Il trattamento dell'iperkaliemia

Giovambattista Desideri
UO Geriatria e Lungodegenza
Dipartimento MESVA
Università degli Studi di L'Aquila

Storie di tutti i giorni…..

Stampa

Richiesta: **04047794** del **04/04/2018**

Provenienza: A432 A-Geriatria

Sig. [redacted]

Data Nascita: 01/06/1925
Identificativo Paziente: 00001721
Sesso M Età: 92 Anni

Data di accettazione: 04/04/2018
Data e ora di presa in carico: 04/04/2018 09:41
Data e ora di stampa: 05/04/2018 11:45

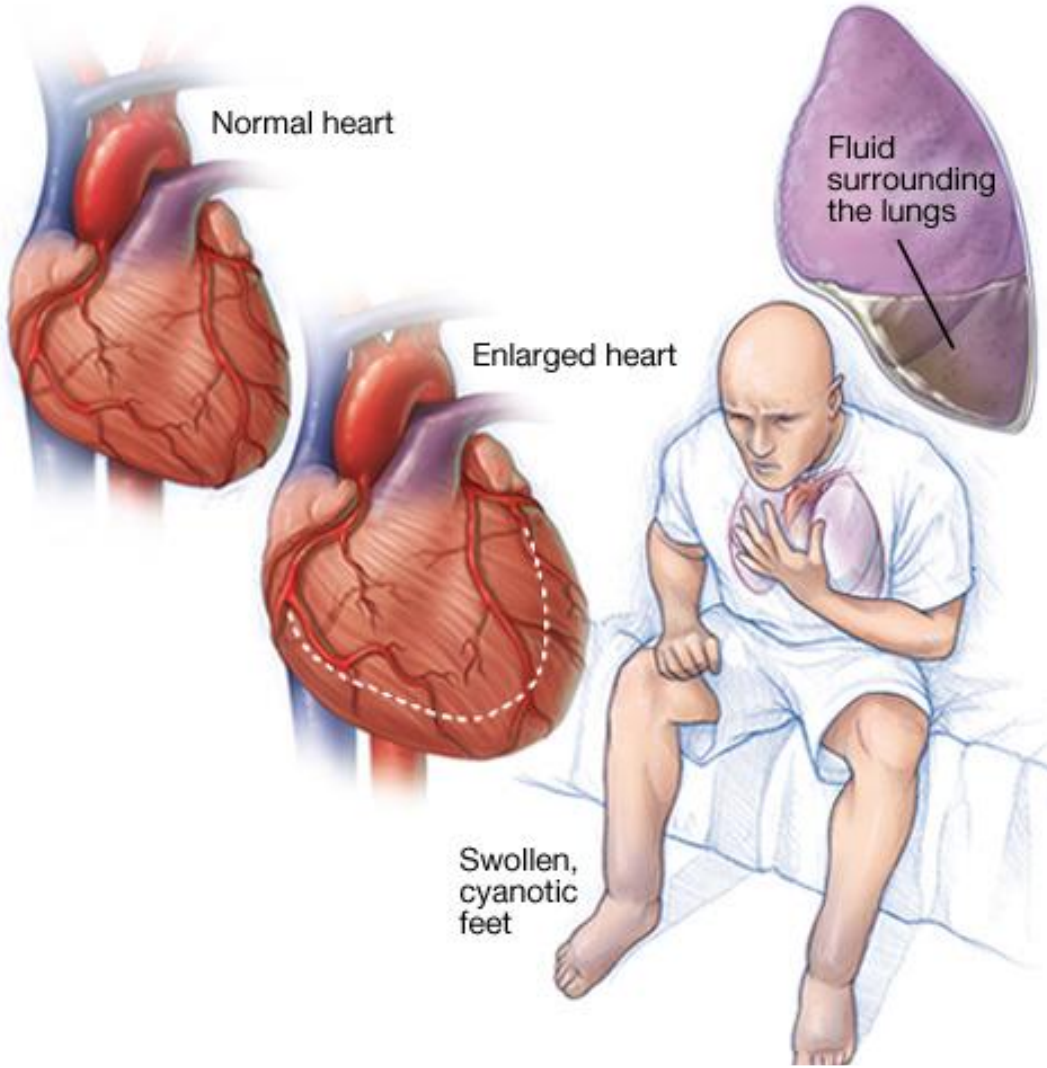
ESAMI IN ROUTINE

Esame	*Esito*		*U.M.*	*Valori di Riferimento*	*Metodica*	*Validatore*
Biochimica Clinica						
S-GLUCOSIO	147	*	mg/dl	60 - 110	(Colorimetrica)	T03
S-UREA	100	*	mg/dl	10 - 50	(Colorimetrico)	T03
S-CREATININA	1.28	*	mg/dl	0.70 - 1.20	(Colorimetrica 2 punti	T03
Filtrato Glomerulare Medio	53		ml/min/1,73 mq	> 60		
Valore calcolato secondo l'equazione MDRD, valido per persone tra 18 - 70 anni caucasiche; moltiplicare per 1.21 se di etnia afro-americana. Valori di eGFR < 60 ml/min/1.73 mq vanno valutati nell'ambito del contesto clinico generale.						
S-SODIO	140		mEq/L	135 - 150	(Ioni selettivi)	T03
S-POTASSIO	6.4	*	mEq/L	3.5 - 5.5	(Ioni selettivi)	T03
S-CALCIO TOTALE	9.2		mg/dl	8.5 - 11.0	(Colorimetrica)	T03
S-COLESTEROLO TOTALE	145		mg/dl	Valore ottimale: 150 - 200 Border line: 200 - 240 Alto: >240	(Colorimetrica)	T03
S-TRIGLICERIDI	51	*	mg/dl	60 - 170	(Colorimetrico)	T03
S-URATO	8.9	*	mg/dl	3.5 - 7.0	(Colorimetrica)	T03
S-PROTEINE TOTALI	7.0		g/dL	6.6 - 8.7	(Colorimetrica)	T03
S-AST-GOT(Aspartato-Amino-Transferasi	22		UI/L	5 - 34	(Cinetica)	T03
S-ALT-GPT(Alanina Amino Transferasi)	21		UI/L	7 - 55	(Cinetica)	T03
S-LATTICO DEIDROGENASI (LDH)	212		UI/L	125 - 220	(Cinetica)	T03
S-CREATINCHINASI (CPK -CK)	140		UI/L	30 - 200	(Cinetica)	T03
S-GAMMA GT (G. Glutamil Transferasi)	69	*	UI/L	12 - 64	(Cinetica)	T03
S-BILIRUBINA TOTALE (BT)	0.75		mg/dl	0.20 - 1.20	(Colorimetrica)	T03
S-FERRO	27	*	µg/dl	65 - 175	(Colorimetrica)	T03
S-Albumina	3.3	*	g/dL	3.5 - 5.0	(Colorimetrica)	T03
Coagulazione						
P-Tempo di Protrombina (PT)						T03

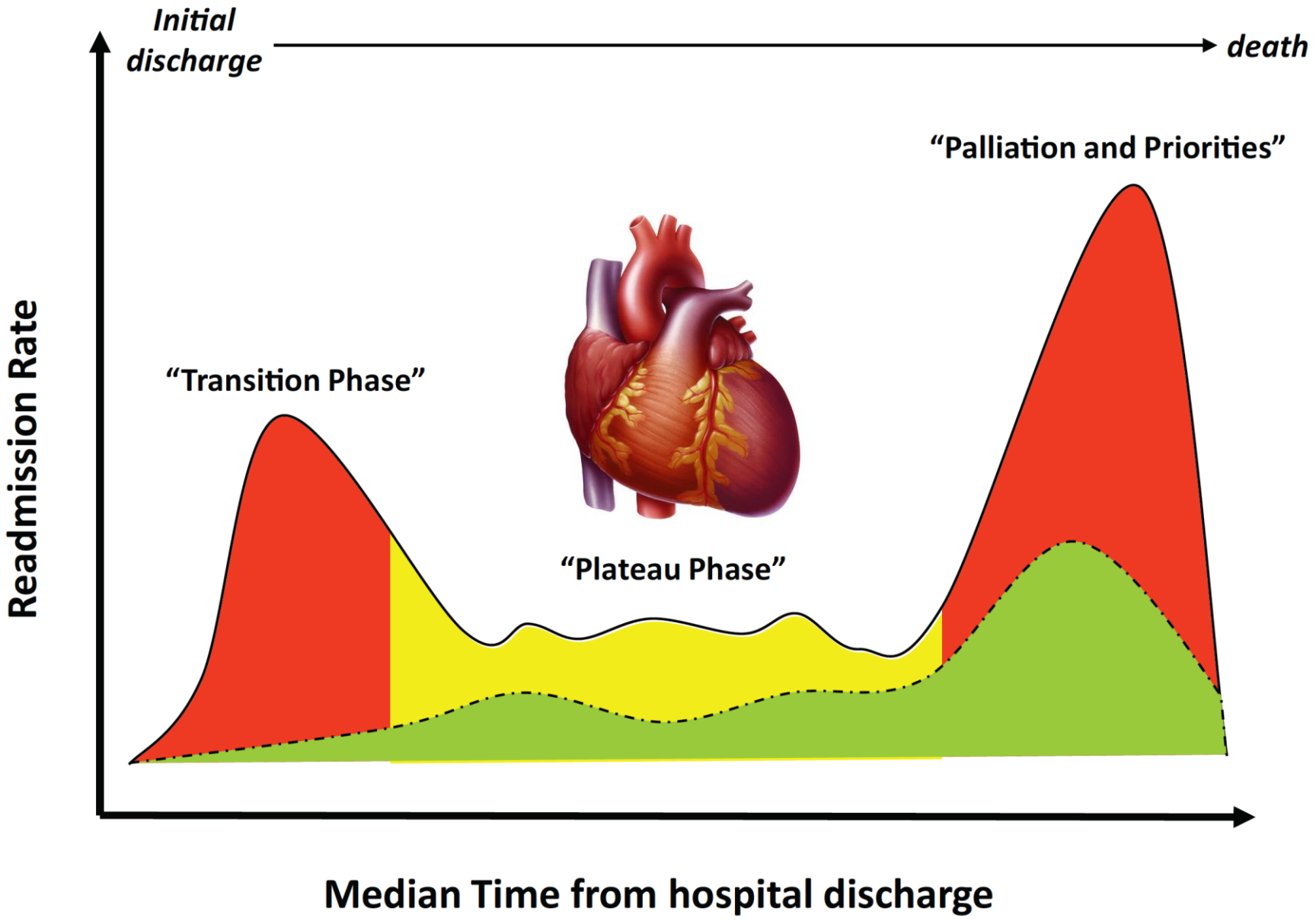
Continua nella pagina seguente

Il laboratorio effettua controllo di qualità interno con sistema UNITY della ditta BIO-RAD, e partecipa al controllo esterno di qualità della Regione ABRUZZO

Referto rilasciato in Copia Conforme; l'originale è disponibile presso il Laboratorio Analisi del P.O. di Avezzano

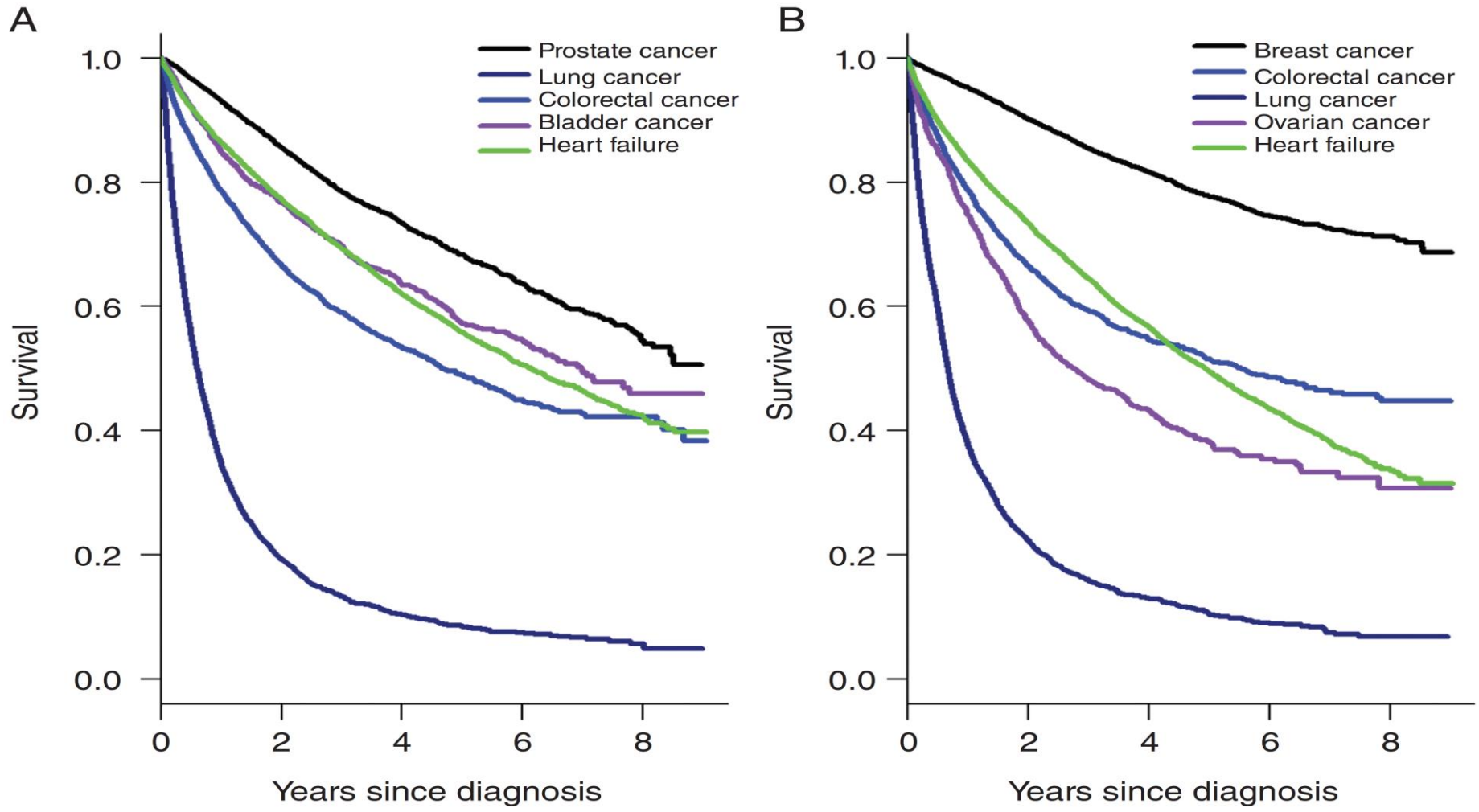


Rehospitalization for Heart Failure



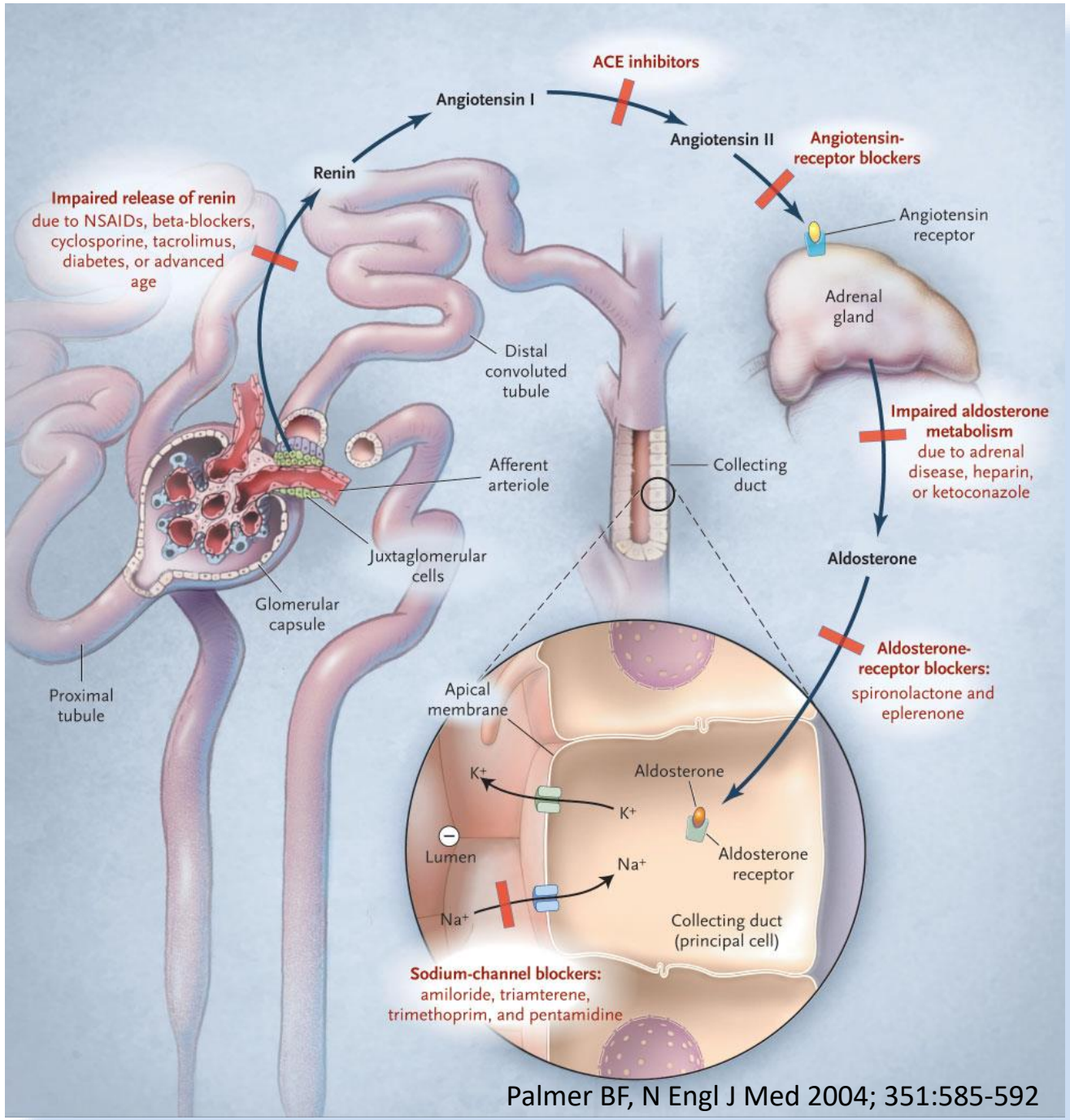
Desai AS et al. Circulation. 2012;126:501-506

Kaplan–Meier curves for overall survival in (A) men or (B) women with different cancer or heart failure

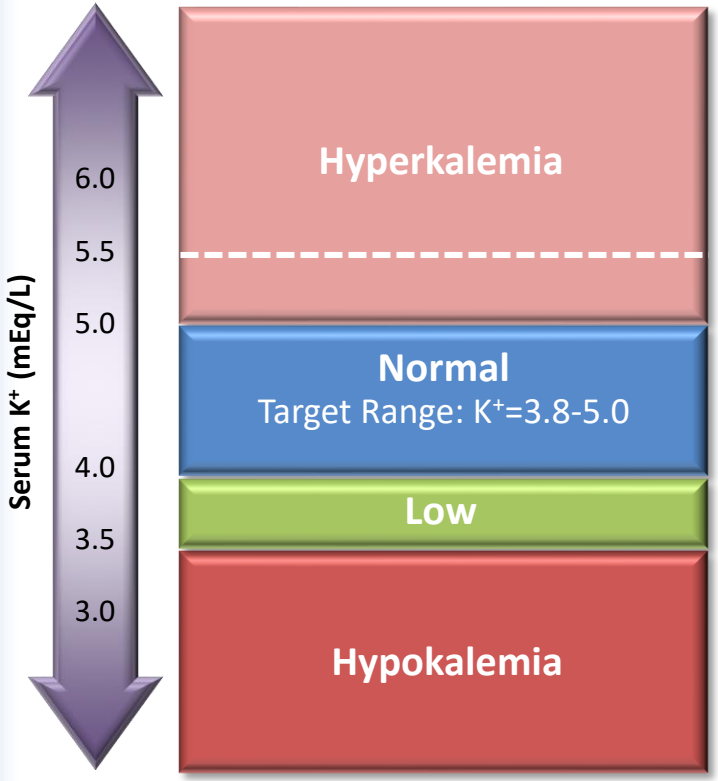


Mamas MA et al. European Journal of Heart Failure (2017) 19, 1095–1104

The RAAS and Regulation of Potassium Excretion in the Kidney



Palmer BF, N Engl J Med 2004; 351:585-592



Management of HFrEF

To reduce mortality - for all patients

ACE-I/ARNI | BB | MRA | SGLT2i

To reduce HF hospitalization/mortality - for selected patients

Volume overload
Diuretics

SR with LBBB ≥ 150 ms — CRT-P/D	*SR with LBBB 130–149 ms or non LBBB≥ 150 ms* — CRT-P/D
Ischaemic aetiology — ICD	*Non-ischaemic aetiology* — ICD
Atrial fibrillation — Anticoagulation	*Atrial fibrillation* — Digoxin, PVI
Coronary artery disease — CABG	*Iron deficiency* — Ferric carboxymaltose
Aortic stenosis — SAVR/TAVI	*Mitral regurgitation* — TEE MV Repair
Heart rate SR>70 bpm — Ivabradine	*Black Race* — Hydralazine/ISDN
ACE-I/ARNI intolerance — ARB	

For selected advanced HF patients

Heart transplantation | MCS as BTT/BTC | Long-term MCS as DT

To reduce HF hospitalization and improve QOL - for all patients

Exercise rehabilitation

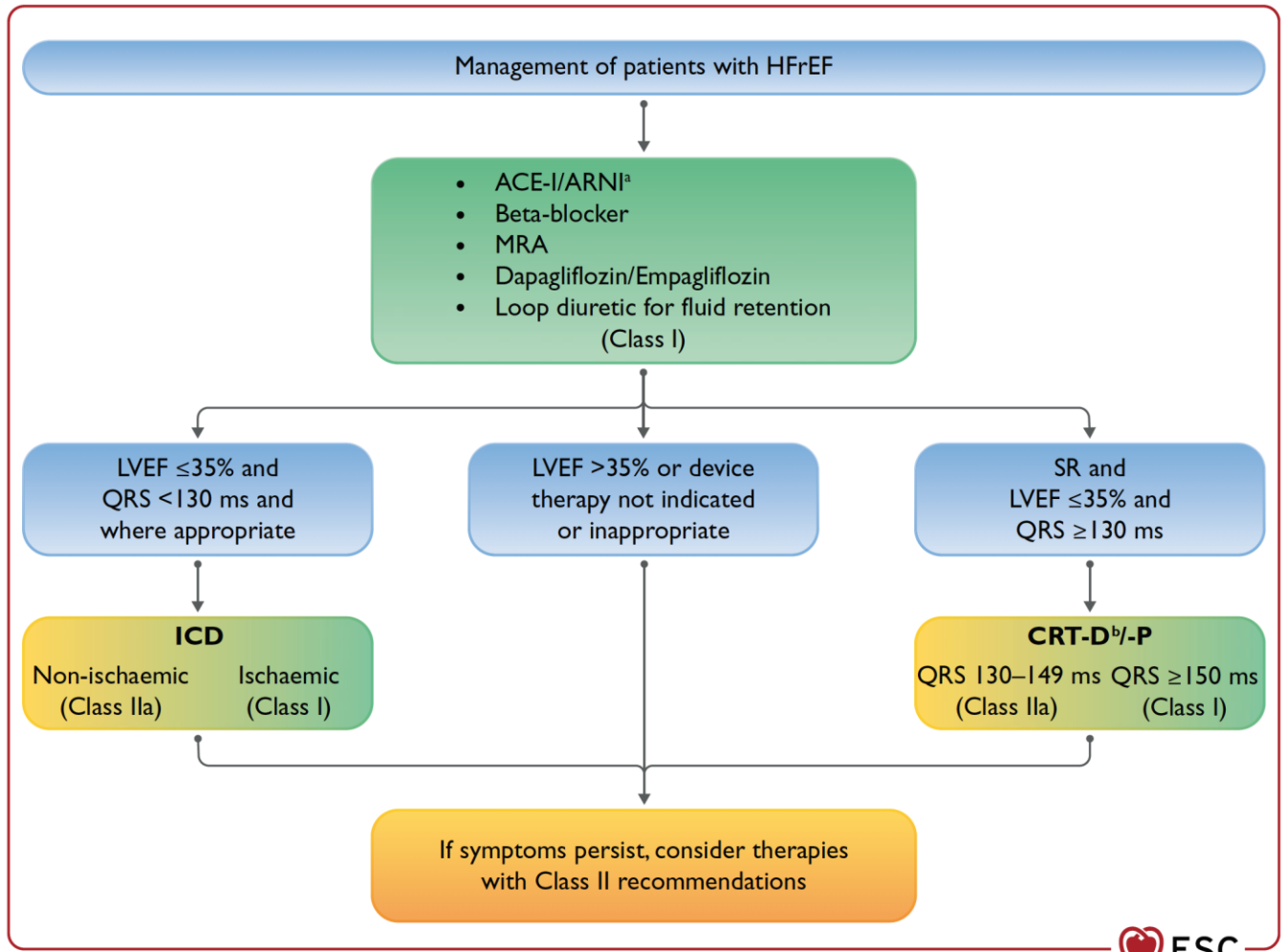
Multi-professional disease management

ESC European Society of Cardiology
European Heart Journal (2021) 42, 3599–3726
doi:10.1093/eurheartj/ehab368

