I PERCORSI APPROPRIATI
ASSISTENZIALI E TERAPEUTICI
IN PREVENZIONE SECONDARIA

Approccio al paziente
ad alto rischio cardiovascolare

10 GIUGNO
2022

CORSO WEBINAR
FAD SINCRONA

Trattamento dell'iperkaliemia nello scompenso cardiaco

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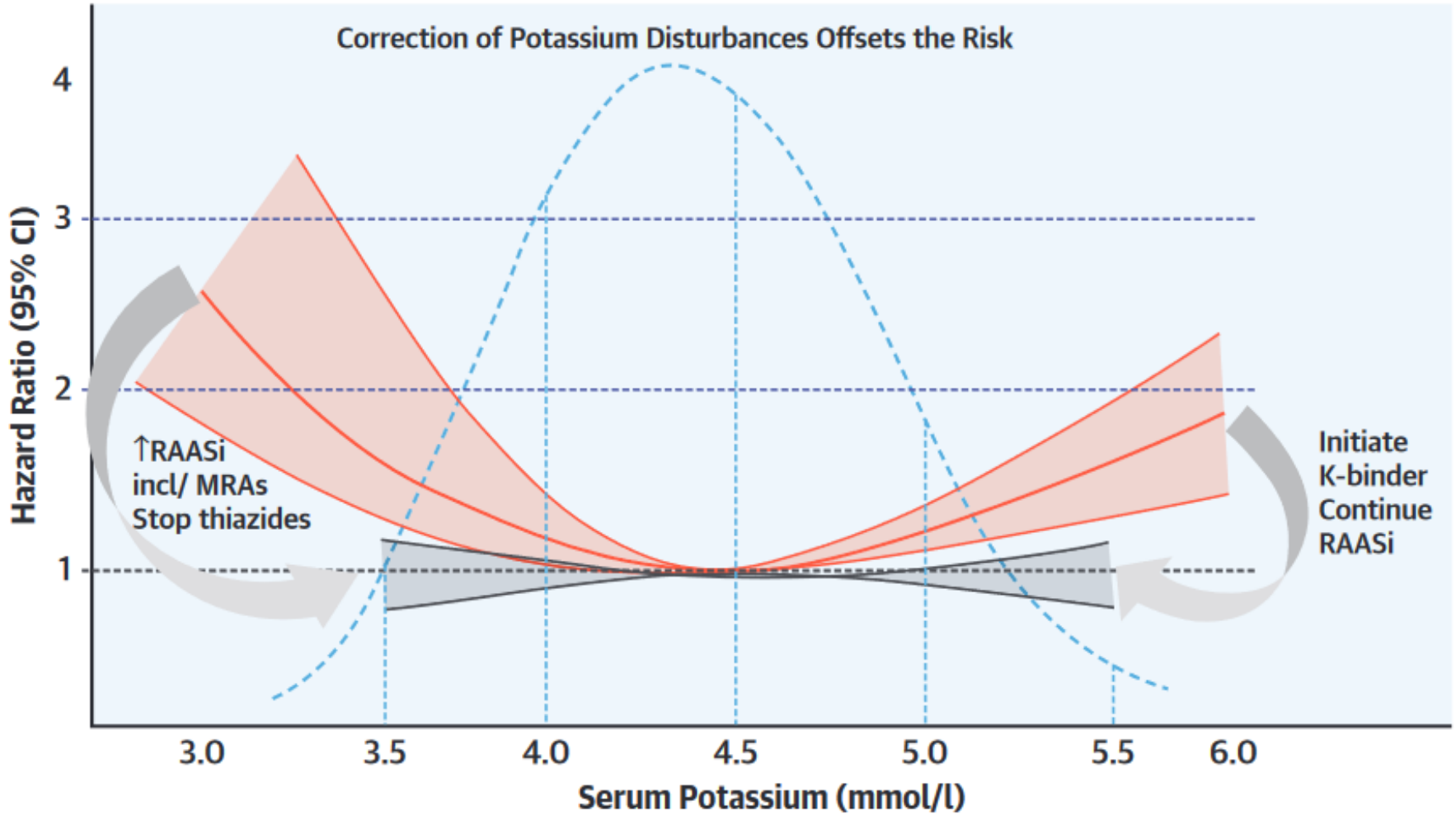
Conflitto d’interesse : NESSUNO

Association of Serum Potassium With All-Cause Death and the Benefit of a Prompt Correction of Dyskalemia



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

European Heart Journal (2016) 37, 2129–2200
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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

The management of acute hyperkalaemia (>6.0 mmol/L) may require a short-term cessation of potassium-retaining agents and RAAS inhibitors, but this should be minimized and RAAS inhibitors should be carefully reintroduced as soon as possible while monitoring potassium levels. A Cochrane review[452] found no trial evidence of major outcome benefits for any emergency therapy regimen for hyperkalaemia. Two new potassium binders (patiromer and sodium zirconium cyclosilicate) are currently under consideration for regulatory approval.[453,454] Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium[455] and preventing recurrent hyperkalaemia in patients with HF and CKD in the context of treatment with RAAS inhibitors.[456]

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

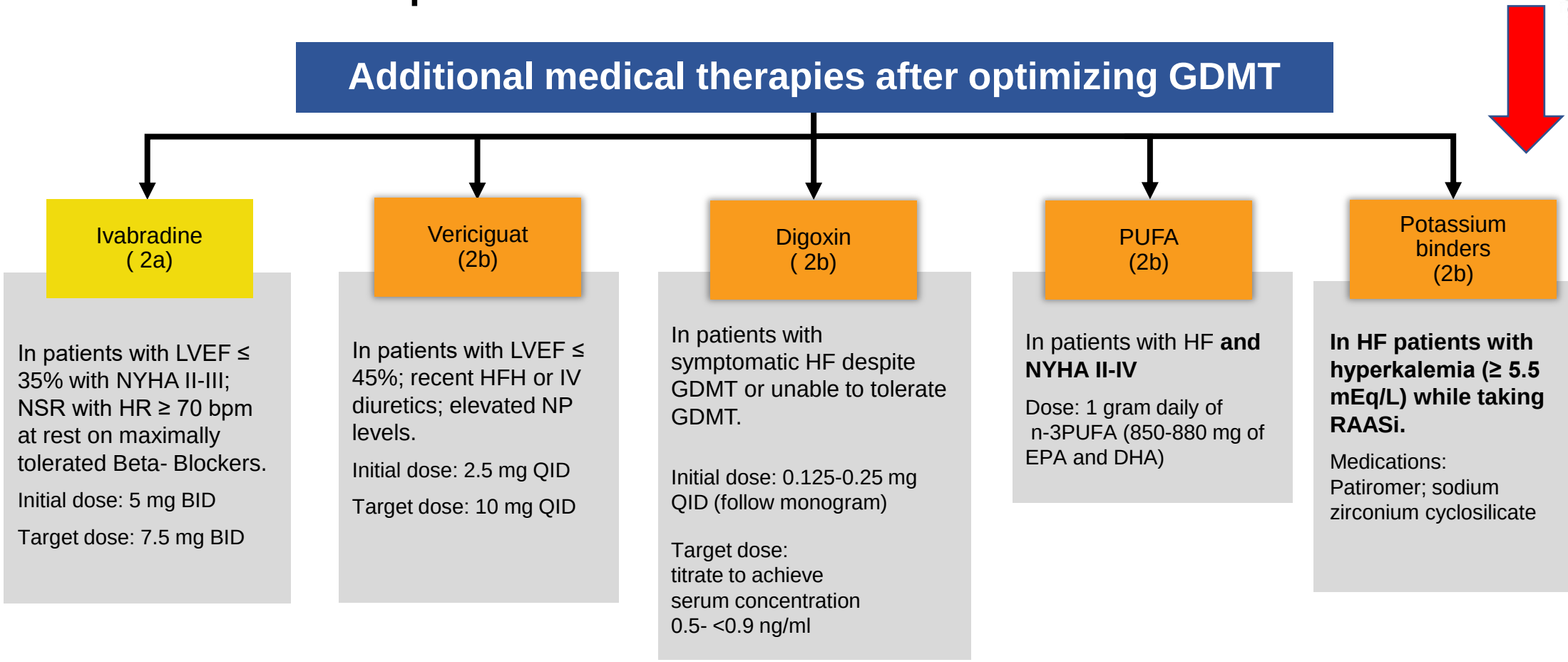
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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

necrosis.[760] Patiromer or SZC increase faecal potassium excretion and act mainly in the colon. Both compounds are effective in normalizing elevated potassium levels, maintaining normokalaemia over time and preventing the recurrence of hyperkalaemia and can be considered for treatment of hyperkalaemia[766–768] (see *Supplementary Table 24*).

Renal dysfunction and hyperkalaemia are the major causes of underuse of RAAS inhibitors, particularly MRA, in clinical practice.[342,753,758,769–771] Administration of the potassium-lowering agents, patiromer or SZC, may allow their initiation or uptitration in a larger proportion of patients. This hypothesis was tested in double-blind, placebo-controlled, randomized trials with patiromer or placebo administration to patients with CKD and hyperkalaemia, or discontinuation of RAAS inhibitors for hyperkalaemia, and with an indication for spironolactone for HF and/or resistant hypertension. Patiromer was more likely to lower serum potassium and decreased episodes of hyperkalaemia than spironolactone initiation and uptitration.[772–775] The ongoing RCT DIAMOND (NCT03888066) is testing the impact on clinical outcomes of a strategy based on patiromer administration, compared with placebo, in patients with HFrEF who are hyperkalaemic while on RAAS inhibitors or with a history of hyperkalaemia with subsequent reduction or discontinuation of a RAAS inhibitor[776,777] (see *Supplementary text 13.1*).

Additional Medical Therapies after GDMT Optimization



Abbreviations: DHA indicates docosaexaenoic acid; EPA, eicosapentaenoic acid; GDMT, guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; HR, heart rate; IV, intravenous; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NSR, normal sinus rhythm; NYHA, New York Heart Association; PUFA, polyunsaturated fatty acid; and RAASi, renin-angiotensin-aldosterone system inhibitors.

