11° CONGRESSO NAZIONALE

CAMPUS Cuore

Quello che le Linee Guida Non Dicono

Napoli
5-6 aprile 2024

Strategie di trattamento dell'iperkaliemia durante terapia con inibitori RAAS

Daniele Masarone

Important points from existing HF guidelines on RAASi therapy

Organisation	Guidelines on RAASi
American Heart Association American Diabetes Association HEART FAILURE ASSOCIATION OF THE ESC HFSA HEART FAILURE SOCIETY OF AMERICA NICE National Institute for Health and Care Excellence	Organisation guidelines consistent in recommending RAASi (ACEi, ARB and MRA):[1–3] • ACEi/ARBs/ARNI/MRA are recommended for symptomatic patients with HF*[3] • **Highest tolerated targeted doses recommended**[1,2]

*Patients with HF with reduced ejection fraction.

ACEi, angiotensin-converting-enzyme inhibitor; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin receptor blocker; ESC-HFA, Heart Failure Association of the European Society of Cardiology; HF, heart failure; HFSA, Heart Failure Society of America; NICE, National Institute for Health and Care Excellence; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

1. Yancy CW, et al. *Circulation.* 2013;128:1810–52; 2. Ponikowski P, et al. *Eur J Heart Fail.* 2016;18:891–975; 3. Lindenfeld J, et al. *J Card Fail.* 2010;16:475–539.

Pharmacological treatments indicated in patients with NYHA class II–IV HFrEF

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

ESC Guidelines HF 2021

Mortality rates improve with RAASi doses approaching guideline-recommended levels

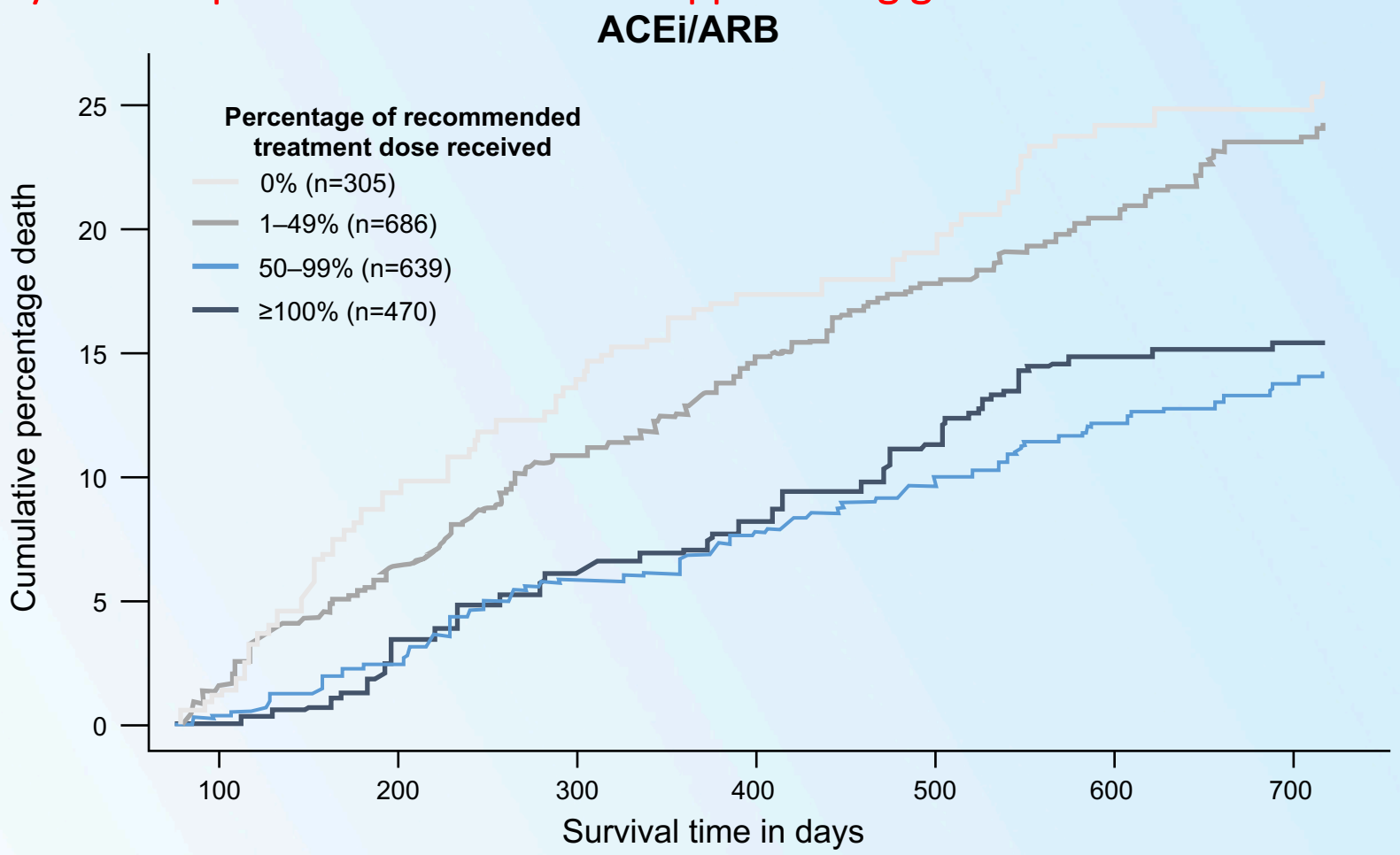
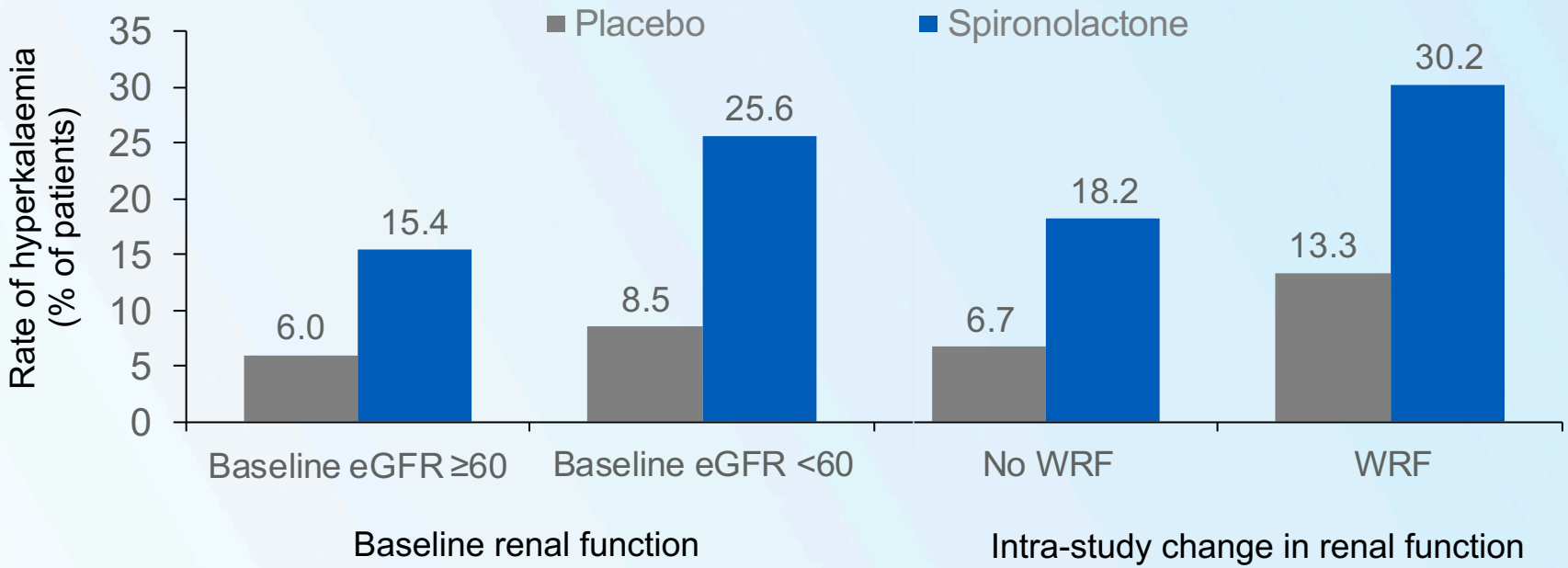


