NEW PARADIGMS IN HEART FAILURE: RAAS INHIBITION AND THE MANAGEMENT OF HYPERKALAEMIA

This symposium took place on 29th August 2015 as a part of the European Society of Cardiology Congress in London, UK

Chair

John McMurray[1]

Speakers

Faiez Zannad,[2] Ileana L. Piña,[3] John McMurray[1]

1. University of Glasgow, Glasgow, UK

2. Henri Poincaré University of Nancy, Nancy, France

3. Montefiore-Einstein Medical Centre, Bronx, New York, USA

Disclosure: John McMurray has no relevant disclosures to declare. Faiez Zannad has acted on steering committees for Bayer, Boston Scientific, Novartis, Pfizer, ResMed, and Takeda; acted as a consultant and advisory board member for Air Liquide, Amgen, CVRx, Relypsa, Servier, St Jude, Stealth Peptide, ZS Pharma, and Quantum Genomics; and received a research grant from Roche Diagnostics. Ileana Piña has acted as a consultant and advisory board member for ZS Pharma.

Acknowledgements: Writing assistance was provided by Dr Lucy Smithers of ApotheCom and funded by ZS Pharma Inc.

Support: The symposium was organised by Medavera, Inc. and supported by an educational grant from ZS Pharma Inc. Authors received honoraria for preparation and delivery of their presentations. The paper is an interpretation of the views of the speakers, but is not written by them. The views and opinions expressed are those of the authors and not necessarily of Medavera, Inc. or ZS Pharma Inc.

Citation: EMJ Cardiol. 2015;3[2]:53-61.

MEETING SUMMARY

This educational symposium discussed advances in blocking the renin–angiotensin–aldosterone system (RAAS) for patients with chronic systolic heart failure (HF), and the issues of managing hyperkalaemia in these patients.

Prof John McMurray introduced the session, outlining the current treatment paradigm and the challenges presented by the associated risks of hyperkalaemia. Prof Faiez Zannad discussed the under-utilisation of life-saving RAAS inhibitor (RAASi) drugs in clinical practice and the benefits to be gained for patients by optimising their use. Prof Ileana Piña reviewed current advances in pharmacological treatments for chronic HF that aim to reduce the risks of renal dysfunction and hyperkalaemia. Finally, Prof John McMurray discussed the potential of new treatment paradigms for improved outcomes in patients with chronic HF.

Symposium Background and Learning Objectives

Treatment with agents that block the RAAS (RAASi) is considered the standard of care (SOC) for patients with systolic HF (HF with reduced ejection fraction [HF-REF]).[1] However, their use is associated with an increased risk of hyperkalaemia.

Hyperkalaemia is defined by an abnormally high concentration of potassium ions in the blood (>5.0 mmol/L according to US guidelines).[2] It can become a chronic, persistent condition that is an ongoing concern for patients with HF, as serum potassium levels >5 mmol/L have been associated with an increased risk of mortality in patients with cardiovascular and renal diseases.[3]

Current practice is to discontinue or reduce the use of RAASi in patients who develop hyperkalaemia. However, lack of knowledge regarding when to titrate, or the failure to titrate, these drugs leads to variation in their use in practice as clinicians attempt to avoid harm. Registries have consistently reported a large gap between real-life practice and recommended practice in international guidelines in the use of these life-saving, evidence-based therapies.[4,5]

With new options for the treatment of hyperkalaemia becoming available, it may be feasible to follow guidelines for directed medical therapy and optimise the use of RAASi, allowing patients to benefit from these life-saving treatments, before considering other therapeutic options.[6]

The learning objectives of the symposium were: 1) To explain why RAASi doses should be optimised and maintained; 2) To review the reasons why target doses are not reached for RAASi; 3) To compare and contrast new pharmacological options for RAAS inhibition and hyperkalaemia management; and 4) To describe the barriers and challenges to RAASi use in HF, in order to identify new paradigms for consideration in achieving better outcomes for HF patients.

Why Aren't We Titrating Optimal RAAS Inhibitor Life-Saving Therapy?

