Short- and Long-Term Associations of Hyperkalemia-related Events on Serum Potassium Time Courses in Patients with Chronic Kidney Disease: A Retrospective Cohort Study Using Electronic Health Records Data from the United States

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Introduction

Hyperkalemia (HK) is defined as an elevated serum potassium (sK+) level and is a potentially life-threatening condition associated with increased premature mortality risk and serious cardiac complications. HK is common in patients with chronic kidney disease, diabetes and heart failure. Management of hyperkalemia involves drugs for membrane stabilization using calcium salts and potassium-shifting agents, while potassium removal is achieved by dialysis, potassium-binding agents and loop diuretics.

Our goal is to observe and assess the immediate and long-term effect of drugs and procedures on the serum potassium level using real life data from OPTUM electronic health records (EHR) database in an exploratory manner. OPTUM EHR database holds patient-level longitudinal information for ~97 million individuals (either commercially insured, Medicare and Medicaid enrolees, or uninsured) of all ages seen at ~700 hospitals and ~7,000 clinics across the US.

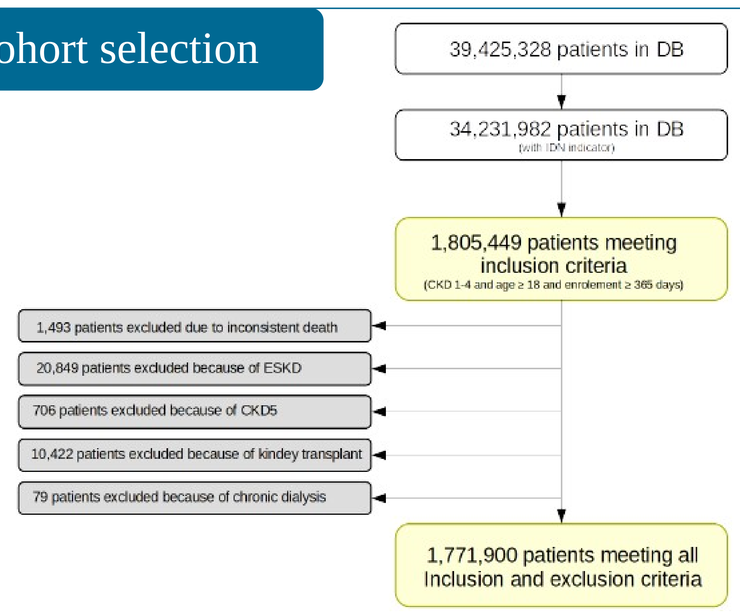
Methods – Cohort selection and definition of HK

Cohort Selection: Using US Optum® electronic health records (~39 M preselected individuals) between 1 January 2009 and 31 December 2020, **we selected patients aged ≥18 years with CKD1-4**. CKD1-4 was defined as ≥2 eGFR values of 15–60 ml/min/1.73m2 and/or ≥2 UACR values ≥30 mg/g at least 90-365 days apart (measurements between the two qualifying measurements were required to be consistent; second qualifying value = index date; prior 365 days = baseline). Patients with evidence of kidney failure, previous haemodialysis, or kidney transplantation were excluded (Figure 1).

Definition of HK events: We identified an episode of HK **using two elevated sK+ values** (≥5.5 mmol/l; from the inpatient setting not more than 2 to 24 hours apart or from the outpatient setting not more than 7 days apart) or one elevated sK+ plus pharmacotherapy or diagnostic code for hyperkalemia not more than 3 days apart.

Time Series: Population-averaged time series were created by aligning incident events of the variables during follow-up and to assess the short-term (days 1-3) and long-term associations (days 20-100) on sK+ levels adjacent to the respective event (see example in Figure 2).

Fig. 1: Cohort selection



Cohort description and selection of risk associated markers

Cohort: Among the 1,771,900 patients meeting the selection criteria, median age was 75 years (interquartile range [IQR] 66–80), 57.7% were women.

Marker pre-selection: Starting with > 5k variables, a bootstrapping multi-variable Cox regression analysis suggested 300 baseline variables affecting HK risk and sK+ level in the follow-up period. Top variables associated with elevated HK risk included:

- **diagnosis of HK** (Median Hazard Ratio [HR], 2.85; IQR, 2.68-3.04)
- **diagnosis of liver cirrhosis** (HR, 2.1; 1.94-2.36)
- **prescription of sodium polystyrene sulfonate** (HR, 2.71; 2.62-3.04)
- **prescription of ion exchange resins** (HR, 2.7; 2.49-2.96);

Variables associated with a decreased HK risk were:

- **prescription of atenolol/chlorthalidone** (HR: 0.57; 0.55-0.58)
- **prescription of tretinoin** (HR: 0.58; 0.57-0.59) prescriptions.

