Communication

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The cardiovascular outcomes of finerenone in patients with chronic kidney disease and type 2 diabetes: A meta-analysis of randomized clinical trials

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SUMMARY Recently, a few randomized control trials (RCTs) suggested that finerenone has been shown to reduce cardiovascular events in patients with CKD and DM-2. We aimed to analyze the cardiovascular benefits of using finerenone in patients with CKD and DM-2. Electronic databases were systematically searched to identify only RCTs comparing finerenone versus placebo. Pooled risk ratios (RR) and their 95% confidence intervals (CI) were calculated using random-effects models. Three RCTs were included, with a total of 13,847 patients. Compared with the placebo group, the use of finerenone was associated with significantly lower rates of cardiovascular events (RR: 0.88; 95% CI: 0.80, 0.96; $p < 0.01$), which was mainly driven by lower hospitalizations for heart failure (RR: 0.79; 95% CI: 0.66, 0.94; $p = 0.01$). However, there were no significant differences between groups in terms of cardiovascular death (RR: 0.88; 95% CI: 0.76, 1.02; $p = 0.09$), non-fatal myocardial infarction (RR: 0.91; 95% CI: 0.74, 1.12; $p = 0.38$), non-fatal stroke (RR: 0.99; 95% CI: 0.80, 1.22; $p = 0.90$).

Keywords finerenone, chronic kidney disease, type 2 diabetes, mineralocorticoid, meta-analysis

Patients with chronic kidney disease (CKD) and diabetes mellitus type 2 (DM-2) have increased cardiovascular morbidity and mortality due to enhanced and over-activation of mineralocorticoid receptors, leading to widespread inflammation and fibrosis affecting the heart, kidneys, and peripheral vessels (*1*). Aldosterone is a mineralocorticoid hormone, which increases proteinuria and affects cardiomyocytes, endothelial cells, and vascular smooth muscle cells by causing chronic inflammation that leads to fibrosis and remodeling of the heart and kidneys. Thus, the use of aldosterone antagonists might reverse these pathophysiological remodeling. Finerenone (BAY 94–8862) is a novel third-generation nonsteroidal selective mineralocorticoid receptor antagonist that has been shown to reduce cardiovascular events in patients with CKD and DM-2 (*2-4*). However, data from randomized controlled trials (RCTs) are limited. Therefore, we aim to conduct a meta-analysis of solely RCTs to evaluate the effects of finerenone on cardiovascular outcomes in patients with CKD and DM-2.

Our Systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched PubMed, EMBASE, Scopus, Web of Science, Cochrane Central, and Google Scholar for RCTs comparing finerenone versus placebo among patients with CKD and DM-2. We performed our search from inception to January 7th, 2022. Our eligibility criteria included; type of study: RCTs; type of subject: patients with CKD and DM-2; type of intervention: studies that evaluated the effect of finerenone compared to placebo; the primary outcome was cardiovascular events defined as death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure; secondary outcomes included the individual primary outcome composite. We calculated risk ratios (RRs) with their 95% confidence intervals (CIs) using the random-effects model. All analyses were performed using RevMan manager v5.3 software.

We identified three RCTs (*2-4*) with 13,847 total patients (finerenone = 7,246 *vs*. placebo = 6,601) with a median follow up was 1.6 years. The mean age was 64.7 ± 8.7 years and 70.3% were male. The

