Hong Kong Society of
Congenital and Structural Heart Disease

Frontiers in Heart Failure Management

A symposium on "Frontiers in Heart Failure Management" was held by Hong Kong Society of Congenital and Structural Heart Disease on 18th November 2021. It was a great opportunity to have two internationally recognized speakers, Professor Marco Metra and Professor Giuseppe Rosano to share with us the latest research findings on "The Four Pillars in Heart Failure: Who and When?" and "Emerging Concepts of Hyperkalaemia Management in Heart Failure Patients: Looking Beyond Potassium".

The Four Pillars in Heart Failure: Who and When?

Prof. Marco Metra MD

- Director, Cardiology, University and Civil Hospitals of Brescia
- Editor-in-Chief, The European Journal of Heart Failure
- Co-chairman, European Society of Cardiology Heart Failure Guidelines

Current Issues with Traditional HF Treatments

Traditionally, ARB/ACEI, beta-blocker and MRA have been central treatments to HFrEF patients as highlighted in previous guidelines[1]. In practice, getting patients to targeted doses has been far from desired (See figure 1)[2]. Part of this reason for suboptimal dosing or discontinuation is due to the need for individualized treatment of patients where patients' background such as blood pressure have to be taken into consideration as shown in figure 2[3]. The latest guideline for HFrEF treatment now includes SGLT2-inhibitors as an additional pillar to the previously established treatment (See figure 3)[4]. This is primarily due to clinical trials proving significant reductions in HF morbidity or mortality outcomes irrespective of pre-existing HF treatments being used (See figure 7)[5-8].

Figure 1 - Use of Guideline-Directed Medical Therapy among patients with chronic HFrEF[2]

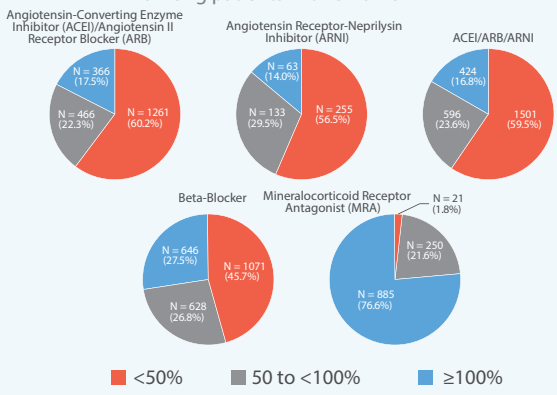


Figure 2 - Important characteristics when considering medical therapy in heart failure patients[3]

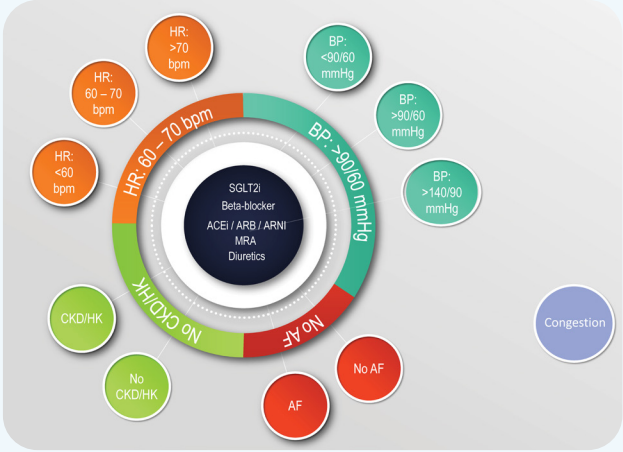


Figure 3 - 2021 ESC Guidelines recommendations for HFrEF[4]

Recommendations	Class	Level
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

Figure 4 - Comparison of the clinical benefits of the 4 HFrEF treatments[9]

Early relative risk reduction			Initiation and optimization of medication dosing				
Outcomes	Change, %	CDMMT	Day1	Day7-14	Day14-28	Day21-42	After day 42
CV death or HF hospitalization	-42	ARNI	Initiate at low dose	Continue	Titrate, as tolerated	Titrate, as tolerated	• Maintenance or additional titration of the 4 foundational therapies • Consideration of EP device therapies or transcatheter mitral valve repair • Consideration of add-on medications or advanced therapies, if refractory • Manage comorbidities
Death	-25	β-Blocker	Initiate at low dose	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated	
CV death or HF hospitalization	-37	MRA	Initiate at low dose	Continue	Titrate, as tolerated	Continue	
Death, HF hospitalization, or emergency/urgent visit for worsening HF	-58	SGLT2i	Initiate	Continue	Continue	Continue	