Figure shows adjusted mortality rate for patients receiving 0, 1–49, 50–99% or ≥100% of the recommended ACEi/ARB dose together with the risk set sizes at each time point.
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; RAASi, renin-angiotensin-aldosterone system inhibitor.
Ouwerkerk W, et al. *Eur Heart J.* 2017;0:1–10.

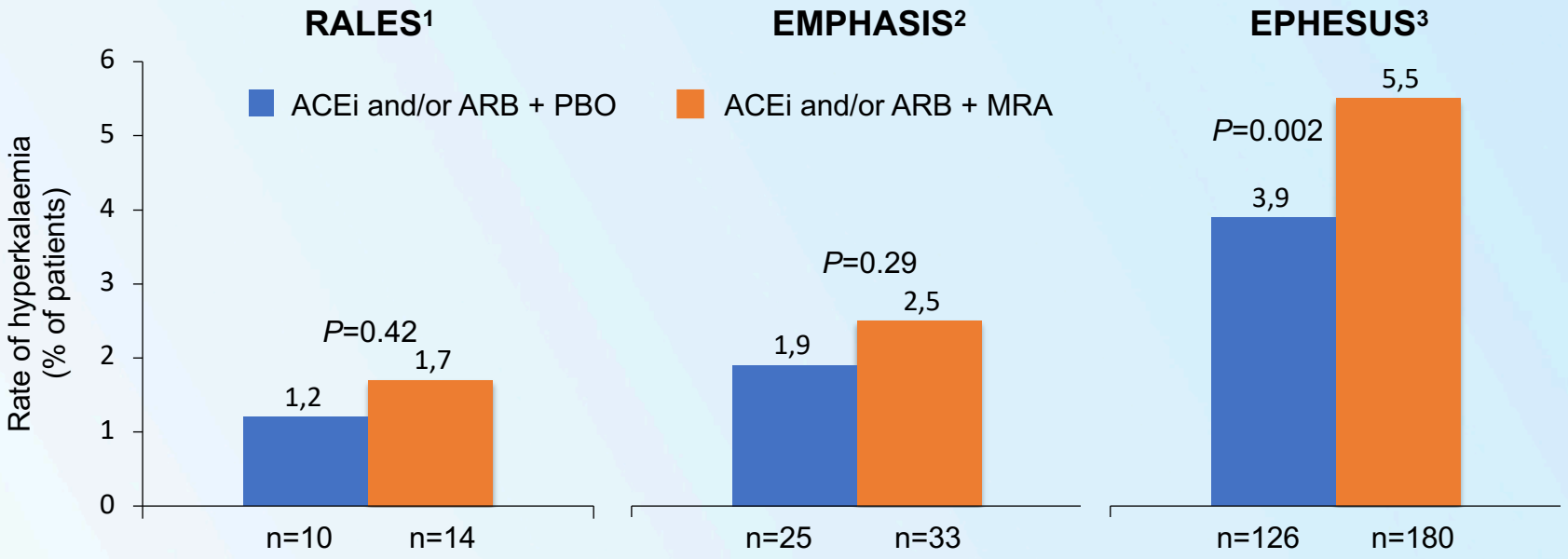
Renal function, spironolactone and hyperkalaemia in patients with HF: RALES analysis*

Impaired renal function and spironolactone use are associated with increased hyperkalaemia (>5.5 mEq/L) rates in patients with HF



Vardeny O, et al. J Am Coll Cardiol. 2012;60:2082–9

Risk of hyperkalaemia consistently increases in RAASi-treated patients, despite exclusion of patients at risk

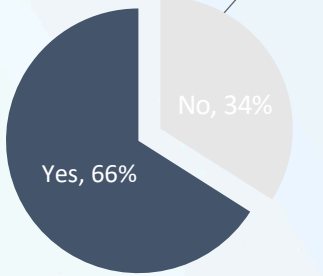


	RALES[1]	EMPHASIS[2]	EPHESUS[3]
Renal exclusion (mg/dL)	SrCr >2.5	GFR <30	SrCr >2.5
Potassium exclusion (mEq/L)	K^+ >5	K^+ >5	K^+ >5
Treatment	Spironolactone 25–50mg QD + ACEi placebo + ACEi	Eplerenone 25–50mg QD + ACEi and/or ARB placebo + ACEi and/or ARB	Eplerenone 25–50mg QD + ACEi or ARB placebo + ACEi or ARB

1.Pitt B, et al. N Engl J Med. 1999;341:709–17;
2. Zannad F, et al. N Engl J Med. 2011;364:11–21;
3. Pitt B, et al. N Engl J Med. 2003;348:1309–21.

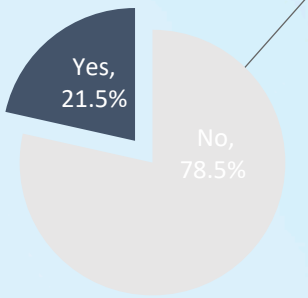
RAASi therapy is often withheld due to hyperkalaemia

ACEi



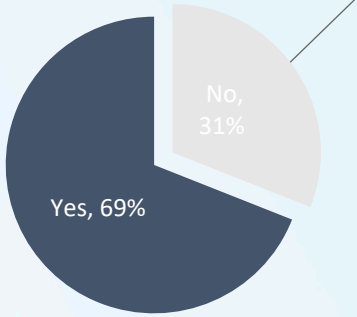
Contraindicated	**22.3%**
Not tolerated	**62.5%**
Reasons	
Cough	55.9%
Hypotension	22.5%
Worsening renal function	11.8%
Hyperkalaemia	3.9%
Other reasons	**15.2%**

ARB



Not indicated	**79.1%**
Contraindicated	**6.6%**
Not tolerated	**6.4%**
Reasons	
Hypotension	48.1%
Worsening renal function	26.7%
Cough	7.2%
Hyperkalaemia	5.5%
Other reasons	**7.9%**

