A.S.L. CN1
Azienda Sanitaria Locale
di Cuneo, Mondovì e Savigliano

Strategie terapeutiche adiuvanti: ferro ed iperpotassiemia quali armi a disposizione ?

Mauro Feola

SC Cardiologia
Ospedale Regina Montis Regalis Mondovi' (CN)

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

Agenda

a) Ruolo dell'iposideremia nelle differenti gradi di gravita' dello scompenso cardiaco e nello scompenso sistolico.

b) Ruolo dell'iposideremia nel paziente con scompenso cardiaco acuto e cronico.

c) L'iperkaliemia nel paz. Affetto da scompenso cardiaco.

d) Il trattamento dell'ipekaliemia.

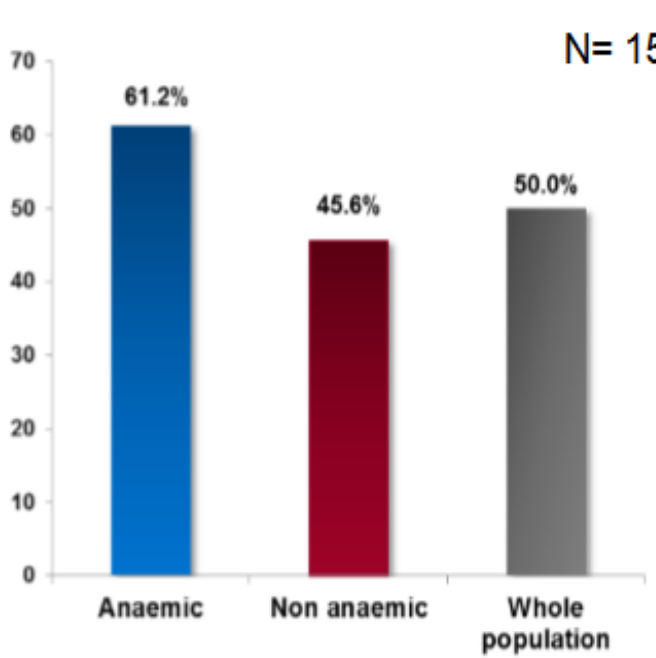
Iron deficiency: definizione

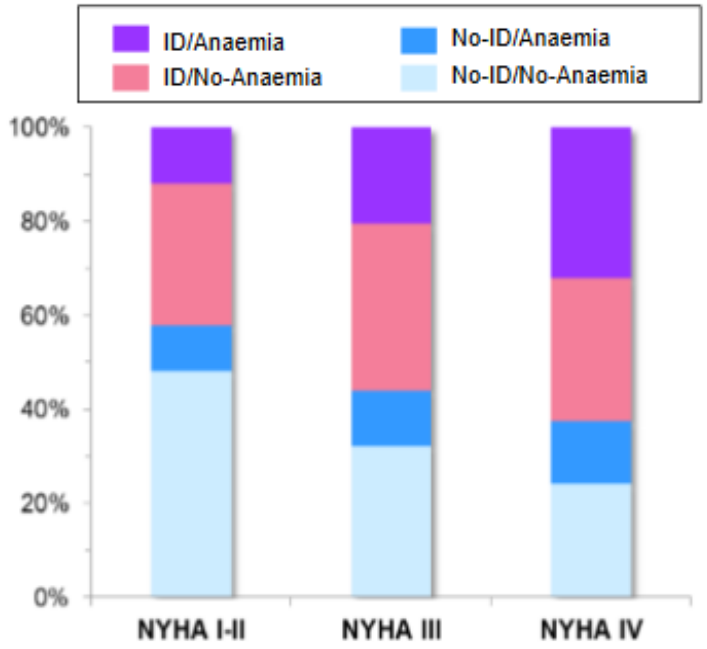
La carenza di ferro è una condizione in cui la disponibilità del ferro non è sufficiente a soddisfare le esigenze dell'organismo e che può essere presente con o senza anemia

Maria Domenica Cappellini
Am J Hematol. 2017 Jun 13. doi: 10.1002/ajh.24820

Prevalenza della carenza marziale nello scompenso cardiaco

Prevalence of iron deficiency in CHF patients





"Disease severity, assessed by NYHA class and NT-proBNP levels, proved to be powerful and independent predictors of a disordered iron status"

Iron deficiency definition used:

- Serum ferritin <100 µg/L or
- Serum ferritin <299 µg/L if TSAT <20%

Adapted from Klip IT, et al. *Am Heart J* 2013;165:575-82.

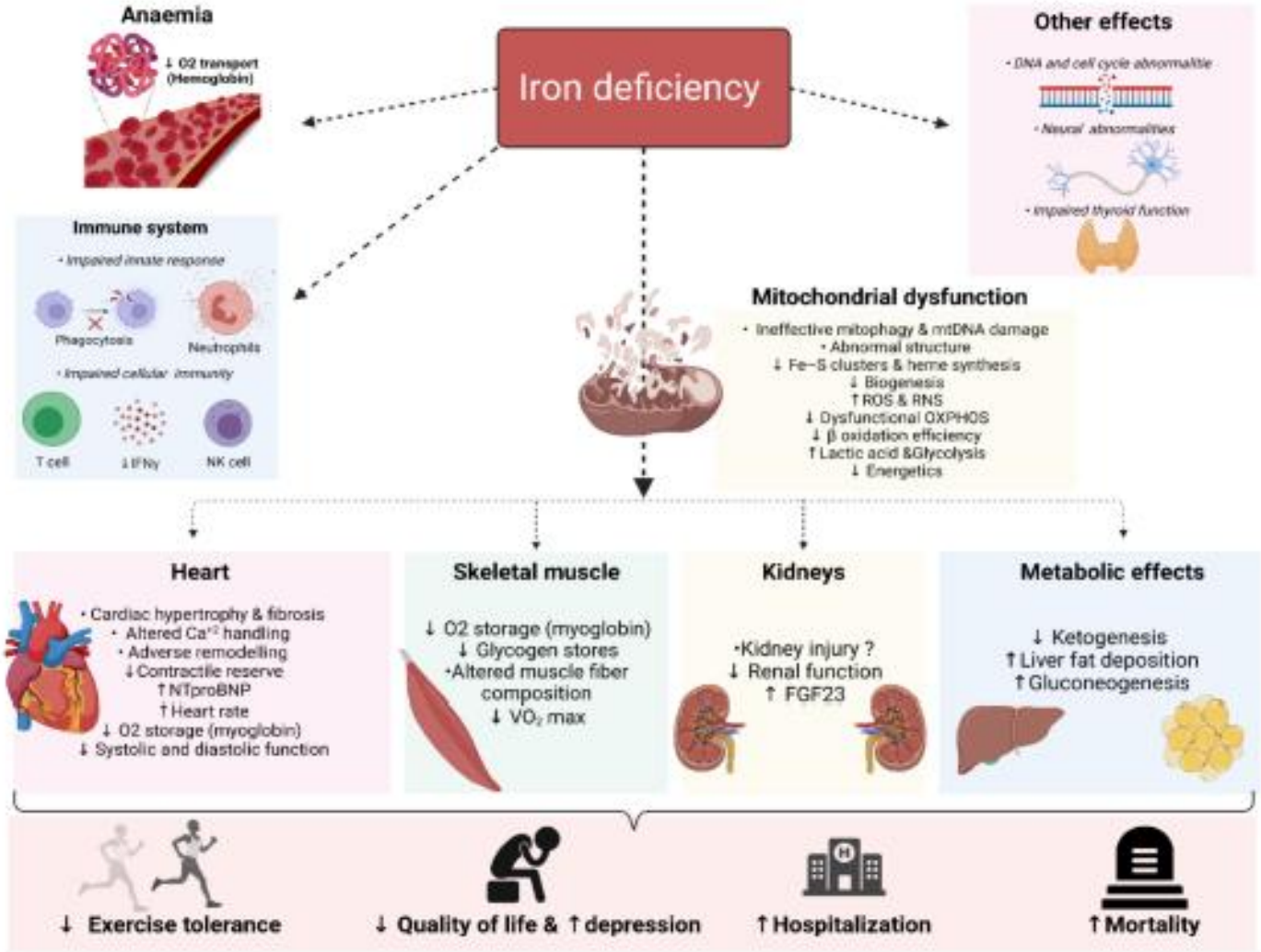
Journal of
Clinical Medicine

MDPI

Review

Iron Deficiency in Heart Failure: Mechanisms and Pathophysiology

Ridha I. S. Alnuwaysir, Martijn F. Hoes, Dirk J. van Veldhuisen, Peter van der Meer and Niels Grote Beverborg *



FAIR-HF STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D.,
Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D.,
Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,*
Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D.,
Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D.,
Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D.,
Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D.,
for the FAIR-HF Trial Investigators†

ABSTRACT

Anker SD et al. *N Engl J Med.* 2009;361:2436-48

FAIR-HF – Material and Methods

Aim

To determine whether the correction of Iron Deficiency, with or without anaemia, with the use of Ferinject® confers symptomatic benefits in patients with chronic heart failure (CHF)

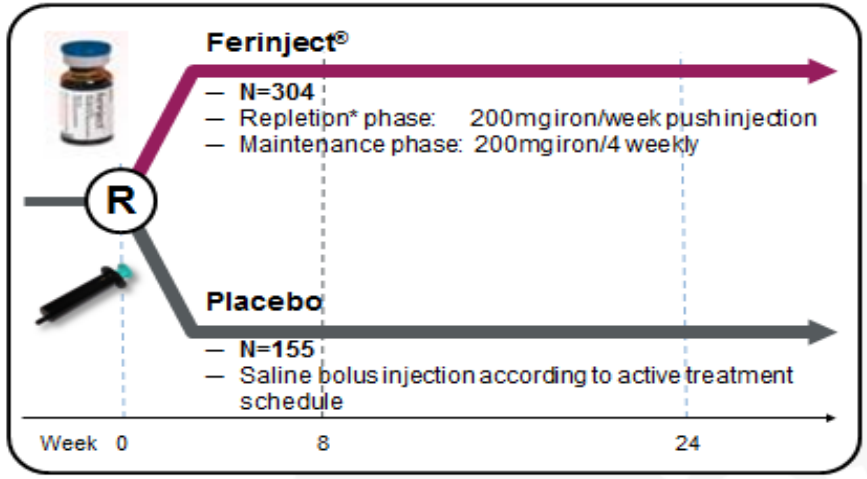
- **Primary endpoints:**
  - Self-reported PGA at Week 24
  - NYHA function class at Week 24
- **Secondary endpoints:**
  - 6 minutes walk test distance (Weeks 4, 12, 24)
  - Health-related QoL (Weeks 4, 12, 24)

✓ **Inclusion criteria**

- CHF of NYHA class II-III, LVEF≤40-45% (for NYHA class II and III, respectively)
- Hb: 9.5–13.5g/dL
- Iron Deficiency:
  serum ferritin <100 µg/L or <300 µg/L +TSAT <20%

