Practical experience and model for optimizing RAASi-based therapy

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Breaking barriers in guideline-based RAASi therapy: Solving issues with hyperkalemia

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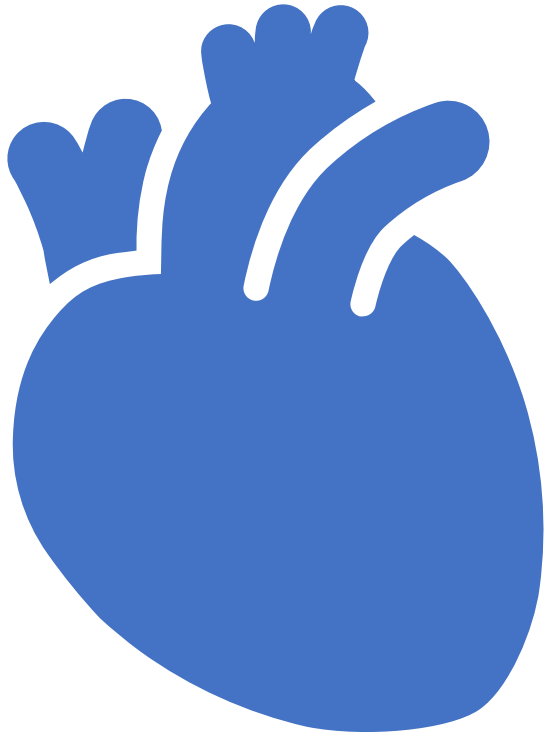

Practical Experience and Model for Optimizing RAASi-Based Therapy

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Speaker disclosures

Dr Aaron Wong

- Received funding for education and attends courses from Servier, Novartis, Menarini, Pharmacosmos, NAPP
- Principal Investigator for TRANSITION-HF, IRONMAN, RelieHF , DAPA-MI, VICTOR-HF, Realize K trials
- Received speaker’s fees and consultation fees from Novartis, AstraZeneca , Pharmacosmos, Menarini, Boehringer Ingelheim, Lilly, Bayer and Roche

RAASI therapy is recommended by multiple organisations for the treatment of HF, CKD and T2DM

NICE National Institute for Health and Care Excellence

American Heart Association®

KDIGO Kidney Disease: Improving Global Outcomes

American Diabetes Association.

ESC European Society of Cardiology

HFSA Heart Failure Society of America

Heart Failure Association of the ESC

1. Yancy CW, *et al. Circulation* 2013;128:1810–52; 2. Ponikowski P, *et al. Eur Heart J.* 2016;37:2129–200; 3. Lindenfeld J, *et al. J Card Fail.* 2010;16:475–539; 4. National Institute for Health and Care Excellence. Chronic heart failure in adults: diagnosis and management. 2018. Available at: http://www.nice.org.uk/guidance/ng106/ (accessed April 2020).
2021 ESC Guidelines, McDonagh TA, et al. *Eur Heart J* 2021;42:3599–3726
Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2020;98(4S):S1–S115; 2. American Diabetes Association. *Diabetes Care* 2022;45:S144–S174

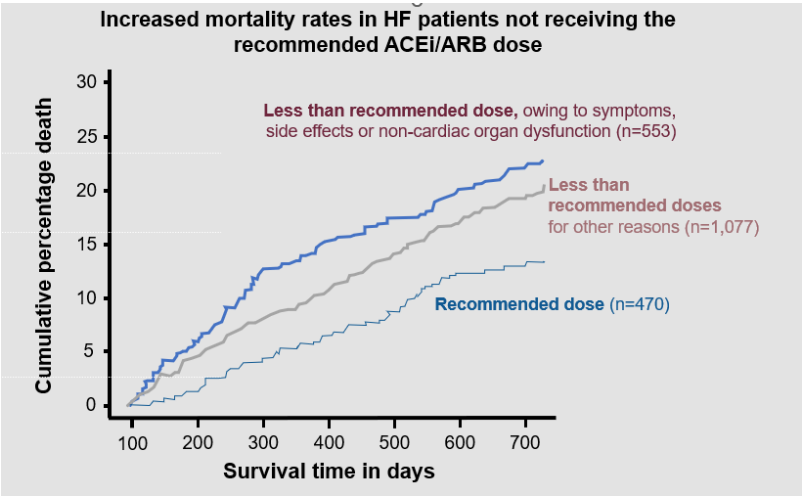
Sub-maximal dosing and discontinuation of RAASi are associated with poor patients outcomes