SGLT-2 Inhibitor – An Outstanding 4th Pillar in HFrEF Treatment

The meta-analysis in figure 4 shows the benefits of using the different classes of medication for HFrEF[9]. The outcome benefits of using an SGLT-2 inhibitor are impressive, providing a 58% reduction in the composite of death, HF hospitalization or emergency / urgent visit for worsening HF[9]. Further still it highlights the ease of initiation with no dose up-titration required for SGLT-2 inhibitors when compared to the other existing treatments. This vastly simplifies the considerations needed when individualizing patient treatment as compared to ARNI, beta-blocker and MRA[9]. Though the 2021 ESC Guidelines for HF recommends quadruple therapy for all HFrEF patients with no restrictions in which treatment to be initiated first, there are expert suggestions to use the rapid sequencing model which places an SGLT-2 inhibitor as first line therapy combined with a beta-blocker while ARNI is placed as step 2[4,10]. Initiating an SGLT-2 inhibitor before ARNI has its advantages as it has minimal effect on blood pressure and a reduced risk of hyperkalaemia as shown in figure 6[11]. It shows using an SGLT-2 inhibitor earlier provides more favorable effects as well as more compatible options of other guideline-directed medical therapies[11].

Figure 5 - Conventional sequencing vs rapid sequencing[10]

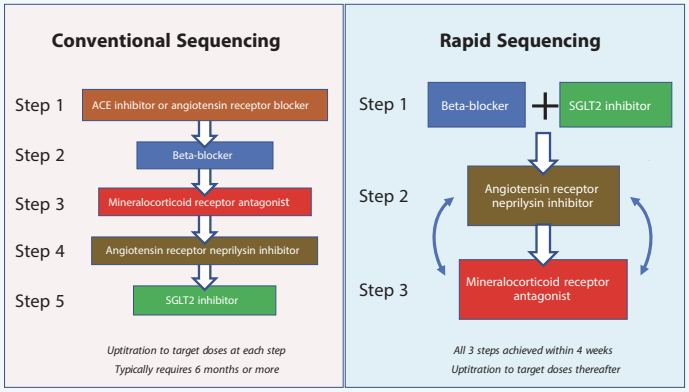


Figure 6 - Potential clinical benefits of SGLT-2 inhibitors vs ARNI[11]

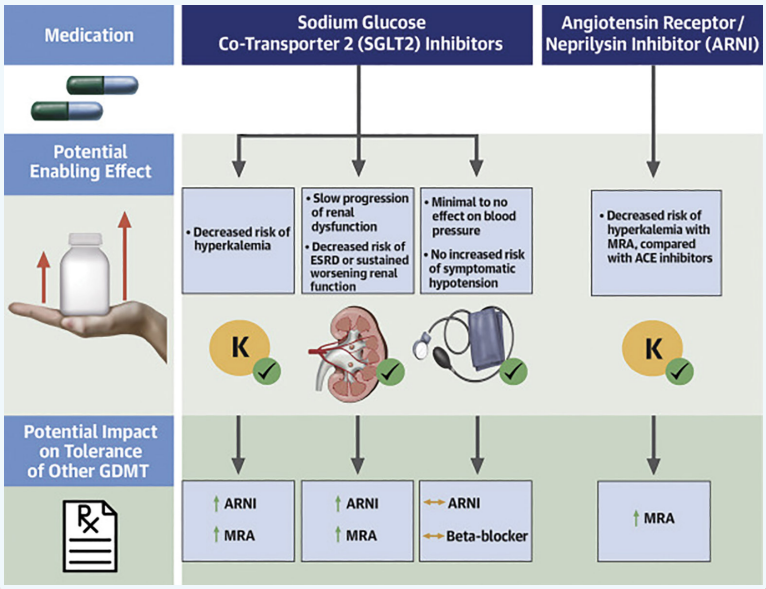


Figure 7 - Mortality benefits of dapagliflozin in DAPA-HF trial[5]

