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ORIGINAL RESEARCH

Impact of Sodium Zirconium Cyclosilicate Plus Renin–Angiotensin–Aldosterone System Inhibitor Therapy on Short-Term Medical Costs in Hyperkalemia: OPTIMIZE II Real-World Study

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ABSTRACT

Introduction: Patients receiving cardiorenal-protective renin–angiotensin–aldosterone system inhibitors (RAASis) are at increased risk of developing hyperkalemia, which is associated with increased medical costs. The aim of this study was to evaluate the impact of adding sodium zirconium cyclosilicate (SZC) therapy on 3-month medical costs in patients who experienced hyperkalemia while receiving RAASi therapy.

Methods: The retrospective OPTIMIZE II study used medical and pharmacy claims data from IQVIA PharMetrics® Plus. Patients aged ≥ 18 years who received SZC (≥ 60 day supply over 3 months' follow-up) and continued RAASi between July 2019 and December 2021 (Continue RAASi + SZC cohort) were 1:1 exact and propensity score matched with patients who discontinued RAASi after hyperkalemia diagnosis and did not receive SZC (Discontinue RAASi + no SZC cohort). The primary outcome was hyperkalemia-related medical costs to payers over 3 months; all-cause medical and pharmacy costs were also analyzed.

Results: In the Continue RAASi + SZC (n = 467) versus Discontinue RAASi + no SZC (n = 467) cohort, there were significant reductions in mean per-patient hyperkalemia-related medical costs (reduction of $2216.07; p = 0.01) and all-cause medical costs (reduction of $6102.43; $p < 0.001$); mean hyperkalemia-related inpatient medical costs and all-cause

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inpatient and emergency department medical costs were significantly reduced. The reduction in all-cause medical cost in the Continue RAASi + SZC cohort offset an increase in the mean per-patient all-cause pharmacy cost (increase of $3117.71; $p < 0.001$).

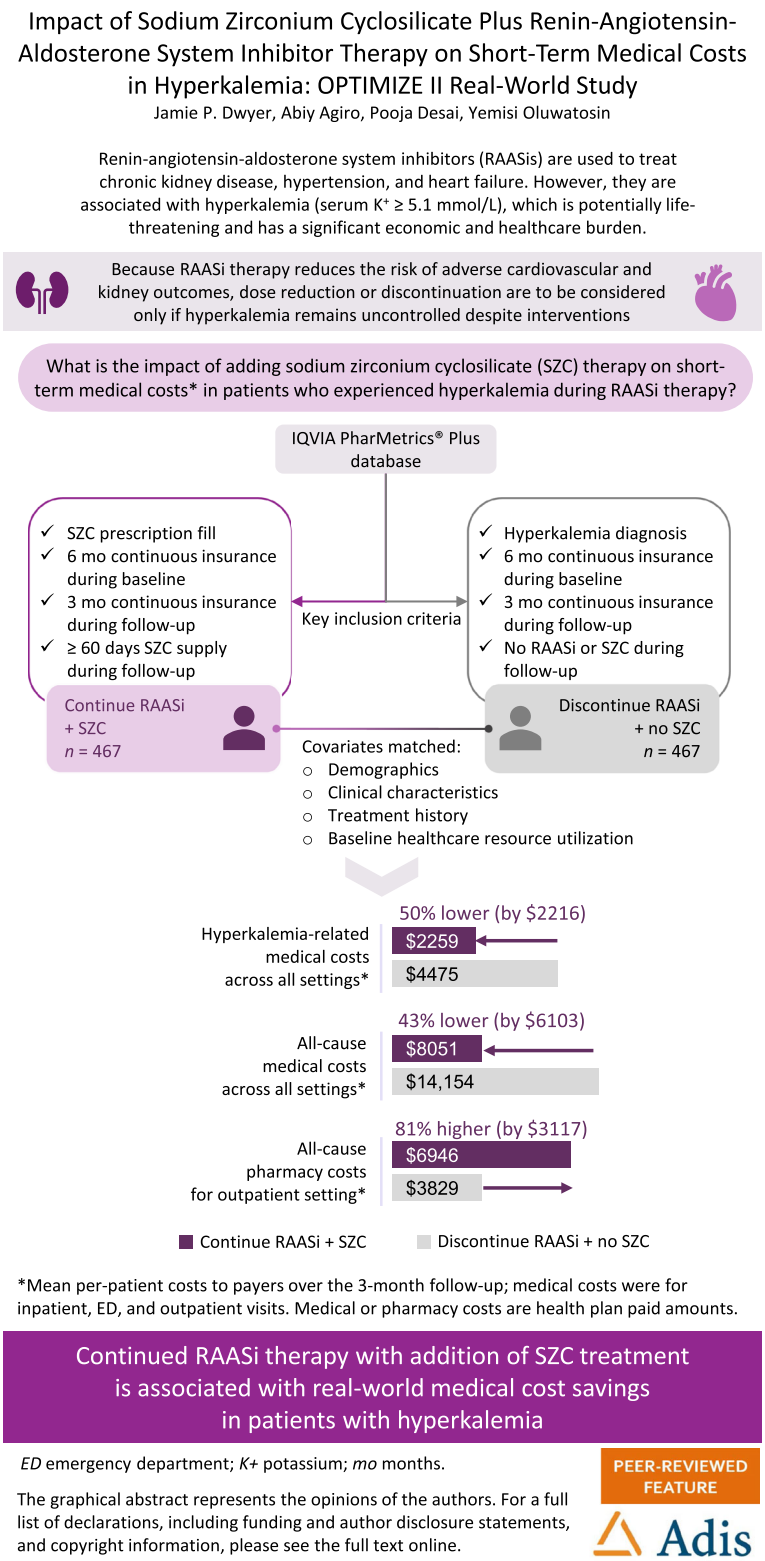
Conclusion: RAASi therapy has well-established cardiorenal benefits. In OPTIMIZE II, management of RAASi-induced hyperkalemia with SZC was associated with lower hyperkalemia-related and all-cause medical costs than RAASi discontinuation without SZC, demonstrating medical cost savings with maintaining RAASi therapy with SZC.