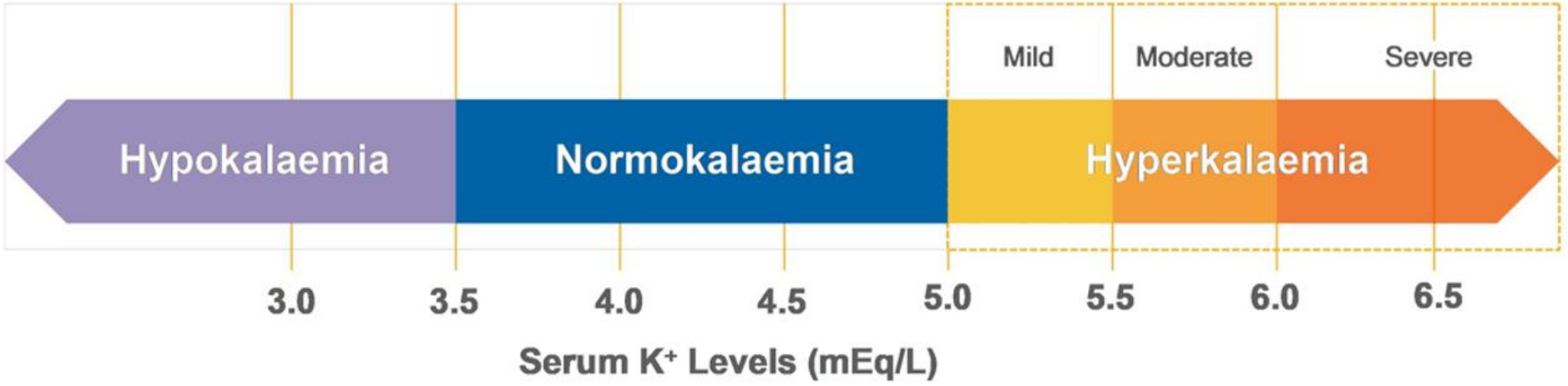
Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

IPERKALIEMIA : RISK MARKER OR RISK FACTOR?

- L'iperkaliemia si definisce come livello del potassio plasmatico al disopra del valore di riferimento normale (3.0-5.0 mEq/L).

  Sono stati utilizzati valori soglia diversi per indicare livelli diversi di gravità (>5.0, >5.5, o >6 mEq/L)

- L'iperkaliemia ha una prevalenza del 2-3% nella popolazione generale, ma nei pazienti con IRC la prevalenza può arrivare al 50%
- L'iperkaliemia abitualmente è asintomatica, ma, se non trattata, può comportare conseguenze cardiache gravi ed anche extracardiache (sintomi neuromuscolari, acidosi metabolica,…)



Kovesdy CP. *Am J Med*. 2015;128:1281–7.

I problemi da trattare

- Perché è importante l'Iperkaliemia?
- Incidenza dell'Iperkaliemia e fattori di rischio in pazienti con IRC e /o SC
- L'impegno clinico e di risorse
- Limiti delle strategie attuali di trattamento
- Sfide future nella gestione di pazienti complessi con iperkaliemia

CKD, chronic kidney disease; HF, heart failure

I problemi da trattare

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Even small increases in K^+ are strongly associated with mortality in a critical care setting

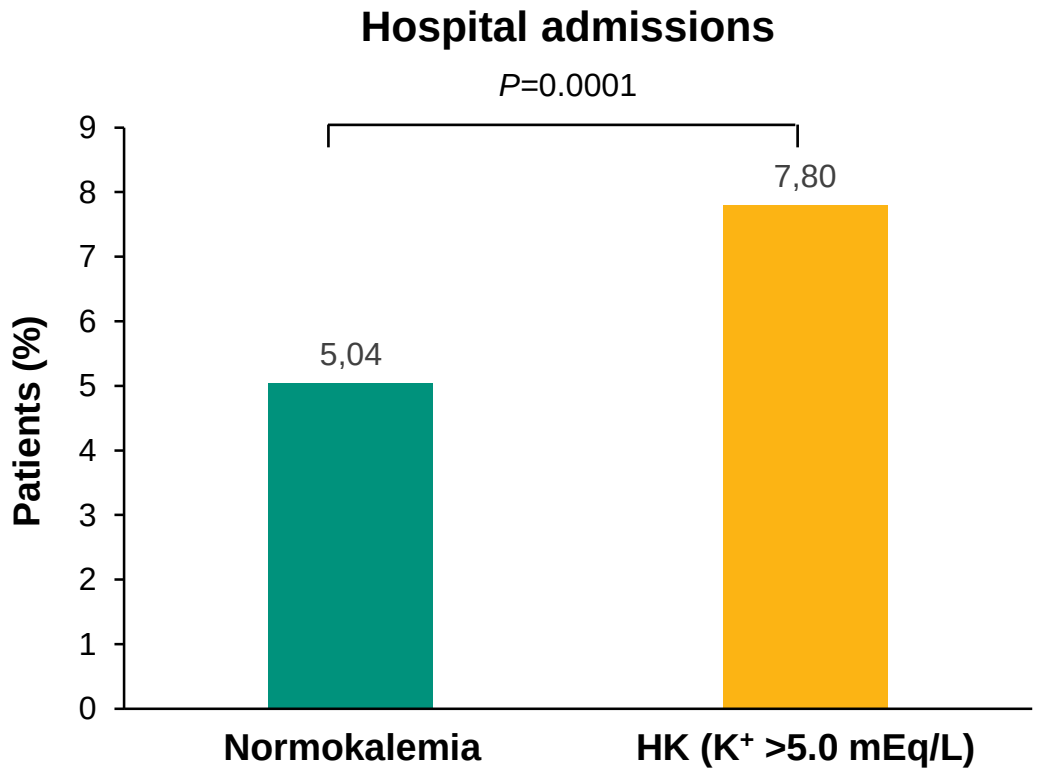
K^+ level	5.5–6.0 mEq/L	6.0–6.5 mEq/L	≥6.5 mEq/L
OR (95% CI)	1.64 (1.44, 1.86)	1.75 (1.46, 2.09)	1.77 (1.52, 2.05)
P value	<0.0001[a]	<0.0001[a]	<0.0001[a]

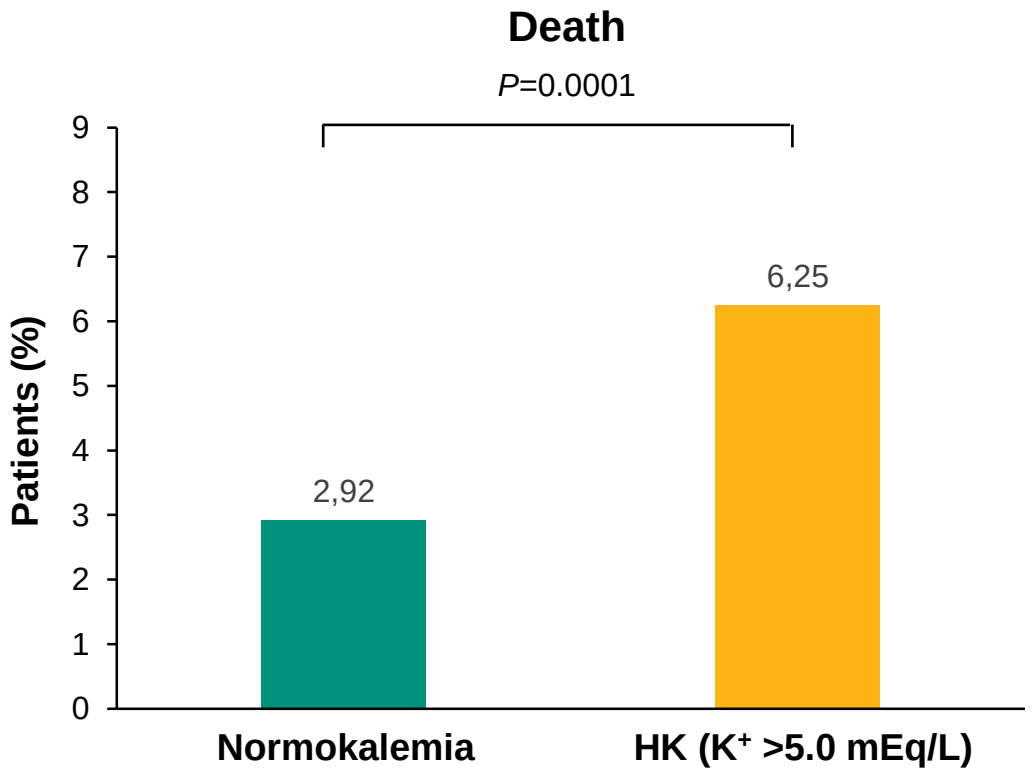
- K^+ concentration was a particularly strong predictor of all-cause mortality with a significant risk gradient across K^+ groups:
  - The adjusted ORs for in-hospital mortality were 1.64, 1.75 and 1.77 in patients with K^+ values of 5.5–6.0, 6.0–6.5 and ≥6.5 mEq/L, respectively, compared with those in the 4.0–4.5 mEq/L group (*P*<0.0001 for all comparisons)

[a]Significant difference vs K^+ 4.0–4.5 mEq/L
CI, confidence interval; OR, odds ratio
McMahon GM, et al. *Intensive Care Med* 2012;38:1834–1842

HK is associated with a higher incidence of hospital admissions and death in patients with HF and HTN

Retrospective US cohort (N=15,803) of patients with established CVD (HF and HTN) treated with antihypertensive medications





CVD, cardiovascular disease; HF, heart failure; HK, hyperkalemia; HTN, hypertension

