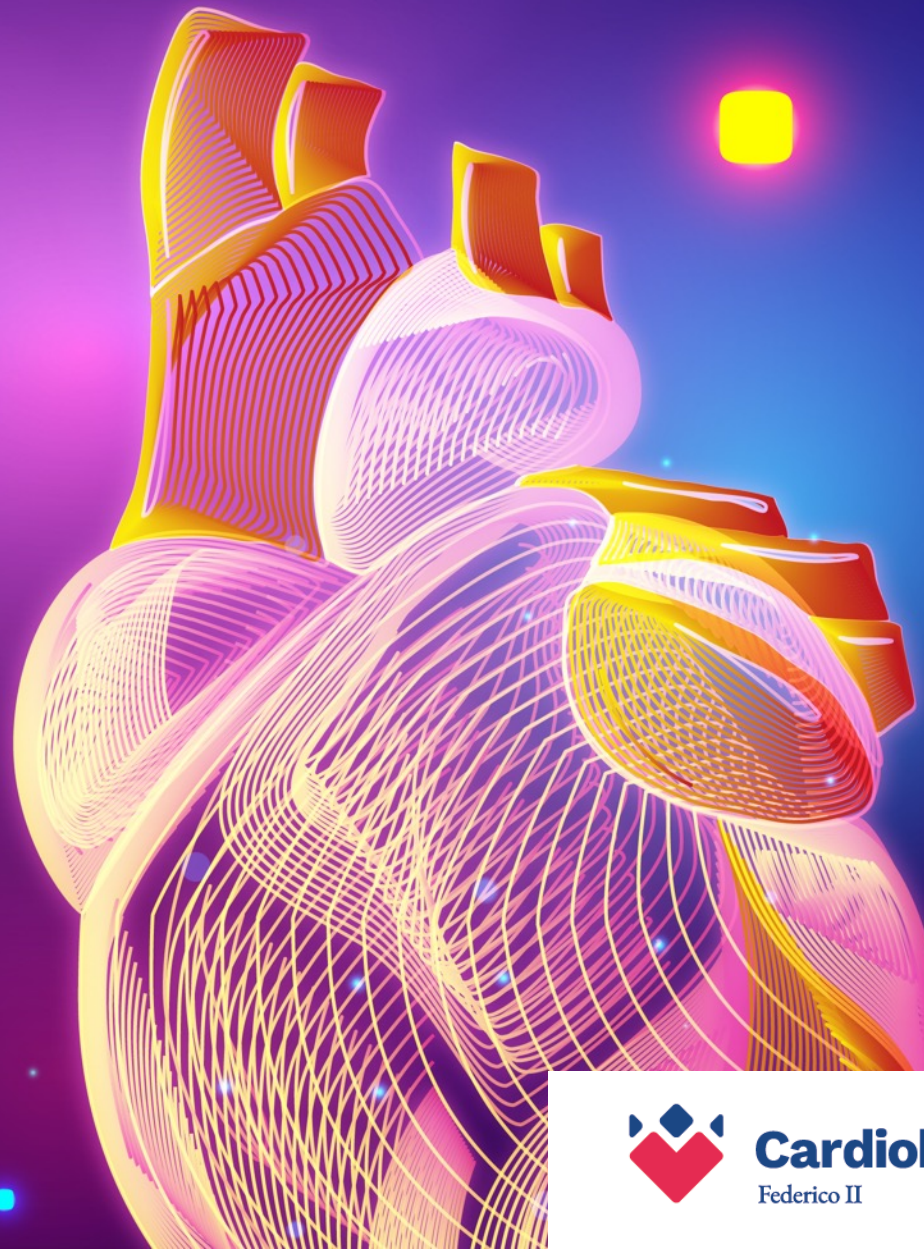
29 SETTEMBRE 2023

CARDIOLOGIA RIABILITATIVA E PREVENTIVA 2023

PALAZZO ALABARDIERI, NAPOLI

STEFANIA PAOLILLO

Gestione e modulazione dell'iperpotassiemia nell'insufficienza cardiaca



AICPR
FORMERLY GICR-IACPR
Associazione Italiana di Cardiologia Clinica, Preventiva e Riabilitativa

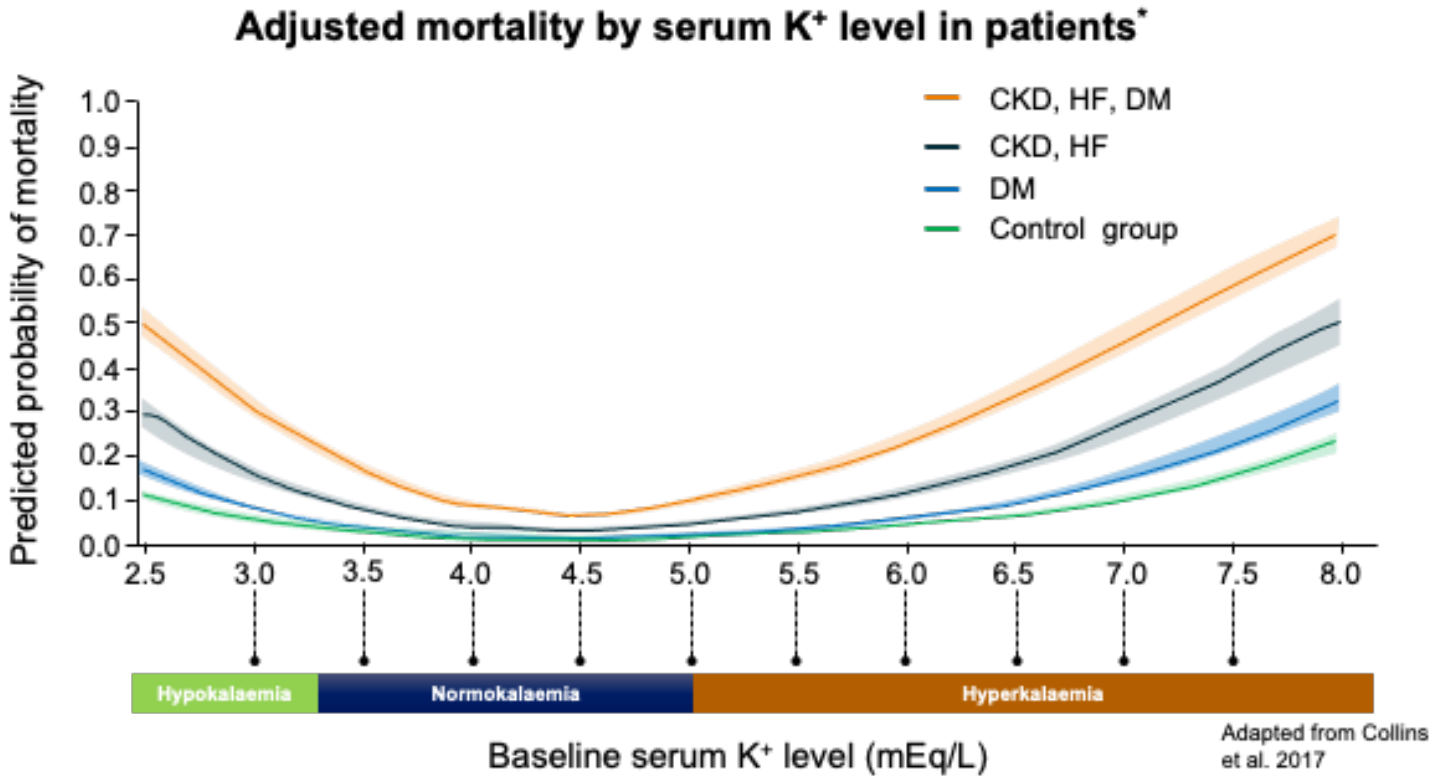
CONGRESSO REGIONALE AICPR CAMPANIA

RESPONSABILE SCIENTIFICO: PROF. ANTONIO CITTADINI

Cardiologia
Federico II

Relazione tra alterazioni del K^+ e mortalità

- Relazione ***U-shaped*** tra K^+ sierico e mortalità per tutte le cause in pazienti con comorbidità
- Mortalità aumentata per ogni ***0.1 mEq/l*** di K^+ <4 mEq/l e ≥5 mEq/l



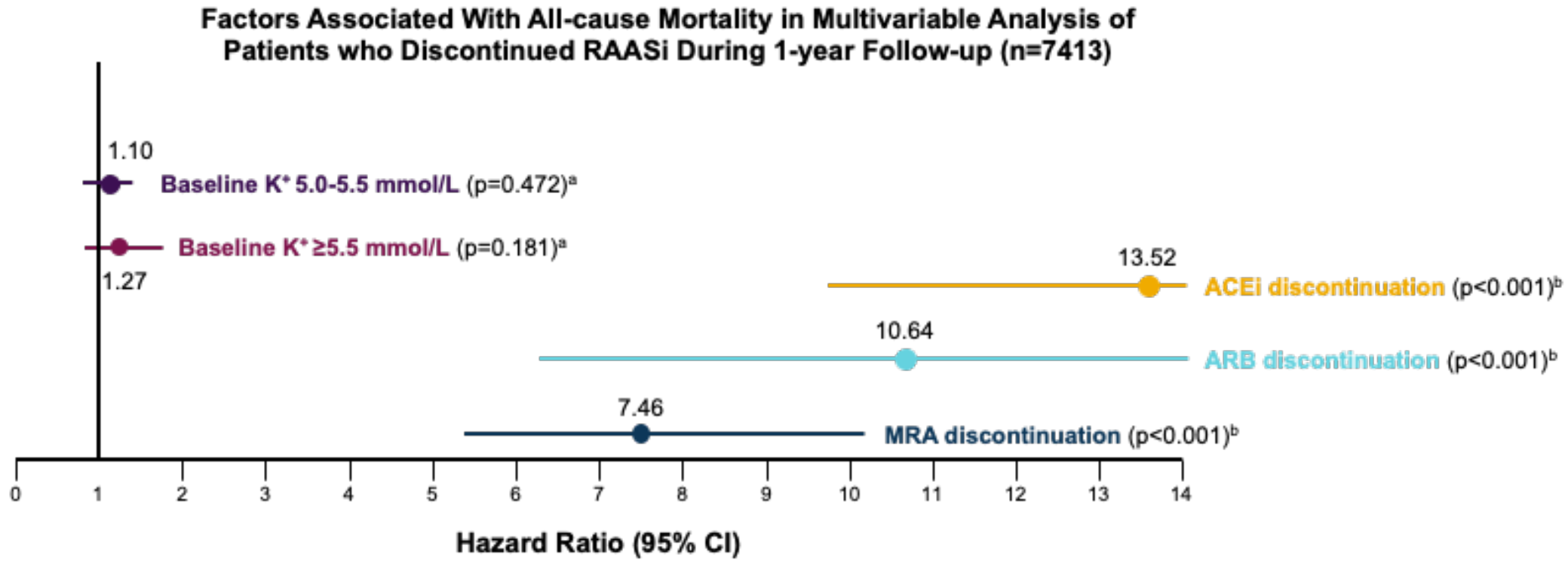
Is hyperkalaemia in heart failure a risk factor or a risk marker?

Figure 1 Hyperkalaemia is a risk marker for poor outcomes by leading to dose reduction or discontinuation of renin–angiotensin–aldosterone system inhibitors (RAASi).

