Efficacy and Safety of finerenone therapy in patients with cardiovascular and chronic kidney diseases in type 2 diabetes mellitus: a systematic review and meta-analysis

Mahima Khatri Mahima Khatri[1], Kamran Mahfooz[1], Kiran Saleem[1], Sidra Khalil[1], Maria Ali[1], Muhammad Usman[1], Uroosh Tariq Khanzada[1], Taha Nadeem[1], Fatima Tanveer[1], Rohit Kumar[1], Vikash Kumar karmani [1], Satesh Kumar [1], and Sumeet kumar[1]

[1]Affiliation not available

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Abstract

Background and Aims: Finerenone, a nonsteroidal MR antagonist (MRA), enhances renal and cardiovascular outcomes in patients with type 2 diabetes (T2DM). Finerenone's safety and effectiveness in renal function are debatable. This meta-analysis evaluates the efficacy and safety of treatments for patients with diabetic kidney disease.

Methods: To find relevant RCTs, the databases PubMed, Embase, and Google Scholar were searched. Finerenone's effects were quantified using estimated pooled mean differences (MDs) and relative risks with 95% confidence intervals (CIs).

Results: This meta-analysis combines seven double-blind trials involving patients with CKD and type 2 diabetes who were randomly assigned to finerenone or placebo. The primary efficacy time-to-event outcomes were cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, heart failure hospitalization, kidney failure, a sustained 57% decrease in estimated glomerular filtration rate from baseline over 4 weeks, or renal death. In this meta-analysis of 39,995 patients, treatment with Finerenone was associated with a lower risk of death due to cardiovascular and renal outcomes than placebo (RR = 0.86 [0.80, 0.93] p=0.0002; I2= 0%) and (RR = 0.56 [0.17, 1.82] p=0.34; I2= 0%), respectively. Finerenone treatment was also associated with a marginally lower risk of serious adverse events (RR = 0.95 [0.92, 0.97] p 0.0001; I2= 0%), but no overall difference in the risk of adverse events was found between the two groups (RR = 1.00 [0.99, 1.01] p=0.56; I2= 0%).

Conclusion: The administration of finerenone decreases the likelihood of end-stage kidney disease, renal failure, cardiovascular death, and hospitalization. Therefore, we propose that patients with T2DM and CKD undergo finerenone therapy.

Keywords: Diabetes, Chronic kidney disease, CKD, Cardiovascular disease, Finerenone, Non-steroidal Mineralocorticoid receptor antagonist, Meta-analysis.

Highlights:

- Finerenone reduces the risk of cardiovascular-related mortality and hospitalization, as well as nonfatal MI.
- Finerenone reduces the risk of renal failure, end-stage renal disease, decline in eGFR, and death from renal causes.
- In addition, finerenone decreases the risk of death and hospitalization from any cause.
- Finerenone posed a comparable risk of adverse events compared to placebo, but the risk of serious adverse events was lower.

Introduction:

Heart failure (HF) is not a solitary pathological condition but rather a clinical syndrome comprising of cardinal symptoms (such as shortness of breath, ankle edema, and fatigue) that may be backed by signs (such

as high jugular venous pressure, pulmonary crackles, and peripheral edema). It is caused by structural or functional abnormalities of the heart that results in increased intraventricular pressures and low cardiac output at rest or during activity.[1] The prevalence of heart failure (HF) is rising and affecting at least 26 million individuals worldwide. 1–2 % of the general population is diagnosed with HF, and 5–10% of those aged 65 and older have the diagnosis.[2] According to the American College of Cardiology/American Heart Association Joint Committee Clinical Practice Guidelines, left ventricular ejection fraction (LVEF) is important in the categorization of patients with HF because of differences in survival rate and response to therapeutic interventions and because most clinical studies select patients based on ejection fraction (EF). Heart failure with reduced ejection fraction (HFrEF) is defined as LVEF40%. In contrast, HF with preserved EF (HFpEF) represents at least 50% of the HF cohort, and its prevalence is rising.[3] HF, type 2 diabetes mellitus (T2DM), and chronic kidney disease (CKD) are significant pandemics of the 21st century.[1] It is now well-known that cardiovascular disease (CVD) is the major cause of this comorbidity and contributes to approximately 60–75 % of fatalities among people with diabetes. Diabetes increases the risk of cardiovascular disease by two to four, and its presence in patients with cardiovascular disease is one of the strongest predictors of bad clinical outcomes.[4] Despite current interventions, patients with CKD and T2DM have substantial residual cardiorenal morbidity and mortality. The risks of renal failure advancement and cardiovascular problems rise with the intensity and stage of CKD. In contrast to individuals with advanced kidney disease, who are more likely to progress to dialysis, patients with better preserved estimated glomerular filtration rate (eGFR) have a higher lifetime risk of the cardiovascular burden of diseases, such as heart failure, myocardial infarction (MI), stroke, or cardiovascular death.[5]

Diabetes is the major cause of chronic kidney disease (CKD), which affects 30% to 40% of individuals with diabetes. Diabetes affects 537 million people worldwide, or one in every ten, and the figure is anticipated to rise to 783 million by 2040.[7] As a result, diabetic kidney disease (DKD) is one of the most devastating complications of diabetes and the leading cause of kidney failure. Chronic kidney disease (CKD) caused by diabetes mellitus is currently diagnosed as diabetic nephropathy, which commences with microalbuminuria and then a steady decline in renal function. It is diagnosed pathologically by distinctive disease processes, such as increased mesangial substrate, nodular lesions, and tubulointerstitial fibrosis.[6] Various interdisciplinary therapies, including ACE inhibitors, SGLT2 inhibitors, and mineralocorticoid receptor antagonists, have been proposed based on critical pathophysiological pathways. Some of them are effective in illnesses such as diabetes and chronic kidney disease. These therapies impact not only diabetics and people with the chronic renal disease but also the physiology of the heart.[6] Increasing evidence points to pathological overactivation of the mineralocorticoid receptor (MR) as a significant predictor of CKD progression and associated morbidity and death. Furthermore, recent research indicates that overactivation of the mineralocorticoid receptor (MR) causes inflammation and fibrosis in the heart, kidneys, and vasculature, accelerating the course of CKD and cardiovascular disease. Therefore, several studies have indicated that inhibiting the mineralocorticoid receptor pharmacologically lowers albuminuria, kidney fibrosis, glomerular lesions, and inflammation in preclinical models of CKD in T2D; favorable cardiovascular benefits have also been noted. Despite clinical studies demonstrating that mineralocorticoid receptor antagonists (MRAs) have an anti-albuminuric impact in diabetic kidney disease, the risk of hyperkalemia accompanied by their usage has restricted their use and evaluation for severe renal and cardiovascular outcomes.[9] Nevertheless, side effects such as hyperkalemia are avoided with concomitant other drugs; hence MR antagonism is being investigated as a novel therapy regimen to delay the progression of CKD.[8]

Finerenone is a revolutionary, selective, nonsteroidal MR antagonist (MRA) with anti-inflammatory and anti-fibrotic properties in experimental renal and cardiovascular diseases trials.[5] According to studies, the incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (the primary composite outcome) is dramatically reduced in finerenone-treated individuals. Additionally, severe and adverse events associated with pneumonia are less frequent with finerenone compared to placebo.[10]

Meta-analysis is a statistical, systematic, epidemiological research strategy used to critically assess previous research findings to conclude that body of research. The results of a meta-analysis may provide a more

precise estimate of the effect of a treatment or risk factor for disease, or other outcomes, than any individual study contributing to the pooled analysis. Because few randomized controlled trials have been performed to examine the efficacy and safety profile of finerenone on chronic kidney disease and cardiovascular outcomes in Type 2 Diabetes, most of the studies have yielded contradictory results due to various adverse effect profiles. Therefore, we carried out a comprehensive systematic review and meta-analysis to determine the precise role of finerenone in patients with CKD and Type 2 diabetes. To the best of our knowledge, this is the first meta-analysis that compares the effects of finerenone therapy versus placebo in patients with CKD and T2D.

Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[11].

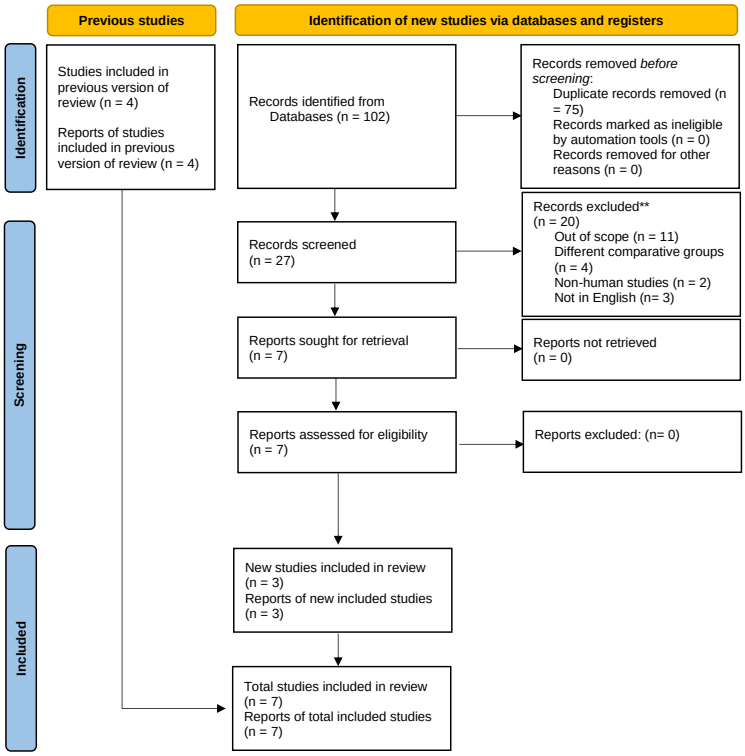

Figure 1: This is a caption

Search strategy and study selection:

PubMed (Medline) and Cochrane were searched in depth from the time of inception of the study to August 1st, 2022. Literature and preprints were identified through searches of ClinicalTrials.gov, Google Scholar, and Medrxiv. A search strategy was created using keywords and Medical Subject Headings (MESH terms) which included [Finerenone OR Non-steroidal mineralocorticoid receptor antagonist OR Non-steroidal MRA] AND [Cardiac outcomes OR Cardio renal outcomes] AND [Type 2 diabetes OR Diabetes Mellitus]. The search methodology is described in full in the Supplementary Table S1. The search results were returned without any sort of restriction or filtering. Text written in a language other than English was translated using Google's built-in translate service. To find applicable studies, a manual search of reviews was carried

out. Titles, full texts, and abstracts of studies were screened by two reviewers (MK and SK) independently. To further eliminate duplicates, we imported the relevant studies into Endnote X9 (Clarivate Analytics, US).

