Challenges of managing hyperkalemia in HF patients with CKD while maintaining RAASi therapy

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Disclosures

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- personal fees from Abbott
- personal fees from TEVA
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- personal fees from GETZ
- personal fees from Menarini
- personal fees from Hikma

HK is frequent among cardiorenal patients

Advanced stages of CKD[1,a]

Up to **40–50%** of patients, especially in those with T2D and on RAASi therapy

Haemodialysis[2,3,b,c]

≈ 25% of patients despite receiving haemodialysis[d,e]

Heart failure[4,a,f]

Up to **≈40%** of patients with severe HF[f] on spironolactone 50 mg

Diabetes mellitus[5,a]

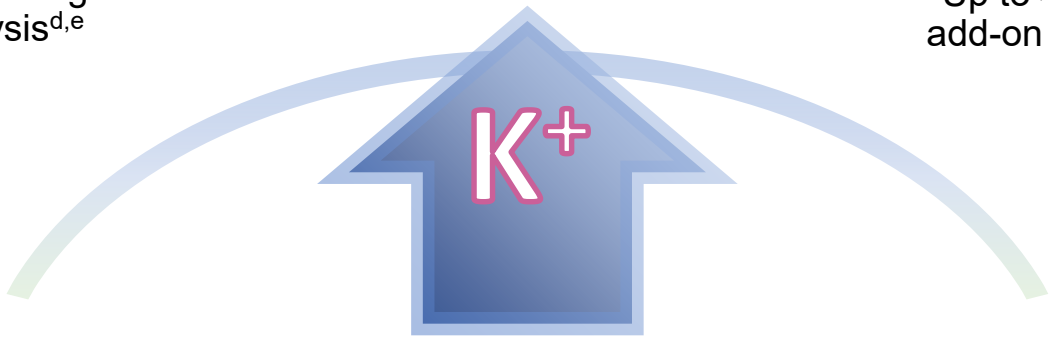
≈17% over 3-year period

Resistant hypertension[6,7,g]

Up to **≈8–17%** with add-on MRA therapy

General population[1,a]

2–3%

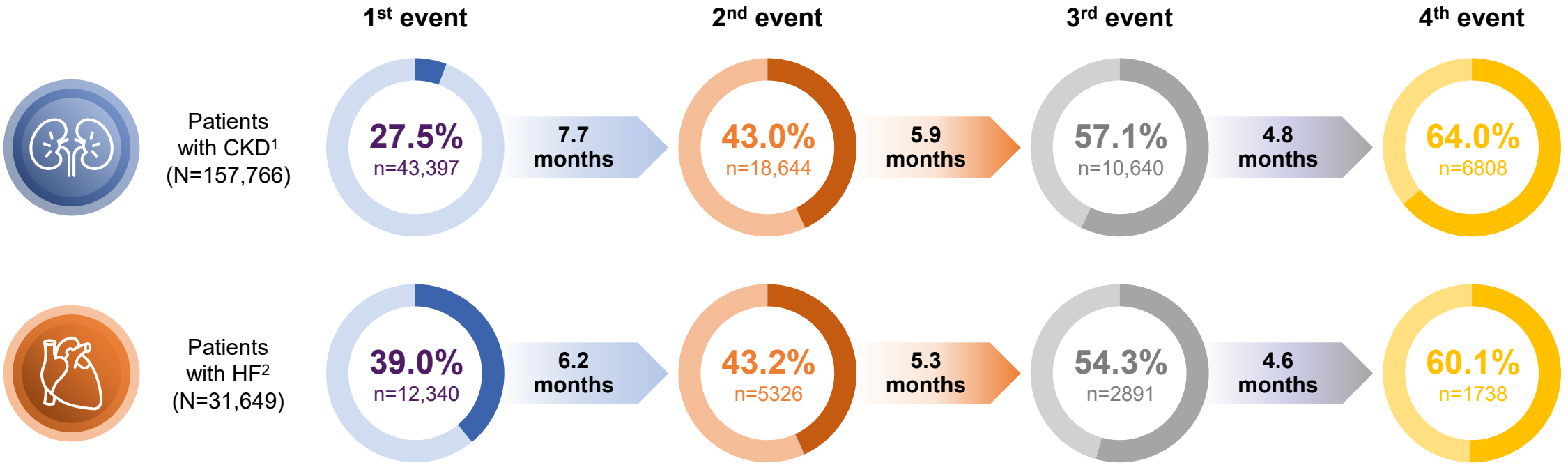


- [a]HK defined as sK^+ >5.0 mmol/L;[1,4,5] [b]HK defined as sK^+ >5.5 mmol/L;[2] [c]When reported, most studies in this systematic review defined HK as sK^+ ≥5.5 mmol/L[3]; [d]Included patients who received haemodialysis for >120 days;[2] [e]Included patients with end-stage renal disease receiving haemodialysis three times weekly (mean vintage time on haemodialysis, where reported, was 42.3 months);[3] [f] New York Heart Association class III or IV and left ventricular ejection fraction <35%;[4] [g]HK defined as persistent sK^+ >5.5 mmol/L (or one reading of sK^+ ≥6.0 mmol/L)[7]
- CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; sK^+, serum potassium; T2D, Type 2 diabetes
- 1. Kovesdy CP. *Nat Rev Nephrol* 2014;10:653–662; 2. Xu H, et al. *Nephrol Dial Transplant* 2017;32(Suppl. 3):iii563; 3. Bem D, et al. *Ren Fail* 2021;43:241–254; 4. Vardeny O, et al. *Circ Heart Fail* 2014;7:573–579; 5. Nilsson E, et al. *Int J Cardiol* 2017;245:277–284; 6. Chomicki J, et al. *J Am Soc Hypertens* 2014;8:e30; 7. Khosla N, et al. *Am J Nephrol* 2009;30:418–424

Patients with CKD and HF have recurrent hyperkalaemia episodes, with successively shorter time between the episodes[1,2]

Population-based cohort study linking individual data from hospital, prescription and laboratory databases in patients from the Danish National Patient Registry in northern Denmark (population 1.8 million) from 2000 to 2012[1,2]

Proportion of patients with recurrent hyperkalaemia events[a] and median time to event

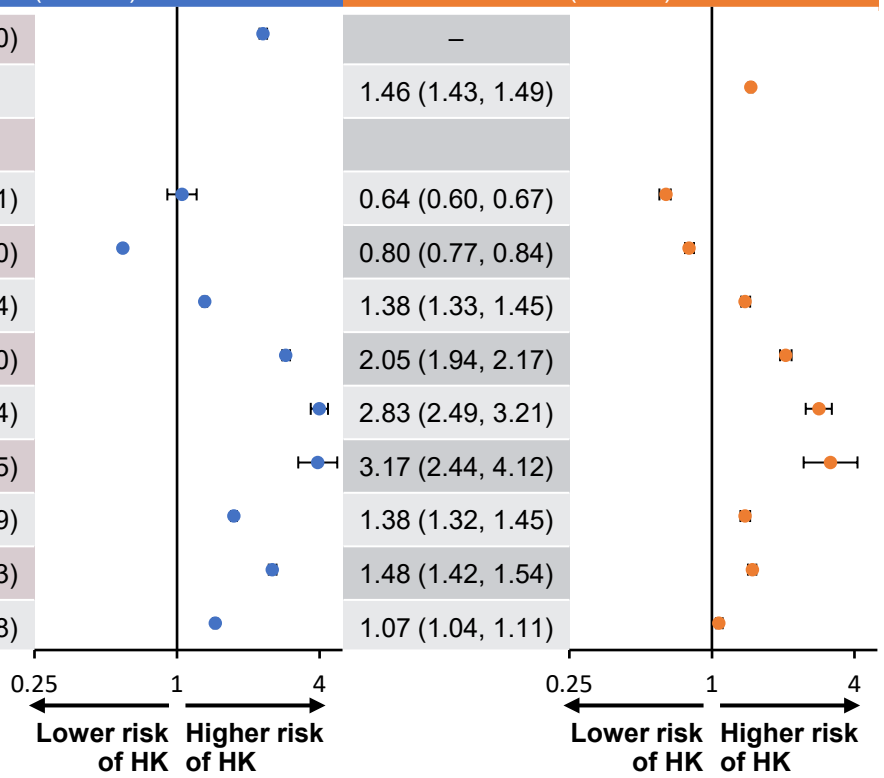


- [a]A hyperkalaemia event was defined as sK+ >5.0 mmol/L not preceded by a prior episode of elevated potassium within the previous month[1,2]
- CKD, chronic kidney disease; HF, heart failure; sK^+, serum potassium
- 1. Thomsen RW, et al. *Nephrol Dial Transplant* 2018;33:1610–1620; 2. Thomsen RW, et al. *J Am Heart Assoc* 2018;7:e008912.

