NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Patiromer for treating hyperkalaemia [ID877]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Patiromer for treating hyperkalaemia [ID877]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Patiromer for treating hyperkalaemia

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	British Society for Heart Failure	Background and general comments: Patients with heart failure and reduced ejection fraction (HFREF) derive major prognostic benefit from with angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), sacubitril/valsartan, beta blockers and mineralocorticoid receptor antagonists (MRAs) [data summarised in ESC guidelines, 1]. For many of these drugs, the benefit is additive. For example, the combination of sacubitril/valsartan, beta blocker and MRA results in a reduction of all-cause mortality with a hazard ratio of 0.37 against placebo [2]. Renin angiotensin aldosterone inhibitors (RAASi) may lead onto hyperkalaemia, in particular in patients with co-existent chronic kidney disease (CKD). In some instances this may result in clinicians stopping or reducing doses of one or more RAASi. The British Society for Heart Failure (BSH) feel that the management of hyperkalaemia during co-existent RAASi use should be directed according to the strength of indication for the RAASi. That is when the drugs have clear prognostic benefit (i.e. HFREF or post MI left ventricular systolic dysfunction or CKD with albuminuria) every effort should be made to ensure their continuation at highest possible dose. This is very different to when they are used to treat hypertension – here many other good alternatives exist and switching the drug to a different class seems very appropriate, if problems such as moderate or severe hyperkalaemia ensue. Similarly if a patient has heart failure with preserved ejection fraction (HFPEF) RAASi have not been shown to be of prognostic benefit. The BSH, Renal Association (RA) and Think Kidneys have published guidelines on the management of changes in renal function and potassium on initiation and up titration of RAASi in patients with heart failure [3]. 1. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2129-2200Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, Cope S. 2. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. Circ Heart Fail 2017;10: pii: e003529 3. https://tinyurl.com/y7yrlk69	Thank you for your comment.
2	Consultee	British Society for Heart Failure	The NICE summary documents are confusing and mix multiple conditions like heart failure, CKD and hypertension and the acute and post-acute/chronic management of hyperkalaemia. It will be almost impossible to make one single recommendation for all of these things. As such the BSH agree that there should not be a very broad indications such as 'hyperkalaemia in adults' for these drugs. However, we feel that availability of novel drugs to lower potassium might be of clinical	Thank you for your comment. The committee considered patiromer within its marketing authorisation and the available clinical evidence.

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			value in the management of a very select cohort patients with HFREF who develop hyperkalaemia in order to facilitate the use of life prolonging drugs (i.e. RAASi) and to prevent development of hyperkalaemia (e.g. potassium >6.0mmol/l). It is uncertain as to how many patients this might effect, but we feel the numbers will be very small. Some patients who develop hyperkalaemia will have other issues such as worsening renal function and/or hypotension, which themselves might limit continued prescribing of RAASi. In summary, by not approving these novel treatments in any clinical scenario patient care may suffer. A suggestion would be restricted use for high risk HFREF patients under secondary care teams (this would for example include compassionate use in advanced heart failure patients with multiple previous admissions who have needed to stop a RAASi due to isolated hyperkalaemia). The BSH feel unable to comment on potential use in patients with severe/end stage renal disease.	
3	Consultee	British Society for Heart Failure	Throughout the document reference is made to the committee and clinical expert highlighting that most clinicians would only treat hyperkalaemia unless the value was 6 mmol/l or more. This is not correct and the BSH feel that this over simplifies the complexity of management of hyperkalaemia. The document mentions that in this case treatment would be as an emergency in secondary care with agents such as insulin/dextrose, calcium gluconate and calcium resonium. It does highlight that RAASi would be stopped or reduced. The BSH feel strongly that in routine clinical practice many clinicians do intervene or 'treat' at potassium values much lower than 6mmol/l. Whilst this may not involve prescription of additional therapy it is commonly a reduction or cessation of ongoing treatment with RAASi. For patients with HFREF, post MI left ventricular systolic dysfunction or CKD with albuminuria this has major adverse implications. 'Section titled: People would welcome an alternative to stopping RAASi'. The BSH agree with this statement but are concerned that the focus of the document is on patients with hypertension and is merely focusing on RAASi as anti-hypertensive agents. They are not just blood pressure lowering drugs - in HFREF, for example, they are disease modifying drugs. See below extract taken from page 7 below: ''The committee concluded that patients and clinicians were keen for new treatments that would allow them to continue to take RAAS inhibitors, but that the harms and benefits of stopping a RAAS inhibitor and switching to an alternative blood pressure lowering treatment would need to be taken into account.''	Thank you for your comment. At the second meeting the committee considered additional evidence supplied by the company on the treatment pathway for hyperkalaemia and clinical expert opinion. The treatment pathway for hyperkalaemia is described in more detail in the FAD, please see section 3.1 of the FAD.
4	Consultee	British Society for Heart Failure	Whilst the BSH agrees that the acute management of severe hyperkalaemia primarily involves treatment such as calcium gluconate, insulin/dextrose and calcium resonium, there may be occasions when novel potassium binders compliment/add to current options. For example, if calcium resonium was not tolerated. Patients often require emergency admission when severe hyperkalaemia is diagnosed; the use of novel potassium binders may allow the patient to be managed safely at home preventing an unnecessary hospitalisation.	Thank you for your comment. The committee considered that patiromer will be used alongside standard care for acute hyperkalaemia and in outpatient care for chronic hyperkalaemia. See section 3.7 of the FAD for further detail.
5	Consultee	British Society for Heart Failure	In summary, the BSH would like NICE to consider use of the new potassium binders for restricted use by secondary care clinicians involved in the management of patients with prognostic indication for RAASi. The BSH are concerned that the NICE evaluation only focuses on the acute presentations with very high potassium levels and fails to consider the downstream adverse effects on patients, associated healthcare costs and adverse outcomes if RAASi are withheld/reduced. The BSH feel unable to comment on potential use in patients with severe/end stage renal disease.	Thank you for your comment. The economic model took into account the long-term impacts of reducing and stopping RAASi. The committee considered that patiromer will be used alongside standard care for acute

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				hyperkalaemia and in outpatient care for chronic hyperkalaemia. See section 3.7 of the FAD for further detail.
6	Consultee	British Society for Heart Failure	The BSH would also highlight that more research is needed, even in the shorter-term with soft heart failure outcomes (e.g. symptoms, QoL, BNP etc). If some use is approved, then the BSH would welcome the prospective collection of data relating to the practicality of use of these medications (e.g. drug interactions and adherence).	Thank you for your comment. The committee made recommendations for further research for patiromer including investigating: mortality, disease progression, patterns of RAAS inhibitor use, healthcare use and health related quality of life. See section 5.1 of the FAD for further detail.
1	Consultee	Pumping Marvellous Foundation	As the patient expert at the committee meeting, I can comment that the committee did not consider or listen to the conversation around why controlling and managing hyperkalaemia in patients with heart failure is important. I blame not only the committee for not having any representation from the clinical heart failure community but also the company for not pressing the case on the needs of the heart failure patient.	Thank you for your comment. Cardiology experts attended the second committee meeting and the committee considered the needs of people with heart failure and hyperkalaemia see sections 3.1 and 3.3 of the FAD.
2	Consultee	Pumping Marvellous Foundation	I am concerned that the meeting didn't take into account the needs of patients with heart failure where their needs are different from those without heart failure eg CKD patients.	Thank you for your comment. The committee considered the needs of people with heart failure and hyperkalaemia see sections 3.1 and 3.3. However, it was not presented with evidence of a differential effect of patiromer in people with chronic kidney disease and people with heart failure.
3	Consultee	Pumping Marvellous Foundation	I believe and witnessed the committee either miss the point of controlling and managing hyperkalaemia in heart failure where the focus was on CKD patients. Heart failure patients have additional needs. People with heart failure always have a need for their kidney function to be checked due to the evidence based triple therapy as indicated in the NICE Chronic Heart Failure Guidelines in Adults 2018. The core medication recommended by NICE includes ACE/ARB and MRA treatments which are considered to increase the likelihood of hyperkalaemia therefore the management of hyperkalaemia helps heart failure patients stay on prognostically significant cost-effective medication as recommended in the current NICE guidelines.	Thank you for your comment. Cardiology experts attended the second committee meeting and the committee considered the needs of people with heart failure and hyperkalaemia see sections 3.1 and 3.3 of the FAD.
4	Consultee	Pumping Marvellous Foundation	I know the committee missed the point as to the value of managing hyperkalaemia and its downstream effect on cost effective pharmacological management of heart failure. The committee was focussed on episodic management of hyperkalaemia in CKD specific patients.	Thank you for your comment. The committee considered the long-term implications of RAASi use see section 3.10 of the FAD.
5	Consultee	Pumping	My feeling was that the committee missed the point. The value of Patiromer to people with heart failure is	Thank you for your comment. The

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		Marvellous Foundation	not managing episodes, it is managing their condition to ensure they maintain their triple therapy through the rollercoaster of managing their prescribing levels. As indicated in the NICE Chronic Heart Failure Guidelines 2018 patients MDT's managing the prescribing regime with an aim to preventing patients being taken off life saving drugs.	committee considered the needs of people with heart failure and hyperkalaemia see sections 3.1 and 3.3 of the FAD.
6	Consultee	Pumping Marvellous Foundation	Whether or not Patiromer has a prognostic value it would ensure people with heart failure maintain their triple therapy drugs if affected by hyperkalaemia which do have significant evidence around their prognostic value and cost effectiveness. This point clearly backups the argument that the committee didn't look or consider the value of Patiromer to people with heart failure.	Thank you for your comment. The committee considered the needs of people with heart failure and hyperkalaemia see sections 3.1 and 3.3 of the FAD.
7	Consultee	Pumping Marvellous Foundation	It is clear that NICE didn't assess the cost effectiveness on treating heart failure patients with Patiromer as the downstream effects were not considered as mentioned already. A patient with heart failure could be said to be more cost effective to the system if managed with triple therapy than one who was not where there ACE/ARD and or MRA was stopped due to Hyperkalaemia.	Thank you for your comment. The committee considered the long-term impacts of reducing and stopping RAASi (see section 3.10 of the FAD).
8	Consultee	Pumping Marvellous Foundation	Patiromer is innovative from the heart failure perspective as it enables people who depend on triple therapy as mentioned above to remain on optimal therapy thus having a prognostic benefit and better QOL. Anecdotally it is not diet that puts people with heart failure into a hyperkaliaemic situation it is the ADE/ARB/ARNI and MRA's they are prescribed.	Thank you for your comment. The committee considered the benefits of patiromer including not needing to change RAASi treatment, however it was aware that other gastrointestinal potassium binders exist and did not consider patiromer a step change in treatment. See section 3.18 of the FAD.
9	Consultee	Pumping Marvellous Foundation	It was a significant failure on behalf of NICE to not include representation from the British Society of Heart Failure or clinical expert with a sub specialty of Heart Failure. In my opinion this dramatically effected the clinical equipoise of the decision that has been made and potentially brings into question the credibility of that decision.	Thank you for your comment. Cardiology experts attended the second committee meeting.
1	Consultee	Renal association	We are concerned that by not approving these novel treatments, at least with restrictions, this will limit optimal patient care and restrict clinicians from treating a cohort of patients with difficult to control potassium values, leading to premature dialysis, serious morbidity, unnecessary hospitalisation and possible mortality.	Thank you for your comment.
2	Consultee	Renal association	We feel that the new potassium binders have a role in facilitating safer use of renin angiotensin blockers (ie ACE inhibitors (ACE-I) or Angiotensin receptor blockers (ARB)) in some patients with CKD and/or cardiac failure. These agents are proven to be of definite clinical benefit in both conditions but can lead to hyperkalaemia; clinicians would choose to use potassium binders at [potassium] > 5.5 mmol/l to prevent [potassium] reaching 6 mmol/l and above . In both patient groups there are many occasions where renin angiotensin blockade has to be reduced or terminated due to hyperkalaemia, leading to increased patient risk.	Thank you for your comment. The committee considered evidence provided by the company that the consensus for cardiologists and nephrologists was to down-titrate or stop RAAS inhibitors at serum potassium levels of more than 6.0 mmol/litre (see section 3.1 of the FAD).
3	Consultee	Renal association	We are concerned that there may have been some misunderstanding concerning the nature of patients suitable for treatment with the new potassium binders. These agents are not intended for acute	Thank you for your comment. At the second meeting the committee

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			management of patients with [potassium] > 6 mmol/l. However, they would provide treatment options, together with dietary restriction, that are currently not available after acute treatment of hyperkalaemia in order to prevent recurrent hyperkalaemia and to facilitate safer use of ACE-I and ARB, necessary treatments for patients with CKD and/or heart failure.	considered additional evidence supplied by the company on the treatment pathway for hyperkalaemia and clinical expert opinion. The treatment pathway for hyperkalaemia is described in more detail in the FAD, please see section 3.1 of the FAD.
4	Consultee	Renal association	We feel that the NICE panel should recognise the importance of the many recurrent and unnecessary hospitalisations that are associated with hyperkalaemia in patients with CKD and/or heart failure. These are associated with major cost, morbidity and mortality. The new potassium binders appear to have the capacity to reduce this burden.	Thank you for your comment. The committee considered that stopping RASSi likely increases the risk of hospitalisation (see section 3.10 of the FAD). The economic model included costs and disbenefits for hospitalisations because of hyperkalaemia (see section 3.12 of the FAD).
5	Consultee	Renal association	Calcium resonium has been available as a potassium binder for decades but most patients suffer gastrointestinal side effects; intestinal necrosis is a very serious but rare complication. We feel that NICE should recommend the use of the novel potassium binders as an alternative for calcium resonium therapy, which remains in guidelines.	Thank you for your comment. The committee took into account gastrointestinal side effects of calcium resonium and considered that patiromer could be used alongside standard care for acute hyperkalaemia 3.7 of the FAD for further detail.
6	Consultee	Renal association	In summary, we would like to see the NICE panel consider permitting use of the new potassium binders for restricted use and prescription by clinicians managing patients with CKD and/or heart failure in a secondary care setting. It is important that this therapeutic option gains real world experience in the UK such that clinicians can establish the use of these agents in a group of patients with multiple comorbidities and limited quality of life until further data becomes available to extend their use to other groups of patients.	Thank you for your comment. The committee considered that patiromer will be used alongside standard care for acute hyperkalaemia and in outpatient care for chronic hyperkalaemia. See section 3.7 of the FAD for further detail.
1	Consultee	Vifor Pharma Group	**Issue: Clinical practice for the management of mild hyperkalaemia (serum potassium levels between 5.5 and 6 mmol/L) in the UK** **Vifor position** The ACD states that in UK clinical practice, patients are not actively treated unless serum potassium exceeds 6.0mmol/L. Vifor contests this and would like to state that multi-morbid CKD patients on life saving RAASi therapy are actively managed at K^+ below 6.0mmol/L by e.g. the modification and possible discontinuation of RAASi dose. Vifor's view is consistent with CKD guidelines including the NICE CG182 as well as with qualitative research that is being conducted for Vifor with practicing UK cardiologists and nephrologists. The ACD does not reflect this as there was no representation of cardiologists (only	Thank you for your comment. The committee considered the needs of people with heart failure and hyperkalaemia see sections 3.1 and 3.3 of the FAD. However, it was not presented with evidence of a differential effect of patiromer in people with chronic kidney disease and people with heart failure.

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			nephrologists) during the submission process.	
1	Consultee	Vifor Pharma Group	We do not consider that the role of the cardiologist and the value that patiromer would provide to patients with heart failure and related comorbidities at risk of hyperkalaemia, has been fully recognised. We propose that in addition to the company being present, a cardiologist is invited to future Appraisal Committee meetings so that this perspective can be adequately captured. Patients with stage 3-4 CKD tend to be treated in primary care (acknowledged in section 3.6 of the ACD) therefore, the population for whom reimbursement is sought, would not be represented adequately by nephrology professionals alone. Since a significant proportion of CKD patients are multi-morbid with Heart Failure (over 40% in both arms of OPAL-HK Part B had heart failure), these patients receive life-saving RAASi therapy. Their raised serum potassium levels are then managed by cardiologists. International and national HF and the NICE guidelines recommend RAASi therapy at the highest-tolerated, optimised doses for HF treatment for their effect on reducing mortality, morbidity and hospitalisations. RAASi are indicated for the treatment of hypertension and CKD for delaying the disease progression and confer well-established cardiovascular benefits. This co-morbid CKD and cardiovascular patient group is the one most likely to benefit from treatment with patiromer as they can continue on optimised RAASi doses and for this reason, it is imperative that the viewpoint of the cardiologist is commensurate with that of the nephrologist.	Thank you for your comment. The committee considered advice from a cardiologist who attended the second committee meeting.
1	Consultee	Vifor Pharma Group	The ACD is inconsistent in the definition of when to treat hyperkalaemia. To evidence: section 3.2 states: “that RAASi discontinuation or dose modification is a strategy to treat HK’ whereas 3.1 states: “The committee and the clinical experts agreed they would not usually consider treating hyperkalaemia at serum potassium levels lower than 6.0 mmol/L”. Further instances are provided below. In addition, the NHS saw fit to issue a (rare) Patient Safety Alert (Ref Nr: NHS/PSA/RE/2018/006) in August 2018. After reports of 35 cardiac arrests from hyperkalaemic patients, the PSA states “These suggest that some Healthcare professionals may not appreciate that clinical assessment, treatment and ongoing monitoring of hyperkalaemia is critical”.	Thank you for your comment. This section of the FAD has been amended.
1	Consultee	Vifor Pharma Group	**Key justifications** While current guidelines do not recommend active pharmacological treatment of Hyperkalaemia (HK) below 6.0mmol/L, they do specify that discontinuation or dose modification of RAAS inhibitors which leads to sub-optimal treatment of patients and subsequent reduced benefit from these therapies. The NICE clinical guideline 182 (Chronic kidney disease in adults: assessment and management) recommends not to routinely start RAAS inhibitors in patients with serum potassium of >5.0mmol/L, and to discontinue RAAS inhibitors at serum potassium >6.0mmol/L. This is similar to the European Society of Cardiology (ESC) 2016 Heart Failure guidelines, where for the use of angiotensin-converting enzyme inhibitors (or angiotensin II receptor blockers) in patients with heart failure with reduced ejection fraction, caution or specialist advice should be sought if the patients serum potassium reaches levels of significant HK which are defined as K^+ of >5.0mmol/L. Other guidelines, including ACCF/AHA heart failure and the Kidney Disease Outcomes Quality Initiative (KDOQI) also recommend dose reduction or discontinuation of RAASi when K^+ exceeds 5.5mmol/L. The latter recommend reducing the ACE inhibitor or ARB dose by 50% at serum potassium levels of >5.0mmol/L, and discontinuation of the ACE inhibitor or ARB if serum potassium does not return to baseline within 2-4 weeks.	Thank you for your comment. The committee considered the evidence provided by the company. The treatment pathway for hyperkalaemia is described in more detail in the FAD, please see section 3.1 of the FAD.

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			Supporting evidence that these approaches are adopted in UK clinical practice comes from a survey of healthcare professionals (4 x Cardiologists and 6 x Nephrologists) conducted for Vifor in November 2018 looking at the impact of hyperkalaemia in managing cardio-renal patients. The survey reported that current practice in the UK is to intervene at a serum potassium value of, on average, 5.6mmol/L. Notably the survey reported differences in to how HK is approached and managed by differing specialities. These differences may be driven by varying considerations not least the desire to optimise heart failure medications. The clinical survey also notes that 60% of participants felt that there is an unmet clinical need that can be met by Patiromer. The reasons for an early intervention included concerns regarding cardiac stability and deterioration in renal function [Kalsi *et al.*, Br J Cardio 2018;25:97-101]. The perspective of these healthcare professionals is directly supportive of the clinical data for patiromer and the thresholds used to initiate an intervention in chronic heart failure, diabetic nephropathy and post myocardial infarction. The survey also noted that many cardiologists seek to maximise RAASi dosing and use patiromer to ensure K+ levels do not reach levels which increase the risk of clinical sequelae. This is further reflected and supported in the findings of the recent Kalsi paper, which also surveyed the opinions of nephrologists and cardiologists in the UK and across Europe on their current management of hyperkalaemia treatment .We note that the Survey by Kalsi *et al.*, [Br J Cardio 2018;25:97-101]. found on average clinician's act to initiate an intervention at K^+ levels of 5.7mmol/L. Modifying RAASi dose to lower serum below 6.0mmol/L is clearly recommended across guidelines and adopted by UK clinicians. Section 3.3 of the ACD confirms that: "at lower levels, the RAAS inhibitor dose would more likely be reduced rather than stopped" This confirms how clinical experts have agreed that patients with levels below 6.0mmol/L will be treated in the UK. The clinical survey notes that clinicians would prefer the ability to maintain RAASi dose and maximise clinical benefit whilst utilising a serum potassium lowering agent in some patients. Comorbid patients (post MI, HF, CKD, DM) face life at high risk, medication that allows them to tolerate the optimum dose of life-prolonging medicines must be a goal of treatment. The long term cardiovascular and reno-protective benefits of RAASi are well documented, NICE Clinical Guideline 182 recommends the use of a renin-angiotensin system antagonist in CKD patients. The same guideline also states: "when hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked". Use of patiromer allows for optimisation of RAASi therapy directly aligned to this recommendation.	
1	Consultee	Vifor Pharma Group	**<u>Amendments to ACD</u>** **ACD states (section 3.1)** The committee and the clinical experts agreed they would not usually consider treating hyperkalaemia at serum potassium levels lower than 6.0 mmol/L.	Thank you for your comments, section 3.1 of the FAD has been amended.

