ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΜΕΤΑΜΟΣΧΕΥΣΕΩΝ
21ο Πανελλήνιο Συνέδριο Μεταμοσχεύσεων
2-4 Δεκεμβρίου 2021
Μέγαρο Μουσικής Αθηνών
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Η νέα εποχή στην αντιμετώπιση της υπερκαλιαιμίας

Ευαγγελία Ντουνούση,
Επίκουρη Καθηγήτρια Νεφρολογίας Πανεπιστημίου Ιωαννίνων

21ο Πανελλήνιο Συνέδριο Μεταμοσχεύσεων, Δεκέμβριος 2021, Μέγαρο Μουσικής Αθηνών

Conflict of interest: Honorarium: **Astra, Sanofi,**
Advisory board**: Faran**

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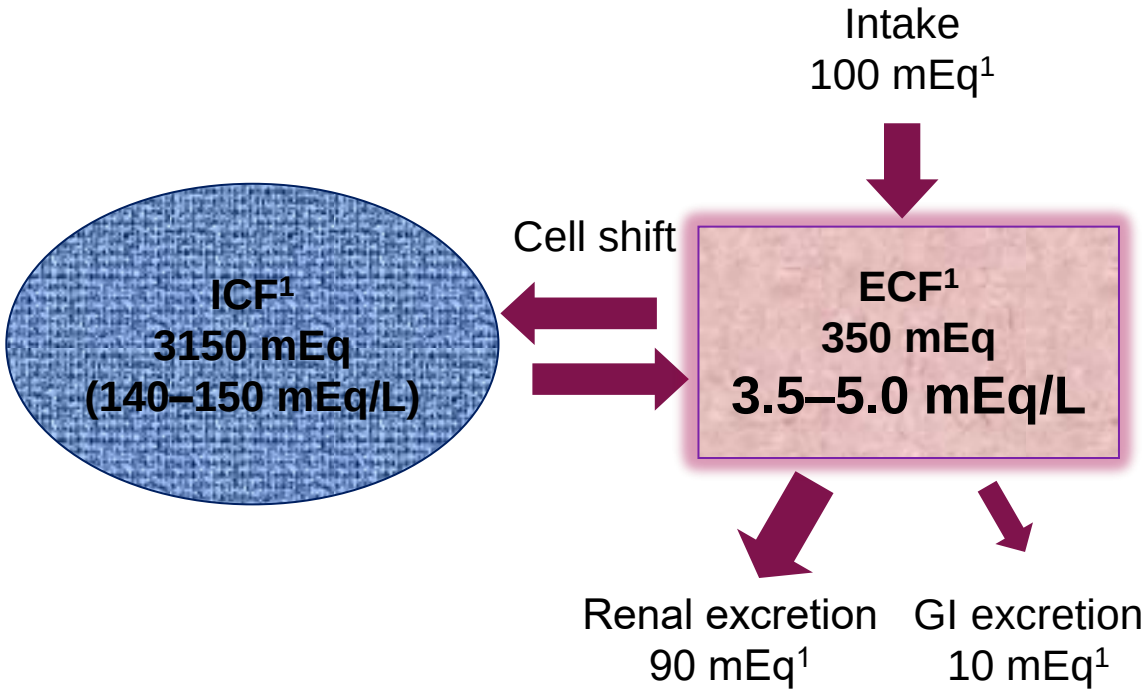
Regulation of K^+ homeostasis



Clinical presentation of HK[2,3]

- ✓ Often asymptomatic
- ✓ In severe HK (K^+ >6.5 mEq/L), patients may present with muscle weakness, paralysis and sudden death
- ✓ Cardiac conduction abnormalities ranging from ECG changes to life-threatening arrhythmias may also occur in severe HK

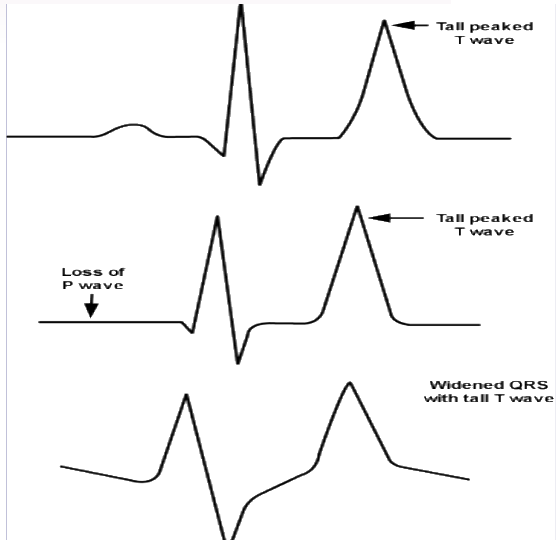
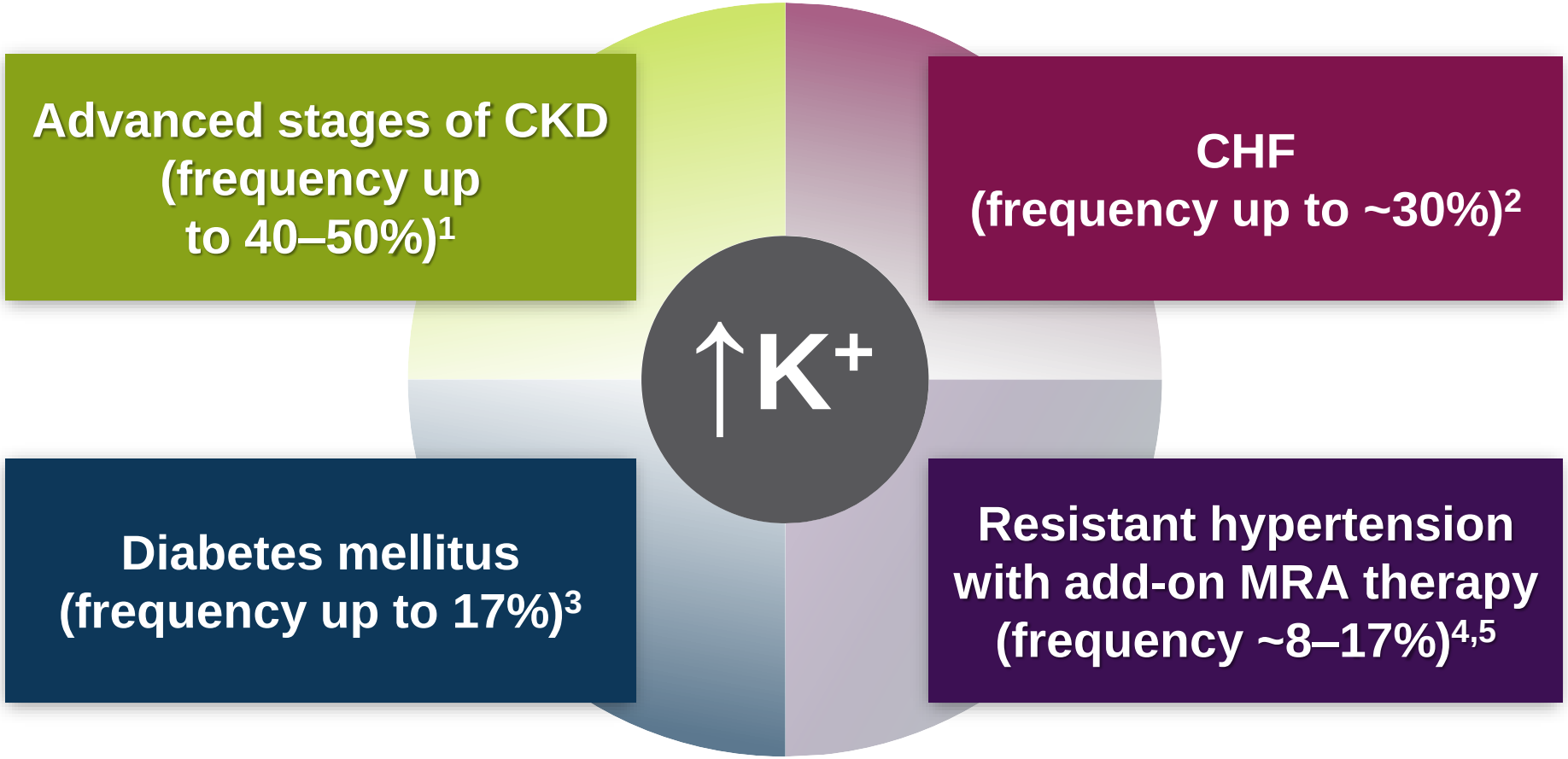


Figure adapted from: Osorio FV, Linas SL[1]ECF, extracellular fluid; ECG, electrocardiogram; GI, gastrointestinal; HK, hyperkalemia; ICF, intracellular fluid

1. Osorio FV, Linas SL. Disorders of potassium metabolism. In: Schrier RW (ed.). *Atlas of Diseases of the Kidney, Vol. 1*; Oxford: Wiley-Blackwell; 1999; 2. Rastergar A, Soleimani M. *Postgrad Med J* 2001;77:759–764; 3. Pfortmüller CA et al. *Eur J Intern Med* 2013;24:e59–e60

Patient subgroups with a high incidence of HiK



HiK is defined as K^+ >5.0 mEq/L[6]

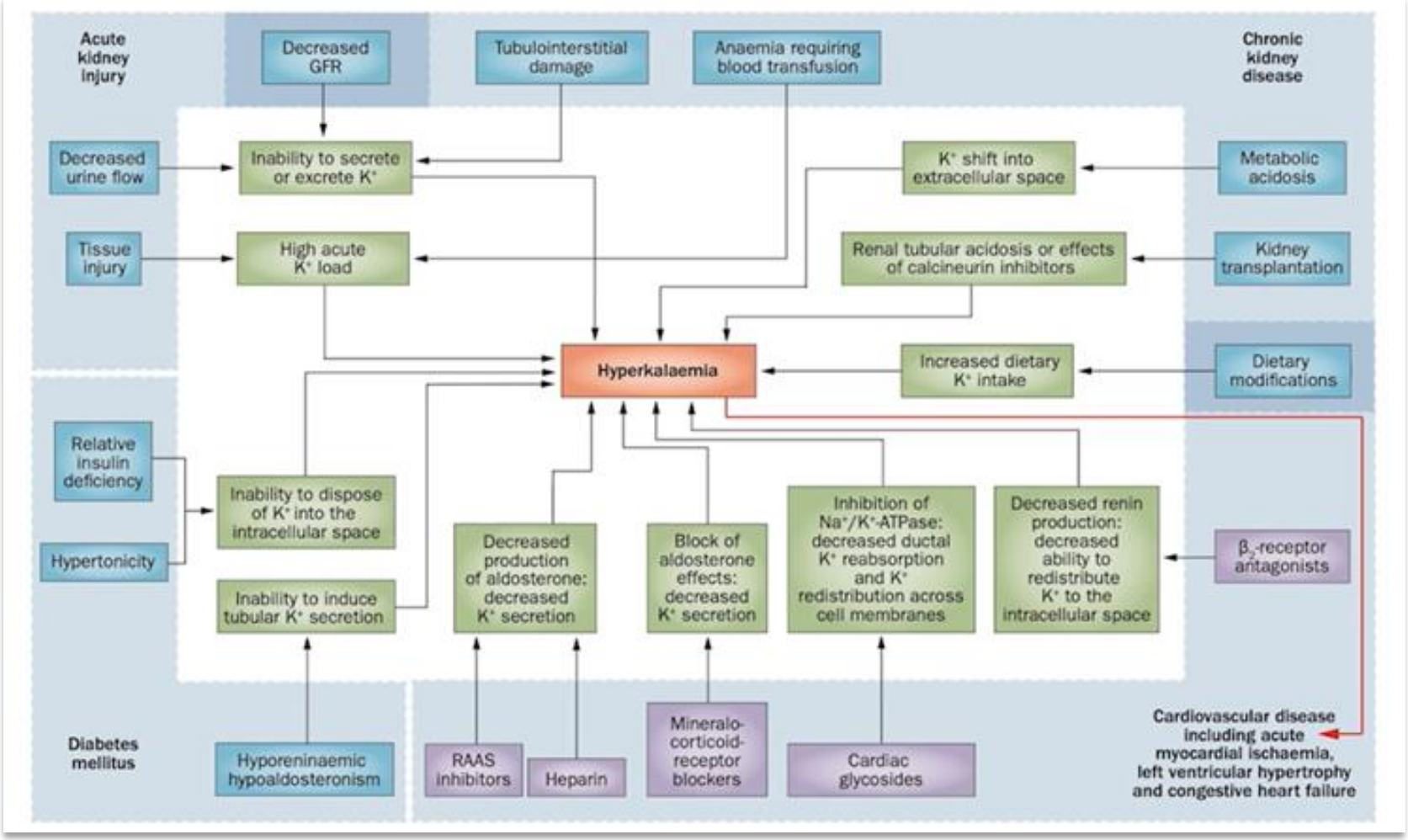
CHF, chronic heart failure; CKD, chronic kidney disease; HF, heart failure; HiK, hyperkalaemia; MRA, mineralocorticoid receptor antagonist

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. *ERA-EDTA*, Madrid, 2017. Poster presentation SP313; 4. Chomicki J, et al. Presented at ASH Annual Scientific Meeting & Exposition; 16th–20th May 2014; New York, NY, USA; P-10; 5. Khosla N, et al. *Am J Nephrol* 2009;30:418–424; 6. Yancy CW, et al. Circulation. 2017;136:e137–e161.

Mechanisms of hyperkalemia in kidney disease – AKI & CKD

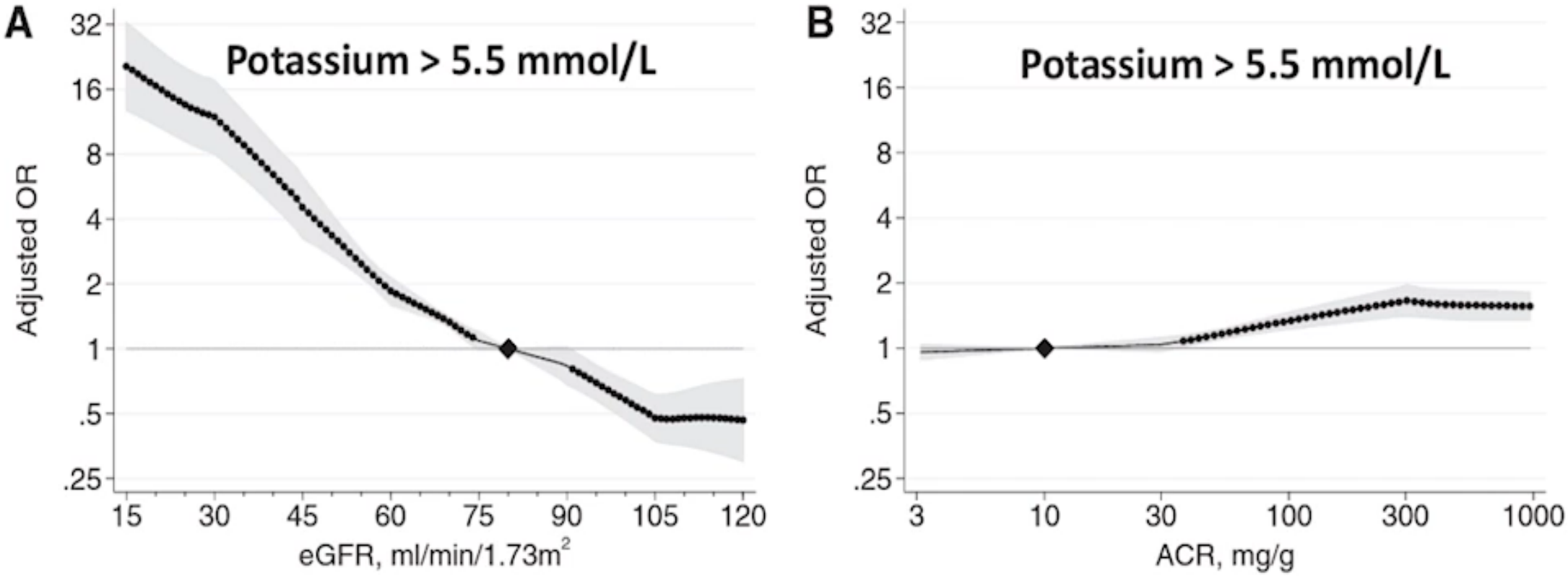
Decreased urine flow
Decreased GFR
Tubulo-interstitial damage
Metabolic acidosis
Tissue injury
Anemia requiring blood transfusion
Kidney transplantation (RTA, CNIs)
Dietary intake

Pharmaceutical Treatments
RAASi
MRAs
Heparin
B-blockers
Cardiac glycosides



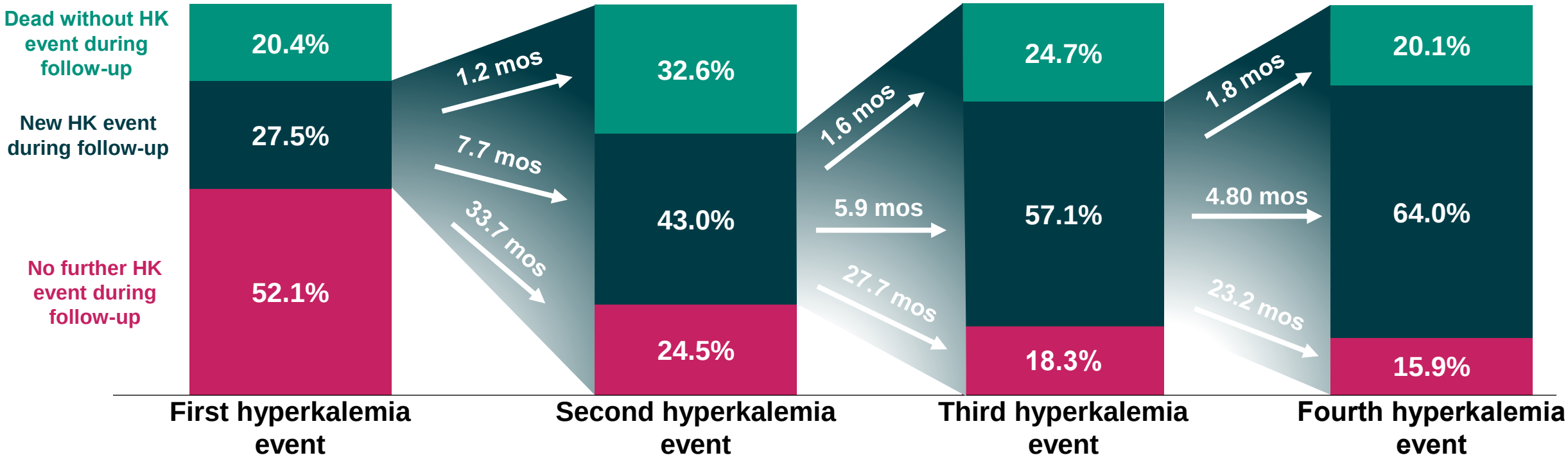
Kovesdy, C., 2014. Management of hyperkalaemia in chronic kidney disease. Nature Reviews Nephrology, 10(11), pp.653-662. http://www.nature.com/doifinder/10.1038/nrneph.2014.168.

