kidney and dialysis

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The Impact of Potassium Binders on Mortality in Patients with Hyperkalemia: A Single-Center Study

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Abstract: Hyperkalemia is associated with an increased risk of mortality and is a common complication in patients with chronic kidney disease (CKD). Despite the prevalence of hyperkalemia, current real-world data suggest that serum potassium levels are not effectively managed in clinical practice. The potential benefit of potassium binders in reducing the risk of death has not been thoroughly investigated. Therefore, this retrospective cohort study aimed to investigate the potential impact of potassium binders on mortality risk in patients with CKD by analyzing electronic medical records. The study included 1689 patients with CKD and hyperkalemia (serum potassium level > 5.0 mEq/L), who visited Kawasaki Medical School Hospital between January 2014 and December 2018. The patients were divided into two groups: those without CPS (calcium polystyrene sulphonate) treatment (CPS_OFF) and those with CPS treatment (CPS_ON). The results showed that the incidence of death was significantly higher in the CPS_OFF group than in the CPS_ON group (22.3% vs. 19.6%, $p < 0.001$). After propensity score matching, the CPS_ON group had a higher survival rate than the CPS_OFF group (log-rank test, $p = 0.020$). These results suggest that potassium binders may reduce the risk of death in patients with CKD and hyperkalemia. We hope that the results of this cohort study will be confirmed in future RCTs.

Keywords: chronic kidney disease; electronic medical record; hyperkalemia; potassium binder

Citation: Nagasu, H.; Tokuyama, A.; Kanda, E.; Itano, S.; Kishi, S.; Sasaki, T.; Kashihara, N. The Impact of Potassium Binders on Mortality in Patients with Hyperkalemia: A Single-Center Study. *Kidney Dial.* **2023**, *3*, 244–254. https://doi.org/10.3390/kidneydial3030022

Academic Editors: Vladimir Tesar and Francesco Locatelli

Received: 11 May 2023
Revised: 7 June 2023
Accepted: 21 June 2023
Published: 28 June 2023

1. Introduction

Potassium is a vital electrolyte that plays a crucial role in maintaining proper cellular and organ functioning in the human body. The regulation of serum potassium levels is essential to preventing potentially life-threatening complications, as even minor fluctuations in potassium levels can have serious consequences. Hyperkalemia, a condition characterized by elevated serum potassium levels greater than 5.0 mEq/L [1,2], is a significant concern for patients with CKD.

The human body employs a combination of renal and extrarenal mechanisms to maintain a tight range of extracellular potassium levels following dietary potassium load ingestion [3]. The distal tubules of the kidney are particularly important in maintaining potassium homeostasis through the renin-angiotensin-aldosterone system. However, in patients with CKD, the impairment of kidney function leads to a reduced ability to excrete excess potassium, resulting in hyperkalemia.

Hyperkalemia is a major complication of CKD, which affects millions of people worldwide. The consequences of untreated hyperkalemia can be severe, including abnormal heart rhythms and potentially fatal cardiac arrest. Therefore, it is crucial to closely monitor serum potassium levels in CKD patients and to implement interventions such as the use of potassium binders to manage hyperkalemia.

Several clinical conditions affect potassium levels, including CKD, diabetes mellitus and heart failure [4,5]. Some medications, such as renin-angiotensin-aldosterone inhibitors

(RAASi) and nonsteroidal anti-inflammatory drugs, can also increase hyperkalemia risk [6]. Hyperkalemia prevalence, as reported in the most recent observational studies, ranges from 1% to 50% [7–9]; in CKD outpatients in the J-CKD-DB, which is the Japanese CKD database, the prevalence was 8.3% and, in patients with CKD stages G4 and G5, it was 11.6% [10]. In a hospital-based cohort outcome study, dichotomized analysis showed that patients with potassium levels of 6.5 mmol/L or higher had an in-hospital mortality of 31% [11]; these real-world data suggest that serum potassium levels are not controlled well enough in clinical practice.

Hyperkalemia is associated with an increased risk of death, which is only partly explicable by hyperkalemia-induced cardiac arrhythmia. Patients with hyperkalemia have an increased mortality, with a hazard ratio of 7.6 (95% confidence interval [CI]: 7.2–8.0) in the case of serum potassium between 5.1 and 5.4 mEq/L [12]. Furthermore, patients with mild hyperkalemia (serum potassium $\geq$ 5.0 mEq/L) should receive the attention of a physician because they are at risk of further increases in serum potassium to levels that may trigger fatal arrhythmias [13,14].

In the past, sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS) were the only drugs available for the treatment of hyperkalemia. While SPS long-term efficacy has not been evaluated in randomized, placebo-controlled trials, a recent study involving 247 adult patients with a baseline estimated glomerular filtration rate (eGFR) level of 30 $\pm$ 15 mL/min/1.73 m^2 suggested that CPS is effective and safe for controlling mild hyperkalemia in CKD [15]. Despite the effectiveness of potassium binders in managing hyperkalemia, there is currently no evidence to suggest that they reduce the risk of death associated with hyperkalemia. To investigate this question further, a retrospective cohort study was conducted using the electronic medical records of patients with CKD. The study aimed to explore the potential relationship between the use of potassium binders and a reduction in death risk in patients with hyperkalemia. The findings of this study could potentially pave the way for the development of new treatment strategies to manage hyperkalemia and improve patient outcomes.

