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Peer Review File

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Reviewer A

Your study touches an interesting and important topic in clinical practice, and you tried to give a conclusive evidence by using trial sequential analysis (TSA). In overall, I really appreciate the use of TSA in this topic, but most information in the article have been revealed in the previous studies (1). However, many works should be done before publish. My comments are listed below:

INTRODUCTION (minor concern):

Comment 1: It is better to have a brief introduction to point out chronic kidney disease under the context of diabetes mellitus since the most evidence in this meta-analysis are based on diabetic nephropathy.

Reply 1: Thank you very much for your valuable suggestion. According to your suggestion, we added relevant context in the text.

Changes in the text: We added following content in the INTRODUCTION section as advised (see Page 4, line 82-87):

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). 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.

METHODS (Search strategy and information sources; minor concern):

Comment 2: Search details were described very briefly, and I cannot judge the appropriateness of the search strategy. As comprehensively evidence gathering is critical for meta-analysis, a clear information of search strategy is required. I know the search details may be complicated, and those information are probably inappropriate to be presented in the main text. They could be presented in Supplementary.

Reply 2: Thank you very much for your serious review. As you suggested, we added the content of literature search strategy in the supplementary file and the results of searching are as follows:

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

Changes in the text: We added a literature search strategy section in the supplementary file as follows (see supplementary file, S2):

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]))).

METHODS (Study selection and data extraction; major concern):

Comment 3: Urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) in clinical practice are usually observed in multiple time points. Randomized controlled trials also commonly measured these outcomes at multiple time points. The authors did not mention how they dealt the data with multiple time points, and the manuscript also had no information regarding which time point was selected. The authors have to describe how and why they choose data from a specific time point or some time points for each outcome by trial (it could be a table in appendix).

Reply 3: Thank you for your valuable comments. In this meta-analysis, the outcomes of urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) measured are change from baseline visit to the end of study visit. We chose these two time points according to the study design of the randomized controlled trials included in this meta-analysis. These two time points are reported in all the included studies and can be extracted for analysis. Therefore, we chose the data of the change of UACR and eGFR from the time points of baseline visit to the end of study visit to keep consistency in data analysis and for it can be fully extracted from the studies included. In addition, we cannot obtain the data from the same measuring time points to analyze the results due to the inconsistent follow up time. It is better to conduct a subgroup analysis, however, owing to the limited number of the included studies, this cannot be done.

Changes in the text: According to your suggestion, we have modified the METHODS section and added a table in supplementary file in our text as advised (see Page 5, line 125-127 and supplementary file S3):

(4) 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, adverse events including cardiovascular disorders (including cardiac disorders and vascular disorders) and hyperkalemia.

S3. 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 et al, 2015	baseline visit and end of study visit (month 3)	baseline visit and end of study visit (month 3)

Bakris et al, 2020	baseline visit and end of study visit (month 30)	baseline visit and end of study visit (month 30)
Katayama et al, 2017	baseline visit and end of study visit (month 3)	baseline visit and end of study visit (month 3)
Pitt et al, 2013	baseline visit and end of study visit (month 1)	baseline visit and end of study visit (month 1)

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

METHODS (Assessment of risk of bias; minor concern):

Comment 4: The authors stated that "The publication bias was assessed by using the Stata test" in PAGE 5 LINEs 109 to 110. It is better to specify which package and argument they used for detecting publication bias.

Reply 4: Thank you for your valuable comments. According to your suggestion, we specified the package and argument we used to detect the publication bias in the text. In this manuscript, we used Stata software with metabias6 package, version 13.0 (Stata Corporation) to assess the publication bias and a two-tailed P-value less than 0.05 was considered to indicate a statistically significant difference.

Changes in the text: We have modified the METHODS section as follows (see Page 6, line 152-153):

Publication bias was assessed using Stata with the metabias6 package, version 13.0 (Stata Corporation). A two-tailed P-value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS (Characteristics of eligible studies and quality assessment; major concern):

Comment 5: Some critical characteristics were not presented in Table 1, and those information could help clinicians to judge how to apply the findings in their clinical practice. Notably, creatinine, stage of chronic kidney disease, or eGFR at baseline should be presented in Table 1.

