Hyperkalemia Management
A NEW ERA

RENAL
Powered by CVRM

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Why is HK a treatment barrier for CKD and HF?

Which of the following sentences best expresses your opinion about hyperkalemia?

- It is a temporary condition that prevents optimal RAASi therapy
- It is a problem that should be kept under constant that contributes to the progression of chronic disease

Approximately what percentage of your patients are hyperkalemic in your clinical practice?

- < 10%
- 10-15 %
- 20-25%
- > 25%

At what potassium level do you start your management?

- > 5 mEq/L
- > 5.5 mEq/L
- > 6 mEq/L
- > 6.5 mEq/L

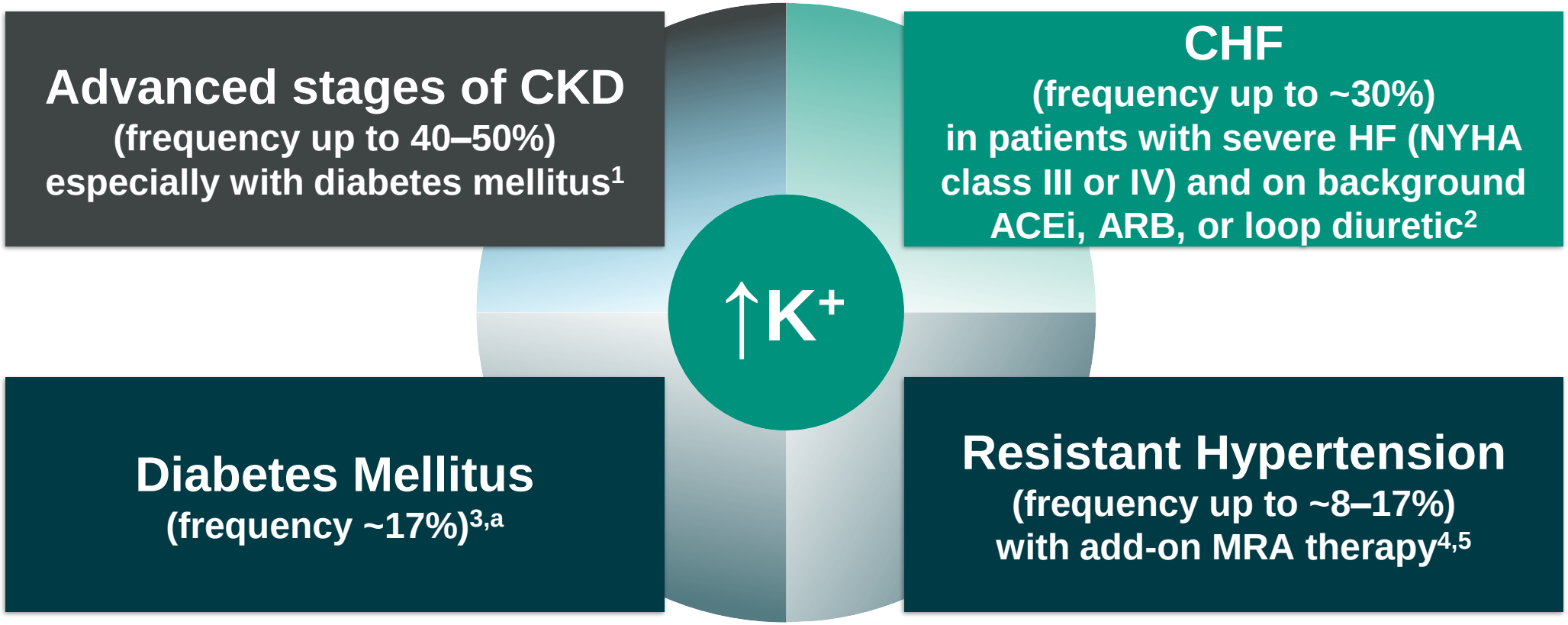
What is your first option to treat Severe hyperkalemia?

- Sodium Bicarbonate
- B2 adrenergic receptors
- Insulin-Glucose
- Dialysis

What is your first option to maintain chronic mild to moderate hyperkalemia?

- Diet Restriction
- Traditional potassium binders (SBS)
- Diuretics
- Down titration or discontinuation of RAAS i

Patient subgroups with a high incidence of hyperkalemia



LOKELMA™ ▼
powder for oral suspension
Sodium zirconium cyclosilicate

Note: Hyperkalemia is defined as K^+ >5.0 mmol/L[1-3] or as persistent K^+ >5.5 mmol/L (or a single reading of K^+ >6.0 mmol/L).[5]
[a]3-year incidence estimate.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CHF = chronic heart failure; CKD = chronic kidney disease; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

1. Kovesdy CP. *Nat Rev Nephrol*. 2014;10:653-662; 2. Vardeny O et al. *Circ Heart Fail*. 2014;7:573-579; 3. Nilsson E et al. *Int J Cardiol*. 2017;245:277-284; 4. Chomicki J et al. *J Am Soc Hypertens*. 2014;8:e30. P-10; 5. Khosla N et al. *Am J Nephrol.* 2009;30:418-424.

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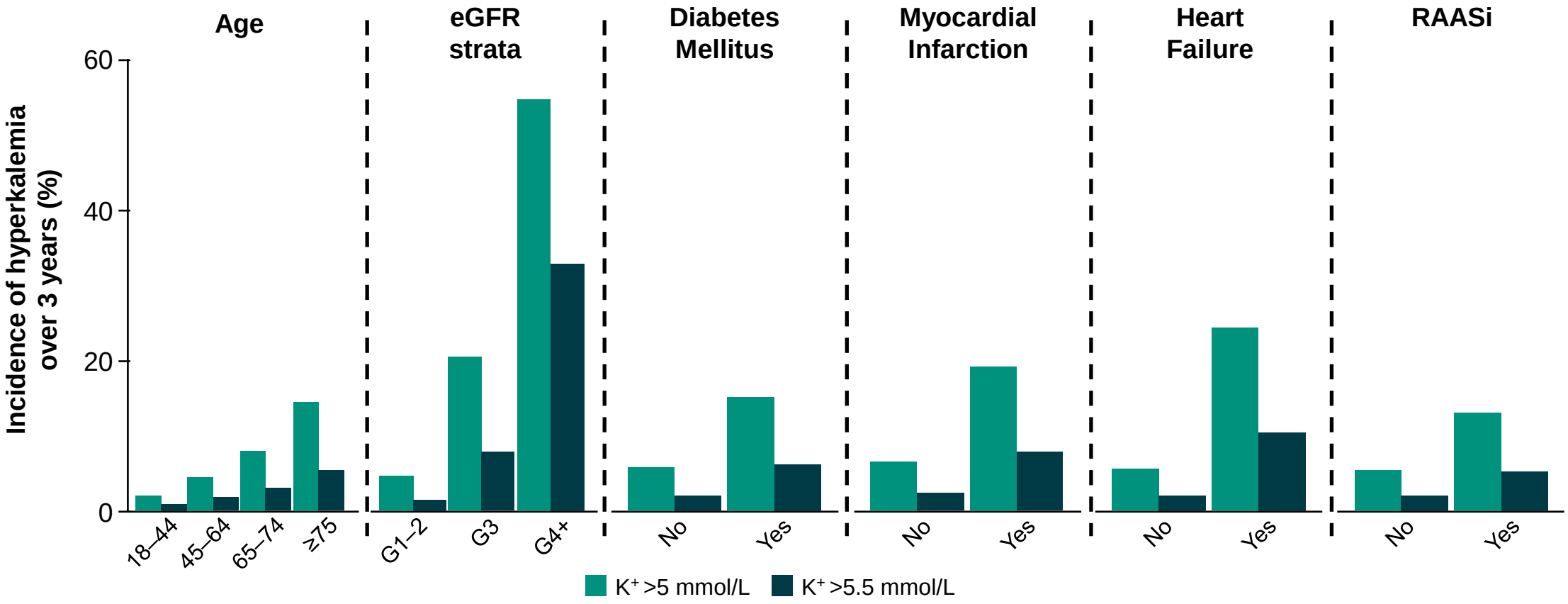
Reduced eGFR observed as a major risk factor for hyperkalemia, along with other comorbidities and common medications

Observational study of 364,955 patients in the SCREAM project who underwent K^+ testing during 2009 and with a recent serum creatinine test to determine eGFR[a]



[a]In the absence of albuminuria information eGFR categories (rather than CKD stages) were defined: G1-2 = eGFR ≥60 mL/min/1.73 m^2; G3 = eGFR ≥30 to <60 mL/min/1.73 m^2; G4+ = eGFR <30 mL/min/1.73 m^2 (including dialysis or transplantation).
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAASi = renin–angiotensin–aldosterone system inhibitor; SCREAM = Stockholm CREAtinine Measurements.
Nilsson E et al. *Int J Cardiol.* 2017;245:277-284.

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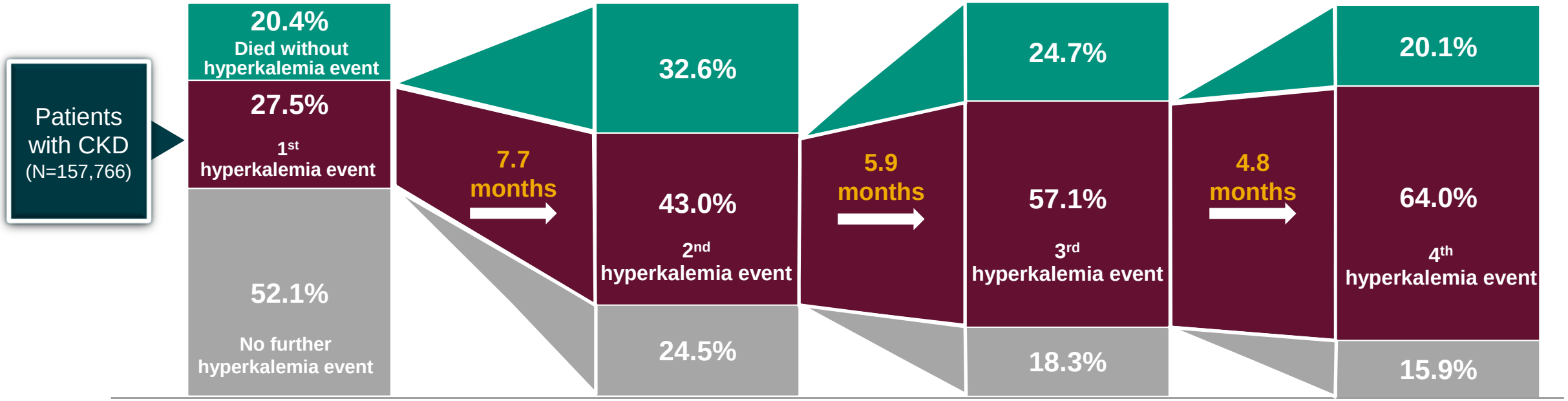
Patients with CKD have recurrent hyperkalemia episodes, with successively shorter time between the episodes

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) during 2000–2012. Patients with a first time diagnosis of CKD were identified



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CKD = chronic kidney disease.

Thomsen RW et al. *Nephrol Dial Transplant*. 2018;33:1610-1620.

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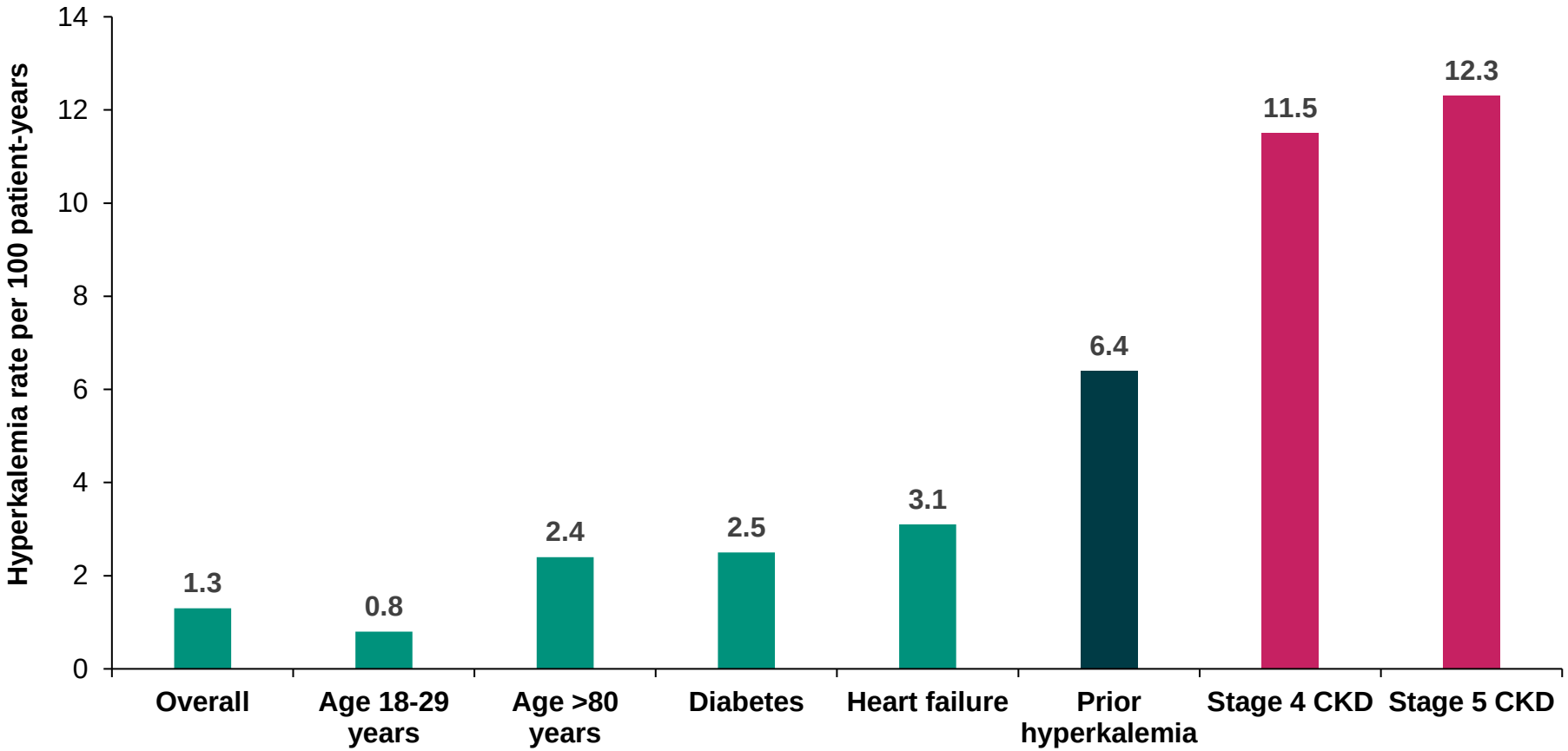
Moderate and severe hyperkalemia was common among RAASi users, especially those with advanced CKD

An observational cohort study of 434,027 patients (moderate hyperkalemia, 78.8%; severe hyperkalemia, 21.2%) with incident and prevalent RAASi users using data from the CPRD and linked Hospital Episode Statistics between 2009 and 2014



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Note: Hyperkalemia defined as moderate (serum K^+ 5.5-6.0 mmol/L) or severe (serum K^+ >6.0 mmol/L). Specific RAASi therapies were not defined.
CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; RAASi = renin-angiotensin-aldosterone system inhibitor.
Gilbertson D et al. *Nephrol Dial Transplant.* 2018;33(suppl 1). Abs SP324.

