The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

New Approach of Hyperkalemia Management to Optimize GDMT in Heart Failure

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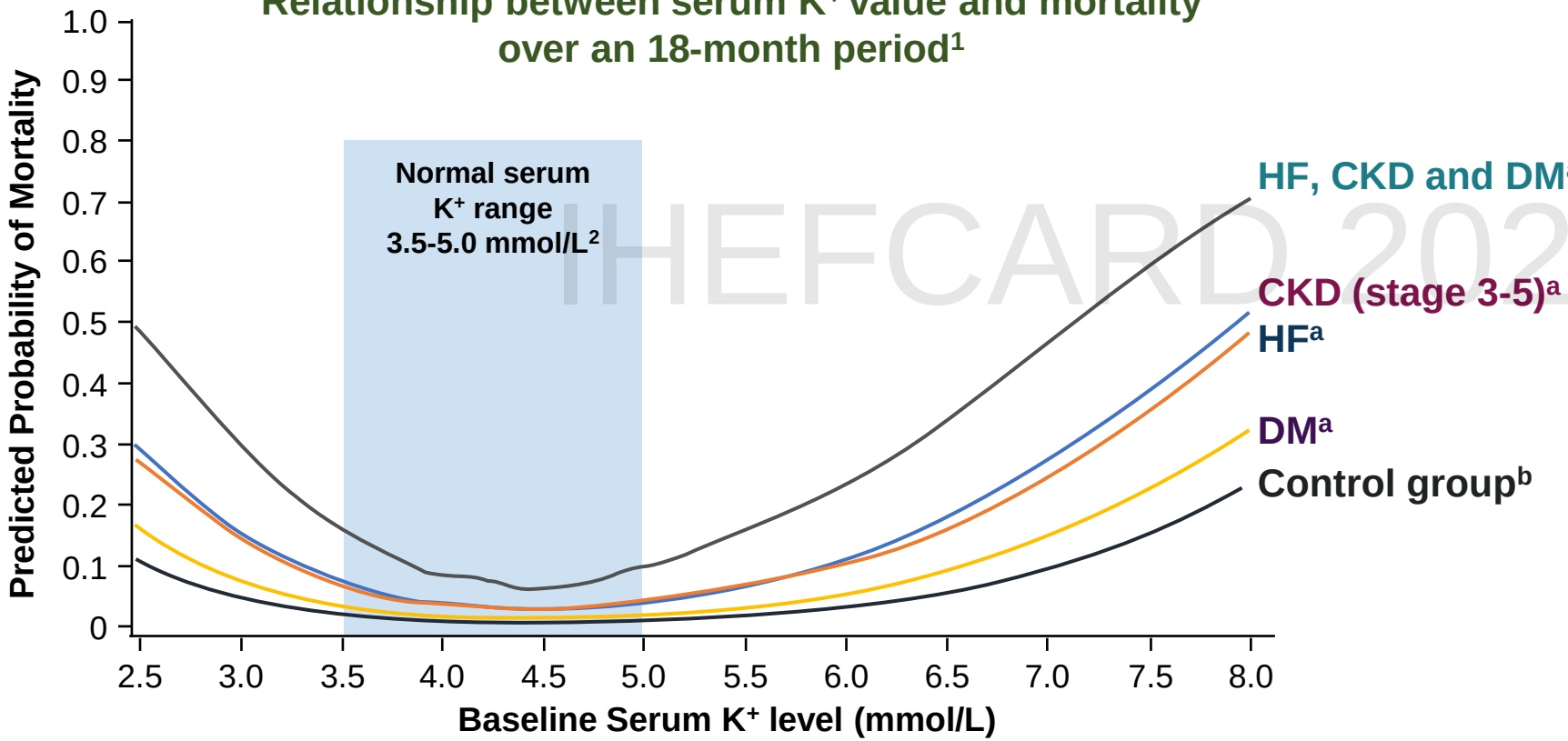
Quick Survey, just raise your hand..

1. Who gives Spironolactone 50 mg (optimal dose) to most of your heart failure patients?
2. If you give Spironolactone lower than that dose (or not give at all), what is the reason?
    1. Worried about worsening renal function
    2. Worried about dropping blood pressure
    3. Fear of hyperkalemia
    4. Didn’t realize the optimal dose is 50 mg

Hyperkalemia associated mortality is higher in patients with comorbidities

Analysis of electronic medical record data from multiple US integrated health delivery networks of 911,698 patients with ≥2 serum K^+ measurements between 2007 and 2012[1]

Relationship between serum K^+ value and mortality over an 18-month period[1]



All-cause mortality was significantly elevated for every 0.1 mmol/L change in serum K^+ <4.0 mmol/L and ≥5.0 mmol/L[1]

[a]Signficant vs. control group; [b]Control group comprised of individuals without known HF, CKD, DM, CVD, or HTN.

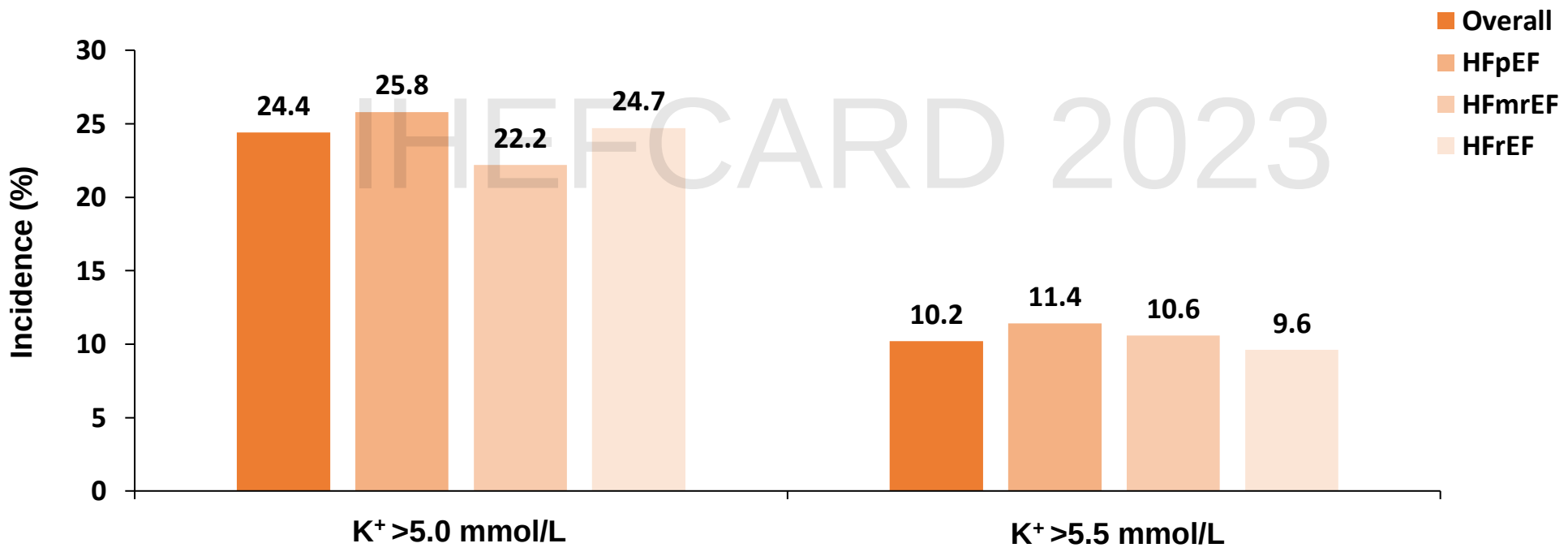
CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; US = United States.