Decreasing eGFR, diabetes and RAASi/MRA therapy are the main risk factors for first hyperkalaemic episode in patients with CKD or HF

Adapted from Thomsen RW, et al. (2018)[1]

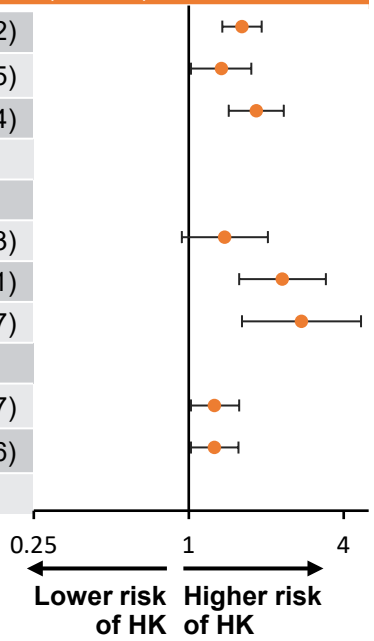
	CKD PR (95% CI)[1,a]	HF PR (95% CI)[2,a]
HF	2.31 (2.23, 2.40)	–
CKD	–	1.46 (1.43, 1.49)
eGFR		
≥60 mL/min/1.73 m²	1.05 (0.91, 1.21)	0.64 (0.60, 0.67)
45–59 mL/min/1.73 m²	0.59 (0.58, 0.60)	0.80 (0.77, 0.84)
30–44 mL/min/1.73 m²	1.31 (1.28, 1.34)	1.38 (1.33, 1.45)
15–29 mL/min/1.73 m²	2.88 (2.78, 3.00)	2.05 (1.94, 2.17)
<15 mL/min/1.73 m²	3.99 (3.67, 4.34)	2.83 (2.49, 3.21)
Dialysis	3.93 (3.25, 4.75)	3.17 (2.44, 4.12)
Diabetes	1.74 (1.69, 1.79)	1.38 (1.32, 1.45)
Spironolactone[b]	2.53 (2.44, 2.63)	1.48 (1.42, 1.54)
ACEi	1.45 (1.42, 1.48)	1.07 (1.04, 1.11)



- **Several other factors have been associated with HK (sK⁺ >5.5 mmol/L) in patients with HF.[3,c]**

Adapted from Savarese G, et al. (2019)[3]

	HF HR (95% CI)[3,d]
Haemoglobin, <120 g/L	1.61 (1.35, 1.92)
Smoker	1.34 (1.02, 1.75)
Hospitalisation at diagnosis	1.83 (1.43, 2.34)
NYHA functional class	
I	Reference
II	1.38 (0.94, 2.03)
III	2.31 (1.57, 3.41)
IV	2.74 (1.61, 4.67)
Ejection fraction, %	
>50	1.26 (1.02, 1.57)
40–49	1.26 (1.02, 1.56)
<40	Reference



- [a]Data from Danish population-based cohort studies. PRs when compared with matched cohort without HK. HK defined as K⁺ >5.0 mmol/L. Relative importance of risk factors increased by higher K⁺ level; [b]Non-steroidal MRAs such as finerenone are associated with lower rates of HK compared with spironolactone;[4] [c]Data from 5848 Swedish patients enrolled in the SwedeHF Registry from 2006 to 2011 and followed-up for 1 year; [d]HK defined as K⁺ >5.5 mmol/L
- ACEi, angiotensin-converting enzyme inhibitor; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HK, hyperkalaemia; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PR, prevalence ratio; RAASi, renin–angiotensin–aldosterone system inhibitor; sK⁺, serum potassium
- 1. Thomsen RW, et al. *Nephrol Dial Transplant* 2018;33:1610–1620; 2. Thomsen RW, et al. *J Am Heart Assoc* 2018;7:e008912; 3. Savarese G, et al. *JACC Heart Fail* 2019;7:65–76;
4. Agarwal R, et al. *Clin Kidney J* 2022;16:293–302

Hyperkalemia is frequent and associated with poor prognosis but…

JACC: HEART FAILURE VOL. 7, NO. 1, 2019

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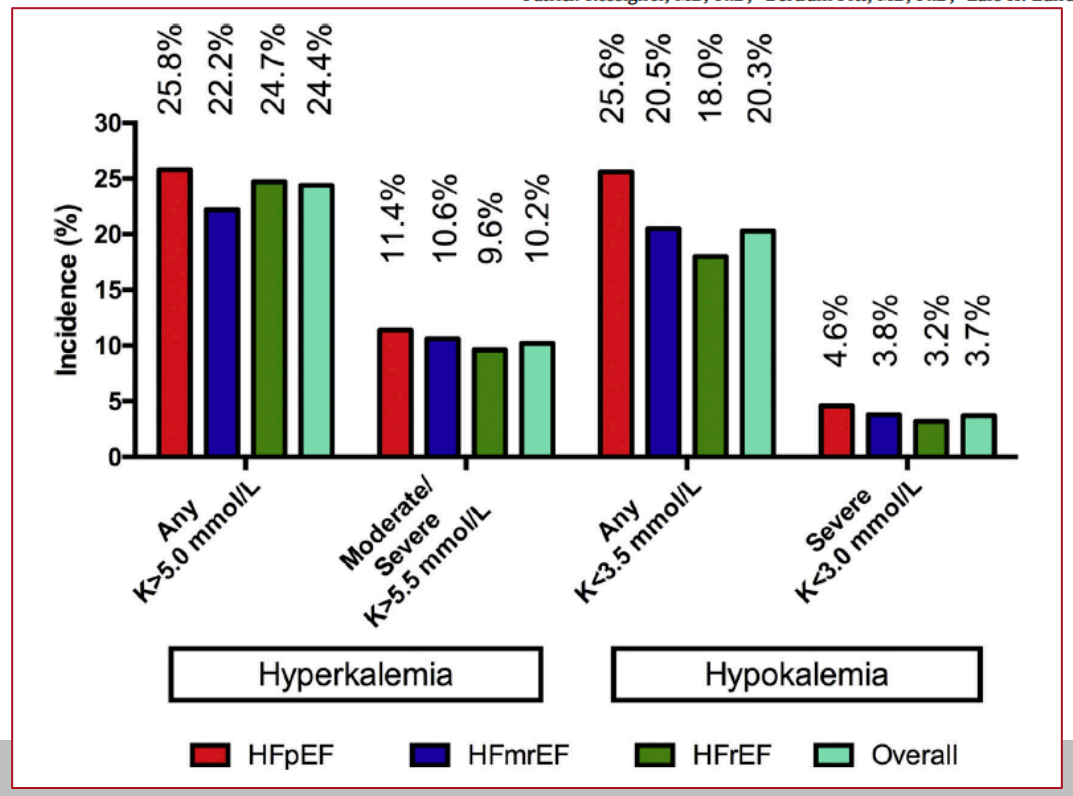
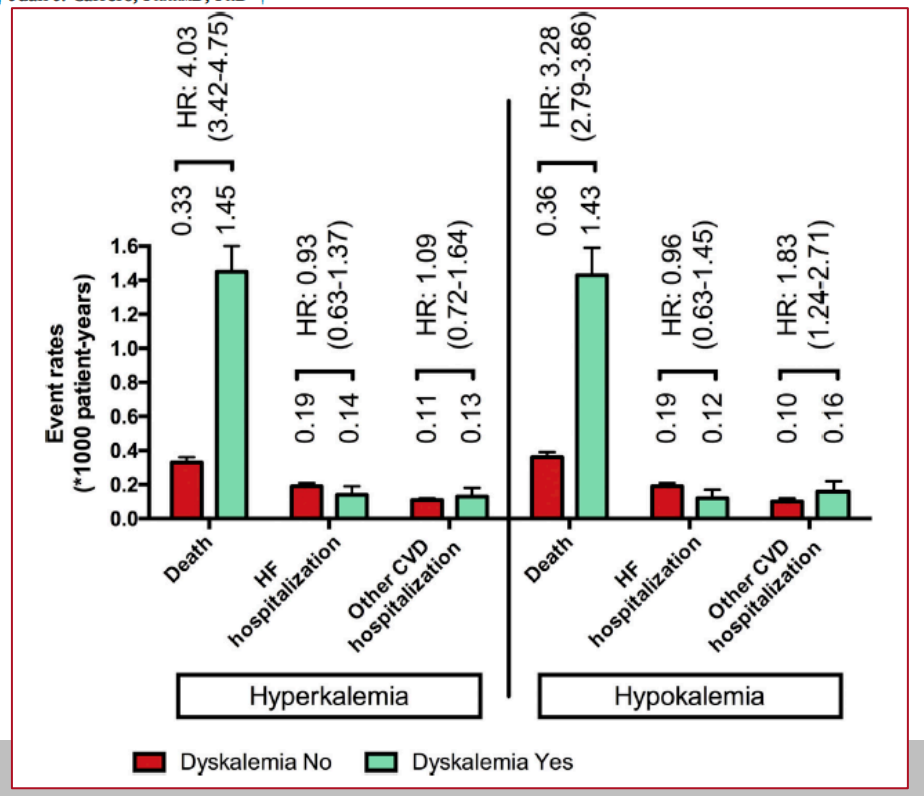
Incidence, Predictors, and Outcome Associations of Dyskalemia in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction

Gianluigi Savarese, MD, PhD,[a,*] Hong Xu, MD,[b,*] Marco Trevisan, MSc,[b] Ulf Dahlström, MD, PhD,[c] Patrick Rossignol, MD, PhD,[d] Bertram Pitt, MD, PhD,[e] Lars H. Lund, MD, PhD,[a,†] Juan J. Carrero, PharmD, PhD[b,†]





.. missed implementation might be even more dangerous

ESC European Society of Cardiology

HFA Heart Failure Association

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES · KDIGO

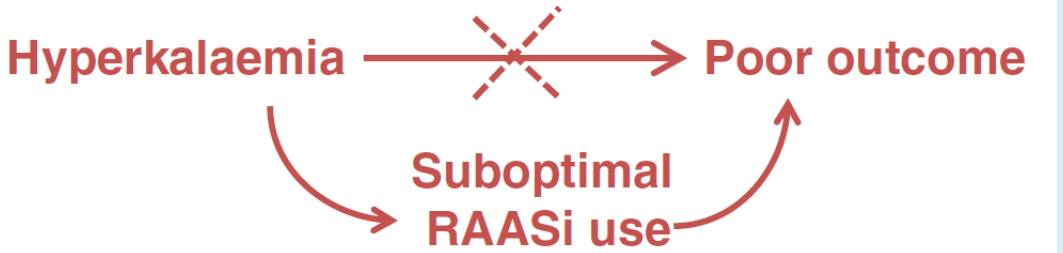


Figure 1 Hyperkalaemia is a risk marker for poor outcomes by leading to dose reduction or discontinuation of renin–angiotensin–aldosterone system inhibitors (RAASi).