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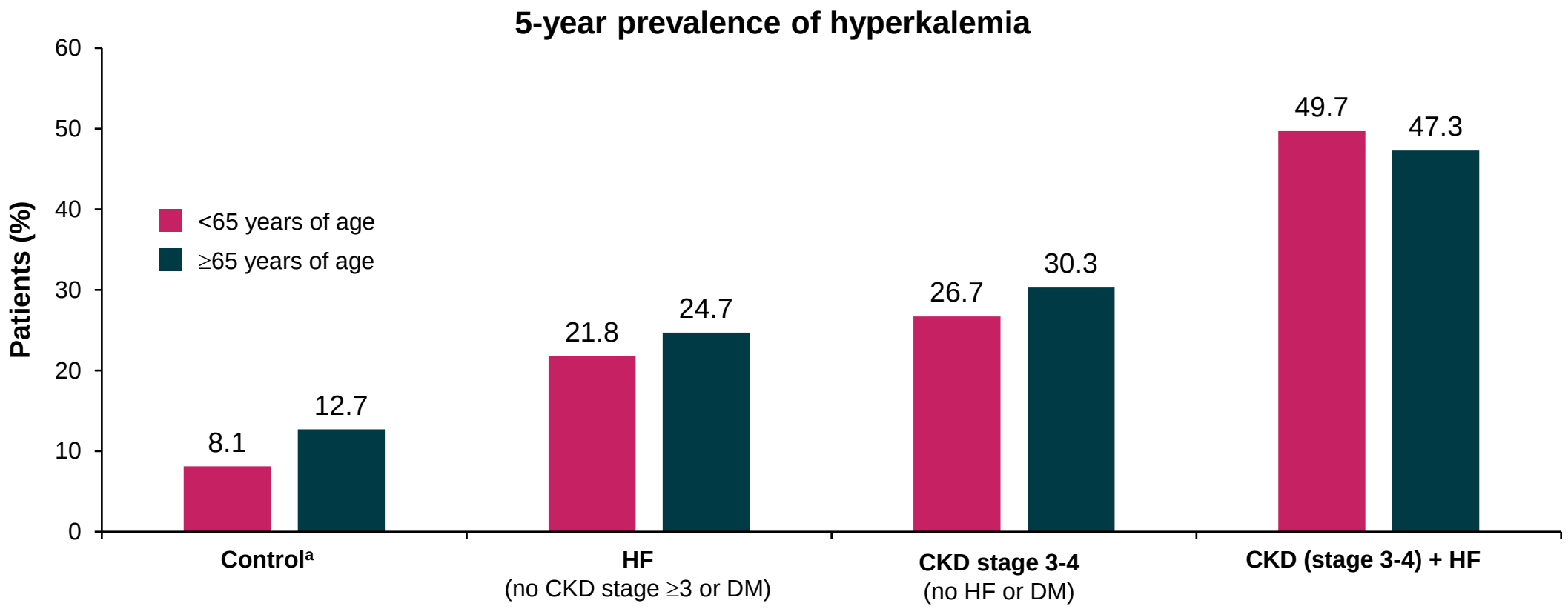
Patients with CKD + HF had an increased prevalence of hyperkalemia

Large US database (N=1.7 million/7 million, including both insured and uninsured) with de-identified medical records (2008-2012) of patients (≥65 years [n=558,308] and <65 years [n=1,072,900]) with various comorbidities and at least one K^+ reading of 2.5-10 mmol/L were evaluated for prevalence of hyperkalemia (K^+ ≥5.1 mmol/L)



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[a]Patients without CKD stages 2–5, HF, DM, or end-stage renal disease.
CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; US = United States.
Latts LM et al. Poster presented at: ISPOR; May 16-20, 2015; Philadelphia, PA. Poster PVC33.

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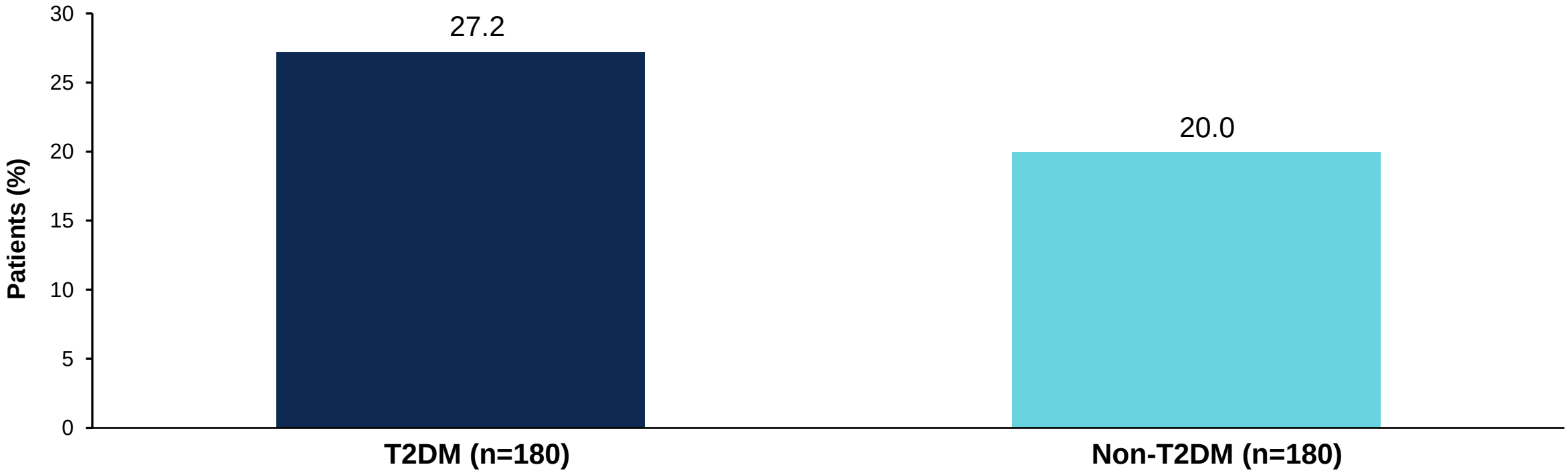
Prevalence of hyperkalemia was higher in patients with CKD and co-existing diabetes compared to control

Nested case-control cohort included CKD stages 2-4[a] patients with T2DM[b] and matched control without T2DM from nephrology outpatient clinic from Greece between January 2007-May 2015



Note: Prevalence of hyperkalemia was defined as K^+ >5 mmol/L or use of sodium polystyrene sulfonate, and further by K^+ >5, ≥5.2, and ≥5.5 mmol/L.
[a]Excluded CKD stage 5 (ESRD and transplant patients). CKD stages were defined according to KDIGO; [b]Diabetes was defined based on ADA or history of T2DM or hypoglycemic agents.
ADA = American Diabetes Association; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; KDIGO = Kidney Disease Improving Global Outcomes; T2DM = Type 2 diabetes mellitus.
Loutradis C et al. *Am J Nephrol*. 2015;42:351–360.

RAASi therapy is recommended for the management of patients with CKD

NDD-CKD patients without diabetes mellitus

- KDIGO recommends that an ARB or ACEi be used in non-diabetic adults with NDD-CKD and urine albumin excretion >300 mg per 24 hours (or equivalent) in whom treatment with BP-lowering drugs is indicated (*1B*)

NDD-CKD patients with diabetes mellitus

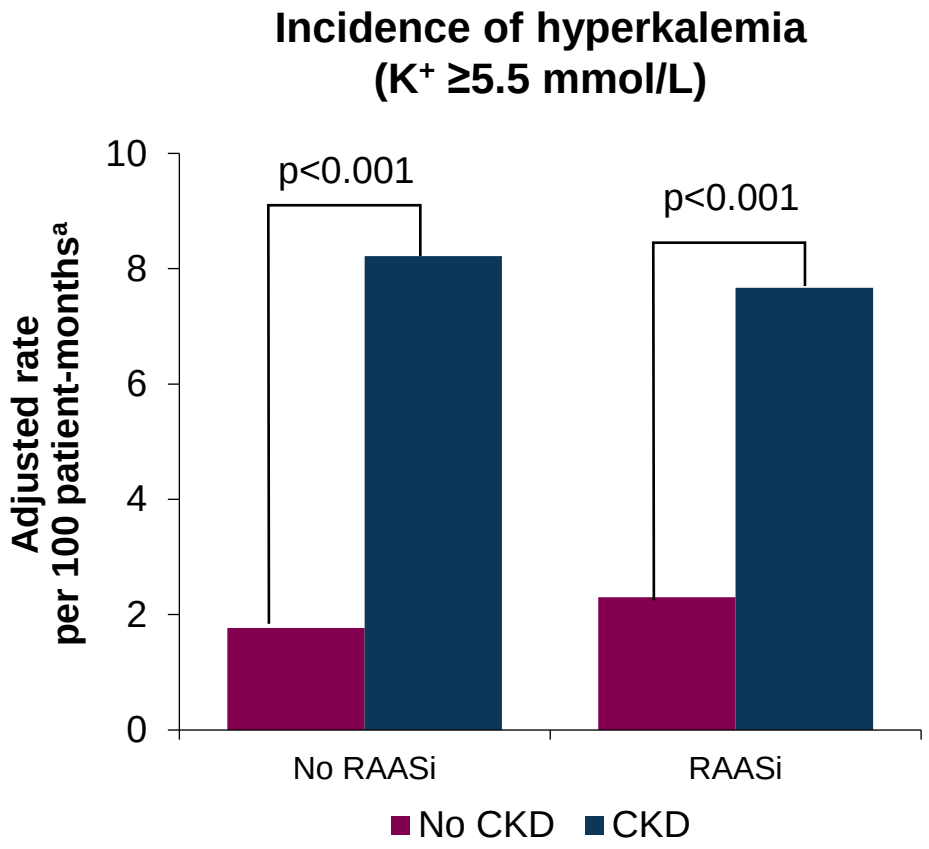
- KDIGO recommends that an ARB or ACEi be used in adults with diabetes and NDD-CKD with urine albumin excretion >300 mg per 24 hours (or equivalent) (*1B*)

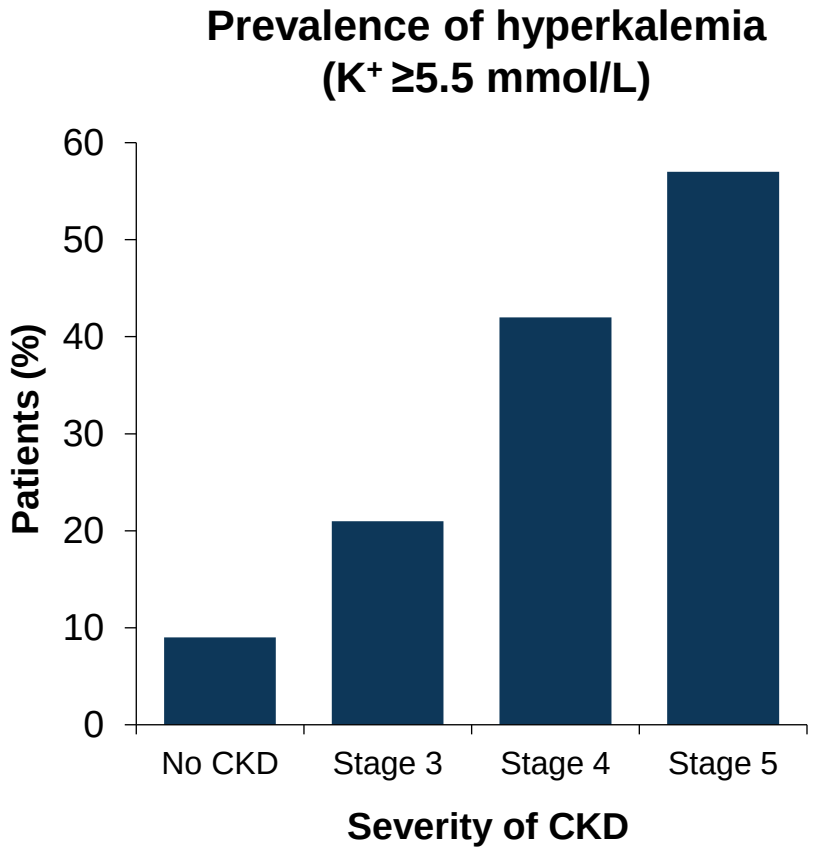
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes; NDD-CKD, nondialysis-dependent chronic kidney disease; RAASi, renin–angiotensin–aldosterone system inhibitor

Kidney Disease Improving Global Outcomes CKD Work Group. *Kidney Int Suppl* 2012;2:337–414

Risk of hyperkalemia increased with CKD ± RAASi use and with the severity of CKD

Retrospective analysis of Veterans Health Administration national healthcare system cohort comprised of 2,103,422 records from 245,808 veterans with at least one hospitalization and serum potassium record during 2005

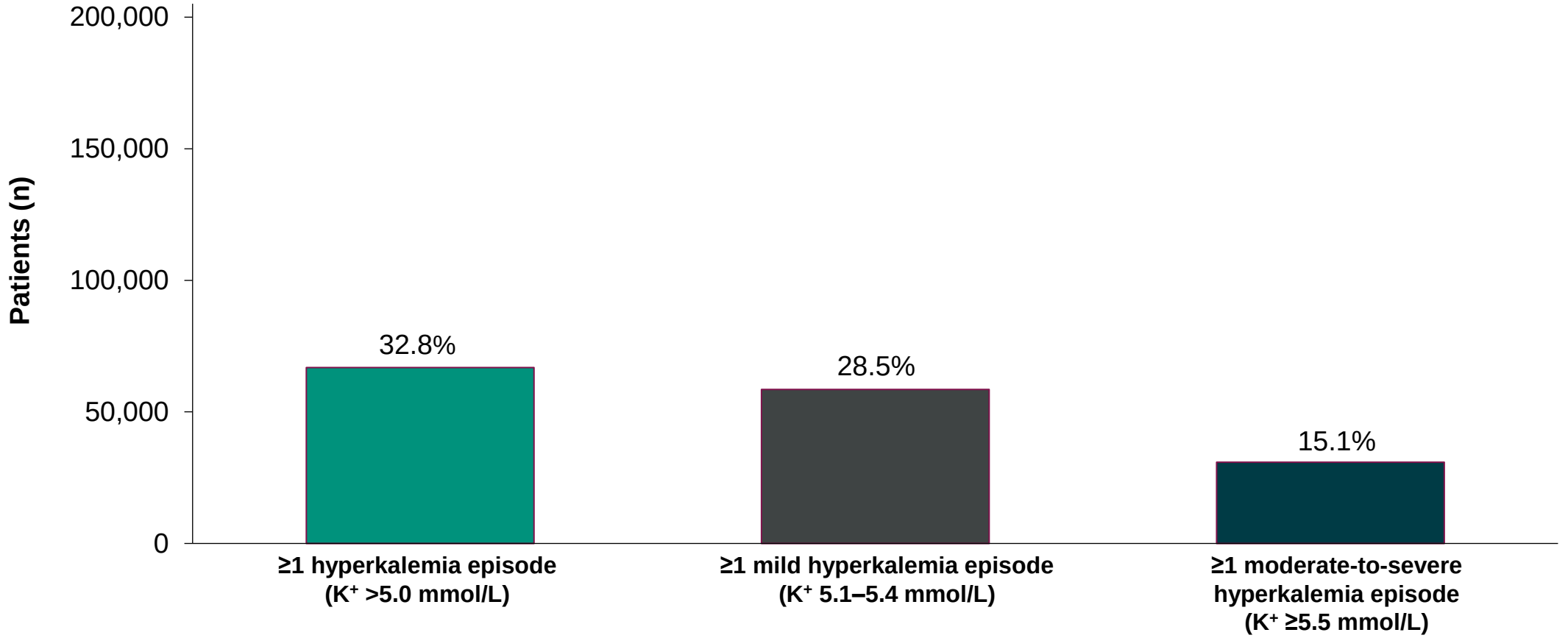




Note: CKD is defined by an eGFR <60 mL/min/1.73 m^2 using the abbreviated Modification of Diet in Renal Disease (MDRD) equation.
[a]Adjusted for confounders; race, gender, age, Charlson Comorbidity Index, cancer, diabetes, CVD, and RAASi treatment within 30 days.
CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; RAASi = renin–angiotensin–aldosterone system inhibitor.
Einhorn LM et al. *Arch Intern Med*. 2009;169:1156-1162.

