Efficacy and Safety of Novel Non-steroidal Mineralocorticoid Receptor Antagonist Finerenone in the Management of Diabetic Kidney Disease: A Meta-analysis

Deep Dutta, Vineet Surana[1], Saptarshi Bhattacharya[2], Sameer Aggarwal[3], Meha Sharma[4]

Departments of Endocrinology and [4]Rheumatology, CEDAR Superspeciality Healthcare, Dwarka, New Delhi, [1]Department of Endocrinology, Manipal Hospitals, New Delhi, [2]Department of Endocrinology, Max Hospitals, Patparganj, New Delhi, [3]Department of Endocrinology, Apex Hospitals, Rohtak, Haryana, India

Abstract

Background: Data are scant on use of finerenone in diabetic kidney disease (DKD). We undertook this meta-analysis to address this knowledge gap. **Methods:** Electronic databases were searched for randomized controlled trials (RCTs) involving diabetes patients receiving finerenone compared to controls. The primary outcome was changes in urine albumin-creatinine ratio (UACR). Secondary outcomes were time to kidney failure (decline in GFR by >40% from baseline over 4 weeks), time to end-stage kidney disease, hospitalization for any cause, death and adverse events reported. **Results:** From initially screened 79 articles, data from 7 RCTs involving 13,783 patients were analyzed (3 in active control group [ACG] defined as having eplerenone/spironolactone as active comparator; 4 in passive control group [PCG] defined as having placebo as controls). Patients receiving finerenone had greater percentage lowering of UACR from baseline as compared to PCG [MD23.82% (95%CI: –24.87 to –22.77); $P < 0.01$; $I^2 = 96\%$] at 90 days, after 2 years [MD 37.9% (95%CI: –38.09 to –37.71); $P < 0.01$] and 4 years [MD 25.20%(95%CI: –25.63 to –24.77);$P < 0.01$] of treatment. Patients receiving finerenone has lower chance of >40% decline in GFR (OR 0.83 [95%CI: 0.75 to 0.92];$P < 0.01$; $I^2 = 0\%$). Patients receiving finerenone had lower occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure, as compared to placebo/eplerenone (OR0.86 [95%CI: 0.78 to 0.95]; $P = 0.003$; $I^2 = 0\%$). TAEs was similar (RR0.97 [95%CI: 0.88–1.07]; $P = 0.56$; $I^2 = 0\%$), but SAEs significantly lower (RR0.91 [95%CI: 0.84 to 0.97]; $P < 0.01$; $I^2 = 0\%$) in finerenone-group compared to controls. **Conclusion:** This meta-analysis provides reassuring data on beneficial impact of finerenone in reducing UACR and GFR decline as compared to placebo. We still lack head-to-head comparison of renal outcomes of finerenone vs eplerenone/spironolactone in DKD.

Keywords: Chronic kidney disease, finerenone, meta-analysis, safety, type-2 diabetes

Introduction

Even after maximal blockade of the renin-angiotensin system (RAS) with an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB), along with the synergistic benefits of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, patients with diabetic kidney disease (DKD) often continue to have residual risk, associated with progression of proteinuria and kidney disease progression.[1] Overactivation of the mineralocorticoid receptor (MR) has been shown to have an independent role in the progression of kidney disease along with cardiovascular disease in people living with diabetes, primarily through increased inflammation and fibrosis.[2] MR antagonism has been shown to reverse some of these pathophysiologic changes at the level of kidneys and heart in animal models.[3] The classical mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone are commonly used in patients with heart failure in addition to ACEIs)/ARBs and beta-blockers to improve cardiovascular outcomes, especially reduce the need for hospital admission and mortality.[4] The

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.ijem_376_21

Address for correspondence: Dr. Deep Dutta, Center for Endocrinology, Diabetes, Arthritis and Rheumatism (CEDAR) Super-speciality Healthcare, Dwarka, New Delhi - 110075, India.
E-mail: deepdutta2000@yahoo.com

Submitted: 21-Aug-2021 **Revised:** 20-Oct-2021
Accepted: 26-Nov-2021 **Published:** 29-Apr-2022

How to cite this article: Dutta D, Surana V, Bhattacharya S, Aggarwal S, Sharma M. Efficacy and safety of novel non-steroidal mineralocorticoid receptor antagonist finerenone in the management of diabetic kidney disease: A meta-analysis. Indian J Endocr Metab 2022;26:198-205.

anti-fibrotic properties of spironolactone have also been found to be useful in reducing portal hypertension in people with chronic liver disease.[5] Common side effects which often limit the use of the above steroidal MRAs include risk of hyperkalemia, renal function deterioration, suppression of male hormone levels leading to gynecomastia in males, and menstrual irregularities in females.[6]

This necessitated the development of a novel non-steroidal selective MRA, finerenone to overcome the inherent limitations of steroidal MRAs. Finerenone has better selectivity than spironolactone and better affinity than eplerenone for mineralocorticoid receptor (MRs), with low affinity of androgen receptor (ARs), progestogen receptor (PRs) and glucocorticoid receptors (GRs).[7] Finerenone's selectivity for MRs is >500 times as compared to ARs, PRs and GRs, thus minimizing the associated side effects.[7] Unlike spironolactone and eplerenone, which have predominant renal effects, finerenone is believed to have equal renal and cardiac effects.[8] Finerenone has been shown to have a more potent anti-inflammatory and antifibrotic effects than steroidal MRAs in preclinical studies.[9] In a meta-analysis published in 2018 involving people living with heart failure, finerenone was shown to have a beneficial impact on reducing circulating levels of NT-proBNP and other surrogate measures of heart failure.[8] A decline in urinary albumin/creatinine ratio (UACR) was also noted in this study.[8] Since then several randomized controlled trials (RCTs) have been published evaluating the role of finerenone in DKD.[10,11] Finerenone has shown to reduce urine albumin excretion with smaller effects on serum potassium as compared to spironolactone.[8] Data are scant on the clinical efficacy and safety of novel non-steroidal MRA in DKD. Hence the aim of this meta-analysis was to evaluate the efficacy and safety of finerenone in DKD.

