

Hyperkalemia Burden and Treatment Pathways in Patients with CKD: Findings From the DISCOVER CKD Retrospective Cohort

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Key Points

- Hyperkalemia (HK) is associated with increased comorbidity burden in patients with CKD.
- Reducing serum potassium levels after HK episodes helps continuation of renin-angiotensin-aldosterone system inhibitor treatment.
- In Japan, HK treatment pathways are more heterogeneous and potassium binders are more commonly prescribed compared with the United Kingdom.

Abstract

Background This analysis used retrospective data from the DISCOVER CKD observational study (NCT04034992) to describe the burden of and treatment pathways for hyperkalemia (HK) in patients with CKD.

Methods Data were extracted from the following databases: UK Clinical Practice Research Datalink (2008–2019) and Japan Medical Data Vision (2008–2017). Patients with CKD (two eGFR measures <75 ml/min per 1.73 m² recorded ≥90 days apart) and HK (at least two serum potassium [sK⁺] measures >5.0 mmol/L) were compared with patients without HK (sK⁺ <5.0 mmol/L); HK index event was the second sK⁺ measurement. Outcomes included baseline characteristics and treatment pathways for key medications (renin-angiotensin-aldosterone system inhibitors [RAASi], diuretics and potassium [K⁺] binders).

Results In the UK Clinical Practice Research Datalink, 37,713 patients with HK and 142,703 patients without HK were included for analysis (HK prevalence 20.9%). In the Japan Medical Data Vision, 5924 patients with HK and 74,272 patients without HK were included for analysis (HK prevalence 7.4%). In both databases, median eGFR was lower and comorbidities such as hypertension, heart failure, type 2 diabetes, and AKI were more prevalent among patients with versus without HK, and most patients were taking RAASi at the time of HK index. Treatment pathways were more heterogeneous in Japan; <0.2% of patients with CKD and HK in the United Kingdom initiated K⁺ binders within 3 months of HK index versus 18.7% in Japan. The proportions of patients with CKD and HK who stopped treatment with diuretics, K⁺ binders, and RAASi during follow-up were 48.7%, 76.5%, and 50.6%, respectively, in the United Kingdom, and 22.9%, 53.6%, and 29.2%, respectively, in Japan.

Conclusions HK was associated with increased comorbidity burden in patients with CKD. Variations in treatment pathways between the United Kingdom and Japan reflect the previous lack of a standardized approach to HK management in CKD.

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Introduction

Hyperkalemia (HK), defined as serum potassium (sK^+) >5.0 mmol/L, is a potentially serious condition that is common in patients with CKD.^{1–3} The combination of CKD and HK is associated with an elevated risk of adverse outcomes and mortality,^{3,4} reduced health-related quality of life,⁵ and increased health care resource utilization and costs.⁶

Guidelines recommend using renin-angiotensin system inhibitors (RASi, comprising angiotensin-converting enzyme inhibitors [ACEi] and angiotensin receptor blockers) at the maximum tolerated dose to delay or prevent CKD progression in patients with or without diabetes.^{7,8} Contemporary data suggest that augmenting RASi with sodium-glucose cotransporter 2 inhibitors (SGLT2i) or non-steroidal mineralocorticoid receptor antagonists (MRA) can improve kidney and cardiovascular outcomes.^{9–12} However, RASi and MRA may also predispose patients to HK,^{13–15} and guidelines recommend assessing sK^+ within 2–4 weeks of initiating or increasing the dose of RASi and at 4 weeks after initiating MRA (and every 4 months thereafter).⁷ Although physicians frequently choose to manage HK by down-titrating or discontinuing RASi, this approach denies patients with CKD the well-reported clinical benefits of RASi and may elevate the risks of adverse clinical outcomes, hospitalization, and mortality.^{16,17} The latest guidelines and Delphi consensus recommendations propose reducing sK^+ first by limiting dietary potassium (K^+) intake, discontinuing any medications (such as nonsteroidal anti-inflammatory drugs) or food supplements/herbal remedies that could impair K^+ excretion, and initiating treatment with K^+ -wasting diuretics or novel K^+ binders (sodium zirconium cyclosilicate [SZC] or patiromer).^{7,8} Moreover, previous studies in patients with diabetes and high cardiovascular risk or with CKD have demonstrated that SGLT2i significantly reduce the risk of HK.¹⁸ Down-titration or discontinuation of renin-angiotensin-aldosterone system inhibitors (RAASi, comprising ACEi, angiotensin receptor blocker, and MRA) is recommended only if all other steps to reduce sK^+ are unsuccessful.^{7,8}

Understanding the burden of and real-world treatment pathways for HK in patients with CKD will help to inform HK management strategies. The aims of this analysis were to use data from DISCOVER CKD to describe: (1) the burden of HK in patients with CKD; (2) treatment pathways for key medications (RAASi, diuretics, and K^+ binders) prescribed within 3 months of HK index; and (3) the characteristics of patients initiating K^+ binders during the observation period. DISCOVER CKD is an ongoing, international, observational study of patients with CKD (ClinicalTrials.gov Identifier: [NCT04034992](https://clinicaltrials.gov/ct2/show/study/NCT04034992)). DISCOVER CKD aims to provide contemporary real-world insights that will improve our understanding of the epidemiology of CKD, and the determinants of clinical and patient-reported outcomes across a range of geographic regions.¹⁹

Methods

Study Design and Patients

Data for this study were extracted from two databases: the UK Clinical Practice Research Datalink (CPRD),²⁰ linked to the Hospital Episode Statistics and Office for National

Statistics databases, from 2008 to 2019; and the Japan Medical Data Vision (MDV-J) from 2008 to 2017.²¹ Inclusion criteria for the DISCOVER CKD study cohort have been described previously.¹⁹ Briefly, the inclusion criteria for this analysis were as follows:

1. Adults aged ≥ 18 years with stage 2–5 CKD, identified by two consecutive eGFR measures of <75 ml/min per 1.73 m² recorded 90–730 days apart on or after January 1, 2008. For patients with eGFR 60–75 ml/min per 1.73 m², one of the following was also required: CKD diagnostic code; a history/presence (code or laboratory measurement) of albuminuria; or a history of kidney transplant; or a confirmed cause of CKD, including IgA nephropathy, GN, lupus nephritis, anti-neutrophil cytoplasm autoantibody nephritis, or polycystic kidney disease.
2. Eligible patients were also required to have at least two sK^+ measures of >5.0 mmol/L. The HK index date was the second sK^+ measurement (>5.0 mmol/L) on or after the CKD index date (Figure 1).