Eligibility criteria:

The included studies were chosen on the basis of the following criteria: study population, intervention, comparison, outcomes of interest, study design, and definition.

- Patient population: adults (aged [?]18 years) with type 2 diabetes and CKD
- Exposure: Maximum tolerated labelled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).
- Comparison: This includes the non-finerenone group which received the usual standard of care or placebo.
- Outcomes of interest: Efficacy and adverse effects of Finerenone
- Study design: Eligible completed randomized clinical trials were extracted to perform the meta-analysis.

Observational studies, case reports, and reviews were excluded from the meta-analysis at screening. Additionally, studies with non-human participants, children <18 years, or pregnant women were not included for analysis.

Data extraction:

Data extraction of the relevant studies included the first author, year of publication, type of study, study follow-up time, total number of patients, and patients who received Finerenone.. From the obtained relevant studies, the baseline characteristics (such as age, gender, and standard therapy) and comorbidities (such as heart disease, hypertension, diabetes mellitus, etc.) of patients in the two groups were also extracted. We accepted the study investigator's definition for all safety and efficacy outcomes. The outcomes extracted are mentioned below.

Efficacy outcomes:

The primary efficacy outcomes were composite of kidney failure: "a sustained decrease of at least 40% in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes. Kidney failure was defined as end-stage kidney disease or an eGFR of less than 15 ml per minute per 1.73 m2; end-stage kidney disease was defined as the initiation of long-term dialysis (for [?]90 days) or kidney transplantation", composite of death from cardiovascular causes: nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Other secondary outcomes were death from any cause, hospitalization for any cause, the change in the urinary albumin-to-creatinine ratio from baseline to month 4, and a composite of kidney failure, a sustained decrease of at least 57% in the eGFR from baseline (equivalent to a doubling of the serum creatinine level) maintained for at least 4 weeks, or death from renal causes.

Safety outcomes:

Safety analyses included assessment of adverse events and central laboratory testing; serum potassium and creatinine levels. Adverse events that occurred during the treatment period were defined as those that started or worsened during finerenone or placebo intake or up to 3 days after any temporary or permanent interruption.

Study quality assessment:

Using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [12], two researchers (MK and SK) evaluated the quality of clinical trials independently. Randomization of participants, selective reporting of outcomes, and the presence of missing data were all evaluated.

Statistical analysis:

The proposed meta-analysis was carried out using Review Manager 5.4 (Cochrane Collaboration). For dichotomous outcomes, we retrieved relative risks (RRs) and 95% confidence intervals (CIs). Mean values and standard deviations were provided for continuous outcomes. Based on a random-effects model and the generic-inverse variance and continuous outcome functions, this meta-analysis presents a pooled effect of relative risks (RRs) and weighted mean differences (WMDs). All results with p-values lower than 0.05 were considered significant. We visualised funnel plots for each outcome to gauge the extent of publication bias.

Heterogeneity between trials was assessed and reported as a percentage using the I2 statistic. The I2 value of 25% indicated low heterogeneity, the range of 25% to 50% indicated moderate heterogeneity, and the range of 50% and above indicated high heterogeneity. Sensitivity analysis was performed to assess the contribution of each study to the overall pooled estimate, which was performed because of the high degree of heterogeneity in the study results.

Ethical approval:

As this was an analysis of publicly accessible data, no approval from the ethical review board was required.

Results

Study selection

The preliminary literature search resulted in the identification of 46 articles. Seven randomized controlled trials[5,10,13-17] were included in this meta-analysis after excluding duplicates and evaluating titles and abstracts. Characteristics of included studies are provided in (Supplementary table S2).

Baseline characteristics ‘

In 7 studies involving a total of 39,995 participants who met the inclusion criteria, 20,368 (50.9%) received Finerenone and 19,627 (49%) received a placebo. Except for Bakris 2015[13] Katayama 2017 [17], which were in phase 2, all included trials were in phase 3. Table 1 and 2 provides information about baseline characteristics, and supplementary tables 3 and 4 provide information about comorbidities, and previous medication history.

Quality assessment and publication bias

According to the Cochrane method of evaluating RCTs, trials of acceptable to good quality were found (Supplementary Table 5). The funnel plots indicated that publication bias had no impact on the quantitative results (Supplementary Figure 1).

Efficacy Outcomes

Composite of kidney failure (Figure 2)

The kidney failure composite included the following outcomes: Kidney failure, End-stage kidney disease, Sustained decrease to 15 ml/min/1.73 m2, Sustained decrease of eGFR by >40% from baseline, and death from renal causes are the criteria for renal failure. Four out of five studies [5,10,14,15] reported renal failure, and the pooled analysis revealed that treatment with Finerenone was associated with a decreased risk of renal failure compared to placebo (RR = 0.91 [0.81, 1.01] p=0.11; I2= 38%). Similarly, End stage kidney disease, Sustained decrease to 15 ml/min/1.73 m2, Sustained decrease of eGFR of >40% from baseline and death from renal causes were reported by 3 of 5 studies[5,10,14], and the pooled analysis demonstrated that treatment with Finerenone was associated with a decreased risk of the aforementioned outcomes compared to placebo (RR = 0.80 [0.69, 0.93] p=0.004; I2= 0%), (RR = 0.82 [0.72, 0.94] p=0.004; I2= 0%), (RR = 0.85 [0.80, 0.90] p <0.00001; I2= 0%) and (RR = 0.56 [0.17, 1.82] p=0.34; I2= 0%), respectively.

Composite Cardiovascular outcomes (Figure 3)

The cardiovascular composite outcomes included cardiovascular-related mortality, hospitalization for heart failure, nonfatal myocardial infarction, and nonfatal stroke. All five studies[5,10,14-16] reported death from cardiovascular causes and hospitalization due to heart failure, and the pooled analysis revealed that treatment

with Finerenone was associated with a significantly decreased risk of death and hospitalization (RR = 0.86 [0.80, 0.93] p=0.0002; I2= 0%), (RR = 0.77 [0.70, 0.84] p 0.00001; I2= 0%), respectively. Non-fatal myocardial infarction and non-fatal stroke were reported in four of the five studies[5,10,14,15], and the pooled analysis revealed that treatment with Finerenone was associated with a decreased risk of non-fatal myocardial infarction (RR = 0.89 [0.78, 1.02] p=0.09; I2= 0%) but there was no difference in risk of non-fatal stroke between the two treatment groups (RR = 1.01 [0.89, 1.14] p=0.93; I2= 0%)

Secondary outcome (Figure 4)

Secondary outcomes included mortality, hospitalization for any cause and Sustained decrease of >/= 57% in eGFR from baseline. 3 of the 5 studies reported all the outcomes [5,10,14]. The pooled analysis revealed that treatment with Finerenone was associated with a reduced risk of the aforementioned outcomes (RR = 0.90 [0.83, 0.97] p=0.006; I2= 0%), (RR = 0.97 [0.94, 0.99] p=0.02; I2= 0%) and (RR = 0.71 [0.64, 0.79] p <0.00001; I2= 0%), respectively.

Safety outcomes

Adverse events (Figure 5)

Three outcomes were used to evaluate adverse events: the total number of patients who experienced any adverse event, adverse events related to the treatment regimen, and adverse events leading to discontinuation of the trial regimen. All seven studies [5,10,13-17]reported the total number of patients experiencing adverse events, and the pooled analysis revealed that the total number of patients experiencing any adverse event was similar in both groups (RR = 1.00 [0.99, 1.01] p=0.56; I2= 0%). However, 5 out of 7 studies[5,10,14,15,16] reported adverse events related to treatment regimen, and the pooled analysis revealed that treatment with Finerenone was associated with a higher risk of adverse events related to the treatment regimen (RR = 1.40 [1.33, 1.46] p <0.00001; I2= 0%). Similarly, adverse events leading to discontinuation of treatment regimen were reported in six out of seven studies [5,10,13-16], and the pooled analysis revealed that treatment with Finerenone was associated with a higher risk of treatment discontinuation compared to placebo (RR = 1.62 [0.84, 3.10] p=0.15; I2 = 98%), respectively. Due to the high heterogeneity of adverse events leading to treatment discontinuation, a sensitivity analysis was performed, which revealed that excluding Gerasimos 2021 [15] reduced heterogeneity and rendered the results statistically significant (RR = 1.22 [1.11, 1.33] p 0.0001; I2= 0%).

