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REVIEW

Epidemiology and risk factors for hyperkalaemia in heart failure

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Abstract

Patients with heart failure (HF), particularly those with impaired renal function receiving renin–angiotensin–aldosterone system inhibitors (RAASis), are at risk of hyperkalaemia; when hyperkalaemia is severe, this can have serious clinical consequences. The incidence, prevalence, and risk factors for hyperkalaemia reported in randomized trials of RAASis may not reflect clinical practice due to exclusion of patients with elevated serum potassium (sK^+) or severe renal impairment: information on patients managed in routine clinical care is important to understanding the actual burden of hyperkalaemia. This paper reviews the available clinical epidemiology data on hyperkalaemia in HF and considers areas requiring further research. Observational studies published since 2017 that focused on hyperkalaemia, included patients with HF, and had ≥1000 participants were considered. Hyperkalaemia occurrence in HF varied widely from 7% to 39% depending on the setting, HF severity, follow-up length, and concomitant medications. Rates were lowest in patients with newly diagnosed HF and highest in patients with greater disease severity; comorbidities, such as chronic kidney disease and diabetes, and RAASi use, reflected commonly identified risk factors for hyperkalaemia in patients with HF. Hyperkalaemia was most often mild; however, from the limited data available, persistence of mild hyperkalaemia was associated with an increased risk of mortality and major adverse cardiovascular events. There were also limited data available on the progression of hyperkalaemia. Recurrence was common, occurring in one-quarter to two-fifths of hyperkalaemia cases. Despite HF guidelines recommending close monitoring of sK^+, 55–93% of patients did not receive appropriate testing before or after initiation of RAASi or in follow-up to moderate/severe hyperkalaemia detection. Many of the observational studies were retrospective and from a single country. There is a need for international, prospective, longitudinal, observational studies, such as the CARE-HK in HF study (NCT04864795), to understand hyperkalaemia's prevalence, incidence, and severity; to identify and characterize cases that persist, progress, and recur; to highlight the importance of sK^+ monitoring when using RAASi; and to assess the impact of newer HF therapies and potassium binders in clinical practice. Data from both clinical trials and observational studies with adjustments for confounding variables will be needed to assess the contribution of hyperkalaemia to clinical outcomes.

Keywords Hyperkalaemia; Heart failure; Epidemiology; Renin–angiotensin–aldosterone system inhibitors; Risk factors

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Introduction

Both hyperkalaemia and hypokalaemia can lead to serious consequences and can constitute clinical emergencies when serum potassium (sK^+) levels are extreme (>6.0 and <2.5 mEq/L, respectively).[1,2] Hyperkalaemia can contribute to peripheral neuropathy and cause renal tubular acidosis and is associated with increased risk of mortality, which is only partially explained by cardiac arrhythmia caused by severe hyperkalaemia, although hyperkalaemia may be an

indirect rather than direct cause of increased mortality in other instances (this is discussed further in a later section).[3,4]

Because the kidneys play a central role in potassium (K^+) homeostasis,[5] and approximately one-third to one-half of patients with heart failure (HF) have renal insufficiency (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), patients with HF may be at greater risk of developing hyperkalaemia.[6] Renin–angiotensin–aldosterone system inhibitor (RAASi) treatments for HF, especially mineralocorticoid receptor antagonists (MRAs), may also cause or exacerbate hyperkalaemia. RAASis, such as angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs), indirectly interfere with angiotensin II-mediated stimulation of aldosterone, decreasing renal blood flow and increasing sK^+, and MRAs directly block the interaction of aldosterone with its receptor, reducing renal K^+ excretion.[7] Other factors that may play a role in the development of hyperkalaemia include the severity of HF, diabetes mellitus, acidosis, exercise, K^+ infusion/oral intake, and advanced age.[8,9]

In patients with HF with reduced ejection fraction [HFrEF; left ventricular ejection fraction (LVEF) ≤40%], RAASis, including ACEis, ARBs, angiotensin receptor–neprilysin inhibitors (ARNis), and MRAs, together with beta-blockers (BBs) and sodium–glucose cotransporter-2 inhibitors (SGLT-2is) have been shown to increase survival, reduce the risk of HF hospitalizations, and improve symptoms.[10–12] These therapies are, therefore, recommended for patients with HFrEF by the latest HF guidelines.[11,12] In a review of hyperkalaemia in clinical trials of RAASis in patients with hypertension, HF, or chronic kidney disease (CKD), the rate of hyperkalaemia (sK^+ >5.5 mEq/L) in patients on RAASi monotherapy was low (≤2%), but was higher (5%) in patients on dual RAASi therapy, and was highest (5–10%) in patients with HF or CKD albeit with small increases in sK^+ of 0.1–0.3 mEq/L and low rates of study discontinuation due to hyperkalaemia.[7] However, a more recent systematic review of clinical trials of ARB, ARNi, and MRA therapies in patients with HFrEF showed rates of hyperkalaemia (sK^+ >5.5 mEq/L) varying from 0.6% to 30.2%,[13] with the lowest rate in the ELITE trial of the ARB, losartan (only hyperkalaemia leading to treatment discontinuation is reported for the study),[14] and the highest rates in the EMPHASIS-HF trial of the MRA, eplerenone (11.8% vs. 7.2% on placebo) (*Figure 1*),[15] as well as a subgroup of patients with worsening renal function on spironolactone in the RALES trial (30.2% vs. 13.3% on placebo).[16] Indeed, the RALES and EPHESUS clinical trials showed patients with an eGFR <60 mL/min/1.73 m^2 receiving the MRAs, spironolactone, or eplerenone, had higher rates of hyperkalaemia (sK^+ >5.5 mEq/L) (22.1–25.6% on an MRA vs. 8.5–13.8% on placebo) as well as a higher proportion of experiencing worsening renal function (eGFR reduced 20–30%) compared with patients receiving placebo (16.9–17% vs. 7–14.7%).[16–18]

In general, conclusions on the extent of hyperkalaemia in HF from interventional clinical trials may be limited by inclusion of carefully selected populations with the patient selection criteria often inherently minimizing the risk of hyperkalaemia: for example, patients with elevated sK^+ and/or CKD may be underrepresented.[19] Furthermore, data on hyperkalaemia in clinical trials may be limited to patients with sK^+ >5.5 or 6.0 mEq/L, and HF therapy discontinuation with hyperkalaemia as a contributing factor may not be reported in all cases. Such limitations in data from interventional clinical trials may consequently impact how these interventions are used in clinical practice—hyperkalaemia and fear of hyperkalaemia have been identified as leading causes of the underuse or underdosing of guideline-directed medical HF therapies in clinical practice.[20–22] Following the results of clinical trials on MRA use in HF described above,[15–18] only 18–33% of patients with HFrEF were found to be treated with an MRA in clinical practice.[23,24] In contrast, other RAASis were found to be used in a greater proportion of patients, with ACEis/ARBs/ARNis used in approximately three-quarters and BBs used in approximately two-thirds of the patients studied in clinical practice.[23,24]

To understand the actual prevalence and incidence of hyperkalaemia and associated risk factors in routine clinical care, observational data are needed. This review assesses the currently available epidemiology data of hyperkalaemia and its risk factors in patients with HF treated in clinical practice and discusses the considerations for future observational studies to further understanding of the epidemiology of this condition in HF.

