STUDY REPORT SYNOPSIS

A cross-sectional study to assess the burden of illness and treatment for management of hyperkalemia in patients with chronic kidney disease or heart failure Description: HK Registry pilot study

Milestones:	CSP finalization	: June 8th, 2020
	First Subject Registration	: July 30th, 2020
	Last Subject Registration	: November 30th, 2020
	Database Lock	: Janualy 18th, 2021
Phase of development:	NA	
Sponsor:	AstraZeneca	
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Background/rationale:

Hyperkalemia occurs in several percent of patients who are being treated as outpatients or in hospitals. Advanced hyperkalemia may lead to fatal cardiac arrhythmias such as asystole or ventricular fibrillation. In addition, hyperkalemia can lead to the cessation of the drugs that cause hyperkalemia, such as RAASi, which may hinder optimal medical care.

Treatment options for patients with chronic hyperkalemia include potassium-restricted diet, diuretics, sodium bicarbonate, and potassium binders. Among these treatment options, the most reasonable and effective drug treatment includes potassium binders. However, side effects such as constipation and gastrointestinal disorders, as well as the distinctive smell and texture of the medication, can cause patients to reduce their intake of these drugs, i.e. adherence can decrease. Such decreases in adherence adversely affect the lives of patients being treated for hyperkalemia.

Health-related Quality of Life (HR-QoL) is generally low in patients with chronic diseases. Lower HR-QoL can be caused by, the symptoms of the disease, the burdens of treatment,

dietary restrictions, and other limitations on daily life. Assessment of HR-QoL is particularly important in patients with hyperkalemia, because the burdens of treatment and of clinical events can be large.

HR-QoL and the burdens of treatment in patients with hyperkalemia are not well understood. Therefore, we are planning a cross-sectional study to quality the burden of disease and of treatment, adherence to prescriptions for therapeutic agents, association with HR-QoLs, and the relationship between HR-QoL and clinical outcomes. This study is a pilot study to obtain the information necessary for planning the aforementioned cohort study.

Objectives:

Primary objective:

To obtain descriptive statistics of PROs which is used in the Hyperkalemia registry study (D9480R00027) to assess their applicability to the patient population studied. Specifically, following information is obtained.

- Descriptive statistics of HR-QoL scales (QGEN-10 / QDIS-7 / SF-36)
- Correlations between HR-QoL scales (QGEN-10 / QDIS-7 / SF-36) and other PROs
- Minimally clinical important difference in QoL for CKD/HF
- Descriptive statistics of compliance scale (Original scale)

Secondary objective:

To describe practice patterns in hyperkalemia patients. Specifically, following information is obtained.

- Proportion of hyperkalemia treatment
- Classification and distribution of treatment pattern (active gradient, dose and dose regimen) for hyperkalemia

Study design:

Descriptive cross-sectional study

Data source:

There are three types of data sources for this study:

i) Physician (Karte)

ii) Medical record

iii) Patient (self-reported questionnaire)

The first two are secondary data collection, and the third is the primary data collection.

Study population:

A hyperkalemia patient, who is receiving outpatient care, with CKD or HF.

Inclusion criteria:

Subjects who meet all following criteria is included in this study.

a) Aged ≥20 years, Male or female

b) Hyperkalemia patients defined as meeting either of the following criteria:

i) Having a history of S-K ≥5.1 mmol/L ≥2 times within 6 months before enrolment

ii) Having a history of S-K ≥5.5 mmol/L once within 6 months before enrolment

iii) Currently treated by potassium binders for the treatment of hyperkalemia at enrolment

c-1) Having been diagnosed as CKD (≥stage 3b) or HFrEF by investigators as defined below:

CKD is diagnosed based on the guidelines of CKD issued by the Japanese Society of Nephrology (JSN, 2018) as being either or both of condition 1 and 2 for ≥3 months

i) Clear sign of kidney impairment based on urinalysis, imaging, blood test, or biopsy.

