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Healthcare resource utilization and cost associated with elevated potassium levels: a Danish population-based cohort study

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Abstract

Objectives: To estimate healthcare costs associated with hyperkalemia (HK) among patients with chronic kidney disease (CKD), heart failure (HF), or diabetes.

Design: This was a cohort study linking laboratory test results from both primary and hospital care for the entire region's population of Northern Denmark with morbidity, mortality, and medication data from Danish national registries.

Setting: Patients with an incident diagnosis of CKD, HF, or diabetes were identified in secondary care (hospitalizations and out-patient visits). First and subsequent HK events were reported, i.e. potassium level >5.0 mmol/L.

Participants: For each patient experiencing HK, a comparison patient without HK was matched on prespecified clinical characteristics.

Primary and secondary outcome measures: The mean costs reported based hospital care, general practice, and dispensed drugs data were measured in 2015 Euros (€) during 6 months before and 6 months after the HK event in the HK patients and the matched non-HK comparisons.

Results: Overall, 17,747 CKD patients, 5,141 HF patients, and 4,183 diabetes patients with a first HK event were included. More than 40% of all patients across the patient groups, had subsequent HK events with successively shorter times between the events. In CKD patients, overall mean costs were €5,598 higher 6 months after HK compared to before HK, while €444 higher in the matched non-HK comparisons, yielding HK-associated costs of €5,154. Corresponding costs associated with a HK event were €6,110 in HF patients, and €4,924 in diabetes patients.

Conclusions: Among CKD, HF, and diabetes patients an incident HK event was common and a large proportion of the patients experienced recurrent HK events with shorter time intervals. Substantial increase in healthcare costs associated with a HK event was observed in the HK patients compared to non-HK patients.

Strengths and limitations of this study

Strengths

- Access to laboratory test results from both primary and hospital care for the entire region's population of Northern Denmark (1,841,902 residents, i.e. 33% of Denmark's population) linkable to nationwide data on morbidity, mortality, and medication.
- Describing corresponding healthcare resource utilization and costs in the main hyperkalaemia (HK) risk groups; patients with chronic kidney disease (CKD), heart failure (HF), or diabetes.
- Reported costs are based on official Diagnosis Related Groups (DRG) and Danish Outpatient Grouping System (DAGS) charges.

Limitations

- Any conclusions concerning causal mechanisms underlying HK outcomes and corresponding costs should be made with caution.
- Rather than precipitating a hospitalization, elevated potassium levels measured during hospitalization may stem from an underlying condition leading to hospitalization.

Background

Hyperkalemia (HK) is defined as serum potassium levels above a reference range, usually above 5.0 mmol/L.[1] HK has been reported to occur in 3–8% of all hospitalized patients, independent of reason for hospitalization, based on single clinic or health insurance based cross-sectional studies.[2-5] Patients older than 65 years with chronic kidney disease (CKD), heart failure (HF), diabetes, or who use renin-angiotensin-aldosterone system inhibitors (RAASi) are at increased risk of experiencing HK.[1, 6-9] An elevated plasma potassium concentration may result in muscle weakness, paralysis, life-threatening effects on cardiac arrhythmias, and sudden death.[6] The latter two have been reported in particular among patients with potassium levels above 6.0 mmol/L.[10, 11] However, recent cohort analyses indicate that potassium levels above 5.0 mmol/L may also predict increased higher risk of cardiovascular events and short-term mortality among patients with an acute hospitalization,[12, 13] as well as among patients with CKD or HF.[14-17]

Although HK has been associated with longer stay during acute hospitalizations, as well as an increased number of intensive care unit (ICU) stays and emergency department visits, [12, 18-20] overall healthcare resource utilization (HRU) and costs associated with HK have not been comprehensively studied in a population-based setting. The aims of this study were to investigate overall HRU and costs associated with HK in a real-world clinical setting in patients with an incident diagnosis of CKD, HF or diabetes.

Methods

Patient and public involvement

This was a cohort study using local and nationwide register data and no patients were involved in the design of the study. The study design is based on previous experience on what type of data clinicians, healthcare providers and payers would be interested in a therapeutic area.

Data sources

This cohort study was conducted in Northern Denmark, using routine laboratory test results from both primary and hospital care for the entire region's population (1,841,902 residents, i.e. 33% of Denmark's population in June 2011).[21] Laboratory data were linked, via mandatory and unique civil personal registration numbers (assigned to each Danish resident), to hospital diagnoses and procedure data maintained in the Danish National Patient Registry (DNPR). The DNPR contains dates of hospital admission and discharge, emergency room visits, and outpatient clinic visits as well as and procedures carried out in the hospital setting.[22] Records of all drugs prescribed in an outpatient setting and dispensed from Danish pharmacies were obtained from the National Prescription Database and the Aarhus Prescription Database.[23, 24] Data on general practitioner (GP) services were retrieved from the National Health Insurance Service Registry (NHISR).[25] This study was approved by an institutional review board.

Study populations

Overall, three disease cohorts with an incident diagnosis of CKD, HF, or diabetes, respectively, were identified between 1 January 2005 and 30 June 2011. An individual diagnosed with more than one of these conditions (such as both incident diabetes and incident

CKD) during the study period could be included in more than one patient cohort, in each case starting on the diagnosis date of the respective disease. Incident CKD was defined as the first occurrence of one of the following: (1) eGFR <60 mL/min/1.73m^2 verified by at least two creatinine measurements more than 90 days apart;[26] (2) an incident hospitalization with a diagnosis of CKD; or (3) hospital-based codes for renal dialysis. Incident HF was defined as the first occurrence of an inpatient hospital admission with a primary or secondary discharge diagnosis of HF.[23, 24, 27] Incident diabetes was defined as the first dispensed prescription for a glucose-lowering drug.[22, 28] Baseline characteristics of the three disease cohorts were described at the time of their first diagnosis of CKD, HF or diabetes respectively.

Hyperkalemia patients and matched non-hyperkalemia comparisons

Within each of the three cohorts, i.e. individuals with CKD, HF, and diabetes respectively, a first HK event for a patient was identified as elevated blood potassium level >5.0 mmol/L not preceded by a prior episode of elevated potassium within the previous month. More severe HK events, >5.5 mmol/L and >6.0 mmol/L, were detected the same way. The incidence of HK per 1,000 person-years was calculated in the three cohorts. Following the first event, subsequent HK events were detected and reported, for potassium levels >5.0 mmol/L, >5.5mmol/L and >6.0 mmol/L respectively. The incidences of subsequent HK event were presented per 1,000 person-years with the median follow-up times between the events, and the healthcare setting where subsequent HK events were detected was reported.

For patients who had experienced HK, a comparison patient who had not experienced HK on the corresponding date was identified, matched on calendar year, age, sex, time since diagnosis, as well as additional prespecified clinical factors specific to each of the three disease cohorts (Table 1).

Hyperkalemia associated healthcare resource use and costs

Among patients who had experienced HK in each of the cohorts with CKD, HF, or diabetes, a total number of hospital admissions (acute or planned non-acute inpatient hospitalizations, including dialysis procedures, ventilator treatment and ICU admissions), hospital outpatient visits, emergency room visits, GP contacts, and drugs prescribed on out-patient basis during the periods 6 months before and 6 months after the incident HK were measured. Difference in overall mean costs of HRU, during the 6 months before the HK event and 6 months after the HK event, was calculated in the HK patients. To control for any changes related to the natural disease course over time, such as CKD or HF progression, the same assessment was conducted in the matched comparisons without HK in each of the three disease cohorts. The costs associated with HK were then estimated as the cost difference after the HK event among the HK patients minus the cost difference during the same period among the non-HK comparisons. Hence, HK-associated costs were derived as a difference-in-difference, in which the difference between costs for HK patients and non-HK comparisons were regarded to be associated to the HK event.

To account for potential early mortality during the 6 months following the index date in both the HK patients and non-HK comparisons, an additional analysis of mean cost per risk-time was performed, where costs were weighted by time-at-risk within the 6 months.

Unit costs

Costs for hospital admissions and outpatient contacts (including emergency room visits) were based on the Diagnosis Related Groups (DRG) and Danish Outpatient Grouping System (DAGS) charges.[29] Costs of GP consultations and contacts such as phone calls, tests, and mileage allowance were calculated based on pre-scheduled fees for GP services.[30] Drug acquisition costs for all drugs prescribed on an outpatient basis were calculated based on

Danish pharmacy retail prices. All unit costs were based on the calendar year in which the resource utilization occurred, and were converted to the year 2015 costs, using the official healthcare sector price index published by Statistics Denmark.[31] All costs were converted to Euros using an average 2015 exchange rate, according to European Central Bank, of 7.46 DKK per Euro.

Results

Among 78,372 patients with CKD, 14,233 patients with HF, and 37,479 patients with diabetes, one or more HK events were experienced by 17,747 (23%) of the CKD patients; 5,141 (36%) of HF patients; and 4,183 (11%) of the diabetes patients. Among patients with a recorded incident diagnosis of CKD, HF or diabetes, patients with HF were older (median age was 79 vs. 76 in CKD patients and 69 in diabetes patients), included more patients with eGFR levels below 30 mL/min/1.73m^2 (42% vs. 37% in CKD patients and 24% in diabetes patients), and had a higher proportion of ACEi users (55%) than the CKD (43%) or diabetes patients (48%) (Table 2).

The incidence rates of HK were 99.0, 256.7, and 45.7 per 1,000 person-years among the CKD, HF and diabetes patients, respectively. The incidence of more severe HK events, >5.5 mmol/L, >6.0 mmol/L, was lower across the three disease cohorts. Among the HF patients, more patients had more severe HK (>5.5 mmol/L) (18%), compared to the CKD patients (10%) and diabetes patients (4%). The baseline characteristics of the patients with more severe HK events (>5.5 mmol/L and >6.0 mmol/L) and those of their matched comparisons without HK are reported in Supplementary Tables 1 and 2. A large proportion of the patients experienced a second HK event; 44% of the CKD patients, 44% of the HF patients, and 45% of the diabetes patients. Among these surviving patients an increasing proportion suffered subsequent HK events (>5.0 mmol/L), and the time between HK events was successively shorter for the subsequent events (Figure 1–3). After an initial HK event, milder subsequent HK events (>5.0 mmol/L) were more frequently detected in primary care, whereas severe subsequent HK events (>6.0 mmol/L) were predominantly diagnosed in the hospital setting. (Figure 1-3)

Among the CKD patients with the HK event, mean numbers of acute hospital admissions increased from 0.8 during the period of 6 months before HK to 1.2 during the period of 6 months after HK. Among the HF patients with the HK event, corresponding admissions increased from 1.3 to 1.5 and among the diabetes patients with the HK event from 0.7 to 1.0. Mean costs of acute admissions with ventilator treatment and ICU stay were higher after HK by 5.2-fold and 4.6-fold respectively in CKD patients, 4.6-fold and 3.7-fold in HF patients, and 8.4-fold and 6.0-fold in diabetes patients (Table 3). Among the matched non-HK comparisons in the same period, minor differences in mean numbers of non-acute hospitalizations, and outpatient and GP visits were observed. The mean difference in total costs among HK patients between 6 months before and 6 months after HK was €5,598 in CKD patients, €5,211 in HF patients, and €4,712 in diabetes patients. In comparison, the mean difference in total costs among the matched non-HK patients between 6 months before and 6 months after the index date was €444 in CKD patients, €-898 in HF patients, and €-212 in diabetes patients, resulting in HK-associated costs of €5,154 in patients with CKD, €6110 in patients with HF, and €4,924 in patients with diabetes. Compared to the cost pattern prior to the HK event, this resulted in higher costs of 72% in CKD patients, 52% in HF patients, and 72% diabetes patients. The HK-associated costs were higher in patients with more severe HK events (>5.5 mmol/L and >6.0 mmol/L) (Supplementary Table 3 and 4). The higher costs after an incident HK and the cost amplification by HK severity are depicted in Figure 4.

Considering the high mortality 6 months after the HK event among the HK patients compared with the matched non-HK comparisons, (26% vs. 7% mortality in CKD patients, 35% vs. 15% mortality in HF patients, and 19% vs. 4% mortality in diabetes patients), the HK-associated costs within 6 months weighted by time-at-risk were estimated; €8,391 in CKD patients, €11,213 in HF patients, and €6,793 in diabetes patients (Supplementary Table 5).

Discussion

This population-based cohort study provides an overview of incidences of HK event and the corresponding HRU and costs, in patients with CKD, HF and diabetes during a maximum observation period of 5.5 years in Denmark. Overall, 17,747 CKD patients, 5,141 HF patients, and 4,183 diabetes patients with a first HK event were identified. More than 40% of the patients had subsequent HK events, with successively shorter time between the events.

In CKD patients, the overall mean costs were €5,598 higher after HK event compared to prior HK event while the costs in the matched non-HK comparisons was €444 during the same time period, resulting in a HK-associated cost of €5,154. Corresponding mean costs associated with a first HK event were €6,110 in patients with HF, and €4,924 in patients with diabetes.

The difference in cost incurred by HK patients and non-HK patients was mainly driven by acute hospitalizations, where ICU stays and ventilator treatments were the main contributing components. The mean cost per acute hospitalization, i.e. due to longer hospital stays and/or a hospital episode with complications, was higher among HK patients, which may indicate hospitalization for more severe conditions among the HK patients. Costs for primary care visits and prescribed drugs had a minor impact on the overall cost pattern associated with a HK event.

A larger proportion of HF patients had experienced mild and severe HK events, which occurred closer to the date of HF diagnosis, compared to the corresponding results in the CKD and diabetes patients. Relatively more HK events were detected in the hospital than in the primary care setting among the HF patients. The HF cohort also had a higher mean cost per patient prior to the HK event than had the CKD and diabetes cohort, and a larger absolute increase in mean costs after the HK event compared to the other disease cohort. The mean relative increase in costs associated with HK, was higher among the CKD (72%) and diabetes

patients (72%) compared to the HF patients (52%). However, when taking the higher mortality among the HF patient cohort into account (35% were deceased within 6 months after HF diagnosis), by weighing in patient survival time, a higher relative mean cost increase was still observed for the HF patients compared to the other disease cohort.

For more severe HK episodes (>5.5 mmol/L and >6.0 mmol/L, respectively) a higher mean cost was observed among the CKD and diabetes patients, compared to costs associated with milder HK events. This pattern was not observed among the HF patients, for whom the HK-associated with cost did not differ greatly by the increasing severity of HK events. This finding might be partly explained by high early mortality among HF patients with severe HK.

Following the initial HK event, a larger proportion of the subsequent HK events were detected in a primary care compared to hospital setting. Following an initial HK event, patients would presumably undergo more frequent blood testing in primary care, thus potentially explaining why a larger proportion of the subsequent HK events were detected in primary care.

The few studies investigating HK related costs in the literature, are mostly from the US. Fitch et al.[32] estimated that monthly severity-adjusted CKD costs for HK patients were $4,922 versus $2,036 for those without HK. Castro et al.[33] estimated a monthly cost of $5,994 and an annual cost of $31,884, to manage CKD patients who experienced HK, but without reference to a comparison group. Despite the considerable differences in clinical practice, mode of reimbursement system between the US and European /Nordic healthcare systems, the mean estimates and the magnitude of cost differences between HK and non-HK patients were comparable in the US studies and the current study, i.e. the HK-associated cost was $5,603 in the CKD patients, $6,642 in the HF patients, and $5,353 in the diabetes patients (applying an exchange rate of 1 USD = 6.86 DKK).

This study does not come without limitations. First, any conclusions concerning causal mechanisms underlying HK outcomes and corresponding costs should be made with caution. Rather than precipitating a hospitalization, elevated potassium levels measured during hospitalization may stem from an underlying condition leading to hospitalization (e.g., infection, dehydration, deteriorating kidney function) among the disease cohorts examined. The exact order of events in the pathophysiological pathway leading to a hospitalization is difficult to disentangle, especially for elderly comorbid patients. Therefore, it is not yet known how effective and sustained management of hyperkalemia will affect incidences of HK events and the corresponding costs.

Second, inclusion of patients in the study cohorts was restricted to 2005–2011 due to DRG record availability and feasibility of long-term follow-up. Clinical management of the comorbid conditions that are known risk factors for HK, as well as HK management, may have changed during this period, however pharmacological advancements in HK management have been relatively stagnant.[34, 35]

Third, long-term clinical implications of HK and the corresponding HRU and costs were not investigated. This could however be a field for further work and investigation.

Lastly, information on drugs administered, including those for the management of HK, during hospitalization were not available in the dataset. Therefore, their acquisition costs could not be examined in detail, but included as a part of the cost of each DRG hospital episode.

Conclusions

The costs associated with incident HK were substantial among CKD, HF and diabetes patients, and were mainly driven by increased use of hospital-based care. A large proportion of patients experienced subsequent HK events after a first incident event, with a successively shorter time between events. Our findings indicate that the increased HRU and corresponding costs associated with HK events, as well as the recurring pattern of events among CKD, HF and diabetic patients, can result in a substantial clinical and economic burden for patients, healthcare providers, and payers. Timely detection and effective management of HK among high-risk populations and avoidance of subsequent events may translate not only to clinical benefits for the patients, but may alleviate the economic burden to healthcare providers and payers. Additional research on the long-term costs, particularly for patients with recurrent events of HK, will be useful to inform clinical decision making.

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Declarations

Ethics approval and consent to participate: The ethics approval to utilize patient records from the data sources was granted by an institutional review board in Aarhus University Hospital.

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

KK, PH, EP are employees of AstraZeneca. RWT, SKN, HTS have reported no personal conflicts of interest relevant to this article. The Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, including the present study.

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Authors' contributions: Conception and design: EP, KK, RWT, SKN. Analysis and interpretation of data: SKN, KK, RWT, EP, PH, HTS. Drafting the article: KK, EP, RWT, PH. Revising the article: KK, RWT, PH, EP, HTS, SKN. Providing intellectual content of critical importance to the work described: all authors. Final approval of the version to be published: all authors.

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List of abbreviations

CKD Chronic Kidney Disease

DAGS Danish Outpatient Grouping System

DNPR Danish National Patient Registry

DRG Diagnosis Related Groups

GP General Practitioner

HF Heart Failure

HK Hyperkalemia

HRU Healthcare Resource Utilization

ICU Intensive Care Unit

NHISR National Health Insurance Service Registry

RAASi Renin-Angiotensin-Aldosterone System Inhibitors

Table 1. Matching criteria for hyperkalemia patients and non-hyperkalemia comparisons

Patient cohort	Matching Criteria
Chronic kidney disease	Age, Gender, Charlson Comorbidity Index score, Chronic kidney disease duration, Years since CKD diagnosis, CKD stage based on eGFR level, Presence of Heart Failure, Diabetes or Hypertension, Hyperkalemia-associated drugs[1]
Heart failure	Age, Gender, Charlson Comorbidity Index score, Heart failure duration, Years since heart failure diagnosis, Presence of chronic kidney disease, Diabetes or Hypertension, eGFR level, Hyperkalemia-associated drugs[1]
Diabetes	Age, Gender, Charlson Comorbidity Index score, Diabetes duration, Years since diabetes diagnosis, micro- or macrovascular complications, HbA1c level.

[1]ACEis/ARBs, spironolactone or eplerenone, or potassium supplements at the time of hyperkalemia

Table 2. Baseline characteristics of patients with hyperkalemia (> 5.0 mmol/L) and matched comparisons

	Patients with hyperkalemia			Matched comparisons without hyperkalemia		
	CKD[1]	HF[2]	Diabetes	CKD	HF	Diabetes
Total	17,747 (100%)	5,141 (100%)	4,183 (100%)	17,608 (100%)	5,141 (100%)	4,151 (100%)
Female	8,576 (48.3%)	2,311 (45.0%)	1,635 (39.1%)	8,521 (48.4%)	2,311 (45.0%)	1,631 (39.3%)
Median age (range)	76 (66.4-83.2)	79 (70.4-85.1)	69 (60.0-78.4)	76 (66.6-83.2)	79 (70.4-85.0)	69 (60.1-78.3)
<65	3,923 (22.1%)	781 (15.2%)	1,589 (38.0%)	3,847 (21.8%)	781 (15.2%)	1,571 (37.8%)
65-74	4,461 (25.1%)	1,149 (22.3%)	1,158 (27.7%)	4,447 (25.3%)	1,149 (22.3%)	1,156 (27.8%)
75-84	6,059 (34.1%)	1,919 (37.3%)	1,035 (24.7%)	6,022 (34.2%)	1,919 (37.3%)	1,041 (25.1%)
85+	3,304 (18.6%)	1,292 (25.1%)	401 (9.6%)	3,292 (18.7%)	1,292 (25.1%)	383 (9.2%)
eGFR level[3]						
eGFR ≥60	102 (0.6%)	559 (10.9%)	1,335 (31.9%)	153 (0.9%)	870 (16.9%)	1,955 (47.1%)
eGFR 45-59	5,072 (28.6%)	878 (17.1%)	908 (21.7%)	6,850 (38.9%)	1,230 (23.9%)	1,041 (25.1%)
eGFR 30-44	5,711 (32.2%)	1,459 (28.4%)	906 (21.7%)	5,896 (33.5%)	1,535 (29.9%)	658 (15.9%)
eGFR 15-29	4,665 (26.3%)	1,529 (29.7%)	712 (17.0%)	3,613 (20.5%)	1,123 (21.8%)	259 (6.2%)
eGFR <15	1,968 (11.1%)	607 (11.8%)	283 (6.8%)	910 (5.2%)	237 (4.6%)	59 (1.4%)
Dialysis	229 (1.3%)	109 (2.1%)	38 (0.9%)	132 (0.7%)	47 (0.9%)	19 (0.5%)
Qualifying event of hyperkalemia						
5.0-5.4	13,788 (77.7%)	3,845 (74.8%)	3,440 (82.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5.5-5.9	2,612 (14.7%)	836 (16.3%)	525 (12.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6.0-6.4	730 (4.1%)	259 (5.0%)	122 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6.5-6.9	331 (1.9%)	107 (2.1%)	54 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥7.0	286 (1.6%)	94 (1.8%)	42 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Main risk factors						
Diabetes	4,779 (26.9%)	1,453 (28.3%)	4,183 (100%)	4,406 (25.0%)	1,186 (23.1%)	4,151 (100%)
CKD	17,747 (100%)	3,478 (67.7%)	2,094 (50.1%)	17,608 (100%)	3,081 (59.9%)	1,562 (37.6%)
Heart failure	3,499 (19.7%)	5,141 (100%)	735 (17.6%)	3,056 (17.4%)	5,141 (100%)	504 (12.1%)
Hypertension	13,080 (73.7%)	4,422 (86.0%)	3,042 (72.7%)	14,933 (84.8%)	4,433 (86.2%)	2,852 (68.7%)
Other comorbidities						
MI[4]	2,756 (15.5%)	1,533 (29.8%)	637 (15.2%)	2,978 (16.9%)	1,598 (31.1%)	655 (15.8%)

HF	3,183 (17.9%)	0 (0.0%)	683 (16.3%)	2,955 (16.8%)	0 (0.0%)	494 (11.9%)
PVD[5]	2,294 (12.9%)	857 (16.7%)	466 (11.1%)	2,232 (12.7%)	766 (14.9%)	410 (9.9%)
CVD[6]	3,257 (18.4%)	1,075 (20.9%)	630 (15.1%)	3,745 (21.3%)	1,128 (21.9%)	761 (18.3%)
Any malignant disease	4,086 (23.0%)	928 (18.1%)	727 (17.4%)	3,883 (22.1%)	917 (17.8%)	751 (18.1%)
Afib or flutter	3,867 (21.8%)	2,151 (41.8%)	828 (19.8%)	3,360 (19.1%)	2,056 (40.0%)	609 (14.7%)
VHD[7]	1,698 (9.6%)	1,007 (19.6%)	284 (6.8%)	1,432 (8.1%)	874 (17.0%)	181 (4.4%)
Charlson comorbidity index						
0	4,180 (23.6%)	991 (19.3%)	1,454 (34.8%)	4,455 (25.3%)	1,110 (21.6%)	1,505 (36.3%)
1	3,864 (21.8%)	1,159 (22.5%)	928 (22.2%)	3,868 (22.0%)	1,284 (25.0%)	948 (22.8%)
2	3,962 (22.3%)	1,053 (20.5%)	738 (17.6%)	3,839 (21.8%)	1,000 (19.5%)	702 (16.9%)
≥3	5,741 (32.3%)	1,938 (37.7%)	1,063 (25.4%)	5,446 (30.9%)	1,747 (34.0%)	996 (24.0%)
Medications						
ACEis	7,682 (43.3%)	2,802 (54.5%)	2,025 (48.4%)	7,710 (43.8%)	2,545 (49.5%)	1,649 (39.7%)
ARBs	3,762 (21.2%)	977 (19.0%)	954 (22.8%)	4,829 (27.4%)	951 (18.5%)	923 (22.2%)
Spironolactone	4,017 (22.6%)	1,934 (37.6%)	891 (21.3%)	2,799 (15.9%)	1,513 (29.4%)	438 (10.6%)
Potassium supplements	6,010 (33.9%)	3,010 (58.5%)	1,214 (29.0%)	5,997 (34.1%)	3,031 (59.0%)	969 (23.3%)

[1]Chronic kidney disease; [2]Heart failure; [3]mL/min/1.73m^2; [4]Myocardial infarction; [5]Peripheral vascular disease; [6]Cerebrovascular disease; [7]Valvular heart disease

Table 3. Healthcare resource use and costs (€) associated with elevated potassium level >5.0 mmol/L

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=17,747**					**N=17,608**			
Acute hospitalizations[1]	3,721	(0.78)	8,325	(1.21)	4,603	1,805	(0.41)	2,227	(0.46)	423	4,181
Dialysis	27	(0.00)	126	(0.01)	99	18	(0.00)	32	(0.00)	14	85
Ventilator	512	(0.02)	2,646	(0.07)	2,134	247	(0.01)	385	(0.01)	138	1,996
ICU	685	(0.04)	3,155	(0.13)	2,470	319	(0.02)	474	(0.02)	155	2,315
Non-acute hospitalizations	1,678	(0.30)	2,798	(0.34)	1,120	1,104	(0.18)	1,107	(0.18)	3	1,117
Outpatient visits	1,508	(4.42)	1,512	(5.06)	4	1,019	(3.10)	1,054	(3.22)	35	-31
GP consultations	82	(4.42)	77	(4.17)	-5	76	(4.11)	75	(4.03)	-2	-3
GP contacts	168	(14.21)	176	(14.67)	8	125	(11.33)	132	(11.65)	7	1
Prescriptions	603	(22.91)	470	(18.56)	-133	571	(21.08)	549	(20.78)	-22	-111
Overall cost	7,760	-	13,358	-	5,598	4,700	-	5,144	-	444	5,154
Heart failure											
Number of patients			**N=5,141**					**N=5,141**			
Acute hospitalizations	5,887	(1.30)	9,801	(1.53)	3,914	5,009	(1.12)	4,219	(0.93)	-790	4,704

Dialysis	86	(0.01)	154	(0.02)	68	36	(0.01)	31	(0.00)	-5	73
Ventilator	645	(0.02)	2,949	(0.09)	2,304	615	(0.02)	426	(0.01)	-190	2,494
ICU	942	(0.06)	3,515	(0.15)	2,572	842	(0.05)	636	(0.04)	-206	2,779
Non-acute hospitalizations	1,785	(0.29)	3,226	(0.33)	1,441	1,848	(0.28)	1,699	(0.24)	-148	1,589
Outpatient visits	1,385	(4.84)	1,453	(5.62)	68	1,070	(4.03)	1,161	(4.63)	91	-23
GP consultations	94	(5.04)	82	(4.40)	-12	94	(5.07)	89	(4.81)	-5	-7
GP contacts	232	(18.17)	215	(16.77)	-17	195	(16.06)	192	(15.76)	-4	-14
Prescriptions	671	(27.68)	490	(20.89)	-182	646	(25.89)	604	(25.59)	-42	-140
Overall cost	10,055	-	15,266	-	5,212	8,862	-	7,964	-	-898	6,110
Diabetes											
Number of patients			**N=4,183**					**N=4,151**			
Acute hospitalizations	3,102	(0.66)	6,914	(0.98)	3,812	1,213	(0.28)	1,092	(0.25)	-121	3,933
Dialysis	33	(0.00)	74	(0.01)	41	9	(0.00)	-	(0.00)	-9	50
Ventilator	264	(0.01)	2,230	(0.06)	1,966	148	(0.00)	121	(0.00)	-27	1,993
ICU	447	(0.03)	2,666	(0.11)	2,218	169	(0.01)	166	(0.01)	-3	2,222
Non-acute hospitalizations	1,330	(0.23)	2,232	(0.29)	901	671	(0.12)	611	(0.12)	-60	962
Outpatient visits	1,296	(4.01)	1,378	(4.74)	82	904	(2.67)	881	(2.63)	-23	105
GP consultations	93	(4.99)	89	(4.79)	-4	82	(4.45)	77	(4.17)	-5	1
GP contacts	183	(15.99)	188	(16.24)	5	137	(12.51)	133	(11.91)	-5	10
Prescriptions	569	(22.48)	485	(19.48)	-85	472	(18.07)	474	(18.93)	2	-86
Overall cost	6,573	-	11,285	-	4,712	3,480	-	3,268	-	-212	4,924

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Figure titles and legends

Figure 1. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with chronic kidney disease and split between diagnosis setting of hyperkalemia

Figure 2. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with heart failure and split between diagnosis setting of hyperkalemia

Figure 3. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with diabetes and split between diagnosis setting of hyperkalemia

Figure 4. Cost of healthcare utilization 6 months before and 6 months after hyperkalemia, in chronic kidney disease, heart failure, and diabetes patients, HK patients vs. matched non-HK comparisons

Supplementary Files

File Name: Additional Files.

Title of Data: Supplementary Tables

Description of Data:

Supplementary Table 1. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.5 mmol/L) and matched comparisons without hyperkalemia.

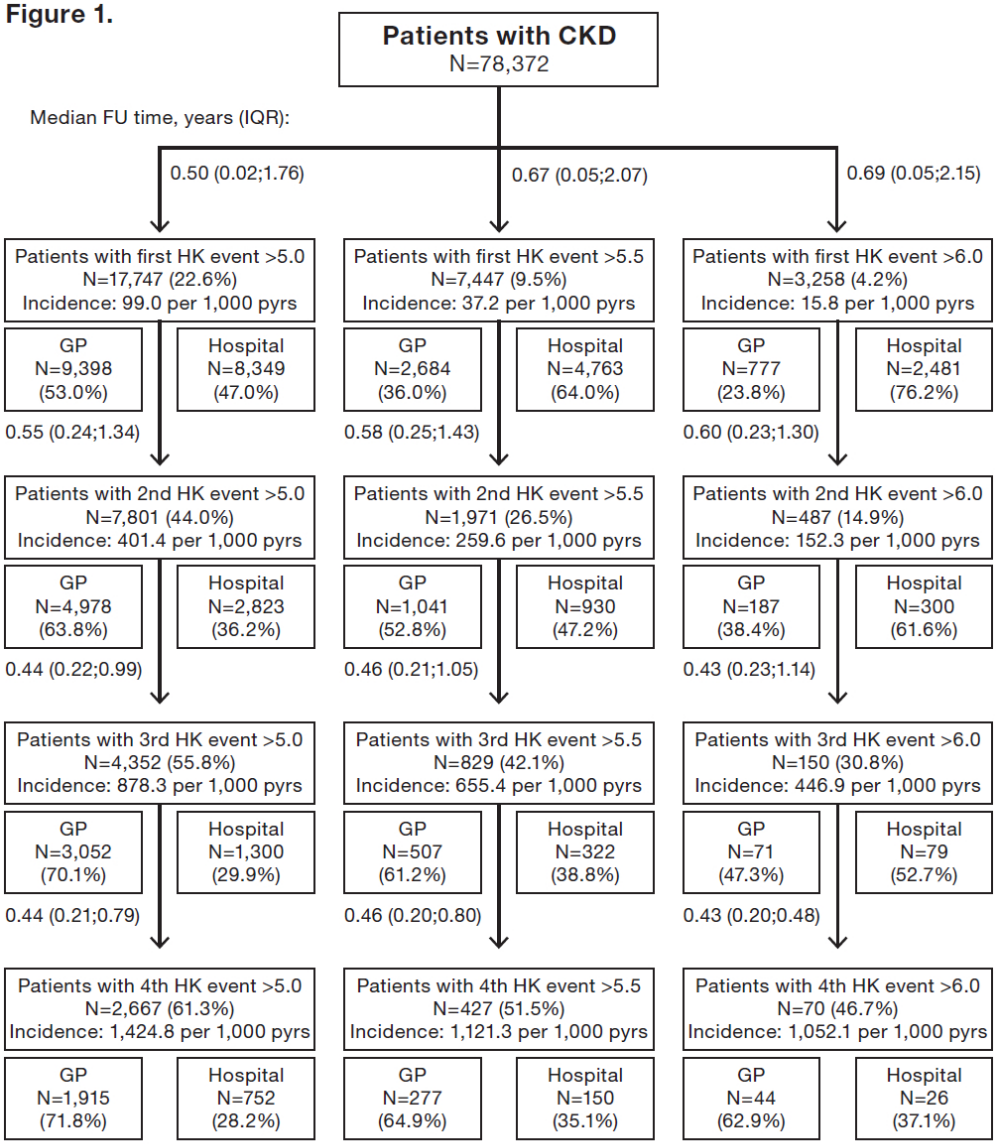
Supplementary Table 2. Baseline characteristics of patients with hyperkalemia (serum potassium above 6.0 mmol/L) and matched comparisons without hyperkalemia.