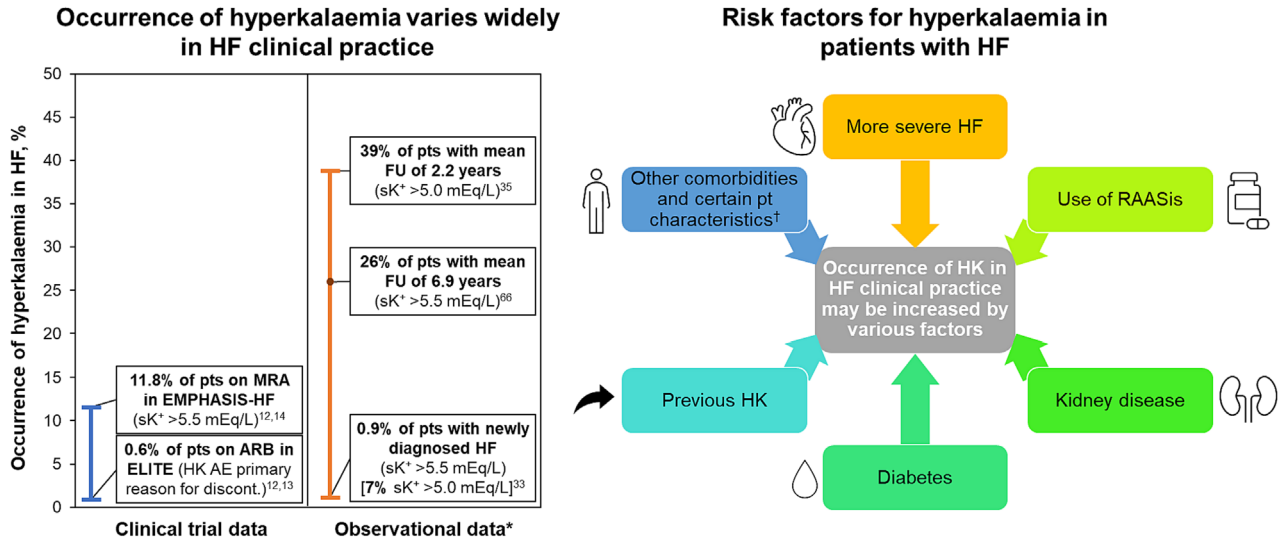
Selection of observational studies

Observational studies published since 2017, focused on the occurrence of hyperkalaemia, that included patients with HF and had ≥1000 participants were found by searching of MEDLINE using PubMed and were supplemented by author recommendations. Data have been referred to as prevalence or incidence as stated in the cited reference and as prevalence in instances where prevalence or incidence is not stated and new cases are not specified. Most of the identified references are of retrospective studies; only two prospective studies were identified, both of which are patient registries.[25,26]

Prevalence and incidence of hyperkalaemia

Hyperkalaemia is typically defined as sK^+ >5.0 mEq/L,[27] with mild, moderate, and severe hyperkalaemia defined as sK^+ >5.0 to ≤5.5, >5.5 to ≤6.0, and >6.0 mEq/L, respectively.[28] The prevalence of hyperkalaemia is infrequent

Figure 1 Hyperkalaemia (HK) occurrence, risk factors, and key areas for future research in patients (pts) with heart failure (HF). *See *Table 1* for further information on the observational studies cited. †See *Box 1* for details of comorbidities and patient (pt) characteristics. ‡Four pillars of therapy include angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ARBs)/angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists (MRAs), beta-blockers, and sodium–glucose cotransporter-2 inhibitors. AE, adverse event; discont., discontinuation; FU, follow-up; GDMT, guideline-directed medical therapy; RAASis, renin–angiotensin–aldosterone system inhibitors; sK^+, serum potassium.



There is a need for international prospectively designed observational studies with complete and systematic data collection to better understand hyperkalaemia occurrence, persistence, progression and monitoring, and the impact of GDMT using the four pillars of HF therapy‡ in HF clinical practice

in the general population (0.035%[25]), and patients with hyperkalaemia commonly have CKD, diabetes, or HF (58.9%, 39.7%, and 11.3%, respectively, vs. 1.1%, 13.1%, and 1.3%, respectively, in matched non-hyperkalaemic controls).[25] In clinical practice, the prevalence of hyperkalaemia ranged from 2.6% to 12.8% overall[29,30] and from 8.6% to 25.0% in patients with HF and/or CKD,[29–31] and the crude rate of hyperkalaemia was more than double in patients with HF than in patients overall (491 vs. 224 events per 1000 patient-years; Supporting Information, *Table S1*).[32] Overall, the majority of cases of hyperkalaemia in these studies were mild.[31–33]

In patients with HF, the prevalence of hyperkalaemia varied from 7% to 23% within 6 months prior to study inclusion to up to 1 year of follow-up,[25,29,30,34,35] and the incidence varied from 25% to 39% in studies with 1–3 years of follow-up (*Figure 1*).[31,36–38] Occurrence of hyperkalaemia varied depending on the care setting, severity of HF, length of follow-up, and concomitant medication exposure (*Table 1* and Supporting Information, *Table S1*), with cases more frequently mild than moderate/severe.[25,32,34,35,38] Over time, the incidence of hyperkalaemia in patients with HF can be large: in one study, the incidence was 39% with a mean follow-up of 2.2 years, and the cumulative incidences for hyperkalaemia were 25% within the first year and 32% within 3 years of HF diagnosis.[36] Notably, patients with HF and comorbidities, such as Stage 3a–5 CKD, had an even higher incidence (26–48%) of hyperkalaemia within the first year.[36] The lowest prevalence of hyperkalaemia in these studies (6.6%) was in patients with newly diagnosed HF.[34] The rate of hyperkalaemia in patients with newly diagnosed HF was also lower than in HF overall (323.5 vs. 490.6 per 100 patient-years).[24,44] In agreement with this, patients with more severe HF as determined by higher New York Heart Association (NYHA) functional class and lower LVEF were observed to have higher rates of hyperkalaemia,[25,41] with one of these studies identifying higher NYHA functional class as an independent predictor for hyperkalaemia.[23]

Patients with HF requiring more than two non-urgent care or emergency department (ED) visits at least 2 years apart,[41] or admitted to a hospital for HF,[25,42] have a high likelihood of hyperkalaemia (61% and 4.6–12.9%, respectively) (*Table 1*). Similarly, patients with HF and hyperkalaemia may require acute-care hospitalization or ED visits, although neither HF nor hyperkalaemia was specified as the reason for these visits.[34,36] For example, in one of these studies, 74% of patients with HF who developed hyperkalaemia had any acute-care hospitalization 6 months after hyperkalaemia vs. 53% of patients 6 months before the hyperkalaemia event [before–after risk ratio, 1.41; 95% confidence interval (CI), 1.38–1.44].[36]

Table 1 Prevalence and incidence of hyperkalaemia and hypokalaemia and risk factors for hyperkalaemia in studies of patients with HF

Study	Population studied	Years	Overall *n* and population breakdown	Prevalence		Risk factors for hyperkalaemia
				Hyperkalaemia	Hypokalaemia	
Retrospective cohort study of US nationwide Veterans Administration database in the United States[34]	Newly diagnosed HF	2005–13	Overall with HF: 142 087	Prevalence within 6 months prior to HF diagnosis[a] • 5.7% mild • 0.9% moderate/severe • 3.3% transient (one occurrence), 1.1% intermittent (>once but ≤50% measurements), and 0.4% persistent (>50% of measurements) within a year	Prevalence within 6 months prior to HF diagnosis[a] • 3.0% • 20.4% mild (3.5–3.9 mEq/L)	RR (95% CI) with strong associations with moderate/severe: • Age: 0.85 (0.80–0.90) • Black race: 0.58 (0.49–0.70) • eGFR <60 mL/min/1.73 m^2: 2.18 (2.04–2.32) • BMI: 0.88 (0.84–0.92) • Diabetes: 1.45 (1.23–1.70) • Loop/thiazide diuretics: 0.63 (0.56–0.71) • Potassium-sparing diuretics: 1.46 (1.24–1.72) • Anti-hypertensive drugs: 0.76 (0.68–0.86)
Retrospective study at a single tertiary hospital in Belgium[39]	HF	2000–17	Overall with HF: 2977: data on first 400 patients with full data available HFrEF: 46% AF: 36% COPD: 19% HT: 64% Dyslipidaemia: 66% DM: 33% In HFrEF: ACEis/ARBs: 74% BBs: 73%	Prevalence at mean follow-up of 6.9 years • 26% moderate/severe • 12% severe • 9% recurrence • One sK^+≥5.5 mmol/L during follow-up gave 6.57 higher odds (95% CI 3.14–13.80, $P < 0.001$) for recurrence	NA	Multivariate analysis OR (95% CI) • DM: 1.80 (1.03–3.19), $P = 0.040$ • Creatinine: 2.37 (1.45–3.85), $P < 0.001$
Retrospective cohort study of five health units in Italy[40]	HF	2010–17	Overall with HF: 8270	Prevalence[a] moderate/severe • 14%	NA	NA
SHAPE retrospective cohort study of general practice setting in Australia[35]	HF with sK^+ data	2013–18	Overall with HF: 17 405 HT: 41% COPD/asthma: 25% Depression/anxiety: 18% Severe renal impairment: 6% ACEis: 37% ARBs: 32% Spironolactone: 17%	Prevalence at time of HF diagnosis[a] • 10.8% mild • 1.9% moderate/severe	Prevalence at time of HF diagnosis[a] • 1.2%	NA