Serious adverse events (Figure 6)

Serious adverse events were evaluated based on the following three outcomes: the number of patients experiencing a serious adverse event, the number of serious adverse events related to the trial regimen, and the number of serious adverse events leading to trial discontinuation. Six out of 7 studies [5,10,13-17] reported the aforementioned outcomes, and the pooled analysis revealed that the number of patients experiencing serious adverse events was marginally lower in the Finerenone group compared to the placebo group (RR = 0.95 [0.92, 0.97] p < 0.0001; I2 = 0%). Similarly, the risk of treatment discontinuation due to serious adverse events was marginally lower in the Finerenone group compared to the placebo group (RR = 0.94 [0.83, 1.07] p= 0.38; I2= 0%), whereas risk of serious adverse events related to trial regimen was higher in patients treated with Finerenone (RR = 1.36 [1.13, 1.64] p = 0.001; I2= 0%).

Hyperkalemia (Figure 7)

The following outcomes were used to assess hyperkalemia: The investigator reported hyperkalemia, hyperkalemia related to the trial regimen, and the trial regimen's permanent discontinuation due to hyperkalemia. Four out of five studies[5,10,14,15] reported investigator-reported hyperkalemia, and the pooled analysis revealed that treatment with Finerenone was associated with a significantly increased risk of hyperkalemia (RR = 2.20 [1.90, 2.55] p 0.00001; I2= 77%). Due to the high heterogeneity, a leave one out analysis was performed, which revealed that excluding Betram 2021 [10] reduced heterogeneity (RR = 2.03 [1.89, 2.18] p < 0. 00001; I2= 0%).

On the other hand, five out of seven studies[5,10,13-17] reported hyperkalemia related to the trial regimen, and the pooled analysis revealed that Finerenone was associated with a significantly increased risk of hyperkalemia related to the treatment regimen. Similarly, six of seven studies[5,10,13-16] reported permanent discontinuation of treatment regimen due to hyperkalemia, and the pooled analysis revealed that treatment with Finerenone was associated with a significantly higher risk of treatment discontinuation due to hyperkalemia compared to placebo (RR = 2.59 [1.92, 3.50] p 0.00001; I2= 40%).

Serious Hyperkalemia (Figure 8)

Serious hyperkalemia was assessed by examining two outcomes: serious hyperkalemia and hyperkalemia-related hospitalization. The above-mentioned outcomes were reported in five out of seven studies [5,10,14-16], and the pooled analysis revealed that treatment with Finerenone was associated with a significantly increased risk of serious hyperkalemia and hospitalization due to hyperkalemia (RR = 4.25 [3.11, 5.83] p 0. 00001; I2= 0%) and (RR = 5.94 [4.04, 8.75] p 0. 00001; I2= 0%), respectively.

Hypokalemia (Figure 9)

Three out of five studies [5,10,14] reported investigator-reported hypokalemia, and the pooled analysis revealed that treatment with Finerenone was associated with a significantly lower risk of hypokalemia compared to patients treated with placebo (RR = 0.47 [0.38, 0.57] p 0. 00001; I2= 0%).

Renal related adverse events (Figure 10)

The following outcomes were studied for renal-related adverse events: acute kidney injury, hospitalization due to acute kidney injury, discontinuation of trial regimen due to acute kidney injury and hospitalization due to acute renal failure. Four out of seven studies[5,10,14,15] reported acute kidney injury, and the pooled analysis revealed that treatment with Finerenone was associated with a slightly lower risk of acute kidney injury (RR = 0.94 [0.84, 1.05] p= 0.30, I2= 0%) whereas hospitalization due to acute kidney injury, discontinuation of treatment regimen due to acute kidney injury and hospitalization due to acute renal failure was reported by three out of seven studies [5,10,14] and the pooled analysis revealed that the risk of hospitalization due to acute kidney injury and risk of hospitalization due to acute renal failure was similar in both treatment groups, (RR = 0.99 [0.80, 1.22] p=0.91; I2= 0%) and (RR = 0.97 [0.80, 1,18] p= 0.76; I2= 0%) respectively, whereas the risk of discontinuation of treatment regimen due to acute kidney injury was higher in Finerenone group (RR = 1.38 [0.69, 2.75] p = 0. 37; I2= 0%)

Adverse events affecting [?]5% of patients in either group

Hyperkalemia, nasopharyngitis, arthralgia, back pain, urinary tract infection, diarrhea, anemia, hypertension, upper respiratory tract infection, peripheral edema, decreased GFR, hypoglycemia, dizziness, bronchitis, constipation, and pneumonia were adverse events affecting 5% of patients in either group. Patients treated with Finerenone had an increased risk of hyperkalemia, anemia, decreased eGFR, dizziness, upper respiratory tract infection, diarrhea, and arthralgia, but a decreased risk of hypoglycemia, pneumonia, peripheral edema, constipation, UTI, bronchitis, nasopharyngitis, and hypertension. Table 3 details the adverse events that affected five percent of the population.

Discussion:

Diabetes is the most prevalent cause of chronic kidney disease (CKD) and a risk factor for its development to end-stage renal disease. Patients with diabetes and chronic kidney disease are at a very high risk for cardiovascular (CV) disease, the leading cause of morbidity and mortality.[18] Activation of the RAAS, hypertension, hyperglycemia, dyslipidemia, and proteinuria are well-established risk factors for diabetic kidney disease development. Angiotensin converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and, more recently, renin inhibitors are therefore routinely administered to these patients. Full doses of these medications slow but do not prevent the deterioration in renal function.[19] Increasing data indicates that mineralocorticoid receptor (MR) signaling is implicated in the development of renal damage, resulting to glomerular and tubular sclerosis independent of angiotensin II. Therefore, mineralocorticoid

receptor antagonists (MRAs) have been identified as a dynamic approach for slowing the advancement of CKD progression in patients with residual kidney disease. [20,21] Finerenone, a new MRA have exhibited clinically significant effects on improving renal outcomes and decreasing cardiovascular mortality and morbidity among patients with CKD and T2D. [18] A recent study of FIDELIO-DKD revealed that finerenone decreases the probability of new-onset atrial fibrillation or flutter as well as the risk of kidney or cardiovascular events, regardless of underlying arrhythmia history. In a recent review of FIGARO-DKD in patients with T2D and CKD without a history of symptomatic HFrEF, finerenone resulted to a substantial reduction in the likelihood of clinically significant time-to-event HF outcomes and lowered the likelihood of new-onset hospitalization for HF by 32% compared to placebo. [15,16]

In the total population, patients in the finerenone therapy group had a lower risk of cumulative kidney outcomes such as renal failure, sustained drop to 15 ml/min/1.73 m2, sustained fall of eGFR of >40% from baseline, and mortality from renal etiology as compared to placebo. Similarly, phase 2 trials (ARTS, ARTS-DN, and ARTS-HF) examined the safety and efficacy of different oral dosages of finerenone in diabetic patients with albuminuria taking ACE inhibitors or ARBs. Time to kidney failure, sustained 57% eGFR drop, or renal death was considerably lower in the finerenone group than in the placebo group. [22] In contrast, FIGARO-DKD, a phase 3 trial, demonstrated no significant difference in the incidence of the first secondary composite endpoints (time until first occurrence of kidney failure, a 40% drop from baseline in eGFR for four weeks, or deaths from renal etiologies) between finerenone and placebo groups.[10] Considering cardiovascular outcomes, risks of deaths due to cardiovascular outcomes along with hospitalization due to heart failure and non-fatal MI were significantly decrease as reported by major studies. However, finerenone therapy had no effects in reduction of non-fatal stroke as compared to placebo. In a prototype of post-MI heart failure, smaller doses of finerenone (0.1, 0.3, and 1 mg/kg/day) were compared with 100 mg/kg/day of eplerenone. At a dosage of 1 mg/kg per day, finerenone demonstrated therapeutic efficacy; smaller doses had no effect and were equivalent to eplerenone. Following administration of finerenone, both systolic and diastolic LV functions were significantly enhanced, as were cardiac contractility and relaxation. Likewise, finerenone decreased plasma levels of pro-BNP without affecting blood pressure.[23] In the ARTS-HF trial, it was determined that the proportions of patients achieving a reduction in NT-proBNP levels of >30% at the end of 90 days were comparable for all dosages of finerenone and eplerenone. The combined endpoint of all-cause mortality, cardiovascular hospitalization, or emergency presentation for worsening HF was attained by very few participants receiving finerenone compared to those who received eplerenone, except for those receiving the lowest effective dose of finerenone (2.5–5 mg). Individually, all-cause mortality and cardiovascular hospitalization were more prevalent in the eplerenone group than in the finerenone group (all dosages pooled), with analysis of the maximum finerenone dose (10–20mg) revealing a substantially lower likelihood of each event.[24] In all studies, the incidence of adverse events during treatment was comparable between finerenone and placebo. In contrast, discontinuation due to trial regimen was significantly more prevalent in the treatment group.[5,10,13-17]

Numerous studies have defined the effects of finerenone therapy on the baseline potassium level. Our study analyzed the increased incidence of investigator-reported hyperkalemia, the risk of hyperkalemia as a result of the trial regimen, and the discontinuation of the drug due to elevated potassium levels. Also, the incidence of severe hyperkalemia and hospitalizations due to hyperkalemia increased. Different comparative studies indicate that Finerenone has a lower incidence of hyperkalemia than spironolactone, but comparable effects on NT-ProBNP and albuminuria. [25] While eplerenone is the more sustainable alternative to spironolactone, relatively new therapies such as finerenone may be a viable substitute with a reduced risk of hyperkalemia and equivalent cardiovascular and renal benefits to other selective and nonselective MRAs. Finerenone seems to be well tolerated, has a safe pharmacological profile, and has predictable dose-dependent effects.[25] Finerenone was associated with a reduced risk of hypokalemia compared to placebo. Numerous participants in our study had extensive medical (such as cardiovascular and diabetic outcomes) and medication history at baseline (antihypertensive and antihyperglycemic drugs). We discovered that as a patient's heart failure worsens, their kidney function will be compromised to varying degrees. The use of potassium-sparing diuretics increases the risk of hyperkalemia in CHF patients receiving MRA therapy who have renal dysfunction.