Over a 5-year period, ~30% of patients on RAASi therapy experienced at least one hyperkalemia episode

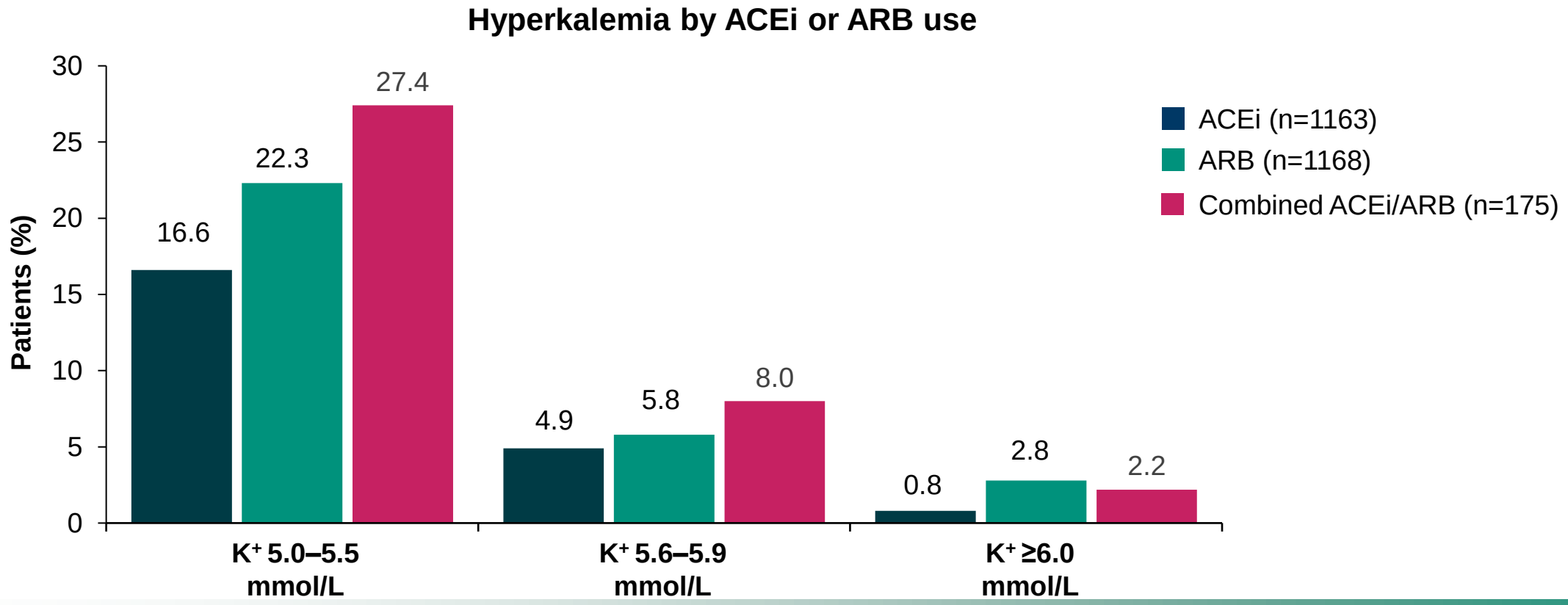
Retrospective analysis of 1,700,000 electronic health records of patients with CKD, heart failure, or diabetes, with at least two serum K^+ readings, and on at least 1 RAASi[a] from Humedica (US) in 2007-2012 (N=205,108)



Note: Patients could have been counted in both the mild or moderate-severe groups, based on the types of episodes experienced.
[a]Includes ACEi, ARBs, direct renin inhibitors, and select MRAs.
ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; US = United States.
Epstein M et al. *Am J Manag Care*. 2015;21(suppl 11):S212–S220.

A significant proportion of patients on ACEi/ARB therapy experience hyperkalemia

Retrospective observational cohort study of 2331 patients on ACEi or ARB therapy from a single center VA Medical Center in the US. Hyperkalemia was observed in 20.4% of patients on ACEi and 31.0% of patients on ARBs. Among patients with diabetes, hyperkalemia was observed in 24% of patients on ACEi (mean GFR 68.7 mL/min) and 37.7% of patients on ARBs (mean GFR 58.7 mL/min)



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Note: Hyperkalemia defined as K^+ >5 mmol/L.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; GFR = glomerular filtration rate; US = United States; VA = Veterans Affairs.
Sadjadi S et al. *Ther Clin Risk Manag*. 2009;5:547–552.

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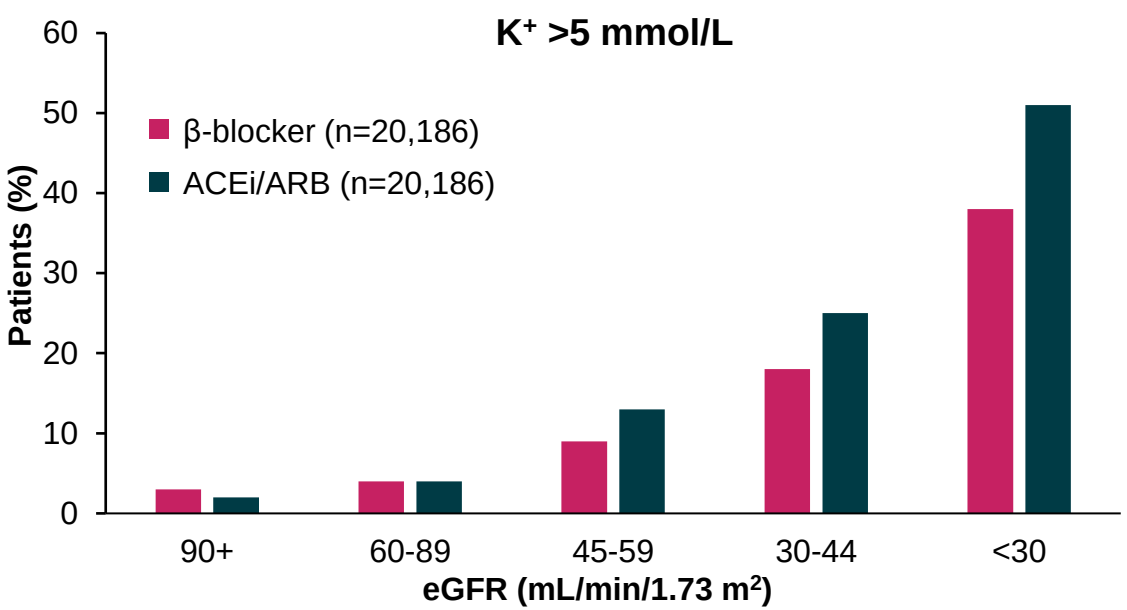
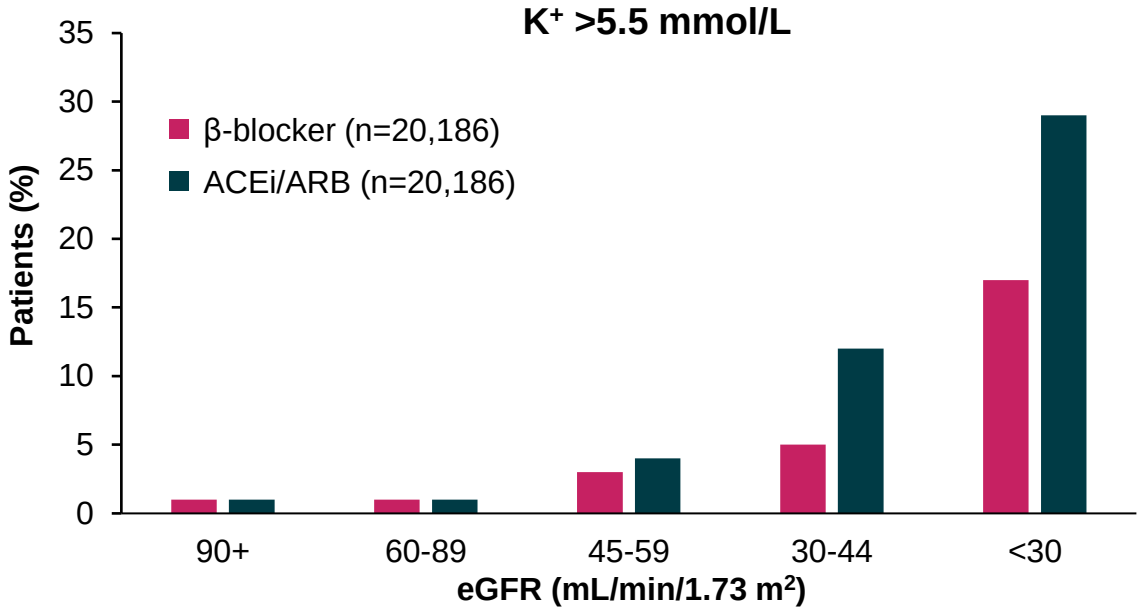
Hyperkalemia rates in the first year of ACEi/ARB therapy increased in patients with lower eGFR

Observational study of 69,426 patients in the SCREAM project who were new ACEi or ARB users with a serum creatinine and K^+ measurement on or within 1 year of dispensing date during January 2007–December 2010. Patients were propensity-matched 1:1 to a cohort of new β-blocker users. Mean K^+ level prior to dispensing medication was 4.1 mmol/L

Proportion of patients with hyperkalemia during the first year of therapy by eGFR status



- Of the 2977 patients who had K^+ >5 mmol/L in the first year, **1000 patients had a recurrent K^+ >5 mmol/L** within the year



- Of the 924 patients who had K^+ >5.5 mmol/L in the first year, **278 patients had a recurrent K^+ >5.5 mmol/L** within the year

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ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; SCREAM = Stockholm CREAtinine Measurements.

Bandak G et al. *J Am Heart Assoc*. 2017;6:e005428.

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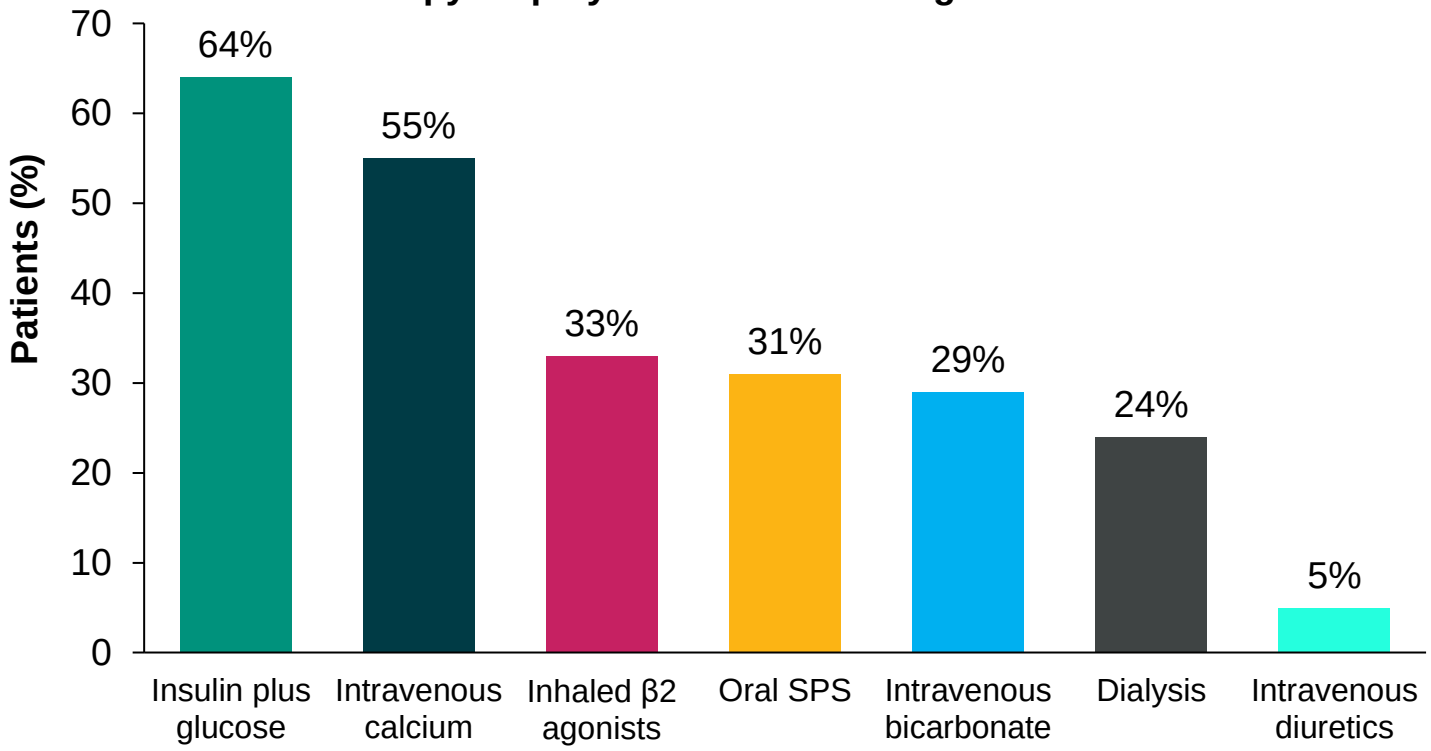
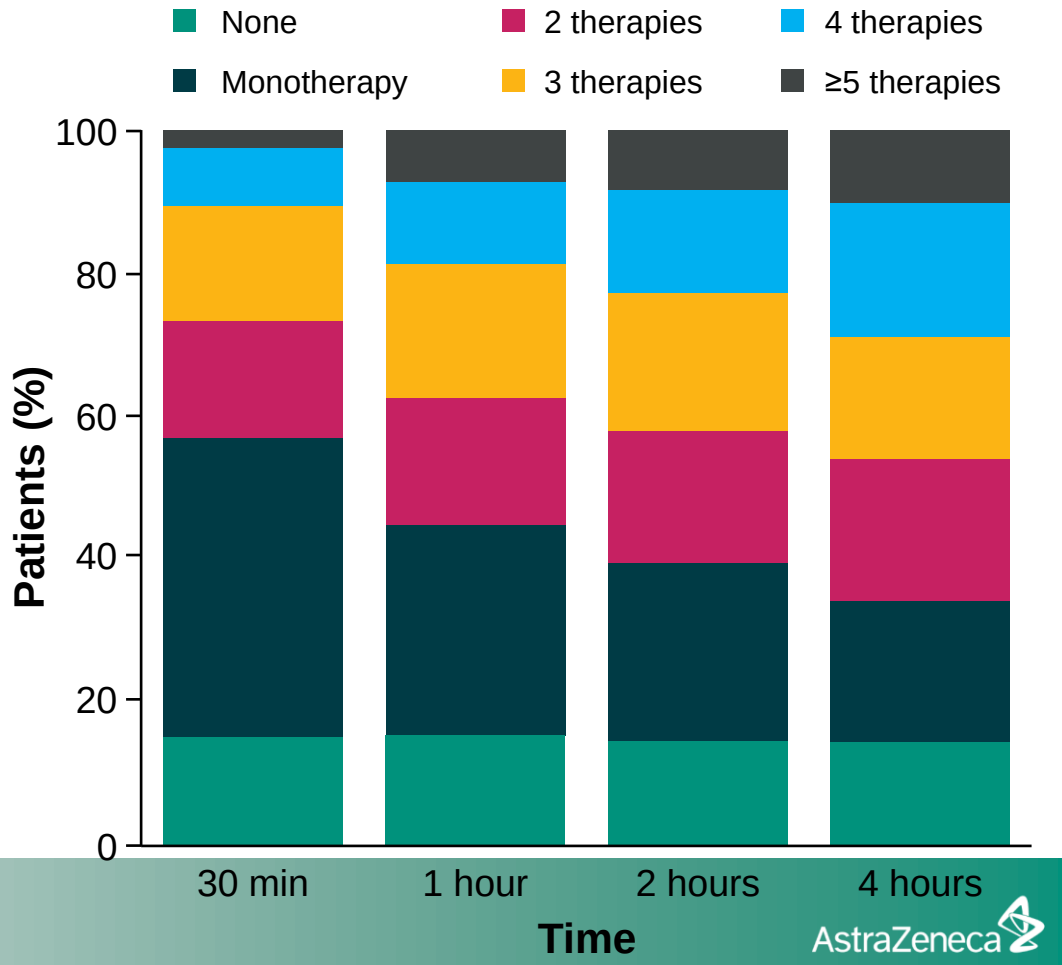
Insulin and glucose were the most common treatment for HK, with the majority of patients receiving multiple interventions within 4 hours

A multicentre, prospective, observational study enrolled 203 patients with HK in the ED at 14 US-based sites from 25th October 2015 to 30th March 2016

Therapy employed in the ED setting within the first 4 hours



Cumulative number of K^+-lowering treatments over time



- The most common therapy employed was insulin plus glucose, which was used alone or in combination with other treatments

