Hyperkalemia

New treatments

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Vincent Esnault – Disclosure

AstraZeneca
Bayer
BEKER
BMS-Pfizer
Boehringer-Ingelheim
ELKENDI
Lilly
MSD
Menarini
Novartis
Vifor Pharma

Hyperkaliemia – New treatments

1/ CKD

Actions to manage hyperkalemia > 5,5 mmol/L

Heart failure +/- CKD

ACEi/ARB + MRA + β-blocker + SGLT2i

↓

Review non-RAASi medications (NSAIDs, trimethoprim)

Assess dietary potassium intakes

KDIGO. Kidney Int 2024:105(Suppl 4S),S117

Potassium absorption rates

Fruits and vegetables
→ fibers slows K^+ absorption
→ sugars stimule insulin → K^+ intracellular transfer
→ alkalizing effect

Animal-based foods
→ high K^+ absorption rate
→ net acid effect: K^+ remains in serum

Processed foods
→ K^+ additives
→ particularly low-salt cure meats

Plant-based foods

Absorption rate
50%–60%

Plant-based foods may have low absorption rate, net alkalizing effect, and carbohydrate content encourages K^+ shifts into intracellular space, minimizing impacts on serum K^+

Animal-based foods

Absorption rate
70%–90%

Animal-based protein has higher absorption and net acid effect results in higher amounts of K^+ remaining in serum

Processed foods

Absorption rate
90%

Potassium salts (often found in processed foods) absorption rate has been reported to be 90%

KDIGO. Kidney Int 2024,105 (Suppl 4S):S117–S314

Actions to manage hyperkalemia > 5,5 mmol/L

Heart failure +/- CKD

ACEi/ARB + MRA + β-blocker + SGLT2i

↓

Review non-RAASi medications (NSAIDs, trimethoprim)

Assess dietary potassium intakes

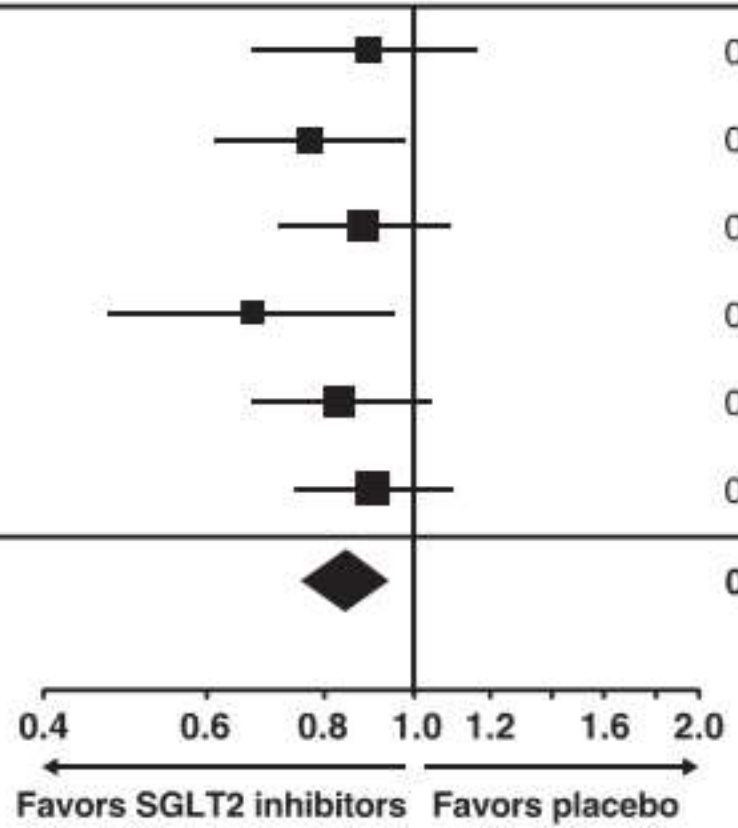
↓ Residual congestion?