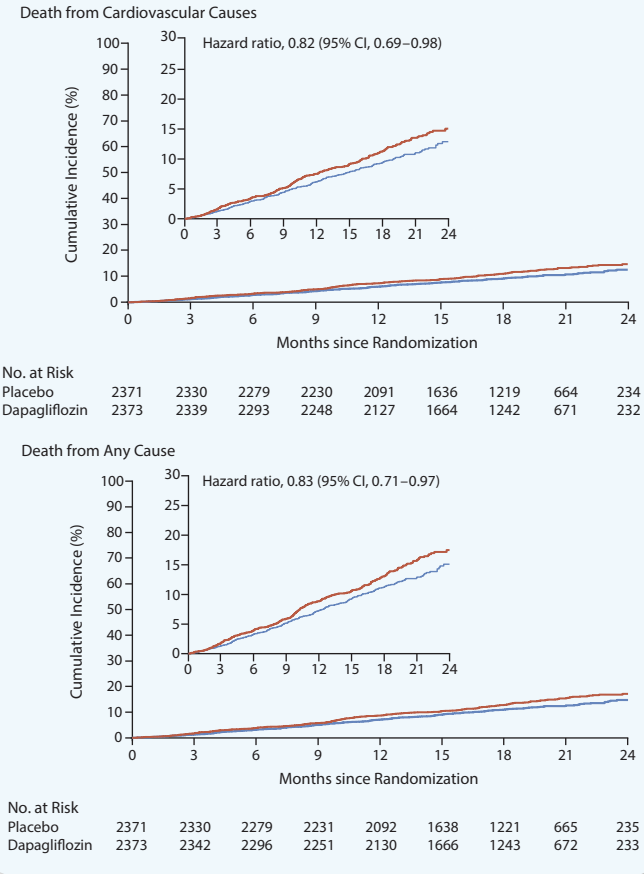
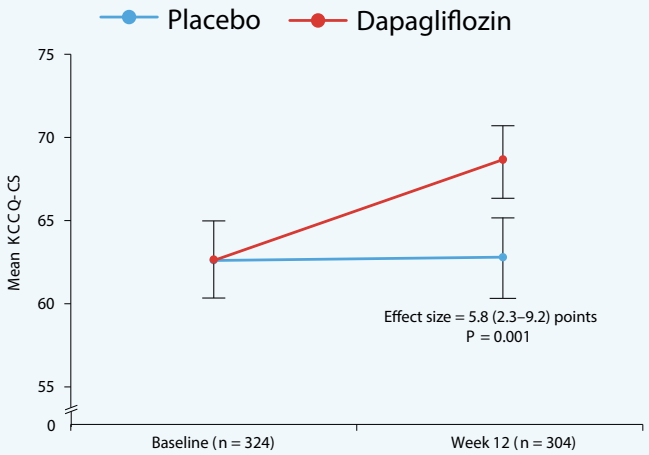


Figure 8 - KCCQ clinical summary score in PRESERVED-HF[12]



Differences in SGLT-2 Inhibitors, Dapagliflozin & Empagliflozin

The 2021 ESC Guidelines recommend dapagliflozin and empagliflozin as the only SGLT-2 inhibitors for HFrEF[4]. Both dapagliflozin and empagliflozin have demonstrated efficacies in the DAPA-HF and EMPEROR-Reduced trials respectively and showing primary composite endpoints comprising similar mortality & morbidity benefits[5,6]. However, it is worth noting that the DAPA-HF trial demonstrated unique mortality benefits with significant reductions in cardiovascular death and all cause death shown in figure 7.

The latest available evidence suggested that SGLT-2 inhibitors are also capable of treating a wider range of HF patients such as those with HFpEF[9,12,13]. In the EMPEROR-Preserved trial, empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with HFpEF, regardless of the diabetes status[13]. A similar outcome trial namely DELIVER for dapagliflozin is going to be presented at ACC in April 2022[9].

On the other hand, dapagliflozin has demonstrated a unique and clinically meaningful symptoms improvement measured by KCCQ clinical summary score (See figure 8) and also a significant increase in 6-minute walk test distance in 12 weeks from the PRESERVED-HF trial, and its benefits were consistent across different baseline LVEF and NYHA functional classes [9,12].