Reply 5: Thank you for your valuable comments. As you suggested, we added the data of eGFR at baseline in Table 1.

Changes in the text: We added the following data of eGFR at baseline in Table 1 (see Table 1).

Source	eGFR at baseline (mL/min/1.73 m²)
Bakris et al, 2015	T:66.9±21.9[a] C:72.2±20.4[a]
Bakris et al, 2020	T:44.4±12.5[a] C:44.3±12.6[a]

Katayama et al, 2017	T:65.23±13.70[a] C:60.88±16.53[a]
Pitt et al, 2013	A:69.1±8.43[a] B:47.0±10.0[a]

RESULTS (Characteristics of eligible studies and quality assessment; major concern):

Comment 6: With regard to baseline characteristics, secondly, HbA1c may be also worth to be shown in Table 1, since this topic highly relates to diabetes mellitus.

Reply 6: Thank you for your valuable comments. As you suggested, we added the data of baseline glycated hemoglobin (or HbA1c) in Table 1.

Changes in the text: We added the data of baseline glycated hemoglobin (or HbA1c) in Table 1 (see Table 1).

Source	Glycated hemoglobin*
Bakris et al, 2015	T:7.6±1.3[a] C:7.6±1.3[a]
Bakris et al, 2020	T:7.7±1.3[a] C:7.7±1.4[a]
Katayama et al, 2017	T:7.22±0.95[a] C:7.28±0.72[a]
Pitt et al, 2013	NA

Abbreviations: 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; [a] Mean ± SD; [b] Mean (range); * data of glycated hemoglobin or Hemoglobin A_{1C}.

RESULTS (Characteristics of eligible studies and quality assessment; major concern):

Comment 7: To my knowledge, this population usually receive other medication, including angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). I am wondering whether the included trials provided relevant medications to patients. It is better to mention baseline medication in Table 1 or in text under subsection of CHARACTERISTICS OF ELIGIBLE STUDIES AND QUALITY ASSESSMENT.

Reply 7: Thank you for your valuable comments. According to your suggestion, we added some relevant information of baseline medication in the text under subsection of CHARACTERISTICS OF ELIGIBLE STUDIES AND QUALITY ASSESSMENT.

Changes in the text: We added the following content in the text under subsection of CHARACTERISTICS OF ELIGIBLE STUDIES AND QUALITY ASSESSMENT (see Page 8, line 182-191):

More patients were taking ARBs than ACEIs. The proportions of patients receiving ACEIs at baseline in the studies conducted by Bakris et al. (2015), Bakris et al. (2020) and Katayama et al. (2017) were 45.7%, 34.2% and 9.4%, respectively. The proportions of patients receiving ARBs in the studies conducted by Bakris et al. (2015), Bakris et al. (2020) and Katayama et al. (2017) 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%. In addition, in the three studies dealing with patients with type 2 diabetes and CKD, nearly all the patients (over 95 percent) were receiving glucose-lowering therapies.

RESULTS (all meta-analysis; major concern):

Comment 8: All the meta-analyses were carried out in random-effects model, and for me, this is appropriate way to pool data due to conceptual heterogeneity. However, the authors indicated that they chose effect model based on heterogeneity. They would like to use fixed-effect model for pooled estimate with low heterogeneity, otherwise they used random-effects model. Methods and actual analysis should be consistent.

Reply 8: Thank you for your valuable comments. According to your suggestion, we checked our manuscript to keep consistency in Methods and actual analysis. We finally chose random-effect model to pool the results of all the studies included in this meta-analysis and had our manuscript modified as advised.

Changes in the text: We have modified the METHODS section as follows (see Page 6, line 148-151):

~~The fixed-effect analytical model was applied to analyze the results of trials with acceptable or no heterogeneity.~~ The random-effect model was applied to pool the results of all the studies included in this meta-analysis regardless of the heterogeneity, and the sensitivity analysis was performed to determine the robustness of the results.