Study design

Multicentre (11 countries), randomised (2:1), placebo-controlled study



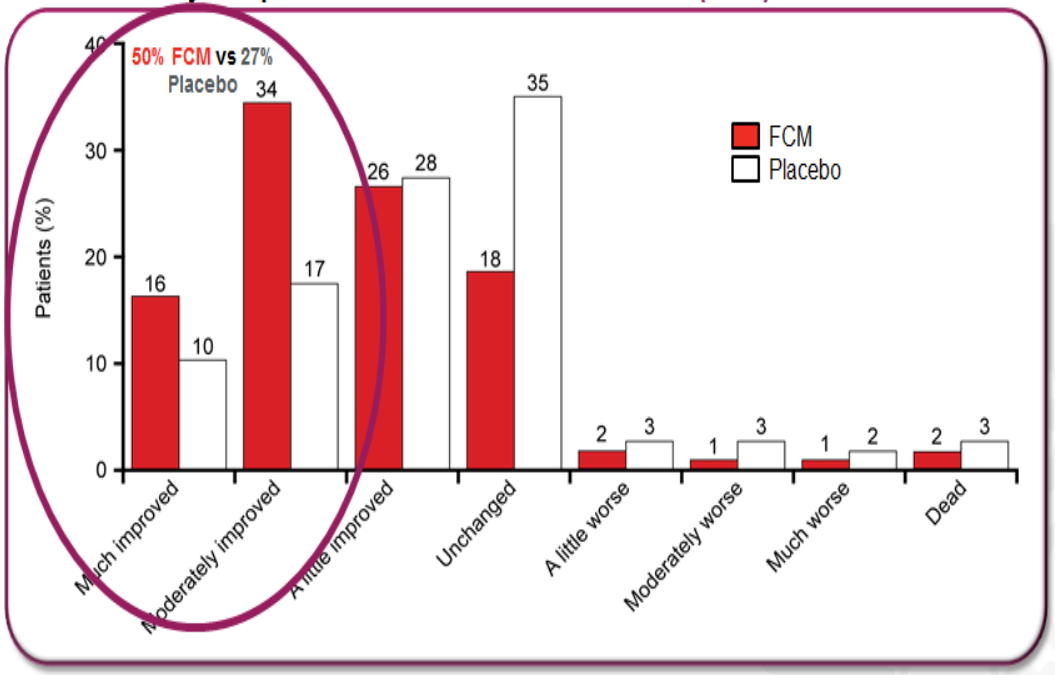
⇨ **Baseline characteristics**

- Average age 67 years
- Females 52-55%
- NYHA class II 17-18%, class III 81-83%
- LVEF 32-33%
- BMI 28kg/m^2

Anker SD et al. *N Engl J Med.* 2009;361:2436-48

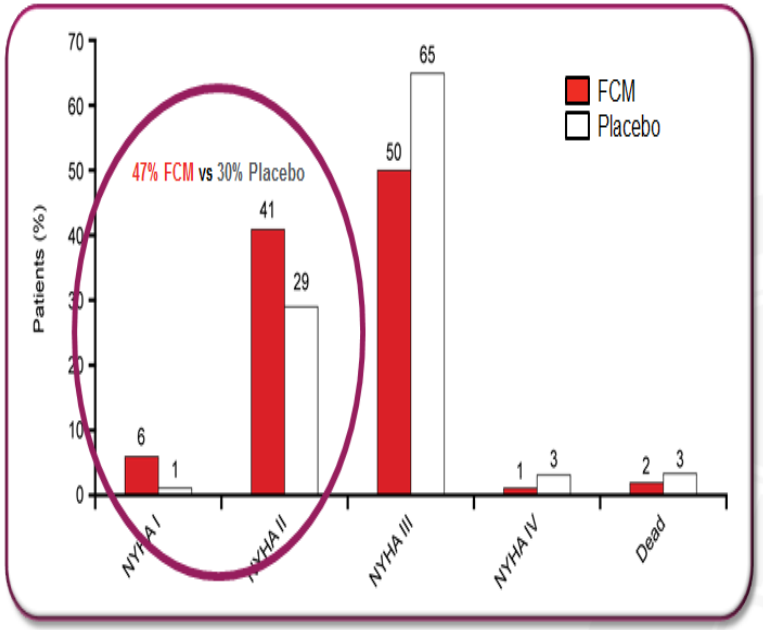
FAIR-HF – Results

Primary Endpoint – Patient Global Assessment (PGA) at Week 24



- Ferinject® improved self-reported PGA scores at week 24
- Odds ratio for better rank: 2.51 (95% CI 1.75, 3.61), P<0.001

Primary Endpoint - NYHA functional class at Week 24



- Ferinject® significantly improved NYHA functional class at week 24
- Odds ratio for improvement by 1 class: 2.40 (95% CI 1.55, 3.71), P<0.001*

CONFIRM-HF STUDY

European Heart Journal (2015) **36**, 657–668
doi:10.1093/eurheartj/ehu385

FASTTRACK ESC HOT LINE
Heart failure/cardiomyopathy

Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

Piotr Ponikowski[1,2]*, Dirk J. van Veldhuisen[3], Josep Comin-Colet[4], Georg Ertl[5,6], Michel Komajda[7], Viacheslav Mareev[8], Theresa McDonagh[9], Alexander Parkhomenko[10], Luigi Tavazzi[11], Victoria Levesque[12], Claudio Mori[12], Bernard Roubert[12], Gerasimos Filippatos[13], Frank Ruschitzka[14], and Stefan D. Anker[15], for the CONFIRM-HF Investigators

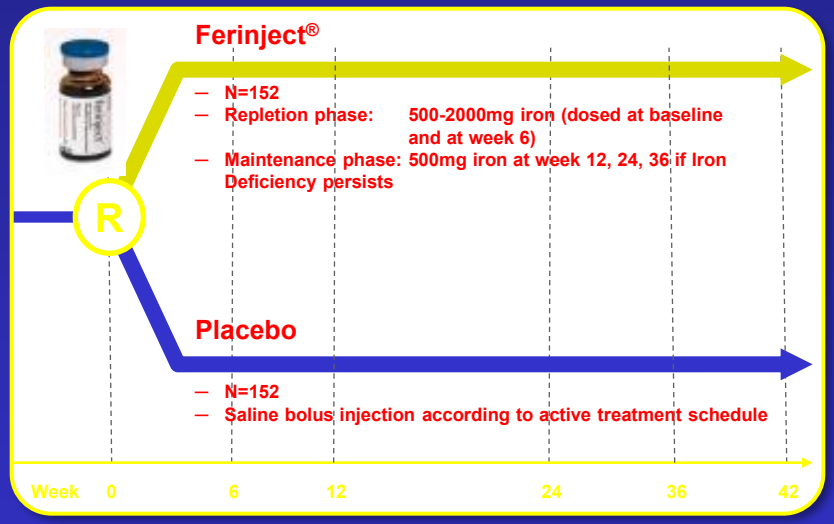
CONFIRM-HF – Material and Methods

Aim
To evaluate the benefits and safety of long-term Ferinject® therapy in Iron Deficiency patients with HF over 52 weeks

- **Primary endpoints:**
  - Change in 6-MWT distance from baseline to Week 24
- **Secondary endpoints (Weeks 6, 12, 24, 36, 52):**
  - NYHA class
  - PGA score
  - 6-MWT distance
  - Fatigue score
  - Health-related QoL (KCCQ and EQ-5D VAS)
  - Rate of hospitalisation for worsening CHF

- ✓ **Inclusion criteria**
  - CHF of NYHA class II or III and LVEF≤45%
  - BNP>100 pg/mL and/or NT-proBNP>400 pg/mL
  - Iron Deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%
  - Hb: <15 g/dL

Study design
Multicentre (9 countries), randomised (1:1), placebo-controlled study

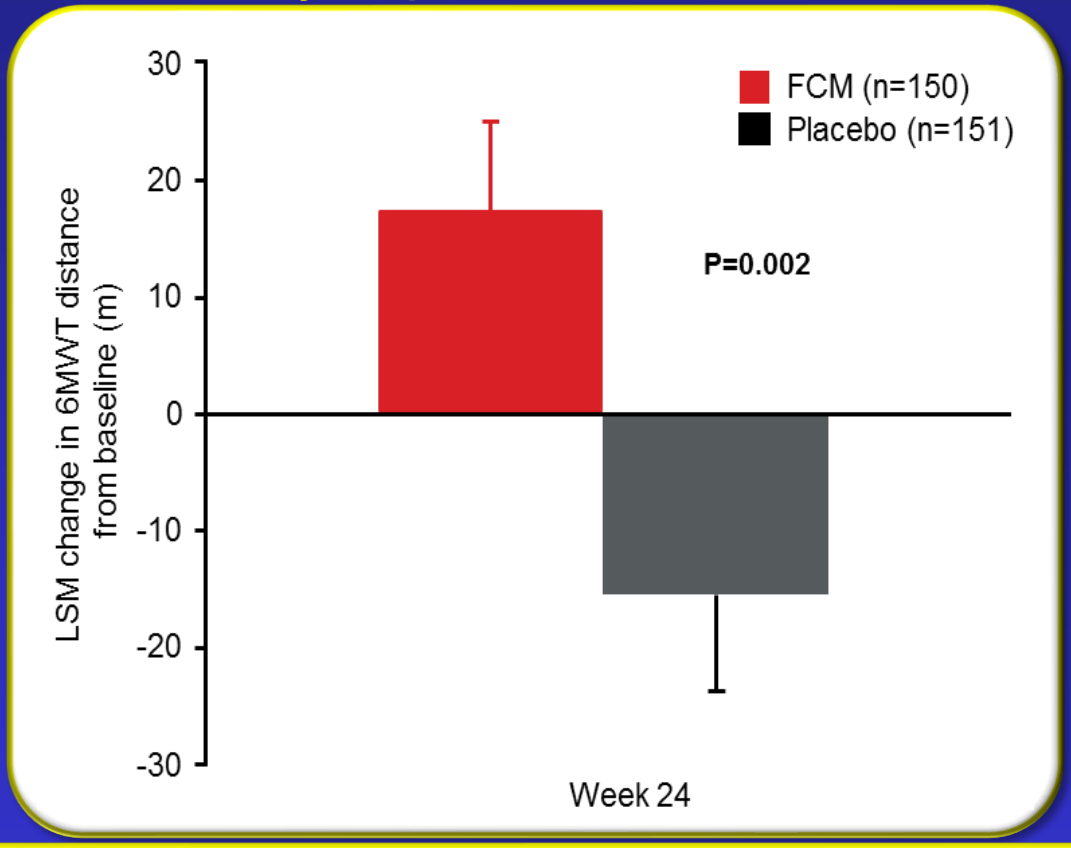


- ⇨ **Baseline characteristics**
  - Average age 69 years
  - Females 45% FCM; 49% placebo
  - NYHA class II 53% FCM; 60% placebo
  - NHYA class III 40% FCM; 47% placebo
  - LVEF 37%
  - BMI 28-28kg/m^2

Ponikowski P et al. *Eur Heart J.* 2015;36:657-68.