HK is one of the major obstacles for implementing GDMT in HFrEF

ESC European Society of Cardiology
European Journal of Heart Failure (2024) 0, 0–0
doi:10.1002/ejhf.3214
RESEARCH ARTICLE

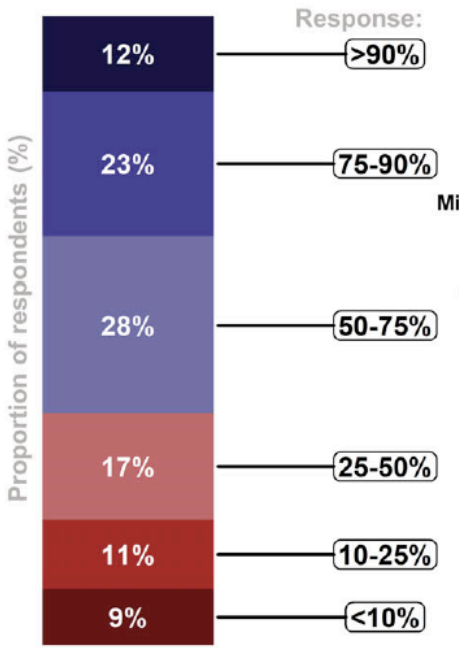
Physician perceptions, attitudes, and strategies towards implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. A survey of the Heart Failure Association of the ESC and the ESC Council for Cardiology Practice

Gianluigi Savarese[1,2*†], Felix Lindberg[1†], Ruxandra M. Christodorescu[3], Marc Ferrini[4], Thomas Kumler[5,6], Konstantinos Toutouzas[7], Giuseppe Dattilo[8], Antoni Bayes-Genis[9,10], Brenda Moura[11], Offer Amir[12], Mark C. Petrie[13], Petar Seferovic[14], Ovidiu Chioncel[15,16], Marco Metra[17], Andrew J.S. Coats[18], and Giuseppe M.C. Rosano[19,20*]

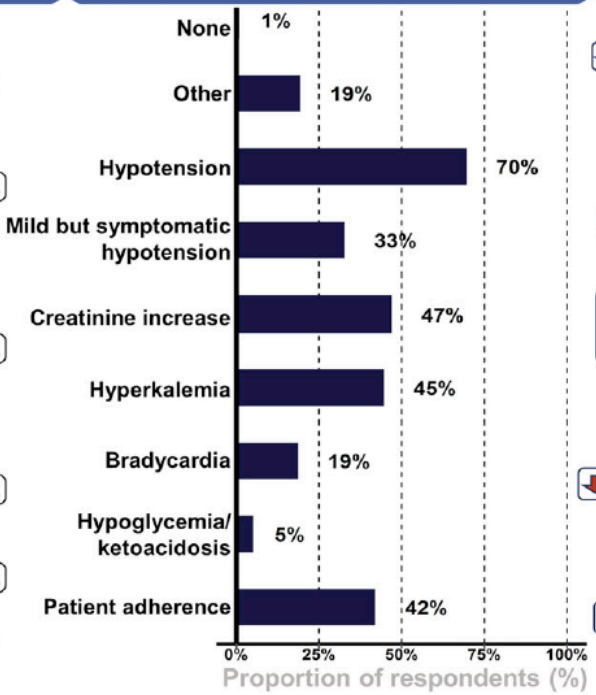
Physician perceptions, attitudes, and strategies towards implementing GDMT in HFrEF
An international survey study from the HFA of the ESC

26-question survey | 432 respondents | 91 countries

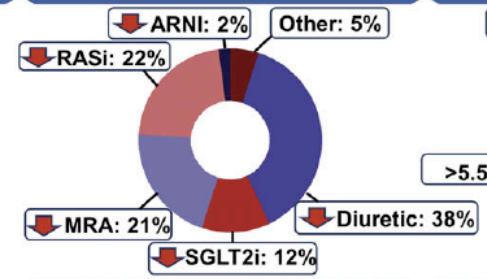
What proportion of HFrEF patients are treated with quadruple therapy?



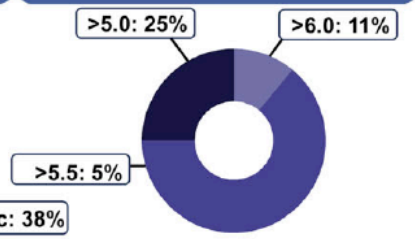
What clinical barriers to implementation are of major importance?



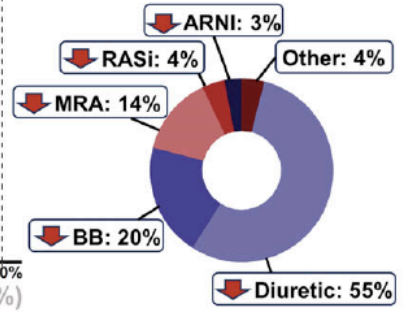
First strategy to manage creatinine increase



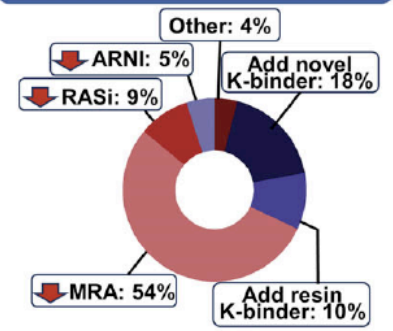
K-level that triggers change in therapy



First strategy to manage hypotension



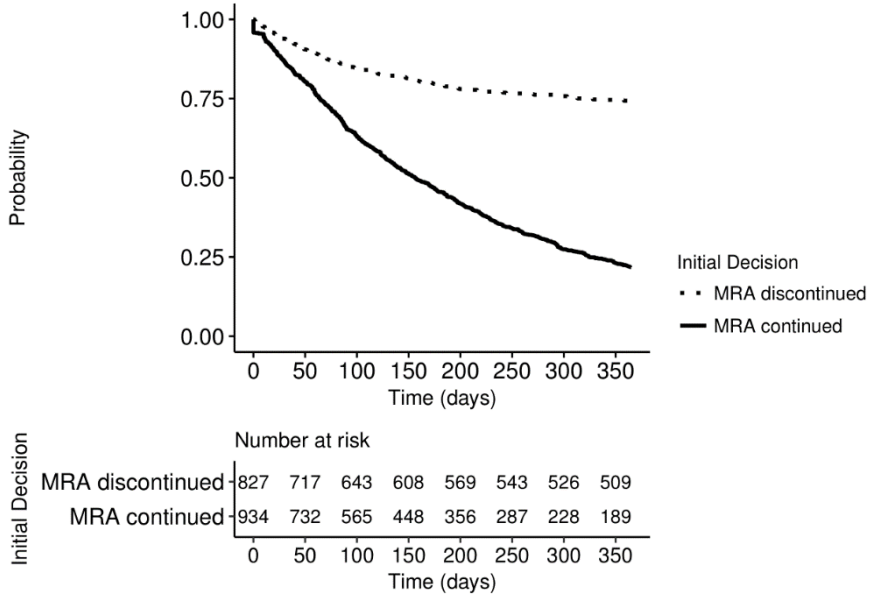
First strategy to manage hyperkalemia



Discontinuation of ACEi/ARB and MRA persists following a HK event

- **19%** of **new MRA** users had **HK within 1 year** (majority within 3 months)[1,a]
- **After HK**, **47% discontinued MRA** and **10% reduced** their **dose**[1]
- **74%** of those who discontinued **MRA did not re-initiate during 1-year follow-up**[1]

Time to MRA cessation in patients who continued therapy after HK and time to MRA re-initiation in those who discontinued[b]



Mean duration of RAASi[c] discontinuation was:[2]