RESULTS (meta-analysis; major concern):

Comment 9: Dialysis or progression to end-stage renal disease (kidney failure) may be key outcomes in this topic, but the present study did not mention any information about these two end points. I have noted that a randomized controlled trial reported

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relevant data on kidney failure (1). I expect to see relevant analysis in RESULTS section or some discussions in DISCUSSION section.

Reply 9: Thank you for your valuable comments. As you suggested, we added some relevant content about the outcome of kidney failure in DISCUSSION section.

Changes in the text: We added the following content in the text under the section of DISCUSSION as advised (see Page 12, line 294-300):

Kidney failure, which is defined as end-stage renal disease (ESRD) or a sustained eGFR of <15 ml per minute per 1.73 m^2 of body-surface area, is also a key outcome worth assessing in CKD patients since CKD will finally progress to renal failure without appropriate treatment. One trial 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.

RESULTS (Figure 2 to 5; major concern):

Comment 10: Defined power was 90% in all TSAs according to figure footnotes, but the authors mentioned they set power 0.8 in METHODS (PAGE 6 LINE 134). Methods and actual analysis should be consistent.

Reply 10: Thank you for your serious review. According to your suggestion, we carefully checked our manuscript to keep consistency in Methods and actual analysis. In this manuscript, we finally chose to use a RR reduction of 10% to estimate the RIS and a power (1-β) of 0.90 to calculate the required information size for all the results.

Changes in the text: We have modified the METHODS section and the figure footnotes as follows (see Page 7, line 165-167 and Page 20, line 495-496):

In this TSA, we estimated the RIS based on a RR reduction of 10%. The type I error (α) was maintained to be 0.05 (two-sided) in this TSA. We used a power (1-β) of 0.90 to calculate the required information size for all the results.

Figure 5 (**D**) Random effects model of the TSA of hyperkalemia. A diversity-adjusted information size of 10275 participants was calculated on the basis of using α=5% (two-sided), β=10% (power-90%), and I^2 =0%.

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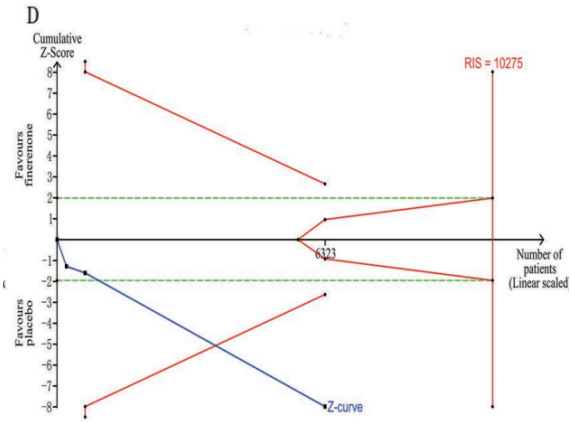


RESULTS (Publication bias; major concern):

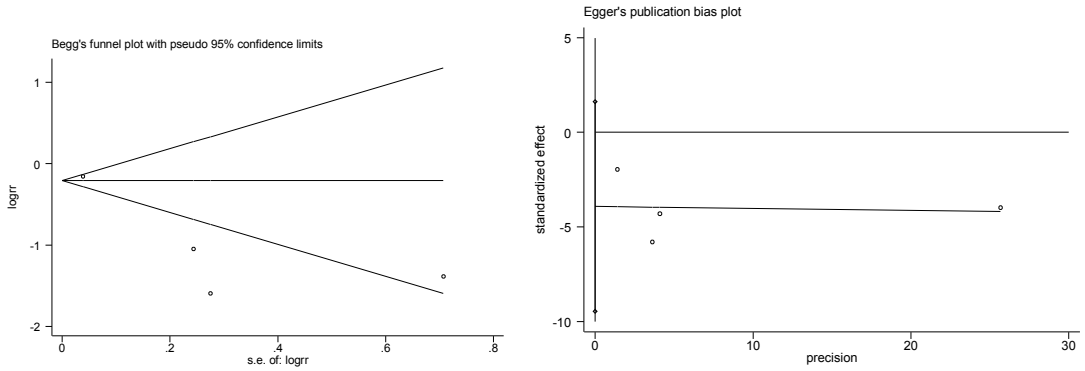
Comment 11: Risk ratio was used for pairwise comparisons of adverse event in consistency model, but log odd ratio was further used for publication bias test. Actually, results sometimes varied by statistical measurements, and these analyses could be conducted using the same statistical measurement. I recommend the authors to use measurement consistently.