MRA

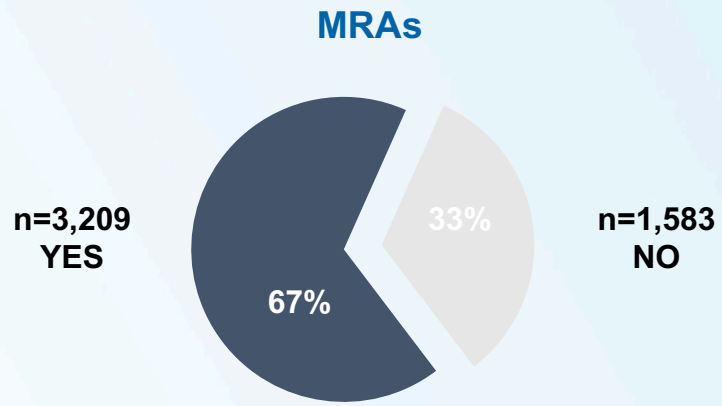


Not indicated	**61.8%**
Contraindicated	**18.9%**
Not tolerated	**14.9%**
Reasons	
Renal dysfunction	51.2%
Hyperkalaemia	31.4%
Gynecomastia	15.3%
Other reasons	**4.5%**

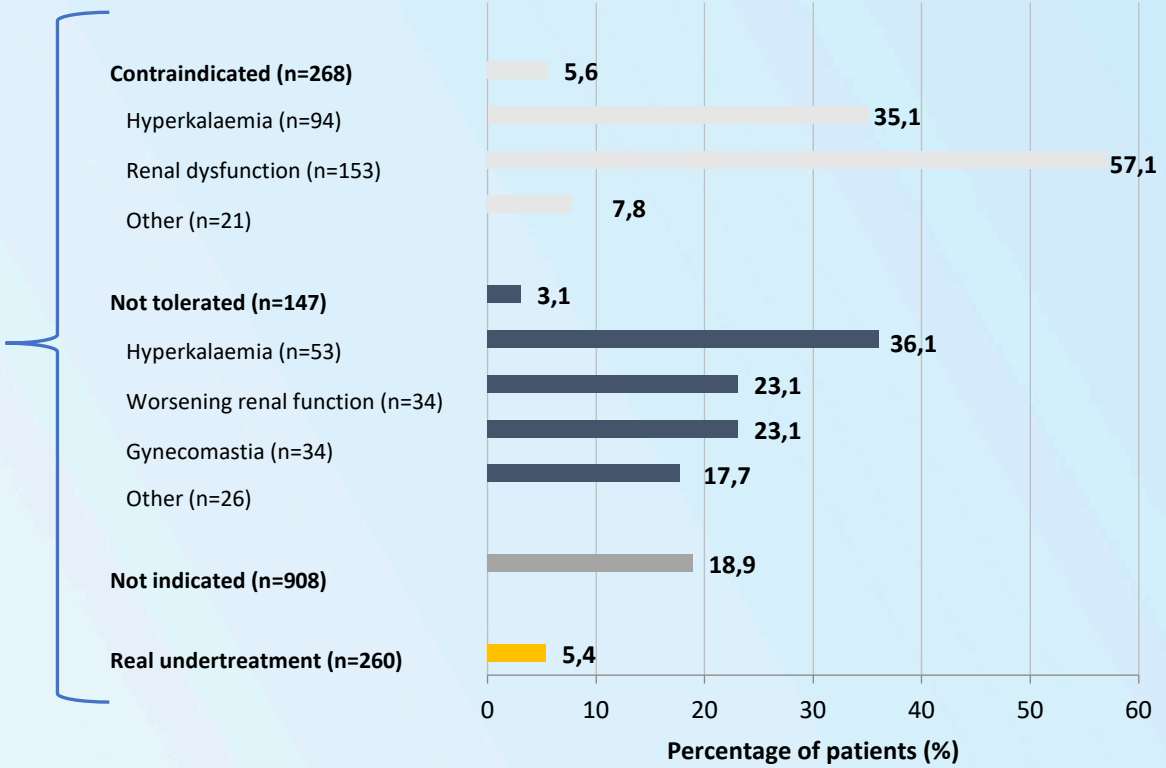
Komajda M, et al. Eur J Heart Fail. 2016;18:514–22.

The ESC registry examined reasons for not following ESC guideline recommendations for RAASi use

Are hospitalised or ambulatory patients with HF treated in accordance with ESC guidelines?



Reason for non-use of recommended treatments (MRA) in patients with HF*



Maggioni AP, et al. Eur J Heart Fail. 2013;15:1173–84.

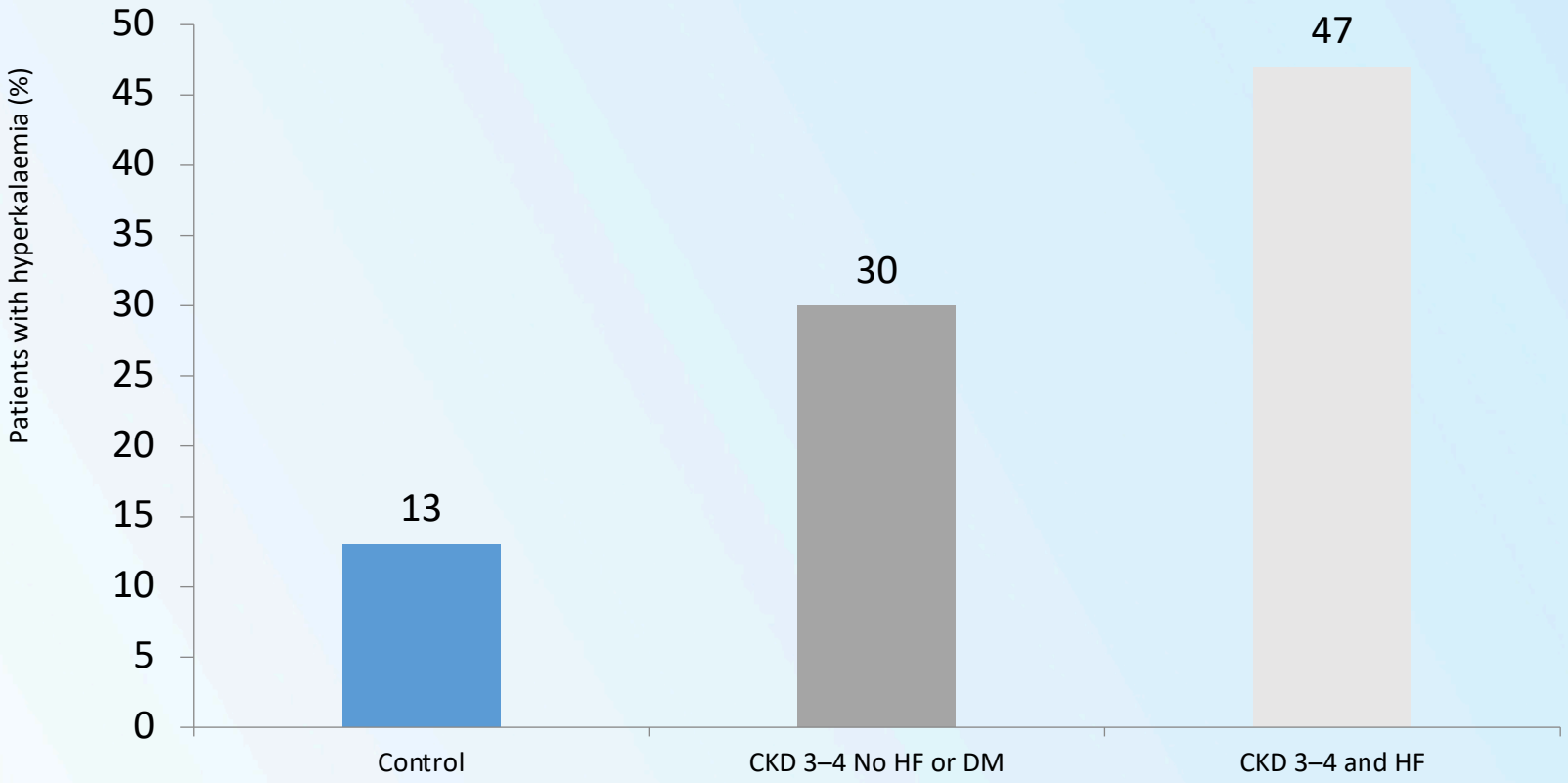
Reasons for underdosing of RAASi therapy
ESC registry

