UTILIZING POTASSIUM BINDERS TO ENABLE RAAS INHIBITION IN HFrEF & HFpEF

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DISCLOSURES

- Financial: Vifor (investigator-initiated study)

OBJECTIVES

- Describe strategies to initiate and optimize RAAS inhibitor therapy in patients with heart failure and chronic hyperkalemia
- Review monitoring guidelines for safe use
- Discuss care integration and team-approach to improve patient outcomes
- Highlight patient education resources

HEART FAILURE BY THE NUMBERS

Most common cause of hospitalization in people aged 65 or older

50% mortality within 5 years of diagnosis

Repeated hospitalizations for ADHF predict mortality

1 OUT OF 4 PATIENTS WITH HEART FAILURE

READMITTED WITHIN 30 DAYS

Benjamin EJ et al. Circulation 137.12 (2018): e67-e492.

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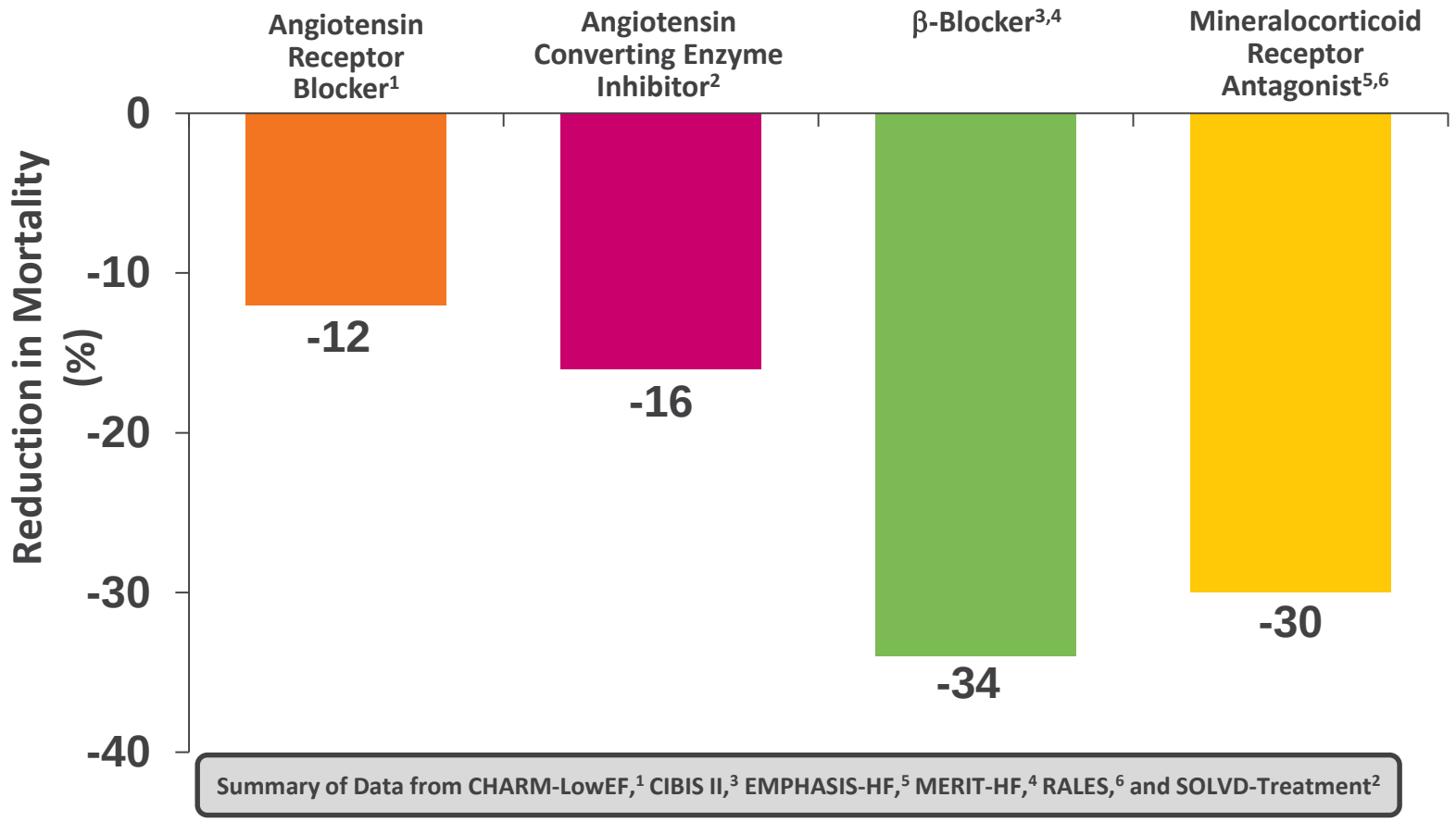
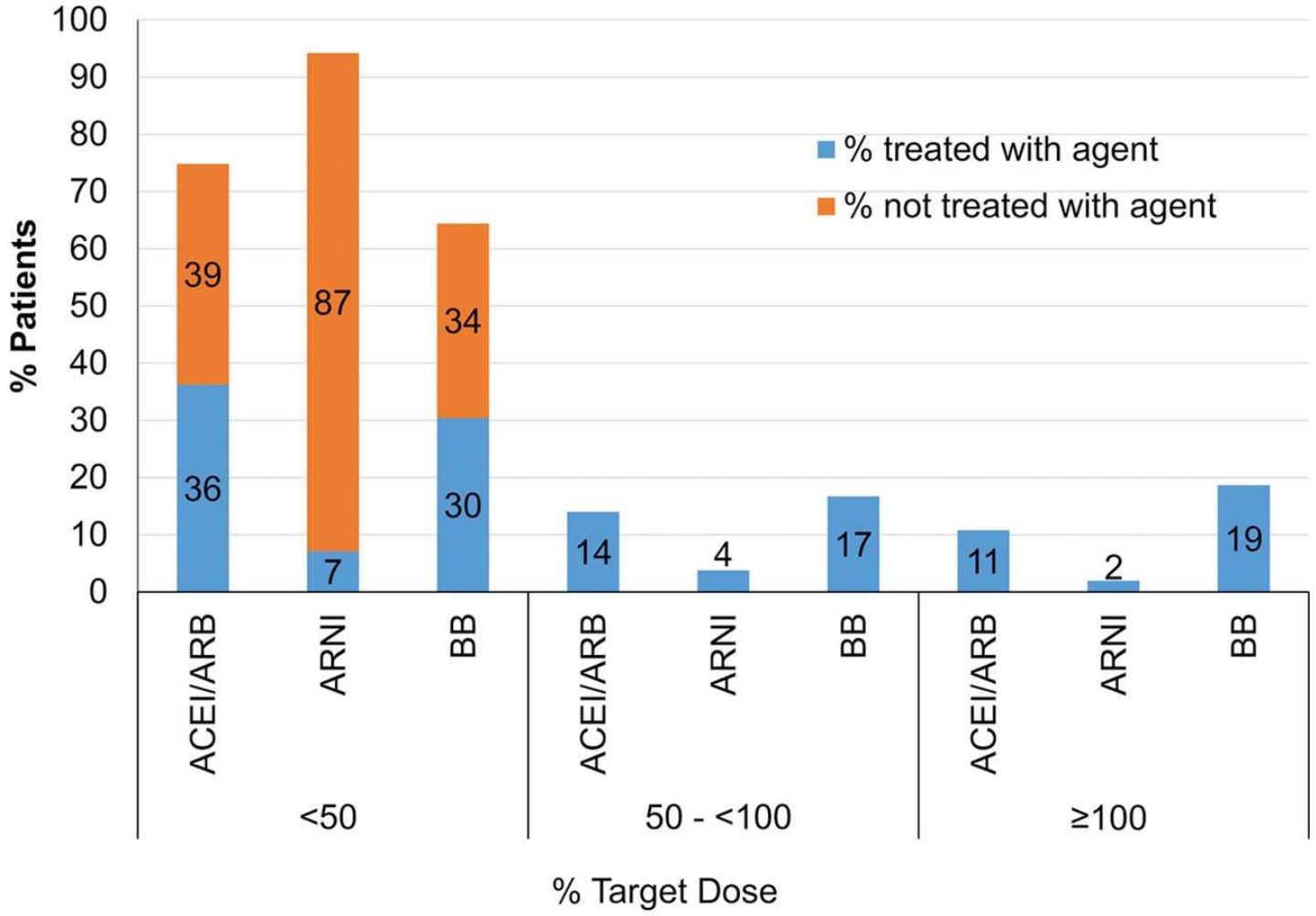
PHARMACOTHERAPY TO REDUCE MORTALITY IN HFrEF



1. Young JB et al. Circulation. 2004;110(17):2618-2626; 2. SOLVD Investigators. N Engl J Med. 1991;325(5):293-302;
3. CIBIS II Investigators. Lancet 1999;353(9146):9-13; 4. MERIT-HF Study Group. Lancet 1999;353(9169):2001-2007;
5. Zannad F et al. N Engl J Med 2011; 364(1):11-21; 6. Pitt B et al. N Engl J Med. 1999;341(10):709-717.

UTILIZATION OF GUIDELINE-DIRECTED MEDICAL THERAPY IN THE REAL WORLD



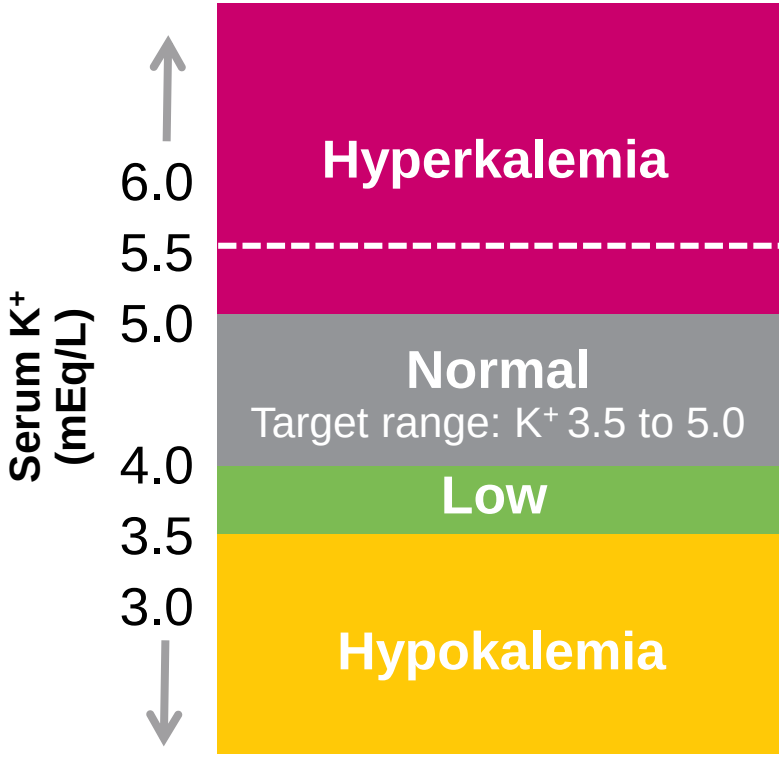
Peri-Okonny PA et al. JACC Heart Fail. 2019;7(4):350-358.

PREVALENCE OF HYPERKALEMIA IN HEART FAILURE

General population	RAAS inhibition	Heart failure
• 2-3%	• 2-10%	• 39%

Palmer BF et al. JAMA. 2015;314:2405-2406. Weir MR et al. Clin J Am Soc Nephrol. 2010;5:531-48.
Bakris GL et al. Kidney Int. 2000;58:2084-92.Thomson RW et al. J Am Heart Assoc. 2018; 7(11):e008912.

WHAT IS HYPERKALEMIA? SERUM POTASSIUM CUTOFF VALUES VARY WIDELY IN STUDIES AND GUIDELINES



- The upper limit of normal (ULN) for serum K^+ levels varies across guidelines and publications
  - Serum K^+ levels of 5.0, 5.5, or 6.0 mEq/L are commonly used cutoffs for ULN

Einhorn LM et al. Arch Intern Med. 2009;169:1156-62; Yancy C, et al. Circulation. 2017;136:r137-2161;
McMurray JJV et al. Eur Heart J. 2012;33:1787-1847; Rastergar A, Soleimani M. Postgrad Med J. 2001;77:759-64.

