UKS
Universitätsklinikum
des Saarlandes

Hyperkaliämie – neue Therapieoptionen

Inzidenz einer Hyperkaliämie

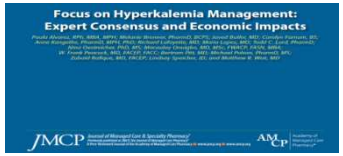


TABLE 2 2014 National Statistics. Principal Diagnosis Only: Outcomes by ICD-9-CM Code 276.7, Hyperpotassemia[8]

	276.7 Hyperpotassemia	Standard Errors
Total number of discharges	40,380	989
LOS, days (mean)	3.3	0.072
LOS, days (median)	2.0	N/A
Charges, $ (mean)	29,181	789
Charges, $ (median)	17,411	N/A
Costs, $ (mean)	7,472	178
Costs, $ (median)	4,863	N/A
Aggregate costs, $	302,665,865	8,478,278
Aggregate charges, $ (the "national bill")	1,181,305,044	36,352,360
In-hospital deaths, n (%)	615 (1.52)	57 (0.14)
Routine discharge, n (%)	27,335 (67.69)	853 (0.74)
Another short-term hospital, n (%)	335 (0.83)	42 (0.10)
Another institution (nursing home, rehab), n (%)	5,960 (14.76)	193 (0.49)
Home health care, n (%)	4,655 (11.53)	177 (0.43)
Against medical advice, n (%)	1,440 (3.57)	99 (0.22)
Missing discharge status, n (%)	a	a

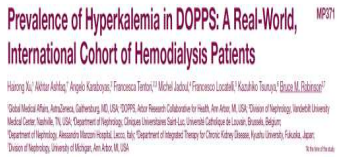
NEDS **Nationwide Emergency Department Sample**

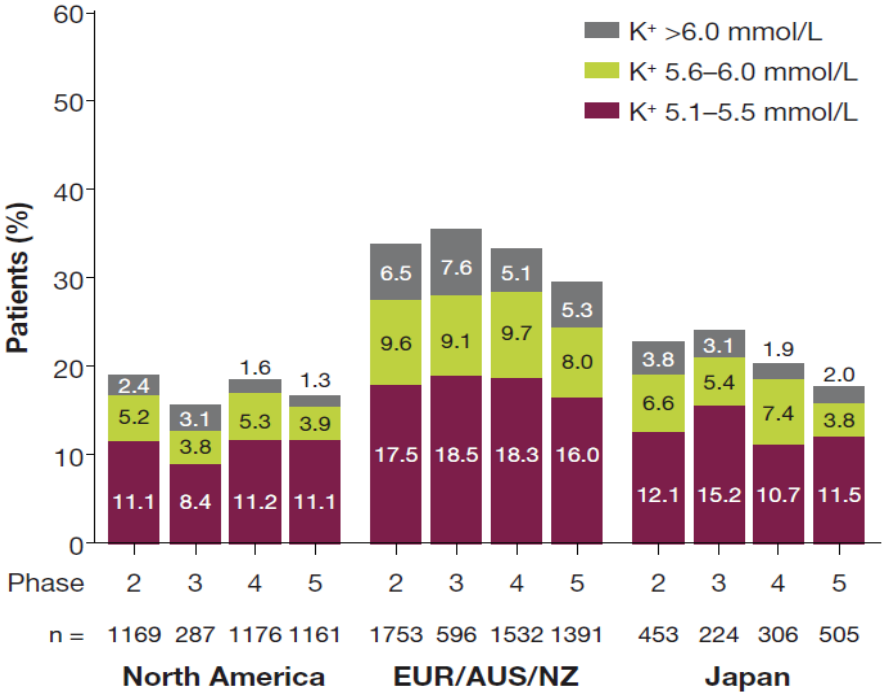
NIS **National Inpatient Sample**

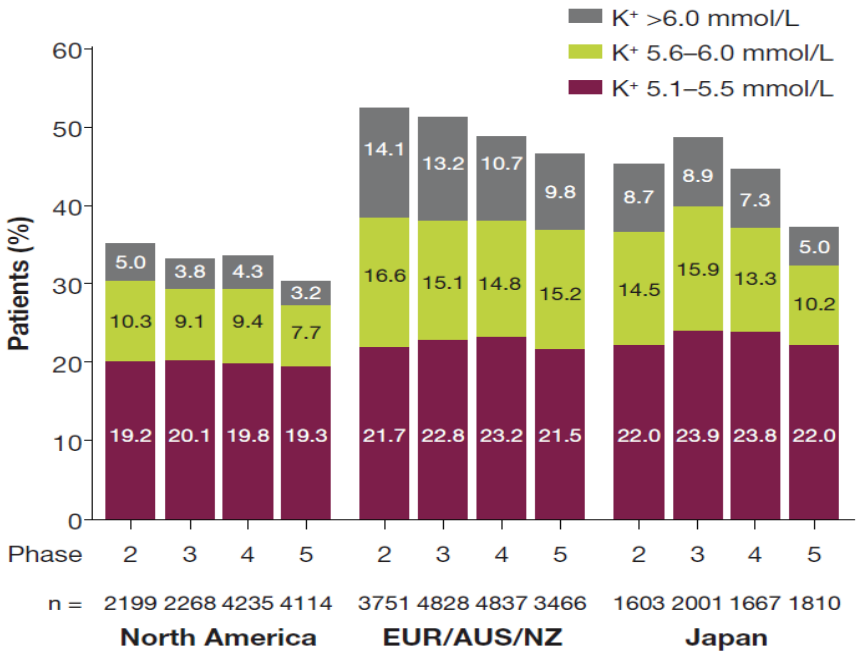
Focus on hyperkalemia management: expert consensus and economic impacts
(3 nephrologists, 2 cardiologists, 2 emergency medicine physicians)

Alvarez et al. ***J Managed Care Pharm*** 2017

Prävalenz einer Hyperkaliämie bei HD


Prevalence of Hyperkalemia in DOPPS: A Real-World, International Cohort of Hemodialysis Patients





Patienten <120 Tage an HD

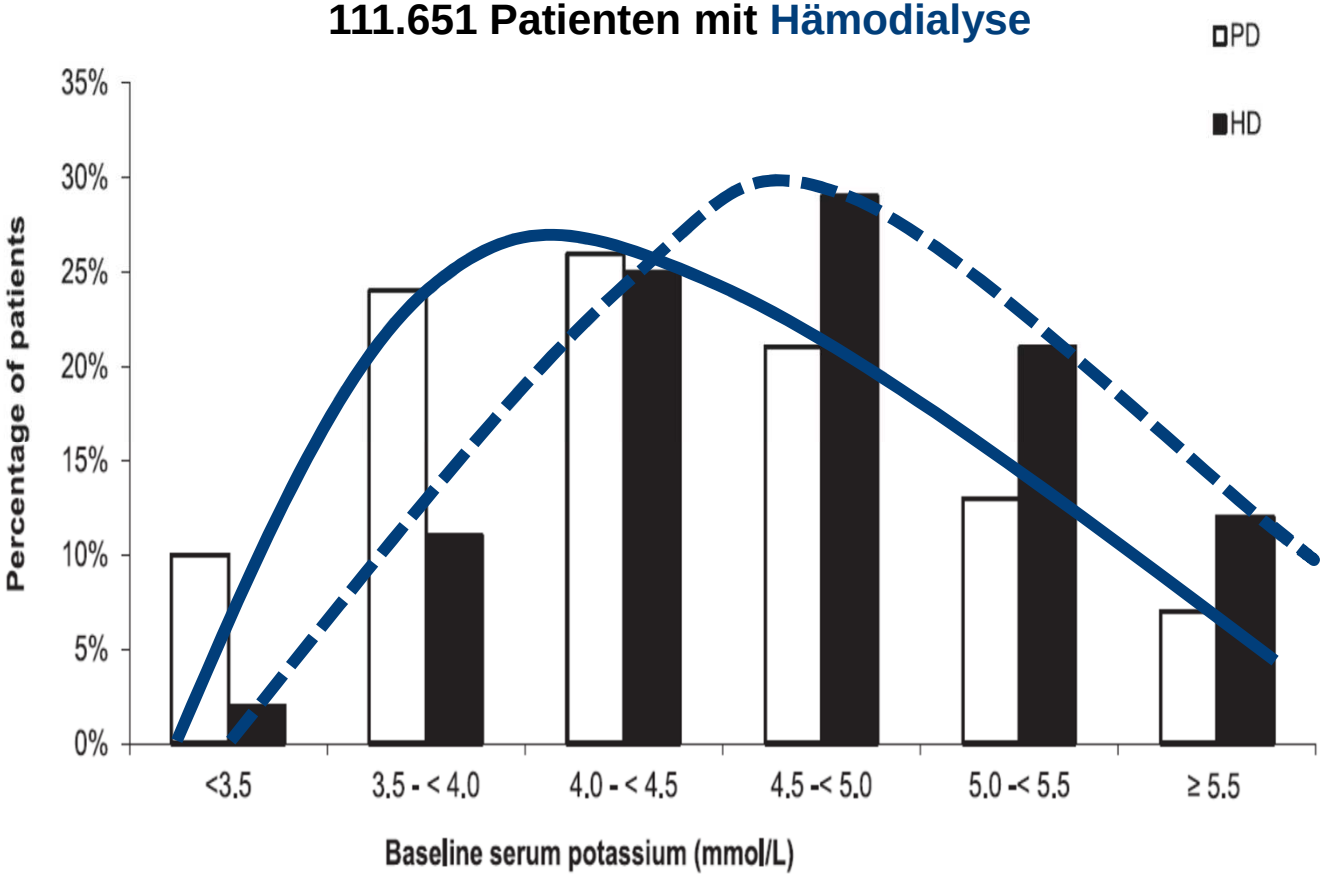
Patienten >120 Tage an HD

Kalium bei HD und PD

Article

Serum Potassium and Cause-Specific Mortality in a Large Peritoneal Dialysis Cohort

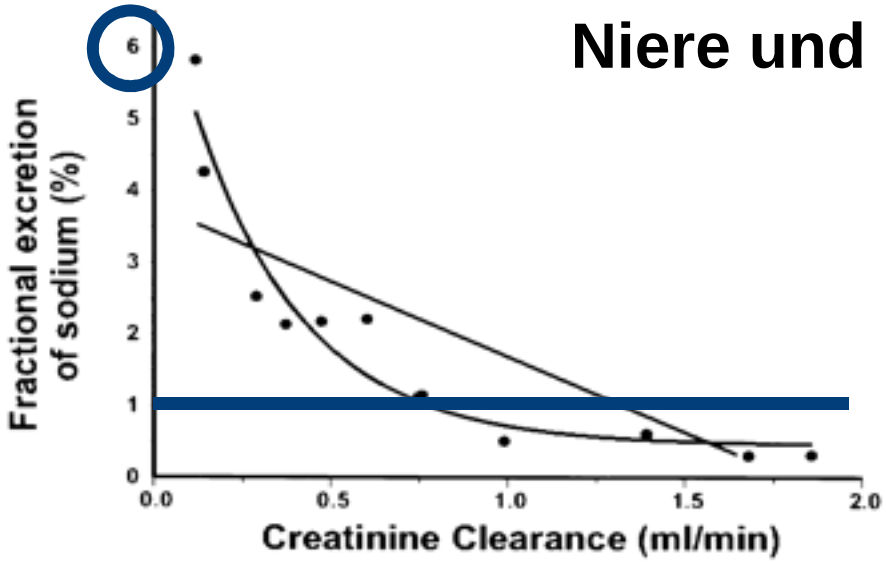
10.468 Patienten mit Peritonealdialyse
111.651 Patienten mit Hämodialyse



