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The role of sodium zirconium cyclosilicate drug utilization in managing hyperkalemia: impact on healthcare resource utilization and on maintenance of renin-angiotensin-aldosterone system inhibitor therapy in Italian clinical practice

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ABSTRACT

Aims: Hyperkalemia (HK) is prevalent in patients with chronic kidney disease (CKD) and heart failure, particularly those on renin-angiotensin-aldosterone system inhibitors (RAASi). However, HK treatment often necessitates RAASi discontinuation. Sodium zirconium cyclosilicate (SZC), reimbursed in Italy since 2021, offers a new treatment option for HK. This study aimed to assess real-world SZC use and resulting economic rebounds in Italy.

Methods: Using administrative databases of healthcare entities covering about 6 million residents, patients with at least one prescription of SZC from Jan-2022 to Jun-2023 were identified. Patients receiving other potassium binders after SZC initiation were excluded. A logistic regression model estimated odds ratios (OR) with 95% confidence interval (95%CI) for predictors of long-term SZC use (>90 days), including age, sex, CKD status, and comorbidities. Univariate regression identified the potential association between each individual predictor and the likelihood of long-term treatment, followed by multivariate analysis adjusted for confounders. A backward stepwise logistic regression method retained only significant predictors, enhancing model accuracy.

Results: The study identified 355 SZC-treated patients (mean age 70.4 years, 64.2% male). CKD was found in 69.3% (47.6% on dialysis), with common comorbidities including hypertension (57.5%), diabetes (43.4%), and heart failure (23.4%). RAASi use was observed in 68.7% before SZC initiation, and RAASi discontinuation was lower in long-term SZC users compared to short-term SZC users (41.2 vs. 56.6%, $p = 0.048$). Short-term SZC treatment (≤90 days) was more frequent (83.1%) and predicted by dialysis (OR = 0.22). Healthcare costs over 6 months averaged €7,943 for short-term users (dialysis: €3,452) and €6,647 for long-term users (dialysis: €1,130).

Conclusions: This real-world study showed that nearly 17% of patients continued SZC therapy for ≥90 days. Long-term therapy was associated with lower RAASi discontinuation and reduced healthcare costs due to hospitalizations and outpatient specialist services, suggesting that SZC can potentially provide clinical and economic benefits for HK management.

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Introduction

Hyperkalemia (HK) is an electrolyte imbalance characterized by serum potassium (sK+) levels exceeding the normal physiological range of 3.5–5.0 mEq/L, with different thresholds indicating severity[1]. Mild HK is typically asymptomatic, but excessively elevated sK + levels can result in life-threatening consequences (i.e. paralysis, and potentially fatal cardiac arrhythmias)[2]. Moreover, severe HK is associated with relevant economic and healthcare burden[3]. Certain patients, particularly those with type 2 diabetes mellitus (T2DM), heart failure, or chronic kidney disease (CKD), are more susceptible to develop HK[4]. In these individuals, HK constitutes a distinct risk factor for overall mortality and hospital admission[5]. Moreover, treatments for heart failure and CKD, such as renin-angiotensin-aldosterone system inhibitors (RAASi), can elevate sK + levels due to their mechanism of action.

For this reason, RAASi therapy is often down-titrated or discontinued among patients with HK[6]. Actually, this current clinical practice is associated with the risk of worsening cardiovascular and renal outcomes and creates a gap between guideline recommendations and real-world practice. The guidelines of European and American cardiology and

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nephrology societies stress the importance of managing HK to enable RAASi therapy at the highest tolerable dose, recommending anti-HK treatments in patients developing HK and suggesting reduction or discontinuation of RAASi as a last resort[7,8]. This notion is further supported by a recent Italian document reinforcing the need for a proper HK management with the use of K-binders when indicated, in order to allow RAASi therapy[6]. Indeed, a recent observational study suggested that HK-related RAASi discontinuation or down-titration was linked to a higher risk of cardiorenal events compared to a maintenance or uptitration of RAASi[9].

Since September 2021, new oral potassium binders like sodium zirconium cyclosilicate (SZC) and patiromer are reimbursed in Italy for chronic HK management. SZC is a non-polymeric, non-absorbable inorganic powder with a microporous structure that selectively binds potassium in exchange for hydrogen and sodium ions. SZC is highly selective for potassium even in the presence of other cations such as calcium and magnesium, reducing sK + levels by capturing it throughout the gastrointestinal tract and increasing fecal K + excretion. SZC starts lowering sK + within one hour of intake, and normokalemia is typically achieved within 24–48 h. Studies have shown that SZC can maintain normokalemia for up to one year, allowing 89% of patients to continue RAASi therapy[10]. The latest guidelines from KDIGO (Kidney Disease: Improving Global Outcomes 2024)[10], from the European Society of Cardiology (ESC 2021)[8] and from the American College of Cardiology/American Heart Association Joint Committee (ACC/AHA/HFSA 2022)[11] for heart failure patients, recognize oral potassium binders like SZC as important for optimizing RAASi use in the setting of HK[7,8].

Recently, a real-world retrospective study in the US using outpatients' data from the HealthVerity warehouse suggested that SZC may decrease HK-related and all-cause hospitalizations, with a stronger association in patients on long-term SZC therapy (>90 days) compared to short-term use (≤90 days)[12].

This study was undertaken to gather real-world data on HK and drug utilization of SZC, focusing specifically on use, dosage, treatment duration of SZC in outpatient setting, healthcare resource utilization (HCRU) related to duration of treatment with SZC (short-term vs. long-term). Moreover, the role of SZC therapy on RAASi maintenance after HK and discontinuation of RAASi (optimization of therapy according to guidelines for the clinical management of CKD) related to duration of treatment with SZC (short-term vs long-term treatment) was also investigated.

