



Efficacy and safety of finerenone in patients with chronic kidney disease: a systematic review with meta-analysis and trial sequential analysis

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Background: The efficacy and safety of finerenone are unknown. Therefore, we performed this meta-analysis to investigate the efficacy and safety of finerenone in patients with chronic kidney disease (CKD).

Methods: We systematically searched for relevant studies in the PubMed, Embase and Cochrane Library databases from database inception until December 2020. We selected randomized controlled trials assessing finerenone treatment in patients with CKD.

Results: Four trials (n=7,048) met the inclusion criteria. Compared with placebo, finerenone significantly reduced the urine albumin-to-creatinine ratio (UACR) in patients with CKD {mean difference (MD), -0.30 [95% confidence interval (CI), -0.50, -0.11], P<0.05}, and trial sequential analysis (TSA) confirmed this result. No significant difference was observed in eGFR in patients with CKD between the finerenone and placebo groups [MD, -0.90 (95% CI, -3.84 to 2.04), P>0.05]. Overall, the frequency of adverse events was similar in the two groups [relative risk (RR), 1.00 (95% CI, 0.98, 1.02), P>0.05], and TSA confirmed this result. However, the finerenone group exhibited a lower risk of cardiovascular disorders and a higher risk of hyperkalemia than the placebo group [RR, 0.92 (95% CI, 0.85, 0.99), P<0.05 and RR, 2.04 (95% CI, 1.77, 2.34), P<0.00001, respectively].

Discussion: This meta-analysis indicated that finerenone confers an important antiproteinuric effect on patients with CKD and reduces the risk of cardiovascular disorders in these patients. Finerenone may be a promising therapy option for patients with CKD.

Trial registration: PROSPERO registration number: CRD42021222404.

Keywords: Efficacy; safety; finerenone; chronic kidney disease (CKD); meta-analysis

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Introduction

Chronic kidney disease (CKD) has become a major public health problem due to its high incidence, poor prognosis and high cost of medical treatment (1). Type 2 diabetes mellitus (T2DM) is the most common cause of CKD and is now globally the single leading cause of end-stage renal disease (ESRD). When type 2 diabetes leads to CKD, the disease is usually referred to as diabetic kidney disease (DKD) or diabetic nephropathy (DN) (2). A substantial proportion of individuals with diabetes develop CKD as a result of their disease and/or other comorbidities, such as hypertension and nephron loss (3). Patients with chronic kidney disease are characterized by a progressive decline in health-related quality of life as well as a high risk of cardiovascular disease (CVD) (4). A variety of factors are involved in the pathophysiological development of CKD, including aldosterone. Aldosterone, a mineralocorticoid hormone, is a downstream target of the activation of the renin-angiotensin system (RAS) that may have an impact on human kidneys due to its potential ability to increase proteinuria and decrease renal function (5). In addition to its effects on the kidney, aldosterone also has the potential to exert effects on the heart. Aldosterone can affect non-epithelial cells such as cardiomyocytes, endothelial cells, vascular smooth muscle cells (VSMCs), mesangial cells, and podocytes via the mineralocorticoid receptor and subsequent genomic events, as well as through nongenomic pathways. Current studies have revealed that aldosterone causes inflammation in various ways, including stimulating the formation of reactive oxygen species (ROS), endothelial exocytosis and adhesion, leading to fibrosis and remodeling in the heart and kidney (6).

In this way, blockade of aldosterone using mineralocorticoid receptor antagonists (MRAs) might be an effective strategy to treat CKD. Several experimental and clinical studies have provided evidence on the moderate renoprotective effect of classic steroidal MRAs (spironolactone and eplerenone) (7-16). However, their use in CKD patients is limited due to its potential risks of hyperkalemia, erectile dysfunction and menstrual disorders (5).

Finerenone (BAY 94–8862) is currently the most advanced third-generation nonsteroidal MRI drug. Preclinical studies have shown that finerenone has a higher selectivity than spironolactone, a better affinity than eplerenone and a lower risk of hyperkalemia (17,18). Researchers have investigated the efficacy and safety of finerenone in recent years. However, its clinical efficacy and safety are still unclear.

Therefore, we decided to undertake a meta-analysis and trial sequential analysis (TSA) to compare the efficacy and safety of finerenone with that of placebo in patients with CKD. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-763>) (19).

Methods

Search strategy and information sources

Electronic databases, including PubMed, Embase, and the Cochrane Library databases, were searched from database inception to December 2020 using items related to “finerenone” and “BAY 94–8862.” Literature search details are shown in [Table S1](#). The search was limited to human subjects, and no language restrictions were applied. An additional search was conducted by manually reviewing conference proceedings and the references of review articles if necessary.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) study design: RCT; (II) comparison: evaluating the efficacy and safety of finerenone with that of placebo; (III) population: conducted on the patients with CKD; and (IV) outcome: assessed at least one of the following outcomes: the change in urinary albumin to creatinine ratio (UACR) from baseline to the end of the study, the change in estimated glomerular filtration rate (eGFR) from baseline to the end of the study (see [Table S2](#) for selected time points), adverse events including cardiovascular disorders (including cardiac disorders and vascular disorders) and hyperkalemia. The exclusion criteria were as follows: (I) studies including patients with heart failure but without CKD or studies including patients with CKD but with data that could not be extracted and analyzed from the published results; and (II) studies such as systemic reviews, comments, case reports, conference abstracts, and editorials.