Table 1 (continued)

Study	Population studied	Years	Overall *n* and population breakdown	Prevalence		Risk factors for hyperkalaemia
				Hyperkalaemia	Hypokalaemia	
			Sacubitril/valsartan: 1%			
Patients requiring an ED visit						
Retrospective study of REDINSCOR II registry in Spain[42]	Hospitalized with AHF	NA	Overall with HF: 1779	Prevalence • 4.6% on admission • 2.7% on discharge	Prevalence • 8.2% on admission • 6.4% on discharge	NA

Retrospective study of Intermountain Healthcare database in the United States[41]	Adults with HF and ≥2 separate, non-urgent care or ED visits	2003–18	Overall with HF: 48 333	Prevalence[a]
				• 61%
					NA	Patients with vs. without hyperkalaemia were significantly ($P < 0.001$) more likely to
						• Be older (73 vs. 71 years)
						• Be male (49% vs. 46%)
						• Have risk factors associated with CVD:
						  ○ HT (90% vs. 73%)
						  ○ Hyperlipidaemia (71% vs. 47%)
						  ○ DM (50% vs. 29%)
						  ○ Smoker (35% vs. 24%)
						  ○ Renal insufficiency (35% vs. 9%)
						  ○ LVEF ≤40% (68% vs. 32%)
						  ○ Previous cardiac diagnosis, e.g.
						  ▪ ASCVD (49% vs. 34%)
						  ▪ AF (42% vs. 33%)
						• Receive baseline medication
						  ○ ACEis (57% vs. 27%)
						  ○ ARBs (26% vs. 11%)
						  ○ Aldosterone inhibitor (17% vs. 4%)
						  ○ Any RAASi (71% vs. 35%)
						• Receive follow-up medication
						  ○ ACEis (47% vs. 40%)
						  ○ ARBs (24% vs. 21%)

Table 1 (continued)

Study	Population studied	Years	Overall *n* and population breakdown	Prevalence		Risk factors for hyperkalaemia
				Hyperkalaemia	Hypokalaemia	
						○ Aldosterone inhibitor (21% vs. 12%) ○ Any RAASi (66% vs. 55%)
Prospective study of IN-HF registry in Italy[25]	Admitted to hospital for AHF or with CHF	2014	Overall: 9315 AHF: 1726 CHF: 7589	Prevalence at inclusion in study • AHF: 8.6% mild and 4.3% moderate/severe (12.9% in total) • CHF: 11.6% mild and 3.6% moderate/severe (14.9% in total)	Prevalence at inclusion in study • AHF: 9.8% • CHF: 2.4%	AHF patients with moderate/severe vs. normokalaemia were more frequently: • Hypotensive (37.8% vs. 18.3%) • Diabetic (54.1% vs. 38.9%) • Have CKD (60.8% vs. 30.3%) • Have LVEF <40% (61.8% vs. 56.6%) • Renally impaired [assessed by a creatinine level >1.5 mg/dL (72.2% vs. 25.6%) and eGFR <30 mL/min/1.73 m^2 (45.1% vs. 10.7%)] • Not treated with ACEis/ARBs + MRAs (32.1% vs. 42.6%) CHF patients with moderate/severe vs. normokalaemia were more frequently: • Older [≥70 years (62.2% vs. 51.0%)] • Female (30.6% vs. 26.8%) • Ischaemic (48.5% vs. 41.9%) • Diabetic (38.2% vs. 25.5%) • Have CKD (51.1% vs. 27.9%) • Renally impaired [assessed by a creatinine level >1.5 mg/dL (51.2% vs. 19.2%) and eGFR <30 mL/min/1.73 m^2 (24.9% vs. 6.2%)] • Not treated with ACEis/ARBs + MRAs (25.8% vs. 39%)

Table 1 (continued)

Study	Population studied	Years	Overall *n* and population breakdown	Incidence		Risk factors for hyperkalaemia
				Hyperkalaemia	Hypokalaemia	

Population-based cohort study in Northern Denmark[36]	Congestive HF	2000–12	Overall with HF: 31 649
			DM: 19%
			CKD: 41%
			HT: 62%
			CVD: 17%
			CPD: 18%
			ACEis: 24%
			ARBs: 11%
			BBs: 31%
			Spironolactone: 11%
			Loop diuretics: 39%
			NSAIDs: 22%
				• Incidence: 39% with a mean follow-up of 2.2 years
				  ○ IR: 178 (95% CI 175–181) per 1000 person-years
				• Cumulative risk: 25% first year and 32% within 3 years of HF diagnosis
				• Stage 3a–5 CKD: 26–48% within first year
				• Median time to first event: 0.34 years
				• In those with a first event, risk of second, third, or fourth event was 43%, 54%, and 60%, respectively
					NA	Prevalence ratio (95% CI) for strongest predictors
						• eGFR (mL/min/1.73 m^2)
						  ○ 30–44: 1.38 (1.33–1.45)
						  ○ 15–29: 2.05 (1.94–2.17)
						  ○ <15: 2.83 (2.49–3.21)
						  ○ Dialysis: 3.17 (2.44–4.12)
						• DM: 1.38 (1.32–1.45)
						• CKD: 1.46 (1.43–1.49)
						• PVD: 1.34 (1.30–1.43)
						• Spironolactone use: 1.48 (1.42–1.54)

SwedeHF registry in Sweden[37]	HF	2006–11	Overall with HF: 5848
			HT: 30%
			DM: 19%
			MI: 25%
			AF: 37%
			COPD: 16%
			ACEis/ARBs: 81%
			BBs: 83%
			MRAs: 36%
			Diuretics: 75%
				Incidence
				• 24.4% at least once within 1 year of follow-up
				  ○ 25.8% HFpEF
				  ○ 22.2% HFmrEF
				  ○ 24.7% HFrEF
				• 10.2% moderate/severe within 1 year of follow-up
				  ○ 11.4% HFpEF
				  ○ 10.6% HFmrEF
				  ○ 9.6% HFrEF
					Incidence
					• 20.3% at least once within 1 year of follow-up
					  ○ 25.6% HFpEF
					  ○ 20.5% HFmrEF
					  ○ 18.0% HFrEF
					• 3.7% had sK^+ <3.0 mEq/L within 1 year of follow-up
					  ○ 4.6% HFpEF
					  ○ 3.8% HFmrEF
					  ○ 3.2% HFrEF
						HR (95% CI) with strongest associations ($P < 0.05$)
						• Women: 0.86 (0.77–0.97)
						• BL sK^+ (mEq/L)
						  ○ 3.5 to <4: 0.79 (0.70–0.89)
						  ○ 4 to <4.5: ref
						  ○ 4.5–5: 1.49 (1.30–1.72)
						• eGFR (mL/min/1.73 m^2)
						  ○ 90+: ref
						  ○ 60–89: 1.46 (1.13–1.87)
						  ○ 45–59: 2.01 (1.53–2.65)
						  ○ 30–44: 2.68 (2.02–3.56)
						  ○ <30: 4.10 (3.04–5.53)
						• Hb <120 g/L: 1.43 (1.27–1.61)
						• DM: 1.33 (1.16–1.51)
						• COPD: 1.22 (1.06–1.40)
						• Hospitalization at diagnosis: 2.01 (1.72–2.36)
						• NYHA

