5th iHEF CARD

The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Indonesian Working Group on Heart Failure and Cardiometabolic Disease

World Heart Failure Society

HEART FAILURE SOCIETY (SINGAPORE)

Optimizing GDMT in HF: Advanced Therapeutics for Managing Heart Rate and Hyperkalemia

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June, 12-14 2025

Sheraton Grand Jakarta Gandaria City, Jakarta, Indonesia

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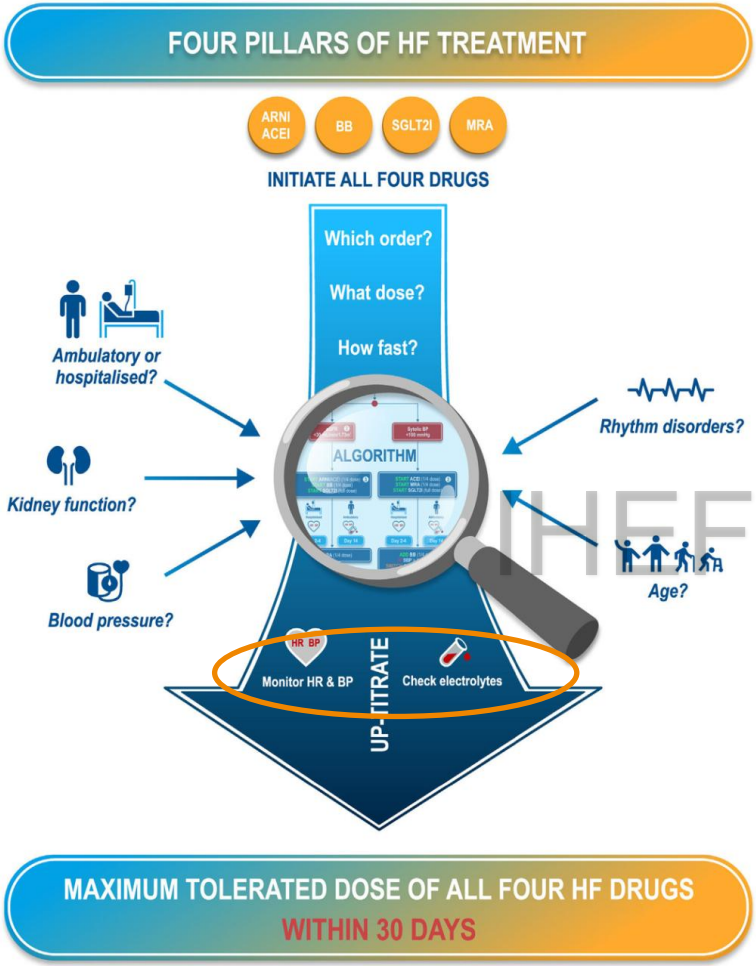
Disclosures

- This lecture has received financial support from

PT. Astra Zeneca

- I have the following financial relationship to disclose :

  Speaker honoraria from : Boehringer Ingelheim, Novartis, Astra Zeneca, Otsuka, Servier, Pfizer, Darya Varia, Menarini, Merc, Zuellig Pharma



Optimizing GDMT in HFrEF

	Beta-blocker	Mineralocorticoid receptor blocker	Neprilysin inhibitor	Inhibitor of renin–angiotensin system
Status I Receiving treatment consistent with strategy described in the landmark trial demonstrating a survival benefit	In sinus rhythm and receiving a trial-proven beta-blocker at target doses (carvedilol 25 mg twice daily, metoprolol succinate 200 mg once daily, or bisoprolol 10 mg daily)	Receiving spironolactone or eplerenone at target doses, (spironolactone ≥25 mg daily or eplerenone 50 mg daily)	Receiving target doses of sacubitril/valsartan (97/103 mg twice daily)	Receiving sacubitril/valsartan
	In sinus rhythm and receiving subtarget doses of a trial-proven beta-blocker; was prescribed higher doses, but these could not be maintained because of documented clinically relevant bradycardia or intolerable drug-related symptoms, which persisted despite adjustment of other medications or In atrial fibrillation or atrial flutter and is receiving carvedilol, metoprolol succinate, or bisoprolol	Receiving spironolactone or eplerenone at subtarget doses; was prescribed higher doses, but these could not be maintained because of documented serum K^+ ≥5.5 mmol/L or intolerable drug-related adverse effects, which persisted despite adjustment of other medications	Receiving subtarget doses of sacubitril/valsartan; was prescribed higher doses, but these could not be maintained because of documented symptomatic hypotension, doubling of serum creatinine, serum K^+ ≥5.5 mmol/L, or intolerable drug-related adverse effects, which persisted despite adjustment of other medications	Receiving enalapril ≥10 mg twice daily or equivalent or Receiving candesartan 32 mg daily or valsartan 160 mg twice daily or Receiving subtarget doses of ACE inhibitor, candesartan or valsartan; was prescribed higher doses, but these could not be maintained because of documented symptomatic hypotension, doubling of serum creatinine, serum K^+ ≥5.5 mmol/L, or intolerable drug-related symptoms, which persisted despite adjustment of other medications

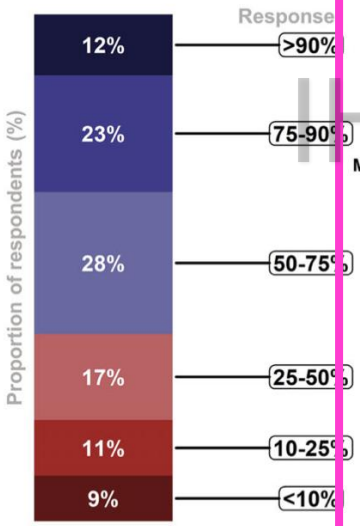
Girerd N, et al.Rev Esp Cardiol.2023
Packer M, et al. Eur Heart J.2020

Physician perceptions, attitudes, and strategies towards implementing GDMT in HFrEF

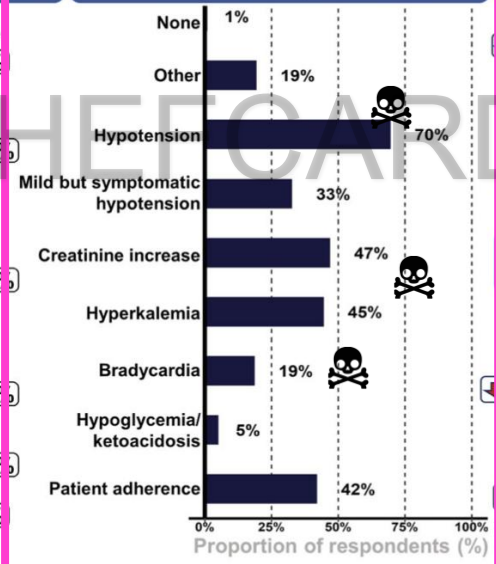
An international survey study from the HFA of the ESC

26-question survey | 432 respondents | 91 countries

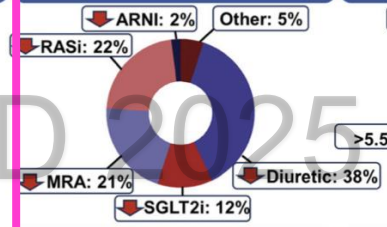
What proportion of HFrEF patients are treated with quadruple therapy?



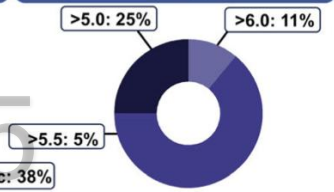
What clinical barriers to implementation are of major importance?



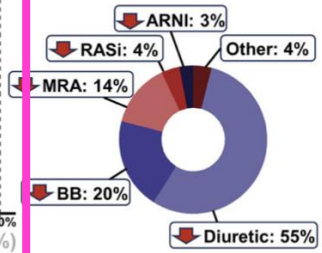
First strategy to manage creatinine increase



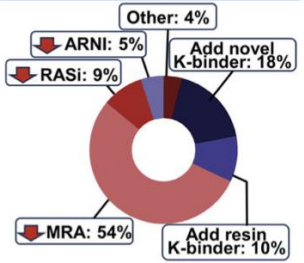
K-level that triggers change in therapy



First strategy to manage hypotension



First strategy to manage hyperkalemia



Savarese G, et al.
Eur Heart J.2024

HR in HFrEF: Prognostic and Therapeutic Target

Association of Heart Rate and Outcomes in a Broad Spectrum of Patients With Chronic Heart Failure

CME

Results From the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) Program

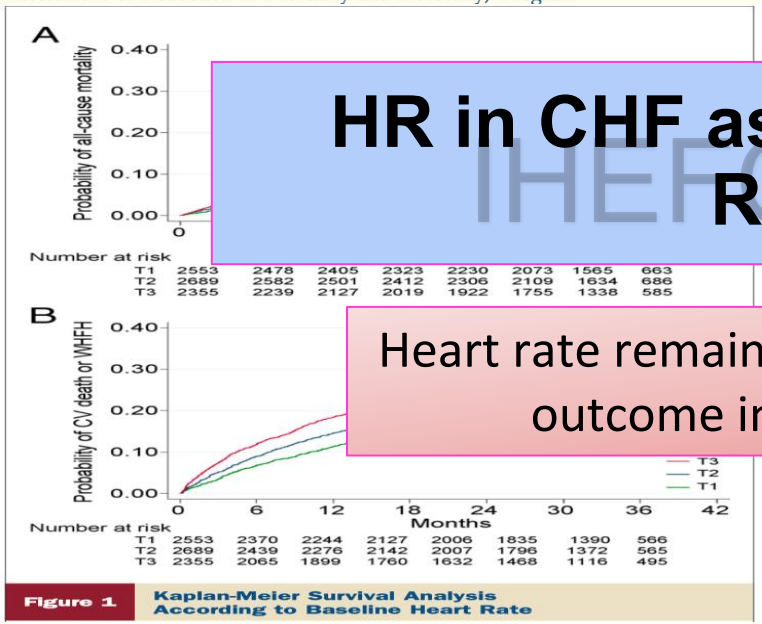
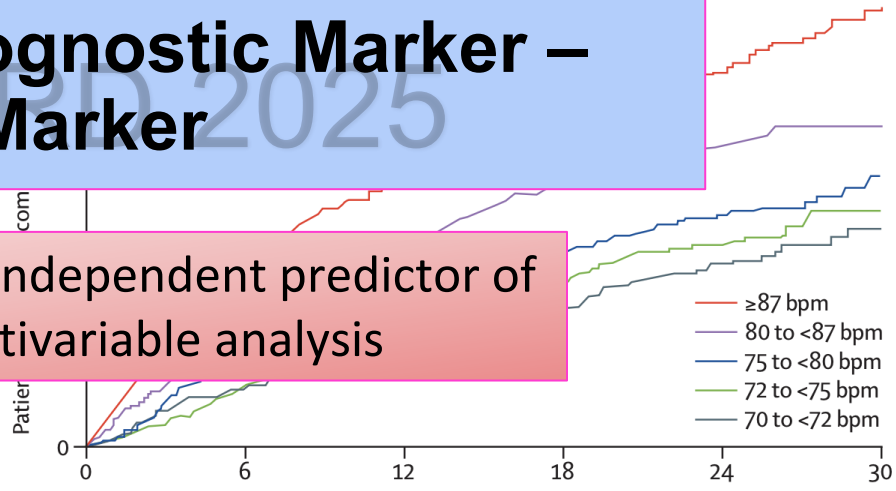


Figure 1 Kaplan-Meier Survival Analysis According to Baseline Heart Rate

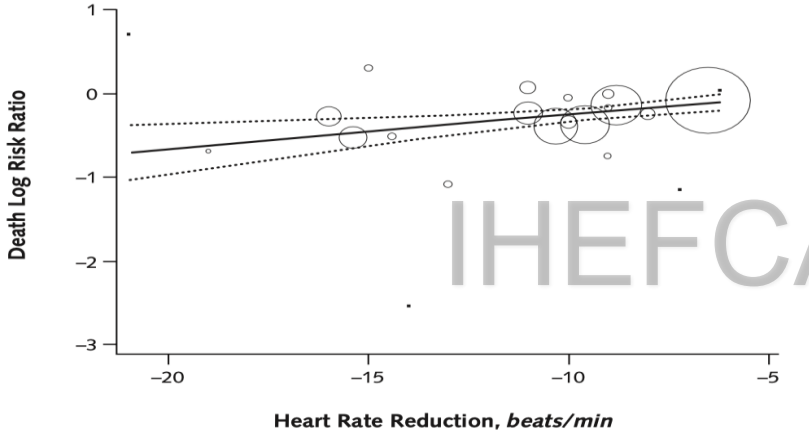
SHIFT
Systolic Heart failure treatment with the If inhibitor ivabradine Trial



