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# Treatment Patterns of Patients with Hyperkalaemia Receiving Sodium Zirconium Cyclosilicate in Greece: A Multicenter Prospective Study

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## Abstract

**Background/Objectives**: Hyperkalaemia affects 2–4% of the general population. Real-world data in Greece are currently limited. The SHIELD study assessed treatment patterns and disease management of patients with hyperkalaemia in Greece. **Methods**: This prospective, multicenter, observational study was conducted in 12 hospital-based nephrology and cardiology units across Greece, with 11 having enrolled patients. The study enrolled patients with hyperkalaemia and chronic kidney disease (CKD) on dialysis or not, or heart failure (HF) under RAASi/MRAs, receiving sodium zirconium cyclosilicate (SZC), with a 6-month follow-up. **Results**: Overall, 125 patients participated in the study (51.2% CKD non-dialysis, 25.6% CKD on dialysis, and 23.2% HF patients receiving RAASi/MRAs), with a mean age of 64.7 years. At SZC initiation, the overall median serum potassium was 5.6 mmol/L (range: 5.1–7.7). At Visits 1, 2, and 3, the most frequently reported potassium monitoring interval was monthly (44.8%, 40.0%, and 41.4%, respectively). The overall median eGFR as calculated by CKD-EPI 2021 equation changed from 30.0 mL/min/1.73 $m^2$ at baseline to 24.5 at 3 months, and 27.0 at 6 months. CKD non-dialysis patients mostly received 10 g SZC daily, dialysis patients 5 g on non-dialysis days and HF patients 5 g daily, with limited changes over time. SZC plus an RAASi/MRA, mostly ARBs (72.2%), was administered to 63.2% of patients at baseline and 3 months, increasing to 69.0% at 6 months. A total of 84.8% of patients received antihypertensive, 56.8% lipid-lowering, 39.2% antiplatelet, 40.0% antidiabetic and 4.8% corticosteroid agents. **Conclusions**: The SHIELD study provides real-world evidence on patient characteristics, monitoring practices, and treatment patterns, including the combination of SZC and RAASi/MRAs, in patients with hyperkalaemia in Greece.

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**Keywords:** chronic kidney disease; heart failure; hyperkalaemia; observational prospective study; sodium zirconium cyclosilicate

## 1. Introduction

Hyperkalaemia is generally defined as a serum or plasma potassium level higher than 5.0 mEq/L [1,2] and can be classified as mild (>5.0 to <5.5 mEq/L), moderate (5.5 to 6.0 mEq/L) and severe (>6.0 mEq/L) [3], with thresholds varying across guidelines [3,4]. In the general population, its prevalence is approximately 2–4%, increasing substantially among patients with chronic kidney disease (CKD), heart failure (HF), and those treated with renin–angiotensin–aldosterone system inhibitors (RAASi) [5] and/or mineralocorticoid receptor antagonists (MRAs) [6–8]. In hospital settings, the reported incidence varies widely (1–10%), reflecting heterogeneity in patient characteristics, monitoring frequency, and diagnostic criteria [5,8,9].

Current clinical guidelines emphasize the importance of hyperkalaemia management to maintain treatment with disease-modifying drugs, such as RAASi and MRAs, in high-risk patients. Recently, several guidelines have introduced potassium binder use in selected patients with advanced CKD, on dialysis or not, or HF with persistent hyperkalaemia who are not receiving optimal RAASi/MRA therapy [10].

Sodium zirconium cyclosilicate (SZC) is an orally administered, inorganic crystalline compound approved in 2018 for the treatment of adults with hyperkalaemia. Clinical trials in patients with CKD and HF have demonstrated that SZC effectively lowers serum potassium and maintains normokalaemia, with a generally mild to moderate safety profile [11–13]. Nevertheless, real-world data on SZC use remain limited, particularly in local clinical practice across CKD populations.

The SHIELD study was conducted in Greece to record treatment patterns and disease management of patients with hyperkalaemia and CKD (under dialysis or not), or HF receiving RAASi/MRAs, treated with SZC in routine care of hospital- and clinic-based nephrology, or cardiology units.

## 2. Materials and Methods

### *2.1. Study Design and Objectives*

The SHIELD study was a national, multicenter, prospective, observational study, recording patient characteristics, routine clinical practice and treatment patterns in hyperkalaemia patients with CKD under dialysis or not, or HF, all treated with SZC as per SmPC in Greece. The study was conducted in 12 hospital-based nephrology and cardiology units across Greece, with 11 having enrolled patients, over three visits (baseline, 3 and 6 months). Total duration was 12 months, comprising up to 6 months of recruitment and 6 months of follow-up per patient. The study was designed and conducted in compliance with the Declaration of Helsinki, the European Union General Data Protection Regulation (GDPR), the Guidelines for Good Pharmacoepidemiology Practices (GPP), applicable national regulations, and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. All participants provided written informed consent and were notified about their withdrawal rights. The study was first approved by the Scientific Council of University Hospital of Larissa (approval number: 48186) and was registered at ClinicalTrials.gov. (ClinicalTrials.gov ID: NCT06185660, https://clinicaltrials.gov/study/NCT06185660?rank=1) (accessed on 1 October 2026). Table 1 presents the study's primary and secondary objectives.

**Table 1.** Primary and secondary study objectives.

| |
|---|
| Primary objective |
| • To describe the treatment patterns and patient characteristics of patients with hyperkalaemia receiving SZC, by recording any pharmacological and other intervention administered, including dose and frequency of administration at baseline and at 3 and 6 months. |
| Secondary objectives |
| • To describe hyperkalaemia management by assessing the following:<br>- RAASi/MRAs dose modification or discontinuation, by recording RAASi/MRAs dose and frequency of administration at baseline and at 3 and 6 months<br>- Potassium level that initiates intervention, by recording serum potassium value at treatment onset, if available, at baseline<br>- Frequency of serum potassium level monitoring, as per investigators' practice, by recording serum potassium test frequency (not serum potassium values) at baseline and at 3 and 6 months<br>- Adherence to treatment with SZC, by recording the number of patients receiving SZC at baseline and at 3 and 6 months<br>- Patient characteristics, by recording information on gender, age, race, medical history/comorbidities at baseline, and by recording alcohol/tobacco/exercise habits at baseline and at 3 and 6 months. |

### *2.2. Study Population and Eligibility Criteria*

Adults with hyperkalaemia (serum potassium > 5.0 mmol/L) treated with SZC were consecutively enrolled, including patients with non-dialysis CKD, dialysis-dependent CKD, or HF receiving RAASi/MRA therapy. Inclusion and exclusion criteria are illustrated in Table 2.