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

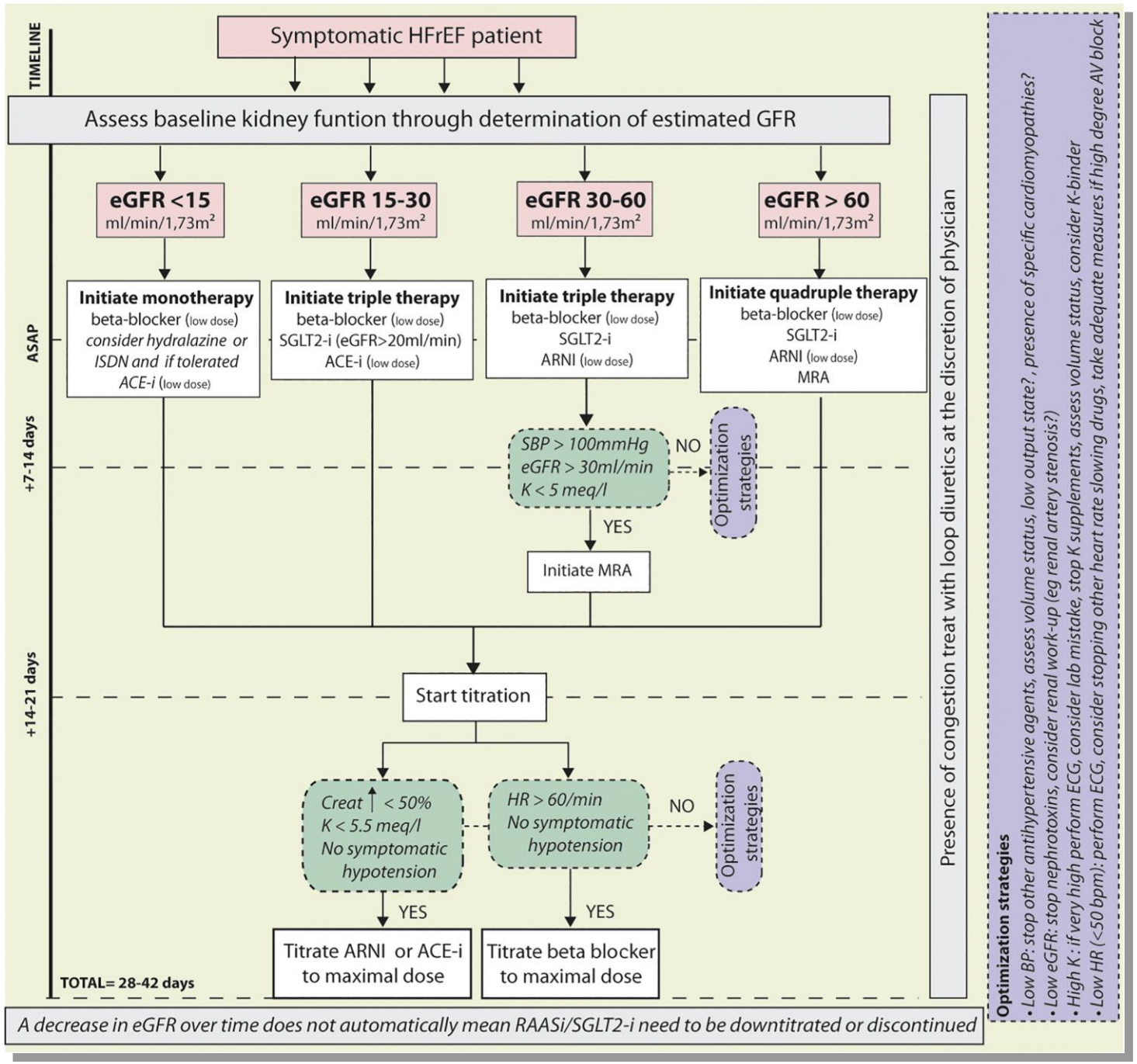
Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

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



ESC European Society of Cardiology
European Journal of Heart Failure (2022) 24, 603–619
doi:10.1002/ejhf.2471
POSITION PAPER

Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology

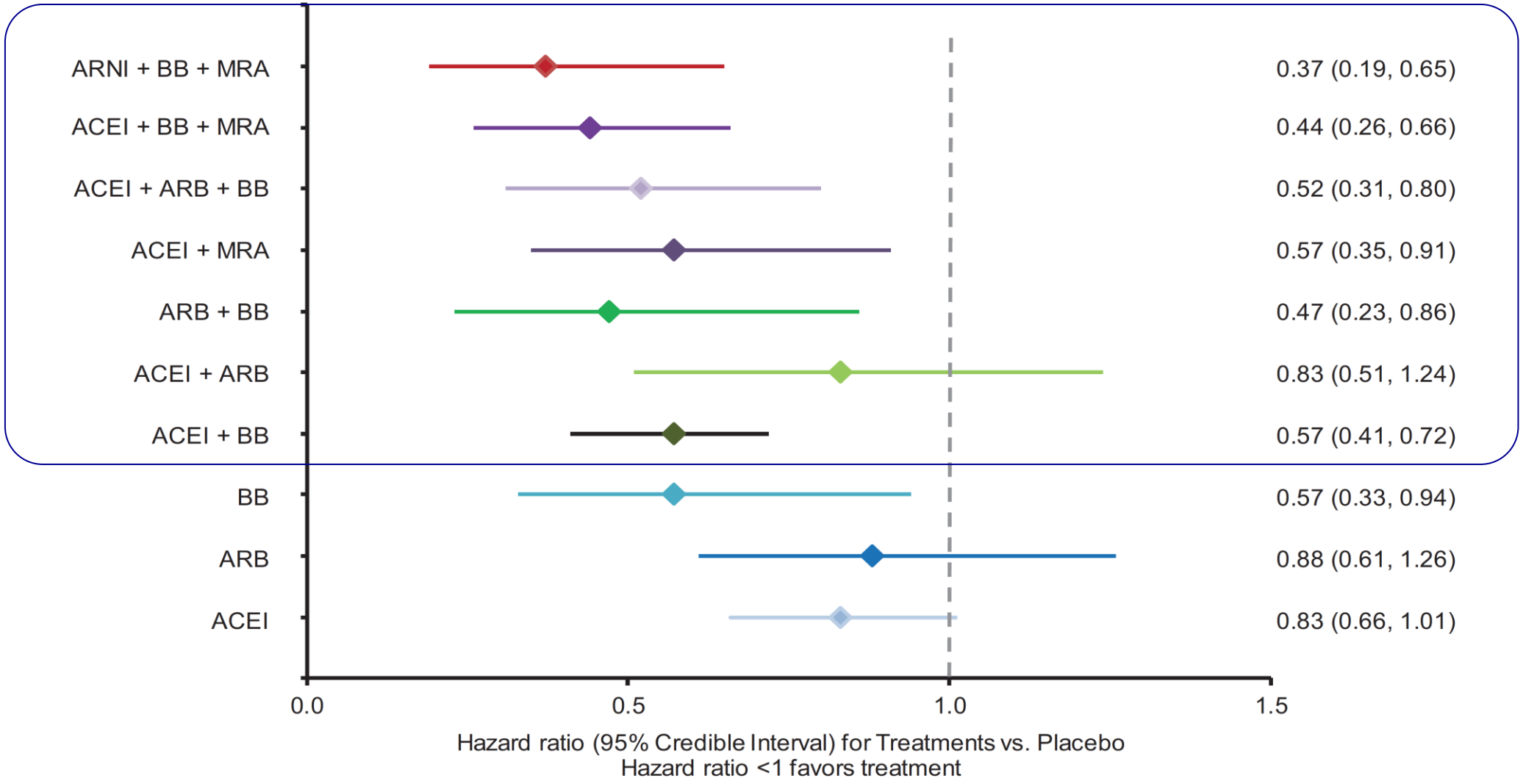


Mullens W et al. Eur J of Heart Failure (2022) 24, 603–619

Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction

A Network Meta-Analysis

All-cause mortality



Burnett H et al. Circ Heart Fail. 2017;10:e003529.

HIGH RAASI DOSES OFFER BETTER CV PROTECTION FOR PATIENTS WITH HF

ATLAS[1]

Double-blind, prospective trial assessing the effects of lisinopril on CV outcomes in patients with HF (NYHA II–IV) with ejection fraction ≤30%

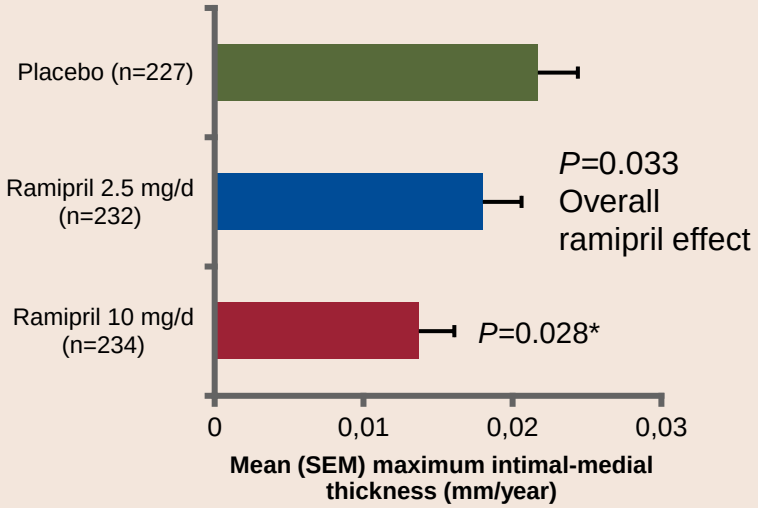
Compared with low-dose, patients receiving **high-dose lisinopril** had**:**

- **8%** risk reduction of **all-cause mortality** **HR 0.92**; *P*=0.128
- **10%** risk reduction of **CV mortality** **HR 0.90**; *P*=0.073
- **13%** fewer **hospitalisations** 3,819 vs 4,397; *P*=0.021
- **24%** **lower** risk of **HF hospitalisation** 1,199 vs 1,576; *P*=0.002

SECURE[2]

Double-blind, prospective trial evaluating the effects of long-term ramipril and vitamin E on atherosclerosis progression in patients at high risk of CV events

Compared with low-dose RAASi, **high-dose RAASi** may be **more effective** at reducing atherosclerosis progression in patients with **high-risk of CV events**



HEAAL[3]

Double-blind, prospective trial investigating effects of high-dose vs low-dose losartan on clinical outcomes in patients with HF

Compared with low-dose, patients receiving **high-dose losartan had:**

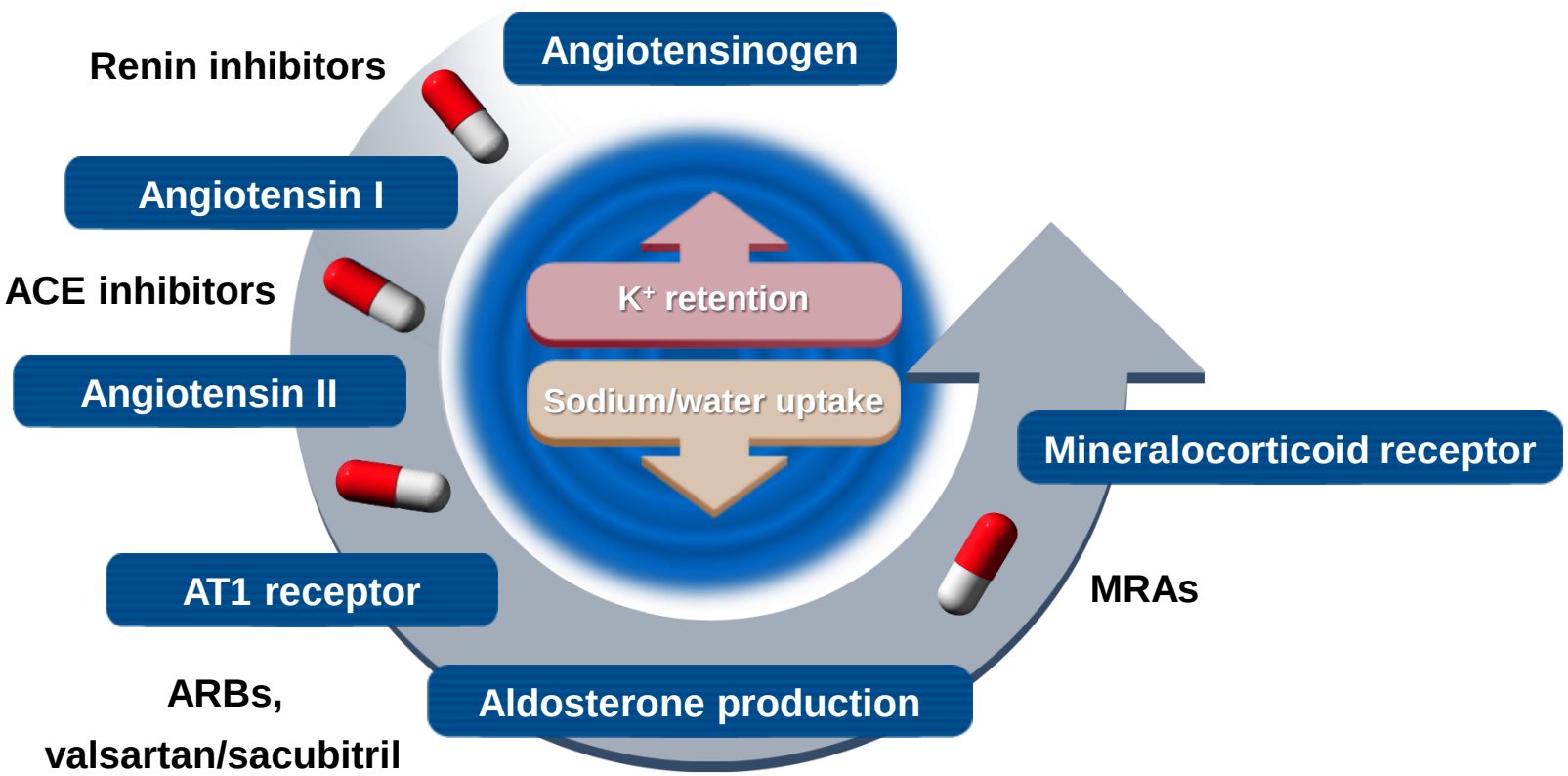
- **10%** risk reduction of **all-cause mortality** or **HF hospitalisation** **HR 0.90**; *P*=0.027
- **13%** risk reduction of **HF hospitalisation** **HR 0.87**; *P*=0.025
- **9%** risk reduction of **CV mortality** or **CV hospitalisation** **HR 0.91**; *P*=0.034
- **12%** risk reduction of **CV mortality** or **HF hospitalisation** **HR 0.88**; *P*=0.011

*vs placebo. See slide notes for abbreviations.

1. Packer M, *et al*. *Circulation*. 1999;100:2312–18; 2. Lonn EM, *et al*. *Circulation*. 2001;103:919–25; 3. Konstam MA, *et al*. *Lancet* 2009;374:1840–8.

ALL RAASI INCREASE SERUM POTASSIUM LEVELS

Hyperkalaemia is an inherent risk in the treatment of HF with RAASi



ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; AT1, angiotensin II receptor type 1; HF, heart failure; K^+, potassium; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

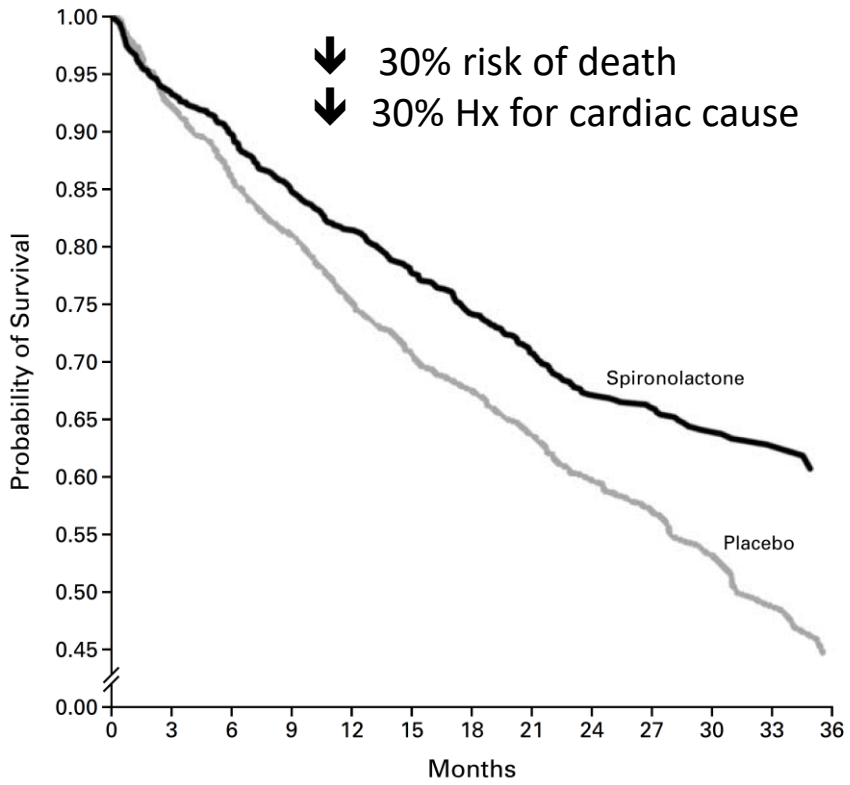
Palmer BF. *New Engl J Med.* 2004;351:585–92; Ponikowski P, *et al*. *Eur Heart J.* 2016;37:2129–200.

The New England
Journal of Medicine

VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

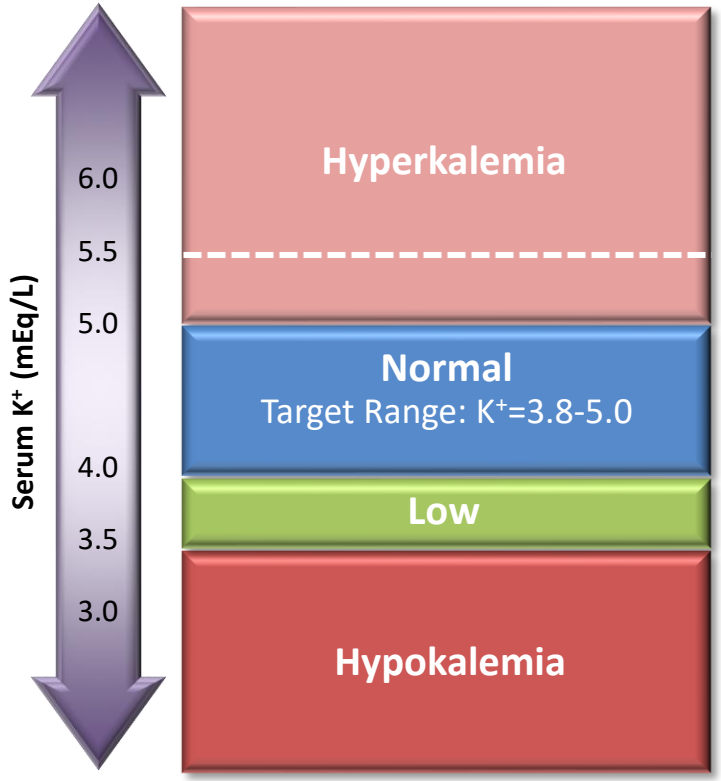
BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*



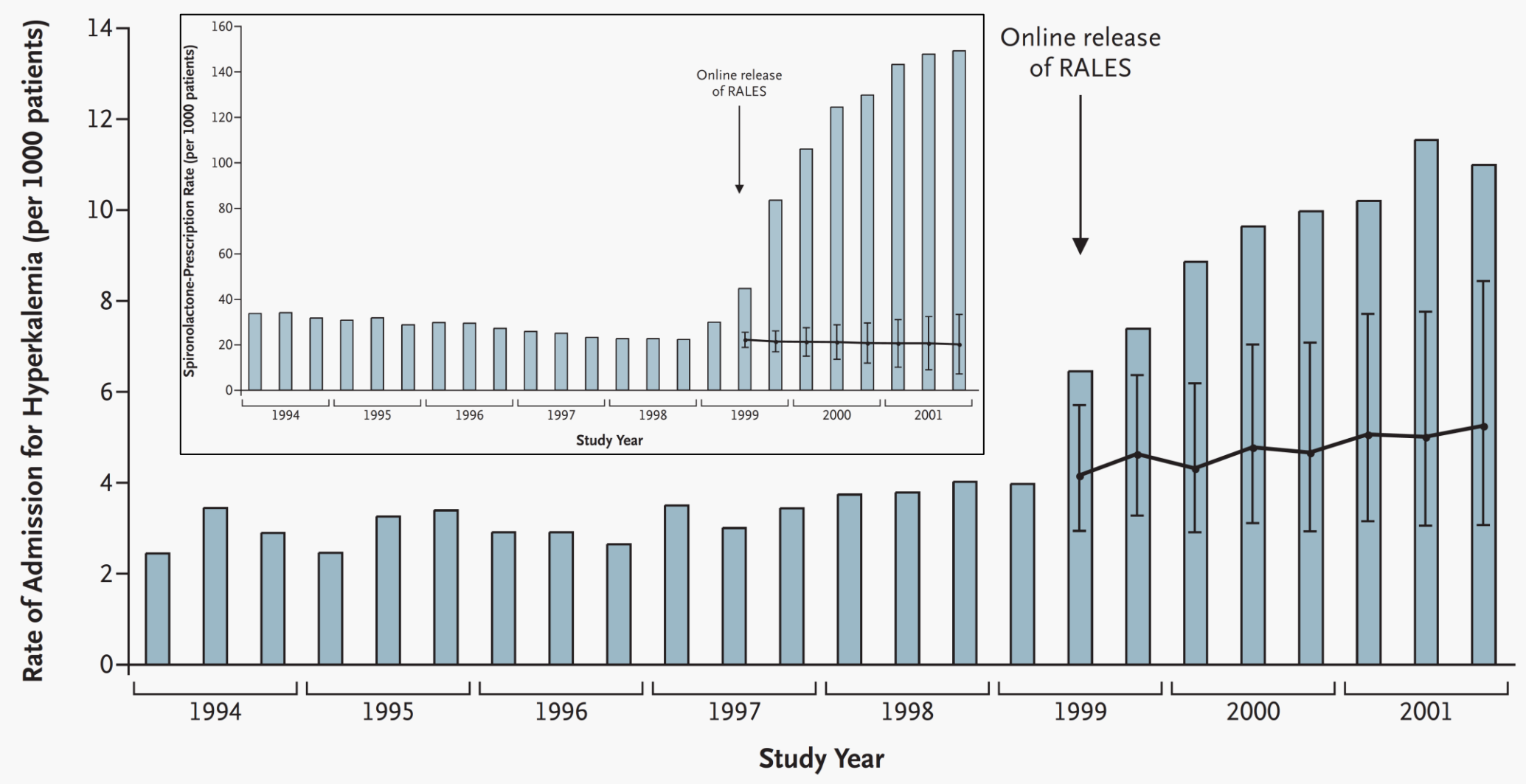
NO. AT RISK

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Pitt B et al. N Eng J Med 1999