Methods

Data source

This retrospective observational analysis used the administrative databases of a sample of Italian Local Health Units (LHUs), covering around 6 million health-assisted individuals. These databases store all data concerning the healthcare resources reimbursed by the Italian National Health Service (INHS), namely: beneficiaries' database containing patients' demographic data; pharmaceutical database providing the Anatomical-Therapeutic Chemical (ATC) code and marketing authorization code [AIC (Autorizzazione all'Immissione in Commercio) code] of drug dispensed, number of packages, number of units per package, and prescription date; hospitalization database recording data on all hospital admissions and discharges, including diagnoses coded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis-related groups (DRGs) with the DRG-related charges; and laboratory database for biochemical and hematological tests.

Approval has been obtained from the ethics committees of the involved Local Health Units. The dataset used consists solely of anonymized data.

Study design and study population

The present study has an observational, descriptive, longitudinal design and is based on secondary data extracted from administrative flows. Adult patients with at least one prescription of SZC (ATC V03AE10) from January 2022 to June 2023 (inclusion period) were included in this study. The index-date was defined as the date of the first SZC prescription during the inclusion period. Patients with at least 12 months of data available before and 6 months after the index-date were considered eligible. Patients with a prescription of other potassium binders such as patiromer (ATC V03AE09) or resins (ATC V03AE01) after the index-date were excluded from the analysis. Characteristics of patients were evaluated prior to the index-date (characterization period) in terms of previous hospitalization (searched in all available period prior to the index-date and listed with corresponding ICD-9-CM codes in Supplementary Table 1) or previous treatments (searched in the year before the index-date and listed with corresponding ATC codes in Supplementary Table 2).

The severity of HK was evaluated according to the established sK + thresholds (mild HK: sK+ ≤5.5 mmol/L; moderate HK: sK+ 5.5–6.0 mmol/L; severe HK: sK+ >6.0 mmol/L)[13], and analyzed across overall SZC-treated patients (herein referred to as "Overall SZC-treated cohort") and dialysis-dependent patients (herein referred to as "Dialysis SZC-treated cohort").

To investigate RAASi treatment patterns, a further analysis was conducted on a subcohort of participants with at least one filled prescription of any RAASi medication during the follow-up period or before index-date, with a lookback period up to 6 months (herein referred to as "RAASi-treated cohort").

Definition of SZC dosage

At index-date, the dosage of SZC was derived from AIC of packages supplied to patients. In Italy, SZC is available as oral suspension (powder) of 5 g per sachet and 10 g per sachet. SZC is indicated with the following dosing scheme: for correction phase at 10 g dosage three times per day (for a maximum of 72 h), and for maintenance phase at of 5/10 g dosages per day or 5 g every other day. Besides, for dialysis patients, up to 15 g can be used (either using three sachets of 5 g or one of 10 g plus one of 5 g).

Definition of treatment duration

In this study, treatment duration was evaluated using treatment persistence as a proxy, calculated based on filled prescriptions. Persistence was measured through two variables, which provide complementary insights: proportion of days covered (PDC) and continuous treatment period (CTP). CTP was assessed using the Refill-Gap method. Each supplied package is considered to cover 30 days, with an allowance for a grace period of 15 days. The proportion of patients treated long-term was defined as the proportion of patients who hag a number of days covered >90 days with a continuous treatment period ≥3 months. The proportion of patients treated for ≥180 days was calculated on those having a number of days covered ≥180 days with a PDC_B ≥80% (see below).

Definition of drug adherence

Adherence to SZC prescriptions was assessed during the follow-up period by the *PDC*, calculated as the ratio between the number of days of medication supplied and the observation time, assuming that a dose covers one day of treatment. *PDC* was calculated in two different ways. *PDC* over the follow-up period (PDC_A), which is equal to:

$$PDC_A = \frac{Days\ Covered}{Days\ of\ FollowUp}; \tag{1}$$

and *PDC* over the continuous treatment period (PDC_B), which is equal to:

$$PDC_B = \frac{Days\ Covered}{Days\ of\ Continuous\ Treatment} \tag{2}$$

The days of continuous treatment were assessed using the Refill-Gap method. Each supplied pack is considered to cover 30 days, plus a grace period of 15 days.

PDC_A considers the entire follow-up period, assessing the proportion of days in which the patient had medication available relative to the total observation time. It provides an overall view of adherence, capturing both treatment persistence and potential discontinuations.

PDC_B considers the period during which the patient continuously received SZC without prolonged interruptions. This approach isolates adherence during the treatment phase, without being influenced by definitive discontinuations.

The classification of adherence levels, following the methodology of previous studies[14–16], used the following PDC cut-offs: less than 40% was considered low adherence, 40–80% was moderate adherence, and greater than or equal to 80% was high adherence.

Definition of treatment patterns with RAASi

Treatment discontinuation was defined according to the refill-gap method. After a filled prescription of one RAASi, a patient is classified as a "discontinuator" if no refill was recorded after the period covered by the filled prescription (computed on the supplied amount of drug and daily defined dose) plus a grace period of two months.

Treatment start was defined as a filled prescription of a RAASi occurring after the index-date in patients with no RAASi prescriptions (from 6 months before the index-date) or who discontinued a RAASi drug before the index-date (discontinuation defined as above, with discontinuation lasting for at least one month after the grace period).

HCRU and healthcare costs

Mean HCRU were calculated per alive patients during the first 6 months of follow-up period for drug treatments, hospitalizations admissions and outpatient specialist services (OSS) in terms of laboratory tests, specialist visits, diagnostic procedures.

