Challenges in RAASi optimization: Hyperkalemia Management

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*Consultant: Bayer, Merck, Relypsa+, Pfizer, Astra Zeneca, Boehringer Ingelheim, Forrest Laboratories, SC Pharmaceuticals+, KPB biosciences+, PharMain+, Tricida+, Aurasence+, DaVinci Therapeutics+, Sarfez, Stealth Peptides +Stock options

A case of hyperkalaemia during RAASi use

- 78-year old female
- 6 years history of severe heart failure with reduced ejection fraction post AMI
- Chronic AF – rate ~65/min
- Blood pressure: 124/72 mmHg
- Renal function and electrolytes:

  eGFR: 45 ml/min/1.73 m^2, Na^+ 136 mmol/L,
  K^+ 5.7 mmol/L (was 4.8 mmol/L before Spironolactone)

Treatment:

Perindopril 4 mg od; furosemide 80 mg od; bisoprolol 5 mg od; warfarin 2 mg od; atorvastatin 20 mg od; spironolactone 50 mg od

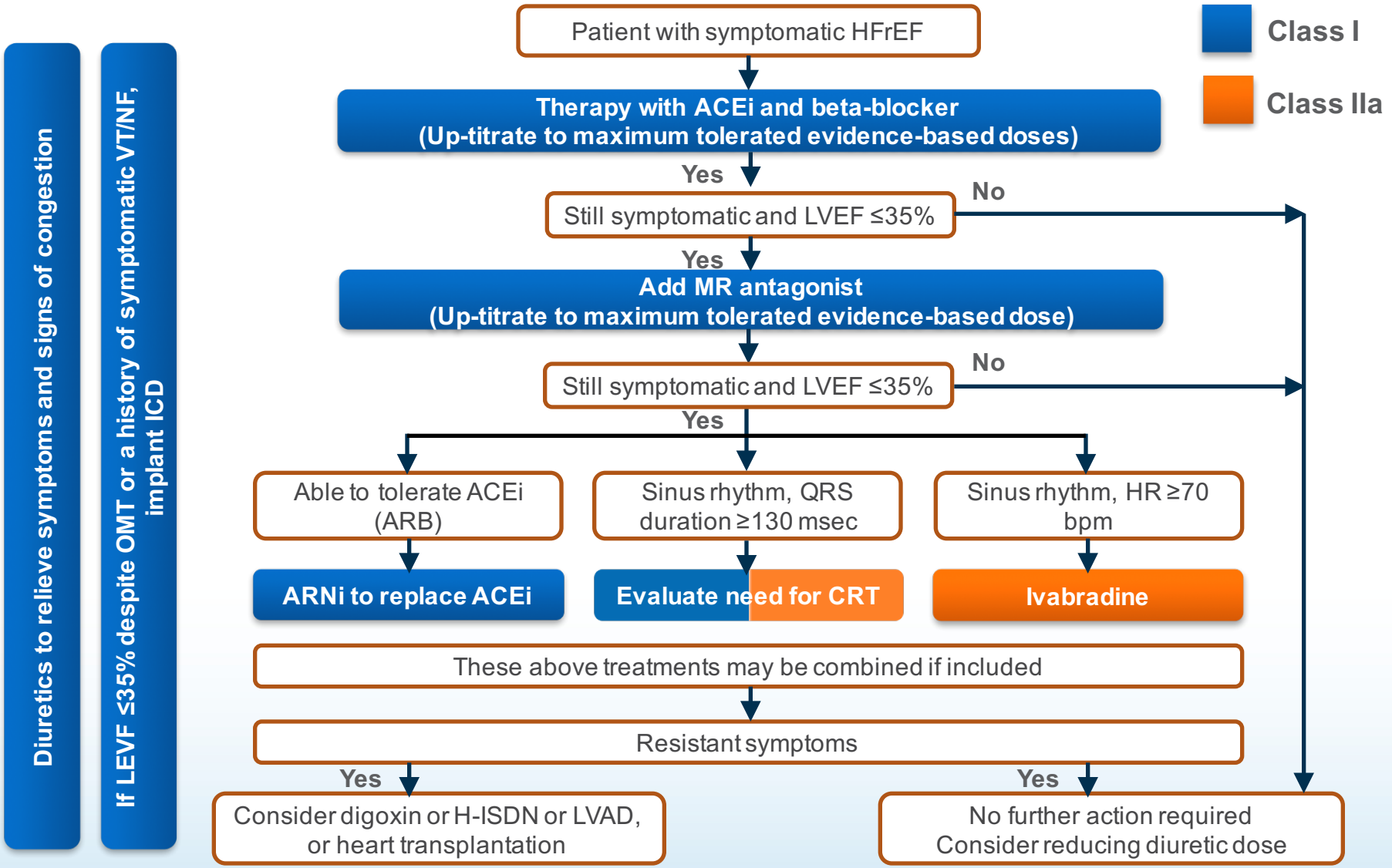
What would you do?

—Stop spironolactone?

—Reduce dose of spironolactone?

—Something else?

Patient's treatment in line with ESC HFrEF guidelines 2016



Ponikowski P, et al. *Eur Heart J.* 2016;37:2129–200.

Adding a mineralocorticoide (MRA) to an ACE improves patient outcomes

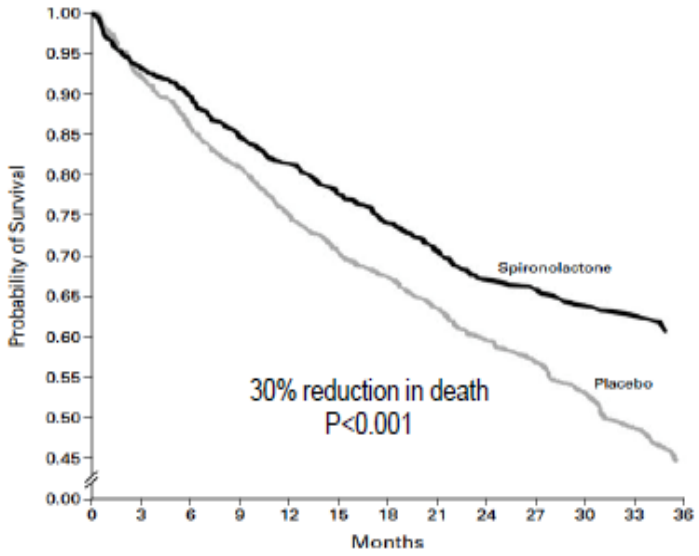
RALES and EMPHASIS – Heart Failure
MRA Improved Survival in HF Patients

RALES[1]

VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*

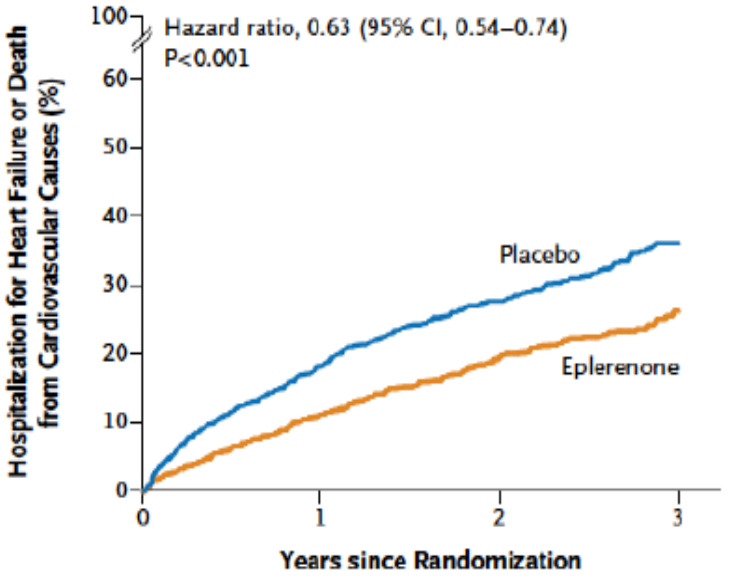


EMPHASIS[2]

ESTABLISHED IN 1812 JANUARY 6, 2011 VOL. 364 NO. 1

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

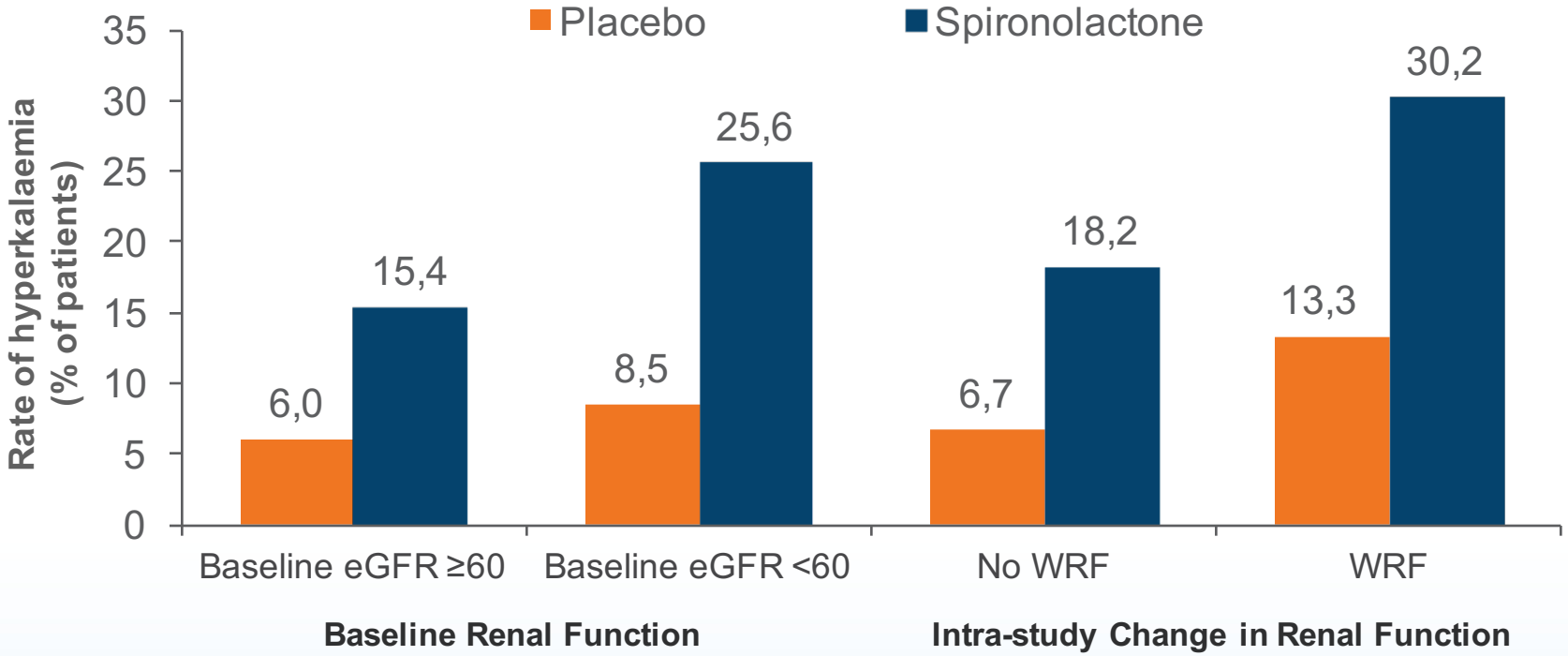
Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*



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

MRA use increases the risk of HK, especially in patients with CKD and a decline in renal function after RAASi initiation

