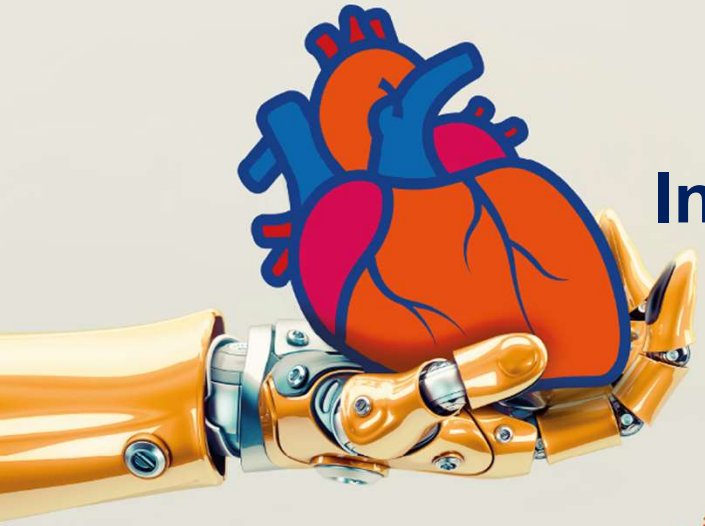


17° Meeting
CardioLucca
Heart Brings Heart 2023
Lucca, 22-24 Giugno 2023
Centro Congressi Auditorium San Francesco

Inquadramento clinico e nuove opportunità terapeutiche nell'iperkaliemia

Gianfranco Sinagra MD, FESC
Dipartimento Cardiotoracovascolare – SC Cardiologia
Ospedale di Cattinara (TS) – ASUGI
Università di Trieste
gianfranco.sinagra@asugi.sanita.fvg.it

17° Meeting
CardioLucca
Heart Brings Heart 2023

Lucca,
22-24 Giugno
2023
Centro Congressi
Auditorium San Francesco

DISCLOSURE INFORMATION

Prof. Gianfranco Sinagra

Negli ultimi due anni ho avuto i seguenti rapporti con soggetti portatori di interessi commerciali in campo sanitario

Novartis, Bayer, Astrazeneca, Bruno Farmaceutici, Boston Scientific, Vifor Pharma, Menarini, Akcea Therapeutics, Alfasigma

Relatore a congressi

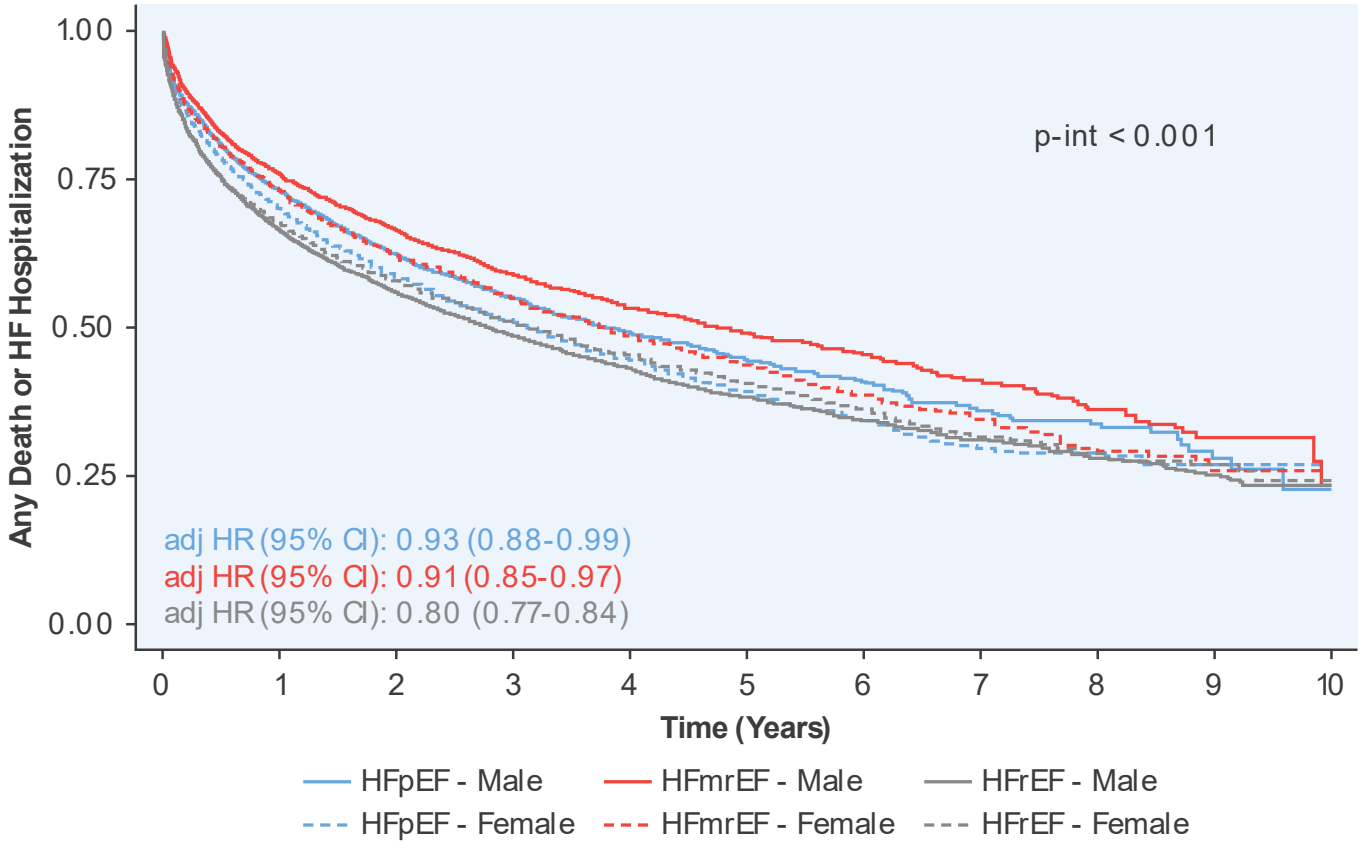
Novartis, Impulse Dynamics, Biotronik

Consulenze e Collaborazione scientifica occasionale

Ai sensi dell'Art. 10 L.675 del 31/12/1996 e dell'Art. 76, comma 4 dell'Accordo Stato-Regioni del 02/02/2017 e del paragrafo 4.5 del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

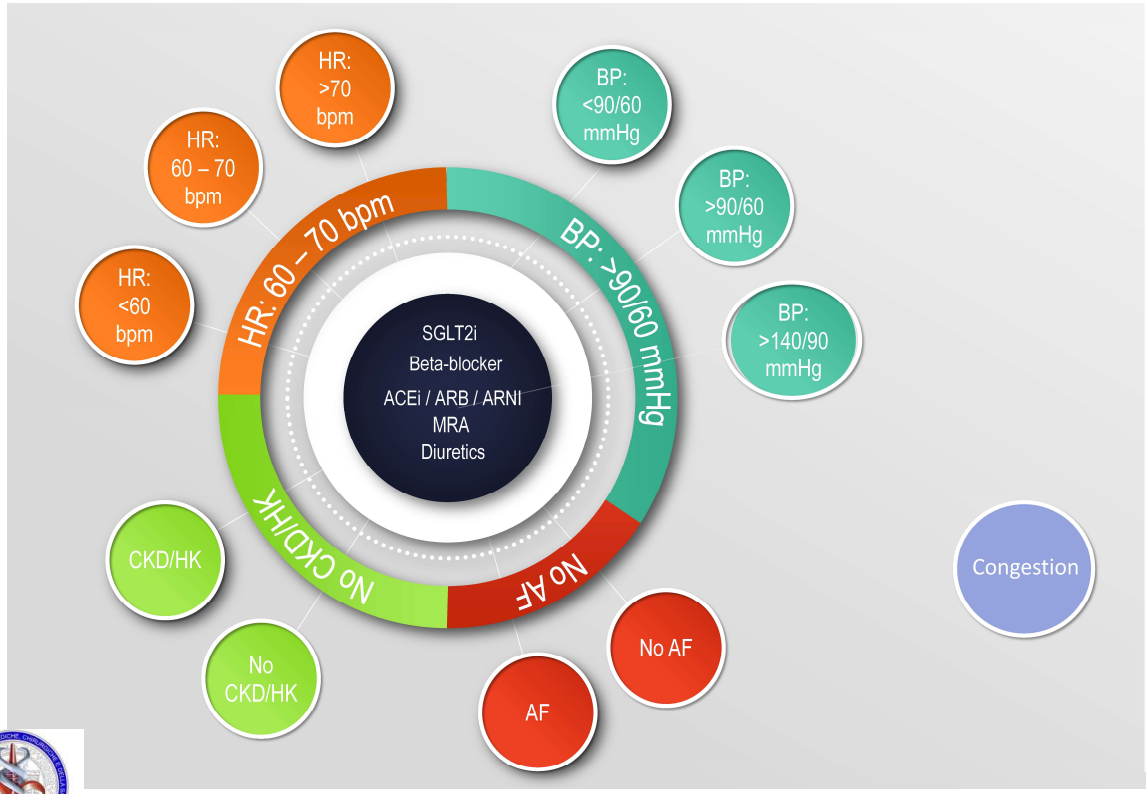
Primary Outcome

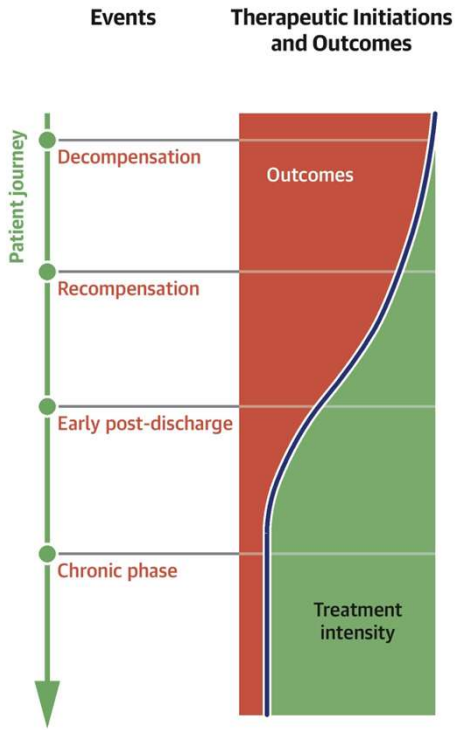
Any Death or HF Hospitalization



J Am Coll Cardiol HF 2019;7:505–15

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology



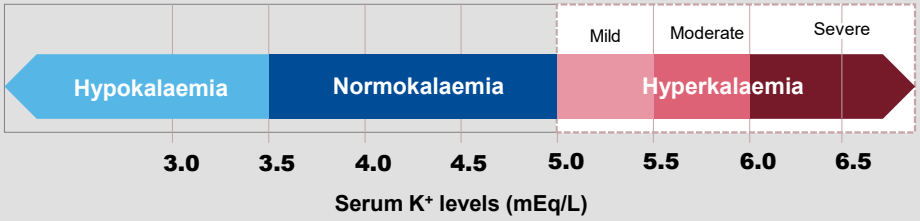


Rosano et al, European Journal of Heart Failure (2021) doi:10.1002/ejhf.2206

HYPERKALAEMIA CAN BE A SERIOUS, CHRONIC DISORDER WITH CLINICAL CONSEQUENCES

Definition

- Typically defined as serum K^+ levels **>5.0 mEq/L**[1]
- Hyperkalaemia may be further classified as **mild**, **moderate** or **severe**[2]



Adapted from Di Lullo, *et al.* 2019[2]

> "***Chronic*** *or* ***recurrent*** *hyperkalaemia is defined as K^+ levels >5 mEq/L repetitively measured over a 1-year period*"[3]

Signs and Symptoms

- Often **asymptomatic** until patient exhibits **serious consequences**[1,4]
- Can occur **with or without** ECG changes[5]
- Patients may present with **muscle weakness, twitching, cramping** or **paralysis**[4]