2. Materials and Methods

Study design and participants: This is a retrospective cohort study, wherein data from the electronic medical records of patients with CKD at Kawasaki Medical School Hospital were used. The study design is shown in Figure 1.

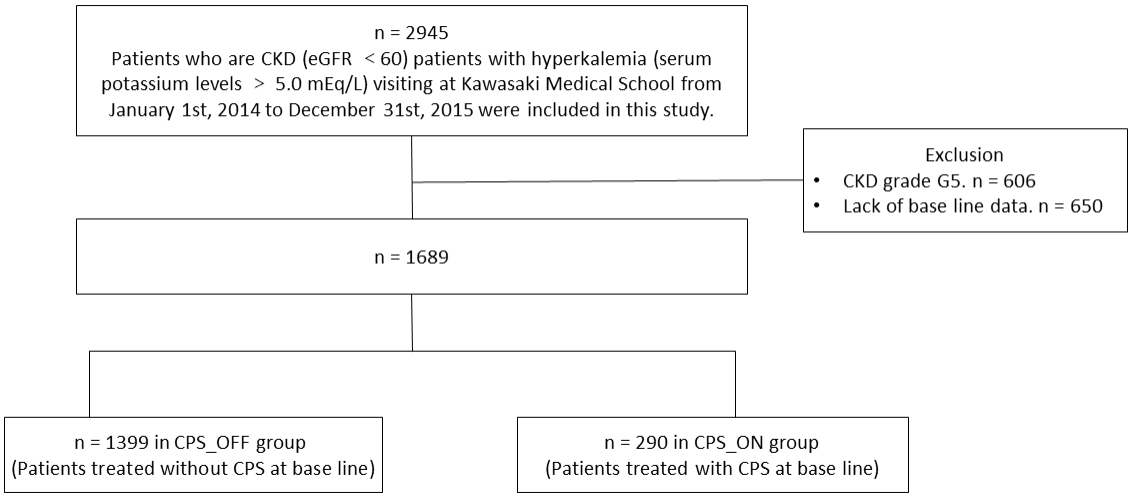


Figure 1. Flowchart of study population. Of these, 2945 were CKD patients with hyperkalemia (serum potassium levels > 5.0 mEq/L) who first visited between 1 January 2014 and 31 December 2015, and they were included in this study. We excluded CKD G5 from this study. We also excluded CKD patients without the required laboratory data.

We extracted data for patients who visited the Kawasaki Medical School Hospital more than once from 1 January 2014 to 31 December 2018. Of these, 2945 patients with CKD with hyperkalemia (serum potassium levels > 5.0 mEq/L) who first visited between 1 January 2014 and 31 December 2015 were included in this study. We excluded CKD G5 from this study. We also excluded CKD patients without the required laboratory data. CPS is used as a potassium binder at the Kawasaki Medical School. In the end, 1689 CKD patients were enrolled and included in the analysis.

Age, sex, eGFR, serum potassium, creatinine, high sensitive C-reactive protein (CRP), hemoglobin, uric acid (UA), total cholesterol (TC), sodium (Na), serum albumin, blood glucose (BG), CPS usage (Kalimate and Argamate), RAASi usage (an angiotensin II receptor blocker, an angiotensin-converting enzyme inhibitor, a mineral corticoid receptor antagonist) and death date comprised the extracted data. A 90-day observation period was used. The primary outcome was death. We defined the patients, at baseline date, treated with CPS as CPS_ON and without CPS as CPS_OFF. We further divided the patients into four groups, CPS_OFF-RAASi_OFF, CPS_OFF-RAASi_ON, CPS_ON-RAASi_OFF and CPS_ON-RAASi_ON, based on the baseline data.

Statistical analyses were conducted as follows. Baseline statistics were reported as mean ± standard deviation (SD) for normally distributed data and as median and interquartile range for non-normally distributed data. The baseline patient characteristics and outcomes were compared using appropriate statistical tests such as the chi-square test, *t*-test or Mann–Whitney U test. The survival rate was evaluated using Kaplan–Meier survival curves, and the log-rank test was used to assess statistical significance. A Cox proportional hazards model was used to compare the risks of death between the groups while adjusting for baseline characteristics. Hazard ratios with 95% confidence intervals (CIs) were reported as the results. To reduce the baseline characteristic bias between the CPS_ON and CPS_OFF groups, a propensity score-matched analysis was conducted. The following factors were included in a logistic regression model as covariates to calculate the propensity score: age, sex, ln(eGFR), potassium levels, serum albumin levels and hemoglobin levels. Nearest-neighbor matching replacement with a caliper width of 0.2 logits of the standard deviation was used to create a one-to-one match between the groups. The survival analysis was then conducted. All statistical analyses were performed using R version 3.5.0. Statistical significance was defined as $p < 0.05$, two-tailed.

3. Results

3.1. Baseline Characteristics and Outcomes

Of the 1689 study patients, 1399 were in the CPS_OFF group and 290 in the CPS_ON group; Table 1 shows the baseline characteristics.