	At target, n (%)	Not at target, n (%)	Reason for not at target, n (%)	
ACEi (n=4,710)	1,380 (29.3)	3,330 (70.7)	1,123 (33.7)	Still in up-titration
			866 (26.0)	Symptomatic hypotension
			264 (7.9)	Worsening renal function
			85 (2.6)	Hyperkalaemia
			29 (0.9)	Cough
			5 (0.2)	Angio-oedema
			958 (28.8)	Other/unknown
ARB (n=1,500)	362 (24.1)	1,138 (75.9)	369 (32.4)	Still in up-titration
			295 (25.9)	Symptomatic hypotension
			115 (10.1)	Worsening renal function
			25 (2.2)	Hyperkalaemia
			1 (0.1)	Angio-edema
MRA (n=4,226)	1,290 (30.5)	2,936 (69.5)	864 (29.4)	Still in up-titration
			350 (11.9)	Hyperkalaemia
			284 (9.7)	Worsening renal function
			60 (2.0)	Gynecomastia
			1,378 (46.9)	Other/unknown

Maggioni AP, et al. Eur J Heart Fail. 2013;15:1173–84.

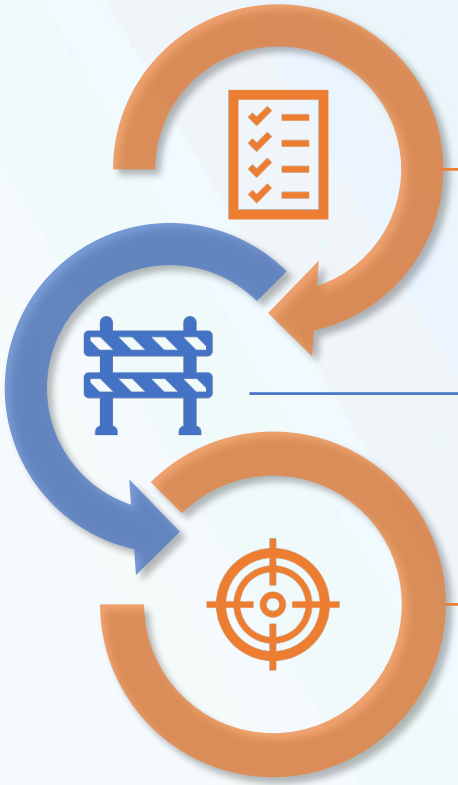
Risk for hyperkalaemia is highest in older patients with advanced CKD, DM and HF

5-year database prevalence of hyperkalaemia* in patients aged ≥65 years†



*Hyperkalaemia defined as highest reported potassium value ≥5.1 mEq/L in 2008–12; †Based on analysis of 1.63 million persons with potassium readings on two dates (2008–2012), with >1 value between 2.5 and 10 mEq/L. Control population composed of patients without CKD Stages 2–5, HF, DM or ESRD.
CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HF, heart failure.
Latts LM, et al. Presented at: ISPOR 2015, Philadelphia, PA: Poster#PVC33.

Overview: Rethinking Hyperkalemia to Optimize RAASi Therapy



CKD and HF treatment guidelines recommend RAASi[a] therapy to improve patient outcomes[1-4]

- RAASi should be initiated and titrated to the highest approved dose that is tolerated

Despite the proven benefits of RAASi therapy, hyperkalemia can be a barrier to achieving and maintaining guideline-recommended doses[1-8]

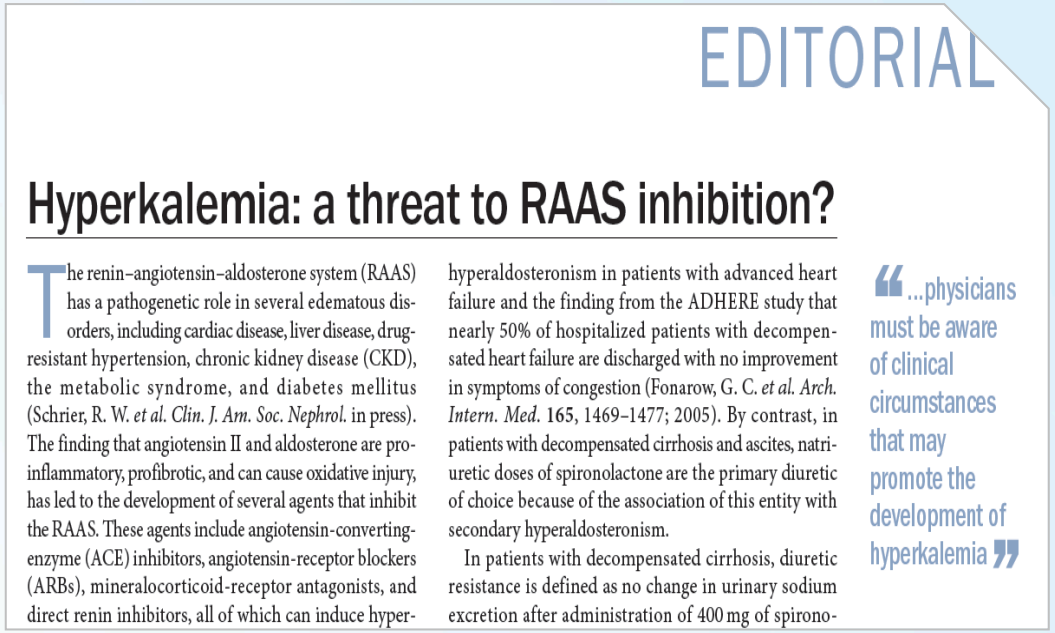
Based on the current evidence, CKD and HF treatment guidelines now include the use of novel K^+ binders as an option for controlling K^+ to enable optimal RAASi[a] therapy[1-4,9]

[a]KDIGO 2020 clinical practice guideline for diabetes management in CKD and KDIGO 2021 clinical practice guideline for the management of blood pressure in CKD define RASi therapy as ACEi or ARB.[1,2] 2021 ESC HF guidelines for the diagnosis and treatment of acute and chronic heart failure define RAASi therapy as ACEi, ARNI, and MRA.[3] 2022 AHA/ACC/HFSA guideline for the management of HF define RAASi therapy as ACEi, ARB, ARNi, and MRA.[4]

ACC = American College of Cardiology; ACEi = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CKD = chronic kidney disease; ESC = European Society of Cardiology; HF = heart failure; HFSA = Heart Failure Society of America; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; RASi = renin-angiotensin system inhibitor.

References in slide notes.

The risk of hyperkalaemia is one of the principal factors limiting RAASi use



EDITORIAL

Hyperkalemia: a threat to RAAS inhibition?