Unravelling the interplay between hyperkalaemia, renin–angiotensin–aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry

European Journal of Heart Failure (2020) **22**, 1378–1389

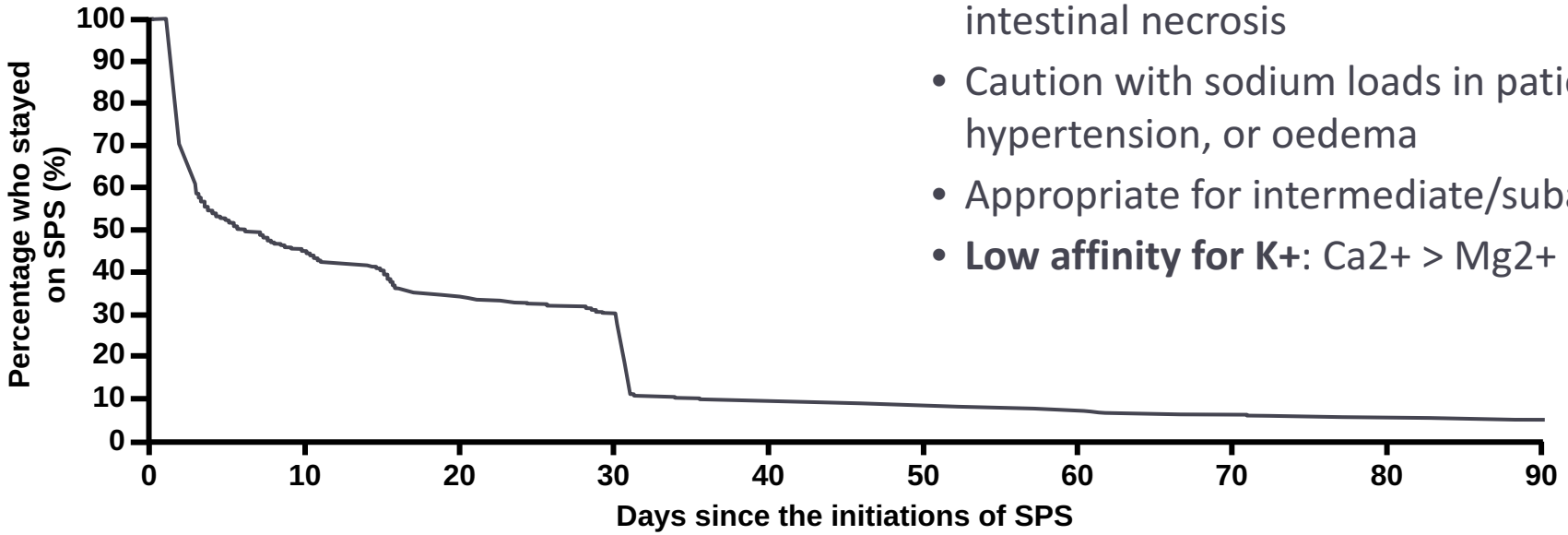
Analysis of outpatients with chronic HF for whom intravenous HF therapy (diuretics, inotropes, or vasodilators) was used and who had a baseline K^+ measurement (N=9222) and were enrolled in the ESC-HFA-EORP Heart Failure Long-Term Registry in 31 European countries between April 2011 and May 2017



Limiti degli approcci storici utilizzati per il trattamento dell'iperkaliemia

Dietary potassium restriction of 50–75 mEq/day[1]	• Many cardio-renal patients already have other restricted diets • Potassium is a common ingredient in many foods • Restricts consumption of healthy foods (e.g., the DASH diet)
RAASi reduction	• Limiting the dose or discontinuing treatment of drugs known to be effective in these populations
Non-potassium sparing diuretics	• Efficacy depends on residual renal function • Important side effects including increased risk for gout and diabetes, volume contraction, worsening of renal function, and reduced potassium excretion
Sodium bicarbonate	• Usually reserved for patients with severe acidosis • May require multiple pills and medication adjustments, as difficult to give salt to patients with CKD/CVD without exacerbating volume status or BP
Traditional potassium binders (CPS and SPS)	• Limited safety and efficacy data • Not well tolerated and their use can be associated with life-threatening side effects including intestinal necrosis • Risk of hypokalaemia: treatment should be discontinued when sK^+ falls below 5.0 mEq/L • SPS: Precaution related to sodium R/W evidence confirm caution with use of SPS Associated with higher risk of severe and minor GI adverse events

Sodium polystyrene sulphonate



- No consistent evidence of efficacy
- Maximum effect may take 6 hours
- **Serious GI adverse** events reported, including fatal cases of intestinal necrosis
- Caution with sodium loads in patients with congestive HF, hypertension, or oedema
- Appropriate for intermediate/subacute care only
- **Low affinity for K+**: Ca2+ > Mg2+ > K+ and NH4+ > Na+

Chaitman M, et al. *PT* 2016;41:43–50; 2
Lepage L, et al. *Clin J Am Soc Nephrol* 2015;10:2136–2142; 3

Nuovi farmaci per il trattamento dell'iperkaliemia

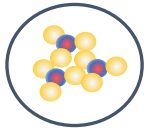
Characteristic	SODIUM POLYSTYRENE SULFONATE	PATIROMER	SODIUM ZIRCONIUM CYCLOSILICATE
FDA approval			
Structure	Benzene, diethenyl-polymer, with ethenylbenzene, sulfonated, sodium salt, organic polymer	100-μm bead, organic polymer	Octahedral, micropore ring 3Å diameter, inorganic crystal
Mechanism of action	Binds Na^+, K^+, Ca^{2+}, or Mg^2 High selectivity for Ca^{+2} (68) Works mostly in colon (68)	Ca^{2+} loaded polymer and Ca^{2+}-K^+ exchanger Binds K^+, Na^+, Ca^{2+}, or Mg^2 Works mostly in colon (68)	Selectivity for K^+ Works in entire GI tract (68)
Administration	15-60 g, up to 4 times daily (85)	8.4 g once daily and can be advanced to 16.8 g to 25.2 g at weekly intervals (60)	5-15 g, once daily, oral (71)
Storage temperature	Room temperature (43)	2°C-8°C (60)	Room temperature (71)
Efficacy			
Normalize serum K^+	Variable and not known	48 to 72 h (60)	2.2 h (mean) (69)
Normokalemia maintained	Variable and not known	52 weeks (so far known) (61)	52 weeks (so far known) (79)
Safety			
Edema	Not known	None	1.3% (14 days) (69), 7.9% (28 days) (69)
Worsening of CKD	Not known	6.3% (over 52 weeks) (61)	Not known
Mild to moderate GI AE	Variable (53)	15% (52 weeks) (61)	5.3% (open-label phase) (69) 1.8% (maintenance phase) (69)
Severe GI AE	Colonic necrosis: case reports (43,86)	None	None
Hypomagnesemia	Reported (85)	7.2%-24% (56,60,61)	None
Hypokalemia/increased QTc	Reported (87)	3%-5.6% (61,63)	0%-11% (69), dose-dependent
Calcium	Reported hypercalcemia (85)	Possible hypocalcemia (88), rare	None
Phosphosphate	Not known	None to minimal (56,63)	None

Sarwaar et al. JACC 2016

Patiromer

Na+ free Polymer

- A novel next-generation, Na+ free, insoluble spherical polymer with improved physical properties
- Suitable for patients who cannot tolerate even a small increase in sodium load



Mechanism of action

- Carboxylate groups of patiromer bind to K^+ in exchange for Ca^{2+} not Na^+, as the exchange cation

High-K^+ binding capacity

- Patiromer has a 1.5- to 2.5-fold higher potassium-binding capacity than other polymers and has been designed to maintain strong binding capacity in the colon

Uniform shape and defined particle size

- Spherical, smooth, uniform microbeads with free-flowing properties that may minimise undesirable GI effects

Non-absorbed

- With an average bead size of ~100 µm, determined by laser diffraction, Patiromer particles are too large to be absorbed during transit through the GI tract

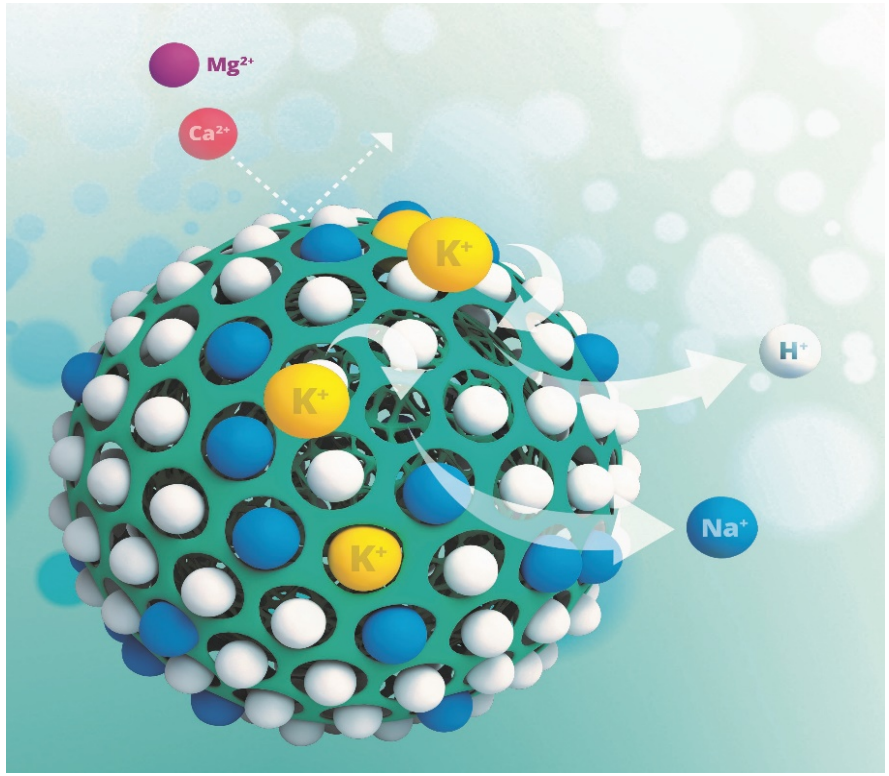
Administration

- Once a day, starting dose 8.4 g (may be increased or decreased by 8.4 g as necessary to reach the desired target range, up to a maximum dose of 25.2 g daily

Li L, et al. J Cardiovasc Pharmacol Ther. 2016;21(5):456–65. 2. Patiromer® EU SmPC, 2019.

Sodio Zirconio Ciclosilicato

SZC preferentially captures for K^+ in exchange for Na^+ and H^+, even in the presence of Ca^{2+} and Mg^{2+}



No effect on serum Ca^{2+} and Mg^{2+} concentrations

- Inorganic crystalline potassium binder; not a polymer
- Exchanges H^+ and Na^+ for K^+
- Highly selective for K^+; binding site width and K^+ ionic diameter are similar
- Insoluble, highly stable, and does not expand in water
- Not systemically absorbed
- Each 5 g of sodium zirconium cyclosilicate contains 400 mg of sodium.

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

Nuovi farmaci per il trattamento dell'iperkaliemia: come?

	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%)

G Ital Cardiol 2021;22(12 Suppl 1):e8-e12

Nuovi farmaci per il trattamento dell'iperkaliemia: quando?

<table>
<tr><th>K^+ levels</th><th>K^+- lowering agents</th><th>RAASi/ARNI</th><th>Monitoring</th></tr>
<tr><td>4.5 – 5.0 mEq/L</td><td>Do not use</td><td rowspan="2">Optimize treatment up to maximally tolerated doses</td><td rowspan="3">Close monitoring of K+ levels</td></tr>
<tr><td>5.0 – 6.5 mEq/L</td><td rowspan="2">Start/maintain treatment with K^+- lowering agents</td></tr>
<tr><td>> 6.5 mEq/L</td><td>Discontinue/Reduce</td></tr>
</table>

Rosano et al. ESC Expert Consensus 2018

Patiromer

Ottimizzazione della terapia con RAASi – DIAMOND trial

Patiromer use in patients with heart failure and reduced ejection fraction (HFrEF) with hyperkalemia (HK)

Study design

1195

Patients with HFrEF and hyperkalemia or a history of hyperkalemia

878

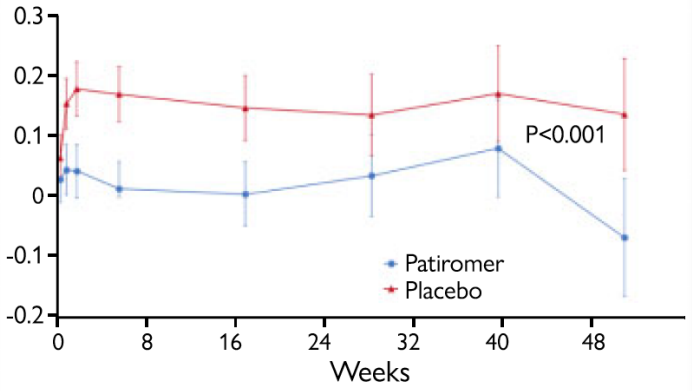
Patients were randomized and completed run-in (where K^+ levels controlled with patiromer and RAASi dose optimized)

439 Placebo

439 Patiromer

Primary endpoint

Mean change in serum potassium (mmol/L) from baseline (95% confidence interval (CI))



	Day	Weeks						
	3	1	2	6	18	30	42	54
Patiromer	409	406	402	376	273	183	104	66
Placebo	416	409	397	361	270	184	106	74

Secondary endpoints

	Patiromer (n=439)	Placebo (n=439)	Hazard/rate ratio (95% CI)	P-value
Hyperkalemia events with serum K^+> 5.5 mmol/L	61 (13.9)	85 (19.4)	0.63 (0.45-0.87)	0.006
Maintained MRA target dose	61 (13.9)	83 (18.9)	0.62 (0.45-0.87)	0.006
Total number of hyperkalemia events	225	316	0.66 (0.53-0.81)	<0.001

0.3 1 3.0
RR or HR* (95% CI)
Favours Patiromer Favours Placebo

	Win ratio (95% CI)	P-value
Hyperkalemia-related morbidity-adjusted events*	1.53 (1.23-1.91)	<0.001
Win-ratio for RAASi use score	1.25 (1.003-1.564)	0.048

