




ORIGINAL ARTICLE

Hyperkalaemia management and related costs in chronic kidney disease patients with comorbidities in Spain

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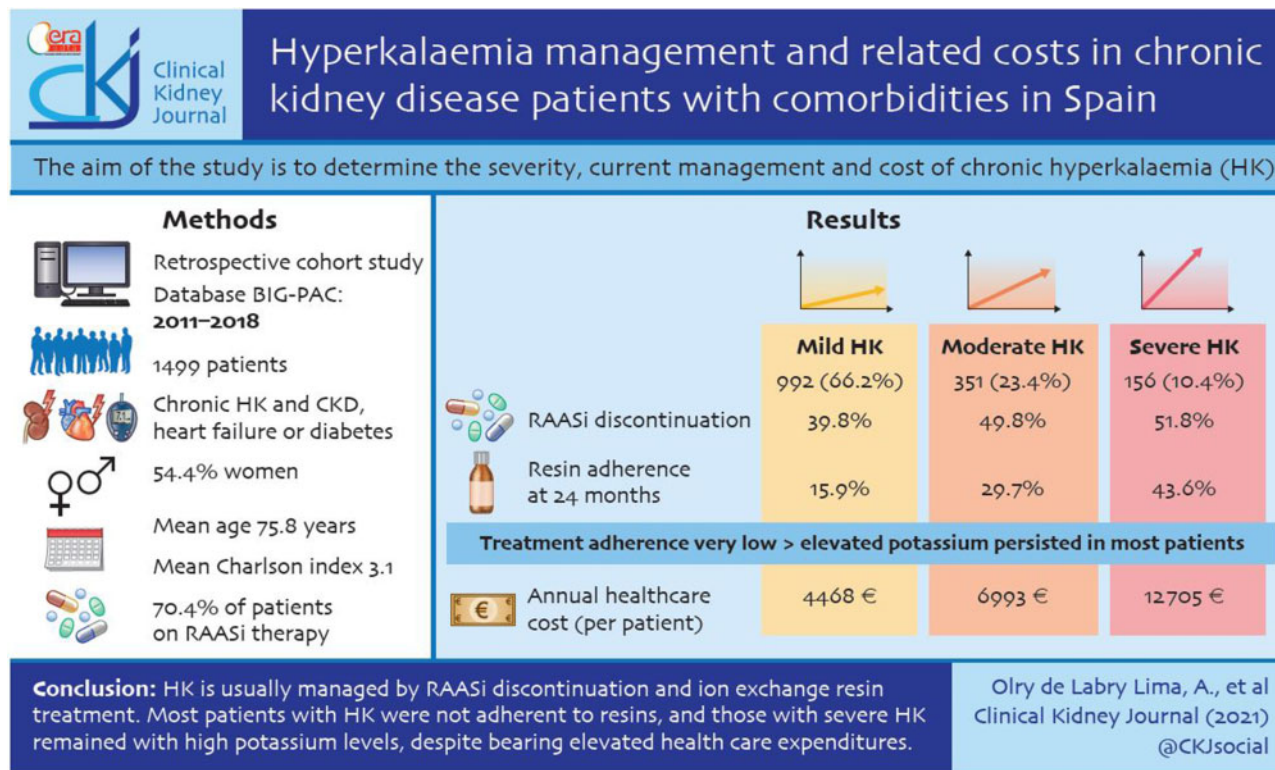
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GRAPHICAL ABSTRACT



ABSTRACT

Background. Hyperkalaemia (HK) is a common electrolyte disorder in patients with chronic kidney disease (CKD) and/or treated with renin–angiotensin–aldosterone system inhibitors (RAASi). The aim of this study is to determine the severity, current management and cost of chronic HK.

Methods. We performed a retrospective cohort study of patients with chronic HK and CKD, heart failure or diabetes mellitus between 2011 and 2018. The study follow-up was 36 months.

Results. A total of 1499 patients with chronic HK were analysed: 66.2% presented with mild HK, 23.4% with moderate HK and 10.4% with severe HK. The severity was associated with CKD stage. Most patients (70.4%) were on RAASi therapies, which were frequently discontinued (discontinuation rate was 39.8, 49.8 and 51.8% in mild, moderate and severe HK, respectively). This RAASi discontinuation was similar with or without resin prescription. Overall, ion-exchange resins were prescribed to 42.5% of patients with HK and prescriptions were related to the severity of HK, being 90% for severe HK. Adherence to resin treatment was very low (36.8% in the first year and 17.5% in the third year) and potassium remained elevated in most patients with severe HK. The annual healthcare cost per patient with HK was €5929, reaching €12 705 in severe HK. Costs related to HK represent 31.9% of the annual cost per HK patient and 58.8% of the specialized care cost.

