But what to do if the potassium level goes up

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Disclosures

- Research Grants
  - AstraZeneca, Boehringer Ingelheim, Pfizer
- Clinical Trial Leadership/Consultant
  - 35Pharma, Alnylam, Amgen, Applied Therapeutics, Astra Zeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Imbria Pharmaceuticals, Janssen, Lexicon Pharmaceuticals, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, scPharmaceuticals, Structure Therapeutics, Vifor Pharma, Youngene Therapeutics
- Honoraria
  - Astra Zeneca, Boehringer Ingelheim, Novo Nordisk
- Other Research Support
  - AstraZeneca
- Stock Options
  - Artera Health, Saghmos Therapeutics

Off label use of therapies may be discussed

The Patient

50-year-old male

- No prior history of CVD or other chronic conditions
- No smoking, no alcohol use
- Presents at the ER with progressive dyspnoea for 3 months
- Since 2 weeks, shortness of breath with minimal activity
- Previously had no exertional symptoms

On physical examination

- BMI: 31.4; BP: 150/82 mmHg
- Heart: 78 bpm, systolic murmur
- Lungs: rales bilaterally
- Extremities: trace peripheral oedema, pulses and neuro intact

bpm, beats per minute; BMI, body mass index; ECG, electrocardiogram; ER, emergency room

Clinical characteristics

Assessments

Biomarker	Value
Haemoglobin	10.1 mmol/L
NT-proBNP	**2.058 ng/L**
Creatinine	**159 µmol/L**
hs-troponin T	38 ng/L
eGFR	**43 mL/min/1.73 m^2**
TSH	2.1 mE/L
FT4	16.2 pmol/L
Sodium	134 mmol/L
Total cholesterol	4.0 mmol/L
Serum K^+	**5.3 mmol/L**
LDL cholesterol	2.7 mmol/L
Ferritin	70 ng/mL
Transferrin saturation	14%

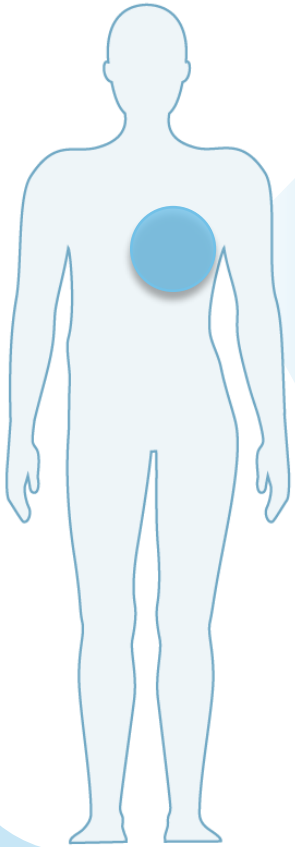
Current medications

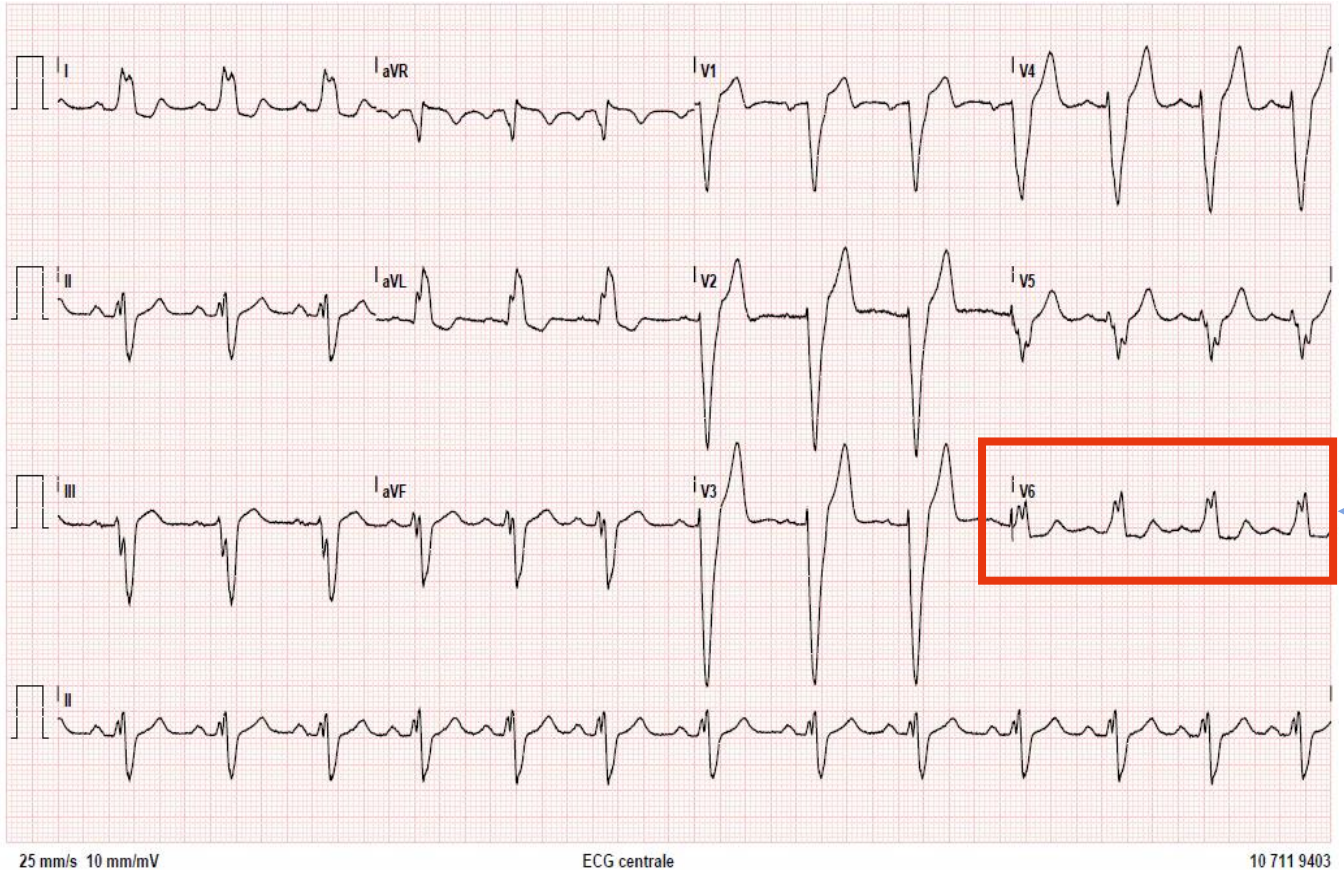
- No current medication

eGFR, estimated glomerular filtration rate; FT4, thyroxine; hs, high-sensitivity; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid-stimulating hormone

Electrocardiogram

Vent rate:	78	BPM
PR int:	195	ms
QRS dur:	185	ms
QT/QTc:	419/452	ms
P-R-T axes:	47 -50	66