Methods

Methodology

The meta-analysis was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[12] The predefined protocol has been registered in PROSPERO having Registration number of CRD42021269052. All randomized controlled trials (RCTs) published till August 2021 were considered for this meta-analysis. This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[12]

The PICOS criteria were used to screen and select the studies for this meta-analysis with patients (P) being people with DKD; intervention (I) being use of finerenone for managing DKD; control (C) being patients either on placebo or any other approved medication for managing DKD; outcomes (O) being evaluated were impact on urine ACR, electrolytes and any adverse effects noted; and (S) being studies included which were RCTs. DKD is different studies have been defined as people living with diabetes either having microalbuminuria (urine ACE 30-300 mg/gm) or macroalbuminuria (urine ACR > 300 mg/gm) and/or GFR < 90 ml/min/1.73 m^2.[10,11] Only patients with type-2 diabetes (T2DM) with chronic kidney disease also known as DKD were considered for this meta-analysis. Patients with other forms of diabetes were excluded. Only those studies were included in this meta-analysis which had at least 2 treatment arms/groups, with one of the groups having patients with DKD on finerenone either alone or a part of standard DKD treatment regimen and the other arm/group receiving either placebo or any other medication in place of finerenone, either alone or as a part of standard DKD treatment regimen.

The primary outcome was to evaluate changes in urine ACR. Secondary outcomes were to evaluate time to kidney failure (defined as decline in GFR by >40% from baseline over at least 4 weeks), time to development of end-stage kidney disease (ESRD) defined as need for renal replacement therapy (RRT) for >90 days or eGFR <15 ml/min/1.73 m^2, doubling of serum creatinine, hospitalization for any cause, death due to any cause, adverse events reported, hypoglycemia and glycemic parameters. Analysis of renal outcomes was done based on whether the control group received an active comparator (any other MRAs like spironolactone or eplerenone) – labeled here as the active control group (ACG) or a placebo/any other medication – labeled as passive control Group (PCG).

Search method for identification of studies

Detailed electronic databases of Medline (Via PubMed), Embase (via Ovid SP), Cochrane central register of controlled trials (CENTRAL) (for trials only), ctri.nic.in, clinicaltrials.gov, global health, and Google scholar were searched using a Boolean search strategy: (finerenone) AND (diabetes).

Data extraction and study selection

Data extraction was carried out independently by two authors using standard data extraction forms. Details have been elaborated elsewhere.[13] Patient characteristics of the included studies are elaborated in Table 1.

Assessment of risk of bias in included studies

Three authors independently assessed the risk of bias using the risk of bias assessment tool in Review Manager (Revman), version 5.3 (The Cochrane Collaboration, Oxford, UK 2014) software. Selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias were looked for. Details have been elaborated elsewhere.[13]

Measures of treatment effect

For continuous variables, the outcomes were expressed as mean differences (MD). For dichotomous outcomes results were expressed as risk ratios (RR) with 95% confidence intervals (CI). For adverse events, results were expressed as post-treatment absolute risk differences. RevMan 5.3 was used for comparing MD of the different outcomes.

Assessment of heterogeneity

Heterogeneity was initially assessed by studying the forest plot generated for the outcomes. Subsequently, heterogeneity was

Table 1: Characteristics of patients in the different randomized controlled trials evaluated in this meta-analysis on use of finerenone in diabetic kidney disease

Study details	Number of patients	Patient characteristics and nature of controls	Duration of study
Bakris 2015[10]	821	Phase-2 RCT; type-2 diabetes (T2DM) with diabetic kidney disease (DKD); baseline GFR was 67.9±21.9 ml/min/1.73 m^2; baseline HbA1c was 7.6±1.3%	90 days
Bakris 2020[17]	5674	Phase-3 RCT; T2DM with DKD; baseline GFR was 44.3±12.4 ml/min/1.73 m^2; baseline HbA1c was 7.7±1.35%	30 months
Filippatos 2016[19]	1066	Phase-2 RCT; T2DM with DKD with heart failure with reduced ejection fraction; baseline GFR was 53.4±10.13 ml/min/1.73 m^2	90 days
Katayama 2017[11]	96	Phase-3 RCT; T2DM with DKD; baseline GFR was 64.1±12.1 ml/min/m^2; baseline HbA1c was 7.23±0.88%	90 days
Pitt 2013[18]	457	Phase-2 RCT; T2DM with DKD along with heart failure with reduced ejection fraction; baseline GFR was 51.1±9.92 ml/min/1.73 m^2	30 days
Pitt 2021[20]	7437	Phase-3 RCT; T2DM with DKD; baseline GFR was 67.8±21.7 ml/min/1.73 m^2	3.4 years
Sato 2016[16]	72	Phase-2 Japanese RCT; T2DM with DKD with heart failure with reduced ejection fraction; baseline GFR was 44.9.4±11.45 ml/min/1.73 m^2	90 days

T2DM: type-2 diabetes; GFR: glomerular filtration rate

analyzed using a χ^2 test on N–1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test.[14,15] Details have been elaborated elsewhere.[13]

Data synthesis

Data was pooled as random-effects model for the analysis of outcomes. Forrest plots were plotted with the left side of graph favoring finerenone and the right side of graph favoring control using RevMan 5.3 software.