Conclusions. HK was usually managed by RAASi discontinuation and ion-exchange resin treatment. Most patients with HK were non-adherent to resins and those with severe HK remained with high potassium levels, despite bearing elevated healthcare expenditures.

Keywords: chronic kidney disease, diabetes, heart failure, hyperkalaemia, renin–angiotensin–aldosterone system inhibitors

INTRODUCTION

Hyperkalaemia (HK) is a common electrolyte disorder characterized by increased serum potassium concentration >5.0 mEq/L [1] and increased risk for life-threatening events such as cardiac

arrhythmias and sudden death [2]. In fact, HK is associated with an increased risk of all-cause mortality [3]. The prevalence of HK varies between 2.7% and 39%, being more prevalent in patients with comorbidities such as chronic kidney disease (CKD), diabetes mellitus or heart failure (HF) [4–8]. A study

conducted in Spain in patients with chronic cardiovascular, metabolic and renal conditions reported a prevalence of HK of 2.7% [4]. The NEFRONA study in CKD patients reported an HK prevalence of 5.1 to 11.6% [9]; similarly, Crespo-Leiro *et al.* [8] observed rates in HF patients between 4.3% and 8.2%.

HK is usually associated with a loss of renal function, since as much as 90% of potassium is eliminated by urine. CKD, diabetes mellitus and the use of renin-angiotensin-aldosterone system inhibitors (RAASi) [10, 11] are major risk factors for HK. Nevertheless, main guidelines for the treatment of CKD [Kidney Disease: Improving Global Outcomes (KDIGO) and Kidney Disease Outcomes Quality Initiative] and HF (European Society of Cardiology, American College of Cardiology Foundation, American Heart Association and Heart Failure Society of America) recommend the use of RAASi [12] to reduce disease progression and increase survival in patients with advanced CKD (Stage ≥ 3), diabetes or chronic HF [1, 13–22].

Treatment strategies for HK are classified as acute (emergency) or chronic (maintenance). Treatment of acute or life-threatening HK is well-defined, including the haemodialysis indications [14]. However, the chronic management of HK is challenging.

The main objective of acute/emergency treatment of HK is to avoid potentially fatal arrhythmias. This is achieved by stabilizing the myocardial cell membranes, promoting the movement of extracellular potassium into the cell and encouraging the elimination of this cation from the body in the shortest possible time. In contrast, the objective of chronic treatment is to maintain stable serum potassium levels in the long term.

However, current treatments for HK have numerous restrictions and limitations that make their use in clinical practice difficult and, in turn, increase uncertainty about efficacy and safety. Intermittent treatment with cation exchange resins [calcium polystyrene sulfonate (CPS) and sodium polystyrene sulfonate (SPS)] is used, although it has important limitations [7], such as poor tolerability, severe gastrointestinal complications including intestinal necrosis, risk of hypokalaemia and lack of long-term efficacy and safety studies [7, 8]. Moreover, a recent study reported that approximately one-quarter of the patients receiving CPS do not adhere to treatment [23]. Consequently, in the absence of effective pharmacological alternatives for the management of HK, many doctors prefer to avoid this treatment option and decide to reduce or stop RAASi [24].

Accordingly, a study from Spain showed that only 25.9% of patients received target doses of RAASi, mainly because of HK, thus precluding the benefit of RAASi treatment demonstrated in clinical trials both in diabetic and non-diabetic CKD and in HF patients with reduced ejection fraction [24]. Ouwerkerk *et al.* [25] reported that reaching <50% of the recommended angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and β -blocker dose was associated with an increased risk of death and/or HF hospitalization. In line with these results, Epstein *et al.* [26] reported that cardiorenal adverse events/mortality and mortality occurred in 34.3 and 11.0% of patients who discontinued RAASi and 24.9 and 8.2% of patients on submaximum doses [26].

HK was associated with increasing costs in the US Medicare system [27]. However, there is a lack of studies describing HK management, treatment adherence and economic burden on the National Health System from any European country.

Thus the main objective of this study was to describe the usual management of chronic HK in patients with CKD, HF or diabetes mellitus, the impact of HK on the use of RAASi, the

level of adherence to CPS or SPS and the economic impact of chronic HK on the Spanish health system.

MATERIALS AND METHODS

Design

This was a retrospective cohort study. The data were extracted from the dissociated and anonymized database BIG-PAC and managed by Big Data Healthcare specialists on Real Life Data [28]. The BIG-PAC database contains data of 1.9 million patients treated in health centres in Spain, which includes seven regional health systems. This database is part of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, a network of institutions coordinated by the European Medicines Agency. The members of this network are public institutions and contract and research organizations involved in research in pharmacoepidemiology and pharmacovigilance. According to the Organic Law on Data Protection (Organic Law 3/2018 of 5 December), the BIG-PAC database lacked information that would allow identification of the patient. The study was classified by the Spanish Agency for Medicines and Healthcare Products as EPA-OD (Post Authorization Studies Other Designs) and was subsequently approved by the Clinical Research Ethics Committee of Bellvitge University Hospital on 24 October 2019 (reference PR339/19).