Keywords: Cost; Healthcare resource utilization; Hyperkalemia; Potassium; Renin–angiotensin–aldosterone inhibitor; Sodium zirconium cyclosilicate

PLAIN LANGUAGE SUMMARY

Renin–angiotensin–aldosterone system inhibitors (RAASis) are a standard drug therapy for high blood pressure, heart failure, or chronic kidney disease to reduce the risk of kidney disease progression, death, and cardiovascular events including stroke, heart attack, and hospitalization for heart failure. However, RAASis can cause abnormal increases in blood potassium (hyperkalemia), which can be life-threatening. RAASi discontinuation is often used to resolve hyperkalemia. In contrast, treatment with sodium zirconium cyclosilicate (SZC) to reduce potassium levels can allow patients with hyperkalemia to continue taking RAASis. We studied the effect of adding SZC on medical costs paid by health insurance for patients who experienced hyperkalemia while taking RAASis. We used insurance claims data to compare medical costs (costs for inpatient, emergency department, and outpatient visits) over a 3-month period for 467 patients continuing RAASis and adding SZC with those for a matching group of 467 patients who discontinued RAASis and did not take SZC after a hyperkalemia diagnosis. Average medical costs per patient were lower for the Continue RAASi + SZC group versus the Discontinue RAASi + no SZC group, with reductions of $2216.07 for hyperkalemia-related medical costs and $6102.43 for all-cause medical costs. Although the average all-cause pharmacy cost per patient was higher for the Continue RAASi + SZC group, the increase of $3117.71 was less than the reduction in average all-cause medical cost. Our study shows that for patients who develop hyperkalemia while taking RAASis, continuing RAASis and adding SZC can lower medical costs versus discontinuing RAASis and not adding SZC.

Graphical abstract:



Key Summary Points

Why carry out this study?

Renin–angiotensin–aldosterone system inhibitor (RAASi) discontinuation is often used to resolve hyperkalemia, although previous studies have shown that treatment with an oral potassium binder such as sodium zirconium cyclosilicate (SZC) allows most patients who experience hyperkalemia while on RAASi therapy to continue RAASi treatment.

Although it is well established that hyperkalemia is associated with increased healthcare resource utilization and costs, there are limited data on the impact of newer potassium binders such as SZC on medical costs in patients who develop hyperkalemia during RAASi treatment.

What did the study ask?

The aim of this real-world study was to evaluate medical costs to payers over 3 months' follow-up in commercially insured patients in the USA who developed hyperkalemia while on RAASi therapy; the authors used medical and pharmacy claims data to compare costs for matching cohorts of patients who continued RAASis and added SZC and patients who discontinued RAASis and did not add SZC after hyperkalemia diagnosis.

What was learned from the study?

Continued RAASi therapy and treatment with SZC was associated with significant reductions in mean per-patient hyperkalemia-related and all-cause medical costs (costs for inpatient, emergency department, and outpatient visits) compared with discontinued RAASi therapy and no SZC; although mean per-patient all-cause pharmacy costs were higher for patients who continued RAASi with SZC, this was offset by the reduction in all-cause medical costs.

The results of this study demonstrate that, in patients with RAASi-induced hyperkalemia, adding SZC and continuing RAASi treatment instead of discontinuing RAASi therapy can lead to medical cost savings in real-world clinical practice.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.23799072.

INTRODUCTION

Renin–angiotensin–aldosterone system inhibitors (RAASis) are a class of disease-modifying drugs that slow kidney disease progression and have also been shown to reduce the risk of death in patients with chronic kidney disease (CKD), heart failure (HF) with reduced ejection fraction, and diabetic kidney disease [1–7]. However, due to their mechanism of action, RAASis are known to be associated with hyperkalemia [8, 9], defined as serum potassium levels of 5.1 mmol/L or more [8, 10]. In addition, patients with CKD and/or HF have an increased risk of hyperkalemia compared with the general population regardless of RAASi use [11–13]. Hyperkalemia is potentially life-threatening [14] and is associated with a significant economic and healthcare burden [15–21].