Reply 11: Thank you for your valuable comments and serious review. According to your suggestion, we revised our manuscript carefully to keep consistency in pairwise comparisons of adverse event in consistency model and publication bias test. In this manuscript, we finally chose to use risk ratio to analyze the results of adverse events.

Changes in the text: As you suggested, we have modified the RESULTS section and the supplementary file as follows (see Page 10-11, line 249-258 and supplementary file S4):

No potential publication bias was observed in the outcomes of adverse events and UACR (P = 0.497 and P = 0.602 for the Begg's test, P = 0.924 and P = 0.463 for the Egger's test respectively, see supplementary file S6 and S4) among the included studies but the publication bias was detected in the efficacy outcomes of eGFR. 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.

S4. Publication bias of funnel plot for adverse events.



RESULTS (Publication bias; minor concern):

Comment 12: The authors declared that "No potential publication bias was observed in the outcomes of adverse events…" in PAGE 8 LINE 197, but the statement is based on an underpowered test due to limited numbers of studies. In fact, actual publication bias may not be detected by limited evidence although Egger's test is non-significant. It is better to tone down the statement.

Reply 12: Thank you for your valuable comments and serious review. Indeed, the number of the studies included in this text is really small, thus the actual publication bias may not be able to be observed via Begg's test and Egger's test. Although publication bias was not detected in the outcomes of adverse events and UACR through Begg's test and Egger's test (P = 0.497 and P = 0.602 for the Begg's test, P = 0.924 and P = 0.463 for the Egger's test respectively), the funnel plots of these two outcomes were apparently asymmetric which indicated that publication bias may actually exist in this study. Therefore, we modified our text to tone down this statement as advised.

Changes in the text: According to your suggestion, we have modified the RESULTS section as follows (see Page 10-11, line 249-258):

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 supplementary files S4 and S5) 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 supplementary file S6). 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.

RESULTS (Publication bias; major concern):

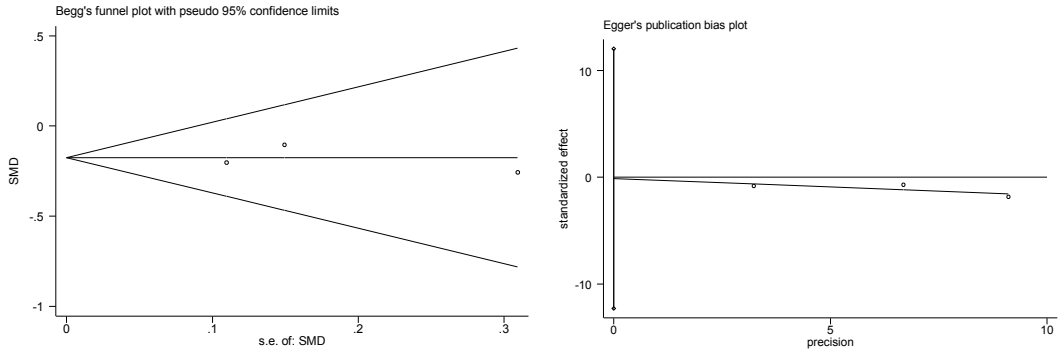
Comment 13: Another point about publication bias is that the author mentioned the publication bias behind pooled estimates of UACR and eGFR, while they did not provide any statistics. I encourage the authors to provide full information of the analyses in Supplementary.

