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REVIEW

Efficacy and safety of finerenone in chronic kidney disease associated with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials

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Abstract

Purpose The main objective was to evaluate the clinical efficacy and safety of finerenone in patients with CKD associated with T2D, especially with regard to renal and cardiovascular protection.

Methods Eight databases were searched. Mean difference (MD) with 95% confidence interval (CI) of the outcomes and risk ratio (RR) were calculated as the effect measure.

Results Four trials ($n=13{,}510$) were included. Compared to placebo groups, the urinary albumin-to-creatinine ratio (UACR) mean ratio, along with the proportion of patients with a decreased eGFR (≥ 40%) and end-stage kidney disease (ESKD), was significantly lower (*MD*: −0.30 (95% *CI*: −0.32, −0.28), $p<0.00001$; *RR*: 0.85 (95% *CI*: 0.78, 0.93), $p=0.0002$; *RR*: 0.80 (95% *CI*: 0.65, 0.99), $p=0.04$, respectively). Furthermore, the proportion of patients with cardiovascular events (CVs) was significantly lower (*RR*: 0.88 (95% *CI*: 0.80, 0.96), $p=0.003$). In terms of safety, while the increase in serum potassium concentration and the incidence of hyperkalemia were significantly higher in the finerenone groups (*MD*: 0.16 (95% *CI*: 0.07, 0.26), $p=0.00006$; *RR*: 2.03 (95% *CI*: 1.83, 2.26), $p<0.00001$, respectively), the all-cause mortality and the incidence of adverse events (AEs) were similar to placebo (*RR*: 0.90 (95% *CI*: 0.80, 1.00), $p=0.05$; *RR*: 1.00 (95% *CI*: 0.98, 1.01), $p=0.65$, respectively).

Conclusion The observed renal and cardiovascular benefits of finerenone were significant and did not cause unacceptable side-effects. Finerenone may represent a promising therapeutic tool for CKD associated with T2D.

Keywords Finerenone · Chronic kidney disease · Type 2 diabetes · Systematic review · Meta-analysis

Introduction

It has been reported that 40% of patients with diabetes mellitus (DM) eventually develop chronic kidney disease (CKD) [1], which leads to a three-fold higher risk of cardiovascular death [1–5]. However, to date, the treatment of CKD in patients associated with type 2 diabetes (T2D) is still challenging with regard to protecting the kidneys and reducing the risk of cardiovascular events (CVs) [4]. An increasing body of evidence indicates that pathophysiological overactivation of the mineralocorticoid receptor (MR) is important for both kidney and cardiovascular diseases via a mechanism that promotes oxidative stress, inflammation, and fibrosis [6–8]. Steroidal mineralocorticoid receptor antagonists (MRAs), including the first-generation spironolactone and the second-generation eplerenone, have been strongly recommended for patients with CKD and chronic heart failure (CHF) [9–11]. As a non-steroidal third-generation MRA, finerenone (BAY 94–8662), which has greater selectivity for the MR over other steroid hormone receptors such as spironolactone and also has improved affinity for MR when compared to eplerenone while maintaining very low affinity for the glucocorticoid, progesterone, and androgen receptors,

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thus reducing off-target side effects such as gynecomastia and irregular menstruation [12–14]. In addition, finerenone also reduces cofactor recruitment to the MR, thereby reducing the downstream expression of pro-inflammatory and pro-fibrotic factors following MR overactivation [15]. Furthermore, comparative pre-clinical studies have revealed the favorable properties of finerenone with regard to cardiorenal end-organ protection [16]. Thus, finerenone may effectively address the unmet medical need for kidney and cardiovascular protection in patients with CKD and T2D.

The Food and Drug Administration (FDA) in the USA has approved finerenone to reduce the risk of kidney function decline, kidney failure, cardiovascular death, non-fatal heart attacks, and hospitalization for heart failure in adults with chronic kidney disease associated with T2D [17]. The current meta-analysis was to validate the efficacy and safety of finerenone for CKD associated with T2D based on randomized controlled trials (RCTs), thus providing more comprehensive evidence for supporting its clinical application.

Materials and methods

This review complies with the PRISMA 2020 statement [18, 19] (Supplementary Table 1).

Search strategy

We comprehensively searched the PubMed, Embase, Cochrane Library, ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI), WanFang and Chongqing VIP Information databases, and SinoMed, from inception until August 2022 for RCTs investigating the utility of finerenone for CKD associated with T2D in adults. We also searched the reference lists of all identified publications to identify further studies (Supplementary Table 2).

Inclusion 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 — patients with CKD associated with T2D, and (IV) outcome — assessment of at least one of the following outcomes: (i) kidney outcomes — urinary albumin-to-creatinine ratio (UACR) mean rario from baseline, change in estimated glomerular filtration rate (eGFR), proportion of patients with ≥ 40% decrease in eGFR post-baseline, incidence of end-stage kidney disease (ESKD); (ii) cardiovascular outcomes — incidence of CVs; and (iii) changes in serum potassium concentration, incidence of hyperkalemia, all-cause mortality, and adverse events (AEs).

