

Introduction: Guidelines, RAASi and hyperkalaemia: the clinical dilemmas in heart failure

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**Clinical dilemmas in heart failure:
Weighing the balance of RAASi and hyperkalaemia**



Introduction: Guidelines, RAASi and hyperkalaemia: the clinical dilemmas in heart failure

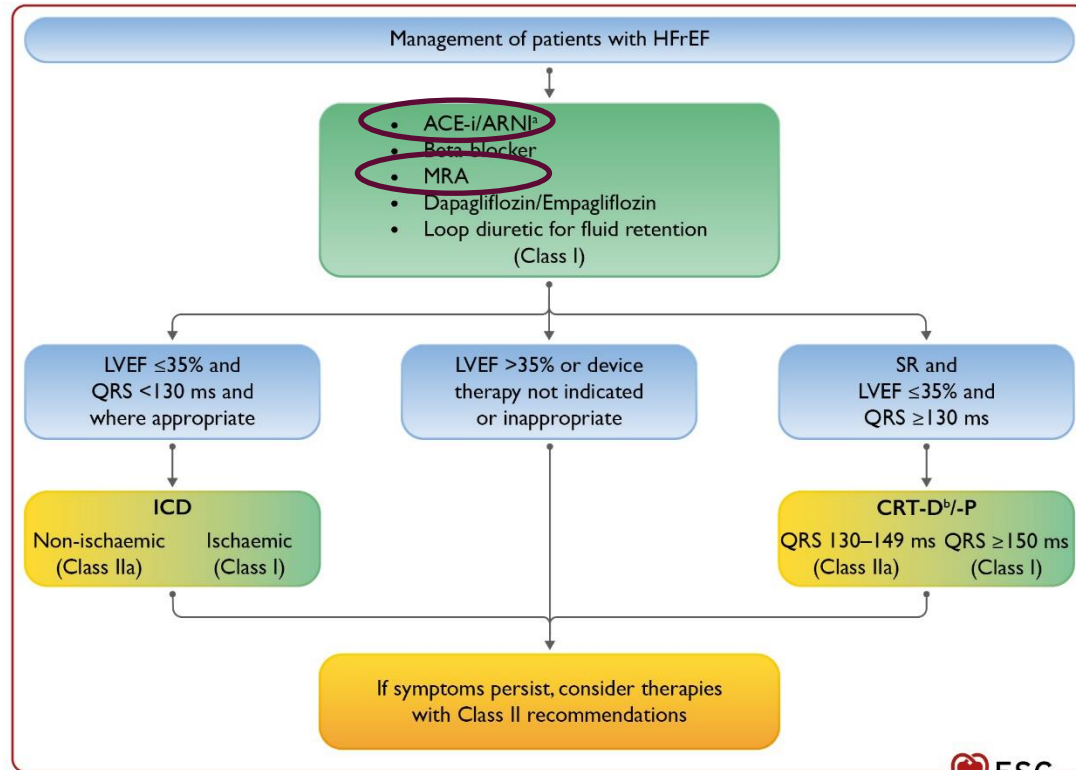
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Declarations: Lecture and/or advisory fees over the last three years from:

Astra Zeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Gore, Impulse Dynamics, Respicardia, Viatrix