+ Thiazide, Furosemide, Sacubitril

KDIGO. Kidney Int 2024:105(Suppl 4S),S117

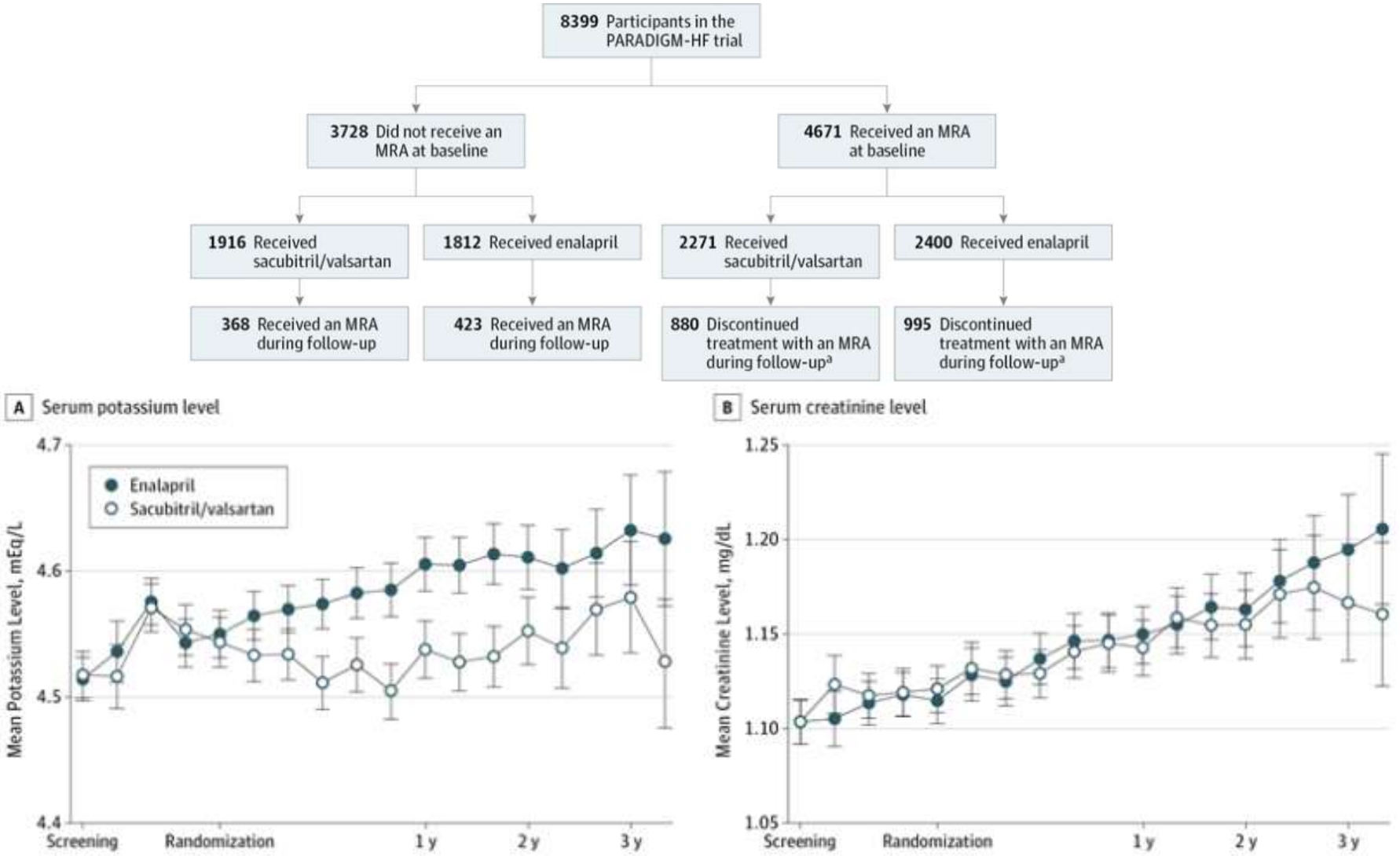
SGLT2i reduce the risk of hyperkalemia

	SGLT2 inhibitors		Placebo		Hazard Ratio (95% CI)
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	
CANVAS Program	137/5795	8.2	85/4347	9.2	0.89 (0.67, 1.17)
CREDENCE	121/2202	21.6	154/2199	27.9	0.77 (0.61, 0.98)
DAPA-CKD	159/1455	56.9	179/1451	65.3	0.88 (0.71, 1.09)
DECLARE-TIMI 58	53/8582	1.6	78/8578	2.3	0.67 (0.47, 0.95)
EMPA-REG OUTCOME	216/4687	17.2	124/2333	20.5	0.83 (0.67, 1.04)
VERTIS CV	291/5493	18.7	157/2745	21.2	0.90 (0.74, 1.09)
Overall (I^2=0.0%; $P_{heterogeneity}$=0.71)					**0.84 (0.76, 0.93)** P<0.001



Neuen. Circulation 2022,145,1460-70

Sacubitril lowers serum potassium levels



Desai. JAMA Cardiol 2017,2:79-85

Actions to manage hyperkalemia > 5,5 mmol/L

Heart failure +/- CKD

ACEi/ARB + MRA + β-blocker + SGLT2i

↓

Review non-RAASi medications (NSAIDs, trimethoprim)

Assess dietary potassium intakes

↓ Residual congestion?

+ Thiazide, Furosemide, Sacubitril

↓ Acidosis ?

+ Bicarbonate

↓ Persistent hyperkalemia?

+ K^+ binders

KDIGO. Kidney Int 2024:105(Suppl 4S),S117

Potassium binders / sodium

The data below are provided for indicative purposes only. This is not a direct clinical comparison

	Sodium Polystyrene Sulfonate	Sodium Zirconium Cyclosilicate
Selectivity	Binds K^+, Ca^{2+} et Mg^{2+}	Binds K^+
Site of K^+ exchange	Large intestine	Small and large intestine
Delay for serum K^+ decrease	Unknown	1 hour
Study length	7 days	1 year
Calcium content	0 g	0 g
Sodium content	1500 mg / 15 g measuring spoon	400 mg / 5 g sachet 800 mg / 10 g sachet
Molecular structure	Polymeric resin	Non-polymeric
Distance from other medications	≥ 3 h	≥ 2 h (if pH dependant)
Storage conditions imposed	Closed recipient	None

SZC. Summary of product characteristics. Updated January 11, 2024.; Palmer BF. kidney disease-diet, renin-angiotensin-aldosterone system inhibitor therapy, and hemodialysis. *Mayo Clin Proc.* 2020;95(2):339-354.
Stavros F, Yang A, Leon A, et al. *PLoS One.* 2014;9(12):e114686. : Packham DK, Rasmussen HS, Lavin PT, et al. *N Engl J Med.* 2015;372(3):222-231. ; Spinowitz BS, Fishbane S, Pergola PE, et al. *Clin J Am Soc Nephrol.* 2019;14(6):798-809.
Lepage L, Dufour AC, Doiron J, et al. *Clin J Am Soc Nephrol.* 2015;10(12):2136-2142.; Clegg DJ, Cody M, Palmer BF*Mayo Clin Proc.* 2017;92(8):1248-1260. ; Bakris G, Weir M, Epstein MJ *Cardiovasc Dis Diagn.* 2016;4(2):237.; Beccari MV, Meaney CJ. *Core Evid.* 2017;12:11-24.

Potassium binders / calcium

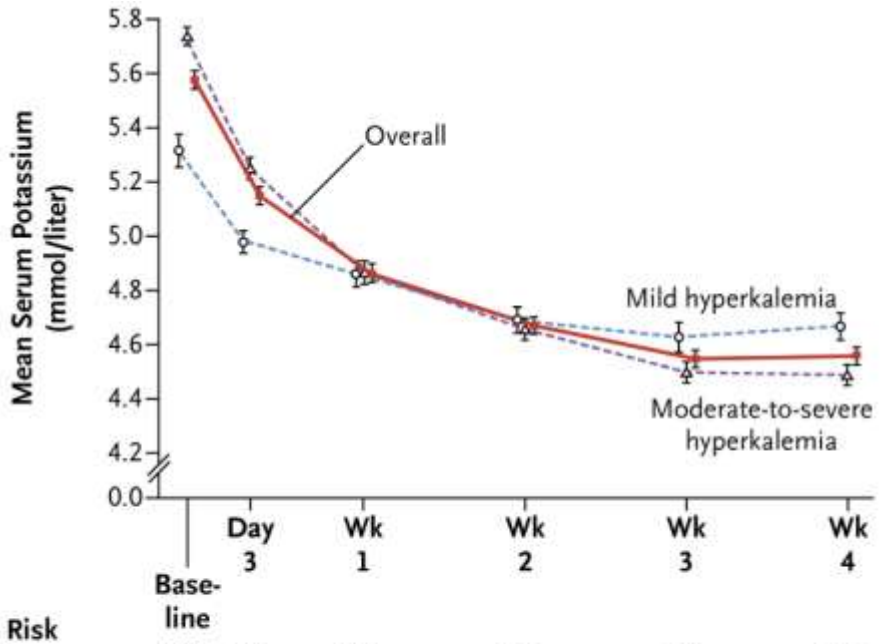
The data below are provided for indicative purposes only. This is not a direct clinical comparison

	Polystyrene Sulfonate de Calcium	Patiromer
Selectivity	Binds K^+	Binds K^+ et Mg^{2+}
Site of K^+ exchange	Large intestine	Large intestine
Delay for serum K^+ decrease	Unknown	7 hours
Study length	7 days	1 year
Calcium content	1,44 g / 20 g measuring spoon (x3)	1,6 g / 8,4 g sachet (x3)
Sodium content	0	0
Molecular structure	Polymeric resin	Polymeric resin
Distance from other medications	≥ 3 h	≥ 3 h
Storage conditions imposed	Fridge at 2-8°C	Fridge at 2-8°C

Palmer BF. *Mayo Clin Proc.* 2020;95(2):339-354. ; Resonium A. Summary of product characteristics. Sanofi; January 2024.; Pitt B, Bakris GL. *Hypertension.* 2015;66(4):731-738. ; Veltassa. Summary of product characteristics. Vifor France, Inc; January 2024. Clegg DJ, Cody M, Palmer BF. *Mayo Clin Proc.* 2017;92(8):1248-1260. ; Bakris G, Weir M, Epstein M. *J Cardiovasc Dis Diagn.* 2016;4(2):237.; Beccari MV, Meaney CJ. *Core Evid.* 2017;12:11-24.; Li L, Harrison SD, Cope MJ, et al. *J Cardiovasc Pharmacol Ther.* 2016;21(5):456-465.

