

Serum Potassium Concentrations Shape Heart Failure Risk

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The precise serum potassium concentration associated with optimal outcomes in heart failure (HF) has remained undefined, particularly regarding potential differences between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).¹ A recent individual patient data meta-analysis clarifies that the optimal range for both HF subtypes is narrower than previously assumed, with concentrations outside 4.0-4.5 mmol/L linked to increased mortality.

KEY TAKEAWAYS

- ° The Pivot: The optimal serum potassium range for heart failure patients is now defined as 4.0-4.5 mmol/L, irrespective of ejection fraction.
- ° The Data: Serum potassium concentrations outside 4.0-4.5 mmol/L were associated with increased all-cause mortality (HR 1.25, 95% CI 1.18-1.33, p<0.001).
- ° The Action: Clinicians should aim to maintain serum potassium within 4.0-4.5 mmol/L in all heart failure patients, adjusting diuretic and RAAS inhibitor regimens as necessary.

The optimal serum potassium concentration in patients with heart failure (HF) has been a subject of ongoing debate, with uncertainty regarding whether the safe range differs between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).¹ Current guidelines often recommend a broad target range, but the clinical implications of maintaining potassium within a narrower, more precise window have not been fully elucidated. This ambiguity has led to varied clinical practices in managing electrolyte balance, particularly in patients receiving diuretics and renin-angiotensin-aldosterone system (RAAS) inhibitors, which can significantly influence potassium levels.¹

Potassium plays a critical role in cardiac electrophysiology, muscle contraction, and nerve function. Deviations from normal serum potassium levels can predispose patients to cardiac arrhythmias, which are a common cause of morbidity and mortality in HF. Both hypokalaemia and hyperkalaemia can destabilise myocardial cell membranes, altering resting membrane potential and action potential duration, thereby increasing the risk of life-threatening ventricular arrhythmias. Given the high prevalence of HF globally and the significant burden of associated mortality and hospitalisations, refining the management of modifiable risk factors like electrolyte imbalances holds substantial clinical importance.

What the study did

A recent individual patient data meta-analysis, published in the *European Heart Journal*, aimed to define the optimal serum potassium concentrations in HF patients and to determine if this range varied by ejection fraction subtype.¹ The meta-analysis included data from multiple clinical trials and observational studies, pooling individual patient

data to achieve sufficient statistical power. The primary outcome was all-cause mortality, with secondary outcomes including cardiovascular mortality and HF hospitalisation. The researchers categorised serum potassium concentrations into predefined ranges and used Cox proportional hazards models to assess the association between potassium levels and outcomes, adjusting for relevant covariates such as age, sex, renal function, and concomitant medications.¹

The methodology involved a systematic search of major medical databases for studies reporting serum potassium levels and clinical outcomes in HF patients. Inclusion criteria focused on studies with individual patient data available, allowing for a more granular analysis than traditional aggregate data meta-analyses. The researchers performed rigorous data harmonisation across studies to ensure consistency in variable definitions and outcome ascertainment. Statistical analyses accounted for potential within-study and between-study heterogeneity. The study population encompassed a diverse range of HF patients, including those with varying etiologies of HF, different stages of disease severity, and a broad spectrum of comorbidities, reflecting real-world clinical practice.

The meta-analysis included a substantial cohort of HF patients, comprising both HFrEF and HFpEF populations. The key finding was that serum potassium concentrations outside the range of 4.0-4.5 mmol/L were consistently associated with an increased risk of all-cause mortality. Specifically, both hypokalaemia (potassium <4.0 mmol/L) and hyperkalaemia (potassium >4.5 mmol/L) were linked to adverse outcomes. For every 0.5 mmol/L deviation from the 4.0-4.5 mmol/L range, there was a statistically significant increase in the risk of all-cause mortality. Patients with serum potassium 4.5 mmol/L also demonstrated an elevated risk of all-cause mortality (HR 1.18, 95% CI 1.12-1.24, $P=0.001$).

Crucially, the study found no significant difference in the optimal serum potassium range between HFrEF and HFpEF patients. The association between potassium concentrations and mortality remained consistent across both HF subtypes, suggesting a universal target range for all HF patients. The findings were robust across various subgroups, including those with different baseline renal function and those receiving different classes of HF medications. The study also reported similar trends for cardiovascular mortality and HF hospitalisation, although the strongest association was observed for all-cause mortality.¹

While the meta-analysis provides strong evidence for a narrower optimal potassium range, it is important to acknowledge certain limitations. As an observational analysis of pooled data, it cannot establish causality definitively. Confounding by indication, where patients with more severe disease or specific comorbidities might be more prone to potassium derangements, could still influence the results despite extensive adjustments. Furthermore, the study relied on serum potassium measurements taken at specific time points, which may not fully capture the dynamic nature of potassium fluctuations in individual patients. The frequency of potassium monitoring and the methods used for potassium correction were not uniformly reported across all included studies, potentially introducing variability. Future prospective trials designed to actively manage potassium within this newly defined optimal range would provide further validation and could inform more precise guideline recommendations.¹

CLINICAL IMPLICATIONS

This meta-analysis from Ono, Chimura, and Docherty provides a much-needed clarification for managing heart failure patients. The finding that a serum potassium range of 4.0-4.5 mmol/L is optimal for both HFrEF and HFpEF patients simplifies a previously ambiguous area. Clinicians should now be more proactive in titrating diuretics, RAAS inhibitors, and mineralocorticoid receptor antagonists to maintain potassium within this tighter window. This will likely necessitate more frequent electrolyte monitoring, particularly during dose adjustments or in patients with fluctuating renal function.

The implications for patient safety are clear. Reducing the incidence of both hypokalaemia and hyperkalaemia, which are known to predispose to arrhythmias and other adverse events, should translate into improved outcomes. This precision in electrolyte management could also influence the uptake and optimal dosing of newer HF therapies, such as SGLT2 inhibitors, which have a relatively neutral effect on potassium but are often used in conjunction with agents that do. Guideline bodies like NICE and ESC should consider updating their recommendations to reflect this narrower, evidence-based target range, providing clearer guidance for primary care and specialist cardiology alike.

From an industry perspective, this data might encourage the development of novel potassium-binding agents or more finely tuned diuretic formulations that allow for better control of serum potassium without compromising other therapeutic benefits. Pharmaceutical companies with existing HF portfolios, particularly those manufacturing RAAS inhibitors, should highlight the importance of careful electrolyte monitoring in their educational materials, reinforcing the need for clinicians to manage potassium within this newly defined optimal range to maximise patient benefit and minimise risk.

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REFERENCES

1. Ono R, Chimura M, Docherty KF. Optimal serum potassium concentrations in heart failure: an individual patient data meta-analysis. Eur Heart J 2026.

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