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RESEARCH ARTICLE

Management of patients with heart failure at high risk of hyperkalaemia: The CARE-HK in HF registry

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Aims Patients with heart failure (HF) at high risk for hyperkalaemia are underrepresented in prospective HF registries. The CARE-HK in HF registry sought to characterize prospectively the clinical profile, management, and outcomes for patients with HF at high risk of hyperkalaemia.

Methods and results CARE-HK in HF was a multinational prospective registry of outpatients with HF (regardless of left ventricular ejection fraction [LVEF]) treated with an angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker/angiotensin receptor–neprilysin inhibitor (ACEI/ARB/ARNI) and either receiving or potential candidate for a mineralocorticoid receptor antagonist (MRA). All patients were at increased risk of hyperkalaemia, defined as hyperkalaemia at baseline, prior hyperkalaemia, or estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2. Outcomes included

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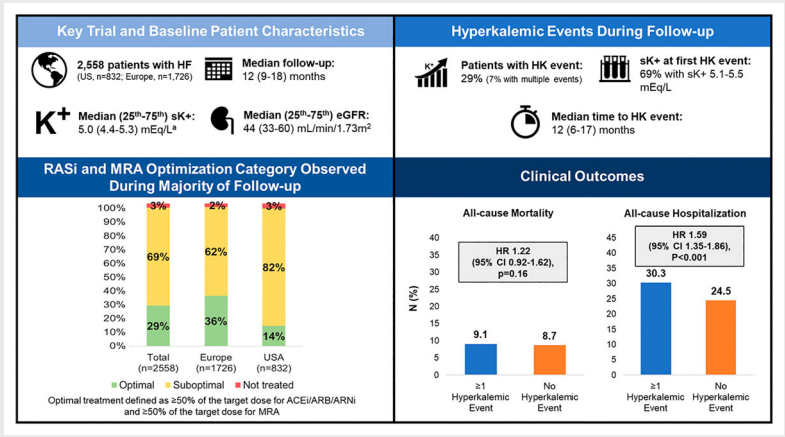
frequency of hyperkalaemic events (defined by clinician report with associated potassium value), achievement of renin–angiotensin system inhibitor (RASi) optimization (defined as ≥50% target doses for ACEI/ARB/ARNI and MRA), medication changes following hyperkalaemic episodes, and clinical events. Overall, 2558 patients from 111 sites across nine countries were included. Median (25th–75th) age was 73 (65–80) years, 32% were women, 61% had LVEF ≤40%, and 40% had prior laboratory evidence of hyperkalaemia. Median baseline eGFR and serum potassium were 44 (33–60) ml/min/1.73 m^2 and 5.0 (4.4–5.3) mEq/L, respectively. Over a median follow-up of 12.3 (9.4–18.1) months, 29% of patients had a hyperkalaemic event, and 7% had multiple events. In characterizing treatment prescribed for most of follow-up, 29% of patients received optimal RASi/MRA therapy, 69% received suboptimal RASi/MRA therapy, and 3% received no RASi/MRA. In the 30 days following the first hyperkalaemic event, RASi/MRA was down-titrated or discontinued in 3.6% of cases. Potassium binder use was low (patiromer 9.1%, sodium zirconium cyclosilicate 5.9%). Compared with patients without a hyperkalaemic event, patients experiencing a hyperkalaemic event had similar risk of all-cause mortality (hazard ratio [HR] 1.22, 95% confidence interval [CI] 0.92–1.62, $p = 0.16$) and a higher risk of subsequent hospitalization (HR 1.59, 95% CI 1.35–1.86, $p < 0.001$).

Conclusions In this contemporary multinational prospective registry of patients with HF at high risk for hyperkalaemia, hyperkalaemic events were common but infrequently associated with RASi/MRA modification or potassium binder use. Fewer than one in three patients received optimal RASi/MRA therapy for the majority of follow-up, and hyperkalaemic events were associated with higher risk of adverse clinical outcomes.
Clinical Trial Registration: ClinicalTrials.gov NCT04864795.

Graphical Abstract



Primary results of the CARE-HK in HF registry. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HK, hyperkalaemia; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; sK+, serum potassium. [a]Defined as the most recent value prior to study enrolment. Optimal: ≥50% of the target dose for ACEI/ARB/ARNI and ≥50% of the target dose for MRA. Suboptimal: <50% of the guideline-recommended dose for all ACEI/ARB/ARNI and/or <50% of the guideline-recommended dose for MRA. Not treated: no ACEI/ARB/ARNI and MRA.

Keywords Heart failure • Hyperkalaemia • Registry • Quality improvement • Chronic kidney disease

Introduction

Despite strong clinical trial evidence and guideline recommendations, many patients with heart failure (HF) do not receive medications proven to improve morbidity and mortality.[1–3] Even when medications are prescribed, dosing in routine clinical practice usually falls short of levels achieved in clinical trials.[1,2] These large and widespread gaps in the use and dosing of guideline-directed medical therapy (GDMT) continue for both branded and unbranded medications and may be particularly

notable for renin–angiotensin system inhibitors (RASi) and mineralocorticoid receptor antagonists (MRA).[1,4] For example, despite Class I guideline recommendations, a contemporary nationwide analysis of US patients hospitalized for HF with reduced ejection fraction found that only 29% of patients were prescribed angiotensin receptor–neprilysin inhibitor (ARNI) and 41% were prescribed MRA.[3,5,6]