Results

A total of 79 articles were found after the initial search [Figure 1]. Following the screening of the titles, abstracts, followed by full-texts, the search was reduced down to 21 studies that were evaluated in detail for inclusion in this meta-analysis [Figure 1]. Seven RCTs in people with DKD which fulfilled all criteria were analyzed in this meta-analysis.[10,11,16-20] The paper by Filippatos *et al.*[21] was *post hoc* analysis of original RCT by Bakris *et al*.[10] Hence the results of study by Filippatos *et al.*[21] have been analyzed with results of Bakris *et al.*[10] in this meta-analysis to avoid patient duplication.

In some of the RCTs, different doses of finerenone were evaluated ranging from 1.25 mg/day to 20 mg/day. For this meta-analysis, outcomes patients receiving finerenone 10 mg/d were compared to controls. Finerenone 10 mg/d dose for used for analysis as it was the most commonly used dose among all the 6 RCTs. Of the 6 RCTs included in this meta-analysis, subgroup analysis was done based on the nature of the control group. Four studies (Bakris 2015[10], Katayama 2017[11], Bakris 2020[17], Pitt 2021[20]) had placebo in the control group, hence were analyzed as the PCG. Three studies (Sato 2016[16], Filippatos 2016[19] and Pitt 2013[18]) had eplerenone/spironolactone as the active control, hence were analyzed as the ACG. The active controls in the studies by Sato *et al.*[16] and Filippatos *et al.*[19] was eplerenone 25 mg/day. The active control in the study by Pitt *et al.*[18] was spironolactone 50 mg/day. The median follow-up duration in the study by Bakris *et al.*[10] and Pitt *et al.*[20] was 2.6 and 3.4 years respectively. The total follow-up duration in the studies by Katayama *et al.*,[11] Filippatos 2016 [19], Sato *et al.*,[16] and Bakris *et al.*[17] was 90 days. The study by Pitt *et al.*[18] had the shortest follow-up duration of 42 days. The details of the studies included in this meta-analysis have been elaborated in Table 1.

Risk of bias in the included studies

The summaries of risk of bias of the 7 studies included in the meta-analysis have been elaborated in Figure 2a, Figure 2b and Supplementary Table 1. Random sequence generation, allocation concealment, performance bias, detection bias and reporting bias were low risk of bias in all seven studies (100%). Incomplete outcome data (attrition bias) was low risk in six out of seven studies (85.71%). Source of funding, especially pharmaceutical, authors from pharmaceutical organizations and conflict of interests were looked into "other bias" section. Other biases were at high risk in all 7 studies (100%) [Figure 2a and b].

Effect of finerenone on primary outcomes

Urine albumin creatinine ratio (UACR)

Data from 2 studies involving 214 people with DKD was analyzed to find out impact of finerenone on percent reduction in UACR as compared to placebo, after 90 days treatment. Individuals receiving finerenone had significantly greater percentage lowering of UACR from baseline as compared to PCG [MD -23.82% (95% CI: -24.87 – -22.77); $P < 0.01$; $I^2 = 96\%$ (considerable heterogeneity); Figure 3a]. Data from one study (Bakris *et al.* 2020) involving 3666 and 1690 people with DKD was analyzed to find impact of finerenone on percent reduction in UACR as compared to placebo, after 2 and 4 years treatment respectively. Individuals receiving finerenone had significantly greater percentage lowering of UACR from baseline as compared to PCG after 2 years [MD -37.9% (95% CI: -38.09 – -37.71); $P < 0.01$] and 4 years [MD -25.20% (95% CI: -25.63 – -24.77); $P < 0.01$] of treatment.

