Optimizing medical therapy in Patients with Heart Failure and Chronic Kidney Disease

Michelle Lew, PharmD, BCPS, BCCP

Scripps memorial Hospital, La Jolla

October 2020

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 guideline directed medical therapy in patients with heart failure with 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

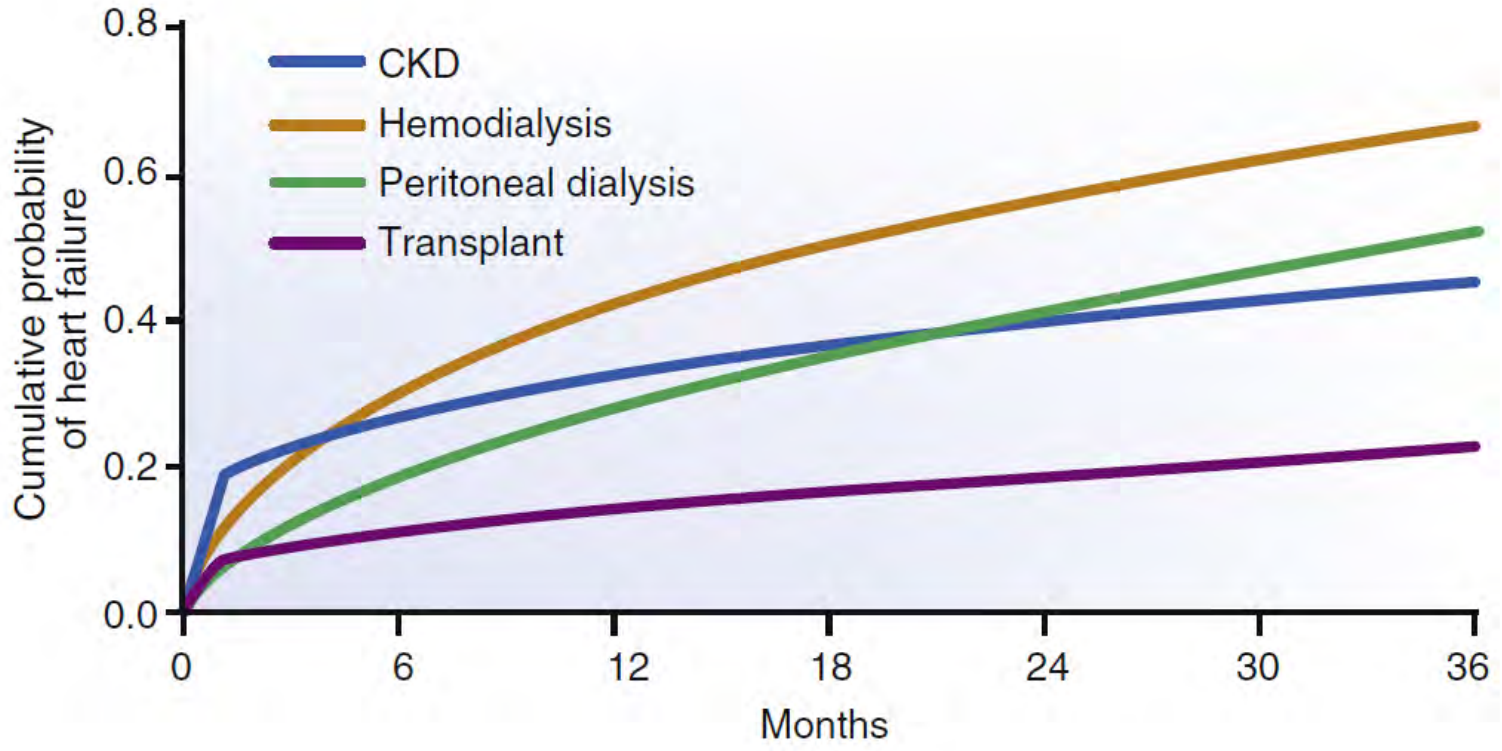
TEST QUESTIONS

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 which is attributed to continued RAAS therapy

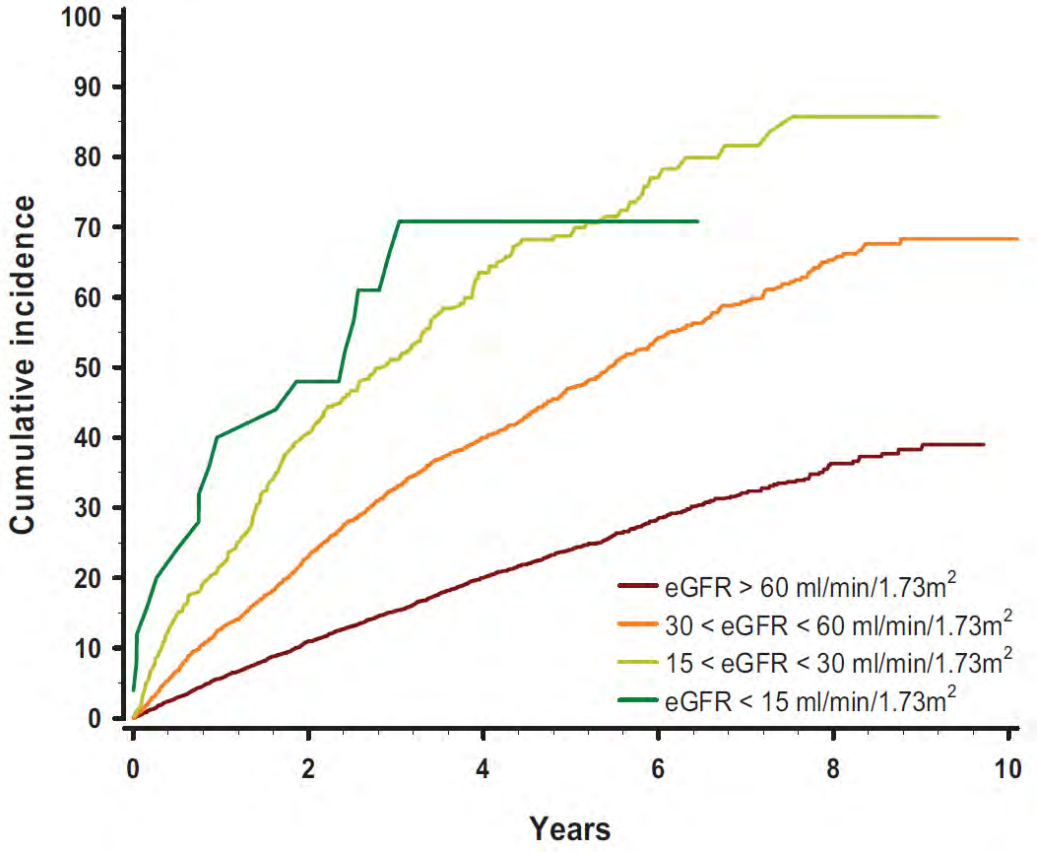
Cumulative Probability of Heart Failure in Populations with CKD, Dialysis, and a Kidney Transplant



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.