LOKELMA™ powder for oral suspension
Sodium zirconium cyclosilicate

ED, emergency department; HK, hyperkalaemia; SPS, sodium polystyrene sulphonate

Peacock FW, et al. *J Emerg Med* 2018;55:741–750

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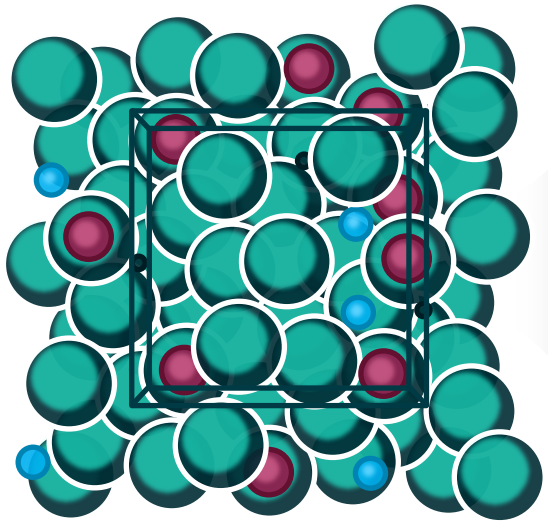
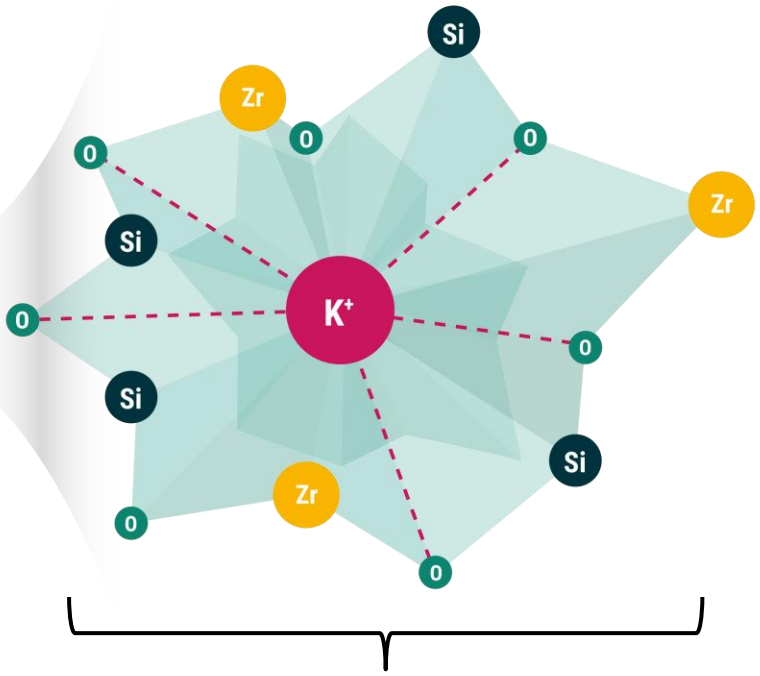
Lokelma: A New Solution

LOKELMA crystal structure

LOKELMA is indicated for the treatment of HK in adults[1]



Chemical formula:
$H_6Na_2O_9Si_3Zr^{+2}$



Average binding-site width: 3 Å

Key molecular characteristics:[1,3]

- Inorganic crystalline zirconium silicate compound
- Not a polymer
- Insoluble, highly stable, and does not expand in water
- Not systemically absorbed
- High affinity for K^+ [a]
- Exchanges Na^+ and H^+ for K^+

LOKELMA™▼ powder for oral suspension Sodium zirconium cyclosilicate

[a]In vitro activity does not always equate to clinical efficacy; images are illustrative only
HK, hyperkalemia
1. AstraZeneca AB. LOKELMA▼ EU Summary of Product Characteristics 2019; 2. US National Institutes of Health National Center for Biotechnology Information PubChem Open Chemistry Database. Compound summary: sodium zirconium cyclosilicate (CID 91799284). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/91799284#section=Top (Accessed February 2019); 3. Stavros F, et al. *PLoS One* 2014;9:e114686

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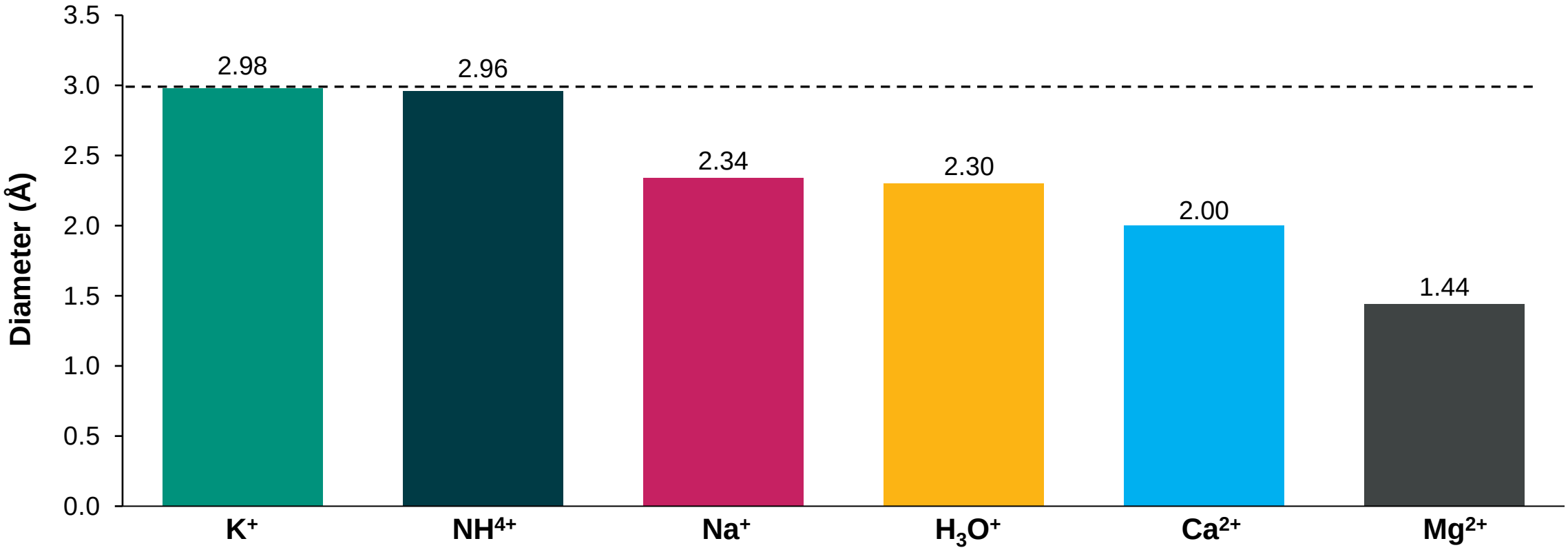
Relative diameters of major cations[a]



K^+ and NH^{4+} ions, owing to similar ionic diameters, 'fit' best into the LOKELMA pores, which are ~3 Å in size

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Sodium zirconium cyclosilicate

[a]Unhydrated

Stavros F, et al. *PLoS One* 2014;9:e114686

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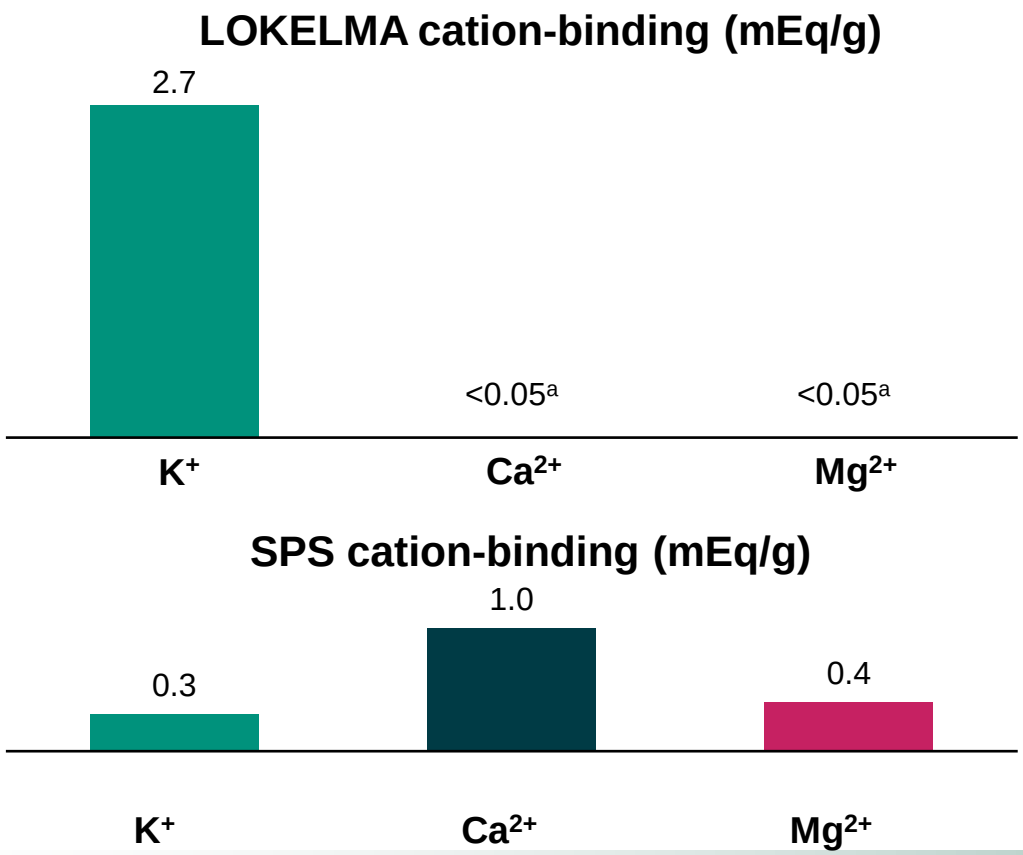
LOKELMA and SPS: Selectivity for K^+

- In vitro studies were designed to examine the ion exchange capacities of LOKELMA and SPS
- K^+, Ca^{2+}, and Mg^{2+} concentration ratio of 1:1:1



- LOKELMA displayed 9.3× more K^+-binding capacity than SPS
- LOKELMA was >125× more selective for K^+ than SPS
- SPS was more selective for Mg^{2+} and Ca^{2+} than for K^+
- LOKELMA and SPS have not been studied in head-to-head clinical trials and *in vitro* effects do not necessarily equate to efficacy, therefore no superiority of efficacy or other clinical benefit should be implied.

LOKELMA™ powder for oral suspension
Sodium zirconium cyclosilicate

[a]Exchange capacity for Ca^{2+} and Mg^{2+} was <LOD (<0.05)
LOD, limit of detection; SPS, sodium polystyrene sulfonate
Adapted from: Stavros F, et al. *PLoS One* 2014;9:e114686

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Lokelma efficacy & safety

ZS-004 (HARMONIZE) + ZS-004E (Extension)

Study Designs

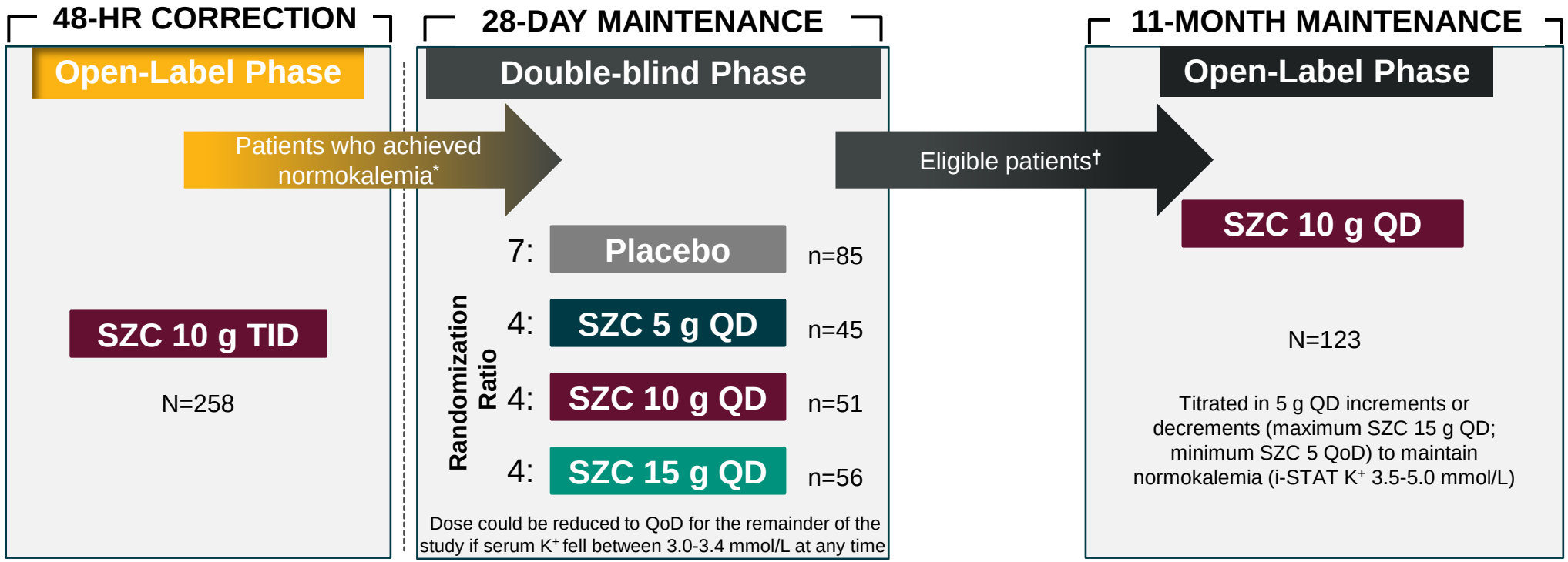
crystalize HARMONIZE & Extension

ZS-004[1]

Phase III, multicenter, 2-phase prospective study in patients with serum K^+ ≥5.1 mmol/L at 44 nephrology, cardiology, general research sites in US, South Africa, and Australia

ZS-004E (EXTENSION)[2]

Extension phase of patients who completed ZS-004 at 30 sites in US, South Africa, and Australia



*Proceeded to maintenance phase if patient achieved normokalemia (i-STAT K^+ 3.5-5.0 mmol/L) by morning of study Day 3; †Two patients with i-STAT K^+ >5.5 mmol/L at the end of ZS-004 entered the correction phase of ZS-004E where they received SZC 10 g TID and proceeded to the 11-month maintenance phase within 1 day once normokalemia (i-STAT K^+ 3.5-5.0 mmol/L) was achieved. The remaining patients with i-STAT K^+ 3.5-5.5 mmol/L at the end of ZS-004 immediately entered the 11-month maintenance phase to receive SZC 10 g QD.
QoD = every other day; SZC = sodium zirconium cyclosilicate; US = United States.

1. Kosiborod M et al. Article and protocol. *JAMA*. 2014;312:2223-2233; 2. Roger SD et al. Article and supplementary material. *Am J Nephrol.* 2019;50:473-480.

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ZS-004 (HARMONIZE) + ZS-004E (Extension)
Efficacy Endpoints

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HARMONIZE & Extension

	ZS-004[1]	ZS-004E[2]
Primary	**Randomized Maintenance Phase:** • Comparison of mean serum K^+ levels between placebo and each SZC treatment group from Day 8 to Day 29	Proportion of patients with mean serum K^+ ≤5.1 mmol/L during 11-month maintenance phase (Day 8 through Day 337)
Key Secondary	**Open-label Correction Phase:** • Change from baseline in serum K^+ levels at all time intervals • Proportion of patients achieving normokalemia by 24 and 48 hours • Time to K^+ normalization **Randomized Maintenance Phase:** • Proportion of patients with mean K^+ level <5.1 mmol/L during Days 8 to 29	Proportion of patients with average serum K^+ ≤5.5 mmol/L during 11-month maintenance phase (Day 8 through Day 337)

Note: Normokalemia defined as serum K^+ 3.5–5.0 mmol/L.
1. Kosiborod M et al. *JAMA*. 2014;312:2223-2233; 2. Roger SD et al. *Am J Nephrol.* 2019;50:473-480.