The renin–angiotensin–aldosterone system (RAAS) has a pathogenetic role in several edematous disorders, including cardiac disease, liver disease, drug-resistant hypertension, chronic kidney disease (CKD), the metabolic syndrome, and diabetes mellitus (Schrier, R. W. *et al. Clin. J. Am. Soc. Nephrol.* in press). The finding that angiotensin II and aldosterone are pro-inflammatory, profibrotic, and can cause oxidative injury, has led to the development of several agents that inhibit the RAAS. These agents include angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), mineralocorticoid-receptor antagonists, and direct renin inhibitors, all of which can induce hyperaldosteronism in patients with advanced heart failure and the finding from the ADHERE study that nearly 50% of hospitalized patients with decompensated heart failure are discharged with no improvement in symptoms of congestion (Fonarow, G. C. *et al. Arch. Intern. Med.* **165**, 1469–1477; 2005). By contrast, in patients with decompensated cirrhosis and ascites, natriuretic doses of spironolactone are the primary diuretic of choice because of the association of this entity with secondary hyperaldosteronism.

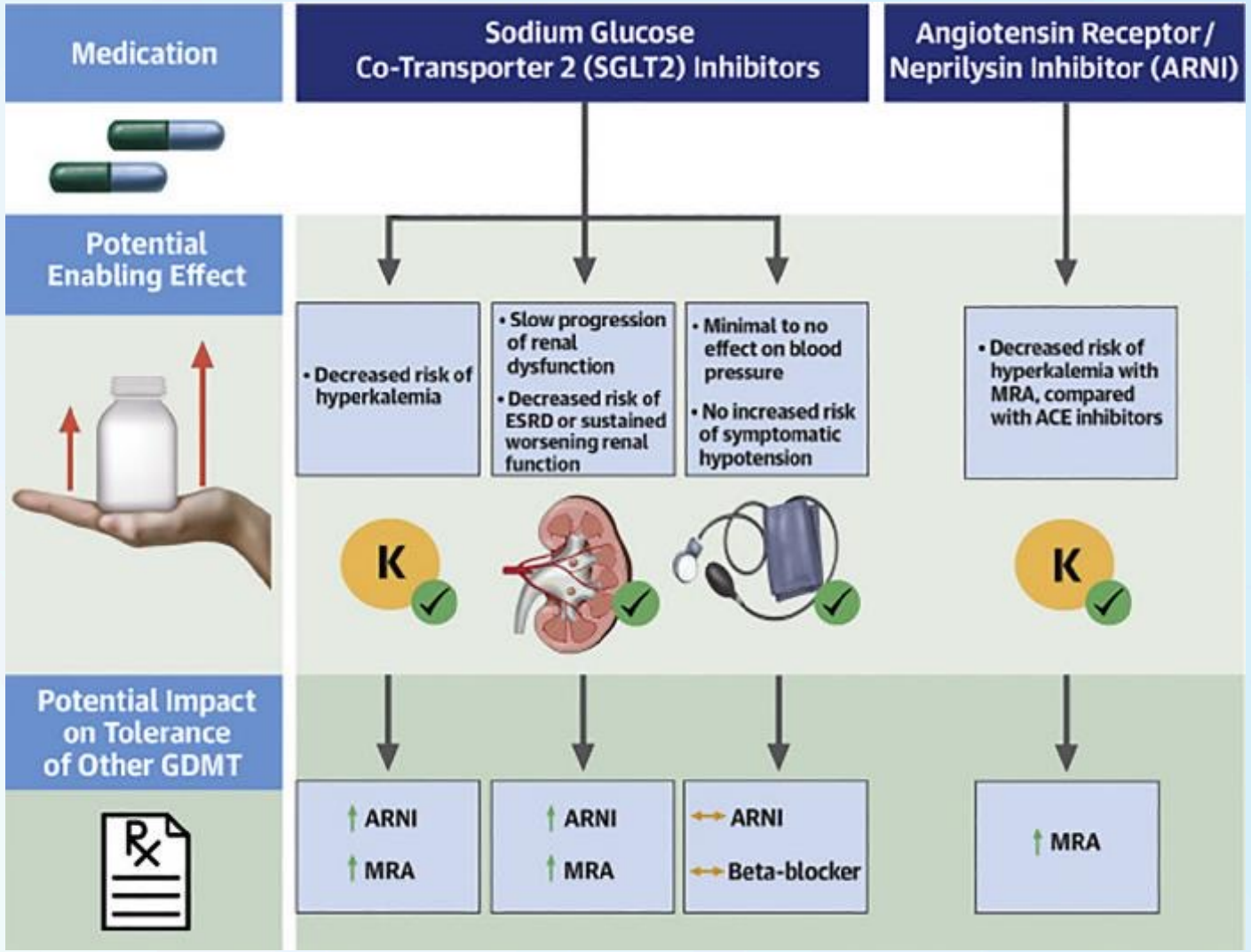
In patients with decompensated cirrhosis, diuretic resistance is defined as no change in urinary sodium excretion after administration of 400 mg of spirono-

"...physicians must be aware of clinical circumstances that may promote the development of hyperkalemia"

"An extensive study of patients with CKD or heart failure who were treated with RAAS inhibitors revealed an incidence of hyperkalaemia of 5–10%"

– Weir M, Rolfe M. *Clin J Am Soc Nephrol.* 2010;5:531–48

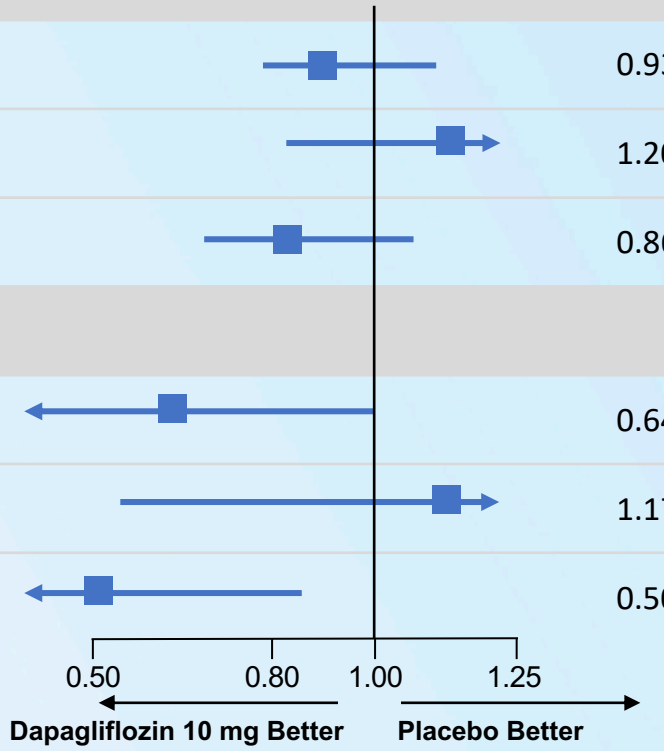
Schrier RW. Nat Rev Nephrol. 2010;6:245–6.



Greene SJ, Butler J, Metra M. Eur J Heart Fail. 2021 Jul 14. doi: 10.1002/ejhf.2301.

