THE ONGOING MANAGEMENT OF HYPERKALAEMIA IN CHRONIC KIDNEY DISEASE PATIENTS: CASES FOR CLINICAL DECISIONS

This symposium took place on 30th May 2015 as part of the 52nd European Renal Association — European Dialysis and Transplant Association (ERA-EDTA) Congress in London, UK

Chairperson

David C. Wheeler[1]

Speakers

Francesco Locatelli,[2] Adrian Covic,[3] David C. Wheeler[1]

1. University College London, London, UK
2. Alessandro Manzoni Hospital, Lecco, Italy
3. Grigori T Popa University, Iasi, Romania

Disclosure: David C. Wheeler received honoraria from ZS Pharma for consultancy and speaking commitments. Francesco Locatelli was a member of an advisory board of ZS Pharma. Adrian Covic is a speaker and consultant for ZS Pharma.
Acknowledgements: Writing assistance was provided by Dr Ana Rodríguez de Ledesma, apothecom scopemedical ltd.
Support: The symposium was organised by Medavera, Inc. and supported by an educational grant from ZS Pharma. Authors received honoraria for preparation and delivery of their presentations. The views and opinions expressed are those of the authors and not necessarily of Medavera, Inc. or ZS Pharma.
Citation: EMJ Nephrol. 2015;3[1]:46–55.

MEETING SUMMARY

This educational symposium provided an insight into the most current clinical evidence of the efficacy and safety of renin—angiotensin—aldosterone system inhibitors (RAASis) for patients with chronic kidney disease (CKD). The programme provided an opportunity to discuss ways to optimise and maintain RAASis in this population by introducing CKD patient cases and the dilemmas of their clinical presentation, and novel treatment options, including benefits, harms, and potential consequences.

Prof David C. Wheeler introduced the debate about the use of RAASis and the associated risk of hyperkalaemia in CKD patients. Prof Francesco Locatelli discussed the management of blood pressure (BP) in CKD and reviewed the most current guidelines for the prevention of hyperkalaemia in this population. Prof Adrian Covic presented the controversies around the use of RAASis in specific group populations. Survival, cardiovascular events (CVEs), and progression of CKD were the main points of his presentation. Finally, Prof David C. Wheeler discussed the latest research on novel therapies for the management of hyperkalaemia.

Welcome and Introductions

Professor David C. Wheeler

Treatment with agents that block the renin—angiotensin—aldosterone system, the so-called RAASis, are considered to be the standard of care for patients with CKD.[1] However, their use has been associated with an increased risk of hyperkalaemia. Hyperkalaemia, a condition defined by an abnormally high concentration of potassium (K^+) in the blood (>5 mmol/l according to the Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines)[2] is of special concern to health providers treating patients with CKD. Whether acute or chronic, hyperkalaemia may increase the risk of adverse CVEs in this population.[1,3,4] The current

practice is to discontinue or reduce the use of RAASis and/or other drugs associated with the development of hyperkalaemia.[5]

Current guidelines recommend the use of RAASis to control BP in patients with CKD, proteinuria and heart failure.[2,6] However, the risk of hyperkalaemia limits the titration of these drugs and leads to variation in practice as clinician attempt to avoid harm.[7,8] Several trials have assessed combinations of RAASis in various populations with different medications and doses, but such combination therapies are also limited by the high risk of hyperkalaemia (and acute kidney injury [AKI]).[9] The use of RAASis may become more problematic as kidney disease advances, with an increased risk of hyperkalaemia in those with more severely impaired kidney functions. Strategies for the management of hyperkalaemia in the acute setting include: intravenous insulin and dextrose, oral polystyrene sulfonate resins, and inhaled beta-adrenergic agonists.[10] These agents have side-effects, some of which are potentially harmful, and are not suitable for use in the longer term. In this symposium the potential of two new therapeutic agents for the management of hyperkalaemia in a chronic setting was discussed.

The learning objectives of the symposium were: 1) to explain why RAASi doses should be optimised and maintained, especially aldosterone blockade in late-stage CKD; 2) to identify why RAASi medications delay CKD progression; 3) to evaluate current Kidney Disease: Improving Clinical Outcomes (KDIGO) and KDOQI guideline recommendations for BP treatment in CKD patients and subsequent management of hyperkalaemia; and 4) to contrast the mechanism of action of organic polymer resins and new therapies for hyperkalaemia.

Chronic Kidney Disease Patients at Risk for Hyperkalaemia: Review of Current Guidelines

Professor Francesco Locatelli

The distribution of electrolytes in our bodies determines the chemical and physical reactions that occur within the fluids. Changes in K^+ concentration are of paramount importance in determining its effects on the heart,[11] and while K^+ equilibrates freely and rapidly within the extracellular fluid, its stable concentration and balance needs to be maintained in order to help the heart and other muscles to work properly.

