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Prevalence, clinical impact and costs of hyperkalaemia: Special focus on heart failure

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Abstract

Background: Hyperkalaemia is a potential life-threatening electrolyte abnormality. Although renin-angiotensin-aldosterone system inhibitors (RAASi) are potentially life-saving, they may contribute to hyperkalaemia.

Methods: The prevalence, comorbidities, comedications and 1-year outcomes of patients admitted or treated for hyperkalaemia were investigated in a large healthcare administrative database including 12 533 230 general population inhabitants. A similar analysis was performed in the Italian Network on Heart Failure (IN-HF), a cardiology registry of 1726 acute and 7589 chronic HF patients, stratified by serum potassium. General practice healthcare costs related to hyperkalaemia were also assessed. Hyperkalaemia was defined by hospital coding, potassium-binder prescription or serum levels (mild: 5-5.4, moderate-severe: ≥5.5 mmol/L).

Results: In the general population, the prevalence of hyperkalaemia was 0.035%. After excluding patients on haemodialysis, hyperkalaemia in the community (n = 2314) was significantly and directly associated with diabetes, chronic kidney disease, HF, RAASi prescriptions, 1-year hospitalisations and threefold annual healthcare costs, compared to age- and sex-matched non-hyperkalaemic subjects (n = 2314). In the IN-HF registry, hyperkalaemia affected 4.3% of acute and 3.6% of chronic patients and was significantly associated with diabetes, kidney disease and lesser use of RAASi, compared to normokalaemic patients. Among patients hospitalised for acute HF, those with hyperkalaemia at entry had significantly higher 1-year all-cause mortality compared with normokalaemic patients, even after adjustment for available confounders.

Conclusions: Hyperkalaemia in the general population, although uncommon, was associated with increased hospitalisations and tripling of healthcare costs. Among HF patients, hyperkalaemia was common and associated with underuse of RAASi; in acutely decompensated patients, it remained independently associated with 1-year all-cause mortality.

KEYWORDS

health care costs, heart failure, hospitalisation, hyperkalaemia, mortality, renin-angiotensin-aldosterone inhibitors

1 | INTRODUCTION

Hyperkalaemia is common in patients with chronic kidney disease (CKD) and heart failure (HF); its occurrence increases markedly when patients are prescribed one or more renin-angiotensin-aldosterone system inhibitors (RAASi), that is any combination of angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA) or angiotensin receptor-neprilysin inhibitors (ARNI).[1] RAASi are strongly recommended in patients with HF and/or CKD, as they reduce all-cause mortality and the need for rehospitalisation in patients with impaired left ventricular ejection fraction,[2,3] as well as proteinuria and decline of glomerular filtration rate in patients with CKD.[4] RAASi are typically not prescribed or discontinued in the presence or for fear of hyperkalaemia, as the latter (like hypokalaemia) can lead to cardiac arrhythmias and increased mortality.[5] About one in five patients with moderate-severe CKD develops hyperkalaemia (>5.5 mmol/L) and many have recurrent episodes.[6]

The availability of new oral potassium binders[7,8] has rekindled an interest in the epidemiology, treatment and prevention of hyperkalaemia, specifically in HF patients with reduced left ventricular ejection fraction. In these patients, the use of RAASi at appropriate doses is growing in order to offer their benefits to all patients, but may be hampered by the presence or fear of hyperkalaemia. What happens in current clinical practice is not clear. Epidemiological studies including administrative data and specialty registries provide information on different aspects of current management.

The present study aimed firstly to analyse an unselected community setting of more than 12 million subjects to assess: (a) the prevalence of hyperkalaemia in the general population, (b) its comorbidities and (c) related healthcare costs. Moreover, to gain information on hyperkalaemia in the setting of HF, we analysed the Italian Network on Heart Failure (IN-HF) registry database in order to assess: (d) the prevalence, comorbidities, comedications and prognostic impact of hyperkalaemia among acute (hospitalised) and chronic (outpatient) HF patients.

2 | METHODS

2.1 | Community database

Administrative data flows (the same periodically sent to the Italian Health Ministry) were transferred from several local Italian health authorities to the nonprofit Ricerca e Salute (ReS) Foundation, whose database is physically located within the Consorzio Interuniversitario del Nord Est italiano per il Calcolo Automatico (CINECA) Institution. CINECA is a large, nonprofit consortium of Italian Universities, established in 1969, equipped with supercomputing tools that allow ReS to ensure: (a) quality and (b) security of data management at International standards. Retrospective analyses were carried out on the ReS population-based database that links demographics, drug prescriptions, hospital records and outpatient specialist examinations and procedures.

Demographics were made anonymous. Dose, number of packages, dispensing date and cost of medicinal products or generics reimbursed by the Italian National Health System (INHS) were obtained from free-filled prescriptions. Anatomical therapeutic chemical classification[9] was used. Hospital diagnoses and procedures were defined by the ninth International Classification of Disease (ICD-IX-CM).[10,11] Outpatient specialist examinations and invasive/noninvasive diagnostic or interventional procedures, as defined by national classifications, were also recorded. Given the anonymous analysis of administrative data for institutional purposes, ethical approval was not required.