Serious clinical consequences of HK

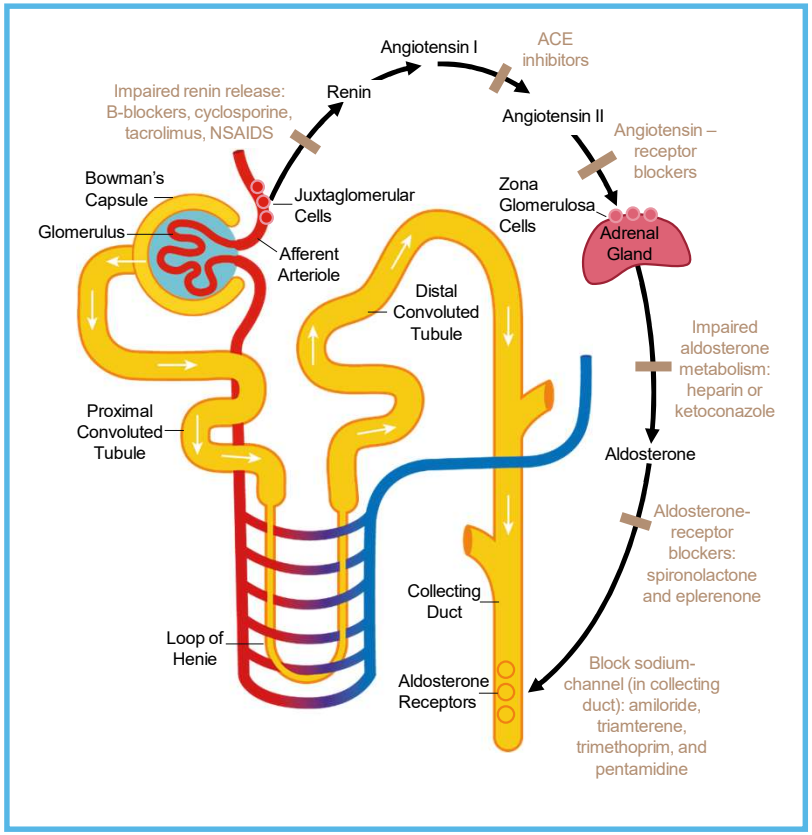
Arrhythmias such as ventricular fibrillation[1,4]

Emergency department visits and hospitalisations[6]

Sudden death[1]

1. Rastergar A, *et al. Postgrad Med J*. 2001;77:759–64; 2. Di Lullo, *et al. Cardiorenal Med*. 2019;9:8–21; 3. Rosano GMC, *et al. Eur Heart J*. 2019;4:180–88; 4. Kraft MD, *et al. Am J Health-Syst Pharm*. 2005;62:1663–82; 5. Montford JR and Linas S. *J Am Soc Nephrol*. 2017;28:3155–65; 6. Kovesdy CP. *Rev Endocr Metab Disord*. 2017;18:41–7.

MECHANISM LEADING TO HYPERKALAEMIA



Renal function often declines with progressive HF resulting in reduced GFR and impaired potassium excretion[1]

ACEi/ARBs further influence urinary potassium excretion by interfering with the stimulatory effect of angiotensin II on aldosterone secretion in the adrenal gland[1]

Aldosterone receptor blockers inhibit the action of aldosterone, impairing potassium excretion[1]

A large proportion of patients receiving RAASI are at increased risk of hyperkalaemia as approximately one third to one half of patients with HF have renal insufficiency (eGFR <60 mL/min/1.73 m^2)[2]

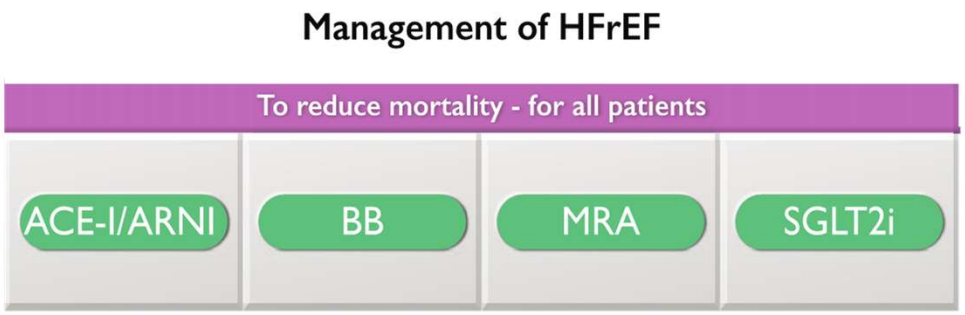
1. Palmer BF, *et al. N Engl J Med.* 2004;351:585–92; 2. Shlipak MG. *Ann Intern Med.* 2003;138:917–24.

HFrEF

ESC GUIDELINES

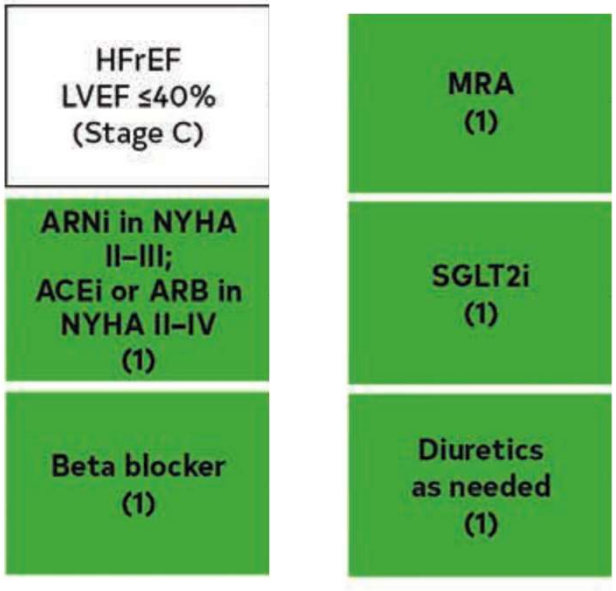
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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



AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines



JACC: HEART FAILURE EXPERT PANEL PAPER

JACC: HEART FAILURE VOL. 9, NO. 1, 2021
JANUARY 2021:1–12

Treatment of HF in an Era of Multiple Therapies

Statement From the HF Collaboratory

TABLE 1 Baseline Therapy in the Various Heart Failure Trials

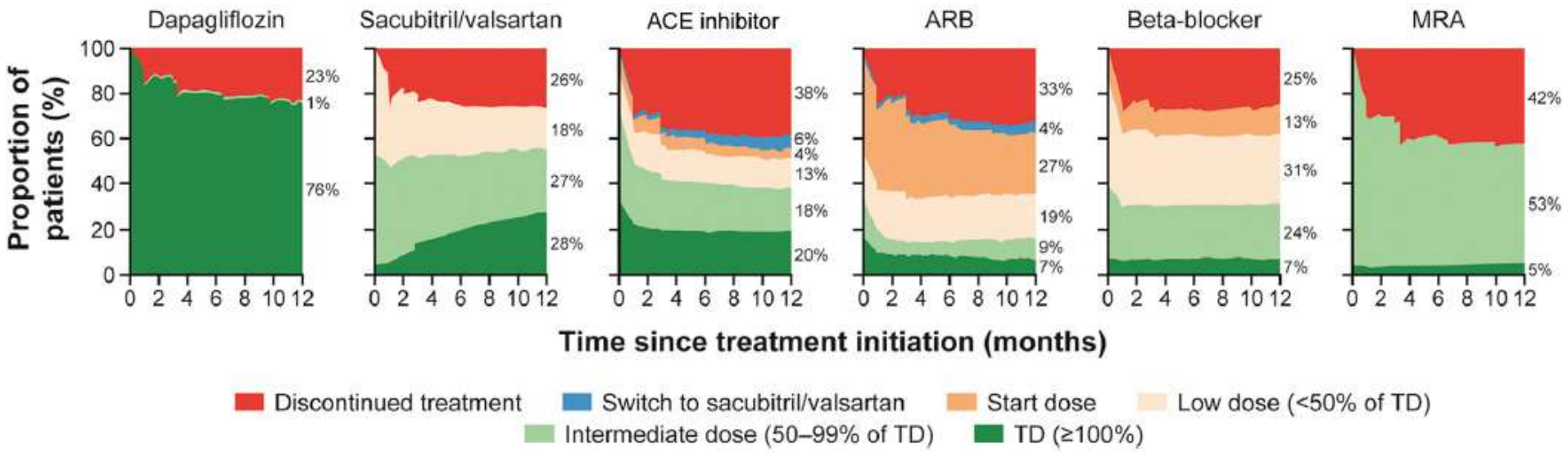
Therapy	Trial (Year)	ACE Inhibitors/ Angiotensin Receptor Blockers	Beta-Blocker	Mineralocorticoid Receptor Antagonist	Angiotensin Receptor Neprilysin Inhibitor
ACE inhibitors	CONSENSUS (1987)	-	<5%	50%-55%	-
	SOLVD (1991)	-	8%	9%	-
	V-HeFT II (1991)	-	Not reported	Not reported	-
Beta-blockers	USCS (1996)	>95%	-	Not reported	-
	MERIT-HF (1999)	>95%	-	Not reported	-
	CIBIS-II (1999)	>95%	-	Not reported	-
Mineralocorticoid receptor antagonist	RALES (1999)	92%	10%-11%	-	-
	EMPHASIS-HF (2011)	93%-94%	86%-87%	-	-
Combination vasodilator	A-HeFT (2004)	86%-87%	73%-74%	38%-40%	-
I_f channel blocker	SHIFT (2010)	90%	93%	60%	-
Angiotensin receptor neprilysin inhibitor	PARADIGM-HF (2014)	100%	93%	56%	-
Sodium-glucose cotransporter 2 inhibitor	DAPA-HF (2019)	94%	96%	71%	11%
	EMPEROR- Reduced (2020)	70%	95%	71%	20%
Soluble guanylate cyclase stimulator	VICTORIA (2020)	74%	93%	70%	15%

Heart Failure Drug Treatment—Inertia, Titration, and Discontinuation

A Multinational Observational Study (EVOLUTION HF)

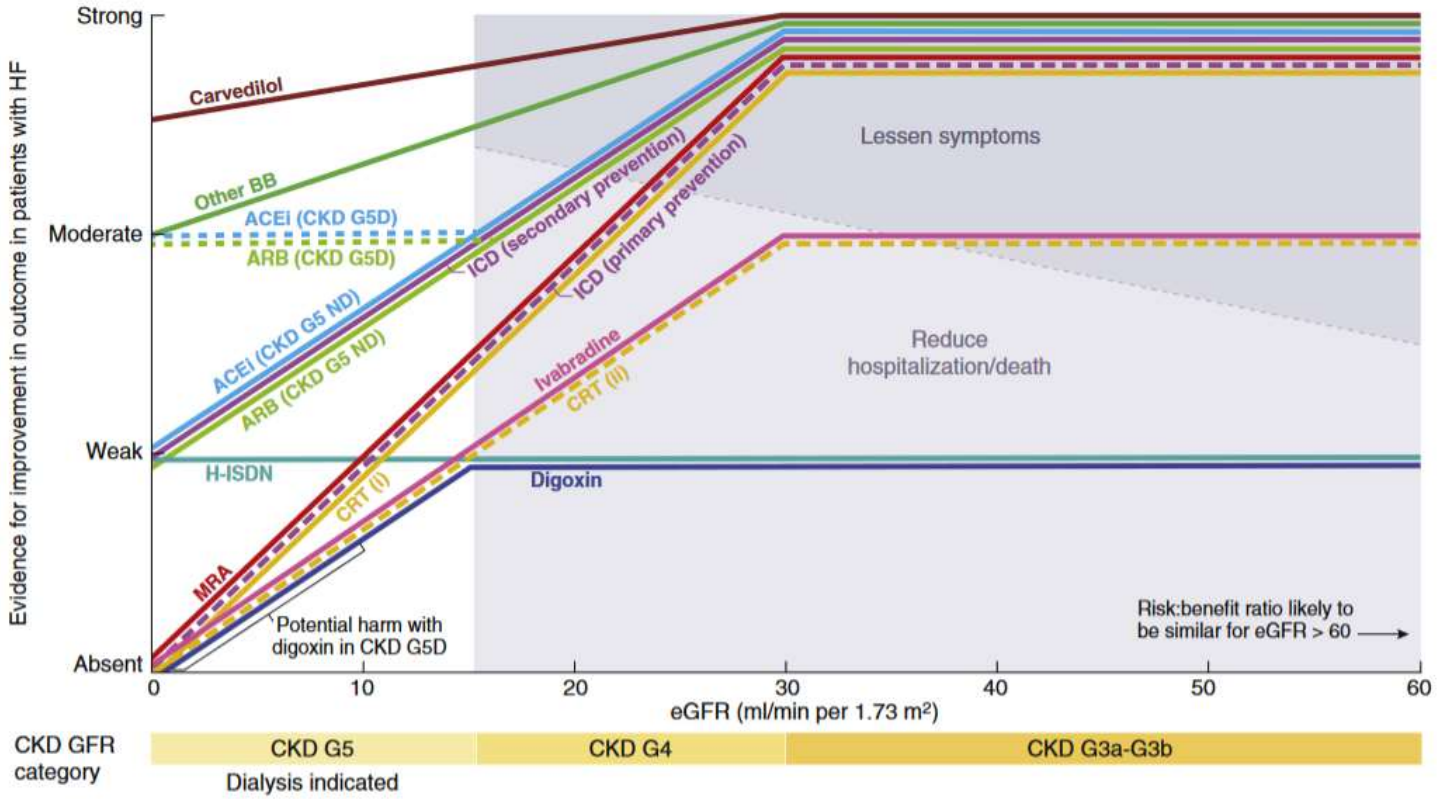
Gianluigi Savarese, MD, PhD,[a,b] Takuya Kishi, MD, PhD,[c] Orly Vardeny, PharmD, MS,[d] Samuel Adamsson Eryd, PhD,[e] Johan Bodegård, MD, PhD,[f] Lars H. Lund, MD, PhD,[a,b] Marcus Thuresson, PhD,[g] Biykem Bozkurt, MD, PhD[h]

JACC: HEART FAILURE



Percentages may not sum to exactly 100% because of rounding. TD = target dose; other abbreviations as in Figure 1.

Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference



CRT (i) = QRS > 120 ms, LBBB QRS morphology, EF ≤ 35% or QRS > 130 ms, EF ≤ 30%
CRT (ii) = QRS > 150 ms

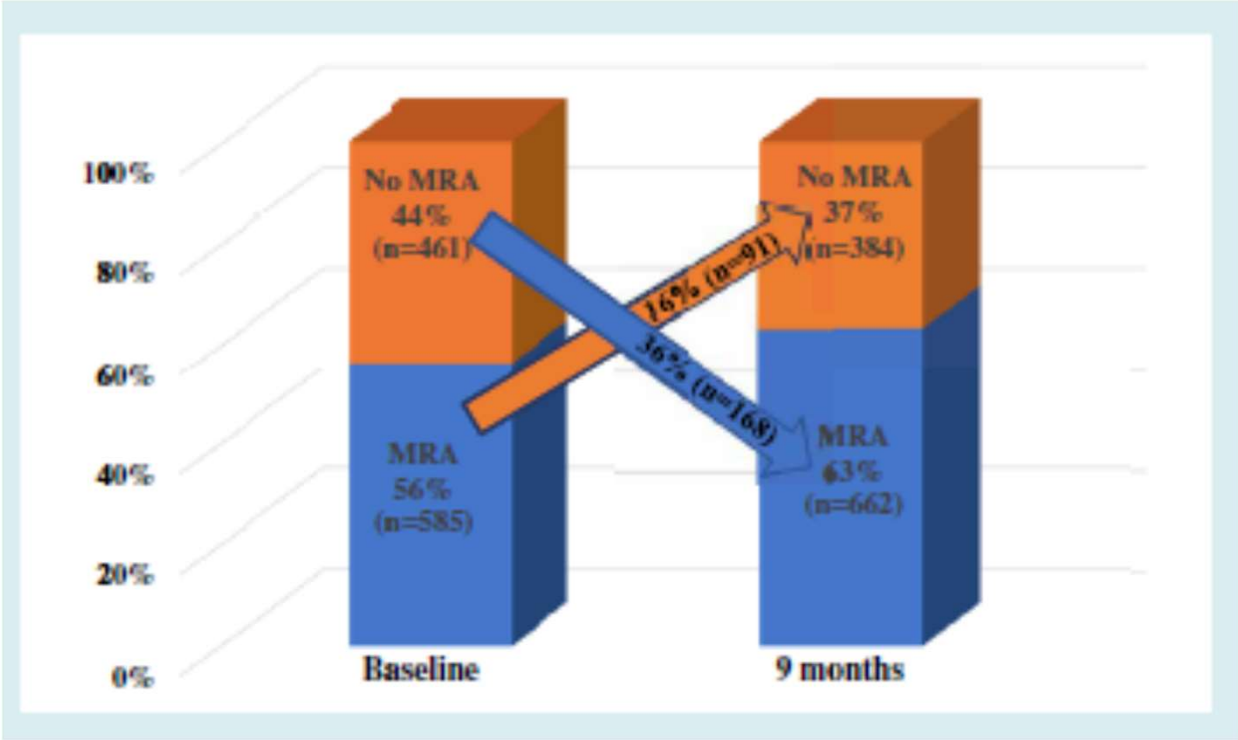
Loop diuretics (p.o./i.v.) (furosemide, bumetanide, torsemide) and thiazide diuretics (metolazone [p.o.], chlorothiazide [i.v.]) = benefit uncertain

Kidney International 2019;95:1304–1317

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.900

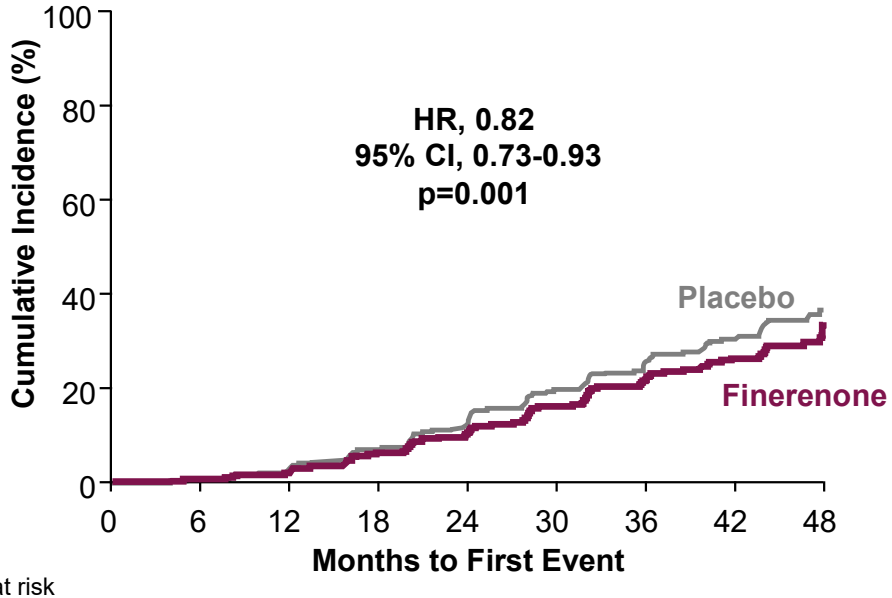
Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF

João Pedro Ferreira[1,2], Patrick Rossignol[1], Jean-Loup Machu[1], Abhinav Sharma[3,4], Nicolas Girerd[1], Stefan D. Anker[5], John G. Cleland[6], Kenneth Dickstein[7,8], Gerasimos Filippatos[9], Hans L. Hillege[10], Chim C. Lang[11], Jozine ter Maaten[10,12], Marco Metra[13], Leong Ng[14], Piotr Ponikowski[15], Nilesh J. Samani[16], Dirk J. van Veldhuisen[10], Aeilko H. Zwinderman[17], Adriaan Voors[10], and Faiez Zannad[1]*



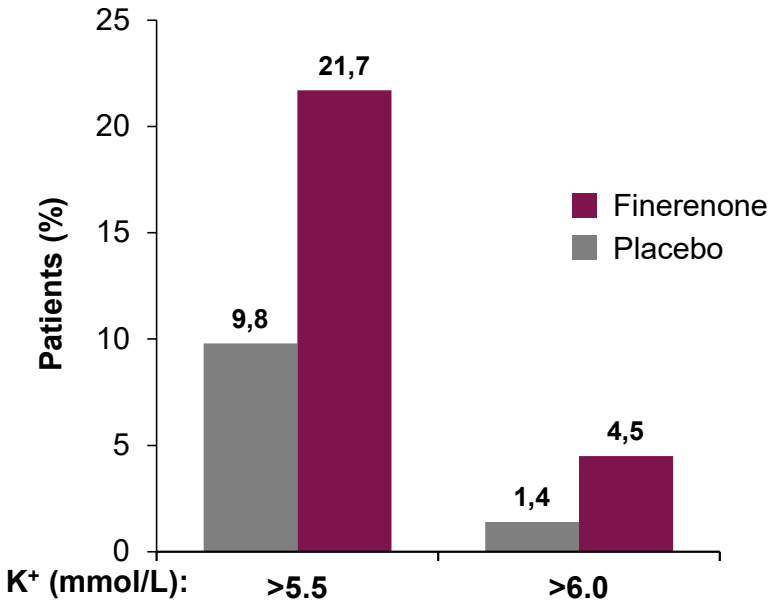
FIDELIO-DKD: Finerenone decreased the risk of CKD progression in patients with T2DM but was associated with hyperkalemia

Time to first event of kidney failure, sustained decrease in eGFR[a], or death from renal causes
(Primary composite endpoint)



No. at risk									
Placebo	2841	2724	2586	2379	1758	1248	792	453	82
Finerenone	2833	2705	2607	2397	1808	1274	787	441	83

Incidence of Hyperkalemia



Treatment discontinued due to hyperkalemia:
Finerenone, 2.3% (n=64) vs. placebo, 0.9% (n=25)

[a]Sustained decrease in eGFR defined as at least 40% reduction in eGFR from baseline over a period of at least 4 weeks.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; FIDELIO-DKD = Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; HR = hazard ratio; T2DM = Type 2 diabetes mellitus.

Bakris GL et al. *N Engl J Med*. 2020;383:2219-2229.

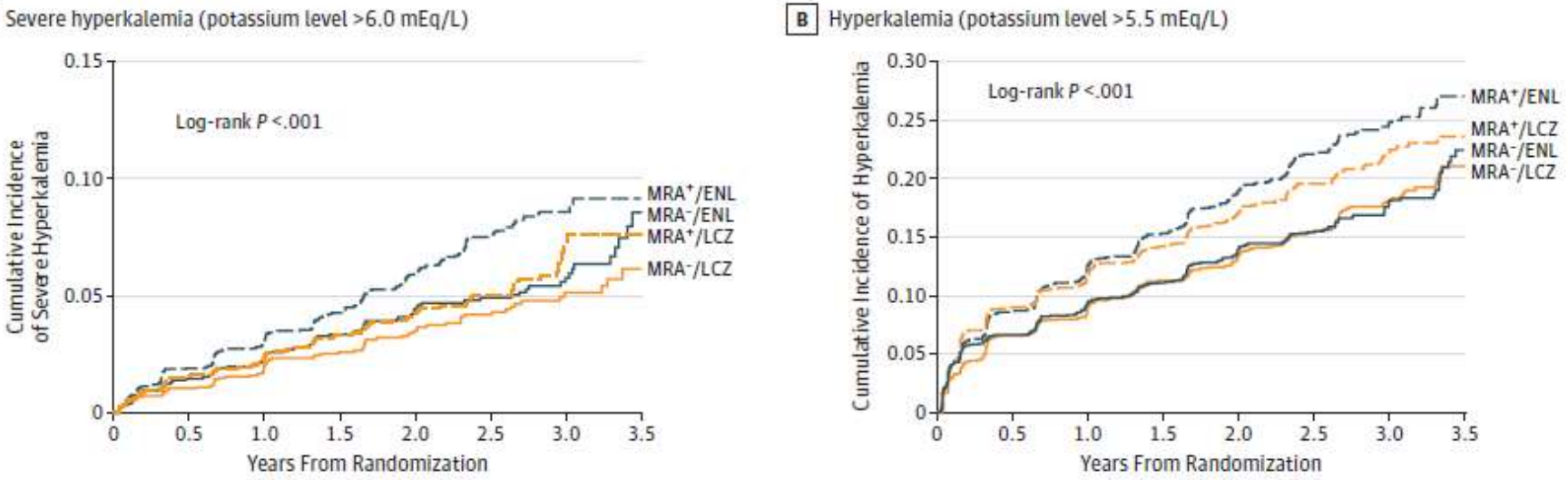
JAMA Cardiology | Original Investigation

Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril

A Secondary Analysis of the PARADIGM-HF Trial

JAMA Cardiology

Figure 3. Time to Development of Severe Hyperkalemia (A) and Hyperkalemia (B) According to Mineralocorticoid Receptor Antagonist (MRA) Use at Baseline and Treatment Assignment



No. at risk

MRA⁻/ENL	1812	1717	1612	1409	1117	845	524	124
MRA⁻/LCZ	1916	1833	1731	1511	1235	885	523	133
MRA⁺/ENL	2400	2246	2110	1658	1132	733	353	86
MRA⁺/LCZ	2271	2152	2040	1619	1105	696	363	93