In addition to angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and aldosterone antagonists, hyperkalaemia can be caused by other mechanisms including dietary ingestion, acidosis, hyperglycaemia (diabetes), hyporeninaemic hypoaldosteronism, oliguria, and certain drugs.[2] Foods with high K^+ content (>250 mg/100 g) include fruits, vegetables, and meats, among others (e.g. nuts, brand cereals, chocolate, tea, mussels).[2] Drugs that impair renin—aldosterone function (e.g. ACEis, ARBs, aldosterone antagonists, β-blockers) or alter K^+ distribution (e.g. insulin agonists, hypertonic solutions, K^+ and herbal supplements, K^+-sparing diuretics, cyclosporine, tacrolimus, trimethoprim, and lithium) can cause hyperkalaemia in CKD.[2] Errors in the sampling (e.g. haemolysed red blood cells, inappropriate sample handling, erroneous reporting, equipment malfunction) should also be taken into consideration when determining clinical factors influencing the presence of hyperkalaemia.[2]

Management of blood pressure in chronic kidney disease — what do the current guidelines recommend?

For adult non-diabetic CKD patients, the 2012 KDIGO guideline recommends the use of BP-lowering drugs (ACEis or ARBs) where indicated, if urine albumin excretion is 30-300 mg (Level 2D) or >300 mg (Level 1B) over a 24-hour period.[2] CKD patients often have reduced capacity for K^+ excretion, which occurs when the glomerular filtration rate (GFR) falls. While ACEis and ARBs are valuable BP-reducing agents in CKD,[2] they can increase the risk of hyperkalaemia and paradoxically reduce the level of GFR; in this context, their role in slowing the progression of CKD needs to be evaluated, in particular in patients with renal artery stenosis, increased renal artery resistance, or reduced intravascular volume in general.[2] If hyperkalaemia occurs in CKD patients under ACEi medication, possible interventions include dietary advice, dosing reduction, or adding a K^+-losing diuretic. Current evidence does not support discontinuing ACEis and ARBs in patients with advanced CKD in an effort to preserve residual kidney function; discontinuation may be recommended due to the risk of hyperkalaemia

and in cases of undercurrent clinical problems (e.g. fever, diarrhoea, vomiting, hypotension, etc.).[2]

Popular and widely recommended weight-loss diets are commonly high in K^+ and protein, and may therefore increase the risk of hyperkalaemia and favour CKD. Moreover, as their potential benefits and harms have not been specifically addressed in the CKD population, the use of these diets in these patients is not recommended.[6] Aldosterone antagonists such as spironolactone have proven to be beneficial in non-CKD patients with HF, including HF after myocardial infarction. However, because of the risk of hyperkalaemia and reduction in GFR in CKD patients, aldosterone antagonist therapy should be considered with caution in this population.[6] In 2004, following the results of the Randomized Aldactone Evaluation Study (RALES)[12] that showed significant improvements in outcomes following treatment with spironolactone in patients with severe HF, there was a dramatic increase in the prescription rate of this drug. The increased use of spironolactone was, however, associated with an increased rate in hospital admissions and deaths due to the hyperkalaemia—spironolactone—ACEi-related interaction.[12] These results highlight the importance of close monitoring and judicious use of these agents in patients with CKD, especially with concomitant ACEi or ARB medication.

The risk of hyperkalaemia in CKD populations highlights the need not only to take into consideration their diet, but also to put into place other measures aiming to reduce the risk of hyperkalaemia. As mentioned, these measures include reducing ACEi intake or adding a K^+-losing diuretic. In general, the use of ACEi, ARB, and aldosterone antagonists should be carefully evaluated in patients using concomitant medications (painkillers, non-steroidal anti-inflammatory drugs, K^+-sparing diuretics) or patients with underlying conditions (non-dialysis patients, transplant patients) that can increase the risk of hyperkalaemia. While thiazides are known to potentiate the effect of other antihypertensive agents, particularly ACEis and ARBs, they also reduce the risk of hyperkalaemia.[6]

The KDOQI guidelines[2] detail measures to lower serum K^+ for prevention and management of hyperkalaemia due to ACEis or ARBs in CKD and/or according to baseline serum K^+. Acute interventions with the use of Ca^{2+} salts are recommended by the National Institute for Health and Care Excellence (NICE)-accredited collaboration between the Renal Association and the Resuscitation Council (UK).[13] These guidelines highlight the need to implement K^+ and BP monitoring for the prevention and identification of hyperkalaemia and, overall, the need to be prepared to treat severe complications in CKD patients.[13,14]

Controlling serum K^+ is an important goal in the maintenance of haemodialysis.[15] Hyperkalaemic patients who achieve K^+ balance through haemodialysis have better survival rates.[15] Studies have concluded on the association of certain modifiable dialysis practices with mortality.[15,16] A high dialytic removal of K^+ does not necessarily prevent a rapid post-dialysis rebound of plasma K^+, and therefore patients with marked hyperkalaemia should be monitored closely post-dialysis.[17] High dialysate bicarbonate levels have also been shown to be associated with a faster decrease in serum K^+.[18] This finding could have an impact on patients with life-threatening pre-conventional haemodialysis hyperkalaemia.[18]

In summary, there is compelling evidence on the importance of maintaining a good concentration and balance of K^+, not only for controlling the risks related to hyperkalaemia but also for controlling the risks related to hypokalaemia. It should be noted that: 1) the use of dialysate K^+ <3 mmol/l is very common and leads to low post-haemodialysis K^+ levels; 2) the risk of sudden death is higher for patients in haemodialysis units where more patients have dialysate K^+ below 3 mmol/l; 3) higher risk with low dialysate K^+ is especially clear for patients with pre-haemodialysis serum K^+ <5 mmol/L; and 4) use of profiled K^+ dialysate concentration reduces arrhythmogenic risk.