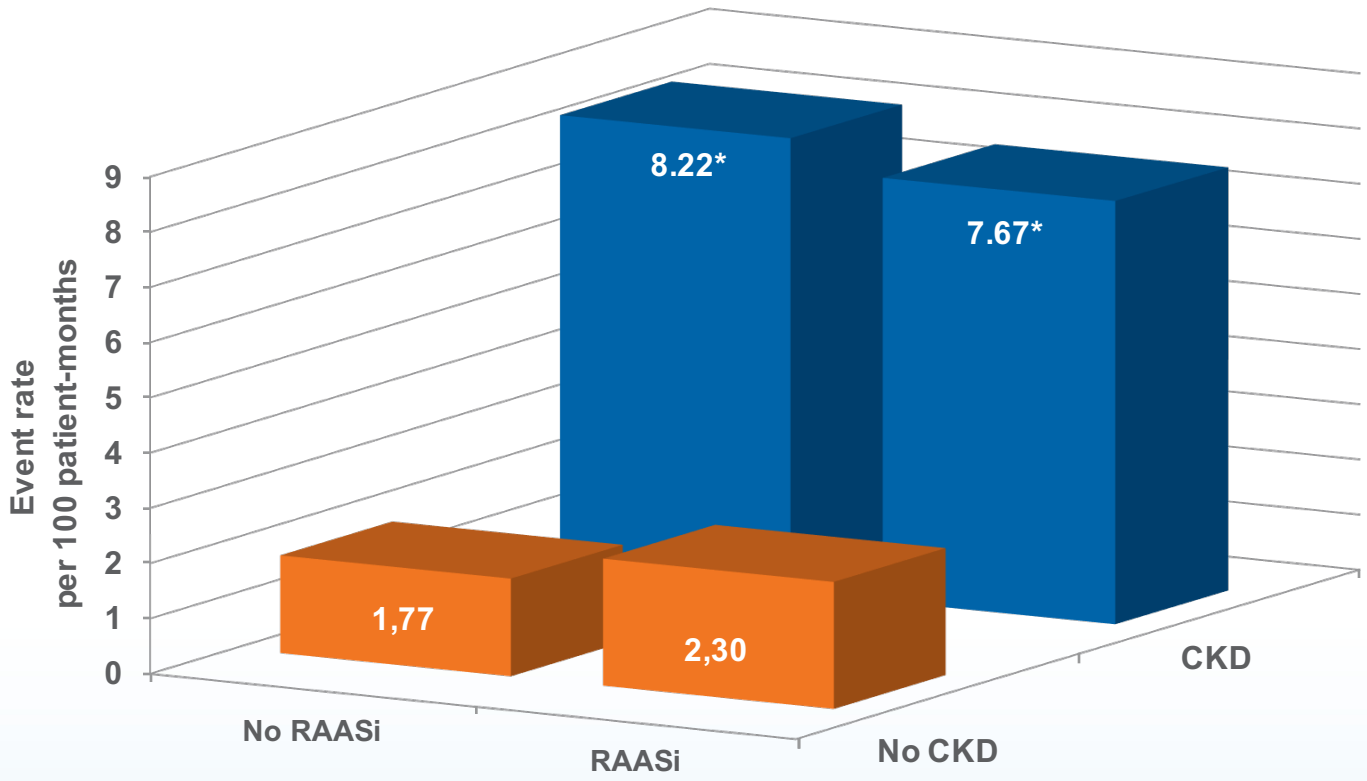
RALES study



eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonists; WRF, worsening renal function

Vardeny O, et al. *J Am Coll Cardiol.* 2012;60:2082–89.

Hyperkalaemia at hospital admission: CKD and/or RAASi



*p <0.0001 versus no CKD

Event rate adjusted for: race, gender, age, CCI, cancer, diabetes, CVD, and RAAS blocker treatment within 30 days. CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CVD, cardiovascular disease; RAASi, renin-angiotensin-aldosterone system inhibitor

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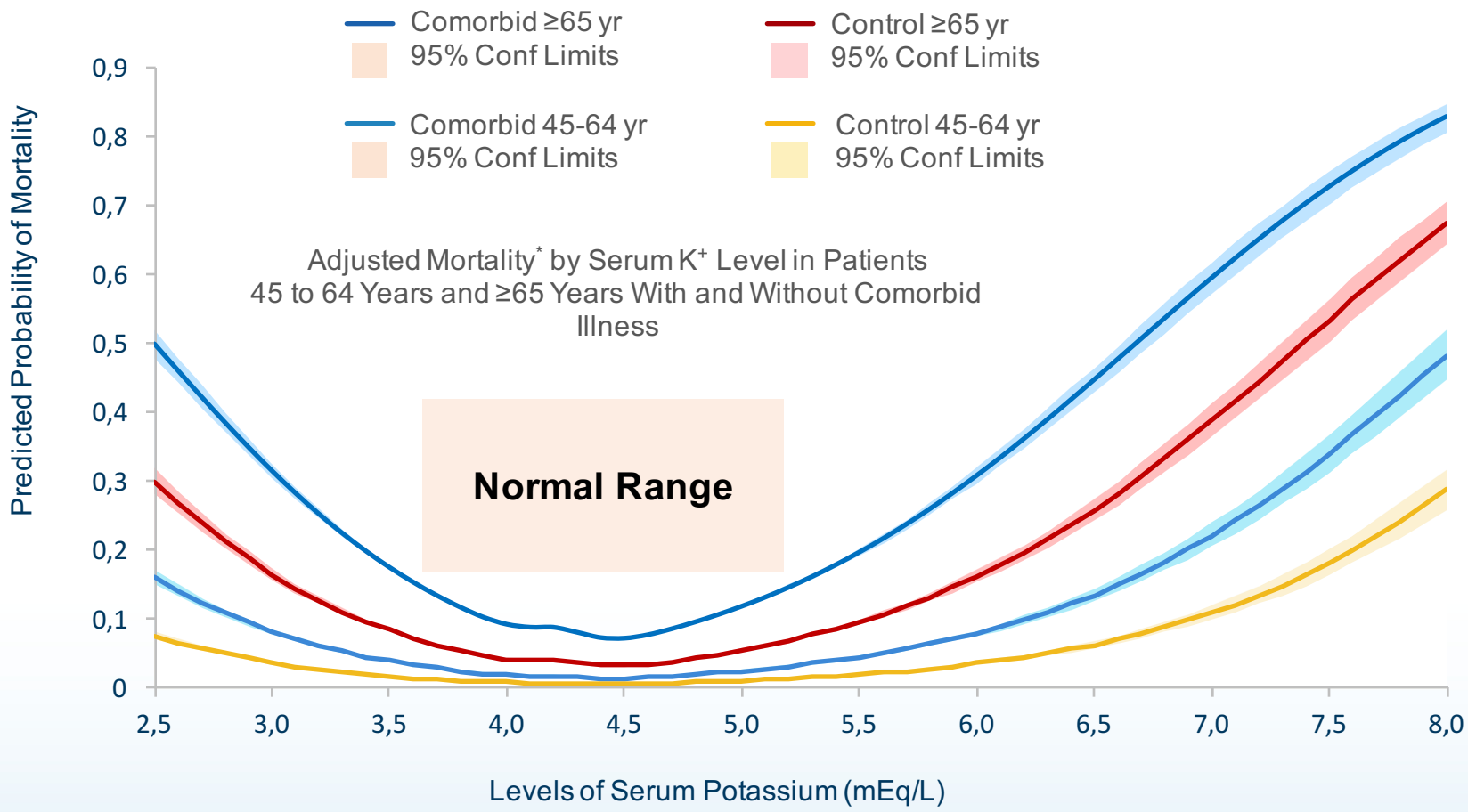
Adapted from: Einhorn LM, et al. Arch Intern Med 2009;169:1156–62.

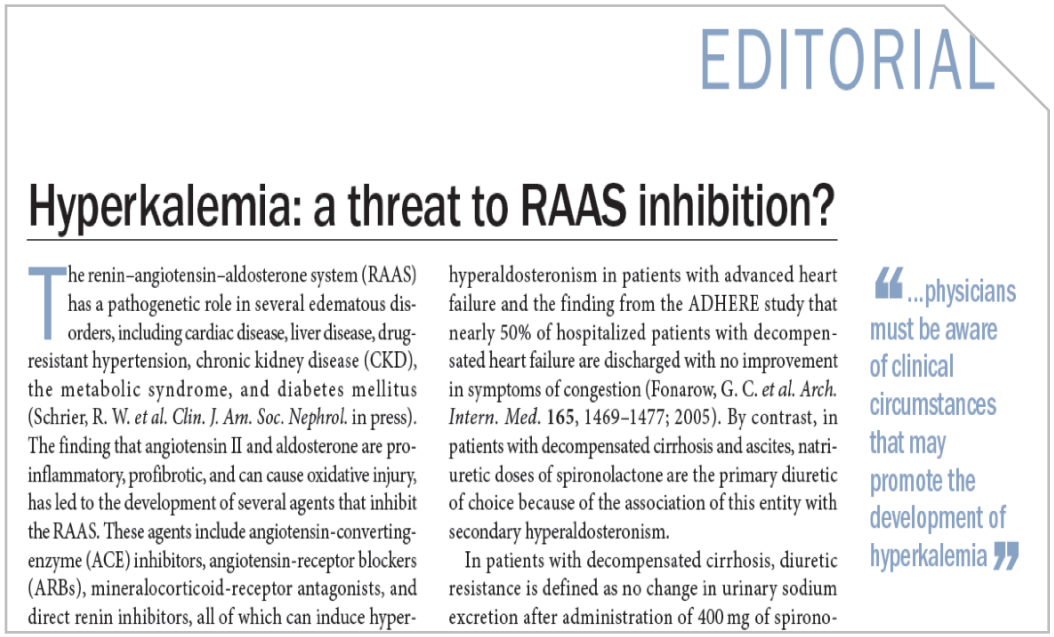
The risk for HK is increased with age and comorbidities



* Evaluated through de-identified medical records (2007-2012) of individuals with ≥2 mEq/L serum K^+ readings (Humedica, Cambridge, MA). Spline analyses were performed to assess mortality at 0.1 mEq/L increments of serum K^+ after adjusting for covariates and interactions. **Comorbid patients are those with diabetes, heart failure, CKD stages 3-5, cardiovascular disease, or hypertension**.

Pitt B, et al. AHA. 2014.

The risk of HK is 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-

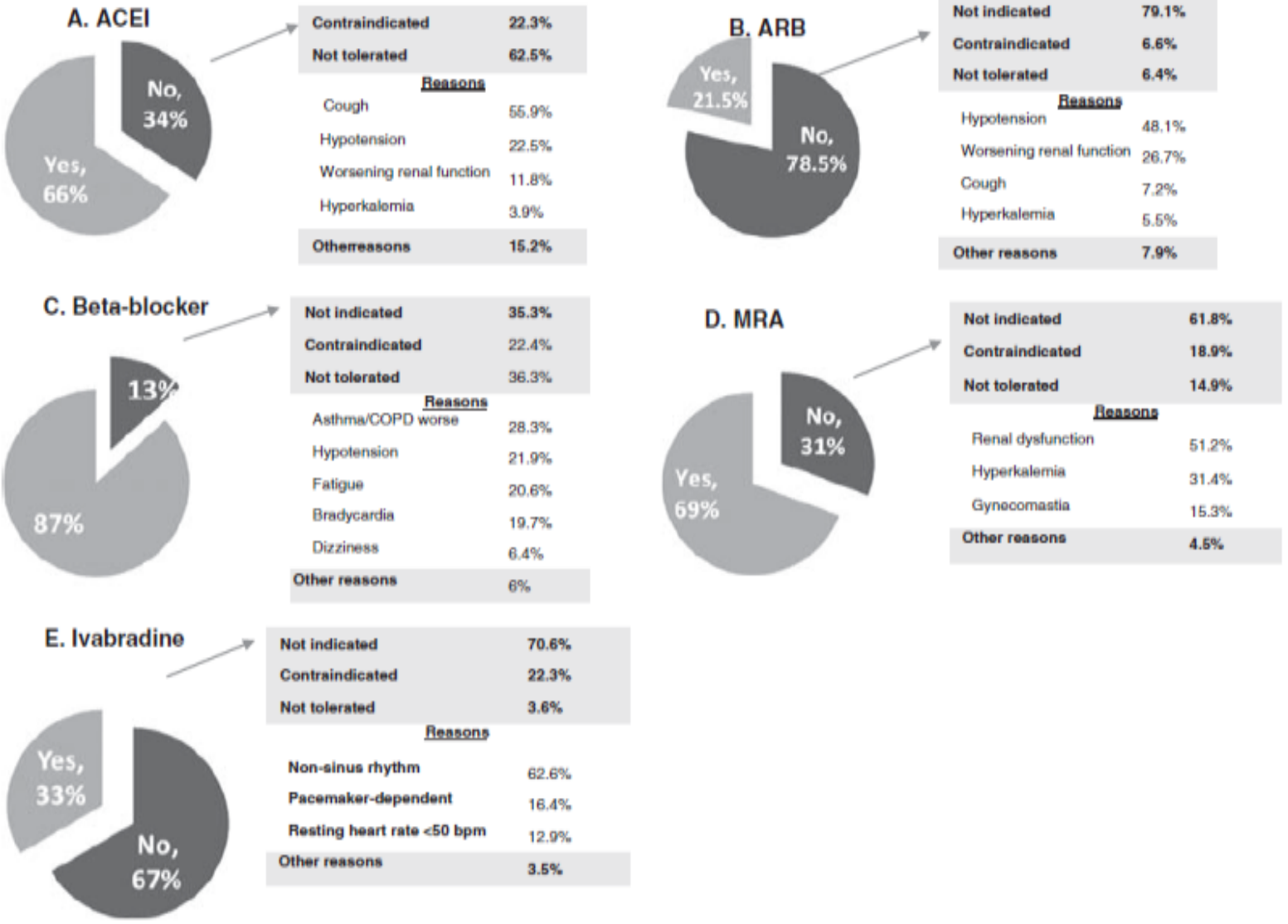
> "...physicians must be aware of clinical circumstances that may promote the development of hyperkalemia"

