Changing the outlook for a chronic HF patient:
optimizing RAASi treatment through long-term potassium control

Understanding the Risk of Hyperkalaemia in Heart Failure

Piotr Ponikowski, MD, PhD, FESC
Centre for Heart Disease, University Hospital,
Medical University, Wroclaw, Poland

Disclosures

Consultancy fees and speaker’s honoraria from:

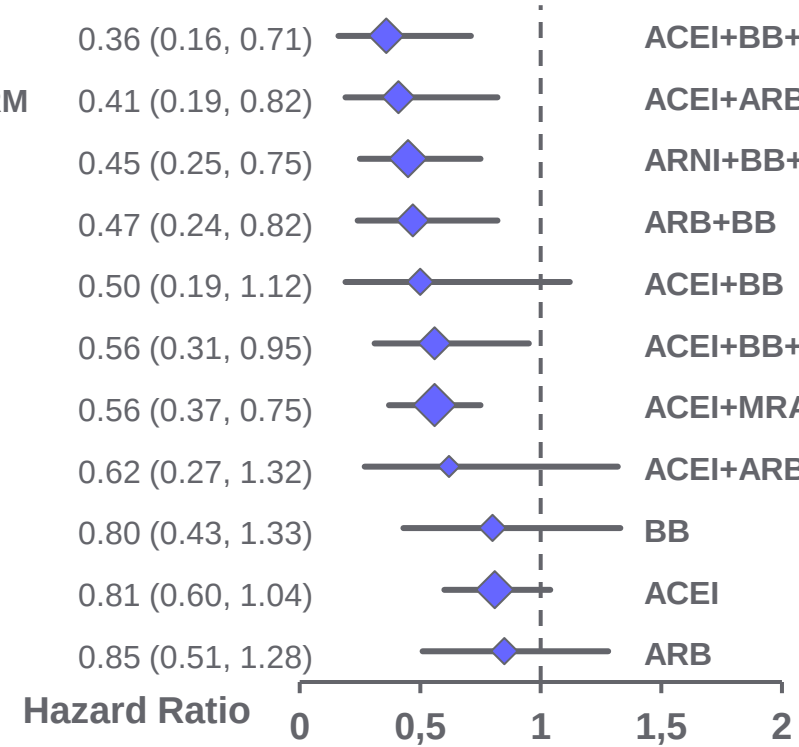
Vifor Pharma, Amgen, Servier, Novartis, Berlin Chemie, Bayer, Pfizer, Cibiem, Coridea, Impulse Dynamics, Renal Guard Solutions, Boehringer Ingelheim, AstraZeneca, BMS

Research grant: Vifor Pharma

Increasing or Incremental Combinations of Recommended Therapies are Consistent with Improved Outcomes: A Network Meta-Analysis of RCTs in HFrEF

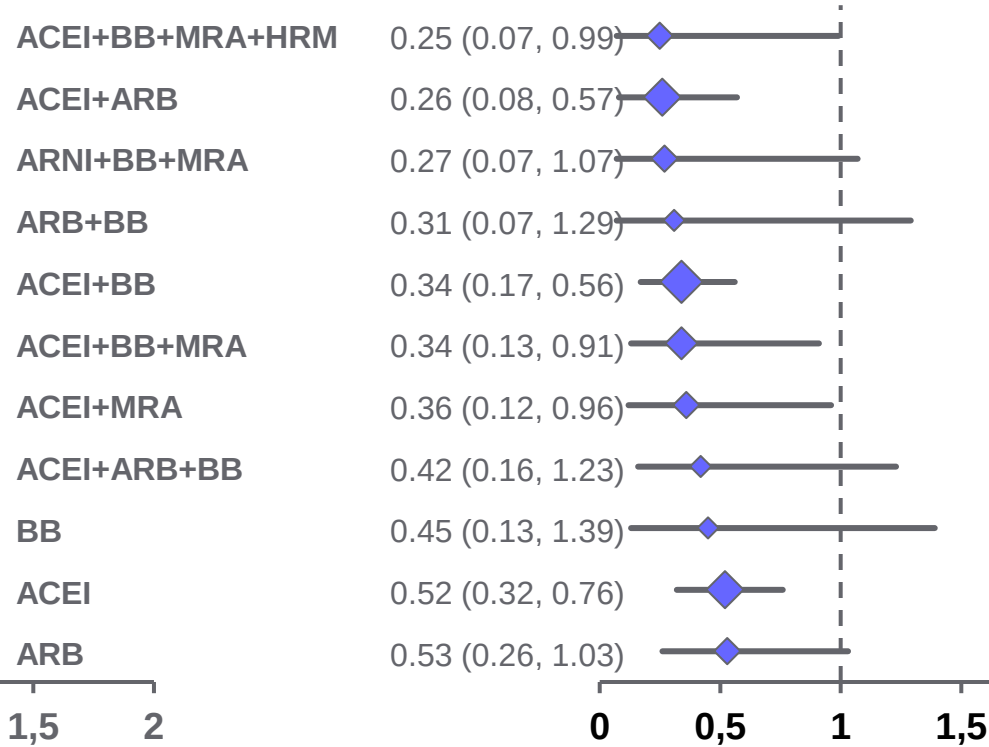
Cardiovascular mortality [1]

