



**PHARMACY  
VISION  
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# OPTIMIZING MEDICAL THERAPY IN PATIENTS WITH HEART FAILURE AND CHRONIC KIDNEY DISEASE

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# DISCLOSURE

I have no conflict of interest to disclose.



## LEARNING OBJECTIVES

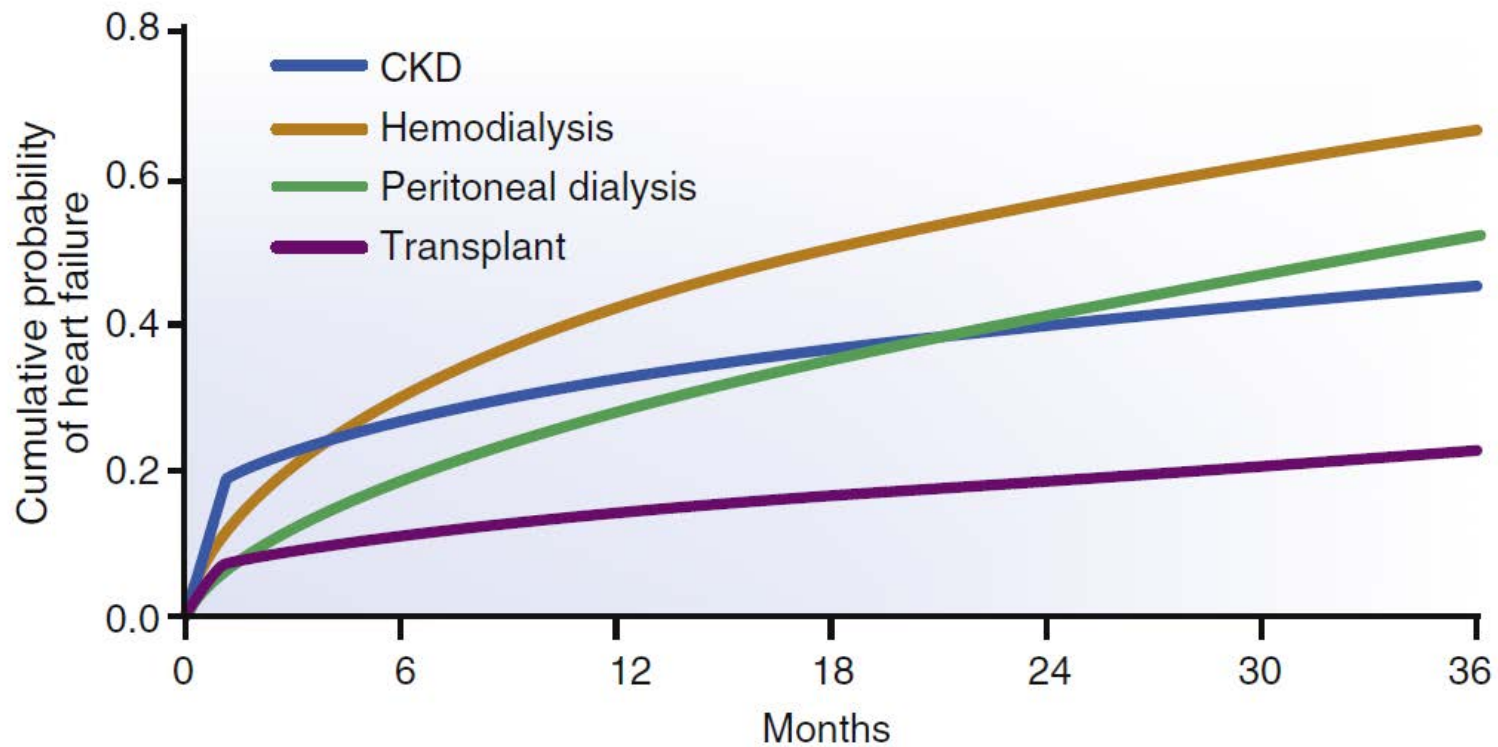
- Describe the relationship between heart failure and kidney disease and the limitations in assessment of renal function in the clinical setting
- Discuss evidence supporting guidelines directed medical therapy in patients with heart failure and reduced ejection fraction with a focus on patients with chronic kidney disease
- Evaluate the role of potassium binders for optimization of medical therapy in this complex patient population



## TEST QUESTIONS

- 1) True/False – Worsening renal function without congestion upon hospital discharge for HF patients has been associated with poorer outcomes when compared to those without worsening renal function
- 2) True/False – Mineralocorticoid antagonists (MRAs) have unclear benefit in those with HFrEF and CKD but are associated with higher rates of hyperkalemia
- 3) True/False – Novel potassium binders have shown mortality benefit in HF patients that have been attributed to continued RAAS therapy

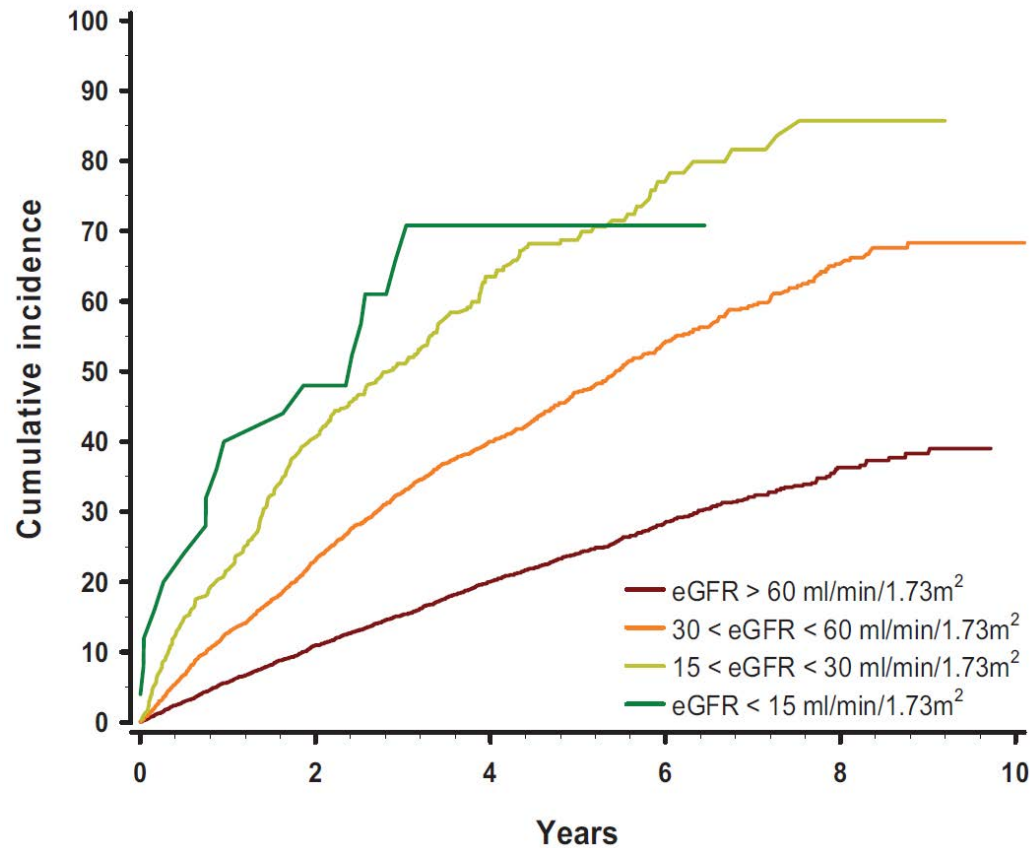
# Cumulative Probability of Heart Failure in Populations with CKD, Dialysis, and a Kidney Transplant



CKD: chronic kidney disease

House AA et al. *Kidney International* 2019. 95:1304-1317.

# Cumulative Incidence of Death by Worsening eGFR in Patients with Systolic Heart Failure



eGFR: estimated glomerular filtration rate

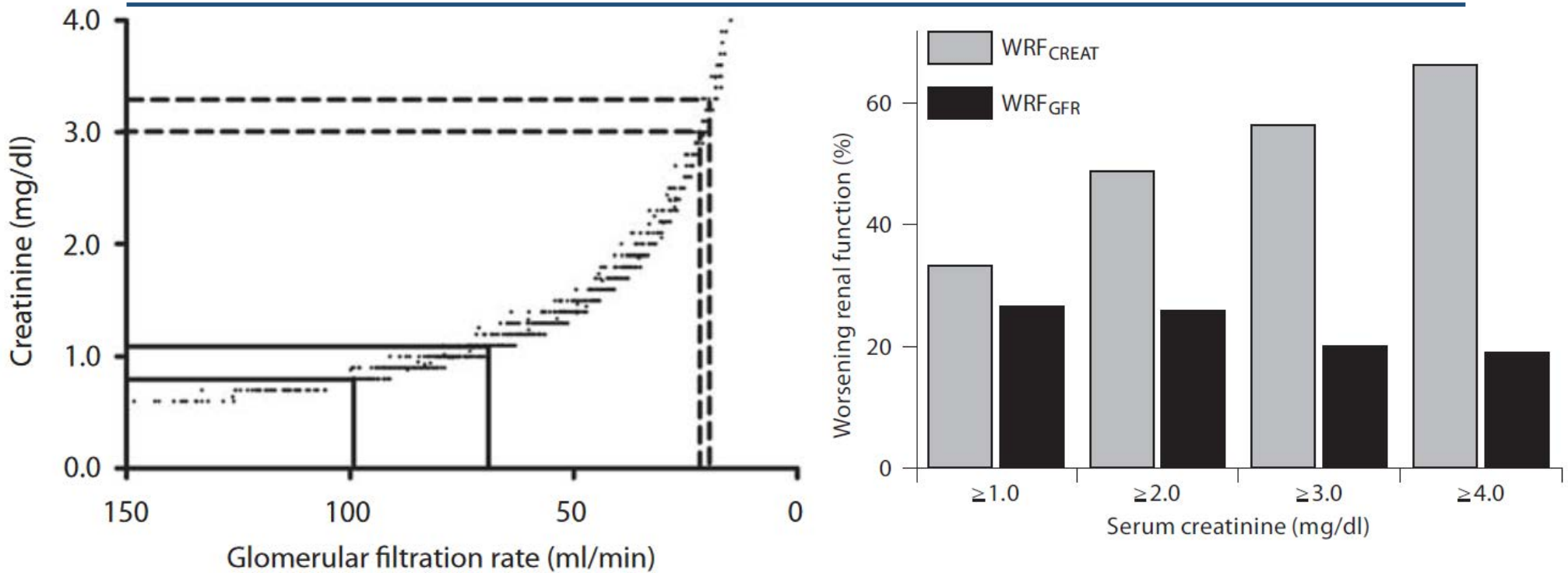
Bosselmann H et al. *Circ Heart Fail* 2013;6:1124-1131.