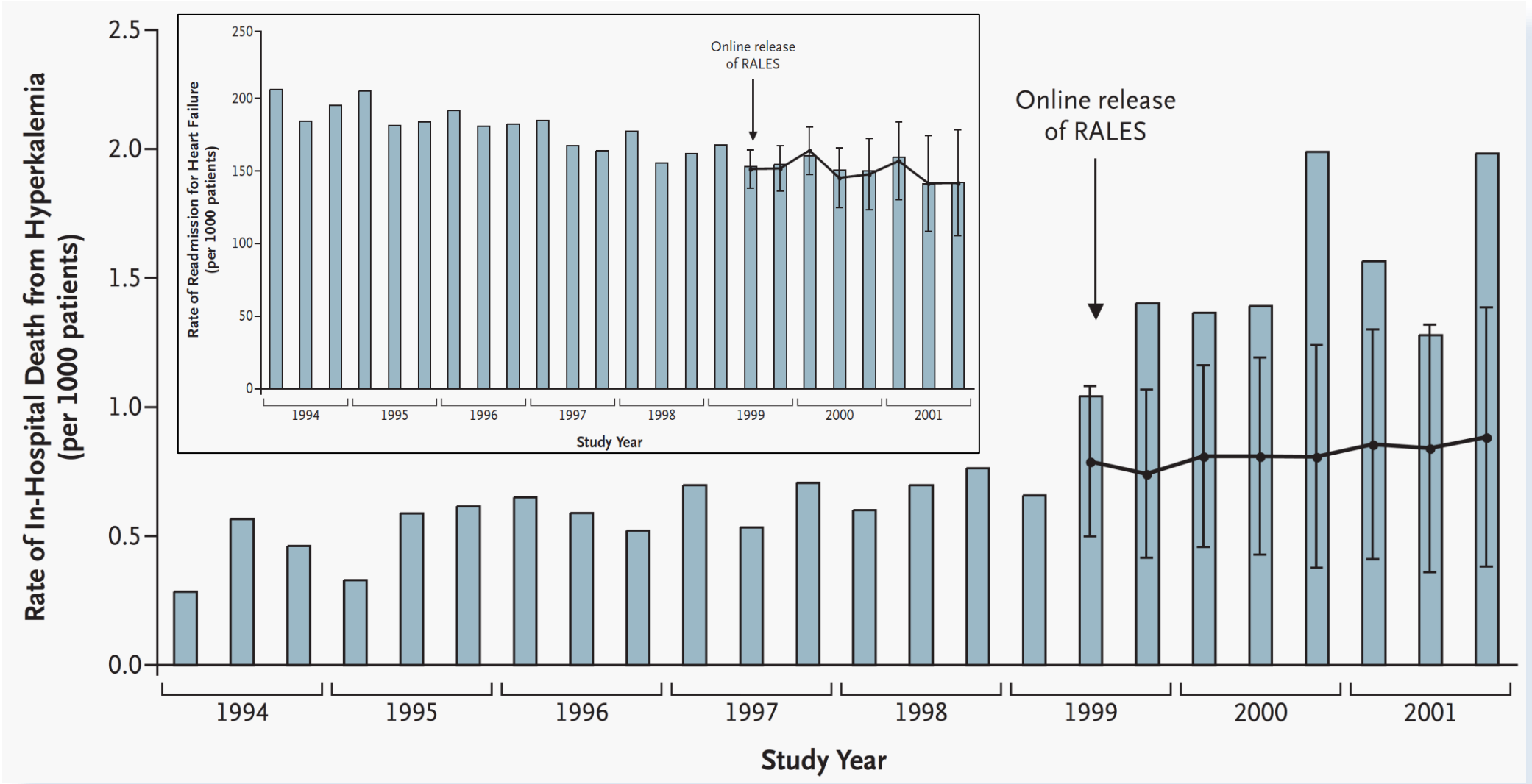


Rate of hospital admission for hyperkalemia among patients recently hospitalized for HF who were receiving ACE-I



Juurlink DN et al. N Engl J Med 2004;351:543-51.

Rate of hospital admission for hyperkalemia among patients recently hospitalized for HF who were receiving ACE-I



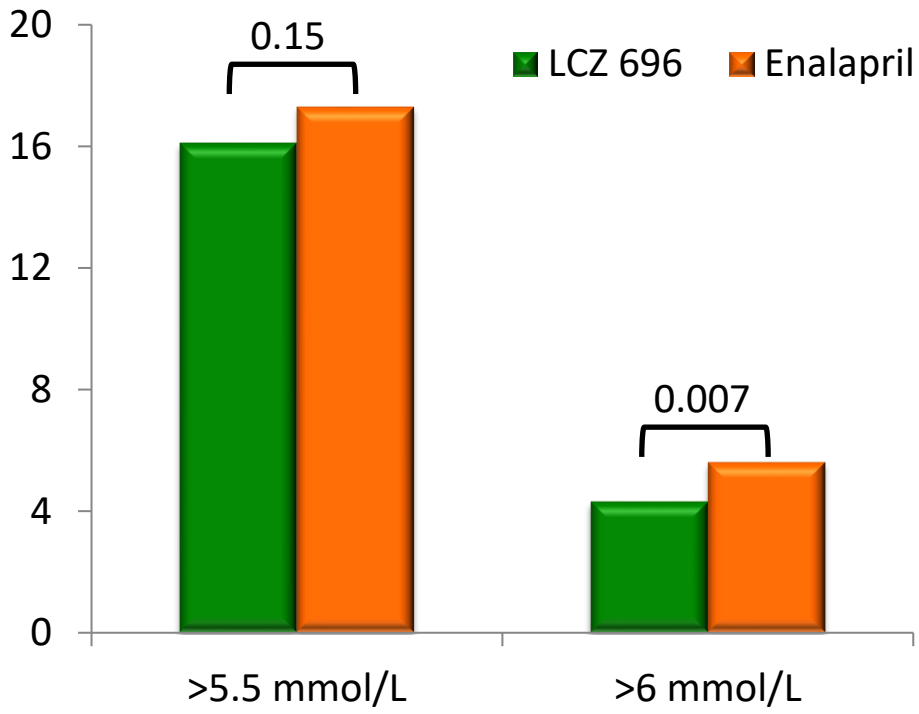
Juurlink DN et al. N Engl J Med 2004;351:543-51.

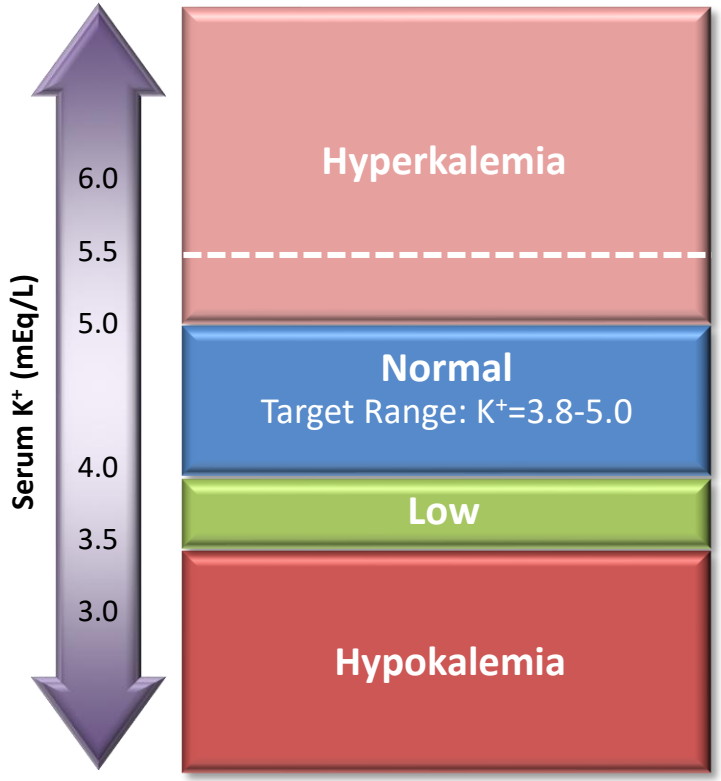
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

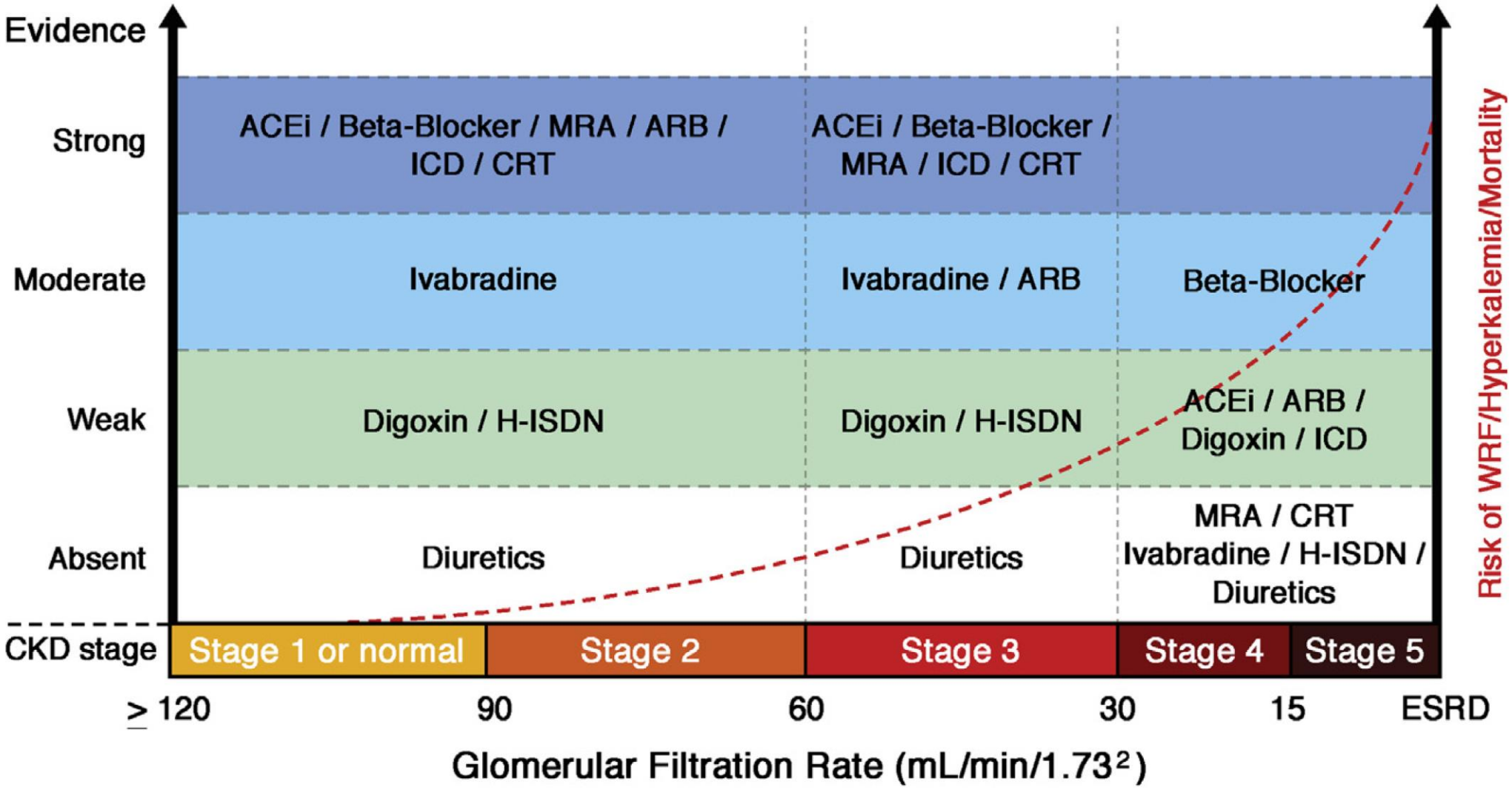
John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*





McMurray JJV et al. N Engl J Med 2014;371:993-1004.

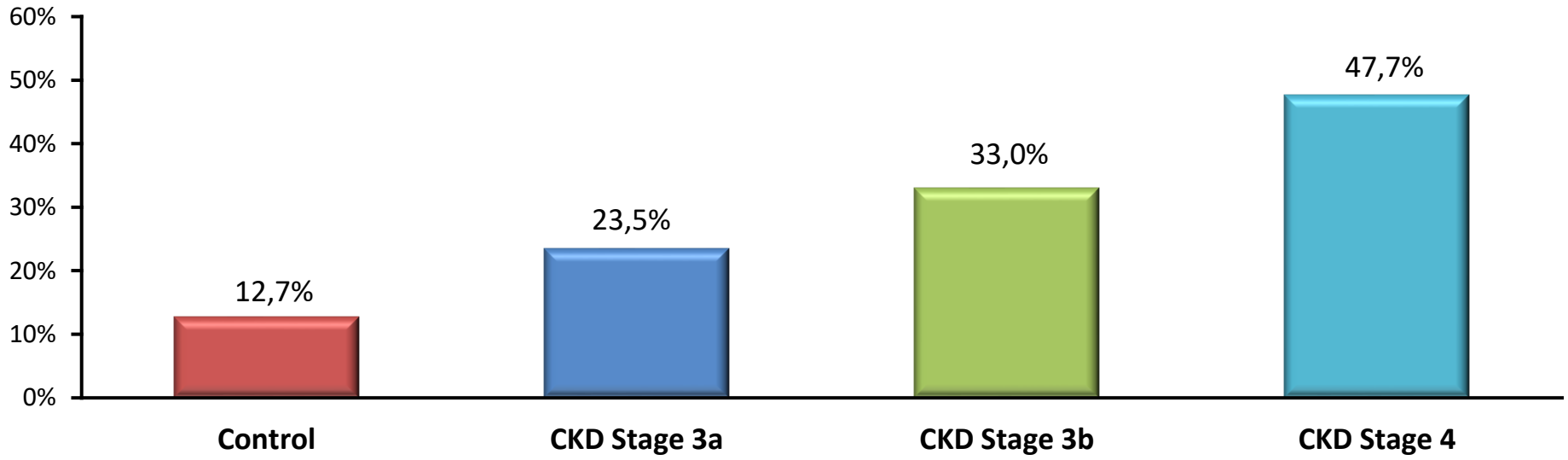
Current Evidence on Treatment of Patients With Chronic Systolic Heart Failure and Renal Insufficiency



Damman K et al. J Am Coll Cardiol 2014;63:853–71

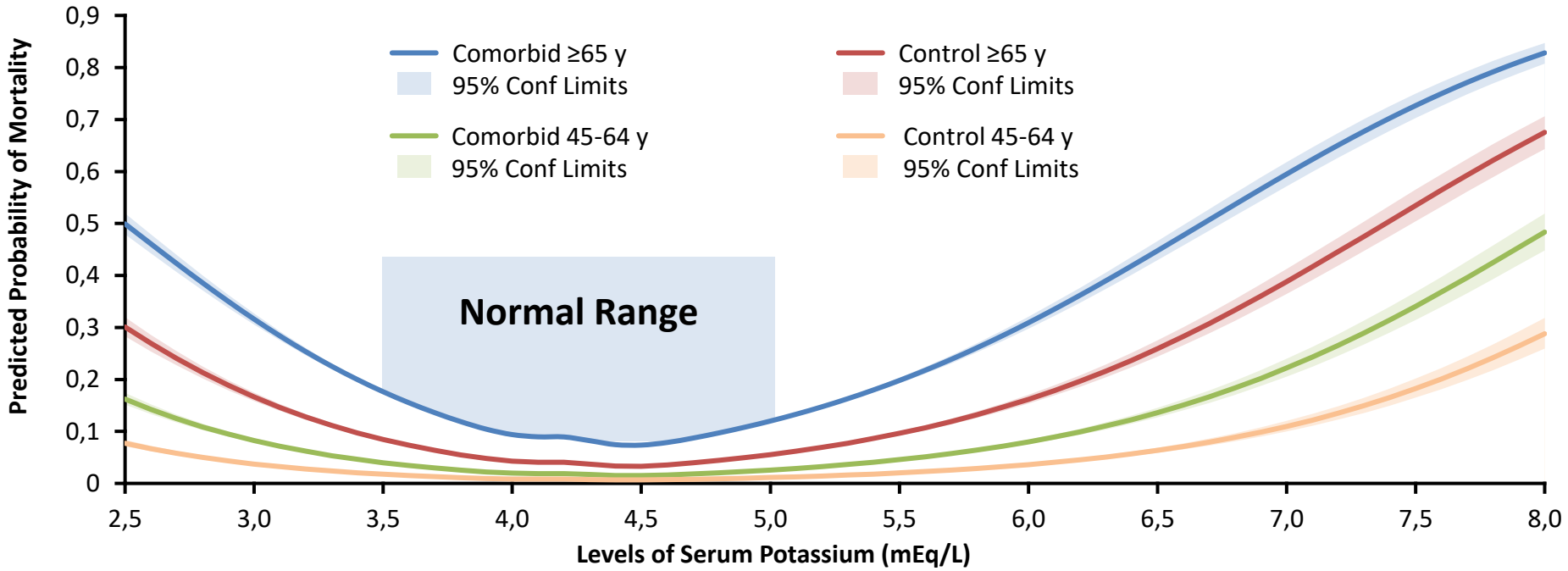
Hyperkalemia Is Prevalent Among Older Populations With Advanced Kidney Disease

5-Year Database Prevalence of Hyperkalemia
Control Population vs CKD Stages 3a, 3b, and 4 in Patients ≥65 Years



- CKD: chronic kidney disease
- Based on an analysis of 1.63 million persons aged ≥5 years with K^+ readings on 2 dates (2008-2012), with >1 K^+ value between 2.5 and 10 mEq/L during 2008-2012. Control population composed of patients ≥65 years without CKD stages 2-5, heart failure, diabetes, or end-stage renal disease (ESRD).
- Hyperkalemia defined as highest reported K^+ value ≥5.1 mEq/L in 2008-2012.
- Data on file. Relypsa, Inc., Redwood City, CA. Data source: Humedica, Cambridge, MA.

Adjusted Mortality* by Serum K^+ Level in Patients 45 to 64 Years and ≥65 Years With and Without Comorbid Illness

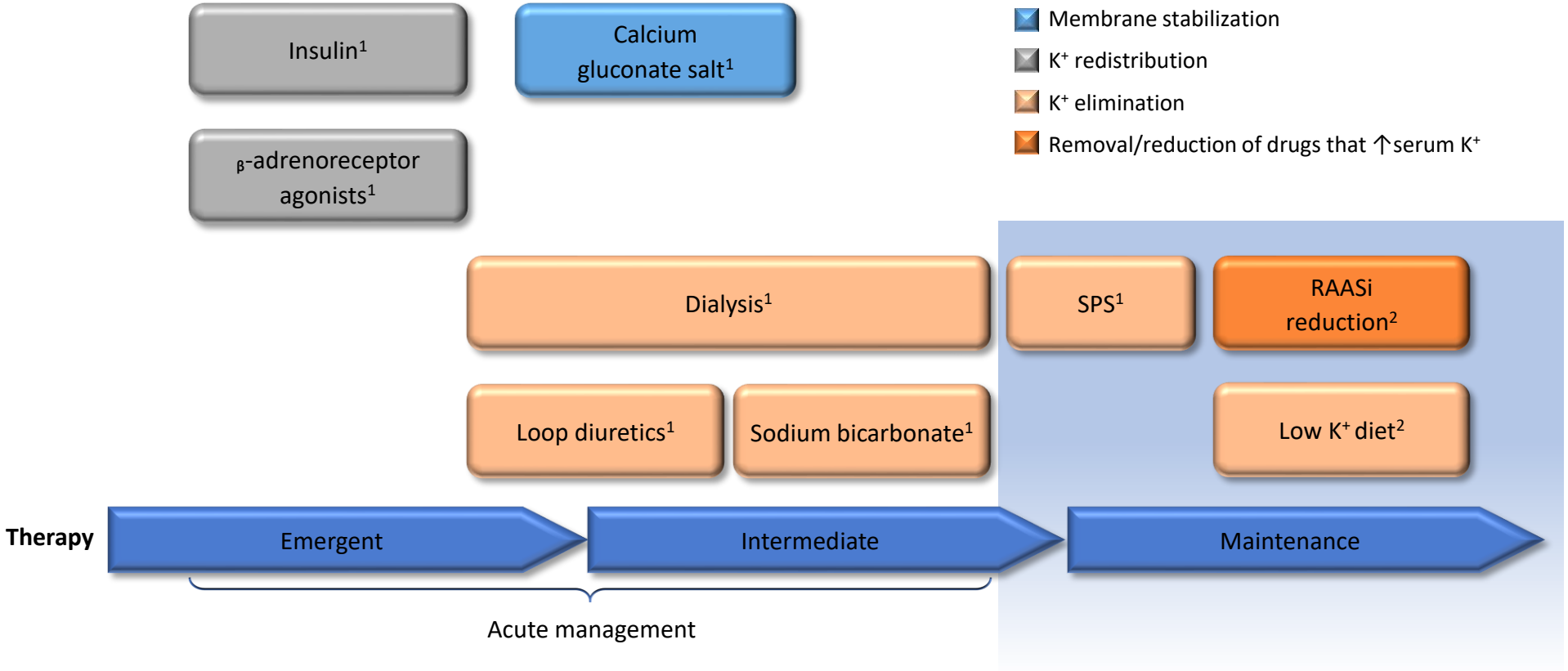


Increases in mortality remained after adjustments for demographic characteristics and comorbidities

*Evaluated through de-identified medical records (2007-2012) of individuals with ≥2 mEq/L serum K^+ readings (Humedica, Cambridge, MA). Spline analyses were performed to assess mortality at 0.1 mEq/L increments of serum K^+ after adjusting for covariates and interactions. Comorbid patients are those with diabetes, heart failure, CKD stages 3-5, cardiovascular disease, or hypertension.

Pitt B, et al. 2014 AHA Scientific Sessions; November 15-19, 2014; Chicago, IL; Poster 2443.