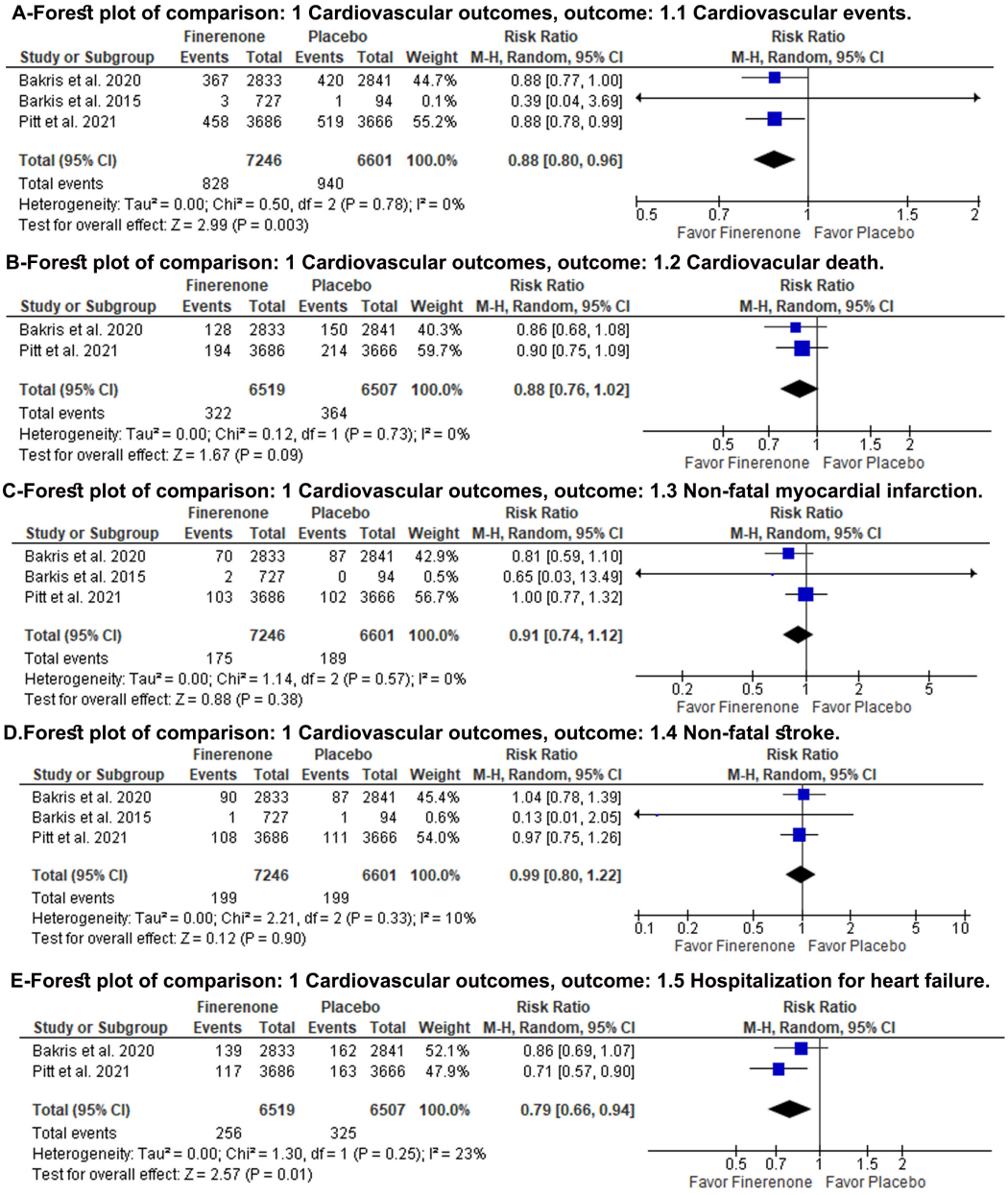

Figure 1. Forest plot comparing the clinical outcomes among patients who received finerenone. (A) Cardiovascular events; **(B)** Cardiovascular death; **(C)** Non-fatal myocardial infarction; **(D)** Non-fatal stroke; **(E)** Hospitalization for heart failure. df: degrees of freedom; I2: I-squared; M-H: Mantel-Haenszel variance; CI: confidence interval.

mean hemoglobin A1c was 7.6% ± 1.24 with mean estimated glomerular filtration rate (eGFR) of 54.9 ±15.5mL/min/1.73m2. Compared to the placebo group, finerenone was associated with significantly lower rates of cardiovascular events (RR: 0.88; 95% CI: 0.80,0.96; $p < 0.01$) (Figure 1). Finerenone was associated with significantly lower heart failure hospitalizations (RR: 0.79; 95% CI: 0.66, 0.94; $p = 0.01$) compared to placebo. However, there were no significant differences between groups in terms of cardiovascular death (RR: 0.88; 95% CI: 0.76, 1.02; $p = 0.09$), non-fatal myocardial infarction (MI) (RR: 0.91; 95% CI: 0.74, 1.12; $p = 0.38$), non-fatal stroke (RR: 0.99; 95% CI: 0.80, 1.22; $p = 0.90$) (Figure 1).

This meta-analysis showed that finerenone was associated with a statistically significant reduction in cardiovascular events, mainly driven by lower hospitalization for heart failure compared to placebo. However, there were no significant differences in terms of cardiovascular death, non-fatal MI, or non-fatal stroke.

In patients with DM-2 and CKD with albuminuria > 30 mg/g and eGFR > 30 mL/min/1.73 m^2, current guidelines recommend sodium-glucose cotransporter-2 inhibitors (SGLT2i) added to angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) to reduce the risk of end-stage renal disease (ESRD) and cardiovascular mortality (*5*). However, despite the use of ACEi (or ARB) and

SGLT2i, the risk of progression to ESRD is still high (*6*). Currently, there is growing evidence that the overactivation of mineralocorticoid receptors contributes to the progression of CKD. Therefore, first-generation aldosterone antagonists -which competitively inhibit aldosterone-dependent sodium-potassium exchange channels in the distal convoluted tubule (such as spironolactone and eplerenone) have been used in patients CKD and DM-2 to reduce mortality and hospitalization despite having side effects, such as hyperkalemia (*7*). Finerenone is a novel medication that demonstrated a lower incidence of hyperkalemia (*8*) and a significant reduction in albuminuria compared to spironolactone (*2*). In our study, we found that finerenone reduced overall cardiovascular events and hospitalization for heart failure but not cardiovascular death, non-fatal MI, or non-fatal stroke. This is likely due to the low sample size and events rates of the included RCTs for these clinical outcomes.

The RALES trial evaluated the effect of spironolactone versus placebo on morbidity and mortality for patients with severe heart failure (*9*). The patients included in our study were similar to the patients in the RALES trial (9) regarding age, sex, and race. However, the RALES trial focused on patients with heart failure (New York Heart Association class IV) with a left ventricular ejection fraction of no more than 35 percent (*9*). Meanwhile, our article focused on patients with type 2 diabetes and CKD. Therefore, more RCTs are needed to compare the spironolactone to finerenone.

The main limitations to our meta-analysis are the low number of included RCTs in our analysis, low events rate, and had relatively short follow-up duration. Therefore, more RCTs are still needed to shed more light on the growing interest in finerenone.

In conclusion, among patients with CKD and DM-2, finerenone is associated with lower risks of cardiovascular events and heart failure hospitalizations compared with placebo. Further large clinical trials and long-term follow-up with a focus on cost-effectiveness are needed.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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