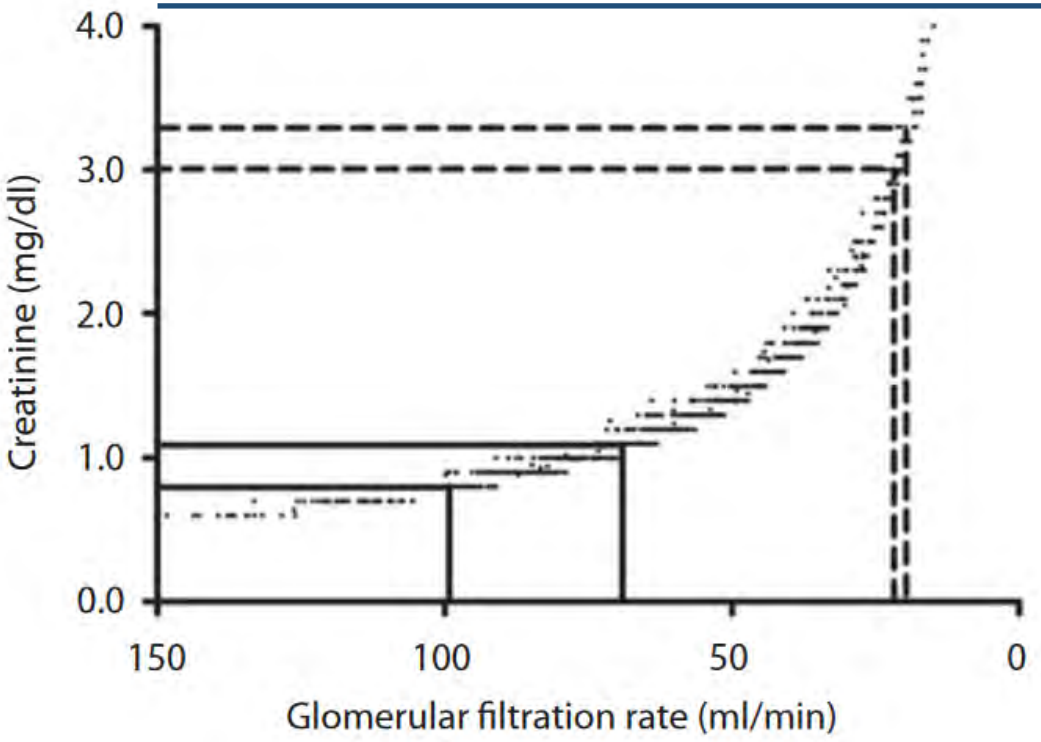
Classification of Cardiorenal Syndrome

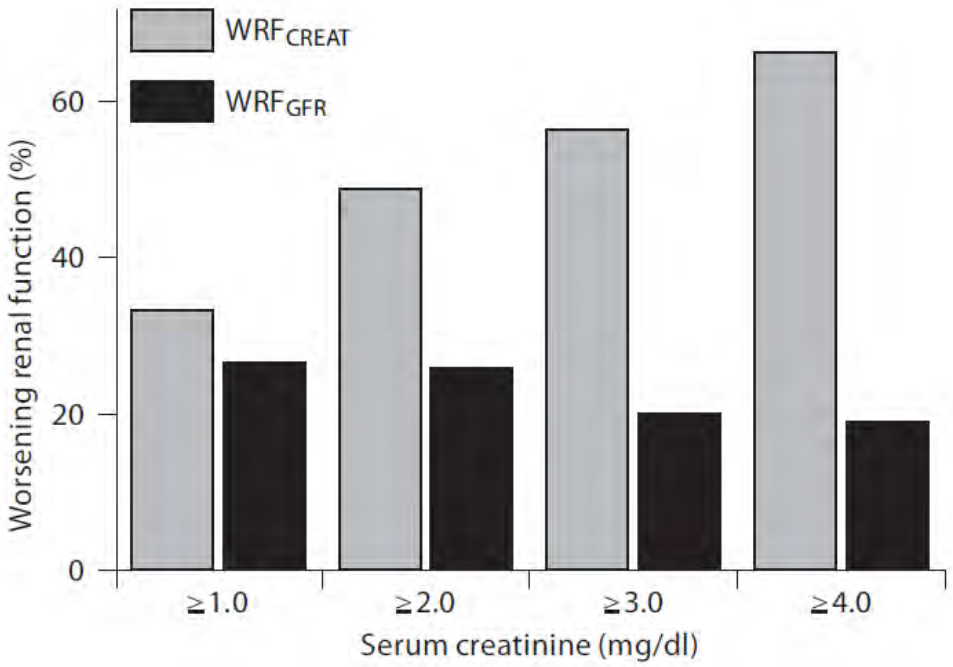
Phenotype	Nomenclature	Description	Clinical Example
Type 1 CRS	Acute CRS	HF resulting in AKI	ACS resulting in cardiogenic shock and AKI, AHF resulting in AKI
Type 2 CRS	Chronic CRS	Chronic HF resulting in CKD	Chronic HF
Type 3 CRS	Acute renocardiac syndrome	AKI resulting in AHF	HF in the setting of AKI from volume overload, inflammatory surge, and metabolic disturbances in uremia
Type 4 CRS	Chronic renocardiac syndrome	CKD resulting in chronic HF	LVH and HF from CKD-associated cardiomyopathy
Type 5 CRS	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

Rangaswami J et al. *Circulation* 2019:139:e840-e878.

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

Testani JM et al. *Cardiology* 2010.116:206-212.

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)
Hemodynamic	
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)
Clinical	
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)
Hemoconcentration	
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)
Plasma Volume	
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 ≥ 0.3 mg/dL) at discharge associated with worse outcomes compared to patients without congestion and WRF

HR: hazard ratio; CI: confidence interval

Fudim M et al. *Am Heart J* 2018.204:163-73.

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

McCallum W et al. *J Am Coll Cardiol HF* 2020.8:537-47.

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
MERIT-HF	NYHA FC II-IV; LVEF ≤ 0.40 (N = 3991)	Metoprolol succinate vs placebo	None	All-cause mortality: 7.2% vs 16.8% (RR 0.34; 95% CI 0.19 – 0.47)
CIBIS-II	NYHA FC III-IV; LVEF ≤ 0.35 (N = 2647)	Bisoprolol vs placebo	SCr ≥ 3.4 mg/dl	All-cause mortality: 12% vs 17% (HR 0.66; 95% CI 0.51 – 0.81)
COPERNICUS	LVEF ≤ 0.52 (N = 2289)	Carvedilol vs placebo	SCr > 2.8 mg/dl	Annual mortality: 12.8% vs 19.7% (RR 0.65; 95% CI 0.64 – 0.87)
SENIORS	≥70 years; CHF diagnosis or LVEF ≤ 0.35 within 6 months (N = 2128)	Nebivolol vs placebo	Significant renal dysfunction	All-cause mortality or cardiovascular hospital admission: 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

Berthe C et al. *Lancet* 1999.353:2001-07. Brunhuber KW et al. *Lancet* 1999.353:9-13. Packer M et al. *Circulation* 2002.106:2194-2199. Flather MD et al. *Eur Heart J* 2005.26:215-225.

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 $eGFR_{MDRD}$ <45

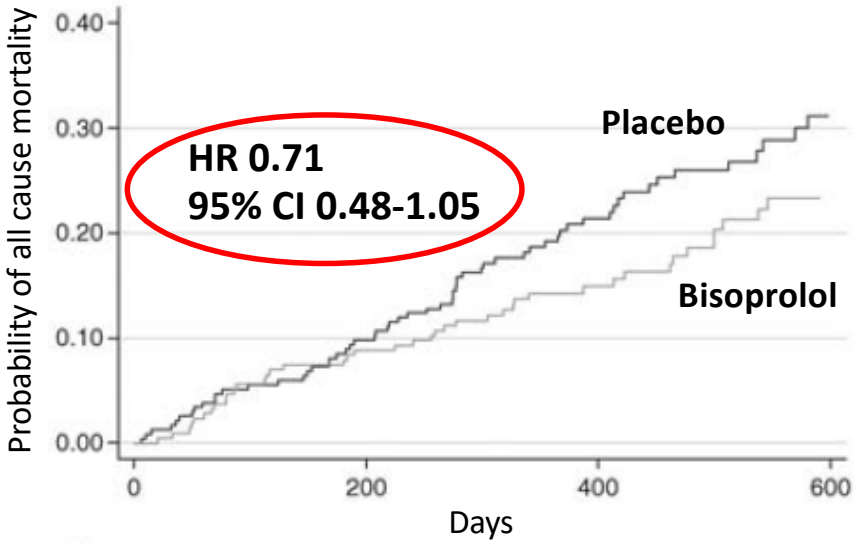
MDRD: Modification of Diet in Renal Disease

Ghali JK et al. *J Cardiac Fail* 2009.15:310-318.