Supplementary Table 3. Healthcare resource use and costs (€) associated with elevated potassium level >5.5 mmol/L in at year 2015

Supplementary Table 4. Healthcare resource use and costs (€) associated with elevated potassium level >6.0 mmol/L in at year 2015

Supplementary Table 5. Healthcare resource use and costs (€) associated with elevated potassium level >5.0 mmol/L at year 2015, weighted by time-at-risk

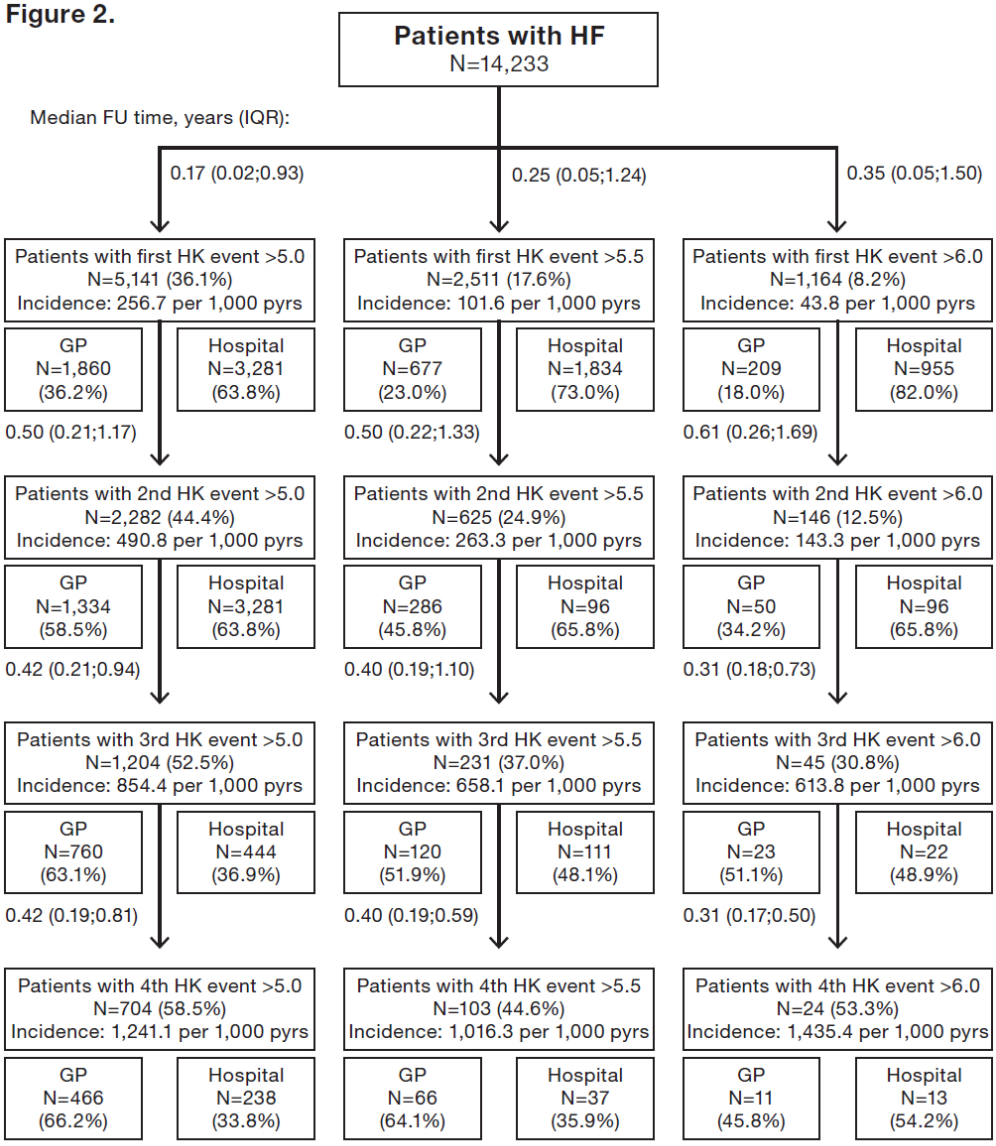
Figure 1.



*CKD: Chronic kidney disease, FU: Follow-up, IQR: Interquartile Range, HK: Hyperkalemia, GP: General practitioner.

Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with chronic kidney disease and split between diagnosis setting of hyperkalemia

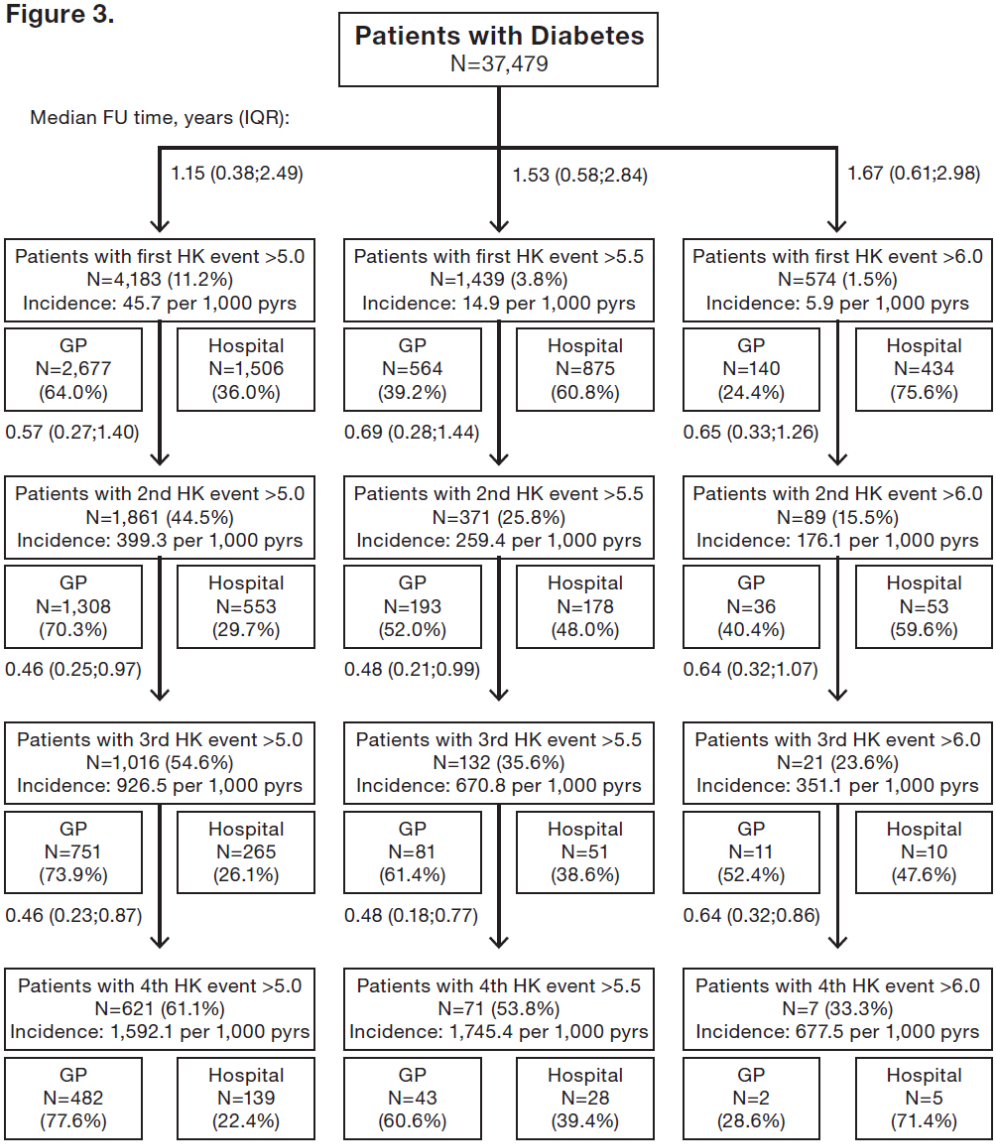
Figure 2.



*HF: Heart failure, FU: Follow-up, IQR: Interquartile Range, HK: Hyperkalemia, GP: General practitioner.

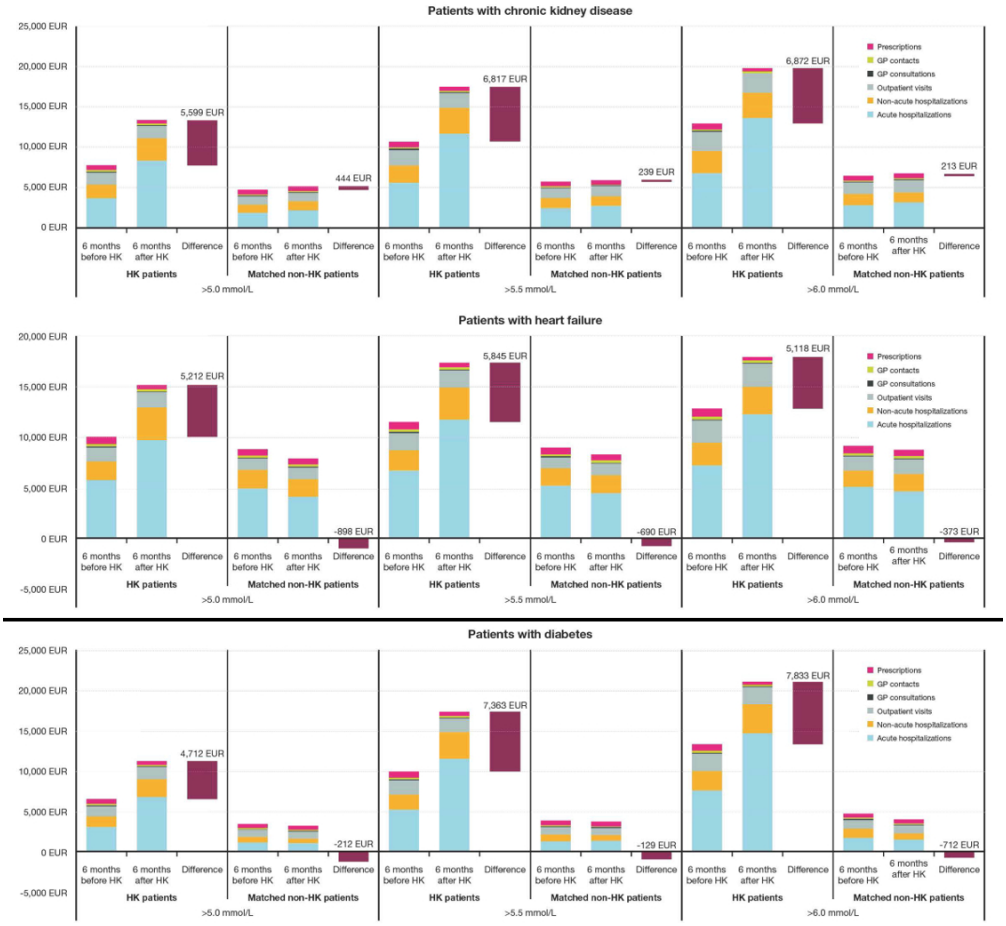
Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with heart failure and split between diagnosis setting of hyperkalemia

Figure 3.



*FU: Follow-up, IQR: Interquartile Range, HK: Hyperkalemia, GP: General practitioner.

Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with diabetes and split between diagnosis setting of hyperkalemia



Cost of healthcare utilization 6 months before and 6 months after hyperkalemia, in chronic kidney disease, heart failure, and diabetes patients, HK patients vs. matched non-HK comparisons

297x277mm (96 x 96 DPI)

Supplementary Table 1. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.5 mmol/L) and matched comparisons without hyperkalemia.

	Patients with hyperkalemia			Matched comparisons without hyperkalemia		
	CKD[1]	HF[2]	Diabetes	CKD	HF	Diabetes
Total	7,447 (100%)	2,511 (100%)	1,439 (100%)	7,391 (100%)	2,511 (100%)	1,436 (100%)
Female	3,359 (45.1%)	1,142 (45.5%)	580 (40.3%)	3,361 (45.5%)	1,142 (45.5%)	579 (40.3%)
Median age (range)	76 (65.5-82.9)	79 (70.5-85.1)	71 (61.4-79.7)	76 (65.7-83.0)	79 (70.5-85.1)	72 (61.8-79.8)
<65	1,781 (23.9%)	373 (14.9%)	479 (33.3%)	1,728 (23.4%)	373 (14.9%)	476 (33.1%)
65-74	1,802 (24.2%)	548 (21.8%)	398 (27.7%)	1,794 (24.3%)	548 (21.8%)	401 (27.9%)
75-84	2,499 (33.6%)	955 (38.0%)	391 (27.2%)	2,498 (33.8%)	955 (38.0%)	393 (27.4%)
85+	1,365 (18.3%)	635 (25.3%)	171 (11.9%)	1,371 (18.5%)	635 (25.3%)	166 (11.6%)
eGFR level[3]						
eGFR ≥60	28 (0.4%)	144 (5.7%)	240 (16.7%)	85 (1.2%)	310 (12.3%)	536 (37.3%)
eGFR 45-59	1,023 (13.7%)	250 (10.0%)	216 (15.0%)	1,897 (25.7%)	482 (19.2%)	372 (25.9%)
eGFR 30-44	1,935 (26.0%)	568 (22.6%)	329 (22.9%)	2,368 (32.0%)	706 (28.1%)	286 (19.9%)
eGFR 15-29	2,636 (35.4%)	940 (37.4%)	393 (27.3%)	2,156 (29.2%)	746 (29.7%)	145 (10.1%)
eGFR <15	1,613 (21.7%)	518 (20.6%)	229 (15.9%)	756 (10.2%)	194 (7.7%)	44 (3.1%)
Dialysis	212 (2.8%)	91 (3.6%)	31 (2.2%)	106 (1.4%)	40 (1.6%)	13 (0.9%)
Qualifying event of hyperkalemia						
5.5-5.9	5,228 (70.2%)	1,719 (68.5%)	1,056 (73.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6.0-6.4	1,279 (17.2%)	460 (18.3%)	223 (15.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6.5-6.9	511 (6.9%)	181 (7.2%)	89 (6.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥7.0	429 (5.8%)	151 (6.0%)	71 (4.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Main risk factors						
Diabetes	2,316 (31.1%)	809 (32.2%)	1,439 (100%)	1,990 (26.9%)	679 (27.0%)	1,436 (100%)
CKD	7,447 (100%)	1,887 (75.1%)	907 (63.0%)	7,391 (100%)	1,686 (67.1%)	683 (47.6%)
Heart failure	1,773 (23.8%)	2,511 (100%)	351 (24.4%)	1,579 (21.4%)	2,511 (100%)	238 (16.6%)
Hypertension	5,754 (77.3%)	2,199 (87.6%)	1,141 (79.3%)	6,334 (85.7%)	2,215 (88.2%)	1,074 (74.8%)
Other comorbidities						
MI[4]	1,255 (16.9%)	790 (31.5%)	232 (16.1%)	1,482 (20.1%)	827 (32.9%)	289 (20.1%)
HF	1,617 (21.7%)	0 (0.0%)	328 (22.8%)	1,551 (21.0%)	0 (0.0%)	234 (16.3%)
PVD[5]	1,111 (14.9%)	472 (18.8%)	210 (14.6%)	1,054 (14.3%)	411 (16.4%)	199 (13.9%)
CVD[6]	1,414 (19.0%)	542 (21.6%)	264 (18.3%)	1,646 (22.3%)	521 (20.7%)	309 (21.5%)
Any malignant disease	1,920 (25.8%)	463 (18.4%)	312 (21.7%)	1,824 (24.7%)	464 (18.5%)	312 (21.7%)
Afib or flutter	1,800 (24.2%)	1,048 (41.7%)	351 (24.4%)	1,574 (21.3%)	1,046 (41.7%)	250 (17.4%)
VHD[7]	820 (11.0%)	529 (21.1%)	124 (8.6%)	668 (9.0%)	445 (17.7%)	106 (7.4%)
Charlson comorbidity index						
0	1,328 (17.8%)	381 (15.2%)	334 (23.2%)	1,474 (19.9%)	464 (18.5%)	362 (25.2%)
1	1,451 (19.5%)	511 (20.4%)	292 (20.3%)	1,486 (20.1%)	578 (23.0%)	312 (21.7%)
2	1,750 (23.5%)	486 (19.4%)	292 (20.3%)	1,661 (22.5%)	468 (18.6%)	285 (19.8%)
≥3	2,918 (39.2%)	1,133 (45.1%)	521 (36.2%)	2,770 (37.5%)	1,001 (39.9%)	477 (33.2%)
Medications						
ACEis	3,402 (45.7%)	1,350 (53.8%)	694 (48.2%)	3,312 (44.8%)	1,305 (52.0%)	626 (43.6%)
ARBs	1,627 (21.8%)	503 (20.0%)	337 (23.4%)	1,987 (26.9%)	470 (18.7%)	333 (23.2%)
Spironolactone	2,124 (28.5%)	1,057 (42.1%)	442 (30.7%)	1,395 (18.9%)	861 (34.3%)	192 (13.4%)
Potassium supplements	2,837 (38.1%)	1,487 (59.2%)	544 (37.8%)	2,719 (36.8%)	1,454 (57.9%)	380 (26.5%)

[1]Chronic kidney disease; [2]Heart failure; [3]mL/min/1.73m^2; [4]Myocardial infarction; [5]Peripheral vascular disease; [6]Cerebrovascular disease; [7]Valvular heart disease

Supplementary Table 2. Baseline characteristics of patients with hyperkalemia (serum potassium above 6.0 mmol/L) and matched comparisons without hyperkalemia.

	Patients with hyperkalemia			Matched comparisons without hyperkalemia		
	CKD[1]	HF[2]	Diabetes	CKD	HF	Diabetes
Total	3,258 (100%)	1,164 (100%)	574 (100%)	3,250 (100%)	1,164 (100%)	585 (100%)
Female	1,435 (44.0%)	523 (44.9%)	213 (37.1%)	1,428 (43.9%)	523 (44.9%)	215 (36.8%)
Median age (range)	75 (64.7-82.4)	79 (69.8-84.8)	72 (62.1-80.4)	75 (65.1-82.6)	79 (69.7-84.8)	72 (62.3-80.4)
<65	836 (25.7%)	185 (15.9%)	184 (32.1%)	803 (24.7%)	185 (15.9%)	187 (32.0%)
65-74	794 (24.4%)	265 (22.8%)	163 (28.4%)	798 (24.6%)	265 (22.8%)	167 (28.5%)
75-84	1,052 (32.3%)	431 (37.0%)	165 (28.7%)	1,064 (32.7%)	431 (37.0%)	169 (28.9%)
85+	576 (17.7%)	283 (24.3%)	62 (10.8%)	585 (18.0%)	283 (24.3%)	62 (10.6%)
eGFR level[3]						
eGFR ≥60	10 (0.3%)	39 (3.4%)	55 (9.6%)	48 (1.5%)	127 (10.9%)	211 (36.1%)
eGFR 45-59	246 (7.6%)	62 (5.3%)	56 (9.8%)	646 (19.9%)	162 (13.9%)	135 (23.1%)
eGFR 30-44	633 (19.4%)	188 (16.2%)	106 (18.5%)	972 (29.9%)	307 (26.4%)	126 (21.5%)
eGFR 15-29	1,166 (35.8%)	456 (39.2%)	178 (31.0%)	1,004 (30.9%)	388 (33.3%)	74 (12.6%)
eGFR <15	1,039 (31.9%)	355 (30.5%)	157 (27.4%)	484 (14.9%)	133 (11.4%)	18 (3.1%)
Dialysis	164 (5.0%)	64 (5.5%)	21 (3.7%)	79 (2.4%)	31 (2.7%)	6 (1.0%)
Qualifying event of hyperkalemia						
6.0-6.4	2,002 (61.4%)	713 (61.3%)	358 (62.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6.5-6.9	711 (21.8%)	258 (22.2%)	127 (22.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥7.0	545 (16.7%)	193 (16.6%)	89 (15.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Main risk factors						
Diabetes	1,060 (32.5%)	412 (35.4%)	574 (100%)	963 (29.6%)	327 (28.1%)	585 (100%)
CKD	3,258 (100%)	910 (78.2%)	389 (67.8%)	3,250 (100%)	835 (71.7%)	306 (52.3%)
Heart failure	845 (25.9%)	1,164 (100%)	166 (28.9%)	720 (22.2%)	1,164 (100%)	104 (17.8%)
Hypertension	2,530 (77.7%)	1,041 (89.4%)	478 (83.3%)	2,759 (84.9%)	1,056 (90.7%)	457 (78.1%)
Other comorbidities						
MI[4]	544 (16.7%)	358 (30.8%)	107 (18.6%)	622 (19.1%)	393 (33.8%)	132 (22.6%)
HF	780 (23.9%)	0 (0.0%)	153 (26.7%)	706 (21.7%)	0 (0.0%)	102 (17.4%)
PVD[5]	501 (15.4%)	219 (18.8%)	81 (14.1%)	497 (15.3%)	206 (17.7%)	97 (16.6%)
CVD[6]	603 (18.5%)	244 (21.0%)	110 (19.2%)	750 (23.1%)	255 (21.9%)	138 (23.6%)
Any malignant disease	882 (27.1%)	226 (19.4%)	134 (23.3%)	818 (25.2%)	207 (17.8%)	154 (26.3%)
Afib & flutter	812 (24.9%)	488 (41.9%)	153 (26.7%)	711 (21.9%)	508 (43.6%)	102 (17.4%)
VHD[7]	389 (11.9%)	272 (23.4%)	55 (9.6%)	308 (9.5%)	201 (17.3%)	48 (8.2%)
Charlson comorbidity index						
0	516 (15.8%)	145 (12.5%)	99 (17.2%)	599 (18.4%)	197 (16.9%)	109 (18.6%)
1	598 (18.4%)	217 (18.6%)	107 (18.6%)	601 (18.5%)	254 (21.8%)	118 (20.2%)
2	759 (23.3%)	225 (19.3%)	122 (21.3%)	729 (22.4%)	211 (18.1%)	131 (22.4%)
≥3	1,385 (42.5%)	577 (49.6%)	246 (42.9%)	1,321 (40.6%)	502 (43.1%)	227 (38.8%)
Medications						
ACEis	1,516 (46.5%)	659 (56.6%)	304 (53.0%)	1,485 (45.7%)	599 (51.5%)	262 (44.8%)
ARBs	711 (21.8%)	231 (19.8%)	128 (22.3%)	843 (25.9%)	249 (21.4%)	158 (27.0%)
Spironolactone	1,024 (31.4%)	533 (45.8%)	203 (35.4%)	637 (19.6%)	429 (36.9%)	82 (14.0%)
Potassium supplements	1,319 (40.5%)	723 (62.1%)	230 (40.1%)	1,202 (37.0%)	664 (57.0%)	168 (28.7%)

[1]Chronic kidney disease; [2]Heart failure; [3]mL/min/1.73m^2; [4]Myocardial infarction; [5]Peripheral vascular disease; [6]Cerebrovascular disease; [7]Valvular heart disease

Supplementary Table 3. Healthcare resource use and costs (€) associated with elevated potassium level >5.5 mmol/L in at year 2015

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=7,447**					**N=7,391**			
Acute hospitalizations[1]	5,633	(1.05)	11,682	(1.57)	6,050	2,456	(0.52)	2,762	(0.52)	306	5,744
Dialysis	51	(0.01)	253	(0.02)	202	58	(0.00)	71	(0.01)	12	190
Ventilator	1,165	(0.03)	4,092	(0.11)	2,927	420	(0.01)	554	(0.01)	134	2,793
ICU	1,477	(0.06)	4,810	(0.19)	3,333	516	(0.03)	698	(0.03)	182	3,151
Non-acute hospitalizations	2,116	(0.38)	3,206	(0.36)	1,090	1,279	(0.21)	1,161	(0.19)	-118	1,208
Outpatient visits	1,933	(5.62)	1,881	(6.25)	-52	1,187	(3.60)	1,278	(3.71)	91	-143
GP consultations	86	(4.62)	68	(3.69)	-17	80	(4.30)	75	(4.05)	-5	-13
GP contacts	197	(16.16)	180	(14.60)	-17	138	(12.37)	139	(12.23)	1	-18
Prescriptions	676	(25.61)	440	(17.39)	-236	616	(22.45)	579	(21.93)	-37	-199
Overall cost	10,641	-	17,458	-	6,817	5,755	-	5,994	-	238	6,578
Heart failure											
Number of patients			**N=2,511**					**N=2,511**			
Acute hospitalizations	6,760	(1.42)	11,803	(1.69)	5,044	5,309	(1.14)	4,535	(0.96)	-774	5,818
Dialysis	157	(0.02)	217	(0.02)	60	48	(0.01)	42	(0.01)	-6	66
Ventilator	925	(0.03)	3,930	(0.11)	3,006	615	(0.02)	629	(0.02)	14	2,992
ICU	1,302	(0.07)	4,759	(0.20)	3,457	828	(0.05)	817	(0.04)	-12	3,468
Non-acute hospitalizations	1,992	(0.30)	3,135	(0.32)	1,143	1,681	(0.24)	1,781	(0.24)	100	1,043
Outpatient visits	1,739	(5.70)	1,748	(6.15)	9	1,080	(4.16)	1,147	(4.72)	66	-57
GP consultations	93	(4.97)	71	(3.81)	-22	95	(5.11)	89	(4.80)	-6	-16
GP contacts	253	(19.52)	210	(16.01)	-44	202	(16.60)	201	(16.46)	-1	-43
Prescriptions	732	(30.16)	446	(18.84)	-286	677	(26.90)	601	(25.96)	-76	-210
Overall cost	11,569	-	17,413	-	5,844	9,044	-	8,354	-	-690	6,535
Diabetes											
Number of patients			**N=1,439**					**N=1,436**			
Acute hospitalizations	5,298	(0.97)	11,553	(1.49)	6,255	1,345	(0.31)	1,421	(0.32)	77	6,179
Dialysis	97	(0.01)	210	(0.02)	113	17	(0.00)	-	(0.00)	-17	129
Ventilator	926	(0.03)	4,161	(0.11)	3,235	129	(0.00)	205	(0.01)	77	3,158
ICU	1,326	(0.06)	4,842	(0.20)	3,516	179	(0.01)	244	(0.01)	65	3,450
Non-acute hospitalizations	1,868	(0.32)	3,298	(0.36)	1,429	878	(0.16)	722	(0.14)	-156	1,586
Outpatient visits	1,795	(5.45)	1,752	(6.02)	-43	896	(2.95)	875	(2.91)	-21	-23
GP consultations	98	(5.26)	79	(4.27)	-19	85	(4.61)	79	(4.29)	-6	-13
GP contacts	225	(18.88)	200	(16.49)	-25	146	(13.16)	143	(12.64)	-3	-22
Prescriptions	723	(27.36)	488	(19.00)	-235	542	(20.76)	522	(20.74)	-20	-215

Overall cost	10,007	-	17,370	-	7,363	3,892	-	3,763	-	-129	7,492

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Supplementary Table 4. Healthcare resource use and costs (€) associated with elevated potassium level >6.0 mmol/L in at year 2015

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=3,258**					**N=3,250**			
Acute hospitalizations[1]	6,834	(1.22)	13,617	(1.84)	6,783	2,823	(0.59)	3,230	(0.60)	407	6,376
Dialysis	100	(0.02)	368	(0.03)	268	24	(0.00)	90	(0.01)	66	201
Ventilator	1,552	(0.04)	4,402	(0.12)	2,850	406	(0.01)	620	(0.02)	215	2,636
ICU	1,920	(0.08)	5,309	(0.23)	3,389	574	(0.03)	772	(0.04)	199	3,190
Non-acute hospitalizations	2,682	(0.43)	3,161	(0.36)	478	1,395	(0.24)	1,235	(0.21)	-160	638
Outpatient visits	2,409	(6.72)	2,405	(7.49)	-4	1,462	(4.24)	1,464	(4.38)	2	-6
GP consultations	86	(4.60)	61	(3.29)	-25	83	(4.47)	75	(4.06)	-8	-17
GP contacts	211	(16.91)	175	(13.74)	-36	148	(13.09)	149	(12.89)	1	-37
Prescriptions	701	(26.42)	376	(15.24)	-325	572	(22.04)	542	(21.60)	-30	-294
Overall cost	12,923	-	19,795	-	6,872	6,483	-	6,696	-	213	6,659
Heart failure											
Number of patients			**N=1,164**					**N=1,164**			
Acute hospitalizations	7,307	(1.57)	12,306	(1.77)	4,999	5,188	(1.17)	4,697	(1.01)	-491	5,490
Dialysis	174	(0.03)	243	(0.03)	69	99	(0.01)	82	(0.01)	-17	86
Ventilator	862	(0.03)	3,798	(0.10)	2,936	383	(0.02)	724	(0.02)	341	2,595
ICU	1,323	(0.08)	5,047	(0.22)	3,724	572	(0.06)	878	(0.05)	306	3,418
Non-acute hospitalizations	2,171	(0.31)	2,789	(0.29)	618	1,600	(0.26)	1,724	(0.23)	124	494
Outpatient visits	2,246	(7.03)	2,300	(7.33)	54	1,364	(4.79)	1,453	(5.27)	89	-36
GP consultations	91	(4.87)	58	(3.12)	-33	96	(5.14)	87	(4.68)	-9	-24
GP contacts	273	(20.71)	188	(14.34)	-85	200	(16.78)	196	(16.17)	-4	-80
Prescriptions	806	(32.25)	372	(15.96)	-435	734	(28.52)	653	(27.53)	-81	-354
Overall cost	12,895	-	18,013	-	5,118	9,182	-	8,809	-	-373	5,491
Diabetes											
Number of patients			**N=574**					**N=585**			
Acute hospitalizations	7,686	(1.19)	14,758	(1.81)	7,072	1,798	(0.41)	1,567	(0.35)	-230	7,303
Dialysis	109	(0.01)	361	(0.03)	252	-	(0.00)	-	(0.00)	-	252
Ventilator	1,876	(0.05)	5,670	(0.13)	3,794	31	(0.00)	256	(0.01)	225	3,569
ICU	2,399	(0.11)	6,981	(0.26)	4,583	156	(0.01)	180	(0.01)	24	4,558
Non-acute hospitalizations	2,333	(0.32)	3,602	(0.39)	1,270	1,112	(0.17)	766	(0.14)	-346	1,616
Outpatient visits	2,193	(6.70)	2,140	(7.25)	-53	1,123	(3.65)	1,015	(3.42)	-109	55
GP consultations	101	(5.42)	73	(3.90)	-29	90	(4.84)	81	(4.36)	-9	-19
GP contacts	232	(19.28)	195	(15.77)	-37	166	(14.40)	158	(13.41)	-8	-28
Prescriptions	790	(29.47)	399	(16.95)	-391	519	(20.31)	509	(20.60)	-10	-381

Overall cost	13,334	-	21,167	-	7,833	4,808	-	4,096	-	-712	8,545

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Supplementary Table 5. Healthcare resource use and costs (€) associated with elevated potassium level >5.0 mmol/L at year 2015, weighted by time-at-risk

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of time-at-risk by half-year term	**17,747**		**14,107**			**17,608**		**16,918**			
Acute hospitalizations[1]	3,721	(0.78)	10,473	(1.52)	6,751	1,805	(0.41)	2,318	(0.48)	514	6,238
Dialysis	27	(0.00)	158	(0.01)	131	18	(0.00)	33	(0.00)	15	116
Ventilator	512	(0.02)	3,329	(0.09)	2,817	247	(0.01)	401	(0.01)	154	2,663
ICU	685	(0.04)	3,970	(0.16)	3,284	319	(0.02)	493	(0.02)	174	3,110
Non-acute hospitalizations	1,678	(0.30)	3,520	(0.43)	1,842	1,104	(0.18)	1,152	(0.18)	48	1,794
Outpatient visits	1,508	(4.42)	1,902	(6.37)	394	1,019	(3.10)	1,097	(3.35)	78	316
GP consultations	82	(4.42)	97	(5.24)	15	76	(4.11)	78	(4.19)	1	14
GP contacts	168	(14.21)	222	(18.46)	54	125	(11.33)	138	(12.12)	13	41
Prescriptions	603	(22.91)	591	(23.35)	-12	571	(21.08)	571	(21.63)	1	-12
Overall cost	7,760	-	16,805	-	9,045	4,700	-	5,354	-	654	8,391
Heart failure											
Number of time-at-risk by half-year term	**N=5,141**		**N=3,702**			**N=5,141**		**N=4,655**			
Acute hospitalizations	5,887	(1.30)	13,611	(2.12)	7,724	5,009	(1.12)	4,659	(1.03)	-349	8,074
Dialysis	86	(0.01)	214	(0.02)	127	36	(0.01)	35	(0.00)	-2	129
Ventilator	645	(0.02)	4,096	(0.12)	3,451	615	(0.02)	470	(0.02)	-145	3,596
ICU	942	(0.06)	4,881	(0.21)	3,939	842	(0.05)	703	(0.04)	-140	4,079
Non-acute hospitalizations	1,785	(0.29)	4,480	(0.45)	2,695	1,848	(0.28)	1,877	(0.26)	29	2,666
Outpatient visits	1,385	(4.84)	2,018	(7.80)	633	1,070	(4.03)	1,282	(5.11)	212	421
GP consultations	94	(5.04)	113	(6.11)	19	94	(5.07)	98	(5.31)	4	15
GP contacts	232	(18.17)	298	(23.29)	66	195	(16.06)	212	(17.41)	16	50
Prescriptions	671	(27.68)	680	(29.02)	8	646	(25.89)	667	(28.27)	21	-13
Overall cost	10,055	-	21,201	-	11,147	8,862	-	8,795	-	-67	11,213
Diabetes											
Number of time-at-risk by half-year term	**N=4,183**		**N=3,572**			**N=4,151**		**N=4,073**			
Acute hospitalizations	3,102	(0.66)	8,097	(1.15)	4,995	1,213	(0.28)	1,113	(0.25)	-100	5,095
Dialysis	33	(0.00)	86	(0.01)	53	9	(0.00)	-	(0.00)	-9	62
Ventilator	264	(0.01)	2,612	(0.07)	2,347	148	(0.00)	123	(0.00)	-25	2,373
ICU	447	(0.03)	3,122	(0.13)	2,675	169	(0.01)	169	(0.01)	-0	2,675
Non-acute hospitalizations	1,330	(0.23)	2,614	(0.34)	1,283	671	(0.12)	623	(0.12)	-49	1,332
Outpatient visits	1,296	(4.01)	1,613	(5.56)	318	904	(2.67)	898	(2.69)	-6	324

GP consultations	93	(4.99)	104	(5.61)	11	82	(4.45)	79	(4.25)	-4	15
GP contacts	183	(15.99)	220	(19.02)	38	137	(12.51)	135	(12.14)	-2	40
Prescriptions	569	(22.48)	568	(22.82)	-2	472	(18.07)	483	(19.30)	11	-13
Overall cost	6,573	-	13,216	-	6,643	3,480	-	3,331	-	-149	6,792

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

†Cost weighted by time-at-risk was calculated as overall cost within the 6-month period divided by the total number of person in half-year term

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

Healthcare resource utilization and cost associated with elevated potassium levels: a Danish population-based cohort study

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 1 and 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 9
Bias	9	Describe any efforts to address potential sources of bias Page 11 and 13
Study size	10	Explain how the study size was arrived at Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 8
		(*b*) Describe any methods used to examine subgroups and interactions Page 8
		(*c*) Explain how missing data were addressed Page 8 and 14
		(*d*) If applicable, explain how loss to follow-up was addressed Not applicable

		(*e*) Describe any sensitivity analyses Not don in this study. Do in the "sister" clinical publications
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram Figure 1-3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 10
		(b) Indicate number of participants with missing data for each variable of interest Not applicable
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time Page 10 and 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Page 10 and 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses See supplementary data
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 13 and 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 15
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 15
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Healthcare resource utilization and cost associated with elevated potassium levels: a Danish population-based cohort study

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Healthcare resource utilization and cost associated with elevated potassium levels: a Danish population-based cohort study

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Abstract

Objectives: To investigate healthcare costs associated with hyperkalemia (HK) among patients with chronic kidney disease (CKD), heart failure (HF), or diabetes.

