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Research Article

Cardiovascular and Renal Outcomes of the New Kid on the Block: FiFi Analysis

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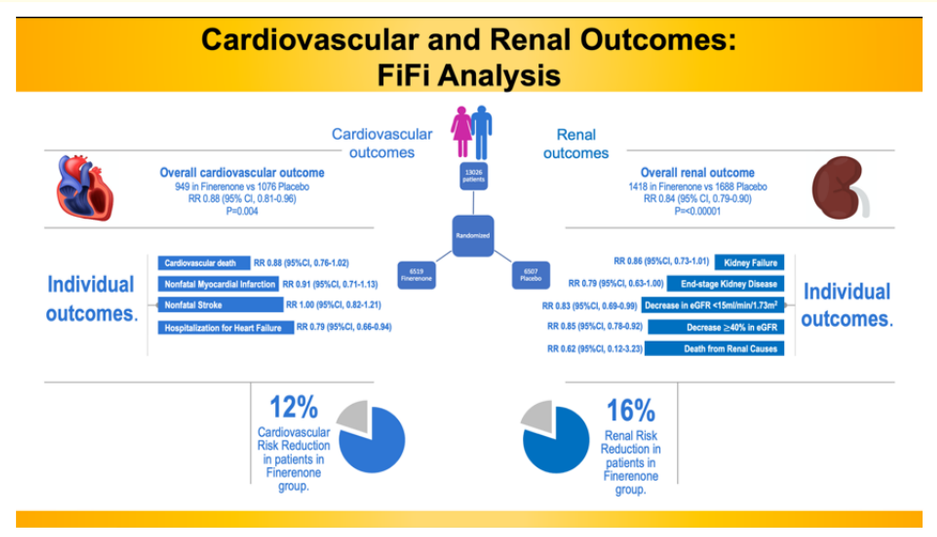
Abstract

Finerenone is a selective nonsteroidal mineralocorticoid receptor antagonist that has been shown to reduce the urinary albumin-to-creatinine ratio in patients with CKD treated with a renin angiotensin system blocker, improving cardiovascular injury while having smaller effects on serum potassium levels than spironolactone. We aim to assess whether nonsteroidal mineralocorticoid receptor antagonists are effective in the treatment of patients with type 2 diabetes and chronic kidney disease using a systematic review approach. We searched PubMed and screened the resulting records on 10 September 2021. A total of 13026 participants were included in this analysis. Overall cardiovascular outcomes were significantly lower in the finerenone group (RR 0.88 (95% CI 0.81 to 0.96; I2 = 0%; p = 0.004). Cardiovascular death had an RR of 0.88 (95% CI 0.76 to 1.02; I2 = 0%), nonfatal myocardial infarction had an RR of 0.91 (95% CI 0.74 to 1.13; I2 = 8%), and heart failure hospitalizations had an RR of 0.79 (95% CI 0.66 to 0.64; I2 = 23%; p = 0.001). Overall renal outcomes were significantly lower in the finerenone group (RR 0.84 (95% CI 0.79 to 0.90; I2 = 0%; p ≤ 0.00001). Death from renal causes had an RR of 0.86 (95% CI 0.73 to 1.01; I2 = 0%). End-stage kidney disease was lower in the intervention arm (p = 0.05) (RR 0.79 (95% CI 0.63 to 1.00; I2 = 10%). These results suggest that finerenone might have an additional protective effect on the cardiovascular and renal systems that is non-existent with the use of spironolactone and eplerenone.

Keywords: *Mineralocorticoid; Receptor; Heart Failure; Chronic Kidney Disease; Type 2 Diabetes*

Graphical Abstract



Introduction

Classical mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, have proven to be effective in the reduction of major adverse cardiovascular events (MACEs) in patients with heart failure with reduced ejection fraction (HFrEF) and post-acute myocardial infarction complicated by left ventricle (LV) dysfunction [1-3].

Mineralocorticoid receptor (MR) expression in the kidney and in a variety of other tissues and its activation could lead to tissue injury. Aldosterone plays a major role in sodium reabsorption and blood pressure regulation. MR activation in the cardiovascular (CV) system has been shown to promote hypertension, fibrosis, and inflammation [4].