(*Continues*)

Table 1 (continued)

Study	Population studied	Years	Overall *n* and population breakdown	Incidence		Risk factors for hyperkalaemia
				Hyperkalaemia	Hypokalaemia	
						○ I: ref ○ II: 1.33 (1.06–1.66) ○ III: 1.72 (1.36–2.17) ○ IV: 2.05 (1.45–2.88) • BBs: 0.81 (0.70–0.94) • MRAs: 1.85 (1.66–2.07)
Retrospective cohort study of Clinical Practice Research Datalink in the United Kingdom[38]	Adults with newly diagnosed HF	2006–15	Overall with HF: 21 334 DM: 15% Arrhythmia: 21% CPD: 14% RAASis: 63% Diuretics: 61% ACEis: 51% BBs: 45%	Over 3 years of follow-up • Incidence: 35.9% ○ IR: 323.5 (95% CI 319.1–327.9) per 1000 patient-years • 19.5% mild • 12.8% moderate/severe ○ IR: 79.9 (95% CI 77.8–82.1) per 1000 patient-years • 3.6% severe ○ IR: 16.1 (95% CI 15.1–17.1) per 1000 patient-years	Over 3 years of follow-up • Incidence: 9.2% ○ IR: 51.7 (95% CI 49.9–53.4) per 1000 patient-years	NA

ACEis, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AHF, acute heart failure; ARBs, angiotensin receptor blockers; ASCVD, atherosclerotic cardiovascular disease; BBs, beta-blockers; BL, baseline; BMI, body mass index; CHF, chronic heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPD, chronic pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; ED, emergency department; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; 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; HR, hazard ratio; HT, hypertension; IN-HF, Italian Network on Heart Failure; IR, incidence rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRAs, mineralocorticoid receptor antagonists; NA, not available; NSAIDs, non-steroidal anti-inflammatory drugs; NYHA, New York Heart Association; OR, odds ratio; PVD, peripheral vascular disease; RAASis, renin–angiotensin–aldosterone system inhibitors; RR, rate ratio; SHAPE, Study of Heart Failure in the Australian Primary CarE Setting; sK^+, serum potassium; SwedeHF, Swedish HF.
Mild, moderate, and severe hyperkalaemia defined as sK^+ >5.0 to ≤5.5, >5.5 to ≤6.0, and >6.0 mEq/L, respectively. Hypokalaemia defined as sK^+ <3.5 mEq/L.
[a]Prevalence was not stated in the paper, but reference was made to all patients with hyperkalaemia out of those tested and new cases were not specified.

Prevalence and incidence of hypokalaemia

Hypokalaemia is typically defined as sK^+ <3.5 mEq/L.[11] The prevalence and incidence of hypokalaemia have also been assessed in observational studies, including patients overall (incidence 13.6% over 3 years),[31] patients older than 55 years (prevalence 1.0–1.2% per year),[29] and patients with HF (prevalence 1.2–9.8% within 6 months prior to or at the time of study inclusion, varying by setting and severity of HF, and incidence 24% over 1 year of follow-up) (*Table 1* and Supporting Information, *Table S1*).[25,34,35,37,42]

Prevalence and incidence of hyperkalaemia in patients on renin–angiotensin–aldosterone system inhibitors

The prevalence and incidence of hyperkalaemia have also been specifically studied in patients receiving RAASi therapies in clinical practice, including some patients with HF,[22,43,44] as well as being studied in HFrEF specifically,[26] with recent systematic review/meta-analyses of patients prescribed with RAASis[45] or an ARNi specifically[46,47] (*Table 2*).

In RAASi (ACEis, ARBs, and MRAs) users, the prevalence of hyperkalaemia was 64.5% overall (71.6% in new RAASi users) in a large retrospective cohort study in the United Kingdom with an incidence rate of moderate/severe hyperkalaemia of 1.30 (95% CI 1.28–1.32) per 100 patient-years.[44] In studies of new users of ACEis/ARBs[43] and MRAs,[22] incidence of hyperkalaemia was 5.6% and 18.5%, respectively, with both studies showing that the incidence was higher compared with propensity score-matched cohorts of new BB users who were not on ACEis/ARBs and MRAs (4.4% and 6.4%, respectively).

In terms of HF specifically, one study of patients treated with ACEis/ARBs (74%), BBs (83%), and/or MRAs (55%) found the prevalence of hyperkalaemia to be 8% overall and 12.3% at 9 months of follow-up after up-titration of ACEis/ARBs.[26] In a systematic review of observational and interventional studies of patients with HFrEF prescribed with RAASis, the occurrence (prevalence and incidence were considered altogether) of moderate/severe hyperkalaemia was 2.0–38.2% (1.6–23.6% severe) in observational studies with combined use of RAASis vs. 2.8–19.0% for moderate/severe hyperkalaemia (0.5–5.6% severe) in interventional studies of RAASis.[45] Furthermore, in observational studies, there was a 4-fold to 13-fold increase in risk of hyperkalaemia when spironolactone or another MRA was added to background ACEi and/or ARB therapy, which is higher than risk estimates in clinical trials.[45] In a systematic review/meta-analysis of patients with HFrEF prescribed with sacubitril/valsartan in clinical practice, the incidence rate of moderate/severe hyperkalaemia was 12 (95% CI 5–19) per 100 person-years,[46] which was slightly higher than the 10 and 7.3 per 100 patient-years in MRA-treated and non-MRA-treated participants, respectively, in the PARADIGM-HF study.[49] Overall, these values suggest that there is a higher prevalence and incidence of moderate/severe hyperkalaemia in clinical practice than clinical trials. However, in another systematic review/meta-analysis of patients with HFrEF prescribed with sacubitril/valsartan in observational studies, the incidence of moderate/severe hyperkalaemia was 2.1% in men and 2.3% in women with a follow-up of 2–12 months[47] vs. 7.2–16.1% in randomized controlled trials.[49–51] Nuechterlein *et al*.[47] speculate that this lower incidence in observational studies than clinical trials could be due to less frequent sK^+ monitoring in clinical practice than clinical trials, and this is discussed further in a later section.

Observational studies of RAASis have focused on ACEis, ARBs, and MRAs (primarily spironolactone), with systematic review/meta-analysis of ARNis focused on sacubitril/valsartan. There is a lack of data from clinical practice on newer HF therapies. A meta-analysis of clinical trial data suggested that there was a lower relative risk of hyperkalaemia with ACEi/ARB treatment combined with finerenone than combined with eplerenone or spironolactone in patients with diabetic nephropathy.[52] Data from FIDELIO-DKD have shown that finerenone was independently associated with hyperkalaemia in patients with CKD and type 2 diabetes,[53] and data from the FIDELITY pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials, comprising 7.7% of patients with HF (patients with symptomatic HFrEF were excluded), have shown higher rates of hyperkalaemia (14.0% vs. 6.9%), serious hyperkalaemia (1.1% vs. 0.2%), and permanent discontinuation due to hyperkalaemia (1.7% vs. 0.6%) in patients receiving finerenone than placebo.[54] Furthermore, in FIDELITY, hyperkalaemia was reported more frequently in patients with poorer eGFRs.[55,56] However, an indirect comparison of clinical trial data showed lower rates of moderate/severe hyperkalaemia in patients treated with finerenone than those treated with spironolactone and a K^+ binder (11.6% vs. 35.4%).[57] The rate of hyperkalaemia with finerenone in patients with HFrEF will be established when data from the Phase 3 FINEARTS trial (NCT04435626) are available in 2024.[58] Results from DAPA-HF indicate that hyperkalaemia is less frequent in patients treated with MRAs in combination with dapagliflozin than in combination with placebo,[59] but, as yet, there are no studies of hyperkalaemia prevalence and/or incidence in patients with HF treated with SGLT-2is in clinical practice. Given that there may be differences in the prevalence and incidence of hyperkalaemia between clinical trials and observational studies, data on hyperkalaemia in patients with HF receiving these newer therapies in clinical practice are warranted.

