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RESEARCH ARTICLE

Effects of hyperkalaemia and non-adherence to renin–angiotensin–aldosterone system inhibitor therapy in patients with heart failure in Italy: a propensity-matched study

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Aims The aims of this study were to evaluate if the risk of cardiovascular events and all-cause mortality was higher in the presence of hyperkalaemia (HK) in patients with heart failure (HF) treated with renin–angiotensin–aldosterone system inhibitors (RAASi), and to investigate in this cohort the increased risk of cardiovascular events and all-cause mortality among HK patients with non-optimal adherence to RAASi therapy.

Methods and results In this retrospective cohort study based on administrative databases of five Italian Local Health Units, all adult patients with a HF diagnosis between January 2010 and December 2017 were included only if they were prescribed RAASi therapy during the first 3 months after the index date, that corresponded to the date of first HF diagnosis during the inclusion period. Patients were considered to have HK if serum potassium level was ≥5.5 mmol/L. A propensity score matching was applied before evaluation of hazard ratios. Patients with HK were 37% ($P < 0.001$) and 70% ($P < 0.001$), respectively, more at risk of cardiovascular events and of dying for all-cause mortality compared to non-HK patients. Among the HK group, patients non-adherent to RAASi therapy had a 39% ($P = 0.105$) higher risk of cardiovascular events and a twofold increased risk ($P < 0.001$) of all-cause death.

Conclusion Findings from this real-world study showed that in a cohort of HF patients under RAASi therapy, subjects with HK had an enhanced risk of cardiovascular events or death compared to patients without HK. Moreover, in HK patients, sub-optimal adherence to RAASi therapy was associated with an increased risk of all-cause mortality.

Keywords Hyperkalaemia • Adherence • Renin–angiotensin–aldosterone system inhibitors • Heart failure • Real world

Introduction

Renin–angiotensin–aldosterone system (RAAS) inhibition by angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRA) represents a milestone in the current pharmacological treatment of heart failure (HF) (in addition to beta-blockers).[1] According to the latest European Society of Cardiology (ESC) HF guidelines, RAAS inhibitors (RAASi) are recommended as first-line treatment in all symptomatic patients (New York Heart Association class II–IV) with HF and reduced ejection fraction[2], unless contraindicated or not tolerated, to reduce mortality and

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morbidity. ACEi are also recommended in patients with asymptomatic left ventricular systolic dysfunction to reduce the risk of HF development, HF hospitalization and death.

Providing patients with optimal dose of these drugs guided by randomized controlled trials is of paramount importance and mandatory to obtain positive results, because not achieving recommended RAASi dose is associated with worse outcome.

However, literature data show that in vulnerable patients, the use of RAASi is associated with the risk of developing hyperkalaemia (HK) (serum potassium concentration of ≥5.5 mmol/L) with possible related complications.[3,4] Thus, the risk of HK has limited the use of one of the most effective treatment for chronic HF, especially if poor renal function coexists as frequently occurs in chronic HF, and recommended dosages of RAASi are rarely achieved in clinical practice.[5]

Information available from real-life clinical studies on the outcomes after RAASi reduction/discontinuation is limited.[6,7] That is, whether RAASi reduction/discontinuation carries a worse prognosis than HK in patients with chronic HF is still poorly known.

Accordingly, the aim of this study was twofold: (i) to assess the increased risk of occurrence of cardiovascular (CV) events and all-cause mortality in the presence of HK in an Italian cohort of propensity score-matched HF patients, and (ii) to assess in the same cohort the risk of occurrence of CV events and all-cause mortality associated with sub-optimal adherence to RAASi therapy among HK patients.