The hyperkalaemic patient cohort was identified, between 1 January and 31 December 2014, as patients who either were hospitalised and discharged alive with a primary or secondary ICD-IX-CM diagnosis of hyperkalaemia or had received at least one prescription of sodium polystyrene sulphonate. For patients not receiving dialysis during 2013-2015, a nested case-control analysis was conducted that compared hyperkalaemic patients (cases) to non-hyperkalaemic subjects (controls) identified in 2014 and matched for age, gender and area of residency in a 1:1 ratio.

From the earliest date of either hospital discharge or potassium-binder prescription (index date), each patient and controls were followed for a year up to 31 December 2015 or until death (whichever came first). Comorbidities and drugs known to be generally associated with hyperkalaemia were identified in the year preceding the index date. Mean costs per capita during follow-up were assessed for cardiovascular and noncardiovascular drugs (public prices reimbursed by the INHS), hospitalisations (national tariffs, according to 2008 Diagnostic-Related Grouping) and outpatient specialist care (national tariffs). Only direct INHS resources were considered.

2.2 | IN-HF registry

The IN-HF registry is a nationwide prospective observational study conducted within hospital cardiology institutions across Italy. Data collection was centralised and web based. Chronic HF patients were enrolled during routine outpatient visits; the diagnosis of chronic HF was left to the attending cardiologist with the recommendation to follow the diagnostic rules described in the most recent ESC guidelines.[2] Acute HF patients were enrolled if treated intravenously with diuretics or vasodilators or inotropes after admission to a cardiology ward for worsening or de novo acute HF. Exclusion criteria were age <18 years or unwillingness to participate. Patients were followed for 1 year.

Details on study design and methods are published elsewhere.[12,13] Specifically, clinical status during follow-up was ascertained by visit or by telephone interview for those unable to attend the clinic. Cause of death was ascertained by hospital records, death certificates, autopsy records or contacting the patient's general practitioner or referring cardiologist. Consecutiveness of enrolment was recommended but not checked by site visits. Patients gave written informed consent to the anonymous handling of their data. Local Institutional Review Boards approved the study according to national rules. Decisions on drugs and diagnostic/therapeutic procedures were left to the participating cardiologists. Contemporary guidelines on the management of acute and chronic HF were discussed, and adherence was encouraged during investigator meetings. HF patients were stratified by baseline potassium: <3.5 (hypokalaemia), 3.5-4.9 (normokalaemia), 5-5.4 (mild hyperkalaemia) and ≥5.5 mmol/L (moderate-to-severe hyperkalaemia).

Categorical variables are presented as percentages, continuous variables as means and standard deviations (SD) if normally distributed and as medians and interquartile ranges (IQR) if not. Variables were compared by chi-square test, *t* test or Mann-Whitney *U* test as appropriate. A multivariable analysis of HF patients was conducted to identify independent predictors of 1-year all-cause mortality and hospitalisations. Included in the model were statistically significant variables at hospital entry on univariable analysis, as well as variables considered of specific clinical interest, namely: age, gender, systolic blood pressure (SBP), chronic obstructive pulmonary disease, CKD (defined as American National Kidney Foundation stage ≥2), history or ECG evidence of atrial fibrillation (AF), ischaemic heart disease, haemoglobin <12 g/dL, sodium <136 mEq/L, creatinine >1.5 mg/dL or blood urea nitrogen (BUN) >50 mg/dL. Age and SBP were analysed as continuous variables, blood chemistry values as categorical variables using clinical cut-offs. Drug treatment was not included in the multivariable analysis. Associations between variables and 1-year outcomes are expressed as hazard ratios with 95% confidence intervals; time to event curves was compared by log-rank test. Analyses were performed using SAS system software (SAS Institute Inc); a two-sided *P*-value < .05 was considered statistically significant. Reporting of the study conforms to broad EQUATOR guidelines.[14]

3 | RESULTS

3.1 | Hyperkalaemia in the general population

From a community of 12 533 230 inhabitants, 3732 adult subjects (35.4 × 100 000) experienced hyperkalaemia as defined