ZS-004 (HARMONIZE) + ZS-004E (Extension)
Key Inclusion and Exclusion Criteria

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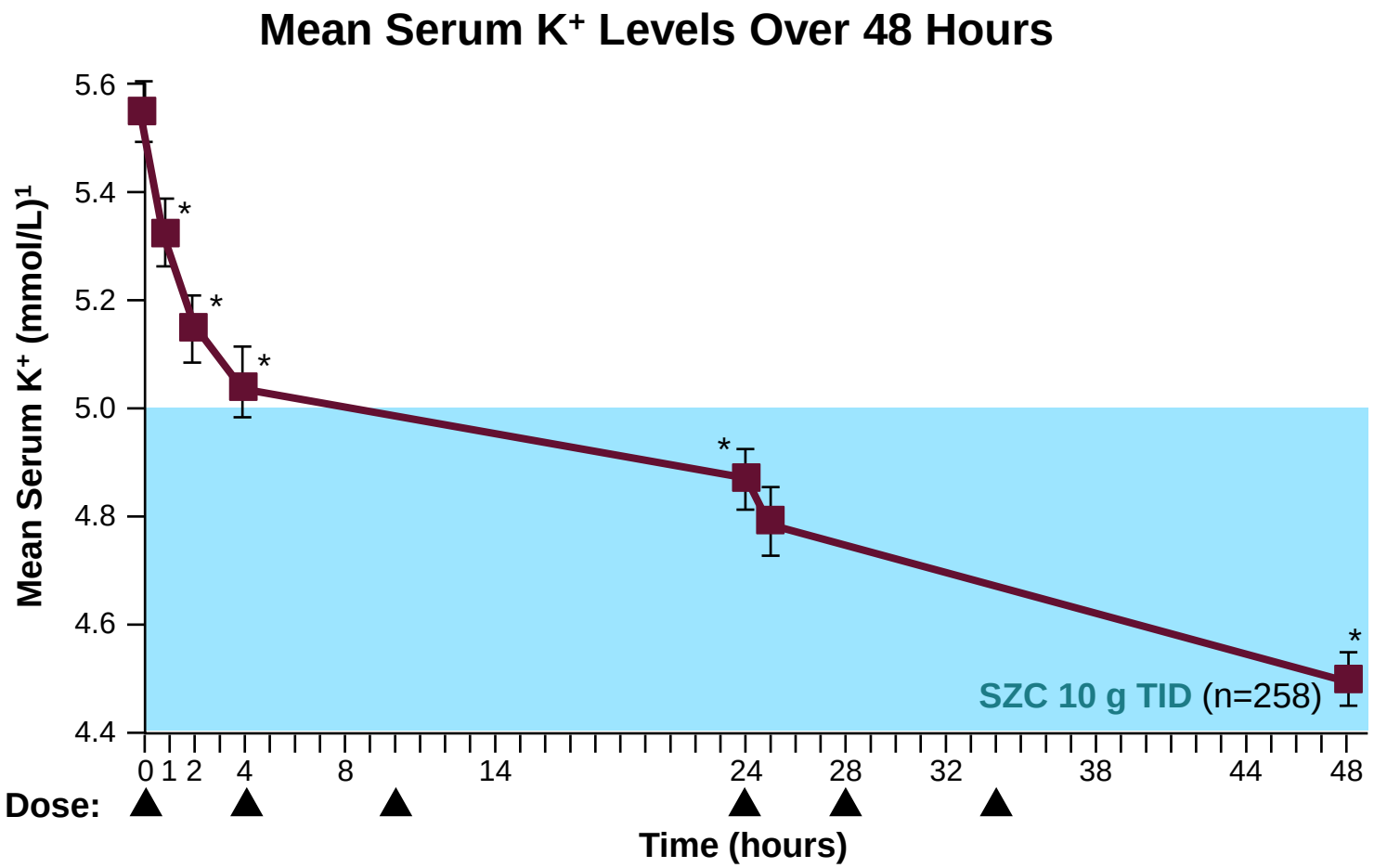
	ZS-004[1]	ZS-004E[2]
Key Inclusion Criteria	• >18 years of age • Two consecutive i-STAT K^+ values ≥5.1 mmol/L, with no upper limit at entry • Ability to have repeated blood draws	• Completed ZS-004 randomized dosing phase or discontinued due to hypo- or hyperkalemia and able to start ZS-004E dosing within 2 days after last ZS-004 dose • i-STAT K^+ 3.5–6.2 mmol/L at ZS-004 study Day 29 visit, OR a mean i-STAT K^+ 3.5–6.2 mmol/L for 2 consecutive measurements at 0 and 60 minutes on correction phase Day 1/maintenance phase Day 1 if discontinued ZS-004 study due to hypo- or hyperkalemia
Key Exclusion Criteria	• Dialysis • Cardiac arrhythmia requiring immediate treatment • Active treatment with resins (eg, SPS or sevelamer acetate), calcium acetate, calcium carbonate, or lanthanum carbonate within 7 days • Treatment with lactulose, Xifaxan®, or other non-absorbed antibiotics for hyperammonemia within 7 days • Diabetic ketoacidosis • Pseudohyperkalemia	• Dialysis • Cardiac arrhythmia requiring immediate treatment • Received alternative treatment for hyperkalemia during ZS-004 study • Diabetic ketoacidosis • Pseudohyperkalemia

SPS = sodium polystyrene sulfonate.
1. Kosiborod M et al. Article and protocol. *JAMA*. 2014;312:2223-2233; 2. Roger SD et al. Supplementary material. *Am J Nephrol.* 2019;50:473-480.

Correction for Acute patient Profiles

ZS-004 (HARMONIZE)
Correction Phase: Efficacy Endpoints



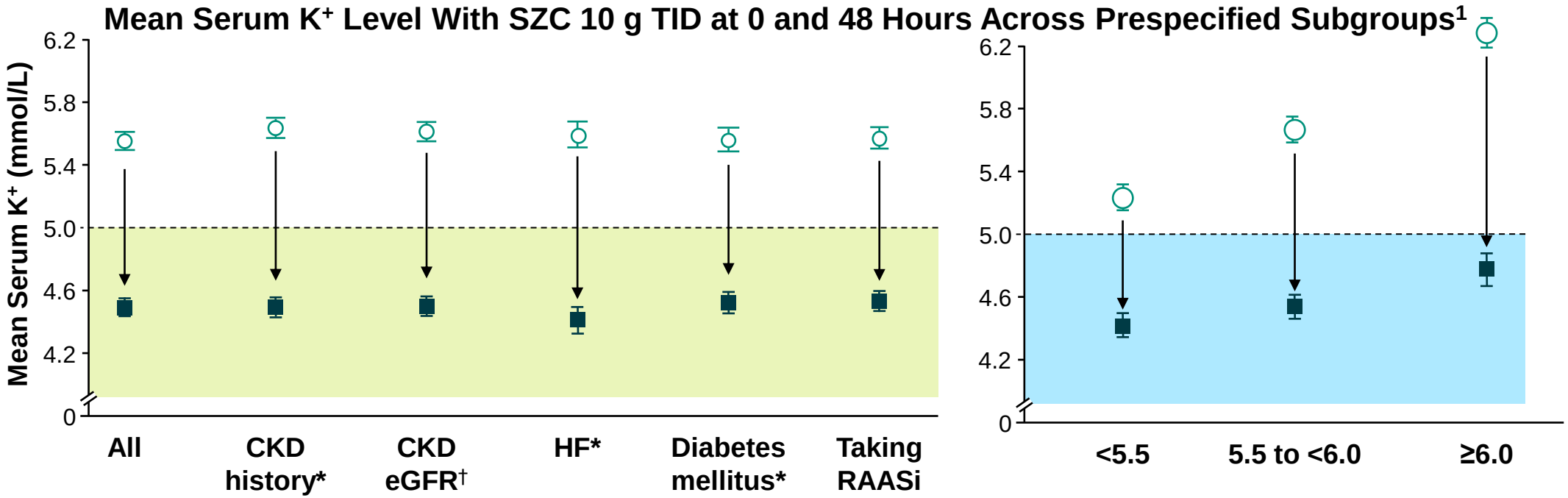
- K^+ decreased by 0.2, 0.4, 0.5, 0.7, and 1.1 mmol/L at 1, 2, 4, 24, and 48 hours, respectively ($p<0.001$)[1]
- Median time to K^+ normalization was 2.2 hours (IQR, 1.0 to 22.3)[1]
- Patients achieving normokalemia:
  - K-M estimates (ITT population)[1]
    - 84% of patients by 24 hours
    - 98% of patients by 48 hours

Note: Normokalemia defined as serum K^+ 3.5–5.0 mmol/L. Error bars indicate 95% CI.
*p<0.001 vs. baseline.
IQR = interquartile range; ITT = intent-to-treat; K-M = Kaplan-Meier; SZC = sodium zirconium cyclosilicate.
1. Kosiborod M et al. *JAMA*. 2014;312:2223-2233; 2. LOKELMA Summary of Product Characteristics.

ZS-004 (HARMONIZE)

Correction Phase: Mean Serum K^+ Levels in Predefined Subgroups

SZC consistently reduced serum K^+, regardless of comorbidities, use of RAASi therapy, or baseline K^+ level[1-3]



No. of patients:						
○ Baseline	258	169	179	94	170	180
■ 48 hours	251	163	172	92	166	173

No. of patients:			
○ Baseline	119	100	39
■ 48 hours	115	99	37

Note: Normokalemia defined as serum K^+ 3.5–5.0 mmol/L. Error bars indicate 95% CI.
*The definitions used to identify subjects with baseline comorbid conditions (across the ZS Pharma clinical development program) were based on custom lists of preferred terms. AstraZeneca has elected to use more recognized definitions that are based on the standardized Medical Dictionary for Regulatory Activities query (narrow) for each comorbid condition. For example, in the original HF population (n=94), the mean change from baseline in K^+ was -1.173 mmol/L at 48 hours. Based on the AstraZeneca re-analysis, the percentage of patients with HF is 11% (28/251) with a mean change in K^+ of -1.196 mmol/L at 48 hours.[3]; †Baseline eGFR <60 mL/min/1.73 m^2.
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; RAASi = renin–angiotensin–aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.
1. Kosiborod M et al. *JAMA*. 2014;312:2223-2233; 2. LOKELMA Summary of Product Characteristics; 3. In House Data, AstraZeneca Pharmaceuticals LP. LOKELMA (sodium zirconium cyclosilicate) oral suspension. Subgroups based on comorbid conditions at baseline in ZS clinical studies. Doc ID-003819479. April 4, 2018.

Maintance for Chronic patient Profiles

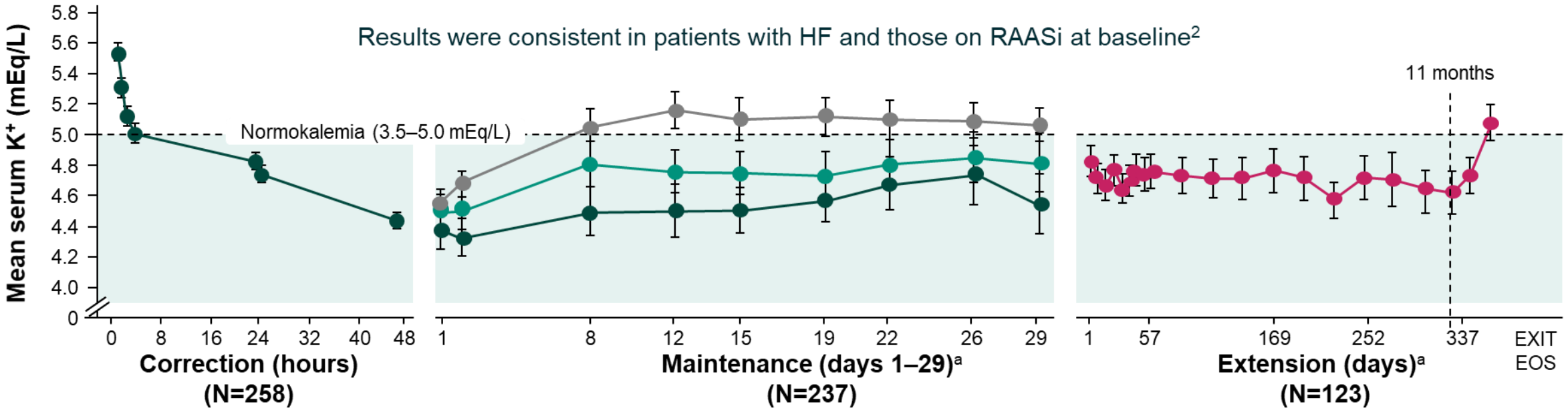
ZS-004 (HARMONIZE) + ZS-004E (Extension)

Mean Serum K⁺ Levels Across Correction, Maintenance, and Extension Phases

- 88% of patients receiving LOKELMA 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]

Mean serum K⁺ levels across correction, maintenance, and extension phases[1]

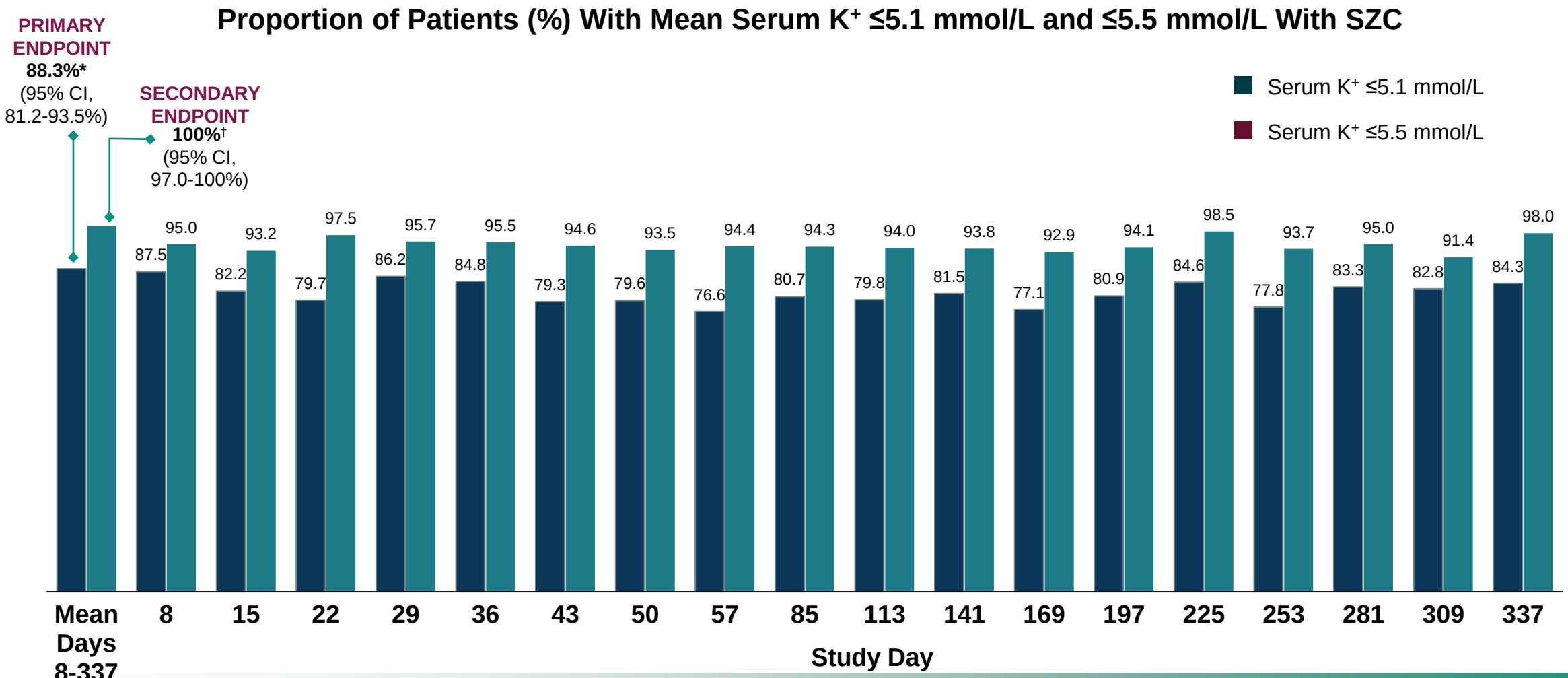
Results were consistent in patients with HF and those on RAASi at baseline[2]



Note: Normokalemia defined as serum K⁺ 3.5–5.0 mmol/L. Error bars indicate 95% CI.
*p<0.001 vs. baseline; †p<0.001 vs. placebo during Days 8-29; ‡ITT population in Extension-MP consisted of patients who received ≥1 SZC dose with any post-Extension-CP BL safety data and post-Extension-MP serum K⁺ measurements. Off-drug values were recorded at 7±1 days following the last dose of SZC; §Mean SZC doses to maintain normokalemia were 10 g QD in 73.2%, >10 g QD in 13.0%, <10 g QD in 13.8% of patients.
BL = baseline; CP = correction phase; ITT = intent-to-treat; MP = maintenance phase; SZC = sodium zirconium cyclosilicate.
1. Kosiborod M et al. *JAMA*. 2014;312:2223-2233; 2. Roger SD et al. Article and supplementary material. *Am J Nephrol.* 2019;50:473-480.

ZS-004E (Extension)

Mean Serum K^+ ≤5.1 mmol/L and ≤5.5 mmol/L (ITT Population)



*Unadjusted proportion, p<0.001 vs. the expected 50%; †Unadjusted proportion, p<0.001 vs. the expected 60%.
ITT = intent-to-treat; SZC = sodium zirconium cyclosilicate.
Roger SD et al. *Am J Nephrol.* 2019;50:473-480.

ZS-004E (Extension)

RAASi Dosing During the Study

Of the 38 patients who were *RAASi-naïve* at extension phase baseline

11% — **Initiated** RAASi therapy

Of the 83 patients who received *RAASi* at the start of the extension maintenance phase

78% — **Maintained** same RAASi dose

8% — **Increased** RAASi dose

4% — **Added** another RAASi

4% — **Discontinued** RAASi dose

4% — **Changed** RAASi dose*

2% — **Switched** RAASi therapy

*Multiple dose increases and decreases.
RAASi = renin–angiotensin–aldosterone system inhibitor.
Roger SD et al. *Am J Nephrol.* 2019;50:473-480.