Design: Before-after cohort study of patients with HK and matched patients without HK.

Setting: Population-based databases covering primary and secondary care for the entire of Northern Denmark.

Participants: Patients with a first incident record of CKD (n=78,372), HF (n=14,233), or diabetes (n=37,479) during 2005-2011. Among all patients experiencing a first HK event (potassium level >5.0 mmol/L), healthcare costs were compared during 6 months before and 6 months after the HK event. The same cost assessment was conducted 6 months before and after a matched index date in a comparison cohort of patients without HK.

Primary and secondary outcome measures: Mean costs of hospital care, general practice, and dispensed drugs, converted to 2018 Euros (€).

Results: Overall, 17,747 (23%) CKD patients, 5,141 (36%) HF patients, and 4,183 (11%) diabetes patients with a first HK event were identified. More than 40% of all HK patients across the patient groups, had subsequent HK events with successively shorter times between the events. In CKD patients, overall mean costs were €5,518 higher 6 months after versus before first HK, while €441 higher in matched CKD patients without HK, yielding HK-associated costs of €5,077. Corresponding costs associated with a HK event were €6,018 in HF patients, and €4,862 in diabetes patients.

Conclusions: Among CKD, HF, and diabetes patients an incident HK event was common, and a large proportion of the patients experienced recurrent HK events. Substantial increase

in healthcare costs associated with a HK event was observed in the HK patients compared to non-HK patients. These results are important to better understand the potential economic impact of HK among high-risk comorbid patients in a real-wold setting and help inform decision making for clinicians and healthcare providers.

Strengths and limitations of this study

Strengths

- Access to laboratory test results from both primary and hospital care for the entire region's population of Northern Denmark (1,841,902 residents, i.e. 33% of Denmark's population) linkable to nationwide data on morbidity, mortality, and medication.
- Describing healthcare resource utilization and corresponding costs in three main hyperkalemia (HK) risk groups; patients with chronic kidney disease (CKD), heart failure (HF), or diabetes.
- Reported costs based on official Diagnosis Related Groups (DRG) and Danish Outpatient Grouping System (DAGS) charges.

Limitations

- Any conclusions concerning causal mechanisms underlying HK outcomes and corresponding costs should be made with caution.
- Rather than precipitating a hospitalization, elevated potassium levels may stem from an underlying condition that led to the hospitalization.

Background

Hyperkalemia (HK) is defined as serum potassium levels above a reference range, usually above 5.0 mmol/L, although more severe potassium cut-off levels are often used in treatment decision guidelines (e.g. >5.5 or >6.0 mmol/L) [1, 2]. HK has been reported to occur in 3–8% of all hospitalized patients, independent of reason for hospitalization, based on single clinic or health insurance based cross-sectional studies[3-5]. Patients older than 65 years with chronic kidney disease (CKD), heart failure (HF), diabetes, or who use renin-angiotensin-aldosterone system inhibitors (RAASi) are at increased risk of experiencing HK[1, 6-9]. An elevated

.plasma potassium concentration may result in muscle weakness, paralysis, life-threatening effects on cardiac arrhythmias, and sudden death[7]. The latter two have been reported among patients with potassium levels above 6.0 mmol/L[10, 11]. However, recent cohort analyses indicate that potassium levels above 5.0 mmol/L may also predict increased higher risk of cardiovascular events and short-term mortality among patients with an acute hospitalization, as well as among patients with CKD or HF[12-17].

HK has been associated with longer stay during acute hospitalizations, as well as an increased number of intensive care unit (ICU) stays and emergency department visits, primarily in the US healthcare system setting[11, 17-19]. However, the overall healthcare resource utilization (HRU) and costs associated with HK have not been comprehensively studied in a full population-based setting outside the US. To better understand the potential impact of new emerging drug therapies for HK, it is important to assess the true burden of HRU and costs in patients with HK events occurring in real-life, even if HK-related costs are unlikely to be causally driven by HK alone. The aims of this study were to investigate overall HRU and costs associated with HK in a real-world clinical setting in patients with an incident diagnosis of CKD, HF or diabetes.

Methods

Patient and public involvement

This was a cohort study using local and nationwide register data and no patients were involved in the design of the study. The study design is based on previous experience on data that are of interest to healthcare providers.

Data sources

This cohort study was conducted in Northern Denmark, using routine laboratory test results from both primary and hospital care for the entire region's population (1,841,902 residents, i.e. 33% of Denmark's population in June 2011) [20, 21]. Laboratory data were linked, via mandatory and unique civil personal registration numbers (assigned to each Danish resident), to hospital diagnoses and procedure data maintained in the Danish National Patient Registry (DNPR). The DNPR contains dates of hospital admission and discharge, emergency room visits, and outpatient clinic visits as well as and procedures carried out in the hospital setting[22]. Records of all drugs prescribed in an outpatient setting and dispensed from Danish pharmacies were obtained from the National Prescription Database and the Aarhus Prescription Database[21, 23]. Data on general practitioner (GP) services were retrieved from the National Health Insurance Service Registry (NHISR) [24]. This study was approved by an institutional review board.

Study populations with CKD, HF, or diabetes

Overall, three disease cohorts with a first incident record of CKD, HF, or diabetes, respectively, were identified between 1 January 2005 and 30 June 2011, based on a combination of laboratory, drug prescription, and hospital contact data. To ensure that our patients reflect true real-world disease cohorts with various possible comorbidities, an individual detected with

more than one of these conditions (such as both incident diabetes and later incident CKD) during the study period could be included in more than one patient cohort, in each case starting on the detection date of the respective disease. Incident CKD was defined as the first occurrence of one of the following: (1) eGFR <60 mL/min/1.73m^2 verified by at least two creatinine measurements more than 90 days apart; (2) an incident hospitalization with a diagnosis of CKD; or (3) hospital-based codes for renal dialysis [15]. Incident HF was defined as the first occurrence of an inpatient hospital admission with a primary or secondary discharge diagnosis of HF[25]. Incident diabetes was defined as the first dispensed prescription for a glucose-lowering drug[26]. To maximise the likelihood that the diseases were truly incident, we ensured that individuals had no previous record of the disease in question before study start (1 January 2005). Available look-back periods were back to 1977 for hospital codes (CKD or HF), to 1998 for prescription data (diabetes), and to 2000 for laboratory data (CKD).

Hyperkalemia events

Within each of the three cohorts, i.e. individuals with a first record of CKD, HF, and diabetes respectively, we followed individuals for a first incident HK event occurring after being recorded for the first time with the respective disease. A HK event for a patient was identified as elevated blood potassium level >5.0 mmol/L not preceded by a prior episode of elevated potassium within the previous month[15, 25, 26].Thus, a patient with a first record of e.g. heart failure was eligible to have a first incident HK event as heart failure patient from the date of her first heart failure cohort entry, only if she had no previous HK event or if she had a previous HK event more than one month before the date of her first heart failure cohort entry. More severe HK events, >5.5 mmol/L and >6.0 mmol/L, were detected the same way. The incidence of HK per 1,000 person-years was calculated in the three cohorts. Following the first event, subsequent HK events were detected and reported, for potassium levels >5.0 mmol/L, >5.5 mmol/L and >6.0 mmol/L respectively. The incidences of subsequent HK events were

presented per 1,000 person-years within the median follow-up times between the events, and the healthcare setting where subsequent HK events were detected was reported.

Hyperkalemia associated healthcare resource utilization and costs

The overall self-controlled before-after analytic design is demonstrated in Figure 1. Among patients who had experienced HK in each of the cohorts with CKD, HF, or diabetes, we assessed the total number of hospital admissions (acute or planned non-acute inpatient hospitalizations, including dialysis procedures, ventilator treatment and ICU admissions), hospital outpatient visits, emergency room visits, GP contacts, and drugs prescribed on an out-patient basis, during the periods 6 months *before* and 6 months *after* the incident HK event. The difference in overall HRU and resulting costs, during the 6 months before the HK event and 6 months after the HK event, was then calculated for each HK patient. If a HK-patient was diagnosed with HK on 1 April 2008 for example, the total costs in the first six months after HK would be his or her costs from 1 April 2008 to 31 September 2008, minus his or her costs from 1 October 2007 to 31 March 2008 (Figure 1).

To control for any changes in HRU and costs related to the natural disease course over time, such as CKD or HF progression, we selected a group of matched comparisons without HK within each disease cohort. Thus, for each patient who developed HK, we selected, by nearest neighbour matching, one comparison patient among those who were alive and had not yet developed HK on the index date of the corresponding matched HK patient, and who was as similar as possible for a range of matching factors. These factors are shown in Figure 1 and included: gender, patient age (in years), calendar year of first record of the disease, disease duration (in days), Charlson Comorbidity Index score (0, 1, 2, 3+), as well as additional pre-specified clinical factors specific to each of the three disease cohorts (Figure 1).

The total costs associated with HK were then estimated as the cost difference 6 months before and after the HK event among the HK patients minus the cost difference during the same period among the non-HK comparisons (Figure 1). Hence, HK-associated costs were derived as a *difference-in-difference*, in which the difference between costs for HK patients and non-HK comparisons were regarded to be associated with the HK event (Figure 1) [27].

To account for early mortality during the 6 months following the index date in both the HK patients and non-HK comparisons, an additional analysis of mean cost per risk-time was performed, where costs were weighted by time-at-risk within the 6 months. We also conducted a supplementary analysis in which the difference-in-difference costs were restricted to costs 1 month before the HK event and 1 month after the HK event.

Unit costs

Costs for hospital admissions and outpatient contacts (including emergency room visits) were based on the Diagnosis Related Groups (DRG) and Danish Outpatient Grouping System (DAGS) charges[28]. Costs of GP consultations and contacts such as phone calls, tests, and mileage allowance were calculated based on pre-scheduled fees for GP services in the Danish Healthcare system[24]. Drug acquisition costs for drugs prescribed on an outpatient basis were calculated based on Danish pharmacy retail prices[29]. All unit costs were based on the calendar year in which the resource utilization occurred, using the official healthcare sector price index published by Statistics Denmark[30]. All costs were converted to Euros using an average 2018 exchange rate, according to the European Central Bank, of 7.45 DKK per Euro.

Results

Among 78,372 patients with CKD, 14,233 patients with HF, and 37,479 patients with diabetes, one or more HK events were experienced by 17,747 (23%) of the CKD patients; 5,141 (36%) of HF patients; and 4,183 (11%) of the diabetes patients. Among the 27,071 patients with HK,

those with HF were older (median age was 79 vs. 76 in CKD patients and 69 in diabetes patients), included more patients with eGFR levels below 30 mL/min/1.73m^2 (42% vs. 37% in CKD patients and 24% in diabetes patients), and had a higher proportion of ACEi users (55%) than the CKD (43%) or diabetes patients (48%) (Table 1). Similar differences by disease group were observed for the 26,900 comparison patients without HK (Supplementary Table S1)

HK incidence

The incidence rates of HK were 99.0, 256.7, and 45.7 per 1,000 person-years among the CKD, HF and diabetes patients, respectively (Figures 2-4). The incidence of more severe HK events, >5.5 mmol/L, >6.0 mmol/L, was lower across the three disease cohorts. Among the HF patients, more patients had more severe HK (>5.5 mmol/L) (18%), compared to the CKD patients (10%) and diabetes patients (4%). The baseline characteristics of the patients with more severe HK events (>5.5 mmol/L and >6.0 mmol/L) and of their matched comparisons without HK are reported in Supplementary Tables S2 and S3. A large proportion of the patients with a first HK event experienced a second HK event; 44% of the CKD patients, 44% of the HF patients, and 45% of the diabetes patients. Among these surviving patients an increasing proportion suffered subsequent HK events (>5.0 mmol/L), and the time between HK events was successively shorter for the subsequent events (Figure 2-4). After an initial HK event (>5.0 mmol/L), subsequent HK events were more frequently detected in primary care than in hospitals, whereas for patients with severe HK events (>6.0 mmol/L), subsequent HK events were predominantly diagnosed in the hospital setting (Figure 2-4).

HRU and costs associated with HK

Among the CKD patients with a HK event, mean numbers of acute hospital admissions increased from 0.8 during the period of 6 months before HK to 1.2 during the period of 6 months after HK (Table 2). Among the HF patients with a HK event, corresponding acute

admissions increased from 1.3 to 1.5 and among the diabetes patients with a HK event from 0.7 to 1.0. One-third (diabetes) to one-half (HF) of the HK patients experienced an acute admission at the time of their HK event; ICD-10 chapters for primary discharge diagnoses for these admissions are shown in Supplementary Table S4. Mean costs of acute admissions with ventilator treatment and ICU stay were much higher after versus before HK, by 5.2-fold and 4.6-fold respectively in CKD patients, 4.6-fold and 3.7-fold in HF patients, and 8.5-fold and 6.0-fold in diabetes patients (Table 2). Among the matched non-HK comparisons in the same period, minor differences in mean numbers of non-acute hospitalizations, and outpatient and GP visits were observed. The mean difference per patient in total costs among HK patients between 6 months before and 6 months after HK was €5,518 in CKD patients, €5,141 in HF patients, and €4,650 in diabetes patients (Table 2, Figure 5). In comparison, the mean difference in total costs among the matched non-HK patients between 6 months before and 6 months after the index date was €441 in CKD patients, €-887 in HF patients, and €-212 in diabetes patients, resulting in estimated HK-associated costs of €5,076 (95% CI 4,690 to 5,463) in patients with CKD, €6,018 (95% CI 5,234 to 6,802) in patients with HF, and €4,862 (95% CI 4,156 to 5,568) in patients with diabetes. Overall, costs after HK increased by 71% in CKD patients, 52% in HF patients, and 70% in diabetes patients. The HK-associated costs were higher in patients with more severe HK events (>5.5 mmol/L and >6.0 mmol/L) (Supplementary Table S5 and S6). The higher costs after versus before incident HK and the cost amplification by HK severity are shown in Table 2 and depicted in Figure 5.

Considering the high mortality 6 months after the HK event among the HK patients compared with the matched non-HK comparisons, (27% vs. 7% mortality in CKD patients, 35% vs. 15% mortality in HF patients, and 19% vs. 4% mortality in diabetes patients, data not shown), the HK-associated costs within 6 months weighted by time-at-risk were estimated; €8,291 (95%

CI 7,823 to 8,704) in CKD patients, €11,078 (95% CI 10,031 to 12,034) in HF patients, and €6,719 (95% CI 5,943 to 7,440) in diabetes patients (Supplementary Table S7).

When restricting the calculations to costs 1 month before the HK event and 1 month after the HK event, HK-associated costs were €4,017 (95% CI 3,785 to 4,249) in CKD patients, €5,140 (95% CI 4,672 to 5,607) in HF patients, and €3,678 (95% CI 3,280 to 4,076) in diabetes patients (Supplementary Table S8)

Discussion

This population-based cohort study provides an overview of incidences of HK event and the corresponding HRU and costs, in patients with CKD, HF and diabetes during a maximum observation period of 5.5 years in Denmark. Overall, 17,747 CKD patients, 5,141 HF patients, and 4,183 diabetes patients with a first HK event were identified. More than 40% of the patients had subsequent HK events, with successively shorter time between the events.

In CKD patients, the overall mean costs were €5,518 higher after HK event compared to prior HK event while the costs in the matched non-HK comparisons was €441 during the same time period, resulting in a HK-associated cost of €5,076. Corresponding mean costs associated with a first HK event were €6,018 in patients with HF, and €4,862 in patients with diabetes.

The difference in cost incurred by HK patients and non-HK patients was mainly driven by acute hospitalizations, where ICU stays and ventilator treatments were the main contributing components. The mean cost per acute hospitalization, i.e. due to longer hospital stays and/or a hospital episode with complications, was higher among HK patients, which may indicate hospitalization for more severe conditions among the HK patients. Costs for primary care visits and prescribed drugs had a minor impact on the overall cost pattern associated with a HK event.

A larger proportion of HF patients had experienced mild and severe HK events, which occurred closer to the date of HF diagnosis, compared to the corresponding results in the CKD and diabetes patients. Relatively more HK events were detected in the hospital than in the primary care setting among the HF patients. The HF cohort also had a higher mean cost per patient prior to the HK event than had the CKD and diabetes cohort, and a larger absolute increase in mean costs after the HK event compared to the other disease cohort. The mean relative increase in costs associated with HK, was higher among the CKD (71%) and diabetes patients (70%) compared to the HF patients (52%). However, when taking the higher mortality among the HF patient cohort into account (35% were deceased within 6 months after HF diagnosis), by weighing in patient survival time, a higher relative mean cost increase was still observed for the HF patients compared to the other disease cohort.

For more severe HK episodes (>5.5 mmol/L and >6.0 mmol/L, respectively) a higher mean cost was observed among the CKD and diabetes patients, compared to costs associated with milder HK events. This pattern was not observed among the HF patients, for whom the HK-associated with cost did not differ greatly by the increasing severity of HK events. This finding might be partly explained by the particularly high early mortality among HF patients with severe HK.

Following the initial HK event, a larger proportion of the subsequent HK events were detected in a primary care compared to hospital setting. Following an initial HK event, patients would presumably undergo more frequent blood testing in primary care, thus potentially explaining why a larger proportion of the subsequent HK events were detected in primary care.

The few existing studies investigating HK related costs in the literature, are mostly from the US. Fitch et al. estimated that monthly severity-adjusted CKD costs for HK patients were $4,922 versus $2,036 for those without HK[31]. Castro et al. estimated a monthly cost of

$5,994 and an annual cost of $31,884, to manage CKD patients who experienced HK, but without reference to a comparison group[32]. Probably related to the considerable differences in clinical practice and in reimbursement system between the US and European /Nordic healthcare systems, the mean estimates and the magnitude of cost differences between HK and non-HK patients were generally higher in the US studies than in the current study, i.e. our HK-associated costs converted to USD were $5,837 in the CKD patients, $6,921 in the HF patients, and $5,591 in the diabetes patients (applying an exchange rate of 1 Euro = 1.15 USD).

This study does not come without limitations. First, any conclusions concerning causal mechanisms underlying HK outcomes and corresponding costs should be made with caution. Rather than precipitating a hospitalization, elevated potassium levels measured during a hospitalization may stem from an underlying condition that led to hospitalization (e.g., infection, dehydration, deteriorating kidney function) among the disease cohorts examined[25, 26]. We observed a variety of acute disease diagnoses, typically for an elderly highly comorbid patient population. On the other hand, HK itself may have had a bearing on the acute hospitalization and its severity and course, and HK may also have directly led to admissions, e.g. through muscle weakness, cardiac problems, resulting falls, etc. The exact order of events in the pathophysiological pathway leading to a hospitalization is difficult to disentangle, especially for elderly comorbid patients. Therefore, it is not yet predictable how the effective and sustained management of hyperkalemia will affect the corresponding costs associated with HK occurrence.

Second, our study is reliant on routine care ICD-10 codes for morbidity data and therefore, the possibility of coding errors cannot be ruled out. Furthermore, we did not have access to detailed clinical data for e.g. severity of heart failure, such as ejection fraction or New York Heart Association Functional Classification, or for exact type of diabetes, which remains uncertain based on treatment modality and hospital codes alone.

Third, inclusion of patients in the study cohorts was restricted to 2005–2011 due to DRG record availability and feasibility of long-term follow-up. Clinical management of the comorbid conditions that are known risk factors for HK, as well as HK management, may have changed during this period, however pharmacological advancements in HK management have been relatively stagnant within this time period[33, 34].

Fourth, long-term clinical implications of HK and the corresponding HRU and costs were not investigated. This could however be a field for further work and investigation.

Lastly, information on drugs administered during hospitalizations, including those for the management of HK, were not available in the dataset. Therefore, their acquisition costs could not be examined in detail, but only included as a part of the cost of each DRG hospital episode.

Conclusions

The costs associated with incident HK were substantial among CKD, HF and diabetes patients, and were mainly driven by increased use of hospital-based care. A large proportion of patients experienced subsequent HK events after a first incident event, with a successively shorter time between events. Our findings indicate that the high HRU and corresponding costs associated with HK events, as well as the recurring pattern of events among CKD, HF and diabetes patients, constitute a substantial clinical and economic burden for patients, healthcare providers, and payers. With our observational study design, it was not possible to determine whether HK was the direct cause of hospital admissions and increased HRU. However, since HK is at least partly contributing to the substantial adverse health outcomes observed, timely detection and management of HK among high-risk populations and avoidance of subsequent events may translate not only to clinical benefits for the patients but may also alleviate the economic burden for healthcare providers and payers. Additional research on the long-term costs, particularly for patients with recurrent events of HK, will be useful to inform clinical decision making.

Declarations

Ethics approval and consent to participate: The ethics approval to utilize patient records from the data sources was granted by an institutional review board in Aarhus University Hospital.

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

KK, PH, EP are employees of AstraZeneca. RWT, SKN, HTS have reported no personal conflicts of interest relevant to this article. The Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, including the present study.

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Authors' contributions: Conception and design: EP, KK, RWT, SKN. Analysis and interpretation of data: SKN, KK, RWT, EP, PH, HTS. Drafting the article: KK, EP, RWT, PH. Revising the article: KK, RWT, PH, EP, HTS, SKN. Providing intellectual content of critical importance to the work described: all authors. Final approval of the version to be published: all authors.

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List of abbreviations

CKD	Chronic Kidney Disease
DAGS	Danish Outpatient Grouping System
DNPR	Danish National Patient Registry
DRG	Diagnosis Related Groups
GP	General Practitioner
HF	Heart Failure
HK	Hyperkalemia
HRU	Healthcare Resource Utilization
ICU	Intensive Care Unit
NHISR	National Health Insurance Service Registry
RAASi	Renin-Angiotensin-Aldosterone System Inhibitors

Table 1. Baseline characteristics of patients with hyperkalemia (> 5.0 mmol/L)

	Patients with hyperkalemia		
	Chronic kidney disease	**Heart failure**	**Diabetes**
Total	17,747 (100%)	5,141 (100%)	4,183 (100%)
Female	8,576 (48.3%)	2,311 (45.0%)	1,635 (39.1%)
Age (years)			
Median age (range)	76 (66.4-83.2)	79 (70.4-85.1)	69 (60.0-78.4)
<65	3,923 (22.1%)	781 (15.2%)	1,589 (38.0%)
65-74	4,461 (25.1%)	1,149 (22.3%)	1,158 (27.7%)
75-84	6,059 (34.1%)	1,919 (37.3%)	1,035 (24.7%)
85+	3,304 (18.6%)	1,292 (25.1%)	401 (9.6%)
eGFR level[1]			
eGFR ≥60	102 (0.6%)	559 (10.9%)	1,335 (31.9%)
eGFR 45-59	5,072 (28.6%)	878 (17.1%)	908 (21.7%)
eGFR 30-44	5,711 (32.2%)	1,459 (28.4%)	906 (21.7%)
eGFR 15-29	4,665 (26.3%)	1,529 (29.7%)	712 (17.0%)
eGFR <15	1,968 (11.1%)	607 (11.8%)	283 (6.8%)
Dialysis	229 (1.3%)	109 (2.1%)	38 (0.9%)
Qualifying event of hyperkalemia			
5.0-5.4	13,788 (77.7%)	3,845 (74.8%)	3,440 (82.2%)
5.5-5.9	2,612 (14.7%)	836 (16.3%)	525 (12.6%)
6.0-6.4	730 (4.1%)	259 (5.0%)	122 (2.9%)
6.5-6.9	331 (1.9%)	107 (2.1%)	54 (1.3%)
≥7.0	286 (1.6%)	94 (1.8%)	42 (1.0%)
Main risk factors			
Diabetes	4,779 (26.9%)	1,453 (28.3%)	4,183 (100%)
CKD	17,747 (100%)	3,478 (67.7%)	2,094 (50.1%)
Heart failure	3,499 (19.7%)	5,141 (100%)	735 (17.6%)
Hypertension	13,080 (73.7%)	4,422 (86.0%)	3,042 (72.7%)
Other comorbidities			
MI[2]	2,756 (15.5%)	1,533 (29.8%)	637 (15.2%)

HF	3,183 (17.9%)	0 (0.0%)	683 (16.3%)
PVD[3]	2,294 (12.9%)	857 (16.7%)	466 (11.1%)
CVD[4]	3,257 (18.4%)	1,075 (20.9%)	630 (15.1%)
Any malignant disease	4,086 (23.0%)	928 (18.1%)	727 (17.4%)
Afib or flutter	3,867 (21.8%)	2,151 (41.8%)	828 (19.8%)
VHD[5]	1,698 (9.6%)	1,007 (19.6%)	284 (6.8%)
Charlson comorbidity index			
0	4,180 (23.6%)	991 (19.3%)	1,454 (34.8%)
1	3,864 (21.8%)	1,159 (22.5%)	928 (22.2%)
2	3,962 (22.3%)	1,053 (20.5%)	738 (17.6%)
≥3	5,741 (32.3%)	1,938 (37.7%)	1,063 (25.4%)
Medications			
ACEis	7,682 (43.3%)	2,802 (54.5%)	2,025 (48.4%)
ARBs	3,762 (21.2%)	977 (19.0%)	954 (22.8%)
Spironolactone	4,017 (22.6%)	1,934 (37.6%)	891 (21.3%)
Potassium supplements	6,010 (33.9%)	3,010 (58.5%)	1,214 (29.0%)

[1]mL/min/1.73m^2; [2]Myocardial infarction; [3]Peripheral vascular disease; [4]Cerebrovascular disease; [5]Valvular heart disease

Table 2. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€) (95% CI)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=17,747**					**N=17,608**			
Acute hospitalizations[1]	3,666	(0.78)	8,200	(1.21)	4,535	1,778	(0.41)	2,194	(0.46)	416	4,118 (3,816;4,421)
Dialysis	27	(0.00)	124	(0.01)	97	17	(0.00)	31	(0.00)	14	83 (50;116)
Ventilator	504	(0.02)	2,607	(0.07)	2,103	243	(0.01)	380	(0.01)	136	1,966 (1,747;2,185)
ICU	675	(0.04)	3,108	(0.13)	2,433	314	(0.02)	467	(0.02)	153	2,281 (2,053;2,508)
Non-acute hospitalizations	1,653	(0.30)	2,757	(0.34)	1,104	1,087	(0.18)	1,091	(0.18)	3	1,101 (922;1,279)
Outpatient visits	1,593	(4.42)	1,597	(5.06)	4	1,077	(3.10)	1,113	(3.22)	37	-32 (-124;60)
GP consultations	85	(4.42)	80	(4.17)	-5	79	(4.11)	77	(4.03)	-2	-3 (-5;-2)
GP contacts	174	(14.21)	183	(14.67)	9	130	(11.33)	137	(11.65)	8	1 (-3;5)
Prescriptions	583	(22.91)	455	(18.57)	-128	554	(21.08)	533	(20.78)	-21	-108 (-122;-93)
Overall cost	7,754	-	13,272	-	5,518	4,705	-	5,146	-	441	5,076 (4,690;5,463)
Heart failure											
Number of patients			**N=5,141**					**N=5,141**			
Acute hospitalizations	5,799	(1.30)	9,655	(1.53)	3,856	4,934	(1.12)	4,156	(0.93)	-778	4,634 (4,028;5,240)

Dialysis	85	(0.01)	152	(0.02)	67	36	(0.01)	31	(0.00)	-5	72 (1;142)
Ventilator	636	(0.02)	2,905	(0.09)	2,270	606	(0.02)	419	(0.01)	-187	2,457 (2,040;2,873)
ICU	928	(0.06)	3,462	(0.15)	2,534	830	(0.05)	627	(0.04)	-203	2,737 (2,311;3,163)
Non-acute hospitalizations	1,759	(0.29)	3,178	(0.33)	1,419	1,820	(0.28)	1,674	(0.24)	-146	1,565 (1,172;1,959)
Outpatient visits	1,463	(4.84)	1,535	(5.62)	73	1,130	(4.03)	1,226	(4.63)	96	-24 (-160;112)
GP consultations	97	(5.04)	85	(4.40)	-13	98	(5.07)	92	(4.81)	-5	-7 (-11;-4)
GP contacts	241	(18.17)	223	(16.77)	-18	203	(16.06)	199	(15.76)	-4	-14 (-24;-4)
Prescriptions	647	(27.68)	470	(20.89)	-176	622	(25.89)	583	(25.59)	-40	-136 (-166;-107)
Overall cost	10,006	-	15,147	-	5,141	8,807	-	7,930	-	-877	6,018 (5,234;6,802)
Diabetes											
Number of patients			**N=4,183**					**N=4,151**			
Acute hospitalizations	3,056	(0.66)	6,810	(0.98)	3,755	1,195	(0.28)	1,076	(0.25)	-119	3,874 (3,301;4,447)
Dialysis	33	(0.00)	72	(0.01)	40	9	(0.00)	0	(0.00)	-9	49 (-3;101)
Ventilator	260	(0.01)	2,197	(0.06)	1,936	146	(0.00)	119	(0.00)	-27	1,963 (1,571;2,356)
ICU	440	(0.03)	2,626	(0.11)	2,185	166	(0.01)	163	(0.01)	-3	2,189 (1,778;2,599)
Non-acute hospitalizations	1,311	(0.23)	2,198	(0.29)	888	661	(0.12)	602	(0.12)	-60	947 (651;1,244)
Outpatient visits	1,369	(4.01)	1,455	(4.74)	87	955	(2.67)	931	(2.63)	-24	111 (-50;271)
GP consultations	97	(4.99)	92	(4.79)	-4	86	(4.45)	80	(4.17)	-5	1 (-2;5)
GP contacts	189	(15.99)	195	(16.24)	6	143	(12.51)	138	(11.91)	-5	10 (2;19)
Prescriptions	548	(22.48)	467	(19.48)	-81	458	(18.08)	459	(18.93)	1	-82 (-109;-54)
Overall cost	6,569	-	11,218	-	4,650	3,497	-	3,285	-	-212	4,862 (4,156;5,568)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Figure titles and legends

Figure 1. Overall study design and matching factors

Figure 2. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with chronic kidney disease and split between diagnosis setting of hyperkalemia

Figure 3. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with heart failure and split between diagnosis setting of hyperkalemia

Figure 4. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with diabetes and split between diagnosis setting of hyperkalemia

Figure 5. Mean cost of healthcare utilization 6 months before and 6 months after hyperkalemia, in chronic kidney disease, heart failure, and diabetes patients, HK patients vs. matched non-HK comparisons

Supplementary Files

File Name: Additional Files.