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

– (Weir, M & Rolfe, M. *Clin. J. Am. Soc. Nephrol.* **5**, 531–548; 2010)

Nature Reviews Nephrology 6, 245-246 (May 2010) | Robert W. Schrier

European healthcare professionals are withholding RAASi due to HK



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

PARADIGM-HF study: Despite novel approaches to RAASi therapy, hyperkalaemia is still an issue with ARNIs

- PARADIGM-HF selected a population at low risk for hyperkalemia prior to randomization
- Excluded patients with eGFR <30 mL/min/1.73 m^2
- Excluded patients with a serum [K^+] of more than 5.2 mEq/L at screening (or >5.4 mEq/L at randomization)
- Had a run-in phase on ACEi that excluded 6% of patients due to AEs, then a run-in phase on LCZ-696 that excluded another 6% of patients due to AEs, which selected a population that would be at low risk for hyperkalaemia

- But hyperkalaemia rates remained high despite a carefully selected population
- >5.5 mEq/L: 16.1% LCZ-696 vs 17.3% ACEi (*P*=0.15)
- >6.0 mEq/L: 4.3% LCZ-696 vs 5.6% ACEi (*P*=0.007)

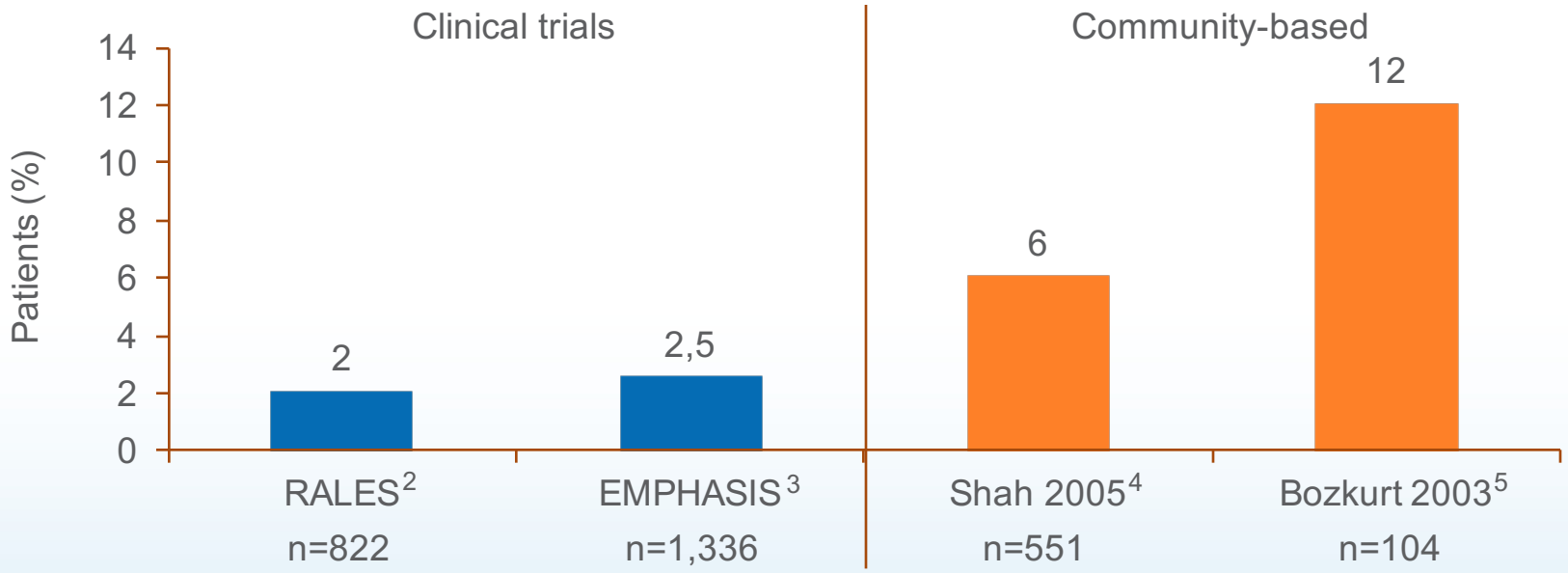
1 mEq/L = 1 mmol/L

AE, adverse event; ACEi, angiotensin converting enzyme inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor ARNI, angiotensin receptor-neprilysin inhibitor

McMurray JJ, et al. *N Engl J Med*. 2014;371:993–1004.

The incidence of hyperkalaemia in real-world studies far exceeds that seen in clinical trials[1]

Hyperkalaemia with spironolactone in real-world vs clinical trials in patients with heart failure



1. Desai AS. *Curr Heart Failure Rep*. 2009;6:272–80; 2. Pitt B, et al. *N Engl J Med*. 1999;341:709–17; 3. Zannad F, et al. *N Engl J Med*. 2011;364:11–21; 4. Shah KB, et al. *J Am Coll Cardiol*. 2005;46:845–49; 5. Bozkurt B, et al. *J Am Coll Cardiol*. 2003;41:211–14.

Patients who experience HK once are at greater risk of recurrent HK events

~50% of patients with hyperkalaemia*

had 2 or more recurrences within 1 year

Some patients experienced

>20 recurrent episodes within 1 year†

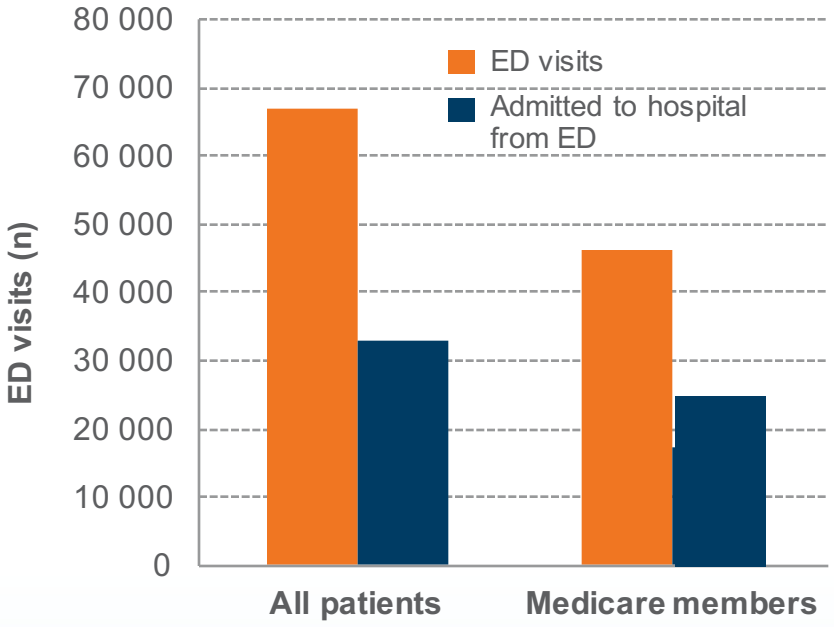
HK, hyperkalaemia

*Hyperkalaemia was defined as serum [K^+] ≥5.5 mEq/L (1 mEq/L = 1 mmol/L); †70 individuals (0.21%) had more than 20 episodes in 1 year

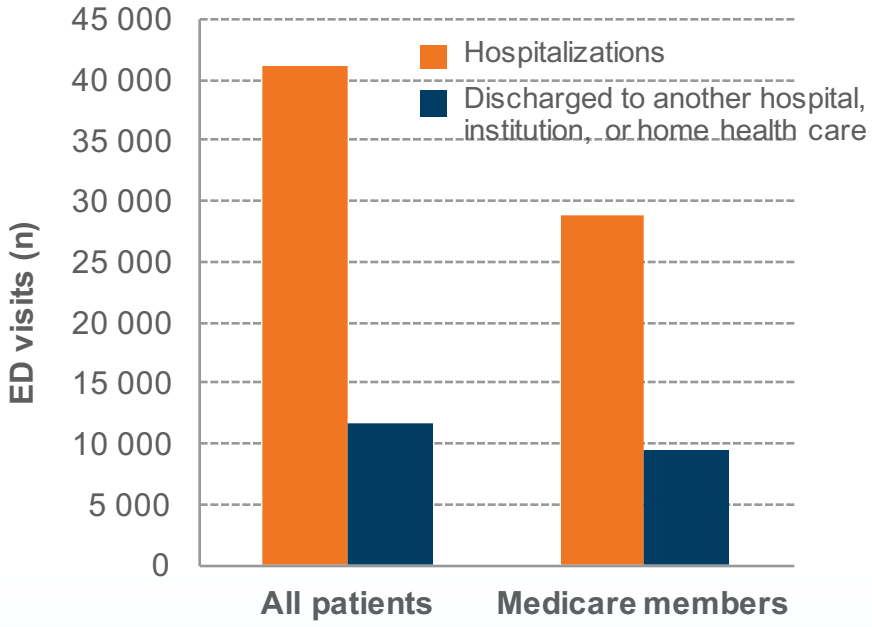
Einhorn LM, et al. *Arch Intern Med*. 2009;169:1156–62.

Hyperkalemia Contributes to ED Visits, Hospitalizations, and Health Care Costs

2011 ED Visits
Primary Diagnosis of Hyperkalemia



2011 Hospitalizations
Primary Diagnosis of Hyperkalemia



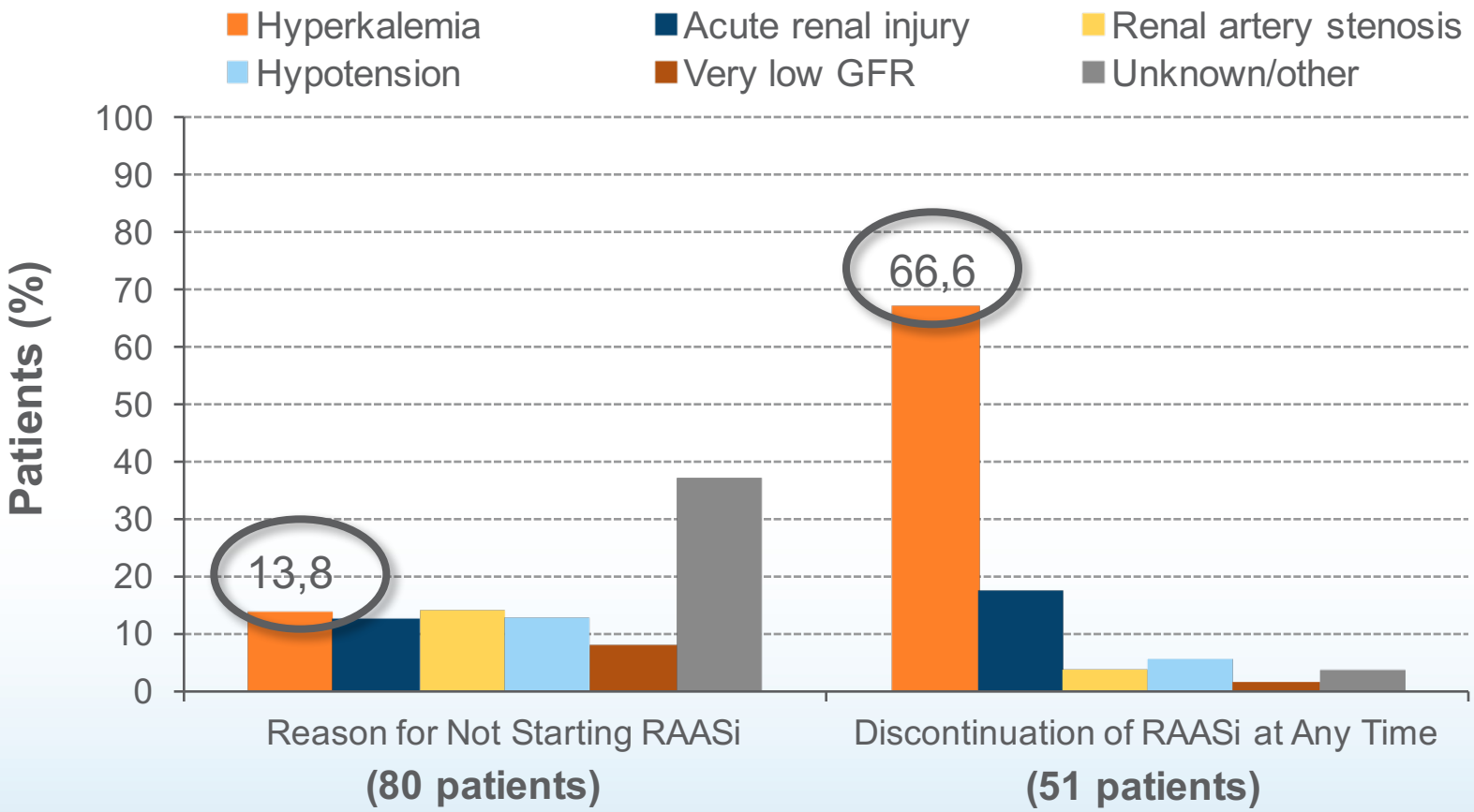
- In 2011, the estimated total annual hospital charges for Medicare admissions with hyperkalemia as primary diagnosis were ~$697 million
- Average Medicare LOS was 3.2 days; mean charges of $24,085 per stay
- One-third were discharged to another short-term hospital, institution, or home health care

ED: emergency department, LOS: length of stay.

Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. http://hcupnet.ahrq.gov/HCUPnet.jsp. Accessed October 21, 2014.

Hyperkalemia Is a Leading Reason for Not Starting RAASi and the Major Reason for Discontinuation of RAASi in CKD Patients

- 279 CKD patients
- Baseline mean GFR was 33.3 mL/min/1.73 m^2 and the serum K^+ was 4.73 mEq/L



Yildirim T, et al. *Ren Fail.* 2012;34(9):1095-1099.

Poor monitoring of serum [K^+] levels after the initiation of MRA therapy in real-world studies

- Evaluation of 10,443 Medicare beneficiaries with heart failure and incident MRA therapy

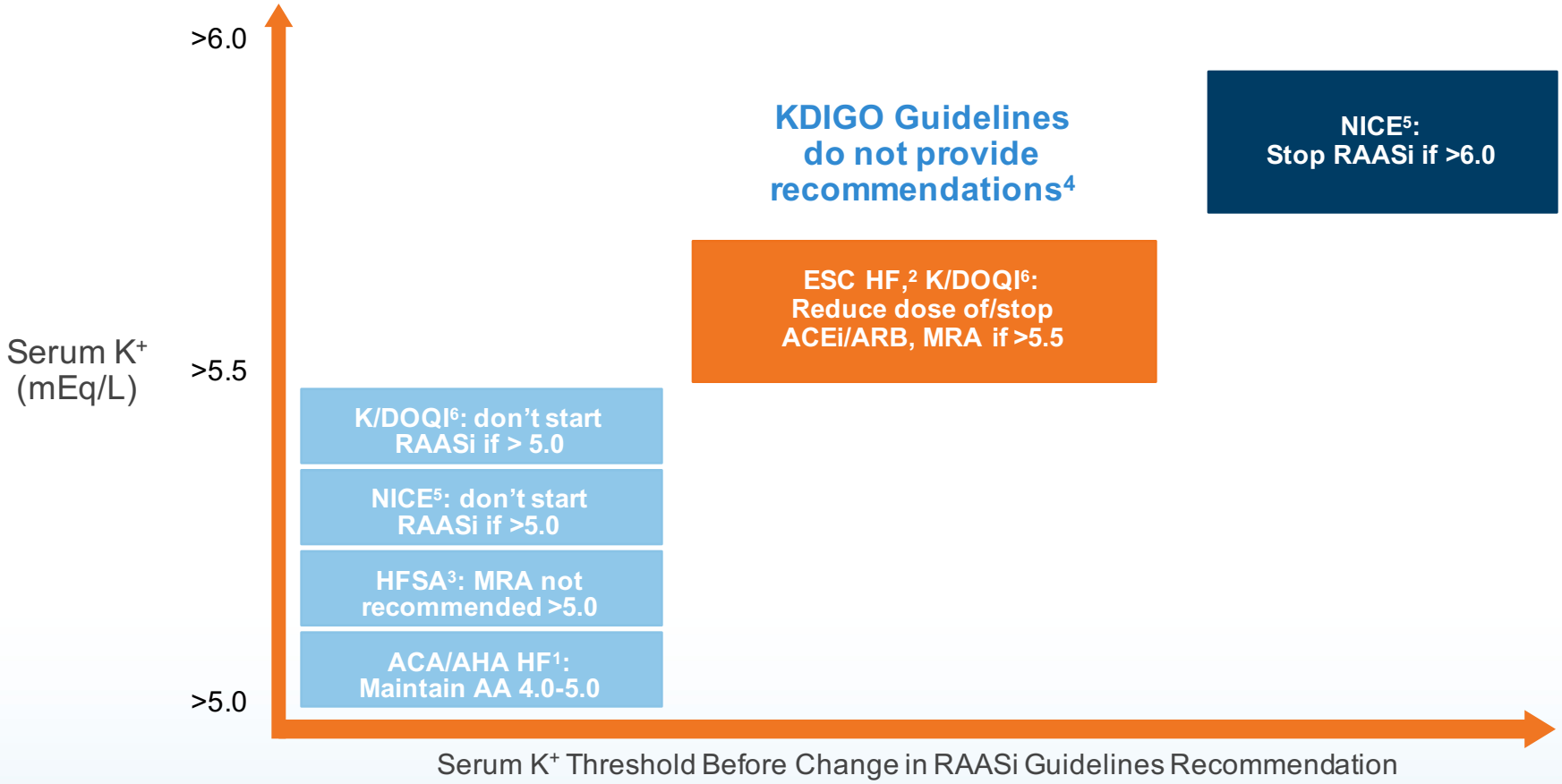
- 91.6% of patients had serum [K^+] first measured in the 120 days prior to MRA initiation
- However, only 13.3% had guideline suggested measurement of serum [K^+] in the early (1–10 days) follow-up period (11–90 days after MRA initiation)
- Overall, 55% of patients did not receive any monitoring of serum [K^+] in the early post-initiation period and 22.3% did not receive any monitoring of serum [K^+] during the extended follow-up period

Regular monitoring of serum [K^+] is needed in clinical practice after patients start MRA therapy

MRA, mineralocorticoid receptor antagonist

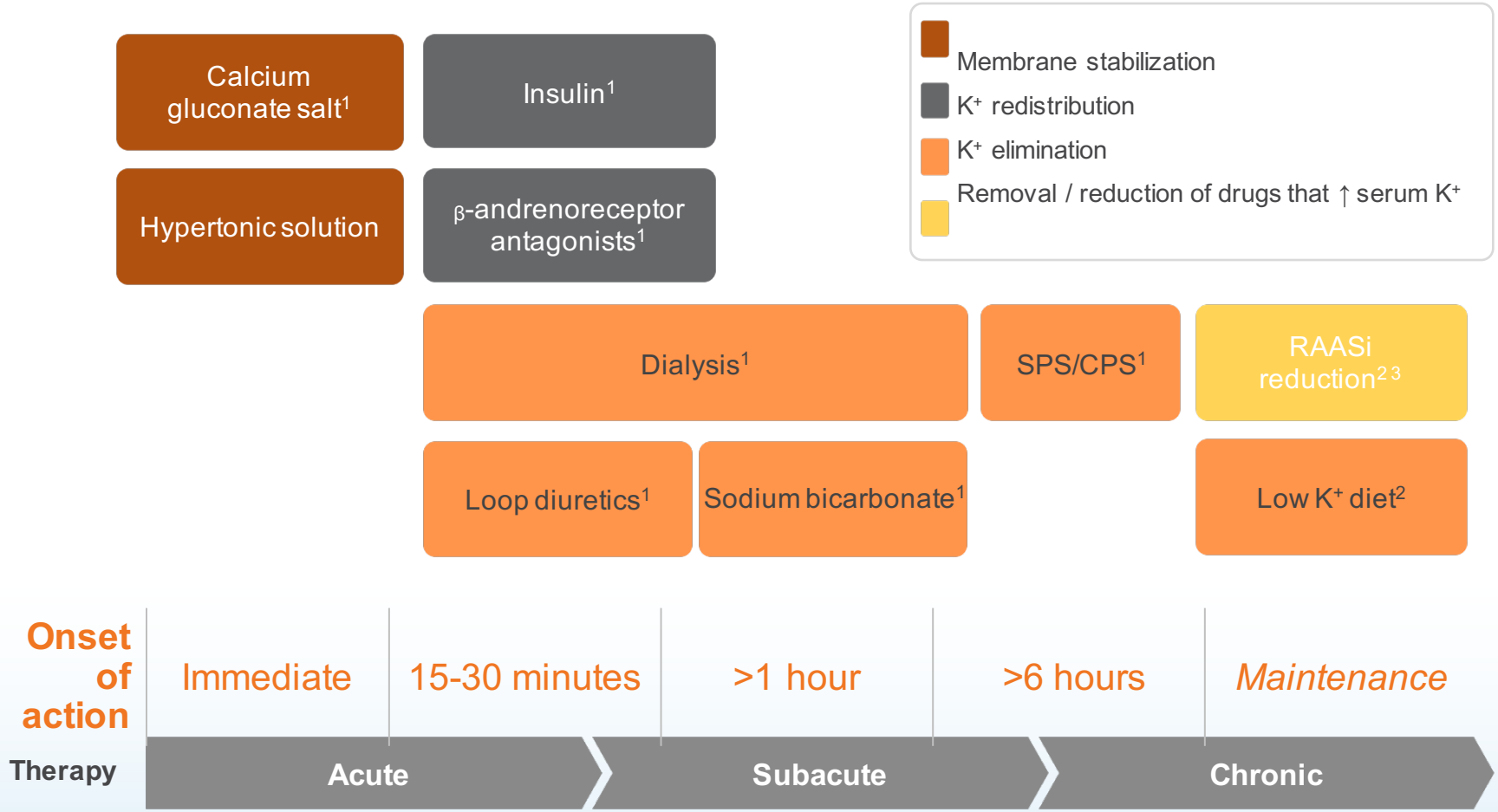
Cooper, LG, et al. *JAMA*. 2015;314:1973–75.

Guidelines recommend dose reduction or discontinuation if HK is a problem during RAASi therapy



[1] Yancy CW, et al. J Am Coll Cardiol. 2013 June 5 [E-pub ahead of print]. [2] McMurray JJ, et al. Eur Heart J. 2012;33(14):1787-1847. [3] Heart Failure Society of America, Lindenfeld J, et al. J Card Fail. 2010;16(6):e1-e194. [4] KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3(1). [5] National Institute for Health and Care Excellence (NICE) [UK]. Chronic kidney disease (CG73): Early identification and management of chronic kidney disease in adults in primary and secondary care. 2008. http://www.nice.org.uk/CG73. http://www.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm#table131.

Current treatment options for hyperkalaemia: No effective long term option



Note: SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate

[1] Weisberg L. Crit Care Med. 2008; 36 (12):3246-3251. [2] Palmer BF, et al. N Engl J Med. 2004;351(6):585-592. [3] National Kidney Foundation. Guideline www.kidney.org/professionals/KDOQI/guidelines_bp/guide_11.htm

Many Patients Are Already on Low Carb and Low Salt: Hyperkalemia Now Adds Potassium Restrictions

What's Left to Eat?