Risk of hyperkalemia by GFR and ACR



Kovesdy et al. (2018). Serum potassium and adverse outcomes across the range of kidney function: A CKD PROGNOSIS CONSORTIUM meta-analysis. European Heart Journal, 39(17), 1535–1542. https://doi.org/10.1093/eurheartj/ehy100

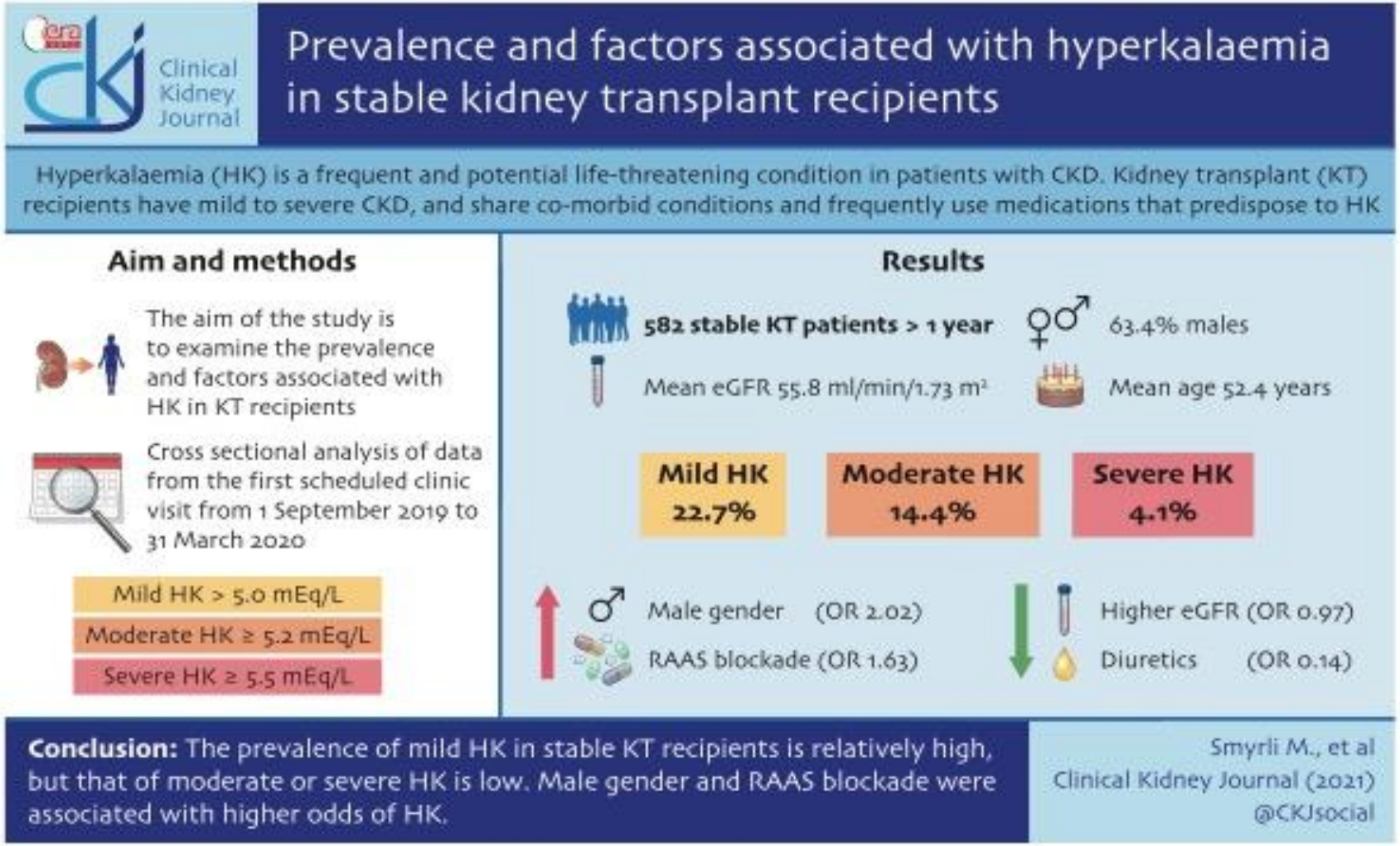
Recurrent HK episodes are common in CKD patients, with successively shorter time between the episodes



The incidence rate of HK [K+ level >5.0 mmol/L] in primary or hospital care was assessed in a population-based cohort of 157766 all newly diagnosed CKD patients in northern Denmark

Population-based cohort study linking individual data from mandatory hospital, prescription, and laboratory databases in northern Denmark (population 1.8 million) during 2000–2012 (N=157,766)
CKD, chronic kidney disease; HK, hyperkalemia
Adapted from: Thomsen RW, et al. *Nephrol Dial Transplant* 2018;33:1610–1620

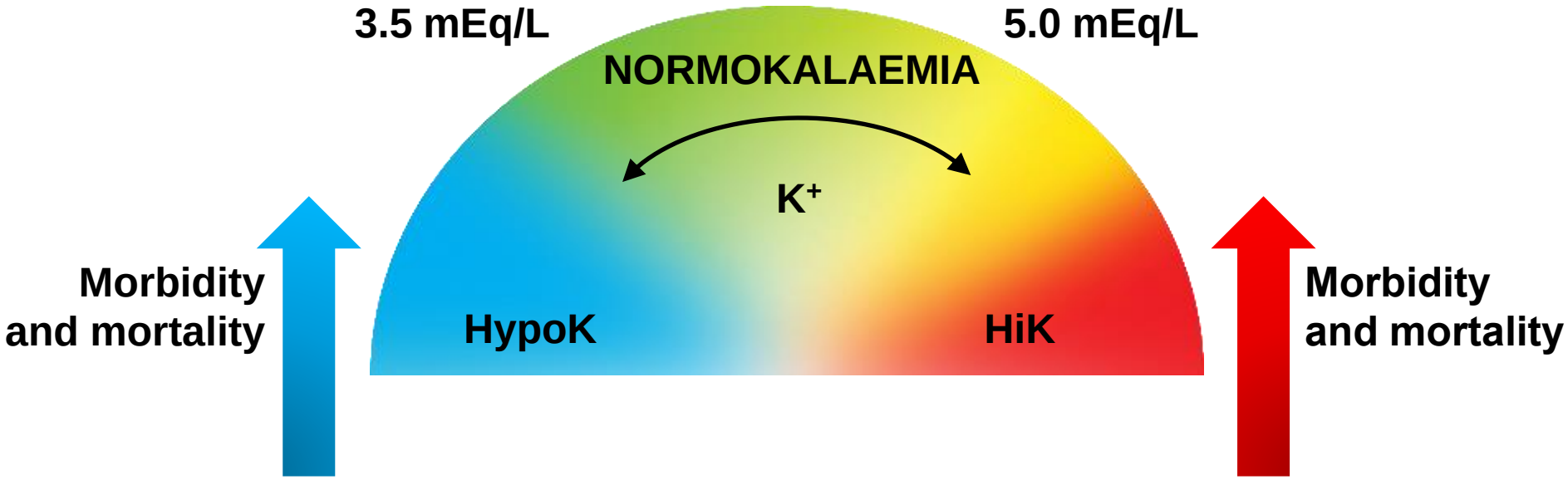
Prevalence and factors associated with hyperkalaemia in stable kidney transplant recipients



Smyrli M…Boletis I, Marinaki S. Clinical Kidney Journal, 2021, 1–8

HiK is associated with increased morbidity and mortality

- As serum K^+ levels deviate from normal levels, rates of morbidity (including MACE) and mortality increase[1–5]

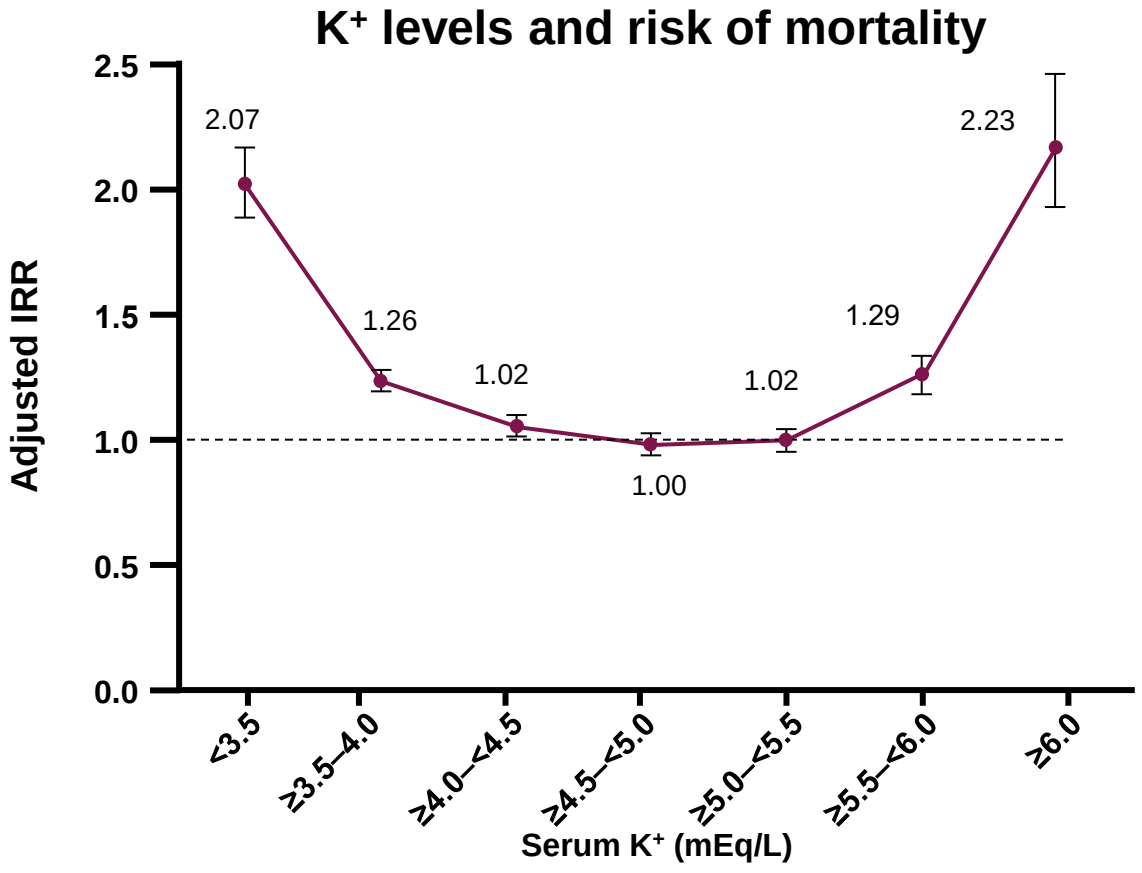


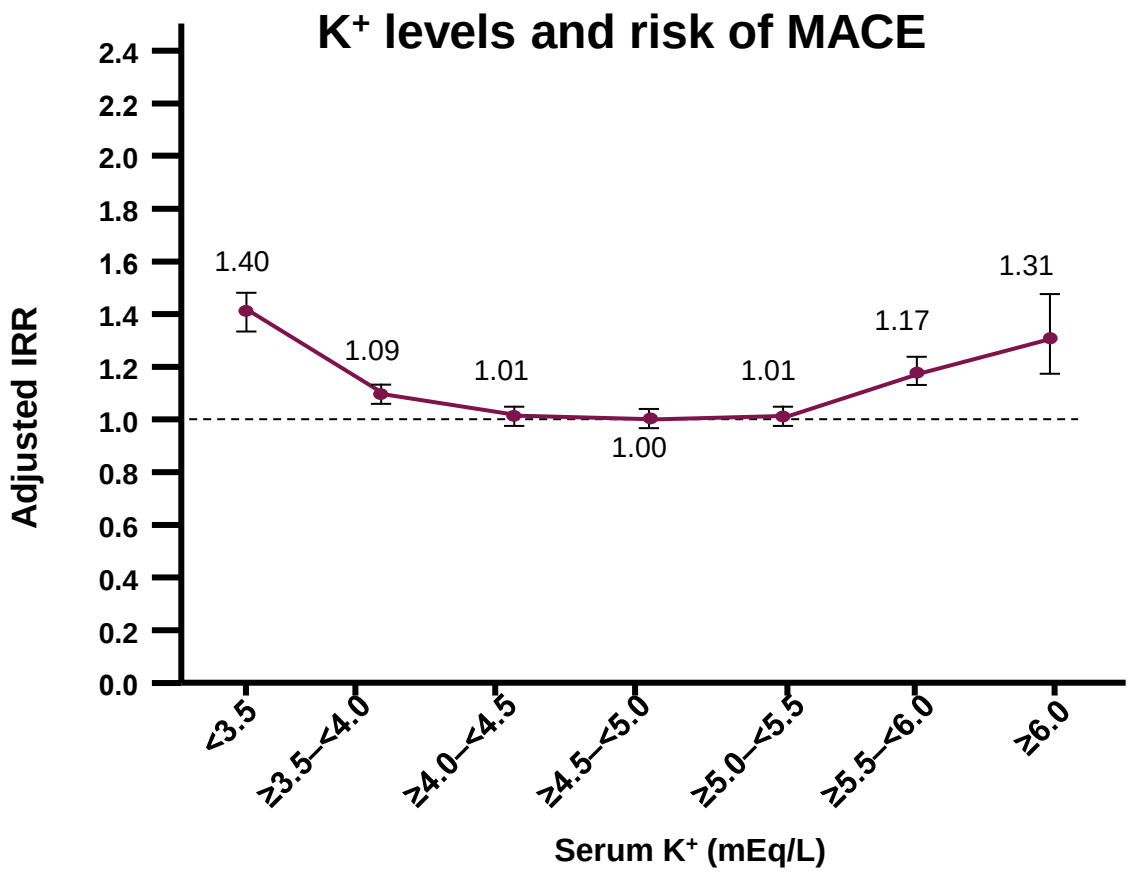
CV, cardiovascular; HiK, hyperkalaemia; HypoK, hypokalaemia; MACE, major adverse cardiovascular events

1. Luo J, et al. *Clin J Am Soc Nephrol* 2016;11:90–100; 2. McMahon GM, et al. *Intensive Care Med* 2012;38:1834–1842; 3. Hayes J, et al. *Nephron Clin Pract* 2012;120:c8–c16; 4. An JN, et al. *Crit Care* 2012;16:R225; 5. Goyal A, et al. *JAMA* 2012;307:157–164

Recent studies confirm high serum K^+ levels are associated with increased risk of mortality and MACE in CKD – U shape association

- Retrospective observational study of 191,964 CKD patients from the CPRD – UK (stage 3a–5nonD) between 2006-2015
- Mean follow-up time of 4.96y, mean eGFR: 50.96 mL/min/1.73m2, **48.06%** received RAASi therapy, mean K^+ 4.47 mmol/L

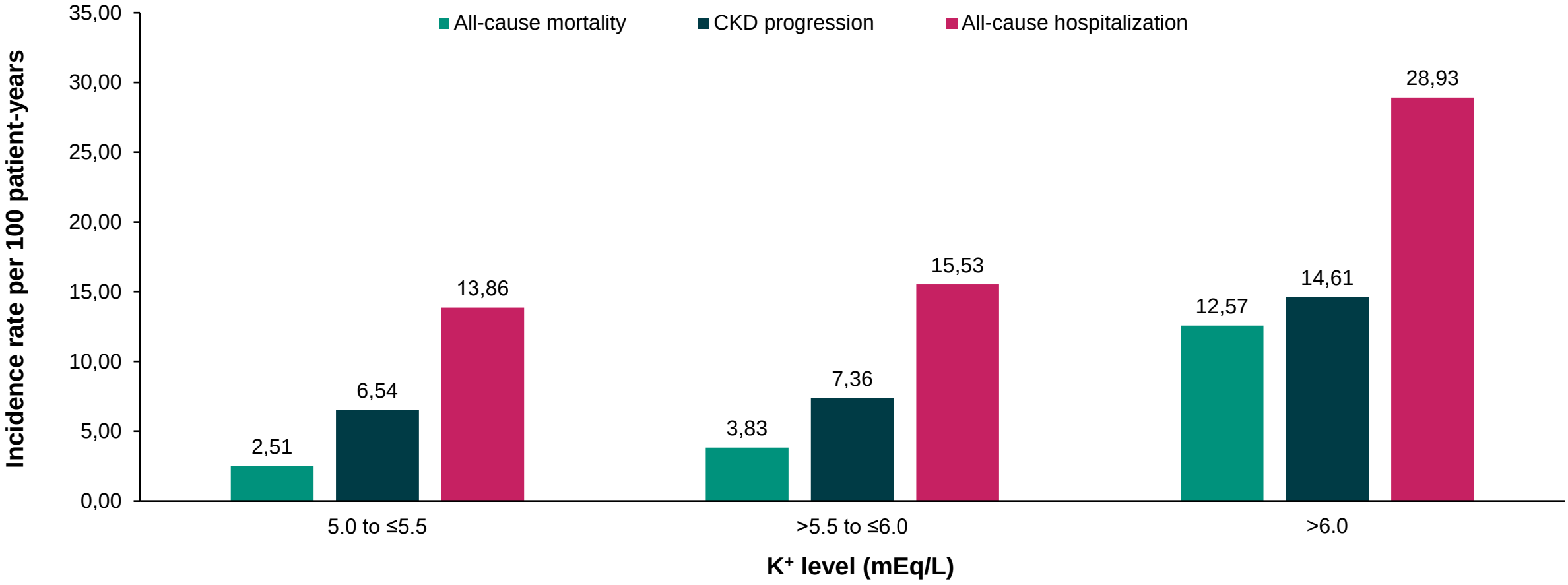




CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; HES, hospital episode statistics; IRR, incident risk ratio; MACE, major adverse cardiovascular events

Qin L, McEwan P, Evans M, Bergenheim K, Horne L, Grandy S; MO067. The Relationship Between Serum K^+ and Incidence Rates of Major Adverse Cardiovascular Events and Mortality in UK Patients With CKD. *Nephrol Dial Transplant*. 2017;32(Suppl 3):iii73–iii74, by permission of the European Renal Association–European Dialysis and Transplant Association.