CONFIRM-HF – Results

Primary Endpoint - 6-MWT at Week 24

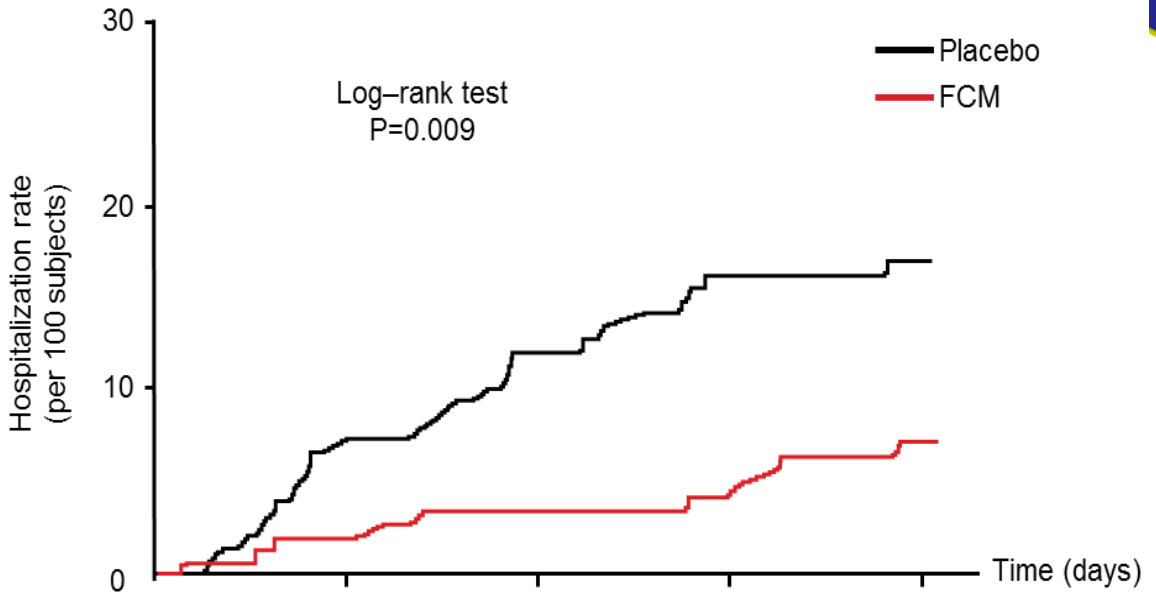


- The treatment of stable, symptomatic, iron-deficient HF patients with Ferinject® results in significant improvement in functional capacity at week 24 and over a 1-year period

Ponikowski P et al. *Eur Heart J.* 2015;36:657-68.

CONFIRM-HF – Results

Secondary Endpoints - First hospitalisation due to worsening CHF



No. of subjects at risk of time to first hospitalisation	0	90	180	270	360
Placebo	151	138	127	117	78
FCM	150	140	131	126	77

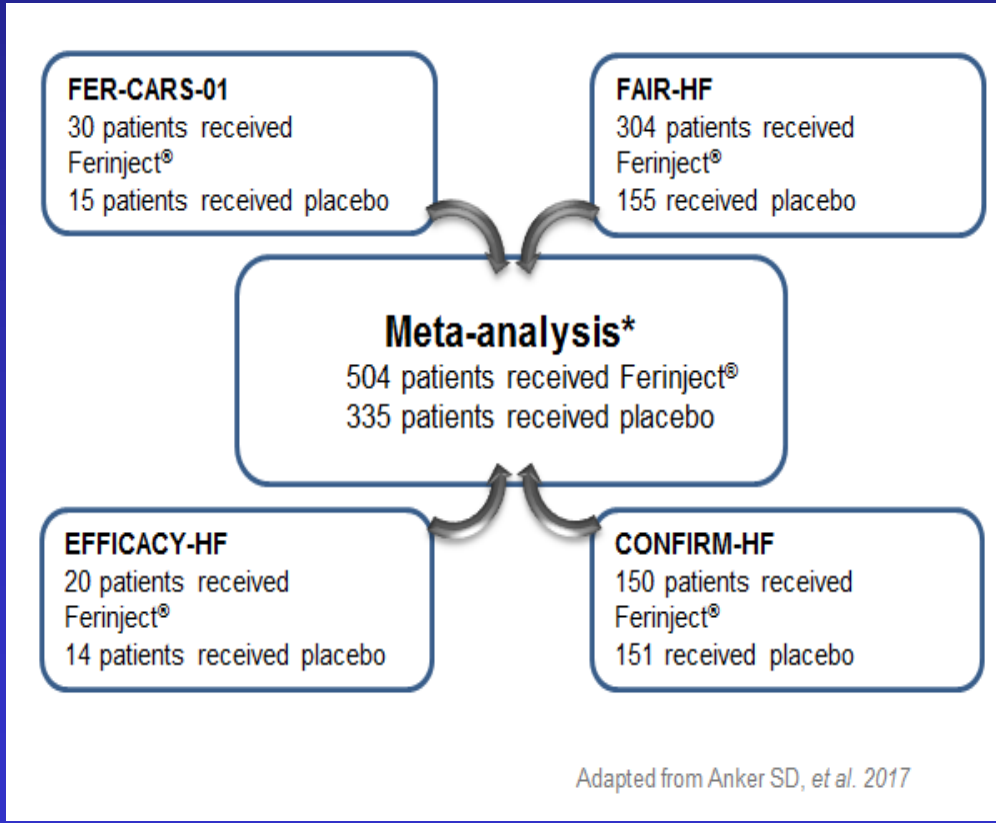
➢ **Ferinject® significantly reduced the risk of hospitalisations for worsening CHF (by 61%)**

Ponikowski P et al. *Eur Heart J.* 2015;36:657-68.

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.823

Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis

Stefan D. Anker[1]*, Bridget-Anne Kirwan[2,3], Dirk J. van Veldhuisen[4], Gerasimos Filippatos[5], Josep Comin-Colet[6], Frank Ruschitzka[7], Thomas F. Lüscher[7], Gregory P. Arutyunov[8], Michael Motro[9], Claudio Mori[10], Bernard Roubert[10], Stuart J. Pocock[3], and Piotr Ponikowski[11]



RECURRENT HOSPITALISATION & MORTALITY OUTCOMES (META-ANALYSIS)

- The FCM in CHF meta-analysis primary efficacy outcome of recurrent CV hospitalisations and CV death represent clinical priorities in HF management[1]

Primary efficacy outcome

Recurrent CV hospitalisations and CV death

Secondary outcomes

Recurrent HF hospitalisations and CV death
Recurrent CV hospitalisations and all cause death
Recurrent HF hospitalisations and all cause death
Recurrent HF hospitalisations
Recurrent CV hospitalisations
CV death
All cause death
Incidence and frequency of adverse events

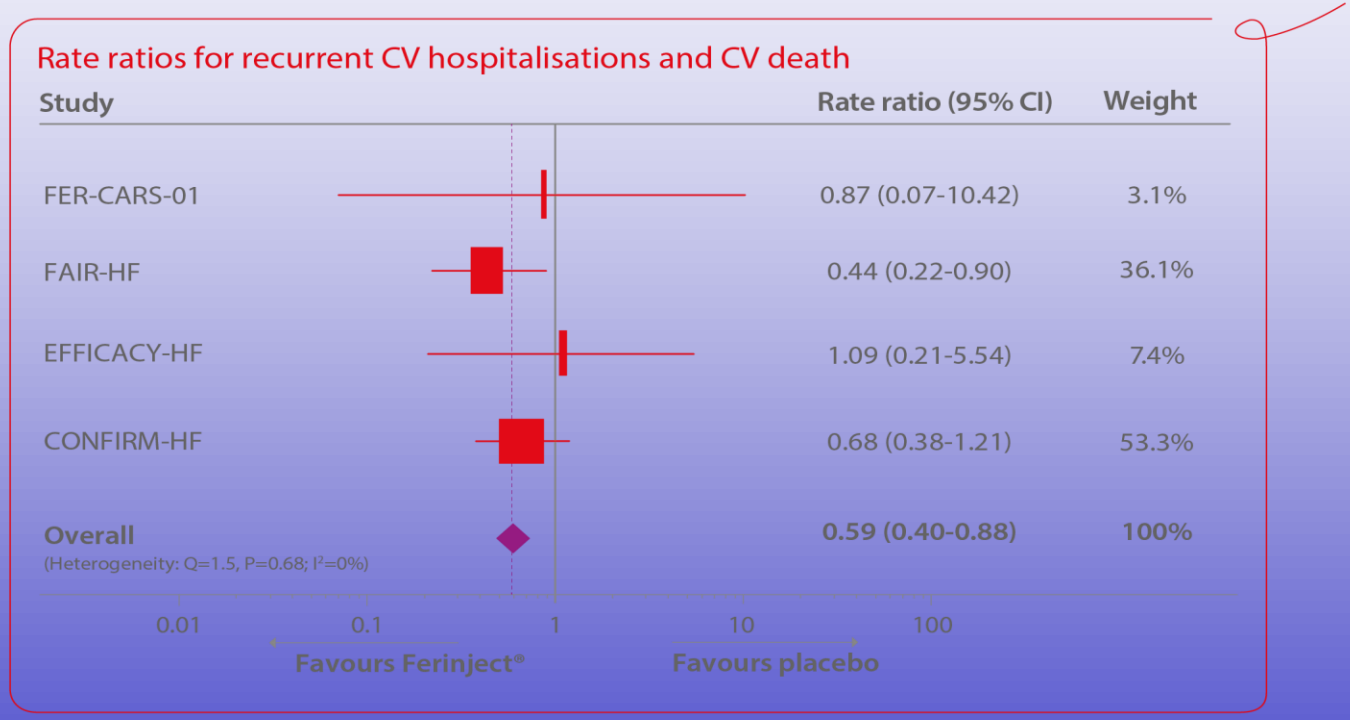
All outcomes were assessed in recurrent event analyses and backed up by time-to-first event analyses.