Jain N, et al. *Am J Cardiol* 2012;109:1510–1513

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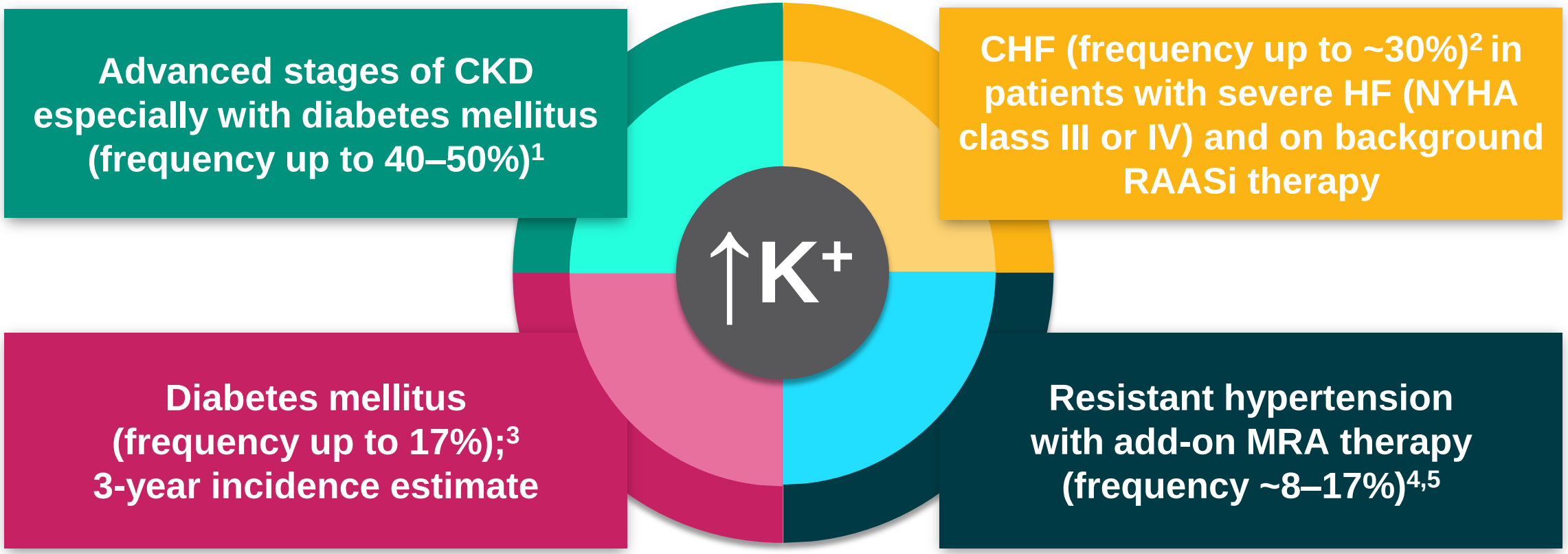
Certain patient subgroups have a high incidence of HK

The incidence of HK in the general population is 2–3%[1]



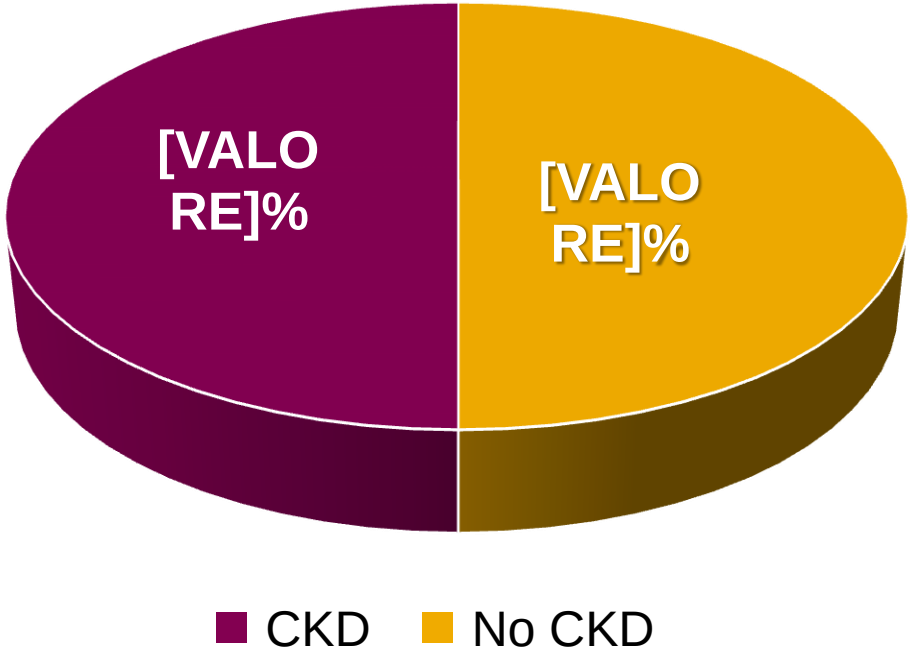
HK is defined as K^+ >5.0 mEq/L[6]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHF, chronic heart failure; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalemia; NYHA, New York Heart Association; MRA, mineralocorticoid receptor antagonist

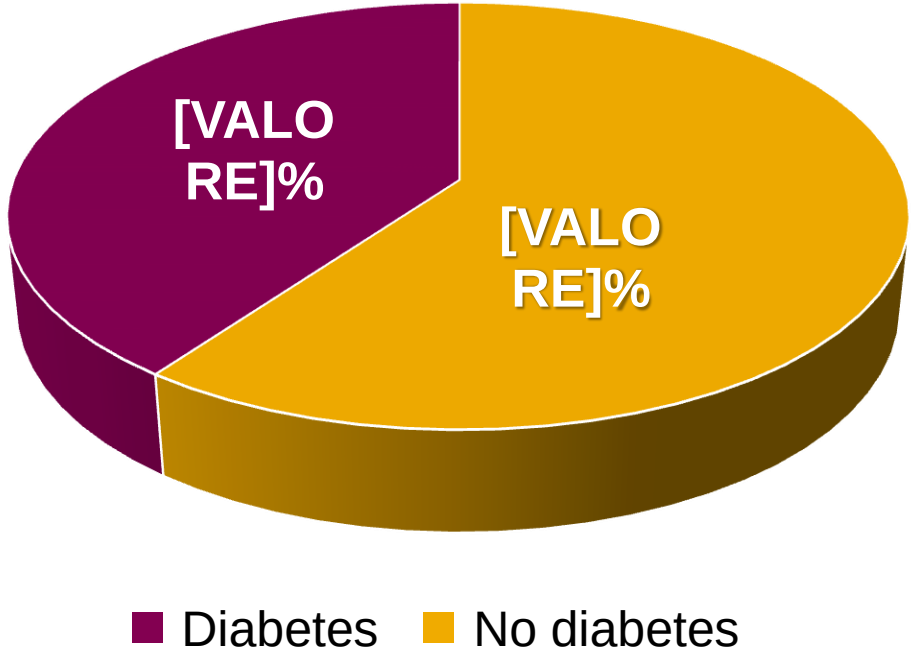
1. Kovesdy CP. *Nat Rev Nephrol* 2014;10:653–662; 2. Vardeny O, et al. *Circ Heart Fail* 2014;7:573–579; 3. Nilsson E, et al. Presented at 54th Congress of the European Renal Association – European Dialysis and Transplant Association; June 3rd–6th, 2017; Madrid, Spain; poster SP313; 4. Chomicki J, et al. Presented at American Society of Hypertension Annual Scientific Meeting and Exposition; May 16th–20th, 2014; New York, NY, USA; P-10; 5. Khosla N, et al. *Am J Nephrol* 2009;30:418–424; 6. Yancy CW, et al. *Circulation* 2017;136:e137–e161

Conditions associated with HiK often co-exist

Up to ~50% of patients with HF also have CKD



Diabetes is present in ~40% of patients hospitalised for acute HF



CKD, chronic kidney disease; HF, heart failure; HiK, hyperkalaemia

Aguilar D. *Circ Heart Fail* 2016;9:e003316

I problemi da trattare

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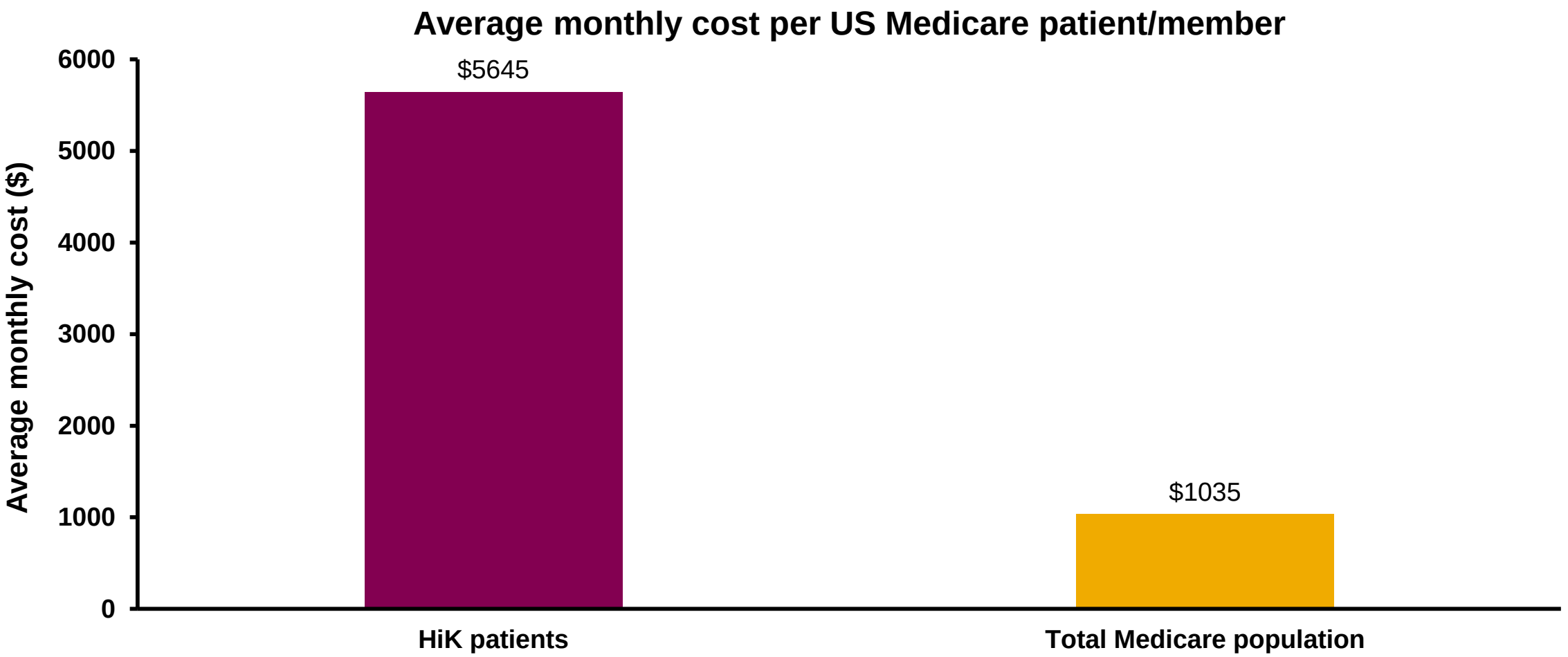
HiK is associated with higher healthcare costs