RAASi therapy is recommended by clinical guidelines for the management of HFrEF

Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction

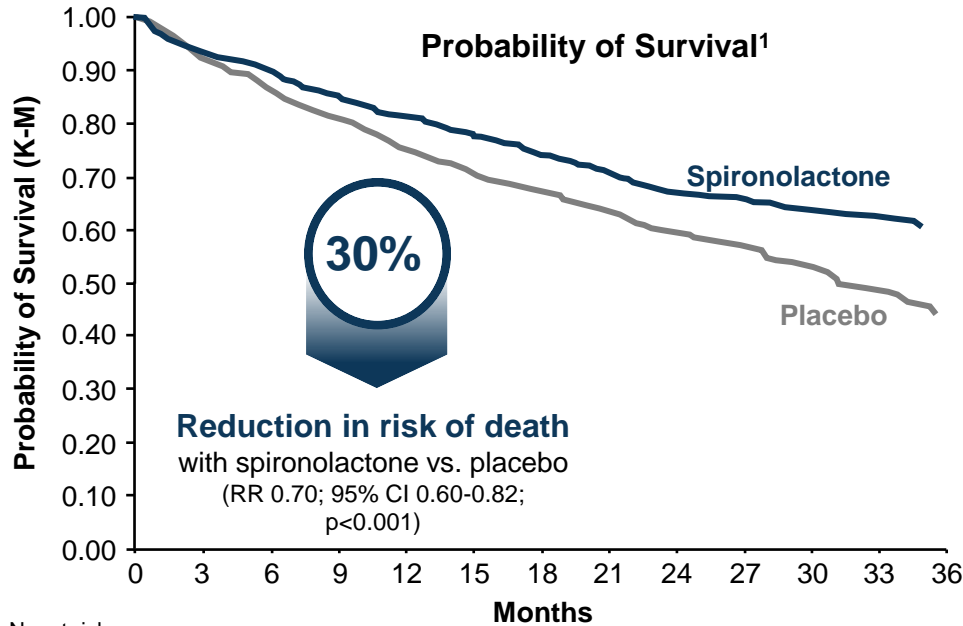


ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves (on a 12-lead electrocardiogram); SR = sinus rhythm.

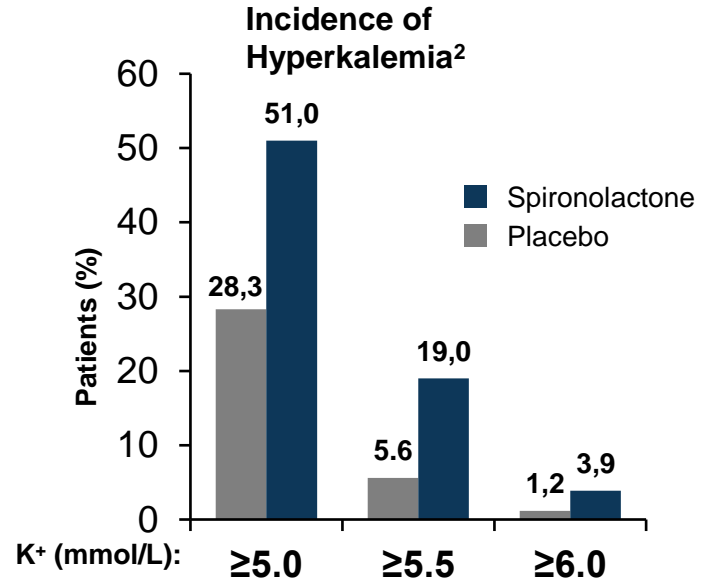
^aAs a replacement for ACE-I.

^bWhere appropriate. Class I=green. Class IIa=Yellow.

RALES: Spironolactone decreased mortality in patients with heart failure but was associated with increased hyperkalemia



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

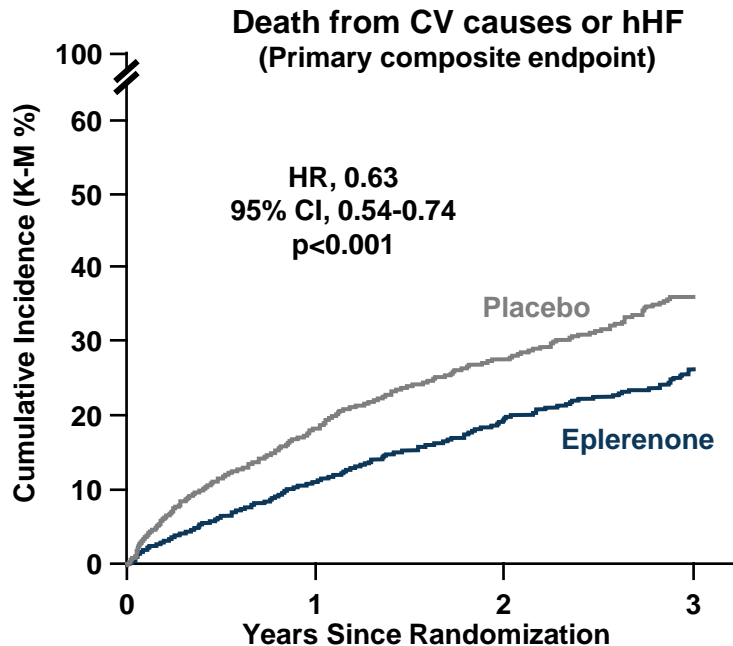


Treatment discontinued due to serious hyperkalemia (K⁺ ≥6.0 mmol/L)¹: spironolactone, n=3 vs. placebo, n=1

