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BRIEF REPORT

Sodium Zirconium Cyclosilicate for Renin–Angiotensin–Aldosterone System Inhibitor Optimization in Patients with Heart Failure with Reduced Ejection Fraction: A Retrospective Analysis

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ABSTRACT

Introduction: In this retrospective analysis, we evaluate the effectiveness of the potassium (K^+) binder sodium zirconium cyclosilicate (SZC) in maintaining normokalemia and facilitating the initiation, optimization, and maintenance of renin–angiotensin–aldosterone system inhibitors (RAASi) in patients with heart failure (HF) with reduced ejection fraction (HFrEF).

Methods: A total of 44 patients with HFrEF and a history of hyperkalemia who were receiving SZC to enable the prescription of RAASi were identified from two district general hospital sites. Retrospective analysis was performed to determine biochemical response, alterations in pharmacotherapy, and subsequent HF outcomes following initiation of SZC.

Results: Mean K^+ was reduced by 0.9 mmol/L within 1 month of initiation of SZC; mean K^+ after 12 months of treatment was 4.8 mmol/L with a median (interquartile range) duration of treatment of 13 (8.4–15.1) months. Following SZC treatment, 100% of patients received an angiotensin receptor–neprilysin inhibitor (18% increase) and 93% received a mineralocorticoid receptor antagonist (41% increase), with 59% and 37% achieving guideline-recommended dosing, respectively. Ninety-one percent of patients were able to receive triple or quadruple therapy with the addition of a beta-blocker and a sodium glucose co-transporter 2 inhibitor. Reduced rates of hospitalization for HF (HHF) were observed with 12 episodes per 100 patient-years recorded (reduced from 21) in addition to improvements in mean left ventricular ejection fraction (29–36%) and median N-terminal pro-B-type natriuretic peptide (3458–2055 ng/L, 45% median reduction). Renal function (creatinine clearance increased from 48.4 to 49.3 ml/min) and systolic blood pressure (decreased from 124 to 122 mmHg) were similar following optimization, and no tolerability issues were identified.

Conclusions: Extended real-world treatment with the K^+ binder SZC was effective at maintaining normokalemia, and was associated with a greater uptake of RAASi, a reduced rate of HHF, and improvements in cardiac biomarkers in patients with HFrEF.

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Keywords: Heart failure; Hyperkalemia; Renin–angiotensin–aldosterone system inhibitor; Sodium zirconium cyclosilicate

Key Summary Points

Renin–angiotensin–aldosterone inhibitors (RAASi) are commonly used for treatment of heart failure with reduced ejection fraction (HFrEF) in accordance with guideline recommendations.

Patients receiving RAASi are at increased risk of developing hyperkalemia, which can provoke life-threatening arrhythmias and often lead to interruption, cessation, or suboptimal dosing of these life-extending therapies.

This retrospective analysis evaluates the effectiveness of the potassium binder sodium zirconium cyclosilicate (SZC) in maintaining normokalemia and facilitating the initiation, optimization, and maintenance of RAASi in patients with HFrEF.

SZC was well tolerated in this real-world group of high-risk patients with HFrEF, was effective at maintaining normokalemia, and was associated with a greater uptake of RAASi, a greater number of patients achieving guideline-recommended dosages, a reduced rate of hospitalization for heart failure, and improvements in cardiac biomarkers.

INTRODUCTION

Renin–angiotensin–aldosterone inhibitors (RAASi) are established pharmacotherapy for the treatment of heart failure (HF) with reduced ejection fraction (HFrEF), recommended by guidelines owing to the associated improvements in patient survival, symptoms, and reduced rates of hospitalization [1–3]. However, patients receiving RAASi are at increased risk of developing hyperkalemia (HK) [4–7]. Recent international guidelines have recommended potassium (K^+) binders to allow initiation and optimization of RAASi in patients with HF and chronic kidney disease (CKD) and stopping and down-titrating RAASi should be the last resort if the risk of HK cannot be mitigated [8–10].