Methods

Data source

This observational retrospective cohort study was conducted by integrating the administrative and laboratory databases of five Local Health Units (LHUs) distributed throughout the Italian territory, accounting for approximately 5% of the total population. Data were collected from the following databases: (i) beneficiaries' database for demographic data; (ii) pharmaceutical database to retrieve information related to drugs reimbursed by the Italian National Health Service (INHS) as Anatomical-Therapeutic Chemical (ATC) code, number of packages, number of units per package, unit cost per package, and prescription date; (iii) hospitalization database providing all hospitalization data including admission and discharge dates, primary and secondary discharge diagnoses recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); (iv) outpatient specialist services database, which contains information on visits, services, laboratory and instrumental diagnostic exams supplied in outpatient settings reimbursed by the INHS; and (v) laboratory analysis registries that allowed to collect data on potassium level.

In order to guarantee patients' privacy, an anonymous univocal numeric code was assigned to each subject included in the study, in full compliance with the European General Data Protection Regulation (GDPR 2016/679). No identifiers related to patients were provided to the authors. The patient code in each database allowed electronic linkage between all different databases. All the results of the analyses were produced as aggregated summaries, which are not possible to assign, either directly or indirectly, to individual patients. Informed consent was not required for using encrypted retrospective information for research purposes. According to the Italian law regarding the conduction of observational analysis,[8] the Local Ethics Committees of each participating LHU have been notified of this study and approved it.

Cohort definition

All adult patients (≥18 years) with a primary hospitalization discharge diagnosis of HF (ICD-9-CM code: 428) from 1 January 2010 to 31 December 2017 (enrolment period) were enrolled. The index date (ID) was defined as the first date of hospitalization discharge related to HF during the enrolment period. All patients were characterized in the 12 months before the ID (characterization period). Only the patients with a HF diagnosis that presented at least one RAASi prescription with ATC code C09 [ACEi plain (ATC code: C09A), ACEi combinations (ATC code: C09B), ARB plain (ATC code: C09C), ARB combinations (ATC code: C09D), other agents acting on the renin–angiotensin system (ATC code: C09X)] during the 3 months after the ID were included in the analysis. Included patients were observed from ID to 31 December 2017 (follow-up period). The exclusion criteria concerned co-diagnosis of chronic kidney disease (ICD-9-CM code: 585), presence of dialysis (ICD-9-CM code: V560), results of serum potassium level tests not available and patients transferred to a different LHU during the study period.

Study variables

Serum potassium level was tested during the 3 months before and after ID; patients were considered as having high potassium level (HK) if they presented a serum potassium level ≥5.5 mmol/L; HK onset was defined as the first detected serum potassium level ≥5.5 mmol/L. Patients with hypokalaemia were included in the non-HK cohorts. Pharmaco-utilization was analysed during the 12 months after ID in terms of adherence to RAASi therapy, which was calculated by using the proportion of days covered (PDC), i.e. the ratio between the number of days of medication supplied and days of observation (365 days), multiplied by 100. Patients were considered as adherent to therapy if they had a PDC >80%. PDC is considered as one of the most reliable method to measure adherence in chronic therapies and the standard threshold of 80% is widely accepted as the likelihood of achieving the most clinical benefits.[9,10]

Data collected at baseline included demographic characteristics as well as RAASi prescription and hospitalization related to HF during the characterization period. Previous treatments analysed were diuretic drugs (ATC code: C03, except for ATC code: C03DA), aldosterone antagonists (ATC code: C03DA), beta-blocking agents (ATC code: C07), lipid-modifying agents (ATC code: C10) and antidiabetic agents (ATC code: A10).

Comorbidities were assessed using the Charlson Comorbidity Index,[11] which assigns a weighted score to each concomitant disease identified from discharge diagnoses/pharmaceutical prescriptions recorded during the characterization period.

Cardiovascular events analysed during follow-up were: acute myocardial infarction (ICD-9-CM code: 410), other acute and subacute forms of ischaemic heart disease (ICD-9-CM code: 411), angina pectoris (ICD-9-CM code: 413), other forms of chronic ischaemic heart disease (ICD-9-CM code: 414), cerebrovascular disease (ICD-9-CM code: 430-438), atherosclerosis (ICD-9-CM code: 440) and other peripheral vascular disease (ICD-9-CM code: 443). For the estimation of hazard ratios (HRs), patients that experienced the events analysed (CV events and death) during the 3 months after ID were excluded.