Rates of adverse clinical outcomes increase with severity of hyperkalemia



Horne L, et al. Presented at 54th European Renal Association – European Dialysis and Transplant Association Congress; June 3rd–6th, 2017; Madrid, Spain; poster MP380 (retrospective analysis)

On the other hand…Potassium has many benefits

- Many studies have shown that potassium deficiency increases the progression of CKD
- Chronic hypoK^+ leads to increase proximal tubule ammoniogenesis which stimulates complement activation leading to inflammation and fibrosis
- Significantly inverse association between K+ intake and BP in hypertensive adults

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 (until diuresis is present)
- Increased risk of gout and diabetes depending on choice of diuretic
- May produce 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 utilization of renal/ cardioprotective RAASi therapy

Traditional potassium binders (SPS)[2–4]

- No long-term efficacy has been evaluated
- Gastric irritation, anorexia, nausea, vomiting, constipation, and occasionally diarrhea may occur
- Hard, gritty texture and unpleasant taste may reduce palatability

DASH, Dietary Approaches to Stop Hypertension; HK, hyperkalemia; RAASi, renin–angiotensin–aldosterone system inhibitor; SPS, sodium polystyrene sulfonate

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. Sanofi-Aventis US LLC. Kayexalate US Prescribing Information 2018; 4. Zann V, et al. *Drug Des Devel Ther* 2017;11:2663–2673

Note: ACE/ARB Discontinuation Associated with MACE/ Mortality in CKD G4

Cohort

3,909 patients from Geisinger Health System on ACE/ARB whose eGFR decreased below 30 ml/min/1.73 m^2 **(2004-2018)**

Mean age 74 years

62% women

Methods

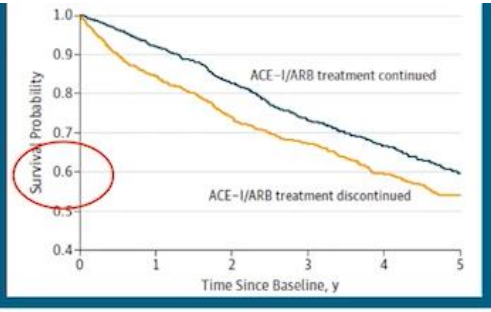
People who discontinued therapy

1:1 propensity matching **1,205 in each group**

People who continued therapy

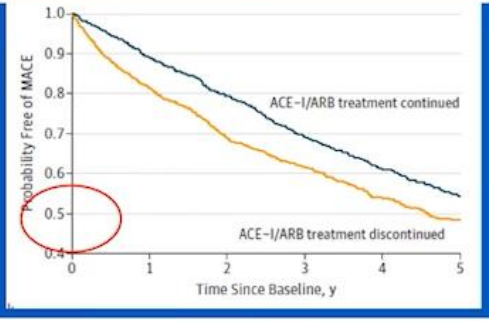
Conclusions Continuation of ACE/ARB therapy may be protective for mortality and major adverse cardiovascular events in advanced CKD without precipitating higher risk of ESKD (*In press, JAMA-IM*)

Death



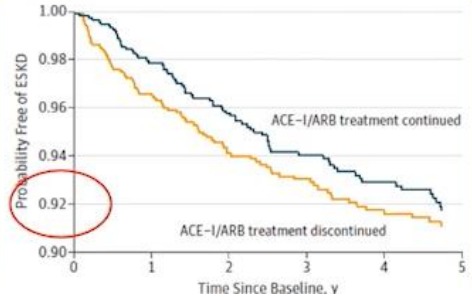
HR 1.39 (95% CI: 1.20-1.60)

MACE



HR 1.37 (95% CI: 1.20-1.56)

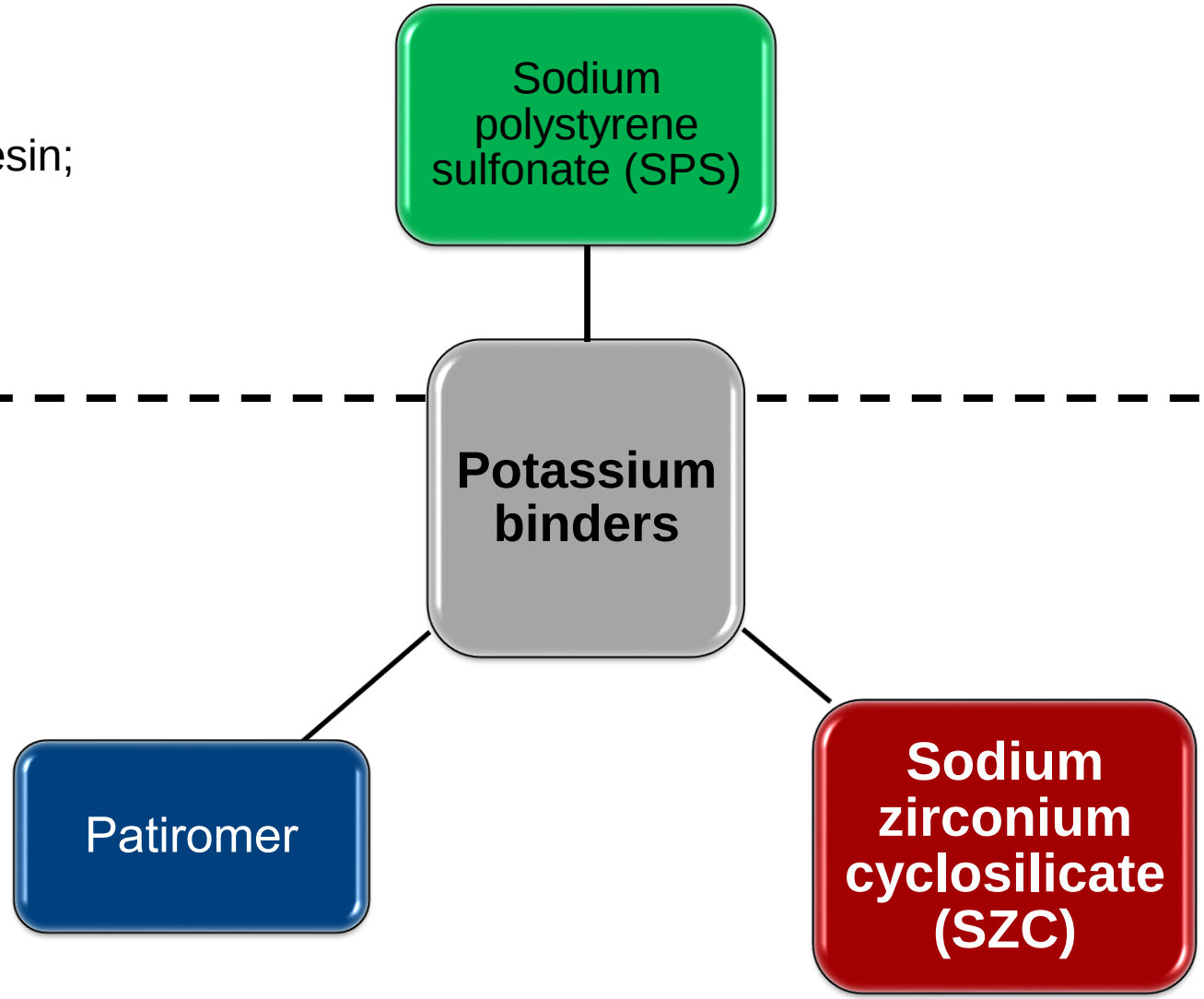
ESKD



HR 1.19 (95% CI: 0.86-1.65)

Available potassium binders

- **SPS**: approved 1958
- Nonspecific sodium cation-exchange resin; may also bind calcium and magnesium



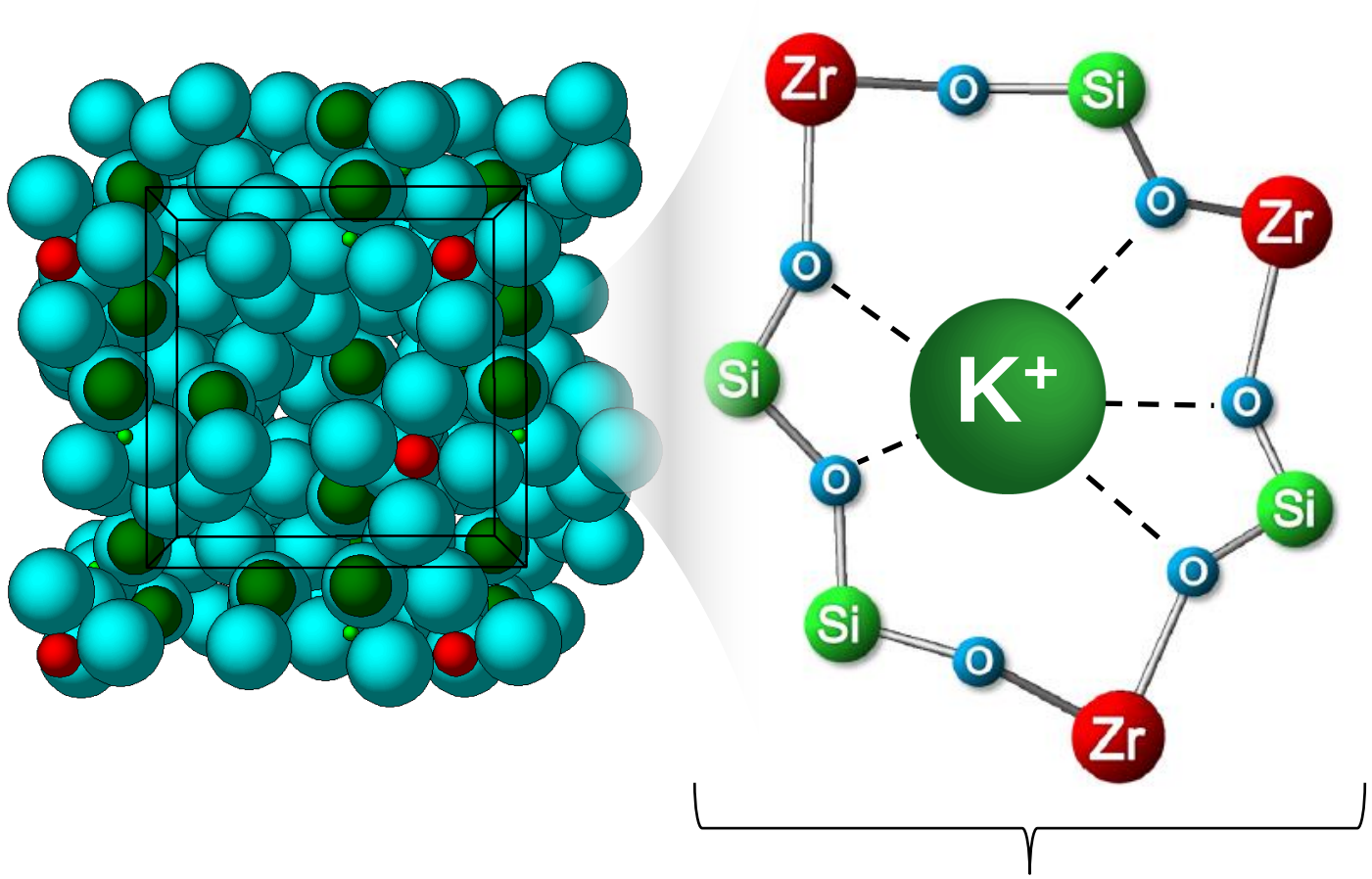
Newer binders in 21st century

- **Patiromer**: approved 2015/EU 2017
- Nonspecific cation-binding in exchange for calcium
- **SZC**: approved 2018/EU 2019
- Highly selective; preferentially captures K^+ ions

• [a]SPS was FDA-approved prior to the Kefauver–Harris Drug Amendments in 1962, which required drug manufacturers' to prove effectiveness of their product[3]

1. Chaitman M, et al. *P T* 2016;41:43–50; 2. Sanofi. Resonium A EU Summary of Product Characteristics 2019; 3. Sterns RH, et al. *J Am Soc Nephrol* 2010;21:733–735; 4. Garimella PS, Jaber BL. *Am J Kidney Dis* 2016;67:545–547; 5. Vifor Fresenius Medical Care Renal Pharma France. Veltassa (Patiromer) EU Summary of Product Characteristics 2018; 6. AstraZeneca AB. LOKELMA▼ EU Summary of Product Characteristics 2020

Sodium zirconium cyclosilicate (SZC): Crystal Structure



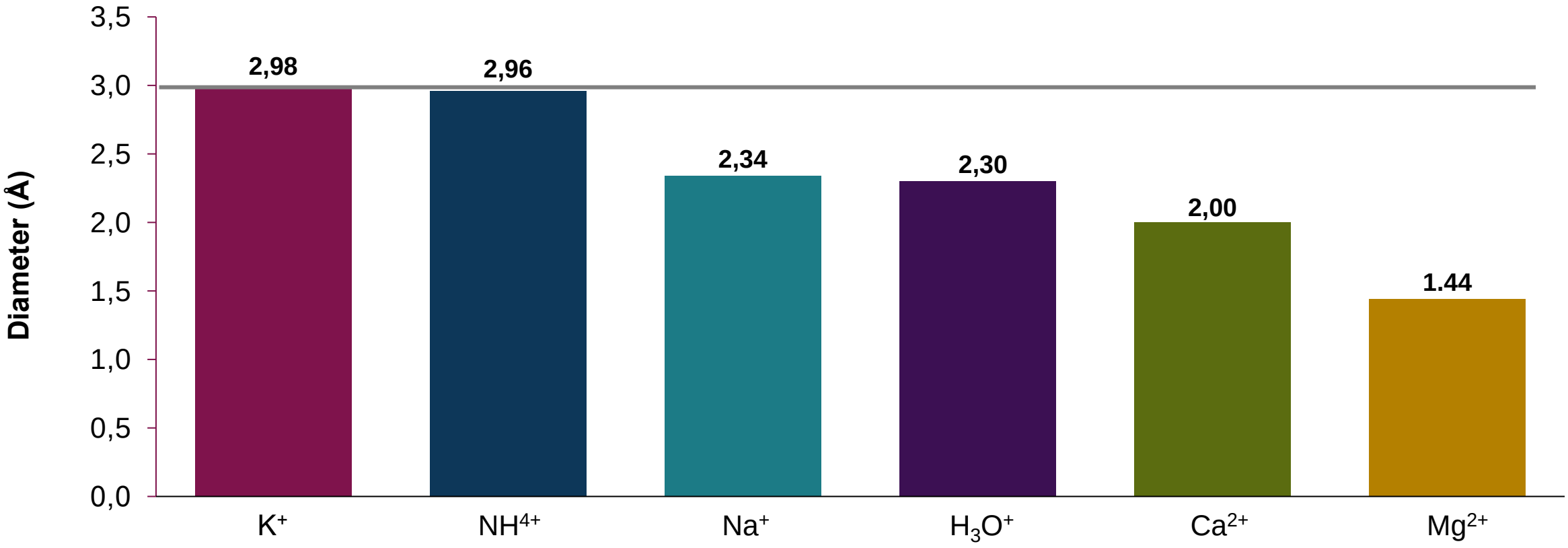
Average Binding-Site Width: 3 Å

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

SZC = sodium zirconium cyclosilicate.

Stavros F, et al. *PLoS One*. 2014;9:e114686 . Characterization of structure and function of ZS-9, a K^+ selective ion trap. *PLoS One*. 2014;9:e114686.

Relative Diameters of Major Cations*

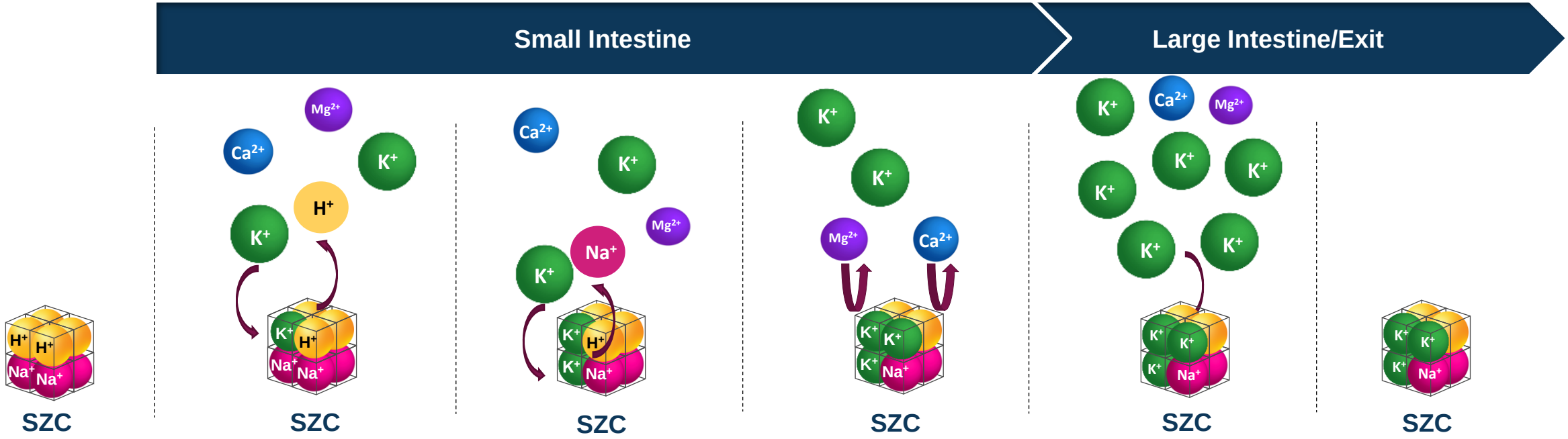


K^+ and NH^{4+} ions, owing to similar ionic diameters, "fit" best into the SZC pores, which are ~3 Å in size

*Unhydrated.
SZC = sodium zirconium cyclosilicate.