ii) GFR <45 mL/min/1.73m^2

Within the routine clinical practice, GFR is estimated by serum creatinine, gender, and age using following the formulation.

eGFR creat (mL/min/1.73m^2) = 194 x serum creatinine (mg/dL)$^{-1.094}$ x age (years)$^{-0.287}$ (for female patients, x 0.739)

≥Stage 3b CKD is defined based on the following eGFR categories:

i) Stage 3b: 30 mL/min/1.73m^2 ≤ eGFR <45 mL/min/1.73m^2

ii) Stage 4: 15 mL/min/1.73m^2 ≤ eGFR <30 mL/min/1.73m^2

iii) Stage 5: eGFR <15 mL/min/1.73m^2

c-2) Patients with HFrEF is enrolled if patients meet following criteria within 6 months:

i) EF ≤40%（No special limitation for EF measuring instrument/method）

ii) NYHA class II-IV

d) Provision of signed, written, and detailed informed consent

Exclusion criteria:

Patients who meet following exclusion criteria isn't enrolled in the study:

a) Currently on any chronic RRT (including hemodialysis or peritoneal dialysis >30 days, or kidney transplant) within 6 months before enrolment

b) Patients with acute kidney injury* within 6 months before enrolment

c) Patients who took blood transfusion within 6 months before enrolment

d) Patients who took potassium supplements within 6 months before enrolment

e) Active malignancy or life expectancy of less than 6 months.

f) GI disturbance/chronic diarrhoea/stoma that, investigator judges, the condition or treatment has a significant impact on S-K values.

g) Autoimmune disease that, investigator judges, the condition or treatment has a significant impact on S-K values.

h) Patients whose lab data have suspicion for pseudohyperkalemia(abnormality in the sample, a history of severe leukocyte or thrombocytopenia)

i) Patients who are pregnant, lactating, or planning to become pregnant

j) Current participation in clinical trials, i.e. interventional studies

k) Presence of any condition below, in the opinion of the investigator,

i) Which places the subject at undue risk

ii) Which potentially jeopardizes the quality of the data to be generated.

iii) Patients may not perform protocol-defined tasks for physical or mental reasons

iv) Patients may not understand the contents of self-reporting questionnaire and answer to the questions on his/her own

v) Which researchers judge inappropriate

*The definition of acute kidney injury is in accordance with the following KDIGO clinical guidelines.

1. ΔsCr ≥ 0.3 mg/dL (within 48 hours)

2. 1.5 x increase from the base value of sCr (within 7 days)

3. Urine volume 0.5 mL/kg/hr or less lasts more than 6 hours

If meet one of 1-3, to diagnose AKI.

Statistical methods:

For continuous variables, we compute and report the means, standard deviations, medians, minima, and maxima. For categorical variables, we compute and report frequencies and percentages. Missing of data is reported. These descriptive statistics is also computed and reported for subgroups defined by the following categories: CKD and HF, CKD stage, NYHA functional classification, EF, prescription or non-prescription of potassium binders, category of potassium binder prescribed, and socioeconomic status. The categories are defined using both clinical cut-offs and distribution-based cut-offs (the latter of course can be done only after the data are collected [e.g., clinical characteristics, socio-demographic factors]). Correlations among the various PRO indices is also investigated.

Primary Objective(s)：

For QGEN-10 and QDIS-7 scores、

• By entire population and interesting subgroups, descriptive statistics (distribution, average, SD, median) will be computed.

•The difference in distribution between subgroups will be presented as the difference in mean values between groups.

•Correlation with scores of other PRO as external criteria will be computed.

•HR-QoL distribution by PGIS level will be computed to estimate MID**

For the score of the medication compliance scale

•By entire population and interesting subgroups, descriptive statistics will be computed.

•Correlation with scores of other PRO as external criteria will be computed.