Patiromer : efficacy in CKD

OPAL-HK, phase 3,
243 CKD stage 3-4 treated with SRAAi, kalemia 5,1-6,5 mmol/L
run-in patiromer 4 weeks 1 - 2 sachets per day (8,4 - 16,8 g/day)
→ at W4 if K 3,8-5 mmol/L randomized to stop patiromer for 8 weeks
→ 24% excluded for ineffectiveness

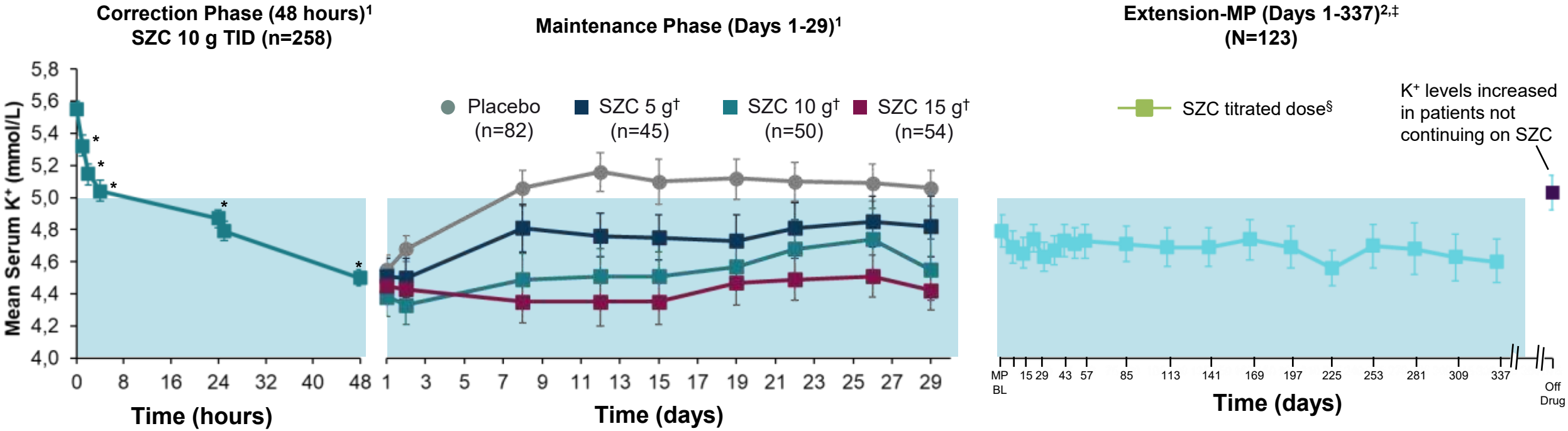


No. at Risk						
Overall	243	217	237	228	221	219
Mild hyperkalemia	92	80	90	87	85	85
Moderate-to-severe hyperkalemia	151	137	147	141	136	134

Weir. NEJM 2015,374,211-221

SZC : efficacy in CKD

HARMONIZE (ZS-004), phase 3, open-label
251 CKD with kalemia > 5 mmol/L (43% 5-5,5, 46% 5,5-6, 11% 6-6,5 mmol/L), 70% SRAAi
→ SZC 10gx3 /jday during 48h → PBO ou SZC 5-15gx1/day during 28 days → SZC 5-10gx1/day during 12 months



K⁺ ≤ 5 mmol/L: 84% at H24 and 98% at H48

92,8% adjusted mean K+ ≤ 5.1 mmol/L

Kosiborod. JAMA 2014,312,2223-33

Roger. Am J Nephrol 2019,50,473-80

Patiromer : side effects

OPAL-HK, phase 3,
243 CKD stage 3-4 treated with SRAAi, kalemia 5,1-6,5 mmol/L
run-in patiromer 4 weeks 1 - 2 sachets per day (8,4 - 16,8 g/day)
→ at W4 if K 3,8-5 mmol/L randomized to stop patiromer for 8 weeks

Table 2. Adverse Events during the Initial Treatment Phase and through the Safety Follow-up Period for That Phase.*

Adverse Event	No. of Patients (%)
≥1 Adverse event†	114 (47)
Constipation	26 (11)
Diarrhea	8 (3)
Hypomagnesemia	8 (3)
Nausea	8 (3)

Table 3. Adverse Events during the Randomized Withdrawal Phase and through the Safety Follow-up Period for That Phase.*

Adverse Event	Placebo (N=52)	Patiromer (N=55)
	no. of patients (%)	
≥1 Adverse event	26 (50)†	26 (47)
Headache	4 (8)	2 (4)
Supraventricular extrasystoles	1 (2)	2 (4)
Constipation	0	2 (4)
Diarrhea	0	2 (4)
Nausea	0	2 (4)

Weir. NEJM 2015,374,211-221

SZC: gastrointestinal side effects vs placebo

ZS-003 Correction

48h + 12 days	Placebo (N=158)	SZC 5g (N=157)	SZC 10g (N=143)
Gastrointestinal side effects	8 (5.1)	6 (3.8)	5 (3.5)

ZS-004 Maintenance

48h + 28 days	Placebo (N=85)	SZC 5g (N=45)	SZC 10g (N=51)
Gastrointestinal side effects	12 (14.1)	3 (6.7)	1 (2.0)

Sorbitol free

Oedema with SZC

258 patients, SZC 10gx3/day for 2 days (correction phase)
237 patients with K 3,5-5 mmol/L at H48
→ randomized: SZC 5 g/jour (n = 45)
SZC 10 g/jour (n = 51)
SZC 15 g/jour (n = 56)
placebo (n = 85)
→ Follow-up 28 days (double blind)

ZS-004		Placebo (N=85)	SZC 5g (N=45)	SZC 10g (N=51)	SZC 15g (N=56)
	Oedema	2,4 %	2,2 %	5,9 %	16,1 %

→ 5g sachet = 400mg Na (1g NaCl)
→ 10g sachet = 800mg Na (2g NaCl)
(NB: 15g SPS measuring spoon = 1500mg Na)

Kosiborod. JAMA 2104,312,2223-33

REALIZE-K - Tolerance

	SZC (n=101)	Placebo (n=101)
Adverse Events		
Any AE, n (%)	65 (64)	64 (63)
Any serious AE, n (%)	23 (23)	22 (22)
AEs leading to discontinuation, n (%)	6 (6)	6 (6)
Serious AEs leading to discontinuation, n (%)	3 (3)	2 (2)
Cardiac failure serious AEs, n (%)	12 (12)	4 (4)
Peripheral oedema AEs, n (%)	6 (6)	2 (2)
AE with outcome of death, n (%)	1 (1)	2 (2)
Cardiovascular death, n (%)	1 (1)	1 (1)
Hypokalemia, n (%)	7 (7)	0 (0)

Patients (%)	SZC (n=99)	Placebo (n=96)
NT-proBNP ≤4000 pg/ml at baseline	4%	1.2%
NT-proBNP >4000 pg/ml at baseline	29%	6%

SZC group: older(+ 4 years)
- 12 ml/min/1.73m2 (eGFR)

Kosiborod. REALIZE-K. J Am Coll Cardiol 2025,85,971-984

SZC and Patiromer: product specificities

The data are provided for indicative purposes only. This is not a direct clinical comparison

	Sodium Zirconium cyclosilicate	Patiromer
Correction phase (48h)	10g x 3 /day	8,4g / day (no dosing charge)
Maintenance phase	5 - 10g / day	8,4g - 16,8g / day (progressive up-titration)
Delay for serum K^+ decrease	1 hour	7 hours
Gastro-intestinal side effects	Comparable with placebo	Comparable with SPS
UE risk management plan		
Important identified risks	None	Hypomagnesemia
Important potential risks	Congestive heart failure	Increased risk of hypercalcemia Increased risk of intestinal perforation
Missing data	None	Pregnant or lactating women, Patients < 18 years old