Type 2 diabetes is the leading cause of chronic kidney disease (CKD), which in turn exacerbates cardiovascular risk in this group of patients [5,6].

The role of MRs in CV diseases is based on the use of pharmacological MRAs, as they have a beneficial effect in several clinical trials. To date, two MRAs (spironolactone and eplerenone) have been used in humans. Finerenone is a selective nonsteroidal mineralocorticoid receptor antagonist that has been shown to reduce the urinary albumin-to-creatinine ratio in patients with CKD treated with a renin angiotensin system (RAS) blocker, improving cardiovascular injury while having smaller effects on serum potassium levels than spironolactone [7,8].

Aim of the Study

We aim to assess whether nonsteroidal MRA is effective in the treatment of patients with type 2 diabetes and chronic kidney disease and to keep up-to-date with the evolving evidence base using a systematic review approach.

Methods

Criteria for considering studies for this review.

Types of studies

We included randomized controlled clinical trials (RCTs). We made specific adaptations related to the research question if necessary.

To assess the efficacy of nonsteroidal mineralocorticoid receptor antagonists in type 2 diabetes patients with CKD, we included RCTs, as this study design, if performed appropriately, provides the best evidence for experimental therapies in highly controlled therapeutic settings.

We used the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions [9].

We included the following formats, if sufficient information was available on study design, characteristics of participants, interventions, and outcomes: full-text publications.

We did not apply any limitation with respect to the length of follow-up.

Types of participants

We included adults with a confirmed diagnosis of type 2 diabetes and chronic kidney disease (as described in the studies), and we did not exclude any studies based on sex, ethnicity, disease severity, or setting.

Types of interventions

We included the following interventions: any type or dose of nonsteroidal mineralocorticoid receptor antagonist (Finerenone).

We included the following comparisons: Finerenone versus standard care (plus placebo).

Outcomes

The cardiovascular outcomes were a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

The renal outcomes were a composite of the first occurrence of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR for a period of at least 4 weeks, or death from renal causes. Kidney failure was defined as end-stage kidney disease or as a sustained eGFR of less than 15 ml per minute per $1.73m^2$ for a period of at least 4 weeks. End-stage kidney disease was defined as the initiation of chronic dialysis (for ≥ 90 days) or kidney transplantation.

Statistical analysis

For continuous outcomes, we recorded the mean, standard deviation (SD) and total number of participants in both the treatment and control groups. Where continuous outcomes used the same scale, we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we performed analyses using the standardized mean difference (SMD). For dichotomous outcomes, we recorded the number of events and total number of participants in both the treatment and control groups. We reported the pooled risk ratio (RR) with a 95% CI.

We assessed the heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. We used the I^2 statistic and visual examination to assess possible heterogeneity (I^2 statistic > 30% to signify moderate heterogeneity, I^2 statistic > 75% to signify considerable heterogeneity) [10]. If the I^2 statistic was above 80%, we planned to explore potential causes through sensitivity and subgroup analyses. However, none of our analyses demonstrated an I^2 statistic > 80%.

Statistical analyses were performed using the Revman software package (Review Manager, Version 5.4. Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration).

Results

We searched all databases and screened the resulting records through 16 April 2021.

We searched PubMed and screened the resulting records on 10 September 2021. The search was limited to the past 5 years. We included two studies, two of which were multicenter platform RCTs [11,12].

A total of 13026 participants were included in this comparison, of whom 6519 were randomized to nonsteroidal mineralocorticoid receptor antagonist (Finerenone) and 6507 to standard care (plus placebo).

The baseline characteristics of the included studies are shown in table 1. Overall, there was a predominance of males, constituting 69% of patients. The patients' mean age was 64 ± 9.4 years. Patients had a mean hemoglobin A1C of 7.7%, systolic blood pressure of 136 mmHg, and a mean estimated glomerular filtration rate of 56 ml/min/$1.73m^2$.