Therapy vs Placebo	HR (95% CI)
ARNI+BB+MRA	0.36 (0.16, 0.71)
ACEI+BB+MRA+HRM	0.41 (0.19, 0.82)
ACEI+BB+MRA	0.45 (0.25, 0.75)
ACEI+ARB+BB	0.47 (0.24, 0.82)
ARB+BB	0.50 (0.19, 1.12)
ACEI+MRA	0.56 (0.31, 0.95)
ACEI+BB	0.56 (0.37, 0.75)
BB	0.62 (0.27, 1.32)
ACEI+ARB	0.80 (0.43, 1.33)
ACEI	0.81 (0.60, 1.04)
ARB	0.85 (0.51, 1.28)



Heart failure hospitalizations [1]

Therapy vs Placebo	HR (95% CI)
ACEI+BB+MRA+HRM	0.25 (0.07, 0.99)
ACEI+ARB	0.26 (0.08, 0.57)
ARNI+BB+MRA	0.27 (0.07, 1.07)
ARB+BB	0.31 (0.07, 1.29)
ACEI+BB	0.34 (0.17, 0.56)
ACEI+BB+MRA	0.34 (0.13, 0.91)
ACEI+MRA	0.36 (0.12, 0.96)
ACEI+ARB+BB	0.42 (0.16, 1.23)
BB	0.45 (0.13, 1.39)
ACEI	0.52 (0.32, 0.76)
ARB	0.53 (0.26, 1.03)

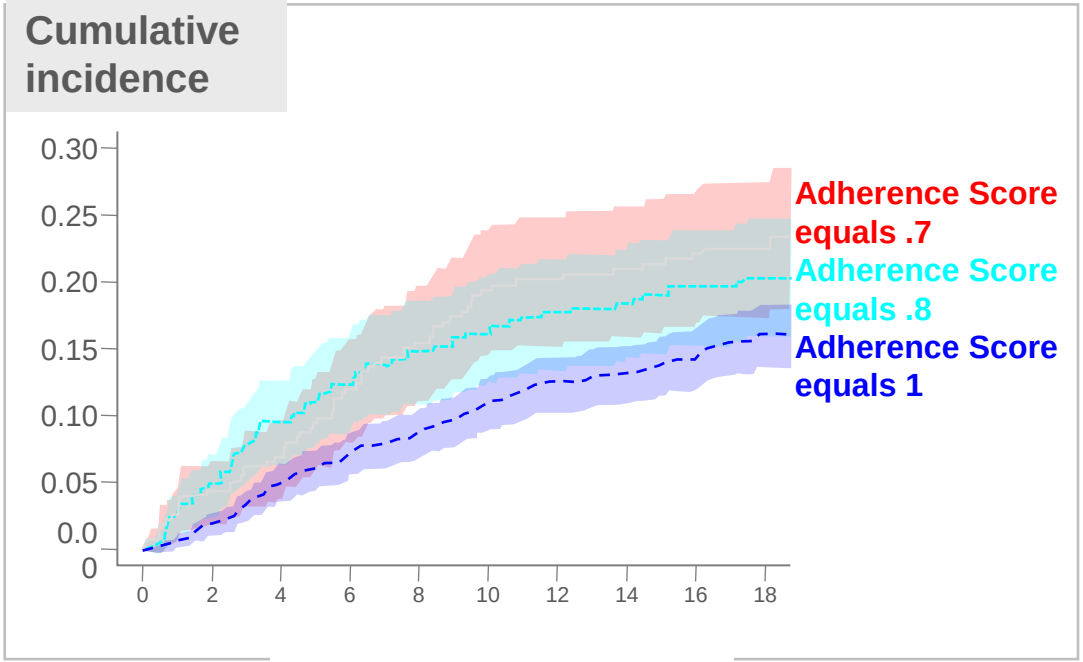


Komajda M et al. *Eur J Heart Fail*. 2018;20(9):1315-1322.

Better Adherence to Recommended Therapies is Associated with Improved Outcomes, in the Real-World Setting

6118 patients with HFrEF with 18-month follow-up from the QUALIFY international registry [1]

The association between physicians' adherence to guideline-recommended treatment expressed as a score (0-1) & hospitalization attributable to HF or CV death[1]



Adherence Score: based on prescription and dosages of main HF medications [1]

0 for non use (if indicated)

1 for each use in dosages ≥50% TD* [1]

0.5 for each use of in dosages <50% TD* : [1]

- ACE inhibitors (or ARB if ACE inhibitors not tolerated)
- Beta-blockers
- MRA (if NYHA class II-IV)
- HR modulator (if NYHA class II-IV + LVEF ≤35% + Sinus rhythm + HR ≥70 bpm + available in the country)

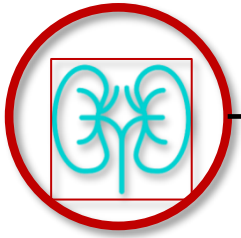
* 100%TD for MRA

Komajda M et al. Eur J Heart Fail. 2019:21(7):921-929

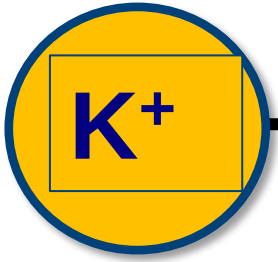
What Are the Limitations to RAAS pathway inhibition?