HiK, hyperkalaemia

Fitch K, et al. Presented at the AMCP 2016; 19th–22nd April 2016; San Francisco, CA, USA; E62

I problemi da trattare

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HK treatment options are associated with limitations

Low-K^+ diet[1]

- Difficult to adhere to
- Limiting K^+-rich foods can cause constipation
- Contradicts DASH diet; may worsen chronic hypertension

Diuretics[1]

- Efficacy depends on residual renal function (until diuresis is present)
- Increased risk of gout and diabetes depending on choice of diuretic
- May produce volume contraction, decreased distal nephron flow, worsening of kidney function and reduced K^+ excretion depending on choice of diuretic

Discontinuation or dose-reduction of RAASi[a] therapy[1]

- Stopping or suboptimal utilization of renal/ cardioprotective RAASi therapy

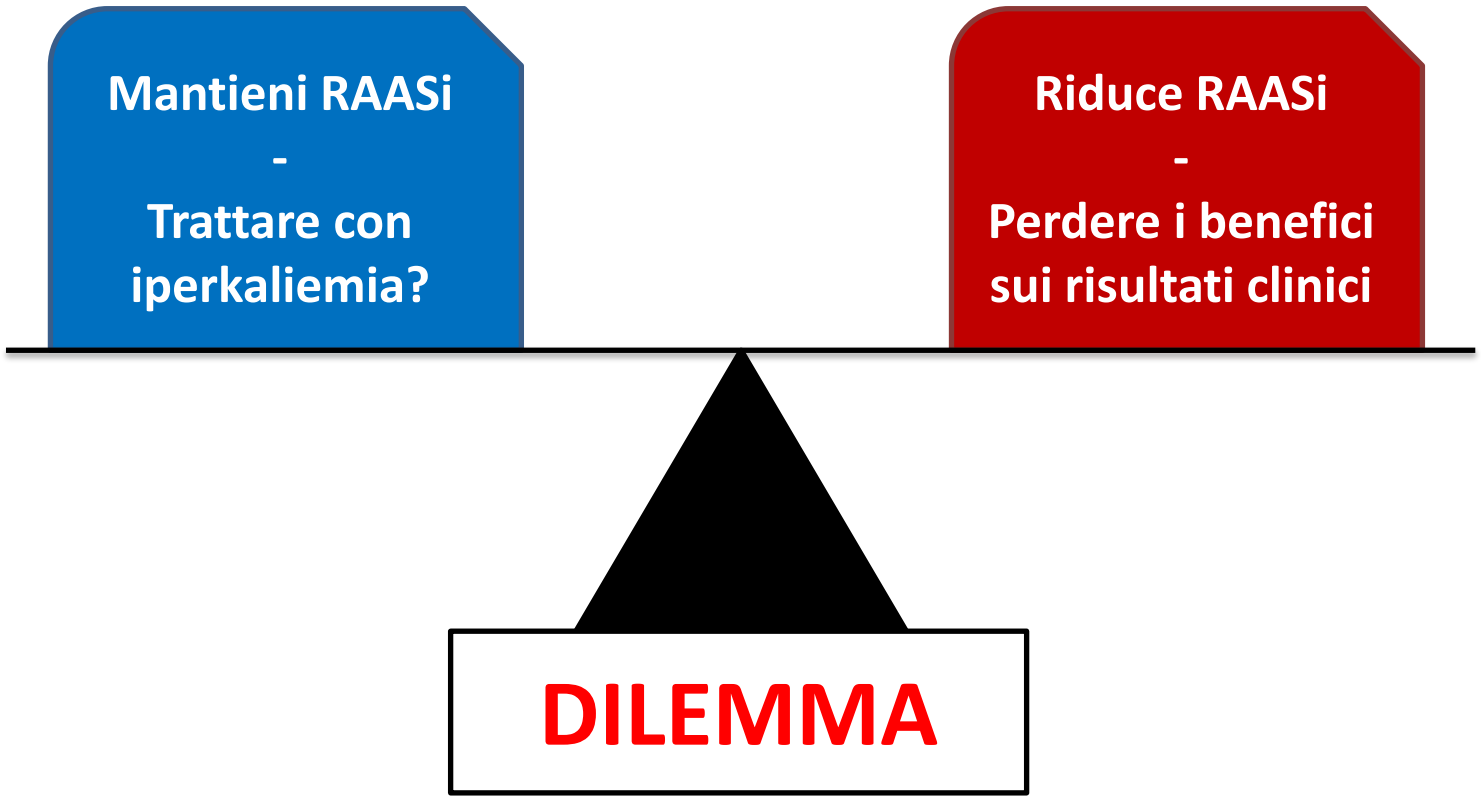
Traditional K^+ binders, e.g. SPS[1–3]

- No consistent evidence of efficacy
- Gastric irritation, anorexia, nausea, vomiting, constipation and occasionally diarrhea may occur
- Hard, gritty texture and unpleasant taste may reduce palatability

Sodio Polisterene Sulfonato

[a]Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists
DASH, Dietary Approaches to Stop Hypertension; HK, hyperkalemia; RAASi, renin–angiotensin–aldosterone system inhibitor; SPS, sodium polystyrene sulfonate
1. Dunn J, et al. *Am J Manag Care* 2015;21:S307–S315; 2. Sanofi. Kayexalate Prescribing Information 2010; 3. Zann V, et al. *Drug Des Devel Ther* 2017;11:2663–2673;

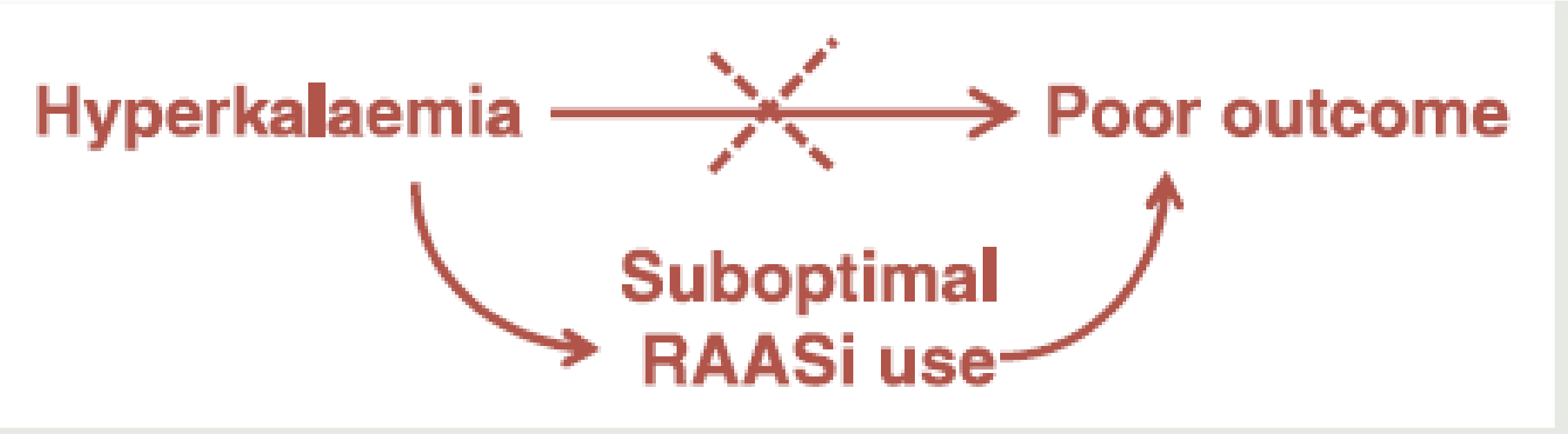
Il Problema: Iperkalemia Vs benefici RAASi



RAASi: inibizione del sistema renina-angiotensina-aldosterone

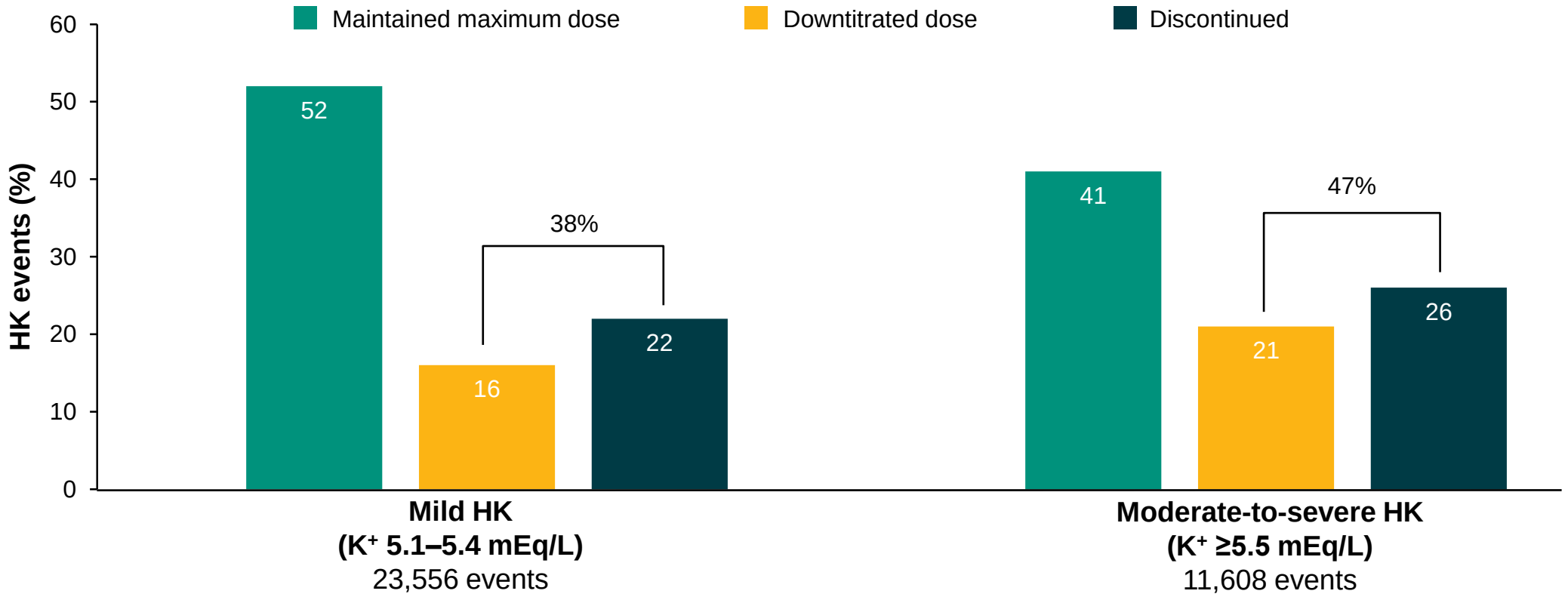
Palmer BF, et al. N Engl J Med 2004;351:585-92