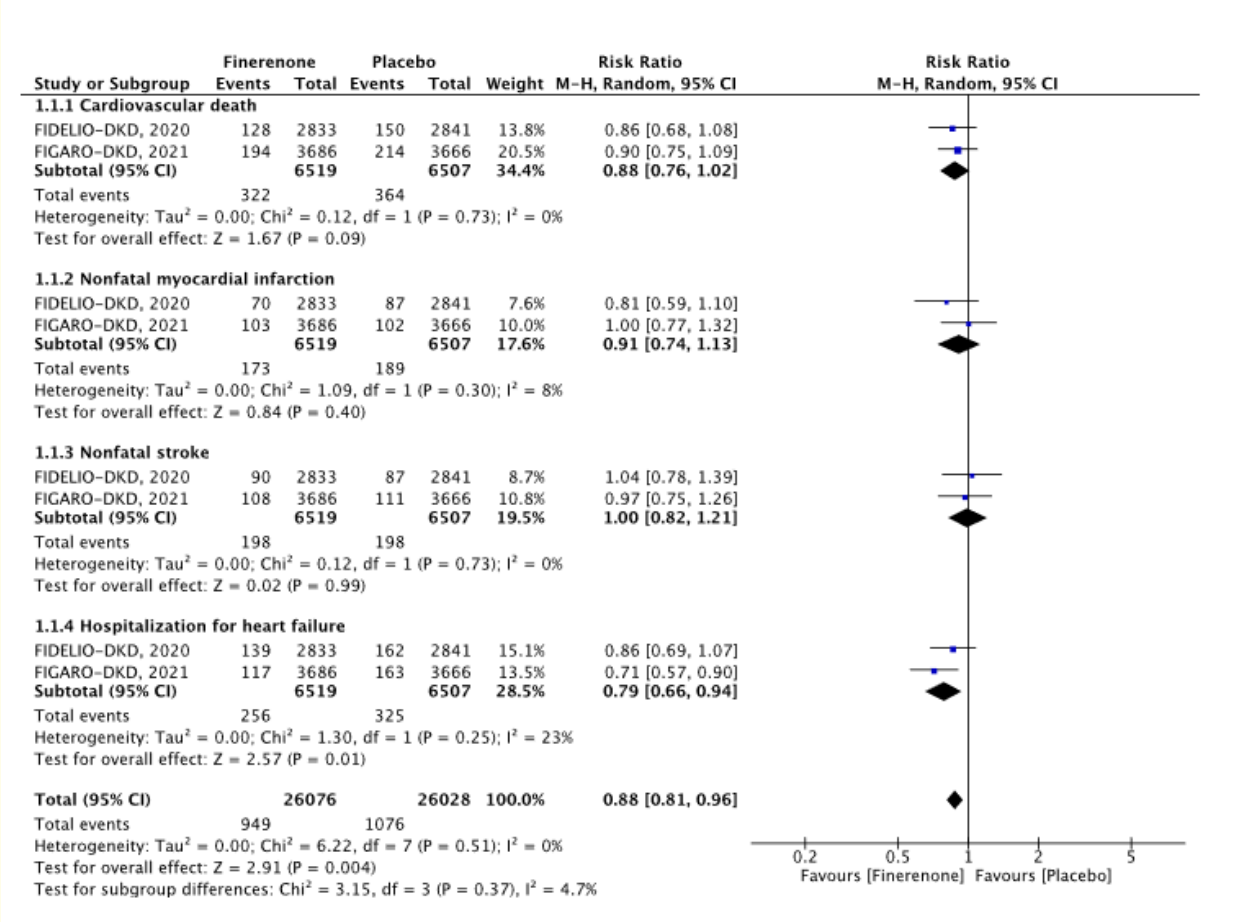
Baseline patient characteristics	Fidelio-DKD	Figaro-DKD
Study type (randomized/double-blind)	Yes	Yes
Median follow-up period (years)	2.6	3.4
N	5674	7352
Age, mean/SD	65.6 ± 9.1	64.1 ± 9.8
Sex (male), n (%)	3983 (70.2)	5105 (69.4)
Race/Ethenic group		
Black	264 (4.7)	258 (3.5)
White	3592 (63.3)	5277 (71.8)
Asian	1440 (25.4)	1454 (19.8)
Hemoglobin A1C (%)	7.7 ± 1.3	7.7 ± 1.4
Systolic blood pressure (mmHg)	138.0 ± 14.4	135.8 ± 14.0
Estimated GFR (ml/min/1.73 m^2)		
Mean	44.3 ± 12.6	67.8 ± 21.7
Distribution, n (%)		
≥ 60 ml/min/1.73 m^2	656 (11.6)	4539 (61.7)
45 to < 60 ml/min/1.73 m^2	1900 (33.5)	1534 (20.9)
25 to < 45 ml/min/1.73 m^2	2981 (52.5)	1251 (17.0)
< 25 ml/min/1.73 m^2	135 (2.4)	27 (0.4)
Urinary albumin-to-creatinine ratio‡		
Median (IQR)	852 (446 - 1634)	308 (108 - 740)
Distribution, n (%)		
< 30	23 (0.4)	207 (2.8)
30 to < 300	685 (12.1)	3414 (46.4)
≥ 300	4963 (87.5)	3729 (50.7)
Serum potassium - mmol/liter	4.37 ± 0.46	4.33 ± 0.43
Baseline medications, n (%)		
ACE inhibitor§	1942 (34.2)	7343 (99.9)*
Angiotensin-receptor blocker§	3725 (65.7)	*
Diuretic	3214 (56.6)	3496 (47.6)
Statin	4215 (74.3)	5184 (70.4)
Glucose-lowering therapy, n (%)	5524 (97.4)	7196 (97.9)
Insulin	3637 (64.1)	3993 (54.3)
GLP-1 receptor agonist	394 (6.9)	550 (7.5)
SGLT2 inhibitor	259 (4.6)	618 (8.4)

