Use of sodium zirconium cyclosilicate for up-titration of renin–angiotensin–aldosterone system inhibitor therapy in patients with heart failure: a case series

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Background
Patients often receive suboptimal dosing of renin–angiotensin–aldosterone system inhibitor (RAASi) therapy over concerns of hyperkalaemia. However, studies have shown associations between suboptimal dosing or interruptions to therapy and adverse clinical events. Therefore, effective treatments for hyperkalaemia that can enable optimal RAASi therapy are needed. This case series examines eight patients whose commencement on the novel potassium binder sodium zirconium cyclosilicate (SZC) allowed for the initiation and/or up-titration of RAASi therapy.

Case summary
Eight patients aged 64–87 years with heart failure (HF) with reduced ejection fraction all developed hyperkalaemia (serum potassium (sK+) >5.0 mmol/L) while receiving RAASi therapy. Following initiation of SZC, all patients experienced eventual stabilization of sK+ levels. All patients were able to initiate, restart, or up-titrate RAASi therapy with five patients achieving optimal medical therapy. Left ventricular ejection fraction improved in four patients, two patients are now re-classified as New York Heart Association Class I, and an additional patient had improved exercise tolerance. Follow-up for Patient 8 is still ongoing.

Discussion
These real-world cases demonstrate that use of SZC to manage hyperkalaemia in patients with HF is feasible and allows optimization of RAASi therapy.

Keywords
Sodium zirconium cyclosilicate • Heart failure • Renin–angiotensin–aldosterone system inhibitors • Hyperkalaemia • Case report

Learning points
• Patients on renin–angiotensin–aldosterone system inhibitor (RAASI) therapy often receive suboptimal dosing and are deprived of the full clinical benefits of this treatment due to its potential to cause hyperkalaemia.
• The use of sodium zirconium cyclosilicate to lower serum potassium levels can allow for the initiation, restarting, and up-titration of RAASi therapy in patients with heart failure, allowing the achievement of optimal medical therapy.

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Introduction

Heart failure (HF) is a major cause of morbidity and mortality, characterized by frequent hospital readmissions with decompensated HF. Treatment of HF with reduced ejection fraction (HFrEF) focuses on renin-angiotensin-aldosterone system inhibitors (RAASis). These include angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), angiotensin-receptor-neprilysin inhibitor (sacubitril–valsartan), and mineralocorticoid receptor antagonists (MRAAs). RAASi reduce all-cause mortality and hospitalization in patients with HF.

Hyperkalaemia—elevated serum potassium (sK⁺)—a potential complication of RAASi, can lead to cardiac arrhythmias, cardiac arrest, and sudden death, and can be classified as mild, moderate, or severe (sK⁺ 5.0–5.5, 5.5–6.0, or >6.0 mmol/L, respectively). Hyperkalaemia is associated with an increased risk of all-cause mortality in patients with HF and often leads to treatment interruption in patients receiving RAASi. Temporary omission of RAASi may reduce the risk of adverse clinical outcomes; however, failure to initiate or restart or reluctance to up-titrator can be detrimental to long-term.

Suboptimal and interrupted RAASi treatment is associated with adverse clinical events, including stroke and myocardial infarction (MI), and increased mortality. Current guidelines recommend against abrupt withdrawal of RAASi. Therefore, effective treatments for hyperkalaemia that enable optimal RAASi treatment are needed.

Patients who develop hyperkalaemia should be counselled on a low potassium diet to help lower sK⁺ levels. However, such a diet can be challenging in itself, and pharmacotherapies may be required to maintain normokalaemia.

The gastrointestinal potassium binder sodium zirconium cyclosilicate (SZC) selectively captures potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal tract, thereby reducing sK⁺ concentration and removing potassium from the body through increased faecal excretion. Other oral potassium binders such as sodium polystyrene sulfonate and patiromer have also been approved. Adverse gastrointestinal effects have been associated with sodium polystyrene sulfonate when combined with sorbitol. Oedema-related events have been observed with SZC, with frequency increasing with higher doses used. Increase in serum bicarbonate concentration has also been observed with SZC, although it has been suggested that this may be a potential benefit for patients with chronic kidney disease (CKD). The efficacy of SZC on lowering and maintaining sK⁺ in HF and its use in facilitating the continuation and dose-optimization of RAASi prevented by hyperkalaemia has been established in clinical trials. However, further long-term research is needed. Here, we report a case series of eight patients with HFrEF who initiated SZC to reduce sK⁺, allowing for the initiation, restart, and up-titrator of RAASi to achieve optimal medical therapy (OMT).