Title of Data: Supplementary Tables

Description of Data:

Supplementary Table S1. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.0 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 5.0 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients vs their matched comparisons are shown.

Supplementary Table S2. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.5 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 5.5 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients vs their matched comparisons are shown.

Supplementary Table S3. Baseline characteristics of patients with hyperkalemia (serum potassium above 6.0 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 6.0 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients vs their matched comparisons are shown.

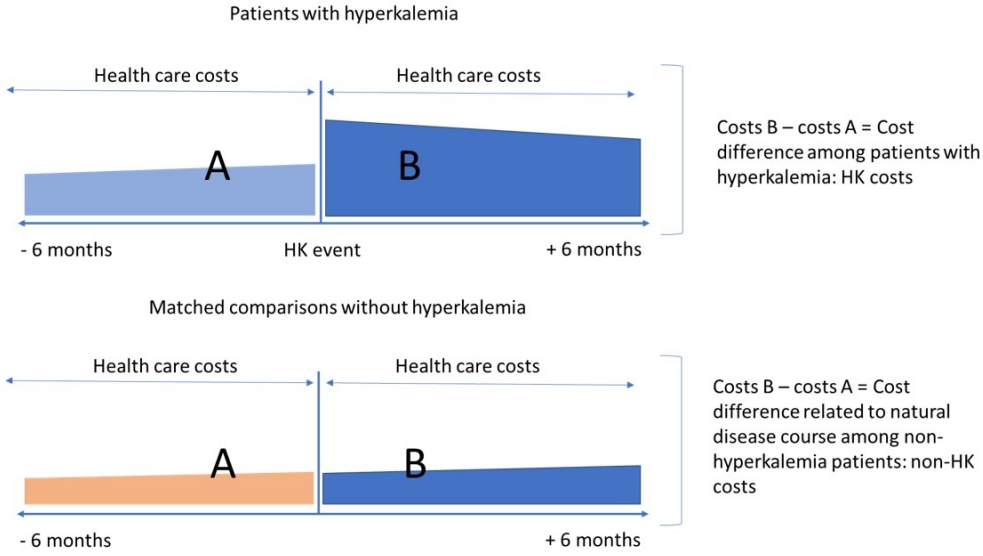
Supplementary Table S4: Primary (first-listed) discharge diagnoses during acute hospital admissions during which HK occurred.

Supplementary Table S5. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.5 mmol/L.

Supplementary Table S6. Healthcare resource use and mean costs (€) associated with elevated potassium level >6.0 mmol/L.

Supplementary Table S7. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L, weighted by time-at-risk.

Supplementary Table S8. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L 1 month before and after HK.



The costs associated with hyperkalemia = HK costs - non-HK costs

Matching criteria for hyperkalemia patients and comparison patients without hyperkalemia

Patient cohort	Matching criteria
Chronic kidney disease	Age, gender, Charlson Comorbidity Index score, chronic kidney disease duration, calendar year of CKD diagnosis, CKD stage based on eGFR level, presence of heart failure, diabetes or hypertension, hyperkalemia-associated drugs[1]
Heart failure	Age, gender, Charlson Comorbidity Index score, heart failure duration, calendar year of heart failure diagnosis, presence of chronic kidney disease, diabetes or hypertension, eGFR level, hyperkalemia-associated drugs[1]
Diabetes	Age, gender, Charlson Comorbidity Index score, diabetes duration, calendar year of diabetes diagnosis, micro- or macrovascular complications, HbA1c level

[1]ACEis/ARBs, spironolactone or eplerenone, or potassium supplements at the time of hyperkalemia

Figure 1. Overall study design and matching factors

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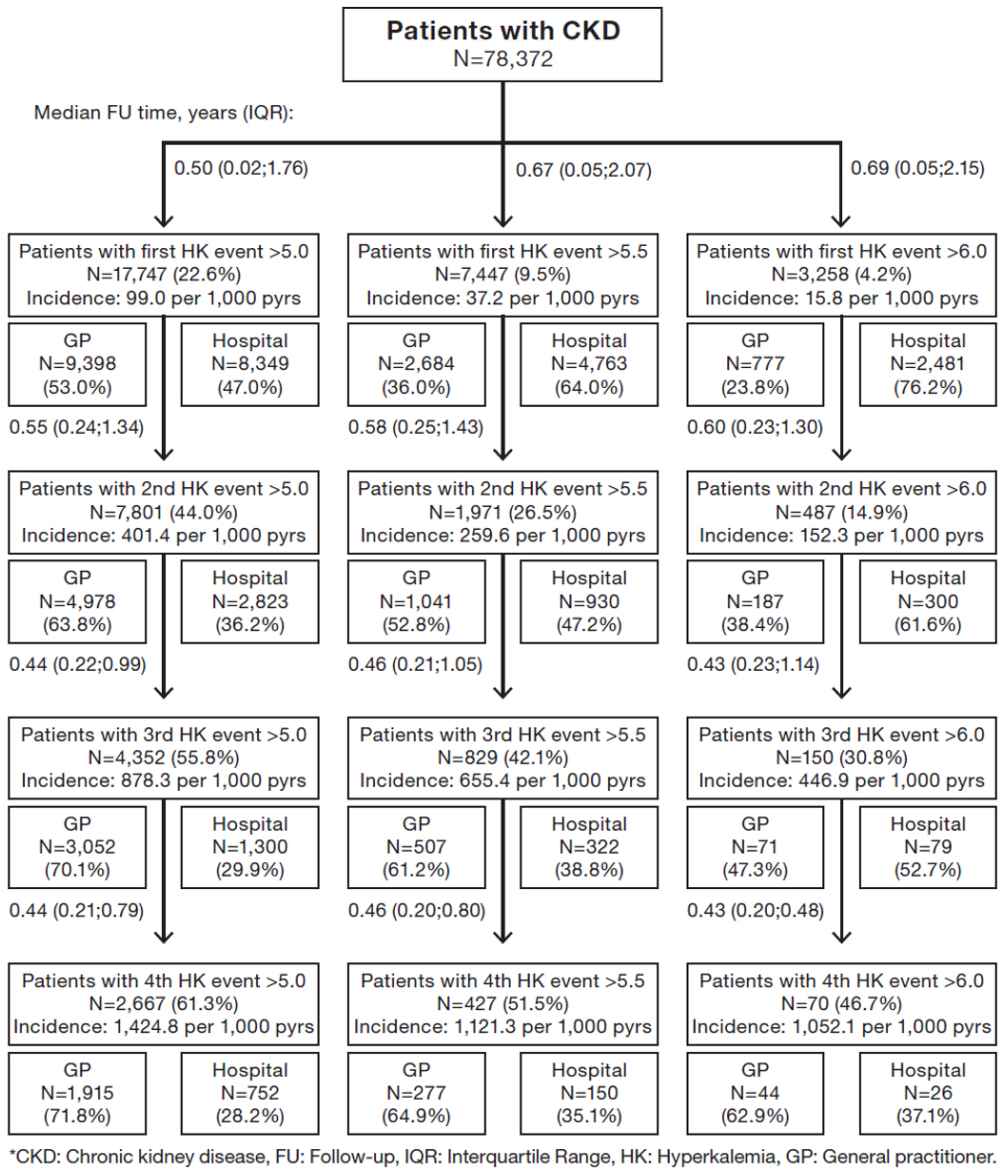

Figure 2. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with chronic kidney disease and split between diagnosis setting of hyperkalemia

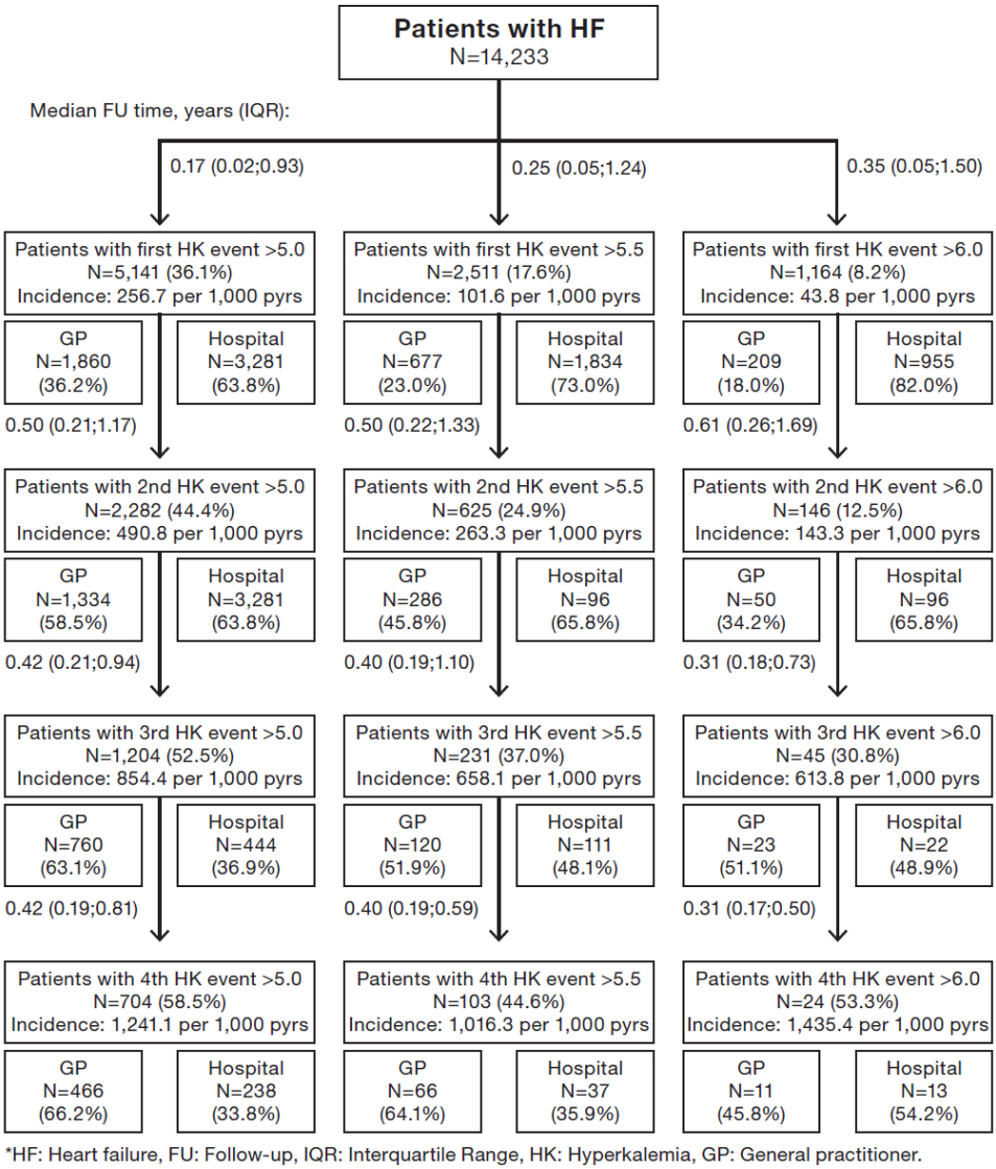

Figure 3. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with heart failure and split between diagnosis setting of hyperkalemia

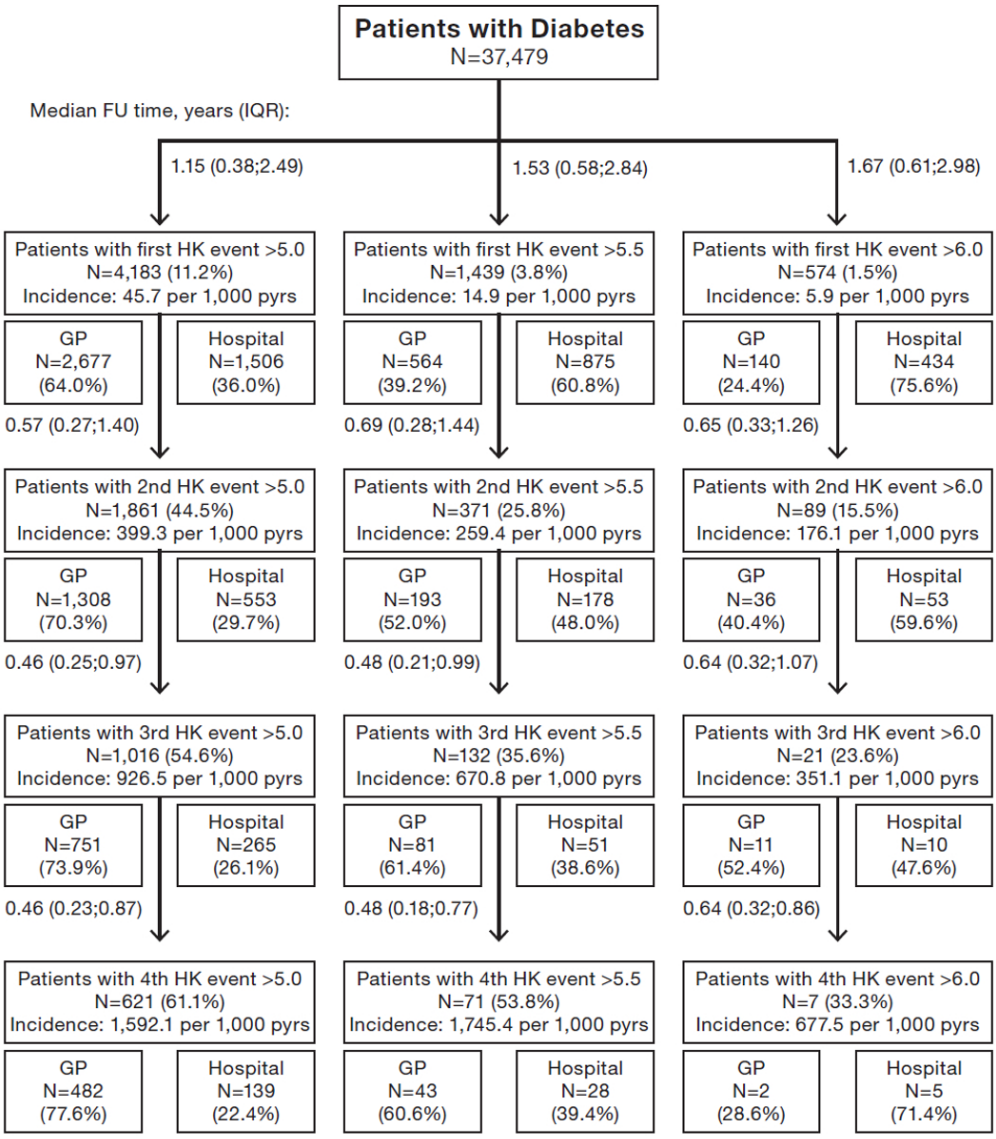

Figure 4. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with diabetes and split between diagnosis setting of hyperkalemia

Figure 5. Mean cost of healthcare utilization 6 months before and 6 months after hyperkalemia, in chronic kidney disease, heart failure, and diabetes patients, HK patients vs. matched non-HK comparisons

191x168mm (150 x 150 DPI)

Supplementary Table S1. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.0 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 5.0 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients vs their matched comparisons are shown.

	Patients with hyperkalemia			Matched comparisons without hyperkalemia					
	CKD[1]	HF[2]	Diabetes	CKD	PR[3]	HF	PR[3]	Diabetes	PR[3]
Total	17,747 (100%)	5,141 (100%)	4,183 (100%)	17,608 (100%)	1.00 (1.00-1.00)	5,141 (100%)	1.00 (1.00-1.00)	4,151 (100%)	1.00 (1.00-1.00)
Female	8,576 (48.3%)	2,311 (45.0%)	1,635 (39.1%)	8,521 (48.4%)	1.00 (0.98-1.02)	2,311 (45.0%)	1.00 (0.96-1.04)	1,631 (39.3%)	0.99 (0.94-1.05)
Median age (range)	76 (66.4-83.2)	79 (70.4-85.1)	69 (60.0-78.4)	76 (66.6-83.2)	. (.-.)	79 (70.4-85.0)	. (.-.)	69 (60.1-78.3)	. (.-.)
<65	3,923 (22.1%)	781 (15.2%)	1,589 (38.0%)	3,847 (21.8%)	1.01 (0.97-1.05)	781 (15.2%)	1.00 (0.91-1.10)	1,571 (37.8%)	1.00 (0.95-1.06)
65-74	4,461 (25.1%)	1,149 (22.3%)	1,158 (27.7%)	4,447 (25.3%)	1.00 (0.96-1.03)	1,149 (22.3%)	1.00 (0.93-1.07)	1,156 (27.8%)	0.99 (0.93-1.07)
75-84	6,059 (34.1%)	1,919 (37.3%)	1,035 (24.7%)	6,022 (34.2%)	1.00 (0.97-1.03)	1,919 (37.3%)	1.00 (0.95-1.05)	1,041 (25.1%)	0.99 (0.92-1.06)
85+	3,304 (18.6%)	1,292 (25.1%)	401 (9.6%)	3,292 (18.7%)	1.00 (0.95-1.04)	1,292 (25.1%)	1.00 (0.94-1.07)	383 (9.2%)	1.04 (0.91-1.19)
eGFR level[4]									
eGFR ≥60	102 (0.6%)	559 (10.9%)	1,335 (31.9%)	54 (0.3%)	0.66 (0.52-0.85)	99 (1.9%)	0.64 (0.58-0.71)	160 (3.9%)	0.68 (0.64-0.72)
eGFR 45-59	5,072 (28.6%)	878 (17.1%)	908 (21.7%)	153 (0.9%)	0.73 (0.71-0.76)	870 (16.9%)	0.71 (0.66-0.77)	1,955 (47.1%)	0.87 (0.80-0.94)
eGFR 30-44	5,711 (32.2%)	1,459 (28.4%)	906 (21.7%)	6,850 (38.9%)	0.96 (0.93-0.99)	1,230 (23.9%)	0.95 (0.89-1.01)	1,041 (25.1%)	1.37 (1.25-1.50)
eGFR 15-29	4,665 (26.3%)	1,529 (29.7%)	712 (17.0%)	5,896 (33.5%)	1.28 (1.23-1.33)	1,535 (29.9%)	1.36 (1.27-1.46)	658 (15.9%)	2.73 (2.38-3.12)
eGFR <15	1,968 (11.1%)	607 (11.8%)	283 (6.8%)	3,613 (20.5%)	2.15 (1.99-2.31)	1,123 (21.8%)	2.56 (2.22-2.96)	259 (6.2%)	4.76 (3.61-6.28)
Dialysis	229 (1.3%)	109 (2.1%)	38 (0.9%)	910 (5.2%)	1.72 (1.39-2.13)	237 (4.6%)	2.32 (1.65-3.26)	59 (1.4%)	1.98 (1.15-3.44)
Qualifying event of hyperkalemia									
5.5-5.9	13,788 (77.7%)	3,845 (74.8%)	3,440 (82.2%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.0-6.4	2,612 (14.7%)	836 (16.3%)	525 (12.6%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.5-6.9	730 (4.1%)	259 (5.0%)	122 (2.9%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
≥7.0	331 (1.9%)	107 (2.1%)	54 (1.3%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
Main risk factors									
Diabetes	4,779 (26.9%)	1,453 (28.3%)	4,183 (100%)	4,406 (25.0%)	1.08 (1.04-1.11)	1,186 (23.1%)	1.23 (1.15-1.31)	4,151 (100%)	1.00 (1.00-1.00)
CKD	17,747 (100%)	3,478 (67.7%)	2,094 (50.1%)	17,608 (100%)	1.00 (1.00-1.00)	3,081 (59.9%)	1.13 (1.10-1.16)	1,562 (37.6%)	1.33 (1.27-1.40)
Heart failure	3,499 (19.7%)	5,141 (100%)	735 (17.6%)	3,056 (17.4%)	1.14 (1.09-1.19)	5,141 (100%)	1.00 (1.00-1.00)	504 (12.1%)	1.45 (1.30-1.61)
Hypertension	13,080 (73.7%)	4,422 (86.0%)	3,042 (72.7%)	14,933 (84.8%)	0.87 (0.86-0.88)	4,433 (86.2%)	1.00 (0.98-1.01)	2,852 (68.7%)	1.06 (1.03-1.09)
Other comorbidities									
MI[5]	2,756 (15.5%)	1,533 (29.8%)	637 (15.2%)	2,978 (16.9%)	0.92 (0.88-0.96)	1,598 (31.1%)	0.96 (0.90-1.02)	655 (15.8%)	0.97 (0.87-1.07)
HF	3,183 (17.9%)	0 (0.0%)	683 (16.3%)	2,955 (16.8%)	1.07 (1.02-1.12)	0 (0.0%)	. (.-.)	494 (11.9%)	1.37 (1.23-1.53)
PVD[6]	2,294 (12.9%)	857 (16.7%)	466 (11.1%)	2,232 (12.7%)	1.02 (0.97-1.08)	766 (14.9%)	1.12 (1.02-1.22)	410 (9.9%)	1.13 (0.99-1.28)
CVD[7]	3,257 (18.4%)	1,075 (20.9%)	630 (15.1%)	3,745 (21.3%)	0.86 (0.83-0.90)	1,128 (21.9%)	0.95 (0.88-1.03)	761 (18.3%)	0.82 (0.75-0.90)
Any malignant disease	1,920 (25.8%)	463 (18.4%)	312 (21.7%)	3,589 (20.4%)	1.01 (0.97-1.05)	848 (16.5%)	0.98 (0.90-1.07)	695 (16.7%)	0.96 (0.87-1.06)
Afib or flutter	3,660 (20.6%)	833 (16.2%)	674 (16.1%)	3,360 (19.1%)	1.14 (1.10-1.19)	2,056 (40.0%)	1.05 (1.00-1.10)	609 (14.7%)	1.35 (1.23-1.48)
VHD[8]	1,698 (9.6%)	1,007 (19.6%)	284 (6.8%)	1,432 (8.1%)	1.18 (1.10-1.26)	874 (17.0%)	1.15 (1.06-1.25)	181 (4.4%)	1.56 (1.30-1.87)
Charlson comorbidity index									
0	4,180 (23.6%)	991 (19.3%)	1,454 (34.8%)	4,455 (25.3%)	0.93 (0.90-0.97)	1,110 (21.6%)	0.89 (0.83-0.96)	1,505 (36.3%)	0.96 (0.90-1.02)
1	3,864 (21.8%)	1,159 (22.5%)	928 (22.2%)	3,868 (22.0%)	0.99 (0.95-1.03)	1,284 (25.0%)	0.90 (0.84-0.97)	948 (22.8%)	0.97 (0.90-1.05)
2	3,962 (22.3%)	1,053 (20.5%)	738 (17.6%)	3,839 (21.8%)	1.02 (0.98-1.06)	1,000 (19.5%)	1.05 (0.97-1.14)	702 (16.9%)	1.04 (0.95-1.15)
≥3	5,741 (32.3%)	1,938 (37.7%)	1,063 (25.4%)	5,446 (30.9%)	1.05 (1.01-1.08)	1,747 (34.0%)	1.11 (1.05-1.17)	996 (24.0%)	1.06 (0.98-1.14)
Medications									

ACEis	7,682 (43.3%)	2,802 (54.5%)	2,025 (48.4%)	7,710 (43.8%)	0.99 (0.97-1.01)	2,545 (49.5%)	1.10 (1.06-1.14)	1,649 (39.7%)	1.22 (1.16-1.28)
ARBs	3,762 (21.2%)	977 (19.0%)	954 (22.8%)	4,829 (27.4%)	0.77 (0.74-0.80)	951 (18.5%)	1.03 (0.95-1.11)	923 (22.2%)	1.03 (0.95-1.11)
Spironolactone	4,017 (22.6%)	1,934 (37.6%)	891 (21.3%)	2,799 (15.9%)	1.42 (1.36-1.49)	1,513 (29.4%)	1.28 (1.21-1.35)	438 (10.6%)	2.02 (1.82-2.24)
Potassium supplements	6,010 (33.9%)	3,010 (58.5%)	1,214 (29.0%)	5,997 (34.1%)	0.99 (0.97-1.02)	3,031 (59.0%)	0.99 (0.96-1.03)	969 (23.3%)	1.24 (1.16-1.34)

[1]Chronic kidney disease; [2]Heart failure; [3]Prevalence ratio of each characteristic in patients with hyperkalemia versus matched comparisons without hyperkalemia; [4]mL/min/1.73m^2; [5]Myocardial infarction; [6]Peripheral vascular disease; [7]Cerebrovascular disease; [8]Valvular heart disease

Supplementary Table S2. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.5 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 5.5 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients (serum potassium above 5.5 mmol/L) vs their matched comparisons are shown.

	Patients with hyperkalemia			Matched comparisons without hyperkalemia					
	CKD[1]	HF[2]	Diabetes	CKD	PR[3]	HF	PR[3]	Diabetes	PR[3]
Total	7,447 (100%)	2,511 (100%)	1,439 (100%)	7,391 (100%)	1.00 (1.00-1.00)	2,511 (100%)	1.00 (1.00-1.00)	1,436 (100%)	1.00 (1.00-1.00)
Female	3,359 (45.1%)	1,142 (45.5%)	580 (40.3%)	3,361 (45.5%)	0.99 (0.96-1.03)	1,142 (45.5%)	1.00 (0.94-1.06)	579 (40.3%)	1.00 (0.91-1.09)
Median age (range)	7,447 (100%)	2,511 (100%)	1,439 (100%)	76 (65.7-83.0)	. (.-.)	79 (70.5-85.1)	. (.-.)	72 (61.8-79.8)	. (.-.)
<65	76 (65.5-82.9)	79 (70.5-85.1)	71 (61.4-79.7)	1,728 (23.4%)	1.02 (0.97-1.08)	373 (14.9%)	1.00 (0.88-1.14)	476 (33.1%)	1.00 (0.91-1.11)
65-74	1,781 (23.9%)	373 (14.9%)	479 (33.3%)	1,794 (24.3%)	1.00 (0.94-1.06)	548 (21.8%)	1.00 (0.90-1.11)	401 (27.9%)	0.99 (0.88-1.11)
75-84	1,802 (24.2%)	548 (21.8%)	398 (27.7%)	2,498 (33.8%)	0.99 (0.95-1.04)	955 (38.0%)	1.00 (0.93-1.07)	393 (27.4%)	0.99 (0.88-1.12)
85+	2,499 (33.6%)	955 (38.0%)	391 (27.2%)	1,371 (18.5%)	0.99 (0.92-1.06)	635 (25.3%)	1.00 (0.91-1.10)	166 (11.6%)	1.03 (0.84-1.26)
eGFR level[4]									
eGFR ≥60	28 (0.4%)	144 (5.7%)	240 (16.7%)	85 (1.2%)	0.33 (0.21-0.50)	310 (12.3%)	0.46 (0.38-0.56)	536 (37.3%)	0.45 (0.39-0.51)
eGFR 45-59	1,023 (13.7%)	250 (10.0%)	216 (15.0%)	1,897 (25.7%)	0.54 (0.50-0.57)	482 (19.2%)	0.52 (0.45-0.60)	372 (25.9%)	0.58 (0.50-0.67)
eGFR 30-44	1,935 (26.0%)	568 (22.6%)	329 (22.9%)	2,368 (32.0%)	0.81 (0.77-0.85)	706 (28.1%)	0.80 (0.73-0.89)	286 (19.9%)	1.15 (1.00-1.32)
eGFR 15-29	2,636 (35.4%)	940 (37.4%)	393 (27.3%)	2,156 (29.2%)	1.21 (1.16-1.27)	746 (29.7%)	1.26 (1.16-1.36)	145 (10.1%)	2.70 (2.27-3.22)
eGFR <15	1,613 (21.7%)	518 (20.6%)	229 (15.9%)	756 (10.2%)	2.12 (1.95-2.29)	194 (7.7%)	2.67 (2.29-3.12)	44 (3.1%)	5.19 (3.79-7.11)
Dialysis	212 (2.8%)	91 (3.6%)	31 (2.2%)	106 (1.4%)	1.98 (1.58-2.50)	40 (1.6%)	2.28 (1.58-3.29)	13 (0.9%)	2.38 (1.25-4.53)
Qualifying event of hyperkalemia									
5.5-5.9	5,228 (70.2%)	1,719 (68.5%)	1,056 (73.4%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.0-6.4	1,279 (17.2%)	460 (18.3%)	223 (15.5%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.5-6.9	511 (6.9%)	181 (7.2%)	89 (6.2%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
≥7.0	429 (5.8%)	151 (6.0%)	71 (4.9%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
Main risk factors									
Diabetes	2,316 (31.1%)	809 (32.2%)	1,439 (100%)	1,990 (26.9%)	1.16 (1.10-1.21)	679 (27.0%)	1.19 (1.09-1.30)	1,436 (100%)	1.00 (1.00-1.00)
CKD	7,447 (100%)	1,887 (75.1%)	907 (63.0%)	7,391 (100%)	1.00 (1.00-1.00)	1,686 (67.1%)	1.12 (1.08-1.16)	683 (47.6%)	1.33 (1.24-1.42)
Heart failure	1,773 (23.8%)	2,511 (100%)	351 (24.4%)	1,579 (21.4%)	1.11 (1.05-1.18)	2,511 (100%)	1.00 (1.00-1.00)	238 (16.6%)	1.47 (1.27-1.71)
Hypertension	5,754 (77.3%)	2,199 (87.6%)	1,141 (79.3%)	6,334 (85.7%)	0.90 (0.89-0.92)	2,215 (88.2%)	0.99 (0.97-1.01)	1,074 (74.8%)	1.06 (1.02-1.10)
Other comorbidities									
MI[5]	1,255 (16.9%)	790 (31.5%)	232 (16.1%)	1,482 (20.1%)	0.84 (0.79-0.90)	827 (32.9%)	0.96 (0.88-1.04)	289 (20.1%)	0.80 (0.69-0.94)
HF	1,617 (21.7%)	0 (0.0%)	328 (22.8%)	1,551 (21.0%)	1.03 (0.97-1.10)	0 (0.0%)	. (.-.)	234 (16.3%)	1.40 (1.20-1.63)
PVD[6]	1,111 (14.9%)	472 (18.8%)	210 (14.6%)	1,054 (14.3%)	1.05 (0.97-1.13)	411 (16.4%)	1.15 (1.02-1.29)	199 (13.9%)	1.05 (0.88-1.26)
CVD[7]	1,414 (19.0%)	542 (21.6%)	264 (18.3%)	1,646 (22.3%)	0.85 (0.80-0.91)	521 (20.7%)	1.04 (0.93-1.16)	309 (21.5%)	0.85 (0.74-0.99)
Any malignant disease	1,690 (22.7%)	422 (16.8%)	284 (19.7%)	1,682 (22.8%)	1.00 (0.94-1.06)	422 (16.8%)	1.00 (0.88-1.13)	298 (20.8%)	0.95 (0.82-1.10)
Afib or flutter	1,800 (24.2%)	1,048 (41.7%)	351 (24.4%)	1,574 (21.3%)	1.13 (1.07-1.20)	1,046 (41.7%)	1.00 (0.94-1.07)	250 (17.4%)	1.40 (1.21-1.62)
VHD[8]	820 (11.0%)	529 (21.1%)	124 (8.6%)	668 (9.0%)	1.22 (1.11-1.34)	445 (17.7%)	1.19 (1.06-1.33)	106 (7.4%)	1.17 (0.91-1.50)
Charlson comorbidity index									
0	1,328 (17.8%)	381 (15.2%)	334 (23.2%)	1,474 (19.9%)	0.89 (0.84-0.96)	464 (18.5%)	0.82 (0.73-0.93)	362 (25.2%)	0.92 (0.81-1.05)
1	1,451 (19.5%)	511 (20.4%)	292 (20.3%)	1,486 (20.1%)	0.97 (0.91-1.03)	578 (23.0%)	0.88 (0.80-0.98)	312 (21.7%)	0.93 (0.81-1.08)
2	1,750 (23.5%)	486 (19.4%)	292 (20.3%)	1,661 (22.5%)	1.05 (0.99-1.11)	468 (18.6%)	1.04 (0.93-1.16)	285 (19.8%)	1.02 (0.88-1.18)
≥3	2,918 (39.2%)	1,133 (45.1%)	521 (36.2%)	2,770 (37.5%)	1.05 (1.00-1.09)	1,001 (39.9%)	1.13 (1.06-1.21)	477 (33.2%)	1.09 (0.99-1.21)
Medications									

ACEis	3,402 (45.7%)	1,350 (53.8%)	694 (48.2%)	3,312 (44.8%)	1.02 (0.98-1.06)	1,305 (52.0%)	1.03 (0.98-1.09)	626 (43.6%)	1.11 (1.02-1.20)
ARBs	1,627 (21.8%)	503 (20.0%)	337 (23.4%)	1,987 (26.9%)	0.81 (0.77-0.86)	470 (18.7%)	1.07 (0.96-1.20)	333 (23.2%)	1.01 (0.88-1.15)
Spironolactone	2,124 (28.5%)	1,057 (42.1%)	442 (30.7%)	1,395 (18.9%)	1.51 (1.42-1.60)	861 (34.3%)	1.23 (1.14-1.32)	192 (13.4%)	2.30 (1.97-2.68)
Potassium supplements	2,837 (38.1%)	1,487 (59.2%)	544 (37.8%)	2,719 (36.8%)	1.04 (0.99-1.08)	1,454 (57.9%)	1.02 (0.98-1.07)	380 (26.5%)	1.43 (1.28-1.59)

[1]Chronic kidney disease; [2]Heart failure; [3]Prevalence ratio of each characteristic in patients with hyperkalemia versus matched comparisons without hyperkalemia; [4]mL/min/1.73m^2; [5]Myocardial infarction; [6]Peripheral vascular disease; [7]Cerebrovascular disease; [8]Valvular heart disease

Supplementary Table S3. Baseline characteristics of patients with hyperkalemia (serum potassium above 6.0 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 6.0 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients (serum potassium above 6.0 mmol/L) vs their matched comparisons are shown.