RAASi Use in Chronic Kidney Disease

Professor Adrian Covic

Angiotensin II has been implicated in a number of pathophysiological processes leading to hypertension, end-organ damage, HF, and death.[19] To date, there is compelling evidence for the end-organ benefit when using RAASis, including in non-diabetic CKD patients, patients with diabetes, and patients who are undergoing dialysis or kidney transplantation (KTx).[20-23]

Diabetic patients

In patients with diabetic nephropathy, RAASis are the cornerstone of treatment, and their beneficial effects have been demonstrated across each stage of disease progression.[24] The KDIGO guidelines recommend ACEis or ARBs as primary prevention of CKD in diabetic nephropathy patients to reduce GFR, and in normotensive patients with albuminuria levels >30 mg of albumin per g of creatinine per 24 hours to reduce microalbuminuria.[6] However, no benefit has been confirmed in normotensive patients with normoalbuminuria.[6]

In a recent meta-analysis of 35 clinical trials and involving up to 32,827 patients with diabetes mellitus (DM), treatment with ACEis reduced all-cause mortality, cardiovascular (CV) mortality, and major CVEs, but not stroke.[25] ARBs had no beneficial effect on these outcomes.[25] In a systematic review and Bayesian network meta-analysis of 63 randomised clinical trials (RCTs) involving 36,917 participants, ACEis showed superior ranking positions in all outcomes (mortality, requirement for dialysis, and doubling of serum creatinine [SCr] levels) versus ARBs.[26] The study showed that the combination therapy of ACEi plus Ca^{2+} channel blocker was the best treatment for reducing mortality, followed by ACEi plus a diuretic, ACEis, Ca^{2+} channel blockers, ARBs, and β-blockers. Compared with placebo, only ACEis significantly reduced the doubling of SCr levels.

In a systematic review and meta-analysis study of 9 clinical trials with 9,797 participants, the effect of RAASis on all-cause mortality and CV mortality in DM patients with advanced CKD was not significantly different compared with control groups (placebo or other antihypertensive drugs).[27] However, patients treated with ACEis experienced a mild 10% reduction in the risk of developing non-fatal CVEs and a 19% risk reduction in the need for renal replacement and doubling of the SCr.[27] These results indicate a small but beneficial effect of ACEis on the survival of patients with more advanced CKD. Combination therapy with ACEis and ARBs has no beneficial effect on survival or CV symptoms in patients with diabetes nephropathy.[28] Moreover, the combination therapy has been associated with an increased risk of AKI, hyperkalaemia, and hypotension, highlighting the potential concern related to the use of double blockade in this population.[28-30]

Non-diabetic chronic kidney disease patients

In a recent analysis conducted with non-dialysis-dependent patients with CKD, ACEi—ARB administration was associated with greater survival over a 6-year period compared with an untreated group.[31] The study involved 141,413 USA veterans with a mean estimated GFR (eGFR) of 50±13 ml/min/1.73 m^2 who had been previously unexposed to the double blockade.[31]

Do patients with early CKD benefit from RAASis? In people with Stage 3 CKD, ACEi use has been shown to impact the all-cause mortality or CVEs in a meta-analysis of 4 RCTs involving 2,177 participants.[32] The results of this study did not confirm the effectiveness of ACEis or ARBs in patients with early (Stage 1-3) CKD who do not have DM.[32]

Do patients with advanced CKD benefit from RAASis? In a prospective study involving 28,497 hypertensive adult patients with advanced CKD (Cr >6 mg/dl), ACEi—ARB therapy reduced the risk for initiating long-term dialysis or death by 6% in a median follow-up of 7 months.[33] The renal benefit of ACEi—ARB use was consistent across most patient subgroups, as was that of ACEi or ARB monotherapy.[33] Compared with non-users, the ACEi—ARB users had a higher hyperkalaemia-associated hospitalisation rate, but the risk of pre-dialysis mortality caused by hyperkalaemia was not significantly increased.[33]

In a small study (n=68) conducted with hypertensive elderly patients with advanced CKD (Stage 4 and 5, not on dialysis), there was an improvement in eGFR 24 months after stopping ACEis or ARBs.[34]

Patients on dialysis

In a meta-analysis involving 1,679 dialysis patients, antihypertensive medications (primarily ACEis or ARBs) were associated with lower risk of all-cause mortality and CV mortality than control regimens.[35] The effect of ACEis and ARBs on haemodialysis was evaluated in an analysis of 8 RCTs involving 837 patients on dialysis.[36] Although ACEi or ARB use was associated with reduced left ventricular mass, it was not associated with a lower risk of CVEs.[36] However, the analysis included very small studies and were of limited duration and so may have been underpowered to detect these differences.[37]