L’iperkaliemia è un marker prognostico negativo in quanto provoca la riduzione o la sospensione degli inibitori del sistema renina- angiotensina - aldosterone



Downtitration or discontinuation of RAASi therapy is common following a HK event[a]

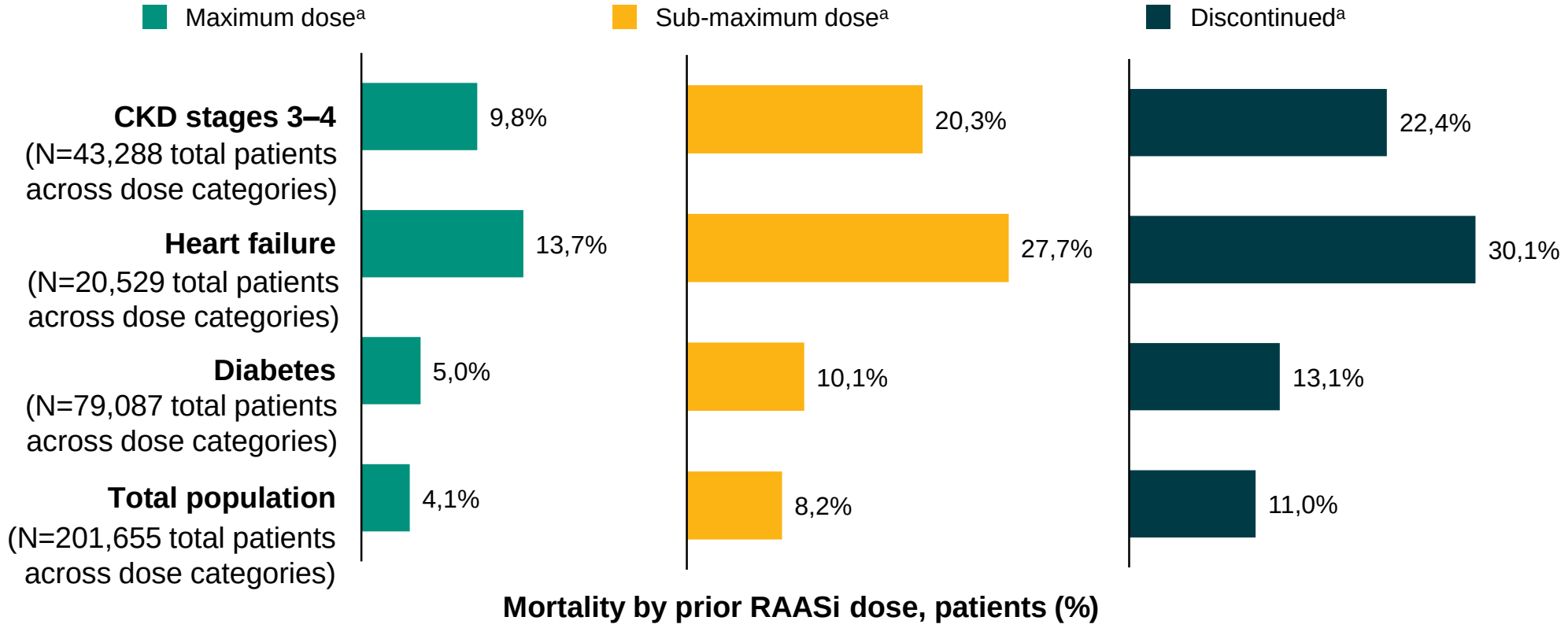
Retrospective analysis of a US database of electronic health records (N>200,000) of patients with various comorbidities and at least two serum K^+ readings



[a]In those receiving maximum doses of RAASi therapy; for the remaining events, the data period following an event was not sufficient to determine subsequent RAASi dose level
HK, hyperkalemia; RAASi, renin–angiotensin–aldosterone system inhibitor
Adapted from Epstein M, et al. *Am J Manag Care* 2015;21(Suppl. 11):S212–S220

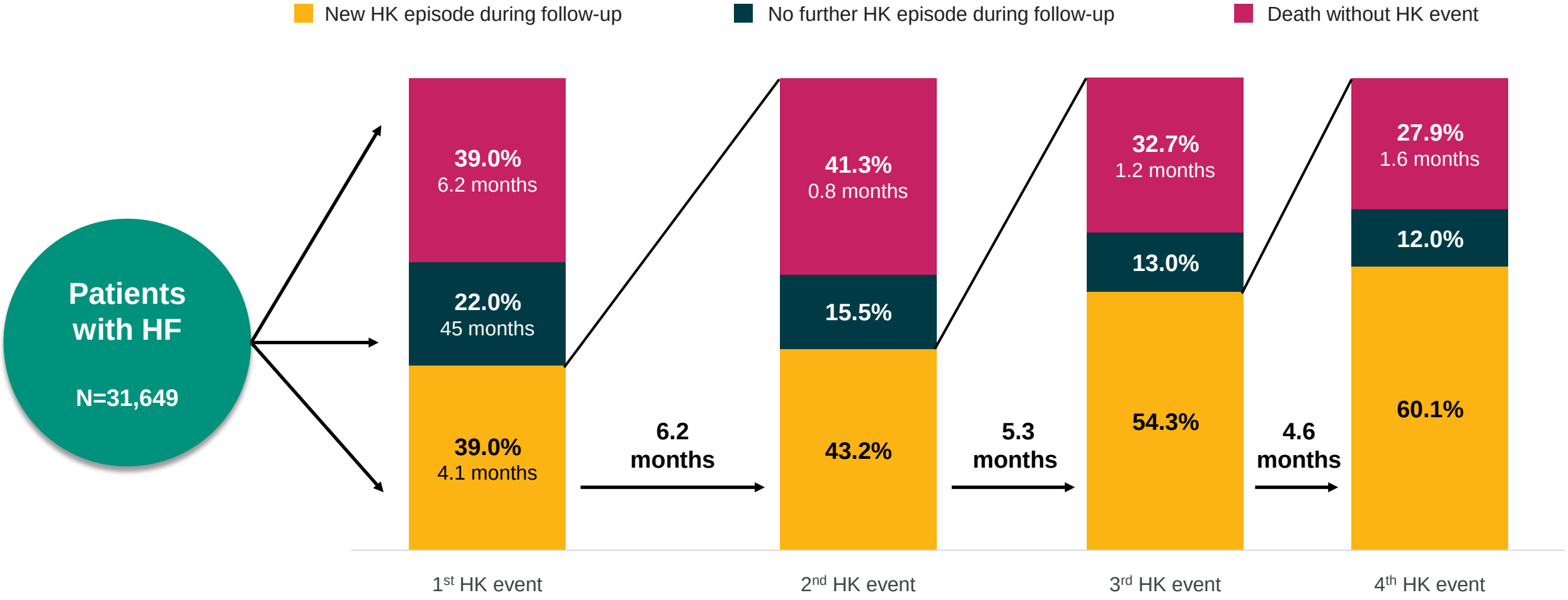
Suboptimal dosing of RAASi therapy is associated with doubling of mortality across patient subtypes

HK among patients on ≥1 RAASi prescription in a retrospective study over a 5-year period; data include any services provided in hospitals as well as office and outpatient setting