Reply 13: Thank you for your valuable comments. As you suggested, we added the pooled results of the publication bias of UACR (P = 0.602 for the Begg's test and P = 0.463 for the Egger's test) and eGFR (P = 0.602 for the Begg's test and P = 0.041 for the Egger's test) in the RESULTS section and Supplementary. However, due to the limited number of the studies included in this text, the actual publication bias may not be able to be observed via Begg's test and Egger's test. So even though publication bias was not detected in the outcomes of UACR through Begg's test and Egger's test, the funnel plots of it were apparently asymmetric which indicated that publication bias may actually exist in this study. Therefore, further research is needed to assess the potential publication bias more accurately and achieve a more reliable conclusion.

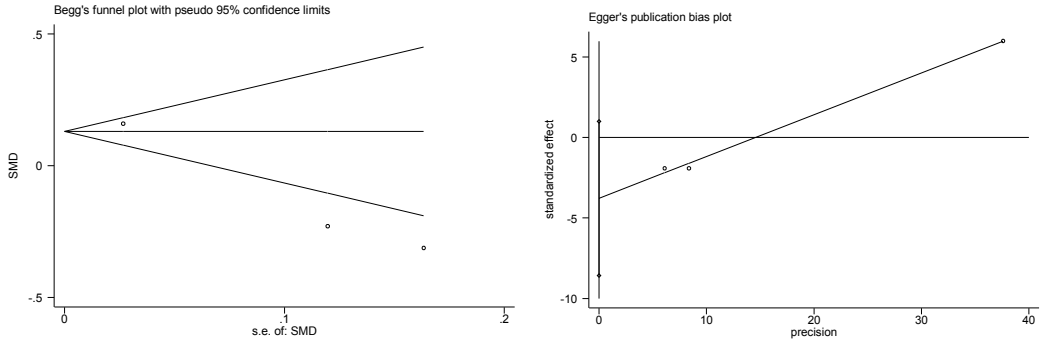
Changes in the text: We added the following content in the RESULTS section and supplementary file as advised (see Page 10, line 249-258 and supplementary file S5 and S6 and):

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 supplementary files S4 and S5) 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 supplementary file S6). 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.

S5. Publication bias of funnel plot for UACR.



S6. Publication bias of funnel plot for eGFR.



DISCUSSION (minor concern):

Comment 14: For clinical practice, readers may want to know how baseline treatments affect the effects of finerenone. If it is possible, the authors could discuss how effects of finerenone might vary with other medications.

Reply 14: Thank you for your valuable comments. According to your suggestion, we added some relevant content in the text in DISCUSSION section to further discuss how the effects of concomitant medications with finerenone might vary with other medications that are most commonly used by the patients included in this study and how effects of finerenone might vary with other mineralocorticoid receptor antagonists (MRAs).

Changes in the text: We added the following content in the text under the section of DISCUSSION as advised (see Page 13, line 314-327):

Current research has reported that compared with eplerenone, finerenone has a much better effect on preventing cardiac fibrosis and improving strain parameters in mice. Hence, future research on finerenone is necessary to explore its efficacy and safety versus 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. 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.

Reviewer B

Comment 1: In this meta-analysis, it has to be specified in the part of data analysis the method which was used to estimate the between−study variance and its uncertainty.

Reply 1: Thank you for your serious review and valuable comments. In this meta-analysis, we initially planned to use subgroup analysis and sensitivity analysis to estimate the potential sources of between-study variance (heterogeneity) and its uncertainty. However, owing to the limited number of included studies, subgroup analysis was not conducted finally. Heterogeneity across the trials was assessed using the I^2 statistic, Q statistic and tau-squared test, and $I^2 > 50$ % indicated significant heterogeneity. In this study, heterogeneity between the included studies was not observed in the outcomes of UACR and adverse events, whereas a high level of heterogeneity between studies was found in the outcome of eGFR (MD, -0.90 [95% CI, −3.84 to 2.04], P =0.55, I^2 =86% [95% CI, 68.5% to 95.9%], Chi^2 = 13.89, P =0 .0001, tau^2 =0.08 [95% CI, 0.01 to 3.54]). And then we apply a sensitivity analysis to further investigate the results of eGFR. We found that no between−study variance was observed and the results of eGFR were significantly changed (a significant difference was found in eGFR in finerenone group compared with placebo group) if one study (1) was excluded from analysis (MD, −2.32 [95% CI, −4.18 to −0.45], P =0.01, I^2 =0%, Chi^2 = 0.10, P =0.76, tau^2 =0). However, due to the limited number of included studies, future research is needed to further evaluate this outcome and achieve a more reliable result.