Study population

Adult patients (≥ 18 years) diagnosed with chronic HK (defined as at least two episodes of HK in 12 months, separated by at least 2 weeks) and diagnosed with CKD, heart failure or diabetes mellitus that required healthcare for an episode of HK between 1 January 2011 and 31 December 2018 in seven of the Spanish regional health systems were included. The study follow-up period was 36 months. Exclusion criteria were the following: CKD Stage 5, potassium supplements, Addison's disease, congenital adrenal hyperplasia, hyperkalaemic periodic paralysis, patients with missing or inconsistent data and patient death during the study period (Figure 1).

Study variables

Chronic HK was considered as a dependent variable and was categorized as mild (5.1–5.4 mEq/L), moderate (5.5–6.0 mEq/L) or severe (≥ 6.1 mEq/L) [1]. Sociodemographic variables included age and sex. Clinical variables included systolic and diastolic blood pressure (mmHg), body mass index, heart failure severity, Charlson comorbidity index (CCI), serum creatinine, glomerular filtration rate, renal disease stage and associated comorbidities. Variables associated with the use of health services due to HK included hospitalization, emergency department medical visits and medical specialist visits whose codes were related to HK.

Measuring instruments

We used the following measuring instruments: CCI (a description of a patient's life expectancy at 10 years based on the presence of comorbidities and other factors such as age) [29, 30], the New York Heart Association scale of heart failure severity rating [31], treatment adherence [32] (percentage of prescriptions collected from the pharmacy office in relation to the total number of prescriptions) with CPS or SPS in the different HK severity groups and costs, which were obtained from regional tariffs lists [33] and from the National Institute of Statistics (INE) [34].

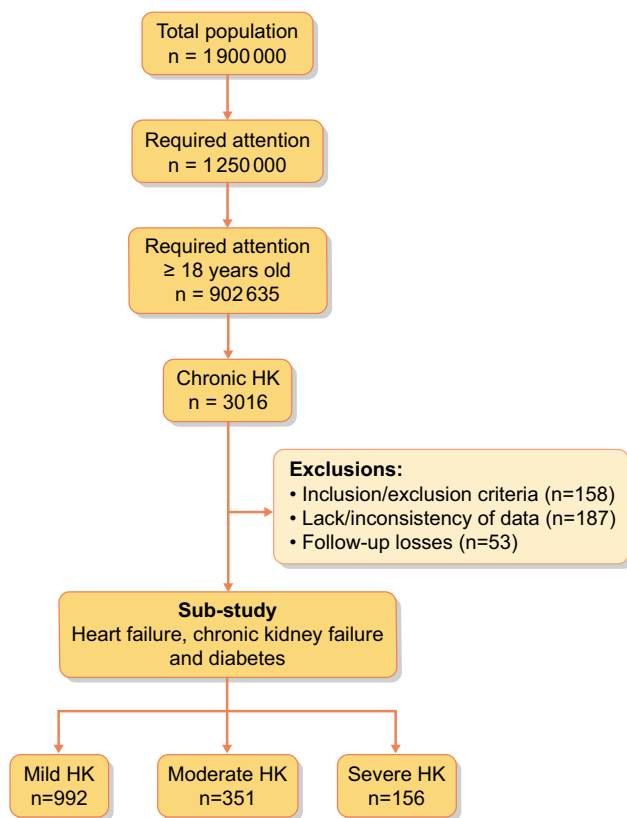


FIGURE 1: Patient flow chart.

Data analysis and statistics

A descriptive statistical analysis was performed using absolute and relative frequencies for the qualitative data, while the quantitative data were described using the mean and standard deviation (SD). The normality of the distributions was checked with the Kolmogorov–Smirnov test and the adherence was quantified by applying Kaplan–Meier survival curves (median time). For comparisons between actuarial curves, the tablecloth–Cox log-rank test was used. In the bivariate analysis, the Student’s t-test, analysis of variance, chi-square and non-parametric Mann–Whitney–Wilcoxon test were used.

To determine the costs of the patients with HK, we obtained data about the use of resources from the database and we used unit costs from regional tariffs lists and from the INE. Prescriptions (acute, chronic or upon request) were quantified according to the recommended retail price per package at the time of prescription (Bot Plus database) [35]. The total cost was expressed as the mean cost per patient (annual mean). The mean use of resources per patient was obtained from the database and was multiplied by the unit costs for each resource to obtain the total costs per patient. These costs have been calculated for all the subgroups taken into account during the study (mild, moderate, and severe HK and total population included in the study).

Finally, a multivariable analysis evaluated the incremental cost burden associated with HK severity. Specifically, generalized linear models with gamma error distribution and log link were fit to the data. Explanatory variables included HK severity, age, sex, concomitant medication, resins treatment and prevalent comorbid conditions.

