



## Cardiovascular and Renal Treatment in Heart Failure Patients With Hyperkalemia or High Risk of Hyperkalemia: Rationale and Design of the CARE-HK in HF Registry

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**Abbreviations:** ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNi, angiotensin-receptor-neprilysin inhibitor; BB, beta blockers; CARE-HK, Cardiovascular and Renal Treatment in Heart Failure Patients with Hyperkalemia or at High Risk of Hyperkalemia; CKD, chronic kidney disease; HR, hazard ratio; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalemia; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; K<sup>+</sup>, potassium; RAASi, renin–angiotensin–aldosterone system inhibitor; sK<sup>+</sup>, serum potassium; SGLT2i, sodium–glucose cotransporter-2 inhibitor

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See page 9 for disclosure information.

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## ABSTRACT

**Background:** Despite guideline recommendations, many patients with heart failure (HF) do not receive target dosages of renin-angiotensin-aldosterone system inhibitors (RAASi) in clinical practice due, in part, to concerns about hyperkalemia (HK).

**Methods and Results:** This noninterventional, multinational, multicenter registry (NCT04864795; 111 sites in Europe and the USA) enrolled 2558 eligible adults with chronic HF (mostly with reduced ejection fraction [HFrEF]). Eligibility criteria included use of angiotensin-converting-enzyme inhibitor/angiotensin-II receptor blocker/angiotensin-receptor-neprilysin inhibitor, being a candidate for or treatment with a mineralocorticoid receptor antagonist, and increased risk of HK (eg, current serum potassium  $> 5.0$  mmol/L), history of HK in the previous 24 months, or estimated glomerular filtration rate  $< 45$  mL/min/1.73 m<sup>2</sup>). Information on RAASi and other guideline-recommended therapies was collected retrospectively and prospectively ( $\geq 6$  months). Patients were followed according to local clinical practice, without study-specific visits or interventions. The main objectives were to characterize RAASi treatment patterns compared with guideline recommendations, describe RAASi modifications following episodes of HK, and describe RAASi treatment in patients treated with patiomer. Baseline characteristics for the first 1000 patients are presented.

**Conclusions:** CARE-HK is a multinational prospective HF registry designed to report on the management and outcomes of patients with HF at high risk for HK in routine clinical practice. (*J Cardiac Fail* 2024;00:1–11)

**Key Words:** Heart failure, renin–angiotensin–aldosterone system inhibitor, hyperkalemia, clinical practice study.

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## Introduction

Patients with heart failure (HF) may experience debilitating symptoms and are at significantly increased risk for disease progression, hospitalization and death.<sup>1</sup> Current HF guidelines strongly recommend treating patients with HF and reduced left ventricular ejection fraction (LVEF  $\leq 40\%$ ) (HFrEF) with renin-angiotensin-aldosterone system inhibitors (RAASi) at the maximally tolerated or target dosages that have been shown to reduce morbidity and mortality rates in randomized clinical trials.<sup>2,3</sup> Guidelines provide weaker recommendations to consider RAASi therapy in patients with HF with mildly reduced ejection fraction (LVEF 41%–49%) (HFmrEF).<sup>2,3</sup> In the US HF guidelines, RAASi therapy may also be considered in patients with HF and preserved ejection fraction (LVEF  $\geq 50\%$ ) (HFpEF), particularly in patients on the lower end of this LVEF spectrum.<sup>2</sup> However, in clinical practice, target dosages of RAASi are often not achieved or sustained. These gaps in RAASi implementation are due, in part, to clinician concerns regarding hyperkalemia (HK) (defined as serum potassium  $[sK^+] > 5.0$  mmol/L), particularly in patients with chronic kidney disease (CKD).<sup>4</sup> Indeed, HK has been associated with adverse outcomes in patients with HF, which may be, in part, related to clinicians discontinuing or down-titrating dosages of RAASi, owing to the fear of HK.<sup>5,6</sup>

HK is common in patients with HF; up to 24% of patients experience at least 1 episode of HK  $> 5.0$  mmol/L over 12 months of follow-up, and 10% experiencing moderate or severe HK  $> 5.5$  mmol/L.<sup>7</sup> The risk of HK is higher in patients with CKD and certain other comorbidities

(eg, diabetes mellitus) and with certain therapies (eg, RAASi, including mineralocorticoid receptor antagonists [MRAs]).<sup>7,8</sup> Following the first episode of HK, the risk of recurrent HK increases, with a tendency for successively shorter intervals between episodes.<sup>5</sup> Despite evidence that lower dosages of RAASi are not as effective as target dosages,<sup>9,10</sup> RAASi are commonly down-titrated or temporarily or permanently discontinued in patients with HF who have comorbidities, potentially contributing to adverse outcomes.<sup>11,12</sup> Therefore, patients with HF at particular risk of HK are generally at higher risk of poor clinical outcomes yet less likely to be treated with disease-modifying medications.

Given the risk of HK in patients with HF receiving RAASi, both European and US HF guidelines, as well as CKD guidelines, recommend monitoring serum potassium ( $sK^+$ ) levels in patients taking RAASi.<sup>2,3,13</sup> Furthermore, HF guidelines provide recommendations for the management of chronic HK, including consideration of the use of potassium ( $K^+$ ) binders as a potential strategy, which may allow for safer initiation, and continued use or up-titration of RAASi in a larger proportion of patients.<sup>2,3</sup> However, despite the potential role as enabling strategies for RAASi use, the effectiveness of  $K^+$  binders to improve outcomes by facilitating RAASi optimization in routine clinical practice has not yet been established.<sup>2</sup>

Patient registries can be used to monitor treatment patterns and associated outcomes in routine clinical practice, particularly for the patients at highest risk, in whom comorbidities or adverse events (or concern regarding them) frequently result in treatment deviating from optimal guideline-recommended medical therapy. Previous

large observational studies have highlighted that a substantial proportion of patients with HF do not receive optimal guideline-recommended medical therapy, receive it only after substantial delays, and/or experience high rates of treatment discontinuation.<sup>14–20</sup> Reasons for these treatment gaps have included a range of factors, from contraindication and intolerance of treatments to inadequate access to therapies and therapeutic inertia,<sup>21</sup> with HK identified as 1 key reason for the discontinuation of MRAs.<sup>15</sup> However, there are limited longitudinal data regarding the reasons for treatment decisions, particularly in patients most at risk for HK.