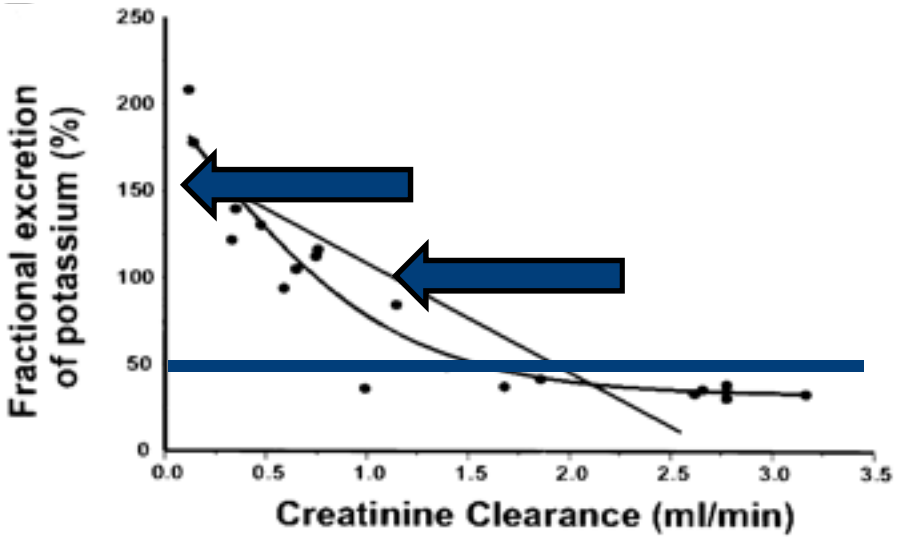
Niere und Kalium

Altered expression of Na transporters NHE-3, NaPi-II, Na-K-ATPase, BSC-1, and TSC in CRF rat kidneys

TAE-HWAN KWON,[1] JØRGEN FRØKIAER,[2] PATRICIA FERNÁNDEZ-LLAMA,[3] ARVID B. MAUNSBACH,[1] MARK A. KNEPPER,[3] AND SØREN NIELSEN[2]
[1]Department of Cell Biology, Institute of Anatomy, University of Aarhus, [2]Department of Clinical Physiology, Aarhus University Hospital and Institute of Experimental Clinical Research, DK-8000 Aarhus, Denmark; and [3]Laboratory of Kidney and Electrolyte Metabolism, National Heart, Lung and Blood Institute, Bethesda, Maryland 20892-1603



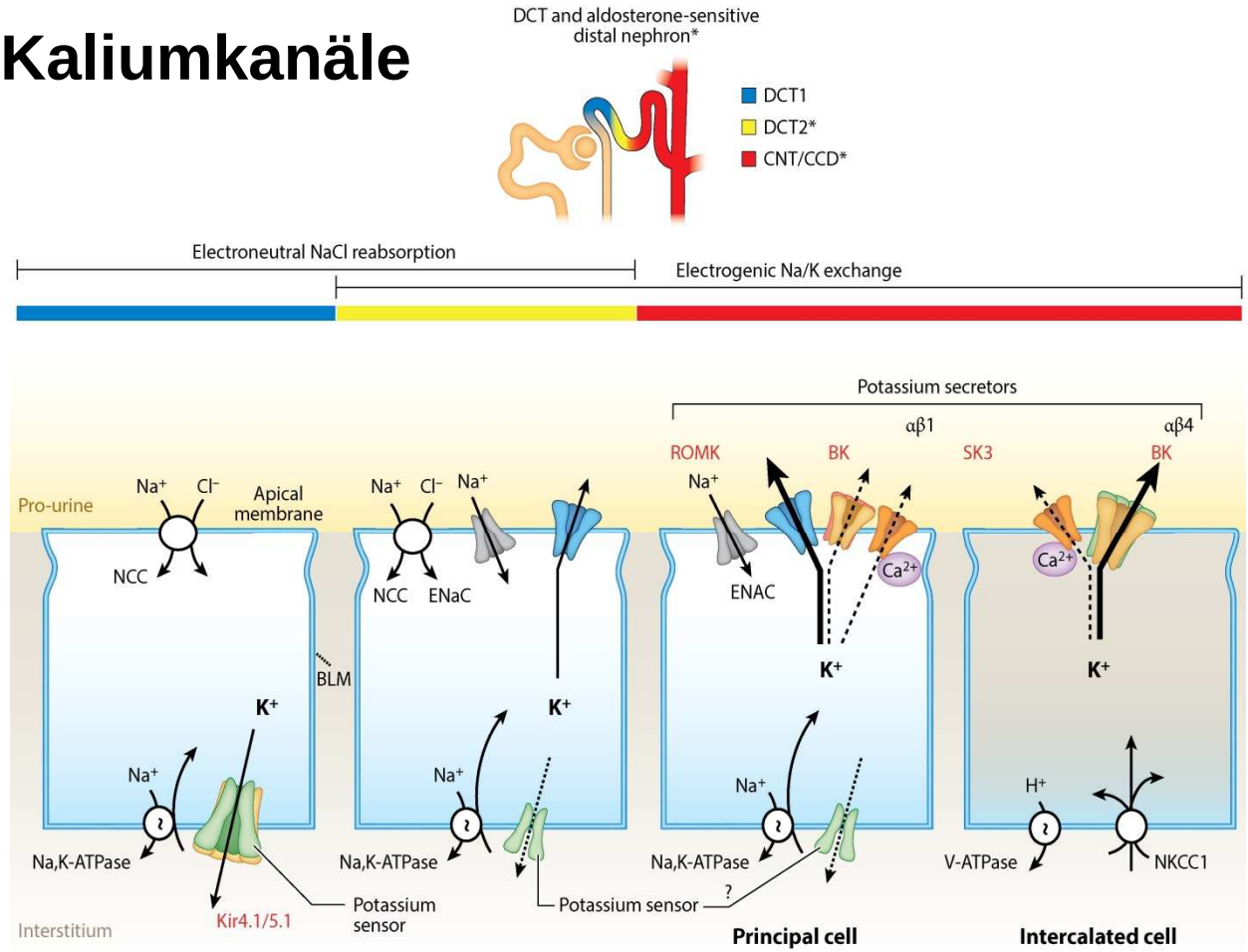
Fraktionelle Natriumausscheidung im 5/6 Nephrektomiemodell der Ratte

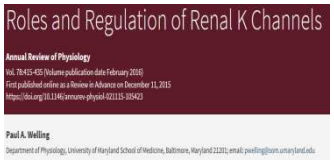


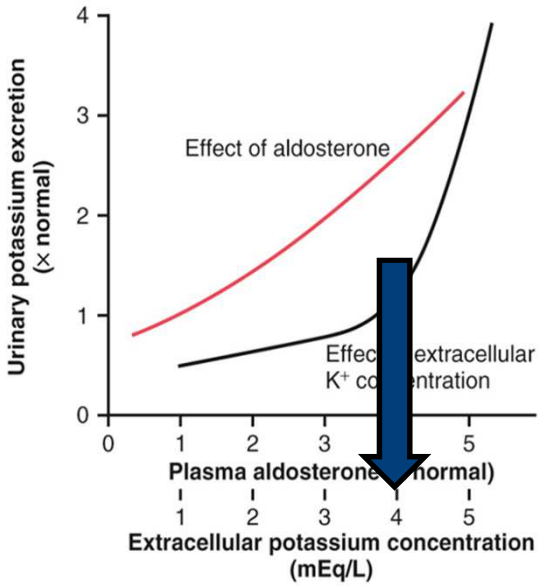
Fraktionelle Kaliumausscheidung im 5/6 Nephrektomiemodell der Ratte

Kwon et al. ***Am J Physiol – Renal Physiol*** 1999

Kaliumkanäle







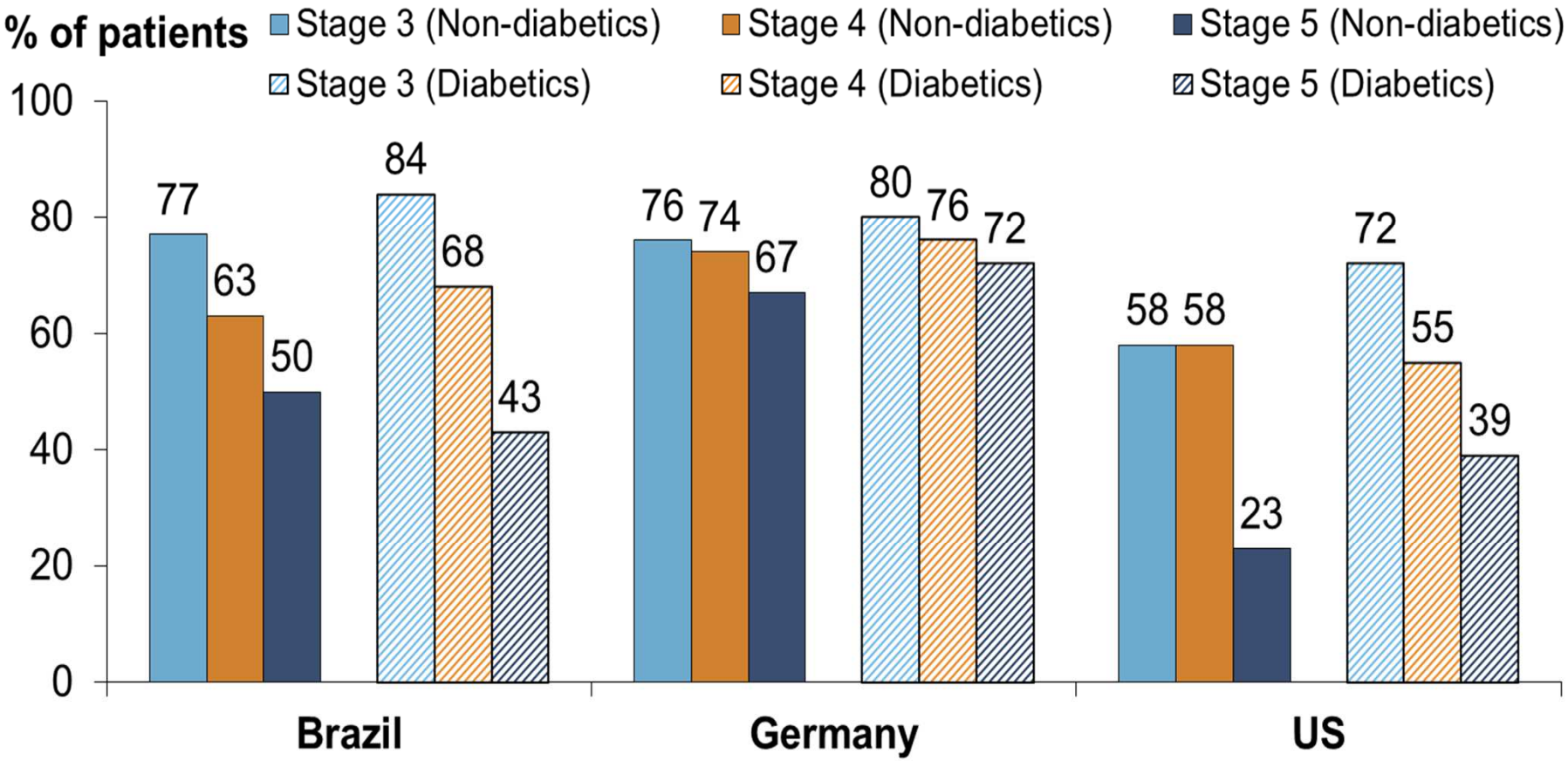
ROMK renal outer medullary potassium channels
BK big-conductance potassium channels
SK3 small-conductance potassium channels