Dapagliflozin may attenuate the risk of moderate/severe hyperkalemia in patients treated with an MRA at baseline

Endpoint	Dapagliflozin 10 mg n/N	Dapagliflozin 10 mg Rate per 100 pt-yrs	Placebo n/N	Placebo Rate per 100 pt-yrs	HR (95% CI)
Mild Hyperkalemia (>5.5 mmol/L)					
All patients	245/2298	8.2	262/2310	8.8	0.93 (0.78, 1.11)
No MRA at baseline	63/661	7.1	58/684	6.5	1.20 (0.84, 1.72)
MRA at baseline	182/1637	8.6	204/1626	9.8	0.86 (0.70, 1.05)
Moderate/Severe Hyperkalemia (>6.0 mmol/L)					
All patients	36/2364	1.1	51/2364	1.6	0.64 (0.42, 0.99)
No MRA at baseline	13/676	1.4	11/697	1.1	1.17 (0.52, 2.62)
MRA at baseline	23/1688	1.0	40/1667	1.7	0.50 (0.29, 0.85)

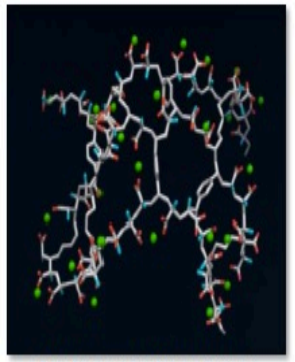


HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; MRA = mineralocorticoid-receptor antagonist; n = number of events; pt-yrs = patient-years.

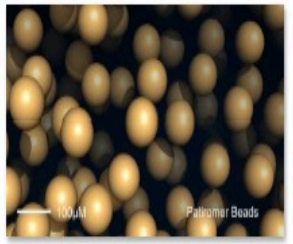
Kristensen SL. Presented at: ESC Congress - The Digital Experience; August 29-September 1, 2020.

Patiromer

- Orally administered, nonabsorbed calcium-based potassium-binding polymer[a]
- Indicated for the treatment of hyperkalemia[b]
  - Not an emergency treatment for life-threatening hyperkalemia
- Designed to be fully ionized at the physiological pH of the colon[a]
- Mechanism of action[a]
  - Exchanges calcium for potassium in the colon
- Drug-drug interactions: take 3 hours apart from other oral medications[b]



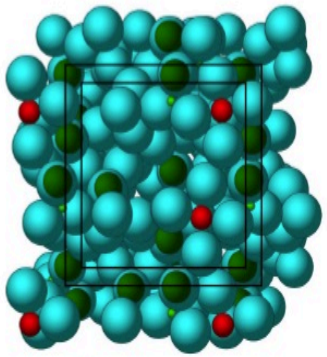
High-capacity polymer

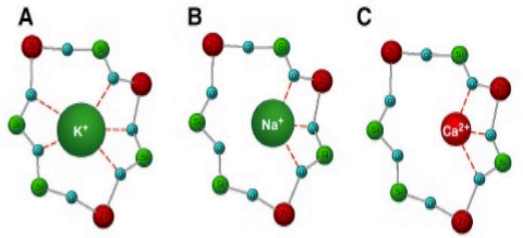


Uniform, spherical patiromer beads

Sodium Zirconium Cyclosilicate (ZS-9)

- Inorganic, crystalline potassium binder
- Orally administered
- Sodium-based, potassium-selective, cation-exchanger
- Primarily active in the gastrointestinal tract





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]

K-levels 4.5 - 5.0 mEq/L

Not on maximal tolerated guideline-recommended target dose of RAASi

Initiate/up-titrate RAASi therapy and closely monitor K-levels.

If K-levels >5.0 mEq/L initiate an approved K-lowering agent.

K-levels >5.0 - ≤6.5 mEq/L

Not on maximal tolerated guideline-recommended target dose of RAASi

Iniitiate an approved K-lowering agent.

If K-levels <5.0 mEq/L detected, up-titrate RAASi therapy

K-level should be closely monitored and K-lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified

K-levels >5.0 - ≤6.5 mEq/L

On maximal tolerated guideline-recommended target dose of RAASi

Treatment with K

lowering may be initiate

K-level should be closely monitored and K-lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified

K-levels >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

1 mEq= 1 mmol

ESC Working Group Cardiovascular Pharmacotherapy

2021 ESC GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE

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

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

Sodium zirconium cyclosilicate and patiromer 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.