	Patients with hyperkalemia			Matched comparisons without hyperkalemia					
	CKD[1]	HF[2]	Diabetes	CKD	PR[3]	HF	PR[3]	Diabetes	PR[3]
Total	3,258 (100%)	1,164 (100%)	574 (100%)	3,250 (100%)	1.00 (1.00-1.00)	1,164 (100%)	1.00 (1.00-1.00)	585 (100%)	1.00 (1.00-1.00)
Female	1,435 (44.0%)	523 (44.9%)	213 (37.1%)	1,428 (43.9%)	1.00 (0.95-1.06)	523 (44.9%)	1.00 (0.91-1.09)	215 (36.8%)	1.01 (0.87-1.17)
Median age (range)	75 (64.7-82.4)	79 (69.8-84.8)	72 (62.1-80.4)	75 (65.1-82.6)	. (.-.)	79 (69.7-84.8)	. (.-.)	72 (62.3-80.4)	. (.-.)
<65	836 (25.7%)	185 (15.9%)	184 (32.1%)	803 (24.7%)	1.04 (0.96-1.13)	185 (15.9%)	1.00 (0.83-1.21)	187 (32.0%)	1.00 (0.85-1.19)
65-74	794 (24.4%)	265 (22.8%)	163 (28.4%)	798 (24.6%)	0.99 (0.91-1.08)	265 (22.8%)	1.00 (0.86-1.16)	167 (28.5%)	0.99 (0.83-1.19)
75-84	1,052 (32.3%)	431 (37.0%)	165 (28.7%)	1,064 (32.7%)	0.99 (0.92-1.06)	431 (37.0%)	1.00 (0.90-1.11)	169 (28.9%)	1.00 (0.83-1.19)
85+	576 (17.7%)	283 (24.3%)	62 (10.8%)	585 (18.0%)	0.98 (0.88-1.09)	283 (24.3%)	1.00 (0.87-1.15)	62 (10.6%)	1.02 (0.73-1.42)
eGFR level[4]									
eGFR ≥60	10 (0.3%)	39 (3.4%)	55 (9.6%)	48 (1.5%)	0.21 (0.11-0.41)	127 (10.9%)	0.31 (0.22-0.44)	211 (36.1%)	0.27 (0.20-0.35)
eGFR 45-59	246 (7.6%)	62 (5.3%)	56 (9.8%)	646 (19.9%)	0.38 (0.33-0.44)	162 (13.9%)	0.38 (0.29-0.51)	135 (23.1%)	0.42 (0.32-0.56)
eGFR 30-44	633 (19.4%)	188 (16.2%)	106 (18.5%)	972 (29.9%)	0.65 (0.60-0.71)	307 (26.4%)	0.61 (0.52-0.72)	126 (21.5%)	0.86 (0.68-1.08)
eGFR 15-29	1,166 (35.8%)	456 (39.2%)	178 (31.0%)	1,004 (30.9%)	1.16 (1.08-1.24)	388 (33.3%)	1.18 (1.05-1.31)	74 (12.6%)	2.45 (1.92-3.13)
eGFR <15	1,039 (31.9%)	355 (30.5%)	157 (27.4%)	484 (14.9%)	2.14 (1.94-2.36)	133 (11.4%)	2.67 (2.23-3.20)	18 (3.1%)	8.89 (5.53-14.28)
Dialysis	164 (5.0%)	64 (5.5%)	21 (3.7%)	79 (2.4%)	2.07 (1.59-2.70)	31 (2.7%)	2.06 (1.35-3.15)	6 (1.0%)	3.57 (1.45-8.77)
Qualifying event of hyperkalemia									
5.5-5.9									
6.0-6.4	2,002 (61.4%)	713 (61.3%)	358 (62.4%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.5-6.9	711 (21.8%)	258 (22.2%)	127 (22.1%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
≥7.0	545 (16.7%)	193 (16.6%)	89 (15.5%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
Main risk factors									
Diabetes	1,060 (32.5%)	412 (35.4%)	574 (100%)	963 (29.6%)	1.10 (1.02-1.18)	327 (28.1%)	1.26 (1.12-1.42)	585 (100%)	1.00 (1.00-1.00)
CKD	3,258 (100%)	910 (78.2%)	389 (67.8%)	3,250 (100%)	1.00 (1.00-1.00)	835 (71.7%)	1.09 (1.04-1.14)	306 (52.3%)	1.30 (1.18-1.43)
Heart failure	845 (25.9%)	1,164 (100%)	166 (28.9%)	720 (22.2%)	1.17 (1.07-1.28)	1,164 (100%)	1.00 (1.00-1.00)	104 (17.8%)	1.63 (1.31-2.02)
Hypertension	2,530 (77.7%)	1,041 (89.4%)	478 (83.3%)	2,759 (84.9%)	0.91 (0.89-0.94)	1,056 (90.7%)	0.99 (0.96-1.01)	457 (78.1%)	1.07 (1.01-1.13)
Other comorbidities									
MI[5]	544 (16.7%)	358 (30.8%)	107 (18.6%)	622 (19.1%)	0.87 (0.79-0.97)	393 (33.8%)	0.91 (0.81-1.02)	132 (22.6%)	0.83 (0.66-1.04)
HF	780 (23.9%)	0 (0.0%)	153 (26.7%)	706 (21.7%)	1.10 (1.01-1.21)	0 (0.0%)	. (.-.)	102 (17.4%)	1.53 (1.22-1.91)
PVD[6]	501 (15.4%)	219 (18.8%)	81 (14.1%)	497 (15.3%)	1.01 (0.90-1.13)	206 (17.7%)	1.06 (0.90-1.26)	97 (16.6%)	0.85 (0.65-1.12)
CVD[7]	603 (18.5%)	244 (21.0%)	110 (19.2%)	750 (23.1%)	0.80 (0.73-0.88)	255 (21.9%)	0.96 (0.82-1.12)	138 (23.6%)	0.81 (0.65-1.01)
Any malignant disease	767 (23.5%)	200 (17.2%)	121 (21.1%)	746 (23.0%)	1.03 (0.94-1.12)	192 (16.5%)	1.04 (0.87-1.25)	147 (25.1%)	0.84 (0.68-1.04)
Afib or flutter	812 (24.9%)	488 (41.9%)	153 (26.7%)	711 (21.9%)	1.14 (1.04-1.24)	508 (43.6%)	0.96 (0.87-1.06)	102 (17.4%)	1.53 (1.22-1.91)
VHD[8]	389 (11.9%)	272 (23.4%)	55 (9.6%)	308 (9.5%)	1.26 (1.09-1.45)	201 (17.3%)	1.35 (1.15-1.59)	48 (8.2%)	1.17 (0.81-1.69)
Charlson comorbidity index									
0	516 (15.8%)	145 (12.5%)	99 (17.2%)	599 (18.4%)	0.86 (0.77-0.96)	197 (16.9%)	0.74 (0.60-0.90)	109 (18.6%)	0.93 (0.72-1.18)
1	598 (18.4%)	217 (18.6%)	107 (18.6%)	601 (18.5%)	0.99 (0.90-1.10)	254 (21.8%)	0.85 (0.73-1.00)	118 (20.2%)	0.92 (0.73-1.17)
2	759 (23.3%)	225 (19.3%)	122 (21.3%)	729 (22.4%)	1.04 (0.95-1.14)	211 (18.1%)	1.07 (0.90-1.26)	131 (22.4%)	0.95 (0.76-1.18)
≥3	1,385 (42.5%)	577 (49.6%)	246 (42.9%)	1,321 (40.6%)	1.05 (0.99-1.11)	502 (43.1%)	1.15 (1.05-1.25)	227 (38.8%)	1.10 (0.96-1.27)

Medications									
ACEis	1,516 (46.5%)	659 (56.6%)	304 (53.0%)	1,485 (45.7%)	1.02 (0.97-1.07)	599 (51.5%)	1.10 (1.02-1.19)	262 (44.8%)	1.18 (1.05-1.33)
ARBs	711 (21.8%)	231 (19.8%)	128 (22.3%)	843 (25.9%)	0.84 (0.77-0.92)	249 (21.4%)	0.93 (0.79-1.09)	158 (27.0%)	0.83 (0.67-1.01)
Spironolactone	1,024 (31.4%)	533 (45.8%)	203 (35.4%)	637 (19.6%)	1.60 (1.47-1.75)	429 (36.9%)	1.24 (1.13-1.37)	82 (14.0%)	2.52 (2.01-3.17)
Potassium supplements	1,319 (40.5%)	723 (62.1%)	230 (40.1%)	1,202 (37.0%)	1.09 (1.03-1.16)	664 (57.0%)	1.09 (1.02-1.16)	168 (28.7%)	1.40 (1.19-1.64)

[1]Chronic kidney disease; [2]Heart failure; [3]Prevalence ratio of each characteristic in patients with hyperkalemia versus matched comparisons without hyperkalemia; [4]mL/min/1.73m^2; [5]Myocardial infarction; [6]Peripheral vascular disease; [7]Cerebrovascular disease; [8]Valvular heart disease

Supplementary Table S4: Primary (first-listed) discharge diagnoses during acute hospital admissions during which HK occurred.

	CKD[1]			HF[2]			Diabetes		
Chapter	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)
Number of patients		**N=17,747**			**N=5,141**			**N=4,183**	
Number of patients with acute hospital admission		**N=7,069**			**N=2,897**			**N=1,288**	
Event during acute hospital admission	7,069	39.8%	100%	2,897	56.4%	100%	1,288	30.8%	100%
Infectious diseases	432	2.4%	6.1%	108	2.1%	3.7%	88	2.1%	6.8%
Neoplasms	471	2.7%	6.7%	68	1.3%	2.3%	70	1.7%	5.4%
Hematological diseases	163	0.9%	2.3%	44	0.9%	1.5%	20	0.5%	1.6%
Endocrine, nutritional and metabolic disorders	455	2.6%	6.4%	125	2.4%	4.3%	167	4.0%	13.0%
Mental and behavioral disorders	40	0.2%	0.6%	12	0.2%	0.4%	8	0.2%	0.6%
Diseases of the nervous system	57	0.3%	0.8%	13	0.3%	0.4%	21	0.5%	1.6%
Diseases of the eye and adnexa	2	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%
Diseases of the ear and mastoid process	3	0.0%	0.0%	0	0.0%	0.0%	1	0.0%	0.1%
Diseases of the circulatory system	1,377	7.8%	19.5%	1,280	24.9%	44.2%	213	5.1%	16.5%

	CKD[1]			HF[2]			Diabetes		
Chapter	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)
Diseases of the respiratory system	1,054	5.9%	14.9%	516	10.0%	17.8%	207	4.9%	16.1%
Diseases of the digestive system	797	4.5%	11.3%	183	3.6%	6.3%	147	3.5%	11.4%
Diseases of the skin and subcutaneous tissue	42	0.2%	0.6%	12	0.2%	0.4%	12	0.3%	0.9%
Musculoskeletal and connective tissue diseases	100	0.6%	1.4%	27	0.5%	0.9%	20	0.5%	1.6%
Diseases of the genitourinary system	623	3.5%	8.8%	121	2.4%	4.2%	76	1.8%	5.9%
Pregnancy, childbirth and the puerperium	3	0.0%	0.0%	0	0.0%	0.0%	8	0.2%	0.6%
Perinatal conditions	1	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%
Congenital malformations	6	0.0%	0.1%	2	0.0%	0.1%	1	0.0%	0.1%
Symptoms, signs and abnormal findings	487	2.7%	6.9%	124	2.4%	4.3%	87	2.1%	6.8%
Injuries	543	3.1%	7.7%	127	2.5%	4.4%	84	2.0%	6.5%
External causes of morbidity and mortality	1	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%

	CKD[1]			HF[2]			Diabetes		
Chapter	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)
Health status factors and health services contact	412	2.3%	5.8%	135	2.6%	4.7%	58	1.4%	4.5%

[1]Chronic kidney disease; [2]Heart failure;

Supplementary Table S5. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.5 mmol/L.

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€) (95% CI)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=7,447**					**N=7,391**			
Acute hospitalizations[1]	5,549	(1.05)	11,508	(1.57)	5,959	2,419	(0.52)	2,720	(0.52)	301	5,658 (5,074;6,242)
Dialysis	50	(0.01)	249	(0.02)	199	57	(0.00)	69	(0.01)	12	187 (111;263)
Ventilator	1,147	(0.03)	4,031	(0.11)	2,883	414	(0.01)	545	(0.01)	132	2,752 (2,323;3,180)
ICU	1,455	(0.06)	4,739	(0.19)	3,283	508	(0.03)	688	(0.03)	179	3,104 (2,668;3,539)
Non-acute hospitalizations	2,085	(0.38)	3,158	(0.36)	1,073	1,260	(0.21)	1,144	(0.19)	-116	1,189 (875;1,504)
Outpatient visits	2,042	(5.62)	1,987	(6.25)	-55	1,254	(3.60)	1,350	(3.71)	96	-151 (-315;13)
GP consultations	89	(4.62)	71	(3.69)	-18	83	(4.30)	78	(4.05)	-5	-13 (-16;-11)
GP contacts	204	(16.16)	187	(14.60)	-17	143	(12.37)	144	(12.23)	1	-19 (-25;-12)
Prescriptions	654	(25.61)	426	(17.39)	-228	597	(22.45)	559	(21.93)	-38	-190 (-215;-164)
Overall cost	10,623	-	17,337	-	6,715	5,756	-	5,996	-	240	6,475 (5,752;7,197)
Heart failure											
Number of patients			**N=2,511**					**N=2,511**			
Acute hospitalizations	6,659	(1.42)	11,628	(1.69)	4,969	5,230	(1.14)	4,467	(0.96)	-762	5,731 (4,797;6,664)

Dialysis	155	(0.02)	214	(0.02)	59	47	(0.01)	41	(0.01)	-6	65 (-70;199)
Ventilator	911	(0.03)	3,872	(0.11)	2,961	606	(0.02)	620	(0.02)	14	2,947 (2,302;3,592)
ICU	1,282	(0.07)	4,688	(0.20)	3,406	816	(0.05)	805	(0.04)	-11	3,417 (2,719;4,115)
Non-acute hospitalizations	1,962	(0.30)	3,088	(0.32)	1,126	1,656	(0.24)	1,755	(0.24)	99	1,027 (439;1,616)
Outpatient visits	1,837	(5.70)	1,847	(6.15)	10	1,141	(4.16)	1,211	(4.72)	70	-60 (-282;162)
GP consultations	96	(4.97)	73	(3.81)	-23	98	(5.11)	92	(4.80)	-6	-17 (-22;-11)
GP contacts	263	(19.52)	218	(16.01)	-46	210	(16.60)	209	(16.46)	-1	-44 (-59;-29)
Prescriptions	704	(30.16)	429	(18.84)	-276	650	(26.90)	579	(25.96)	-70	-205 (-251;-159)
Overall cost	11,521	-	17,283	-	5,761	8,985	-	8,314	-	-671	6,432 (5,223;7,642)
Diabetes											
Number of patients			**N=4,183**					**N=4,151**			
Acute hospitalizations	5,219	(0.97)	11,380	(1.49)	6,161	1,325	(0.31)	1,400	(0.32)	75	6,086 (4,757;7,415)
Dialysis	96	(0.01)	207	(0.02)	111	16	(0.00)	0	(0.00)	-16	128 (-23;278)
Ventilator	912	(0.03)	4,099	(0.11)	3,186	127	(0.00)	202	(0.01)	76	3,111 (2,142;4,080)
ICU	1,306	(0.06)	4,770	(0.20)	3,463	176	(0.01)	241	(0.01)	65	3,399 (2,382;4,416)
Non-acute hospitalizations	1,840	(0.32)	3,249	(0.36)	1,408	865	(0.16)	711	(0.14)	-154	1,562 (927;2,197)
Outpatient visits	1,896	(5.45)	1,850	(6.02)	-46	946	(2.95)	924	(2.91)	-22	-24 (-304;257)
GP consultations	102	(5.26)	82	(4.27)	-19	89	(4.61)	82	(4.29)	-6	-13 (-19;-7)
GP contacts	234	(18.88)	208	(16.49)	-26	151	(13.16)	148	(12.64)	-3	-23 (-39;-7)
Prescriptions	694	(27.36)	469	(19.01)	-225	532	(20.76)	513	(20.74)	-19	-207 (-275;-139)
Overall cost	9,985	-	17,238	-	7,253	3,907	-	3,779	-	-128	7,381 (5,802;8,961)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Supplementary Table S6. Healthcare resource use and mean costs (€) associated with elevated potassium level >6.0 mmol/L.

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€) (95% CI)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=3,258**					**N=3,250**			
Acute hospitalizations[1]	6,732	(1.22)	13,414	(1.84)	6,682	2,781	(0.59)	3,182	(0.60)	401	6,281 (5,320;7,242)
Dialysis	99	(0.02)	362	(0.03)	264	24	(0.00)	89	(0.01)	65	198 (71;325)
Ventilator	1,529	(0.04)	4,337	(0.12)	2,808	400	(0.01)	611	(0.02)	211	2,597 (1,906;3,287)
ICU	1,891	(0.08)	5,230	(0.23)	3,338	565	(0.03)	761	(0.04)	195	3,143 (2,434;3,851)
Non-acute hospitalizations	2,642	(0.43)	3,113	(0.36)	471	1,374	(0.24)	1,217	(0.21)	-157	628 (131;1,125)
Outpatient visits	2,545	(6.72)	2,541	(7.49)	-4	1,544	(4.24)	1,546	(4.38)	2	-6 (-306;293)
GP consultations	89	(4.60)	63	(3.29)	-26	86	(4.47)	78	(4.06)	-8	-18 (-22;-13)
GP contacts	219	(16.91)	181	(13.74)	-37	154	(13.09)	155	(12.89)	1	-38 (-50;-27)
Prescriptions	676	(26.42)	364	(15.24)	-312	555	(22.04)	524	(21.60)	-31	-281 (-321;-241)
Overall cost	12,904	-	19,678	-	6,774	6,494	-	6,702	-	208	6,565 (5,392;7,738)
Heart failure											
Number of patients			**N=1,164**					**N=1,164**			
Acute hospitalizations	7,199	(1.57)	12,123	(1.77)	4,924	5,111	(1.17)	4,627	(1.01)	-484	5,408 (3,949;6,867)

Dialysis	171	(0.03)	239	(0.03)	68	97	(0.01)	80	(0.01)	-17	85 (-77;246)
Ventilator	849	(0.03)	3,741	(0.10)	2,892	377	(0.02)	714	(0.02)	336	2,556 (1,581;3,531)
ICU	1,303	(0.08)	4,972	(0.22)	3,669	564	(0.06)	865	(0.05)	301	3,368 (2,320;4,415)
Non-acute hospitalizations	2,139	(0.31)	2,747	(0.29)	608	1,577	(0.26)	1,698	(0.23)	122	487 (-376;1,349)
Outpatient visits	2,373	(7.03)	2,430	(7.33)	57	1,440	(4.79)	1,535	(5.27)	94	-37 (-418;343)
GP consultations	94	(4.87)	60	(3.12)	-34	100	(5.14)	90	(4.68)	-10	-25 (-32;-17)
GP contacts	283	(20.71)	195	(14.34)	-88	208	(16.78)	203	(16.17)	-4	-83 (-106;-61)
Prescriptions	776	(32.25)	358	(15.96)	-418	707	(28.52)	631	(27.53)	-76	-342 (-417;-267)
Overall cost	12,863	-	17,913	-	5,050	9,141	-	8,784	-	-358	5,407 (3,508;7,307)
Diabetes											
Number of patients			**N=574**					**N=585**			
Acute hospitalizations	7,571	(1.19)	14,537	(1.81)	6,966	1,771	(0.41)	1,544	(0.35)	-227	7,193 (4,624;9,762)
Dialysis	108	(0.01)	356	(0.03)	248	0	(0.00)	0	(0.00)	0	248 (-35;532)
Ventilator	1,848	(0.05)	5,585	(0.13)	3,737	30	(0.00)	252	(0.01)	221	3,516 (1,544;5,488)
ICU	2,363	(0.11)	6,877	(0.26)	4,514	154	(0.01)	177	(0.01)	24	4,490 (2,497;6,484)
Non-acute hospitalizations	2,298	(0.32)	3,548	(0.39)	1,251	1,095	(0.17)	754	(0.14)	-341	1,591 (454;2,729)
Outpatient visits	2,317	(6.70)	2,261	(7.25)	-56	1,187	(3.65)	1,072	(3.42)	-115	59 (-441;559)
GP consultations	105	(5.42)	75	(3.90)	-30	93	(4.84)	84	(4.36)	-9	-20 (-30;-10)
GP contacts	240	(19.28)	202	(15.77)	-38	173	(14.40)	164	(13.41)	-9	-29 (-57;-2)
Prescriptions	759	(29.47)	381	(16.95)	-378	508	(20.31)	494	(20.60)	-15	-363 (-493;-234)

Overall cost	13,291	-	21,006	-	7,715	4,828	-	4,112	-	-715	8,430 (5,481;11,379)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Supplementary Table S7. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L, weighted by time-at-risk.

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of time-at-risk by half-year term	**17,747**		**14,107**			**17,608**		**16,918**			
Acute hospitalizations[1]	3,666	(0.78)	10,316	(1.52)	6,651	1,778	(0.41)	2,284	(0.48)	506	6,145 (5,760;6,511)
Dialysis	27	(0.00)	156	(0.01)	129	17	(0.00)	33	(0.00)	15	114 (77;158)
Ventilator	504	(0.02)	3,279	(0.09)	2,775	243	(0.01)	395	(0.01)	152	2,623 (2,326;2,898)
ICU	675	(0.04)	3,910	(0.16)	3,235	314	(0.02)	486	(0.02)	172	3,063 (2,768;3,343)
Non-acute hospitalizations	1,653	(0.30)	3,468	(0.43)	1,815	1,087	(0.18)	1,135	(0.18)	48	1,767 (1,567;1,981)
Outpatient visits	1,593	(4.42)	2,009	(6.37)	416	1,077	(3.10)	1,159	(3.35)	82	334 (228;429)
GP consultations	85	(4.42)	101	(5.24)	16	79	(4.11)	81	(4.19)	1	14 (12;16)
GP contacts	174	(14.21)	230	(18.46)	56	130	(11.33)	143	(12.12)	13	43 (39;47)
Prescriptions	583	(22.91)	572	(23.36)	-11	554	(21.08)	555	(21.63)	1	-12 (-27;3)
Overall cost	3,666	(0.78)	10,316	(1.52)	6,651	1,778	(0.41)	2,284	(0.48)	506	6,145 (5,760;6,511)
Heart failure											

Number of time-at-risk by half-year term	**N=5,141**		**N=3,702**			**N=5,141**		**N=4,655**			
Acute hospitalizations	5,799	(1.30)	13,409	(2.12)	7,609	4,934	(1.12)	4,590	(1.03)	-344	7,954 (7,063;8,676)
Dialysis	85	(0.01)	211	(0.02)	126	36	(0.01)	34	(0.00)	-2	127 (49;229)
Ventilator	636	(0.02)	4,035	(0.12)	3,399	606	(0.02)	463	(0.02)	-143	3,542 (3,039;4,127)
ICU	928	(0.06)	4,808	(0.21)	3,880	830	(0.05)	692	(0.04)	-138	4,018 (3,457;4,607)
Non-acute hospitalizations	1,759	(0.29)	4,414	(0.45)	2,655	1,820	(0.28)	1,849	(0.26)	29	2,626 (2,163;3,105)
Outpatient visits	1,463	(4.84)	2,132	(7.80)	669	1,130	(4.03)	1,354	(5.11)	224	445 (283;614)
GP consultations	97	(5.04)	117	(6.11)	20	98	(5.07)	102	(5.31)	4	16 (12;20)
GP contacts	241	(18.17)	310	(23.29)	69	203	(16.06)	220	(17.41)	17	52 (41;63)
Prescriptions	647	(27.68)	653	(29.02)	7	622	(25.89)	644	(28.27)	21	-14 (-45;13)
Overall cost	10,006	-	21,035	-	11,029	8,807	-	8,758	-	-49	11,078 (10,031;12,034)
Diabetes											
Number of time-at-risk by half-year term	**N=4,183**		**N=3,572**			**N=4,151**		**N=4,073**			
Acute hospitalizations	3,056	(0.66)	7,976	(1.15)	4,920	1,195	(0.28)	1,096	(0.25)	-98	5,019 (4,427;5,627)
Dialysis	33	(0.00)	85	(0.01)	52	9	(0.00)	0	(0.00)	-9	61 (7;118)
Ventilator	260	(0.01)	2,572	(0.07)	2,312	146	(0.00)	121	(0.00)	-25	2,337 (1,929;2,792)
ICU	440	(0.03)	3,075	(0.13)	2,635	166	(0.01)	166	(0.01)	-0	2,635 (2,216;3,076)
Non-acute hospitalizations	1,311	(0.23)	2,575	(0.34)	1,264	661	(0.12)	614	(0.12)	-48	1,312 (975;1,650)
Outpatient visits	1,369	(4.01)	1,704	(5.56)	336	955	(2.67)	948	(2.69)	-6	342 (176;520)

GP consultations	97	(4.99)	108	(5.61)	12	86	(4.45)	82	(4.25)	-4	15 (12;19)
GP contacts	189	(15.99)	228	(19.02)	39	143	(12.51)	140	(12.14)	-2	41 (33;49)
Prescriptions	548	(22.48)	547	(22.82)	-1	458	(18.08)	467	(19.30)	10	-11 (-37;17)
Overall cost	6,569	-	13,138	-	6,570	3,497	-	3,348	-	-149	6,719 (5,943;7,440)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

†Cost weighted by time-at-risk was calculated as overall cost within the 6-month period divided by the total number of person in half-year term

Supplementary Table S8. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L 1 month before and after HK.

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€) (95% CI)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=17,747**					**N=17,608**			
Acute hospitalizations[1]	1,378	(0.27)	4,925	(0.65)	3,547	450	(0.10)	810	(0.15)	360	3,187 (2,984;3,391)
Dialysis	11	(0.00)	63	(0.00)	52	7	(0.00)	21	(0.00)	14	38 (13;62)
Ventilator	221	(0.01)	1,864	(0.05)	1,643	77	(0.00)	195	(0.00)	119	1,524 (1,359;1,688)
ICU	311	(0.01)	2,248	(0.09)	1,936	99	(0.00)	234	(0.01)	134	1,802 (1,630;1,974)
Non-acute hospitalizations	494	(0.07)	1,418	(0.13)	924	217	(0.03)	324	(0.05)	107	817 (705;929)
Outpatient visits	302	(1.01)	327	(1.19)	25	198	(0.58)	213	(0.64)	16	9 (-10;29)
GP consultations	16	(0.81)	21	(1.08)	5	14	(0.73)	15	(0.80)	1	4 (3;4)
GP contacts	47	(3.28)	56	(4.21)	9	26	(2.14)	28	(2.35)	3	6 (5;8)
Prescriptions	101	(4.17)	94	(3.92)	-7	94	(3.63)	94	(3.69)	0	-7 (-11;-4)
Overall cost	2,338	-	6,841	-	4,503	999	-	1,485	-	486	4,017 (3,785;4,249)
Heart failure											
Number of patients			**N=5,141**					**N=5,141**			
Acute hospitalizations	2,164	(0.46)	6,149	(0.87)	3,984	1,727	(0.39)	1,921	(0.40)	194	3,790 (3,377;4,203)

Dialysis	19	(0.00)	69	(0.01)	50	12	(0.00)	8	(0.00)	-5	55 (-1;110)
Ventilator	320	(0.01)	2,242	(0.07)	1,923	190	(0.01)	246	(0.01)	56	1,867 (1,540;2,194)
ICU	460	(0.03)	2,640	(0.12)	2,180	299	(0.02)	353	(0.02)	54	2,126 (1,796;2,456)
Non-acute hospitalizations	500	(0.08)	1,750	(0.14)	1,250	563	(0.08)	439	(0.07)	-124	1,374 (1,141;1,607)
Outpatient visits	290	(1.09)	287	(1.19)	-3	222	(0.85)	231	(0.91)	9	-12 (-40;15)
GP consultations	19	(0.98)	20	(1.02)	1	19	(1.00)	18	(0.94)	-1	2 (1;3)
GP contacts	66	(4.35)	63	(4.38)	-3	49	(3.54)	44	(3.24)	-5	2 (-2;6)
Prescriptions	114	(5.25)	99	(4.65)	-15	110	(4.92)	112	(4.99)	2	-16 (-23;-10)
Overall cost	3,154	-	8,368	-	5,213	2,690	-	2,764	-	74	5,140 (4,672;5,607)
Diabetes											
Number of patients			**N=574**					**N=585**			
Acute hospitalizations	1,081	(0.22)	3,980	(0.51)	2,899	211	(0.05)	170	(0.05)	-41	2,940 (2,593;3,288)
Dialysis	10	(0.00)	25	(0.00)	15	0	(0.00)	0	(0.00)	0	15 (-12;42)
Ventilator	99	(0.00)	1,591	(0.05)	1,493	9	(0.00)	2	(0.00)	-7	1,500 (1,217;1,783)
ICU	192	(0.01)	1,876	(0.08)	1,684	20	(0.00)	22	(0.00)	2	1,682 (1,399;1,965)
Non-acute hospitalizations	478	(0.07)	1,150	(0.11)	673	109	(0.02)	102	(0.02)	-7	680 (489;870)
Outpatient visits	268	(0.91)	305	(1.12)	37	164	(0.49)	161	(0.48)	-2	40 (6;74)
GP consultations	17	(0.88)	25	(1.27)	7	15	(0.77)	14	(0.71)	-1	8 (7;10)
GP contacts	43	(3.31)	60	(4.69)	16	26	(2.20)	24	(2.10)	-2	18 (15;21)
Prescriptions	98	(4.18)	89	(3.85)	-10	78	(3.20)	77	(3.16)	-2	-8 (-14;-2)
Overall cost	1,985	-	5,608	-	3,623	603	-	547	-	-56	3,678 (3,280;4,076)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectivel

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

Healthcare resource utilization and cost associated with elevated potassium levels: a Danish population-based cohort study

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 1 and 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 9
Bias	9	Describe any efforts to address potential sources of bias Page 11 and 13
Study size	10	Explain how the study size was arrived at Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 8
		(*b*) Describe any methods used to examine subgroups and interactions Page 8
		(*c*) Explain how missing data were addressed Page 8 and 14
		(*d*) If applicable, explain how loss to follow-up was addressed Not applicable

		(*e*) Describe any sensitivity analyses Not don in this study. Do in the "sister" clinical publications
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram Figure 1-3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 10
		(b) Indicate number of participants with missing data for each variable of interest Not applicable
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time Page 10 and 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Page 10 and 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses See supplementary data
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 13 and 14
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Healthcare resource utilization and cost associated with elevated potassium levels: a Danish population-based cohort study

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Healthcare resource utilization and cost associated with elevated potassium levels: a Danish population-based cohort study

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Abstract

Objectives: To investigate healthcare costs associated with hyperkalemia (HK) among patients with chronic kidney disease (CKD), heart failure (HF), or diabetes.