Case presentation

Full patient characteristics, laboratory measures, and treatments before and after SZC initiation are summarized in Table 1.

Patient 1

A 65-year-old woman presented to her general practitioner (GP) with a past medical history (PMH) of type 1 diabetes mellitus, hypertension (HTN), chronic obstructive pulmonary disease, CKD, coronary artery bypass grafting (CABG), and cardiac resynchronisation therapy pacemaker. She was referred to the HF clinic for over 2-year follow-up with breathlessness and orthopnoea and significant HFrEF (left ventricular ejection fraction [LV EF] 32%), with N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 8697 ng/L. Average systolic blood pressure (SBP) was ~140–150 mmHg. At first review, she was on an ACEi at 50% of the optimal dose. Attempts to optimize her RAASi were limited by hyperkalaemia (sK⁺ 6.0 mmol/L) and fluctuating renal function. Bendroflumethiazide was prescribed to improve blood pressure control and kaliuresis, but this caused hyponatraemia and sK⁺ remained prohibitively high. Sodium zirconium cyclosilicate (SZC) 5 g once a day (o.d.) was introduced at sK⁺ 5.8 mmol/L to enable up-titrator of sacubitril–valsartan from 12.5% to 50% of the optimal dose after ACEI discontinuation. Despite this, the patient was admitted with decompensated HF requiring intravenous diuretics. During that admission, her sacubitril–valsartan dose was optimized, an MRA was introduced at 50% of the optimal dose, and SZC was stopped due to normokalaemia. Blood tests 1-week post-discharge showed sK⁺ at 5.8 mmol/L, so SZC 5 g o.d. was restarted. The MRA was omitted and reintroduced at alternate daily dosing, SZC was increased to 10 g o.d. and MRA was increased to optimal dosage. The most recent sK⁺ was 4.1 mmol/L with the patient on OMT. The latest NT-proBNP level was 5142 ng/L.

Patient 2

A 72-year-old woman with a PMH of atrial fibrillation (AF) and hyperthyroidism presented to her GP with exertional breathlessness and significant HFrEF (LVEF 32%), with N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 2897 ng/L. Transthoracic echocardiogram (TTE) confirmed severe HFrEF (LVEF 25%). She was prescribed sacubitril–valsartan and spironolactone with sK⁺ of 4.6 mmol/L. Subsequent sK⁺ ranged 5.1–5.5 mmol/L, which, together with asymptomatic hypotension, prevented further RAASi optimization. SZC 5 g o.d. was initiated and sacubitril–valsartan was maintained when sK⁺ increased to 6.2 mmol/L. Since then, subsequent clinical letters show an average SBP of ~120 mmHg and sK⁺ has remained <5.1 mmol/L, and she could continue RAASi with OMT. A repeat TTE showed significant improvement in left ventricular (LV) function (LVEF 47%).

Patient 3

An 87-year-old woman with a PMH of HTN, permanent AF, and previous bilateral mastectomy and lung nodules was referred to the HF service by her GP after worsening breathlessness and orthopnoea. A TTE revealed HFrEF (LVEF 27%) with moderate left atrial dilatation. She was clinically well, maintained good exercise tolerance [New York Heart Association (NYHA) Class II], and was euolaemic, but was also hypertensive during her initial consultation. Sacubitril–valsartan was initiated to improve LV function and up-titrator to 49/51 mg twice a day (b.i.d.), but recurrent episodes of hyperkalaemia prohibited further RAASi up-titrator. sK⁺ ranged 4.9–5.8 mmol/L over the previous 12 months.
## Timeline

