

### Transcript Details

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The Impact of Finerenone Plus Empagliflozin on Hyperkalemia in the CONFIDENCE Trial

### Announcer:

Welcome to DataPulse from ASN Kidney Week 2025 on ReachMD. This activity, titled “The Impact of Finerenone Plus Empagliflozin on Hyperkalemia in the CONFIDENCE Trial” is provided by Medcon International.

### Dr. Agarwal:

Hello. This is Dr. Rajiv Agarwal. I'm a staff nephrologist at the VA Medical Center at Indianapolis, Indiana, and I'm joining you here from Houston, the Kidney Week 2025, to present you the late-breaking findings of the CONFIDENCE trial.

The CONFIDENCE trial was a double-blind, randomized controlled trial in patients with type 2 diabetes and chronic kidney disease to test the hypothesis whether the simultaneous initiation of empagliflozin and finerenone would be better than either of the component therapies over 180 days. The primary endpoint was the mean reduction in urine albumin-to-creatinine ratio from baseline to 180 days.

We reported these results in the *New England Journal of Medicine* in June of 2025. Here, we are reporting the side effect of hyperkalemia in these participants.

Hyperkalemia is an important adverse effect of renin-angiotensin system inhibitor therapy and often leads to dose interruption or permanently stopping these drugs. So understanding why it happens, how it happens is important.

So we already reported that hyperkalemia is approximately twice as often seen in finerenone-containing regimens. Here, we analyze what are the factors that lead to a mean change from baseline in serum potassium and also determine what are the factors that determine the risk of hyperkalemia.

And then we ask whether the hyperkalemia makes any difference to the outcome of reduction in UACR from baseline to day 180. And for that, we did a causal mediation analysis—asked if hyperkalemia is in the causal pathway of efficacy of these drugs.

So what did we find? Well, first, there were a small number of people who had hyperkalemia: approximately 40 people in the combination group, 48 in the finerenone group, and 25 in the empagliflozin group who had any hyperkalemia. If you look at the numbers who had hyperkalemia—severe hyperkalemia, defined as more than 6—there were only about a dozen people in the finerenone-containing groups and approximately 5 people in the empagliflozin group.

So we find that the distribution of hyperkalemia is even, over time, demonstrated by Kaplan–Meier curves. But what we went about asking, what are the determinants of the change from baseline in mean level of potassium?

Well, first is obvious: it is the finerenone-containing regimen. But next, very important, is the baseline level of potassium. And that's really interesting, because what we found was that the lower the potassium, the more likely that it's going to go up. Regardless of therapy, whether you are on finerenone, empagliflozin, or the combination, if you're starting at about a potassium of 3.5, it will go up. But if you're starting with a potassium of 5, it doesn't change in the finerenone-containing groups, but it goes down in the empagliflozin group.

The second thing we found was that eGFR is an important determinant of hyperkalemia and also a mean change in potassium; that's self-evident. When we look at the adjusted odds ratio for hyperkalemia, besides finerenone, again, it was the mean potassium level. Every milliequivalent increased the odds of hyperkalemia by ninefold. And there was an 11% increase in the risk of hyperkalemia by adjusted odds ratio for every 5 mL decline in eGFR.

Finally, when we look at the causation, we find there's absolutely no effect of the occurrence or lack of occurrence of hyperkalemia on the improvement in uACR from baseline.

So in summary, what we find is that the improvement in potassium is absent, whether we look at the mean change from baseline in potassium or we look at hyperkalemia, when we compare the finerenone alone with finerenone plus empagliflozin.

So how does this compare with other trials? The other trials actually show very clearly that SGLT2 inhibitors mitigate hyperkalemia. So why is this trial showing there is no effect? In part, it is because the potassium stress induced by finerenone is very small. It is only 0.18 when we compare it to placebo. When you compare it to other therapies—for example, spironolactone or aldosterone synthase inhibitors—it's about 0.3. So if the potassium stress is less and empa works when there's a potassium stress, it's no surprise that we didn't find an effect.

So evidence of absence is not absence of evidence. So we really cannot say that SGLT2 inhibitors don't work to mitigate hyperkalemia. It's just in the context of this trial, where potassium stress is less with finerenone, that we are finding that empagliflozin is not as effective.

That's, in summary, what we found. Here again, I'm Dr. Rajiv Agarwal joining you from Houston. Thanks for listening in.

**Announcer:**

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