Professor Faiez Zannad

RAASi have a proven benefit in reducing deaths in HF patients, and international guidelines, such as those published by the European Society of Cardiology (ESC), recommend their use in patients with systolic HF.[1] Our analysis of the ESC Heart Failure Long-term Registry shows that not all patients who are eligible for these drugs are being treated with them. In this registry, <10% of eligible ambulatory patients with chronic HF are not treated with either angiotensin-converting enzyme inhibitors (ACEi) or aldosterone receptor blockers (ARBs) and beta-blockers, while around 30% of patients eligible for mineralocorticoid receptor antagonists (MRAs) are not being treated either.[4] While the majority of eligible patients in this registry were receiving RAASi, many were not receiving them at their target dose (70.7% of those on ACEi, 75.9% of those on ARBs, 82.5% of those on beta-blockers, and 69.5% of those on MRAs).[4] Previous reports in the literature from the US show higher rates of underuse, such as 80% of eligible patients receiving an ACEi or ARB, 86% receiving a beta-blocker, but only 36% receiving an MRA in the IMPROVE HF registry of outpatient cardiology practices.[7]

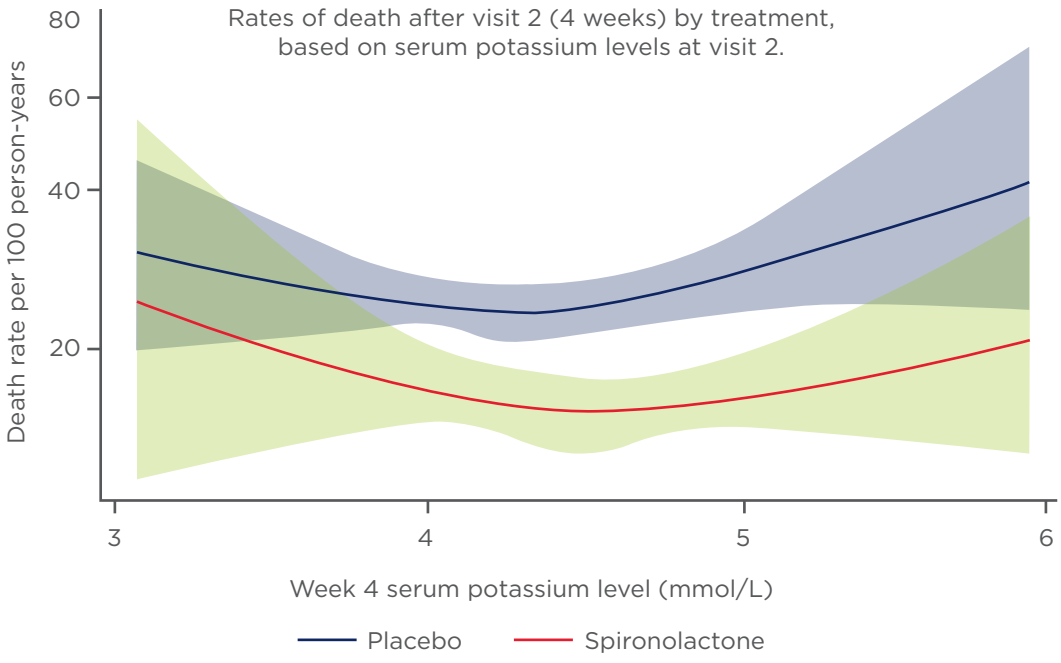

Figure 1: Mortality in the RALES study population in relation to serum potassium levels.
p<0.0001 for comparison between spironolactone and placebo. Shaded areas represent 95% confidence intervals.

The main reasons for underuse of these treatments are chronic kidney disease (CKD) and hyperkalaemia.[4,8] Hyperkalaemia is a serious threat to HF patients and is associated with increased mortality.[3] Our findings from the ESC registry study and the IMPROVE HF registry suggest that concern over these serious risks leads clinicians to discontinue RAASi or use them at doses below the guidelines' recommended target: approximately 60% of patients on ACEi or ARBs and approximately 70% of patients on beta-blockers were below the target dose at baseline and 2 years later. This is of concern as it has been shown that patients who do not receive RAASi at discharge from hospitalisation for HF have double the 30-day risk of death or readmission.[9]

Even in patients with severe renal disease, treatment with RAASi can reduce mortality.[10] The range of potassium levels in clinical trials may be underestimated, since patients with multiple comorbidities or moderate-to-severe renal impairment have typically been excluded.[11-14] In clinical practice, cardiologists treating patients with HF may have to deal with higher rates of hyperkalaemia, depending on the patient population and severity of CKD.[3,15-19] An understanding of the mechanism of action of RAASi shows that elevations in potassium levels are a common feature of all RAASi, and increases in mortality rates were seen at levels >5.0 mmol/L in the original studies (Figure 1).[20] Patients with risk factors for hyperkalaemia, including older age, diabetes, and CKD, are also those who receive the greatest absolute benefit from RAASi therapy.[3,13]