HK is defined as serum or plasma K^+ >5.0 mmol/L, with severity classed as mild (>5.0 to <5.5 mmol/L), moderate (5.5–6.0 mmol/L) or severe (>6.0 mmol/L) [11]. HK, if left untreated, can lead to fatal arrhythmias or result in cessation or down-titration of guideline-recommended RAASi therapies in those who need them the most [8, 10]. However, discontinuation and down-titration of RAASi have been associated with adverse outcomes in patients with HF and CKD [10, 12, 13].

Physician inertia may also prevent patients at risk of HK receiving RAASi at target doses, particularly given the numerous clinical manifestations of HK [12, 14]. One approach is to induce kaliuresis by prescribing loop or thiazide diuretics; however, this is of limited value in patients with hypotension and renal impairment, often encountered in chronic HF. Besides RAASi-induced HK, HF itself is a risk factor for HK, as are prevalent comorbidities such as CKD, diabetes mellitus, hypertension, and older age [4, 15, 16]. Patients with HF often have recurrent HK episodes, with progressively shorter intervals between episodes and more time spent in hospital [10, 17, 18]. As recommended by a 2022 international Delphi consensus, HK should be recognized as a predictable, treatable, and manageable side effect of optimal HF/CKD therapies [19]. The challenge facing clinicians is therefore in maintaining the delicate balance between avoiding significant HK whilst continuing or optimizing essential RAASi [10, 14, 20, 21].

Emerging strategies to overcome HK as a barrier to RAASi use include the novel K^+ binders sodium zirconium cyclosilicate (SZC) and patiromer, which lower serum K^+ concentrations through cation exchange of sodium and calcium, respectively, in the alimentary canal, causing increased fecal excretion of K^+ [22, 23]. While these agents have shown effectiveness in the acute treatment of HK and enabling RAASi optimization [24, 25], experience of these agents in real-world settings or periods exceeding 12 months in HF populations is limited. However, two previous studies of SZC treatment in patients with HFrEF and HK

demonstrated stabilization and/or reduction in serum K^+ concentrations, subsequent RAASi up-titration and, as a result, improved cardiac function due to positive changes in left ventricular ejection fraction (LVEF) [26, 27]. In this retrospective analysis, we describe the experience of our HF service in using SZC to enable patients with HFrEF with HK to receive RAASi at target or maximally tolerated doses.

In this retrospective analysis, we evaluated patients with HFrEF receiving long-term SZC in our outpatient cohort. We studied changes in RAASi therapies, serum K^+ levels, hospitalization for decompensated HF or HK, HF outcomes (including LVEF and N-terminal pro B-natriuretic peptide [NT-proBNP]), and survival.

METHODS

Study Population

Patients with the diagnosis of HFrEF (LVEF ≤ 40%) who were receiving the K^+ binder SZC between July 2020 and October 2022 were studied. Forty-nine patients were identified, of whom five were excluded from analysis because of non-adherence with SZC ($n=2$), in-patient prescribing only ($n=2$), and intermittent prescribing ($n=1$). All patients had multidisciplinary team input with the involvement of a cardiologist specializing in HF.

Ethical Approval

This retrospective study was submitted to Cwm Taf Morgannwg University Health Board Research & Development department. As the study was recognized as a service evaluation, using evidence-based medicines and no data collected beyond that of routine clinical care, formal approval from the research ethics committee was not required.

Baseline Characteristics

Baseline demographic data were collected, including age, sex, systolic/diastolic blood pressure, LVEF percentage, and New York Heart Association (NYHA) functional classification. Comorbidities and previous cardiac interventions were recorded. NT-proBNP concentration, estimated glomerular filtration rate (eGFR; ml/min/1.73 m^2) prior to initiation of K^+ binder and following optimization of RAASi therapy, and serial serum K^+ (in mmol/l) level were recorded throughout the optimization process of RAASi. HF medication classes, doses, and percentage of guideline-recommended dose were recorded.

Study Outcomes

Serum K^+ concentrations (mmol/l) were recorded 6 months pre-initiation of SZC, at initiation of SZC, and up to 24 months post-initiation of SZC. Prescriptions and doses of RAASi were recorded before and after initiation of SZC, until guideline-recommended dosage or maximum tolerated dosages were achieved. Measurements of NT-proBNP and LVEF were recorded prior to initiation of K^+ binders to enable RAASi, and following optimization.