Consequently, it is essential to monitor serum potassium levels. Finerenone has fewer detrimental effects on blood potassium and eGFR than spironolactone or eplerenone·[26]Finerenone therapy was associated with a slight reduction in the risk of acute kidney injury (AKI), while the risk of hospitalization due to AKI and ARF (acute renal failure) remained unchanged. Data supporting the potential MR antagonism as a curative method for preventing the acute and long-term implications of renal ischemia/reperfusion has accumulated in recent years. The majority of studies demonstrating the protective effect of MR antagonism in AKI and its advantage against CKD progression have used steroidal MR antagonists.[27] In patients with CKD and T2DM, the benefits of finerenone outweigh the risks associated with its discontinuation due to AKI.

Our meta-analysis has several benefits (1) As a result of the inclusion of additional studies, the sample size of our meta-analysis is more significant than that of previous meta-analyses, lending credibility to our findings. (2) Various plots and tests, including the funnel plot, Egger's test, and Begg's test, were used to calculate publication biases, which revealed no publication bias. (3) The effect of heterogeneous studies on the pooled estimate was determined by a sensitivity analysis. Despite the fact that this analysis produced sufficient statistical evidence, some limitations should be acknowledged. (1) First, the follow-up periods for most studies varied, with some reporting longer periods. Long-term follow-ups are more useful when assessing the efficacy of this therapy in patients with chronic diseases such as CKD and T2DM. (2) A few studies used different doses of finerenone at different time intervals, and the majority of studies did not include doses of finerenone or control groups, which may have created uncertainty. (3) Half of the studies conducted on patients with CKD and T2DM failed to report vital renal and cardiovascular outcomes, such as the number of End-stage kidney disease patients, deaths from renal as well as cardiovascular causes, etc.

Conclusion: According to our meta-analysis, finerenone therapy is associated with favorable renal and cardiovascular outcomes, including a reduction in the risk of end-stage kidney disease and renal failure, as well as a significant decrease in death and hospitalization due to cardiovascular outcomes. The therapy's favorable therapeutic profile enables it to counteract potassium fluctuations. Therefore, we recommend this therapy in patients with T2DM and CKD. Additionally, additional RCTs of standard quality are required to investigate the additional effects of finerenone therapy in CKD patients with T2DM.

Declarations of interest

None

Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in the article.

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None

Author's contributions

Mahima Khatri: Protocol development, Data collection, Data analysis, Manuscript writing.

Satesh Kumar: Protocol development, Data collection, Data analysis, Manuscript writing.

Kiran Saleem: Data collection, Data analysis, Manuscript writing.

Maria Ali: Data collection, Manuscript writing.

Sidra Khalil: Manuscript writing.

Sumeet Kumar: Protocol development, Data collection.

Muhammad Usman: Protocol development.

Taha Nadeem: Protocol development, Manuscript writing.

Fatima Tanveer: Data analysis, Manuscript editing.

Rohit kumar: Data analysis, Manuscript editing.

Muhammad Shehryar: Data analysis, Manuscript editing.

Vikash Kumar Karmani: Data analysis, Manuscript editing.

Uroosh Tariq Khanzada : Protocol development, Manuscript writing.

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Legends to figures:

Figure 1: Prisma flow chart

Figure 2: Composite of kidney failure; A= Kidney failure, B= End-stage kidney disease, C= Sustained decrease to 15 ml/min/1.73 m2, D= Sustained decrease of eGFR by > 40% from baseline, E= Death from renal causes, RR= Relative risk, CI= confidence interval, I2= heterogeneity

Figure 3: Composite Cardiovascular outcomes; A= Cardiovascular-related mortality, B= Hospitalization for heart failure, C= Non-fatal MI, D= non-fatal stroke, RR= Relative risk, CI= confidence interval, I2= heterogeneity

Figure 4: Secondary outcomes; A= Mortality due to any cause, B= Hospitalization for any cause, C= Sustained decrease of >/= 57% in eGFR from baseline, RR= Relative risk, CI= confidence interval, I2= heterogeneity

Figure 5: Adverse events; A= Total number of patients experiencing adverse events, B= Adverse events related to the treatment regimen, C= Adverse events leading to discontinuation of treatment, RR= Relative risk, CI= confidence interval, I2= heterogeneity

Figure 6: Serious adverse events: A= Total number of patients experiencing serious adverse events, B= Adverse events related to the trial regimen, C= Adverse events leading to discontinuation of trial, RR= Relative risk, CI= confidence interval, I2= heterogeneity

Figure 7: Hyperkalemia: A= Investigator reported hyperkalemia, B=Hyperkalemia related to the trial regimen, C= Permanent discontinuation of trial regimen due to hyperkalemia, RR= Relative risk, CI= confidence interval, I2= heterogeneity

Figure 8: Serious Hyperkalemia: A=Total number of patients with serious hyperkalemia, B= Hospitalization due to hyperkalemia, RR= Relative risk, CI= confidence interval, I2= heterogeneity.

Figure 9: Hypokalemia, RR= Relative risk, CI= confidence interval, I2= heterogeneity

Figure 10: Renal related adverse events: A= Acute kidney injury, B= Hospitalization due to acute kidney injury, discontinuation of trial regimen due to acute kidney injury, C= Discontinuation of treatment regimen

due to acute kidney injury, D = Hospitalization due to acute renal failure, RR= Relative risk, CI= confidence interval, I2= heterogeneity

Table 3: Adverse events affecting >/= 5% of patients in either group.

Adverse Event	Risk Ratio	95% confidence interval	P value
Hyperkalemia	2.07	1.94-2.21	<0.00001
Nasopharyngitis	0.97	0.90-1.04	0.35
Hypertension	0.73	0.68-0.79	<0.00001
Anemia	1.07	0.99-1.17	0.10
Diarrhea	1.02	0.94-1.11	0.66
Upper respiratory tract infection	1.02	0.93-1.11	0.69
Decline in eGFR	1.30	1.15-1.47	<0.0001
Urinary tract infection	0.97	0.88-1.06	0.51
Back pain	1.01	0.93-1.10	0.74
Peripheral edema	0.65	0.60-0.70	<0.00001
Hypoglycemia	0.87	0.77-0.99	0.04
Dizziness	1.04	0.94-1.414	0.43
Arthralgia	1.06	0.97-1.15	0.17
Bronchitis	0.97	0.88-1.06	0.49
Constipation	0.91	0.80-1.03	0.14
Pneumonia	0.70	0.64-0.77	<0.00001

Study	Study design	Total no. of patients	No. of patients	No. of patients	Age (Mean ±SD)	Age (Mean ±SD)	Male sex No. (%)	Male sex No. (%)	BMI kg/m2 (Mean ±SD)	BMI kg/m2 (Mean ±SD)	HBA1C% (Mean ±SD)	HBA1C% (Mean ±SD)	Systolic blood pressure (Mean ±SD)	Systolic blood pressure (Mean ±SD)	Di bl pr su (M ±
			Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Fi
Bakris (2015)[13]	RCT	821	727	94	63.9± 9.2	63.2±8.6	570 (78.4)	69 (73.4)	31.7± 5.5	32.4± 5.2	7.58± 1.2	7.6± 1.3	137.9±14	139.9±14	77 9.7
Katayama (2017)[17]	RCT	96	84	12	62.4± 9.9	66.7± 9	67 (79.7)	10 (83.3)	27± 74.1	26.6± 3.2	7.21± 0.9	7.28± 0.7	137.2± 14.8	135.7± 16.9	77 10
Bakris (2020)[14]	RCT	5674	2833	2841	65.4± 8.9	65.7±9.2	1953 (68.9)	2030 (71.5)	31.1± 6.0	31.1± 6.0	7.7± 1.3	7.7± 1.4	138.1±14	138.0± 14.4	75 ±
Bertram (2021)[10]	RCT	7352	3686	3666	64.1± 9.7	64.1±10	2528 (68.6)	2577 (70.3)	31.5± 6.0	31.4± 5.9	7.7± 1.4	7.7± 1.4	135.8±14	135.7± 14.1	76 ±
Gerasimos (2021)[15]	RCT	5674	2833	2841	65.5± 8.8	65.8±9	1953 (68.9)	2030 (71.4)	31.1± 6	31.1± 6	7.7± 1.3	7.7± 1.4	138± 14.3	138± 14.4	75 9.7
Agarwal (2022)[5]	RCT	13026	6519	6507	64.7± 9.4	64.8 ± 9.7	4481 (68.7)	4607 (70.8)	N/A	N/A	7.7± 1.4	7.7 ± 1.4	136.8 ± 14.2	136.7± 14.3	76 ±
Gerasimos (2022)[16]	RCT	7352	3686	3666	64.4± 9.34	65.1± 9.41	2528 (68.5)	2577 (70.2)	32.28± 6.2	31.84± 5.9	7.8± 1.4	7.79± 1.3	135.7± 13.7	135.3± 13.9	77 9.6