Study selection and data extraction

Two reviewers (ZF and CL) independently performed the study selection and data extraction. All disagreements between the two reviewers were resolved by third-party adjudication (QH). A standard form designed according to the Cochrane checklist was used to collect data from

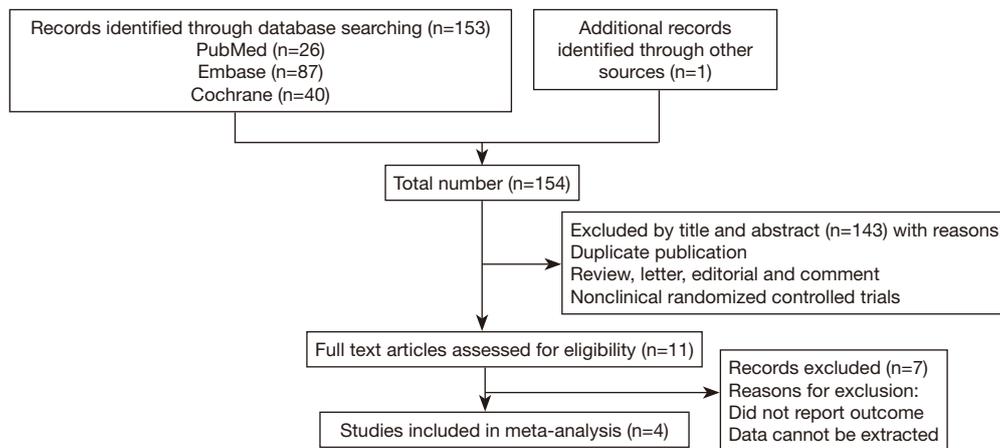


Figure 1 Flow diagram of the study selection process for the meta-analysis.

each study. The extracted data included first author, year of publication, study setting, patient characteristics, sample size, doses of treatment, control, and follow-up.

Assessment of risk of bias

Assessment of risk of bias was performed by two reviewers (ZF and CL) according to the Cochrane Collaboration's risk-of-bias assessment tool in Review Manager 5.3. Publication bias was assessed by using Stata (version 13.0).

Statistical analysis

Dichotomous outcomes were reported using relative risks (RRs) with 95% confidence intervals (CIs), whereas continuous outcomes (UACR and eGFR) were reported using mean differences (MDs) with 95% CIs. Heterogeneity across the trials was assessed using the I^2 statistic, Q statistic and tau-squared test, and $I^2 > 50\%$ indicated significant heterogeneity (20). R software (version 3.6.1) was used to calculate the 95% CIs of these results. The random-effects model was applied to pool the results of all the studies included in this meta-analysis regardless of the heterogeneity, and sensitivity analysis was performed to determine the robustness of the results. Subgroup analysis was conducted to investigate the potential sources of between-study heterogeneity. Publication bias was assessed using Stata with the metabis6 package, version 13.0 (Stata Corporation). A two-tailed P value less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using Review Manager, version 5.3 (RevMan, The Cochrane

Collaboration, Oxford, United Kingdom). If the mean or standard deviation of UACR or eGFR could not be directly obtained from the trials, we estimated the mean and deviation from the sample size, median, range and/or interquartile range (21).

Trial sequential analysis

Trial sequential analysis (TSA) was used in the meta-analyses to reduce the risk of reaching a false-positive or false-negative conclusion (22). When the cumulative Z-curve crossed the trial sequential monitoring boundary or entered the futility area, a sufficient level of evidence for the anticipated intervention effect was reached, and no further trials were needed. If the Z-curve did not cross any of the boundaries and the required information size (RIS) had not been reached, evidence was insufficient to obtain a conclusion, and more trials were needed to confirm the results (23). In this TSA, we estimated the RIS based on an RR reduction of 10%. The type I error (α) was maintained at 0.05 (two-sided) in this TSA. We used a power ($1-\beta$) of 0.90 to calculate the required information size for all the results. The control event proportion was calculated based on the comparator group (24). The TSA was conducted using TSA Version 0.9.5.10 Beta (www.ctu.dk/tsa).

Results

Characteristics of eligible studies and quality assessment

The study selection process is depicted as a flow diagram in *Figure 1*. After the removal of duplicates and studies

that failed to meet the inclusion criteria, 11 articles were retrieved for detailed assessment. Seven articles were excluded because they did not report outcomes or the data could not be extracted from the articles. In total, 4 RCTs (25-28) involving 7,048 participants were included in this meta-analysis. The characteristics of the included trials and patient demographic data are summarized in *Table 1*. Three studies (25,27,28) were phase 2 clinical trials, and the other study (26) was a phase 3 clinical trial. These trials were reported between 2013 and 2020. The number of patients included in each study ranged from 96 to 5,674, and the follow-up ranged from 1 to 30 months. Most of the patients involved in these trials received concomitant medication at baseline, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and drugs used for diabetes treatment. More patients were taking ARBs than ACEIs. The proportions of patients receiving ACEIs at baseline in the studies conducted by Bakris *et al.* [2015] (25), Bakris *et al.* [2020] (26) and Katayama *et al.* [2017] (27) were 45.7%, 34.2% and 9.4%, respectively. The proportions of patients receiving ARBs in the studies conducted by Bakris *et al.* [2015] (25), Bakris *et al.* [2020] (26) and Katayama *et al.* [2017] (27) were 55.1%, 65.7% and 90.6%, respectively. Pitt *et al.* also described the number of patients who were receiving agents acting on the renin-angiotensin system (RAS), and the proportion of these patients was 95.4% (28). In addition, in the three studies (25-27) dealing with patients with type 2 diabetes and CKD, nearly all the patients (over 95 percent) were receiving glucose-lowering therapies. Review Manager 5.3 was used to evaluate the overall quality of the articles. The quality of the studies is shown in *Figure S1*. All studies had low selection bias.

Efficacy outcomes

Urine albumin-to-creatinine ratio (UACR)

UACR is an important indicator of treatment efficacy and is closely related to the improvement and prognosis of CKD. Three studies (n=329) (25,27,28) displayed a difference in the urine albumin-to-creatinine ratio between the finerenone and placebo groups. A significantly greater reduction in the urine albumin-to-creatinine ratio among patients with CKD was observed in the finerenone group than in the placebo group [MD, -0.30 (95% CI, -0.50 to -0.11), $P=0.003$, $I^2=0\%$ (95% CI, 0.0% to 40.6%), $\text{Chi}^2=0.03$, $P=0.98$, $\tau^2=0$ (95% CI, 0 to 0.17); *Figure 2A*], and TSA confirmed this result (the cumulative Z-curve crossed the

conventional boundary and the trial sequential monitoring boundary; *Figure 2B*). In addition, we compared the clinical effectiveness of finerenone at doses of 10 and 20 mg once daily. The pooled analysis showed that doses of both 10 and 20 mg once daily appear to be efficacious at reducing the UACR [MD, -0.24 (95% CI, -0.46 to -0.01), $P=0.04$, $I^2=0\%$ and MD, -0.35 (95% CI, -0.57 to -0.13), $P=0.002$, $I^2=0\%$, respectively; *Figure 3A,B*]. However, the TSA result only suggested the treatment effect of the finerenone dose of 20 mg/d on reducing UACR, for the cumulative Z curve of the dose of 10 mg/d just crossed the conventional boundary but did not cross the trial sequential monitoring boundary (*Figure 3C*) and the cumulative Z curve of the dose of 20 mg/d crossed the conventional boundary and the sequential monitoring boundary (*Figure 3D*).