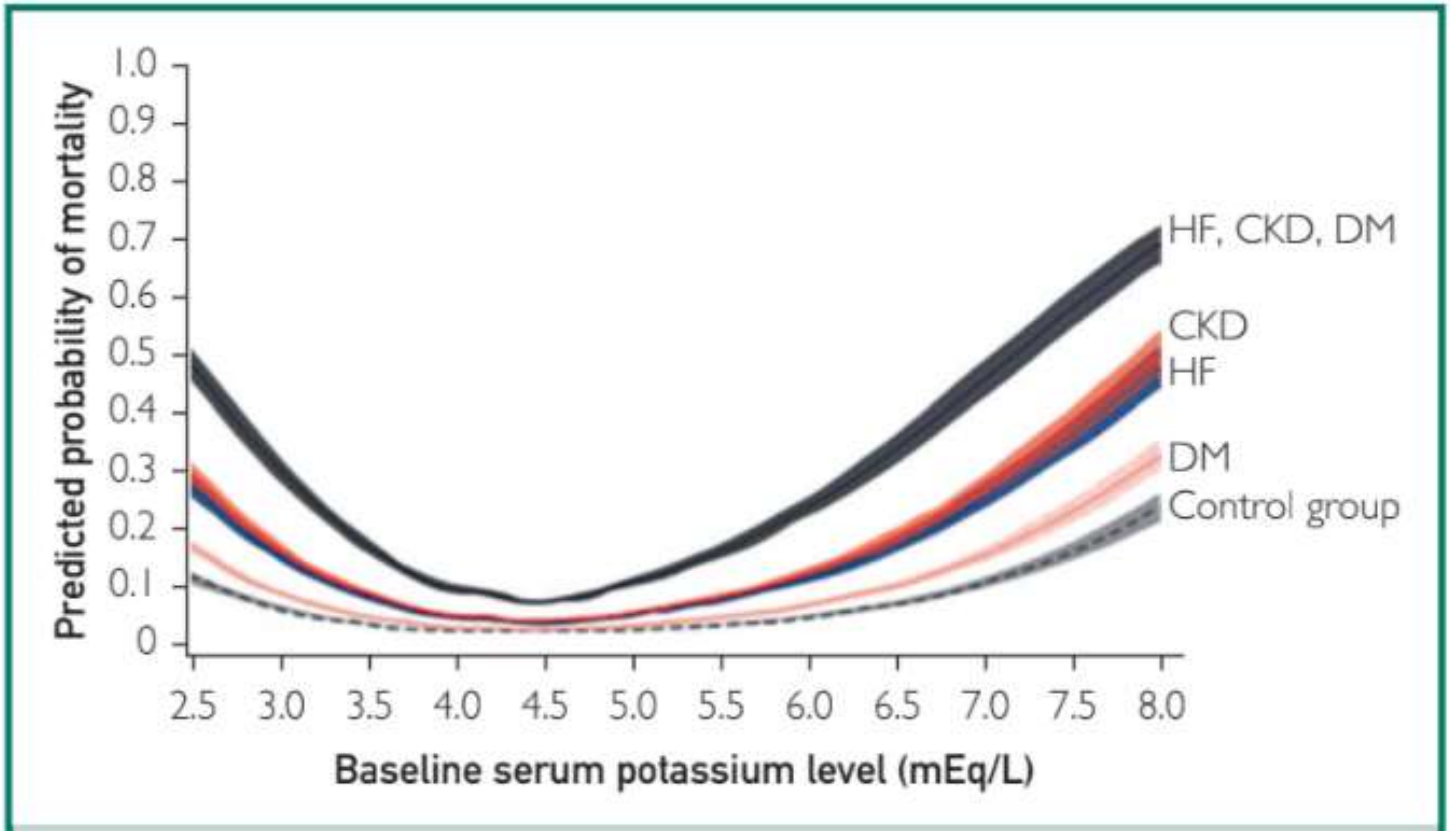
No. at risk

MRA⁻/ENL	1812	1618	1487	1282	989	735	446	110
MRA⁻/LCZ	1916	1705	1574	1352	1081	754	439	110
MRA⁺/ENL	2400	2048	1849	1430	941	592	283	70
MRA⁺/LCZ	2271	1954	1808	1419	945	589	307	82

MAYO CLINIC

Clinical Management of Hyperkalemia

Biff F. Palmer, MD; Juan Jesus Carrero, PharmD, PhD; Deborah J. Clegg, PhD; Gates B. Colbert, MD; Michael Emmett, MD; Steven Fishbane, MD; Debra J. Hain, PhD, APRN, AGPCNP-BC; Edgar Lerma, MD; Macaulay Onuigbo, MD; Anjay Rastogi, MD; Simon D. Roger, MD; Bruce S. Spinowitz, MD; and Matthew R. Weir, MD



Risk of DysK in HF patients

JACC: HEART FAILURE
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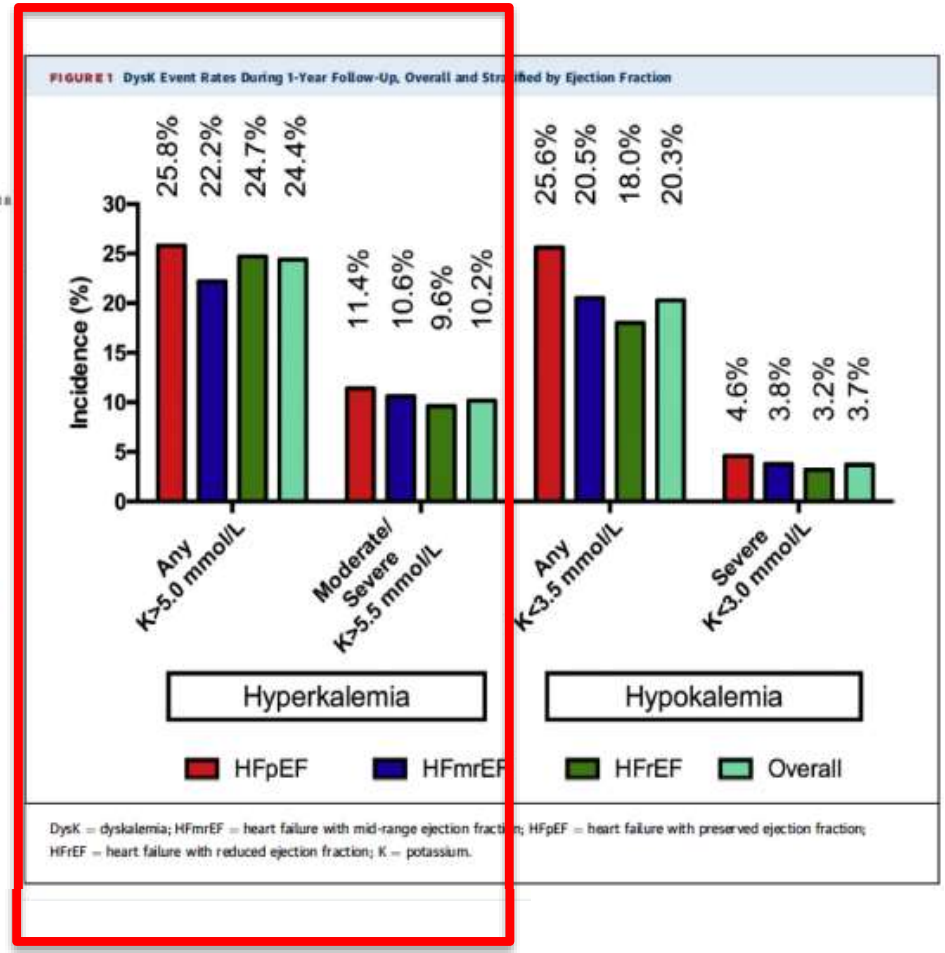
VOL. ■, NO. ■, 2018

Incidence, Predictors, and Outcome Associations of Dyskalemia in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction

Gianluigi Savarese, MD, PhD,[a,*] Hong Xu, MD,[b,*] Marco Trevisan, MSc,[b] Ulf Dahlström, MD, PhD,[c] Patrick Rossignol, MD, PhD,[d] Bertram Pitt, MD, PhD,[e] Lars H. Lund, MD, PhD,[a,†] Juan J. Carrero, PharmD, PhD[b,†]

SwedeHF
Heart Failure Registry



Worse outcome in HF patients with DysK

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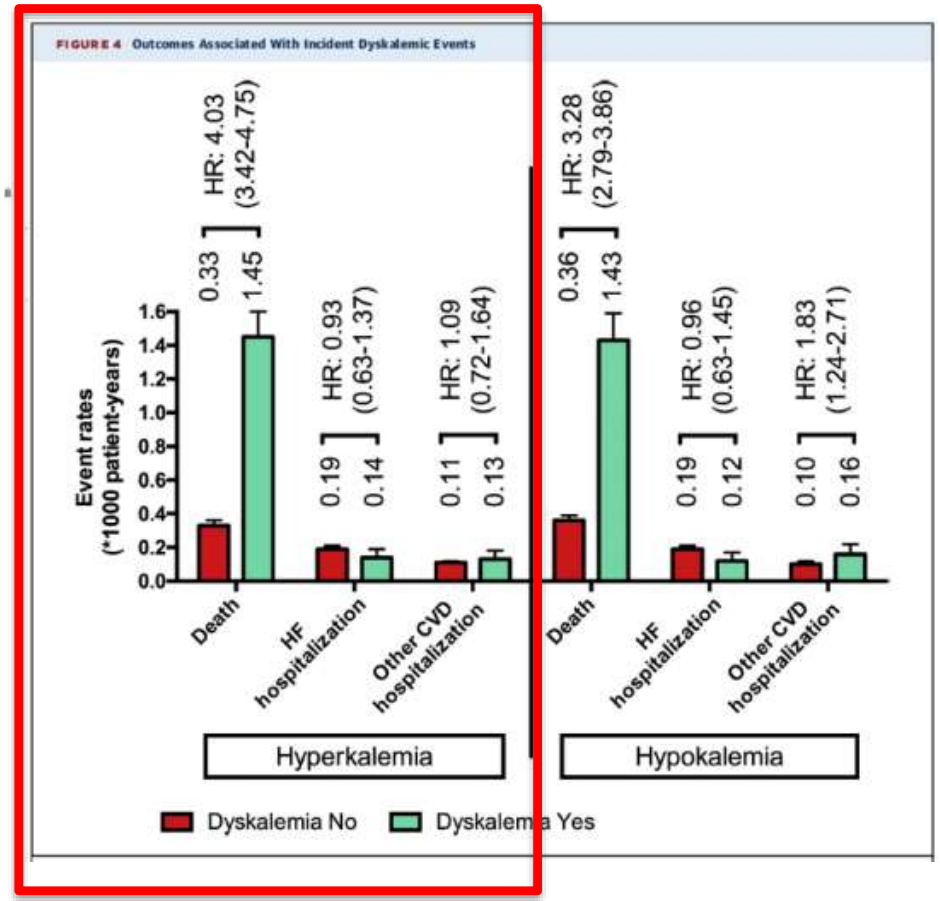
Incidence, Predictors, and Outcome Associations of Dyskalemia in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction

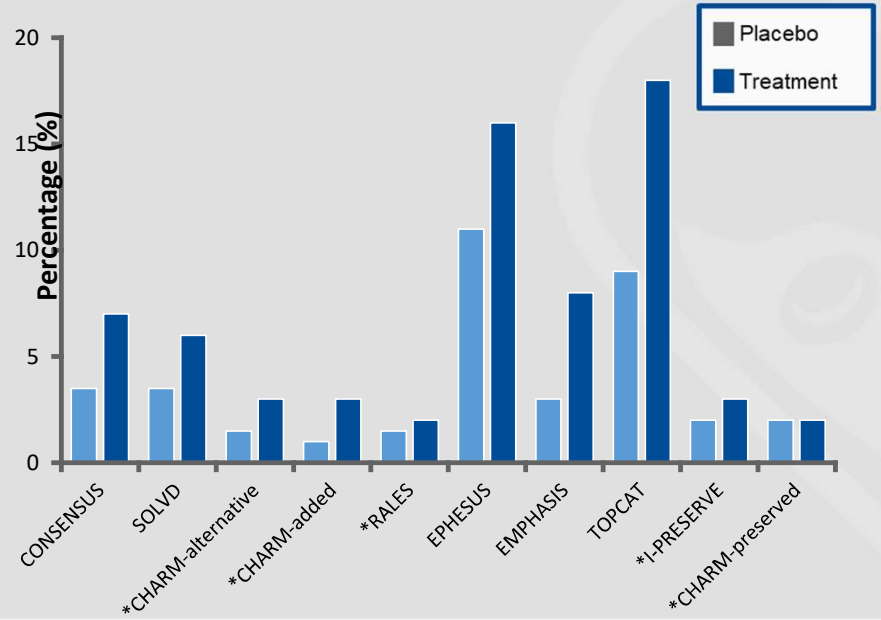
Gianluigi Savarese, MD, PhD,[a,*] Hong Xu, MD,[b,*] Marco Trevisan, MSc,[b] Ulf Dahlström, MD, PhD,[c] Patrick Rossignol, MD, PhD,[d] Bertram Pitt, MD, PhD,[e] Lars H. Lund, MD, PhD,[b,†] Juan J. Carrero, PharmD, PhD[b,†]