CARE-HK in HF (Cardiovascular and Renal Treatment in Heart Failure Patients with Hyperkalemia or at High Risk of Hyperkalemia) is the first dedicated, prospective HF registry designed to study the management of patients with HF and current or at high risk for HK. The CARE-HK in HF registry aims to evaluate RAASi treatment patterns in clinical practice compared with guideline-recommended medical therapy and describe RAASi treatment modifications following episodes of HK. Reasons for RAASi treatment decisions provided by clinicians may help to identify potential barriers to guideline-recommended medical therapy. The association of the K<sup>+</sup> binder, patiomer, with RAASi treatment patterns is also evaluated by comparing patients receiving patiomer with those not receiving any K<sup>+</sup> binder in routine clinical practice.

## Methods

### Study Design and Population

The CARE-HK in HF Registry (NCT04864795) is a noninterventional, multinational, multicenter study that seeks to evaluate RAASi treatment patterns in clinical practice compared with guideline-recommended medical therapy.

The CARE-HK in HF registry planned to enroll at least 2000 patients and up to 5000 patients who had a diagnosis of chronic HF for at least 3 months prior to providing informed consent to participate. Enrollment took place at 111 sites in Europe and the USA over a period of approximately 24 months. Patients were followed prospectively until study completion, for a minimum of 6 months (Fig. 1). At enrollment, data concerning RAASi use were retrospectively ascertained from at least the time of HF diagnosis or for 24 months prior to enrollment (whichever was shorter), and then were prospectively collected until the study's completion. When appropriate and possible, dates of diagnosis, initiation of treatments, and selected laboratory results supporting HF diagnosis and risk of HK were collected from before the 24 months prior to enrollment. The study was embedded within routine clinical care with no study-mandated visits, treatments or procedures; the study protocol did not provide treatment recommendations, and all decisions about disease management were at the discretion of the treating physician.

In addition to the diagnosis of chronic HF in the medical records at least 3 months prior to giving informed consent, other key inclusion criteria were: (1) treatment with RAASi (angiotensin-converting-enzyme inhibitor [ACEi]/angiotensin-II receptor blocker [ARB]/angiotensin-receptor-neprilysin inhibitor [ARNi]); (2) either treatment with or candidate for treatment with an MRA; and (3) at increased risk of HK. Increased risk of HK was defined as at least 1 of the following criteria: current HK ( $sK^+ > 5.0$  mmol/L) at enrollment, documented HK in the 24 months prior to enrollment, or  $eGFR < 45$  mL/min/1.73 m<sup>2</sup> or CKD stage  $\geq 3b$ . Key exclusion criteria were patients on renal replacement therapy or mechanical circulatory support. The goal was for patients with HF<sub>r</sub>EF or HF<sub>mr</sub>EF to comprise at least 80% of the total sample. Therefore, the enrollment of patients with HF<sub>p</sub>EF (LVEF  $\geq 50\%$ ) was capped once they had exceeded 20% of the sample. A full description of the eligibility criteria is provided in Table 1.

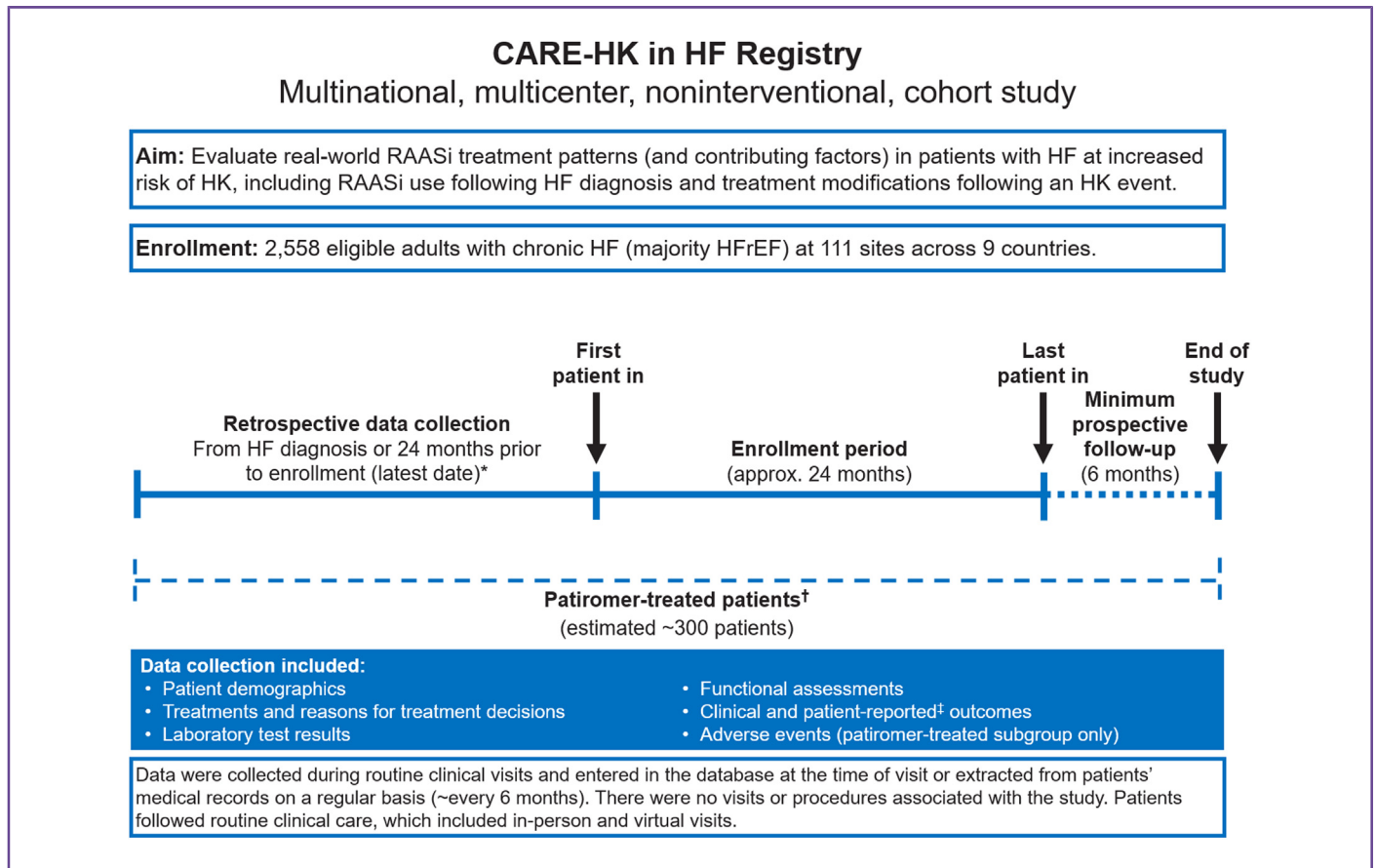
This study was conducted under the guidelines for Good Pharmacoepidemiology Practice issued by the International Society for Pharmacoepidemiology, Good Clinical Practice, the Declaration of Helsinki and its amendments, and any applicable national guidelines. Local independent ethics committee/institutional review board approval was required prior to enrollment of patients, and each patient provided informed consent before any data collection.