RESULTS

Basal and clinical characteristics

A total of 1499 patients diagnosed with chronic HK were included, of which 992 (66.2%) had mild HK, 351 (23.4%) had moderate HK and 156 (10.4%) had severe HK (Table 1). Of the total population, 54.4% were women and the mean age was 75.8 ± 9.2 years. The mean CCI was 3.1, with an average of 4.0 comorbidities per patient. The most frequent comorbidities were hypertension, diabetes mellitus, dyslipaemia, CKD, HF and obesity. As expected, the severity of HK was directly related to the severity of CKD and HF. As shown in Table 2, 70.4% of patients with HK were taken RAASi.

Use of resins and adherence to treatment

Ion-exchange resins were frequently prescribed in patients with HK (Table 2), directly related with its severity. Indeed, resins were prescribed in nearly 90% of patients with severe HK.

The mean duration of resin treatment per year depended on the severity of HK and was 85, 140 and 181 days in patients with mild, moderate and severe HK, respectively. However, only one-third of the patients (36.8%) were adherent to resins during the first year. This percentage decreased over time and was very low at the end of the study, with only 17.5% of patients adherent in the third year (Figure 2). Furthermore, resin adherence was associated with the severity of HK.

RAASi management and potassium concentration

RAASi treatment was frequently discontinued in all HK groups, with an average discontinuation rate of 43.3%, with higher discontinuation observed in patients treated with resins (51%) (Table 3). Table 4 presents the evolution of the potassium concentration depending on the severity of HK and treatment with ion-exchange resins and RAASi. Most patients with mild and moderate HK had a normal potassium concentration at 36 months, independent of RAASi treatment. However, potassium levels remained elevated in patients with severe HK, even in those treated with ion-exchange resins, despite the fact that potassium reduction was higher in those patients. Severe HK patients on resins decreased to the mild range or lower limit of the moderate range and had a 2- to 7-fold greater reduction in serum potassium than patients with severe HK in whom resins were not prescribed, although patients without resins were very few (Table 4).

Resource use and HK-associated costs

Patients with chronic HK needed a mean of 9.1 hospital visits and 1.3 emergency room visits and were hospitalized for a mean of 3.6 days. Nevertheless, the number of hospitalization days varied according to the severity of HK, ranging from 1.5 days in patients with mild HK to 14 days in patients with severe HK.

Overall, the annual healthcare cost per patient with chronic HK was €5929, with a direct relationship to the severity of HK (Figure 3). Primary care costs accounted for 45.8% and specialized care costs for 54.2% of the overall cost. Of the annual healthcare cost per patient, 31.9% was attributable to HK.

Concerning specialized care costs, the annual cost per patient was €3213, and again this was directly related to the severity of HK (Figure 4a). In addition, 58.8% of the specialized care costs were attributable to HK. Of these costs, 5.3% were related to

Table 1. Baseline characteristics (demographics and morbidity) of the sample by study groups

Characteristics	Total (N = 1499)	Mild HK (n = 992)	Moderate HK (n = 351)	Severe HK (n = 156)	P-value
Sociodemographics					
Age (years), mean (SD)	75.8 (9.2)	75.6 (8.7)	76.1 (10.5)	76.8 (9.5)	<0.001
Range (years), %					
18–44	0.7	0.4	1.4	0.6	0.175
45–64	11.3	11.8	9.7	12.2	
65–74	23.9	23.9	24.5	22.4	
≥75	64.1	63.9	64.4	64.7	
Sex (female), %	54.4	53.6	56.7	53.8	0.738
General comorbidity					
Number of diagnoses, mean (SD)	4.0 (1.6)	4.0 (1.5)	4.0 (1.6)	4.3 (1.7)	<0.001
CCI, n (%)	3.1 (1.7)	3.0 (1.7)	3.1 (1.8)	3.5 (1.8)	<0.001
1	21.9	23.5	20.5	14.7	0.005
2	20.3	20.4	21.7	17.3	
3+	57.8	56.1	57.8	67.9	
Associated comorbidities, %					
Hypertension	76.7	76.7	77.2	75.0	0.085
Diabetes mellitus	73.3	74.8	69.5	72.4	0.233
Dyslipaemia	54.4	55.4	51.9	53.2	0.885
Kidney failure (GF <60)	44.4	41.2	49.0	54.5	<0.001
Heart failure	32.4	32.2	31.1	36.5	0.086
Obesity	28.8	30.5	24.5	26.9	0.981
Ischaemic heart disease	24.9	25.0	25.1	24.4	0.474
Asthma and COPD	23.5	22.8	23.1	28.8	0.018
Stroke	13.0	13.1	11.7	15.4	0.242
Depressive syndrome	12.0	9.9	14.5	19.9	<0.001
Malignant neoplasms	9.8	8.9	10.5	14.1	0.194
Active smokers	8.5	9.0	7.4	7.7	0.138
Anthropometric-biochemical parameters, mean (SD)					
Systolic blood pressure (mmHg)	133.4 (18.9)	134.0 (19.0)	132.0 (19.4)	132.8 (16.8)	0.279
Diastolic blood pressure (mmHg)	79.0 (11.8)	78.9 (11.8)	78.7 (12.0)	79.8 (11.1)	0.958
Body mass index (kg/m ²)	29.1 (4.6)	29.3 (4.8)	28.6 (4.1)	29.3 (4.4)	0.059
Glomerular filtration rate (mL/min/1.73 m ²)	67.9 (24.0)	69.6 (22.5)	67.0 (25.5)	59.0 (27.2)	<0.001
Kidney disease stage, %					
CKD 1	20.5	21.1	23.6	9.6	0.078
CKD 2	35.5	38.3	27.4	35.9	0.097
CKD 3	37.2	34.2	41.9	45.5	<0.001
CKD 4	6.9	6.5	7.1	9.0	0.149
NYHA scale, %					
1	33.8	36.1	34.9	19.3	0.173
2	27.2	27.3	23.9	33.3	0.043
3	27.2	21.9	36.0	40.4	0.235
4	11.8	14.8	5.2	7.0	0.038