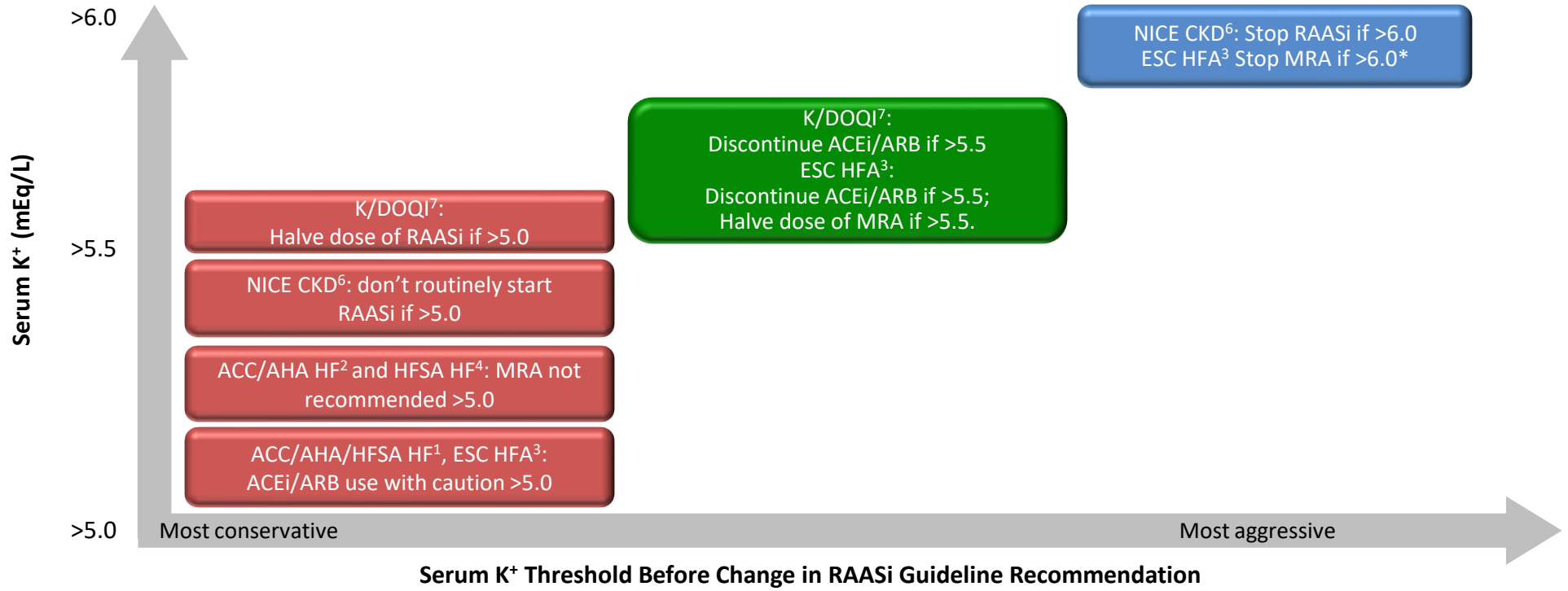
Traditional Treatment Options for Hyperkalemia



RAASi: renin-angiotensin-aldosterone system inhibitor, SPS: sodium polystyrene sulfonate

1. Weisberg L. *Crit Care Med*. 2008;36(12):3246-3251. 2. Palmer BF, et al. *N Engl J Med.* 2004;351(6):585-592.

Guidelines Recommend RAASi Dose Modifications With Increasing Serum K+



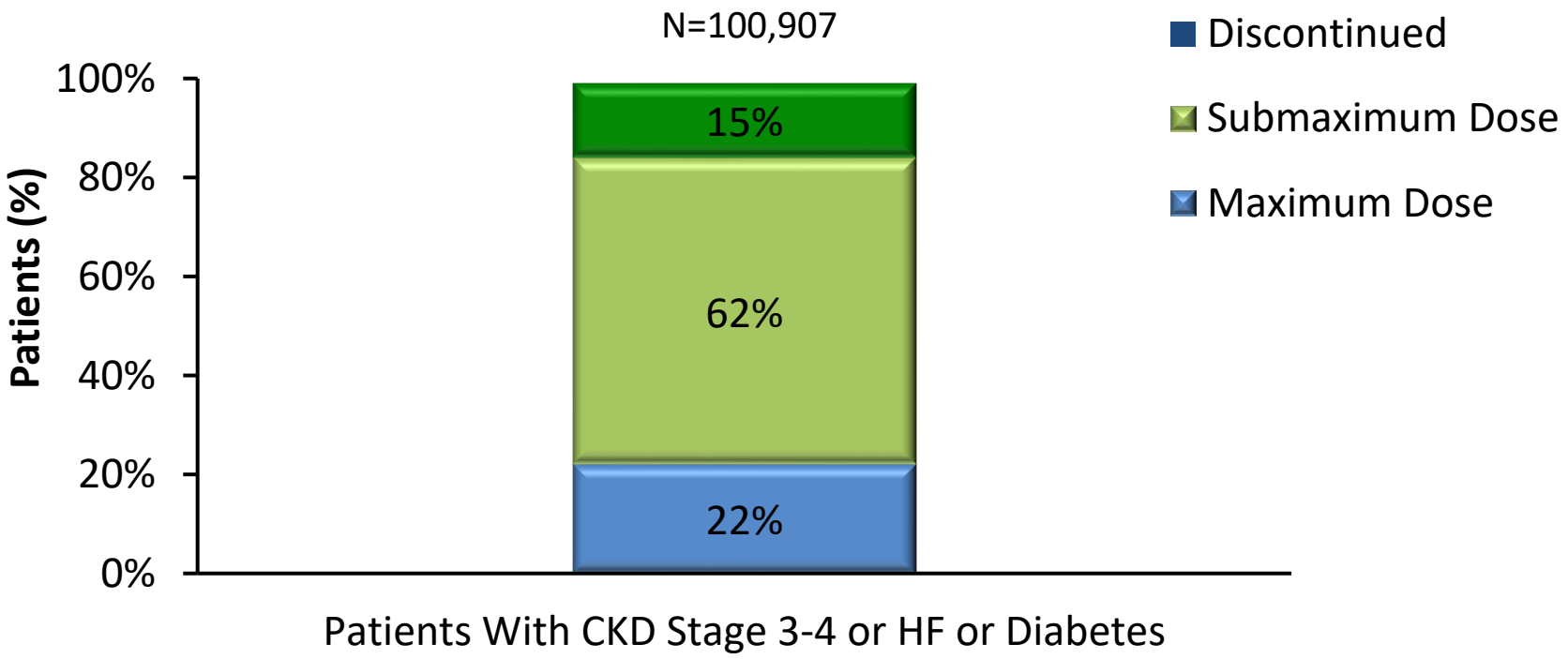
KDIGO Guidelines do not provide recommendations[5]

**ESC HFA: Management of acute hyperkalemia (>6.0) may require a short-term cessation of K+-retaining agents and RAASi, but this should be minimized and RAASi should be carefully reintroduced as soon as possible while monitoring K+ levels.*[3]

1. *Yancy CW, et al. Circulation. 2016;134:[Epub ahead of print].* ***2.*** *Yancy CW, et al. Circulation. 2013;128:1810-1852.* ***3.*** *Ponikowski P, et al. European Heart Journal. 2016 May 20. pii: ehw128. [Epub ahead of print].* ***4.*** *Heart Failure Society of America, Lindenfeld J, et al. J Card Fail. 2010;16(6):475-539.*
5. *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3(1).* ***6.*** *National Institute for Health and Clinical Excellence (NICE) [UK]. Chronic kidney disease (partial update): Early identification and management of chronic kidney disease in adults in primary and secondary care. 2014. https://www.nice.org.uk/guidance/cg182/evidence/update-full-guideline-191905165.* ***7.*** *National Kidney Foundation. Guideline 11. http://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed February 17, 2015.*

Few Patients Are on Maximum RAASi

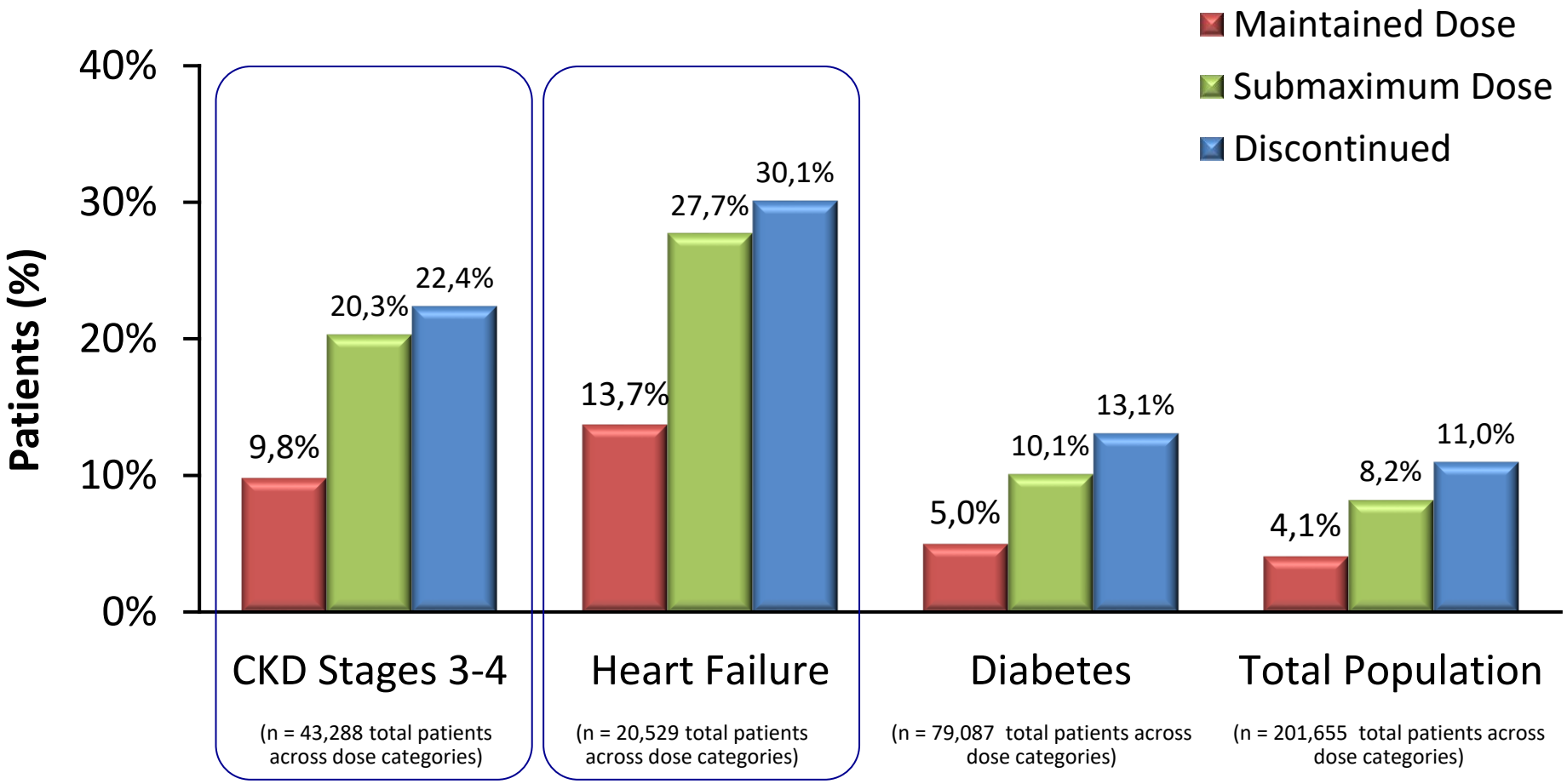
- Distribution of RAASi Dose Levels in Patients With CKD Stage 3-4 or Heart Failure or Diabetes



- RAASi prescriptions were classified by dose level using the following dose categories:
  - **"Maximum,"** defined as the labeled dose
  - **"Submaximum,"** defined as any RAASi dose lower than the labeled dose
  - **"Discontinued,"** defined as the absence of RAASi prescriptions for >390 days subsequent to prior prescription

Epstein M, et al. *Am J Manag Care.* 2015;21:S212-S220.

Percent Mortality by Prior RAASi Dose



Epstein M, et al. *Am J Manag Care.* 2015;21:S212-S220.

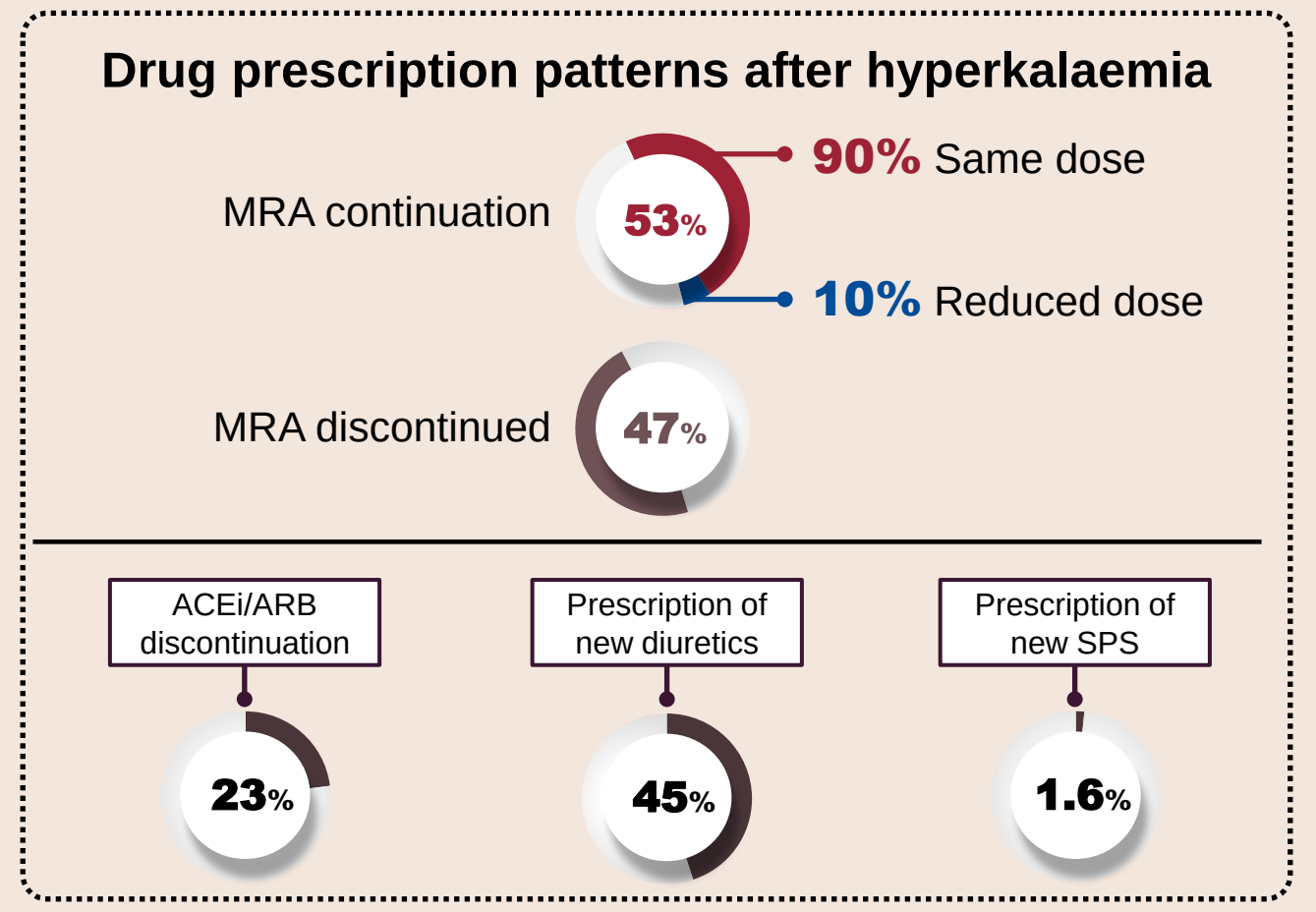
RAASI ARE FREQUENTLY DISCONTINUED OR REDUCED IN PATIENTS WITH HF AFTER A HYPERKALAEMIA EVENT

Objective

This study investigated the 1-year incidence and clinical HK predictors, and quantified drug prescription changes after an episode of HK in 13,726 Swedish patients initiating MRA therapy during 2007–2010

MRA discontinuation

- Discontinuation rates were higher after moderate/severe (K^+ >5.5 mEq/L) and <3 months from MRA initiation
- Participants with CKD carried the highest risk of MRA discontinuation

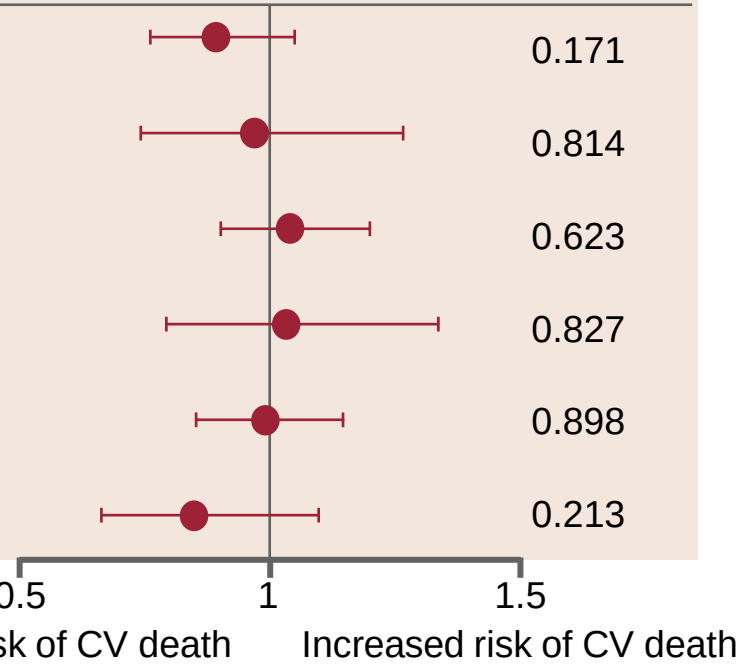


See slide notes for abbreviations.
Trevisan M, *et al. Eur J Heart Fail.* 2018;20:1217–26.

UNRAVELLING THE INTERPLAY BETWEEN HK, RAASI USE AND CLINICAL OUTCOMES

Risk of CV death due to HK was no longer statistically significant after controlling for RAASi therapy discontinuation; data from the ESC-HFA-EORP Heart Failure Long-term Registry (n~9000)

Mediator	K^+ at baseline, mEq/L	Risk of CV death HR (95% CI)	*P*-value
ACEi discontinuation	5–5.5	0.89 (0.76, 1.05)	0.171
	>5	0.97 (0.74, 1.27)	0.814
ARB discontinuation	5–5.5	1.04 (0.90, 1.20)	0.623
	>5	1.03 (0.79, 1.34)	0.827
MRA discontinuation	5–5.5	0.99 (0.85, 1.15)	0.898
	>5	0.85 (0.66, 1.10)	0.213



Is HK a risk marker for RAASi discontinuation rather than being a risk factor for worse outcomes?

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CV, cardiovascular; ESC-HFA-EORP, European Society of Cardiology Heart Failure Association EURObservational Research Programme; HK, hyperkalaemia; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.
Rossignol P, *et al. Eur J Heart Fail.* 2020;22:1378–89.

HYPERKALAEMIA AS A RISK MARKER IN HEART FAILURE

Hyperkalaemia is not a risk factor for poor outcomes

Hyperkalaemia ⊘→ **Poor outcomes**

- A **U-shaped relationship** between K^+ and poor outcomes has been observed in HF and CKD[1–3]
- However, multivariable adjustment varies and data for the association of hyperkalaemia with worse outcomes are **inconsistent**[4]

Hyperkalaemia is a risk marker for poor outcomes

Hyperkalaemia → **Suboptimal RAASi use** → **Poor outcomes**

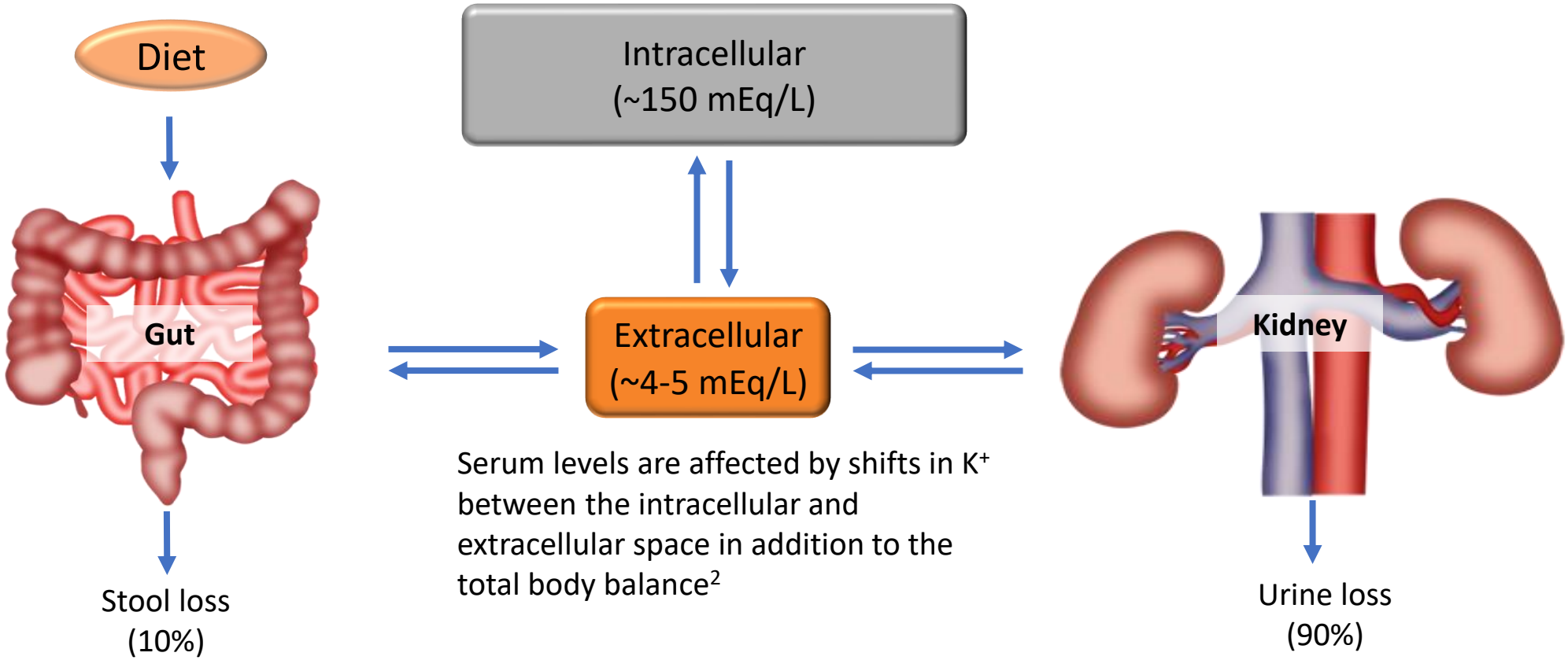
- According to several clinical trials, the benefit of RAASi was **not attenuated by hyperkalaemia**[5–7]
- Instead, real-world studies have demonstrated that suboptimal use of RAASi due to hyperkalaemia have been **associated with poor clinical outcomes**[8,9]

The main goal for patients with HFrEF and concomitant CKD and/or hyperkalaemia should be to optimise RAASi use[1]

CKD, chronic kidney disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor.

1. Lund LH and Pitt B. *Eur J Heart Fail*. 2018;20:931–2; 2. Luo J, *et al. Clin J Am Soc Nephrol.* 2016;11:90–100; 3. Aldahl M, *et al. Eur Heart J.* 2017;38:2890–96;
4. Martens P, *et al. Acta Cardiol.* 2020;1–9 doi: 10.1080/00015385.2020.1771885; 5. Vardeny O, *et al. Circ Heart Fail.* 2014;7:573–9; 6. Rossignol P, *et al. Circ Heart Fail.* 2014;7:51–8; 7. Beusekamp JC, *et al. Eur J Heart Fail.* 2018;20:923–30;
8. Epstein M, *et al. Am J Manag Care.* 2015;21:S212–20; 9. Rossignol P, *et al. Eur J Heart Fail.* 2020;22:1378–89.

