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EDITORIAL COMMENT

Is hyperkalaemia in heart failure a risk factor or a risk marker? Implications for renin–angiotensin–aldosterone system inhibitor use

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This article refers to 'Potassium and the use of renin–angiotensin–aldosterone system inhibitors in heart failure with reduced ejection fraction: data from BIOSTAT-CHF' by J.C. Beusekamp *et al.*, published in this issue on pages 923–930.

For clinicians caring for patients with heart failure (HF), acute or chronic kidney disease (CKD), and/or diabetes mellitus, dyskalaemia and optimization of diuretics and renin–angiotensin–aldosterone system inhibitors (RAASi) are everyday concerns. Although we understand cellular and renal potassium regulation, surprisingly little is known about the causal relationships between these syndromes, drug effects, and outcomes.

In this issue of the Journal, Beusekamp *et al.*[1] studied potassium, use of RAASi drugs, and outcomes in patients with HF and reduced ejection fraction (HFrEF) from the well characterized longitudinal BIOSTAT-CHF cohort. At baseline, hypokalaemia ($K < 3.5$ mEq/L) was present in 6.9% and hyperkalaemia ($K > 5.0$ mEq/L) in 8.0%. In unadjusted and adjusted Cox models, neither hypo- or hyperkalaemia, nor increases or decreases in potassium at 9 months, were significantly associated with the composite outcome of all-cause death or HF hospitalization up to 2 years. However, in univariable and several multivariable logistic regression models, higher baseline potassium was associated with lower odds of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) uptitration. So is hyperkalaemia a risk marker or a risk factor for poor outcomes in HF?

Does dyskalemia cause poor outcomes? Several studies indicate that the relationship between potassium and outcomes exhibits a U-shaped relationship in HF and/or CKD.[2,3] However, the extent of multivariable adjustment in these studies has been variable. In the present analysis, hypo- or hyperkalaemia were not significantly associated with outcomes. However, the sample size of 1666 was modest and a closer examination reveals nominal hazard ratios substantially above 1.0 for baseline hypo- but not hyperkalaemia. Similarly, in a study of 13 015 patients in the Swedish HF Registry, in univariable analysis, the relationship between potassium and long-term outcomes was U-shaped, but in multivariable analyses, hypo- but not hyperkalaemia was associated with worse outcomes.[4] Taken together, these data suggest that hyperkalaemia is not a risk factor but a risk marker, but a risk marker for what?

Does hyperkalaemia attenuate the benefit of RAASi drugs? In RALES[5] and EMPHASIS-HF[6] the benefit of mineralocorticoid receptor antagonists was independent of potassium levels and persisted even with severe hyperkalaemia. In BIOSTAT-CHF, there was no interaction between baseline potassium, potassium increases, or 9-month potassium levels and the benefit of uptitrating RAASi. In an analysis of patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 in the Swedish HF Registry, ACEi/ARB use was associated with the same benefit as in patients with eGFR ≥ 30 mL/min/1.73 m^2, and as demonstrated in randomized trials of ACEi/ARB in HFrEF.[7]

So what is the problem with hyperkalaemia? We believe BIOSTAT-CHF and other studies show that it is primarily not a risk factor but a risk marker that leads to suboptimal use of RAASi, especially mineralocorticoid receptor antagonists, which in turn is causative in poor outcomes (*Figure 1*). Numerous studies have demonstrated suboptimal use and/or dosing of RAASi in the real world, that this underuse is associated with worse outcomes,[8–11] and that quality improvement efforts improve use of evidence-based HF drugs and ultimately outcomes.[12] In the present analysis, the salient finding was that hyperkalaemia at baseline was associated with failure to uptitrate RAASi, consistently in univariable analysis and in several multivariable models.

What can be done? Taken together, these findings suggest that the main goal for patients with HFrEF and concomitant CKD

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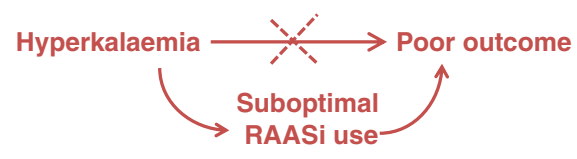

Figure 1 Hyperkalaemia is a risk marker for poor outcomes by leading to dose reduction or discontinuation of renin–angiotensin–aldosterone system inhibitors (RAASi).

and/or hyperkalaemia should be to optimize RAASi use. This can potentially be achieved by diligent monitoring of renal function and electrolytes and persistence in attempting to introduce and uptitrate these agents. Indeed, while eGFR <30 mL/min/1.73 m^2 or potassium >5.0–5.2 mEq/L were exclusion criteria for most RAASi drug trials, the European Society of Cardiology HF guidelines recommend that these drugs not be dose-reduced or discontinued until potassium goes above 5.5 mEq/L.[13] Another possibility is using novel potassium binders to enable RAASi use. Both patiromer and sodium zirconium cyclosilicate were shown to be effective in lowering potassium and maintaining normokalaemia in patients with HF and hyperkalaemia.[14,15] Whether such a strategy can enable use of RAASi agents and translate into improved outcomes in patients with HFrEF and CKD and/or hyperkalaemia remains to be shown.

Conflict of interest: none declared.

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