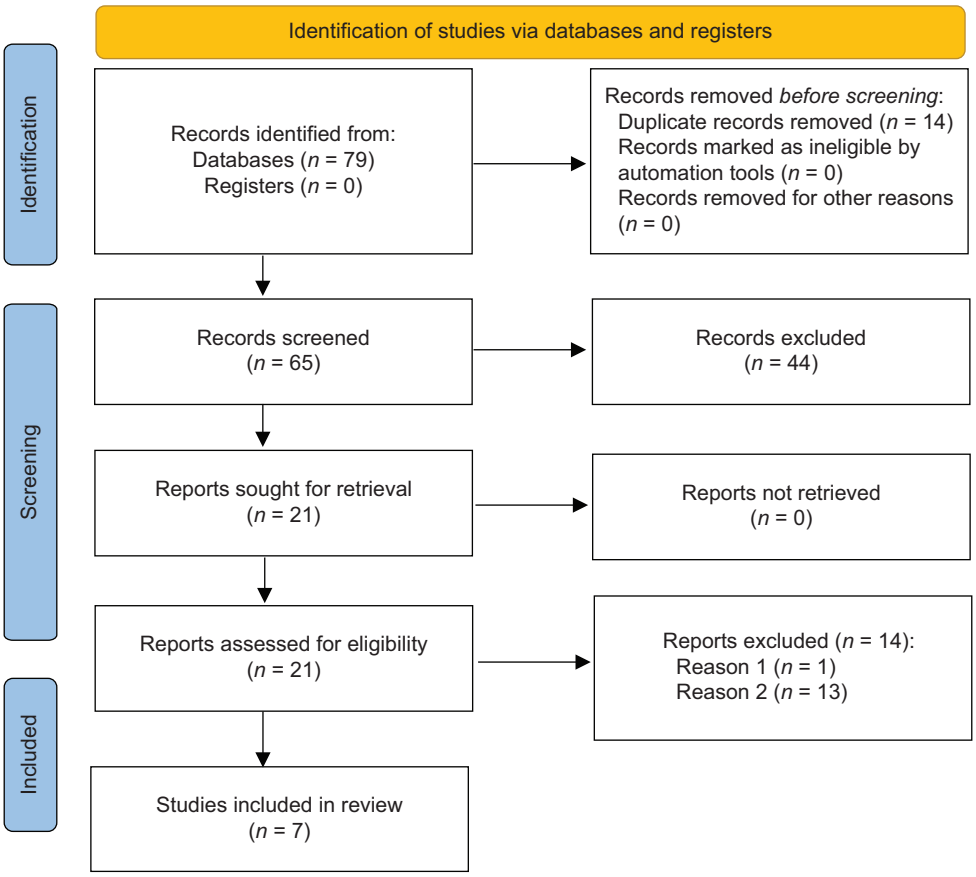


Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis. Reason-1: One study by Filippatos *et al.* (2021) was post-hoc analysis of the original RCT by Bakris *et al.* (2020). Hence the results of the study has not been presented seperately; Reason-2: did not fulfil the inclusion and exclusion criteria; RCT: randomized controlled trial

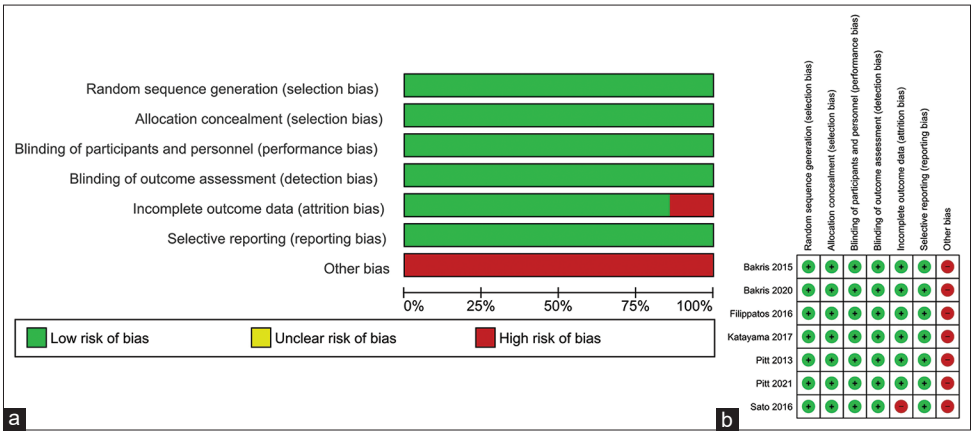


Figure 2: a. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; b: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Data from one study involving 175 patients (Bakris *et al.* 2015) was analyzed to find out how many patients had >40% decline in UACR from baseline after 90 days of therapy with finerenone as compared to placebo. Patient receiving finerenone had significantly higher rates of achieving >40% decline in UACR [Odds Ratio (OR) 2.51 (95% CI: 1.21 – 5.19); $P = 0.01$]. Similar date was not available for finerenone vs. ACG.

Effect of finerenone on secondary outcomes

Glomerular filtration rate (GFR)

Data from 4 studies (13,238 patients) and 3 studies (13,050 patients) were analyzed to find out how many patients had >40% and >57% decline in GFR respectively, when receiving finerenone as compared to those receiving placebo (PCG). Patients receiving finerenone has

a significantly lower chance of having >40% decline [OR 0.83 (95% CI: 0.75 – 0.92); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 3b] and 57% decline [OR 0.70 (95% CI: 0.60 – 0.82); $P < 0.01$; Figure 3c] in GFR as compared to PCG. Data from 1 study (Filippatos 2016[19]; 261 patients) and 2 studies (Filippatos 2016[19] and Sato 2016[16]; 283 patients) were analyzed to find out how many patients had >40% and >57% decline in GFR respectively, when receiving finerenone as compared to those receiving eplerenone (ACG). Patients receiving finerenone had similar chance of having >40% decline in GFR as compared to controls receiving eplerenone [OR 0.80 (95% CI: 0.13 – 4.90); $P = 0.81$]. OR calculation was not possible for >57% decline in GFR as none of the patients in the studies by Filippatos 2016[19] and Sato 2016[16]. had >57% decline in GFR by the end of the study [Figure 3d].

Composite cardiac outcomes (CCO)

CCO in the different studies were defined as the combined occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure. Data from 3 studies (13,390 patients) were analyzed to find out the occurrence of CCO when receiving finerenone as compared to controls. Patients receiving finerenone has significantly lower CCO as compared to those receiving placebo or eplerenone [OR 0.86 (95% CI: 0.78 – 0.95); $P = 0.003$; $I^2 = 0\%$ (low heterogeneity); Figure 4a].

Data from 3 studies (13,052 patients) were analyzed to find out the occurrence of hospitalization for heart failure when receiving finerenone as compared to controls. Patients receiving finerenone had lower hospitalization for heart failure, but not statistically significant, as compared to those receiving placebo or eplerenone [OR 0.78 (95% CI: 0.66 – 0.92); $P = 0.003$; $I^2 = 0\%$ (low heterogeneity); Figure 4b].