Patients' ineligible for inclusion were those with <1 year of medical history available or with a diagnosis of cancer on or within 1 year of the index date,¹⁹ and those on dialysis.

Study Variables and Outcomes

All available covariates for the DISCOVER CKD cohort have been described.¹⁹ Patient characteristics pertinent to the present analyses included age, sex, laboratory findings, CKD stage and treatment status, medication prescriptions, comorbidities (including hypertension, heart failure, type 2 diabetes [T2D], and AKI), and sK^+ . Laboratory data and medication prescriptions for patients with and without HK were based on data captured on or within 12 months of the index date. The number of patients with CKD and HK who were taking key medications any time from 3 months before to 3 months after HK index, up to the end of follow-up, was assessed in each database (Figure 1). Key medications included RAASi, diuretics (comprising loop diuretics and/or thiazide diuretics), and K^+ binders (comprising calcium polystyrene sulfonate/sodium polystyrene sulfonate [C/SPS], patiromer, and/or SZC).

Sankey plots were used to visualize chronological treatment pathways for key medications. Sankey plots are flow diagrams used to emphasize flow, movement, or change from one state to another or one time to another, for example, for visualizing the trajectory of a population that experienced an event.^{22,23} The x axis represents steps or time points. The total height of the y axis represents the full sample (100%). Different states or times are represented as nodes, and the connections between nodes are referred to as arcs. Arcs represent the proportion of the sample transitioning from one node to the next. Pathway analyses included treatments initiated before CKD but overlapping with the CKD index date. Days from partially overlapping treatment durations were brought forward and added to the subsequent treatment. Pathways that contained fewer than five patients were excluded. Treatments were considered to have been stopped if a key medication was not taken for 90 days. The observation period encompassed 3 months before and after the HK index event.

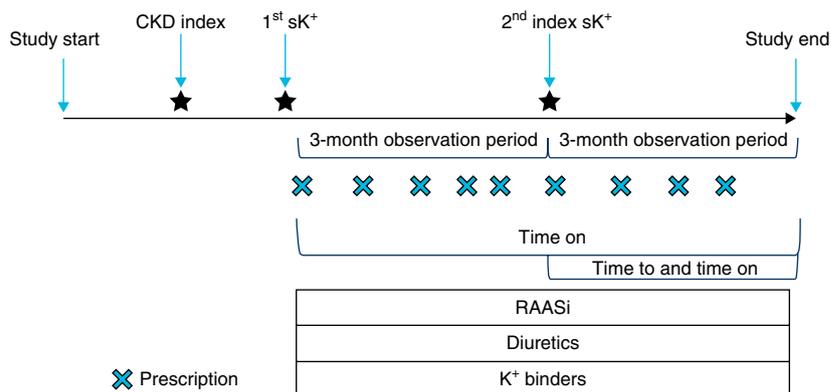


Figure 1. Study design and observation periods. Diuretics included thiazide and loop diuretics. K⁺ binders included C/SPS, patiromer, and SZC. RAASi included ACEi, ARB, and MRAs. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C/SPS, calcium polystyrene sulfonate/sodium polystyrene sulfonate; K⁺, potassium; MRA, mineralocorticoid receptor antagonists; RAASi, renin-angiotensin-aldosterone system inhibitors; sK⁺, serum potassium; SZC, sodium zirconium cyclosilicate.

Statistical Analyses

Baseline/index characteristics were summarized descriptively for each database/cohort and were stratified by CKD stage and HK severity. Treatment pathways were summarized descriptively for each database/cohort. Sankey plots were generated using R Statistical Software. Summary statistics were generated using Python Statistical Software.

Results

Patient Attrition

The DISCOVER CKD retrospective cohort included data pertaining to 425,246 patients in the UK CPRD and 128,624 patients in the MDV-J. The UK CPRD included 180,416 patients with CKD, with ($n=37,713$) and without ($n=142,703$) HK, who were eligible for analysis. The MDV-J included 80,196 patients with CKD, with ($n=5924$)

and without ($n=74,272$) HK, who were eligible for analysis (Figure 2).

Baseline Characteristics of Patients with CKD, with or without HK

Patients with CKD and HK comprised 20.9% of eligible patients in the UK CPRD and 7.4% of eligible patients in the MDV-J. Most patients with HK had mild HK (sK⁺ 5.0–5.5 mmol/L) in both databases (70.2%–72.5%) (Figure 3). In both databases, median age was slightly higher in patients with versus without HK. Patients with HK had lower median eGFR and a higher prevalence of comorbidities (hypertension, heart failure, T2D, and AKI) compared with those without HK (Tables 1 and 2). Regardless of HK status, the prevalence of hypertension, heart failure, and T2D was higher in Japan compared with the United

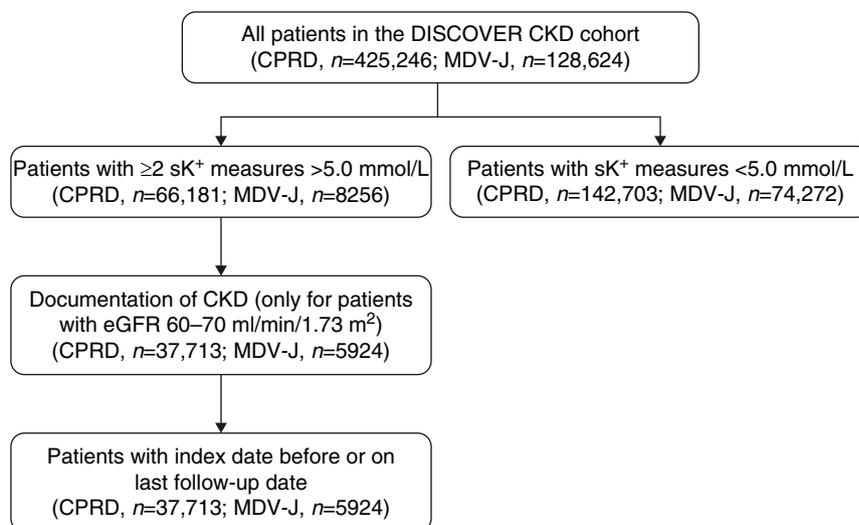


Figure 2. Attrition of patients during the screening process by database. CPRD, Clinical Practice Research Datalink; MDV-J, Japan Medical Data Vision.