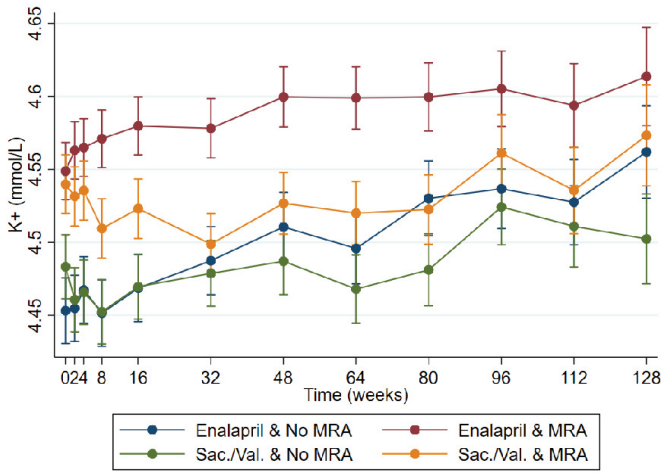
2.4 years
in patients with CKD

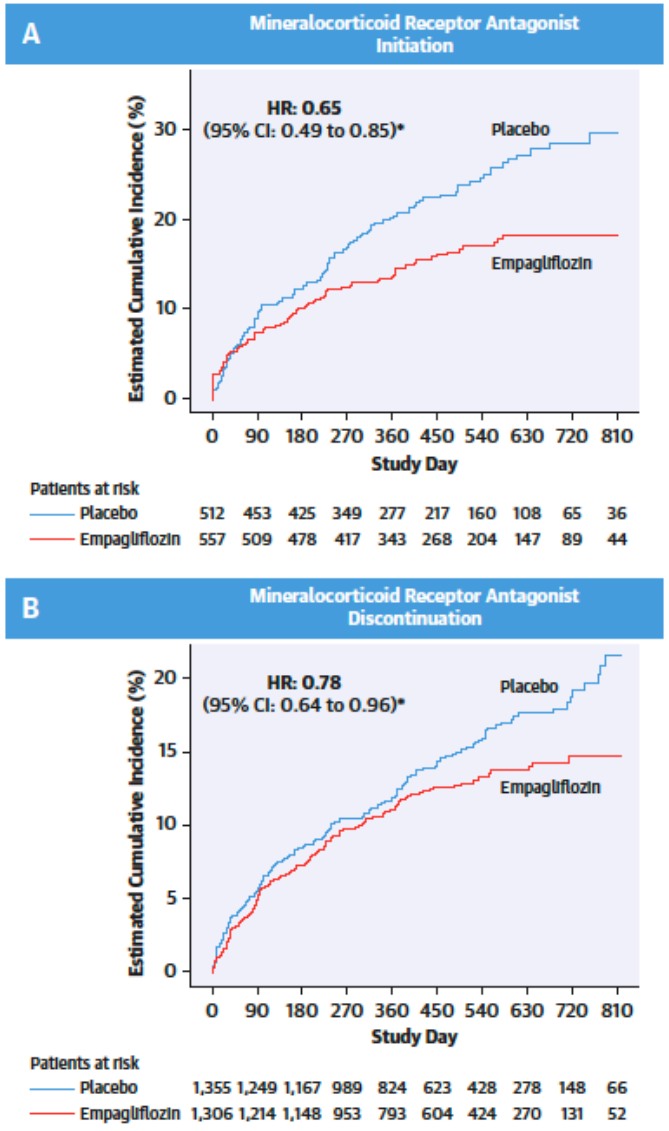
1.9 years
in patients with HF

- [a]This is a Swedish population study; [b]MRA cessation was defined as absence of new dispensation of MRA within 30 days after patient's most recent supply expired. For example, those receiving a 90-day supply of MRA had 120 days from their previous purchase to refill it; [c]RAASi defined as ACEi, ARB or MRA[2]
- ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor
- 1. Trevisan M, et al. *Eur J Heart Fail* 2018;20:1217–1226; 2. Linde C, et al. *J Am Heart Assoc* 2019;8:e012655

Drugs helping each other: ARNi and SGLT2i for better K homeostatis

PARADIGMHF





Ferreira. EJHF 2020

Ferreira, J.P. et al. J Am Coll Cardiol. 2021;77(11):1397-407.

Circulation

ORIGINAL RESEARCH ARTICLE

Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials

CANVAS Program

CREDENCE

DAPA-CKD

DECLARE-TIMI 58

EMPA-REG OUTCOME

VERTIS CV

	n/N SGLT2i	n/N Placebo	Hazard ratio (95%CI)	Study: P for interaction	Subgroup: P for interaction
Overall	**977/28,214**	**777/21,653**	**0.84 (0.76, 0.93)**	**0.71**	
HbA1c ≤8%	495/14,298	382/11,073	0.90 (0.78, 1.03)	0.86	0.19
HbA1c >8%	481/13,888	394/10,553	0.79 (0.69, 0.90)	0.47	
eGFR ≥60 mL/min/1.73m^2	521/21,511	335/16,273	0.90 (0.79, 1.04)	0.89	0.20
eGFR <60 mL/min/1.73m^2	456/6,699	442/5,379	0.79 (0.70, 0.91)	0.54	
UACR <30 mg/g	377/15,823	224/11,814	0.90 (0.77, 1.07)	0.93	0.23
UACR ≥30 mg/g	585/11,957	549/9,515	0.80 (0.70, 0.90)	0.39	
No heart failure	735/24,305	604/18,701	0.82 (0.73, 0.92)	0.40	0.31
Heart failure	242/3,909	173/2,952	0.92 (0.74, 1.13)	0.37	
No RAAS inhibitor use	118/4,730	107/3,512	0.56 (0.43, 0.74)	0.65	0.002
RAAS inhibitor use	859/23,534	670/18,141	0.89 (0.79, 0.99)	0.32	
No diuretic use	519/16,054	398/12,260	0.84 (0.73, 0.96)	0.88	0.97
Diuretic use	458/12,160	379/9,393	0.84 (0.73, 0.97)	0.38	
No MRA use	895/26,861	729/20,732	0.83 (0.75, 0.92)	0.93	0.25
MRA use	82/1,353	48/921	1.04 (0.72, 1.52)	0.47	

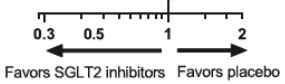


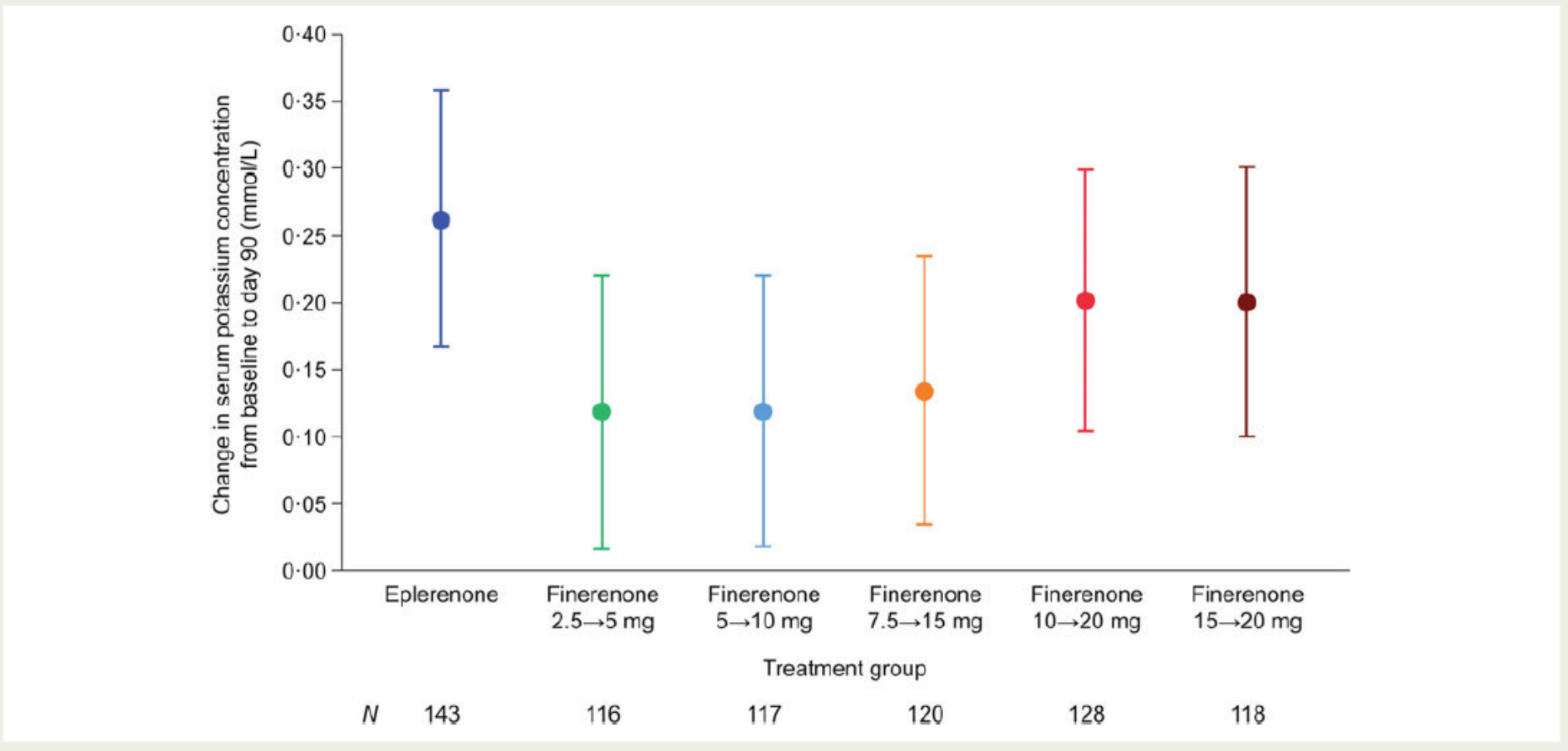
Figure 3. Effect of SGLT2 inhibitors on serious hyperkalemia (central laboratory–determined serum potassium ≥6.0 mmol/L) according to baseline participant characteristics.
eGFR indicates estimated glomerular filtration rate; HbA1c, glycohemoglobin; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose cotransporter 2 inhibitor; and UACR, urinary albumin-to-creatinine ratio;