The resulting per-patient costs, expressed in euros (€), were calculated for all drug prescriptions, HK-related treatments, cardiorenal treatments, all-cause hospitalizations, HK-related hospitalizations (identified by ICD-9-CM code 276.7), OSS (excluding dialysis) and dialysis procedures. HK-related drug refers to the prescription of SZC, and cardiorenal drug refers to the prescription of RAASi, beta-blockers, calcium channel blockers, loop diuretics, digitalis, nitrates.

Outlier values (those costs exceeding more than 3-times standard deviation over the mean value) were excluded. This cost analysis was conducted from the perspective of the INHS. Drug costs were assessed based on the INHS purchase prices. Hospitalization costs were determined using Diagnosis-Related Group (DRG) tariffs, which represent the reimbursement rates provided by the INHS to healthcare providers. The costs of outpatient specialty services were defined according to the tariffs applied in each region.

Statistical analysis

Continuous variables were presented as the mean with standard deviation (SD), while categorical variables were shown as frequencies and percentages. For inferential testing, a *p* value of less than 0.05 was considered statistically significant. Using a logistic regression model, the presence of long-term treatment versus short-term was evaluated for the predictive factors by estimating the odds ratio (OR) association measure with 95% confidence interval (95% CI). The predictors were entered as dichotomous covariates (depending on whether the condition occurred or not) except for CKD, which was a categorical variable, with absence of CKD used as reference category. The potential predictors age, as a continuous variable, and sex, with female as reference category, were also evaluated.

To identify predictors of long-term treatment with SZC, univariate and multivariate logistic regression analyses were conducted. The univariate regression analysis was first implemented to evaluate the association between each individual predictor and the likelihood of long-term treatment. This initial analysis helped to screen potential predictors that might be associated with long-term treatment duration. Then, a multivariate logistic regression analysis was performed to account for the influence of multiple predictors simultaneously and to adjust for potential confounders. The multivariate model included all potential predictors identified in the univariate regression analysis, with the estimates for each predictor adjusted for the presence of the others. This comprehensive approach provided a more robust evaluation of the factors influencing long-term treatment. To refine the model, a backward stepwise logistic regression method was employed, retaining only those predictors that were significant based on Wald's test of the regression coefficient ($p < 0.2$). This stepwise approach ensured that the final model included only the most relevant predictors, improving the accuracy and interpretability of the results. To refine the model, a backward stepwise logistic regression approach was utilized, retaining only predictors that are significant on Wald's test. The reference category for CKD stage remained unchanged. All the analyses were conducted using Stata SE version 17.0 (StataCorp, College Station, TX, USA).

Results

Hyperkalemia patients treated with sodium zirconium cyclosilicate

From a sample of about 6 million Italian health-assisted citizens, according to the inclusion and exclusion criteria, 355 patients with at least one SZC prescription were identified. As shown in Table 1, the mean age was 70.4 years (SD 14.1), and there was a slight predominance of male sex (64.2%). The average follow-up period was 9.3 months (SD 2.8). CKD was highly prevalent in the cohort (69.3%): almost half of them (47.6%) were on dialysis treatment, whereas the remaining were distributed across CKD stages (15.0% Stage 3a/3b, 17.1% Stage 4, and 11.8% Stage 5). Other prevalent conditions were hypertension (57.5%), heart failure (23.4%), and diabetes mellitus (43.4%). Only 2.3% of the patients had been hospitalized for HK in the year prior to the index-date. In the cohort, 27.3% of patients were treated with resins for HK within the 12 months before the index-date, and less than 4 patients was treated with patiromer. Moreover, 68.7% of patients received RAASi in the 6 months before the index-date, specifically 67% prescribed with one or more RAASi among angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blockers (ARBs), or angiotensin receptor-neprilysin inhibitors (ARNI), and 15.5% with mineralocorticoids (MRA).

Within the 12 months before the index-date, the severity of HK based on the maximum sK+ level measurement was categorized as follows: 43.9% had no measurement recorded in the administrative database, 14.1% had mild HK (≤5.5 mmol/L), 13.0% had moderate HK (>5.5 and ≤6.0 mmol/L), and 29.0% had severe HK (>6.0 mmol/L). Among patients on dialysis, severe HK was more common (Table 2).

Table 1. Baseline demographic and clinical characteristics of patients prescribed with SZC.

	Overall SZC-treated cohort ($N = 355$)
Age at index-date, mean (SD)	70.4 (14.1)
Age groups	
18–65 Years, *n* (%)	115 (32.4%)
66–70 years, *n* (%)	45 (12.7%)
71–80 years, *n* (%)	104 (29.3%)
>80 years, *n* (%)	91 (25.6%)
Male gender, *n* (%)	228 (64.2%)
Follow-up (months), mean (SD)	9.3 (2.8)
Patients previously treated for HK#	
Resins, *n* (%)	97 (27.3%)
Patiromer, *n* (%)	<4
Patients previously treated for HK°	
Resins, *n* (%)	152 (42.8%)
Patiromer, *n* (%)	<4
Previous treatment with RAASi, *n* (%)^	244 (68.7%)
ACEi/ARB/ARNI, n (%)	238 (67%)
MRA, n (%)	55 (15.5%)
Comorbidity profile	
Patients previously hospitalized for HK#	8 (2.3%)
CKD, n (%)	246 (69.3%)
Unspecified, *n* (%)	18/246 (7.3%)
Stage 1 (high or normal eGFR), *n* (%)	<4
Stage 2a/2b (mildly reduced eGFR), *n* (%)	<4
Stage 3a/3b (mildly/moderately reduced eGFR), *n* (%)	37/246 (15.0%)
Stage 4 (severely reduced eGFR), *n* (%)	42/246 (17.1%)
Stage 5 (kidney failure), *n* (%)	29/246 (11.8%)
Dialysis, *n* (%)	117/246 (47.6%)
Hemodialysis, *n* (%)	91/117 (77.8%)
Peritoneal dialysis, *n* (%)	5/117 (4.3%)
Heart failure, *n* (%)	83 (23.4%)
Hypertension, *n* (%)	204 (57.5%)
Diabetes, *n* (%)	154 (43.4%)
Type 1, *n* (%)	6/154 (3.9%)
Type 2, *n* (%)	132/154 (85.7%)

#During 12 months before index-date; °during all available period before index-date; ^during 6 months before index-date.
Abbreviations. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; MRA, mineralocorticoid; RAASi, Renin-angiotensin-aldosterone system inhibitors.