# Classification of Cardiorenal Syndrome

Phenotype	Nomenclature	Description	Clinical Example
<b>Type 1 CRS</b>	Acute CRS	HF resulting in AKI	ACS resulting in cardiogenic shock and AKI, AHF resulting in AKI
<b>Type 2 CRS</b>	Chronic CRS	Chronic HF resulting in CKD	Chronic HF
<b>Type 3 CRS</b>	Acute renocardiac syndrome	AKI resulting in AHF	HF in the setting of AKI from volume overload, inflammatory surge, and metabolic disturbances in uremia
<b>Type 4 CRS</b>	Chronic renocardiac syndrome	CKD resulting in chronic HF	LVH and HF from CKD-associated cardiomyopathy
<b>Type 5 CRS</b>	Secondary CRS	Systemic process resulting in HF and kidney failure	Amyloidosis, sepsis, cirrhosis

CRS: cardiorenal syndrome; AHF: acute heart failure; AKI: acute kidney injury; ACS: acute coronary syndrome; LVH: left ventricular hypertrophy

# Limitations of Estimating Worsening Renal Function Using Serum Creatinine



Association between increases in creatinine and WRF is largely dependent on baseline renal function

WRF: worsening renal function

# Worsening Renal Function in Acute Decompensated Heart Failure

## Worsening Renal Function and Decongestion at Discharge and Death at Day 180

Measures of Congestion	HR (95% CI)
<b>Hemodynamic</b>	
WRF + Congestion	5.42 (2.57 – 11.46)
No WRF + Congestion	2.20 (0.78 – 6.22)
WRF + No congestion	0.88 (0.29 – 2.62)
<b>Clinical</b>	
WRF + Congestion	3.46 (1.89 – 6.31)
No WRF + Congestion	1.20 (0.61 – 2.38)
WRF + No congestion	0.52 (0.20 – 1.35)

Measures of Congestion	HR (95% CI)
<b>Hemoconcentration</b>	
WRF + Congestion	3.16 (1.40 – 7.17)
No WRF + Congestion	1.74 (0.77 – 3.97)
WRF + No congestion	2.32 (1.01 – 5.32)
<b>Plasma Volume</b>	
WRF + Congestion	3.41 (1.49 – 7.80)
No WRF + Congestion	2.08 (0.90 – 4.78)
WRF + No congestion	2.02 (0.84 – 4.86)

Persistent congestion with concomitant WRF (creatinine  $\geq$  0.3 mg/dL) at discharge associated with worse outcomes compared to patients without congestion and WRF

HR: hazard ratio; CI: confidence interval

# Worsening Renal Function in Acute Decompensated Heart Failure

Decline in eGFR is associated with higher risk of death when interpreted alone

HR: 1.10 [95% CI: 1.07 – 1.31] per every 30% decline in eGFR

Decline in BNP and increases in hematocrit are associated with lower risk of death when interpreted alone

HR: 0.78 [95% CI: 0.72 – 0.84] per 50% decrease in BNP

HR: 0.89 [95% CI: 0.84 - 0.95] per every 3% increase in hematocrit

Decline in kidney function needs to be interpreted in the context of changes in decongestion and hemoconcentration

Association between decline in kidney function and death is modified by the change in markers of decongestion and hemoconcentration

## Incidence of Heart Failure by CKD and Microalbuminuria

Predictor	Outcome	HR (95% CI)	P-value
CKD	Overall HF	1.24 (1.01 – 1.51)	0.04
	HFpEF	1.10 (0.81 – 1.51)	0.53
	HFrEF	1.36 (0.99 - 1.86)	0.06
Microalbuminuria	Overall HF	1.71 (1.25 – 2.34)	<0.0001
	HFpEF	1.26 (0.78 – 2.03)	0.34
	HFrEF	2.10 (1.35 – 3.26)	0.01

Microalbuminuria predictive of the incidence of overall HF and HFrEF

CKD predictive of the incidence of overall HF but not HFrEF

HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction

Nayor M et al. Eur J Heart Fail 2017;19:615-623.



# Guideline Directed Medical Therapy for Patients with Heart Failure and Chronic Kidney Disease

## Beta Blockers in Heart Failure with Reduced Ejection Fraction

Trial	Patient population	Treatment arms	Renal Exclusion	Outcome
<b>MERIT-HF</b>	NYHA FC II-IV; LVEF $\leq$ 0.40 (N = 3991)	Metoprolol succinate vs placebo	None	<u>All-cause mortality:</u> 7.2% vs 16.8% (RR 0.34; 95% CI 0.19 – 0.47)
<b>CIBIS-II</b>	NYHA FC III-IV; LVEF $\leq$ 0.35 (N = 2647)	Bisoprolol vs placebo	SCr $\geq$ 3.4 mg/dl	<u>All-cause mortality:</u> 12% vs 17% (HR 0.66; 95% CI 0.51 – 0.81)
<b>COPERNICUS</b>	LVEF $\leq$ 0.52 (N = 2289)	Carvedilol vs placebo	SCr $>$ 2.8 mg/dl	<u>Annual mortality:</u> 12.8% vs 19.7% (RR 0.65; 95% CI 0.64 – 0.87)
<b>SENIORS</b>	$\geq$ 70 years; LVEF $\leq$ 0.35 within 6 months (N = 2128)	Nebivolol vs placebo	Significant renal dysfunction	<u>All-cause mortality or cardiovascular hospital admission:</u> 31.1% vs 35.3% (HR 0.86; 95% CI 0.74 – 0.99)

NYHA: New York Heart Association; FC: functional class; LVEF: left ventricular ejection fraction; SCr: serum creatinine

Heart Failure and Chronic Kidney Disease:

## Benefit of Metoprolol CR/XL in Chronic Kidney Disease

	No. of events (rate) Placebo/Meto CR/XL	HR (95% CI)
Total Mortality		
eGFR <45	44(21.7)/24(9.1)	0.41 (0.25 – 0.68)
eGFR ≤ 45 ≥ 60	61(12.2)/39(8.3)	0.68 (0.45 – 1.02)
eGFR > 60	112(8.9)/80(6.4)	0.71 (0.54 – 0.95)
All-cause mortality/all-cause hospitalization		
eGFR <45	135(98.4)/112(54.8)	0.58 (0.45 – 0.75)
eGFR ≤ 45 ≥ 60	213(54.6)/176(47.6)	0.87 (0.71 – 1.06)
eGFR > 60	417(39.2)/348(32.7)	0.83 (0.72 – 0.95)
All-cause mortality/HF hospitalization		
eGFR <45	81(45.4)/50(20.2)	0.44 (0.31 – 0.63)
eGFR ≤ 45 ≥ 60	133(29.2)/86(19.8)	0.68 (0.52 – 0.89)
eGFR > 60	224(18.8)/172(14.5)	0.75 (0.62 – 0.92)

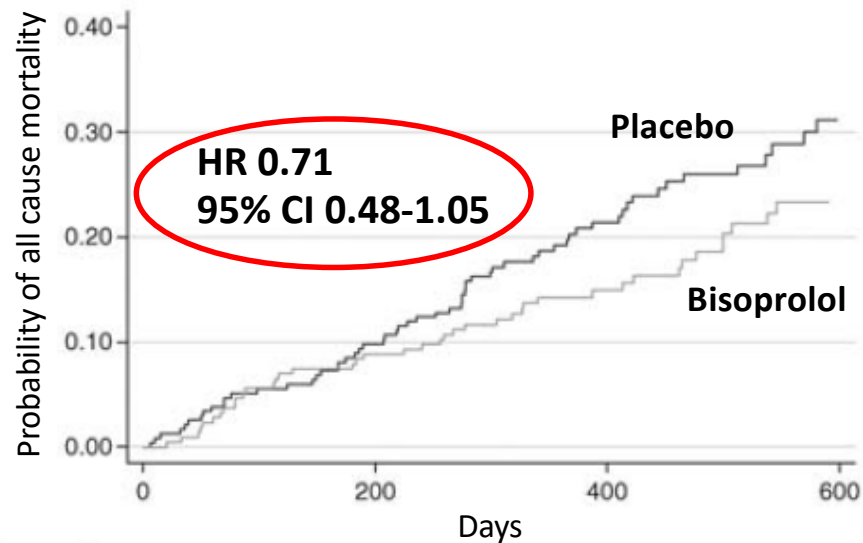
Benefit of metoprolol CR/XL sustained for eGFR<sub>MDRD</sub> <45