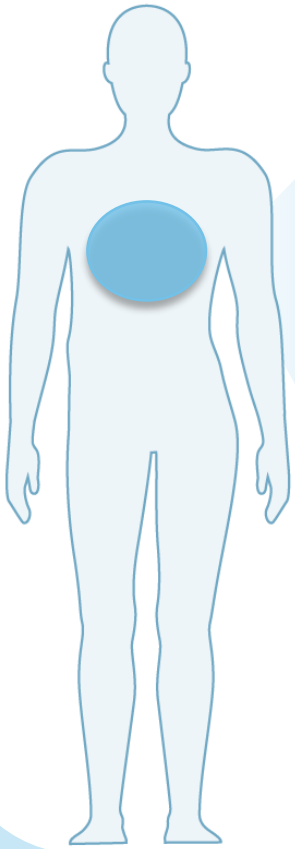


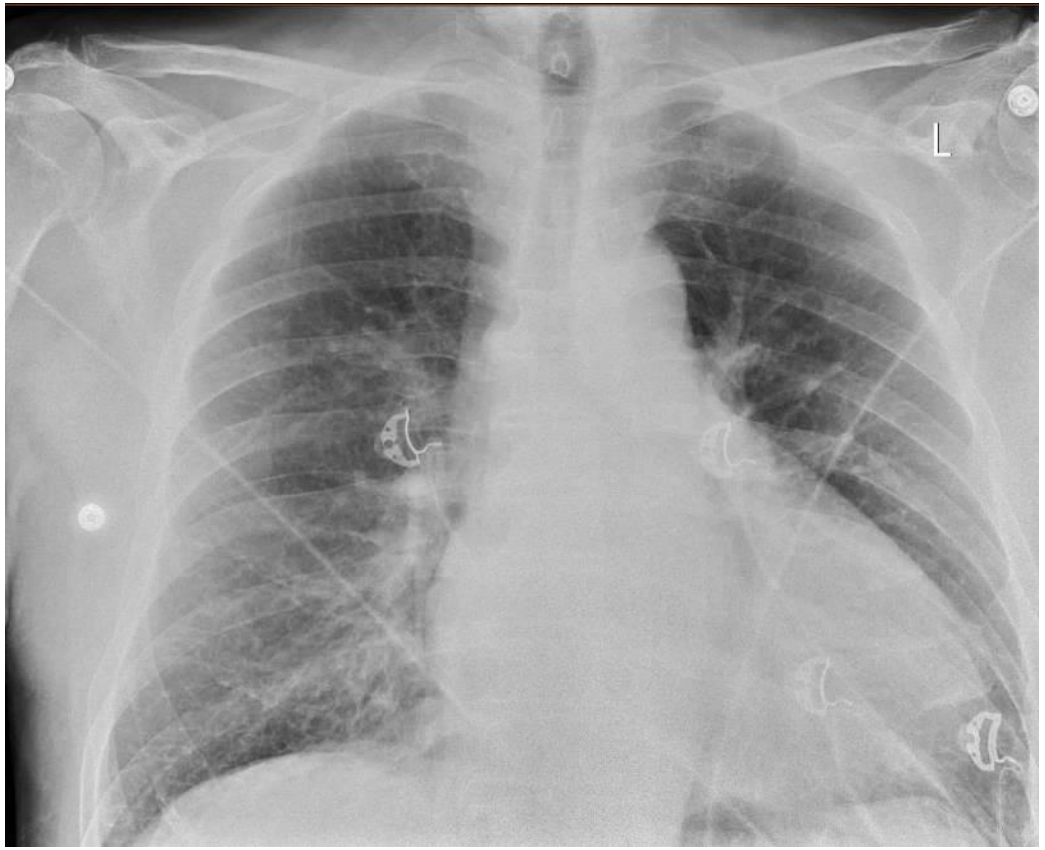


Sinus rhythm with left bundle branch block

BPM, beats per minute

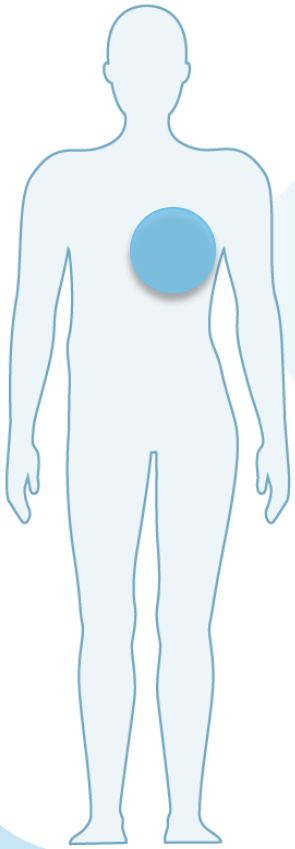
Chest radiograph

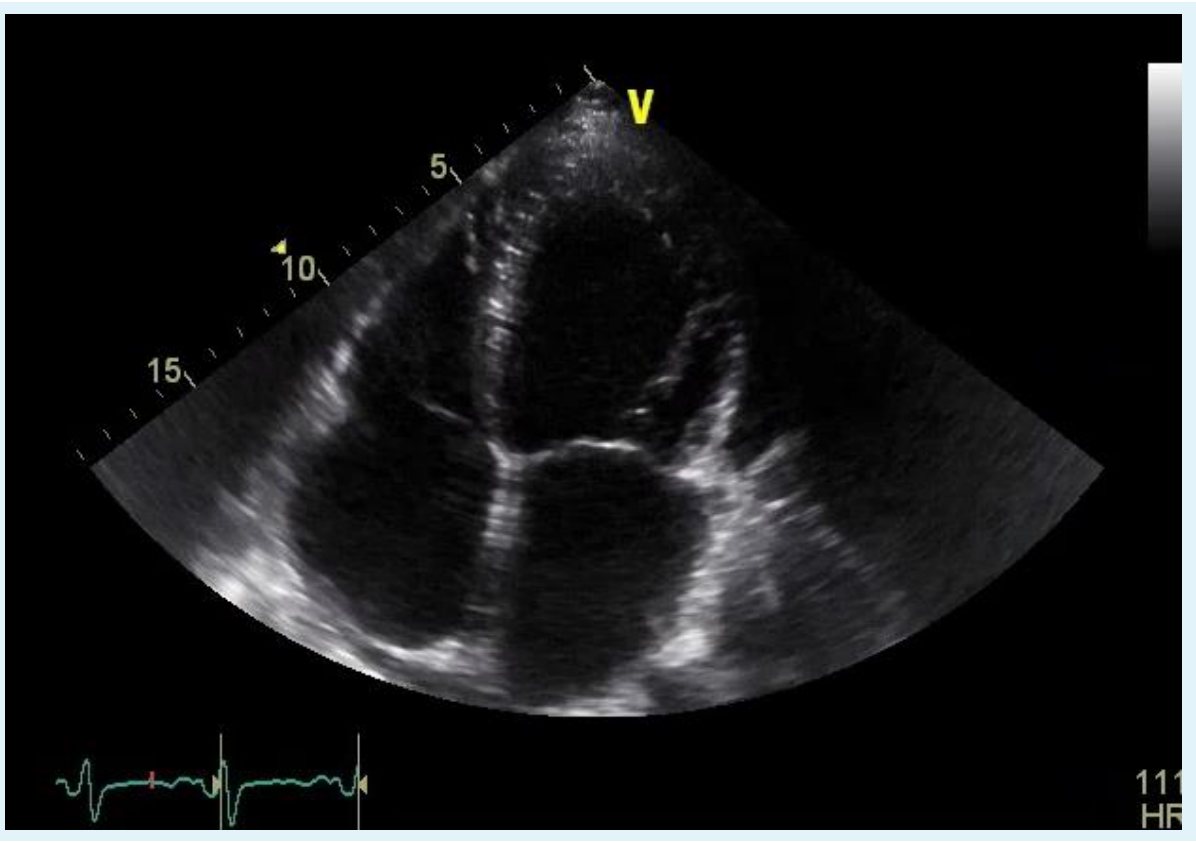




- Kerley B lines
- Volume overload

Echocardiogram



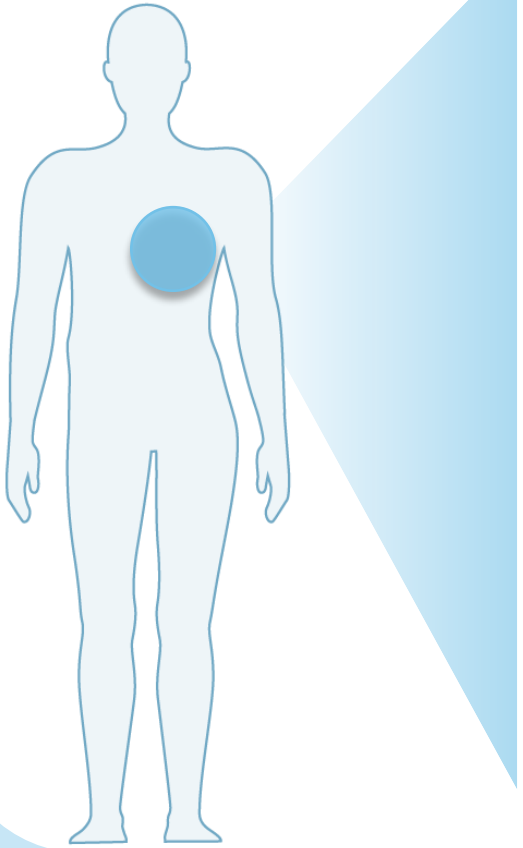


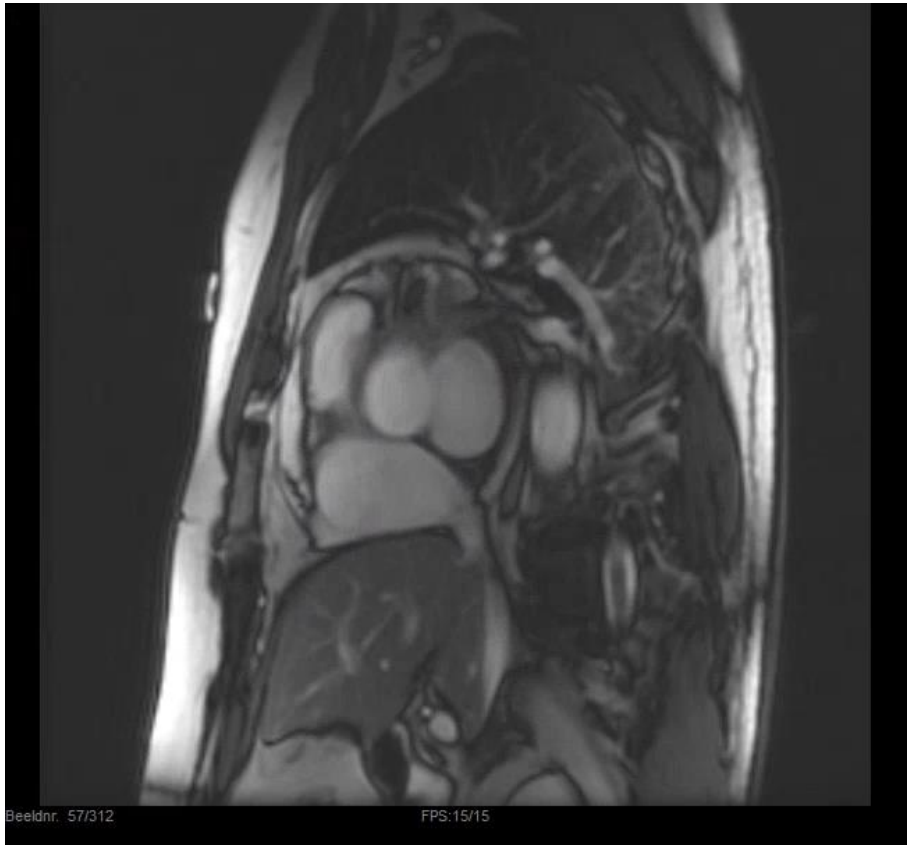
LVEF: 20%

Moderate MR/TR

LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TR, tricuspid regurgitation

Cardiac MRI





No late enhancement (excludes myocarditis)