ACEi

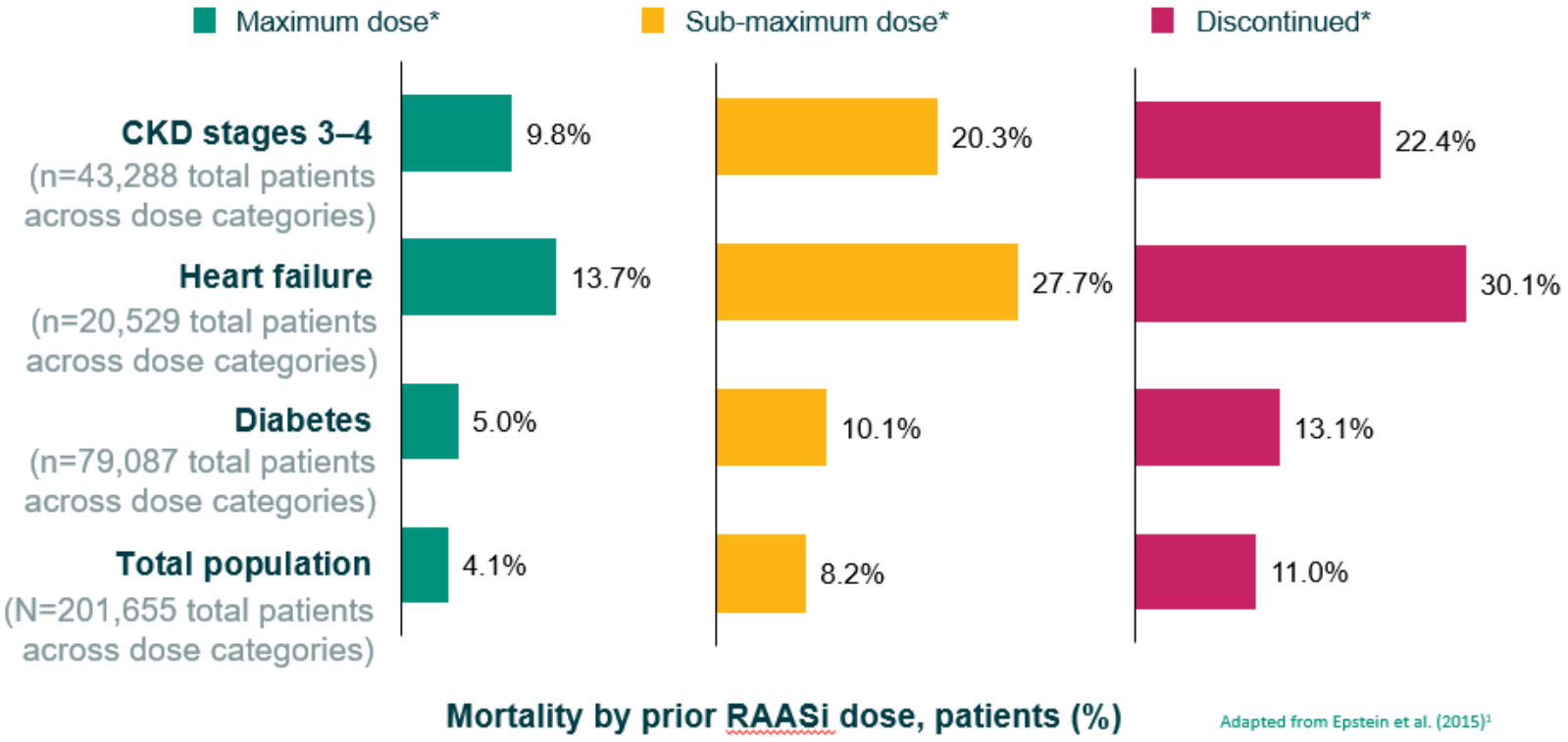
ARB

ARNI

MRA



Ouwerkerk W, *et al. BIOSTAT-CHF. Eur Heart J.*2017;38:1883–90.