These data demonstrate that increased survival can be achieved in patients with HF who are at risk of hyperkalaemia due to the development of new hyperkalaemia therapies, through the use of algorithm-based, life-saving RAASi treatment, and by monitoring of potassium and creatinine levels.[13,21] If hyperkalaemia occurs, clinical outcomes can be optimised by the prompt recognition and management of hyperkalaemia, and the new potassium binders can potentially treat hyperkalaemia without the need to reduce or discontinue RAASi, allowing patients to continue benefitting from reduced mortality and hospitalisation.[6]

New Pharmacological Options for Heart Failure

Professor Ileana L. Piña

The treatment of HF today is complex, with challenging patients who present in clinics with more comorbidities and more advanced disease. The goals of treatment remain unchanged and aim to alleviate symptoms, reduce excess extracellular fluid volume, improve haemodynamics, maintain renal function and perfusion to vital organs, prevent hospital admissions, avoid disease progression, and reduce deaths. Optimising chronic therapy for HF patients is a key part of these goals.

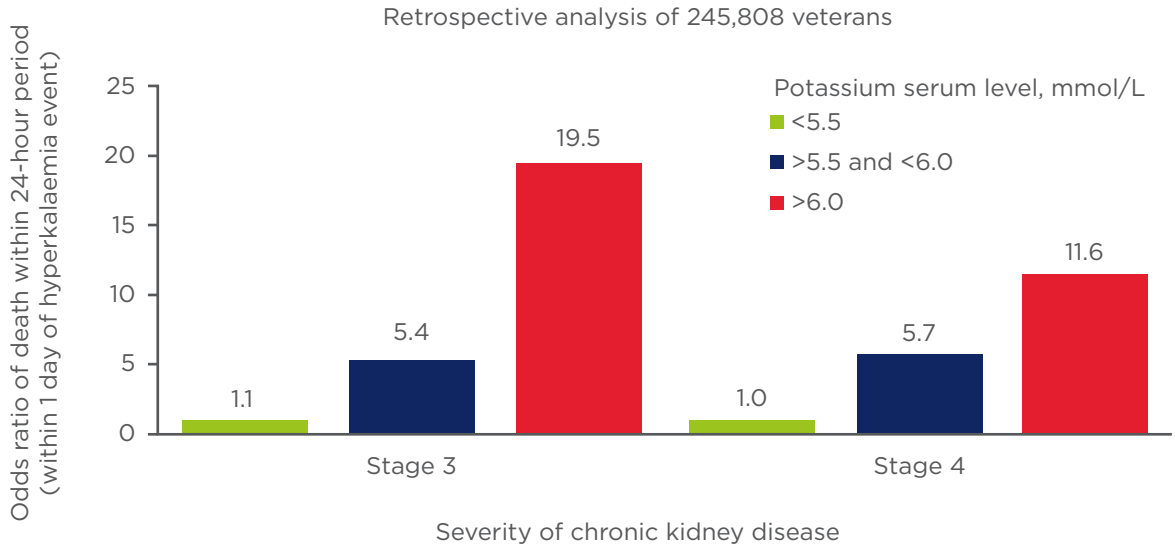

Figure 2: Risk of mortality in relation to serum potassium levels in a retrospective cohort of patients with heart failure and chronic kidney disease.[3]

Current treatment options for patients with systolic HF are limited by issues of hypotension, reductions in renal function, and hyperkalaemia. Exciting advances in pharmacological treatments for HF may overcome these limitations by addressing new targets. Currently, treatments for HF target the sympathetic nervous system, the RAAS, sodium and water retention, and loss of contractility. The question is whether the new drugs in development (vasodilators, synthetic natriuretic peptides, sinus node inhibitors, neutral endopeptidase inhibitors [used with ARBs or an angiotensin receptor neprilysin inhibitor such as valsartan/sacubitril (LCZ696)], actin–myosin binders, and potassium binders) will be subject to the same limitations or not.