LVEF: 22%

LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging

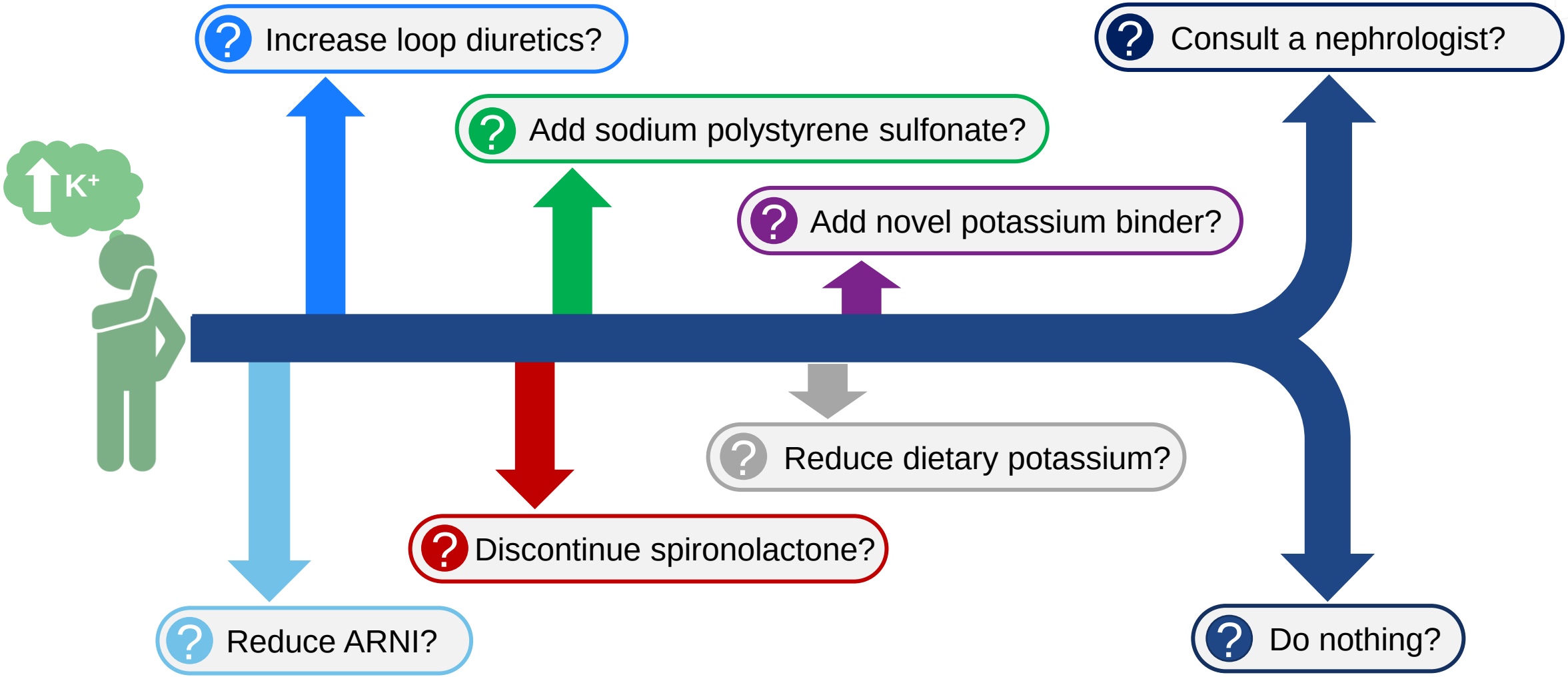
Uptitration of GDMT

After 3 months

- Sacubitril/valsartan 49/51 mg BID
- Carvedilol 12.5 mg BID, Furosemide 20 mg BID
- Dapagliflozin 10 mg
- Spironolactone 12.5 mg **(potassium: 5.8 mmol/L)**

BID, twice daily

What next?


Increase loop diuretics?
Consult a nephrologist?
Add sodium polystyrene sulfonate?
K+
Add novel potassium binder?
Reduce dietary potassium?
Discontinue spironolactone?
Reduce ARNI?
Do nothing?

Interactive question 1

What is the next step for this patient?

A. Discontinue spironolactone
B. Reduce ARNI
C. Increase loop diuretic
D. Add sodium polystyrene sulfonate (SPS)
E. Add novel potassium binder

Interactive question 1

What is the next step for this patient?

A. Discontinue spironolactone

B. Reduce ARNI

C. Increase loop diuretic

D. Add sodium polystyrene sulfonate (SPS)

E. Add novel potassium binder

And what is the nephrologist's opinion?

James Burton, MD

Leicester, United Kingdom

Traditional HK treatment options are associated with limitations

Low-K^+ diet[1]

- Difficult to adhere to
- Limiting K^+-rich foods can cause constipation
- Contradicts DASH diet; may worsen chronic hypertension

Diuretics[1]

- Efficacy depends on residual renal function
- Increased risk of gout and diabetes
- May result in:
  - Volume contraction
  - Decreased distal nephron flow
  - Worsening of kidney function and reduced K^+ excretion depending on choice of diuretic

Discontinuation or dose reduction of RAASi therapy[1]

- Stopping or suboptimal utilisation of guideline-recommended renoprotective/ cardioprotective RAASi therapy

Traditional K^+ binders (sodium polystyrene sulphonate)[2–4]

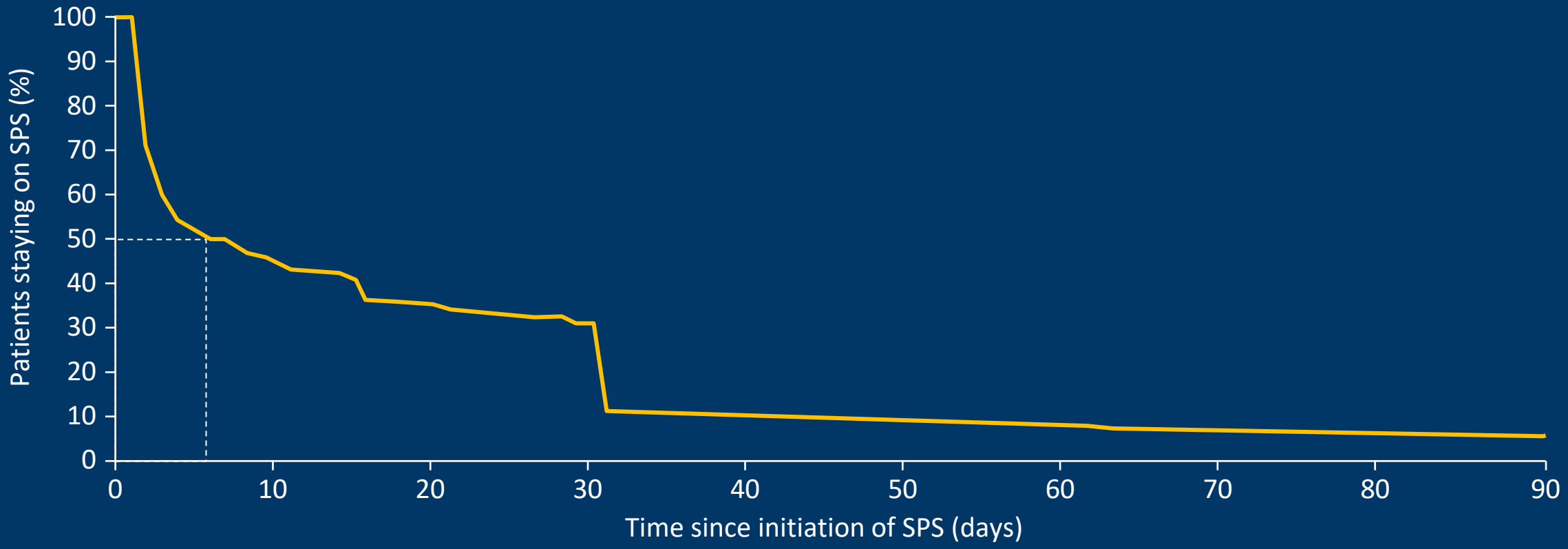
- No long-term efficacy has been evaluated
- GI side effects
- Hard, gritty texture and unpleasant taste may reduce palatability

DASH, Dietary Approaches to Stop Hypertension; HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor

1. Dunn J, et al. *Am J Manag Care* 2015;21:S307–S315; 2. Chaitman M, et al. *P T* 2016;41:43–50; 3. Sodium polystyrene sulphonate Prescribing Information (last updated 2018); 4. Zann V, et al. *Drug Des Devel Ther* 2017;11:2663–2673

The median SPS treatment duration was 7 days

Discontinuation of SPS among 4559 patients from a large US claims database study (1st January 2010 – 31st December 2014); patients had to have ≥1 SPS prescription fill and ≥31 days of continuous enrolment