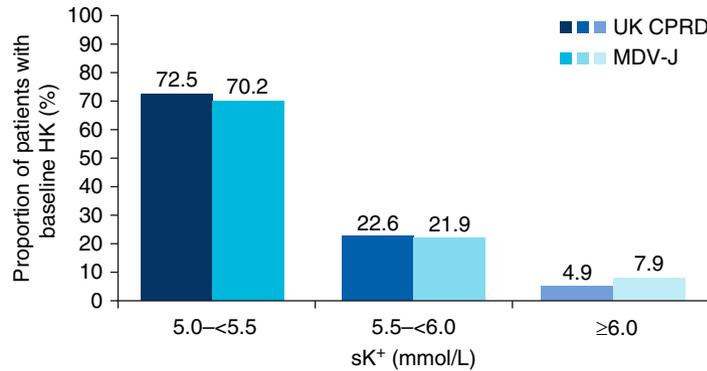


Figure 3. Proportion of patients with baseline HK stratified by severity. HK, hyperkalemia.

Kingdom; the prevalence of AKI was low and comparable between the two databases (Tables 1 and 2).

Regardless of HK status, RAASi were the most commonly taken key medication at baseline, followed by diuretics, MRA, and K⁺ binders (Tables 1 and 2). More patients were taking MRA or K⁺ binders in Japan compared with the United Kingdom; in the United Kingdom, <0.1% of patients were taking K⁺ binders at baseline. In both databases, the proportion of patients taking RAASi was higher among those with HK compared with those without HK, regardless of CKD stage (Tables 1 and 2).

Treatment Pathways for Key Medications in Patients with CKD and HK

The treatment pathways analysis (Sankey plots) of patients with a key medication initiated within 3 months of HK index date included 27,007 and 4191 patients from the UK CPRD and MDV-J, respectively. Treatment pathways differed between the United Kingdom and Japan. In the United Kingdom, RAASi, either alone or in combination with diuretics, were the most common treatment taken by patients in 3 months before and after HK index; treatment with diuretics alone was less common (Figure 4A). Fewer than one fifth of patients in the United Kingdom were prescribed alternative treatments for HK, including K⁺ binders (Figure 4A). Among those patients who were taking RAASi after HK index, the majority continued to take RAASi alone rather than in combination with diuretics (Figure 4B). Among those patients who were not taking RAASi as a monotherapy after HK index, approximately two-thirds took RAASi in combination with a diuretic; the remainder took diuretics alone (Figure 4C).

In Japan, treatment pathways in patients with CKD and HK were more heterogeneous compared with the United Kingdom. RAASi, either alone or in combination with diuretics, were the most common treatment taken in 3 months before and after HK index, followed by diuretics alone; in addition, a smaller proportion of patients were taking K⁺ binders, alone or in combination with one or more other medications (Figure 5A). Among those patients who were taking RAASi after HK index, the majority took RAASi alone rather than in combination with another medication (Figure 5B). Among those patients who did not take RAASi monotherapy after HK index, many continued taking

RAASi in combination with a diuretic; smaller proportions took RAASi in combination with K⁺ binders, with or without diuretics (Figure 5C).

Proportions of Patients with CKD and HK Who Stopped Treatment with Key Medications during Follow-Up

The proportions of patients with CKD and HK who stopped taking diuretics, K⁺ binders, or RAASi during follow-up were 48.7%, 76.5%, and 50.6%, respectively, in the UK CPRD, and 22.9%, 53.6%, and 29.2%, respectively, in the MDV-J (Figure 6A). The proportions of patients stopping these key medications were higher in the United Kingdom compared with Japan, regardless of HK severity (Figure 6, B–D). Within each country, the proportions of patients stopping these key medications were generally similar for patients with or without AKI at baseline (Supplemental Table 1).

Characteristics of Patients Initiating K⁺ Binders within 3 Months of HK Index

In the United Kingdom, very few (<0.2%; *n*=51/27,007) patients with CKD and HK initiated K⁺ binders within 3 months of HK index, compared with 18.7% (*n*=785/4189) of patients in Japan (Table 3). Compared with patients in the United Kingdom, patients in Japan initiating treatment with K⁺ binders had lower median sK⁺ levels (5.6 versus 6.0 mmol/L), higher median age (81 versus 70 years), and lower median eGFR (25.0 versus 31.4 ml/min per 1.73 m²). Hypertension was the most common comorbidity among patients in the United Kingdom and Japan (62.7% and 87.4%, respectively), followed by T2D in the United Kingdom (37.3%) and heart failure in Japan (65.0%). At the time of initiating treatment with K⁺ binders, similar proportions of patients in the United Kingdom and Japan were already taking RAASi (approximately 61%) or diuretics (approximately 55%–60%); fewer were taking MRA (approximately 20%–25%).

