

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

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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

1. Beusekamp JC, Tromp J, van der Wal HH, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Metra M, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Rossignol P, Zannad F, Voors AA, van der Meer P. Potassium and the use of renin-angiotensin-aldosterone system inhibitors in heart failure with reduced ejection fraction: data from BIOSTAT-CHF. *Eur J Heart Fail.* 2018 Jan 12.
2. Luo J, Brunelli SM, Jensen DE, Yang A. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. *Clinical journal of the American Society of Nephrology : CJASN.* 2016 Jan 7;11(1):90-100.
3. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, Krogager ML, Kober L, Torp-Pedersen C, Sogaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J.* 2017 Oct 7;38(38):2890-6.

4. Cooper LB, Benson L, Mentz RJ, Savarese G, DeVore AD, Carrero JJ, Dahlström U, Anker SD, Lainscak M, Hernandez A, Pitt B, Lund LH. Association Between Serum Potassium Level and Outcomes in Heart Failure

With Reduced Ejection Fraction: A Cohort Study From the Swedish Heart

Failure Registry. ACC 20172017.

5. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, Pitt B, Solomon SD, Randomized Aldactone Evaluation Study I. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail.* 2014 Jul;7(4):573-9.

6. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Girerd N, Bakris G, Pitt B, Zannad F. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail.* 2014 Jan;7(1):51-8.

7. Edner M, Benson L, Dahlstrom U, Lund LH. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. *Eur Heart J.* 2015 Jun 11.

8. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *The American journal of managed care.* 2015 Sep;21(11 Suppl):S212-20.

9. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. *Eur J Heart Fail.* 2016 May;18(5):503-11.

10. Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozd J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavaliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L, Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2013 Oct;15(10):1173-84.

11. Ferreira JP, Rossignol P, Machu JL, Sharma A, Girerd N, Anker SD, Cleland JG, Dickstein K, Filippatos G, Hillege HL, Lang CC, Ter Maaten J, Metra M, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Voors A, Zannad F. Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. *Eur J Heart Fail.* 2017 Jun 05.

12. Lund LH, Carrero, J.J., Farahmand, B., Henriksson, K.M., Jonsson, Å., Jernberg, T., Dahlström, U. Association between enrolment in a heart failure quality registry and subsequent mortality – a nationwide cohort study. *Eur J Heart Fail.* 2017;in press.

13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M, Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European

Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2016 Aug;18(8):891-975.

14. Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, Christ-Schmidt H, Berman L, Weir MR. Effect of patiomer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail.* 2015 Oct;17(10):1057-65.

15. Anker SD, Kosiborod M, Zannad F, Pina IL, McCullough PA, Filippatos G, van der Meer P, Ponikowski P, Rasmussen HS, Lavin PT, Singh B, Yang A, Deedwania P. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail.* 2015 Oct;17(10):1050-6.

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



