OPTIMISING RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITOR THERAPY IN HEART FAILURE AND RESISTANT HYPERTENSION: CHALLENGES AND SOLUTIONS

This Lorraine University organised, educational event took place on the 30th August 2016 as a part of the European Society of Cardiology (ESC) Congress in Rome, Italy

Moderator

Faiez Zannad[1]

Faculty

Stefan D. Anker,[2] Luis M. Ruilope,[3] Mikhail Kosiborod[4]

1. CHU Vandœuvre-lès-Nancy, Nancy, France

2. Department of Cardiology and Pneumology, University Medical Center Göttingen, Göttingen, Denmark

3. Hospital 12 de Octubre, Madrid, Spain

4. University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA

Disclosure: Dr Ruilope has served as speaker/advisor for Amgen, AstraZeneca, Bayer, Daiichi-Sankyo, Medtronic, Novartis, Relypsa, Servier, Sanofi, Theravance, and Vifor. Prof Kosiborod has received research grants from AstraZeneca, Gilead Sciences, Sanofi, and Genentech and served as a consultant for or on the advisory board of AstraZeneca, Amgen, Boehringer-Ingelheim, Sanofi, Eli Lilly, Novo Nordisk, Merck (Diabetes), GSK, ZS Pharma, Takeda, and Glytec. He has been on the speaker's bureau for Amgen. Prof Zannad has received steering committee fees from Bayer, Pfizer, Novartis, Boston Scientific, Resmed, Takeda, General Electric, and Boehringer-Ingelheim, acted as a consultant for Amgen, CVRx, Quantum Genomics, Relypsa, ZS Pharma, AstraZeneca, and Janssen and is the founder of Cardiorenal and CVCT. Prof Anker has no relevant disclosures to declare.

Acknowledgements: Writing assistance was provided by Kaedy Bryson of Ashfield Healthcare Communications Ltd., supported by AstraZeneca.

Support: Organised by Lorraine University, Nancy, France; supported by an unrestricted educational grant from AstraZeneca.

Citation: EMJ. 2016;1[4]:19-26.

MEETING SUMMARY

Renin-angiotensin-aldosterone system (RAAS) inhibitor therapy has been shown to be beneficial in patients with reduced left ventricular systolic function after an acute myocardial infarction, chronic systolic heart failure, and resistant hypertension. Although RAAS inhibitors are widely regarded as life-saving drugs, their use is often associated with changes in renal function, reducing elimination of potassium from the body. This can result in elevated concentrations of serum potassium, known as hyperkalaemia, which can in turn lead to potentially life-threatening conduction abnormalities and cardiac arrhythmias, and is associated with increased risk of death.

RAAS inhibitors are intrinsically linked to hyperkalaemia, with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and mineral corticoid receptor antagonists all increasing serum potassium levels. The consequences of this side effect are treatment discontinuation or underdosing in patients with heart failure, which may contribute to a higher rate of heart failure-related hospitalisations and deaths. However, since the benefits of RAAS inhibitors outweigh the risks of hyperkalaemia, there remains the need to overcome these challenges rather than withdraw treatment.

Treatment options currently available for reducing potassium concentrations have many limitations, including uncertain efficacy, potential safety issues, as well as the fact that many therapies are temporising,

only reducing serum potassium levels for a short amount of time, rather than eliminating excess potassium from the body. The clinical need to improve hyperkalaemia treatment options has led to the emergence of two novel agents: patiromer, which has been approved in the USA, and sodium zirconium cyclosilicate (SZC) which is currently in the clinical development stage. Studies have shown that these two new agents are efficacious in terms of achieving and maintaining normal potassium levels for up to 1 year and are well tolerated.

Introduction

Treatment with RAAS inhibitors is instrumental in the treatment of patients with heart failure with reduced ejection fraction (HFrEF) to reduce heart failure-related hospitalisations and deaths. According to 2016 European Society of Cardiology (ESC) guidelines, three out of four life-saving drug classes in this patient group have RAAS inhibitor properties.[1] Large-scale randomised clinical trials have demonstrated the critical value of RAAS inhibitors. In a prospective propensity score-matched study of heart patients, all-cause mortality was significantly higher when RAAS inhibitors were not used.[2] Furthermore, in a retrospective study of 205,108 patients, discontinuing RAAS inhibitors or administering them at a submaximal dose was associated with a higher death rate.[3]

The class of RAAS inhibitors is broad, including ACE inhibitors, angiotensin receptor blockers, and aldosterone receptor blockers (Figure 1). However, due to their mechanisms of action, the use of RAAS inhibitors increases serum potassium ion concentrations. Given the risk of hyperkalaemia, RAAS inhibitors are frequently discontinued, underdosed, or just not given to patients with heart failure that are eligible for these life-saving medications.[4] Hence, there is a substantial unmet need for optimisation and maintenance of RAAS inhibitor therapy. Developing novel and better strategies for the management of hyperkalaemia is an integral part of addressing this clinical need.