Table 1: *Baseline studies and patients characteristics.*

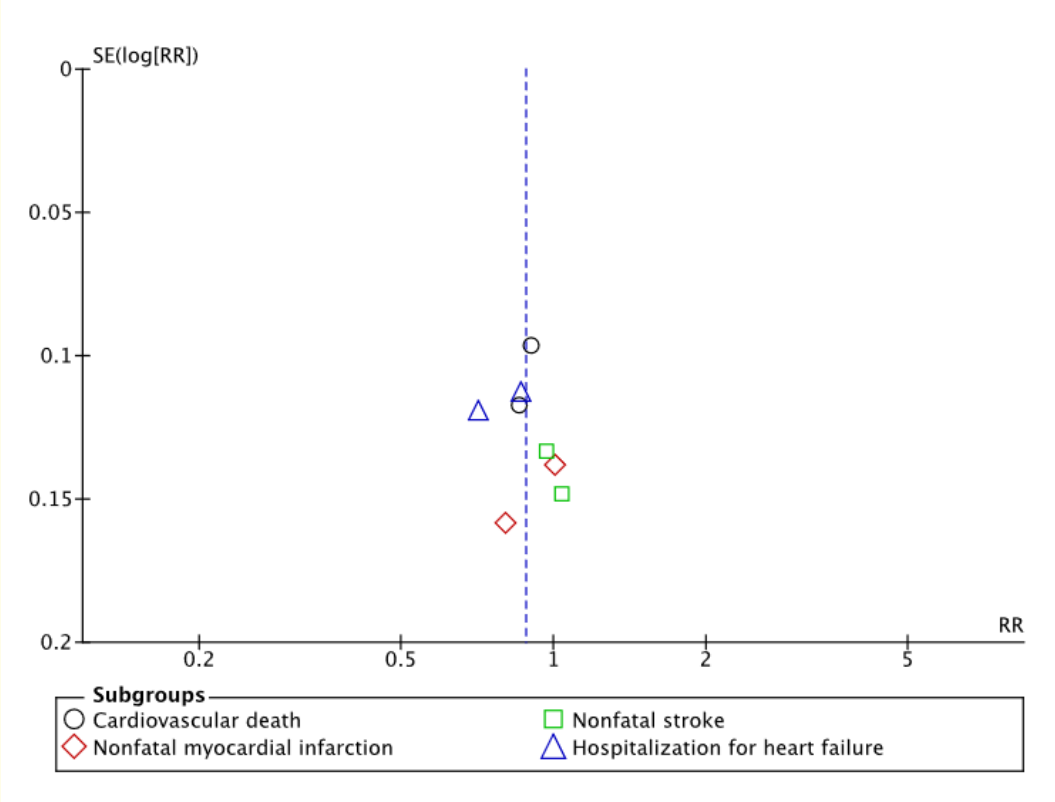
*Plus–minus values are means ± SD. Percentages may not total 100 because of rounding. GLP-1 denotes glucagon-like peptide-1, and SGLT2 sodium–glucose cotransporter 2. *Some patients were not treated with either an ACE inhibitor or an angiotensin-receptor blocker at baseline; patients received treatment with both an ACE inhibitor and an angiotensin-receptor blocker. ‡The ratio was calculated with albumin measured in milligrams and creatinine measured in grams.*