Heart Failure and Chronic Kidney Disease:

Benefit of Bisoprolol in Chronic Kidney Disease

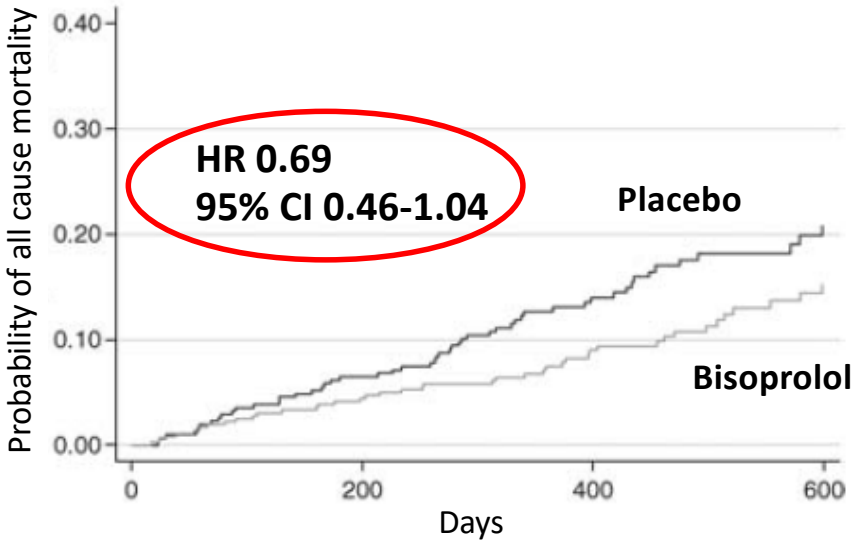
All-Cause Mortality with eGFR < 45 ml/min/1.73m²



Number at risk

Placebo	235	211	129	56
Bisoprolol	215	196	127	63

All-Cause Mortality with eGFR ≥ 45 to <60 ml/min/1.73m²



Number at risk

Placebo	308	288	190	89
Bisoprolol	361	345	228	108

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

Castagno D et al. *Eur J Heart Fail* 2010.12:607-616.

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^2?

HF: heart failure; CV: cardiovascular

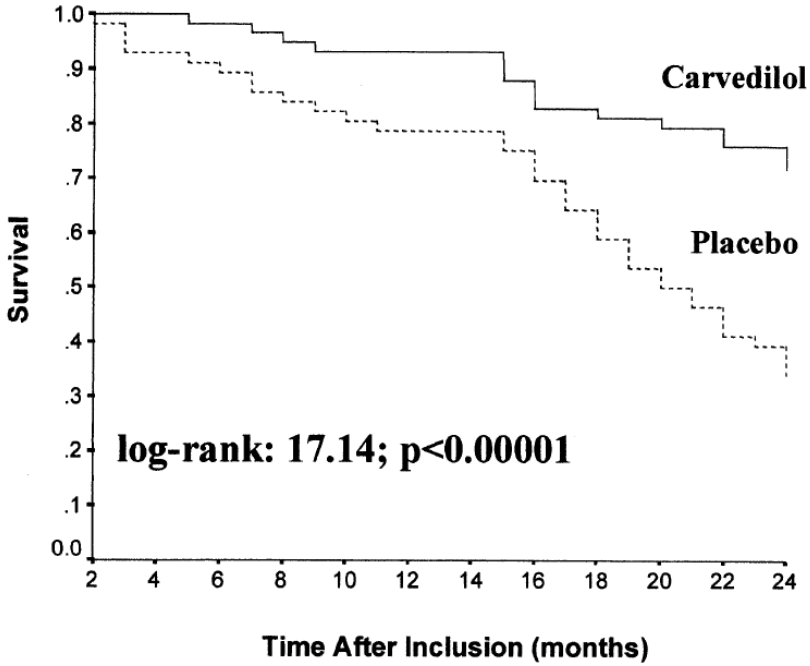
Wali RK et al. *Circ Heart Fail* 2011.4:18-26.

Heart Failure and Chronic Kidney Disease:

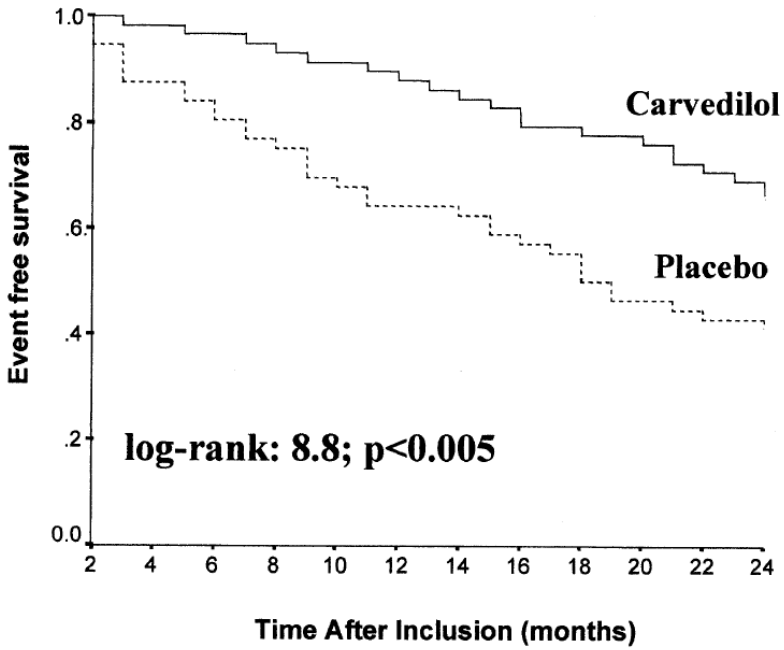
Benefit of Carvedilol in Hemodialysis

- 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

Cardiovascular Death



All-Cause Hospital Admission



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

Cice G et al. *J Am Coll Cardiol* 2001.37:407-11.

Cice G et al. *J Am Coll Cardiol* 2003. 41:1438-44.

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
Hemodialysis cohort				
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)	
Nondialysis cohort				
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

Weir MA et al. *J Am Soc Nephrol* 2015.26:987-996. Tieu A et al. *Clin J Am Soc Nephrol* 2018.13:604-611.

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%

Badve SV et al. *J Am Coll Cardiol* 2011.58:1152-61.

Summary:

Beta Blockers in Heart Failure and Chronic Kidney Disease

- 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^2

- There is conflicting evidence for the benefit of beta blockers in patients with CKD, primarily due to the low number of participants included studies

- Carvedilol may be preferable in patients on hemodialysis

ACC: American College of Cardiology; AHA: American Heart Association; KDIGO: Kidney Disease Improving Global Outcomes

Yancy CW et al. *Circulation* 2013.128:e240-e327. Yancy CW et al. *Circulation* 2016.134:e282-e293. KDIGO 2012 clinical practice guideline. *Kidney Int* 2013.3(1):1-150.

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

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

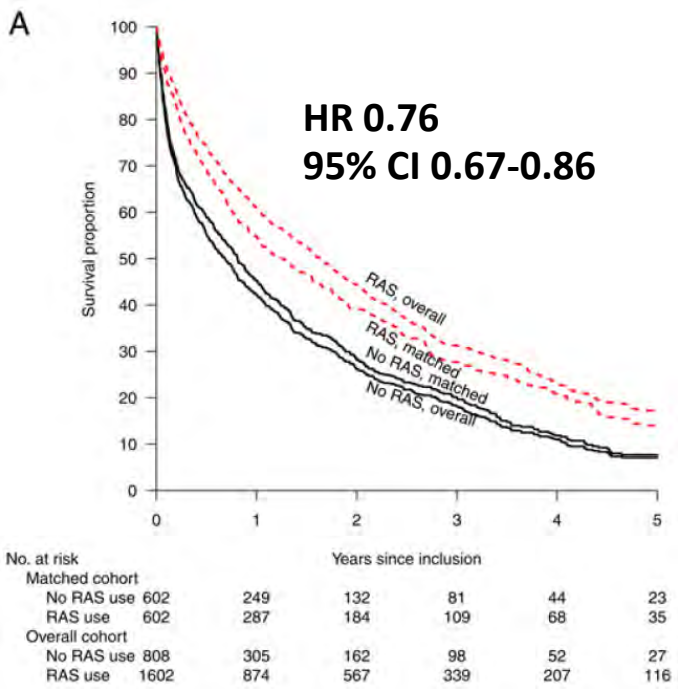
CHF: congestive heart failure; CV: cardiovascular

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.