1. Collins AJ et al. *Am J Nephrol.* 2017;46:213–221; 2. NKF. What is hyperkalemia? Reviewed February 8, 2016.

~25% of patients with HF experience hyperkalemia

HF patients (N=5848) that were registered with SwedeHF Registry for the first time and resided in Stockholm between 2006 and 2010 and had a measured serum creatinine and plasma K^+ level

Incidence of Hyperkalemia Overall and by Ejection Fraction[a] During 1-year Follow-up



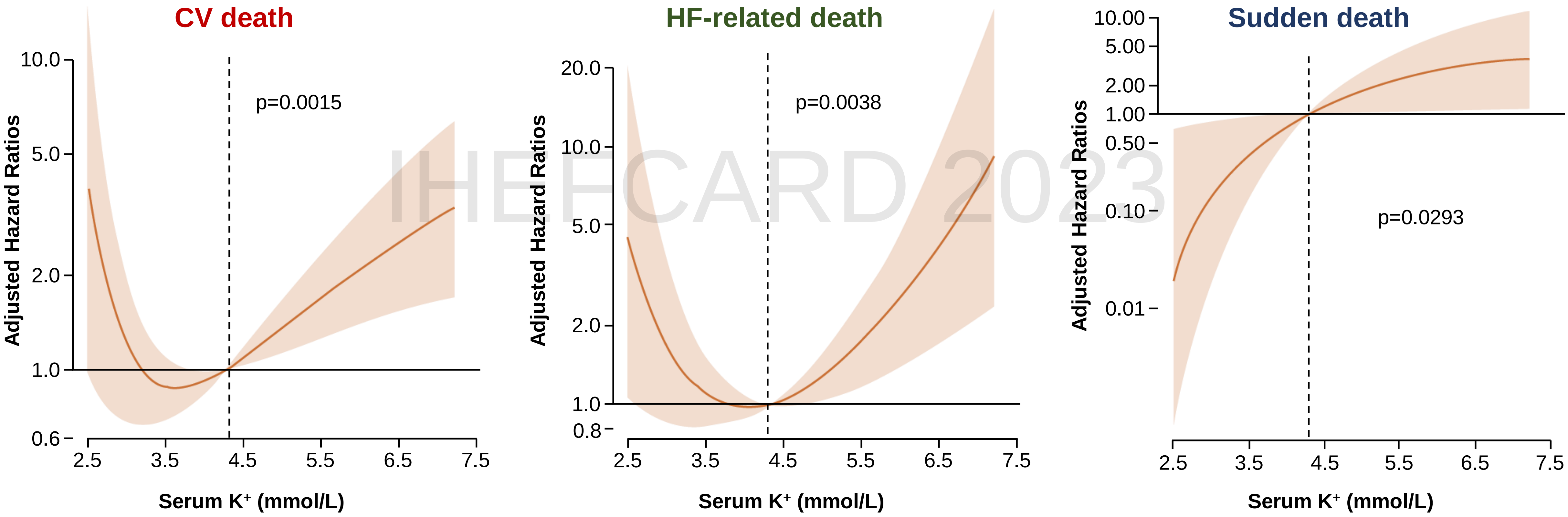
[a]HFpEF = EF ≥50%, HFmrEF = EF 40-49%, HFrEF = EF <40%.

EF = ejection fraction; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; SwedeHF = Swedish Heart Failure Registry.

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

Persistent hyperkalemia in patients with HF is associated with a higher risk of mortality compared to those who achieved or maintained normokalemia

Retrospective analysis of 2164 patients discharged from an acute HF admission between January 2008 and July 2016 with a total of 16,116 K^+ observations from a single center (median follow-up of 2.79 years)

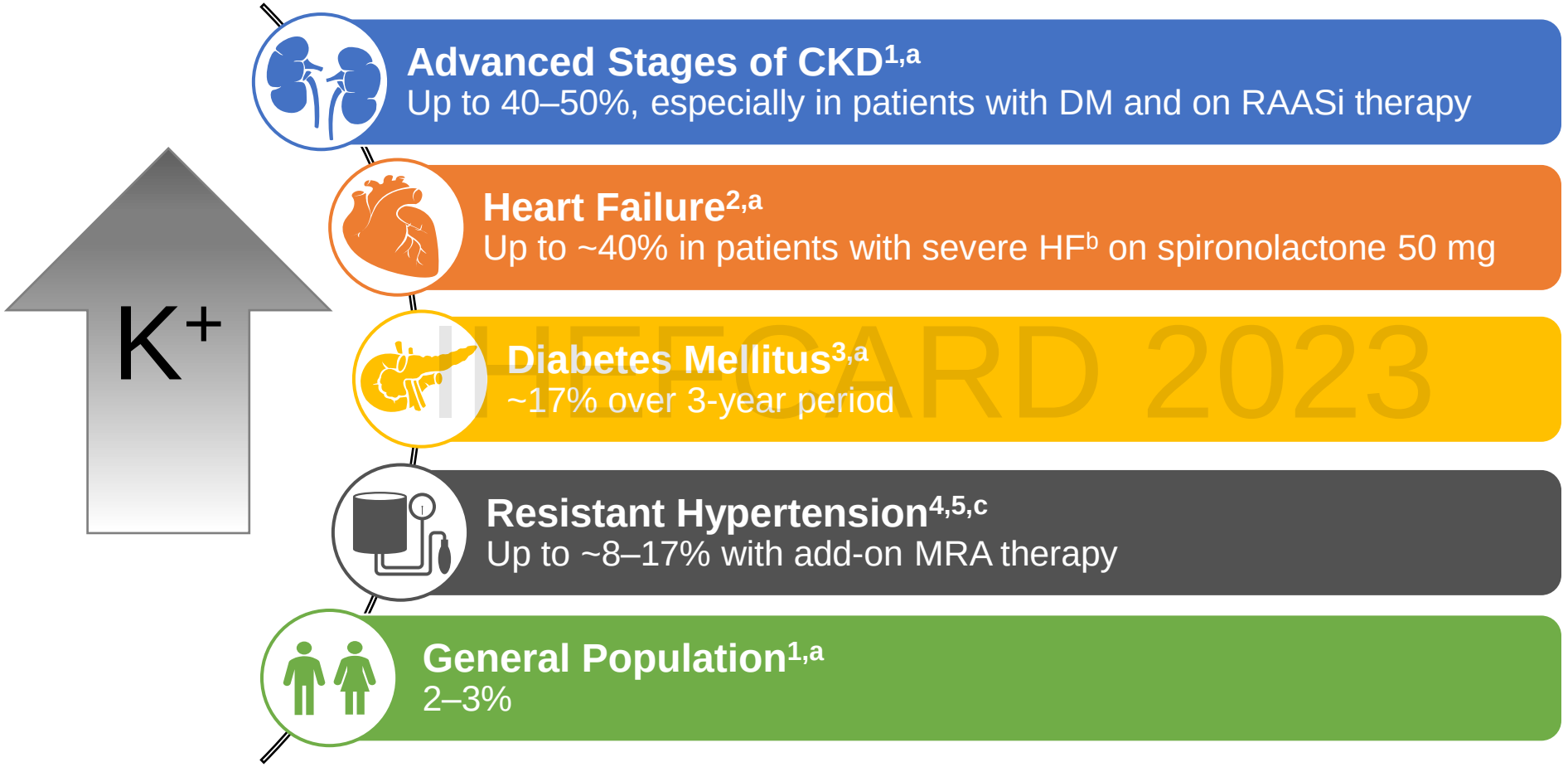


Note: Hypokalemia defined as K^+ <3.5 mmol/L, normokalemia as K^+ 3.5-5.0 mmol/L, and hyperkalemia as K^+ >5.0 mmol/L. Shaded area represents the 95% CI and the risk-gradient trajectory was centered at the median K^+ value in the sample of 4.3 mmol/L.

CV = cardiovascular; HF = heart failure.

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

Cardiorenal patients are at increased risk of hyperkalemia



[a]Hyperkalemia defined as K^+ >5.0 mmol/L;[1-3] [b]NYHA class III or IV and LVEF <35%;[2] [c]Hyperkalemia defined as persistent K^+ >5.5 mmol/L (or 1 reading of K^+ ≥6.0 mmol/L).[5]

CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RAASi = renin–angiotensin–aldosterone system inhibitor.

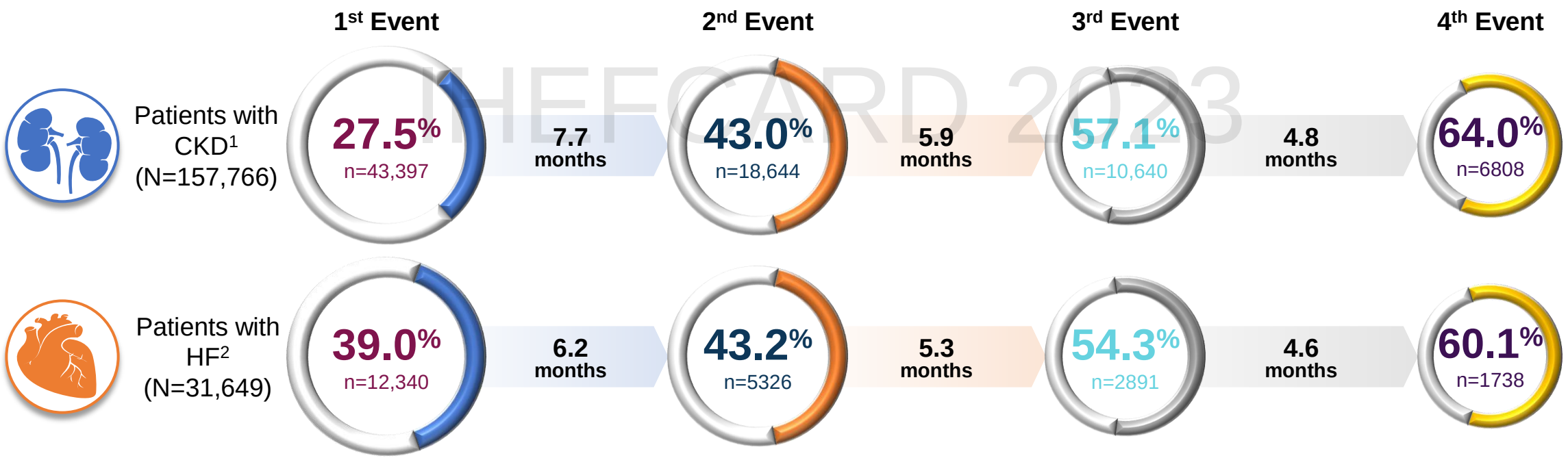
1. Kovesdy CP. *Nat Rev Nephrol*. 2014;10:653-662; 2. Vardeny O et al. *Circ Heart Fail*. 2014;7:573-579; 3. Nilsson E et al. *Int J Cardiol*. 2017;245:277-284; 4. Chomicki J et al. *J Am Soc Hypertens*. 2014;8:e30. P-10; 5. Khosla N et al. *Am J Nephrol.* 2009;30:418-424.