European Journal of Internal Medicine 119 (2024) 109–117

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

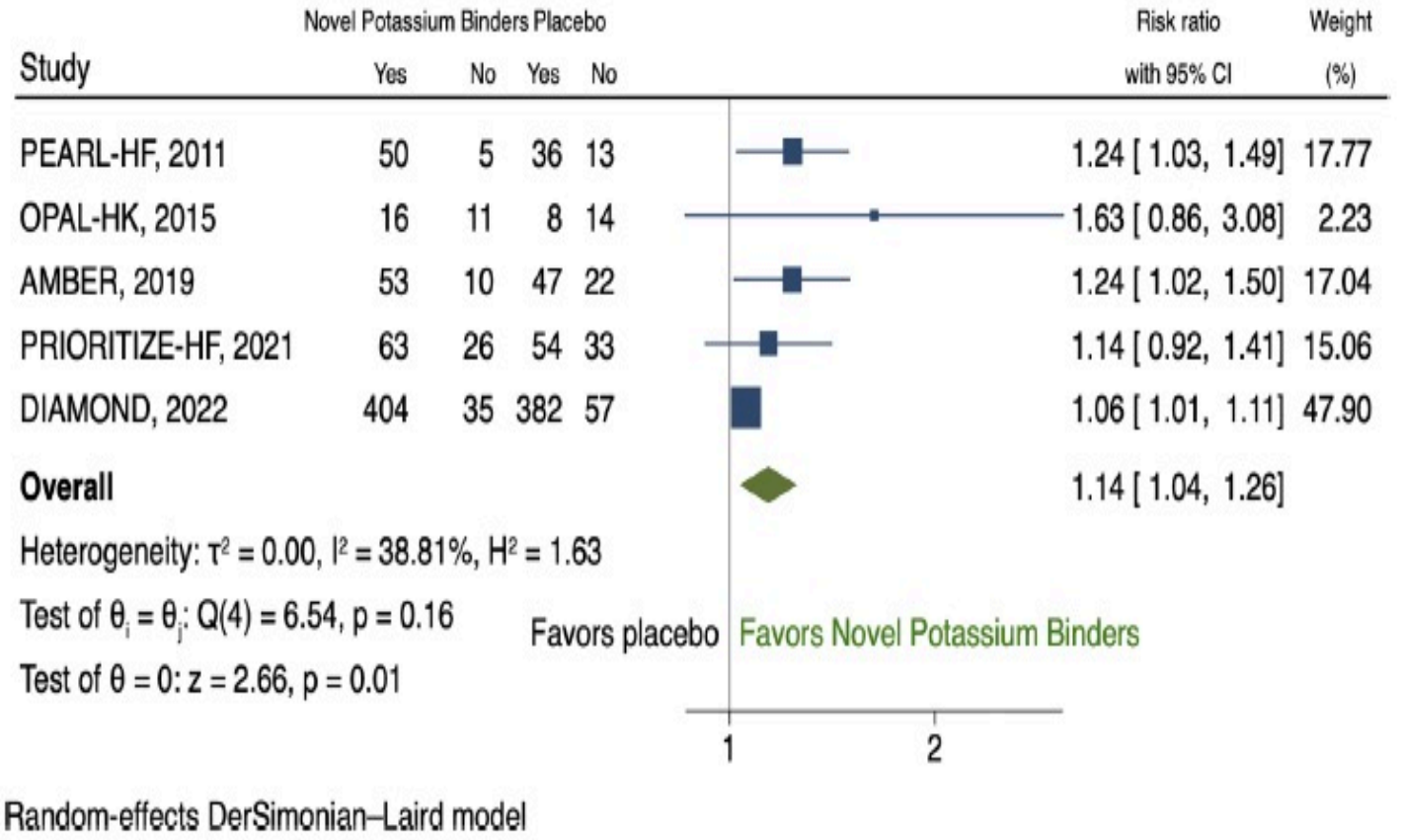
Original article

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

Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy

Optimization of RAASi therapy



European Journal of Internal Medicine 119 (2024) 109–117

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

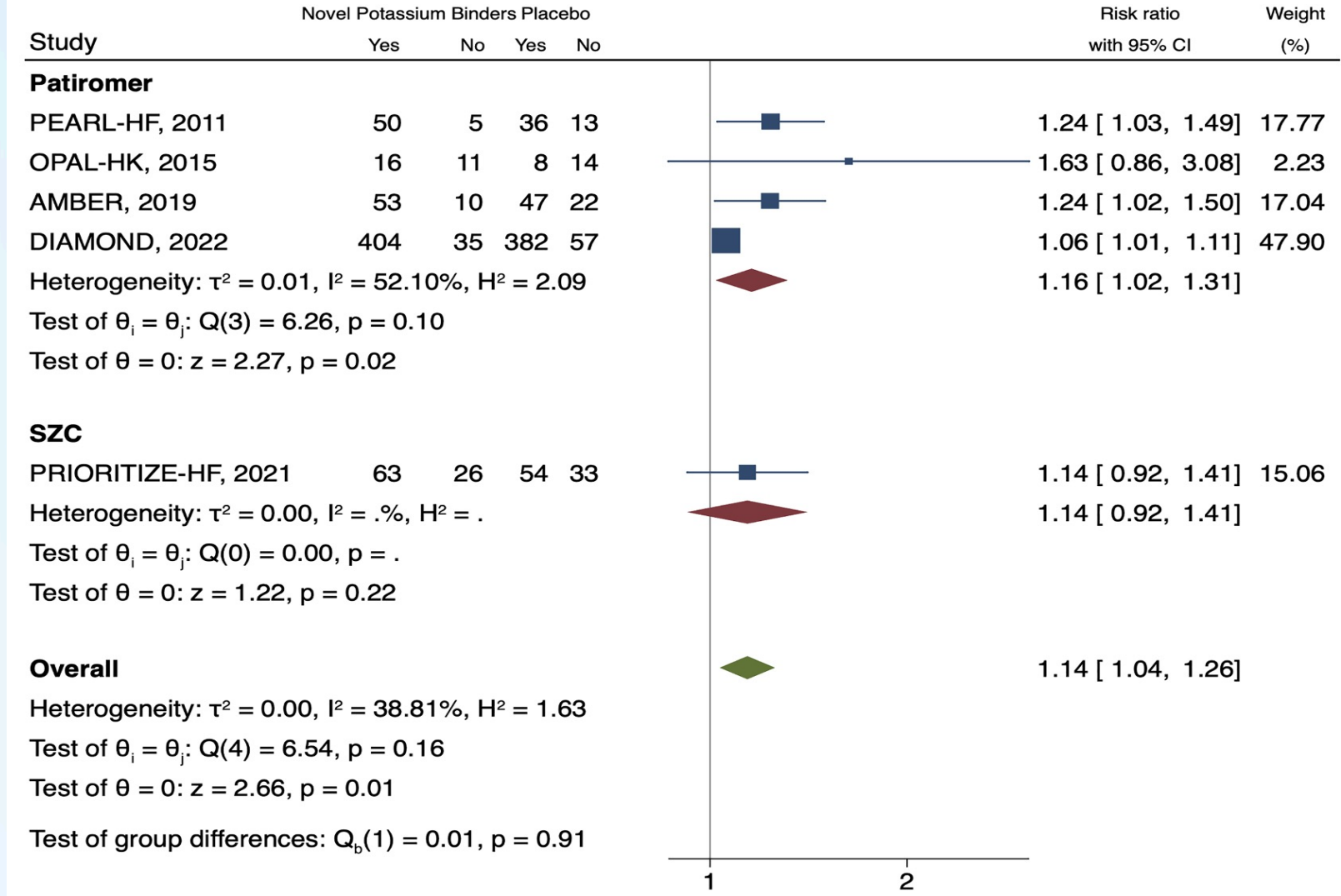
Original article

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

Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy

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



RESEARCH ARTICLE

Predictors for repeated hyperkalemia and potassium trajectories in high-risk patients — A population-based cohort study

Kasper Adelborg[1]*, Sia Kromann Nicolaisen[1], Pål Hasvold[2], Eirini Palaka[3], Lars Pedersen[1], Reimar Wernich Thomsen[1]

1 Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, **2** AstraZeneca Nordic, Medical Department, Etterstad, Oslo, Norway, **3** AstraZeneca, Global Payer Evidence, Cambridge, United Kingdom

* kade@clin.au.dk

- **Repeated hyperkalemia was common among the explored cohorts.**
- **The first hyperkalemia event was an indicator of increased median potassium levels.**
- **Predictors may identify patients likely to benefit from intensified monitoring and intervention.**

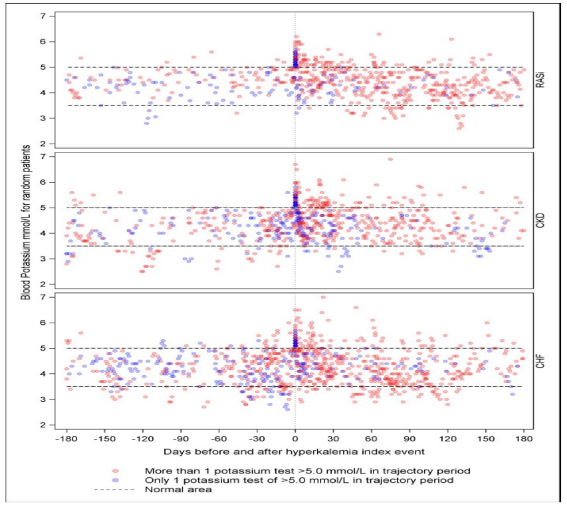


Fig 2. All potassium test results for 50 randomly sampled individuals in three cohorts before and after first hyperkalemia event, by patients with one and more than one hyperkalemia event. Abbreviations: CHF, chronic heart failure; CKD, chronic kidney disease; RASi, renin angiotensin system inhibitors Patients were at risk of hyperkalemia before their first hyperkalemia event if they did not fulfil the criteria for chronic heart failure, chronic kidney disease, and RASi treatment, respectively.

https://doi.org/10.1371/journal.pone.0218739.g002

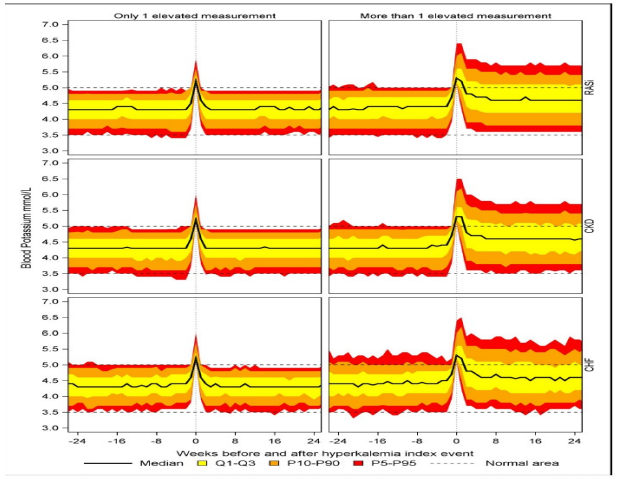


Fig 1. Median potassium levels (mmol/L) in the three patient cohorts before and after a first hyperkalemia event. Data are shown separately for patients with one and more than one hyperkalemia event during the 6 months trajectory period. Abbreviations: CHF, chronic heart failure; CKD, chronic kidney disease; RASi, renin angiotensin system inhibitors Patients were at risk of hyperkalemia before their first hyperkalemia event if they did not fulfil the criteria for chronic heart failure, chronic kidney disease, and RASi treatment, respectively.