Less risk of HK with finerenone vs. eplerenone

European Heart Journal (2016) 37, 2105–2114
doi:10.1093/eurheartj/ehw132

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease

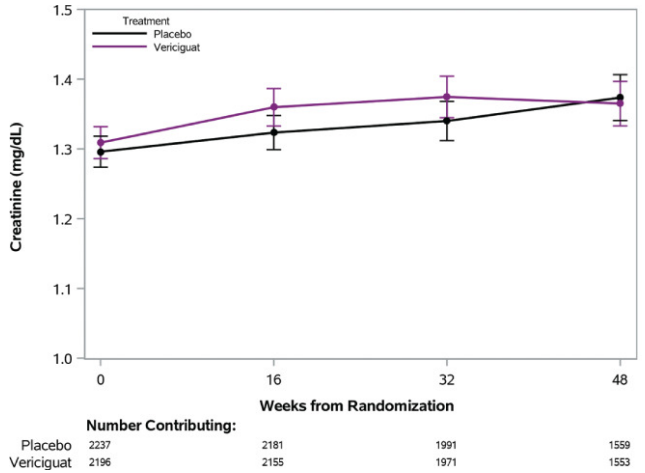


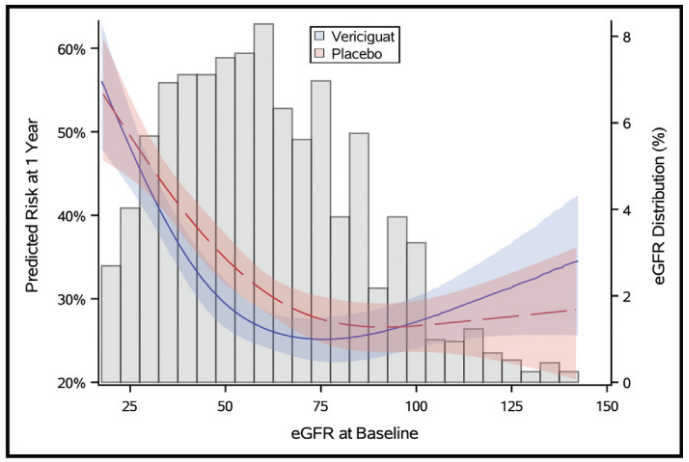
Not all HF treatments increase K: Focus on patient profiles!

ESC European Society of Cardiology
European Journal of Heart Failure (2021) 23, 1313–1321
doi:10.1002/ejhf.2221

RESEARCH ARTICLE

Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: insights from the VICTORIA (Vericiguat Global Study in Subjects with HFrEF) trial





Potassium				0.68
Baseline	4.49 (0.011)	4.51 (0.011)	–	
Week 16	4.44 (0.012)	4.48 (0.011)	−0.025 (−0.054 to 0.003)	0.08
Week 32	4.46 (0.012)	4.50 (0.012)	−0.031 (−0.061 to −0.001)	0.043
Week 48	4.48 (0.013)	4.50 (0.013)	−0.015 (−0.048 to 0.019)	0.39

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 14, 2021 VOL. 384 NO. 2

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

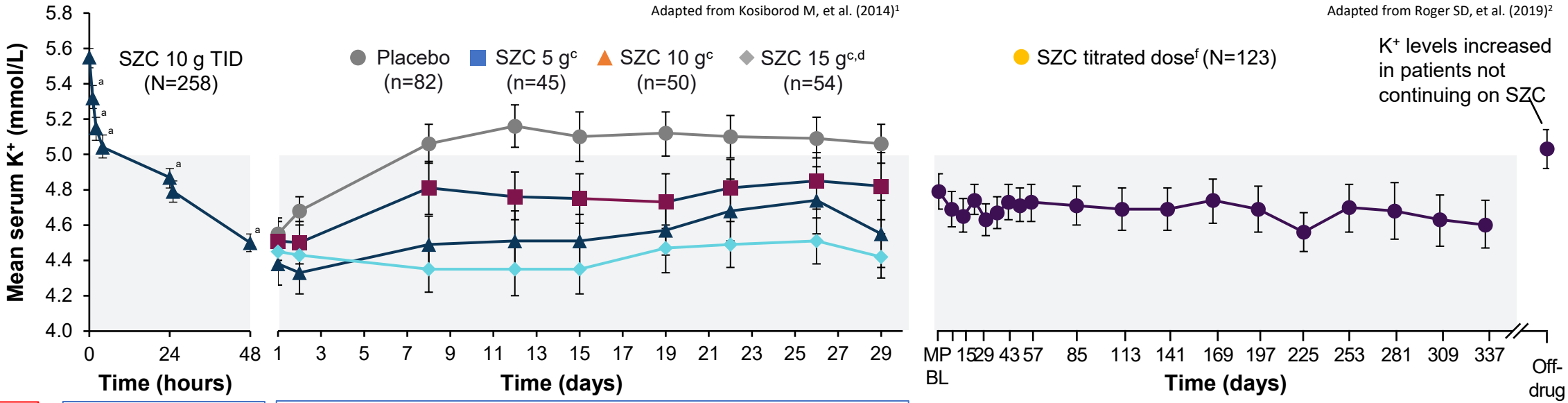
Potassium – mmol/liter			
At wk 24	−0.01±0.57	−0.01±0.57	0.00 (−0.03 to 0.03)
At wk 48	−0.03±0.59	−0.02±0.58	−0.01 (−0.04 to 0.02)
Creatinine — mg/dl			
At wk 24	0.03±0.33	0.02±0.32	0.01 (−0.01 to 0.02)
At wk 48	0.06±0.39	0.05±0.38	0.01 (−0.01 to 0.03)

SZC provided K^+ reduction as soon as 1 hour and sustained K^+ control for up to 1 year

258 outpatients with hyperkalemia (serum potassium ≥5.1 mEq/L)

ZS-004 (HARMONIZE)[1] | **ZS-004E (11-month extension)[2]**

Open-label CP (48 hours)[1] | **Randomised, double-blind maintenance phase (days 1–29; QD dosing[b])[1]** | **Open-label maintenance phase (days 1-337)[2,e]**



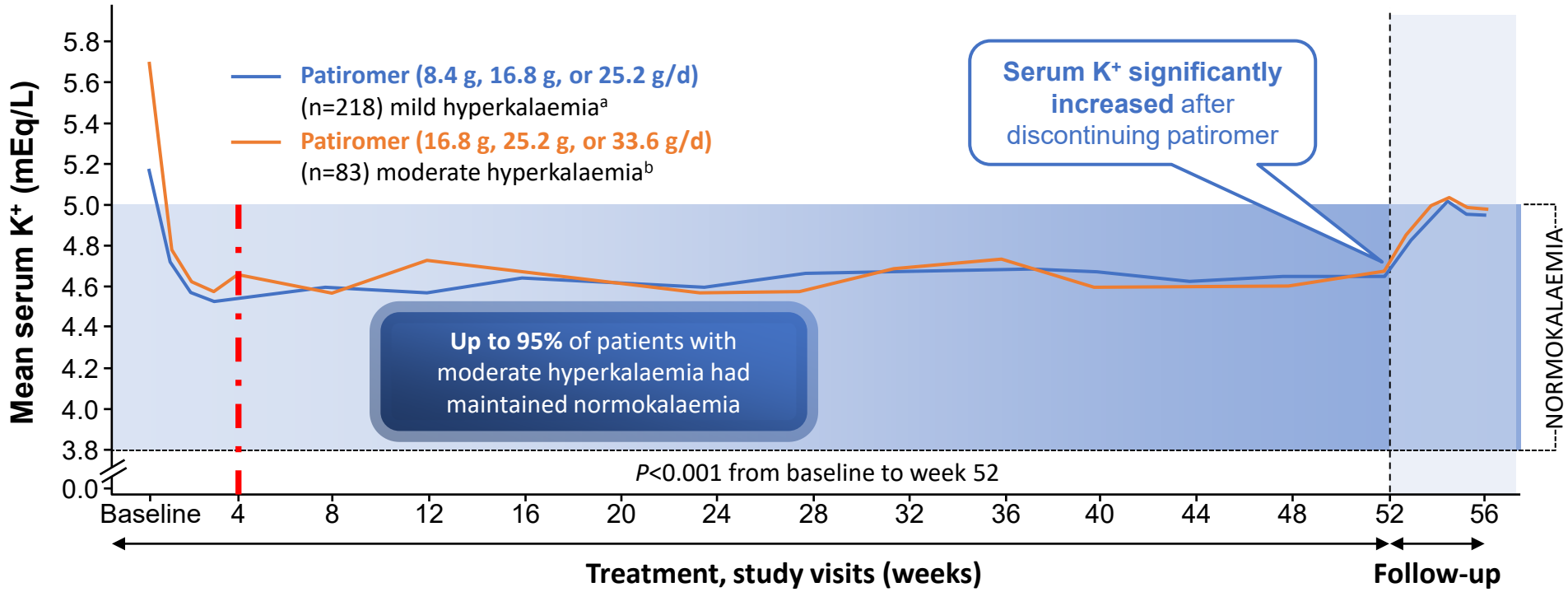
All	98% normoK	80-94% vs. 46% normoK at day 28% with SZC
HF	93% normoK	83-92% vs. 40% normoK at day 28% with SZC