| Patient | Age | Diagnosis                              | Before sodium zirconium cyclosilicate (SZC) | Initiating SZC                                                                 | Stabilized on SZC                                                                 | Optimal medical therapy achieved? |
|---------|-----|----------------------------------------|---------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------|
| 1       | 65  | Heart failure with reduced ejection fraction (HFrEF) | On angiotensin-converting enzyme inhibitor at 50% of optimal dose Serum potassium (sK⁺) 6.0 mmol/L Bendroflumethiazide prescribed | SZC 5 g once a day (o.d.) initiated at sK⁺ 5.8 mmol/L Sacubitril–valsartan up-titrated to 50% of optimal dose Admitted with decompensated heart failure (9 days) Sacubitril–valsartan dose 100% optimized Mineralocorticoid receptor antagonists (MRA) initiated at 50% optimal dose SZC stopped due to normokalaemia One-week post-discharge sK⁺ 5.8 mmol/L SZC restarted at 5 g o.d. MRA stopped, reintroduced at alternate daily dosing SZC increased to 10 g o.d. MRA increased to optimal dosing | Most recent sK⁺ 4.1 mmol/L | Yes |
| 2       | 72  | HFrEF                                   | sK⁺ 4.6 mmol/L Sacubitril–valsartan and spironolactone prescribed Subsequent sK⁺ levels between 5.1 and 5.5 mmol/L | sK⁺ has remained below 5.1 mmol/L Sacubitril–valsartan dosing maintained MRA restarted | | |
| 3       | 87  | HFrEF                                   | Sacubitril–valsartan prescribed and up-titrated sK⁺ ranged from 4.9 to 5.8 mmol/L over 12 months | | | |
| 4       | 64  | HFrEF                                   | History of hyperkalaemia over 2 years with renin–angiotensin–aldosterone system inhibitor (RAAS) therapy | SZC 5 g o.d. initiated at sK⁺ 5.8 mmol/L Sacubitril–valsartan dosing maintained | | |
| 5       | 79  | HFrEF                                   | sK⁺ 5.8 mmol/L Losartan and spironolactone stopped | | | |
| 6       | 81  | Ischaemic HFrEF                         | History of hyperkalaemia Sacubitril–valsartan prescribed Sacubitril–valsartan stopped at sK⁺ 6.3 mmol/L | SZC 10 g three times daily (TID) initiated, followed by 5 g o.d. Sacubitril–valsartan restarted at sK⁺ 4.6 mmol/L sK⁺ rose to 6.0 mmol/L after 1 week | sK⁺ stabilized at ~5.0 mmol/L Weight gain and abdominal distension 4 weeks after commencing SZC Low-dose furosemide prescribed | In progress |
| 7       | 75  | HFrEF coronavirus 2019                  | Sacubitril–valsartan and eplerenone prescribed sK⁺ 3.7 mmol/L | | | |
| 8       | 69  | HFrEF                                   | sK⁺ ranging from 5.0 to 5.7 mmol/L Thiazide prescribed RAASI withheld sK⁺ 6.5 mmol/L | | | |