Patients with kidney transplantation

According to some studies, the use of ACEis and ARBs may help to reduce the high incidence of death and/or renal allograft failure in patients undergoing transplantation.[38,39] In a retrospective open cohort study involving 2,031 kidney transplant recipients, the use of ACEi—ARB combination has been associated with a prolonged patient and graft survival 10 years after KTx.[39] In a longitudinal study of 990 single-renal recipients, the use of ACEi—ARB was also associated with a reduction of the mortality risk in a median 14-month period after transplantation, but no significant improvements in graft survival were observed.[38] In a more recent large-scale retrospective study of prospectively collected data involving 29,251 kidney transplant recipients, the use of ACEi—ARB resulted in similar CVE rates to those observed in non ACEi—ARB users.[40] Therefore, despite the wide use of RAASis after KTx, the evidence for an improvement remains mixed.[40]

Table 1: Patient cases at a glance.

Current history	Discussion	Message
An everyday clinical case, by Francesco Locatelli (Case 1)		

- A patient with CKD treated with an ACEi who develops hyperkalaemia and metabolic acidosis
- High-to-normal BP
	- What to do first: correct metabolic acidosis or directly hyperkalaemia?
	- If you correct acidosis (e.g. sodium bicarbonate), then hyperkalaemia may persist – *then what?*
	  - Use diuretic as first step (e.g. furosemide; thiazides or chlorthalidone could be added in some situations)
	  - Then, control hyperkalaemia with a resin and withdraw the ACEi if hyperkalaemia persists
		- In case of complications (e.g. fever, diarrhoea, vomiting), treatment with diuretics and ACEis, ARBs, and aldosterone antagonists should be stopped to avoid hypotension, hyperkalaemia, and further deterioration of renal function

An emergency case, by Adrian Covic (Case 2)		
Male, 56-years-old, came to the emergency room - 'Some diarrhoea' in the past 3 days; back pain treated with over-the-counter non-steroidal anti-inflammatory drugs in the past week - In 2003 (43-year-old): diagnosed with Type 2 diabetes mellitus, treated with insulin - In 2014 (55-year-old): diabetic kidney disease; proteinuria 0.78 g/day; eGFR 58 ml/min; medication included ACEis, β-blockers, and insulin - Upon clinical evaluation: dehydrated; biochemistry: eGFR 40 ml/min; normal K^+ level; proteinuria 0.8 g/day Treatment • Fluids • ACEis were stopped temporarily, eGFR recovered	**After 6 months** - Periodical evaluation; euvolaemic; BP 145/95 mmHg; proteinuria 2.1 g/day; eGFR 45 ml/min; K^+ 5.2 mmol/l; no back pain; compliant Treatment • Spironolactone 12.5 mg/day was added to his medication regimen	**A month later** - Euvolaemic; BP 135/85 mmHg; proteinuria 1.2 g/day; stationary eGFR 40 ml/min; hyperkalaemia K^+ 6.0 mmol/l - Cardiologist: stop ACEi + magnetic resonance imaging, switch to Ca^{2+} channel blockers and β-blockers

CKD: chronic kidney disease; ACEi: angiotensin-converting enzyme inhibitor; BP: blood pressure; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate.

How about novel strategies?

Aldosterone antagonists can be added to prevent further progression of CKD.[41] In a systematic review of 27 RCTs, the use of aldosterone antagonists alone or in combination with an ACEi or ARB (or both) reduced proteinuria and BP in adults with mild-to-moderate CKD.[41] However, because aldosterone antagonists can cause or exacerbate hyperkalaemia, only one-third of those patients hospitalised for HF are being recommended.[42,43]

In summary, there is compelling evidence demonstrating that RAASis, in particular ACEis, increase survival and slow CKD progression at an early stage. Evidence also indicates that non-fatal CVEs and CKD progression are prevented in advanced-stage CKD, but there is uncertainty regarding the benefits of RAASis in patients undergoing dialysis and transplantation. Dual blockade with ACEis and ARBs does not necessarily correlate with improved morbidity and mortality in CKD patients. Finally, some short-term clinical studies have shown renoprotective effects of aldosterone blockade. By discussing two different clinical cases of CKD the speakers discussed practical steps for improving the management of hyperkalemia in such patients (Table 1).

New Strategies in the Management of Hyperkalaemia

Professor David C. Wheeler

Do we have therapies to control K^+ levels and allow the continuing/increasing use of RAASis?

Prof Wheeler introduced his presentation by contrasting two patients with hyperkalaemia, one in an acute setting and the other in a chronic setting (Table 2).