P: statistical significance (difference between mild HK and severe HK; CKD1: CKD-EPI 91–≤130 mL/min/1.73 m²; CKD 2: CKD-EPI 59–≤90 mL/min/1.73 m²; CKD 3: CKD-EPI 31–≤60 mL/min/1.73 m²; CKD4: CKD-EPI 15–30 mL/min/1.73 m²; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration (refers to the equation used to assess estimated glomerular filtration rate); COPD, chronic obstructive pulmonary disease; GF, glomerular filtration; NYHA, New York Heart Association.

Table 2. Use of resins (CPS and SPS) and concomitant medication related to HK

	Total (N = 1499)	Mild HK (n = 992)	Moderate HK (n = 351)	Severe HK (n = 156)	P-value
Prescription of CPS or SPS					
Patients, %	42.5	30.3	55.7	89.9	<0.001
Concomitant medication related to HK					
Number of drugs, mean (SD)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (1.1)	0.248
C09—Renin-angiotensin system, %	70.4	71.4	70.4	64.7	0.712
C03C—Loop diuretics, %	36.6	34.8	37.9	44.9	<0.001
C07A—β-blockers, %	31.9	31.9	30.5	35.3	0.195
M01A—Anti-inflammatory and anti-rheumatic, %	19.3	20.6	17.9	14.1	0.078
C03E—Diuretics and potassium-sparing products, ^a %	0.8	0.8	0.9	0.6	0.703

P: statistical significance (difference between mild HK and severe HK).

^aATC code C03E group includes mineralocorticoid receptor antagonist.

hospital emergencies, 8.1% represented the cost of treatment with resins, 24.7% were related to hospital medical visits and 61.9% were associated with hospitalization (Figure 4b).

DISCUSSION

This study found that chronic HK in CKD patients with comorbidities in Spain was usually managed with ion-exchange resins and RAASi discontinuation. However, patients were reluctant to maintain resin intake, even those patients with severe HK. The most relevant finding in this study is that HK remained uncontrolled in patients with severe HK and was associated with high

numbers of hospitalizations and high healthcare costs. It is also noteworthy that severe HK patients on resins had a 2- to 7-fold greater reduction in serum potassium than patients with severe HK in whom resins were not prescribed.

It has been described that potassium levels >5 mEq/L increase the risk of life-threatening events such as cardiac arrhythmias and sudden death [36]. Therefore, in the present study, we considered HK when potassium was ≥5.1 mEq/L. Patients with CKD show the highest risk of HK, particularly if they are diabetic and treated with RAASi [37]. Accordingly, in this study, most patients were older, diabetic with CKD Stages 2 and 3 and receiving RAASi.

The usual recommendation for patients with CKD and HK is dietary potassium restriction. Unfortunately this information was lacking in this study. However, there is no definitive evidence supporting this recommendation and recent KDIGO guidelines state that although dietary potassium restriction is a valid strategy to treat acute HK, ‘generalized dietary potassium restriction in people with CKD may deprive them from other beneficial effects and nutrient of potassium-rich diets’ [38]. Regarding management of HK in CKD patients with comorbidities, this study confirms previous findings from observational studies [37] describing RAASi cessation as a common practice, and this study found RAASi discontinuation in 43.3% of the entire cohort. RAASi improve kidney and patient survival in CKD, particularly in diabetics and, theoretically, RAASi discontinuation may be associated with worse outcome in this population. Nevertheless, further studies are needed, as this assumption has not yet been proved.