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			This should be amended to read: The committee and the clinical experts agreed they would not usually consider using currently available potassium lowering therapies in the emergency treatment of hyperkalaemia at serum potassium levels lower than 6.0 mmol/L. The committee and the Nephrology clinical experts agreed that although practice differs between individuals, at serum potassium levels between 5.0 and 6.0 mmol/L, the RAAS inhibitor dose would more likely be reduced, rather than stopped because the perceived benefits of being on RAASi treatment outweigh the risks of having a serum potassium level of between 5 and 6mmol/L.	
1	Consultee	Vifor Pharma Group	**ACD states (section 3.8)** A key outcome for clinicians would be the proportion of people whose serum potassium levels drop to below 6.0 mmol/L, the level above which NICE's guideline on chronic kidney disease recommends stopping RAAS inhibitors, but this was not an outcome in the OPAL-HK trial. **The following text should be added:** In addition, the percentage of patients with a potassium level above 5.5 mmol/L whose potassium level falls to below 5.5 mmol/L on patiromer therapy is of relevance as this has a direct influence on the patients' benefit from RAAS inhibitors.	Thank you for your comment. This section of the FAD has been amended.
1	Consultee	Vifor Pharma Group	**ACD states (section 3.10)** However, the committee recalled its earlier conclusion that the population did not reflect the population who would have treatment in the NHS (see section 3.6). **Please delete**	Thank you for your comment. This section of the FAD has been amended.
1	Consultee	Vifor Pharma Group	**ACD states (section 3.10)** It agreed that the current evidence did not address how and when hyperkalaemia would be treated in the NHS Therefore, the committee concluded that the estimates of cost effectiveness were not relevant for decision-making. **The text should be amended to** It agreed that further evidence would be valuable to address how and when hyperkalaemia would be treated in the NHS.	Thank you for your comment. This section of the FAD has been amended.
2	Consultee	Vifor Pharma Group	**Issue: The ACD states that a treatment effect is observed in OPAL-HK (between 5.0–6.0mmol/L but not in a clinically meaningful range for the NHS.** **<u>Vifor position</u>**	Thank you for your comment. The committee considered patiromer within its marketing authorisation and the available trial data. The company updated its basecase in

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			The efficacy of patiromer has been accepted by regulatory authorities including the European Medicines Agency (EMA). The use of patiromer has not been restricted by these authorities to any range of serum potassium .In addition, on the basis of the evidence provided for the previous comment, Vifor contests that OPAL-HK does not provide efficacy data for patiromer in the clinically meaningful range of serum potassium. Please see point 1 with regards to the clinically meaningful range of serum potassium for patients with HF and CKD. Kalsi *et al.*, [Br J Cardio 2018;25:97-101] and a further recent survey of clinicians in the NHS clinical treatment setting demonstrates that K levels of 5.0-6.0mmol/L are clinically meaningful and levels at which clinicians, particularly cardiologists would seek to make changes to treatment in the UK **<u>Key justifications</u>** The label states no restriction on the starting level of serum potassium. The European Medicines Agency (EMA) has accepted the efficacy of patiromer as summarised in the European Public Assessment Report (EPAR) on the basis of results observed in OPAL-HK. The report has previously been provided as part of the original submission. On this basis, the company believes that patiromer has been shown to be (and been accepted by regulators), as efficacious in reducing serum potassium. It must be noted that a publication by Dasgupta [Dasgupta 2016] in the E-journal of Cardiology also acknowledged the efficacy of patiromer: "[Two] new potassium binders (patiromer and [sodium zirconium cyclosilicate) are (….). Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium and preventing recurrent hyperkalaemia in patients with HF and CKD in the context of treatment with RAAS inhibitors". As per the data provided for the previous comment, HK in patients across the UK is actively managed via RAASi modification at serum potassium below 6.0. This was a consistent message from the aforementioned Vifor survey and is aligned to the clinical guidelines specified above. Therefore, Vifor believe that the efficacy data from OPAL-HK is of direct relevance to UK clinical practice. In addition, Vifor are able to provide data from their clinical trial programme and real-world studies which confirm the efficacy of patiromer at serum potassium levels above 6.0mmol/L. Analysis of sub-groups with baseline K^+ levels of 6.0mmol/L or above confirm that there is no lack of efficacy with patiromer in these patients: <u>Randomised data</u> In the majority of the studies, the cut off for HK inclusion was 5.5mEq/L and not 6 mEq/L. However, there were several patients records with serum potassium >6.0mEq/L <u>TOURMALINE</u> • Cut off was 5.5mEq/L (41% of total patients) with 42 patients having serum potassium >5.5, seven patients had serum potassium>6.0 with one >6.5,	response to the ACD to include patients with serum potassium of 6.0mmol/litre or more.

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			• Baseline serum potassium was 5.75mEq/L and the change from baseline (SD) was -0.80 (0.595) vs base line 5.39 in overall population and a change of -0.57 (0.548) • 82% were responders vs. 86% responders in group with serum potassium<5.5 (primary objective), with no difference with food or without food groups Bushinsky D et al, Kidney International (2015) 88 1427-1433 • 8 patients had hyperkalaemia > 6mEq/L (mean (s.e.)=6.14 (0.04) mEq/l). In a prespecified secondary analysis, mean changes in serum potassium over time in these two subgroups were consistent with those seen in the overall population. • For patients with moderate and severe HK respectively, the mean (s.e.) change from baseline at 7 h was − 0.17 (0.07) mEq/l (95% CI=− 0.31, − 0.03) and − 0.29 (0.15)mEq/l (95% CI=−0.61, 0.04), respectively Bushinsky D *et al*, Am J Nephrol 2016;44:404–410 • Patiromer was evaluated in haemodialysis patients • Mean serum potassium was 5.93 mEq/L with 3 Patients with serum potassium > 6.0mEq/L • serum potassium decrease in these patients was greater -1.4, (-1.5.-0.7mEq/L) than in overall population (-0.6 +/- 0.2mEq/L) OPAL-HK • Although serum potassium cut off was 5.5mEq/L,11 patients had serum potassium ≥ 6.5mEq/L (central lab measures) • Results for these patients were included in the >5.5 and <6.5 mEq/L group. There is no mention of any difference in efficacy nor safety in these subgroups of patients Real-world data Extensive and robust real world evidence also exists which shows that the effectiveness of patiromer at K^+ levels above 6.0 is consistent with, or better than, at lower levels. Relevant studies include: Rowan c *et al*, poster THPO780 ASN 2017 • 527 patients in daVita HD centres were initiated on patiromer between Dec 2015 and Dec 2016 • 21% of patients had 6.0 ≤ serum potassium ≤6.5 mEq/L and 18.% ≥6.5mEq/L • Average decrease was respectively -0.73mEq/L and -1.40mEq/L after 90 days • Rowan *et al* shows greatest K^+ reduction with higher baseline K^+ Frenova Chatoth D *et al*, poster TH-PO779, ASN 2017 • US RW study of HK in ESRD • 317 patients in US Frenova Kidney centres were initiated on patiromer between Oct 2015 and Oct 2016 • Mean baseline serum potassium was 6.2 mEq/L • 60 patients had >6.5 mEq/L subgroup and mean serum potassium decrease was 1.3mEq/L by	

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			week 1 compared to no decrease and -0.6mEq/L respectively in patients with serum potassium ≤5.5 and >5.5 -<6.5 mEq/ In the Desai and Kovesdy posters (ASN 2018), there were, respectively, 64 patients with serum potassium ≥6.0 and 30 patients with 6.0 ≤ serum potassium ≤6.5 mEq/L, but with notable difference in outcomes	
2	Consultee	Vifor Pharma Group	**Amendments to ACD** **ACD states (section 1 Why the committee made these recommendations)** However, these results may not be relevant to NHS clinical practice because in the trial most people had a lower level of serum potassium than would be treated in the NHS. **This should be removed**	Thank you for your comment, this section has been amended in the FAD.
2	Consultee	Vifor Pharma Group	**ACD states (section 3.7)** However, the serum potassium levels in both arms were within the range that would not be treated in the NHS and therefore the difference was not clinically meaningful. The committee recognised that OPAL-HK included patients with serum potassium levels that would not be treated in the NHS. **This text should be removed.**	Thank you for your comment. This section of the FAD has been amended.
2	Consultee	Vifor Pharma Group	**ACD states (Section 3.8)** A key outcome for clinicians would be the proportion of people whose serum potassium levels drop to below 6.0 mmol/L, the level above which NICE's guideline on chronic kidney disease recommends stopping RAAS inhibitors, but this was not an outcome in the trial. **This should be removed**	Thank you for your comment. This section of the FAD has been amended.
2	Consultee	Vifor Pharma Group	**ACD states (Section 3.8)** The follow-up in OPAL-HK was short, and at the end of part B (8 weeks), the average serum potassium levels of people who were randomised to placebo was 5.2 mmol/L, lower than the level that would be treated. Also, the difference in serum potassium levels on patiromer compared with placebo was not clinically meaningful (see section 3.7). It was unclear whether, without further treatment, serum potassium levels would rise to a level needing treatment **This should be amended to read** The follow-up in OPAL-HK was short, and at the end of part B (8 weeks), the average serum potassium levels of people who were randomised to placebo was 5.2 mmol/L. It was unclear whether, without further	Thank you for your comment. This section of the FAD has been amended.

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			treatment, serum potassium levels would rise to a level needing treatment	
2	Consultee	Vifor Pharma Group	**ACD states (Section 3.11)** The committee concluded that the company had focused its submission on a population with serum potassium levels reflecting a wider range than would usually be treated in the NHS (see section 3.1). Also, OPAL-HK included people with even lower serum potassium levels. The committee agreed that focussing on people with serum potassium levels of 6.0 mmol/L or more would reflect clinical practice in the NHS. **This should be amended to read:** The committee concluded that the company had focused its submission on a population with serum potassium levels reflecting a wider range than would have received previously available potassium reducing measures in the NHS (see section 3.1). However, the committee recognised that people with serum potassium levels of 5.0 - 6.0 mmol/L might experience some modification or reduction of their RAAS inhibitor therapy thus preventing these patients from gaining the maximum treatment benefit	Thank you for your comment. This section of the FAD has been amended.
2	Consultee	Vifor Pharma Group	**ACD states (Section 3.12)** There was no evidence for a difference in serum potassium levels on standard care and while having patiromer for a population who would have NHS treatment **This should be removed**	Thank you for your comment. This section of the FAD has been amended.
2	Consultee	Vifor Pharma Group	**ACD states (Section 3.13)** Also the population in the model, and therefore the cost-effectiveness results, could not be generalised to NHS clinical practice. **This should be removed**	Thank you for your comment. This section of the FAD has been amended.
3	Consultee	Vifor Pharma Group	**Issue: RAASi discontinuation in OPAL-HK is protocol driven and is not reflective of UK clinical practice. OPAL-HK does not explore the impact of RAASi dose modification as would happen below 6.0mmol/L** **Vifor position** As described for comment 1, RAASi dose modification or discontinuation has been used as a strategy to manage serum potassium between 5.0 and 6.0mmol/L in the UK. OPAL-HK evaluates discontinuation rates using a level of 5.5mmol/L which is consistent with UK clinical practice as established from clinical guidelines and the aforementioned survey of UK clinicians. Vifor acknowledges that OPAL-HK does not provide data relating to RAASi dose modification. **Key justifications**	Thank you for your comment. The committee considered additional evidence provided by the company, the FAD has been amended to reflect this.

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			Current guidelines (ACCF/AHA HF (1), KDOQI (2) on RAASi management make recommendations to reduce or stop ACEi/ARB and MRA if serum potassium>5.5. Others (ESC-HF (3) and NICE (4)) recommend stopping RAASi if serum potassium is >5.0mEq/L or >6.0mEq/L. In line with guidelines, in the OPAL-HK study, the serum potassium threshold for taking action (RAASI down titration or discontinuation) was at 5.5mEq/L. The Part A titration algorithm specified discontinuation of the RAASi dose if (a) if the serum potassium level was ≥ 6.5 mEq/L or if (b) the serum potassium level was ≥ 5.1 mEq/L and the subject was receiving the maximum dose of patiromer (50.4 g/day patiromer). Similarly, in Part B, RAASi was stopped at serum potassium ≥ 5.1 mEq/L after the second titration of patiromer (or placebo) or at any time if serum potassium ≥ 6.0 mEq/L, that is aligned with clinical practice in UK and NICE guidelines with regards to HK management. The objective was to ensure patient safety (in the placebo group) by avoiding a serum potassium range associated with cardiac complications, which is aligned with clinical practice in UK. In a recent retrospective analysis assessing the maintenance of RAASi therapy in HK patients (>5.0mEq/L) receiving RAASi medication and either patiromer, SPS or no K^+ binder (Desai N *et al*, poster SA-PO712 ASN 2018) patiromer showed the highest rates of RAASi continuation in both continuous exposure (CE) and intention to treat (ITT) exposure at 6 months post index (87%) compared to 72%, and 57% respectively in the SPS, and no K^+ binder cohorts. In addition, the patiromer cohort had approximately 1/3 of the patients on guideline-recommended doses, and the majority of those who remained in the CE cohort at 6 months maintained their dose. In another retrospective cohort evaluating the health resource utilization (HRU) among US veterans with hyperkalaemia (>5.1mEq/L) treated with patiromer or SPS,(Kovesdy *et al*, poster FR-PO304, ASN 2018) the greater reduction in electrolyte-related (ED) visits and hospitalisations was observed after initiating patiromer (ITT and CE) (respectively -23.1%, for patiromer and -5.7%, for SPS) Patients continuously exposed to patiromer did not experience any ED or hospital readmissions at 1, 3, or 6 months (-1.2%, -3.8%, 7.7%, respectively, for patiromer, and -0.5%, -0.9%, and -0.4%, respectively, for SPS).	
3	Consultee	Vifor Pharma Group	**<u>Amendments to ACD</u>** **ACD states (Section 3.10)** The committee recognised that the placebo arm may not reflect NHS practice, in which RAAS inhibitors may be stopped in a population with chronic kidney disease at values of serum potassium closer to 6.0 mmol/L than to 5.5 mmol/L. **This should be deleted**	Thank you for your comment. This section of the FAD has been amended.
3	Consultee	Vifor Pharma Group	**ACD states (Section 3.10)** The committee concluded that the trial was not designed to assess the use of RAAS inhibitors and the	Thank you for your comment. This section of the FAD has been amended.

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			differences seen were mostly driven by a different protocol for stopping RAAS inhibitors between patiromer and placebo. **This text should be replaced by** The committee concluded that the trial was not designed to assess the use of RAAS inhibitors and the differences seen were mostly driven by a different protocol for stopping RAAS inhibitors between patiromer and placebo. However, part A of the trial showed in an uncontrolled setting that treatment with patiromer was associated with some patients moving from a level of potassium at which RAAS inhibitor therapy might be modified (5.5 to 6.0 mmol/L) to a level where modification would not be needed (below 5.0 mmol/L). In Part B, the company agreed that there are differences in the management of HK between treatment arms. However this is because RAASi modification is the only current treatment approach whereas patiromer offers the first alternative for 60 years in Europe while allowing for RAASi maintenance.	
4	Consultee	Vifor Pharma Group	**Issue: Stage 5 and dialysis patients are excluded; this is a population where there is a need to treat** **<u>Vifor position</u>** While there is an unmet need for the management of HK in CKD stage 5 and dialysis patients this is also true for stage 3-4 patients as clarified in comment 1 above. Reimbursement was sought for the latter population only on the basis of available, robust, randomised data. There were insufficient patient numbers in OPAL-HK and AMETHYST-DN who were classified as stage 5 or ESRD (n=21) to allow for a robust analysis. Therefore, Vifor are seeking reimbursement in stage 3-4 disease only. However, data for patients with later stage disease indicates patiromer is effective in these patients. **<u>Key justifications</u>** While the focus of the current submission is for CKD stage 3-4, the company offers the following additional information **Patients with CKD 5 non-dialysis:** Out of the 547 patients included in studies RLY5016-301 (OPAL) and RLY5016-205 (AMETHYST), 188 patients had a baseline eGFR <30 mL/min/1.73 m2, and 21 patients had a baseline eGFR of <15 mL/min/1.73 m2. In those patients with severe CKD, patiromer provided both clinically meaningful and statically significant reductions in serum potassium, without the risk of more drug-related adverse events. **Week 4 Efficacy Analysis of Serum potassium for eGFR Subgroups - Studies 205 and 301 [table received, not reproduced in comments table]** **Patients with CKD 5 on dialysis:** A small (N=6) study, RLY5016-201 (Bushinsky *et al* (11)), assessed the safety, efficacy, and pharmacodynamic effects of patiromer in an open-label, multiple dose, phase 2 study in hyperkalaemic haemodialysis (HD) patients for 7 consecutive days	Thank you for your comment.

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			Serum potassium values over time during the pre-treatment week and the patiromer treatment week. **HD treatments are indicated by arrows.** [figure received, not reproduced in comments table] This data suggests that patiromer is no less effective in patients with CKD 5 on dialysis or not on dialysis than earlier stages of CKD. In addition, there is high medical need for a safe and effective treatment for hyperkalaemia in these patients.	
4	Consultee	Vifor Pharma Group	**<u>Amendments to ACD</u>** **ACD states (Section 3.6)** The committee recognised that there was a need for a treatment option for hyperkalaemia for people with chronic kidney disease stage 5 or on dialysis. However it noted that the company had not provided evidence for these populations. **This should be amended to** The committee recognised that there was a need for a treatment option for hyperkalaemia for people with chronic kidney disease stage 5 or on dialysis. However it noted that the company had not provided evidence for these populations on the basis of the available evidence.	Thank you for your comment. This section of the FAD has been amended.
5	Consultee	Vifor Pharma Group	**Issue: There is no evidence that patiromer prolongs survival** **<u>Vifor position</u>** Vifor accept that there is no direct evidence linking patiromer with survival benefit. However, there is robust published evidence to support the long-term benefit of RAASi optimisation in relation to mortality as well as the incidence of cardiovascular events. **<u>Key justifications</u>** The mortality benefit of RAASi optimisation in stage 3-4 CKD patients has been shown in Epstein *et al* 2015 where mortality was 22.4%, 20.3% and 9.8% in patients who were RAASi discontinued, using submaximal doses and maintained on RAASi, respectively (n=43,288) There are many observational studies published that demonstrate a U-shape curve association with increased mortality in hypokalaemia (serum potassium<3.8mmol/l) and hyperkalaemia (serum potassium levels >5mmol/l) in CKD patients. Overall these trials looked at 242,206 CKD and dialysis patients with	Thank you for your comment. The committee considered the evidence presented by the company for the long-term benefit of RAASi (see section 3.10 of the the FAD). However, did not see evidence showing a direct link between lowering serum potassium and long-term outcomes (see section 3.11 of the FAD).

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			different races over 1-5 years, and the U shape survival patterns were consistent in these trials (Hayes 2012, Wang 2013, Luo 2016,Nakhoul 2015,Torlen2012, Kim 2017). Furthermore in an individualised data meta-analysis the risk of serum potassium >5.5 mmol/L was related to lower eGFR and higher albuminuria. The risk relationship between K^+ levels and adverse outcomes was U-shaped with the adjusted hazard ratio for all-cause mortality of 1.22 [95% confidence interval (CI) 1.15–1.29] at 5.5 mmol/L (Kovesdy *et al* 2018).	
5	Consultee	Vifor Pharma Group	**Amendments to ACD** **ACD states (Section 3.12)** There is no evidence that patiromer prolongs survival. OPAL-HK did not collect data on the effect of patiromer on long-term outcomes such as progression of kidney disease, cardiovascular events or mortality **This should be amended to read:** There is limited evidence that patiromer prolongs survival. OPAL-HK did not collect data on the effect of patiromer on long-term outcomes such as progression of kidney disease, cardiovascular events or mortality	Thank you for your comment. This section of the FAD has been amended.
6	Consultee	Vifor Pharma Group	**Issue: Committee concern of potential for increased risk of death due to hypokalaemia** **Vifor position** All patients in OPAL-HK were receiving a RAASi medication at baseline and 42% were HF patients. Then, bringing patients into a range of 3.8-5.0mmol/L should not be associated with an increased risk of death as noted by the committee. **Key justifications** Although the normokalaemia range is defined within the interval of 3.5 to <5,1 and hypokalaemia by serum potassium <3.5 mmol/L, the target range defined by the company was 3.8 to <5.1 while hypokalaemia definition remains at serum potassium value <3.5 mEq/L, **Goyal *et al* (JAMA 2012)** described that among inpatients with acute myocardial infarction), the lowest mortality was observed in those with (postadmission) serum potassium levels between 3.5 and <4.5 mmol/L compared with those who had higher or lower potassium levels [figure received, not reproduced in comments table] **Matsushita *et al*,** (T4044 — 2016 AHA) could assess the mortality rate among a population of 78,652	Thank you for your comment. The committee considered the assumption in the company's updated basecase which removed the direct link between serum potassium and mortality to be reasonable (see section 3.12 of the FAD).