The study revealed that a greater number of patients were treated with renin-angiotensin-aldosterone system inhibitors (RAASi) in the CPS_ON group compared to the CPS_OFF group. Notably, the CPS_ON group exhibited lower estimated glomerular filtration rate (eGFR) and hemoglobin levels, while their potassium levels were significantly higher than those observed in the CPS_OFF group. The observed differences in eGFR, hemoglobin levels, and potassium levels between the CPS_ON and CPS_OFF groups may be attributed to the effects of RAASi treatment, which can lead to changes in kidney function, blood cell production and electrolyte balance.

3.2. Relationship between CPS Use and Death

The usefulness of the CPS was first examined over a 90-day observation period. During the observation period up to 90 days, the Kaplan–Meier curve for the primary endpoint showed that the CPS_ON group had a higher survival rate than the CFS_OFF group (log-rank test, $p = 0.007$; Figure 2).

Table 1. Baseline characteristics of patients grouped by CPS treatment.

	All ***n* = 1689**	**CPS_OFF** ***n* = 1399**	**CPS_ON** ***n* = 290**	***p***
Demographic characteristic				
Age (years)	77.0 [69.0, 83.0]	77.0 [69.0, 83.0]	75.0 [69.0, 81.0]	0.010
Male (*n*, %)	1039 (61.5%)	852 (60.9%)	187 (64.5%)	0.254
Medication				
CPS (*n*, %)	290 (17.2%)	0 (0.0%)	100 (100.0%)	–
RAASi (*n*, %)	724 (42.9%)	535 (38.2%)	189 (65.2%)	<0.001
Laboratory measurement				
K (mEq/L)	5.1 [5.0, 5.4]	5.1 [5.0, 5.3]	5.2 [5.1, 5.5]	<0.001
Hb (g/dL)	11.6 ± 2.5	11.7 ± 2.5	11.2 ± 2.2	<0.001
eGFR (ml/min/1.73 m^2)	41.7 [29.8, 51.1]	43.2 [31.8, 52.0]	33.0 [25.7, 44.1]	<0.001
TC (mg/dL)	168.0 [140.0, 203.0]	169.0 [140.0, 204.0]	164.0 [140.0, 195.3]	0.208
Albumin (g/dL)	3.7 [3.0, 4.1]	3.7 [3.0, 4.1]	3.6 [3.1, 4.0]	0.182
BG (mg/dL)	107.0 [94.0, 137.0]	107.0 [94.0, 137.0]	107.5 [94.0, 138.0]	0.984

Continuous variables are shown as mean ± SD or median [interquartile range]. Categorical variables are shown as *n* (%). Abbreviations: CPS, calcium polystyrene sulfonate; RAASi, renin–angiotensin–aldosterone system inhibitor; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; TC, total cholesterol; and BG, blood glucose.

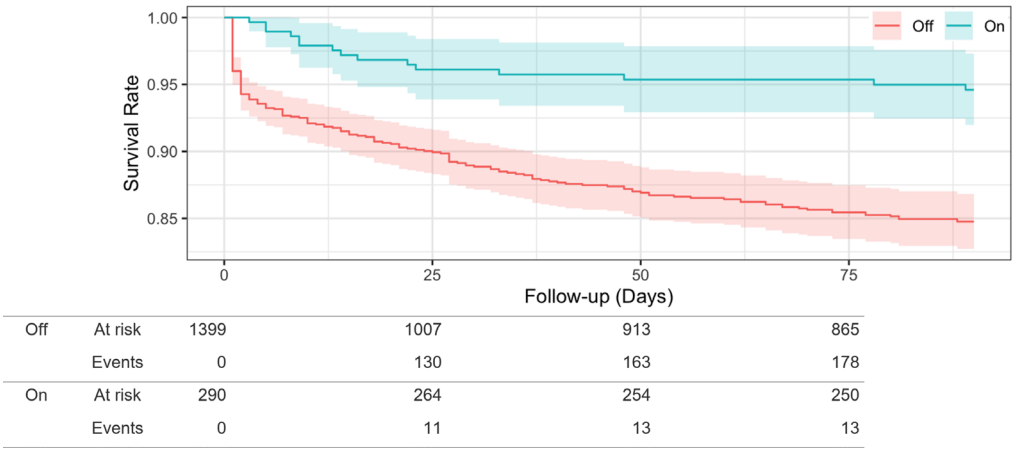


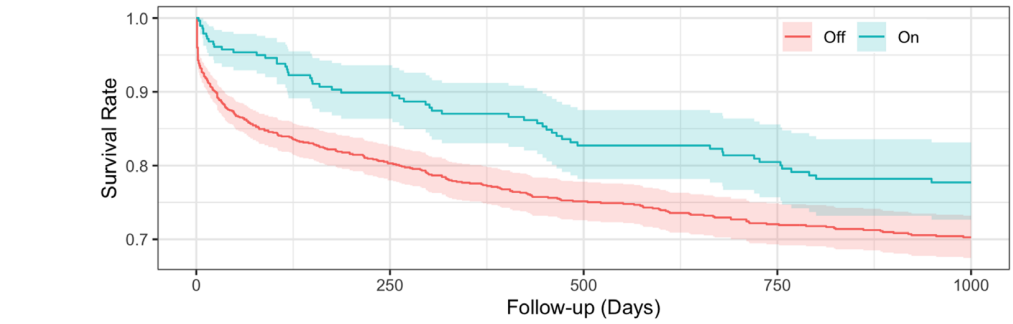
Figure 2. Survival rates in the original study population. Kaplan–Meier curves for the primary outcome over 90 days.