CHF = chronic heart failure; HF = heart failure; CV = cardiovascular

1. Anker SD *et al. Eur J Heart Fail* 2017; epub ahead of print. DOI:10.1002/ejhf.823.

FCM WAS ASSOCIATED WITH REDUCED RECURRENT CV HOSPITALISATIONS AND CV DEATH

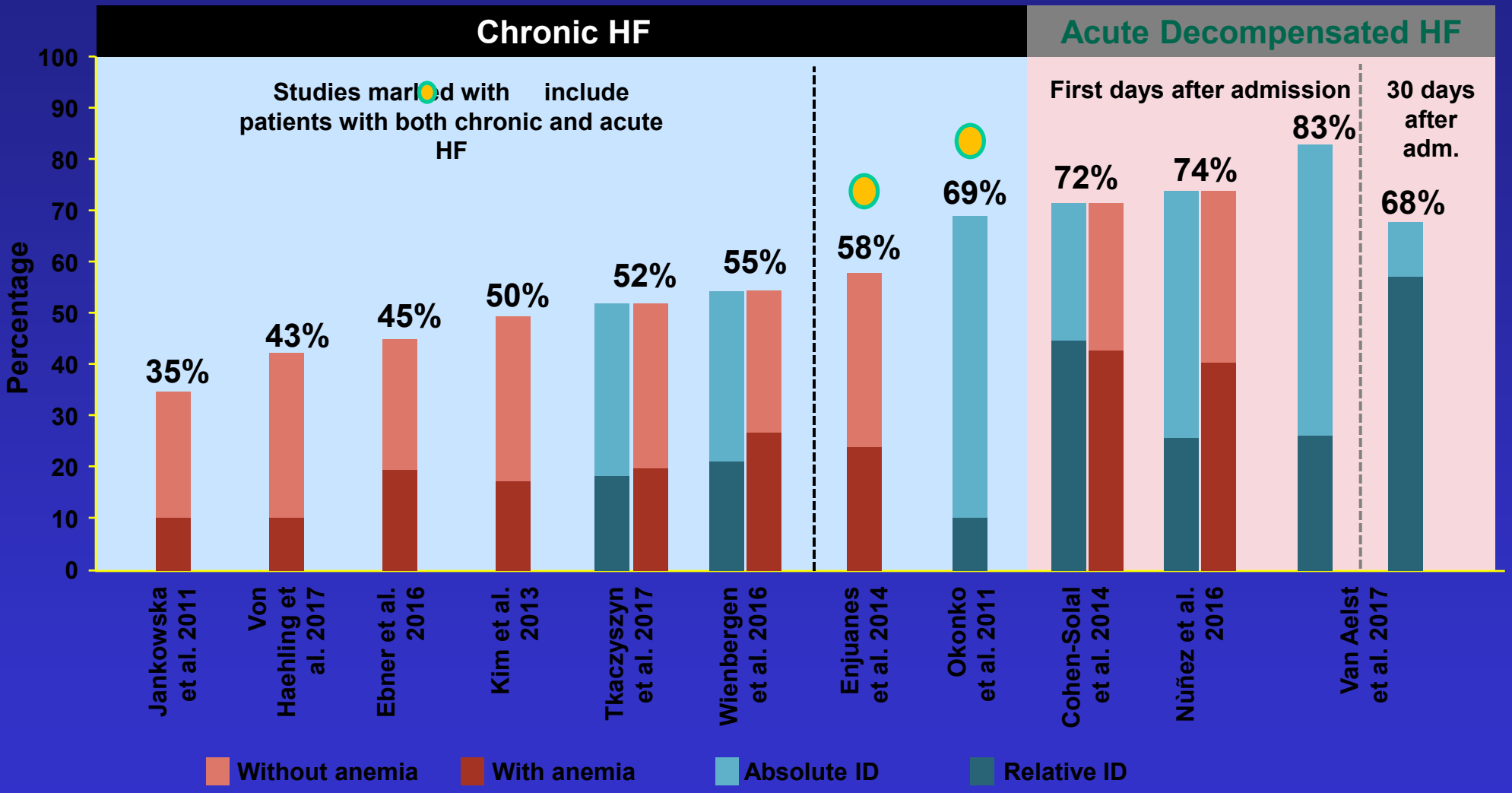
- **FCM was associated with a significantly lower rate (41% relative risk reduction) of recurrent CV hospitalisations and CV death versus placebo, in patients with systolic CHF and iron deficiency**



1. Anker SD *et al. Eur J Heart Fail* 2017; epub ahead of print. DOI:10.1002/ejhf.823.

ID IS COMMON IN HF

ESPECIALLY DURING ACUTE EXACERBATIONS



- Adapted from Rocha BML et al. *J Am Coll Cardiol*. 2018;71(7):782-793.

THE LANCET

Volume 376 · Number 9734 · Pages 1–68 · July 3–9, 2010 www.thelancet.com

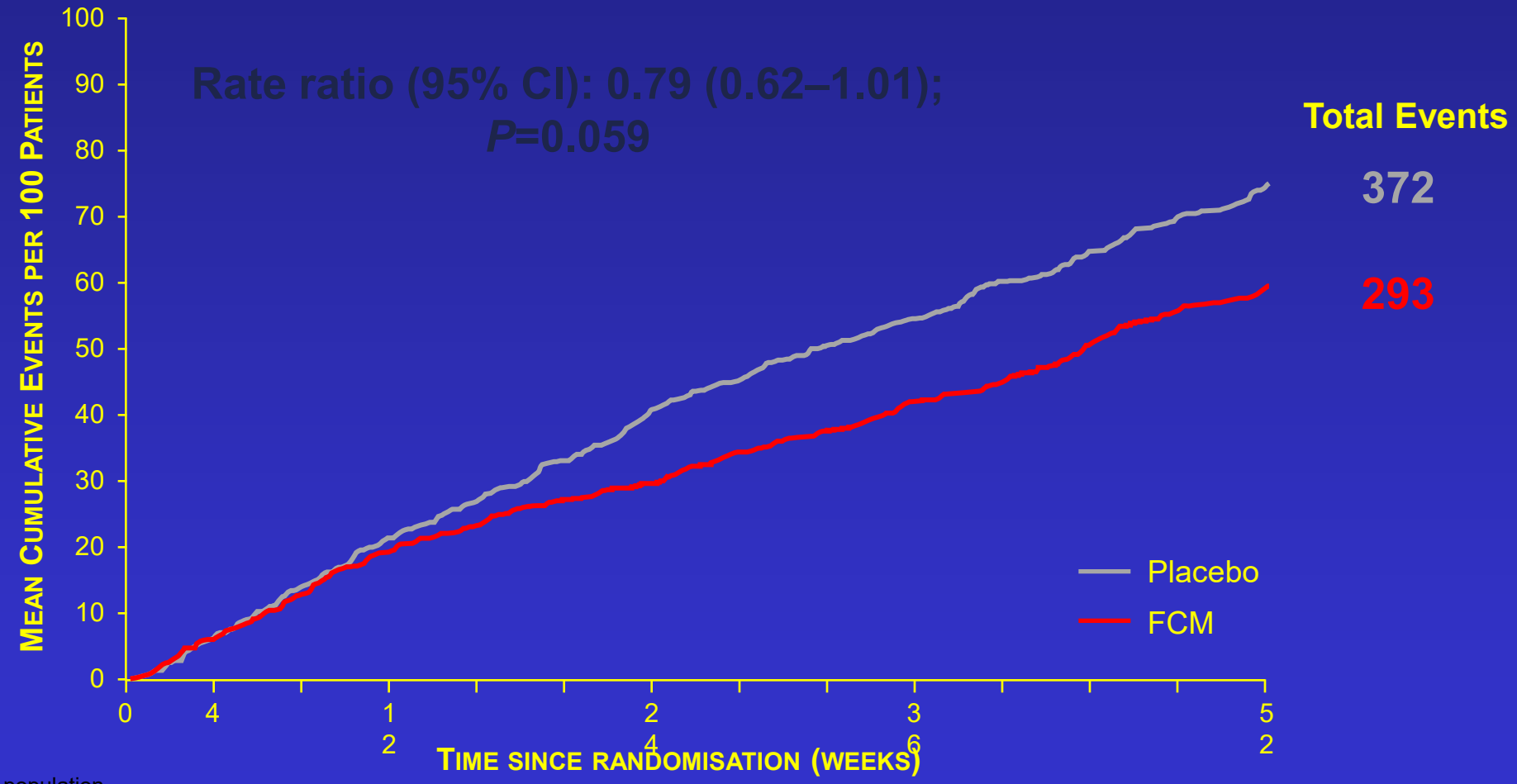
Articles

Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial

*Piotr Ponikowski, Bridget-Anne Kirwan, Stefan D Anker, Theresa McDonagh, Maria Dorobantu, Jarosław Drozdz, Vincent Fabien, Gerasimos Filippatos, Udo Michael Göhring, Andre Keren, Irakli Khintibidze, Hans Kragten, Felipe A Martinez, Marco Metra, Davor Milicic, José C Nicolau, Marcus Ohlsson, Alexander Parkhomenko, Domingo A Pascual-Figal, Frank Ruschitzka, David Sim, Hadi Skouri, Peter van der Meer, Basil S Lewis, Josep Comin-Colet, Stephan von Haehling, Alain Cohen-Solal, Nicolas Danchin, Wolfram Doehner, Henry J Dargie, Michael Motro, Javed Butler, Tim Friede, Klaus H Jensen, Stuart Pocock, Ewa A Jankowska, on behalf of the AFFIRM-AHF investigators**

TOTAL HF HOSPITALISATION AND CV DEATH

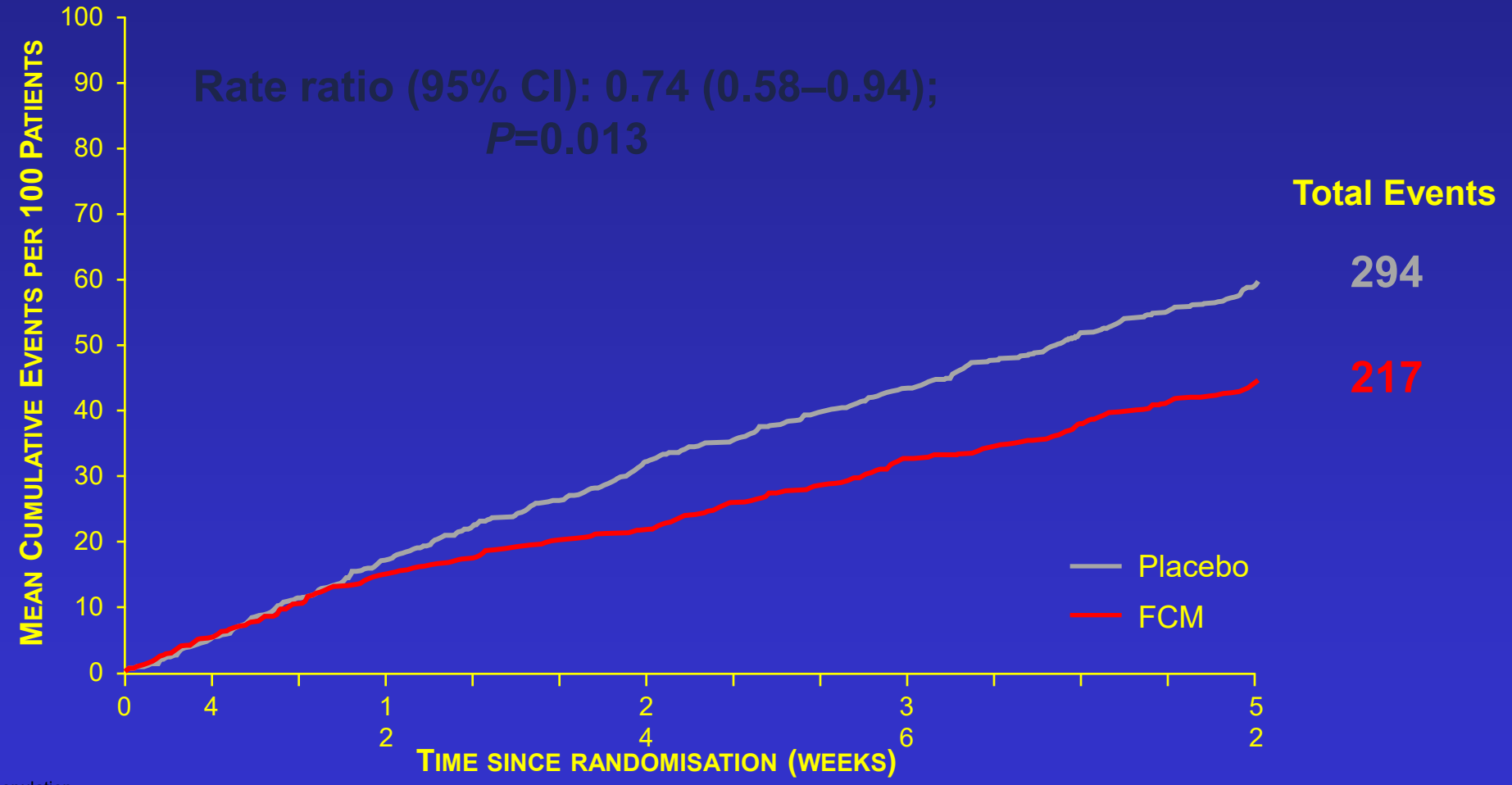
PRIMARY ENDPOINT



- mITT population.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

TOTAL HF HOSPITALIZATIONS
COMPONENT OF PRIMARY ENDPOINT

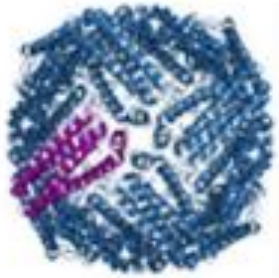
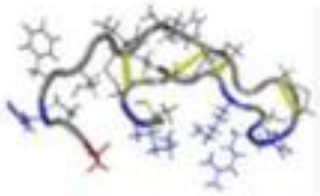