Among patients in the United Kingdom with CKD and HK who initiated K⁺ binders, median eGFR was 31.4 ml/min per 1.73 m² (Table 3), which was lower than the median eGFR of all eligible patients in the UK CPRD with or without HK (52.0–55.3 ml/min per 1.73 m²), although higher than the median eGFR of those patients with CKD stages 4–5 (≤25.3 ml/min per 1.73 m²) (Table 1). The

Table 1. Baseline characteristics of patients with and without hyperkalemia from the UK Clinical Practice Research Datalink

CKD Stage	Without Hyperkalemia						With Hyperkalemia					
	2	3	4	5	Unspecified	Any	2	3	4	5	Unspecified	Any
Demographics												
Patients, n (%)	13,361 (9.4)	122,052 (85.5)	2952 (2.1)	1052 (0.7)	3286 (2.3)	142,703 (100)	5196 (13.8)	27,218 (72.2)	2790 (7.4)	459 (1.2)	2050 (5.4)	37,713 (100)
Age, median (IQR), yr	66 (58–74)	74 (66–82)	81 (70–89)	64 (50–77)	61 (47–74)	74 (64–82)	70 (63–77)	76 (69–83)	79 (69–86)	73 (57–83)	67 (59–75)	75 (67–82)
Female, %	48.8	61.2	60.7	44.9	51.8	59.7	49.7	52.6	52.9	42.5	46.1	51.8
Race, %												
Asian	3.7	0.8	0.8	2.8	2.6	1.1	3.3	1.0	1.1	2.2	4.7	1.5
Black or African American	2.4	0.8	0.5	1.7	2.4	1.0	1.3	0.3	0.4	2.0	0.9	0.5
White	78.4	56.7	53.0	59.8	60.3	58.8	82.8	42.5	63.4	65.6	69.1	51.3
Other	1.6	0.6	0.6	1.6	2.3	0.7	1.1	0.5	0.5	0.9	1.4	0.6
Unknown	14.0	41.1	45.1	34.1	32.5	38.4	11.5	55.7	34.6	29.4	23.9	46.0
Laboratory results, median (IQR)												
eGFR, ml/min per 1.73 m ²	69.2 (65.1–72.3)	54.1 (48.5–57.6)	25.3 (21.4–28.1)	9.5 (1.0–14.5)	63.4 (40.0–81.6)	55.3 (49.0–59.0)	66.1 (62.9–70.2)	47.7 (40.5–53.9)	24.8 (20.8–27.7)	11.2 (8.0–13.4)	82.4 (78.7–87.7)	52.0 (40.4–62.9)
sK ⁺ , mmol/L	4.4 (4.1–4.7)	4.4 (4.1–4.7)	4.5 (4.2–4.9)	4.6 (4.1–5.0)	4.4 (4.1–4.6)	4.4 (4.1–4.7)	5.3 (5.1–5.4)	5.3 (5.1–5.5)	5.3 (5.2–5.6)	5.5 (5.2–5.9)	5.3 (5.1–5.5)	5.3 (5.1–5.5)
UACR, mg/g	37.1 (14.3–85.0)	15.9 (6.2–57.5)	53.1 (12.9–265.5)	31.0 (8.0–449.7)	31.5 (8.0–123.9)	22.1 (7.4–66.4)	22.1 (8.0–80.3)	23.9 (8.6–88.5)	62.8 (15.9–262.8)	276.0 (45.1–1000.0)	27.7 (8.9–97.4)	24.7 (8.5–93.8)
Comorbidities, %												
Hypertension	62.8	52.6	58.3	52.8	42.3	53.5	59.8	65.4	68.1	66.7	59.6	64.5
Heart failure	5.1	6.1	13.0	21.4	6.3	6.2	8.1	14.0	22.2	17.0	9.0	13.5
T2D	57.0	11.1	15.3	23.2	11.8	15.6	42.6	31.9	29.4	27.7	52.3	34.3
AKI	2.4	1.8	9.5	21.4	7.6	2.3	4.5	5.0	15.6	32.5	6.0	6.1
Prescriptions, %												
RAASi	60.4	39.7	45.1	36.8	32.0	41.6	62.3	69.3	70.1	54.5	62.0	67.8
MRA	3.4	3.4	7.6	4.5	2.8	3.4	6.2	11.6	15.8	8.5	6.5	10.9
Diuretics	35.1	38.5	54.8	37.0	26.6	38.2	25.7	40.7	54.5	47.5	27.5	39.0
K ⁺ binders	<0.1	<0.1	0	0.6	0.1	<0.1	<0.1	0.1	0.3	1.3	0.2	0.1

CKD stage included patients with a generic CKD code. Diuretics included thiazide and loop diuretics. Potassium binders included calcium polystyrene sulfonate/sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate. Renin-angiotensin-aldosterone system inhibitor included angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and MRA. IQR, interquartile range; K⁺, potassium; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; sK⁺, serum potassium; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

Table 2. Baseline characteristics of patients with and without hyperkalemia from the Japan Medical Data Vision

CKD Stage	Without Hyperkalemia						With Hyperkalemia					
	2	3	4	5	Unspecified	Any	2	3	4	5	Unspecified	Any
Demographics												
Patients, <i>n</i> (%)	5062 (6.8)	32,591 (43.9)	3216 (4.3)	3429 (4.6)	29,974 (40.4)	74,272 (100)	408 (6.9)	2938 (49.6)	1553 (26.2)	845 (14.3)	180 (3.0)	5924 (100)
Age, median (IQR), yr	65 (54–75)	77 (69–84)	84 (76–89)	75 (66–85)	80 (71–87)	78 (69–85)	75 (67–83)	79 (72–86)	82 (75–88)	77 (67–86)	78 (68–86)	80 (71–86)
Female, %	60.0	53.1	58.4	40.5	45.4	50.1	46.3	47.9	52.2	47.7	43.9	48.7
Laboratory results, median (IQR)												
eGFR, ml/min per 1.73 m ²	68.9 (64.4–72.3)	51.6 (44.8–56.3)	24.8 (21.0–27.8)	8.5 (6.1–11.8)	81.2 (53.8–94.9)	52.4 (43.8–57.9)	65.3 (62.0–69.8)	42.5 (35.9–49.5)	23.0 (19.3–26.3)	9.0 (5.8–12.3)	83.6 (77.5–96.5)	34.1 (21.6–47.5)
sK ⁺ , mmol/L	4.1 (3.9–4.4)	4.2 (4.0–4.5)	4.4 (4.0–4.8)	4.4 (3.9–4.9)	4.1 (3.9–4.4)	4.2 (4.0–4.5)	5.2 (5.1–5.4)	5.2 (5.1–5.4)	5.3 (5.2–5.6)	5.4 (5.2–5.8)	5.2 (5.1–5.4)	5.3 (5.1–5.5)
Comorbidities, %												
Hypertension	49.4	64.6	72.7	68.4	83.2	71.6	75.0	82.8	88.0	81.1	70.6	83.0
Heart failure	32.6	43.3	65.0	71.6	86.4	62.2	53.2	60.7	68.9	62.7	54.4	62.4
T2D	23.6	28.4	35.7	42.6	44.0	35.4	40.0	46.0	44.9	50.2	42.2	45.8
AKI	0.9	1.3	6.5	8.9	6.0	3.7	6.1	4.8	9.3	14.0	6.1	7.4
Prescriptions, %												
RAASi	24.8	32.4	30.3	23.4	43.2	35.7	47.3	55.3	57.9	46.2	40.0	53.6
MRA	2.8	6.5	12.6	7.3	17.9	11.2	12.5	20.9	28.0	14.7	19.4	21.3
Diuretics	8.3	17.1	39.0	35.3	47.4	30.5	31.1	40.7	59.2	52.9	40.0	46.6
K ⁺ binders	0.1	0.5	4.0	7.4	14.2	6.4	6.4	9.7	17.8	22.4	13.9	13.5