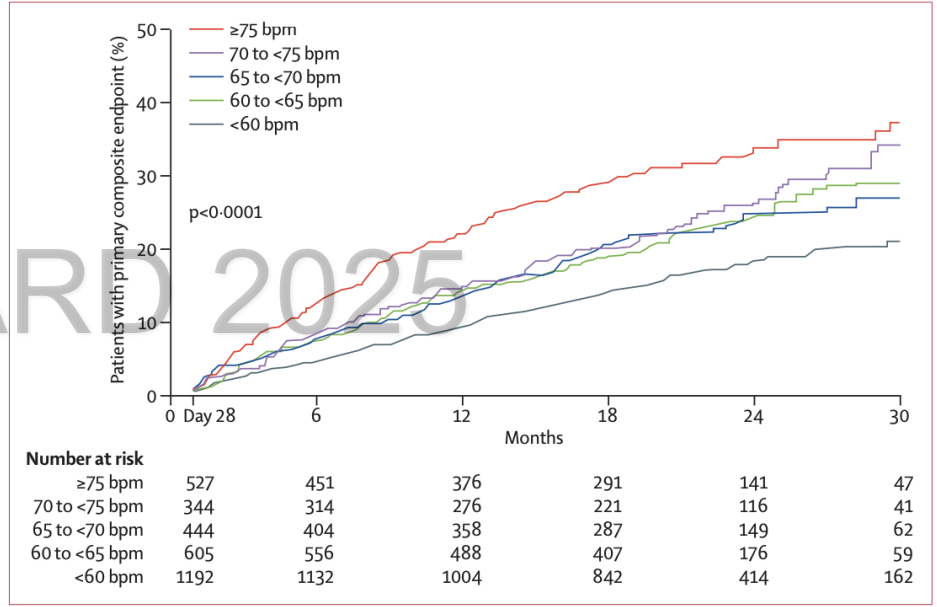
HR in CHF as Prognostic Marker – Risk Marker

Heart rate remained an independent predictor of outcome in a multivariable analysis

HR in HFrEF: Prognostic and Therapeutic Target



The mortality logarithm of relative risk is plotted against the reduction in heart rate. Circles are the observed estimates; size is based on the inverse of the SE of each trial. The 3 lines are the fitted and the upper and lower bounds of the 95% CIs.



Number at risk						
≥75 bpm	527	451	376	291	141	47
70 to <75 bpm	344	314	276	221	116	41
65 to <70 bpm	444	404	358	287	149	62
60 to <65 bpm	605	556	488	407	176	59
<60 bpm	1192	1132	1004	842	414	162

HR is a risk factors – therapeutic target:

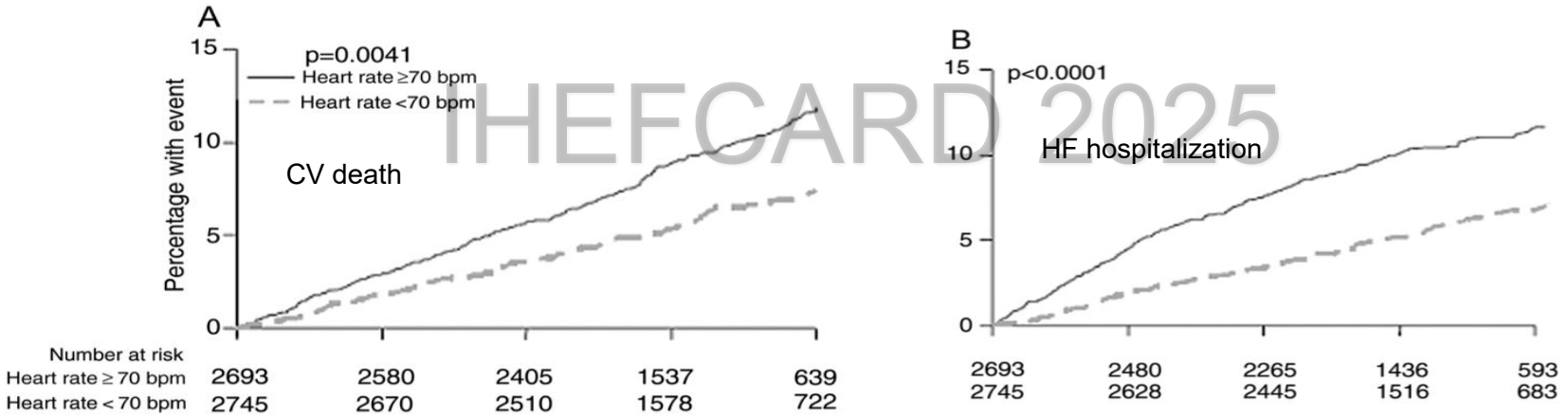
For every reduction in heart rate of 5 beats/min, the relative risk for death decreased by 45%

McAlister F, et al. Ann Intern Med.2009

Target HR in HFrEF

Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial

Michael Böhm, Karl Swedberg, Michel Komajda, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators



HF drugs with heart rate-lowering effects in CHF

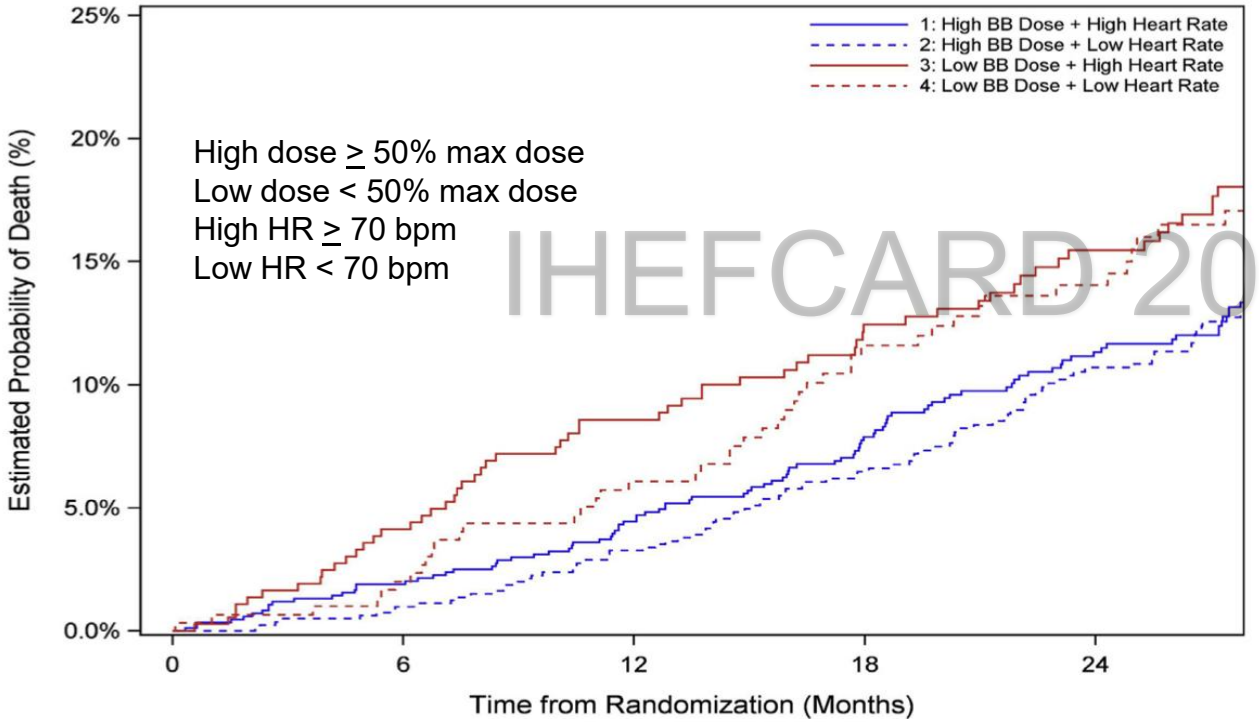
Drug		Mechanism of action	HF indication
Beta-blockers	IA	Blocks adrenergic activity; slows sinus rate and prolongs AV conduction.	HF-rEF with sinus rhythm or AF; HF-pEF with AF
Ivabradine	IIA	Selective inhibi current (I slows sinu	
Digoxin		Increases vag inhibits sy slows sinu	
Verapamil		Blocks high v slows sinu	
Amiodarone		Blocks potas antiadrene slows sinu	

BB effect beyond HR :

- Block the activity of endogenous catecholamines → reduce adrenergic tone, slowing HR in sinus rhythm (negative chronotropic effect)
- Reduction in free-fatty acid use
- Reduced apoptosis of cardiac myocytes
- Antioxidant and anti-endothelin effects
- Improve cardiac function and reduce CV hospitalizations, sudden death, and overall mortality

Dobre D, et al.Eur Heart J.2014

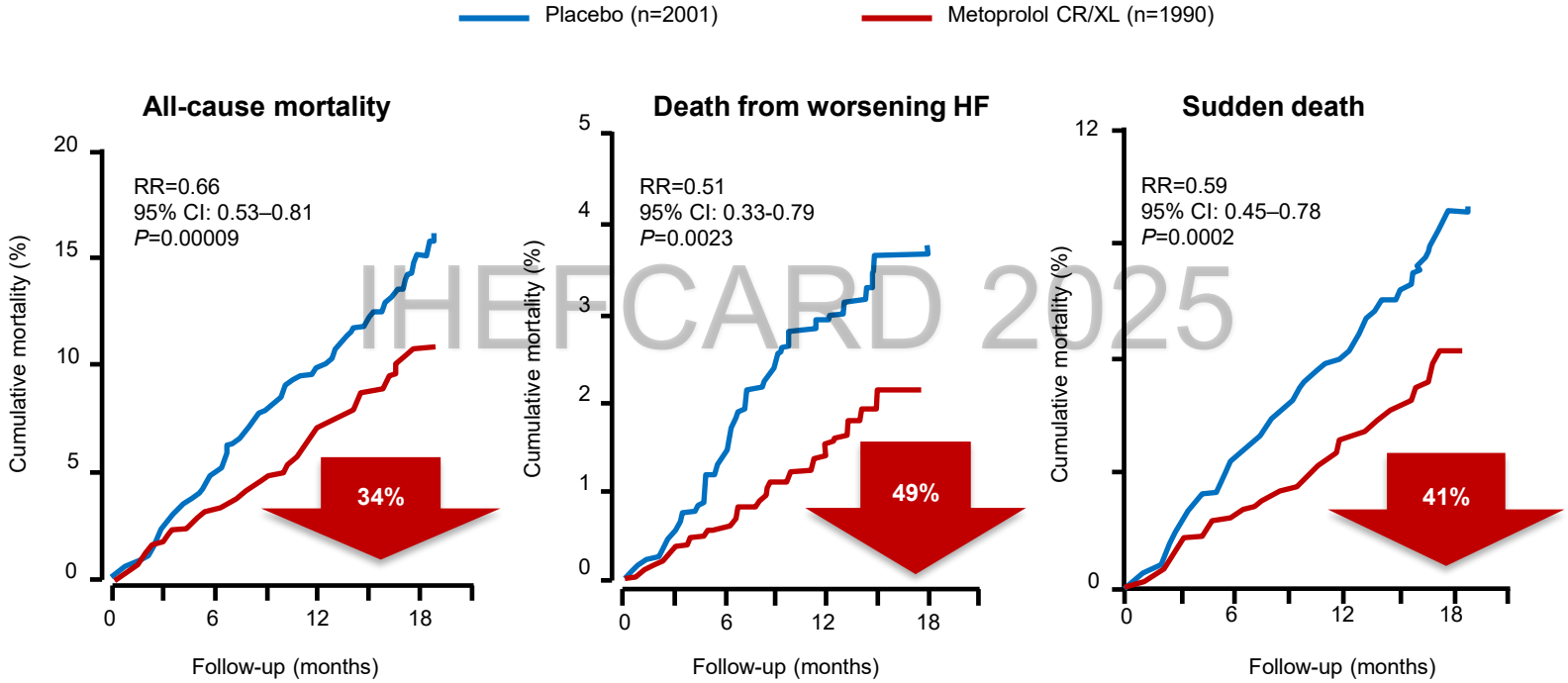
Optimizing HF therapy along with managing HR



Beta- blocker use associated with a lower risk of death but did not change the association between heart rate and mortality (p for interaction = 0.55)

Fiuzat M, et al.J Am Coll Cardiol.2016
Castagno D, et al.J Am Coll Cardiol.2012

MERIT-HF: Metoprolol Succinate (CR/XL) Significantly Reduced All-Cause Mortality, Death from Worsening HF and Sudden Death



Deedwania PC, et al. Eur Heart J. 2004;25(15):1300-9

MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-2007.