Strategies for the management of hyperkalemia include dietary modifications to reduce potassium intake as well as treatment with diuretics, sodium bicarbonate, and potassium binders (also known as gastrointestinal cation exchangers) [16, 22]. Previously, reduction of the RAASi dose or discontinuation of RAASi therapy entirely was recommended for patients who experience hyperkalemia while receiving RAASi therapy [8, 22]. This management strategy poses a therapeutic dilemma because discontinuation of RAASi therapy can lead to worse cardiovascular and kidney outcomes and

increased risk of hospitalization and mortality [8]. Therefore, updated Kidney Disease Improving Global Outcomes and American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines recommend RAASi dose reduction or discontinuation as a last resort, only if hyperkalemia remains uncontrolled despite interventions [6, 7].

Newer treatment options for patients who develop hyperkalemia while receiving RAASi therapy include sodium zirconium cyclosilicate (SZC) and patiromer. In clinical trials, these therapies have been shown to effectively treat hyperkalemia and up to 89% of patients remained on RAASi therapy [6, 7, 23, 24]. In addition, real-world evidence also showed that about 83% of patients with hyperkalemia treated with SZC maintained RAASi therapy [25]. However, although there is clear evidence that hyperkalemia is associated with increased healthcare resource utilization [15–18, 20], there are limited data on whether these newer potassium binders may reduce medical costs in patients who develop hyperkalemia while receiving RAASi therapy. To address this, the current real-world study aimed to describe the impact of adding the newer potassium binder, SZC, on 3-month medical costs in patients who experienced hyperkalemia while receiving RAASi therapy.

METHODS

Data Source

The source for all data used in this study was the PharMetrics® Plus closed claims database, which was accessed via the Instant Health Data (IHD) platform (Panalgo, Boston, MA). This database is representative of the commercially insured US national population for patients under 65 years of age.

Ethical Approval

This study used de-identified patient data in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and was therefore considered exempt from institutional review board approval or requirement for informed consent from individual patients, as per article 45 §CFR 164.514(e). This study was performed in accordance with the Declaration of Helsinki of 1964 and its later amendments.

The authors received permission to access and use medical and pharmacy claims data from the PharMetrics Plus database under license from IQVIA Inc. and as per signed agreement between AstraZeneca and IQVIA Inc.

Study Design and Sample Selection

OPTIMIZE II (Real-World Cost Outcomes Following Adoption of Sodium Zirconium Cyclosilicate to Utilize RAASi therapy) was a noninterventional, retrospective, propensity score matched, observational cohort study.

Data from patients aged 18 years or older who were receiving RAASi therapy, defined as any angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor neprilysin inhibitor, or mineralocorticoid receptor antagonist/aldosterone receptor antagonist, at baseline before a diagnosis of hyperkalemia were collected.

Patients were divided into two cohorts: Continue RAASi + SZC and Discontinue RAASi + no SZC. The Continue RAASi + SZC cohort consisted of patients on RAASi therapy who were prescribed at least 60 days' supply of SZC following at least one diagnosis of hyperkalemia between July 2019 and December 2021 and had at least one prescription of RAASi therapy filled during the 3-month follow-up period. The Discontinue RAASi + no SZC cohort consisted of patients on RAASi therapy who discontinued RAASi therapy and did not fill an SZC prescription following at least one diagnosis of hyperkalemia between July 2019 and December 2021; RAASi discontinuation was determined by an absence of RAASi therapy prescription fills during the 3-month follow-up period.

All patients were required to have continuous medical and pharmacy insurance coverage

of at least 6 months before (baseline period) and at least 3 months after (follow-up period) the index date. The index date was defined as the date of the first SZC prescription fill for the Continue RAASi + SZC cohort and as the date of the first diagnosis of hyperkalemia during the study period for the Discontinue RAASi + no SZC cohort. For patients with an index date in July 2019, the lookback period for the baseline period started from January 2019.

Study Measurements and Outcomes

The objectives of this analysis were to evaluate the impact of SZC therapy on short-term (3-month) hyperkalemia-related medical (non-pharmacy) costs in the inpatient, emergency department (ED), and outpatient settings, all-cause medical (non-pharmacy) costs in these practice settings, and all-cause outpatient pharmacy costs in patients who developed hyperkalemia while on RAASi therapy.

Patient demographics, characteristics, treatments, and all-cause healthcare resource utilization and costs were assessed during the 6-month baseline period. Persistence with SZC and RAASi therapy was assessed in the Continue RAASi + SZC cohort during the 3-month follow-up period. The use of other oral potassium binder therapy (sodium polystyrene sulfonate [SPS] or patiromer) during the follow-up period was assessed in both cohorts. The primary outcome was hyperkalemia-related medical costs to payers over the 3-month follow-up period in any treatment setting. Hyperkalemia-related medical costs included: inpatient admission with a diagnosis code for hyperkalemia in any diagnosis position; ED visit with a diagnosis code for hyperkalemia in any diagnosis position; and outpatient visit with a diagnosis code for hyperkalemia in any diagnosis position. The secondary outcome was hyperkalemia-related medical costs to payers over the 3-month follow-up period in the individual settings (inpatient, ED, or outpatient). All-cause medical costs for all settings and for the individual settings and all-cause outpatient pharmacy costs to payers during 3 months' follow-up were also analyzed as exploratory outcomes. Medical cost outcomes did not include pharmacy costs. ED visits that resulted in inpatient admission were counted as inpatient hospitalizations. Costs were based on the amounts paid by the health plan and were adjusted for inflation to 2021 constant United States dollars (USD). The costs were final payment amounts that were fully adjudicated by health plans. Health plan paid amounts for pharmacy costs do not exclude additional rebates and discounts provided to health plans.