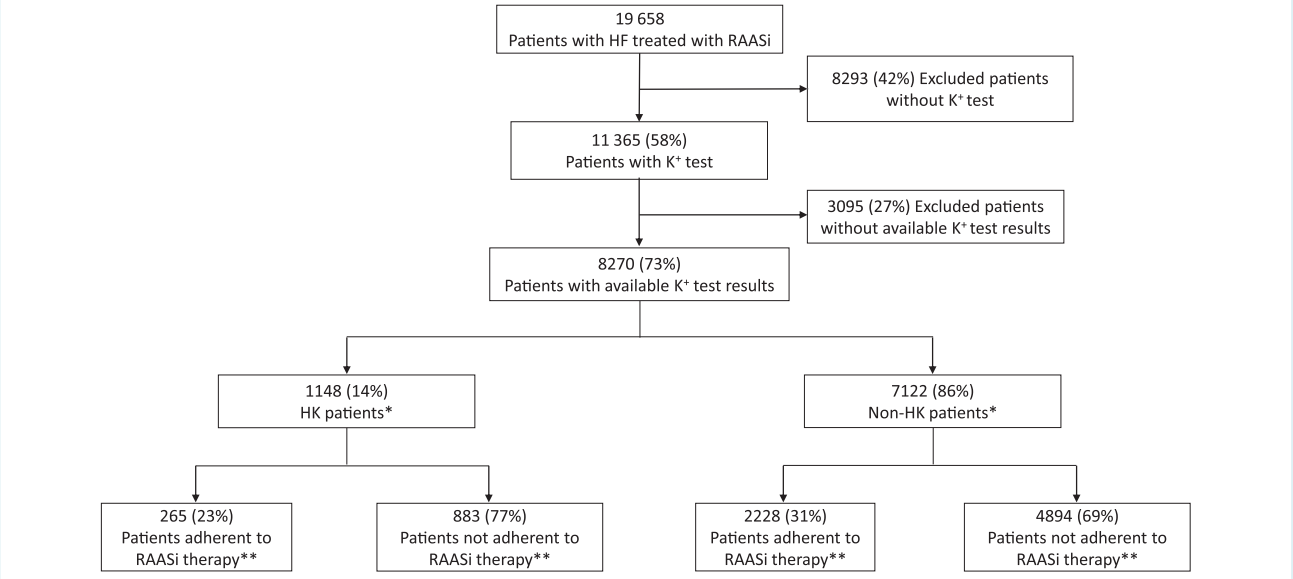

Figure 1 Flow-chart of included patients. HF, heart failure; HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor. *Patients were considered as having HK if they presented a serum potassium level ≥5.5 mmol/l. **Patients were considered as adherent to therapy if they had a proportion of days covered >80%.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD), categorical variables were expressed as numbers and percentages. Clinical and demographic characteristics were evaluated and compared among patients with and without HK. Given the non-randomized nature of the study, to minimize selection bias, a multivariable analysis was performed using propensity score matching (PSM), that was determined using a logistic regression model from which the probability of being HK or non-HK was calculated for each patient. The probability was stratified in quintiles, and the two cohorts were matched 1:1 within each quintile. The analysis performed after PSM considered and included in the model the following potentially confounding variables: age, gender, Charlson Comorbidity Index, presence of treatments (RAASi, diuretics, aldosterone antagonists, beta-blocking agents, lipid-modifying agents, antidiabetics) or hospitalization prior the ID. Model discrimination was assessed using the c statistic, and model calibration using the Hosmer–Lemeshow test.