### Notes:
- **SZC for optimizing RAAS inhibitor therapy in heart failure**
- Optimal medical therapy achieved? indicates whether the patient achieved optimal medical therapy.
| Patient | Gender | Age | Baseline LVEF (%) | Baseline NT-proBNP (ng/L) | Previous sk⁺ > 6.0 mmol/L | sk⁺ (Pre) (mmol/L) | Creatinine (Pre) (µmol/L) | CrCl (Pre) (mL/min) | sK⁺ (Post) (mmol/L) | Creatinine (Post) (µmol/L) | CrCl (Post) (mL/min) | ACEi/ARB/ARNi (Pre) | MRA (Pre) | ACEi/ARB/ARNi (Post) | MRA (Post) | ACEi/ARB/ARNi initiated/continued/up-titrated | MRA initiated/continued/up-titrated | OMT achieved | Latest NT-proBNP (ng/L) | Absolute NT-proBNP difference (ng/L) | Latest LVEF (%) | Absolute LVEF difference (%) | SZC allowing initiation/maintenance/up-titrations of RAASi |
|---------|--------|-----|------------------|--------------------------|----------------------------|------------------------|-------------------------|------------------------|------------------------|--------------------------|------------------------|-------------------------|-----------|------------------------|----------|----------------------------|-----------------------------|---------------|-----------------------|-------------------------------|------------------|-------------------------|--------------------------------------------------|
| Patient 1 | Female | 65  | 32%              | 8697                     | Yes                        | 5.8                    | 154                     | 35                     | 4.4                    | 162                     | 34                      | 1/2 × 24/26 mg b.i.d. | NA               | Yes                   | Eplerenone | Yes                        | Yes               | Yes               | Yes                   | -3555            | -2078                   | Initiation and up-titrations of RAASi         |
| Patient 2 | Female | 72  | 25%              | 2897                     | Yes                        | 6.2                    | 122                     | 45                     | 4.6                    | 82                       | 66                      | 49/51 mg b.i.d. | Spironolactone | 25 mg o.d. | 49/51 mg b.i.d. (on hold) | NA             | No               | No                   | 5142             | NA                      |                          |
| Patient 3 | Female | 87  | 27%              | 2568                     | No                         | 5.8                    | 154                     | 26                     | 5.0                    | 158                     | 25                      | 49/51 mg b.i.d. | Spironolactone | 25 mg o.d. | 49/51 mg b.i.d. (on hold) | NA             | No               | No                   | 4646             | 10291                   |                          |
| Patient 4 | Male   | 64  | 13%              | 5437                     | Yes                        | 5.8                    | 166                     | 54                     | 4.7                    | 178                     | 50                      | 97/103 mg b.i.d. | NA               | Yes                   | Eplerenone | Yes                        | Yes               | Yes               | Yes                   | 1351             | -773                    |                          |
| Patient 5 | Male   | 79  | 35%              | 2124                     | No                         | 5.8                    | 125                     | 54                     | 4.4–5.4                | 166                     | 41                      | 97/103 mg b.i.d. (on hold) | NA             | No               | No                   | 10291            | 17341                   |                          |
| Patient 6 | Male   | 81  | 28%              | 3736                     | Yes                        | 6.3                    | 205                     | 55                     | 5.2                    | 215                     | 27                      | 24/26 mg b.i.d. | NA               | Yes                   | Eplerenone | Yes                        | Yes               | Yes               | Yes                   | 21077            | -7292                   |                          |
| Patient 7 | Male   | 75  | 15%              | >35000                    | No                         | 5.4                    | 170                     | 27                     | 4.4–4.8                | 180                     | 30                      | 49/51 mg b.i.d. | NA               | Yes                   | Eplerenone | Yes                        | Yes               | Yes               | Yes                   | 27708            | -1110                   |                          |
| Patient 8 | Female | 69  | 40%              | 2173                     | Yes                        | 6.5                    | 105                     | 67                     | 4.6–5.2                | 90                       | 78                      | 49/51 mg b.i.d. | NA               | Yes                   | NA             | Yes               | No                    | 1063             | 27708                   |                          |

Reference ranges: sk⁺, 3.5–5.3 mmol/L; creatinine, 58–110 µmol/L (male) and 46–92 µmol/L (female).
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; b.i.d., twice a day; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NA, not applicable; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; o.d., once a day; OMT, optimal medical therapy; RAASi, renin–angiotensin–aldosterone system inhibitor; sk⁺, serum potassium; SZC, sodium zirconium cyclosilicate.

*Pre and post are relative to SZC treatment.

Based on actual body weight.
Routine urea and electrolytes revealed an sK\(^+\) of 5.8 mmol/L. Further optimization of RAASi therapy was restricted due to the recurrent nature of the hyperkalaemia. In view of the severely reduced EF with elevated NT-proBNP of 2568 ng/L, SZC was initiated at 5 g o.d. to enable further up-titration of sacubitril–valsartan and maintained at 97/103 mg b.i.d.; sK\(^+\) dropped to 4.5 mmol/L. Recent echocardiography showed improved LV function (LVEF 43%).