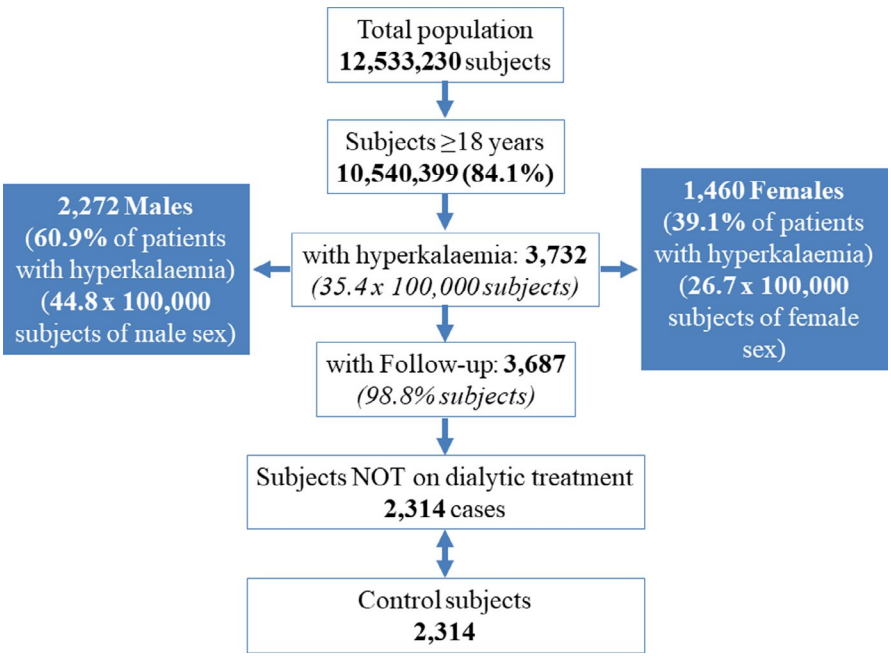
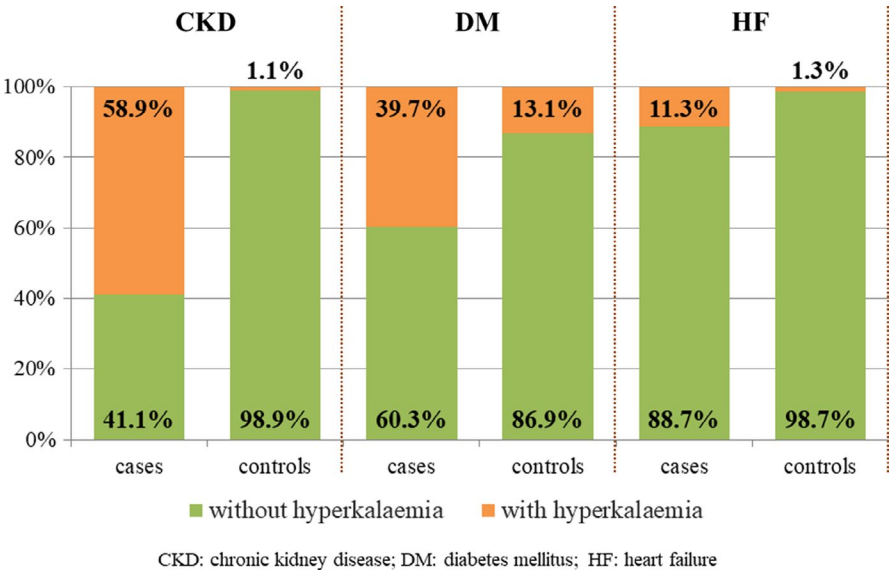


FIGURE 1 Community study population: hyperkalaemic patients in a large sample drawn from the general population



CKD: chronic kidney disease; DM: diabetes mellitus; HF: heart failure

FIGURE 2 Prevalence of CKD, DM and HF in patients with (cases) or without hyperkalaemia (matched controls), drawn from a large community sample

TABLE 1 Average annual healthcare costs of hyperkalaemic cases (not on haemodialysis) and of subjects without hyperkalaemia (controls) in a large sample drawn from the general population

	Cases		Controls	
Administrative flow	**Average cost per case (n = 2314)**	**% of total cost**	**Average cost per control (n = 2314)**	**% of total cost**
Drugs	€ 1868	27.5	€ 539	29.2
Sodium polystyrene sulphonate	€ 75	4.0	€ 0	0.0
Other drugs	€ 1793	96.0	€ 539	100.0
CV drugs	€ 383	20.5	€ 183	34.0
Non-CV drugs	€ 1410	75.5	€ 355	66.0
Hospitalisations	€ 4265	62.8	€ 1006	54.6
At index event	€ 952	22.3	€ 2	0.2
After index event	€ 3313	77.7	€ 1004	99.8
Specialty visits	€ 653	9.6	€ 298	16.2
Total	€ 6786	100.0	€ 1843	100.0

above in the year 2014. Of these, 1373 were on dialytic treatment (36.7%) and 45 (1.2%) lacked follow-up information. Thus, the final study population consisted of 2314 hyperkalaemic cases and 2314 age-, sex- and residency-matched non-hyperkalaemic controls (Figure 1). Mean age (±SD) of cases and controls was 73 ± 14 years; 39% were female. CKD was reported in 58.9% of cases and in 1.1% of controls. Diabetes and HF were reported in 39.7% and 11.3% of cases vs 13.1% and 1.3% of controls (Figure 2). Figure S1 shows the rates of the most prescribed drugs among hyperkalaemic cases and corresponding controls. During the 1-year follow-up, 56.7% of cases were admitted to hospital at least once, vs 14.7% of controls. For the INHS, the average annual cost per hyperkalaemic subject was 6786€, vs 1843€ for controls, with hospitalisation being the most important cost driver (Table 1).