Patiromer sorbitex calcium (RLY5016S; cross-linked polymer of calcium 2-fluoroprop-2-enoate with diethenylbenzene and octa-1,7-diene, combination with D-glucitol) and sodium zirconium cyclosilicate (ZS-9; silicic acid [H_2SiO_3], sodium zirconium [4+] salt [3:2:1], hydrate) are two novel compounds for the treatment of hyperkalaemia.[44,45] Patiromer is a non-absorbable polymer that enhances K^+ excretion by the exchange of Ca^{2+}, predominantly in the distal colon. ZS-9 is a non-absorbable cation trap that selectively binds K^+ in exchange for H^+ and Na^+; it binds K^+ immediately upon ingestion. New research indicates that both compounds are promising drugs in the treatment of hyperkalaemia.

In a two-part, single-blind, Phase III study (the OPAL-HK study) patiromer decreased the serum K^+ levels and reduced the risk of hyperkalaemia recurrence compared with placebo in patients with CKD.[44] The approximate sorbitol content of the drug product at starting doses of 4.2 g and 8.4 g patiromer (each given BID) used in the current study were 2 g and 4 g per dose (i.e. 4 g and 8 g daily), respectively. During the first 4 weeks, if a first recurrent hyperkalaemic event occurred, an up-titration of patiromer in the patiromer group and a dose reduction of RAASi medication for the placebo group was required. In either group, if a subsequent elevation in serum potassium occurred (≥5.1 mmol/l), discontinuation of RAASi medication was required. During the second 4 weeks, an up-titration of patiromer in the patiromer group and a dose reduction of RAASi medication in the placebo group was required. The study comprised 237 CKD patients with hyperkalaemia (K^+ 5.1-<6.5 mmol/l) who received at least one dose of patiromer and had at least one post-dose K^+ measurement, and who were on RAASis. Patients with baseline K^+ of 5.1-<6.5 mEq/l received patiromer (4.2 or 8.4 g twice daily initially) for 4 weeks. Doses were adjusted in order to reach and maintain a target K^+ level according to a prespecified algorithm. At the end of the 4 weeks, 76% of patients reached the predefined K^+ target range of 3.8-<5.1 mmol/l; the mean change in serum K^+ from baseline to Week 4 was statistically significant, indicating the effectiveness of patiromer. At the end of this 4-week period, patients with a baseline K^+ level of 5.5-<6.5 mmol/l in whom the level decreased to 3.8-<5.1 mmol/l entered an 8-week randomised withdrawal phase (follow-up phase). Throughout the 8-week period, the recurrence of hyperkalaemia occurred in a significantly lower proportion of patients in the patiromer group (15%) compared with the placebo group (60%; $p<0.001$).[44] Constipation was the most frequent adverse event (AE) (11% of patients across both groups) during the initial phase (Table 3). No serious gastrointestinal (GI) events were reported during this phase. Mild-to-moderate constipation, diarrhoea, and nausea were the most common GI events reported with patiromer (each in 4% of patients) during the follow-up period. Overall, rates of AEs in the patiromer groups were similar to those in the placebo group.

Table 2: An acute versus chronic case of hyperkalaemia.

A case of acute hyperkalaemia (Case 3)	A case of chronic hyperkalaemia (Case 4)
• Young patient brought into the emergency room with acute kidney injury; K^+ 8.5 mmol/l; electrocardiographic changes of hyperkalaemia Treatment options • Insulin 10 units + 50 ml 50% glucose (intravenous) • Polystyrene sulfonate resins (e.g. resonium; oral or rectal) • β-adrenergic agonists (e.g. salbutamol; inhaled)	• 56-year-old male, with known CKD; Type 2 diabetes mellitus for 8 years • Previous non-ST segment elevation myocardial infarction; heart failure (New York Heart Association Stage 2) • eGFR 32 ml/min/1.73 m^2 • Dipstick protein +++, albumin: creatinine ratio 124 mg/mmol • HbA_{1c} 77 mmol/mol on metformin 500 mg • Cholesterol 6.3 mmol/l on simvastatin 20 mg • BP 165/95 mmHg on bendroflumethiazide 2.5 mg and irbesartan 150 mg; serum K^+ 6.5 mmol/l

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; BP: blood pressure; HbA_{1c}: glycated haemoglobin.

Table 3: Patients with adverse events in the OPAL-HK study, number of patients (%).[44]

Adverse event	Initial treatment phase and through the safety follow-up period for that phase*	
≥1 Adverse event†	114 (47)	
Constipation	26 (11)	
Diarrhoea	8 (3)	
Hypomagnesaemia	8 (3)	
Nausea	8 (3)	
Anaemia	7 (3)	
Chronic renal failure	7 (3)	
≥1 Serious adverse event‡	3 (1)	
	Randomised withdrawal phase and through the safety follow-up period for that phase*	
	Placebo (n=52)	**Patiromer (n=55)**
≥1 Adverse event	26 (50)†	26 (47)
Headache	4 (8)	2 (4)
Supraventricular extrasystoles	1 (2)	2 (4)
Constipation	0	2 (4)
Diarrhoea	0	2 (4)
Nausea	0	2 (4)
≥1 Serious adverse event	1 (2)	0

*The safety follow-up period was 1 to 2 weeks after discontinuation of the study drug. Events are listed in the initial/safety phase if they occurred in at least 3% of the 243 patients overall; and in the randomised withdrawal phase if they occurred in at least 4% of patients in the patiromer group.