CKD PPS

The Chronic Kidney Disease Outcomes and Practice Patterns Study

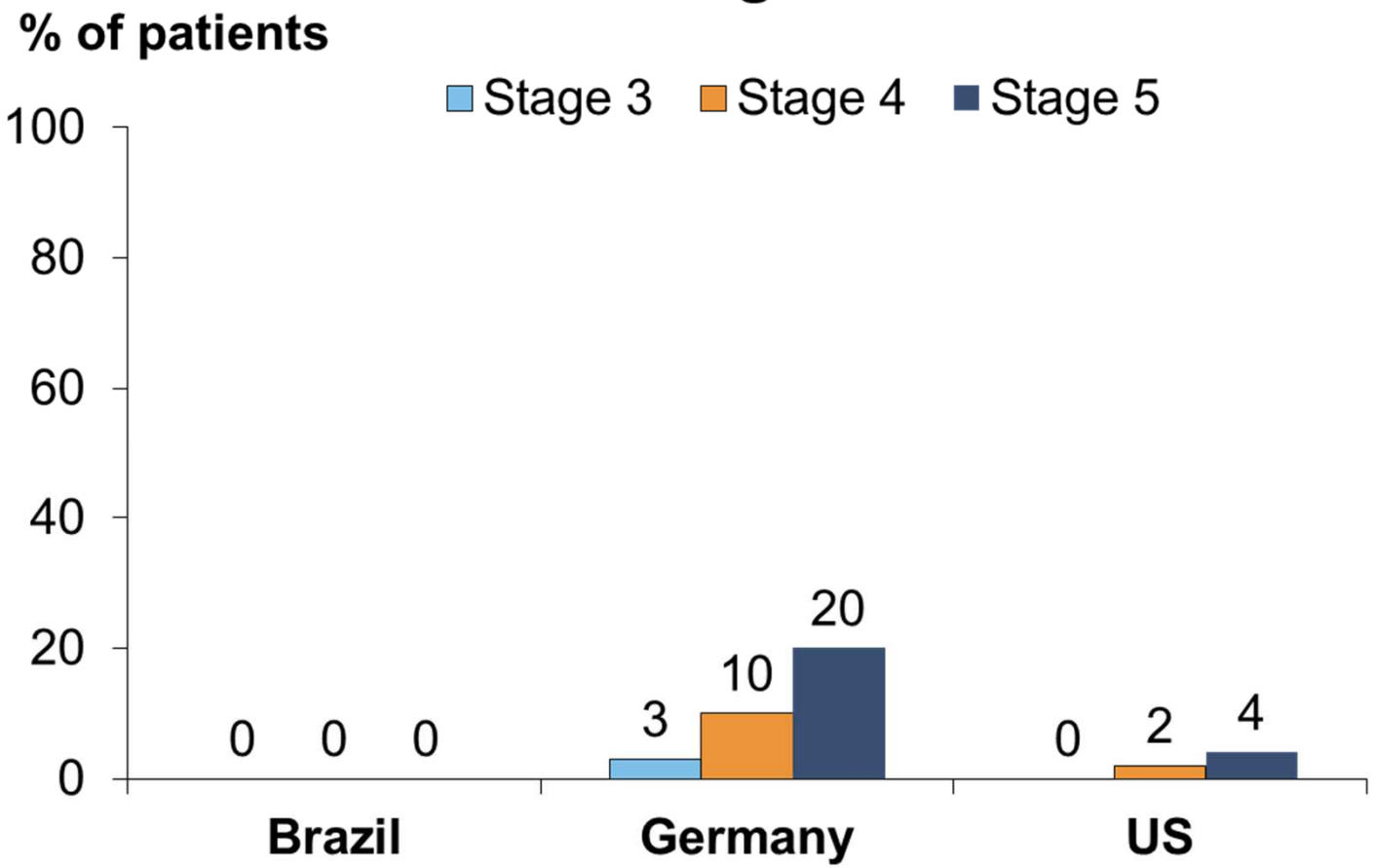
International prospective cohort study with CKD patients **(eGFR <60 mL/min/1.73m²)** followed through the dialysis transition period; **5,959** patients enrolled between 2013 and 2016

RAASi*



* Includes ACEi (Angiotensin converting enzyme inhibitor) or ARB (Angiotensin II receptor blocker), direct renin inhibitors, and aldosterone receptor antagonists

K-binding resins‡



‡Na-based (e.g. Kayexalate) or Ca-based (e.g. Calcium Resonium)

Therapie der Hyperkaliämie

Core Evidence
Dovepress
REVIEW

Clinical utility of patiromer, sodium zirconium cyclosilicate, and sodium polystyrene sulfonate for the treatment of hyperkalemia: an evidence-based review

Pharmacologic property	Sodium polystyrene sulfonate (SPS)[11]	Patiromer calcium sorbitex[20–22]	Sodium zirconium cyclosilicate[18,23–25]
Brand name	Kayexalate	Veltassa	None (not FDA-approved)
Mechanism of action	Binds potassium in the gastrointestinal tract and facilitates excretion in the feces	Binds potassium in the gastrointestinal tract and facilitates excretion in the feces	Binds potassium in the gastrointestinal tract and facilitates excretion in the feces
Selectivity for potassium ion	Nonselective; also binds calcium and magnesium	Selective; also binds magnesium	Highly selective; nine times the potassium-binding capacity compared to SPS; also binds ammonium
Sodium content	1,500 mg sodium per 15 g dose	No sodium content	Approximately 1,000 mg sodium per 10 g dose
Sorbitol content	20 g sorbitol per 15 g dose	4 g sorbitol per 8.4 g dose	No sorbitol content
Onset of effect	Variable; 2–6 hours	7–48 hours	1–6 hours
Duration of effect	Variable; 6–24 hours	12–24 hours	Unclear; appears to be 4–12 hours based on trial data
Dosing	15 g PO one to four times per day	8.4 g PO once daily with a meal; titrated to 25.2 g/day based on response	10 g PO three times daily with meals for acute treatment; 5, 10, or 15 g PO once daily with breakfast for chronic treatment (not approved; based on trial data)
Preparation(s)/ administration	Liquid or powder for suspension; mix with water (3–4 mL per g of drug) and administer within 24 hours	Powder for suspension; mix with water (90 mL) and administer immediately; store in refrigerator (36–46°F or 2–8°C); use within 3 months upon removal from refrigerator	White, tasteless powder for suspension; mix vigorously with water (240 mL) and administer immediately

Beccary & Meanay. ***Core Evidence*** 2017

Resonium A (Natrium Polystyrensulfonat)

DANGERS OF RESONIUM A IN THE TREATMENT OF HYPERKALÆMIA IN RENAL FAILURE

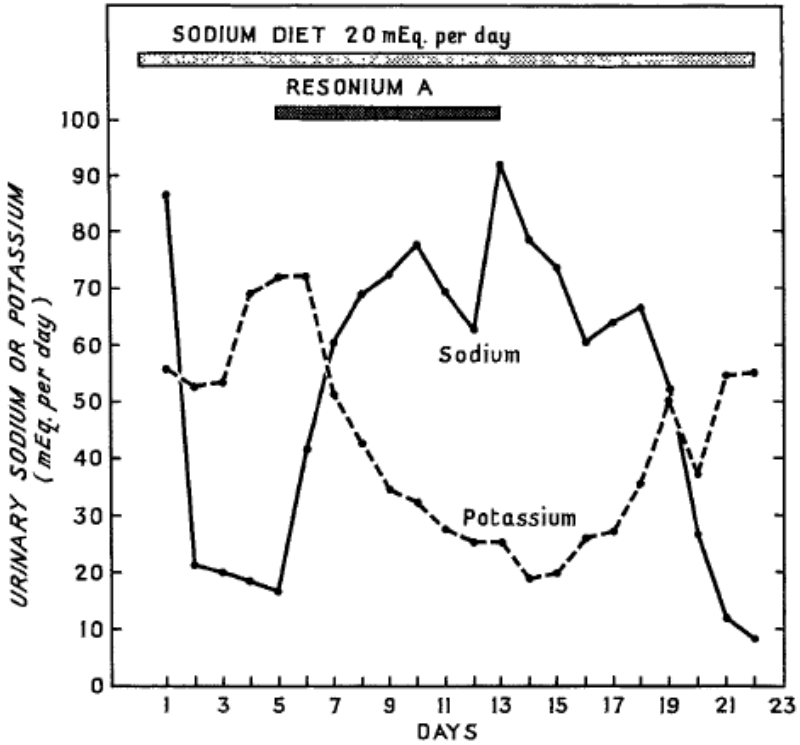
G. M. BERLYNE
M.B. Manc., M.R.C.P.
LECTURER IN MEDICINE

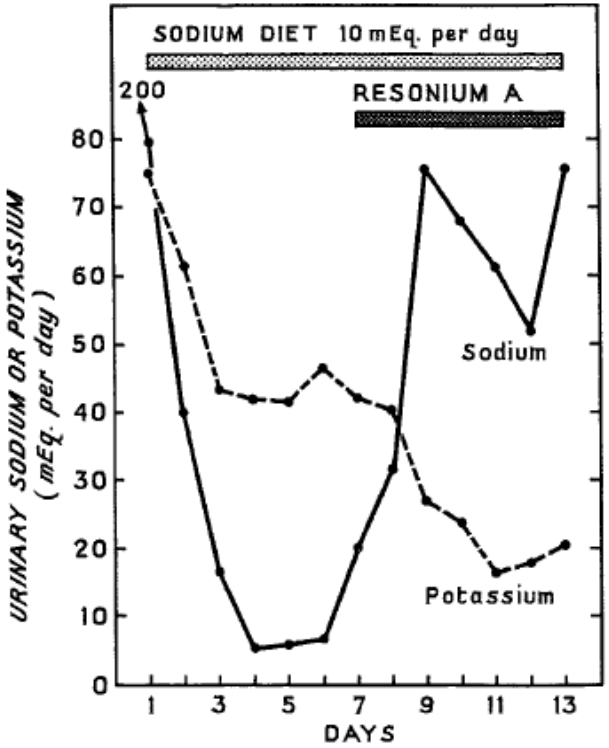
K. JANABI
M.B. Baghdad, M.R.C.P.E.
RESEARCH FELLOW

A. B. SHAW
M.B. Lond., M.R.C.P.
MEDICAL RESEARCH COUNCIL RESEARCH FELLOW

UNIVERSITY DEPARTMENT OF MEDICINE,
ROYAL INFIRMARY, MANCHESTER, 13

- Zulassung 1958 durch die FDA
- Kationenaustauscher = Austausch von Na^+ gegen K^+ Ionen!
- SPS enthält 4 mmol Na^+/g und bindet ca. 1 mmol K^+/g
- CPS enthält Ca^{++} anstelle von Na^+





Berlyne et al. ***Lancet*** 1966

Resonium A (Natrium Polystyrensulfonat)