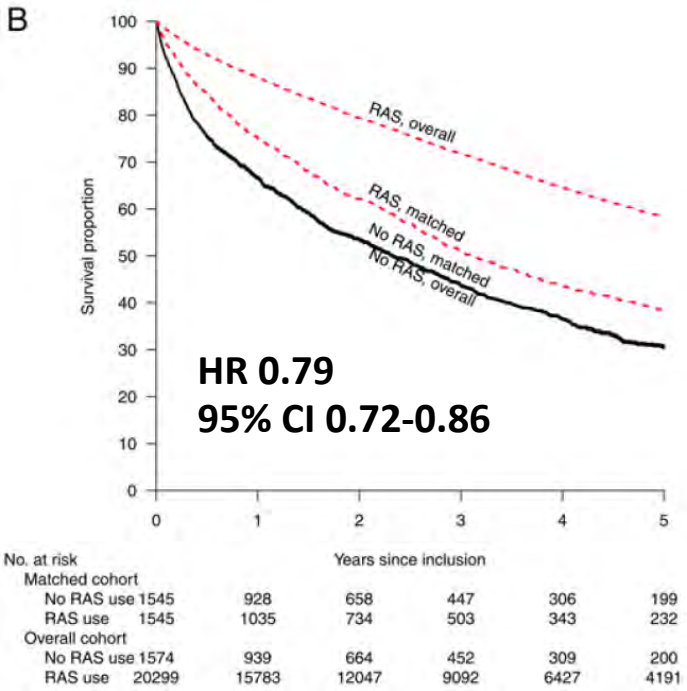
Heart Failure and Chronic Kidney Disease:

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

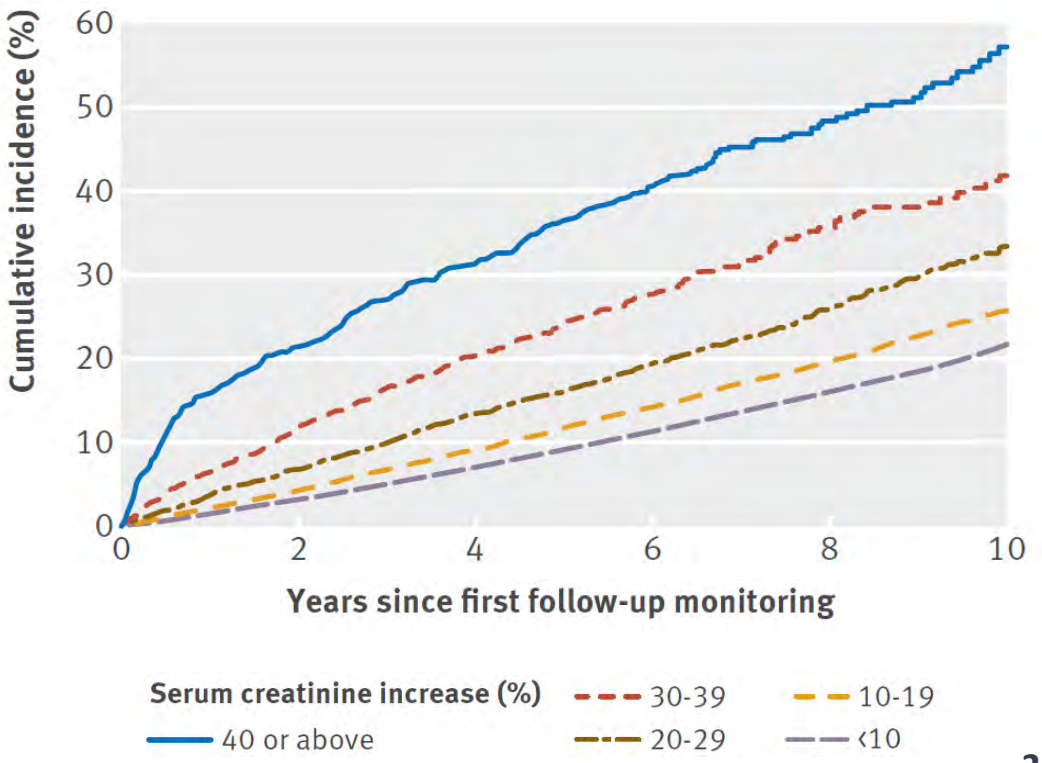
Edner M et al. *Eur Heart J* 2015.36:2318-2326.

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)
Chronic kidney disease		
Stage 3b (GFR 30-44)	143 (6.9)	4502 (3.7)
Stage 4 (GFR 15-29)	42 (2.0)	694 (0.6)
Comorbidities		
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)
Co-medications		
Loop diuretics	594 (28.6)	8693 (7.2)
K^+ 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

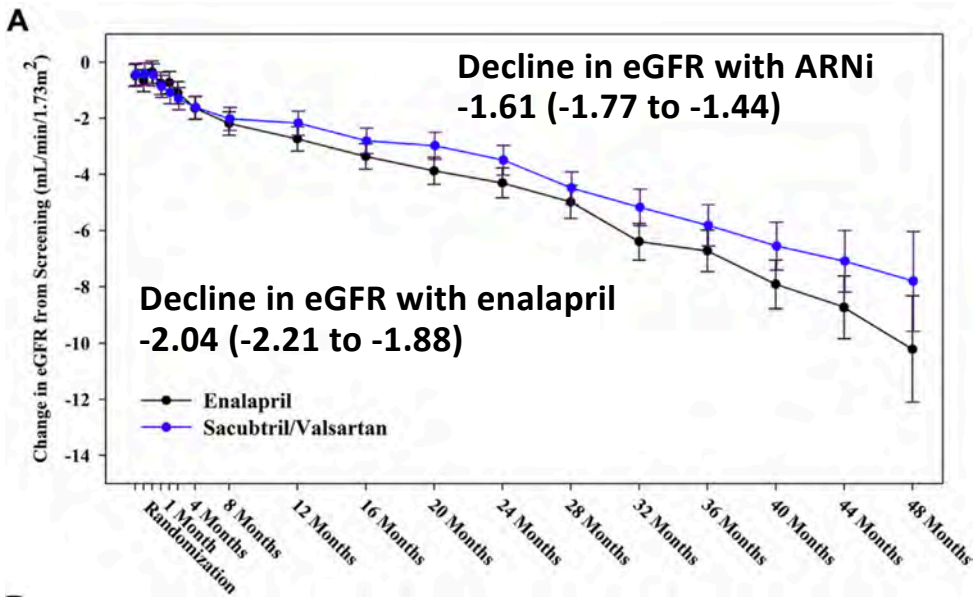


Schmidt M et al. *BMJ* 2017.356:j791.

Heart Failure and Chronic Kidney Disease:

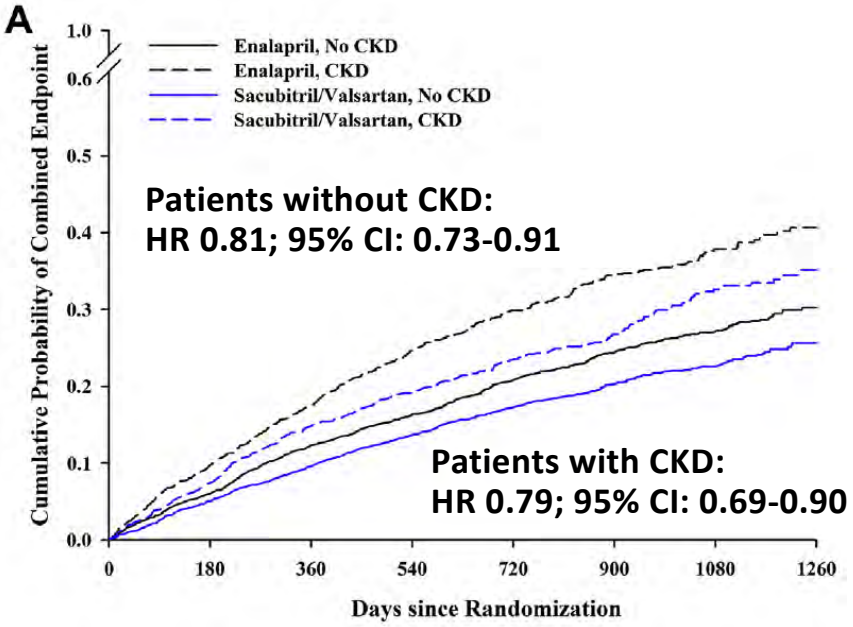
Benefit of Sacubitril/Valsartan in Chronic Kidney Disease

Change in eGFR Stratified by Treatment



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)

Damman K et al. *J Am Coll Cardiol HF* 2018.6:489-98.