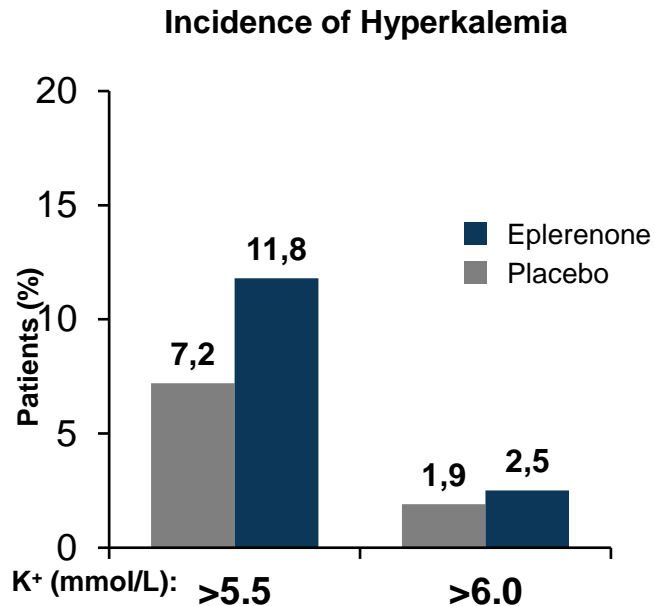
K-M = Kaplan-Meier; RALES = Randomized Aldactone Evaluation Study; RR = relative risk.

1. Pitt B et al. *N Engl J Med.* 1999;341:709–717; 2. Vardeny O, et al. *Circ Heart Fail* 2014;7:573–579.

EMPHASIS-HF: Eplerenone reduced CV mortality and hHF in patients with HF but was associated with increased hyperkalemia



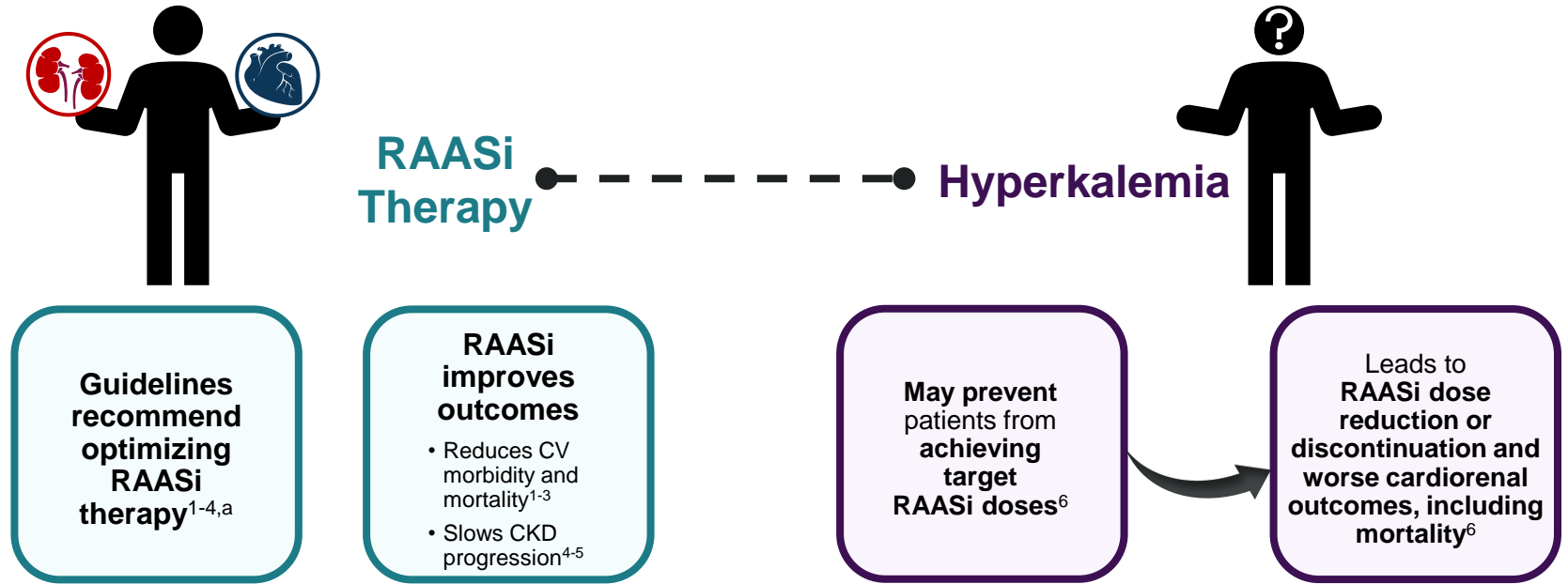
No. at risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232



Treatment discontinued due to hyperkalemia:
Eplerenone, 1.1% (n=15) vs. placebo, 0.9% (n=12)

CV = cardiovascular; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; K-M = Kaplan-Meier.