Note: Normokalaemia defined as serum K^+ 3.5–5.0 mmol/L and patients on dialysis were excluded from these studies.[1,2] Error bars indicate 95% CIs
[a]P<0.001 vs baseline;[1] [b]If a patient's K^+ value was between 3.0–3.4 mmol/L at any time during the randomised phase, the dose was reduced from QD to QOD for the remainder of the study;[1] [c]P<0.001 vs placebo during days 8–29;[1] [d]The extended maintenance group contained a small proportion (11%) of patients treated with 15 g once daily which is not approved for use in nonhaemodialysis patients[4]; [e]Maintenance SZC dosing was initiated at 10 g QD and titrated in 5 g increments or decrements to maintain i-STAT K^+ 3.5–5.0 mmol/L (minimum 5 g QOD; maximum 15 g QD). Off-drug values were recorded at 7±1 days following the last dose of SZC[2]; [f]Mean SZC doses to maintain normokalaemia were 10 g QD in 73.2% and <10 g QD in 13.8% of patients
BL, baseline; CI, confidence interval; CP, correction phase; MP, maintenance phase; QD, once daily; QOD, once every other day; SZC, sodium zirconium cyclosilicate; TID, three times daily
1. Kosiborod M, et al. *JAMA* 2014;312:2223–2233; 2. Roger SD, et al. *Am J Nephrol* 2019;50:473–480;

With patiromer, up to 95% of patients with hyperkalaemia taking RAASi maintained normokalaemia over 1 year

306 outpatients with type 2 diabetes (eGFR 15 to <60 mL/min/1.73 m2 and serum potassium level >5.0 mEq/L) on RAASi

AMETHYST-DN 1-YEAR STUDY: Mean change in serum K⁺ over 1 year



83.1–92.7% of patients with mild HK and 77.4–95.1% of patients with moderate HK maintained K⁺ levels within target range (3.8–5.0 mEq/L) during the MP through week 52

Phase 2, multicentre, open-label, dose-ranging, randomised clinical trial (AMETHYST-DN), conducted in 48 sites in Europe from June 2011 to June 2013 evaluating patiromer in 306 outpatients with Type 2 diabetes (eGFR 15 to <60 mL/min/1.73 m^2 and serum potassium level >5.0 mEq/L). All patients received RAASi prior to and during study treatment

[a]Serum potassium >5.0 to 5.5 mEq/L; [b]Serum potassium >5.5 to <6.0 mEq/L

eGFR, estimated glomerular filtration rate; HK, hyperkalaemia; MP, maintenance phase; RAASi, renin–angiotensin–aldosterone system inhibitor

Bakris GL, et al. *JAMA* 2015;314:151–161

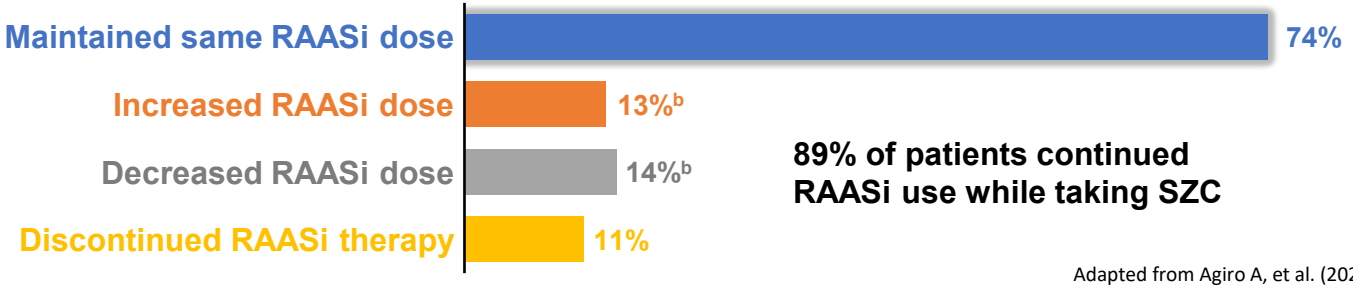
Majority of patients on recent oral K binders maintain or increase their RAASi therapy

Sodium zirconium cyclosilicate

ZS-005 (phase 3)[1,a]

Adapted from Spinowitz B, et al. (2019)[1]

Of the 483 patients who received RAASi therapy at the start of CP:

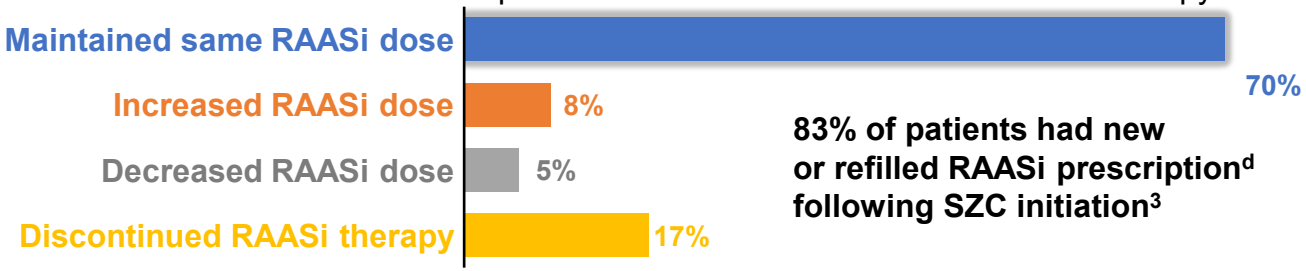


89% of patients continued RAASi use while taking SZC

Adapted from Agiro A, et al. (2023)[2]

OPTIMIZE I (real-world evidence)[2,c]

Of the 589 patients who initiated SZC while on RAASi therapy:



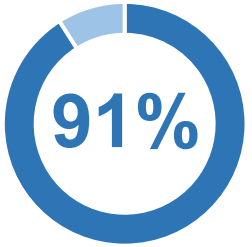
83% of patients had new or refilled RAASi prescription[d] following SZC initiation[3]

Patiromer

PEARL-HF[4,e]

HF + ([K requiring d/c RAASi] or [eGFR<60])

Of the patients who received spironolactone 25 mg/day:

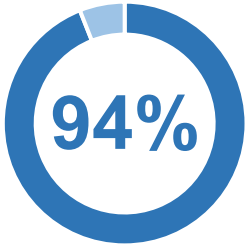


of patients taking patiromer (n=55) were able to increase their spironolactone dose to 50 mg/day, **compared to 74%** of patients taking placebo (n=49)

OPAL-HK[5,f]

eGFR 15-59; K 5.1-6.4; RAASi

Of the 105 patients who received at least one RAASi at baseline:



of patients taking patiromer (n=55) continued RAASi use, **compared with 44%** of patients taking placebo (n=52)

Note: RAASi included ACEi, ARB and MRA in the ZS-005 study,[1] and ACEi, ARB, ARNI, MRA and direct renin inhibitor in the OPTIMIZE I study[3]

[a]A pre-specified exploratory analysis of a phase 3, open-label, single-arm, 12-month study in adult outpatients with HK (i-STAT K^+ ≥5.1 mmol/L) who were not on dialysis;[1] [b]Non-mutually exclusive; [c]A retrospective, non-comparative cohort study utilising US insurance claims data in adult outpatients with an HK diagnosis who initiated SZC in an outpatient setting (index date), while receiving RAASi therapy between January 2018 and June 2020;[2] [d]New or refilled RAASi prescription was defined as different fill or refill of same RAASi within 90 days of ending their index RAASi[3]; [e]A multinational prospective randomized double-blind pilot study[4]; [f]A multinational,single-blind, two-phase prospective trial study[5]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CP, correction phase; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate

1. Spinowitz B, et al. *Clin J Am Soc Nephrol* 2019;14:798–809; 2. Agiro A, et al. Presented at National Kidney Foundation Spring Clinical Meetings; 11–15 April 2023; poster 282; 3. Agiro A, et al. *Adv Ther* 2023;40(6):2886–2901; 4. Pitt B, et al. *Eur Heart J* 2011;32:820–828; 5. Weir MR, et al. *N Engl J Med* 2015;372:211–221

The DIAMOND study indicates that RAASi optimisation may be possible with the newer oral potassium binders

Trial description

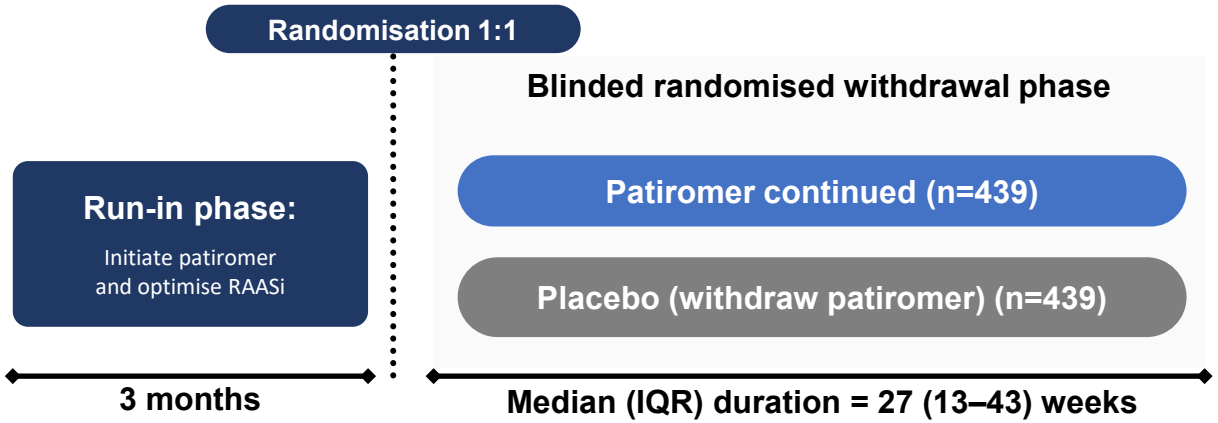
Phase 3b multinational, multicentre, double-blind, placebo-controlled, randomised withdrawal, parallel group trial.