Safety

The most common adverse event noted across RCTs was hyperkaliemia. Other common mild adverse events were nasopharyngitis, decreased GFR, diarrhea, back pain, dizziness, arthralgias, constipation, edema and anemia. Data from 6 studies (13,595 patients) was analyzed to evaluate the impact of finerenone on the occurrence of total adverse events (TAEs). The occurrence of TAEs was not statistically different in patients receiving finerenone as compared to controls [Risk ratio (RR) 0.97 (95% CI: 0.88 – 1.07); $P = 0.56$; $I^2 = 0\%$ (low heterogeneity); Figure 4c]. Data from four studies (13,409 patients) were analyzed to evaluate the impact of finerenone on the occurrence of severe adverse events (SAEs). The occurrence of SAEs was significantly lower in patients receiving finerenone as compared to controls [RR 0.91 (95% CI: 0.84 – 0.97); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 4d]. Data from 3 studies (13,315 patients) was analyzed to evaluate the impact of finerenone on the occurrence of hyperkaliemia. Hyperkaliemia

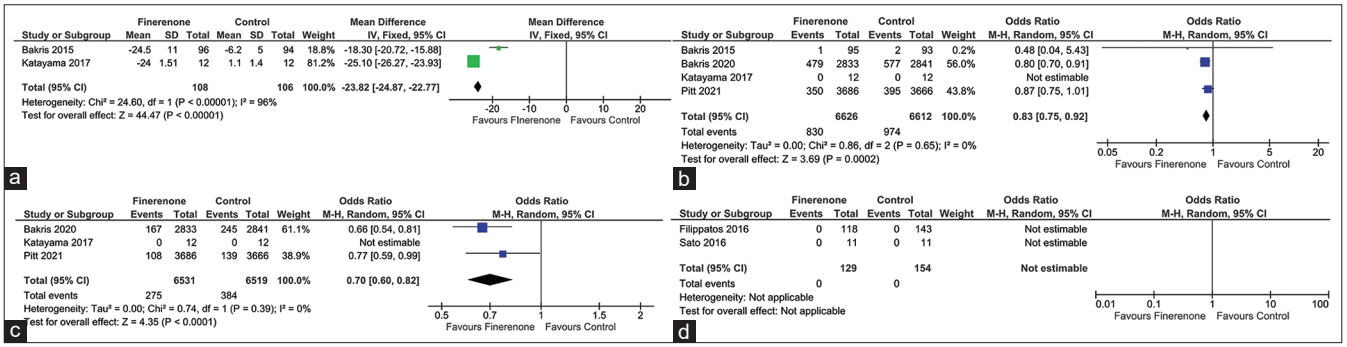


Figure 3: Forest plot highlighting the impact of finerenone on (a) Percent reduction in UACR at 90 days as compared to PCG; (b) >40% decline in GFR as compared to PCG; (c) >57% decline in UACR as compared to PCG; (d) >57% decline in UACR as compared to ACG

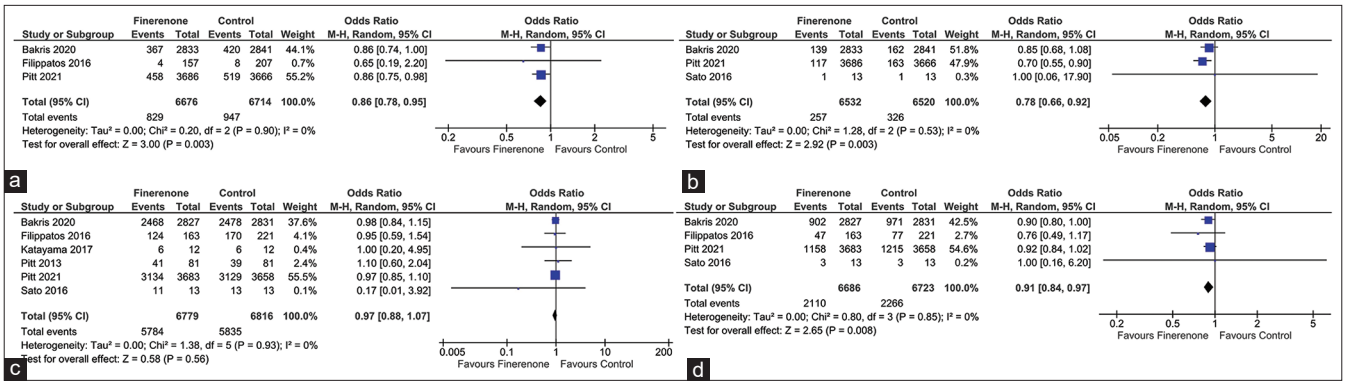


Figure 4: Forest plot highlighting the impact of finerenone on (a) Composite cardiac outcomes; (b) hospitalization for heart failure; (c) Total adverse events (TAEs); (d) Severe adverse events (SAEs)

was significantly higher in patients receiving finerenone as compared to controls [RR 2.19 (95% CI: 1.94 – 2.48); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 5a]. Data from 2 studies (13,026 patients) were analyzed to evaluate the impact of finerenone on death from any cause, hospitalization for any cause and progression to end-stage kidney disease (ESRD). Finerenone use was associated with reduced death from any cause [RR 0.89 (95% CI: 0.79 – 1.00); $P = 0.05$; $I^2 = 0\%$ (low heterogeneity); Figure 5b], hospitalization for any cause [RR 0.94 (95% CI: 0.88 – 1.01); $P = 0.09$; $I^2 = 0\%$ (low heterogeneity); Figure 5c], or progression to ESRD [RR 0.79 (95% CI: 0.62 – 1.01); $P = 0.06$; $I^2 = 10\%$ (low heterogeneity); Figure 5d], all of which approached statistical significance.

Data from 1 study (Pitt *et al.*, 2021) was analyzed to evaluate the impact of finerenone on occurrence of gynecomastia. The occurrence of gynecomastia was not statistically different in patients receiving finerenone as compared to controls [RR 0.99 (95% CI: 0.63 – 1.57); $P = 0.98$].

Metabolic parameters

Data from 2 studies were analyzed to evaluate the impact of finerenone on systolic blood pressure after 2 years (9969 patients) and 4 years (2390 patients) of clinical use. Finerenone use was associated with statistically significant lowering of SBP as compared to placebo after 2 years [MD -2.49 mm Hg (95% CI: -2.98 – 2.00); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); supplementary Figure 1a] but not 4 years [MD -1.57 mm Hg (95% CI: -3.34 – 0.21); $P = 0.08$; $I^2 = 64\%$ (moderate heterogeneity); supplementary Figure 1b] of clinical use.