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-HF	
	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

Solomon Sd et al. *Eur J Heart Fail* 2016.18:1238-1243.

Summary:

RAS Inhibitors in Heart Failure and Chronic Kidney Disease

- 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^2

- KDIGO guidelines also recommend against routine discontinuation of these agents when GFR< 30 ml/min/1.73^2 as they remain nephroprotective

- Current evidence supports the use of ARNis in patients with HF and CKD although more studies are needed

Yancy CW et al. *Circulation* 2013.128:e240-e327. Yancy CW et al. *Circulation* 2016.134:e282-e293. KDIGO 2012 clinical practice guideline. *Kidney Int* 2013.3(1):1-150.

Mineralocorticoid Receptor Antagonists in Heart Failure with Reduced Ejection Fraction

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

Pitt B et al. *N Engl J Med* 1999.341:709-17. Pitt B et al. *N Engl J Med* 2003.348:1309-21. Zannad F et al. *N Engl J Med* 2011.364:11-21.

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
Effect of MRA on All-cause Mortality			
Overall	✓		0.78 (0.62 – 0.97) 55.0%
Incidence of MACE			
Overall	✓		0.65 (0.50 – 0.83) 67.1%
Complication of Heart Failure Subgroup Analysis			
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**

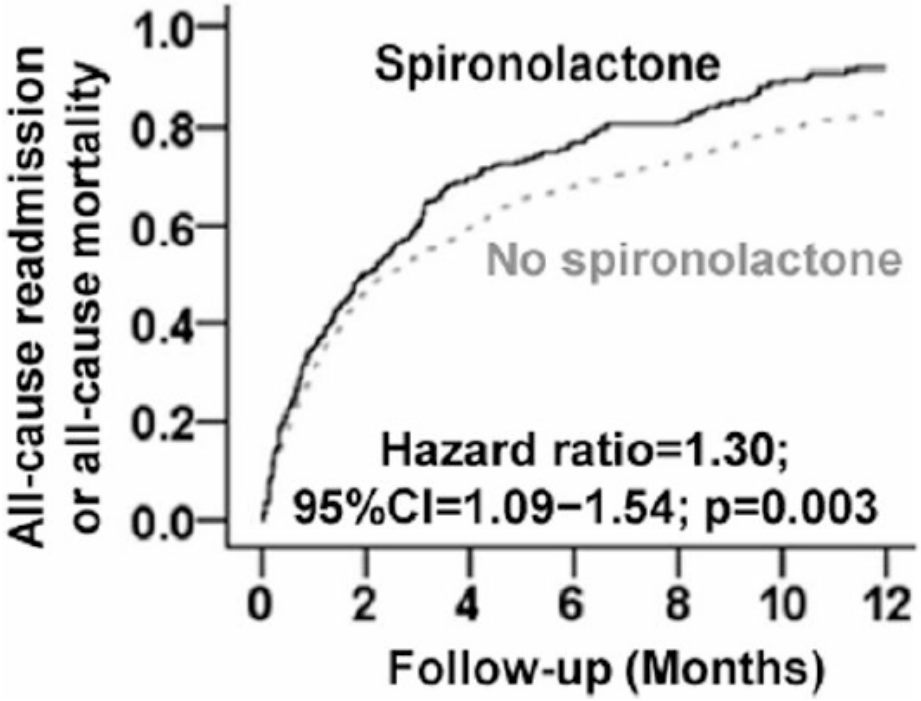
MRA: mineralocorticoid receptor antagonist; MACE: major adverse cardiovascular events

Lu R et al. *Int Urol Nephrol* 2016.48:1499-509.

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^2



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

Inampudi C et al. *Am J Cardiol* 2014.114:79-82.

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

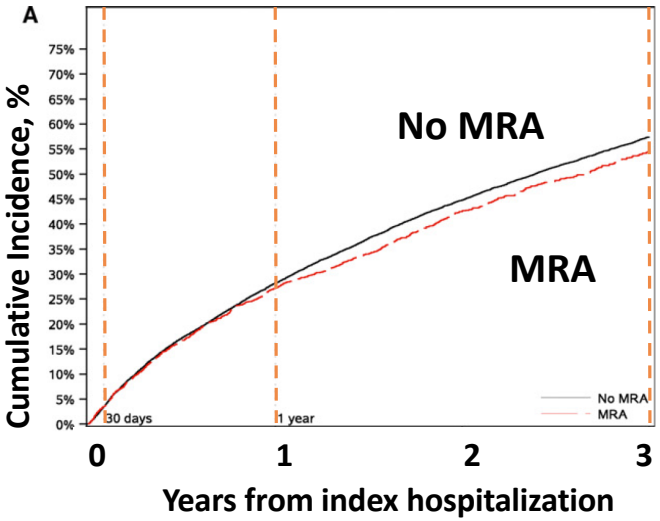
Inampudi C et al. *Am J Cardiol* 2014.114:79-82.

Heart Failure and Chronic Kidney Disease:

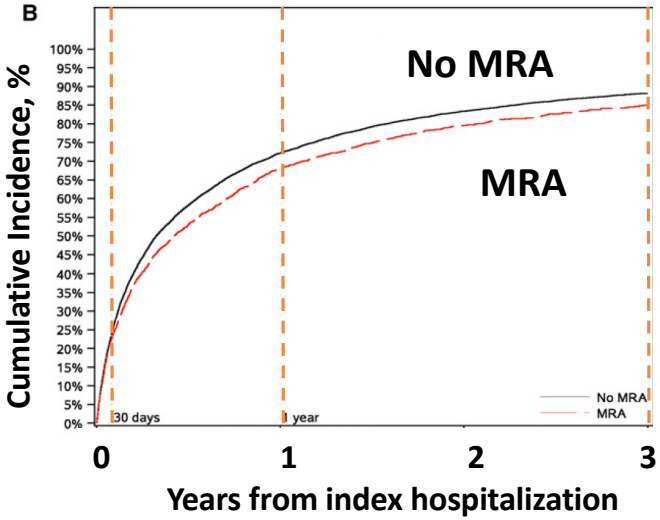
Benefit of MRAs in Chronic Kidney Disease