Data extraction

Two reviewers (MZ and WB) extracted data from the original trials independently. Study characteristics (first author, publication year, location, sample size, intervention and control, period of treatment, duration of follow-up, and phase of clinical trial), characteristics of the patients (inclusion criteria, mean age, proportion of men, baseline eGFR, and baseline UACR), reported outcomes (UACR, eGFR, ESKD, CV events, serum potassium concentration, hyperkalemia, all-cause mortality, AEs), and information relating to methodology were extracted.

Quality assessment

The risk of bias was assessed by two investigators (WB and MZ) independently, using the Cochrane Collaboration's tool. If necessary, any disagreement was resolved by consensus with a third author (NL). In addition, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was employed to evaluate the quality of evidence contributing to each estimate [20]. And the tool GRADEpro (www.gradepro.org) was used to evaluate all outcome indicators.

Statistical analysis

Data entry and analysis were conducted using Microsoft Excel (Microsoft, Redmond, WA, USA) and ReviewManager (RevMan) 5.4.1. Mean difference (MD) with 95% confidence interval (CI) of the outcomes and risk ratio (RR) were calculated as the effect measure. The I^2-statistic was calculated for heterogeneity, as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity. A fixed-effects model was chosen if $I^2 < 50\%$; otherwise, the random-effects model was used. Subgroup or sensitivity analysis was conducted to explore the underlying causes of heterogeneity in treatment outcomes. Accordingly, publication bias was only examined if > 10 comparative studies were included for analysis [20]. Upon the inclusion of several subgroups for analysis (finerenone dose ≥ 10 mg/d), outcomes were pooled. In cases where standard deviations of UACR, eGFR, or serum potassium concentration could not be directly obtained from the trials, we estimated means and deviations from the CI [20].

Results

Study characteristics

Following our search, we identified 295 relevant articles. Of these, 92 were duplicated. Subsequently, 203 titles and

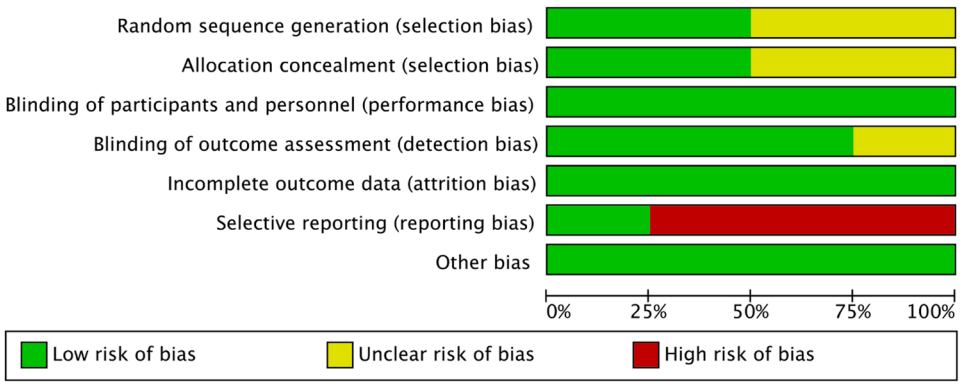

Fig. 1 Risk of bias graph: data for each risk-of-bias item presented as percentages across all included studies

abstracts were screened, with 5 articles for full-text screening. Finally, 4 eligible studies [4, 21–23] (13,510 participants) were included in our analysis of the efficacy and safety of finerenone for CKD associated with T2D. Supplementary Fig. 1 shows the screening process and Supplementary Table 3 presents the main characteristics of the included RCTs. All trials reported the clinical benefits of finerenone and AEs in patients with CKD associated with T2D.

Evaluation of the risk of bias for selected studies

None of the RCTs had an overall low risk of bias. All RCTs [4, 21–23] were categorized as low risk of bias for the blinding of participants and personnel as well as for incomplete outcome data and other items. Three RCTs [4, 21, 23] had a high risk of reporting bias for selective reporting, since some outcomes mentioned in a pre-specified analysis plan were not reported. Two RCTs [4, 23] had an unclear selection risk of bias for sequence generation and allocation concealment. One RCT [22] had an unclear selection risk of bias for the blinding of outcome assessment. The risks of bias assessments for the included trials are shown in Fig. 1.

Meta-analysis

UACR mean ratio from baseline

Four trials [4, 21–23] compared the mean ratio of UACR between finerenone ($n = 6618$) and placebo ($n = 6308$) in groups of patients with CKD associated with T2D. The UACR mean ratio from baseline was significantly lower in the finerenone group than that of placebo group (*MD*: −0.30, 95% *CI*: (−0.32, −0.28), $p < 0.00001$) (Fig. 2).