Among the barriers to the implementation of RASi and MRA in clinical practice, the real and perceived risk of hyperkalaemia (HK) is considered a major challenge.[7] The risk of HK may be particularly high in patients with multiple comorbidities such as chronic kidney disease (CKD) and diabetes, conditions that both complicate clinical management and increase risks of clinical worsening and death.[8] As such, despite the heightened risks of poor outcomes and similar relative (and generally greater absolute) benefits with GDMT, these patients may be paradoxically less likely to receive disease-modifying therapies.[9] To compound matters, patients with or at high risk for HK have generally been underrepresented in prospective HF registries. Thus, there are few data documenting the exact nature and magnitude of care gaps in current practice in this patient population, and how RASi and MRA treatment, as well as use of potassium binders, may vary across world regions.[1,2,10–12] A better understanding of contemporary treatment patterns of patients with HF at high risk of HK, including clinical decisions regarding RASi, MRA, and potassium binder use, may inform targeted initiatives to improve patient outcomes and quality of care. In this context, the CARE-HK in HF (Cardiovascular and Renal Treatment in Heart Failure Patients with Hyperkalaemia or at High Risk of Hyperkalaemia) registry is the first prospective multinational registry specifically designed to examine the clinical management of patients with HF, either with active HK or at high risk of HK. We present the primary results of the CARE-HK in HF registry, examining clinical characteristics of participants, baseline and longitudinal treatment patterns, and downstream risks of HK events, including associated clinical outcomes.

Methods

Study design and patient population

The design of the CARE-HK in HF registry has been previously described.[13] In brief, CARE-HK is a prospective, observational, non-interventional, multinational study of adult outpatients with HF across the spectrum of left ventricular ejection fraction (LVEF). Eligible patients had a diagnosis of chronic HF for ≥3 months prior to enrolment, ≥1 measurement of LVEF within the prior 24 months, active treatment with angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB)/ARNI, and active treatment with or eligibility for MRA therapy. Patients were also required to be at increased risk of HK, as defined by ≥1 of the following: serum potassium (sK+) >5.0 mEq/L at enrolment, history of HK >5.0 mEq/L within the prior 24 months, and/or estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2 or documented stage 3b CKD. Key exclusion criteria included active renal replacement therapy/dialysis or mechanical circulatory support and disease other than HF, limiting expected survival to <1 year. Patients were eligible for CARE-HK regardless of LVEF, but enrolment of patients with LVEF ≥50% was capped in an effort to target 20% of total participants.

Baseline patient data were abstracted from medical records and recorded in an electronic case report form. The registry included both retrospective and prospective components. At enrolment, data on RASi and MRA use and dosing (including initiation and discontinuation dates) and episodes of HK were retrospectively ascertained from at least the time of initial HF diagnosis or 24 months prior to enrolment, whichever was more recent. After enrolment, all patients in CARE-HK were prospectively followed for a minimum of 6 months. The registry was embedded within routine clinical care with no study-specific mandatory visits, treatments, or procedures. The study protocol did not provide treatment recommendations, and all decisions on disease management were at the discretion of treating clinicians. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, the protocols were approved by the institutional review boards/ethics committees at each site, and all participants provided written informed consent.

Objectives and study endpoints

CARE-HK included multiple pre-specified primary endpoints (online supplementary *Table S1*). One primary endpoint was the proportion of patients achieving RASi/MRA optimization over time. RASi/MRA optimization categories included 'optimal' treatment (defined as ≥50% of target dose for ACEI/ARB/ARNI, and ≥50% of target dose for MRA), 'suboptimal' treatment (defined as <50% of guideline-recommended dose for all ACEI/ARB/ARNI, and/or <50% of guideline-recommended dose for MRA), and 'not treated' (defined as no dose of ACEI/ARB/ARNI and MRA) (online supplementary *Table S2*). An additional primary endpoint was the percentage of patients with RASi/MRA dose modification in response to an HK event, with specific subcategories including medication down-titration and medication interruption/discontinuation.

In addition, the current report analysed the following key outcomes of interest: (i) the frequency, severity, and timing of HK events during follow-up (with HK events defined by the local clinician and with collection of corresponding sK+ data); (ii) longitudinal use and dosing of GDMT; (iii) use of potassium binders, including specific agents; and (iv) incidence rates of all-cause death and all-cause hospitalization.

Statistical analysis

The sample size calculation for the registry was performed to ensure sufficient precision estimates based on the half-width of the 95% confidence interval (CI) under different scenarios. For 2000 patients in the full analysis set, there would be a precision estimate of 2.2% overall. Precision around all estimates would remain under 5% for any subgroup with at least 500 patients and 7% for any subgroup with at least 200 patients. Enrolment was planned to continue until either a total of at least 2000 patients and/or 300 patiromer-treated patients was reached.

Patients enrolled in the United States and Europe were compared in terms of their baseline characteristics, hyperkalaemic events, medication use, and outcomes. Continuous variables were reported as median (25th–75th percentile), and categorical variables were recorded as frequencies and percentages. Continuous variables were compared using Wilcoxon–Mann–Whitney test, and categorical variables were assessed using chi-square test or exact tests, as appropriate.

By design, the registry included both retrospective (i.e. chart review data capture extending up to 24 months prior to baseline) and prospective time periods. The current report focused on the prospective

post-enrolment time period. To complement data from the prospective period only, select analyses were repeated to be inclusive of the combined retrospective and prospective study period.

Endpoints were pre-specified to be analysed descriptively without statistical adjustment.

The frequency of HK events was calculated, and the median time-to-first event was determined using the Kaplan–Meier method. HK events were defined by clinician report but were further characterized by the sK+ associated with the event. During prospective follow-up, use and dosing of GDMT were assessed over 6-month increments of post-baseline follow-up (among those with available follow-up data for each period), up to 30 months. Medication dosing was reported as the percentage of guideline-recommended target dose that was prescribed (online supplementary *Table S2*). For analyses of RASi/MRA optimization, rates of optimal, suboptimal, and no treatment were primarily analysed according to the treatment prescribed for the majority of study follow-up (i.e. defined as treatment prescribed for the highest percentage of the follow-up period duration). In a complementary analysis, RASi/MRA optimization was examined by the best optimization category (optimal, suboptimal, no treatment) achieved at any point during the follow-up.