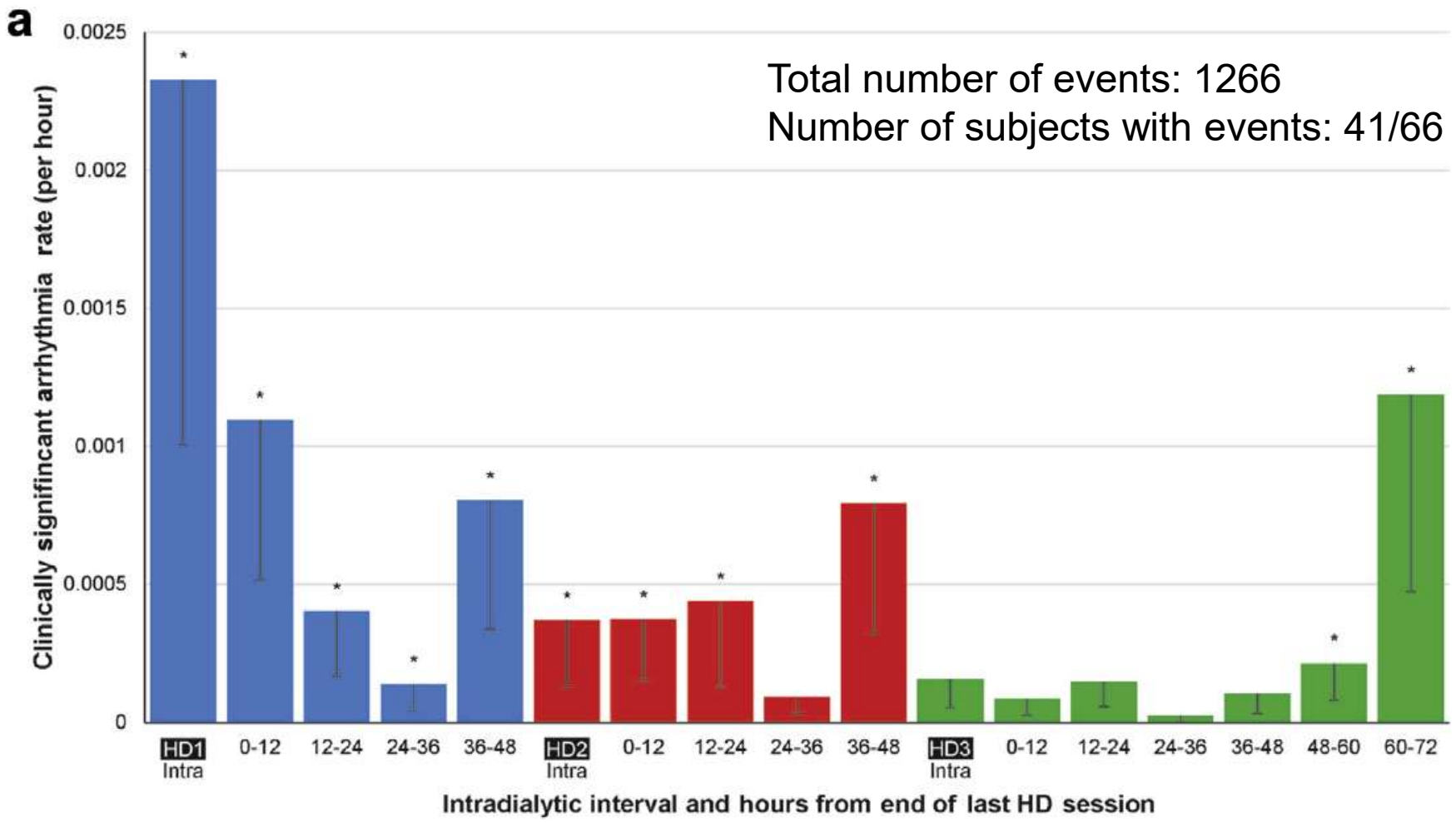
SmPC Patiromer / ZS
UE risk management plan – Patiromer / ZS

Hyperkaliemia – New treatments

1/ CKD

2/ Hemodialysis

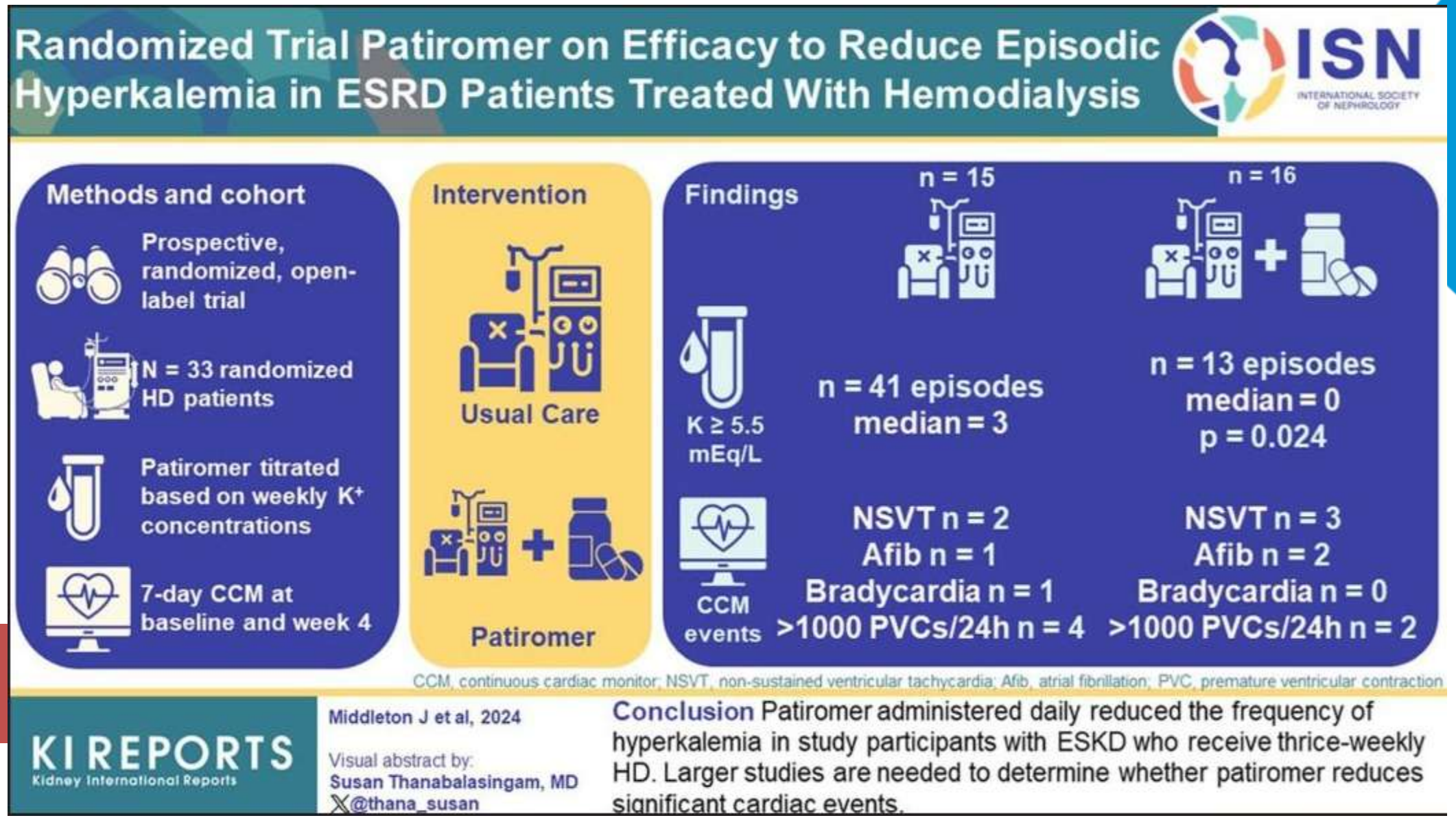
Clinically significant arrhythmias in HD