**Table 2.** Inclusion and exclusion criteria.

| |
|---|
| Inclusion criteria |
| • Signed informed consent form<br>• Age ≥ 18 years at the time of consent<br>• Patients treated with sodium SZC for hyperkalaemia at the time of enrolment and who had started receiving SZC at least 10 days before enrolment<br>• Patients diagnosed with hyperkalaemia (S-$K^+$ > 5.0 mmol/L), and with CKD not on dialysis (Group 1) or on dialysis (Group 2), or with HF, receiving RAASi/MRAs therapy (Group 3) |
| Exclusion criteria |
| • Patients who were pregnant, breast-feeding, or planning to become pregnant<br>• Patients participating in another clinical trial<br>• Presence of a condition that, in the opinion of the investigator: (i) would put the subject at undue risk, or (ii) would potentially jeopardize the quality of the data to be generated, or (iii) would, for some other reason, make the patient inappropriate for this study |

### *2.3. Data Source*

Sites and investigators were selected nationwide to represent the national management of CKD patients (dialysis or non-dialysis), or HF patients receiving RAASi/MRAs, treated with SZC as per SmPC. Site selection was based on a documented feasibility assessment of physician qualifications, prior study participation, and experience with similar studies. Data was collected prospectively during study visits according to routine clinical practice, while patients' medical histories were retrieved retrospectively from medical charts. Data sources

included routine clinical assessments, physician notes, and medical charts. Physicians recorded patient management as per standard care. Documentation from routine clinical practice, as provided by the investigators, was used as source documentation, and relevant data were entered into the eCRF to ensure that study data accurately reflected common clinical practice.

### *2.4. Statistical Analysis*

The study was descriptive; therefore, no formal hypothesis was tested. Descriptive statistics were used for the presentation of the data. For continuous variables, the number of observations and of missing or not available data, mean, standard deviation (SD), median (Q2), interquartile range (IQR: 25th–75th percentile), minimum, and maximum were calculated for primary and secondary endpoints. Categorical variables were summarized using frequencies, percentages, and the number of missing data. Missing and partial data were reported as observed. All analyses were performed by a designated contract research organization (CRO) using the SAS® statistical package (version 9.4; SAS Institute Inc., Cary, NC, USA).

## 3. Results

### *3.1. Patient Disposition and Characteristics at Baseline*

A total of 125 patients were enrolled in the study, comprising 64 patients (51.2%) with CKD not on dialysis (Group 1), 32 (25.6%) with CKD on dialysis (Group 2), and 29 (23.2%) with HF receiving RAASi/MRAs therapy (Group 3). Overall, 116 patients (92.8%) completed the study, while 9 patients (7.2%) discontinued (Figure 1). Baseline characteristics are shown in Table S1.

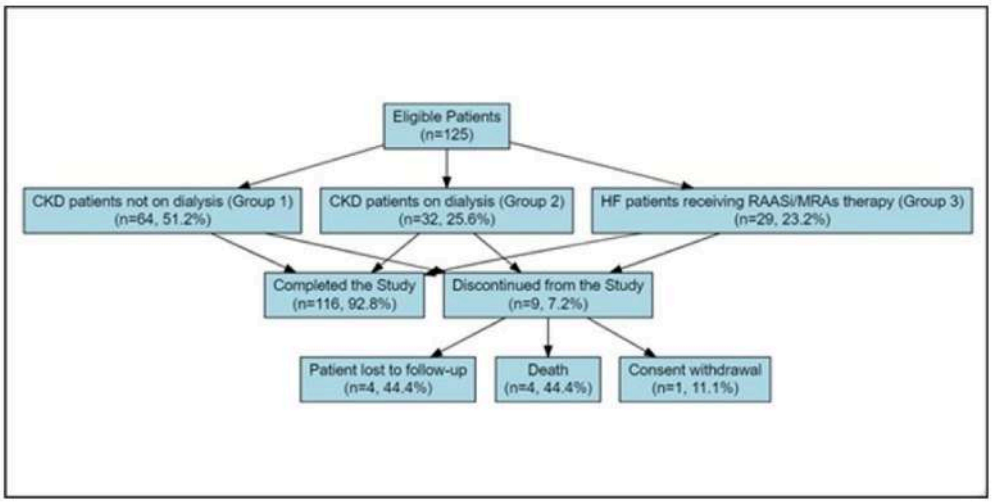



**Figure 1.** Patient disposition.

### *3.2. BMI and Lifestyle Habits*

BMI, exercise status, smoking behavior, alcohol intake, and dietary restrictions were assessed at each study visit. The overall median BMI was 26.6 kg/m$^2$ with minimal variations across visits. A sedentary lifestyle was the most frequently reported exercise status at baseline (48.8%), and across follow-up visits. Most of the overall patient population had never smoked (62.4%) and most participants (56%) reported never consuming alcohol. Lifestyle and dietary habits are summarized in Table S2.

### *3.3. Medical History and Disease Characteristics*

Baseline disease characteristics varied across study groups (Table 3). Kidney dysfunction was the predominant cause of hyperkalaemia in Groups 1 and 2 (92.2% and 100%, respectively), while heart failure predominated in Group 3 (69.0%), and dietary factors were most frequently reported in dialysis CKD patients (40.6%). Regarding the coexistence of hyperkaleamia causes, the most frequently reported combinations were kidney dysfunction and pharmacological treatment (20.0% of patients) and kidney dysfunction and dietary factors (16.0% of patients). At treatment initiation, median serum potassium was 5.6 mmol/L (range: 5.1–7.7) overall, with the highest value observed in dialysis patients (6.1 mmol/L, range: 5.2–7.7).

**Table 3.** Medical History and Disease Characteristics stratified by Patient Study Groups.

| | **Patient Study Groups** | | | |
|---|---|---|---|---|
| | **CKD Patients Not on Dialysis (Group 1) N = 64 (51.2%)** | **CKD Patients on Dialysis (Group 2) N = 32 (25.6%)** | **HF Patients Receiving RAASi/MRAs Therapy (Group 3) N = 29 (23.2%)** | **Total N = 125 (100.0%)** |
| **Cause of Hyperkalaemia, N (%)** [1] | | | | |
| Kidney dysfunction | 59 (92.2%) | 32 (100.0%) | 16 (55.2%) | 107 (85.6%) |
| Pharmacological treatment | 22 (34.4%) | 5 (15.6%) | 10 (34.5%) | 37 (29.6%) |
| Heart Failure | 1 (1.6%) | 0 (0.0%) | 20 (69.0%) | 21 (16.8%) |
| Diet | 14 (21.9%) | 13 (40.6%) | 1 (3.4%) | 28 (22.4%) |
| Other | 2 (3.1%) | 0 (0.0%) | 0 (0.0%) | 2 (1.6%) |
| Constipation [2] | 1 (50.0%) | 0 (0.0%) | 0 (0.0%) | 1 (50.0%) |
| Hyporeninemic Hypoaldosteronism [2] | 1 (50.0%) | 0 (0.0%) | 0 (0.0%) | 1 (50.0%) |
| **Serum potassium (S-$K^+$) value at hyperkalaemia treatment initiation (mmol/L)** | | | | |
| Median (min, max) | 5.6 (5.1, 7.2) | 6.1 (5.2, 7.7) | 5.5 (5.1, 5.9) | 5.6 (5.1, 7.7) |
| Missing N (%) | 2 (3.1%) | 3 (9.4%) | 0 (0.0%) | 5 (4%) |
| **Treatment with sodium zirconium cyclosilicate before enrolment (months)** | | | | |
| Median (min, max) | 2.4 (0.3, 21.8) | 4.1 (0.3, 18.5) | 1.1 (0.3, 21.7) | 2.2 (0.3, 21.8) |
| **Family History of Kidney Disease N** (%) | | | | |
| Yes | 4 (6.2%) | 10 (31.2%) | 2 (6.9%) | 16 (12.8%) |
| No | 57 (89.1%) | 22 (68.8%) | 23 (79.3%) | 102 (81.6%) |
| Unknown | 3 (4.7%) | 0 (0.0%) | 4 (13.8%) | 7 (5.6%) |
| **Family History of Heart Disease N** (%) | | | | |
| Yes | 0 (0.0%) | 1 (3.1%) | 1 (3.4%) | 2 (1.6%) |
| No | 54 (84.4%) | 31 (96.9%) | 23 (79.3%) | 108 (86.4%) |
| Unknown | 10 (15.6%) | 0 (0.0%) | 5 (17.2%) | 15 (12.0%) |