†During the initial treatment phase (i.e. excluding the safety follow-up period), one or more adverse events were reported in 107 patients (44%), and one or more serious adverse events were reported in 2 patients (1%). During the randomised withdrawal phase (i.e. excluding the safety follow-up period), one or more adverse events were reported in 24 patients (46%) in the placebo group.

‡The serious adverse events included atrial fibrillation (in 1 patient), enterococcal endocarditis (in 1), escherichia bacteraemia (in 1), urinary tract infection (in 1), sub therapeutic anticoagulant blood levels (in 1), and chronic renal failure (in 1).

The results showed that patiromer is effective in decreasing serum K^+ levels, and also in reducing the risk of hyperkalaemia in patients with CKD who are receiving RAASis and who develop hyperkalaemia.

In a multicentre, two-stage, double-blind, placebo-controlled Phase III study (the ZS-003 study), ZS-9 was effective in reducing hyperkalaemia among patients with comorbidities such as HF, CKD, DM, and on concurrent medications for management of their disease.[46] The study involved 753 patients with hyperkalaemia (K^+ 5.0-6.5 mmol/l), most of whom were on RAASis (75%) and/or had eGFR <60 ml/min/1.73 m^2 (67%).[46] Initially, patients were randomised to receive ZS-9 (1.25, 2.5, 5, or 10 g) or placebo three times daily for 48 hours (acute phase); then patients with normokalaemia at 48 hours were randomised to receive ZS-9 or placebo once daily on Days 3-14 (maintenance phase).[46] Compared with placebo, the reduction in serum K^+ was significant as early as 1 hour after administration of 10 g ZS-9, and maintained after 24 hours (89% of patients) and 48 hours (98%) (Figure 1); both the 5 g and 10 g daily doses of ZS-9 were significantly superior to placebo in maintaining normokalaemia during the maintenance period (p=0.008 and p<0.001, respectively). Patients on placebo returned to hyperkalaemic range. Overall the safety profile of ZS-9 was similar to that of placebo where the rates of AEs observed were similar between groups (25% for both groups). The incidence of GI and systemic AEs was low in both groups. The most common AE at all doses and during both study phases was diarrhoea, with a frequency of 1.8% with ZS-9 versus 2.5% with placebo during the initial phase, and 1.7% versus 2.2% during the maintenance phase, respectively.

The efficacy and safety of ZS-9 has also been evaluated in a more recent Phase III study (the HARMONIZE study).[47] The study involved 258 outpatients with hyperkalaemia (K^+ ≥5.1 mmol/l) who received ZS-9 initially three times daily during the first 48-hour open-label phase.[47] Forty-eight hours after treatment, ZS-9 reduced serum K^+ to within normal levels in 98% of patients. The median time to normalisation was 2.2 hours. First statistical efficacy was at 1 hour, 84% normal within 24 hours. Patients achieving normokalaemia (n=237; 3.5-5 mmol/l) were then randomised to receive ZS-9 (5, 10, or 15 g) or placebo for 28 days. Compared with placebo, all doses of the drug resulted in the continued maintenance of normokalaemia (80% of patients with 5 g, 90% with 10 g, and 94% with 15 g) over a period of 28 days (Figure 2).[47]