The issues around optimising RAAS inhibitor therapy in heart failure and resistant hypertension were discussed by international experts at a Lorraine University, Nancy, France, organised, educational event held during the ESC Congress 2016 in Rome. These challenges and solutions included predicting the risk of hyperkalaemia, preventing the development of hyperkalaemia, monitoring serum potassium, and novel agents for treating hyperkalaemia.

Renin-Angiotensin-Aldosterone System and Potassium Homeostasis

RAAS is a complex system that plays a vital role in maintaining arterial blood pressure, water, and electrolyte balance in the body. Renin regulates the first step of the RAAS by converting angiotensinogen to angiotensin I (Figure 1). Angiotensin I is then activated by the enzyme ACE to form angiotensin II.

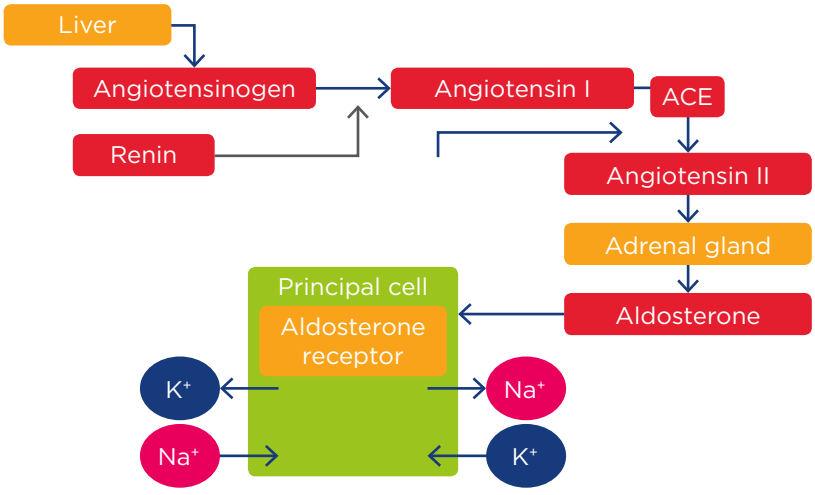

Figure 1: Schematic diagram summarising the renin-angiotensin-aldosterone system.
ACE: angiotensin-converting enzyme.

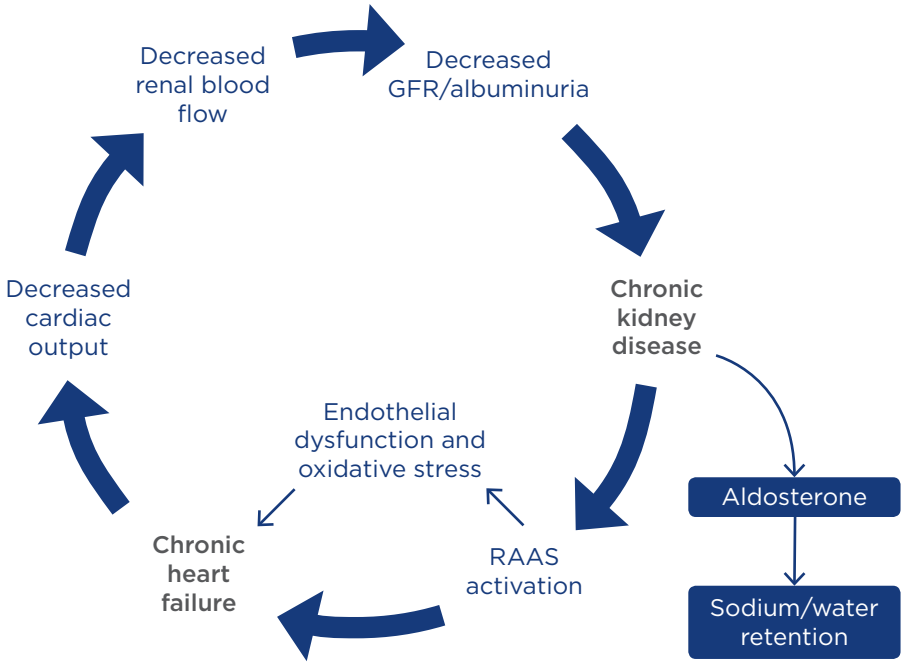

Figure 2: Role of the renin-angiotensin-aldosterone system in chronic heart failure linking to chronic kidney disease.
GFR: glomerular filtration rate; RAAS: renin-angiotensin-aldosterone system.