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

SZC Binds K^+ Throughout the GI Tract*

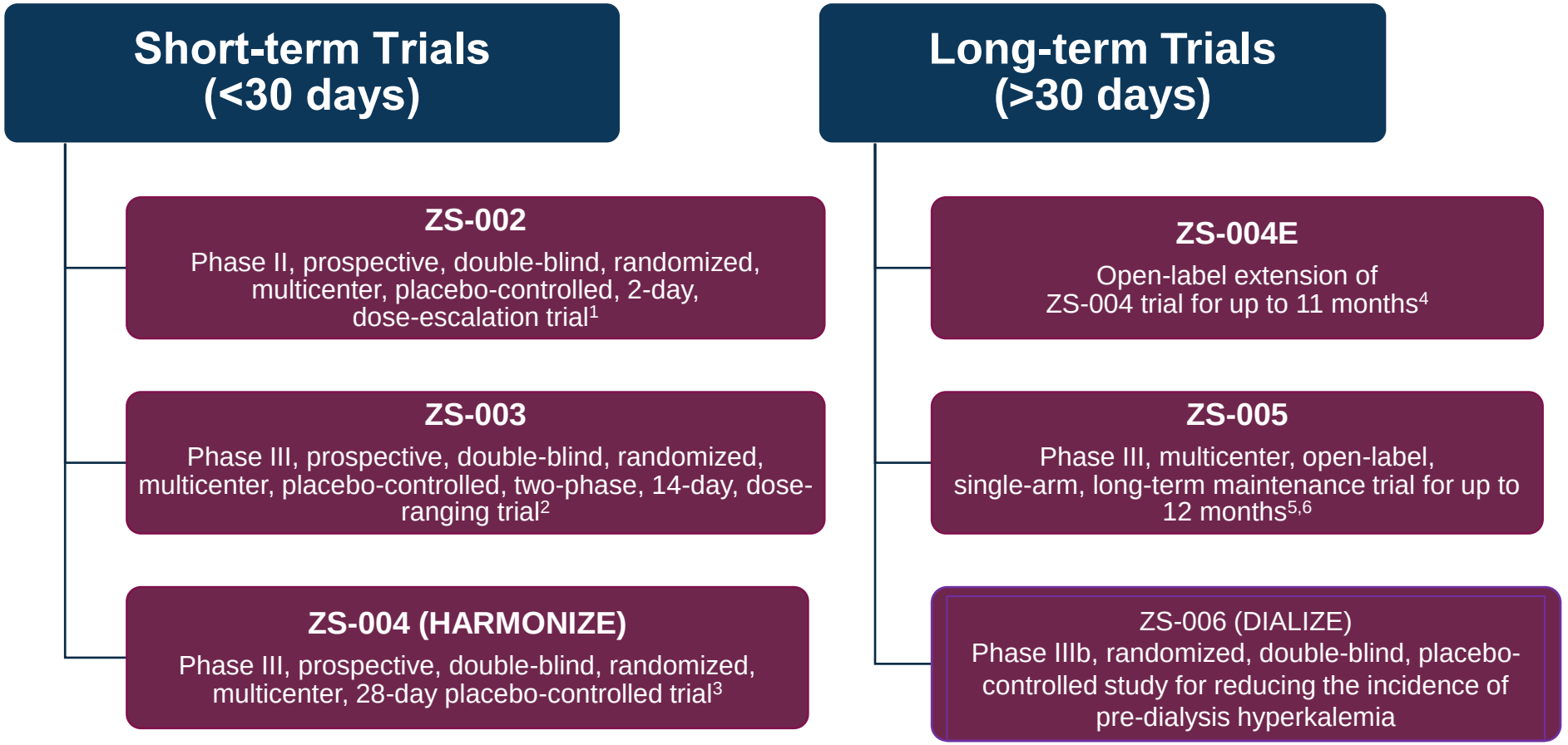


- Based on in vitro data, SZC may begin working immediately in the small intestine to preferentially capture K^+
- K^+ is exchanged for sodium and hydrogen

*For illustrative purposes only.
SZC = sodium zirconium cyclosilicate.

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

SZC Development Program



SZC = sodium zirconium cyclosilicate.

1. Ash SR, et al. *Kidney Int*. 2015;88:404-411. 2. Packham DK, et al. *N Engl J Med*. 2015;372:222-231. 3. Kosiborod M, et al. *JAMA*. 2014;312:2223-2233. 4. ZS Pharma, Inc. http://www.clinicaltrials.gov/show/NCT02107092. 5. Packham DK, et al. Poster presented at: ASN Kidney Week; October 31-November 5, 2017; New Orleans, LA. Poster FR-PO1074. 6. Fishbane S, et al. Poster presented at: ASN Kidney Week; October 31-November 5, 2017; New Orleans, LA. Poster TH-PO1112.

ZS-003

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sodium Zirconium Cyclosilicate in Hyperkalemia

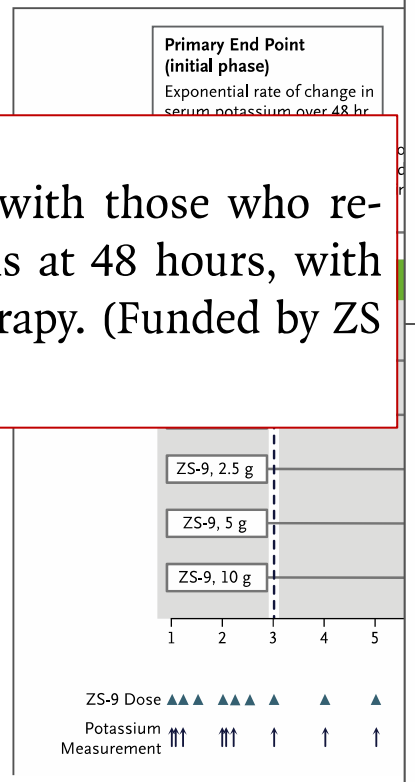
David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.

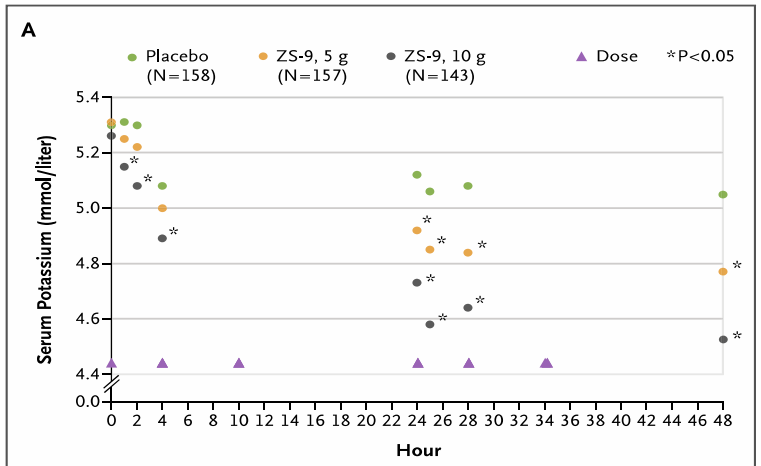
CONCLUSIONS

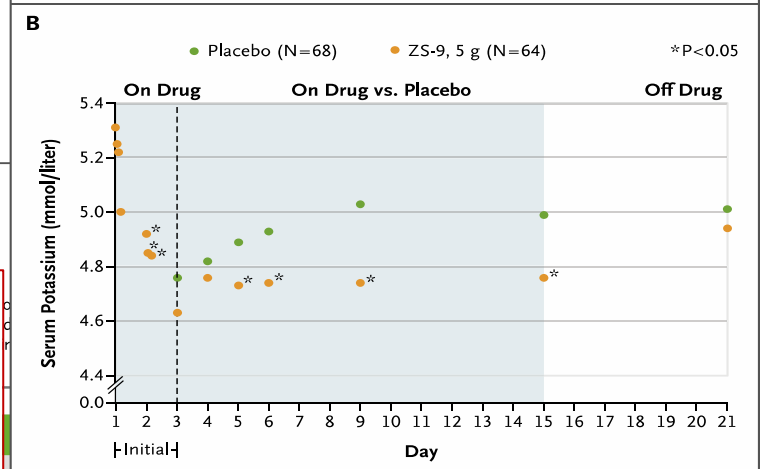
Patients with hyperkalemia who received ZS-9, as compared with those who received placebo, had a significant reduction in potassium levels at 48 hours, with normokalemia maintained during 12 days of maintenance therapy. (Funded by ZS Pharma; ClinicalTrials.gov number, NCT01737697.)

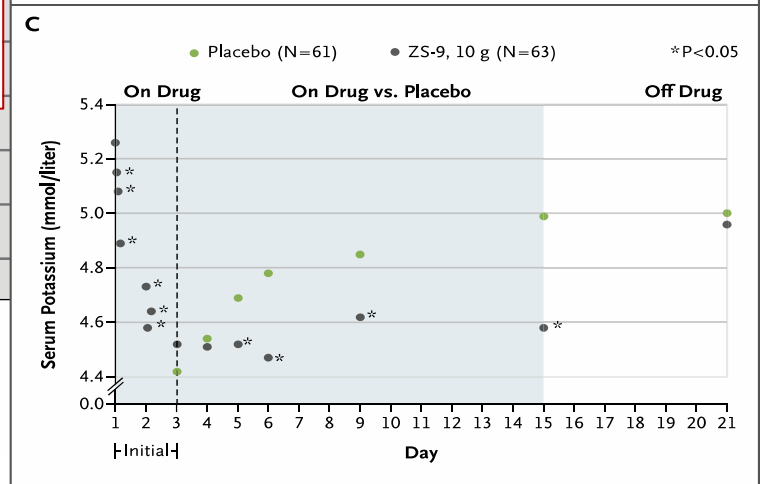
60% had diabetes

40% had a history of heart failure









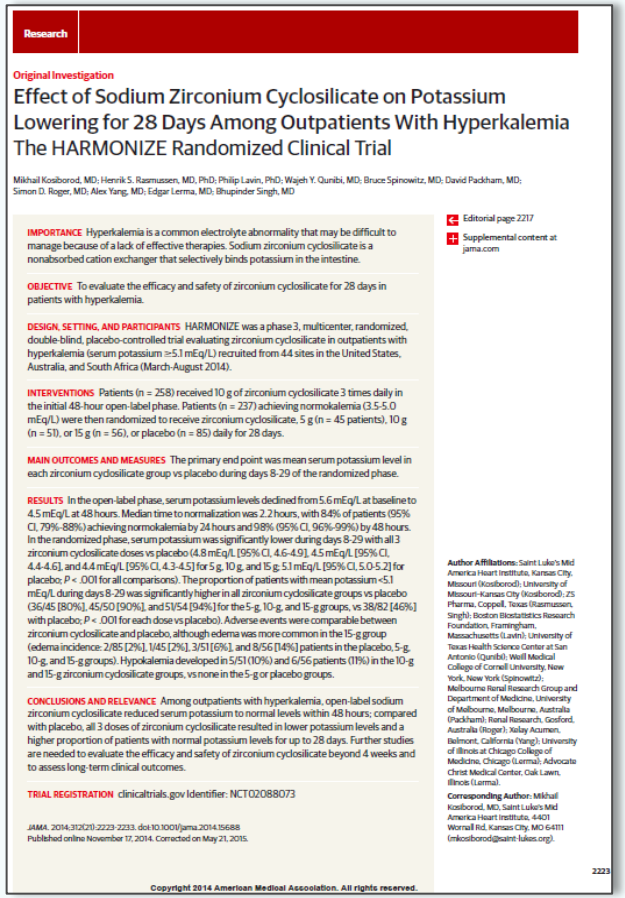
Packham et al. N Engl J Med 2015;372:222-31.

ZS-004

Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients with Hyperkalemia: The HARMONIZE Randomized Clinical Trial[1]

ZS-004E

Efficacy and Safety of Sodium Zirconium Cyclosilicate for Treatment of Hyperkalemia: An 11-Month Open-Label Extension of HARMONIZE[2]



Research

Original Investigation

Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia
The HARMONIZE Randomized Clinical Trial

Mikhail Kosiborod, MD; Henrik S. Rasmussen, MD, PhD; Philip Lavin, PhD; Wajeh Y. Qunibi, MD; Bruce Spinowitz, MD; David Packham, MD; Simon D. Roger, MD; Alex Yang, MD; Edgar Lerma, MD; Bhupinder Singh, MD

Editorial page 2217

Supplemental content at jama.com

IMPORTANCE Hyperkalemia is a common electrolyte abnormality that may be difficult to manage because of a lack of effective therapies. Sodium zirconium cyclosilicate is a nonabsorbed cation exchanger that selectively binds potassium in the intestine.

OBJECTIVE To evaluate the efficacy and safety of zirconium cyclosilicate for 28 days in patients with hyperkalemia.

DESIGN, SETTING, AND PARTICIPANTS HARMONIZE was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating zirconium cyclosilicate in outpatients with hyperkalemia (serum potassium ≥5.1 mEq/L) recruited from 44 sites in the United States, Australia, and South Africa (March-August 2014).

INTERVENTIONS Patients (n = 258) received 10 g of zirconium cyclosilicate 3 times daily in the initial 48-hour open-label phase. Patients (n = 237) achieving normokalemia (3.5-5.0 mEq/L) were then randomized to receive zirconium cyclosilicate, 5 g (n = 45 patients), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days.

MAIN OUTCOMES AND MEASURES The primary end point was mean serum potassium level in each zirconium cyclosilicate group vs placebo during days 8-29 of the randomized phase.

RESULTS In the open-label phase, serum potassium levels declined from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 hours. Median time to normalization was 2.2 hours, with 84% of patients (95% CI, 79%-88%) achieving normokalemia by 24 hours and 98% (95% CI, 96%-99%) by 48 hours. In the randomized phase, serum potassium was significantly lower during days 8-29 with all 3 zirconium cyclosilicate doses vs placebo (4.8 mEq/L [95% CI, 4.6-4.9], 4.5 mEq/L [95% CI, 4.4-4.6], and 4.4 mEq/L [95% CI, 4.3-4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI, 5.0-5.2] for placebo; $P < .001$ for all comparisons). The proportion of patients with mean potassium <5.1 mEq/L during days 8-29 was significantly higher in all zirconium cyclosilicate groups vs placebo (36/45 [80%], 45/50 [90%], and 51/54 [94%] for the 5-g, 10-g, and 15-g groups, vs 38/82 [46%] with placebo; $P < .001$ for each dose vs placebo). Adverse events were comparable between zirconium cyclosilicate and placebo, although edema was more common in the 15-g group (edema incidence: 2/85 [2%], 1/45 [2%], 3/51 [6%], and 8/56 [14%] patients in the placebo, 5-g, 10-g, and 15-g groups). Hypokalemia developed in 5/51 (10%) and 6/56 patients (11%) in the 10-g and 15-g zirconium cyclosilicate groups, vs none in the 5-g or placebo groups.

CONCLUSIONS AND RELEVANCE Among outpatients with hyperkalemia, open-label sodium zirconium cyclosilicate reduced serum potassium to normal levels within 48 hours; compared with placebo, all 3 doses of zirconium cyclosilicate resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days. Further studies are needed to evaluate the efficacy and safety of zirconium cyclosilicate beyond 4 weeks and to assess long-term clinical outcomes.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02088073

JAMA. 2014;312(21):2223-2233. doi:10.1001/jama.2014.15688
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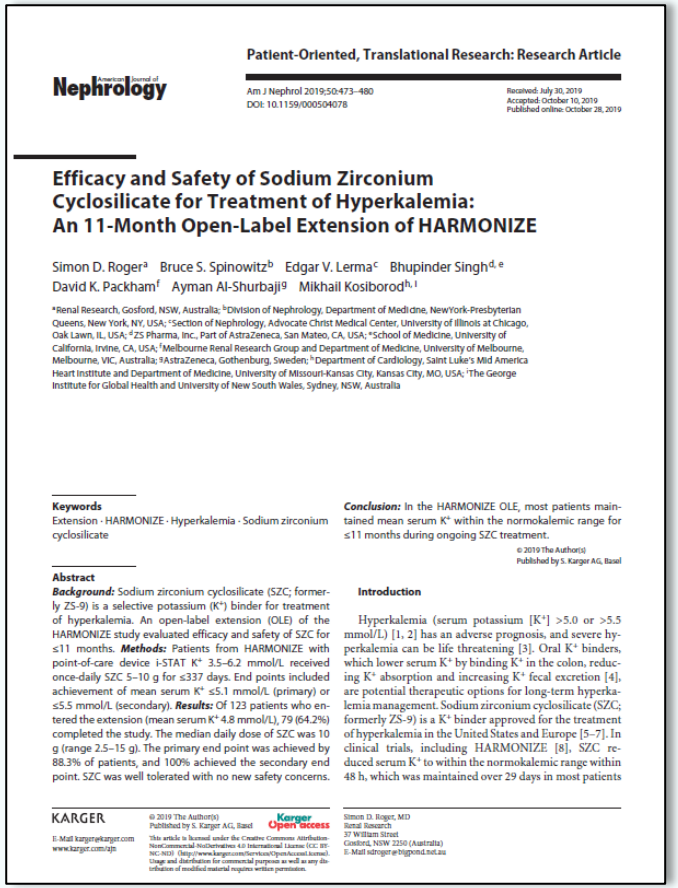

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Efficacy and Safety of Sodium Zirconium Cyclosilicate for Treatment of Hyperkalemia: An 11-Month Open-Label Extension of HARMONIZE

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Keywords
Extension · HARMONIZE · Hyperkalemia · Sodium zirconium cyclosilicate

Abstract

Background: Sodium zirconium cyclosilicate (SZC; formerly ZS-9) is a selective potassium (K^+) binder for treatment of hyperkalemia. An open-label extension (OLE) of the HARMONIZE study evaluated efficacy and safety of SZC for ≤11 months. ***Methods:*** Patients from HARMONIZE with point-of-care device i-STAT K^+ 3.5–6.2 mmol/L received once-daily SZC 5–10 g for ≤337 days. End points included achievement of mean serum K^+ ≤5.1 mmol/L (primary) or ≤5.5 mmol/L (secondary). ***Results:*** Of 123 patients who entered the extension (mean serum K^+ 4.8 mmol/L), 79 (64.2%) completed the study. The median daily dose of SZC was 10 g (range 2.5–15 g). The primary end point was achieved by 88.3% of patients, and 100% achieved the secondary end point. SZC was well tolerated with no new safety concerns. ***Conclusion:*** In the HARMONIZE OLE, most patients maintained mean serum K^+ within the normokalemic range for ≤11 months during ongoing SZC treatment.