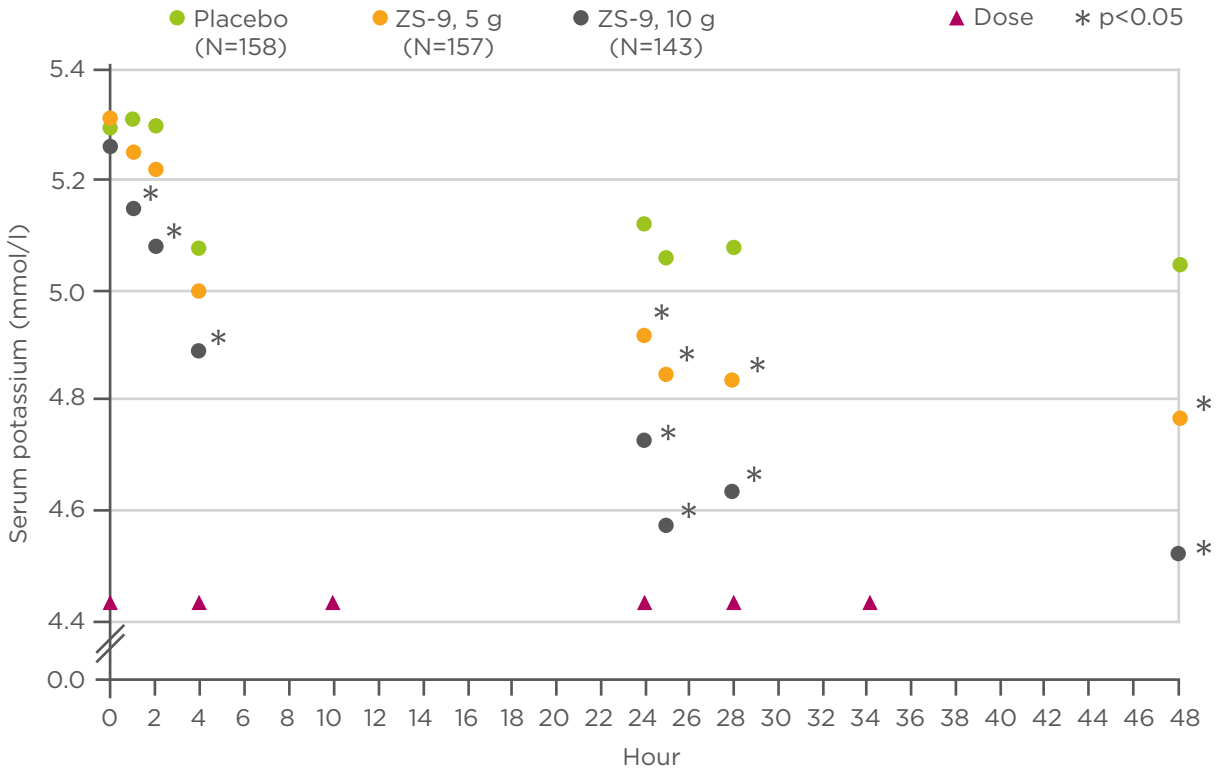
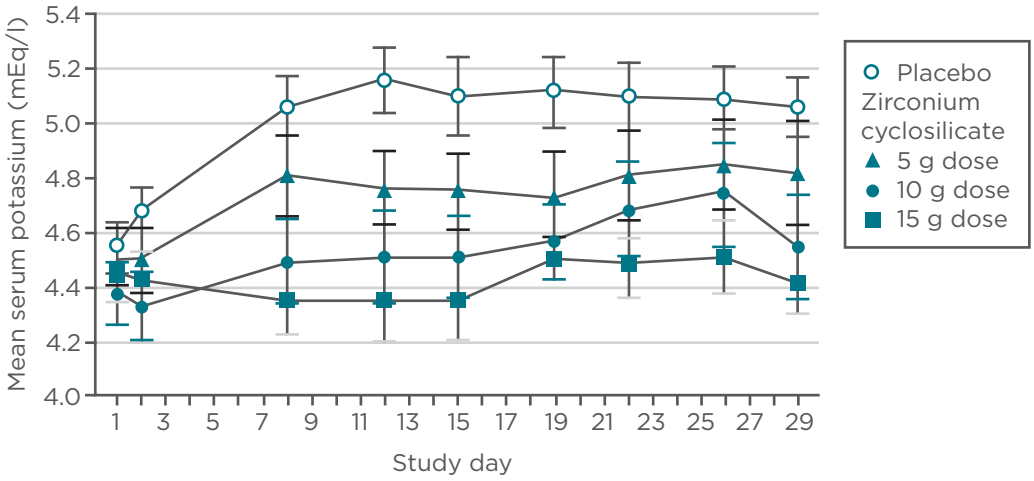


Figure 1: ZS-9 is associated with significantly lower serum K^+ levels than placebo during the acute phase.[46]



No. of patients

Placebo	82	81	81	80	80	78	77	74	73
5 g dose	45	45	45	44	44	43	43	42	39
10 g dose	50	49	50	47	47	47	45	45	38
15 g dose	54	54	54	53	52	51	51	51	43

Figure 2: All doses of ZS-9 maintained normokalaemia during the randomised phase of the HARMONIZE study.[47]

Adapted with permission from Kosiborod M et al.[47] 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.

ZS-9 and patiromer sorbitex calcium are two promising advanced therapies for the treatment of hyperkalaemia. The studies conducted with patiromer and ZS-003 excluded patients with K^+ levels >6.5 mmol/l, whereas the HARMONIZE study had no upper limit of serum potassium level for patient inclusion. The study included patients with K^+ levels up to 7.2 mmol/l. However, all studies described excluded patients who were hospitalised and/or on dialysis.[47] Further studies to determine the long-term efficacy and safety of these new therapies for the treatment of hyperkalaemia in CKD and HF are currently ongoing.

REFERENCES

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

2. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43(5 Suppl 1):S1-290.

3. Heerspink HJ et al. The effect of ramipril and telmisartan on serum potassium and its association with cardiovascular and renal events: results from the ONTARGET trial. Eur J Prev Cardiol. 2014;21(3): 299-309.

4. Patel UD et al. Quality of care and outcomes among patients with heart failure and chronic kidney disease: A Get With the Guidelines -- Heart Failure Program study. Am Heart J. 2008;156(4):674-81.

5. Kidney Disease Outcomes Quality Initiative. KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. 2004. Available at: http://www2.kidney.org/professionals/KDOQI/guidelines_bp/. Last accessed: 3 July 2015.

6. Kidney Disease Improving Global Outcomes. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. 2012. Available at: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO_BP_GL.pdf. Last accessed: 3 July 2015.