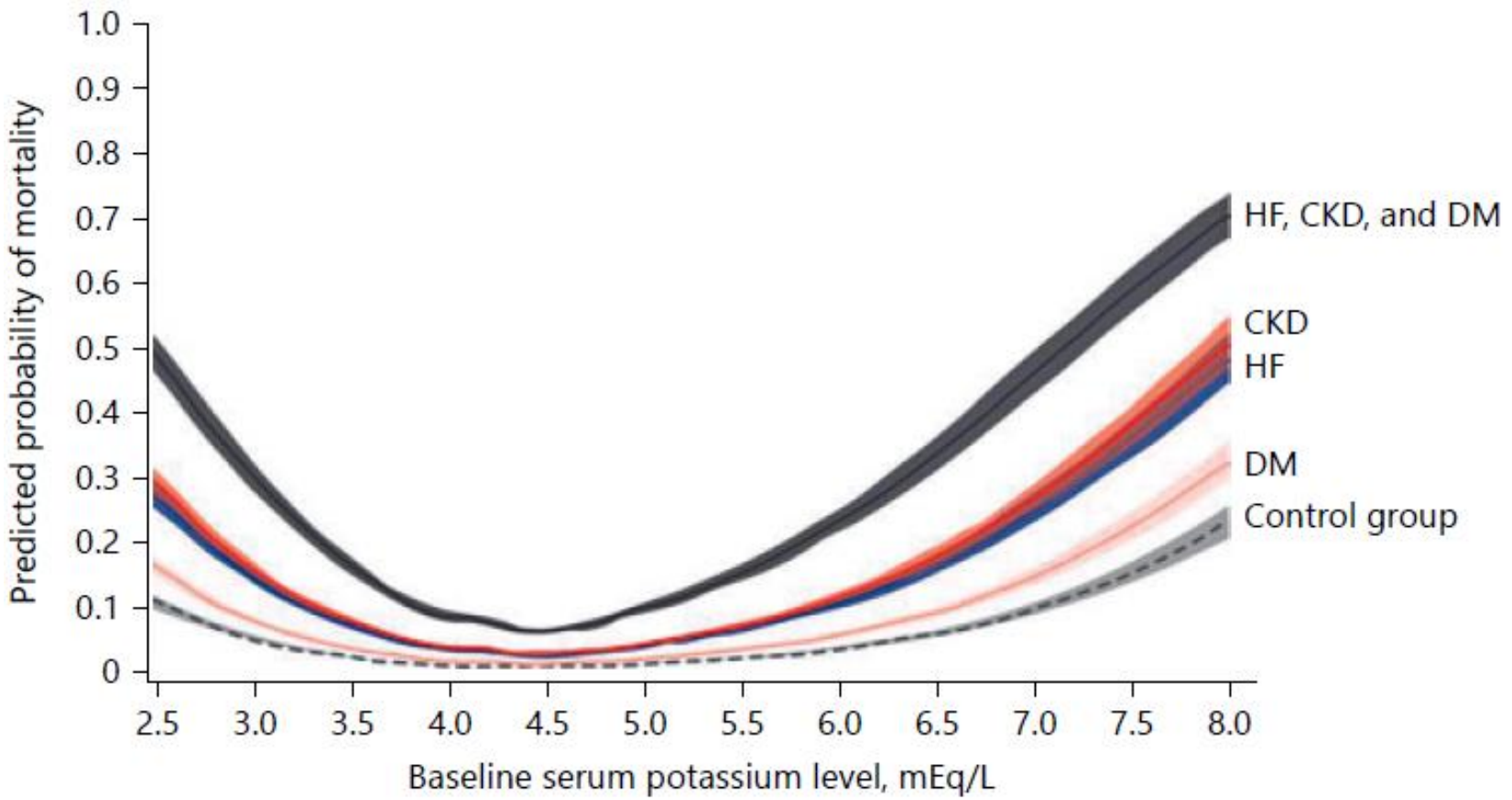
CAUSES OF HYPERKALEMIA

Mechanism	Causes*
Increased K^+ load	• Dietary intake • Drug-induced: potassium supplements, herbal supplements, packed RBC infusions
Altered K^+ distribution	• Metabolic: acidosis, hyperglycemia (in diabetes) • Drug-induced: insulin antagonists, hypertonic solutions, digoxin, β-blockers
Reduced K^+ excretion	• Metabolic: hyporeninemic, hypoaldosteronism, oliguria • Drug-induced: potassium-sparing diuretics, cyclosporine, tacrolimus, pentamidine, trimethoprim, lithium
Impaired renin-aldosterone function	• Drug-induced: ACEIs, ARBs, ARNIs, MRAs, β-blockers, heparin, NSAIDs, COX-2 inhibitors
Reduced GFR/hypovolemia	• Metabolic: acidosis, HF, dehydration • Drug-induced: antihypertensives, diuretics
Laboratory error	• Hemolyzed RBCs, inappropriate sample handling, erroneous reporting, equipment malfunction

*Not all-inclusive table

NKF K/DOQI website. Guideline 11: Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in CKD.

ADJUSTED MORTALITY ACCORDING TO POTASSIUM AND COMORBID CONDITIONS



Spline analysis adjusted for covariates showing serum potassium as a continuous variable with all cause mortality in HF, CKD, DM, and combined vs control group.

Collins AJ, et al. Am J Nephrol 2017;46:213-21.

THE GREY ZONE: UNDERAPPRECIATED

- Hyperkalemia: K+ > 5mEq/L
- Severe hyperkalemia: K+ > 6.5 mEq/L
  - Need for acute care
- Grey zone: when to start worrying about potassium and what to do?

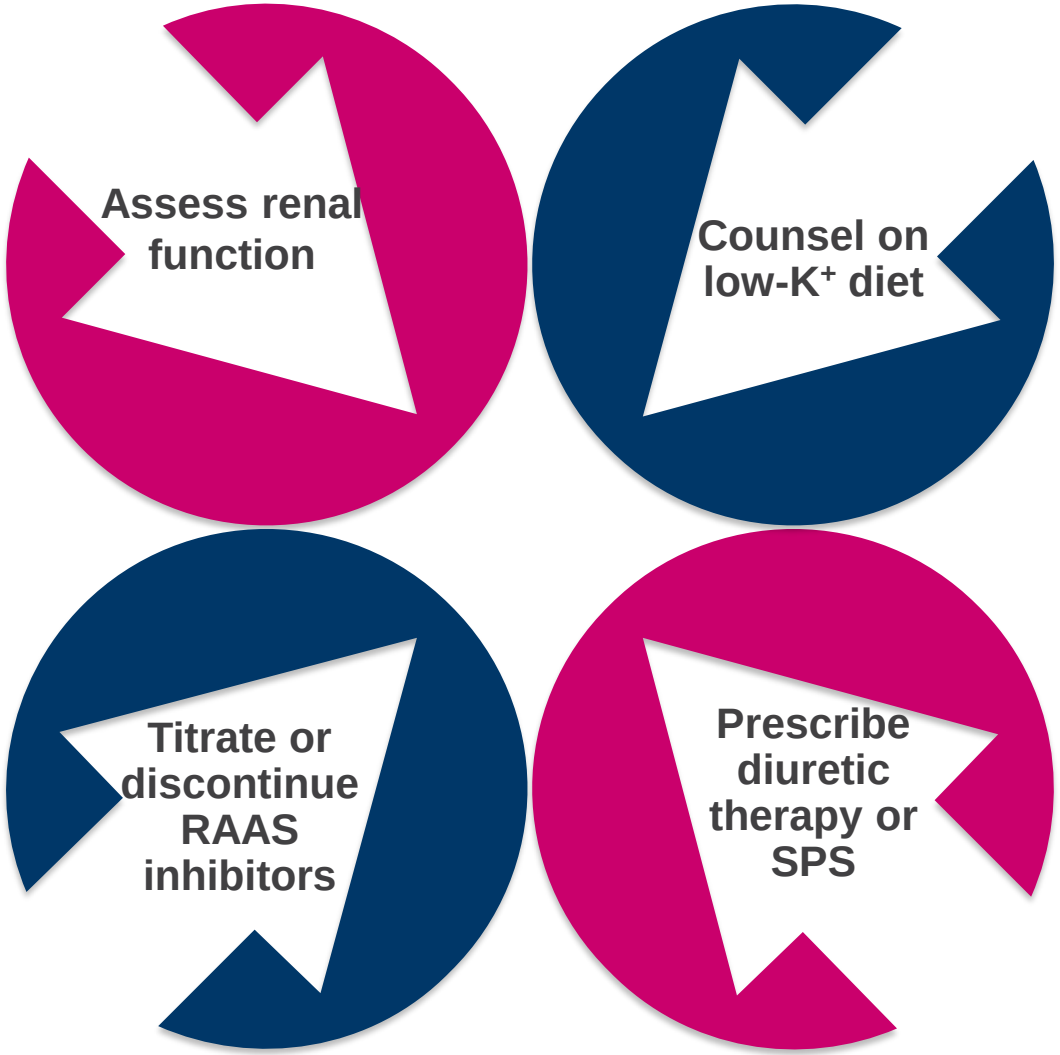
Action	K >5 mEq/L	K >5.5 mEq/L
ED visit	1.2%	3.1%
Repeat serum K measurement	**18.4%**	**44.3%**
Rx SPS	0.7%	4.7%
Rx/Incr diuretic	5.6%	9.2%
D/C ACEI or ARB	**10.5%**	**24.3%**
Decr ACEI or ARB	2.6%	4.8%
D/C K-sparing diuretic	**23%**	**48.5%**
Decr K-sparing diuretic	1.4%	1.1%

Chang AR et al. Hypertension. 2016;67:1181–88.

HYPKERLAMIA IS A COMPLEX CLINICAL CHALLENGE

- Comorbidities such as CKD, DM & HF place patients at high risk of hyperkalemia
- RAAS inhibitors used to treat comorbidities can further increases risk
- However, discontinuing therapy increases risk of CV events and mortality
- Comorbidities rarely are cured resulting in lifelong balance of lifestyle, medications and monitoring

MANAGEMENT OF CHRONIC HYPERKALEMIA BEFORE ERA OF NEW POTASSIUM BINDERS



Kidney Disease Outcomes Quality Initiative. Am J Kidney Dis. 2004;43(suppl 1):S1-S290; Palmer BF et al. N Engl J Med. 2004;351:585-92.

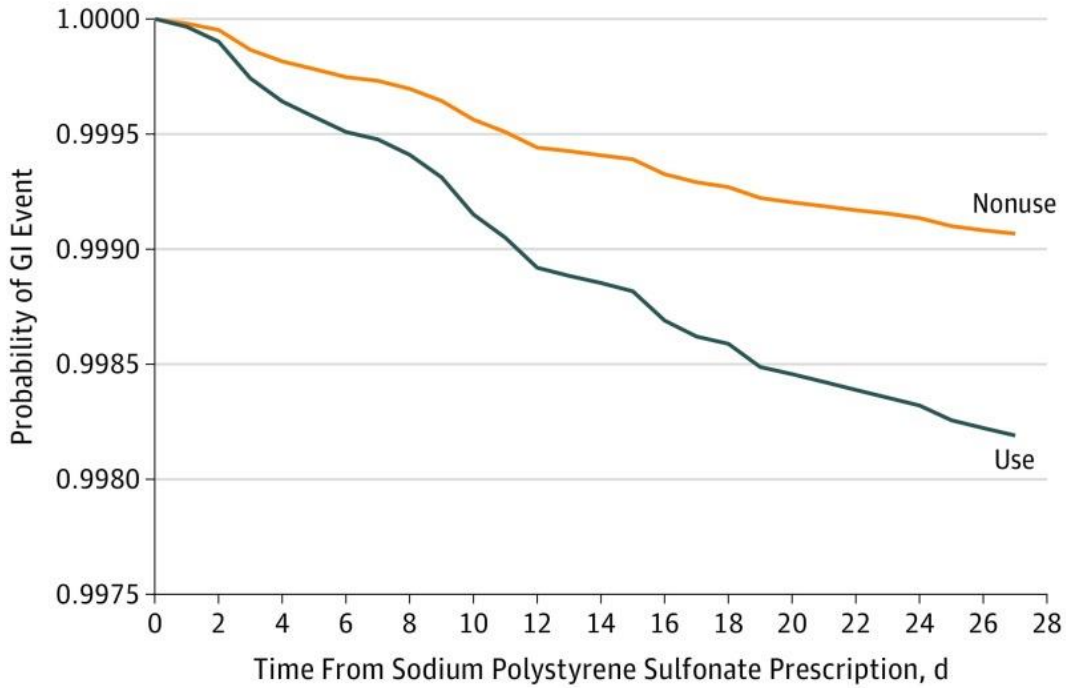
LIMITATIONS OF CHRONIC HYPERKALEMIA STRATEGIES

Treatment Focuses on Diet Changes, Removal of Therapies That Increase Serum K^+ and SPS

RAAS inhibitor reduction	• Dose limiting or discontinuing increases risk of morbidity and mortality in patients with heart failure
SPS	• Warnings related to serious GI AEs and colonic necrosis • Precaution related to Na^+
Dietary K^+ restriction of 50–75 mEq/day	• K^+ is a common ingredient in many foods • Restricts consumption of healthy foods (DASH Diet) • Low-K^+ diet often expensive

SPS: NOT APPROPRIATE FOR OUTPATIENT USE

- Population-based, retrospective matched cohort study of older adults (≥ 66 years) dispensed SPS in outpatient setting
- SPS associated with higher risk of ED visit or hospitalization for GI ADE (intestinal ischemia/thrombosis, ulceration) compared with non-use



HR 1.94 (95% CI: 1.10 3.41)

Noel JA et al. JAMA Intern Med. 2019;179(8):1025-33.