Table 2 Prevalence and incidence of hyperkalaemia and risk factors for hyperkalaemia in patients on RAASis

Study	Population studied	Years	Overall *n* and population breakdown	Prevalence and incidence of hyperkalaemia	Risk factors for hyperkalaemia
Studies on RAASis Retrospective cohort study of UK Clinical Practice Research Datalink–Hospital Episodes Statistics[44]	RAASi users (ACEi, ARB, and MRA)	2009–15	Overall RAASi users: 434 027 • HF: 32 462 (8%) New RAASi users: 154 275 • HF: 8592 (6%) Overall and new RAASi users: Type 1 or 2 diabetes: 19% and 12% Ischaemia: 23% and 18% Stage 3 CKD: 14% and 8% Stage 4/5 CKD: 1% and 1% ACEi: 75% ARBs: 23% MRA: 2%	• Overall and new RAASi users at any time before RAASi use ○ Prevalence[a]: 64.5% and 71.6% • Of those with history of hyperkalaemia (overall and new RAASi users): ○ 91% and 91% mild ○ 7.3% and 7.6% moderate ○ 1.6% and 1.4% severe • IR moderate/severe: 1.30 (95% CI 1.28–1.32) per 100 patient-years • IR (95% CI) first moderate/severe per 100 patient-years with vs. without history hyperkalaemia: ○ New RAASi users ▪ 3.41 (3.28–3.54) vs. 0.74 (0.71–0.77) ○ All RAASi users ▪ 3.13 (3.08–3.19) vs. no history of hyperkalaemia: 0.63 (0.61–0.64)	IR first moderate/severe higher with: • Older age • History of moderate/severe hyperkalaemia • Stage 4/5 CKD • Comorbidities ○ Diabetes type 1 or 2 ○ Hyperlipidaemia ○ Ischaemia ○ MI ○ HF ○ Arrhythmia ○ AF ○ CVD ○ COPD ○ Chronic liver disease
Studies on MRAs Observational study including all Stockholm citizens in Sweden[22]	New MRA users (primarily spironolactone)	2007–10	Overall: 13 726 HF: 6302 (46%) HT: 64% DM: 25% ACEis: 38% ARBs: 28% BBs: 63% Thiazide/loop diuretics: 68% NSAIDs: 18% Other BP-lowering: 31%	Incidence • 18.5% ≥ 1 event within a year: 14.9% mild and 7.1% moderate/severe, the majority within the first 3 months of therapy ○ HF subgroup: 26.2% ≥1 event, 10.87% moderate/severe • 6.4% ≥1 event within a year in propensity score-matched cohort new users of BBs not on MRAs: 2% moderate/severe	HR (95% CI) • <45 years: ref • 45–64 years: 1.56 (1.12–2.16) • 65–74 years: 1.75 (1.26–2.42) • >74 years: 2.00 (1.45–2.76) • eGFR (mL/min/1.73 m^2) ○ >60: ref ○ 45–60: 1.49 (1.34–1.65) ○ 30–45: 2.08 (1.84–2.33) ○ <30: 2.51 (2.09–3.02) • sK^+ (mmol/L)

(*Continues*)

Table 2 (continued)

Study	Population studied	Years	Overall *n* and population breakdown	Prevalence and incidence of hyperkalaemia	Risk factors for hyperkalaemia
					○ 4–5: ref ○ >5.0: 2.78 (2.17–3.58) • Comorbidities ○ PVD: 1.19 (1.07–1.32) ○ HF: 1.29 (1.17–1.43) ○ DM: 1.63 (1.50–1.77) • Concomitant medications ○ ACEis: 1.54 (1.41–1.69) ○ ARBs: 1.17 (1.06–1.28) ○ BBs: 1.12 (1.02–1.23) ○ Thiazide/loop diuretics: 1.52 (1.36–1.70)
Studies on ACEis/ARBs Cohort study of SCREAM project in Sweden[43]	New ACEi/ARB users with creatinine and K^+ monitoring	2007–10	Overall: 52 996 with sK^+ measured HF: 4797 (9%) DM: 11% CAD, CVD, or PVD: 16% NSAIDs: 27% Other diuretics: 24% K^+-sparing diuretics: 5% BBs: 42%	Incidence • 5.6%: 1.7% moderate/severe and 0.63% severe ○ Of those who developed hyperkalaemia, 33.6% had another episode within the year • 4.4%: 1.4% moderate/severe in a propensity score-matched cohort of new users of BBs not on ACEis/ARBs (*n* = 20 186)	OR (95% CI), $P < 0.001$ unless stated for mild (moderate similar) • Female: 0.83 (0.76–0.90) • sK^+: 1.19 (1.17–1.20) • eGFR (mL/min/1.73 m^2) ○ <60: 1.93 (1.80–2.07) ○ >60: 1.24 (1.18–1.31) • DM: 1.64 (1.47–1.82) • Congestive HF: 1.57 (1.40–1.76) • CAD, CVD, and PVD: 1.12 (1.01–1.24), $P = 0.031$ • ACEi (vs. ARB): 1.17 (1.03–1.32), $P = 0.012$ • K-sparing diuretics: 2.06 (1.80–2.35) • Other diuretics: 1.12 (1.01–1.24), $P = 0.032$
Prospective BIOSTAT-CHF international study[26,48]	HFrEF treated with ACEis/ARBs and/or BBs	2010–12	Overall with HF: 1666 DM: 32% MI: 38% AF: 43% HT: 59% eGFR < 60 mL/min/1.73 m^2: 45%	Prevalence[a] • 8% overall: 2% moderate/severe ○ 19% Slovenia, 13% Poland, 12% Serbia, and 11% Greece	Hyperkalaemia vs. normokalaemia • eGFR <45 mL/min/1.73 m^2: 33% vs. 20% • Prior eGFR <60 mL/min/1.73 m^2: 61% vs. 43% • MRA: 63% vs. 55%

(*Continues*)

Table 2 (continued)

Study	Population studied	Years	Overall *n* and population breakdown	Prevalence and incidence of hyperkalaemia	Risk factors for hyperkalaemia
			COPD: 17% ACEis/ARBs: 74% BBs: 83% MRAs: 55% Diuretics: 100% Digoxin: 18%	• 12.3% 9 months after up-titration of ACEis/ARBs	• Digoxin: 14% vs. 19%
Studies on ARNis					
Systematic review/ meta-analysis of real-world studies[46]	European patients with HFrEF prescribed with sacubitril/ valsartan	2014–20	Overall with HF: 1076 in six studies Prior HF hospitalization: 17% HT: 28% DM: 99% AF: 22% ACEis: 82% ARBs: 82% BBs: 99.6% MRAs: 99.6% Diuretics: 81% Digoxin: 4%	• IR moderate/severe[b]: 12 (95% CI 5–19) per 100 person-years ○ IR moderate/severe: 10 and 7.3 per 100 patient-years in MRA-treated and non-MRA-treated participants in PARADIGM-HF, respectively[52]	NA
Systematic review/ meta-analysis of observational studies[47]	HFrEF prescribed with sacubitril/valsartan	2015–20	Overall with HF: 8981 in 10 studies DM: 68% males and females HT: 36% males and 55% females BBs: 67% males and 65% females	• Incidence moderate/severe ○ 2.1% in men and 2.3% in women with a follow-up of 2–12 months ○ 13.2–16.1% in randomized controlled trials of sacubitril/ valsartan[50,51] ○ 7.2% vs. 9.4% in MRA-treated and non-MRA-treated participants in PARADIGM-HF, respectively[49]	NA

ACEis, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; ARNis, angiotensin receptor–neprilysin inhibitors; BBs, beta-blockers; BP, blood pressure; CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; HT, hypertension; IR, incidence rate; K^+, potassium; MI, myocardial infarction; MRAs, mineralocorticoid receptor antagonists; NA, not available; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PVD, peripheral vascular disease; RAASis, renin–angiotensin–aldosterone system inhibitors; SCREAM, Stockholm CREAtinine Measurements; sK^+, serum potassium.
Mild, moderate, and severe hyperkalaemia defined as sK^+ >5.0 to ≤5.5, >5.5 to ≤6.0, and >6.0 mEq/L, respectively. Hypokalaemia defined as sK^+ <3.5 mEq/L.
[a]Prevalence was not stated in the paper, but reference was made to all patients with hyperkalaemia out of those tested and new cases were not specified.
[b]Moderate/severe hyperkalaemia was not stated in the paper, but reference was made to IR of moderate/severe hyperkalaemia in Desai *et al*. when comparing data.

