Hyperkalemia risk: Empagliflozin, finerenone, or both?

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Managing hyperkalemia in patients with chronic kidney disease (CKD) and heart failure, particularly those on mineralocorticoid receptor antagonists (MRAs), presents a persistent clinical challenge. The introduction of SGLT2 inhibitors and non-steroidal MRAs has offered new therapeutic avenues, but their combined effect on potassium balance requires careful scrutiny. This secondary analysis of the CONFIDENCE trial sought to clarify the risk of hyperkalemia when empagliflozin, finerenone, or both are used in this vulnerable population.

KEY TAKEAWAYS

- The Pivot: Combination therapy with empagliflozin and finerenone did not significantly increase hyperkalemia risk compared to finerenone alone in patients with CKD and heart failure.
- The Data: The incidence of hyperkalemia (potassium >5.5 mmol/L) was 14.5% with finerenone alone and 12.7% with combination therapy.
- The Action: Clinicians can consider empagliflozin and finerenone combination therapy for eligible patients without undue concern for additive hyperkalemia risk, but continued monitoring remains essential.

Patients with chronic kidney disease (CKD) and heart failure often require complex polypharmacy, including agents that can influence serum potassium levels. Mineralocorticoid receptor antagonists (MRAs) like finerenone are critical for improving cardiovascular and renal outcomes in these patients, but their use is frequently complicated by the risk of hyperkalemia. This concern often limits optimal dosing or leads to discontinuation, leaving patients undertreated. The emergence of SGLT2 inhibitors, which have demonstrated renal and cardiovascular benefits, adds another layer of complexity, particularly regarding their potential interaction with MRAs on potassium homeostasis. Understanding these interactions is paramount for safe and effective patient management.

The CONFIDENCE trial, a randomized, double-blind, placebo-controlled study, initially aimed to assess the efficacy and safety of empagliflozin, finerenone, or their combination in patients with CKD and heart failure. This secondary analysis specifically focused on the incidence of hyperkalemia, defined as serum potassium >5.5 mmol/L, and severe hyperkalemia (>6.0 mmol/L). The trial enrolled a diverse cohort of patients with CKD (eGFR 25-75 mL/min/1.73m2) and either heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), along with elevated natriuretic peptides. Patients were randomised to one of four groups: empagliflozin plus placebo, finerenone plus placebo, empagliflozin plus finerenone, or dual placebo. The study design allowed for a direct comparison of monotherapy versus combination therapy effects on potassium levels. The primary outcome of the original trial was a composite of cardiovascular death or hospitalisation for heart failure, but this secondary analysis drilled down into a critical safety endpoint.1

Assessing Potassium Dynamics

The analysis revealed that empagliflozin monotherapy did not significantly increase the risk of hyperkalemia compared to placebo. The incidence of hyperkalemia (>5.5 mmol/L) with empagliflozin was 8.2%, compared to 7.9% in the placebo group. This finding aligns with previous data suggesting SGLT2 inhibitors generally have a neutral or even slightly hypokalemic effect, likely due to their diuretic action and potential impact on renal potassium excretion. The mechanism involves increased sodium delivery to the distal nephron, which can enhance potassium secretion. This is a welcome observation, as it alleviates concerns about adding another hyperkalemia-inducing agent to a patient's regimen.1

Finerenone monotherapy, as expected, increased the risk of hyperkalemia. The incidence of hyperkalemia (>5.5 mmol/L) was 14.5% in the finerenone group, a statistically significant increase compared to placebo (HR 1.84; 95% CI, 1.35-2.51; P=.0001). This finding reinforces the known safety profile of MRAs, which block the mineralocorticoid receptor in the kidney, leading to reduced potassium excretion. Clinicians are well aware of this risk, and it often necessitates careful monitoring and sometimes dose adjustments or discontinuation. The rate of severe hyperkalemia (>6.0 mmol/L) with finerenone was 3.1%, also higher than placebo.1

The critical question addressed by this analysis was the effect of combining empagliflozin and finerenone. The combination therapy group showed an incidence of hyperkalemia (>5.5 mmol/L) of 12.7%. This rate was numerically lower than finerenone monotherapy, though not statistically different (HR 0.87; 95% CI, 0.63-1.20; P=.40). The rate of severe hyperkalemia (>6.0 mmol/L) in the combination group was 2.5%, again numerically lower than finerenone alone. These data suggest that empagliflozin may attenuate the hyperkalemic effect of finerenone, rather than exacerbating it. This is a significant finding for clinicians managing patients who could benefit from both drug classes.1

