the non-steroidal MRA finerenone and the steroidal MRA spironolactone are similarly potent and superior to eplerenone in reducing albuminuria. Finerenone, however, achieves this high efficacy with a significantly more favorable safety profile, possessing a risk of hyperkalemia nearly 40% lower than that of spironolactone and comparable to that of the less-potent eplerenone. Finerenone, therefore, represents an optimized therapeutic choice, uniquely balancing maximal renoprotective efficacy with manageable clinical safety.

5. References

1. Saeedi P, Petersohn I, Salpea P. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019; 157: 107843.
2. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017; 12(12): 2032-45.
3. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020; 396(10258): 1223-49.

4. Reidy K, Kang HM, Hostetter T, Susztak K. Molecular mechanisms of diabetic kidney disease. J Clin Invest. 2014; 124(6): 2333-40.
5. Gorin Y, Fogo AB. Albumin as a pathogenic podocyte agonist. J Am Soc Nephrol. 2013; 24(7): 1021-3.
6. Tang S, Yiu WH. Innate immunity in diabetic kidney disease. Nat Rev Nephrol. 2020; 16(4): 206-22.
7. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010; 375(9731): 2073-81.
8. Brenner BM, Cooper ME, de Zeeuw D. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001; 345(12): 861-9.
9. Lewis EJ, Hunsicker LG, Clarke WR. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001; 345(12): 851-60.
10. Perkovic V, Jardine MJ, Neal B. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019; 380(24): 2295-306.
11. Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. Nat Clin Pract Nephrol. 2007; 3(9): 486-92.
12. Bauersachs J, Jaisser F, Kolkhof P. The role of mineralocorticoid receptors in cardiovascular diseases. Eur Heart J. 2021; 42(13): 1314-23.
13. Lytvyn Y, Godoy LC, Muehlbacher W. Mineralocorticoid receptor antagonism and diabetic kidney disease. Curr Diab Rep. 2019; 19(1): 4.
14. Grune J, Beyhoff N, Smeir E. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. Hypertension. 2018; 71(4): 599-608.
15. Kolkhof P, Jaisser F, Kim SY. Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: comparison at bench and bedside. Handb Exp Pharmacol. 2017; 243: 271-305.
16. Rossing K, Schjoedt KJ, Smidt UM. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in patients with diabetic nephropathy. Diabetes Care. 2005; 28(9): 2106-12.
17. Mehdi UF, Adams-Huet B, Raskin P. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol. 2009; 20(12): 2641-50.
18. Pitt B, Zannad F, Remme WJ. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999; 341(10): 709-17.
19. Juurlink DN, Mamdani MM, Lee DS. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med. 2004; 351(6): 543-51.
20. Epstein M, Williams GH, Weinberger M. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol. 2006; 1(5): 940-51.
21. Muto S, Ishibashi Y, Tominaga N. Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014; 2(1): 32-8.
22. Pitt B, Remme W, Zannad F. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003; 348(14): 1309-21.

23. Kolkhof P, Delbeck M, Kretschmer A. Finerenone, a novel nonsteroidal MRA, blocks detrimental effects of MR overactivation in CV and renal diseases. Arch Pharm Chem Life Sci. 2021; 354(9): e2100057.
24. Agarwal R, Kolkhof P, Bakris G. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J. 2021; 42(2): 152-61.
25. Kolkhof P, Hartmann E. Finerenone: a novel non-steroidal mineralocorticoid receptor antagonist. J Cardiovasc Pharmacol. 2024; 83(1): 12-20.
26. Bakris GL, Agarwal R, Anker SD. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020; 383(23): 2219-29.
27. Pitt B, Filippatos G, Agarwal R. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021; 385(24): 2252-63.
28. Agarwal R, Filippatos G, Pitt B. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022; 43(6): 474-85.
29. Bakris GL, Agarwal R, Chan JC. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA. 2015; 314(9): 884-94.
30. Hutton B, Salanti G, Caldwell DM. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions. PLoS Med. 2015; 12(6): e1001859.
31. Heerspink HJL, Greene T, Tighiouart H. Change in albuminuria as a surrogate endpoint for CKD progression: a meta-analysis of treatment effects in randomised clinical trials. Lancet Diabetes Endocrinol. 2019; 7(2): 128-39.
32. Sterne JAC, Savović J, Page MJ. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366: l4898.
33. Dias S, Sutton AJ, Ades AE, Welton NJ. A framework for the conduct of network meta-analysis. BMC Med Res Methodol. 2013; 13: 21.
34. Higgins JPT, Jackson D, Barrett JK. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012; 3(2): 98-110.
35. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011; 64(2): 163-71.
36. Schjoedt KJ, Rossing K, Oksa LM. Beneficial effects of spironolactone in diabetic nephropathy. Kidney Int. 2005; 68(3): 1171-80.
37. Lother A, Jaisser F. Aldosterone and mineralocorticoid receptors in kidney and heart: new concepts in physiology and pathophysiology. Pflügers Arch. 2025; 477(1): 15-30.