3.2 | Hyperkalaemia in patients admitted for HF

Among the 1726 acute HF patients included in the IN-HF registry, 169 (9.8%) presented a potassium level <3.5 mmol/L, 1335 (77.3%) between 3.5 and 4.9 mmol/L, 148 (8.6%) between 5 and 5.4 mmol/L and 74 (4.3%) ≥5.5 mmol/L. Table 2 reports the clinical characteristics of the four different groups. Hospitalised HF patients with moderate-to-severe hyperkalaemia (≥5.5 mmol/L) were more frequently hypotensive, with a history of diabetes mellitus and CKD, with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 and treated significantly less frequently with RAASi compared with hospitalised HF patients without hyperkalaemia. In contrast, patients with hypokalaemia at hospital entry presented less frequently renal dysfunction, had a higher left ventricular

TABLE 2 Characteristics of patients admitted for acute heart failure (n = 1726) stratified by potassium levels

	Serum potassium at entry (mmol/L)				
	<3.5 (n = 169)	**3.5-4.9 (n = 1335)**	**5-5.4 (n = 148)**	**≥5.5 (n = 74)**	***P*-value**
Age (y), median [IQR]	72 [63-80]	75 [66-81]	74 [68-82]	77 [69-82]	.11
Females, %	42.0	40.8	41.9	44.6	.92
BMI (kg/m^2), median [IQR]	27 [24-31]	27 [24-31]	27 [24-30]	27 [24-30]	.73
SBP (mm Hg), median [IQR]	130 [110-160]	130 [110-150]	129 [110-150]	120 [100-145]	.04
SBP <110 mm Hg, %	23.8	18.3	21.2	37.8	.0003
HR (bpm), median [IQR]	90 [75-107]	90 [74-110]	89 [71-105]	92 [75-110]	.68
Ischaemic aetiology, %	41.7	41.6	49.3	42.5	.36
Treated hypertension, %	62.1	58.9	62.8	56.8	.66
Diabetes, %	30.2	38.9	52.0	54.1	<.0001
History of AF or AF occurred during hospitalisation, %	44.4	46.8	41.9	33.8	.12
Prior stroke/TIA, %	9.5	9.3	6.1	8.1	.62
CKD, %	26.0	30.3	47.3	60.8	<.0001
EF <40%, % available for 1623 pts	52.2	56.6	65.9	61.8	.08
EF (%), median [IQR] available for 1623 pts	37 [26-50]	35 [26-46]	35 [25-42]	33 [25-41]	.03
Moderate/severe mitral regurgitation, % available for 1325 pts	69.4	74.9	24.6	42.3	.03
Serum creatinine (mg/dL), median [IQR]	1.00 [0.90-1.30]	1.16 [0.94-1.52]	1.41 [1.12-2.02]	1.90 [1.50-2.90]	<.0001
Serum creatinine >1.5 mg/dL, %	15.2	25.6	43.8	72.2	<.0001
eGFR <30 mL/min/1.73 m^2, %	8.1	10.7	28.8	45.1	<.0001
Pharmacological treatment at discharge (1592 pts discharged alive)					
ACEi/ARBs, %	75.2	75.9	69.6	62.5	.07
Beta-blockers, %	55.4	62.8	63.7	57.1	.27
MRAs, %	69.4	53.4	42.2	42.9	<.0001
ACEi/ARBS + MRAs, %	49.7	42.6	31.9	32.1	.008
Digitalis, %	26.1	25.3	17.0	17.9	.11

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BMI, body mass index; bpm, beats per minute; CKD, chronic kidney disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HR, heart rate; IQR, interquartile range; MRAs: mineralocorticoid receptor antagonists; SBP, systolic blood pressure; TIA, transient ischaemic attack.

ejection fraction and were treated more frequently with MRAs and digitalis compared to those without. One-year all-cause and cardiovascular (CV) mortality were significantly higher in hyperkalaemic vs normokalaemic hospitalised HF patients, while re-hospitalisations occurred at similar rates (upper Table 3 and Figure 3, panel A). Multivariable analysis confirmed the independent association of increasing levels of potassium with 1-year all-cause mortality.

3.3 | Hyperkalaemia in patients with chronic HF

Among the 7589 chronic HF patients included in the IN-HF registry, 183 (2.4%) presented a potassium level <3.5 mmol/L, 6250 (82.4%) between 3.5 and 4.9 mmol/L, 881 (11.6%) between 5 and 5.4 mmol/L and 275 (3.6%) ≥5.5 mmol/L. Table 4 reports the clinical characteristics of the four different groups. Chronic HF patients with hyperkalaemia were older, with a more frequent history of ischaemic disease, diabetes mellitus and CKD vs normokalaemic patients. Renal dysfunction assessed by a higher creatinine level and a lower eGFR was significantly more frequent in hyperkalaemic patients, and, similarly to acute HF, recommended treatments such as RAASi were prescribed less frequently. Patients with hypokalaemia, instead, more frequently were female, in advanced New York Heart Association class, diagnosed AF, prior stroke and mitral regurgitation, and receiving MRAs and digitalis compared to those without.