Hyperkalemia is common in patients with HFrEF/HFmrEF (particularly in patients with CKD and diabetes

Hyperkalemia represents one of the main clinical factors that limit the achievement of OMT

Appropriate use of potassium binders can help physicians achieve the OMT

Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

Muthiah Vaduganathan, Brian L Claggett, Pardeep S Jhund, Jonathan W Cunningham, João Pedro Ferreira, Faiez Zannad, Milton Packer, Gregg C Fonarow, John J V McMurray, Scott D Solomon

Summary

Background Three drug classes (mineralocorticoid receptor antagonists [MRAs], angiotensin receptor–neprilysin inhibitors [ARNIs], and sodium/glucose cotransporter 2 [SGLT2] inhibitors) reduce mortality in patients with heart failure with reduced ejection fraction (HFrEF) beyond conventional therapy consisting of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and β blockers. Each class was previously studied with different background therapies and the expected treatment benefits with their combined use are not known. Here, we used data from three previously reported randomised controlled trials to estimate lifetime gains in event-free survival and overall survival with comprehensive therapy versus conventional therapy in patients with chronic HFrEF.

Methods In this cross-trial analysis, we estimated treatment effects of comprehensive disease-modifying pharmacological therapy (ARNI, β blocker, MRA, and SGLT2 inhibitor) versus conventional therapy (ACE inhibitor or ARB and β blocker) in patients with chronic HFrEF by making indirect comparisons of three pivotal trials, EMPHASIS-HF (n=2737), PARADIGM-HF (n=8399), and DAPA-HF (n=4744). Our primary endpoint was a composite of cardiovascular death or first hospital admission for heart failure; we also assessed these endpoints individually and assessed all-cause mortality. Assuming these relative treatment effects are consistent over time, we then projected incremental long-term gains in event-free survival and overall survival with comprehensive disease-modifying therapy in the control group of the EMPHASIS-HF trial (ACE inhibitor or ARB and β blocker).

Findings The hazard ratio (HR) for the imputed aggregate treatment effects of comprehensive disease-modifying therapy versus conventional therapy on the primary endpoint of cardiovascular death or hospital admission for heart failure was 0·38 (95% CI 0·30–0·47). HRs were also favourable for cardiovascular death alone (HR 0·50 [95% CI 0·37–0·67]), hospital admission for heart failure alone (0·32 [0·24–0·43]), and all-cause mortality (0·53 [0·40–0·70]). Treatment with comprehensive disease-modifying pharmacological therapy was estimated to afford 2·7 additional years (for an 80-year-old) to 8·3 additional years (for a 55-year-old) free from cardiovascular death or first hospital admission for heart failure and 1·4 additional years (for an 80-year-old) to 6·3 additional years (for a 55-year-old) of survival compared with conventional therapy.

Interpretation Among patients with HFrEF, the anticipated aggregate treatment effects of early comprehensive disease-modifying pharmacological therapy are substantial and support the combination use of an ARNI, β blocker, MRA, and SGLT2 inhibitor as a new therapeutic standard.

Funding None.

Published Online
May 21, 2020
https://doi.org/10.1016/S0140-6736(20)30748-0

See Online/Comment
https://doi.org/10.1016/S0140-6736(20)30929-6

Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (M Vaduganathan MD, B L Claggett PhD, J W Cunningham MD, Prof S D Solomon MD); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK (P S Jhund PhD, Prof J J V McMurray MD); Université de Lorraine INSERM, Centre d'Investigations Cliniques Plurithématique 1433, INSERM U1116, CHRU de Nancy, F-CRIN INI-CRCT, Nancy, France (J Pedro Ferreira MD, Prof F Zannad MD); Department of Physiology and Cardiothoracic Surgery, University of Porto, Porto, Portugal (J Pedro Ferreira); Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA (Prof M Packer MD); Imperial College, London, UK (Prof M Packer); and Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles Medical Center, Los Angeles, CA, USA (Prof G C Fonarow MD)

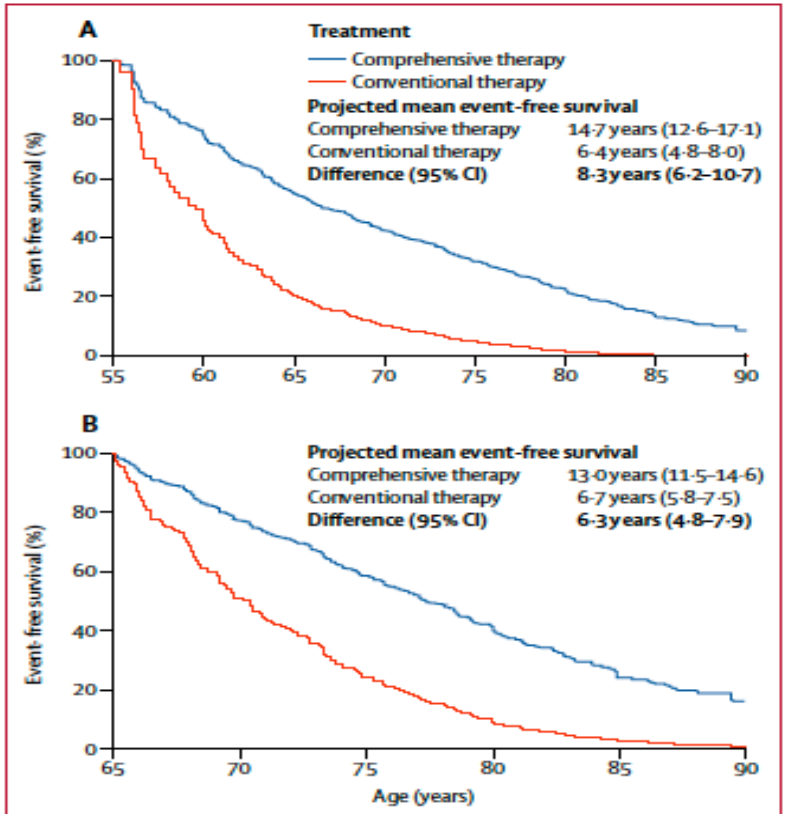


Figure 2: **Event-free survival with comprehensive disease-modifying therapy vs conventional therapy**
Kaplan-Meier estimated curves for patients starting at age 55 years (A) and 65 years (B) for primary endpoint event-free survival. Comprehensive therapy (simulated) consisted of an ARNI, β blocker, MRA, and SGLT2 inhibitor; conventional therapy (EMPHASIS-HF[6] control group) consisted of an ACE inhibitor or ARB and β blocker. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. SGLT2 inhibitor=sodium/glucose cotransporter 2 inhibitor.