Changes in eGFR from baseline

Three trials [21–23] compared eGFR values between finerenone ($n = 3094$) and placebo ($n = 2826$) in groups of patients with CKD associated with T2D. The decrease

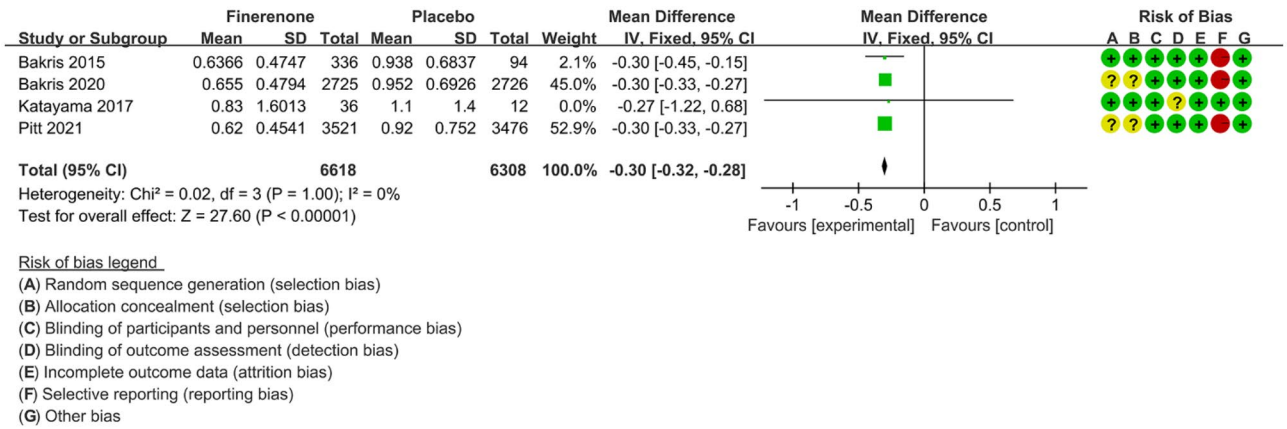

Fig. 2 Meta-analysis results of mean ratio of UACR from baseline for finerenone and placebo patient groups

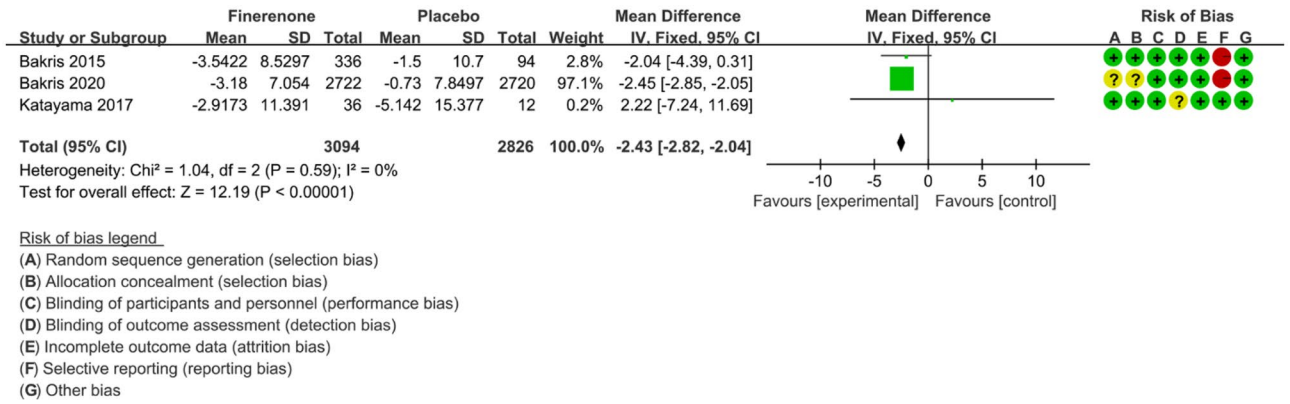

Fig. 3 Meta-analysis results of changes in eGFR from baseline for finerenone and placebo patient groups

in eGFR from baseline within 4 months was significantly higher with finerenone than for placebo (MD: −2.43 (95% *CI*: −2.82, −2.04), $p < 0.00001$) (Fig. 3).

Proportion of patients with ≥ 40% decrease in eGFR

Three trials [4, 21, 23] compared the proportion of patients showing a ≥ 40% decrease in eGFR from baseline between the finerenone ($n = 6852$) and placebo ($n = 6600$) groups. The proportion of patients was significantly lower for the finerenone groups than the placebo treatment groups (*RR*: 0.85 (95% *CI*: 0.78, 0.93), $p = 0.0002$) (Fig. 4).

Proportion of patients with ESKD

Two trials [4, 23] compared the proportion of patients with ESKD following treatment with finerenone ($n = 6519$) *versus* placebo ($n = 6507$). Overall, there was a significantly lower proportion of patients with ESKD in the finerenone groups than in the placebo groups (*RR*: 0.80 (95% *CI*: 0.65, 0.99), $p = 0.04$) (Fig. 5).

Proportion of patients with CVs

The proportion of patients with CVs between groups treated with finerenone ($n = 6861$) *versus* placebo ($n = 6604$) was compared in three trials [4, 21, 23] and it was significantly lower in the finerenone groups than in the placebo groups (*RR*: 0.88 (95% *CI*: 0.80, 0.96), $p = 0.003$) (Fig. 6).