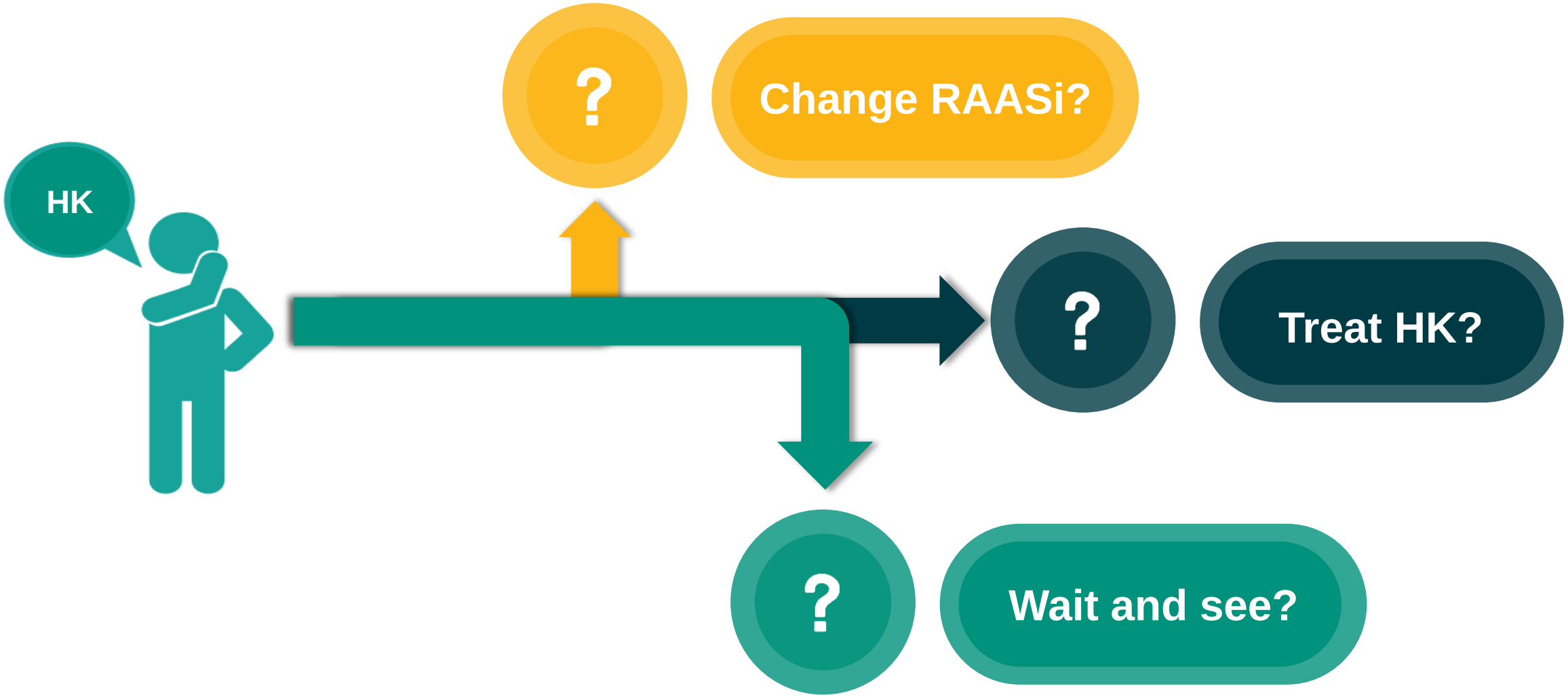
[a]In those receiving maximum doses of RAASi therapy; inclusion criteria required 12 months of data prior to index date.
CKD, chronic kidney disease; RAASi, renin–angiotensin–aldosterone system inhibitor
Adapted from Epstein M, et al. *Am J Manag Care* 2015;21(Suppl. 11):S212–S220

Many patients with HF have recurrent HK episodes, with successively shorter time between the episodes



Population-based cohort study linking individual data from mandatory hospital, prescription, and laboratory databases in Northern Denmark (population 1.8 million) during 2000–2012 (N=31,649)
HF, heart failure; HK, hyperkalemia
Adapted from: Thomsen RW, et al. *J Am Heart Assoc* 2018;7:e008912

Are we optimally managing patients with HK?



HK, hyperkalemia; RAASi, renin–angiotensin–aldosterone system inhibitor
Khanna A, et al. *Am J Med* 2009;122:215–221

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Modificare il paradigma terapeutico della gestione dell'iperkalemia per abilitare e ottimizzare la terapia RAASi

Bertram Pitt, MD
University of Michigan School of Medicine

Gestione dei livelli di potassio sierico nei pazienti con sc e ridotta funzionalità renale

- Consiglia al paziente di evitare alimenti ad elevato contenuto di potassio
- Aggiusta il dosaggio dei farmaci che possono aumentare i livelli di potassio nel momento in cui inserisci in terapia gli antagonisti recettoriali dell'aldosterone
  - controlla la potassiemia e la funzione renale dopo 2-3 giorni e ripeti a 7 giorni
  - controlla mensilmente per i primi 3 mesi e successivamente ogni 3 mesi

Utilita' della collaborazione con l'ambulatorio infermieristico dedicato

Farmaci nuovi ed emergenti
leganti del potassio

- **2 nuovi leganti del potassio**
  - ***Patiromer***
    - Meccanismo di azione: polimero di scambio cationico di nuova generazione non assorbito che lega il potassio in scambio con il calcio prevalentemente nel colon distale e aumenta l'escrezione fecale di potassio
  - ***Sodio zirconio ciclosilicato (SZC, ZS-9)***
    - Meccanismo di azione: scambiatore inorganico di cationi con struttura cristallina che trattiene il potassio lungo l'intera lunghezza del tratto gastrointestinale. Scambia il sodio con il potassio.

The NEW ENGLAND JOURNAL of MEDICINE

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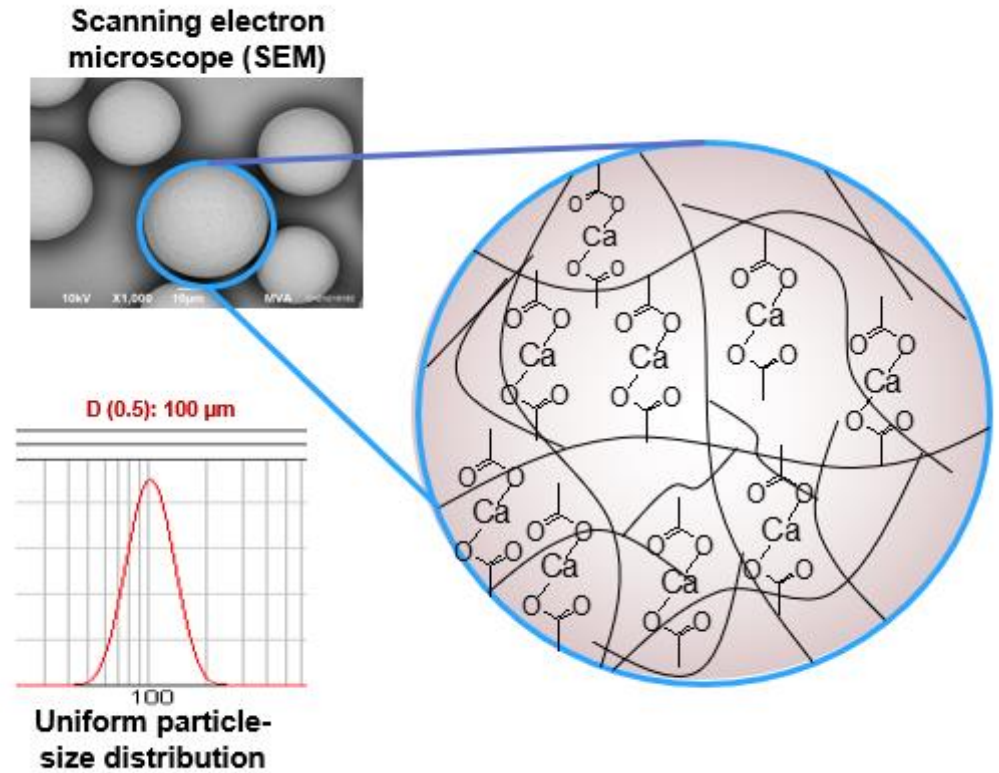
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

CONCLUSIONS

In patients with chronic kidney disease who were receiving RAAS inhibitors and who had hyperkalemia, patiromer treatment was associated with a decrease in serum potassium levels and, as compared with placebo, a reduction in the recurrence of hyperkalemia. (Funded by Relypsa; OPAL-HK ClinicalTrials.gov number, NCT01810939.)



WHAT DATA WE HAVE FOR PATIROMER ENABLING RAASI?

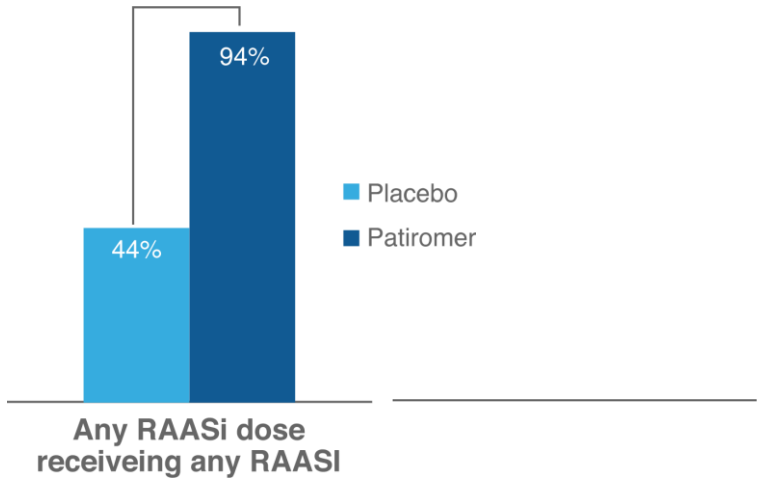
EU SmPC: Treatment of hyperkalemia[1]

Patiromer enabled substantially more patients to:

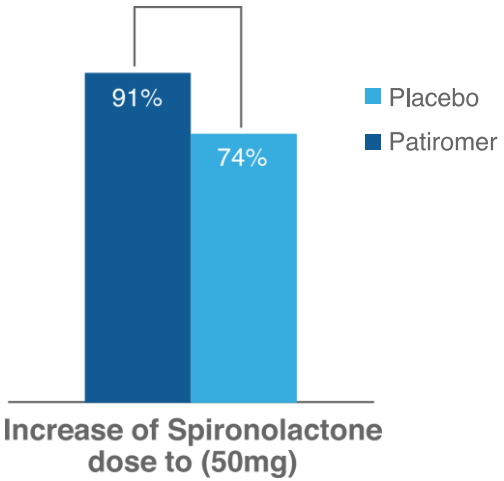
- Remain on their RAASi medication at the end of the study, compared with those given placebo[2]
- Initiate and up-titrate spironolactone in patients with HF and advanced CKD with rHTN[3,4]

Patiromer:

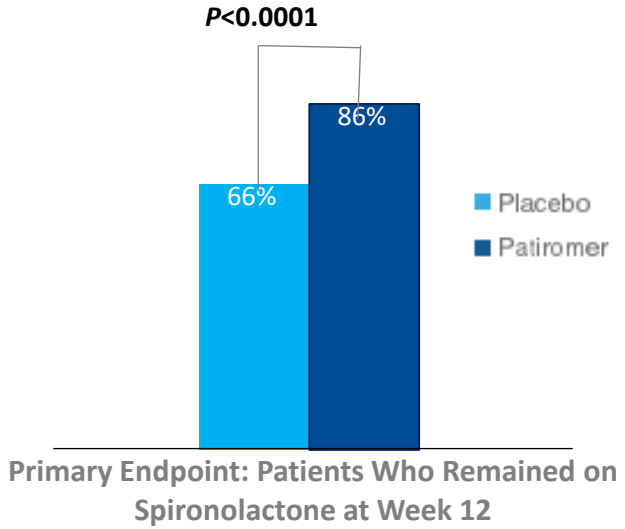
- **OPAL Weir NEJM 2015[2]**
  GFR 15-59; K^+ 5.1-6.4; RAASi; 42-49% HF
  8w randomized withdrawal → 60% v 15% recurrence