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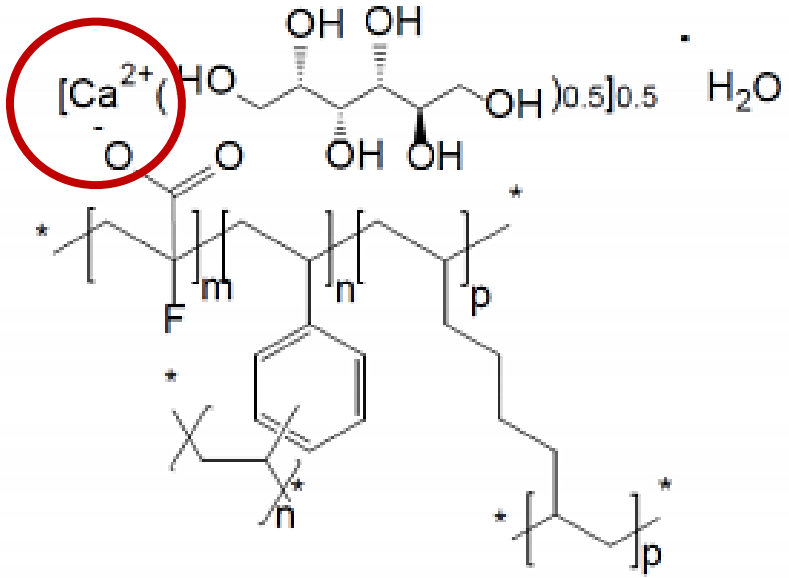
PATIROMER CALCIUM SORBITEX

- Primary effect in colon
  - Exchanges Ca++ for K+
- Available as
    - 8.4 g, 16.8 g, 25.2 g powder packets
    - Must be refrigerated, stable for 3 months at room temperature
    - Take with or without food
    - Starting dose 8.4 g once daily
    - Titrate weekly
- Onset of action: 7 hours
- DDI interactions: separate administration by 3 hours



m = number of 2-fluoro-2-propenoate groups

m = 0.91

n, p = number of crosslinking groups

n + p = 0.09

H_2O = associated water

* = indicates an extended polymeric network

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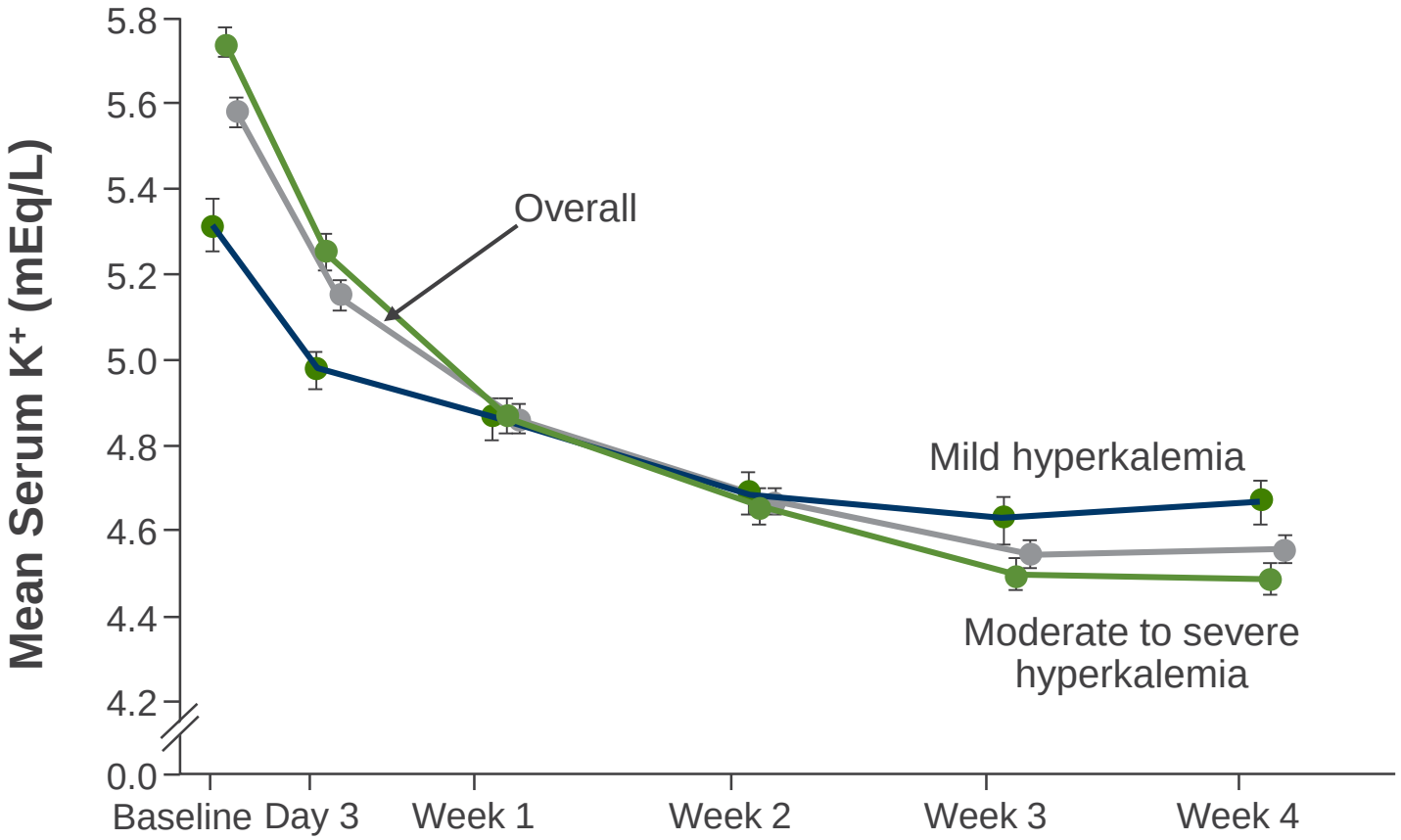
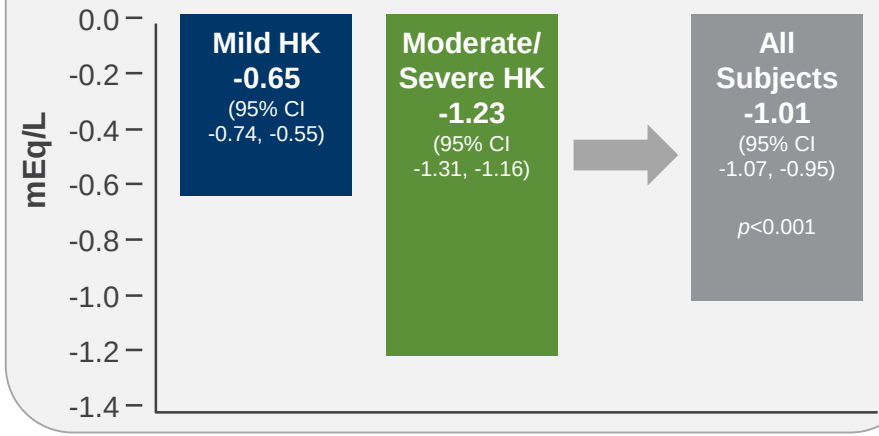
ONSET: OPAL-HK

76% of subjects had serum K^+ in the target range (3.8 to <5.1 mEq/L) at week 4



Primary Efficacy Endpoint:
Mean Change from Baseline to Week 4 (All Subjects)



Weir MR et al. N Engl J Med. 2015;372(3):211-221.

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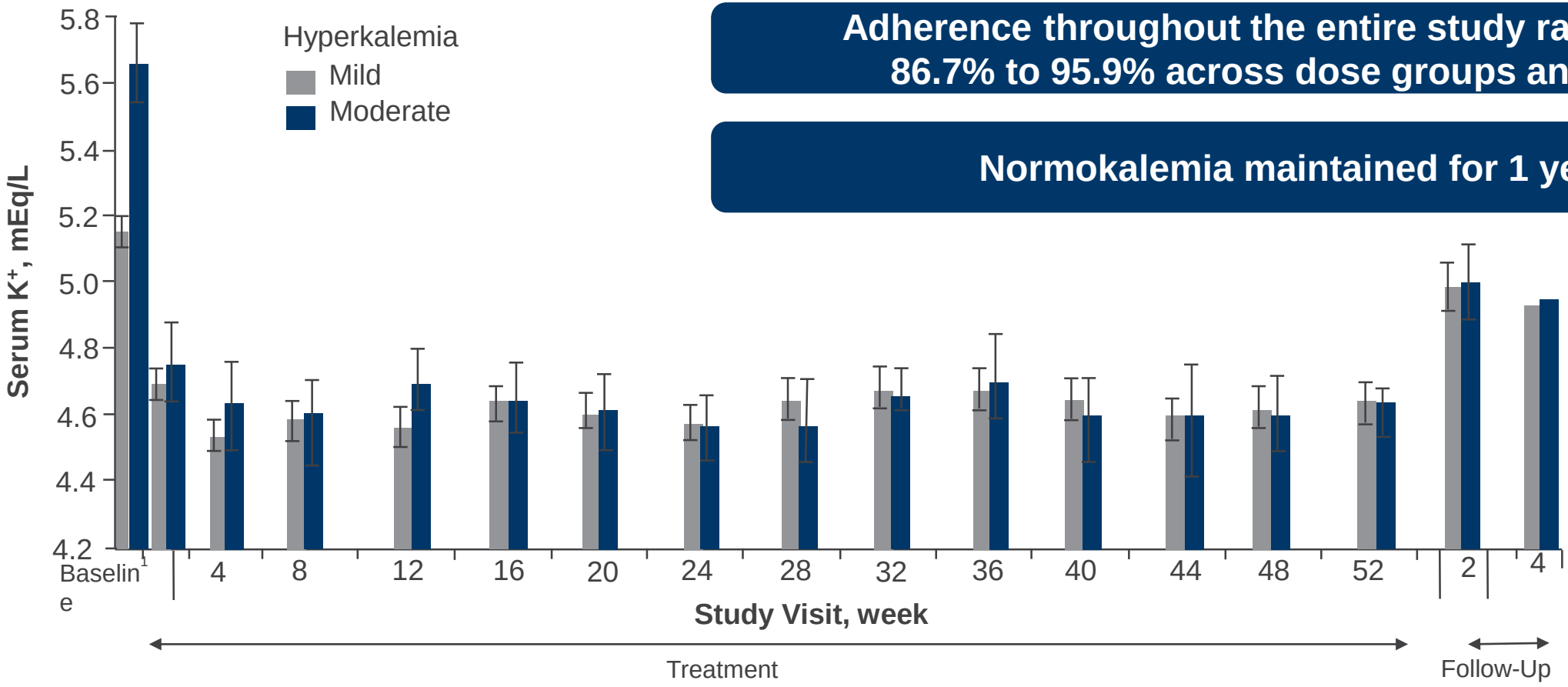
LONG TERM EFFICACY: AMETHYST-DN



Adherence throughout the entire study ranged from 86.7% to 95.9% across dose groups and strata

Normokalemia maintained for 1 year

Bakris G et al. JAMA. 2015;314:151-161.