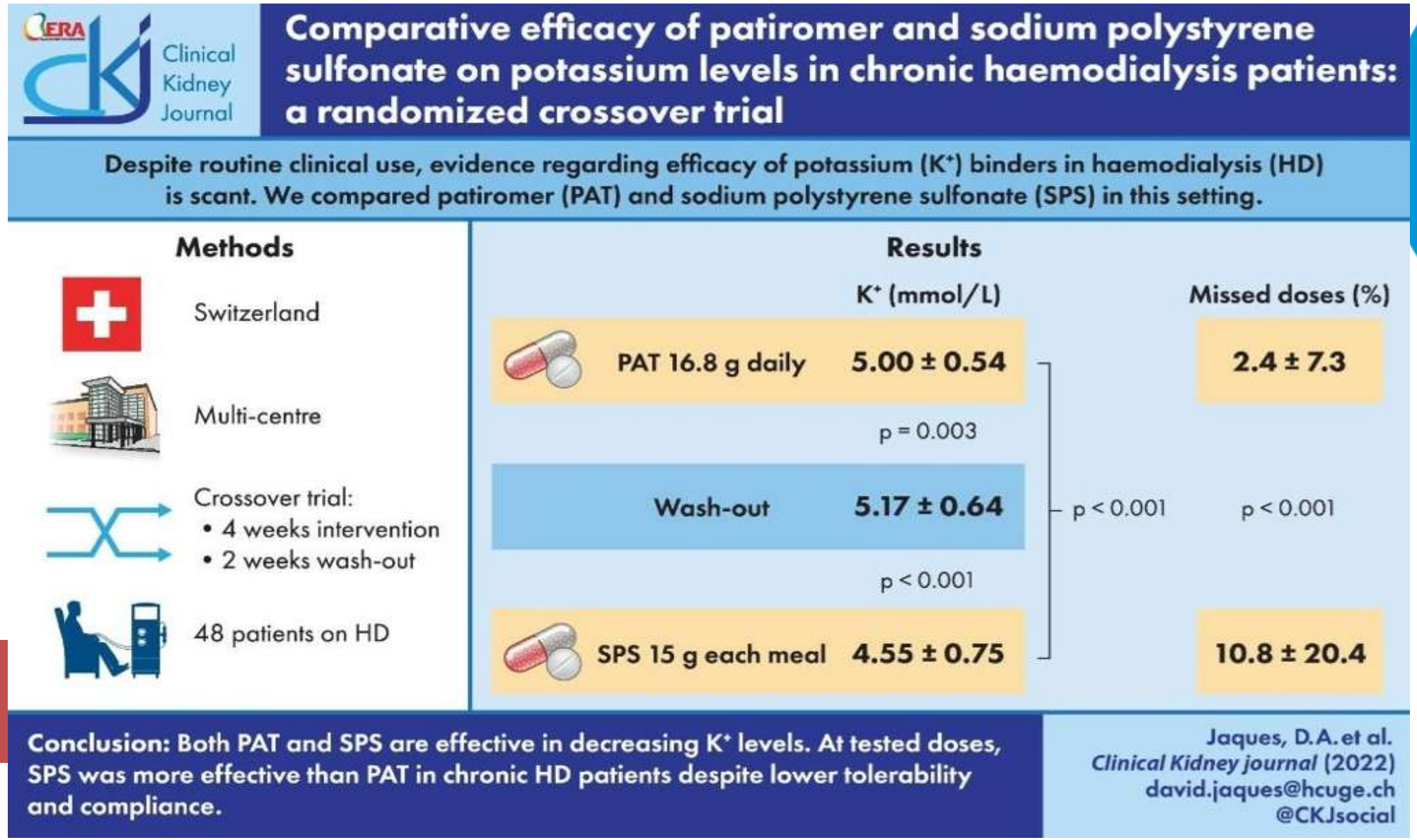
Total number of events: 1266
Number of subjects with events: 41/66 patients

Roy-Chaudhury. KI 2018,93,941-51

Patiromer: efficacy vs placebo in HD



Patiromer: efficacy vs SPS in HD



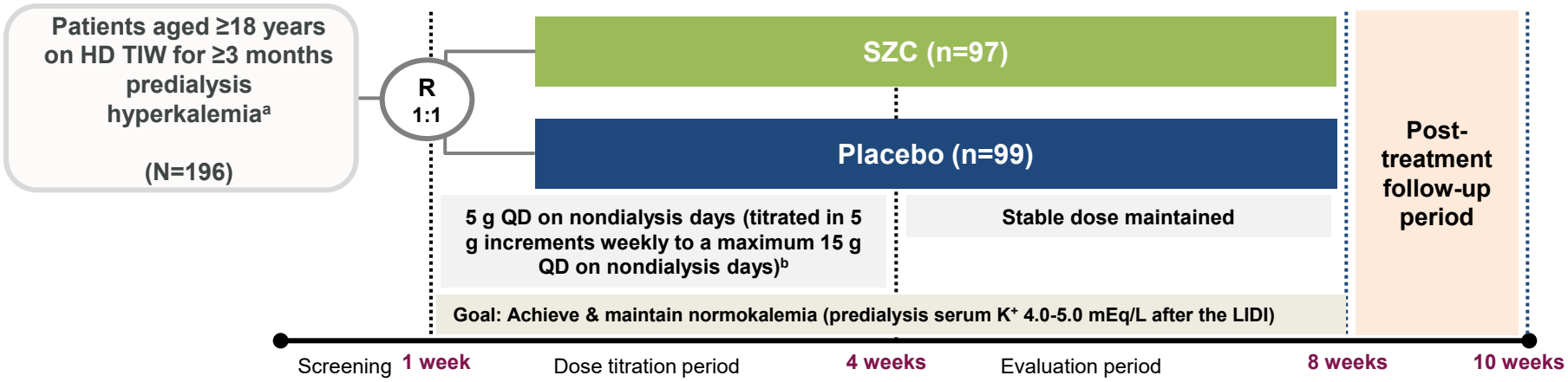
Patiromer: tolerance vs SPS in HD

	Washout	PAT	SPS
K^+ value (mmol/L)	5.17 ± 0.64	5.00 ± 0.54[a,b]	4.55 ± 0.75[a,b]
Calcium (mmol/L)	2.26 ± 0.18	2.27 ± 0.17	2.24 ± 0.19[a]
Phosphate (mmol/L)	1.64 ± 0.47	1.56 ± 0.47[a]	1.67 ± 0.43
Magnesium (mmol/L)	0.89 ± 0.13	0.86 ± 0.14[a]	0.87 ± 0.16
Missed doses (%)		2.4 ± 7.3[b]	10.8 ± 20.4[b]
Tolerability (0–10 scale)		6.9 ± 1.9[b]	6.0 ± 2.4[b]
GI side effect (study weeks), *n* (%)		35 (26.3)[c]	31 (24.6)[c]