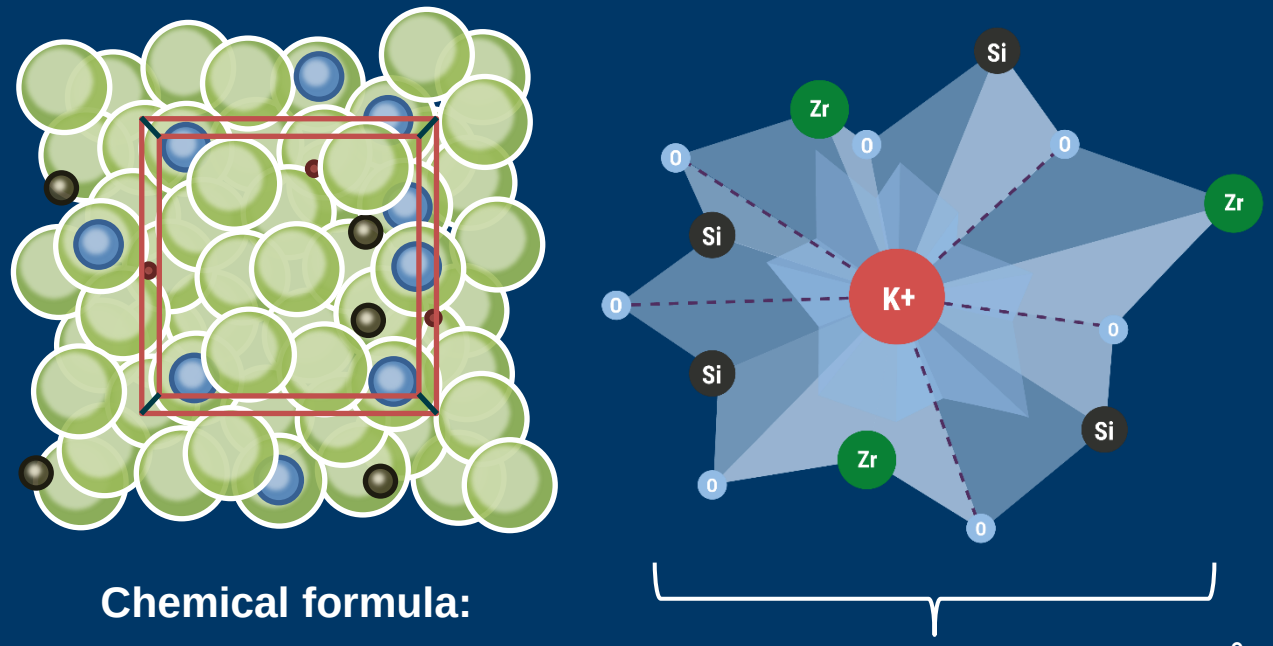


SPS, sodium polystyrene sulphonate

Betts K, et al. Presented at American Society of Nephrology Kidney Week 2016; 15th–20th November 2016; Chicago, IL; FR-PO786

Novel K^+ binders for treating Hyperkalemia in adults

Sodium zirconium cyclosilicate crystal structure[1,2]

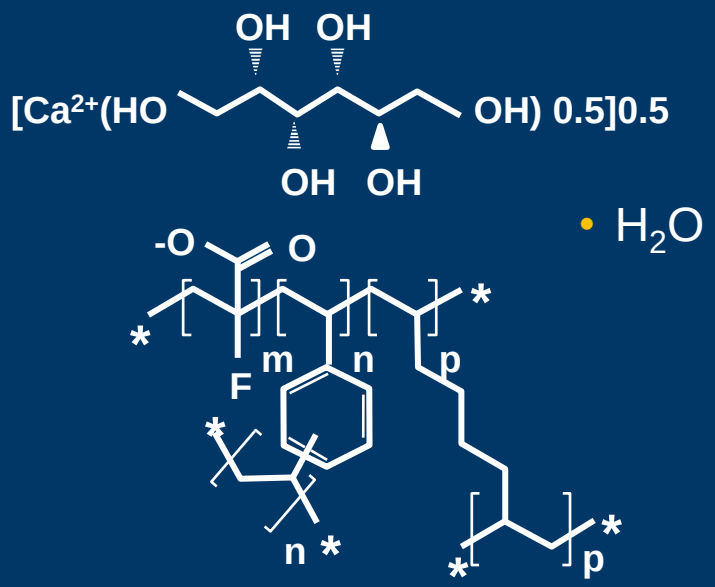


Chemical formula:

$H_6Na_2O_9Si_3Zr^{+2}$

Average binding-site width: 3 Å

Patiromer molecular structure[3]



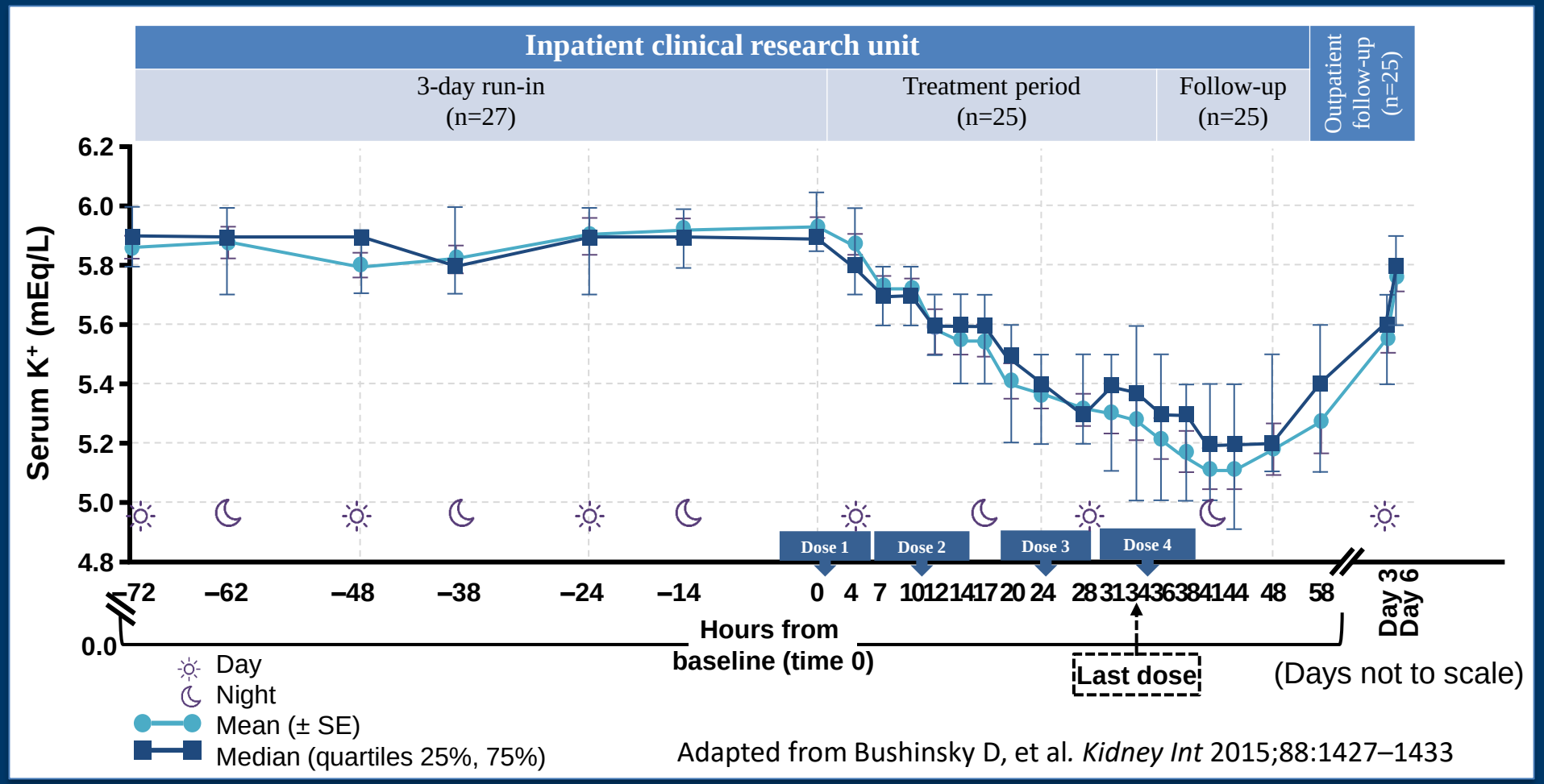
m = number of 2-fluoro-2-proprenoate groups
n, p = number of crosslinking groups
H_2O = associated water
*Indicates an extended polymeric network

1. Stavros F, et al. *PLoS One* 2014;9:e114686; 2. US National Institutes of Health, National Center for Biotechnology Information. PubChem Open Chemistry Database Compound Summary for CID 91799284. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/91799284#section=Top (Accessed July 2019); 3. Patiromer US Prescribing Information 2016

Patiromer selected efficacy data

The onset of action with patiromer is 4–7 hours

A phase 1, open label study to evaluate the onset of hyperkalemia in patients with CKD taking at least one RAASi (N=25)[1]



Adapted from Bushinsky D, et al. *Kidney Int* 2015;88:1427–1433

- The primary end point was the change in serum potassium from baseline during the 48 h after the first dose
- There was a change in serum K^+ from baseline during the 48 hours after the first dose of patiromer
- SZC and patiromer data are from separate studies so data is not directly comparable. No head-to-head data is available