TABLE 3 One-year mortality and hospitalisations of patients with acute or chronic heart failure stratified by potassium levels

Patients with acute HF					
A. Univariate analysis					
	Serum potassium at entry (mmol/L)				***P*-value**
	<3.5 (n = 169)	**3.5-4.9 (n = 1335)**	**5-5.4 (n = 148)**	**≥5.5 (n = 74)**	
All-cause death, %	24.9	22.0	37.8	50.0	<.0001
CV death, %	14.8	17.2	25.7	41.9	<.0001
Hospitalised pts[a], %	36.3	29.4	32.6	37.5	.19
Pts hospitalised for CV cause[a], %	23.6	23.3	24.4	26.8	.94
Pts hospitalised for HF[a], %	17.2	15.9	11.1	23.2	.19
B. Multivariable analysis. Associations between variables and outcomes are expressed as hazard ratios and 95% confidence intervals, with normokalaemia as reference					
	Serum potassium at entry (mmol/L)				
	<3.5 (n = 169)	**3.5-4.9 (n = 1335)**	**5-5.4 (n = 148)**	**≥5.5 (n = 74)**	
All-cause death[b] Hazard ratio (95% CI)	1.15 (0.82-1.61)	1	1.42 (1.05-1.91)	1.73 (1.21-2.49)	
All-cause hospitalisations[c] Hazard ratio (95% CI)	1.19 (0.89-1.60)	1	1.11 (0.81-1.53)	1.24 (0.78-1.98)	
Patients with chronic HF					
A. Univariate analysis					
	Serum potassium (mmol/L)				***P*-value**
	<3.5 (n = 183)	**3.5-4.9 (n = 6250)**	**5-5.4 (n = 881)**	**≥5.5 (n = 275)**	
All-cause death, %	14.2	7.1	7.0	9.5	.002
CV death, %	11.5	5.0	4.9	8.0	.0002
All-cause hospitalisations, %	31.2	22.0	25.2	24.0	.003
CV hospitalisation, %	23.0	15.9	18.2	18.6	.02
HF hospitalisation, %	11.5	8.5	9.4	9.8	.40
B. Multivariable analysis. Associations between variables and outcomes are expressed as hazard ratios and 95% confidence intervals, with normokalaemia as reference.					
	Serum potassium (mmol/L)				
	<3.5 (n = 183)	**3.5-4.9 (n = 6250)**	**5-5.4 (n = 881)**	**≥5.5 (n = 275)**	
All-cause death[d] Hazard ratio (95% CI)	1.48 (0.98-2.25)	1	0.92 (0.70-1.20)	1.04 (0.69-1.58)	
All-cause hospitalisations[e] Hazard ratio (95% CI)	1.22 (0.93-1.61)	1	1.09 (0.94-1.26)	1.003 (0.78-1.30)	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, heart rate; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; Pts, patients; SBP, systolic blood pressure; TIA, transient ischaemic attack.

[a]1592 pts discharged alive.; [b]Variables inserted: age, SBP, HR (as continuous), female gender, clinical presentation at entry [NYHA III, NYHA IV, acute pulmonary oedema, cardiogenic shock, unknown, NYHA III as reference], worsening vs de novo HF, BMI [<22, 22-25, 26-30, >30, unknown, >30 as reference], ischaemic heart disease, stroke/TIA, peripheral arterial disease, renal dysfunction, peripheral congestion, mitral regurgitation [no, yes, unknown, no as reference], creatinine at entry >1.5 [no, yes, unknown, no as reference], ACEi/ARBs, MRA, beta-blockers, prior hospitalisation.; [c]Variables inserted: age, SBP at discharge (as continuous), female gender, worsening vs de novo HF, smoking habit [no, current, former, unknown, no as reference], renal dysfunction, previous device, creatinine at entry >1.5 [no, yes, unknown, no as reference], peripheral congestion and NYHA III-IV at discharge, ACEi/ARBs, MRA and beta-blockers at discharge.; [d]Variables inserted: age, SBP, HR (as continuous), female gender, BMI [<22, 22-25, 26-30, >30, >30 as reference], NYHA III-IV, ejection fraction [<40, 40-50, >50, unknown, >50 as reference], ischaemic heart disease, treated hypertension, peripheral vascular disease and renal dysfunction [no, yes, unknown, no as reference], previous device, rales, peripheral oedema, atrial fibrillation (history or during hospitalisation), mitral regurgitation [no, yes, unknown, no as reference], creatinine at entry >1.5 [no, yes, unknown, no as reference], ACEi/ARBs, beta-blockers, MRA.; [e]Variables inserted: age, SBP, HR, BMI (as continuous), female gender, NYHA III-IV, ejection fraction [<40, 40-50, >50, unknown, >50 as reference], ischaemic heart disease, smoking habit [no, current, former, unknown, no as reference], diabetes, stroke/TIA, peripheral arterial disease [no, yes, unknown, no as reference], renal dysfunction [no, yes, unknown, no as reference], malignancy, previous device, peripheral oedema, rales, atrial fibrillation (history or during hospitalisation), mitral regurgitation [no, yes, unknown, no as reference], creatinine at entry >1.5 [no, yes, unknown, no as reference], uric acid at entry >6.9 [no, yes, unknown, no as reference], ACEi/ARBs, beta-blockers, MRA.