Therapeutic dilemma in managing hyperkalemia while optimizing RAASi therapy



^aACCF/AHA, ACC/AHA/HFSA, and ESC HF guidelines define RAASi therapy as ACEi, ARB, MRA, and ARNi. KDIGO 2020 clinical practice guideline for diabetes management in CKD define RAASi therapy as ACEi or ARB.

ACC = American College of Cardiology; ACCF = American College of Cardiology Foundation; ACEi = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor–neprilysin inhibitor; CKD = chronic kidney disease; CV = cardiovascular; ESC = European Society of Cardiology; HFSA = Heart Failure Society of America; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

1. Ponikowski P et al. *Eur Heart J*. 2016;37:2129-2200; 2. Yancy CW et al. *J Am Coll Cardiol*. 2013;62:e147-e239; 3. Yancy CW et al. *Circulation*. 2017;136:e137-e161; 4. KDIGO Diabetes Work Group. *Kidney Int Suppl*. 2020;98:S1-S115; 5. KDIGO Blood Pressure Work Group. *Kidney Int Suppl*. 2012;2:337-4146; 6. Epstein M et al. *Am J Manag Care*. 2015;21(suppl 11):S212–S220.

In real world practice, discontinuation of RAASi therapy persists following a hyperkalemia event



76%

of patients were **not reintroduced to MRA therapy** during the subsequent year¹

Mean duration of RAASi discontinuation was:²

2.4 years

in patients with CKD



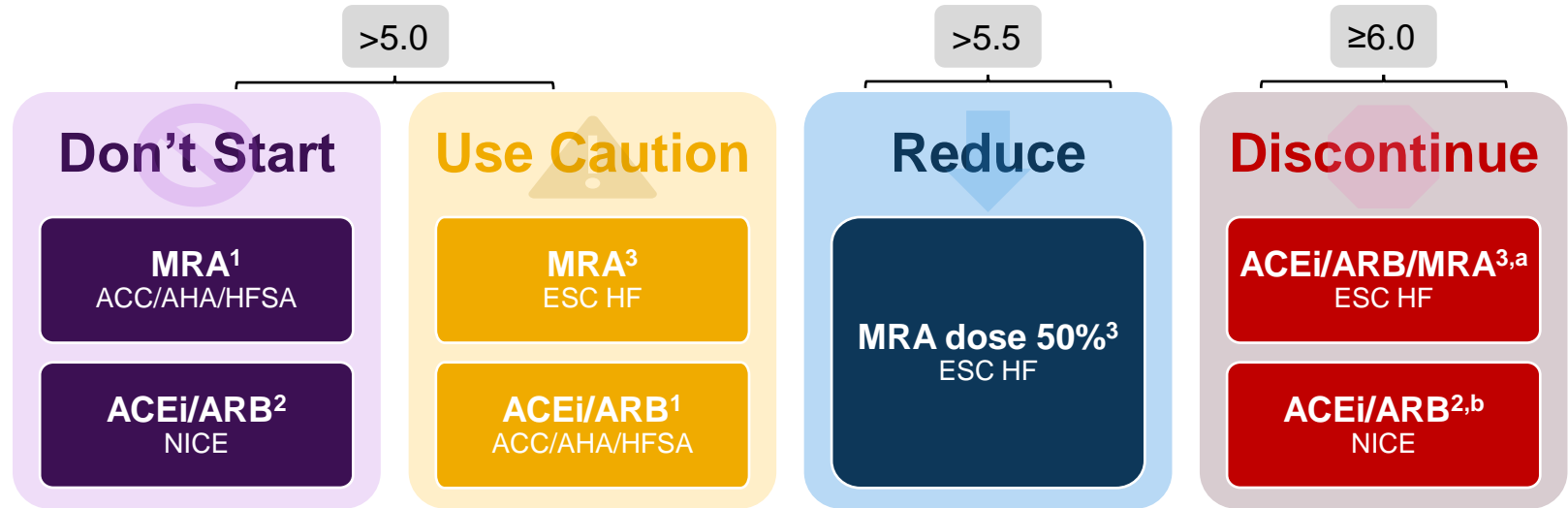
1.9 years

in patients with HF



Guideline-recommended management of RAASi in setting of hyperkalemia

Guideline Recommended Management of RAASi Based on Serum K⁺ (mmol/L)