Analysis of treatment adherence and duration

At index-date, 67.9% of patients received a 5 g dosage of SZC, and 7% received a 10 g dosage during follow-up. Besides, 32.1% of patients received a 5 g dosage of SZC at index-date, and 12.3% received a 5 g dosage during follow-up. Regarding the duration of treatment, 83.1% of patients were classified as short-term treated (≤90 days), while 16.9% were classified as long-term treated (>90 days). Only 7.6% of patients were treated for at least 180 days. Treatment adherence was assessed using two metrics: PDC_A and PDC_B. Over the follow-up period (PDC_A), 22.3% of patients were adherent ($PDC_A \geq 80$), 30.1% had moderate adherence ($40 \leq PDC_A < 80$), and 47.6% had low adherence ($PDC_A < 40$). Over the continuous treatment period (PDC_B), 59.2% of patients were adherent, 32.1% had moderate adherence, and 8.7% had low adherence (Figure 1).

HCRU and direct healthcare costs associated with use of SZC in short and long-term treated patients

The study examined the average HCRU per patient treated with SZC over the first 6 months of follow-up, excluding deaths. The analysis included 328 patients, stratified by short-term (≤90 days, $N = 269$) and long-term (>90 days, $N = 59$) treatment durations. On average, patients had 16.7 (SD 8.2) drug prescriptions. Short-term treated patients had a mean of 16.2 (SD 8.3) prescriptions, while long-term treated patients had a higher mean of 18.9 (SD 7.4) prescriptions. The number of HK-related drug prescriptions averaged 3.1 (SD 1.8); short-term treated patients averaged 2.5 (SD 1.4) prescriptions, whereas long-term treated patients averaged more at 5.6 (SD 1.1) prescriptions. For cardiorenal drug prescriptions, the mean was 5.6 (SD 3.9), with a median of 5.0. Short-term patients had a mean of 5.3 (SD 3.7) prescriptions, and long-term patients had a mean of 6.6 (SD 4.3) prescriptions. The average number of hospitalizations was 0.4 (SD 0.9), and HK-related hospitalizations were rare. Outpatient specialist services averaged 18.8 (SD 28.3). Short-term treated patients had a mean of 20.8 (SD 29.6) services, compared to 9.7 (SD 18.6) services for long-term treated patients (Table 3).

Table 2. Distribution of patients based on sK + level in overall SZC-treated cohort and in dialysis SZC-treated cohort.

	Overall SZC-treated cohort ($N = 355$)
Severity of HK	
No measurement, *n* (%)	156 (43.9%)
Mild (≤5.5 mmol/L), *n* (%)	50 (14.1%)
Moderate >5.5 and ≤6.0 mmol/L, *n* (%)	46 (13.0%)
Severe >6.0 mmol/L, *n* (%)	103 (29.0%)
	Dialysis SZC-treated cohort ($N = 117$)
No measurement, *n* (%)	31 (26.5%)
Mild (≤5.5 mmol/L), *n* (%)	10 (8.6%)
Moderate >5.5 and ≤6.0 mmol/L, *n* (%)	17 (14.5%)
Severe >6.0 mmol/L, *n* (%)	59 (50.4%)

Abbreviations. HK, hyperkalemia; SZC, sodium zirconium cyclosilicate.

The average healthcare costs per patient treated with SZC over the first 6 months of follow-up, excluding deaths and outliers, were analyzed and stratified by short-term (≤90 days, $N = 263$) and long-term (>90 days, $N = 59$) treatment durations (Figure 2). For short-term treated patients, the mean drug costs were €2,471, with HK-related drugs accounting for €876.65 and cardiorenal drugs for €116. The mean hospitalization costs were €1,321, with HK-related hospitalizations contributing for €36. The costs for OSS, excluding dialysis, were €699, while OSS-dialysis costs were €3,452. The total healthcare cost per patient was €7,943.02, with total HK-related costs amounting to €913. In contrast, long-term treated patients had higher mean drug costs of €3,672, with HK-related drugs costing €1,961 and cardiorenal drugs €249. The mean hospitalization costs for these patients were €1,271, with no costs attributed to HK-related hospitalizations. The costs for OSS, excluding dialysis, were €574, and OSS-dialysis costs were €1,130. The total healthcare cost per patient for the long-term treated group was €6,647, with total HK-related costs at €1,961 (Figure 3).