Track fluid intake	Avoid alcohol	Limit caffeine	Low protein in severe CKD

Hyperkalemia

Loop diuretics are effective in lowering serum potassium

- However, Loop diuretics are associated with hypochloremia (serum chloride <96 meq/L) resulting in:
  - Diuretic Resistance
  - Renal Dysfunction
  - If persistent 14 days after hospitalization for Acute HF reduced survival

Hyperkalemia

- Reducing the dose or discontinuing the use of a RAASi is an effective strategy to reduce serum K^+ and the clinical consequences of hyperkalemia
- However discontinuing a RAASi in a patient with HFREF and or CKD places the patient at increased risk of CV death

Potassium Lowering Drugs

Table 2. Comparison of Existing and New Potential Therapies for Chronic Hyperkalemia

Characteristic	Kayexylate	Patiromer	ZS-9
Clinical pharmacology	Cation-exchange resin, exchanges sodium for H^+ in stomach, then exchange for H^+ for other cations in large intestine	Nonabsorbed organic polymer[28,29]; preferentially binds K+ in the colon	Inorganic polymer; negative charge to framework enables cation exchange[28,29]
Clinical trials	No	Yes	Yes
Efficacy	Observed decreases in serum potassium between 0.82 and 1.14 mEq/L depending on dose[29]	Mean reduction in serum potassium at week 4 −1.01 mmol/L; 76% with normokalemia after 4 wk;[17] 60% placebo vs 15% patiromer had recurrent serum K+ ≥5.5 mmol/L during 8-week withdrawal phase[17]	Mean initial reduction in serum potassium (48 h) −0.46 to −1.1 mEq/L depending on dose[16,20]; 98% achieved normokalemia within 48 h; 71%–85% depending on ZS-9 dose maintained normokalemia during 28 day follow-up vs 48% with placebo[20]
Safety	Risk of acute bowel necrosis, hypernatremia, diarrhea, and gastrointestinal intolerance[15]	Mild-to-moderate constipation most commonly reported (11% during initial treatment phase and 4% patiromer vs 0% placebo during 8-wk randomized withdrawal phase), hypokalemia (5%–6%), hypomagnesemia (3% in OPAL-HK, 7.2% in AMETHYST-DN, and 24% in PEARL-HF)	Gastrointestinal disorder reported in 2.1%–8.7% of ZS-9 patients (depending on dose and period of study) vs 2.4%–7.4% of placebo patients, hypokalemia (≈10% depending on dose), edema (2.4%)

Pitt B, et al. Hyp 2015; 66:731

SPS (Kayexalate) and CPS are the only current drugs that remove excess potassium from the body

- Sodium polystyrene sulfonate was approved for the treatment of hyperkalaemia by the FDA in 1958 and in France in 1980

- SPS is a cation-exchange resin that is administered orally or rectally[2]
- In 2009, the FDA added gastrointestinal safety warnings and precautions to the label[1,2]
  - intestinal necrosis (particularly with concomitant sorbitol) which may be fatal, and other serious gastrointestinal adverse reactions
- Resin is a source of sodium – caution is advised in patients who cannot tolerate increases in sodium load (i.e. severe CHF, severe HTN, marked oedema or renal damage)[2]
- Not an option for long-term use

CHF, congestive heart failure; FDA, Food and Drug Administration; HTN, hypertension; SPS, sodium polystyrene sulfonate SPS sodium polystyrene sulfonate CPS, calcium polystyrene sulfonate

1. Sterns RH, et al. *J Am Soc Nephrol*. 2010;21:733–35; 2. Kayexalate® (sodium polystyrene sulfonate) [Package Insert]. Sanofi-Aventis US LLC, Bridgewater, NJ; 2016.

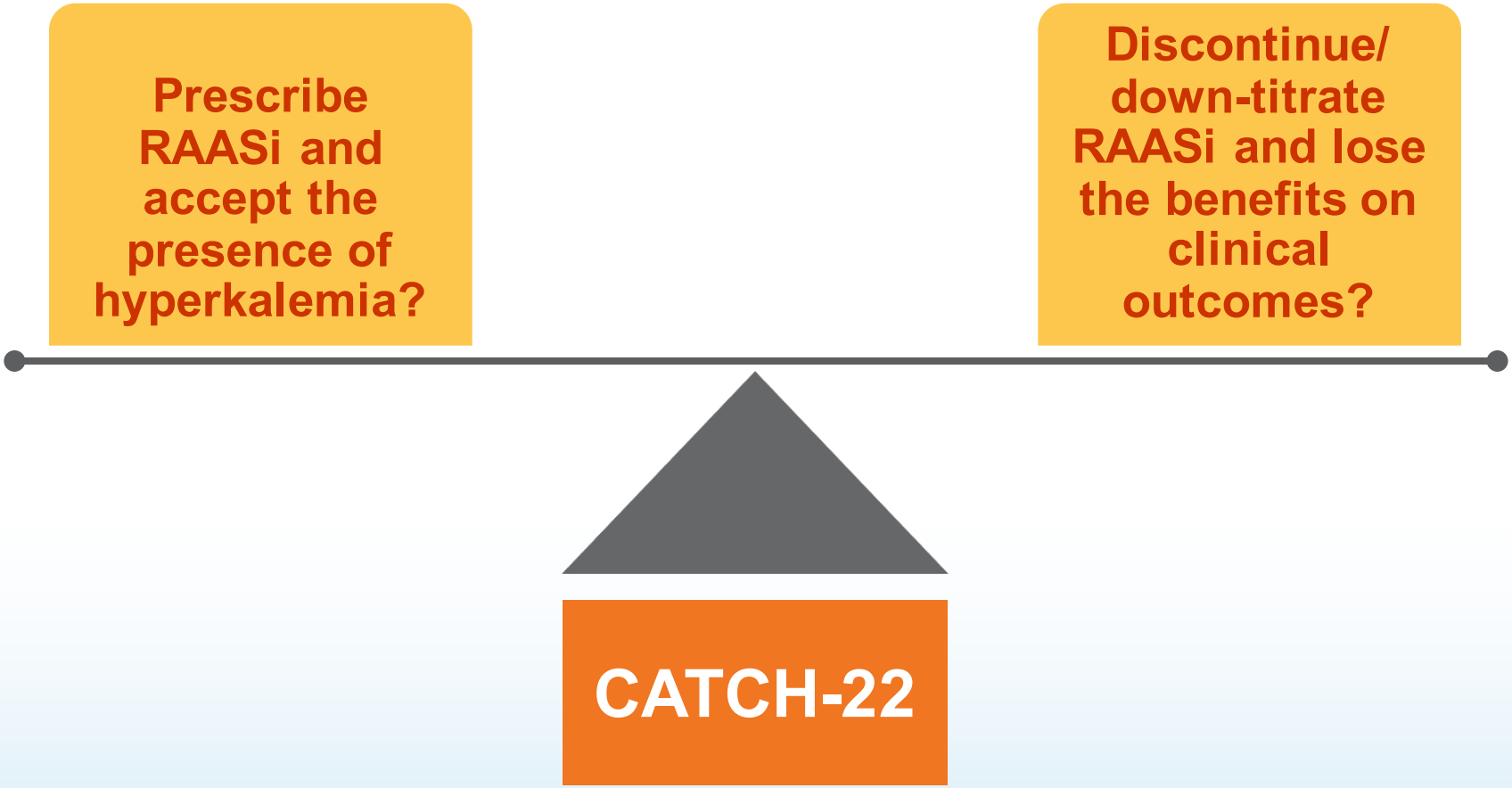
Sodium Polystyrene Sulfonate (SPS)

- SPS removes 0.5-1.0 mg of K^+ in exchange for 2-3 mg of Na^+
- A single daily dose of SPS contains approximately 60 mg of Na^+
- Administration of SPS to patients with renal failure and hyperkalemia is associated with:
  - Worsening edema
  - Weight gain
  - Poor blood pressure control

Nasir, K. et al; J. Ayub Med Coll Abbottabad2014; 26:455

Patients who benefit the most from RAASi therapy are the patients at greatest risk of hyperkalaemia

Catch 22: Hyperkalemia vs RAASi benefits?



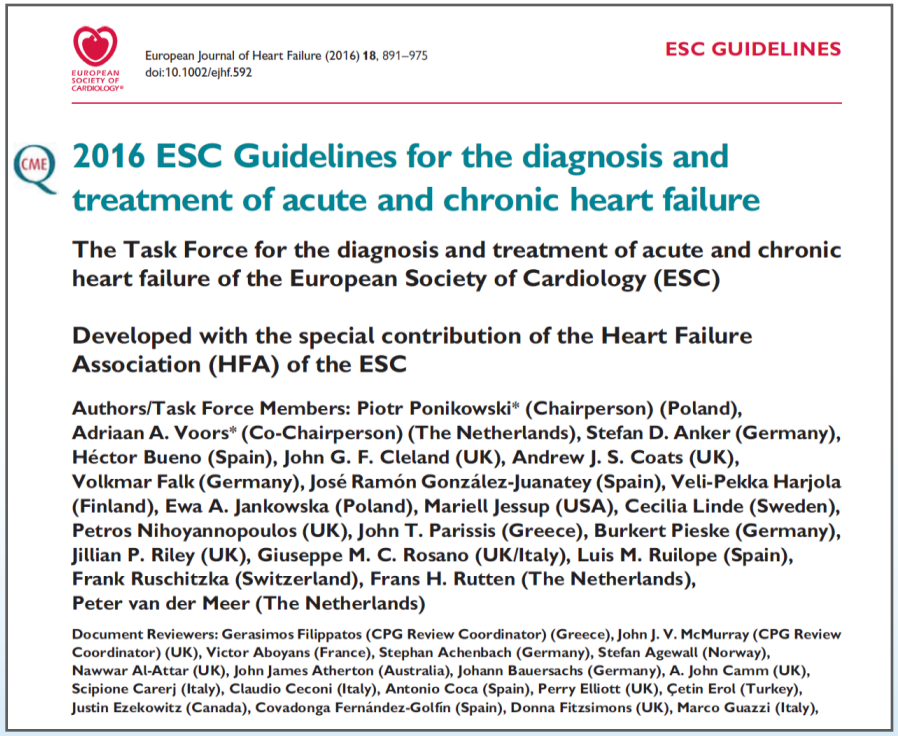
RAASi, renin-angiotensin-aldosterone system inhibitor

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

ECS Guidelines for heart failure 2016: New option?

"Two new potassium binders (patiromer and sodium zirconium cyclosilicate) are currently under consideration for regulatory approval.

Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium and preventing recurrent hyperkalemia in patients with HF and CKD in the context of treatment with RAAS inhibitors."



European Journal of Heart Failure (2016) **18**, 891–975
doi:10.1002/ejhf.592

ESC GUIDELINES

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)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

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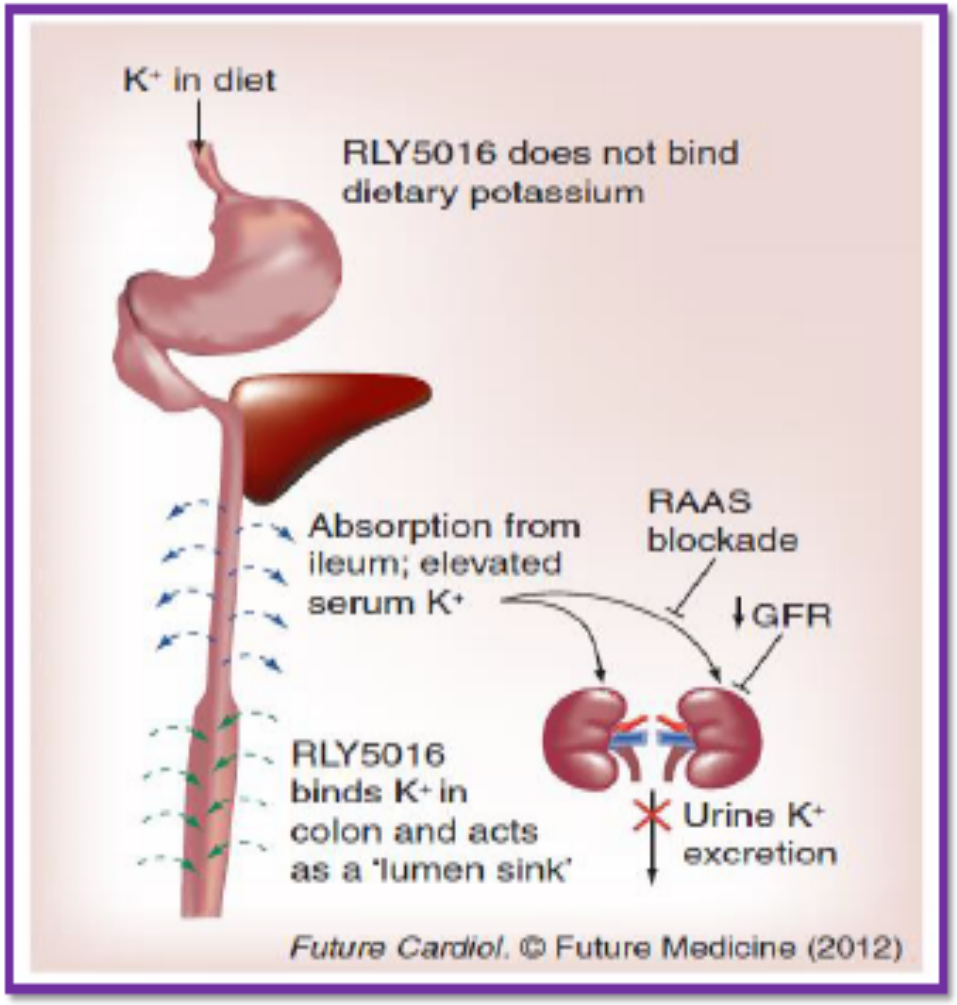
Ponikowski P et al. Rev Esp Cardiol (Engl Ed). 2016 Dec;69(12):1167. doi: 0.1016/j.rec.2016.11.005.