CKD stage included patients with a generic CKD code. Diuretics included thiazide and loop diuretics. Potassium binders included calcium polystyrene sulfonate/sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate. Renin-angiotensin-aldosterone system inhibitor included angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and MRA. IQR, interquartile range; K⁺, potassium; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; sK⁺, serum potassium; T2D, type 2 diabetes.

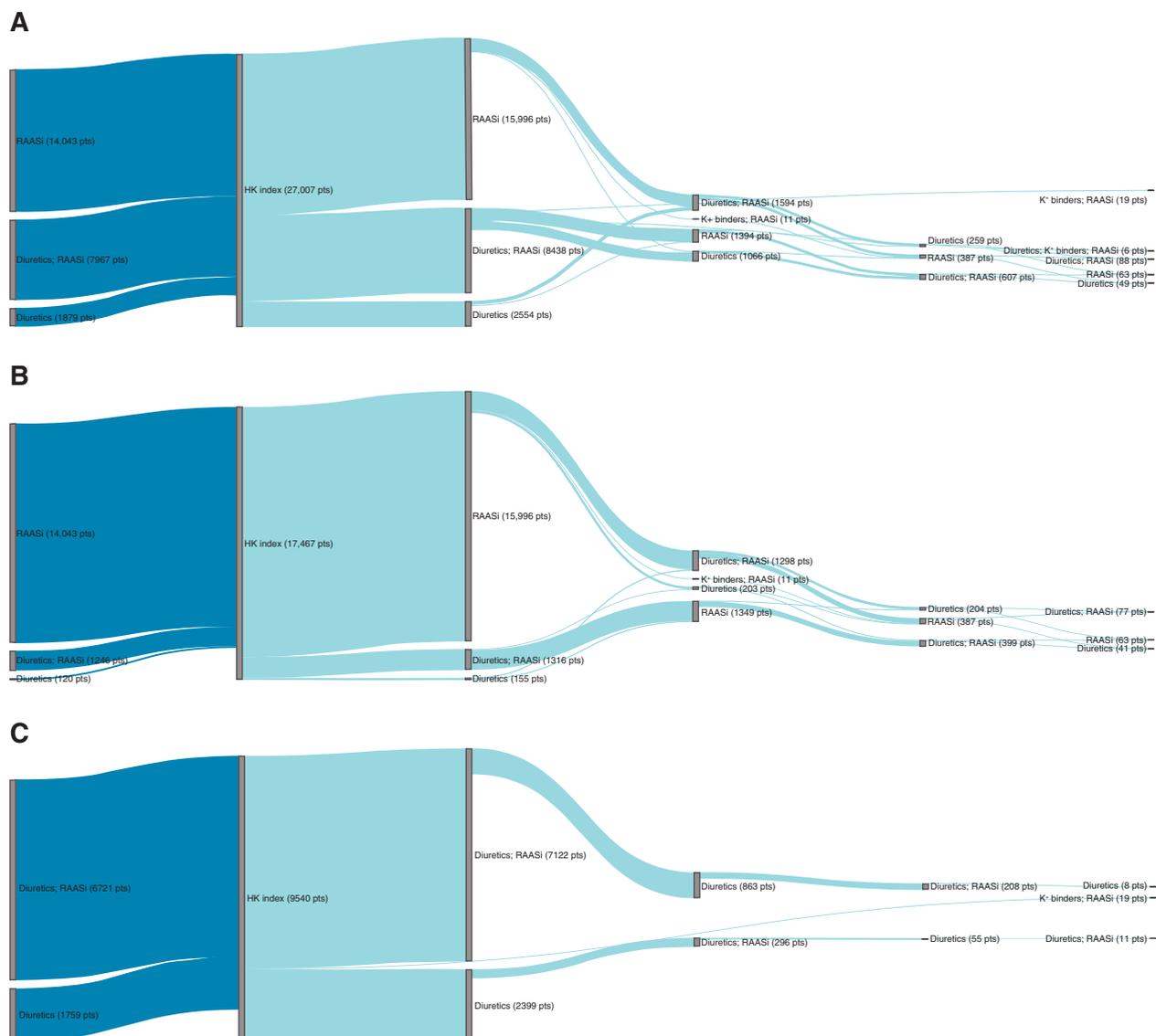


Figure 4. Treatment pathways for key medications in patients with CKD in the UK CPRD. (A) overall, (B) in patients prescribed RAASi after the HK index date, and (C) in patients not prescribed RAASi after the HK index date. Diuretics included thiazide and loop diuretics. K⁺ binders included C/SPS, patiromer, and SZC. RAASi included ACEi, ARBs, and MRAs. pts, patients.

median urine albumin-to-creatinine ratio (UACR) was 299.6 mg/g (Table 3), which was higher than the median UACR of all eligible patients in the UK CPRD with or without HK (22.1–24.7 mg/g), although comparable with the median UACR of patients with CKD stage 5 and HK (276.0 mg/g) (Table 1). The comorbidity burden among patients initiating K⁺ binders (Table 3) was higher than that recorded for all eligible patients without HK but comparable with that recorded for all eligible patients with HK (Table 1). Similar trends were observed within the MDV-J (Tables 2 and 3).