Evidence based BB for HFrEF Therapy

ESC 2021

Beta-blockers	Starting dose	Target dose
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*
Metoprolol succinate (CR/XL)	12.5-25 mg *o.d.*	200 mg *o.d.*
Nebivolol*	1.25 mg *o.d.*	10 mg *o.d.*

*Indicates a treatment **not shown to reduce CV or all-cause mortality** in patients with heart failure (or shown to be non-inferior to a treatment that does).

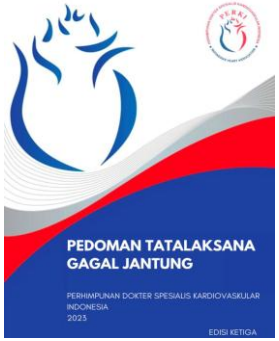
McDonagh TA, Metra M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur H Journal (2021) 00, 1-128

Only Bisoprolol, Carvedilol, and Metoprolol Succinate are indicated in HFrEF to reduce CV/all-cause mortality.

2022 AHA/ACC/HFSA Heart Failure Guideline: recommendations for B-blockers in HFrEF

COR	LOE	RECOMMENDATION
1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations (1-3).
Value Statement: High Value (A)		2. In patients with HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value (4-8).

Heidenreich et al. AHA/ACC/HFSA Heart Failure Guideline JACC VOL. 79, NO. 17, MAY 3, 2022:e263–e421e264



Indonesian Journal of Cardiology
Indonesian J Cardiol 2024:45:68-103
pISSN: 2830-3105 / eISSN: 2964-7304
doi: 10.30701/ijc.1671

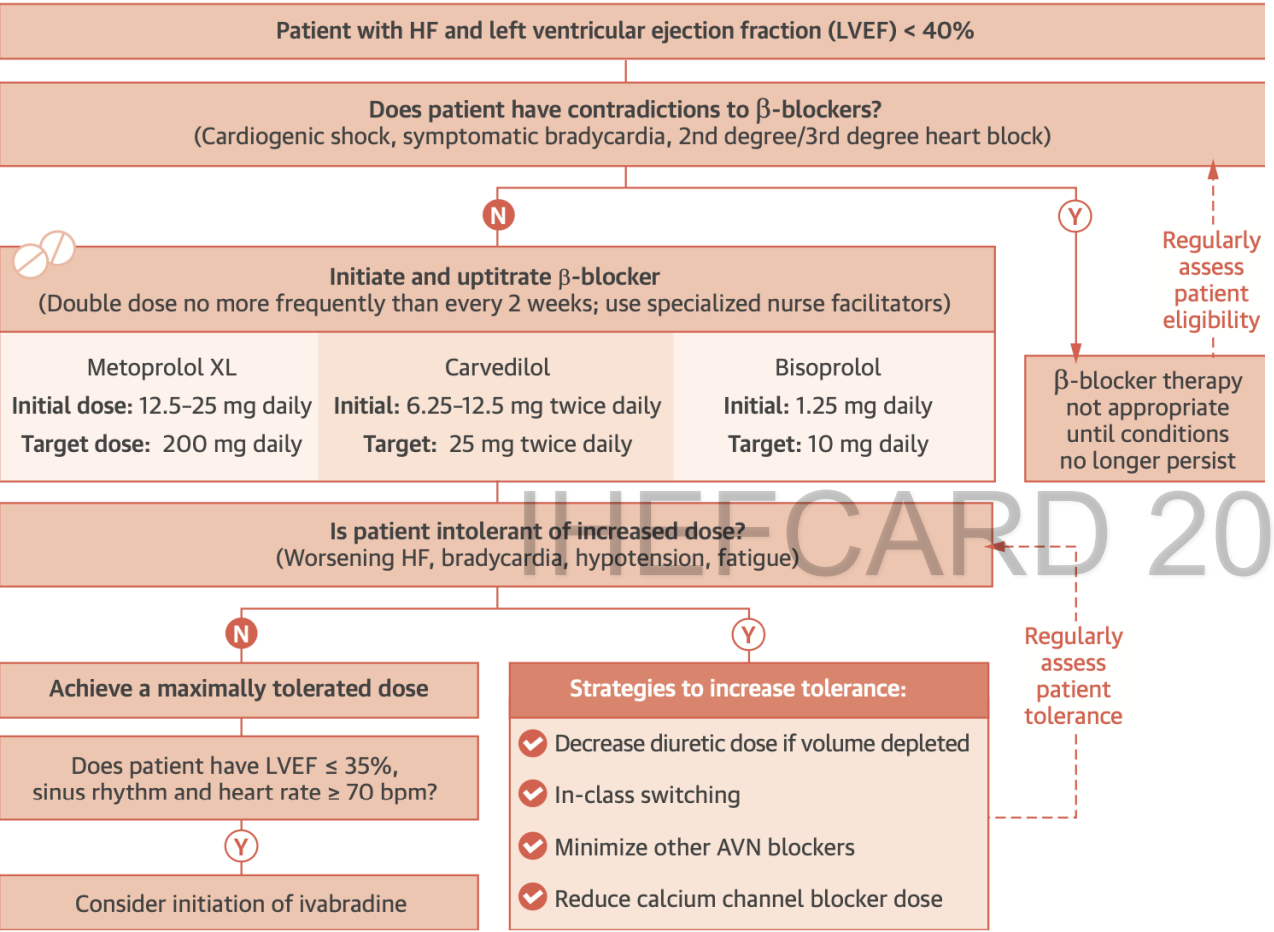
Guideline

2023 Indonesian Guidelines for Heart Failure Treatment: Working Group on Heart Failure and Cardiometabolic Diseases, Indonesian Heart Association

Dian Yaniarti Hasanah,[1] Edrian Zulkarnain,[2] Habibie Arifianto,[3] Hawani Sasmaya Prameswari,[4] Leonardo Paskah Suciadi,[5] Paskariatne Probo Dewi Yamin,[6] Rarsari Soerarso,[1] Siti Elkana Nauli,[7] Vebiona Kartini Prima Putri,[8] Wahyu Aditya Soedarsono,[6] Yuke Sarastri.[9]

Rekomendasi	COR	LOE
ACE-I direkomendasikan untuk semua pasien gagal jantung HfrEF untuk mengurangi rawat ulang akibat perburukan gagal jantung, dan meningkatkan angka kesintasan pasien.	I	A
Penyekat-*β* direkomendasikan untuk semua pasien gagal jantung HfrEF yang stabil untuk mengurangi perawatan rumah sakit karena perburukan gagal jantung, dan menurunkan mortalitas	I	A

Penyekat-*β*		
Bisoprolol	1.25 (1 kali sehari)	10 (1 kali sehari)
Carvedilol	3.125 (2 kali sehari)	25 (2 kali sehari)
Metoprolol	12.5-25 (1 kali sehari)	200 (1 kali sehari)
Nebivolol	1.25 (1 kali sehari)	10 (1 kali sehari)



Bhatt, A.S. et al. J Am Coll Cardiol. 2017;69(20):2542-50.

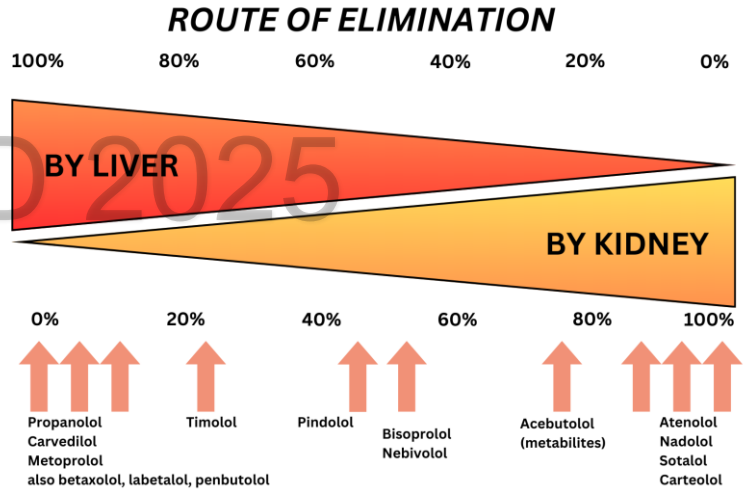
- Synchronize between targeting the dose and targeting the HR → always try to optimize dose while monitoring HR and at least achieve target HR (55-65 bpm)
- Individualized steps depend on patient tolerability

Heterogeneity Within the β-blocker Class

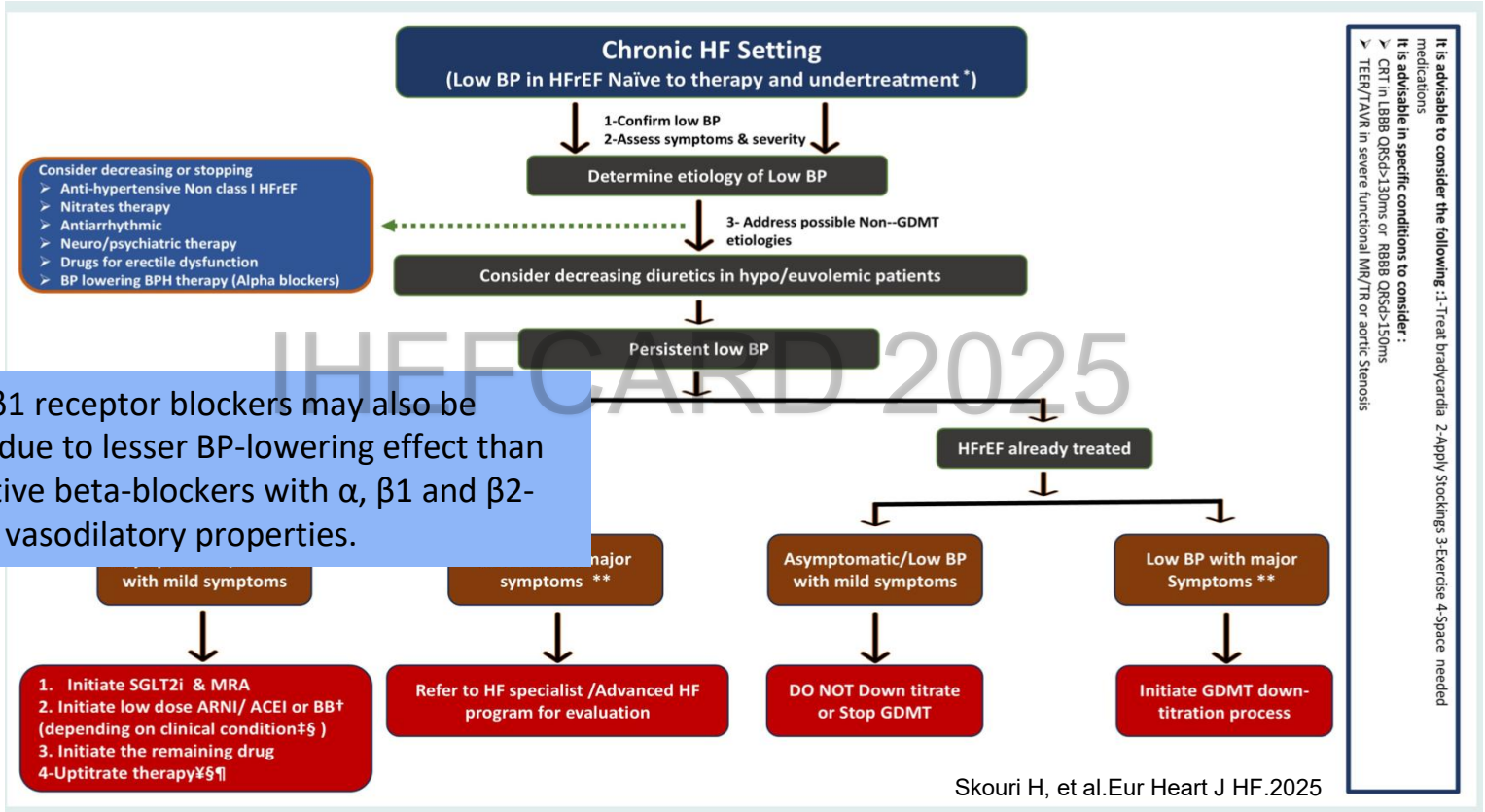
TABLE 1 Pharmacologic Properties of Commonly Prescribed β-Blockers

Drug	β1/β2 Selectivity (Cardio-Selectivity)	ISA	Half-Life	Additional Properties
Second generation				
Bisoprolol	++	0	9-12	
Metoprolol	++	0	3-7	
Atenolol	+	0	6-9	
Third generation				
Carvedilol	0	0	7-10	α1-receptor inhibition mediated vasodilation
Nebivolol	+++	0	8-27	L-arginine/nitric oxide mediated vasodilation

Adapted with permission from Poirier and Tobe (25).
+ = relatively higher affinity for β1 versus β2 receptors.