Serelaxin is a new vasodilator drug that has shown efficacy for the primary endpoint of dyspnoea relief in acute HF in the RELAX-AHF trial.[22,23] Notably, the risk of cardiovascular death was significantly reduced at 6 months with SOC plus serelaxin versus SOC plus placebo (hazard ratio [HR]: 0.63, 95% confidence interval [CI]: 0.41–0.96; p=0.028), and this is now being investigated further in the ongoing RELAX-AHF-2 prospective mortality trial (NCT01870778). It is also of interest that the serelaxin group showed fewer increases in creatinine and blood urea nitrogen, indicating fewer patients at risk of reduced renal function versus the placebo group.[22,23]

Ularitide is a synthetic natriuretic peptide that causes vasodilation, diuresis, and natriuresis. It has demonstrated symptom relief and vasodilation with preserved renal function in Phase I and II trials, and is currently in a Phase III trial for safety and efficacy on clinical status and mortality outcome safety in acute HF (TRUE-AHF).[24,25] This trial aims to enrol patients within the first few hours of presenting at the hospital as there is evidence that treating patients as early as possible is beneficial.[24]

Ivabradine inhibits the sinus node by targeting the I_f pacemaker current sodium channel and hence reducing heart rate. This drug was recently approved in Europe and the USA on the basis of the SHIFT trial, which demonstrated improvements in the primary endpoint of cardiovascular mortality and hospitalisations (HR for the combined primary endpoint: 0.82, 95% CI: 0.75–0.90; p<0.001). This was driven by reductions in hospitalisations more than reductions in cardiovascular mortality.[26] Analysis of factors influencing outcomes showed that ivabradine was more effective in patients with high baseline heart rate, and in fact only about half of the patients (56%) in the trial were receiving >50% of their target dose of beta-blocker, confirming the challenge of optimising patients' chronic heart therapy.

Loss of contractility has traditionally been treated with inotropes, but their use is restricted by increased mortality. The novel selective cardiac myosin activator omecamtiv mecarbil (OM) is a promising new drug in development that does not change left ventricle contractility (dP/dt), but strengthens and prolongs it without increasing oxygen consumption in the myocardium.[27,28] In the Phase II ATOMIC-AHF trial of OM in HF, despite the study not reaching its primary endpoint of dyspnoea relief, the response appeared to be better in the cohort of patients given higher doses of the drug.[28] Further trials to assess the efficacy of this new approach in treating loss of contractility are ongoing.

An important advance in the treatment of patients with HF has been the development of potassium binders to address the need for hyperkalaemia management, in particular for hyperkalaemia resulting from RAAS inhibition. The clinical evidence base for the use of RAASi to benefit both post-myocardial infarction and chronic HF patients is strong, and hence their use is recommended by international guidelines.[2] RAASi treatment, particularly in combination with comorbidities such as CKD and/or diabetes, contributes to hyperkalaemia development in these patients. While hyperkalaemia can be controlled to some extent in clinical trials with careful patient selection and monitoring,[11,12,29] this is not representative of real-life patient populations in whom hyperkalaemia rates are notably higher.[11,30-32] These real-world rates of potassium levels ≥5.0 mmol/L, combined with the increasing prevalence of patients with combined HF, CKD, and diabetes, leads to many patients not being given RAASi because of the risk of hyperkalaemia.[33,34] It is in the best interests of clinicians and patients to manage hyperkalaemia, since it contributes to increased costs through emergency department visits and hospitalisations,[35] and increases the risk of death in HF and renal disease patients (Figure 2).[3,36]

Patients find it difficult to control potassium levels through diet alone, and since the 1950s the only pharmacological option in the USA for reducing potassium has been sodium polystyrene sulfonate

(Kayexalate®), which is neither a pleasant nor benign treatment.[37] Therefore, the availability of potassium binders is particularly welcome in order to make it possible for more patients to benefit from life-saving RAASi therapy. Zirconium cyclosilicate (ZS-9) is an insoluble, non-absorbed zirconium silicate that preferentially and selectively traps potassium ions, and is eliminated in stools (Figure 3). It has a rapid onset of action due to the selective mechanism of trapping potassium ions that starts in the upper gastrointestinal tract. ZS-9 normalises serum potassium in a median time of 2.2 hours, and consistently maintains normokalaemia across a range of patients receiving RAASi.[38,39] Another agent, patiromer sorbitex calcium, is a non-specific, organic polymer that binds potassium primarily in the colon and is then eliminated in stools. Its slow onset and low response rate of action may limit its usefulness; however, it appears to maintain normokalaemia.[40]

There are also developments in RAASi to treat HF-REF that may have less severe effects on potassium levels, in particular the non-steroidal MRA finerenone. Studies indicate that this drug's effects on potassium levels and renal function are dose-related; trials are ongoing.[41]