Table 2 shows the incidence of death, which was higher in the CPS_OFF group than in the CPS_ON group (22.3% vs. 19.6%, $p < 0.001$).

Table 2. Incident of death in both group.

	All ***n* = 1689**	**CPS_OFF Group** ***n* = 1399**	**CPS_ON Group** ***n* = 290**	***p***
Death, *n* (%)	367 (11.8%)	185 (13.2%)	15 (5.2%)	<0.001
Observation period, median days (interquartile range)	90 (26, 90)	90 (18, 90)	90 (90, 90)	<0.001

In addition to the previously discussed findings, the study conducted an extended observation period of up to 1000 days, followed by a Kaplan–Meier curve analysis to evaluate the survival rate of patients in the CPS_ON and CPS_OFF groups. The results of the analysis revealed that the survival rate was significantly higher in the CPS_ON group compared to the CPS_OFF group (log-rank test, $p = 0.0001$), as demonstrated in Figure 3.



Off	At risk	1399	749	631	557	486
	Events	0	228	274	299	312
On	At risk	290	223	192	178	156
	Events	0	27	44	49	55

Figure 3. Survival rates in the original study population. Kaplan–Meier curves for the primary outcome over 1000 days.

The interaction between CPS and RAASi was also insignificant ($p = 0.73$), and the adjusted Cox proportional hazard model showed that the CPS_ON group was 0.67 times less likely to have the primary outcome than the CPS_OFF group (Table 3).

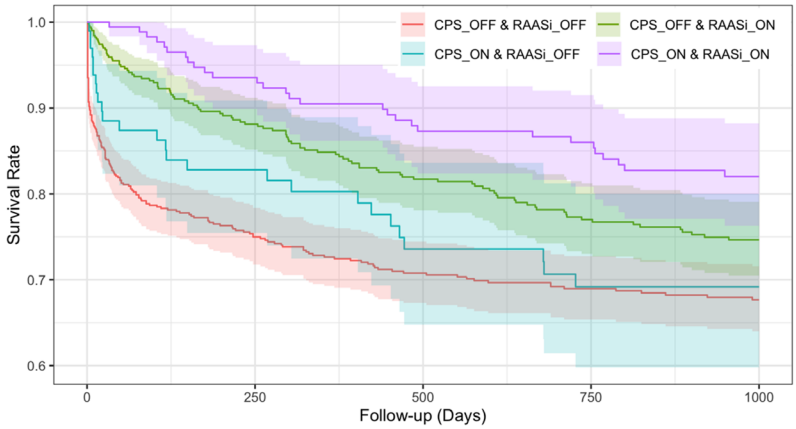
Table 3. Association of CPS treatment with the primary outcome.

	Hazard Ratio (95% CI)	***p***
Age (years)	1.02 (1.01, 1.03)	<0.001
Male	1.46 (1.16, 1.84)	0.002
ln(eGFR)	0.75 (0.56, 1.02)	0.063
Albumin (g/dL)	0.31 (0.27, 0.36)	<0.001
K (mEq/L)	2.50 (2.16, 2.89)	<0.001
UA (mg/dL)	1.07 (1.02, 1.13)	0.008
TC (mg/dL)	1.00 (1.00, 1.00)	0.272
BG (mg/dL)	1.00 (1.00, 1.00)	0.004
CPS (On:1)	0.66 (0.49, 0.88)	0.006
RASSi (On:1)	0.61 (0.49, 0.76)	<0.001
Na (mEq/L)	0.98 (0.96, 1.00)	0.041
Hb (g/dL)	0.98 (0.93, 1.03)	0.432

The hazard ratio of the CPS_ON group to the CPS_OFF group is shown. The multivariate Cox proportional hazard model was adjusted for baseline characteristics such as age, sex, ln(eGFR), serum albumin levels, serum potassium levels, serum uremic acid levels, serum total cholesterol levels, serum blood glucose levels, serum natrium levels, RAS treatment and hemoglobin levels.

Although there was no interaction between CPS and RAASi, a stratified analysis was performed to consider the possibility that the effect of CPS may be mediated by RAASi. We further divided the patients into four groups: CPS_OFF-RAASi_OFF, CPS_OFF-RAASi_ON,

CPS_ON-RAASi_OFF and CPS_ON-RAASi_ON. The Kaplan–Meier curves are shown in Figure 4.



CPS_OFF & RAASi_OFF	At risk	864	393	323	289	247
	Events	0	175	196	204	209
CPS_OFF & RAASi_ON	At risk	535	356	308	268	239
	Events	0	53	78	95	103
CPS_ON & RAASi_OFF	At risk	101	68	55	46	43
	Events	0	16	23	26	26
CPS_ON & RAASi_ON	At risk	189	155	137	132	113
	Events	0	11	21	23	29

Figure 4. Survival rates in the original study population. We divided the patients into four groups: CPS_OFF-RAASi_OFF, CPS_OFF-RAASi_ON, CPS_ON-RAASi_OFF and CPS_ON-RAASi_ON. Kaplan–Meier curves for the primary outcome over 1000 days.