Design: Before-after cohort study of patients with HK and matched patients without HK.

Setting: Population-based databases covering primary and secondary care for the entire of Northern Denmark.

Participants: Patients with a first incident record of CKD (n=78,372), HF (n=14,233), or diabetes (n=37,479) during 2005-2011. Among all patients experiencing a first HK event (potassium level >5.0 mmol/L), healthcare costs were compared during 6 months before and 6 months after the HK event. The same cost assessment was conducted 6 months before and after a matched index date in a comparison cohort of patients without HK.

Primary and secondary outcome measures: Mean costs of hospital care, general practice, and dispensed drugs, converted to 2018 Euros (€).

Results: Overall, 17,747 (23%) CKD patients, 5,141 (36%) HF patients, and 4,183 (11%) diabetes patients with a first HK event were identified. More than 40% of all HK patients across the patient groups, had subsequent HK events with successively shorter times between the events. In CKD patients, overall mean costs were €5,518 higher 6 months after versus before first HK, while €441 higher in matched CKD patients without HK, yielding HK-associated costs of €5,077. Corresponding costs associated with a HK event were €6,018 in HF patients, and €4,862 in diabetes patients.

Conclusions: Among CKD, HF, and diabetes patients an incident HK event was common, and a large proportion of the patients experienced recurrent HK events. Substantial increase

in healthcare costs associated with a HK event was observed in the HK patients compared to non-HK patients. These results are important to better understand the potential economic impact of HK among high-risk comorbid patients in a real-wold setting and help inform decision making for clinicians and healthcare providers.

Strengths and limitations of this study

Strengths

- Access to laboratory test results from both primary and hospital care for the entire region's population of Northern Denmark (1,841,902 residents, i.e. 33% of Denmark's population) linkable to nationwide data on morbidity, mortality, and medication.
- Describing healthcare resource utilization and corresponding costs in three main hyperkalemia (HK) risk groups; patients with chronic kidney disease (CKD), heart failure (HF), or diabetes.
- Reported costs based on official Diagnosis Related Groups (DRG) and Danish Outpatient Grouping System (DAGS) charges.

Limitations

- Any conclusions concerning causal mechanisms underlying HK outcomes and corresponding costs should be made with caution.
- Rather than precipitating a hospitalization, elevated potassium levels may stem from an underlying condition that led to the hospitalization.

Background

Hyperkalemia (HK) is defined as serum potassium levels above a reference range, usually above 5.0 mmol/L, although more severe potassium cut-off levels are often used in treatment decision guidelines (e.g. >5.5 or >6.0 mmol/L) [1, 2]. HK has been reported to occur in 3–8% of all hospitalized patients, independent of reason for hospitalization, based on single clinic or health insurance based cross-sectional studies[3-5]. Patients older than 65 years with chronic kidney disease (CKD), heart failure (HF), diabetes, or who use renin-angiotensin-aldosterone system inhibitors (RAASi) are at increased risk of experiencing HK[1, 6-9]. An elevated

.plasma potassium concentration may result in muscle weakness, paralysis, life-threatening effects on cardiac arrhythmias, and sudden death[7]. The latter two have been reported among patients with potassium levels above 6.0 mmol/L[10, 11]. However, recent cohort analyses indicate that potassium levels above 5.0 mmol/L may also predict increased higher risk of cardiovascular events and short-term mortality among patients with an acute hospitalization, as well as among patients with CKD or HF[12-17].

HK has been associated with longer stay during acute hospitalizations, as well as an increased number of intensive care unit (ICU) stays and emergency department visits, primarily in the US healthcare system setting[11, 17-19]. However, the overall healthcare resource utilization (HRU) and costs associated with HK have not been comprehensively studied in a full population-based setting outside the US. To better understand the potential impact of new emerging drug therapies for HK, it is important to assess the true burden of HRU and costs in patients with HK events occurring in real-life, even if HK-related costs are unlikely to be causally driven by HK alone. The aims of this study were to investigate overall HRU and costs associated with HK in a real-world clinical setting in patients with an incident diagnosis of CKD, HF or diabetes.

Methods

Patient and public involvement

This was a cohort study using local and nationwide register data and no patients were involved in the design of the study. The study design is based on previous experience on data that are of interest to healthcare providers.

Data sources

This cohort study was conducted in Northern Denmark, using routine laboratory test results from both primary and hospital care for the entire region's population (1,841,902 residents, i.e. 33% of Denmark's population in June 2011) [20, 21]. Laboratory data were linked, via mandatory and unique civil personal registration numbers (assigned to each Danish resident), to hospital diagnoses and procedure data maintained in the Danish National Patient Registry (DNPR). The DNPR contains dates of hospital admission and discharge, emergency room visits, and outpatient clinic visits as well as and procedures carried out in the hospital setting[22]. Records of all drugs prescribed in an outpatient setting and dispensed from Danish pharmacies were obtained from the National Prescription Database and the Aarhus Prescription Database[21, 23]. Data on general practitioner (GP) services were retrieved from the National Health Insurance Service Registry (NHISR) [24]. This study was approved by an institutional review board.

Study populations with CKD, HF, or diabetes

Overall, three disease cohorts with a first incident record of CKD, HF, or diabetes, respectively, were identified between 1 January 2005 and 30 June 2011, based on a combination of laboratory, drug prescription, and hospital contact data. To ensure that our patients reflect true real-world disease cohorts with various possible comorbidities, an individual detected with

more than one of these conditions (such as both incident diabetes and later incident CKD) during the study period could be included in more than one patient cohort, in each case starting on the detection date of the respective disease. Incident CKD was defined as the first occurrence of one of the following: (1) eGFR <60 mL/min/1.73m^2 verified by at least two creatinine measurements more than 90 days apart; (2) an incident hospitalization with a diagnosis of CKD; or (3) hospital-based codes for renal dialysis [15]. Incident HF was defined as the first occurrence of an inpatient hospital admission with a primary or secondary discharge diagnosis of HF[25]. Incident diabetes was defined as the first dispensed prescription for a glucose-lowering drug[26]. To maximise the likelihood that the diseases were truly incident, we ensured that individuals had no previous record of the disease in question before study start (1 January 2005). Available look-back periods were back to 1977 for hospital codes (CKD or HF), to 1998 for prescription data (diabetes), and to 2000 for laboratory data (CKD).

Hyperkalemia events

Within each of the three cohorts, i.e. individuals with a first record of CKD, HF, and diabetes respectively, we followed individuals for a first incident HK event occurring after being recorded for the first time with the respective disease. A HK event for a patient was identified as elevated blood potassium level >5.0 mmol/L not preceded by a prior episode of elevated potassium within the previous month[15, 25, 26].Thus, a patient with a first record of e.g. heart failure was eligible to have a first incident HK event as heart failure patient from the date of her first heart failure cohort entry, only if she had no previous HK event or if she had a previous HK event more than one month before the date of her first heart failure cohort entry. More severe HK events, >5.5 mmol/L and >6.0 mmol/L, were detected the same way. The incidence of HK per 1,000 person-years was calculated in the three cohorts. Following the first event, subsequent HK events were detected and reported, for potassium levels >5.0 mmol/L, >5.5 mmol/L and >6.0 mmol/L respectively. The incidences of subsequent HK events were

presented per 1,000 person-years within the median follow-up times between the events, and the healthcare setting where subsequent HK events were detected was reported.

Hyperkalemia associated healthcare resource utilization and costs

The overall self-controlled before-after analytic design is demonstrated in Figure 1. Among patients who had experienced HK in each of the cohorts with CKD, HF, or diabetes, we assessed the total number of hospital admissions (acute or planned non-acute inpatient hospitalizations, including dialysis procedures, ventilator treatment and ICU admissions), hospital outpatient visits, emergency room visits, GP contacts, and drugs prescribed on an out-patient basis, during the periods 6 months *before* and 6 months *after* the incident HK event. The difference in overall HRU and resulting costs, during the 6 months before the HK event and 6 months after the HK event, was then calculated for each HK patient. If a HK-patient was diagnosed with HK on 1 April 2008 for example, the total costs in the first six months after HK would be his or her costs from 1 April 2008 to 31 September 2008, minus his or her costs from 1 October 2007 to 31 March 2008 (Figure 1).

To control for any changes in HRU and costs related to the natural disease course over time, such as CKD or HF progression, we selected a group of matched comparisons without HK within each disease cohort. Thus, for each patient who developed HK, we selected, by nearest neighbour matching, one comparison patient among those who were alive and had not yet developed HK on the index date of the corresponding matched HK patient, and who was as similar as possible for a range of matching factors. These factors are shown in Figure 1 and included: gender, patient age (in years), calendar year of first record of the disease, disease duration (in days), Charlson Comorbidity Index score (0, 1, 2, 3+), as well as additional pre-specified clinical factors specific to each of the three disease cohorts (Figure 1).

The total costs associated with HK were then estimated as the cost difference 6 months before and after the HK event among the HK patients minus the cost difference during the same period among the non-HK comparisons (Figure 1). Hence, HK-associated costs were derived as a *difference-in-difference*, in which the difference between costs for HK patients and non-HK comparisons were regarded to be associated with the HK event (Figure 1) [27].

To account for early mortality during the 6 months following the index date in both the HK patients and non-HK comparisons, an additional analysis of mean cost per risk-time was performed, where costs were weighted by time-at-risk within the 6 months. We also conducted a supplementary analysis in which the difference-in-difference costs were restricted to costs 1 month before the HK event and 1 month after the HK event. The confidence intervals in the main analysis were calculated based on the assumption that the *difference-in-difference* followed a t-distribution. The confidence intervals in the sub-analysis where the costs were weighted by time-at-risk were calculated based on bootstrapping.

Unit costs

Costs for hospital admissions and outpatient contacts (including emergency room visits) were based on the Diagnosis Related Groups (DRG) and Danish Outpatient Grouping System (DAGS) charges[28]. Costs of GP consultations and contacts such as phone calls, tests, and mileage allowance were calculated based on pre-scheduled fees for GP services in the Danish Healthcare system[24]. Drug acquisition costs for drugs prescribed on an outpatient basis were calculated based on Danish pharmacy retail prices[29]. All unit costs were based on the calendar year in which the resource utilization occurred, using the official healthcare sector price index published by Statistics Denmark[30]. All costs were converted to Euros using an average 2018 exchange rate, according to the European Central Bank, of 7.45 DKK per Euro.

Results

Among 78,372 patients with CKD, 14,233 patients with HF, and 37,479 patients with diabetes, one or more HK events were experienced by 17,747 (23%) of the CKD patients; 5,141 (36%) of HF patients; and 4,183 (11%) of the diabetes patients. Among the 27,071 patients with HK, those with HF were older (median age was 79 vs. 76 in CKD patients and 69 in diabetes patients), included more patients with eGFR levels below 30 mL/min/1.73m^2 (42% vs. 37% in CKD patients and 24% in diabetes patients), and had a higher proportion of ACEi users (55%) than the CKD (43%) or diabetes patients (48%) (Table 1). Similar differences by disease group were observed for the 26,900 comparison patients without HK (Supplementary Table S1)

HK incidence

The incidence rates of HK were 99.0, 256.7, and 45.7 per 1,000 person-years among the CKD, HF and diabetes patients, respectively (Figures 2-4). The incidence of more severe HK events, >5.5 mmol/L, >6.0 mmol/L, was lower across the three disease cohorts. Among the HF patients, more patients had more severe HK (>5.5 mmol/L) (18%), compared to the CKD patients (10%) and diabetes patients (4%). The baseline characteristics of the patients with more severe HK events (>5.5 mmol/L and >6.0 mmol/L) and of their matched comparisons without HK are reported in Supplementary Tables S2 and S3. A large proportion of the patients with a first HK event experienced a second HK event; 44% of the CKD patients, 44% of the HF patients, and 45% of the diabetes patients. Among these surviving patients an increasing proportion suffered subsequent HK events (>5.0 mmol/L), and the time between HK events was successively shorter for the subsequent events (Figure 2-4). After an initial HK event (>5.0 mmol/L), subsequent HK events were more frequently detected in primary care than in hospitals, whereas for patients with severe HK events (>6.0 mmol/L), subsequent HK events were predominantly diagnosed in the hospital setting (Figure 2-4).

HRU and costs associated with HK

Among the CKD patients with a HK event, mean numbers of acute hospital admissions increased from 0.8 during the period of 6 months before HK to 1.2 during the period of 6 months after HK (Table 2). Among the HF patients with a HK event, corresponding acute admissions increased from 1.3 to 1.5 and among the diabetes patients with a HK event from 0.7 to 1.0. One-third (diabetes) to one-half (HF) of the HK patients experienced an acute admission at the time of their HK event; ICD-10 chapters for primary discharge diagnoses for these admissions are shown in Supplementary Table S4. Mean costs of acute admissions with ventilator treatment and ICU stay were much higher after versus before HK, by 5.2-fold and 4.6-fold respectively in CKD patients, 4.6-fold and 3.7-fold in HF patients, and 8.5-fold and 6.0-fold in diabetes patients (Table 2). Among the matched non-HK comparisons in the same period, minor differences in mean numbers of non-acute hospitalizations, and outpatient and GP visits were observed. The mean difference per patient in total costs among HK patients between 6 months before and 6 months after HK was €5,518 in CKD patients, €5,141 in HF patients, and €4,650 in diabetes patients (Table 2, Figure 5). In comparison, the mean difference in total costs among the matched non-HK patients between 6 months before and 6 months after the index date was €441 in CKD patients, €-887 in HF patients, and €-212 in diabetes patients, resulting in estimated HK-associated costs of €5,076 (95% CI 4,690 to 5,463) in patients with CKD, €6,018 (95% CI 5,234 to 6,802) in patients with HF, and €4,862 (95% CI 4,156 to 5,568) in patients with diabetes. Overall, costs after HK increased by 71% in CKD patients, 52% in HF patients, and 70% in diabetes patients. The HK-associated costs were higher in patients with more severe HK events (>5.5 mmol/L and >6.0 mmol/L) (Supplementary Table S5 and S6). The higher costs after versus before incident HK and the cost amplification by HK severity are shown in Table 2 and depicted in Figure 5.

Considering the high mortality 6 months after the HK event among the HK patients compared with the matched non-HK comparisons, (27% vs. 7% mortality in CKD patients, 35% vs. 15% mortality in HF patients, and 19% vs. 4% mortality in diabetes patients, data not shown), the HK-associated costs within 6 months weighted by time-at-risk were estimated; €8,291 (95% CI 7,823 to 8,704) in CKD patients, €11,078 (95% CI 10,031 to 12,034) in HF patients, and €6,719 (95% CI 5,943 to 7,440) in diabetes patients (Supplementary Table S7).

When restricting the calculations to costs 1 month before the HK event and 1 month after the HK event, HK-associated costs were €4,017 (95% CI 3,785 to 4,249) in CKD patients, €5,140 (95% CI 4,672 to 5,607) in HF patients, and €3,678 (95% CI 3,280 to 4,076) in diabetes patients (Supplementary Table S8)

Discussion

This population-based cohort study provides an overview of incidences of HK event and the corresponding HRU and costs, in patients with CKD, HF and diabetes during a maximum observation period of 5.5 years in Denmark. Overall, 17,747 CKD patients, 5,141 HF patients, and 4,183 diabetes patients with a first HK event were identified. More than 40% of the patients had subsequent HK events, with successively shorter time between the events.

In CKD patients, the overall mean costs were €5,518 higher after HK event compared to prior HK event while the costs in the matched non-HK comparisons was €441 during the same time period, resulting in a HK-associated cost of €5,076. Corresponding mean costs associated with a first HK event were €6,018 in patients with HF, and €4,862 in patients with diabetes.

The difference in cost incurred by HK patients and non-HK patients was mainly driven by acute hospitalizations, where ICU stays and ventilator treatments were the main contributing components. The mean cost per acute hospitalization, i.e. due to longer hospital stays and/or a

hospital episode with complications, was higher among HK patients, which may indicate hospitalization for more severe conditions among the HK patients. Costs for primary care visits and prescribed drugs had a minor impact on the overall cost pattern associated with a HK event.

A larger proportion of HF patients had experienced mild and severe HK events, which occurred closer to the date of HF diagnosis, compared to the corresponding results in the CKD and diabetes patients. Relatively more HK events were detected in the hospital than in the primary care setting among the HF patients. The HF cohort also had a higher mean cost per patient prior to the HK event than had the CKD and diabetes cohort, and a larger absolute increase in mean costs after the HK event compared to the other disease cohort. The mean relative increase in costs associated with HK, was higher among the CKD (71%) and diabetes patients (70%) compared to the HF patients (52%). However, when taking the higher mortality among the HF patient cohort into account (35% were deceased within 6 months after HF diagnosis), by weighing in patient survival time, a higher relative mean cost increase was still observed for the HF patients compared to the other disease cohort.

For more severe HK episodes (>5.5 mmol/L and >6.0 mmol/L, respectively) a higher mean cost was observed among the CKD and diabetes patients, compared to costs associated with milder HK events. This pattern was not observed among the HF patients, for whom the HK-associated with cost did not differ greatly by the increasing severity of HK events. This finding might be partly explained by the particularly high early mortality among HF patients with severe HK.

Following the initial HK event, a larger proportion of the subsequent HK events were detected in a primary care compared to hospital setting. Following an initial HK event, patients would presumably undergo more frequent blood testing in primary care, thus potentially explaining why a larger proportion of the subsequent HK events were detected in primary care.

The few existing studies investigating HK related costs in the literature, are mostly from the US. Fitch et al. estimated that monthly severity-adjusted CKD costs for HK patients were $4,922 versus $2,036 for those without HK[31]. Castro et al. estimated a monthly cost of $5,994 and an annual cost of $31,884, to manage CKD patients who experienced HK, but without reference to a comparison group[32]. Probably related to the considerable differences in clinical practice and in reimbursement system between the US and European /Nordic healthcare systems, the mean estimates and the magnitude of cost differences between HK and non-HK patients were generally higher in the US studies than in the current study, i.e. our HK-associated costs converted to USD were $5,837 in the CKD patients, $6,921 in the HF patients, and $5,591 in the diabetes patients (applying an exchange rate of 1 Euro = 1.15 USD).

This study does not come without limitations. First, any conclusions concerning causal mechanisms underlying HK outcomes and corresponding costs should be made with caution. Rather than precipitating a hospitalization, elevated potassium levels measured during a hospitalization may stem from an underlying condition that led to hospitalization (e.g., infection, dehydration, deteriorating kidney function) among the disease cohorts examined[25, 26]. We observed a variety of acute disease diagnoses, typically for an elderly highly comorbid patient population. On the other hand, HK itself may have had a bearing on the acute hospitalization and its severity and course, and HK may also have directly led to admissions, e.g. through muscle weakness, cardiac problems, resulting falls, etc. The exact order of events in the pathophysiological pathway leading to a hospitalization is difficult to disentangle, especially for elderly comorbid patients. Therefore, it is not yet predictable how the effective and sustained management of hyperkalemia will affect the corresponding costs associated with HK occurrence.

Second, our study is reliant on routine care ICD-10 codes for morbidity data and therefore, the possibility of coding errors cannot be ruled out. Furthermore, we did not have access to detailed

clinical data for e.g. severity of heart failure, such as ejection fraction or New York Heart Association Functional Classification, or for exact type of diabetes, which remains uncertain based on treatment modality and hospital codes alone.

Third, inclusion of patients in the study cohorts was restricted to 2005–2011 due to DRG record availability and feasibility of long-term follow-up. Clinical management of the comorbid conditions that are known risk factors for HK, as well as HK management, may have changed during this period, however pharmacological advancements in HK management have been relatively stagnant within this time period[33, 34].

Fourth, long-term clinical implications of HK and the corresponding HRU and costs were not investigated. This could however be a field for further work and investigation.

Lastly, information on drugs administered during hospitalizations, including those for the management of HK, were not available in the dataset. Therefore, their acquisition costs could not be examined in detail, but only included as a part of the cost of each DRG hospital episode.

Conclusions

The costs associated with incident HK were substantial among CKD, HF and diabetes patients, and were mainly driven by increased use of hospital-based care. A large proportion of patients experienced subsequent HK events after a first incident event, with a successively shorter time between events. Our findings indicate that the high HRU and corresponding costs associated with HK events, as well as the recurring pattern of events among CKD, HF and diabetes patients, constitute a substantial clinical and economic burden for patients, healthcare providers, and payers. With our observational study design, it was not possible to determine whether HK was the direct cause of hospital admissions and increased HRU. However, since HK is at least partly contributing to the substantial adverse health outcomes observed, timely detection and management of HK among high-risk populations and avoidance of subsequent events may translate not only to clinical benefits for the patients but may also alleviate the economic burden for healthcare providers and payers. Additional research on the long-term costs, particularly for patients with recurrent events of HK, will be useful to inform clinical decision making.

Declarations

Ethics approval and consent to participate: The ethics approval to utilize patient records from the data sources was granted by an institutional review board in Aarhus University Hospital.

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

KK, PH, EP are employees of AstraZeneca. RWT, SKN, HTS have reported no personal conflicts of interest relevant to this article. The Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, including the present study.

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Authors' contributions: Conception and design: EP, KK, RWT, SKN. Analysis and interpretation of data: SKN, KK, RWT, EP, PH, HTS. Drafting the article: KK, EP, RWT, PH. Revising the article: KK, RWT, PH, EP, HTS, SKN. Providing intellectual content of critical importance to the work described: all authors. Final approval of the version to be published: all authors.

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List of abbreviations

CKD	Chronic Kidney Disease
DAGS	Danish Outpatient Grouping System
DNPR	Danish National Patient Registry
DRG	Diagnosis Related Groups
GP	General Practitioner
HF	Heart Failure
HK	Hyperkalemia
HRU	Healthcare Resource Utilization
ICU	Intensive Care Unit
NHISR	National Health Insurance Service Registry
RAASi	Renin-Angiotensin-Aldosterone System Inhibitors

453 Table 1. Baseline characteristics of patients with hyperkalemia (> 5.0 mmol/L)

	Patients with hyperkalemia		
	Chronic kidney disease	**Heart failure**	**Diabetes**
Total	17,747 (100%)	5,141 (100%)	4,183 (100%)
Female	8,576 (48.3%)	2,311 (45.0%)	1,635 (39.1%)
Age (years)			
Median age (range)	76 (66.4-83.2)	79 (70.4-85.1)	69 (60.0-78.4)
<65	3,923 (22.1%)	781 (15.2%)	1,589 (38.0%)
65-74	4,461 (25.1%)	1,149 (22.3%)	1,158 (27.7%)
75-84	6,059 (34.1%)	1,919 (37.3%)	1,035 (24.7%)
85+	3,304 (18.6%)	1,292 (25.1%)	401 (9.6%)
eGFR level[1]			
eGFR ≥60	102 (0.6%)	559 (10.9%)	1,335 (31.9%)
eGFR 45-59	5,072 (28.6%)	878 (17.1%)	908 (21.7%)
eGFR 30-44	5,711 (32.2%)	1,459 (28.4%)	906 (21.7%)
eGFR 15-29	4,665 (26.3%)	1,529 (29.7%)	712 (17.0%)
eGFR <15	1,968 (11.1%)	607 (11.8%)	283 (6.8%)
Dialysis	229 (1.3%)	109 (2.1%)	38 (0.9%)
Qualifying event of hyperkalemia			
5.0-5.4	13,788 (77.7%)	3,845 (74.8%)	3,440 (82.2%)
5.5-5.9	2,612 (14.7%)	836 (16.3%)	525 (12.6%)
6.0-6.4	730 (4.1%)	259 (5.0%)	122 (2.9%)
6.5-6.9	331 (1.9%)	107 (2.1%)	54 (1.3%)
≥7.0	286 (1.6%)	94 (1.8%)	42 (1.0%)
Main risk factors			
Diabetes	4,779 (26.9%)	1,453 (28.3%)	4,183 (100%)
CKD	17,747 (100%)	3,478 (67.7%)	2,094 (50.1%)
Heart failure	3,499 (19.7%)	5,141 (100%)	735 (17.6%)
Hypertension	13,080 (73.7%)	4,422 (86.0%)	3,042 (72.7%)
Other comorbidities			
MI[2]	2,756 (15.5%)	1,533 (29.8%)	637 (15.2%)

HF	3,183 (17.9%)	0 (0.0%)	683 (16.3%)
PVD[3]	2,294 (12.9%)	857 (16.7%)	466 (11.1%)
CVD[4]	3,257 (18.4%)	1,075 (20.9%)	630 (15.1%)
Any malignant disease	4,086 (23.0%)	928 (18.1%)	727 (17.4%)
Afib or flutter	3,867 (21.8%)	2,151 (41.8%)	828 (19.8%)
VHD[5]	1,698 (9.6%)	1,007 (19.6%)	284 (6.8%)
Charlson comorbidity index			
0	4,180 (23.6%)	991 (19.3%)	1,454 (34.8%)
1	3,864 (21.8%)	1,159 (22.5%)	928 (22.2%)
2	3,962 (22.3%)	1,053 (20.5%)	738 (17.6%)
≥3	5,741 (32.3%)	1,938 (37.7%)	1,063 (25.4%)
Medications			
ACEis	7,682 (43.3%)	2,802 (54.5%)	2,025 (48.4%)
ARBs	3,762 (21.2%)	977 (19.0%)	954 (22.8%)
Spironolactone	4,017 (22.6%)	1,934 (37.6%)	891 (21.3%)
Potassium supplements	6,010 (33.9%)	3,010 (58.5%)	1,214 (29.0%)

454 [1]mL/min/1.73m^2; [2]Myocardial infarction; [3]Peripheral vascular disease; [4]Cerebrovascular disease; [5]Valvular heart disease

Table 2. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€) (95% CI)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=17,747**					**N=17,608**			
Acute hospitalizations[1]	3,666	(0.78)	8,200	(1.21)	4,535	1,778	(0.41)	2,194	(0.46)	416	4,118 (3,816;4,421)
Dialysis	27	(0.00)	124	(0.01)	97	17	(0.00)	31	(0.00)	14	83 (50;116)
Ventilator	504	(0.02)	2,607	(0.07)	2,103	243	(0.01)	380	(0.01)	136	1,966 (1,747;2,185)
ICU	675	(0.04)	3,108	(0.13)	2,433	314	(0.02)	467	(0.02)	153	2,281 (2,053;2,508)
Non-acute hospitalizations	1,653	(0.30)	2,757	(0.34)	1,104	1,087	(0.18)	1,091	(0.18)	3	1,101 (922;1,279)
Outpatient visits	1,593	(4.42)	1,597	(5.06)	4	1,077	(3.10)	1,113	(3.22)	37	-32 (-124;60)
GP consultations	85	(4.42)	80	(4.17)	-5	79	(4.11)	77	(4.03)	-2	-3 (-5;-2)
GP contacts	174	(14.21)	183	(14.67)	9	130	(11.33)	137	(11.65)	8	1 (-3;5)
Prescriptions	583	(22.91)	455	(18.57)	-128	554	(21.08)	533	(20.78)	-21	-108 (-122;-93)
Overall cost	7,754	-	13,272	-	5,518	4,705	-	5,146	-	441	5,076 (4,690;5,463)
Heart failure											
Number of patients			**N=5,141**					**N=5,141**			
Acute hospitalizations	5,799	(1.30)	9,655	(1.53)	3,856	4,934	(1.12)	4,156	(0.93)	-778	4,634 (4,028;5,240)

Dialysis	85	(0.01)	152	(0.02)	67	36	(0.01)	31	(0.00)	-5	72 (1;142)
Ventilator	636	(0.02)	2,905	(0.09)	2,270	606	(0.02)	419	(0.01)	-187	2,457 (2,040;2,873)
ICU	928	(0.06)	3,462	(0.15)	2,534	830	(0.05)	627	(0.04)	-203	2,737 (2,311;3,163)
Non-acute hospitalizations	1,759	(0.29)	3,178	(0.33)	1,419	1,820	(0.28)	1,674	(0.24)	-146	1,565 (1,172;1,959)
Outpatient visits	1,463	(4.84)	1,535	(5.62)	73	1,130	(4.03)	1,226	(4.63)	96	-24 (-160;112)
GP consultations	97	(5.04)	85	(4.40)	-13	98	(5.07)	92	(4.81)	-5	-7 (-11;-4)
GP contacts	241	(18.17)	223	(16.77)	-18	203	(16.06)	199	(15.76)	-4	-14 (-24;-4)
Prescriptions	647	(27.68)	470	(20.89)	-176	622	(25.89)	583	(25.59)	-40	-136 (-166;-107)
Overall cost	10,006	-	15,147	-	5,141	8,807	-	7,930	-	-877	6,018 (5,234;6,802)
Diabetes											
Number of patients			**N=4,183**					**N=4,151**			
Acute hospitalizations	3,056	(0.66)	6,810	(0.98)	3,755	1,195	(0.28)	1,076	(0.25)	-119	3,874 (3,301;4,447)
Dialysis	33	(0.00)	72	(0.01)	40	9	(0.00)	0	(0.00)	-9	49 (-3;101)
Ventilator	260	(0.01)	2,197	(0.06)	1,936	146	(0.00)	119	(0.00)	-27	1,963 (1,571;2,356)
ICU	440	(0.03)	2,626	(0.11)	2,185	166	(0.01)	163	(0.01)	-3	2,189 (1,778;2,599)
Non-acute hospitalizations	1,311	(0.23)	2,198	(0.29)	888	661	(0.12)	602	(0.12)	-60	947 (651;1,244)
Outpatient visits	1,369	(4.01)	1,455	(4.74)	87	955	(2.67)	931	(2.63)	-24	111 (-50;271)
GP consultations	97	(4.99)	92	(4.79)	-4	86	(4.45)	80	(4.17)	-5	1 (-2;5)
GP contacts	189	(15.99)	195	(16.24)	6	143	(12.51)	138	(11.91)	-5	10 (2;19)
Prescriptions	548	(22.48)	467	(19.48)	-81	458	(18.08)	459	(18.93)	1	-82 (-109;-54)
Overall cost	6,569	-	11,218	-	4,650	3,497	-	3,285	-	-212	4,862 (4,156;5,568)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Figure titles and legends

Figure 1. Overall study design and matching factors

Figure 2. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with chronic kidney disease and split between diagnosis setting of hyperkalemia

Figure 3. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with heart failure and split between diagnosis setting of hyperkalemia

Figure 4. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with diabetes and split between diagnosis setting of hyperkalemia

Figure 5. Mean cost of healthcare utilization 6 months before and 6 months after hyperkalemia, in chronic kidney disease, heart failure, and diabetes patients, HK patients vs. matched non-HK comparisons

Supplementary Files

File Name: Additional Files.

Title of Data: Supplementary Tables

Description of Data:

Supplementary Table S1. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.0 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 5.0 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients vs their matched comparisons are shown.

Supplementary Table S2. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.5 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 5.5 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients vs their matched comparisons are shown.

Supplementary Table S3. Baseline characteristics of patients with hyperkalemia (serum potassium above 6.0 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 6.0 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients vs their matched comparisons are shown.