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

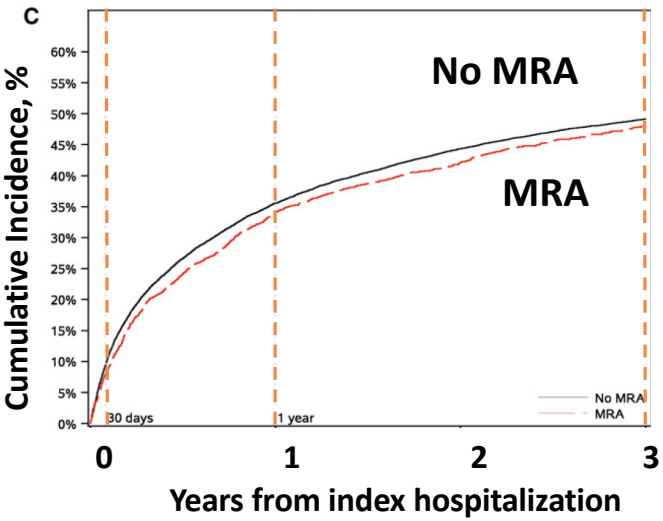
Mortality



All-Cause Hospitalization



Heart Failure Hospitalization



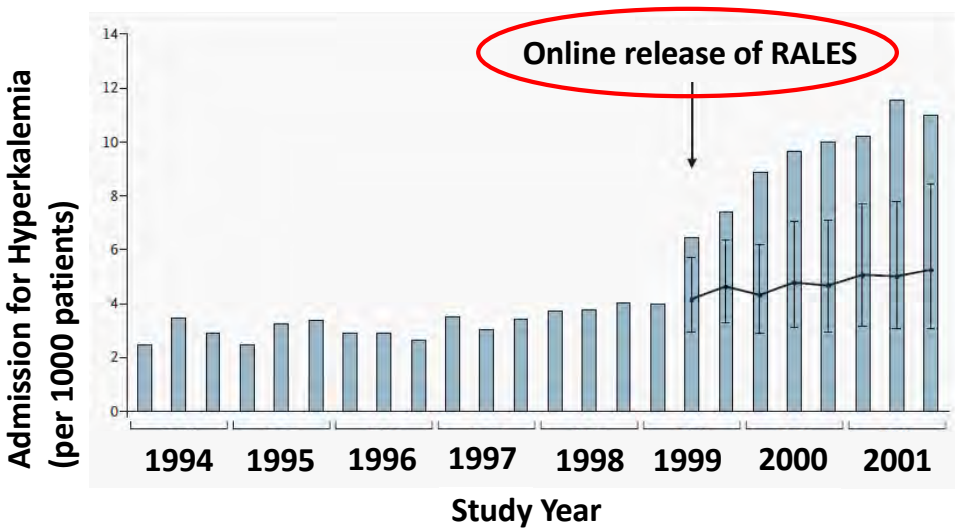
After adjustment for patient-specific characteristics and other medications (i.e. ACEi/ARB, beta-blockers, anticoagulants, digoxin, diuretics, lipid-lowering agents), **MRA on discharge not associated with difference in mortality outcome.**

Cooper LB et al. *J Am Heart Assoc* 2017.6(2):e006540.

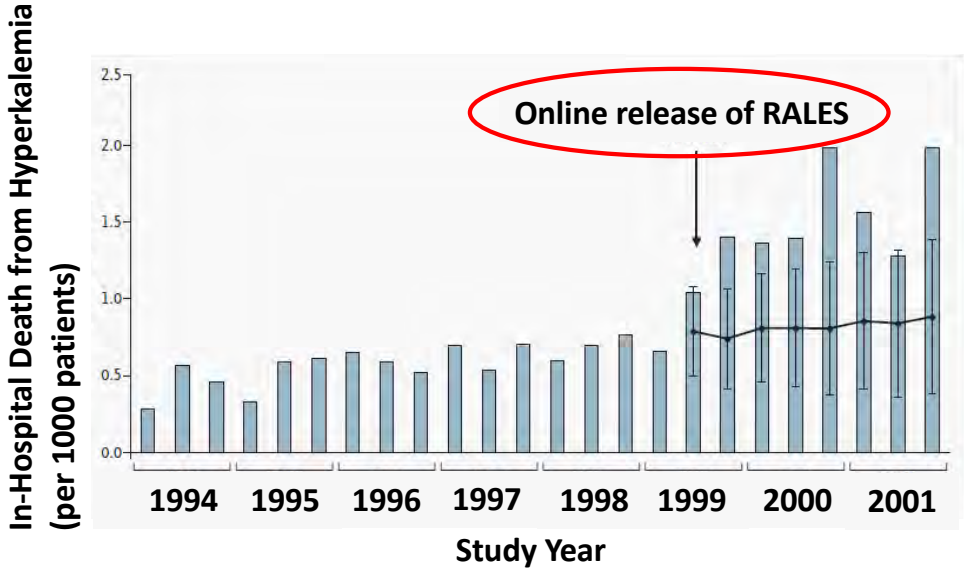
Heart Failure and Chronic Kidney Disease:

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

Juurlink DN et al. *N Engl J Med 2004.351:543-51.*

Summary:

MRAs in Heart Failure and Chronic Kidney Disease

- 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^2 due to the concern for hyperkalemia

- KDIGO guidelines recommend starting at a lower dose in patients with GFR< 45 ml/min/1.73 m^2

- KDIGO guidelines also recommend against routine discontinuation of these agents when GFR< 30 ml/min/1.73^2 as they remain nephroprotective

- MRAs have unclear benefit in those with HFrEF and CKD but are associated with higher rates of hyperkalemia

Yancy CW et al. *Circulation* 2013.128:e240-e327. Yancy CW et al. *Circulation* 2016.134:e282-e293. KDIGO 2012 clinical practice guideline. *Kidney Int* 2013.3(1):1-150.

Potassium Binders for Patients with Heart Failure and Chronic Kidney Disease

Potassium Binders for Hyperkalemia

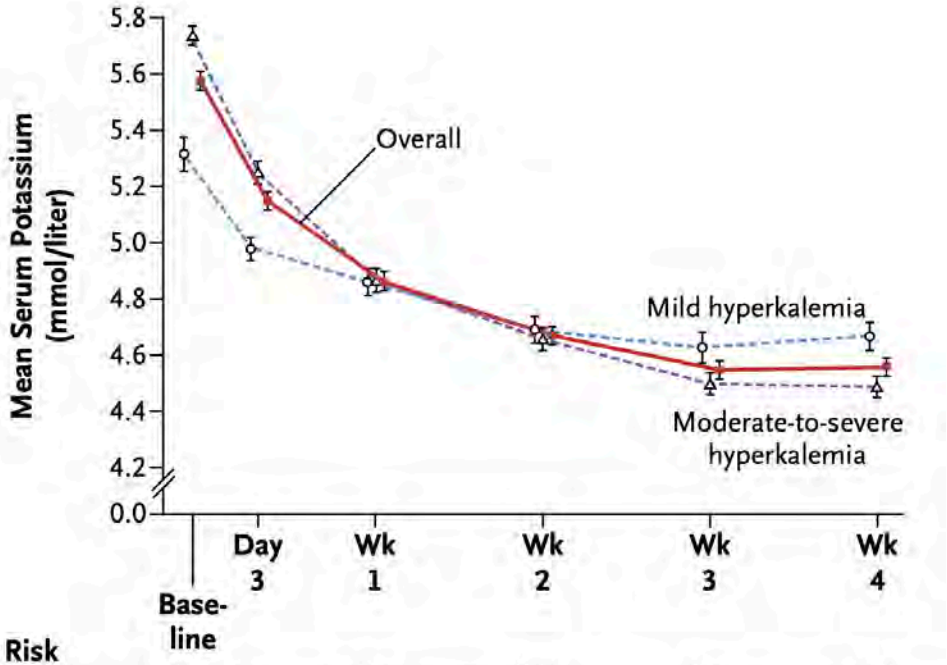
Drug	MOA	Onset of Action	Dose	Adverse Events	Administration Considerations
Patiromer Calcium	Non-absorbed, cation exchange polymer; calcium-sorbitol counterion; binds potassium in the lumen of GI tract increasing fecal potassium excretion	7 hours	8.4 g/day. Up-titrate at 1-week intervals to a max of 25.2 g/day	Constipation, diarrhea, nausea, hypomagnesemia	Administer other oral medications at least 3 hours before or after
Sodium Zirconium Cyclosilicate (SZC)	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 2 hours before or after
Sodium Polystyrene Sulfonate (SPS)	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; bowel necrosis	Administer other oral medications at least 3 hours before or after

Veltassa [package insert]. 2018 Lokelma [package insert]. 2020 Kayexalate [package insert]. 2018