Data from 2 studies were analyzed to evaluate the impact of finerenone on HbA1c after 2 years (9847 patients) and 4 years (2360 patients) of clinical use. Finerenone had no significant impact on HbA1c as compared to placebo after 2 years [MD 0.02% (95% CI: -0.05 – 0.08); $P = 0.62$; $I^2 = 46\%$ (moderate heterogeneity); supplementary Figure 1c] and 4 years [MD 0.11% (95% CI: -0.01 – 0.23); $P = 0.08$; $I^2 = 0\%$ (low heterogeneity); supplementary Figure 1d] of clinical use. Data from 2 studies were analyzed to evaluate the impact of finerenone on body weight after 2 years (7244 patients) and 4 years (2386 patients) of clinical use. Finerenone had no significant impact on weight as compared to placebo after 2 years [MD -0.01 kg (95% CI: -1.01 – 0.99); $P = 0.99$; $I^2 = 0\%$ (low heterogeneity); supplementary Figure 1e] and 4 years [MD 0.33 kg (95% CI: -1.13 – 1.78); $P = 0.66$; $I^2 = 0\%$ (low heterogeneity); supplementary Figure 1f] of clinical use.

Finerenone use was associated with significantly decreased occurrence of new onset atrial fibrillation as noted in the study by Bakris *et al.* 2020 ($n = 5213$) [OR 0.70 (95% CI: 0.52 – 0.93); $P = 0.01$].

Discussion

Finerenone has been shown to be more effective than eplerenone in reducing cardiac and renal hypertrophy, proteinuria and circulating levels of plasma prohormone of B-type natriuretic peptide (BNP).[22] Our meta-analysis showed that finerenone is highly effective in reducing in urine protein loss in people living with DKD. This benefit is over and above the benefits seen with use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), as most of the patients in the trials were already on one of these medications. Compared to placebo there was an additional -28.2% reduction in UACR. However similar direct comparison between finerenone and eplerenone/spironolactone us currently not available and should be an area of future research.

This meta-analysis showed that finerenone is superior to controls with regards to delaying the progression of DKD. Patients on finerenone had a much slower decline of GFR as compared to those on placebo. Data from only 1 study was available directly comparing GFR outcomes of finerenone vs eplerenone. In that study finerenone was found to be comparable to eplerenone in terms of delaying the decline in GFR in people with DKD.

Finerenone has a beneficial impact on cardiovascular outcomes on people with DKD. Patients on finerenone in this meta-analysis had a much lower combined occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure as compared to those on placebo. Over 4 years of clinical use, finerenone

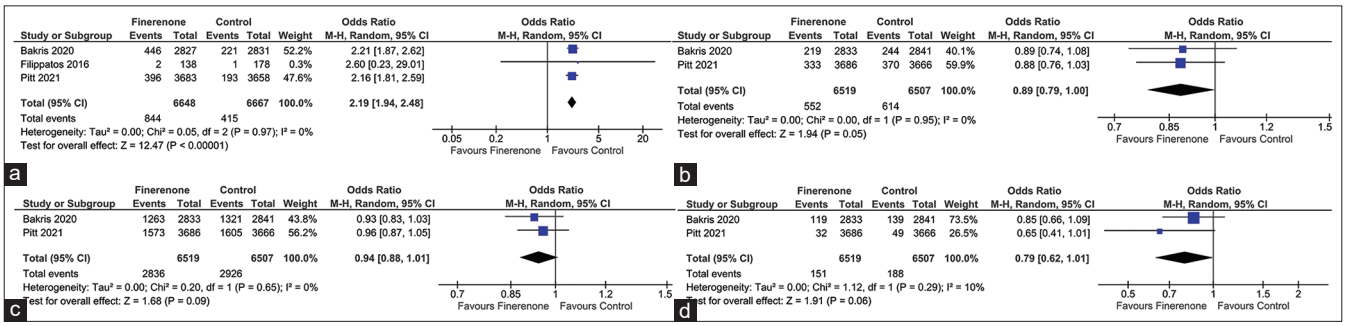


Figure 5: Forest plot highlighting the impact of finerenone on (a) Hyperkalemia (b): All cause death; (c): hospitalization for any cause; (d): progression to end-stage kidney disease (ESRD)

has no impact on HbA1c or body weight. Finerenone use is associated with reduction in SBP over 2 years of clinical use, which tended to wane off by 4 years of use. The cause for this decline needs further evaluation. The beneficial impact on blood pressure would also have contributed to the beneficial impact on cardiovascular outcomes. Finerenone use has been associated with reduced occurrence of atrial fibrillation in one of the RCTs.

Our analysis highlighted that finerenone at 10-20 mg/day is well tolerated with no increased occurrence of TAEs as compared to those receiving placebo/eplerenone/spironolactone. In fact the occurrence of SAEs were significantly lower in patients on finerenone as compared to placebo/eplerenone/spironolactone. No increased occurrence of hormonal side effects like gynecomastia or impotence was noted with finerenone, problems which are common with spironolactone. Hyperkaliemia continues to be a problem with finerenone use in DKD in all the RCTs. The occurrence of hyperkalemia was lower with finerenone as compared to spironolactone as per the report by Pitt *et al*.[18] Hence there remains need for more head-to-head comparison of side effect profile of finerenone vs spironolactone/eplerenone. As of today, a good clinical practice should be to periodically monitor serum electrolytes in patients initiated on finerenone.