Fig. 2: Detailed potassium time series (SPS, Spironolactone)

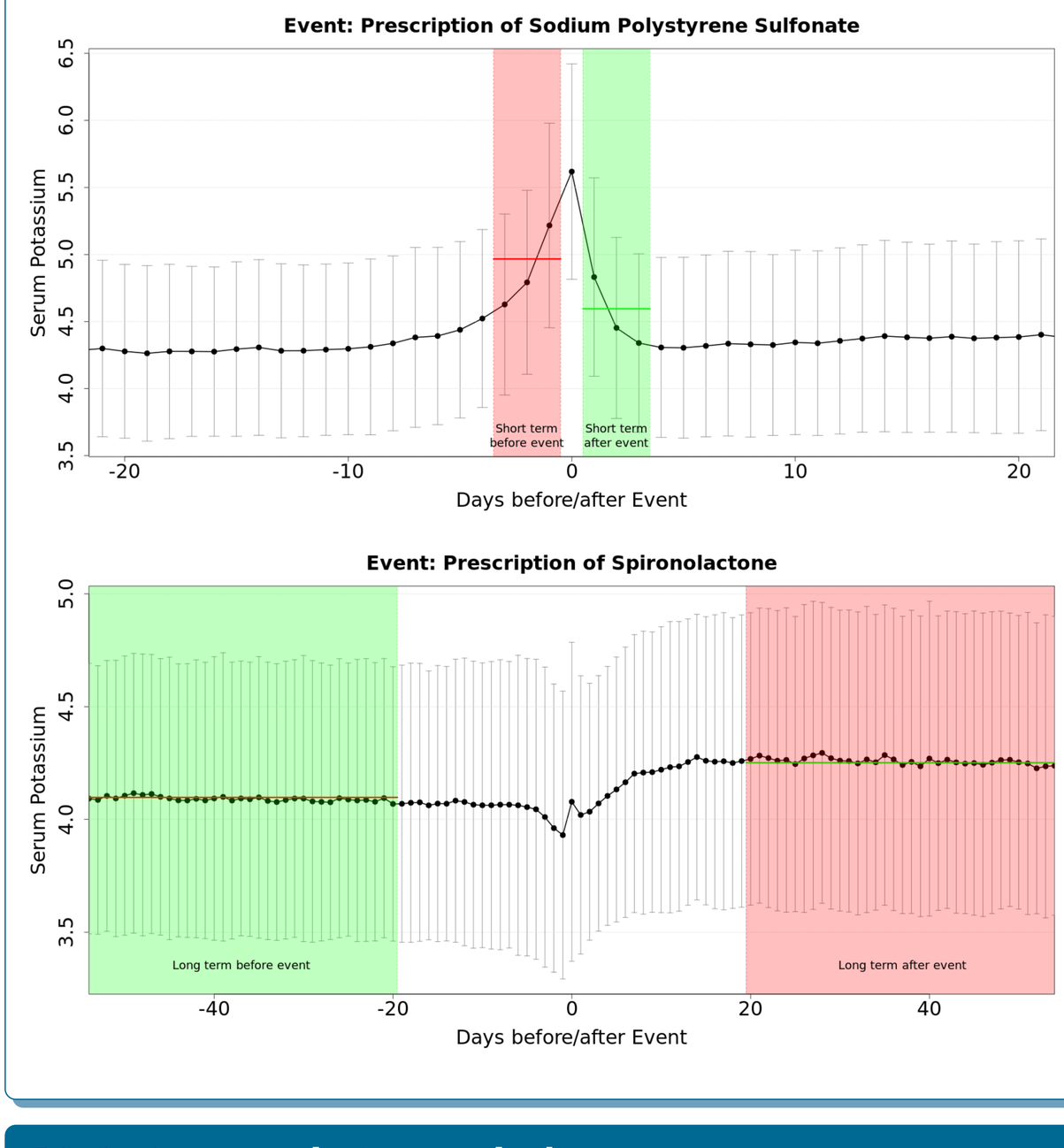
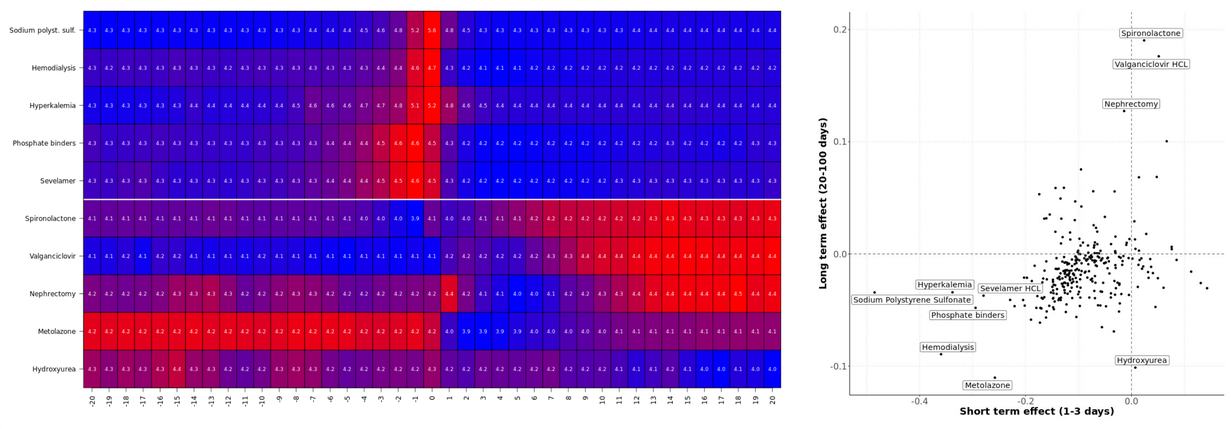