Hyperkalemia is an ongoing threat in cardiorenal patients

Patients with CKD and HF have recurrent hyperkalemia episodes, with successively shorter time between the episodes[1,2]

Population-based cohort study linking individual data from hospital, prescription, and laboratory databases in patients from the Danish National Patient Registry in Northern Denmark (population 1.8 million) during 2000–2012[1,2]

Proportion of Patients With Recurrent Hyperkalemia Events[a] and Median Time to Event



[a]A hyperkalemia event was defined as blood K^+ >5.0 mmol/L not preceded by a prior episode of elevated potassium within the previous month.[1,2]

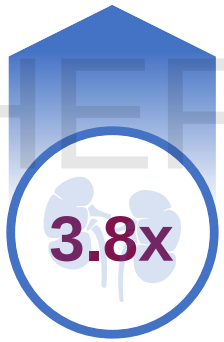
CKD = chronic kidney disease; HF = heart failure.

1. Thomsen RW et al. *Nephrol Dial Transplant*. 2018;33:1610-1620; 2. Thomsen RW et al. *J Am Heart Assoc.* 2018;7:e008912.

Hyperkalemia is associated with an increase in hospitalizations in patients with CKD and HF

Population-based cohort studies linking individual data from hospital, prescription, and laboratory databases in patients from the Danish National Patient Registry in northern Denmark (population 1.8 million) during 2000–2012. Patients with a first-time diagnosis of CKD (N=157,766) and HF were identified (N=31,649)[1,2]

Compared to matched patients without hyperkalemia, **hospitalizations 6 months after index date** were:



higher in patients with CKD and hyperkalemia[1]
(HR 3.78; 95% CI: 3.69-3.87)

higher in patients with HF and hyperkalemia[2]
(HR 2.75; 95% CI: 2.65-2.85)

Note: Hyperkalemia defined as K^+ >5.0 mmol/L.[1,2]

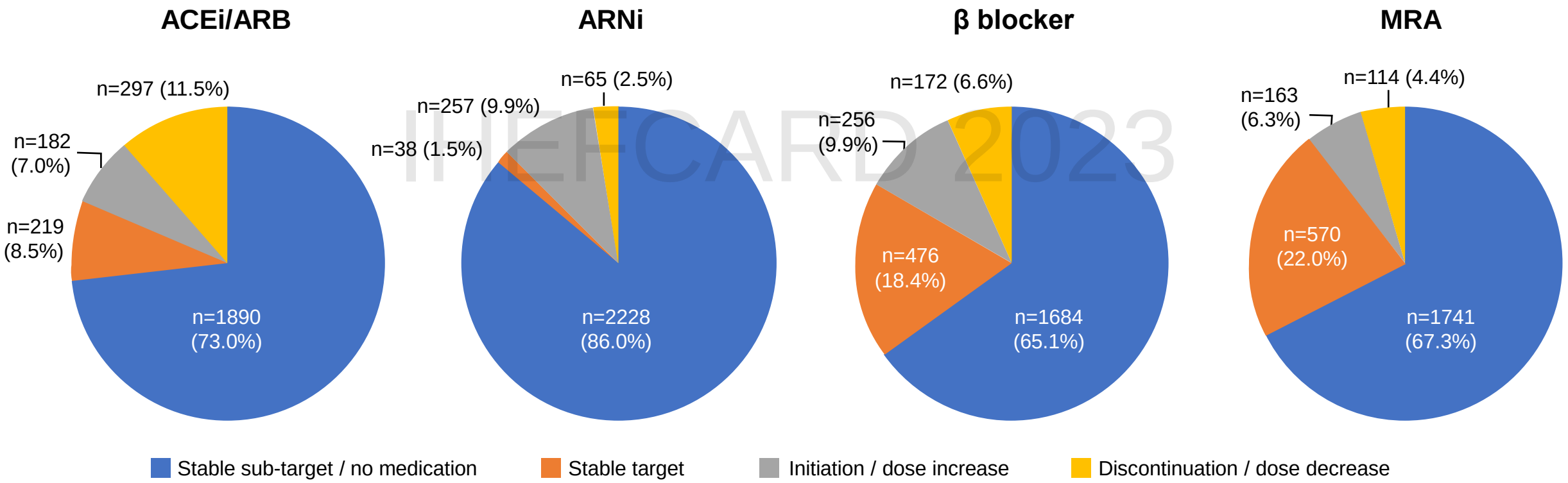
CKD = chronic kidney disease; HF = heart failure; HR = hazard ratio.

1. Thomsen RW et al. *Nephrol Dial Transplant*. 2018;33:1610-1620; 2. Thomsen RW et al. *J Am Heart Assoc.* 2018;7:e008912.

Approximately 90% of patients with chronic HF are either not on target dose, or their RAASi therapy has been down-titrated or discontinued

The CHAMP-HF registry included outpatients in the USA with chronic HFrEF receiving at least one oral medication for management of HF (N=2588)

Dose of medication at 12-month follow-up compared with baseline



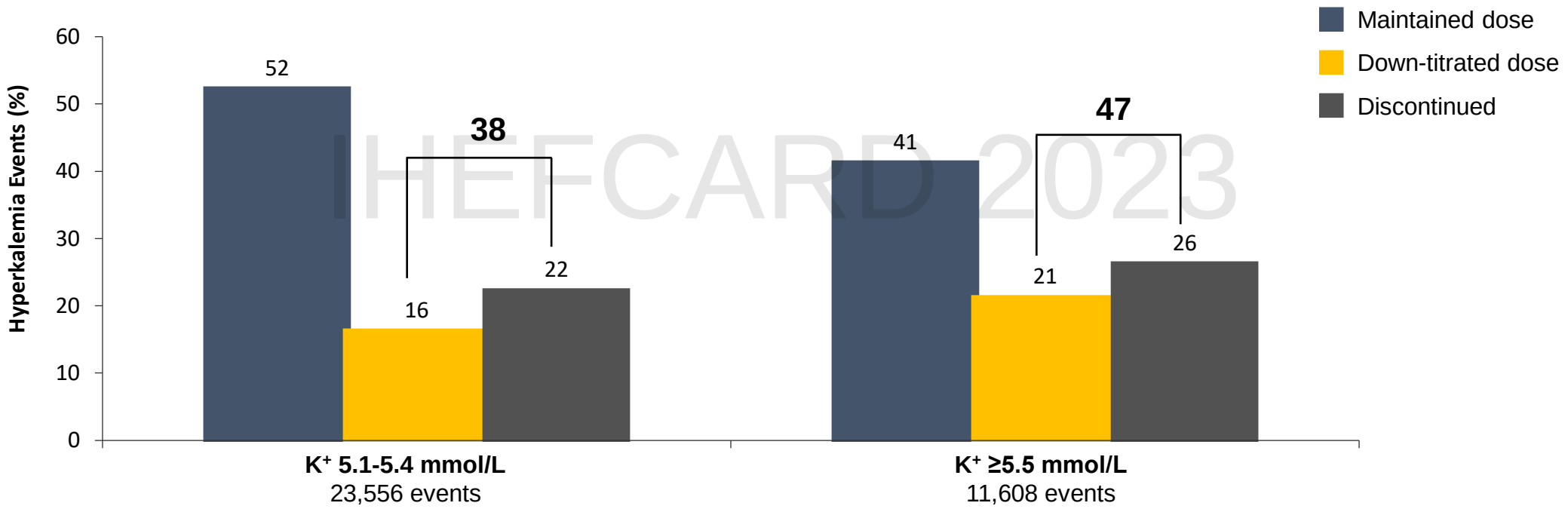
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor

Greene SJ, et al. *J Am Coll Cardiol* 2019;73:2365–2383

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

Retrospective analysis of a US database of electronic health records (Humedica; N>200,000) of patients ≥5 years of age with various comorbidities and with at least 1 outpatient RAASi prescription from 2007-2012. An event-level analysis was used to examine RAASi dose changes following 218,813 hyperkalemia events.