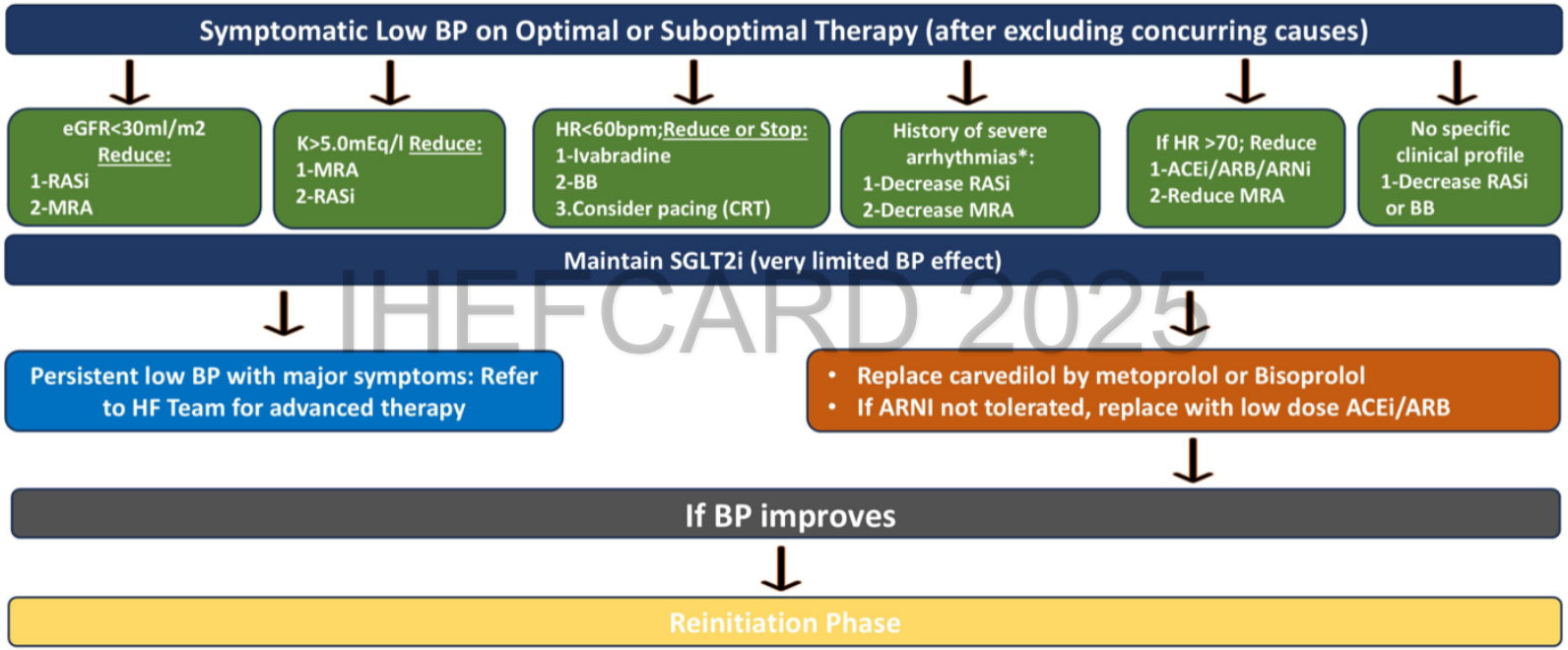


Joseph P, et al.J Am Coll Cardiol.2019



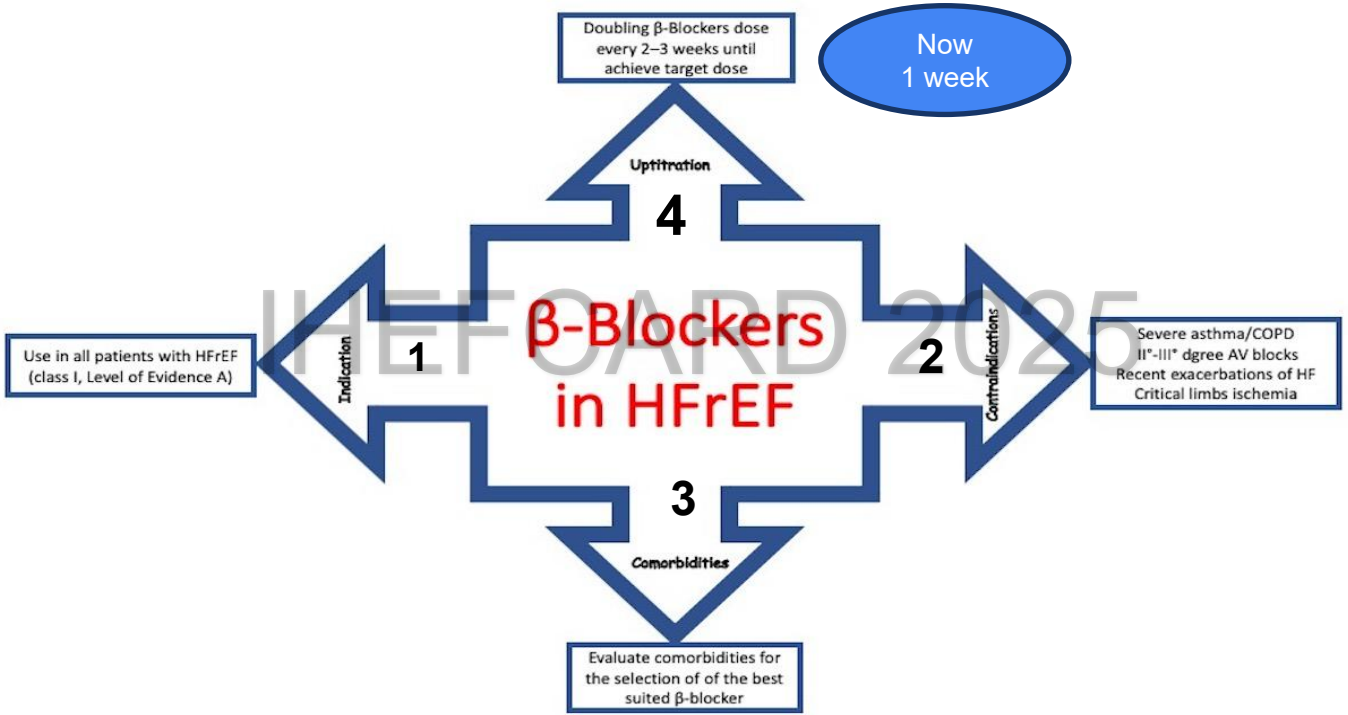
Selective β1 receptor blockers may also be preferred due to lesser BP-lowering effect than non-selective beta-blockers with α, β1 and β2-blocker or vasodilatory properties.

Skouri H, et al.Eur Heart J HF.2025



Skouri H, et al.Eur Heart J HF.2025

Key Messages :
Strategy in choosing BB in HFrEF



Male, 34 y.o

- Consult by nephrologist with SOB
- DOE since 1 month ago despite HD
- Routinely HD 2x a week

D/ Hypertensive CMP CHF (HFrEF) NYHA III
HTN
CKD e.c hypertensive nephrosclerosis, agenesis renal sin
Hyperkalemia

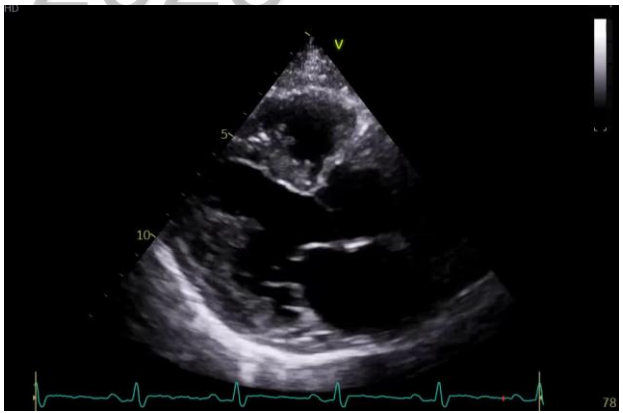
Physical examinations:

- BP 150/100 mmHg
- HR 110 bpm
- JVP HJR +
- Rales bilateral at basal lungs
- Ext bipedal edema +

Lab test :
Hb 10.5 gr/dL
Cr 5.8 mg/dL eGFR 12 ml/m/1.73 m2
K 5.6 mEq/L

ECG : ST, LVH with LV strain

Echo 10/24: reduced EF 34.4% global hypokinetic



Th/ :
- Sodium zirconium cyclosilicate (SZC) 10 gr TID continue with HD, maintenance 10 gr OD in non dialysis day
- ARNI 50 mg BD – non dialysis day
- Metoprolol XL 25 mg OD
- Refer to dietician
- Early follow up to HF clinic for K evaluation

Within 2 months manage to OMT with K in normal level (4.8 – 5.2 mEq/L)

Th/:
- ARNI 100 mg BD
- Metoprolol XL 100 mg OD
- Sodium zirconium cyclosilicate (SZC) 5 gr on 3x/week and non dialysis day

In 6 months

Echo 12/24 : Concentric LVH, dilated LA, LVEF 44.5% (Simpson's Biplane) DD gr. I, Normal RV contractility

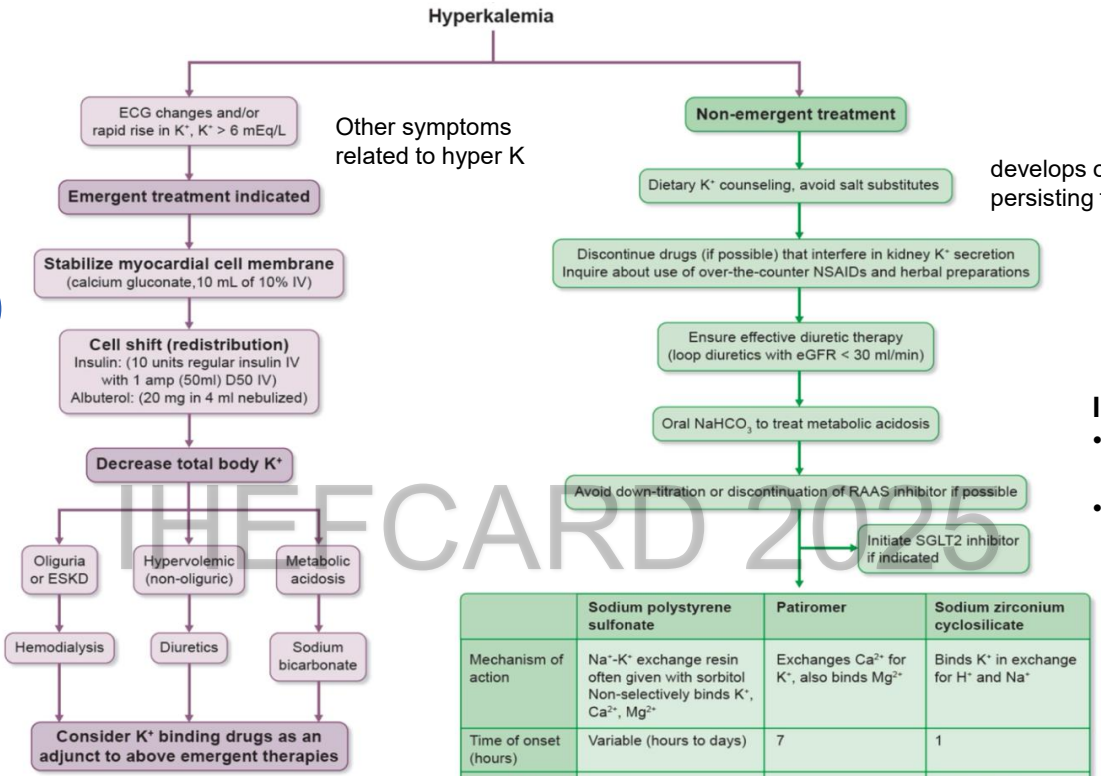
HF improved → Plan for Renal Transplantation