HF hospitalization and admissions due to HK were recorded from patients' electronic health records, 2 years prior to initiation with SZC and until the end of the analysis period.

Data Analyses

Statistical analysis was conducted using Prism (V10.2.0 for Mac, GraphPad Software, Boston, MA, USA). A $p<0.05$ was accepted as being statistically significant. Kruskal–Wallis supported by Dunn's post hoc test was used to determine statistical differences in serum K^+ levels between pre- and post-initiation of SZC. Two-sided Fisher's exact tests were used to determine statistical differences in the percentage of patients achieving the guideline-recommended dosage between the pre- and post-initiation of SZC. McNemar's test was used to determine the

level of statistical differences between pre- and post-initiation of SZC for the number of HFrEF therapies patients are taking. Mann–Whitney tests were used to determine statistical differences between pre- and post-initiation of SZC for LVEF and NT-proBNP. The Wilcoxon signed-rank test was used to determine statistical differences in patient morbidity between pre- and post-initiation of SZC.

RESULTS

Forty-four patients were included out of 49 identified patients; mean age was 75 years, 27% were female, mean systolic blood pressure was 124 mmHg, mean diastolic blood pressure was 70 mmHg, and mean baseline LVEF was 29%. Median baseline NT-proBNP concentration was 3458 ng/l. At baseline, six patients (14%) were NYHA class I, 15 patients (36%) class II, 20 patients (48%) class III, and one patient (2%) was recorded as class IV severity. Comorbidities are listed in Table 1. Seven (16%) patients had a history of percutaneous coronary intervention, six (14%) patients had coronary artery bypass graft surgery, three (6.8%) had a cardiac resynchronization therapy pacemaker, and one (2%) patient had an implantable cardioverter-defibrillator (Table 1).

Serum K^+

At initiation of SZC, mean sK^+ was 5.7 mmol/l; 34% of patients had mild HK (5.0–5.5 mmol/l), 36% had moderate HK (5.5–6.0 mmol/l), and 30% had severe HK (>6.0 mmol/l). One month following initiation of SZC, 59% of patients achieved normokalemic status and a further 39% achieved a K^+ <5.5 mmol/l (Figs. 1, 2).

RAASi Therapies

The K^+ binder SZC was associated with higher prescription rates of guideline-directed medical therapy in patients with HFrEF; 93% of patients were able to receive a mineralocorticoid receptor antagonist (MRA; 37% increase) and 100% of patients were able to receive an angiotensin

Table 1 Baseline characteristics

Characteristic	*n* = 44
Age, years, mean ± SD	75.0 ± 22
Female, *n* (%)	12 (27)
Blood pressure, mmHg	124/70
Systolic blood pressure, mean ± SD (*n*)	124 ± 19 (42)
Diastolic blood pressure, mean ± SD (*n*)	70 ± 14 (42)
Clinical features of heart failure	
Mean LVEF, % ± SD	28.7 ± 20
Median NT-proBNP, ng/l (IQR)	3458 (2163–6437)
NYHA functional class, *n* (%)	
I	6 (14)
II	15 (36)
III	20 (48)
IV	1 (2)
Comorbidities, *n* (%)	
Atrial fibrillation	22 (50)
Anemia	13 (30)
Cancer	5 (11)
Chronic kidney disease*	38 (86)
Stage 1 (eGFR > 90 ml/min/1.73 m^2)	0 (0)
Stage 2 (eGFR 60–89 ml/min/1.73 m^2)	8 (18)
Albuminuria < 3 mg/mmol	6 (13)
Albuminuria 3–30 mg/mmol	2 (5)
Albuminuria > 30 mg/mmol	0 (0)
Stage 3a (eGFR 45–59 ml/min/1.73 m^2)	10 (23)
Stage 3b (eGFR 30–44 ml/min/1.73 m^2)	15 (34)
Stage 4 (eGFR 15–29 ml/min/1.73 m^2)	11 (25)
Stage 5 (eGFR < 15 ml/min/1.73 m^2)	0 (0)
COPD	8 (18)
Cerebrovascular disease	8 (18)