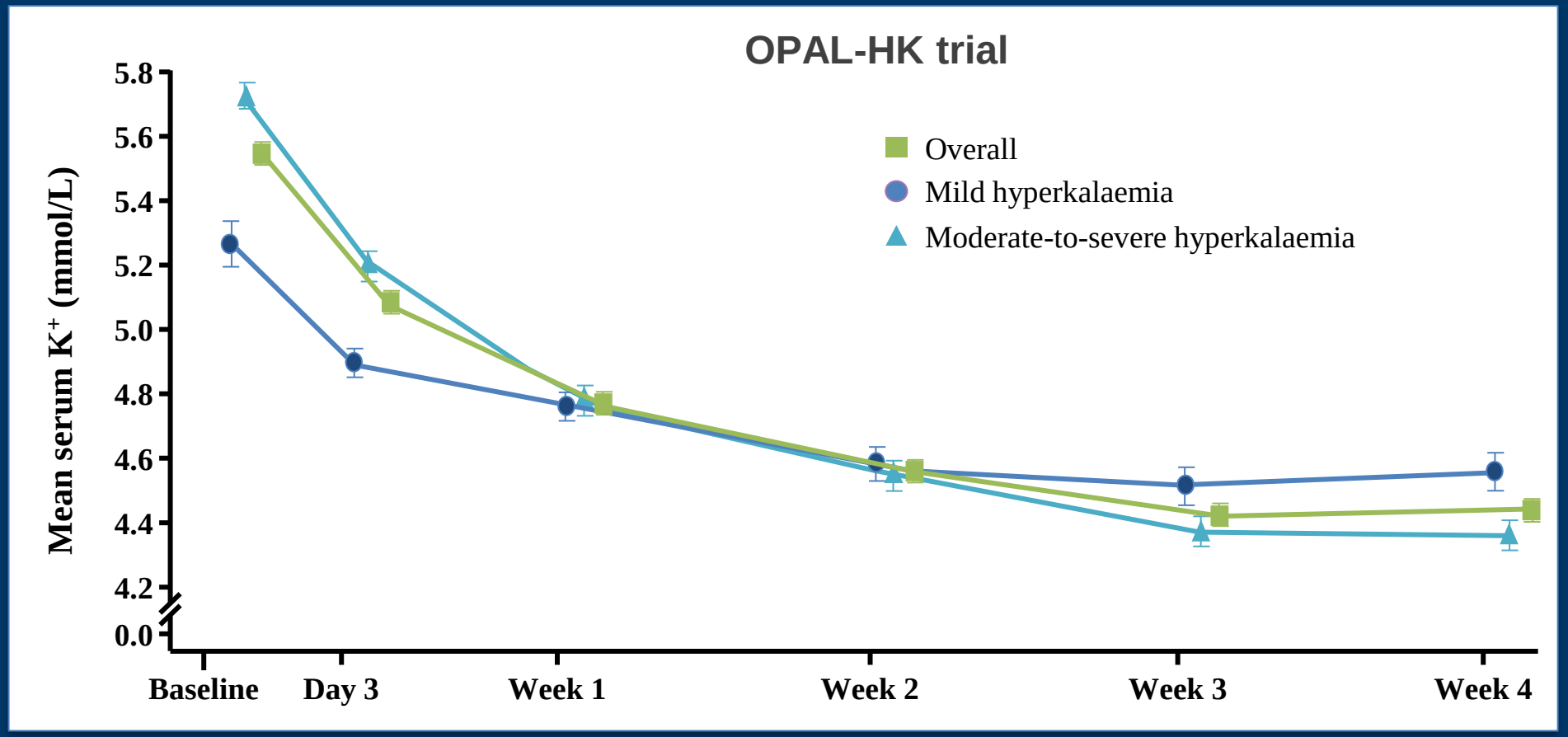
Significant reductions occurred at all assessments from 7–48 h ($P \leq 0.004$ at 7 h and 10 h; $P < 0.001$ for 12–48 h)

At the end of the run-in phase, patients with a serum K^+ 5.5–6.5 mEq/L entered the treatment period and began patiromer 8.4g twice daily with meals for 2 days for a total of four doses (at 0, 10, 24, and 34 h)

Both SZC and patiromer are not indicated to maximise RAASi dosing

Patiromer maintained normal K^+ levels for up to 4 weeks

A two-phase study in patients with hyperkalaemia and CKD taking at least one RAASi (N=243)
Comorbidities/treatment at baseline: T2DM (57%); HF (42%); MI (25%); hypertension (97%)



- The primary efficacy end point was the mean change in the serum potassium level from baseline to week 4
- The mean (±SE) change in the serum potassium level was −1.01±0.03 mmol/L (P<0.001)
- SZC and patiromer data are from separate studies so data is not directly comparable. No head-to-head data is available

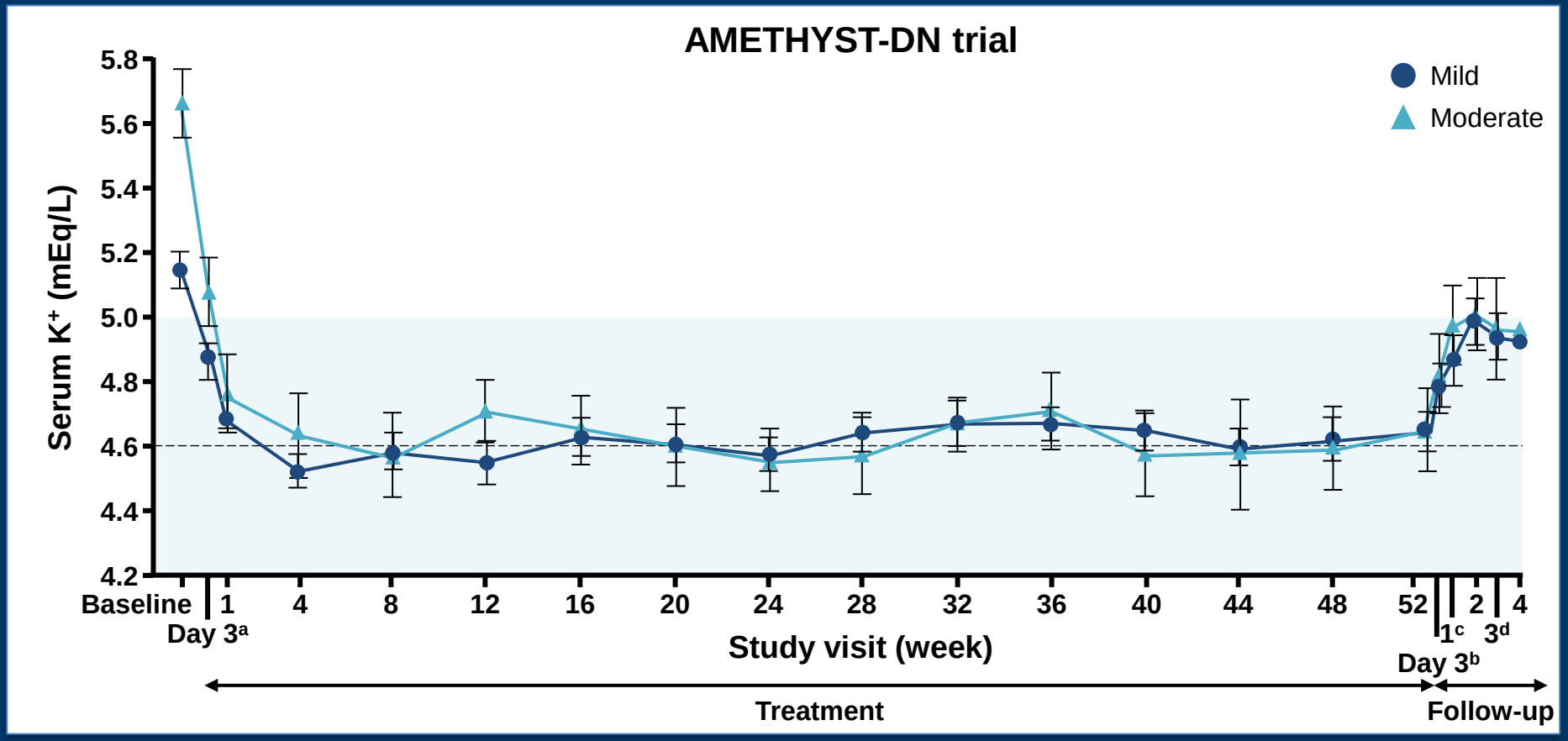
Adapted from Weir MR, et al. N Engl J Med 2015;372:211–221

Patients with a serum K^+ level 5.1–<5.5 mEq/L received 4.2 g of patiromer twice daily and patients with a serum K^+ 5.5–<6.5 received 8.4 g patiromer twice daily. During the 4 weeks the dose could be adjusted to reach and maintain a target K^+ level based on a pre-specified algorithm

Both SZC and patiromer are not indicated to maximise RAASi dosing

Patiromer maintained normal serum K^+ levels for up to 1 year

A phase 2, open label, randomised study in patients on stable doses of RAASi with mild or moderate hyperkalemia (N=306)
Comorbidities/treatment at baseline: CKD (65%), HF (35%), T2DM (100%), hypertension (100%)



- The primary efficacy end point was mean change in serum potassium level from baseline to week 4:
  - (Moderate hyperkalaemia) 0.87 (95% CI, 0.60-1.14) mEq/L for the 16.8 g/d; group, 0.97 (95% CI, 0.70-1.23) mEq/L for the 25.2 g/d group (P<0.001)
- From week 4 through week 52, significant (P<0.001) mean decreases from baseline in serum potassium levels were observed at each monthly time point in patients with mild and moderate hyperkalaemia
- SZC and patiromer data are from separate studies so data is not directly comparable. No head-to-head data is available

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

[a]At treatment day 3, there were 202 patients with mild hyperkalaemia and 82 with moderate hyperkalaemia; [b]At follow-up day 3, there were 163 patients with mild hyperkalaemia and 58 with moderate hyperkalaemia; [c]At follow-up week 1, there were 154 patients with mild hyperkalaemia and 57 with moderate hyperkalaemia; [d]At follow-up week 3, there were 126 patients with mild hyperkalaemia and 48 with moderate hyperkalaemia

Eligible patients were stratified by baseline serum K^+ level (stratum 1: >5.0-5.5 mEq/L; stratum 2: >5.5-<6.0 mEq/L) and were randomly assigned in a 1:1:1 ratio to 1 of 3 patiromer starting doses per stratum (stratum 1: 4.2 g, 8.4 g or 12.6 g twice daily [8.4 g/d, 16 g/d, 25.2 g/d]; stratum 2: 4.2 g, 8.4 g or 12.6 g twice daily [16.8 g/d, 25.2 g/d, 33.6 g/d]. The patiromer dose could be titrated upward or downward in a stepwise fashion to the individualised effective dose to maintain control of serum K^+ level. The 33.6 g daily dose is not indicated for use.