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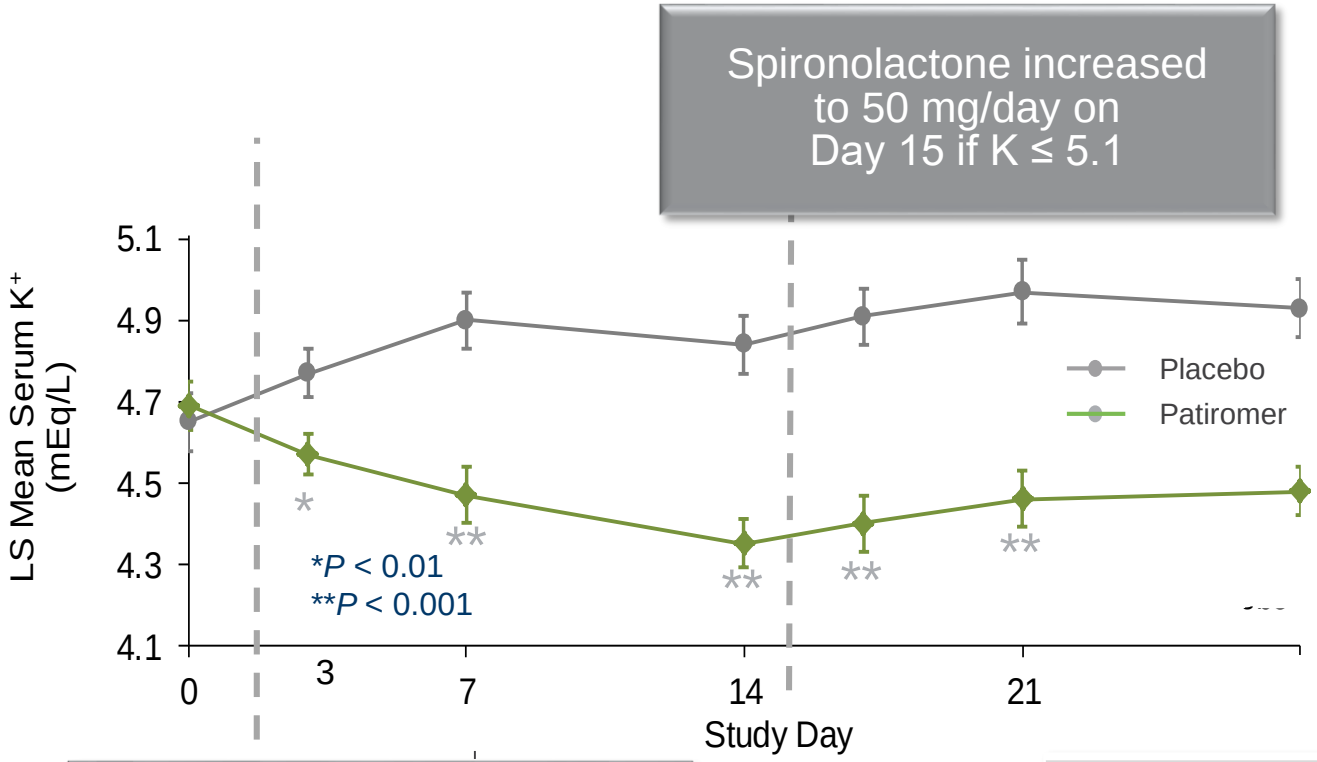
RAASi ENABLEMENT: PEARL-HF



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

Pitt B et al. Eur Heart J. 2011;32(7):820-828.

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ADVERSE DRUG EVENTS: AMETHYST-DN

Adverse event	Mild HK (n = 220)	Moderate HK (n = 84)	Overall (n = 304)
Hypomagnesemia†	15 (7%)	11 (13%)	26 (9%)
Worsening of HTN	14 (6%)	10 (12%)	24 (8%)
Worsening of CKD	14 (6%)	14 (17%)	28 (9%)
Diarrhea	12 (6%)	5 (6%)	17 (6%)
Constipation	11 (5%)	8 (10%)	19 (6%)
Hypoglycemia†	4 (2%)	6 (7%)	10 (3%)

Bakris G et al. JAMA. 2015;314:151-161.

DRUG-DRUG INTERACTIONS

>50% Interaction	30%–50% Interaction	<30% Interaction
Amlodipine Cinacalcet Ciprofloxacin Levothyroxine Quinidine Trimethoprim	Clopidogrel Lithium Metoprolol Verapamil Warfarin	Allopurinol Amoxicillin Apixaban Aspirin Atorvastatin Cephalexin Digoxin Glipizide Lisinopril Phenytoin Rivaroxaban Spironolactone Valsartan

- In vitro binding studies as part of FDA requirement
  - 28 drugs tested
  - 50% of tested drugs were bound by patiromer

DRUG-DRUG INTERACTIONS

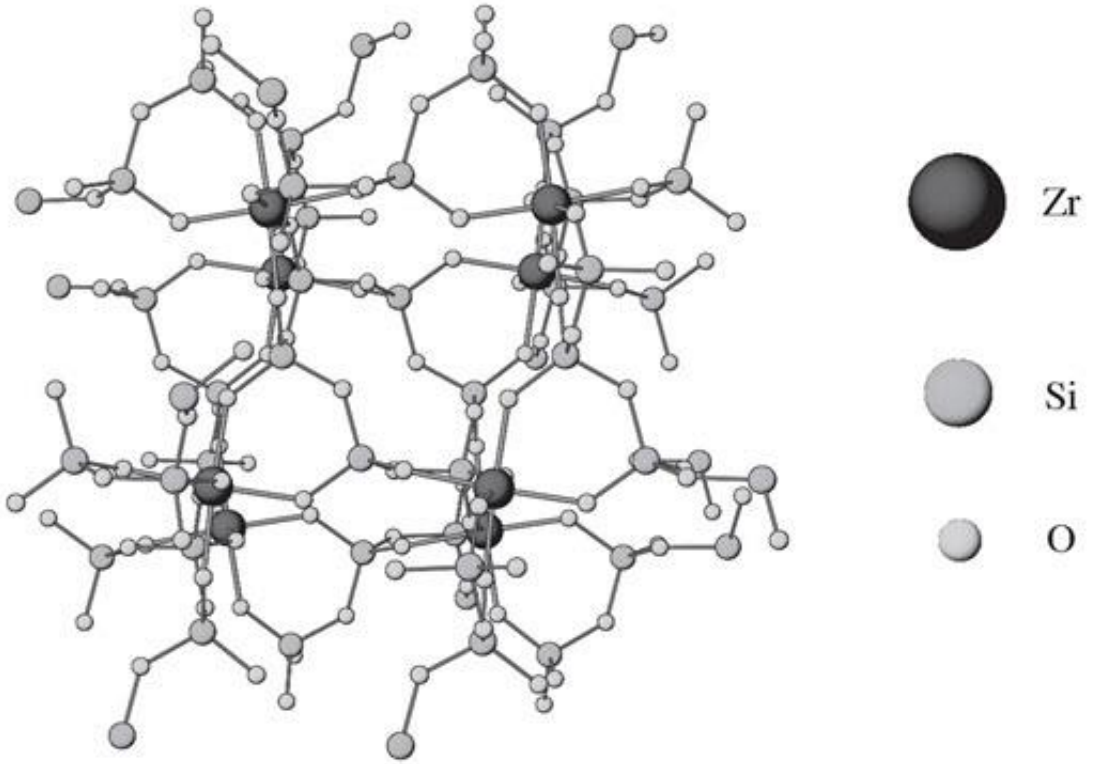
Drugs Evaluated
Amlodipine
Cinacalcet
Ciprofloxacin*
Clopidogrel
Furosemide
Levothyroxine*
Lithium
Metformin*
Metoprolol
Trimethoprim
Verapamil
Warfarin

- *In vivo* studies conducted to further answer question
  - 12 medications studied
  - Low risk of drug-drug interactions with other oral medications
- Administer other oral medications at least 3 hours before or 3 hours after

*Patiromer decreased systemic exposure of these medications

SODIUM ZIRCONIUM CYCLOSILICATE (SZC)

- Traps potassium throughout intestine
  - Exchanges Na+ and H+ for K+
- Available as
  - 5 g, 10 g, powder packets
  - Mix with water
  - Take with or without food
  - Starting dose 10 grams TID for up to 48 hours
  - Maintenance dose 5 grams every other day to 15 g daily
  - Titrate weekly
- Onset of action: 1 hour
- DDI interactions: separate administration by 2 hours



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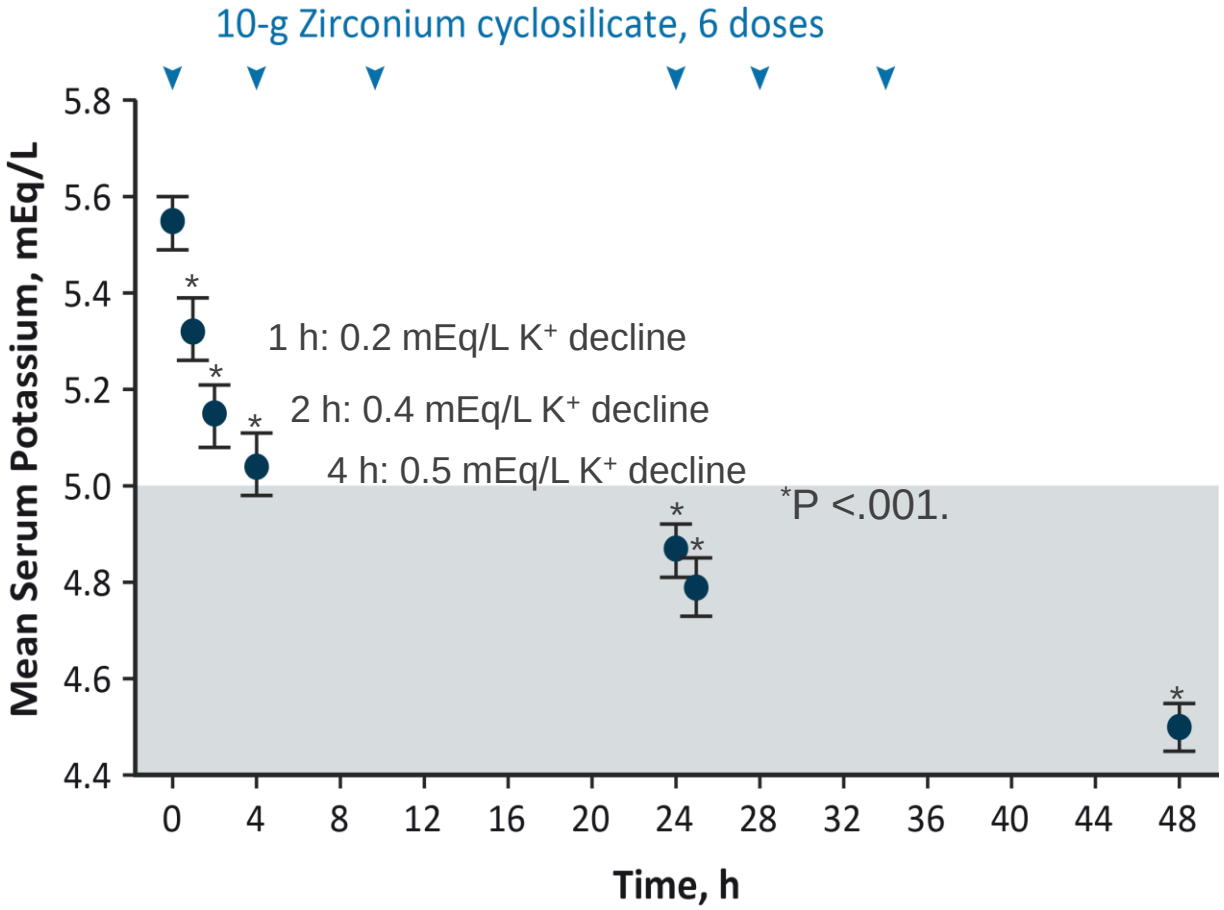
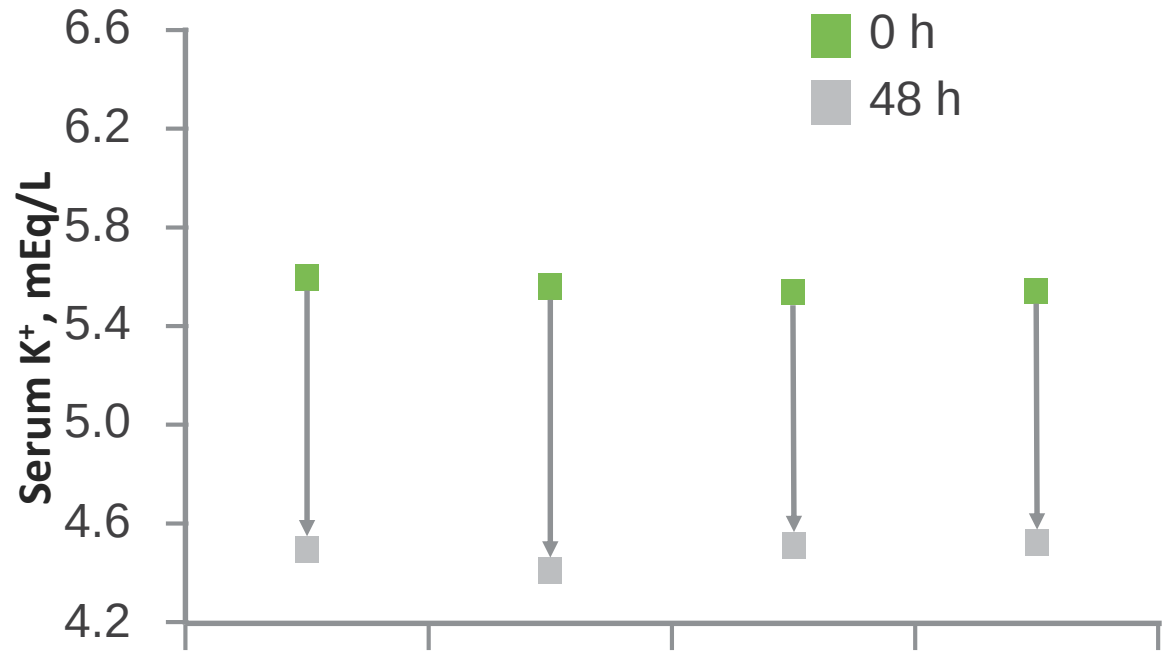
ONSET: HARMONIZE