Statistical Analyses

On the basis of a recent study of the impact of patiromer with continued RAASi therapy on costs in patients with hyperkalemia, which showed statistically significant reductions in all-cause medical costs when assessed in 232 matched pairs [26], it was estimated that the same number of patients would be required in this analysis. An initial sample count from PharMetrics Plus found that approximately 3394 patients had at least one outpatient fill of SZC therapy.

To balance the Continue RAASi + SZC and Discontinue RAASi + no SZC cohorts, exact and propensity score matching were used to adjust for differences in baseline variables (patient demographics, comorbidities, medications, and healthcare resource use) during the 6-month baseline period (Supplementary Material Table S1). Because health plan paid costs in real-world settings are sensitive to outliers, patients in the top 0.5% of medical costs were excluded from all cohorts before matching.

Patients in the two cohorts were exact matched on highly relevant factors before the propensity score matching procedure. The exact matching characteristics were age less than 65 years, baseline CKD, baseline end-stage kidney disease, baseline history of hyperkalemia, and baseline all-cause inpatient admissions. To preserve sample size and statistical power, the exact matching was limited to these five binary variables. A multivariable logistic regression model was used to estimate a propensity score, with 1:1 matching of cases and controls using a 0.02 caliper value without replacement. A

standardized mean difference threshold value of less than 0.2 was used to judge the adequacy of the multivariable regression adjustment and define the balance of covariates between matched cohorts.

Patient demographics, characteristics, treatments, and costs were assessed using descriptive statistics, with mean ± standard deviation (SD) and median and interquartile range (IQR) used for continuous variables and number and percentage of patients used for categorical variables. The differences in medical costs were compared between the matched cohorts using one-way analysis of variance tests for statistical significance to generate *p*-values. Costs were calculated and reported as mean (SD) cost per patient over the 3-month follow-up period.

All statistical analyses were performed within the IHD platform that is integrated with R, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). An analytic dataset was not downloaded from the IHD platform.

RESULTS

There were 406,765 patients with a diagnosis of hyperkalemia and 4615 who filled an SZC therapy prescription between July 1, 2019 and December 31, 2021 (Supplementary Material Table S2). Of the total patients with hyperkalemia, 19,888 patients met the inclusion criteria: 486 and 19,402 in the Continue RAASi + SZC and Discontinue RAASi + No SZC cohorts, respectively. After exact and propensity score matching, each cohort included 467 patients.

There were no significant differences between the two matched cohorts with regard to baseline demographics, clinical characteristics, treatments, or healthcare resource utilization, with all standardized mean differences between groups less than 0.2 (Table 1). In the Continue RAASi + SZC cohort, the mean ± SD age was 60.5 ± 13.8 years, 67.9% of patients were male, and 75.2% had CKD. In the Discontinue RAASi + No SZC cohort, the mean ± SD age was 61.3 ± 13.3 years, 69.0% of patients were male, and 75.2% had CKD. The most common hyperkalemia-related comorbidities in both patient cohorts were hypertension (91.0% of Continue RAASi + SZC cohort; 93.8% of Discontinue RAASi + No SZC cohort) and type 2 diabetes (63.4% of Continue RAASi + SZC cohort; 69.6% of Discontinue RAASi + No SZC cohort).

Prescribed Medications

In the Continue RAASi + SZC cohort, more than half of the patients were prescribed a 90-day supply of SZC, with a mean ± SD total supply of 99 ± 34.9 days. In this cohort, patients had a high persistence with both SZC and RAASi therapy, with mean ± SD proportion of days covered of 0.84 ± 0.17 for SZC and 0.96 ± 0.12 for RAASi; median (IQR) for proportion of days covered was 0.92 (0.66–0.97) for SZC and 1.00 (1.00–1.00) for RAASi. Only 9 (1.9%) patients in the Continue RAASi + SZC cohort were prescribed another oral potassium binder (SPS or patiromer) during the 3-month follow-up period. To preserve the real-world applicability of this study, these patients were not excluded or censored from the analysis. Few patients ($n = 44$; 9.4%) in the Discontinue RAASi + No SZC cohort started treatment with a non-SZC oral potassium binder (SPS or patiromer) during the 3-month follow-up period. Again, these patients were not excluded or censored from the analysis to preserve the real-world applicability of this study.