There was a significant difference between the CPS_OFF-RAASi_OFF and CPS_ON-RAASi_OFF groups ($p < 0.001$), but not between the CPS_OFF-RAASi_ON and CPS_ON-RAASi_ON groups ($p = 0.969$). The results showed that the effect of the CPS was particularly pronounced in the RAASi-treated group.

3.3. Propensity Score-Matched Analysis

The patients were matched between the two main groups (Table 4) according to propensity score.

Table 4. Base line data after PS matching.

	All ***n* = 578**	**CPS_OFF** ***n* = 289**	**CPS_ON** ***n* = 289**	***p***	***ASD***
Demographic characteristic					
Age (years)	76 [69.0, 83.0]	78 [69, 84]	75 [69, 81]	0.084	0.144
Male	367 (63.6%)	181 (31.3%)	186 (32.1%)	0.730	0.036
Medication					
CPS	289 (50.0%)	0 (0.0%)	289 (100.0%)	-	-
RAASi	377 (64.3%)	189 (32.6%)	188 (32.5%)	1	0.007
Laboratory measurement					
K (mEq/L)	5.2 [5, 5.4]	5.35 [5, 5.4]	5.2 [5.1, 5.5]	0.975	0.03
Hb (g/dL)	11.0 ± 2.4	11.05 ± 2.47	11.15 ± 2.2	0.592	0.045
eGFR (mL/min/1.73 m^2)	33.8 [25.15, 45.22]	35.27 [24.61 46.5]	33.10 [25.8, 43.9]	0.978	0.002
TC (mg/dL)	166 [141, 199]	168 [141, 202]	164 [140.0, 195]	0.804	0.021
Albumin (g/dL)	3.6 [3.1, 4.0]	3.7 [3.1,4.1]	3.6 [3.1, 4.0]	0.426	0.066
BG (mg/dL)	107 [94, 138]	107 [138, 94]	108 [94.0, 138.0]	0.58	0.046

Continuous variables are shown as mean ± SD or median [interquartile range]. Categorical variables are shown as *n* (%). SD, standard deviation; *ASD*, absolute standardized difference. *p*-value is shown for the chi-squared test, unpaired *t*-test and Mann–Whitney U test.

The incidence of death was higher in the CPS_OFF group than that in the CPS_ON group (Table 5).

Table 5. Incident of death in both group after PS matching.

	All ***n* = 578**	**CPS_OFF Group** ***n* = 289**	**CPS_ON Group** ***n* = 289**	***p***
Death, n (%)	119 (20.5)	64 (11%)	55 (9.5)	
Observation period, median days (interquartile range)	601.36 (907.75)	440 (978)	1000 (715)	<0.004

In the Kaplan–Meier curves for the primary outcome, the survival rate was lower in the CPS_OFF group than that in the CPS_ON group (log-rank test, $p = 0.020$) (Figure 5).

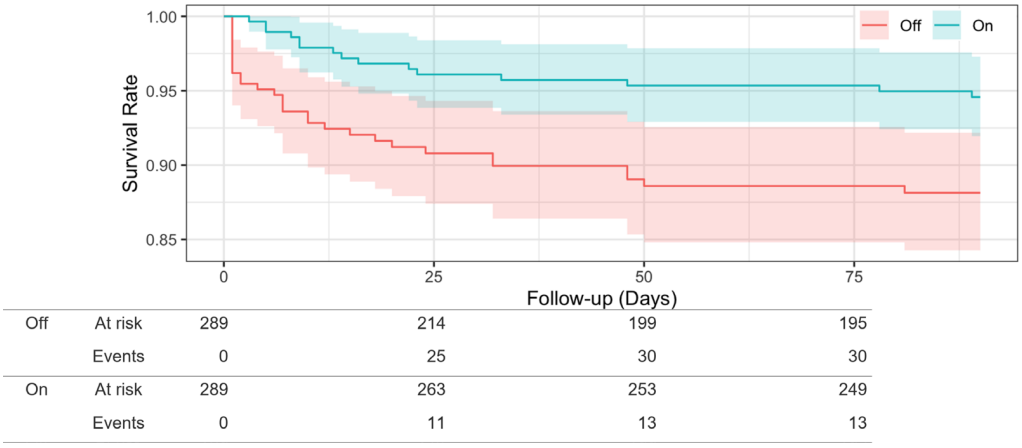


Figure 5. Survival rates in the propensity-score-matched population. Kaplan–Meier curves for the primary outcome over 90 days.

4. Discussion

In this study, survival analysis showed that CPS administration reduced the risk of death in patients with CKD, and this effect was maintained after propensity score matching. To the best of our knowledge, no clinical studies have previously investigated whether potassium binders reduce the risk of death in patients with CKD with hyperkalemia, which has been reported to reduce life expectancy.

There are many confounding factors and interactions between abnormal potassium levels and life expectancy. For instance, renal dysfunction, heart failure and diabetes mellitus all reduce life expectancy and are risk factors for hyperkalemia. Another possible factor is that patients with hyperkalemia have a lower rate of use of RAASi medications. NICE guidelines recommend that anti-RAAS treatments not be offered to patients with CKD if pre-treatment serum potassium exceeds 5.0 mEq/L. RAAS inhibition treatment was discontinued in 25% of patients with hyperkalemia in 194,456 outpatients in the Geisinger Health System [16]. Due to these possible confounding factors, it is unclear how correcting abnormal potassium levels will contribute to improved life expectancy. Therefore, we conducted a propensity-score-matched analysis to resolve this question.