Table 1: Baseline characteristics of included studies

SD: Standard deviation, HBA1C: glycated hemoglobin, BMI: Body mass index

Study	eGFR (Mean±SD)	eGFR (Mean±SD)	eGFR >/= 60 ml/min/1.73m2 NO. (%)	eGFR >/= 60 ml/min/1.73m2 (%)	eGFR 45 to < 60 ml/min/1.73m2 NO. (%)	eGFR 45 to < 60 ml/min/1.73m2 (%)	eGFR \ 25 to < 45 ml/min/1.73m2 NO. (%)	eGFR \ 25 to < 45 ml/min/1.73m2 (%)	eGFR < 25 ml/min/1.73m2 NO. (%)	eGFR < 25 ml/min/1.73m2 (%)	urinary albumin to creatinine ratio (Mean±SD)	urinary albumin to creatinine ratio (Mean±SD)	UACR >/= 30 NO. (%)	UACR >/= 30 (%)	UACR to 30 NO. (%
	Fineren one	Placebo	Fineren one	Placebo	Fineren one	Placebo	Fineren one	Placebo	Fineren one	Placebo	Fineren one	Placebo	Fineren one	Placebo	Fineron
Bakris (2015)[13]	66.9±21.8	72.2±20.4	N/A	N/A	302 (41.5)	26 (27.7)	N/A	N/A	N/A	N/A	190±649	182.9±58	N/A	N/A	N/
Katayama (2017)[17]	65.2±13.7	60.8±16.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	217.6±221.4	256.8±166.3	N/A	N/A	N/
Bakris (2020)[14]	44.4±12.5	44.3±12.6	318 (11.2)	338 (11.9)	972 (34.3)	928 (32.7)	1476 (52.1)	1505 (53.0)	66 (2.3)	69 (2.4)	833±219.8	867±220.7	11 (0.4)	12 (0.4)	35 (1
Bertram (2021)[16]	67.6±21.7	68.0±21.7	2285 (62.0)	2254 (61.5)	745 (20.2)	789 (21.5)	641 (17.4)	610 (16.6)	15 (0.4)	12 (0.3)	302±119.2	315±114.8	109 (3.0)	98 (2.7)	17 (4
Gerasimos (2021)[15]	44.3±12.5	44.3±12.5	318 (11.2)	338 (11.8)	972 (34.3)	928 (32.6)	1476 (52.1)	1505 (52.9)	66 (2.3)	69 (2.4)	831±146.5	867.5±221.7	11 (0.3)	12 (0.4)	35 (1
Agarwal (2022)[5]	57.5±21.6	57.7±21.8	2603 (39.9)	2592 (39.8)	1717 (26.3)	1717 (26.4)	2117 (32.5)	2115 (32.5)	81 (1.2)	81 (1.2)	514±172.42	515±178.7	120 (1.8)	110 (1.7)	20 (3
Gerasimos (2022)[16]	65.95±21.5	65.61±21.83	2285 (61.9)	2354 (64.2)	745 (20.2)	789 (21.5)	641 (17.3)	610 (16.6)	15 (0.4)	12 (0.3)	289.4±118.3	283.8±116.8	109 (2.9)	98 (2.6)	17 (4

Table 2: Baseline characteristics of included studies

eGFR: estimated glomerular filtration rate, UACR: urinary albumin to creatinine ratio

A

Study or Subgroup	Finerinone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bakris 2020 [14]	208	2833	235	2841	25.4%	0.89 [0.74, 1.06]	2020
Bertram 2021 [10]	46	3686	62	3666	8.0%	0.74 [0.51, 1.08]	2021
Gerasimos 2021 [15]	441	2833	435	2841	38.3%	1.02 [0.90, 1.15]	2021
Agarwal 2022 [5]	254	6519	297	6507	28.3%	0.85 [0.72, 1.01]	2022
Total (95% CI)		**15871**		**15855**	**100.0%**	**0.91 [0.81, 1.02]**	
Total events	949		1029				

Heterogeneity: Tau² = 0.01; Chi² = 4.81, df = 3 (P = 0.19); I² = 38%
Test for overall effect: Z = 1.60 (P = 0.11)

Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Decreased Kidney failure Increased Kidney failure

B

Study or Subgroup	Finerinone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bakris 2020 [14]	208	2833	235	2841	25.4%	0.89 [0.74, 1.06]	2020
Bertram 2021 [10]	46	3686	62	3666	8.0%	0.74 [0.51, 1.08]	2021
Gerasimos 2021 [15]	441	2833	435	2841	38.3%	1.02 [0.90, 1.15]	2021
Agarwal 2022 [5]	254	6519	297	6507	28.3%	0.85 [0.72, 1.01]	2022
Total (95% CI)		**15871**		**15855**	**100.0%**	**0.91 [0.81, 1.02]**	
Total events	949		1029				

Heterogeneity: Tau² = 0.01; Chi² = 4.81, df = 3 (P = 0.19); I² = 38%
Test for overall effect: Z = 1.60 (P = 0.11)

Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Decreased Kidney failure Increased Kidney failure

Figure 2: This is a caption

A

Study or Subgroup	Finerinone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bakris 2020 [14]	128	2833	150	2841	12.0%	0.86 [0.68, 1.08]	2020
Bertram 2021 [10]	194	3686	214	3666	17.7%	0.90 [0.75, 1.09]	2021
Gerasimos 2021 [15]	128	2833	150	2841	12.0%	0.86 [0.68, 1.08]	2021
Agarwal 2022 [5]	322	6519	364	6507	29.7%	0.88 [0.76, 1.02]	2022
Gerasimos 2022 [16]	290	3686	351	3666	28.6%	0.82 [0.71, 0.95]	2022
Total (95% CI)		**19557**		**19521**	**100.0%**	**0.86 [0.80, 0.93]**	
Total events	1062		1229				

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 4 (P = 0.95); I² = 0%
Test for overall effect: Z = 3.67 (P = 0.0002)

Risk Ratio M-H, Random, 95% CI
0.7 0.85 1 1.2 1.5
Dec death (cardio) Inc death (cardio)

B

Study or Subgroup	Finerinone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bakris 2020 [14]	139	2833	162	2841	17.4%	0.86 [0.69, 1.07]	2020
Bertram 2021 [10]	117	3686	163	3666	15.6%	0.71 [0.57, 0.90]	2021
Gerasimos 2021 [15]	139	2833	162	2841	17.4%	0.86 [0.69, 1.07]	2021
Agarwal 2022 [5]	256	6519	352	6507	34.1%	0.73 [0.62, 0.85]	2022
Gerasimos 2022 [16]	117	3686	163	3666	15.6%	0.71 [0.57, 0.90]	2022
Total (95% CI)		**19557**		**19521**	**100.0%**	**0.77 [0.70, 0.84]**	
Total events	768		1002				

Heterogeneity: Tau² = 0.00; Chi² = 3.29, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 5.68 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI
0.7 0.85 1 1.2 1.5
Dec hospitalization(HF) Inc hospitalization(HF)

Figure 3: This is a caption

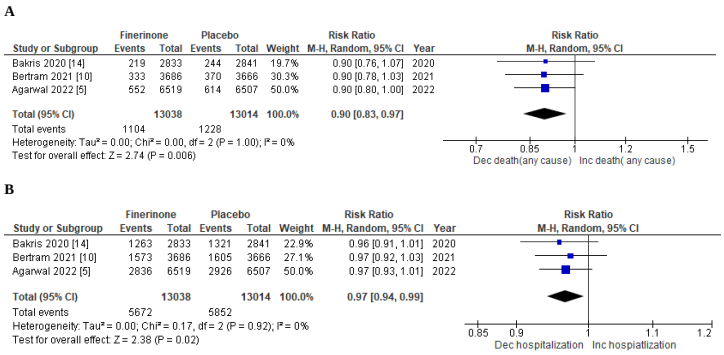
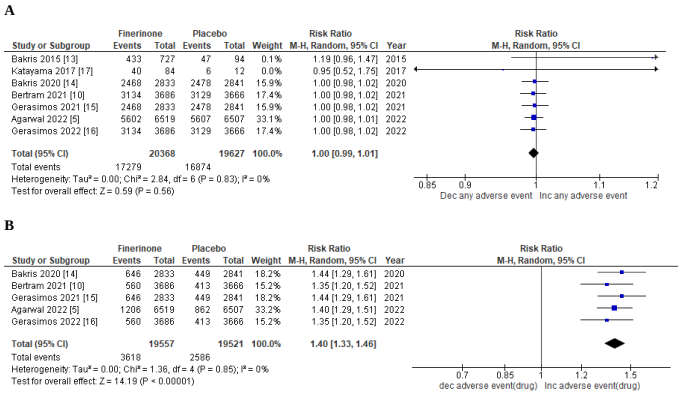