Table 1 continued

Characteristic	*n* = 44
Hypertension	27 (61)
Ischemic heart disease	24 (55)
PCI	7 (16)
CABG	6 (14)
LBBB	10 (23)
Diabetes mellitus	17 (39)
Type 1	1 (2)
Type 2	16 (36)
Medication and device use, *n* (%)	
ACEi (ramipril)	3 (7)
ARB	0 (0)
ARNi (sacubitril/valsartan)	36 (82)
ACEi/ARB/ARNi	39 (89)
MRA (spironolactone/eplerenone)	23 (52)
Beta-blocker (bisoprolol/carvedilol)	35 (80)
SGLT2i (dapagliflozin)	29 (66)
Loop diuretic (furosemide/bumetanide)	13 (30)
ICD	1 (2)
CRT	
CRT-P	3 (6.8)
CRT-D	0 (0)

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNi* angiotensin receptor–neprilysin inhibitor, *CABG* coronary artery bypass graft, *COPD* chronic obstructive pulmonary disease, *CRT* cardiac resynchronization therapy, *CRT-D* cardiac resynchronization therapy defibrillator, *CRT-P* cardiac resynchronization therapy pacemaker, *eGFR* estimated glomerular filtration rate, *ICD* implantable cardioverter-defibrillator, *IQR* interquartile range, *LBBB* left bundle branch block, *LVEF* left ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonist, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *PCI* percutaneous coronary intervention, *SD* standard deviation, *SGLT2i* sodium glucose co-transporter 2 inhibitor

*Chronic kidney disease defined as per Kidney Disease Improving Global Outcomes guidelines 2024 [8]

receptor–neprilysin inhibitor (ARNi; 11% increase) following initiation of SZC (Table 2). The proportion of patients receiving a guideline-recommended dose also improved with a 27% increase in MRA ($p<0.05$) and a 43% ($p<0.05$) increase in angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/ARNi. Patients who were not able to receive the guideline-recommended dose were still able to take higher doses; the mean dose of MRA increased from 13 to 31 mg/day and the mean percentage of guideline-recommended dose for ACEi/ARB/ARNi increased by 30–74%, which is equivalent to a mean dose of 296 mg/day of ARNi (sacubitril/valsartan).

There was a two-fold increase in the percentage of patients prescribed "four-pillar therapy" (32–64%; $p<0.05$), with 91% of patients prescribed three or more agents (Table 3). At the time of data retrieval, 41% of patients had a duration of treatment with SZC of < 12 months, 45% of patients had between 12 and 24 months, and 14% of patients had > 24 months. Median duration of treatment was 13 months.

HF Outcomes/Hospitalizations

Following optimization of RAASi therapy, a reduction in NT-proBNP was observed in 79% of patients (median, 2055 ng/l; $p<0.05$). There was a 7% increase in mean LVEF (29–36%; $n=35$; $p<0.05$). There were no significant changes in blood pressure and renal function. Hospitalization rates for decompensated HF were 21 per 100 patient-years in the 2 years preceding SZC; this reduced to 12 per 100 patient-years on SZC ($p<0.05$). HK hospitalizations, recorded 2 years prior to initiation of SZC and post-initiation, were 8 per 100 patient-years (Table 3).

Tolerability/Compliance

The tolerability of SZC was 100% during the study period. As this was a real-world evaluation, compliance was assumed through continued monitoring of serum K^+ levels whilst receiving SZC; suspected non-adherence resulted in clinical review for patient education and reassurance.