Modification of RASi/MRA was assessed following a patient's first HK event observed during follow-up. Time intervals for analysis of RASi/MRA de-escalation included within 3 days and within 30 days following the hyperkalaemic event. RASi/MRA de-escalation was further subcategorized as down-titration versus interruption/discontinuation. Modification events were counted as long as ≥1 RASi or MRA agent was modified (e.g. down-titration of ACEI with no change in MRA would count as a down-titration event).

All-cause mortality and hospitalization outcomes were ascertained via local investigator report. There was no centralized adjudication or clinical events committee in CARE-HK, and cause-specific mortality and hospitalization events were not available for this report. Hazard ratios (HR) (with 95% CI) for mortality were computed using a Cox's proportional hazards method to perform a time-to-event analysis from enrolment to death with a time-dependent covariate for the first HK episode. HR (with 95% CI) for the all-cause hospitalization endpoint were computed using a Cox's proportional hazards method to perform a time-to-event analysis of the first hospitalization following the first HK episode (or enrolment for those with no HK episode) in the prospective period.

Missing data were not imputed (with the exception of partial dates). Two-tailed $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study population

Between 6 April 2021 and 31 August 2023, the CARE-HK registry enrolled 2688 patients across nine countries. Among all enrolled patients, 130 (4.8%) were excluded from the full analysis set due to pre-specified exclusions (eligibility criteria not met, lack of required comorbidity data, major protocol deviation). The remaining 2558 (95.2%) patients met pre-specified criteria for the full analysis set and comprised the study cohort for analysis. Median (25th–75th percentile) prospective follow-up for patients in the full analysis set was 12.3 (9.4–18.1) months.

Patient characteristics by global region

Among 2558 patients in the full analysis set, the median (25th–75th percentile) age was 73 (65–80) years, 31.5% were female, 93.6% were White race, and 61.2% had an LVEF ≤40% (*Table 1*). Overall, 832 (32.5%) were enrolled in the U.S. and 1726 (67.5%) were enrolled in Europe. Compared with Europe, patients enrolled in the U.S. were more frequently Black race and with LVEF >40%, and tended to have higher rates of multiple comorbidities. Overall, median eGFR was 44 (33–60) ml/min/1.73 m^2 and similar in both geographic regions.

Regarding baseline medical therapy, overall rates of ARNI, beta-blocker, MRA, and sodium–glucose co-transporter 2 inhibitor (SGLT2i) use were 56.5%, 85.9%, 62.2%, and 60.5%, respectively (*Figure 1A*). Patients enrolled in Europe were more frequently prescribed ARNI, MRA, and SGLT2i, whereas patients in the U.S. were more frequently prescribed a loop or thiazide diuretic (*Table 1*). Among patients with LVEF ≤40%, 48.1% were prescribed quadruple medical therapy (i.e. simultaneous ACEI/ARB/ARNI, beta-blocker, MRA, and SGLT2i), including 58.7% of patients from Europe and 21.2% of patients from the U.S. (*Figure 1B*).

Baseline serum potassium and history of hyperkalaemia

Among all patients in the full analysis set, the median (25th–75th percentile) most recent sK+ level prior to enrolment was 5.0 (4.4–5.3) mEq/L (*Table 2*). This was lower in the U.S. (4.6 [4.2–5.1] mEq/L) than in Europe (5.1 [4.6–5.4] mEq/L). In total, 12.0% of patients had a baseline sK+ >5.5 mEq/L, and 2.5% of patients had a baseline sK+ >6.0 mEq/L.

Regarding risk factors for HK required for study eligibility (i.e. current HK, prior HK, and/or eGFR <45 ml/min/1.73 m^2), most patients met criteria by both clinician assessment and laboratory criteria (*Table 2*). Approximately one-third of patients had combined risk factors for HK, including CKD stage 3b or worse in combination with current or prior HK.

Hyperkalaemic events during follow-up

Among the 2558 total patients, during prospective follow-up, 746 (29.2%) experienced ≥1 HK event as defined by the clinician (*Table 3*). Of these patients with HK events, the median (25th–75th percentile) number of events was 1 (1–2) with a maximum of 8. The median time-to-first HK event was 11.8 (6.0–16.6) months. In total, 188 (7.3%) patients experienced ≥2 HK events, and 58 (2.3%) experienced ≥3 HK events. The proportion of patients experiencing ≥1 HK event was higher among patients in Europe (32.1%) than in the U.S. (23.1%). In terms of the sK+ level associated with the first HK event, 68.9% of cases overall had an sK+ of 5.1–5.5 mEq/L, 23.4% had an sK+ of 5.6–6.0 mEq/L, and 7.7% had an sK+ of >6.0 mEq/L.

When combining the retrospective and prospective periods of the study, 1724 (67.4%) patients experienced a clinician-defined HK event, with a median number of HK events for these patients of 1 (1–2) and a maximum number of 11 (online supplementary *Table S3*).