Jaques. Clin Kidney J 2022,15,1908–1914

SZC: efficacy vs placebo in HD - methods

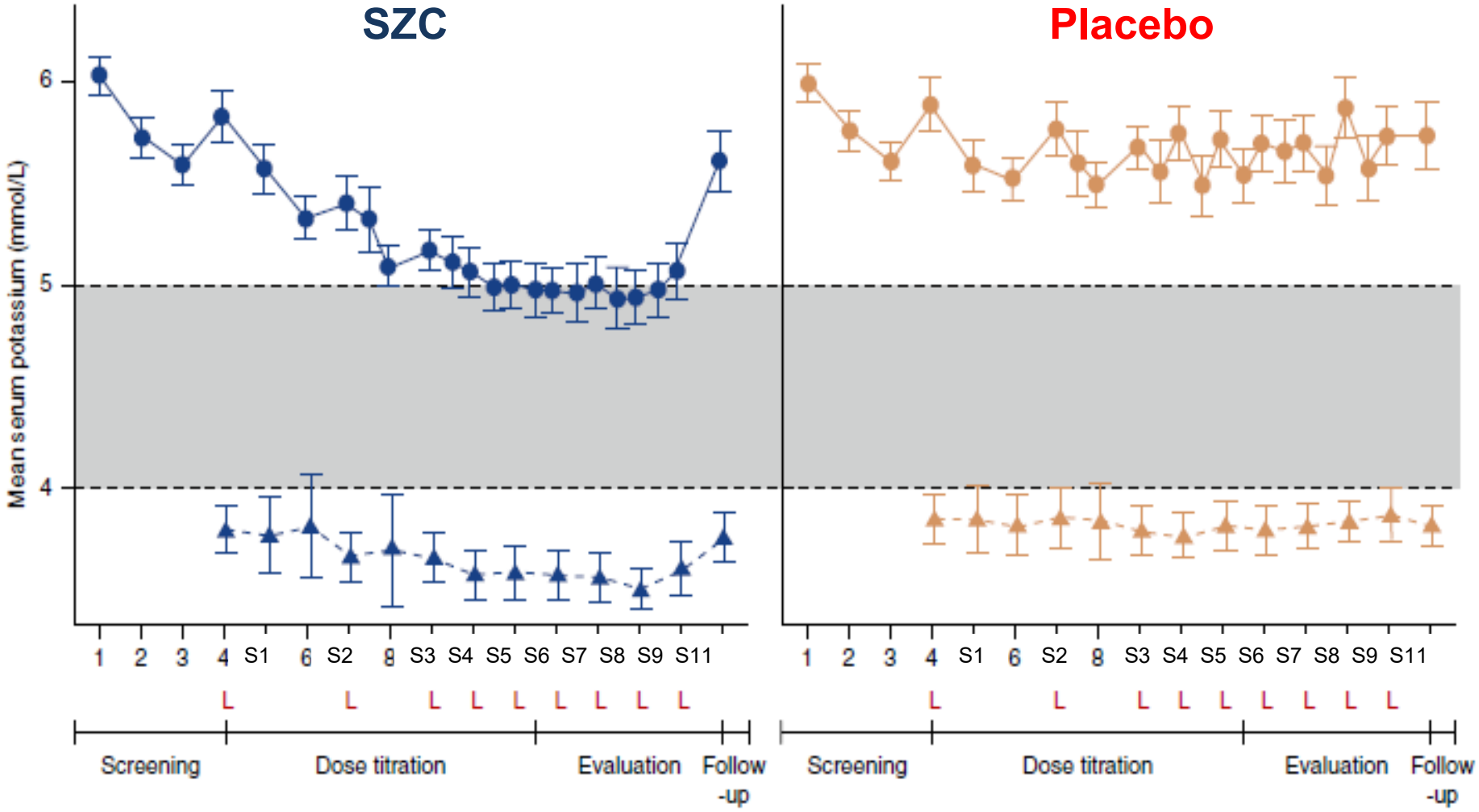
Phase IIIb, randomized, double-blind, placebo-controlled, multicenter trial
to evaluate the efficacy and safety of SZC for the treatment of hyperkalemia in ESRD patients on stable HD



- USA
- Mean age 55.7 (SZC) and 60 years (placebo)
- HD since 7.9 years
- Diabetes 34%
- 89% AVF

Fishbane. JASN 2019,30,1723–1733

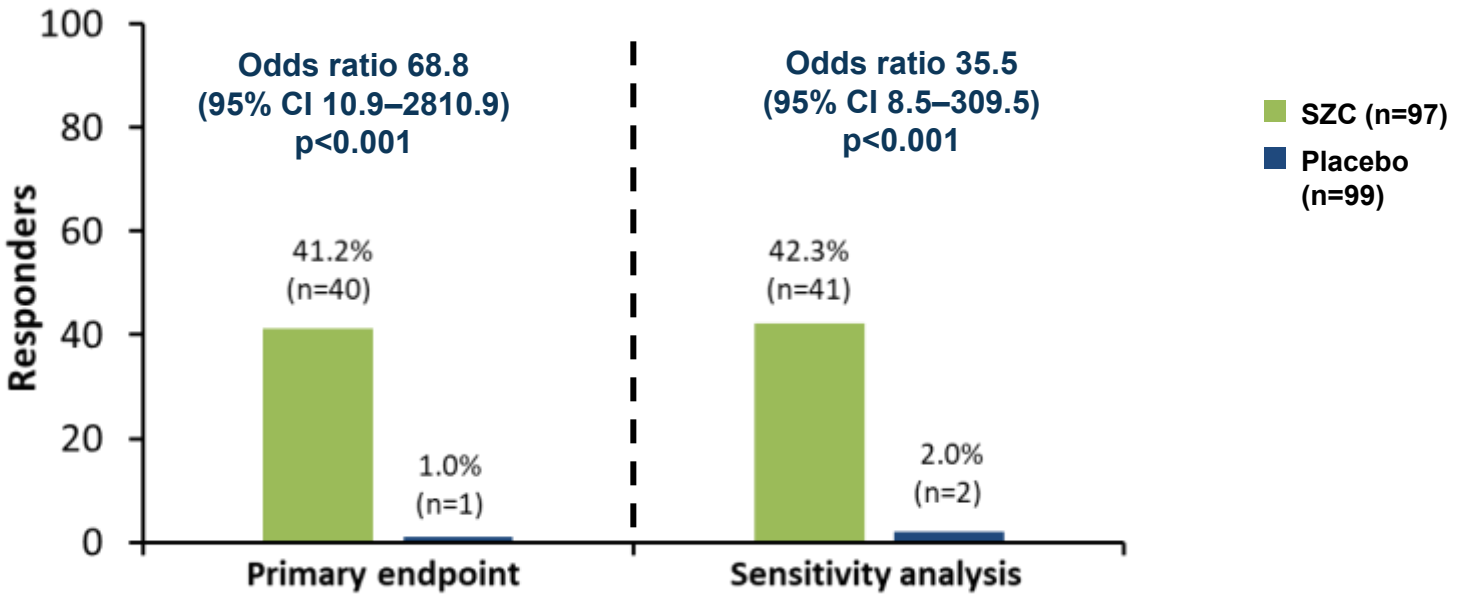
SZC: efficacy vs placebo in HD - results



Fishbane. JASN 2019,30,1723–1733

SZC vs placebo in HD
Primary efficacy endpoint

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 mEq/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.

