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ORIGINAL RESEARCH ARTICLE

Economic Evaluation of Patiromer in Patients with Concomitant Heart Failure and Chronic Kidney Disease in Italy

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Abstract

Background Hyperkalaemia (HK), in patients with heart failure (HF) with and without chronic kidney disease (CKD), is potentially life-threatening. Risk of HK is further heightened in those patients receiving renin–angiotensin–aldosterone system inhibitors (RAASi), used to reduce cardiovascular morbidity and mortality in HF. Patiromer, an oral potassium (K^+) binder, has been shown to reduce the risk of HK and enable optimal RAASi dosing. We evaluated the cost-effectiveness of patiromer in HF patients with CKD in the Italian setting, utilising results from the recent DIAMOND clinical trial, which assessed long-term use of patiromer in HK management.

Methods An established Markov model was adapted to include data from DIAMOND using the National Health Service (NHS) perspective. In DIAMOND, patients received patiromer during a run-in period (up to 12 weeks) to achieve optimal RAASi without HK. However, this led to low mean K^+ concentrations in the placebo arm, resulting from a legacy effect of patiromer in the run-in phase of the trial. Therefore, the DIAMOND population was adjusted to a real-world population to better represent the K^+ levels in the standard of care (SoC) arm. Mean K^+ concentration for baseline and the patiromer arm was calculated from the overall population at baseline (screening phase) and after treatment (end of run-in period), respectively. Lifetime trajectories were estimated for quality-adjusted life years (QALYs), life years (LYs) and costs.

Results The economic evaluation model calculated a discounted total average cost per patient of €109,900 for patiromer and €64,847 for SoC. Patiromer generated a gain of 1.97 LYs (1.55 QALYs) compared with SoC. The incremental cost-effectiveness ratio (ICER) for patiromer was €29,060/QALY gained versus SoC.

Conclusion Applying DIAMOND data, patiromer is deemed to be cost-effective at a willingness-to pay threshold of €40,000 per QALY gained in Italy.

Key Points for Decision Makers

Using patiromer as a treatment for hyperkalaemia in patients with concomitant heart failure and chronic kidney disease is cost-effective in Italy compared with standard of care.

Patiromer enables RAASi therapy maintenance, reduces chronic hyperkalaemia and increases life expectancy compared with standard of care.

1 Introduction

The burden of heart failure (HF) is significant, particularly when accompanied by concomitant chronic kidney disease (CKD). Patients with HF and CKD present a substantial clinical and economic burden, characterised by increased morbidity, mortality and healthcare costs. In Italy, HF prevalence is estimated at 1.4% and risk increases with age, with nearly 15% of people over 85 years of age affected [1, 2]. A study in an Italian primary care setting reported that over 51% of those with chronic HF also had CKD [3]. Overall, these patients experience worsened clinical outcomes, including hospitalisation rates, reduced quality of life and mortality compared with those with

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either condition alone. Patients with HF and CKD are also at increased risk of hyperkalaemia (HK), which leads to increased risk of cardiovascular events, hospitalisations and death [4–6].

Treatment for patients with HF and CKD is complex. Renin–angiotensin–aldosterone system inhibitors (RAASi) offer significant benefits in improving cardiovascular outcomes, including reduced morbidity and mortality, and are recommended by several clinical practice guidelines [7–10]. RAASi treatment alone increases the risk of HK in this at-risk population, and following a moderate or severe case of HK in patients with HF and CKD, RAASi use is often down-titrated to a sub-optimal dose or permanently discontinued [6, 10, 11].

The management of HF patients is complicated as sub-optimal dosing or discontinuation of RAASi after a hyperkalaemic event reduces the risk of HK but increases the risk of other adverse events (AEs) including HF, myocardial infarction, stroke and death [12, 13]. A UK real-world evidence (RWE) study investigating the burden of HK found HK to be associated with an increased risk of both RAASi discontinuation and mortality [14]. As well as impacting on health, recurrent HK events create an economic burden, with a recent Italian study modelling the effect of persistent HK versus normokalaemia on costs demonstrating the value of maintaining normal K^+ levels, resulting in a lifetime saving per patient of €16,059 [15]. This was also noted in another study of an Italian population, where HK was more prevalent in people with HF compared with the general population and will therefore result in elevated healthcare costs [15, 16]. Similarly, HK events are associated with increased healthcare costs and resource utilisation across other European countries [17–20]. There are a range of treatment options for those who have had mild HK, including enteral K^+ exchangers and loop diuretics, but they can cause serious side effects and the data on their efficacy to date are limited [21–23]. Therefore, there is a need for a HK chronic treatment in HF with CKD populations that allows continued RAASi use, thereby reducing the clinical and financial burden associated with HK events.

OPAL-HK and the more recent DIAMOND clinical trials have demonstrated the efficacy and safety profile of an alternative treatment for HK in the form of patiromer, an oral potassium (K^+) binder which reduces K^+ levels and enables the continuation of optimal RAASi dosing in patients with HF and CKD [24–26]. Previous cost-effectiveness analyses of patiromer in several European countries have been conducted, showing an economic case for its use, but were conducted using data from the smaller OPAL-HK clinical trial [27–29].

1.1 Objective

This study aimed to evaluate the cost-effectiveness of patiromer in patients with concomitant HF and CKD in Italy, utilising data from the DIAMOND clinical trial [24].

2 Methods

A previously published Markov model [27] was adapted to estimate the course of HF and CKD disease progression in patients with HK, treated with either patiromer or standard of care (SoC), using data from the DIAMOND trial [27]. The aim was to estimate the costs and benefits associated with utilising patiromer for HK management from an Italian NHS perspective.

2.1 Trial Design and Patient Population

The DIAMOND trial was a prospective phase 3b multinational, multicentre, double-blind, randomised withdrawal, parallel-group, placebo-controlled trial that was designed to evaluate whether patiromer treatment in patients who developed HK while receiving RAASi medications would result in improved K^+ concentration and in turn lead to optimisation of RAASi use, consistent with guidelines [30] (ClinicalTrials.gov: NCT03888066).

The patient population for this analysis was adults ≥ 18 years old with New York Heart Association (NYHA) class II–IV, heart failure and left ventricular ejection fraction (LVEF) of ≤ 40% and HK defined as serum K^+ of > 5.0 mmol/l with diagnosed CKD and receiving a stable RAASi dose [31]. Baseline patient demographics and clinical characteristics of DIAMOND have been described previously [24, 31]. Subjects were required to have HK at screening (defined by two K^+ values of > 5.0 mEq/L) while receiving an angiotensin-converting enzyme inhibitor (ACE)/angiotensin receptor blocker (ARB)/angiotensin receptor/neprilysin (ARN) inhibitor, and/or a mineralocorticoid receptor antagonist (MRA).