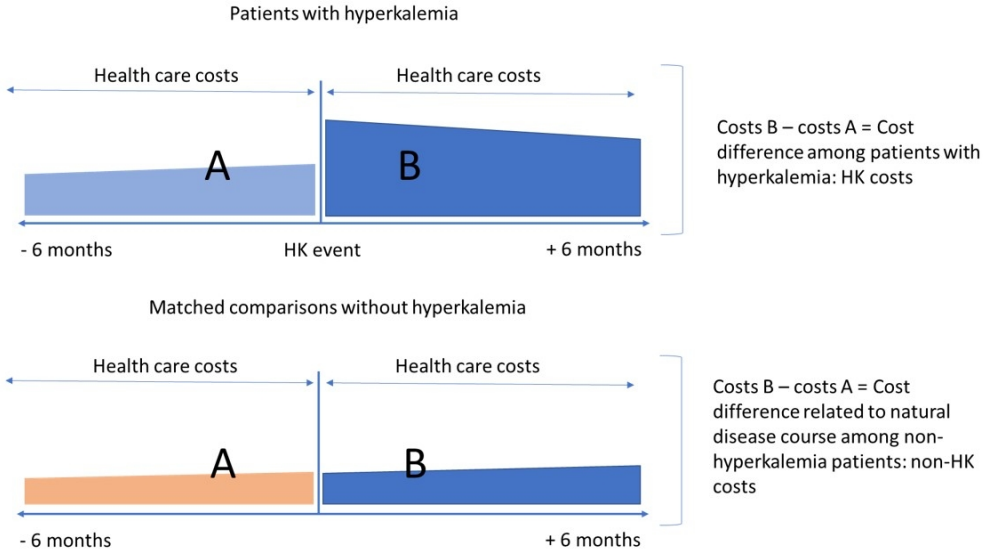
Supplementary Table S4: Primary (first-listed) discharge diagnoses during acute hospital admissions during which HK occurred.

Supplementary Table S5. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.5 mmol/L.

Supplementary Table S6. Healthcare resource use and mean costs (€) associated with elevated potassium level >6.0 mmol/L.

Supplementary Table S7. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L, weighted by time-at-risk.

Supplementary Table S8. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L 1 month before and after HK.



The costs associated with hyperkalemia = HK costs - non-HK costs

Matching criteria for hyperkalemia patients and comparison patients without hyperkalemia

Patient cohort	Matching criteria
Chronic kidney disease	Age, gender, Charlson Comorbidity Index score, chronic kidney disease duration, calendar year of CKD diagnosis, CKD stage based on eGFR level, presence of heart failure, diabetes or hypertension, hyperkalemia-associated drugs[1]
Heart failure	Age, gender, Charlson Comorbidity Index score, heart failure duration, calendar year of heart failure diagnosis, presence of chronic kidney disease, diabetes or hypertension, eGFR level, hyperkalemia-associated drugs[1]
Diabetes	Age, gender, Charlson Comorbidity Index score, diabetes duration, calendar year of diabetes diagnosis, micro- or macrovascular complications, HbA1c level

[1]ACEis/ARBs, spironolactone or eplerenone, or potassium supplements at the time of hyperkalemia

Figure 1. Overall study design and matching factors

190x208mm (150 x 150 DPI)

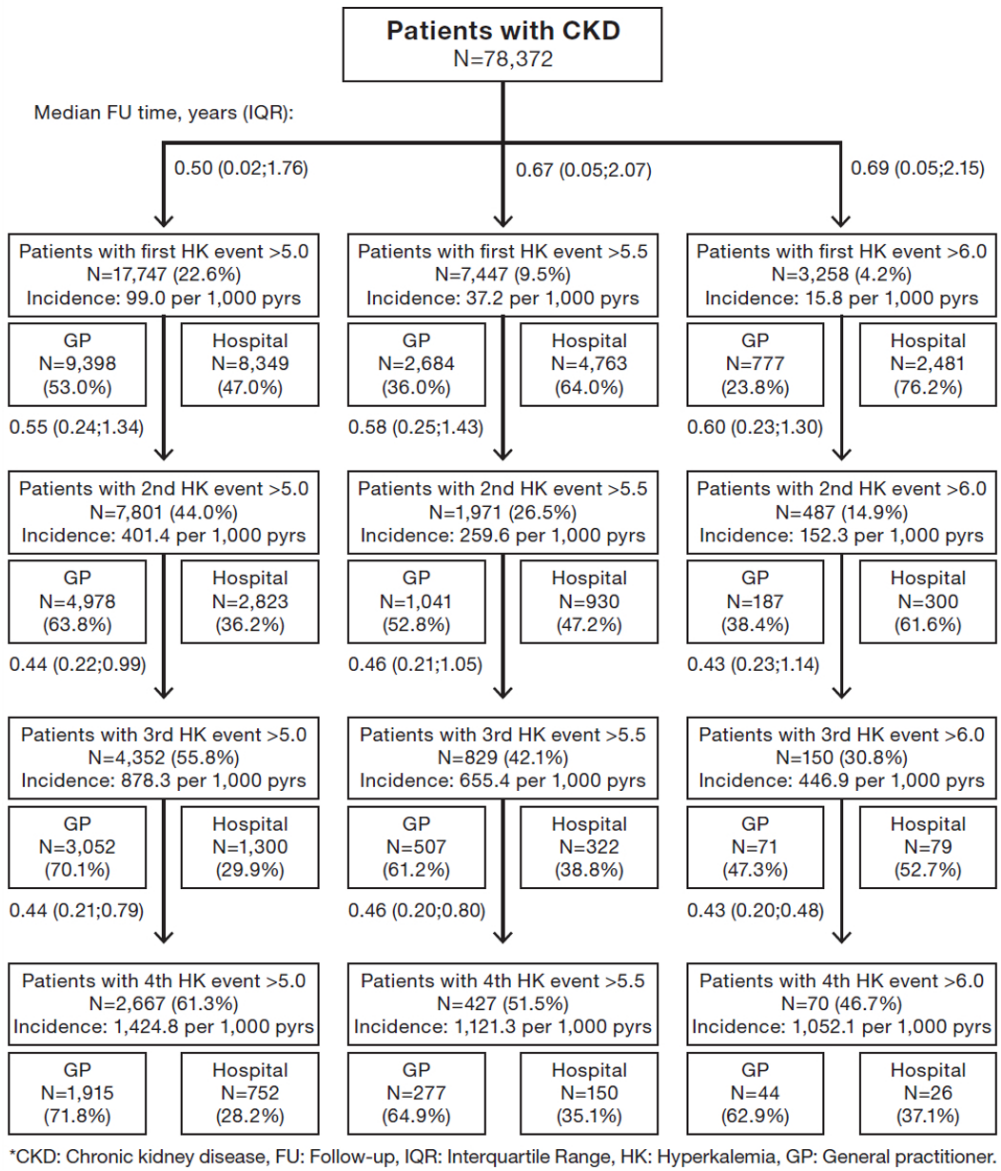


Figure 2. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with chronic kidney disease and split between diagnosis setting of hyperkalemia

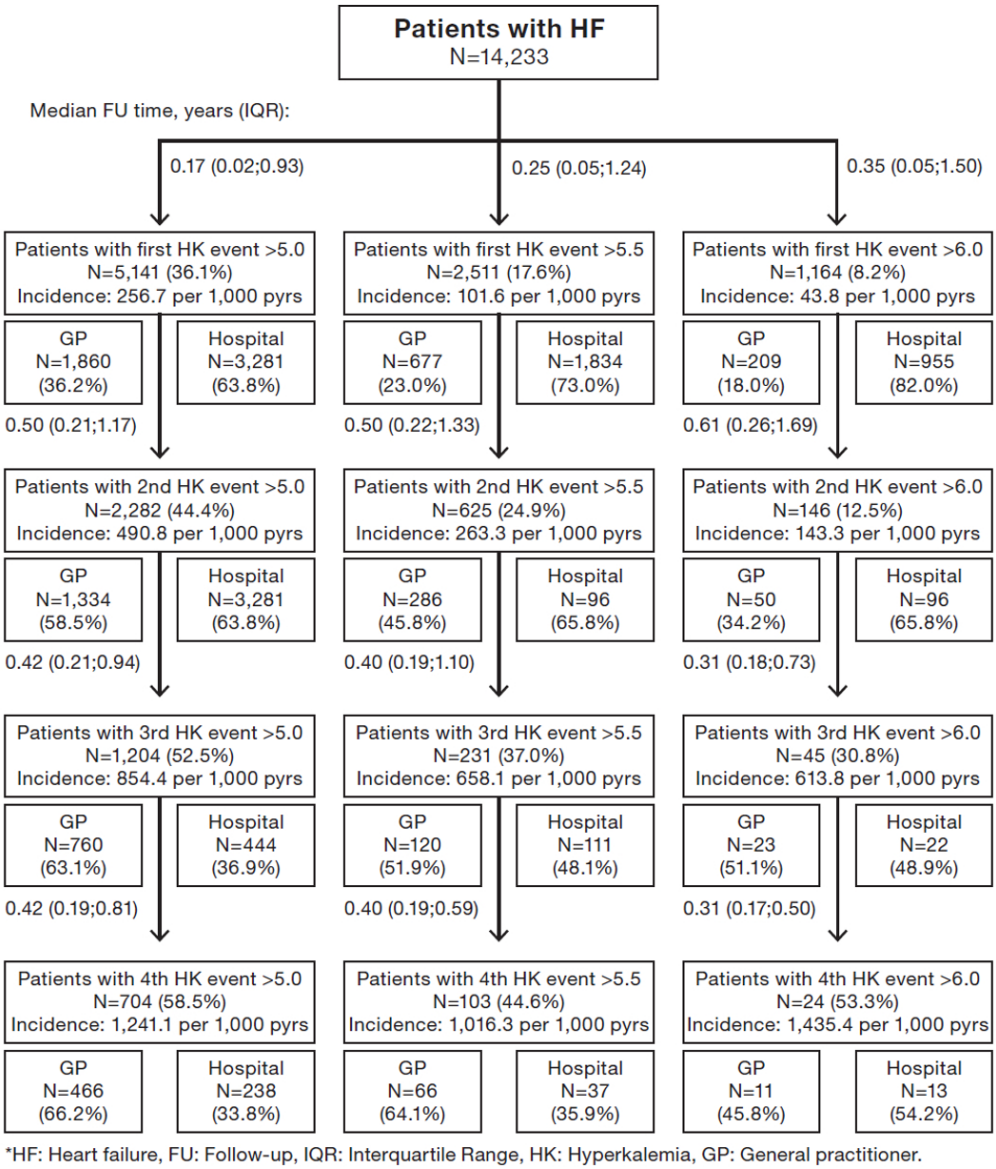


Figure 3. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with heart failure and split between diagnosis setting of hyperkalemia

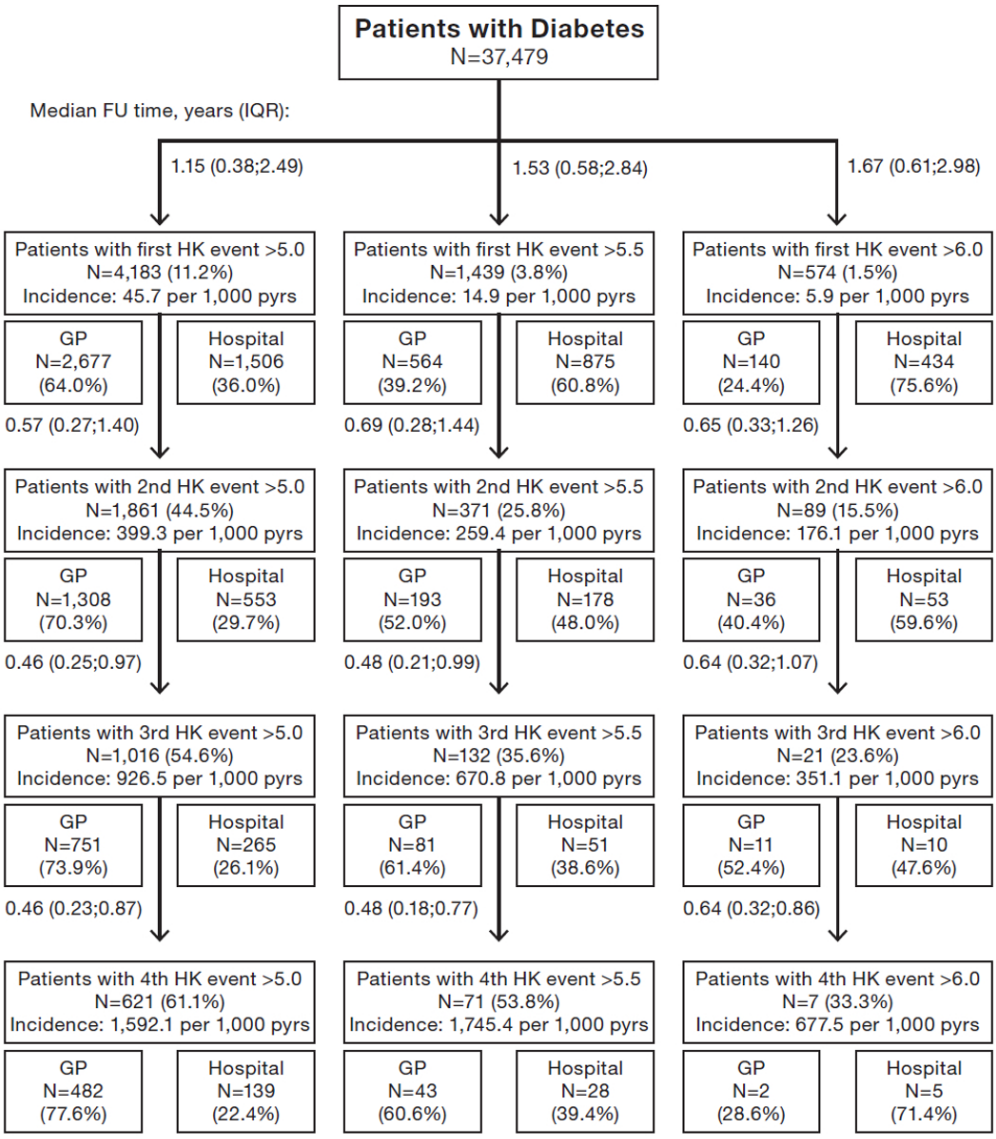


Figure 4. Risks of developing first and subsequent events with elevated potassium level >5.0, >5.5, and >6.0 mmol/L in patients with diabetes and split between diagnosis setting of hyperkalemia

Figure 5. Mean cost of healthcare utilization 6 months before and 6 months after hyperkalemia, in chronic kidney disease, heart failure, and diabetes patients, HK patients vs. matched non-HK comparisons

191x168mm (150 x 150 DPI)

Supplementary Table S1. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.0 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 5.0 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients vs their matched comparisons are shown.

	Patients with hyperkalemia			Matched comparisons without hyperkalemia					
	CKD[1]	HF[2]	Diabetes	CKD	PR[3]	HF	PR[3]	Diabetes	PR[3]
Total	17,747 (100%)	5,141 (100%)	4,183 (100%)	17,608 (100%)	1.00 (1.00-1.00)	5,141 (100%)	1.00 (1.00-1.00)	4,151 (100%)	1.00 (1.00-1.00)
Female	8,576 (48.3%)	2,311 (45.0%)	1,635 (39.1%)	8,521 (48.4%)	1.00 (0.98-1.02)	2,311 (45.0%)	1.00 (0.96-1.04)	1,631 (39.3%)	0.99 (0.94-1.05)
Median age (range)	76 (66.4-83.2)	79 (70.4-85.1)	69 (60.0-78.4)	76 (66.6-83.2)	. (.-.)	79 (70.4-85.0)	. (.-.)	69 (60.1-78.3)	. (.-.)
<65	3,923 (22.1%)	781 (15.2%)	1,589 (38.0%)	3,847 (21.8%)	1.01 (0.97-1.05)	781 (15.2%)	1.00 (0.91-1.10)	1,571 (37.8%)	1.00 (0.95-1.06)
65-74	4,461 (25.1%)	1,149 (22.3%)	1,158 (27.7%)	4,447 (25.3%)	1.00 (0.96-1.03)	1,149 (22.3%)	1.00 (0.93-1.07)	1,156 (27.8%)	0.99 (0.93-1.07)
75-84	6,059 (34.1%)	1,919 (37.3%)	1,035 (24.7%)	6,022 (34.2%)	1.00 (0.97-1.03)	1,919 (37.3%)	1.00 (0.95-1.05)	1,041 (25.1%)	0.99 (0.92-1.06)
85+	3,304 (18.6%)	1,292 (25.1%)	401 (9.6%)	3,292 (18.7%)	1.00 (0.95-1.04)	1,292 (25.1%)	1.00 (0.94-1.07)	383 (9.2%)	1.04 (0.91-1.19)
eGFR level[4]									
eGFR ≥60	102 (0.6%)	559 (10.9%)	1,335 (31.9%)	54 (0.3%)	0.66 (0.52-0.85)	99 (1.9%)	0.64 (0.58-0.71)	160 (3.9%)	0.68 (0.64-0.72)
eGFR 45-59	5,072 (28.6%)	878 (17.1%)	908 (21.7%)	153 (0.9%)	0.73 (0.71-0.76)	870 (16.9%)	0.71 (0.66-0.77)	1,955 (47.1%)	0.87 (0.80-0.94)
eGFR 30-44	5,711 (32.2%)	1,459 (28.4%)	906 (21.7%)	6,850 (38.9%)	0.96 (0.93-0.99)	1,230 (23.9%)	0.95 (0.89-1.01)	1,041 (25.1%)	1.37 (1.25-1.50)
eGFR 15-29	4,665 (26.3%)	1,529 (29.7%)	712 (17.0%)	5,896 (33.5%)	1.28 (1.23-1.33)	1,535 (29.9%)	1.36 (1.27-1.46)	658 (15.9%)	2.73 (2.38-3.12)
eGFR <15	1,968 (11.1%)	607 (11.8%)	283 (6.8%)	3,613 (20.5%)	2.15 (1.99-2.31)	1,123 (21.8%)	2.56 (2.22-2.96)	259 (6.2%)	4.76 (3.61-6.28)
Dialysis	229 (1.3%)	109 (2.1%)	38 (0.9%)	910 (5.2%)	1.72 (1.39-2.13)	237 (4.6%)	2.32 (1.65-3.26)	59 (1.4%)	1.98 (1.15-3.44)
Qualifying event of hyperkalemia									
5.5-5.9	13,788 (77.7%)	3,845 (74.8%)	3,440 (82.2%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.0-6.4	2,612 (14.7%)	836 (16.3%)	525 (12.6%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.5-6.9	730 (4.1%)	259 (5.0%)	122 (2.9%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
≥7.0	331 (1.9%)	107 (2.1%)	54 (1.3%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
Main risk factors									
Diabetes	4,779 (26.9%)	1,453 (28.3%)	4,183 (100%)	4,406 (25.0%)	1.08 (1.04-1.11)	1,186 (23.1%)	1.23 (1.15-1.31)	4,151 (100%)	1.00 (1.00-1.00)
CKD	17,747 (100%)	3,478 (67.7%)	2,094 (50.1%)	17,608 (100%)	1.00 (1.00-1.00)	3,081 (59.9%)	1.13 (1.10-1.16)	1,562 (37.6%)	1.33 (1.27-1.40)
Heart failure	3,499 (19.7%)	5,141 (100%)	735 (17.6%)	3,056 (17.4%)	1.14 (1.09-1.19)	5,141 (100%)	1.00 (1.00-1.00)	504 (12.1%)	1.45 (1.30-1.61)
Hypertension	13,080 (73.7%)	4,422 (86.0%)	3,042 (72.7%)	14,933 (84.8%)	0.87 (0.86-0.88)	4,433 (86.2%)	1.00 (0.98-1.01)	2,852 (68.7%)	1.06 (1.03-1.09)
Other comorbidities									
MI[5]	2,756 (15.5%)	1,533 (29.8%)	637 (15.2%)	2,978 (16.9%)	0.92 (0.88-0.96)	1,598 (31.1%)	0.96 (0.90-1.02)	655 (15.8%)	0.97 (0.87-1.07)
HF	3,183 (17.9%)	0 (0.0%)	683 (16.3%)	2,955 (16.8%)	1.07 (1.02-1.12)	0 (0.0%)	. (.-.)	494 (11.9%)	1.37 (1.23-1.53)
PVD[6]	2,294 (12.9%)	857 (16.7%)	466 (11.1%)	2,232 (12.7%)	1.02 (0.97-1.08)	766 (14.9%)	1.12 (1.02-1.22)	410 (9.9%)	1.13 (0.99-1.28)
CVD[7]	3,257 (18.4%)	1,075 (20.9%)	630 (15.1%)	3,745 (21.3%)	0.86 (0.83-0.90)	1,128 (21.9%)	0.95 (0.88-1.03)	761 (18.3%)	0.82 (0.75-0.90)
Any malignant disease	1,920 (25.8%)	463 (18.4%)	312 (21.7%)	3,589 (20.4%)	1.01 (0.97-1.05)	848 (16.5%)	0.98 (0.90-1.07)	695 (16.7%)	0.96 (0.87-1.06)
Afib or flutter	3,660 (20.6%)	833 (16.2%)	674 (16.1%)	3,360 (19.1%)	1.14 (1.10-1.19)	2,056 (40.0%)	1.05 (1.00-1.10)	609 (14.7%)	1.35 (1.23-1.48)
VHD[8]	1,698 (9.6%)	1,007 (19.6%)	284 (6.8%)	1,432 (8.1%)	1.18 (1.10-1.26)	874 (17.0%)	1.15 (1.06-1.25)	181 (4.4%)	1.56 (1.30-1.87)
Charlson comorbidity index									
0	4,180 (23.6%)	991 (19.3%)	1,454 (34.8%)	4,455 (25.3%)	0.93 (0.90-0.97)	1,110 (21.6%)	0.89 (0.83-0.96)	1,505 (36.3%)	0.96 (0.90-1.02)
1	3,864 (21.8%)	1,159 (22.5%)	928 (22.2%)	3,868 (22.0%)	0.99 (0.95-1.03)	1,284 (25.0%)	0.90 (0.84-0.97)	948 (22.8%)	0.97 (0.90-1.05)
2	3,962 (22.3%)	1,053 (20.5%)	738 (17.6%)	3,839 (21.8%)	1.02 (0.98-1.06)	1,000 (19.5%)	1.05 (0.97-1.14)	702 (16.9%)	1.04 (0.95-1.15)
≥3	5,741 (32.3%)	1,938 (37.7%)	1,063 (25.4%)	5,446 (30.9%)	1.05 (1.01-1.08)	1,747 (34.0%)	1.11 (1.05-1.17)	996 (24.0%)	1.06 (0.98-1.14)
Medications									

ACEis	7,682 (43.3%)	2,802 (54.5%)	2,025 (48.4%)	7,710 (43.8%)	0.99 (0.97-1.01)	2,545 (49.5%)	1.10 (1.06-1.14)	1,649 (39.7%)	1.22 (1.16-1.28)
ARBs	3,762 (21.2%)	977 (19.0%)	954 (22.8%)	4,829 (27.4%)	0.77 (0.74-0.80)	951 (18.5%)	1.03 (0.95-1.11)	923 (22.2%)	1.03 (0.95-1.11)
Spironolactone	4,017 (22.6%)	1,934 (37.6%)	891 (21.3%)	2,799 (15.9%)	1.42 (1.36-1.49)	1,513 (29.4%)	1.28 (1.21-1.35)	438 (10.6%)	2.02 (1.82-2.24)
Potassium supplements	6,010 (33.9%)	3,010 (58.5%)	1,214 (29.0%)	5,997 (34.1%)	0.99 (0.97-1.02)	3,031 (59.0%)	0.99 (0.96-1.03)	969 (23.3%)	1.24 (1.16-1.34)

[1]Chronic kidney disease; [2]Heart failure; [3]Prevalence ratio of each characteristic in patients with hyperkalemia versus matched comparisons without hyperkalemia; [4]mL/min/1.73m^2; [5]Myocardial infarction; [6]Peripheral vascular disease; [7]Cerebrovascular disease; [8]Valvular heart disease

Supplementary Table S2. Baseline characteristics of patients with hyperkalemia (serum potassium above 5.5 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 5.5 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients (serum potassium above 5.5 mmol/L) vs their matched comparisons are shown.

	Patients with hyperkalemia			Matched comparisons without hyperkalemia					
	CKD[1]	HF[2]	Diabetes	CKD	PR[3]	HF	PR[3]	Diabetes	PR[3]
Total	7,447 (100%)	2,511 (100%)	1,439 (100%)	7,391 (100%)	1.00 (1.00-1.00)	2,511 (100%)	1.00 (1.00-1.00)	1,436 (100%)	1.00 (1.00-1.00)
Female	3,359 (45.1%)	1,142 (45.5%)	580 (40.3%)	3,361 (45.5%)	0.99 (0.96-1.03)	1,142 (45.5%)	1.00 (0.94-1.06)	579 (40.3%)	1.00 (0.91-1.09)
Median age (range)	7,447 (100%)	2,511 (100%)	1,439 (100%)	76 (65.7-83.0)	. (.-.)	79 (70.5-85.1)	. (.-.)	72 (61.8-79.8)	. (.-.)
<65	76 (65.5-82.9)	79 (70.5-85.1)	71 (61.4-79.7)	1,728 (23.4%)	1.02 (0.97-1.08)	373 (14.9%)	1.00 (0.88-1.14)	476 (33.1%)	1.00 (0.91-1.11)
65-74	1,781 (23.9%)	373 (14.9%)	479 (33.3%)	1,794 (24.3%)	1.00 (0.94-1.06)	548 (21.8%)	1.00 (0.90-1.11)	401 (27.9%)	0.99 (0.88-1.11)
75-84	1,802 (24.2%)	548 (21.8%)	398 (27.7%)	2,498 (33.8%)	0.99 (0.95-1.04)	955 (38.0%)	1.00 (0.93-1.07)	393 (27.4%)	0.99 (0.88-1.12)
85+	2,499 (33.6%)	955 (38.0%)	391 (27.2%)	1,371 (18.5%)	0.99 (0.92-1.06)	635 (25.3%)	1.00 (0.91-1.10)	166 (11.6%)	1.03 (0.84-1.26)
eGFR level[4]									
eGFR ≥60	28 (0.4%)	144 (5.7%)	240 (16.7%)	85 (1.2%)	0.33 (0.21-0.50)	310 (12.3%)	0.46 (0.38-0.56)	536 (37.3%)	0.45 (0.39-0.51)
eGFR 45-59	1,023 (13.7%)	250 (10.0%)	216 (15.0%)	1,897 (25.7%)	0.54 (0.50-0.57)	482 (19.2%)	0.52 (0.45-0.60)	372 (25.9%)	0.58 (0.50-0.67)
eGFR 30-44	1,935 (26.0%)	568 (22.6%)	329 (22.9%)	2,368 (32.0%)	0.81 (0.77-0.85)	706 (28.1%)	0.80 (0.73-0.89)	286 (19.9%)	1.15 (1.00-1.32)
eGFR 15-29	2,636 (35.4%)	940 (37.4%)	393 (27.3%)	2,156 (29.2%)	1.21 (1.16-1.27)	746 (29.7%)	1.26 (1.16-1.36)	145 (10.1%)	2.70 (2.27-3.22)
eGFR <15	1,613 (21.7%)	518 (20.6%)	229 (15.9%)	756 (10.2%)	2.12 (1.95-2.29)	194 (7.7%)	2.67 (2.29-3.12)	44 (3.1%)	5.19 (3.79-7.11)
Dialysis	212 (2.8%)	91 (3.6%)	31 (2.2%)	106 (1.4%)	1.98 (1.58-2.50)	40 (1.6%)	2.28 (1.58-3.29)	13 (0.9%)	2.38 (1.25-4.53)
Qualifying event of hyperkalemia									
5.5-5.9	5,228 (70.2%)	1,719 (68.5%)	1,056 (73.4%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.0-6.4	1,279 (17.2%)	460 (18.3%)	223 (15.5%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.5-6.9	511 (6.9%)	181 (7.2%)	89 (6.2%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
≥7.0	429 (5.8%)	151 (6.0%)	71 (4.9%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
Main risk factors									
Diabetes	2,316 (31.1%)	809 (32.2%)	1,439 (100%)	1,990 (26.9%)	1.16 (1.10-1.21)	679 (27.0%)	1.19 (1.09-1.30)	1,436 (100%)	1.00 (1.00-1.00)
CKD	7,447 (100%)	1,887 (75.1%)	907 (63.0%)	7,391 (100%)	1.00 (1.00-1.00)	1,686 (67.1%)	1.12 (1.08-1.16)	683 (47.6%)	1.33 (1.24-1.42)
Heart failure	1,773 (23.8%)	2,511 (100%)	351 (24.4%)	1,579 (21.4%)	1.11 (1.05-1.18)	2,511 (100%)	1.00 (1.00-1.00)	238 (16.6%)	1.47 (1.27-1.71)
Hypertension	5,754 (77.3%)	2,199 (87.6%)	1,141 (79.3%)	6,334 (85.7%)	0.90 (0.89-0.92)	2,215 (88.2%)	0.99 (0.97-1.01)	1,074 (74.8%)	1.06 (1.02-1.10)
Other comorbidities									
MI[5]	1,255 (16.9%)	790 (31.5%)	232 (16.1%)	1,482 (20.1%)	0.84 (0.79-0.90)	827 (32.9%)	0.96 (0.88-1.04)	289 (20.1%)	0.80 (0.69-0.94)
HF	1,617 (21.7%)	0 (0.0%)	328 (22.8%)	1,551 (21.0%)	1.03 (0.97-1.10)	0 (0.0%)	. (.-.)	234 (16.3%)	1.40 (1.20-1.63)
PVD[6]	1,111 (14.9%)	472 (18.8%)	210 (14.6%)	1,054 (14.3%)	1.05 (0.97-1.13)	411 (16.4%)	1.15 (1.02-1.29)	199 (13.9%)	1.05 (0.88-1.26)
CVD[7]	1,414 (19.0%)	542 (21.6%)	264 (18.3%)	1,646 (22.3%)	0.85 (0.80-0.91)	521 (20.7%)	1.04 (0.93-1.16)	309 (21.5%)	0.85 (0.74-0.99)
Any malignant disease	1,690 (22.7%)	422 (16.8%)	284 (19.7%)	1,682 (22.8%)	1.00 (0.94-1.06)	422 (16.8%)	1.00 (0.88-1.13)	298 (20.8%)	0.95 (0.82-1.10)
Afib or flutter	1,800 (24.2%)	1,048 (41.7%)	351 (24.4%)	1,574 (21.3%)	1.13 (1.07-1.20)	1,046 (41.7%)	1.00 (0.94-1.07)	250 (17.4%)	1.40 (1.21-1.62)
VHD[8]	820 (11.0%)	529 (21.1%)	124 (8.6%)	668 (9.0%)	1.22 (1.11-1.34)	445 (17.7%)	1.19 (1.06-1.33)	106 (7.4%)	1.17 (0.91-1.50)
Charlson comorbidity index									
0	1,328 (17.8%)	381 (15.2%)	334 (23.2%)	1,474 (19.9%)	0.89 (0.84-0.96)	464 (18.5%)	0.82 (0.73-0.93)	362 (25.2%)	0.92 (0.81-1.05)
1	1,451 (19.5%)	511 (20.4%)	292 (20.3%)	1,486 (20.1%)	0.97 (0.91-1.03)	578 (23.0%)	0.88 (0.80-0.98)	312 (21.7%)	0.93 (0.81-1.08)
2	1,750 (23.5%)	486 (19.4%)	292 (20.3%)	1,661 (22.5%)	1.05 (0.99-1.11)	468 (18.6%)	1.04 (0.93-1.16)	285 (19.8%)	1.02 (0.88-1.18)
≥3	2,918 (39.2%)	1,133 (45.1%)	521 (36.2%)	2,770 (37.5%)	1.05 (1.00-1.09)	1,001 (39.9%)	1.13 (1.06-1.21)	477 (33.2%)	1.09 (0.99-1.21)
Medications									

ACEis	3,402 (45.7%)	1,350 (53.8%)	694 (48.2%)	3,312 (44.8%)	1.02 (0.98-1.06)	1,305 (52.0%)	1.03 (0.98-1.09)	626 (43.6%)	1.11 (1.02-1.20)
ARBs	1,627 (21.8%)	503 (20.0%)	337 (23.4%)	1,987 (26.9%)	0.81 (0.77-0.86)	470 (18.7%)	1.07 (0.96-1.20)	333 (23.2%)	1.01 (0.88-1.15)
Spironolactone	2,124 (28.5%)	1,057 (42.1%)	442 (30.7%)	1,395 (18.9%)	1.51 (1.42-1.60)	861 (34.3%)	1.23 (1.14-1.32)	192 (13.4%)	2.30 (1.97-2.68)
Potassium supplements	2,837 (38.1%)	1,487 (59.2%)	544 (37.8%)	2,719 (36.8%)	1.04 (0.99-1.08)	1,454 (57.9%)	1.02 (0.98-1.07)	380 (26.5%)	1.43 (1.28-1.59)

[1]Chronic kidney disease; [2]Heart failure; [3]Prevalence ratio of each characteristic in patients with hyperkalemia versus matched comparisons without hyperkalemia; [4]mL/min/1.73m^2; [5]Myocardial infarction; [6]Peripheral vascular disease; [7]Cerebrovascular disease; [8]Valvular heart disease

Supplementary Table S3. Baseline characteristics of patients with hyperkalemia (serum potassium above 6.0 mmol/L), and matched comparisons without hyperkalemia (no serum potassium above 6.0 mmol/L). Prevalence ratios (with 95% CIs) of characteristics in hyperkalemia patients (serum potassium above 6.0 mmol/L) vs their matched comparisons are shown.