In conclusion, SGLT-2 inhibitors provide additional benefits to HFrEF treatment in both efficacy and convenience to achieve optimized treatment of such patients. With the emerging evidence, SGLT-2 inhibitors may also become an effective treatment for HFpEF in the near future.

Prof. Giuseppe Rosano MD, PhD

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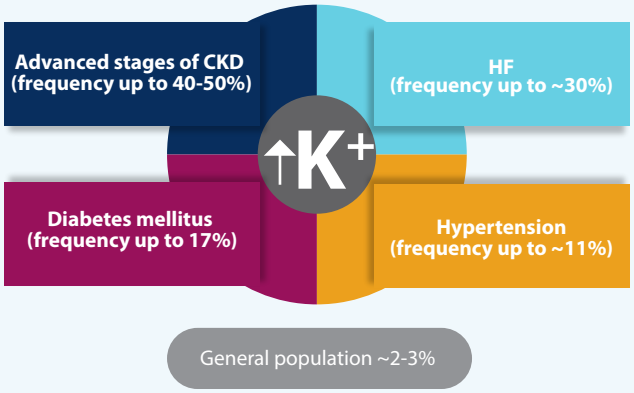
- Director, MSc Heart Failure, St George's University of London
- President-elected, Heart Failure Association of the European Society of Cardiology

Hyperkalaemia in Patients with Chronic Diseases

Figure 9 - Patient subgroups with a high incidence of hyperkalaemia[15]



Hyperkalaemia, defined by >5 mEq/l of potassium level in the body, is one of the most common electrolyte abnormalities in patients with chronic diseases and RAASI therapy[14,15]. High incidence of hyperkalaemia is often seen in patients with advanced stages of chronic diseases (See figure 9)[15]. The severity and some of the causes of hyperkalaemia can be seen in figure 10. Signs and symptoms of hyperkalaemia include generalized muscle weakness, flaccid paralysis, paresthesia of the hands and feet, lethargy, confusion and palpitations[15]. The pathology of hyperkalaemia might be abnormal net release of potassium from cells due to trauma, metabolic acidosis, haemolytic states, and the treatment goals are to induce potassium flux into intracellular space and remove it from the body to prevent cardiac arrhythmias[15]. In addition, with chronic, recurrent hyperkalaemia, ongoing treatment is required[15].

Effective control of hyperkalaemia in patients with chronic diseases and RAASI therapy is important. Often, patients with chronic diseases like heart failure, are prescribed with RAASI therapy like ACEI, ARB and MRA, but high incidence of hyperkalaemia was seen in these patients[16,17]. Up to 40% of patients with NYHA class III/IV HF with concomitant high dose MRA have been reported to have hyperkalaemia[18]. In a 5-year observational study that included 205,108 patients with hyperkalaemia who were on RAASi therapy, 32.8% had at least 1 hyperkalaemia event, and 28.5% and 15.1% were observed with at least 1 mild, and moderate-to-severe hyperkalaemia events respectively[15,16]. About 70% of patients prescribed with guideline-recommended ACEI, ARB and MRA doses were not at target doses, and hyperkalaemia is often the reason of down-titrating or discontinuing the RAASi therapy[15,16,19]. In the study, 38% of patients experienced mild hyperkalaemia and 47% of them experienced moderate-to-severe hyperkalaemia, had sub-maximum dose of or discontinued the RAASi therapy[15,16].

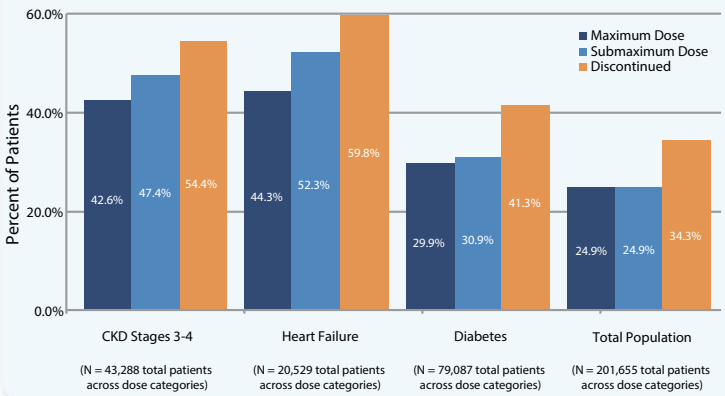
Over half of the patients with HF had sub-maximum dose or discontinued experienced an adverse outcome or died (See figure 11), in other words, the mortality is associated with decreasing the RASSI dose[15,16]. High serum potassium is also found to be associated with increased mortality in CKD patients[15,20]. Therefore, effective control of hyperkalaemia in patients with chronic diseases to keep the RASSi therapy on optimal dose is important, as Prof. Rosano pointed out.