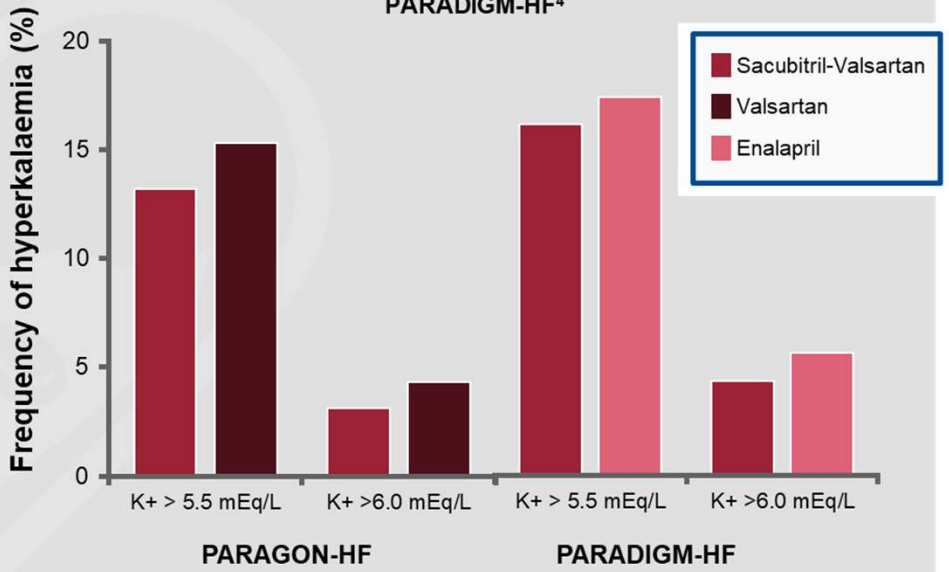
RAASI USE IS ASSOCIATED WITH HIGHER RISK OF HYPERKALAEMIA

High incidence of hyperkalaemia can be observed in the treatment arms of clinical trials involving RAASI as monotherapy, despite exclusion of patients at risk[1,2]

Incidence of hyperkalaemia in the treatment arm in trials in HF[1]



Hyperkalaemia rates in PARAGON-HF[3] and PARADIGM-HF[4]



* Hyperkalaemia defined as >6.0 mEq/L.

1. Tromp T and van der Meer P. *Eur Heart J Suppl.* 2019;21(Suppl A):A6–11; 2. Desai AS. *Curr Heart Fail Rep.* 2009;6:272–80;
3. Solomon SD, *et al. N Engl J Med.* 2019; 381:1609–20; 4. McMurray JJV, *et al. N Engl J Med.* 2014;371:993–1004.

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Incidence, Predictors, and Outcome Associations of Dyskalemia in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction

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Predictors of DysK

TABLE 2 Baseline Characteristics Associated With 1-Year Risk of Hypokalemia and Hyperkalemia

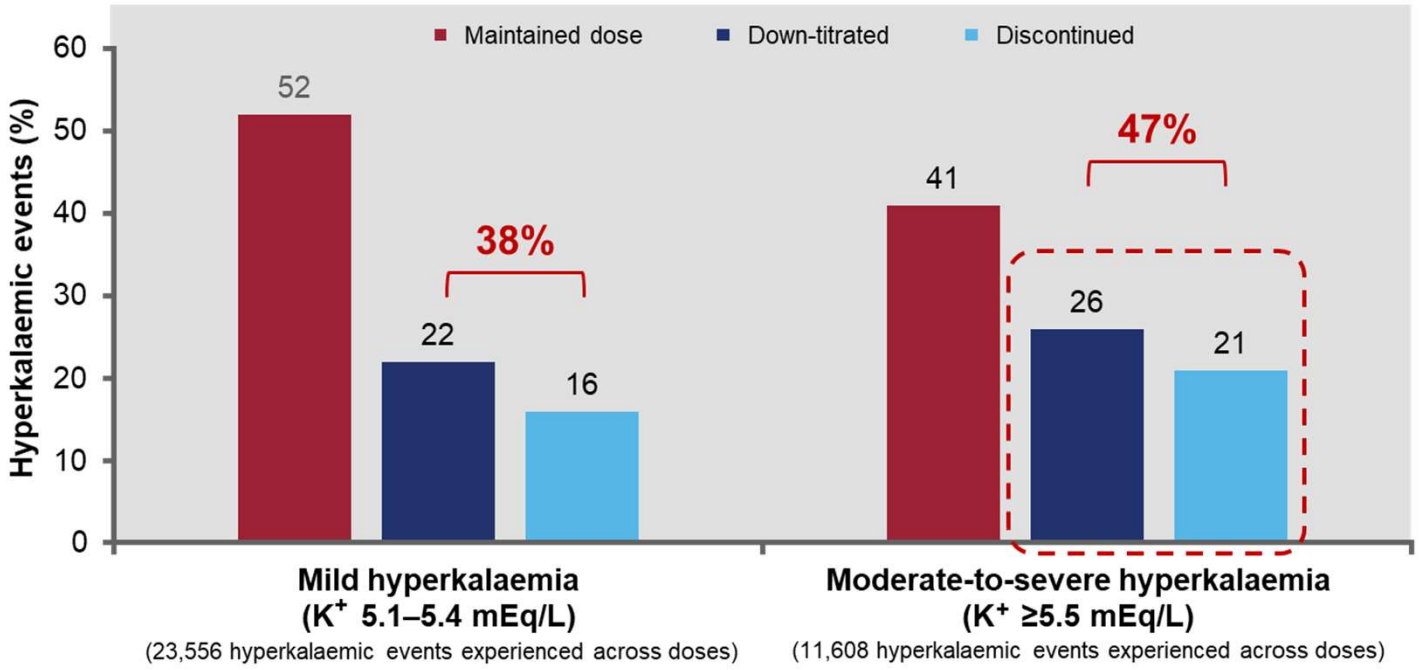
	Any Hyperkalemia (K+ >5.0 mmol/l)		Any Hypokalemia (K+ <3.5 mmol/l)	
	HR	95% CI	HR	95% CI
Age, per 5 yrs	1.01	0.98-1.04	1.02	0.99-1.06
Women	0.86*	0.77-0.97	1.33‡	1.18-1.51
Smoker	1.11	0.93-1.33	0.93	0.76-1.14
Baseline potassium strata				
3.5-<4.0 mmol/l	0.79‡	0.70-0.89	1.52‡	1.34-1.72
4.0-<4.5 mmol/l	Ref.		Ref.	
4.5-5.0 mmol/l	1.49‡	1.30-1.72	0.85	0.71-1.03
Baseline eGFR strata				
90+ ml/min per 1.73 m^2	Ref.		Ref.	
60-89 ml/min per 1.73 m^2	1.46†	1.13-1.87	1.11	0.87-1.42
45-59 ml/min per 1.73 m^2	2.01‡	1.53-2.65	0.96	0.74-1.26
30-44 ml/min per 1.73 m^2	2.68‡	2.02-3.56	1.13	0.85-1.50
<30 ml/min per 1.73 m^2	4.10‡	3.04-5.53	1.64†	1.22-2.21
Hemoglobin, <120 g/l	1.43‡	1.27-1.61	1.23†	1.08-1.40
Hypertension	1.00	0.89-1.13	0.97	0.85-1.11
Diabetes mellitus	1.33‡	1.16-1.51	0.96	0.82-1.11
Myocardial infarction	0.99	0.87-1.12	1.19*	1.03-1.37
Stroke or TIA	1.05	0.87-1.26	1.01	0.82-1.25
PAD	1.20	0.95-1.51	1.12	0.86-1.44

TABLE 2 Baseline Characteristics Associated With 1-Year Risk of Hypokalemia and Hyperkalemia

	Any Hyperkalemia (K+ >5.0 mmol/l)		Any Hypokalemia (K+ <3.5 mmol/l)	
	HR	95% CI	HR	95% CI
Atrial fibrillation	1.04	0.93-1.16	1.13*	1.00-1.28
COPD	1.22†	1.06-1.40	1.34‡	1.16-1.55
Liver disease	1.26	0.82-1.94	1.24	0.72-2.14
Alcoholism	1.46*	1.05-2.04	1.67†	1.16-2.42
Cancer (3 yrs)	1.30*	1.03-1.64	1.22	0.94-1.58
Hospitalization at diagnosis	2.01‡	1.72-2.36	2.04‡	1.69-2.45
NYHA functional class				
I	Ref.		Ref.	
II	1.33*	1.06-1.66	1.23	0.98-1.55
III	1.72‡	1.36-2.17	1.66‡	1.31-2.10
IV	2.05‡	1.45-2.88	1.99‡	1.38-2.88
EF strata				
>50%	1.06	0.92-1.22	1.17*	1.00-1.36
40%-49%	0.99	0.86-1.14	1.10	0.94-1.28
<40%	Ref.		Ref.	
ACE/ARB	1.07	0.93-1.23	0.63‡	0.54-0.72
Beta-blockers	0.81†	0.70-0.94	0.83*	0.71-0.96
MRAs	1.85‡	1.66-2.07	1.08	0.95-1.22
Diuretics	1.10	0.94-1.29	1.38‡	1.16-1.64

ELEVATED K^+ WAS ASSOCIATED WITH DOSE REDUCTION OR DISCONTINUATION OF RAASI*

Patients on maximal RAASI dose had their treatment reduced or stopped after a hyperkalaemic event nearly half the time



* Patients with CKD at Stages 3–5 were enrolled in the study. Only those patients who were on maximum RAASI dose were included within this part of the study (which is why the total numbers do not equal 100%).

Epstein M, *et al. Am J Manag Care*. 2015;21:S212–20.

Cosa possiamo concretamente fare:

- **Possiamo verificare aspetti nutrizionali e dare suggerimenti;**
- **Possiamo rimodulare le dosi dei RAASi;**
- **Possiamo utilizzare la K+ dispersione dei diuretici ansa/ tiazidici;**
- **Possiamo sfruttare la K+ dispersione degli SGLT2;**
- **K+ binders**

RASSEGNA

Iperpotassiemia nello scompenso cardiaco: nuove soluzioni per un vecchio problema

Simona Romani, Aldostefano Porcari, Enrico Fabris, Gianfranco Sinagra

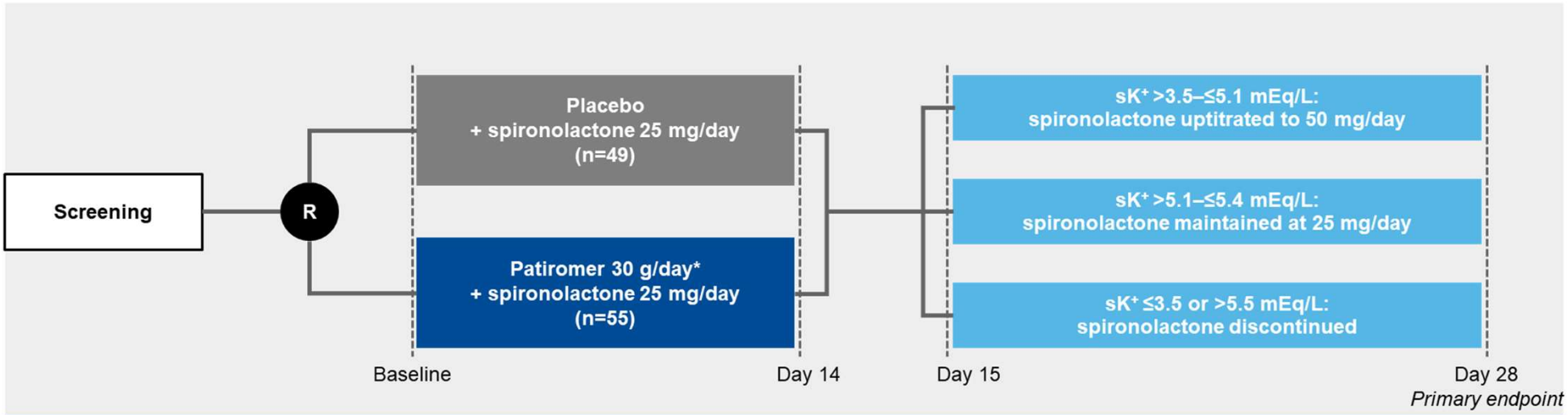
Dipartimento Cardiovascolare, Azienda Sanitaria Universitaria Integrata (ASUITS) e Università degli Studi di Trieste, Trieste