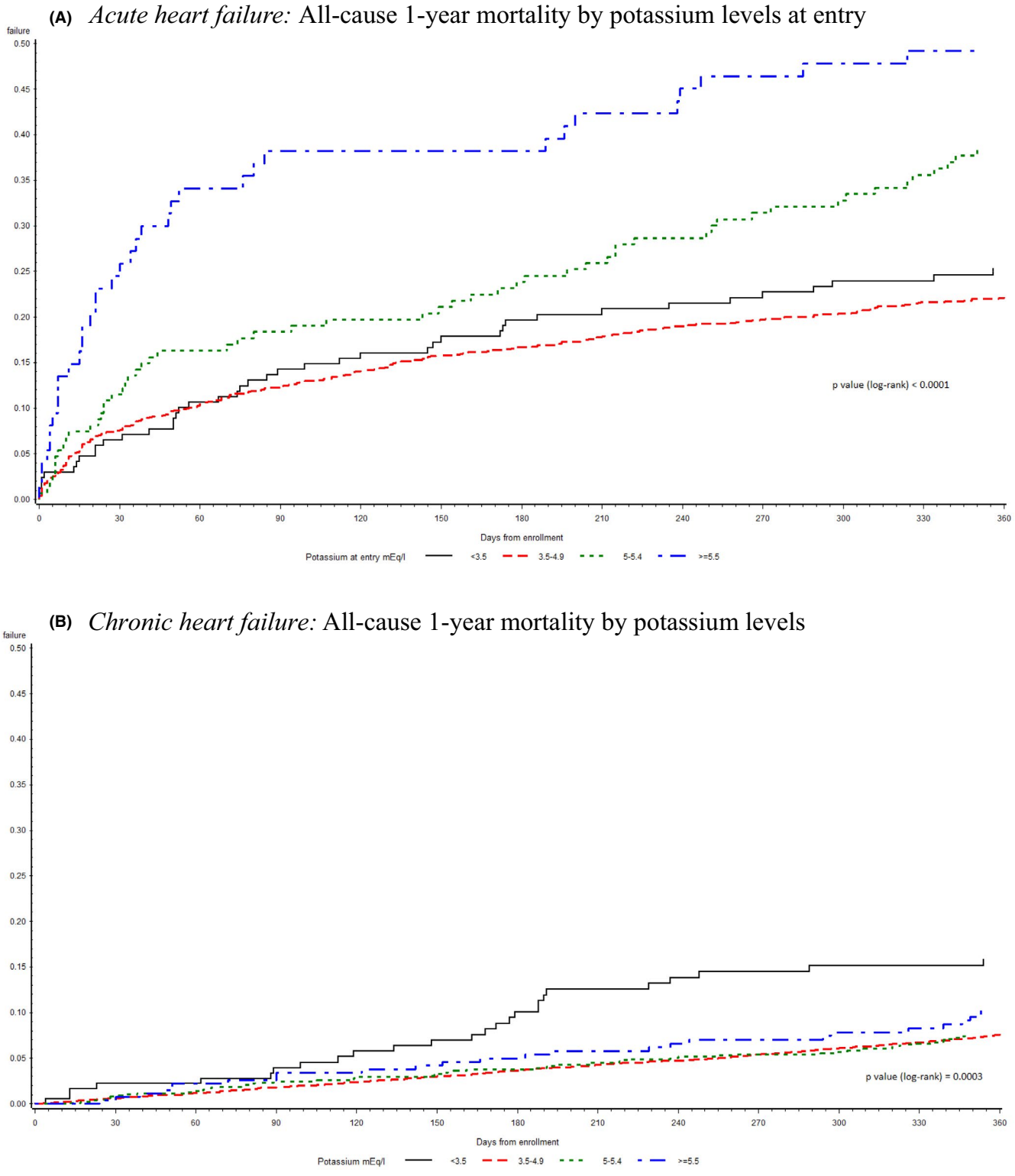


FIGURE 3 HF-study population: all-cause 1-year mortality in acute (A) or chronic (B) HF patients stratified by serum potassium levels. Panel A—Acute heart failure: All-cause 1-year mortality by potassium levels at entry. Panel B—Chronic heart failure: All-cause 1-year mortality by potassium levels

One-year all-cause and CV mortality rates were numerically higher and significantly different at univariate analysis (Figure 3, panel B) among hypokalaemic and hyperkalaemic chronic HF patients vs normokalaemic ones, but the differences did not reach conventional statistical significance after multivariable analysis (lower Table 3). No significant differences among groups were observed for the occurrence of HF hospitalisations (Table 3).