Trial objective

To assess the effects of patiromer compared with placebo on sK^+ in patients with HF.

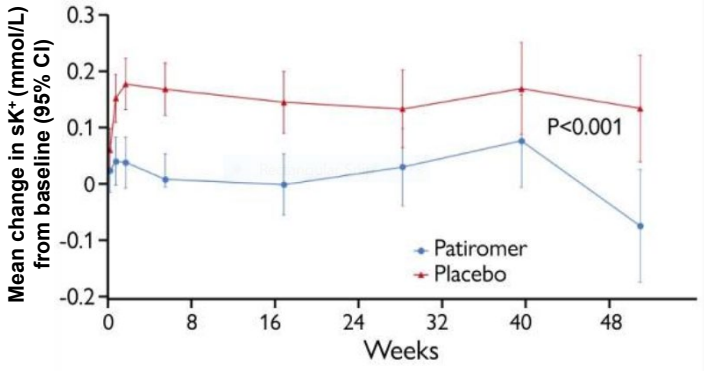
Eligibility criteria

- Adults (≥18 years) with a history of symptomatic HFrEF
- Outpatient treatment or hospitalisation within 1 year
- Mild-to-moderate renal impairment
- High sK^+ (>5.0 mEq/L) while treated for HF, or history of high sK^+ leading to change in HF therapy



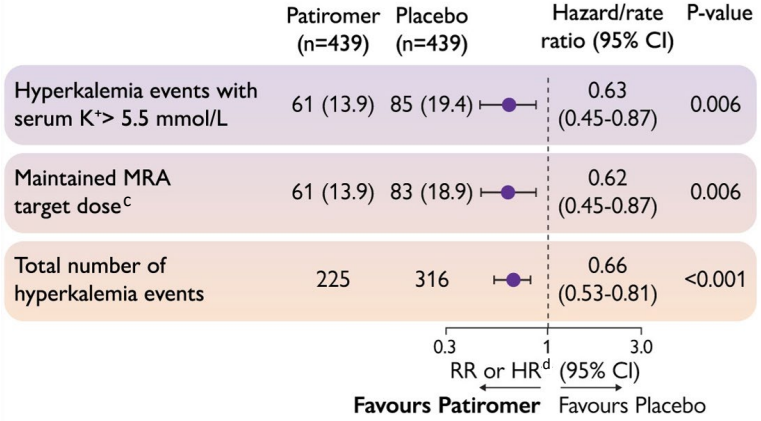
Primary endpoint[a]

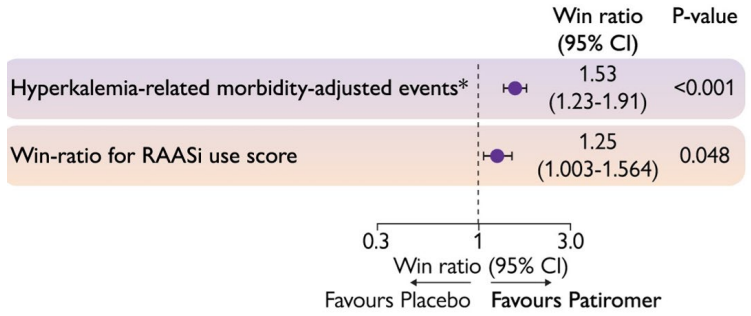
The adjusted mean change in sK^+ from randomisation to study end was +0.03 mmol/L (95% CI: −0.01, 0.07) in the patiromer group and +0.13 mmol/L (95% CI: 0.09, 0.16) in the placebo group.[b]



Secondary endpoints

Patiromer was superior to placebo in all secondary outcomes.





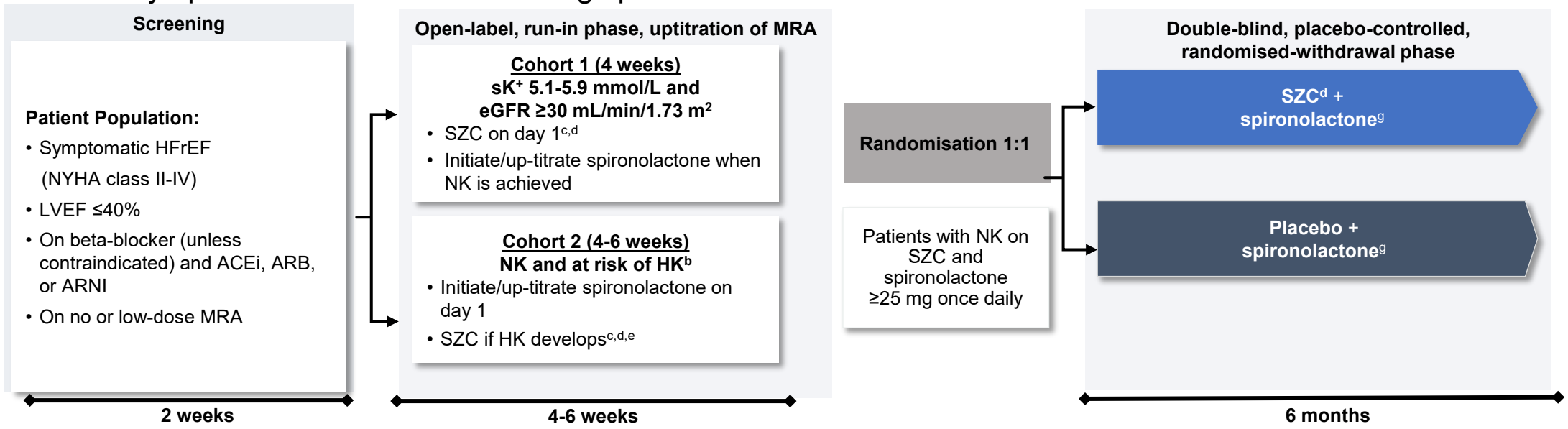
[a]Owing to slow enrolment rates, changing hospitalisation patterns, lower than expected event rates, and the uncertainty of the COVID-19 pandemic, the primary endpoint was revised during the study from time to first occurrence of cardiovascular death or cardiovascular hospitalisation to changes in sK^+ levels from the baseline; [b]A significantly greater mean change from baseline in sK^+ was reported for participants with eGFR <45 mL/min/1.73 m^2 (−0.19; 95% CI: −0.26, −0.12) compared with participants with eGFR ≥45 mL/min/1.73 m^2 (−0.08; 95% CI: −0.11, −0.04; *P*=0.003; [c]MRA target dose of 50 mg daily spironolactone or eplerenone, respectively; [d]Morbidity adjusted HK-related outcomes were tested in a hierarchical manner with the following sequence: CV death, CV hospitalisation, total HK events > 6.5 mMol/L, > 6.0–6.5 mMol/L and >5.0–6.0 mMol/L

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range)MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; sK^+, serum potassium

Butler J, et al. *Eur Heart J* 2022;43:4362–4373

REALIZE-K Study Design

Phase 4, double-blind, placebo-controlled, randomised-withdrawal trial evaluating SZC for the management of HK in patients with symptomatic HFrEF and receiving spironolactone



Primary Endpoint:

Per visit, Month 1-6, response is defined by

- Having potassium (sK+) within 3.5-5.0 mEq/L as assessed by central laboratory AND
- Being on spironolactone ≥25 mg daily AND
- Not using rescue therapy for HK during the last month

Note: NK defined as sK^+ 3.5-5.0 mmol/L; HK defined as sK^+ >5.0 mmol/L.

[b] Defined as either having a history of HK within the prior 24 months and eGFR ≥30 mL/min/1.73 m^2, or sK^+ ≥4.5 mmol/L and eGFR 30-60 mL/min/1.73 m^2 and/or age >75 years.

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04676646 Accessed on January 24th 2024; Last Update Posted Nov 7th 2023

An European perspective from HF community

Management of HK in patients with CVD and indication for RAASi therapy

K level 4.5–5.0 mEq/L[a]

Not on maximal tolerated guideline-recommended target dose of RAASi therapy

→ Initiate/up-titrate RAASi therapy and closely monitor K levels

→ If K level >5.0 mEq/L, initiate an approved K-lowering agent

K level >5.0 to ≤6.5 mEq/L[a]

Not on maximal tolerated guideline-recommended target dose of RAASi therapy

→ Initiate an approved K-lowering agent

→ If K level <5.0 mEq/L is detected, up-titrate RAASi therapy

→ K level should be closely monitored and K-lowering treatment should be maintained[b]

On maximal tolerated guideline-recommended target dose of RAASi therapy

→ Treatment with a K-lowering agent may be initiated

→ K level should be closely monitored and K-lowering treatment should be maintained[b]

K level >6.5 mEq/L[a]

On either maximal/sub-maximal tolerated, guideline-recommended target dose of RAASi therapy

→ Discontinue/reduce RAASi therapy

→ Treatment with a K-lowering agent may be initiated as soon as K level >5.0 mEq/L

→ K level should be closely monitored

Chronic or recurrent HK

Not on maximal tolerated guideline-recommended target dose of RAASi therapy

→ RAASi therapy should be optimised and an approved sK^+-lowering agent may be initiated as soon as sK^+ level >5.0 mEq/L

→ Maintain treatment[b] and K level should be closely monitored

- [a]1 mEq/L= 1 mmol/L; [b]Unless another aetiology for hyperkalaemia is identified
- CVD, cardiovascular disease; HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor; sK^+, serum potassium
- Rosano G, et al. *Eur Heart J Cardiovasc Pharmacother* 2018;4:180–188

What do the nephrologists say?