MDRD: Modification of Diet in Renal Disease

Heart Failure and Chronic Kidney Disease:

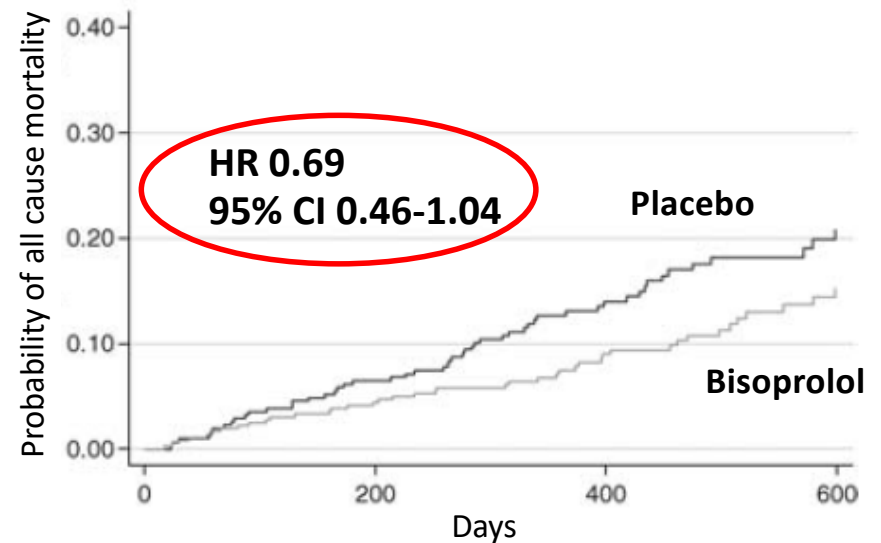
## Benefit of Bisoprolol in Chronic Kidney Disease

All-Cause Mortality with eGFR < 45 ml/min/1.73m<sup>2</sup>



Number at risk					
Placebo	235	211	129	56	
Bisoprolol	215	196	127	63	

All-Cause Mortality with eGFR ≥ 45 to <60 ml/min/1.73m<sup>2</sup>



Number at risk					
Placebo	308	288	190	89	
Bisoprolol	361	345	228	108	

Benefit in patients with HFrEF consistent regardless of baseline renal function?

Heart Failure and Chronic Kidney Disease:

## Benefit of Carvedilol in Chronic Kidney Disease

	Carvedilol vs. Placebo (HR, 95% CI)		
	eGFR <45 (CKD stage 3b)	eGFR ≥ 45-60 (CKD stage 3a)	eGFR > 60 (Non-CKD)
	N = 544 versus 572	N = 749 versus 701	N = 822 versus 829
All-cause mortality	0.94 (0.72 – 1.23)	0.63 (0.47 – 0.84)	0.59 (-.43 – 0.81)
HF mortality	0.86 (0.61 – 1.21)	0.52 (0.35 – 0.77)	0.58 (0.34 – 0.99)
CV Death or hospitalization for HF	0.92 (0.75 – 1.13)	0.62 (0.50 – 0.77)	0.78 (0.63 – 0.98)
Sudden cardiac death	1.04 (0.64 – 1.71)	0.62 (0.41 – 0.94)	0.58 (0.37 – 0.92)

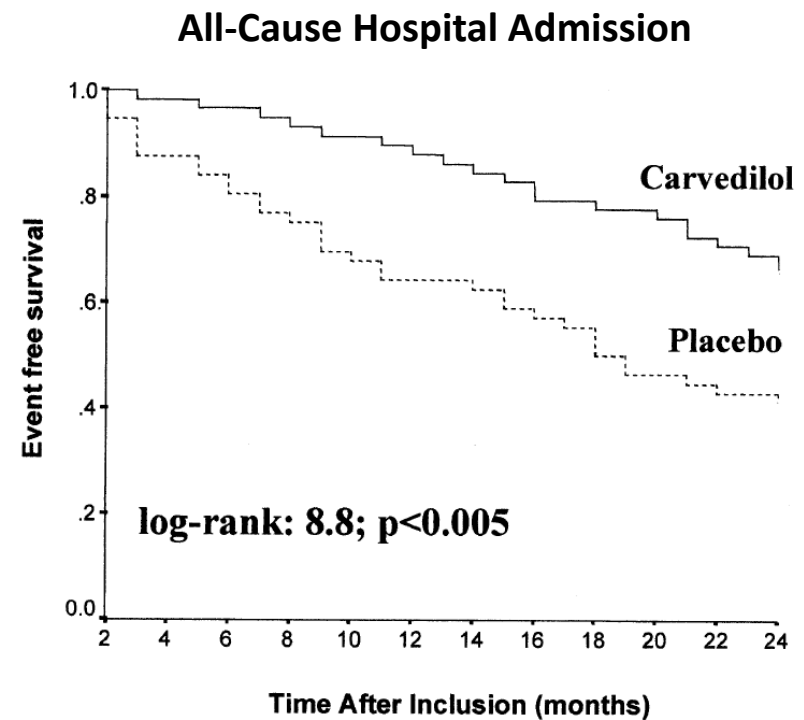
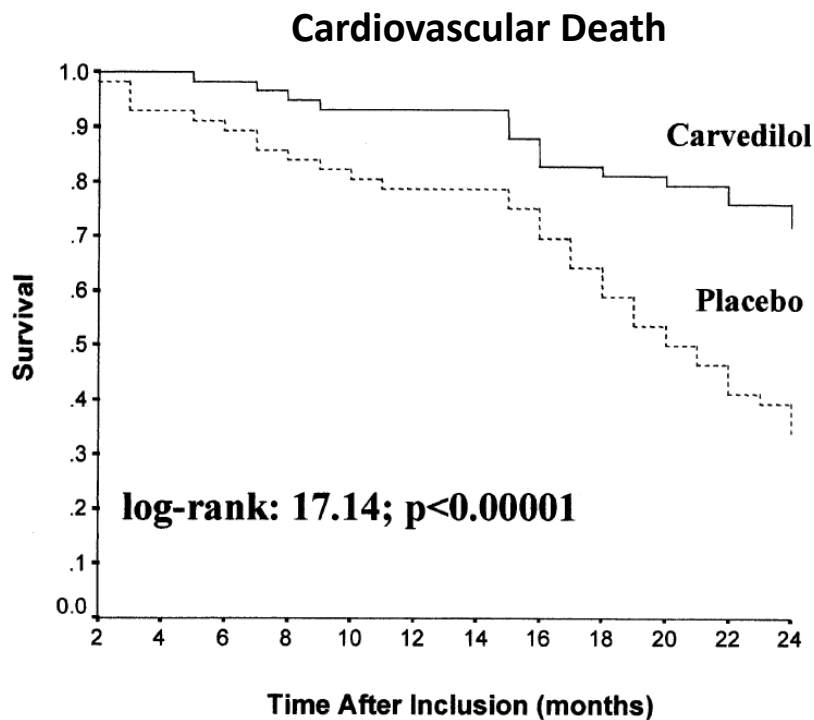
No benefit with carvedilol in patients with eGFR <45 mL/min/1.73 m<sup>2</sup>?

HF: heart failure; CV: cardiovascular

Heart Failure and Chronic Kidney Disease:

## Benefit of Carvedilol in Hemodialysis

- HR and SBP significantly decreased after 1 month and remained significant for 12 months
- Significant increase in LVEF and reduction of LVEDV/LVESV after 6 months of therapy



HR: heart rate; SBP: systolic blood pressure; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume

Heart Failure and Chronic Kidney Disease:

## Dialyzability of Beta Blockers and Clinical Outcomes

High Dialyzability	Low Dialyzability
Atenolol Acebutolol Metoprolol	Bisoprolol Propranolol (Carvedilol)

### All-Cause Mortality at 180 Days

Variable	Patients (n)	No. of Events (%)	RR (95% CI)	P-value
<b>Hemodialysis cohort</b>				
High-dialyzability beta blockers	3294	182 (5.5)	1.4 (1.1 – 1.8)	<0.01
Low-dialyzability beta blockers	3294	135 (4.1)	1 (referent)	
<b>Nondialysis cohort</b>				
High-dialyzability beta blockers	13,586	186 (1.4)	1.0 (0.9 – 1.3)	0.71
Low-dialyzability beta blockers	13,586	179 (1.3)	1 (referent)	

Initiation of high versus low-dialyzability beta blockers associated with higher risk of death at 180 days

Heart Failure and Chronic Kidney Disease:

## Risks of Beta Blockers in Chronic Kidney Disease/Hemodialysis

Adverse Events	More Likely Compared to Placebo	No Difference When Compared to Placebo	RR (95% CI) I-squared statistic
Bradycardia	✓		4.92 (3.20 – 7.55) 0.0%
Hypotension	✓		5.08 (3.48 – 7.41) 0.0%
Hyperkalemia		✓	2.16 (0.12 – 37.92) 68.2%
Medication Discontinuation		✓	1.17 (0.66 – 2.09) 59.2%

Summary:

## Beta Blockers in Heart Failure and Chronic Kidney Disease

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- ACC/AHA guidelines support the use beta blockers in all patients with stable HFrEF
- KDIGO guidelines recommend a 50% dose reduction in people with GFR <30 ml/min/1.73 m<sup>2</sup>
- There is conflicting evidence for the benefit of beta blockers in patients with CKD, primarily due to the low number of participants included in these
- Carvedilol may be preferable in patients on hemodialysis