Patients, n	CKD	HF	Diabetes	RAASi
0 h	179	94	170	180
48 h	172	92	166	173

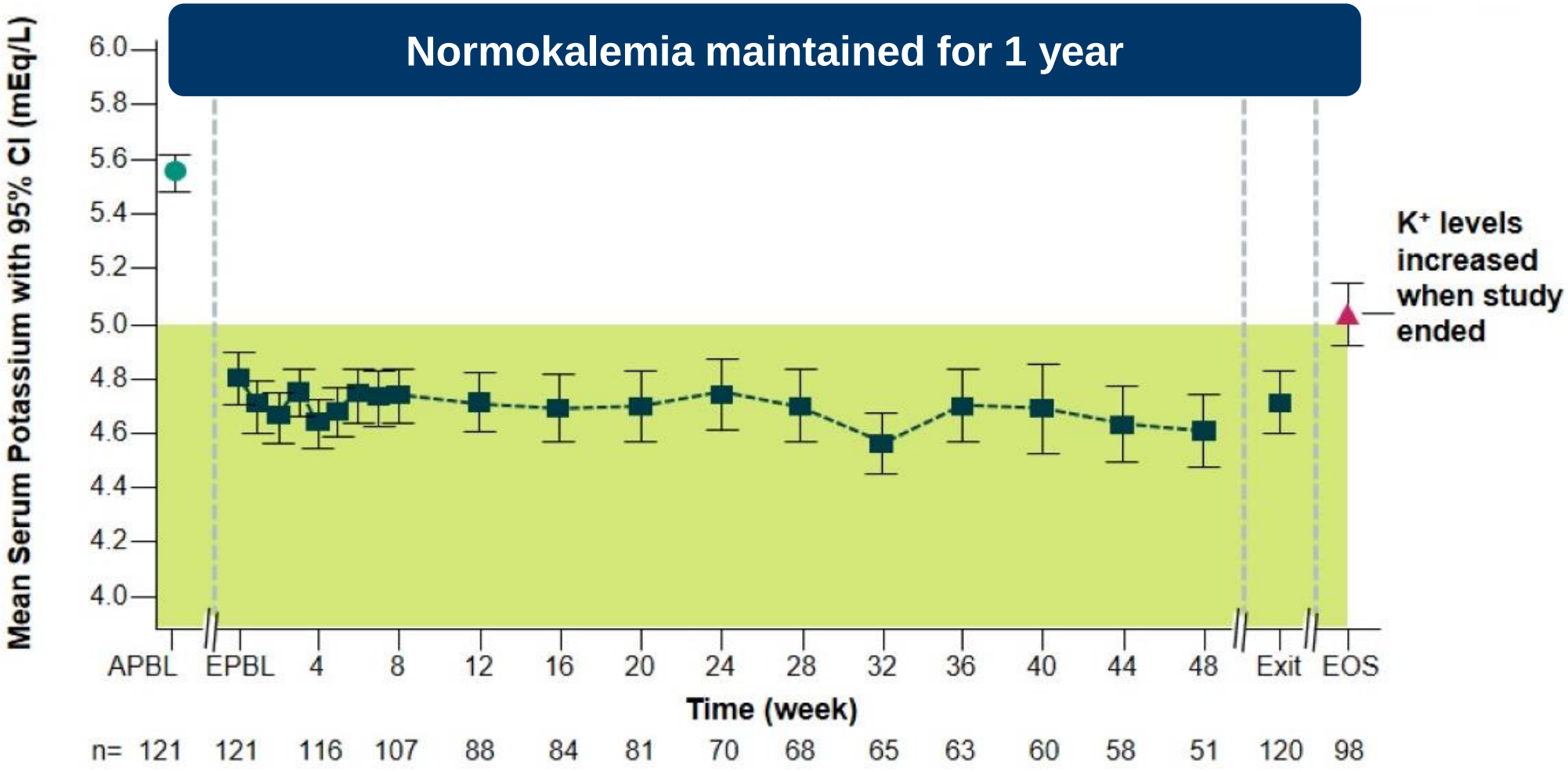
Kosiborod M, et al. JAMA. 2014;312:2223-33.

ADVERSE DRUG EVENTS: HARMONIZE

		SZC Dose Group		
	Placebo (n=85)	5 g (n=45)	10 g (n=51)	15 g (n=56)
Constipation	6 (7.1)	0	1 (2.0)	1 (1.8)
Edema	2 (2.4)	1 (2.2)	3 (5.9)	8 (14.3)
Hypokalemia	0	0	5 (9.8)	6 (10.7)

Kosiborod M, et al. JAMA. 2014;312:2223-33.

LONG-TERM EFFICACY: HARMONIZE EXTENSION



Spinowitz BS. Clin J Am Soc Nephrol. 2019;14(6):798-809.

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DRUG-DRUG INTERACTIONS

- *In vitro* studies
  - 39 drugs tested
  - 23 demonstrated measurable interaction
- Primary interaction mechanism related to SZC's potential to transiently increase gastric pH

No *In Vitro* Reaction
Allopurinol
Apixaban
Aspirin
Captopril
Cyclosporine
Digoxin
Ethinyl Estradiol
Lisinopril
Magnesium
Metformin
Phenytoin
Prednisone
Quinapril
Spironolactone
Ticagrelor

DRUG-DRUG INTERACTIONS

- *In vivo* studies
  - 9 medications studied
    - Dabigatran (⇩ systemic exposure)
    - Furosemide (⇧ systemic exposure
    - Atorvastatin (⇧ systemic exposure)
- Administer other oral medications at least 2 hours before or 2 hours after

Drugs Evaluated

Amlodipine
Atorvastatin*
Clopidogrel
Dabigatran*
Furosemide*
Glipizide
Levothyroxine
Losartan
Warfarin

SUMMARY OF NOVEL POTASSIUM BINDERS

- Studied in patients with HF, CKD and DM
- Effective in treating hyperkalemia
- Well-tolerated
- Safety and efficacy data for up to 1 year
- DDI issues ‘manageable’
- Hypokalemia is uncommon
- Rebound hyperkalemia when stopped

BALANCING RAAS INHIBITOR USE AND HYPERKALEMIA

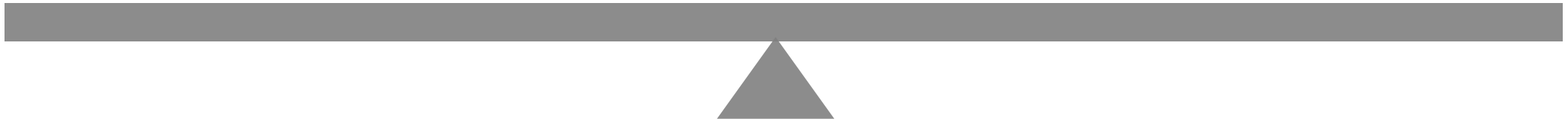
Chronic Management Challenges

RAAS inhibitors: ACE inhibitors, ARBs, aldosterone blockers

- Guidelines recommended (ACCF/AHA and HFSA)
- Proven outcomes benefit in HF

Potential risks of RAAS inhibitor therapy

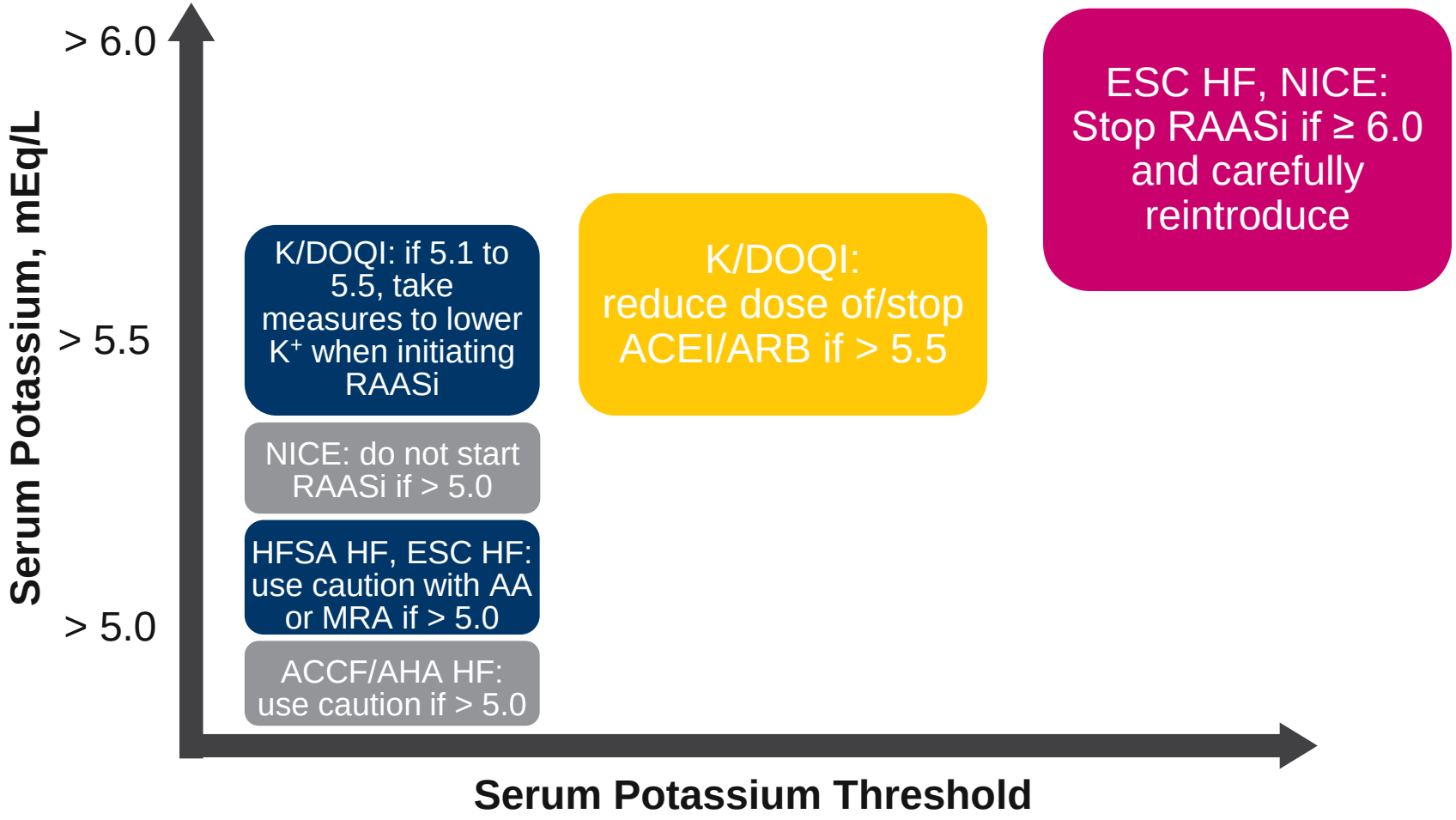
- Risk of increased serum potassium
- Utilization limited by risk of hyperkalemia
- Up to 65% of patients with HF are suboptimally dosed



Resolve the competing issue (hyperkalemia) so patients can remain on appropriate drugs that lower mortality