Normal Potassium Distribution[1,2]



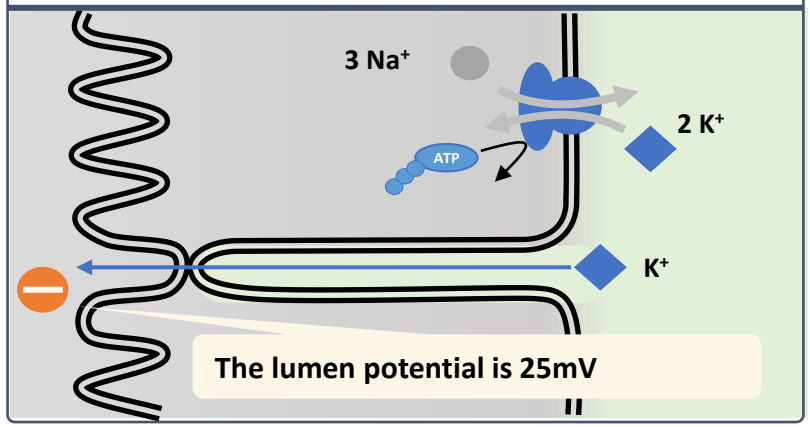
Serum levels are affected by shifts in K^+ between the intracellular and extracellular space in addition to the total body balance[2]

1. Evans KJ, Greenberg A. *J Intensive Care Med*. 2005;20(5):272-290.
2. Brown RS. *Am J Med*. 1984;77(5A):3-10.

The Response to Elevated Serum K^+ Levels Is an Increase in Colonic K^+ Secretion Using 2 Mechanisms

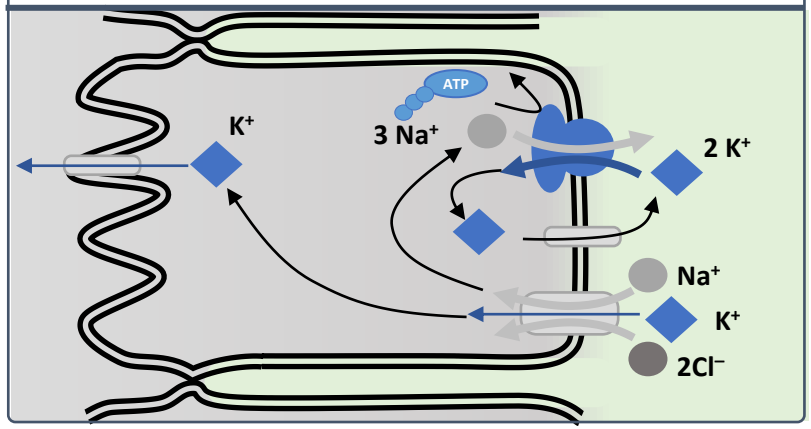
Passive secretion

- Responsible for net colonic K^+ secretion
- Paracellular secretion (extracellular to intracellular space across tight junctions)
- Greatest in the distal end of the colon



Active secretion

- Occurs throughout the colon
- Mechanistically follows the "pump-leak" model
  - Basolateral uptake of K^+ via Na^+/K^+ pump and $Na^+/K^+/Cl^-$ cotransporter
  - Efflux of K^+ through BK channels



BK: big K^+; Cl^-: chloride; Na^+, sodium.

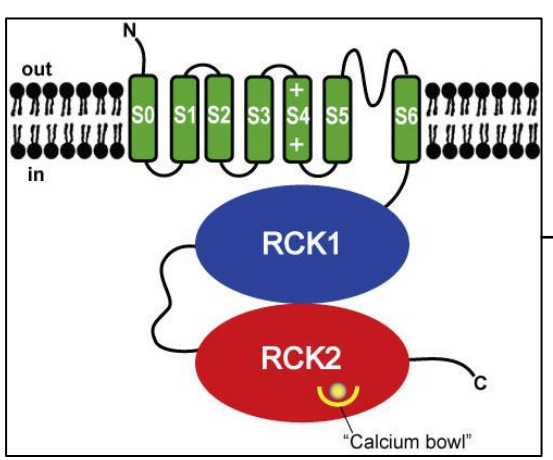
Binder HJ. In: Boron WF, Boulpaep EI, eds. *Medical Physiology.* Philadelphia, PA: Elsevier; 2005:931-946.

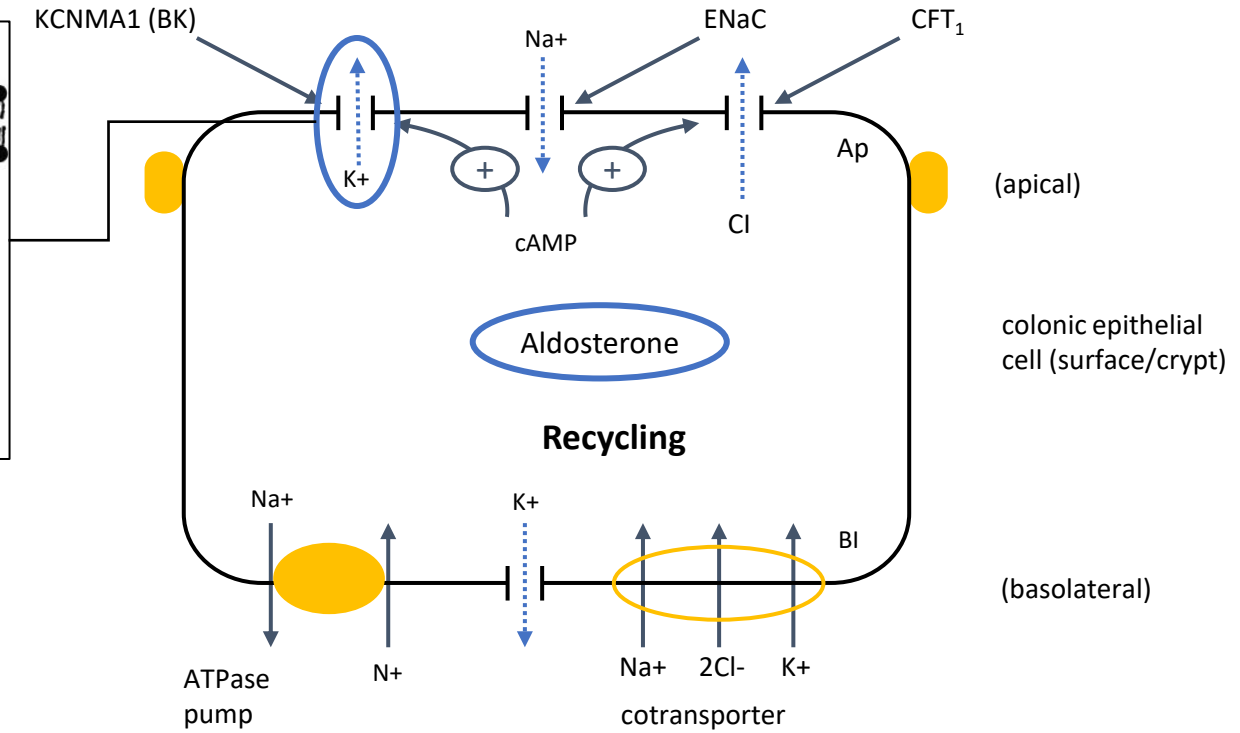
CKD and ESRD Adaptation Includes Increased K^+ Secretion in the Colon

In CKD and ESRD patients, active K^+ secretion is increased (>70 mEq/day)[1]

Increased BK channel expression and concentration on the colonic epithelial cell apical surface[2]

As CKD progresses, BK channel content increases independent of plasma K+ concentration, transmucosal potential difference, or aldosterone status[2]



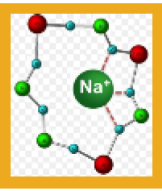
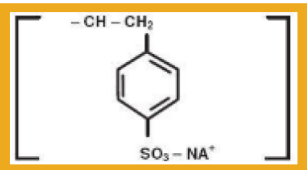
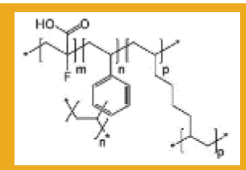


Channels:
KCNMA1 (BK) = electrogenic K^+ secretion
ENaC = electrogenic Na^+ absorption
CFTR = electrogenic Cl^- secretion

ESRD: end-stage renal disease

1. Mathialahan T, et al. *J Pathol*. 2005;206(1):46-51. 2. Sandle GI, et al. *Q J Med*. 2009;159:1-5.

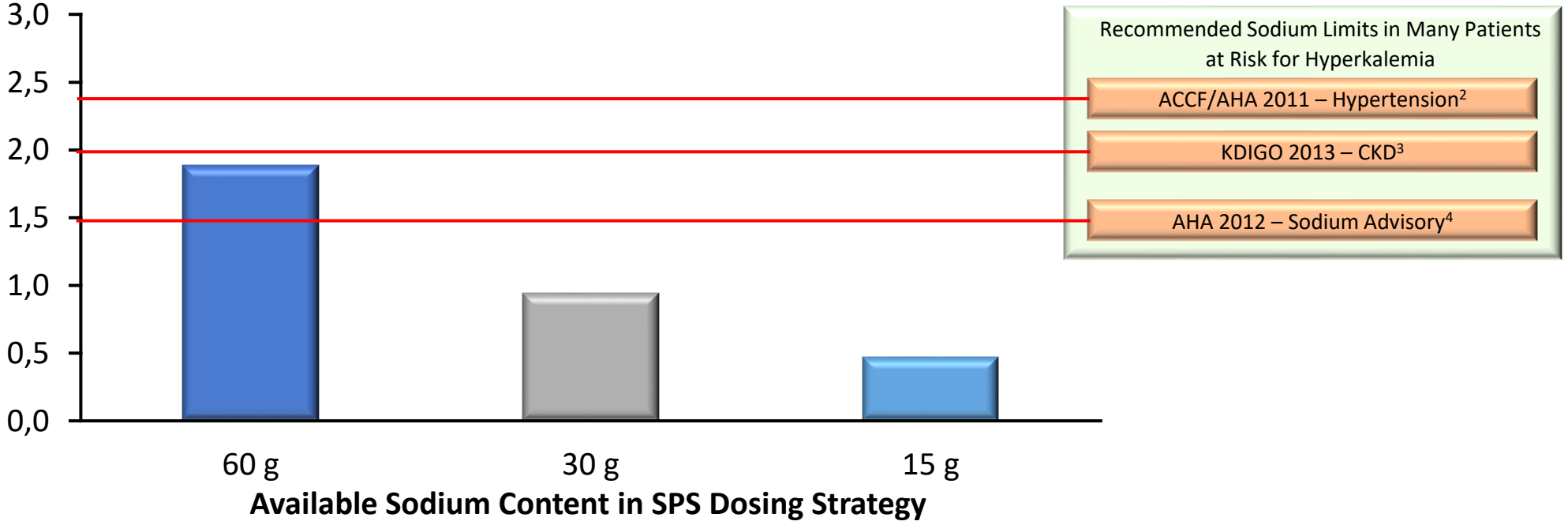
Comparison of Key Potassium Binders1

	ZS-9[1] 	SPS[1] 	Patiromer[1] 
Type of compound	Non-absorbed, insoluble inorganic crystal	Non-absorbed, organic polymer in a sorbitol base	Non-absorbed, organic polymer and sorbitol complex
Mechanism of action	Selective potassium binding in exchange for Na^+ and H^+	Non-specific cation binding in exchange for sodium	Non-specific cation binding in exchange for Ca^{2+}
Route of administration	Oral	Oral or rectal	Oral
Formulation	Oral suspension (Dissolvable tablet if FDA-approved[2])	Suspension in sorbitol or dissolvable powder	Oral suspension
Location of potassium binding	Entire intestinal tract	Colon	Distal colon predominantly

1. GarimellaPS, et al. *Am J Kidney Disease* 2016;Epub ahead of print; 2. Chaitman M et al. *PT*. 2016;41(1):43–50.

Sodium Polystyrene Sulfonate and Sodium Content

SPS Contains 9.4% sodium by weight (4.1 mEq/g)[1]



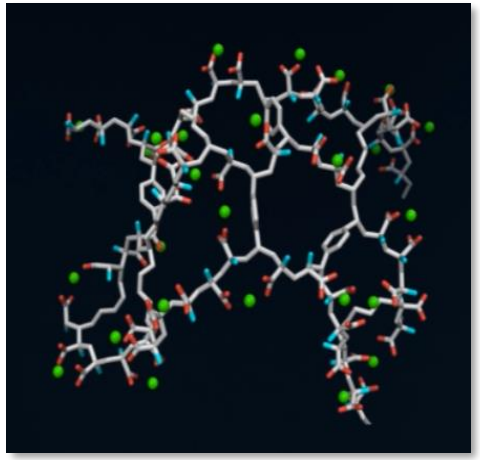
Since the in vivo efficiency of SPS is about 33%, approximately 1/3 of the resin's actual sodium content is being delivered to the body[1]

SPS dosing may use up a sizable portion of a sodium-restricted patient's daily sodium allowance

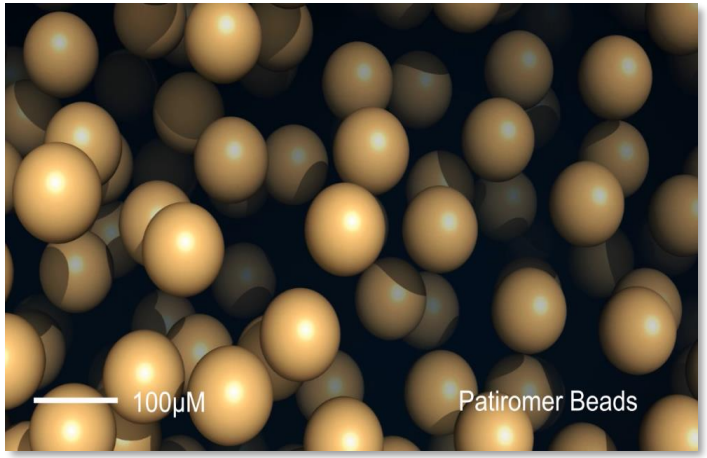
1. Kayexelate [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2010.
2. Whelton P, et al. *Circulation*. 2012;126:2880-2889.
3. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1).
4. Aronow WS, et al. *Circulation.* 2011;123:2434 -2506.

Patiromer Is a Novel, Sperical, Non-absorbed K^+ Binder

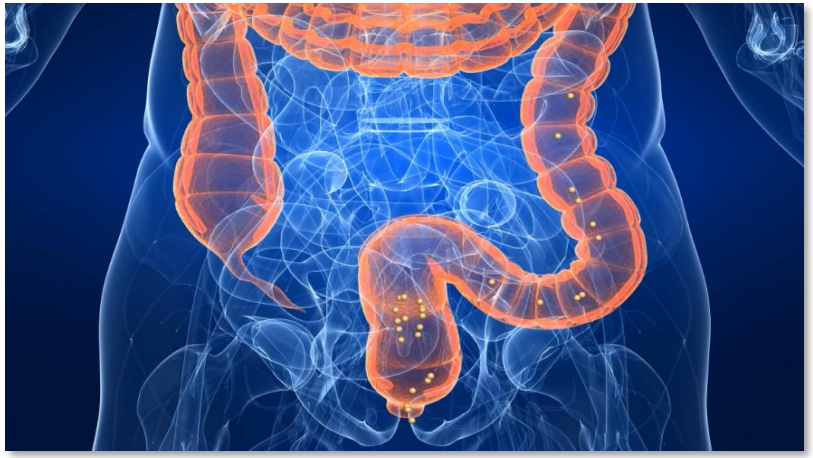
- High-capacity K^+ binder
- Average bead size (100 µM) is too large for patiromer to be absorbed from the gastrointestinal tract, enabling patiromer to be passed through the entire GI tract and absorb more K^+
- Uniform spherical shape, size, and low-swelling beads ratio



High-capacity polymer



Uniform, spherical patiromer beads

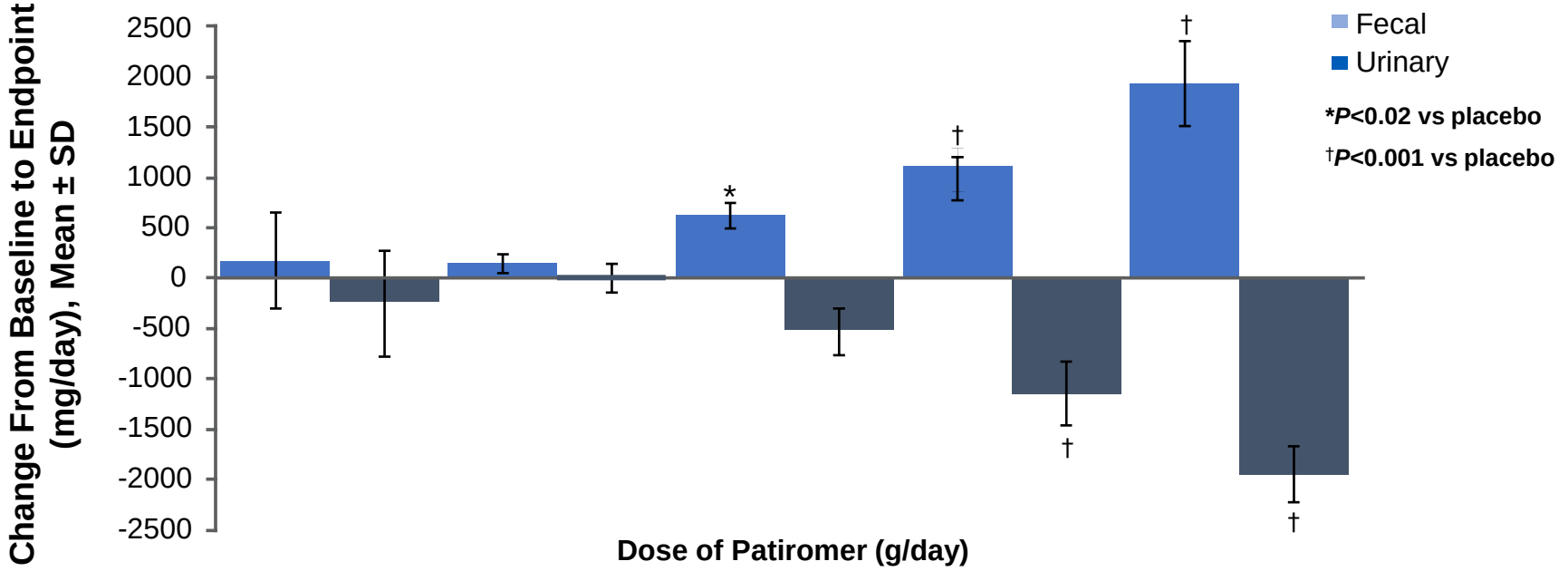


Patiromer travels through the gastointestinal tract over 24-72 hours

Patiromer is fully ionized at the physiologic pH of the colon for optimal ion exchange. Carboxylate groups of patiromer bind to K^+, which is primarily in the colon due to upregulation of BK channels in colonic epithelial cells. Patiromer beads are excreted, leading to removal of excess K^+ and reduction of serum K^+ levels. Ca^{2+} is exchanged for K^+

Li L, et al. *J Cardiovasc Pharmacol Ther.* 2016;doi:10.1177/107428416629549.

Patiromer Increases Fecal and Decreases Urinary K^+ Excretion in Healthy Volunteers



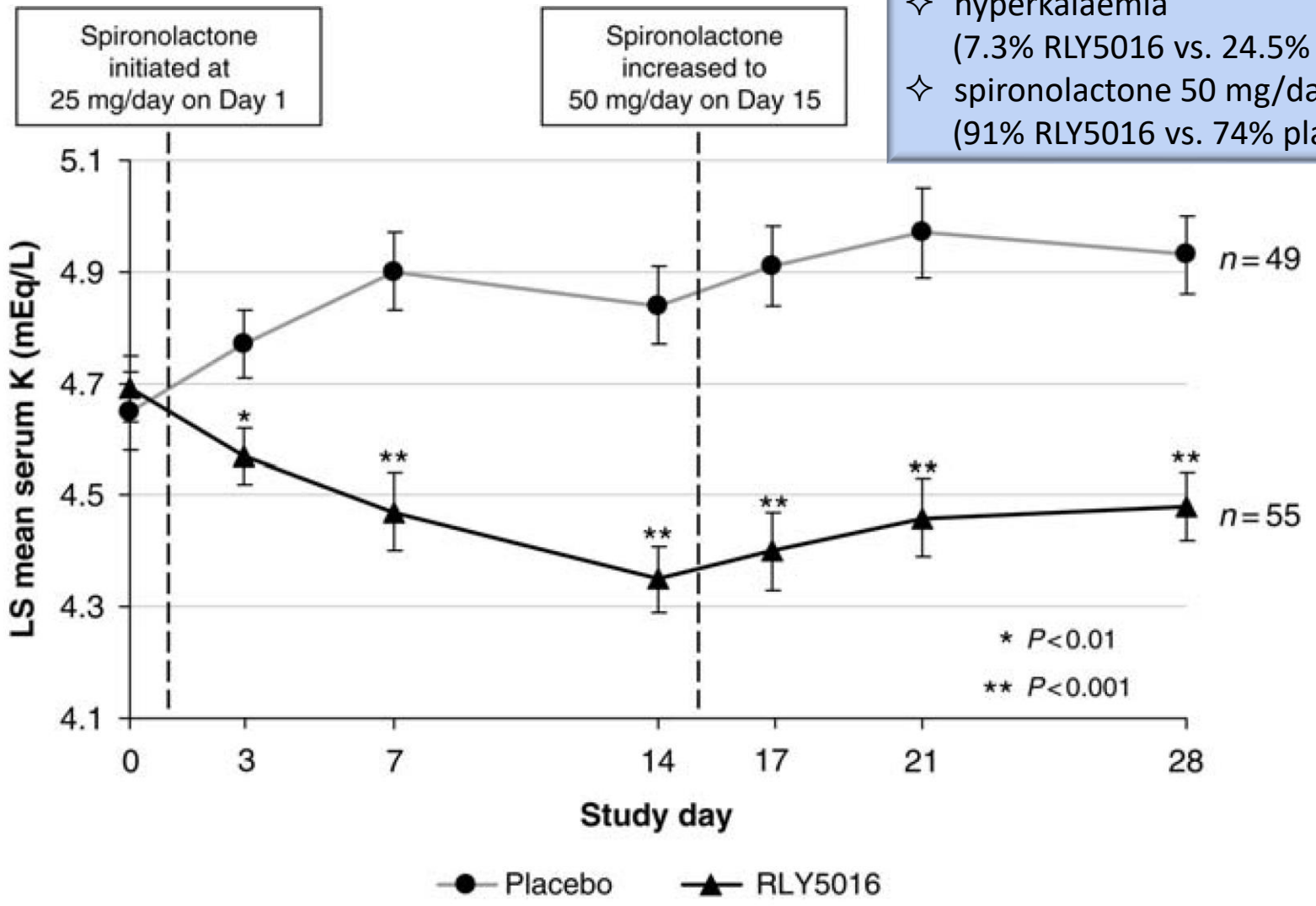
	Placebo	0.8	4.2	8.4	16.8
	n=8	n=6	n=6	n=6	n=6
Baseline Fecal Excretion	768.1±297.9	758.1±91.5	794.0±198.9	676.5±114.5	862.0±172.6
Baseline Urinary Excretion	3644.9±468.3	3493.7±570.4	3447.2±446.6	3765.5±325.8	3748.8±248.5

SD: standard deviation.

Li L, et al. *J Cardiovasc Pharmacol Ther*. 2016;doi:10.1177/1074248416629549.