Table 1 Baseline characteristics by geographic region

	Overall ($n = 2558$)	U.S. ($n = 832$)	Europe ($n = 1726$)	p-value
Age, years	73 (65–80)	73 (65–79)	73 (65–80)	0.60
Women	805 (31.5)	325 (39.1)	480 (27.8)	<0.001
Race				<0.001
White	2139 (93.6)	706 (85.4)	1433 (98.3)	
Black	98 (4.3)	91 (11.0)	7 (0.5)	
Other	48 (2.1)	30 (3.6)	18 (1.2)	
Left ventricular ejection fraction (%)	38 (30–48)	40 (30–55)	37 (30–45)	
Left ventricular ejection fraction				<0.001
≤40%	1561 (61.2)	435 (52.3)	1126 (65.5)	
41%–49%	386 (15.1)	102 (12.3)	284 (16.5)	
≥50%	604 (23.7)	295 (35.5)	309 (18.0)	
NYHA class[a]				<0.001
I	289 (16.6)	63 (13.5)	226 (17.7)	
II	1058 (60.7)	262 (56.0)	796 (62.4)	
III	376 (21.6)	133 (28.4)	243 (19.1)	
IV	20 (1.1)	10 (2.1)	10 (0.8)	
Duration of heart failure, months	40.5 (14.1–86.8)	42.7 (16.0–76.8)	38.0 (13.6–92.8)	0.87
Vital sign and laboratory data				
Systolic blood pressure (mmHg)	120 (110–135)	122 (110–134)	120 (109–135)	0.02
Heart rate (bpm)	69 (61–78)	72 (65–81)	67 (60–75)	<0.001
Body mass index (kg/m^2)[b]				<0.001
<18.5	29 (1.7)	10 (1.4)	19 (1.9)	
18.5–24.9	465 (27.0)	139 (19.9)	326 (31.9)	
25.0–29.9	614 (35.6)	217 (31.0)	397 (38.8)	
≥30	615 (35.7)	334 (47.7)	281 (27.5)	
eGFR (ml/min/1.73 m^2)[c]	44 (33–60)	43 (34–57)	44 (33–61)	0.66
eGFR (ml/min/1.73 m^2)[c]				0.02
<15	24 (1.1)	3 (0.5)	21 (1.3)	
15–29	352 (15.7)	93 (14.1)	259 (16.4)	
30–44	799 (35.7)	257 (39.1)	542 (34.3)	
45–59	503 (22.5)	160 (24.3)	343 (21.7)	
≥60	464 (20.7)	116 (17.6)	348 (22.0)	
Medical history				
Hypertension	1895 (78.5)	761 (93.7)	1134 (70.8)	<0.001
Coronary artery disease	1383 (57.3)	493 (60.7)	890 (55.6)	0.02
Cerebrovascular disease	350 (14.5)	115 (14.2)	235 (14.7)	0.74
Peripheral artery disease	330 (13.7)	107 (13.2)	223 (13.9)	0.62
Type 2 diabetes	1157 (47.9)	449 (55.3)	708 (44.2)	<0.001
Atrial fibrillation	1158 (48.0)	383 (47.2)	775 (48.4)	0.57
Chronic kidney disease	1638 (67.9)	589 (72.5)	1049 (65.6)	<0.001
COPD	398 (16.5)	179 (22.0)	219 (13.7)	<0.001
Sleep apnoea	374 (15.5)	223 (27.5)	151 (9.4)	<0.001
Medical therapy				
ACEI	549 (21.5)	203 (24.4)	346 (20.0)	0.01
ACEI ≥50% target dose	345 (13.5)	144 (17.3)	201 (11.6)	<0.001
ARB	507 (19.8)	245 (29.4)	262 (15.2)	<0.001
ARB ≥50% target dose	226 (8.8)	98 (11.8)	128 (7.4)	<0.001
ARNI	1446 (56.5)	382 (45.9)	1064 (61.6)	<0.001
ARNI ≥50% target dose	780 (30.5)	147 (17.7)	633 (36.7)	<0.001
MRA	1590 (62.2)	363 (43.6)	1227 (71.1)	<0.001
MRA ≥50% target dose	1335 (52.2)	289 (34.7)	1046 (60.6)	<0.001
Beta-blocker	2134 (85.9)	677 (82.6)	1457 (87.5)	<0.001
Beta-blocker ≥50% target dose	1236 (48.3)	321 (38.6)	915 (53.0)	<0.001
SGLT2i	1503 (60.5)	282 (34.4)	1221 (73.3)	<0.001

Table 1 (Continued)

	Overall ($n = 2558$)	U.S. ($n = 832$)	Europe ($n = 1726$)	*p*-value
Loop diuretic	1360 (53.2)	546 (65.6)	814 (47.2)	<0.001
Thiazide diuretic	117 (4.6)	63 (7.6)	54 (3.1)	<0.001
Quadruple medical therapy (EF ≤40%)[d]	734 (48.1)	92 (21.2)	642 (58.7)	<0.001
Heart failure device therapy				
Implantable cardioverter-defibrillator	177 (6.9)	61 (7.3)	116 (6.7)	0.57
Cardiac resynchronization therapy	135 (5.3)	26 (3.1)	109 (6.3)	<0.001

Data represent median (25th–75th percentile) or *n* (%) with percentage calculated among patients with available data.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium–glucose co-transporter 2 inhibitor.
[a]NYHA data were missing for 815 patients overall (U.S. $n = 364$; Europe $n = 451$).
[b]Body mass index data were missing for 835 patients overall (U.S. $n = 132$; Europe $n = 703$).
[c]Most recent eGFR at enrolment collected in the electronic case report computed with CKD-EPI formula.
[d]Defined as simultaneous prescription of ACEI/ARB/ARNI, beta-blocker, MRA, SGLT2i among patients with EF ≤40% at enrolment (overall $n = 1527$; U.S. $n = 433$; Europe $n = 1094$).

