Clinical outcomes associated with sodium zirconium cyclosilicate for treating hyperkalaemia in patients receiving haemodialysis

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Introduction

Patients with end-stage kidney disease (ESKD) require kidney replacement therapy, typically in the form of haemodialysis three times per week, to remove excess fluid and waste products.[1] Patients with ESKD are at risk of developing hyperkalaemia, defined as a serum potassium (sK^+) above the normal range of 3.5–5.0 mmol/L, between haemodialysis sessions,[2,3] and many individuals with ESKD have persistently elevated predialysis sK^+ despite haemodialysis, which is associated with increased risk of adverse outcomes.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective cohort study of haemodialysis practices, including in Italy. A recent analysis of DOPPS-Italy data found that higher peak sK^+ levels over time were associated with an increased risk of all-cause mortality, cardiovascular (CV) death and hospitalisation.[4] Therefore, there remains an unmet need to manage hyperkalaemia in ESKD patients who are receiving haemodialysis.

In the DIALIZE trial, sodium zirconium cyclosilicate (SZC) significantly increased the proportion of patients with ESKD who maintained predialysis sK^+ 4.0–5.0 mmol/L vs placebo.[5]

Objectives

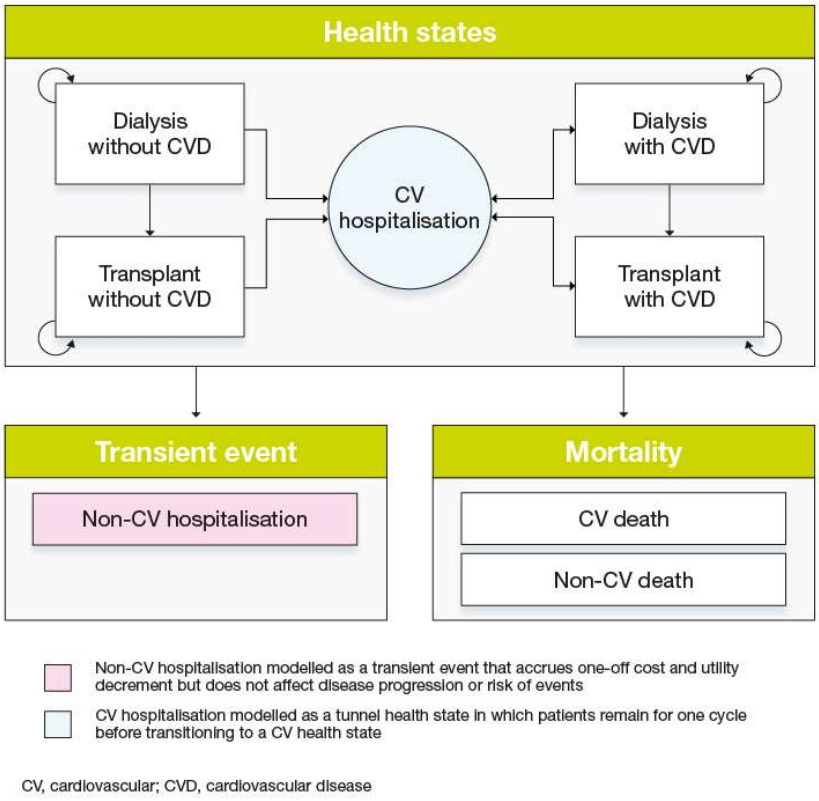
This study aimed to understand the impact of SZC vs placebo on clinical outcomes in individuals with ESKD on haemodialysis in Italy, reflecting the additional risks of a history of CV disease and incorporating the potential impact on kidney transplants.

Methods

A semi-Markov state transition model was used to predict the effect of SZC versus standard care on clinical outcomes over a lifetime (40 years) horizon. The model utilised a 112-day cycle length to match the frequency at which patient's peak sK^+ were recorded in the DOPPS-Italy study.[4]

The model comprised seven health states: dialysis with and without cardiovascular disease (CVD), kidney transplant with and without CVD, CV hospitalisation, CV and non-CV death. Non-CV hospitalisation was modelled as an event (Figure 1).

Figure 1. Semi-Markov model structure



CV, cardiovascular; CVD, cardiovascular disease

Baseline patient characteristics were sourced from DOPPS-Italy, with a mean age of 67.99, 59.7% male and 29.0% with a history of cardiovascular disease.[4]

Event rates of hospitalisations and deaths were taken from the DOPPS-Italy study[4] and adjusted using hazard ratios (HRs) stratified by sK^+ from published DOPPS-Italy data (Table 1).