### Data Sources

Data were extracted from patients' medical records and/or collected during routine clinical visits, and participants who provided additional consent for the collection of patient-reported outcomes were requested to complete the Kansas City Cardiomyopathy Questionnaire (KCCQ) to measure HF-related health status at enrollment and approximately every 6 months. Medical histories were collected for up to 24 months prior to enrollment or from time of HF diagnosis (whichever was shorter). Data collection included demographics, HF diagnosis details, HF disease severity (New York Heart Association [NYHA] classification and LVEF) and signs and symptoms, comorbidities (eg, CKD), kidney function, treatments details (RAASi, K<sup>+</sup> control, HF-related or HF-relevant concomitant medications), and reasons for treatment decisions, laboratory test results, procedures, and clinical events (occurrence of HK, hospitalizations and mortality), as well as safety data in patiomer-treated patients.

### Objectives and Study Endpoints

The primary and secondary objectives and endpoints are detailed in Supplementary Table 1 and Supplementary Table 2, respectively. The primary objectives are to describe RAASi treatment patterns in patients with HF and compare them with treatment guideline



**Fig. 1.** CARE-HK in HF Registry Study Design. \*Data were retrospectively extracted from medical records. When appropriate and possible, dates of diagnosis, initiation of treatments and selected laboratory results supporting HF diagnosis and HK risk were collected from before the 24 months prior to enrollment. <sup>†</sup>The study protocol did not recommend the use of any specific treatments; no study medication was provided as part of participation. All decisions on therapeutic or diagnostic procedures, treatments, or management of the disease were at the full discretion of the treating physician. <sup>‡</sup>Patients who provided additional consent for the collection of patient-reported outcomes were requested to complete the KCCQ to measure HF-related health status at enrollment and approximately every 6 months. CARE-HK, Cardiovascular and Renal Treatment in Heart Failure Patients with Hyperkalemia or at High Risk of Hyperkalemia; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalemia; KCCQ, Kansas City Cardiomyopathy Questionnaire; RAASi, renin–angiotensin–aldosterone system inhibitor.

**Table 1** Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>• Aged <math>\geq 18</math> years</li> <li>• Diagnosis of chronic HF for at least 3 months prior to the signature of informed consent</li> <li>• At least 1 record of LVEF in the 24 months prior to enrollment</li> <li>• Treated with ACEi, ARB, or ARNi at enrollment</li> <li>• Treated with or is a candidate for an MRA per a relevant treatment guideline (eg, HF, CKD, resistant hypertension) at enrollment</li> <li>• Increased risk of HK due to <math>\geq 1</math> of the following criteria:               <ul style="list-style-type: none"> <li>◦ Current HK (<math>sK^+ &gt; 5.0</math> mmol/L) at enrollment</li> <li>◦ Documented HK in the 24 months prior to signature of informed consent</li> <li>◦ eGFR <math>&lt; 45</math> mL/min/1.73 m<sup>2</sup></li> </ul> </li> <li>• Sufficient cognitive ability to participate in the study</li> </ul>	<ul style="list-style-type: none"> <li>• Treated with renal replacement therapy or mechanical circulatory support</li> <li>• Presenting other diseases with an expected survival of less than 1 year</li> <li>• Participating in, or being screened for, an interventional trial—with the exception of patients participating in clinical trials relating to SARS-CoV-2</li> <li>• Intolerant to MRAs for reasons other than HK or renal impairment</li> </ul>

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blockers; ARNi, angiotensin-receptor-neprilysin inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HK, hyperkalemia; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2;  $sK^+$ , serum potassium.

recommendations (ie, RAASi optimization) during the overall (retrospective and prospective) observation period and to describe RAASi treatment modifications following episodes of HK ( $sK^+ > 5.0$  mmol/L) at short- and long-term intervals. RAASi treatment optimization categories include: optimal treatment, defined as  $\geq 50\%$  of guideline-recommended target dosages, and suboptimal treatment, defined as  $< 50\%$  of guideline-recommended target dosages, or not treated if no RAASi treatment is prescribed. These definitions were prespecified and consistent with prior publications.<sup>18,22–24</sup> Additional RAASi treatment optimization definitions may be added to improve precision and account for the dynamic treatment patterns.