Following screening, eligible subjects were enrolled into a single-blinded run-in phase with weekly visits. The purpose of the run-in phase was to control K^+ levels with patiromer while simultaneously optimising the use and doses of RAASi medications, including MRA (titrated to 50 mg/day). Patiromer was titrated up to a maximum of three packs/day (8.4 g/pack). After the run-in phase, lasting up to 12 weeks, subjects underwent a double-blind randomisation in a 1:1 ratio, to receive either continued patiromer or placebo (patiromer withdrawal). The K^+ levels were measured at screening, at baseline (after the run-in phase, prior to being assigned to a treatment arm),

at day 3, at weeks 1, 2, 6 and 18 and every 3 months until the end of the study. The median follow-up time was 27 weeks.

The primary analysis endpoint for the DIAMOND RCT was the mean change in serum K^+ levels between day 1/baseline (end of run-in phase) and study completion (end-of-study visit). Secondary outcome measures included the total number of cardiovascular hospitalisations and mortality.

2.2 Economic Model

The Markov cohort model was used to predict the natural course of CKD and HF progression over a lifetime horizon, in line with Health Information and Quality Authority technology assessment guidelines [32]. The model followed a monthly cycle and disease progression simulated over a lifetime. Costs and quality-adjusted life years (QALYs) were discounted at 3% per annum.

2.2.1 Disease Progression

All patients entered the model with both HF and CKD (Fig. 1), with baseline characteristics and details of modelled cohort characteristics provided in Online Resource 1. The model progressed patients through estimated glomerular filtration rate (eGFR) stages 1 to 5 and HF progression through NYHA categories I to IV, independently of one another, according to health state transition probabilities (Table 1). Transition probabilities within CKD stages were dependent on RAASi usage, and major adverse cardiovascular event (MACE) risk was applied depending on CKD stage, RAASi usage and K^+ level. Patients left the model when the death health state occurred; mortality rates were influenced by dialysis, transplant, CKD stage, K^+ level and RAASi usage [33–37]. Additional information on mortality rates is provide in Online Resource 1.

The model captured the value of each treatment as each patient progressed by recording the incidence of HK and RAASi down-titration or discontinuation. Three levels of RAASi usage were included: maximum (optimal), down-titrated (sub-optimal) and off. At cohort initialisation, RAASi use for patiromer was based on DIAMOND trial data and for SoC it was approximated based on published RAASi discontinuation rates and HK baseline distribution. Additionally, monthly probability of RAASi discontinuation, down-titration for different K^+ levels (≤ 5, > 5 to ≤ 5.5, > 5.5 to ≤ 6, > 6) and returning to RAASi max following discontinuation or down-titration was assessed on the basis of Linde et al.'s RWE study [14]. The probability of

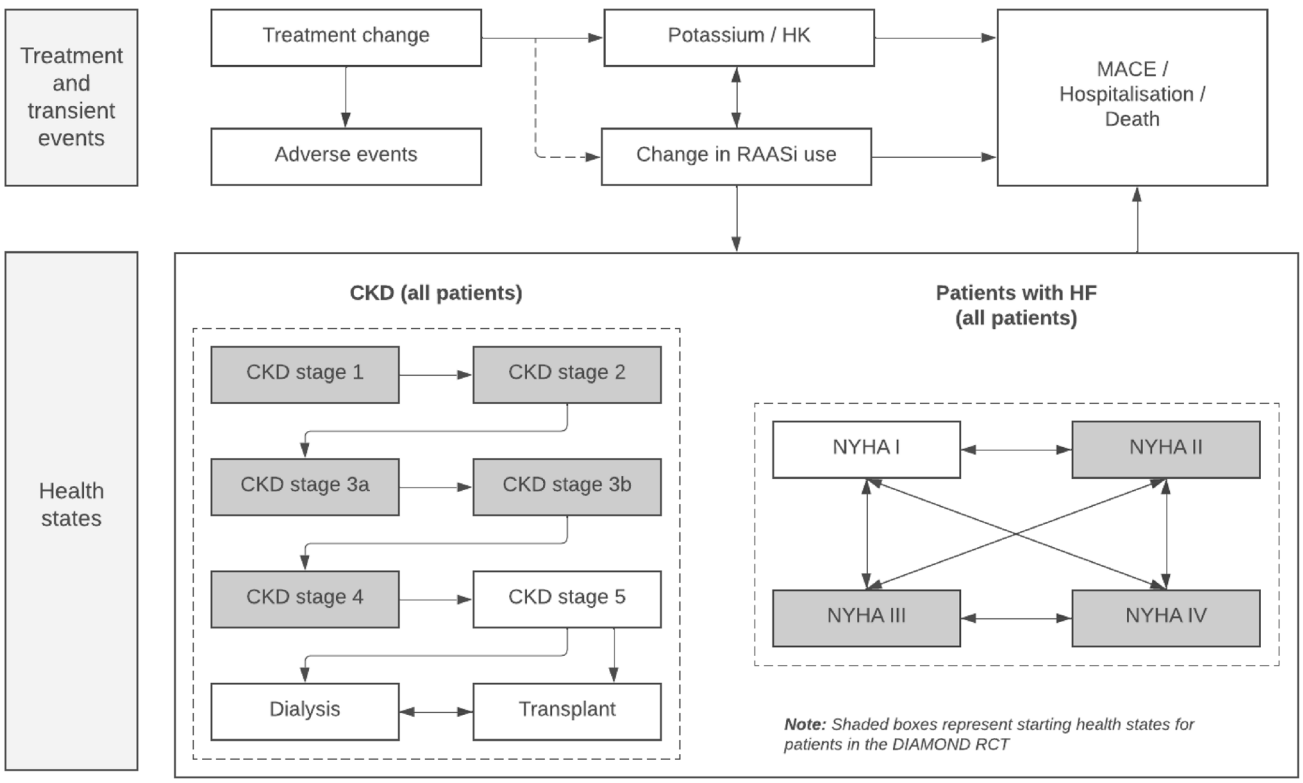

Fig. 1 Model structure. States highlighted in grey represent starting health states. *CKD* chronic kidney disease, *HF* heart failure, *HK* hyperkalaemia, *MACE* major adverse cardiovascular event, *NYHA* New York Heart Association, *RAASi* renin-angiotensin-aldosterone system inhibitor

Table 1 Model inputs controlling initiation and management of RRT (RRT module)