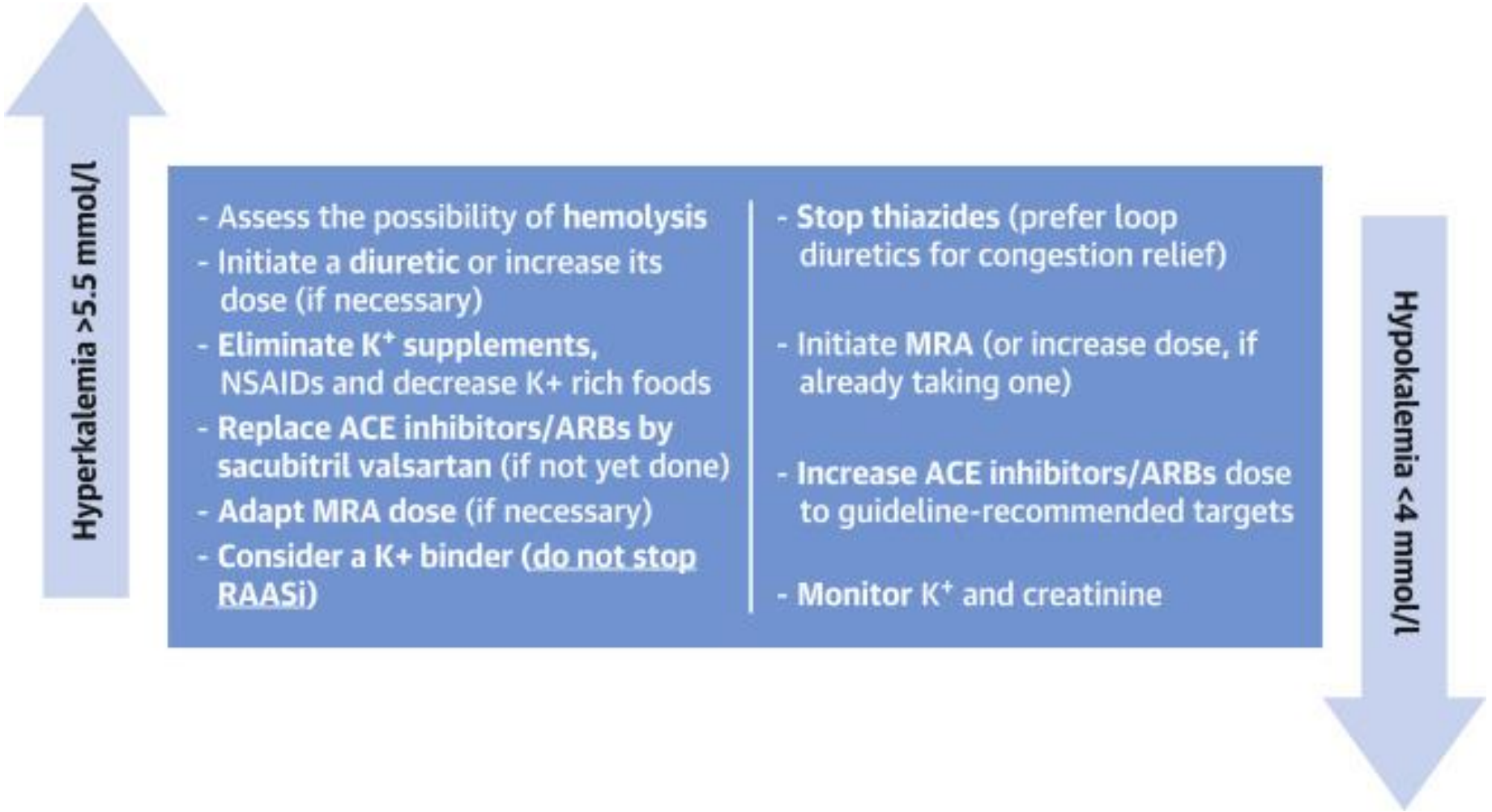
Epstein M et al. Am J Manag Care. 2015;11:S212-20.

GUIDELINE RECOMMENDATIONS: RAAS INHIBITOR USE BASED ON SERUM POTASSIUM LEVEL



Yancy CW et al. Circulation. 2017;136:r137-2161;Lindenfeld J et al. J Card Fail. 2010;16:e1-e194;
Ponikowski P et al. Eur J Heart Fail. 2016;37:2129-2200; NICE website. Clinical guideline [CG182]; K/DOQI. Am J Kidney Dis. 2004;43:S1-S290.

MANAGEMENT OF DYSKALEMIA IN PATIENTS WITH HEART FAILURE



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

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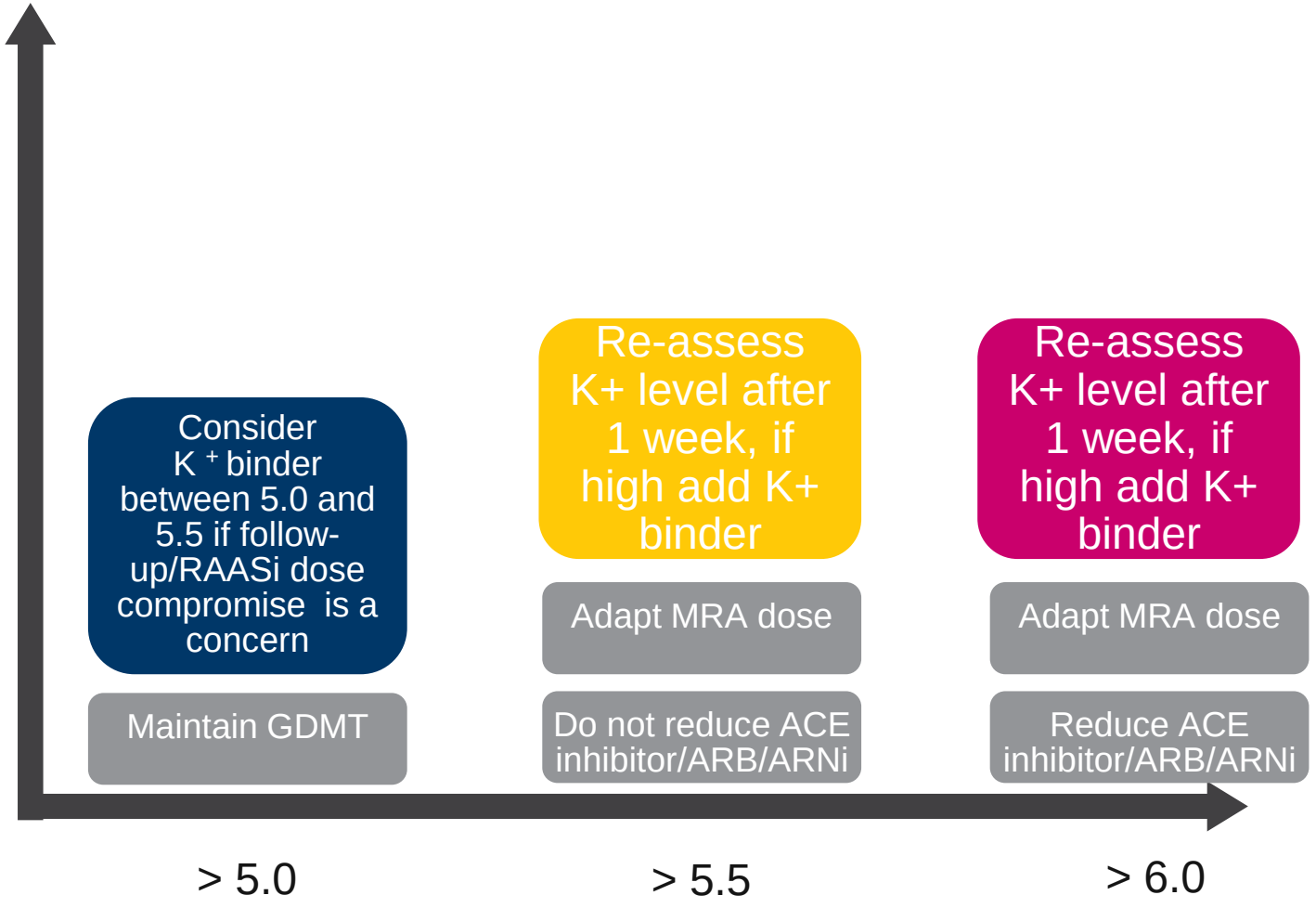
JACC RECOMMENDATIONS: POTASSIUM BINDER INITIATION BASED ON SERUM POTASSIUM LEVEL



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

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ROLE OF THE PHARMACIST IN HYPERKALEMIA MANAGEMENT

- **Appropriate assessment of hyperkalemia and management requires a thorough understanding of the underlying mechanisms and evidence-based recommendations regarding risk versus benefits of RAAS inhibition in patients with HFrEF and HFpEF**
- Pharmacists can play an integral role by:
  - Recognizing agents that may contribute to hyperkalemia
  - Providing strategies to enable RAAS inhibition
  - Assisting with drug selection and dosing of agents used to treat hyperkalemia
  - Counseling patients and other health care providers on use of available potassium binding agents

PATIENT CASE: THE GREY ZONE

- CK is a 76-year-old male referred to outpatient HF team after 2 recent hospitalizations for acute decompensated HF
  - Hyperkalemia documented in EMR as an “allergy” to RAAS inhibitors
  - Unable to tolerate metformin

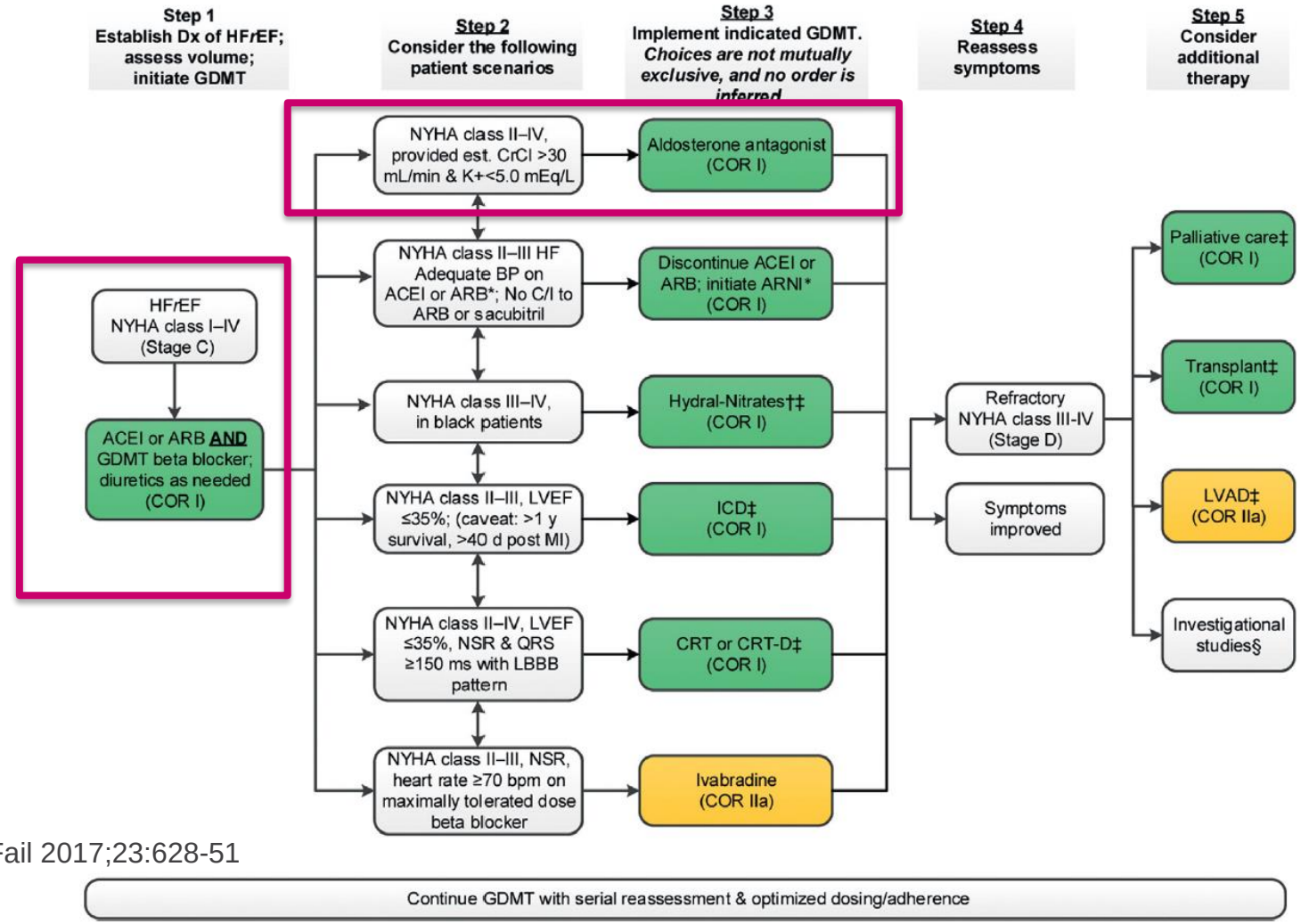
Past Medical History	Hypertension HFpEF (NYHA Class III EF 55%) Chronic kidney disease stage 3A Diabetes mellitus Atrial fibrillation Obesity
Labs	Serum creatinine: 1.6 mg/dL Estimated GFR: 52 mL/min/m^2 Potassium: 4.9 mEq/L NT-proBNP: 4500 pg/mL
Vitals	BP: 148/94 HR: 72 BMI: 32
Medications	Amlodipine 10mg daily Carvedilol 6.25mg BID Torsemide 40 mg BID Rivaroxaban 15mg daily Liraglutide 1.8mg daily

POLL QUESTION

Should CK receive dual RAAS inhibition with an ACE inhibitor/ARB and aldosterone antagonist?