Estimated glomerular filtration rate (eGFR)

Three studies (n=5,974) (25,26,28) reported a change in eGFR in patients with CKD. The results demonstrated that there was no significant difference in eGFR between the finerenone group and the placebo group [MD, -0.90 (95% CI, -3.84 to 2.04), $P=0.55$]. Heterogeneity was observed among the included studies [$I^2=86\%$ (95% CI, 68.5% to 95.9%), $\text{Chi}^2=13.89$, $P=0.0001$, $\tau^2=0.08$ (95% CI, 0.01 to 3.54)] (*Table 2*). Therefore, we applied a sensitivity analysis to further investigate the eGFR results. We found that no between-study variance was observed, and the eGFR results were significantly changed (a significant difference was found in eGFR between the finerenone group and the placebo group) if one study was excluded from the analysis [MD, -2.32 (95% CI, -4.18 to -0.45), $P=0.01$, $I^2=0\%$, $\text{Chi}^2=0.10$, $P=0.76$, $\tau^2=0$] (26). However, due to the limited number of included studies, further research is needed to achieve a more reliable result.

Adverse events

Four studies (n=6,039) (25-28) showed that the overall frequency of adverse events was similar between the finerenone and placebo groups [RR, 1.00 (95% CI, 0.98, 1.02), $P=0.84$, $I^2=0\%$ (95% CI, 0.0% to 5.9%), $\text{Chi}^2=0.47$, $P=0.93$, $\tau^2=0$ (95% CI, 0 to 0.05); *Figure 4A*], and TSA confirmed this result (the cumulative Z curve crossed the futility boundary and reached the required information size, *Figure 4B*). In addition, we compared the incidence of total adverse events at doses of 10 and 20 mg once daily separately. No significant differences were observed between the finerenone and placebo groups in either the 10 or 20 mg/d

Table 1 The basic characteristics of the studies included in this meta-analysis

Source	Region	Setting	Renal disease	eGFR at baseline (mL/min/1.73 m ²)	Glycated hemoglobin* (%)	No. of patients (M/F)	Mean age, years	Treatment	Control	Follow-up, months
Bakris et al., 2015	23 countries	Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter	Type 2 DN	T: 66.9±21.9 ^a C: 72.2±20.4 ^a	T: 7.6±1.3 ^a C: 7.6±1.3 ^a	T: 727 (570/157) C: 94 (69/25)	T: 64.33±9.20 ^a C: 63.26±8.68 ^a	Finerenone 1.25, 2.5, 5, 7.5, 10, 15, 20 mg	Placebo	3
Bakris et al., 2020	48 countries	Phase 3, randomized, double-blind, placebo-controlled, multicenter	Type 2 diabetes and CKD	T: 44.4±12.5 ^a C: 44.3±12.6 ^a	T: 7.7±1.3 ^a C: 7.7±1.4 ^a	T: 2,833 (1,953/880) C: 2,841 (2,030/811)	T: 65.4±8.9 ^a C: 65.7±9.2 ^a	Finerenone 10, 20 mg	Placebo	30
Katayama et al., 2017	Japan	Phase 2b, randomized, double-blind, placebo-controlled, multicenter	Type 2 DN	T: 65.23±13.70 ^a C: 60.88±16.53 ^a	T: 7.22±0.95 ^a C: 7.28±0.72 ^a	T: 84 (67/17) C: 12 (10/2)	T: 62.41±9.80 ^a C: 66.75±9.02 ^a	Finerenone 1.25, 2.5, 5, 7.5, 10, 15, 20 mg	Placebo	3
Pitt et al., 2013	10 countries	Phase 2, randomized, double-blind, placebo-controlled, parallel-group multicenter	Heart failure with reduced ejection fraction and mild (A) or moderate (B) chronic kidney disease (eGFR 30–60 mL/min/1.73 m ²)	A: 69.1±8.43 ^a B: 47.0±10.0 ^a	NA	A: 65 (52/13) B: 392 (312/80)	A: 66.3 [42–85] ^b B: 72.1 [40–89] ^b	Finerenone 2.5, 5, 10 mg	Placebo	1

C, control group; CKD, chronic kidney disease; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; NA, not available; T, treatment group; UACR, urinary albumin-creatinine ratio; ^aMean ± SD; ^bMean (range); * data of glycated hemoglobin or Hemoglobin A_{1c}.