Change in RAASi Dose Subsequent to a Hyperkalemia Event in Patients at Maximum RAASi Dose



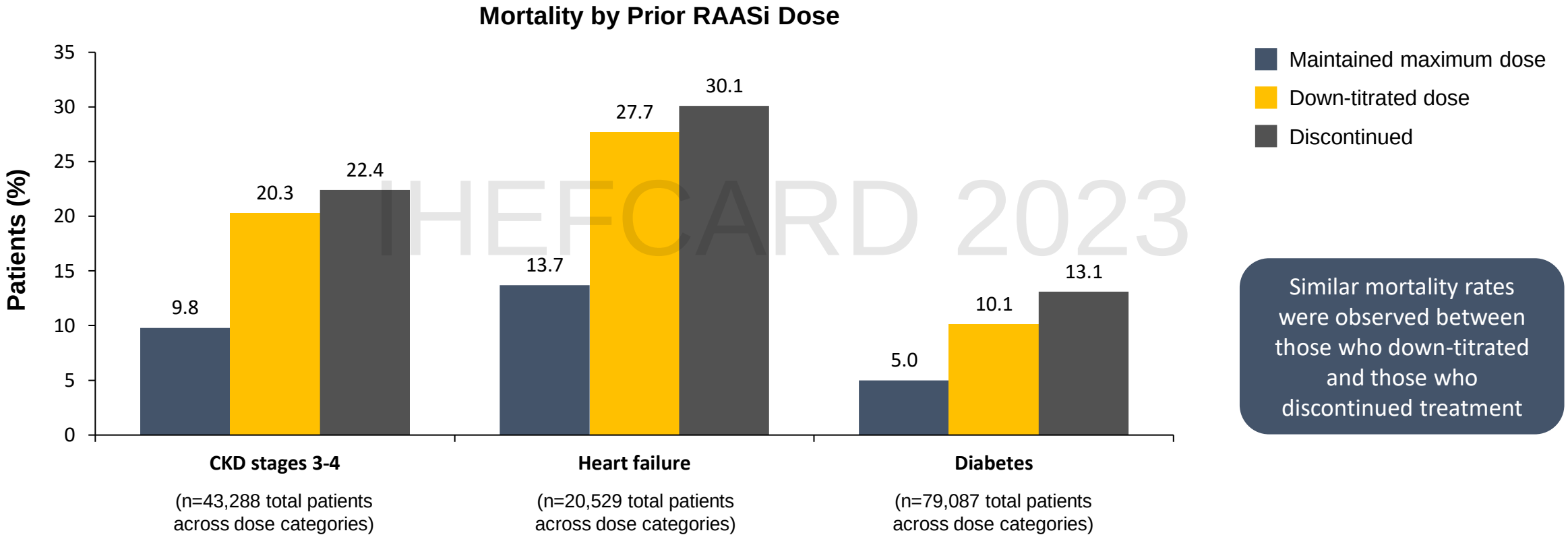
Note: Hyperkalemia defined as K^+ >5.0 mmol/L. RAASi includes ACEi, ARB, direct renin inhibitor, and select MRA. For the remaining events not shown in the graph, the data period following a hyperkalemia event was not sufficient to determine subsequent RAASi dose level in these patients.

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 is associated with doubling of mortality across patient subtypes

Retrospective analysis of a US database of electronic health records (Humedica; N>200,000) of patients ≥5 years of age with various comorbidities and with at least 1 outpatient RAASi prescription from 2007-2012



Similar mortality rates were observed between those who down-titrated and those who discontinued treatment

Note: RAASi includes ACEi, ARB, direct renin inhibitor, and select MRA.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; 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.

Guidelines recommend RAASi therapy for patients with CKD and/or HF

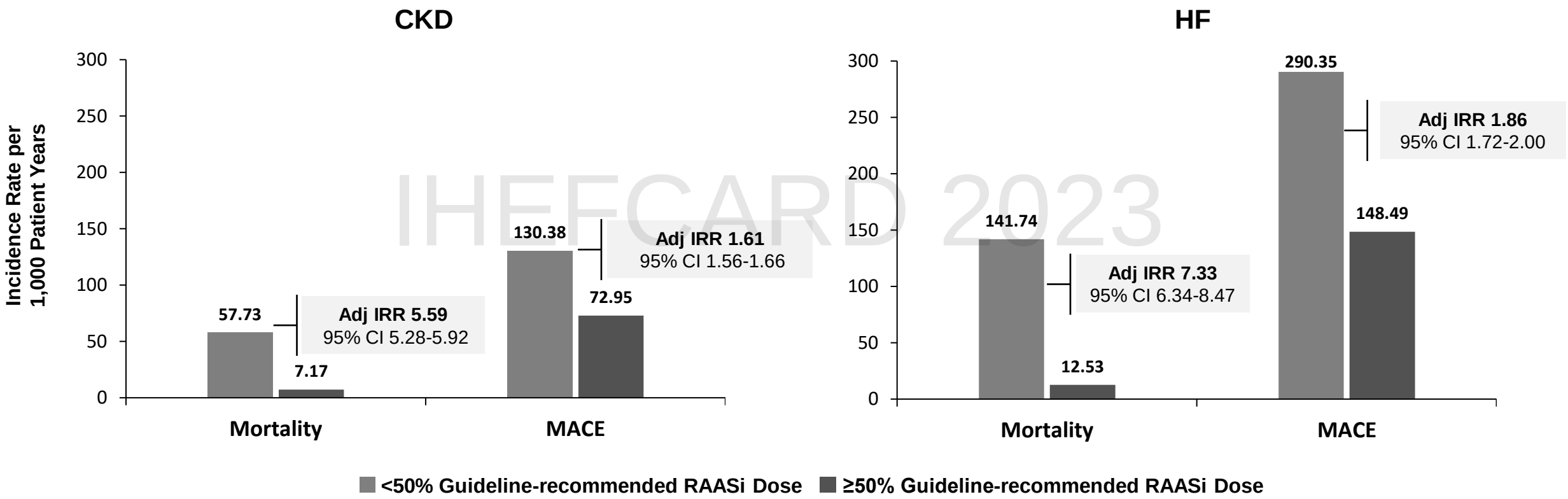
	CKD Guidelines (KDIGO 2020 Diabetes in CKD[1]; 2021 BP in CKD[2])	HF Guidelines (2021 ESC[3]; 2022 AHA/ACC/HFSA[4])
Optimize RAASi to reduce risk of morbidity and mortality	ACEi or ARB should be administered using the highest approved dose that is tolerated[1,2,a,b]	ACEi/ARNi and an MRA should be uptitrated to guideline recommended doses (or to maximally tolerated doses, if that is not possible)[3,4,c,d]
Monitor for HK	Serum K^+,[1-4] renal function,[1-4] and diuretic[4] dosing should be carefully monitored at RAASi[e] initiation and closely monitored thereafter to minimize the risk of HK and renal insufficiency	
Treat HK to enable patients to remain on optimized RAASi	HK associated with ACEi or ARB use can often be managed by measures to reduce K^+ rather than decreasing dose or stopping the ACEi or ARB[1,2]	The use of K^+ binders[f] has been shown to lower K^+ levels and enable treatment with a RAASi[3,4,g]
Discontinue RAASi as last resort	Reduce dose or stop ACEi or ARB as last resort[1]	Discontinuation of RAASi should occur only when HK cannot be managed with a K^+ binder. Reduce dose or stop RAASi as last resort[3,4]

[a]Recommendation (*1B*) in the KDIGO 2020 guideline: Level 1 = "We recommend" and Grade B = Moderate quality of evidence;[1] [b]In the KDIGO 2021 guideline, this is a practice point that is used to provide guidance to clinicians when a systematic review was not completed or was performed but did not find sufficient evidence to warrant a recommendation. It is not graded for strength or evidence quality;[2] [c]Recommendation (IA) in the 2021 ESC guideline: Class I = Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective and Level of Evidence A = Data derived from multiple randomized clinical trials or meta-analysis;[3] [d]Recommendation (1A) in the 2022 AHA/ACC/HFSA guideline: Class 1 = Strong (benefit >>> risk) and Level of Evidence A = High-quality evidence from more than 1 RCT; meta-analyses of high-quality RCTs; one or more RCTs corroborated by high-quality registry studies;[4] [e]ACEi or ARB in the KDIGO[1,2] and 2021 ESC guidelines[3], and MRA in the 2022 AHA/ACC/HFSA guideline;[4] [f]K^+ binders such as SZC and patiromer;[3,4] [g]ACEi, ARNI, and MRA in the 2021 ESC guideline[3] and ACEi, ARB, ARNi, and MRA in the 2022 AHA/ACC/HFSA guideline.[4]

Abbreviations and references in slide notes.