Fishbane. JASN 2019,30,1723–1733

SZC: tolerance vs placebo in HD

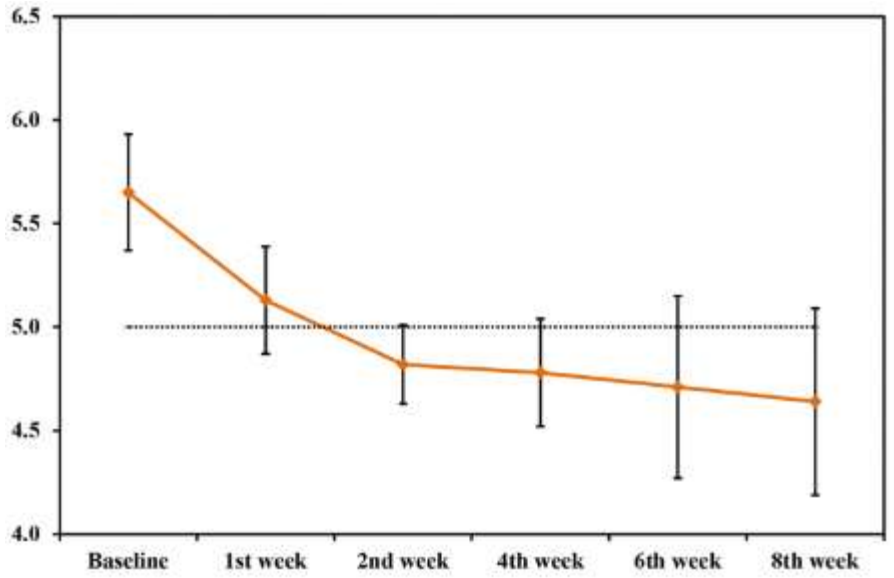
AE	No. (%) of Patients	
	SZC, *n*=97	PBO, *n*=99
Any AE	40 (41.7)	46 (46.5)
Any serious AE[a]	7 (7.3)	8 (8.1)
AE leading to discontinuation of treatment	4 (4.2)	2 (2.0)
Death	1 (1.0)	0 (0.0)
AEs in >2% patients		
Constipation	4 (4.2)	3 (3.0)
Diarrhea	4 (4.2)	6 (6.1)
Headache	3 (3.1)	2 (2.0)
Nasopharyngitis	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)

Fishbane. JASN 2019,30,1723–1733

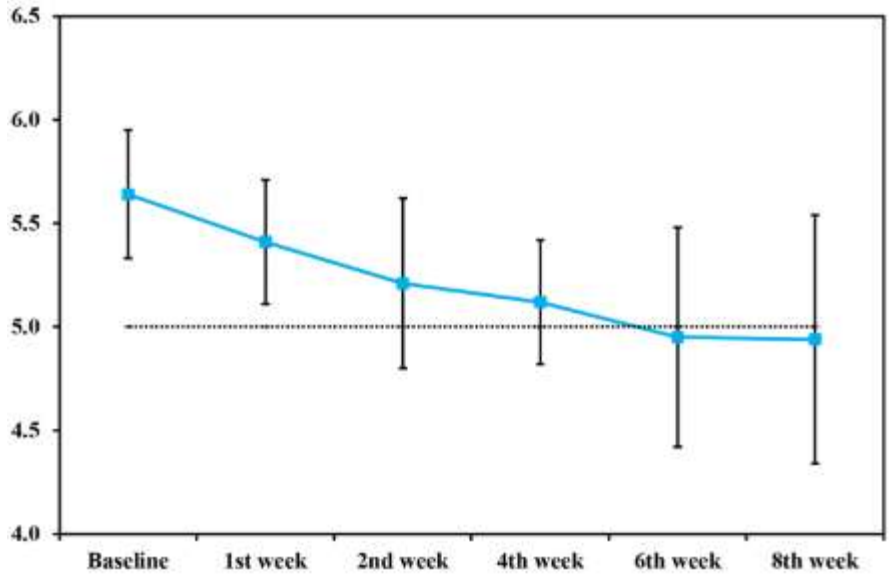
SZC: efficacy vs SPS in HD

Prospective, double-blinded, randomized multicenter clinical trial
120 HD patients with predialysis serum potassium > 5 mmol/L after the long interdialytic interval
→ randomized to SZC (5 g, 3 times/wk on non-dialysis days, 15 gm/wk)
or SPS (15 g, 3 times/wk on non-dialysis days, 45 gm/wk) for 8 weeks.
→ primary outcome: change in serum potassium through the 8 weeks of the study

Mean serum K+ (95% CI) after long interdialytic interval (mmoml/L)



SZC



SPS

Elsayed. BMC Nephrol 2025,26:227

SZC: tolerance vs SPS in HD

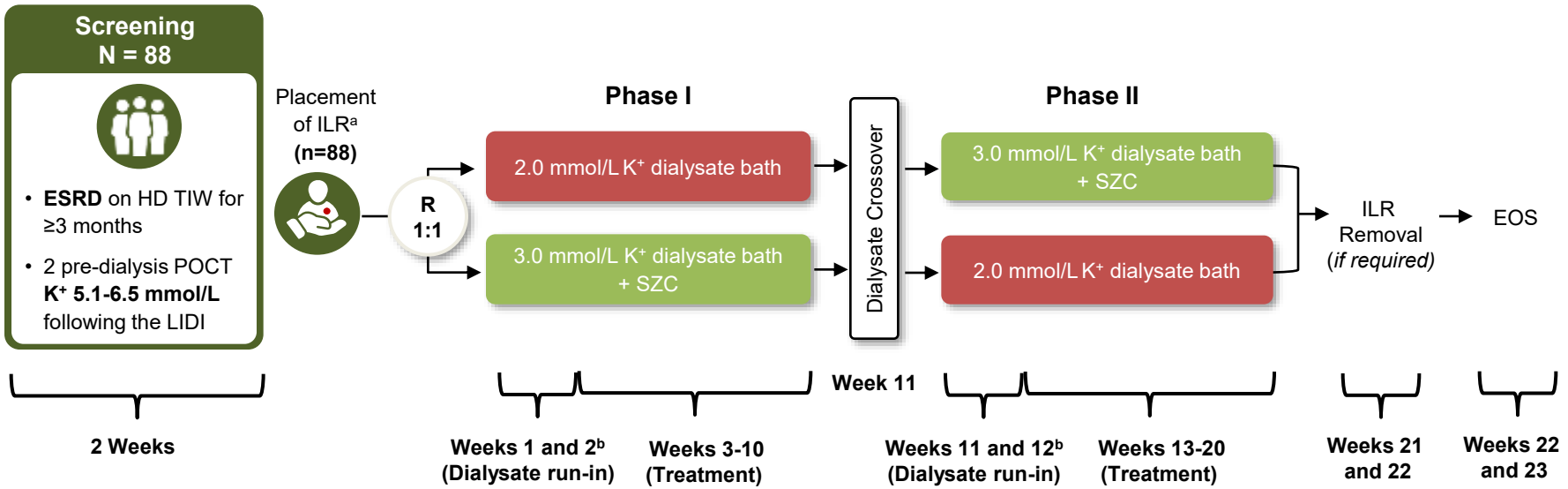
Prospective, double-blinded, randomized multicenter clinical trial
120 HD patients with predialysis serum potassium > 5 mmol/L after the long interdialytic interval
→ randomized to SZC (5 g, 3 times/wk on non-dialysis days, 15 gm/wk)
or SPS (15 g, 3 times/wk on non-dialysis days, 45 gm/wk) for 8 weeks.