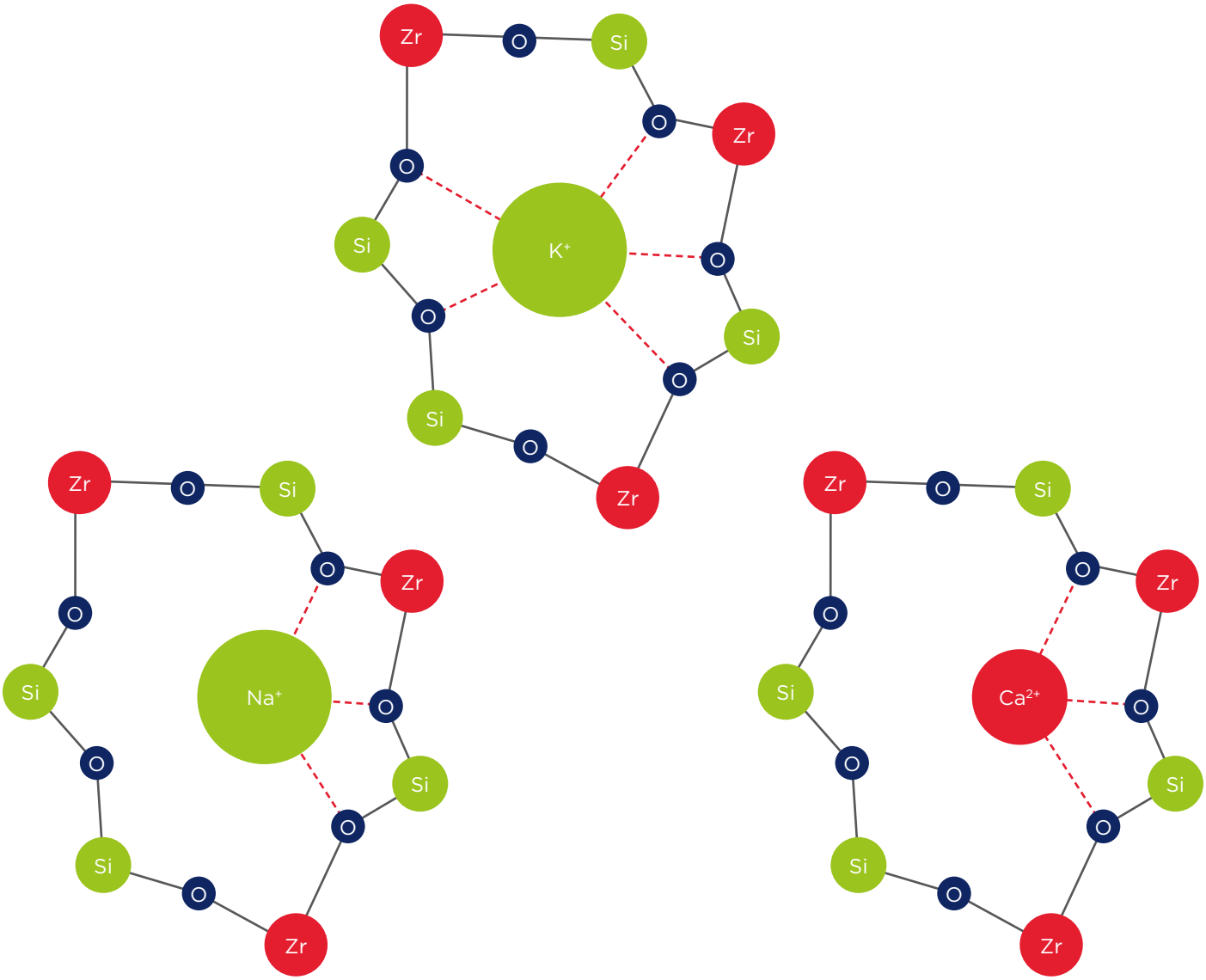

Figure 3: Mechanism of action of ZS-9 in binding potassium.
Similarly to physiological potassium channels, the pore size of ZS-9 is such that only potassium ions (K^+) interact strongly and are selectively captured.
ZS-9: Zirconium cyclosilicate.
Reproduced with permission from Stavros F et al. Characterization of structure and function of ZS-9, a K^+ selective ion trap. PLoS One. 2014;9(12):e114686.