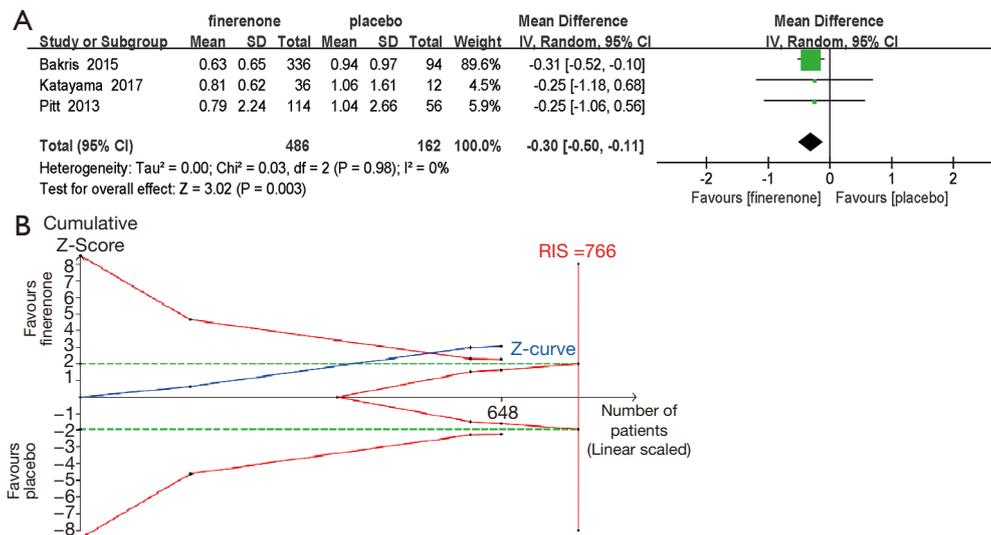


Figure 2 The efficacy outcomes of finerenone *vs.* placebo. (A) Forest plot of the mean UACR (urine albumin-to-creatinine ratio) to that at baseline. (B) Random effects model of the TSA of UACR. A diversity-adjusted information size of 766 participants was calculated on the basis of using $\alpha=5\%$ (two-sided), $\beta=10\%$ (power 90%), and $I^2=0\%$. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary (dashed green line) and the trial sequential monitoring boundary (solid red line). Data were analyzed using information on doses of at least 10 mg/d.

groups (Table 2). However, the risk of cardiovascular disorders and hyperkalemia related to finerenone was different between the finerenone and placebo groups (Figure 5).

Cardiovascular disorders

Four trials (n=6,039) (25–28) investigated the incidence of cardiovascular disorders in the finerenone and placebo groups. In patients with CKD, a lower risk of cardiovascular disorders was found in the finerenone group than in the placebo group [RR, 0.92 (95% CI, 0.85, 0.99), P=0.03, I²=0%; Figure 5A], but TSA could not confirm this result (the cumulative Z-curve just crossed the conventional boundary but did not cross the trial sequential monitoring boundary; Figure 5C).

Hyperkalemia

Four studies (n=6,039) (25–28) indicated a difference in the relative risk of hyperkalemia between the finerenone and placebo groups. The use of finerenone was associated with a higher relative risk of hyperkalaemia than placebo in patients with CKD [RR, 2.04 (95% CI, 1.77, 2.34), P<0.00001, I²=0%; Figure 5B], and TSA suggested that the evidence to reach this conclusion was sufficient, as the cumulative Z-curve crossed both the conventional boundary and the trial sequential monitoring boundary (Figure 5D).

Publication bias

No potential publication bias was observed in the outcomes of adverse events and UACR (P=0.497 and P=0.602 for Begg's test, P=0.924 and P=0.463 for Egger's test, respectively, see Figures S2,S3) among the included studies, but publication bias was detected in the efficacy outcomes of eGFR (P=0.602 for Begg's test and P=0.041 for Egger's test, see Figure S4). However, due to the limited number of included trials, the actual publication bias may not be able to be observed via this method. Although publication bias was not detected in the outcomes of adverse events and UACR through Begg's test and Egger's test, the funnel plots of these two outcomes were apparently asymmetric, which indicated that publication bias may actually exist in this meta-analysis. Therefore, further research is needed to assess the potential publication bias more accurately and achieve a more reliable conclusion.

Discussion

Finerenone (BAY 94–8862), a novel nonsteroidal, selective mineralocorticoid receptor antagonist (MRA), is the third generation of MRAs. Finerenone has a better selectivity than spironolactone and a stronger MR-binding affinity