Both SZC and patiromer are not indicated to maximise RAASi dosing

Interactive question 2

All of the following are correct statements about the DIAMOND trial, except?

A. Majority of patients with HFrEF and prior history of or at high risk for HK were optimized on MRA with patiromer

B. More patients were able to be maintained on optimal MRA, and fewer had hyperkalemia with patiromer vs placebo

C. Patiromer was well tolerated

D. Patiromer reduced the risk of CV death and HF hospitalizations

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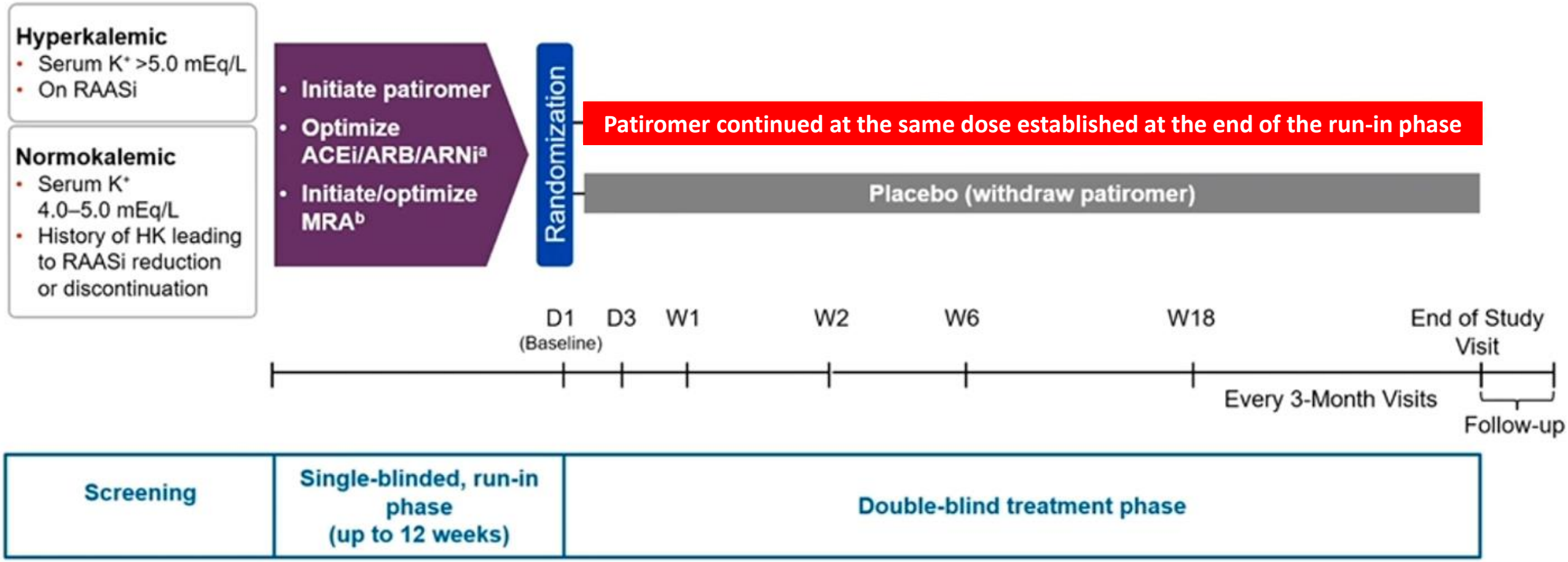
DIAMOND Study: Design[1,2]



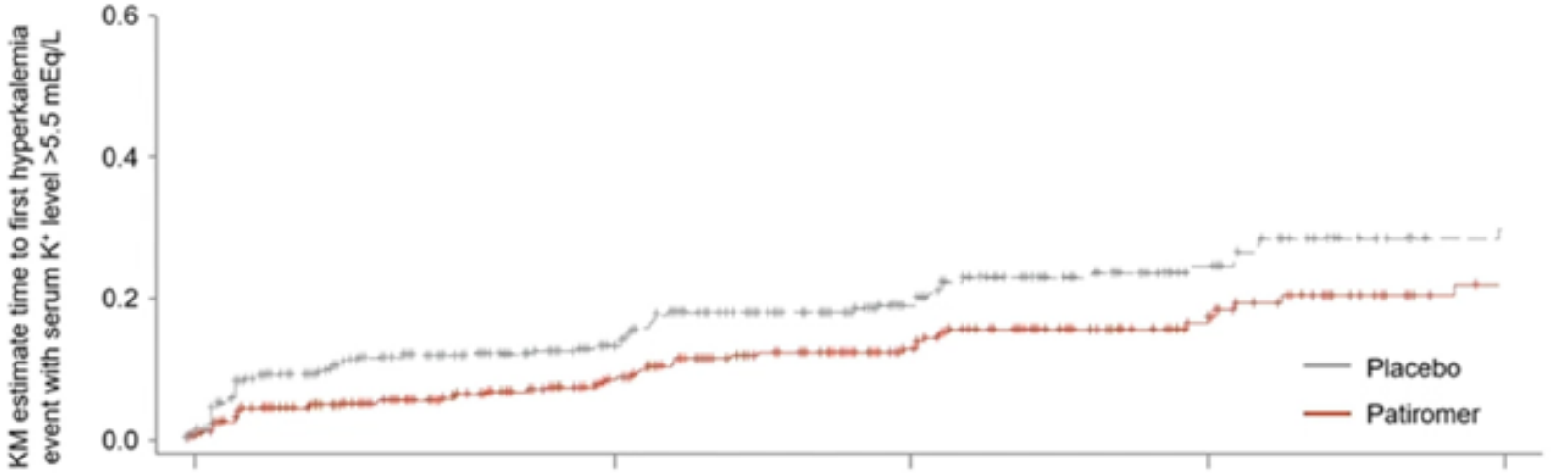
Note: Follow-up after the end of study visit included a K^+ assessment visit within 2 weeks of patiromer/placebo discontinuation and/or follow up phone call at least 2 weeks after the end of the study visit.

[a]≥50% recommended dose of ACEi/ARB/ARNI. [b]50 mg of MRA (spironolactone or eplerenone).

1. Butler J on behalf of the DIAMOND trial committees and investigators. Presented at: ACC Annual Scientific Session; April 2-4, 2022; Washington DC, United States.
2. Butler J, et al. *Eur J Heart Fail.* 2022;24(1):230-238.

DIAMOND Study: Secondary Endpoint
Time to first hyperkalemia event with sK+>5.5 mEq/L

Patiromer (N=439) n (%)	Placebo (N=439) n (%)	HR (95% CI)	P value
61 (13.9)	85 (19.4)	0.63 (0.45, 0.87)	0.006



Number at Risk (Events)					
Patiromer	414 (9)	249 (32)	156 (44)	89 (49)	52 (53)
Placebo	406 (18)	233 (55)	146 (69)	83 (76)	53 (81)

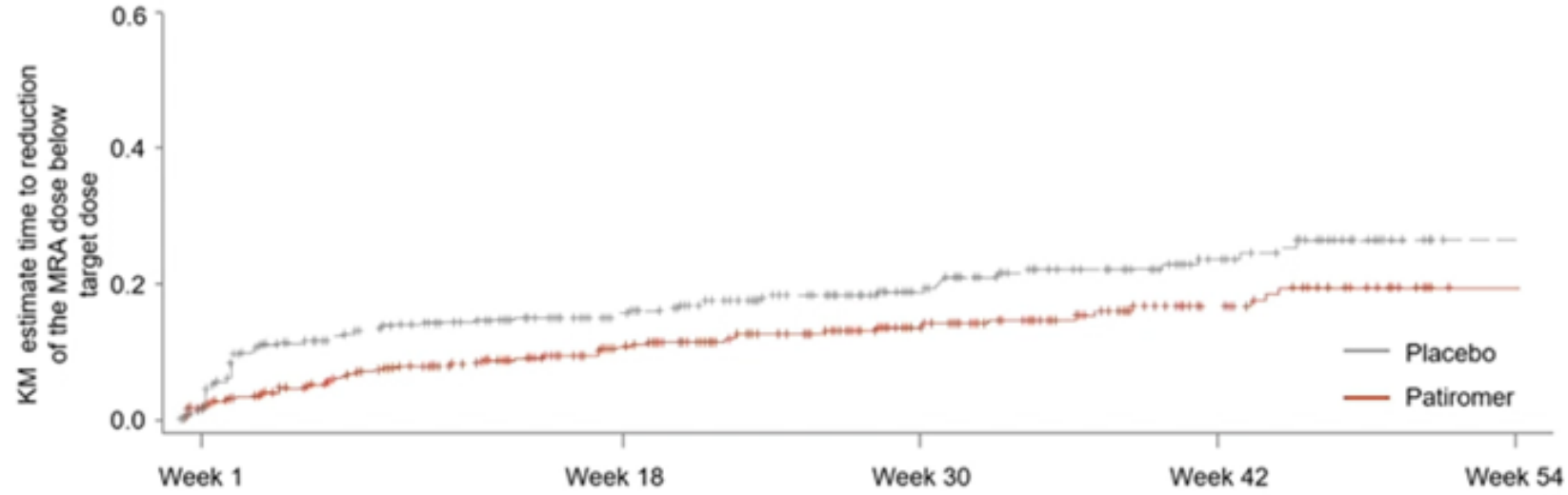
Note: Participants without an event are censored at the last K^+ measurement data or at data cut-off, whichever comes first.