	SZC group (n = 60)	SPS group (n = 60)	Comparison bet. groups *p*
Serious AE	2 (3.3%)	3 (5%)	1.000
AE causing drug discontinuation	0	1 (1.6%)	1.000
GIT AEs			
- Diarrhea	1 (1.6%)	2 (3.3%)	1.000
- Constipation	2 (3.3%)	3 (5%)	1.000
- Nausea	0 (0.0)	2 (3.3%)	0.495
Headache	1 (1.6%)	1 (1.6%)	1.000
Hypokalemia	0	0	-
Poor palatability	2 (3.3%)	17 (28.3%)	< 0.001*

Elsayed. BMC Nephrol 2025,26:227

ADAPT: methods

Prospective, open-label, randomized, cross-over, phase IV study sponsored by AstraZeneca
→ compare SZC + 3 mmol/L K^+ versus 2 mmol/L K^+ dialysate bath
→ 88 adult HD patients
→ to reduce the incidence of post-dialysis atrial fibrillation and other clinically significant cardiac arrhythmias



[a]Subcutaneous recorder with left parasternal border for continuous cardiac monitoring and placed using local anesthesia on a non-dialysis day;

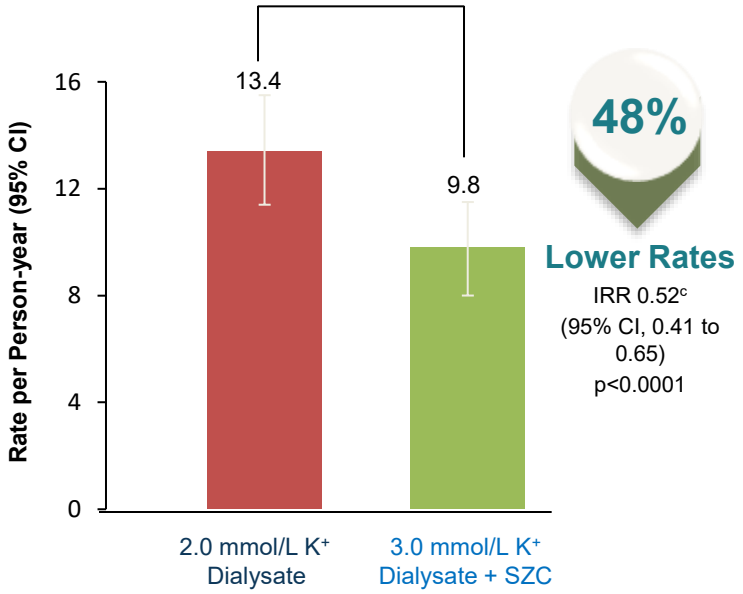
[b]To allow dialysate and SZC equilibration with SZC starting dose of 5 g (4 days per week) on non-dialysis days (uptitrated weekly in 5 g increments up to 15 g to maintain serum K^+ 4.0-5.5 mmol/L).

EOS = end of study; ESRD = end-stage renal disease; HD = hemodialysis; **ILR = implantable loop recorder; LIDI = long interdialytic interval; POCT = point of care testing;** R = randomization; SZC = sodium zirconium cyclosilicate; TIW = three times a week.

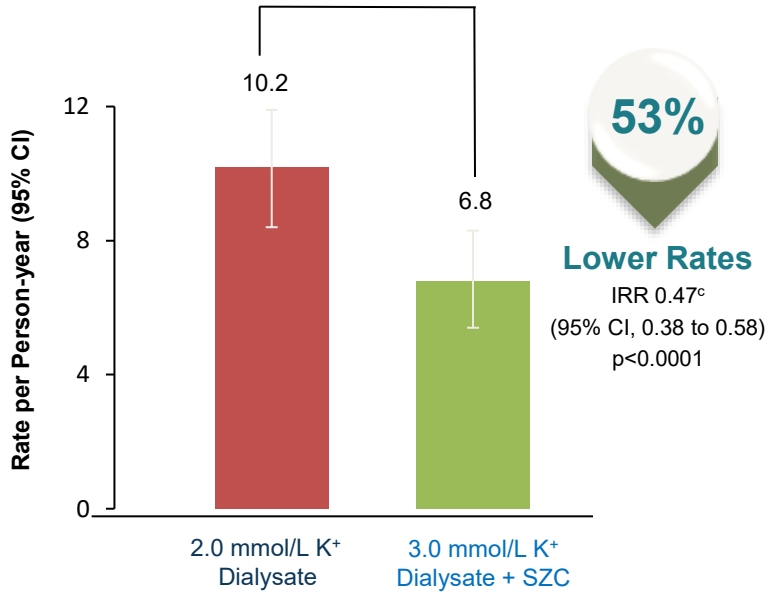
Charytan. Kidney Int 2025,107,169–179

ADAPT: results

AF Rate[a] (Primary Endpoint): for ≥2 minutes



CSCA Rate[b] (First Secondary Efficacy Endpoint): asystole (≥3 seconds), bradycardia (≤40 bpm ≥6 seconds), supraventricular and ventricular tachycardia (≥130 bpm ≥30 seconds each)



[a]Overall 296 AF episodes (n=9) were recorded, of which, 123 events were in 6 participants on 3.0 mmol/L K^+ dialysate and SZC and 173 events were in 7 participants on 2.0 mmol/L K^+ dialysate;

[b]Overall 217 CSCA events were recorded, of which, 86 events were in 11 participants on 3.0 mmol/L K^+ dialysate and SZC and 131 events in 13 patients on 2.0 mmol/L K^+ dialysate

Charytan. Kidney Int 2025,107,169–179

Hyperkalemia – new treatments

1/ Actions to manage hyperkalemia > 5,5 mmol/L

- Review non-RAASi medications (NSAIDs, trimethoprim)
- Assess dietary potassium intakes: processed foods and animal-based food
- Control residual congestion: SGLT2i, thiazide, furosémide, sacubitril
- Control acidosis: Na bicarbonate
- K^+ binders

2/ Control HK during hemodialysis to prevent cardiac arrhythmias

- Predialysis serum potassium target after long interdialytic interval: 4-5,5 mmol/L
- K^+ dialysate bath 3 mmol/L with K^+ binders

Hyperkalemia – new treatments

3/ SZC :

Median time for K+ < 5 mmol/L = 2,2 h
and 98% success after 48h correction phase
Gastro-intestinal side effects comparable with placebo (it is not a resin)
Increase diuretic dosage in patients with HFrEF
No storage condition imposed

4/ Patiromer

Median time for K+ < 5 mmol/L > 3 days
Gastro-intestinal side effects comparable with SPS (it is a resin)
Important identified risk of hypomagnesemia
Excluded in patients taking calcium salt,
or with history of hypercalcemia,
or severe gastrointestinal disorders
Store in a fridge at 4-8°C: must be used within 6 months after being removed from refrigeration