Is hyperkalemia in heart failure a risk factor or risk marker? - Implications for RAASi use

Lars H. Lund MD PhD\textsuperscript{1,2*}, Bertram Pitt MD\textsuperscript{3}

(1) Karolinska Institutet, Department of Medicine, Stockholm, Sweden
(2) Karolinska University Hospital, Heart and Vascular Theme, Stockholm, Sweden
(3) University of Michigan, Department of Medicine, Ann Arbor, Michigan, USA

*Correspondence
Lars H. Lund MD, PhD
Department of Medicine, Karolinska Institutet
171 76 Stockholm, Sweden
Fax: +46-8- 311044
Phone: +46-8-51770000
email: lars.lund@alumni.duke.edu

For clinicians caring for patients with heart failure (HF), acute or chronic kidney disease (CKD), and/or diabetes mellitus, dyskalemia and optimization of diuretics and renin-angiotensin-aldosterone system inhibitors (RAASi) are every-day 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, hypokalemia (K <3.5 mEq/L) was present in 6.9% and hyperkalemia (K >5.0 mEq/L) in 8.0%. In unadjusted and adjusted Cox models, neither hypo- or hyperkalemia, 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 inhibitors (ACEi) / angiotensin receptor blockers (ARB) up-titration. So is hyperkalemia a risk marker or a risk factor for poor outcomes in HF?

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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 hyperkalemia were not significantly associated with outcomes. However the sample size of n=1,666 was modest and a closer examination reveals nominal hazard ratios substantially above 1.0 for baseline hypo- but not hyperkalemia. 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 hyperkalemia was associated with worse outcomes (4). Taken together, these data suggest that hyperkalemia is not a risk factor but a risk marker, but a risk marker for what?

Does hyperkalemia attenuate the benefit of RAASi drugs? In RALES (5) and EMPHASIS (6) the benefit of mineralocorticoid receptor antagonists (MRAs) was independent of potassium levels and persisted even with severe hyperkalemia. In BIOSTAT-CHF, there was no interaction between baseline potassium, potassium increases, or 9 month potassium levels and the benefit of up-titrating RAASi. In an analysis of patients with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m2 in the Swedish HF Registry, ACEi/ARB use was associated with the same benefit as in patients with eGFR ≥30 ml/min/1.73 m2, and as demonstrated in randomized trials of ACEi/ARB in HFrEF (7).

So what is the problem with hyperkalemia? 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 MRAs, which in turn is causative in poor outcomes (Figure). 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 hyperkalemia at baseline was associated with failure to up-titrate 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 and/or hyperkalemia 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 up-titrate these agents. Indeed, while eGFR <30 ml/min/1.73 m2 or potassium >5.0-5.2 mEq/L were exclusion criteria for most RAASI drug trials, the ESC 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 normokalemia in patients with HF and hyperkalemia (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 hyperkalemia remains to be shown.

REFERENCES


**FIGURE.** Hyperkalemia is a risk marker for poor outcomes, by leading to dose reduction or discontinuation of RAASi drugs.