## Renin-Angiotensin System Inhibitors in Heart Failure with Reduced Ejection Fraction

Trial	Patient population	Treatment arms	Renal Exclusion	Outcome
<b>Angiotensin-converting enzyme inhibitors (ACEi)</b>				
<b>CONSENSUS</b>	NYHA FC IV (N = 253)	Enalapril vs placebo	SCr > 3.4 mg/dl	<u>6-month mortality:</u> 26% vs 44% (RR = 0.60; p = 0.002)
<b>SOLVD-Treatment (N = 2569)</b>	LVEF ≤ 0.35	Enalapril vs placebo	SCr > 2 mg/dl	<u>All-cause mortality:</u> 35.2% vs 39.7% (RR 0.84; 95% CI 0.74-0.95)
<b>SOLVD-Prevention (N = 4228)</b>				14.8% vs 15.8% (RR 0.08; p = 0.30)
<b>SAVE</b>	Post-MI; LVEF ≤ 0.40 (N = 2231)	Captopril vs placebo	SCr > 2.5 mg/dl	<u>All-cause mortality:</u> 20% vs 25% (RR 0.81; 95% CI 0.63 – 0.96)
<b>Angiotensin II receptors blockers (ARB)</b>				
<b>Val-HeFT</b>	NYHA FC II-IV; LVEF ≤ 0.40 (N = 5010)	Valsartan vs placebo	SCr > 2.5 mg/dl	<u>All-cause mortality, cardiac arrest with resuscitation, HF hospitalization, IV therapy:</u> 28.8% vs 32.1% (RR 0.87; 95% CI 0.77 – 0.97)
<b>CHARM-Alternative</b>	NYHA FC II-IV; LVEF ≤ 0.40 (N = 2028)	Candesartan vs placebo	SCr ≥ 3 mg/dl	<u>Cardiovascular death or CHF hospitalization:</u> 33% vs 40% (HR 0.70; 95% CI 0.60 – 0.81)
<b>Angiotensin receptor-neprilysin inhibitor (ARNi)</b>				
<b>PARADIGM – HF</b>	NYHA FC II-IV; LVEF ≤ 0.40 (N = 8399)	Sacubitril/valsartan vs enalapril	eGFR < 30 ml/min/1.73m <sup>2</sup>	<u>CV death or first hospitalization for worsening HF:</u> 21.8% vs 26.5% (HR 0.80; 0.73 – 0.87)

CHF: congestive heart failure; CV: cardiovascular

CONSENSUS Trial Study Group. *N Engl J Med* 1987.316:1429-1435.  
SOLVD Investigators. *N Engl J Med* 1991.325:293-302.

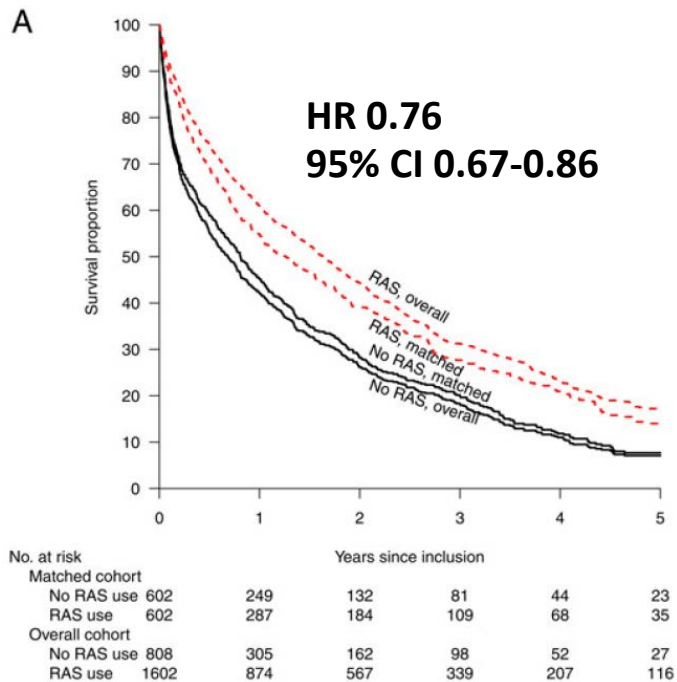
SOLVD Investigators. *N Engl J Med* 1992.327:685-91.  
Pfeffer MA et al. *N Engl J Med* 1992;327:669-77.

Cohn JN et al. *N Engl J Med* 2001.345:1667-75.  
Granger CB et al. *Lancet* 2003.362:772-776.

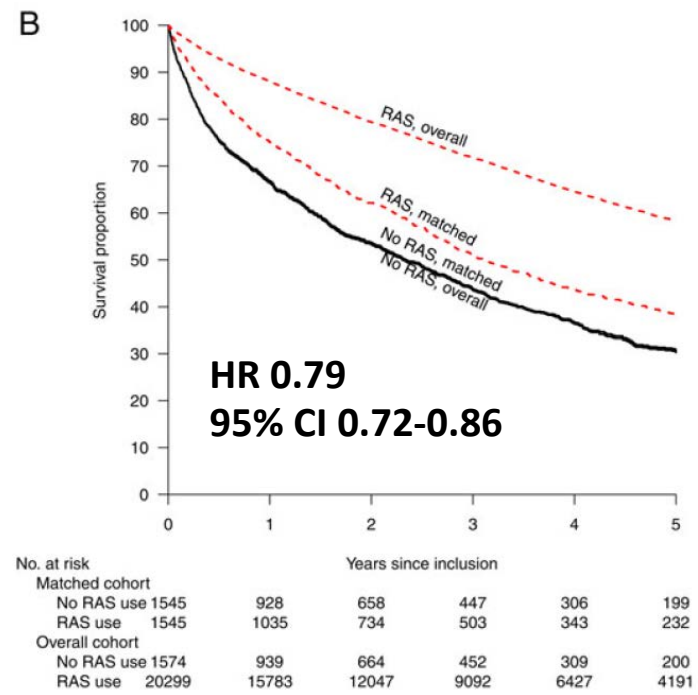
McMurray JV et al. *N Engl J Med* 2014.371:993-1004.

# Heart Failure and Chronic Kidney Disease: Benefit of ACEi/ARBs in Chronic Kidney Disease

## Survival With Severe Renal Insufficiency



## Survival Without Severe Renal Insufficiency



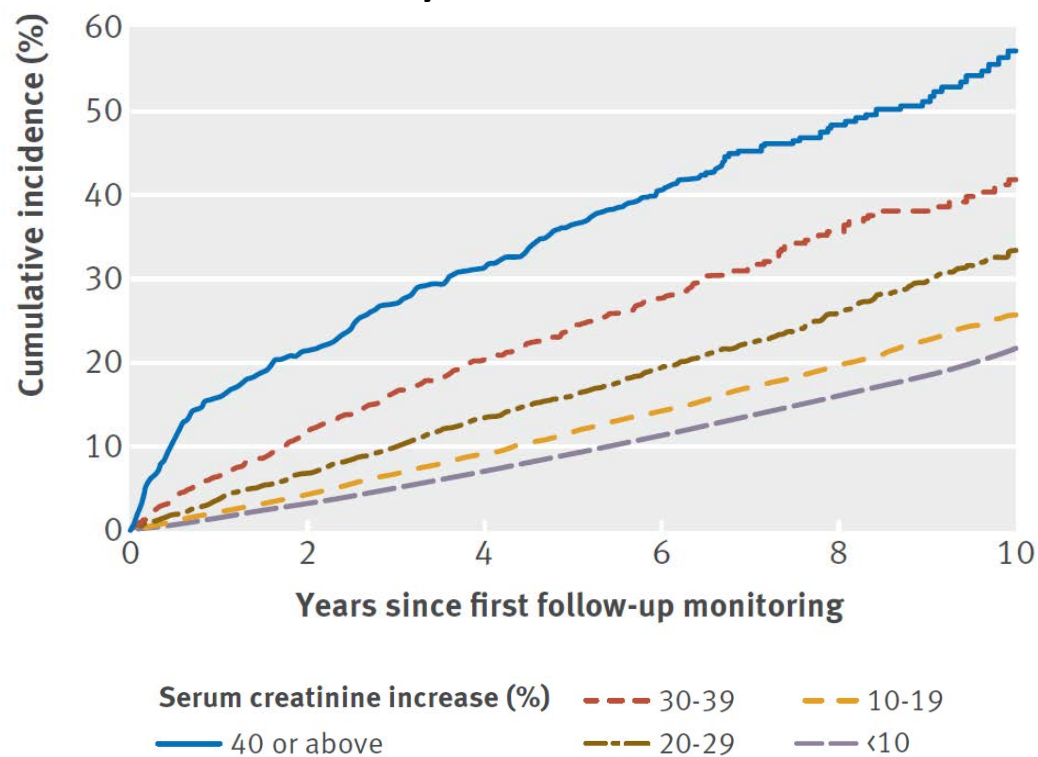
Overall survival worse in patients with severe renal insufficiency but risk reduction associated with ACEi/ARB similar in both cohorts

Heart Failure and Chronic Kidney Disease:

## Risks of ACEi/ARBs in Chronic Kidney Disease

Baseline Characteristic	SCr ↑ after starting ACEi/ARB	
	≥30% (N = 2078)	<30% (N=120,285)
<b>Chronic kidney disease</b>		
Stage 3b (GFR 30-44)	143 (6.9)	4502 (3.7)
Stage 4 (GFR 15-29)	42 (2.0)	694 (0.6)
<b>Comorbidities</b>		
Previous MI	219 (10.5)	5468 (4.5)
Heart failure	395 (19.0)	5756 (4.8)
Arrhythmia	358 (17.2)	8122 (6.8)
PAD	124 (6.0)	3044 (0.6)
<b>Co-medications</b>		
Loop diuretics	594 (28.6)	8693 (7.2)
K <sup>+</sup> sparing diuretics	183 (8.87)	2354 (2.0)
Beta blockers	493 (23.7)	20474 (17.0)

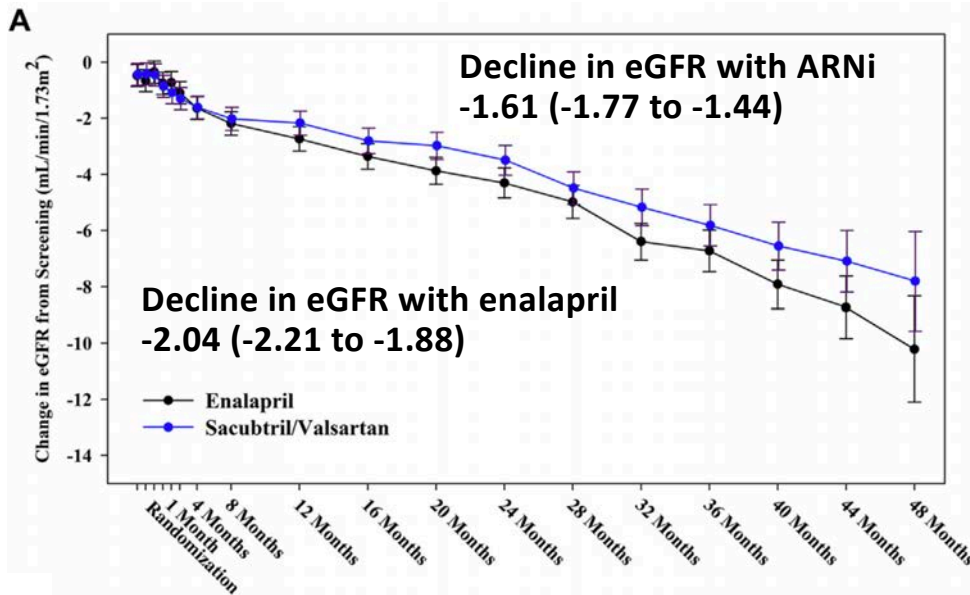
**Cumulative Mortality According to Levels of Creatinine Increase After Renin-Angiotensin System Blockade**



Heart Failure and Chronic Kidney Disease:

## Benefit of Sacubitril/Valsartan in Chronic Kidney Disease

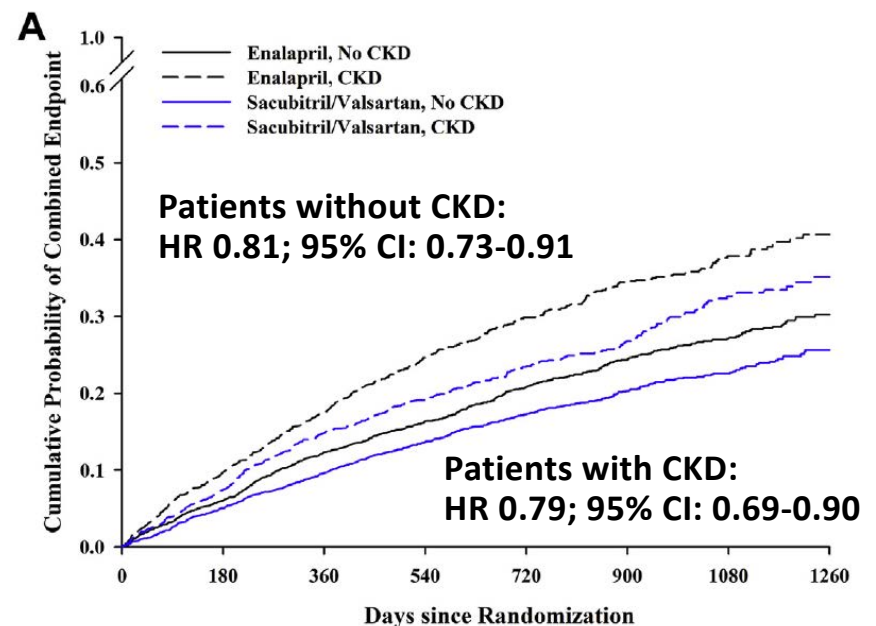
### Change in eGFR Stratified by Treatment



Difference in decline in eGFR between ARNi and enalapril:  
0.44 (0.21 to 0.67); p-value <0.001

Efficacy in preserving renal function consistent among groups with and without CKD

### Composite of CV Death and First Hospitalization for HF by Treatment Group and CKD



Absolute risk reduction with sacubitril/valsartan greater in patients with CKD (3.7 vs. 2.1 fewer patients per 100 patient-years)

Heart Failure and Chronic Kidney Disease:

## Risk of ARNi in Chronic Kidney Disease

### Adverse Events from Trials Comparing Neprilysin/RAS inhibition with RAS Inhibition Alone

	IMPRESS		OVERTURE		PARADIGM-HG	
	Omapatrilat (N = 289)	Lisinopril (N = 284)	Omapatrilat (N = 2884)	Enalapril (N = 2884)	Sacubitril/ valsartan (N = 4817)	Enalapril (N = 4212)
Symptomatic hypotension	10%	6%	19.5%	11.5%	14%	9.2%
Creatinine elevation or impaired renal function	1.8%	6.1%	6.8%	10.1%	3.3%	4.5%
Potassium elevation	3.6%	2.1%	NR	NR	4.3%	5.6%

Neprilysin/RAS inhibition have increased rates of hypotension although have decreased rates of renal impairment and potassium elevation

RAS: Renin angiotensin system

Summary:

## RAS Inhibitors in Heart Failure and Chronic Kidney Disease

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- ACC/AHA guidelines suggest caution when using an ACE inhibitor or ARB in patients with serum creatinine  $>3$  mg/dL
- KDIGO guidelines recommend starting at a lower dose in patients with GFR  $<45$  ml/min/ $1.73$  m<sup>2</sup>
- KDIGO guidelines also recommend against routine discontinuation of these agents when GFR  $< 30$  ml/min/ $1.73$  m<sup>2</sup> as they remain nephroprotective
- Current evidence supports the use of ARNis in patients with HF and CKD although more studies are needed

# Mineralocorticoid Receptor Antagonists in Heart Failure with Reduced Ejection Fraction

Trial	Patient population	Treatment arms	Renal Exclusion	Outcome
<b>RALES</b>	NYHA FC III-IV; LVEF $\leq$ 0.35 (N = 1663)	Spironolactone vs placebo	SCr > 2.5 mg/dl	<u>Death from any cause:</u> 35% vs 46% (RR = 0.70; 95% CI 0.60-0.82)
<b>EPHESUS</b>	3-14 days post-MI; LVEF $\leq$ 0.40 (N=6632)	Eplerenone vs placebo	SCr $\geq$ 2.5 mg/dl	<u>Death from any cause:</u> 14.4% vs 16.7% (RR 0.85; 95% CI 0.75-0.96)  <u>Death from CV causes or first hospitalization for CV event:</u> 26.7% vs 30.0% (RR 0.87; 95% CI 0.79-0.95)
<b>EMPHASIS-HF</b>	NYHA FC II; LVEF $\leq$ 0.30 (N = 2737)	Eplerenone vs placebo	eGFR < 30 ml/min/1.73m <sup>2</sup>	<u>Death from CV causes or first hospitalization for HF:</u> 18.3% vs 25.9% (HR 0.66; 95% CI 0.56-0.78)

Heart Failure and Chronic Kidney Disease:

## Benefit of MRAs in Chronic Kidney Disease

	Favors MRAs	No Difference Compared to Placebo	RR (95% CI) I-squared statistic
<b>Effect of MRA on All-cause Mortality</b>			
Overall	✓		0.78 (0.62 – 0.97) 55.0%
<b>Incidence of MACE</b>			
Overall	✓		0.65 (0.50 – 0.83) 67.1%
<b>Complication of Heart Failure Subgroup Analysis</b>			
Heart failure		✓	0.85 (0.71 – 1.01) 59.4%

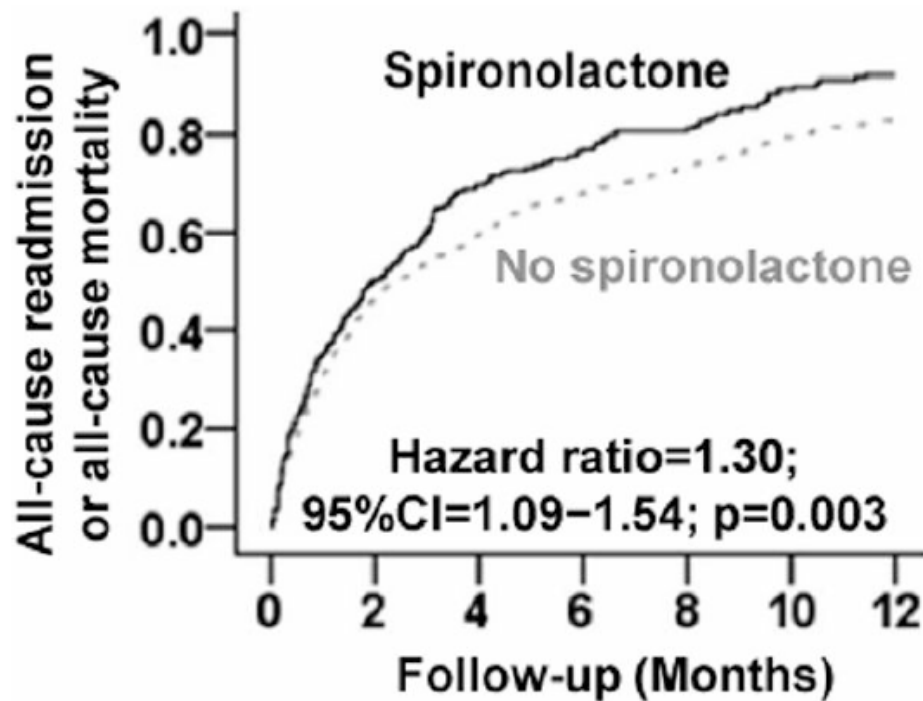
MRA use in general population with CKD associated with reduced all-cause mortality, but **benefits not seen in HF subanalysis**