Figure 4: This is a caption



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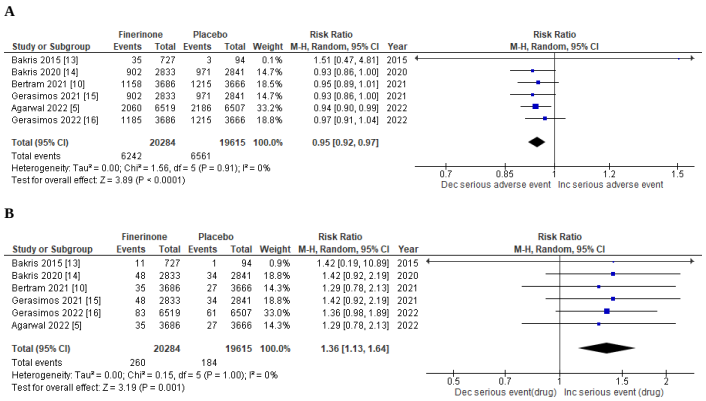
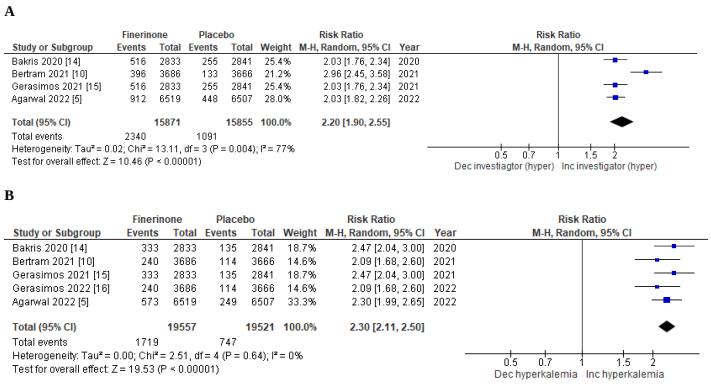


Figure 6: This is a caption



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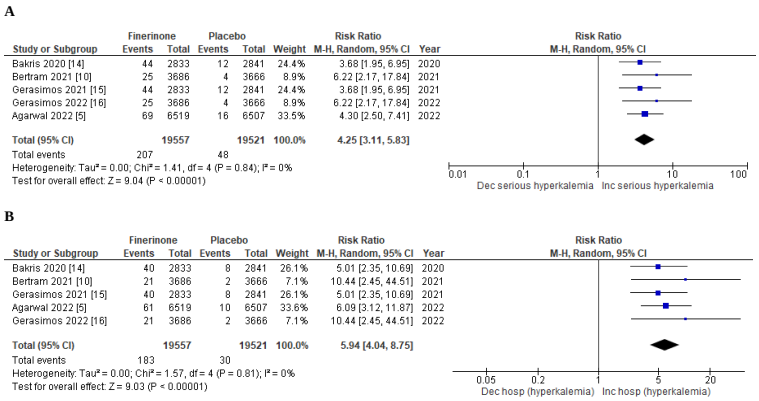

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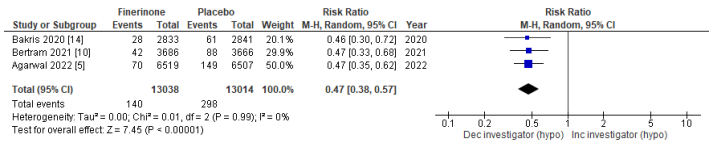

Figure 9: This is a caption

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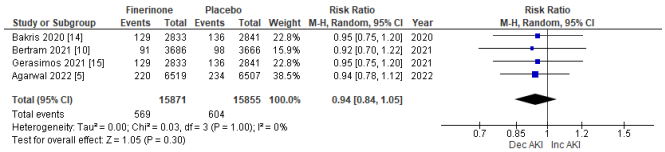

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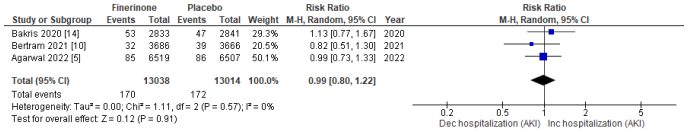


C

Figure 10: This is a caption

Supplementary Table 1: Detailed search strategy

Database	Search Strategy	Results
PubMed	(("finerenone"[Supplementary Concept] OR "finerenone"[All Fields] OR ("Non-steroidal"[All Fields] AND ("mineralocorticoid receptor antagonists"[Pharmacological Action] OR "mineralocorticoid receptor antagonists"[MeSH Terms] OR ("mineralocorticoid"[All Fields] AND "receptor"[All Fields] AND "antagonists"[All Fields]) OR "mineralocorticoid receptor antagonists"[All Fields] OR ("mineralocorticoid"[All Fields] AND "receptor"[All Fields] AND "antagonist"[All Fields]) OR "mineralocorticoid receptor antagonist"[All Fields])) OR ("Non-steroidal"[All Fields] AND ("microbiol resour announc"[Journal] OR "med res arch"[Journal] OR "mra"[All Fields]))) AND ((("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields])) OR ("Cardio-renal"[All Fields] AND ("outcome"[All Fields] OR "outcomes"[All Fields]))) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "type 2 diabetes"[All Fields] OR ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]))))	47
Google Scholar	((((Finerenone) OR (Non-steroidal mineralocorticoid receptor antagonist)) OR (Non-steroidal MRA)) AND ((Cardiac outcomes) OR (Cardio-renal outcomes))) AND ((Type 2 diabetes) OR (Diabetes mellitus))	30
Embase	((((Finerenone) OR (Non-steroidal mineralocorticoid receptor antagonist)) OR (Non-steroidal MRA)) AND ((Cardiac outcomes) OR (Cardio-renal outcomes))) AND ((Type 2 diabetes) OR (Diabetes mellitus))	25

Supplementary Table 2: Characteristics of included studies

Characteristics	Bakris 2015 [13]	Bakris 2020 [14]	Betram 2021 [10]	Gerasimos 2021 [15]	Gerasimos 2022 [16]	Agarwal 2022 [5]	Katayama 2017 [17]
Study name	Effect of Finerenone on Albuminuria in Patients with Diabetic Nephropathy a Randomized Clinical Trial	Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes	Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes	Finerenone and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Type 2 Diabetes	Finerenone Reduces Risk of Incident Heart Failure in Patients with Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial	Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis	A randomized controlled study of finerenone versus placebo in Japanese patients with type 2 diabetes mellitus and diabetic nephropathy
Patients, n	812	5674	7352	5674	7352	13,026	2013
Enrolment initiation	2013	2015	2015	2015	2015	2015	2014
Enrolment completion	2014	2020	2021	2018	2018	2021	2015
Year of completion	2015	2020	2021	2020	2022	2021	2017
Follow up duration	90	2.6 years	3.4 years	2.57 years	3.4	3 years	90 days
Population	Patients with diabetes and high or very high	Patients with CKD and type 2 diabetes	patients with CKD and type 2 diabetes	Patients with chronic kidney disease and type 2 diabetes	patients with albuminuric chronic kidney	Patients with CKD and type 2 diabetes	Japanese patients with T2DM and albuminuria ≥

	albuminuria who are receiving an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.				disease and type 2 diabetes.		30 mg/g and receiving therapy with a RAS blocker
Trial type	Multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase 2B	Phase 3, randomized, double-blind, placebo-controlled, multicentre clinical trail	Phase 3, multicentre, randomized, double-blind, placebo-controlled, event-driven clinical trial.	Phase III randomized, double-blind, placebo-controlled, parallel-group, event-driven trial	Randomized, double-blind, placebo-controlled, multicentre, phase III trial	Two phase III, multicentre, double-blind trials	Multicentre, randomized, double-blind, placebo-controlled, phase 2b study.
Inclusion criteria	-Type 2 Diabetes - UACRs in two of three first morning samples, with both being ≥300 mg/g (≥34 mg/mmol; very high albuminuria) or both being ≥30– <300 mg/g (≥3.4– <34 mg/mmol; high albuminuria) plus an estimated	-Adults (≥18 years of age) with type 2 diabetes and CKD treated with an ACE inhibitor or ARB at the maximum dose on the manufacturer's label that did not cause unacceptable side effects.	-Male or female patient aged ≥18 years. - Patient with type 2 diabetes (T2D) as defined by the American Diabetes Association in the 2010 Standards of Medical Care in Diabetes. - Patient with a diagnosis of chronic kidney disease.\	- Patients aged ≥18 years with a clinical diagnosis of T2D and moderately elevated albuminuria - eGFR (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula) ≥25 to <60 mL per min per 1.73 m2	- Patients aged ≥18 years with a clinical diagnosis of T2D and moderately elevated albuminuria - eGFR (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula) ≥25 to <60 mL per min per 1.73 m2	-Age ≥18 years -T2D and CKD defined as UACR 30– <300 mg/g, eGFR 25– <60 mL/min/1.73 m2, and diabetic retinopathy, or UACR 300– 5000 mg/g and eGFR 25– <75 mL/min/1.73 m2 -Maximum tolerated dose	- Japanese subjects with type 2 diabetes mellitus and a clinical diagnosis of DN (Diabetic Nephropathy) treated with at least the minimal recommended dose of an Angiotensin Converting Enzyme Inhibitor (ACEI) and/or

	glomerular filtration rate eGFR ≥30 mL/min/1.73 m2.	- Patient with prior treatment with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). - Patient with serum potassium ≤4.8 mmol/L at both the run-in visit and the screening visit - For women of child-bearing potential, a negative pregnancy test at screening visit and agreeing to use adequate contraception. - Patient with ability to understand and follow study-related instructions. - Patient providing written	- history of diabetic retinopathy, or severely elevated albuminuria - on stable treatment with a maximum tolerated labelled dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 4 weeks before the screening visit. - A serum potassium ≤4.8 mEq/L	- history of diabetic retinopathy, or severely elevated albuminuria - on stable treatment with a maximum tolerated labelled dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 4 weeks before the screening visit. - A serum potassium ≤4.8 mEq/L	of an RAS inhibitor -Serum potassium ≤4.8 mmol/L	Angiotensin Receptor Blocker (ARB) - Subjects with a clinical diagnosis of Diabetic Nephropathy. - Serum potassium </=4.8 mmol/L at both the run-in visit and the screening visit