Discussion

The general prevalence of HK, usually defined as $sK^+ \geq 5$ mmol/L, is reported to be 14%–20% among patients with CKD.^{24–28} HK prevalence is also reported to increase

with declining eGFR,^{29,30} with a prevalence of 54% reported in one study of patients with eGFR <20 ml/min per 1.73 m².³¹ In this analysis, HK prevalence in the MDV-J database (7.4%) was lower than estimates from other studies, whereas HK prevalence in the UK CPRD database (20.9%) was more comparable with the published literature. In both databases, most of the patients with HK had stage 3 CKD, and those with HK and stage 2–4 CKD had lower median eGFR compared with patients without HK. There was a trend toward higher comorbidity burden (hypertension, heart failure, T2D, and AKI) among patients with HK compared with patients without HK, regardless of CKD stage. Comorbidities were more commonly observed in Japan compared with the United Kingdom, which may be related to country-specific sociodemographic factors as well as the timing of dialysis initiation in each country. Previous analyses have reported greater burdens of heart failure and

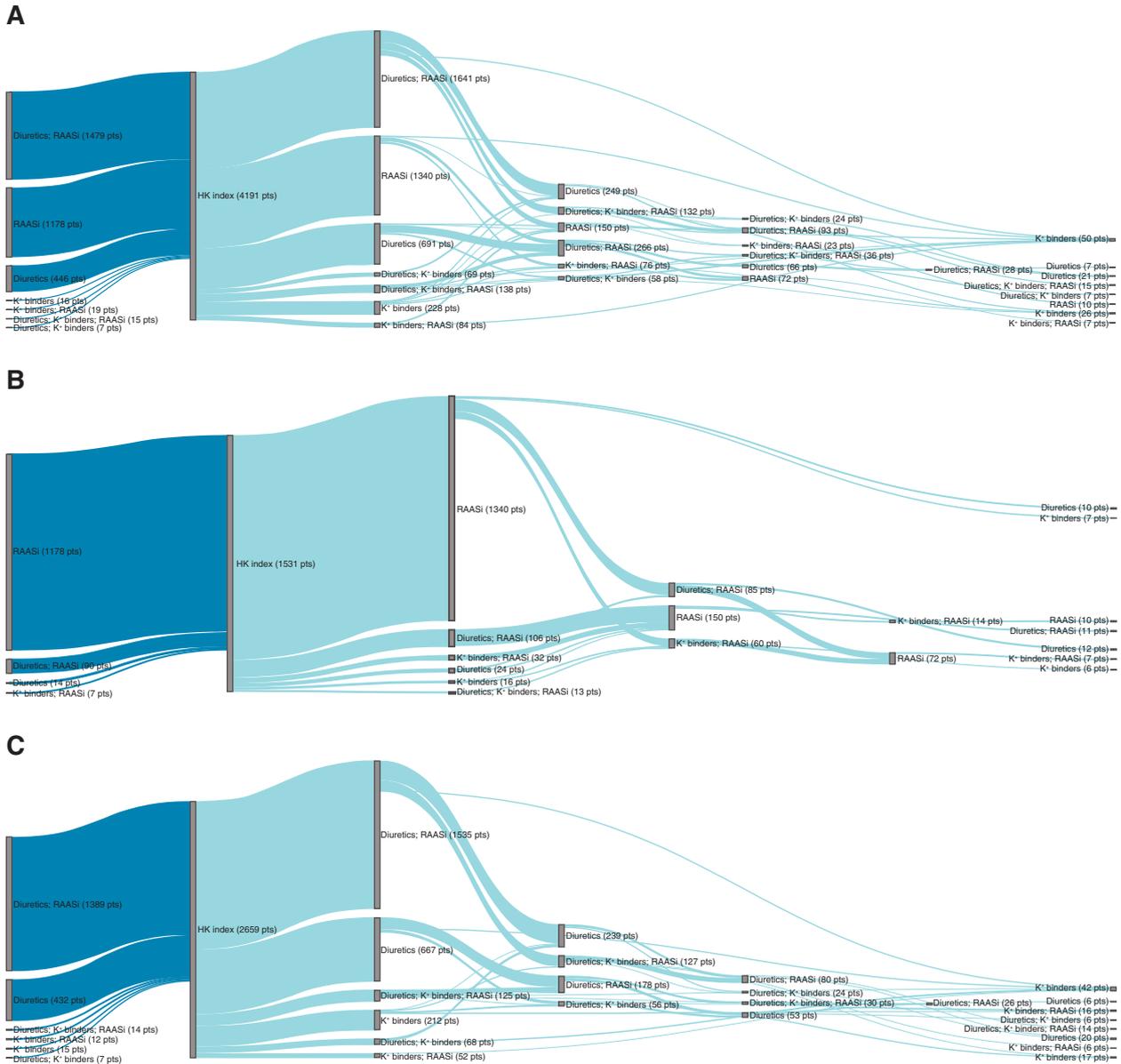


Figure 5. Treatment pathways for key medications in patients with CKD in the MDV-J. (A) overall, (B) in patients prescribed RAASi after the HK index date, and (C) in patients not prescribed RAASi after the HK index date. Diuretics included thiazide and loop diuretics. K⁺ binders included C/SPS, patiromer, and SZC. RAASi included ACEi, ARBs, and MRAs.

diabetes in Japan than in the United Kingdom.^{32,33} Furthermore, patients with CKD in Japan initiate dialysis at lower eGFR levels compared with patients in the United Kingdom^{34,35}; thus, more patients with comorbidities in the UK CPRD were potentially excluded from this analysis owing to dialysis compared with patients in the MDV-J.