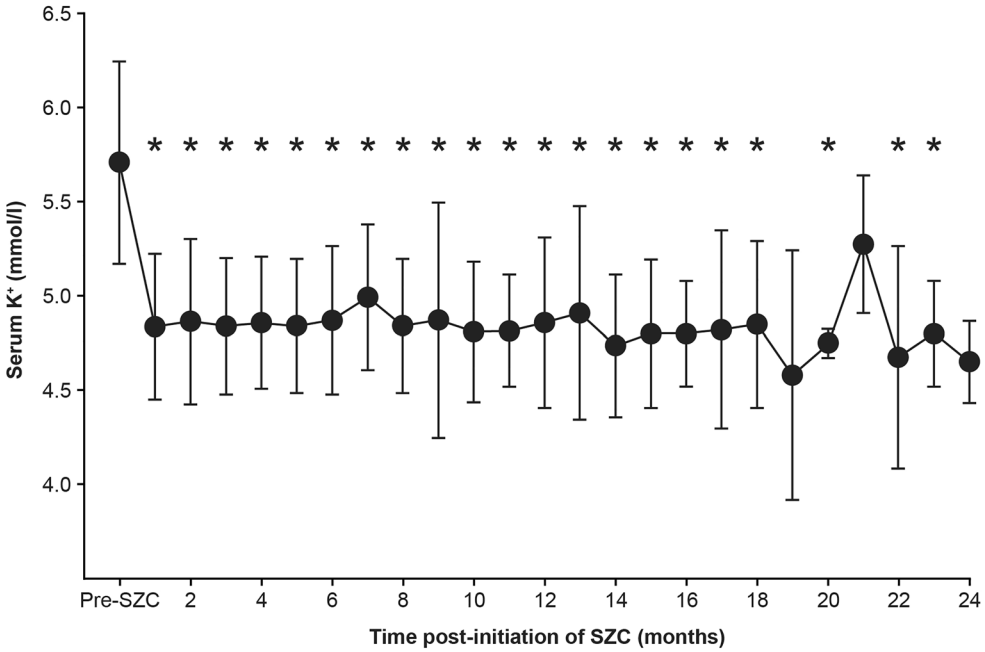

Fig. 1 Average serum K^+ concentration (mmol/l) ± SD pre-initiation of SZC and post-initiation of SZC. Overall, serum K^+ concentration was significantly ($p < 0.0001$, Kruskal–Wallis test) lower post-initiation of SZC compared with pre-SZC baseline. *$p < 0.05$ versus pre-SZC. *K^+* potassium, *SD* standard deviation, *SZC* sodium zirconium cyclosilicate

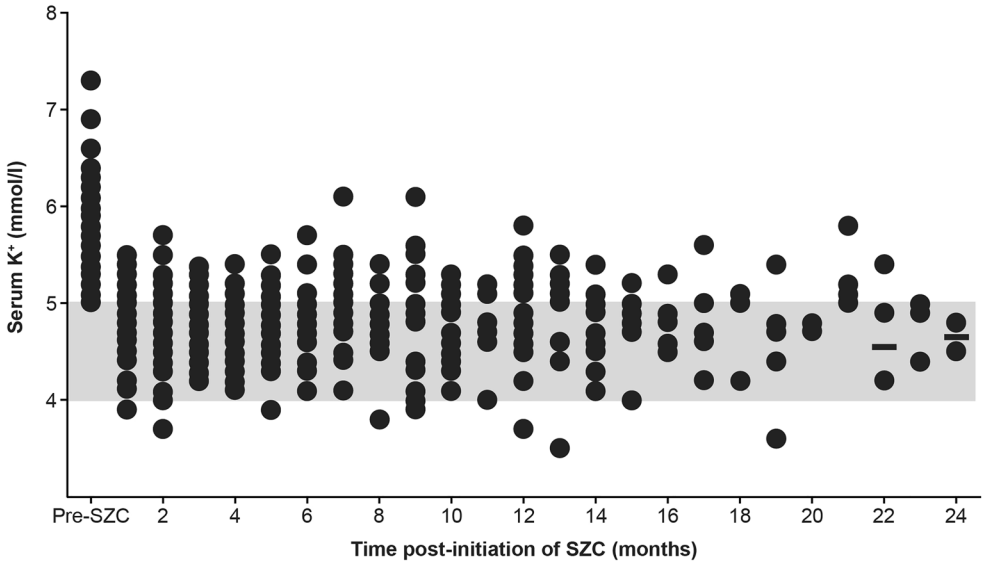

Fig. 2 Individual serum K^+ concentration (mmol/l) pre-initiation of SZC and post-initiation of SZC. Shading indicates normokalemia range as defined by the European Society of Cardiology. Overall, serum K^+ concentration was significantly lower ($p < 0.0001$, Kruskal–Wallis test) post-initiation of SZC compared with pre-SZC baseline. $p < 0.05$ versus pre-SZC. *K^+* potassium, *SD* standard deviation, *SZC* sodium zirconium cyclosilicate