Risk factors for hyperkalaemia

Characteristics of patients with hyperkalaemia include older age,[30,31,60,61] particularly in patients >80 years old,[60] being male[61,62] (although a higher proportion with hyperkalaemia were female in one study[30]), and being non-White.[62] Patients with comorbidities such as HF,[31,61] more advanced CKD,[29,31,61,62] reduced renal function,[32,60] diabetes,[29–31,61] hypertension,[30,31,61] higher Charlson Comorbidity Index (CCI),[30] and peripheral vascular disease[31,61] were also at increased risk of hyperkalaemia. Patients receiving ACEis,[29,31,61] ARBs,[29,31,61] MRAs,[31,61] and/or BBs[31] and/or not receiving loop/thiazide diuretics or other blood pressure medication[31,61] were at increased risk of hyperkalaemia (*Table 1* and Supporting Information, *Table S1*). Likewise, in studies of patients receiving RAASis (ACEis, ARBs, and MRAs),[44] MRAs,[22] and ACEis/ARBs,[43] similar characteristics as those mentioned above were observed in patients with hyperkalaemia (*Table 2*).

Similarly, in patients with HF specifically, there were a number of factors relating to patient characteristics, comorbidities, and the severity and treatment of HF that have been identified as risks for hyperkalaemia (*Box 1* and *Figure 1*). Factors such as impaired kidney function and diabetes were commonly identified as risk factors for hyperkalaemia in patients with HF.[25,26,34,36,37,41,45] While, in most studies, RAASis[45] including ACEis,[41] ARBs,[41] and MRAs[26,36,37,41] were identified as risk factors for hyperkalaemia in patients with HF, there was one study that showed that no treatment with ACEis/ARBs + MRAs[25] was a risk factor for hyperkalaemia. This finding could be related to the discontinuation of ACEis/ARBs + MRAs in patients who previously developed hyperkalaemia.

Box 1 Summary of risk factors for hyperkalaemia in HF

Patient characteristics

- Older/advanced age[25,41,45] although also younger age[34]
- Non-Black race[34]
- Lower BMI[34]
- Male[25,41] although also female[37]
- Higher baseline sK^+[37,45]
- Previous hyperkalaemia[36]
- Hb < 120 g/L[37]
- Smoker[41]
- Haematocrit <0.36[45]

Comorbidities

- Lower eGFR/higher creatinine/renal insufficiency[25,26,34,36,37,41]
- Dialysis[36]
- CKD[25,36,45]
- Diabetes[25,34,36,37,41,45]
- PVD[36]
- COPD[37]
- Hypertension[41] although also hypotension (in AHF)[25]
- Hyperlipidaemia[41]
- Ischaemia[25]

HF severity/therapies

- Higher NYHA functional class[37]
- LVEF ≤ 40%[25,41]
- Requires hospitalization[37]
- No use of loop/thiazide diuretics[34]
- No use of other anti-hypertensive drugs[34]
- No use of digoxin[26]
- RAASis:
  - ACEis[41]
  - ARBs[41]
  - MRAs[26,36,37,41]
    - ACEis/ARBs + MRAs[45]
    - Although also no treatment with ACEis/ARBs + MRAs[25]
  - No use of BBs[37]
- Use of K^+-sparing diuretics[34] plus trimethoprim or ACEi[45]

ACEis, angiotensin-converting enzyme inhibitors; AHF, acute heart failure; ARBs, angiotensin receptor blockers; BBs, beta-blockers; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; K^+, potassium; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; PVD, peripheral vascular disease; RAASis, renin–angiotensin–aldosterone system inhibitors; sK^+, serum potassium.

No observational studies have so far identified risk factors for hyperkalaemia in patients with HF receiving ARNis. However, clinical trial data from PARADIGM-HF showed that severe hyperkalaemia was less likely during treatment with MRAs plus sacubitril/valsartan than MRAs plus enalapril [2.2 vs. 3.1 per 100 patient-years; hazard ratio (HR) 1.37 (95% CI 1.06–1.76), $P = 0.02$].[49]

Persistence, progression, and recurrence of hyperkalaemia

There is limited evidence available on the persistence of hyperkalaemia in the observational studies identified. One study of patients with newly diagnosed HF defined hyperkalaemia by the frequency of occurrence: transient

hyperkalaemia was one occurrence; intermittent hyperkalaemia was more than one occurrence, but ≤50% of sK^+ measurements were elevated; and persistent hyperkalaemia as >50% of sK^+ measurements were elevated.[34] This study found that the prevalence was 3.3%, 1.1%, and 0.4% for transient, intermittent, and persistent hyperkalaemia, respectively, with the highest risk of mortality in those with persistent [adjusted HR 1.7 (95% CI 1.5–1.9)], followed by intermittent [adjusted HR 1.3 (95% CI 1.2–1.4)], and transient [adjusted HR 1.3 (95% CI 1.3–1.4)] hyperkalaemia.[34] However, these mortality rates likely also reflect the underlying pathologies of the patients and treatments they receive. Similarly, in a study including a broader population of patients with sK^+ measurements in clinical practice, with the same definitions of hyperkalaemia as the previous study, even mild hyperkalaemia was associated with adverse clinical and economic consequences in cases where the hyperkalaemia was persistent or recurrent.[63] The risk of major adverse cardiovascular events (MACEs) was higher in patients with persistently recurring hyperkalaemia than those with transient hyperkalaemia [HR 2.31 (95% CI 2.20–2.43), $P < 0.001$].[63] Again, the risk of MACE likely also reflects the characteristics and treatment of the patients studied in each cohort. For example, CCI was higher (4.3 vs. 3.1) and RAASi use was lower (ACEi 30% vs. 48%; ARB 13% vs. 18%; MRA 37% vs. 25%) in patients with hyperkalaemia that was persistently recurring than when it was transient.[63] Indeed, hyperkalaemia has been suggested as a risk marker for RAASi discontinuation, and a large European registry study of patients with HF showed that after adjusting for RAASi (ACEi, ARB, or MRA) discontinuation, hyperkalaemia was no longer associated with increased mortality.[4] A further study of patients with Stage 3–5 CKD, a third of whom also had HF, found a greater effect of transient (<50% of sK^+ measurements were elevated) than chronic (>50% of sK^+ measurements were elevated) hyperkalaemia on increasing the risk of MACE vs. the reference of normokalaemia [HR 1.36 (95% CI 1.29–1.44) and HR 1.16 (95% CI 1.05–1.28), respectively].[61] In this study, patients with transient hyperkalaemia also had an increased risk of hyperkalaemia on MRAs vs. patients with chronic hyperkalaemia [odds ratio 1.76 (95% CI 1.66–1.87) and odds ratio 1.26 (95% CI 1.10–1.45), respectively].