Changes in serum potassium concentrations

Four trials [4, 21–23] compared changes in the serum potassium levels in finerenone-treated ($n = 6735$) *versus* placebo ($n = 6469$) groups of patients with CKD associated with

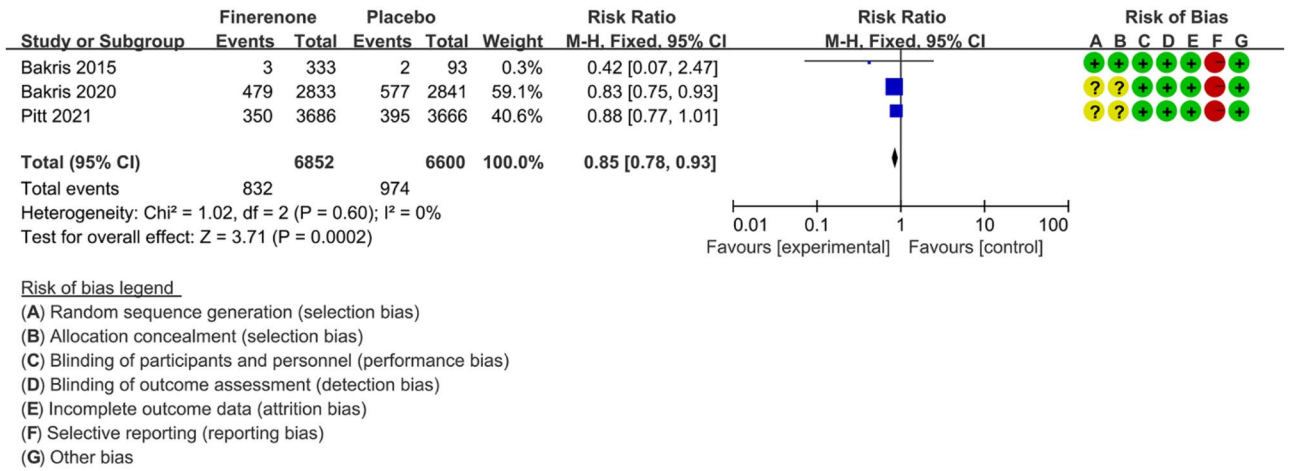

Fig. 4 Meta-analysis results of the proportion of patients with ≥ 40% decrease in eGFR in finerenone versus placebo patient groups

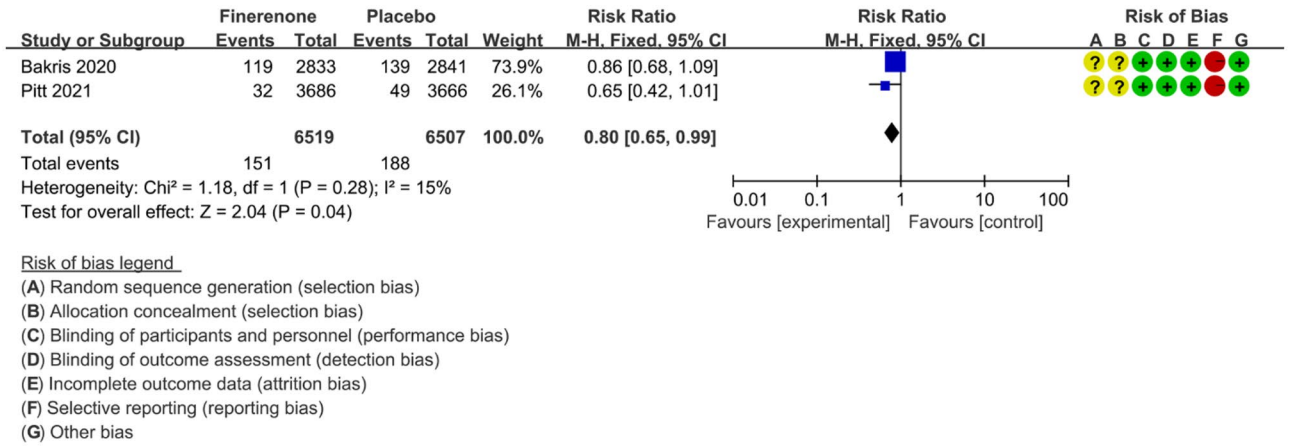

Fig. 5 Meta-analysis results of the efficacy of finerenone versus placebo for ESKD

T2D. The increase in serum potassium was significantly higher in the finerenone groups than in the placebo groups (*MD*: 0.16 (95% *CI*: 0.07, 0.26), $p = 0.0006$) (Fig. 7).

Proportion of patients with hyperkalemia

The proportion of patients with hyperkalemia in finerenone ($n = 6852$) *versus* placebo ($n = 6583$) groups was compared in three trials [4, 21, 23], and it was significantly higher in the finerenone groups than the placebo groups (*RR*: 2.03 (95% *CI*: 1.83, 2.26), $p < 0.00001$) (Fig. 8).

All-cause mortality

The all-cause mortality in finerenone ($n = 6555$) *versus* placebo ($n = 6519$) groups was compared in three trials [4, 22, 23], and there was no significant difference in all-cause mortality between the finerenone and placebo groups (*RR*: 0.90 (95% *CI*: 0.80, 1.00), $p = 0.05$) (Fig. 9).

Proportion of patients with AEs

Four trials [4, 21–23] compared the proportion of patients with AEs in finerenone ($n = 6888$) *versus* placebo ($n = 6595$) groups. Overall, there was no significant difference in incidence of AEs between the finerenone and placebo groups (*RR*: 1.00 (95% *CI*: 0.98–1.01), $p = 0.65$) (Fig. 10).