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			newly diagnosed HF veterans (vs average over 6 months prior to HF diagnosis) and link it to all-cause mortality in 142,087 patients based upon their serum potassium level [figure received, not reproduced in comments table] Hypokalaemia (defined as <4 mEq/L) was observed in 24.5% whereas hyperkalaemia (≥5 mEq/L) was seen in 8.4%. For hypokalaemia, lower cumulative survival compared to normal levels (4-<5 mEq/L) was found only below 3.5 mEq/L (prevalence of 4.0%), particularly in the first 5-6 years **Adahl *et al* (EHJ, 2017)** describe association of serum potassium levels with mortality in chronic heart failure patients and based upon the below intervals, 4.2-4.4mmol/L being the reference interval [figure received, not reproduced in comments table] Levels within the lower and upper levels of the normal serum potassium range (3.5–4.1 mmol/L and 4.8–5.0 mmol/L, respectively) were associated with a significant increased short-term risk of death in chronic heart failure compared to reference interval of 4.2-4.4 on a 90 day period. However, potassium below 3.5 mmol/L and above 5.0 mmol/L was associated with increased mortality. [figure received, not reproduced in comments table] **A Collins *et al* (Am J Nephrol 2017)** evaluated the association of serum potassium with all-cause mortality in patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. [figure received, not reproduced in comments table] In an adjusted model, all-cause mortality was significantly elevated for every 0.1 mEq/L change in potassium <4.0 mEq/L and ≥ 5.0 mEq/L and was differentially greater in those with HF, CKD, or DM. Hypokalaemia was defined **as mild** (3.5–<4.0 mmol/L) or **moderate-to-severe** (<3.5 mmol/L). Unadjusted 18-month mortality ranged from 34.8 to 55.6% with mild to severe hypokalemia compared to patients in the range of 4.0 to 5.0mmol/L. **Vardeny O, *et al.*** (Circ Heart Failure. 2014) demonstrated that patients with HF benefit from spironolactone at all serum potassium levels (including at serum potassium<4.0) compared to patients receiving placebo. [figure received, not reproduced in comments table] In summary, although there is some evidence that patients with serum potassium 3.8-4 may have a higher mortality risk compared to patients within a range of 4.2 to 4.5 (or 5.0) there is also evidence that patients undergoing RAASi medication have reduced risk or mortality compared to those not receiving RAASi medication for same serum potassium levels, that include serum potassium <4	

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			Vifor Position The second Periodic Safety Update Report (PSUR) for Veltassa (patiromer) issued on June 2018 reported until 20 April 2018 11.609 adverse drug reactions (ADRs). Out of these ADRs, 524 serious adverse events were reported from spontaneous and solicited post marketing sources. During this reporting period, no new safety signal has been detected in any clinical trials and from post marketing experience and there has been no ongoing or closed signal, In particular, a very low number of patients experienced an hypokalaemia episode (defined as serum potassium <3.5 mmol/l) in the phase 2-3 clinical program that is reflected in the EU SmPC where hypokalaemia is not listed as an adverse event. Similarly only 53 hypokalaemic post marketed cases were notified during the reporting period. The benefit/risk profile for Veltassa has not changed and remains positive" (ASP-PAT-EU-PSUR V2.0, June 2018)	
6	Consultee	Vifor Pharma Group	**Amendments to ACD** **ACD states (Section 3.12)** The normal range (as defined by the company; 3.8 mmol/L to 5.1 mmol/L) overlapped with the category of serum potassium (3.5 to 3.9 mmol/L) associated with an increased risk of death compared with serum potassium values of 4.5 mmol/L to 4.9 mmol/L. The committee was concerned that if the associations between serum potassium and death were true, using patiromer to lower serum potassium to the levels proposed by the company could actually increase the risk of death. **This text should be amended to** The normal serum potassium range (as defined by the company; 3.8 mmol/L to 5.1 mmol/L) overlapped with the category of serum potassium (3.5 to 3.9 mmol/L) associated with an increased risk of death compared with serum potassium values of 4.5 mmol/L to 4.9 mmol/L. While the committee was concerned that associations between serum potassium and death may be based on truth, the continual use of optimised RAASi dosing provides proven mortality benefit.	Thank you for your comment. This section of the FAD has been amended.
7	Consultee	Vifor Pharma Group	**Additional amendments** **ACD states (Section 3.2)** The Committee considered that patiromer could have a role in treating life threatening HK. It would not replace intravenous insulin and glucose but it might replace calcium resonium. **and** Committee concluded that managing acute life threatening HK and chronic HK differed and that patiromer had a potential role in both **Vifor comments**	Thank you for your comment. The committee considered that patiromer could be used alongside standard care for acute hyperkalaemia and in outpatient care for chronic hyperkalaemia. See section 3.7 of the FAD for further detail.

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			Vifor request NICE to correct this conclusion as the role of patiromer will be in the treatment of chronic HK and not in the acute life-threatening situation. Therefore calcium resonium should not be considered a comparator of patiromer.	
7	Consultee	Vifor Pharma Group	**ACD states (Section 3.2)** Treatment of persistent HK includes diet and stopping or reducing RAAS inhibitors **This should be amended to read** Treatment of persistent HK includes diet and reducing RAAS inhibitors at serum potassium levels between 5.0 and 6.0mmol/L or stopping if levels exceed 6.0mmol/L.	Thank you for your comment.
1	Web comment	Clinical expert	Introduction Heart failure is both common and serious. When heart failure is associated with a reduced left ventricular ejection fraction (HFrEF), renin-angiotensin-aldosterone-system inhibitors (RAASi) combined with diuretics, beta-blockers and, for those with a prolonged QRS duration, cardiac resynchronization therapy (CRT) devices, improve symptoms and reduce morbidity and mortality. However, many patients also have renal dysfunction and/or diabetes, which increases the risk of developing hyperkalaemia with RAASi and beta-blockers. Hyperkalaemia and clinicians' fear of hyperkalaemia are important reasons for many patients not achieving NICE (and other) guideline-recommended doses of these agents.	Thank you for your comment.
2	Web comment	Clinical expert	Why are Patients with Heart Failure Prescribed RAASi? There are two main reasons to treat a patient with HFrEF with RAASi. The reason most prominently stated in guidelines is the impact of RAASi on morbidity and mortality. This may be partly mediated by correction and prevention of hypokalaemia but improvement in cardiac function and structure (remodelling) and reduction in congestion also probably play an important role. However, from a patient's perspective, the most important reason for taking a RAASi may be to improve symptoms (which may lead to a reduction in hospitalisation for worsening congestion). For these patients, withdrawal of RAASi is not a satisfactory response to hyperkalaemia. A treatment for hyperkalaemia that permitted initiation and maintenance of RAASi to treat symptoms and signs and improve well-being in patients with heart failure would have high clinical value. Hyperkalaemia (and the fear of hyperkalaemia) may prevent effective treatment to control symptoms. It is for this reason (rather than possible benefits on mortality) that I believe there is a current, important role for potassium-binding agents for heart failure.	Thank you for your comment.
3	Web comment	Clinical expert	What Do Guidelines Say about Hyperkalaemia? Current NICE guidelines on heart failure refer frequently to the need to measure serum potassium but refrain from making specific recommendations based on serum potassium. The 2010 NICE guideline on heart failure recommended a reduction in dose or cessation of a mineralo-corticoid antagonist (MRA) when serum potassium exceeded 5.5mmol/L. SIGN guidelines recommend "Serum potassium should be monitored to maintain its concentration in the range 4–5 mmol/l and adjustments in therapy should be made to prevent both hypokalaemia and hyperkalaemia" and "If potassium rises to >5.5 mmol/l or creatinine increases by >100% or to above 310	Thank you for your comment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			micromol/l the ACE inhibitor/ARB should be stopped and specialist advice sought" and "If K+ rises above 5.5 mmol/l or creatinine rises to >220 micromol/l reduce the dose (of MRA) to 25 mg on alternate days and monitor blood chemistry closely. If K+ rises ≥6.0 mmol/l or creatinine to 310 micromol/l stop spironolactone immediately and seek specialist advice." The SIGN Guidelines also recommend caution in the use of all RAASi when serum potassium is >5.0mmol/L. The ESC Guidelines on heart failure recommend caution with the use of RAASi when serum potassium is >5.0mmol/L and temporary cessation when serum potassium is >6.0mmol/L. American guidelines also suggest caution in the use of RAASi when serum potassium is >5.0mmol/L. In summary, guidelines urge caution in the use of RAASi when serum potassium is >5.0mmol/L and to maintain serum potassium in the range 4.0 to 5.0mmol/L. This is consistent with clinical practice.	
4	Web comment	Clinical expert	Background Information The National (England & Wales) Audit for Heart Failure reports that 83% of patients with HF with HFrEF are prescribed an ACE inhibitor or angiotensin receptor blocker (ARB) and 53% a MRA at discharge [National Heart Failure Audit April 2015 – March 2016, section 2.3.1]. The Audit Report states: "Had the patients identified within this audit cycle as having HFrEF, who left hospital on none of the three disease modifying drugs, been prescribed all three, then an additional 169 patients would likely have been alive at the time of censor. With more comprehensive prescription and dose optimisation across the audit there is the ability to prevent numerous additional deaths." Hyperkalaemia is a common complication of RAASi in some groups of patients. A retrospective cohort study of patients with chronic kidney disease (CKD) registered in the Clinical Practice Research Datalink (CPRD) GP practices in Scotland found that the prevalence of hyperkalaemia in patients with heart failure and CKD stage 3 was 23.3% and in CKD stage 4, 40% [Hyperkalaemia in CKD: Incidence, Prevalence and Impact on RAAS Inhibitor treatment in Primary Care in Scotland, figure 3]. After an episode of hyperkalaemia, 10.7% of patients discontinued RASSi and in 21.4% it was down-titrated [figure 4]. BIOSTAT-CHF, a prospective study including UK centres, investigated the up-titration of RAASi in 2,516 patients with HFrEF. Only 22% achieved guideline-recommended doses. Those who achieved <50% had an increased risk of hospitalization (or death) due to heart failure [Ouwerkerk W, et al. Eur Heart J. 2017; Figure 2]. Another large European registry of 12,440 HF patients reported that while 92% of hospitalized HF patients were prescribed the recommended RAASi therapy as per ESC guidelines, less than 30% were up-titrated to the recommended target dose [Maggioni AP, et al. Eur J Heart Fail. 2013]. These results were confirmed also in QUALIFY, an international, prospective survey assessing physicians' adherence to guideline-recommended medications for the treatment of HFrEF. Only 87% were treated with ACEi/ARB and only 69% were treated with MRAs [Komajda M, et al. Eur J Heart Fail. 2016]. Hyperkalemia in Chronic Kidney Disease: Incidence, Prevalence and Impact on RAAS Inhibitors treatment in Primary Care in Scotland, figure 3 [figure received, not reproduced in comments table] Hyperkalemia in Chronic Kidney Disease: Incidence, Prevalence and Impact on RAAS Inhibitors treatment in Primary Care in Scotland, figure 4 [figure received, not reproduced in comments table]	Thank you for your comment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Ouwerkerk W, et al. Eur Heart J. 2017; Figure 2 [figure received, not reproduced in comments table]	
5	Web comment	Clinical expert	Treatment of Hyperkalaemia Treatment options for the long-term management and/or prevention of hyperkalaemia are currently limited to reducing dietary potassium, increasing the dose of diuretics and/or reducing or stopping medications that increase serum potassium, including RAASi, especially MRAs, and beta-blockers. The latter strategy may not be appropriate for symptomatic patients. Hyperkalaemia may be treated in the short-term with calcium resonium [Calcium Resonium SmPC 2014]. Long-term use should be avoided due to potential severe gastrointestinal side effects such as bowel necrosis [Calcium Resonium SmPC 2014]. The efficacy and safety of calcium resonium has not been studied in substantial, long-term trials [Sterns RH et al. J Am Soc Nephrol 2010]. The Expert Consensus on the management of hyperkalaemia in cardiovascular disease treated with RAASi coordinated by the working group on cardiovascular pharmacotherapy of the ESC states: “Patients with CKD and heart failure are at increased risk of hyperkalaemia and ~50% experience two or more yearly recurrences. A substantial proportion of patients receiving RAASi therapy have their therapy down-titrated or more often discontinued even after a single episode of hyperkalaemia. Since RAASi therapy reduces mortality and morbidity in patients with cardiovascular disease, steps should, when hyperkalaemia develops, be considered to lower K+ and enable patients to continue their RAASi therapy. The use of such measures is especially important in those with the most to gain from RAASi therapy.” Patiromer, and potentially zirconium cyclosilicate, provides an alternative long-term strategy to withdrawal of RAASi for the management of hyperkalaemia in patients with heart failure. I believe this will improve the management of patients who require RAASI for the control of symptoms of heart failure, which will potentially also reduce the risk of hospitalisation for heart failure and mortality.	Thank you for your comment. The committee considered the alternative treatments available for reducing serum potassium and the side effects of calcium resonium. It considered that patiromer could be used alongside standard care for acute hyperkalaemia and in outpatient care for chronic hyperkalaemia. See section 3.7 of the FAD for further detail.
1	Consultee	Royal College of Pathologists	No comments	Thank you for your response.

NICE National Institute for Health and Care Excellence

Patiromer for treating hyperkalaemia [ID877]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: 1. has all of the relevant evidence been taken into account? 2. are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? 3. are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: 1. could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; 2. could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Vifor Pharma Group (incorporating Vifor Pharma UK Limited and Vifor Fresenius Medical Care Renal Pharma UK Limited)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Brinley Jackson

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this

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Patiromer for treating hyperkalaemia [ID877]

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	table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Issue: Clinical practice for the management of mild hyperkalaemia (serum potassium levels between 5.5 and 6 mmol/L) in the UK** **Vifor position** The ACD states that in UK clinical practice, patients are not actively treated unless serum potassium exceeds 6.0mmol/L. Vifor contests this and would like to state that multi-morbid CKD patients on life saving RAASi therapy are actively managed at K^+ below 6.0mmol/L by e.g. the modification and possible discontinuation of RAASi dose. Vifor's view is consistent with CKD guidelines including the NICE CG182 as well as with qualitative research that is being conducted for Vifor with practicing UK cardiologists and nephrologists. The ACD does not reflect this as there was no representation of cardiologists (only nephrologists) during the submission process. We do not consider that the role of the cardiologist and the value that patiromer would provide to patients with heart failure and related comorbidities at risk of hyperkalaemia, has been fully recognised. We propose that in addition to the company being present, a cardiologist is invited to future Appraisal Committee meetings so that this perspective can be adequately captured. Patients with stage 3-4 CKD tend to be treated in primary care (acknowledged in section 3.6 of the ACD) therefore, the population for whom reimbursement is sought, would not be represented adequately by nephrology professionals alone. Since a significant proportion of CKD patients are multi-morbid with Heart Failure (over 40% in both arms of OPAL-HK Part B had heart failure), these patients receive life-saving RAASi therapy. Their raised serum potassium levels are then managed by cardiologists. International and national HF and the NICE guidelines recommend RAASi therapy at the highest-tolerated, optimised doses for HF treatment for their effect on reducing mortality, morbidity and hospitalisations. RAASi are indicated for the treatment of hypertension and CKD for delaying the disease progression and confer well-established cardiovascular benefits. This co-morbid CKD and cardiovascular patient group is the one most likely to benefit from treatment with patiromer as they can continue on optimised RAASi doses and for this reason, it is imperative that the viewpoint of the cardiologist is commensurate with that of the nephrologist. The ACD is inconsistent in the definition of when to treat hyperkalaemia. To evidence: section 3.2 states: "that RAASi discontinuation or dose modification is a strategy to treat HK' whereas 3.1 states: "The committee and the clinical experts agreed they would not usually consider treating hyperkalaemia at serum potassium levels lower than 6.0 mmol/L". Further instances are provided below. In addition, the NHS saw fit to issue a (rare) Patient Safety Alert (Ref Nr: NHS/PSA/RE/2018/006) in August 2018. After reports of 35 cardiac arrests from hyperkalaemic patients, the PSA states "These suggest that some Healthcare professionals may not appreciate that clinical assessment, treatment and ongoing monitoring of hyperkalaemia is critical". **<u>Key justifications</u>** While current guidelines do not recommend active pharmacological treatment of Hyperkalaemia (HK) below 6.0mmol/L, they do specify that discontinuation or dose modification of RAAS inhibitors which leads to sub-optimal treatment of patients and subsequent reduced benefit from these therapies. The NICE clinical guideline 182 (Chronic kidney disease in adults: assessment and management) recommends not to routinely start RAAS inhibitors in patients with serum potassium of >5.0mmol/L,

	and to discontinue RAAS inhibitors at serum potassium >6.0mmol/L. This is similar to the European Society of Cardiology (ESC) 2016 Heart Failure guidelines, where for the use of angiotensin-converting enzyme inhibitors (or angiotensin II receptor blockers) in patients with heart failure with reduced ejection fraction, caution or specialist advice should be sought if the patients serum potassium reaches levels of significant HK which are defined as K^+ of >5.0mmol/L. Other guidelines, including ACCF/AHA heart failure and the Kidney Disease Outcomes Quality Initiative (KDOQI) also recommend dose reduction or discontinuation of RAASi when K^+ exceeds 5.5mmol/L. The latter recommend reducing the ACE inhibitor or ARB dose by 50% at serum potassium levels of >5.0mmol/L, and discontinuation of the ACE inhibitor or ARB if serum potassium does not return to baseline within 2-4 weeks. Supporting evidence that these approaches are adopted in UK clinical practice comes from a survey of healthcare professionals (4 x Cardiologists and 6 x Nephrologists) conducted for Vifor in November 2018 looking at the impact of hyperkalaemia in managing cardio-renal patients. The survey reported that current practice in the UK is to intervene at a serum potassium value of, on average, 5.6mmol/L. Notably the survey reported differences in to how HK is approached and managed by differing specialities. These differences may be driven by varying considerations not least the desire to optimise heart failure medications. The clinical survey also notes that 60% of participants felt that there is an unmet clinical need that can be met by Patiromer. The reasons for an early intervention included concerns regarding cardiac stability and deterioration in renal function [Kalsi *et al*., Br J Cardio 2018;25:97-101]. The perspective of these healthcare professionals is directly supportive of the clinical data for patiromer and the thresholds used to initiate an intervention in chronic heart failure, diabetic nephropathy and post myocardial infarction. The survey also noted that many cardiologists seek to maximise RAASi dosing and use patiromer to ensure K+ levels do not reach levels which increase the risk of clinical sequelae. This is further reflected and supported in the findings of the recent Kalsi paper, which also surveyed the opinions of nephrologists and cardiologists in the UK and across Europe on their current management of hyperkalaemia treatment .We note that the Survey by Kalsi *et al*., [Br J Cardio 2018;25:97-101]. found on average clinician's act to initiate an intervention at K^+ levels of 5.7mmol/L. Modifying RAASi dose to lower serum below 6.0mmol/L is clearly recommended across guidelines and adopted by UK clinicians. Section 3.3 of the ACD confirms that: "at lower levels, the RAAS inhibitor dose would more likely be reduced rather than stopped" This confirms how clinical experts have agreed that patients with levels below 6.0mmol/L will be treated in the UK. The clinical survey notes that clinicians would prefer the ability to maintain RAASi dose and maximise clinical benefit whilst utilising a serum potassium lowering agent in some patients. Comorbid patients (post MI, HF, CKD, DM) face life at high risk, medication that allows them to tolerate the optimum dose of life-prolonging medicines must be a goal of treatment. The long term cardiovascular and reno-protective benefits of RAASi are well documented, NICE Clinical Guideline 182 recommends the use of a renin-angiotensin system antagonist in CKD patients. The same guideline also states: "when hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked". Use of patiromer allows for optimisation of RAASi therapy directly aligned to this recommendation. **<u>Amendments to ACD</u>** **ACD states (section 3.1)** The committee and the clinical experts agreed they would not usually consider treating hyperkalaemia at serum potassium levels lower than 6.0 mmol/L.

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	This should be amended to read: The committee and the clinical experts agreed they would not usually consider using currently available potassium lowering therapies in the emergency treatment of hyperkalaemia at serum potassium levels lower than 6.0 mmol/L. The committee and the Nephrology clinical experts agreed that although practice differs between individuals, at serum potassium levels between 5.0 and 6.0 mmol/L, the RAAS inhibitor dose would more likely be reduced, rather than stopped because the perceived benefits of being on RAASi treatment outweigh the risks of having a serum potassium level of between 5 and 6mmol/L. **ACD states (section 3.8)** A key outcome for clinicians would be the proportion of people whose serum potassium levels drop to below 6.0 mmol/L, the level above which NICE's guideline on chronic kidney disease recommends stopping RAAS inhibitors, but this was not an outcome in the OPAL-HK trial. **The following text should be added:** In addition, the percentage of patients with a potassium level above 5.5 mmol/L whose potassium level falls to below 5.5 mmol/L on patiromer therapy is of relevance as this has a direct influence on the patients' benefit from RAAS inhibitors. **ACD states (section 3.10)** However, the committee recalled its earlier conclusion that the population did not reflect the population who would have treatment in the NHS (see section 3.6). **Please delete** **ACD states (section 3.10)** It agreed that the current evidence did not address how and when hyperkalaemia would be treated in the NHS Therefore, the committee concluded that the estimates of cost effectiveness were not relevant for decision-making. **The text should be amended to** It agreed that further evidence would be valuable to address how and when hyperkalaemia would be treated in the NHS.
2	**Issue: The ACD states that a treatment effect is observed in OPAL-HK (between 5.0–6.0mmol/L but not in a clinically meaningful range for the NHS.** **<u>Vifor position</u>** The efficacy of patiromer has been accepted by regulatory authorities including the European Medicines Agency (EMA). The use of patiromer has not been restricted by these authorities to any range of serum potassium .In addition, on the basis of the evidence provided for the previous comment, Vifor contests that OPAL-HK does not provide efficacy data for patiromer in the clinically meaningful range of serum potassium. Please see point 1 with regards to the clinically meaningful range of serum potassium for patients with HF and CKD. Kalsi *et al.*, [Br J Cardio 2018;25:97-101] and a further recent survey of clinicians in the NHS clinical treatment setting demonstrates that K levels of 5.0-6.0mmol/L are clinically meaningful and levels at which clinicians, particularly cardiologists would seek to make changes to treatment in the UK

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Key justifications

The label states no restriction on the starting level of serum potassium. The European Medicines Agency (EMA) has accepted the efficacy of patiromer as summarised in the European Public Assessment Report (EPAR) on the basis of results observed in OPAL-HK. The report has previously been provided as part of the original submission. On this basis, the company believes that patiromer has been shown to be (and been accepted by regulators), as efficacious in reducing serum potassium.

It must be noted that a publication by Dasgupta [Dasgupta 2016] in the E-journal of Cardiology also acknowledged the efficacy of patiromer:

"[Two] new potassium binders (patiromer and [sodium zirconium cyclosilicate) are (….). Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium and preventing recurrent hyperkalaemia in patients with HF and CKD in the context of treatment with RAAS inhibitors".

As per the data provided for the previous comment, HK in patients across the UK is actively managed via RAASi modification at serum potassium below 6.0. This was a consistent message from the aforementioned Vifor survey and is aligned to the clinical guidelines specified above. Therefore, Vifor believe that the efficacy data from OPAL-HK is of direct relevance to UK clinical practice.