It must be noted that similar anti-proteinuria effects have been noted with SGLT2 inhibitors such as empagliflozin, canagliflozin, dapagliflozin and sotagliflozin among patients with DKD in different trials. In the study by Pitt *et al*.,[20] only 8% of patients on finerenone were receiving SGLT2i. As of now, we do not have enough data on whether finerenone can be used with SGLT2i for additional benefits in reducing proteinuria and remains an important area of future research. Also in must be remembered that the results of this meta-analysis is applicable only in patients with albuminuric DKD, and not in patients with non-albuminuric DKD.

To conclude, this meta-analysis provides us with reassuring data on the beneficial impact of finerenone in reducing urine protein loss and delaying the decline in GFR as compared to placebo in people with albuminuric DKD. However we still lack head to head comparison of renal outcomes of finerenone vs eplerenone/spironolactone in DKD. Such studies are warranted in the near future.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Li H, Lu W, Wang A, Jiang H, Lyu J. Changing epidemiology of chronic kidney disease as a result of type 2 diabetes mellitus from 1990 to 2017: Estimates from Global Burden of Disease 2017. J Diabetes Investig 2021;12:346-56.
2. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: Pathophysiological basis. Kidney Int 2019;96:302-19.
3. Guo C, Martinez-Vasquez D, Mendez GP, Toniolo MF, Yao TM, Oestreicher EM, *et al*. Mineralocorticoid receptor antagonist reduces renal injury in rodent models of types 1 and 2 diabetes mellitus. Endocrinology 2006;147:5363-73.
4. Konikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
5. De BK, Dutta D, Som R, Biswas PK, Pal SK, Biswas A. Hemodynamic effects of propranolol with spironolactone in patients with variceal bleeds: a randomized controlled trial. World J Gastroenterol 2008;14:1908-13.
6. Parthasarathy HK, Menard J, White WB, Young WF Jr, Williams GH, Williams B, *et al*. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens 2011;29:980–90.
7. Fagart J, Hillisch A, Huyet J, Bärfacker L, Fay M, Pleiss U, *et al*. A new mode of mineralocorticoid receptor antagonism by a potent and selective nonsteroidal molecule. J Biol Chem 2010;285:29932–40.
8. Pei H, Wang W, Zhao D, Wang L, Su GH, Zhao Z. The use of a novel non-steroidal mineralocorticoid receptor antagonist finerenone for the treatment of chronic heart failure: A systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e0254. doi: 10.1097/MD.0000000000010254.
9. Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B. Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: Comparison at bench and bedside. Handb Exp Pharmacol 2017;243:271-305.
10. 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. N Engl J Med 2020;383:2219-29.
11. Katayama S, Yamada D, Nakayama M, Yamada T, Myoishi M, Kato M, *et al*. ARTS-DN Japan study group. A randomized controlled study of finerenone versus placebo in Japanese patients with type 2 diabetes mellitus and diabetic nephropathy. J Diabetes Complications 2017;31:758-65.
12. Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
13. Dutta D, Jindal R, Kumar M, Mehta D, Dhall A, Sharma M. Efficacy and safety of once weekly thyroxine as compared to daily thyroxine in managing primary hypothyroidism: A systematic review and meta-analysis. Indian J Endocr Metab 2021;25:76-85.
14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and metaanalyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
15. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
16. Sato N, Ajioka M, Yamada T, Kato M, Myoishi M, Yamada T, *et al*. A randomized controlled study of finerenone vs. eplerenone in Japanese patients with worsening chronic heart failure and diabetes and/or chronic kidney disease. Circ J 2016;80:1113-22.
17. Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, *et al*. Effect of finerenone on albuminuria in patients with diabetic nephropathy: A randomized clinical trial. JAMA 2015;314:884-94.
18. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, *et al*. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: A randomized, double-blind trial. Eur Heart J 2013;34:2453-63.
19. Filippatos G, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, *et al*. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/

or chronic kidney disease. Eur Heart J 2016;37:2105-14.
20. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, *et al*. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021. doi: 10.1056/NEJMoa2110956.
21. Filippatos G, Bakris GL, Pitt B, Agarwal R, Rossing P, Ruilope LM, *et al*. Finerenone reduces new-onset atrial fibrillation in patients with chronic kidney disease and type 2 diabetes. J Am Coll Cardiol 2021;78:142-52.
22. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Barfacker L, *et al*. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. J Cardiovasc Pharmacol 2014;64:69–78.

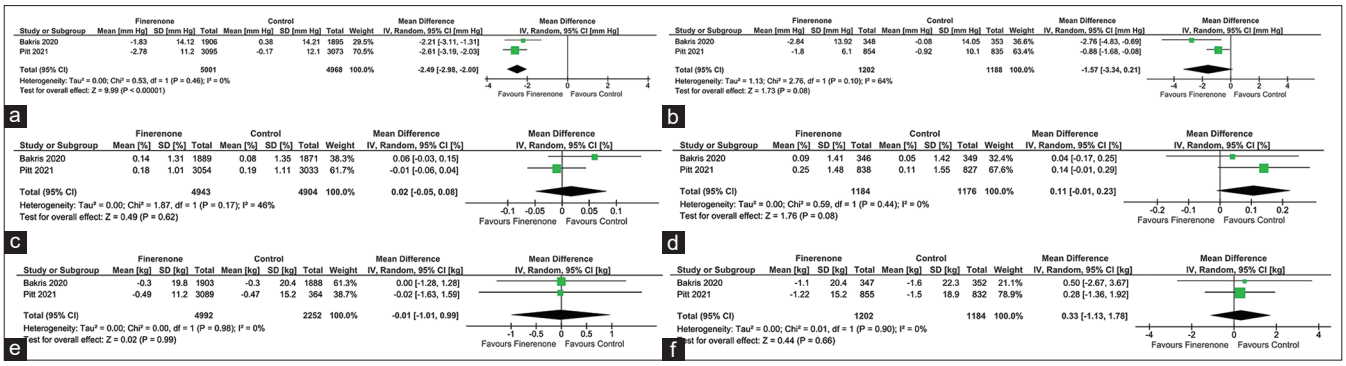
Supplementary Table 1: Risk of bias assessment table