Einhorn et al. studied the effect of CKD (eGFR < 60 mL/min/1.73 m^2) on the incidence of hyperkalemia and death within 1 day of onset in a cohort of US veterans [17]. Regardless of the presence or absence of renin-angiotensin system inhibitors, patients with CKD had a higher incidence of hyperkalemia, and the odds of death within 1 day after the onset of moderate hyperkalemia ($5.5 \leq$ serum potassium < 6.0 mEq/L) and severe hyperkalemia (serum potassium $\geq$ 6.0 mEq/L) were significantly higher than for CKD and

normal potassium levels. Furthermore, when analyzed according to the stage of CKD, the association between hyperkalemia and death was stronger in the earlier stages. However, these results were obtained from observational studies and did not directly indicate the prognostic impact of controlling serum potassium levels.

In end-stage renal failure, it was unclear whether the discontinuation of RAASi prolongs renal prognosis. The STOP-ACEi trial was conducted to investigate this point [18]. In this trial, the discontinuation of RAASi in patients with advanced chronic kidney disease did not result in clinically significant changes in eGFR or group differences in the rate of long-term decline in eGFR. However, there was a trend toward an increase, although not significant, in the RAASi discontinuation group with respect to cardiovascular events. In a large observational study, Fu et al. found an increased incidence of major cardiovascular events and death in patients who discontinued RAASi [19]. Based on these results, several clinical studies have been conducted with the outcome of whether the use of potassium binders is useful for the continued use of RAASi. Recent randomized, controlled trials have reported that two newer potassium-binder patiromer and sodium zirconium cyclosilicate (ZS-9) effectively and safely reduce serum potassium levels in patients with CKD taking RAASi medications. Those patients receiving submaximal doses or those who discontinued RAASi therapy had worse outcomes than those receiving maximal doses of RAASi medications, including a higher incidence of CV events, a more rapid progression of kidney disease and increased mortality [20]. The use of extended-release patiromer, a potassium binder, is associated with a relatively high continuation rate of RAASi therapy and decreased hospitalization rates [21]. On the other hand, patients with hyperkalemia who adhere to RAASi regimens have a higher risk of total mortality than non-adherent patients [22]. In another clinical trial, the use of SZC has been shown to be useful in maximizing RAASi dosing in patients with advanced CKD and HF. Thus, the use of RAASi as a benefit of potassium control is sufficient [23]. Furthermore, these results have led to the current DIAMOND trials [24]. The primary outcomes of these trials are the amount of RAS used and the continuation rate. While it cannot be ascertained whether the CPS has a direct prognostic role, it is possible that the increased use of RAASi was a factor. Future RCTs should examine the impact of potassium binders on life outcomes.

In the present study, we also examined the effect of CPS on mortality with and without RAASi medication, but no interaction was found, which was therefore not explanatory of the effect of CPS on the risk of death.

A healthy diet, including at least four to five servings of fruit and vegetables per day, is recommended in order to prevent major chronic diseases, such as cardiovascular disease, diabetes and cancer [25,26]. Evidence from observational studies suggests an association between higher consumption of fruit and vegetables and a 10–20% lower risk of all-cause mortality, largely driven by reduced cardiovascular mortality [27,28]. Patients with hyperkalemia are usually on a restricted diet, including reduced fruit and raw vegetable intake. Thus, alkaline substances intake is reduced, which may affect life expectancy. Potassium-binding agents may therefore allow patients with CKD at risk for hyperkalemia to receive the other benefits of a potassium-rich diet. To examine this, Na-Cl levels were analyzed as an indicator of acidosis and found to be significantly related to life expectancy. However, the prognosis was better in cases of acidemia (data not shown). Our data set does not contain dietary information. Therefore, it is unclear whether the diet was altered by CPS administration. The inability to correct for such confounding factors is a major limitation. Thus, it is necessary to consider the possibility that CPS administration may have contributed to the improvement in prognosis through behavioral changes, rather than through the correction of potassium levels.

This study, while informative, has some limitations that must be considered. The results of this study are a retrospective cohort study and caution should be exercised in interpreting the results. Certain correlations have been reported between the results of observational studies and RCTs using PS matching [29]. On the other hand, it has been found that discrepancies between the results of RCTs and observational studies cannot be

removed. This has been attributed to the lack of control over confounding in the latter. Although some discrepancies between studies of different designs are to be expected, it is the unpredictability of discrepancies that most undermines the reliability of the results of observational studies and limits their application. Therefore, only an RCT can prove whether the results of this study are truly correct. One notable limitation is that only CPS was used as the potassium binder due to the single-center nature of the study, making it difficult to determine the effect of SPS. CPS and SPS have different calcium content, with SPS exchanging sodium for potassium, while CPS avoids hypervolemia by exchanging calcium for potassium [30]. Thus, it remains unclear whether the observed prognostic effect of CPS in this study is due to its ability to lower potassium levels or whether it is specific to CPS itself. Another limitation of this study is the absence of data on complications, blood pressure and causes of death, which are missing due to the limitations of the dataset. As a result, it is not possible to conduct a detailed investigation into the causes of death in relation to potassium binders. It is important to consider these limitations when interpreting the findings of this study and to conduct further research to address these gaps in knowledge.