Parameter	Mean	SE	Source
Monthly transition probability			
CKD stage 1 to CKD stage 2	10.000%	1.000%*	Elbasha et al. [42]
CKD stage 2 to CKD stage 3a	0.838%	0.240%	
CKD stage 3a to CKD stage 3b	0.838%	0.240%	
CKD stage 3b to CKD stage 4	1.220%	0.311%	
CKD stage 4 to CKD stage 5	0.701%	0.070%*	
CKD stage 5 to dialysis	12.640%	1.614%	Cooper et al. [60]; time to dialysis of 7.4 months converted to exponential rate and subsequently to probability
CKD stage 5 to transplant	1.675%	0.168%*	NHSBT [37] (table 3.1 and fig. 3.12); UK Renal Registry 8th report [61] (Table 5.5)
Dialysis to transplant	2.759%	0.276%*	NHSBT [37] (table 3.13); UK Renal Registry 23rd report (2021) [33]
Dialysis to death	0.846%	0.085%*	UK Renal Registry 23rd report (2021) [33] (table 3.9)
Transplant to dialysis (graft failure)	0.193%	0.019%*	NHSBT [37] (tables 6.1 and 6.2; weighted by values in fig. 5.1); Karim et al. [62]
Transplant to death	0.323%	0.032%*	
CKD progression odds ratio			
On RAASi: CKD stage 1 to CKD stage 2	1.00	0.06	Assumption
On RAASi: CKD stage 2 to CKD stage 3a	1.00	0.06	Assumption
On RAASi: CKD stage 1 to CKD stage 2	0.62	0.06*	Xie et al. [63]
On RAASi: CKD stage 1 to CKD stage 2	0.62	0.06*	Xie et al. [63]
On RAASi: CKD stage 1 to CKD stage 2	0.62	0.06*	Xie et al. [63]

*SE assumed 10% of the mean

eGFR estimated glomerular filtration rate, *HF* heart failure, *NHSBT* NHS Blood and Transplant, *RAASi* renin–angiotensin–aldosterone system inhibitor, *RRT* renal replacement therapy, *SE* standard error

CKD progression, death in CKD patients, MACE in CKD and HF patients, hospitalisations in CKD and HF patients, and HK events was influenced by RAASi usage. In addition, hospitalisations (defined as any hospitalisation) and major adverse cardiovascular events (MACE; defined as HF, ischaemic stroke, coronary heart disease and peripheral arterial disease, leading to hospitalisation) were also recorded within the model as transient events with patient health state (CKD and HF), RAASi treatment and HK severity influencing the probability of each outcome. The rate of hospitalisation was dependent on CKD and NYHA stage, and RAASi usage and K^+ level. There was no maximum number of MACE events an individual could experience; the incidence of MACE events was influenced by RAASi usage (optimal, sub-optimal, off), K^+ level and CKD stage. Subsequent MACE events were not influenced by previous MACE. For MACE and mortality events, if a patient has both CKD and HF, the higher risk is taken. In the blinded treatment phase and including assessments recorded after the end of DIAMOND trial, AEs including hypokalaemia (mild-severe), hypomagnesemia, diarrhoea, constipation, nausea, any AE leading to withdrawal and any serious AE were recorded. Owing to the low incidence of AE leading to withdrawal and severe AEs in the DIAMOND clinical trial (similar proportions were recorded in both the patiromer and placebo groups; AEs leading to withdrawal were 2.7% and 2.5%, respectively, and there was a 0.2% rate of severe AE events in both groups) [24], AEs were not modelled in the present analysis. Additional model details are provided in Online Resource 2.

2.2.2 Costs

Each modelled health state and event was associated with direct medical costs, as shown in Online Resource 3. Costs were applied from the perspective of the Italian healthcare system and inflated to 2022 values [38–41].

A literature search was undertaken to identify costs estimates for HF and CKD health states [42–44]. For each patient, RAASi status (optimal, down-titrated and discontinued) and severity of HK events (mild HK: K^+ 5.0–5.5 mmol/L; moderate HK: K^+ 5.5 to $\leq$ 6 mmol/L; and severe HK: $K^+ > 6$ mol/L) were used to inform healthcare resource usage. In addition, costs for different events including end-stage kidney disease (ESKD)-related events (dialysis complications, transplant procedures and dialysis access), major events (MACE and hospitalisations) and medical visits and tests associated with HK management were taken from published literature and country reference unit costs. Health state costs associated with HF disease management were estimated as zero to avoid double counting (costs for HF event costs, MACE and hospitalisation were included).

Patient death was assumed to incur no cost. A recent National Institute for Health and Care Excellence (NICE) technology appraisal for the treatment of HK (TA599) was used to inform resource use for HK management [45].

The acquisition cost of patiromer was €10.81 per 8.4 g per day. Three annual costs for RAASi use were calculated by per patient and subgroup: €175.89 for optimal, €87.95 for sub-optimal (down-titrated) and €0.00 for discontinued RAASi, based on the average patient drug usage (informed by the Italian clinical members of the study team on the basis of their clinical expertise and knowledge). There was no stopping rule (stopping after a predefined time period) for patiromer, and it was assumed it would be continued throughout the patient's lifetime or until discontinuation occurs.

2.2.3 Utility Inputs

Utility weights were applied to calculate QALYs, with one QALY representing 1 year of life in perfect health. Italian age-dependent utility estimates informed the baseline utility of the trial population. Both CKD and HF health state utilities and event disutilities were applied to calculate QALYs per arm for each cycle, but to avoid double counting, HF health state utilities were assumed to be unity. Italian utility data for health state and event components was used where available. Where Italian-based data were unavailable, estimates based on other country settings were applied. Full details on the applied utility weights are detailed in Online Resource 4.

2.2.4 Mean K^+ Concentration

All participants (treatment and SoC) of the DIAMOND trial received, by protocol, patiromer therapy during an initial 12-week run-in phase, to standardise baseline RAASi therapy and K^+ levels. This approach meant that, after randomisation and up until the end of the DIAMOND study, the mean K^+ concentration of the placebo arm is influenced by the legacy effect of patiromer treatment received during the run-in phase [24]. However, this does not provide a realistic mean K^+ value for informing the SoC arm of the cost-effectiveness model. Instead, the clinical outcomes from SoC reflect the continual beneficial effect from the previous patiromer treatment, as shown in Butler et al. [24].

To better represent the mean K^+ levels for SoC in this analysis, data from a RWE study by Linde et al. [14], with a comparable patient profile to DIAMOND, with a large cohort size of 21,334 UK HF/CKD patients with $K^+ \geq 5.0$ mmol/L, was used to better represent the performance of mean K^+ levels in SoC in this cost-effectiveness analysis.