The present study provides interesting data regarding treatment with ion-exchange resins. Indeed, resins were prescribed in 42.5% of patients and in nearly 90% of patients with severe HK. Surprisingly, there is limited high-quality evidence supporting the efficacy of ion-exchange resins in patients with CKD, whereas there are some concerns regarding safety. SPS prescription was associated with increased hospitalization for gastrointestinal adverse events [39, 40], including intestinal necrosis when given with sorbitol [41]. Moreover, ion-exchange resins should be given in patients with normal bowel function and with caution, since they can produce significant gastrointestinal binding of other drugs, limiting their correct

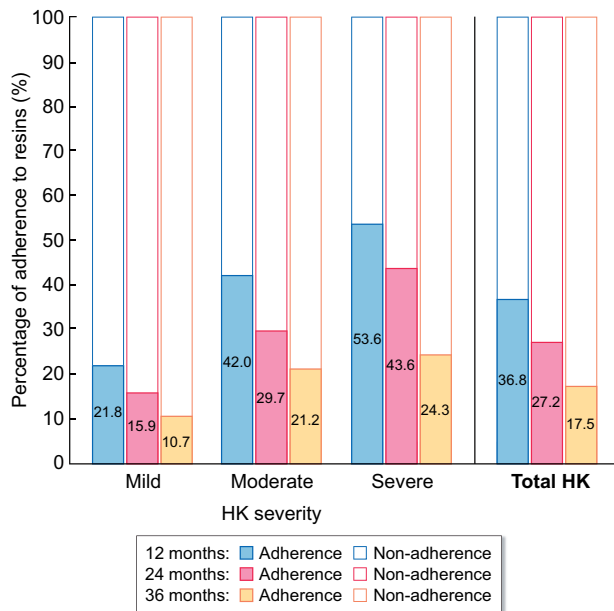


FIGURE 2: CPS and SPS adherence according to HK severity.

Table 3. Use of RAASi

	Total (N = 1499)	Mild HK (n = 992)	Moderate HK (n = 351)	Severe HK (n = 156)	P-value
Total sample (N = 1449)					
Initial period, n (%)	1199 (80.0)	800 (80.6)	285 (81.2)	114 (73.1)	
After 36 months, n (%)	680 (45.4)	482 (48.6)	143 (40.7)	55 (35.3)	0.002
% of RAASi discontinuation	-43.3	-39.8	-49.8	-51.8	<0.001
P-value*	<0.001	<0.001	<0.001	<0.001	
Patients without CPS or SPS (n = 863)					
Initial period, n (%)	698 (72.0)	561 (79.6)	127 (89.4)	10 (62.5)	
After 36 months, n (%)	440 (51.0)	366 (51.9)	69 (48.6)	5 (31.3)	0.002
% of RAASi discontinuation	-37.0	-34.8	-45.7	-50.0	<0.001
P-value*	<0.001	<0.001	0.002	NS	
Patients with CPS or SPS (n = 636)					
Initial period, n (%)	490 (77.0)	231 (80.5)	161 (77.0)	98 (70.0)	
After 36 months, n (%)	240 (37.7)	114 (39.7)	79 (37.8)	47 (33.6)	0.002
% of RAASi discontinuation	-51.0	-50.6	-50.9	-52.0	0.0871
P-value*	<0.001	<0.001	<0.001	0.002	

NS: not significant; P: statistical significance (difference between mild HK and severe HK).
*Statistical significance (difference between initial period and HK after 36 months).

Table 4. Evolution of average potassium levels according to RAASi use (mEq/L)