A. Yes
B. No

ACCF/AHA GUIDELINES FOR RAAS INHIBITION IN HFrEF



Yancy CW et al. J Card Fail 2017;23:628-51

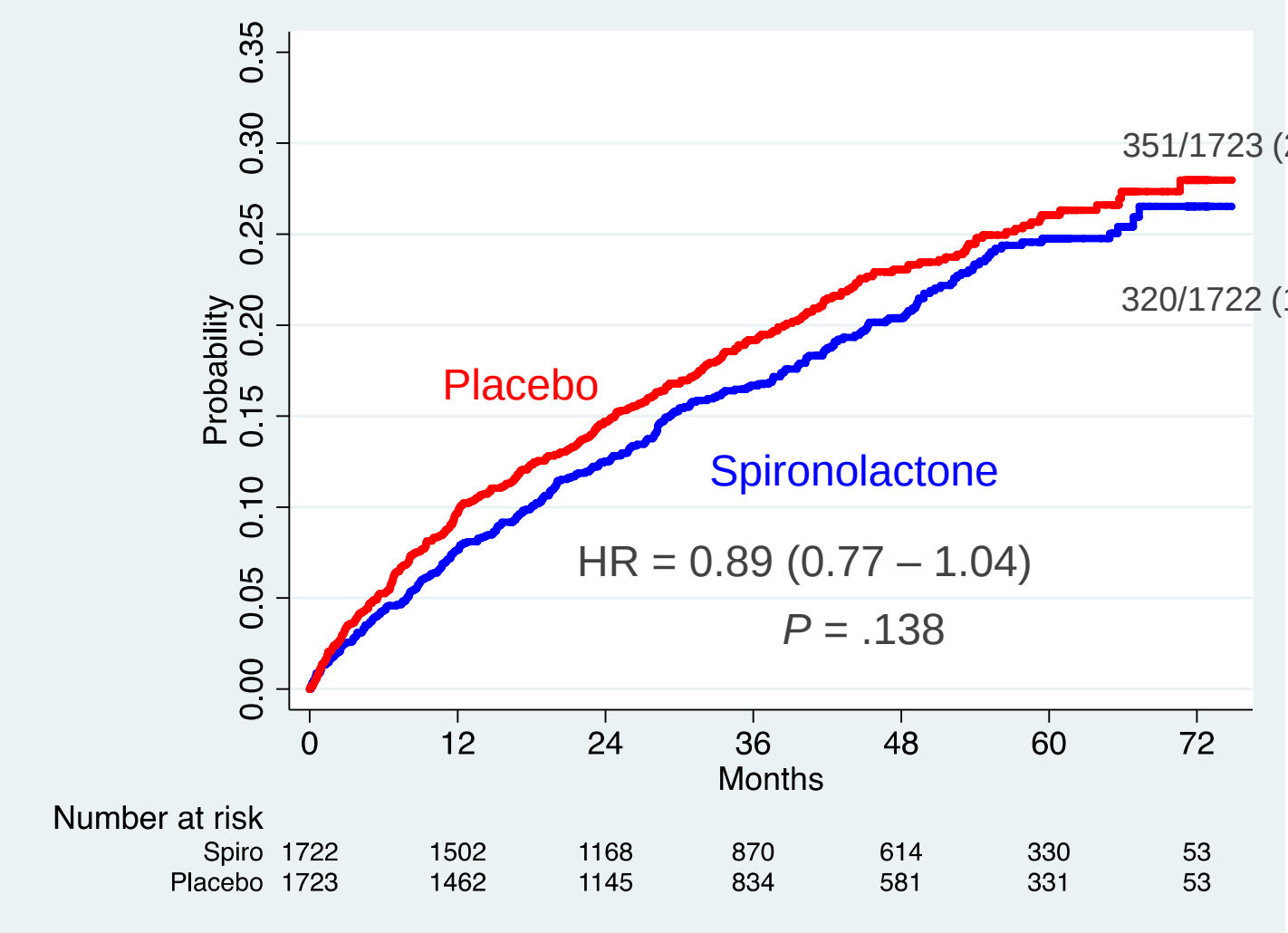
ACCF/AHA GUIDELINES FOR RAAS INHIBITION IN HFpEF

- In appropriately selected patients with HFpEF an aldosterone antagonist might be considered to decrease hospitalizations
    - EF >= 45%
    - Elevated BNP levels of HF admission within 1 year
    - SrCr < 2.5 mg/dL and K < 5.0 mEq/L

- 2013 recommendation remains current for the use of ARBs to decrease hospitalizations for patients with HFpEF

Yancy CW et al. J Card Fail 2017;23:628-51; Yancy CW et al. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.

1° OUTCOME: CV DEATH, HF HOSPITALIZATION OR RESUSCITATED CARDIAC ARREST



Pitt B et al. N Engl J Med. 2014;370:1383-92.

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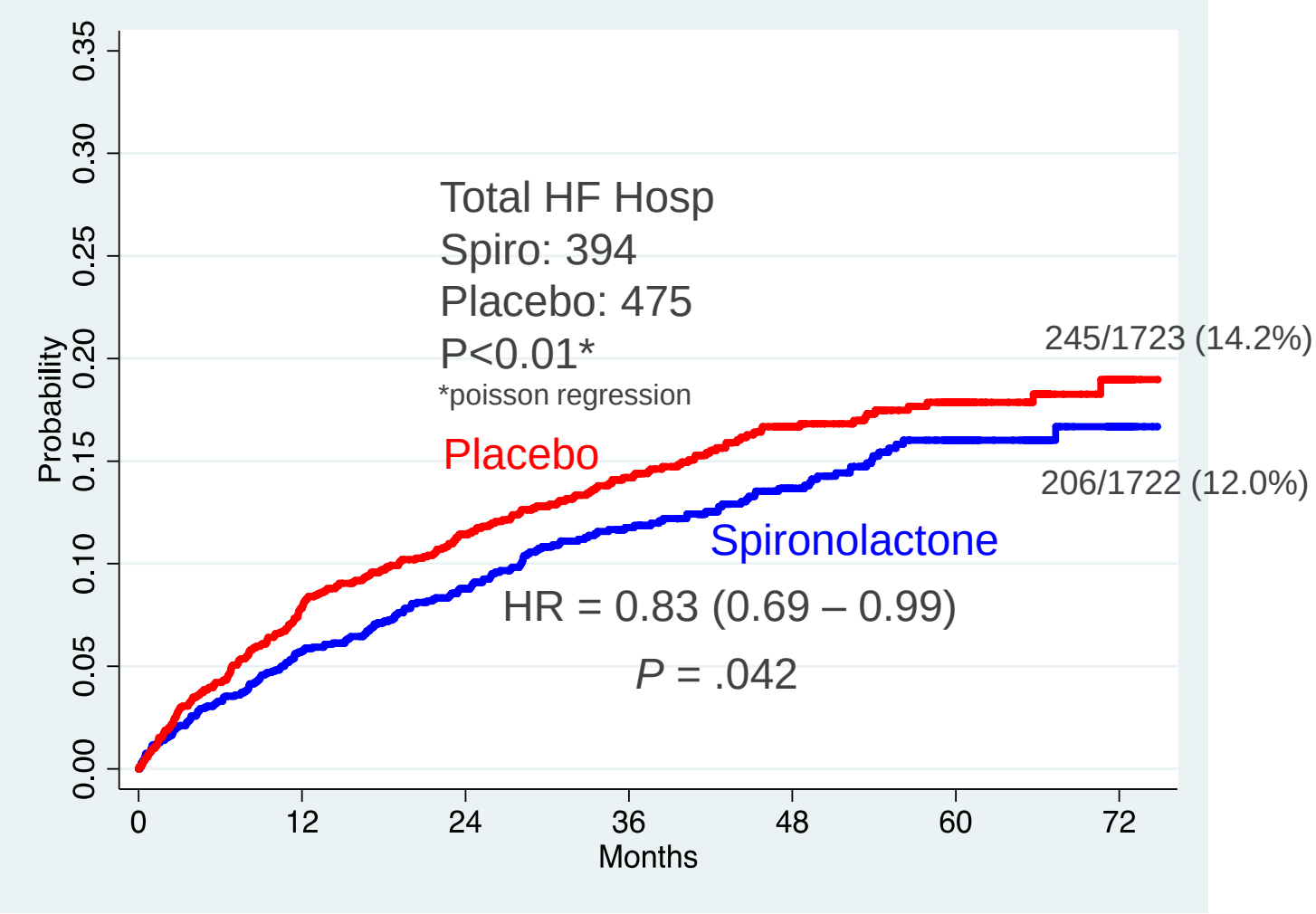
HEART FAILURE HOSPITALIZATIONS



Pitt B et al. N Engl J Med. 2014;370:1383-92.

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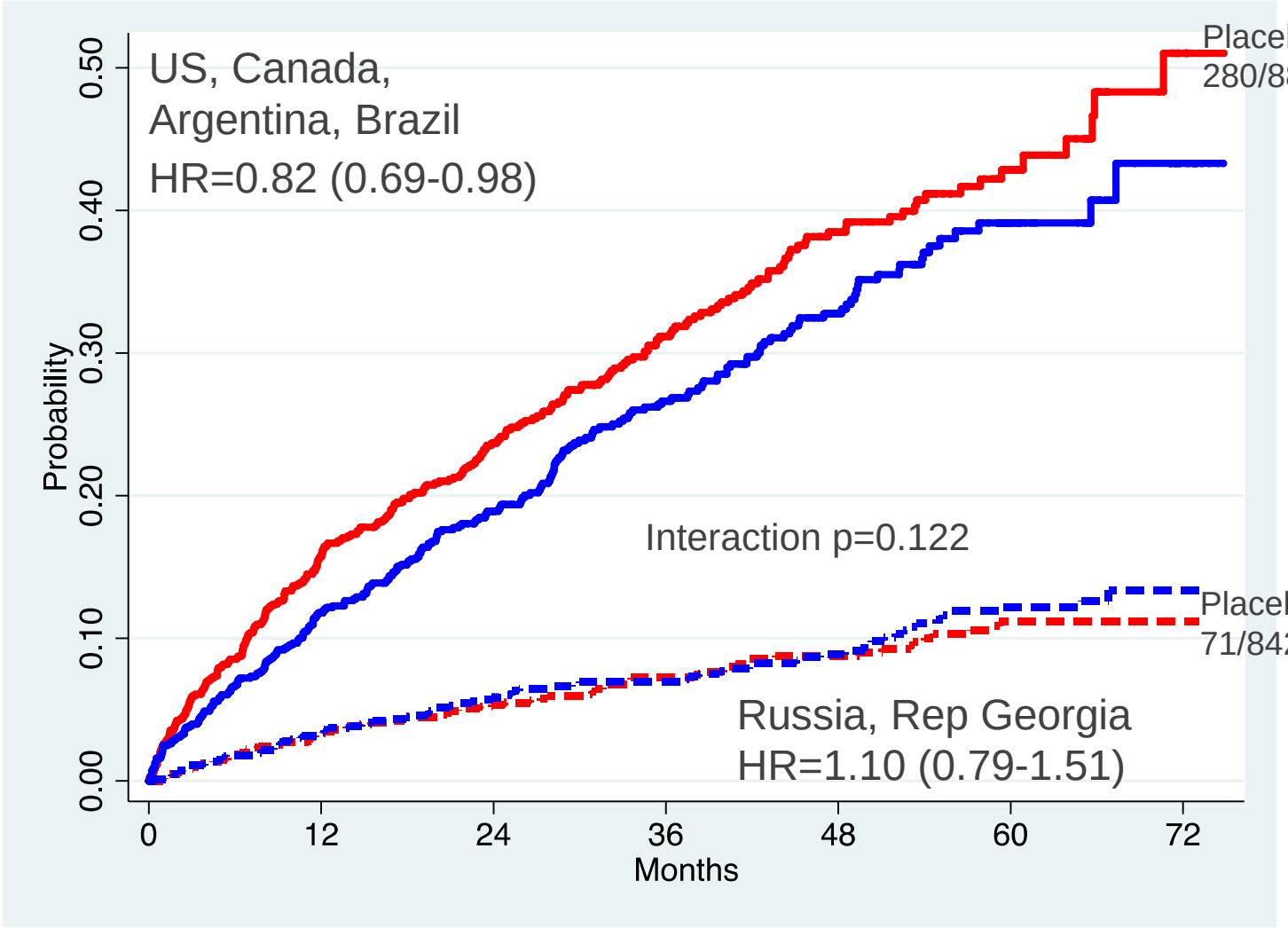
EXPLORATORY (POST-HOC): PLACEBO VS. SPIRONOLACTONE BY REGION



Pitt B et al. N Engl J Med. 2014;370:1383-92.