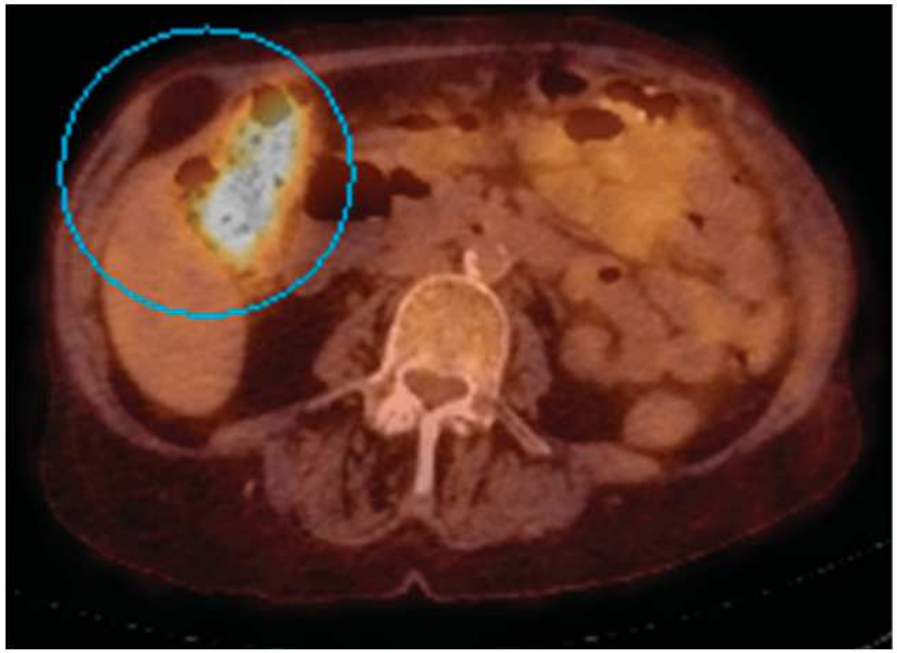

http://www.kidney-international.org make your diagnosis

© 2013 International Society of Nephrology

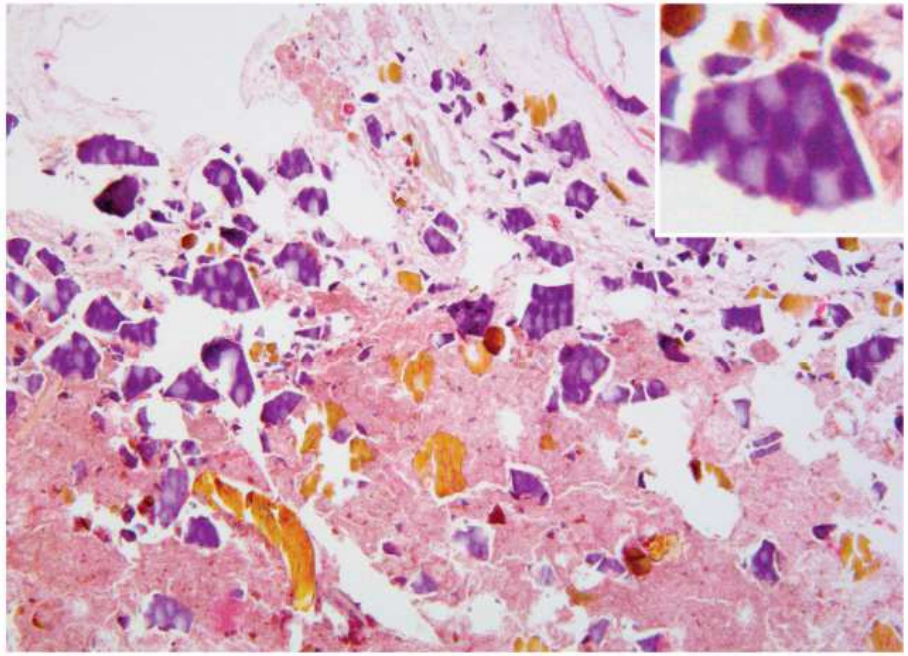
Kidney International (2013) 84, 1057–1059; doi:10.1038/ki.2013.140

The Case | A kidney transplant patient with ileocecal inflammation

Mohamad Zaidan[1,2,3], Alexandre Loupy[1,2], Alexandre Rousperthe[4], Pierre Philippe Massaad[5], Frank Martinez[1,2], Christophe Legendre[1,2] and Marie-France Mamzer-Bruneel[1,2]



PET: 18FDG-uptake in der Ileocoecalregion



Lichtmikroskopie: basophile Kristalle

Natrium Zirconium Cyclosilikat (ZS-9)

Research

Original Investigation

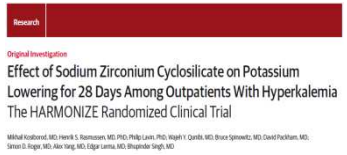
Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia
The HARMONIZE Randomized Clinical Trial

	Open-Label Phase (Zirconium Cyclosilicate, 10 g) (n = 258)	Randomized Phase			
		Placebo Group (n = 85)	Zirconium Cyclosilicate Dose Group		
			5 g (n = 45)	10 g (n = 51)	15 g (n = 56)
Age, mean (SD), y	64.0 (12.7)	64.3 (12.1)	61.5 (16.9)	63.8 (10.0)	64.9 (12.9)
Sex, No. (%)					
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, No. (%)					
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, mean (SD), kg	87.9 (22.9)	85.1 (18.6)	89.6 (23.9)	87.4 (25.6)	87.2 (18.6)
Serum potassium, mean (SD), mEq/L	5.6 (0.4)	4.6 (0.4)	4.5 (0.4)	4.4 (0.4)	4.5 (0.4)
Serum potassium, No. (%)					
<5.5 mEq/L	119 (46.1)	43 (50.6)	23 (51.1)	19 (37.3)	24 (42.9)
5.5 to <6.0 mEq/L	100 (38.8)	30 (35.3)	17 (37.8)	23 (45.1)	26 (46.4)
≥6.0 mEq/L	39 (15.1)	12 (14.1)	5 (11.1)	9 (17.6)	6 (10.7)
eGFR,[a] mean (SD), mL/min/1.73 m^2	46.3 (30.5)	48.0 (28.8)	48.0 (30.7)	44.7 (30.7)	44.9 (29.5)
eGFR, No. (%)					
<60 mL/min/1.73 m^2	179 (69.4)	52 (61.2)	31 (68.9)	38 (74.5)	41 (73.2)
≥60 mL/min/1.73 m^2	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), pg/mL[b]	125.9 (170)	101.3 (106.5)	174.6 (228.6)	100.6 (143.7)	151.6 (216.8)
Comorbidities, No. (%)					
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 medication, No. (%)	180 (69.8)	61 (71.8)	33 (73.3)	36 (70.6)	33 (58.9)

- noch nicht zugelassen
- hochselektive K^+-Bindung
- Wirkeintritt nach **1-2 Stunden**

Kosiborod et al. ***JAMA*** 2014

Natrium Zirconium Cyclosilikat (ZS-9)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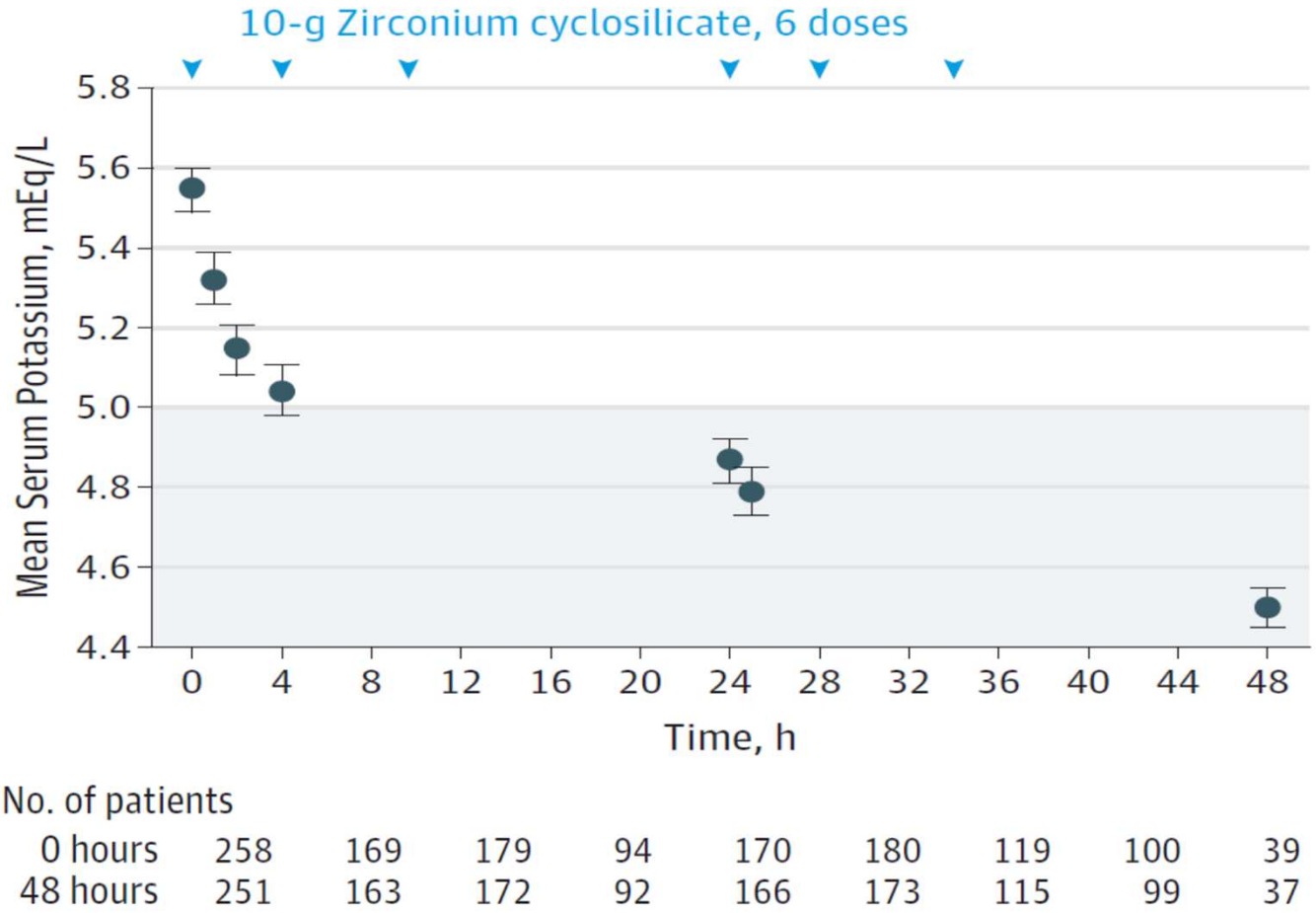
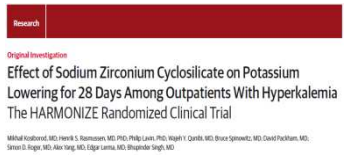
Mikhail Kosiborod, MD; Henrik S. Rasmussen, MD, PhD; Philip Lavin, PhD; Wajeh Y. Qunibi, MD; Bruce Spinowitz, MD; David Packham, MD; Simon D. Roger, MD; Alex Yang, MD; Edgar Lerma, MD; Bhupinder Singh, MD



Open-label Phase

Kosiborod et al. ***JAMA*** 2014

Natrium Zirconium Cyclosilikat (ZS-9)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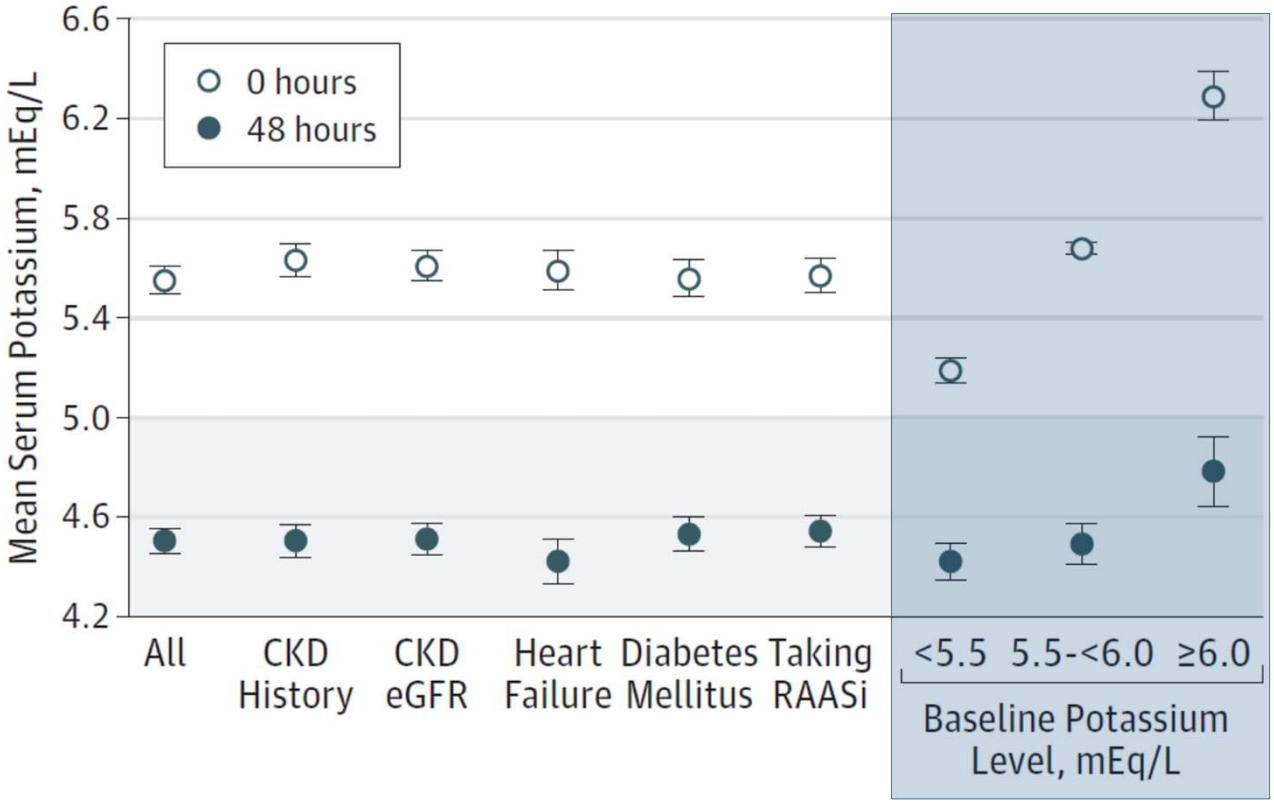
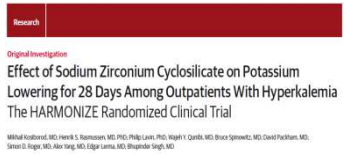