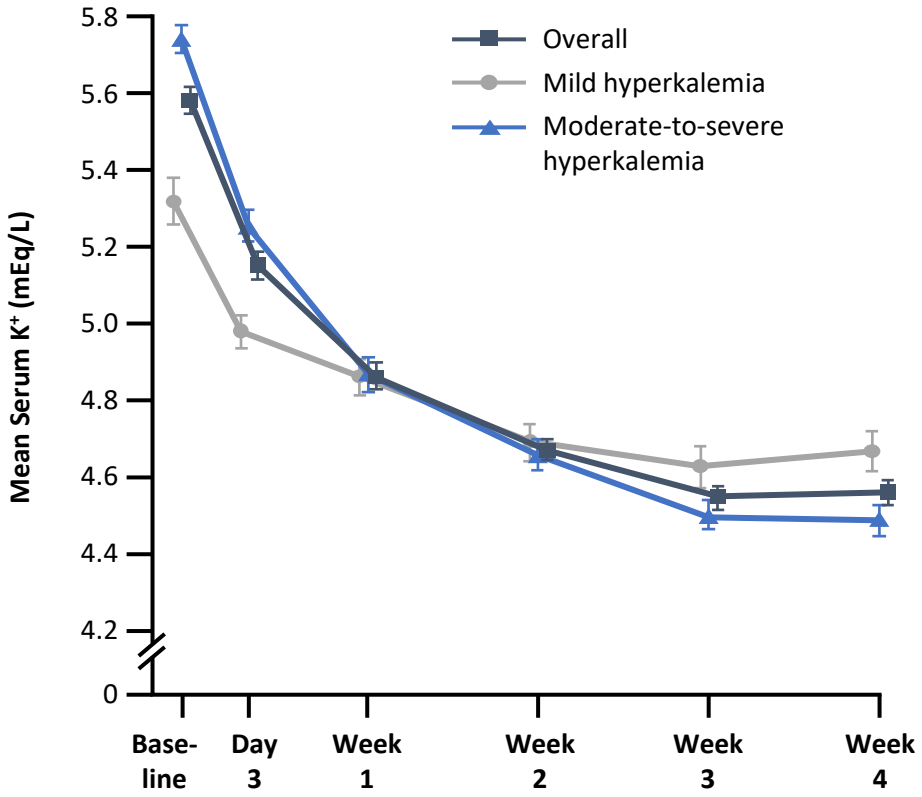
Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with **chronic heart failure (the PEARL-HF)** trial

- hyperkalaemia (7.3% RLY5016 vs. 24.5% placebo, P . 0.015)
- spironolactone 50 mg/day (91% RLY5016 vs. 74% placebo, P . 0.019).



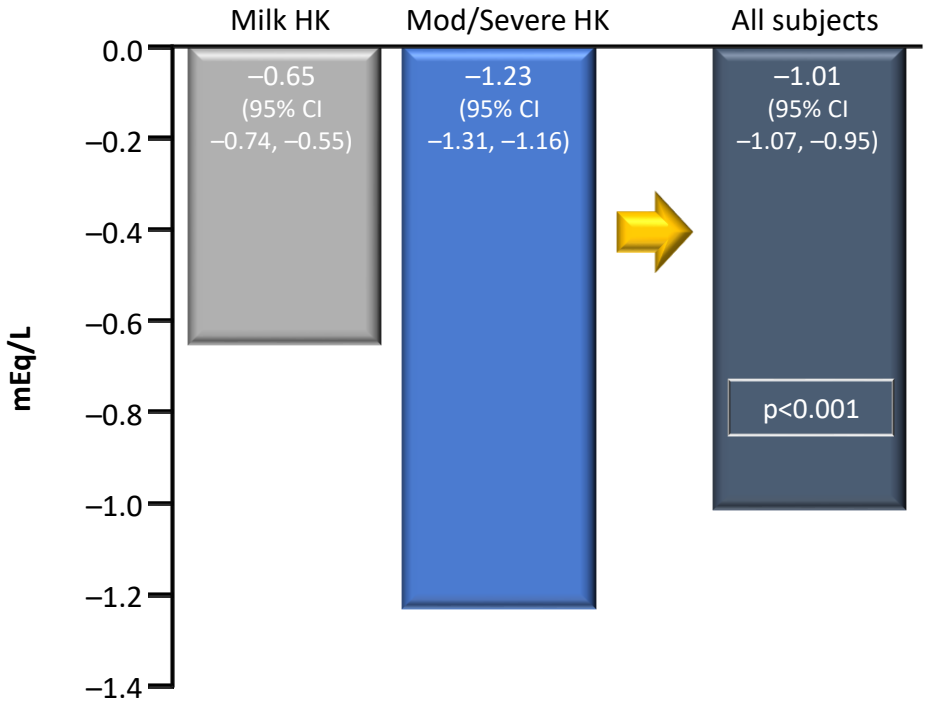
Pitt B et al. European Heart Journal (2011) 32, 820–828

OPAL-HK Part A: Primary and Secondary Efficacy Endpoints



HK; hyperkalemia.

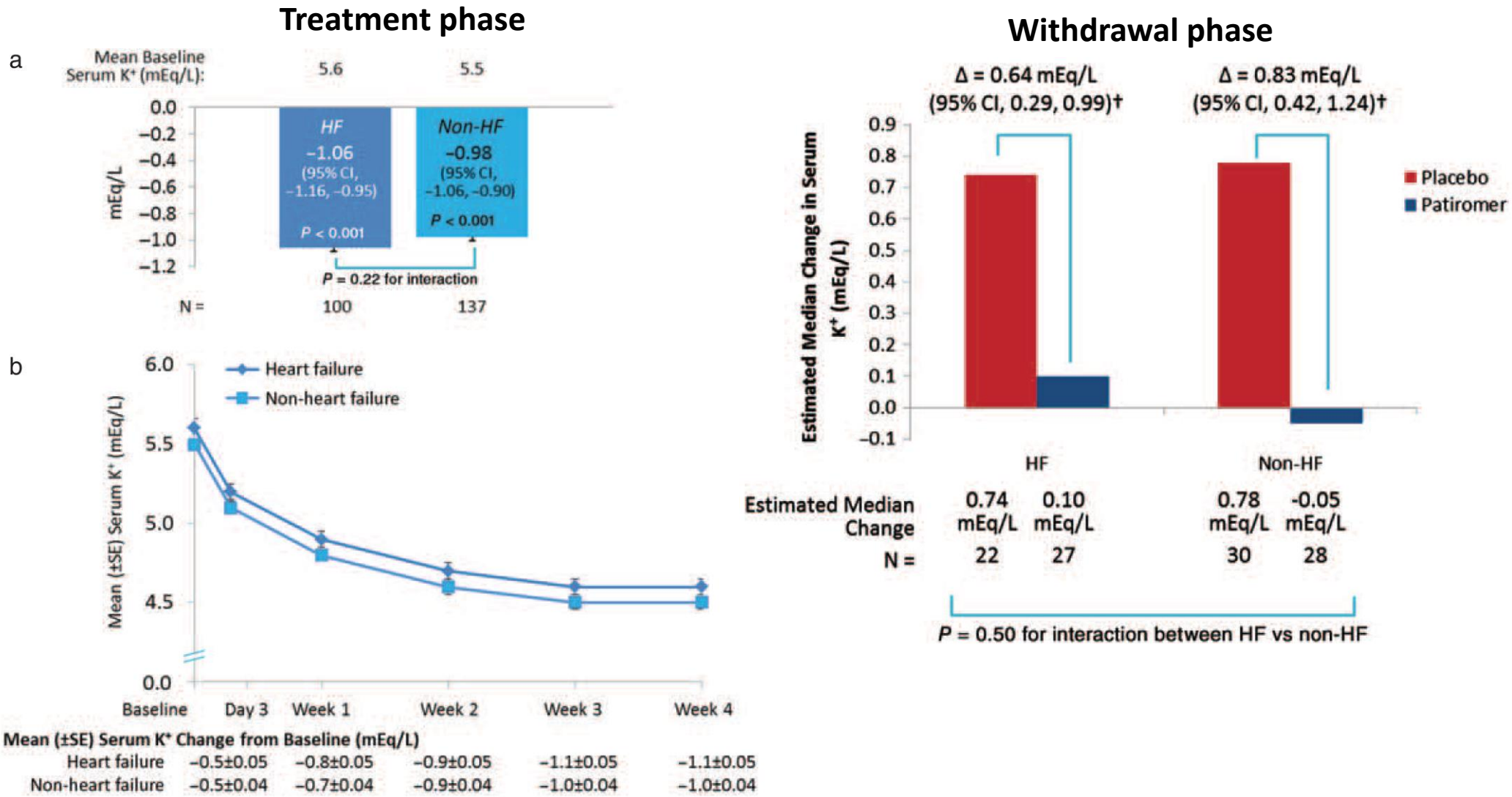
Primary efficacy endpoint:
mean change from baseline to Week 4 (all subjects)



Secondary Efficacy Endpoint:
76% of subjects had serum K^+ in the target range (3.8 to <5.1 mEq/L) at week 4

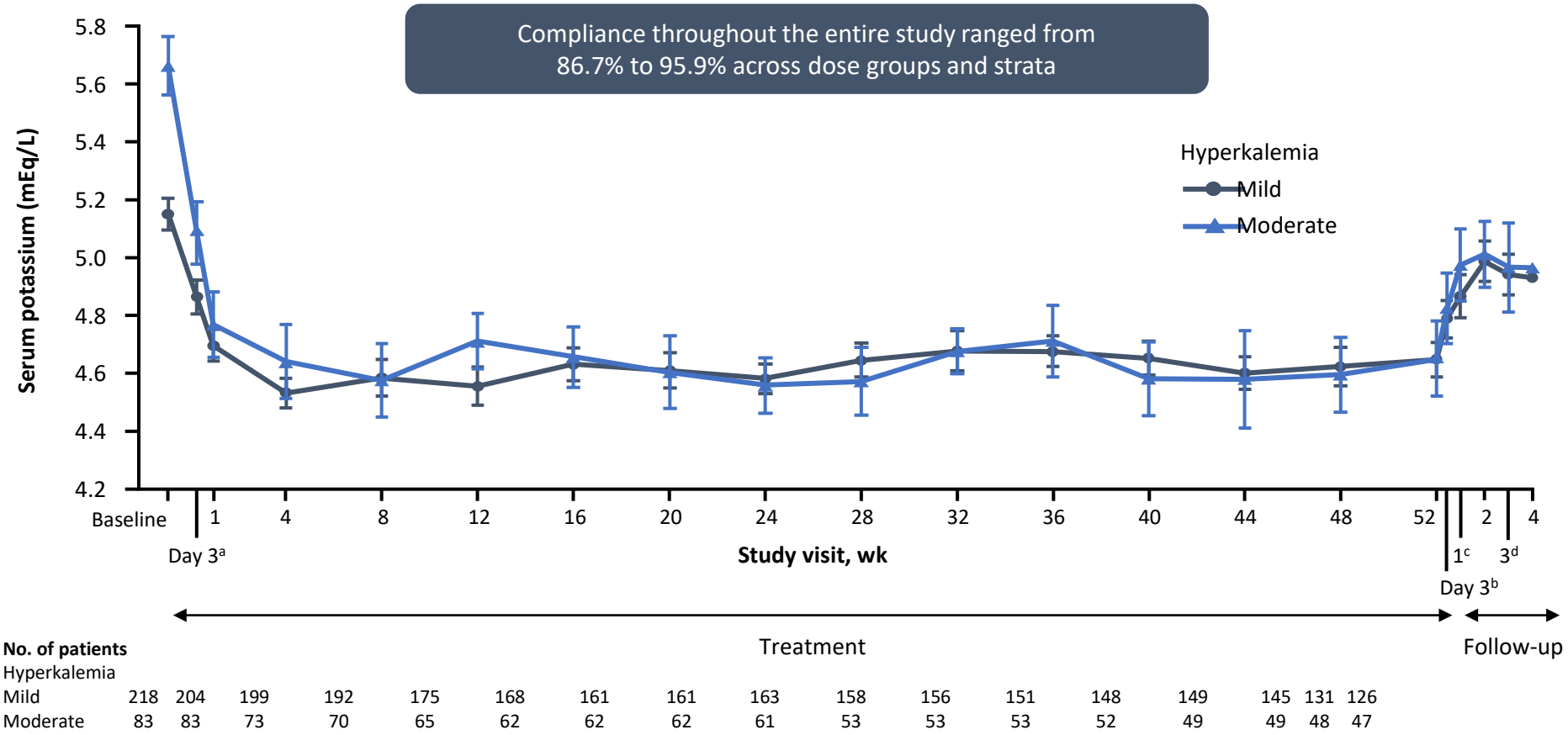
Weir MR, et al. *N Engl J Med.* 2015;372(3):211-221.

Effect of patiromer on reducing serum K+ and preventing recurrent hyperkalaemia in patients with HF and CKD on RAAS inhibitors: OPAL-HK



Pitt B et al. European Journal of Heart Failure (2015) 17, 1057–1065

Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial



All serum K^+ analyses are based on central lab values; 3 patients (2 with mild HK and 1 with moderate HK) did not have a central lab serum K^+ value at baseline and therefore are not included in the analysis at this timepoint. *At all timepoints, $P<0.001$ (2-sided t-test) for least-squares mean changes from baseline and week 52 (or from last dose of patiromer received during the study).

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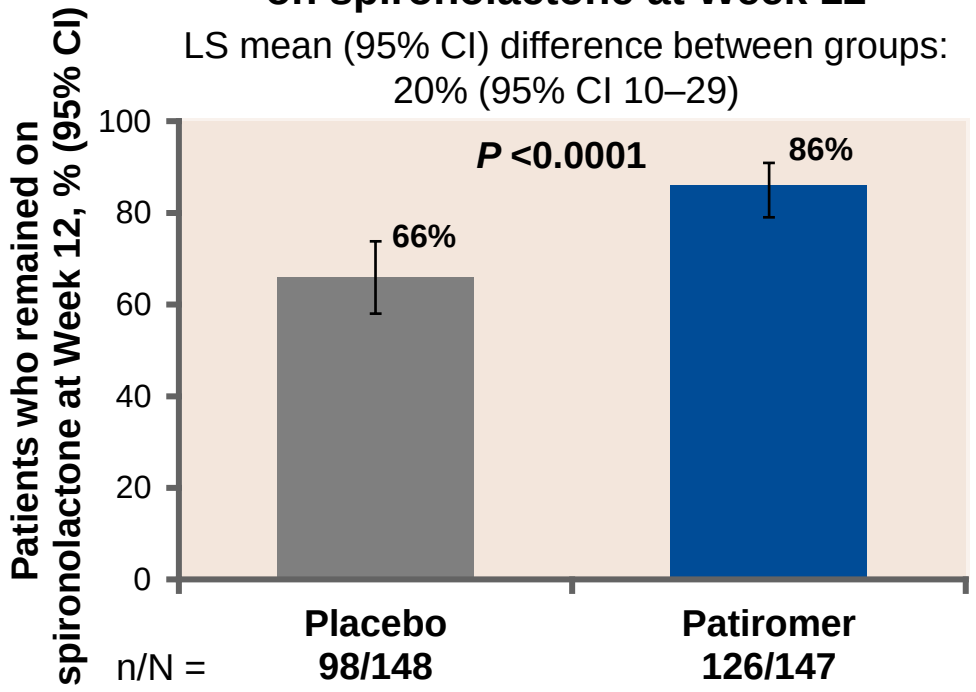
Bakris G, et al. *JAMA*. 2015;314(2):151-161.

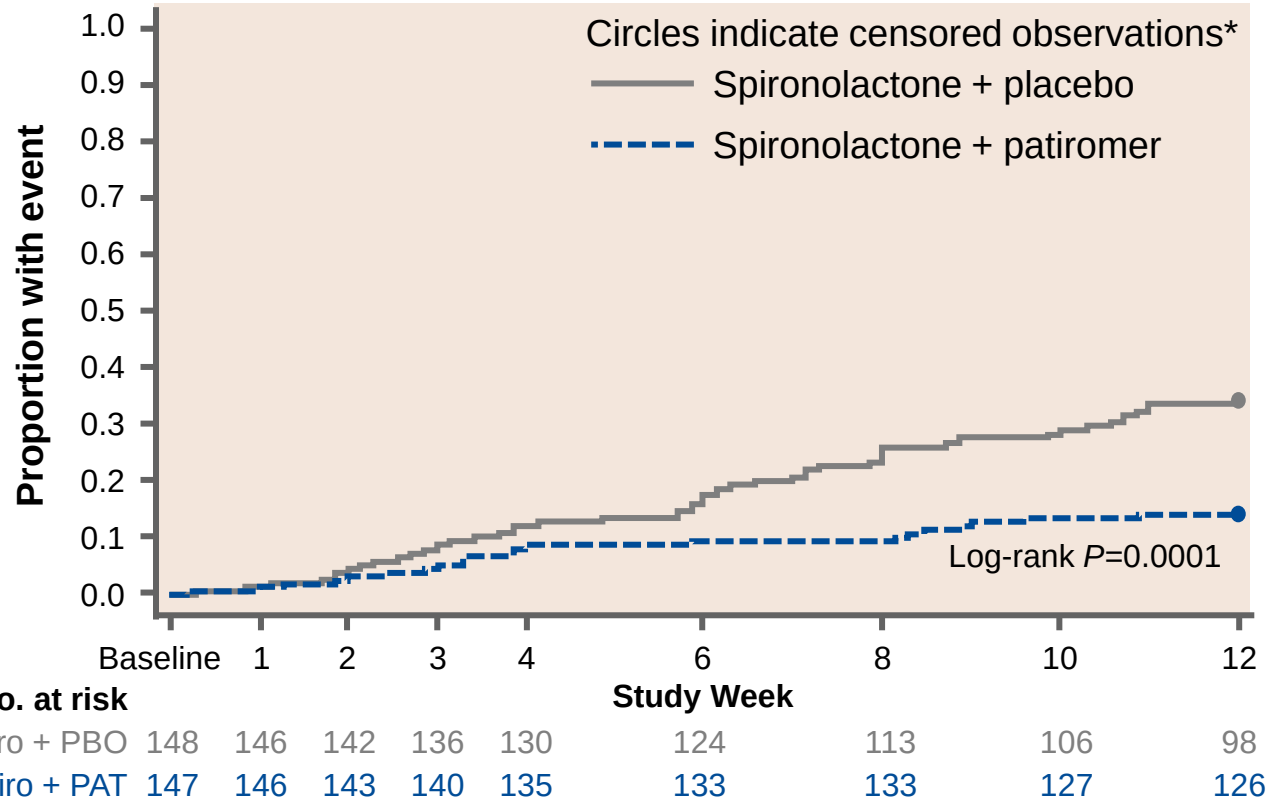
AMBER KEY RESULTS: ITT POPULATION

Primary endpoint: Patients who remained on spironolactone at Week 12

LS mean (95% CI) difference between groups: 20% (95% CI 10–29)



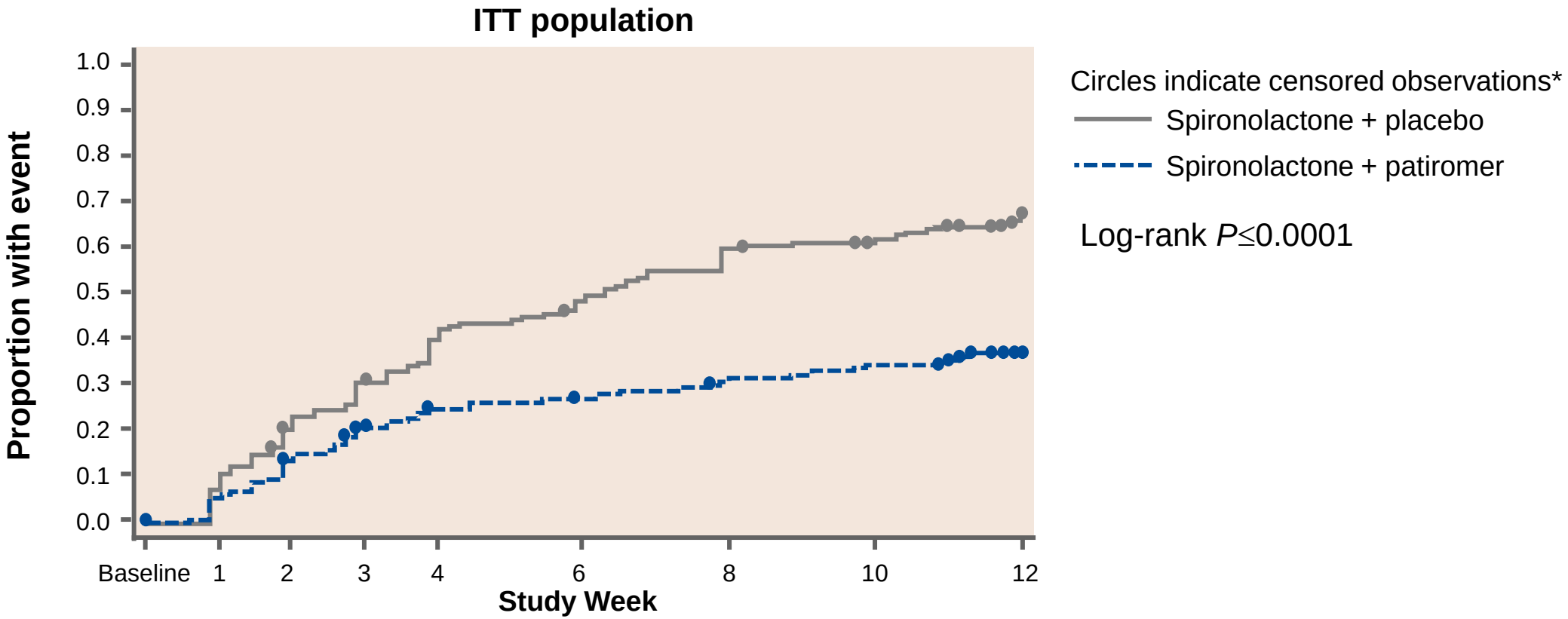
Time to discontinuation of spironolactone



In advanced CKD with resistant hypertension, patiromer enables more persistent use of spironolactone

*Patients who completed 12 weeks of study treatment and had not had any event are censored at Week 12.
CI, confidence interval; CKD, chronic kidney disease; ITT, intention-to-treat; LS, least squares; PAT, patiromer; PBO, placebo; spiro, spironolactone.
Agarwal R, *et al. Lancet.* 2019;394:1540−50.

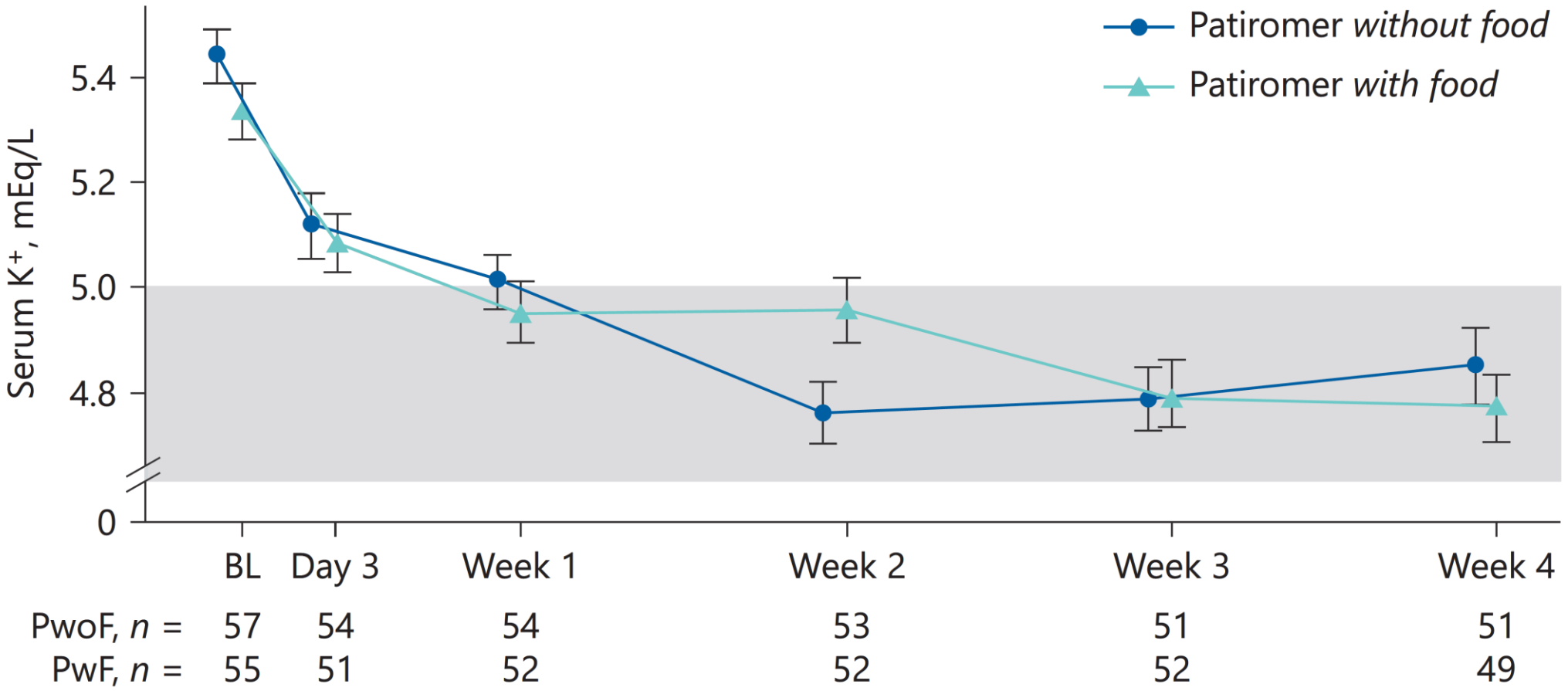
AMBER: TIME TO SERUM K^+ ≥5.5 MEQ/L



Among patients treated with placebo, **2 out of 3 developed hyperkalaemia**
Patiromer reduced this risk by half

*Patients who did not have any event are censored on the last date with serum K^+ assessment.
ITT, intention-to-treat; K^+, potassium.
Agarwal R, *et al. Lancet.* 2019;394:1540−50.