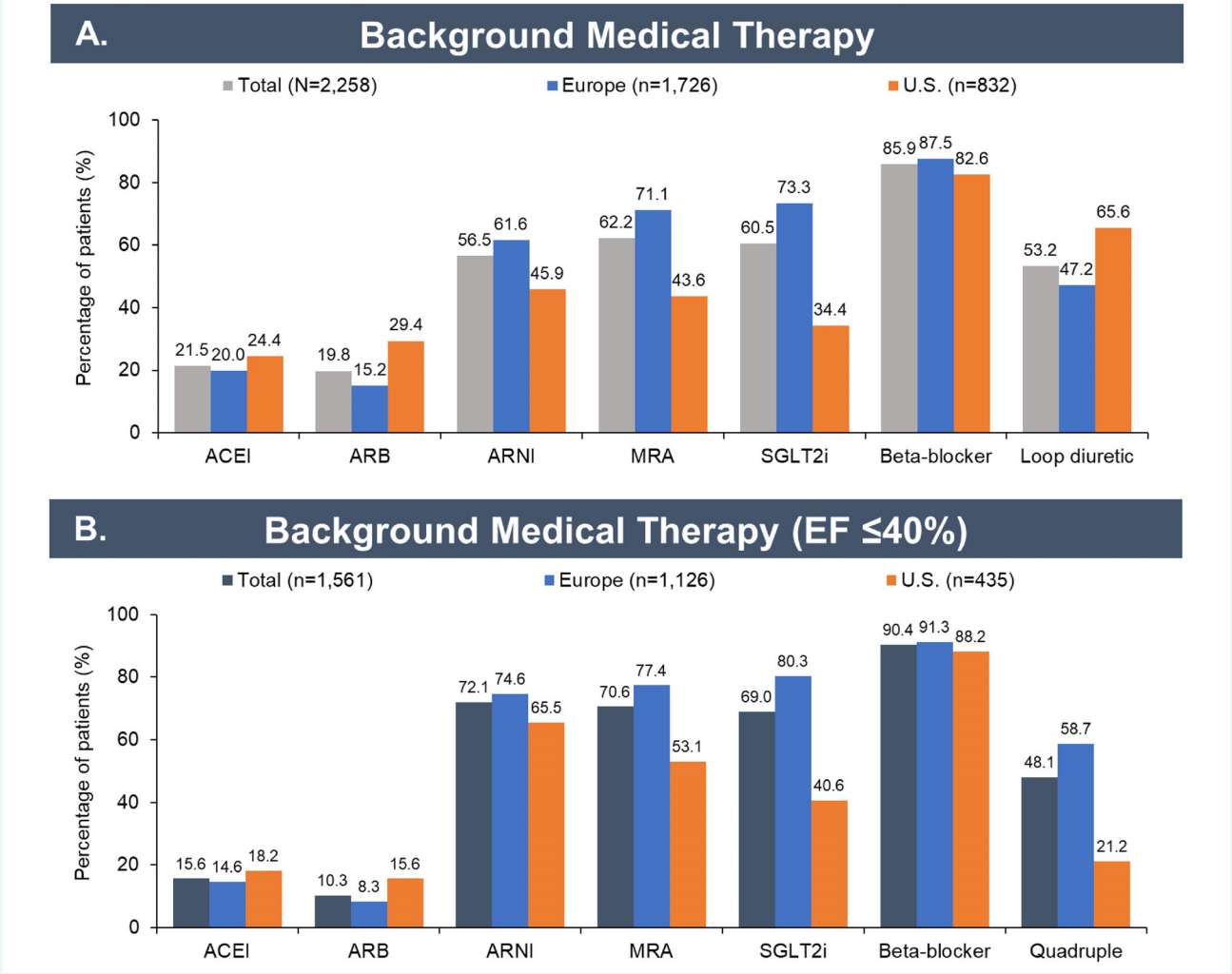


Figure 1 Background medical therapy. Percentage computed among all patients from the full analysis set (*A*) and among patients with ejection fraction (EF) ≤40% (*B*). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

Table 2 Baseline serum potassium and risk factors for hyperkalaemic events

	Overall ($n = 2558$)	U.S. ($n = 832$)	Europe ($n = 1726$)	*p*-value
Baseline serum potassium				
Serum potassium (mEq/L)[a]	5.0 (4.4–5.3)	4.6 (4.2–5.1)	5.1 (4.6–5.4)	<0.001
Serum potassium (mEq/L)[a]				<0.001
≤5.0	1243 (52.5)	557 (70.3)	686 (43.5)	
5.1–5.5	841 (35.5)	197 (24.9)	644 (40.8)	
5.6–6.0	226 (9.5)	32 (4.0)	194 (12.3)	
6.1–6.5	46 (1.9)	4 (0.5)	4.2 (2.7)	
>6.5	13 (0.5)	2 (0.3)	11 (0.7)	
Risk factors for hyperkalaemic events				
Increased risk of HK defined by clinician[b]	2253 (88.1)	702 (84.4)	1551 (89.9)	<0.001
Reason for increased risk of HK defined by clinician				<0.001
Current HK only	396 (17.6)	60 (8.5)	336 (21.7)	
History of HK only	557 (24.7)	213 (30.3)	344 (22.2)	
CKD stage ≥3b or eGFR <45 ml/min/1.73 m^2 only	584 (25.9)	257 (36.6)	327 (21.1)	
Current HK + CKD stage ≥3b	296 (13.1)	34 (4.8)	262 (16.9)	
History of HK + CKD stage ≥3b	420 (18.6)	138 (19.7)	282 (18.2)	
Increased risk of HK defined by laboratories	2401 (93.9)	773 (92.9)	1628 (94.3)	0.16
Reason for increased risk of HK defined by laboratories[b]				<0.001
Current HK only	477 (19.9)	98 (12.7)	379 (23.3)	
History of HK only	624 (26.0)	246 (31.8)	378 (23.2)	
CKD stage 3b or eGFR <45 ml/min/1.73 m^2 only	518 (21.6)	231 (29.9)	287 (17.6)	
Current HK + CKD stage ≥3b	376 (15.7)	62 (8.0)	314 (19.3)	
History of HK + CKD stage ≥3b	406 (16.9)	136 (17.6)	270 (16.6)	

Data represent median (25th–75th percentile) or *n* (%).
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HK, hyperkalaemia.
[a]Most recent value prior to study enrolment (from renin–angiotensin system inhibitor initiation date or 24 months prior to enrolment, whichever happened last).
[b]Defined as current HK (within 3 months prior to enrolment); history of HK (within 24 months prior to enrolment) or CKD stage ≥3b (within 24 months prior or up to 3 months after enrolment).