Introduction

Hyperkalemia (serum potassium [K^+] >5.0 or >5.5 mmol/L) [1, 2] has an adverse prognosis, and severe hyperkalemia can be life threatening [3]. Oral K^+ binders, which lower serum K^+ by binding K^+ in the colon, reducing K^+ absorption and increasing K^+ fecal excretion [4], are potential therapeutic options for long-term hyperkalemia management. Sodium zirconium cyclosilicate (SZC; formerly ZS-9) is a K^+ binder approved for the treatment of hyperkalemia in the United States and Europe [5–7]. In clinical trials, including HARMONIZE [8], SZC reduced serum K^+ to within the normokalemic range within 48 h, which was maintained over 29 days in most patients

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

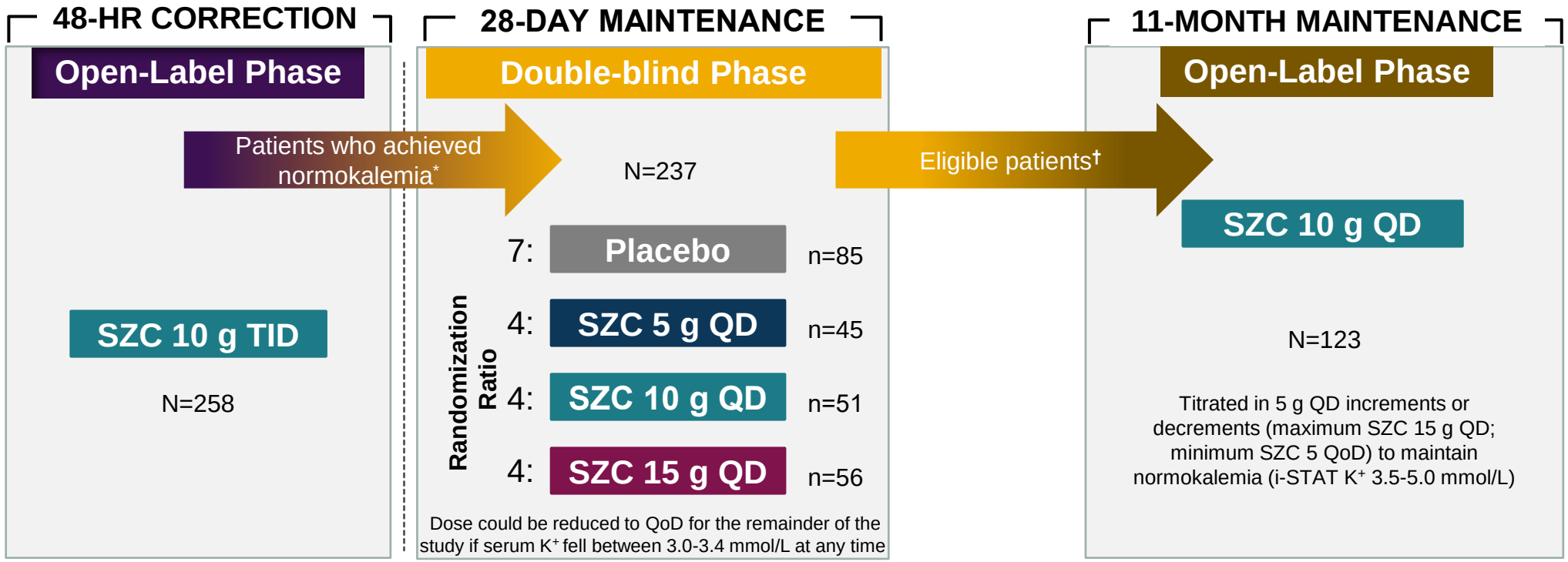
ZS-004 (HARMONIZE) + ZS-004E (Extension)
Study Designs

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 with meals 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.

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.

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

crystalize
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

	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.

ZS-004 (HARMONIZE)
Patient Demographics and Baseline Characteristics

	Correction Phase	Maintenance Phase			
Parameter	**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)**
Age, years, mean (SD),	64.0 (12.7)	64.3 (12.1)	61.5 (16.9)	63.8 (10.0)	64.9 (12.9)
Sex, n (%)					
Male	149 (57.8)	44 (51.8)	27 (60.0)	27 (52.9)	40 (71.4)
Female	109 (42.2)	41 (48.2)	18 (40.0)	24 (47.1)	16 (28.6)
Race, n (%)					
White	215 (83.3)	73 (85.9)	36 (80.0)	44 (86.3)	46 (82.1)
Black/African American	37 (14.3)	10 (11.8)	8 (17.8)	5 (9.8)	9 (16.1)
Asian	5 (1.9)	3 (3.5)	0	1 (2.0)	1 (1.8)
Other	3 (1.2)	1 (1.2)	1 (2.2)	1 (2.0)	0
Weight, kg, mean (SD)	87.9 (22.9)	85.1 (18.6)	89.6 (23.9)	87.4 (25.6)	87.2 (18.6)
Comorbidities, n (%)					
Chronic kidney disease	169 (65.5)	50 (58.8)	29 (64.4)	36 (70.6)	37 (66.1)
Heart failure	94 (36.4)	26 (30.6)	18 (40.0)	18 (35.3)	25 (44.6)
Diabetes mellitus	170 (65.9)	54 (63.5)	26 (57.8)	38 (74.5)	39 (69.6)
RAASi medications, n (%)	180 (69.8)	61 (71.8)	33 (73.3)	36 (70.6)	33 (58.9)

RAASi = renin–angiotensin–aldosterone system inhibitors; SD = standard deviation; SZC = sodium zirconium cyclosilicate.

Kosiborod M et al. *JAMA*. 2014;312:2223-2233.

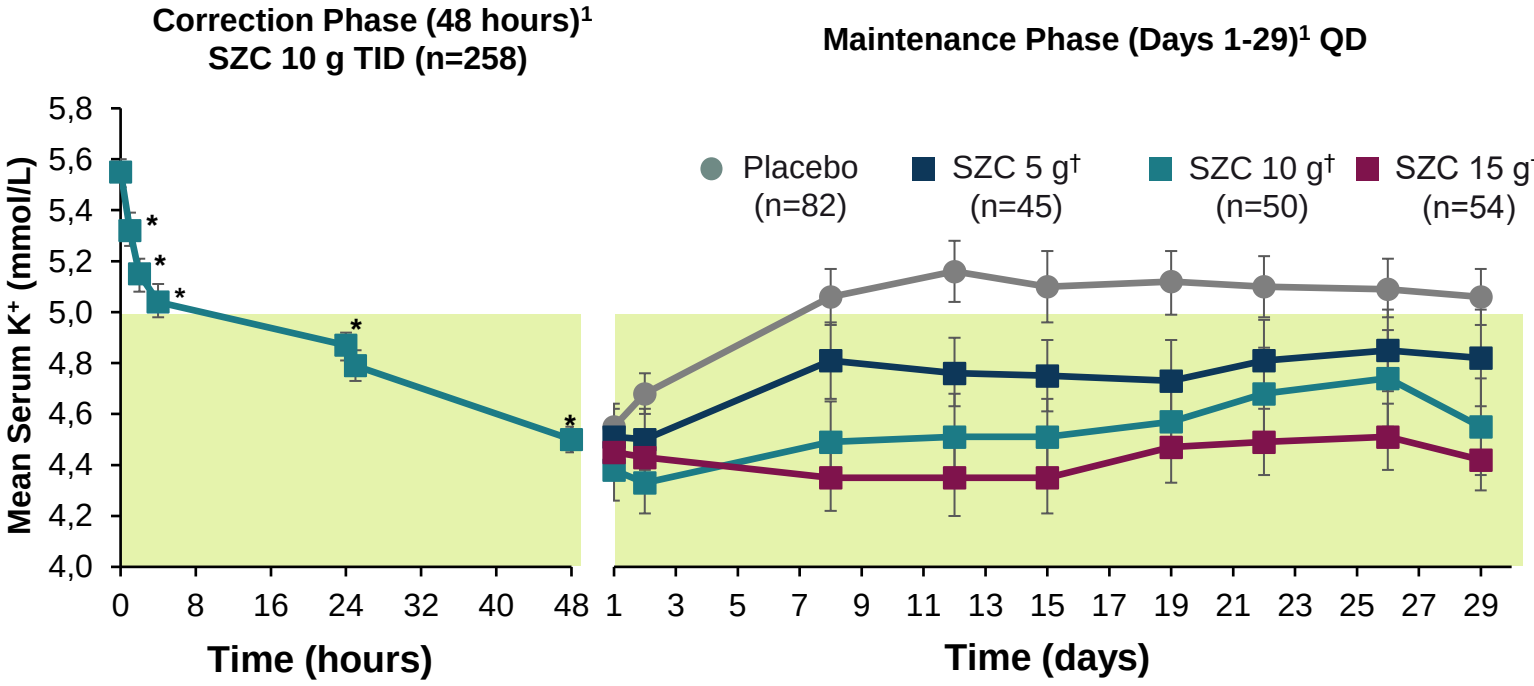
ZS-004 (HARMONIZE)
Patient Demographics and Baseline Characteristics (cont'd)

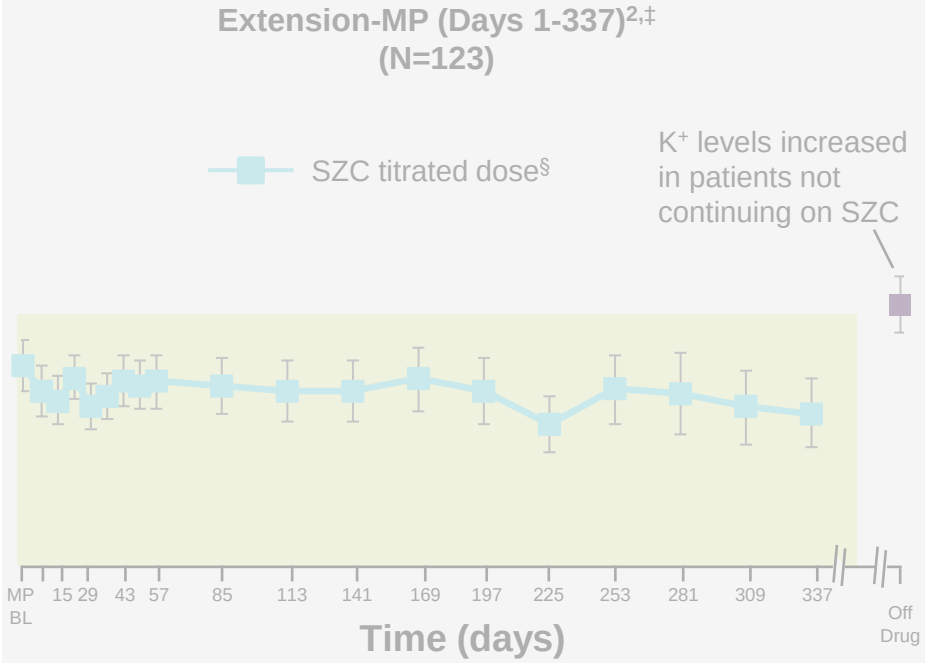
Parameter	Correction Phase	Maintenance Phase			
	SZC 10 g TID (n=258)	Placebo QD (n=85)	SZC 5 g QD (n=45)	SZC 10 g QD (n=51)	SZC 15 g QD (n=56)
eGFR,* mL/min/1.73 m2, mean (SD)	46.3 (30.5)	48.0 (28.8)	48.0 (30.7)	44.7 (30.7)	44.9 (29.5)
eGFR, mL/min/1.73 m^2, n (%)					
<60	179 (69.4)	52 (61.2)	31 (68.9)	38 (74.5)	41 (73.2)
≥60	72 (27.9)	28 (32.9)	12 (26.7)	13 (25.5)	15 (26.8)
Not reported	7 (2.7)	5 (5.9)	2 (4.4)	0	0
Brain natriuretic peptide,† mean (SD)	125.9 (170)	101.3 (106.5)	174.6 (228.6)	100.6 (143.7)	151.6 (216.8)
Serum K$^+$,‡ mmol/L, mean (SD)	5.6 (0.4)	4.6 (0.4)	4.5 (0.4)	4.4 (0.4)	4.5 (0.4)
Serum K$^+$, mmol/L, n (%)					
<5.5	119 (46.1)	43 (50.6)	23 (51.1)	19 (37.3)	24 (42.9)
5.5 to <6.0	100 (38.8)	30 (35.3)	17 (37.8)	23 (45.1)	26 (46.4)
≥6.0	39 (15.1)	12 (14.1)	5 (11.1)	9 (17.6)	6 (10.7)

*Calculated from the Modification of Diet in Renal Disease Study equation; †US sites only, measured at open-label baseline; ‡Baseline serum potassium was measured up to 1 day prior to initial SZC/placebo administration.

Kosiborod M et al. Article and protocol. *JAMA*. 2014;312:2223-2233.

ZS-004 (HARMONIZE) + ZS-004E (Extension)
Mean Serum K^+ Levels Correction, Maintenance and Extension Phases





88% of patients receiving SZC maintained an average serum K^+ of <5.1 mmol/L over 11 months

Mean decreases in serum K^+ from HARMONIZE-CP BL were observed at every time point during the Extension-MP, ranging from –1.0 to –0.8 mmol/L (–17.8 to –14.4%; p ≤0.001 for all)

Note: Normokalemia defined as serum K^+ 3.5–5.0 mmol/L. Error bars indicate 95% CI.

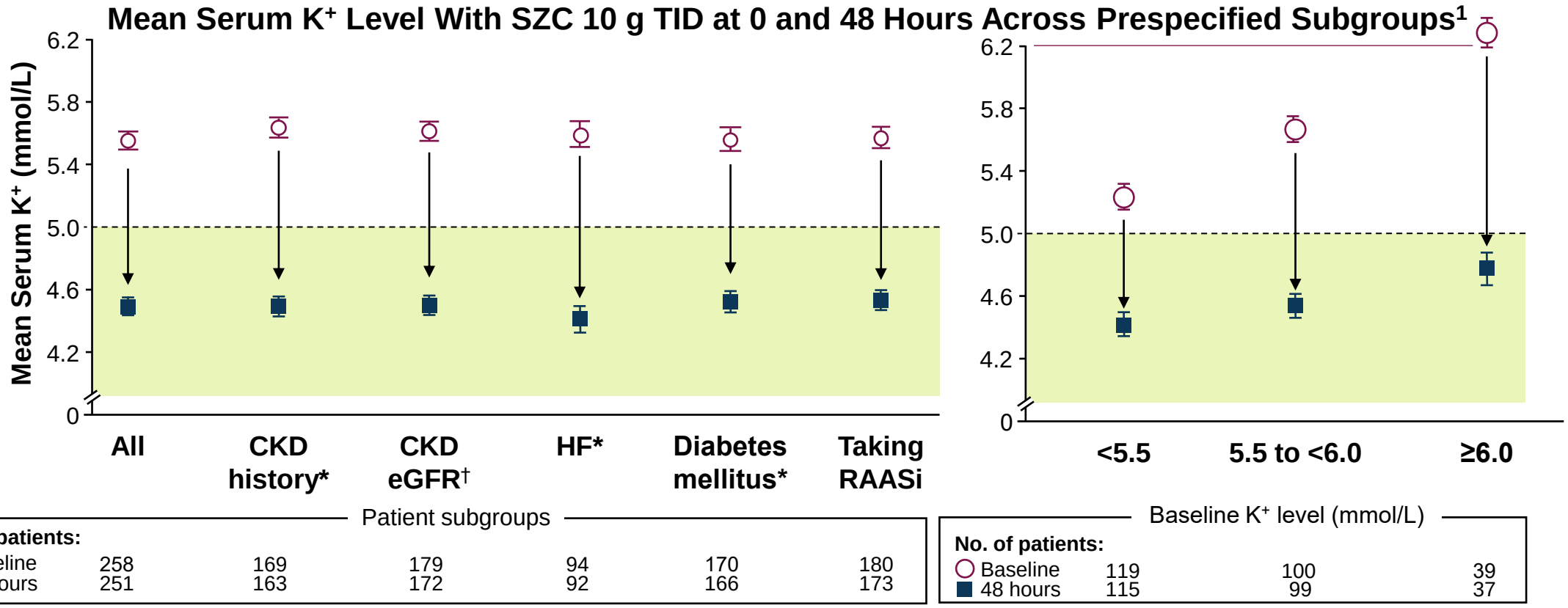
*p<0.001 vs. baseline; †p<0.001 vs. placebo during Days 8-29; ‡ITT population in Extension-MP consisted of patients who received ≥1 SZC dose with any post-Extension-CP BL safety data and post-Extension-MP serum K^+ measurements. Off-drug values were recorded at 7±1 days following the last dose of SZC; §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-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]



Note: Normokalemia defined as serum K^+ 3.5–5.0 mmol/L. Error bars indicated 95% CI.