TABLE 4 Characteristics of patients with chronic heart failure (n = 7589) stratified by potassium levels

	Serum potassium (mmol/L)				
	<3.5 (n = 183)	**3.5-4.9 (n = 6250)**	**5-5.4 (n = 881)**	**≥5.5 (n = 275)**	***P*-value**
Age (y), median [IQR]	71 [62-78]	70 [60-77]	71 [62-78]	73 [65-79]	<.0001
Age (y) ≥70, %	57.4	51.0	56.3	62.2	<.0001
Females, %	35.5	26.8	23.6	30.6	.003
BMI (kg/m^2), median [IQR]	25 [23-29]	26 [23-29]	26 [23-29]	26 [23-29]	.52
SBP (mm Hg), median [IQR]	120 [110-140]	130 [110-140]	125 [110-140]	130 [115-140]	.18
HR (bpm), median [IQR]	75 [65-86]	71 [64-80]	72 [63-82]	74 [64-86]	.04
NYHA III-IV, %	43.2	23.9	24.2	25.8	<.0001
Ischaemic aetiology, %	39.4	41.9	48.2	48.5	.0007
Treated hypertension, %	32.2	28.5	31.6	27.6	.20
Diabetes, %	29.0	25.5	30.0	38.2	<.0001
History of AF or AF during hospitalisation, %	43.1	33.6	31.3	37.3	.01
Prior stroke/TIA, %	12.6	7.7	7.6	10.6	.03
CKD, % available for 4004 pts	33.3	27.9	39.5	51.1	<.0001
EF <40%, % available for 5249 pts	69.7	64.2	63.5	64.0	.57
EF (%), median [IQR] available for 5249 pts	32 [25-45]	35 [28-43]	35 [28-44]	35 [29-44]	.24
Moderate/severe mitral regurgitation, % available for 4657 pts	33.8	18.6	18.1	17.3	.0002
Serum creatinine (mg/dL), median [IQR] available for 7205 pts	1.2 [0.9-1.5]	1.1 [0.9-1.4]	1.3 [1.0-1.7]	1.6 [1.1-2.0]	<.0001
Serum creatinine >1.5 mg/dL, % available for 7205 pts	21.5	19.2	33.2	51.2	<.0001
eGFR <30 mL/min/1.73 m^2, % available for 7057 pts	8.8	6.2	13.4	24.9	<.0001
ACEi/ARBs, %	80.3	87.6	87.9	79.3	<.0001
Beta-blockers, %	60.1	60.9	61.2	60.4	.99
MRAs, %	62.3	44.6	41.5	33.1	<.0001
ACEi or ARBS+MRAs, %	53.0	39.0	36.8	25.8	<.0001
Digitalis, %	39.3	33.6	30.2	26.9	.008

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BMI, body mass index; bpm, beats per minute; CKD, chronic kidney disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HR, heart rate; IQR, interquartile range; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack.

4 | DISCUSSION

Hyperkalaemia is receiving renewed attention following recent clinical trials testing innovative oral potassium binders.[7,8,14,15] Focus on hyperkalaemia is justified by concerns regarding this often asymptomatic and potentially life-threatening electrolyte disorder and by the associated under-prescription of beneficial potassium-sparing medications in patients with HF or CKD. We investigated the current burden and clinical epidemiology of hyperkalaemia in the general population and, more specifically, in HF patients using two large contemporary databases: the administrative ReS database and the IN-HF cardiology registry.

The most important emerging findings are as follows:

- in the general population, patients with hyperkalaemia are more frequently affected by CKD, diabetes and HF, and use more RAASi than matched controls. Although

hyperkalaemia in the community was uncommon (0.035% in the present analysis), over 50% of those affected were admitted to hospital during a 1-year follow-up, with tripling of yearly healthcare costs compared with non-hyperkalaemic individuals of the same age, sex and area of residency;
- in patients with acute and chronic HF, the prevalence of hyperkalaemia is two orders of magnitude greater than in the general population (3.6%-4.3%) and is associated with underuse of RAASi; diabetes mellitus and CKD were the most frequent comorbidities;
- among those admitted for acute HF, 1-year all-cause and CV mortality rates are high (>40%) and hyperkalaemia remains a significant predictor of increased 1-year all-cause mortality, even after adjustment for relevant prognostic factors;
- among chronic HF patients, 1-year mortality is <10% and hyperkalaemia, although associated with numerically higher rates of total and CV mortality, was not a significant independent predictor of death;
- hypokalaemia in both acute and chronic HF patients showed a numerically higher mortality rate compared with normokalaemic patients, but was not independently associated with all-cause mortality at 1 year.