Traditionally guidelines focused on reducing the risk of hyperkalemia rather than its management¹⁻³

Note: KDIGO 2012 clinical practice guideline for the management of blood pressure in chronic kidney disease do not specifically address management of RAASi in patients with hyperkalemia.⁴

^aMay require short-term cessation of K⁺ retaining agents and RAASi, but this should be minimized and RAASi should be reintroduced as soon as possible while monitoring K⁺ levels; ^bIf other drugs known to promote HK have been discontinued.

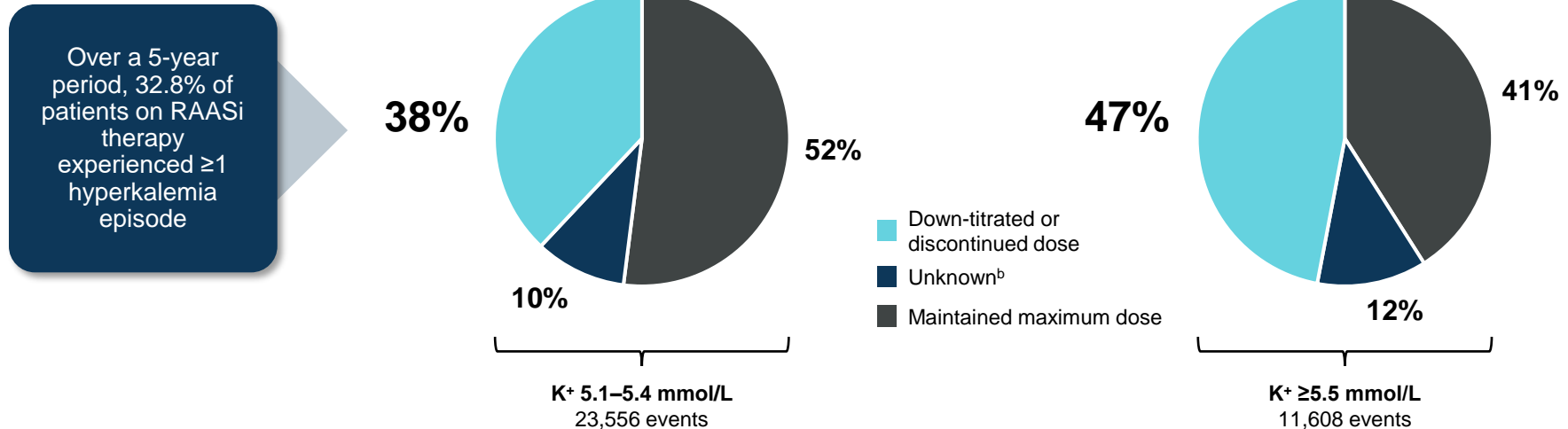
ACC = American College of Cardiology; ACEi = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; ESC = European Society of Cardiology; HF = heart failure; HFSA = Heart Failure Society of America; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid receptor antagonist; NICE = National Institute for Health and Care Excellence; RAASi = renin-angiotensin-aldosterone system inhibitor.

1. Yancy CW et al. *Circulation*. 2017;136:e137-e161; 2. NICE. Chronic kidney disease in adults: assessment and management (CG182). Updated January 16, 2015; 3. Ponikowski P et al. Article and web addenda. *Eur Heart J*. 2016;37:2129-2200; 4. KDIGO Blood Pressure Work Group. *Kidney Int Suppl*. 2012;2:337-414.

Down-titration or discontinuation of RAASi therapy is common following a hyperkalemia event

Retrospective analysis of electronic health records (N>200,000) of patients with various comorbidities, with at least 2 serum K⁺ readings, and on at least 1 RAASi from Humedica (US) in 2007-2012

Patients (%) with change in RAASi dose subsequent to a hyperkalemic event^a



Note: RAASi includes ACEi, ARBs, direct renin inhibitors, and select MRAs.