Table 3 Hyperkalaemic events during follow-up

	Overall ($n = 2558$)	U.S. ($n = 832$)	Europe ($n = 1726$)	*p*-value
Patients with ≥1 HK event[a]	746 (29.2)	192 (23.1)	554 (32.1)	<0.001
Number of HK events per patient[a,b]	1 (1–2)	1 (1–2)	1 (1–1)	
1 HK event	558 (21.8)	139 (16.7)	419 (24.3)	
2 HK events	130 (5.1)	35 (4.2)	95 (5.5)	
≥3 HK events	58 (2.3)	18 (2.2)	40 (2.3)	
Number of HK events by serum potassium at first HK event[a,c]				0.11
5.1–5.5 mEq/L	510 (68.9)	145 (75.5)	365 (66.6)	
5.6–6.0 mEq/L	173 (23.4)	33 (17.2)	140 (25.5)	
>6.0 mEq/L	57 (7.7)	14 (7.3)	43 (7.8)	

Data reflect median (25th–75th percentile) or *n* (%).
HK, hyperkalaemia.
[a]HK event occurring during prospective follow-up, defined by the clinician.
[b]Number of HK events per patient, percentage calculated among patients with ≥1 HK event.
[c]Percentage calculated among 740 patients overall with ≥1 HK event and serum potassium data available (U.S. $n = 192$; Europe $n = 548$).

Guideline-directed medical therapy prescription over time

In general, during prospective follow-up, the proportion of patients prescribed different GDMTs for HF remained stable or decreased over time (online supplementary *Figure S1*). In terms of RASi/MRA therapies, ARNI was prescribed among 58.9% of patients during the first 6 months of follow-up, with stepwise declines in prescription rate at each 6-month follow-up interval to a low of 41.3% at >24- to 30-month follow-up. A similar pattern was observed for MRA, with a prescription rate of 64.4% during the first 6 months of follow-up, with subsequent declines to a low of 41.3% by

>24–30 months. Prescription rates for ACEI (21.4%–26.1%) and ARB (20.7%–21.7%) remained relatively stable over time.

Renin–angiotensin system inhibitor and mineralocorticoid receptor antagonist optimization over time

When patients were assessed by the RASi/MRA optimization category observed during the majority of the follow-up period, 28.7% of patients received optimal RASi/MRA, 68.5% received suboptimal RASi/MRA therapy, and 2.8% received no RASi/MRA therapy (*Graphical Abstract*; online supplementary *Figure S2*). Corresponding proportions of patients achieving optimal RASi/MRA in Europe and the U.S. were 35.6% and 14.4%, respectively. The proportion achieving RASi/MRA optimization were higher when describing patients by the best RASi/MRA optimization category achieved at any point during prospective follow-up. By this measure, 33.8% of patients achieved optimal RASi/MRA therapy, 66.2% achieved suboptimal RASi/MRA, and zero were prescribed no RASi/MRA therapy.

When considering the combined retrospective and prospective periods and the majority of total study period, 22.7% were prescribed optimal RASi/MRA, 62.5% were prescribed suboptimal RASi/MRA, and 14.8% were not prescribed any RASi/MRA (online supplementary *Figure S3*). When describing patients by the best RASi/MRA optimization category achieved at any time during the retrospective or prospective periods, the proportion of patients achieving optimal RASi/MRA was 36.9%.

Renin–angiotensin system inhibitor and mineralocorticoid receptor antagonist modification in response to hyperkalaemic event

When considering the first HK event among the 746 (29.2%) patients with ≥1 HK event during prospective follow-up, RASi/MRA de-escalation following HK occurred within 3 days in 15 (2.0%) patients and within 30 days in 27 (3.6%) patients. Within 3 days, 7 (0.9%) patients were managed with RASi down-titration, and 8 (1.1%) patients were managed with interruption/discontinuation. Corresponding data for the 30-day period following the HK event were 13 (1.7%) and 16 (2.1%) patients, respectively (with two patients having both down-titration and interruption/discontinuation within 30 days). When considering any HK event that occurred during prospective follow-up, 6.3% of events were followed by RASi modification within 3 days and 10.5% of events were followed by RASi modification within 30 days.

Among the 746 patients with ≥1 HK event during prospective follow-up, at the time of a HK event, 146 (19.6%) patients were prescribed an ACEI, 118 (15.8%) were prescribed an ARB, 457 (61.3%) were prescribed ARNI, and 521 (69.8%) were prescribed MRA (online supplementary *Table S4*). In the 3 days following the first HK event, rates of RASi/MRA de-escalation were 0% for ACEI, 0% for ARB, 1.1% for ARNI, and 1.9% for MRA. Corresponding rates in the 30 days following the first HK event were 1.4%, 0%, 2.0%, and 4.0%, respectively. Results for RASi and MRA de-escalation were similarly low when considering the time periods following any HK event, and when separately considering U.S. versus Europe.

Use of potassium binders

Across the entire study period, 234 (9.1%) patients were prescribed patiromer, 150 (5.9%) were prescribed sodium zirconium cyclosilicate, 62 (2.4%) were prescribed calcium polystyrene sulfonate, and 48 (1.9%) were prescribed sodium polystyrene sulfonate (online supplementary *Table S5*). For all four agents, the most common reason for use was to treat HK, while use for purposes of maintaining normokalaemia or up-titrating/initiating RASi/MRA was less common. Compared with the U.S., prescriptions of patiromer, sodium zirconium cyclosilicate, and calcium polystyrene sulfonate were more frequent among patients enrolled in Europe, while prescription rates of sodium polystyrene sulfonate were similar in both regions.