In addition, Vifor are able to provide data from their clinical trial programme and real-world studies which confirm the efficacy of patiromer at serum potassium levels above 6.0mmol/L. Analysis of sub-groups with baseline K^+ levels of 6.0mmol/L or above confirm that there is no lack of efficacy with patiromer in these patients:

Randomised data

In the majority of the studies, the cut off for HK inclusion was 5.5mEq/L and not 6 mEq/L. However, there were several patients records with serum potassium >6.0mEq/L

TOURMALINE

- Cut off was 5.5mEq/L (41% of total patients) with 42 patients having serum potassium >5.5, seven patients had serum potassium>6.0 with one >6.5,
- Baseline serum potassium was 5.75mEq/L and the change from baseline (SD) was -0.80 (0.595) vs base line 5.39 in overall population and a change of -0.57 (0.548)
- 82% were responders vs. 86% responders in group with serum potassium<5.5 (primary objective), with no difference with food or without food groups

Bushinsky D et al, Kidney International (2015) 88 1427-1433

- 8 patients had hyperkalaemia > 6mEq/L (mean (s.e.)=6.14 (0.04) mEq/l). In a prespecified secondary analysis, mean changes in serum potassium over time in these two subgroups were consistent with those seen in the overall population.
- For patients with moderate and severe HK respectively, the mean (s.e.) change from baseline at 7 h was − 0.17 (0.07) mEq/l (95% CI=− 0.31, − 0.03) and − 0.29 (0.15)mEq/l (95% CI=−0.61, 0.04), respectively

Bushinsky D *et al*, Am J Nephrol 2016;44:404–410

- Patiromer was evaluated in haemodialysis patients
- Mean serum potassium was 5.93 mEq/L with 3 Patients with serum potassium > 6.0mEq/L
- serum potassium decrease in these patients was greater -1.4, (-1.5.-0.7mEq/L) than in overall population (-0.6 +/- 0.2mEq/L)

OPAL-HK

- Although serum potassium cut off was 5.5mEq/L,11 patients had serum potassium ≥ 6.5mEq/L (central lab measures)
- Results for these patients were included in the >5.5 and <6.5 mEq/L group. There is no mention of any difference in efficacy nor safety in these subgroups of patients

Real-world data

Extensive and robust real world evidence also exists which shows that the effectiveness of patiromer at K^+ levels above 6.0 is consistent with, or better than, at lower levels. Relevant studies include:

Rowan c *et al*, poster THPO780 ASN 2017

- 527 patients in daVita HD centres were initiated on patiromer between Dec 2015 and Dec 2016
- 21% of patients had 6.0 ≤ serum potassium ≤6.5 mEq/L and 18.% ≥6.5mEq/L
- Average decrease was respectively -0.73mEq/L and -1.40mEq/L after 90 days
- Rowan *et al* shows greatest K^+ reduction with higher baseline K^+

Frenova Chatoth D *et al*, poster TH-PO779, ASN 2017

- US RW study of HK in ESRD
- 317 patients in US Frenova Kidney centres were initiated on patiromer between Oct 2015 and Oct 2016
- Mean baseline serum potassium was 6.2 mEq/L
- 60 patients had >6.5 mEq/L subgroup and mean serum potassium decrease was 1.3mEq/L by week 1 compared to no decrease and -0.6mEq/L respectively in patients with serum potassium ≤5.5 and >5.5 -<6.5 mEq/

In the Desai and Kovesdy posters (ASN 2018), there were, respectively, 64 patients with serum potassium ≥6.0 and 30 patients with 6.0 ≤ serum potassium ≤6.5 mEq/L, but with notable difference in outcomes

Amendments to ACD

ACD states (section 1 Why the committee made these recommendations)

However, these results may not be relevant to NHS clinical practice because in the trial most people had a lower level of serum potassium than would be treated in the NHS.

This should be removed

ACD states (section 3.7)

However, the serum potassium levels in both arms were within the range that would not be treated in the NHS and therefore the difference was not clinically meaningful. The committee recognised that OPAL-HK included patients with serum potassium levels that would not be treated in the NHS.

This text should be removed.

ACD states (Section 3.8)

A key outcome for clinicians would be the proportion of people whose serum potassium levels drop to below 6.0 mmol/L, the level above which NICE's guideline on chronic kidney disease recommends stopping RAAS inhibitors, but this was not an outcome in the trial.

	This should be removed **ACD states (Section 3.8)** The follow-up in OPAL-HK was short, and at the end of part B (8 weeks), the average serum potassium levels of people who were randomised to placebo was 5.2 mmol/L, lower than the level that would be treated. Also, the difference in serum potassium levels on patiromer compared with placebo was not clinically meaningful (see section 3.7). It was unclear whether, without further treatment, serum potassium levels would rise to a level needing treatment **This should be amended to read** The follow-up in OPAL-HK was short, and at the end of part B (8 weeks), the average serum potassium levels of people who were randomised to placebo was 5.2 mmol/L. It was unclear whether, without further treatment, serum potassium levels would rise to a level needing treatment **ACD states (Section 3.11)** The committee concluded that the company had focused its submission on a population with serum potassium levels reflecting a wider range than would usually be treated in the NHS (see section 3.1). Also, OPAL-HK included people with even lower serum potassium levels. The committee agreed that focussing on people with serum potassium levels of 6.0 mmol/L or more would reflect clinical practice in the NHS. **This should be amended to read:** The committee concluded that the company had focused its submission on a population with serum potassium levels reflecting a wider range than would have received previously available potassium reducing measures in the NHS (see section 3.1). However, the committee recognised that people with serum potassium levels of 5.0 - 6.0 mmol/L might experience some modification or reduction of their RAAS inhibitor therapy thus preventing these patients from gaining the maximum treatment benefit **ACD states (Section 3.12)** There was no evidence for a difference in serum potassium levels on standard care and while having patiromer for a population who would have NHS treatment **This should be removed** **ACD states (Section 3.13)** Also the population in the model, and therefore the cost-effectiveness results, could not be generalised to NHS clinical practice. **This should be removed**
3	**Issue: RAASi discontinuation in OPAL-HK is protocol driven and is not reflective of UK clinical practice. OPAL-HK does not explore the impact of RAASi dose modification as would happen below 6.0mmol/L** **<u>Vifor position</u>** As described for comment 1, RAASi dose modification or discontinuation has been used as a strategy to manage serum potassium between 5.0 and 6.0mmol/L in the UK. OPAL-HK evaluates discontinuation rates using a level of 5.5mmol/L which is consistent with UK clinical practice as

established from clinical guidelines and the aforementioned survey of UK clinicians. Vifor acknowledges that OPAL-HK does not provide data relating to RAASi dose modification.

Key justifications

Current guidelines (ACCF/AHA HF (1), KDOQI (2) on RAASi management make recommendations to reduce or stop ACEi/ARB and MRA if serum potassium>5.5. Others (ESC-HF (3) and NICE (4)) recommend stopping RAASi if serum potassium is >5.0mEq/L or >6.0mEq/L.

In line with guidelines, in the OPAL-HK study, the serum potassium threshold for taking action (RAASI down titration or discontinuation) was at 5.5mEq/L. The Part A titration algorithm specified discontinuation of the RAASi dose if (a) if the serum potassium level was ≥ 6.5 mEq/L or if (b) the serum potassium level was ≥ 5.1 mEq/L and the subject was receiving the maximum dose of patiromer (50.4 g/day patiromer).

Similarly, in Part B, RAASi was stopped at serum potassium ≥ 5.1 mEq/L after the second titration of patiromer (or placebo) or at any time if serum potassium ≥ 6.0 mEq/L, that is aligned with clinical practice in UK and NICE guidelines with regards to HK management. The objective was to ensure patient safety (in the placebo group) by avoiding a serum potassium range associated with cardiac complications, which is aligned with clinical practice in UK.

In a recent retrospective analysis assessing the maintenance of RAASi therapy in HK patients (>5.0mEq/L) receiving RAASi medication and either patiromer, SPS or no K^+ binder (Desai N *et al*, poster SA-PO712 ASN 2018) patiromer showed the highest rates of RAASi continuation in both continuous exposure (CE) and intention to treat (ITT) exposure at 6 months post index (87%) compared to 72%, and 57% respectively in the SPS, and no K^+ binder cohorts. In addition, the patiromer cohort had approximately 1/3 of the patients on guideline-recommended doses, and the majority of those who remained in the CE cohort at 6 months maintained their dose.

In another retrospective cohort evaluating the health resource utilization (HRU) among US veterans with hyperkalaemia (>5.1mEq/L) treated with patiromer or SPS,(Kovesdy *et al*, poster FR-PO304, ASN 2018) the greater reduction in electrolyte-related (ED) visits and hospitalisations was observed after initiating patiromer (ITT and CE) (respectively -23.1%, for patiromer and -5.7%, for SPS) Patients continuously exposed to patiromer did not experience any ED or hospital readmissions at 1, 3, or 6 months (-1.2%, -3.8%, 7.7%, respectively, for patiromer, and -0.5%, -0.9%, and -0.4%, respectively, for SPS).

Amendments to ACD

ACD states (Section 3.10)

The committee recognised that the placebo arm may not reflect NHS practice, in which RAAS inhibitors may be stopped in a population with chronic kidney disease at values of serum potassium closer to 6.0 mmol/L than to 5.5 mmol/L.

This should be deleted

ACD states (Section 3.10)

The committee concluded that the trial was not designed to assess the use of RAAS inhibitors and the differences seen were mostly driven by a different protocol for stopping RAAS inhibitors between patiromer and placebo.

This text should be replaced by

The committee concluded that the trial was not designed to assess the use of RAAS inhibitors and

	the differences seen were mostly driven by a different protocol for stopping RAAS inhibitors between patiromer and placebo. However, part A of the trial showed in an uncontrolled setting that treatment with patiromer was associated with some patients moving from a level of potassium at which RAAS inhibitor therapy might be modified (5.5 to 6.0 mmol/L) to a level where modification would not be needed (below 5.0 mmol/L). In Part B, the company agreed that there are differences in the management of HK between treatment arms. However this is because RAASi modification is the only current treatment approach whereas patiromer offers the first alternative for 60 years in Europe while allowing for RAASi maintenance.

Patiromer for treating hyperkalaemia [ID877]

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4	**Issue: Stage 5 and dialysis patients are excluded; this is a population where there is a need to treat** **Vifor position** While there is an unmet need for the management of HK in CKD stage 5 and dialysis patients this is also true for stage 3-4 patients as clarified in comment 1 above. Reimbursement was sought for the latter population only on the basis of available, robust, randomised data. There were insufficient patient numbers in OPAL-HK and AMETHYST-DN who were classified as stage 5 or ESRD (n=21) to allow for a robust analysis. Therefore, Vifor are seeking reimbursement in stage 3-4 disease only. However, data for patients with later stage disease indicates patiromer is effective in these patients. **Key justifications** While the focus of the current submission is for CKD stage 3-4, the company offers the following additional information **Patients with CKD 5 non-dialysis:** Out of the 547 patients included in studies RLY5016-301 (OPAL) and RLY5016-205 (AMETHYST), 188 patients had a baseline eGFR <30 mL/min/1.73 m2, and 21 patients had a baseline eGFR of <15 mL/min/1.73 m2. In those patients with severe CKD, patiromer provided both clinically meaningful and statically significant reductions in serum potassium' without the risk of more drug-related adverse events. **Week 4 Efficacy Analysis of Serum potassium for eGFR Subgroups - Studies 205 and 301** **Baseline eGFR** / **eGFR < 15 (N=21)** / **eGFR ≥ 15 (N=514)** / **eGFR < 30 (N=188)** / **eGFR ≥ 30 (N=347)** **Change from Baseline** Mean (SD): -1.12 (0.632) / -0.84 (0.587) / -0.91 (0.639) / -0.82 (0.563) SE of Mean: 0.163 / 0.027 / 0.051 / 0.031 LS Mean (SEM): -1.28 (0.162) / -0.83 (0.021) / -0.92 (0.043) / -0.80 (0.023) 95% CI: (-1.64, -0.92) / (-0.87, -0.79) / (-1.00, -0.84) / (-0.85, -0.76) p-value: <.0001 / <.0001 / <.0001 / <.0001 **Patients with CKD 5 on dialysis:** A small (N=6) study, RLY5016-201 (Bushinsky *et al* (11)), assessed the safety, efficacy, and pharmacodynamic effects of patiromer in an open-label, multiple dose, phase 2 study in hyperkalaemic haemodialysis (HD) patients for 7 consecutive days **Serum potassium values over time during the pre-treatment week and the patiromer treatment week.** **HD treatments are indicated by arrows.**

Patiromer for treating hyperkalaemia [ID877]

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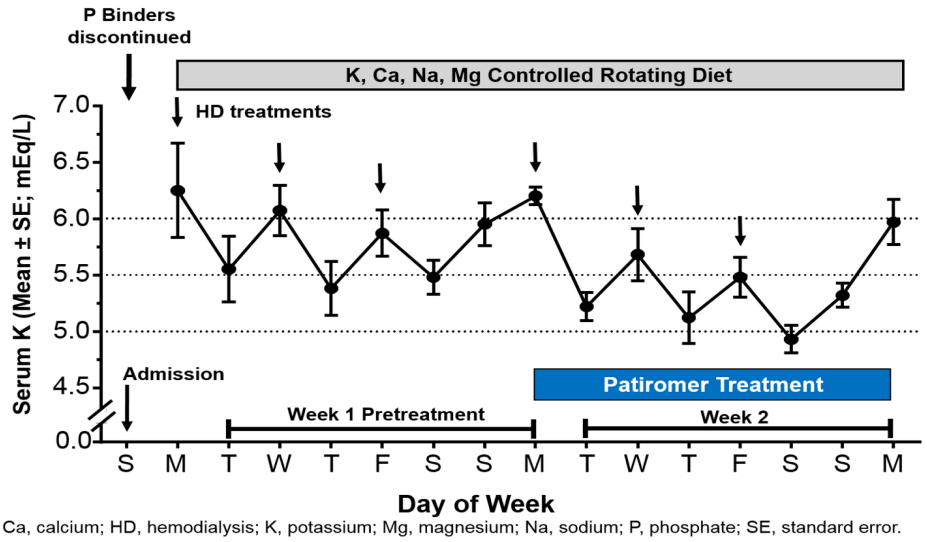


Ca, calcium; HD, hemodialysis; K, potassium; Mg, magnesium; Na, sodium; P, phosphate; SE, standard error.

This data suggests that patiromer is no less effective in patients with CKD 5 on dialysis or not on dialysis than earlier stages of CKD. In addition, there is high medical need for a safe and effective treatment for hyperkalaemia in these patients.

Amendments to ACD

ACD states (Section 3.6)

The committee recognised that there was a need for a treatment option for hyperkalaemia for people with chronic kidney disease stage 5 or on dialysis. However it noted that the company had not provided evidence for these populations.

This should be amended to

The committee recognised that there was a need for a treatment option for hyperkalaemia for people with chronic kidney disease stage 5 or on dialysis. However it noted that the company had not provided evidence for these populations on the basis of the available evidence.

5

Issue: There is no evidence that patiromer prolongs survival

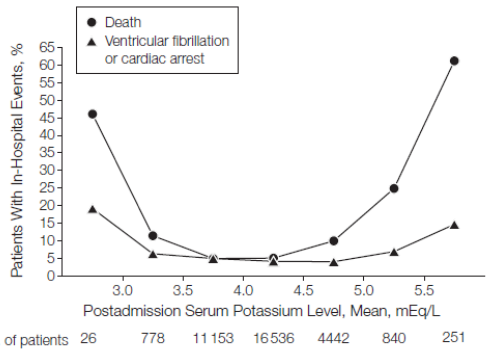
Vifor position

Vifor accept that there is no direct evidence linking patiromer with survival benefit. However, there is robust published evidence to support the long-term benefit of RAASi optimisation in relation to mortality as well as the incidence of cardiovascular events.

Key justifications

The mortality benefit of RAASi optimisation in stage 3-4 CKD patients has been shown in Epstein *et al* 2015 where mortality was 22.4%, 20.3% and 9.8% in patients who were RAASi discontinued, using submaximal doses and maintained on RAASi, respectively (n=43,288)

There are many observational studies published that demonstrate a U-shape curve association with increased mortality in hypokalaemia (serum potassium<3.8mmol/l) and hyperkalaemia (serum potassium levels >5mmol/l) in CKD patients. Overall these trials looked at 242,206 CKD and dialysis patients with different races over 1-5 years, and the U shape survival patterns were consistent in

	these trials (Hayes 2012, Wang 2013, Luo 2016,Nakhoul 2015,Torlen2012, Kim 2017). Furthermore in an individualised data meta-analysis the risk of serum potassium >5.5 mmol/L was related to lower eGFR and higher albuminuria. The risk relationship between K^+ levels and adverse outcomes was U-shaped with the adjusted hazard ratio for all-cause mortality of 1.22 [95% confidence interval (CI) 1.15–1.29] at 5.5 mmol/L (Kovesdy *et al* 2018). **Amendments to ACD** **ACD states (Section 3.12)** There is no evidence that patiromer prolongs survival. OPAL-HK did not collect data on the effect of patiromer on long-term outcomes such as progression of kidney disease, cardiovascular events or mortality **This should be amended to read:** There is limited evidence that patiromer prolongs survival. OPAL-HK did not collect data on the effect of patiromer on long-term outcomes such as progression of kidney disease, cardiovascular events or mortality
6	**Issue: Committee concern of potential for increased risk of death due to hypokalaemia** **Vifor position** All patients in OPAL-HK were receiving a RAASi medication at baseline and 42% were HF patients. Then, bringing patients into a range of 3.8-5.0mmol/L should not be associated with an increased risk of death as noted by the committee. **Key justifications** Although the normokalaemia range is defined within the interval of 3.5 to <5,1 and hypokalaemia by serum potassium <3.5 mmol/L, the target range defined by the company was 3.8 to <5.1 while hypokalaemia definition remains at serum potassium value <3.5 mEq/L, **Goyal *et al* (JAMA 2012)** described that among inpatients with acute myocardial infarction), the lowest mortality was observed in those with (postadmission) serum potassium levels between 3.5 and <4.5 mmol/L compared with those who had higher or lower potassium levels **Figure 3.** Rates of In-Hospital Mortality and of the Composite of Ventricular Fibrillation or Cardiac Arrest by Mean Postadmission Serum Potassium Level  Each x-axis interval is equal to or greater than the lower limit of the interval and less than the upper limit. The first interval includes all serum potassium levels less than 3.0 mEq/L; the last interval includes all levels equal to or greater than 5.5 mEq/L. Numbers of events and event rates are listed in Table 2.

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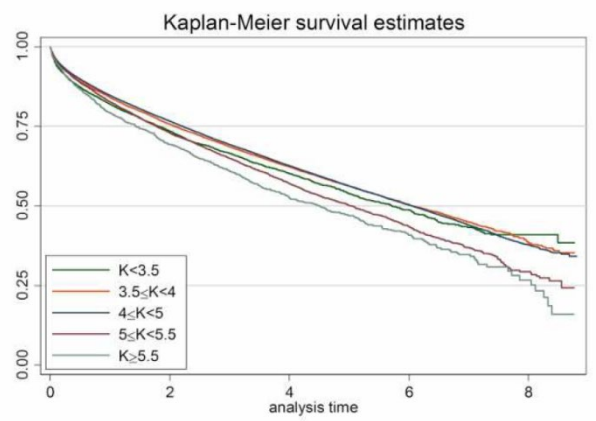
Matsushita *et al*, (T4044 — 2016 AHA) could assess the mortality rate among a population of 78,652 newly diagnosed HF veterans (vs average over 6 months prior to HF diagnosis) and link it to all-cause mortality in 142,087 patients based upon their serum potassium level



Hypokalaemia (defined as <4 mEq/L) was observed in 24.5% whereas hyperkalaemia (≥5 mEq/L) was seen in 8.4%. For hypokalaemia, lower cumulative survival compared to normal levels (4-<5 mEq/L) was found only below 3.5 mEq/L (prevalence of 4.0%), particularly in the first 5-6 years

Adahl *et al* (EHJ, 2017) describe association of serum potassium levels with mortality in chronic heart failure patients and based upon the below intervals, 4.2-4.4mmol/L being the reference interval

Table I Pre-defined potassium intervals

Potassium	Serum potassium concentration
Interval 1 (Hypokalaemia)	2.8–3.4 mmol/L
Interval 2	3.5–3.8 mmol/L
Interval 3	3.9–4.1 mmol/L
Interval 4 (Reference interval)	4.2–4.4 mmol/L
Interval 5	4.5–4.7 mmol/L
Interval 6	4.8–5.0 mmol/L
Interval 7 (Mild hyperkalaemia)	5.1–5.5 mmol/L
Interval 8 (Severe hyperkalaemia)	5.6–7.4 mmol/L

Levels within the lower and upper levels of the normal serum potassium range (3.5–4.1 mmol/L and 4.8–5.0 mmol/L, respectively) were associated with a significant increased short-term risk of death in chronic heart failure compared to reference interval of 4.2-4.4 on a 90 day period.
However, potassium below 3.5 mmol/L and above 5.0 mmol/L was associated with increased mortality.

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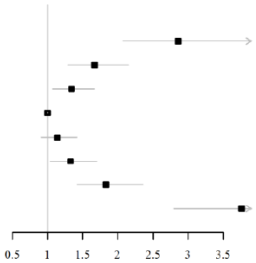
Parameter	HR	95% low	95% high	P-value
K:2.8-3.4 mmol/L	2.86	2.08	3.94	<0.01
K:3.5-3.8 mmol/L	1.67	1.29	2.15	<0.01
K:3.9-4.1 mmol/L	1.34	1.07	1.67	0.01
K:4.2-4.4 mmol/L	1			
K:4.5-4.7 mmol/L	1.14	0.91	1.42	0.25
K:4.8-5.0 mmol/L	1.33	1.04	1.70	0.02
K: 5.1-5.5 mmol/L	1.83	1.42	2.36	<0.01
K:5.6-7.4 mmol/L	3.76	2.80	5.05	<0.01



A Collins *et al* (Am J Nephrol 2017) evaluated the association of serum potassium with all-cause mortality in patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes.

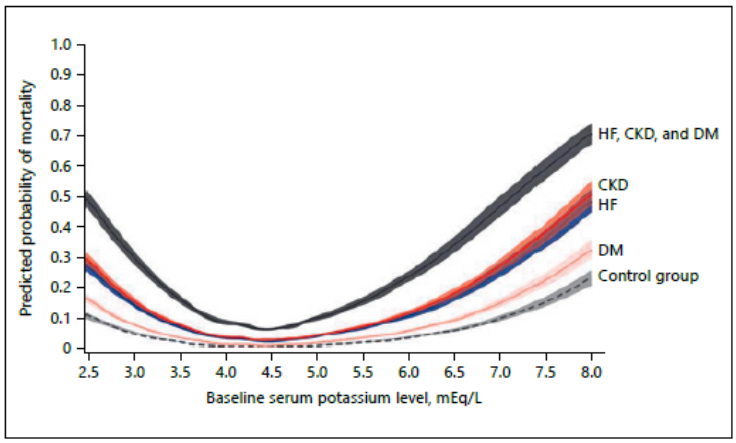
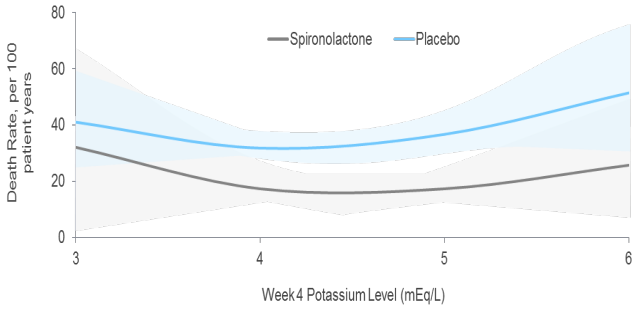


Fig. 2. Spline analysis adjusted for covariates, showing serum potassium as a continuous variable with all-cause mortality over the distribution of potassium values (2.5–8.0 mEq/L) in HF, CKD, DM, and combined cohort compared to controls. Data for patients with baseline serum potassium of 8.1–10.0 mEq/L are not reported because the sample size was small ($n = 138$). CKD, chronic kidney disease; DM, diabetes mellitus, HF, heart failure.