No. of patients

0 hours	258	169	179	94	170	180	119	100	39
48 hours	251	163	172	92	166	173	115	99	37

Open-label Phase

Natrium Zirconium Cyclosilikat (ZS-9)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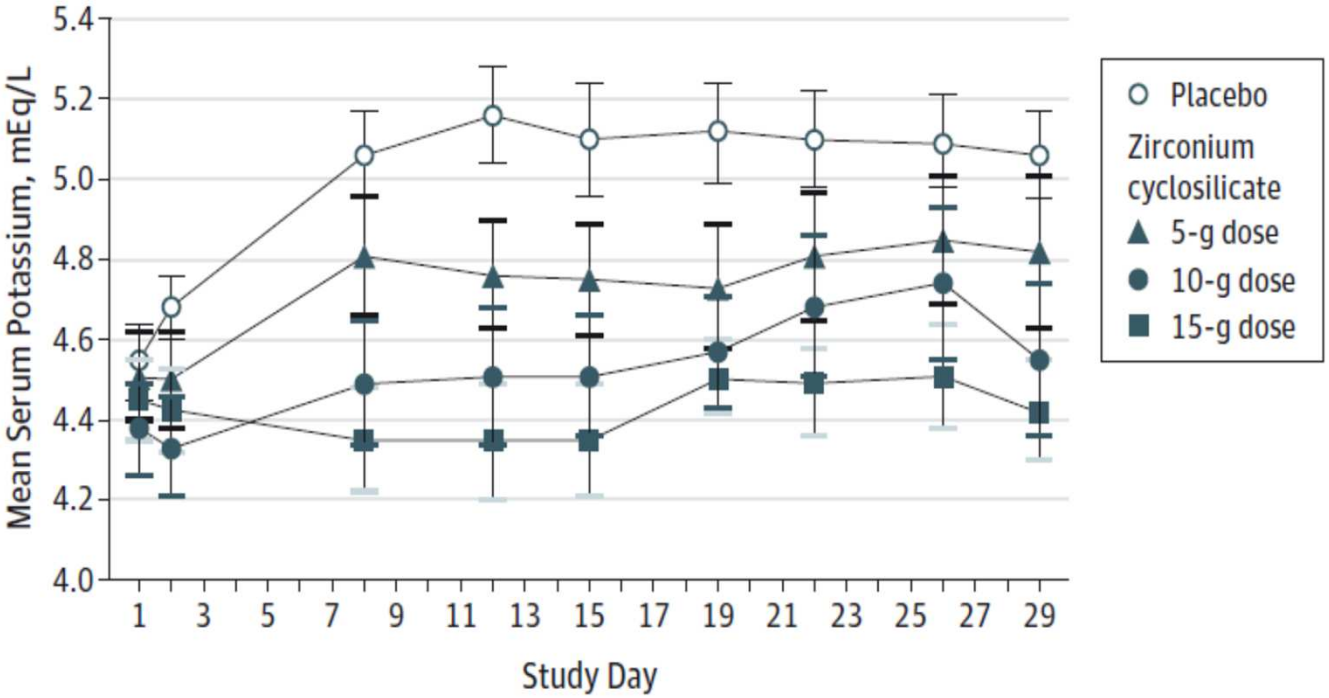
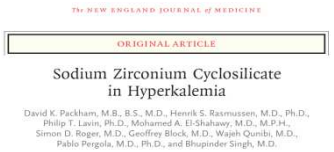


No. of patients

Placebo	82	81	81	80	80	78	77	74	73
5-g dose	45	45	45	44	44	43	43	42	39
10-g dose	50	49	50	47	47	47	45	45	38
15-g dose	54	54	54	53	52	51	51	51	43

Randomisierte doppel-blinde Phase

Natrium Zirconium Cyclosilikat (ZS-9)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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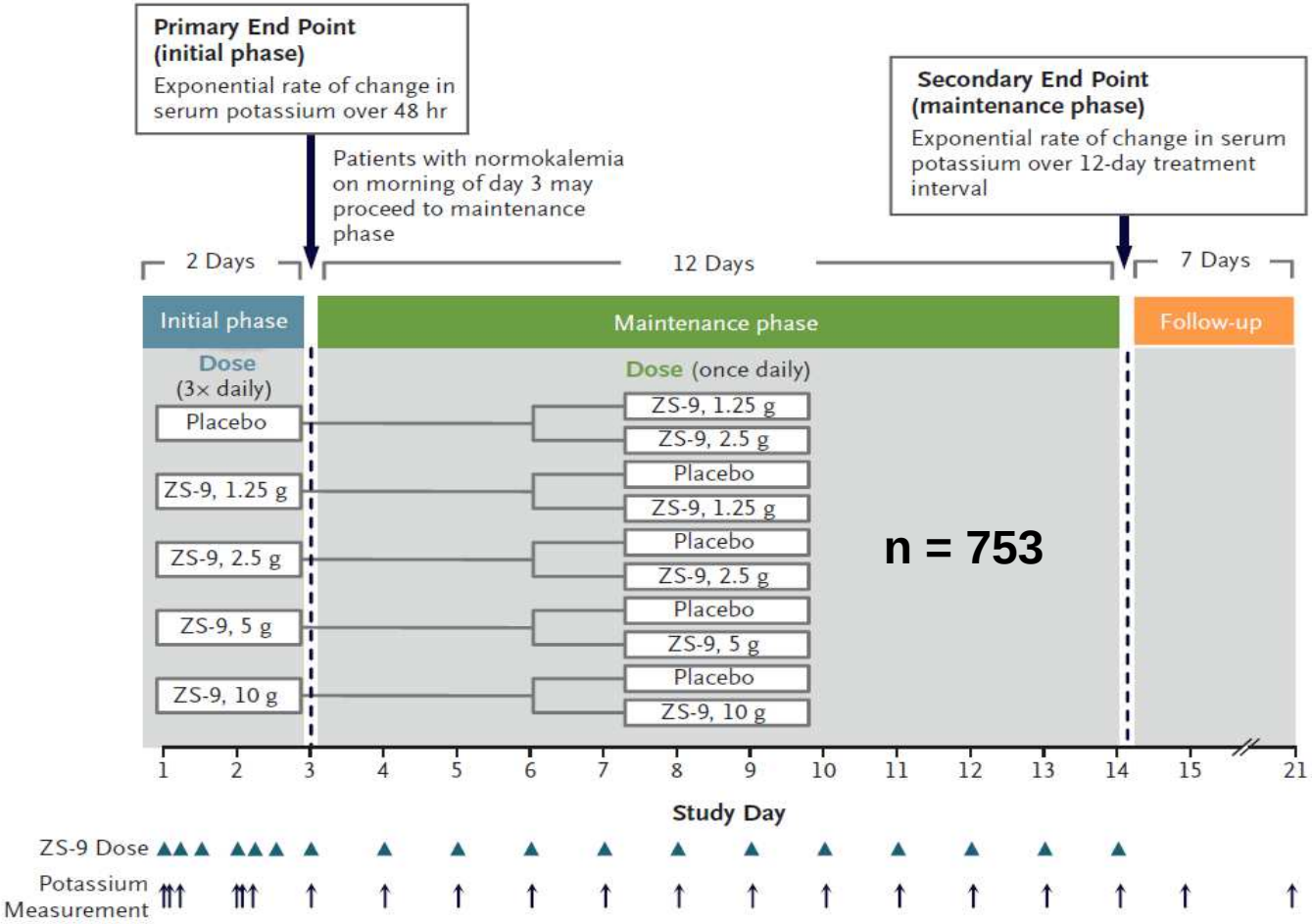
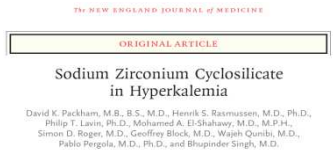
David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.



Packham et al. ***N Engl J Med*** 2015

Natrium Zirconium Cyclosilikat (ZS-9)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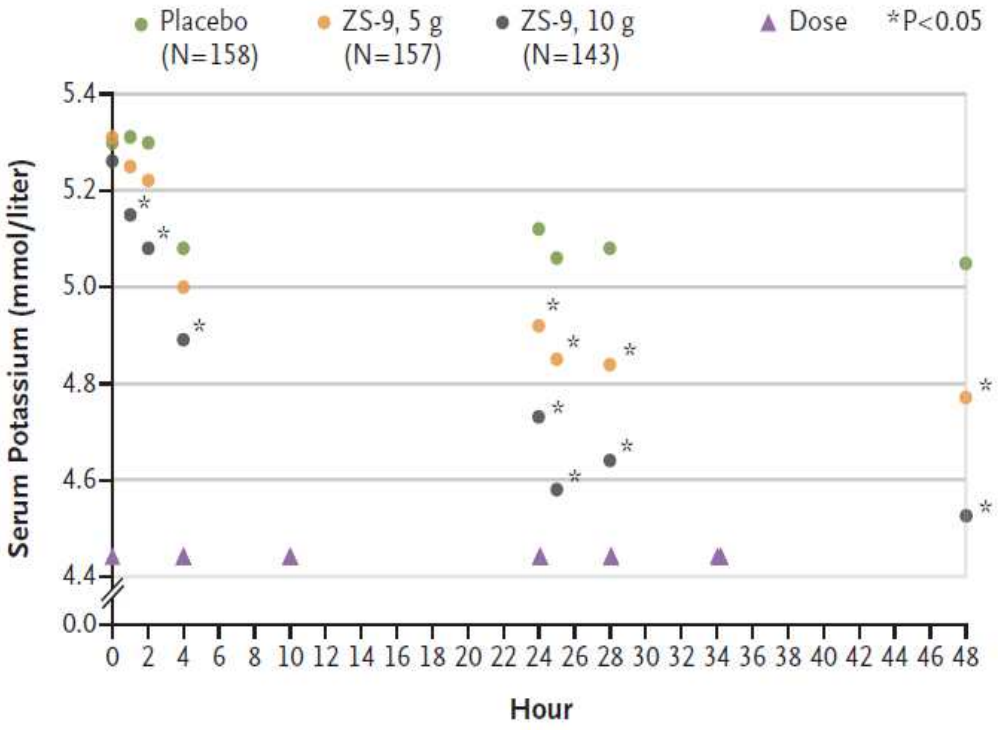
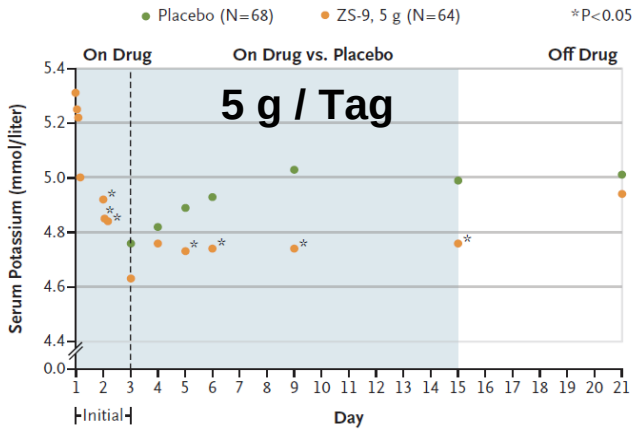
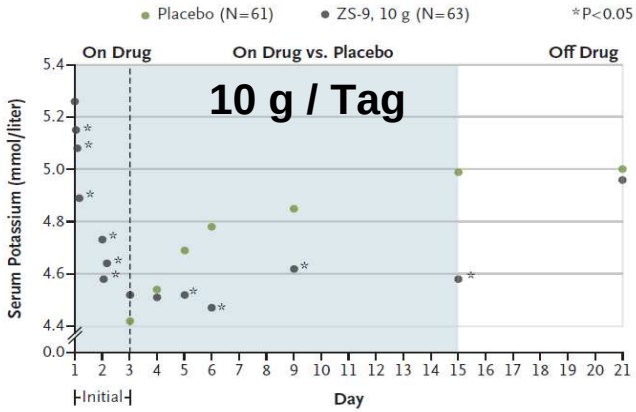
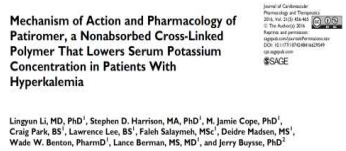