GIORNALE ITALIANO DI CARDIOLOGIA

	Sodio polistirene sulfonato	Patiromer calcio sorbitolo	Sodio zirconio ciclosilicato
Meccanismo d'azione	Resina contenente Na che viene scambiato con un altro catione (K, Ca o Mg)	Resina contenente Ca che viene scambiato col K	Composto inorganico non polimerico che agisce come scambiatore Na-K
Formulazione	Polvere per sospensione orale e rettale	Polvere per sospensione orale	Polvere per sospensione orale
Dosaggi	Per os: 15 g 1-4 volte/die Per via rettale: 30 g 1-2 volte/die	Dose iniziale: 8.4 g/die Dose massima: 25.2 g/die	Dose iniziale: 10 g 3 volte/die per max 3 giorni Dose di mantenimento: max 10 g/die
Temperatura di conservazione	Temperatura ambiente	2-8°C	Temperatura ambiente
Inizio d'azione	1-2 h	4-7 h	1 h
Proprietà farmacocinetiche	Non assorbito nel tratto GI Eliminato con le feci	Non assorbito nel tratto GI Eliminato con le feci	Non assorbito nel tratto GI Eliminato con le feci
Effetti collaterali	Disturbi GI: anoressia, nausea, vomito, stipsi, diarrea Disturbi elettrolitici: ritenzione sodica, ipopotassiemia e ipocalcemia	Disturbi GI: stipsi (6.2%) diarrea (3%), dolore addominale (2.9%) Disturbi elettrolitici: ipomagnesemia (5.3%)	Disturbi elettrolitici: ipopotassiemia (2.3%) Edema (5.7%): ritenzione di liquidi, edema generalizzato o localizzato, ipervolemia
Effetti collaterali gravi	Ischemia GI	Nessuno	Nessuno

Romani S, Sinagra G et al. G Ital Cardiol 2019;20(10):543-551

PEARL-HF STUDY DESIGN



Primary Endpoint: mean change of serum K^+ from baseline to the end of the study (Day 28).
Secondary Endpoint: proportion of patients with serum K^+ 5.5 mEq/L at any time during the trial and the proportion of patients whose spironolactone dose could be increased to 50 mg/day.

Inclusion criteria

CHF, indicated to receive spironolactone and sK^+ 4.3–5.1 mEq/L **AND** CKD (eGFR <60 mL/min/1.73 m^2) and on ≥1 ACEi/ARB or BB **OR** documented HK that led to discontinuation of ACEi/ARB or BB within 6 months

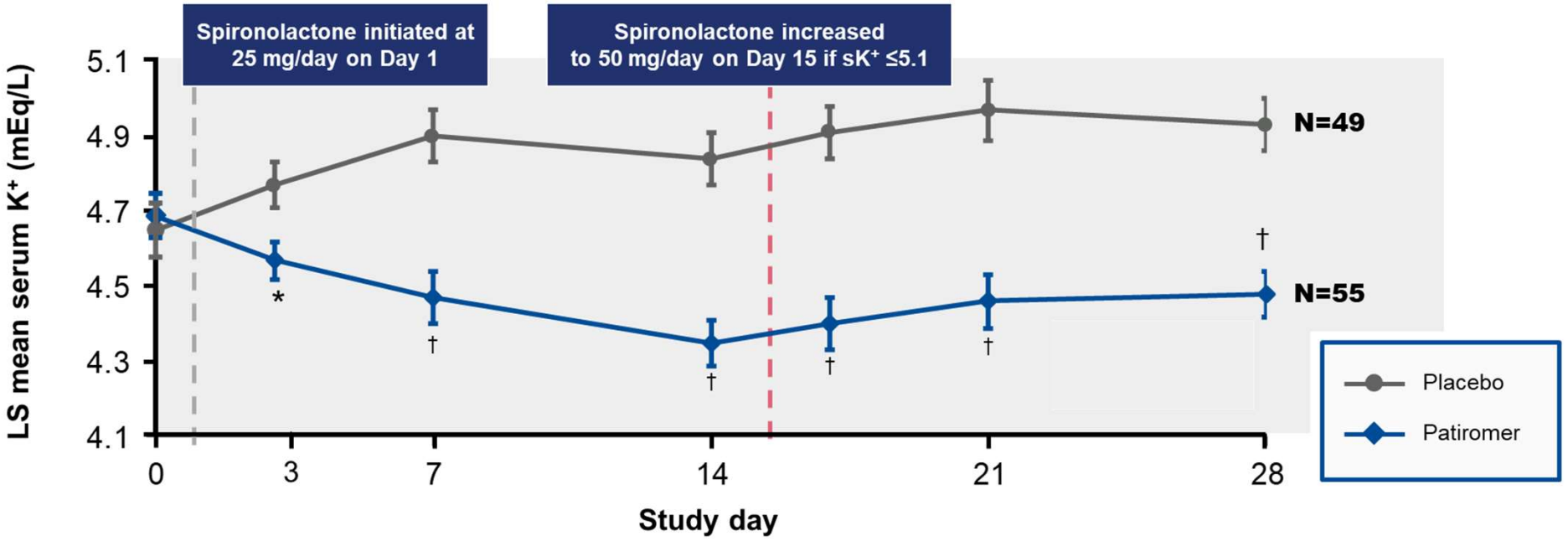
Baseline comorbidities/ treatment

- **100%** with HF
- **55%** with CKD
- **32%** with T2DM
- **98%** receiving RAASI

* RLY5016.

Pitt B, *et al. Eur Heart J*. 2011;32:820–8.

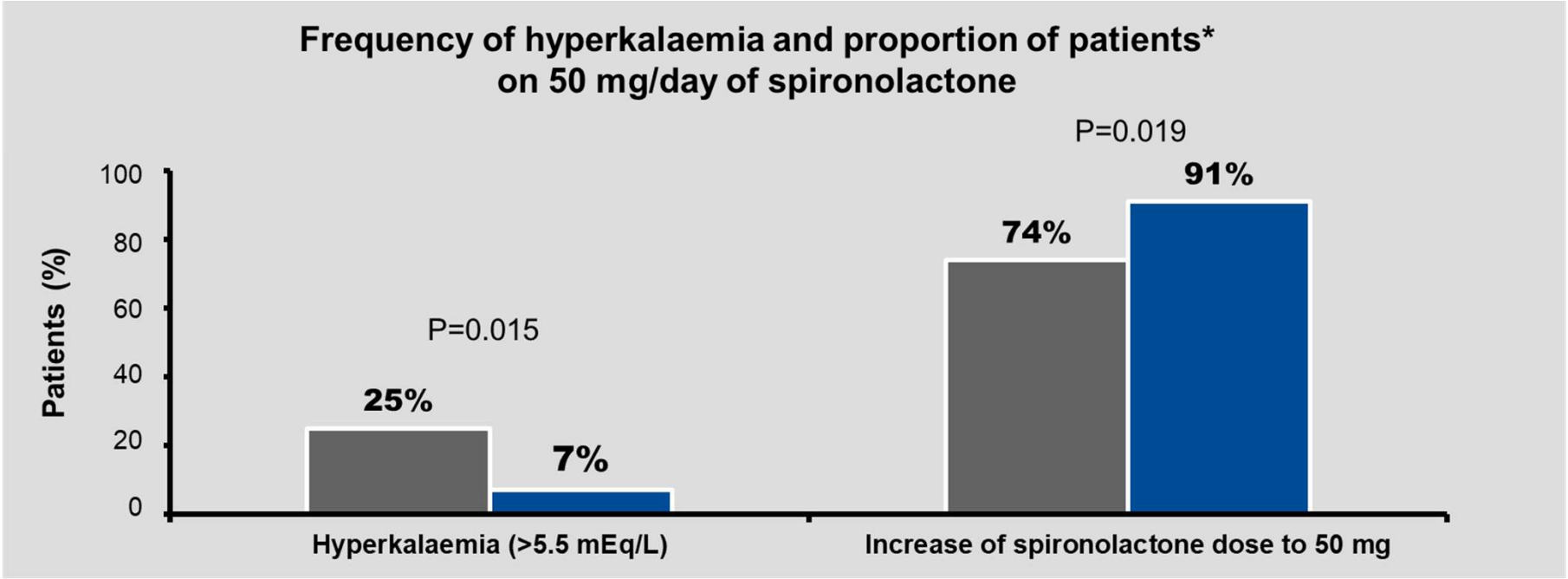
PEARL-HF: PATIROMER SIGNIFICANTLY LOWERED SERUM K^+ LEVELS COMPARED WITH PLACEBO



Difference in response between treatment groups was **statistically significant** at every measured time point, starting at Day 3 (2 days after initiation of study medication), and continued through to Day 28

* *P* <0.01; † *P* <0.001.
Pitt B, *et al. Eur Heart J.* 2011;32:820–8.

PEARL-HF: PATIROMER ALLOWS FOR SPIRONOLACTONE DOSE INCREASE

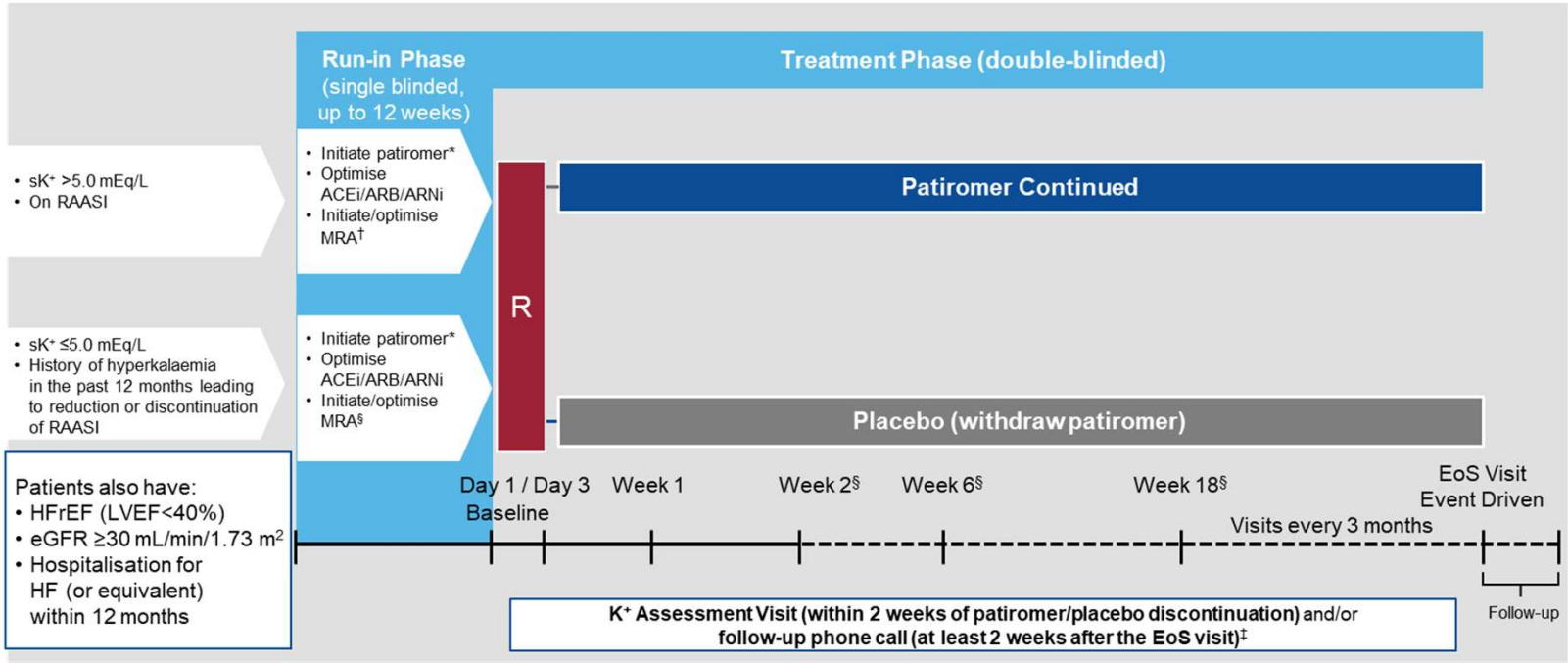


Significantly more patients in the **patiromer** group were able to have their spironolactone dose **increased** to 50 mg/day compared with patients in the placebo group

Pitt B, *et al. Eur Heart J.* 2011;32:820–8.