0.3 1 3.0
Win ratio (95% CI)
Favours Placebo **Favours Patiromer**

European Heart Journal (2022) **00**, 1–12

Patiromer

Ottimizzazione della terapia con RAASi – DIAMOND trial

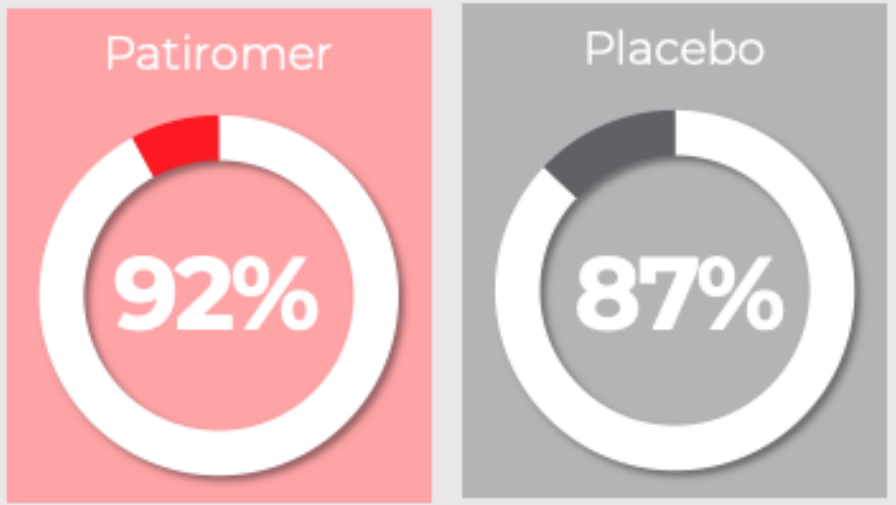
Patients treated with patiromer were:

26% LESS LIKELY **to have MRA dose reduced/discontinued or have K^+ >5.5 mmol**
21.6% vs 26.7%; HR (95% CI): 0.74 (0.57; 0.97); P=0.030

36% LESS LIKELY **to have MRA discontinued**
4.6% vs 7.1%; HR (95% CI): 0.64 (0.36; 1.12); P=0.117

26% LESS LIKELY **to have ACEi/ARB/ARNi discontinued**
2.7% vs 3.6%; HR (95% CI): 0.74 (0.35; 1.57); P=0.438

Patients at EoS on
≥50% of target dose of ACEi/ARB/ARNi
+
≥25 mg daily MRA dose

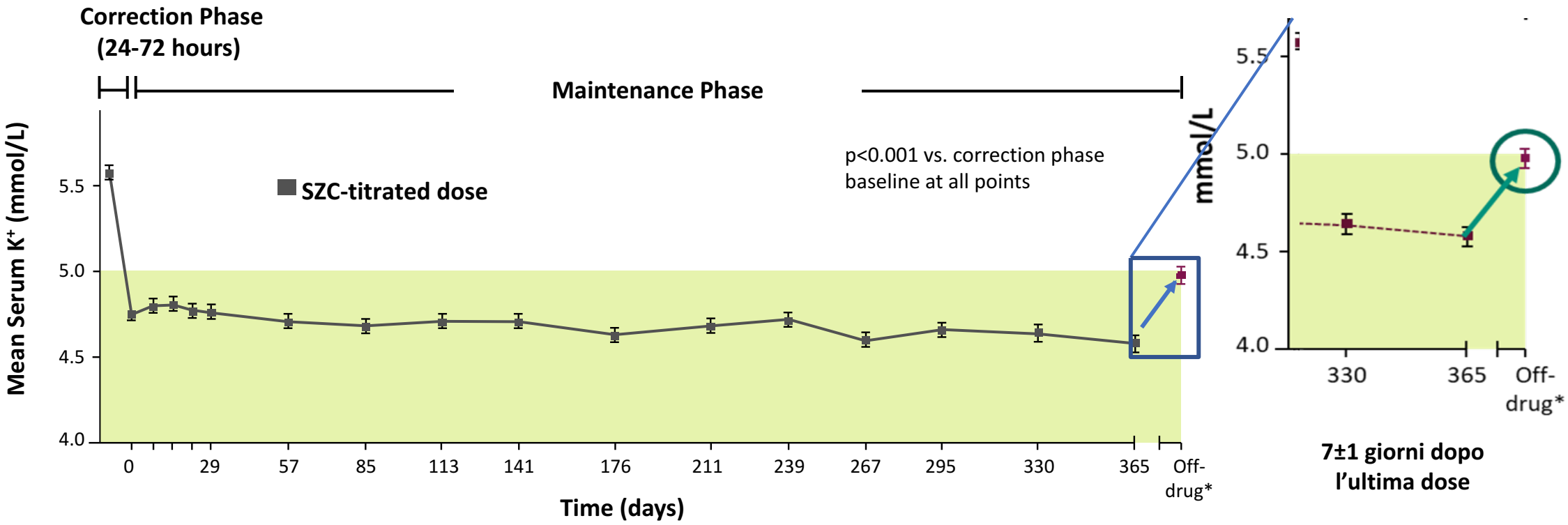


ARR: 5%
NNT: 20
P=0.015

European Heart Journal (2022) **00**, 1–12

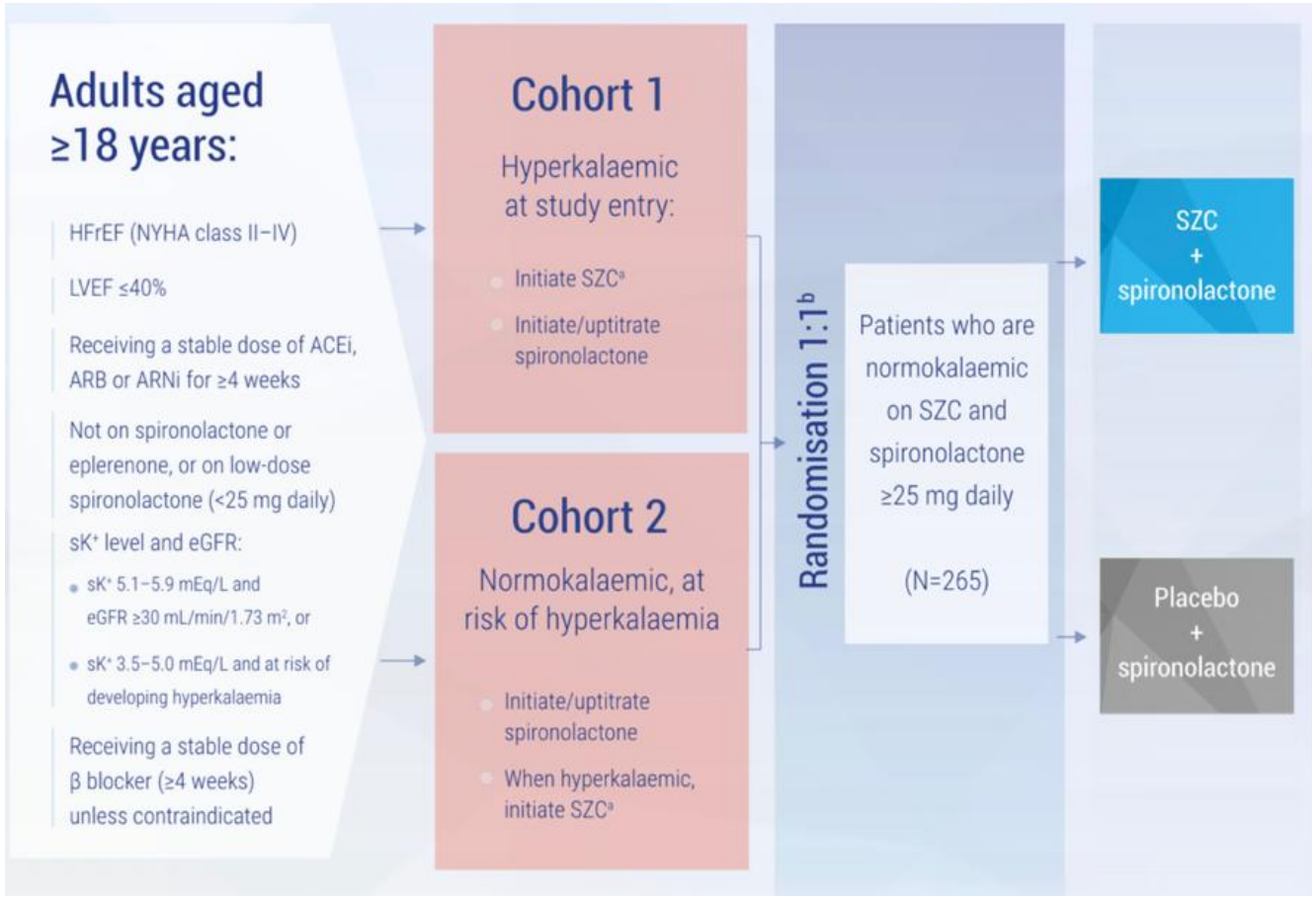
SZC

Controllo dell'iperK⁺



SZC

Ottimizzazione della terapia con RAASi – REALIZE-K trial



Primary Endpoint:[2]
Occurrence of patients receiving SZC vs. placebo who are normokalemic and on spironolactone ≥25 mg daily at EOT, and did not use rescue therapy for HK during the randomized withdrawal phase

ZS-005

RAASi Dosing During the Study

Of the 263 patients who are *RAASi-naïve* at baseline

14% **Initiated** RAASi therapy

Of the 483 patients who received *RAASi* at the start of the initial phase

74% **Maintained** same RAASi dose

13% **Increased** RAASi dose*

14% **Decreased** RAASi dose*

11% **Discontinued** RAASi dose

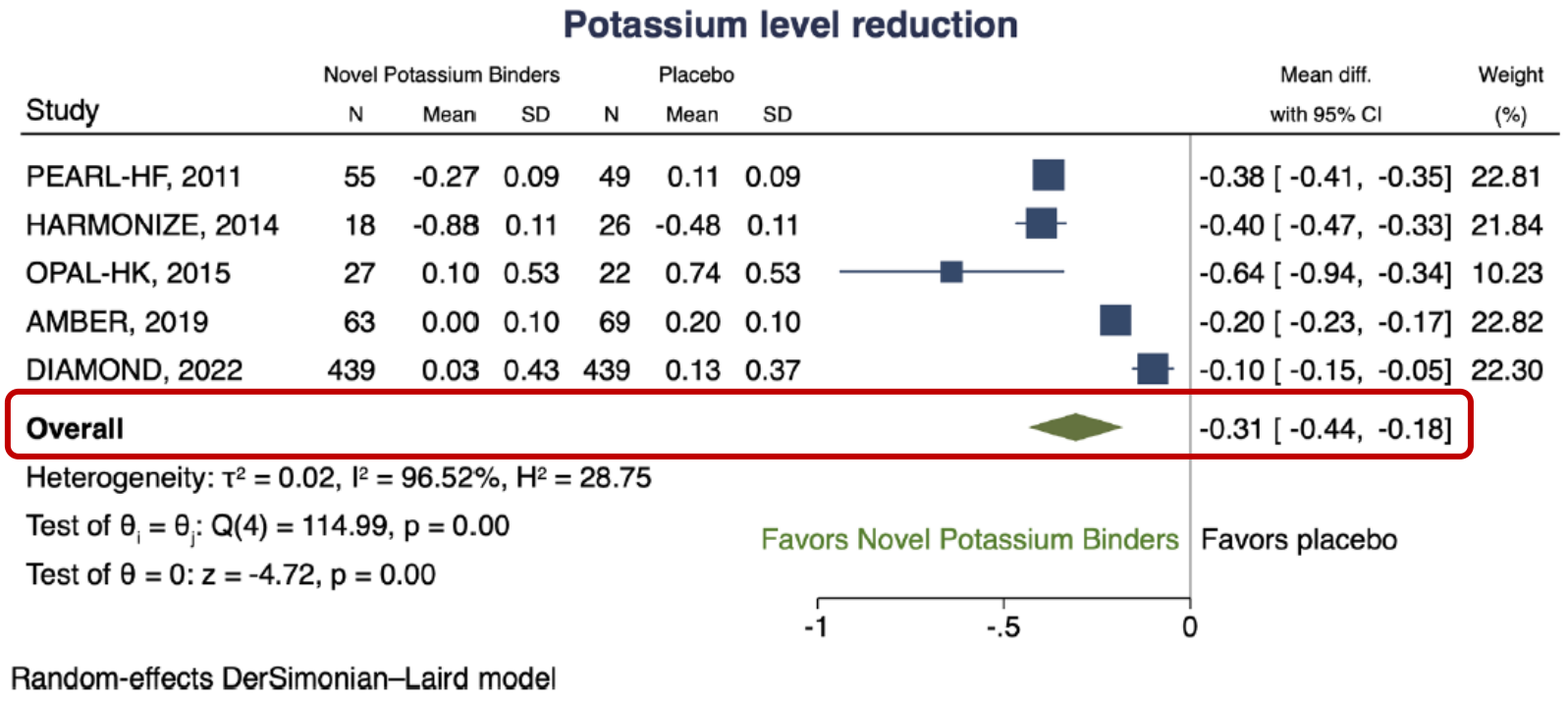
*Nonmutually exclusive.

Spinowitz BS et al. Clin J Am Soc Nephrol. 2019;14(6):798-809.