Owing to differing population characteristics between DIAMOND and the RWE study, an indirect treatment comparison (ITC) was conducted to inform mean K^+ values for the baseline and patiromer arm of the cost-effectiveness model. This calculated adjusted estimates of serum K^+ concentrations, at screening phase and end of run-in phase, respectively, for the DIAMOND [24] study population that would be expected if the population were identical to that observed in the comparator RWE study [14]. Note that the mean K^+ value at the screening phase of the trial was used as the "baseline" in the model while that at the end of the run-in phase of the trial was used as the "after patiromer treatment" value in the model.

A matching adjusted indirect comparison (MAIC) was deemed to be the most appropriate ITC methodology, as outlined in NICE DCU27 [46] and Signorivitch et al. [47]. It allows individual patient-level data from an index study to be reweighted to match aggregate patient characteristics of a comparator study [45, 47]. Study outcomes are subsequently reweighted in a comparable manner, allowing the effect of the intervention in the index study to be estimated in a population similar to that of the comparator study. Here, individual patient data from the index trial were reweighted to provide weighted patient characteristics of the trial that matched patient characteristics of the RWE cohort [14].

For the unanchored MAIC analyses (i.e. where there is no connected network of evidence for the treatments of interest), all prognostic factors (PFs) and treatment effect modifiers (TEMs) variables were included as covariates for adjustment. Variables were identified from a review of patiromer literature and considered to be PFs or TEMs [14, 24]. Subsequently, these variables were used as the matching variables in the analysis, and included age, region (proportion in European region), sex (proportion male), diabetes (proportion with diabetes flag) and eGFR. Since baseline serum K^+ was the outcome of interest in the MAIC, it was not included as a matching variable.

Population reweighting (Online Resource 5) indicated that there was sufficient overlap between the DIAMOND and Linde et al. study populations and that it was feasible to use MAIC to derive adjusted serum K^+ concentrations. The MAIC produced an effective sample size of 254, based on the matching variables listed above; this was a reduction from the 878 patients from the DIAMOND trial.

Baseline characteristics before and after matching were similar; the reweighting of the patiromer population was successful for the five variables on which the populations were matched (Table 2). To further investigate the matching of covariates, which were not adjusted, a Love plot was created (Online Resource 5). The proportions of patients using ACEIs, ARBs and MRAs differed at baseline. However, since all patients in the DIAMOND study received RAASi at baseline, adjustment of RAASi use was not possible. Similarly, it was not possible to match the populations using MRAs, as 99.9% of the patients in DIAMOND

used MRAs at baseline. Whilst the two populations are well matched on variables such as age, sex, region, eGFR and diabetes, there were some differences between the RWE and adjusted populations.

To enable the calculation of mean serum K^+ concentrations at screening (used as the baseline K^+ level in the model) and baseline (end of run-in, used as the "after patiromer treatment" value in the model) for patients from the DIAMOND trial, MAIC weights were applied to the patients in DIAMOND [24], adjusted to a population similar to the RWE study [14]. The mean serum K^+ concentration values at baseline (after run-in) and after patiromer are presented in Table 3.

Table 3. Mean serum K^+ level inputs

	Mean serum K^+ concentration (mmol/L)
Baseline[†]	4.840
Post-patiromer[†]	4.634
Post-SoC[‡]	5.239

K^+ potassium, *RWE* real world evidence, *SoC* standard of care

[†]Baseline and patiromer mean K^+ concentrations were derived from MAIC analysis, utilising data from DIAMOND and RWE [14, 24]

[‡]Patients in the SoC arm of the DIAMOND trial had lower mean K^+ concentration levels compared with patients from the real world, thus the mean K^+ concentration value was based on the weighted average of RWE data

2.3 Analysis

2.3.1 Base Case

The model was utilised to assess the lifetime impact of patiromer use compared with SoC for the treatment of HK in patients with HF and CKD. The primary model outcome was the incremental cost-effectiveness ratio (ICER) and represents the extra cost per QALY gained. The ICER was calculated as the difference in cost between the treatment (patiromer) and SoC arms divided by the differences in QALYs. The treatment was considered cost-effective if the ICER was less than the willingness-to-pay (WTP) threshold of €40,000/QALY gained [48–52].

2.3.2 Sensitivity Analyses

Deterministic sensitivity analysis and probabilistic sensitivity analysis were conducted to quantify the level of confidence in the ICERs, and incremental net monetary benefit (INMB) and analyse uncertainty in clinical and economic outcomes. A deterministic sensitivity analysis assessed the impact of individual parameters on the model outcomes, using lower and upper values (bounds of 95% confidence intervals or minimum and maximum values). For the probabilistic sensitivity analysis, patient characteristics and demographics were sampled using a normal distribution; transition probabilities, utility and disutility values were sampled using a beta distribution; costs were sampled using a gamma distribution; and hazard ratios and odds ratios were sampled using a log-normal distribution.

2.3.3 Scenario Analyses

A scenario analysis was performed to determine the effect if both the patiromer and SoC cohorts were to have the same RAASi usage distribution at model entry. The values for patiromer from the DIAMOND clinical trial were applied to the SoC cohort. Additional scenario analyses were performed to explore the effect of varying baselines characteristics of the model population. These included patients grouped according to CKD severity, denoted by baseline eGFR. Patients with CKD stage 3a (eGFR 45–59 mL/min/1.73 m^2) and stage 3b (eGFR 30–44 mL/min/1.73 m^2) and stage 4 (eGFR 15–29 mL/min/1.73 m^2) were analysed for the cost and benefit implications of patiromer at different stages of the CKD pathway. Furthermore, patients with history of HK were adopted as a subgroup, in which patients reporting at baseline with normokalaemia (serum $K^+ \leq 5$) were excluded from the model analysis. A final scenario analysis was performed to determine the impact of including HF disease management costs alongside the CKD

Table 2 Baseline characteristics of DIAMOND trial before and after adjustment compared with baseline characteristics of RWE study

Variable	Patiromer unadjusted (DIAMOND trial)	Placebo (RWE study)	Patiromer adjusted
Age (years)	66.401	73.320	73.320
Proportion male	0.734	0.611	0.611
Proportion European	0.862	1.000	0.999
eGFR (ml/min/1.73 m^2)	63.703	64.680	64.680
Proportion diabetic	0.396	0.201	0.201

eGFR estimated glomerular filtration rate, *RWE* real-world evidence

disease management costs; the NYHA-dependent costs were sourced from Rognoni 2019 [53].