- mITT population.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

Redefining Iron Deficiency in Patients With Chronic Heart Failure

Milton Packer, MD; Stefan D. Anker, MD, PhD; Javed Butler, MD, MPH, MBA; John G.F. Cleland, MD; Paul R. Kalra, MD; Robert J. Mentz, MD; Piotr Ponikowski, MD; Khawaja M. Talha, MBBS

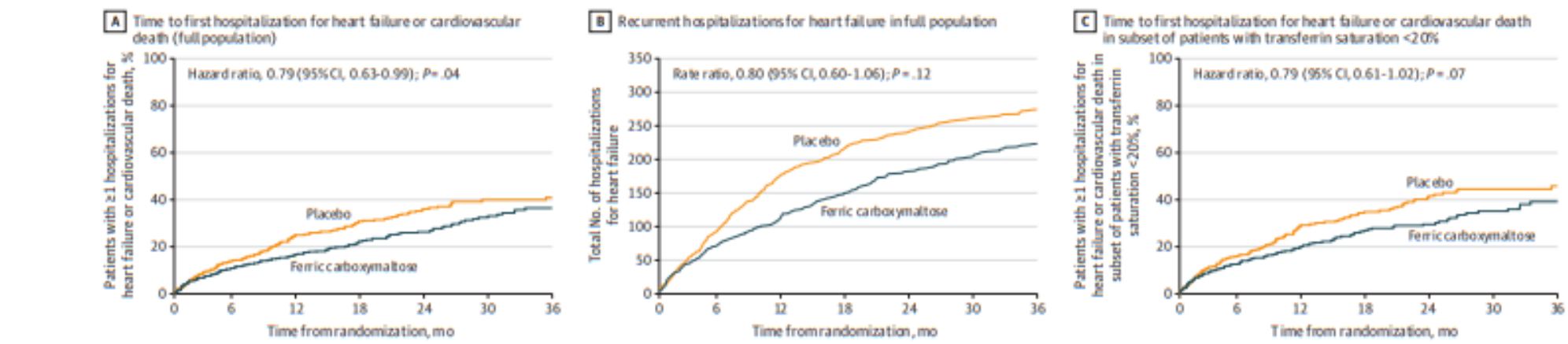
Ferritin	Transferrin saturation	Hepcidin	Soluble transferrin receptor
			
Intracellular storage of iron in nonreactive form	Bloodstream transport of iron in nonreactive form	Efflux of iron out of cells into bloodstream	Entry of iron into cells from the bloodstream
Produced in response to increases in intracellular iron and to inflammation	Reflects iron availability and delivery to target tissues	Produced in response to increases in serum iron and to inflammation	Produced when cytosolic iron levels are low
< 15-20 μg/L indicative of iron depletion, but rarely seen in heart failure	TSAT < 20% generally indicative of favorable response to IV iron	Higher values generally indicative of functional iron deficiency	Higher values generally indicative of intracellular iron deficiency
Values > 15-20 μg/L not helpful in identifying iron deficiency	Uncertain sensitivity of TSAT in discerning effects of IV iron on exercise capacity	Assays often measure fragments and are not standardized	Assays are not standardized and reflect erythroblast (not myocyte) demands

JAMA | Original Investigation

Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency
The FAIR-HF2 DZHK05 Randomized Clinical Trial

Stefan D. Anker, MD, PhD; Tim Friede, PhD; Javed Butler, MD, MPH; Khawaja M. Talha, MBBS; Marius Placzek, PhD; Monika Diek, MA; Anna Nosko, PhD; Adriane Stas, BA; Stefan Kluge, MD; Dominik Jarczak, MD; Geraldine deHeer, MD; Meike Rybczynski, MD; Antoni Bayés-Genís, MD, PhD; Michael Böhm, MD; Andrew J. S. Coats, MD; Frank Edelmann, MD; Gerasimos Filippatos, MD; Gerd Hasenfuß, MD; Wilhelm Haverkamp, MD; Mitja Lainscak, MD, PhD; Ulf Landmesser, MD; Iain C. Macdougall, MD; Bela Merkely, MD, PhD, DSc; Burkert M. Pieske, MD; Fausto J. Pinto, MD, PhD; Tienush Rassaf, MD; Jennifer K. Visser-Rogers, PhD; Giuseppe Rosano, PhD; Maurizio Volterrani, MD; Stephan von Haehling, MD, PhD; Markus S. Anker, MD; Wolfram Doehner, MD, PhD; Hüseyin Ince, MD; Friedrich Koehler, MD; Gianluigi Savarese, MD; Muhammad Shahzeb Khan, MD, MSc; Ursula Rauch-Kröhnert, MD; Tommaso Gori, MD; Teresa Trenkwalder, MD; Ibrahim Akin, MD; Christina Paitazoglou, MD; Iwona Kobielusz-Gembala, MD; Luca Kuthi, MD; Norbert Frey, MD; Manuela Licka, MD; Stefan Kääb, MD; Karl-Ludwig Laugwitz, MD; Piotr Ponikowski, MD, PhD; Mahir Karakas, MD, PhD, MBA

Figure 2. Cumulative Incidence of the Primary End Points



	A							B							C						
No. at risk																					
Placebo	547	384	272	194	140	84	63	547	431	324	250	193	130	98	380	249	171	126	86	60	44
Ferric carboxymaltose	558	416	317	223	173	110	75	558	454	361	273	213	145	103	368	269	197	144	118	76	50
No. of events																					
Placebo	1	72	43	19	12	7	1	0	102	79	40	21	19	13	1	57	34	12	11	4	1
Ferric carboxymaltose	0	61	23	18	10	13	5	0	78	41	32	31	25	16	0	48	18	15	4	8	4
No. censored																					
Placebo	3	87	69	59	42	49	20	3	95	82	63	45	56	26	3	70	44	33	29	22	15
Ferric carboxymaltose	2	79	76	76	40	50	30	2	86	79	77	51	54	35	2	58	45	38	22	34	22

The overall median follow-up was 16.6 months (IQR, 7.9-29.9 months). For parts A-C, the median follow-up was 17.3 months (IQR, 8.2-30.9 months) in the ferric carboxymaltose group vs 16.0 months (IQR, 8.7-28.7 months) in the placebo group.

Agenda

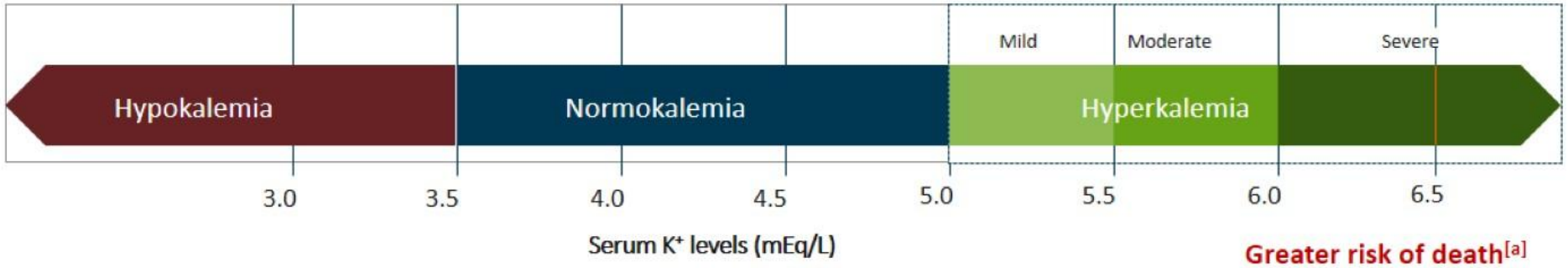
a) Ruolo dell'iposideremia nelle differenti gradi di gravita' dello scompenso cardiaco e nello scompenso sistolico.

b) Ruolo dell'iposideremia nel paziente con scompenso cardiaco acuto e cronico.

c) L'iperkaliemia nel paz. Affetto da scompenso cardiaco.

d) Il trattamento dell'ipekaliemia.