Cardiovascular outcomes

Overall cardiovascular death, 322 of 6519 participants in the intervention group died compared with 364 of 6507 participants in the control (placebo) group. The RR of death was 0.88 (95% CI 0.76 to 1.02; I^2 = 0%; random-effects model). Nonfatal myocardial infarction occurred in 173 of 6519 participants in the intervention group compared with 189 of 6507 participants in the placebo group (RR 0.91 (95% CI 0.74 to 1.13; I^2 = 8%; random-effects model). Nonfatal stroke occurred in 322 of 6519 participants in the intervention group versus 198 of 6507 participants in the placebo group (RR 1.00 (95% CI 0.82 to 1.21; I^2 = 0%; random-effects model). Hospitalizations for heart failure were significantly lower in the intervention (finerenone) group (256 of 6519 participants) than in the placebo group (325 of 6507 participants) (RR 0.79 (95% CI 0.66 to 0.64; I^2 = 23%; p = 0.001; random-effects model). Although there was no significant difference in cardiovascular death, nonfatal MI or stroke between the two groups, the overall cardiovascular outcomes were significantly lower in the finerenone group than in the standard care group (949/6519 vs 1076/6507) (RR 0.88 (95% CI 0.81 to 0.96; I^2 = 0%; p = 0.004; random-effects model) (Plot 1).



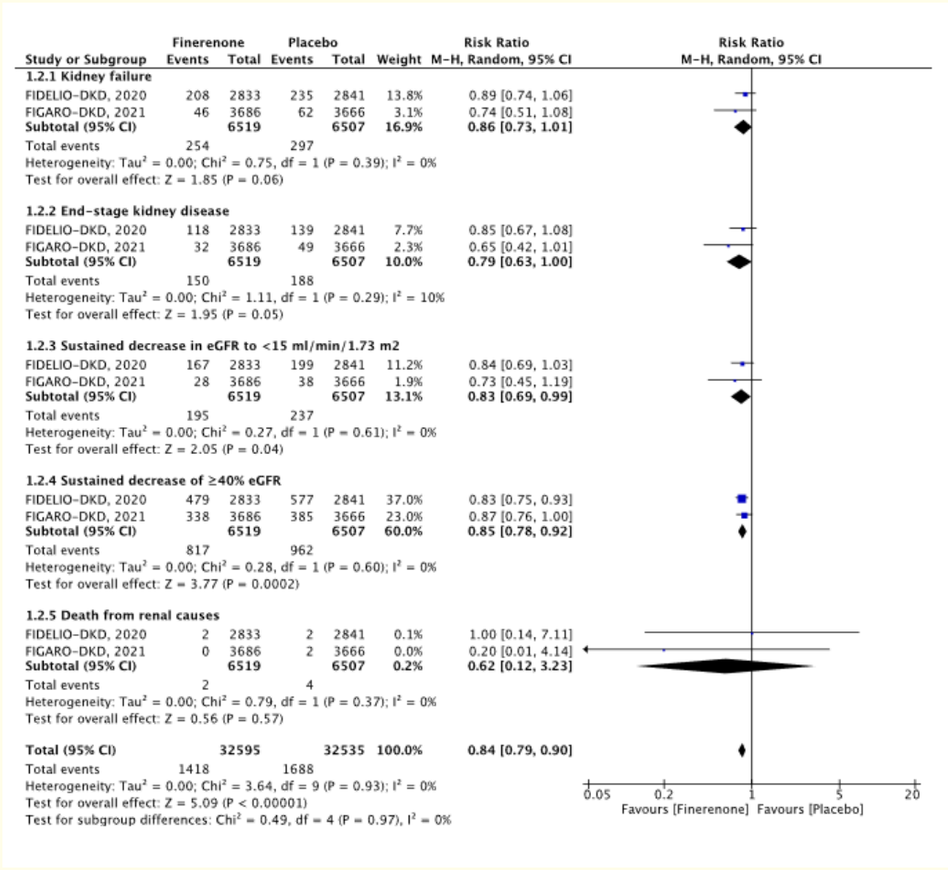
Plot 1: *Comparison 1: Finerenone plus standard care versus standard care (plus placebo), Outcome 1: Cardiovascular outcomes.*