Optimizing RAASi therapy in patients with CKD and HF was associated with decreased 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 2015[1]

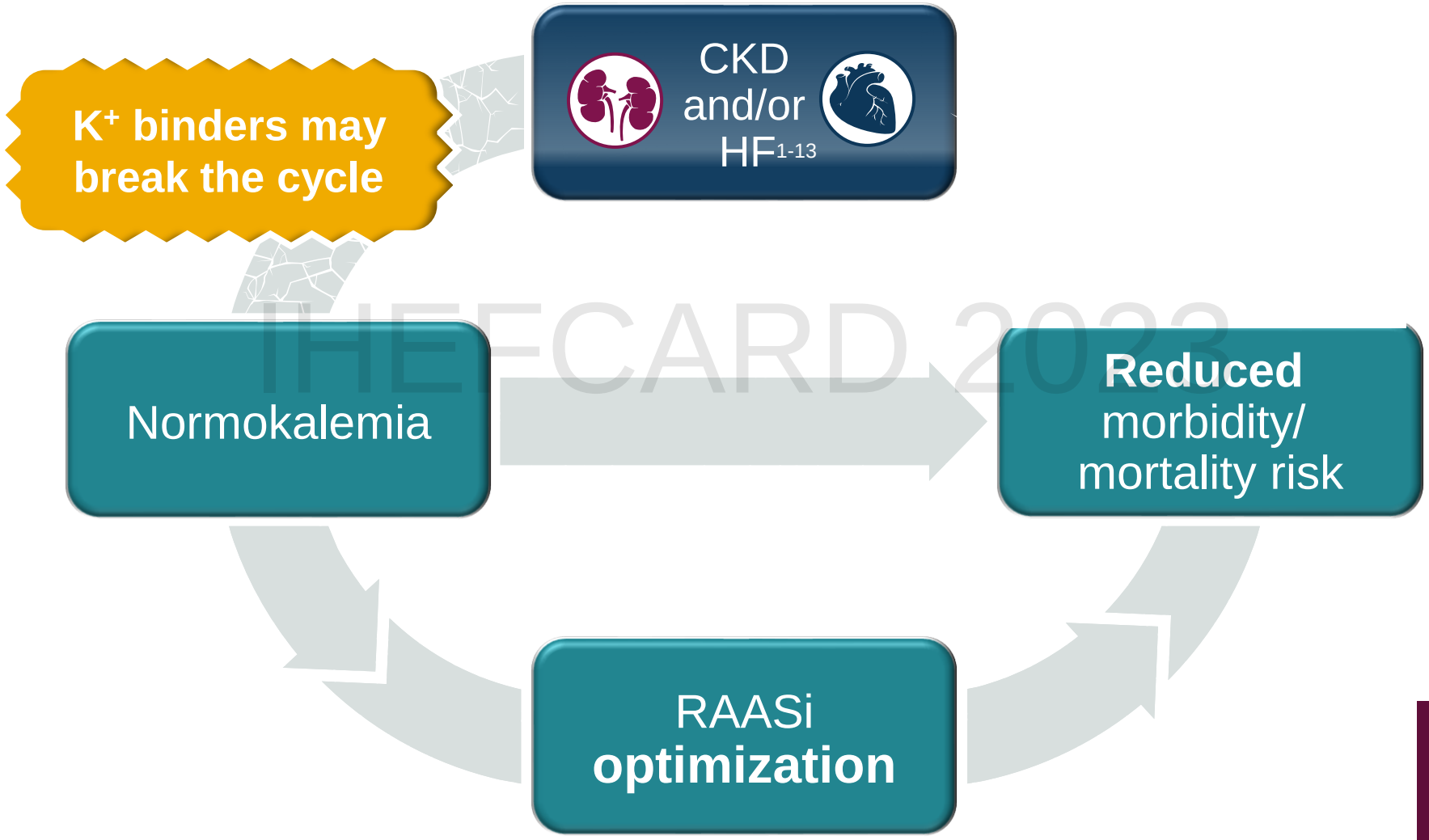


Note: Non-fatal MACE defined as a composite of non-fatal arrhythmia, HF, myocardial infarction, and stroke. Poison models were used to estimate adjusted IRRs and included covariates to control for patient characteristics and clinical histories. RAASi included specific ACEi, ARB, and MRA and the recommended dose was based on ESC 2016 guidelines[2] for the treatment of HF.[1]

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 events; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

1. Linde C et al. *J Am Heart Assoc.* 2019;8:e012655; 2. Pomikowski P et al. *Eur Heart J.* 2016;37:2129-2200.

Clinical consequences of hyperkalemia and suboptimal RAASi use



Note: For illustrative purposes only.
Abbreviations and references in slide notes.

In patients with HF, guidelines state the use of K^+ binders[a] to manage HK which may enable RAASi therapy

2021 ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HEART FAILURE[1]

Management of patients with chronic or recurrent HK on RAASi therapy:

- RAASi should be optimized when K^+ levels are <5.0 mmol/L
- An approved K^+ lowering agent[a] may be initiated as soon as K^+ levels are confirmed as >5.0 mmol/L
- Closely monitor K^+ levels
- Maintain K^+ lowering treatment unless alternative treatable etiology for HK is identified

K^+ Level	On Target RAASi Dose[b]	Guidance
4.5 to 5.0 mmol/L	No	• Initiate/up-titrate RAASi therapy to optimal doses • Closely monitor K^+ levels
>5.0 to ≤6.5 mmol/L	No	• Should initiate treatment with a K^+ lowering agent[a] • Closely monitor K^+ levels and maintain K^+ lowering agent[a] • If K^+ <5.0 mmol/L are detected, up-titrate RAASi therapy
	Yes	• May initiate treatment with a K^+ lowering agent • Closely monitor K^+ levels and maintain K^+ lowering agent[a]
>6.5 mmol/L	Yes or No	• Discontinue/reduce RAASi therapy • May initiate treatment with a K^+ lowering agent[a] • Closely monitor K^+

2022 AHA/ACC/HFSA GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE[2]

Recommendation	COR	LOE
In patients with HF who experience HK (serum K^+ ≥5.5 mmol/L) while taking a RAASi,[c] the effectiveness of K^+ binders[a] to improve outcomes by facilitating continuation of RAASi therapy is uncertain	2b	B-R

Sodium zirconium cyclosilicate and patiromer have been shown to lower K^+ levels and enable treatment with a RAASi[c] in patients with HF

[a]Patiromer or sodium zirconium cyclosilicate;[1,2] [b]Defined as maximal tolerated, guideline-recommended target dose of RAASi, which includes ACEi, MRA, or ARNi;

[c]RAASi includes ACEi, ARB, ARNi, and MRA.

ACC = American College of Cardiology; ACEi = angiotensin-converting enzyme inhibitors; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; COR = class of recommendation; ESC = European Society of Cardiology; HF = heart failure; HFSA = Heart Failure Society of America; HK = hyperkalemia; LOE = level of evidence; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

1. McDonagh TA et al. Article and supplementary data. *Eur Heart J*. 2021;42:3599-3726; 2. Heidenreich PA et al. In press-corrected proof. *J Am Coll Cardiol.* 2022.

Traditional hyperkalemia treatment options are associated with limitations

Low-K^+ diet[1]	Diuretics[1]	Traditional K^+ binders eg, SPS[1-5]	Discontinuation or dose-reduction of RAASi therapy[1]
• Difficult to adhere to • Limiting K^+-rich foods can cause constipation • Contradicts DASH diet; may worsen chronic hypertension	• Efficacy depends on residual renal function (until diuresis is present) • Increased risk of gout and diabetes depending on choice of diuretic • May produce volume contraction, decreased distal nephron flow, worsening of kidney function, and reduced K^+ excretion depending on choice of diuretic	• Long-term efficacy has not been evaluated • Gastric irritation, anorexia, nausea, vomiting, constipation and occasionally diarrhea may occur • High risk of hospitalizations or death due to serious GI AEs[a] • Hard, gritty texture and unpleasant taste may reduce palatability	• Stopping or suboptimal utilization of renal/ cardioprotective RAASi therapy

[a]Based on 2 retrospective analyses where primary outcome was a composite of adverse GI events (hospitalization or emergency department visit with intestinal ischemia/thrombosis, GI ulceration/perforation, or resection/ostomy within 30 days of initial SPS prescription in elderly patients[4] and hospitalization or death due to intestinal ischemia or thrombosis, GI ulcers and perforation) in adult patients.[5]

AE = adverse event; DASH = Dietary Approaches to Stop Hypertension; GI = gastrointestinal; RAASi = renin-angiotensin-aldosterone system inhibitor; SPS = sodium polystyrene sulfonate.