In terms of progression of hyperkalaemia (i.e. when sK^+ increases further and hyperkalaemia becomes more severe), there is also limited evidence available from observational studies. One study of patients with mild hyperkalaemia, which included patients with HF, assessed sK^+ over 2 years and found that 16.9% progressed to moderate/severe hyperkalaemia and 8.7% progressed to severe hyperkalaemia.[62]

There is evidence that recurrence of hyperkalaemia occurs in approximately one-quarter to two-fifths of hyperkalaemia cases in a large healthcare setting,[31] after ED discharge,[64] in RAASi users,[43] in MRA users,[22] and in patients with HF.[34,36] RAASi users had an increased risk of moderate or severe hyperkalaemia if they had a history of hyperkalaemia than if they did not [rate of 3.41 (95% CI 3.28–3.54) vs. 0.74 (95% CI 0.71–0.77) per 100 patient-years].[44] In patients with HF and a first hyperkalaemia event, risk of second, third, or fourth event was 43%, 54%, and 60%, respectively.[36]

Frequency of potassium monitoring

The most recent HF guidelines recommend closely monitoring sK^+ levels of patients with HF initiating or receiving ACEi/ARB/ARNi/MRA therapy.[11,12] However, low rates of sK^+ monitoring have been observed in clinical practice (*Table 3*).[31,32,34,43,65] For example, although the majority of patients with HF (83.0–95.5%) had sK^+ measured in the course of a year,[31,34] many patients (55.4–92.8%) did not receive appropriate testing before or after initiation of MRAs[65] or ACEi/ARB,[43] or in follow-up to moderate/severe hyperkalaemia detection.[34] In comparison, patients in clinical trials, such as PARADIGM-HF, were evaluated every 2–8 weeks during the initial 4-month double-blind treatment phase, with sK^+ assessed at every study visit and further checks advised for any patient with an sK^+ >5.3 mEq/L.[49,50]

Notably, in a large retrospective cohort study in the United Kingdom of patients with at least one of HF, resistant hypertension, diabetes, Stage 3+ CKD, dialysis, and/or RAASi use (ACEis, ARBs, MRAs, and renin inhibitors), the crude rate of hyperkalaemia was highest in patients with HF and lowest in patients receiving RAASis (490.6 vs. 211.0 per 1000 patient-years).[32] Additionally, the frequency of sK^+ tests was highest in patents with HF and lowest in patients receiving RAASis (crude rate 2429.3 vs. 1216.2 per 1000 patient-years).[32] James *et al*.[32] speculate that these data may reflect a heightened awareness of hyperkalaemia in patients with HF, discontinuation of RAASis following hyperkalaemia in these patients, and/or treatment of patients with RAASis who lack the comorbidities that may increase their hyperkalaemia risk and who therefore did not require frequent sK^+ monitoring. The accuracy of presented data on prevalence and incidence of hyperkalaemia or hypokalaemia may be influenced by the perceived risk of these conditions in that patient population and resulting frequency of testing, completeness of test results in clinical records, and/or lack of data capture of laboratory results within the research databases used for observational analyses. Patients perceived to be at risk of hyperkalaemia are also more likely to have sK^+ monitored and hyperkalaemia diagnosed.[31,38,43,65] For example, higher proportions of mild and moderate/severe as well as recurrent hyperkalaemia were detected in one study with more frequent testing, with odds ratio for hyperkalaemia detection of 4.17 (95% CI 3.99–4.36) for 3–4 sK^+ tests per year and 17.26 (95% CI 16.58–17.97) for >4 sK^+ tests per year.[43]

Table 3 Frequency of potassium monitoring in patients with HF and/or on RAASis

Study	Population studied	Years	Overall *n* and population breakdown	Frequency of sK^+ measurements
Cohort study of claims data from the Centers for Medicare and Medicaid Services Virtual Research Data Center[65]	HF initiating MRAs	May–September 2011	Overall with HF: 10 443 CKD: 45.4% ACEi/ARB: 53.3%	• Overall, 7.2% received appropriate testing before and after MRA initiation • 13.3% and 29.9% received appropriate laboratory testing during early and extended follow-up, respectively • 55.4% and 22.3% received no testing during the early or extended follow-up, respectively • AF, anaemia, CKD, COPD, hypothyroidism, osteoporosis, and diuretic use associated with a greater likelihood of appropriate laboratory testing
Cohort study of SCREAM project in Sweden[43]	New ACEi/ARB users with creatinine and K^+ monitoring	2007–10	Overall: 52 996 with sK^+ measured HF: 4797 (9%) DM: 11% CAD, CVD, or PVD: 16% NSAIDs: 27% Other diuretics: 24% K^+-sparing diuretics: 5% BBs: 42%	• 34% of new ACEi or ARB users had sK^+ checked within 1 month of treatment initiation • 24% had not had sK^+ checked within 1 year after ACEi or ARB initiation ○ sK^+ more likely to be checked than not if older and with HF, DM, CAD, lower eGFR (87 vs. 94 mL/min/1.73 m^2, $P < 0.001$), and higher prevalence of eGFR <60 mL/min/1.73 m^2 (10.6% vs. 4.3%, $P < 0.001$) ○ Baseline sK^+: 4.1 mmol/L both with and without sK^+ monitoring
Retrospective cohort study of SCREAM project in Sweden[31]	Adults with ≥1 ambulatory serum creatinine measurement in inpatient or outpatient care within the preceding year	2006–11	Overall: 364 955 with K^+ measured HF: 29 684 (8%) HT: 54% CVD: 19% DM: 16% On RAASis: 23%	• Number of tests/year overall and in HF ○ No tests: 24.5% and 4.5% ○ Of those tested overall and in HF: ▪ 1–2 tests: 69.4% and 31.3% ▪ 3–4 tests: 16.7% and 24.8% ▪ >4 tests: 13.9% and 43.9% • More frequent sK^+ tests if older, men, and with DM, HT, CVD, and low eGFR • More frequent sK^+ tests associated with increased use of all studied medications
Retrospective cohort study of Clinical Practice Research Datalink in the United Kingdom[38]	Adults with newly diagnosed HF	2006–15	Overall with HF: 21 334 DM: 15% Arrhythmia: 21% CPD: 14% RAASis: 63% Diuretics: 61% ACEis: 51% BBs: 45%	• Median (inter-quartile range): 1.85 (1.06–3.27) per year • Hyperkalaemia more frequently detected in patients with ≥1.85 than <1.85 sK^+ measurements per year (17.8% vs. 13.8%, $P < 0.001$)
Retrospective cohort study of US nationwide Veterans Administration database in the United States[34]	Newly diagnosed HF	2005–13	Overall with HF: 142 087	• 83% had ≥1 measurement of sK^+ within a year of incident HF • 43.4% with moderate/severe hyperkalaemia received repeated measurement of sK^+ within 2 weeks
Retrospective cohort study of Clinical Practice Research Datalink and linked Hospital	≥1 of condition: HF, resistant HT, diabetes, Stage 3+	2003–18	Overall: 931 460 HF: 84 210 (9%) Resistant HT: 34%	• Crude rate (95% CI) of testing per 1000 patient-years ○ HF: 2429.25 (2423.17–2435.34): highest rate of cohorts studied ○ RAASis: 1216.19 (1214.99–1217.40): lowest rate of cohorts studied

(*Continues*)

Table 3 (continued)

Study	Population studied	Years	Overall *n* and population breakdown	Frequency of sK^+ measurements
Episode Statistics databases in the United Kingdom[32]	CKD, dialysis, and/or RAASis		Diabetes: 31% Stage 3+ CKD: 31% Dialysis: 0.5% RAASi use: 81% RAASis and in no other group: 28%	

ACEis, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BBs, beta-blockers; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPD, chronic pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HT, hypertension; K^+, potassium; MRAs, mineralocorticoid receptor antagonists; NSAIDs, non-steroidal anti-inflammatory drugs; PVD, peripheral vascular disease; RAASis, renin–angiotensin–aldosterone system inhibitors; SCREAM, Stockholm CREAtinine Measurements; sK^+, serum potassium.

Another factor that could be considered along with the frequency of sK^+ measurements may be seasonal variations in sK^+ levels. One Japanese study of sK^+ measured in an ED showed that moderate/severe hyperkalaemia prevalence was higher in winter than summer months in patients with both preserved (2.9% vs. 1.1%) and reduced renal function (14.4% vs. 9.7%).[60] This agrees with other studies of haemodialysis patients in Japan and the United States, which showed higher sK^+ in winter than summer months.[63–65] This seasonal variation in sK^+ levels may be due to such factors as seasonal trends in the consumption of vegetables and fruits, loss of K^+ through sweat and urine in hot weather, and seasonal variations in serum aldosterone levels.