Certainty of evidence

The quality of evidence was downgraded for risk of bias and upgraded for large effect. Following comprehensive analysis,

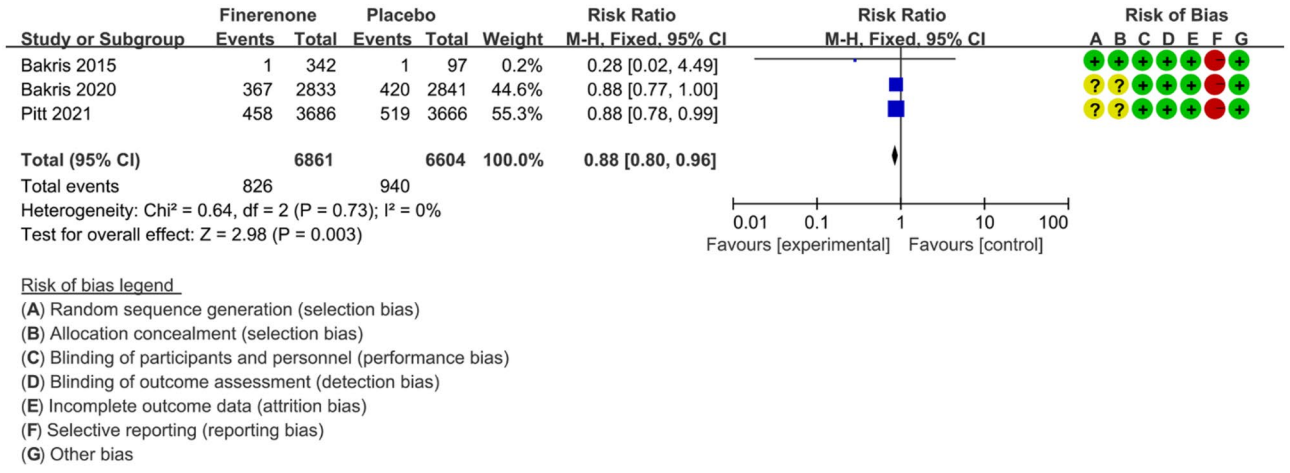

Fig. 6 Meta-analysis results of the effect of finerenone versus placebo on CVs

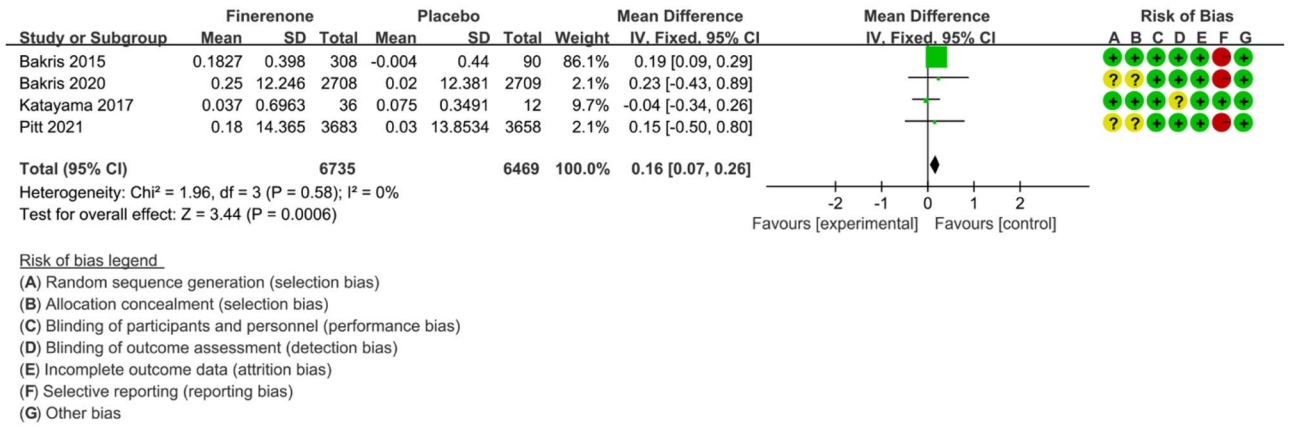

Fig. 7 Meta-analysis results of changes in serum potassium concentration between finerenone and placebo patient groups

we generated a summary of findings table which showed that all outcome indicators were of moderate quality or high quality (Supplementary Table 4).

Publication bias

Publication bias was not examined because all outcome indicators were observed in less than 10 studies.

Discussion

The "Kidney Disease: Improving Global Outcomes (KDIGO)" 2020 Clinical Practice Guideline [24] suggests that patients with diabetes, hypertension, and albuminuria (UACR > 30 mg/g) should receive renin-angiotensin system (RAS) inhibitors including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor II blockers (ARB) at the maximal tolerated dose, with close monitoring of serum potassium and serum creatinine levels within 2 to 4 weeks of initiation of when the dose is changed. Eligible patients in all four trials were treated with RAS inhibitors. In addition, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) [23] and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) [4] trials included patients who received an ACE inhibitor or ARB at the maximum dose on the manufacturer's label that did not cause unacceptable side effects, plus well-controlled glycated hemoglobin and BP levels, thereby addressing the problems that needed to be corrected to meet the predefined endpoints [6].