DIAMOND: THE CARDIOVASCULAR OUTCOME STUDY FOR PATIROMER

878 Pts; 13 weeks; 67 yrs; 42% DM; GFR >30 ml/min/1.73 mq; K+ >5.5 13.9 vs 19.4 % p 0.006; RAASi reduction > placebo; HK related outcomes > placebo



Study endpoints

Primary

- Time to first occurrence of CV death or CV hospitalisation

Secondary

- Proportion of subjects on ≥50% of guideline-recommended target dose of RAASI medications
- Total HF hospitalisations
- KCCQ

Objective: To determine if patiromer treatment of patients who develop HK while receiving RAASI will result in RAASI continuation per HF treatment guidelines and thereby decrease the occurrence of CV death and CV hospitalisation events compared with placebo

* Start at 8.4 g/day and up-titrate as necessary up to 25.2 g/day. Subject must return within 1 week (± 3 days) after patiromer initiation or dose adjustment to assess K+ levels; † Initiate selected MRA, up-titrate to 50 mg/day; ‡ If the K+ Assessment Visit is at 2 weeks after the EoS Visit, then the follow-up phone call is not required; § If there are changes to ACEi, ARB, ARNi and/or MRA dose or sK+ varies outside of the intended range, unscheduled weekly or monthly visits should occur until stability returns. NCT03888066. Available at: clinicaltrials.gov/ct2/show/NCT03888066 (accessed July 2020).

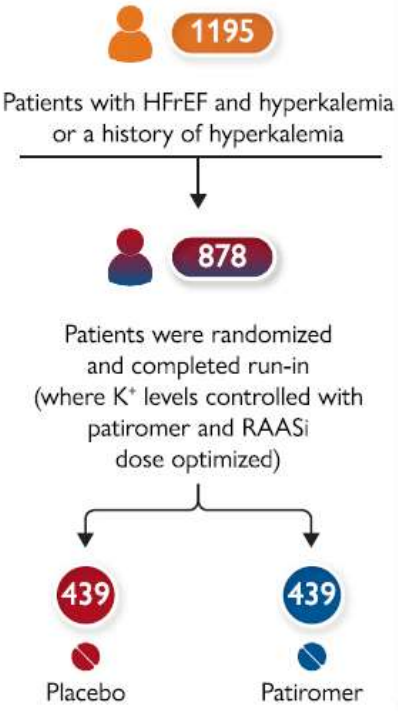
Eur Heart J; 2022; 43; 4362 - 4373

Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial

European Heart Journal (2022) **43**, 4362–4373
https://doi.org/10.1093/eurheartj/ehac401

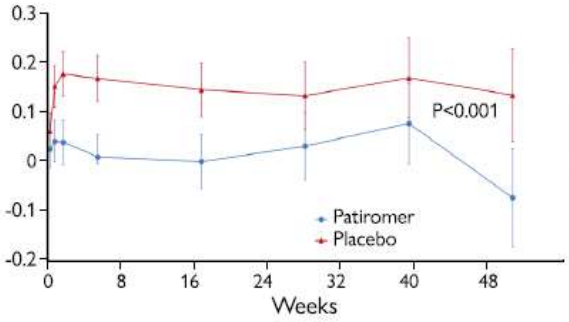
Patiromer use in patients with heart failure and reduced ejection fraction (HFrEF) with hyperkalemia (HK)

Study design



Primary endpoint

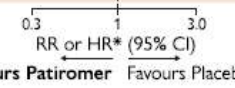
Mean change in serum potassium (mmol/L) from baseline (95% confidence interval (CI))



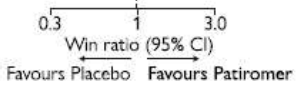
	Day	Weeks						
	3	1	2	6	18	30	42	54
Patiromer	409	406	402	376	273	183	104	66
Placebo	416	409	397	361	270	184	106	74

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



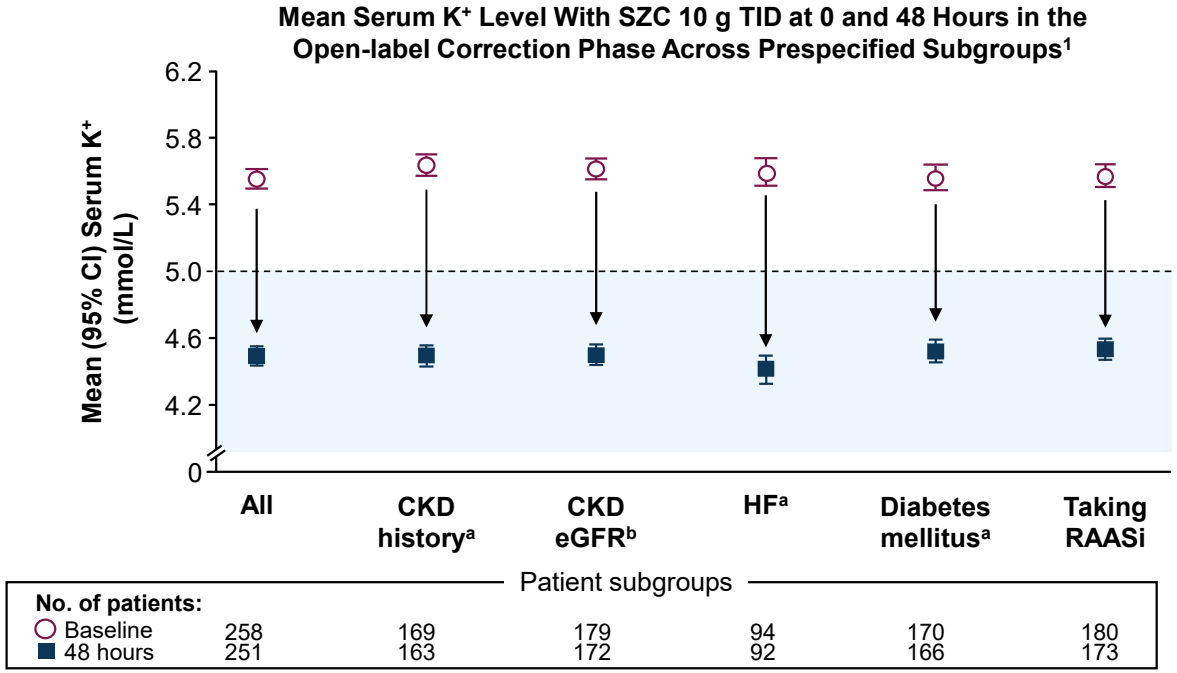
	Win ratio (95% CI)	P-value
Hyperkalemia-related morbidity-adjusted events*	1.53 (1.23-1.91)	<0.001
Win-ratio for RAASi use score	1.25 (1.003-1.564)	0.048



*Morbidity-adjusted hyperkalemia-related outcomes were tested in a hierarchical manner with the following sequence: cardiovascular death, cardiovascular hospitalization, total hyperkalemia events >6.5 mmol/L, >6.0–6.5 mmol/L, and >5.0–6.0 mmol/L

Efficacy of SZC was similar across all patient subgroups, including those receiving RAASi therapy

ZS-004 (HARMONIZE)[1]



Note: Normokalemia defined as serum K^+ 3.5-5.0 mmol/L and patients on dialysis were excluded from the study. RAASi was not defined in the study.

[a]Data shown is based on definitions used to identify patients with baseline comorbid conditions (across the ZS Pharma clinical development program) using custom lists of preferred terms. AstraZeneca has elected to use more recognized definitions that are based on the standardized Medical Dictionary for Regulatory Activities query (narrow) for each comorbid condition. For example, in the original HF population (n=94), the mean change from baseline in K^+ was -1.173 mmol/L at 48 hours. Based on the AstraZeneca re-analysis, the percentage of patients with HF is 11% (28/251) with a mean change in K^+ of -1.196 mmol/L at 48 hours;[2] [b]Baseline eGFR <60 mL/min/1.73 m^2.[1]

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; RAASi = renin–angiotensin–aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

1. Kosiborod M et al. *JAMA*. 2014;312:2223-2233; 2. In House Data, AstraZeneca Pharmaceuticals LP. LOKELMA (sodium zirconium cyclosilicate) oral suspension. Subgroups based on comorbid conditions at baseline in ZS clinical studies. Doc ID-003819479. April 4, 2018.

SZC provided rapid K^+ reduction within 48 hours and sustained K^+ control for up to 1 year

ZS-004 (HARMONIZE)[1] | **ZS-004E (11-MONTH EXTENSION)[3]**

Open-label CP (48 hours)[1]
SZC 10 g TID (n=258)

Randomized, Double-blind MP (Days 1-29)[1,b]
Placebo (n=82) | SZC 5 g[c] (n=45) | SZC 10 g[c] (n=50) | SZC 15 g[c] (n=54)

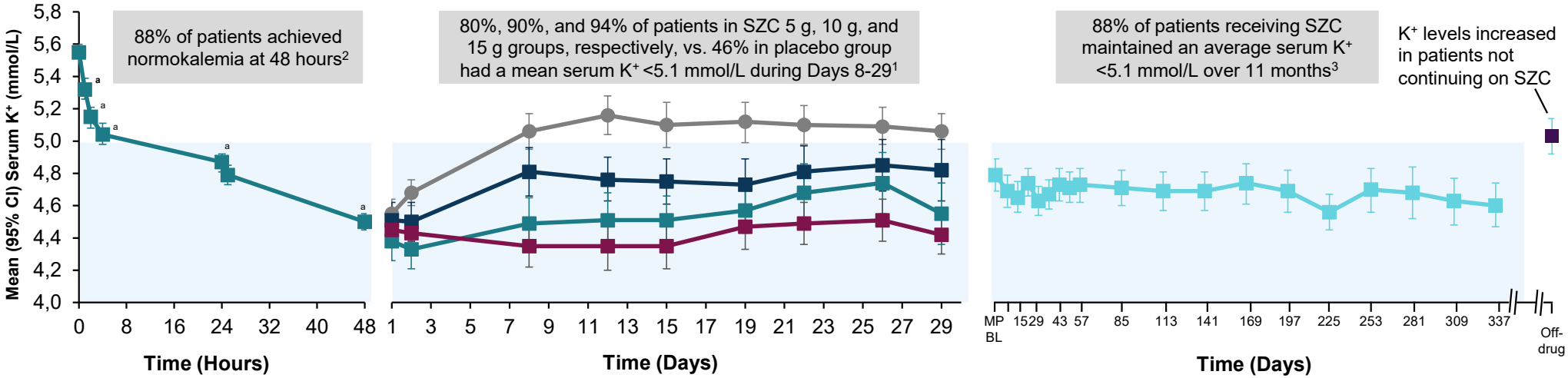
Open-label MP (Days 1-337)[3,d]
SZC titrated dose[e] (N=123)

88% of patients achieved normokalemia at 48 hours[2]

80%, 90%, and 94% of patients in SZC 5 g, 10 g, and 15 g groups, respectively, vs. 46% in placebo group had a mean serum K^+ <5.1 mmol/L during Days 8-29[1]

88% of patients receiving SZC maintained an average serum K^+ <5.1 mmol/L over 11 months[3]

K^+ levels increased in patients not continuing on SZC



Note: Normokalemia defined as serum K^+ 3.5-5.0 mmol/L and patients on dialysis were excluded from these studies.[1,3]

[a]p<0.001 vs. baseline;[1] [b]If a patient's K^+ value was between 3.0-3.4 mmol/L at any time during the randomized phase, the dose was reduced from QD to QOD for the remainder of the study;[1] [c]p<0.001 vs. placebo during Days 8-29;[1] [d]Maintenance SZC dosing was initiated at 10 g QD and titrated in 5 g increments or decrements to maintain i-STAT K^+ 3.5–5.0 mmol/L (minimum 5 g QOD; maximum 15 g QD). Off-drug values were recorded at 7±1 days following the last dose of SZC;[3] [e]Mean SZC doses to maintain normokalemia were 10 g QD in 73.2%, >10 g QD in 13.0%, <10 g QD in 13.8% of patients.[3]

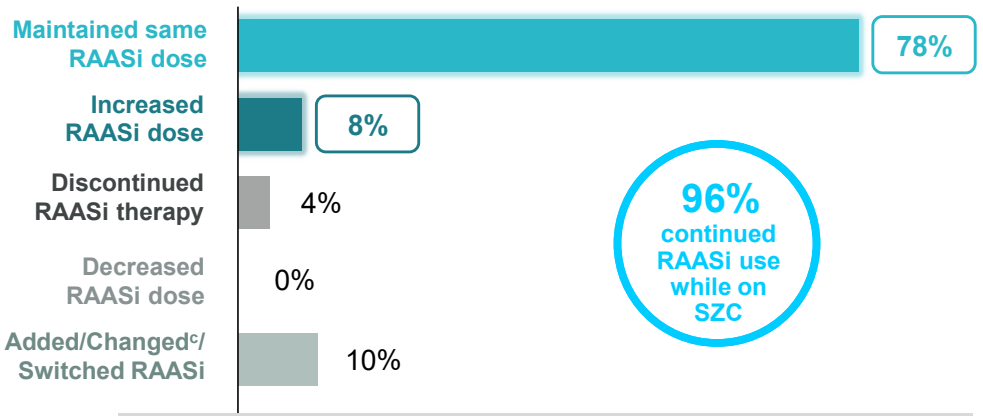
BL = baseline; CP = correction phase; MP = maintenance phase; QOD = every other day; SZC = sodium zirconium cyclosilicate.