The future prospects for the treatment of HF are exciting, with new drugs and new targets providing a wider range of options for treatment, as well as allowing better use of currently available RAASi by addressing hyperkalaemia. Lessons learned from previous trials serve to inform future studies with regards to earlier intervention and refining the choice of patient population through biomarkers. Improvement is also needed in patients' transition from acute care to chronic HF therapy in order to prevent hospital readmissions.[42]

Paradigm Shifts in the Pharmacological Management of Heart Failure

Professor John McMurray

The past 30 years have seen several paradigm shifts in the treatment of HF, which have resulted in consistent international guidelines owing to the strong evidence base for the drugs that are used today.[1,2] The core therapies for HF are beta-blockers, ACEi, ARBs, and MRAs, and there are additional roles for devices or additional drugs in selected subsets of patients. Is it possible to improve further on the current paradigm?

The recent PARADIGM-HF trial suggests that it will be possible to go beyond RAASi, not just blocking harmful neurohumoral pathways but also augmenting potentially beneficial effects. The new paradigm would aim to harness endogenous protective systems and replace existing treatments rather than adding to them. The best understood protective pathways in the heart are the natriuretic peptides, which can be augmented by inhibiting neprilysin. Neprilysin breaks down natriuretic peptides and a range of other vasoactive substances, including bradykinin, adrenomedullin, and substance P, as well as angiotensin II. Coupling neprilysin inhibition with RAASi (angiotensin receptor neprilysin inhibition [ARNi]) has the potential to reset the neurohumoral balance in patients with HF.[43,44]

The PARADIGM-HF trial compared the efficacy of ARNi versus ACEi in patients with HF-REF. Beta-blocker and MRA therapy was permitted according to guidelines. Patients were excluded if their potassium levels rose above 5.2 mmol/L during a run-in period, first on enalapril then on valsartan. The run-in was intended to identify patients susceptible to hypotension and angioedema but also excluded patients predisposed to hyperkalaemia from the trial population. The trial was stopped early due to the significant benefits demonstrated by ARNi, both for cardiovascular mortality (HR: 0.80, 95% CI: 0.71–0.89; p<0.001) and HF hospitalisations (HR: 0.79, 95% CI: 0.71–0.89; p<0.001).[43] This treatment gave incremental benefits even for patients who were treated with the full combination of beta-blocker, MRA, and ACEi.[44]

Safety data from PARADIGM-HF suggest that ARNi may be better tolerated than the ACEi comparator, enalapril. There were fewer patients in the ARNi arm with creatinine levels ≥2.5 mg/dL and slightly fewer patients with serious hyperkalaemia (potassium levels ≥6.0 mmol/dL: 5.6% on enalapril versus 4.3% on valsartan), although still a very high rate of moderate-to-severe hyperkalaemia (potassium levels ≥5.5 mmol/L: 17.3% on enalapril versus 16.1% on valsartan).[43] It has yet to be determined whether these improvements in safety and efficacy are sufficient for this new treatment to replace existing ARB or ACEi therapy.

Another potential change to the HF treatment paradigm is to inhibit the RAAS with a direct renin inhibitor in order to target the rate-limiting step of the cascade. The ATMOSPHERE trial comparing the efficacy of the direct renin inhibitor aliskiren with enalapril, both singly and in combination, on mortality and hospitalisation in patients with HF (NCT00853658), will be reporting in early 2016.[45]

Non-steroidal MRAs, which aim to have a reduced effect on renal function, may also change the treatment paradigm. The Phase IIb ARTS-HF trial of finerenone versus eplerenone was reported at the 2015 ESC Congress,[46] and a Phase III trial is planned to compare finerenone with eplerenone in patients with HF and Type 2 diabetes or CKD, who are at risk of hyperkalaemia, for efficacy in reducing mortality and hospitalisation.

As already mentioned, improvements in treatment paradigms can be anticipated with the availability of potassium binders that can treat or prevent hyperkalaemia. This could allow more patients to benefit from RAASi while reducing the risks associated with hyperkalaemia.

Further improvements to the treatment paradigm may be available owing to the development of a new RAASi. TRV(120)027 is a biased angiotensin II type 1 receptor (AT1R) ligand that selectively activates the beneficial beta-arrestin pathway, but blocks the alternative detrimental pathway from

the AT1R. It is currently being tested in a Phase II proof-of-concept trial in patients with acute HF.[47]

In summary, blocking the RAAS is the core of current treatment of HF. We have the hope of better ways of inhibiting this system through addressing new targets, such as neprilysin and renin. Hyperkalaemia and renal insufficiency remain the Achilles heel of current RAASi therapy and prevent many people from benefitting from these treatments, but this may be addressed by the new RAASi with reduced effects on potassium levels or renal function, or by using potassium binders to manage hyperkalaemia.