Patiromer (RLY5016) is a Polymer That Binds Potassium in the Colon



Hyperkalemia

Hyperkalemia is most commonly caused by chronic kidney disease (CKD), or the use of RAAS blockade drugs that limit urinary K^+ excretion and increase serum K^+ level

Patiromer (RLY5016)

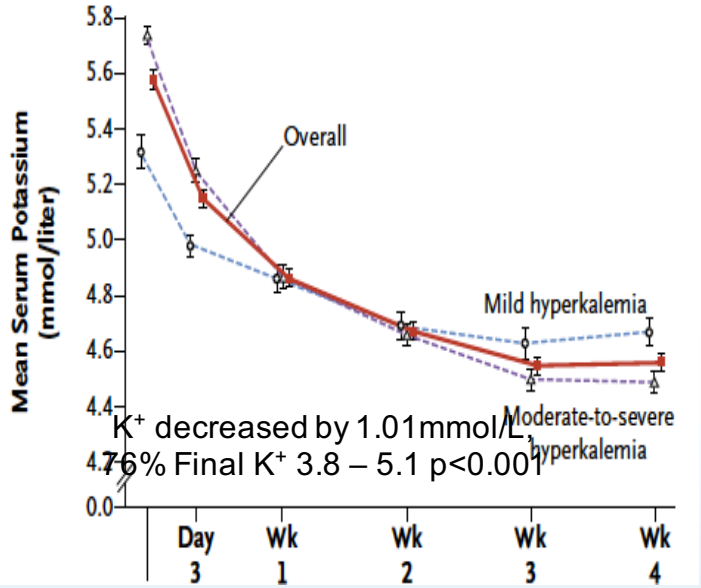
- Patiromer is a non-absorbed K^+ binding polymer
- Patiromer binds K^+ in colon (not dietary K^+)
- Patiromer acts as a "sink" to increase colonic K^+ excretion

Buysse JM et al. 2012 Future Cardiol. 8:17-28

ESTABLISHED IN 1812 JANUARY 15, 2015 VOL. 372 NO. 3

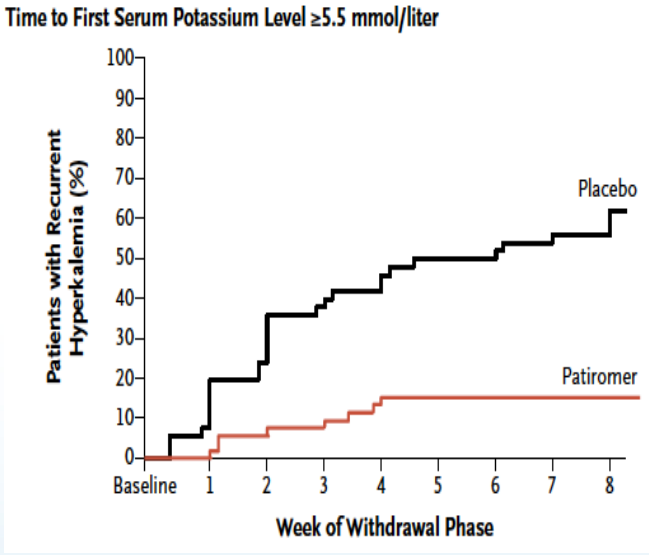
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

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*



K^+ decreased by 1.01mmol/L, 76% Final K^+ 3.8 – 5.1 p<0.001

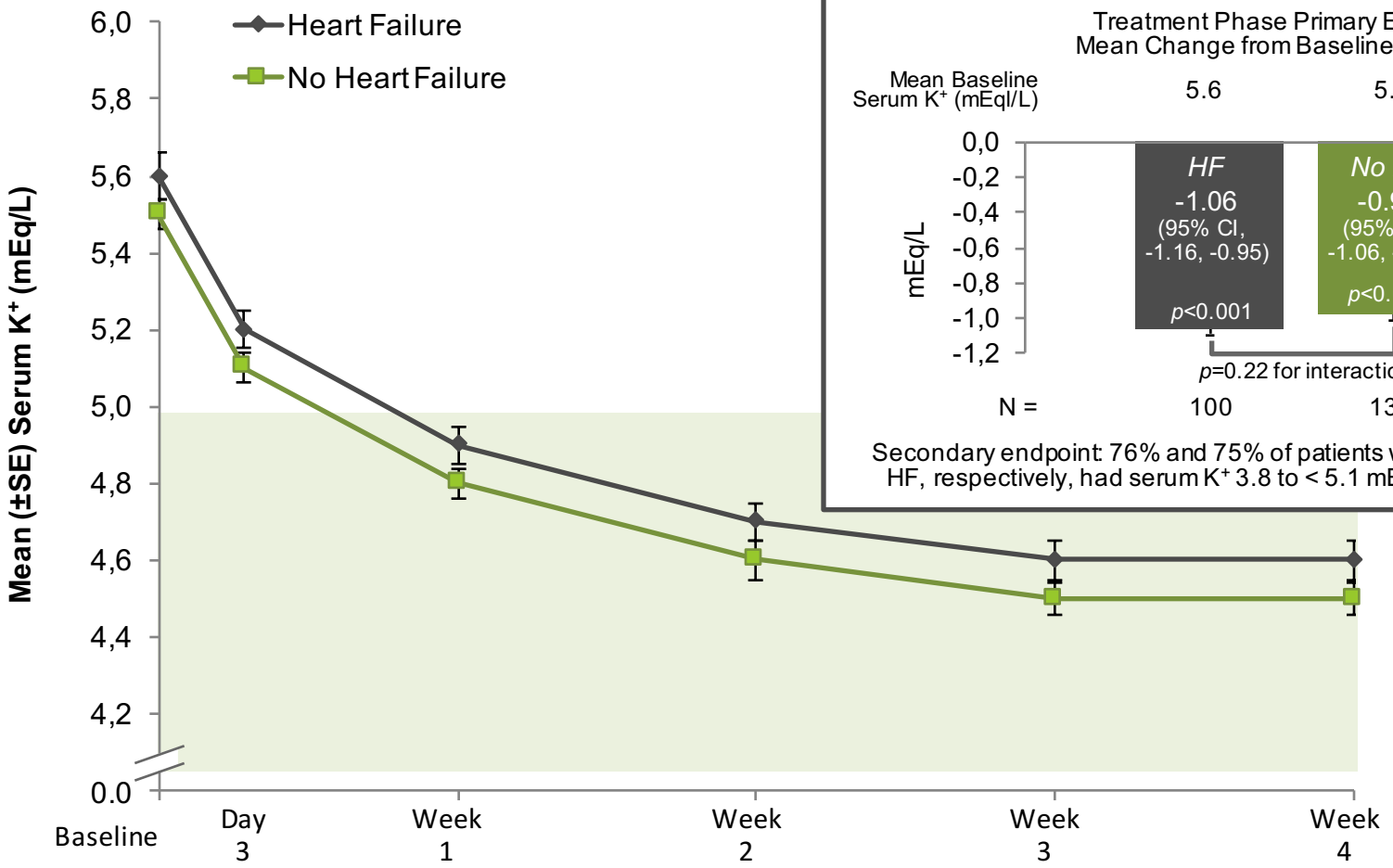
Mean age 64yrs, eGFR: 35, K^+ 5.6mmol/L



K^+ rise to ≥5.5mmol/L:
Placebo 60%, Patiromer 15%, p<0.001

Weir M et al. *NEJM* 2015;372:211–21.

Primary Endpoint: Mean Change in Serum K+ From Baseline to Week 4 During the Treatment Phase (Part A)



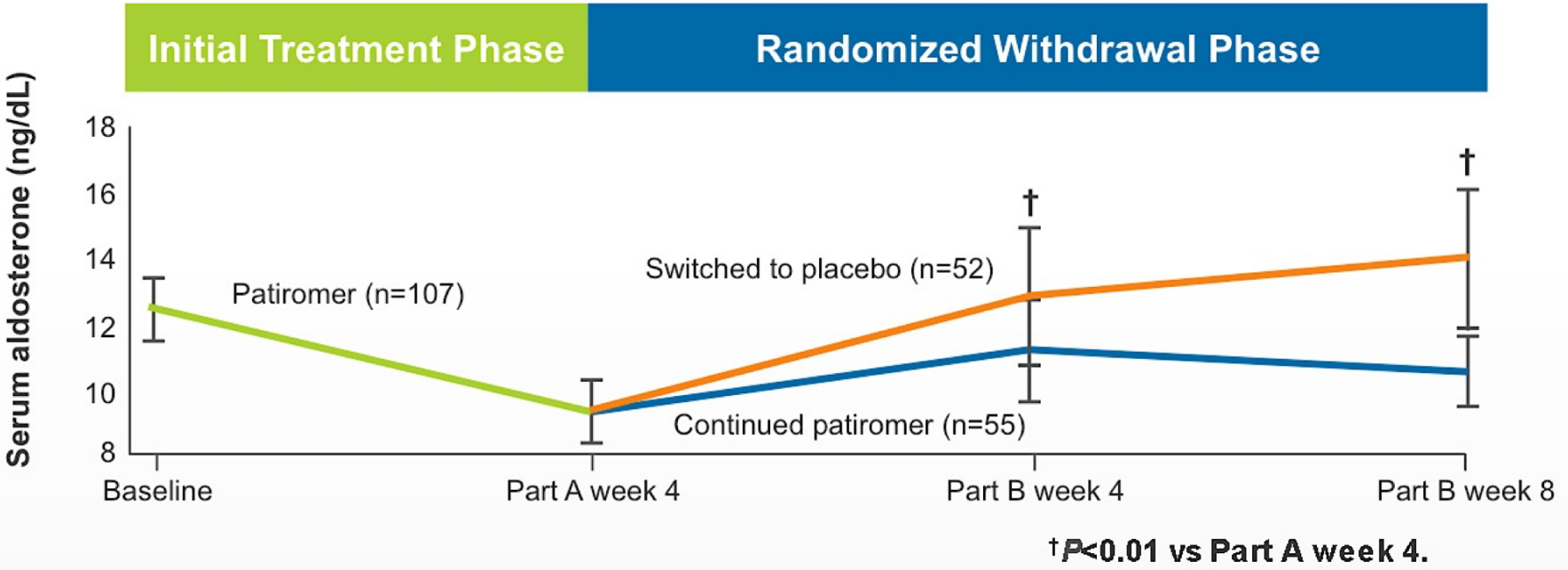
Mean (±SE) serum K⁺ change from baseline (mEq/L)					
Heart failure	-0.5±0.05	-0.8±0.05	-0.9±0.05	-1.1±0.05	-1.1±0.05
No heart failure	-0.5±0.04	-0.7±0.04	-0.9±0.04	-1.0±0.04	-1.0±0.04

CI: 95% confidence interval; HF: heart failure; K⁺: potassium; SE: standard error.

From Pitt B, et al. *Eur J Heart Fail.* 2015;17:1057-1065. © 2015 The Authors, published by John Wiley & Sons Ltd on behalf of the European Society of Cardiology; licensed under a Creative Commons Attribution-NonCommercial-NoDerivs License.