What can we learn from this case?
Hyperkalemia is not an obstacle for OMT

Define the severity of Hyper-K

- Mild : 5.1 – 5.5 mEq/L
- Moderate : 5.6 – 6 mEq/L
- Severe : > 6 mEq/L

Emergent (acute) or non-emergent (chronic)



Other symptoms related to hyper K

develops over a more extended period, often persisting for weeks, months

	Sodium polystyrene sulfonate	Patiromer	Sodium zirconium cyclosilicate
Mechanism of action	Na^+-K^+ exchange resin often given with sorbitol Non-selectively binds K^+, Ca^{2+}, Mg^{2+}	Exchanges Ca^{2+} for K^+, also binds Mg^{2+}	Binds K^+ in exchange for H^+ and Na^+
Time of onset (hours)	Variable (hours to days)	7	1
Binding site	Colon	Colon	Entire intestinal tract
Commonly reported adverse reactions and precautions	Diarrhea, metabolic alkalosis, hypernatremia, volume overload, rarely colonic necrosis. Must separate dose from other oral drugs by at least 3 hours	Constipation, diarrhea, flatulence, hypomagnesemia. Must separate dose from other oral drugs by at least 3 hours	Constipation,diarrhea, edema. Can increase gastric pH potentially interfering with drugs having pH-dependent solubility

In our case :

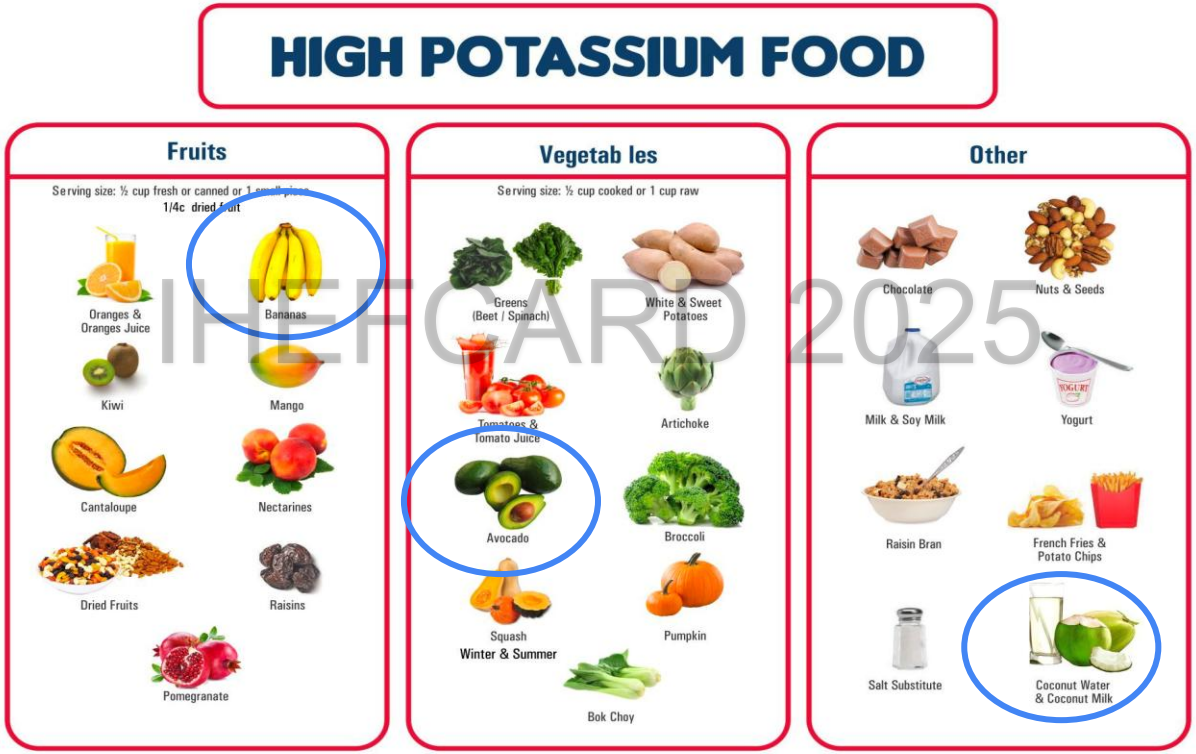
- No specific symptoms related to hyper K
- No significant ECG changes

Palmer BF, et al. Oxford University.2024

Hyper K^+ in HF

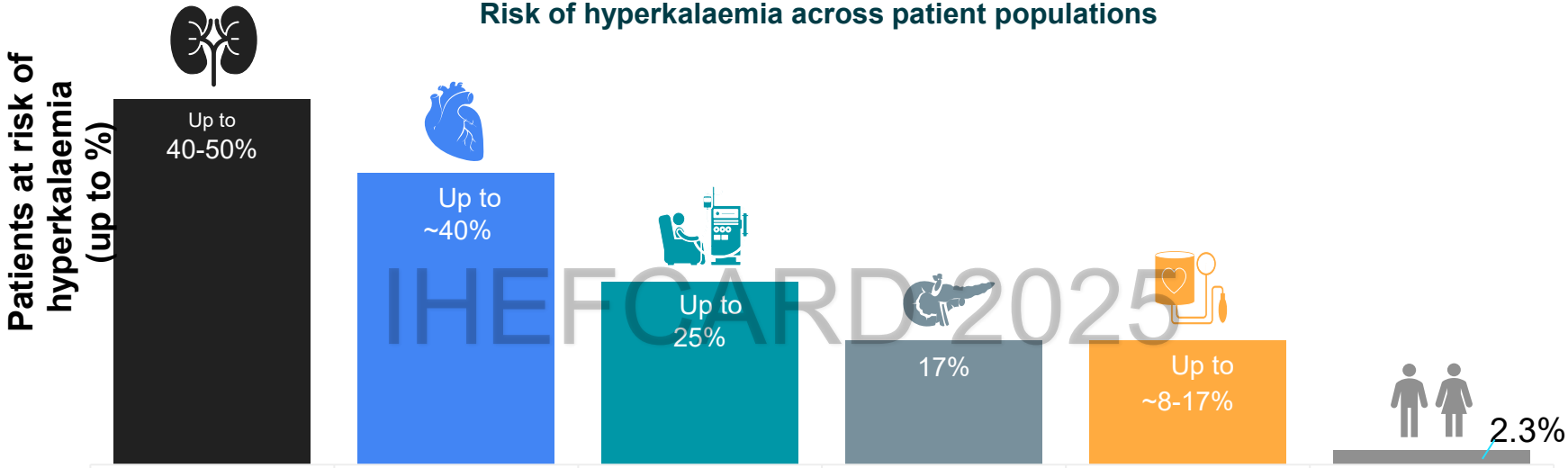
- Excess dietary intake of foods high in K
- Inherent Hyper K : DM, CKD, hormonal disorder, etc
- Treatment-related : RAASi, MRA, NSAIDs, diuretic

1. Hyper K in HF :
Excess dietary intake of foods high in K



2. Inherent Hyper K related to comorbidities in HF

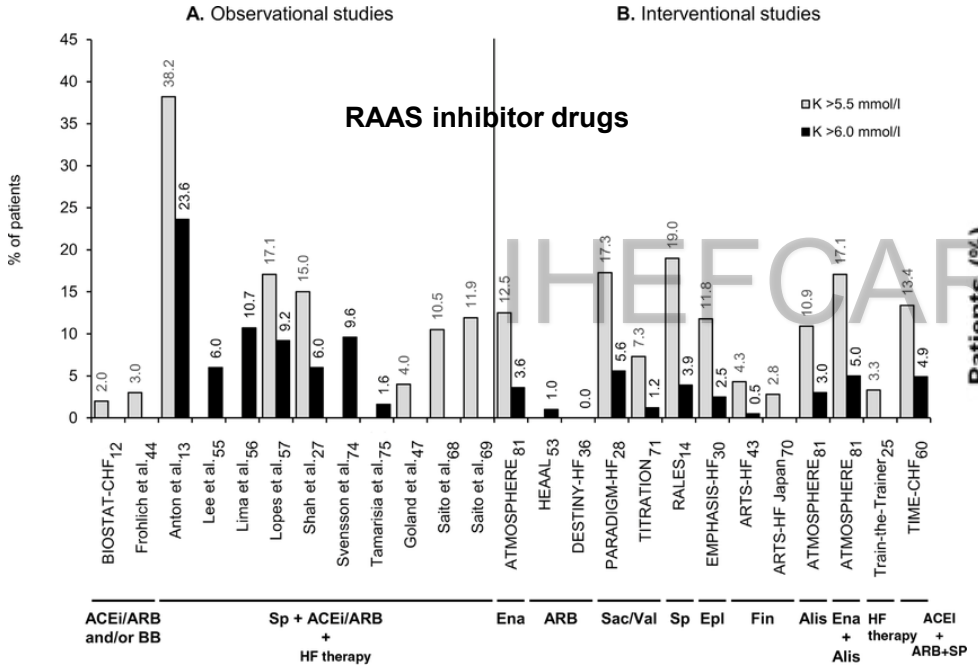
Risk of hyperkalaemia across patient populations

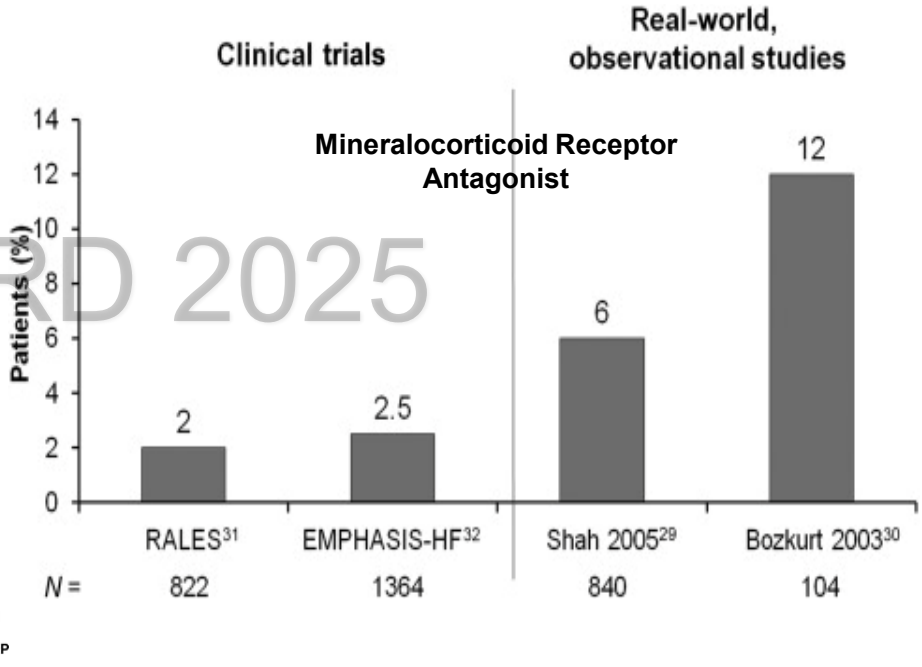


[a]Definition of hyperkalaemia varied from K+ >5.0 mmol/L to ≥5.5 mmol/L;[1,2,5] [b]NYHA Class III or IV and LVEF <35%;[2] [c]Hyperkalaemia defined as K+ >5.5 mmol/L in patients who received hemodialysis for >120 days;[3] [d]When reported, most studies in this systematic review defined hyperkalaemia as serum K+ ≥5.5 mmol/L and included patients with end stage kidney disease receiving hemodialysis TIW (mean vintage time on hemodialysis, where reported, was 42.3 months);[4] [e]Hyperkalaemia defined as persistent K+ >5.5 mmol/L (or 1 reading of K+ ≥6.0 mmol/L).[7]