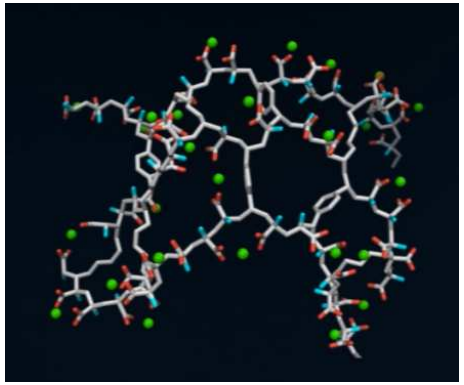




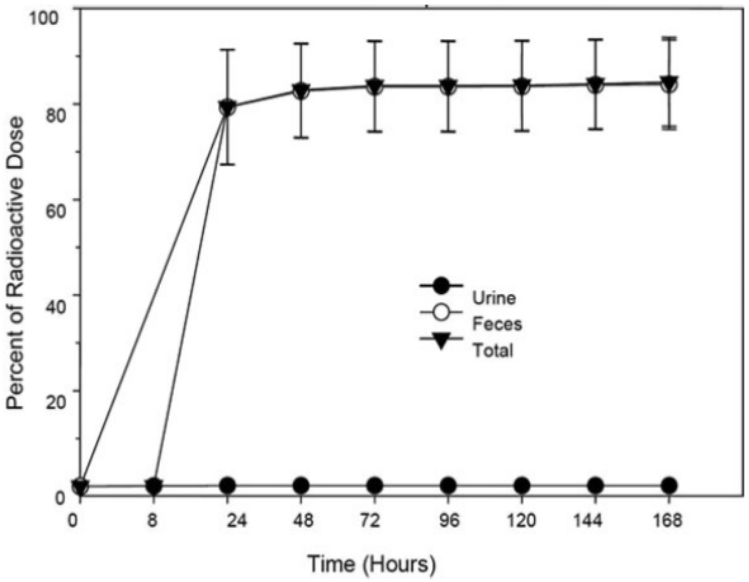
Patiromer


Mechanism of Action and Pharmacology of Patiromer, a Nonabsorbed Cross-Linked Polymer That Lowers Serum Potassium Concentration in Patients With Hyperkalemia

Lingyun Li, MD, PhD[1], Stephen D. Harrison, MA, PhD[1], M. Jamie Cope, PhD[1], Craig Park, BS[1], Lawrence Lee, BS[1], Faleh Salaymeh, MSc[1], Deidre Madsen, MS[1], Wade W. Benton, PharmD[1], Lance Berman, MS, MD[1], and Jerry Buysse, PhD[2]



- **Polymere** mit hoher Bindungskapazität für Kalium
- zu groß (100 µM) für gastrointestinale Resorption
- Passage dauert 24 bis 72 Stunden
- Wirkeintritt nach ca. 7 Stunden
- **K^+ wird gegen Ca^{++} ausgetauscht**



Li et al. ***J Cardiovasc Pharmacol Ther*** 2016

OPAL-HK Studie

The NEW ENGLAND JOURNAL of MEDICINE
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Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Witten, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

Characteristic	Initial Treatment Phase	Randomized Withdrawal Phase	
	Overall (N=243)	Placebo (N=52)	Patiromer (N=55)
Male sex — no. (%)	140 (58)	30 (58)	28 (51)
Age — yr	64.2±10.5	65.0±9.1	65.5±9.4
White race — no. (%)†	239 (98)	52 (100)	55 (100)
Type 2 diabetes — no. (%)	139 (57)	33 (63)	34 (62)
Heart failure — no. (%)	102 (42)	22 (42)	27 (49)
Myocardial infarction — no. (%)	60 (25)	14 (27)	18 (33)
Hypertension — no. (%)	236 (97)	50 (96)	54 (98)
Serum potassium — mmol/liter	5.6±0.5	5.9±0.4	5.9±0.6
Estimated GFR — ml/min/1.73 m^2‡	35.4±16.2	39.0±20.4	38.6±20.7
RAAS-inhibitor use — no. (%)‡	243 (100)	52 (100)	55 (100)
ACE inhibitor	170 (70)	38 (73)	37 (67)
Angiotensin II–receptor blocker	92 (38)	16 (31)	24 (44)
Aldosterone antagonist	22 (9)	4 (8)	4 (7)
Renin inhibitor	2 (1)	0	0
Dual RAAS blockade§	41 (17)	6 (12)	10 (18)
Receiving maximal dose¶	106 (44)	21 (40)	21 (38)
Non–RAAS-inhibitor diuretic use — no. (%)‡	132 (54)	27 (52)	28 (51)
Thiazide	70 (29)	11 (21)	16 (29)
Loop	77 (32)	20 (38)	16 (29)

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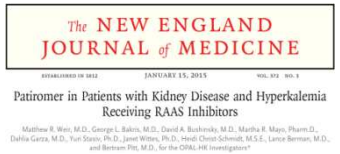
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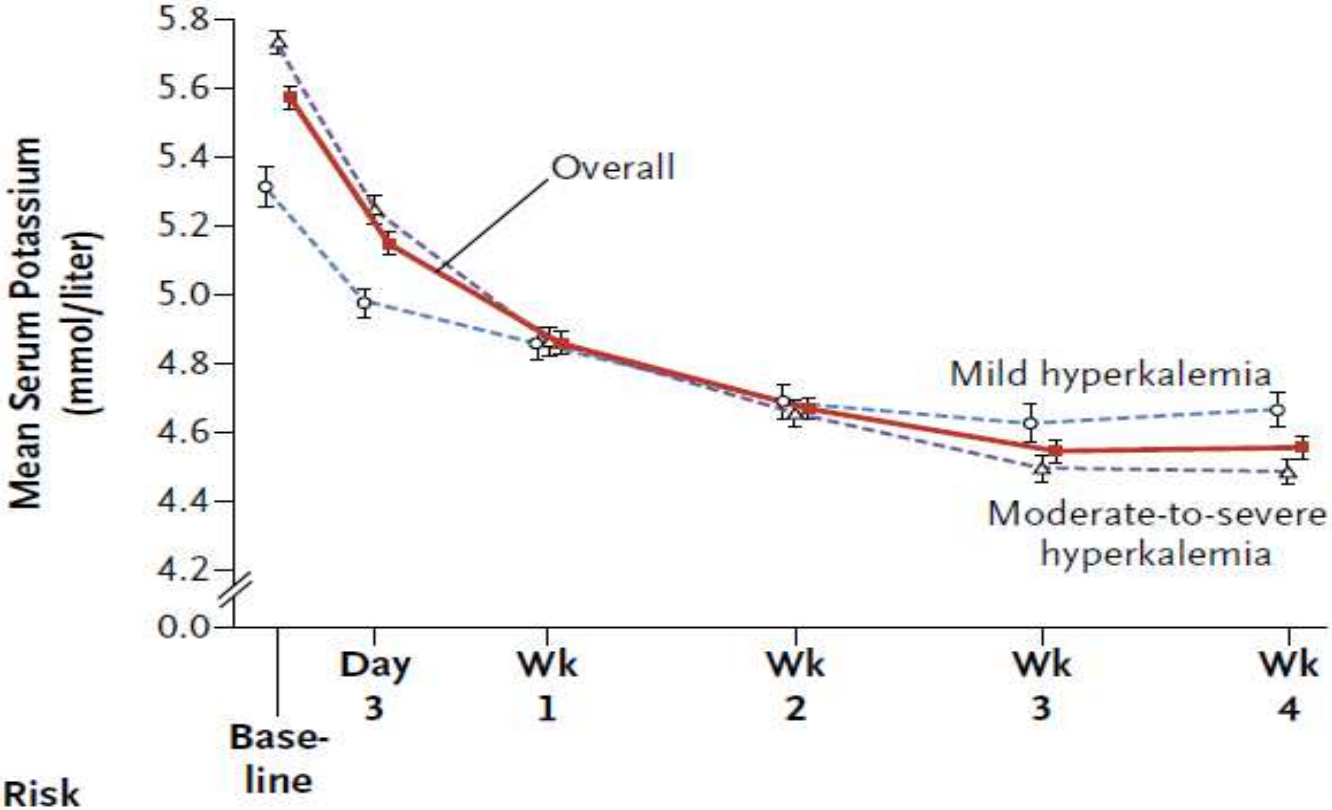

No. at Risk	Base-line	Day 3	Wk 1	Wk 2	Wk 3	Wk 4
Overall	243	217	237	228	221	219
Mild hyperkalemia	92	80	90	87	85	85
Moderate-to-severe hyperkalemia	151	137	147	141	136	134

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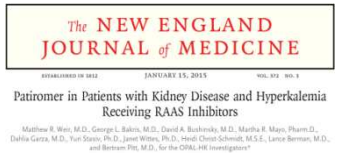
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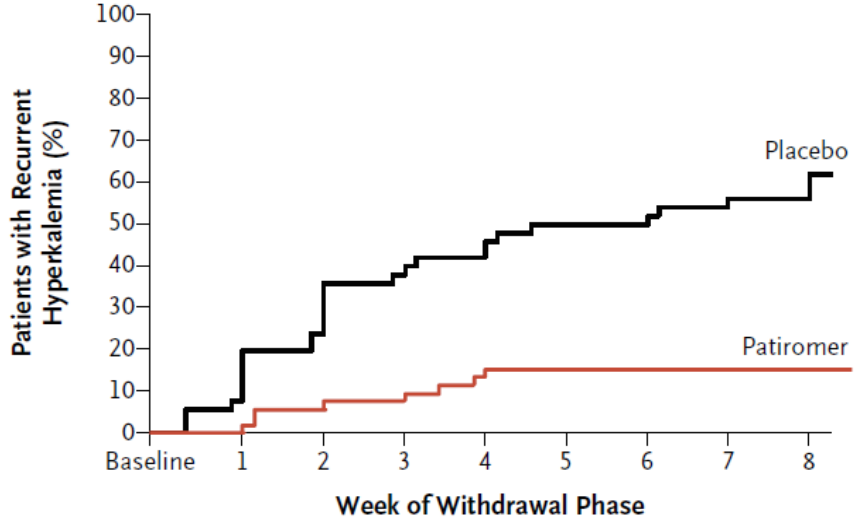
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