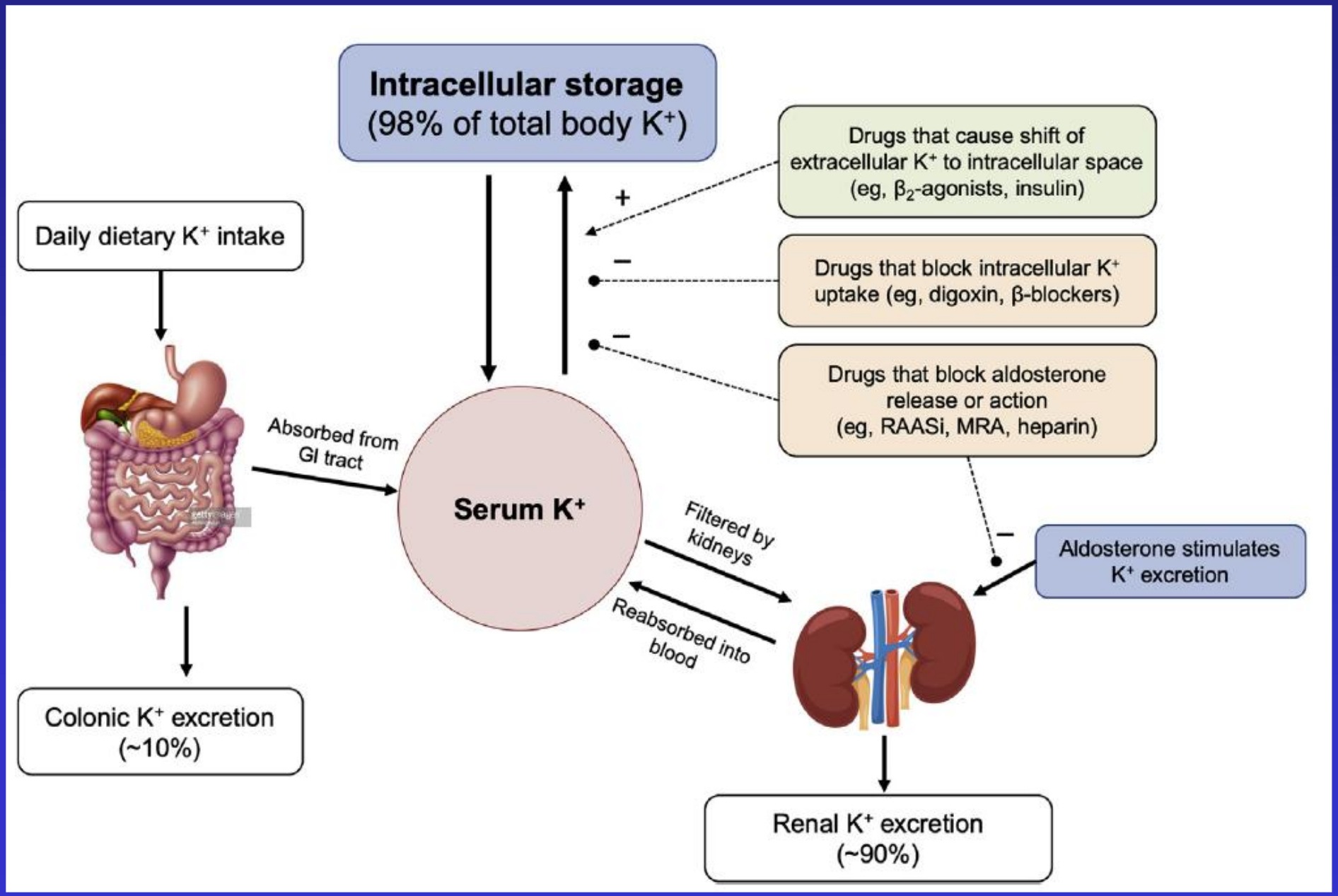
Definition of Hyperkalemia



- Definitions vary, but typically defined as K^+ levels > 5.0 mEq/L[b,c]
- Hyperkalemia may be further classified as mild, moderate, or severe[b]
- Serum K^+ can elevate quickly and unexpectedly,[d,e] and hyperkalemia can recur frequently in high-risk populations
- Disorders of K^+ levels profoundly affect membrane excitability and nerve, muscle, and cardiac function

a. Peacock WF, et al. J Emerg Med. 2018;55:741-750; b. Rastegar A, et al. Postgrad Med J. 2001;77:759-764;c. Kovesdy CP. Nat Rev Nephrol. 2014;10:653-662; d. Weiner D, et al. J Am Soc Nephrol. 1998;9:1535-1543; e. Hollander-Rodriguez JC, et al. Am Fam Phys. 2006;73:283-290.

Pathophysiology of Hyperkalemia in HF

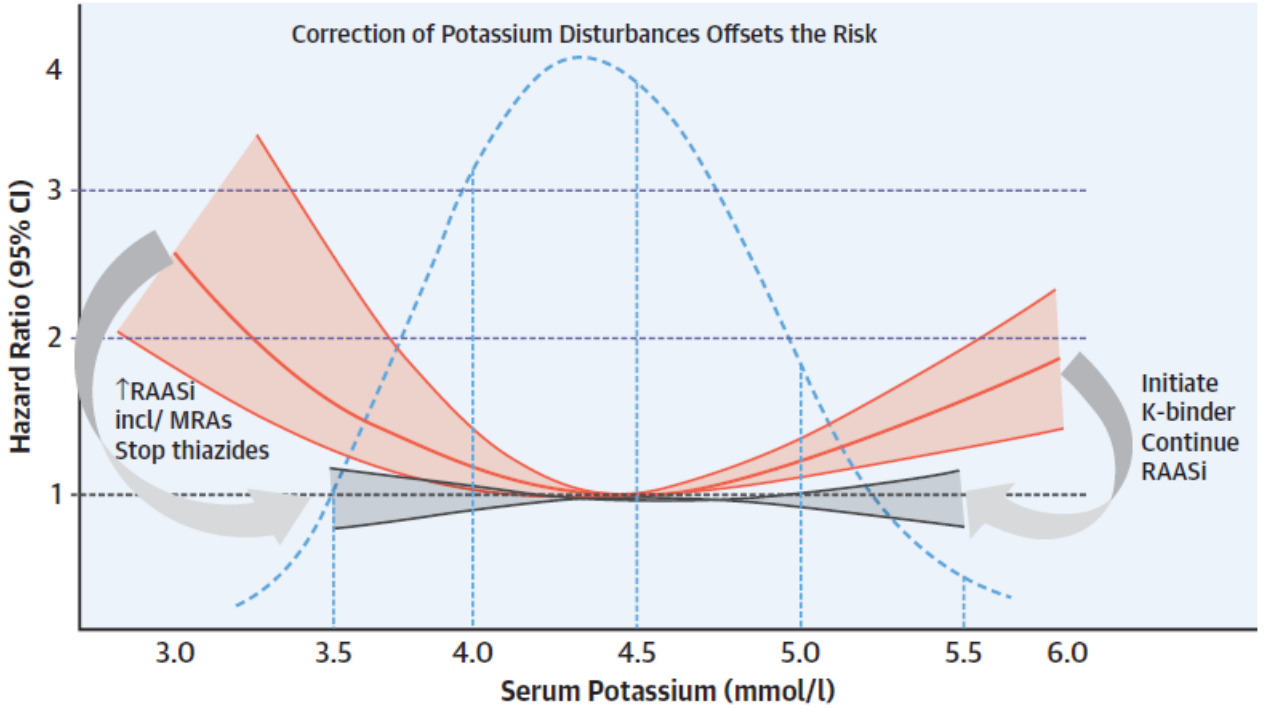


Abnormalities of Potassium in Heart Failure

JACC State-of-the-Art Review

VOL. 75, NO. 22, 2020

CENTRAL ILLUSTRATION Association of Serum Potassium With All-Cause Death and the Benefits of a Prompt Correction of Dyskalemia



Ferreira, J.P. et al. J Am Coll Cardiol. 2020;75(22):2836-50.

↑ = increase; incl = include; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin aldosterone inhibitor.

Hyperkalaemia in Heart Failure

Umar Ismail, Kiran Sidhu and Shelley Zieroth

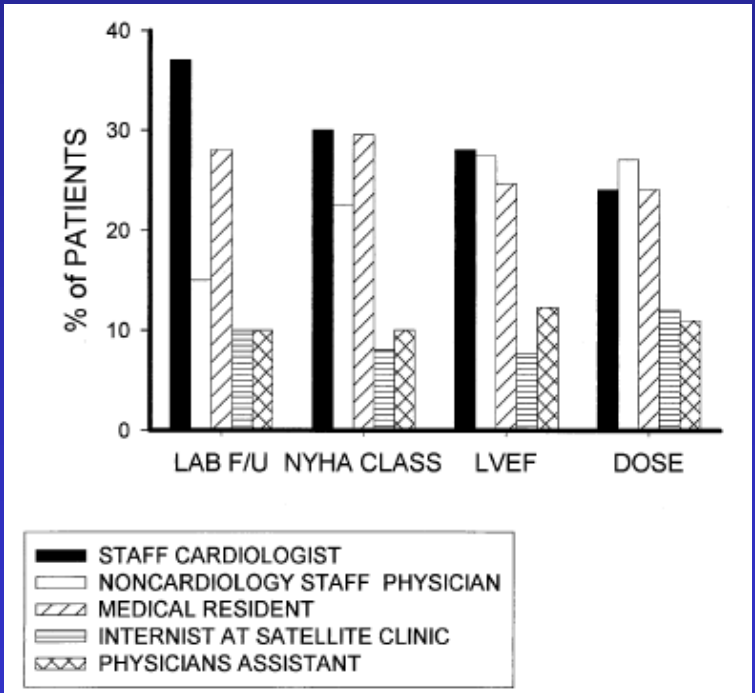
Table 1: Common Aetiologies for Hyperkalaemia in Heart Failure Patients

- Increased potassium supplementation from diet
- Metabolic shifts
  - Hyperglycaemia
  - Metabolic acidosis
- Iatrogenic
  - Renin–angiotensin–aldosterone system inhibitors
  - Angiotensin–neprilysin inhibitors
  - Digoxin
  - β-blockers
- Chronic kidney disease
- Type IV renal tubular acidosis

Cardiac failure review **vol. 7**
e10. 12 May. 2021

Complications of Inappropriate Use of Spironolactone in Heart Failure: When an Old Medicine Spirals Out of New Guidelines

Biykem Bozkurt, MD,* Ildiko Agoston, MD,* A. A. Knowlton, MD†
Houston, Texas



12% iperkaliemia grave
3% necessita' di un PM

	Study Cohort (n = 104)	RALES Trial (n = 82
NYHA (% patients)		
I	4.5	0
II	4.5	0.5
III	15.3	72
IV	10.3	27
Undocumented	65.4	0
% Patients with LVEF < 35	54.8	100
Medications (% patients)		
Loop diuretics	90.4	100
ACE inhibitors	79.8	95
Digitalis	55.7	75
Potassium supplements	40.4	29
Beta-blockers	34.6	11
Mean dose of ACE inhibitors		
Captopril (mg/day)	120 ± 12	63.4
Lisinopril (mg/day)	23 ± 2	15.5
Mean dose of beta-blockers		
Metoprolol (mg/day)	72.3 ± 10	not reported
Mean dose of spironolactone (mg/day)	40.7 ± 3.1	26
% Patients continued on potassium supplements	40.4	29
% Patients with renal insufficiency at baseline	30.7	excluded
% Patients with diabetes mellitus	46.2	not reported

Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

David N. Juurlink, M.D., Ph.D., Muhammad M. Mamdani, Pharm.D., M.P.H., Douglas S. Lee, M.D., Alexander Kopp, B.A., Peter C. Austin, Ph.D., Andreas Laupacis, M.D., and Donald A. Redelmeier, M.D.

Mean dose 26 mg/die

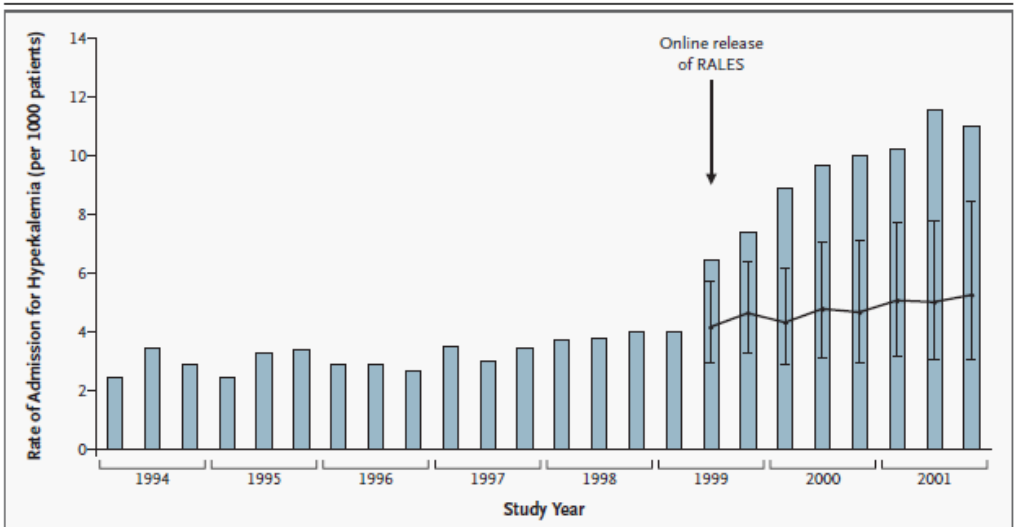


Figure 2. Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of hospital admission for hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected admission rates for hyperkalemia derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