Original article

Novel potassium binders to optimize RAASi therapy in heart failure: A systematic review and meta-analysis

Stefania Paolillo [1,*], Christian Basile [1], Simona Dell'Aversana, Immacolata Esposito, Alfonsina Chirico, Angela Colella, Gennaro Esposito, Mariafrancesca Di Santo, Maria Francesca Fierro, Francesca Carbone, Federica Marzano, Chiara Amato, Paola Gargiulo, Pasquale Perrone Filardi



Random-effects DerSimonian–Laird model

Potassium levels reduction

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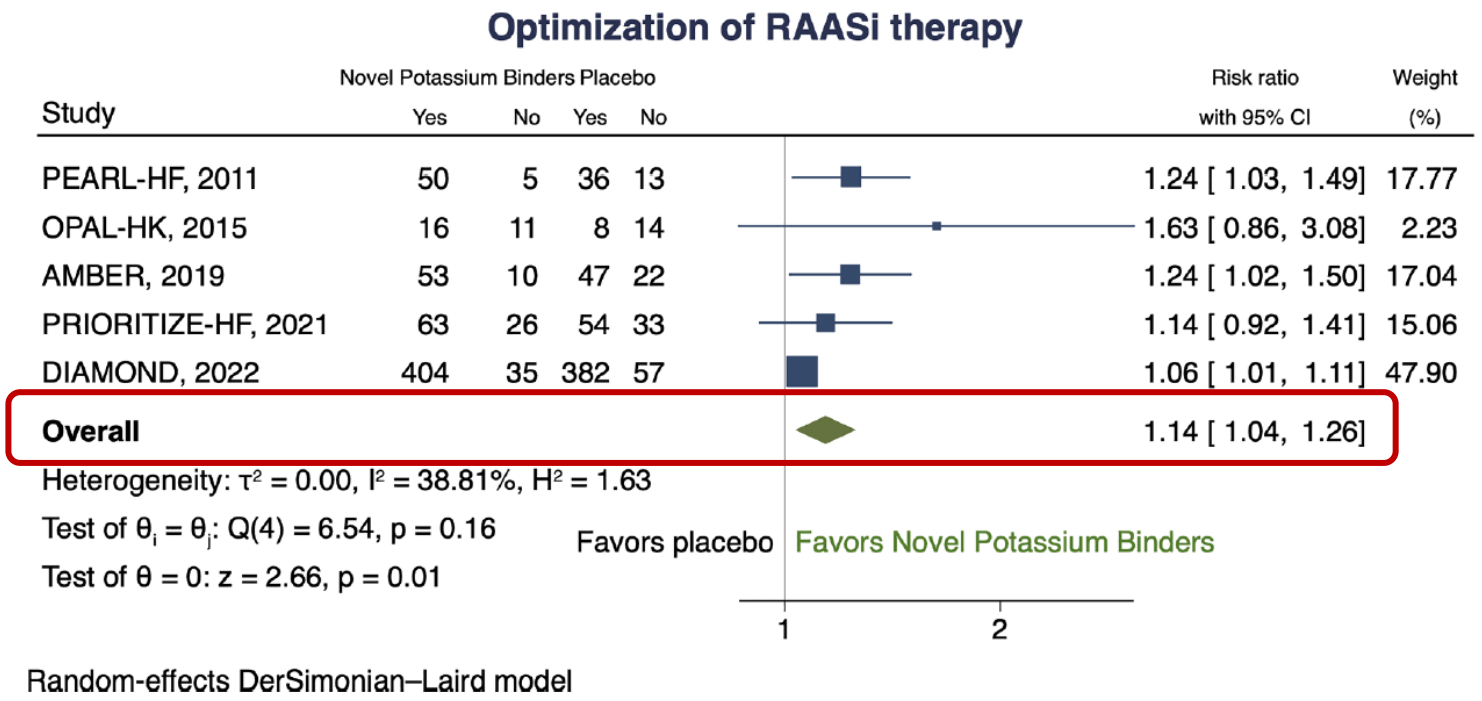
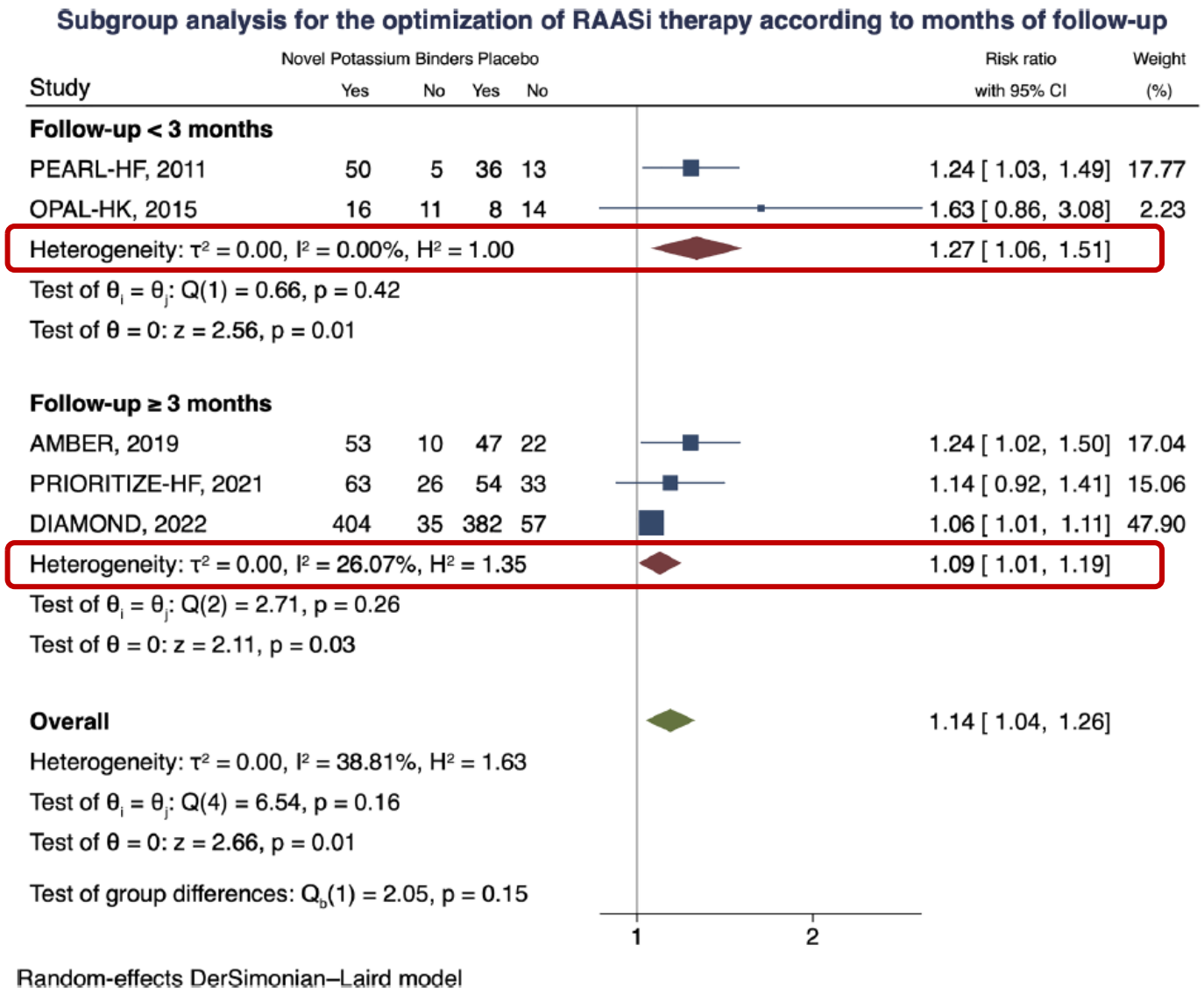


Optimization of RAASi therapy

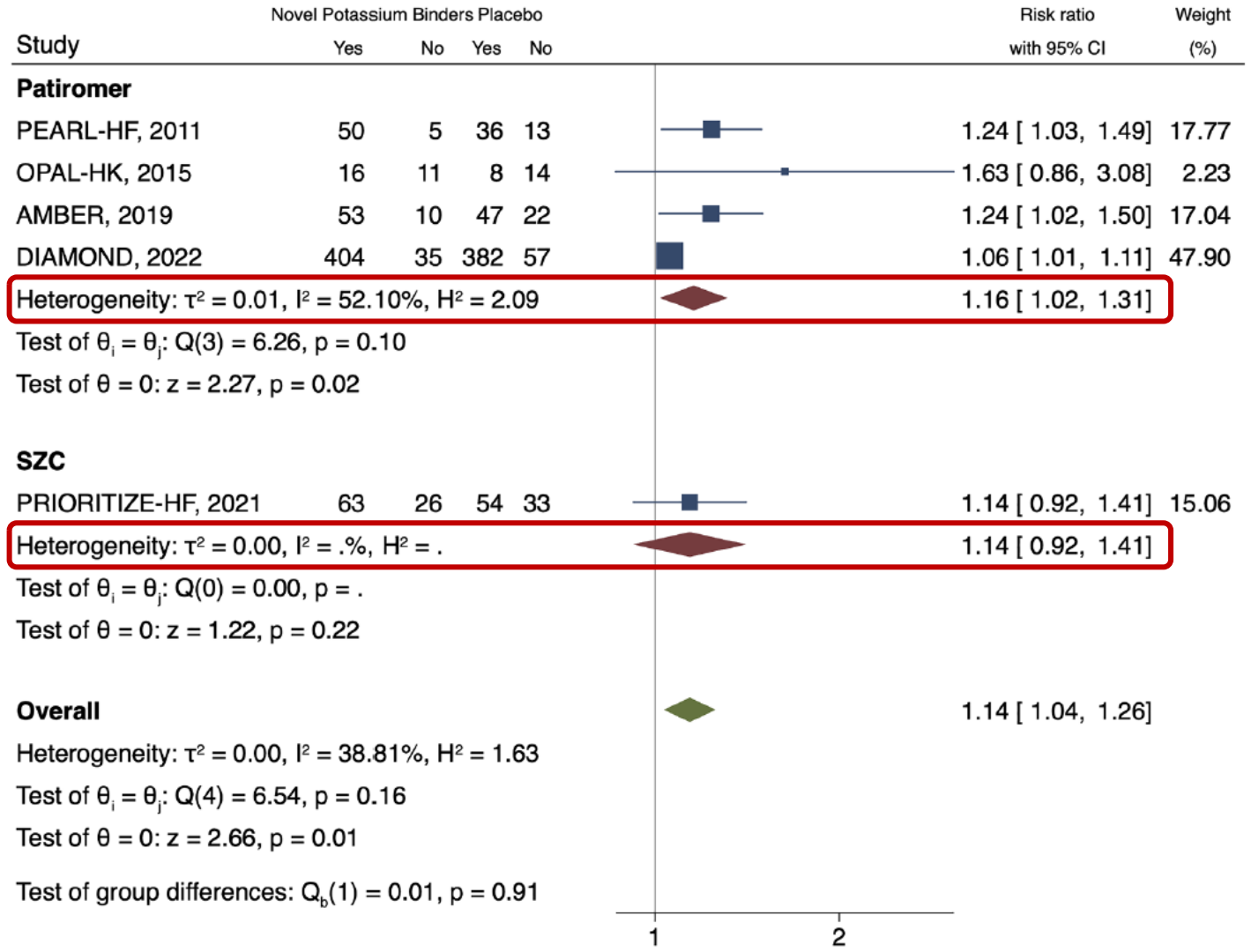


Follow-up <3 months

Follow-up ≥3 months

Paolillo et al. EJIM 2023

Subgroup analysis for the optimization of RAASi therapy according to the Novel Potassium Binder



PATIROMER

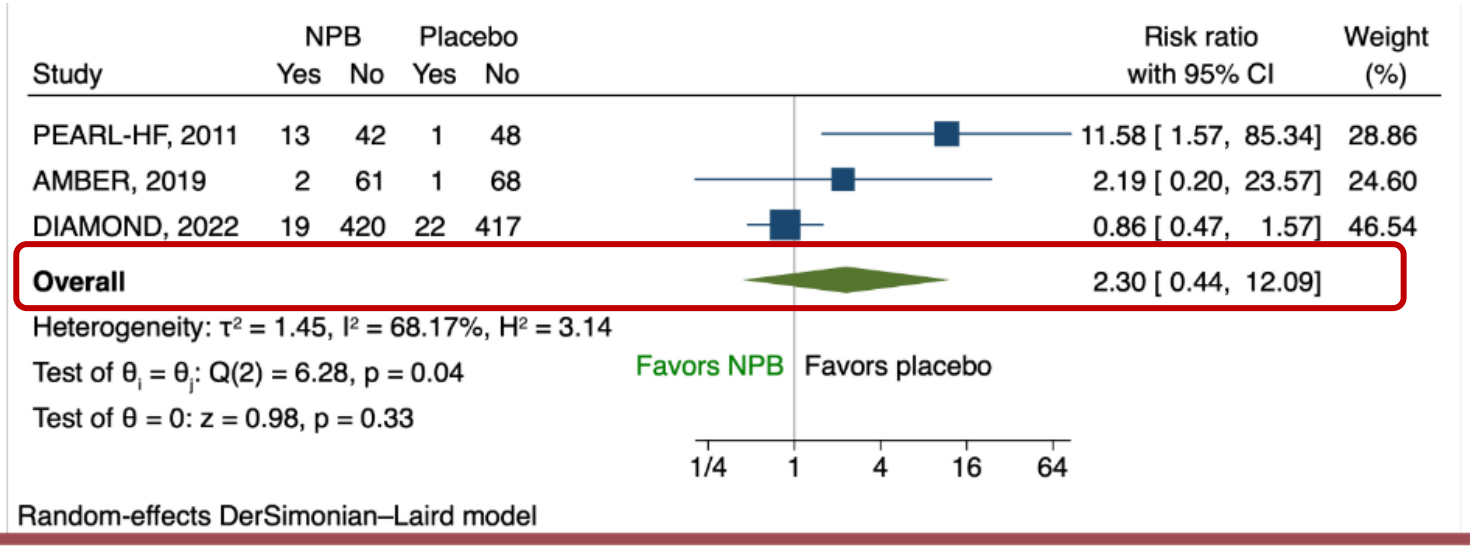
SZC

Paolillo et al. EJIM 2023

New therapeutic approaches for hyperkalemia
Patiromer and Sodium Zirconium Cyclosilicate (SZC)