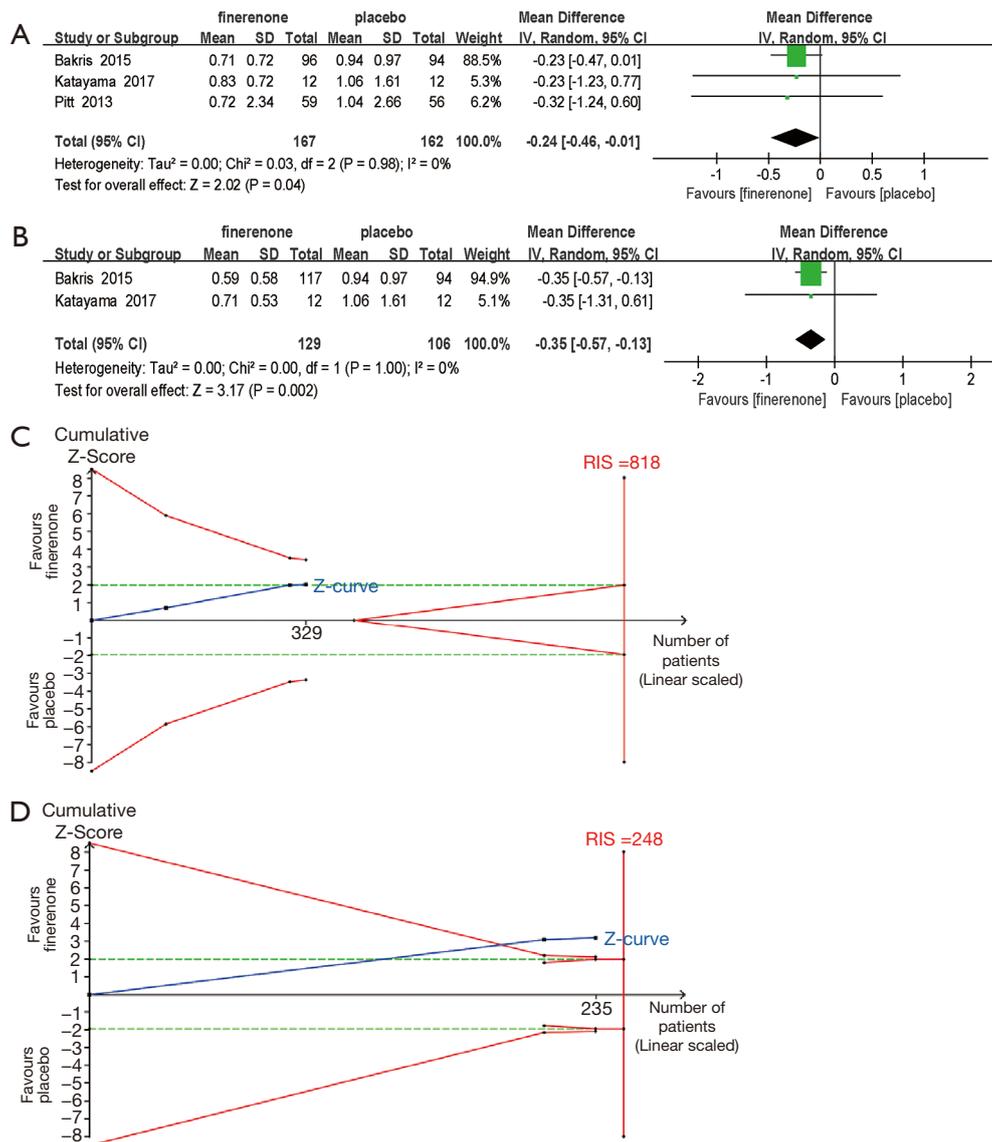


Figure 3 The UACR results for different doses. (A) Forest plot comparing the mean UACR (urine albumin-to-creatinine ratio) to that at baseline in the 10 mg group. (B) Forest plot of the UACR in the 20 mg group. (C) TSA for 10 mg finerenone. A diversity-adjusted information size of 818 participants was calculated on the basis of using $\alpha=5\%$ (two-sided), $\beta=10\%$ (power 90%), and $I^2=0\%$. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary (dashed green line) but did not cross the trial sequential monitoring boundary (solid red line). (D) TSA for 20 mg finerenone. A diversity-adjusted information size of 248 participants was calculated on the basis of using $\alpha=5\%$ (two-sided), $\beta=10\%$ (power 90%), and $I^2=0\%$. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary (dashed green line) and the trial sequential monitoring boundary (solid red line).

than eplerenone (classic steroidal MRAs) (17,18). In this meta-analysis, we used a dose of at least 10 mg/d to assess the overall efficacy and safety of finerenone for its best potential effect (29,30) and compared the outcomes of UACR and total adverse events at doses of 10 and 20 mg of

finerenone separately. In addition, we further used TSA to provide more conservative estimates and to establish more sufficient and conclusive evidence of the outcomes.

Previous meta-analyses have not yet evaluated this topic since finerenone is a relatively new drug. In this updated

Table 2 Comparison of the other outcomes of finerenone

Outcomes	Dose	Number of studies	Mean difference (95% CI)	Test for effect (P value)	Heterogeneity I ² (P value)
eGFR	≥10 mg q.d.	3 (22,23,25)	-0.90 (-3.84, 2.04)	0.55	86% (0.001)
Adverse events	10 mg q.d.	3 (22,24,25)	1.09 (0.89, 1.32)	0.41	0% (0.61)
Adverse events	20 mg q.d.	2 (22,24)	1.05 (0.82, 1.35)	0.68	0% (0.58)

CI, confidence interval; eGFR, estimated glomerular filtration rate, (mL/min/1.73m²); q.d., once daily; UACR, urine albumin-to-creatinine ratio.

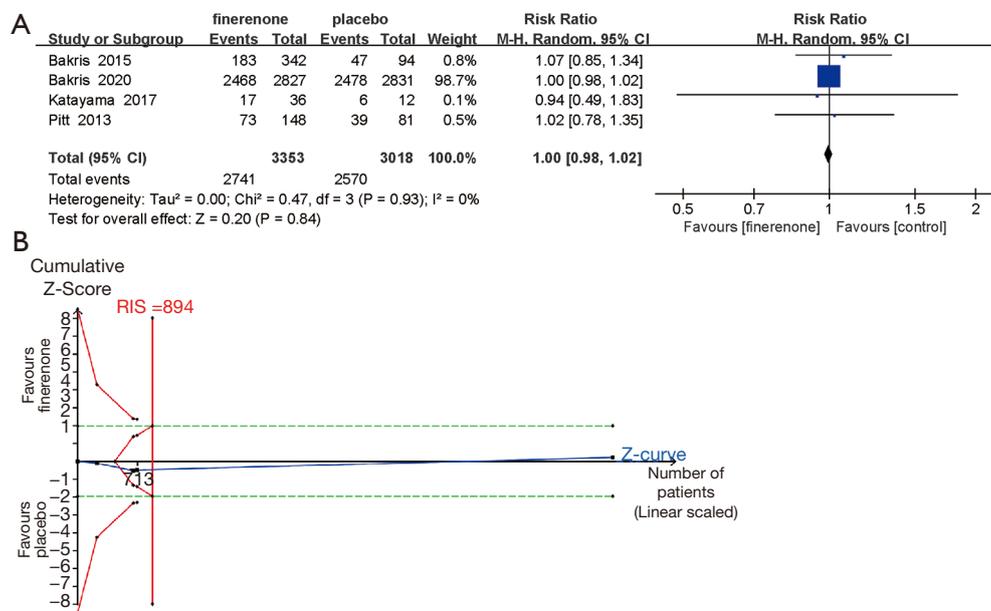


Figure 4 The incidence of adverse events in the finerenone and placebo groups. (A) Forest plot of the adverse events. (B) Random effects model of the TSA of adverse events. A diversity-adjusted information size of 894 participants was calculated on the basis of using $\alpha=5\%$ (two-sided), $\beta=10\%$ (power 90%), and $I^2=0\%$. The solid blue line represents the cumulative Z-curve, which crossed the futility boundary (solid red line).

meta-analysis with the largest sample size to date, we found (I) there was a significant decrease in UACR in the finerenone treatment groups compared with the UACR in the placebo group in patients with CKD, and TSA confirmed this result; (II) doses of both 10 and 20 mg once daily seem to be efficacious at reducing UACR, and TSA confirmed the effectiveness of 20 mg, with no increase in the risk of adverse events; (III) there were no statistically significant changes in eGFR between the two groups; (IV) the incidence of adverse events was similar in the two groups in patients with CKD, and TSA suggested this conclusion was reliable; (V) compared with placebo, finerenone greatly reduced the risk of cardiovascular disorders in CKD patients, but TSA did not prove this result; and (VI) more

episodes of hyperkalemia were observed in the finerenone groups than the placebo groups, and TSA could confirm this result.