Hypotension[1]
(real or perceived)

Rise in serum
creatinine/eGFR↓[1]



Rise in K^+
HK diagnosis[1]



RAASi

Initial reaction

ACEi / ARB / ARNi limitations

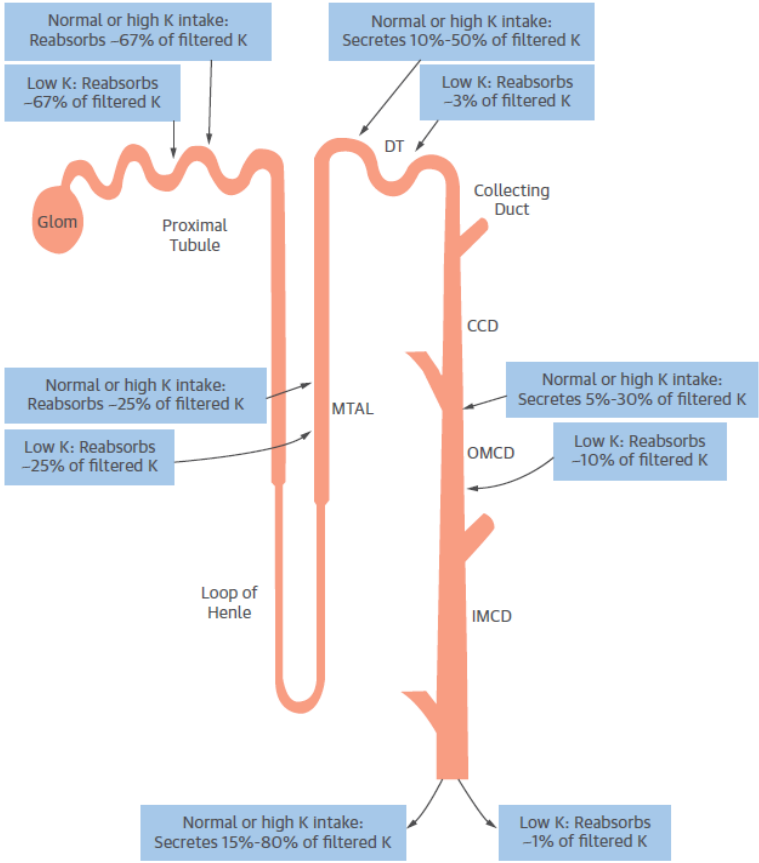
On admission for ADHF [1]

Limitations in existing MRA or initiation of MRA [1]

1. Clark AL, et al. Heart 2019;105:904–910.

The world of potassium

- The most abundant cation in the body; **98% intracellular** (~140 mmol/L), 2% extracellular (3.8-5.0 mmol/L)
- Complex regulation of **intracellular /extracellular shifts with active uptake and passive leak**
- **Long-term K^+ homeostasis -** mainly **renal excretion** (influenced by aldosterone), 5-10% in the colon;
- Most of **K^+** freely filtered by the glomerulus, absorbed in the proximal tubule and loop of Henle; **10% reaches the distal tubule - RAAS effect**
- **Short-term K^+ homeostasis** - **skeletal muscle** (total skeletal muscle pool 225 x extracellular **K^+** content)
- Definition of **hyperkalaemia:**
  - **>5.0 – 5.5 mmol/L – mild**
  - **>5.5 – 6.0 mmol/L – moderate**
  - **> 6.0 mmol/L – severe**



Sarwar CMS et al. *JACC 2016;68:1575-89*
Nyirenda MJ et al. *BMJ.* 2009;339:bmj.b41114

Causes of Hyperkalaemia

EXCESS K^+ INTAKE

- **Potassium supplement**, diet
- Enteral nutrition (eg, formulas with high electrolyte content)

K^+ REDISTRIBUTION

- Acidosis
- Hyperglycaemia
- **Insulin deficiency or resistance**
- **Certain drugs (eg, digoxin)**
- Strenuous exercise
- Haemolysis
- Tissue damage (eg, rhabdomyolysis, burns, or trauma)
- Tumour lysis syndrome