3 Results

3.1 Base Case Analysis

Base case cost-effectiveness results are summarised in Table 4. The modelled outcomes show that each patient incurred significant total lifetime costs of €64,847 in the SoC arm. Introducing patiromer led to an increase in total lifetime cost per patient compared with SoC, amounting to €45,053 over a lifetime horizon. Despite this increased cost, patiromer treatment demonstrated significant clinical benefits compared with SoC, with gains in both LYs and QALYs; patients in Italy gained an average of 1.973 LYs and 1.550 QALYs. When compared with the SoC, patiromer was associated with a deterministic INMB of €16,961 and an ICER of €29,060 per QALY gained, thus suggesting that patiromer is cost-effective compared with SoC, considering a WTP threshold of €40,000/QALY gained.

The cost increase associated with patiromer treatment, compared with SoC, was partially offset by cost savings from HK events (€786 per patient) and RAASi titration (€192 per patient), as presented in Table 4. The additional cost in the patiromer arm is mainly attributable to drug cost and direct medical costs associated with longer lifespans, leading to more time for experiencing HF, CKD and other events, highlighting the importance of considering lifespan implications in cost-effectiveness evaluations. Further, the majority of QALY gains in the patiromer arm were attributable to the additional time spent in CKD stages 2–4.

In the patiromer cohort, a reduction in moderate and severe HK events per patient (− 12.66 and − 0.13, respectively), up-titration/restarting RAASi events (− 1.38), down-titration events (− 0.78) and discontinuation of RAASi (− 1.72) was observed when compared with SoC (Fig. 2). Further, in those treated with patiromer, event rates for MACE and hospitalisation were slightly increased (0.19 and 1.35, respectively), with similar numbers of dialysis (0.020), transplant (0.02) and dialysis complication events (0.003) compared with SoC. Note that the increased life expectancy in the patiromer arm led to the increases observed in MACE and hospitalisations.

Table 4 Base-case cost-effectiveness results

	Patiromer	SoC	Difference
Clinical effectiveness (discounted)			
Total life years	10.036	8.036	1.973
QALY breakdown (discounted)			
CKD stage 1	0.102	0.100	0.002
CKD stage 2	2.354	2.058	0.296
CKD stage 3a	2.427	1.870	0.557
CKD stage 3b	1.610	1.274	0.336
CKD stage 4	1.094	0.817	0.277
CKD stage 5	0.028	0.024	0.004
Dialysis	0.078	0.064	0.014
Transplant	0.283	0.217	0.066
MACE	− 0.009	− 0.009	0.000
Hospitalisation	− 0.010	− 0.008	− 0.002
Total QALYs	7.958	6.407	1.550
Costs (discounted)			
Treatment	€32,726	€0	€32,726
HK	€252	€1038	− €786
Medical by $K^{+\dagger}$	€0	€0	€0
HF‡	€0	€0	€0
CKD	€21,851	€17,301	€4550
RRT	€15,834	€12,625	€3209
MACE	€11,727	€11,321	€406
Hospitalisation	€26,142	€21,693	€4449
RAASi drug usage	€1318	€627	€691
RAASi titration	€51	€243	− €192
Death	€0	€0	€0
Total costs	€109,900	€64,847	€45,053
NMB	€208,410	€191,449	€16,961
Cost-effectiveness results			
Cost per life years gained			€22,837
Cost per QALY gained			€29,060

CKD chronic kidney disease, *HF* heart failure, *HK* hyperkalaemia, K^+ potassium, *MACE* major adverse cardiovascular event, *NMB* net monetary benefit, *QALY* quality-adjusted life year, *RAASi* renin–angiotensin–aldosterone system inhibitors, *RRT* renal replacement therapy, *SoC* standard of care

†Medical costs relating to K^+ assumed to be zero as costs accounted for elsewhere

‡Health state costs associated with HF were assumed to be zero to avoid double counting

3.2 Deterministic Sensitivity Analysis

Results of the deterministic sensitivity analysis presenting the ten most influential parameters are shown in Fig. 3. The deterministic sensitivity analyses revealed that K^+ levels had the highest impact on the cost-effectiveness results.

3.3 Probabilistic Sensitivity Analysis

Assuming a cost-effectiveness threshold of €40,000 per QALY gained, patiromer was cost-effective in 71.6% of 1000 iterations compared with SoC (Fig. 4).

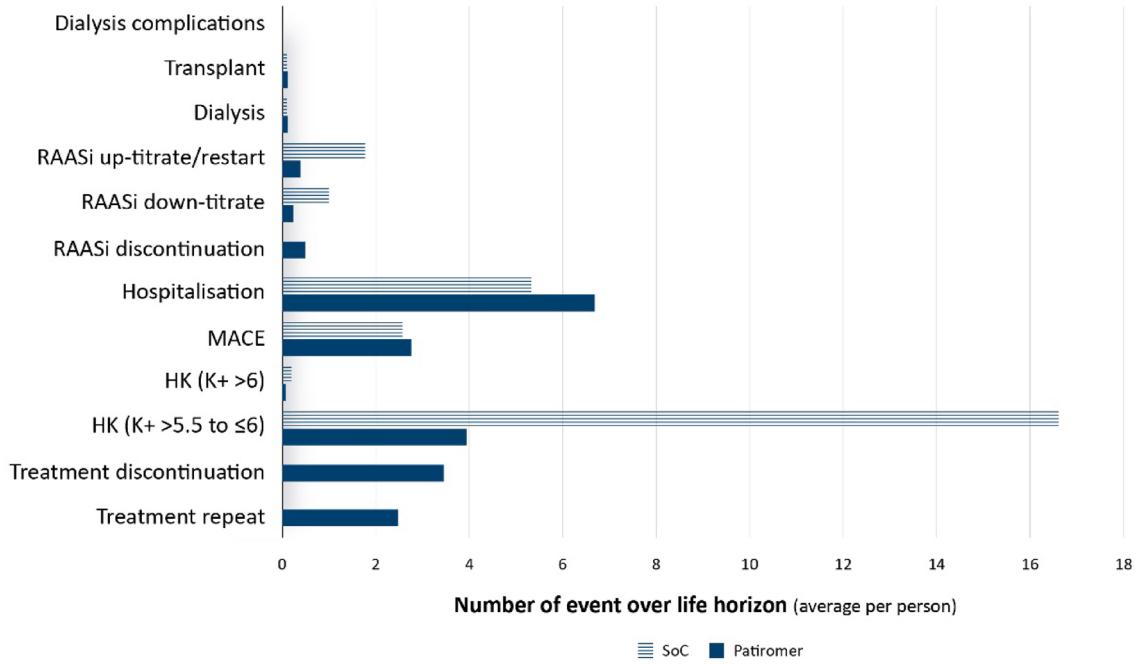

Fig. 2 Clinical outcomes. Striped and blue bars represent SoC and patiromer respectively. *HK* Hyperkalaemia, *MACE* major adverse cardiac event, *RAASi* renin-angiotensin-aldosterone system inhibitor, *SoC* standard of care