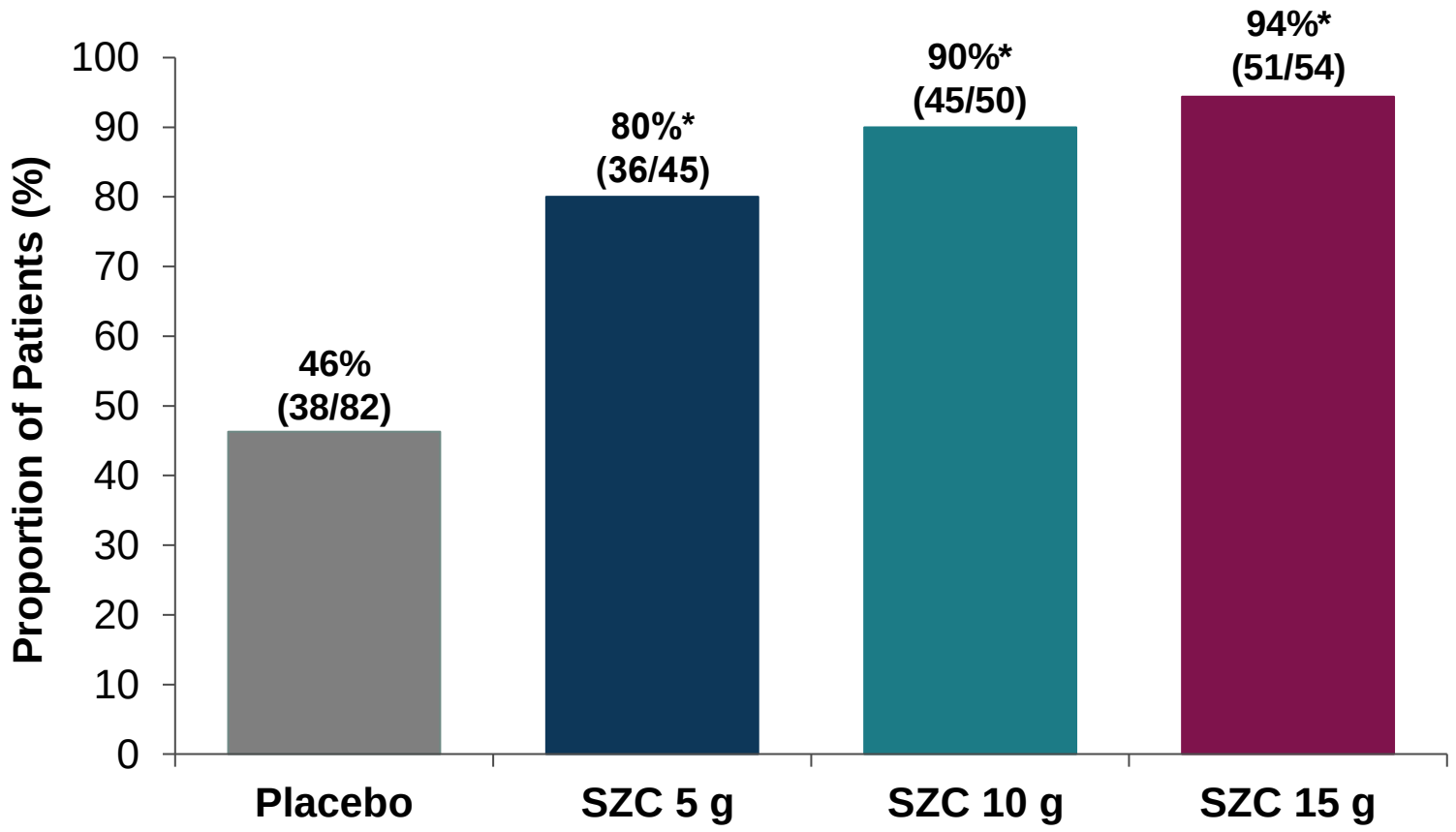
*The definitions used to identify subjects with baseline comorbid conditions (across the ZS Pharma clinical development program) were based on custom lists of preferred terms. AstraZeneca has elected to use more recognized definitions that are based on the standardized Medical Dictionary for Regulatory 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.[1]

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.

ZS-004 (HARMONIZE)

Maintenance Phase: Patients With Mean Serum K^+ <5.1 mmol/L During Days 8–29

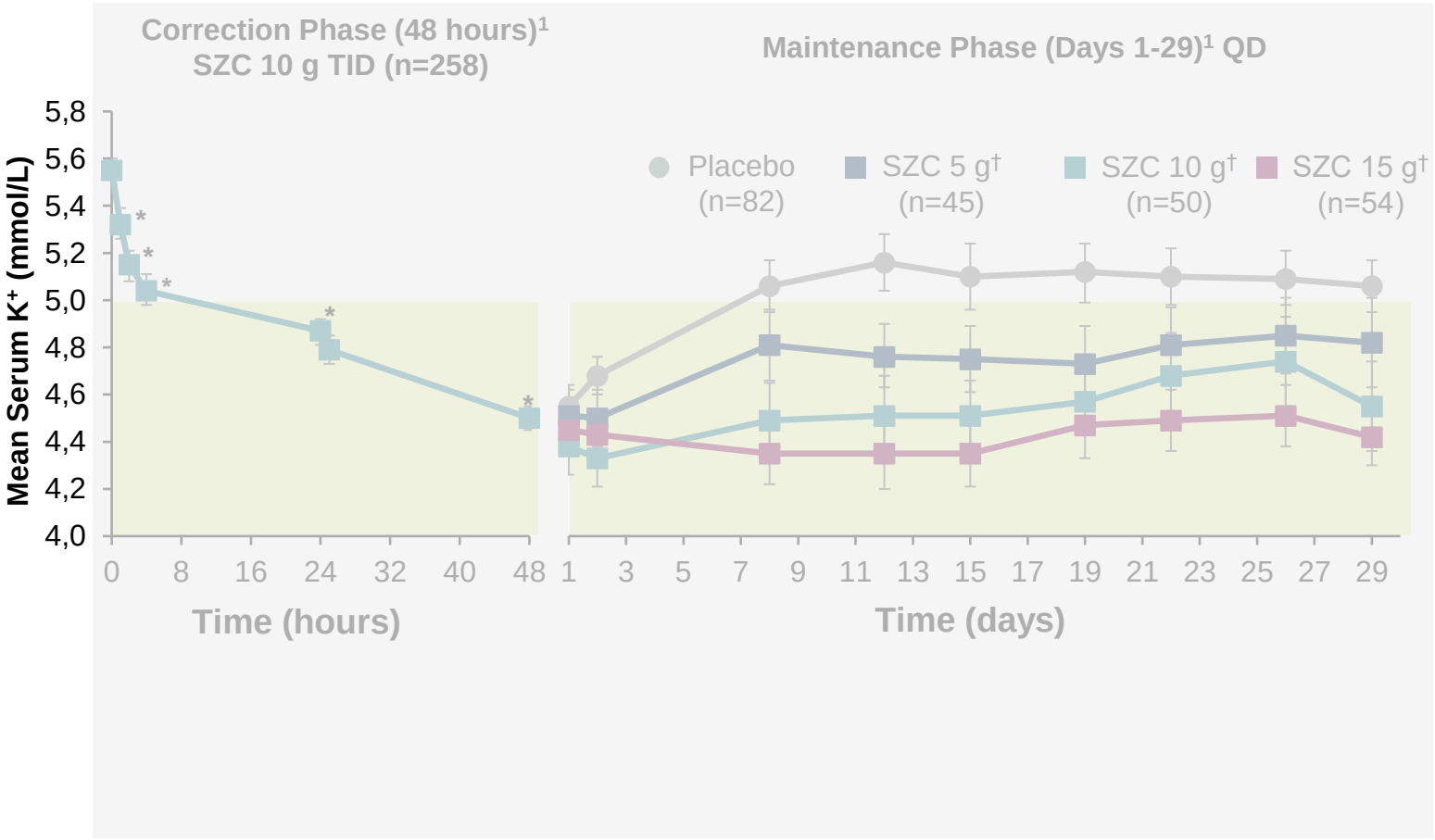


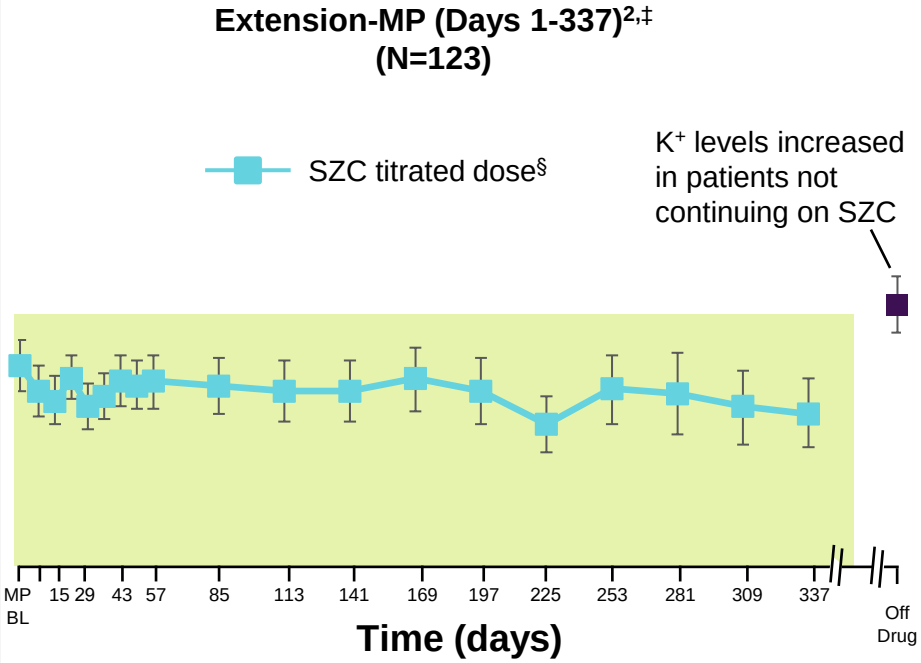
*p<0.001 vs. placebo.

SZC = sodium zirconium cyclosilicate.

Kosiborod M et al. *JAMA*. 2014;312:2223-2233.

ZS-004E (Extension)
Mean Serum K⁺ Levels in Extension Phases





88% of patients receiving SZC maintained an average serum K⁺ of <5.1 mmol/L over 11 months

Mean decreases in serum K⁺ from HARMONIZE-CP BL were observed at every time point during the Extension-MP, ranging from –1.0 to –0.8 mmol/L (–17.8 to –14.4%; p ≤0.001 for all)

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)
RAASi Dosing During the Study

Of the 83 (68%) 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% Changed** RAASi dose*
- **2% Switched** RAASi therapy
- **4% Discontinued** RAASi therapy

Of the 38 RAASi-naïve patients at extension phase baseline:

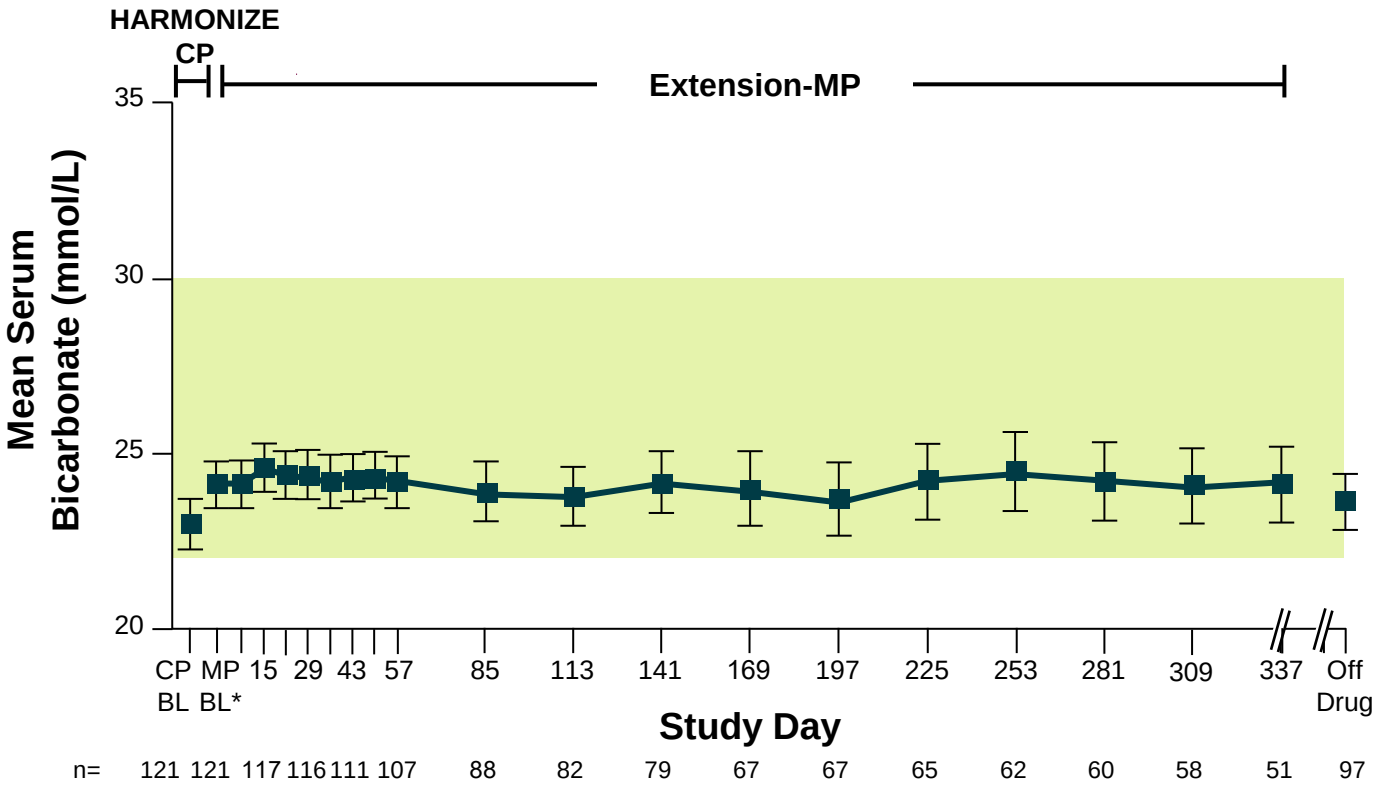
- **11% Initiated** RAASi therapy

*Multiple dose increases and decreases.

RAASi = renin–angiotensin–aldosterone system inhibitor.

Roger SD et al. *Am J Nephrol.* 2019;50:473-480.

ZS-004E (Extension)
Effect of SZC on Serum Bicarbonate Levels Over Time



- Among pooled data from all SZC doses, mean serum bicarbonate levels:
  - Increased from HARMONIZE-CP baseline to Extension-MP baseline (23.0 vs. 24.1 mmol/L)
  - Maintained throughout the Extension-MP (24.1 mmol/L at Day 337)
- After SZC cessation, mean serum bicarbonate returned to baseline levels (23.6 mmol/L)

Sustained increases in serum bicarbonate were observed during the Extension-MP

Note: Normal serum bicarbonate defined as 22–30 mmol/L. Error bars indicate 95% CI. Data from all SZC doses were pooled. Off-drug values were recorded at 7±1 days following the last dose of SZC.

*Extension-MP BL.

BL = baseline; CP = correction phase; MP = maintenance phase; SZC = sodium zirconium cyclosilicate.

Roger SD et al. Article and supplementary material. *Am J Nephrol.* 2019;50:473-480.

ZS-004E (Extension)
Adverse Events

Extension-MP Safety Population,* N=123	n (%)
Adverse Events Occurring in ≥5% of Patients	**82 (66.7)**
Constipation†	7 (5.7)
Hypertension‡	15 (12.2)
Peripheral edema	10 (8.1)
Urinary tract infection	11 (8.9)
AEs leading to discontinuation in ≥2 patients	**11 (8.9)**
Electrocardiogram QT interval prolonged§	2 (1.6)
SAEs leading to discontinuation	**6 (4.9)‖**
Serious Adverse Events in ≥2 Patients	**24 (19.5)**
Chronic obstructive pulmonary disease	2 (1.6)
Congestive cardiac failure	2 (1.6)
Pneumonia	2 (1.6)
Urinary tract infection	2 (1.6)

- 16 patients (13%) reported SMQ edema, of which 11 had significant risk factors for fluid overload–related events, including history of heart failure, diastolic dysfunction, CKD, edema, lymphedema, or venous insufficiency¶
- No clinically meaningful changes in weight or blood pressure were observed
- 2 patients experienced hyperkalemia as an AE (1 was considered a serious AE and 1 lead to discontinuation), both patients has a serum K^+ of 7.0 mmol/L at discontinuation

Note: Interpretation of safety results are limited as study was open-label and lacked a placebo comparator arm.

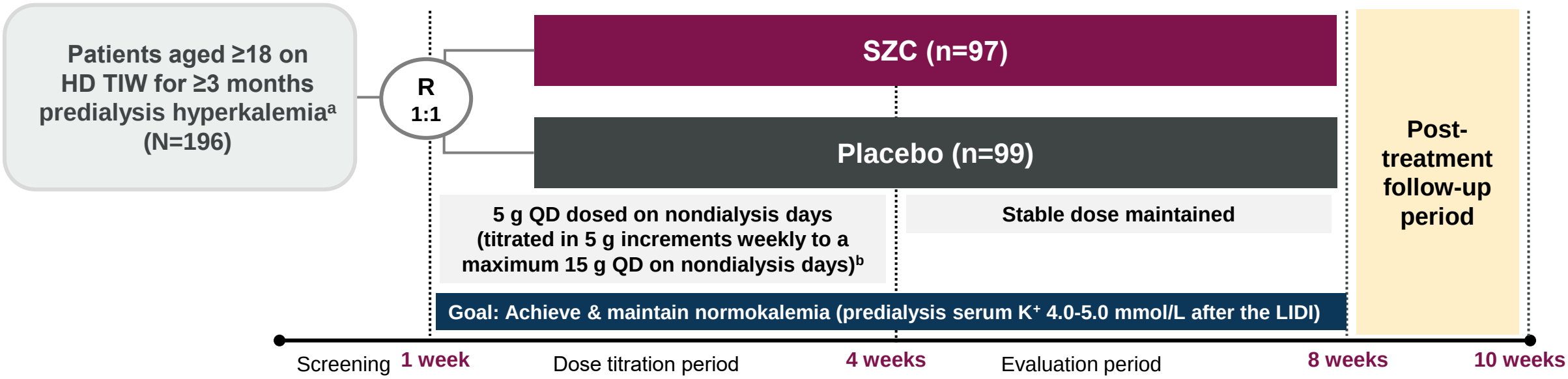
*Extension-MP safety population included all patients who received ≥1 dose of SZC during the extension-MP and had any post–extension-correction phase baseline safety data; †Overall, 23 patients (18.7%) reported gastrointestinal disorders. Nausea, vomiting, diarrhea were each reported in 3.3% of patients; ‡As reported by site with no specific threshold. Hypertension was rated as mild (n=7; 46.7%) or moderate (n=8; 53.3%) in severity and only 1 case was considered related to SZC by the investigator. No patients discontinued study medication due to an AE of hypertension; §Non-serious; possibly related to SZC; ‖Including cardiac failure, acute myocardial infarction, hyperkalemia, chronic obstructive pulmonary disease, localized infection, and diabetic foot infection. No SAEs were considered related to SZC; ¶SMQ edema includes preferred terms from the Standardized MedDRA Queries for hemodynamic edema, effusions, and fluid overload; In the 16 patients, there were 17 SMQ edema events. None of the edema events led to discontinuation.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; MP = maintenance phase; SAE = serious adverse event; SMQ = Standardized Medical Dictionary for Regulatory Activities query; SZC = sodium zirconium cyclosilicate.