REDUCED K^+ EXCRETION

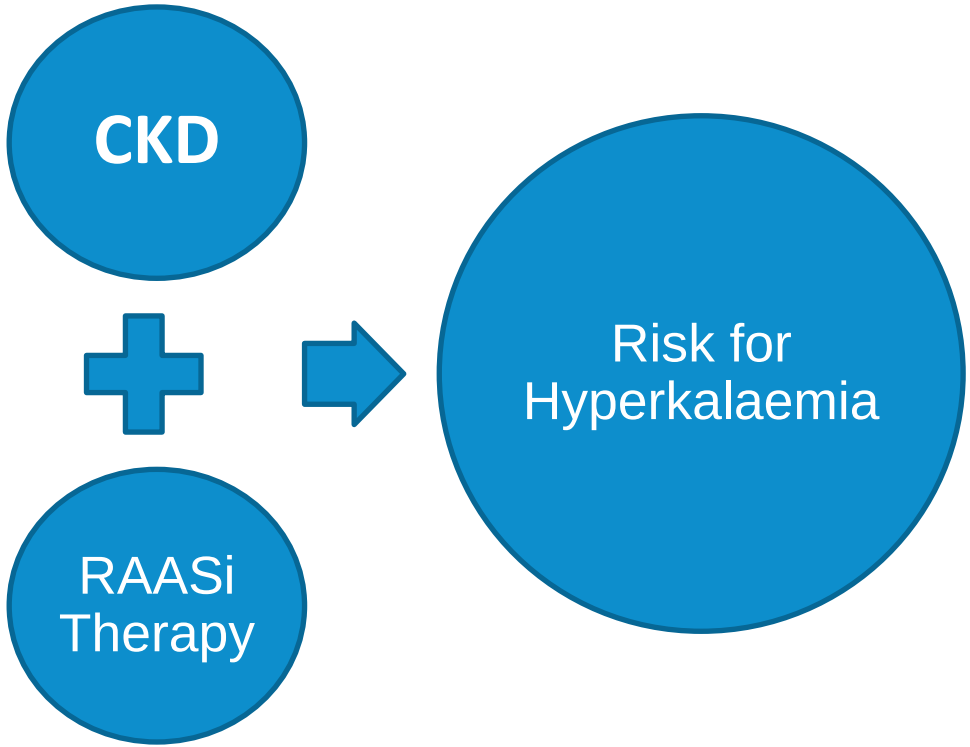
- **HF**
- **Impaired renal function**
- **T2DM**
- Obstructive uropathy
- Diseases with low levels of, or lack of response to, aldosterone
- **RAAS inhibition**

Lehnhardt A, et al. Pediatr Nephrol. 2011;26:377-384; Nyirenda MJ, et al. BMJ. 2009;339:b4114

Cardiorenal Patients on RAAS Inhibitor Therapy Are at Increased Risk of Hyperkalaemia

- The majority of patients at risk for HK have some level of underlying kidney disease[a-c]
- HK risk increases as kidney function continues to decline

- Treatment with RAAS inhibitors increases HK risk[a-c]
- Other agents linked to elevated K include NSAIDs, diuretics, beta-blockers, heparin, and digoxin



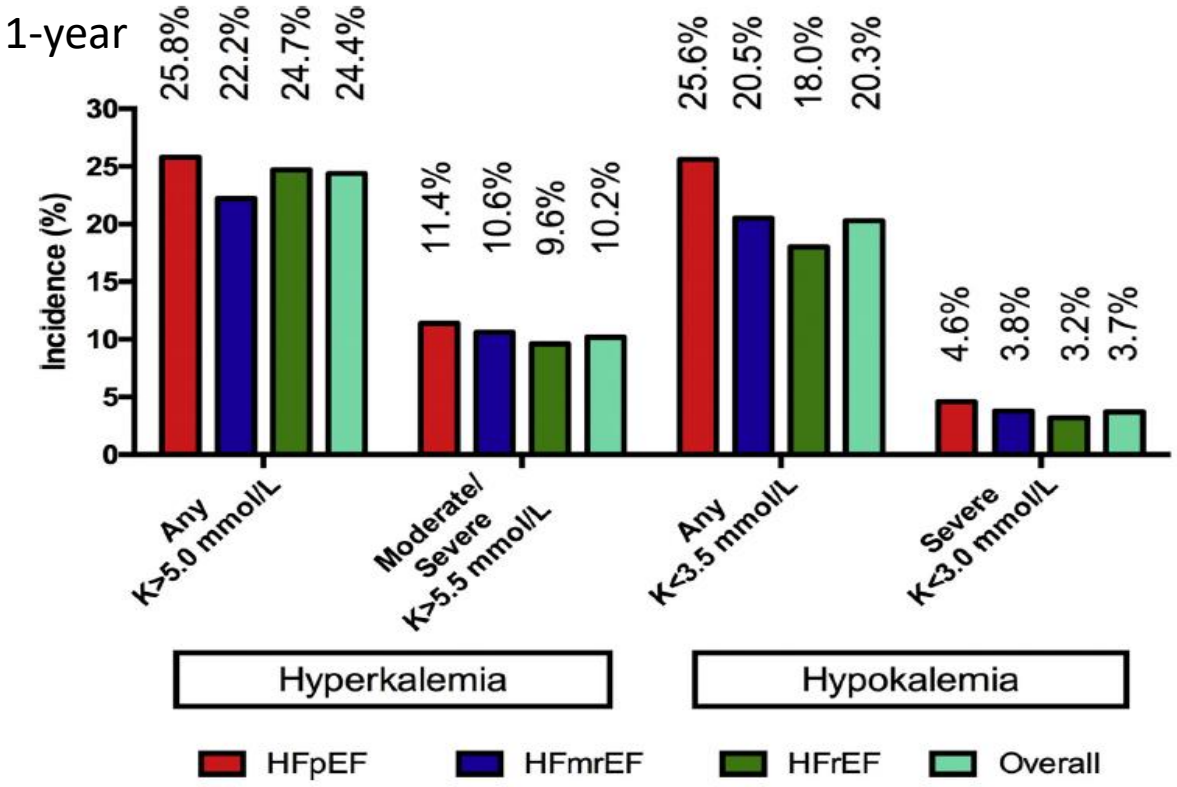
a. Dunn JD, et al. Am J Manag Care. 2015;21:S307-S315;
b. b. Einhorn LM, et al. Arch Intern Med. 2009;169:1156-1162; c. Kovesdy CP. Am J Med. 2015;128:1281-1287.