CONCEPT K
Rethinking Hyperkalemia

KDIGO 2021 Clinical Practice Guideline for the Management of BP: Use of RAASi can often be managed by measures to reduce the serum K^+ levels rather than decreasing the dose or stopping RAASi

Selected practice points

- Strategies to control chronic hyperkalemia include dietary potassium restriction; discontinuation of potassium supplements, certain salt substitutes, and hyperkalemic drugs; adding potassium-wasting diuretics and oral potassium binders

- In CKD patients receiving RASSi who develop hyperkalemia, the latter can be controlled with newer oral potassium binders in many patients, with the effect that RASi can be continued at the recommended dose

Refer to KDIGO guidelines for more details and further practice points
UK prescribing and adverse event reporting information is available at: https://medicines.astrazeneca.co.uk/content/dam/multibrand/uk/en/prescribinginformation/lokelma-pi.pdf
BP, blood pressure; CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; RAASi, renin–angiotensin–aldosterone system inhibitor; RASi, renin–angiotensin system inhibitor
Kidney Disease: Improving Global Outcomes Blood Pressure Work Group. *Kidney Int* 2021;99(3S):S1–S87

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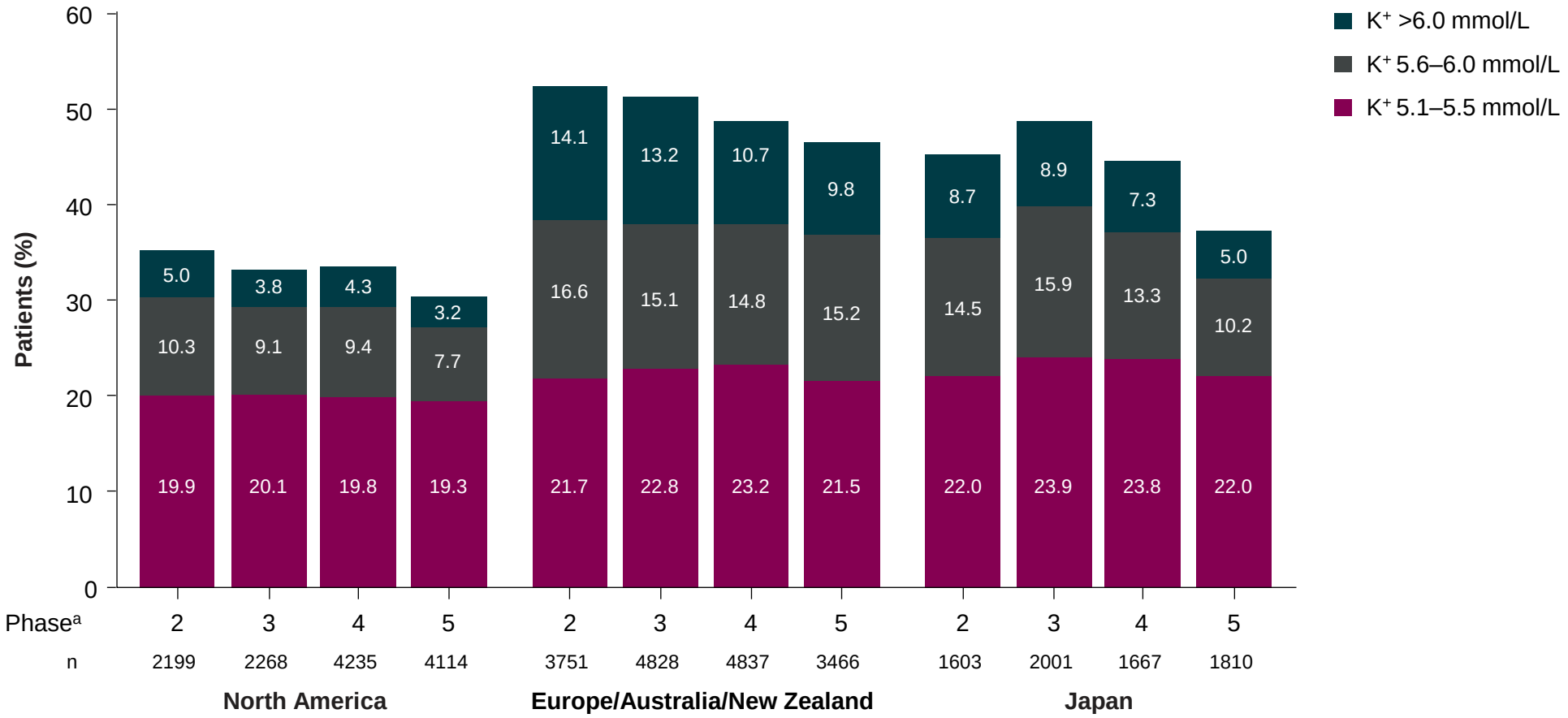
ESRD: Patient's on Dialysis What's next?

Hyperkalemia is prevalent in 30-50% of long-term hemodialysis patients

Analysis of data from an international, prospective cohort study (DOPPS) Phases 2–5 (2002–2015) in 37,852 patients with long-term dialysis (>120 days) with prevalent hyperkalemia (median follow-up 1.6 years) by various regions



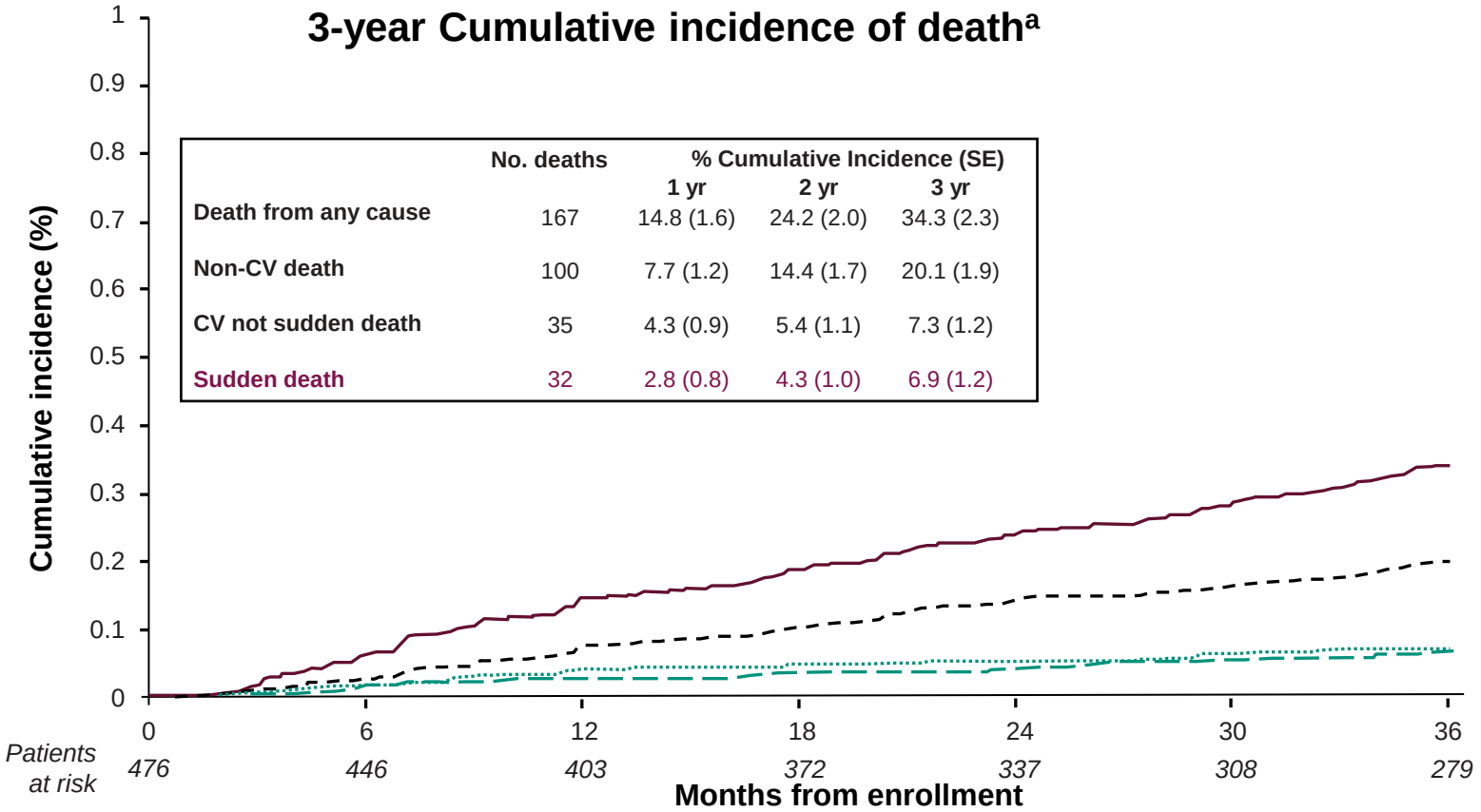
Note: Timing of K^+ measurement in relation to the hemodialysis cycle was not described in the study.
[a]Phase 2 = 2002-2004, Phase 3 = 2005-2008, Phase 4 = 2009-2011, Phase 5 = 2012-2015.
DOPPS = Dialysis Outcomes and Practice Patterns Study.
Xu H et al. Poster presented at: ERA-EDTA Congress; June 3-6, 2017; Madrid, Spain; Poster MP371.

Sudden cardiac death accounted for ~20% of total deaths of patients on chronic hemodialysis

Observational cohort study of 476 chronic hemodialysis patients receiving dialysis TIW who were followed from June 2003 to June 2006 from 5 dialysis centers in Italy (56% on dialysis for >36 months)

3-year Cumulative incidence of death[a]

	No. deaths	% Cumulative Incidence (SE)		
		1 yr	2 yr	3 yr
Death from any cause	167	14.8 (1.6)	24.2 (2.0)	34.3 (2.3)
Non-CV death	100	7.7 (1.2)	14.4 (1.7)	20.1 (1.9)
CV not sudden death	35	4.3 (0.9)	5.4 (1.1)	7.3 (1.2)
Sudden death	32	2.8 (0.8)	4.3 (1.0)	6.9 (1.2)



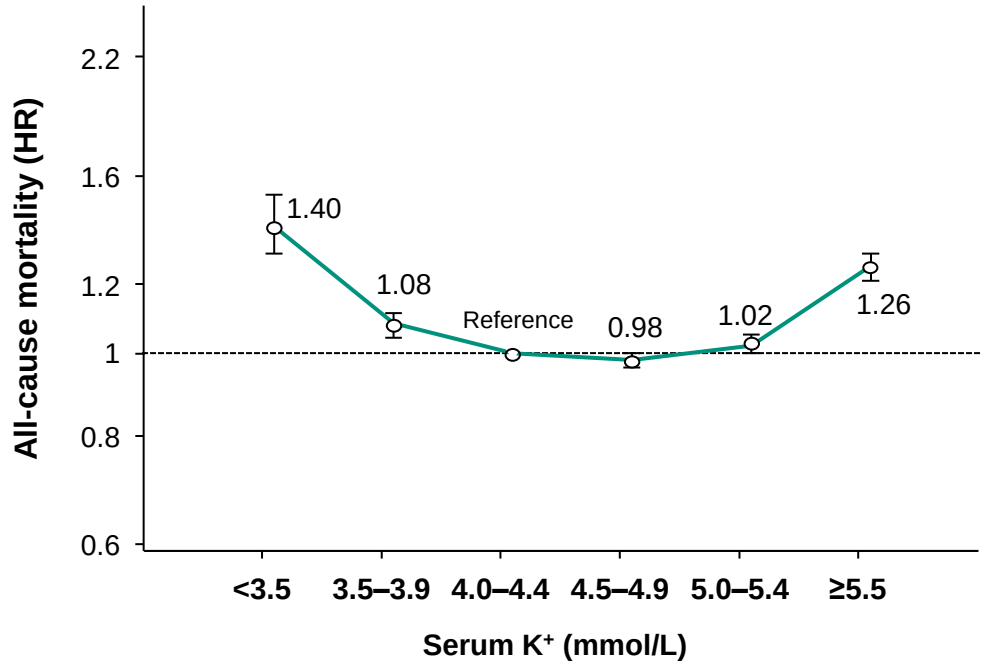
- Risk of sudden death was independently associated with the presence of atrial fibrillation, diabetes mellitus and predialytic hyperkalemia[b]

[a]Deaths were classified as CV only if causes of death included documented heart diseases. Sudden death was defined as unexpected natural death occurring within 1 hour after the onset of symptoms; [b]Diagnosis of hyperkalemia was made based on ≥3 predialysis serum K^+ concentrations of ≥6.0 mmol/L in the last 6 months before recruitment into the study.
CV = cardiovascular; SE = standard error; TIW = three times weekly.
Genovesi S et al. *Nephrol Dial Transplant*. 2009;24:2529–2536.

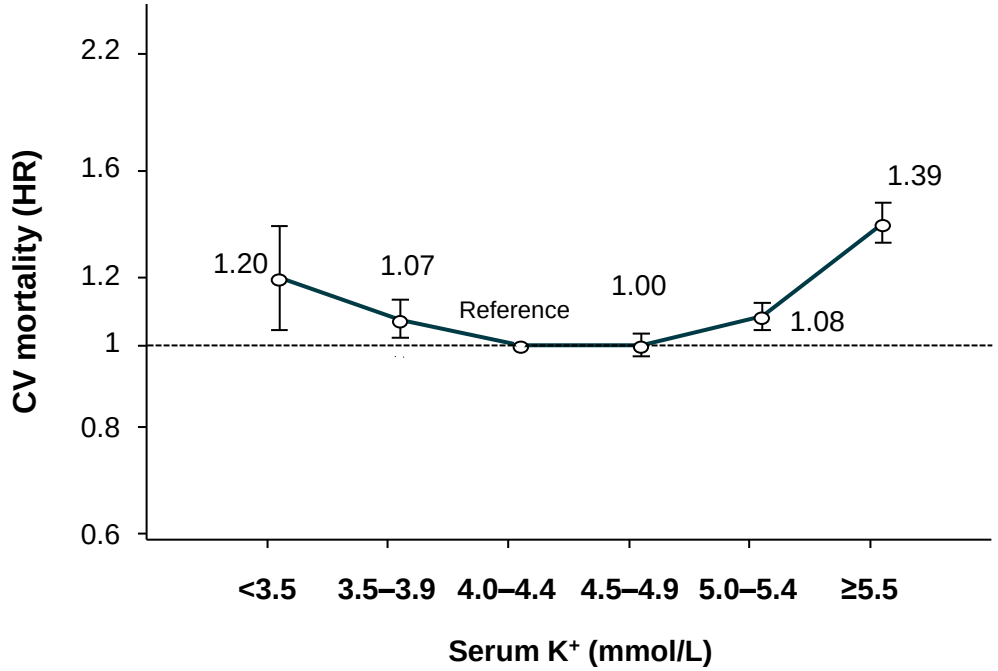
Hyperkalemia is associated with an increased risk of all-cause and CV mortality in patients receiving hemodialysis

Observational cohort study between July 2001 and June 2006 in 111,651 hemodialysis patients from US DaVita facilities

Risk of all-cause mortality by serum K^+



Risk of CV mortality by serum K^+



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Note: Hyperkalemia defined as K^+ ≥5.0 mmol/L and data based on 111,434 hemodialysis patients used as reference vs. peritoneal dialysis patients in the same cohort. The timing of K^+ measurement in relation to the hemodialysis cycle was not described in the study.
CV = cardiovascular; HR = hazard ratio; US = United States.
Torlén K et al. *Clin J Am Soc Nephrol*. 2012;7:1272–1284.