Considerations for future observational studies of hyperkalaemia

Occurrence of hyperkalaemia in HF varied widely in the region of 7–39% depending on the setting, severity of HF, length of follow-up, and concomitant medication exposure.[25,29–31,34–38] Rates were notably higher in patients with HF than general populations,[25,29–31] and within HF populations, were lowest in patients with newly diagnosed HF,[32,34,38] and were highest in patients with greater disease severity,[25,37,41] comorbidities such as CKD,[36] visits to the ED or hospital,[25,41,42] and RAASi use.[26,36,37,41,45] Because there is evidence to show that the comorbidities of CKD and diabetes[25,26,34,36,37,41,45] and the use of RAASis (ACEis, ARBs, and MRAs)[26,36,37,41,45] are risk factors for hyperkalaemia in patients with HF, it will be important to understand how these risk factors are modified in patients with HFrEF receiving the recently recommended combination of ACEis/ARBs/ARNis, MRAs, BBs, and SGLT-2is[11,12] in clinical practice. This knowledge will help to ensure the optimal treatment of HF with guideline-directed medical therapies while minimizing the risk of hyperkalaemia.

Hyperkalaemia in patients with HF was most often mild[25,32,34,35,38]; however, it has been shown that even mild hyperkalaemia is associated with an increased risk of mortality and MACEs when hyperkalaemia persists.[34,63] A notable difference between using observational study and clinical trial data to assess the clinical consequences of hyperkalaemia or hypokalaemia is that patients are not necessarily selected in observational studies as they are in clinical trials, for example, on the basis of sK^+ and specific HF severity, with the exclusion of other potentially confounding conditions, such as Stage 5 CKD. Therefore, the resultant population may consist of patients with differing disease severities and a mixture of additional prognostically relevant conditions, which may require a variety of different treatment approaches, adding a layer of complexity to the findings. Although propensity score matching can be used to match for factors such as CKD stage

or CCI, unmeasured confounding factors will inevitably remain. A combination of data from both clinical trials and well-characterized observational studies with appropriate adjustments for confounding variables may eventually show the true contribution of deviations in sK^+ to clinical outcomes.

There is limited evidence available on the persistence as well as the progression of hyperkalaemia in clinical practice. Limited existing studies indicate that there are proportions of patients for whom hyperkalaemia persists[34] or progresses.[62] Because persistent hyperkalaemia has been associated with adverse clinical consequences that may be mitigated by earlier medical management, it would be valuable to assess in more detail how frequently this occurs in clinical practice as well as characterize these patients to further understand the subsequent clinical implications. A number of studies have shown that recurrence of hyperkalaemia is common and prior hyperkalaemia (or higher baseline sK^+) is a risk factor for the future development of hyperkalaemia.[22,29,31,34,36,43,64] This finding supports frequent monitoring of sK^+ particularly in patients with a history of hyperkalaemia, which is supported by HF guidelines.[11,12] However, low rates of sK^+ monitoring have been observed in clinical practice,[31,32,34,43,65] with factors such as perceived risk and risk profiles for hyperkalaemia and/or frequency/data capture of sK^+ monitoring having an impact. Notably, recent studies on sK^+ monitoring have been lacking. Insufficient sK^+ monitoring in clinical practice will have an impact not only on prevalence and incidence data but also on the prompt detection and treatment of the condition. Therefore, it is important to determine whether the insufficient sK^+ monitoring observed in clinical practice reflects a lack of ordering of tests and/or a lack of documentation of laboratory findings in observational datasets. A lack of perceived necessity and/or record of sK^+ monitoring could be addressed with increased awareness of the importance of sK^+ monitoring per guidance after initiating or changing RAASi dose.

Notably, many of the observational studies on hyperkalaemia have been retrospective and usually from a single country. These studies may have incomplete data collection related to the limitations of documentation such as a lack of coding for hyperkalaemia, no claim records for non-reimbursed (out-of-pocket) RAASis, and missing or incomplete test result records. Thus, there is a need for international prospectively designed studies with complete and systematic data collection.

The CARE-HK in HF study (NCT04864795) is a prospective observational study that aims to understand RAASi treatment patterns in clinical practice and adoption of guideline-directed medical therapy recommendations.[69] Longitudinal data on patients with HF and history of hyperkalaemia or at high risk of hyperkalaemia will be gathered in this study to provide evidence on the impact of new HF guideline implementation and use of the newer therapies such as ARNis, SGLT-2is, and finerenone on hyperkalaemia in clinical practice.

Both the European Society of Cardiology HF guidelines and the American Heart Association/American College of Cardiology/Heart Failure Society of America HF guidelines provide recommendations on RAASi use depending on the degree of hyperkalaemia, with dose reductions or treatment discontinuation advised, as well as recommending to avoid or monitor use of K^+-retaining drugs (K^+-sparing diuretics) when using MRAs.[11,12] It is also a standard clinical recommendation that patients with CKD and chronic hyperkalaemia should avoid foods high in potassium, but the clinical effectiveness of this advice is uncertain.[70] Management of hyperkalaemia with K^+ binders in patients with HF on RAASis was recently included in the European HF guidelines, with K^+ binders potentially allowing initiation or up-titration of RAASis in a larger proportion of patients.[11] However, the American HF guidelines highlight that the effectiveness of K^+ binders to improve outcomes by facilitating RAASi is uncertain, and this is an area for future research.[12] Importantly, data on the use of K^+ binders and their impact on RAASi treatment decisions in patients with HF will also be collected in CARE-HK in HF to help understand the value of K^+ binders to enable RAASi treatment.

Conclusions

Occurrence of hyperkalaemia in HF varied widely in the region of 7–39% depending on the setting, severity of HF, length of follow-up, and concomitant medication exposure. Rates of hyperkalaemia were highest in patients with commonly identified risk factors for hyperkalaemia in HF, such as CKD and diabetes, and the use of RAASis. Cases of hyperkalaemia were mostly mild, but there are patients for whom hyperkalaemia persists, progresses, or recurs, which was associated with an increased risk of mortality and MACEs. Despite HF guidelines recommending close monitoring of sK^+, low rates of monitoring are observed in clinical practice, which impacts not only the understanding of prevalence and incidence of hyperkalaemia but also the prompt detection and treatment of the condition. Further international prospective longitudinal observational studies are therefore warranted to better understand the prevalence, incidence, and severity of hyperkalaemia; characterize and identify cases of hyperkalaemia that persist, progress, and recur; highlight the importance of sK^+ monitoring in clinical practice; and assess the impact of newer therapies, such as ARNis, SGLT-2is, finerenone, and K^+ binders (*Figure 1*).

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Conflict of interest

D.E.G. reported consultancy fees from Vifor. G.F. reported lecture fees and/or advisory and/or trial committee membership by Bayer, Boehringer Ingelheim, Servier, Novartis, Impulse Dynamics, Vifor, Medtronic, Cardior, Novo Nordisk and Research Grants from the European Union. A.J.S.C. reported honoraria and/or lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, Respicardia, and Viatris. F.P. reported consulting fees from Vifor Pharma and Novo Nordisk; honoraria from Servier, Pfizer, Novartis, and Boehringer Ingelheim. N.R.D works under contract with the Centers for Medicare and Medicaid Services to develop and maintain performance measures used for public reporting and pay for performance programs and reports research grants and consulting for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Cytokinetics, Merck, Novartis, SCPharmaceuticals, and Vifor. G. M.C.R reports no conflict of interest. J.G.F.C reports honoraria from CSL Vifor as a member of the steering committee of CARE-HK and is supported by a British Heart Foundation Centre of Research Excellence (grant number RE/18/6/34217). J.K. and A.R.d.A. are employees of CSL Vifor.

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Supporting information

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

Table S1. Prevalence and incidence of hyperkalaemia and hypokalaemia, and risk factors for hyperkalaemia in studies that include patients with HF.

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