Angiotensin II, in turn, results in the release of aldosterone. The system is regulated through a negative feedback mechanism.

When RAAS is activated, release of angiotensin II increases sympathetic nervous system activity, inducing endothelial dysfunction and oxidative stress, stimulating vasoconstriction, sodium and water retention, and increasing arterial blood pressure. Furthermore, aldosterone stimulates sodium reabsorption, which in turn causes potassium secretion. Over time this can lead to adverse cardiovascular effects, and ultimately contribute to the development and progression of heart failure (Figure 2). Progressive cardiac dysfunction can in turn lead to reduced renal perfusion (which may further stimulate RAAS activation) thus linking chronic heart failure to chronic kidney disease.[5]

Role of Renin-Angiotensin-Aldosterone System Inhibitors

RAAS inhibitors interfere with the RAAS system at various levels and lead to favourable cardiovascular effects in patients with heart failure. There is much evidence to show that RAAS inhibitors confer significant benefits to patients suffering from HFrEF. Studies have shown that ACE inhibitors, such as enalapril, improved mortality[6] and left ventricular function,[7] while early intervention with captopril prevented or reversed progressive left ventricular remodelling.[8] Angiotensin receptor blockers, such as candesartan, reduced cardiovascular death and hospitalisation for heart failure,[9] while spironolactone improved mortality and hospitalisation in patients with symptomatic heart failure with reduced systolic function,[10] which may in part be due to spironolactone reducing cardiac remodelling.[11] Eplerenone has been demonstrated to reduce cardiovascular death and hospitalisation for heart failure in patients with heart failure symptoms after myocardial infarction and in those with chronic symptomatic heart failure with reduced systolic function,[12] while combined angiotensin receptor blockade and neprilysin inhibition improved cardiovascular morbidity and mortality to a greater extent than using an ACE inhibitor (enalapril) alone.[13]

RAAS inhibitors also have proven clinical benefits in patients with hypertension. A meta-analysis of 26 large scale clinical trials involving 146,838 patients, of which two-thirds were hypertensive, showed that treatment with ACE inhibitors or angiotensin receptor blockers reduced the risk of stroke, heart disease, and heart failure by ≤27%.[14]

RAAS inhibitors were also shown to reduce mortality in hypertensive patients in a meta-analysis of 20 cardiovascular morbidity-mortality trials (N=158,998), where RAAS inhibitor treatment reduced all-cause mortality by 5% (hazard ratio [HR]: 0.95; 95% confidence interval [CI]: 0.91–1.00; p=0.032), and cardiovascular mortality by 7% (HR: 0.93; 95% CI: 0.88–0.99; p=0.018).[15]

Causes and Risks of Hyperkalaemia

As stated above, due to blocking the RAAS system, RAAS inhibitors can cause reduced elimination of potassium by affecting potassium handling in the kidney, subsequently leading to hyperkalaemia.[16] A meta-analysis of five randomised controlled trials involving 553 patients showed that the RAAS inhibitor spironolactone, despite being highly effective at reducing resistant hypertension, raised serum potassium levels.[17] The risks of hyperkalaemia include conduction system abnormalities and serious arrhythmias.[18,19] Furthermore, in epidemiological studies it has been associated with an increased risk of mortality.[20] For example, a retrospective analysis of patients with hypertension and heart failure showed that hyperkalaemia (defined as serum potassium ≥5.1 mEq/L) was associated with increased hospital admissions[21] as well as increased in-hospital mortality.[22]