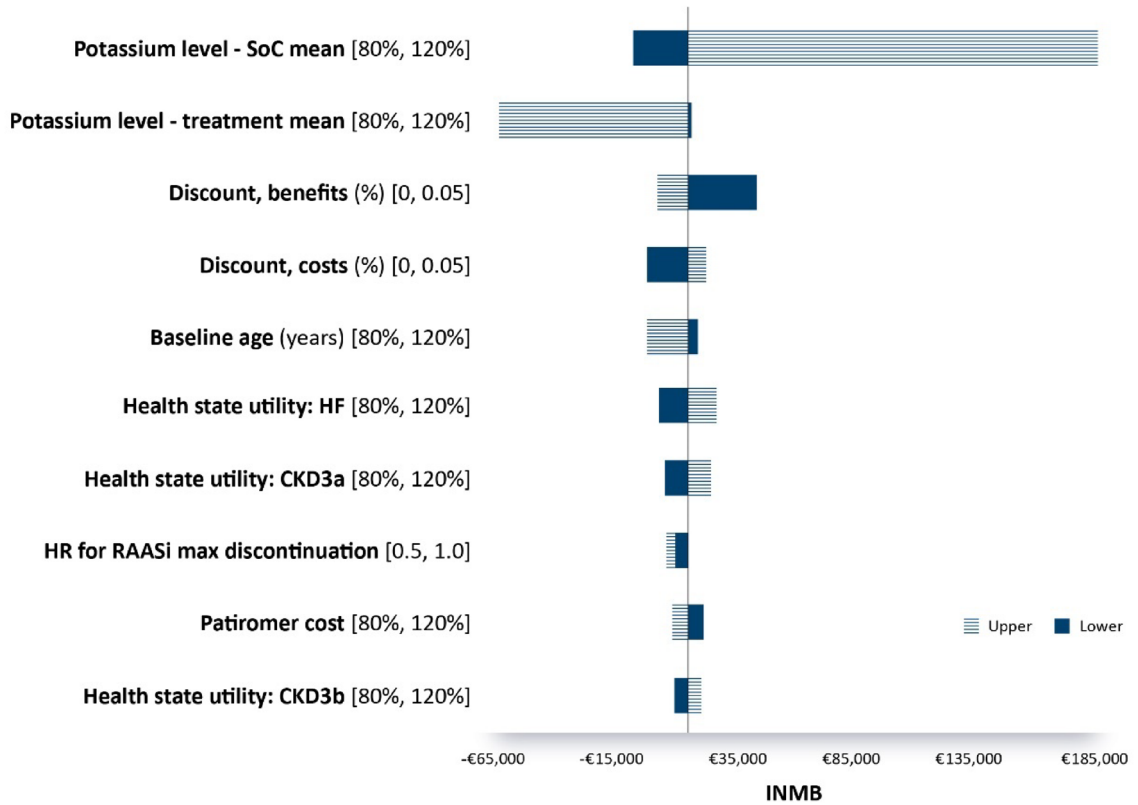

Fig. 3 Deterministic sensitivity analysis. *CKD* chronic kidney disease, *HF* heart failure, *HR* hazard ratio, *INMB* incremental net monetary benefit, *RAASi* renin-angiotensin-aldosterone system inhibitor, *SoC* standard of care.

3.4 Scenario Analyses

In the scenario where the RAASi distribution at model entry was assumed to be the same for patiromer and SoC, the impact on results was negligible, with the ICER increasing by only 0.2% from €29,060 to €29,124 (Table 5).

In the base case, patients entered the model at CKD stage 1–4, with 62.11% of the cohort entering the model with normokalaemia. Since each CKD stage is associated with distinct clinical risks, outcomes and costs, scenarios with all patients (100%) initiating the model at a specific CKD stage (3a, 3b or 4) were explored (Table 5) to determine the stage at which treatment is most cost-effective. Over a lifetime horizon, the lowest ICER was observed at mild to moderate