The primary endpoints of the study are the percentage of patients by RAASi optimization overall; the percentage of patients by RAASi dose modification in response to an HK episode (downtitration, interruption, discontinuation, no change); and the percentage of patients by RAASi treatment modifications (uptitration, downtitration, interruptions, discontinuations) after HK episodes.

Following data analysis, if a sufficient number of patients were prescribed patiromer in routine practice, an additional primary objective describing RAASi treatment patterns and comparing them with treatment guideline recommendations (ie, RAASi optimization) in patiromer-treated patients will be evaluated. The primary endpoints for this analysis are a comparison of the percentage of patients with RAASi treatment optimization between patiromer-treated and untreated patients following HK episodes at long-term intervals and a description of RAASi treatment patterns in patiromer-treated patients following episodes of HK at short-term and long-term intervals.

### Statistical Considerations

The primary endpoint analyses are descriptive in nature, and the sample size calculation was performed with the goal of ensuring sufficient precision in descriptive outcomes based on the half-width of the 95% confidence interval (CI) under differing scenarios. For 5000 patients, there would be a precision estimate of 1.4% overall, and for 2000 patients, there would be a precision estimate of 2.2% overall. Precision around all estimates would be predicted to remain under 5% for any subgroup with at least 500 patients and under 7% for any subgroup with at least 200 patients.

A sample size estimate was performed for the patiromer comparative analyses, to define the minimum patiromer-treated patient population required. To observe an improvement in RAASi treatment optimization of 10% between patients treated with patiromer and patients not treated with any  $K^+$  binder (at 80% power, 5% significance, and comparing 2 proportions), with a ratio of 2 treated patients to 1 untreated patient, approximately

300 patiromer-treated patients would be required. Enrollment was planned to continue until either a total of at least 2000 patients and/or 300 patiromer-treated patients was reached, and the projections for numbers of patiromer-treated patients were evaluated to make decisions regarding further enrollment.

One interim analysis for baseline characteristics was prespecified once 1000 patients were enrolled.

## Results

### Patients Enrolled in the CARE-HK in HF Registry

Enrollment into the CARE-HK in HF Registry has completed and, as of database lock on March 28, 2024, there were 2558 patients enrolled and eligible for the full analysis set. The first 1000 patients for the full analysis set were enrolled by February 16, 2023, and were included in the current prespecified interim analysis of baseline characteristics. This group comprised 589 patients from Europe and 411 from the US. Demographics, clinical characteristics and RAASi treatment at enrollment for the first 1000 eligible patients are reported in Table 2, overall and by region.

The median (interquartile range [IQR]) age at enrollment was 73.0 (65.0–80.0) years; 63.1% of patients were male, and 91.7% were White. HF diagnosis occurred a median (IQR) of 46.4 (16.3–95.2) months prior to enrollment, and median (IQR) LVEF at enrollment was 39.0% (30.0–50.0), with 57.3%, 16.1% and 26.6% of patients having an LVEF of  $\leq 40\%$  (HF<sub>r</sub>EF),  $> 40$ – $< 50\%$  (HF<sub>mr</sub>EF), and  $\geq 50\%$  (HF<sub>p</sub>EF), respectively. Based on the distribution of LVEF phenotype enrolled in this interim analysis, and close monitoring of the LVEF phenotypes being enrolled in the registry, prespecified capping of enrollment for patients with HF<sub>p</sub>EF was triggered on April 18, 2023. Subsequently, the registry continued to enroll patients with HF and LVEF of  $< 50\%$  only.

The majority of patients (95.1%) had  $\geq 1$  reported comorbidity, the most common of which was hypertension (77.5%), followed by CKD (58.7%), coronary artery disease (55.0%) and atrial fibrillation (46.3%). The median (IQR) most recent eGFR measurement was 42 (33–56) mL/min/1.73 m<sup>2</sup>. The median most recent  $sK^+$  was 5.0 (4.4–5.3) mmol/L. Overall, 11.1% of patients had their most recent  $sK^+ > 5.5$  mmol/L.

Overall, 59.6% of patients were prescribed an MRA at enrollment. Reasons for contraindication, nonprescription or lack of tolerability for those not receiving an MRA included previous HK (39.6%), worsening kidney function (37.7%), risk of HK (36.5%), advanced CKD (stage  $\geq 4$  or eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>; 13.8%), and rise in  $sK^+$  (9.4%). HF<sub>r</sub>EF was the most common indication for treatment with an MRA (64.3%) as well as for treatment with an ACEi, ARB or ARNi (66.3%). Among patients with HF<sub>r</sub>EF, the use of other guideline-directed medications for HF at

**Table 2** Patient demographics, characteristics and use of RAASi treatment at enrollment for first 1000 patients in the full analysis set.