1. Kovesdy CP. *Nat Rev Nephrol*. 2014;10(11):653-662. 2. Vardeny O et al. *Circ Heart Fail*. 2014;7(4):573-579. 3. Xu H, et al. Poster presented at: 54th ERA-EDTA Congress; June 3-6, 2017; Madrid, ES. 4. Bem D et al. Article and supplementary material. *Kidney Int*. 2009;30(5):448-424

3. Hyper K in HF meds study





Exclusion for low eGFR, hyper K baseline

Epstein M, et al.ISN.2016
Fonseca C, et al.Rev Port Cardiol.2020

Risk of Hyper K is independent from worsening kidney function

TABLE 3 Adverse Events According to eGFR Categories

Outcome/eGFR Category[a]	Event-Rate[b] Placebo n/N (%)	Event-Rate[b] MRA n/N (%)	OR (95% CI)	Interaction *P* for Trend[c]
Hyperkalemia				0.002
>90	52/803 (6.5)	85/865 (9.8)	1.57 (1.13-2.19)	
61-90	226/2,788 (8.1)	311/2,759 (11.3)	1.44 (0.88-2.35)	
46-60	167/1,600 (10.4)	295/1,580 (18.7)	1.97 (1.32-2.94)	
31-45	100/903 (11.1)	225/889 (25.3)	2.72 (2.02-3.67)	
≤30	27/157 (17.2)	49/162 (30.2)	2.09 (1.38-3.15)	
Worsening kidney function				0.39
>90	207/772 (26.8)	262/843 (31.1)	1.23 (0.99-1.53)	
61-90	588/2,688 (21.9)	738/2,668 (27.7)	1.37 (1.15-1.62)	
46-60	309/1,533 (20.2)	410/1,515 (27.1)	1.47 (1.28-1.68)	
31-45	180/853 (21.1)	248/851 (29.1)	1.54 (1.21-1.95)	
≤30	21/147 (14.3)	39/153 (25.5)	2.05 (1.24-3.41)	

Ferreira JP,et al.J Am Coll Cardiol HF.2022

ATHENA TRIAL : Hyper K might not be dose related

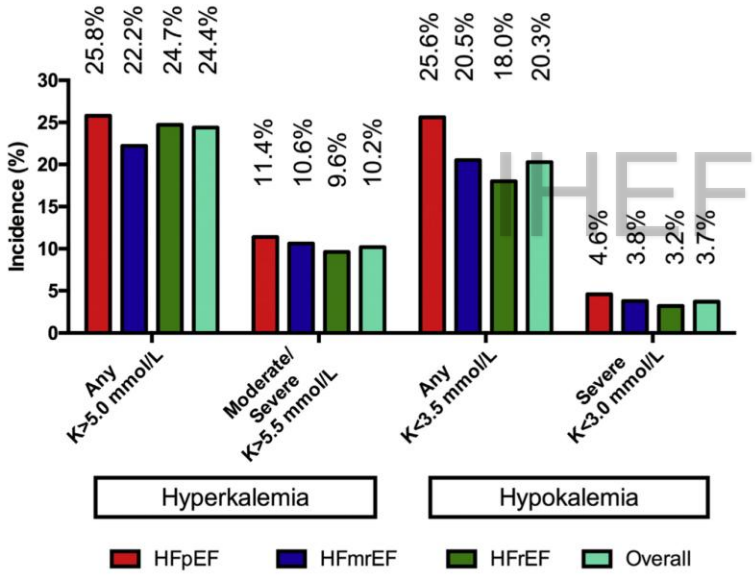
Table 3. Changes in Serum Potassium Concentration and Renal Function

Change	Median (25th-75th) Usual Care Alone	Median (25th-75th) High-Dose Spironolactone	Mean (SD) Usual Care Alone	Mean (SD) High-Dose Spironolactone	*P* Value
Change in Serum Potassium, mEq/L (to Convert to Millimoles per Liter, Multiply by 1.0)					
24-h	0.00 (−0.40 to 0.30)	0.00 (−0.30 to 0.30)	0.01 (0.56)	−0.00 (0.47)	.50
48-h	0.10 (−0.30 to 0.40)	0.10 (−0.10 to 0.40)	0.04 (0.52)	0.16 (0.46)	.02
72-h	0.20 (−0.40 to 0.55)	0.20 (−0.20 to 0.60)	0.09 (0.62)	0.22 (0.52)	.08
96-h	0.20 (−0.30 to 0.60)	0.30 (0.00 to 0.70)	0.15 (0.69)	0.31 (0.54)	.08
Change in Serum Creatinine, mg/dL (to Convert to Micromoles per Liter, Multiply by 88.4)					
24-h	0.05 (−0.05 to 0.20)	0.05 (−0.03 to 0.17)	0.07 (0.18)	0.06 (0.17)	.76
48-h	0.02 (−1.10 to 0.20)	0.10 (−0.03 to 0.02)	0.10 (0.27)	0.09 (0.20)	.67
72-h	0.08 (−0.08 to 0.22)	0.10 (−0.03 to 0.28)	0.13 (0.33)	0.12 (0.26)	.85
96-h	0.10 (−0.02 to 0.33)	0.10 (−0.05 to 0.27)	0.16 (0.30)	0.15 (0.30)	.77
Change in Estimated Glomerular Filtration Rate, mL/min/1.73 m^2					
24-h	−1.95 (−8.46 to 2.79)	−2.58 (−7.83 to 1.53)	−2.75 (9.43)	−2.54 (10.80)	.87
48-h	−1.59 (−9.65 to 3.71)	−4.12 (−8.87 to 1.89)	−3.34 (12.52)	−3.33 (11.15)	.95
72-h	−3.70 (−12.06 to 4.09)	−3.71 (−10.67 to 0.87)	−4.47 (13.37)	−4.53 (12.05)	.82
96-h	−5.53 (−13.11 to 0.79)	−4.35 (−11.06 to 1.74)	−5.56 (13.85)	−4.13 (11.58)	.56

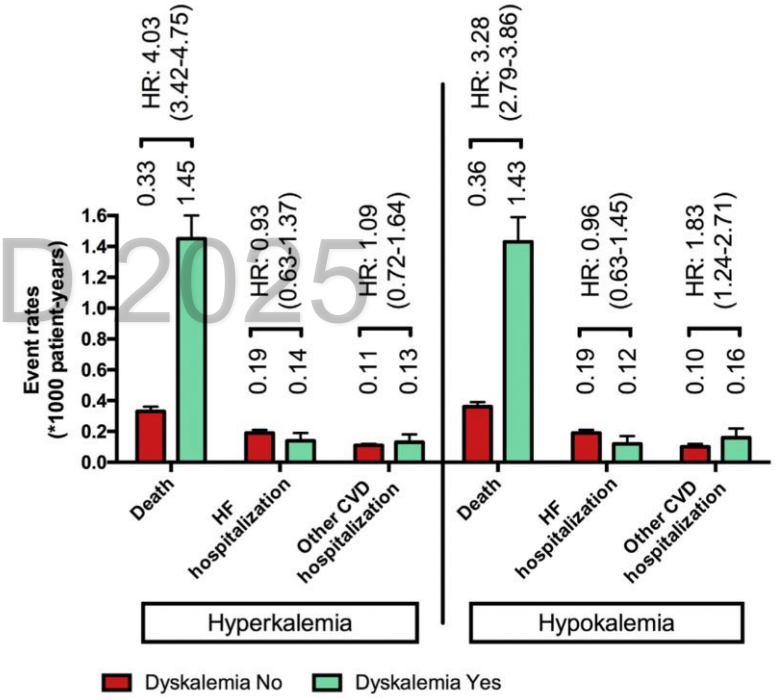
Butler J, et al.J Am Coll Cardiol HF 2016

Incidence, Predictors, and Outcome Associations of Dyskalemia in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction

Gianluigi Savarese, MD, PhD,[a,*] Hong Xu, MD,[b,*] Marco Trevisan, MSc,[b] Ulf Dahlström, MD, PhD,[c] Patrick Rossignol, MD, PhD,[d] Bertram Pitt, MD, PhD,[e] Lars H. Lund, MD, PhD,[a,†] Juan J. Carrero, PharmD, PhD[b,†]



IMPACT on HF outcome?



European Journal of Heart Failure (2018) **20**, 931–932
doi:10.1002/ejhf.1175

EDITORIAL COMMENT

Is hyperkalaemia in heart failure a risk factor or a risk marker? Implications for renin–angiotensin–aldosterone system inhibitor use

Lars H. Lund[1,2]* and Bertram Pitt[3]

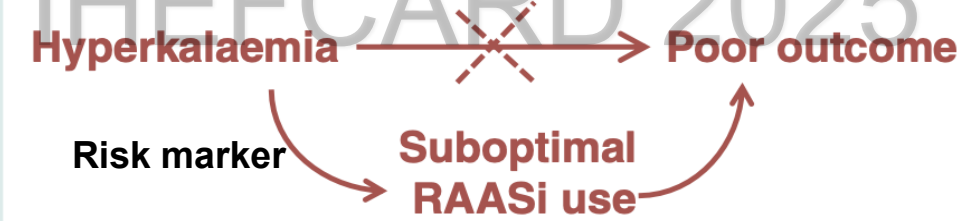
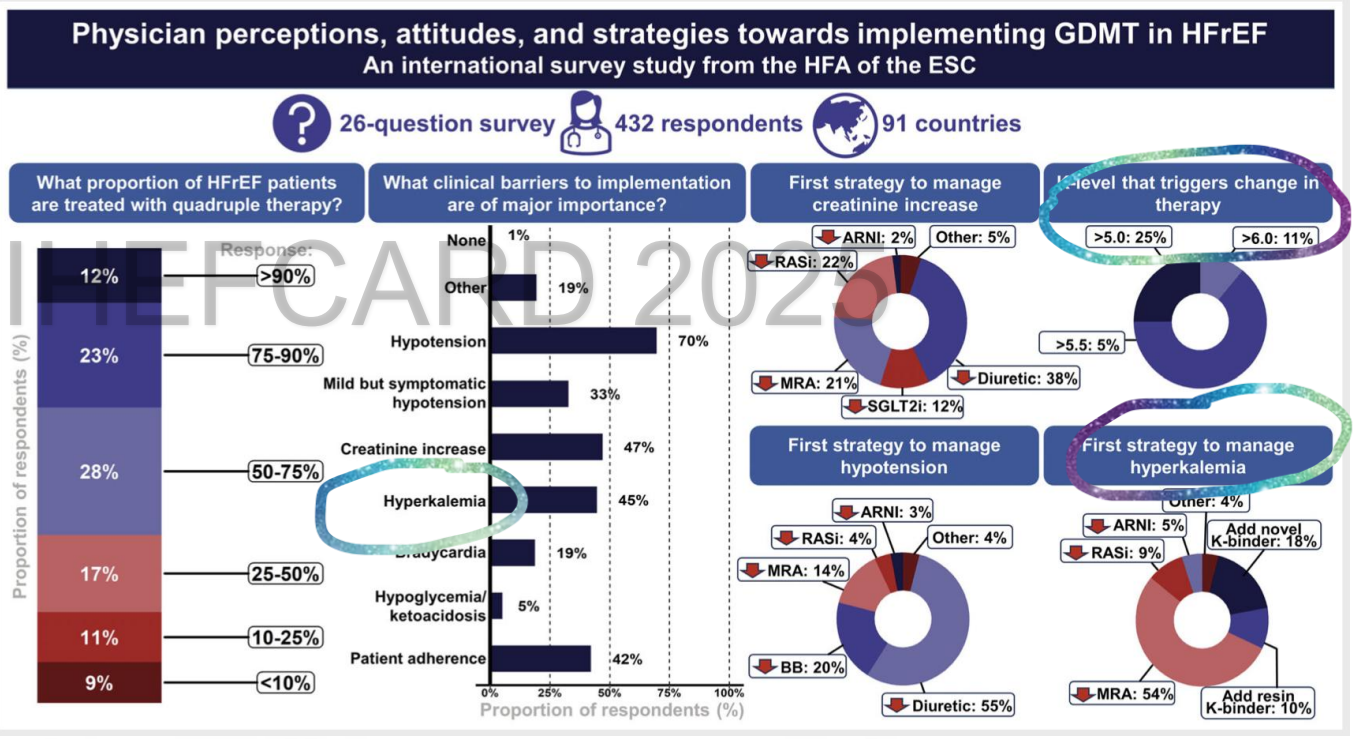


Figure 1 Hyperkalaemia is a risk marker for poor outcomes by leading to dose reduction or discontinuation of renin–angiotensin–aldosterone system inhibitors (RAASi).