4.1 | Hyperkalaemia in the general population

In an Italian community of over 12 million subjects, hyperkalaemia, defined by hospital diagnosis or by the need of potassium-binder prescriptions (Figure 1), was not frequent, in agreement with observations from North America.[16] As reported by others,[17-20] most cases were associated with CKD, diabetes mellitus and/or HF (Figure 2). In the general population, we additionally found a greater than threefold risk of hospitalisation and healthcare costs in the year that followed diagnosis of hyperkalaemia, both of which might be abatable by specific and safe treatments. A possible cause of hyperkalaemia is the use of RAASi, such as ACE inhibitors, angiotensin receptor blockers, MRAs or ARNI[17,21]; these medications are specifically recommended for the clinical conditions in which hyperkalaemia more frequently occurs. As a consequence, hyperkalaemia is generally a deterrent for the use of these potentially life-saving therapies, determining, in addition to the negative role of hyperkalaemia itself, an unfavourable impact on patients with CKD, HF or diabetes.[21-23] Large observational studies have demonstrated an association between hyperkalaemia and an increased risk of death.[21,24-26] Until recently, there has been a dearth of drugs for the long-term prevention of hyperkalaemia; urgent treatments, in addition to diuretics and dialysis, involve the administration of sodium polystyrene sulphonate, intravenous insulin-glucose or sodium bicarbonate and nebulised beta-agonists[17] that may be contraindicated in diabetic or HF patients. Since the new potassium binders are not yet reimbursed by the Italian NHS, in our cohort the treatment of hyperkalaemia did not substantially change over time, with patients generally being treated with sodium polystyrene sulphonate. The availability of oral drugs able to safely treat hyperkalaemia[27] and, even more relevantly, to prevent the occurrence of hyperkalaemia in high-risk patients, allowing the initiation or continuation of RAASi therapy at optimal doses, could likely reduce the negative impact of this severe electrolyte imbalance on patients' outcomes.

4.2 | Impact of hyperkalaemia in patients with HF

Some decades ago, when only digitalis and diuretics were used to treat HF patients, hypokalaemia was frequent and worrisome. Nowadays, the widespread use of RAASi, while shown to improve patients' outcomes, is also associated with an increased risk of hyperkalaemia.[5] In the IN-HF registry database, HF patients developed hyperkalaemia rather frequently (3.6%-4.3%) with possible recurrent episodes. The risk of hyperkalaemia in HF patients is generally strongly associated with some degree of reduced kidney function and diabetes mellitus.[5] In the IN-HF registry, CKD affected 61% of hyperkalaemic acute HF patients and was twice as common than in patients with normal or reduced potassium values (<3.5 or 3.5-4.9 mmol/L) (Table 2). Importantly, our data in a contemporary Italian registry confirm that hyperkalaemia is still associated with severe clinical outcomes and death in HF patients, generally owing to life-threatening ventricular arrhythmias or progression of renal dysfunction.[5,20,23] Our analyses further confirm the following: (a) the strict association between CKD or diabetes and hyperkalaemia in both acute and chronic HF patients, (b) the fact that hyperkalaemic patients are treated less frequently with RAASi, (c) the graded relation between serum levels of potassium and 1-year all-cause and CV mortality among patients admitted for decompensation; in these patients, mortality remains very high, and hyperkalaemia was confirmed as an independent predictor of 1-year all-cause mortality.

4.3 | Strengths and limitations

4.3.1 | Population-based database

Advantages of administrative data include the breadth of coverage and the ability to perform long-term follow-up of

drug prescriptions and hospitalisations. Although the present database covers only one fifth of the entire Italian population, the analysed sample appropriately represents Italy as a whole in terms of demographics (Figure S2). As in all administrative data sets, the type and number of variables were limited, with lack of some baseline clinical, diagnostic and prognostic measures.

4.3.2 | IN-HF registry

Its main advantage is the fact that participating centres are part of a major Italian cardiology network. Its limitations are related to its strengths, in that patients were enrolled in cardiology centres and, therefore, do not include patients who died in emergency wards, or those admitted to noncardiac wards or those followed by general practitioners or internal medicine doctors. Hence, this registry does not depict the whole epidemiology of HF, but rather the epidemiology as managed by cardiologists. The absence of periodical potassium determinations is a potential limitation, common to many investigations including ours.

4.4 | Conclusions

The present analysis of two contemporary Italian databases indicates that hyperkalaemia in the community occurs more frequently in patients with CKD, diabetes mellitus, HF and in those treated with drugs that inhibit the RAAS. Over 50% of community patients with hyperkalaemia needed hospital admission at 1 year with consequent elevated costs for the local NHS. Among acute HF patients, our analysis confirms that hyperkalaemia remains an independent predictor of all-cause mortality. In both acute and chronic HF patients, hyperkalaemia was associated with underuse of life-saving treatments such as RAASi. This, in addition to the risk of death from hyperkalaemia itself, is bound to have an unfavourable impact on patients' outcomes. The role of new oral potassium binders to treat hyperkalaemia (and likely probably also to maintain normokalaemia over time) needs to be further investigated with the aim of allowing the continuation of RAASi treatments at appropriate doses in patients with this potentially life-threatening electrolyte abnormality or in those at high risk of developing it.

CONFLICT OF INTEREST

APM reports receiving personal fees from Bayer, Fresenius, Novartis for the participation in study committees outside the present work. FA reports receiving speaker or consultancy fees from Amgen, Bayer, B-I, BMS/Pfizer and Daiichi Sankyo outside the present work. SC, MI, CP, LD and NM report no conflicts of interest to disclose.

AUTHORS CONTRIBUTIONS

All authors contributed to the whole content of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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