Meeting Impression

ESC Heart Failure Congress 2016, May 23, 2016, Florence, Italy

OPTIMIZING RAAS INHIBITION IN HEART FAILURE: NOVEL TREATMENT CONSIDERATIONS FOR THE MANAGEMENT OF HYPERKALAEMIA

During the ESC Heart Failure Congress 2016, held in Florence, Italy, the Physicians' Academy for Cardiovascular Education (PACE) organised a satellite symposium that elaborated on beneficial and unwanted effects of RAAS inhibition in heart failure. Hyperkalaemia is a common comorbid condition, which is often the reason that patients receive suboptimal treatment. Also when potassium levels are high, a patient still benefits from RAAS-inhibiting treatment. During this symposium, it was discussed how hyperkalaemia can be monitored and managed. Two novel agents are under investigation to treat hyperkalaemia and can help in optimally treating patients with heart failure.

TOPICS

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The future of HF management: How does potassium binding fit within pharmacological treatment of heart failure?
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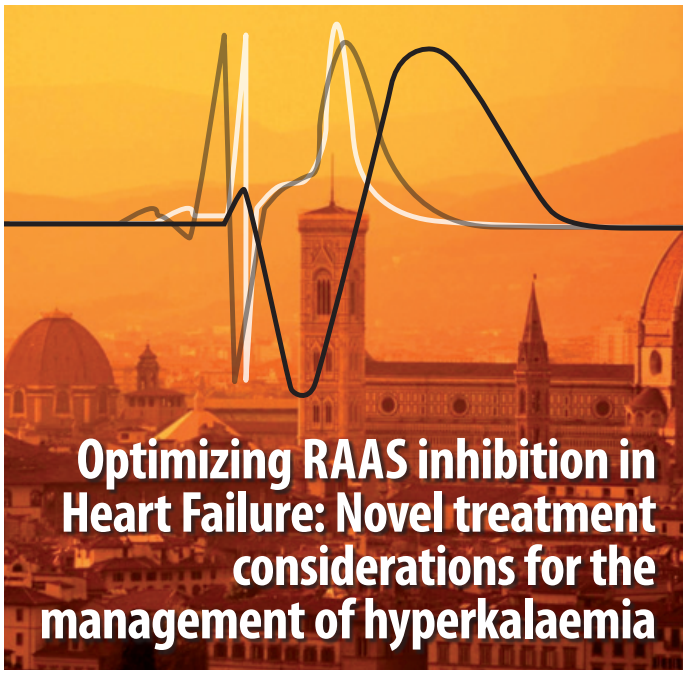

The renin-angiotensin-aldosterone-system (RAAS) has a significant role in the pathology of cardiovascular (CV) diseases and diabetic kidney disease. Renin, angiotensinogen, angiotensin-converting enzyme (ACE) and angiotensin I and II (Ang I and II) are key proteins of RAAS signalling, that ultimately lead to stimulation of renal sodium retention and aldosterone secretion, vasoconstriction and activation of the sympathetic nervous system.
As a result, blood pressure (BP) increases. Inhibition of RAAS signalling by specific inhibitors, like ACE-inhibitors and angiotensin II receptor blockers (ARBs) or mineralocorticoid receptor antagonists (MRAs), is often used for the treatment of CV diseases such as hypertension, heart failure (HF) and chronic kidney disease.

RAAS inhibition in heart failure: corner stone of therapy & potassium homeostasis

Faiez Zannad, MD – *CHU, Nancy University, Nancy France*

Prof. Zannad explained the implementation of RAAS inhibitors (RAASi) for the treatment of HF in clinical practice and their clinical impact. He showed that RAASi are frequently omitted or discontinued in clinical practice, although HF guidelines strongly recommend the use of RAASi for several indications. Data of the ESC heart failure registry revealed that while ACEi or ARBs were quite frequently prescribed by practitioners, MRAs were not offered to ~30% of the eligible HF patients with reduced ejection fraction (HFrEF)[1]. In addition and more importantly, patients who did receive medication, were frequently underdosed, because these patients were at increased risk

for concomitant adverse events[2-4]. These adverse events comprised mainly persistent and consistent hyperkalaemia and/or worsening renal function. Unfortunately, these events are frequently associated with HF[2-4].

In a retrospective study, the frequency of underdosing of RAASi was independent of risk factors such as chronic kidney disease (CKD) and diabetes, and was noted in about two third of patients. Furthermore, discontinuation was observed in 15-25% of patients[5]. A dramatic effect on mortality in patients that did not receive or discontinued therapy with RAASi was reported by a Swedish registry[6]. The risk doubled compared with patients receiving the therapy, regardless of having renal insufficiency. A second study showed similar results for patients with stage 3-4 CKD, HF and diabetes and remarkably, mortality rates were almost comparable for patients who received reduced doses and those who discontinued. These increased risks of mortality are similar for all types of RAASi.