[1] More than one cause of hyperkalaemia could be reported per patient. [2] Percentages are based on the number of patients for whom 'Other' was reported as a cause of hyperkalaemia. N = Number of patients in each category and in the overall population.

Comorbidities were highly prevalent (96.8%) across groups, with hypertension (76.9%), dyslipidaemia (51.2%), type 2 diabetes (43.8%), and hyperuricaemia (26.4%) being the most common (Table S3).

### *3.4. Laboratory Assessments*

Laboratory monitoring results across visits, as well as group-stratified results, are summarized in Tables 4 and S4, respectively. Overall, renal function evaluation indicated a median CKD-EPI eGFR change from 30.0 mL/min/1.73 $m^2$ (IQR: 9.5–42.0) at baseline to 24.5 (IQR: 7.0–37.0) at 3 months, with a slight increase to 27.0 (IQR: 8.0–38.0) at 6 months (Table 4). CKD non-dialysis patients maintained stable function [median CKD-EPI eGFR 33.4 (IQR: 25.0–43.0), 35.0 (IQR: 25.5–42.5), and 34.0 mL/min/1.73 $m^2$ (IQR: 27.5–42.0) at baseline, 3, and 6 months, respectively), dialysis patients had persistently low eGFR (5.0 mL/min/1.73 $m^2$ at all visits), while in HF patients, it declined progressively [from 40.50 mL/min/1.73 $m^2$ (IQR: 29.3–60.0) at baseline to 26.0 mL/min/1.73 $m^2$ (IQR: 11.3–35.3) at 3 months and 18.0 mL/min/1.73 $m^2$ (IQR: 8.5–28.5) at 6 months] (Table S4). An additional analysis was performed to further evaluate eGFR in the HF group with available data at all visits. eGFR showed a slight decrease from a mean of 24.6 mL/min/1.73 $m^2$ (SD 12.4, median 28.5, range 8–49) at Visit 1, to 23.6 mL/min/1.73 $m^2$ (SD 13.8, median 26.0, range 5–47) at Visit 2, and finally 20.1 mL/min/1.73 $m^2$ (SD 12.6, median 18.0, range 5–44) at Visit 3. Other laboratory parameters, including serum urea, uric acid, and phosphorus, demonstrated modest visit-to-visit fluctuations without consistent trajectories across study groups (Table S4).

**Table 4.** Vital signs and Laboratory Monitoring for the Overall Population, across visits.

| | **Visit 1 Baseline (N = 125)** | **Visit 2 (3 Months) (N = 115)** | **Visit 3 (6 Months) (N = 116)** |
|---|---|---|---|
| **Vital signs** [1] | | | |
| **Patients with recorded vital signs testing results N (%)** | **115 (92.0%)** | **105 (91.3%)** | **114 (98.3%)** |
| **Resting heart Rate (Beats/min)** | | | |
| N | 115 | 105 | 110 |
| Median (Min, Max) | 70.0 (52, 108) | 69.0 (51, 99) | 70.0 (48, 97) |
| Missing N (%) | 0 (0.0%) | 0 (0.0%) | 2 (1.8%) |
| Not Available N (%) | 0 (0.0%) | 0 (0.0%) | 2 (1.8%) |
| IQR | 65.0–75.0 | 64.0–74.0 | 65.0–75.0 |
| **Systolic Blood pressure (mmHg)** | | | |
| N | 115 | 105 | 111 |
| Median (Min, Max) | 130.0 (90, 180) | 128.0 (100, 177) | 129.0 (83, 169) |
| Missing N (%) | 0 (0.0%) | 0 (0.0%) | 2 (1.8%) |
| Not Available N (%) | 0 (0.0%) | 0 (0.0%) | 1 (0.9%) |
| IQR | 120.0–140.5 | 121.0–135.0 | 120.0–135.0 |
| **Diastolic Blood pressure (mmHg)** | | | |
| N | 115 | 105 | 111 |
| Median (Min, Max) | 75.0 (49, 106) | 74.0 (57, 96) | 76.0 (44, 96) |
| Missing N (%) | 0 (0.0%) | 0 (0.0%) | 2 (1.8%) |
| Not Available N (%) | 0 (0.0%) | 0 (0.0%) | 1 (0.9%) |
| IQR | 69.0–80.0 | 69.0–80.0 | 70.0–80.0 |