			informed consent before any study-specific criteria				
Exclusion criteria	-If they received concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or a potassium-sparing diuretic that could not be discontinued for the run-in and treatment periods	- Known significant non-diabetic kidney disease, including clinically relevant renal artery stenosis - Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued ≥4 weeks prior to the screening visit - Concomitant therapy with both ACEi and ARBs which cannot be discontinued for the purpose of the study - Concomitant therapy with potent	- Known significant non-diabetic kidney disease, including clinically relevant renal artery stenosis. - Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued ≥4 weeks prior to the screening visit. - Concomitant therapy with both ACEi and ARBs which cannot be discontinued for the purpose of the study - Concomitant therapy with potent	Patients were excluded if they had: -Known nondiabetic kidney disease. -Chronic symptomatic heart failure with reduced ejection fraction (New York Heart Association Class II–IV). -A recent history of dialysis for acute kidney failure. - A kidney transplant. - Uncontrolled hypertension.	Patients were excluded if they had: -Known nondiabetic kidney disease. -Chronic symptomatic heart failure with reduced ejection fraction (New York Heart Association Class II–IV). -A recent history of dialysis for acute kidney failure. - A kidney transplant. - Uncontrolled hypertension.	-Non-diabetic kidney disease -Uncontrolled hypertension -HbA1c >12% -SBP <90 mmHg -Chronic symptomatic HFrEF	Patients were excluded if they had: -Known nondiabetic kidney disease. -Chronic symptomatic heart failure with reduced ejection fraction (New York Heart Association Class II–IV). -A recent history of dialysis for acute kidney failure. - A kidney transplant. - Uncontrolled hypertension.

		cytochrome P450 isoenzyme 3A4. - Any other condition or therapy, which would make the patient unsuitable for this study and will not allow participation for the full planned study period (e.g., active malignancy or other condition limiting life expectancy to <12 months)	cytochrome P450 isoenzyme 3A4. - Any other condition or therapy, which would make the patient unsuitable for this study and will not allow participation for the full planned study period (e.g., active malignancy or other condition limiting life expectancy to <12 months)				
Treatment	Finerenone, 1.25 to 20 mg once daily	Patients with an eGFR of 25 to less than 60 ml per minute per 1.73 m2 at the screening visit received an initial dose of 10 mg once daily, and those with an eGFR of 60 ml per minute per 1.73 m2 or more at the screening	patients with an eGFR at the screening visit of 25 to less than 60 ml per minute per 1.73 m2 received an initial dose of 10 mg once daily, and those with an eGFR of at least 60 ml per minute per 1.73 m2 received an	Initial dose of study drug was either 10 or 20 mg OD based on an eGFR at the screening visit of 25 to <60 or ≥60 mL per min per 1.73 m2, respectively. Study drug up titration from 10 to 20 mg OD was encouraged	Initial dose of study drug was either 10 or 20 mg OD based on an eGFR at the screening visit of 25 to <60 or ≥60 mL per min per 1.73 m2, respectively. Study drug up titration from 10 to 20 mg OD was encouraged	Oral finerenone (10 or 20 mg)	Finerenone (1.25 mg, 2.5 mg, 5 mg, 7.5 mg or 10 mg)

		visit received an initial dose of 20 mg once daily. An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month.	initial dose of 20 mg once daily.	from month 1 onwards, provided the serum potassium was ≤4.8 mEq/L and eGFR was stable.	from month 1 onwards, provided the serum potassium was ≤4.8 mEq/L and eGFR was stable.		
Primary outcomes	ratio of the urinary albumin-creatinine ratio (UACR) at day 90 vs at baseline	Composite of kidney failure.	- Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.	- Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.	- Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.	-Time to kidney failure -Sustained ≥40% decrease in eGFR from baseline - Renal death	Change of urinary albumin-to creatinine ratio
Secondary outcomes	-Proportion of patients with adverse and serious adverse events. -Change in serum potassium levels. - The incidence of serum potassium levels of 5.6 mmol/L or higher and	- Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. - Death from any cause. - Hospitalization for any cause. - Change in the	- composite of the first occurrence of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR for a period of at least 4 weeks, or death from renal causes. - Hospitalization	- composite of the first occurrence of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR for a period of at least 4 weeks, or death from renal causes. - Hospitalization	- composite of the first occurrence of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR for a period of at least 4 weeks, or death from renal causes. - Hospitalization	Time to CV death - non-fatal MI, -non-fatal stroke -HHF	Change in serum potassium concentration

	higher than 6.0 mmol/L -The incidence of a decrease in eGFR of 30% or more, 40% or more, and 57%. -The change in UACR at day 30 and day 60 relative to baseline.	urinary albumin-to-creatinine ratio from baseline to month 4, - composite of kidney failure.	for any cause. - death from any cause. - The change in the urinary albumin-to-creatinine ratio from baseline to month 4. - A kidney composite outcome, the first onset of kidney failure. - A sustained decrease from baseline of at least 57% in the eGFR for a period of at least 4 weeks	for any cause. - death from any cause. - The change in the urinary albumin-to-creatinine ratio from baseline to month 4. - A kidney composite outcome, the first onset of kidney failure. - A sustained decrease from baseline of at least 57% in the eGFR for a period of at least 4 weeks	for any cause. - death from any cause. - The change in the urinary albumin-to-creatinine ratio from baseline to month 4. - A kidney composite outcome, the first onset of kidney failure. - A sustained decrease from baseline of at least 57% in the eGFR for a period of at least 4 weeks

N= number of patients

Supplementary Table 3: Co-morbidities of patients included in the study

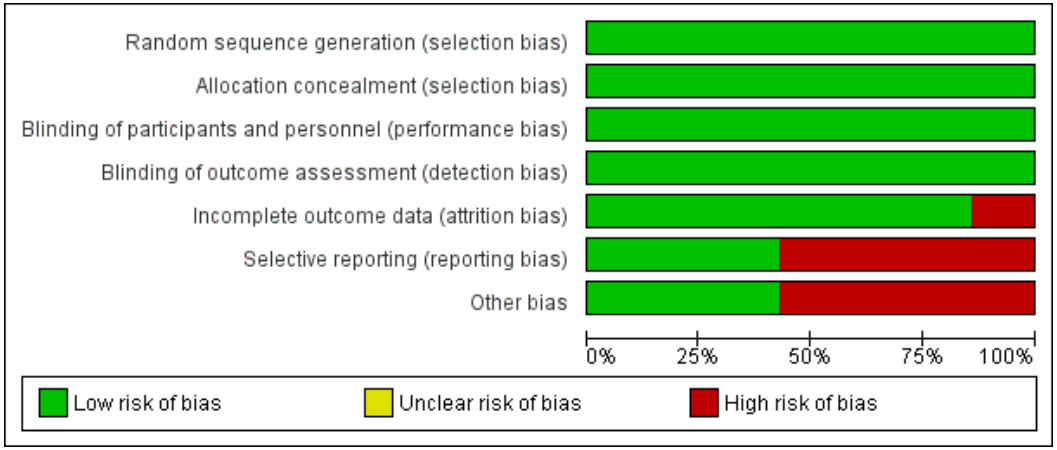
Study	Hypertension No. (%)		Diabetic retinopathy No. (%)		Diabetic neuropathy No. (%)		History of cardiovascular diseases No. (%)		Heart failure No. (%)		Peripheral arterial occlusive disease No. (%)		Ischemic stroke No. (%)	
	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo
Bakris (2015)[13]	685(94.2)	89 (94.7)	149(20.4)	19 (20.2)	139(19.1)	27(28.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Katayama (2017)[17]	84 (100)	12 (100)	40 (47.6)	5 (41.7)	30 (35.7)	6 (50)	15(17.8)	3(25)	N/A	N/A	N/A	N/A	N/A	N/A
Bakris (2020)[14]	2737 (96.6)	2768 (97.4)	1312 (46.3)	1351 (47.6)	738 (26.1)	716 (25.2)	1303 (46.0)	1302 (45.8)	195 (6.9)	241 (8.5)	470 (16.6)	453 (15.9)	329 (11.6)	360 (12.7)
Bertram (2021)[10]	3544 (96.1)	3517 (95.9)	1193 (32.4)	1098 (30.0)	1046 (28.4)	990 (27.0)	1676 (45.5)	1654 (45.1)	290 (7.9)	281 (7.7)	587 (15.9)	575 (15.7)	442 (12.0)	425 (11.6)
Gerasimos (2021)[15]	2737(96.6)	2768(97.3)	1312(46.3)	1351(47.5)	742(26.1)	722(25.4)	1303(45.9)	1302(45.8)	195 (6.8)	241(8.4)	N/A	N/A	N/A	N/A
Agarwal (2022)[5]	6281 (96.3)	6285 (96.6)	2505 (38.4)	2449 (37.6)	1788 (27.4)	1712(26.3)	2979 (45.7)	2956 (45.4)	485 (7.4)	522 (8.0)	1057 (16.2)	1028 (15.8)	771 (11.8)	785 (12.1)
Gerasimos (2022)[16]	3436(93.2)	3398(92.6)	N/A	N/A	N/A	N/A	1676(45.4)	1654(45.1)	290 (7.8)	281 (7.6)	N/A	N/A	N/A	N/A