In an adjusted model, all-cause mortality was significantly elevated for every 0.1 mEq/L change in potassium <4.0 mEq/L and ≥ 5.0 mEq/L and was differentially greater in those with HF, CKD, or DM.

Hypokalaemia was defined **as mild** (3.5–<4.0 mmol/L) or **moderate-to-severe** (<3.5 mmol/L). Unadjusted 18-month mortality ranged from 34.8 to 55.6% with mild to severe hypokalemia compared to patients in the range of 4.0 to 5.0mmol/L.

Vardeny O, *et al*. (Circ Heart Failure. 2014) demonstrated that patients with HF benefit from spironolactone at all serum potassium levels (<u>including at serum potassium<4.0</u>) compared to patients receiving placebo.



In summary, although there is some evidence that patients with serum potassium 3.8-4 may have a higher mortality risk compared to patients within a range of 4.2 to 4.5 (or 5.0) there is also evidence that patients undergoing RAASi medication have reduced risk or mortality compared to those not receiving RAASi medication for same serum potassium levels, that include serum potassium <4

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	Vifor Position The second Periodic Safety Update Report (PSUR) for Veltassa (patiromer) issued on June 2018 reported until 20 April 2018 11.609 adverse drug reactions (ADRs). Out of these ADRs, 524 serious adverse events were reported from spontaneous and solicited post marketing sources. During this reporting period, no new safety signal has been detected in any clinical trials and from post marketing experience and there has been no ongoing or closed signal, In particular, a very low number of patients experienced an hypokalaemia episode (defined as serum potassium <3.5 mmol/l) in the phase 2-3 clinical program that is reflected in the EU SmPC where hypokalaemia is not listed as an adverse event. Similarly only 53 hypokalaemic post marketed cases were notified during the reporting period. The benefit/risk profile for Veltassa has not changed and remains positive" (ASP-PAT-EU-PSUR V2.0, June 2018) **<u>Amendments to ACD</u>** **ACD states (Section 3.12)** The normal range (as defined by the company; 3.8 mmol/L to 5.1 mmol/L) overlapped with the category of serum potassium (3.5 to 3.9 mmol/L) associated with an increased risk of death compared with serum potassium values of 4.5 mmol/L to 4.9 mmol/L. The committee was concerned that if the associations between serum potassium and death were true, using patiromer to lower serum potassium to the levels proposed by the company could actually increase the risk of death. **This text should be amended to** The normal serum potassium range (as defined by the company; 3.8 mmol/L to 5.1 mmol/L) overlapped with the category of serum potassium (3.5 to 3.9 mmol/L) associated with an increased risk of death compared with serum potassium values of 4.5 mmol/L to 4.9 mmol/L. While the committee was concerned that associations between serum potassium and death may be based on truth, the continual use of optimised RAASi dosing provides proven mortality benefit.
	<u>Additional amendments</u> **ACD states (Section 3.2)** The Committee considered that patiromer could have a role in treating life threatening HK. It would not replace intravenous insulin and glucose but it might replace calcium resonium. **and** Committee concluded that managing acute life threatening HK and chronic HK differed and that patiromer had a potential role in both **Vifor comments** Vifor request NICE to correct this conclusion as the role of patiromer will be in the treatment of chronic HK and not in the acute life-threatening situation. Therefore calcium resonium should not be considered a comparator of patiromer. **ACD states (Section 3.2)** Treatment of persistent HK includes diet and stopping or reducing RAAS inhibitors **This should be amended to read**

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	Treatment of persistent HK includes diet and reducing RAAS inhibitors at serum potassium levels between 5.0 and 6.0mmol/L or stopping if levels exceed 6.0mmol/L.

Insert extra rows as needed

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T4044 — 2016 [Board 4044] AHA

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2. Complete the disclosure about links with, or funding from, the tobacco industry.
3. Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
4. Do not paste other tables into this table – type directly into the table.
5. Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
6. Do not include medical information about yourself or another person from which you or the person could be identified.
7. Do not use abbreviations
8. Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
9. If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pumping Marvellous Foundation
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

Patiromer for treating hyperkalaemia [ID877]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	As the patient expert at the committee meeting, I can comment that the committee did not consider or listen to the conversation around why controlling and managing hyperkalaemia in patients with heart failure is important. I blame not only the committee for not having any representation from the clinical heart failure community but also the company for not pressing the case on the needs of the heart failure patient.
2	I am concerned that the meeting didn't take into account the needs of patients with heart failure where their needs are different from those without heart failure eg CKD patients.
3	I believe and witnessed the committee either miss the point of controlling and managing hyperkalaemia in heart failure where the focus was on CKD patients. Heart failure patients have additional needs. People with heart failure always have a need for their kidney function to be checked due to the evidence based triple therapy as indicated in the NICE Chronic Heart Failure Guidelines in Adults 2018. The core medication recommended by NICE includes ACE/ARB and MRA treatments which are considered to increase the likelihood of hyperkalaemia therefore the management of hyperkalaemia helps heart failure patients stay on prognostically significant cost-effective medication as recommended in the current NICE guidelines.
4	I know the committee missed the point as to the value of managing hyperkalaemia and its downstream effect on cost effective pharmacological management of heart failure. The committee was focussed on episodic management of hyperkalaemia in CKD specific patients.
5	My feeling was that the committee missed the point. The value of Patiromer to people with heart failure is not managing episodes, it is managing their condition to ensure they maintain their triple therapy through the rollercoaster of managing their prescribing levels. As indicated in the NICE Chronic Heart Failure Guidelines 2018 patients MDT's managing the prescribing regime with an aim to preventing patients being taken off life saving drugs.
6	Whether or not Patiromer has a prognostic value it would ensure people with heart failure maintain their triple therapy drugs if affected by hyperkalaemia which do have significant evidence around their prognostic value and cost effectiveness. This point clearly backups the argument that the committee didn't look or consider the value of Patiromer to people with heart failure.
7	It is clear that NICE didn't assess the cost effectiveness on treating heart failure patients with Patiromer as the downstream effects were not considered as mentioned already. A patient with heart failure could be said to be more cost effective to the system if managed with triple therapy than one who was not where there ACE/ARD and or MRA was stopped due to Hyperkalaemia.
8	Patiromer is innovative from the heart failure perspective as it enables people who depend on triple therapy as mentioned above to remain on optimal therapy thus having a prognostic benefit and better QOL. Anecdotally it is not diet that puts people with heart failure into a hyperkaliaemic situation it is the ADE/ARB/ARNI and MRA's they are prescribed.
9	It was a significant failure on behalf of NICE to not include representation from the British Society of Heart Failure or clinical expert with a sub specialty of Heart Failure. In my opinion this dramatically effected the clinical equipoise of the decision that has been made and potentially brings into question the credibility of that decision.

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Heart Failure (BSH)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted], on behalf of British Society for Heart Failure Board

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Background and general comments:** Patients with heart failure and reduced ejection fraction (HFREF) derive major prognostic benefit from with angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), sacubitril/valsartan, beta blockers and mineralocorticoid receptor antagonists (MRAs) [data summarised in ESC guidelines, 1]. For many of these drugs, the benefit is additive. For example, the combination of sacubitril/valsartan, beta blocker and MRA results in a reduction of all-cause mortality with a hazard ratio of 0.37 against placebo [2]. Renin angiotensin aldosterone inhibitors (RAASi) may lead onto hyperkalaemia, in particular in patients with co-existent chronic kidney disease (CKD). In some instances this may result in clinicians stopping or reducing doses of one or more RAASi. The British Society for Heart Failure (BSH) feel that the management of hyperkalaemia during co-existent RAASi use should be directed according to the strength of indication for the RAASi. That is when the drugs have clear prognostic benefit (i.e. HFREF or post MI left ventricular systolic dysfunction or CKD with albuminuria) every effort should be made to ensure their continuation at highest possible dose. This is very different to when they are used to treat hypertension – here many other good alternatives exist and switching the drug to a different class seems very appropriate, if problems such as moderate or severe hyperkalaemia ensue. Similarly if a patient has heart failure with preserved ejection fraction (HFPEF) RAASi have not been shown to be of prognostic benefit. The BSH, Renal Association (RA) and Think Kidneys have published guidelines on the management of changes in renal function and potassium on initiation and up titration of RAASi in patients with heart failure [3]. 1. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37:**2129-2200Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, Cope S. 2. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Circ Heart Fail* 2017;10: pii: e003529 3. https://tinyurl.com/y7yrlk69
2	The NICE summary documents are confusing and mix multiple conditions like heart failure, CKD and hypertension and the acute and post-acute/chronic management of hyperkalaemia. It will be almost impossible to make one single recommendation for all of these things. As such the BSH agree that there should not be a very broad indications such as 'hyperkalaemia in adults' for these drugs. However, we feel that availability of novel drugs to lower potassium might be of clinical value in the management of a very select cohort patients with HFREF who develop hyperkalaemia in order to facilitate the use of life prolonging drugs (i.e. RAASi) and to prevent development of hyperkalaemia (e.g. potassium

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	>6.0mmol/l). It is uncertain as to how many patients this might effect, but we feel the numbers will be very small. Some patients who develop hyperkalaemia will have other issues such as worsening renal function and/or hypotension, which themselves might limit continued prescribing of RAASi. In summary, by not approving these novel treatments in any clinical scenario patient care may suffer. A suggestion would be restricted use for high risk HFREF patients under secondary care teams (this would for example include compassionate use in advanced heart failure patients with multiple previous admissions who have needed to stop a RAASi due to isolated hyperkalaemia). The BSH feel unable to comment on potential use in patients with severe/end stage renal disease.
3	Throughout the document reference is made to the committee and clinical expert highlighting that most clinicians would only treat hyperkalaemia unless the value was 6 mmol/l or more. This is not correct and the BSH feel that this over simplifies the complexity of management of hyperkalaemia. The document mentions that in this case treatment would be as an emergency in secondary care with agents such as insulin/dextrose, calcium gluconate and calcium resonium. It does highlight that RAASi would be stopped or reduced. The BSH feel strongly that in routine clinical practice many clinicians do intervene or 'treat' at potassium values much lower than 6mmol/l. Whilst this may not involve prescription of additional therapy it is commonly a *reduction or cessation* of ongoing treatment with RAASi. For patients with HFREF, post MI left ventricular systolic dysfunction or CKD with albuminuria this has major adverse implications. 'Section titled: People would welcome an alternative to stopping RAASi'. The BSH agree with this statement but are concerned that the focus of the document is on patients with hypertension and is merely focusing on RAASi as anti-hypertensive agents. They are not just blood pressure lowering drugs - in HFREF, for example, they are disease modifying drugs. See below extract taken from page 7 below: ''The committee concluded that patients and clinicians were keen for new treatments that would allow them to continue to take RAAS inhibitors, but that the harms and benefits of stopping a RAAS inhibitor and **switching to an alternative blood pressure lowering treatment** would need to be taken into account.''
4	Whilst the BSH agrees that the acute management of severe hyperkalaemia primarily involves treatment such as calcium gluconate, insulin/dextrose and calcium resonium, there may be occasions when novel potassium binders compliment/add to current options. For example, if calcium resonium was not tolerated. Patients often require emergency admission when severe hyperkalaemia is diagnosed; the use of novel potassium binders may allow the patient to be managed safely at home preventing an unnecessary hospitalisation.
5	In summary, the BSH would like NICE to consider use of the new potassium binders for restricted use by secondary care clinicians involved in the management of patients with prognostic indication for RAASi. The BSH are concerned that the NICE evaluation only focuses on the acute presentations with very high potassium levels and fails to consider the downstream adverse effects on patients, associated healthcare costs and adverse outcomes if RAASi are withheld/reduced. The BSH feel unable to comment on potential use in patients with severe/end stage renal disease.
6	The BSH would also highlight that more research is needed, even in the shorter-term with soft heart failure outcomes (e.g. symptoms, QoL, BNP etc). If some use is approved, then the BSH would welcome the prospective collection of data relating to the practicality of use of these medications (e.g. drug interactions and adherence).

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Renal Association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No new disclosures from last submission**] Was present as expert at NICE Meeting during review of drugs – therefore heard all comments during the open meeting
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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1	We are concerned that by not approving these novel treatments, at least with restrictions, this will limit optimal patient care and restrict clinicians from treating a cohort of patients with difficult to control potassium values, leading to premature dialysis, serious morbidity, unnecessary hospitalisation and possible mortality.
2	We feel that the new potassium binders have a role in facilitating safer use of renin angiotensin blockers (ie ACE inhibitors (ACE-I) or Angiotensin receptor blockers (ARB)) in **some** patients with CKD and/or cardiac failure. These agents are proven to be of definite clinical benefit in both conditions but can lead to hyperkalaemia; clinicians would choose to use potassium binders at [potassium] > 5.5 mmol/l to **prevent** [potassium] reaching 6 mmol/l and above . In both patient groups there are many occasions where renin angiotensin blockade has to be reduced or terminated due to hyperkalaemia, leading to increased patient risk.
3	We are concerned that there may have been some misunderstanding concerning the nature of patients suitable for treatment with the new potassium binders. These agents are not intended for acute management of patients with [potassium] > 6 mmol/l. However, they would provide treatment options, together with dietary restriction, that are currently not available **after acute treatment** of hyperkalaemia in order to prevent recurrent hyperkalaemia and to facilitate safer use of ACE-I and ARB, necessary treatments for patients with CKD and/or heart failure.
4	We feel that the NICE panel should recognise the importance of the many recurrent and unnecessary hospitalisations that are associated with hyperkalaemia in patients with CKD and/or heart failure. These are associated with major cost, morbidity and mortality. The new potassium binders appear to have the capacity to reduce this burden.
5	Calcium resonium has been available as a potassium binder for decades but most patients suffer gastrointestinal side effects; intestinal necrosis is a very serious but rare complication. We feel that NICE should recommend the use of the novel potassium binders as an alternative for calcium resonium therapy, which remains in guidelines.
6	In summary, we would like to see the NICE panel consider permitting use of the new potassium binders for restricted use and prescription by clinicians managing patients with CKD and/or heart failure in a secondary care setting. It is important that this therapeutic option gains real world experience in the UK such that clinicians can establish the use of these agents in a group of patients with multiple comorbidities and limited quality of life until further data becomes available to extend their use to other groups of patients.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Royal College of Pathologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments
	None to add

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Example 1	We are concerned that this recommendation may imply that ……..
1	
2	
3	
4	
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6	

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have received honoraria from advisory boards from Vifor and AstraZeneca and my institution is in receipt of a grant from Vifor.
Name of commentator person completing form:	John G F Cleland Professor of Cardiology, Imperial College, London Director of the Robertson Centre for Biostatistics & Clinical Trials, University of Glasgow

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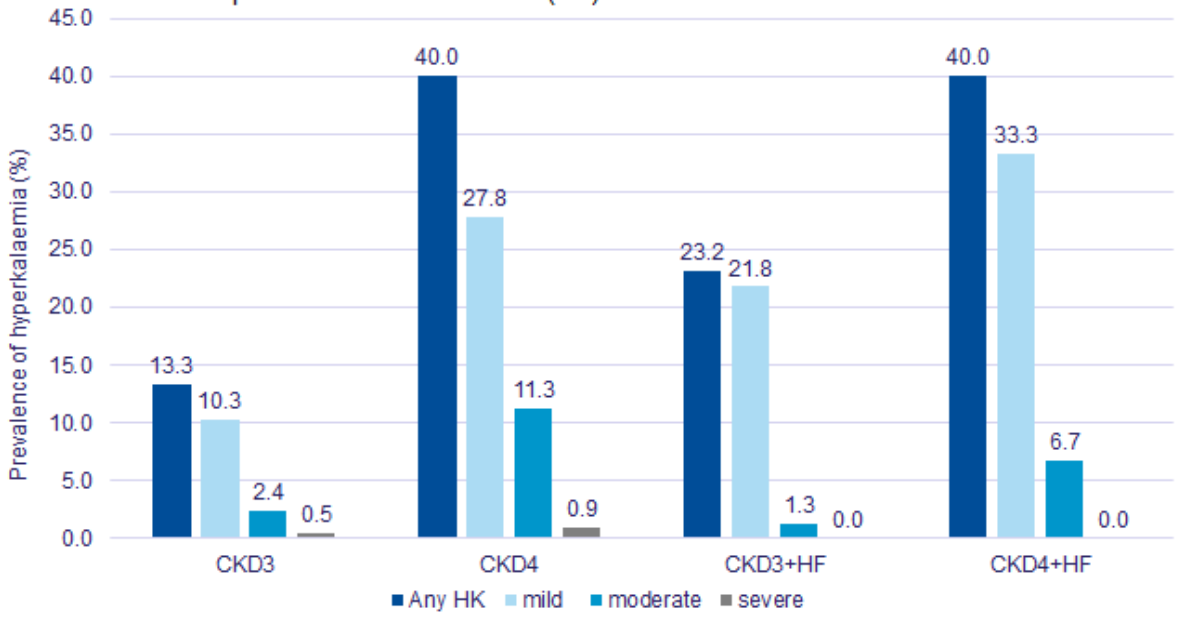
	Introduction Heart failure is both common and serious. When heart failure is associated with a reduced left ventricular ejection fraction (HFrEF), renin-angiotensin-aldosterone-system inhibitors (RAASi) combined with diuretics, beta-blockers and, for those with a prolonged QRS duration, cardiac resynchronization therapy (CRT) devices, improve symptoms and reduce morbidity and mortality. However, many patients also have renal dysfunction and/or diabetes, which increases the risk of developing hyperkalaemia with RAASi and beta-blockers. Hyperkalaemia and clinicians' fear of hyperkalaemia are important reasons for many patients not achieving NICE (and other) guideline-recommended doses of these agents.
1	**Why are Patients with Heart Failure Prescribed RAASi?** There are two main reasons to treat a patient with HFrEF with RAASi. The reason most prominently stated in **guidelines** is the impact of RAASi on morbidity and mortality. This may be partly mediated by correction and prevention of hypokalaemia but improvement in cardiac function and structure (remodelling) and reduction in congestion also probably play an important role. However, **from a patient's perspective**, the most important reason for taking a RAASi may be to improve symptoms (which may lead to a reduction in hospitalisation for worsening congestion). For these patients, withdrawal of RAASi is not a satisfactory response to hyperkalaemia. A treatment for hyperkalaemia that permitted initiation and maintenance of RAASi to treat symptoms and signs and improve well-being in patients with heart failure would have high clinical value. Hyperkalaemia (and the fear of hyperkalaemia) may prevent effective treatment to control symptoms. It is for this reason (rather than possible benefits on mortality) that I believe there is a current, important role for potassium-binding agents for heart failure.
2	**What Do Guidelines Say about Hyperkalaemia?** Current NICE guidelines on heart failure refer frequently to the need to measure serum potassium but refrain from making specific recommendations based on serum potassium. The 2010 NICE guideline on heart failure recommended a reduction in dose or cessation of a mineralo-corticoid antagonist (MRA) when serum potassium exceeded 5.5mmol/L. SIGN guidelines recommend "Serum potassium should be monitored to maintain its concentration in the range 4–5 mmol/l and adjustments in therapy should be made to prevent both hypokalaemia and hyperkalaemia" **and** "If potassium rises to >5.5 mmol/l or creatinine increases by >100% or to above 310 micromol/l the ACE inhibitor/ARB should be stopped and specialist advice sought" **and** "If K+ rises above 5.5 mmol/l or creatinine rises to >220 micromol/l reduce the dose (of MRA) to 25 mg on alternate days and monitor blood chemistry closely. If K+ rises ≥6.0 mmol/l or creatinine to 310 micromol/l stop spironolactone immediately and seek specialist advice." The SIGN Guidelines also recommend caution in the use of all RAASi when serum potassium is >5.0mmol/L. The ESC Guidelines on heart failure recommend caution with the use of RAASi when serum potassium is

	>5.0mmol/L and temporary cessation when serum potassium is >6.0mmol/L. American guidelines also suggest caution in the use of RAASi when serum potassium is >5.0mmol/L. In summary, guidelines urge caution in the use of RAASi when serum potassium is >5.0mmol/L and to maintain serum potassium in the range 4.0 to 5.0mmol/L. This is consistent with clinical practice.
3	**Background Information** The National (England & Wales) Audit for Heart Failure reports that 83% of patients with HF with HFrEF are prescribed an ACE inhibitor or angiotensin receptor blocker (ARB) and 53% a MRA at discharge *[National Heart Failure Audit April 2015 – March 2016, section 2.3.1]*. The Audit Report states: "*Had the patients identified within this audit cycle as having HFrEF, who left hospital on none of the three disease modifying drugs, been prescribed all three, then an additional 169 patients would likely have been alive at the time of censor. With more comprehensive prescription and dose optimisation across the audit there is the ability to prevent numerous additional deaths*." Hyperkalaemia is a common complication of RAASi in some groups of patients. A retrospective cohort study of patients with chronic kidney disease (CKD) registered in the Clinical Practice Research Datalink (CPRD) GP practices in Scotland found that the prevalence of hyperkalaemia in patients with heart failure and CKD stage 3 was 23.3% and in CKD stage 4, 40% *[Hyperkalaemia in CKD: Incidence, Prevalence and Impact on RAAS Inhibitor treatment in Primary Care in Scotland, figure 3]*. After an episode of hyperkalaemia, 10.7% of patients discontinued RASSi and in 21.4% it was down-titrated *[figure 4]*. BIOSTAT-CHF, a prospective study including UK centres, investigated the up-titration of RAASi in 2,516 patients with HFrEF. Only 22% achieved guideline-recommended doses. Those who achieved <50% had an increased risk of hospitalization (or death) due to heart failure *[Ouwerkerk W, et al. Eur Heart J. 2017; Figure 2]*. Another large European registry of 12,440 HF patients reported that while 92% of hospitalized HF patients were prescribed the recommended RAASi therapy as per ESC guidelines, less than 30% were up-titrated to the recommended target dose *[Maggioni AP, et al. Eur J Heart Fail. 2013]*. These results were confirmed also in QUALIFY, an international, prospective survey assessing physicians' adherence to guideline-recommended medications for the treatment of HFrEF. Only 87% were treated with ACEi/ARB and only 69% were treated with MRAs *[Komajda M, et al. Eur J Heart Fail. 2016]*. ***Hyperkalemia in Chronic Kidney Disease: Incidence, Prevalence and Impact on RAAS Inhibitors treatment in Primary Care in Scotland, figure 3***