Costs

Over the 3-month follow-up period, mean hyperkalemia-related medical (non-pharmacy) costs were 49.5% lower per patient in the Continue RAASi + SZC cohort ($2259.24 ± $13,739.50) compared with those for the Discontinue RAASi + No SZC cohort ($4475.31 ± $13,828.22), with a significant difference in mean per-patient medical cost of $2216.07 ($p = 0.01$) between cohorts (Fig. 1). This significant difference in hyperkalemia-related medical costs was driven by a significant reduction in mean hyperkalemia-related inpatient medical costs in the Continue RAASi +

Table 1 Baseline demographics, clinical characteristics, treatments, and healthcare resource utilization

	Discontinue RAASi + No SZC cohort (*n* = 467)	Continue RAASi + SZC cohort (*n* = 467)	Standardized mean difference
Age, years			
Mean ± SD	61.3 ± 13.3	60.5 ± 13.8	0.06
Median (IQR)	61 (54–70)	61 (52–70)	
Sex, *n* (%)			
Female	145 (31.1)	150 (32.1)	0.02
Male	322 (69.0)	317 (67.9)	
Payer, *n* (%)			
Commercial	319 (68.3)	350 (74.9)	0.15
Medicare advantage	148 (31.7)	117 (25.1)	
US census region, *n* (%)			
Midwest	140 (30.0)	131 (28.1)	0.03
Northeast	48 (10.3)	60 (12.8)	
South	204 (43.7)	210 (45.0)	
West	75 (16.1)	66 (14.1)	
Charlson comorbidity index score			
Mean ± SD	2.65 ± 1.98	2.47 ± 1.69	0.10
Comorbidities during baseline, *n* (%)			
CKD	351 (75.2)	351 (75.2)	0.00
ESKD	87 (18.6)	87 (18.6)	0.00
Heart failure	90 (19.3)	78 (16.7)	0.07
Type 2 diabetes	325 (69.6)	296 (63.4)	0.13
Hypertension	438 (93.8)	425 (91.0)	0.10
CAD	125 (26.8)	97 (20.8)	0.15
Dyslipidemia	307 (65.7)	304 (65.1)	0.01
Arrythmia	40 (8.6)	41 (8.8)	0.01
Prior hyperkalemia	265 (56.7)	265 (56.7)	0.00
COVID-19	13 (2.9)	14 (3.0)	0.01
Treatments during baseline, *n* (%)			
Dialysis	59 (12.6)	58 (12.4)	0.01
Cardiovascular medications[a]	453 (97.0)	445 (95.3)	0.08

Table 1 continued

	Discontinue RAASi + No SZC cohort (n = 467)	Continue RAASi + SZC cohort (n = 467)	Standardized mean difference
Glucose-lowering medications[b]	255 (54.6)	252 (54.0)	0.01
Medications during baseline, n (%)			
Potassium binders	85 (18.2)	88 (18.8)	0.02
RAASi therapy[c]	467 (100.0)	467 (100.0)	0.00
Healthcare resource utilization during baseline, n (%)			
All-cause inpatient hospitalizations	81 (17.3)	81 (17.3)	0.00
All-cause ED visits	126 (27.0)	100 (21.4)	0.14
All-cause medical costs during baseline, $US			
Mean ± SD	13,027.42 ± 23,185.04	13,479.94 ± 25,896.46	0.02
Median (IQR)	3191.04 (896.49–13,764.48)	2220.27 (558.54–12,054.71)	
Hyperkalemia-related medical costs during baseline, $US			
Mean ± SD	3726.41 ± 12,776.29	2358.07 ± 8953.14	0.15
Median (IQR)	26.36 (0–486.80)	19.13 (0–363.46)	

CAD coronary artery disease, *CKD* chronic kidney disease, *ED* emergency department, *ESKD* end-stage kidney disease, *IQR* interquartile range, *RAASi* renin–angiotensin–aldosterone system inhibitor, *SD* standard deviation, *SZC* sodium zirconium cyclosilicate, *US* United States

[a]Cardiovascular medications: alpha blockers, beta blockers, calcium channel blockers, anticoagulants, antiplatelets, lipid-lowering drugs, loop diuretics, and thiazide diuretics

[b]Glucose-lowering medications: metformin, sulfonylureas, dipeptidylpeptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, insulin, and thiazolidinediones

[c]RAASi therapy: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists/aldosterone receptor antagonists

SZC cohort ($1697.12 ± $12,688.32) versus the Discontinue RAASi + No SZC cohort ($3861.10 ± $13,690.18) with a significant reduction in mean per-patient medical cost of 56.1% ($2163.98; $p = 0.02$; Fig. 2a). There were no significant differences between cohorts in hyperkalemia-related ED and outpatient medical costs over the 3-month follow-up period. Median (IQR) hyperkalemia-related medical costs are presented in the Supplementary Material (Table S3).