Butler J on behalf of the DIAMOND trial committees and investigators. Presented at: ACC Annual Scientific Session; April 2-4, 2022

DIAMOND Study: Secondary Endpoint

Time to reduction of the MRA dose below target dose[a]

Patiromer (N=439) n (%)	Placebo (N=439) n (%)	HR (95% CI)	P value
61 (13.9)	83 (18.9)	0.62 (0.45, 0.87)	0.006



Number at Risk (Events)

Patiromer	417 (8)	256 (40)	169 (48)	98 (52)	62 (55)
Placebo	399 (18)	238 (61)	156 (70)	89 (77)	56 (80)

Note: Participants without an event are censored at end of study date or date where MRA target dose could not be determined or at data cut off, whichever comes first. Participants not on MRA target dose at baseline are censored on day 1.

[a]Target dose defined as 50 mg of spironolactone or eplerenone

Butler J on behalf of the DIAMOND trial committees and investigators. Presented at: ACC Annual Scientific Session; April 2-4, 2022

SZC selected efficacy data

Interactive question 3

All of the following are correct about SZC, except?

A. It is an inorganic crystal
B. It significantly reduces K levels within 1 hour
C. Can maintain K levels in normal range for up to 1 year
D. Effects on RAASi optimization in HFrEF being evaluated in REALIZE-K trial
E. Has only been tested in patients with mild hyperkalemia

Interactive question 3

All of the following are correct about SZC, except?

A. It is an inorganic crystal

B. It significantly reduces K levels within 1 hour

C. Can maintain K levels in normal range for up to 1 year

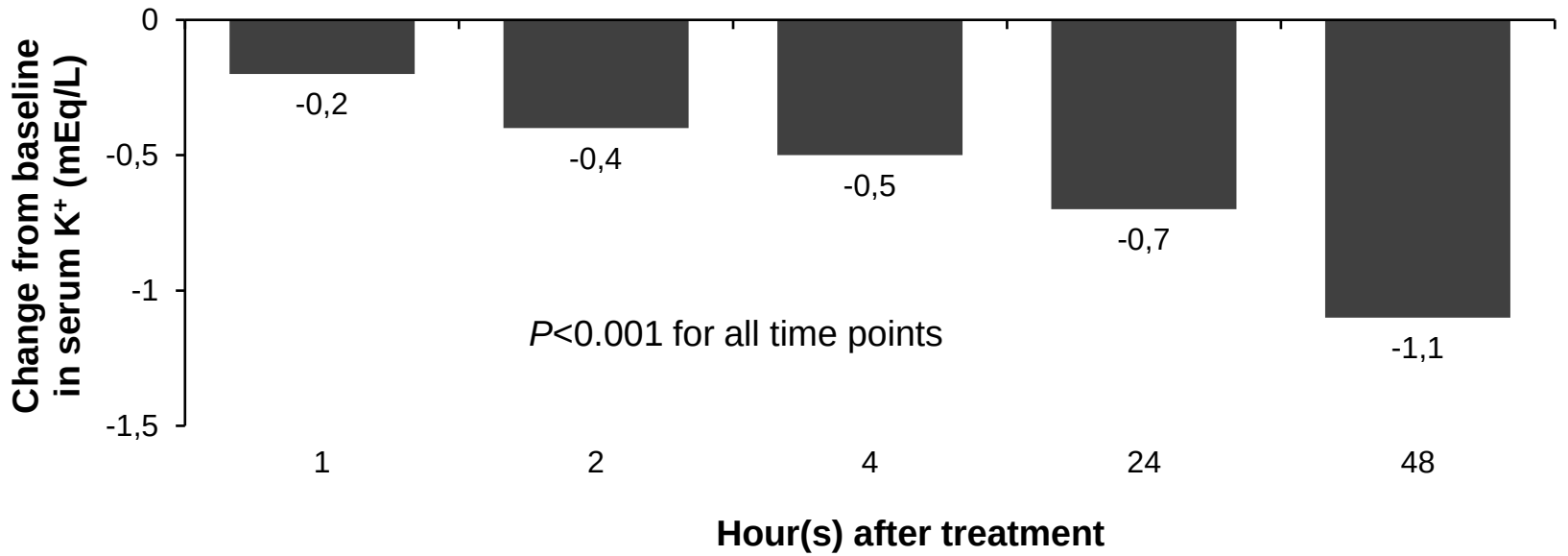
D. Effects on RAASi optimization in HFrEF being evaluated in REALIZE-K trial

E. Has only been tested in patients with mild hyperkalemia

SZC: Onset of action at 1 hour (HARMONIZE 004)

- One dose of SZC significantly reduced serum K^+ levels (–0.2 mEq/L) at 1 hour vs baseline ($P<0.001$)[1,2]
- 98% of patients achieved normokalemia during the 48-hour correction phase[1]

Mean serum K^+ level with SZC 10 g three times daily for 48 hours (N=258)[a,1]



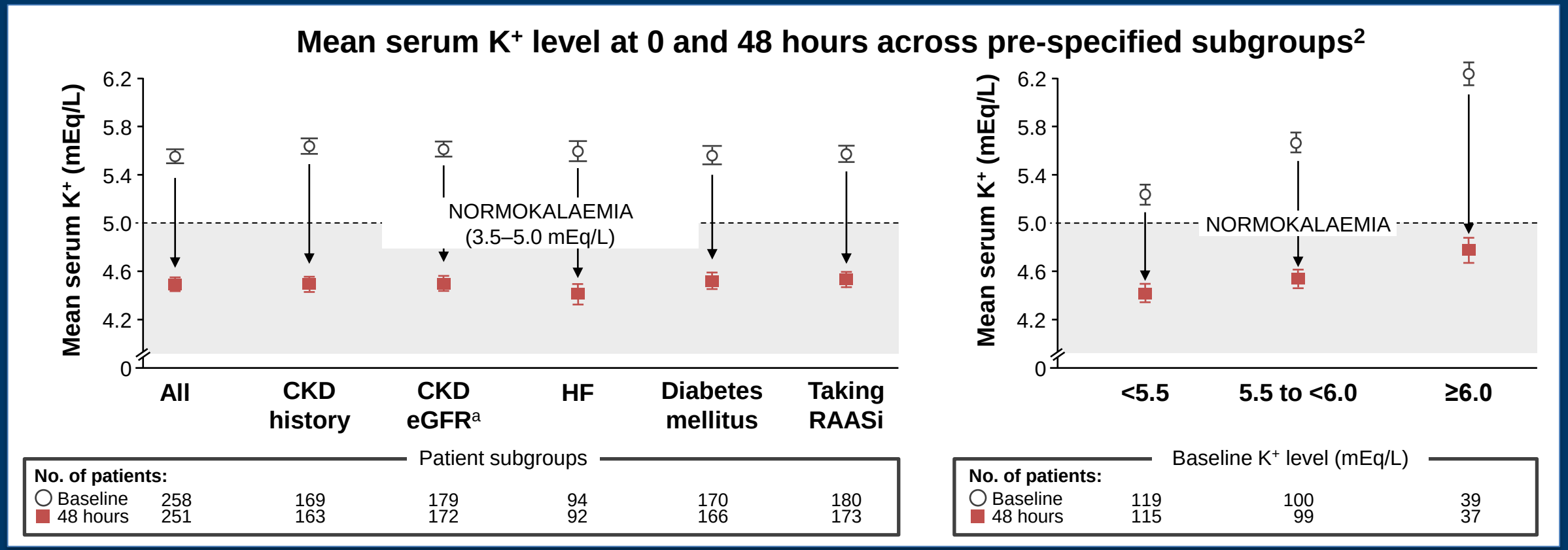
Open-label phase mean baseline serum K^+: **5.6 mEq/L**

[a]In the open-label 48-h phase of the HARMONIZE trial SZC, sodium zirconium cyclosilicate

1. Kosiborod M, et al. *JAMA* 2014;312:2223–2233; 2. SZC Singapore Prescribing Information (June 2020)

SZC: Predictable serum K+ reduction across patient types (HARMONIZE 004)

- SZC consistently reduced serum K^+, regardless of comorbidities, use of RAASi therapy or baseline K^+ level[1]