Patiromer for treating hyperkalaemia [ID877]

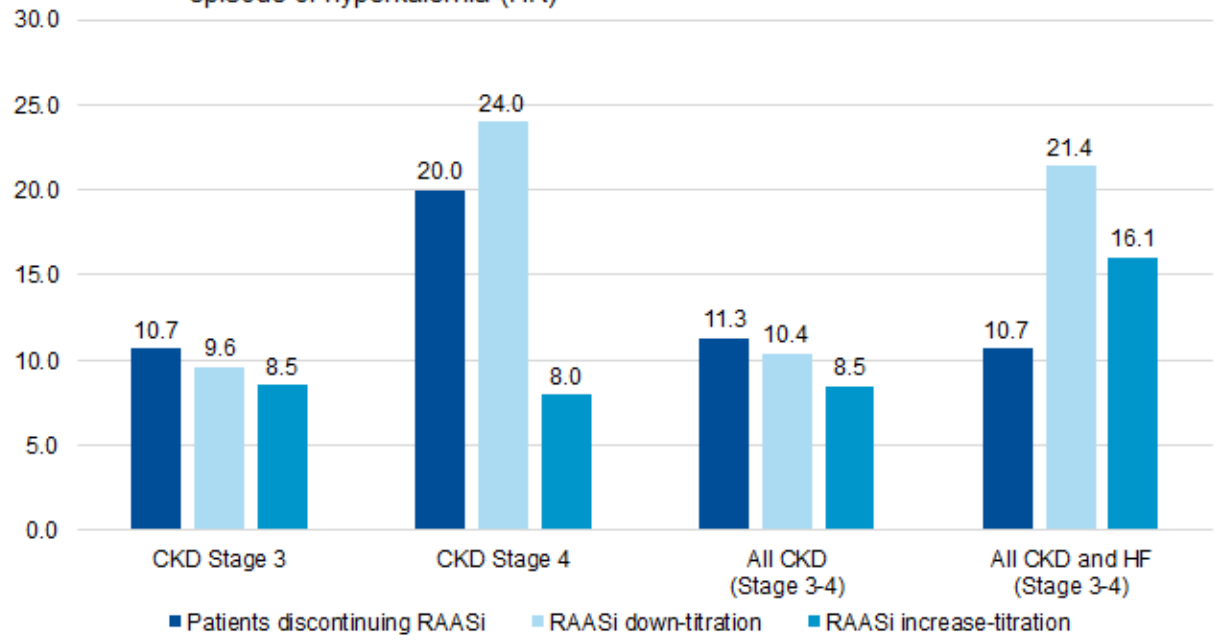
Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

Figure 3. Prevalence of hyperkalemia (HK) by CKD stage in the absence and presence of Heart Failure (HF)



Hyperkalemia in Chronic Kidney Disease: Incidence, Prevalence and Impact on RAAS Inhibitors treatment in Primary Care in Scotland, figure 4

Figure 4. Percentage of patients with changes to RAASi treatment after an episode of hyperkalemia (HK)



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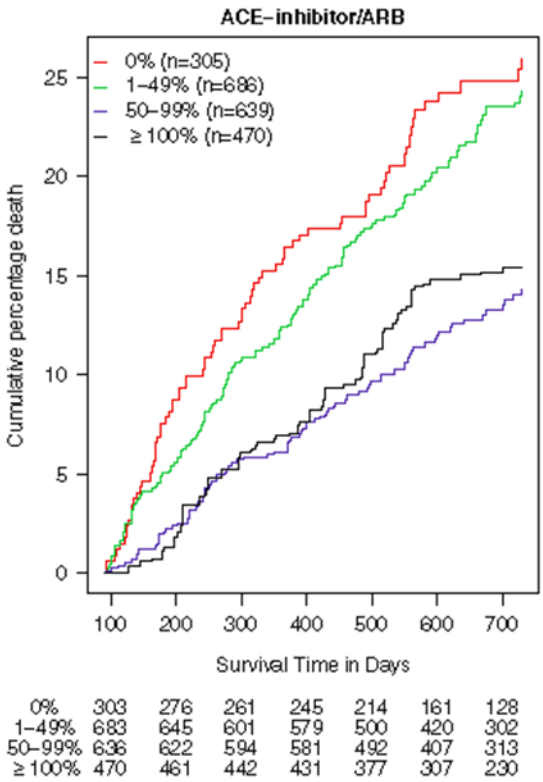
	Ouwerkerk W, et al. Eur Heart J. 2017; Figure 2 
4	**<u>Treatment of Hyperkalaemia</u>** Treatment options for the long-term management and/or prevention of hyperkalaemia are currently limited to reducing dietary potassium, increasing the dose of diuretics and/or reducing or stopping medications that increase serum potassium, including RAASi, especially MRAs, and beta-blockers. The latter strategy may not be appropriate for symptomatic patients. Hyperkalaemia may be treated in the short-term with calcium resonium *[Calcium Resonium SmPC 2014].* Long-term use should be avoided due to potential severe gastrointestinal side effects such as bowel necrosis *[Calcium Resonium SmPC 2014].* The efficacy and safety of calcium resonium has not been studied in substantial, long-term trials [Sterns RH et al. J Am Soc Nephrol 2010]. The Expert Consensus on the management of hyperkalaemia in cardiovascular disease treated with RAASi coordinated by the working group on cardiovascular pharmacotherapy of the ESC states: *"*Patients with CKD and heart failure are at increased risk of hyperkalaemia and ~50% experience two or more yearly recurrences. A substantial proportion of patients receiving RAASi therapy have their therapy down-titrated or more often discontinued even after a single episode of hyperkalaemia. Since RAASi therapy reduces mortality and morbidity in patients with cardiovascular disease, steps should, when hyperkalaemia develops, be considered to lower K+ and enable patients to continue their RAASi therapy.

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	The use of such measures is especially important in those with the most to gain from RAASi therapy." Patiromer, and potentially zirconium cyclosilicate, provides an alternative long-term strategy to withdrawal of RAASi for the management of hyperkalaemia in patients with heart failure. I believe this will improve the management of patients who require RAASI for the control of symptoms of heart failure, which will potentially also reduce the risk of hospitalisation for heart failure and mortality.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Patiromer for treating hyperkalaemia [ID877]

Company evidence submission 2 (response to Appraisal Consultation)

June 2019

File name	Version	Contains confidential information	Date
ID877_Patiromer_EvidenceSubmission2_07June2019_v1.0	**1.0**	**Yes**	**07/06/2019**

List of Abbreviations

Abbreviation	Definition
ACD	Appraisal consultation document
ACE	Angiotensin-converting-enzyme
ACEi	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
AEs	Adverse events
AOBP	Automated office blood pressure
ARB	Angiotensin II receptor blocker
ARNi	angiotensin receptor-neprilysin inhibitors
AUC	Area under the curve
BHBIA	British Healthcare Business Intelligence Association
BMI	Body mass index
BNF	British National Formulary
CCB	Calcium channel blocker
CCV	Cerebrovascular
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CHAMP-HF	Change the Management of Patients with Heart Failure
CKD	Chronic kidney disease
CKD3	Chronic kidney disease stage 3
CKD4	Chronic kidney disease stage 4
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
DDD	Defined daily dose
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence review group
ESC	European Society of Cardiology
ESRD	End-stage renal disease
GDMT	Guideline-directed medical therapy
GP	General practitioner
HD	Haemodialysis
HF	Heart failure

HFrEF	Heart failure with reduce ejection fraction
H-ISDN	Hydralazine and isosorbide dinitrate
HK	Hyperkalaemia
HR	Hazard ratio
K+	Potassium
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
IQR	Inter-quartile range
IRR	Incidence rate ratios
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan Meier
LBBB	Left bundle branch block
LSM	Least square mean
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LYG	Life years gained
MA	Meta-analysis
MACE	Major adverse cardiovascular events
MDRD	Modification of diet in renal disease
MI	Myocardial infarction
MSV	Mandatory safety visits
MRA	Mineralocorticoid receptor antagonists
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
NRLS	National Reporting and Learning System
NSAID	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association
OLM	Olmesartan medoxomil
OMT	Optimal medical therapy
OR	Odds ratio
PAD	Peripheral artery disease
PAS	Patient access scheme

PD	Peritoneal dialysis
PICOS	Population, Intervention(s), Comparators, Outcomes and Study design
PMF	Pumping Marvellous Foundation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRSSU	Personal Social Services Research Unit
PSA	Patient safety alert
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PTCA	Percutaneous transluminal coronary angioplasty
PY	Patient years
QALY	Quality-adjusted life years
RAASi	Renin-angiotensin-aldosterone system inhibitors
RHTN	Resistant hypertension
RR	Relative risk
SD	Standard deviation
SLR	Systematic literature review
SMR	Standardised mortality ratios
SmPC	Summary of product characteristics
SPS/CPS	Sodium/calcium polystyrene sulfonate
STA	Single Technology Appraisal
SZC	Sodium zirconium cyclosilicate
TLR	Targeted literature review
TCM	Traditional Chinese medicine
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WHO	World Health Organization

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1. Executive Summary

1.1 Introduction

Patiromer (Veltassa®) is indicated in Europe for the treatment of hyperkalaemia in adults. Hyperkalaemia is potentially life-threatening and the risk of chronic hyperkalaemia is increased by the use of renin-angiotensin-aldosterone system inhibitors (RAASi), which are often used in patients with chronic kidney disease (CKD) with or without heart failure (HF). RAASi-induced hyperkalaemia often leads to the discontinuation, dose reduction, or even non-initiation of these protective and life-saving RAASi treatments. This poses a clinical dilemma in that RAASi therapy is a globally recommended management approach in patients with CKD with or without HF but hyperkalaemia prevents optimal guideline recommended use. Patiromer offers an innovative solution for the enablement of optimal RAASi therapy through potassium (K+) control that in turn enables the reno-protective, cardiovascular and mortality benefits related to RAAS inhibition in patients with CKD with or without HF. Further, hyperkalaemia in itself is associated with increased mortality risk for which long-term use of patiromer offers a solution.

When patiromer was reviewed by the National Institute for Health and Care Excellence (NICE) in 2018, the following concerns were raised:

(1) clinical trial results may not be relevant to clinical practice because in the trial most people had a lower level of serum potassium than would be treated in the National Health Service (NHS) (≥6.0 mmol/L according to NICE clinical guideline 182),

(2) there was no evidence to show that patiromer extends life or improves quality of life compared with standard care in people who would have treatment for hyperkalaemia in the NHS, and

(3) because of the lack of relevant clinical-effectiveness evidence, the cost-effectiveness estimates for patiromer were not valid.

Vifor were concerned that the scoping document clearly identified heart failure patients as an important population for consideration whereas the STA process only sought to discover current practice from the nephrology clinical community. In failing to seek the current treatment practice of cardiologists in this process, the cardiology clinician and patient views and experiences were not considered. Vifor research informed that in the UK, cardiologists actively manage patients with hyperkalaemia to enable optimal RAASi treatment below a K+ level of 6.0. The clinical need to manage hyperkalaemia is quite different to a nephrology perspective since cardiologists are more likely to intervene at lower serum potassium levels due to the sensitivity of heart failure patients to changes in serum K+, with associated risks including the development of life-threatening arrhythmias.

Vifor conducted additional research to address these concerns for resubmission to NICE. This document summarises the additional work undertaken, relevant findings, and updates made to the economic analysis.

1.2 Clinical evidence

Vifor undertook a review of clinical evidence and current UK management guidelines, and conducted physician and patient surveys to establish:

(1) the importance of controlling hyperkalaemia in patients needing or receiving RAASi therapy;

(2) the prevalence and consequence of sub-optimal RAASi treatment due to hyperkalaemia and the benefit of RAASi enablement; and

(3) the generalisability of patiromer to NHS practice, including the variation in serum potassium levels that triggers management of hyperkalaemia in clinical practice and how it is most appropriately managed by nephrologists and cardiologists.

The clinical review shows that RAASi-induced hyperkalaemia prevents its optimal use, with guidelines showing that current hyperkalaemia management is limited to RAASi modification, non-initiation and dietary control, all of which are recommended at serum potassium levels below 6.0mmol/L. Studies show that target guideline recommended dosing of RAASi is only achieved in 22% of patients with HF and only 19%-26% of patients with CKD. Since both suboptimal dosing of RAASi and hyperkalaemia are associated with increased risk of morbidity and mortality in patients with CKD and/or HF, an efficacious treatment for hyperkalaemia could contribute to better outcomes in these patients, enabling optimal guideline recommended RAASi dosing.

A survey of 112 healthcare professionals found the level of serum potassium cited as requiring treatment ranged from 4.9-6.6 mmol/L (1). This clearly shows that RAASi modification (and thus current management of hyperkalaemia) occurs below serum levels of 6.0 mmol/L in clinical practice and that treatment thresholds differed among specialists. This observation was corroborated by results from the physician survey, which shows that physicians in England have a maximal tolerable, serum potassium threshold of between 5.5-5.9 mmol/L in clinical practice. Both nephrologists and cardiologists would actively manage serum potassium below 6.0 mmol/L by reducing or discontinuing RAASi. Notably, cardiologists are likely to manage patients at lower serum potassium levels (≥5.5 mmol/L) than nephrologists. This approach to care has been recognised in the recent Appraisal Consultation document (ACD) for STA ID1293 where clinical expert input also validated a need for treatment below 6.0mmol/L.

Considering these findings, the placebo arm of OPAL-HK trial can be regarded as reflective of UK clinical practice for the management of hyperkalaemia given this involves RAASi modification and dietary control at serum potassium levels treated in the NHS. The wider patiromer clinical trial programme and feedback from a clinician working group of nephrologists and cardiologists

engaged by Vifor confirms the RAASi enabling benefit of patiromer in a range of high-need patient groups including CKD and/or HF (OPAL-HK, PEARL-HF, AMBER) and diabetes (AMETHYST-DN).

Physicians in the working group see a clear unmet need for effective longer-term hyperkalaemia management such as patiromer. Physicians advise that patiromer, when made available on the NHS, will enable treatment optimisation and initiation of life-saving RAASi therapy. In a survey of patients with HF and hyperkalaemia, most responders (83%) said they would find it extremely or very beneficial to have a treatment that ensured they could stay on the optimum dosage of their HF medications.

1.3 Targeted literature reviews

The following specific concerns were raised by the Evidence Review Group (ERG) and NICE relating to data used in the economic model:

(1) the data on the impact of RAASi on CV events, mortality and CKD progression were not sourced systematically;

(2) the risk of progressing to ESRD was over-estimated;

(3) the relationship between serum potassium levels and mortality and other long-term outcomes was uncertain and a systematic review of the evidence for this relationship was not provided, and

(4) it may be inappropriate to use clinical-effectiveness data for people starting RAASi from the Xie et al network meta-analysis (NMA) to model the benefits forgone if RAASi therapy is stopped.

Vifor therefore undertook targeted literature reviews (TLRs) to address these concerns.

Initially, published systematic literature reviews (SLRs) and meta-analyses (MA) were reviewed for relevant and robust data. This was followed by a review of published single studies (randomised and non-randomised) to find alternative data which could be used in the absence of relevant data from SLRs or MAs.

Findings of the TLRs confirmed that RAASi has a positive impact on outcomes including reducing the risk of CV events, mortality and renal progression. Studies showed that RAASi provides a significant delay in progression to end stage renal disease (ESRD) in patients with CKD, and that stopping RAASi treatment or sub-optimal RAASi dosing in patients with CKD leads to an increased risk of CV events, mortality and renal progression.

The TLR identified both SLRs/MAs and observational studies that highlighted the association between serum potassium levels and mortality. The volume and consistency of evidence shows that hypokalaemia and hyperkalaemia are associated with increased morbidity and mortality risk. Further, the use of RAASi reduced mortality risk across serum potassium categories. Mortality risk generally increases at serum potassium levels >5.0 mmol/L, again highlighting the need to control serum potassium below the current CKD treatment guideline level of ≥6.0 mmol/L.

Studies showed that increasing serum potassium levels are associated with an increasing incidence of RAASi discontinuation. Since stopping treatment with RAASi or sub-optimal RAASi dosing in patients with CKD leads to an increased risk of CV events, mortality and renal progression and given the impact of hyperkalaemia on patient mortality and morbidity, strategies that control serum potassium and avoid RAASi discontinuation could impart significant health benefits to patients with CKD.

The TLR identified the Xie et al. NMA as the most appropriate source of long-term efficacy data for use in the economic model. Additional evidence supported using the Xie et al. NMA to inform the relative risks in the economic model whereby the benefits of starting RAASi are modelled as equivalent to the benefits foregone upon discontinuing.

In conclusion, the TLRs increased the robustness of inputs used in the economic model and verified the long-term benefits of RAASi therapy and the long-term implications of hyperkalaemia in patients with CKD.

1.4 Clinical Practice Research Datalink (CPRD) analysis

To address the concern raised by NICE that differences between CKD stage 3 (CKD3) and CKD stage 4 (CKD4) may not be captured by combining the health states in the economic model, Vifor undertook an analysis of patient data from the CPRD database to understand the difference in movements between potassium categories by CKD stage. The analysis included 9,751 patients in England with CKD and a RAASi prescription. The monthly probabilities of transitioning between serum potassium categories (defined as ≤5.0 mmol/L, >5.0 to ≤5.5 mmol/L, >5.5 to ≤6.0 mmol/L, and >6.0 mmol/L) for patients with CKD3 and CKD4 were captured separately, which enabled differences between the stages to be accounted for when used in the model. The inclusion of CPRD also enabled the inclusion of serum potassium data in CKD patients based on a UK population so improving the generalisability of results to a UK setting.

Demographic and clinical characteristics of patients identified in the CPRD were compared with patients in OPAL-HK trial. Patients in the CPRD were generally older and healthier than patients in the OPAL-HK trial (fewer co-morbidities, lower mean serum potassium level, higher mean eGFR) at index. This may be attributable to differences in the level of care they were receiving. Since the CPRD population are managed in primary care they may be healthier than the OPAL-HK population who were managed by nephrologists and cardiologists in an outpatient setting.

1.5 Economic model update

To address concerns raised by the ERG and NICE on the original economic model, several structural changes have been implemented in the model. These included accounting for Part A of OPAL-HK, improving the generalisability of the results to UK clinical practice (CPRD), allowing for RAASi dose modification, including adverse events due to patiromer, and refining the patient population included in the model to account for differences in how nephrologists and cardiologists

manage hyperkalaemia. Changes were made based on evidence gathered from the additional research conducted for this updated submission.

The population used in model was updated to align with NICE's view and with the company's research with nephrologists and cardiologists, in particular on the serum potassium levels which would determine treatment in UK clinical practice. Therefore, the updated economic analysis was conducted to assess the cost-effectiveness of initiating patiromer in adult patients with CKD 3-4 with HF with a serum potassium level of ≥5.5 mmol/L, and adult patients with CKD 3-4 and no HF with a serum potassium level of >6mmol/L. Therefore, the updated population excluded patients from OPAL-HK with CKD and no HF with a starting serum potassium level of 5.5-6.0 mmol/L. Patiromer was compared with standard of care i.e. dietary modification and RAASi dose modification.

The base case analysis adheres to the NICE reference case adopting the NHS and Personal and Social Services (PSS) in England and Wales perspective, considering only costs incurred by the NHS, and a lifetime horizon.

Patients were treated with patiromer for 52 weeks reflecting the longest duration of treatment observed in the patiromer clinical trial programme, from AMETHYST-DN. Scenario analyses evaluate the impact of treatment durations based on the longest observed real-world usage for patiromer from US claims data ([redacted]) and OPAL-HK (84 days). The latter was selected on the basis of the recent ACD for STA ID1293 where NICE have proposed the recommendation of another technology for treating hyperkalaemia in adults only if the drug is stopped after 28 days of maintenance treatment, or earlier if hyperkalaemia resolves. This duration is based on the length of the clinical data driving the analysis. Vifor provide an equivalent scenario for a treatment duration of 84 days based on the length of OPAL-HK. Vifor are also investigating the long-term impact of patiromer on RAASi enablement and subsequent CV endpoints (hospitalisation and death) compared with placebo in the phase 3b DIAMOND study. Primary endpoint results are expected in December 2021.

Following the updates, the base-case deterministic analysis showed that patiromer is cost-effective (ICER=£18,893), with a probability of being cost effective at NICE thresholds of £20,000 and £30,000 per QALY of 38% and 94%, respectively. Patiromer remains cost effective under various scenario settings including varied treatment durations, alternative utility values, and alternative cohort starting ages.

2. Clinical evaluation

Key messages
• Chronic hyperkalaemia (HK) often manifests in patients with chronic kidney disease (CKD) and/or heart failure (HF) treated with renin-angiotensin-aldosterone system inhibitors (RAASi). Hyperkalaemia is potentially life-threatening, however, questions remain about when and how it is most appropriately managed. • A survey of 112 healthcare professionals found the level of serum potassium (K+) cited as requiring treatment ranged from 4.9-6.6 mmol/L, thus revealing uncertainty surrounding treatment initiation and confirming that serum levels <6.0 mmol/L are treated in clinical practice. This finding was supported by separate surveys conducted with UK nephrologists and cardiologists to determine how hyperkalaemia is managed in current UK practice. • There is a clinical dilemma as RAASi therapy is a globally recommended management approach in patients with CKD with or without HF with demonstrably significant clinical and pharmacoeconomic benefits, but hyperkalaemia commonly prevents optimal use. • Patiromer offers an innovative option for the enablement of optimal RAASi therapy through potassium control that in turn preserves the benefits related to RAAS inhibition in patients with CKD with or without HF. • Suboptimal dosing of RAASi in patients with CKD and/or HF is associated with increased morbidity and mortality. Efficacious management of hyperkalaemia could enable guideline recommended dosing of RAASi thus contributing to better outcomes in patients with CKD with or without HF.