"Dose reduction or discontinuation is not always needed, as hyperkalaemia is just a very expected adverse event of RAASi"

However, said Zannad, 'dose reduction or discontinuation is not always needed, as hyperkalaemia is just a very expected adverse event of RAASi'. Potassium levels quickly rise after induction of RAASi, but the risk of hyperkalaemia is low if you monitor potassium properly. Only potassium levels above 5.5 mmol/L increase the risk of mortality[7], meaning that there is not much concern when potassium levels are elevated but stay below 5 mmol/L. Therefore, discontinuation of RAASi is not needed when levels are below this line and only dose reduction or temporary dose reduction should be considered. Moreover, if a patient has hyperkalaemia, this does not deny the patient from benefit: it was demonstrated that also patients with high potassium levels benefit from spironolactone treatment, since patients with high and low potassium levels had a similar decreased risk of death as placebo-treated patients[7]. Comparable results have also been shown with eplerenone for HFrEF patients[8].

Hence, Zannad emphasised that patients be maintained on RAASi medication when they are at risk of hyperkalaemia, thereby offering patients a life-saving therapy. Hyperkalaemia can be prevented by monitoring potassium levels, which can be done by e.g. telemedicine. Discontinuation and reinitiating medication can be guided by an algorithm, for instance as used in EMPHASIS-HF[8]. Moreover, this algorithm provides information about how frequently potassium levels should be checked. Unfortunately, it has been shown that measurements of potassium are not regularly executed in common practice[9]. In the nearby future, new potassium binders may optimise RAASi therapy, by allowing uptitration of the dose of RAASi. However, their preventive value needs to be investigated.

Hyperkalaemia: novel treatment strategies to manage potassium levels in heart failure

Peter van der meer, MD – *University Medical Center Groningen, Groningen, The Netherlands*

Several therapeutic options exist for hyperkalaemia. Insulin, beta-adrenergic agonists and sodium bicarbonate are used in acute situations. In case of very high potassium levels, dialysis can be done. This is, however, invasive and expensive and therefore not a preferable option. For chronic treatment, kayexalate and resonium calcium are indicated. These drugs exchange potassium for calcium. These medications have, however, severe side effects, for instance affecting the gastrointestinal tract. Therefore, there is a need for new treatment options for hyperkalaemia that are effective, safe and well-tolerated. Patiromer and ZS-9 (sodium zirconium cyclosilicate) are two novel potassium binders that are currently under investigation. By binding to potassium, potassium levels in the circulation are lowered.

One of few trials evaluating patiromer is the AMETHYST-DN trial, which included 306 diabetic patients that had low eGFR (15-60 mL/min), who were on RAAS inhibition (RAASi) and had potassium levels >5mmol/L[10]. The efficacy and safety of low- and high dose patiromer treatment were evaluated. For both conditions a significant decrease in potassium levels was seen, which remained stable and increased again upon withdrawal of the treatment. Adverse events were modest and included worsening of CKD, hypomagnesaemia, worsening of hypertension, constipation, diarrhoea and hypoglycaemia. However, it was difficult to determine whether these adverse events were truly related to treatment, as this trial did not include a placebo group for comparison.

Another study with patiromer is the PEARL-HF trial, which investigated the efficacy and safety of patiromer in 104 spironolactone-treated (25 mg/day) HF patients with high risk for hyperkalaemia (history of hyperkalaemia or eGFR <60 mL/min), in order to evaluate whether the dose of spironolactone could be enhanced when patiromer was used[11]. This showed that potassium levels clearly decreased when patients were treated with patiromer, in contrast to potassium levels of placebo-treated patients, which increased upon spironolactone treatment. After 2 weeks, spironolactone dose was uptitrated to 50 mg/day, and resulted a slight potassium level increase in both groups.

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This translated into an efficacy (number of patients with hyperkalaemia) that was significantly higher in de patiromer versus the placebo group. However, 6% of the patients treated with patiromer were hypokalaemic (3.5 mmol/L), versus none in the placebo group. But most importantly, 91% of the patiromer-treated patients could tolerate 50 mg/day spironolactone instead of 74% of the placebo-treated patients, which was a significant difference. Adverse events were also slightly more common in patiromer-treated patients, however there was no difference in the frequency of serious side effects or events leading to discontinuation.