	Patients with hyperkalemia			Matched comparisons without hyperkalemia					
	CKD[1]	HF[2]	Diabetes	CKD	PR[3]	HF	PR[3]	Diabetes	PR[3]
Total	3,258 (100%)	1,164 (100%)	574 (100%)	3,250 (100%)	1.00 (1.00-1.00)	1,164 (100%)	1.00 (1.00-1.00)	585 (100%)	1.00 (1.00-1.00)
Female	1,435 (44.0%)	523 (44.9%)	213 (37.1%)	1,428 (43.9%)	1.00 (0.95-1.06)	523 (44.9%)	1.00 (0.91-1.09)	215 (36.8%)	1.01 (0.87-1.17)
Median age (range)	75 (64.7-82.4)	79 (69.8-84.8)	72 (62.1-80.4)	75 (65.1-82.6)	. (.-.)	79 (69.7-84.8)	. (.-.)	72 (62.3-80.4)	. (.-.)
<65	836 (25.7%)	185 (15.9%)	184 (32.1%)	803 (24.7%)	1.04 (0.96-1.13)	185 (15.9%)	1.00 (0.83-1.21)	187 (32.0%)	1.00 (0.85-1.19)
65-74	794 (24.4%)	265 (22.8%)	163 (28.4%)	798 (24.6%)	0.99 (0.91-1.08)	265 (22.8%)	1.00 (0.86-1.16)	167 (28.5%)	0.99 (0.83-1.19)
75-84	1,052 (32.3%)	431 (37.0%)	165 (28.7%)	1,064 (32.7%)	0.99 (0.92-1.06)	431 (37.0%)	1.00 (0.90-1.11)	169 (28.9%)	1.00 (0.83-1.19)
85+	576 (17.7%)	283 (24.3%)	62 (10.8%)	585 (18.0%)	0.98 (0.88-1.09)	283 (24.3%)	1.00 (0.87-1.15)	62 (10.6%)	1.02 (0.73-1.42)
eGFR level[4]									
eGFR ≥60	10 (0.3%)	39 (3.4%)	55 (9.6%)	48 (1.5%)	0.21 (0.11-0.41)	127 (10.9%)	0.31 (0.22-0.44)	211 (36.1%)	0.27 (0.20-0.35)
eGFR 45-59	246 (7.6%)	62 (5.3%)	56 (9.8%)	646 (19.9%)	0.38 (0.33-0.44)	162 (13.9%)	0.38 (0.29-0.51)	135 (23.1%)	0.42 (0.32-0.56)
eGFR 30-44	633 (19.4%)	188 (16.2%)	106 (18.5%)	972 (29.9%)	0.65 (0.60-0.71)	307 (26.4%)	0.61 (0.52-0.72)	126 (21.5%)	0.86 (0.68-1.08)
eGFR 15-29	1,166 (35.8%)	456 (39.2%)	178 (31.0%)	1,004 (30.9%)	1.16 (1.08-1.24)	388 (33.3%)	1.18 (1.05-1.31)	74 (12.6%)	2.45 (1.92-3.13)
eGFR <15	1,039 (31.9%)	355 (30.5%)	157 (27.4%)	484 (14.9%)	2.14 (1.94-2.36)	133 (11.4%)	2.67 (2.23-3.20)	18 (3.1%)	8.89 (5.53-14.28)
Dialysis	164 (5.0%)	64 (5.5%)	21 (3.7%)	79 (2.4%)	2.07 (1.59-2.70)	31 (2.7%)	2.06 (1.35-3.15)	6 (1.0%)	3.57 (1.45-8.77)
Qualifying event of hyperkalemia									
5.5-5.9									
6.0-6.4	2,002 (61.4%)	713 (61.3%)	358 (62.4%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
6.5-6.9	711 (21.8%)	258 (22.2%)	127 (22.1%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
≥7.0	545 (16.7%)	193 (16.6%)	89 (15.5%)	0 (0.0%)	(-)	0 (0.0%)	(-)	0 (0.0%)	(-)
Main risk factors									
Diabetes	1,060 (32.5%)	412 (35.4%)	574 (100%)	963 (29.6%)	1.10 (1.02-1.18)	327 (28.1%)	1.26 (1.12-1.42)	585 (100%)	1.00 (1.00-1.00)
CKD	3,258 (100%)	910 (78.2%)	389 (67.8%)	3,250 (100%)	1.00 (1.00-1.00)	835 (71.7%)	1.09 (1.04-1.14)	306 (52.3%)	1.30 (1.18-1.43)
Heart failure	845 (25.9%)	1,164 (100%)	166 (28.9%)	720 (22.2%)	1.17 (1.07-1.28)	1,164 (100%)	1.00 (1.00-1.00)	104 (17.8%)	1.63 (1.31-2.02)
Hypertension	2,530 (77.7%)	1,041 (89.4%)	478 (83.3%)	2,759 (84.9%)	0.91 (0.89-0.94)	1,056 (90.7%)	0.99 (0.96-1.01)	457 (78.1%)	1.07 (1.01-1.13)
Other comorbidities									
MI[5]	544 (16.7%)	358 (30.8%)	107 (18.6%)	622 (19.1%)	0.87 (0.79-0.97)	393 (33.8%)	0.91 (0.81-1.02)	132 (22.6%)	0.83 (0.66-1.04)
HF	780 (23.9%)	0 (0.0%)	153 (26.7%)	706 (21.7%)	1.10 (1.01-1.21)	0 (0.0%)	. (.-.)	102 (17.4%)	1.53 (1.22-1.91)
PVD[6]	501 (15.4%)	219 (18.8%)	81 (14.1%)	497 (15.3%)	1.01 (0.90-1.13)	206 (17.7%)	1.06 (0.90-1.26)	97 (16.6%)	0.85 (0.65-1.12)
CVD[7]	603 (18.5%)	244 (21.0%)	110 (19.2%)	750 (23.1%)	0.80 (0.73-0.88)	255 (21.9%)	0.96 (0.82-1.12)	138 (23.6%)	0.81 (0.65-1.01)
Any malignant disease	767 (23.5%)	200 (17.2%)	121 (21.1%)	746 (23.0%)	1.03 (0.94-1.12)	192 (16.5%)	1.04 (0.87-1.25)	147 (25.1%)	0.84 (0.68-1.04)
Afib or flutter	812 (24.9%)	488 (41.9%)	153 (26.7%)	711 (21.9%)	1.14 (1.04-1.24)	508 (43.6%)	0.96 (0.87-1.06)	102 (17.4%)	1.53 (1.22-1.91)
VHD[8]	389 (11.9%)	272 (23.4%)	55 (9.6%)	308 (9.5%)	1.26 (1.09-1.45)	201 (17.3%)	1.35 (1.15-1.59)	48 (8.2%)	1.17 (0.81-1.69)
Charlson comorbidity index									
0	516 (15.8%)	145 (12.5%)	99 (17.2%)	599 (18.4%)	0.86 (0.77-0.96)	197 (16.9%)	0.74 (0.60-0.90)	109 (18.6%)	0.93 (0.72-1.18)
1	598 (18.4%)	217 (18.6%)	107 (18.6%)	601 (18.5%)	0.99 (0.90-1.10)	254 (21.8%)	0.85 (0.73-1.00)	118 (20.2%)	0.92 (0.73-1.17)
2	759 (23.3%)	225 (19.3%)	122 (21.3%)	729 (22.4%)	1.04 (0.95-1.14)	211 (18.1%)	1.07 (0.90-1.26)	131 (22.4%)	0.95 (0.76-1.18)
≥3	1,385 (42.5%)	577 (49.6%)	246 (42.9%)	1,321 (40.6%)	1.05 (0.99-1.11)	502 (43.1%)	1.15 (1.05-1.25)	227 (38.8%)	1.10 (0.96-1.27)

Medications									
ACEis	1,516 (46.5%)	659 (56.6%)	304 (53.0%)	1,485 (45.7%)	1.02 (0.97-1.07)	599 (51.5%)	1.10 (1.02-1.19)	262 (44.8%)	1.18 (1.05-1.33)
ARBs	711 (21.8%)	231 (19.8%)	128 (22.3%)	843 (25.9%)	0.84 (0.77-0.92)	249 (21.4%)	0.93 (0.79-1.09)	158 (27.0%)	0.83 (0.67-1.01)
Spironolactone	1,024 (31.4%)	533 (45.8%)	203 (35.4%)	637 (19.6%)	1.60 (1.47-1.75)	429 (36.9%)	1.24 (1.13-1.37)	82 (14.0%)	2.52 (2.01-3.17)
Potassium supplements	1,319 (40.5%)	723 (62.1%)	230 (40.1%)	1,202 (37.0%)	1.09 (1.03-1.16)	664 (57.0%)	1.09 (1.02-1.16)	168 (28.7%)	1.40 (1.19-1.64)

[1]Chronic kidney disease; [2]Heart failure; [3]Prevalence ratio of each characteristic in patients with hyperkalemia versus matched comparisons without hyperkalemia; [4]mL/min/1.73m^2; [5]Myocardial infarction; [6]Peripheral vascular disease; [7]Cerebrovascular disease; [8]Valvular heart disease

Supplementary Table S4: Primary (first-listed) discharge diagnoses during acute hospital admissions during which HK occurred.

	CKD[1]			HF[2]			Diabetes		
Chapter	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)
Number of patients		**N=17,747**			**N=5,141**			**N=4,183**	
Number of patients with acute hospital admission		**N=7,069**			**N=2,897**			**N=1,288**	
Event during acute hospital admission	7,069	39.8%	100%	2,897	56.4%	100%	1,288	30.8%	100%
Infectious diseases	432	2.4%	6.1%	108	2.1%	3.7%	88	2.1%	6.8%
Neoplasms	471	2.7%	6.7%	68	1.3%	2.3%	70	1.7%	5.4%
Hematological diseases	163	0.9%	2.3%	44	0.9%	1.5%	20	0.5%	1.6%
Endocrine, nutritional and metabolic disorders	455	2.6%	6.4%	125	2.4%	4.3%	167	4.0%	13.0%
Mental and behavioral disorders	40	0.2%	0.6%	12	0.2%	0.4%	8	0.2%	0.6%
Diseases of the nervous system	57	0.3%	0.8%	13	0.3%	0.4%	21	0.5%	1.6%
Diseases of the eye and adnexa	2	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%
Diseases of the ear and mastoid process	3	0.0%	0.0%	0	0.0%	0.0%	1	0.0%	0.1%
Diseases of the circulatory system	1,377	7.8%	19.5%	1,280	24.9%	44.2%	213	5.1%	16.5%

	CKD[1]			HF[2]			Diabetes		
Chapter	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)
Diseases of the respiratory system	1,054	5.9%	14.9%	516	10.0%	17.8%	207	4.9%	16.1%
Diseases of the digestive system	797	4.5%	11.3%	183	3.6%	6.3%	147	3.5%	11.4%
Diseases of the skin and subcutaneous tissue	42	0.2%	0.6%	12	0.2%	0.4%	12	0.3%	0.9%
Musculoskeletal and connective tissue diseases	100	0.6%	1.4%	27	0.5%	0.9%	20	0.5%	1.6%
Diseases of the genitourinary system	623	3.5%	8.8%	121	2.4%	4.2%	76	1.8%	5.9%
Pregnancy, childbirth and the puerperium	3	0.0%	0.0%	0	0.0%	0.0%	8	0.2%	0.6%
Perinatal conditions	1	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%
Congenital malformations	6	0.0%	0.1%	2	0.0%	0.1%	1	0.0%	0.1%
Symptoms, signs and abnormal findings	487	2.7%	6.9%	124	2.4%	4.3%	87	2.1%	6.8%
Injuries	543	3.1%	7.7%	127	2.5%	4.4%	84	2.0%	6.5%
External causes of morbidity and mortality	1	0.0%	0.0%	0	0.0%	0.0%	0	0.0%	0.0%

	CKD[1]			HF[2]			Diabetes		
Chapter	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)	Total number of patients admitted with the current chapter	Percentage (out of the cohort)	Percentage (out of the cohort with admissions)
Health status factors and health services contact	412	2.3%	5.8%	135	2.6%	4.7%	58	1.4%	4.5%

[1]Chronic kidney disease; [2]Heart failure;

Supplementary Table S5. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.5 mmol/L.

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€) (95% CI)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=7,447**					**N=7,391**			
Acute hospitalizations[1]	5,549	(1.05)	11,508	(1.57)	5,959	2,419	(0.52)	2,720	(0.52)	301	5,658 (5,074;6,242)
Dialysis	50	(0.01)	249	(0.02)	199	57	(0.00)	69	(0.01)	12	187 (111;263)
Ventilator	1,147	(0.03)	4,031	(0.11)	2,883	414	(0.01)	545	(0.01)	132	2,752 (2,323;3,180)
ICU	1,455	(0.06)	4,739	(0.19)	3,283	508	(0.03)	688	(0.03)	179	3,104 (2,668;3,539)
Non-acute hospitalizations	2,085	(0.38)	3,158	(0.36)	1,073	1,260	(0.21)	1,144	(0.19)	-116	1,189 (875;1,504)
Outpatient visits	2,042	(5.62)	1,987	(6.25)	-55	1,254	(3.60)	1,350	(3.71)	96	-151 (-315;13)
GP consultations	89	(4.62)	71	(3.69)	-18	83	(4.30)	78	(4.05)	-5	-13 (-16;-11)
GP contacts	204	(16.16)	187	(14.60)	-17	143	(12.37)	144	(12.23)	1	-19 (-25;-12)
Prescriptions	654	(25.61)	426	(17.39)	-228	597	(22.45)	559	(21.93)	-38	-190 (-215;-164)
Overall cost	10,623	-	17,337	-	6,715	5,756	-	5,996	-	240	6,475 (5,752;7,197)
Heart failure											
Number of patients			**N=2,511**					**N=2,511**			
Acute hospitalizations	6,659	(1.42)	11,628	(1.69)	4,969	5,230	(1.14)	4,467	(0.96)	-762	5,731 (4,797;6,664)

Dialysis	155	(0.02)	214	(0.02)	59	47	(0.01)	41	(0.01)	-6	65 (-70;199)
Ventilator	911	(0.03)	3,872	(0.11)	2,961	606	(0.02)	620	(0.02)	14	2,947 (2,302;3,592)
ICU	1,282	(0.07)	4,688	(0.20)	3,406	816	(0.05)	805	(0.04)	-11	3,417 (2,719;4,115)
Non-acute hospitalizations	1,962	(0.30)	3,088	(0.32)	1,126	1,656	(0.24)	1,755	(0.24)	99	1,027 (439;1,616)
Outpatient visits	1,837	(5.70)	1,847	(6.15)	10	1,141	(4.16)	1,211	(4.72)	70	-60 (-282;162)
GP consultations	96	(4.97)	73	(3.81)	-23	98	(5.11)	92	(4.80)	-6	-17 (-22;-11)
GP contacts	263	(19.52)	218	(16.01)	-46	210	(16.60)	209	(16.46)	-1	-44 (-59;-29)
Prescriptions	704	(30.16)	429	(18.84)	-276	650	(26.90)	579	(25.96)	-70	-205 (-251;-159)
Overall cost	11,521	-	17,283	-	5,761	8,985	-	8,314	-	-671	6,432 (5,223;7,642)
Diabetes											
Number of patients			**N=4,183**					**N=4,151**			
Acute hospitalizations	5,219	(0.97)	11,380	(1.49)	6,161	1,325	(0.31)	1,400	(0.32)	75	6,086 (4,757;7,415)
Dialysis	96	(0.01)	207	(0.02)	111	16	(0.00)	0	(0.00)	-16	128 (-23;278)
Ventilator	912	(0.03)	4,099	(0.11)	3,186	127	(0.00)	202	(0.01)	76	3,111 (2,142;4,080)
ICU	1,306	(0.06)	4,770	(0.20)	3,463	176	(0.01)	241	(0.01)	65	3,399 (2,382;4,416)
Non-acute hospitalizations	1,840	(0.32)	3,249	(0.36)	1,408	865	(0.16)	711	(0.14)	-154	1,562 (927;2,197)
Outpatient visits	1,896	(5.45)	1,850	(6.02)	-46	946	(2.95)	924	(2.91)	-22	-24 (-304;257)
GP consultations	102	(5.26)	82	(4.27)	-19	89	(4.61)	82	(4.29)	-6	-13 (-19;-7)
GP contacts	234	(18.88)	208	(16.49)	-26	151	(13.16)	148	(12.64)	-3	-23 (-39;-7)
Prescriptions	694	(27.36)	469	(19.01)	-225	532	(20.76)	513	(20.74)	-19	-207 (-275;-139)
Overall cost	9,985	-	17,238	-	7,253	3,907	-	3,779	-	-128	7,381 (5,802;8,961)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Supplementary Table S6. Healthcare resource use and mean costs (€) associated with elevated potassium level >6.0 mmol/L.

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€) (95% CI)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=3,258**					**N=3,250**			
Acute hospitalizations[1]	6,732	(1.22)	13,414	(1.84)	6,682	2,781	(0.59)	3,182	(0.60)	401	6,281 (5,320;7,242)
Dialysis	99	(0.02)	362	(0.03)	264	24	(0.00)	89	(0.01)	65	198 (71;325)
Ventilator	1,529	(0.04)	4,337	(0.12)	2,808	400	(0.01)	611	(0.02)	211	2,597 (1,906;3,287)
ICU	1,891	(0.08)	5,230	(0.23)	3,338	565	(0.03)	761	(0.04)	195	3,143 (2,434;3,851)
Non-acute hospitalizations	2,642	(0.43)	3,113	(0.36)	471	1,374	(0.24)	1,217	(0.21)	-157	628 (131;1,125)
Outpatient visits	2,545	(6.72)	2,541	(7.49)	-4	1,544	(4.24)	1,546	(4.38)	2	-6 (-306;293)
GP consultations	89	(4.60)	63	(3.29)	-26	86	(4.47)	78	(4.06)	-8	-18 (-22;-13)
GP contacts	219	(16.91)	181	(13.74)	-37	154	(13.09)	155	(12.89)	1	-38 (-50;-27)
Prescriptions	676	(26.42)	364	(15.24)	-312	555	(22.04)	524	(21.60)	-31	-281 (-321;-241)
Overall cost	12,904	-	19,678	-	6,774	6,494	-	6,702	-	208	6,565 (5,392;7,738)
Heart failure											
Number of patients			**N=1,164**					**N=1,164**			
Acute hospitalizations	7,199	(1.57)	12,123	(1.77)	4,924	5,111	(1.17)	4,627	(1.01)	-484	5,408 (3,949;6,867)

Dialysis	171	(0.03)	239	(0.03)	68	97	(0.01)	80	(0.01)	-17	85 (-77;246)
Ventilator	849	(0.03)	3,741	(0.10)	2,892	377	(0.02)	714	(0.02)	336	2,556 (1,581;3,531)
ICU	1,303	(0.08)	4,972	(0.22)	3,669	564	(0.06)	865	(0.05)	301	3,368 (2,320;4,415)
Non-acute hospitalizations	2,139	(0.31)	2,747	(0.29)	608	1,577	(0.26)	1,698	(0.23)	122	487 (-376;1,349)
Outpatient visits	2,373	(7.03)	2,430	(7.33)	57	1,440	(4.79)	1,535	(5.27)	94	-37 (-418;343)
GP consultations	94	(4.87)	60	(3.12)	-34	100	(5.14)	90	(4.68)	-10	-25 (-32;-17)
GP contacts	283	(20.71)	195	(14.34)	-88	208	(16.78)	203	(16.17)	-4	-83 (-106;-61)
Prescriptions	776	(32.25)	358	(15.96)	-418	707	(28.52)	631	(27.53)	-76	-342 (-417;-267)
Overall cost	12,863	-	17,913	-	5,050	9,141	-	8,784	-	-358	5,407 (3,508;7,307)
Diabetes											
Number of patients			**N=574**					**N=585**			
Acute hospitalizations	7,571	(1.19)	14,537	(1.81)	6,966	1,771	(0.41)	1,544	(0.35)	-227	7,193 (4,624;9,762)
Dialysis	108	(0.01)	356	(0.03)	248	0	(0.00)	0	(0.00)	0	248 (-35;532)
Ventilator	1,848	(0.05)	5,585	(0.13)	3,737	30	(0.00)	252	(0.01)	221	3,516 (1,544;5,488)
ICU	2,363	(0.11)	6,877	(0.26)	4,514	154	(0.01)	177	(0.01)	24	4,490 (2,497;6,484)
Non-acute hospitalizations	2,298	(0.32)	3,548	(0.39)	1,251	1,095	(0.17)	754	(0.14)	-341	1,591 (454;2,729)
Outpatient visits	2,317	(6.70)	2,261	(7.25)	-56	1,187	(3.65)	1,072	(3.42)	-115	59 (-441;559)
GP consultations	105	(5.42)	75	(3.90)	-30	93	(4.84)	84	(4.36)	-9	-20 (-30;-10)
GP contacts	240	(19.28)	202	(15.77)	-38	173	(14.40)	164	(13.41)	-9	-29 (-57;-2)
Prescriptions	759	(29.47)	381	(16.95)	-378	508	(20.31)	494	(20.60)	-15	-363 (-493;-234)

Overall cost	13,291	-	21,006	-	7,715	4,828	-	4,112	-	-715	8,430 (5,481;11,379)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

Supplementary Table S7. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L, weighted by time-at-risk.

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of time-at-risk by half-year term	**17,747**		**14,107**			**17,608**		**16,918**			
Acute hospitalizations[1]	3,666	(0.78)	10,316	(1.52)	6,651	1,778	(0.41)	2,284	(0.48)	506	6,145 (5,760;6,511)
Dialysis	27	(0.00)	156	(0.01)	129	17	(0.00)	33	(0.00)	15	114 (77;158)
Ventilator	504	(0.02)	3,279	(0.09)	2,775	243	(0.01)	395	(0.01)	152	2,623 (2,326;2,898)
ICU	675	(0.04)	3,910	(0.16)	3,235	314	(0.02)	486	(0.02)	172	3,063 (2,768;3,343)
Non-acute hospitalizations	1,653	(0.30)	3,468	(0.43)	1,815	1,087	(0.18)	1,135	(0.18)	48	1,767 (1,567;1,981)
Outpatient visits	1,593	(4.42)	2,009	(6.37)	416	1,077	(3.10)	1,159	(3.35)	82	334 (228;429)
GP consultations	85	(4.42)	101	(5.24)	16	79	(4.11)	81	(4.19)	1	14 (12;16)
GP contacts	174	(14.21)	230	(18.46)	56	130	(11.33)	143	(12.12)	13	43 (39;47)
Prescriptions	583	(22.91)	572	(23.36)	-11	554	(21.08)	555	(21.63)	1	-12 (-27;3)
Overall cost	3,666	(0.78)	10,316	(1.52)	6,651	1,778	(0.41)	2,284	(0.48)	506	6,145 (5,760;6,511)
Heart failure											

Number of time-at-risk by half-year term	**N=5,141**		**N=3,702**			**N=5,141**		**N=4,655**			
Acute hospitalizations	5,799	(1.30)	13,409	(2.12)	7,609	4,934	(1.12)	4,590	(1.03)	-344	7,954 (7,063;8,676)
Dialysis	85	(0.01)	211	(0.02)	126	36	(0.01)	34	(0.00)	-2	127 (49;229)
Ventilator	636	(0.02)	4,035	(0.12)	3,399	606	(0.02)	463	(0.02)	-143	3,542 (3,039;4,127)
ICU	928	(0.06)	4,808	(0.21)	3,880	830	(0.05)	692	(0.04)	-138	4,018 (3,457;4,607)
Non-acute hospitalizations	1,759	(0.29)	4,414	(0.45)	2,655	1,820	(0.28)	1,849	(0.26)	29	2,626 (2,163;3,105)
Outpatient visits	1,463	(4.84)	2,132	(7.80)	669	1,130	(4.03)	1,354	(5.11)	224	445 (283;614)
GP consultations	97	(5.04)	117	(6.11)	20	98	(5.07)	102	(5.31)	4	16 (12;20)
GP contacts	241	(18.17)	310	(23.29)	69	203	(16.06)	220	(17.41)	17	52 (41;63)
Prescriptions	647	(27.68)	653	(29.02)	7	622	(25.89)	644	(28.27)	21	-14 (-45;13)
Overall cost	10,006	-	21,035	-	11,029	8,807	-	8,758	-	-49	11,078 (10,031;12,034)
Diabetes											
Number of time-at-risk by half-year term	**N=4,183**		**N=3,572**			**N=4,151**		**N=4,073**			
Acute hospitalizations	3,056	(0.66)	7,976	(1.15)	4,920	1,195	(0.28)	1,096	(0.25)	-98	5,019 (4,427;5,627)
Dialysis	33	(0.00)	85	(0.01)	52	9	(0.00)	0	(0.00)	-9	61 (7;118)
Ventilator	260	(0.01)	2,572	(0.07)	2,312	146	(0.00)	121	(0.00)	-25	2,337 (1,929;2,792)
ICU	440	(0.03)	3,075	(0.13)	2,635	166	(0.01)	166	(0.01)	-0	2,635 (2,216;3,076)
Non-acute hospitalizations	1,311	(0.23)	2,575	(0.34)	1,264	661	(0.12)	614	(0.12)	-48	1,312 (975;1,650)
Outpatient visits	1,369	(4.01)	1,704	(5.56)	336	955	(2.67)	948	(2.69)	-6	342 (176;520)

GP consultations	97	(4.99)	108	(5.61)	12	86	(4.45)	82	(4.25)	-4	15 (12;19)
GP contacts	189	(15.99)	228	(19.02)	39	143	(12.51)	140	(12.14)	-2	41 (33;49)
Prescriptions	548	(22.48)	547	(22.82)	-1	458	(18.08)	467	(19.30)	10	-11 (-37;17)
Overall cost	6,569	-	13,138	-	6,570	3,497	-	3,348	-	-149	6,719 (5,943;7,440)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectively.

†Cost weighted by time-at-risk was calculated as overall cost within the 6-month period divided by the total number of person in half-year term

Supplementary Table S8. Healthcare resource use and mean costs (€) associated with elevated potassium level >5.0 mmol/L 1 month before and after HK.

	Patients with hyperkalemia					Matched comparisons without hyperkalemia					Difference within the cohort – Difference within the comparisons (€) (95% CI)
	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the cohort (€)	6 months before (€)	(Mean number of events)	6 months after (€)	(Mean number of events)	Difference within the comparisons (€)	
Chronic kidney disease											
Number of patients			**N=17,747**					**N=17,608**			
Acute hospitalizations[1]	1,378	(0.27)	4,925	(0.65)	3,547	450	(0.10)	810	(0.15)	360	3,187 (2,984;3,391)
Dialysis	11	(0.00)	63	(0.00)	52	7	(0.00)	21	(0.00)	14	38 (13;62)
Ventilator	221	(0.01)	1,864	(0.05)	1,643	77	(0.00)	195	(0.00)	119	1,524 (1,359;1,688)
ICU	311	(0.01)	2,248	(0.09)	1,936	99	(0.00)	234	(0.01)	134	1,802 (1,630;1,974)
Non-acute hospitalizations	494	(0.07)	1,418	(0.13)	924	217	(0.03)	324	(0.05)	107	817 (705;929)
Outpatient visits	302	(1.01)	327	(1.19)	25	198	(0.58)	213	(0.64)	16	9 (-10;29)
GP consultations	16	(0.81)	21	(1.08)	5	14	(0.73)	15	(0.80)	1	4 (3;4)
GP contacts	47	(3.28)	56	(4.21)	9	26	(2.14)	28	(2.35)	3	6 (5;8)
Prescriptions	101	(4.17)	94	(3.92)	-7	94	(3.63)	94	(3.69)	0	-7 (-11;-4)
Overall cost	2,338	-	6,841	-	4,503	999	-	1,485	-	486	4,017 (3,785;4,249)
Heart failure											
Number of patients			**N=5,141**					**N=5,141**			
Acute hospitalizations	2,164	(0.46)	6,149	(0.87)	3,984	1,727	(0.39)	1,921	(0.40)	194	3,790 (3,377;4,203)

Dialysis	19	(0.00)	69	(0.01)	50	12	(0.00)	8	(0.00)	-5	55 (-1;110)
Ventilator	320	(0.01)	2,242	(0.07)	1,923	190	(0.01)	246	(0.01)	56	1,867 (1,540;2,194)
ICU	460	(0.03)	2,640	(0.12)	2,180	299	(0.02)	353	(0.02)	54	2,126 (1,796;2,456)
Non-acute hospitalizations	500	(0.08)	1,750	(0.14)	1,250	563	(0.08)	439	(0.07)	-124	1,374 (1,141;1,607)
Outpatient visits	290	(1.09)	287	(1.19)	-3	222	(0.85)	231	(0.91)	9	-12 (-40;15)
GP consultations	19	(0.98)	20	(1.02)	1	19	(1.00)	18	(0.94)	-1	2 (1;3)
GP contacts	66	(4.35)	63	(4.38)	-3	49	(3.54)	44	(3.24)	-5	2 (-2;6)
Prescriptions	114	(5.25)	99	(4.65)	-15	110	(4.92)	112	(4.99)	2	-16 (-23;-10)
Overall cost	3,154	-	8,368	-	5,213	2,690	-	2,764	-	74	5,140 (4,672;5,607)
Diabetes											
Number of patients			**N=574**					**N=585**			
Acute hospitalizations	1,081	(0.22)	3,980	(0.51)	2,899	211	(0.05)	170	(0.05)	-41	2,940 (2,593;3,288)
Dialysis	10	(0.00)	25	(0.00)	15	0	(0.00)	0	(0.00)	0	15 (-12;42)
Ventilator	99	(0.00)	1,591	(0.05)	1,493	9	(0.00)	2	(0.00)	-7	1,500 (1,217;1,783)
ICU	192	(0.01)	1,876	(0.08)	1,684	20	(0.00)	22	(0.00)	2	1,682 (1,399;1,965)
Non-acute hospitalizations	478	(0.07)	1,150	(0.11)	673	109	(0.02)	102	(0.02)	-7	680 (489;870)
Outpatient visits	268	(0.91)	305	(1.12)	37	164	(0.49)	161	(0.48)	-2	40 (6;74)
GP consultations	17	(0.88)	25	(1.27)	7	15	(0.77)	14	(0.71)	-1	8 (7;10)
GP contacts	43	(3.31)	60	(4.69)	16	26	(2.20)	24	(2.10)	-2	18 (15;21)
Prescriptions	98	(4.18)	89	(3.85)	-10	78	(3.20)	77	(3.16)	-2	-8 (-14;-2)
Overall cost	1,985	-	5,608	-	3,623	603	-	547	-	-56	3,678 (3,280;4,076)

[1]Acute hospitalizations with procedures of interest including dialysis, ventilator, and ICU are presented, respectivel

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

Healthcare resource utilization and cost associated with elevated potassium levels: a Danish population-based cohort study

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 1 and 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 9
Bias	9	Describe any efforts to address potential sources of bias Page 11 and 13
Study size	10	Explain how the study size was arrived at Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 8
		(*b*) Describe any methods used to examine subgroups and interactions Page 8
		(*c*) Explain how missing data were addressed Page 8 and 14
		(*d*) If applicable, explain how loss to follow-up was addressed Not applicable

		(*e*) Describe any sensitivity analyses Not don in this study. Do in the "sister" clinical publications
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram Figure 1-3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 10
		(b) Indicate number of participants with missing data for each variable of interest Not applicable
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time Page 10 and 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Page 10 and 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses See supplementary data
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 13 and 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 15
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 15
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.