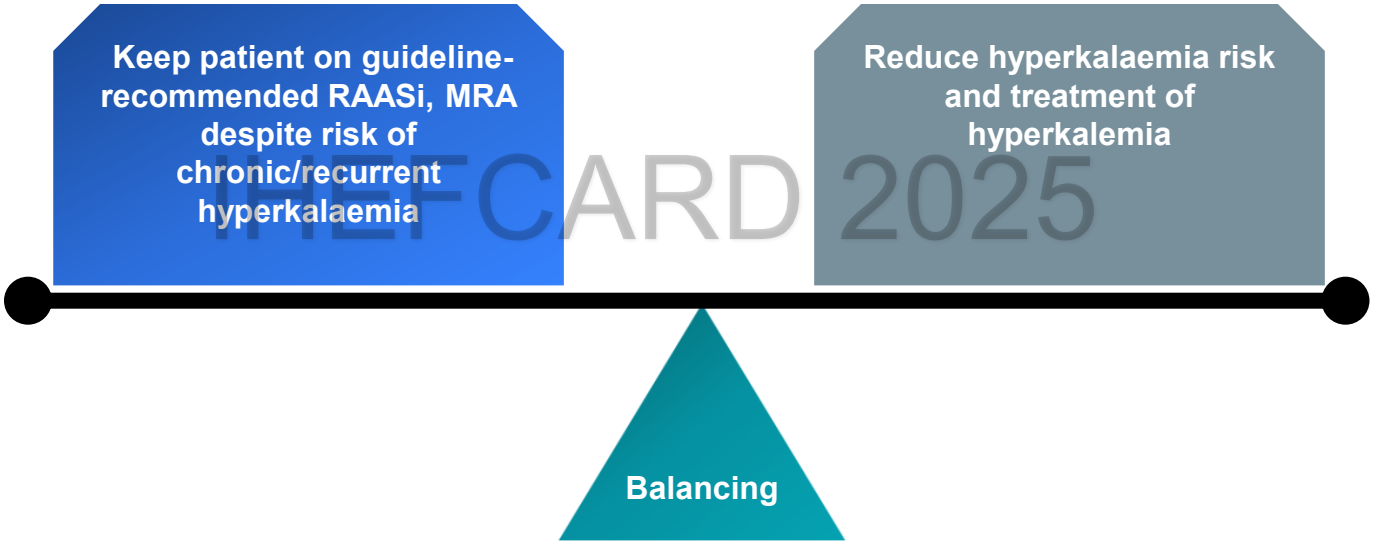
ESC European Society of Cardiology
European Journal of Heart Failure (2024) 26, 1408–1418
doi:10.1002/ejhf.3214

RESEARCH ARTICLE

Physician perceptions, attitudes, and strategies towards implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. A survey of the Heart Failure Association of the ESC and the ES for Cardiology Practice



How to win the Hyper K 'battle' in OMT HF?



Hyperkalemia treatment options with limitations

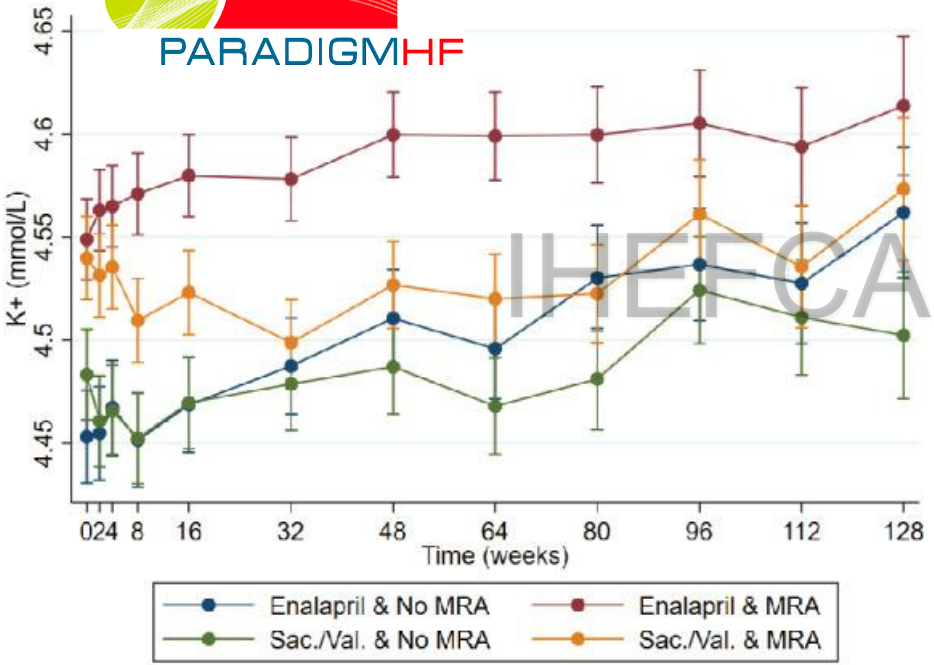
Low-K^+ diet[1]	Diuretics[1]	Traditional K^+ binders eg, SPS[1-5]	Discontinuation or dose-reduction of RAASi therapy[1]
• Difficult to adhere to • Limiting K^+-rich foods can cause constipation • Contradicts DASH diet; may worsen chronic hypertension	• Efficacy depends on residual renal function (until 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

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.

Choose The Right Treatment Combination

The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

PARADIGMHF



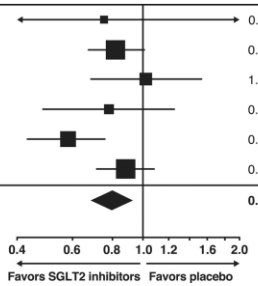
Circulation
Volume 145, Issue 19, 10 May 2022; Pages 1460-1470
https://doi.org/10.1161/CIRCULATIONAHA.121.057736

ORIGINAL RESEARCH ARTICLE

Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials

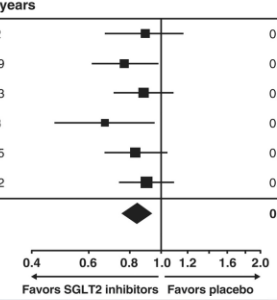
Time to first hyper K

	SGLT2 inhibitors n/N	SGLT2 inhibitors Events per 1000 patient-years	Placebo n/N	Placebo Events per 1000 patient-years	Hazard Ratio (95% CI)
CANVAS Program	8/5795	0.4	7/4347	0.6	0.75 (0.27, 2.11)
CREDENCE	169/2202	30.7	203/2199	37.4	0.82 (0.67, 1.01)
DAPA-CKD	48/1455	33.0	47/1451	32.0	1.02 (0.68, 1.54)
DECLARE-TIMI 58	30/8582	0.9	38/8578	1.1	0.78 (0.48, 1.26)
EMPA-REG OUTCOME	104/4687	7.7	88/2333	13.4	0.58 (0.43, 0.76)
VERTIS CV	243/5493	15.4	134/2745	17.7	0.88 (0.71, 1.09)
Overall (I^2=29.5%; $P_{heterogeneity}$=0.21)					**0.80 (0.68, 0.93)** P=0.004



Serious hyper K (≥ 6 mmol/L)

	SGLT2 inhibitors n/N	SGLT2 inhibitors Events per 1000 patient-years	Placebo n/N	Placebo Events per 1000 patient-years	Hazard Ratio (95% CI)
CANVAS Program	137/5795	8.2	85/4347	9.2	0.89 (0.67, 1.17)
CREDENCE	121/2202	21.6	154/2199	27.9	0.77 (0.61, 0.98)
DAPA-CKD	159/1455	56.9	179/1451	65.3	0.88 (0.71, 1.09)
DECLARE-TIMI 58	53/8582	1.6	78/8578	2.3	0.67 (0.47, 0.95)
EMPA-REG OUTCOME	216/4687	17.2	124/2333	20.5	0.83 (0.67, 1.04)
VERTIS CV	291/5493	18.7	157/2745	21.2	0.90 (0.74, 1.09)
Overall (I^2=0.0%; $P_{heterogeneity}$=0.71)					**0.84 (0.76, 0.93)** P<0.001



Add on Potassium Binder

	Traditional Potassium Binder	Novel Potassium Binder	
	Calcium polystyrene sulfonate (CPS)	Patiromer	Sodium zirconium cyclosilicate (SZC)
Mechanism	Nonspecific calcium cation-exchange resin[1]	Nonspecific cation binding in exchange for calcium[3]	Selective potassium binding in exchange for sodium and hydrogen[3]
Onset	Action may be delayed for 1 to 2 days[1]	4 to 7 hours[4]	1 hour[5]
Dosing	15 g orally 3 to 4 times daily[2] 30 g given as retention enema once daily[2]	8.4 g orally once daily (recommended starting dose)[4]	10 g orally 3 times daily for a maximum of 72 hours (starting dose)[5*] 5 g orally once daily (recommended starting maintenance dose)[5]
Indication	No RCT study	Treatment of HK in adults; there is limited data on the use in patients requiring dialysis and in patients with serum K^+ levels greater than 6.5 mmol/L[4]	Treatment of HK in adults; there is limited experience in patients with serum K^+ levels greater than 6.5 mmol/L[5]
Location		Predominantly distal colon[3]	Entire intestinal tract[3]
Adverse events	Cases of intestinal necrosis, which may be fatal, and other serious GI adverse events have been reported[2]	Hypomagnesaemia and mild to moderate GI side effects (for example, constipation)[4]	Hypokalaemia and oedema-related events[5]
Drug Interactions	Antacids, laxatives, digitalis, sorbitol, lithium, levothyroxine[2] Administer at least 3 hours before or 3 hours after other oral medications[2]	Separate by at least 3 hours from other oral medications[4]	Administer at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH–dependent bioavailability[5]

*Dose differs for patients on haemodialysis- refer to SmPC for more information.[4]
References and abbreviations in slide notes.
FDA = US Food and Drug Administration; GI = gastrointestinal; HK = hyperkalaemia; SmPC = Summary of Product Characteristics.