MRA: mineralocorticoid receptor antagonist

Heart Failure and Chronic Kidney Disease:

## Benefit of MRAs in Chronic Kidney Disease

Propensity Score-Adjusted 1-Year All-Cause Readmission or All-Cause Mortality in Patients with LVEF <45% and est. GFR <45ml/min/1.73m<sup>2</sup>



Increased risk of all-cause readmission or all-cause mortality within one year among patients on spironolactone

Heart Failure and Chronic Kidney Disease:

## Benefit of MRAs in Chronic Kidney Disease

### Associations of Discharge Prescription of Spironolactone with Outcomes at 30 days Post-Discharge Among Medicare Beneficiaries

	% (total events/total patients) Spironolactone on discharge		Hazard ratio (95% CI); p-value	
	No	Yes	Unadjusted	Propensity score adjusted
All-cause readmission	25% (237/933)	30% (61/207)	1.19 (0.90-1.57);p=0.233	1.41 (1.04-1.90);p=0.027
Heart failure readmission	12% (116/933)	12% (25/207)	0.97 (0.63-1.49);p=0.872	0.90 (0.57-1.41);p=0.635
All-cause mortality	8% (75/933)	8% (17/207)	1.01 (0.60-1.72);p=0.961	1.05 (0.60-1.82);p=0.866
All-cause mortality or readmission	31% (285/933)	34% (70/207)	1.13 (0.87-1.47);p=0.352	1.31 (0.99-1.72);p=0.058

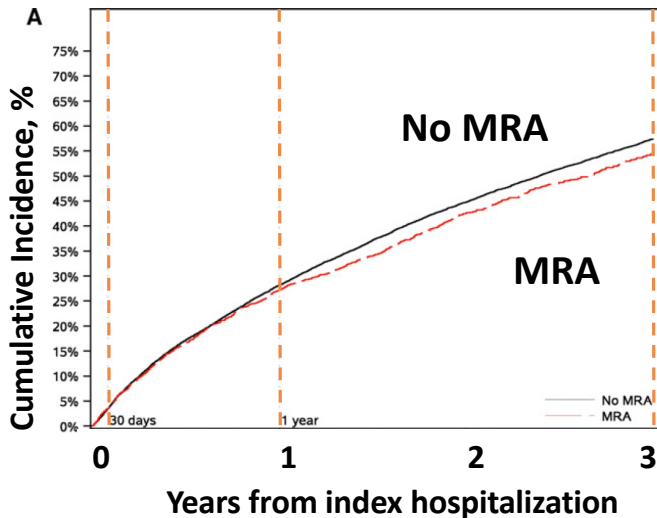
MRA prescription at discharge for patients with HFrEF and CKD associated with increased readmission rates and combined endpoint for all-cause mortality or readmission at 1-year

Heart Failure and Chronic Kidney Disease:

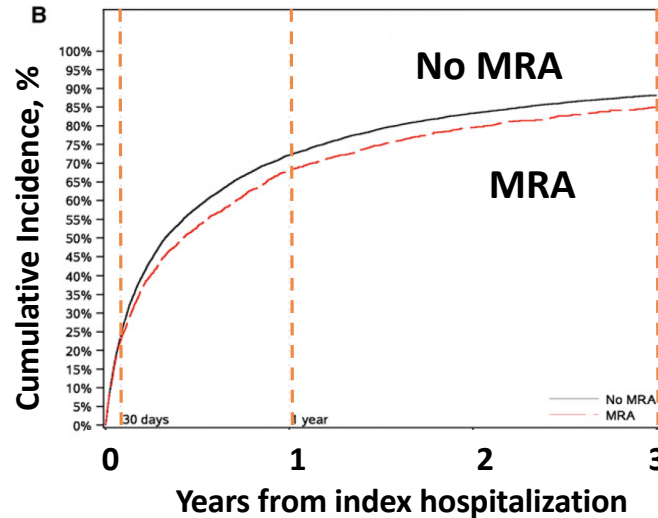
## Benefit of MRAs in Chronic Kidney Disease

Association of MRA Discharge Prescription with 30-day, 1-year or 3-year Mortality for Hospitalized Patients with HF and Type II DM or a SCr >2.0 mg/dl

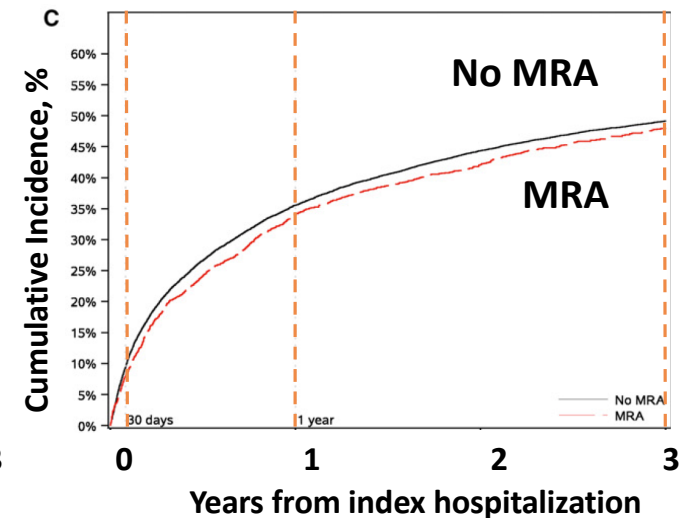
Mortality



All-Cause Hospitalization



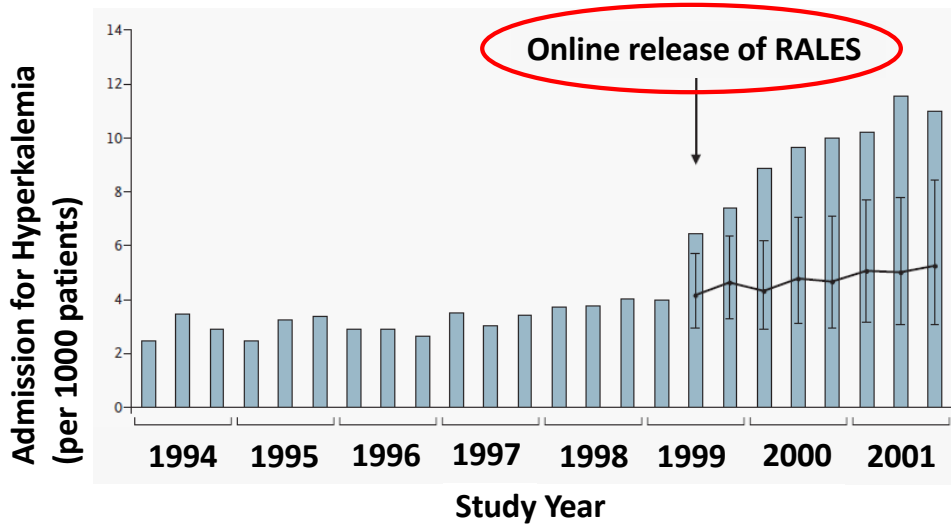
Heart Failure Hospitalization



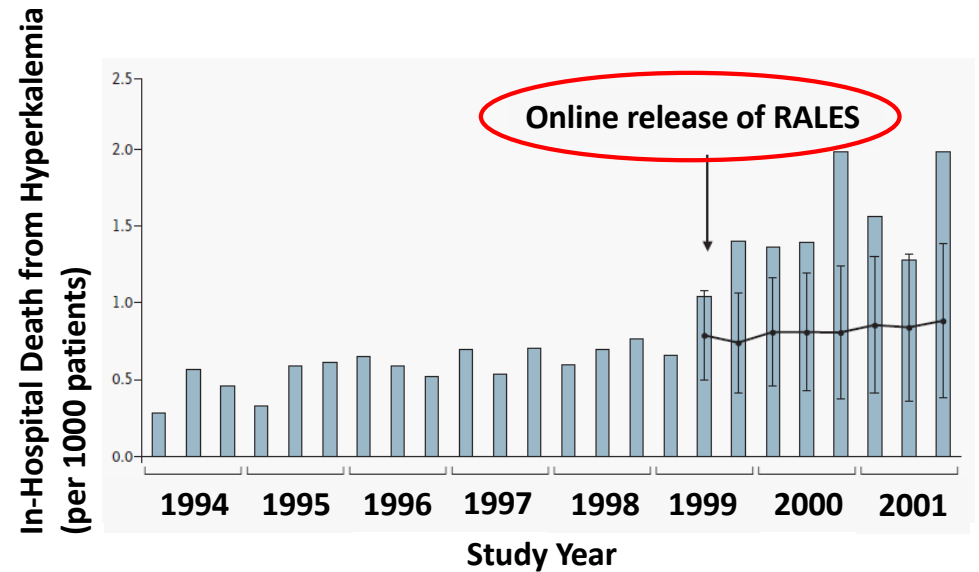
After adjustment for patient-specific characteristics and other medications (i.e. ACEi/ARB, beta-blockers, anticoagulants, digoxin, diuretics, lipid-lowering agents), **MRA on discharge not associated with difference in outcomes.**