Key concerns raised by the committee
• What is the unmet need in the management of hyperkalaemia in patients with CKD with or without HF? • What are the benefits of maintaining serum K+ in these patients? • The patient population treated in OPAL-HK is not reflective of UK clinical practice as patients would not routinely be managed at serum K+ <6.0.

2.1 Objective

In their Appraisal consultation document (ACD) on patiromer for treating hyperkalaemia, the National Institute for Health and Care Excellence (NICE) raised the concerns that:

- Trial results showed that continuing patiromer was associated with lower serum potassium (K+) than stopping patiromer, however, the benefit of this to patients in clinical practice was unclear.
- Hyperkalaemia at serum K+ levels lower than 6.0 mmol/L would not normally be treated in National Health Service (NHS) clinical practice.
- Clinical trial results may not be relevant to UK clinical practice because in the trial most people had a lower level of serum K+ than would be treated in the NHS.

Therefore, the aim of the clinical evidence review was to:

- Investigate renin-angiotensin-aldosterone system inhibitor (RAASi) treatment enablement in patients with chronic kidney disease (CKD) and/or heart failure (HF) with hyperkalaemia to establish:
    - The importance of controlling hyperkalaemia in patients receiving RAASi therapy
    - Reveal the variation in serum K+ levels that triggers hyperkalaemia treatment initiation in clinical practice in the UK.
    - The level and consequence of sub-optimal RAASi treatment due to hyperkalaemia and the benefit of RAASi enablement in this patient population.
- Assess the generalisability of patiromer clinical trial programme to UK practice.

This clinical evaluation will highlight the importance of RAASi enablement in patients with HF through potassium control, a key co-morbidity in patients with CKD.

2.2 Summary of clinical data

The technology, patiromer (Veltassa®), is a novel, next-generation, non-absorbed, sodium-free, cation exchange polymer that binds excess potassium. Patiromer is indicated in Europe for the treatment of hyperkalaemia in adults.

Hyperkalaemia is a serious medical condition that can cause muscle weakness, paralysis and cardiac arrhythmia's leading to cardiac arrest and death, with a resulting mortality rate of up to 30%. (2, 3) A Patient Safety Alert (PSA) published by the National Health Service (NHS) in 2018 showed that between 2014 and 2017, 35 patients suffered cardiac arrest while hyperkalaemic.(4)

Hyperkalaemia results from a combination of intrinsic and extrinsic factors.(5-7) Intrinsic factors include underlying disease, for example chronic kidney disease (CKD) or heart failure (HF) (8). Common extrinsic factors are drugs that impair physiologic responses to hyperkalaemia such as various medications, among which RAASi.(5, 9, 10)

There is currently no standard treatment for chronic hyperkalaemia and it is mainly based on RAASi therapy non-initiation, down-titration or withdrawal.(2, 3) Otherwise there are three pharmacological options: Sodium/calcium polystyrene sulfonate (SPS/CPS) which is not suitable

for extended use; sodium zirconium cyclosilicate which is currently undergoing assessment and outside of the remit of this document and patiromer.(5)

Angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) such as spironolactone are RAASi medications. Each class has been shown to reduce mortality and morbidity in patients with HF with reduced left ventricular ejection fraction (HFrEF) and are recommended by the European Society of Cardiology (ESC 2016) Guidelines and the NICE HF Guidelines.(11, 12). Both ACEi or ARB plus MRA are recommended in all symptomatic HF patients as part of what is known as triple therapy which consists of an ACE/ ARB + beta blocker + MRA. Potentially all patients with persisting HF symptoms (New York Heart Association [NYHA] Class II–IV) and a left ventricular ejection fraction (LVEF) ≤35% despite treatment with an ACE-I (or ARB) and a beta-blocker should be prescribed triple therapy to improve symptoms, reduce the risk of HF hospitalisation and increase survival (11). Cole et al. provided an estimate of lifespan benefit from triple therapy using a method that any clinician can replicate. The summary from the publication is that “triple therapy triples lifespan”.(13)

Despite the evidence from multiple clinical trials informing national (NICE) and international (ESC) guidelines, the reality in the UK is different. The National Heart Failure Audit (14) showed the number of patients discharged from hospital on triple therapy after an admission for HF is only 44% [Table 4 of the National Heart Failure Audit].

One contributing factor to these low numbers is because RAASi can increase serum potassium levels. Elevation from baseline serum potassium levels then often lead to non-initiation, down-titration or discontinuation of protective and life-extending treatments with RAASi (15-19).

BIOSTAT-CHF, a prospective European study, investigating the up-titration of ACEi/ARB in 2516 patients with HFrEF noted that only 22% achieved the guideline recommended dose and those patients reaching <50% had an increased risk of death and/or hospitalisation due to HF (19).

In QUALIFY, an international prospective observational longitudinal survey, less than two-thirds of the patients (65.7%) were treated with ACEi, only 21.5% of the patients were on ARBs and 69.3% were treated with MRAs. Hyperkalaemia was a reason in 3.9% of patients not taking ACEi, in 5.5% of patients not taking ARBs and in 31.4% of patients not taking MRAs (15).

Both dose reduction of RAASi and higher levels of serum potassium in patients with HF have been shown to be associated with increased mortality risk in clinical studies (18, 20). Thus, efficacious treatment of hyperkalaemia could contribute to better outcomes of patients with HF enabling guideline recommended dose of RAASi.

Kalsi et al. (1) recently published the results of a survey conducted across 112 (81% UK based) Healthcare Professionals confirming that hyperkalaemia is considered as a common and important clinical issue for patients receiving RAASi which may limit the use of RAASi and impact on improving prognosis in the cardiorenal population. In this survey, the majority of professionals (70%) felt that hyperkalaemia would affect the use of RAAS blocking medications in up to a quarter

of their patients, with the minority (10%) having this concern for half of their patient population. Across all respondents, the serum potassium level cited as requiring treatment ranged from 4.8 – 6.6 mmol/L. Higher values of hyperkalaemia prompting treatment were more likely to be cited by nephrologists. The reasons given for consideration of intervention at an earlier level of potassium included concerns regarding cardiac stability (31.5%) and deterioration in renal function (15.7%).(1)

The results from Kalsi et al. (1) were corroborated in research conducted in the UK via a modified Delphi process (see Section 2). Maximal tolerable, serum potassium thresholds exist in UK clinical practice. The vast majority of cardiologists and a significant proportion of nephrologists will take action at serum potassium levels between 5.5 mmol/L and 5.9 mmol/L by either stopping or reducing RAASi (data shown in Section 3).

In patients with CKD, despite guidelines for the use of RAASi therapy, the only current recommendations for managing hyperkalaemia are the non-initiation, down-titration or discontinuation of RAASi, thus foregoing the proven benefits that these drugs provide. For example, the NICE Clinical Guideline 182 advise that patients with pre-treatment serum potassium >5.0 mmol/L should not routinely be offered RAASi therapy and where serum potassium increases to ≥6.0 mmol/L RAASi should be discontinued.(21)

Molnar et al., assessed 141,413 non-dialysis patients with CKD and found that RAASi were prescribed at the target guideline recommended dose in 19% to 26% of patients, at submaximal dose in 58% to 65% of patients and were discontinued during follow-up in 14% to 16% of patients. Cardio-renal adverse events (AEs)/mortality and mortality occurred in 34.3% and 11.0% of patients who discontinued RAASi, 24.9% and 8.2% of patients on submaximal doses, and 24.9% and 4.1% of patients on maximum doses, respectively.(22)

In the RENAAL study (23) it was established that losartan, along with conventional antihypertensive treatment as needed, conferred strong renal protection in patients with type 2 diabetes and nephropathy.

In the REIN study (24) ACEi had a greater effect than other antihypertensive drugs on proteinuria and the progressive decline in glomerular filtration rate (GFR) in patients with diabetic nephropathy.

The ESC Guidelines published in 2016 (11) shows the clear place of “Triple therapy” (which consists of an ACE/ARB + beta blocker + MRA) in a treatment strategy for the use of drugs in patients with HFrEF. The importance of guideline adherence on prognosis has been recently highlighted by the QUALIFY global survey in 7092 patients with HFrEF. In this registry good adherence to guidelines was associated with a significant prognostic benefit, the adherence score was good in 67%, moderate in 25%, and poor in 8% of patients and the proportion of patients at target dose and at ≥50% of target dose was 27.9% and 63.3% for ACEi and 6.9% and 39.5% for ARBs, respectively (2, 15).

In a recent publication from the Change the Management of Patients With Heart Failure (CHAMP-HF) Registry, investigating the target doses of heart failure medical therapy and blood pressure, it

was seen that <20% of chronic HFrEF patients eligible for beta blockers and ACEI/ARB/angiotensin receptor-neprilysin inhibitors (ARNi) were receiving target doses.(25)

The working group on Cardiovascular Pharmacotherapy of the European Society of Cardiology states in the Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with RAASis “since RAASi therapy reduces mortality and morbidity in patients with cardiovascular disease, steps should, when hyperkalaemia develops, be considered to lower K^+ level and enable patients to continue their RAASi therapy. The use of such measures are especially important in those patients with the most to gain from RAASi therapy”.(2)

In the very recently published “Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology” Consensus report the following considerations:

"- Patiromer and ZS-9 may be considered in patients with HF with or without CKD to manage hyperkalaemia. In selected patients these therapies may enable use of MRAs and other RAASis in more patients and at higher doses, but it is not known whether this will improve patient outcomes.

- Patiromer and ZS-9 may be considered in selected patients with HF with or without CKD in order to enable up-titration of MRA while avoiding hyperkalaemia." (26)

Patiromer (Veltassa®) is a novel, next-generation, non-absorbed, sodium-free, cation-exchange polymer that binds excess K+ in the lumen of the gastrointestinal tract and increases faecal potassium excretion for the treatment of hyperkalaemia in adult patient (27). Furthermore, patiromer offers an innovative solution for the enablement of optimal RAASi therapy through potassium control that in turn preserves the benefits related to RAAS inhibition in patients with CKD with or without HF.

Currently, a phase 3b clinical outcome, randomised trial (NCT03888066) is ongoing to determine if patiromer treatment in HFrEF subjects with/ with history of hyperkalaemia by enabling and optimising RAASi therapy in accordance with HF treatment guidelines will result in decreasing the occurrence of cardiovascular (CV) death and CV hospitalisation events compared with placebo treatment, which is reflective of the standard of care. (28) An overview of the DIAMOND study is found in Appendix 10.1.6.

2.3 Clinical context

2.3.1 Summary of decision problem

A summary of the decision problem and a description of the technology being appraised can be found in Table 37 and Table 38 in the Appendix 10.1.1. In summary, patiromer is a non-absorbed, sodium-free, cation-exchange polymer that contains a calcium-sorbitol counterion. Patiromer

increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction in serum potassium levels. Patiromer has a marketing authorisation for the treatment of hyperkalaemia although, based on the available clinical evidence, the decision problem addressed in this submission is for adult patients with stage 3-4 chronic kidney disease (and other co-morbidities such as heart failure and diabetes) and hyperkalaemia treated with RAASi therapy.

2.3.2 Hyperkalaemia

Potassium is the most abundant intracellular cation and it plays a key role in the cellular function of nerve and muscle tissue, including maintenance of normal heart rhythm. Potassium disorders or dyskalaemias (hypo or hyperkalaemia) are relatively common in clinical practice and are associated with an increase in all-cause mortality over an 18-month follow-up. Mortality risk was lowest with serum potassium values between 4.0 and 5.0 mmol/L, both in those with and without CKD, heart failure, diabetes mellitus, and CV disease.(29)

The standard normal range of serum potassium is typically considered to be 3.5–5.0 mmol/L.(30) Hypokalaemia occurs when serum potassium drops below the normal range, while hyperkalaemia is defined as serum potassium levels above the upper limit of normal, typically defined as >5.0 mmol/L.(6) Hyperkalaemia may be further classified as mild, moderate, or severe based on the serum potassium level.(3) In 2018, the working group on Cardiovascular Pharmacotherapy of the European Society of Cardiology stated in their Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with RAASi “the severity of hyperkalaemia can be classified as mild (>5.0 to <5.5 mmol/L) to moderate (5.5 to 6.0 mmol/L) and to severe at thresholds (>6.0 mmol/L)”.(2)

Hyperkalaemia is a serious medical condition that can cause muscle weakness, paralysis, and cardiac arrhythmias leading to cardiac arrest and death, with a resulting mortality rate of up to 30%.(2, 3) Chronic hyperkalaemia is a serious medical condition that often manifests in patients with CKD and/or heart failure.(3)

In August 2018, a PSA was published by the NHS (NHS/PSA/RE/2018/006) entitled, “Resources to support safe and timely management of hyperkalaemia (high level of potassium in the blood)”. It states that over a recent three-year period, the National Reporting and Learning System (NRLS) received 35 reports of patients suffering cardiac arrest in the setting of hyperkalaemia.(4) These suggest that some healthcare professionals may not appreciate that clinical assessment, treatment and ongoing monitoring of hyperkalaemia is time critical.

2.3.3 RAASi therapy and hyperkalaemia

Hyperkalaemia, usually defined as serum potassium concentrations greater than 5.0 mmol/L, is widely recognised as a direct and life-threatening complication, although questions remain about when and how to correct it.(5)

The NHS PSA titled “Resources to support safe and timely management of hyperkalaemia” from August 2018, states clearly “Hyperkalaemia is a potentially life-threatening emergency which can be corrected with treatment”.(4)

Hyperkalaemia most often results from the failure of renal adaptation to potassium imbalance resulting from a combination of intrinsic and extrinsic factors.(5-7, 10)

Intrinsic factors include disease whilst common extrinsic factors are drugs that impair physiologic responses to hyperkalaemia e.g. various inhibitors of the RAAS, and potassium intake e.g. a diet rich in potassium, or potassium supplements.(5, 9, 10)

RAASi medications include ACEi (e.g. ramipril), ARB (Sartan medications), direct renin inhibitors (e.g. aliskerin), MRA (e.g. spironolactone) and ARNi (e.g. sacubitril/valsartan).

Patient groups that are most susceptible to the development of hyperkalaemia include those groups for whom there is unequivocal evidence for prognostic benefits from RAASi agents; for example, patients with CKD, diabetes mellitus, or HF.(5, 10, 18, 29)

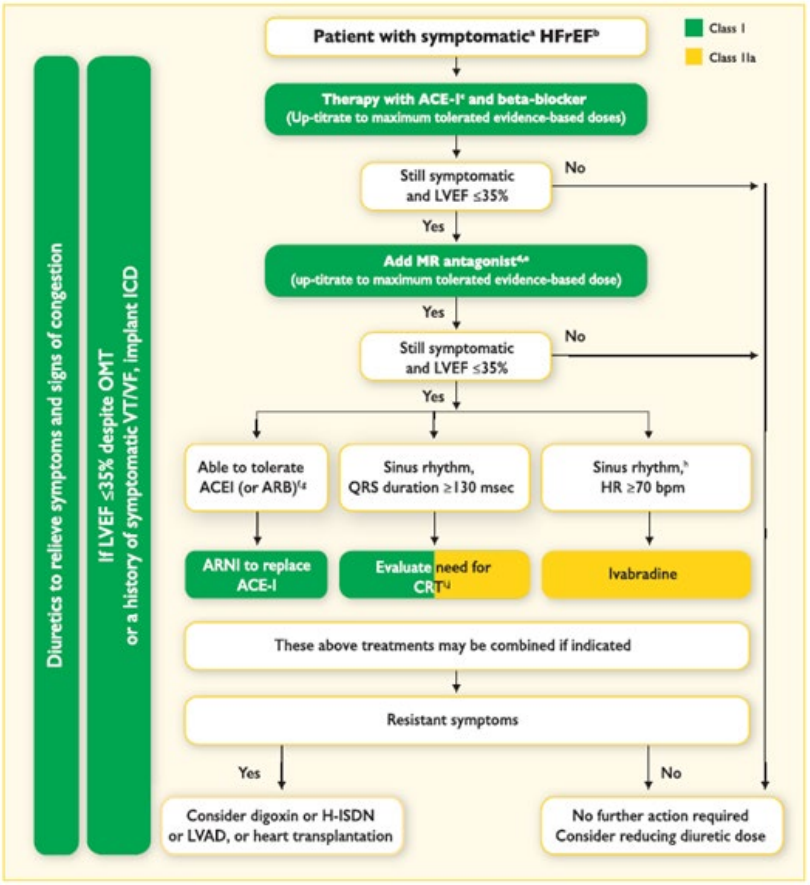
In the clinical setting, congestive heart failure and CKD often co-exist in patients. An intricate equilibrium between the CV and renal system is maintained through the renin angiotensin–aldosterone axis and autonomic nervous system. Progression to end stage renal failure may be slowed by RAAS inhibition in patients with pre-existing renal dysfunction.(31)

RAASi are also the basis of the treatment of arterial hypertension and in hypertensive patients an MRA must be implemented before resistant hypertension is diagnosed (32). RAASi have an overwhelming evidence of benefit (2, 32).

Heart failure comprises a wide range of patients, from those with normal LVEF to those with reduced LVEF (typically considered as 40% HFrEF).(11) ACEis are a class of RAASis shown to reduce mortality and morbidity in patients with HFrEF and are recommended, by the ESC 2016 Guidelines, in all symptomatic HFrEF patients. MRA such as spironolactone and eplerenone are also RAASis. Both are recommended in all symptomatic patients as part of what is known as “Triple therapy”, which consists of an ACE/ARB + beta blocker + MRA. Triple therapy has been shown to have a prognostic benefit in HFrEF and is the guideline recommended pharmacological regime for HFrEF in the ESC 2016 and NICE guidelines (11, 12). Potentially all patients with persisting HF symptoms (NYHA Class II–IV) and an LVEF ≤35% despite treatment with an ACE-I (or ARB) and a beta-blocker should be prescribed triple therapy to improve symptoms, reduce the risk of HF hospitalisation and increase survival.

The treatment strategy for the use of drugs and devices in patients with HFrEF taken from the 2016 ESC guidelines (11) is shown in Figure 1. It clearly shows the recommendation that all symptomatic HFrEF patients are given the RAASis ACEi and potentially MRA.

Figure 1: Treatment strategy for patients with HFrEF



Source: ESC Guidelines (11)

Note: Green indicates a class 1 recommendation, yellow indicates a class IIa recommendation.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; HFrEF,heart failure with reduced ejection fraction; H-ISDN, hydralazine and isosorbide dinitrate; HR, heart rate; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NT-proBNP N-terminal pro-B type natriuretic peptide; NYHA ¼ New York Heart Association; OMT,optimal medical therapy; VF, ventricular fibrillation; VT, ventricular tachycardia.

a Symptomatic= NYHA Class II-IV. bHFrEF=LVEF <40%. cIf ACEi not tolerated/contra-indicated, use ARB. dIf MR antagonist not tolerated/contra-indicated, use ARB. eWith a hospital admission for HF within the last 6 months or with elevated natriuretic peptides. FWith an elevated plasma natriuretic peptide level. GIn doses equivalent to enalapril 10 mg b.i.d. h With a hospital admission for HF within the previous year. I CRT is recommended if QRS ≥ 130 msec and LBBB (in sinus rhythm). J CRT should/may be considered if QRS ≥ 130 msec with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place.

The National Heart Failure Audit (14) showed that 83% of patients with HFrEF discharged after a hospital admission are prescribed an ACEi or ARB and 53% an MRA treatment. A more challenging outcome was the number of patients discharged on triple therapy which is only 44% [Table 4 of the National Heart Failure Audit] (14).

Since RAASi have the potential to increase K^+ levels, RAASi-induced hyperkalaemia often limits the use of these drugs thereby offsetting their survival benefits. The negation of the survival benefit comes from the non-prescription of RAASi. In hypertensive patients without risk factors for hyperkalaemia, the incidence of hyperkalaemia with RAASi monotherapy is <2% and increases to ~5% with dual RAAS inhibition and to 5–10% when dual therapy is administered in patients with HF or chronic kidney disease.(5, 20, 33)

High serum potassium levels often lead to discontinuation or down-titration of protective and life-saving treatments with RAASi (15-19).

BIOSTAT-CHF, a prospective European study, investigated the up-titration of ACEi/ARB in 2516 HFrEF patients noted that only 22% achieved the guideline recommended dose and those patients reaching <50% had an increased risk of death and/or hospitalisation due to HF (19).

A large European registry of 12,440 HF patients reported that while 92% of hospitalized HF patients were prescribed the recommended RAASi therapy as per ESC guidelines, less than 30% were up-titrated to the recommended target dose. Hyperkalaemia was one of the reasons for not achieving the target RAASi dose: in 11.9% of cases for MRAs, in 2.6% of cases for ACEi and in 2.2% of cases for ARBs.(16)

The European results were confirmed also in QUALIFY, an international prospective observational longitudinal survey that assesses physicians' adherence to guideline-recommended medications for the treatment of HFrEF. Less than two-thirds of the patients (65.7%) were treated with ACEi, only 21.5% of the patients were on ARBs and 69.3% were treated with MRAs. Among the reasons for not prescribing the drugs, hyperkalaemia was a reason in 3.9% of patients not taking ACEi, in 5.5% of patients not taking ARBs, and in 31.4% of patients not taking MRAs.(15)

In a targeted retrospective chart review conducted in five European countries including UK with data from 1457 patients (239 in the UK) with chronic hyperkalaemia (≥2 hyperkalaemia episodes [serum potassium ≥5.5 mmol/L) within 12 months], the RAASi use declined from the first to the second hyperkalaemic episode. A total of 326 hospitalisations due to recurrent hyperkalaemia or underlying comorbidities were documented for 307 patients (21.1% of all patients, 1.2 [0.6] hospitalisations/ patient). This included 121 hospitalisations related to hyperkalaemia and 100 hospitalisations for cardiovascular reasons (34). In the HFrEF subgroup the proportions of patients reaching guideline recommended doses of spironolactone and ramipril (the most used RAASi in this chart review) were significantly reduced at the second hyperkalaemic episode (34).