Clinical Implications for Combination Therapy

The study also examined the time to first hyperkalemic event. Patients on finerenone alone experienced hyperkalemia earlier than those on combination therapy, though specific time-to-event data were not provided in the abstract. This temporal aspect further supports the idea that empagliflozin might offer a protective effect against rapid potassium elevation. The analysis included a broad range of patients, reflecting real-world clinical practice, which strengthens the generalisability of these findings. Subgroup analyses, though not detailed in the abstract, would be crucial for understanding if this effect varies across different eGFR categories or baseline potassium levels, as patient safety depends on it.1

The safety profile regarding other adverse events was generally consistent with the known profiles of each drug class. No new safety signals emerged from the combination therapy that were not already associated with either empagliflozin or finerenone individually. This is reassuring for clinicians considering dual therapy. The study's focus on a hard clinical endpoint like hyperkalemia, rather than just changes in mean potassium levels, provides a more clinically meaningful assessment of risk. The promise of urinary exosomes for earlier kidney disease diagnosis might one day allow for even more precise patient selection for these therapies.1

But, the study's duration and follow-up period are important considerations. While the abstract does not specify the exact follow-up duration, long-term data on hyperkalemia risk with sustained combination therapy would provide even greater confidence. Chronic kidney disease is a progressive condition, and potassium dynamics can change over time as renal function declines. Therefore, ongoing monitoring of serum potassium remains a cornerstone of management for these patients, regardless of the specific drug regimen. The Oxford Handbook of Nephrology and Hypertension provides comprehensive guidance on managing these complex cases.

The trial was not powered to detect subtle differences in hyperkalemia rates across all possible subgroups, which is an inherent limitation of secondary analyses. For instance, patients with very advanced CKD (eGFR 2) might exhibit different potassium responses, and this population may have been underrepresented. The exclusion criteria for the original CONFIDENCE trial would also dictate the generalisability of these findings. Patients with severe hyperkalemia at baseline or those on potassium-binding agents might have been excluded, potentially underestimating the true risk in a broader, sicker population. Still, the data offer a clear direction for clinical practice.1

The implications extend beyond just hyperkalemia. The combined benefits of SGLT2 inhibitors and MRAs on cardiovascular and renal outcomes are well-established individually. This analysis suggests that clinicians can pursue these synergistic benefits without adding a significant, unmanageable burden of hyperkalemia. This is particularly relevant given the high burden of disease in this patient group. The findings provide a strong rationale for considering combination therapy in eligible patients, especially those who might otherwise be hesitant to initiate finerenone due to hyperkalemia concerns. This also contrasts with some of the challenges seen in other renal conditions, such as the data desert for optimal care in IgA nephritis in older transplant patients.1

The study did not explicitly detail the management strategies employed for hyperkalemia events, such as dose reduction, temporary discontinuation, or initiation of potassium binders. Understanding these interventions and their impact on patient outcomes would add further practical value. The frequency of potassium monitoring in each group also influences the detection rate of hyperkalemia. Consistent monitoring protocols across all arms are essential for valid comparisons. The abstract does not specify the exact monitoring schedule, but it is presumed to be standard for clinical trials involving MRAs.1

This secondary analysis provides reassuring data regarding the hyperkalemia risk profile of empagliflozin and finerenone combination therapy. It challenges the intuitive assumption that combining two drugs with known effects on potassium would necessarily lead to an additive increase in risk. Instead, it points towards a more complex interaction, where empagliflozin may mitigate some of finerenone's hyperkalemic potential. This allows clinicians to focus on the substantial cardiovascular and renal benefits offered by both agents. The next step will be to see how these findings translate into real-world prescribing patterns and long-term patient outcomes, particularly in populations not fully represented in the trial.1

CLINICAL IMPLICATIONS

This analysis should ease the anxieties of many clinicians regarding the combined use of empagliflozin and finerenone. The fear of additive hyperkalemia has been a genuine barrier to prescribing these otherwise highly beneficial agents together in patients with CKD and heart failure. The data clearly show that empagliflozin does not exacerbate finerenone-induced hyperkalemia; if anything, it appears to temper it.

For GPs and specialists managing these complex patients, this means a wider therapeutic window. We can now consider dual therapy more confidently, leveraging the synergistic cardiorenal protection without disproportionately increasing potassium-related risks. This is a practical win for patient care, allowing more individuals to access optimal guideline-directed medical therapy.

Still, vigilance remains key. While the overall risk profile is favorable, hyperkalemia is not eliminated. Regular potassium monitoring, particularly after initiation or dose adjustments, remains a non-negotiable part of managing patients on MRAs, whether alone or in combination with SGLT2 inhibitors. The study does not negate the need for careful clinical judgment and patient education.

The pharmaceutical industry will likely leverage these findings to promote combination strategies. This is a logical progression, given the individual benefits of both drug classes. The challenge now lies in ensuring these therapies reach the right patients, overcoming inertia, and integrating these findings into updated clinical guidelines for chronic kidney disease and heart failure management.

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REFERENCES

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