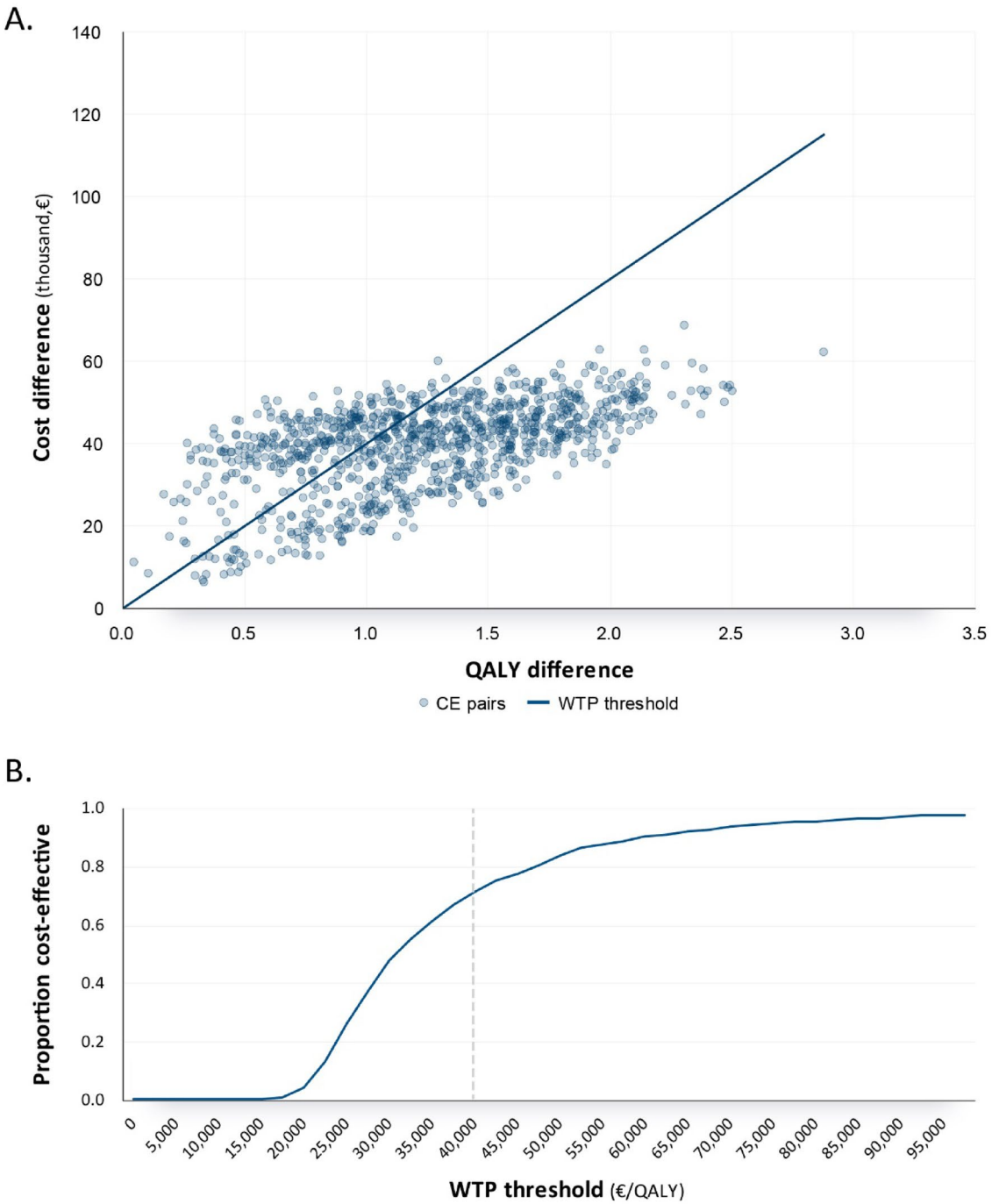

Fig. 4 Probabilistic sensitivity analysis results. *CE* cost-effectiveness, *QALY* quality adjusted life year, *WTP* willingness-to-pay

Table 5 Scenario analysis results

Scenario	Intervention	Total costs (€)	Total LYs	Total QALYs	ICER Cost per QALY gained[¥]
Equal RAASi usage at baseline	Patiromer	109,900	10.036	7.958	€29.124
	SoC	64,837	8.067	6.410	
	Incremental	45,063	1.969	1.547	
CKD stage 3a[†]	Patiromer	105,558	10.080	7.886	€28,402
	SoC	61,749	8.108	6.344	
	Incremental	43,809	1.972	1.542	
CKD stage 3b[†]	Patiromer	148,798	9.822	7.399	€34,900
	SoC	95,221	7.776	5.864	
	Incremental	53,577	2.046	1.535	
CKD stage 4[†]	Patiromer	199,582	9.367	6.582	€42,200
	SoC	137,269	7.289	5.106	
	Incremental	62,313	2.078	1.477	
Patients with a history of HK[‡]	Patiromer	109,948	10.036	7.958	€29,043
	SoC	64,903	8.062	6.407	
	Incremental	45,045	1.973	1.551	
Including HF management costs	Patiromer	141,548	10.036	7.958	€33,087
	SoC	90,252	8.063	6.407	
	Incremental	51,296	1.973	1.550	

All costs shown are discounted

CKD chronic kidney disease, *HF* heart failure, *HK* hyperkalaemia, *ICER* incremental cost-effectiveness ratio, *QALY* quality adjusted life year, *RAASi* renin-angiotensin-aldosterone system inhibitor, *SoC* standard of care, *LYs* life years

‡Calculated assuming that 0% of patients are with normokalaemia at baseline (cohort initialisation)

[†]Calculated assuming that 100% of patients are in a particular CKD stage at baseline (cohort initialisation)

[¥]Willingness to pay threshold: €40,000

stages of CKD with an ICER of €28,402/QALY gained for stage 3a and €34,900/QALY gained for stage 3b. The highest ICER was for CKD stage 4, resulting in €42,200/QALY gained.

A further scenario was constructed to evaluate the cost-effectiveness of patiromer in those with a history of HK, where all patients with $K^+ \leq 5.0$ mmol/L were excluded. In this population, ICER was comparable to the base case (€29,043 per QALY gained), meaning that the model outcome is not influenced by baseline K^+ values.

In the scenario where HF disease management costs were included alongside CKD disease management costs, the ICER was slightly increased when compared with the base case (€33,087 versus €29,043 per QALY gained).

4 Discussion

In this study, we determined that patiromer is a cost-effective treatment for HK in patients with concomitant HF and CKD in Italy, using data from the DIAMOND trial. A Markov state-transition framework model was chosen for this analysis as individual patient-level simulations are typically subject to patient-level stochastic variability, and convergence (particularly when differences between treatment arms might be small) may be difficult to achieve without running an extremely large number of simulations. In contrast, a Markov model assumes that heterogeneity between patients can be captured by a set of homogeneous health states.

The base case simulation indicated an ICER of €29,060 per QALY gained, almost 27% lower than an Italian WTP threshold of €40,000 per QALY gained [48–52]. Patiromer was cost-effective in the scenario where all patients entered the model with the same RAASi usage distribution. Patiromer was also cost-effective in all scenarios where baseline characteristics were varied, except at CKD stage 4, underlining how early treatment is potentially more effective compared with late intervention. In addition, cost-effectiveness was maintained in a scenario where all the patients reporting at baseline with normokalaemia were excluded from analysis, implying that patiromer remains cost-effective in patients with any level of K^+ at baseline. In the scenario where HF disease management costs were included alongside CKD disease management costs, an increase in the ICER was

seen. This represents a conservative approach because there is a risk of overlap/double counting when including both CKD and HF disease management costs, however patiromer cost-effectiveness was still maintained.

Sensitivity analyses revealed that, among the clinical inputs, the model was most sensitive to K^+ levels, in both the patiromer and SoC arms. However, general inputs such as discount rate and baseline characteristics also impacted the results. The probabilistic sensitivity analysis results showed that the modelled data are robust, with 71.6% of 1000 iterations indicating that patiromer remained under the WTP threshold.

Economic evaluation of patiromer has been reported previously in Europe, mainly utilising data from the short-term clinical trial, OPAL-HK [27–29, 54, 55]. A study by Gonzalez-Juanatey et al. investigated the cost-effectiveness of patiromer for the management of HK in patients with CKD with or without HF from a Spanish health care perspective [54]. Patiromer treatment versus usual care resulted in greater QALYs (5.76 versus 5.57, respectively) and life years (7.73 versus 7.50, respectively) with an incremental cost of €3574, yielding an ICER of €19,092 per QALY gained. Another cost-effectiveness study by Widen et al. assessed the impact of patiromer in HK patients with CKD from a Swedish health care perspective [29]. Patiromer was cost-effective at a WTP threshold of €52,804 per QALY gained, with a gain of 0.14 QALYs and an incremental cost of €6109 compared with SoC. This resulted in an ICER of €43,307 per QALY gained. A further study evaluated the costs and effectiveness associated with patiromer treatment in HK management in patients with CKD from a healthcare perspective in Austria [44]. Compared with SoC, patiromer was cost-effective and associated with greater QALYs (5.48 compared with 4.90) and an incremental cost of €10.96. The ICER was €18,979 per QALY gained. Together, these studies show that patiromer is a cost-effective treatment in HK management in patients with HF and/or CKD. Nevertheless, published literature demonstrates the challenges of utilising data from small, short-term clinical trials, such as OPAL-HK, which are less able to accurately predict long-term outcomes [56]. Our results align with the previous cost-effectiveness studies using data from the recent DIAMOND trial.