"The novel potassium binders patiromer and ZS-9 are highly effective in lowering serum potassium levels"

ZS-9 is the other new potassium binder, which is more selective. Several large trials have been performed with ZS-9, the most important being a multicentre phase 3 trial[12] that included all kinds of patients with hyperkalaemia (n=753) receiving different doses of ZS-9 or placebo. This revealed a significant dose-dependent decrease in potassium levels within hours. Upon withdrawal of the drug, potassium levels increased again. The safety profile of ZS-9 seems very promising with no differences between ZS-9 and placebo-treated patients in adverse events such as gastrointestinal events.

In addition, another ZS-9 study in 94 HF patients showed a significant decrease in potassium levels when patients were treated with ZS-9 for 48 hours, which quickly increased in patients who were randomised to placebo after these 48 hours. However, potassium levels reached around 4.5 mmol/L in patients that remained on ZS-9 (several doses). Also in this study, a favourable safety profile was observed, although there was a marginal increase in the frequency of peripheral oedema in patients treated with the highest ZS-9 dose. However, whether this is related to the doses and the underlying mechanism is as yet unclear.

In summary, the novel potassium binders patiromer and ZS-9 have a favourable safety profile when compared to that of the older potassium binders. They both resulted in a quick decrease of potassium levels, which enabled dose uptitration of spironolactone. It remains to be investigated whether this will also result in an improved long-term outcome.

The future of HF management: How does potassium binding fit within pharmacological treatment of heart failure

Kenneth Dickstein, MD – *University of Bergen, Stavanger University Hospital, Stavanger, Norway*

Dickstein started off outlining the concept that HF is not a disease but a syndrome with multiple causes and converges many symptoms, making it a very large and heterogeneous population. This population is rapidly growing and prevalence estimates depend on how HF is defined. The costs of treating HF are enormous and are largely due to hospitalisation (60-65% of all costs).

Next to direct HF treatment, a substantial part of HF management is represented by treatment of concomitant therapeutic effects. In HF, guidelines recommend to use medications such as ACEi, ARBs and MRAs, which block the neurohormonal angiotensin system. Overactivity of this system dominates and worsens patient's symptoms. Activity of this system is not only affected by the body itself but can also be affected by treatment, such as increased aldosterone plasma levels upon diuretic therapy.

"A substantial part of HF management is represented by treatment of concomitant therapeutic effects"

To improve management, several trials have been done to block the angiotensin system more strongly, such as VALIANT in 2003, CHARM-added in 2003, ValHeFT in 2002 and RESOLVD in 1999, including for example combination therapy of ACEi and ARBs. Nevertheless, these demonstrated only non-inferiority or slight benefit and included an increased frequency of adverse events such as worsening renal function and hyperkalaemia[13]. Also the renin inhibitor aliskiren and the ACEi enalapril were tested as monotherapy as well as in combination, in patients with HF (ATMOSPHERE and PARADIGM trials)[14]. This showed no difference in terms of long-term clinical outcome between monotherapy and combination therapy, however a significantly higher frequency of hyperkalaemia development was observed when treated with combination therapy, compared to monotherapy. This was even more apparent when MRAs were used at baseline.

A new agent in clinical trial that may improve HF management is LCZ696 (sacubitril/valsartan or ARNI therapy)[15]. However, a study suggested that prior therapy optimisation resulted in a high frequency of patients with a contraindication for ARNI therapy as a result of side effects, such as hyperkalaemia.
Overall, the barriers of HF treatment with RAAS inhibition are similar to those that have been observed over the last

20 years, including creatinine increase, hypotension and risk for hyperkalaemia, as was demonstrated by the RALES, EPHESUS and EMPHASIS trial[16-18].

Nevertheless, insights have emerged on how to manage hyperkalaemia in HF. One study found eGFR<45 mL/min/1.73 m^2, baseline K^+>4.5 mEq/L on diuretics and BMI<26 kg/m^2 as predictors of hyperkalaemia (K^+>5.5 mEq/L)[19] and risk factors for hyperkalaemia with use of RAAS inhibitors include chronic kidney disease, decompensated HF, diabetes, volume depletion with decreased GFR and advanced age[20]. Standard care in case of hyperkalaemia includes a low potassium diet, assessing renal function, reviewing medication history, titrating or discontinuing RAASi, applying diuretic therapy and/or potassium binder therapy.

Hyperkalaemia in at-risk patients is associated with increased mortality and frequent visits to the emergency department when potassium levels increase. Fear of hyperkalaemia can therefore be in the way of prescribing or optimally dosing RAAS inhibitor therapy. Indeed, uptake of guideline-recommended therapy for eligible patients is poor. If hyperkalaemia can be prevented with new agents such as patiromer and ZS-9, this will allow better treatment of a larger number of HF patients.

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