## STUDY REPORT SYNOPSIS

# D9480R00033 PRECEDE-K

# Hyperkalaemia Prevalence, Recurrence and Treatment in Haemodialysis: A Prospective Multi-Centre Cohort Study

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| **Milestones:** | Study protocol approved | Q4. 2020 |
| | First subject/patient in | Q2. 2021 |
| | Last subject/patient in | Q4. 2021 |
| | Last subject/patient last visit | Q3. 2022 |
| | Final database lock | Q4. 2022 |
| | Clinical study report approved | Q1. 2023 |
| **Phase of development:** | IV | |
| **Protocol No.** | D9480R00033 | |
| **Sponsor:** | AstraZeneca | |
| **Report Date** | 03 Feb 2023 | |

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

## Background/rationale:

Hyperkalaemia (HK) is a potentially life-threatening electrolyte imbalance, typically defined as a serum potassium concentration > 5.0 mmol/L. Due to its detrimental effects on cardiac electrophysiology and neuromuscular function, HK has been proved to be associated with several adverse clinical outcomes, including significant arrythmia, hospitalization and associated length of stay, and all-cause mortality. Hyperkalaemia is common in patients with kidney failure due to diminished renal potassium excretion. Hyperkalaemia is prevalent in 30-50% of end-stage renal disease (ESRD) patients under maintenance haemodialysis (HD) worldwide, and is recognized as a risk factor for sudden death and all-cause mortality in HD patients. Chinese patients with ESRD have different spectrum of chronic kidney disease (CKD), different dietary style and treatment patterns, thus may have distinct characteristics of HK occurrence and recurrence. There is no evidence on the occurrence, recurrence, and the treatment of HK in HD patients in China. In the present study, we aimed to evaluate the prevalence and recurrence of HK in Chinese HD patients and to understand the treatment pattern of HK in China.

## Objectives:

- **Primary Objective**

- To describe the prevalence of HK in HD patients

- **Secondary Objectives**

- To describe the recurrence of HK in HD patients
- To describe the intradialytic potassium shift at long interdialytic interval (LIDI) in HD patient
- To describe the potassium level at LIDI and short interdialytic interval (SIDI)
- To describe the pattern of treating HK with potassium binders in HD patients.

## Study Design:

This was a prospective, cohort study. This study utilized primary data collected by investigators from 15 sites in China. End-stage renal disease patients on HD treatment were enrolled and followed up for 24 weeks.

## Data Source:

This study primarily collected data from 15 HD centers in China. HD centers were selected as study sites from tertiary and secondary hospitals in different areas across China. Patients who were eligible and consent to participate in the study were enrolled consecutively as per protocol and without personal preference from investigators. Investigators were physicians specialized in nephrology or dialysis. Investigators were qualified in terms of experience and ability to perform the study. Data were collected and entered into the electronic case report form (eCRF). The investigator was responsible for ensuring that the required data was collected and entered into the eCRF.

## Study Population:

This study was to include approximate 600 ESRD patients receiving HD treatment twice a week or thrice a week.

The primary endpoint was the proportion of patients experiencing HK anytime at enrolment and during a 24-week follow-up, the previous reported proportion of patients experiencing HK was 73.8% during a 2-year follow-up and 58% during a 4-month follow-up. It was assumed that for this study, the proportion of patients experiencing HK was between 58% and 73.8% during the 24-week follow-up. So, 600 patients provided a precision (half width of 95% confidence interval) estimate of 3.5% to 3.9%, which was clinically accepted.

## Inclusion Criteria:

Patients were eligible to be included in the study only if all of the following criteria applied:

1. Patient aged ≥ 18 years at the time of signing the informed consent.
2. Patients with ESRD and on haemodialysis (HD)
3. The HD treatment frequency was ≥ 2 sessions per week.
4. Capable of giving signed informed consent

## Exclusion Criteria:

Patients were excluded from the study if any of the following criteria applied:

1. Acute kidney injury
2. Expected to receive renal transplantation within 6 months
3. Intracranial haemorrhage or elevated intracranial pressure within one month before enrolment
4. Shock that could not be corrected by drugs within one month before enrolment
5. Failure to establish vascular access
6. Had been receiving peritoneal dialysis
7. Not suitable for this study judged by investigators

## Outcome(s):

### Primary Endpoint

- Proportion of patients experiencing any HK (defined as serum potassium > 5.0 mmol/L) at the study enrolment or during a 24-week follow-up

### Secondary Endpoints:

- Proportion of patients experiencing HK recurrence (defined as any HK event after the first HK event) within 1, 2, 3, 4, 5 or 6 months (if applicable) during a 24-week follow-up including enrolment assessment. A HK event was defined as any serum $K^+$ > 5.0 mmol/L within an interdialytic interval, which is usually two to three days.
- Proportion of patients with 2, 3, 4, 5, 6 or more than 6 events of HK during a 24-week follow-up including enrolment assessment
- Intradialytic potassium shift (defined as the difference between pre- and post-dialysis $K^+$)at LIDI during the first week after patient enrolment