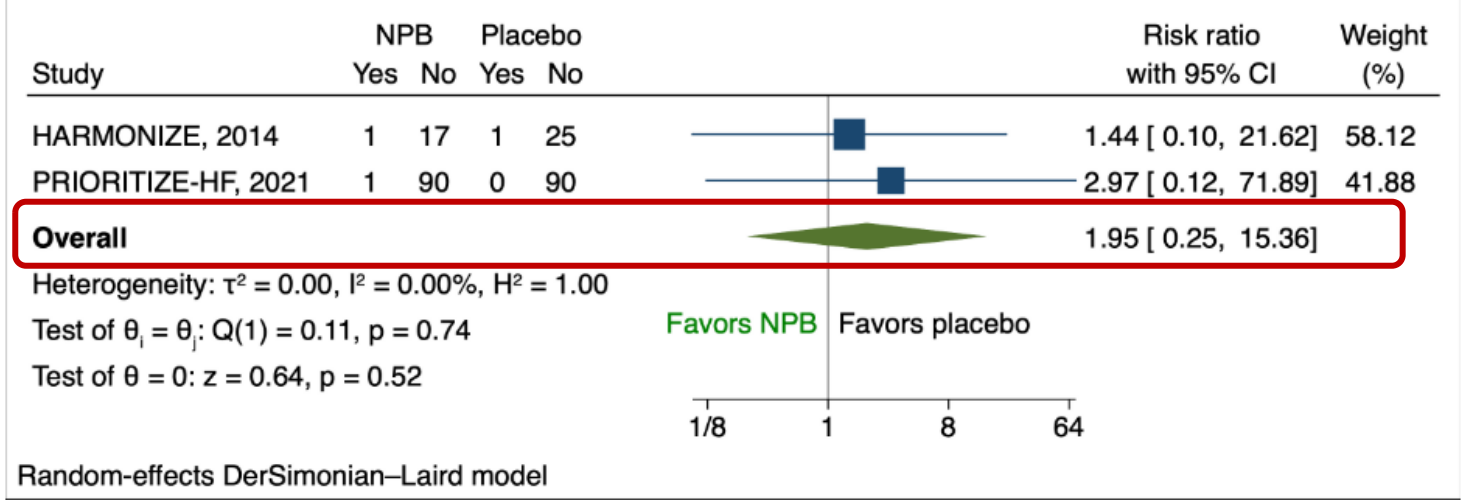
EFFICACY	SAFETY CONCERNS
○ Effective and sustained reduction of serum K^+ levels ○ Reduction of recurrent hyperkalemia events ○ Reduction of severe hyperkalemia (> 5.5 mEq/L) events ○ Effective in CKD and HF ○ Optimization of RAASi/ARNI therapy	○ GI effects – *both* ○ Edema – *SZC at high doses* ○ Hypomagnesemia – *patiromer* ○ Hypokalemia - *both* ○ Bicarbonate increase - *SZC*

A



Patiromer ipomagnesemia

B



SZC edema

Paolillo et al. EJIM 2023

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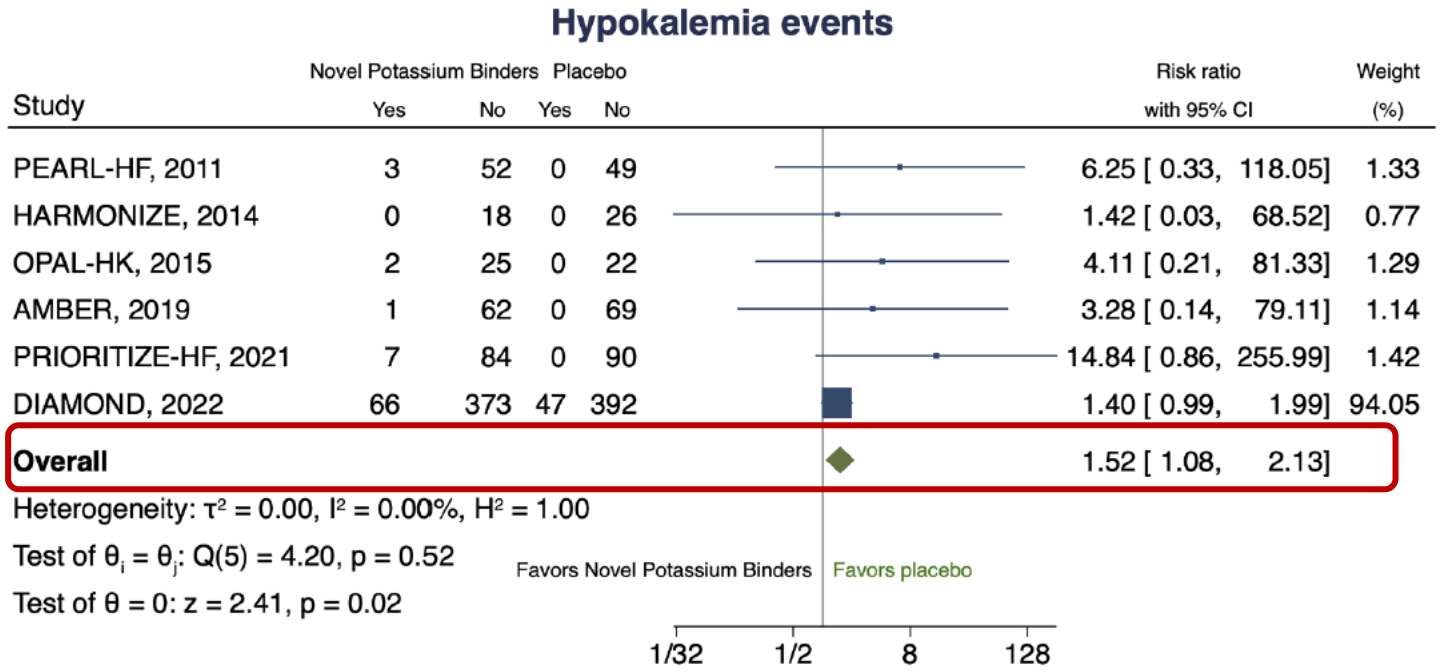

IPOKALIEMIA

EJIM 2023

Original article

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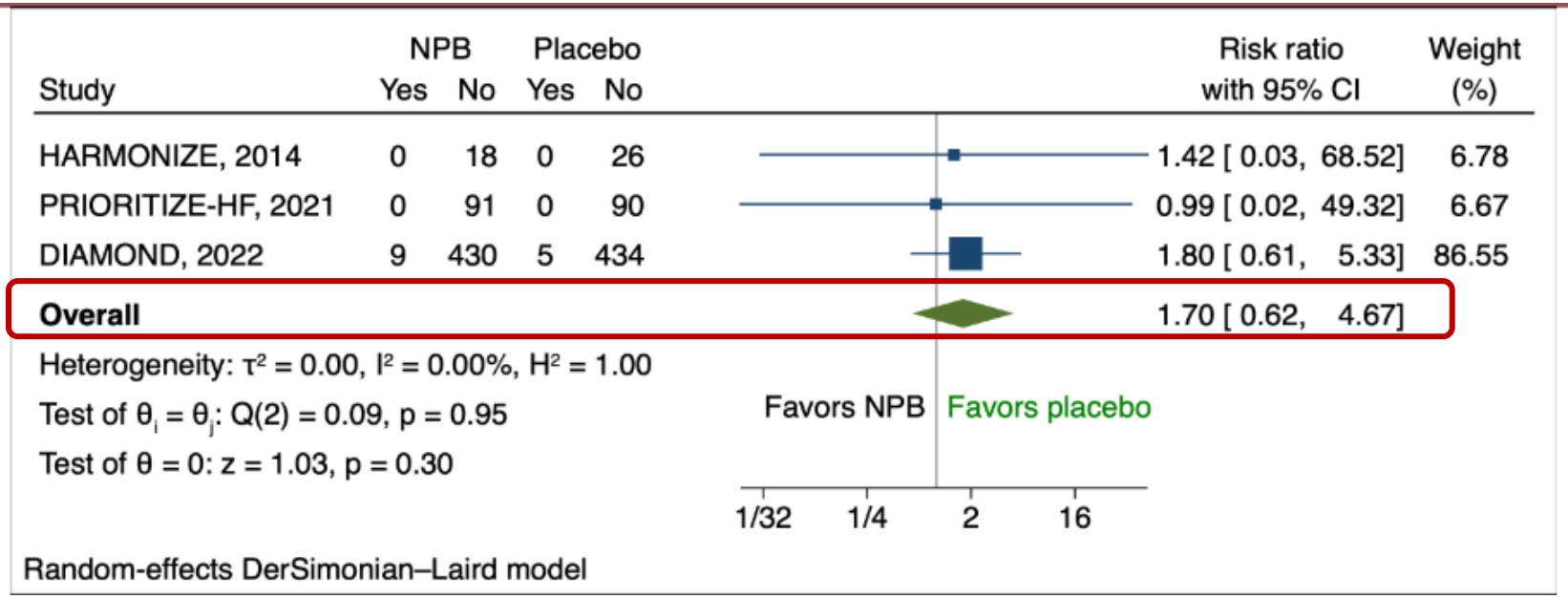
Stefania Paolillo [1,*], Christian Basile [1], Simona Dell'Aversana, Immacolata Esposito, Alfonsina Chirico, Angela Colella, Gennaro Esposito, Mariafrancesca Di Santo, Maria Francesca Fierro, Francesca Carbone, Federica Marzano, Chiara Amato, Paola Gargiulo, Pasquale Perrone Filardi



IPOKALIEMIA SEVERA <3.5 mEq/L

EJIM 2023

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Patiromer and Sodium Zirconium Cyclosilicate (SZC)