Predictors of treatment duration: univariate and multivariate regression analysis

As shown in Table 4, the univariate analysis revealed that previous therapy with RAASi during the 6 months before the index-date (OR 2.60, 95% CI: 1.27–5.35) was a significant predictor of

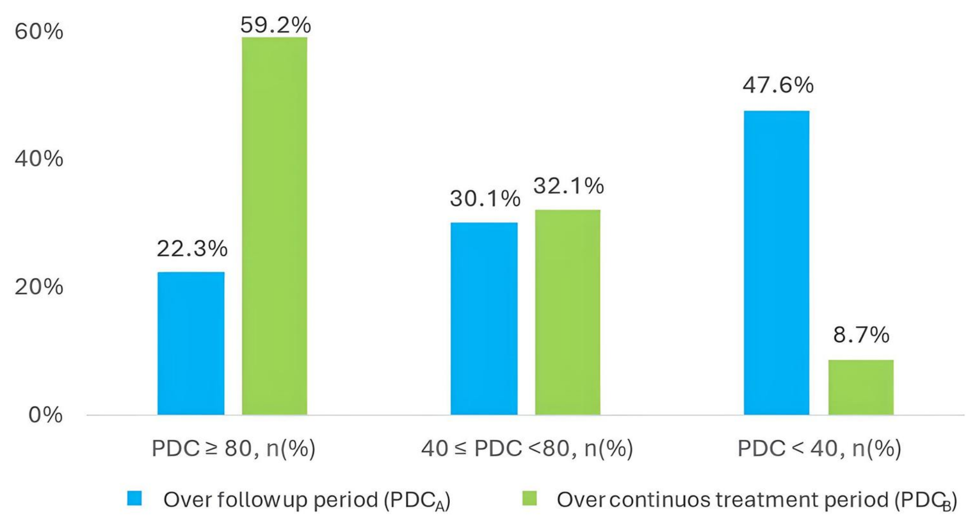

Figure 1. Treatment adherence in the PDC_A and PDC_B groups assuming the consumption of 1 dose/day. Abbreviations. PDC, proportion of days covered.

Table 3. Average HCRU per patient during the first 6 months of follow-up, stratified by duration of treatment.

	SZC-treated patients ($N = 328$)	Short-term ($N = 269$)	Long-term ($N = 59$)
Number of drug prescriptions	16.7 (8.2); 16.0	16.2 (8.3); 15.0	18.9 (7.4); 19.0
Number of HK-related drug prescriptions	3.1 (1.8); 3.0	2.5 (1.4); 2.0	5.6 (1.1); 6.0
Number of cardiorenal drug# prescriptions	5.6 (3.9); 5.0	5.3 (3.7); 5.0	6.6 (4.3); 6.0
Number of hospitalizations	0.4 (0.9); 0.0	0.4 (0.9); 0.0	0.3 (0.5); 0.0
Number of HK-related hospitalizations	0.0 (0.1); 0.0	0.0 (0.1); 0.0	0.0 (0.0); 0.0
Number of outpatient specialist services	18.8 (28.3); 6.0	20.8 (29.6); 6.0	9.7 (18.6); 4.0

Data are given as mean (SD) and median.
HK-related drug refers to the prescription of (at least one ATC code): SZC, patiromer and polystyrensulphonate; #cardiorenal drug refers to the prescription of (at least one ATC code): RAASi, beta-blockers, calcium channel blockers, loop diuretics, digitalis, nitrates.
Abbreviations. HK, hyperkalemia; RAASi, renin-angiotensin-aldosterone system inhibitors, SD, standard deviation; SZC, sodium zirconium cyclosilicate.

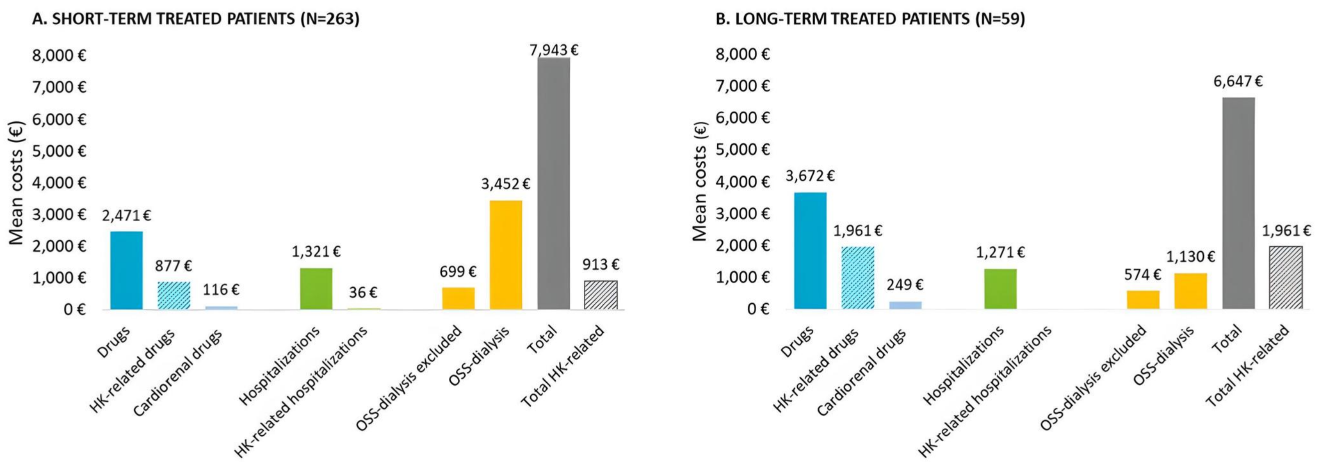

Figure 2. Average healthcare costs per patient during the first 6 months of follow-up, stratified by duration of treatment. Mean annual healthcare costs in the short-term (A) and long-term (B) treated patients prescribed with SZC. Abbreviations. HK, hyperkalemia; OSS, outpatient specialist services.