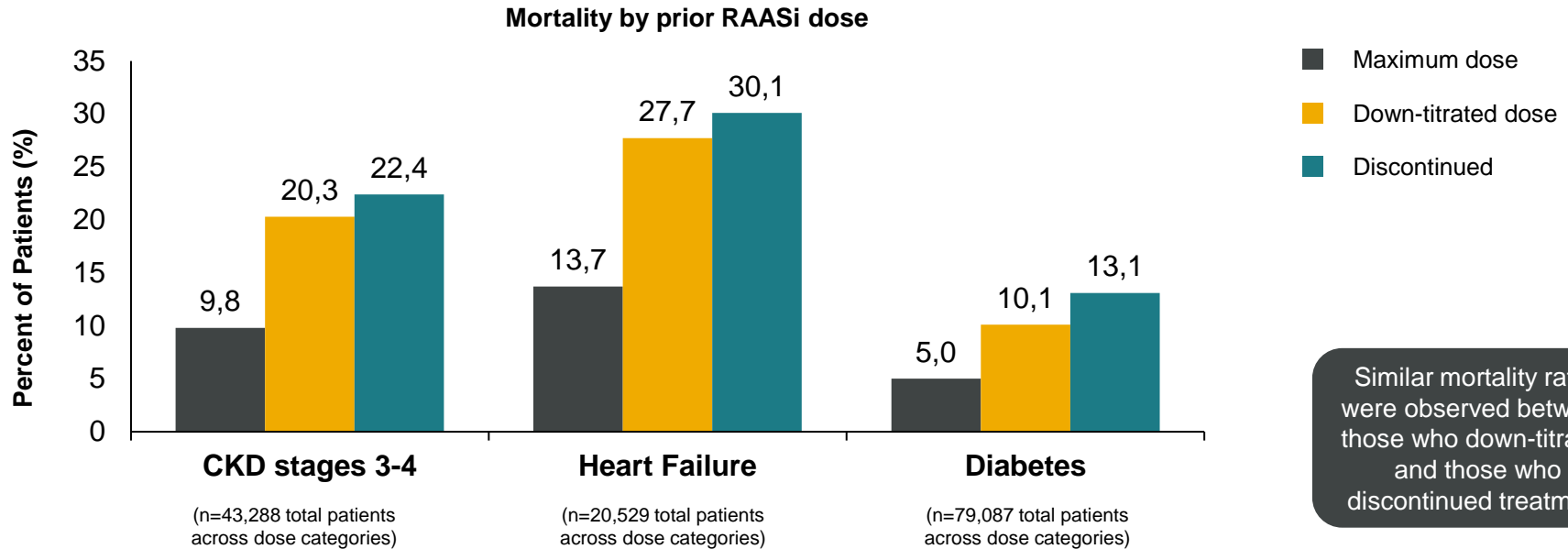
^aIn those receiving maximum dose of RAASi therapy; ^bThe data period following a hyperkalemia event was not sufficient to determine subsequent RAASi dose level in these patients.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; US = United States.

Epstein M et al. *Am J Manag Care.* 2015;21(suppl 11):S212–S220.

Down-titration or discontinuation of RAASi therapy due to HK is associated with doubling of mortality across patient subtypes

Retrospective analysis of electronic health records (N>200,000) of patients with various comorbidities, with at least two serum K⁺ readings, and on at least 1 RAASi from Humedica (US) in 2007-2012



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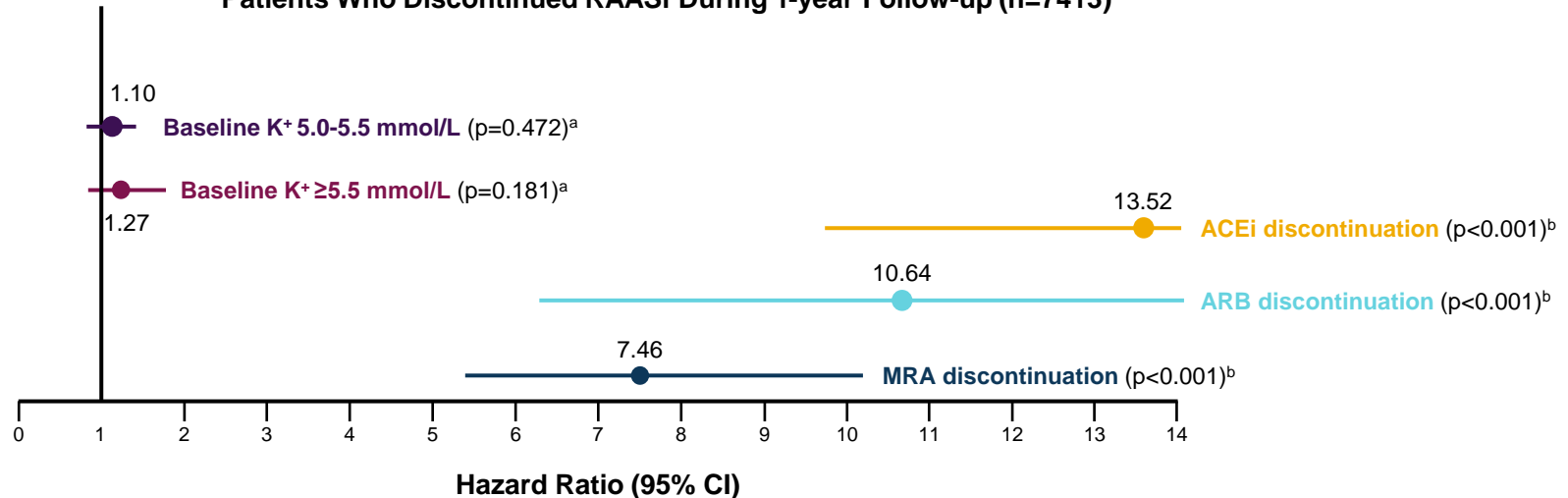
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RAASi discontinuation rather than Hyperkalemia at baseline was strongly associated with all-cause mortality in patients with HF during 1-year follow-up