Incidence rate of all-cause mortality was calculated as the total number of deaths for all-cause per 100 person-years in each group. Cox proportional hazard model was used to estimate HR before and after PSM; the proportional hazards assumption was tested using Schoenfeld residuals. In the present study, we report the analysis performed after PSM. The Cox model considering the population pre-PSM is published elsewhere.[12] Statistical significance was accepted at $P < 0.05$.

All analyses were performed using Stata SE version 12.0 (StataCorp, College Station, TX, USA).

Results

A total of 19 658 patients with a primary diagnosis of HF and treated with RAASi within 90 days of hospitalization discharge were identified during the enrolment period. For 8270 of them, results on serum potassium level test were available, and therefore they were included in the analysis. A flow-chart showing the eligibility criteria applied is presented in *Figure 1*. Patients with HK ($n = 1148$) accounted for 14% of patients included and the remaining 86% ($n = 7122$) were without HK (non-HK). Adherence to RAASi therapy was observed in 265 (23%) HK patients, while 883 (77%) of them were non-adherent according to our definition.

Demographic and clinical characteristics at baseline before and after PSM are reported in *Table 1*. HK patients (49.9% male) were older than non-HK (54% male), as their mean age ± SD was 77.7 ± 9.9 and 76.3 ± 11.5 years ($P < 0.001$), respectively. After PSM, mean age was 78.0 ± 10 and 78.1 ± 10.7 years for HK and non-HK patients, respectively (not statistically significant). The proportion of patients with previous RAASi prescriptions (84.4%) and hospitalization (3%) during the characterization period was higher in the HK group than in the non-HK group (77.6% and 1.2%, respectively; $P < 0.001$). After PSM, the difference between RAASi prescription was not statistically significant anymore (84.8% in HK and 84.3% in non-HK groups). At ID, aldosterone antagonists were prescribed to 46.2% and 39.1% of HK and non-HK patients, respectively. Previous pharmacological treatments observed during the characterization period are reported in *Table 1*. An increment of the diuretic dosage was observed in 9.6% of HK and 8.6% of non-HK patients before PSM, and in 9.0% of HK and 8.0% of non-HK patients after PSM. Mean number of potassium and creatinine tests before and after inclusion is shown in *Table 2*. In the PSM cohort, 0.6% of HK patients used sodium polystyrene sulfonate. All-cause mortality incidence rate was estimated to be 15.6/100 person-years for HK patients and 9.1/100 person-years for non-HK patients.

Table 1 Demographic characteristics, previous treatments and comorbidities of included patients before and after propensity score matching

	Before PSM			After PSM		
	HK patients	Non-HK patients	*P*-value	HK patients	Non-HK patients	*P*-value
Patients, *n*	1148	7122		1000	1000	
Age (years), mean ± SD	77.7 ± 9.9	76.3 ± 11.5	<0.001	78.0 ± 10.0	78.1 ± 10.7	0.829
Male sex, *n* (%)	573 (49.9)	3843 (54.0)	0.011	500 (50.0)	506 (50.6)	0.788
CCI, mean ± SD	1.80 ± 1.47	1.48 ± 1.31	<0.001	1.73 ± 1.47	1.67 ± 1.43	0.355
Previous RAASi use, *n* (%)	969 (84.4)	5524 (77.6)	<0.001	848 (84.8)	843 (84.3)	0.757
Previous HF hospitalization, *n* (%)	34 (3.0)	85 (1.2)	<0.001	33 (3.3)	19 (1.9)	0.050
Previous treatments, *n* (%)						
Diuretics	769 (67.0)	4095 (57.5)	<0.001	669 (66.9)	641 (64.1)	0.188
Aldosterone antagonists	236 (20.6)	998 (14.0)	<0.001	204 (20.4)	194 (19.4)	0.575
Beta-blocking agents	628 (54.7)	3629 (51.0)	0.018	537 (53.7)	529 (52.9)	0.720
Lipid-modifying agents	522 (45.5)	2891 (40.6)	0.002	430 (43.0)	422 (42.2)	0.718
Antidiabetics	446 (38.9)	1919 (26.9)	<0.001	375 (37.5)	378 (37.8)	0.890

CCI, Charlson Comorbidity Index; HF, heart failure; HK, hyperkalaemia; PSM, propensity score matching; RAASi, renin–angiotensin–aldosterone system inhibitor; SD, standard deviation.