Panel Discussion

Prof McMurray invited Prof Piña to explain the pros and cons of the two different potassium binders discussed in the symposium. Prof Piña explained that, whereas ZS-9 was a binder with a structure that literally caged potassium ions preferentially, patiromer was an organic polymer that, when mixed with water, absorbed potassium in a non-specific manner in the colon. Potassium levels rise again after withdrawal of both binders. She noted that the best ways to use the binders were not yet determined – for example, whether they should only be used sporadically when hyperkalaemia occurred, or be prescribed concomitantly when mineralocorticoids were initiated. It would be reasonable to raise the dose of RAASi therapy in patients with controlled potassium levels. Both drugs have been followed-up for 1 year. In addition, more information was needed on their effects on other electrolytes, such as sodium, calcium, and magnesium. Prof Zannad noted that patiromer, as an organic polymer, would expand in the gastrointestinal tract, and that ZS-9, because it is an ion trap, would not expand. However, in the absence of a head-to-head trial, he could not compare the tolerability of the two therapies, although the overall safety of both appeared to be good in their respective trials.

A general practitioner from the UK confirmed the problem raised by the panel with regard to patients having their RAASi discontinued when they are hospitalised, and that non-cardiologist healthcare professionals (HCPs) were focussing too much on acute renal injury. He called for more education in hospitals regarding the balance of risk and benefit for RAASi and ways to stop hyperkalaemia. Prof Zannad agreed that the evidence from trials indicated that increases of 10–15% in creatinine were not a cause for concern, and that there was a need to educate HCPs on the importance of uptitrating a treatment once the problem has been reversed, since the benefit of RAASi on mortality is greater than the potential harm from increased creatinine. On the other hand, the risks of hyperkalaemia secondary to RAASi therapy are real and monitoring treatment is necessary. Prof Zannad emphasised that HF is a chronic disease that needs chronic, adaptive therapy with regular monitoring of patients, which has become more feasible with the advent of 'telemedicine'.

The final question was regarding advice on the rate at which RAASi could be uptitrated, following the message from the symposium that a patient's dose should ideally be optimised by the time they leave hospital, since further optimisation after discharge is unlikely. The panel agreed that this depended on the condition of the individual patient, and that the paradigm of 'start low, go slow' was good advice where time and resources allowed weekly uptitration. Prof McMurray noted that in the UK, where the median hospital stay is 8 days, most patients can be titrated to a full dose of ACEi by the time they are discharged, with HF nurses monitoring electrolyte levels after the patient goes home. Prof Piña's practice in the USA, where the mean hospital stay is 4.5 days, was to uptitrate doses daily while managing the diuretics by dose reduction, but this required experience with the drugs because creatinine levels were affected. Where shorter hospital stays are the norm, faster-acting agents would make it easier to optimise a patient's dose by the time they were discharged.

Conclusions

RAAS inhibition is a proven, life-saving therapy for patients with HF, and RAASi are recommended by international guidelines. However, there is still underuse of these treatments and many patients are not receiving optimal doses of RAASi recommended for clinical benefit. Hyperkalaemia is a key barrier to the optimal use of RAASi. New, safe, and efficacious therapies to address hyperkalaemia are being made available, which may allow patients with HF and a risk of hyperkalaemia to benefit from increased survival due to RAASi therapy. New RAASi with fewer undesirable effects could become available, with the potential to improve the paradigm for the treatment of HF.

REFERENCES

1. McMurray JJ et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847.

2. Yancy CW et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-e239.

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

4. Maggioni AP et al; 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;15(10):1173-84.

5. Gheorghiade M et al. Medication dosing in outpatients with heart failure after implementation of a practice-based performance improvement intervention: findings from IMPROVE HF. Congest Heart Fail. 2012;18(1):9-17.

6. Packham DK, Kosiborod M. Potential New Agents for the Management of Hyperkalemia. Am J Cardiovasc Drugs. 2015. [Epub ahead of print].

7. Fonarow GC et al. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Circ Heart Fail. 2008;1(2):98-106.

8. Shirazian S et al. Underprescription of renin-angiotensin system blockers in moderate to severe chronic kidney disease. Am J Med Sci. 2015;349(6):510-5.

9. Di Tano G et al. The 30-day metric in acute heart failure revisited: data from IN-HF Outcome, an Italian nationwide cardiology registry. Eur J Heart Fail. 2015;doi:10.1002/ejhf.290. [Epub ahead of print].