Hyperkalaemia is common with RAASi

Trial	Drug studied	Population	Outcome	Hyperkalaemia rates
RENAAL[1,2]	Losartan vs placebo	CKD, DM (Diabetic Nephropathy)	**16% risk reduction**	**38% >5.0 mmol/L;** **11% >5.5 mmol/L**
IDNT[3,4]	Irbesartan vs amlodipine vs placebo	CKD, DM (Diabetic Nephropathy)	**20% risk reduction**	**18.6% >6.0 mmol/L**
RALES[5,6]	Spironolactone vs placebo	Moderate–severe HF	**30% risk reduction**	**2% in RALES >6.0 mmol/L;** **13% >5.5 mmol/L** **(25 mg in RALES pilot)**
EPHESUS[7,8]	Eplerenone vs placebo	HF post-MI	**15% risk reduction**	**16% >5.5 mmol/L** **5.5% >6.0 mmol/L**
EMPHASIS-HF[9,10]	Eplerenone vs placebo	Mild HF	**37% risk reduction**	**12% >5.5 mmol/L** **2.5% >6.0 mmol/L**
PARADIGM-HF	Sacubitril/valsartan vs placebo	Moderate HF	**20% risk reduction**	**16 % vs 17.3% > 5.5 mmol/L**

1. Brenner BM et al. *N Engl J Med.* 2001;345:861-9; 2. Miao Y et al. *Diabetologia.* 2011;54:44-50. 3. Lewis EJ, et al. *N Engl J Med.* 2001;345:851-60;
4. Avapro Highlights of Prescribing Information. Bridgewater, NJ: Sanofi-Aventis; 2014; 5. Pitt B, et al. *N Engl J Med.* 1999;341:709-17;
6. The RALES Investigators. *Am J Cardiol*. 1996 15;78:902-7; 7. Pitt B et al. *N Engl J Med*. 2003;348:1309-21; 8. Pitt B et al. *Circulation*. 2008 14;118:1643-50;
9. Zannad F et al. *N Engl J Med.* 2011;364:11-21; 10. Eschalier R *et al. J Am Coll Cardiol.* 2013 22;62:1585-93

Incidence, Predictors, and Outcome Associations of Dyskalaemia in HF With Preserved, Mid-Range, and Reduced Ejection Fraction



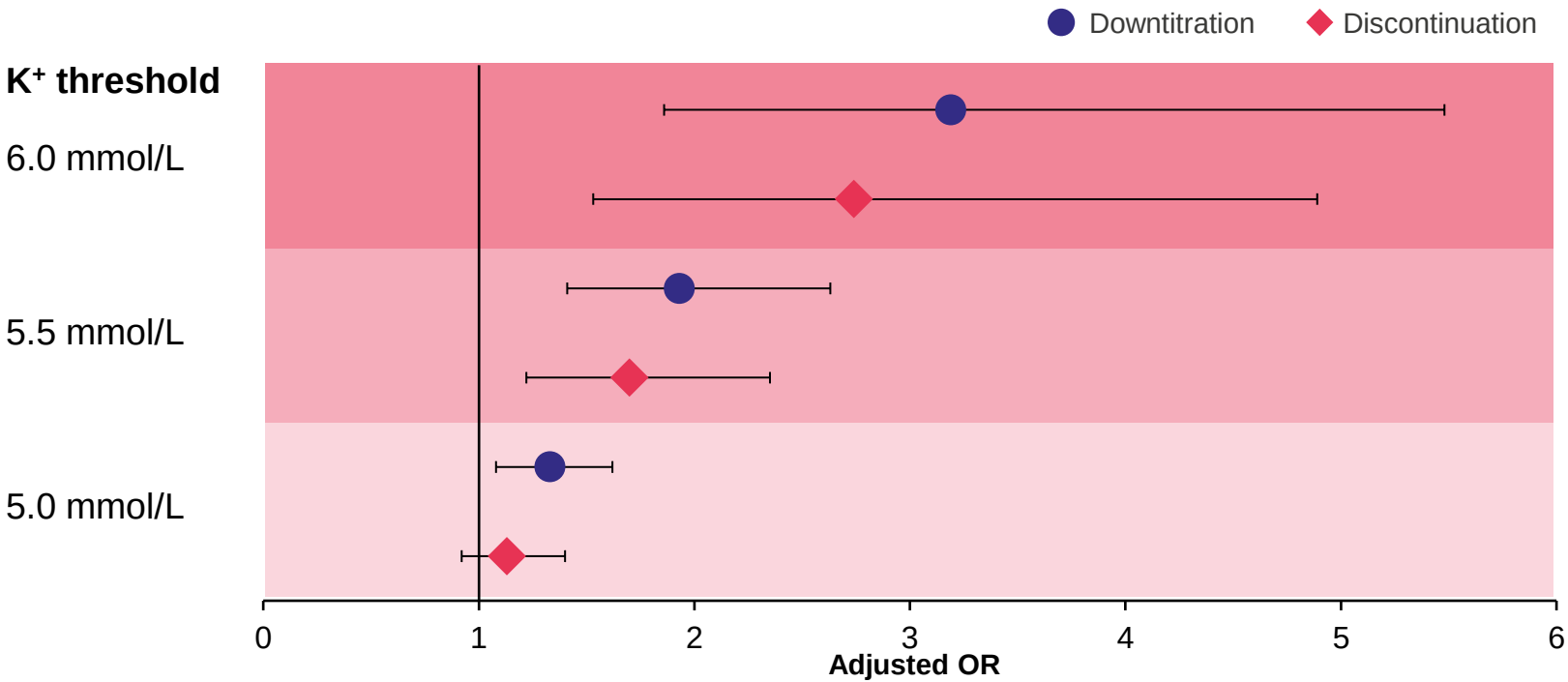
Risk markers for HK:

- male sex
- baseline K 4.5-5.0 mmol/L
- lower eGFR
- Hb <120 g/dL
- DM history
- COPD
- ↑NYHA class
- use of MRA
- non-use of BB

Savarese G et al. JACC Heart Fail. 2019;7:65-76

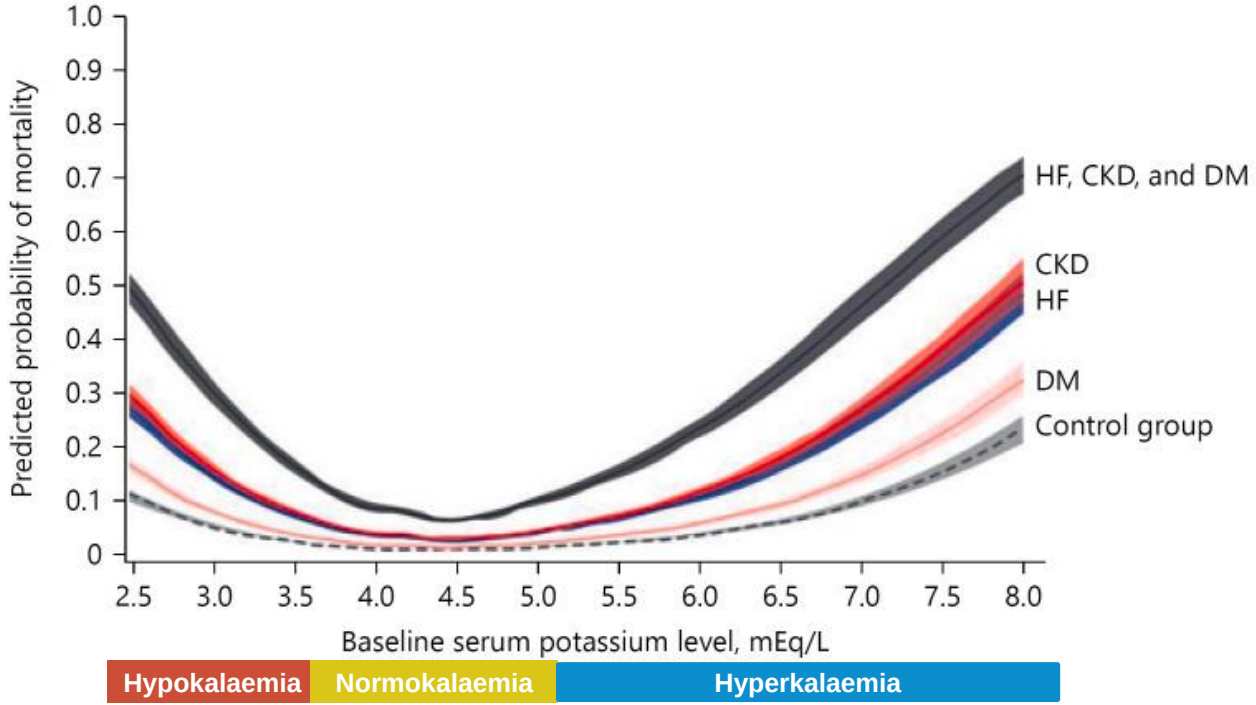
Elevated serum K^+ is associated with an increased risk of RAASi downtitration or discontinuation in patients with HF

Adjusted odds ratios (95% CIs) for dose modification of RAASi stratified by serum potassium threshold for HF patients



Linde C, et al. *Am Heart Assoc* 2019;8:e012655

Elevated Serum Potassium Is Associated With Increased Mortality in At-Risk Populations