Hyperkalaemic events and clinical outcomes

During prospective follow-up, 225 (8.8%) patients died, and 764 (29.9%) patients were hospitalized (*Table 4*). Risks of death were similar among patients who experienced ≥1 HK event (9.1%) compared with those who did not (8.7%) (HR 1.22 [95% CI 0.92–1.62]; $p = 0.16$). Risk of all-cause hospitalization was greater following a first HK event (30.3%) than those without an HK event (24.5%) (HR 1.59 [95% CI 1.35–1.86]; $p < 0.001$), with consistent findings in the U.S. and Europe.

Discussion

In this prospective, multinational registry of patients with HF and risk factors for HK, nearly one in three patients experienced ≥1 HK event over a median follow-up of 12 months. Although the use of GDMT at baseline was generally higher in CARE-HK than in most prior HF registries, and all patients were prescribed RASi at baseline by design, only a minority of patients received optimal RASi/MRA therapy during the majority of follow-up. Instead, across all classes of GDMT, use and dosing of medication either remained stable or declined over time. Despite a high frequency of clinician-defined HK events, these episodes were infrequently associated with RASi/MRA modification or the use of potassium binders by treating clinicians. HK events were not significantly associated with risk of death, but were associated with substantially higher risk of hospitalization, consistent with the potential role of HK in complicating the management of this patient population. Significant differences in patient profiles, rates of HK, and use of GDMT and potassium binders were observed between the U.S. and Europe.

To our knowledge, the CARE-HK in HF registry is the first prospective observational study specifically examining the clinical profile and treatment patterns for patients with HF with active HK or at high risk for HK. In this context, the median baseline

Table 4 Clinical outcomes for patients with and without hyperkalaemic events during follow-up

	With ≥1 hyperkalaemic event *n* (%)	No hyperkalemic event *n* (%)	Hazard ratio (95% CI), *p*-value[a]
Overall cohort	(*n* = 746)	(*n* = 1812)	
All-cause mortality	68 (9.1)	157 (8.7)	1.22 (0.92–1.62), $p = 0.16$
All-cause hospitalization[b]	226 (30.3)	444 (24.5)	1.59 (1.35–1.86), $p < 0.001$
U.S.	(*n* = 192)	(*n* = 640)	
All-cause mortality	23 (12.0)	78 (12.2)	1.25 (0.79–1.99), $p = 0.34$
All-cause hospitalization[b]	75 (39.1)	206 (32.2)	1.65 (1.27–2.15), $p < 0.001$
Europe	(*n* = 554)	(*n* = 1172)	
All-cause mortality	45 (8.1)	79 (6.7)	1.32 (0.92–1.90), $p = 0.13$
All-cause hospitalization[b]	151 (27.3)	238 (20.3)	1.67 (1.36–2.05), $p < 0.001$

CI, confidence interval; HK, hyperkalaemia.
[a]Hazard ratio with 95% CI for the mortality outcome was computed using a Cox's proportional hazards method to perform a time-to-event analysis from enrolment to death with a time-dependent covariate for the first HK episode. Hazard ratio (with 95% CI) for hospitalizations was computed using a Cox's proportional hazards method to perform a time-to-event analysis of the first hospitalization following the first HK episode (or enrolment for those with no HK episode) in the prospective period.
[b]For the hyperkalaemic event group, data reflect only all-cause hospitalizations that occurred subsequent to the first hyperkalaemic event during prospective follow-up.

sK+ (5.0 mEq/L) and eGFR (44 ml/min/1.73 m^2) in CARE-HK are notable and identify a study cohort previously underrepresented in prior nationwide and global HF registries.[1,2,10] For example, among U.S. registries, <20% of patients with available data in the Change the Management of Patients with Heart Failure (CHAMP-HF) registry had eGFR <45 ml/min/1.73 m^2, and the majority had eGFR ≥60 ml/min/1.73 m^2.[1,14] The median sK+ in CHAMP-HF was 4.3 mmol/L.[15] Similarly, across many European HF registries, the median eGFR was approximately 60 ml/min/1.73 m^2, and the median sK+ was approximately 4.3 mEq/L.[2,10,16] This unique and enriched patient profile in CARE-HK was validated by a high rate of hyperkaleamic events during follow-up.

An important feature of CARE-HK was its multinational design with enrolment across both the U.S. and Europe. Although most HF registries have historically been confined to a single country, enrolment across nine countries broadens the potential applicability of study conclusions while also facilitating direct comparison of clinical profiles, practice patterns, and quality of care across world regions. Many relevant patient characteristics varied between the U.S. and Europe, with U.S. patients more frequently having preserved LVEF, obesity, and many comorbidities. Moreover, baseline sK+ was lower in the U.S. (median 4.6 vs. 5.1 mEq/L), which may explain the lower rate of HK events compared with Europe. Despite similarities in patient age and eGFR, and higher baseline sK+, the use of background HF medical therapy was consistently higher in Europe than the U.S., with higher rates of ARNI, MRA, beta-blocker, and SGLT2i. This pattern of background therapy persisted when confined to patients with LVEF ≤40%, with a higher rate of quadruple medical therapy among patients from Europe (58.7%) as compared with the U.S. (21.2%). Such geographic variation in background HF therapy has also been frequently seen in global HF trials, and highlights the importance of additional efforts to improve GDMT optimization, particularly in the U.S.[17]