**Table 4.** *Cont.*

| | Visit 1 Baseline (N = 125) | Visit 2 (3 Months) (N = 115) | Visit 3 (6 Months) (N = 116) |
|---|---|---|---|
| **Biochemistry Testing** | | | |
| **Patients with recorded biochemistry testing results N (%)** | 115 (92.0%) | 94 (81.7%) | 100 (86.2%) |
| **Serum biochemistry tests** | | | |
| **Urea (mg/dL)** | | | |
| N | 113 | 94 | 98 |
| Median (Min, Max) | 96.0 (34.0, 311.0) | 93.5 (27.0, 282.0) | 98.5 (32.0, 209.0) |
| Not Available N (%) | 2 (1.7%) | - | 2 (2.0%) |
| IQR | 74.0–133.5 | 74.0–124.0 | 71.0–127.0 |
| **Glucose (mg/dL)** | | | |
| N | 100 | 82 | 82 |
| Median (Min, Max) | 102.5 (33.0, 228.0) | 100.0 (63.0, 275.0) | 102.0 (54.0, 223.0) |
| Missing N (%) | 1 (0.9%) | - | 1 (1.0%) |
| Not Available N (%) | 14 (12.2%) | 12 (12.8%) | 17 (17.0%) |
| IQR | 88.0–124.5 | 89.0–118.0 | 88.0–120.0 |
| **Uric acid (mg/dL)** | | | |
| N | 80 | 71 | 76 |
| Median (Min, Max) | 6.3 (3.3, 11.5) | 6.2 (2.1, 10.2) | 6.0 (4.1, 10.2) |
| Missing N (%) | 1 (0.9%) | - | - |
| Not Available N (%) | 34 (29.6%) | 23 (24.5%) | 24 (24.0%) |
| IQR | 5.6–7.4 | 5.2–7.3 | 5.2–7.0 |
| **Phosphorus (mg/dL)** | | | |
| N | 96 | 82 | 94 |
| Median (Min, Max) | 4.1 (2.4, 12.5) | 4.0 (1.8, 8.5) | 4.1 (1.4, 9.0) |
| Missing N (%) | 1 (0.9%) | - | - |
| Not Available N (%) | 18 (15.7%) | 12 (12.8%) | 6 (6.0%) |
| IQR | 3.6–5.1 | 3.4–4.7 | 3.5–5.1 |
| **CPK (IU/L)** | | | |
| N | 55 | 47 | 50 |
| Median (Min, Max) | 86.0 (19.0, 303.0) | 97.0 (20.0, 411.0) | 110.00 (18.0, 373.0) |
| Missing N (%) | 3 (2.6%) | 1 (1.1%) | 1 (1.0%) |
| Not Available N (%) | 57 (49.6%) | 46 (48.9%) | 49 (49.0%) |
| IQR | 46.0–119.0 | 64.0–174.0 | 50.0–174.0 |
| **Renal function** | | | |
| **Patients with recorded eGFR results N (%)** | 113 (90.4%) [2] | 94 (81.7%) | 95 (81.9%) |
| **Serum Creatinine (mg/dL)** | | | |
| N | 112 | 94 | 95 |
| Median (Min, Max) | 2.2 (0.6, 18.7) | 2.5 (1.0, 17.8) | 2.5 (0.9, 18.6) |
| IQR | 1.6–5.9 | 1.8–7.2 | 1.8–7.0 |

**Table 4.** *Cont.*

| | Visit 1 Baseline (N = 125) | Visit 2 (3 Months) (N = 115) | Visit 3 (6 Months) (N = 116) |
|---|---|---|---|
| **CKD-EPI eGFR (ml/min/1.73 m$^2$)** | | | |
| N | 112 | 94 | 95 |
| Median (Min, Max) | 30.0 (3.0, 102.0) | 24.5 (3.0, 82.0) | 27.0 (3.0, 94.0) |
| IQR | 9.5–42.0 | 7.0–37.0 | 8.0–38.0 |
| **Clinically Significant Abnormalities N (%)** | | | |
| Yes | - | - | - |
| No | 112 (100.0%) | 94 (100.0%) | 95 (100.0%) |

Not available, n (%) indicates tests that were not available/reported for the corresponding visit; Missing, n (%) indicates that it was not recorded whether the test was performed. [1] Percentages are based on the number of patients with reported vital signs measurements at each visit. [2] Data was not available for one patient. IQR = Interquartile range (25th–75th percentile), N = Number of patients in each category and in the overall population.

Serum potassium monitoring frequency varied across study groups and visits (Table 5). At baseline, monthly testing predominated overall (44.8%). By 3 and 6 months, monthly monitoring was most common in dialysis patients (82.8% and 79.3%, respectively), whereas testing every 3 months became prevalent in non-dialysis (52.6% and 51.7%, respectively for visits 2 and 3) and HF patients (62.1–66.7%, respectively, for visits 2 and 3).

**Table 5.** Serum Potassium Testing Frequency across visits, stratified by patient study groups.

| | Patient Study Groups | | | |
|---|---|---|---|---|
| **Visit 1 Baseline** | **CKD patients not on dialysis (Group 1) N = 64 (51.2%)** | **CKD patients on dialysis (Group 2) N = 32 (25.6%)** | **HF patients receiving RAASi/MRAs therapy (Group 3) N = 29 (23.2%)** | **Total N = 125 (100.0%)** |
| **Current Serum Potassium Testing Frequency N (%)** | | | | |
| Per week | 0 (0.0%) | 1 (3.1%) | 0 (0.0%) | 1 (0.8%) |
| Per 2 weeks | 9 (14.1%) | 5 (15.6%) | 0 (0.0%) | 14 (11.2%) |
| Per month | 23 (35.9%) | 25 (78.1%) | 8 (27.6%) | 56 (44.8%) |
| Per 2 months | 7 (10.9%) | 1 (3.1%) | 5 (17.2%) | 13 (10.4%) |
| Per 3 months | 21 (32.8%) | 0 (0.0%) | 13 (44.8%) | 34 (27.2%) |
| Not Available | 4 (6.2%) | 0 (0.0%) | 3 (10.3%) | 7 (5.6%) |
| **Visit 2 3 months** | **CKD patients not on dialysis (Group 1) N = 57 (49.6%)** | **CKD patients on dialysis (Group 2) N = 29 (25.2%)** | **HF patients receiving RAASi/MRAs therapy (Group 3) N = 29 (25.2%)** | **Total N = 115 (100.0%)** |
| **Current Serum Potassium Testing Frequency N (%)** | | | | |
| Per week | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Per 2 weeks | 4 (7.0%) | 4 (13.8%) | 0 (0.0%) | 8 (7.0%) |
| Per month | 13 (22.8%) | 24 (82.8%) | 9 (31.0%) | 46 (40.0%) |
| Per 2 months | 10 (17.5%) | 0 (0.0%) | 0 (0.0%) | 10 (8.7%) |
| Per 3 months | 30 (52.6%) | 1 (3.4%) | 18 (62.1%) | 49 (42.6%) |
| Not Available | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Other | - | - | 2 (6.9%) | 2 (1.7%) |

**Table 5.** *Cont.*

| | Patient Study Groups | | | |
|---|---|---|---|---|
| **Visit 3 6 months** | **CKD patients not on dialysis (Group 1) N = 60 (51.7%)** | **CKD patients on dialysis (Group 2) N = 29 (25.0%)** | **HF patients receiving RAASi/MRAs therapy (Group 3) N = 27 (23.3%)** | **Total N = 116 (100.0%)** |
| **Current Serum Potassium Testing Frequency N (%)** | | | | |
| Per week | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Per 2 weeks | 2 (3.3%) | 5 (17.2%) | 0 (0.0%) | 7 (6.0%) |
| Per month | 17 (28.3%) | 23 (79.3%) | 8 (29.6%) | 48 (41.4%) |
| Per 2 months | 8 (13.3%) | 0 (0.0%) | 0 (0.0%) | 8 (6.9%) |
| Per 3 months | 31 (51.7%) | 1 (3.4%) | 18 (66.7%) | 50 (43.1%) |
| Not Available | 2 (3.3%) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) |
| Per 6 months | - | - | 1 (3.7%) | 1 (0.9%) |

N = Number of patients in each category and in the overall population.