Treatment pathways for key medications initiated within 3 months of the HK index date were more heterogeneous in Japan compared with the United Kingdom. In Japan, various combinations of RAASi, diuretics, and K⁺ binders were prescribed. In the United Kingdom, the most commonly prescribed key medications were RAASi or diuretics. Very few patients in the United Kingdom were prescribed K⁺ binders (<0.2% versus 18.7% of patients in Japan) despite having higher median sK⁺ levels (6.0 versus 5.6 mmol/L in

Japan). The Dialysis Outcomes and Practice Patterns Study of hemodialysis practices has already reported substantial variations in the use of K⁺ binders (from 5% in Canada to 42% in France).³⁶ In our study, heterogeneous treatment use and patterns between the United Kingdom and Japan may reflect the greater comorbidity burden observed in Japan; in particular, this might have resulted in the greater use of K⁺ binders (alone or in combination with other key medications) in Japan to manage HK so that treatment with RAASi could be maintained.

Of the patients prescribed RAASi, 50.6% in the United Kingdom and 29.2% in Japan stopped their treatment within 90 days. Evidence supporting the discontinuation of RAASi is limited to one very small observational study of 52 patients with CKD stage 4–5, which noted improved

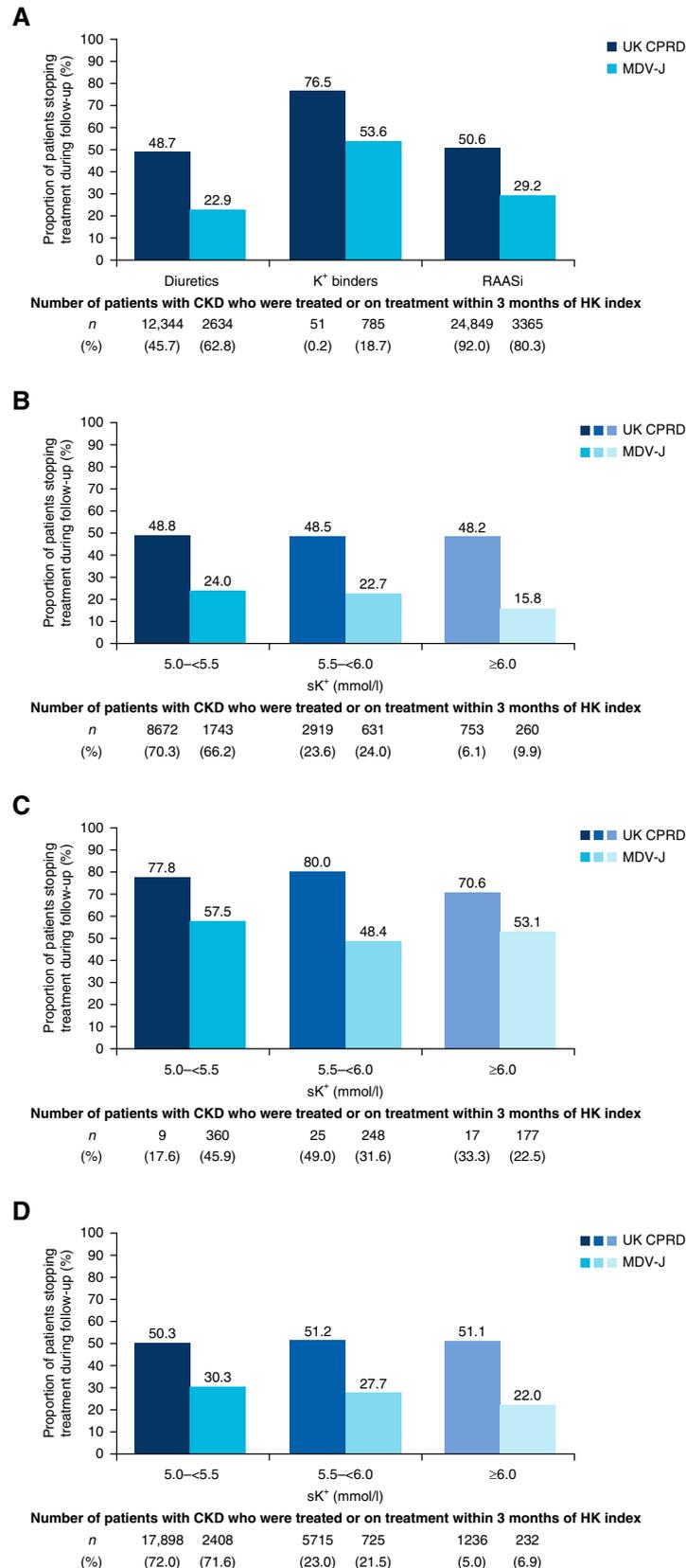


Figure 6. Proportions of patients with CKD and HK who stopped treatment with key medications during follow-up. (A) overall, and stratified by HK severity in patients taking (B) diuretics, (C) K⁺ binders, or (D) RAASi. End of follow-up contributed to a high proportion of censoring for all databases. Diuretics included thiazide and loop diuretics. K⁺ binders included C/SPS, patiromer, and SZC. RAASi included ACEi, ARBs, and MRAs. K⁺ binders are only intended for the short-term management of acute HK.

Table 3. Characteristics of patients with CKD and hyperkalemia initiating potassium binders within 3 months of hyperkalemia index

Variable	UK CPRD (N=27,007)	MDV-J (N=4189)
Patients, <i>n</i> (%)	51 (<0.2)	785 (18.7)
Age, median (IQR), yr	70 (56–79)	81 (73–87)
Female, %	23.5	47.9
Laboratory results, median (IQR)		
eGFR, ml/min per 1.73 m ²	31.4 (19.9–41.9)	25.0 (15.1–34.2)
sK ⁺ , mmol/L	6.0 (5.7–6.4)	5.6 (5.3–6.0)
UACR, mg/g	299.6 (22.1–830.1)	NA
Comorbidities, %		
Hypertension	62.7	87.4
Heart failure	13.7	65.0
T2D	37.3	46.5
AKI	9.8	12.2
Prescriptions, %		
K ⁺ binders	100	100
RAASi	60.8	60.9
MRA	19.6	25.4
Diuretics	54.9	60.0