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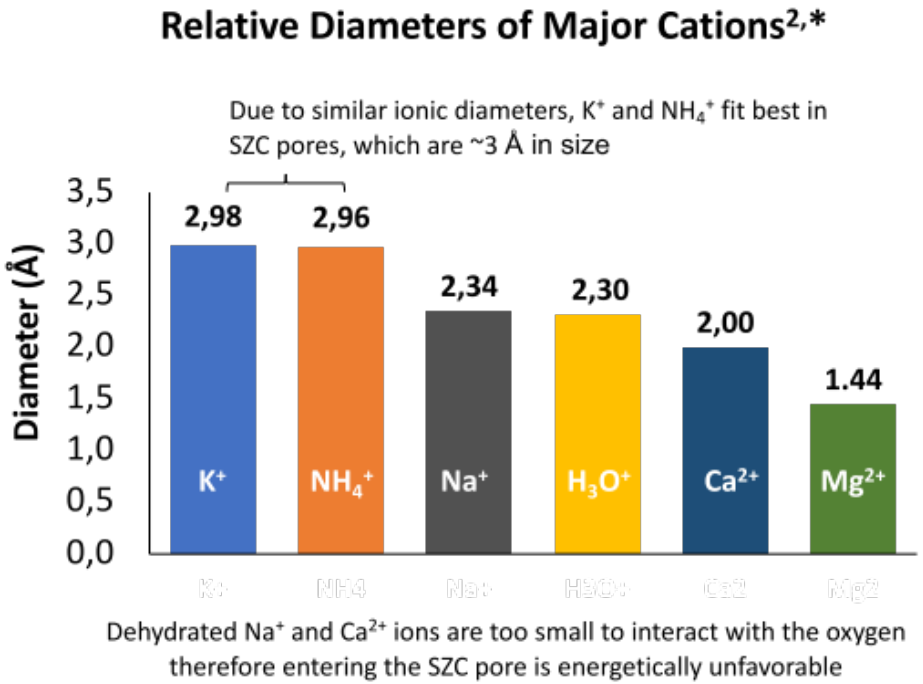
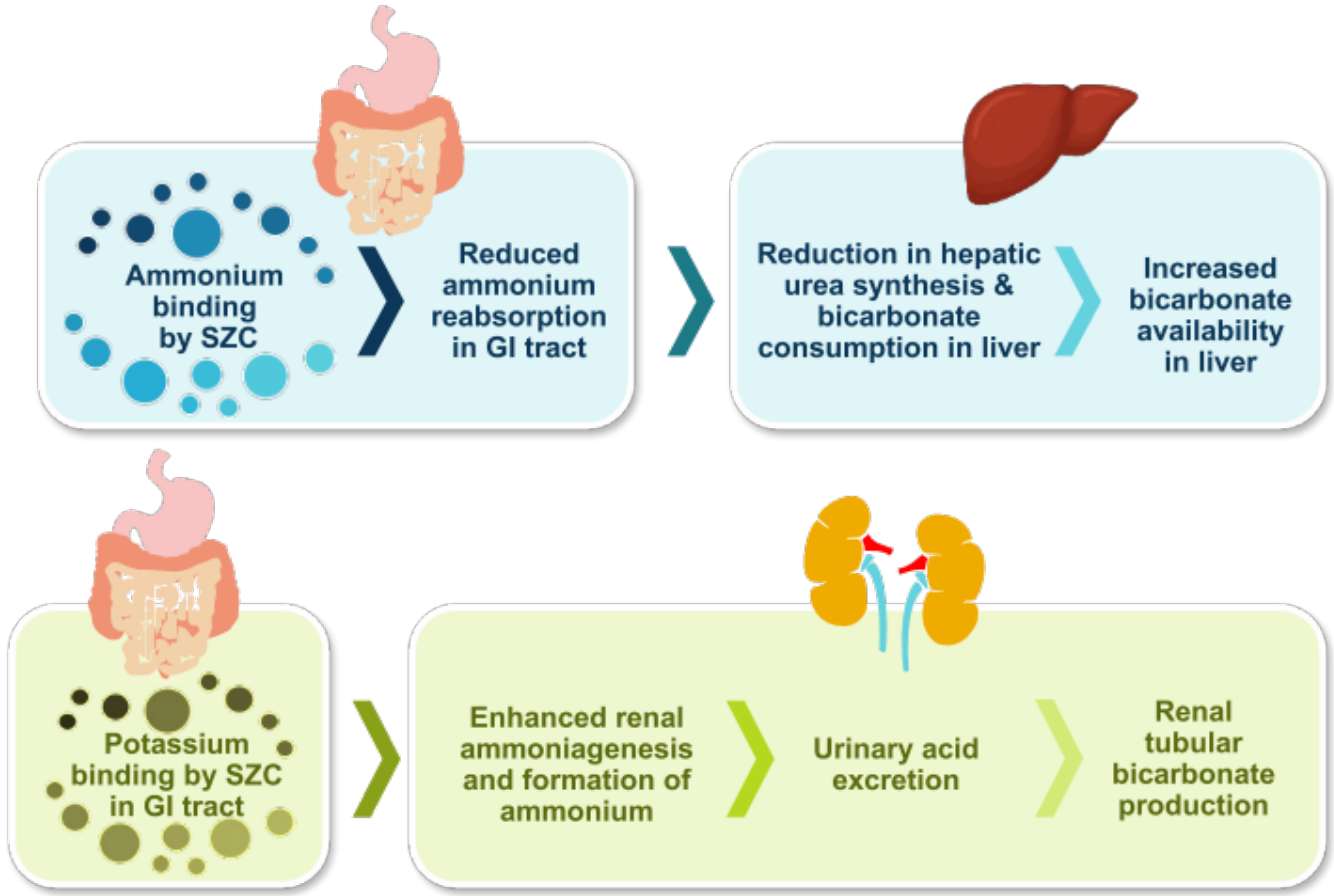
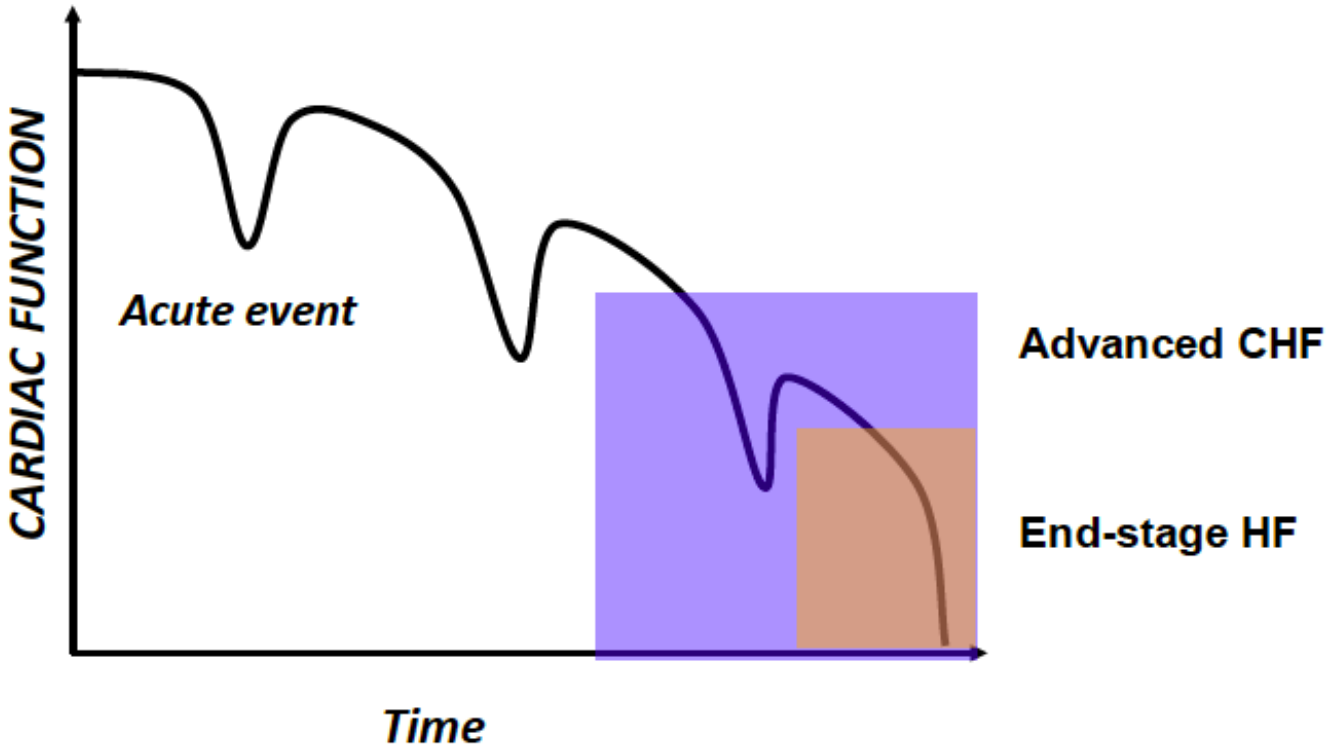
○ Effective and sustained reduction of serum K^+ levels ○ Reduction of recurrent hyperkalemia events ○ Reduction of severe hyperkalemia (> 5.5 mEq/L) events ○ Effective in CKD and HF ○ Optimization of RAASi/ARNI therapy	○ GI effects – *both* ○ Edema – *SZC at high doses* ○ Hypomagnesemia – *patiromer* ○ Hypokalemia - *both* ○ Bicarbonate increase - *SZC*