Mean all-cause medical (non-pharmacy) costs were also significantly reduced over the 3-month follow-up period in the Continue RAASi + SZC cohort ($8051.08 ± $20,167.81) versus the Discontinue RAASi + No SZC cohort ($14,153.51 ± $29,826.25), by 43.1% ($6102.43; $p < 0.001$) per patient (Fig. 1). This significant difference in all-cause medical costs was driven by the significant difference in mean inpatient medical costs and mean ED medical costs. The mean inpatient medical costs were $2899.91 ± $15,860.29 for the Continue RAASi + SZC cohort and $7822.22 ± $23,895.43 for the Discontinue RAASi + No SZC cohort, corresponding to a between-cohort difference of $4922.31 (62.9% reduction; $p < 0.001$; Fig. 2b). Mean ED medical

costs were \$290.50 ± \$1300.07 for the Continue RAASi + SZC cohort and \$724.90 ± \$2569.20 for the Discontinue RAASi + No SZC cohort, resulting in a difference of 59.9% (\$434.40; $p = 0.003$) between cohorts (Fig. 2b). No significant difference in all-cause outpatient medical costs was observed between cohorts.

The reduction in all-cause medical (non-pharmacy) costs in the Continue RAASi + SZC cohort offset an increase in mean all-cause pharmacy costs versus the Discontinue RAASi + No SZC cohort of \$3117.71 ($p < 0.001$) per patient. Over the 3-month follow-up period, patients in the Continue RAASi + SZC cohort had a mean \$6946.29 ± \$13,146.17 all-cause pharmacy cost, while patients in the Discontinue RAASi + No SZC cohort had a mean \$3828.58 ± \$9046.16 all-cause pharmacy cost. Median (IQR) all-cause medical and pharmacy costs are presented in the Supplementary Material (Table S3).

DISCUSSION

In this noninterventional, retrospective study of US medical and pharmacy claims data of patients who experienced hyperkalemia while receiving RAASi therapy, SZC with continued RAASi therapy was associated with reduced hyperkalemia-related and all-cause medical (non-pharmacy) costs compared with no SZC therapy and RAASi discontinuation after hyperkalemia diagnosis. The reduced medical costs with SZC treatment were driven by reductions in hyperkalemia-related and all-cause inpatient medical costs and all-cause ED medical costs. The reduction in all-cause medical costs with SZC treatment offset an increase in all-cause pharmacy costs.

To our knowledge, this is the first study to describe the impact of SZC, a newer potassium binder, on short-term medical costs in patients who developed hyperkalemia while receiving RAASi therapy. A retrospective, propensity score matched cohort study of the newer potassium binder, patiromer, has been reported [26]. That study, which used de-identified data (2016 to 2019) from Optum Clinformatics® Data Mart, found that patiromer-treated patients who continued RAASi therapy ($n = 84$) had a 40% decrease in mean all-cause medical costs over 3 months of \$6209 per patient; mean all-cause medical costs were \$9135 for patients treated with patiromer who continued RAASi versus \$15,344 for matched patients without patiromer treatment who discontinued RAASi therapy after hyperkalemia diagnosis ($p = 0.006$). This reduction was driven by reductions in all-cause outpatient and ED medical costs among patiromer-treated patients who continued RAASi therapy. Inpatient medical costs were not different between matched patients treated with or without patiromer. Hyperkalemia-related medical costs were not assessed in the patiromer study.

The results of the OPTIMIZE II study also support the findings of a real-world analysis that indicated that optimizing RAASi therapy and effectively managing hyperkalemia may reduce medical costs in patients with CKD and/or HF [27].

Prospective randomized controlled trials evaluating the efficacy and safety of continuing RAASi therapy with the addition of SZC treatment in patients with hyperkalemia have been published or are ongoing. REALIZE-K (NCT04676646) is an ongoing, double-blind, placebo-controlled, parallel-group, randomized clinical trial evaluating SZC for the management of hyperkalemia in patients with symptomatic HF with reduced ejection fraction (HFrEF) receiving mineralocorticoid receptor antagonist therapy [28]. This prospective clinical trial will provide long-term safety and efficacy results over a follow-up period of 6 months. The REALIZE-K study is currently recruiting patients and is expected to be completed in July 2024 [28]. PRIORITIZE-HF was a multicenter, double-blind, placebo-controlled, parallel group, randomized clinical trial that evaluated the efficacy and safety of using SZC to intensify RAASi therapy in patients with symptomatic HFrEF [29]. Although the study was terminated prematurely due to the COVID-19 pandemic, 3-month follow-up of 182 randomized patients provided reassuring safety results related to edema. Three (3.3%) patients in the SZC group and 1 (1.1%) patient in the placebo