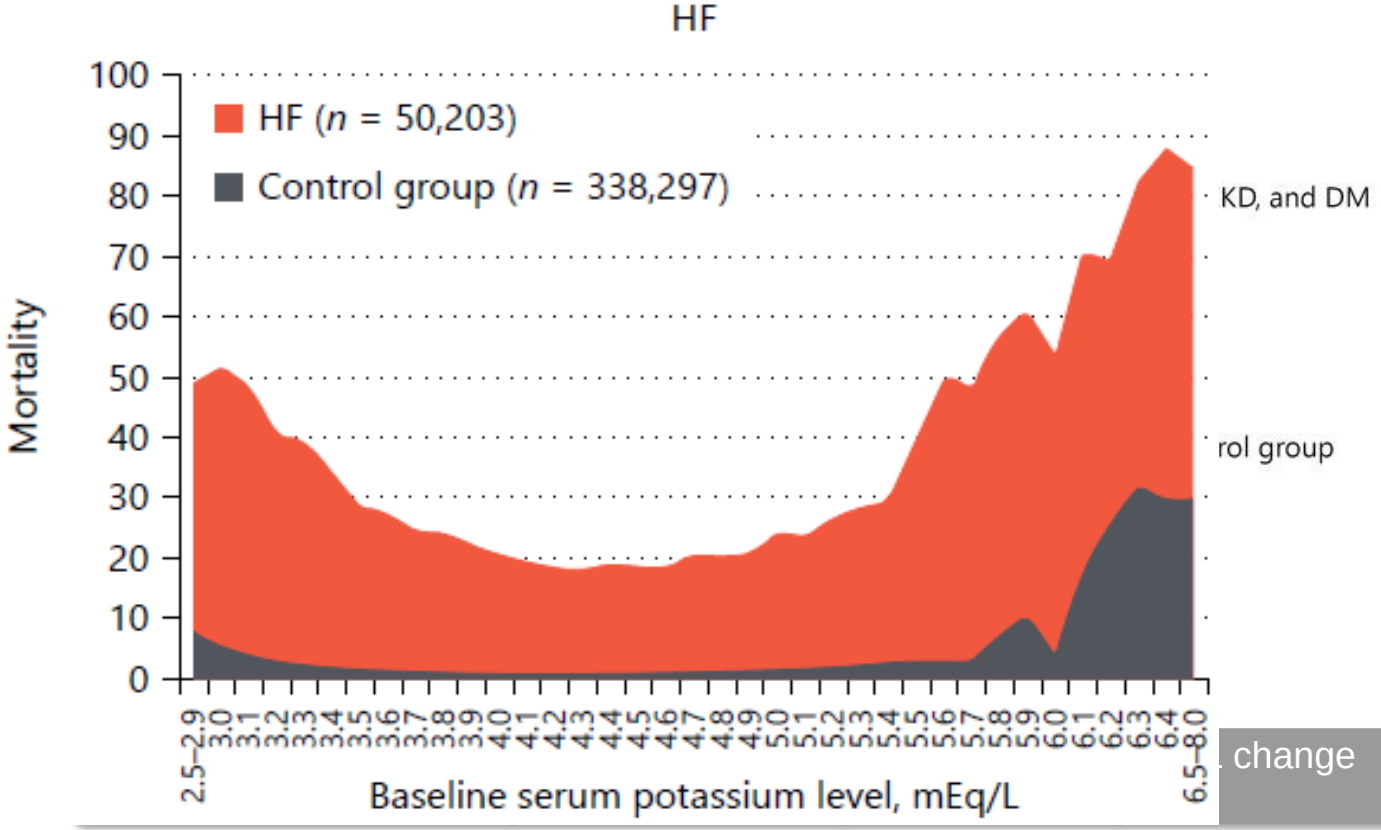


All-cause mortality was significantly elevated for every 0.1 mEq/L change in serum potassium <4.0 mEq/L and ≥5.0 mEq/L

Adjusted Mortality (95% CI*) by Serum Potassium Level

Collins AJ, et al. *Am J Nephrol*. 2017;46:213-221.

Elevated Serum Potassium Is Associated With Increased Mortality in At-Risk Populations