Figure 10 - Severity & causes of hyperkalaemia

Mild	>5 to <5.5 mEq/l
Moderate	5.5-6 mEq/l
Severe	>6 mEq/l

Intake of medications that decreased excretion of potassium	Increased intake of potassium
• Potassium-sparing diuretics • Beta-blockers • Digitalis	• Potassium supplements • Alfalfa • Dandelion

Figure 11 - Mortality rates of patients across RAASi dose categories[17]



Novel Therapeutic Options for Hyperkalaemia

To keep optimal RAASi dose, effective and safe treatments controlling hyperkalaemia in the long-term would be important. Traditionally, patients are prescribed with SPS, which is an ion-exchange resin potassium binder first approved in 1958, only until recently, two novel potassium binders, sodium zirconium cyclosilicate and patiromer have been introduced (See figure 12)[14].

SZC reduces potassium level rapidly in as early as 1 hour[21]. In ZS-003 and HARMONIZE, potassium levels decreased significantly after the first dose and reduced 0.7 mEq/l of potassium significantly after 4 hours in patients with severe hyperkalaemia (See figure 13)[15]. In HARMONIZE and ZS-004E, SZC demonstrated sustained potassium effects for up to 1 year. 88% of patients receiving SZC maintained an average serum potassium of <5.1 mmol/L over 11 months with no dietary restrictions imposed (See figure 14)[15,23]. In the initial phase, normokalaemia was reached by patients on SZC 10g TID within 48 hours (See figure 14)[21]. Entering the maintenance phase, patients with 10g dose maintained the normokalaemia level for 29 days (See figure 14)[15,22]. Then in the extension phase, patients with titrated dose maintained the level for up to 1 year (See figure 14)[15].

Across the prespecified subgroups of patients, including those with CKD history, CKD with eGFR <60 mL/min/1.73 m^2, HF, DM and RAASI therapy, 10g SZC reduced mean serum potassium levels to <5.0 within 48 hours, regardless if the baseline level is <5.5, 5.5 to 6.0 or ≥6.0 mmol/L[15,22]. The long-term efficacy was also demonstrated in the ZS-005 study[15,24].

Regarding safety, over 52 weeks, 5%, 7.6% and 8.2% of constipation, peripheral oedema and worsening hypertension were seen and SZC was generally well tolerated with limited drug-drug interactions[15].

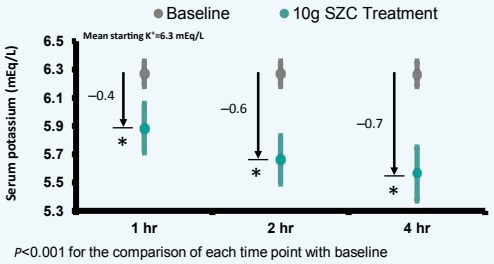
SZC is recommended by the latest 2021 KDIGO and ESC guidelines[15,25]. In 2021 KDIGO Blood Pressure in CKD guideline, newer oral potassium binders should be used to treat hyperkalaemia in patients with RAASi, while decreasing or stopping RAASi dose should be the last resort[15,25]. In 2021 ESC HF guideline, for patients with chronic or recurrent hyperkalaemia on RAASi therapy, potassium binder may be initiated as soon as the level is >5 mEq/l, allowing the initiation or up-titration of RAASi therapy[15]. Other additional therapies may include adding an SGLT-2 inhibitor as it was shown to lower the risk of hyperkalaemia as well as the risk of renal events, CV death and all-cause mortality, which is definitely beneficial in chronic diseases patients[15]. To conclude, SZC enables the possibility of maintaining optimal RAASi dose and is a perfect chronic hyperkalaemia therapy for patients with chronic diseases.