	Total (n = 1,000)	Europe (n = 589)	USA (n = 411)
<b>Demographics</b>			
Age, years <sup>a</sup>	73 (65–80)	74.0 (66–80)	73 (65–79)
Male, n (%) <sup>a</sup>	631 (63.1)	395 (67.1)	236 (57.4)
<b>Race, n (%)<sup>a</sup></b>			
American Indian or Alaska Native	1 (0.1)	0	1 (0.2)
Asian	11 (1.2)	2 (0.4)	9 (2.2)
Black or African American	52 (5.8)	1 (0.2)	51 (12.4)
White	828 (91.7)	488 (99.2)	340 (82.7)
Other	11 (1.2)	1 (0.2)	10 (2.4)
Body mass index, kg/m <sup>2a</sup>	28.1 (24.7–32.0)	27.2 (24.2–30.5)	29.3 (25.7–33.3)
Systolic blood pressure, mmHg <sup>a</sup>	122.0 (110–136)	120.0 (109–135)	123 (110–137)
<b>Serum potassium, mmol/L<sup>a,b</sup></b>			
≤5.0 mmol/L, n (%)	499 (54.5)	237 (44.5)	262 (68.4)
>5.0–5.5 mmol/L, n (%)	315 (34.4)	215 (40.3)	100 (26.1)
>5.5–6.0 mmol/L, n (%)	82 (9.0)	64 (12.0)	18 (4.7)
>6.0–6.5 mmol/L, n (%)	15 (1.6)	12 (2.3)	3 (0.8)
>6.5 mmol/L, n (%)	5 (0.5)	5 (0.9)	0
History of hyperkalemia, n (%) <sup>a,c</sup>	661 (69.6)	412 (71.8)	249 (66.2)
Time since diagnosis of HF to enrollment, months <sup>a,d</sup>	46.4 (16.3–95.2)	46.2 (14.7–100.9)	46.7 (19.4–83.8)
<b>Most recent LVEF, %<sup>a,e</sup></b>			
HFrEF (≤40%), n (%)	39 (30–50)	38 (30–45)	40 (30–55)
HFmrEF (40%–<50%), n (%)	572 (57.3)	365 (62.1)	207 (50.5)
HFpEF (≥50%), n (%)	161 (16.1)	119 (20.2)	42 (10.2)
<b>Most recent CKD stage, n (%)<sup>a,f</sup></b>			
1	42 (4.9)	29 (5.4)	13 (4.1)
2	150 (17.5)	104 (19.3)	46 (14.5)
3a	186 (21.7)	108 (20.0)	78 (24.6)
3b	331 (38.6)	195 (36.1)	136 (42.9)
4	133 (15.5)	92 (17.0)	41 (12.9)
5	15 (1.8)	12 (2.2)	3 (0.9)
Most recent eGFR, mL/min/1.73 m <sup>2 a,g</sup>	42 (33–56)	42 (32–58)	42 (34–54)
<b>Comorbidities<sup>h</sup></b>			
At least one comorbidity, n (%)	951 (95.1)	546 (92.7)	405 (98.5)
Hypertension	775 (77.5)	394 (66.9)	381 (92.7)
Type 1 diabetes	14 (1.4)	8 (1.4)	6 (1.5)
Type 2 diabetes	451 (45.1)	233 (39.6)	218 (53.0)
CKD	587 (58.7)	308 (52.3)	279 (67.9)
Coronary artery disease	550 (55.0)	307 (52.1)	243 (59.1)
Cerebrovascular disease	139 (13.9)	79 (13.4)	60 (14.6)
Peripheral arterial disease	134 (13.4)	82 (13.9)	52 (12.7)
Atrial fibrillation	463 (46.3)	273 (46.3)	190 (46.2)
COPD	184 (18.4)	86 (14.6)	98 (23.8)
Sleep apnea	143 (14.3)	43 (7.3)	100 (24.3)
Liver disease/cirrhosis	31 (3.1)	21 (3.6)	10 (2.4)
Dementia / cognitive decline / Alzheimer's disease	13 (1.3)	5 (0.8)	8 (1.9)
<b>RAASi at enrollment, n (%)<sup>a</sup></b>			
ACEi	240 (24.0)	136 (23.1)	104 (25.3)
ARB	221 (22.1)	97 (16.5)	124 (30.2)
ARNi	529 (52.9)	345 (58.6)	184 (44.8)
MRA	596 (59.6)	429 (72.8)	167 (40.6)
<b>Reason for no MRA treatment, n (%)<sup>a,i</sup></b>			
Contraindicated	121 (33.4)	59 (43.4)	62 (27.4)
Not tolerated	41 (11.3)	21 (15.4)	20 (8.8)
Other	200 (55.2)	56 (41.2)	144 (63.7)
<b>Reason for MRA contraindication or not tolerated, n (%)<sup>a,j</sup></b>			
Previous hyperkalemia	63 (39.6)	33 (42.3)	30 (37.0)
Worsening renal function	60 (37.7)	30 (38.5)	30 (37.0)
Risk of hyperkalemia	58 (36.5)	27 (34.6)	31 (38.3)
Advanced CKD (Stage ≥4 or eGFR <30 mL/min/1.73 m <sup>2</sup> )	22 (13.8)	14 (17.9)	8 (9.9)
Rise in serum potassium	15 (9.4)	13 (16.7)	2 (2.5)
Gynecomastia	0	0	0
Hyponatremia	0	0	0
Other	0	0	0

(Continued)

Table 2. (Continued)

	Total (n = 1,000)	Europe (n = 589)	USA (n = 411)
Other medications of interest <sup>a,k</sup>			
Beta blocker, n (%)	749 (80.6)	425 (80.5)	324 (80.8)
SGLT2i, n (%)	419 (45.1)	322 (61.0)	97 (24.2)

Data are reported as median (quartile 1 – quartile 3) or n (%).