Table 2 Optimization of GDMTs

	Pre-SZC (*n* = 44)	**Post-SZC (*n* = 44)**
Patients prescribed GDMT, *n* (%)		
ACEi (ramipril)	3 (7)	0 (0)
ARB	0 (0)	0 (0)
ARNi (sacubitril/valsartan)	36 (82)	44 (100)
ACEi/ARB/ARNi	39 (89)	44 (100)
MRA (spironolactone/eplerenone)	23 (52)	41 (93)
Beta-blocker (bisoprolol/carvedilol)	35 (80)	37 (84)
SGLT2i (dapagliflozin)	29 (66)	37 (84)
Percentage of guideline-recommended dose, median (% range of guideline-recommended dose; *n*)		
ACEi/ARB/ARNi	50% (13–100; 39)	100% (25–100; 44)
MRA	50% (25–100; 23)	50% (14–150; 41)
Beta-blocker	50% (6–150; 35)	50% (13–100; 37)
SGLT2i	100% (100; 29)	100% (100; 37)
Patients with maintained or increased dose, *n* (%)		
ACEi/ARB/ARNi (*n* = 44)	–	41 (93)
MRA (*n* = 41)	–	39 (95)
Beta-blocker (*n* = 37)	–	34 (92)
SGLT2i (*n* = 37)	–	37 (100)
Patients with increased dose, *n* (%)		
ACEi/ARB/ARNi (*n* = 44)	–	26 (59)
MRA (*n* = 41)	–	29 (71)
Beta-blocker (*n* = 37)	–	15 (41)
SGLT2i (*n* = 37)	–	11 (30)
Patients who achieved guideline-recommended dose, *n/N* (%)		
ACEi/ARB/ARNi	7/39 (18)	26/44 (59)[a]
MRA	2/23 (9)	15/41 (37)[a]

Table 2 continued

	Pre-SZC ($n=44$)	Post-SZC ($n=44$)
Beta-blocker	5/35 (14)	6/37 (16)
SGLT2i	29/29 (100)	37/37 (100)
Diuretic therapies, *n* (%)		
Loop diuretic (furosemide/bumetanide)	13 (30)	11 (25)
Mean dose (expressed as furosemide [mg])	35	51
Median dose (expressed as furosemide [mg])	40	40
Dose range (expressed as furosemide [mg])	20–80	20–160
Thiazide(-like) diuretic	0 (0)	0 (0)
Patients receiving SZC 10 g QD, *n (%)*	–	22 (50)

*ACE*i angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNi* angiotensin receptor–neprilysin inhibitor, *GDMT* guideline-directed medical therapy, *MRA* mineralocorticoid receptor antagonist, *QD* once a day, *SGLT2i* sodium glucose co-transporter 2 inhibitor, *SZC* sodium zirconium cyclosilicate

[a] $p < 0.05$ (Fisher's exact test)

DISCUSSION

RAASi therapy forms part of guideline-directed medical therapy (GDMT) in the management of HF and CKD, but HK can be a barrier to initiating and maintaining RAASi in patients who benefit the most from these therapies [28–30]. Discontinuation or down-titration of RAASi has been shown to be related to adverse cardiorenal outcomes in patients with HF and CKD [10, 12]. Using K^+ binders to control HK is now a recommended strategy to facilitate optimization of RAASi [8, 9].