Roger SD et al. Article and supplementary material. *Am J Nephrol.* 2019;50:473-480.

DIALIZE – ZS006
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



[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® K^+ after the LIDI was >5.0 mmol/L (one weekly dose adjustment). If the predialysis i-STAT 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 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. *J Am Soc Nephrol*. 2019;30:1723-1733.

DIALIZE
Study endpoints

Primary Endpoint	**Percentage of patients maintaining serum K^+ of 4.0–5.0 mmol/L[a] during ≥3 of 4 HD treatments following the LIDI and who did not require rescue therapy[b] during the 4-week evaluation period (responders)**
Secondary Endpoints	
Efficacy	Proportion of patients requiring rescue therapy to reduce serum K^+ in the setting of severe hyperkalemia (serum K^+ >6 mmol/L)[b]
Safety	• Adverse events • Laboratory changes/vital signs, ECG changes • IDWG: difference between predialysis weight after LIDI and postdialysis weight from the previous dialysis session
Post Hoc Analysis	K^+ shift: difference between pre- and postdialysis K^+ K^+ gradient: difference between predialysis K^+ and the dialysate K^+ concentration

[a]Serum K^+ levels will be measured using i-STAT device and central laboratory. Dose adjustments will be made based on predialysis i-STAT K^+ levels; [b]Rescue therapy was any urgent therapeutic intervention considered necessary to reduce serum K^+ for severe hyperkalemia (serum K^+ >6.0 mmol/L). Use of rescue therapy included but was not limited to insulin/glucose, sodium bicarbonate, β-adrenergic agonists, potassium binders (SPS, CPS, patiromer), and any other form of renal replacement therapy including additional dialysis or reduction in dialysate K^+ concentration. Use of rescue therapy was not strictly protocolized and was left to the investigator's clinical judgement to be given in accordance with local practice patterns. No clinically justified therapy for severe acute hyperkalemia was withheld in study patients. Rescue therapy was followed by SZC dose adjustment, if appropriate, and documentation of the event.

CPS = calcium polystyrene sulfonate; ECG = electrocardiogram; HD = hemodialysis; IDWG = interdialytic weight gain; LIDI = long interdialytic interval; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate.

Fishbane S et al. Article and supplemental data. *J Am Soc Nephrol*. 2019;30:1723-1733.

DIALIZE
Baseline demographics

Patient characteristics were generally balanced between treatment groups except for small difference in age distribution where patients on SZC were younger vs. placebo

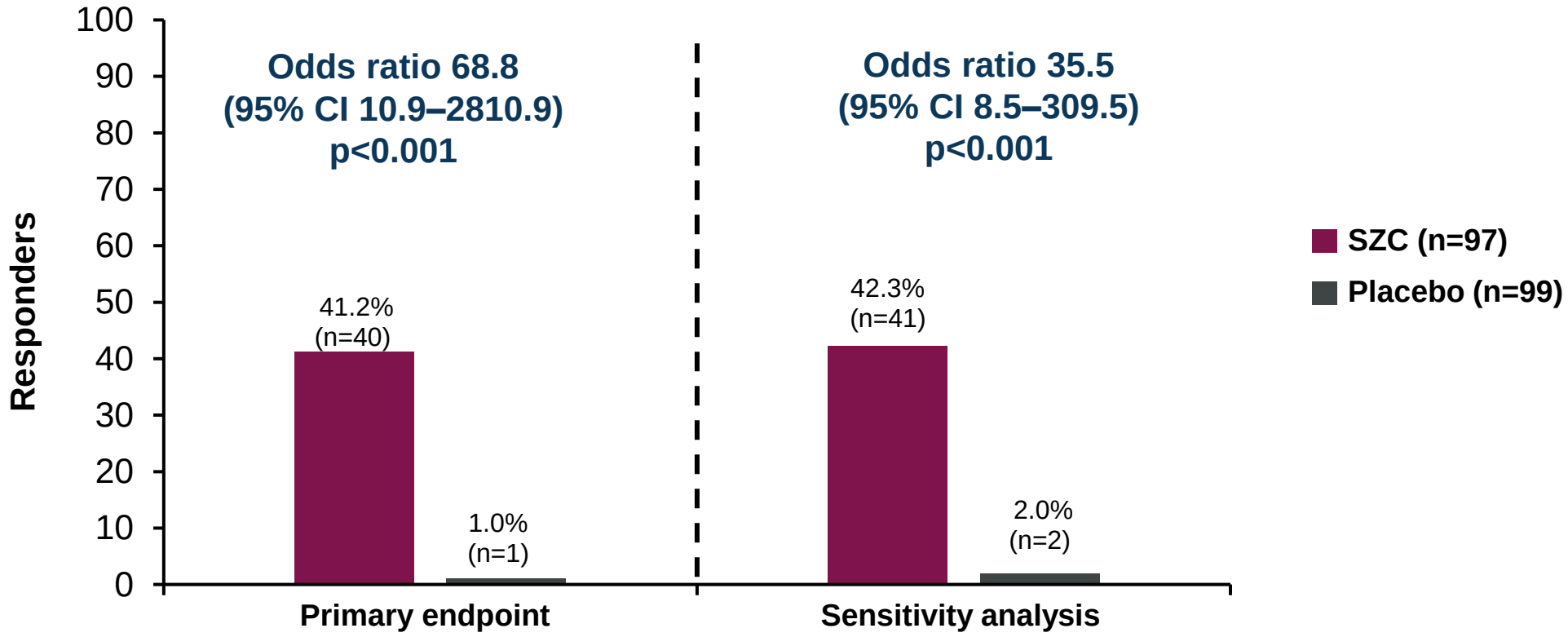
Characteristic	SZC (n=97)	Placebo (n=99)
Age, years (mean ± SD)	55.7 ± 13.8	60.4 ± 13.2
Male, n (%)	57 (58.8)	58 (58.6)
Age group, years, n (%)		
18-50	31 (32.0)	21 (21.2)
51-64	34 (35.1)	32 (32.3)
65-84	32 (33.0)	45 (45.5)
≥85	0 (0.0)	1 (1.0)
Race, n (%)		
White	50 (51.5)	52 (52.5)
African American/Black	11 (11.3)	8 (8.1)
Asian	33 (34.0)	33 (33.3)
American Indian/Alaska Native	1 (1.0)	2 (2.0)
Other	2 (2.1)	4 (4.0)
Height, cm (mean ± SD)	166.4 ± 9.9	165.1 ± 9.2
Weight, kg (mean ± SD)	72.0 ± 22.0	70.0 ± 15.9
BMI, kg/m^2 (mean ± SD)	26.9 ± 7.1	26.7 ± 5.4

BMI = body mass index; SD = standard deviation; SZC = sodium zirconium cyclosilicate.

Fishbane S et al. *J Am Soc Nephrol*. 2019;30:1723-1733.

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]



[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 K^+ data.

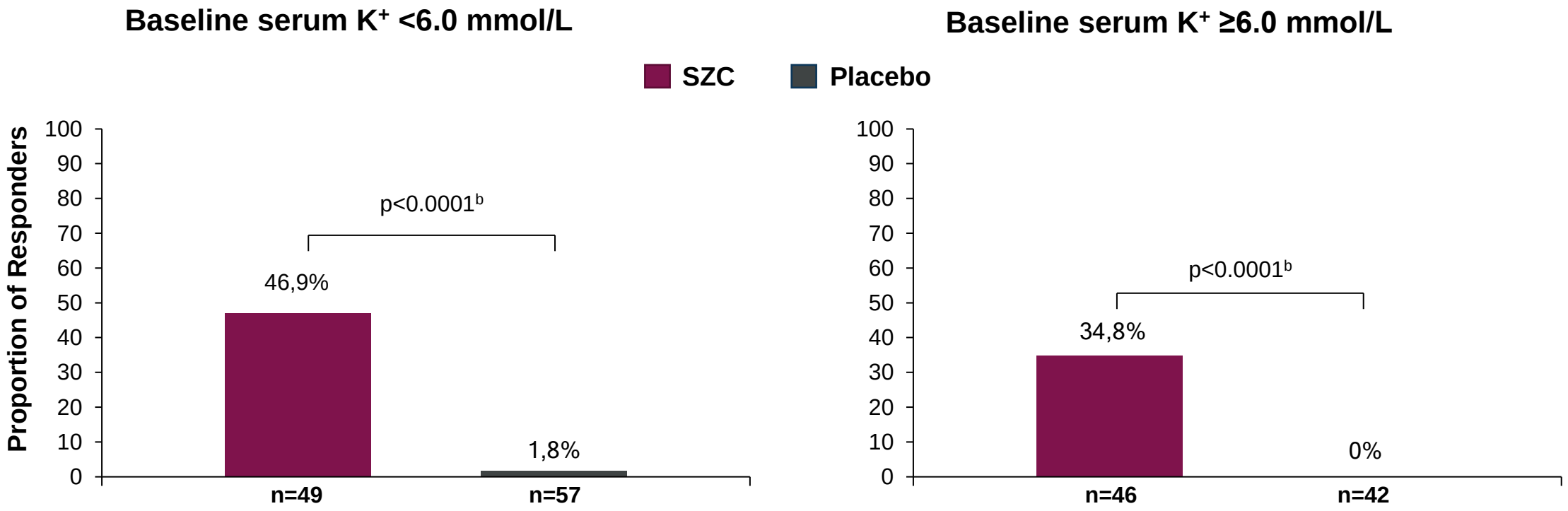
HD = hemodialysis; SZC = sodium zirconium cyclosilicate.

Fishbane S et al. Article and supplemental data. *J Am Soc Nephrol*. 2019;30:1723-1733.

DIALIZE

Post hoc analysis – Proportion of responders by baseline serum K^+

The proportion of responders[a] who maintained a predialysis serum K^+ 4.0-5.0 mmol/L during ≥3 out of 4 HD treatments was significantly higher with SZC than placebo, regardless of baseline serum K^+

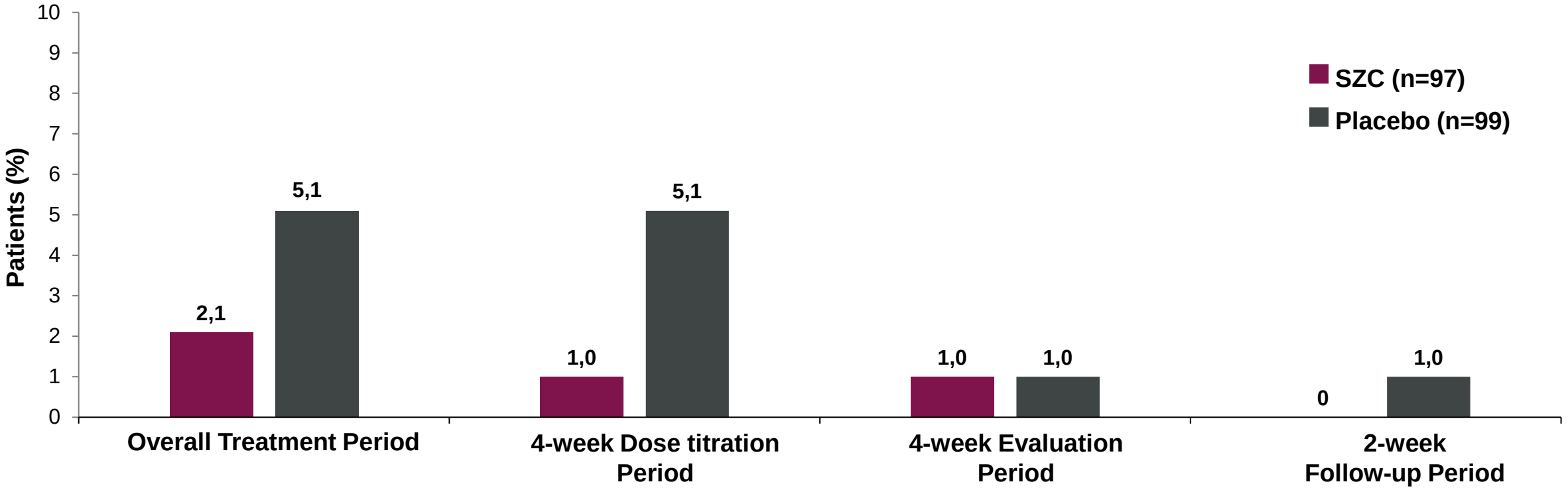


[a]Responders were defined as patients who, during the evaluation period, maintained a predialysis serum K^+ 4.0-5.0 mmol/L during ≥3 out of 4 HD treatments following the long interdialytic interval and who did not receive rescue therapy. [b]p values obtained using a Fisher's exact test.
HD = hemodialysis; SZC = sodium zirconium cyclosilicate.

Fishbane S et al. Presented at: ASN Kidney Week 2019; November 5-10, 2019; Washington, DC.

DIALIZE
Secondary endpoint – Use of rescue therapy

A low percentage of patients on SZC and placebo required rescue therapy[a]



Note: Study period defined using the date of the adverse event requiring rescue therapy.

[a]Rescue therapy was any urgent therapeutic intervention considered necessary to reduce serum K^+ for severe hyperkalemia (serum K^+ >6.0 mmol/L). Rescue therapies included SPS (1.5%), CPS (1.0%), dialysis (1.0%), insulin (1.0%), calcium gluconate (0.5%), furosemide (0.5%), and salbutamol (0.5%).

CPS = calcium polystyrene sulfonate; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate.

Fishbane S et al. *J Am Soc Nephrol*. 2019;30:1723-1733.

DIALIZE
Safety results

AE, n (%)[1]	SZC (n=96)	Placebo (n=99)
Patients with any AE	40 (41.7)	46 (46.5)
Patients with any SAE[a]	7 (7.3)	8 (8.1)
AEs leading to discontinuation	4 (4.2)[b]	2 (2.0)
Death	1 (1.0)[c]	0 (0.0)
AEs in >2% of patients		
Constipation	4 (4.2)	3 (3.0)
Diarrhea	4 (4.2)	6 (6.1)
Headache	3 (3.1)	2 (2.0)
Nasopharyngitis	3 (3.1)	5 (5.1)
Hyperkalemia	2 (2.1)	6 (6.1)
Hordeolum (stye)	2 (2.1)	0 (0.0)
Muscle spasms	2 (2.1)	2 (2.0)
Dizziness	1 (1.0)	4 (4.0)
Dyspnea	1 (1.0)	3 (3.0)
Pruritus	1 (1.0)	3 (3.0)
Shunt stenosis	1 (1.0)	3 (3.0)

- Most AEs reported were considered mild or moderate in intensity[1]
- Most common AE was GI disorders, with no difference between groups (19.8% with SZC vs. 17.2% with placebo)[1]
- Throughout the study, there were no clinically meaningful changes in blood pressure or heart rate and there were no clinically significantly abnormal electrocardiogram results[1,2]
- All SAEs were considered not related to the study drug[1]

[a]Including the event with death as an outcome and were considered not related to the study drug; [b]One event of hyperkalemia with SZC led to drug discontinuation and was considered unlikely related to the study drug; [c]SAE of peripheral arterial occlusive disease occurring 69 days after SZC start that led to death. The patient had a concomitant SAE of gangrene of the leg and feet starting 53 days after the first dose of SZC and 6 days after the last dose. It was judged by the investigators as not related to SZC.

AE = adverse event; GI = gastrointestinal; SAE = serious adverse event; SZC = sodium zirconium cyclosilicate.

1. Fishbane S et al. *J Am Soc Nephrol*. 2019;30:1723-1733; 2. In House Data, AstraZeneca Pharmaceuticals LP. CSR D9480C00006. April 26, 2019.