# Heart Failure and Chronic Kidney Disease: Risk of MRAs in Chronic Kidney Disease

### Rate of Hospital Admission for Hyperkalemia Among HF Patients on ACE Inhibitors



### Rate of In-Hospital Death Associated with Hyperkalemia Among HF Patients on ACE Inhibitors



The publication of RALES associated with significant increases in rates of hospital admission for hyperkalemia and in-hospital death

Summary:

## MRAs in Heart Failure and Chronic Kidney Disease

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- ACC/AHA guidelines recommend against using MRAs in men and women with serum creatinine  $> 2.5$  mg/dl and  $>2.0$  mg/dl, respectively, or GFR  $<30$  ml/min/1.73 m<sup>2</sup> due to the concern for hyperkalemia
- KDIGO guidelines recommend starting at a lower dose in patients with GFR  $< 45$  ml/min/1.73 m<sup>2</sup>
- KDIGO guidelines also recommend against routine discontinuation of these agents when GFR  $< 30$  ml/min/1.73<sup>2</sup> as they remain nephroprotective
- MRAs have unclear benefit in those with HFrEF and CKD but are associated with higher rates of hyperkalemia



# Potassium Binders for Patients with Heart Failure and Chronic Kidney Disease

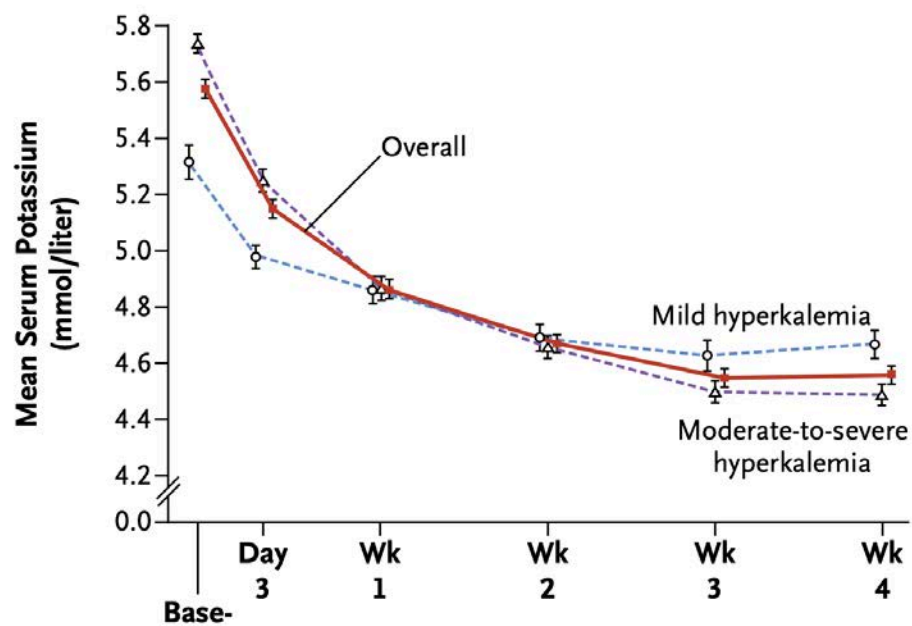
# Potassium Binders for Hyperkalemia

Drug	MOA	Onset of Action	Dose	Adverse Events	Administration Considerations
<b>Patiromer Calcium</b>	Non-absorbed, cation exchange polymer; calcium-sorbitol counterion; binds potassium in the lumen of GI tract increasing fecal potassium excretion	7 hours	8.4 g/day. Up-titrate at 1-week intervals to a max of 25.2 g/day	Constipation, diarrhea, nausea, hypomagnesemia	Administer other oral medications at least <u>6 hours</u> before or after
<b>Sodium Zirconium Cyclosilicate (SZC)</b>	Non-absorbed, zirconium silicate that preferentially binds calcium in exchange for hydrogen and sodium in the lumen of the GI tract increasing fecal potassium excretion	1 hour	10 g three times daily for up to 48 hours, then 10 g once daily. Up-titrate at 1-week intervals to a max of 15 g/day	Edema, hypokalemia in patients on hemodialysis	Administer other oral medications at least <u>2 hours</u> before or after
<b>Sodium Polystyrene Sulfonate (SPS)</b>	Non-absorbed, cation exchange polymer that removes potassium in exchange for sodium in large and small intestine.	Hours to days	Oral: 15 grams one to four times daily Rectal: 30-50 grams once or twice daily	Abdominal pain and distention, GI bleeding, diarrhea, nausea/vomiting; <u>bowel necrosis</u>	Administer other oral medications at least <u>3 hours</u> before or after

# Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors: OPAL-HK Trial (2015)

## Serum Potassium Levels over Time during Initial Treatment Phase

- Double-blind, randomized
- N = 237
- GFR 15 to <60 ml/min/1.73 m<sup>2</sup>
- Serum K 5.1 to < 6.5 mmol/L
- Stable dose of RAASi for ≥ 28 days

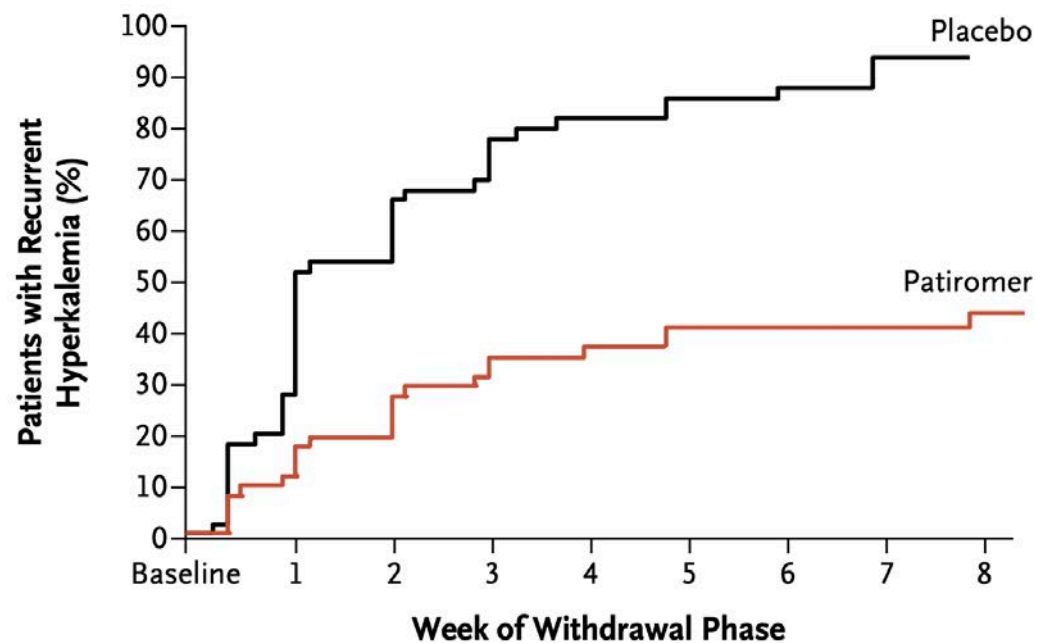


No. at Risk	Base-line	Day 3	Wk 1	Wk 2	Wk 3	Wk 4
Overall	243	217	237	228	221	219
Mild hyperkalemia	92	80	90	87	85	85
Moderate-to-severe hyperkalemia	151	137	147	141	136	134

RAASi: renin-angiotensin-aldosterone system inhibitors

# Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors: OPAL-HK Trial (2015)