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Changes in the text: According to your suggestion, we have modified the METHODS section and the RESULTS section to further explain the method we used to estimate the between−study variance and its uncertainty (see Page 6, line 146-151 and Page 9, line 213-223):

Heterogeneity across the trials was assessed using the I^2 statistic, Q statistic and tau-squared test, and $I^2 > 50\%$ indicated significant heterogeneity. 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.

Three studies (n=5974) 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%], 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%, Chi^2 = 0.10, P =0.76, tau^2 =0). However, due to the limited number of included studies, further research is needed to achieve a more reliable result.

Comment 2: Techniques to assess publication bias such as the symmetry of funnel plots are not very reliable when less than 10 studies are combined.

Reply 2: Thank you for your serious review and valuable comments. As you pointed out, the methods we used to assess publication bias such as the symmetry of funnel plots in this text are not very reliable when less than 10 studies are combined. The Begg's test and Egger's test may not be suitable to pool the results of such a small sample. Publication bias may exist in this study without being detected. Therefore, we modified our text to tone down the statement of publication bias as advised. Future research is necessary to further investigate the potential publication bias among these clinical trials and achieve more reliable results.

Changes in the text: We have modified the RESULTS section to tone down our statements as advised (see Page 10, line 253-258):

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.

Comment 3: In small meta-analyses, heterogeneity statistic I2, is biased as well. The 95% confidence interval of the point estimate I2 and Q statistic had to be reported as well.

Reply 3: Thank you for your serious review and valuable comments. As you suggested, we used R software to calculate the 95% confidence intervals of these results and added the results of the point estimate of I^2, Q and tau^2 statistic into the test.

Changes in the text: We added the results of 95% confidence interval of the point estimate of I^2 and tau^2 statistic in the RESULTS section. The value of Q statistic is also added in the text as advised (see Page 8, line 200-201; Page 9, line 216-217 and Page 9, line 227):

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%], Chi^2 = 0.03, P = 0.98, tau^2 =0 [95% CI, 0 to 0.17]; Fig. 2A).

Three studies (n=5974) reported a change in eGFR in the patients with CKD. The results demonstrated that there was no significant difference in eGFR in finerenone group versus placebo group (MD, -0.90 [95% CI, −3.84 to 2.04], P =0.55).

Heterogeneity was observed between the included studies (I^2 =86% [95% CI, 68.5% to 95.9%], Chi^2 = 13.89, P =0 .0001, tau^2 =0.08 [95% CI, 0.01 to 3.54]) (Table 2).

Four studies (n=6039) 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%], Chi^2 = 0.47, P = 0.93, tau^2 =0 [95% CI, 0 to 0.05]; Fig.4A).

Comment 4: In introduction please explain more about the pathophysiological mechanism of fibrosis and inflammation driven by aldosterone leading to cardiorenal disease.

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Reply 4: Thank you for your valuable comments. As you suggested, we added some relevant content in INTRODUCTION section to further explain the pathophysiological mechanism through which aldosterone stimulates inflammation and fibrosis leading to cardiac and renal injury.

Changes in the text: We added the following content in the text under the section of INTRODUCTION as advised (see Page 4, line 93-99):

In addition to its effects on the kidney, aldosterone also has the potential to exert effects on the heart. Aldosterone can affect nonepithelial 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.

Reference

1. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. New England Journal of Medicine. 349 2020.