Fig. 3: left: potassium profiles; right: short vs. long term effects



Short and long term effect on serum potassium concentration (sK+)

Population averaged time courses for the 300 pre-selected markers show different characteristic shapes with short- (days 1-3) and long-term (days 20-100) associations on serum potassium levels during follow-up. Strongest short-term associations were found for:

- **prescription of sodium polystyrene sulfonate** (-0.485 mmol/L) – see Figure 2
- **procedure: hemodialysis** (-0.36 mmol/L)
- **diagnosis of hyperkalemia** (-0.34 mmol/L)
- **prescription of phosphate binders** (-0.29 mmol/L)
- **prescription of sevelamer** (-0.28 mmol/L).

Major long-term associations were found for:

- **prescription of spironolactone** (+0.19 mmol/L) – see Figure 2
- **prescription of valganciclovir** (+0.18 mmol/L)
- **procedure: partial nephrectomy** (+0.13 mmol/L)
- **prescription of metolazone** (-0.11 mmol/L)
- **prescription of hydroxyurea** (-0.1 mmol/L).

The identified profiles often show distinct patterns. In addition, drugs affecting the serum potassium concentration typically showed either a short term effect or a long term effect (Figure 3).

Limitations, conclusions, outlook

Limitations: Our approach can detect correlations but we can not make a statement about causal relations. E.g. the diagnosis of HK leads to a strong short term decrease of serum potassium but the reason is not the diagnosis itself, but rather the initiation of a treatment.

Conclusions: Our investigation identified and quantified clinical covariates associated with short- and long-term effects on sK+ levels in a large real-world cohort of patients with CKD. These findings highlight clinically relevant risk factors associated with sK+ variability over time which may inform optimal management of patients with CKD.

Outlook: We only investigated the single drug effects. A multi-variate analysis considering correlation of events might help for a better causal interpretation.

[1] van Boemmel-Wegmann S, Bauer C, Schuchhardt J, Hartenstein A, James G, Pessina E, Beeman S, Edfors R, Pecoits-Filho R, Hyperkalemia Incidence in Patients With Non-Dialysis Chronic Kidney Disease: A Large Retrospective Cohort Study from United States Clinical Care, Kidney Medicine (2024), doi:https://doi.org/10.1016/j.xkme.2024.100879.

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Abbreviations: **CKD:** chronic kidney disease; **DB:** database; **eGFR:** estimated glomerular filtration rate; **EHR:** electronic health records; **ESKD:** end stage kidney disease; **HK:** hyperkalemia; **HR:** hazard ratio; **sK+:** serum potassium; **UACR:** urine albumin-creatinine ratio