Table 2 Mean number of potassium and creatinine tests in hyperkalaemia patients 12 months before and after the index date

	Before PSM		After PSM	
	HK patients	Non-HK patients	HK patients	Non-HK patients
Characterization period				
Potassium test, mean number ± SD	2.41 ± 2.44	2.50 ± 2.90	2.44 ± 2.52	2.74 ± 3.03
Creatinine test, mean number ± SD	2.54 ± 3.36	1.95 ± 2.15	2.65 ± 3.58	2.07 ± 2.17
12 months after inclusion				
Potassium test, mean number ± SD	3.04 ± 4.16	2.76 ± 3.94	2.98 ± 4.04	2.70 ± 3.86
Creatinine test, mean number ± SD	3.85 ± 4.44	2.51 ± 2.66	2.07 ± 2.17	2.68 ± 2.93

HK, hyperkalaemia; PSM, propensity score matching; SD, standard deviation.

With the aim to evaluate if HK could be associated with increased risk of CV events or death, the HR after PSM was calculated, and the analysis revealed that compared to non-HK, HK patients had a 37% and 70% higher risk of experiencing CV events and death, respectively (all $P < 0.001$) (*Figure 2* and *Table 3*).

A dramatic reduction of adherence to RAASi therapy was observed among adherent patients after HK onset: only 41.9% of patients remained adherent to therapy, while 36.4% were considered as non-adherent (PDC <80%) and 21.7% discontinued the treatment, as recommended by ESC guidelines.[2] Proportion of patients that discontinued ACEi, ARB and MRA is reported in online supplementary *Table S1*.

In the HK group, incidence rate of all-cause mortality was 12.8/100 person-years among adherent patients and 35.4/100 person-years among patients not adherent to therapy.

After HK onset, non-adherence to RAASi was found to be associated with a 39% increased risk of CV events ($P = 0.105$) and a twofold increased risk of mortality ($P < 0.001$) (*Figure 3* and *Table 4*).

Our results were also confirmed in the pre-PSM cohort previously reported by us,[12] and when the model was adjusted for

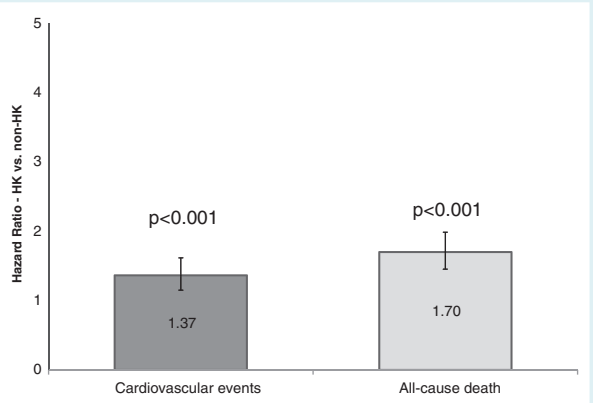

Figure 2 Risk of cardiovascular events or death in hyperkalaemia (HK) vs. non-HK patients.

Table 3 Risk of cardiovascular events, death or dialysis in hyperkalaemia (HK) vs. von-HK patients after propensity score matching