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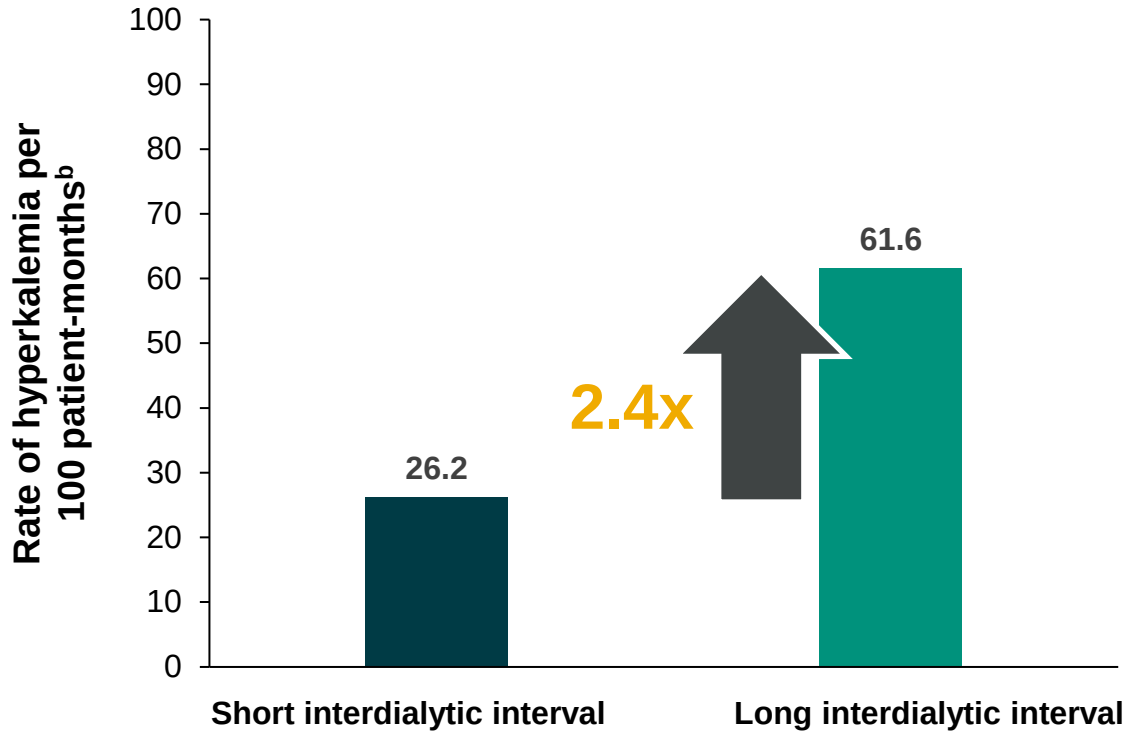
Prevalence of hyperkalemia is 2.4 times higher prior to dialysis after the long interdialytic interval compared to the short interdialytic interval[a]

Retrospective observational study from the USRDS of hemodialysis patients (N=36,888) during 2010 with ≥6 hemodialysis sessions and ≥1 potassium measurement. Hyperkalemia defined as K^+ ≥5.5 mmol/L

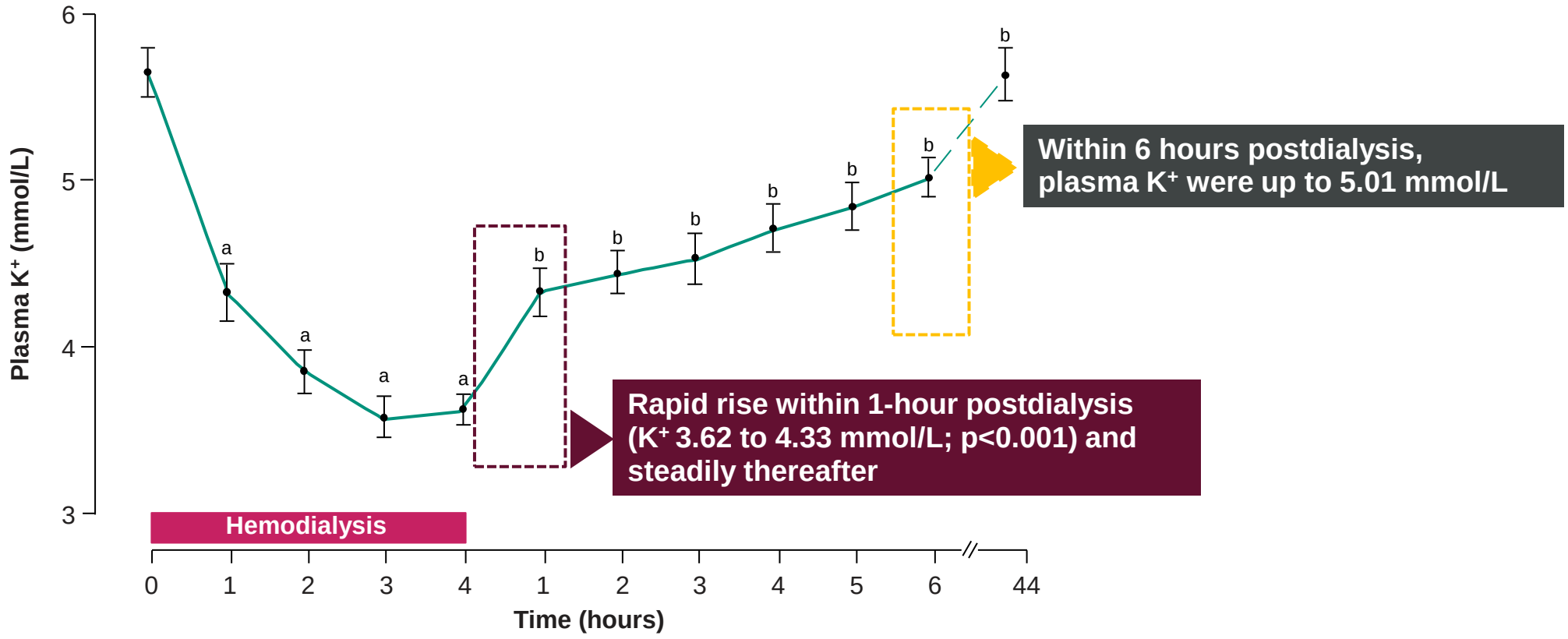


Note: Timing of K^+ measurement in relation to the hemodialysis cycle was not described in the study, but were typically measured once a month during routine sessions.
[a]The hemodialysis schedule was defined as Monday-Wednesday-Friday (M-W-F) or Tuesday-Thursday-Saturday (T-Th-Sa). The day after the long 3-day interval between sessions (long interdialytic interval) was defined as Monday for patients on a M-W-F schedule and as Tuesday for patients on a T-Th-Sa schedule, and the other days were referred to as the short interdialytic interval; [b]Rate of hyperkalemia was computed as a ratio of total number of hyperkalemia episodes and cumulative follow-up time.
USRDS = United States Renal Data System.
Yusuf AA et al. *Am J Nephrol.* 2016;44:179–186.

Within 6 hours after hemodialysis, patients return to being hyperkalemic

Prospective study of 14 patients with ESRD receiving chronic hemodialysis TIW with repeated predialysis levels of K^+ ≥5.5 mmol/L. A standard 4 hour dialysis was performed with dialysate consisting of K^+ 1 mmol/L and bicarbonate 40 mmol/L

K^+ profile during and after hemodialysis



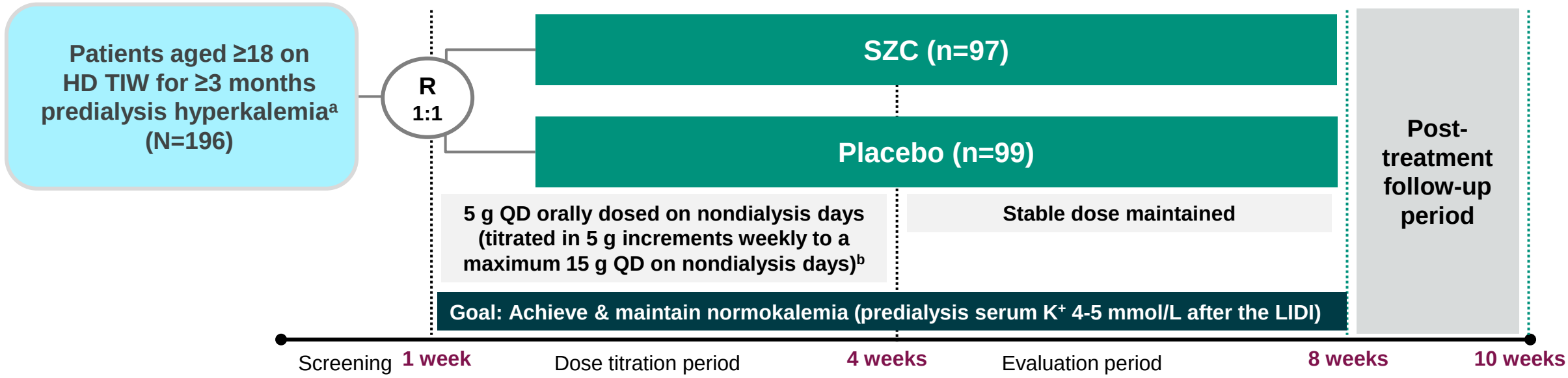
Note: Hyperkalemia defined as K^+ ≥5.0 mmol/L. Serum K^+ measurements were performed on the first weekly hemodialysis day after the long weekend (ie, Monday or Tuesday).
[a]Significantly lower than predialysis value (p<0.001); [b]Significantly higher than end-dialysis value (p<0.001).
ESRD = end stage renal disease; TIW = three times weekly.
Blumberg A et al. *Nephrol Dial Transplant.* 1997;12:1629-1634.

DIALIZE study

A Phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of pre-dialysis hyperkalemia

DIALIZE
Study design

Phase IIIb, randomized, double-blind, placebo-controlled, multicenter trial designed to evaluate the efficacy and safety of SZC for the treatment of hyperkalemia in ESRD patients on stable HD



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[a]Predialysis central laboratory serum K^+ ≥5.5 mmol/L after the LIDI and ≥5.1 mmol/L after at least one short interdialytic interval; [b]During the first 4 weeks of the treatment period, the SZC and placebo doses were adjusted if the predialysis i-STAT serum K^+ after the LIDI was >5.0 mmol/L (one weekly dose adjustment). If the predialysis i-STAT serum K^+ <4.0 mmol/L, dialysate K^+ concentration was increased by 0.5 or 1.0 mmol/L according to standard of care; if local practice did not include increasing dialysate K^+ concentrations or if the dialysate K^+ concentration could not be increased further, the SZC or placebo dose could be reduced by 5 g or held if already dosed at the minimum dose of 5 g. If during the initial 4 weeks, the dose of SZC or placebo was reduced or held and the predialysis i-STAT serum K^+ after the next LIDI was >5.0 mmol/L, every effort was made to increase the dose by 5 g or restart 5 g if it was held.
ESRD = end stage renal disease; HD = hemodialysis; LIDI = long interdialytic interval; R = randomization; SZC = sodium zirconium cyclosilicate; TIW = three times weekly.
Fishbane S et al. Article and supplemental data online ahead of print. *J Am Soc Nephrol.* 2019.

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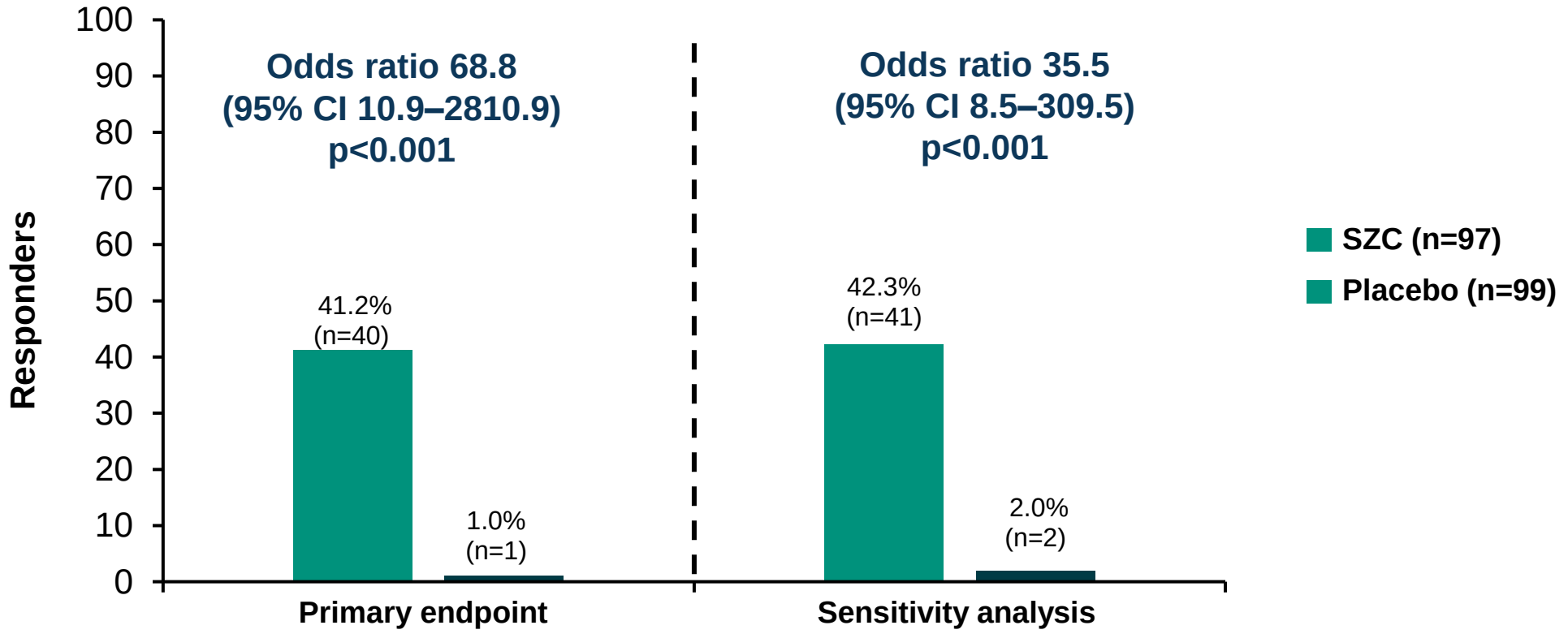
DIALIZE

Primary efficacy endpoint – Proportion of responders

The proportion of responders[a] was significantly higher with SZC than placebo.
Sensitivity analysis results were consistent with the primary analysis.[b]



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[a]Responders were defined as patients who, during the evaluation period, maintained a predialysis serum K^+ 4.0-5.0 mmol/L during ≥3 out of 4 HD treatments following the long interdialytic interval and who did not receive rescue therapy; [b]A sensitivity analysis was conducted to account for nonresponders with missing central laboratory assessment by using adjusted i-STAT serum K^+ data.
HD = hemodialysis; SZC = sodium zirconium cyclosilicate.
Fishbane S et al. Article and supplemental data online ahead of print. *J Am Soc Nephrol.* 2019

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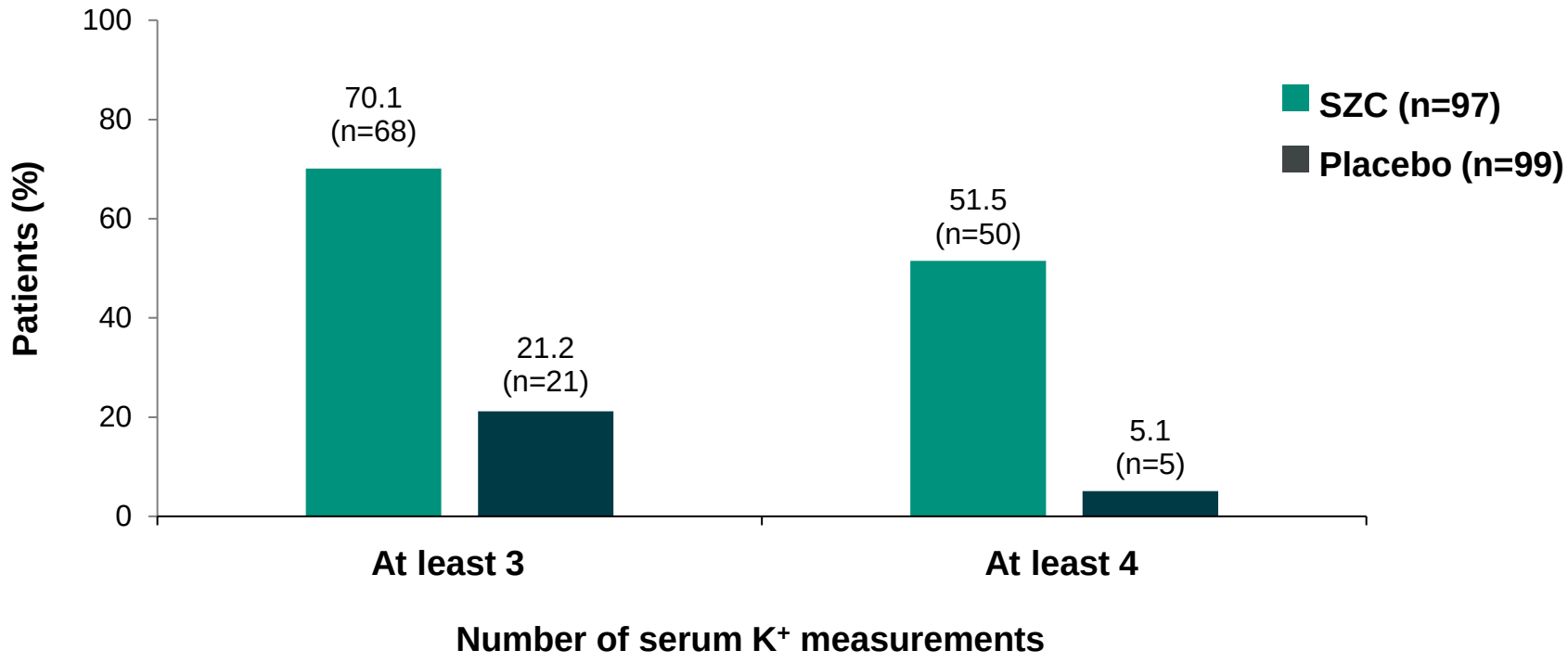
DIALIZE