Epstein M, *et al. Am J Manag Care*. 2015;21:212–20.

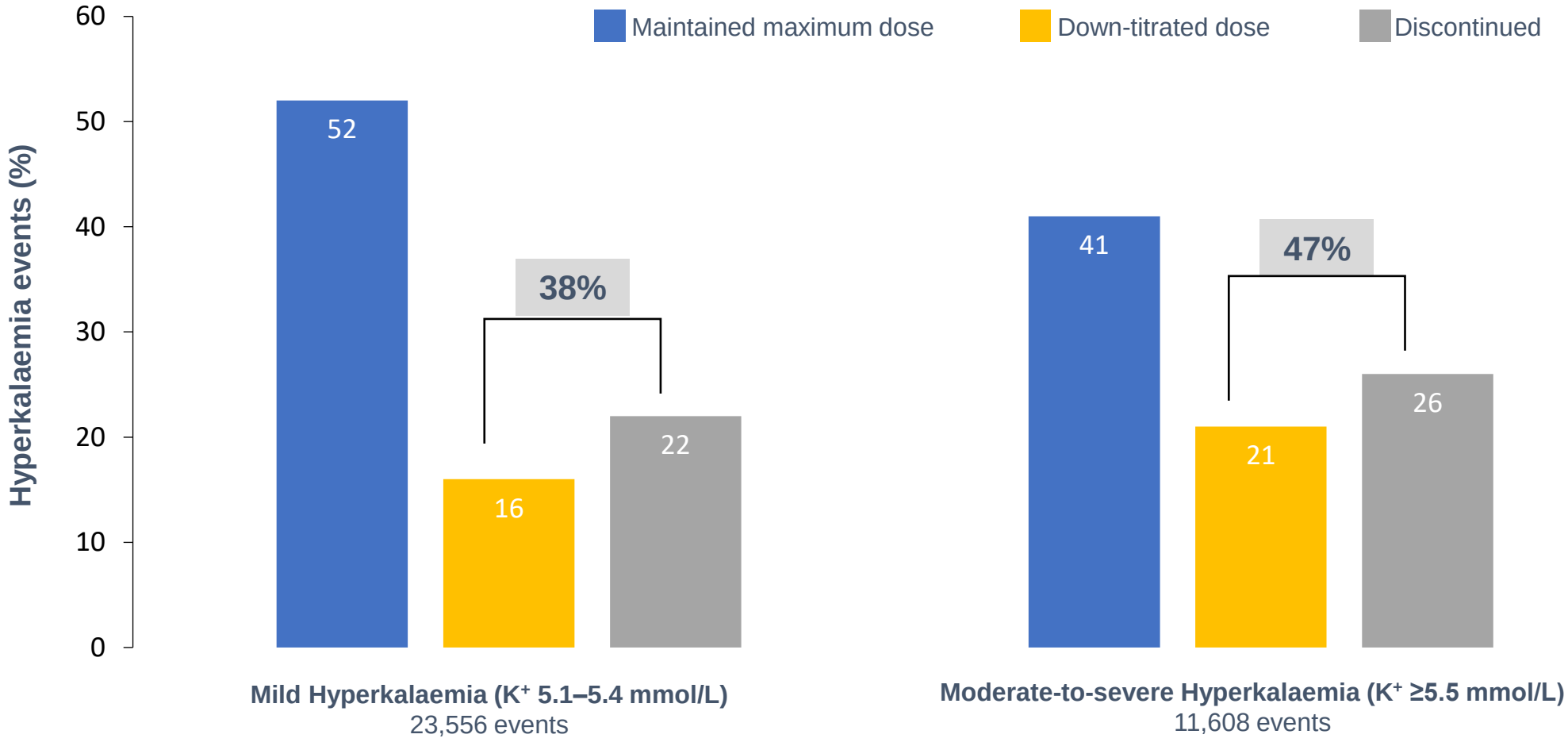
ACEi (Angiotensin-covering enzyme inhibitor); ARB (Angiotensin-receptor blocker); ARNI (Angiotensin receptor-neprilysin inhibitor; MRA (Mineralocorticoid receptor antagonist)