7. Yancy CW et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 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.

8. 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.

9. Persson F, Rossing P. Sequential RAAS blockade: is it worth the risk? Adv Chronic Kidney Dis. 2014;21(2):159-65.

10. Mushiyakh Y et al. Treatment and pathogenesis of acute hyperkalemia. J Community Hosp Intern Med Perspect. 2011;1(4);doi:10.3402/jchimp.v1i4.7372.

11. Austin Community College. Fluid/Electrolyte Balance. Available at: http://www.austincc.edu/apreview/

EmphasisItems/Electrolytefluidbalance.html. Last accessed: 3 July 2015.

12. Juurlink DN et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004;351(6):543-51.

13. The Renal Association. Treatment of Acute Hyperkalaemia in Adults. 2014. Available at: http://www.renal.org/guidelines/joint-guidelines/treatment-of-acute-hyperkalaemia-in-adults#sthash.At4NAN7Y.dpbs. Last accessed: 3 July 2015.

14. Guidelines and Audit Implementation Network. Guidelines for the Treatment of Hyperkalaemia in Adults. 2014. Available at: http://www.gain-ni.org/images/Uploads/Guidelines/GAIN_Guidelines_Treatment_of_Hyperkalaemia_in_Adults_GAIN_02_12_2014.pdf. Last accessed: 3 July 2015.

15. Kovesdy CP et al. Serum and dialysate potassium concentrations and survival in hemodialysis patients. Clin J Am Soc Nephrol. 2007;2(5):999-1007.

16. Jadoul M et al. Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Clin J Am Soc Nephrol. 2012;7(5):765-74.

17. Blumberg A et al. Plasma potassium in patients with terminal renal failure during and after haemodialysis; relationship with dialytic potassium removal and total body potassium. Nephrol Dial Transplant. 1997;12(8):1629-34.

18. Heguilén RM et al. The faster potassium-lowering effect of high dialysate bicarbonate concentrations in chronic haemodialysis patients. Nephrol Dial Transplant. 2005;20(3):591-7.

19. Willenheimer R et al. AT1-receptor blockers in hypertension and heart failure: clinical experience and future directions. Eur Heart J. 1999;20(14):997-1008.

20. Dahlöf B. Effect of angiotensin II blockade on cardiac hypertrophy and remodelling: a review. J Hum Hypertens. 1995;9 Suppl 5:S37-44.

21. Fyhrquist F et al. Role of angiotensin II in blood pressure regulation and in the pathophysiology of cardiovascular disorders. J Hum Hypertens. 1995;9 Suppl 5:S19-24.

22. Beers MH et al. (eds.), The Merck Manual of Diagnosis and Therapy (17th edition) 1999, Whitehouse Station, NJ: Merck Research Laboratories, pp. 1417-27.

23. Anderson S. Mechanisms of injury in progressive renal disease. Exp Nephrol. 1996;4 Suppl 1:34-40.

24. Roscioni SS et al. The effect of RAAS blockade on the progression of diabetic nephropathy. Nat Rev Nephrol. 2014;10(2):77-87.

25. Cheng J et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. JAMA Intern Med. 2014;174(5):773-85.

26. Wu H-Y et al. Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis. BMJ. 2013;347:f6008.

27. Covic A et al. Effect of RAAS blockade in adults with diabetes mellitus and advanced chronic kidney disease not on dialysis: a systematic review and meta-analysis. Nephrol Dial Transplant. 2015;30(suppl 3):iii188.

28. Fried LF et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369(20):1892-903.

29. Makani H et al. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ. 2013;346:f360.

30. Parving HH et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367(23):2204-13.

31. Molnar MZ et al. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. J Am Coll Cardiol. 2014;63(7):650-8.

32. Sharma P et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease. Cochrane Database Syst Rev. 2011;(10):CD007751.

33. Hsu T-W et al. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. JAMA Intern Med. 2014;174(3):347-54.

34. Ahmed AK et al. The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. Nephrol Dial Transplant. 2010;25(12):3977-82.

35. Heerspink HJ et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. Lancet. 2009;373(9668):1009-15.

36. Tai DJ et al. Cardiovascular effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in hemodialysis: a meta-analysis. Clin J Am Soc Nephrol. 2010;5(4):623-30.

37. Chang TI. Systolic blood pressure and mortality in patients on hemodialysis. Curr Hypertens Rep. 2011;13(5):362-9.

38. Hernández D et al. Renin-angiotensin system blockade and kidney transplantation: a longitudinal cohort study. Nephrol Dial Transplant. 2012;27(1):417-22.

39. Heinze G et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. J Am Soc Nephrol. 2006;17(3):889-99.

40. Opelz G, Döhler B. Cardiovascular death in kidney recipients treated with renin-angiotensin system blockers. Transplantation. 2014;97(3):310-5.

41. Bolignano D et al. Aldosterone antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2014;4:CD007004.

42. Komajda M et al. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J. 2003;24(5):464-74.

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

44. Weir MR et al. Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors. N Engl J Med. 2015;372(3):211-21.

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

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

47. 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.