Potential Mechanisms for Increase in Serum Bicarbonate



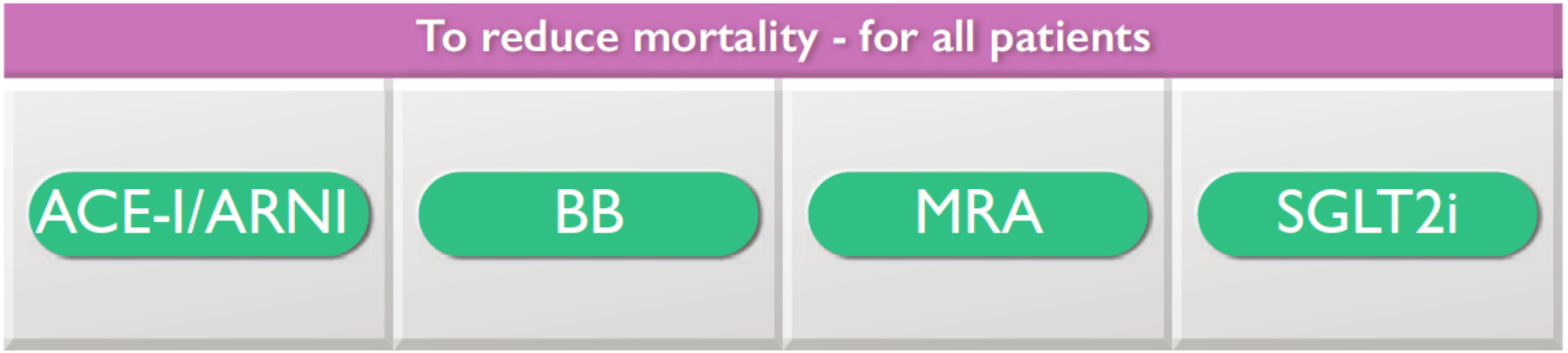


Scompenso cardiaco: storia naturale



Gheorgiade et al. Am J Cardiol 2005

MANAGEMENT OF HFrEF



Vericiguat

Digoxin

ARBs

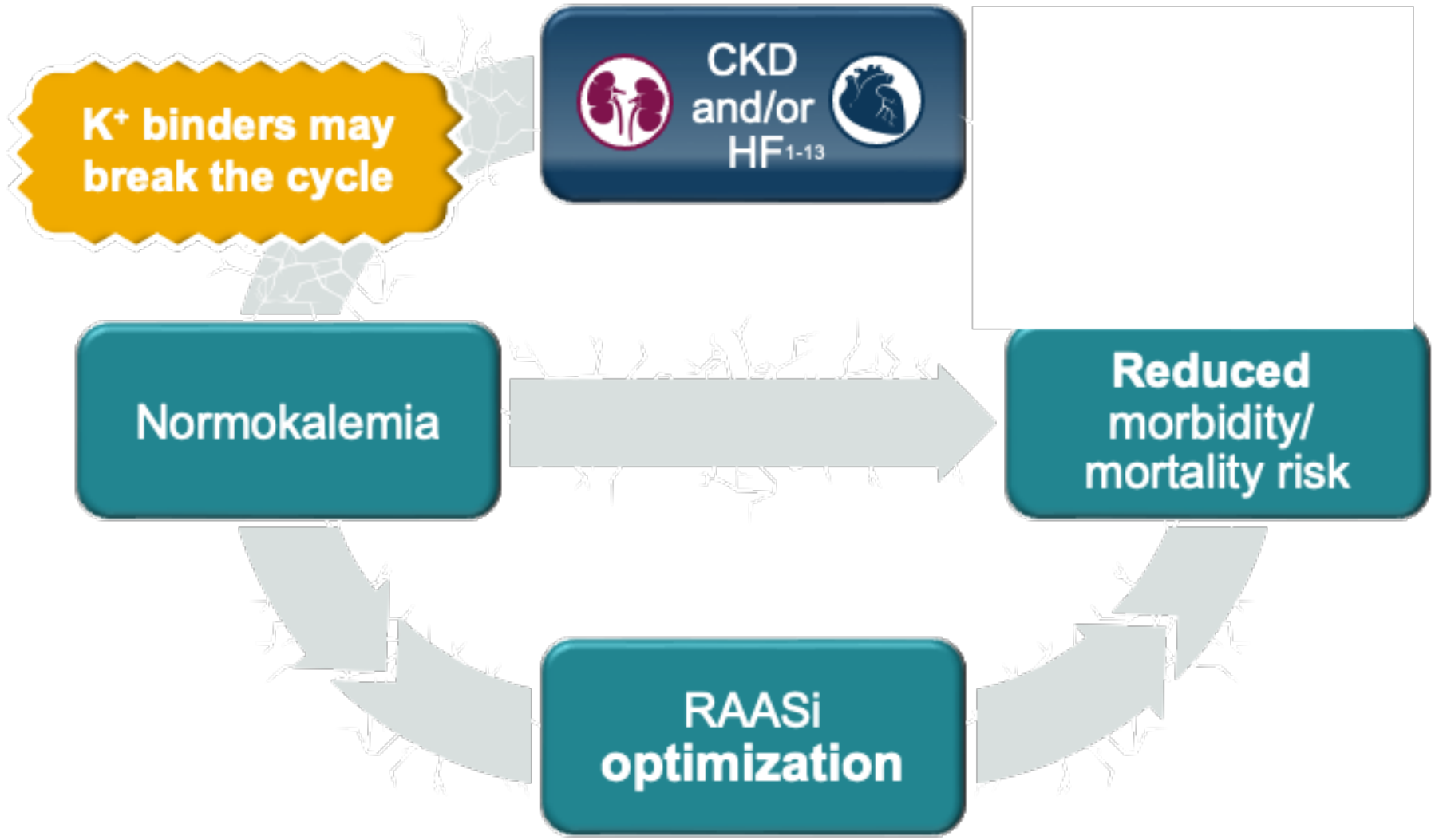
Diuretics

FCM

Hydralazine/ISDN

Ivabradine

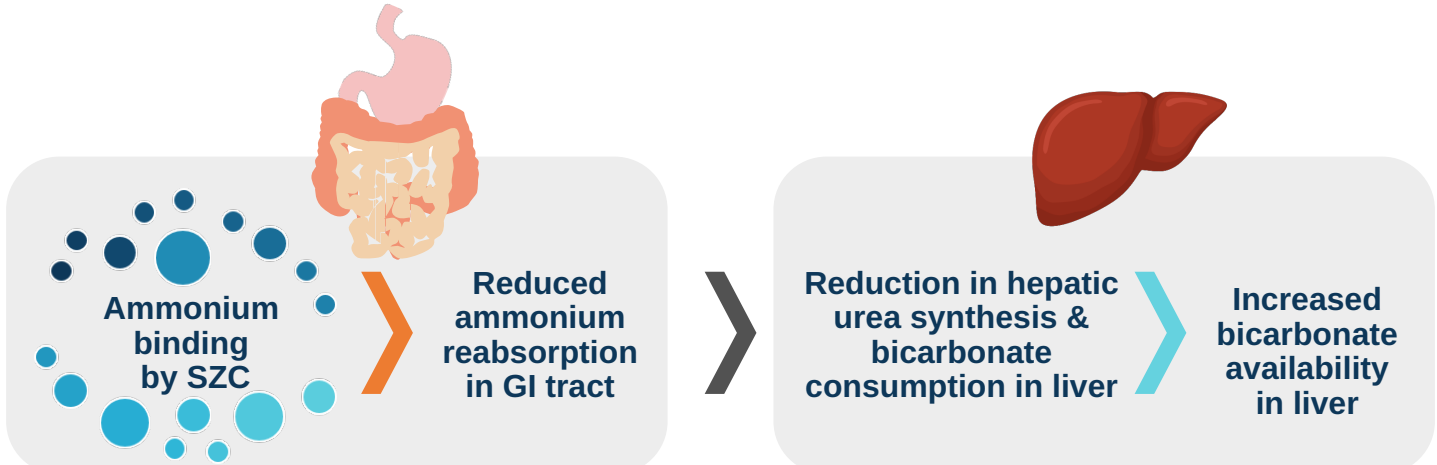
ESC HF Guidelines 2021


K+ binders may break the cycle
CKD and/or HF1-13
Normokalemia
Reduced morbidity/ mortality risk
RAASi optimization

Potential Mechanisms for Increase in Serum Bicarbonate

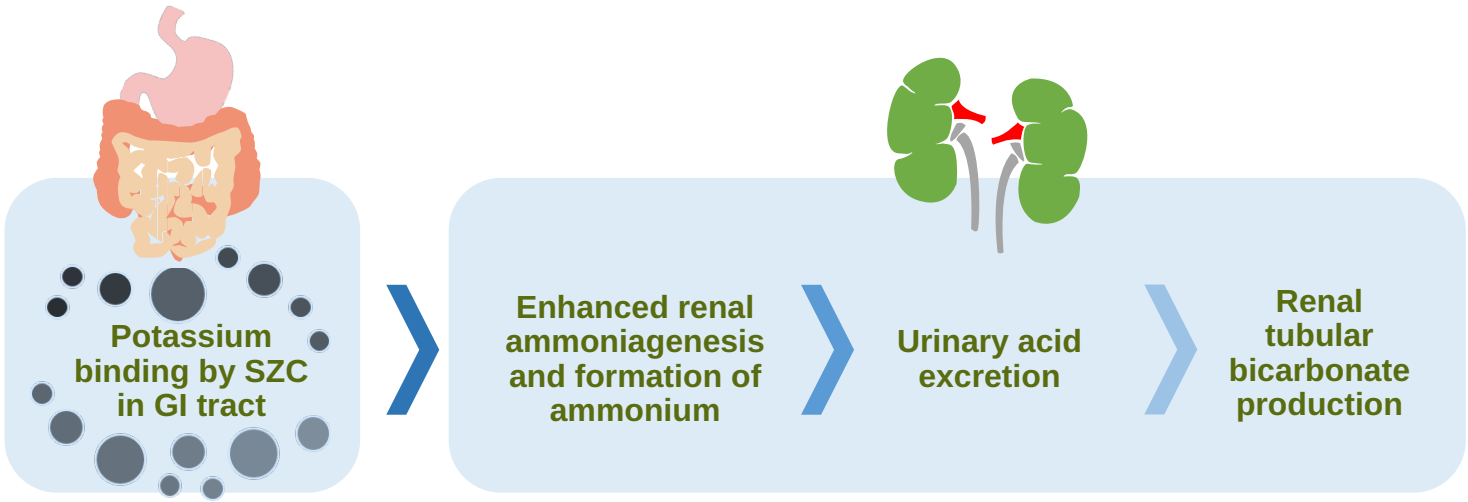
AMMONIUM BINDING HYPOTHESIS:[1,2]

- The micropore opening in SZC is approximately 3.0 Å wide and hence cations such as potassium and ammonium with an ionic diameter of 2.98 Å and 2.96 Å, respectively, will have high affinity to SZC
- Therefore, it is postulated that SZC binds to the ammonium cation



RENAL AMMONIAGENESIS HYPOTHESIS:[1]

- Normalization of serum potassium with SZC may increase renal ammoniagenesis



Further research is needed to determine the exact mechanism behind the increase in serum bicarbonate and its clinical significance

GI = gastrointestinal; SZC = sodium zirconium cyclosilicate.

1. Roger SD et al. *Nephrol Dial Transplant.* 2021;36:871-883; 2. Stavros F et al. *PLoS One.* 2014;9:e114686.

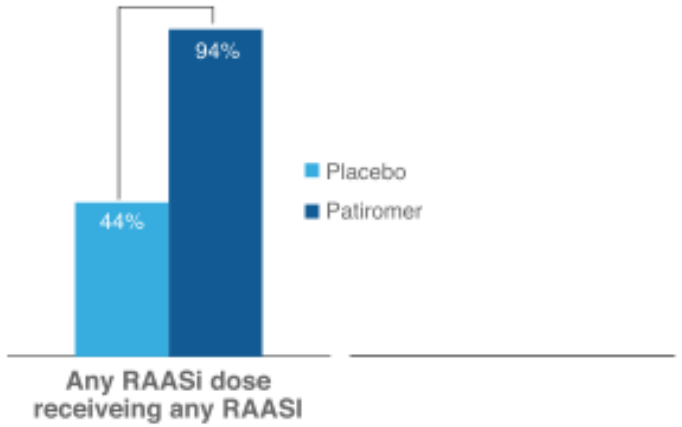
Patiromer

Ottimizzazione della terapia con RAASi

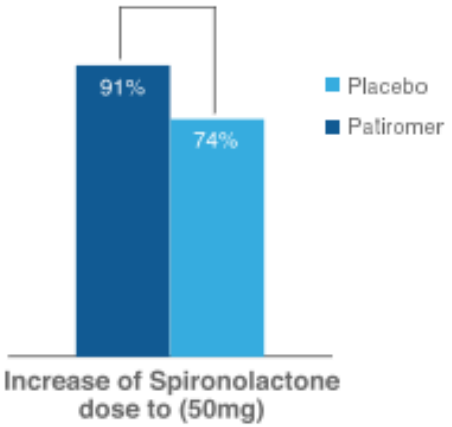
Patiromer enabled substantially more patients to:

- Remain on their RAASi medication at the end of the study, compared with those given placebo
- Initiate and up-titrate spironolactone in patients with HF and advanced CKD with rHTN

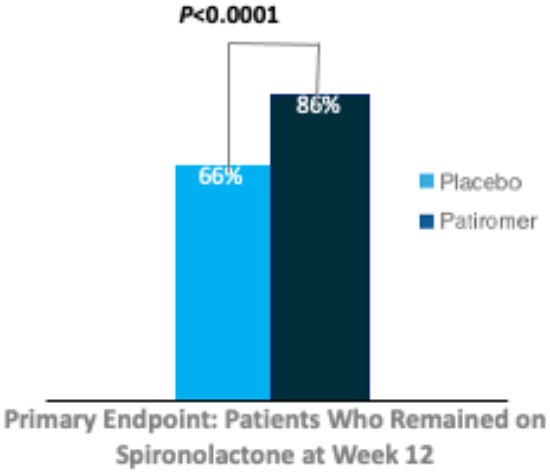
- **OPAL Weir NEJM 2015**
  GFR 15-59; K⁺ 5.1-6.4; RAASi; 42-49% HF
  8w randomized withdrawal → 60% v 15% recurrence



- **PEARL-HF EHJ 2011; n=105**
  HF + ([K⁺ requiring d/c RAASi] or [eGFR<60])
  4w □ normoK in 24% v 7%; prevent recurrence



- **AMBER LANCET 2019; n=295**
  rHTN; eGFR 25-45 mL/min/1.73 m²; sK⁺ 4.3-5.1 mEq/L

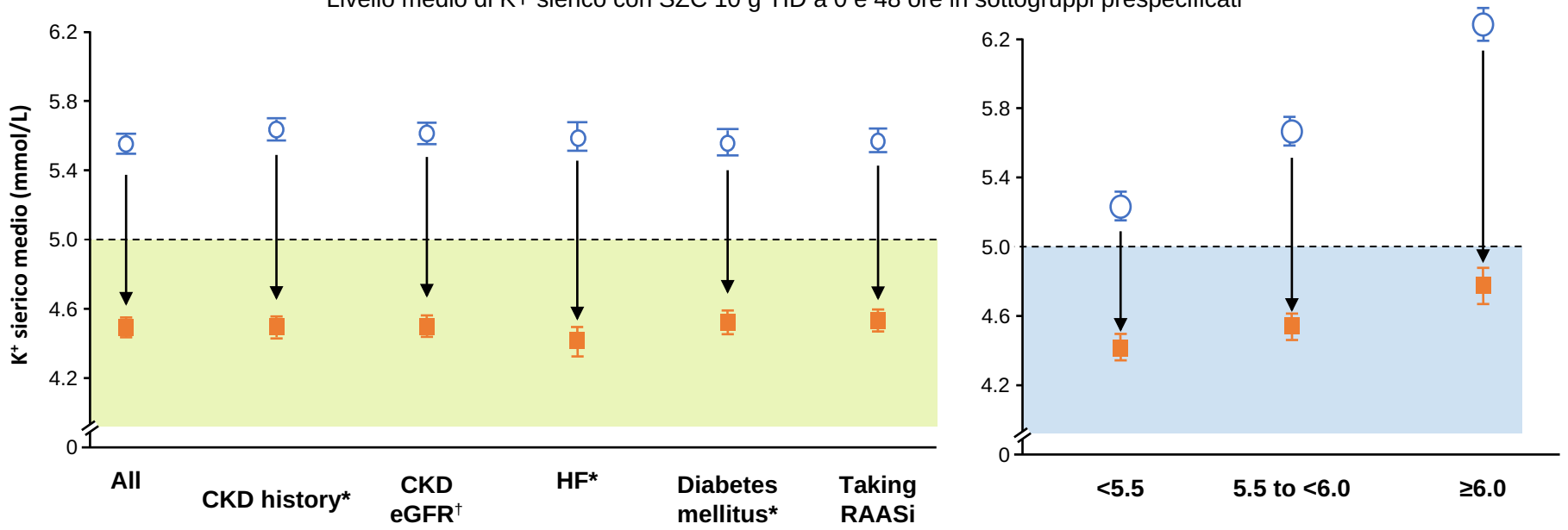


1 Patiromer EU SmPC, 2017. 2. Weir MR, et al. N Engl J Med 2015;372(3):211-21.

3. Pitt B, et al. Eur Heart J 2011;32(7):820-8. 4. Agarwal R, et al. Lancet 2019;394(10208):1540-1550.

SZC ha costantemente ridotto il K+ sierico INDIPENDENTEMENTE dalle comorbidità e dall'uso della terapia RAASi o dal livello basale di K+[1-3]