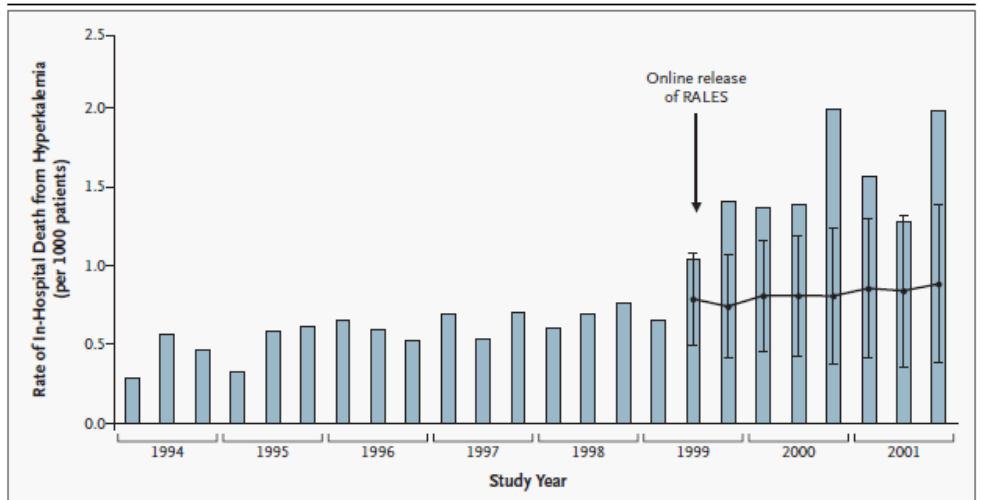


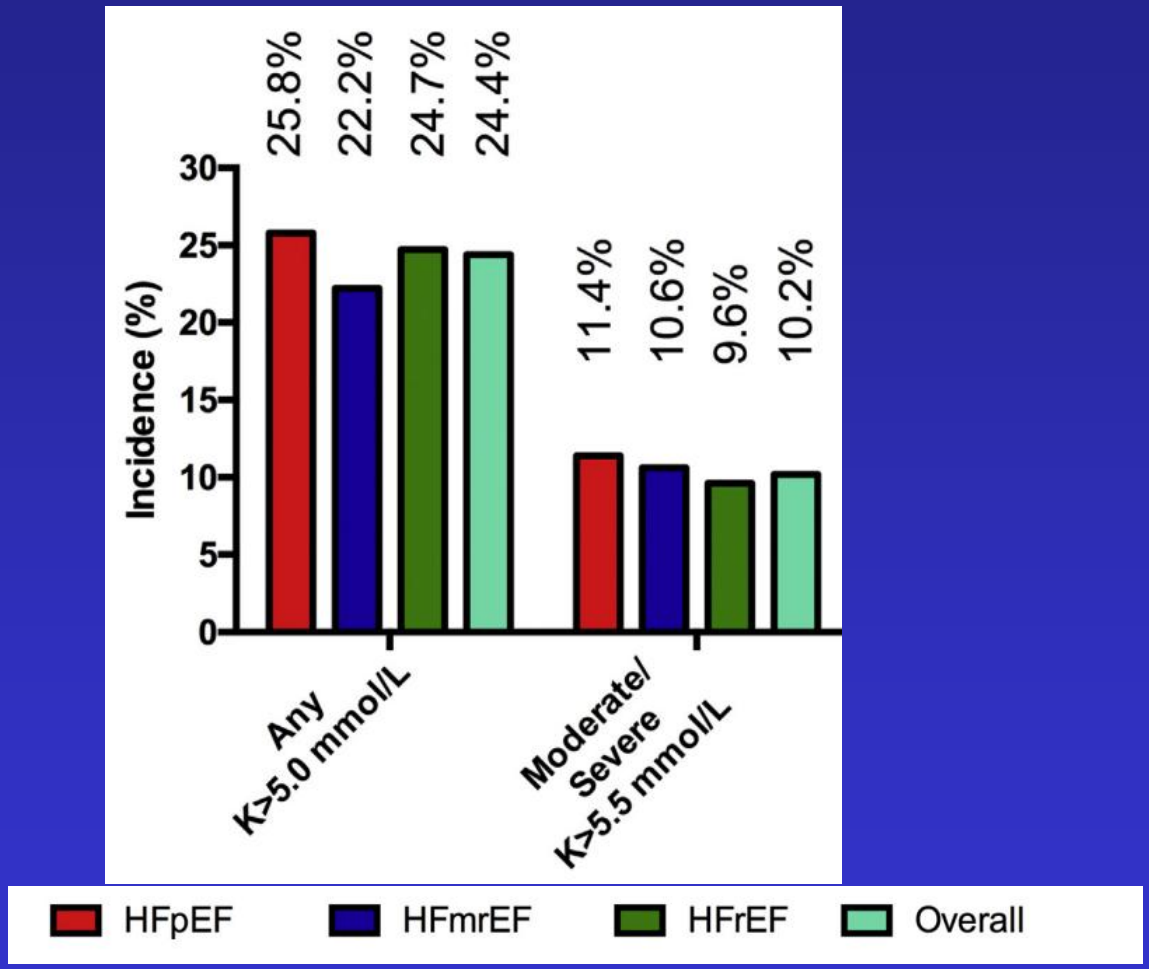
Figure 3. Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of in-hospital death associated with hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected death rates derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

Hyperkalaemia Event Rates During 1-Year Follow-Up, Overall and Stratified by Ejection Fraction

Swedish HF registry
2006-2011

N = 5,848



Savarese G, et al. JACC Heart Fail. 2019

Table 2 Treatment of acute or chronic hyperkalaemia

Promote update of K^+ into the intracellular space	Stimulate Na+/K+-ATPase: • β2-adrenergic agonists (IV, nebulized) • Insulin (IV) ± glucose • Sodium bicarbonate (if metabolic acidosis) • Combination cocktails
Cardiac membrane stabilization	• Calcium chloride or gluconate (IV) • Hypertonic saline (3–5%)
Increase K^+ elimination	• Loop diuretics (IV, oral) to increase renal K^+ excretion • Haemodialysis for removal of K^+ from blood • Cation-exchange resins (sodium polystyrene sulfonate) to enhance faecal K^+ excretion (PO, PR) • Sodium bicarbonate alkalinizes the urine and increases urinary K+ excretion • New K^+ binders: patiromer, sodium zirconium cyclosilicate
Other	• Fludrocortisone (PO) in aldosterone deficiency

IV, intravenous; PO, per os (orally); PR, per rectum; Na, sodium; K, potassium; IV, intravenous; PO, per os.

Rosano GMC et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2018 Jul 1;4(3):180-188.

Brief Review

New Potassium Binders for the Treatment of Hyperkalemia

Current Data and Opportunities for the Future

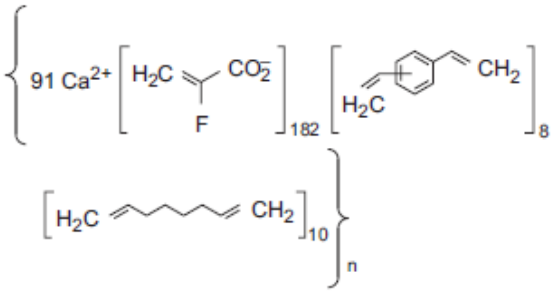
Bertram Pitt, George L. Bakris

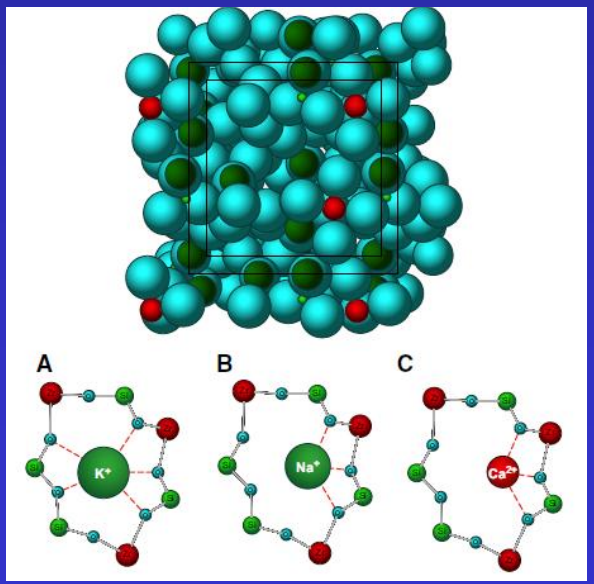
Patiromer

Sodium Zirconium Cyclosilicate

Patiromer Calcium

- Organic polymer
- 2-Propenoic acid, 2-fluoro-, calcium salt (2:1), polymer with diethenylbenzene
- and 1,7-octadiene
- Cross-linked polymer of calcium 2-fluoroprop-2-enoate with diethenylbenzene
- and octa-1,7-diene





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

Tabella 1. Caratteristiche dei principali agenti chelanti del potassio secondo la scheda dell'Agenzia Italiana del Farmaco (AIFA).

	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

Ca, calcio; GI, gastrointestinale; K, potassio; Mg, magnesio; Na, sodio.

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Trial	Criteri di inclusione	Disegno	Endpoint	Risultati
PEARL-HF[36], 2011	≥18 anni SCC con indicazione a MRA K 4.3-5.1 mmol/l eGFR <60 ml/min/1.73 m² o interruzione dei RAASi per iperK	105 pz: placebo vs patiromer 15 g bid per 4 settimane, associati a 25 mg/die di spironolattone, incrementato a 50 mg/die a partire dal giorno 15, se K <5.1 mmol/l	Primario: variazioni del K Secondario: casi di iperK (K >5.5 mmol/l). Pz in spironolattone 50 mg/die	Gruppo patiromer con K più basso di 0.45 mmol/l rispetto al placebo (p=0.001); minore incidenza di iperK (7.3 vs 24.5%, p=0.015) e più pz in spironolattone 50 mg/die (91 vs 74%, p=0.019)
AMETHYST-DN[33], 2015	30-80 anni Diabete mellito tipo 2 eGFR <60 ml/min/1.73 m² RAASi da almeno 28 giorni K >5 e <6 mmol/l	Fase iniziale: 222 pz (5< K ≤5.5 mmol/l) in patiromer 8.4 vs 16.8 vs 25.2 g/die e 84 pz (5.5< K<6 mmol/l) in patiromer 16.8 vs 25.2 vs 33.6 g/die per 8 settimane Fase di mantenimento: 44 settimane modulando la dose di patiromer in base al K	Primario: variazioni del K durante le prime 4 settimane Secondario: variazioni del K durante tutto lo studio	A 4 settimane: nei pz con K basale ≤5.5 mmol/l il K si riduceva di 0.35/0.55 mmol/l e nei pz con K basale >5.5 mmol/l di 0.87/0.97 mmol/l Da 4 a 52 settimane: riduzioni significative di K rispetto al basale ad ogni misurazione mensile
OPAL-HK[34], 2015	Fase iniziale: 18-80 anni eGFR <60 ml/min/1.73 m² 5.1< K <6.5 mmol/l Dose stabile di RAASi da 28 giorni Fase di mantenimento: K basale ≥5.5 mmol/l 3.8< K <5.1 mmol/l al termine della fase iniziale	Fase iniziale: 243 pz in patiromer 4.2 g bid (se K <5.5 mmol/l) o 8.4 g bid (se K ≥5.5 mmol/l) per 4 settimane Fase di mantenimento: 107 pz in patiromer alla stessa dose vs placebo per 8 settimane	Fase iniziale: riduzione del K Fase di mantenimento: differenza nei valori di K dopo le prime 4 settimane di questa fase	Fase iniziale: 76% dei pz raggiunge K tra 3.8 e 5.1 mmol/l, con riduzione media di 1.01 ± 0.03 mmol/l (IC 95% -1.07;-0.95; p<0.001) 4 settimane di mantenimento: pz in placebo +0.72 mmol/l di K vs + 0 mmol/l in patiromer (p<0.001)