Common Reasons for Stopping/ Reducing/ Not up-titrating RAASi Therapy

- Hyperkalaemia
- Renal Function
- Age
- Hypotension
- Perceived Frailty
- Inertia
- Others

Caroline, et al. Adherence and Discontinuation of Optimal heart Failure Therapies According to Age: A Danish Nationwide Study. JAHA Volume 11, Issue 19, 2022,
Patel et al. Kidney Function and outcomes in patients Hospitalised with Heart Failure. JACC, 2021
Smith et al. Evaluation of the Usage and Dosing of GDMT for HFrEF in Clinical Practice. Journal of Pharmacy Practice. Vol 35, Issue 5, 2022

Down-titration Or Discontinuation Of RAASi Therapy Is Common Following A Hyperkalaemic Event [1]

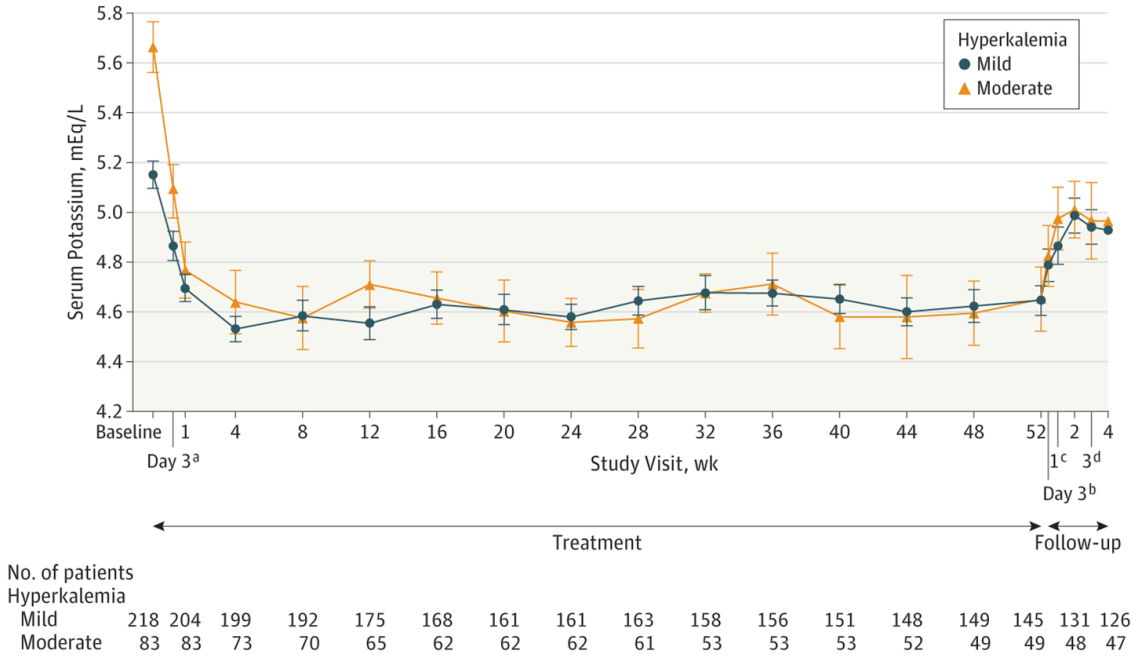


RAASi: Renin-angiotensin-aldosterone System Inhibitor

1. Epstein M, *et al. Am J Manag Care*. 2015;21:212–20.

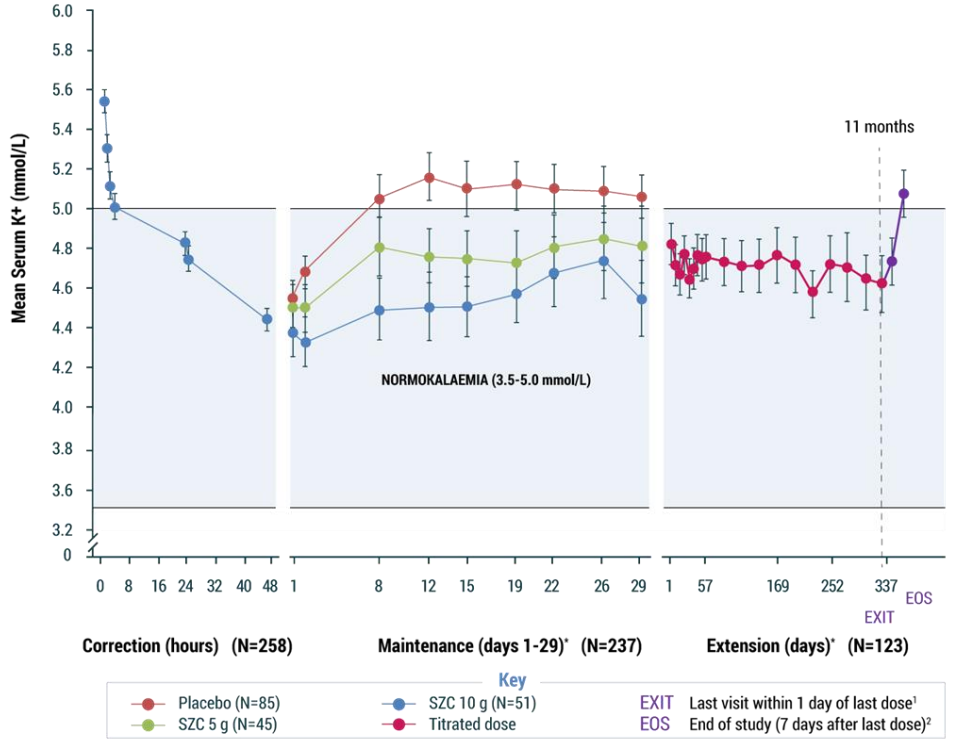
Two Novel Potassium Binders

Patiromer



Bakris GL et al. JAMA 2015;314(2):151-61

Sodium Zirconium Cyclosilicate



Kosiborod M, et al. *JAMA* 2014;312:2223–2233

Use of sodium zirconium cyclosilicate for up-titration of renin-angiotensin-aldosterone system inhibitor therapy in patients with heart failure: real world data

Rhys Williams[1], Alexander James[1], Rhian Donald[1], Kerys Thomas[2], Aaron Wong[1].

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Cwm Taf Morgannwg University Health Board.

[2]Pharmacy Department, Neath Port Tablot Hospital, Baglan Way, Port Talbot, Wales, SA12 7BX. UK.

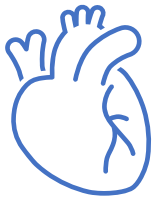
Swansea Bay University Health Board.

Unpublished Data

HFrEF Patients on SZC

Jul 2020- Oct 2022

25 Months



Echocardiography

Blood tests

Serum Potassium Level

NTproBNP

Creatinine

Medications

Hospitalisation

Death

HFrEF: Heart Failure with reduced Ejection Fraction

SZC: Sodium Zirconium Cyclosilicate

Results

Baseline (Prior to initiation of SZC)

44patients

Mean Age 75 years old

27% Female

75% CKD Stage 3b or 4

38% Diabetes

55% IHD

61% Hypertension

50% AF

10% CRT/ICD

Mean Baseline LVEF 29%

NYHA II-III (86%)