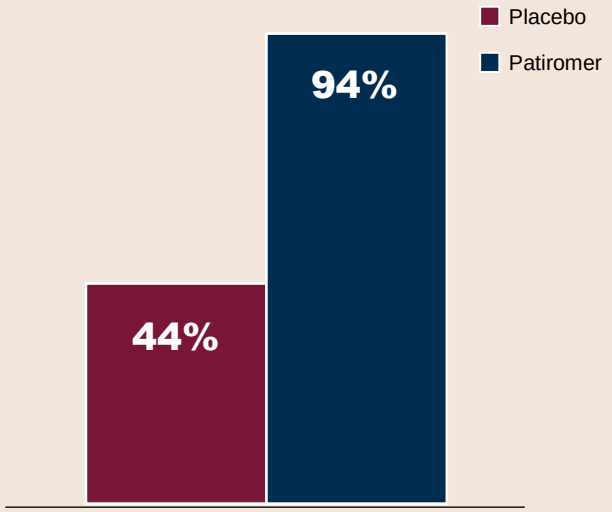
Patiromer is equally effective and well tolerated when taken without food or with food: TOURMALINE study



Pergola PE et al. Am J Nephrol 2017;46:323–332

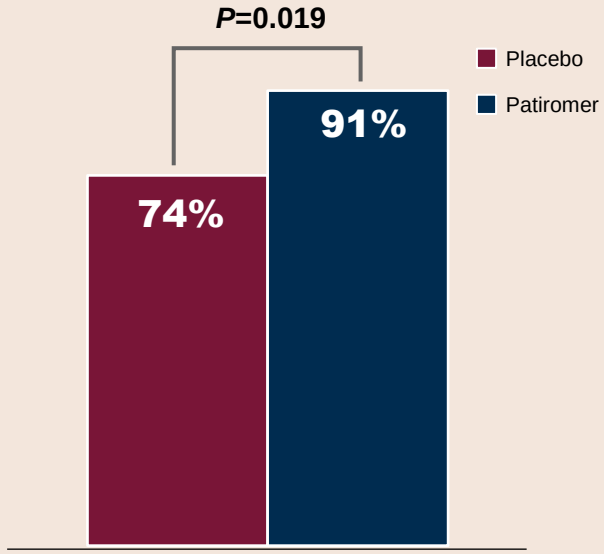
PATIROMER HAS DEMONSTRATED THE **ABILITY TO ENABLE RAASI** IN PLACEBO-CONTROLLED RANDOMISED CLINICAL TRIALS

OPAL Weir NEJM 2015; N=243[1]
eGFR 15–59; K^+ 5.1–6.4; RAASi; 42–49% HF
8w randomised withdrawal → 60% v 15% HK recurrence



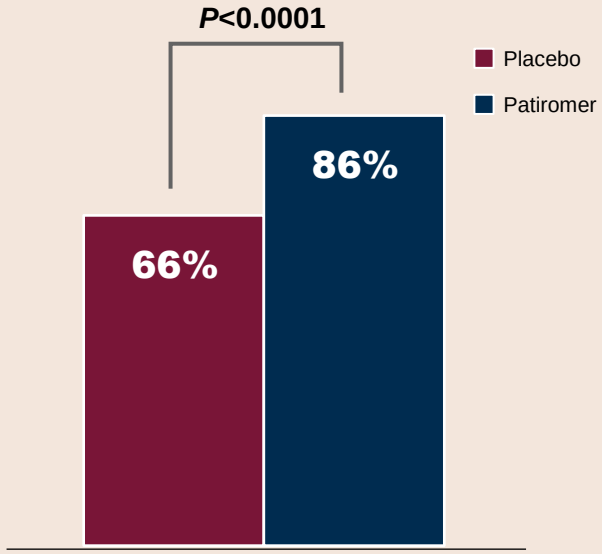
Exploratory endpoint:
Patients receiving any RAASi dose

PEARL-HF EHJ 2011; N=105[2]
HF + ([K^+ requiring d/c RAASi] or [eGFR<60])
normoK; 4w → 25% v 7% hyperkalaemia



Secondary endpoint:
Increase of spironolactone dose to 50 mg

AMBER LANCET 2019; N=295[3]
rHTN; eGFR 25–45 mL/min/1.73 m^2;
sK^+ 4.3–5.1 mEq/L



Primary endpoint:
Patients who remained on spironolactone at Week 12

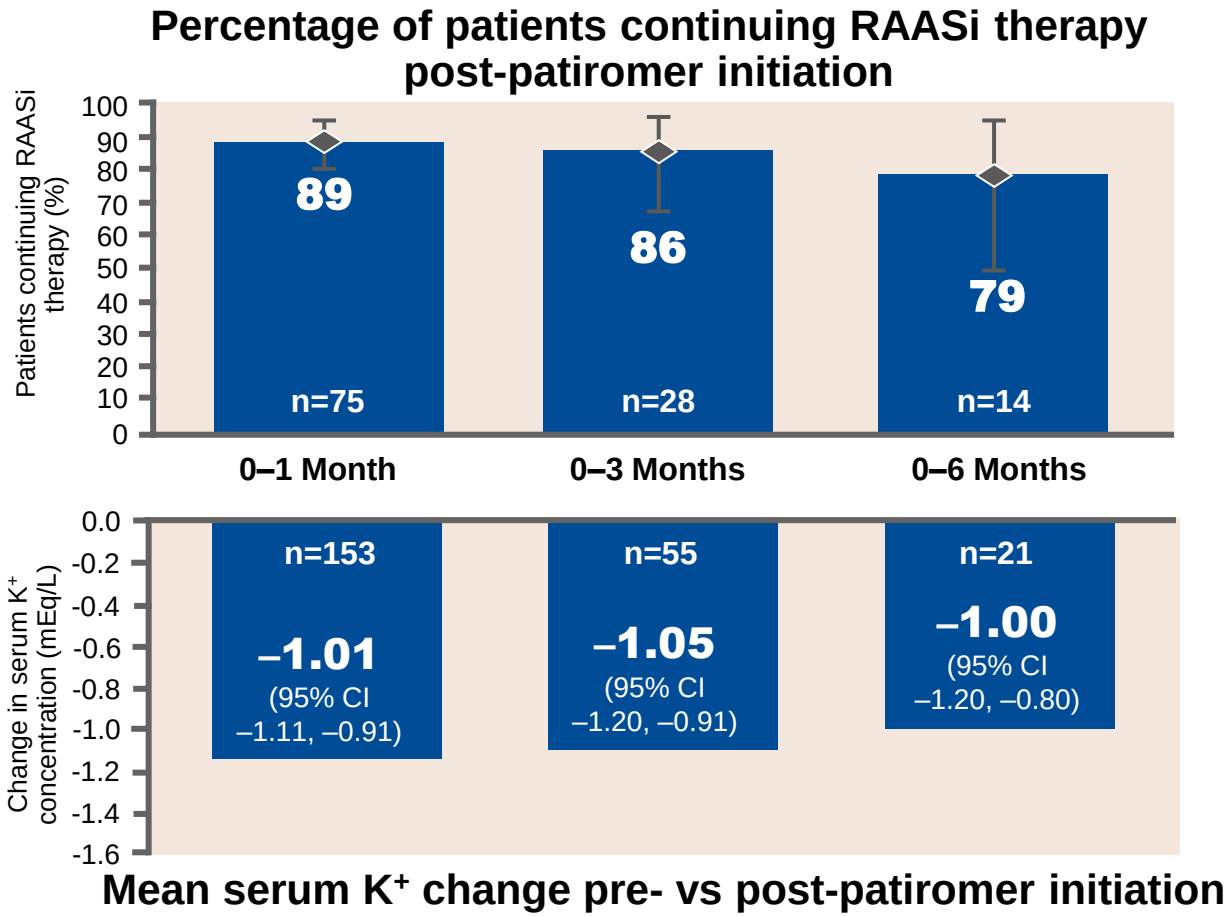
Patiromer enabled substantially more patients to:

- Remain on their RAASi medications at the end of the study, compared with those given placebo[1]
- Initiate and up-titrate spironolactone in patients with HF and advanced CKD with rHTN[2,3]

CKD, chronic kidney disease; d/c, discontinuation; eGFR, estimated glomerular filtration rate; HF, heart failure; HK, hyperkalaemia; K^+, potassium; normoK, normokalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor; rHTN, resistant hypertension; sK^+, serum potassium.

1. Weir MR, *et al. N Engl J Med.* 2015;372:211–21; 2. Pitt B, *et al. Eur Heart J.* 2011;32:820–8. 3. Agarwal R, *et al. Lancet.* 2019;394:1540–50.

REAL-WORLD MANAGEMENT OF HYPERKALAEMIA WITH PATIROMER IS ASSOCIATED WITH HIGH RATES OF RAASI CONTINUATION



CI, confidence interval; K^+, potassium; US, united states; RAASi, renin-angiotensin-aldosterone system inhibitor.
Kovesdy CP, *et al. Postgrad Med.* 2020;132:176–83.

Study

A retrospective, observational cohort study of 288 US Veterans with hyperkalaemia (K^+ ≥5.1 mEq/L)

Objective

To evaluate patiromer utilisation, RAASi continuation and serum K^+ levels post-patiromer initiation

Findings

- **K^+ concentration reductions post-patiromer** initiation averaged –1.0 mEq/L (*P*<0.001)
- Through 6 months post index, **RAASi therapy was continued in ~80%** of patients treated with patiromer

PATIROMER: SAFETY AND TOLERABILITY PROFILE

Summary of the safety profile

- Most AEs reported from trials were GI disorders, with **constipation (6.2%)**, **hypomagnesaemia (5.3%)**, **diarrhoea (3%)**, **abdominal pain (2.9%)** and **flatulence (1.8%)** being the most common
- Most frequently reported GI-related AEs were generally **mild-to-moderate in nature, did not appear to be dose-related, generally resolved spontaneously or with treatment, and none was reported as serious**

Hypomagnesaemia

- Hypomagnesaemia was mild-to-moderate, with **no patient developing a serum magnesium level <1 mg/dL (0.4 mEq/L)**. Serum magnesium should be **monitored for at least 1 month after initiating treatment**, and magnesium supplementation considered in patients who develop low serum magnesium levels

Interactions

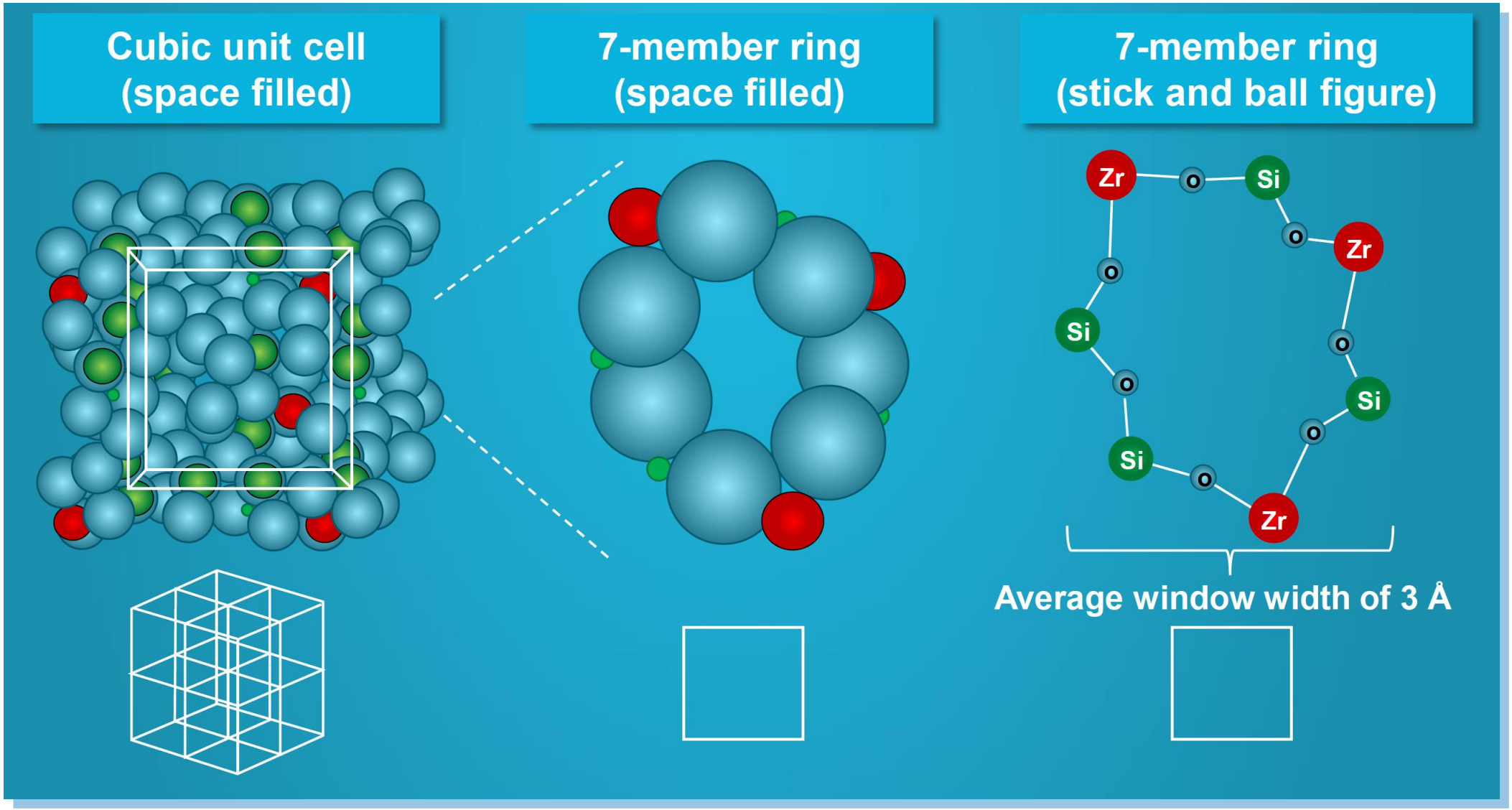
- Patiromer has the potential to bind some oral co-administered medications, which could decrease their GI absorption
- As a precautionary measure, administration of patiromer should be **separated by at least 3 hours from other oral medications**

AE, adverse event; GI, gastrointestinal.
Patiromer EU Summary of Product Characteristics, 2019.

LIST OF ADVERSE REACTIONS IN CLINICAL STUDIES

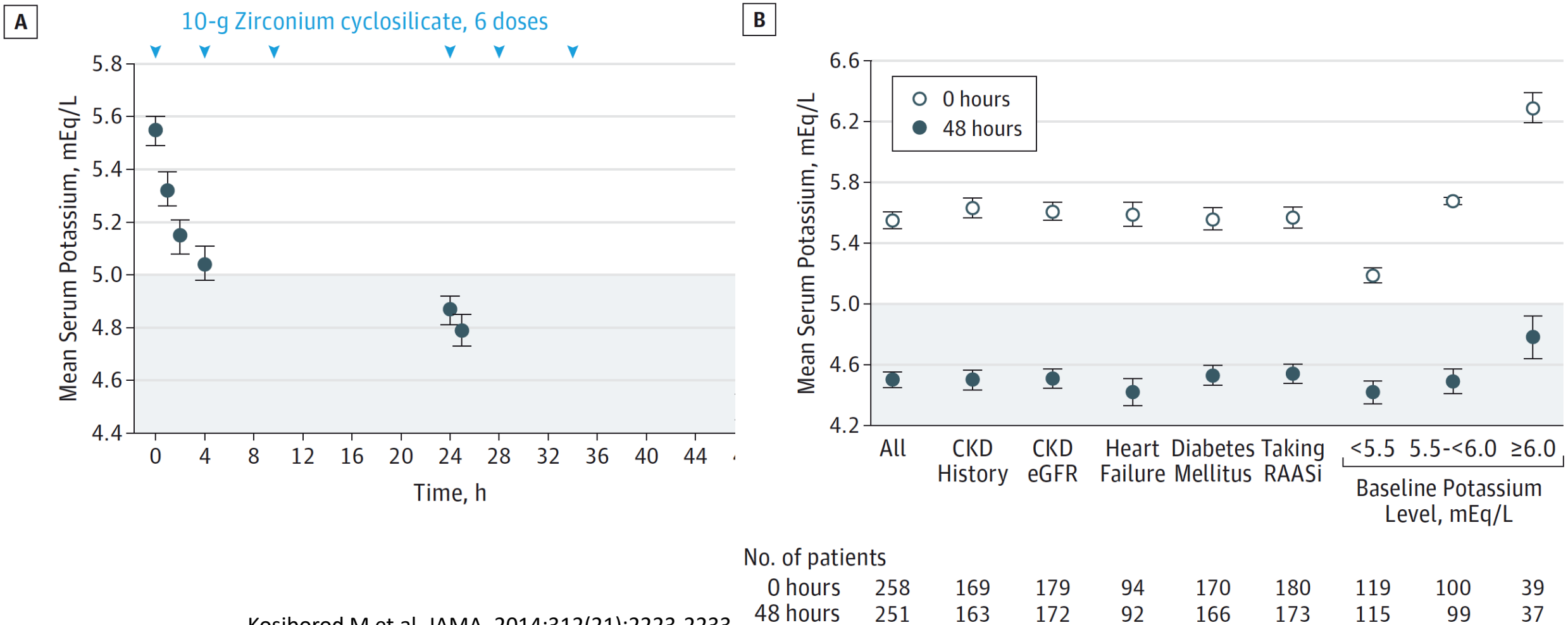
System Organ Class	Common	Uncommon
Metabolism and nutrition disorders	Hypomagnesaemia	
Gastrointestinal disorders	Constipation Diarrhoea Abdominal pain Flatulence	Nausea Vomiting

Characterization of structure and function of ZS-9, a K^+ selective ion trap



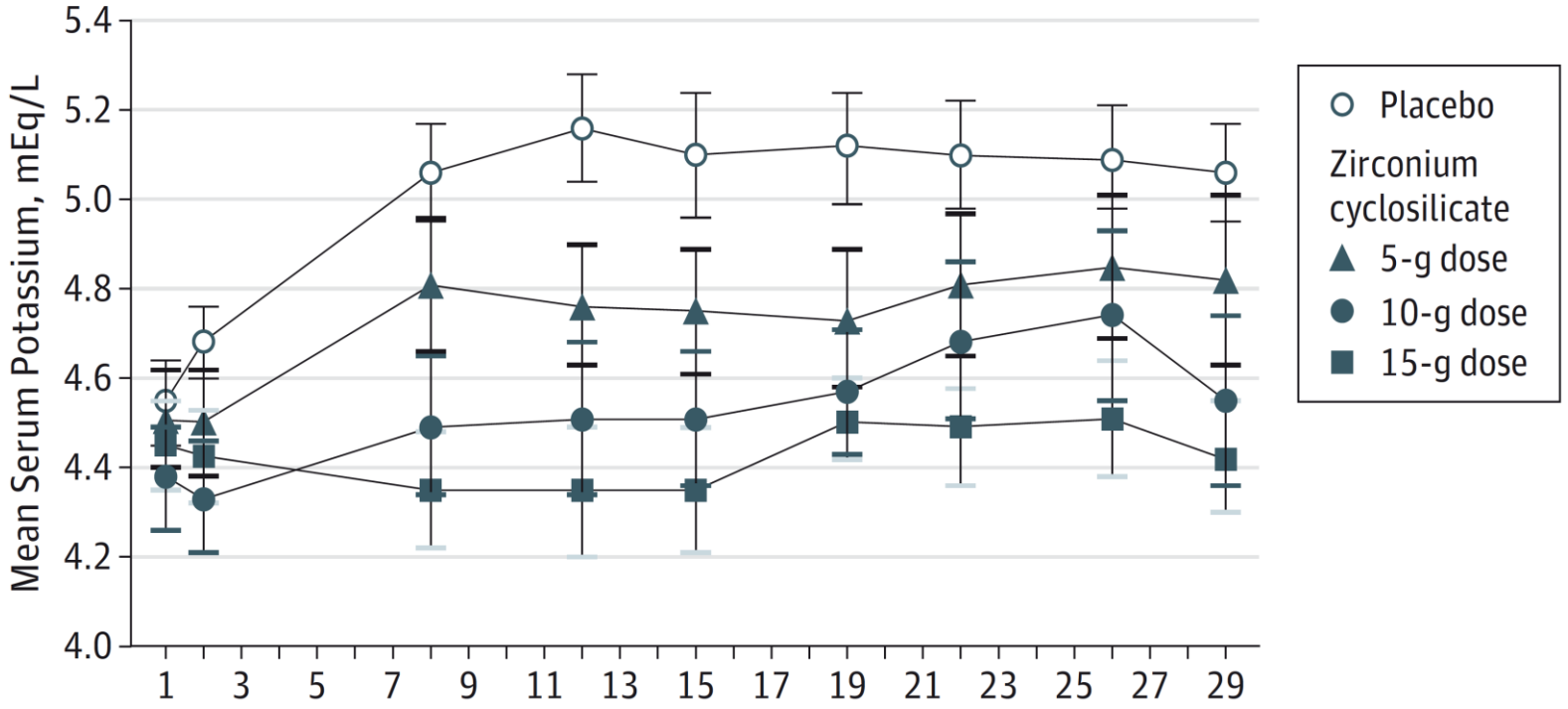
Stavros F, et al. PLoS One 2014;9:e114686

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



Kosiborod M et al. JAMA. 2014;312(21):2223-2233.

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



Comorbidities, No. (%)	Open label	placebo	5 g	10 g	15 g
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)

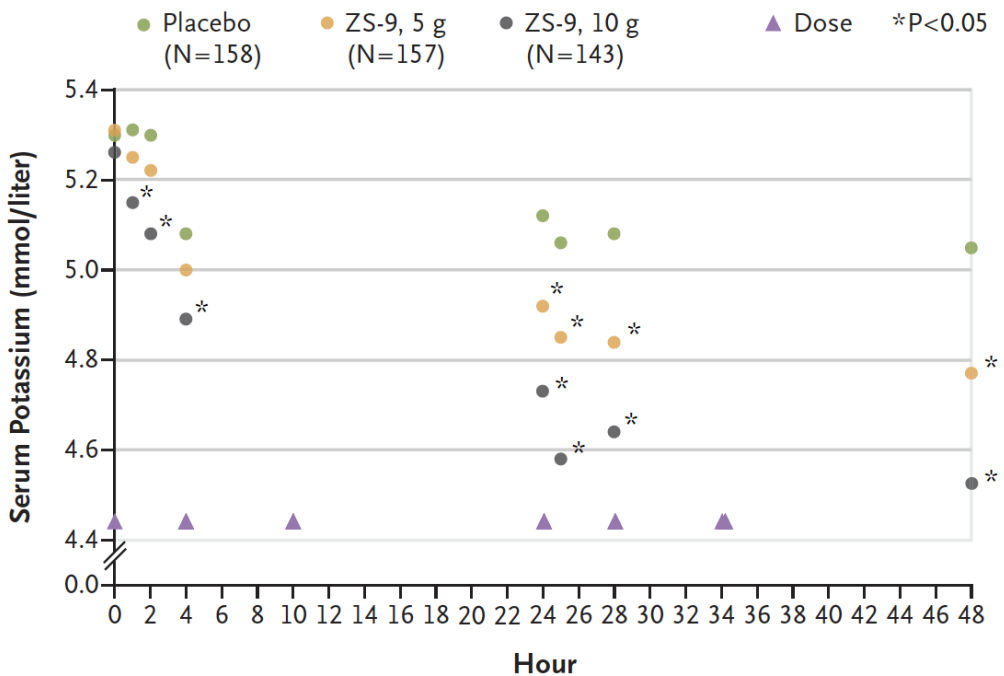
Kosiborod M et al. JAMA. 2014;312(21):2223-2233.