Table 1. Clinical event parameters

	CV hospitalisation	All-cause hospitalisation	CV mortality	All-cause mortality
Event rate for $sK^+ \leq 5.0$ mmol/L (per 1,000 patient-years)	106.0	558.0	58.0	148.0
HR for sK^+ 5.1–5.5 mmol/L	1.85	1.31	1.13	1.32
HR for sK^+ 5.6–6.0 mmol/L	1.65	1.09	0.92	1.17
HR for $sK^+ \geq 6.0$ mmol/L	1.64	1.37	1.56	1.38

CV, cardiovascular; HR, hazard ratio; sK^+, serum potassium

A transplantation rate of 34.9 per 1,000 patient-years was derived from Italian registry data,[6] with a mortality HR of 0.49 (relative to dialysis) modelled for transplant based on a systematic review and meta-analysis.[7]

The base case modelled the effect of SZC versus placebo based on data from DIALIZE (Table 2).

Table 2. sK^+ model parameters

sK^+	SZC		Placebo	
	Mean	SD	Mean	SD
sK^+ after a long interdialytic interval	5.001	0.596	5.751	0.671
sK^+ after a short interdialytic interval	4.960	0.650	5.590	0.690
sK^+ after haemodialysis	3.569	0.540	3.842	0.571

SD, standard deviation; sK^+, serum potassium; SZC, sodium zirconium cyclosilicate

Peak sK^+ over a 112-day period were derived based on normal deviates using the mean and SD as reported in Table 2. The mean peak sK^+ levels were derived through 1,000 bootstrap replications and used to inform a distribution across the sK^+ categorisation as presented in Table 1.

An annual risk of 0.006 was used for the discontinuation of SZC derived from DIALIZE; upon discontinuation patients' sK^+ follow the trajectories informed by the placebo arm of DIALIZE.

Results

SZC treatment was estimated to reduce overall hospitalisations by 30.2 per 1,000 patients over the modelled time horizon compared with placebo (Table 3; Figure 2; Figure 3). CV deaths were also reduced compared with placebo, by 55.1 CV deaths per 1,000 patients. The incremental increase in life years of 0.289 led to 6.9 more kidney transplants per 1,000 patients associated with SZC treatment compared with placebo over the modelled time horizon

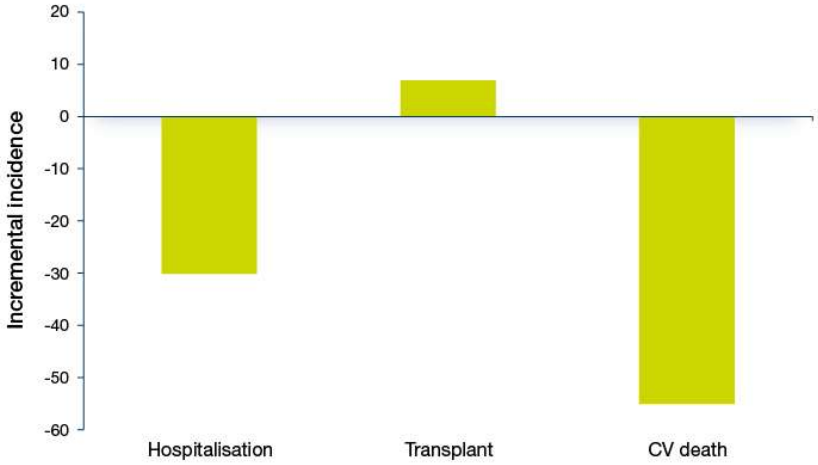
Table 3. Modelled number of events per 1,000 patients over a lifetime horizon

Outcome	SZC	Placebo	Incremental
Hospitalisation	3,350.1	3,380.2	-30.2
Transplant	159.7	152.8	6.9
CV deaths	378.5	433.6	-55.1