10. 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.

11. 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.

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

13. Rossignol P et al; Writing group of 10th Global Cardio Vascular Clinical Trialist forum held on December 6th-7th 2013 in Paris, France. Time to retrieve the best benefits from renin angiotensin aldosterone system (RAAS) inhibition in heart failure patients with reduced ejection fraction: lessons from randomized controlled trials and registries. Int J Cardiol. 2014;177(3):731-3.

14. Rossignol P et al. 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;7(1):51-8.

15. Jarman PR et al. Hyperkalaemia in diabetes: prevalence and associations. Postgrad Med J. 1995;71(839):551-2.

16. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch Intern Med. 1998;158(1):26-32.

17. Sarafidis PA et al. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. Clin J Am Soc Nephrol. 2012;7(8):1234-41.

18. Stevens MS, Dunlay RW. Hyperkalemia in hospitalized patients. Int Urol Nephrol. 2000;32(2):177-80.

19. Uijtendaal EV et al. Frequency of laboratory measurement and hyperkalaemia in hospitalised patients using serum potassium concentration increasing drugs. Eur J Clin Pharmacol. 2011;67(9):933-40.

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. Raebel MA et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Pharmacoepidemiol Drug Saf. 2007;16(1):55-64.

22. Metra M et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. J Am Coll Cardiol. 2013;61(2):196-206.

23. Teerlink JR et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013;381(9860):29-39.

24. Anker SD et al. Ularitide for the treatment of acute decompensated heart failure: from preclinical to clinical studies. Eur Heart J. 2015;36(12):715-23.

25. Cardiorentis. Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure (TRUE-AHF). NCT01661634. https://www.clinicaltrials.gov/ct2/show/NCT01661634?term=NCT01661634&rank=1.

26. Swedberg K et al; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875-85.

27. Malik FI et al. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. Science. 2011;331(6023):1439-43.

28. Teerlink JR. A Phase 2 Study of Intravenous Omecamtiv Mecarbil, a Novel Cardiac Myosin Activator, in Patients with Acute Heart Failure. Available at: www.clinicaltrialresults.org. Last accessed: 8 October 2015.

29. Pitt B et al; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309-21.

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

31. Bozkurt B et al. Complications of inappropriate use of spironolactone in heart failure: when an old medicine spirals out of new guidelines. J Am Coll Cardiol. 2003;41(2):211-4.

32. Shah KB et al. The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. J Am Coll Cardiol. 2005;46(5):845-9.

33. Albert NM et al. Use of aldosterone antagonists in heart failure. JAMA. 2009;302(15):1658-65.

34. Go AS et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.

35. Healthcare Cost and Utilization Project. US Agency for Healthcare Research and Quality 2015. Available at: http://hcupnet.ahrq.gov/HCUPnet.jsp. Last accessed: 8 October 2015.

36. Pitt B et al. Effect of Cardiovascular Comorbidities on the Mortality Risk Associated with Serum Potassium. Poster 2443. AHA 2014 Scientific Sessions, 19 Nov 2014.

37. US Food and Drug Administration. Sanofi-aventis U.S.LLC. KAYEXALATE® Product Information. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm186845.htm. Last accessed: 8 October 2015.

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

39. Anker SD et al. 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;doi:10.1002/ejhf.300. [Epub ahead of print].

40. Weir MR et al. New agents for hyperkalemia. N Engl J Med. 2015;372(16):1570-1.

41. Pitt B et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J. 2013;34(31):2453-63.

42. Patel SR, Pina IL. From acute decompensated to chronic heart failure. Am J Cardiol. 2014;114(12):1923-9.

43. 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.

44. McMurray JJ. Neprilysin inhibition to treat heart failure: a tale of science, serendipity, and second chances. Eur J Heart Fail. 2015;17(3):242-7.

45. Novartis Pharmaceuticals. Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbi-mortality in Patients With Chronic Heart Failure (ATMOSPHERE). NCT00853658. https://www.clinicaltrials.gov/ct2/show/NCT00853658?term=aliskiren+enalapril&rank=2.

46. Pitt B et al. Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. Eur J Heart Fail. 2015;17(2):224-32.

47. Felker GM et al. Heart failure therapeutics on the basis of a biased ligand of the angiotensin-2 type 1 receptor. Rationale and design of the BLAST-AHF study (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure). JACC Heart Fail. 2015;3(3):193-201.