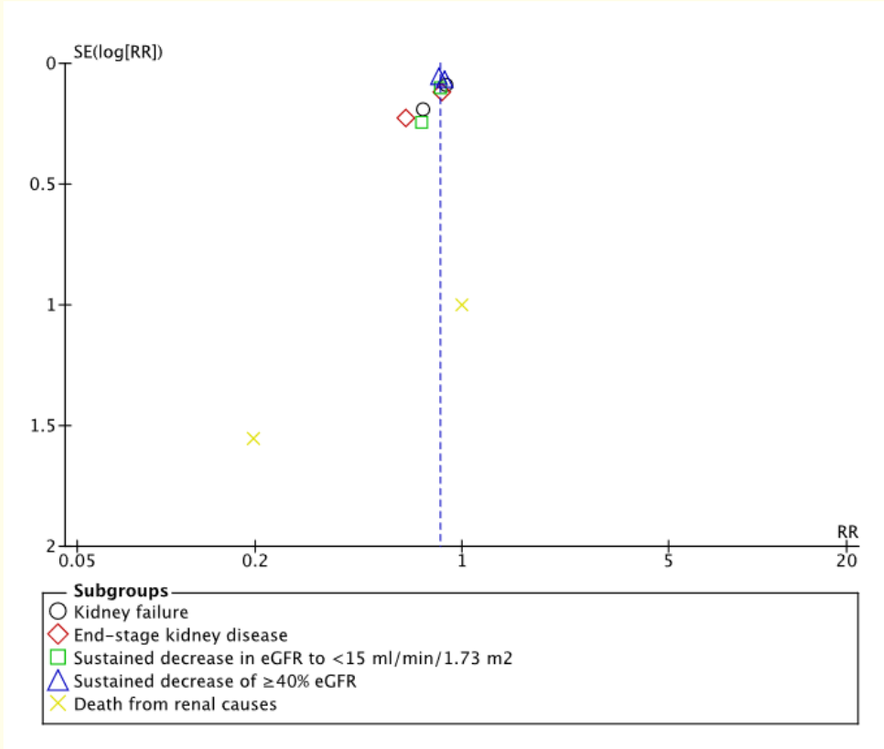
Funnel Plot 1: *Showing low risk of bias in cardiovascular outcomes.*

Renal outcomes

Overall, 254 of 6519 participants in the intervention group developed kidney failure compared with 297 of 6507 participants in the placebo group. The RR of death was 0.86 (95% CI 0.73 to 1.01; I^2 = 0%; random-effects model). The difference was nonsignificant (p = 0.06). End-stage kidney disease was significantly lower (p = 0.05) in participants in the intervention group (150 of 6519) than in 188 of 6507 participants in the placebo group (RR 0.79 (95% CI 0.63 to 1.00; I^2 = 10%; random-effects model). A sustained decrease in eGFR less than 15 ml/min/1.73m^2 occurred in 195 of 6519 participants in the intervention group versus 237 of 6507 participants in the placebo group (RR 0.83 (95% CI 0.69 to 0.99; p = 0.04; I^2 = 0%; random-effects model). A sustained decrease from baseline of at least 40% in the eGFR was significantly lower in the finerenone group (817 of 6519 participants) than in the placebo group (998 of 6507 participants) (RR 0.85 (95% CI 0.78 to 0.92; I^2 = 0%; p = 0.0002; random-effects model). No significant difference was noticed with regard to death from renal causes between the two groups (2/6519 vs 4/6507; p = 0.57). Nonetheless, overall renal outcomes were significantly lower in the finerenone group than in the standard care group (1418/6519 vs 1688/6507) (RR 0.84 (95% CI 0.79 to 0.90; I^2 = 0%; p ≤ 0.00001) (Plot 2).