1. Dunn J et al. *Am J Manag Care.* 2015;21:S307–S315; 2. SPS Suspension Prescribing Information, CMP Pharma, Inc. March 2018; 3. Zann V et al. *Drug Des Devel Ther.* 2017;11:2663–2673; 4. Noel JA et al. *JAMA Intern Med.* 2019;179:1025-1033; 5. Laureati P et al. *Nephrol Dial Transplant.* 2020;35:1518-1526.

Comparison With Other K^+ Binders

	Sodium Zirconium Cyclosilicate	Patiromer	Sodium Polystyrene Sulfonate
Selectivity	Binds K^+ [1,a]	Binds K^+ and Mg^{2+} [2]	Binds K^+, Ca^{2+}, and Mg^{2+} [3]
Site of K^+ Capture in Lumen of GI Tract	Small and large intestines[4,b]	Primarily colon[5,c]	Primarily large intestine[5]
Time to Initial K^+ Reduction	1 hour[1,6,d]	7 hours[7]	Not provided in the labeling information[3]
Longest Duration Studied Prospectively	1 year[1,8,d]	1 year[7]	7 days[9]
Calcium Content	0 g[10]	1.6 g per 8.4 g of patiromer[11]	0 g[10]
Sodium Content for Recommended Maintenance Dose Range	400 mg QOD–1200 mg daily[1,d,e]	0[12]	1500–6000 mg daily[12,f]
Molecular Composition	Non-polymer[2]	Polymer[2]	Polymer[2]
Spacing of Other Medications	At least 2 hours before or 2 hours after Lokelma[1]	At least 3 hours before or 3 hours after patiromer[7]	At least 3 hours before or 3 hours after SPS[3]
Storage	Does not require special storage conditions[1]	Refrigerate at 2-8°C (36-46°F)[7]	None stated[3]

Note: Clinical pharmacology does not correlate with efficacy or safety. SZC has not been compared to other K^+ binders in prospective, head-to-head, controlled clinical trials. This data is for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.

[a]In vitro, SZC has a high affinity for K^+, even in the presence of other cations such as Ca^{2+} and Mg^{2+};[4] [b]In vitro study; based on simulated intestinal fluid;[4] [c]Based on nonclinical and early phase studies[13]; [d]Clinical data in patients not on dialysis; [e]The sodium content/unit dose of SZC is 400 mg/5 g,[1] but the amount released and subsequently absorbed per a given dose of SZC has not been formally quantified; [f]The sodium content/unit dose of SPS is 1500 mg/15 g.[12]

GI = gastrointestinal; QOD = every other day; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate.

1. LOKELMA Summary of product characteristics. Updated August 16, 2022; 2. Palmer BF. *Mayo Clin Proc.* 2020;95(2):339-354; 3. Resonium A. Summary of product characteristics. Sanofi; November 2021; 4. Stavros F et al. *PLoS One*. 2014;9(12):e114686; 5. Pitt B et al. *Hypertension*. 2015;66(4):731-738; 6. Packham DK et al. *N Engl J Med*. 2015;372(3):222-231; 7. Veltassa. Summary of product characteristics. Vifor; June 2022; 8. Spinowitz BS et al. *Clin J Am Soc Nephrol*. 2019;14(6):798-809; 9. Lepage L et al. *Clin J Am Soc Nephrol.* 2015;10(12):2136-2142; 10. Clegg DJ et al. *Mayo Clin Proc.* 2017;92(8):1248-1260; 11. Bakris G et al. Letter. *J Cardiovasc Dis Diagn*. 2016;4(2):237; 12. Beccari MV. *Core Evid.* 2017;12:11-24; 13. Li L et al. *J Cardiovasc Pharmacol Ther*. 2016;21(5):456-465.

In real world practice, SZC has been used to manage hyperkalemia in patients with HFrEF and allowed optimization of RAASi therapy

Case series of 8 patients with HFrEF who developed hyperkalemia (serum K^+ >5.0 mmol/L) while receiving RAASi therapy[a] and initiated SZC therapy

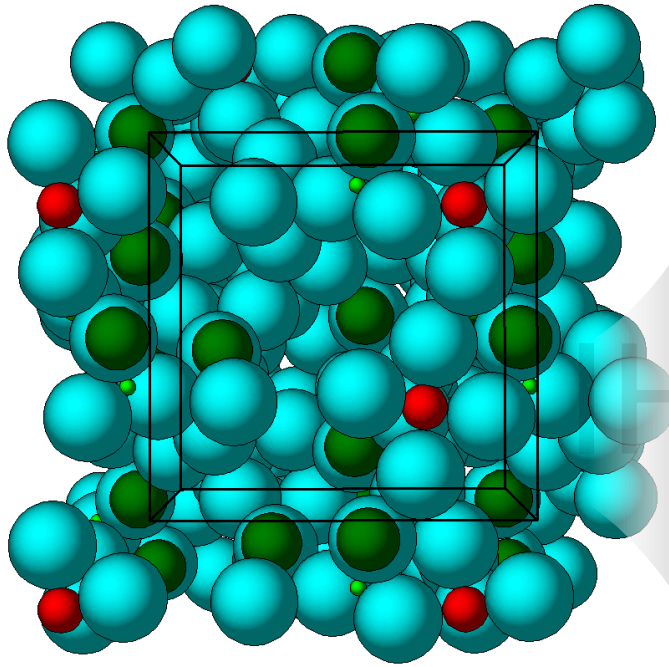
Patient	Baseline LVEF (%)	Serum K^+ (mmol/L)		RAASi Therapy		Change in RAASi therapy	OMT achieved
		At SZC initiation	Most recent post-SZC	Before SZC	After SZC		
1	32	**5.8**	**4.1**	Sacubitril/valsartan 1/2 x 24/26 mg BID	Sacubitril/valsartan 97/103 mg BID Eplerenone 50 mg QD	Initiation & up-titration	Yes
2	25	**6.2**	**<5.1**	Sacubitril/valsartan 49/51 mg BID (on hold) Spironolactone 25 mg QD	Sacubitril/valsartan 49/51 mg BID Spironolactone 25 mg QD	Maintenance	Yes
3	27	**5.8**	**4.5**	Sacubitril/valsartan 49/51 mg BID	Sacubitril/valsartan 97/103 mg BID	Up-titration	In progress
4	13	**5.8**	**4.7**	Sacubitril/valsartan 97/103 mg BID (on hold)	Sacubitril/valsartan 97/103 mg BID Spironolactone 25 mg QD	Initiation & up-titration	Yes
5	35	**5.8**	**<5.2**	NR	Sacubitril/valsartan 97/103 mg BID Eplerenone 25 mg QD	Initiation & up-titration	Yes
6	28	**6.3**	**~5.0**	Sacubitril/valsartan 24/26 mg BID	Sacubitril/valsartan 24/26 mg BID	Maintenance	Yes
7	15	**5.4**	**4.4–4.8**	Sacubitril/valsartan 49/51 mg BID Eplerenone 25 mg QD	Sacubitril/valsartan 49/51 mg BID Eplerenone 50 mg QD	Initiation & up-titration	In progress
8	40	**6.5**	**4.7–5.1**	Sacubitril/valsartan 49/51 mg BID	Sacubitril/valsartan 49/51 mg BID Spironolactone 12.5 mg QD	Initiation & up-titration	In progress

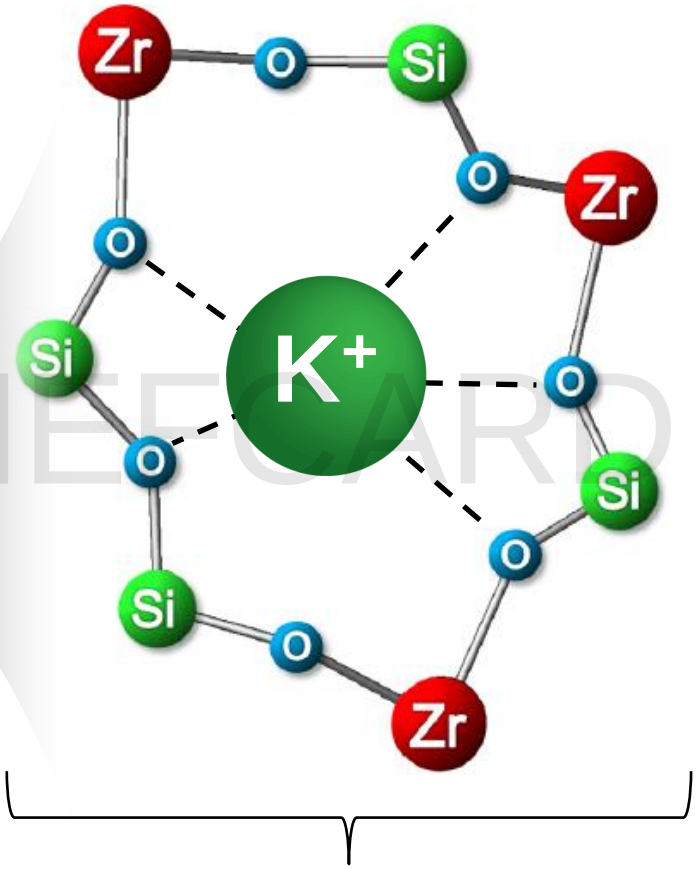
[a]Patient selection for this case series was critical, as patients with low blood pressure or significant kidney dysfunction are unlikely to benefit from this approach as initiation or further up-titration of RAASi therapy may be limited by such factors. Four patients were male, and all were between 65 and 87 years old.

HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NR = not reported; OMT = optimal medical therapy; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

Williams R et al. Article and supplementary data. *Eur Heart J Case Rep*. 2021;5:ytab281.

SZC Crystal Structure





Average Binding-Site Width: 3 Å

- Inorganic crystalline potassium binder; not a polymer
- Exchanges H^+ and Na^+ for K^+
- Highly selective for K^+; binding site width and K^+ ionic diameter are similar
- Insoluble, highly stable, and does not expand in water
- Not systemically absorbed

O = oxygen atom; Si = silicon atom; SZC = sodium zirconium cyclosilicate; Zr = zirconium atom.

Stavros F et al. *PLoS One*. 2014;9(12):e114686.

SZC provided rapid K^+ reduction within 48 hours and sustained K^+ control for up to 1 year

ZS-004 (HARMONIZE)[1] | **ZS-004E (11-MONTH EXTENSION)[3]**

Open-label CP (48 hours)[1]
SZC 10 g TID (n=258)

Randomized, Double-blind MP (Days 1-29)[1,b]
Placebo (n=82) | SZC 5 g[c] (n=45) | SZC 10 g[c] (n=50) | SZC 15 g[c] (n=54)

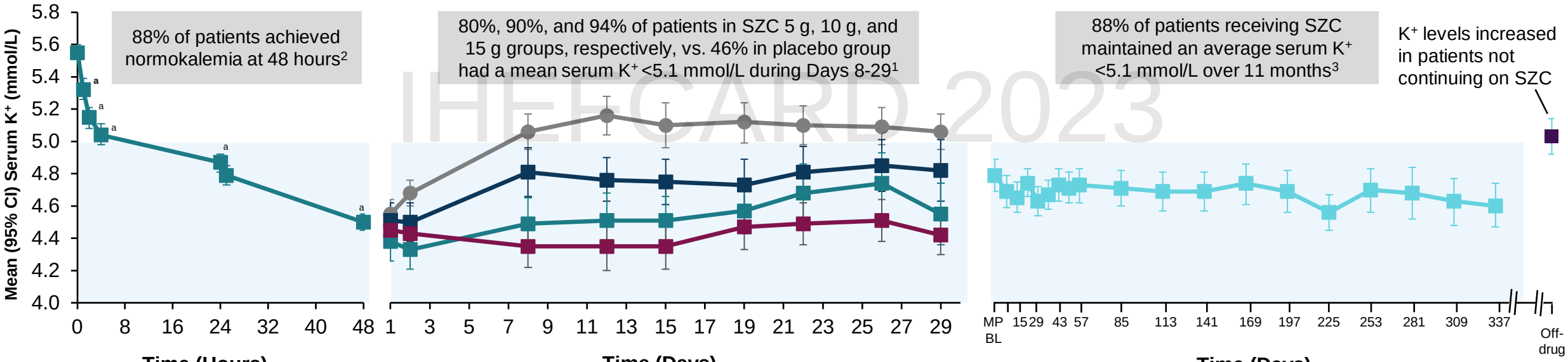
Open-label MP (Days 1-337)[3,d]
SZC titrated dose[e] (N=123)

88% of patients achieved normokalemia at 48 hours[2]

80%, 90%, and 94% of patients in SZC 5 g, 10 g, and 15 g groups, respectively, vs. 46% in placebo group had a mean serum K^+ <5.1 mmol/L during Days 8-29[1]

88% of patients receiving SZC maintained an average serum K^+ <5.1 mmol/L over 11 months[3]

K^+ levels increased in patients not continuing on SZC



Note: Normokalemia defined as serum K^+ 3.5-5.0 mmol/L and patients on dialysis were excluded from these studies.[1,3]

[a]p<0.001 vs. baseline;[1] [b]If a patient's K^+ value was between 3.0-3.4 mmol/L at any time during the randomized phase, the dose was reduced from QD to QOD for the remainder of the study;[1] [c]p<0.001 vs. placebo during Days 8-29;[1] [d]Maintenance SZC dosing was initiated at 10 g QD and titrated in 5 g increments or decrements to maintain i-STAT K^+ 3.5–5.0 mmol/L (minimum 5 g QOD; maximum 15 g QD). Off-drug values were recorded at 7±1 days following the last dose of SZC;[3] [e]Mean SZC doses to maintain normokalemia were 10 g QD in 73.2%, >10 g QD in 13.0%, <10 g QD in 13.8% of patients.[3]

BL = baseline; CP = correction phase; MP = maintenance phase; QOD = every other day; SZC = sodium zirconium cyclosilicate.

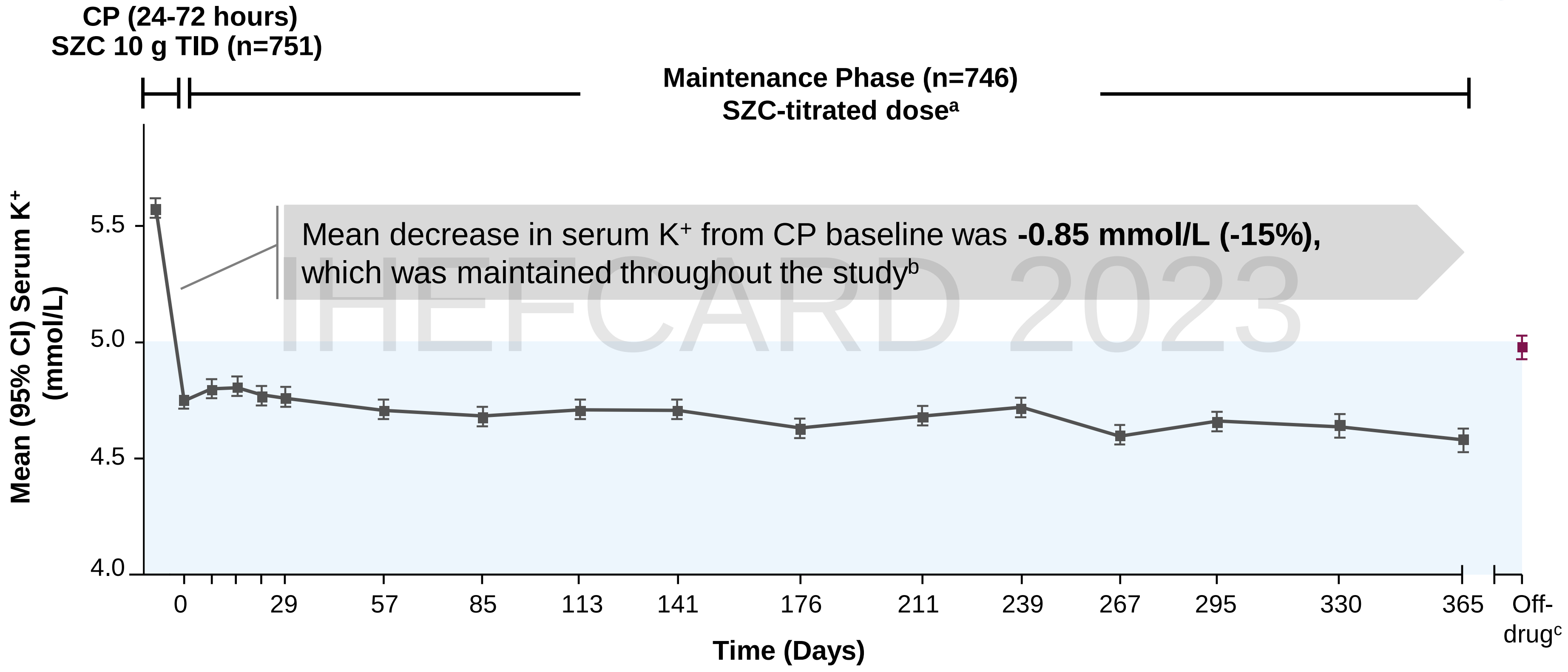
1. Kosiborod M et al. *JAMA*. 2014;312:2223-2233; 2. LOKELMA Summary of product characteristics. Updated January 21, 2021; 3. Roger SD et al. Article and supplementary material. *Am J Nephrol.* 2019;50:473-480.

crystalize HARMONIZE & Extension

In another long-term study, SZC sustained K^+ control over 1 year

ZS-005 (12-MONTH STUDY)

crystalize ZS-005



Note: Normokalemia defined as serum K^+ 3.5-5.0 mmol/L and patients on dialysis were excluded from the study. Data based on ITT population which included all participants who received SZC and had any postbaseline K^+ values measured during the study phase.