### *3.5. Treatment Patterns Across Patient Study Groups*

At baseline, SZC dosing patterns differed across study groups (Figure 2A). CKD non-dialysis patients mostly received 10 g daily (50.0%), while dialysis and HF patients predominantly used 5 g on non-dialysis days (46.9%) and 5 g daily (69.0%), respectively. During follow-up, SZC regimens remained generally unchanged with few dose modifications or treatment discontinuations (Figure 2B–D).

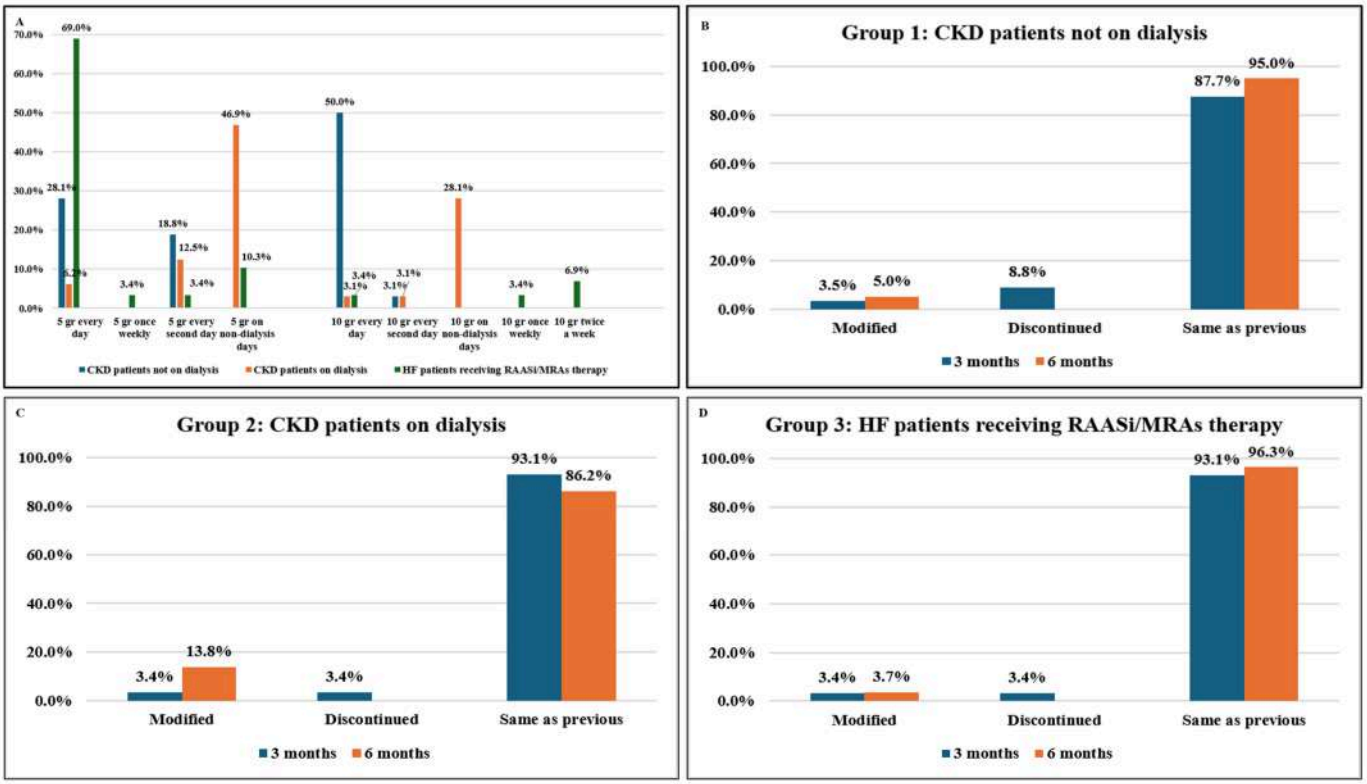



**Figure 2.** SZC dosing regimens at baseline and treatment course during follow-up per patient group. (**A**) Distribution of SZC regimen at baseline in the overall study population, (**B**) Treatment course of SZC in CKD patients not on dialysis (Group 1) at 3 and 6 months ("same regimen as previous visit", "modified", or "discontinued"), (**C**) Treatment course of SZC in CKD patients on dialysis (Group 2) at 3 and 6 months ("same regimen as previous visit", "modified", or "discontinued"), (**D**) Treatment

course of SZC in HF patients receiving RAASi/MRA therapy (Group 3) at 3 and 6 months ("same regimen as previous visit", "modified", or "discontinued"). Percentages represent the proportion of patients receiving each SZC regimen among patients with available data at each study visit.

RAASi/MRA use varied markedly across patient groups (Figure 3A) and remained generally stable (Figure 3B–D). Overall, 63.2% of patients received at least one RAASi/MRA at baseline, with the highest use in HF patients (100.0%), followed by non-dialysis CKD patients (67.2%), and lowest use in dialysis-dependent CKD patients (21.9%). ARBs were the most frequently received RAASi class (72.2%), while MRAs were mainly observed in the HF cohort. Over time, RAASi/MRA treatment patterns were highly stable, with most patients maintaining the same regimen as at the previous visit (96.5% at 3 months and 95.7% at 6 months). Discontinuations and modifications were infrequent.