### Patient 4
A 64-year-old man with a PMH of type 2 diabetes mellitus (T2DM), CKD, HTN, and ischaemic heart disease was diagnosed with HFrEF (LVEF 13%) after being admitted with breathlessness. During follow-up, he developed hyperkalaemia on seven occasions over 2 years (sK\(^+\) ranging 5.4–6.2 mmol/L) during attempts to establish optimal dosing of dual RAASI. He was admitted once with decompensated HF and hyperkalaemia during this follow-up, and referred to a nephrologist after developing cardio-renal syndrome. Persistently elevated sK\(^+\) led to RAASI omission and worsening of his HF symptoms. Sodium zirconium cyclosilicate 5 g o.d. was commenced at sK\(^+\) 5.8 mmol/L. Since then, he has tolerated reintroduction of both sacubitril–valsartan at optimal dose and spironolactone 25 mg o.d. His most recent sK\(^+\) was 4.7 mmol/L. His LVEF has improved to 25% with OMT and he is being considered for a primary prevention implantable cardioverter-defibrillator.

### Patient 5
A 79-year-old man with a PMH of T2DM, peripheral vascular disease, AF, single chamber pacemaker, and HTN was diagnosed with HFrEF during an admission with pneumonia. A TTE showed an LVEF of 35–40%. He was referred to the HF service following discharge. At first review, his sK\(^+\) was 5.8 mmol/L and NT-proBNP was 2124 ng/L. Examinations revealed elevated blood pressure and moderate pedal oedema, but losartan and spironolactone were stopped as a result of his hyperkalaemia. Subsequent sK\(^+\) levels were lower but remained mildly elevated despite no RAASI. SZC was initiated at 5 g o.d. and sacubitril–valsartan at 50 mg b.i.d. when sK\(^+\) reached 5.5 mmol/L. Sacubitril–valsartan was increased to optimal dosing and an MRA introduced at 50% of the optimal dose following SZC initiation. Subsequent sK\(^+\) has remained below 5.2 mmol/L and NT-proBNP has decreased to 1351 ng/L. The patient has achieved OMT.

### Patient 6
An 81-year-old man with a PMH of T2DM, CKD, MI, and curative nephrectomy for renal cell carcinoma presented with ischaemic HFrEF. He was under follow-up in the HF clinic for 3 years, during which he underwent elective angioplasty to a proximal left anterior descending coronary artery lesion for reperfusion following detection of reversible ischaemia. He had a history of hyperkalaemia prior to RAASI treatment. Following commencement of sacubitril–valsartan, his exercise tolerance improved, but mild hyperkalaemia persisted. Blood pressure (SBP ~120–130 mmHg) did not limit up-titrination of RAASI. An sK\(^+\) of 6.3 mmol/L prompted omission of sacubitril–valsartan and a brief admission for emergency hyperkalaemia treatment, with SZC initiated at 10 g three times daily (TID) followed by 5 g o.d. alongside conventional therapy. Sacubitril–valsartan was restarted once sK\(^+\) decreased to 4.6 mmol/L. However, 1 week after commencing SZC 5 g o.d., sK\(^+\) increased to 6.0 mmol/L; SZC was increased to 10 g o.d. His sK\(^+\) level has since stabilized at ~5.0 mmol/L; however, weight gain and abdominal distension 4 weeks after commencing SZC necessitated a period of low-dose furosemide to treat decompensated HF (NT-proBNP had risen to 21 077 ng/L). The patient’s symptoms improved since and can be described as NYHA Class I. He has achieved OMT (unable to tolerate any further increase in sacubitril–valsartan).