In the current meta-analysis, we pooled data for which the dose of finerenone was at least 10 mg/day to optimize potential effects [25]. With regard to kidney outcomes,

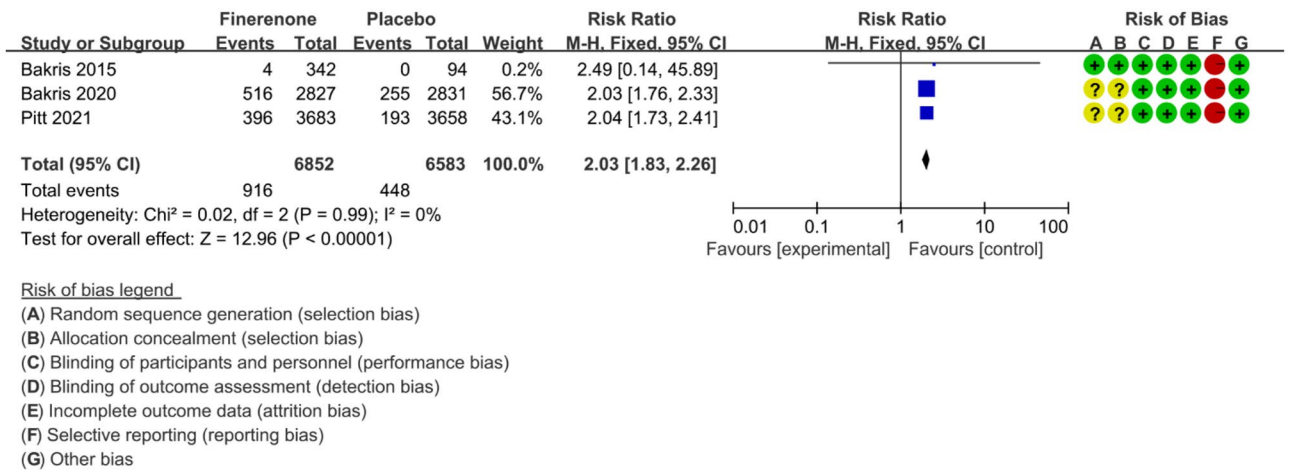

Fig. 8 Meta-analysis results of hyperkalemia in finerenone compared to placebo patient groups

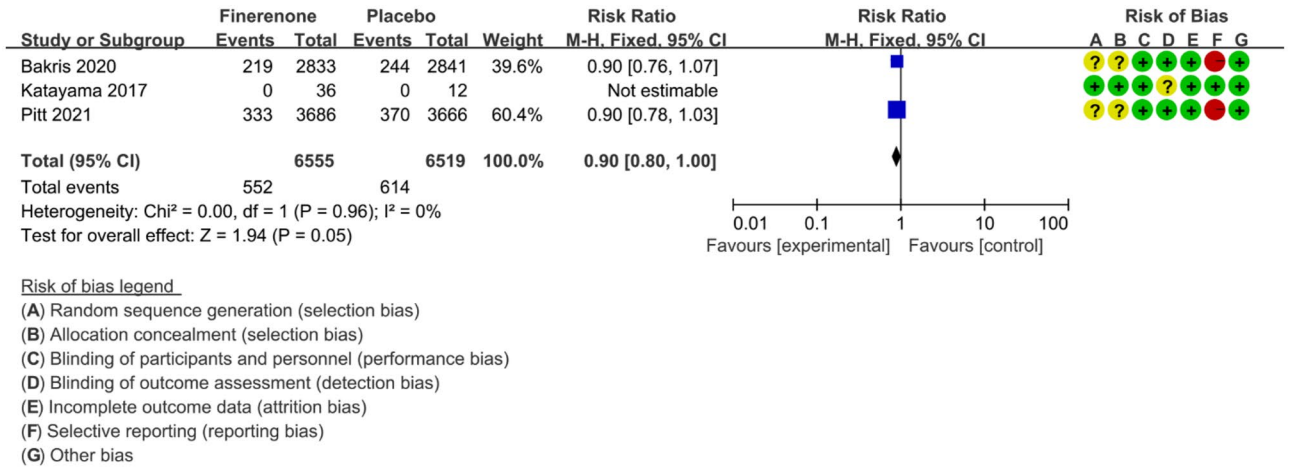

Fig. 9 Meta-analysis results of all-cause mortality in finerenone compared to placebo patient groups

changes in albuminuria are strongly and consistently associated with the risk of ESRD and death in patients with and without DM [26]. We found that the UACR mean ratio from baseline decreased significantly in the finerenone groups comparing with the placebo groups for patients with CKD associated with T2D. Although our meta-analysis found that changes in eGFR from baseline were reduced significantly in the finerenone groups when compared to placebo groups within 4 months, the FIDELIO-DKD trial showed that eGFR decreased more slowly with finerenone than placebo after 4 months, and the reduction in eGFR was smaller with finerenone after approximately 26 months [23]. In addition, a reduction in eGFR by 30 to 40% may be a reliable marker of reduced CKD progression in interventional studies [7]. Our data showed that the relative risk of a sustained ≥ 40% decrease in eGFR was reduced by 15% while that for ESKD was reduced by 20%. These results indicate that finerenone may provide long-term renal benefits for CKD and T2D patients. With regard to cardiovascular outcomes, the proportion of patients with CVs was significantly lower for finerenone than placebo; this was inconsistent with the FIDELITY pooled analysis [27]. Furthermore, the increase in serum potassium concentration and the incidence of hyperkalemia were significantly higher in the finerenone group. The all-cause mortality and the incidence of AEs was similar when compared between the groups. All outcome indicators were of moderate quality or high quality.