Time to First Serum Potassium Level  $\geq 5.1$  mmol/L



**No. at Risk**

Placebo	52	37	24	16	10	8	8	7	1
Patiromer	55	47	42	36	34	30	29	29	23

# Efficacy and Safety of Patiromer in Patients with Chronic HF

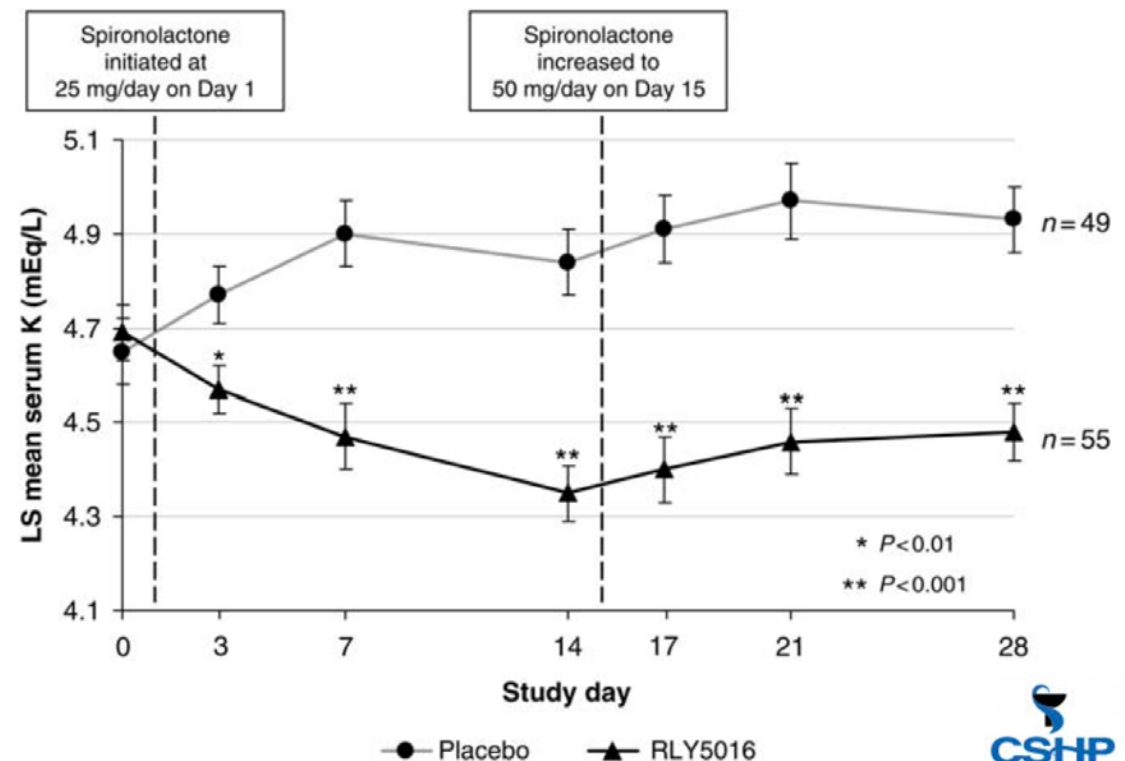
## PEARL-HF Trial (2011)

- Double-blind, randomized trial of 104 patients
- Chronic HF with indication for spironolactone

- GFR <60 ml/min/1.73 m<sup>2</sup> or history of hyperkalemia resulting in discontinuation of RAAS inhibitor

Patients on patiromer had lower serum potassium and were more likely to have spironolactone titrated to 50mg/d

Hypomagnesemia (<1.8 mg/dL) occurred in **24%** of patients in the patiromer group compared to 2% in the placebo group

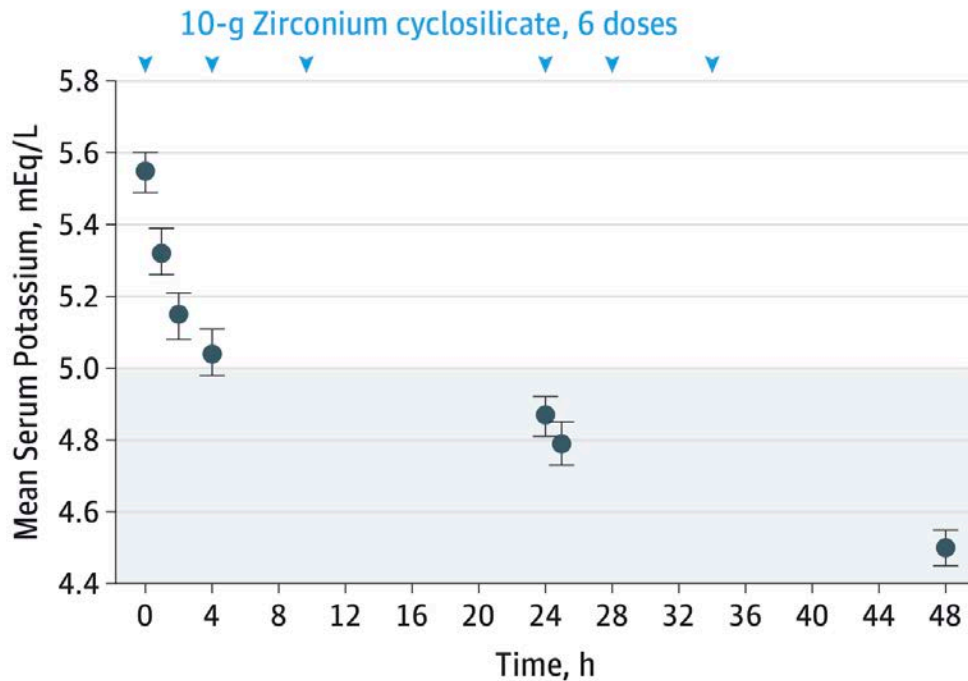


# Effect of SZC on Potassium Lowering for 28 Days Among Outpatients with Hyperkalemia: [HARMONIZE Trial \(2014\)](#)

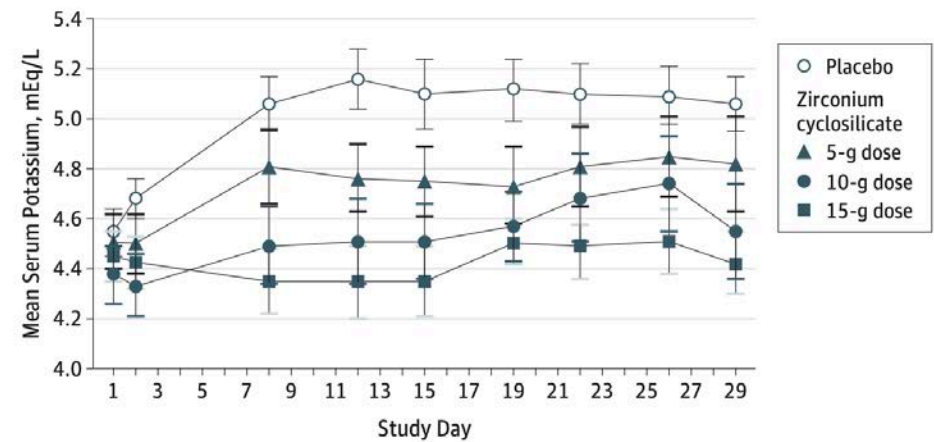
- Double-blind, randomized trial of 258 patients

- Ambulatory patients with a serum potassium  $\geq 5.1$  mEq/L

**Mean Serum Potassium Levels During Open-label Phase**



**Serum Potassium Levels During Randomized Phase**



No. of patients

Placebo	82	81	81	80	80	78	77	74	73
5-g dose	45	45	45	44	44	43	43	42	39
10-g dose	50	49	50	47	47	47	45	45	38
15-g dose	54	54	54	53	52	51	51	51	43

# Effect of SZC on Potassium Lowering for 28 Days Among Outpatients with Hyperkalemia: [HARMONIZE Trial \(2014\)](#)

Effect of SZC consistent across all prespecified subgroups (CKD, HF, DM, taking RAASi)

Most Common Adverse Events:

	Open-label Phase (SZC 10g) (N = 259)	Randomized Phase			
		Placebo Group (N = 85)	Sodium Zirconium Cyclosilicate Dose Group		
			5g (N = 45)	10g (N = 51)	15g (N = 56)
<b>Edema</b>	0	2 (2.4)	1 (2.2)	3 (5.9)	8 (14.3)
<b>Hypokalemia</b>	0	0	0	5 (9.8)	6 (10.7)

Dose-dependent increase in edema and hypokalemia found with SZC

DM: diabetes mellitus

# Potassium Binders for Hyperkalemia

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What about Sodium Polystyrene Sulfonate?

- **FDA Black Box Warning**

- Cases of colonic necrosis and other serious GI adverse events
- Occurs in 0.1 – 0.3% of patients (33% mortality)
- Avoid concomitant administration of sorbitol or in postoperative patient at risk for constipation or impaction

## Potassium Binders for Hyperkalemia

Drug	Average Wholesale Price	Estimated Monthly Cost Based on Average Wholesale Price
<b>Patiromer Calcium</b>	8.4 g: \$48.00 16.8 g: \$35.92 25.2 g: 35.92	\$1400 per month
<b>Sodium Zirconium Cyclosilicate (SZC)</b>	5 g: \$26.98 10 g: \$26.98	\$800 per month
<b>Sodium Polystyrene Sulfonate</b>	Oral 15g/60mL (per mL): \$0.82 Rectal 30g/120mL (per mL): \$0.37	\$10 per month

Ongoing clinical trials:

## Potassium Binders for Hyperkalemia

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Study	ClinicalTrials.gov identifier	Status
Patiromer Utility as an Adjunct Treatment in Patients Needing Urgent Hyperkalemia Management (PLATINUM)	NCT04443608	Not yet recruiting
Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure (DIAMOND)	NCT03888066	Active, not recruiting

Summary:

## Potassium Binders for Hyperkalemia

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- Not incorporated into guidelines yet
- Potassium binders may be beneficial as adjunctive therapy to RAAS inhibitor therapies in patients with CKD experiencing hyperkalemia
- Given the delayed onset of action, patiromer and sodium zirconium cyclosilicate should not be used as emergency treatment for acute hyperkalemia

Summary:

## Optimizing Medical Therapy in Patients with HF and CKD

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- Due to lack of RCTs in patients with HFrEF and CKD, there is little guidance of GDMT in this population
- The benefit of GDMT in this patient population remains largely unknown, although there is a higher risk of adverse drug side effects
- Novel potassium binders show promise in this patient population although more studies are needed



## TEST QUESTIONS

- 1) True/False – Worsening renal function without congestion upon hospital discharge for HF patients has been associated with poorer outcomes when compared to those without worsening renal function
- 2) True/False – MRAs have unclear benefit in those with HFrEF and CKD but are associated with higher rates of hyperkalemia
- 3) True/False – Novel potassium binders have shown mortality benefit in HF patients that have been attributed to continued RAAS therapy



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# QUESTIONS?

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## Additional Resources

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