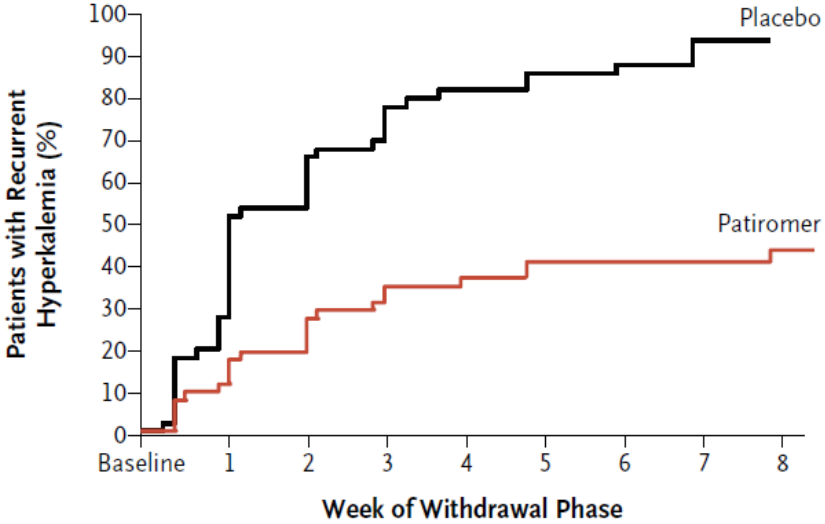
Time to First Serum Potassium Level ≥5.5 mmol/liter



No. at Risk

Placebo	52	46	38	31	29	25	25	23	15
Patiromer	55	53	49	48	45	43	42	42	32

Time to First Serum Potassium Level ≥5.1 mmol/liter



No. at Risk

Placebo	52	37	24	16	10	8	8	7	1
Patiromer	55	47	42	36	34	30	29	29	23

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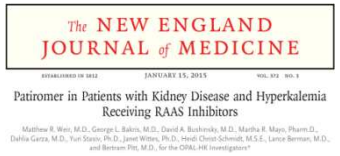
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Adverse Event	Placebo (N=52)	Patiromer (N=55)
	no. of patients (%)	
≥1 Adverse event	26 (50)†	26 (47)
Headache	4 (8)	2 (4)
Supraventricular extrasystoles	1 (2)	2 (4)
Constipation	0	2 (4)
Diarrhea	0	2 (4)
Nausea	0	2 (4)
≥1 Serious adverse event	1 (2)‡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

Weir et al. ***N Engl J Med*** 2015

Post-Hoc Analyse OPAL-HK Studie


clinical investigation www.kidney-international.org

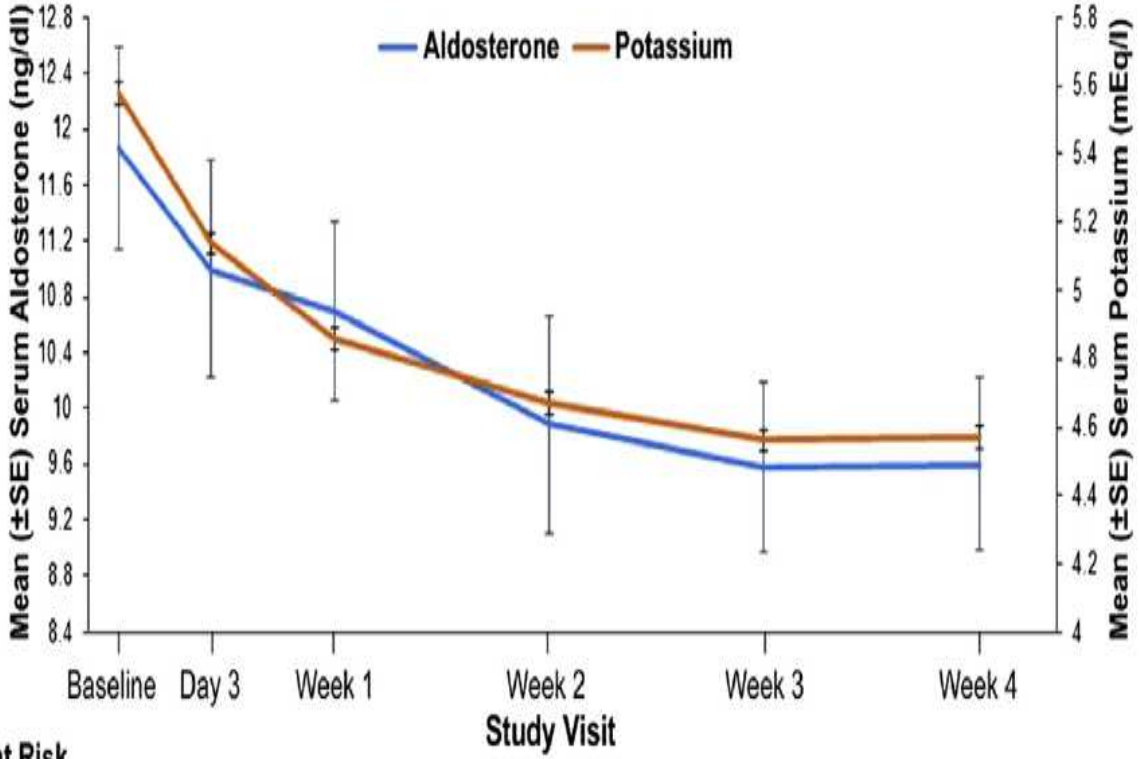
Treatment with patiromer decreases aldosterone in patients with chronic kidney disease and hyperkalemia on renin-angiotensin system inhibitors

OPEN

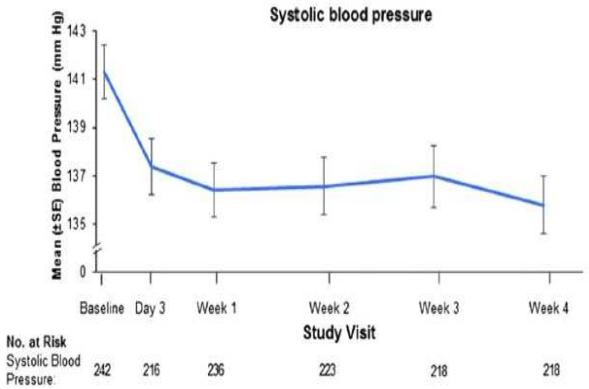
see commentary on page 484

Matthew R. Weir[1], George L. Bakris[2], Coleman Gross[1], Martha R. Mayo[1], Dahlia Garza[1], Yuri Stasiv[3], Jinwei Yuan[3], Lance Berman[3] and Gordon H. Williams[4]

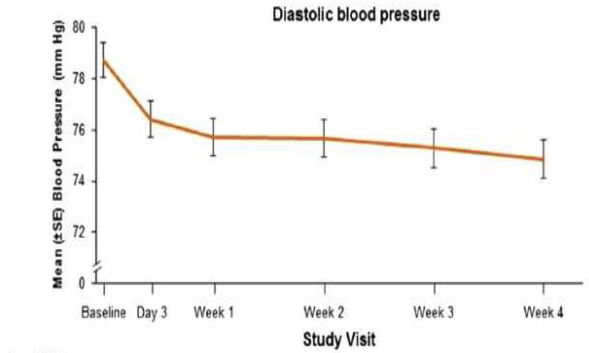
[1]Division of Nephrology, Department of Medicine, University of Maryland, Baltimore, Maryland, USA; [2]University of Chicago, Chicago, Illinois, USA; [3]Relypsa, Redwood City, California, USA; and [4]Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, USA



No. at Risk	Baseline	Day 3	Week 1	Week 2	Week 3	Week 4
Aldosterone	243	215	236	224	218	219
Potassium	243	217	237	228	221	219

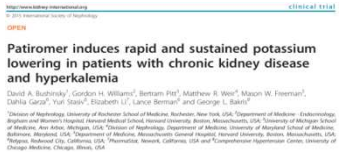


No. at Risk	Baseline	Day 3	Week 1	Week 2	Week 3	Week 4
Systolic Blood Pressure	242	216	236	223	218	218

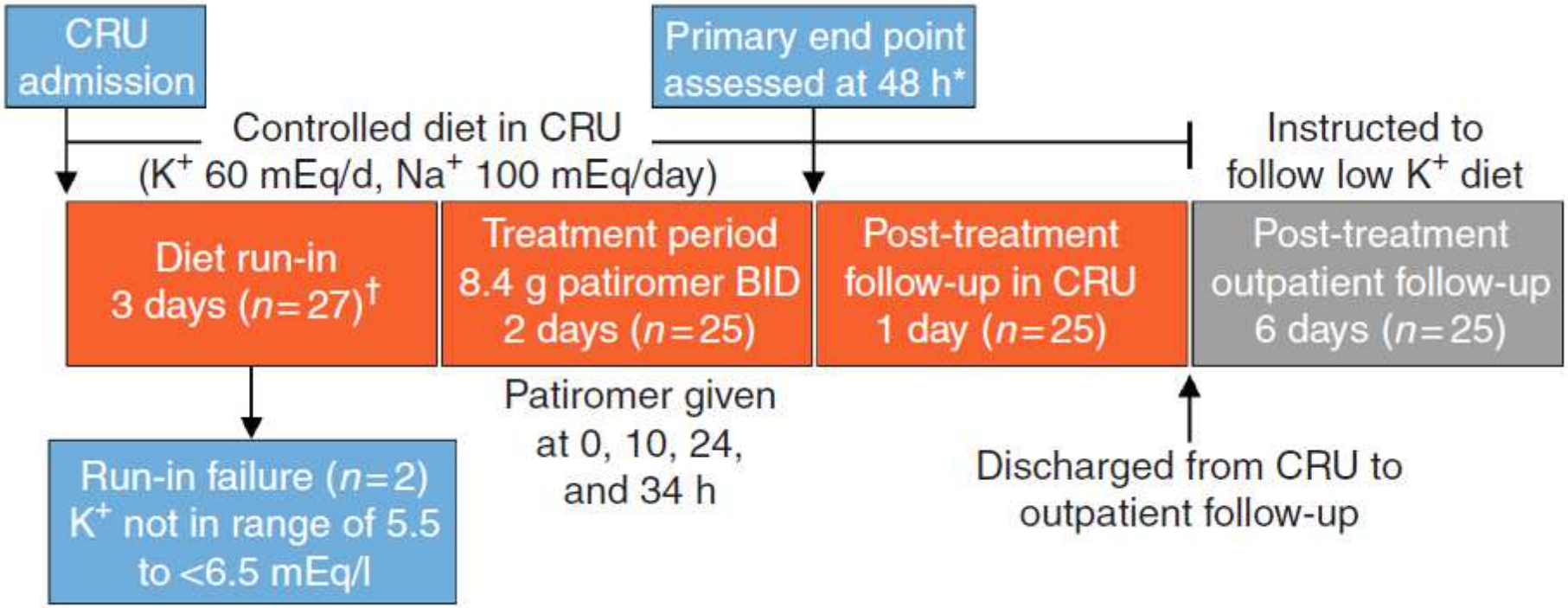


No. at Risk	Baseline	Day 3	Week 1	Week 2	Week 3	Week 4
Diastolic Blood Pressure	242	216	236	223	218	218