	Cardiovascular events		Death	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Non-HK	1	–	1	–
HK	1.37 (1.15–1.62)	<0.001	1.70 (1.46–1.99)	<0.001
Age	1.02 (1.01–1.03)	<0.001	1.06 (1.05–1.07)	<0.001
Male sex	1.49 (1.25–1.78)	<0.001	1.30 (1.11–1.51)	<0.001
CCI	1.13 (1.07–1.21)	<0.001	1.25 (1.19–1.32)	<0.001
Previous hospitalization related to HF	1.07 (0.71–1.61)	0.741	0.91 (0.63–1.31)	0.608
Previous drug treatments				
RAASi use	0.86 (0.66–1.13)	0.275	0.91 (0.71–1.16)	0.436
Diuretics (%)	0.99 (0.81–1.21)	0.923	1.52 (1.26–1.84)	<0.001
Aldosterone antagonists	1.20 (0.97–1.49)	0.087	1.23 (1.01–1.48)	0.036
Beta-blocking agents	1.09 (0.91–1.31)	0.348	0.87 (0.74–1.03)	0.099
Lipid-modifying agents	1.72 (1.05–1.55)	0.013	0.82 (0.70–0.97)	0.020
Antidiabetics	1.28 (1.05–1.55)	0.013	0.91 (0.76–1.08)	0.268
RAASi dosage	1.00 (1.00)	0.714	1.00 (1.00)	0.430

CCI, Charlson Comorbidity Index; CI, confidence interval; HF, heart failure; HR, hazard ratio; PSM, propensity score matching; RAASi, renin–angiotensin–aldosterone system inhibitor.

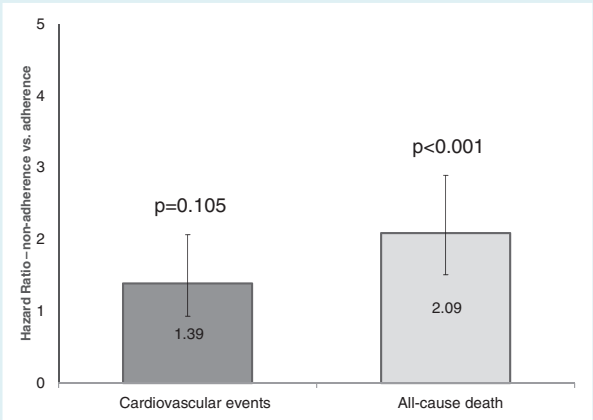

Figure 3 Risk of cardiovascular events or death in hyperkalaemia (HK) patients non-adherent vs. adherent to renin–angiotensin–aldosterone system inhibitor therapy (patients were considered as adherent to therapy if they had a proportion of days covered >80%).

potentially confounding variables (online supplementary *Tables S2* and *S3*).

Discussion

The main finding of the present real-world study is that HF patients with HK who were non-adherent or discontinued RAASi featured an enhanced mortality in comparison to patients who remained adherent to optimal RAASi therapy despite HK.

In particular, our study confirms and extends previous investigations[13,14] showing that compared to non-HK, HK patients had a significantly higher risk of experiencing CV events and death (*Figure 2*).

Table 4 Risk of cardiovascular events or death in patients non-adherent vs. adherent to renin–angiotensin–aldosterone system inhibitor therapy after propensity score matching[a]

	Cardiovascular events		Death	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Adherence	1	–	1	–
Non-adherence	1.39 (0.93–2.07)	0.105	2.09 (1.51–2.90)	<0.001
Age	0.99 (0.97–1.01)	0.514	1.03 (1.01–1.05)	0.002
Male sex	1.69 (1.11–2.57)	0.014	1.60 (1.14–2.25)	0.006
CCI	1.19 (1.06–1.34)	0.003	1.16 (1.05–1.29)	0.004

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.
[a]Due to the small sample size, only age, male gender and CCI were considered.

Additionally, the study confirmed that, accordingly to literature and clinical practice,[5,15] after HK onset, non-adherence or discontinuation of RAASi was observed in the majority of HF patients. Indeed, this translated in a greater incidence of mortality in this sub-group of patients. In this regard, after the onset of HK, non-adherence to RAASi was associated with a higher risk of CV events (39%) and a twofold higher risk of mortality (*Figure 3*). Overall, in the HK group, the incidence rate of all-cause mortality was 12.8/100 person-years among patients adherent and 35.4/100 person-years among patients non-adherent to RAASi therapy.