As albuminuria is a significant predictor of the progression of CKD (31), a decrease in albuminuria is closely related to the protection of renal function. This meta-analysis suggested that compared with placebo, the use of finerenone may have a great advantage in reducing UACR in patients with CKD. The rationale of this approach is that excess aldosterone induces renal and cardiovascular injury because of its proinflammatory and profibrotic effects (32-34). Thus, blockade of aldosterone could be effective for these patients.

However, analysis of the three studies (25,26,28) comparing finerenone to placebo revealed no significant

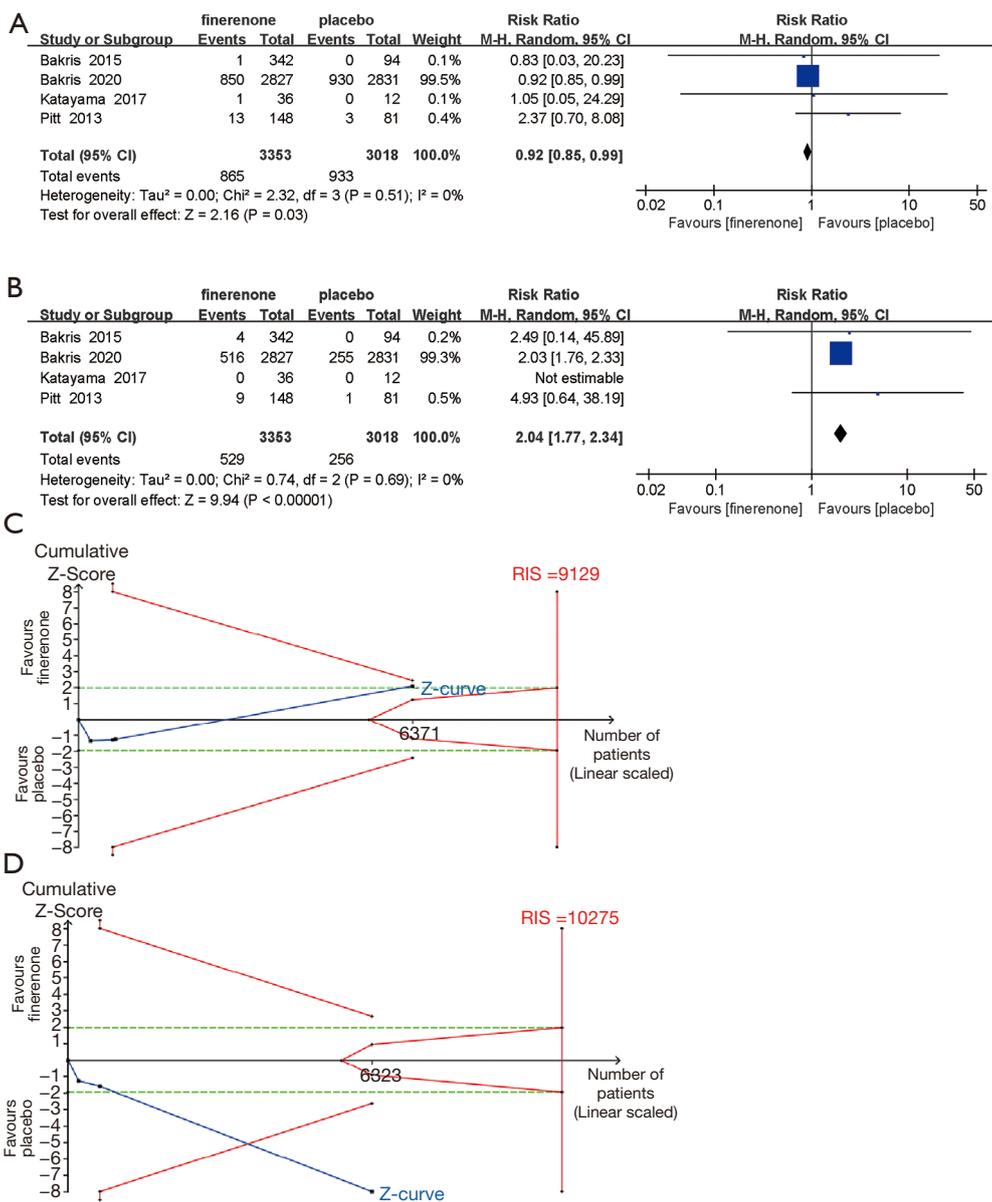


Figure 5 The incidence of cardiovascular disorders and hyperkalemia in the finerenone and placebo groups. (A) Forest plot of cardiovascular disorders. (B) Forest plot of hyperkalemia. (C) Random effects model of the TSA of cardiovascular disorders. A diversity-adjusted information size of 9,129 participants was calculated on the basis of using $\alpha=5\%$ (two-sided), $\beta=10\%$ (power 90%), and $I^2=0\%$. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary (dashed green line) but did not cross the trial sequential monitoring boundary (solid red line). (D) Random effects model of the TSA of hyperkalemia. A diversity-adjusted information size of 10,275 participants was calculated on the basis of using $\alpha=5\%$ (two-sided), $\beta=10\%$ (power 90%), and $I^2=0\%$. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary (dashed green line) and the trial sequential monitoring boundary (solid red line).

changes in eGFR between the two groups. Nevertheless, the change in eGFR in the finerenone group was much different from that in the placebo group and is directly related to the follow-up time (26). A study showed a smaller decrease in eGFR in the finerenone group than in the placebo group in the observation after 12 months, and the trend persisted throughout the trial (26). This result indicates that finerenone may have a long-term benefit for patients with renal diseases. This finding may be of great significance since the patients for whom this treatment might be suitable all have chronic disease and require long-term medication. Therefore, further studies investigating eGFR changes in different periods are needed to assess this outcome.

Kidney failure, which is defined as end-stage renal disease (ESRD) or a sustained eGFR of <15 mL per minute per 1.73 m² of body-surface area (26), is also a key outcome worth assessing in CKD patients since CKD will finally progress to renal failure without appropriate treatment. One trial (26) included in this meta-analysis reported that the incidence of kidney failure was significantly lower in the finerenone group than in the placebo group. This indicates that finerenone may have an effect on ameliorating the progression of CKD and thus benefit patients with CKD.