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HYPERKALEMIA IN TOPCAT

Potassium	Spiro	Placebo	*P* (chi-sq)
Hyperkalemia (≥ 5.5 mmol/L)	322 **(18.7%)**	157 **(9.1%)**	<0.001

No deaths related to hyperkalemia were reported

Pitt B et al. N Engl J Med. 2014;370:1383-92.

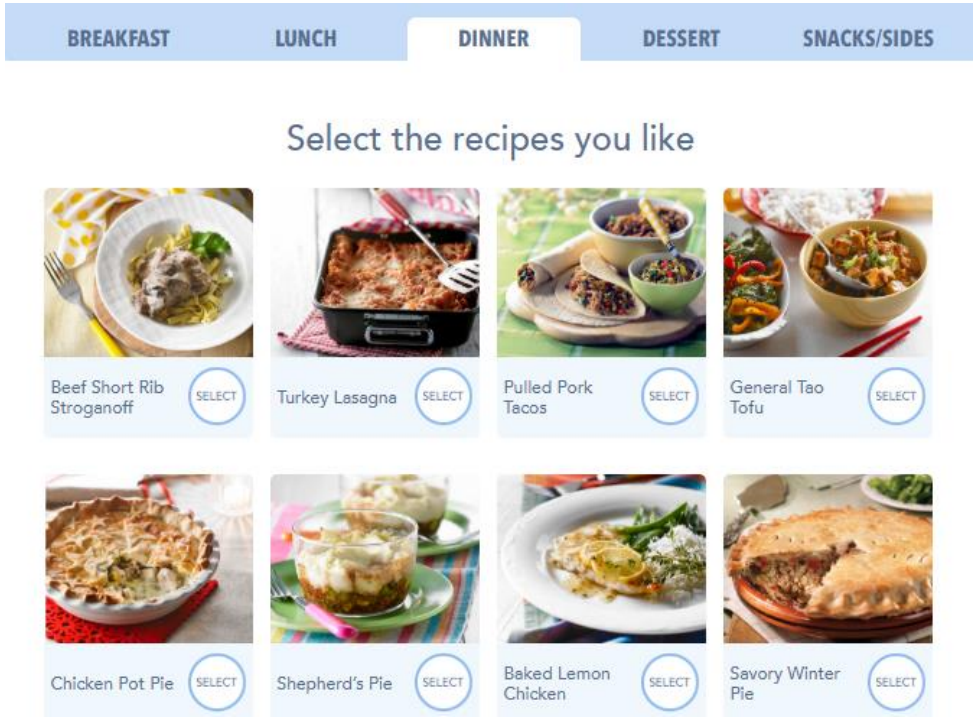
POLL QUESTION

What non-pharmacologic intervention(s) can be utilized to safely initiate an aldosterone antagonist?

A. Dietary counseling
B. Medication review
C. Prior authorization for a potassium binder
D. All of the above

COUNSEL PATIENTS ON DIETARY SOURCES OF POTASSIUM

Food	Portion	K^+ Content, mg
Beans—black, canned	½ cup	903
Beans—lima, canned	1 cup	987
Brussels sprouts	1 cup	446
Clams	19 small	665
Guacamole	½ cup	458
Lentils—boiled	1 cup	731
Mango	1 medium	564
Milk—coconut	8 fl oz	497
Orange juice	8 oz	496
Oysters—raw	6 medium	504
Plantain—cooked	1 cup	716
Potato—baked	1 medium	926
Raisins	1 cup	1086
Spinach—frozen, boiled	1 cup	574
Tomato paste	6 oz	1724



https://www.veltassa.com/patient/resources/#

https://aakp.org/product/download-aakp-nutrition-counter-reference-kidney-patient-electronic-download/

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REVIEW FOR MEDICATION-RELATED SOURCES

Causes	Agent or Medication
Drugs that promote transmembrane potassium shift	Nonselective beta-blockers (eg, propranolol, labetalol, carvedilol), digoxin intoxication, mannitol
Drugs that affect aldosterone secretion	ACE inhibitors (eg, benazepril, lisinopril), direct renin inhibitors (eg, aliskiren), NSAIDs and COX-2 inhibitors (eg, ibuprofen, celecoxib), calcineurin inhibitors (cyclosporine, tacrolimus), heparin
Drugs that cause tubular resistance to action of aldosterone	Aldosterone antagonists (eg, spironolactone, eplerenone) and other potassium-sparing diuretics (eg, amiloride, triamterene), trimethoprim, pentamidine, heparin
Agents that contain potassium	Salt substitutes and alternatives, penicillin G, stored blood products
Other	Succinylcholine, herbal supplements

Ben Salem C et al. Drug Saf. 2014; 37:677-92.

THE ART OF PRIOR AUTHOZIATION

- Receive approval **BEFORE** prescribing
- Use electronic prior authorization (ePA)
  - CoverMyMeds
- Standardize request letter
  - Refer to HF guidelines
  - Highlight safety and efficacy concerns with formulary alternatives (SPS)
- Check for co-pay assistance
  - Manufacturer
  - Patient Access Network

THE GREY ZONE: 1 WEEK LATER

- After dietary counseling, discontinuation of carvedilol, and pre-authorization for patiromer, candesartan 8mg daily and spironolactone 25mg daily initiated
  - CK reports “feeling great” with the following labs and vitals during clinic visit

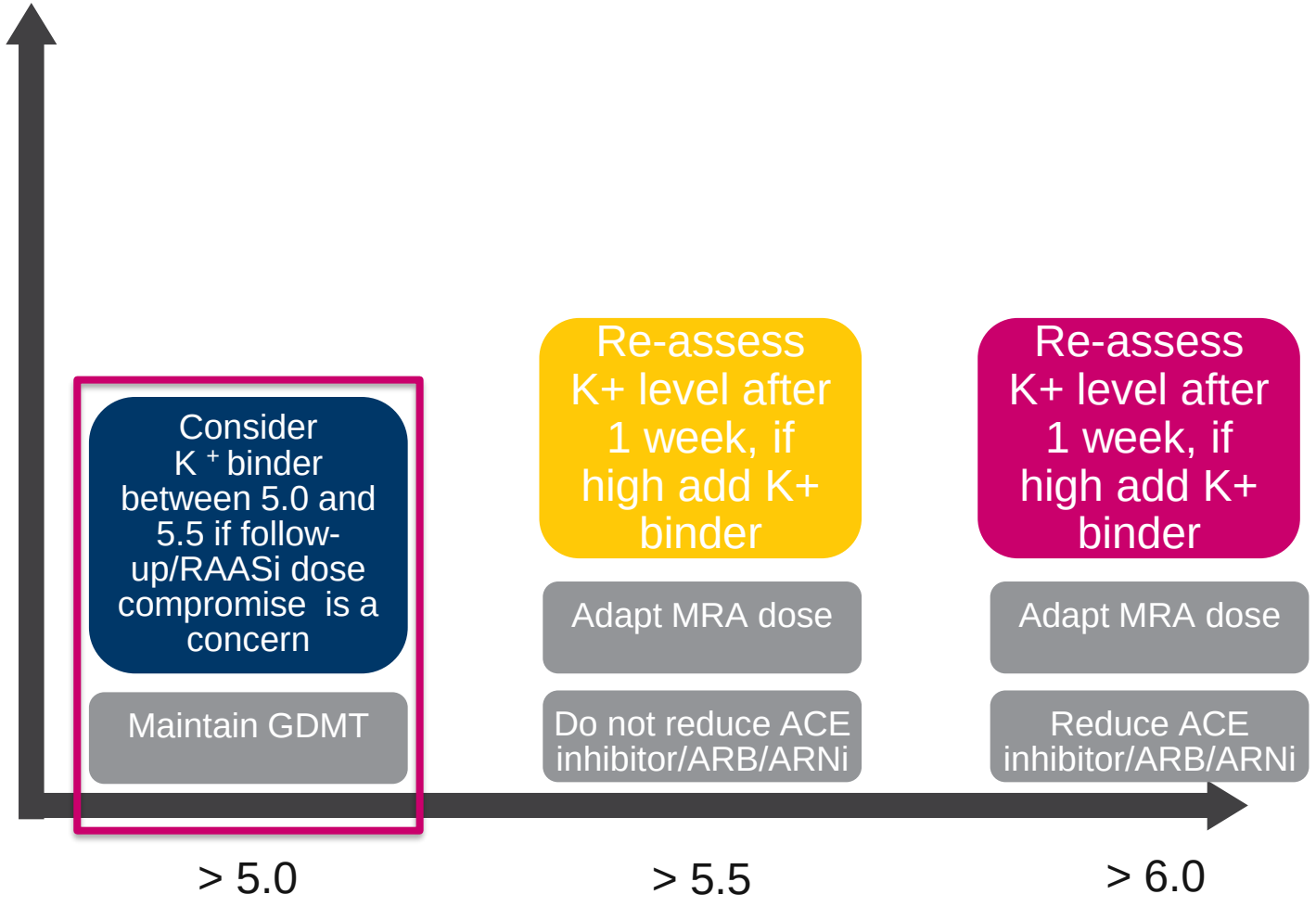
Labs	SrCr: 1.6 mg/dL → 1.7 mg/dL **Potassium: 4.9 mEq/L → 5.5 mEq/L** NT-proBNP: 4500 pg/mL → 2700 pg/mL
Vitals	BP: 148/94 → 132/82 HR: 72 → 78
Medications	Amlodipine 10mg daily **Candesartan 8mg daily** **Spironolactone 25mg daily** Torsemide 20 mg BID Rivaroxaban 15mg daily Liraglutide 1.8mg daily

POLL QUESTION

What approach could be used to treat CK's hyperkalemia?

A. Decrease spironolactone to 12.5 mg daily and candesartan to 4mg daily
B. Initiate patiromer 8.4g daily
C. Discontinue spironolactone until potassium returns to baseline
D. Prescribe SPS 15 g/60 mL x 1 dose

JACC RECOMMENDATIONS: POTASSIUM BINDER INITIATION BASED ON SERUM POTASSIUM LEVEL



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

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THE GREY ZONE: 2 WEEKS LATER

- With prior authorization already obtained patiromer is immediately started
  - CK reports “no taste, no problems” and repeats blood work 5 days later
- Interdisciplinary HF team plan:
  - Up-titrate ARB and aldosterone antagonist
  - Up-titrate potassium binder if needed
  - Add SGLT-2 inhibitor (?)

Labs	SrCr: 1.7 mg/dL → 1.8 mg/dL Potassium: **5.5 mEq/L → 4.6 mEq/L**
Vitals	BP: 148/94 → 132/82 HR: 72 → 78
Medications	Amlodipine 10mg daily **Candesartan 8mg daily** **Spironolactone 25mg daily** Torsemide 20 mg BID **Patiromer 8.4g daily** Rivaroxaban 15mg daily with evening meal Liraglutide 1.8mg daily

UNANSWERED QUESTIONS: PATIROMER

- DIAMOND
  - HFrEF patients with hyperkalemia or history of hyperkalemia
  - Primary endpoint: time to first occurrence of CV death or CV hospitalization

UNANSWERED QUESTIONS: SODIUM ZIRCONIUM CYCLOSILICATE

- PRIORITIZE HF
  - HF patients with hyperkalemia or history of hyperkalemia
  - Primary endpoint: proportion of patients on RAASi
- REALIZE-K
  - HFrEF patients on RAS inhibition with no or low dose aldosterone antagonist
  - Primary endpoint: proportion of patients on spironolactone >= 25mg

SUMMARY

- Hyperkalemia presents a challenge to optimizing RAAS inhibitor therapy in patients with HFrEF and HFpEF
- Management of hyperkalemia starts with proactive monitoring, repeat testing and discussion of patient-centered guideline-directed medical therapy goals
- **Patiromer and sodium zirconium can enable RAAS inhibitor utilization in patients with chronic hyperkalemia and heart failure**
- Pharmacists are integral team members and can promote adoption and implementation of guideline-directed medical therapy and potassium binders into routine clinical practice


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