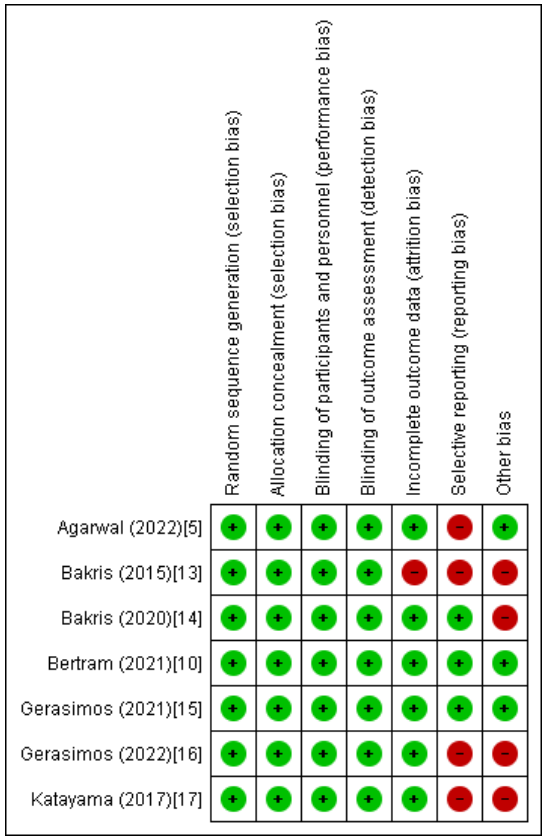
N/A= not applicable

Supplementary Table 4: Medication history of patients included in the history

Study	ACE inhibitor No. (%)		Angiotensin receptor blocker No. (%)		Diuretic No. (%)		Statin No. (%)		Potassium lowering agent No. (%)		Platelet aggregation inhibitors No. (%)		Insulin No. (%)		GLP-1 receptor Agonist No. (%)		SGLT-2 inhibitor No. (%)		Metformin No. (%)		Sulfonylurea No. (%)		Alpha-glucosidase inhibitor No. (%)		DPP-4 inhibitors No. (%)	
	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo
Bakris (2015)[xx]	334 (45.9)	41 (43.6)	397 (54.6)	55 (58.5)	543 (74.6)	76 (80.8)	558 (76.7)	67 (71.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Katayama (2017)[xx]	9 (10.7)	0	75 (89.2)	12 (100)	19 (22.6)	3 (25)	9 (75)	48 (57.1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bakris (2020)[xx]	950 (33.5)	992 (34.9)	1879 (66.3)	1846 (65.0)	1577 (55.7)	1637 (57.6)	2105 (74.3)	2110 (74.3)	70 (2.5)	66 (2.3)	1633 (57.6)	1595 (56.1)	1843 (65.1)	1794 (63.1)	189 (6.7)	205 (7.2)	124 (4.4)	135 (4.8)	1251 (44.2)	1239 (43.6)	654 (23.1)	673 (23.7)	163 (5.8)	161 (5.7)	764 (27.0)	758 (26.7)
Bertram (2021)[xx]	1576 (42.8)	1561 (42.6)	2108 (57.2)	2104 (57.4)	1748 (47.4)	1748 (47.7)	2552 (69.2)	2632 (71.8)	24 (0.7)	22 (0.6)	2044 (55.5)	2029 (55.3)	2023 (54.9)	1970 (53.7)	308 (8.4)	242 (6.6)	314 (8.5)	304 (8.3)	2561 (69.5)	2506 (68.4)	1037 (28.1)	1025 (28.0)	160 (4.3)	172 (4.7)	896 (24.3)	860 (23.5)
Gerasimos (2021)[xx]	995 (33.5)	992 (34.9)	1886 (66.5)	1846 (64.9)	1576 (55.6)	1637 (57.6)	2105 (74.3)	2110 (74.2)	80 (2.8)	82 (2.8)	1633 (57.6)	1595 (56.1)	1843 (65)	1794 (63.1)	189 (6.6)	205 (7.2)	124 (4.3)	135 (4.7)	1251 (44.1)	1239 (43.5)	654 (23)	673 (23.6)	N/A	N/A	764 (26.9)	758 (26.6)
Agarwal (2022)[xx]	2526 (38.7)	2553 (39.2)	3987 (61.2)	3950 (60.7)	3325 (51.0)	3385 (52.0)	4657 (71.4)	4742 (72.9)	94 (1.4)	88 (1.4)	3677 (56.4)	3624 (55.7)	3866 (59.3)	3764 (57.8)	497 (7.6)	447 (6.9)	438 (6.7)	439 (6.7)	3812 (58.5)	3745 (57.6)	1691(25.9)	16968 (26.1)	323 (5)	333 (5.1)	1660 (25.5)	1618 (24.9)
Gerasimos (2022)[xx]	1576 (42.7)	1561 (42.5)	2108 (57.1)	2104 (57.3)	1748 (47.4)	1748 (47.6)	2552 (69.2)	2632 (71.7)	24 (0.6)	22 (0.6)	N/A	N/A	2023 (54.8)	1970 (53.7)	308 (8.3)	242 (6.6)	314 (8.5)	304 (8.2)	2561 (69.4)	2506 (68.3)	1037 (28.1)	1025 (27.9)	N/A	N/A	896 (24.3)	860 (23.4)

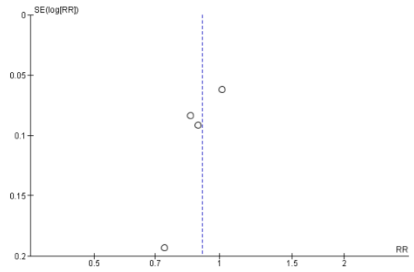
Supplementary Table 5: Quality assessment of included RCTs





Supplementary Figure 1: Funnel plots of efficacy and safety outcomes

A



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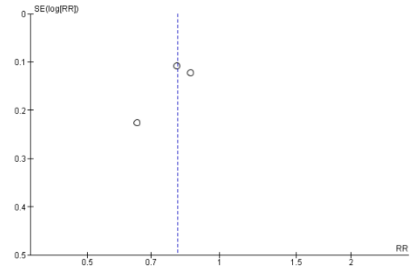

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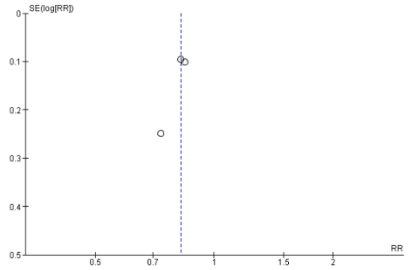

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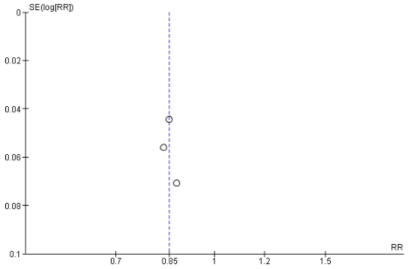

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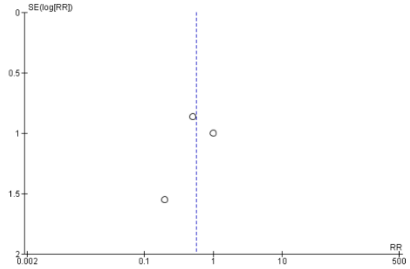
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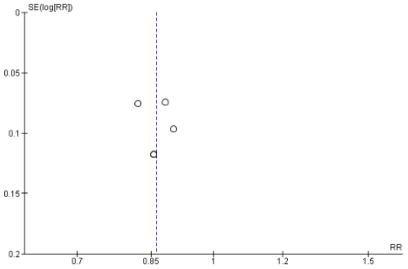
F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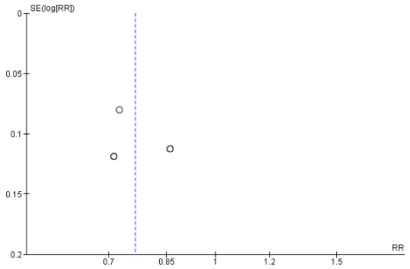

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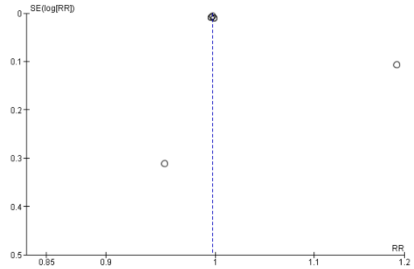
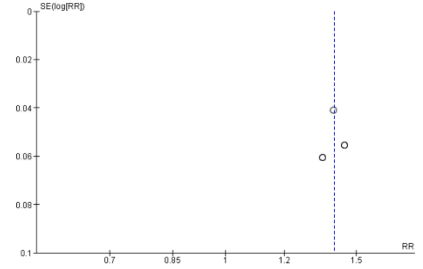
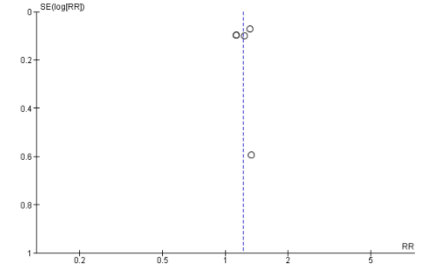


K



L



A= Kidney failure, B= End-stage kidney disease, C= Sustained decrease to < 15 ml/min/1.73m2, D= Sustained decrease to eGFR > 40% from baseline, E= Death from renal causes, F= Death from cardiovascular causes, G= Non-fatal MI, H= Non-fatal Stroke, I= Hospitalization for heart failure, J= Death from any cause, K= Hospitalization for any cause, L= Any adverse event.