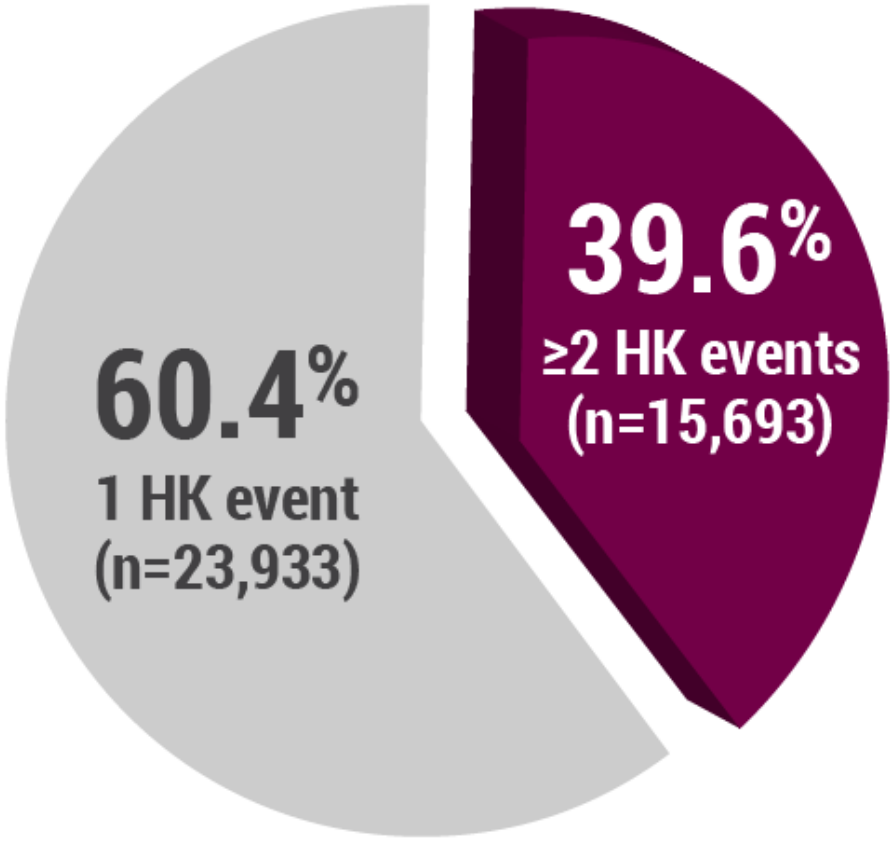
Livello medio di K+ sierico con SZC 10 g TID a 0 e 48 ore in sottogruppi prespecificati



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

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

Hyperkalemia can be Recurrent for Many



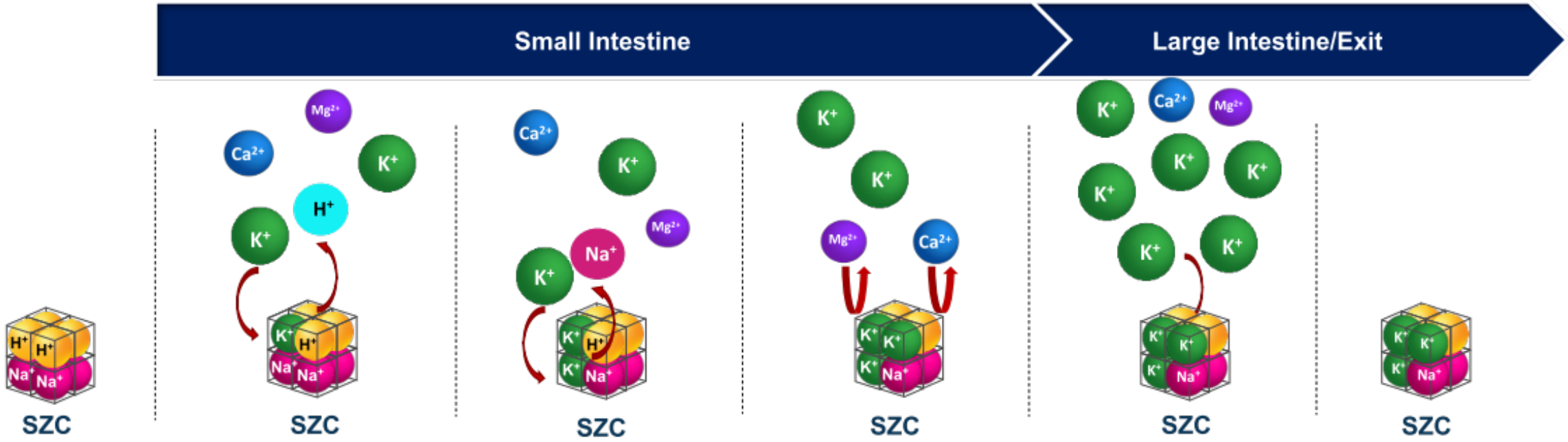
40% of patients with hyperkalemia in the Truven MarketScan® analysis experienced 2 or more hyperkalemic events during the 1-year post-index period

- 15.6% of patients (n=6180) had ≥3 HK events
- 8.2% of patients (n=3234) had ≥4 HK events

Data on file, REF-34835, AstraZeneca Pharmaceuticals LP; 2. Betts KA et al. Kidney Int Rep. 2017;3(2):385-393.

Sodio Zirconio Ciclosilicato

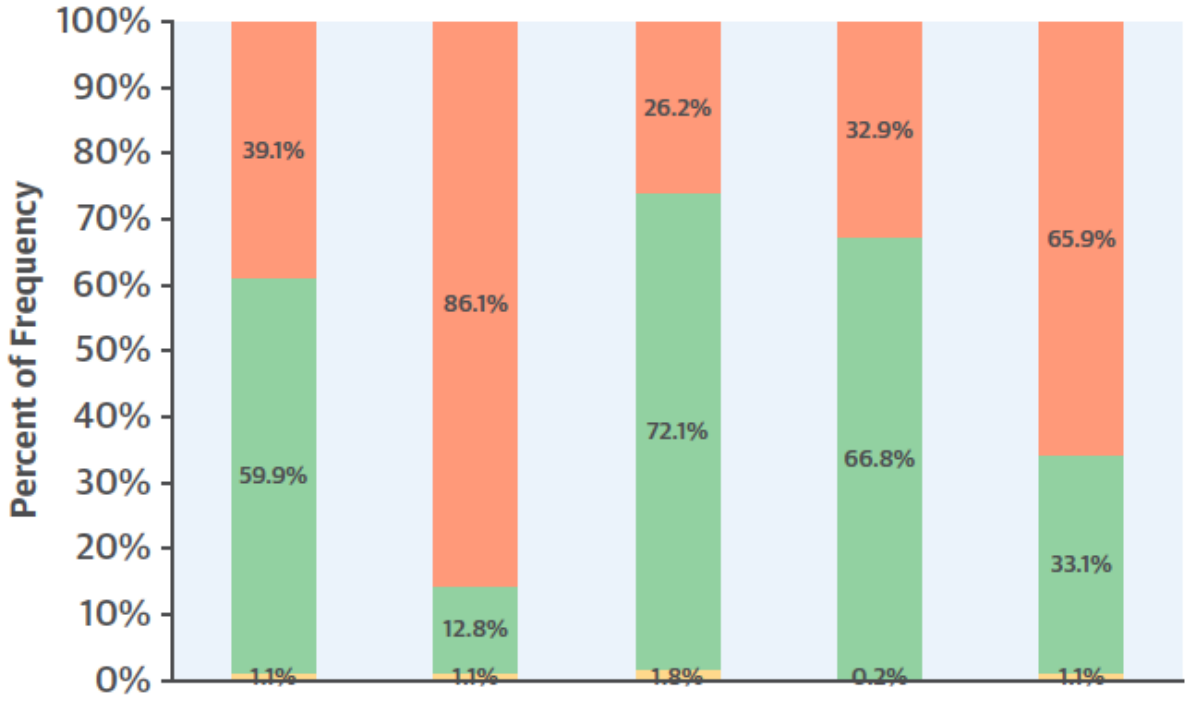
SZC may begin working immediately in the small intestine resulting in the early capture of K^+



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

INTRODURRE RAASi/ARNI IN TERAPIA

A

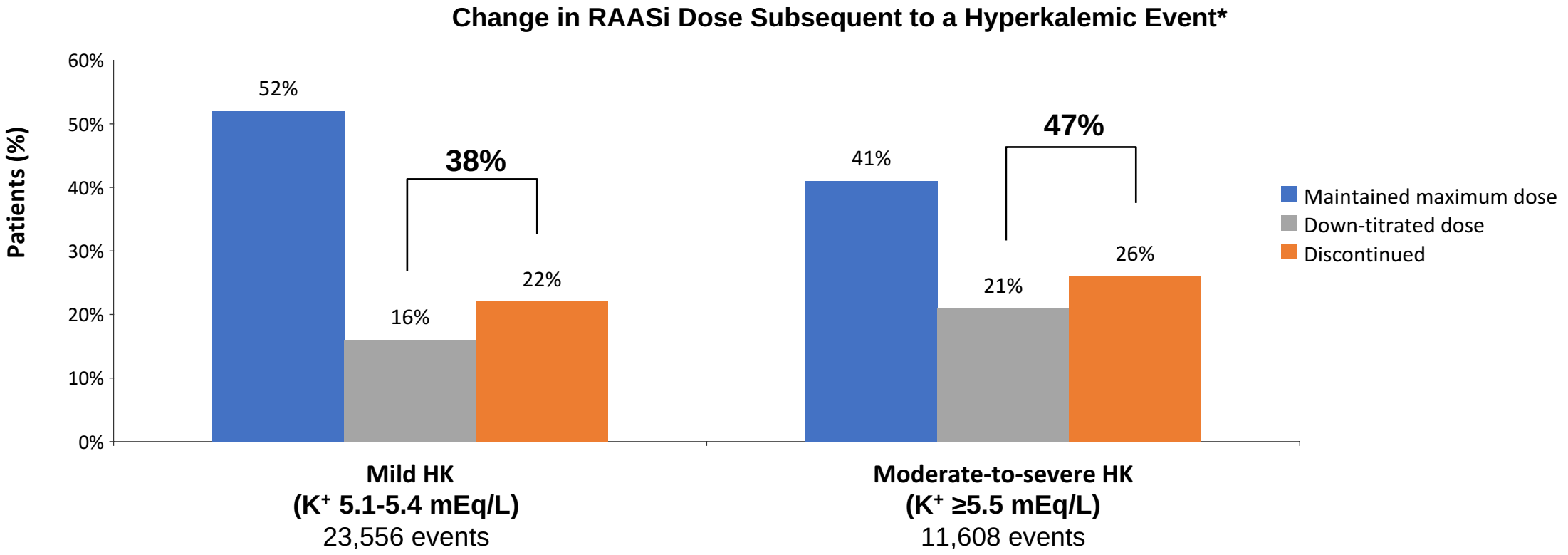


	ACEI/ARB	ARNI	ACEI/ARB/ ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38

CHAMP-HF Registry 2019

Down-titration or Discontinuation of Guideline-recommended RAASi Therapy is Common Following a HK Event

Retrospective Analysis of a US Database of Electronic Health Records (N>200,000) of Patients ≥5 Years of Age With at Least 1 Outpatient RAASi Prescription and at Least Two Serum K^+ Readings



Epstein M et al. Am J Manag Care. 2015;21(suppl 11):S212-S220.

Patiromer

Profilo di Safety

GI disorders

- 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/(0.4 mmol/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

List of adverse reactions in clinical studies

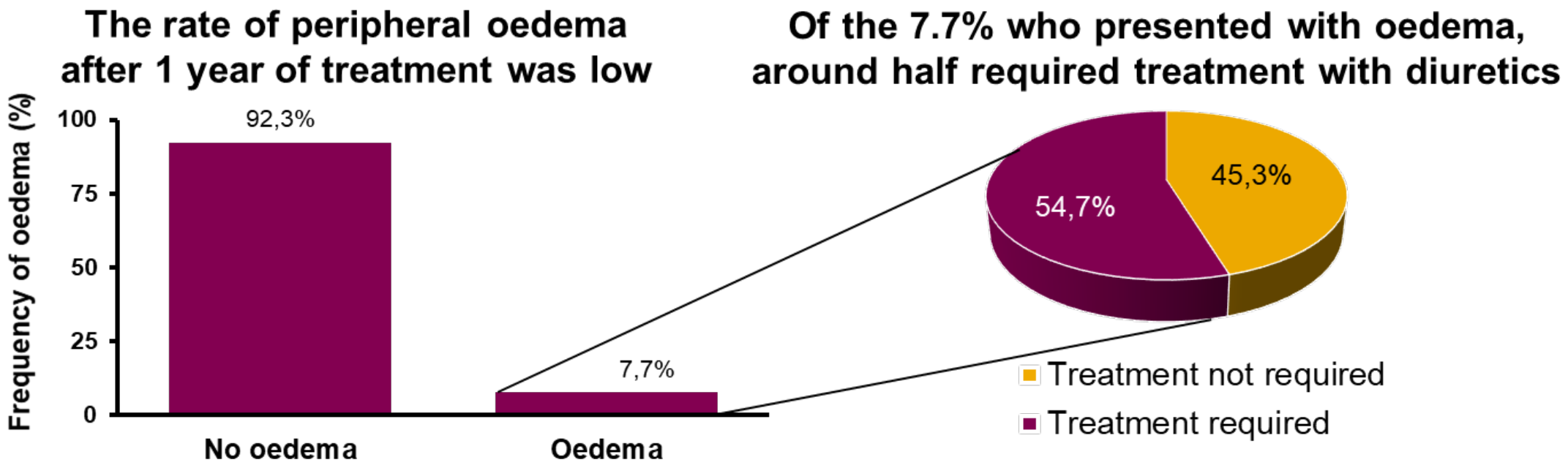
System Organ Class	Common	Uncommon
Metabolism and nutrition disorders	***Hypomagnesaemia***	
Gastrointestinal disorders	Constipation Diarrhoea Abdominal pain Flatulence	Nausea Vomiting

Adapted from Veltassa® EU SmPC, 2019.

Interactions

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

Edema



90% of patients requiring treatment for oedema had prior history of oedema

Tumlin J, et al. Poster presented at American Society of Nephrology 2015; poster 1101.