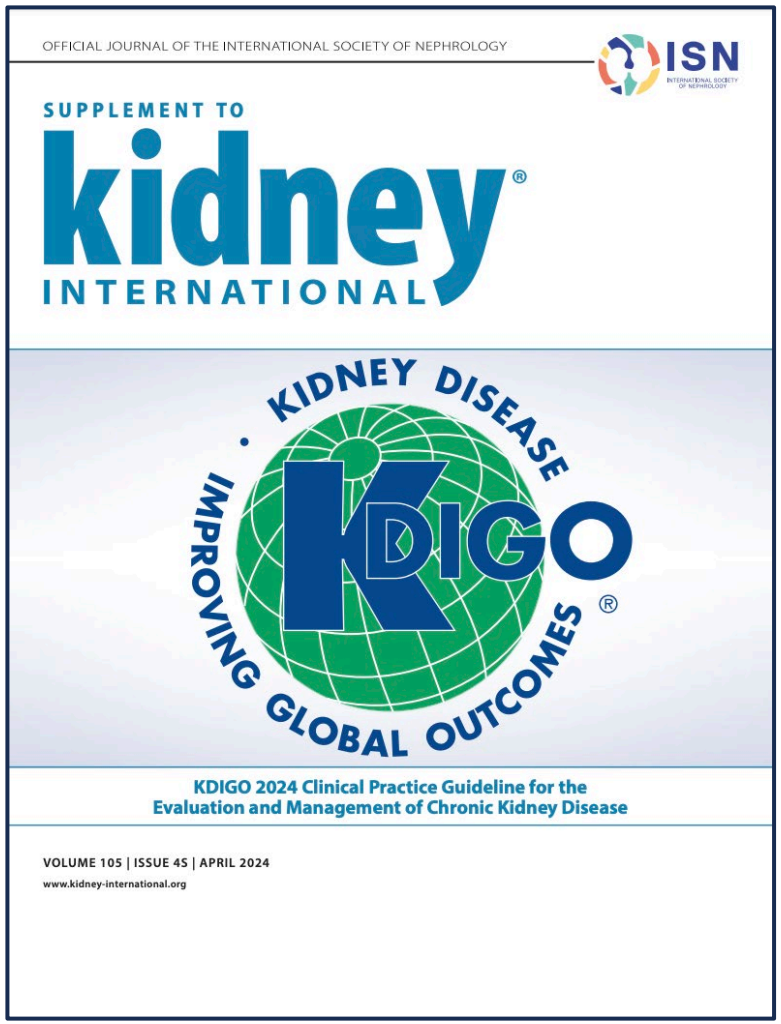
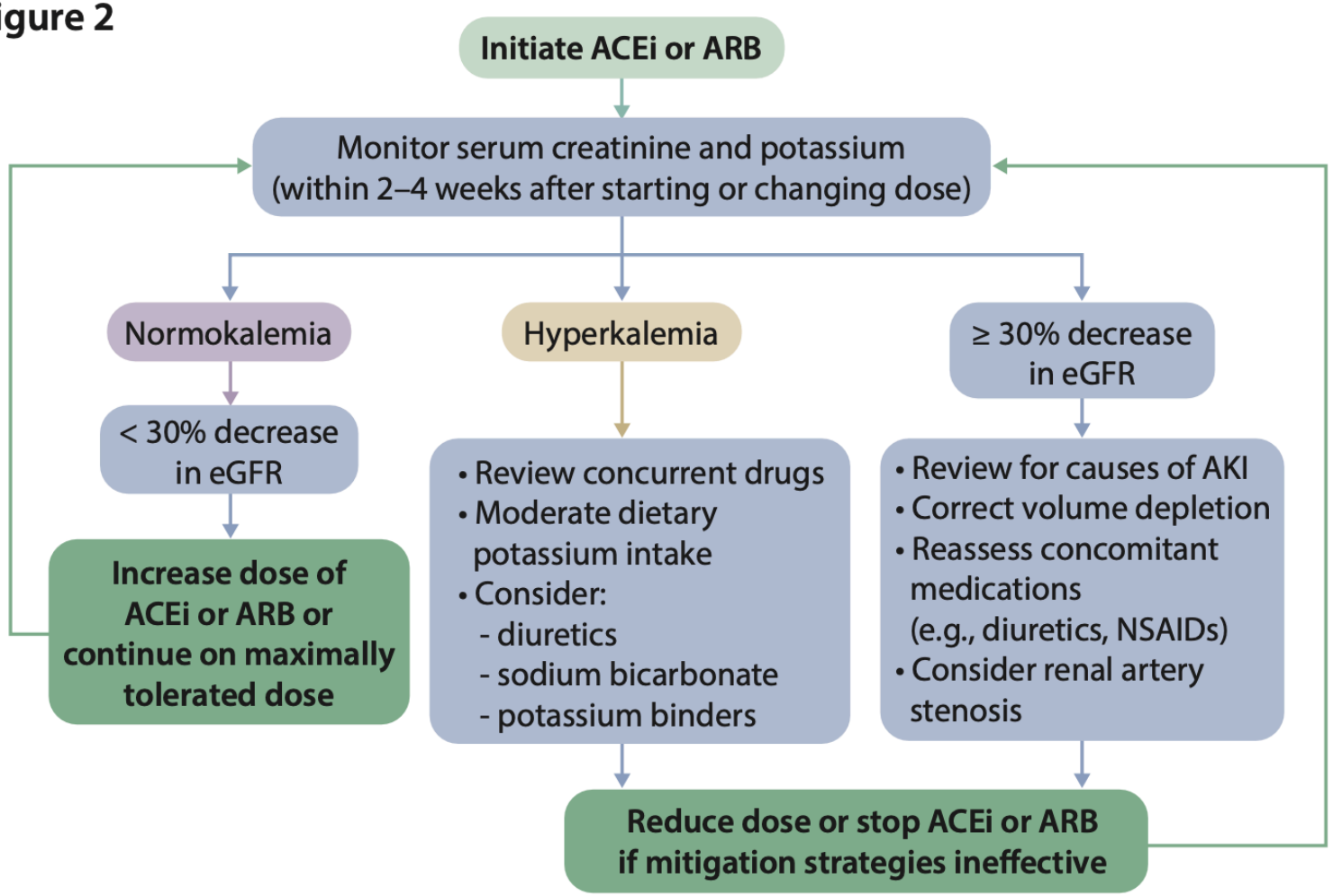


Figure 2



GUARDIAN HK (Guiding Understanding of Recurrence, Decisions, and Implementation Network – Hyperkalaemia) interdisciplinary recommendations for recurrent hyperkalaemia

Duty of care

Identifying patients at risk of HK recurrence

Managing the risk of HK recurrence

Hyperkalaemia

Immediate management per local protocol

Risk assessment for HK recurrence

Identify and correct reversible causes

Identify previous history of HK and/or irreversible risk factors for HK recurrence

Patient at risk of HK recurrence

Yes

No

Consider K^+ binders and additional therapy

Optimise RAASi therapy (up-titrate to optimal dose)

Follow-up

No follow-up for HK

Reducing the risk of HK recurrence should be **standard practice**

It is the **responsibility of all HCPs** to evaluate and address the risk of HK recurrence

If there is **no reversible factor**, treatment to **prevent HK** recurrence should be initiated

Every encounter should be an opportunity to **optimise RAASi**, even in the context of an HK event

Unless the cause of acute HK can be reversed, treatment for recurrent HK is **likely to be indefinite**

The initial aim of HK management should be to normalise sK levels and correct reversible precipitating factors

The risk of HK recurrence should be reduced **without discontinuing or down-titrating disease-modifying therapy such as RAASi**

Long-term conditions and reliance on therapy that interferes with potassium homeostasis should be considered **irreversible factors** associated with HK

A **risk-stratification tool** for HK recurrence is required and could guide management

Additional monitoring of sK levels beyond that for routine comorbidities should not be necessary

HCP, healthcare professional; HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor; sK, serum potassium

The GUARDIAN HK collaborative is organized and funded by AstraZeneca

Summary

- HK is frequently recurrent and associated with poorer outcomes in patients with cardiorenal disease
- Several comorbidities, such as CKD, HF and diabetes, and therapies such as MRAs and RAASi are risk factors for HK
- Following an HK event, down-titration or discontinuation of ACEi/ARB/MRA therapy is common and associated with worse clinical outcomes
- Recent oral potassium binders provide potassium reduction with potential to allow patients to avoid HK recurrence and maintain or increase their RAASi therapy

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Thank You!