Rates of RASi/MRA de-escalation in response to HK events in CARE-HK were lower than expected (e.g. 3.6% within 30 days of first HK event). For example, a prior retrospective analysis of U.S. electronic health record data for patients with HF, CKD, and/or diabetes observed that following an HK event, RASi/MRA therapy was down-titrated in 16–21% of cases and discontinued in 22–27% of cases.[18] Likewise, a retrospective analysis of patients with CKD and HK in Canada observed that 14–35% of patients discontinued RASi within 90 days.[19] Although the exact reason for lower rates of RASi/MRA modification in CARE-HK is unclear, one can speculate that any of multiple potential explanations may have contributed. First, by requiring eligible patients to be receiving baseline RASi therapy despite proven history or high risk of HK, the registry may have selected for patients and managing clinicians unlikely to subsequently modify therapy in response to future HK. The higher use of background medical therapy, compared with other prospective registries, may also support more clinical experience or expertise with patients at risk for HK events among enrolling sites.[1,2] In contrast, patients who had their RASi permanently discontinued previously in response to a prior HK event, as may happen in clinical practice, were not eligible for enrolment in CARE-HK. Second, most HK events occurring in CARE-HK were mild, with an sK+ of 5.1–5.5 mEq/L. Guidelines do not recommend de-escalation of RASi or MRA therapy for episodes of mild HK <5.5 mEq/L, and it is possible that clinicians participating in CARE-HK had increased tolerance for maintaining RASi and MRA therapy.[5,6] Third, it is possible that clinical inertia toward medication changes was a key reason for low rates of RASi modification following HK events. Such clinical inertia has been previously well-documented in clinical practice, with prior HF registries documenting relatively low rates of medication initiations, and in many cases discontinuations, over longitudinal outpatient care.[14,20] Indeed, in CARE-HK, the combination of low rates of RASi modification with HK events, stagnant to declining rates of GDMT prescription during longitudinal follow-up, and low rates of potassium binder initiation could be consistent with a culture of clinical inertia and reluctance toward medication changes.

Despite the minimal change in the use of GDMT during follow-up, baseline use of SGLT2i (60.5%) and ARNI (56.5%) in

CARE-HK was notably higher than previously observed in clinical practice.[1,3,21] Not only may this observation suggest improved uptake of these newer HF therapies in clinical practice, but also both therapies have a potential effect on HK. Specifically, across multiple randomized trials of HF, CKD, and type 2 diabetes populations, SGLT2i treatment consistently mitigates the risk of HK.[22,23] Likewise, ARNI, compared with ACEI, may reduce the risk of HK among patients treated with MRA.[24] Although even greater utilization of SGLT2i and ARNI (instead of ACEI) within CARE-HK may have reduced the rate of hyperkalaemic events observed in the registry, rates of SGLT2i and ARNI were already much higher than typically seen in other clinical practice cohorts.[3,21] In this context, CARE-HK supports a substantial residual risk of 'breakthrough' HK for patients with HF and comorbid CKD in routine clinical practice despite high utilization of SGLT2i and preferential use of ARNI.

Regardless of lower than anticipated rates of GDMT modification in response to HK episodes, higher rates of hospitalization among patients following episodes of HK in CARE-HK are consistent with the clinical relevance of HK and the potential role of HK in complicating patient care. Although cause-and-effect relationships cannot be inferred from this observational study, CARE-HK provides further supporting evidence for HK events as being both common and markers of clinical risk. In this context, CARE-HK may draw needed attention to a particularly vulnerable yet previously understudied subset of the global HF population with severe comorbid kidney disease or prior HK. Dedicated quality improvement initiatives are needed to close gaps in the provision of proven GDMT within this population while simultaneously preventing or treating episodes of HK. The results of the randomized DIAMOND and REALIZE-K trials demonstrated that potassium binder therapy may be helpful for enabling patients with HF and active or prior HK to tolerate long-term RASi and MRA therapy.[11,12]

Limitations

Limitations of this study should be noted. First, the observational nature of this study precludes any definitive assessment of cause-and-effect relationships. For example, in assessing treatment modification and clinical outcomes associated with hyperkalaemic events, the possibility of residual or unmeasured confounding remains. Second, although study sites were selected to reflect a diverse set of clinical practices and investigators across nine countries, data reflect patients from sites that elected to participate and thus may not be generalizable to all care practices. Third, patients in the registry were predominantly male and White race. However, the distribution of race reflects the demographics of many of the enrolling European countries, and the proportion of Black race among U.S. patients (11.0%) was generally consistent with analyses of older HF populations in U.S. clinical practice.[25] Fourth, CARE-HK did not include a clinical event committee and formal event adjudication was not pre-specified. Thus, analyses of cause-specific mortality and cause-specific hospitalization were not feasible. For example, it was not possible to determine the number of hospitalization events specifically due to HK. Fifth, although target doses of RASi and MRA pre-specified for use in CARE-HK were derived from clinical practice guidelines, these target doses are intended for HF with reduced ejection fraction and target doses for patients with LVEF >40% are unclear. Likewise, there is some potential debate over target doses for particular agents. For example, spironolactone 25 mg daily may meet threshold for target dose in U.S. guidelines, whereas 50 mg is the recommended target dose in the European Society of Cardiology guidelines.[5,6] Lastly, data entered within the CARE-HK case report form are based on documentation in the medical record. Despite a prospective study design and measures aimed at lessening any effects of documentation quality and completeness on registry data, inherent limitations may remain. Specifically, it is possible that actual treatment and medication changes implemented by clinicians or received by patients differed from those recorded in the medical record.

Conclusions

In this contemporary multinational prospective registry of patients with HF at high risk of HK, HK events were common but infrequently associated with RASi/MRA modification or potassium binder use. Fewer than one in three patients received optimal RASi/MRA therapy for the majority of follow-up, and HK events were associated with higher risks of hospitalization. Important geographic differences in clinical profile, HK events, and treatment patterns were observed among patients enrolled in the U.S. versus Europe. Targeted strategies are needed to improve the utilization of RASi and MRA while preventing HK in this at-risk population.

Supplementary Information

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

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