RAAS inhibitors are tightly linked with increased serum potassium concentrations, and, consequently, hyperkalaemia in HFrEF and hypertensive patients. Hyperkalaemia is common in patients with hypertension taking blood pressure lowering medications, as demonstrated by a 3-year evaluation of 194,456 patients in the Geisinger Health System, USA. Patients using the following medications at baseline showed an increase in risk of hyperkalaemia (defined as potassium >5 mEq/L), of 54% with ACE inhibitors, 13% with β-blockers and 7% with angiotensin receptor blockers.[23] Although much less frequently used, potassium-sparing diuretics (including aldosterone antagonists, amiloride, and triamterene) were not associated with an increase in risk (HR: 1.00, 95% CI: 0.91–1.10). Loop/thiazide diuretic use at baseline was associated with a decrease in risk for hyperkalaemia.[23] A similar trend was seen with the ACE inhibitor lisinopril in 118 male patients with mild-to-moderate essential hypertension, where reduction in blood pressure was associated with significantly increased serum potassium.[24] Estimates of the incidence of hyperkalaemia in patients with HFrEF who have been treated with optimal medical therapy vary substantially, although it is widely acknowledged that reported rates in clinical trials are an underestimation of the actual rates of hyperkalaemia in clinical practice.[25]

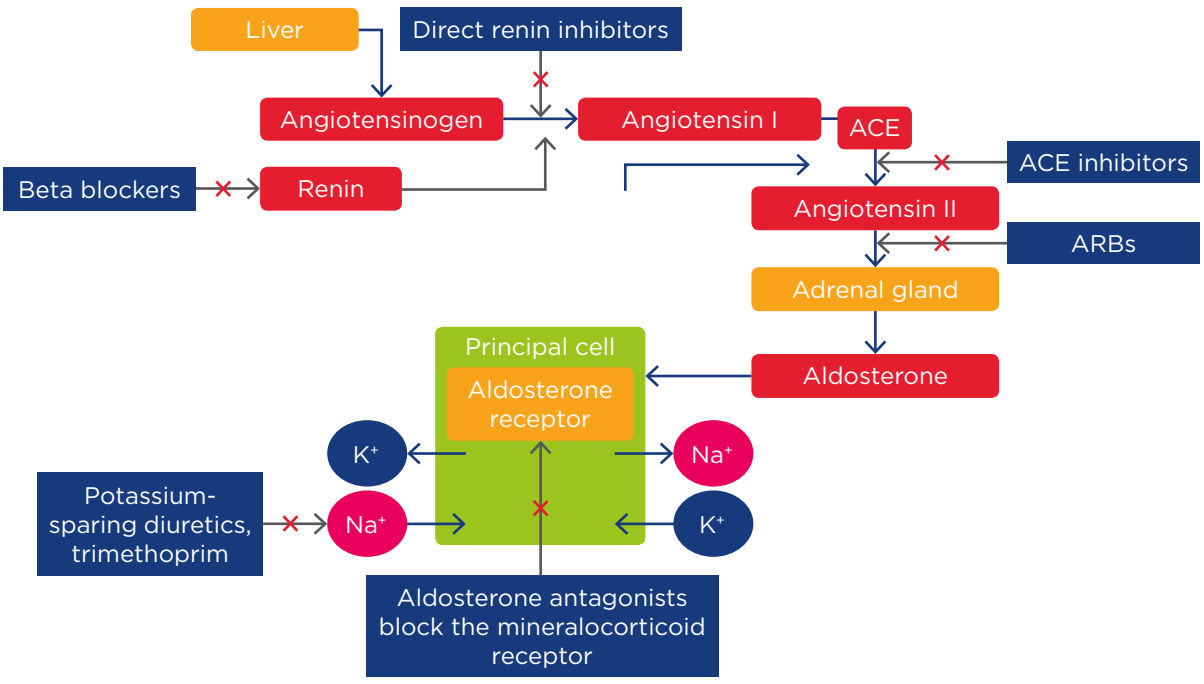

Figure 3: The actions of various renin-angiotensin-aldosterone system inhibitors in causing hyperkalaemia. ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers.

A retrospective analysis of hypertensive patients receiving spironolactone for the treatment of resistant hypertension demonstrated that a 12-fold increase in the rate of patients achieving a satisfactory systolic blood pressure response in a categorical multivariate model was associated with a baseline potassium ion level of <4.5 mEq/L.[26] In hypertensive patients both hyper and hypokalaemia increase mortality risk, as seen from a retrospective analysis of patients included in the Danish National Patient Registry (DNPR) on at least two concomitant antihypertensive drugs (n=44,799).[27]

It is noted that hyperkalaemia can also be caused by other regularly prescribed medications in patients with heart failure and/or hypertension, such as beta blockers and non-steroidal anti-inflammatory drugs, and it is emphasised that alternative hyperkalaemia-reducing agents are required. The actions of various RAAS inhibitors in causing hyperkalaemia are illustrated in Figure 3.