Compared with OPAL-HK, DIAMOND included a larger and more diverse patient population, with CKD stage from 1 to 4 and higher prevalence of HF [24]. This wider representation enhances the generalisability of the findings. Further, the extension of the DIAMOND trial to 54 weeks confirmed the long-term clinical effects of patiromer, showing that decreased K^+ levels seen at week 12 were maintained until week 54 [24, 57].

HK management in Italy poses a significant clinical challenge in HF and CKD, with detrimental effects on patients' outcomes. Despite its well-recognised epidemiological burden and negative impact on HF and CKD prognosis, current therapeutic strategies remain sub-optimal. This is further highlighted by an Italian prospective study by Provenzano et al., which demonstrates the limitations of existing approaches even within the specialised setting of kidney clinics, which are considered the gold standard for managing CKD [58]. This study followed 2443 patients with CKD visiting Italian nephrology clinics and found that HK was frequent (37%) and associated with a greater risk of ESKD. Another observational study by Maggioni et al. investigated the prevalence and clinical impact of HK in HF by utilising data from several local Italian health databases [16]. They reported a significant and direct association between HK and CKD, HF, and a reduction in RAASi use, with greater hospitalisations and tripling of healthcare costs.

These data underscore the urgent need for utilising more effective and well-tolerated therapies, such as patiromer, to manage HK in patients with HF and CKD. Existing options are limited and include discontinuing or reducing beneficial RAASi therapy or rely on short-term interventions such as sodium polystyrene sulphonate. Although patiromer offers a promising alternative by reducing chronic HK and continuation of RAASi therapy and is recommended by the European Society of Cardiology and endorsed by the Italian Society of Nephrology, it is not yet reimbursed by the Italian NHS [30, 59].

4.1 Limitations

Although this study provides valuable insights into the cost-effectiveness of patiromer for the treatment of HK in patients with concomitant HF and CKD in Italy, there are several limitations associated with our analyses. The main challenge was overcoming the legacy effect of patiromer in the SoC arm of the DIAMOND trial, which led to artificially low K^+ levels. To address this limitation and enhance the robustness of the study, a RWE study was sought to better represent K^+ values. The DIAMOND trial and RWE study populations underwent MAIC analysis to adjust the K^+ values at baseline and end of screening. There was good overlap between the DIAMOND and RWE populations, and following the MAIC, these populations were sufficiently matched on a number of key variables. While this approach achieved similarity in key variables between the DIAMOND and RWE populations, there were some limitations. The population overlap was limited, and differences in trial methodologies remain between DIAMOND and RWE [2, 55]. Additionally, as it was not possible to adjust for RAASi usage, it is likely that the estimated K^+ concentrations are slightly higher than would be expected in a RWE population. This is based on the understanding that RAASi usage would lead to higher K^+ concentrations and the percentage of the DIAMOND population using RAASi is higher than the corresponding

number in the RWE population. Thus, we expect that the impact of adjusting for RAASi use would lead to a reduction in K^+ concentrations. As we were unable to adjust for RAASi usage, this reduction has not been observed, leading to the conclusion that K^+ concentrations are expected to be slightly higher than would be expected in the RWE population. On the other hand, the RAASi distribution at cohort initiation in patiromer and comparator arms differed slightly, which partially outweighed the above limitation. The cost-effectiveness analysis extrapolated lifelong outcomes based on K^+ values at only 12 weeks, which introduces inherent uncertainty. However, as DIAMOND was a 54-week trial, we could assess the stability of these values by comparing K^+ levels at both timepoints. Indeed, stable K^+ level was observed between weeks 12 and 54 for patients treated with patiromer. The 54-week data point excluded from the model would have introduced greater uncertainty into the model, since this data point was based on fewer observations. Additionally, as the K^+ value at week 12 was higher than that at week 54 (4.623 versus 4.597), we would expect to see better results for patiromer using the week-54 value, so using the week-12 value is a conservative approach. To ensure the uncertainty assessment was kept within the model, both DSA and PSA were conducted, where the impact of different K^+ levels on analysis results was assessed.

The maximum number of MACE events was uncapped, which could have resulted in higher costs and worsening health outcomes. Further, the increased risk of subsequent MACE events was not captured. However, because the number of MACE events per patient over a lifetime in the model is low, the effect of these assumptions on the overall health and economic outcomes of the model is likely not to be affected.

In addition, the use of a cohort model rather than a patient-level model means that individual patient histories were not used, therefore it was not possible to fully capture the interaction between CKD progression, RAASi titration and HF progression, which would have been possible if using a patient-level model. Our cost-effectiveness analysis relies on a relatively limited body of existing literature, posing potential biases and knowledge gaps and highlighting the need for further research to solidify the evidence base. While our study acknowledges this limitation, it provides a valuable initial exploration in the absence of more robust data.

4.2 Conclusions

These results suggest that, despite an increase in cost associated with patiromer treatment, the significant clinical benefits in terms of extended life and improved quality of life outweigh the additional expense. Considering the WTP threshold of €40,000/QALY gained, our results find patiromer to be a cost-effective treatment option for HK management in patients with concomitant HF and CKD in Italy.

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Declarations

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Author contributors A.R.d.A. conceptualised and designed the study. E.S. was responsible for data analysis. All authors contributed to interpretation of the results, preparation and review of the manuscript, and approval of the final manuscript for publication.

Conflicts of interest A.R.d.A. was an employee of CSL Vifor at the time of original drafts. E.S. and M.H. are employees of Health Economics and Outcomes Research Ltd. Health Economics and Outcomes Research Ltd. received fees from CSL Vifor in relation to this study. E.P. reports consultancy fees from CSL Vifor, AstratZeneca, Astellas and Novartis. M.S. reports consultancy fees from CSL Vifor, Novartis, Merck, Bayer, Abbott, Boehringer Ingelheim, AstraZeneca, Bioventrix, Servier, Novo Nordisk, Cardurion and AnaCardio.

Availability of data and material All data and material relevant to the analysis are presented in the publication or its supplementary material, with the exception of the model itself.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability The model used in this study was provided to the journal's peer reviewers for their reference when reviewing the manuscript, but the model remains the intellectual property of CSL Vifor. The authors will respond to all enquiries regarding the details of the analysis upon reasonable request should these not have been answered by the information provided in the "Methods" section.

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