The renoprotective effects of finerenone are mediated by its anti-inflammatory, antifibrotic, and antioxidative actions [7]. Finerenone controls inflammation by increasing the polarization of M2 macrophages; these are anti-inflammatory macrophages that promote efficient tissue repair and reduce

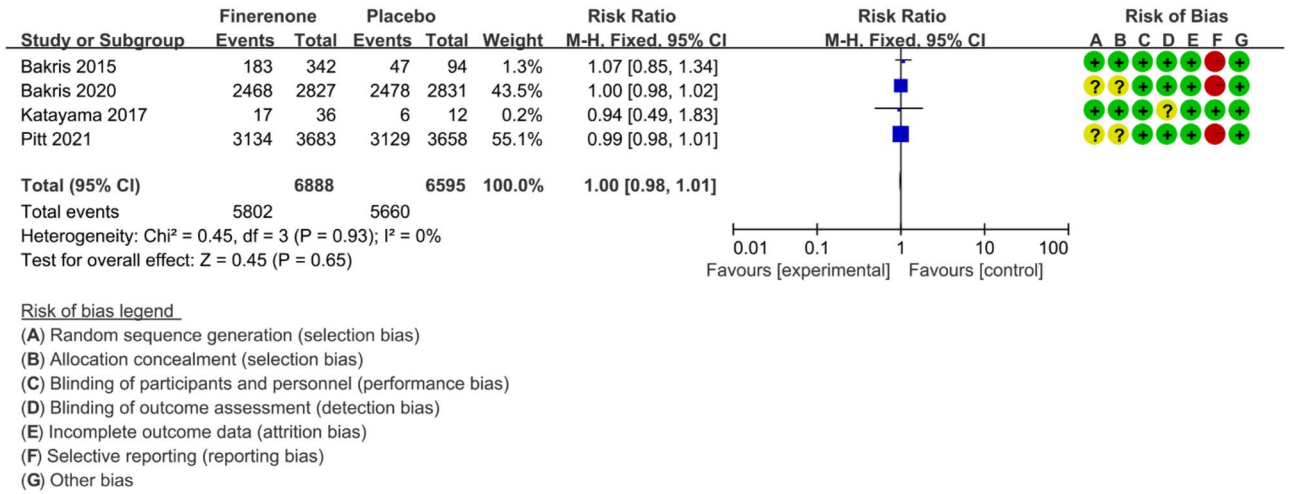

Fig. 10 Meta-analysis results of AEs in finerenone compared to placebo patient groups

the level of fibrosis by interleukin (IL-4) receptor signaling [28]. In addition, finerenone has direct anti-fibrotic properties that result in reduced myofibroblast and collagen deposition, accompanied by a reduction in renal plasminogen activator inhibitor (PAI-1) and naked cuticle 2 (NKD2) expression in a mouse model [29]. Finerenone has additionally been shown to exhibit antioxidative effects by enhancing nitric oxide (NO) bioavailability and improving superoxide dismutase (SOD) activities to improve endothelial dysfunction [30]. Rats treated with finerenone exhibited significantly less extensive tubular injury and kidney injury molecule-1 and neutrophil gelatinase associated to lipolacin levels, thus implying that finerenone can delay the progression of kidney injury [31]. The results of these studies are consistent with the findings of our meta-analysis and indicate that finerenone may have long-term renal benefits for patients with CKD and T2M.

Radio-labeled finerenone shows balanced accumulation between the kidneys and the heart [16]. Further analysis showed that finerenone reduced the risk of clinically important cardiovascular outcomes in patients with CKD and T2D, regardless of pre-existing cardiovascular disease status [4, 27, 32]. Preclinical studies have also demonstrated the anti-fibrotic myocardial effects of finerenone. Treatment with finerenone reduced the expression levels of connective tissue growth factor (CTGF) and completely prevented the aldosterone-induced upregulation of CTGF and lysyl oxidase (LOX), thus implying that finerenone prevented MR-mediated structural remodeling in cardiac fibroblasts [33]. Over the long-term, finerenone reduced both left ventricular (LV) systolic and diastolic diameters, associated with reductions in LV weight and LV collagen density in a rat model of metabolic syndrome [34]. Finerenone reduced cardiac hypertrophy and the levels of plasma prohormone of brain natriuretic peptide (pro-BNP) more efficiently than eplerenone [16]. In addition, finerenone treatment reduced intrinsic arterial stiffness in the mesenteric arteries (MA) of Munich Wistar Frömter (MWF) rats; this effect was associated with changes in elastin organization, the normalization of matrix metalloproteinase (MMP)-2 and MMP-9 activities, and a reduction of oxidative stress. Moreover, a reduction of arterial stiffness was previously shown to correlate with a reduction in albuminuria [35]. Notably, it appears that finerenone has a relatively weak effect on blood pressure (BP). In the Alocorticoid Receptor antagonist Tolerability Study (ARTS) trial, the reductions of systolic BP were significantly smaller in the finerenone group (the dose of 10 mg daily: mean ± standard deviation, − 4.2 ± 15.5 mmHg) than in the spironolactone group (the mean dose of 37 mg daily: − 10.1 ± 15.0 mmHg) [36]. Due to the limited studies on BP, the actual antihypertensive effect of finerenone should be further investigated [34].