Effect of Hyperkalaemia on Renin-Angiotensin-Aldosterone System Inhibitor Use

Due to the significant risks associated with hyperkalaemia, RAAS inhibitor therapy is often altered following hyperkalaemia events, such as maximum doses being downtitrated to a submaximum dose or even discontinuation of the drugs. In turn, this may lead to greater risk of heart failure readmissions and cardiovascular mortality. In comparison, using the maximum RAAS inhibitor dose is associated with a reduced risk of heart failure hospitalisations and cardiovascular death.[3] Indeed, hyperkalaemia is a key reason for both not starting and discontinuing RAAS inhibitors. In a retrospective review of patients with Stage 3–5 chronic kidney disease, past or current hyperkalaemia was the reason for not starting RAAS inhibitor therapy in 14% of patients, and the reason for discontinuation of RAAS inhibitors in 67% of patients.[28] In the 3-year study using the data from the Geisinger Health System, USA of approximately 200,000 patients, both dose reduction and discontinuation were common in patients with a serum potassium concentration of >5.5 mEq/L receiving ACE inhibitors or angiotensin receptor blockers (n=1,715).[23]

Treatment discontinuation or administration of submaximal doses is a suboptimal approach to managing patients with hyperkalaemia. An alternative approach to hyperkalaemia would allow RAAS inhibitors to be used at their maximum dose and consequently reduce the risk of adverse outcomes from both progressive heart failure and hyperkalaemia.

Currently Available Treatments and Their Limitations

Since the incidence of hyperkalaemia is on the rise due in part to the increase in chronic kidney disease, heart failure, and diabetes as well as greater use of RAAS inhibitors in patients that have clear indications for these therapies (those with heart failure, chronic kidney disease, and/or diabetes), its recognition and treatment is becoming more important than ever.[25,29,30] Unfortunately, current hyperkalaemia treatments have several important limitations so the need for new treatment options is becoming more apparent. The only treatment options currently available are temporising agents such as intravenous calcium, alkalinisation agents (such as sodium bicarbonate), glucose and insulin, and loop diuretics. Calcium is used to stabilise the cardiomyocyte membrane, reducing the risk of conduction abnormalities and cardiac arrhythmias in the setting of hyperkalaemia, but does not directly impact potassium concentrations; in addition, it is only effective over a short time period. Sodium bicarbonate and insulin/glucose act quickly (within approximately 5 minutes) to reduce potassium concentration, and so are useful in times of emergency and can be life-saving. However, these agents do not eliminate excess potassium, and effects are not long-lasting. Both calcium and alkalinisation are usually only effective for 30 minutes, whereas glucose and insulin are effective for ~2 hours. Loop diuretics, on the other hand, have a slower onset of effect, taking 20–60 minutes to reduce potassium concentration, and may not be effective in patients with severely impaired renal function; hence these agents are less useful in the case of an emergency.

Sodium polystyrene sulfonate (SPS) has previously been the only treatment that could be used in addition to loop diuretics to eliminate potassium from the body; it is primarily used in a hospital setting. However, SPS is only weakly selective for potassium, and in fact is more selective for calcium

and magnesium than for potassium.[31] Therefore, the only parts of the gastrointestinal tract where there is a high enough concentration of potassium to be bound by SPS is in the distal colon and rectum. It takes a long time for SPS to reach the distal colon and, hence, the onset of action of SPS to bind and remove potassium is slow.[32]

No well-designed clinical trials have been conducted to prove the efficacy of SPS in lowering potassium levels, since the agent was approved before there was a US Food and Drug Administration (FDA) requirement to demonstrate efficacy and safety in large randomised clinical trials. Furthermore, several small studies suggest that sorbitol, rather than SPS, may be responsible at least in part for the potassium-lowering effect. For example, one study compared the total soluble potassium ions in stools following treatment with a combination of sorbitol and SPS. The levels of total soluble potassium with sorbitol and SPS combined was similar to the results with sorbitol alone.[33]

Some safety concerns also exist with a combination of sorbitol and SPS, such as gastrointestinal tolerability issues. Diarrhoea and constipation are common, particularly with chronic use, as well as in hospital and intensive care units. Furthermore, a FDA alert was released in 2009 highlighting reported cases of colon necrosis, possibly caused by SPS crystals following their administration with sorbitol. The recommendation from this alert was to not co-administer SPS and sorbitol; however, this recommendation has proved difficult to follow as most of the SPS prescriptions in the USA are in combination with sorbitol.[34] The safety issues and lack of efficacy data for SPS as well as the limitations of temporising agents therefore emphasise the clinical need for new hyperkalaemia treatments that are effective and well tolerated.