5. Conclusions

In conclusion, this study has shown that patients taking potassium chelators have better outcomes than those not taking them. However, future studies are needed to determine if the findings of this study are relevant to the usefulness of these agents. Our data suggest that CKD patients with hyperkalemia should be treated with these drugs intensively to maintain serum potassium levels in a normal range. The results of this study are based on a cohort study and will have to be proven by RCTs in the future.

Author Contributions: H.N., E.K., S.I. and N.K. conceived the study and design; H.N. and A.T. acquired and analyzed the data; H.N. and A.T. drafted the manuscript; H.N., E.K., S.K., T.S. and N.K. revised the manuscript for important intellectual content; N.K. provided supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Kowa Company, Ltd., Aichi, Japan. (Funding number: 3916).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Board of the Kawasaki Medical School (No. 3916).

Informed Consent Statement: Informed consent was obtained from all subjects who participated in this study on an opt-out basis.

Data Availability Statement: Not applicable.

Conflicts of Interest: This study was funded by Kowa Company, Ltd., Aichi, Japan., a commercial pharmaceutical company manufacturing a medication to treat hyperkalemia. The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results. In accordance with MDPI's policy, and with my ethical obligation as a researcher, Nagasu is reporting that Nagasu receive funding from Kowa Company, Ltd., Aichi, Japan, a company that may be affected by the research reported in the enclosed paper. Nagasu have disclosed those interests fully to MDPI, and I have in place an approved plan for managing any potential conflicts arising from the Kawasaki Medical School.

References

1. Terzi, N.; Piquilloud, L.; Roze, H.; Mercat, A.; Lofaso, F.; Delisle, S.; Jolliet, P.; Sottiaux, T.; Tassaux, D.; Roesler, J.; et al. Clinical review: Update on neurally adjusted ventilatory assist-report of a round-table conference. *Crit. Care* **2012**, *16*, 225. [CrossRef] [PubMed]
2. Palmer, B.F. Regulation of Potassium Homeostasis. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 1050–1060. [CrossRef] [PubMed]
3. Boyd-Shiwarski, C.R.; Subramanya, A.R. The renal response to potassium stress: Integrating past with present. *Curr. Opin. Nephrol. Hypertens.* **2017**, *26*, 411–418. [CrossRef] [PubMed]
4. Palmer, B.F. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N. Engl. J. Med.* **2004**, *351*, 585–592. [CrossRef]
5. Cohn, J.N.; Tognoni, G.; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N. Engl. J. Med.* **2001**, *345*, 1667–1675. [CrossRef]