ORIGINAL ARTICLE

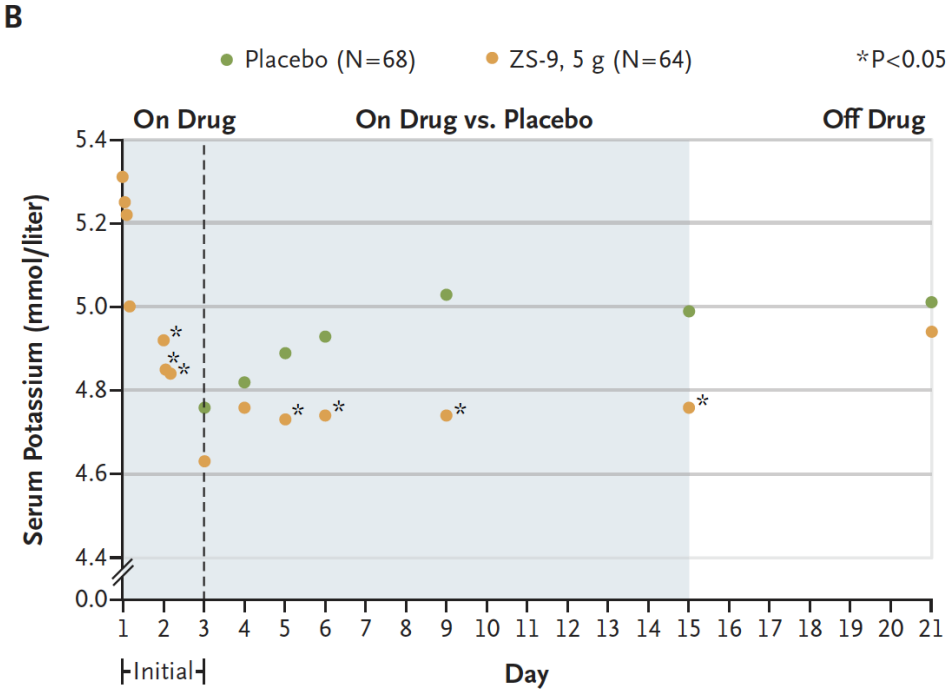
Sodium Zirconium Cyclosilicate in Hyperkalemia

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.

A



B



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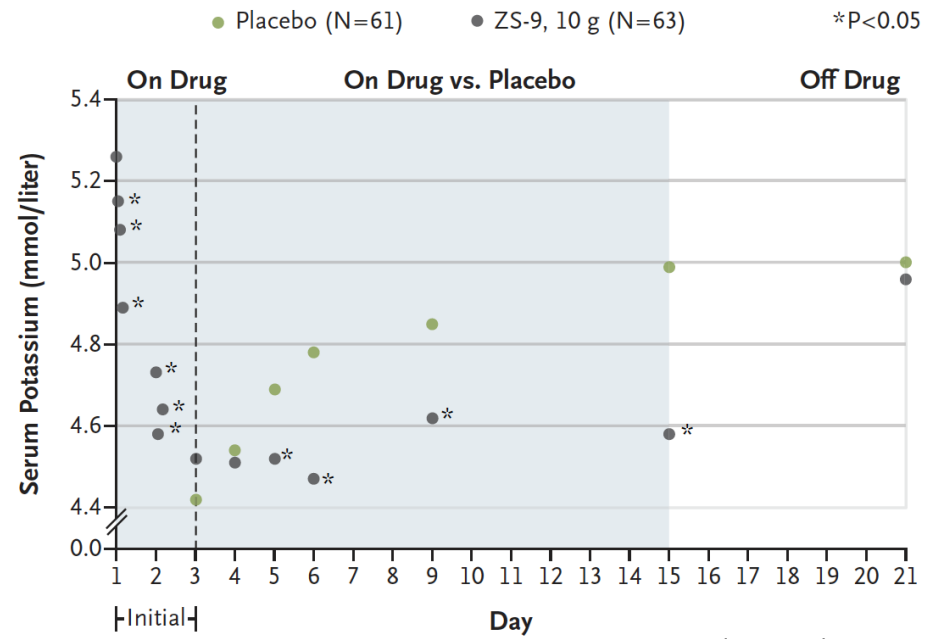

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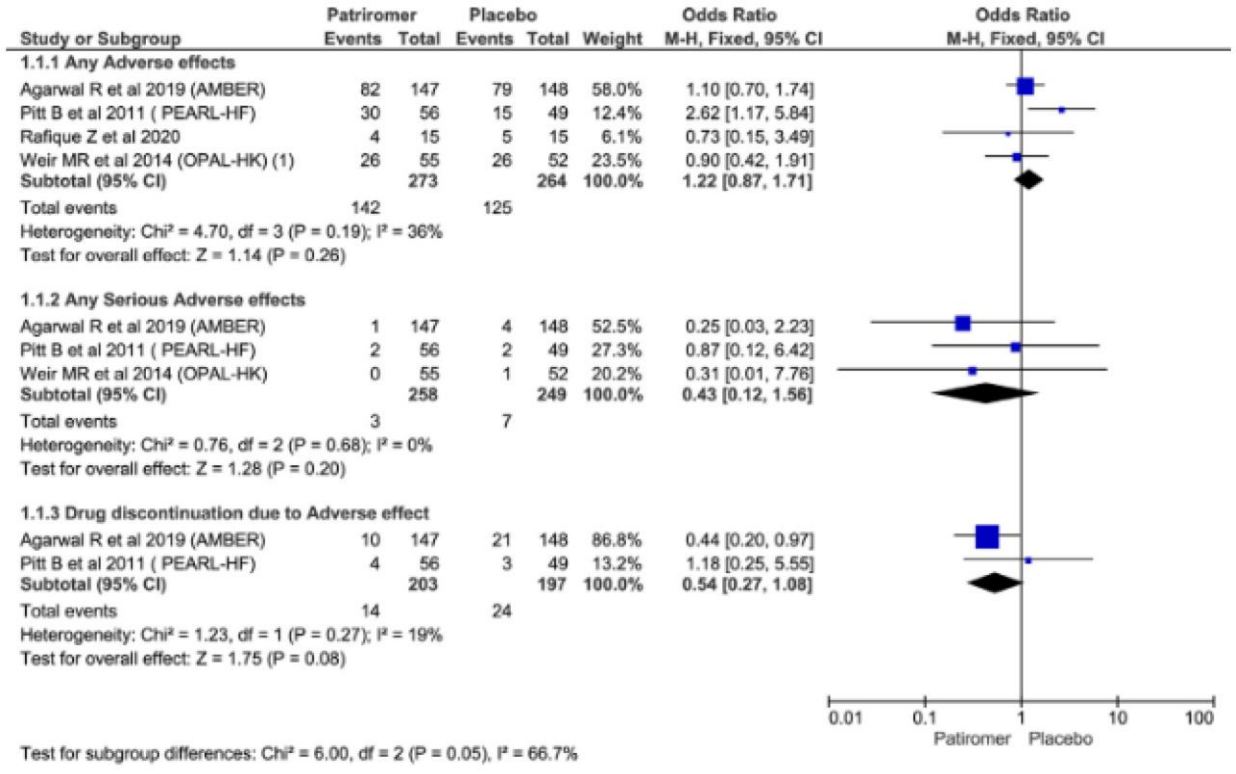

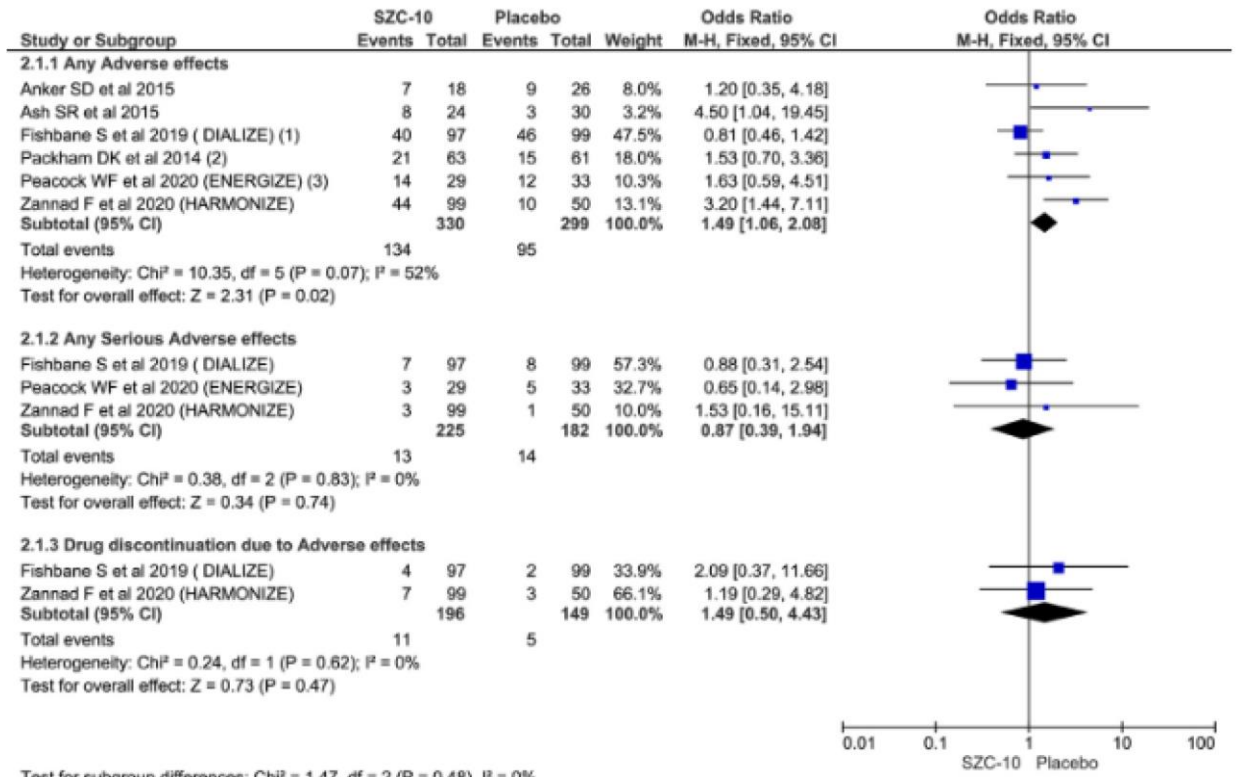

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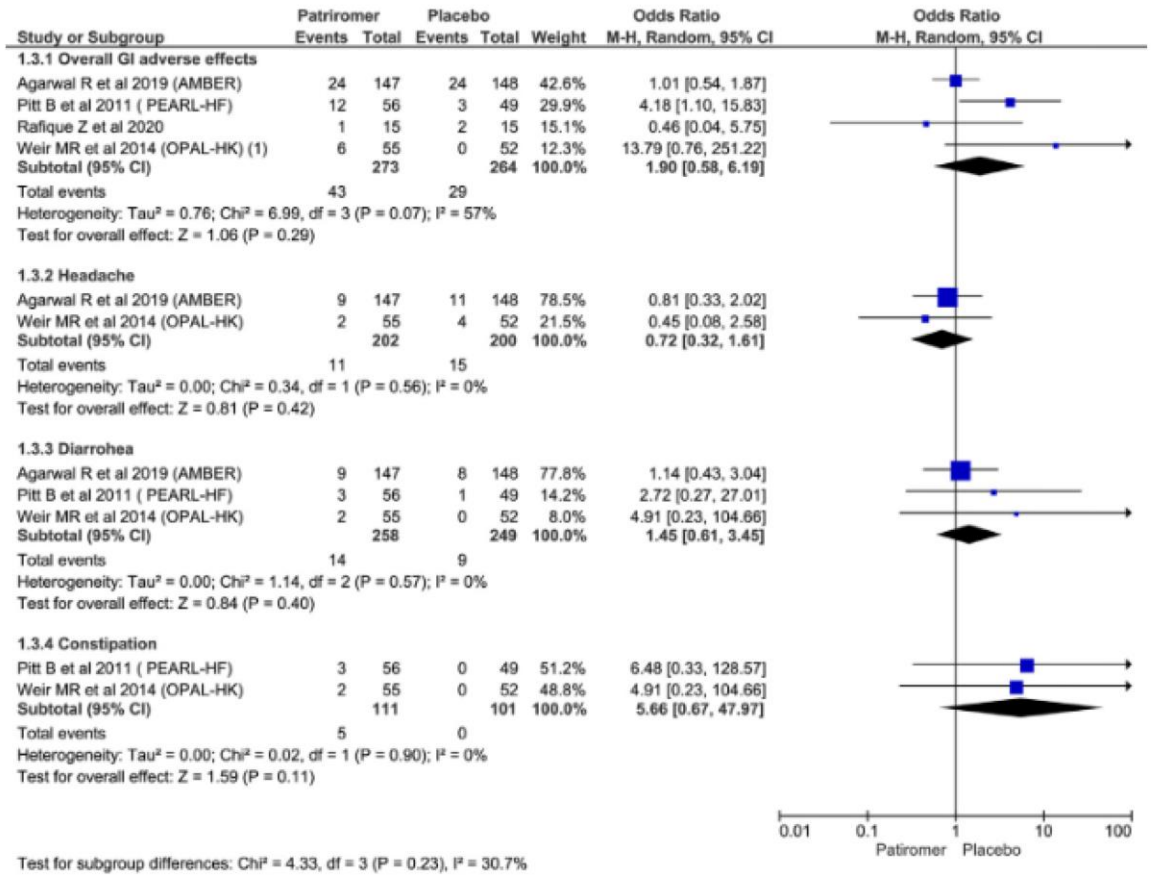

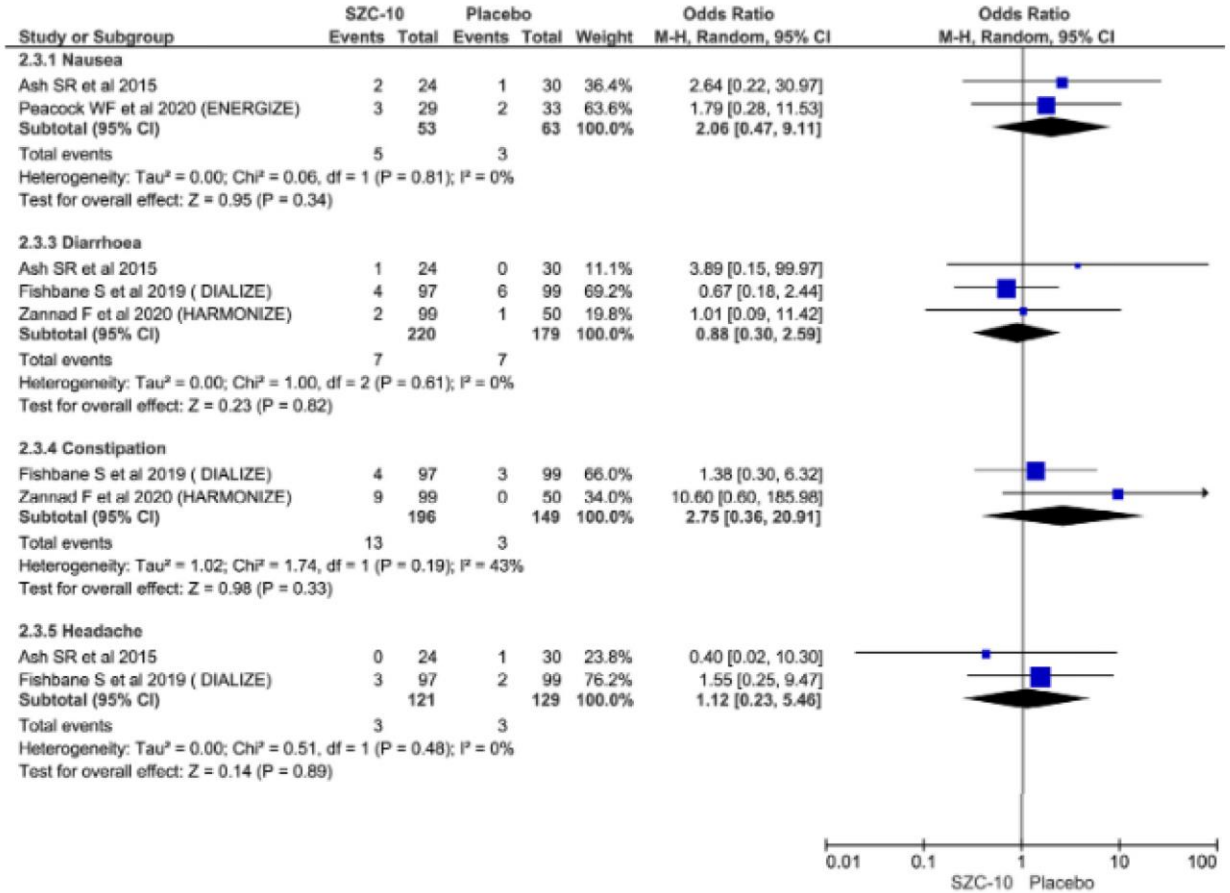

ALLEGATO

Piano terapeutico per la prescrizione dei K-binders

La prescrivibilita' e' consentita a medici ospedalieri
o specialisti nefrologo, cardiologo e internista
Indicazione: trattamento dell'iperK negli adulti
Rimborsabilita' limitata ai pazienti adulti con iperK
persistente (K>5.5 mmol/L) con risposta insufficiente
o controindicazione alle resine

CRITERI DI ELEGGIBILITÀ AL TRATTAMENTO (devono essere soddisfatti entrambi i punti 1 e 2)

1) Diagnosi: Iperkaliemia persistente (livello di potassiemia >5.5mmol/L) in pazienti con risposta insufficiente o controindicazione alle resine (calcio polistirene sulfonato/sodio polistirene sulfonato).

2) Almeno una delle seguenti condizioni (possibilità di scelta multipla):

☑ Insufficienza renale: stadio 3b-CKD in pazienti **con** concomitante terapia con RAASi

☑ Insufficienza renale: stadio 4 o 5-CKD **non in dialisi**, in pazienti **con o senza** concomitante terapia con RAASi

☑ Insufficienza renale: stadio 5-CKD **in dialisi** (solo per sodio zirconio ciclosilicato)

☐ Scompenso cardiaco (frazione di eiezione ≤40%) in pazienti **con** concomitante terapia con RAASi in dose giudicata subottimale.

Proprietà. farmacodinamiche e farmacocinetiche di patiromer e ciclosilicato di sodio e zirconio (SZC)

	SZC	Patiromer
Meccanismo d'azione	Aumenta l'escrezione fecale di K^+ Agisce legando il K^+ già nel primo tratto gastrointestinale	Aumenta l'escrezione fecale di K^+ Agisce legando il K^+ nel tratto gastrointestinale, principalmente nel colon
Assorbimento	Nessuno	Nessuno
Eliminazione	Fecale	Fecale
Forma	Polvere per sospensione orale solubile da miscelare con acqua: 5 g/bustina 10 g/bustina	Polvere per sospensione orale: 8.4 g/bustina 16.8 g/ bustina 25.2 g/bustina
Dose	Iniziale: 10 g tid per os per 48 h Mantenimento: 5 o 10 g/die per os La dose giornaliera può essere aggiustata con incrementi o decrementi di 5 g, con una dose minima di 5 g/die e una dose massima di 10 g/die La dose di mantenimento raccomandata è di 5-15 g/die, massimo 15 g/die solo per i pazienti dializzati	Iniziale: 8.4 g/die per os Mantenimento: aumentare o ridurre la dose se necessario ma non superare 25.2 g/die La dose giornaliera può essere aggiustata ad intervalli di 1 settimana o di durata maggiore, con incrementi di 8.4 g Dosaggi superiori a 50.4 g/die non sono stati testati; dosaggi eccessivi possono provocare ipopotassiemia, nel qual caso devono essere ripristinati normali livelli sierici di K^+
Effetti avversi	Edema (5.7%)* Ipopotassiemia (4.1%)	Stitichezza (7.2%) Ipomagnesiemia (5.3%) Diarrea (4.8%) Ipopotassiemia (4.7%) Nausea (2.3%) Dolori addominali (2%) Flatulenza (2%)

*Gli eventi sono stati osservati solo durante la fase di mantenimento ed erano più comuni nei pazienti trattati con la dose di 15 g. Fino al 53% degli eventi è stato gestito tramite somministrazione di un diuretico o aggiustamento della dose di un diuretico; i restanti soggetti non hanno richiesto alcun trattamento.

Rosano GMC et al. G Ital Cardiol 2021;22(12 Suppl 1):e8-e12

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European Society of Cardiology
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ESC GUIDELINES

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri

European Heart Journal (2021) 00, 1 42

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

- In patients with chronic or recurrent hyperkalaemia on RAAS inhibitors therapy an approved K^+-lowering agent may be initiated as soon as K^+ levels are confirmed as >5.0 mEq/L. Closely monitor K^+ levels. Maintain treatment unless alternative treatable aetiology is identified.
- In patients with chronic or recurrent hyperkalaemia not on maximal tolerated guideline-recommended target dose of RAAS inhibitors, an approved K^+-lowering agent may be initiated as soon as confirmed K^+ levels are >5.0 mEq/L. Closely monitor K^+ levels. Maintain treatment unless alternative treatable aetiology is identified. RAAS inhibitors should be optimized when K^+ levels are <5.0 mEq/L.
- In patients with K^+ levels of 4.5–5.0 mEq/L not on maximal tolerated, guideline-recommended target dose of RAAS inhibitor therapy, RAAS inhibitor therapy can be initiated/uptitrated with a close monitoring of K^+ levels. If K^+ levels rise above 5.0 mEq/L, initiate an approved K^+-lowering agent.
- In patients with K^+ levels of >5.0–≤6.5 mEq/L not on maximal tolerated, guideline-recommended target dose of RAAS inhibitor therapy, an approved K^+-lowering agent should be initiated. If levels <5.0 mEq/L are detected, uptitrate RAAS inhibitor; K^+ level should be closely monitored and K^+-lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified.
- In patients with K^+ levels of >5.0–≤6.5 mEq/L on maximal tolerated, guideline-recommended target dose of RAAS inhibitor therapy, treatment with a K^+-lowering agent may be initiated. K^+ level should be closely monitored and K^+-lowering treatment should be maintained unless alternative treatable aetiology for hyperkalaemia is identified.
- In patients with K^+ levels of >6.5 mEq/L on either maximal or sub-maximal tolerated, guideline-recommended target dose of RAAS inhibitor therapy, it is recommended to discontinue/reduce RAAS inhibitor. Treatment with a K^+-lowering agent may be initiated as soon as K^+ levels >5.0 mEq/L. K^+ level should be closely monitored.

SUMMARY

- **RAASi**, including ACE inhibitors, ARBs and MRAs, are the **cornerstone** of therapy in **heart failure** and **chronic kidney disease**
  - RAASi are proven to **reduce morbidity and mortality** in patients with CVD, preserve kidney function in CKD and delay progression to ESKD
- RAASi are associated with a risk of **hyperkalaemia**

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CVD, cardiovascular disease; ESKD, end-stage kidney disease; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.