Novel Treatment Strategies to Manage Potassium Levels

Two novel agents to treat hyperkalaemia have recently emerged: patiromer and SZC. Patiromer is now approved in the USA; it has been studied in several clinical trials to demonstrate its long-term efficacy at lowering potassium and maintaining normal potassium levels for ≤1 year. The mechanism of action of patiromer is non-specific cation binding in exchange for calcium in the distal colon, reducing potassium levels by ~0.2 mEq/L 7 hours after the first dose, and achieving acceptable potassium levels within several days.[35,36]

A randomised blinded trial tested the efficacy of patiromer compared with placebo in patients with mild and moderate-to-severe hyperkalaemia over 4 weeks. Results from the study found that patiromer was superior to placebo, and effectively controlled potassium levels for ≤4 weeks.[35] Patiromer was subsequently studied for ≤1 year in an open-label single-arm study; the results showed that patiromer could be effective at keeping potassium levels controlled over a sustained period of time. Patiromer has been shown to be well tolerated, but hypomagnesaemia and gastrointestinal side effects, such as mild-to-moderate constipation, have been observed.[37]

SZC is another novel potassium binder and is currently in development. SZC is an inorganic crystalline zirconium silicate compound that is insoluble, highly stable, does not expand in water, is not systemically absorbed, and is highly selective for potassium.[38] The mechanism of action of SZC is through selective potassium binding in exchange for sodium and hydrogen, which appears to occur both in the upper and lower gastrointestinal tract based on its rapid onset of action. SZC has been evaluated in one Phase II and two Phase III randomised clinical trials in >1,000 patients. There is also an ongoing ZS005 open-label safety study evaluating SZC in 750 patients for ≤12 months.[39] Studies have shown that SZC normalised potassium levels in 84% of patients by 24 hours (and 98% of patients by 48 hours), and the median time to potassium normalisation was 2.2 hours;[40] the agent was also highly effective in rapidly reducing potassium levels even among patients with severe hyperkalaemia (potassium levels ≥6.0 mEq/L).[41] SZC is well tolerated, but cases of oedema have been observed at high doses.[42]

These novel agents may therefore contribute to a paradigm shift in the management of hyperkalaemia caused by RAAS inhibitors, by optimising serum potassium concentration in the long-term and enabling optimisation of RAAS inhibitor use (and dose) in patients previously ineligible for these treatments. The optimal ways in which these agents may be incorporated into clinical practice among patients with heart failure and resistant hypertension, and their impact on optimisation of RAAS inhibition and ultimately patient outcomes, remains to be established.

New Agents: Unanswered Questions and Clinical Implications

Patiromer and SZC have been studied primarily in outpatients with hyperkalaemia and not in hospitalised patients. Therefore, their effectiveness and safety in the hospital or emergency settings has not yet been evaluated. There are several other important patient groups in which the use of these novel agents should be studied, including those with end-stage renal disease receiving dialysis. Additional clinical trials are also needed to better document the degree with which these agents can optimise RAAS inhibitor use (and dose) in patients with heart failure and reduced systolic function that are unable to tolerate RAAS inhibitor therapy due to previously documented hyperkalaemia, considered to be at high risk for development of hyperkalaemia, or have contraindications to RAAS inhibitor therapy due to potassium levels >5.5 mEq/L or severe chronic kidney disease.

REFERENCES

1. Ponikowski P et al. 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 Heart J. 2016;37(27):2129-200.

2. Edner M et al. 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;36:2318-26.

3. Epstein M et al. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care. 2015;21(11 Suppl):S212-20.

4. Epstein M. Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: the widening gap between mandated treatment guidelines and the real-world clinical arena. Kidney Int Suppl. 2016; 6(1):20-8.

5. Damman K et al. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. J Am Coll Cardiol. 2014;63(9): 853-71.

6. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293-302.