[a]Maintenance dosing was initiated at SZC 5 g QD and dose was titrated in 5 g increments or decrements to maintain i-STAT K^+ 3.5–5.0 mmol/L (minimum 5 g QOD; maximum 15 g QD). Maximum SZC doses to maintain normokalemia were 5 g QD in 47% of patients, 10 g QD in 41%, and 15 g QD in 12%; [b]p<0.001 vs. CP baseline at all time points; [c]Off-drug values were recorded at 7±1 days following the last dose of SZC.

CP = correction phase; ITT = intention-to-treat; QOD = every other day; SZC = sodium zirconium cyclosilicate.

Spinowitz BS et al. Article and supplementary material. *Clin J Am Soc Nephrol.* 2019;14:798-809.

SZC is generally well tolerated and has limited drug interactions

Safety

1760 patients were evaluated in clinical trials to establish SZC safety profile; 507 patients received SZC for at least 1 year

5.7% of patients reported edema that was generally mild to moderate in severity[a]

4.1% K^+ of patients reported hypokalemia (serum K^+ less than 3.5 mmol/L) that resolved with SZC dose adjustment or discontinuation

Pharmacology and Drug interactions

SZC does not affect serum Ca^{2+} or Mg^{2+} concentrations or urinary Na^+ excretion

SZC is not absorbed or metabolized by the body and there are no expected effects of other medicinal products on the pharmacologic action of SZC

SZC can transiently increase gastric pH and should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability

[a]In up to 47% of patients, edema resolved without treatment. The remainder were managed with diuretic initiation or diuretic dose adjustment.

SZC = sodium zirconium cyclosilicate.

LOKELMA Summary of product characteristics. Updated January 21, 2021.

The safety profile of SZC in patients with HFrEF is consistent with that observed in other SZC clinical trials

crystalize PRIORITIZE-HF

- PRIORITIZE HF was a Phase II, international, multicenter study conducted to evaluate the use of SZC to facilitate the up-titration of RAASi in patients with HFrEF.[1]
- The study was terminated early due to the COVID-19 pandemic and did not fully enroll (N=182 of 280 planned), therefore, the efficacy results are exploratory.[2]

Primary Endpoint

- There was no statistically significant difference between SZC and placebo in the various RAASi treatment categories[a] at 3 months, however, there was a numerical increase in MRA up-titration in the SZC group[1,2]
  - RAASi up-titration was encouraged, but not mandated[2]
  - Despite the majority of patients not being at target dose, many investigators did not uptitrate RAASi even though the patients' lab values and vital signs were normal[2]

Additional Endpoint

- Mean serum K^+ was numerically lower in the SZC group compared to placebo despite a higher proportion of patients in the SZC group being at target MRA dose[2]

Safety

- The safety profile of SZC in this HFrEF patient population was consistent with that observed in other SZC clinical trials[2]
  - Low incidence of edema-related adverse events
  - No indication of increased risk of worsening of HF
  - No cases of severe hypokalemia (serum K^+ <3.0 mmol/L)

[a]Categories: No ACEi/ARB/ARNI or at less than target dose, and no MRA; ACEi/ARB/ARNI at target dose, and no MRA; MRA at less than target dose (below 50 mg daily; irrespective of ACEi, ARB or ARNI dose); MRA at target dose of 50 mg daily (irrespective of ACEi, ARB or ARNI dose).[1,2]

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

1. Study NCT03532009. ClinicalTrials.gov website; 2. In House Data, AstraZeneca Pharmaceuticals LP. CSR D9484C00001.

Summary

In cardiorenal patients:

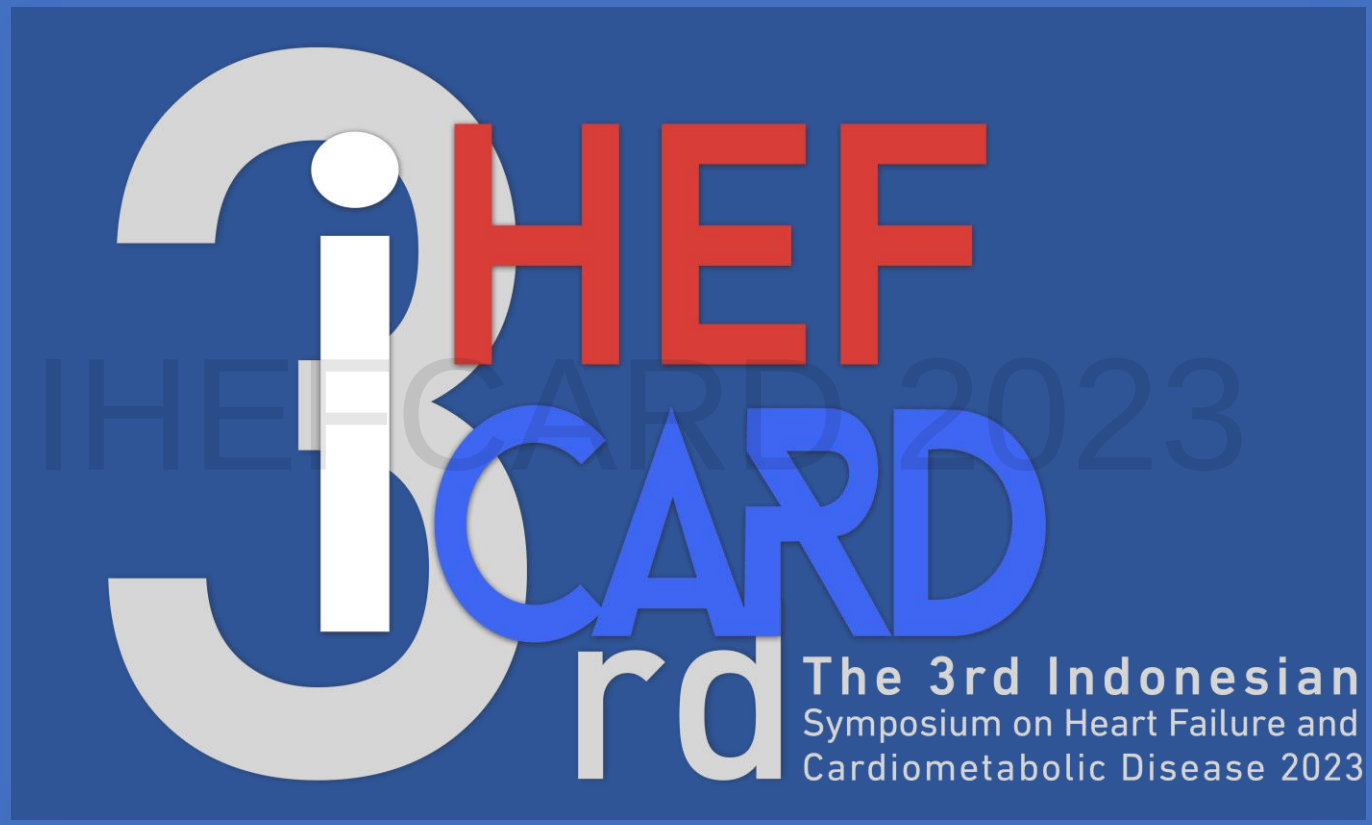
- HK is an **ongoing threat**
- HK is associated with **increased mortality and hospitalizations**

Guidelines recommend RAASi for patients with CKD and HF

- **Treat HK** to enable patients to remain on optimized RAASi
- **Discontinue RAASi as last resort**

Treatment with **SZC**:

- **Rapid and sustained K^+ reduction** for up to 1 year across all patients subgroups, including those on RAASi therapy
- Enabled patients to **continue RAASi dosing**
- **Reduced hospitalizations**
- **Generally, well tolerated**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Cardiometabolic Disease 2023