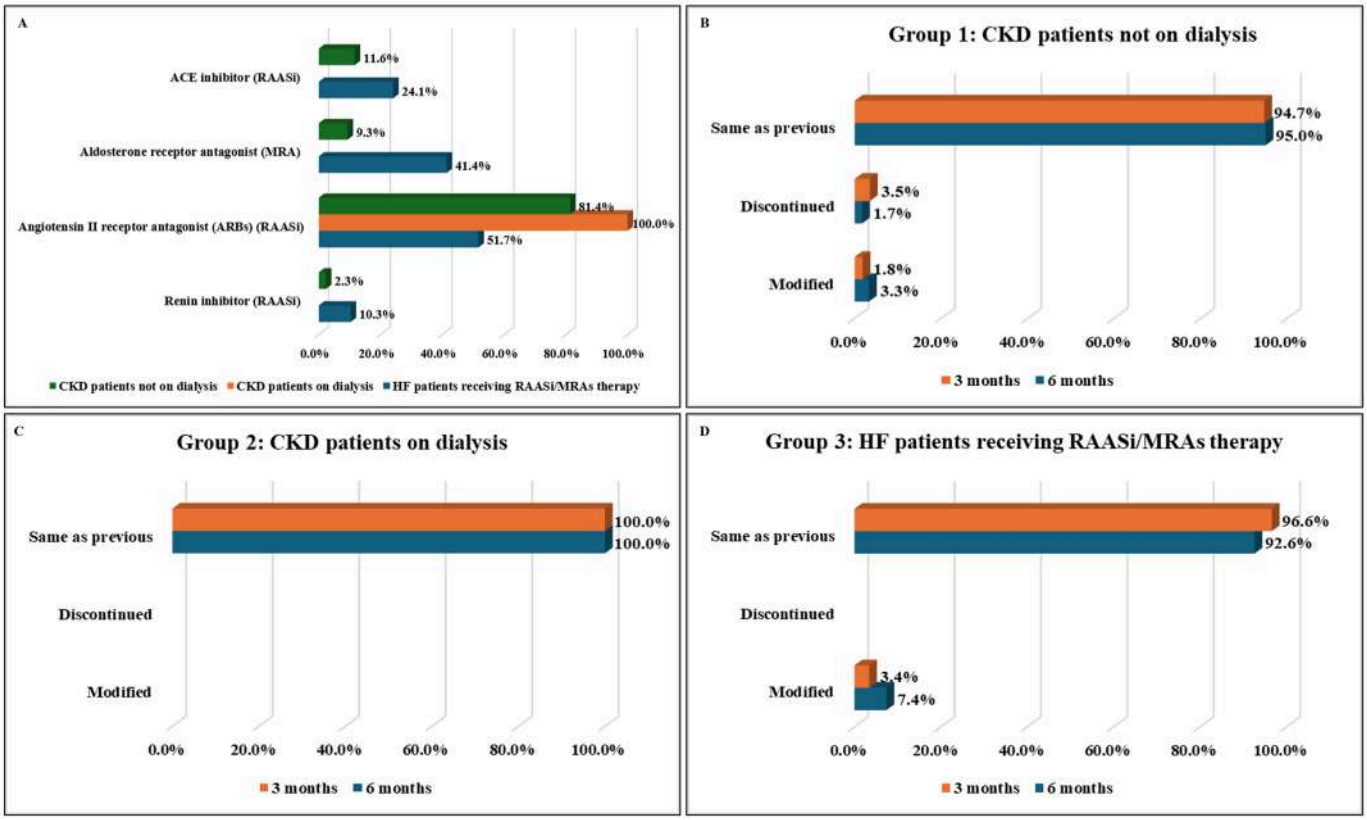



**Figure 3.** RAASi/MRAs treatment patterns across study visits per patient group. (**A**) Distribution of RAASi/MRA treatment classes at baseline per study group, (**B**) Treatment course of RAASi/MRA therapy in CKD patients not on dialysis (Group 1) at 3 and 6 months, (**C**) Treatment course of RAASi/MRA therapy in CKD patients on dialysis (Group 2) at 3 and 6 months, (**D**) Treatment course of RAASi/MRA therapy in HF patients receiving RAASi/MRA therapy (Group 3) at 3 and 6 months. Percentages represent the proportion of patients with available data at each study visit.

Figure 4 details the specific RAASi/MRA classes co-administered with SZC during follow-up. The combination of SZC with at least one RAASi/MRA agent was common, showing distinct group-specific patterns over time. In non-dialysis CKD patients (Figure 4A), SZC was most frequently combined with ARBs (79.1% at 3 months and 77.3% at 6 months among combination-treated patients). Combinations with ACE inhibitors were less frequent, reported in 11.6% of patients at 3 months and 13.6% at 6 months, while MRA co-administration remained low (9.3% and 9.1%, respectively). In dialysis patients (Figure 4B), combination therapy was almost exclusively limited to ARBs. In HF patients receiving RAASi/MRAs (Figure 4C), SZC was combined with a broader range of RAASi/MRA classes, including ARBs and ACE

inhibitors (55.2% and 20.7% of patients respectively, at both 3 and 6 months). MRA use declined over time, from 37.9% at 3 months to 31.0% at 6 months. Overall, combination patterns were largely stable between 3 and 6 months, with ARBs consistently representing the predominant RAASi class across all patient groups.

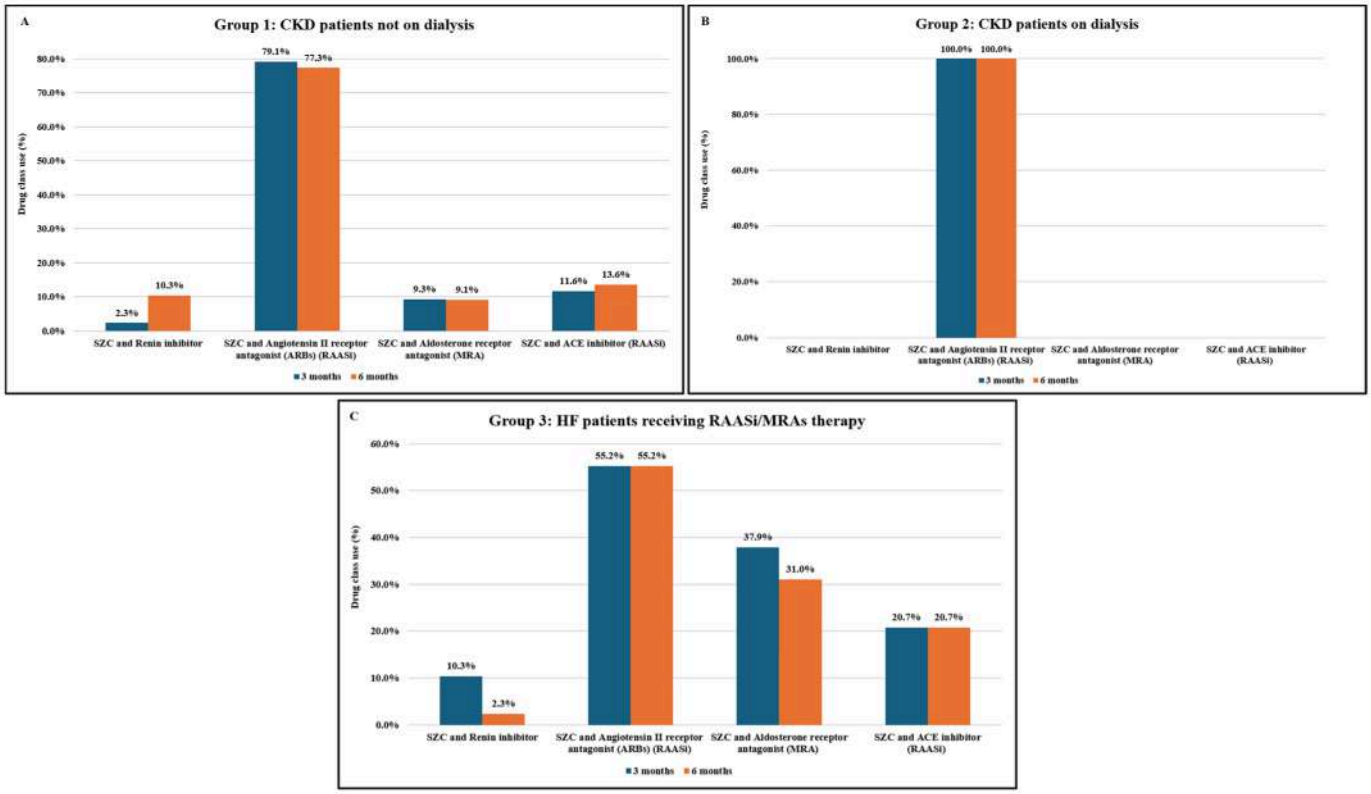



**Figure 4.** Combination treatment patterns of SZC with RAASi/MRA classes during follow-up in (**A**) CKD patients not on dialysis (Group 1), (**B**) CKD patients on dialysis (Group 2) and (**C**) HF patients receiving RAASi/MRAs therapy (Group 3). Percentages represent the proportion of patients receiving SZC in combination with each RAASi/MRA class at 3 and 6 months among patients with available data at each study visit. Patients may have received more than one RAASi/MRA class.