**To estimate the MID, the distribution of HR-QoL scores for each level of PGIS and their differences will be assessed. In addition, the distribution of HR-QoL scores corresponding to

the each level of other external criteria (the indices of disease severity and the SF-36 score), and their differences, as well as the distribution of scores in the entire population will be assessed. Based on these, the MID will be decided by consensus of multiple experts.

Secondary Objective(s):

For treatment patterns of hyperkalemia,

•Determine the proportion of each treatment method will be determined.

•The treatment patterns will be classified in terms of active ingredient name, dose, dose regimen, and proportion of each pattern will be computed.

Results:

A total of 145 patients were registered, 125 patients with CKD and 20 patients with HF responded to the questionnaires. Two among them were judged to have given invalid responses and their data were excluded from further analyses.

Overall, the hyperkalemia patients were elderly (age = 72.48 ± 11.21 years). Their mean serum potassium concentration (S-K) was 4.87 ± 0.48 mg/dl, and 11.72% had values greater than 5.5 mg/dl. More than two thirds of them (70.34 %) were taking a potassium binder. In addition, 65.52% of them were taking renin-angiotensin-aldosterone inhibitors (RAASi). About two thirds of them were taking at least 7 drugs by mouth per day.

Overall, HR-QoL scores were high, and their compliance with prescriptions for medication was good. Therefore, there were no easily assessed differences in HR-QoL or in compliance among sub-groups. Correlations involving HR-QoL scores and medication-compliance scores also could not be assessed clearly, and MIDs could not be estimated.

The situation described above was unexpected. Nonetheless, the following results were obtained.

- PF_N (physical functioning), VT_N (vitality), and MH_N (mental health) did not differ by CKD Stage. However, in the stratum of those aged 65-75, PF_N (physical functioning) was low among those at high CKD stages.

- In these hyperkalemia patients, neither HR-QoL nor medication compliance was associated with the use of potassium binders. In most patients, the dose of potassium binder was lower than specified in the PI. The data were also examined for relationships between HR-QoL scores and S-K concentrations above and below 5.5 mmol/L, but no such relationships were found. When analyzed as a continuous variable, the S-K value was not found to be correlated with HR-QoL score.

- Among patients taking potassium binders in the form of granules and powders, the SF-36 mental summary scores and the QDIS scores tended to be low.

- Among patients taking potassium binders, the percentage who were using RAASi's was low.

Conclusion:

- Overall, HR-QoL and medication-compliance scores were high. These findings may be attributed at least in part to information bias at the time the patients completed the questionnaires.

- PF_N (physical functioning), VT_N (vitality), and MH_N (mental health) did not differ by CKD stage. This finding was strongly confounded by age. An age-stratified analysis showed that in the stratum of those who were 65-75 years old, PF_N was low at high CKD stages.

- The original plan was to estimate MID from associations among the severity of disease, PGIS, and SF-36 scores. We decided not to estimate the MID, mainly because so many of the HR-QOL scores were very high.

- In these hyperkalemia patients, the data were also examined for relationships between HR-QoL scores and S-K concentrations above and below 5.5 mmol/L, but no such relationships were found. Also, the use of a potassium binder was not associated with low HR-QoL or with non-compliance with prescriptions for medications.

- Among patients taking potassium binders, the percentage who were using RAASi's was low.

- As expected, the PHGS and ePCS of QGEN were relatively strongly correrated with the PF_N (Physical Functioning), BP (Bodily Pain)_N, 3PCS, 2PCS_U, and 2PCS_J of the SF-36. Regarding scores on the medication-compliance scales, Q13 part_1 and Q13_overall were relatively strongly correrated with ASK_part_1 and ASK_overall, as expected. The HR-QoL scales and compliance scales used were high in score than predicted in this research, but were observed good correlation with several external criteria (SF-36, ASK-12 and Medical-taking Behaviour scale) , so it was determined those PRO scales're applicable to hyperkalemia patients.

Publications:

- Japan Health Sciences Foundation, Ministry of Health, Welfare, and Labor. (in Japanese) Future perspective of CKD treatment. 2012.