	Total (N = 1499)	Mild HK (n = 992)	Moderate HK (n = 351)	Severe HK (n = 156)	P-value
With RAASi					
n	1199	800	285	114	
Initial period with RAASi, mean (SD)	6.0 (0.7)	5.3 (0.1)	5.7 (0.2)	6.8 (0.6)	<0.001
After 36 months (with RAASi), mean (SD)	5.1 (0.8)	4.7 (0.7)	4.9 (0.6)	5.6 (0.9)	<0.001
Difference	0.9	0.6	0.8	1.2	
P-value*	<0.001	<0.001	<0.001	<0.001	
Without RAASi					
n	300	192	66	42	
Initial period without RAASi, mean (SD)	6.0 (0.8)	5.2 (0.1)	5.7 (0.2)	6.9 (0.7)	<0.001
After 36 months (without RAASi), mean (SD)	5.2 (0.9)	4.7 (0.7)	4.9 (0.6)	5.8 (1.0)	<0.001
Difference	0.8	0.5	0.8	1.1	
P-value*	<0.001	<0.001	<0.001	<0.001	
Without CPS or SPS (n = 863)					
n	698	567	127	4	
Initial period with RAASi, mean (SD)	5.7 (0.4)	5.3 (0.1)	5.7 (0.2)	6.5 (0.4)	<0.001
After 36 months (with RAASi), mean (SD)	5.2 (0.7)	4.9 (0.5)	5.0 (0.4)	5.8 (0.8)	<0.001
Difference	0.5	0.4	0.7	0.7	
P-value*	<0.001	<0.001	0.002	NS	
n	165	147	15	3	
Initial period without RAASi, mean (SD)	5.6 (0.4)	5.2 (0.1)	5.7 (0.2)	6.4 (0.2)	<0.001
After 36 months (without RAASi), mean (SD)	5.3 (0.8)	5.0 (0.6)	5.0 (0.5)	6.2 (0.9)	<0.001
Difference	0.3	0.2	0.7	0.2	
P-value*	<0.001	<0.001	0.002	NS	
With CPS or SPS (n = 636)					
n	501	229	158	114	
Initial period with RAASi, mean (SD)	6.3 (0.8)	5.3 (0.2)	5.7 (0.2)	6.9 (0.4)	<0.001
After 36 months (with RAASi), mean (SD)	4.8 (1.0)	4.3 (0.7)	4.5 (0.7)	5.4 (1.0)	<0.001
Difference	1.5	1.0	1.2	1.5	
P-value*	<0.001	<0.001	<0.001	0.002	
n	135	42	51	42	
Initial period without RAASi, mean (SD)	6.5 (0.9)	5.3 (0.1)	5.7 (0.2)	7.0 (0.7)	<0.001
After 36 months (without RAASi), mean (SD)	5.0 (1.0)	4.0 (0.7)	4.6 (0.7)	5.5 (0.9)	<0.001
Difference	1.5	1.3	1.1	1.5	
P-value*	<0.001	<0.001	<0.001	0.002	

NS: not significant; P: statistical significance (difference between mild HK and severe HK).
*Statistical significance (difference between initial period and HK after 36 months).

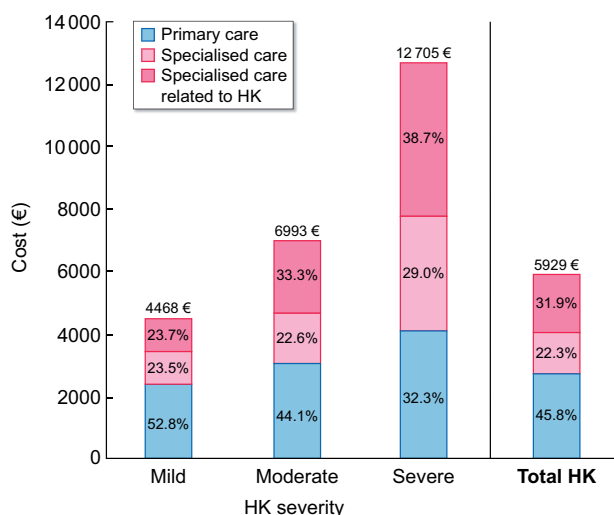


FIGURE 3: Annual total cost per HK patient.

absorption [38]. In this study we found a very low adherence to ion-exchange resins, with only 36.6% and 17.5% of adherent

patients at 1 and 3 years, respectively. Adherence was not related to the severity of HK. Although, in the present study, the occurrence of these potentially severe adverse effects was not confirmed, our hypothesis is that low adherence is related with low tolerance and the discomfort caused by these medications when given chronically. The non-compliance with resins, or potentially with other therapies, may be due to the slightly increased frequency of depressive symptoms in patients with more severe HK. In addition, this study showed that the percentage of normokalaemia (serum potassium <5.0mEq/L) was similar in patients regardless of the use of resins, although it was higher in patients without the use of resins.

The management of chronic HK in the real-world population seems to normalize potassium levels in mild and moderate HK at the expense of RAASi discontinuation and still failed to control HK in patients with severe HK. This finding clearly points out that the effective management of HK remains an unmet need. This fact may put this population at the highest risk of morbimortality, and it is associated with increased health expenditures, as we observed in our study and previously reported by others [4, 27]. In our study, moderate and severe HK entailed 3.5 and 8.7 times more risk for hospitalization compared with mild HK and was associated with an overall annual cost of €6993 and €12 705 per patient, respectively, and a significant part of it directly related to HK complications.