Analysis of outpatients with chronic HF for whom intravenous HF therapy (diuretics, inotropes, or vasodilators) was used and who had a baseline K⁺ measurement (N=9222) and were enrolled in the ESC-HFA-EORP Heart Failure Long-Term Registry in 31 European countries between April 2011 and May 2017

Factors Associated With All-Cause Mortality in Multivariable Analysis of Patients Who Discontinued RAASi During 1-year Follow-up (n=7413)



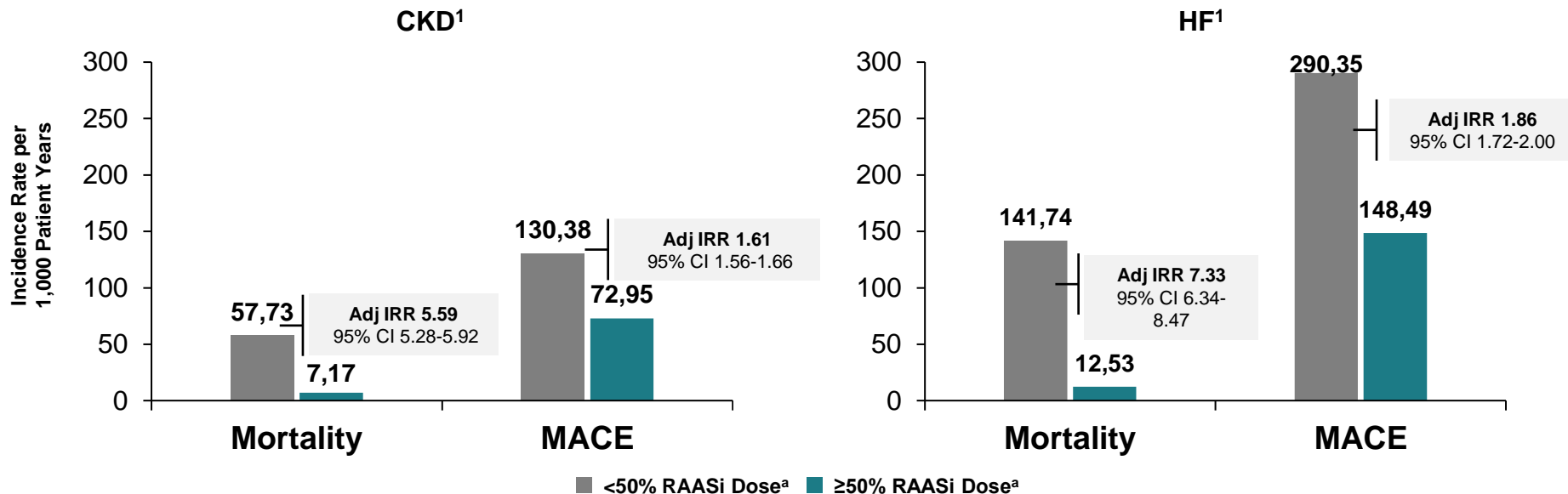
^ap value vs. K⁺ 4.0-5.0 mmol/L; ^bp value vs. no RAASi discontinuation.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ESC-HFA-EORP = The European Society of Cardiology Heart Failure Association EU Observational Research Programme; HF = heart failure; HK = hyperkalemia; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

Rossignol P et al. *Eur J Heart Fail.* 2020;22:1378-1389.