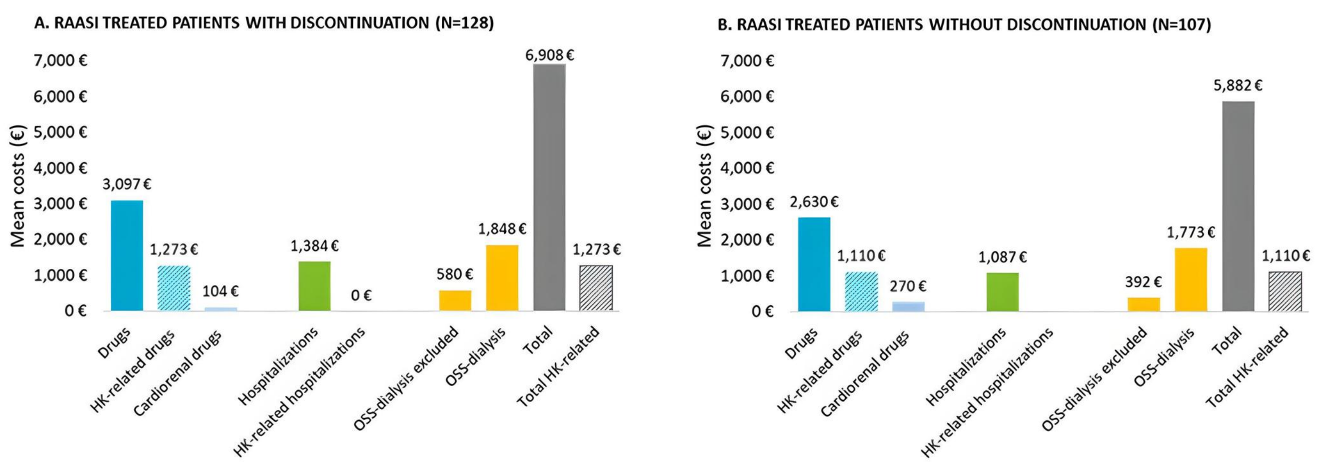

Figure 3. Average healthcare costs per patient during the first 6 months of follow-up, stratified by duration of treatment. Mean annual healthcare costs in RAASi-treated patients who discontinued the therapy (A) and RAASi-treated patients who did not discontinue the therapy (B). Abbreviations. HK, hyperkalemia; OSS, outpatients specialist services; RAASi, renin-angiotensin-aldosterone system inhibitors.

long-term treatment and dialysis was a significant predictor of short-term treatment (OR 0.20, 95% CI: 0.08–0.49). Multivariate regression (Table 5) confirmed the significant predictive value of dialysis on short-term treatment (full model: OR 0.22, 95% CI: 0.08–0.60; simplified model: OR 0.19, 95% CI: 0.08–0.44).

Subgroup analysis: SZC-treated patients with at least one RAASi prescription before and after index-date

Patterns of treatment with RAASi medications, in terms of treatment discontinuation and initiation, were explored a subset of 256 patients (out of the 355 included) on RAASi therapy. This subgroup consisted of patients with at least one filled prescription of any RAASi medication in the time window comprised between the 6 months prior to index-date and the 12-month after the index-date. RAASi discontinuation was observed in 54% of the patients. When stratified by SZC treatment duration, the rate of RAASi was significantly higher in the short-term treated patients compared to the long-term treated ones (56.6 vs. 41.2%, $p = 0.048$). In terms of treatment initiation, 11% of the patients started RAASi therapy after the index-date.

Table 4. Univariate regression analysis for predictors of short and long-term treatment duration (unadjusted effect estimates).

Potential predictors	OR	95% CI
Age at index-date (+1 year)	1.01	0.99–1.03
Male (vs. female)	1.14	0.63–2.05
CKD stage		
Stage 3 (included stages 1,2,3, unspecified)	0.92	0.43–1.97
Stage 4	1.13	0.50–2.56
Stage 5	0.37	0.10–1.32
Dialysis	0.20	0.08–0.49*
Heart failure	1.11	0.58–2.12
Hypertension	0.64	0.37–1.12
Diabetes	0.92	0.52–1.61
Previous treatment with RAASi (during 6 months before index-date)	2.60	1.27–5.35*
Previous treatment for HK (during 12 months before index-date)	1.27	0.69–2.31

Absence of CKD used as reference category; *indicates statistical significance (p-value <0.05).

Table 5. Multivariate regression analysis for predictors of short and long-term treatment duration (adjusted effect estimates).

Potential predictors	OR	95% CI
Full model		
Age at index-date (+1 year)	1.00	0.98–1.02
Male (vs. female)	1.04	0.56–1.96
CKD stage		
Stage 3 (included stages 1, 2, 3, unspecified)	0.96	0.44–2.07
Stage 4	1.13	0.49–2.63
Stage 5	0.36	0.10–1.34
Dialysis	0.22	0.08–0.60*
Heart failure	1.15	0.57–2.34
Hypertension	0.88	0.49–1.60
Diabetes	0.72	0.39–1.32
Previous treatment with RAASi (during 6 months before index-date)	1.44	0.63–3.27
Previous treatment for HK (during 12 months before index-date)	1.51	0.79–2.90
Simplified model		
CKD stage		
Stage 5	0.33	0.09–1.14
Dialysis	0.19	0.08–0.44*
Previous treatment for HK (during 12 months before index-date)	1.60	0.85–3.02

Absence of CKD used as reference category; *indicates statistical significance (p-value <0.05).

Stratification showed that 11.7% of short-term treated patients maintained or initiated RAASi therapy, whereas 7.8% of long-term treated patients did the same.