Restrictions in RAASi therapy in chronic HF patients who either feature HK or high potassium levels, even if often still in the 'normal range' (i.e. potassium level from 3.5 to 5.5 mmol/L), are suggested by current guidelines and observed in real-world clinical practice; however, questions were raised whether this is justified and appropriate.[16] Indeed, previous results showed that potassium levels or increases in potassium levels during RAASi up-titration within the relative 'normal' range did not interfere with the beneficial effects of these therapies and was not associated with worse outcomes,[17] being tolerated by patients. On

the contrary, previous results from the Randomized Aldactone Evaluation Study (RALES) showed that, regardless of the fact that HK did not interfere with the beneficial effects of spironolactone, it was associated with higher mortality rates.[18] This was confirmed by a population-based, time-series analysis of health care Canadian databases after RALES publication: spironolactone prescriptions highly increased in HF patients treated with ACEi, leading to a rise by a factor of about three of both the rate of hospital admission involving a diagnosis of HK and the rate of HK associated with in-hospital death among these patients ($P < 0.001$).[19] In such a perspective, ESC guidelines recommend to strictly monitor potassium level during RAASi therapy and to lower/discontinue RAASi treatment to minimize risks associated with HK. However, discontinuation or lowering of ACEi/ARB dosages was associated with more adverse outcomes,[7,15] suggesting that high potassium levels could contribute to severely adverse outcomes. These findings might have implications for clinical practice, suggesting that lowering potassium levels in patients with HK might lead to improved guideline-directed treatment with ACEi and ARB. These data are important considering the availability of new potassium-lowering drugs,[20] effective in keeping potassium levels within the normal range.[21,22] Hence, data on RAASi therapy and HK must be interpreted in the context of the benefits of RAASi with regard to CV mortality, always controlling for elevated potassium.[23–25]

At present, a tenable approach to maintain optimal RAASi dosages together with adequate potassium levels could be a more frequent, periodic, monitoring of serum potassium which is currently poor,[26,27] along with electrocardiogram, to catch the signs of impending threshold events. Assessment of renal function could also be performed at the same time intervals.

Study limitations

We acknowledge some limitations of the study, mainly due to the descriptive observational nature of the analysis, based on data collected through administrative databases. The first limitation concerns the lack of clinical information in administrative databases that could have been useful to further characterize patients, such as preservation or reduction in ventricular ejection fraction or concomitant presence of hypertension. Therefore, we cannot rule out any impact of unknown/unmeasured confounders. Moreover, a selection bias could be present since potassium level is more likely to be measured in patients at higher risk of dyskalaemia. Another limitation is related to the absence of information on dietary recommendations for altering potassium-rich foods. Ultimately, since data regarding pharmacological treatments were retrieved from pharmaceutical database, the actual use of drugs was not available.

Conclusions

In an unselected population of patients with HF, subjects with HK that were adherent to RAASi therapy experienced a lower mortality rate compared to those who were not adherent, in which a twofold increased risk of death was observed. Our findings are limited to the population analysed; however, they could stimulate further confirmatory investigation on how optimal treatment with RAASi, while minimizing HK-associated risks, can impact morbidity and mortality outcomes in HF patients.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Vifor Pharma Italia purchased the study report that is the basis for this manuscript. This manuscript was developed with Vifor Pharma Italia and CliCon S.r.l. The views expressed here are those of the authors and not necessarily those of the supporters. The agreement signed by Clicon S.r.l. and Vifor Pharma Italia does not create any entityship, joint venture or any similar relationship between parties. Clicon S.r.l. is an independent company. Neither CliCon S.r.l. nor any of their representatives are employees of Vifor Pharma Italia for any purpose. An extract of the manuscript was published in Italian language in G Ital Nefrol 2019;36:2019–vol5 (https://www.ncbi.nlm.nih.gov/pubmed/31580544).
Conflict of interest: none declared.

Appendix

LHUs Study Group

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