- **PEARL-HF EHJ 2011; n=105[3]**
  HF + ([K^+ requiring d/c RAASi] or [eGFR<60])
  4w □ normoK in 24% v 7%; prevent recurrence

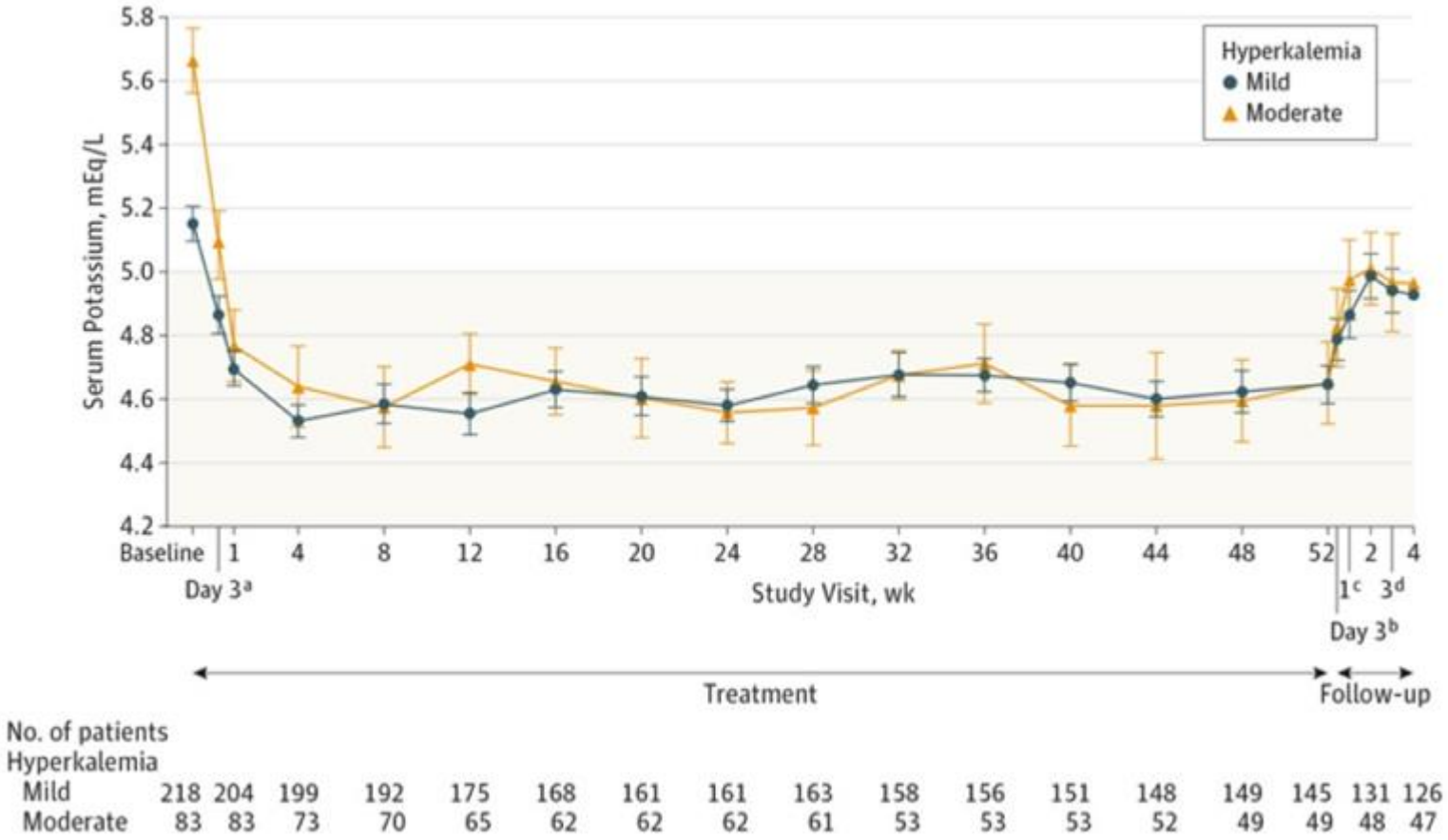


- **AMBER LANCET 2019; n=295[4]**
  rHTN; eGFR 25-45 mL/min/1.73 m^2; sK^+ 4.3-5.1 mEq/L

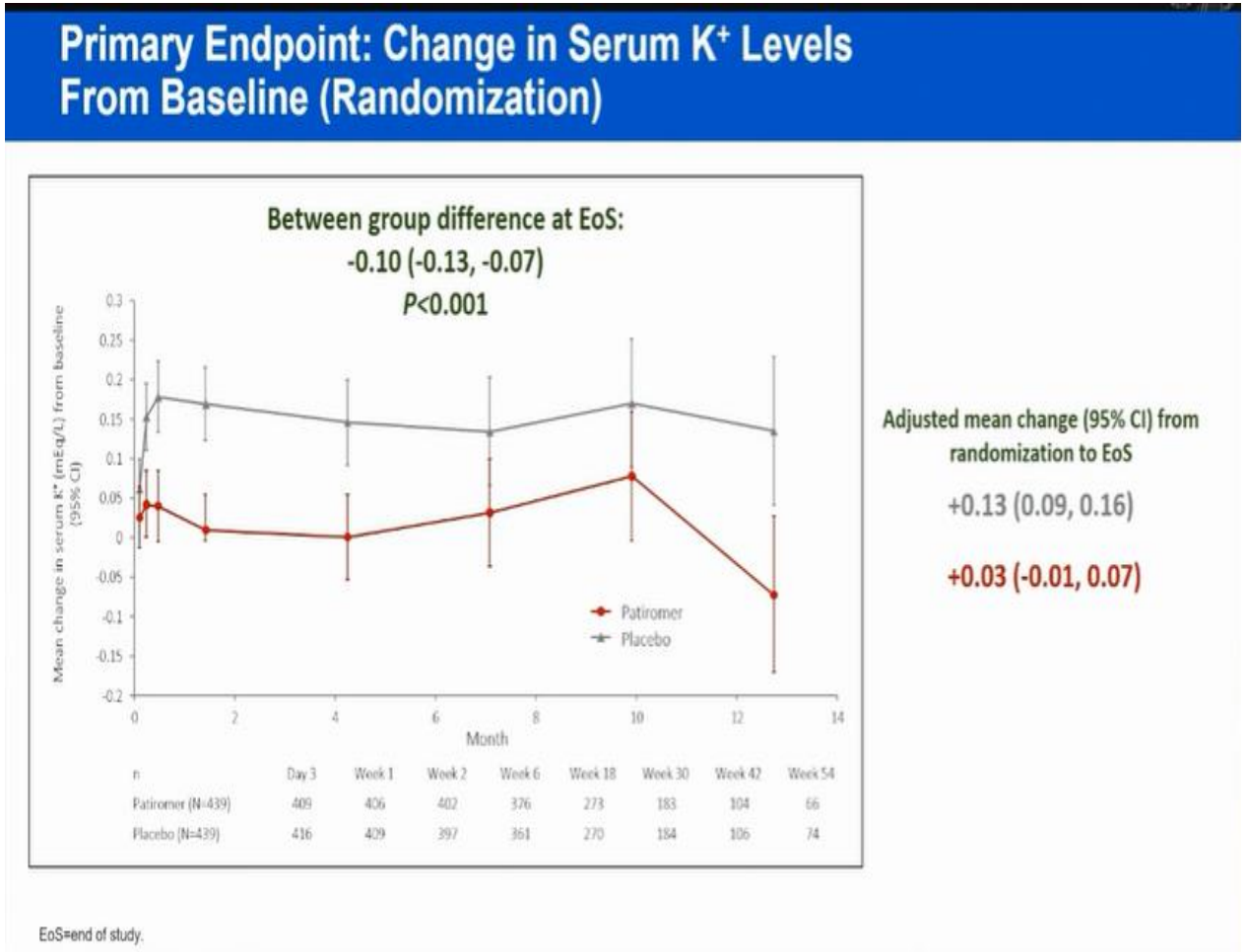


1 Patiromer EU SmPC, 2017. 2. Weir MR, et al. *N Engl J Med* 2015;372(3):211-21. 3. Pitt B, et al. *Eur Heart J* 2011;32(7):820-8. 4. Agarwal R, et al. *Lancet* 2019;394(10208):1540-1550.