Plot 2: *Comparison 1: Finerenone plus standard care versus standard care (plus placebo), Outcome 2: Renal outcomes.*



Funnel Plot 2: *Showing low risk of bias in renal outcomes.*

Discussion

The abovementioned results showed an overall reduction in the relative risk for cardiovascular and renal outcomes in a meta-analysis that combined a significant sample (a total of 13026 participants).

Our pooled-analyses show high-certainty evidence that finerenone compared with placebo or no intervention probably reduces the risk of all-cause mortality, myocardial infarction, and progression of kidney disease in patients with type 2 diabetes-associated kidney disease. When major cardiovascular events, cardiovascular mortality, and hospitalization due to heart failure were assessed, this analysis yielded moderate-certainty evidence suggesting that finerenone compared with placebo or no intervention may reduce the risk. Similarly, moderate-certainty evidence suggests that finerenone compared with placebo or no intervention may reduce the risk of kidney failure, end-stage kidney disease and sustained decrease in estimated glomerular filtration rate. Hence, evidence seems to suggest that finerenone versus placebo or no treatment may result in a 28% reduction in the risk ratio for all-cause mortality, a 9% reduction in nonfatal myocardial infarction, and a 21% reduction in hospitalizations due to heart failure. However, when stroke was assessed, our analysis yielded low-certainty evidence suggesting that finerenone compared with placebo or no intervention may not affect the risk.

A previous report showed that classical MRA therapy in patients with diabetes and chronic kidney disease had lower observed rates of 3-year mortality (54.4% versus 57.5%), 30-day heart failure readmission (7.9% versus 9.5%), and 1-year (68.2% versus 72.2%) and 3-year (84.9% versus 88.2%) all-cause readmission. Benefits were also seen in patients with heart failure post-myocardial infarction, with an early mortality reduction of up to 33% [13-15]. However, a recent randomized controlled trial demonstrated that spironolactone did not delay or prevent the development of confirmed microalbuminuria in patients with type 2 diabetes at high risk of developing microalbuminuria [16].

Classical mineralocorticoid receptor antagonists are often underutilized in clinical practice, possibly due to risks of hyperkalemia and worsening renal function [17,18]. In the present analysis, we did not assess hyperkalemia-associated adverse events, as has been reported in the FIDELITY pooled analysis, showing that it was more frequent with finerenone (12%) vs. placebo (6%) [19].

Slowing chronic kidney disease progression and reducing cardiovascular risk involves multireceptor targeting using ACEi/ARB to treat hypertension, sodium/glucose cotransporter 2 and (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, and lifestyle changes [20,21]. A recent network meta-analysis showed that SGLT-2 inhibitors reduced all-cause and cardiovascular mortality by 23% and 16%, respectively, when compared with placebo. The same analysis reported a 29% reduction in kidney failure with SGLT-2 inhibitor use [22].

Although not all the proposed cardiovascular and renal outcomes obtained were significant from the statistical point of view, the overall analysis showed a reduction of those adverse outcomes with the use of finerenone in comparison with the placebo/standard care group.

Conclusion

These results suggest that finerenone might have an additional protective effect in cardiovascular and renal systems that is non-existent with the use of spironolactone and eplerenone. The large sample used for this analysis gives strength to these findings, which should be further studied with RCTs and real-world data to better understand the molecule and its mechanism of action responsible for the protective cardiovascular and renal effects.

Disclosures

The authors have no conflicts of interest to declare.

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