Overall distributions of concomitant medication categories by patient group are summarized in Table 6. Heart failure and antihypertensive medications (other than RAASi/MRAs) were the most frequently administered drug categories, with 84.8% of the total study population receiving at least one such agent. Lipid-lowering and antidiabetic therapies were also commonly used (56.8% and 40.0% of patients overall, respectively).

At the drug-class level (Figure S1), patterns varied across patient groups. Among heart failure or antihypertensive medications (other than RAASi/MRAs), beta-blockers were the most commonly used class overall (in 66.0% of treated patients). Calcium channel blockers (CCBs) were also frequently administered (62.3%). Diuretics were most commonly used in HF patients (51.9%). Among patients receiving lipid-lowering therapies, statins were the predominant class across all groups, used in 94.4% of treated patients. Antidiabetic therapy was administered to 40.0% of patients overall, with highest use in CKD patients not on dialysis (48.4%) and HF patients (48.3%). Among patients receiving antidiabetic agents, insulin and DPP-4 inhibitors were the most administered classes (66.0% and 44.0% of treated patients, respectively); however, SGLT2 inhibitors were used primarily in non-dialysis CKD and HF patients.

**Table 6.** Overall distribution of concomitant medication categories by patient group.

| | CKD Patients Not on Dialysis (Group 1) | CKD Patients on Dialysis (Group 2) | HF Patients Receiving RAASi/MRAs Therapy (Group 3) | Total |
|---|---|---|---|---|
| | **N = 64 (51.2%)** | **N = 32 (25.6%)** | **N = 29 (23.2%)** | **N = 125 (100.0%)** |
| **Patients receiving at least one Heart Failure or Hypertensive medication (other than RAASi/MRAs), N (%)** | 54 (84.4%) | 25 (78.1%) | 27 (93.1%) | 106 (84.8%) |
| **Patients receiving at least one Lipid Lowering Agent, N (%)** | 39 (60.9%) | 12 (37.5%) | 20 (69.0%) | 71 (56.8%) |
| **Patients receiving at least one Antidiabetic, N (%)** | 31 (48.4%) | 5 (15.6%) | 14 (48.3%) | 50 (40.0%) |
| **Patients receiving at least one Antiplatelet Agent, N (%)** | 24 (37.5%) | 14 (43.8%) | 11 (37.9%) | 49 (39.2%) |
| **Patients receiving at least one Corticosteroid, N (%)** | 2 (3.1%) | 4 (12.5%) | - | 6 (4.8%) |

N: number of patients in each category and in the overall population. Patients may have received more than one medication within or across treatment categories; therefore, percentages may not sum to 100%.

### *3.6. Safety Evaluation*

A total of 28 adverse events (AEs) were recorded in 19 patients (15.8% of the study population). Only one AE (peripheral edema; 3.6%) was considered possibly related to SZC, while the remaining events (96.4%) were assessed as unrelated to study treatment. The most frequently reported were death (4; 21% of patients with at least one AE), followed by hyperkalaemia, hypertension, and acute priapism (2 patients each; 10.5%). Most AEs were severe (60.7%), and serious (64.3%). SZC treatment was not modified in 85.7% of cases, while permanent discontinuation occurred in 3 events (10.7%). Complete recovery/resolution was reported in 39.3% of events and 4 events (14.3%) were fatal.

## 4. Discussion

The SHIELD study is a multicenter, prospective, observational, study describing the real-world management of hyperkalaemia patients with CKD under dialysis or not, or HF, treated with SZC in Greece. Over 6 months, the study provides evidence on potassium monitoring, renal function trends, continued use of SZC, and concomitant medication use, including RAASi/MRAs, in routine clinical practice. While previous studies have established the efficacy and safety of SZC in the management of hyperkalaemia, evidence from routine clinical practice provides complementary insights into its use beyond controlled clinical trial settings. Accordingly, the SHIELD study adds to the existing evidence by documenting treatment patterns and disease management across distinct patient populations in the Greek real-world setting.

At SZC initiation, median serum potassium was 5.6 mmol/L, with all groups exceeding the EMA-defined threshold for hyperkalaemia treatment (>5.0 mmol/L) [11]. Regarding serum potassium monitoring, monthly testing was most common among dialysis patients, whereas testing every 3 months predominated in non-dialysis and HF patients, reflecting guideline recommendations for individualized monitoring based on renal function, car-

diovascular disease, or RAASi therapy administration [14]. This indicates that regular potassium monitoring remains significant for the early identification of recurrent hyperkalaemia and for the long-term management of patients receiving RAASi-based therapies, which are often limited by concerns regarding potassium elevation.

Regarding renal function patterns, a decline was observed in median CKD-EPI eGFR overall from 30.0 mL/min/1.73 $m^2$ at baseline to 24.5 at 3 months, reflecting expected trajectories in patients with CKD and HF, with comorbidities such as hypertension and diabetes [15,16]. This underscores the need for renal function monitoring in this population, under therapies affecting renal hemodynamics.

The SZC regimens remained largely stable throughout the SHIELD study, with high retention rates and only few discontinuations or dose modifications, suggesting that SZC can provide sustained potassium control in routine clinical practice. The most common regimens overall were 5 g and 10 g daily with subgroup-specific approaches maintaining over time. These findings align with clinical trial evidence [17] and guideline recommendations [11], demonstrating that once-daily doses of 5 g or 10 g effectively maintain normokalaemia while supporting individualized therapy based on patient risk, disease severity, and treatment response. These findings indicate that SZC may contribute to sustained hyperkalaemia management and facilitate the continued use of guideline-recommended therapies, including RAASi/MRAs.

In line with this observation, RAASi/MRA therapy remained highly stable over time, with over 95% of patients maintaining their baseline regimen and SZC combination therapy appearing to facilitate continued RAASi/MRA use despite the presence of hyperkalaemia. This high treatment persistence suggests that SZC may enable clinicians to avoid unnecessary dose reduction or discontinuation of guideline-directed therapies. ARBs were the predominant RAASi class, while ACE inhibitors and MRAs were less common but stable over time. These findings align with prior research on RAASi-treated CKD patients with hyperkalaemia [18] and HF patients under similar regimens [19] and further support current guidelines that recommend RAASi/MRAs for both HF [20] and CKD [21].