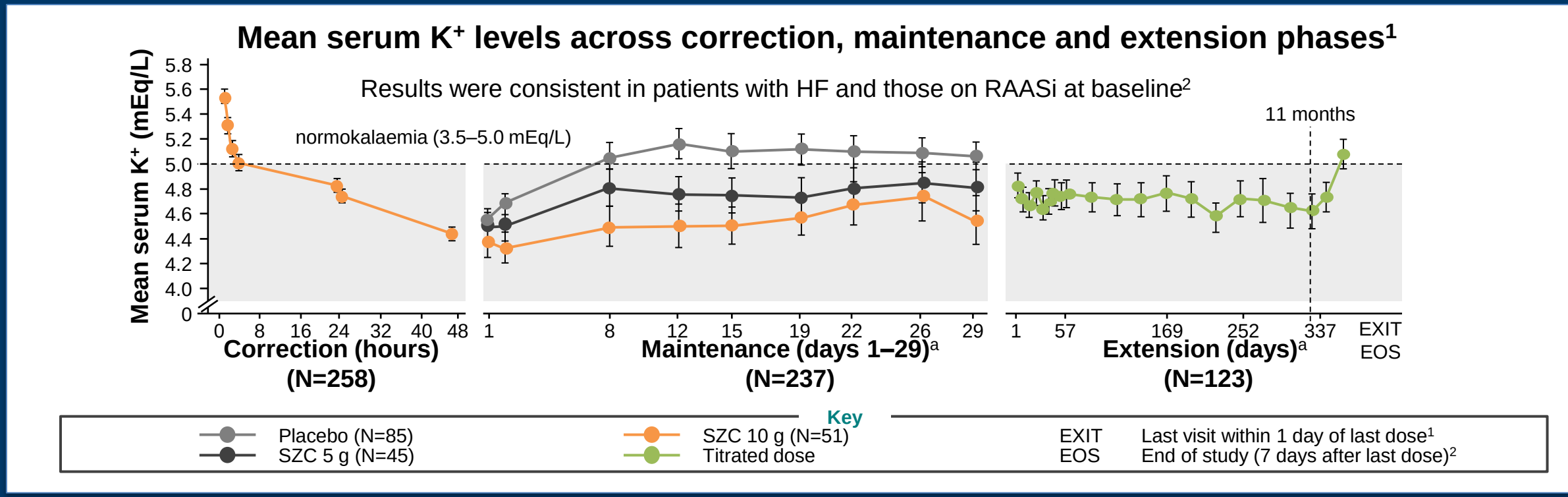
[a]<60 mL/min/1.73 m^2

eGFR, estimated glomerular filtration rate; RAASi, renin–angiotensin–aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate

1. SZC Singapore Prescribing Information (June 2020); 2. Adapted from Kosiborod M, et al. *JAMA* 2014;312:2223–2233

SZC: Sustained K+ control for up to 1 year (HARMONIZE 004)

- 88% of patients receiving SZC maintained an average serum K^+ of <5.1 mEq/L over 11 months[1]
- No dietary restrictions were imposed; patients were instructed to continue their usual diet without any specified alterations[1]

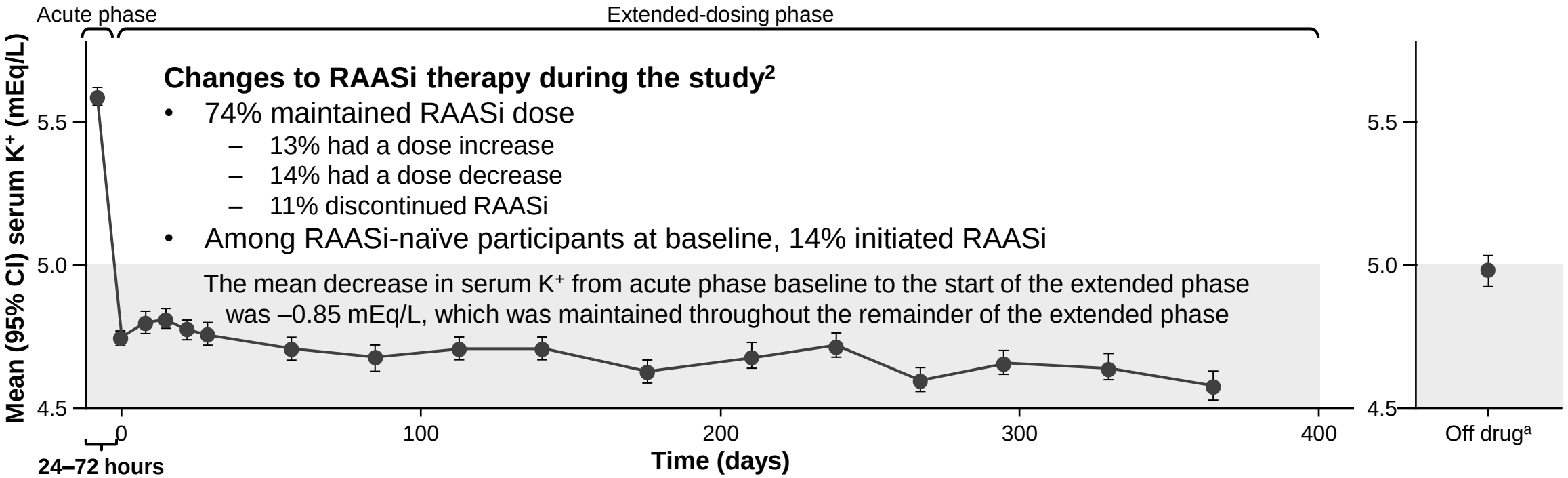


[a]The recommended starting dose for maintenance therapy with SZC is 5 g QD, which may be titrated to 10 g QD as needed. No more that 10 g QD should be used for maintenance therapy. The 5 g QD dose can be downtitrated to 5 g QOD.[1] The extended maintenance group contained a small proportion (11%) of patients who were treated with SZC 15 g QD, which is not a dose that is indicated for use in the EU[1]

1. SZC Singapore Prescribing Information (June 2020); 2. Kosiborod M, et al. *JAMA* 2014;312:2223–2233

Study 005: Sustained K+ control over 1 year

- Outpatients (≥18 years) with HK (serum K^+ ≥5.1 mEq/L) enrolled across 56 sites from Cardiology and Nephrology clinics in USA, Australia, Germany, UK, Netherlands, Romania and South Africa. No dietary restrictions or changes in RAASi were required[1,2]

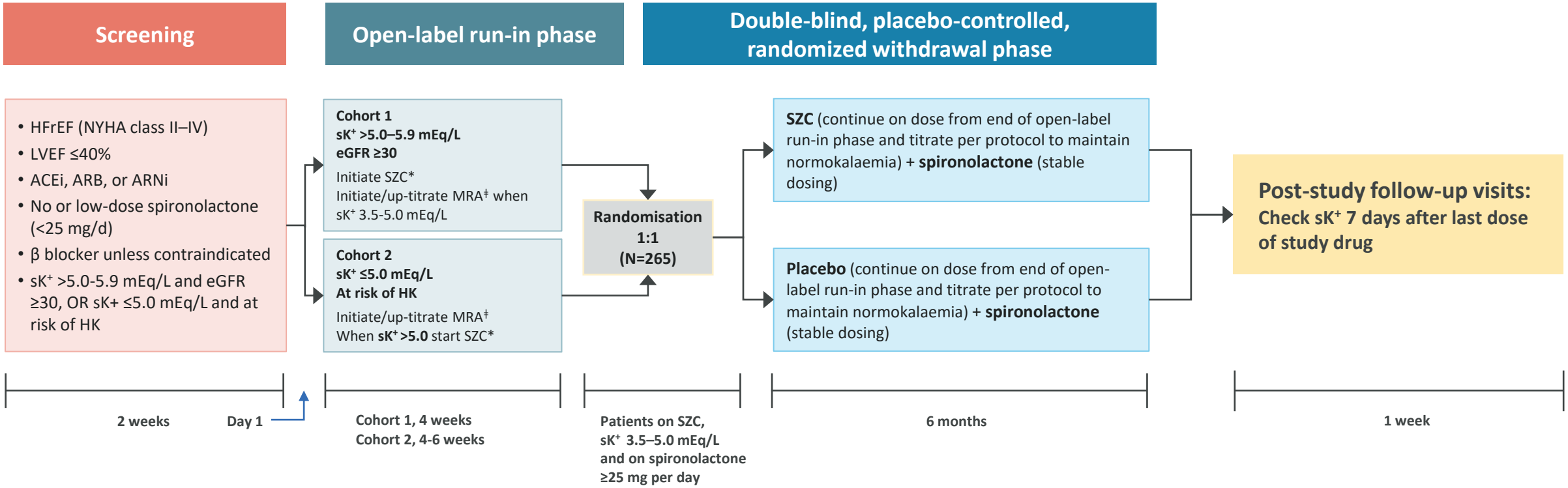


[a]Off-drug values collected 7 (±1) days after the last administration of SZC. The extended maintenance group contained a small proportion (11.7%) of patients who were treated with 15 g QD, which is not a dose indicated for use in the EU.[1] Of 483 RAASi users at baseline, 87% continued or had their dose increased; 11% discontinued[2]

1. Fishbane S, et al. Presented at American Society of Nephrology Kidney Week 2017; 31st October – 5th November 2017; New Orleans, LA, USA; TH-PO1112;
2. Spinowitz B, et al. *Clin J Am Soc Nephrol* 2019;7;14:798–809

REALIZE-K

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



*SZC 10 g TID ≤48 h, then SZC 10 g QD, titrate if needed per protocol to maintain sK 3.5–5.0 (range: 5 g QOD to 15 g QD)

‡Spironolactone maximum dose is 50 mg daily

HK, hyperkalaemia; MRA, mineralocorticoid receptor antagonist; sK+, serum potassium; SZC, sodium zirconium cyclosilicate

Summary

- Prevalence of hyperkalemia will likely continue to increase and is a particular problem because of its association with RAAS inhibitor use
- Typical clinical decision making is to down-titrate or stop RAASi despite benefits
- Marked underuse of GDMT in HFrEF
- Novel K-binders may change the treatment paradigm in favor of optimizing the use and dosing of RAAS inhibitors/MRAs
- Guidelines have acknowledged novel K-binders as a potential treatment option, but have not strongly endorsed their use to date
- Additional evidence regarding effects of K-binders on RAASi enablement may further advance their adoption