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

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

Serum Potassium Levels over Time during Initial Treatment Phase



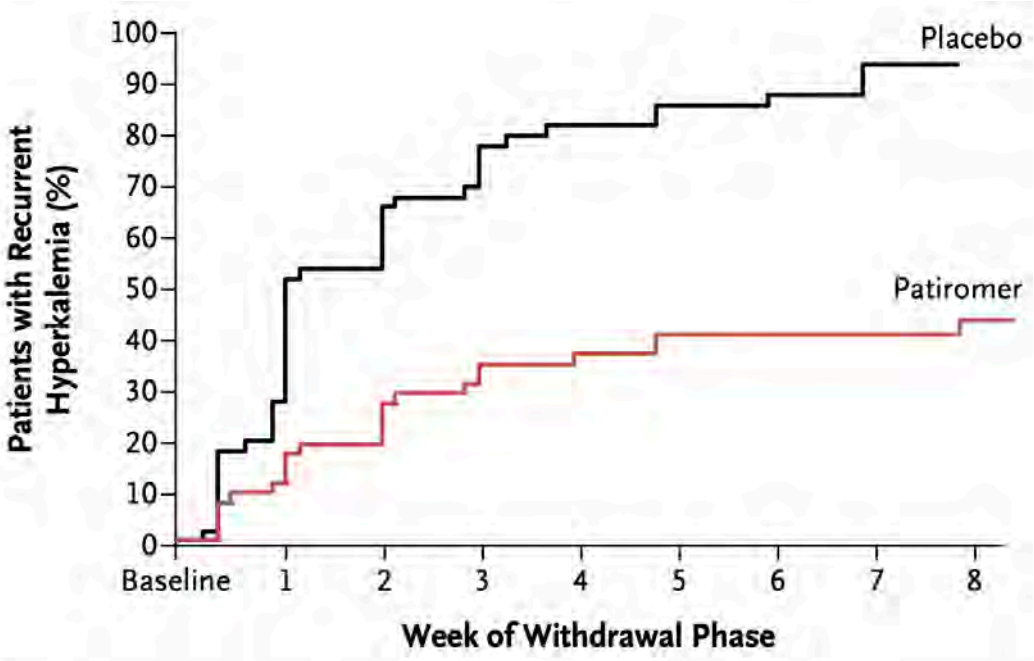
No. at Risk						
Overall	243	217	237	228	221	219
Mild hyperkalemia	92	80	90	87	85	85
Moderate-to-severe hyperkalemia	151	137	147	141	136	134

RAASi: renin-angiotensin-aldosterone system inhibitors

Weir MR et al. *N Engl J Med* 2015.372:211-21.

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

Time to First Serum Potassium Level ≥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

Weir MR et al. *N Engl J Med* 2015.372:211-21.

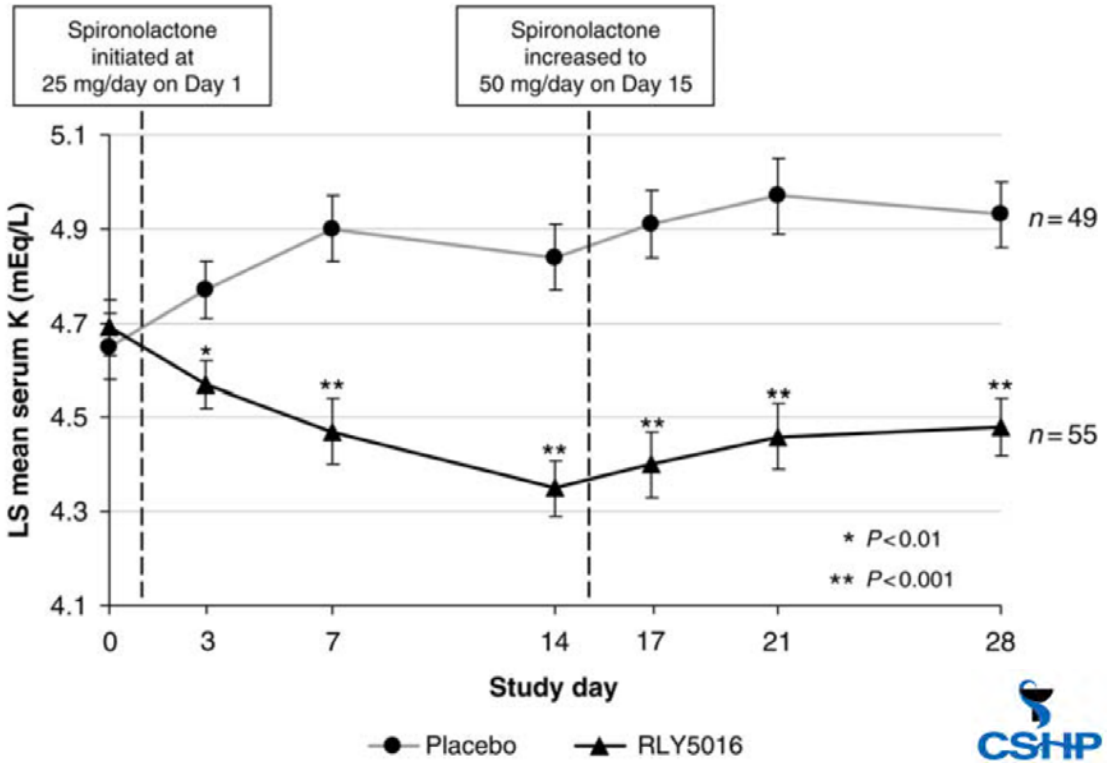
Efficacy and Safety of Patiromer in Patients with Chronic HF

PEARL-HF Trial (2011)

- Double-blind, randomized trial of 104 patients
- Chronic HF with indication for spironolactone
- GFR <60 ml/min/1.73 m^2 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

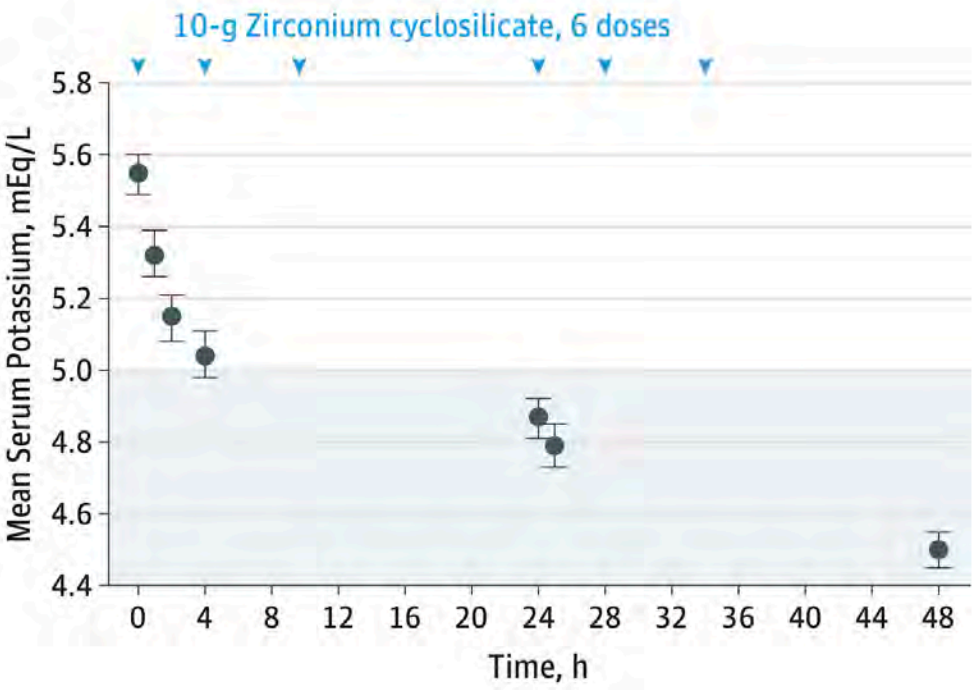


Pitt B et al. *Eur Heart J* 2011.21:820-828.