- Serum $K^+$ at LIDI and SIDI in patients receiving HD thrice a week during the first week after patient enrolment
- Proportion of HK patients treated with any potassium binders including sodium polystyrene sulfonate (SPS), calcium polystyrene sulfonate (CPS) or sodium zirconium cyclosilicate (SZC), and specific proportion of each potassium binder respectively during the 24-week follow up period
- Proportion of HK events treated with any potassium binders including SPS, CPS or SZC among total number of HK events during the 24-week follow up period
- Mean daily dose of SPS, CPS or SZC in patients treated with any potassium binder
- Duration of the treatment of SPS, CPS or SZC in patients treated with any potassium binders

**Exploratory Endpoints:**

- Risk factors for experiencing any HK (defined as serum potassium > 5.0 mmol/L) at the study enrolment or during a 24-week follow-up
- Risk factors for experiencing HK recurrence during a 24-week follow-up

## Statistical Methods:

Statistical methods were primarily descriptive in nature.

For categorical data, the frequency and percentage of patients in each category were presented. Percentages were based on non-missing data unless otherwise specified.

For continuous data, descriptive statistics were presented as the number of patients (n), mean, standard deviation (SD), median, minimum, and maximum.

All successfully enrolled patients fulfilling inclusion/exclusion criteria were included into the Full Analysis Set (FAS), which was primary analysis set for all primary and secondary analyses unless specified otherwise.

**Primary Analysis**

The proportion of patents experiencing any HK at the study enrolment or during a 24-week follow-up were presented by the percentage as well as its 95% confidence interval. Hyperkalaemia was defined as $K^+$ > 5.0 mmol/L while the same summary was generated using a higher threshold of HK as $K^+$ > 5.3 mmol/L, 5.5 mmol/L as well, as sensitivity analysis. The proportion of patients experiencing serum $K^+$ > 6.0 mmol/L, 6.5 mmol/L, 7.0 mmol/L and 7.5 mmol/L was reported as well.

**Secondary Analysis**

Proportion of patients with HK recurrence, multiple times of HK events, patients treated with any potassium binders and specific proportion of each binder was summarized with 95% confidence interval estimate provided as applicable.

Intradialytic potassium shift, serum $K^+$ at LIDI and SIDI was summarized and presented with descriptive statistics as stated above.

Detailed description for secondary analysis and analysis of exploratory endpoints were described in SAP.

## Results:

A total of 600 eligible Chinese HD patients were enrolled in the study, with a mean age of 54 years. 67.2% of male patients. The 3 most common causes of ESRD are primary glomerulonephritis (39%), diabetes kidney disease (28%) and hypertensive renal disease (16%). The study has shown that Chinese HD patients have a heavy disease burden of HK, 60% of HD patients have a medical history of HK (sK+＞5.0 mmol/L) in recent 6 months. The mean pre-dialysis sK+ at LIDI was 4.8 mmol/L at baseline, among these, the prevalence of HK (sK+ ＞5.0 mmol/L) is 40%, with the proportions of sK+＞5.5 mmol/L,＞6.0 mmol/L and＞6.5 mmol/L were 17%, 6%, and 3%, respectively. Majority (97.7%) of dialysate potassium concentration used in China was 2.0mmol/L, with limited use of 2.5 mmol/L (0.5%) and 3.0 mmol/L (1.8%). The mean HD duration is 4 hours and the dialysis frequency of 86% HD patients is three times per week(6% for two times per week and 8% for five times two week). The dialysis adequacy was generally up to standard, with an average urea reduction ratio (URR) of 68% and an average Kt/V of 1.45. Another concern is the fluctuation of blood potassium in Chinese patients during dialysis. The study has shown that sK+ fluctuation between pre- and post-dialysis was 1.4 mmol/L, and the proportions of fluctuation of [0 - < 1], [1 - < 2], [2 - < 3], [≥3] were 24%, 62%, 13% and 1%, respectively. The potassium gradient between serum and dialysate is 2.8 mmol/L, and the proportions of gradients of [1 - < 2], [2 - < 3], [3 - < 4], [≥4] were 14%, 45%, 36% and 5%, respectively.

## Conclusion:

The prevalence and recurrence of hyperkalaemia in Chinese patients with ESRD remain high despite receiving standard adequate HD treatment. This is due to the serum potassium rebound, which could not be effectively controlled.

Findings from this PRECEDE-K suggest the need for effective potassium-lowering treatments on non-dialysis days to control for the hyperkalaemia and the serum potassium fluctuations.