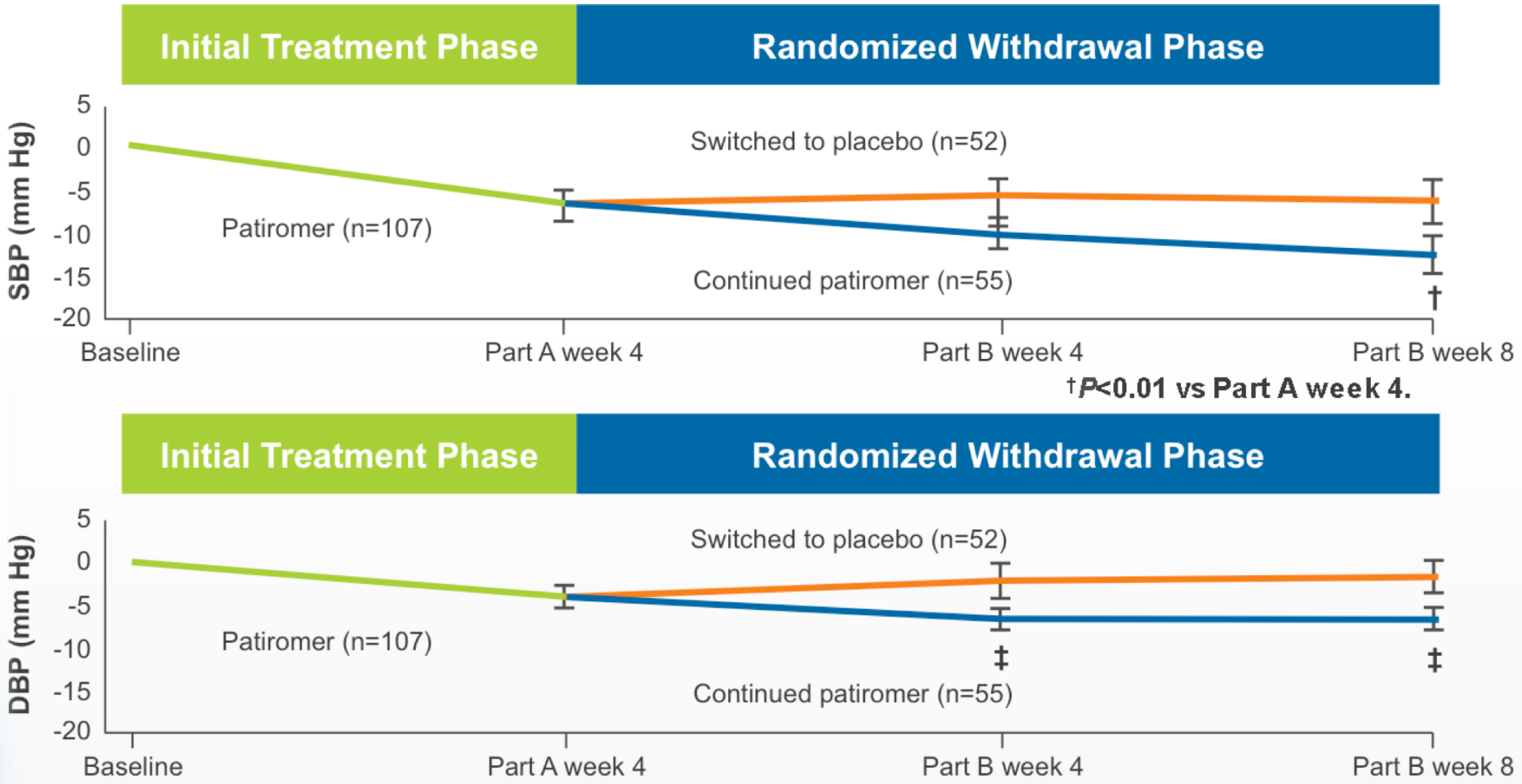
OPAL-HK Part B: Effect of Continuing Versus Discontinuing Patiromer on Mean Serum Aldosterone

Exploratory Endpoint



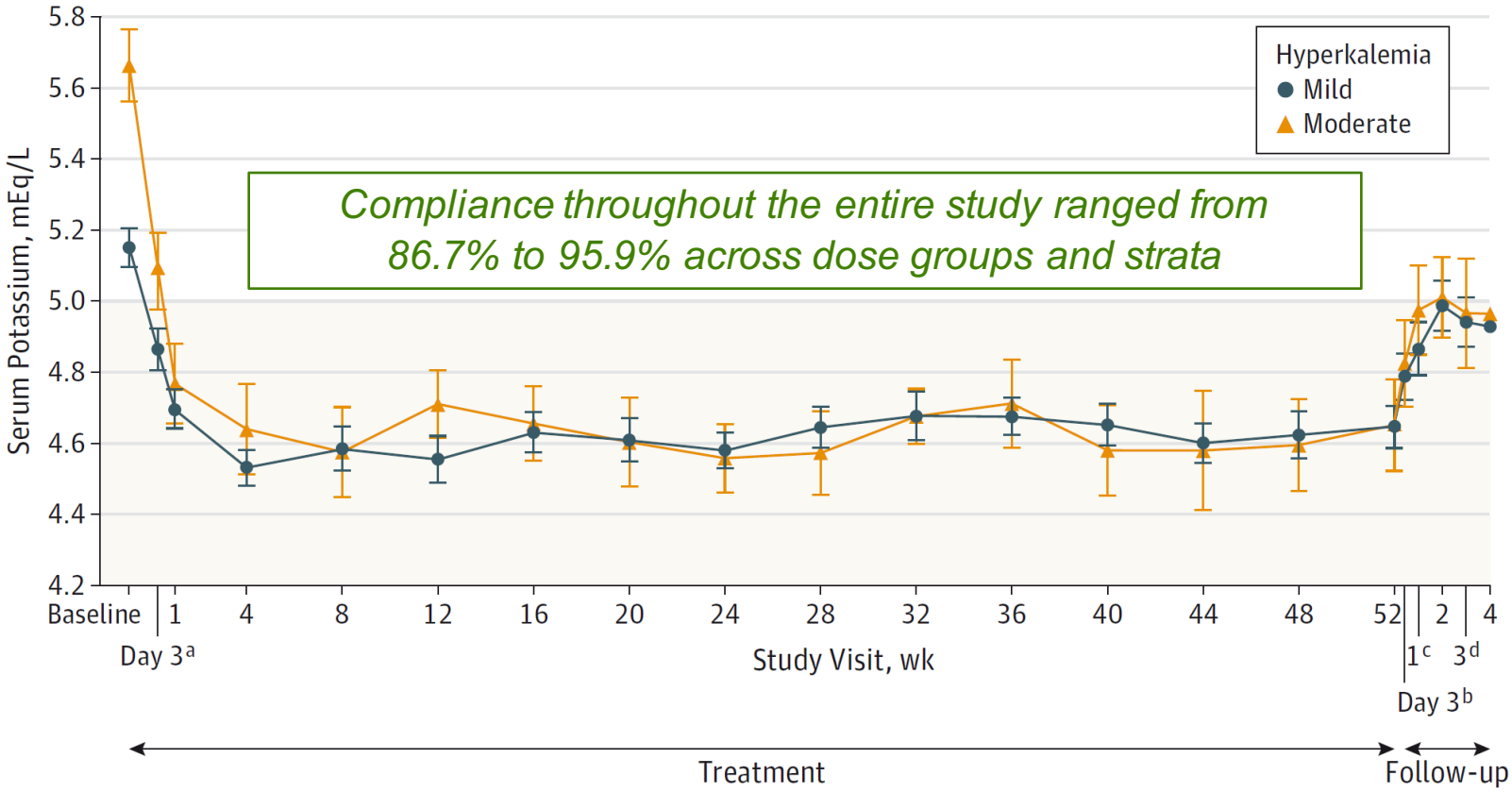
Weir M, et al. Presented at the ASH 2015 Annual Scientific Meeting; New York, NY; May 15-19, 2015. Poster LB-1.

OPAL-HK Part B: Effect of Continuing Versus Discontinuing Patiromer on Mean Serum Systolic and Diastolic BP



Weir M, et al. Presented at the ASH 2015 Annual Scientific Meeting; New York, NY; May 15-19, 2015. Poster LB-1.

AMETHYST-DN: Least Squares Mean (95% CI) Serum K+ Levels Over 52 Weeks and During Posttreatment Follow-up



No. of patients

Hyperkalemia																	
Mild	218	204	199	192	175	168	161	161	163	158	156	151	148	149	145	131	126
Moderate	83	83	73	70	65	62	62	62	61	53	53	53	52	49	49	48	47

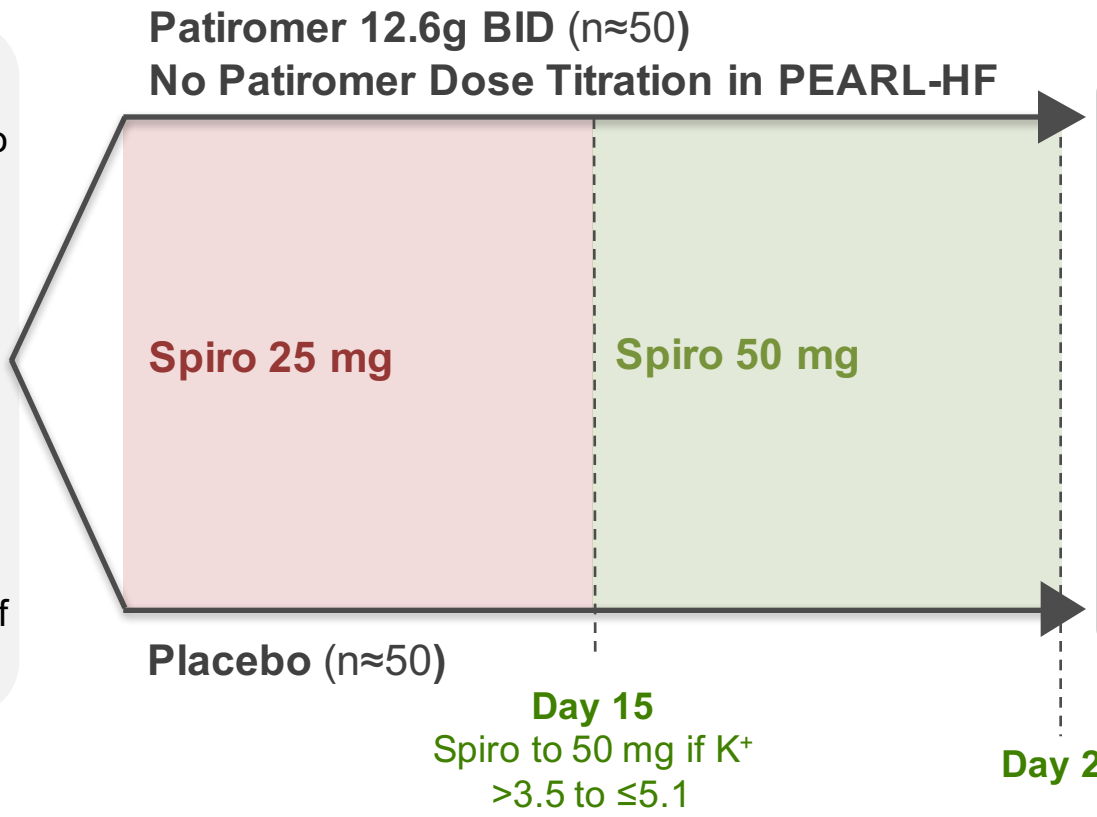
All serum K+ analyses are based on central lab values; 3 patients (2 with mild HK and 1 with moderate HK) did not have a central lab serum K+ value at baseline and therefore are not included in the analysis at this timepoint. * At all timepoints, p<0.001 (2-sided t-test) for lease squares mean changes from baseline and week 52 (or from last dose of patiromer received during the study. BL: baseline, F/Up: follow-up, HK: hyperkalemia.

Bakris G., et al., JAMA 2015; 314:151-61.

PEARL-HF Study Design

Subjects with a history of chronic HF, aged 18 or older, clinically indicated to receive spironolactone with a serum K^+ at screening between 4.3 – 5.1 mEq/L and:

1. CKD (eGFR <60 mL/min) and on ≥ 1 ACEi or ARB or βB; OR
2. Documented Hx hyperK^+ < 6 mo* that led to discontinuation of AA, ACEi or ARB or βB



Endpoints

1°:

Mean change in serum K^+ from BL at Day 28

2°:

% of patients with serum K^+>5.5 mEq/L at any time

% of patients eligible for dose titration to Spiro 50 mg

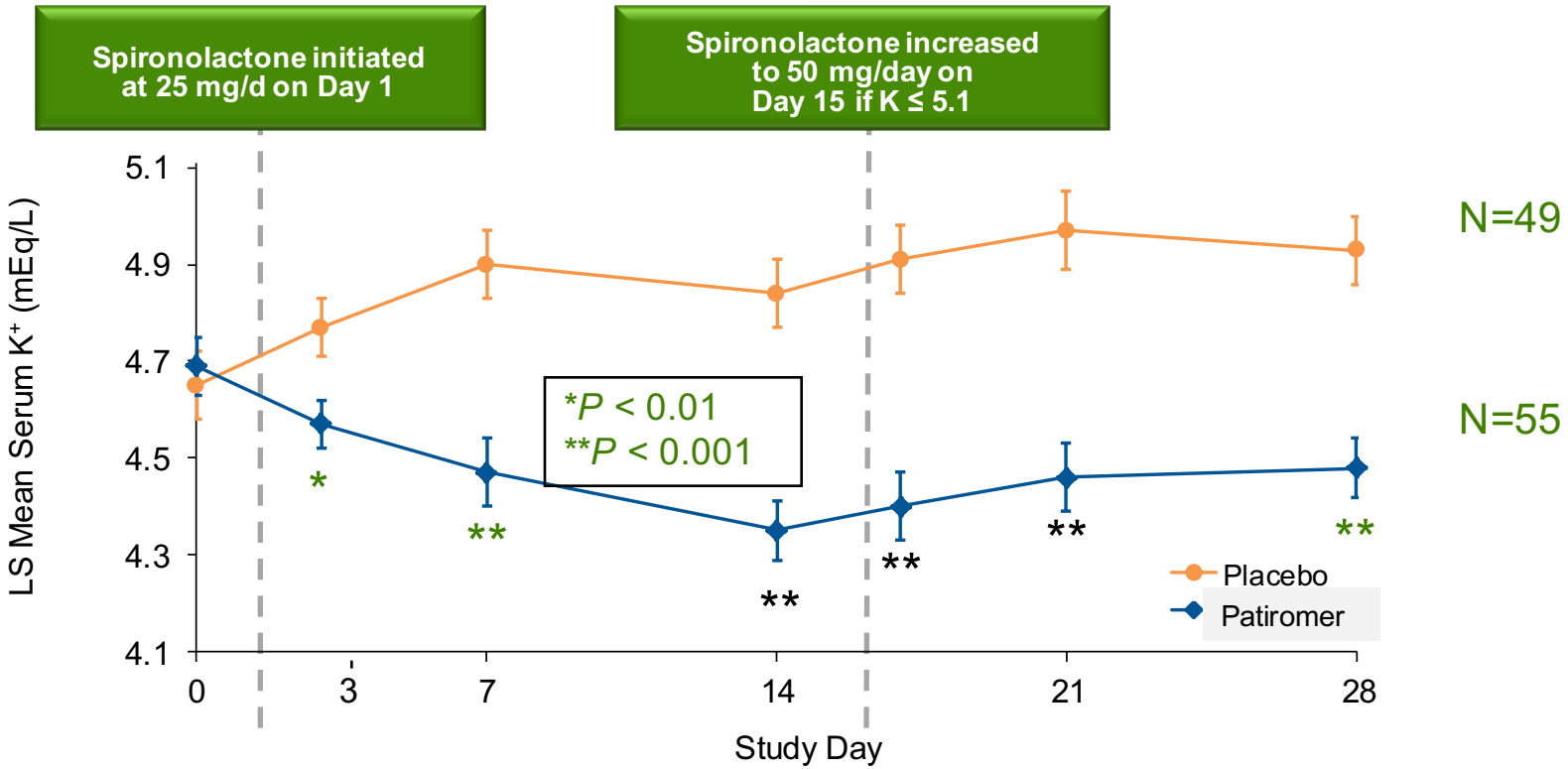
ACEi: angiontensin converting enzyme inhibitor, ARB: angiotension receptor blocker, βB: beta blocker, AA: aldosterone antagonist, Hx: history Spiro: spironolactone.
Note: In the publication, 15g BID (30g total) is reported which refers to dosing calculation that incorporates the weight of the exchange ion and sorbitol complex; Current dosing reflects the active moiety only where 15g BID = 12.6g BID (25.2g total)

* Leading to d/c of RAASi or βB.

Pitt B, Anker SD, Bushinsky DA, et al. Eur Heart J. 2011;32(7):820-828.

PEARL-HF Primary Efficacy Endpoint: Change From Baseline in Serum K+ (LOCF) by Study Visit

Serum K^+ (mEq/L)	Patiromer (n=55)	Placebo (n=49)	P value
Baseline	4.69	4.65	0.664
Change from baseline	-0.22	+0.23	<0.001
Difference Patiromer vs placebo	-0.45		<0.001



LOCF: last observation carried forward.

Pitt B, Anker SD, Bushinsky DA, et al. *Eur Heart J*. 2011;32(7):820-828.

PEARL-HF Secondary Efficacy Endpoint: Proportion of Subjects Able to Increase Spironolactone Dose to 50 mg/day

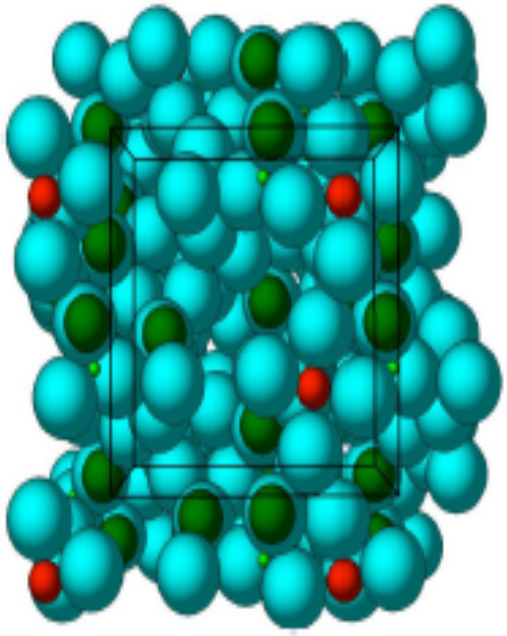
	Patiromer (n=55)	Placebo (n=49)	p value
Subjects able to titrate up spironolactone dose	50 (91%)	36 (74%)	0.019

Pitt B, Anker SD, Bushinsky DA, et al. *Eur Heart J*. 2011;32(7):820-828.

Chemical and physical properties of ZS-9

ZS-9
An orally administered, non-absorbed, selective potassium binder[1]
A selective, high-capacity, inorganic crystalline lattice that selectively traps monovalent cations (e.g. potassium) over divalent cations in the gastrointestinal tract[1]
Has its greatest effects in the duodenum[2]

Structure of ZS-9[2]



Blue spheres=oxygen atoms; red spheres=zirconium atoms, green spheres=silicon atoms

ZS-9, sodium zirconium cyclosilicate.
1. Ash SR et al. Kidney Int 2015;88:404–11; 2. Stavros F et al. PLoS One 2014;9:e114686.

ZS 9

TABLE 4 Clinical Trials With Sodium Zirconium Cyclosilicate

Trial, First Author, Year (Ref #)	Type of Study	Number of Patients (n)	Intervention	Endpoints	Results
ZS-003 Packham et al., 2015 (71)	RCT Double-blinded Phase III	753 patients with K^+ 5.0-6.5 mmol/l 561 patients had eGFR <60 ml/min/1.73 m^2, 502 patients had diabetes, and 300 patients had history of HF	Patients were randomly assigned to thrice-daily: 1. ZS-9 treatment with 1.25, 2.5, 5.0, or 10 g or 2. placebo for 48 h. Patients with K^+ 3.5–4.9 mmol/l at 48 h were randomly assigned to once-daily ZS-9 or placebo on days 3–14.	Potassium levels through 48 h	Reduction of 0.46, 0.54, and 0.73 in the 2.5-, 5-, and 10-g groups, respectively, and 0.25 mmol/l with placebo. At 1 h, a significant reduction was seen after the 10-g dose (-0.11 vs. +0.01 mmol/l in placebo; p = 0.009). At 48 h, 99% of patients treated with 10 g t.i.d. and 94% with 5 g t.i.d. achieved normal K^+. In the maintenance phase, the patients who received 5 g and 10 g ZS-9, serum K^+ levels were maintained at 4.76 mmol/l and 4.58 mmol/l, respectively, compared with >5.10 mmol/l in the placebo group (p < 0.01) after ZS-9 withdrawal. Adverse events: Initial phase (ZS-9 group 12.9% and placebo group 10.8%). Maintenance phase (ZS-9 group 25.1% and placebo group 24.5%).
ZS-002 Ash et al., 2015 (70)	RCT Double-blinded Phase II	90 patients with K^+ 5.0-6.5 mmol/l	Patients were randomly assigned to thrice-daily: 1. ZS-9 treatment with 0.3 (n = 12), 3.0 (n = 24) or 10 g (n = 24) or 2. Placebo (n = 30) for 48 h	Potassium levels through 48 h	Mean baseline serum K^+ was 5.1 mmol/l. Serum K^+ was significantly decreased by 0.92 ± 0.52 mmol/l at 38 h. Urinary potassium excretion significantly decreased with 10-g ZS-9 as compared with placebo at day 2 (+15.8 ± 21.8 mmol/l/24 h vs. +8.9 ± 22.9 mmol/l/24 h). Mild GI adverse events in 20% patients in treatment group vs. 10% in placebo group. Only 90 patients in study.
ZS-004 or HARMONIZE Kosiborod et al., 2014 (69)	RCT Double-blinded Phase III	258 patients with K^+ >5.0 mmol/l	All patients treated with thrice-daily 10 g ZS-9 for 48 h. Patients with normokalemia (3.5–5.0 mmol/l) at 48 h were randomly assigned to receive once-daily 5, 10, or 15 g of ZS-9 or placebo for 28 days	Potassium levels through 8 to 29 days in each group	In the open-label phase, mean K^+ levels decreased from 5.6 to 4.5 mmol/l at 48 h. Median time to normalization was 2.2 h, 84% achieved normokalemia by 24 h and 98% by 48 h. In the randomized phase, K^+ level declined though days 8-29 with all ZS-9 doses vs. placebo (4.8 mmol/l, 4.5 mmol/l, and 4.4 mmol/l for 5 g, 10 g, and 15 g, respectively; 5.1 mmol/l for placebo. The proportion of patients with mean K^+ <5.1 mmol/l during days 8-29 was higher in all treatment groups vs. placebo (80%, 90%, and 94% for the 5-, 10-, and 15-g groups, respectively, vs. 46% with placebo. Edema was more common in the ZS-9, 15-g group (2%, 2%, 6%, and 14% in placebo, 5-g, 10-g, and 15-g groups, respectively). Hypokalemia developed in 10% and 11% in the 10-g and 15-g treatment groups, respectively, vs. none in the 5-g or placebo group.
HARMONIZE HF subgroup Anker et al., 2015 (73)	Double-blinded Phase III	94 patients with K^+ >5.0 mmol/l; 60 receiving RAASi	All patients treated with thrice-daily 10 g ZS-9 for 48 h. Patients with normokalemia (3.5–5.0 mmol/l) at 48 h were randomly assigned to receive once-daily 5 g, 10 g, or 15 g of ZS-9 or placebo for 28 days	Potassium levels through 8 to 29 days in each group	87 (93%) achieved normokalemia after 48 h. In the randomized phase, despite constant RAASi doses, K^+ level declined though days 8-29 with all ZS-9 doses vs. placebo (4.7 mmol/l, 4.5 mmol/l, and 4.4 mmol/l for 5 g, 10 g, and 15 g, respectively; 5.2 mmol/l for placebo. The proportion of patients with mean K^+ <5.1 mmol/l during days 8-29 was higher in all treatment groups vs. placebo (83%, 89%, and 92% for the 5-g, 10-g, and 15-g dose groups, respectively, vs. 40% with placebo. Edema was more common in the maintenance phase, occurring in 1, 2, and 5 patients in the 5-g, 10-g, and 15-g dose groups, respectively, vs. 1 patient in the placebo group.

ZS-003: Phase 3 study

AEs during the maintenance phase		
AEs	Placebo (all arms) n=219	ZS-9 (all arms) n=326
Any event, n (%)	53 (25%)	82 (25%)
Gastrointestinal disorder, n (%)	8 (4%)	18 (6%)
Cardiac disorder, n (%)	2 (1%)	5 (2%)
Urinary tract infection, n (%)	3 (1%)	9 (3%)

AEs, adverse events; ZS-9, sodium zirconium cyclosilicate.

1. Packham DK et al. N Engl J Med 2015;372:222–31.

ZS9: Tolerability in Heart Failure Patients on RAASi from a Phase 3 Study

Incidence of Adverse Events with ZS9 and placebo

Acute Maintenance Phase				
10g ZS9	Placebo	5g ZS9	10gZS9	15gZS9
N=256	N=85	N=45	N=51	N=56
0 (0)	2 (2:4%)	1 (2.2%)	3(5.9%)	8(14.3%)

Peripheral edema

Potassium Binders: Potential Future Clinical Trials

- Evaluate their effectiveness in reducing CV events in patients with CKD, DM, HF and or resistant hypertension in whom RAAS-I have been shown to be effective but who have discontinued a RAAS-I due to hyperkalemia
- Enable the use of RAAS-Is, especially MRAs in patients with an eGFR <30->/=15 ml/min/1.73 m2
- Prevent the occurrence of hyperkalemia and CV events in patients known to benefit from RAAS-Is but who have not been started due to the fear of inducing hyperkalemia

Are Potassium Binders the Solution?

Summary/Conclusions

- Potassium binders are effective in reducing serum potassium and allowing the maintenance or reintroduction of RAASi, especially MRAs in patients with HF and or CKD.
- The long term effectiveness in reducing CV death vs discontinuing or reducing the dose of a RAASi remaining to be determined.

Pitt B, 2017