HCRU and costs among SZC patients treated with RAASi. During the first 6 months of follow-up (excluding deaths), HCRU was evaluated among patients treated with RAASi, stratified by treatment discontinuation. A total of 239 RAASi-treated patients were included in the analysis, with 131 patients experiencing RAASi treatment discontinuation and 108 patients maintaining continuous treatment. On average, patients received 17.7 prescriptions (SD 7.8, median 17.0). Among those with discontinuation, the mean was 17.1 prescriptions (SD 7.9, median 16.0), while patients without discontinuation averaged 18.5 prescriptions (SD 7.8, median 18.0). The mean number of prescriptions related to HK was 3.3 (SD 1.8, median 3.0) across all patients. Patients with discontinuation had a mean of 3.1 (SD 1.8, median 3.0), compared to 3.5 (SD 1.9, median 3.5) for those without discontinuation. Patients averaged 6.5 prescriptions (SD 3.8, median 6.0) for cardiorenal conditions. Those with discontinuation had a mean of 5.6 prescriptions (SD 3.7, median 5.0), while those without discontinuation had a mean of 7.5 prescriptions (SD 3.7, median 7.0). The average number of hospitalizations was 0.4 (SD 0.9, median 0.0) across all patients. Patients with discontinuation averaged 0.5 hospitalizations (SD 0.9, median 0.0), compared to 0.3 hospitalizations (SD 0.8, median 0.0) for those without discontinuation. No HK-related hospitalizations were recorded on average across all patient groups. Patients averaged 14.0 outpatient specialist services (SD 24.8, median 5.0). Patients with discontinuation averaged 15.2 services (SD 27.4, median 4.0), while those without discontinuation averaged 12.6 services (SD 21.4, median 5.0) (Table 6).

In this descriptive analysis of healthcare costs during the initial 6-month follow-up period, RAASi-treated patients were stratified by treatment discontinuation status. Among patients with RAASi treatment discontinuation ($N = 128$), average costs were generally higher across several healthcare expenditure categories compared to those without discontinuation ($N = 107$). Specifically, patients with discontinuation incurred higher average costs for drugs (3,097 € vs. 2,630 €), HK-related drugs (1,273 € vs. 1,110 €), and outpatient specialist services, including dialysis (1,848 € vs. 1,773 €). Additionally, hospitalization costs were elevated among discontinuers (1,384 € vs. 1,087 €).

Discussion

Hyperkalemia can be a persistent condition for several patients, especially those with CKD, diabetes, heart failure,

Table 6. Average HCRU per patient during the first 6 months of follow-up, stratified by duration of treatment discontinuation.

	RAASi-treated patients ($N = 239$)	RAASi-treated patients with discontinuation ($N = 131$)	RAASi-treated patients without discontinuation ($N = 108$)
Number of drug prescriptions	17.7 (7.8); 17.0	17.1 (7.9); 16.0	18.5 (7.8); 18.0
Number of HK-related drug prescriptions	3.3 (1.8); 3.0	3.1 (1.8); 3.0	3.5 (1.9); 3.5
Number of cardiorenal drug# prescriptions	6.5 (3.8); 6.0	5.6 (3.7); 5.0	7.5 (3.7); 7.0
Number of hospitalizations	0.4 (0.9); 0.0	0.5 (0.9); 0.0	0.3 (0.8); 0.0
Number of HK-related hospitalizations	0.0 (0.0); 0.0	0.0 (0.0); 0.0	0.0 (0.0); 0.0
Number of outpatient specialist services	14.0 (24.8); 5.0	15.2 (27.4); 4.0	12.6 (21.4); 5.0

Data are given as mean (SD) and median.
HK-related drug refers to the prescription of (at least one ATC code): SZC, patiromer and polystyrensulphonate; #cardiorenal drug refers to the prescription of (at least one ATC code): RAASi, beta-blockers, calcium channel blockers, loop diuretics, digitalis, nitrates. Abbreviations. HK, hyperkalemia; RAASi, renin-angiotensin-aldosterone system inhibitors, SD, standard deviation; SZC, sodium zirconium cyclosilicate.

emphasizing the necessity of effective long-term therapeutic control of sK+[17]. In the last few years, HK has received renewed attention following the reimbursement of innovative oral potassium binders in Italy in September 2021[18,19]. The focus on HK is justified by concerns about this often asymptomatic and potentially life-threatening electrolyte disorder and the associated under-prescription of beneficial RAASi drugs in patients with heart failure or CKD. We investigated the current use of SZC for the treatment of HK in Italian clinical practice, particularly focusing on treatment patterns, adherence, HCRU, and direct healthcare costs.

From a database including around 6.0 million health-assisted individuals, 355 subjects were treated with SZC from January 2022 to June 2023. The cohort was relatively old (mean age of 70.4 years), predominantly consisting of male subjects (64.2%), and with a major burden of comorbidities. CKD was present in 69.3% of the subjects, with 47.6% of them on dialysis. Other common conditions included arterial hypertension (57.5%), diabetes mellitus (43.4%), and heart failure (23.4%). These findings are consistent with the existing literature on HK management in similar populations[20–24].

The distribution of sK + levels showed that 42.0% of patients had levels $\geq$5.5 mmol/L, with 29.0% specifically experiencing severe HK (>6.0 mmol/L), underscoring the necessity for effective management strategies. Furthermore, almost one-third of patients (27.3%) had previously been treated with resins.

Most of the SZC patients (83.1%) received short-term maintenance treatment ($\leq$90 days) over 6 months of follow-up, with only 16.9% receiving long-term treatment (>90 days).