A major concern of the use of finerenone is its adverse events. Two main adverse events were reported in this study. Compared with placebo, finerenone had less unfavorable effects on cardiovascular disorders in patients with CKD, but TSA could not confirm this result. Thus, more trials are needed to make a more reliable conclusion. In terms of hyperkalemia, the pooled result indicated that compared with placebo, the use of finerenone led to an increased risk of hyperkalemia in patients with CKD, and TSA confirmed this result. This may be associated with the treatment mechanism of MRAs. MRA use increases sodium excretion and decreases potassium excretion in the kidney, resulting in an increase in serum potassium levels (35). Even though the incidence of hyperkalaemia was increased in comparison with that in the placebo group, finerenone is associated with a lower risk than classic steroidal MRAs (spironolactone or eplerenone) according to recent trials and meta-analyses (30,35,36). Current research has reported that compared with eplerenone, finerenone has a much better effect on preventing cardiac fibrosis and improving strain parameters in mice (37). Hence, future research on finerenone is necessary to explore its efficacy and safety versus that of spironolactone and/or eplerenone.

In addition, patients with CKD usually receive a

combination of medications including an antidiabetic prescription medication and/or antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Therefore, it is necessary to consider how the effects of finerenone might vary according to the use of other medications. Current studies have revealed that dual renin-angiotensin-aldosterone system (RAAS) blockade with ACEI plus ARB or ARB plus renin inhibition is associated with an increased risk of serious adverse events such as acute kidney injury or stroke, and no apparent benefits are seen in the context of this kind of medication (38). In contrast, finerenone added to a single RAS blockade seems to be associated with greater reductions in urine albumin or protein excretion than placebo or dual RAS blockade along with fewer episodes of hyperkalaemia (39).

Limitations

Our analysis has some limitations. First, the number of studies included in this analysis was small, and the data for some of the results were scarce. Second, this article only provides preliminary results on the efficacy and safety of finerenone. Third, most of the studies included in the present analysis had a short follow-up period, and only one study had a planned follow-up of 65 months. Thus, further evidence and conclusive results regarding the short-term and long-term efficacy and safety of finerenone in comparison with spironolactone or eplerenone are expected.

Conclusions

This analysis suggests that finerenone confers an important antiproteinuric effect on patients with CKD, with a less unfavorable effect on eGFR. Although a higher risk of hyperkalemia was observed for finerenone than for placebo, the use of finerenone results in a lower incidence of cardiovascular disorders in patients with CKD. Finerenone seems to be a new kind of promising treatment for patients with CKD.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 The literature search strategy and the results of searching in PubMed

Search step	Query	Results
1	(((((Chronic kidney disease[MeSH Major Topic] OR (chronic kidney disease [Title/Abstract])) OR (chronic renal failure[Title/Abstract])) OR (diabetic nephropathy[Title/Abstract])) OR (diabetic kidney disease[Title/Abstract]))	149102
2	((finerenone) OR (BAY 94-8862))	87
3	((((((Randomized controlled trial[Publication Type] OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])) NOT ((Animals[MeSH Terms]) NOT (humans[MeSH Terms]))	2783946
4	(((((Chronic kidney disease[MeSH Major Topic] OR (chronic kidney disease[Title/Abstract])) OR (chronic renal failure[Title/Abstract])) OR (diabetic nephropathy[Title/Abstract])) OR (diabetic kidney disease[Title/Abstract])) AND ((finerenone) OR (BAY 94-8862))) AND (((((((Randomized controlled trial[Publication Type] OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])) NOT ((Animals[MeSH Terms]) NOT (humans[MeSH Terms]))	26

Generally, electronic databases including PubMed, Embase, and the Cochrane Library databases were searched from database inception to December 2020. The search items used were “chronic kidney disease”, “chronic renal failure”, “diabetic nephropathy”, “diabetes mellitus”, and “finerenone”, “BAY 94–8862”, “randomized controlled trial”. The search was limited to human subjects, and no language restrictions were applied. A further search was conducted by manually reviewing conference proceedings and the references of review articles to identify potentially relevant studies. The search terms in PubMed for example, are as follows: ((((((Chronic kidney disease[MeSH Major Topic] OR (chronic kidney disease[Title/Abstract])) OR (chronic renal failure[Title/Abstract])) OR (diabetic nephropathy[Title/Abstract])) OR (diabetic kidney disease[Title/Abstract])) AND ((finerenone) OR (BAY 94-8862))) AND (((((((Randomized controlled trial[Publication Type] OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])) NOT ((Animals[MeSH Terms]) NOT (humans[MeSH Terms]))).

Table S2 The time points of urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) selected for analysis

Study	Selected time points of the outcomes	
	UACR	eGFR
Bakris <i>et al.</i> , 2015	baseline visit and end of study visit (month 3)	baseline visit and end of study visit (month 3)
Bakris <i>et al.</i> , 2020	baseline visit and end of study visit (month 30)	baseline visit and end of study visit (month 30)
Katayama <i>et al.</i> , 2017	baseline visit and end of study visit (month 3)	baseline visit and end of study visit (month 3)
Pitt <i>et al.</i> , 2013	baseline visit and end of study visit (month 1)	baseline visit and end of study visit (month 1)