The increased risk of hyperkalemia may limit the therapeutic use of steroidal MRAs in patients treated with RAS inhibitors [37] and the non-steroidal MRA finerenone is independently associated with hyperkalemia [38]. However, it has been suggested that the balanced heart-relative-to-kidney distribution of finerenone in rodent models may confer a lower risk of electrolyte disturbance, such as hyperkalemia, in clinical research [16, 36]. In addition, results from the pooled analysis of data from the FIDELIO-DKD and FIGARO-DKD trials observed discontinuation rates due to hyperkalemia of 1.7% with finerenone when compared to 0.6% for the placebo, and FIGARO-DKD reported the incidence of serum potassium lev el > 5.5 mmol·L^{-1}/6.0 mmol·L^{-1} was 13.5%/2.3% with finerenone when compared to 2.3%/1.2% for the placebo, which was within the acceptable range [4, 23]. Moreover, the present meta-analysis showed that finerenone increased the serum potassium level by 0.16 mmol/L, and the all-cause mortality and the incidence of AEs were similar between two groups. Routine potassium monitoring and hyperkalemia management strategies might minimize the impact of hyperkalemia, thus providing a basis for the clinical use of finerenone [38].

In general, the comprehensive management of CKD associated with T2D depends on multi-factorial treatment, mainly including strict glycemic and blood pressure control [28, 39–41]. With regard to the agents of choice for the management of hypertension, the blockade of RAS has become an established treatment with which to slow the progression of DKD and reduce CVs [42, 43]. Our meta-analysis suggests that the combination of finerenone with a RAS blocker confers significant benefits for patients with CKD associated with T2D. As 2020 KDIGO Clinical Practice Guideline required, glycemic management for patients with T2D, CKD, and an eGFR ≥ 30 ml/min/1.73 m^2 should include lifestyle therapy, first-line treatment with metformin and sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2i), and additional drug therapy for glycemic control [3]. The administration of SGLT2i results in favorable effects on several biomarkers, including glycemia, blood pressure, weight [44], intrarenal hemodynamics, and albuminuria, [45] and may also reduce the risk of serious cardiovascular complications, kidney disease, and death [46, 47]. In addition, finerenone could improve glucose tolerance by increasing the functionality of interscapular brown adipose tissue (iBAT) by activating the adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)-adipose triglyceride lipase (ATGL)-uncoupling protein (UCP)-1 signaling pathway [48]. Recently, researchers attempted to investigate how the combination of finerenone and empagliflozin works and how safe this treatment is when compared to each treatment alone in adult participants with long-term kidney disease (CKD) and T2D (NCT05254002) is under conducted; more research is expected to provide evidence relating to the efficacy and safety of finerenone when combined with SGLT2i for CKD associated with T2D.

There are several limitations that should be considered. Firstly, our study was limited by the small number of studies; two of the four trials included trials were relatively small, accounting for 4% (484/13,510) of the total sample size.

Secondly, the control intervention in this meta-analysis only included placebo and no data were extracted from studies with positive drug controls. Further research is also expected to provide evidence regarding the efficacy and safety of finerenone compared with positive drug treatment.

Conclusions

Our meta-analysis suggests that finerenone confers significant renal and cardiovascular benefits for CKD and T2D. Although a higher risk of hyperkalemia was observed with finerenone than placebo, the discontinuation rates due to hyperkalemia were infrequent. Importantly, in terms of the all-cause mortality and AEs, there is no significant differences between the finerenone and placebo group. Finerenone plays a role in renal and cardiovascular protections significantly and did not cause unacceptable side-effects. Our findings support the administration of finerenone as a novel promising therapeutic agent for patients with CKD associated with T2D.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-022-03408-w.

Author contribution All authors contributed to the conception, search terms and methodology of the review. MZ, WB, and LS came up with the study idea. MZ, WB, and LS designed the study. MZ and WB completed the database searches and study selection. MZ, WB, and NL completed the assessment of bias of the included studies. MZ and WB extracted data from the included studies. MZ and WB completed the meta-analyses. MZ and WB wrote the first draft of the manuscript. MZ, WB, NL, ZY, and LS completed the critical revision of the manuscript. All authors contributed to the writing or revision of the final manuscript. And all authors have read and approve the final version submitted to this journal.

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Availability of data and material The data that support the findings of this study were sourced directly from the published studies included in this systematic review and meta-analysis.

Declarations

Ethical Approval This study was exempt from full ethical approval by an institutional review board, as no original data was included. There were no interactions with any human or animal participants across the duration of this study.

Consent to participate Not applicable.

Competing interests The authors declare no competing interests.

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