HCRU analysis revealed extensive drug prescriptions and access to outpatient services. As expected, long-term SZC treated patients had a higher consumption of resources driven by the drug component. Nevertheless, long-term treatment with SZC contributed to a 16% healthcare cost reduction compared to short-term treatment. These findings might be explained by the fact that in the long-term, the increased drug costs are feasibly due to the maintenance of RAASi plus potassium binders therapy, in front of reduced total healthcare expenditures, mainly driven by cost savings for dialysis and OSS. Indeed, baseline characteristics differ substantially between long-term and short-term users of SZC. Notably, dialysis status and prior prescription of RAASi within six months before inclusion emerged as significant predictors of short-term SZC use. It may be hypothesized that long-term SZC users represent a less severe patient population compared to short-term users. This could explicate the observed trend toward lower healthcare costs, excluding pharmaceutical expenditures (SZC and RAASi), associated with prolonged SZC use. Specifically, while long-term users incur predictably higher costs related to pharmacological treatment, other healthcare expenditures, such as hospitalizations and outpatient specialist services, appear to be lower, likely reflecting a relatively better overall clinical status. This interpretation is further supported by the predictive association between prior RAASi therapy and long-term SZC use, although statistical significance was observed only in univariate analysis. RAASi treatment is known to elevate serum potassium (sK+) levels, yet it also confers significant prognostic benefits in this patient population.

Our data are in agreement with a recent cost-effectiveness analysis conducted in Norwegian and Swedish clinical settings to predict long-term health economic outcomes of treating HK with SZC versus other therapies. The model revealed that SZC was highly cost-effective in comparison to usual care, showing an incremental cost-effectiveness ratio of €14,838/QALY €14,352/QALY in Norway and Sweden, respectively. As observed in the present real-world analysis, the purchase cost of SZC was largely counterbalanced by cost savings associated with reductions in acute HK events and hospital admissions[25].

Multivariate regression analysis identified dialysis as a significant predictor of short-term treatment, indicating that dialysis patients are less likely to remain on long-term SZC therapy. Conversely, previous RAASi treatment was associated with long-term SZC use, reflecting the ongoing need to manage HK in patients receiving RAASi therapy, which is known to increase sK + levels but also to significantly improve prognosis in these patients.

Subgroup analysis of RAASi-treated patients revealed high rates of RAASi discontinuation (54%), in particular among short-term SZC users, feasibly due to concerns over HK exacerbated by RAASi. These findings suggest that, consistent with previous international reports, in the Italian real clinical practice RAASi therapy is still discontinued (or down-titrated) in patients with HK, preventing patients with CKD or heart failure from getting the full cardiorenal benefits associated with optimal, guideline-directed RAASi use[26]. Interestingly, patients on long-term SZC treatment were able to continue RAASi therapy more frequently than those on short-term SZC, and those who maintained RAASi therapy experienced a 15% reduction in HCRU and the deriving healthcare costs, highlighting the potentially improved management of HK in patients treated with SZC who were still on RAASi therapy. A very recent multinational cohort study in US, Japan and Spain evaluated the likelihood of maintained or up-titrated RAASi therapy after at 6 months from HK in patients with CKD and/or heart failure among SZC users vs. patients without any potassium binder prescription. The aggregated meta-analyzed data across the three countries showed that patients treated with SZC had more chances to maintain guideline-concordant RAASi therapy at 6 months following HK, with respect to those with potassium binder treatment[27].

This study has various limitations. First of all, the observational design; however, the study has a descriptive nature, so no multivariable adjustments or propensity score matching were performed to account for patient differences. Another point is that the study is based on secondary data, and specifically on a retrospective database combining administrative and laboratory data, which was not created for research purposes: this could lead to information bias. Although treatments with SZC and other medications for chronic conditions (such as RAASi) are likely to be prescribed under NHS reimbursement, the mere record of a filled prescription does not confirm that the patient took the drug as prescribed. Additionally, proxies used to measure treatment persistence and implementation in claims data studies are based on numerous assumptions (e.g. daily dose, grace period) that can significantly impact the analysis outcomes, making interpretation challenging. Moreover, since our analysis of HCRU and direct costs during follow-up periods was unadjusted (due to the lack of a comparison group not treated with SZC), these results should be interpreted with caution. Another point that deserves mention is the reliance on the ICD-9-CM coding system currently used in Italy, which, despite updates for emerging conditions such as COVID-19, lacks the specificity and international comparability of ICD-10-CM. This may affect the accuracy and interoperability of health data, potentially impacting cross-national analyses. While efforts to transition to ICD-10 have been underway since 2010, the process remains incomplete, limiting the full adoption of a more detailed and standardized classification system[28].

Nonetheless, the strengths of this study include its large, geographically representative dataset that comprises all adult age groups and the distinction of being the first real-world study of its kind for the use of SZC in Italy.

Conclusion

This study provides a comprehensive overview of SZC use for HK treatment in Italy, revealing important patterns in patient demographics, treatment adherence, healthcare utilization, and direct healthcare costs. The findings indicate that long-term treatment with SZC supports greater persistence with RAASi therapy, which is associated with significant clinical benefits and reduced healthcare costs due to fewer hospitalizations and outpatient services, in turn resulting in a noticeable alleviation of the economic burden due to hospitalizations and outpatients services. The findings emphasize the need for a change of attitude from the clinicians to improve long-term treatment and effective management of HK, especially in patients with significant comorbidities such as CKD and/or heart failure. Future research should focus on interventions to enhance adherence and explore the long-term benefits of SZC in broader patient populations and observation time.

Transparency

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M.G., F.D., V.M., am, N.C., A.R.M. are AstraZeneca employees. The other authors have no competing interest to disclose. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Conceptualization: M.G., M.N., L.D.E.; Data curation: M.L.; Study design and supervision: M.G., F.D., V.M., am, N.C., A.R.M., L.D.E.; Writing – original draft, review & editing: M.N. All authors have read and agreed to the published version of the manuscript.

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Data sharing statement

All data used for the current study are available upon reasonable request to CliCon S.r.l. Società Benefit, which is the body entitled to data treatment and analysis by Local Health Units.

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