Effetti a lungo termine del Patiromer sui livelli di potassio: AMETHYST-DN



Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi for HFrEF - DIAMOND

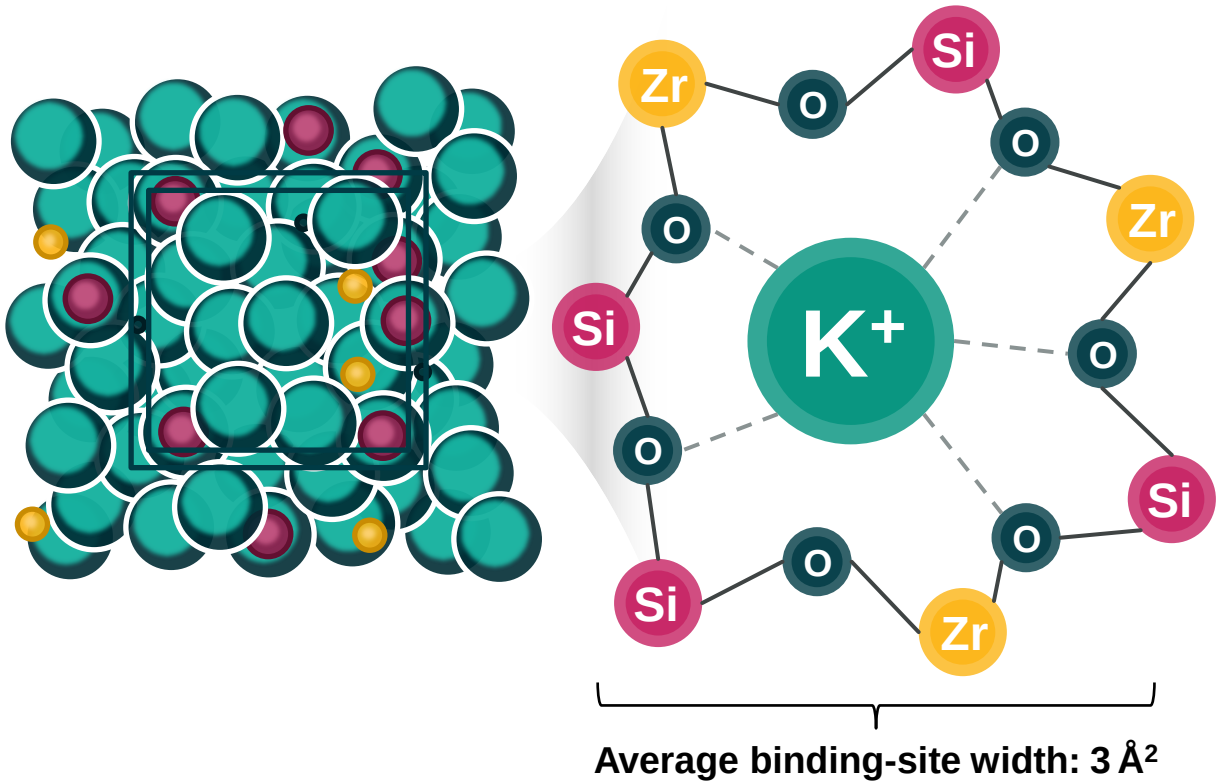


- Most patients (85%) with HFrEF and RAASi-related hyperkalemia could achieve optimal doses of RAASi, including an MRA, when treated with patiromer while maintaining normal serum K^+
- Patiromer treatment maintained lower serum K^+ levels
- Patiromer was associated with a lower incidence of hyperkalemia events and greater proportion of patients being maintained on MRA at target doses
- Patiromer led to a 35% relative risk reduction in the total number of hyperkalemia events
- The win-ratio for morbidity-adjusted hyperkalemia events and the overall RAASi use score were both significantly higher with patiromer treatment

Presented ACC April 2022

Sodio zirconio ciclosilicato ‚ZSC crystal structure

ZSC is indicated for the treatment of HK in adults[1]

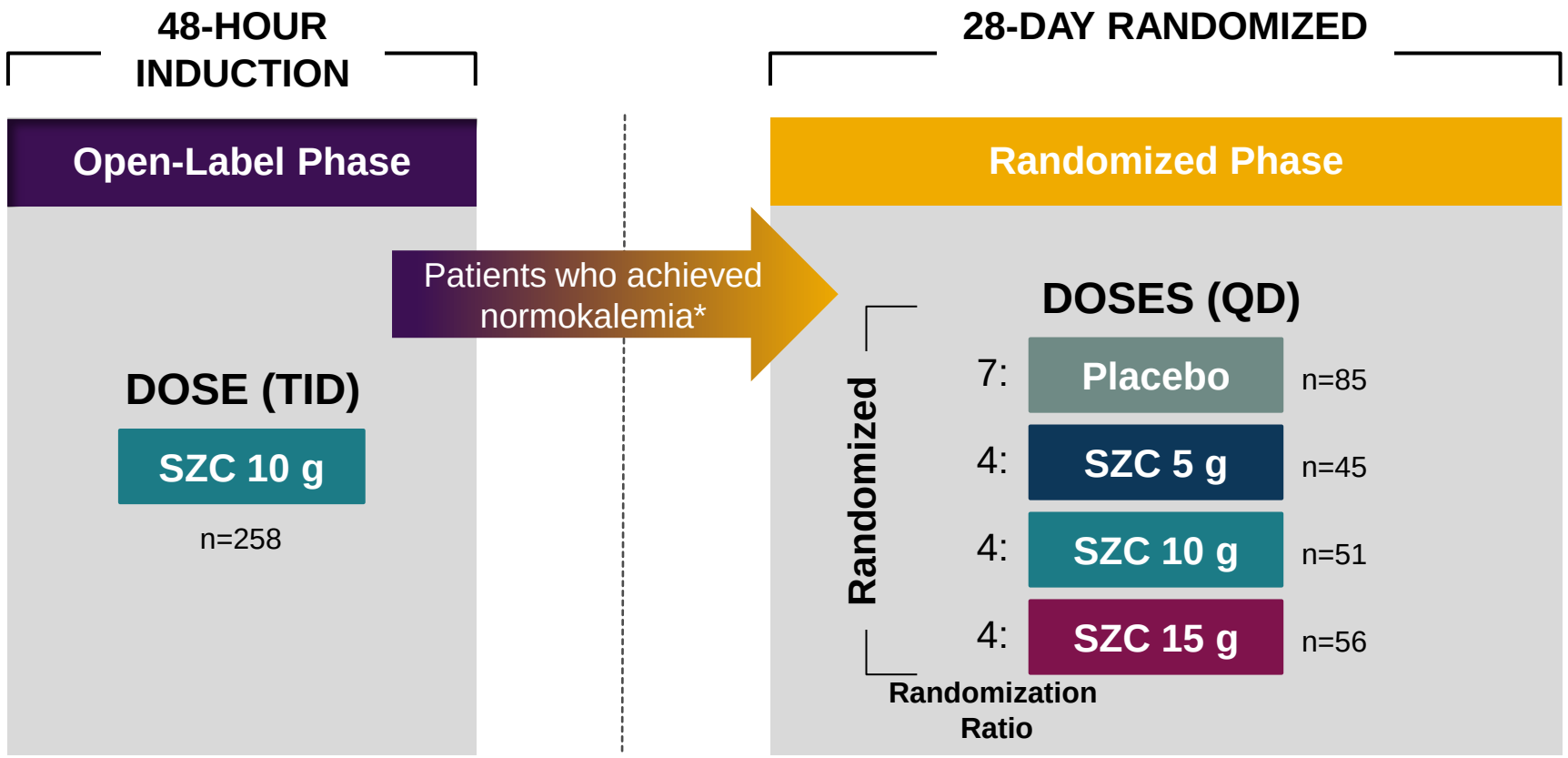


Key molecular characteristics:[1,2]

- Inorganic crystalline zirconium silicate compound
- Not a polymer
- Insoluble, highly stable, and does not expand in water
- Not systemically absorbed
- *High affinity for K^+
- Exchanges Na^+ and H^+ for K^+

*In vitro activity does not always equate to clinical efficacy; images are illustrative only.
HK, hyperkalemia
1. AstraZeneca. LOKELMA Summary of Product Characteristics 2018; 2. Stavros F, et al. *PLoS One* 2014;9:e114686

HARMONIZE (004): Study design



- Entry criteria: serum K^+ ≥5.1 mmol/L
- Primary efficacy endpoint: Mean serum K^+ during days 8–29 of the maintenance phase

*Proceeded to randomized phase if patient achieved normokalemia (i-STAT K^+ 3.5-5.0 mmol/L) by morning of study day 3.
SZC = sodium zirconium cyclosilicate; US = United States.
Kosiborod M et al. *JAMA*. 2014;312:2223-2233.

Study Summary

- Outpatient treatment with SZC 10 g orally TID rapidly (≤72 hours) and reliably normalized K^+ levels in most patients with hyperkalemia; most achieved normokalemia within 24 hours[1]
- In the largest prospective study of hyperkalemia to date, SZC was efficacious in both correcting elevated K^+ into the normal range (within 1 to 3 days) and maintenance of normokalemia in most patients with QD dosing for up to 12 months[2]
- Safety data were consistent with the established safety profile in a similar patient population with hypokalemia in 5.8% of patients[2]
- **These findings support the use of SZC for outpatient treatment of hyperkalemia and maintenance of normokalemia for up to 12 months[2]**
    - **ZSC has a rapid onset of action (within 1 hour of administration)**
    - **ZSC offers sustained K^+ control up to 1 year across all patient types**
    - **ZSC is generally well tolerated**

AE = adverse event; SZC = sodium zirconium cyclosilicate.

1. Packham DK et al. Poster presented at: ASN Kidney Week; October 31-November 5, 2017; New Orleans, LA. Poster FR-PO1074. 2. Fishbane S et al. Poster presented at: ASN Kidney Week; October 31-November 5, 2017; New Orleans, LA. Poster TH-PO1112.

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^+

Conclusioni

- L’iperkaliemia è fortemente prevalente nei paz. con IRC, SC e diabete e in quelli trattati con RAASi
- L’iperkaliemia si associa con aumento delle ospedalizzazioni e della mortalità e può limitare l’uso dei farmaci RAASi
- I trattamenti tradizionali dell’iperkaliemia hanno grossi limiti:
  - breve durata di azione
  - svantaggi, come i diuretici, la dialisi e SPS
  - diete a basso livello di potassio difficili da rispettare
  - ridurre pericolosamente il dosaggio dei RAASi
- ***C’è la reale necessità di una gestione efficace della iperkaliemia senza compromettere il dosaggio ottimale di farmaci salva-vita***
- **I nuovi farmaci chelanti il potassio sono molto promettenti per l’ottimizzazione della terapia nello SC :**
- **efficaci e sicuri nel trattamento dell’iperkaliemia a 1 anno ,**
- **prevedibile effetto dose – risposta,**
- **interferenze con altri farmaci facilmente risolvibili,**
- **ipokaliemia rara,**
- **effetto iperkaliemia *rebound* alla sospensione.**

Diapo di riserva

PIANO TERAPEUTICO AIFA DI PRESCRIVIBILITÀ PER PATIROMER E SODIO ZIRCONIO CICLOSILICATO

La prescrivibilità di questi medicinali è consentita ai soli medici appartenenti a centri ospedalieri o specialisti nefrologo, cardiologo, internista . Validità del piano 6 mesi

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

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

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

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

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

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

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

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CARATTERISTICHE DEI PRINCIPALI AGENTI CHELANTI DEL POTASSIO

	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.

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