The RALES Legacy and Finerenone Use on CKD Patients

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Results from the much-anticipated Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial were published recently. This double-blind, placebo-controlled trial evaluated the effects of the “novel” mineralocorticoid receptor antagonist—finerenone—on kidney and cardiovascular outcomes in patients with advanced CKD and type 2 diabetes mellitus. The study tested the hypothesis that finerenone slows the progression of kidney disease and reduces cardiovascular mortality and morbidity (1).

Finenone (developmental code name BAY 948862) has been described as an effective and selective third-generation nonsteroidal mineralocorticoid receptor antagonist (2). The mechanism of action of finerenone is different than previous “similar” drugs. Although classic mineralocorticoid receptor antagonists bind in the ligand binding domain of the receptor, finerenone causes conformational alterations in the mineralocorticoid receptor through a bulky side chain. The bulky molecule causes the protuberance of the mineralocorticoid receptor helix 12, which has an important role in the activation of the receptor through the binding of key coactivators (2). Although a single oral dose is usually well tolerated, in initial pharmacokinetics studies, exposure to finerenone was higher in patients with moderate and severe kidney function impairment when compared with normal kidney function, with a moderate to high variability among individuals (3).

The medical community reacted with some excitement to the positive results of the trial. The incidence of the primary composite outcome of death from kidney causes or kidney failure, which was considered a persistent reduction of 40% in the eGFR from the baseline, was significantly lower in patients on finerenone than placebo during a median follow-up of 2.6 years (hazard ratio, 0.82; 95% confidence interval, 0.73 to 0.93; P=0.001) (1).

However, certain aspects of this trial warrant further discussion. First, the use of a composite primary outcome requires some caution when interpreting the results (4). Second, after 3 years, the number needed to treat was 29 to prevent one primary outcome event (1).

Comparatively, novel drugs have been proposed to patients with CKD and diabetes mellitus in the past years with superior outcomes: dapagliflozin, atrasentan, and canagliflozin. Dapagliflozin showed a 36% lower relative risk (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.79) than placebo for patients with type 2 diabetes for the primary composite outcome—a sustained decrease in the eGFR of ≥50%, kidney failure, or death from kidney or cardiovascular causes (5). The number needed to treat with dapagliflozin to prevent one primary outcome event was 19—lower than with finerenone. In the Study of Diabetic Nephropathy with Atrasentan, the relative risk of the primary outcome was 35% lower in the atrasentan group than in the placebo group (hazard ratio, 0.65; 95% confidence interval, 0.49 to 0.88; P=0.005). The primary outcome was a composite of doubling of serum creatinine level (sustained for ≥30 days) or kidney failure (eGFR<15 ml/min per 1.73 m² sustained for ≥90 days, maintenance dialysis for ≥90 days, kidney transplantation, or death from kidney failure) (6). The hazard ratio for the comparison of canagliflozin and placebo for the primary outcome (a composite of kidney failure, a doubling of the serum creatinine, or death from kidney or cardiovascular causes) was 0.70—a 30% lower relative risk than placebo (hazard ratio, 0.70; 95% confidence interval, 0.47 to 0.80; P<0.001) (7). Taken together, these recent data suggest that dapagliflozin, atrasentan, and canagliflozin may be better alternatives than finerenone for patients with CKD and diabetes mellitus.

Additionally, FIDELIO-DKD raises another major concern. CKD is a well-recognized risk factor for hyperkalemia, with a prevalence rate ranging from 14% to 20% (8). In line with this concern, the serum potassium levels of patients on finerenone, as well as the incidence of hyperkalemia, were much higher than in patients who were taking placebo in the FIDELIO-DKD trial. Patients in the finerenone group had a higher mean serum potassium level compared with the placebo group. Although the incidences of moderate (>5.5 mEq/L) and severe hyperkalemia (>6.0 mEq/L) were 9.8% and 1.4% in the placebo group, respectively, they were more than two- and three-fold in patients treated with finerenone: 21.7% and 4.5%, respectively. Although no fatal cases were reported, hyperkalemia-related events were twice as likely in patients who used finerenone (18.3%) than in the placebo group (9.0%) (1).

In order to further address these concerns, first we must revisit a seminal study published 20 years ago in the same prestigious journal: the Randomized Aldactone Evaluation Study, widely known by its acronym RALES. In summary, this trial showed that “blocking of mineralocorticoid receptors with spironolactone,
in addition to standard therapy, significantly diminishes morbidity and mortality risk in patients with severe heart failure (9). The incidence of serious hyperkalemia was minimal and had no statistical significance: 14 patients of 841 (2%, $P=0.42$) in the spironolactone group versus ten patients of 822 (1%) in the placebo group. Although 62 patients (8%) in the spironolactone group discontinued treatment due to adverse events, against 40 patients (5%) in the placebo group, this was probably due to a higher incidence of breast pain or gynecomastia among men using spironolactone ($P<0.001$) (9). Conversely, in the FIDELIO-DKD trial, there were many more patients who discontinued the drug due to hyperkalemia in the finerenone group (64 of 2827, 2.3%) compared with the group of patients receiving placebo (25 of 2831, 0.9%) (1).

As expected, rate of prescriptions of spironolactone increased following publication of RALES; however, in parallel, there was also a substantial “unexpected” rise in the

![Figure 1](image-url)

**Figure 1.** Hospital admission and in-hospital death rates associated with hyperkalemia in patients hospitalized with heart failure who were also treated with ACE inhibitors following publication of the Randomized Aldactone Evaluation Study (RALES) study. The bars indicate in a 4-month period, the rate of hospital admission due to hyperkalemia per 1000 patients (A) and the in-hospital death rate associated with hyperkalemia per 1000 patients (B). Starting at the second interval of the year 1999, the line shows the projected rates of hospital admissions due to hyperkalemia (A) and in-hospital death rates associated with hyperkalemia (B) derived from interventional ARIMA models, with 1 bars representing the 95% confidence intervals. ACE, angiotensin-converting enzyme; ARIMA, autoregressive integrated moving average. Adapted from ref. 10, with permission.
number of hospital admissions and deaths associated with iatrogenic hyperkalemia (Figure 1) (10). Beyond its formal landmark results and academic conclusion, RALES taught the medical community, in a harsh manner, a quite intuitive “between the lines” lesson: that results obtained in controlled environments (randomized controlled trials) should be translated to the “real world” with caution (11).

Finally, we are concerned that the positive outcomes of FIDELIO-DKD may lead to wider (and indiscriminate) prescription of finerenone, which could potentially increase drug-induced hyperkalemia cases in the population of patients with CKD. Our previous experience with RALES cautions us about what also might come following publication of impactful results from controlled trials. Whether we actually learned this lesson or whether a substantial part of the RALES legacy has already been forgotten will only be discovered in the years to come (11). Until more robust evidence is available, we must still be careful when deciding to prescribe finerenone to patients with advanced CKD.

Disclosures
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References

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