Optimizing RAASi therapy in patients with CKD and HF may decrease mortality and MACE

An observational, longitudinal cohort study of RAASi-prescribed patients with new-onset CKD (n=100,572) or HF (n=13,113) using data from the CPRD and linked Hospital Episode Statistics between January 2006 and December 2015¹



Note: Non-fatal MACE defined as a composite of nonfatal arrhythmia, HF, myocardial infarction, and stroke. Poisson models were used to estimate adjusted IRRs and included covariates to control for patient characteristics and clinical histories.

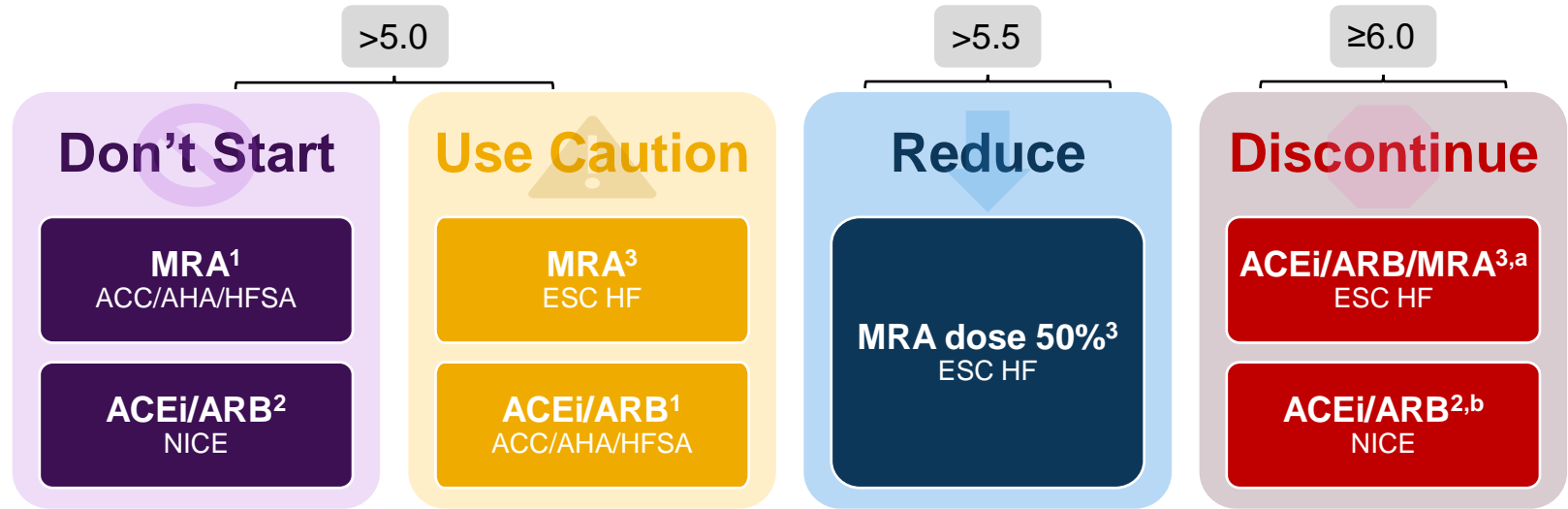
^aRAASi included specific ACEis, ARBs, and MRAs and the recommended dose was based on ESC 2016 guidelines for the treatment of HF.^{1,2}

ACEi = angiotensin-converting enzyme inhibitor; Adj = adjusted; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; ESC = European Society of Cardiology; HF = heart failure; IRR = incidence rate ratio; MACE = major adverse cardiac event; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

1. Linde C et al. *J Am Heart Assoc.* 2019; 2. Ponikowski P et al. *Eur Heart J.* 2016;37:2129-2200.

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Balancing RAAS inhibitor therapy with Potassium Levels

Chronic Management Challenges

RAAS inhibitors

ACEi, ARBs, aldosterone blockers

- Guideline Recommended
- Proven benefits in HF
- Strong evidence of benefit in Diabetic Nephropathy

Potential Risks of RAAS inhibitor therapy

- Hyperkalemia /Increased K⁺
- Limited by Hyperkalemia
- Up to 75% of HF patients are dosed sub-optimally

Can patients with hyperkalemia receive optimal RAASi therapy?

