

Constructing Practical Pathways for RAASi Management: A Review of Emerging Data

This programme is supported by an unrestricted educational grant from AstraZeneca.



CKD and HF treatment guidelines state RAASi therapy should be initiated and titrated to the highest approved dose that is tolerated to improve patient outcomes¹⁻²



Optimising RAASi therapy in patients with CKD and HF is associated with decreased mortality and MACE and down-titration or discontinuation of RAASi therapy is associated with doubling of mortality across patient subtypes.³



Despite this, hyperkalemia (HK) can be a barrier to achieving and maintaining optimal RAASi therapy⁴

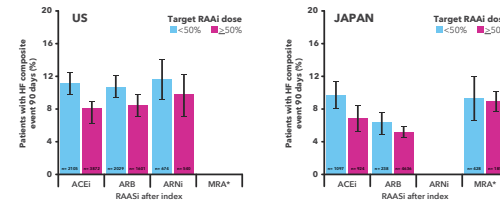


However, HK during optimal RAASi therapy is now a manageable barrier due to the availability of novel potassium (K+) binders, allowing for RAASi optimisation⁵⁻⁷



What ZORA Study Data Tell Us

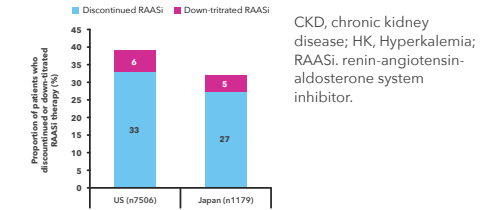
A. Risk of HF composite at 3 months by attainment of guideline-recommended RAASi target dose



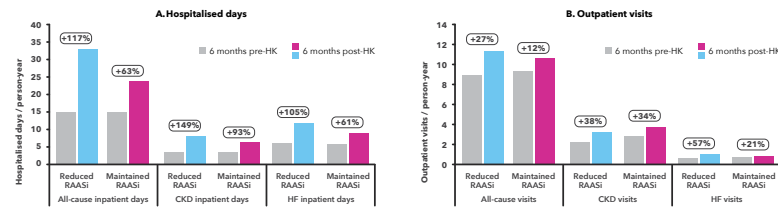
B. Risk of progression to ESKD in patients with CKD Stage 3 or 4 who discontinued or down-titrated versus maintained RAASi therapy following an HK episode

Country	RAASi status	N	Events	Adjusted HR (95% CI) [†]	P-value
US	Maintained	4586	138	(ref)	
	Discontinued	2460	138	1.74 (1.37-2.21)	<0.001
	Down-titrated	460	23	1.60 (1.02-2.49)	0.0039
Japan	Maintained	793	41	(ref)	
	Discontinued	323	26	1.70 (1.01-2.86)	0.045
	Down-titrated	63	n/a	n/a	n/a

Proportion of patients with CKD in the US and Japan who discontinued or down-titrated RAASi therapy following an HK Therapy

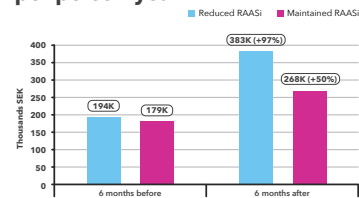


D. Hospitalised days (A) and outpatient visits (B) per person-year during 6 months before and 6 months after the index hyperkalemia event, by RAASi management strategy

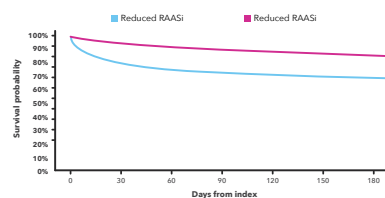


The propensity score matched cohorts included 6998 patients each. †Patients were defined as having reduced or maintained their pre-HK RAASi therapy based on filled prescriptions, or lack thereof within 120 days pre-versus post HK event. CKD chronic kidney disease; RAASi, renin-angiotensin-aldosterone inhibitor.

Healthcare costs 6 months before and after a hyperkalemia event, per person-year

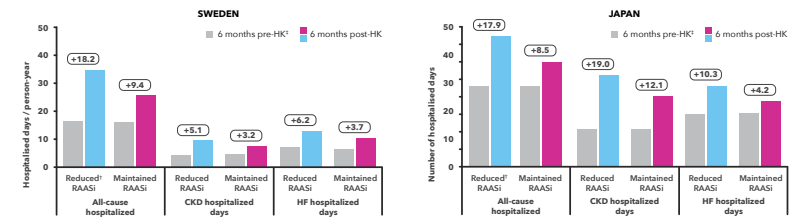


Survival within 6 months from the hyperkalemia event, by RAASi treatment strategy



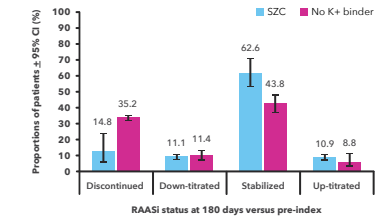
A. RAASi dose <50% of the guideline-directed target dose was associated with a higher immediate risk of adverse HF outcomes. **B.** HK-prompted RAASi therapy reduction is associated with an increased risk of progression to ESKD. **C and D.** Reduction in RAASi was associated with a greater increase in number of hospitalised days, increased risk of all-cause mortality and increased health care costs. **E.** Patients treated with novel K+ inhibitors were substantially more likely to have maintained (stabilised or up-titrated) RAASi therapy at 6 months following a HK episode, relative to patients with no K+ binder treatment.