Figure 12 - Potassium binders comparison[15]

	Sodium polystyrene sulfonate	Patiromer*	Sodium zirconium cyclosilicate
Mechanism of action	Non-specific cation binding	Cation binding	Selective potassium binding
Time to normokalaemia	Unconfirmed efficacy	Within 1 week	84% achieved within 24 hours
Onset of effect	Unknown	Significant reduction 7 hours after first dose	Median time 2.2 hours
Drug-drug interactions	Antacids, laxatives,digitalis, sorbitol, lithium, and thyroxine	3 hours apart from other oral drugs	No clinically meaningful interactions to date
Location of potassium binding	Colon	Distal colon predominantly	Likely to be upper and lower intestinal tract (not proven)
Safety/tolerability	Poor tolerability/adherence, associated with colonic necrosis , hypokalaemia, electrolyte disturbances, and GI side effects	Well tolerated but may cause hypomagnesaemia and GI side effects	Well tolerated, but may cause oedema, mild to moderate GI side effects, and hypokalaemia

*Patiromer is not available in Hong Kong (Jan 2022).

Figure 13 - Potassium levels decreased significantly after the first dose of SZC in severe hyperkalaemia[15]

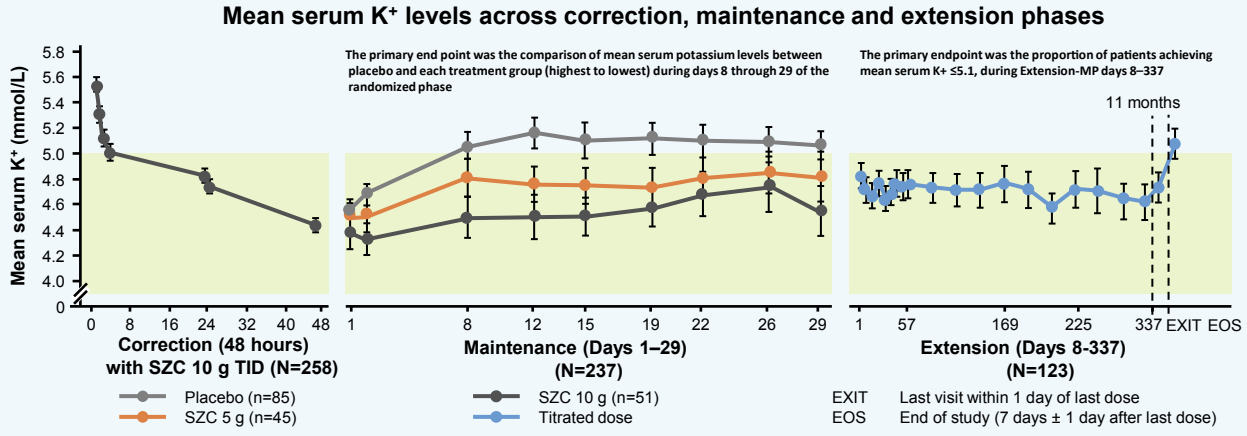


P<0.001 for the comparison of each time point with baseline

Key observations

- Mean starting K+ of 6.3 mEq/L
- Median time to <6.0 mEq/L: 1.1 hours
- Median time to <5.5 mEq/L: 4.0 hours

Figure 14 - Outcomes of HARMONIZE and ZS-004E studies[15]



ACEI=angiotensin-converting-enzyme inhibitor. AF=atrial fibrillation. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor-neprilysin inhibitor. BP=blood pressure. CI=confidence interval. CKD=chronic kidney disease. CV=cardiovascular. EP=electrophysiology. ESC=European Society of Cardiology. ESRD=end-stage renal disease. GDMT=guideline-directed medical therapy. HF=heart failure. HFpEF=heart failure with preserved ejection fraction. HFrEF=heart failure with reduced ejection fraction. HK=hyperkalaemia. HR=hazard ratio. KCCQ=Kansas City Cardiomyopathy Questionnaire. KCCQ-CS=Kansas City Cardiomyopathy Questionnaire clinical summary. LVEF=left ventricular ejection fraction. MRA=aldosterone receptor antagonist. NYHA=New York Heart Association. RAASI=renin-angiotensin-aldosterone system inhibitor. SGLT-2i=sodium-glucose cotransporter-2 inhibitor. SPS=sodium polystyrene sulfonate. SZC=sodium zirconium cyclosilicate.

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