### Patient 7
A 75-year-old man with a PMH of HTN, diverticular disease, and prostate cancer was diagnosed with HFrEF following an emergency admission with breathlessness after testing positive for coronavirus 2019. A TTE demonstrated severe LV impairment (LVEF 15%), and NT-proBNP >35 000 ng/L. He was prescribed sacubitril–valsartan and eplerenone as an inpatient with a pre-discharge sK\(^+\) of 3.7 mmol/L. At first review, the sacubitril–valsartan dose was increased, with sK\(^+\) subsequently rising to 5.4 mmol/L. An electrocardiogram (ECG) showed a sinus rhythm of 68 beats per minute, a broad QRS of 134 ms, and a left bundle branch block-like pattern with T-wave inversion in leads I to AVL, V5, and V6. On examination, no audible murmurs upon auscultation were present, and lung fields sounded clear with evidence of bilateral peripheral oedema. The patient was identified as high-risk for readmission; therefore, SZC was commenced at 5 g o.d. to allow optimization and maintenance of his RAASI. Despite dose-optimization of MRA, his sK\(^+\) has remained between 4.4 and 4.8 mmol/L. Asymptomatic hypotension has prevented further optimization of sacubitril–valsartan; however, at his most recent review, he was classified as NYHA Class I and euvoealaeic, and awaits post-optimization echocardiogram.

### Patient 8
A 69-year-old woman with a PMH of T2DM, HTN, stroke, and ischaemic heart disease has been with the HF team since her MI in 2019, which resulted in a CABG and HFrEF with an LVEF of 40%. Hyperkalaemia has prevented up-titration and maintenance of RAASI; her sK\(^+\) ranges from 5.0 to 5.7 mmol/L. Her HTN and hyperkalaemia were managed with a thiazide diuretic, alongside evidence-based HF therapies. RAASI were withheld due to uncontrolled hyperkalaemia. During her hospital admission with sK\(^+\) of 6.5 mmol/L, no acute hyperkalaemia-associated ECG changes were reported. SZC was initiated at an sK\(^+\) of 6.5 mmol/L. Treatment included SZC 10 g TID, an immediate dose of salbutamol, and temporary withdrawal of sacubitril–valsartan. sK\(^+\) dropped from 6.5 to 5.0 mmol/L within 24 h and SZC dose reduced to 5 g o.d. sK\(^+\) decreased to 4.7 mmol/L prior to discharge. The thiazide diuretic was stopped, sacubitril–valsartan was restarted, and the patient was referred to HF services for follow-up. Repeat blood tests have shown stabilization of sK\(^+\) between 4.7 and 5.1 mmol/L with an aim to further up-titrate HF therapies. A trial of low-dose spironolactone (12.5 mg o.d.) has been facilitated with SZC use but was withdrawn due to worsening postural symptoms.

### Discussion
Concerns over the development of hyperkalaemia in patients receiving RAASI often results in treatment interruption or suboptimal...
dosing, which has been associated with adverse effects and increased mortality.

We successfully used S2C to manage hyperkalaemia in eight patients with HFrEF with deteriorating symptoms, allowing initiation and up-titration of RAASi in all patients (Table 1). Patient selection for this case series was critical, as patients with low blood pressure or significant kidney dysfunction, for example, are unlikely to benefit from this approach as initiation or further up-titration of RAASi would be limited by such factors. This approach allowed all patients to be able to initiate, restart, or up-titrate RAASi with five patients achieving OMT. LVEF improved in four patients, two patients are now re-classified as NYHA Class I, and an additional patient had improved exercise tolerance. Follow-up for Patient 8 is still ongoing. Positive cardiac remodelling, combined with optimal RAASi dosing, could potentially reduce the risk of hospitalization with HF, mortality, and the need for device use (i.e., cardiac resynchronization therapy). This impact could reduce unscheduled care, and costs associated with hospitalization, device use, and follow-up.

Adherence to treatment guidelines for HF has been associated with improved clinical outcomes, yet a recent audit of HF hospital admissions in the UK over 2016–17 reported 53% of patients with HFrEF being discharged on MRA, 83% on an ACEi or ARB, and 87% on beta blockers—but only 44% on all three. Current guidelines suggest considering potassium binders to avoid hyperkalaemia in selected patients with HF treated with RAASi. Trials are currently investigating whether novel potassium binders such as S2C and patiromer will allow patients with HFrEF to achieve guideline-recommended doses of RAASi more often and improve outcomes (Clinicaltrials.gov identifiers: NCT01476646, NCT03532009, NCT03888066, NCT04142788). The results from real-world data demonstrate that use of S2C to manage hyperkalaemia in patients with HF is feasible and allows OMT to be achieved with RAASi therapy.

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