DIALIZE
Post hoc analysis – Hypokalemia events

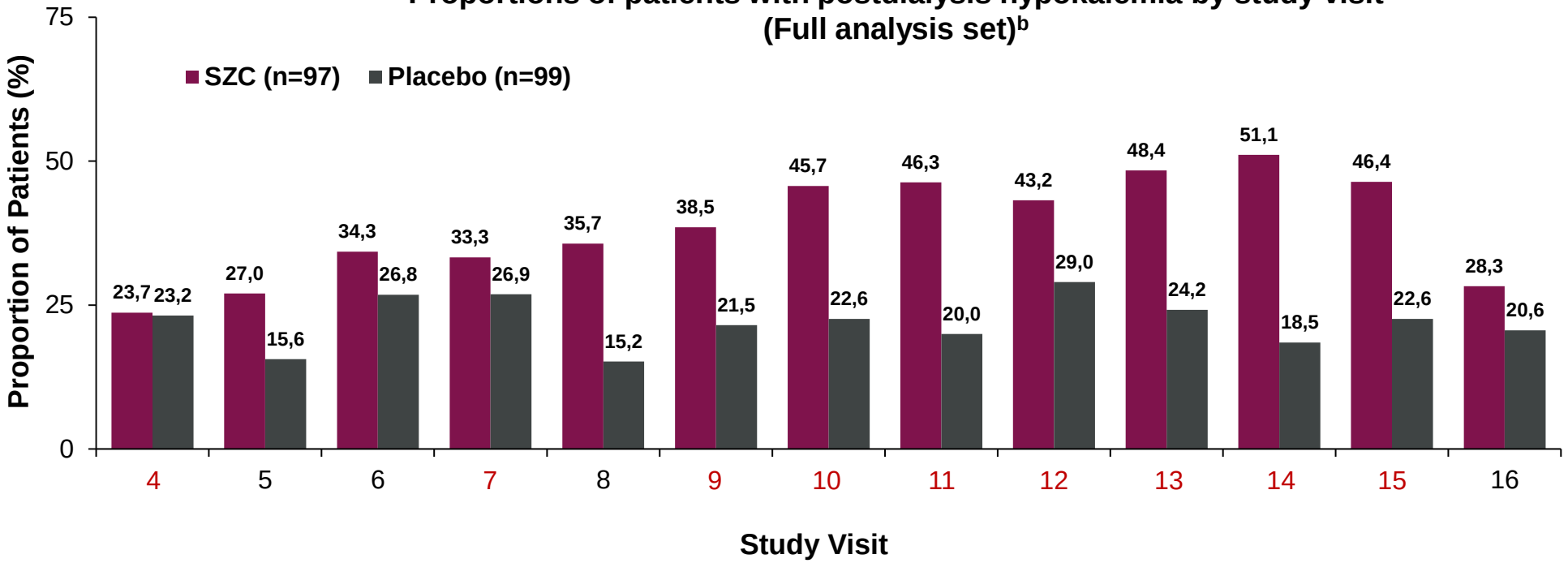
The overall frequency of predialysis hypokalemia was similar between SZC and placebo groups. Conversely, the proportion of patients with postdialysis hypokalemia was greater with SZC at each study visit

Overall frequency of predialysis hypokalemia (Safety analysis set)

SZC (n=96)	
Number of Patients[a] (%)	Instances
5 (5.2)	7

Placebo (n=99)	
Number of Patients[a] (%)	Instances
5 (5.1)	5

Proportions of patients with postdialysis hypokalemia by study visit (Full analysis set)[b]



Note: Hypokalemia was defined as a serum K^+ <3.5 mmol/L.

[a]Percentages are based on the total numbers of patients in the treatment group; [b]Red numbers denote study visits following the LIDI. Percentages are calculated as the number of patients with hypokalemia as the numerator and the number of patients with non-missing serum K^+ measurements as the denominator. No imputation of missing data was conducted.

LIDI = long interdialytic interval; SZC = sodium zirconium cyclosilicate.

Fishbane S et al. Poster presented at: ASN Kidney Week 2020; October 22-25, 2020; Poster PO1051.

DIALIZE
Interdialytic weight gain

Changes in IDWG over time were comparable between treatment groups

IDWG[a] Over Time

	SZC (n=96)			Placebo (n=99)		
	n	IDWG, kg (mean ± SD)	Mean ± SD change from baseline[b]	n	IDWG, kg (mean ± SD)	Mean ± SD change from baseline[b]
Baseline[c]	96	3.0 ± 1.3	—	99	2.9 ± 1.6	—
Visit 11 (Day 29)	95	2.7 ± 3.7	-0.3 ± 3.6	97	2.8 ± 1.5	-0.1 ± 1.5
Visit 15 (Day 57; EOT)	83	3.2 ± 1.3	0.2 ± 1.3	88	2.7 ± 1.6	-0.1 ± 1.6

[a]IDWG was calculated as the difference between current predialysis weight minus previous postdialysis weight (measured at the immediate dialysis session prior to the visit; [b]Based on programmatic calculations; [c]Baseline IDWG was defined as the latest IDWG calculated over the LIDI during screening that occurred immediately prior to Visit 4 (Day 1).

EOT = end of treatment; IDWG = interdialytic weight gain; LIDI = long interdialytic interval; SD = standard deviation; SZC = sodium zirconium cyclosilicate.

Fishbane S et al. Article and supplemental data. *J Am Soc Nephrol*. 2019;30:1723-1733.

Practice Point 3.2.4:

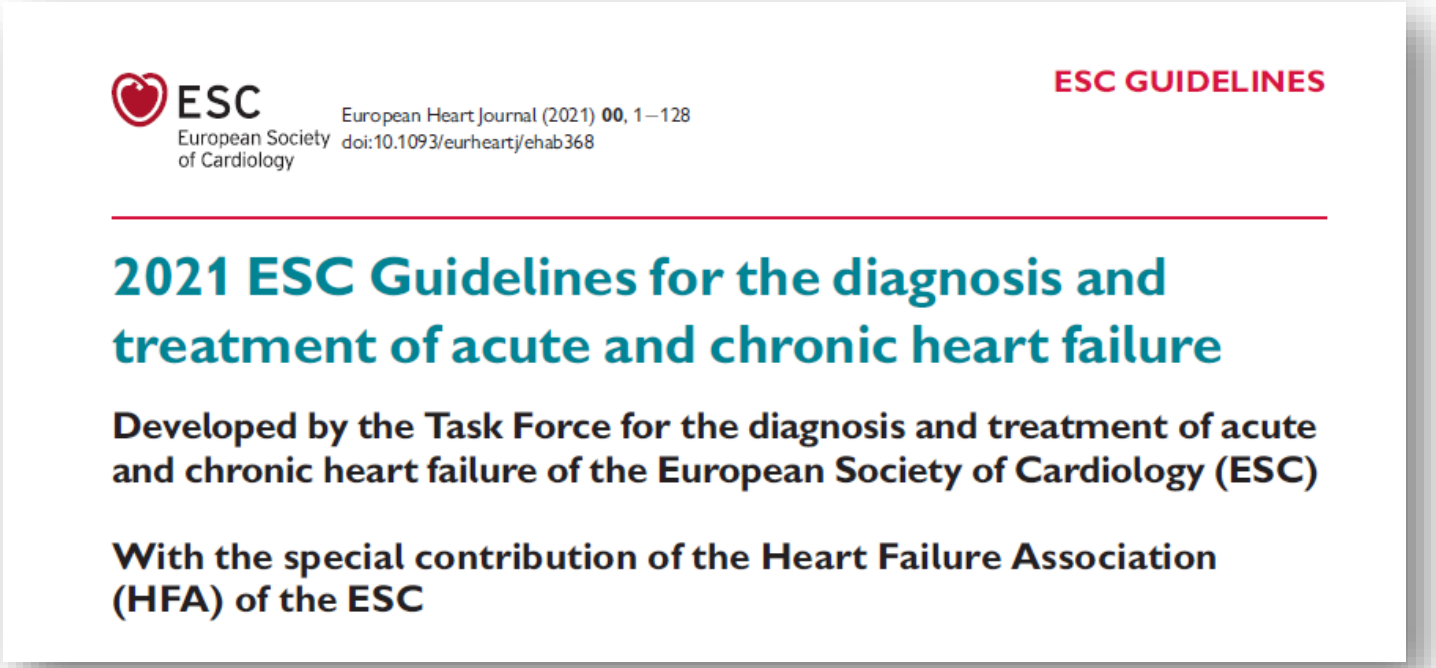
Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi.

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 RASi 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

For the 1st time, a globally recognized Cardiology Guideline lists novel K^+ binders (sodium zirconium cyclosilicate, patiromer and sorbitex calcium) as options to manage hyperkalaemia

- Clearly defined hyperkalaemia
- RAASi uptitration and optimization when K^+ < 5.0 mmol/L
- Clear direction for action with novel K^+ binder >5.0 mmol/L



ESC European Society of Cardiology

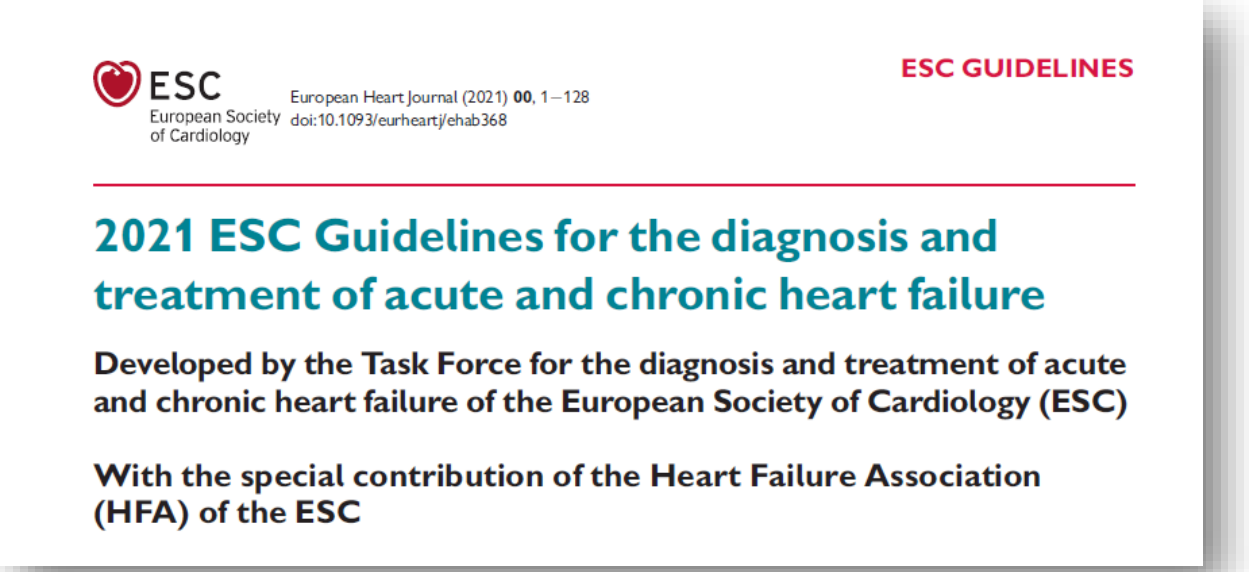
European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC



Low K^+ Diet is not mentioned as option for the management of HK

Loop diuretics are mentioned only in the context of managing life-threatening HK, to help facilitate K^+ loss

SZC and patiromer are described as being 'much better tolerated' than SPS and CPS

SPS **should not** be used in the medium or long term as it may cause severe gastrointestinal side effects, including bowel necrosis

MAINTENANCE DOSING[1]

- **LOKELMA is a daily 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[a,b]**

10 g
for 24 to 48 hours

until normokalemia is achieved[a,b]

Maintenance phase

1×  **/day[a,b]**

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
[a]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; [b]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.

The amount of Na^+ contained in LOKELMA is equivalent to that found in common foods, and is less than the recommended daily amount

LOKELMA contains less than ~8% sodium by total weight[1]

	LOKELMA 5 g[a]	LOKELMA 10 g	Bicarbonate 4.8 g[2]	SPS 60 g[3,b,c]
Estimated Na^+ content	400 mg	800 mg	1311 mg	6000 mg[d]
Salt equivalent:[4]	 ~1/6th tsp	 ~1/3rd tsp	 ~1/2 tsp	 ~2.5 tsp

LOKELMA contains approximately 400mg sodium per 5g dose, equivalent to 20% of the WHO recommended maximum daily intake for sodium. LOKELMA is considered high in sodium. This should be particularly taken into account for those on a low sodium diet.

- The average Western diet includes >3.4 g/day of sodium[4]
- Guidelines recommend daily intake in patients with CKD and HF of <2000 and 1500–3000 mg/day, respectively[5,6]

[a]Recommended daily dose during the maintenance phase;[6] [b]Typical daily dose; [c]SPS is the current standard of care within class for treating hyperkalemia;[7] however, calcium polystyrene sulfonate is another available treatment option;[8] [d]Approximately 1/3 is expected to be delivered to the body

CKD, chronic kidney disease; HF, heart failure; SPS, sodium polystyrene sulfonate

1. Stavros F, et al. *PLoS One* 2014;9:e114686; 2. UK National Institute for Health and Care Excellence. Available at: https://bnf.nice.org.uk/drug/sodium-bicarbonate.html (Accessed June 2020); 3. Sanofi-Aventis US LLC. Kayexalate US Prescribing Information 2018; 4. American Heart Association and American Stroke Association. About Sodium. Available at: https://sodiumbreakup.heart.org/how_much_sodium_should_i_eat (Accessed June 2020); 5. Kidney Disease Improving Global Outcomes CKD Work Group. *Kidney Int Suppl* 2013;3:1–150; 6. Yancy CW, et al. *J Am Coll Cardiol* 2013;62:e147–239; 7. Chaitman M, et al. *P T* 2016;41:43–50; 8. Sanofi. Resonium Calcium Prescribing Information 2018

Oral Administration

- **LOKELMA is a powder for oral suspension, available in 5 g or 10 g doses[1]**
- **Mix LOKELMA with 45 mL of water for oral administration[1]**

45 mL of water

- ✓ Tasteless and odourless[1,2]
- ✓ May be taken with many other medications and with or without food[a1]
- ✓ No special conditions for storage[1]

Ensure patients stir well and drink suspension straight away while still cloudy (powder will not dissolve). Remind patients, if powder settles, to stir again before finishing drink[1]

Please see limited drug-drug Interactions for the types of drugs that cannot be co-administered with LOKELMA.
[a]LOKELMA should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH-dependent bioavailability.
LOKELMA can be taken without spacing of dosing times with oral medications that do not exhibit pH-dependent bioavailability.
1. AstraZeneca. LOKELMA Summary of Product Characteristics, 2020. 2. Stavros F, et al. *PLoS One*. 2014;9(12):e114686.

LOKELMA summary of key characteristics

LOKELMA is indicated for the treatment of hyperkalemia in adults

	LOKELMA
MOA	Preferential K^+-binding in exchange for sodium and hydrogen[1]
Onset of action	As early as 1 hour after the first dose[2]
Efficacy data	Acute treatment and maintenance data up to 1 year[2]
Drug–drug interactions	Should be administered at least 2 hours before or 2 hour after oral medications with clinically meaningful gastric pH-dependent bioavailability[2*]
Location of K^+-binding	Throughout GI tract[2]
Tolerability	Associated with:[2] • Hypokalemia • Edema-related events

There is limited experience in patients with serum potassium concentrations greater than 6.5 mEq/L[2]
*Examples of medicines that should be administered before or after LOKELMA include azole antifungals (ketoconazole, itraconazole, and posaconazole); anti-HIV drugs (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, and rilpivirine); tyrosine kinase inhibitors (erlotinib, dasatinib, and nilotinib)
GI, gastrointestinal; MOA, mechanism of action
1. Garimella PS, Jaber BL. *Am J Kidney Dis* 2016;67:545–547; 2. AstraZeneca AB. LOKELMA EU Summary of Product Characteristics 2020

ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ

Sodium Polystyrene Sulphate (SPS)

- SPS exchanges Na+ for K+ in the GI tract, mainly in the colon.
- One gram of SPS binds 0,5-1,2 mEq of K+ in exchange for 2-3 mEq of Na+
- Each 15 gram dose contains 65,25 mmol of Na+
- Slow effect on serum K+, decrease in K+ may take 4-24 hrs
- Lack of RCT data for FDA approval back in 1958
- FDA advisory September 2009, do NOT administer SPS with sorbitol, due to risk of intestinal necrosis
- Multiple subsequent case reports of intestinal necrosis after SPS given without sorbitol
- 2017 FDA advisory due to drug interactions, advised not taking other medications within 3 hours of SPS

RAASi therapy is recommended for the management of patients with CKD

3.2 Treatment with antihypertensive drugs, including RAS inhibitors (RASi)

Recommendation 3.2.1: We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes *(1B)*.

Recommendation 3.2.2: We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes *(2C)*.

Recommendation 3.2.3: We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes *(1B)*.

KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease
VOLUME 99 | ISSUE 3S | MARCH 2021 www.kidney-international.org

RAASi therapy is recommended for the management of kidney transplant recipients

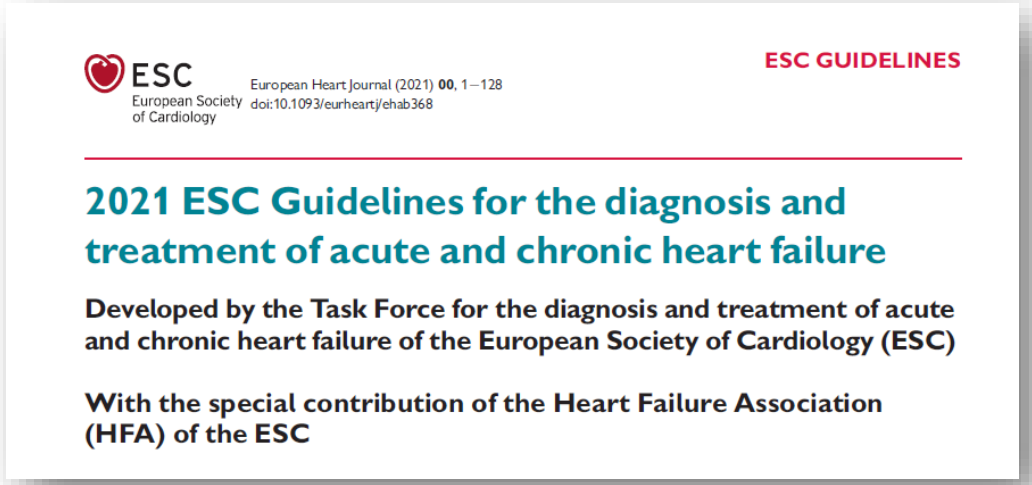
Chapter 4: Blood pressure management in kidney transplant recipients (CKD G1T–G5T)

Practice Point 4.1: Treat adult kidney transplant recipients with high BP to a target BP of <130 mm Hg systolic and <80 mm Hg diastolic using standardized office BP measurement (see Recommendation 1.1).

Recommendation 4.1: We recommend that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients *(1C)*.

KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease
VOLUME 99 | ISSUE 3S | MARCH 2021 www.kidney-international.org

Simple management of hyperkalaemia:



Optimize RAASi

K⁺ Binder K⁺>5.0

Stay on K⁺ Binder

1. *RAASi should be optimized when K^+ levels are <5.0 mEq/L; closely monitor K^+ levels*
2. *An approved K^+ lowering agent should be initiated as soon as K^+ levels are confirmed as >5.0 mEq/L*
3. *Maintain K^+ lowering agent unless alternative treatable aetiology for hyperkalaemia is identified*

- *<u>Note:</u>*
- *RAASi dose reduction or discontinuation is recommended*
- *when sK^+ is >6.5 mEq/L*