Diuretics included thiazide and loop diuretics. Potassium binders included calcium polystyrene sulfonate/sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate. Renin-angiotensin-aldosterone system inhibitor included angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and MRA. CPRD, Clinical Practice Research Datalink; IQR, interquartile range; K⁺, potassium; MDV-J, Japan Medical Data Vision; MRA, mineralocorticoid receptor antagonist; NA, not available; RAASi, renin-angiotensin-aldosterone system inhibitor; sK⁺, serum potassium; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

kidney function and delayed onset of RRT following RAASi discontinuation.³⁷ However, the latest evidence supports the continuation rather than discontinuation of RAASi. In the larger STOP-Angiotensin Converting Enzyme Inhibitors trial of 411 patients with advanced or progressive CKD, discontinuation of RAASi neither increased eGFR nor slowed its decline.³⁸ In two very large retrospective studies of 10,254–434,027 RAASi recipients, discontinuation of RAASi was associated with elevated risks of mortality and major adverse cardiovascular events,^{39,40} findings that were later supported by a meta-analysis of six observational studies.⁴¹

The latest guidelines and Delphi consensus recommendations now propose stopping RAASi only if measures to reduce sK⁺ have first proven unsuccessful.^{7,8} One of those measures is the initiation of treatment with novel K⁺ binders. Of the patients prescribed K⁺ binders in this study, 76.5% in the United Kingdom and 53.1% in Japan stopped their treatment within 90 days. This finding is consistent with data reported from a large US commercial database, which found that 69.3% and 92.3% of 4559 adults treated with sodium polystyrene sulfonate between 2010 and 2014 stopped treatment within 30 and 60 days, respectively.⁴² However, the finding of our study should also be interpreted with caution. First, prescriptions of K⁺ binders in the United Kingdom were limited to just 51 patients. Second, patients with acute HK may have required treatment for only 3 months or less, although we note that almost 25% of patients in the United Kingdom and almost 50% in Japan were still taking their K⁺ binders at the end of the observation periods. Third, while we do not know exactly which K⁺ binders were prescribed, most of the patients in the United Kingdom would not have had access to SZC or patiromer as they were approved for use (in 2018 and 2017, respectively)^{43,44} toward the end of the data extraction

period (2008–2019). Similarly, no patients in Japan would have had access to SZC as it was approved for use (in 2020)⁴⁵ after the data extraction period (2008–2017), whereas patiromer is still not approved. Instead, most of the patients would have been prescribed the traditional K⁺ binders, C/SPS. These exchange resins are often described by patients as being unpalatable.^{46,47} Moreover, they can cause serious gastrointestinal complications,^{48,49} leading many patients to discontinue treatment.⁵⁰ The poor palatability and tolerability of C/SPS may explain the low uptake of K⁺ binders, especially in the United Kingdom, and may have contributed to the large proportion of patients who stopped treatment in both countries. For example, traditional K⁺ binders (C/SPS) have a tendency to worsen constipation,⁵¹ which might have contributed to low prescription rates of K⁺ binders or patients stopping treatment; however, data on constipation events were not available in the analysis databases.

Another measure to enable the continuation of RAASi, including combinations with MRA, is the addition of SGLT2i. Contemporary data from several clinical trials suggest that augmenting RAASi with canagliflozin can improve clinical outcomes in patients with T2D, while dapagliflozin can significantly improve clinical outcomes and reduce the risk of mortality in patients with or without T2D.^{9,10,12} Moreover, the mechanism of action of SGLT2i may also mitigate the risk of HK development.^{18,52} However, SGLT2i use was not yet widespread during the time frame of this study, therefore precluding an evaluation of their impact.

A notable strength of this study is the assessment of baseline characteristics in a large real-world cohort of 43,637 patients with CKD and HK from two different countries. Additional strengths of the analysis include the use of two sK⁺ measures to identify more persistent HK, longitudinal assessment of treatment pathways, data granularity,

the wide range of covariates explored, and the use of databases from primary- and secondary-based care that are generalizable to populations represented by the data sources. An inherent limitation of retrospective observational studies is that conclusions about causality cannot be made. In addition, our results are restricted to the specific health care systems of the United Kingdom and Japan within a particular time frame; thus, extrapolation of results to other populations requires caution.

A notable limitation of this study is the use of real-world data that were not collected for research purposes; as a result, some data were missing. For example, no data on dietary interventions were available, the causes of HK in the patient populations could not be discerned, and UACR data were not available for the MDV-J. Furthermore, metabolic acidosis and prescription of sodium bicarbonate to manage metabolic acidosis can affect the extent of HK; however, these data were not reported consistently across the databases. Key medications were grouped into treatment classes, preventing an analysis of individual medications, while the time frame of the study limited patient exposure to novel K⁺ binders and SGLT2i, both of which feature prominently in the latest guidelines and Delphi consensus recommendations.^{7,8} In addition, the rationale for prescribing, not prescribing, changing, or stopping treatment with key medications could not be discerned, while the reinitiation of treatment was not assessed. There was also potential for underreporting or misclassifying outcomes of interest. Furthermore, the differences between the data sources could affect the data interpretation and treatment approaches. For example, the MDV-J included hospital and claims data, whereas data from the UK CPRD comprised primary care sources linked to hospital data. Therefore, patients in the MDV-J were likely to have a more advanced disease stage or an increased comorbidity burden compared with patients in the UK CPRD due to the secondary care nature of the database. Other studies are assessing the effect of RAASi dose adjustment on clinical outcomes in patients with CKD experiencing an episode of HK, and data from Japan and the United States are already available.¹⁷

In this large, geographically diverse cohort of patients with CKD, HK was generally of mild severity. However, patients with HK had a greater disease burden compared with patients without HK. Prescriptions of key medications varied between the United Kingdom and Japan. This finding is consistent with the observations reported elsewhere and likely reflects a previous lack of consensus on how to manage episodes of HK in patients with CKD. The latest guidelines and Delphi consensus recommendations reinforce the benefits of maintaining RAASi treatment in these patients and propose several measures to reduce sK⁺. Studies are now warranted to determine whether these measures can facilitate the continuation of RAASi treatment and to determine the effect of a second HK episode.

Disclosure

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/KN9/A524>.

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Data Sharing Statement

Data cannot be shared. Secondary datasets used in the study are third-party datasets contracted to be strictly used within AstraZeneca and hence unavailable for data shares.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/KN9/A523>.

Supplemental Table 1. Proportions of patients with CKD and HK who stopped treatment with key medications during follow-up by AKI status at baseline.

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