Patiromer bei CKD

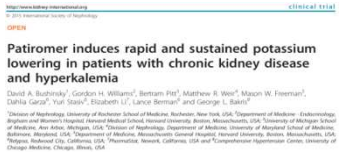

Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia

25 CKD Patienten (eGFR 35 ml/min)
2 x 8,4 g Patiromer täglich für 2 Tage



Bushinsky et al. ***Kidney Int*** 2015

Patiromer bei CKD


clinical trial

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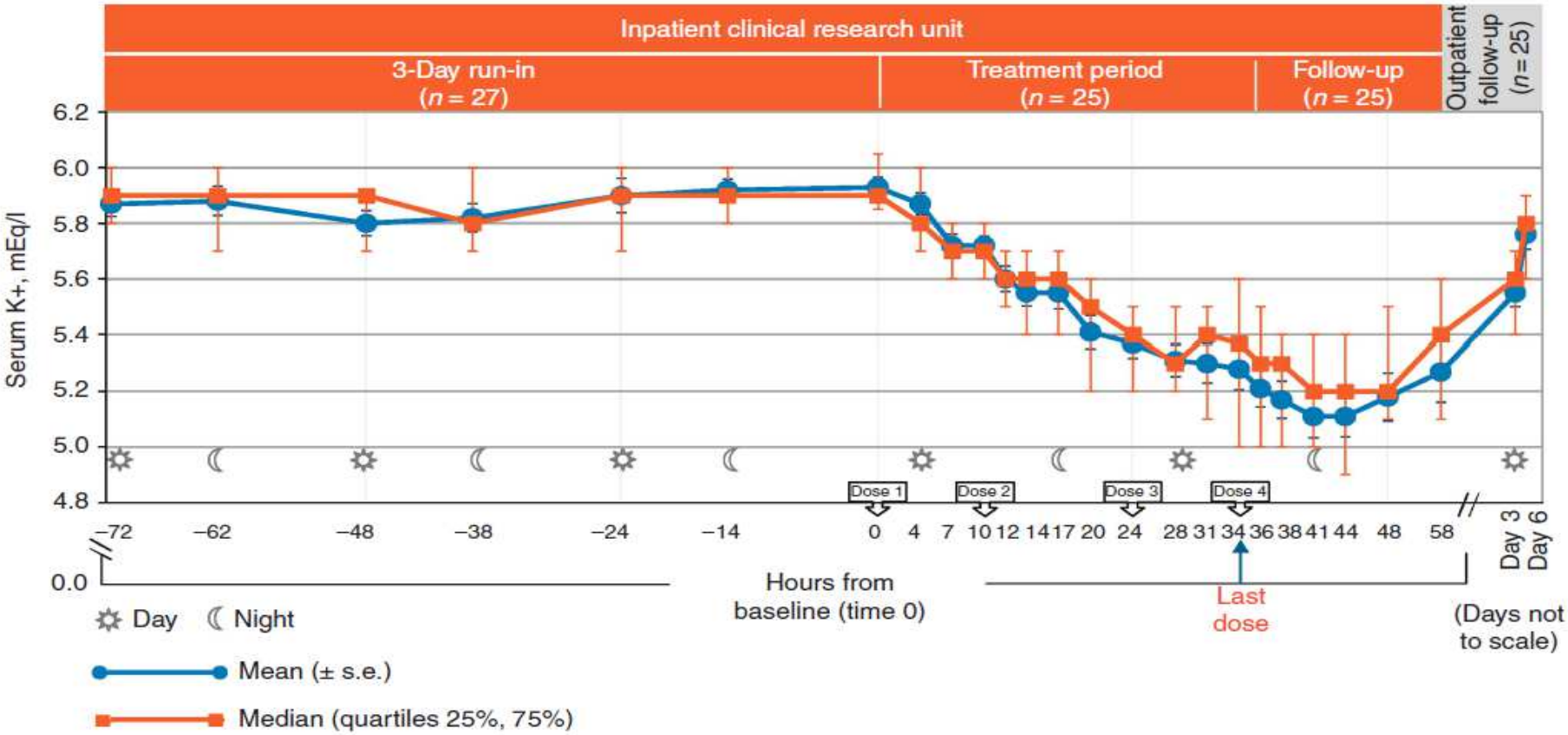
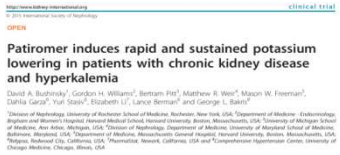
Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia



Patiromer bei CKD


clinical trial

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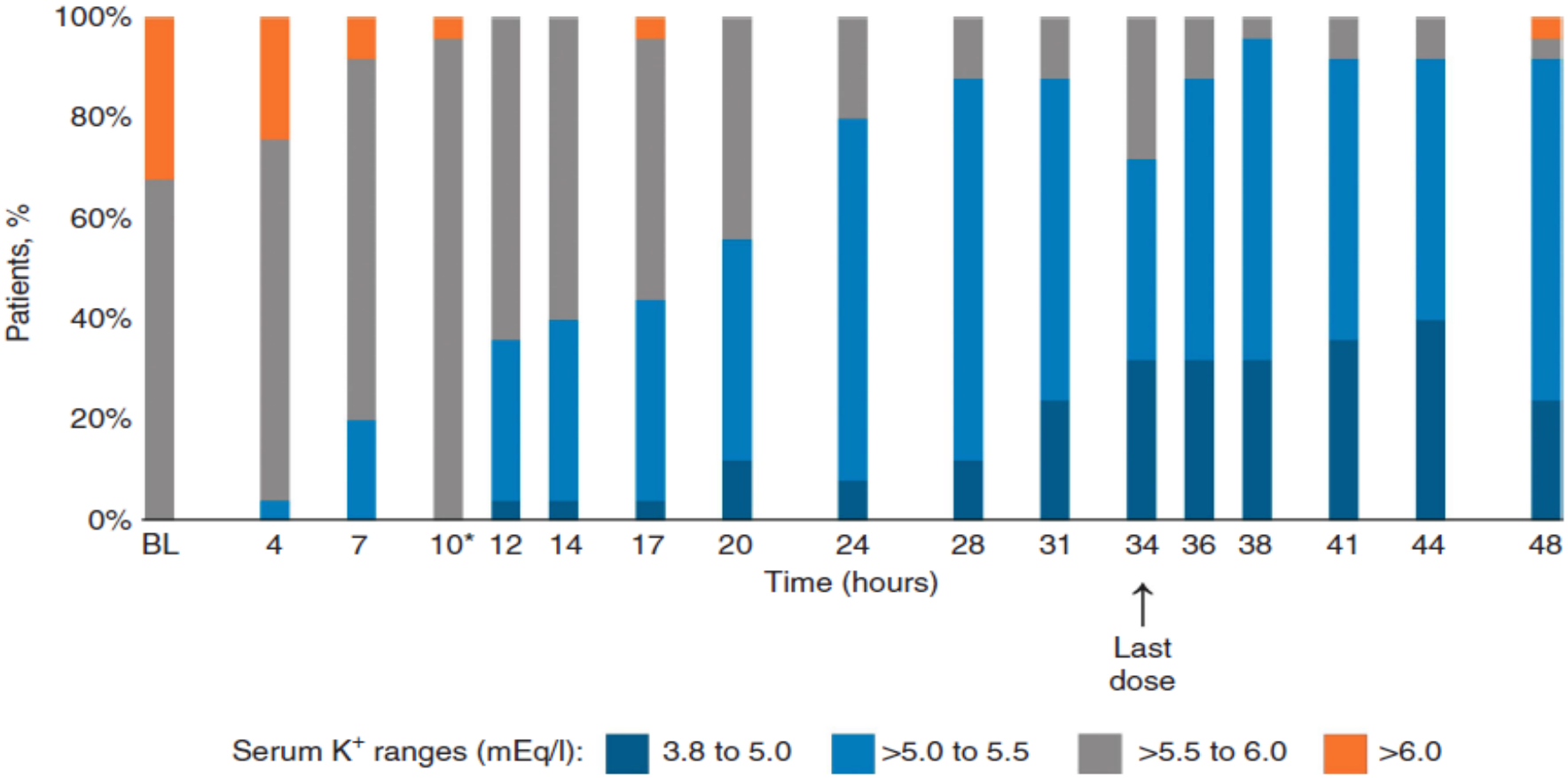
Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia



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Patiromer bei HD


Nephrology

Original Report: Patient-Oriented, Translational Research

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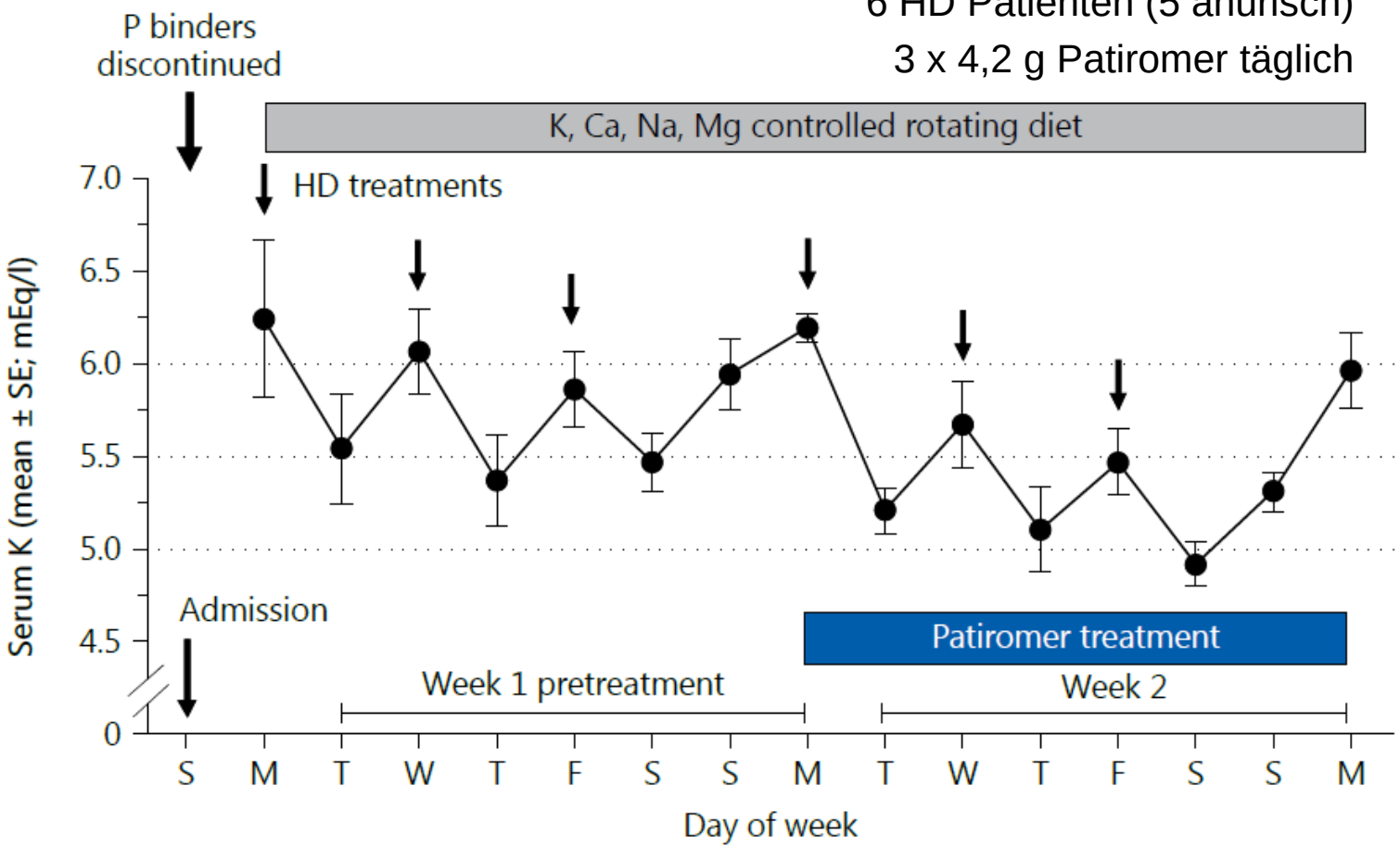
Patiromer Decreases Serum Potassium and Phosphate Levels in Patients on Hemodialysis

David A. Bushinsky[a] Patrick Rossignol[b] David M. Spiegel[c] Wade W. Benton[c] Jinwei Yuan[c] Geoffrey A. Block[d] Christopher S. Wilcox[e] Rajiv Agarwal[f]

6 HD Patienten (5 anurisch)

3 x 4,2 g Patiromer täglich



Bushinsky et al. ***Am J Nephrol*** 2016

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Vielen Dank!