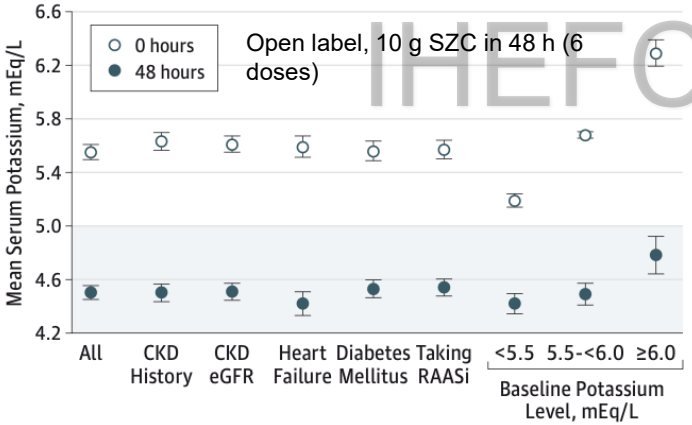
1. Resonium calcium. Prescribing Information. Sanofi-Aventis Canada.
2. Calcium resonium. Summary of product characteristics. Sanofi.
3. Garimella PS, Jaber BL. Patiromer for hyperkalemia in diabetic CKD: a new kid on the block. *Am J Kidney Dis.* 2016;67(4):545-547. doi:10.1053/j.ajkd.2016.01.001
4. Veltassa. Summary of product characteristics. Vifor.
5. Lokelma. Product Information Indonesia. 2023

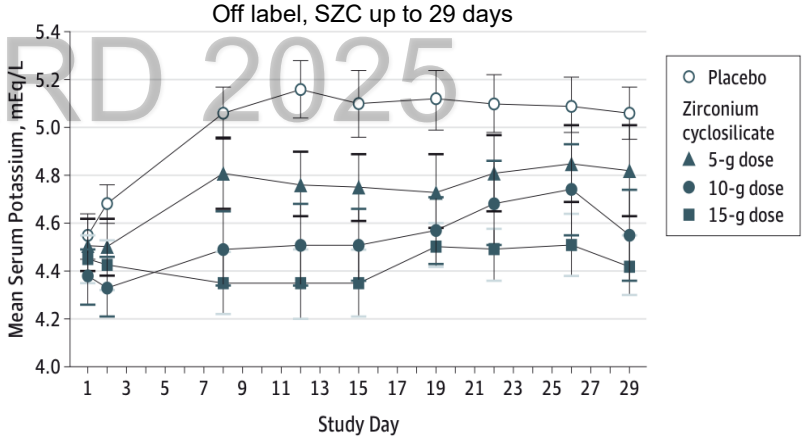
Original Investigation

Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia
The HARMONIZE Randomized Clinical Trial

Mikhail Kosiborod, MD; Henrik S. Rasmussen, MD, PhD; Philip Lavin, PhD; Wajeh Y. Qunibi, MD; Bruce Spinowitz, MD; David Packham, MD; Simon D. Roger, MD; Alex Yang, MD; Edgar Lerma, MD; Bhupinder Singh, MD

Hyper K ≥ 5.1 mEq/L in DM, HF, CKD, RAASi
No situation that require urgent management (arrhythmias, potassium >6.2 mEq/L)

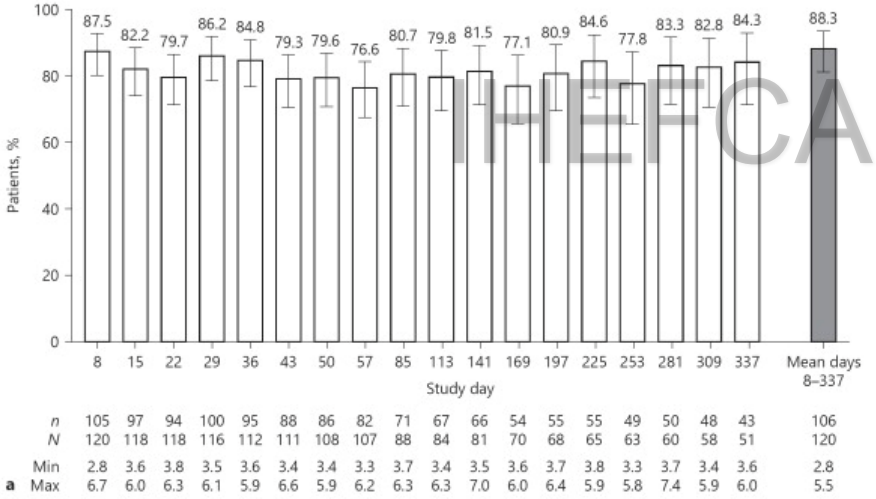




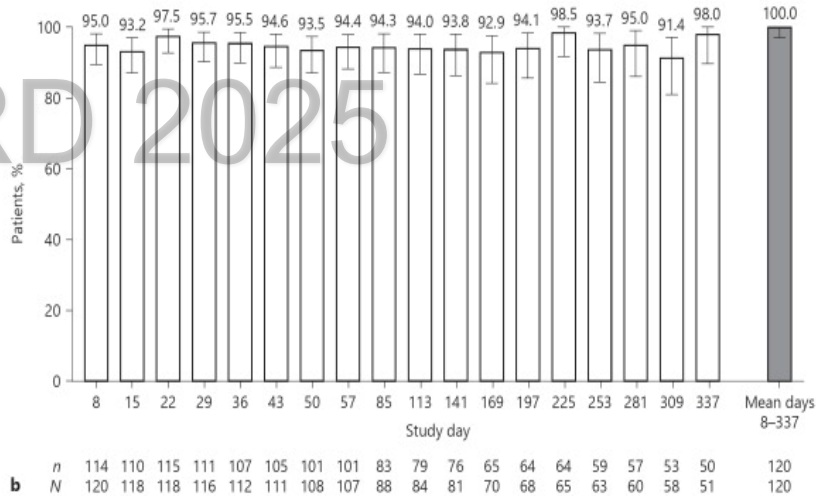
Efficacy and Safety of Sodium Zirconium Cyclosilicate for Treatment of Hyperkalemia: An 11-Month Open-Label Extension of HARMONIZE

once-daily SZC 5–10 g for ≤337 days

≤ 5.1 mEq/L



≤ 5.5 mEq/L

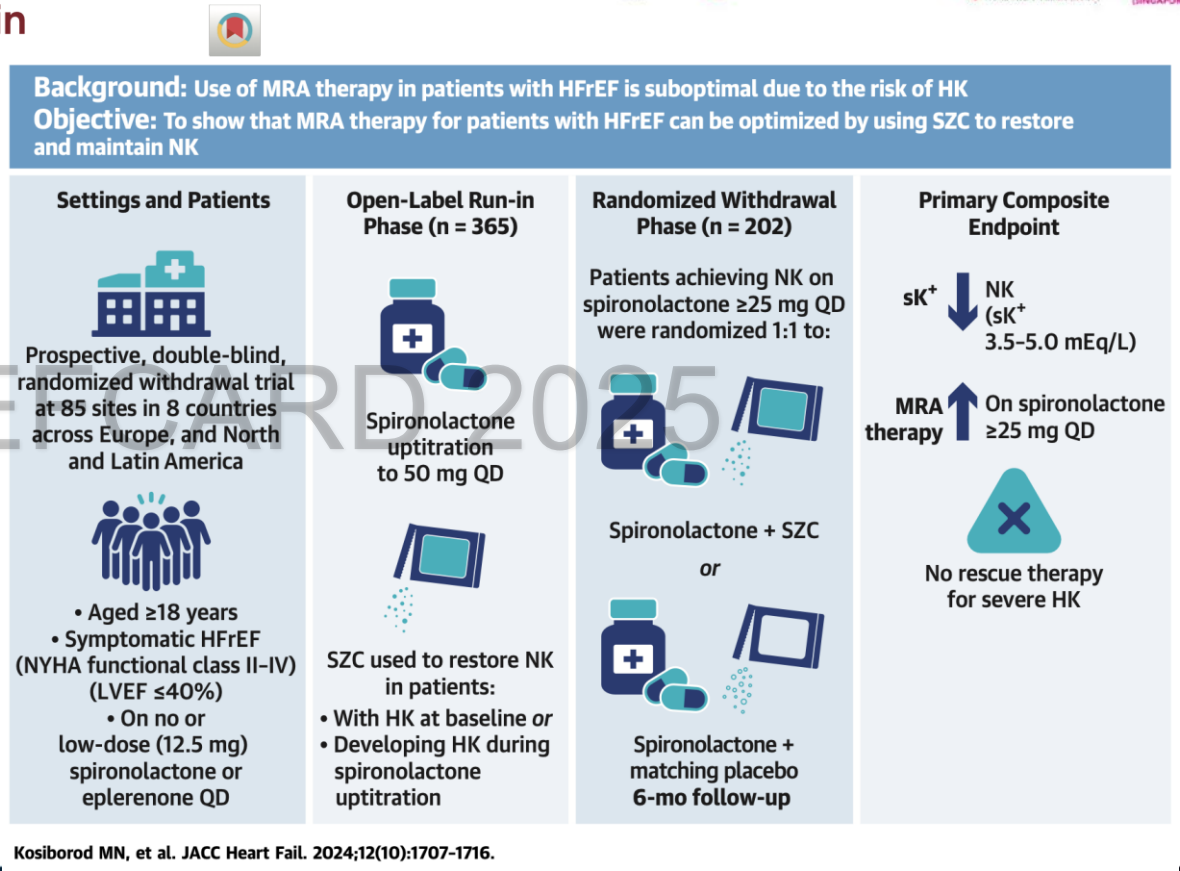


Roger SD et al. Am J Nephrol 2019.

Sodium Zirconium Cyclosilicate in HFrEF and Hyperkalemia

REALIZE-K Design and Baseline Characteristics

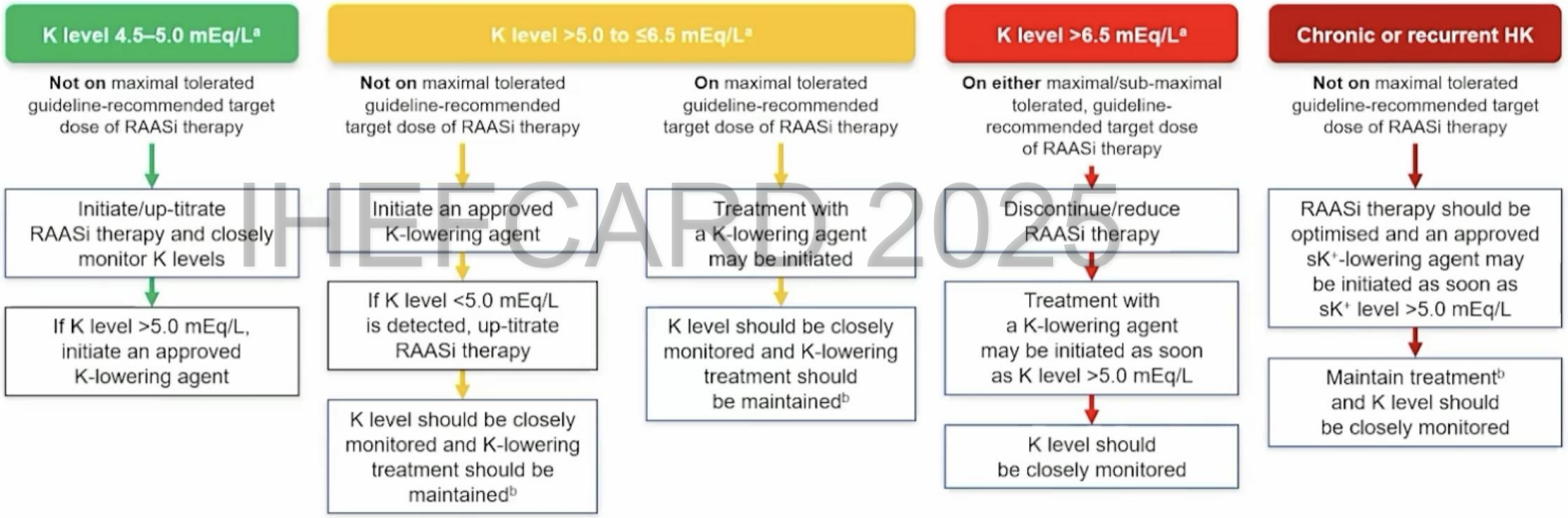
At 6 months, **71% of patients who received SZC achieved the primary endpoint of normokalemia on spironolactone ≥ 25 mg/daily** without rescue therapy for hyperkalemia compared with 36% of those on placebo ($P < 0.001$)



Kosiborod MN, et al. JACC Heart Fail. 2024;12(10):1707-1716.

A European perspective from HF community

Management of HK in patients with CVD and indication for RAASi therapy



a1 mEq/L= 1 mmol/L; bUnless another aetiology for hyperkalaemia is identified
CVD, cardiovascular disease; HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor; sK+, serum potassium
Rosano G, et al. *Eur Heart J Cardiovasc Pharmacother* 2018;4:180–188

Key Message(s)

- Hyper K may become one of the obstacle to OMT but it's not the end of the road to OMT
- Novel PB agents including SZC should be consider for the following conditions in HF patients undergoing or on OMT :
  - Lowering K level in hyper K
  - Maintaining K level and preventing recurrent hyper K
  - Preventing hyper K in HF patient at high risk of hyper K
- SZC generally well tolerated in HF patients for long term use
- Refer to PPK Hyper K from Indonesian HF Working Group

THANK YOU