C. Number of hospitalised days per person-year during 6 months pre- versus post-HK episode in patients who reduced versus maintained RAASi in Sweden (n=6,998 per group) and Japan (n=2,092 per group)



†Patients were defined as having reduced or maintained their pre-HK RAASi therapy based on filled prescriptions, or lack thereof; within 90 days (Japan) or 120 days (Sweden) pre- versus post-HK episode. †1:1 propensity score matching was applied to balance the cohorts on demographics, comorbidities, baseline medications (including RAASi), and hospitalisation days prior to index. CKD, chronic kidney disease; HF, heart failure; Hyperkalemia; RAASi, renin-angiotensin-aldosterone system inhibitor.

E. Meta-analysed proportions of patients who discontinued, down-titrated, stabilised, and up-titrated their RAASi therapy post-index versus pre-index



Despite clear guidelines, real world evidence shows a significant lag in implementation that leads to increased morbidity, mortality and cost. HK is a manageable barrier, novel K+ binders can and should be used to implement GDMT.

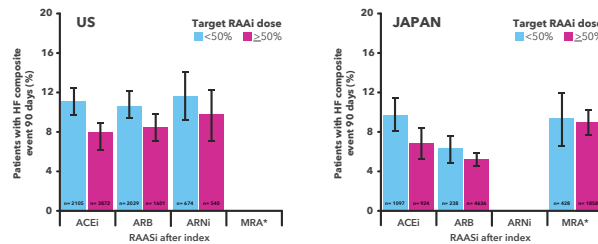
References: 1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int Suppl.* 2020;98:S1-S115. 2. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl.* 2021;99:S1-S8. 3. Epstein M et al. *Am J Manag Care.* 2015;21:S212-S220. 4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726. 5. Shirazian S, Grant CD, Mujeeb S, et al. Underprescription of renin-angiotensin system blockers in moderate to severe chronic kidney disease. *Am J Med Sci.* 2015;349:510-515. 6. Spinoz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol.* 2019;14:798-809. 7. Williams R, James A, Ashton M, et al. Use of sodium zirconium cyclosilicate for up-titration of renin-angiotensin-aldosterone system inhibitor therapy in patients with heart failure: a case series. *Eur Heart J Case Rep.* 2021;5(8):ytb281. doi:10.1093/ehjcr/ytb281

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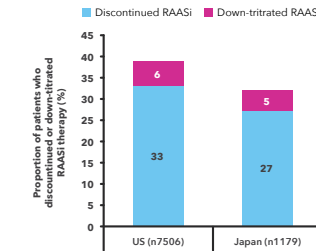
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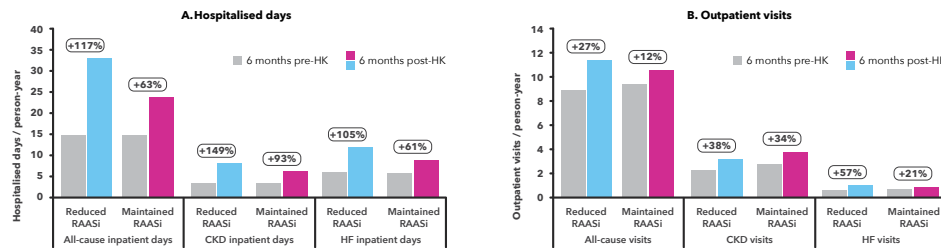
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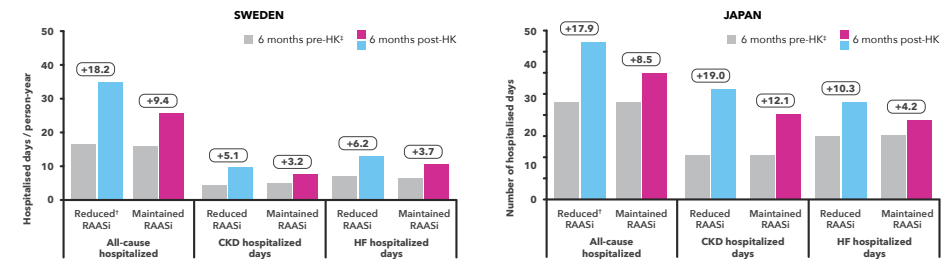
CKD, chronic kidney disease; HK, Hyperkalemia; RAASi, renin-angiotensin-aldosterone system inhibitor.

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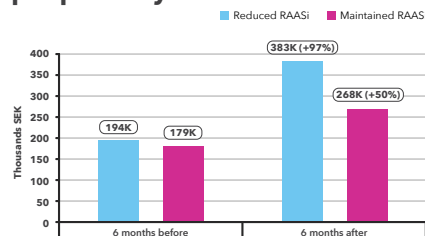
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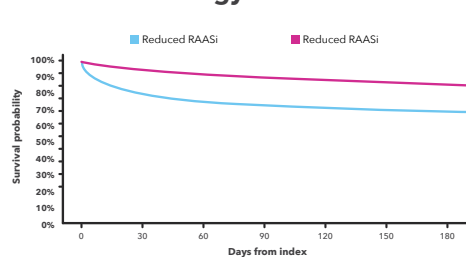


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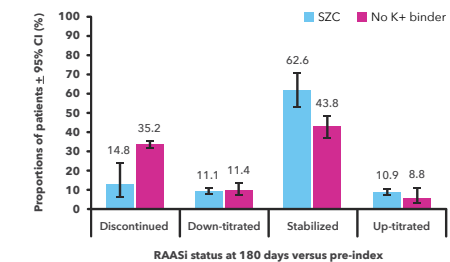
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