30% had HHF hospitalisation in the preceding 24 months

Baseline

NTproBNP 3458 ng/L

sK^+ 5.7mmol/L

Creatinine clearance 48mL/min

32% on Quadruple Therapy

89% ACEi/ARNi

52% MRA

66% SGLT2i

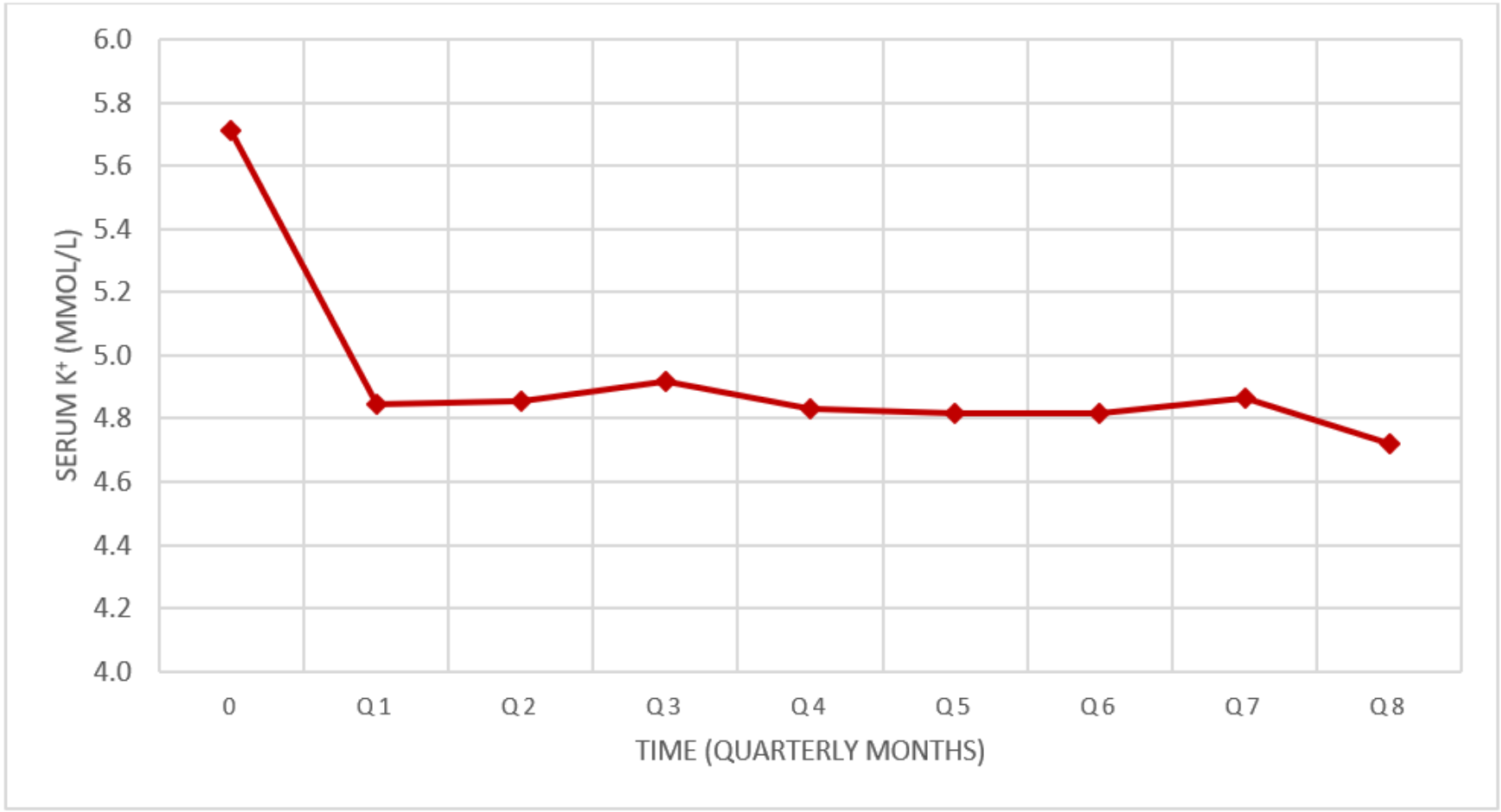
80% Beta Blockers

Increased Uptake and dosing of Guidelines Recommended therapy

	n=44		Pre-SZC		Post-SZC	
ACEi/ARB/ARNI	% patients prescribed	ACEi	7%	90%	0%	100%
		ARB	0%		0%	
		ARNI	82%		100%	
	% guideline recommended dose		50%		73%	
MRA	% patients prescribed		52%		89%	
	% guideline recommended dose		48%		66%	
Loop Diuretics	% patients on loop diuretic therapy		30%		25%	
	% of patients with maintenance / reduction of loop diuretics		-		79%	
HFrEF Treatments	% patients on 'Quadruple therapy' (ACEi/ARB/ARNI + BB + MRA + SGLT2i)		32%		64%	
	% patients on 'Triple therapy' (ACEi/ARB/ARNI +/- BB +/- MRA +/- SGLT2i)		68%		91%	
Dosing of SZC	% of patients receiving 10g once daily dosing		-		50%	

ACEi (Angiotensin-covering enzyme inhibitor); ARB (Angiotensin-receptor blocker); ARNI (Angiotensin receptor-neprilysin inhibitor); BB (beta blocker); dHF (Decompensation of heart failure); HFrEF (Heart failure with reduced ejection fraction); LVEF (Left ventricular ejection fraction); MRA (Mineralocorticoid receptor antagonist); NT-proBNP (N-terminal pro B-type natriuretic peptide); SEs (Side effects); SGLT2i (sodium-glucose co-transporter 2 inhibitor); SZC (sodium zirconium cyclosilicate)

Maintain Normal Serum Potassium level



K⁺, potassium; SZC, sodium zirconium cyclosilicate