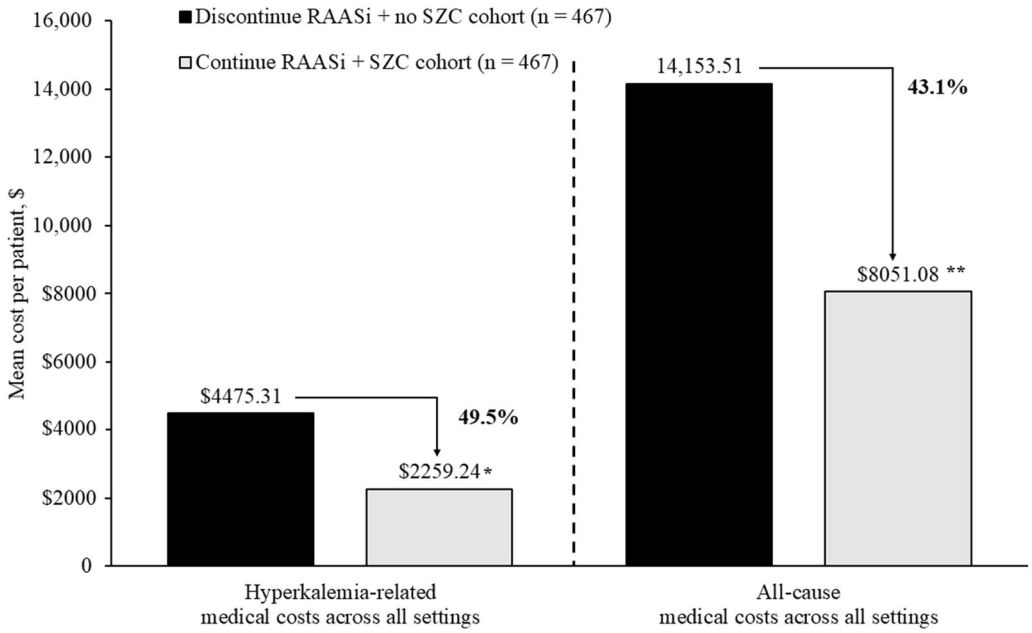


Fig. 1 Hyperkalemia-related and all-cause medical costs to payers across all settings in the Continue RAASi + SZC and Discontinue RAASi + no SZC cohorts over the 3-month follow-up period. Medical costs are adjusted for inflation to 2021 constant US dollars. *$p = 0.01$ vs Discontinue RAASi + No SZC cohort; **$p < 0.001$ vs Discontinue RAASi + No SZC cohort. *RAASi* renin–angiotensin–aldosterone system inhibitor, *SZC* sodium zirconium cyclosilicate

group experienced an edema-related adverse event [29].

The current study has several limitations, most of which are attributable to residual confounding from unobservable factors as a result of the nonrandomized, observational nature of its design and the use of retrospective insurance claims data. Therefore, medical cost reductions could result from factors other than SZC and continued RAASi therapy. In particular, the COVID-19 pandemic could have increased the number of hospitalizations in the study cohorts because COVID-19 has been shown to be associated with hyperkalemia [30]. Although the baseline rate of diagnosed COVID-19 was similar in the matched study cohorts (3%), residual confounding related to COVID-19 cannot be ruled out. Medical and pharmacy claims data do not capture mortality or reasons for treatment discontinuation. The use of medication samples for branded medications, the use of medications paid for entirely out of pocket by patients, and the use of generic medications, including RAASi therapy, that were not billed to insurers are not captured. In addition, data describing serum potassium levels and estimated glomerular filtration rates are not recorded in claims and were therefore not available for analysis, thus limiting our ability to account for the confounding effect of hyperkalemia severity on medical costs. There is potential for exposure misclassification in the comparison group because reasons for RAASi discontinuation after hyperkalemia diagnosis were not captured, so we were unable to determine the clinician's intention to manage hyperkalemia through RAASi discontinuation. The lack of serum potassium values is also a study limitation due to the resulting inability to identify alternative index dates for patients not treated with SZC. The requirement for continuous insurance coverage during the baseline and follow-up periods means the study results may not be generalizable to uninsured patients. Patients who discontinued insurance or switched insurance plans during the follow-up period were also excluded.

