CLINICAL TRIALS

New nonabsorbable potassium-exchange resins in hyperkalaemia

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New data suggest that treatment with patiromer or sodium zirconium cyclosilicate for up to 8 weeks reduces plasma potassium levels in hyperkalaemic patients. If proven safe and effective for long-term use, these therapies might be administered together with intensive renin–angiotensin–aldosterone blockade to reduce adverse effects and renal and cardiovascular risk.

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Hyperkalaemia occurs frequently in patients with chronic kidney disease (CKD) or cardiovascular disease (CVD) and results in increased cardiovascular and renal risk.[1] Increased potassium levels can result from altered renal potassium handling (which may be caused by use of various medications) or derangements in renin or aldosterone synthesis. Indeed, hyperkalaemia is frequently observed during treatment with renin–angiotensin–aldosterone system (RAAS) inhibitors, which are used to lower renal and/or cardiovascular risk in patients with CKD or CVD. Treatment of hyperkalaemia is limited by a lack of safe and effective interventions.[1] Current management consists of moderation of dietary potassium intake, provision of diuretic or bicarbonate and/or prevention of potassium absorption using nonabsorbable cation exchange resins. Sodium or calcium polystyrene sulphonates—the only FDA-approved potassium exchange resins—have a noxious taste, cause diarrhoea and have been associated with rare but serious adverse effects, such as colonic perforations.[2] Now, three recent clinical trials have shown efficacy of two new potassium absorbents for the management of hyperkalaemia.[3–5]

The first study by Weir *et al.* assessed the efficacy of patiromer, a nonabsorbable polymer that binds potassium in exchange for calcium in the colon.[3] This agent, which is administered as a suspension, increases faecal excretion of potassium and consequently decreases plasma potassium levels. In this study, 243 patients with CKD on RAAS inhibitors with serum potassium levels of 5.1–6.5 mmol/l entered an initial 4 week treatment phase during which they received patiromer twice daily. Weir *et al.* report a mean reduction in plasma potassium levels of 1.0 mmol/l at the end of this phase. The 107 patients who reached normokalaemia (plasma potassium levels 3.5–4.9 mmol/l) entered a single-blind withdrawal phase and were randomly assigned to receive patiromer or placebo for a further 8 weeks. The recurrence of hyperkalaemia during this period was significantly higher in the placebo group (60%) than in the patiromer group (15%; $P<0.001$). The most common adverse effect of patiromer therapy was constipation.

> “Treatment of hyperkalaemia is limited by a lack of safe and effective interventions”

The other studies assessed the efficacy of sodium zirconium cyclosilicate (ZS-9) in hyperkalaemic patients with a variety of diseases associated with hyperkalaemia, including CKD, heart failure or diabetes. ZS-9 is a high-specificity inorganic crystal that entraps potassium in the intestinal tract. However, instead of exchanging calcium, ZS-9 exchanges sodium and hydrogen ions for potassium. Packham *et al.* conducted a two-phase, double-blind, dose-finding study of ZS-9 (1.25 g, 2.5 g, 5 g and 10 g) versus placebo.[4] They report that ZS-9 treatment (three times daily for 48 h) acutely and dose-dependently decreased potassium levels; reductions ranged from 0.46 mmol/l in the 2.5 g dose group to 0.73 mmol/l in the 10 g dose group versus an increase of 0.25 mmol/l in the placebo group. During the second phase, patients who had reached normokalaemia received ZS-9 or placebo daily for 11 days. Those who received 5 g or 10 g ZS-9 maintained potassium levels <5 mmol/l, whereas potassium levels increased to >5 mmol/l in the placebo group. A clinical trial by Kosiborod *et al.*[5] tested the effects of 5 g, 10 g or 15 g doses of ZS-9 on potassium levels using a similar study design to the trial by Packham *et al.*[4] Rapid lowering effects of ZS-9 on plasma potassium levels were observed in the initial treatment phase and sustained in the subsequent 28 days of double-blind placebo-controlled treatment. The most frequent adverse effect of ZS-9 was diarrhoea.[4,5]

These new data are promising for management of hyperkalaemia in general, but may also have far-reaching consequences for use of RAAS inhibitors in patients with compromised renal or cardiac function. Recent clinical trials that tested the renal and cardioprotective efficacy of intensive RAAS blockade using combinations of RAAS inhibitors had to be stopped prematurely or showed unexpected outcomes because of hyperkalaemia and other adverse effects.[6–8] These results are likely explained by off-target effects of intensive RAAS inhibition, including the induction of hyperkalaemia, which directly increases renal and cardiovascular risk and thereby offsets the protective effects of lowering of blood pressure and albuminuria. Indeed, a subanalysis of the ONTARGET trial data

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showed that dual compared to single-agent RAAS inhibition increased the risk of hyperkalaemia, which was an independent predictor of long-term renal and cardiovascular outcomes.[9] Effective treatment strategies for at-risk patients should maximize beneficial effects on protective risk markers and minimize detrimental effects on harmful risk markers.

Would management of hyperkalaemia improve the beneficial effects of RAAS inhibition? No data from prospective clinical trials are available but a *post hoc* analysis of the RENAAL trial showed that in patients with diabetic nephropathy, the relative renal risk reduction conferred by losartan increased from 21% to 35% after adjusting for the development of hyperkalaemia.[10] This finding suggests that management of hyperkalaemia would significantly enhance the renoprotective effects of RAAS inhibition.

Given these considerations, should we initiate patiromer or ZS-9 therapy in patients who develop hyperkalaemia during single, dual or even triple-agent RAAS inhibition? Although this strategy is attractive, long-term treatment with these new resins would be required. The recent trials of patiromer and ZS-9 were of short duration; the durability of the beneficial effects and the long-term safety of these agents still have to be ascertained. In addition, whether intensive RAAS inhibition will improve renal and cardiovascular outcomes when hyperkalaemia is controlled using patiromer or ZS-9 has to be addressed in appropriately designed randomized controlled trials with hard outcomes.

Importantly not all trial participants responded to patiromer or ZS-9 therapy; some patients maintained high potassium levels despite treatment. Although elucidating the underlying mechanisms of response variability was not the focus of these trials, the differential responses may be explained by individual differences in food intake. As patiromer and ZS-9 bind potassium in food along the gastrointestinal tract it is conceivable that a high dietary potassium intake might limit the efficacy of these agents. Although participants were advised to avoid a high potassium diet in the study by Weir *et al.*,[3] the dietary intake of potassium was not controlled by protocol in any of the studies. The effects of diet need to be evaluated and could explain the significant differences in drug efficacy reported for patiromer between patient populations residing in Eastern Europe versus Western Europe or the USA.[3]

Patiromer and ZS-9 represent promising therapeutic strategies to treat hyperkalaemia. In the future they may become the first choice therapies for clinicians who aim to maintain plasma potassium levels in the physiological range. Whether these drugs improve the efficacy of intensive RAAS inhibition, and enable us to investigate the effects of dual or even triple RAAS inhibition on renal and cardiovascular outcomes, remains to be addressed in future trials.

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Competing interests
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CORRECTION

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In the version of this article that was initially published online, the withdrawal phase of the study by Weir *et al*. was incorrectly described as double-blind rather than single-blind and ZS-9 was incorrectly described as a nonabsorbable polymer rather than a high-specificity inorganic crystal. The errors have been corrected in the html and pdf versions of the article.