Reduction in Serum Potassium levels following SZC initiation up to 24 months

Improvement in HF Markers and Clinical outcome

	N=44	Pre-SZC	Post-SZC
Heart Failure Markers	LVEF (%)	29%	36%
	Median NT-proBNP (ng/L)	3458ng/L	2055ng/L
	% of patients with reduction of NTproBNP (n=33)	-	79%
	% of patients with reduction of NTproBNP > 800ng/L (n=33)	-	67%
Observations / Biochemical	Mean Creatinine Clearance (mL/min)	49	50
	Mean Blood Pressure (mmHg)	124/70	122/71
Hospitalisation / Mortality	% patients requiring hospitalisation for hyperkalaemia	14%	7%
	% patients requiring hospitalisation for dHF	30%	11%
	% Survival	-	91%
Tolerability	% of patients discontinued on SZC due to SEs	-	3%

ACEi (Angiotensin-covering enzyme inhibitor); ARB (Angiotensin-receptor blocker); ARNI (Angiotensin receptor-neprilysin inhibitor); BB (beta blocker); dHF (Decompensation of heart failure); HFrEF (Heart failure with reduced ejection fraction); LVEF (Left ventricular ejection fraction); MRA (Mineralocorticoid receptor antagonist); NT-proBNP (N-terminal pro B-type natriuretic peptide); SEs (Side effects); SGLT2i (sodium-glucose co-transporter 2 inhibitor); SZC (sodium zirconium cyclosilicate)

Practical guidance for the prescribing and monitoring of Sodium Zirconium Cyclosilicate to allow initiation / maintenance of Heart Failure therapies in Primary Care

Table 1: SZC (Lokelma®) dose adjustment table and monitoring frequency

This table is intended for management of SZC in patients who are clinically well with no acute illness / acute renal injury.