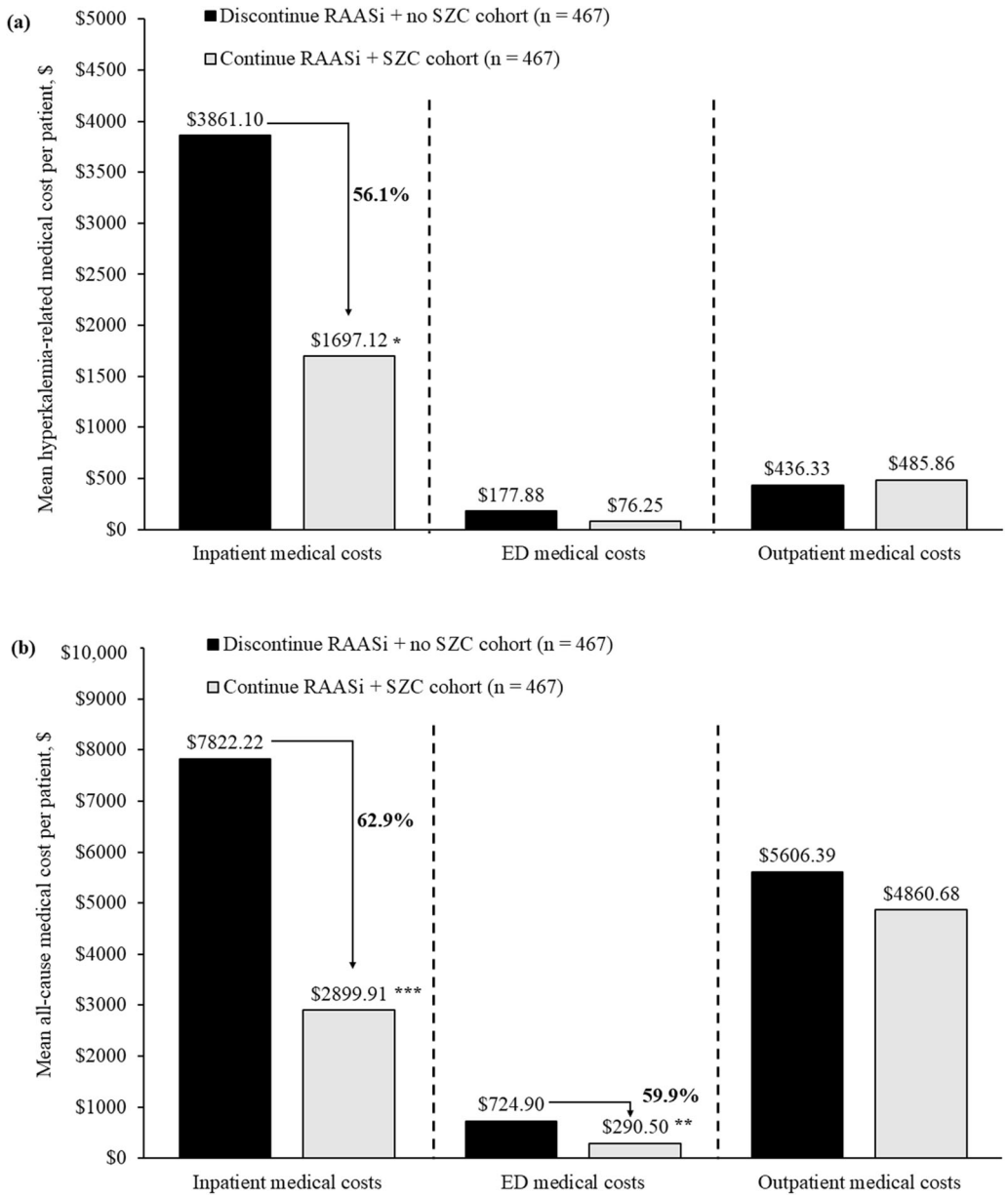


Fig. 2 **a** Hyperkalemia-related and **b** all-cause inpatient, emergency department, and outpatient medical costs to payers in the Continue RAASi + SZC and Discontinue RAASi + No SZC cohorts over the 3-month follow-up period. Medical costs are adjusted for inflation to 2021 constant US dollars. *p = 0.02 vs Discontinue RAASi + No SZC cohort; **p = 0.003 vs Discontinue RAASi + No SZC cohort; ***p = 0.001 vs Discontinue RAASi + No SZC cohort. *ED* emergency department, *RAASi* renin–angiotensin–aldosterone system inhibitor, *SZC* sodium zirconium cyclosilicate

The strengths of this study include the use of a large, geographically representative database and real-world patient data. As such, the patient population included is likely more representative of that seen in clinical practice than the study populations of clinical trials. Furthermore, the results of this study are more likely to reflect real-world medical and pharmacy cost patterns than those of modeled cost-effectiveness studies based on clinical trial results

projected to hypothetical populations. Finally, the use of both exact matching and propensity score matching in these analyses helps mitigate some of the potential biases that arise from real-world analysis of insurance claims data in terms of differences in patient characteristics, baseline comorbidities, medications, healthcare resource utilization, and costs. This matching improves the internal validity of the study.

CONCLUSION

In this real-world study of US patients who experienced hyperkalemia while receiving RAASi therapy, continued RAASi therapy and treatment with SZC was associated with significantly lower hyperkalemia-related and all-cause medical costs compared with those of discontinuing RAASi therapy and no treatment with SZC. The reduced medical costs with SZC treatment were driven by reductions in hyperkalemia-related and all-cause inpatient medical costs and all-cause ED medical costs. Importantly, the reduction in all-cause medical costs with SZC treatment offset an increase in all-cause pharmacy costs. The findings of this study demonstrate that medical cost savings by adding SZC to treat RAASi therapy-induced hyperkalemia, instead of discontinuing RAASi therapy, is achievable in a real-world setting.

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Compliance with Ethics Guidelines. This study used de-identified patient data in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and was therefore considered exempt from institutional review board approval or requirement for informed consent from individual patients, as per article 45 §CFR 164.514(e). This study was performed in accordance with the Declaration of Helsinki of 1964 and its later amendments.

Data Availability. This was a claims database analysis using IQVIA PharMetrics® Plus closed claims data obtained under license from IQVIA Inc. The raw data cannot be publicly shared because it was obtained from IQVIA Inc. and as per signed agreement between AstraZeneca and IQVIA Inc. However, we have provided all relevant data in the manuscript that supports the research objectives and conclusions. We confirm that interested researchers can contact IQVIA Inc. to access the data. For further information on data access, please contact IQVIA Inc.

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