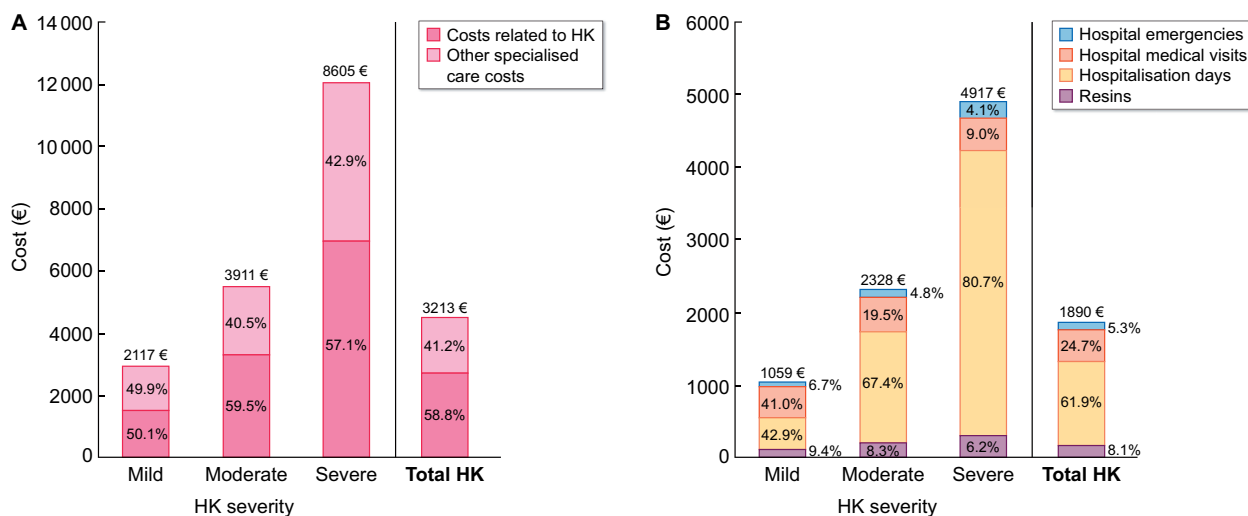


FIGURE 4: (A) Annual specialized care cost per HK patient. (B) annual specialized care costs related to HK.

Chronic HK in CKD patients with comorbidities can be treated with the new potassium binders patiromer [42] and sodium zirconium cyclosilicate [43, 44]. Studies with 12 months of follow-up provided evidence for efficacy in controlling HK, although they also showed some adverse events [38]. Patiromer has been associated with constipation and hypomagnesaemia and sodium zirconium cyclosilicate with oedema. Moreover, as happens with ion-exchange resins, these new agents interfere with the bioavailability of other medications either by direct binding or by gastric pH alteration. Some studies provide promising data regarding the use of patiromer in patients requiring RAAS blockade, demonstrating both efficacy to control HK and to retain RAASi in up to 94% of patients [45] or 87% of patients [46]. Similar results were reported with sodium zirconium cyclosilicate [47].

This study has some limitations. First, the study only includes patients who required healthcare for an episode of HK and thus generated HK-related healthcare. Second, the study does not provide information regarding dietary potassium restriction, as this information is not available in the data source. Finally, the study was designed to ascertain HK management and costs rather than study CKD progression or mortality. However, this study also has some strengths. First, the real-life healthcare database used contains data of 1.9 million patients in Spain. This database is part of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, a network of institutions coordinated by the European Medicines Agency. Second, we were able to follow patients with HK up to 36 months and to precisely analyse the effect of HK on healthcare costs, the use of RAASi, ion-exchange resin adherence and the lack of potassium control in cases of severe HK.

In conclusion, this study points out that there remain unmet needs for chronic HK treatment in patients with comorbidities and CKD. Despite that chronic HK entails a high cost for the National Health System, most patients with severe HK persist uncontrolled and therefore are at risk of HK complications. Moreover, severe HK patients, as well as mild and moderate HK patients, suffer from low adherence to ion-exchange resins and a high proportion of RAASi discontinuation, which may lead to

CKD progression and cardiovascular events. Therefore it is advisable to seek new strategies to tackle chronic HK.

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AUTHORS' CONTRIBUTIONS

M.A., J.D. and J.M.C. participated in the conception or design and analysis and interpretation of data. M.A. and J.M.C. drafted the article. All authors reviewed the draft manuscript, provided intellectual content of critical importance to the work described and read and gave final approval of the version to be published.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract format. A.O.d.L.L. is affiliated with the Escuela Andaluza de Salud Pública, CIBER en Epidemiología y Salud Pública (CIBERESP) and Instituto de Investigación Biosanitaria. O.D.C. is employed by the Servicio Galego de Saúde. J.M.R.-R. is employed by the Hospital Perpetuo Socorro. M.R.G.D.-G. is employed by the Dirección provincial de Sanidad en Albacete. V.A.P. and M.B.d.l.H.D. are employed by Hospital Nuestra Señora del Prado. M.A. is an employee of BCN Health Economics & Outcomes Research S.L., an independent contract health economic organization. J.D. is employed by the University of Barcelona. J.M.C. is affiliated with the University of Barcelona, Bellvitge Biomedical Research Institute (IDIBELL) and Spanish Network for Renal Research (REDINREN). A.O.d.L.L., O.D., J.M.R.-R., V.A.P., M.B.d.l.H.D. and J.M.C. have received consultancy fees from Vifor Fresenius Medical Care Renal Pharma España S.L. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter

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