Serum K⁺ \ Dose	SZC 5mg alternate days	SZC 5g OD	SZC 10g OD	SZC 15g OD (Unlicensed)*
< 3.0 mmol/L	Withhold SZC. Review patient (identify cause) +/- treat hypokalaemia. Discuss with Heart Failure / Renal specialists if required.			
3.0 – 3.4 mmol/L	Discontinue	Reduce to 5g alt days	Reduce to 5g OD	Reduce to 10g OD
3.5 – 3.9 mmol/L	Consider optimisation of RAASi therapies *(see table 2)* Consider dose reduction of SZC.			
4.0 – 4.9 mmol/L	No change			
5.0 – 5.4 mmol/L	Consider increase to 5g OD	Consider increase to 10g OD	Consider increase to 15g OD*	Discuss with HF / Renal team
	No change			
5.5 – 5.9 mmol/L	Increase to 5g OD	Increase to 10g OD	Increase to 15g OD*	Patient Assessment. Consider down-titration of RAASi
> 6.0mmol/L	Follow local guidance for management of hyperkalaemia.			

Adapted from Spinowitz et al. Sodium Zirconium Cyclosilicate among Individuals with Hyperkalaemia: A 12-month phase 3 study. Clin J Am Soc Nephrol. 2019 Jun 7;14(6):798-809.

*15g is an unlicensed dosage and patient should have regular review with their heart failure / renal team.

U&E Monitoring	Within 1-3 days	Within 1 week	Within 2 weeks	Monthly	Every 2 months

Table 2: Patient considerations for the management of serum potassium

	Hypokalaemia	Hyperkalaemia
Worsening HF symptoms	Consider further optimisation of RAASi if able. Review other possible causes for ↓ sK⁺.	Increase SZC as per *table 1* to maintain existing RAASi therapy.
Fluid Overloaded	Decrease / withhold SZC as per *table 1*. Review diuretic therapies.	Review diuretic therapies (Diuretics will ↓ sK⁺) Increase SZC as per *table 1* to maintain existing RAASi therapy.
Hypertension / Normotensive	Consider further optimisation of RAASi if able.	Increase SZC as per *table 1* to maintain existing RAASi therapy.
Hypotension	Decrease / withhold SZC as per *table 1*. Assess symptom burden & review medications.	Increase SZC as per *table 1* to maintain existing RAASi therapy. Assess symptom burden & review medications.
Worsening Renal Function	Decrease / withhold SZC as per *table 1*. See *table 3*. Review fluid status and diuretic therapy.	Increase SZC as per *table 1* +/- reduce RAASi therapy *(table 3)*
Medications	Review medications that may ↓ sK⁺.	Review medications that may ↑ sK⁺.

Adapted from Clark AL et al. Changes in renal function associated with drug treatment in heart failure: national guidance. *Heart*. 2019;**105**:904-910

Table 3: Recommendations for RAASi dosing in response to change in renal function

Clinical assessment of the patient (to assess fluid status, consider baseline renal function and BP) and review of their medication is imperative

	Heart Failure with PRESERVED Ejection Fraction (HFpEF)	Heart Failure with REDUCED Ejection Fraction (HFrEF)
Increase in serum creatinine by < 30%	Consider stop ACEi/ARB/ARNI. Review MRA according to fluid status	Continue unless symptomatic hypotension
Increase in serum creatinine 30 – 50%	Stop RAAS inhibitor	Consider reducing dose / temporary withdrawal*
Increase in serum creatinine > 50%		Temporarily stop RAAS inhibitor*
Severe renal dysfunction (eGFR < 20)		Stop RAAS inhibitor if symptomatic uraemia irrespective of baseline function

Adapted from Clark AL et al. Changes in renal function associated with drug treatment in heart failure: national guidance. *Heart*. 2019;105:904-910

*reinitiate and/or re-titrate when renal function improved.

This Local Guidelines is subject to further revision

Conclusions

- RAASi is the cornerstone for the treatment of HF
- These evidence based medications can improve outcome and dosing is important
- Hyperkalaemia can be a barrier to optimise RAASi therapy
- Selective use of potassium binder can allow optimisation of guideline recommended medications
- Real World Evidence: Potassium binder SZC was well tolerated, effective in maintaining normokalaemia to enable optimisation of RAASi therapy during the study period with improvements in NT-proBNP levels and LVEF
- The applicability of this real-world experience of potassium-binder use will be further expanded upon with the outcomes of randomised clinical trials such as REALIZE-K.