7. Onodera H et al. Enalapril suppresses ventricular remodeling more effectively than losartan in patients with acute myocardial infarction. Am Heart J. 2005;150(4):689.

8. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation. 2000;101(25):2981-8.

9. Granger CB et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362(9386):772-6.

10. Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17.

11. Zannad F et al. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. Circulation. 2000;102(22):2700-6.

12. Zannad F et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21.

13. McMurray JJ et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.

14. Blood Pressure Lowering Treatment Trialists Collaboration; Turnbull F et al. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. J Hypertens. 2007;25(5):951-8.

15. van Vark LC et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158,998 patients. Eur Heart J. 2012;33(16):2088-97.

16. Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cardiovasc Ther. 2012; 30(3):e156-66.

17. Wang C et al. Efficacy and Safety of Spironolactone in Patients with Resistant Hypertension: A Meta-analysis of Randomised Controlled Trials. Heart Lung Circ. 2016;25(10):1021-30.

18. Alfonzo A et al. Treatment of acute hyperkalaemia in adults. The Renal Association. 2014. Available at: http://www.renal.org/guidelines/joint-guidelines/treatment-of-acute-hyperkalaemia-in-adults#sthash.agrRCBCg.dpbs. Last accessed: 1 December 2016.

19. Xi L et al. Associations between serum potassium and sodium levels and risk of hypertension: a community-based cohort study. J Geriatr Cardiol. 2015;12(2):119-26.

20. Vardeny O et al.; Randomized Aldactone Evaluation Study (RALES) Investigators. 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; 7(4):573-9.

21. Jain N et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. Am J Cardiol. 2012; 109(10):1510-3.

22. Khanagavi J et al. Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes. Arch Med Sci. 2014;10(2):251-7.

23. Chang AR et al. Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Health System. Hypertension. 2016;67(6):1181-8.

24. Fogari R et al. Effects of different antihypertensive drugs on plasma fibrinogen in hypertensive drugs on plasma fibrinogen in hypertensive patients. Br J Clin Pharmacol. 1995;39(5):471-6.

25. Desai AS et al. Hyperkalemia in patients with heart failure: incidence, prevalence, and management. Curr Heart Fail Rep. 2009;6(4):272-80.

26. Shlomai G et al. Serum potassium levels predict blood pressure response to aldosterone antagonists in resistant hypertension. Hypertens Res. 2014;37(12): 1037-41.

27. Krogager ML et al. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis

of nationwide registry data. Eur Heart J. 2016. [Epub ahead of print].

28. Yildirim T et al. Major barriers against renin-angiotensin-aldosterone system blocker use in chronic kidney disease stages 3-5 in clinical practice: a safety concern? Ren Fail. 2012;34(9):1095-9.

29. Einhorn LM et al. The frequency of hyperkalemia and its significance in chronic kidney disease. Arch Intern Med. 2009;169(12):1156-62.

30. Raebel MA et al. Diabetes and drug-associated hyperkalemia: effect of potassium monitoring. J Gen Intern Med. 2010;25(4):326-33.

31. Stavros F et al. Characterization of Structure and Function of ZS-9, a K+ Selective Ion Trap. PLoS ONE. 2014;9(12): e114686.

32. Fordtran JS. Speculations on the pathogenesis of diarrhea. Fed Proc. 1967;26(5):1405-14.

33. Emmett M et al. Effect of three laxatives and a cation exchange resin on fecal sodium and potassium excretion. Gastroenterology. 1995;108(3):752-60.

34. U.S. Food and Drug Administration. Kayexalate (sodium polystyrene sulfonate) powder. 2011. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm186845.htm. Last accessed: 7 September 2016.

35. Weir MR et al.; OPAL-HK Investigators. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3): 211-21.

36. Bushinsky DA et al. Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. Kidney Int. 2015;88(6):1427-33.

37. Bakris GL et al.; AMETHYST-DN Investigators. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. JAMA. 2015;314(2):151-61.

38. Stavros F et al. Characterization of structure and function of ZS-9, a K+ selective ion trap. PLoS One. 2014;9(12): e114686.

39. Kosiborod et al. ZS Pharma R&D Analyst Day, NYC, 2014.

40. Kosiborod M et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA. 2014; 312(21):2223-33.

41. Kosiborod M et al. Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. N Engl J Med. 2015; 372(16):1577-8.

42. Packham DK et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med. 2015;372(3):222-31.