UACR, urinary albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

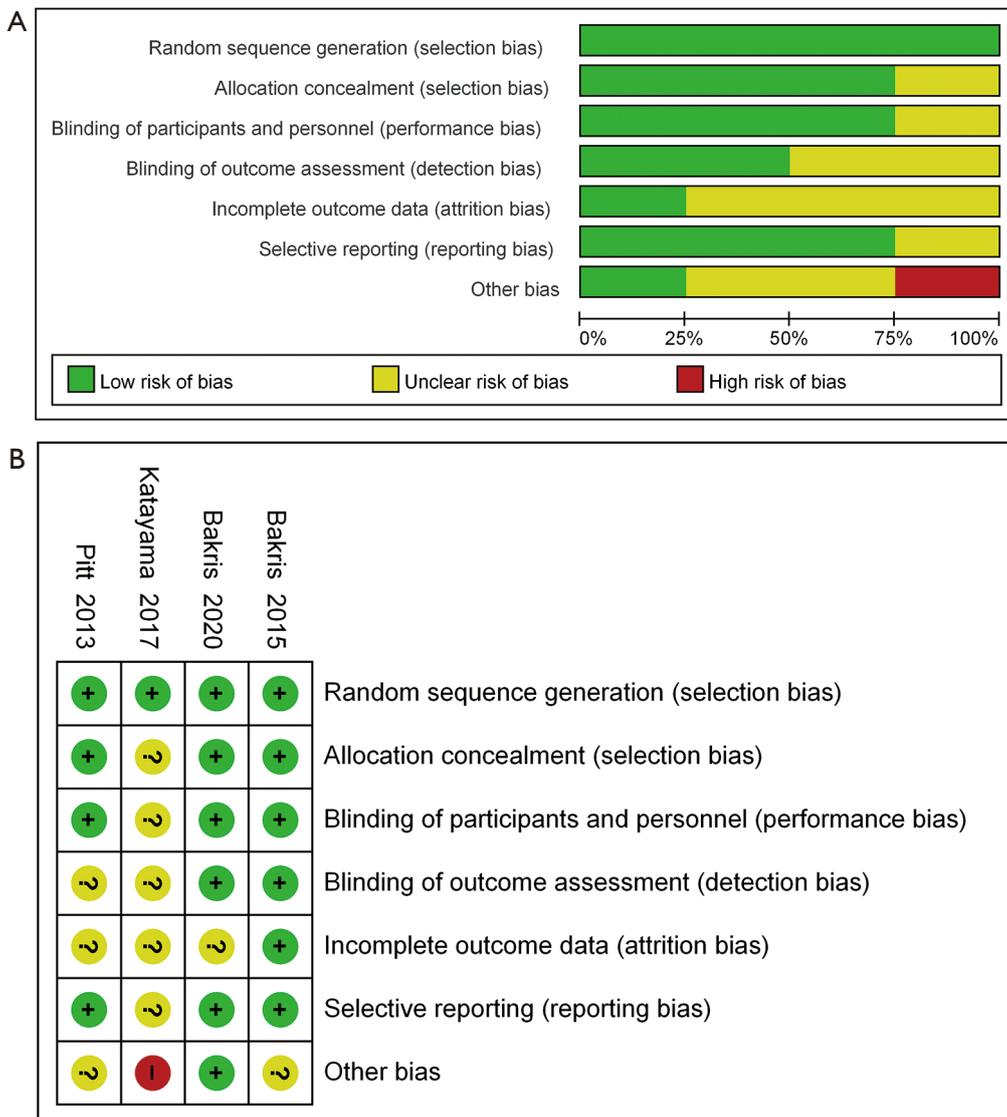


Figure S1 Risk of bias of included studies. (A) Risk of bias graph. (B) Risk of bias summary.

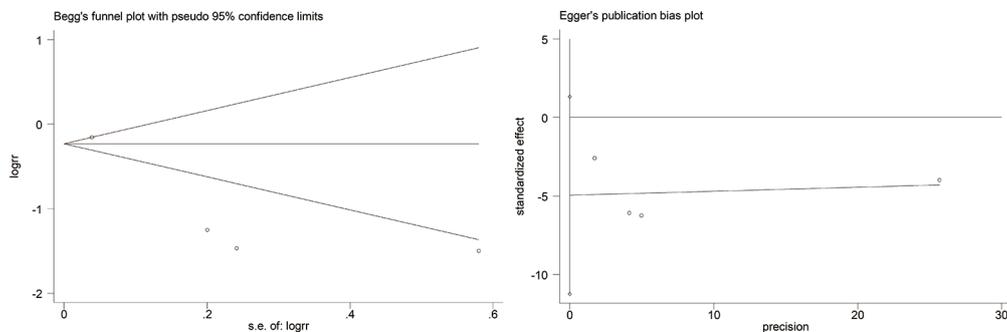


Figure S2 Publication bias of funnel plot for adverse events.

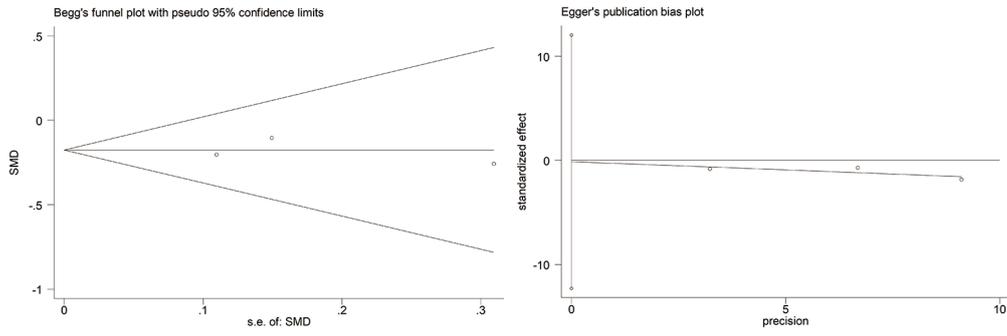


Figure S3 Publication bias of funnel plot for UACR.

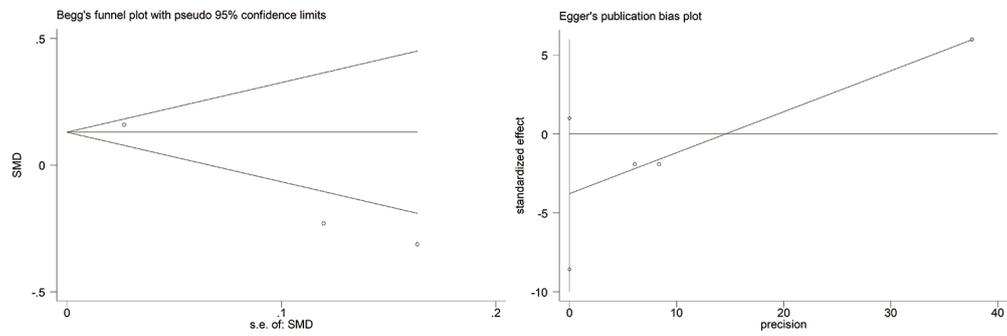


Figure S4 Publication bias of funnel plot for eGFR.