6. Ouwerkerk, W.; Voors, A.A.; Anker, S.D.; Cleland, J.G.; Dickstein, K.; Filippatos, G.; van der Harst, P.; Hillege, H.L.; Lang, C.C.; Ter Maaten, J.M.; et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: A prospective European study. *Eur. Heart J.* **2017**, *38*, 1883–1890. [CrossRef]
7. Hayes, J.; Kalantar-Zadeh, K.; Lu, J.L.; Turban, S.; Anderson, J.E.; Kovesdy, C.P. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: The role of race. *Nephron. Clin. Pract.* **2012**, *120*, c8–c16. [CrossRef]
8. Drawz, P.E.; Babineau, D.C.; Rahman, M. Metabolic complications in elderly adults with chronic kidney disease. *J. Am. Geriatr. Soc.* **2012**, *60*, 310–315. [CrossRef]
9. Sarafidis, P.A.; Blacklock, R.; Wood, E.; Rumjon, A.; Simmonds, S.; Fletcher-Rogers, J.; Ariyanayagam, R.; Al-Yassin, A.; Sharpe, C.; Vinen, K. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 1234–1241. [CrossRef]
10. Sofue, T.; Nakagawa, N.; Kanda, E.; Nagasu, H.; Matsushita, K.; Nangaku, M.; Maruyama, S.; Wada, T.; Terada, Y.; Yamagata, K.; et al. Prevalences of hyperuricemia and electrolyte abnormalities in patients with chronic kidney disease in Japan: A nationwide, cross-sectional cohort study using data from the Japan Chronic Kidney Disease Database (J-CKD-DB). *PLoS ONE* **2020**, *15*, e0240402. [CrossRef]
11. An, J.N.; Lee, J.P.; Jeon, H.J.; Kim, D.H.; Oh, Y.K.; Kim, Y.S.; Lim, C.S. Severe hyperkalemia requiring hospitalization: Predictors of mortality. *Crit. Care* **2012**, *16*, R225. [CrossRef] [PubMed]
12. Kashihara, N.; Kohsaka, S.; Kanda, E.; Okami, S.; Yajima, T. Hyperkalemia in Real-World Patients Under Continuous Medical Care in Japan. *Kidney Int. Rep.* **2019**, *4*, 1248–1260. [CrossRef]
13. Nakhoul, G.N.; Huang, H.; Arrigain, S.; Jolly, S.E.; Schold, J.D.; Nally, J.V., Jr.; Navaneethan, S.D. Serum Potassium, End-Stage Renal Disease and Mortality in Chronic Kidney Disease. *Am. J. Nephrol.* **2015**, *41*, 456–463. [CrossRef]
14. Luo, J.; Brunelli, S.M.; Jensen, D.E.; Yang, A. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. *Clin. J. Am. Soc. Nephrol.* **2016**, *11*, 90–100. [CrossRef] [PubMed]
15. Yu, M.Y.; Yeo, J.H.; Park, J.S.; Lee, C.H.; Kim, G.H. Long-term efficacy of oral calcium polystyrene sulfonate for hyperkalemia in CKD patients. *PLoS ONE* **2017**, *12*, e0173542. [CrossRef]
16. Chang, A.R.; Sang, Y.; Leddy, J.; Yahya, T.; Kirchner, H.L.; Inker, L.A.; Matsushita, K.; Ballew, S.H.; Coresh, J.; Grams, M.E. Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Health System. *Hypertension* **2016**, *67*, 1181–1188. [CrossRef] [PubMed]
17. Einhorn, L.M.; Zhan, M.; Hsu, V.D.; Walker, L.D.; Moen, M.F.; Seliger, S.L.; Weir, M.R.; Fink, J.C. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch. Intern. Med.* **2009**, *169*, 1156–1162. [CrossRef]
18. Bhandari, S.; Mehta, S.; Khwaja, A.; Cleland, J.G.F.; Ives, N.; Brettell, E.; Chadburn, M.; Cockwell, P. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. *N. Engl. J. Med.* **2022**, *387*, 2021–2032. [CrossRef] [PubMed]
19. Fu, E.L.; Evans, M.; Clase, C.M.; Tomlinson, L.A.; van Diepen, M.; Dekker, F.W.; Carrero, J.J. Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcomes: A Nationwide Study. *J. Am. Soc. Nephrol.* **2021**, *32*, 424–435. [CrossRef]
20. Epstein, M.; Reaven, N.L.; Funk, S.E.; McGaughey, K.J.; Oestreicher, N.; Knispel, J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am. J. Manag. Care* **2015**, *21* (Suppl. S11), S212–S220.
21. Desai, N.R.; Rowan, C.G.; Alvarez, P.J.; Fogli, J.; Toto, R.D. Hyperkalemia treatment modalities: A descriptive observational study focused on medication and healthcare resource utilization. *PLoS ONE* **2020**, *15*, e0226844. [CrossRef]
22. Volterrani, M.; Perrone, V.; Sangiorgi, D.; Giacomini, E.; Iellamo, F.; Degli Esposti, L.; on behalf of the LSG. Effects of hyperkalaemia and non-adherence to renin-angiotensin-aldosterone system inhibitor therapy in patients with heart failure in Italy: A propensity-matched study. *Eur. J. Heart Fail* **2020**, *22*, 2049–2055. [CrossRef]
23. Murphy, D.; Ster, I.C.; Kaski, J.C.; Anderson, L.; Banerjee, D. The LIFT trial: Study protocol for a double-blind, randomised, placebo-controlled trial of K(+)-binder Lokelma for maximisation of RAAS inhibition in CKD patients with heart failure. *BMC Nephrol.* **2021**, *22*, 254. [CrossRef]
24. Butler, J.; Anker, S.D.; Siddiqi, T.J.; Coats, A.J.S.; Dorigotti, F.; Filippatos, G.; Friede, T.; Göhring, U.M.; Kosiborod, M.N.; Lund, L.H.; et al. Patiromer for the management of hyperkalaemia in patients receiving renin-angiotensin-aldosterone system inhibitors for heart failure: Design and rationale of the DIAMOND trial. *Eur. J. Heart Fail* **2022**, *24*, 230–238. [CrossRef] [PubMed]
25. Piepoli, M.F.; Hoes, A.W.; Agewall, S.; Albus, C.; Brotons, C.; Catapano, A.L.; Cooney, M.T.; Corra, U.; Cosyns, B.; Deaton, C.; et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur. Heart J.* **2016**, *37*, 2315–2381. [PubMed]
26. American Heart Association Nutrition Committee; Lichtenstein, A.H.; Appel, L.J.; Brands, M.; Carnethon, M.; Daniels, S.; Franch, H.A.; Franklin, B.; Kris-Etherton, P.; Harris, W.S.; et al. Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. *Circulation* **2006**, *114*, 82–96.

27. Wang, X.; Ouyang, Y.; Liu, J.; Zhu, M.; Zhao, G.; Bao, W.; Hu, F.B. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: Systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ* **2014**, *349*, g4490. [CrossRef]
28. Zhan, J.; Liu, Y.J.; Cai, L.B.; Xu, F.R.; Xie, T.; He, Q.Q. Fruit and vegetable consumption and risk of cardiovascular disease: A meta-analysis of prospective cohort studies. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 1650–1663. [CrossRef]
29. Dahabreh, I.J.; Kent, D.M. Can the learning health care system be educated with observational data? *JAMA* **2014**, *312*, 129–130. [CrossRef]
30. Kim, G.H. Pharmacologic Treatment of Chronic Hyperkalemia in Patients with Chronic Kidney Disease. *Electrolytes Blood Press.* **2019**, *17*, 1–6. [CrossRef]