<sup>a</sup>Percentage calculated among all patients with non-missing information

<sup>b</sup>Most recent result collected from RAASi initiation date for HF or 24 months' prior enrollment, whichever happened last, until the day before enrollment

<sup>c</sup>Based on laboratory tests (number of patients with > 5.0 mmol/L) at any time prior to enrollment, until the day before enrollment

<sup>d</sup>Most recent LVEF defined as category reported at the enrollment visit

<sup>e</sup>Time since HF diagnosis, calculated as the difference between enrollment date and HF diagnosis date, divided by 365.25

<sup>f</sup>Most recent result (from eGFR calculated using the CKD EPI-Formula, eGFR collected in the eCRF, or CKD stage collected in the eCRF) collected at enrollment, or the closest data within 3 months prior or after enrollment

<sup>g</sup>eGFR calculated using the CKD-EPI formula collected at enrollment, or the closest data within 3 months prior or after enrollment

<sup>h</sup>Percentage calculated among all patients enrolled

<sup>i</sup>Percentage calculated among patients who did not receive MRA at enrollment (n=362; Europe: n=136; USA: n=226)

<sup>j</sup>Percentage calculated among patients with contraindicated/not tolerated MRA at enrollment (n=159; Europe: n=78; USA: n=81)

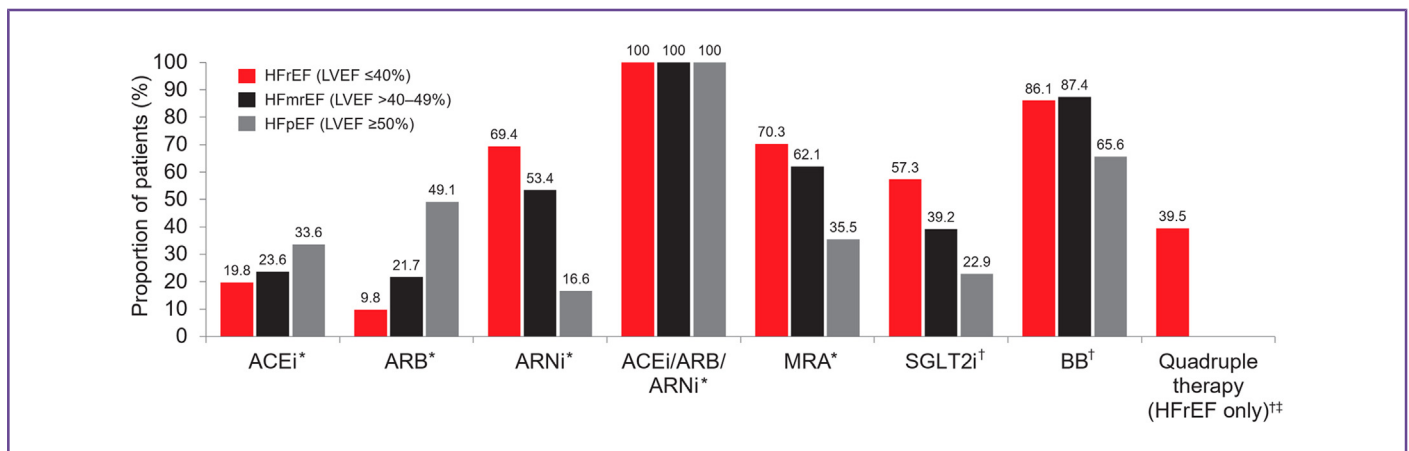
<sup>k</sup>Percentage calculated among patients with at least 1 concomitant medication reported (n=929; Europe: n=528; USA: n=401). Data in the table are based on the full analysis set. ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNi, angiotensin-receptor-neprilysin inhibitor; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eCRF, electronic case-report form; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; Q, quartile; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

enrollment included beta-blockers (BBs) (86.1%) and sodium-glucose cotransporter-2 inhibitors (SGLT2is; 57.3%); 39.5% of patients with HFrEF received quadruple guideline-directed medical therapy (ACEi/ARB/ARNi, MRA, BB, and SGLT2i). Fig. 2 contains further details about the HF treatment prescribed at enrollment, stratified by LVEF subgroup. At any time—either prior to study enrollment or after—17.4% of patients had received treatment with any K<sup>+</sup> binder, and 6.2% had received treatment with patiromer.

## Discussion

The CARE-HK in HF registry is the first global longitudinal study evaluating the clinical care and treatment of patients

with HF at increased risk of HK. The concept for the CARE-HK in HF registry study was based on the belief that adherence to guideline recommendations for RAASi use is associated with improved clinical outcomes for patients with HF. The CARE-HK in HF registry was, therefore, designed to describe the use of guideline-recommended medical therapy in real-world clinical practice, characterize reasons for contraindications or discontinuation of guideline-recommended medical therapy, and study the implications of HK on patterns of care and use of RAASi in patients with HF. Specifically (and uniquely), this study aims to inform the care of a patient population that is in particular need of strategies to improve the use of evidence-based therapies, with a focus on those at risk for HK (current or prior episodes of HK or with kidney dysfunction [eGFR <45 mL/min/1.73 m<sup>2</sup>]). To meet these



**Fig. 2.** Heart failure treatment prescribed at enrollment by LVEF. \*Percentage among total subgroups (HFrEF: n = 572; HFmrEF: n=161; HFpEF: n = 265). †Percentage of patients with available data (HFrEF: n = 531; HFmrEF: n = 143; HFpEF: n = 253). ††Quadruple therapy defined as ACEi, ARB or ARNi and MRA, SGLT2i and BB. ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNi, angiotensin-receptor-neprilysin inhibitor; BB, beta blocker; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

objectives, the CARE-HK in HF registry was designed as a large, multinational study embedded within routine practice. The study aims to provide important data on the impact of HK and perceived risk of HK on clinical decision making and use of RAASis for patients with HF. In parallel, the study may also examine the use of patiomer to manage and prevent HK in an at-risk population and the role of patiomer in facilitating use of RAASis in clinical practice.

The baseline data for the first 1000 patients enrolled in the CARE-HK in HF registry reaffirm the uniqueness of the study's patient population, as compared with prior HF registries and clinical trials.<sup>16,18,22</sup> Among the key characteristics, the median age was 73 years, the median most recent  $sK^+$  was 5.0 mmol/L, and the median most recent eGFR level was 42 mL/min/1.73 m<sup>2</sup>. By comparison, in the CHAMP-HF registry of US outpatients with HF<sub>rEF</sub>, the median age was 68 years, the median baseline  $sK^+$  was 4.3 mmol/L, and the majority of patients had eGFR > 60 mL/min/1.73 m<sup>2</sup>.<sup>16,25,26</sup> In addition to CKD, the initial cohort from CARE-HK also had high rates of comorbidities, with nearly half of patients having histories of diabetes and atrial fibrillation. Taken together, these initial baseline characteristics suggest that CARE-HK successfully enrolled the intended target population, a population generally underrepresented in prior registries and clinical trials and with a high degree of medical complexity, comorbidity and risk of HK.