Iperpotassiemia nello scompenso cardiaco: nuove soluzioni per un vecchio problema

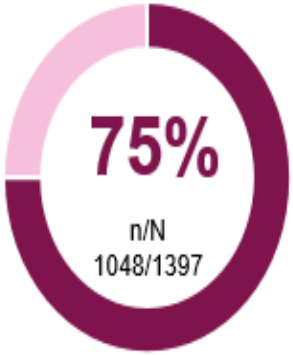
Simona Romani, Aldostefano Porcari, Enrico Fabris, Gianfranco Sinagra

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

Trial	Criteri di inclusione	Disegno	Endpoint	Risultati
ZS-002[41], 2015	>18 anni; eGFR tra 30 e 60 ml/min/1.73 m^2 K 5-6 mmol/l	90 pz: placebo vs ZS-9 alla dose di 0.3 o 3 o 10 g tid per 48 h	Primario: riduzione dei livelli di K Secondario: variazioni nei livelli sierici di Ca, K, Mg e creatinina	Endpoint primario raggiunto nei gruppi in 3 g (p=0.048) e 10 g (p<0.001) di ZS-9 vs placebo Massima riduzione di K (-0.92 mmol/l) nel gruppo 10 g ZS-9 dopo 38 h. Non differenze nei valori di Ca, Mg, Na e creatinina
ZS-003[40], 2015	>18 anni; K 5-6.5 mmol/l	Fase iniziale: 754 pz in ZS-9 1.25 vs 2.5 vs 5 vs 10 g tid vs placebo per 48 h. Fase di mantenimento: pz che raggiungono 3.5<K<4.9 mmol/l randomizzati a dose originaria di ZS-9 1 volta/die o a placebo. Pz inizialmente in placebo randomizzati a 1.25 o 2.5 g/die di ZS-9 per 12 giorni	Fase iniziale: variazioni di K a 48 h Fase di mantenimento: differenze di K tra i gruppi dopo 12 giorni	Fase iniziale: livelli medi di K scesi da 5.3 a 4.9 mmol/l in 2.5 g di ZS-9, a 4.8 mmol/l in 5 g e a 4.6 mmol/l in 10 g (p<0.001). Variazione non significativa in 1.25 g tid Fase di mantenimento: 5 e 10 g/die di ZS-9 superiori al placebo nel mantenere la normopotassiemia (p=0.008 e p<0.001, rispettivamente)
ZS-004 o HARMONIZE[39], 2014	>18 anni; K >5.1 mmol/l	Fase iniziale: 258 pz in 10 g tid di ZS-9 per 48 h Fase di randomizzazione: pz che raggiungono 3<K<5 mmol/l randomizzati a placebo vs ZS-9 a 5 o 10 o 15 g/die per 28 giorni	Primario: variazioni di K nei diversi gruppi durante la fase di randomizzazione Secondario: variazione di K nella fase iniziale	Fase di randomizzazione: K si riduce nei pz in ZS-9 vs placebo (4.8 mmol/l per ZS-9 5 g; 4.5 mmol/l per 10 g; 4.4 mmol/l per 15 g e 5.1 mmol/l per placebo; p<0.01 per ogni dose di ZS-9 vs placebo) Fase iniziale: 84% dei pz con normopotassiemia dopo 24 h e 98% dopo 48 h.
ZS-005[42], 2019	>18 anni K >5.1 mmol/l	Fase iniziale: 751 pz in 10 g tid di ZS-9 per 24/72 h. Fase di mantenimento: raggiunta la normopotassiemia, i pz ricevono 5 g/die di ZS-9, titolabile fino a 15 g per 12 mesi	Primario: percentuale di pz con normopotassiemia dopo la fase iniziale e di mantenimento	Fase iniziale: il 99% dei pz raggiunge la normopotassiemia Fase di mantenimento: 88% dei pz con K <5.1 mmol/l e 99% con K <5.5 mmol/l

Patients Treated With SZC for Hyperkalemia Were Able to Maintain and Increase Their RAASi Therapy

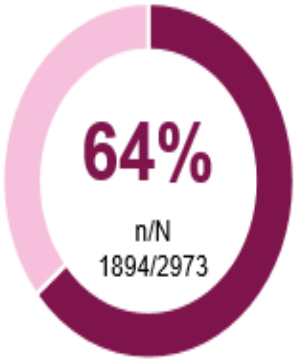
ZORA: Of the patients who received RAASi,[1,a,b]



of patients taking SZC **stabilized or uptitrated their RAASi therapy compared to 54%** of patients who did not receive K^+ binder (n/N=2667/4900)

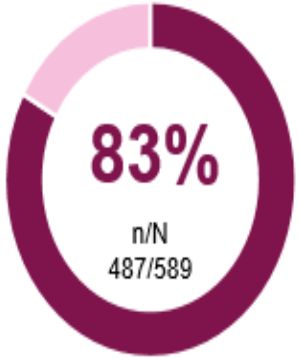
Meta-analyzed across countries, patients who received SZC had **2.5x higher odds of either stabilizing or uptitrating their RAASi therapy** vs those who did not receive any K^+ binders.
(odds ratio: 2.56; 95% CI: 1.92, 3.41)[c]

GALVANIZE RAASi: Of the patients who received RAASi,[2,3,d]



of patients taking SZC were on **optimized[e] RAASi dose** in 6 months

OPTIMIZE I: Of the patients who initiated SZC while on RAASi,[4,5,f]



of patients **continued[g] their RAASi therapy**, in which **8% had an increase** in their dose

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

Javed Butler[1,2*†], Stefan D. Anker[3,4,5,6*†], Lars H. Lund[7,8], Andrew J.S. Coats[9], Gerasimos Filippatos[10,11], Tariq Jamal Siddiqi[1,2], Tim Friede[12,13,14], Vincent Fabien[15], Mikhail Kosiborod[16,17], Marco Metra[18], Ileana L. Piña[19], Fausto Pinto[20], Patrick Rossignol[21,22], Peter van der Meer[23], Cecilia Bahit[24], Jan Belohlavek[25], Michael Böhm[26], Jasper J. Brugts[27], John G.F. Cleland[28], Justin Ezekowitz[29], Antoni Bayes-Genis[30], Israel Gotsman[31], Assen Goudev[32], Irakli Khintibidze[33], Joann Lindenfeld[34], Robert J. Mentz[35], Bela Merkely[36], Eliodoro Castro Montes[37], Wilfried Mullens[38], Jose C. Nicolau[39,40], Aleksandr Parkhomenko[41], Piotr Ponikowski[42], Petar M. Seferovic[43,44], Michele Senni[45], Evgeny Shlyakhto[46], Alain Cohen-Solal[47], Peter Szecsödy[15], Klaus Jensen[15], Fabio Dorigotti[15], Matthew R. Weir[48], and Bertram Pitt[49]

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

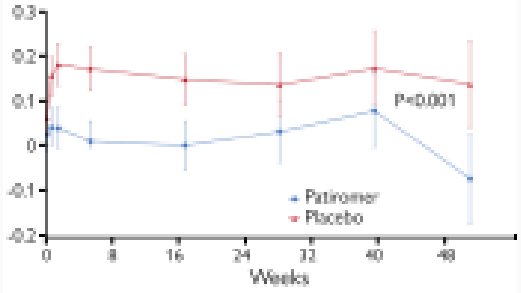
Patients were randomized and completed run-in (where K^+ levels controlled with patiromer and RAASi dose optimized)

439 Placebo

439 Patiromer

Primary endpoint

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



	Day 3	Weeks 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 — 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 — 3.0
Win ratio (95% CI)
Favours Placebo | Favours Patiromer

*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

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2018) 4, 180–188
doi:10.1093/ehjcvp/pvy015
CURRENT OPINION
Heart failure/cardiomyopathy

Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology

Giuseppe M.C. Rosano[1,2]*, Juan Tamargo[3], Keld P. Kjeldsen[4,5,6], Mitja Lainscak[7], Stefan Agewall[8,9], Stefan D. Anker[10,11], Claudio Ceconi[12], Andrew J.S. Coats[1], Heinz Drexel[13,14,15], Gerasimos Filippatos[16], Juan Carlos Kaski[1], Lars Lund[17], Alexander Niessner[18], Piotr Ponikowski[19], Gianluigi Savarese[17], Thomas A. Schmidt[20,21], Petar Seferovic[22], Sven Wassmann[23,24], Thomas Walther[25,26], and Basil S. Lewis[27,28]

Patients	Recommendation
Chronic or recurrent hyperkalaemia on RAASi 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
Chronic or recurrent hyperkalaemia not on maximal tolerated guideline-recommended target dose of RAASi	RAASi should be optimised and 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
K+ levels of 4.5–5.0 mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi therapy	Initiate/up-titrate RAASi therapy and closely monitor K^+ levels. If K^+ levels rise above 5.0 mEq/L, initiate an approved K^+-lowering agent
K+ levels of >5.0–≤6.5 mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi therapy	Initiate an approved K^+-lowering agent. If levels <5.0 mEq/L are detected, up-titrate RAASi - K+ level should be closely monitored and K+ lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified
K+ levels of >5.0–≤6.5 mEq/L on maximal tolerated, guideline-recommended target dose of RAASi 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
K+ levels of >6.5 mEq/L on either maximal sub-maximal tolerated, guideline-recommended target dose of RAASi therapy	Discontinue/reduce RAASi. Treatment with a K^+ lowering agent may be initiated as soon as K^+ levels >5.0 mEq/l. K^+ level should be closely monitored

Journal of
Clinical Medicine

MDPI

Article

Medical Therapy in Patients with Heart Failure: A Delphi Consensus from Italian Cardiologists

Valentina Tardivo [1], Emanuele Venturini [2], Gaetano M. Ruocco [3], Guido Pastorini [4], Elisa Bertone [4] and Mauro Feola [4,*]

Table 7. Use of MRA and ARNi.

	1	2	3	4	5	TOT
In patients with heart failure and reduced systolic function, in case of developing hyperkalemia with associated worsening of renal function, I discontinue MRAs while maintaining therapy with sacubitril/valsartan	11	15	33	28	6	93
	28%			72%		100%
In patients with reduced systolic cardiac function, if hyperkalemia has occurred, I prefer to use "Patiromer" or "Sodium zirconium cyclosilicate" while maintaining therapy with ACE/RAASi/ARNI and MRA	5	7	19	23	39	93
	13%			87%		100%