K^+ binders have shown effectiveness in treating HK and maintaining normokalemia in the HARMONIZE and DIAMOND trials [22, 23], and in our study most serum K^+ levels were within the normal range, including for patients receiving treatment with SZC for 24 months. A 2023 real-world, multicountry, observational study showed that patients on SZC were likely to maintain GDMT following an HK episode [31]. We observed similar findings in our study. Patients who received SZC were more likely to be prescribed GDMT and at guideline-recommended dosages with controlled K^+ level. The REALIZE-K study (ClinicalTrials. gov NCT04676646) is evaluating whether SZC can enable safe and long-term MRA optimization in patients with HFrEF and prevalent/high risk of hyperkalemia [32]. The SCREAM (Stockholm CREAtinine Measurement) project demonstrated that 47% of patients would have their MRA discontinued after a HK episode and 74% of these patients would not have their therapy reinitiated within 12 months [33]. Although discontinuing the MRA reduced the risk of recurrent hyperkalemia by 25% [hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.72–0.79], this also resulted in a 10% increase in cardiovascular mortality or HF hospitalization (HR 1.10, 95% CI 1.06–1.14), clearly demonstrating the importance of continuing MRA therapy in this high-risk population and the potential role for K^+ binder therapies to help maintain patients on these agents [21].

Sodium glucose co-transporter 2 inhibitors (SGLT2i) have been shown to reduce the risk of serious HK by 16% ($p<0.001$) [34]. Secondary analysis from the DAPA-HF study demonstrated

Table 3 Heart failure outcomes

	Pre-SZC	Post-SZC
HFrEF therapies		
Patients prescribed "4 therapies", *n* (%)	14 (32)	27 (64)[a]
Patients prescribed "3 or more therapies", *n* (%)	30 (68)	38 (91)[a]
Heart failure markers		
LVEF, mean ± SD, (*n*)	29 ± 8 (44)	36 ± 11 (41)[b]
Patients with improved LVEF, *n (%)* (*n* = 41)	–	21 (52)
NT-proBNP (ng/l), median (IQR) [*n*]	3458 (2163–6437) [43]	2055 (959–4544) [34][b]
Patients with reduction in NT-proBNP, *n* (%)	–	27 (79)
Patients with reduction in NT-proBNP > 800 ng/l, *n* (%)	–	23 (68)
Observations or biochemical analysis		
eGFR, (eGFR; ml/min/1.73 m^2), mean ± SD (*n*)	43 ± 16.1 (44)	45 ± 14.4 (42)
Systolic blood pressure, mmHg, mean ± SD (*n*)	124 ± 19 (42)	122 ± 18 (43)
Diastolic blood pressure, mmHg, mean ± SD (*n*)	70 ± 14 (42)	71 ± 11 (43)
Hospitalization or mortality		
Patient hospitalization with either dHF or HK, *n* (%)	19 (43)	8 (18)
Hospitalization: dHF		
Patients, *n* (%)	13 (30)	5 (11)
Total no. episodes (per year), *n*	9	6
Per 100 patient-years, average ± SD	21 ± 35	12 ± 45[c]
Hospitalization: HK		
Patients, *n* (%)	6 (14)	3 (7)
Total no. of episodes (per year), *n*	3.5	4
Per 100 patient-years	8	8
Survival, *n* (%)	–	40 (91)

dHF decompensated heart failure, *HFrEF* heart failure with reduced ejection fraction, *HK* hyperkalemia, *LVEF* left ventricular ejection fraction, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *SD* standard deviation, *SZC* sodium zirconium cyclosilicate

[a] $p < 0.05$ versus pre-SZC (McNemar's test)

[b] $p < 0.05$ versus pre-SZC (Mann–Whitney test)

[c] $p < 0.05$ versus pre-SZC (Wilcoxon signed-rank test)

a 50% reduction in the incidence of moderate/severe HK (>6.0 mmol/l) in patients co-prescribed an MRA ($p=0.010$) [35]. SGLT2i were prescribed in 86% of patients during the medicine optimization process in our study. In total, 66% of patients were prescribed an SGLT2i when initiated on SZC. Mean serum K^+ was reduced by 0.02 mmol/l within 12 months and 0.04 mmol/l over 24 months; HK remains a problem even in patients who are already taking SGLT2i. The use of SGLT2i alone is unlikely to enable optimization of RAASi use, and a more definite strategy such as using K^+ binders will need to be considered for further optimization of RAASi.