Multiple prior HF registries and large observational studies have consistently shown gaps in the use and dosing of evidence-based therapy in routine clinical practice.<sup>14–20</sup> Despite strong guideline recommendations, robust clinical trial evidence and multiple quality-improvement initiatives, these gaps have generally persisted over time and across global regions.<sup>14–21</sup> Underuse of medical therapy in HF is notable for RAASi treatment and MRAs in particular, but it has also been observed for SGLT2is.<sup>20</sup> In US clinical practice, among patients with HF<sub>rEF</sub> eligible for therapy, 1 in 4 patients do not receive an ACEi, ARB or ARNi, and 2 of 3 patients do not receive an MRA.<sup>16</sup> Such gaps in use and dosing are generally largest among patients with severe CKD, likely due, in part, to concerns about HK. For example, among US patients hospitalized with HF<sub>rEF</sub>, there are graded reductions in the use of an ACEi or ARB, an ARNi and an MRA with increasing severity of kidney dysfunction.<sup>27</sup> Specifically, among patients with eGFR 30–< 45 mL/min/1.73 m<sup>2</sup> (ie, an eGFR level at which therapies are not contraindicated and where therapeutic efficacy generally remains consistent in clinical trials), only 50% and 26% of patients are prescribed an ACEi/ARB/ARNi and an MRA at discharge, respectively.<sup>27</sup> In this context, initial patient data from the CARE-HK in HF registry showed that less than 60% of patients were prescribed an MRA at enrollment. Previous HK, risk of HK and rise in  $sK^+$ , as well as worsening renal function

and advanced CKD (stage  $\geq 4$  or eGFR < 30 mL/min/1.73 m<sup>2</sup>) were the most common reasons for contraindication or intolerance to MRAs. Future data from the CARE-HK in HF registry will be able to assess how use of RAASi therapy (in particular, MRAs) and SGLT2is change over time and in relation to HK events. Likewise, the registry will allow comparison of prescription rates of guideline-recommended medical therapy between the US and Europe, stratified by LVEF phenotype.

In a setting where guideline-recommended medical therapy is not achieved owing to HK, patiomer may facilitate initiation or ongoing use of RAASis in patients with HF.<sup>28,29</sup> Among 132 patients with HF in the AMBER trial, discontinuation of MRA therapy at 12 weeks occurred in 15.9% (n = 10/63) with patiomer compared with 31.9% (n = 22/69) with placebo ( $P = 0.0504$ ).<sup>28</sup> The DIAMOND trial assessed patiomer for the management of HK among 1195 patients with HF<sub>rEF</sub> and current or prior RAASi-related HK.<sup>29</sup> DIAMOND showed that high dosage of RAASi therapy ( $\geq 50\%$  the target dosage of ACEi, ARB or ARNi, and 50 mg of spironolactone or eplerenone) was achieved in 84.6% of patients following the run-in phase with patiomer and optimization of the RAASi therapy.<sup>29</sup> Patients were then randomized to continued patiomer vs withdrawal, where patients continuing patiomer demonstrated lower risk of HK > 5.5 mmol/L (hazard ratio [HR] 0.63; 95% CI 0.45, 0.87;  $P = 0.006$ ) and MRA dosage reduction (HR 0.62; 95% CI 0.45, 0.87;  $P = 0.006$ ) and fewer total adjusted HK events/100 person-years (77.7 vs 118.2; HR 0.66; 95% CI 0.53, 0.81;  $P < 0.001$ ). The CARE-HK in HF registry will complement these clinical trial data, informing the use of patiomer and its association with risk of HK and enablement of evidence-based therapy for HF in routine clinical practice.

While gaps in medical therapy for HF have been repeatedly shown in clinical practice, the fundamental question of why these gaps exist remains generally unanswered. Multiple potential barriers to achieving guideline-recommended medical therapy have been proposed, including medical-level (eg, true medication intolerance), clinician-level (eg, education/awareness, inertia), patient-level (eg, patient preference, non-adherence/persistence), and system-level (eg, drug formularies, out-of-pocket costs).<sup>17,21</sup> Yet, despite much debate, no specific explanation has been proven dominant or definitive. Although prior research has examined patient or practice factors that are associated with medication changes in patients with HF, there are scarce data specifically within the population at high risk for HK. To address this knowledge gap, the CARE-HK in HF registry will allow examination of factors associated with medication changes. Combined with multiple other domains of clinical data, the study will provide a comprehensive and novel description of the longitudinal patient journey and care for a vulnerable population of patients with HF at high risk for HK.

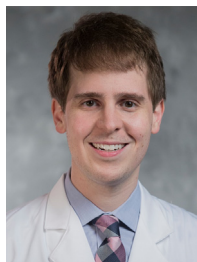


## Conclusions

The CARE-HK in HF registry is a large, multinational, prospective study embedded within clinical practice that will provide a unique opportunity to study the implications of HK on patterns of care and use of RAASis for HF. The registry specifically seeks to enroll a patient population with advanced CKD and high risk of hyperkalemia, a vulnerable patient population that has been underrepresented in prior HF registries. The study will also evaluate the association of patiromer, a novel K<sup>+</sup> binder, with use of guideline-recommended medical therapy and prevention of HK in routine clinical practice. These data will inform HF quality improvement initiatives by both characterizing the current patterns of care, frequency of HK, and clinical events (hospitalizations and mortality) among patients with HF at increased risk of HK, as well as identifying risk factors and potential underlying reasons for gaps in guideline-recommended medical therapy.