Post hoc analysis – Serum K^+ of 3.5-5.5 mmol/L

More patients receiving SZC had a serum K^+ of 3.5-5.5 mmol/L during ≥3 of 4 HD sessions after the LIDI vs. placebo



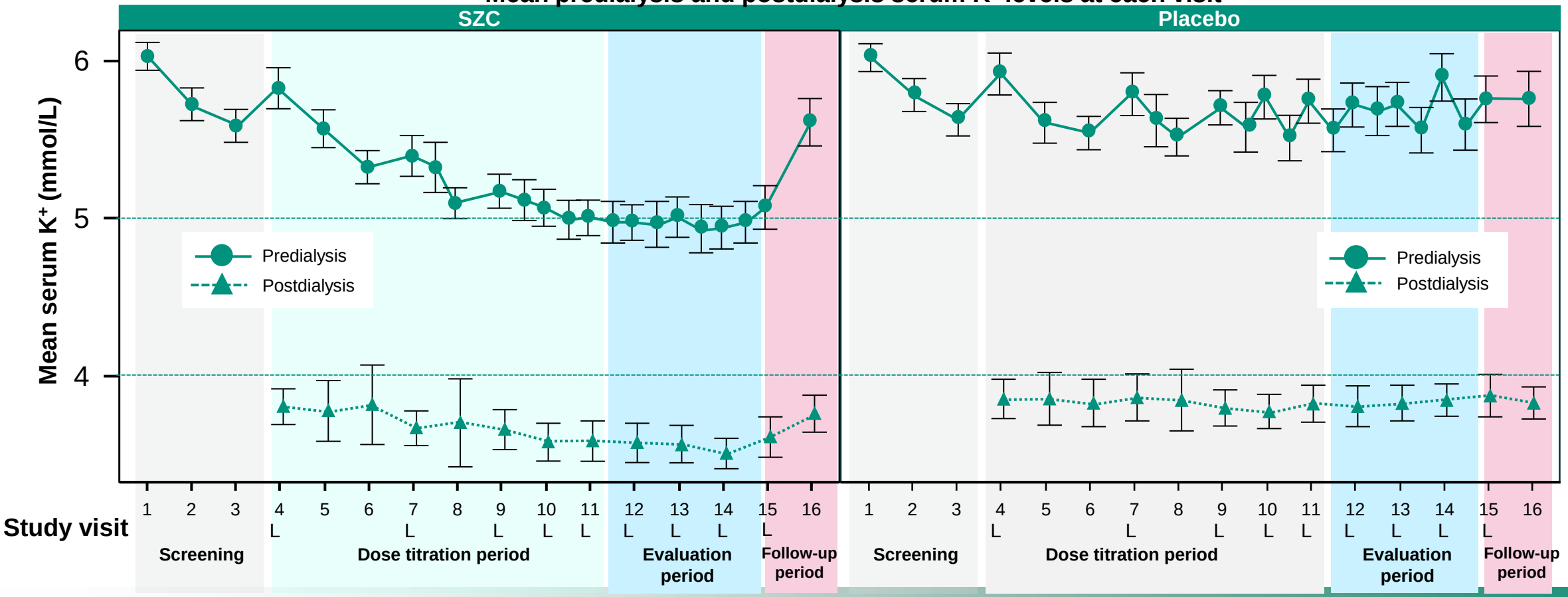
Note: Data based on predialysis serum K^+ values obtained at the LIDI visits in the evaluation period.
HD = hemodialysis; LIDI = long interdialytic interval; SZC = sodium zirconium cyclosilicate.
Fishbane S et al. Article and supplemental data online ahead of print. *J Am Soc Nephrol.* 2019

DIALIZE

Predialysis and postdialysis serum K^+ concentrations

Predialysis and postdialysis mean serum K^+ levels were comparable between the groups at baseline and were lower in the SZC group vs. the placebo group at the end of both the dose titration period and the evaluation period

Mean predialysis and postdialysis serum K^+ levels at each visit

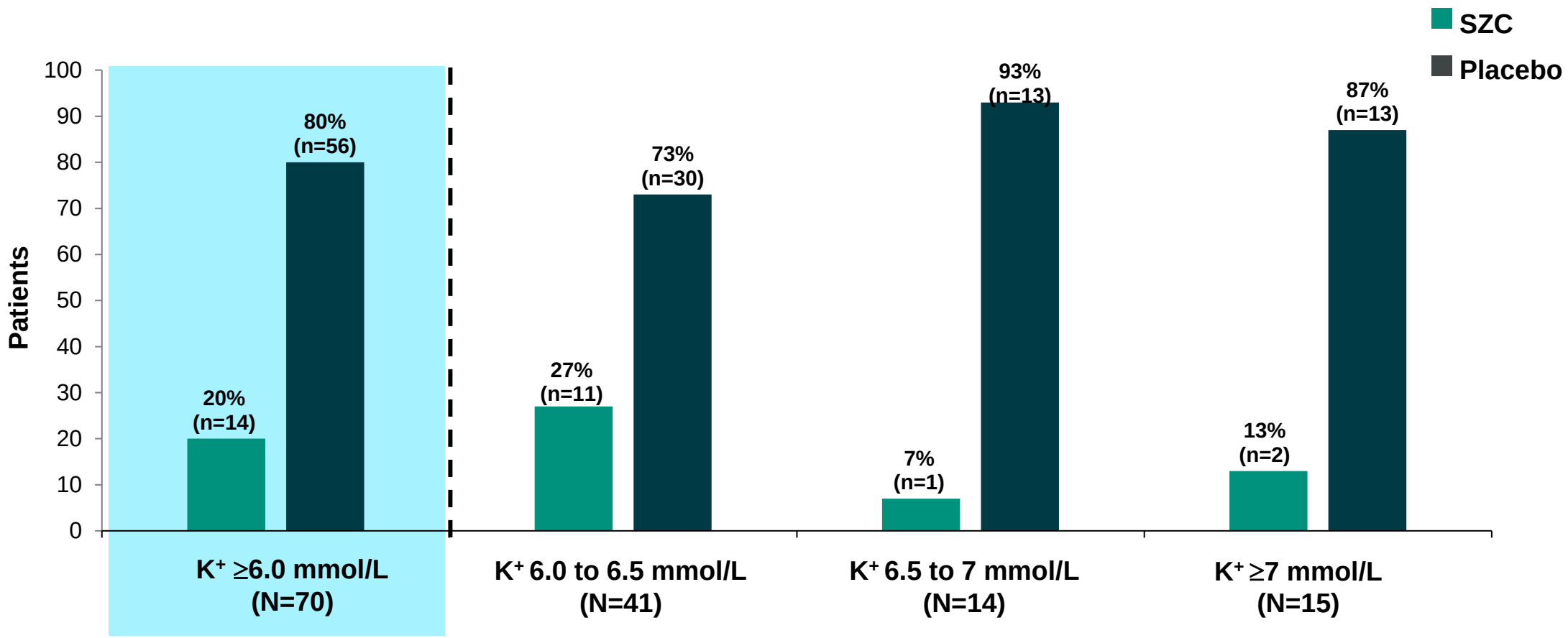


Note: Error bars represent 2 x SD of the mean. Dashed horizontal lines represent the upper and lower limits of normal predialysis serum K^+.
L = visit following the long interdialytic interval; SD = standard deviation; SZC = sodium zirconium cyclosilicate.
Fishbane S et al. Online ahead of print. *J Am Soc Nephrol.* 2019.

DIALIZE

Post hoc analysis – Maximum serum K^+ concentrations

Fewer patients with SZC had serum K^+ ≥6.0 mmol/L following the LIDI during the evaluation period vs. placebo



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Note: Percentages are based on the total number of patients in the serum K^+ concentration strata during the evaluation period.
LIDI = long interdialytic interval; SZC = sodium zirconium cyclosilicate.
Fishbane S et al. Article and supplemental data online ahead of print. *J Am Soc Nephrol.* 2019

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DIALIZE
Summary

- DIALIZE is the first randomized, placebo-controlled trial to evaluate the efficacy and safety of a potassium binder in the treatment of hyperkalemia in patients on HD

- The study met its primary endpoint by demonstrating that significantly more patients with SZC (41%) maintained a predialysis serum K^+ between 4.0-5.0 mmol/L during ≥3 of 4 HD sessions after the LIDI and did not require rescue therapy vs. placebo (1%; p<0.001)
  - More patients receiving SZC (70%) achieved a predialysis serum K^+ between 3.5-5.5 mmol/L during ≥3 of 4 HD sessions after the LIDI vs. placebo (21%)

- There were no differences between SZC and placebo in interdialytic weight gain, a marker of sodium and fluid retention

- SZC was well-tolerated with most adverse events mild or moderate in intensity. The adverse event profiles between the treatment groups were similar, including GI adverse events and hypokalemia

GI = gastrointestinal; HD = hemodialysis; LIDI = long interdialytic interval; SZC = sodium zirconium cyclosilicate.
Fishbane S et al. Article and supplemental data online ahead of print. *J Am Soc Nephrol.* 2019.

CONCEPT K
Rethinking Hyperkalemia

NICE and Renal Association UK recommend using novel K^+ binders to manage HK, minimising the demand for hospital services during the COVID-19 pandemic

Recommendations regarding the use of newer K^+ binders:

For dialysis service delivery

- [Use novel K^+ binders to] support delaying starting dialysis or to treat hyperkalaemia[1]
- Develop individualised plans for patients so that their dialysis schedule can be reduced safely if that becomes necessary – local policies should address the use of fluid restriction and the prescription
of potassium binders to allow the frequency of dialysis to be reduced[2]

For acute kidney injury in the hospital setting

- As options alongside standard care for the emergency management of acute life-threatening hyperkalaemia[3]

UK prescribing and adverse event reporting information is available at: https://medicines.astrazeneca.co.uk/content/dam/multibrand/uk/en/prescribinginformation/lokelma-pi.pdf
COVID-19, coronavirus disease 2019; HK, hyperkalaemia; NICE, UK National Institute for Health and Care Excellence
1. UK National Institute for Health and Care Excellence. COVID-19 rapid guideline: Dialysis service delivery (NG160). Available at: https://www.nice.org.uk/guidance/ng160/resources/covid19-rapid-guideline-dialysis-service-delivery-pdf-66141894031045 (Accessed September 2021); 2. The Renal Association UK. Renal Association commentary on NICE COVID-19 rapid guideline: Dialysis service delivery. Available at: https://ukkidney.org/sites/renal.org/files/RA%20commentary%20on%20NICE%20COVID-19%20rapid%20guideline-%20dialysis%20service%20delivery_Final-2.pdf (Accessed September 2021); 3. UK National Institute for Health and Care Excellence. COVID-19 rapid guideline: Managing COVID-19 (NG191). Available at: https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-covid19-pdf-51035553326 (Accessed September 2021)

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Safety Profile

ZS-004 (HARMONIZE)
Serious Adverse Events

crystalize
HARMONIZE & Extension

Adverse Event, n (%)	Correction Phase	Maintenance Phase			
	SZC 10 g TID (n=258)	Placebo QD (n=85)	SZC 5 g QD (n=45)	SZC 10 g QD* (n=51)	SZC 15 g QD (n=56)
Any serious adverse event	0	0	5 (11.1)	2 (3.9)	3 (5.4)
Cardiac disorders					
Cardiac failure, congestive	0	0	1 (2.2)	0	0
Myocardial infarction	0	0	0	1 (2.0)	0
Gastrointestinal disorders					
Small intestinal obstruction	0	0	1 (2.2)	0	0
General disorders and administration-site conditions					
Generalized edema	0	0	0	0	1 (1.8)
Hepatobiliary disorders					
Hepatotoxicity	0	0	1 (2.2)	0	0
Cellulitis	0	0	0	1 (2.0)	0
Pneumonia	0	0	1 (2.2)	0	1 (1.8)
Psychiatric disorders					
Confusional state	0	0	1 (2.2)	0	0
Respiratory, thoracic, and mediastinal disorders					
Dyspnea	0	0	0	0	1 (1.8)

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*One death of a patient with stage 5 CKD, diabetes, hypertension, and known cardiovascular disease that was due to myocardial infarction, occurred on randomized phase Day 18.
CKD = chronic kidney disease; SZC = sodium zirconium cyclosilicate.
Kosiborod M et al. *JAMA*. 2014;312:2223-2233.

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ZS-004 (HARMONIZE)
Adverse Events

crystalize
HARMONIZE & Extension

Adverse Events Occurring in ≥5% of Patients, n (%)	Correction Phase	Maintenance Phase			
	SZC 10 g TID (n=258)	Placebo QD (n=85)	SZC 5 g QD (n=45)	SZC 10 g QD (n=51)	SZC 15 g QD (n=56)
Any event	20 (7.8)	27 (31.8)	24 (53.3)	15 (29.4)	25 (44.6)
Blood and lymphatic system disorders					
Anemia	0	0	0	0	3 (5.4)
Gastrointestinal disorders*					
Constipation	2 (0.8)	6 (7.1)	0	1 (2.0)	1 (1.8)
General disorders and administration-site conditions					
Edema†	0	2 (2.4)	1 (2.2)	3 (5.9)	8 (14.3)
Metabolism and nutrition disorders					
Hypokalemia (<3.5 mmol/L)‡	0	0	0	5 (9.8)	6 (10.7)
Hypokalemia (reported as AE)	0	0	0	0	1 (1.8)
Infections and infestations					
Nasopharyngitis	0	1 (1.2)	0	0	3 (5.4)
Upper respiratory tract infection	1 (0.4)	1 (1.2)	3 (6.7)	1 (2.0)	1 (1.8)

- No clinically relevant changes in serum electrolytes (Na^+, Mg^{2+}, or Ca^{2+}), vital signs, blood pressure, heart rate, or body weight
- No dose-dependent increase in urinary sodium excretion

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Sodium zirconium cyclosilicate

*Gastrointestinal adverse events were reported in 14% (12/85) in placebo group, 7% (3/45) in SZC 5 g group, 2% (1/51) in SZC 10 g group, and 9% (5/56) in SZC 15 g group; †Included terms edema, generalized edema, or peripheral edema as treatment-emergent adverse event. Of the 14 patients who developed edema, 5 patients in the SZC 15 g group required change in therapy; ‡All cases of hypokalemia were mild (3.0–3.4 mmol/L) and resolved after dose reduction.
AE = adverse event; SZC = sodium zirconium cyclosilicate.
Kosiborod M et al. *JAMA*. 2014;312:2223-2233.

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MAINTENANCE DOSING[1]

- **LOKELMA is a daily maintenance treatment option for hyperkalaemia (for non-dialysis patients)[1]**
- **Recommended dosing of LOKELMA to achieve and sustain normokalaemia[1]**

FOR ADULT (NON-DIALYSIS) PATIENTS

Correction phase

3×  **/day*†**

10 g

for 24 to 48 hours

until normokalemia is achieved*†

Maintenance phase

1×  **/day*†**

5 g

for up to 1 year

To establish minimum effective dose, LOKELMA may be titrated

- Up to **10 g once daily** or
- Down to **5 g once every other day**

No more than **10 g once daily** should be used for maintenance therapy

New SmPC Update Based on DIALIZE Data

FOR HAEMODIALYSIS PATIENTS

RECOMMENDED STARTING DOSE

1×  **/non-dialysis days**

5 g

To establish normokalaemia, the dose may be titrated up or down weekly based on the predialysis serum K^+ after the long interdialytic interval

The dose could be adjusted at intervals of one week in increments of 5 g:

- **Up to 15 g once daily on non-dialysis days**

It is recommended to monitor serum K^+ weekly while the dose is adjusted. To maintain normokalaemia, it is recommended to monitor serum K^+ regularly (e.g., monthly or more frequently based on clinical judgement)

Serum K^+ levels should be monitored regularly during treatment. Monitoring frequency will depend upon a variety of factors, including other medications, progression of CKD and dietary K^+ intake. If severe hypokalaemia should occur, LOKELMA should be discontinued and the patient is re-evaluated.
LOKELMA should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH-dependent bioavailability. Refer to Summary of Product Characteristics for more information including examples of such medicines.

Serum K^+ levels should be monitored periodically during treatment
*If normokalaemia is not achieved within 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered; †Patients who miss a dose should be instructed to take the next usual dose at their normal time.[1]

1. AstraZeneca. LOKELMA Summary of Product Characteristics 2020.

LOKELMA
Powder for oral suspension
Sodium zirconium cyclosilicate

AstraZeneca

THANK YOU