Following initiation of SZC treatment, a reduction in mean K^+ was observed within the first month of therapy, with 58% of patients achieving serum K^+ between 4.0 and 5.0 mmol/l (normokalemia, as defined by the European Society of Cardiology). Biochemical laboratories often use a broader definition of normokalemia (3.5–5.3 mmol/l in local centers); using this parameter, 95% of patients had controlled K^+ levels within the first 28 days of therapy. The rate of hospitalization with an episode of HK was comparable pre- and post-SZC commencement at 8 per 100 patient-years, which is likely explained by ongoing up-titration of RAASi therapy in this group of high-risk patients (mean age, 75 years; CKD stage 3b–4, 59%; diabetes mellitus, 38%).

The initiation of SZC and higher uptake of GDMT had no overall impact on the number of patients requiring loop diuretics (30% pre-SZC, 25% post-SZC); 85% of patients taking loop diuretics before initiation of SZC either saw their diuretic stopped or their dosage decreased, while four patients (9%) had a new diuretic requirement post-SZC.

SZC was well tolerated (100% of patients remained on SZC) with nearly half of the patients receiving the 10-g dose. Peripheral edema and sodium absorption have been noted as potential adverse effects of SZC; in the HARMONIZE study, 69% of patients (11/16) who experienced fluid retention had significant baseline risk factors including history of HF, CKD, lymphedema, or venous insufficiency [36]. Most of these events were seen in the unlicensed dosage study arm (15 g once a day) and no edema-related events led to SZC discontinuation [36].

The European Society of Cardiology recommend a normal sodium intake in patients with chronic HF (up to 5 g salt/day) as it has been associated with improved quality of life and therefore better adherence to a healthy diet compared with a restricted sodium intake [37]. The sodium concentration of SZC and its potential for absorption is also small compared with the oral dosage forms of other common medications, e.g., 4 g (1 g four times daily) of effervescent paracetamol (acetaminophen) contains 2.5 g sodium (equivalent to 6.3 g of salt), whereas a single 10-g sachet of SZC contains 800 mg (2 g salt).

Limitations

This study had a small sample size of 44 patients, which reduces the statistical power and may not be sufficient to be representative of the broader HFrEF population. All results require cautious interpretation. The selection of patients treated with SZC was also at the discretion of the prescribing physicians, which could potentially introduce bias.

CONCLUSION

The use of the K^+ binder SZC was well tolerated in this real-world study of high-risk patients with HF. SZC is effective at controlling K^+ level and enables optimization of GDMT by achieving higher doses.

Ongoing clinical trials such as REALIZE-K are further investigating the impact of K^+ binders on MRA optimization in patients with HFrEF and with, or at risk of, HK. Future studies could assess the effectiveness of SZC in larger patient populations with HFrEF in a randomized setting to remove selection bias and improve statistical power.

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Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Rhys Williams—Speakers Fees, Honorarium, Congress Sponsorship, Joint-Working collaboration: AstraZeneca, Boehringer-Ingelheim, Novartis, Pharmacosmos. William Ford—Has nothing to disclose. Current affiliation: Royal College of Surgeons in Ireland—Bahrain, Al Sayh Muharraq Governorate, Bahrain. Alexander James—Has nothing to disclose. Current affiliation: Derriford Hospital, University Hospitals Plymouth NHS Trust, Plymouth, UK. Kerys Thomas—Speakers Fees, Honorarium: AstraZeneca. Aaron Wong—Speakers Fees, Honorarium, Congress Sponsorship: Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, Menarini, NAPP, Novartis, Pharmacosmos, Servier.

Ethical Approval. This retrospective study was submitted to Cwm Taf Morgannwg University Health Board Research & Development department. As the study was recognized as a service evaluation, using evidence-based medicines and no data collected beyond that of routine clinical care, formal approval from the research ethics committee was not required.

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