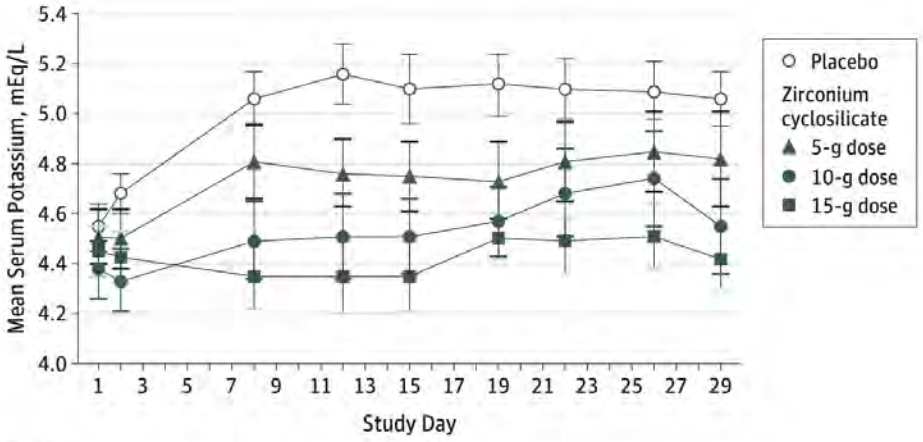
Effect of SZC on Potassium Lowering for 28 Days Among Outpatients with Hyperkalemia: HARMONIZE Trial (2014)

- Double-blind, randomized trial of 258 patients
- Ambulatory patients with a serum potassium ≥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

Kosiborod M et al. *JAMA* 2014.312(21):2223-2233.

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)
Edema – No. (%)	0	2 (2.4)	1 (2.2)	3 (5.9)	8 (14.3)
Hypokalemia – No. (%)	0	0	0	5 (9.8)	6 (10.7)

Dose-dependent increase in edema and hypokalemia found with SZC

DM: diabetes mellitus

Kosiborod M et al. *JAMA* 2014.312(21):2223-2233.

Potassium Binders for Hyperkalemia

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

GI: gastrointestinal

Kovesdy CP. *Am J Med* 2015.128(12):1281-7. Harel Z et al. *Am J Med* 2013.126:264.e9-264.e24. Gerstman BB et al. *Am J Kidney Dis* 1992.20(2):159-161.

Potassium Binders for Hyperkalemia

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

Veltassa [package insert]. 2018

Lokelma [package insert]. 2020

Kayexalate [package insert]. 2018

Ongoing clinical trials:

Potassium Binders for Hyperkalemia

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

- 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

- 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

RCT: randomized control trials; GDMT: guideline directed medical therapy

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 which is attributed to continued RAAS therapy

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 which is attributed to continued RAAS therapy

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 which is attributed to continued RAAS therapy

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 which is attributed to continued RAAS therapy

QUESTIONS?

LEW.MICHELLE@SCRIPPSHEALTH.ORG

Additional Resources

1) House AA et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International* 2019.95:13.4-1317.
2) Bosselmann H et al. Incidence and predictors of end-stage renal disease in outpatients with systolic heart failure. *Circ Heart Fail* 2013.6:1124-1131.
3) Rangaswami J et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies. A scientific statement from the American Heart Association. *Circulation* 2019.139:e870-e878.
4) Testani JM et al. Worsening renal function defined as an absolute increase in serum creatinine is a biased metric for the study of cardio-renal interactions. *Cardiology* 2010.116:206-212.
5) Fudim M et al. Worsening renal function during decongestion among patients hospitalized for heart failure: Findings from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial. *Am Heart J* 2018.204:163-73.
6) McCallum W et al. Acute Kidney Function Declines in the Context of Decongestion in Acute Decompensated Heart Failure. *J Am Coll Cardiol HF* 2020.8:537-47.
7) Nayor M et al. The association of chronic kidney disease and microalbuminuria with heart failure with preserved vs. reduced ejection fraction. *Eur J Heart Fail* 2017.19:615-623.
8) Berthe C et al. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomized intervention trial in congestive heart failure. *Lancet* 1999.353:2001-07.
9) Brunhuber KW et al. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. *Lancet* 1999.353:9-13.
10) Packer M et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002.106:2194-2199.
11) - Flather MD et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure. *Eur Heart J* 2005.26:215-225.
12) Ghali JK et al. The influence of renal function on clinical outcome and response to β-blockade in systolic heart failure: insights from metoprolol CR/XL randomized intervention trial in chronic HF (MERIT-HF). *J Cardiac Fail* 2009.15:310-318.
13) Castagno D et al. Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial. *Eur J Heart Fail* 2010.12:607-616.
14) Wali RK et al. Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: a meta-analysis of randomized trials. *Circ Heart Fail* 2011.4:18-26.
15) Cice G et al. Dilated cardiomyopathy in dialysis patients – beneficial effects of carvedilol: a double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2001.37:407-11.
16) Cice G et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003.41:1438-44.
17) Weir MA et al. Beta-blocker dialyzability and mortality in older patients receiving hemodialysis. *J Am Soc Nephrol* 2015.26:987-996.
18) Tieu A et al. Beta-blocker dialyzability in maintenance hemodialysis patients: A randomized clinical trial. *Clin J Am Soc Nephrol* 2018.13:604-611.
19) Badve SV et al. Effects of beta-adrenergic antagonists in patients with chronic kidney disease. *J Am Coll Cardiol* 2011.58:1152-61.
20) Yancy CW et al. 2013 ACCF/AHA guidelines for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013.128:3240-e327.
21) Yancy CW et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guidelines for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2016.134:e282-93.
22) Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013.3(1):1-150.
23) CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987.316:1429-1435.
24) SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991.325:293-302.
25) SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992.327:685-91.
26) Pfeffer MA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infraction. *N Engl J Med* 1992.327:669-77.
27) Cohn JN et al. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001.345:1667-75.
28) Granger CB et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003.362:772-776.
29) McMurray JV et al. Angiotensin-neprilysis inhibition versus enalapril in heart failure. *N Engl J Med* 2014.371:993-1004.
30) Edner M et al. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. *Eur Heart J* 2018.36:2318-2326.
31) Schmidt M et al. Serum creatinine elevation after renin-angiotensin system blockade and long-term cardiorenal risks: cohort study. *BMJ* 2017.356:j791.
32) Damman K et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *J Am Coll Cardiol HF* 2018.6:489-98.
33) Solomon SD et al. Combined neprilysis and renin-angiotensin system inhibition in heart failure with reduced ejection fraction: a meta-analysis. *Eur J Heart Fail* 2016.18:1238-1243.
34) Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999.341:709-17.
35) Pitt B et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003.348:1309-21.
36) Zannad F et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011.364:11-21.32.
37) Lu R et al. Effects of mineralocorticoid receptor antagonists in left ventricular mass in chronic kidney disease patients: a systematic review and meta-analysis. *Int Urol Nephrol* 2016.48:1499-509.
38) Inampudi C et al. Spironolactone use and higher hospital readmission for Medicare beneficiaries with heart failure, left ventricular ejection fraction <45%, and estimated glomerular filtration rate <45 ml/min/1.73m(2). *Am J Cardiol* 2014.114:79-82.
39) Cooper LB et al. Use of mineralocorticoid receptor antagonists in patients with heart failure and comorbid diabetes mellitus or chronic kidney disease. *J Am Heart Assoc* 2017.6(2):e006540.
40) Juurlink DN et al. Rates of hyperkalemia after publication of the randomized Aldactone evaluation study. *N Engl J Med* 2004.351:543-51.
41) Veltassa (patiromer) [package insert]. Redwood City, CA: Relypsa, Inc.; 2018.
42) Lokelma (sodium zirconium cyclosilicate) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2020.
43) Kayexalate (sodium polystyrene sulfonate) [package insert]. Laval, Quebec: Sanofi-aventis Canada Inc.; 2018.
44) Weir MR et al. Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors. *N Engl J Med* 2015.372:211-21.
45) Pitt B et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011.21:820-828.
46) Kosiborod M et al. Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients with Hyperkalemia: The HARMONIZE Randomized Clinical Trial. *JAMA* 2014.312(21):2223-2233.
47) Kovesdy CP. Management of Hyperkalemia: an update for the internist. *Am J Med* 2015.128(12):1281-7.
48) Harel Z et al. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. *Am J Med* 2013.126:264.e9-264.e24.
49) Gerstman BB et al. Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *Am J Kidney Dis* 1992.20(2):159-161.

CSHP
CALIFORNIA SOCIETY OF HEALTH-SYSTEM PHARMACISTS

SESSION CODE:

PHARMACY VISION 2020

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

CSHP
CALIFORNIA SOCIETY OF HEALTH-SYSTEM PHARMACISTS