## Lay summary

- Guidelines recommend that patients with heart failure with reduced ejection fraction (HFrEF) should receive renin-angiotensin-aldosterone system inhibitors (RAASis) at the target dosages determined in clinical trials to improve outcomes and reduce mortality rates.
- In clinical practice, RAASis may not be initiated, continued or maintained at target dosages owing, in part, to fear of developing high blood potassium levels (known as hyperkalemia) that may have serious consequences.
- The CARE-HK in HF registry aims to characterize RAASi treatment patterns compared with guideline recommendations in patients with heart failure at high risk for hyperkalemia. Closing the gap between clinical practice and guideline recommendations should improve patient outcomes.



STEPHEN J. GREENE

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## References

1. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017;3:7–11.
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American

- College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol* 2022;79:e263–421.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. Group ESCSD. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726.
  4. Vijayakumar S, Butler J, Bakris GL. Barriers to guideline mandated renin-angiotensin inhibitor use: focus on hyperkalaemia. *Eur Heart J Suppl* 2019;21:A20–7.
  5. Thomsen RW, Nicolaisen SK, Hasvold P, Garcia-Sanchez R, Pedersen L, Adelborg K, et al. Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes: a Danish population-based cohort study. *J Am Heart Assoc* 2018;7:e008912.
  6. Núñez J, Bayés-Genis A, Zannad F, Rossignol P, Núñez E, Bodi V, et al. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. *Circulation* 2018;137:1320–30.
  7. Savarese G, Xu H, Trevisan M, Dahlstrom U, Rossignol P, Pitt B, et al. Incidence, predictors, and outcome associations of dyskaemia in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail* 2019;7:65–76.
  8. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol* 2017;46:213–21.
  9. Turgeon RD, Kolber MR, Loewen P, Ellis U, McCormack JP. Higher versus lower doses of ACE inhibitors, angiotensin-2 receptor blockers and beta-blockers in heart failure with reduced ejection fraction: systematic review and meta-analysis. *PLoS One* 2019;14:e0212907.
  10. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: Coordinated by the working group on cardiovascular pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother* 2018;4:180–8.
  11. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015;21:S212–20.
  12. Ferreira JP, Butler J, Rossignol P, Pitt B, Anker SD, Kosiborod M, et al. Abnormalities of potassium in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;75:2836–50.
  13. American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: Standards of medical care in diabetes-2022. *Diabetes Care* 2022;45:S175–84.
  14. Jonsson A, Edner M, Alehagen U, Dahlström U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail* 2010;12:25–31.
  15. Komajda M, Anker SD, Cowie MR, Filippatos GS, Mengelle B, Ponikowski P, et al. Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. *Eur J Heart Fail* 2016;18:514–22.
  16. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol* 2018;72:351–66.
  17. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, et al. Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019;73:2365–83.
  18. Brunner-La Rocca HP, Linssen GC, Smeele FJ, van Drimmelen AA, Schaafsma HJ, Westendorp PH, et al. Contemporary drug treatment of chronic heart failure with reduced ejection fraction: the CHECK-HF Registry. *JACC Heart Fail* 2019;7:13–21.
  19. Rossignol P, Lainscak M, Crespo-Leiro MG, Laroche C, Piepoli MF, Filippatos G, et al. and Heart Failure Long-Term Registry Investigators. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail* 2020;22:1378–89.
  20. Savarese G, Kishi T, Vardeny O, Adamsson Eryd S, Bodegård J, Lund LH, et al. Heart failure drug treatment-inertia, titration, and discontinuation: a multinational observational study (EVOLUTION HF). *JACC Heart Fail* 2023;11:1–14.
  21. Bozkurt B. Reasons for lack of improvement in treatment with evidence-based therapies in heart failure. *J Am Coll Cardiol* 2019;73:2384–7.
  22. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J* 2017;38:1883–90.
  23. Greene SJ, Butler J, Hellkamp AS, Spertus JA, Vaduganathan M, DeVore AD, et al. Comparative effectiveness of dosing of medical therapy for heart failure: from the CHAMP-HF Registry. *J Card Fail* 2022;28:370–84.
  24. Komajda M, Tavazzi L, Swedberg K, Böhm M, Borer JS, Moyne A, et al. investigators. Chronic exposure to ivabradine reduces readmissions in the vulnerable phase after hospitalization for worsening systolic heart failure: a post-hoc analysis of SHIFT. *Eur J Heart Fail* 2016;18:1182–9.
  25. Vaduganathan M, Fonarow GC, Greene SJ, DeVore AD, Albert NM, Duffy CI, et al. Treatment persistence of renin-angiotensin-aldosterone-system inhibitors over time in heart failure with reduced ejection fraction. *J Card Fail* 2022;28:191–201.
  26. Khariton Y, Hernandez AF, Fonarow GC, Sharma PP, Duffy CI, Thomas L, et al. Health status variation across practices in outpatients with heart failure: insights from the CHAMP-HF (Change the Management of Patients With Heart Failure) Registry. *Circ Cardiovasc Qual Outcomes* 2018;11:e004668.
  27. Patel RB, Fonarow GC, Greene SJ, Zhang S, Alhanti B, DeVore AD, et al. Kidney function and outcomes in patients hospitalized with heart failure. *J Am Coll Cardiol* 2021;78:330–43.
  28. Rossignol P, Williams B, Mayo MR, Warren S, Arthur S, Ackourey G, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): results in the pre-specified subgroup with heart failure. *Eur J Heart Fail* 2020;22:1462–71.
  29. Butler J, Anker SD, Lund LH, Coats AJS, Filippatos G, Siddiqi TJ, et al. Patiromer for the management of hyperkalaemia in heart failure with reduced ejection fraction: the DIAMOND trial. *Eur Heart J* 2022;43:4362–73.