	Risk of Bias	Author Judgement
Bakris 2015		
Random Sequence Generation (Selection Bias)	Low Risk	Randomized double blinded placebo controlled, parallel group multicentric study
Allocation Concealment (Selection Bias)	Low Risk	Randomization was done centrally by an interactive voice/web response system using computer-generated randomization lists, and participants, investigators, and the sponsor's clinical team were blinded to the allocation
Blinding Of Participants & Personal (Performance Bias)	Low Risk	Yes, double blinded RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Yes, double blinded RCT
Incomplete Outcome Data (Attrition Bias)	Low RIsk	823 patients were randomized, of which 764 patients completed the study (attrition rate 7.17%)
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	This study was funded by Bayer HealthCare AG. Bayer HealthCare AG, the sponsor, provided financial support for the conduct of the research and preparation of the article. The sponsor could not veto decisions made by the steering committee in the production of this article. Together with the steering committee, the sponsor designed and conducted the study including collection, management, and analysis of data. The members of the steering committee and employees of the sponsor interpreted the data and prepared, reviewed, and approved the manuscript; the sponsor was not involved in the decision to submit the manuscript for publication.
Bakris 2020		
Random Sequence Generation (Selection Bias)	Low Risk	Randomized, double blind, placebo-controlled, multi-center clinical trial
Allocation Concealment (Selection Bias)	Low Risk	Randomization done using computer generated randomization lists
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	5734 patients were randomized, of which 5674 patients' data was used for analysis. Hence attrition rate was 0.01%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	This study was funded by Bayer HealthCare AG. The executive committee in collaboration with the sponsor, Bayer, designed and amended the trial protocol and supervised the conduct of the trial. The sponsor conducted the analyses, and all the authors had access to the data and participated in the interpretation of the data. Medical writing assistance was funded by Bayer
Filippatos 2016		
Random Sequence Generation (Selection Bias)	Low Risk	Active-controlled, randomized, double-blind, parallel-group, clinical trial
Allocation Concealment (Selection Bias)	Low risk	Patients were randomized using a computer program and all participants, clinicians and the sponsor's clinical team were blinded to treatment allocation.
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	1066 patients were randomized out of which 1002 patients data was analysed in the end. Hence the attrition rate was 6%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	The study was designed by the Steering Committee in collaboration with the sponsor (Bayer Pharma AG). The sponsor also had a role in data collection and performed the statistical analysis.
Katayama 2017		
Random Sequence Generation (Selection Bias)	Low Risk	Placebo-controlled, randomized, double-blind, parallel-group, clinical trial
Allocation Concealment (Selection Bias)	Low risk	Patients were randomized using a computer program and all participants, clinicians and the sponsor's clinical team were blinded to treatment allocation.
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	96 patients were randomized out of which 91 patients completed the study. Hence the attrition rate was 5.21%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported

Contd...

Supplementary Table 1: Contd...

	Risk of Bias	Author Judgement
Other Biases	High Risk	The study was funded by Bayer Yakuhin Ltd. Medical writing support was provided by Elizabeth R. Perdeaux PhD of Oxford PharmaGenesis, Oxford, UK and funded by Bayer Yakuhin Ltd.
Pitt 2013		
Random Sequence Generation (Selection Bias)	Low Risk	Randomized, multicenter, double-blinded, placebo-controlled clinical trial
Allocation Concealment (Selection Bias)	Low Risk	The randomization list was generated using a validated automated system that assigned treatment groups to randomization numbers.
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	458 patients from the initially randomized 420 patients completed the study. Hence attrition rate was 8.29%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	This work was supported by Bayer Pharma AG. Editorial work (by C.C. of Oxford Pharma GenesisTM Ltd) was funded by Bayer Pharma AG. Editorial support for the preparation of this manuscript was provided by Dr Charlotte Cookson of Oxford PharmaGenesisTM Ltd.
Pitt 2021		
Random Sequence Generation (Selection Bias)	Low Risk	Randomized, multicenter, double-blinded, placebo-controlled clinical trial
Allocation Concealment (Selection Bias)	Low Risk	The randomization list was generated using a validated automated system that assigned treatment groups to randomization numbers.
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)		7352 patients from the initially randomized 7437 patients completed the study. Hence attrition rate was 1.14%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	This work was supported and funded by Bayer Pharma AG.
Sato 2016		
Random Sequence Generation (Selection Bias)	Low Risk	Randomized, double blind, active-comparator-controlled, parallel-group, study conducted at 31 centers in Japan
Allocation Concealment (Selection Bias)	Low Risk	The randomization listings were generated by the Randomization Management Group of the sponsor using a computer program, and participants, investigators and the sponsor's clinical team were blinded to treatment allocation.
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	High Risk	72 patients from the initially randomized of which 52 patients completed the study. Hence attrition rate was 27.7%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	This study was funded by Bayer Yakuhin Ltd. Charlotte Cookson, DPhil, of Oxford PharmaGenesis, Oxford, UK provided medical writing support, which was funded by Bayer Yakuhin Ltd. The sponsor, Bayer Yakuhin Ltd, provided financial support for the conduct of the research and preparation of the article.



Supplementary Figure 1: a: Forest plot highlighting the impact of finerenone on (a) Systolic blood pressure at 2 years; (b): Systolic blood pressure at 4 years; (c): HbA1c at 2 years; (d): HbA1c at 4 years; (e): Body weight at 2 years; (f): Body weight at 4 years