Concomitant heart failure and antihypertensive medications, excluding RAASi/MRAs, were widely used across the study population, with 84.8% receiving at least one such agent. Beta-blockers, CCBs and diuretics were the most frequently administered classes with patterns differing by patient group and reflecting underlying condition and dialysis status. The 2023 ESH Guidelines recommend combining RAAS blockers with a CCB or thiazide/thiazide like diuretic when eGFR $\geq$ 45 mL/min/1.73 $m^2$ (CKD G1–G3a), replacing thiazides with loop diuretics if eGFR $<$ 30 mL/min/1.73 $m^2$ (CKD G4–G5) [22]. Lipid-lowering therapy was administered to 56.8% of patients, predominantly statins, with cholesterol absorption inhibitors mainly administered in CKD non-dialysis and HF patients. These patterns reflect KDIGO [23] and ESC [20] recommendations of statin-based therapy for cardiovascular risk reduction in CKD and HF populations and observations from the CKDopps study in non-dialysis CKD [24]. Antidiabetic therapy was administered in 40.0% of patients, predominantly insulin and DPP-4 inhibitors, while SGLT2 inhibitors and metformin were administered only in non-dialysis CKD and HF patients. This pattern aligns with real-world data from Greece that reported frequent use of insulin (40.8%) and DPP-4 inhibitors (40.7%) among patients with type 2 diabetes and mild-to-severe CKD under diabetologist care [25]. Collectively, these patterns indicate that patients receiving SZC are managed within a complex therapeutic framework, highlighting the importance of maintaining potassium control to enable continued use of cardiorenal therapies and minimize treatment limitations related to hyperkalaemia.

The study population had a median age of 66.0 years and most participants were male, reflecting epidemiological data of faster CKD progression in men [26], highlighting the

importance of early CKD diagnosis and individualized management, particularly in older patients. Higher BMI values were observed in CKD non-dialysis and HF patients compared with dialysis patients, consistent with observations from the CKD Prognosis Consortium in CKD and high-CV-risk cohorts [27]. Lifestyle assessment indicated predominantly sedentary behavior, highlighting the importance of non-pharmacological interventions, including physical activity, as part of a comprehensive cardiorenal care of CKD patients according to the Italian Society of Nephrology's consensus document [28].

Dietary restrictions were frequent across all groups, with the highest adherence observed in dialysis patients. These findings are consistent with KDIGO 2024 recommendations for a low-salt diet, a higher consumption of plant-based foods compared to animal-based foods and a lower consumption of ultra-processed foods in CKD patients, while also maintaining a protein intake of 0.8 g/kg body weight/d in adults with CKD G3–G5 [21]. Although meta-analyses support low-salt diets for improving renal [29] and HF-related outcomes [30,31], their impact on major clinical endpoints remains uncertain. In addition, dialysis patients represent a unique patient population in whom optimal disease management requires the integration of high adherence to fluid and dietary restrictions [32–34]. The higher adherence observed in this group reflects the fact that patients often view dietary adherence as a key component of hemodialysis care that provides tangible health benefits [33]. Taken together, these real-world data suggest that optimal hyperkalaemia management requires a multidisciplinary approach, combining pharmacological strategies with lifestyle interventions, thereby enabling a more comprehensive approach to long-term cardiorenal care.

Baseline characteristics reflected the expected hyperkalaemia etiologies and comorbidities. Kidney dysfunction and pharmacological treatment were the predominant causes, while heart failure predominated in the HF group, consistent with existing literature [35]. Common comorbidities included arterial hypertension, dyslipidemia and type II diabetes mellitus, frequently associated with hyperkalaemia in clinical practice [36]. These findings highlight patient populations that may benefit most from proactive potassium monitoring and long-term potassium-lowering strategies.

## 5. Limitations

As an observational study, SHIELD has limitations, including variable follow-up timing, missing data, and the absence of a control group. Subgroup analyses included smaller patient numbers, limiting generalizability for specific findings. Furthermore, the coexistence of CKD and HF was not specifically assessed, and its potential influence on patient characteristics and hyperkalaemia management was therefore not explored. Nevertheless, the multicenter and prospective design of the SHIELD study provides valuable real-world insight into hyperkalaemia management with SZC in Greek patients with CKD or HF.

## 6. Conclusions

The SHIELD study provides real-world evidence on SZC use in patients with hyperkalaemia and with underlying CKD (under dialysis or not) or HF, demonstrating high treatment persistence, stable dosing patterns, and continued RAASi/MRAs use in routine clinical practice. However, given the observational, single-arm design and statistical limitations of the study, these findings should be interpreted cautiously. Future controlled studies are warranted to confirm these observations and further clarify the clinical implications of SZC use in these patient populations.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomedicines14112587/s1, Figure S1: Concomitant medication use

by drug class across patient groups, showing the most frequently administered medication categories overall: A. Heart failure and antihypertensive agents, B. Lipid-lowering agents, C. Antidiabetic agents. Percentages represent the proportion of patients in each study group receiving each drug class at baseline. Patients may have received more than one medication within or across drug classes; Table S1: Baseline Characteristics stratified by patient study groups; Table S2: BMI and Lifestyle Habits across visits, stratified by patient study groups; Table S3: Comorbidities and interventions stratified by patient study groups; Table S4: Vital Signs and Laboratory monitoring across visits, stratified by Patient Study Groups.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The raw data supporting the conclusions of this article will be made available by the authors on request.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| ACE | Angiotensin-Converting Enzyme |
| AE/AEs | Adverse Event/Adverse Events |
| ARBs | Angiotensin Receptor Blockers |
| BMI | Body Mass Index |
| CCBs | Calcium Channel Blockers |
| CKD | Chronic Kidney Disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CKDopps | Chronic Kidney Disease Outcomes and Practice Patterns Study |
| CPK | Creatine Phosphokinase |
| CRO | Contract Research Organization |
| CV | Cardiovascular |
| DPP-4 | Dipeptidyl Peptidase-4 |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| EMA | European Medicines Agency |
| ESC | European Society of Cardiology |
| ESH | European Society of Hypertension |
| GDPR | General Data Protection Regulation |
| GPP | Good Pharmacoepidemiology Practices |
| HF | Heart Failure |
| IQR | Interquartile Range |
| KDIGO | Kidney Disease: Improving Global Outcomes |

| | |
|---|---|
| MRA/MRAs | Mineralocorticoid Receptor Antagonist(s) |
| N | Number |
| NCT | National Clinical Trial |
| Q2 | Second Quartile |
| RAASi | Renin–Angiotensin–Aldosterone System Inhibitors |
| S-$K^+$ | Serum Potassium |
| SAS | Statistical Analysis System |
| SD | Standard Deviation |
| SGLT2 | Sodium-Glucose Cotransporter-2 |
| SmPC | Summary of Product Characteristics |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| SZC | Sodium Zirconium Cyclosilicate |

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