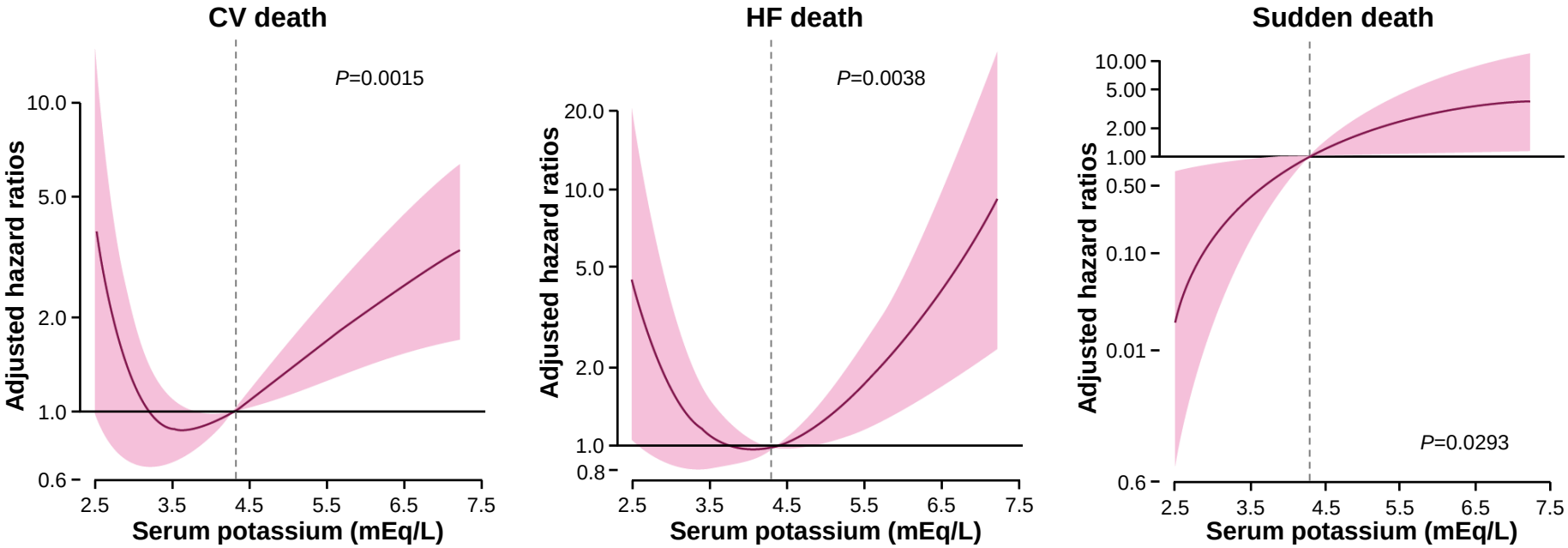


Adjusted Mortality (95% CI*) by Serum Potassium Level

Collins AJ, et al. *Am J Nephrol*. 2017;46:213-221.

HK is associated with a higher risk of CV, HF and sudden death in patients with HF

Retrospective analysis in patients discharged from a previous acute HF admission (N=2164)



Risk-gradient trajectory centred at median potassium value of 4.3 mEq/L

Prospective and consecutive cohort of 2164 patients discharged from acute HF admission between 1st January 2008 and 1st July 2016, with a total of 16,116 potassium observations. Shaded areas represent the 95% CI and are centred at the median of potassium in the sample (4.3 mEq/L)

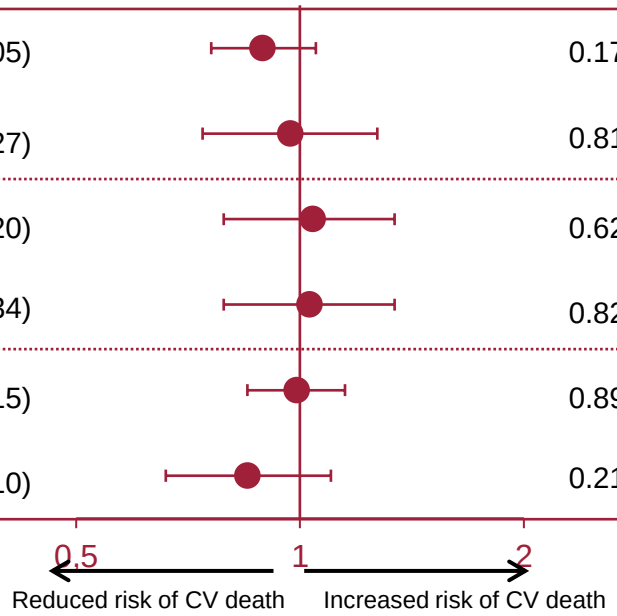
CI, confidence interval; CV, cardiovascular; HF, heart failure; HK, hyperkalaemia

Núñez J, et al. *Circulation* 2018;137:1320–1330

Unravelling the interplay between hyperkalaemia, RAASi use and clinical outcomes.

Risk of CV death due to HK was no longer statistically significant after controlling for RAASi therapy discontinuation; data from the ESC-HFA-EORP Heart Failure Long-term Registry (N=~9000)

Mediator	Potassium at baseline (mmol/L)	Risk of CV death HR (95% CI)	*p*-value
ACEi discontinuation	5-5.5	0.89 (0.76; 1.05)	0.171
	>5	0.97 (0.74, 1.27)	0.814
ARB discontinuation	5-5.5	1.04 (0.90, 1.20)	0.623
	>5	1.03 (0.79, 1.34)	0.827
MRA discontinuation	5-5.5	0.99 (0.85; 1.15)	0.893
	>5	0.85 (0.66; 1.10)	0.213



HK a risk marker for RAASi discontinuation rather than a risk factor for worse outcomes ?

Rossignol P, et al. *Eur J Heart Fail* 2020 [Epub ahead of print]

Managing Hyperkalaemia: recommendations

- **Be wary of clinical inertia**
  - It is important to use maximal doses of RAAS inhibitors to improve patient outcomes
  - Escalate doses when appropriate
- **Regular screening of hyperkalaemia in patients taking RAAS inhibitors is important**
- **Take medical history, including current/past medications (prescription and over-the-counter) to assess increases in the risk for hyperkalaemia**
- **Maintaining use of optimal doses of RAAS inhibitors maximises outcomes for patients**
- **HFA expert consensus meeting report[1]: “Patiromer and ZS-9 may be considered:**
  - in selected patients with HF +/- CKD in order to enable up-titration of MRA while avoiding hyperkalaemia.
  - in patients with HF +/- CKD to manage hyperkalaemia. In selected patients these therapies may enable use of MRAs and other RAASi's in more patients and at higher doses, but it is not known whether this will improve patient outcomes.”

[1]Seferovic PM, et al. Eur Heart J 2019; doi 10.1002/ejhf.1531