CV, cardiovascular; SZC, sodium zirconium cyclosilicate

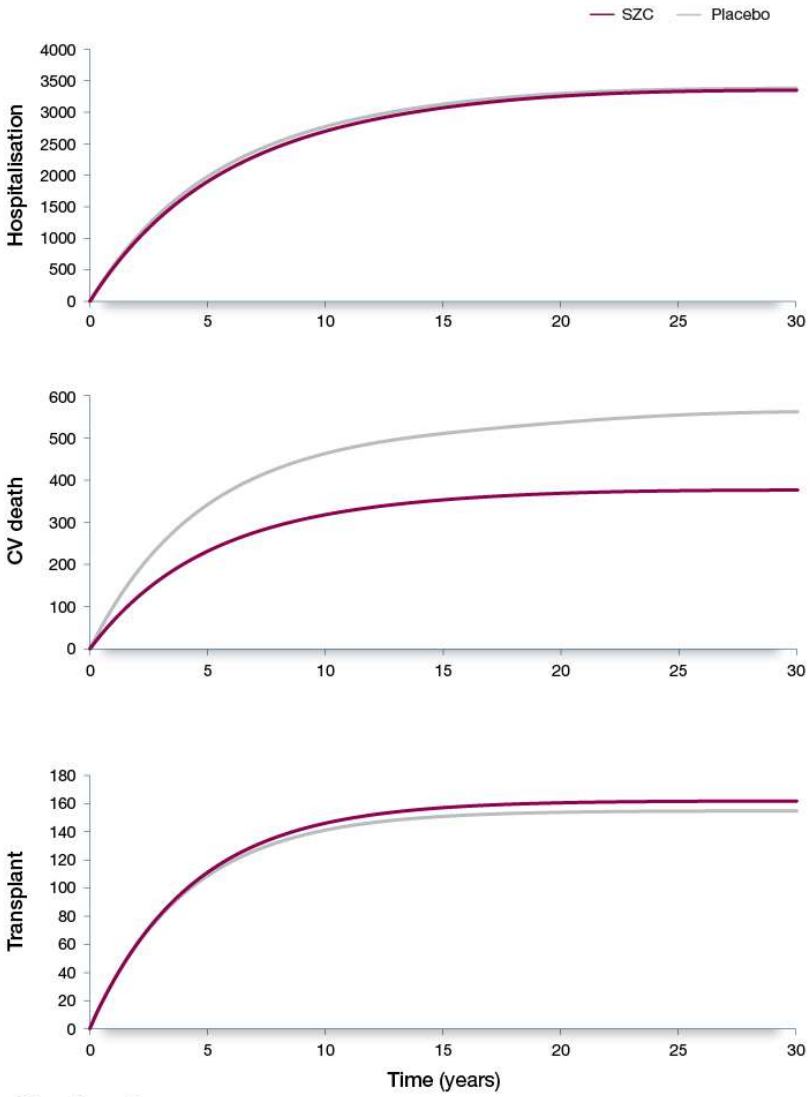
Figure 2. Cumulative incremental incidence

Incremental events presented per 1,000 patients over a lifetime horizon



CV, cardiovascular

Figure 3. Cumulative incidence of clinical outcomes
Total events presented per 1,000 patients



CV, cardiovascular

At a national level, SZC was predicted to results in 1,277 fewer hospitalisations, 293 additional kidney transplants and 2,335 fewer CV deaths, based on a prevalence of 42,375 patients receiving haemodialysis.[6]

Limitations

The model assumed a constant baseline sK^+ distribution, therefore did not account for potential long-term effects of SZC on controlling sK^+ levels, which may underestimate the benefits of SZC. Additionally, the same hospitalisation risks were assumed for patients receiving haemodialysis and those who had undergone transplant. This may lead to an underestimation of the overall benefits of SZC, as the potential reduction in hospitalisations due to the increased number of transplants facilitated by SZC was not captured.

Conclusion

Modelling using trial data from DIALIZE combined with real-world evidence from DOPPS-Italy indicate that management of hyperkalaemia with SZC in patients on haemodialysis has potential benefits including fewer hospitalisations and CV deaths. Treatment with SZC may enhance survival, enabling more patients to benefit from kidney transplantation and experience subsequent improvements in quality of life. Implementing SZC treatment for hyperkalaemia nationally in Italy could potentially alleviate disease burden and optimize healthcare resource utilisation, enhancing healthcare capacity. These findings underscore the importance of considering SZC as a standard intervention for managing hyperkalaemia in patients on haemodialysis.

References

1. Bem D, Sugrue D, Wilding B, et al. The effect of hyperkalemia and long inter-dialytic interval on morbidity and mortality in patients receiving hemodialysis: a systematic review. Ren Fail. 2021;43(1):241-54.
2. Luo J, Brunelli SM, Jensen DE, et al. Association between serum potassium and outcomes in patients with reduced kidney function. Clin J Am Soc Nephrol. 2016;11(1):90.
3. Rossignol P, Lamiral Z, Frimat L, et al. Hyperkalaemia prevalence, recurrence and management in chronic haemodialysis: a prospective multicentre French regional registry 2-year survey. Nephrol Dial Transplant. 2017;32(12):2112-8.
4. Ferraro PM, Bolignano D, Aucella F, et al. Hyperkalemia excursions and risk of mortality and hospitalizations in hemodialysis patients: results from DOPPS-Italy. J Nephrol. 2022;35(2):707-9.
5. Fishbane S, Ford M, Fukagawa M, et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. J Am Soc Nephrol. 2019;30(9):1723.
6. Pani A, Capasso G. Global Dialysis Perspective: Italy. Kidney360. 2022;3(11):1948.
7. Chaudhry D, Chaudhry A, Peracha J, et al. Survival for waitlisted kidney failure patients receiving transplantation versus remaining on waiting list: systematic review and meta-analysis. bmj. 2022;376.