1. Kosiborod M et al. *JAMA*. 2014;312:2223-2233; 2. LOKELMA Summary of product characteristics. Updated January 21, 2021; 3. Roger SD et al. Article and supplementary material. *Am J Nephrol.* 2019;50:473-480.

Long-term SZC clinical studies: most patients who were on RAASi therapy at BSL maintained the same dose or increased their RAASi dose

ZS-004E (11-MONTH EXTENSION)[1,a]

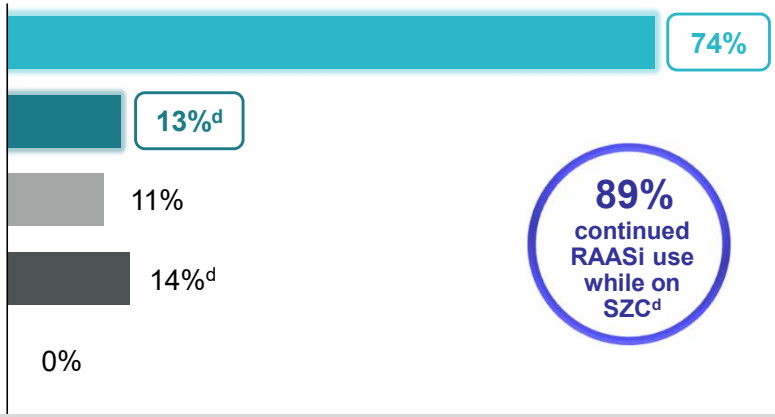
Of the 83 patients who received *RAASi* therapy at the start of the extension maintenance phase (Day 8), to end of treatment (Day 337):



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

ZS-005 (12-MONTH STUDY)[2,b]

Of the 483 patients who received *RAASi* therapy at the start of the correction phase, to end of treatment (Day 365):



Of the 263 patients who were *RAASi-naïve* at baseline:

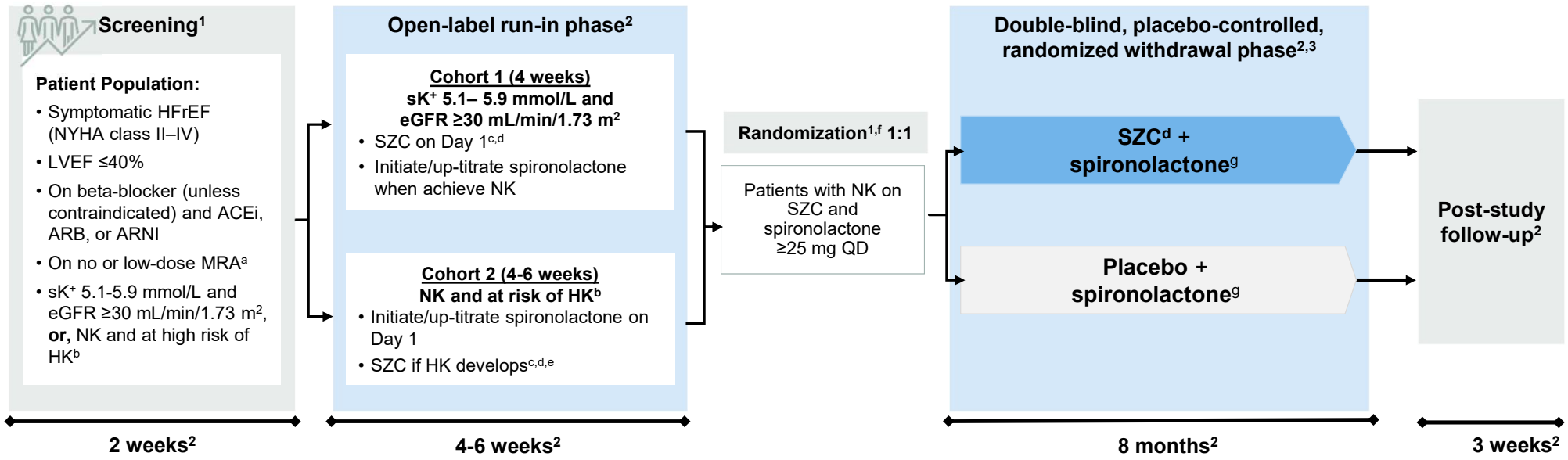
Note: RAASi includes ACEi, ARB, and MRA in ZS-004E and ZS-005 studies.

[a]Phase III, single-arm, open-label extension of the ZS-004 (HARMONIZE) trial evaluating efficacy and safety of SZC for the treatment of HK in outpatients (not on dialysis) for 11 months (N=123); [b]Phase III open-label, single-arm trial evaluating SZC for the treatment of HK in outpatients (not on dialysis) for 12 months (N=751). Changes in RAASi dose were evaluated as a prespecified exploratory analysis; [c]Multiple dose increases and decreases; [d]Non-mutually exclusive.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HK = hyperkalemia; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

1. Roger SD et al. Article and supplementary material. *Am J Nephrol.* 2019;50:473-480; 2. Spinowitz BS et al. Article and supplementary material. *Clin J Am Soc Nephrol.* 2019;14:798-809.

REALIZE-K is an ongoing Phase IV study to evaluate the efficacy and safety of SZC in patients with HFrEF who are optimized on spironolactone[1]



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

Estimated Patient Enrollment: N=265[1]

Estimated Study Completion Date: October 2023[1]

Note: NK defined as sK+ 3.5-5.0 mmol/L; HK defined as sK+ >5.0 mmol/L.[1]

[a]Not on spironolactone or eplerenone, or on low-dose spironolactone (<25 mg daily);[1] [b]Defined as either having a history of HK within the prior 24 months and eGFR ≥30 mL/min/1.73 m², or sK+ ≥4.5 mmol/L and eGFR 30-60 mL/min/1.73 m² and/or age >75 years;[1] [c]SZC 10 g TID ≤48 hours to achieve NK, followed by 10 g QD to maintain NK;[1] [d]SZC dose range from 5 g QOD to 5-15 g QD;[1] [e]Patients who do not develop HK within 4 weeks will be discontinued from the study;[3] [f]Randomization will be stratified by the sK+ cohort determined by central laboratory at the start of the open-label phase (Day 1);[1] [g]Spironolactone to be continued at same dose as administered at the end of run-in phase; dose may be reduced in patients who develop HK despite maximum dose of SZC/placebo.[2]

Abbreviations and References in slide notes.

In patients with HF, guidelines state the use of K^+ binders[a] to manage HK which may enable RAASi therapy

2021 ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HEART FAILURE[1]

Management of patients with chronic or recurrent HK on RAASi therapy:
- RAASi should be optimized when K^+ levels are <5.0 mmol/L
- An approved K^+ lowering agent[a] may be initiated as soon as K^+ levels are confirmed as >5.0 mmol/L
- Closely monitor K^+ levels
- Maintain K^+ lowering treatment unless alternative treatable etiology for HK is identified

K^+ Level	On Target RAASi Dose[b]	Guidance
4.5 to 5.0 mmol/L	No	• Initiate/up-titrate RAASi therapy to optimal doses • Closely monitor K^+ levels
>5.0 to ≤6.5 mmol/L	No	• Should initiate treatment with a K^+ lowering agent[a] • Closely monitor K^+ levels and maintain K^+ lowering agent[a] • If K^+ <5.0 mmol/L are detected, up-titrate RAASi therapy
	Yes	• May initiate treatment with a K^+ lowering agent • Closely monitor K^+ levels and maintain K^+ lowering agent[a]
>6.5 mmol/L	Yes or No	• Discontinue/reduce RAASi therapy • May initiate treatment with a K^+ lowering agent[a] • Closely monitor K^+

2022 AHA/ACC/HFSA GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE[2]

Recommendation	COR	LOE
In patients with HF who experience HK (serum K^+ ≥5.5 mmol/L) while taking a RAASi,[c] the effectiveness of K^+ binders[a] to improve outcomes by facilitating continuation of RAASi therapy is uncertain	2b	B-R

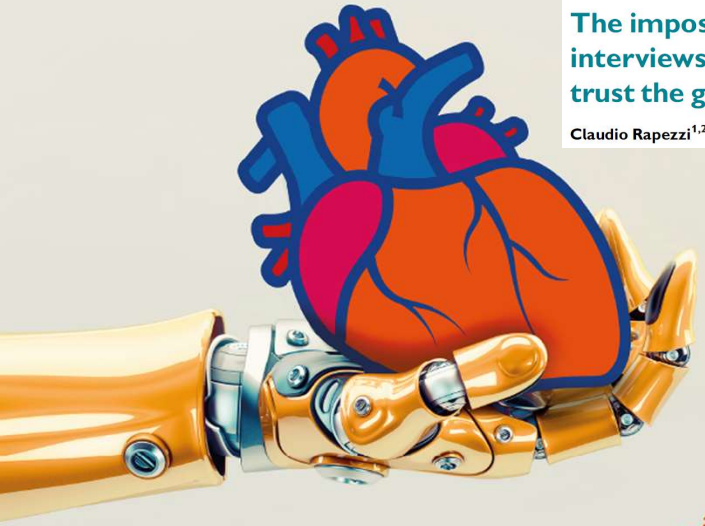
PATIROMER and SZC have been shown to lower K^+ levels and enable treatment with a RAASi[c] in patients with HF

[a]Patiromer or sodium zirconium cyclosilicate;[1,2] [b]Defined as maximal tolerated, guideline-recommended target dose of RAASi, which includes ACEi, MRA, or ARNi;

[c]RAASi includes ACEi, ARB, ARNi, and MRA.

ACC = American College of Cardiology; ACEi = angiotensin-converting enzyme inhibitors; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; COR = class of recommendation; ESC = European Society of Cardiology; HF = heart failure; HFSA = Heart Failure Society of America; HK = hyperkalemia; LOE = level of evidence; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

1. McDonagh TA et al. Article and supplementary data. *Eur Heart J*. 2021;42:3599-3726; 2. Heidenreich PA et al. In press-corrected proof. *J Am Coll Cardiol*. 2022.



17° Meeting

CardioLucca

Heart Brings Heart 2023

Lucca, 22-24 Giugno 2023

Centro Congressi Auditorium San Francesco

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–3
doi:10.1093/eurheartj/ehab187

The impossible interviews—Sherlock Holmes interviews David Sackett: 'how much can we trust the guidelines?'

Claudio Rapezzi[1,2]*, Gianfranco Sinagra[3], Marco Merlo[3], and Roberto Ferrari[1,2]

Table 1 Pros and cons of the clinical guidelines

Six good reasons why we should not follow guidelines

1. They focus on the disease rather than on the patient.
2. Their recommendations are based more often on expert opinions than on solid EBM.
3. They usually refer to studies conducted on relatively young patients with a low comorbidity burden.
4. They deter individual reasoning and suppress the deductive element of diagnostic decision-making in the individual patient.
5. They attenuate scientific curiosity and the motivation for further research by shifting attention from what we (still) don't know to what we know (consolidated evidence).
6. They are the product of a 'lobby' of authors, often with strong links with pharmaceutical or biomedical companies.

Six good reasons why we should use the guidelines

1. They are an exceptional tool summarizing the latest published research.
2. They provide a useful 'checklist' of possible treatments to consider in the individual patient.
3. They explain the general rationale behind each diagnosis.
4. They outline the principles and steps for making diagnostic and therapeutic decisions.
5. They promote a more rational use of economic resources.
6. They provide a convenient line of defense in the event of malpractice charges.

THM

- **20-40% dei casi HF potrebbero porre il tema RAASi-IperK+;**
- **20-40% dei pz trattati potrebbero presentare IperK+;**
- **La rimodulazione dose RAASi (non necessariamente la sospensione) può essere sufficiente in molti casi;**
- **La rivalutazione dinamica della funzione renale;**
- **Contenuto K+ nella dieta…;**
- **K+ binders, che ovviamente approcciano solo il tema K+, non il peggioramento GFR che spesso è a monte;**
- **RAASi protettivi …..**
- **SGLT2i, protettivi e permissivi …..**

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Lucca,
22-24 Giugno
2023
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European Reference Networks

Università degli Studi di Trieste

Master di II livello

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dalla genetica alla gestione multidisciplinare

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- Cardiomiopatie nello sport

Responsabili Scientifici:
Prof. Gianfranco Sinagra
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