Both dose reduction of RAASi and higher levels of serum potassium have been shown to be associated with increased mortality risk in clinical studies.(18, 20). Thus, efficacious treatment of hyperkalaemia could contribute to better outcomes of patients with HF.

2.3.4 Treatment guidelines for management of hyperkalaemia in CKD and HF

Treatment guidelines for management of hyperkalaemia in CKD

Despite guidelines for the use of RAASi therapy in CKD, the only current recommendations for managing chronic hyperkalaemia is the discontinuation of RAASi, thereby foregoing the benefits these drugs provide:

- NICE guidelines for the management of CKD state that RAASi treatment should not be initiated in patients with CKD with serum K+ >5.0 mmol/L and in those receiving RAASis, treatment should be discontinued if the serum K+ reaches ≥6.0 mmol/L (21)
- NICE guidelines [CG182] (21) also advise that patients with pre-treatment serum potassium >5.0 mmol/L should not routinely be offered RAASi therapy

This situation therefore creates a clinical dilemma as RAAS inhibition is a globally recommended management approach with demonstrably significant clinical and pharmacoeconomic benefits (23, 35-37) but hyperkalaemia prevents optimal use.

Treatment guidelines for management of hyperkalaemia in heart failure

Patients with HF have poor cardiac outcomes and mortality.(38) The study by George et al., 2017 shows an association between HF and a significantly higher risk of new onset CKD and rapid decline in kidney function which is associated with a higher risk of mortality. Early diagnosis and treatment strategies aimed at preventing and treating HF may prevent worsening kidney function and mortality in these patients. (38)

“Triple therapy” which consists of an ACE/ARB + beta blocker + MRA is shown clearly in a treatment strategy for the use of drugs in patients with HFrEF in the ESC 2016 guidelines.(11) A study by Cole et al. (13) examined whether clinicians communicate the potential increase in life expectancy when offering treatment to patients with heart failure. This article provides an estimate of lifespan benefit using a method that any clinician can replicate.(13)

Hyperkalaemia, together with worsening renal function (which hyperkalaemia may accompany) and symptomatic hypotension, are the main reasons for discontinuation, dose reduction, or even non-initiation of RAASi therapy in patients with renal and CV diseases offsetting the survival benefits conferred by these drugs (2).

RAASi are the cornerstone of the treatment of patients with CV diseases (HFrEF, arterial hypertension, coronary artery disease, myocardial infarction (MI), left ventricular (LV) hypertrophy), with a Class IA recommendation in current ESC clinical guidelines due to the proven reduction of mortality and morbidity in HFrEF. (2, 11, 39, 40)

A substantial proportion of HF patients experience a RAASi dose adjustment even after a single instance of elevated serum potassium levels. According to the European Society of Cardiology

Heart Failure Long-Term Registry recruiting 12 440 patients with HFrEF, RAASi (ACEi/ARB and MRAs) were used in 92.2% and 67.0% of patients, respectively.(16) This large European registry reported that while 92% of hospitalized HF patients were prescribed the recommended RAASi therapy as per ESC guidelines, less than 30% were up-titrated to the recommended target dose. Hyperkalaemia was one of the reasons for not achieving the target RAASi dose: in 11.9% of cases for MRAs, in 2.6% of cases for ACEi and in 2.2% of cases for ARBs. Less than one-third of patients were on guideline-recommended target doses (29.3% for ACEi, 24.1% for ARB, and 30.5% for MRA). In about a third of the patients not achieving the target dosages, a clear reason was not reported (28.8% for ACEi, 29.3% for ARB, and 46.9% for MRA). Hyperkalaemia was the reason for non-use of ACEi/ARB and MRA in 8.5% and 35.1% of patients, respectively.(2, 16)

Among patients with CKD, RAASi were prescribed at the target guideline recommended dose in 19% to 26% of patients, at submaximal dose in 58% to 65% of patients and were discontinued during follow-up in 14% to 16% of patients. Cardio-renal AEs/mortality and mortality occurred in 34.3% and 11.0% of patients who discontinued RAASi, 24.9% and 8.2% of patients on submaximal doses, and 24.9% and 4.1% of patients on maximum doses, respectively.(2, 22)

Recently, the BIOSTAT-CHF reported that only 22% of patients with HFrEF achieved the recommended treatment dose for ACEi/ARB. Reaching <50% of the recommended dose of ACEi/ARB doses was associated with an increased risk of death and/or HF hospitalisation compared with patients reaching ≥100%.(2, 41)

Kalsi et al. (1) recently published the results of a survey conducted across 112 (81% UK based) Healthcare Professionals confirming that hyperkalaemia is considered as a common and important clinical issue for patients which may limit the use of RAASi, which might impact on improving prognosis in the cardiorenal population. In this survey, the majority of professionals (70%) felt that hyperkalaemia would affect the use of RAAS blocking medications in up to a quarter of their patients, with the minority (10%) having this concern for half of their patient population. Across all respondents, the serum potassium level cited as requiring treatment ranged from 4.8 – 6.6 mmol/l. Higher values of hyperkalaemia prompting treatment were more likely to be cited by nephrologists. The reasons given for consideration of intervention at an earlier level of potassium included concerns regarding cardiac stability (31.5%) and deterioration in renal function (15.7%).(1)

These results from Kalsi et al were corroborated in research conducted in the UK via a modified Delphi process. Maximal tolerable, serum potassium thresholds exist in UK clinical practice. All cardiologists and the majority of nephrologists will take action at serum potassium levels between 5.5 mmol/l and 5.9 mmol/l (data shown in Section 3).

In another recent publication from the CHAMP-HF Registry, investigating the target doses of heart failure medical therapy and blood pressure, it was seen that <20% of chronic HFrEF patients eligible for beta blockers and ACEI/ARB/ARNI were receiving target doses.(25)

The importance of guideline adherence on prognosis has been recently highlighted by the QUALIFY global survey in 7092 patients with HFrEF. In this registry good adherence to guidelines was associated with a significant prognostic benefit, the adherence score was good in 67%, moderate in 25%, and poor in 8% of patients and the proportion of patients at target dose and at ≥50% of target dose was 27.9% and 63.3% for ACEi and 6.9% and 39.5% for ARBs, respectively.(2, 15)

- In the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (11), practical guidance is given in web table 7.4 on the use of ACEi or ARBs in patients with HFrEF.: Cautions and specialist advice should be sought for patients with significant hyperkalaemia (K≥5.0 mmol/L). For worsening renal function and hyperkalaemia: An increase in potassium up to ≤ 5.5 mmol/L is acceptable. If potassium rises to >5.5 mmol/L the ACEi or ARB should be stopped, and specialist advice sought

More detail is given in Appendix 10.1.2.

The working group on Cardiovascular Pharmacotherapy of the European Society of Cardiology states in the Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with RAASis “since RAASi therapy reduces mortality and morbidity in patients with cardiovascular disease, steps should, when hyperkalaemia develops, be considered to lower K^+ level and enable patients to continue their RAASi therapy. The use of such measures are especially important in those patients with the most to gain from RAASi therapy”.(2)

2.3.5 Treatment pathway for hyperkalaemia

A variety of measures are used to manage hyperkalaemia clinically, including discontinuation of hyperkalaemia-inducing drugs such as RAASis, diuretics, diet change, bicarbonates and potassium binders. However, there is insufficient evidence for mid- to long-term hyperkalaemia treatment, or for maintaining hyperkalaemic patients on RAASi therapy by the use of drugs licensed for the acute setting. Therefore, enabling optimal RAASi therapy in adult CKD patients with hyperkalaemia is challenging.

NICE guidelines on the management of CKD in adults recommend non-initiation of RAASi in cases where serum potassium is >5 mmol/L, and discontinuation of RAASi where serum potassium increases to ≥6 mmol/L (42). In patients receiving RAASis with hyperkalaemia, it has been shown that the most common strategy for management of chronic hyperkalaemia is RAASi dose reduction or discontinuation, occurring in 16-21% and 22-27% of patients, respectively.(17) This treatment option exposes the patient to an increased risk of disease progression, morbidity and mortality (43-46).

Another treatment option includes the use of potassium binders, such as CPS/sodium polystyrene sulphonate[1] (SPS; Kayexalate, Resonium A). These cation exchange resins are known to lower K+ levels in the acute setting, however, their transient effect on serum K+, limited long-term data, issues with tolerance, risk of serious gastrointestinal AEs including life threatening intestinal necrosis and sodium load precautions prevent their use for the management of chronic hyperkalaemia (47, 48). Both are contraindicated for treating patients with a serum potassium < 5.0 mmol/L and both require frequent stop and start cycles of drug administration, further complicating chronic dosing (47). Further, SPS should also be administered with caution in patients who cannot tolerate even small increases in sodium load due to the effect of appreciable sodium load. As a result of these issues, it is unlikely that SPS/CPS would be used in the chronic setting and according to UK key opinion leaders, the use of CPS/SPS for chronic hyperkalaemia is insufficiently evidence-based and is subsequently not commonly used (47, 49, 50).

An additional strategy to manage chronic hyperkalaemia is a low K+ diet. However, this is unlikely to be used widely because its value in the management of potassium levels is limited due to the difficulties in changing dietary habits and the prevalence of K+-rich foods making long-term adherence problematic (51).

Currently, for patients with CKD and hyperkalaemia who are also receiving RAASi, no treatment option is available that protects from recurring life-threatening hyperkalaemia and enables optimal RAASi therapy continuation. Therefore, an unmet need exists for treatment of chronic hyperkalaemia in patients where continuation of RAASi therapy would have clear prognostic benefit.

2.3.6 Positioning of patiromer in hyperkalaemia treatment pathway

The Expert consensus document from Rosano et al., 2018 (2) on the management of hyperkalaemia in patients with cardiovascular disease treated with RAASi states very clearly that RAASi therapy reduces mortality and morbidity in patients with cardiovascular disease but can increase K+ levels, therefore therapies aimed at lowering K+ levels and enabling patients to continue RAASi therapy should be considered.(2) The paper also describes two new effective and safe K+ binders, Patiromer and ZS-9. Table 2 describes the management of hyperkalaemia in patients with indication for RAASi therapy.

[1]An ion-exchange resin recommended for the treatment of hyperkalaemia associated with anuria or severe oliguria. Also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis.

Table 2: Management of hyperkalaemia in patients with an indication for RAASi therapy

Patients	Recommendation
Chronic or recurrent hyperkalaemia on RAASi therapy	An approved K+ lowering agent may be initiated as soon as K+ levels are confirmed as >5.0 mmol/L. Closely monitor K+ levels. Maintain treatment unless alternative treatable aetiology is identified
Chronic or recurrent hyperkalaemia not on maximal tolerated guideline-recommended target dose of RAASi	RAASi should be optimised and an approved K+ lowering agent may be initiated as soon as confirmed K+ levels are >5.0 mmol/L. Closely monitor K+ levels. Maintain treatment unless alternative treatable aetiology is identified.
K+ levels of 4.5–5.0 mmol/L not on maximal tolerated, guideline recommended target dose of RAASi therapy	Initiate/up-titrate RAASi therapy and closely monitor K+ levels. If K+ levels rise above 5.0 mmol/L, initiate an approved K+ lowering agent.
K+ levels of >5.0–<6.5 mmol/L not on maximal tolerated, guideline recommended target dose of RAASi therapy	Initiate an approved K+ lowering agent. If levels <5.0 mmol/L are detected, up-titrate RAASi - K+ level should be closely monitored and K+ lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified.
K+ levels of >5.0–<6.5 mmol/L on maximal tolerated, guideline recommended target dose of RAASi therapy	Treatment with a K+ lowering agent may be initiated. K+ level should be closely monitored and K+ lowering treatment should be maintained unless alternative treatable aetiology for hyperkalaemia is identified
K+ levels of >6.5 mmol/L on either maximal sub-maximal tolerated, guideline-recommended target dose of RAASi therapy	Discontinue/reduce RAASi. Treatment with a K+ lowering agent may be initiated as soon as K+ levels >5.0 mmol/l. K+ level should be closely monitored.

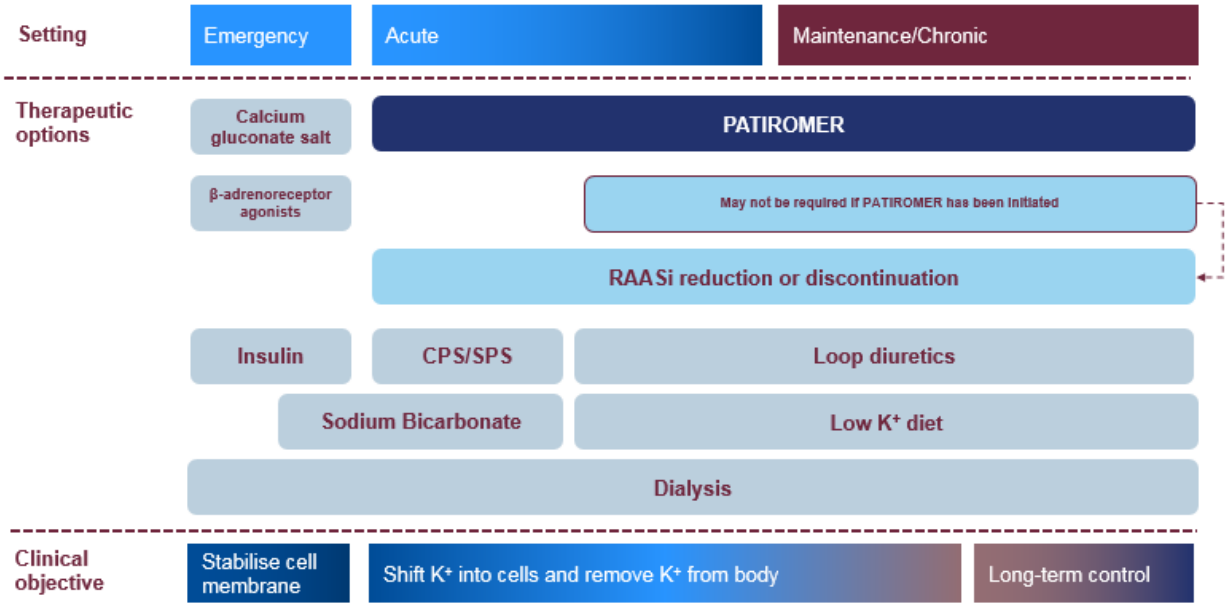
Source: Rosano et al. 2018 (2)

K+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

Patiromer (Veltassa®) is a novel, next-generation, non-absorbed, sodium-free, cation-exchange polymer that binds excess K^+ in the lumen of the gastrointestinal tract and increases faecal potassium excretion for the treatment of hyperkalaemia in adult patients [SmPC]. Furthermore, patiromer offers an innovative solution for maintenance of normokalaemia [AMBER trial results(52), under embargo, are in Appendix 10.1.5] and enablement of RAASi therapy (spironolactone) that in turn preserves the benefits related to RAAS inhibition in patients with CKD and/or HF further burdened with resistant hypertension. In this study a significantly higher proportion of patients on patiromer (86%) compared with placebo (66%) remained on spironolactone treatment at week 12 ($p<0.0001$). Among the patients treated with spironolactone and placebo, 2 out of 3 developed hyperkalaemia; patiromer reduced this risk by half.

Figure 2 shows the position of patiromer in the hyperkalaemia treatment pathway.

Figure 2: Position of patiromer in hyperkalaemia treatment pathway



2.4 Key concerns addressed

Key concerns raised by the committee
• What is the unmet need in the management of hyperkalaemia in patients with CKD with or without HF? • What are the benefits of maintaining serum K+ in these patients? • **The patient population treated in OPAL-HK is not reflective of UK clinical practice as patients would not routinely be managed at serum K+ <6.0** Comparison of guidelines with the OPAL-HK study protocol (and other patiromer trials) show that management of hyperkalaemia is currently limited to RAASi modification and dietary control. It is clear that in UK clinical practice RAASi modification occurs below K+ 6.0 therefore compromising the well-established long-term benefits of these therapies. The paucity of current treatment options means that RAASi optimisation must be compromised to achieve normokalaemia and so an option which allows management of hyperkalaemia and RAASI optimisation would provide significant benefit in the way this consider is managed.

3. Physician opinion and consensus

Key messages

• UK physicians have a maximal tolerable serum K+ threshold of between 5.5-5.9 mmol/l in clinical practice. All cardiologists and most nephrologists will make changes to treatment when serum K+ reaches this threshold.
• Cardiologists and nephrologists recognise the need to manage hyperkalaemia below 6.0 mmol/L
  o 70% of cardiologists would stop or reduce RAASi if serum K+ is between 5.1-5.4 mmol/L and 9% of nephrologists would reduce RAASi dosing at that level.
  o 50% of cardiologists versus 18%-27% (depending on CKD stage) of nephrologists would stop RAASi at serum K+ between 5.5-5.9 mmol/L. 50% of cardiologists and 54% of nephrologists would reduce RAASi dosing at that level.
• Physicians see a clear unmet clinical need for effective longer-term hyperkalaemia management such as patiromer to enable initiation of life-saving RAASi therapy.
• Physicians identified the following patient groups as having the greatest unmet clinical need:
  o CKD patients' stage 3/4, with or without HFrEF
  o Proteinuric CKD patients with progression
  o CKD patients receiving or requiring triple therapy for HFrEF

Key concerns raised by the committee
• The patient population treated in OPAL-HK is not reflective of UK clinical practice as patients would not routinely be managed at serum K+ <6.0

3.1 Objective

In their ACD on patiromer for treating hyperkalaemia, NICE raised concerns that hyperkalaemia at serum K+ levels lower than 6.0 mmol/L would not normally be treated in NHS clinical practice. The aim of the physician surveys was to provide a clear representation of current hyperkalaemia management in NHS England clinical practice

3.2 Methods

A modified Delphi research process was designed to iteratively demonstrate consensus on the following key questions:

- At what point would you consider a patient to be hyperkalaemic?

- When do you start to actively manage serum potassium?
- How do you currently manage hyperkalaemia?
- Does patiromer address an unmet need?
- Define the patient cohorts most suitable for patiromer?

The modification of the Delphi process (reduction of interview rounds and a face-to-face meeting) ensured an agreed position was reached within a given, reasonable timeframe. A summary of the process followed is provided in Appendix 10.2.1.

Physicians were selected for their expertise in their relevant therapy area from centres across England. Participation was based upon availability and interest/willingness to participate. Bias was managed through anonymisation and blinding of participants responses during the telephone interview stages. Participants in the telephone interview stages did not receive honoraria for their participation. However, participants in the working group were paid for their participation. All research was conducted in line with the British Healthcare Business Intelligence Association (BHBIA) Legal and Ethical Guidelines for Healthcare Market Research, overseen by a member of the BHBIA.

A summary of participation at each stage of the Delphi survey process is shown in Table 3.

Table 3: Physician participation at each stage of the modified Delphi survey

Physician survey round	Conducted	Participants	Honoraria
First round physician survey (telephone interviews)	November 2018	10 physicians (6 consultant nephrologists and 4 consultant cardiologists)	Unpaid
Second round physician survey (extended telephone interviews)	February and March 2019	21 physicians (11 consultant nephrologists and 10 consultant cardiologists	Unpaid
Working group (web hosted group discussion and a face-to-face meeting)	February and March 2019	9 physicians (numbers of consultant nephrologist and cardiologist attendees varied based upon availability)	Honoraria paid

3.3 Results

3.3.1.1. First round physician survey - telephone interview

Key outputs from the short survey were:

- Differences exist between nephrologist and cardiologist opinions, however both groups identify the need for a drug that lowers serum potassium levels.
- Both cardiologists and nephrologists identify a need for patiromer, however cardiologists would appear to intervene in treatment pathways at a lower serum K+ level than nephrologists.

- Current practice in the UK suggests that interventions, across both specialities begin at an average serum K+ level of 5.6 mmol/L (range 5.5-6.0 mmol/L).
- Currently, treatment options are limited and difficult. This usually involves dietary restriction and reduction of RAASi (and other medication) dose to reduce serum K+ levels. This is identified as treating at sub-optimal doses which may affect morbidity and mortality.
- 60% of clinicians see a clear unmet clinical need that could be met by allowing patients access to patiromer in the UK. This unmet need is defined as optimisation of RAASi and other medications, as opposed to their withdrawal in response to a patient developing hyperkalaemia.

3.3.1.2. Second round physician survey – extended telephone interviews

Key outputs from the second round physician survey are shown in Table 4.

Table 4: Key outputs from second round physician survey

Key outputs	Cardiologists	Nephrologists
What are the primary treatment objectives in treating patients with CKD and hyperkalaemia	Cardiologist and nephrologist primary treatment objects are: • To keep the patient alive • To reduce cardiovascular risk • To reduce harm from medication toxicity (avoiding incorrect medications or making sure medication is appropriately adjusted) • To maximise and optimise RAASi treatment and minimise hyperkalaemia • To avoid the risk of acute kidney injury • To avoid progression to end stage kidney disease (important but a rare outcome compared to cardiovascular risk)	
How well do current treatment for hyperkalaemia allow clinicians to meet their treatment objectives	Cardiologists and nephrologists consider current hyperkalaemia treatment options to be limiting in their abilities to allow achievement of treatment objectives (see Figure 24 of Appendix 10.2.2)	
What clinical action takes place at varying potassium levels?	70% of cardiologists will stop or reduce RAASi if serum K+ is between 5.1-5.4 mmol/L 100% of cardiologists will stop or reduce RAASi if serum K+ is between 5.5-5.9 mmol/l, this would appear to be the maximal tolerable threshold of serum K+ for cardiologists. • 50% of cardiologists will stop RAASi and 50% will reduce RAASi if serum K+ is between 5.5 mmol/l and 5.9 mmol/l. 90% of cardiologists will stop	9% of nephrologists will reduce RAASi if serum K+ is between 5.1-5.4 mmol/L 18% of nephrologists will stop RAASi and 54% will reduce RAASi if serum K+ is between 5.5-5.9 mmol/L and the patient has CKD stage 3. 27% of nephrologists will stop RAASi and 54% will reduce RAASi if serum K+ is between 5.5-5.9 mmol/L and the patient has CKD stage 4. 90% of nephrologists will stop RAASi if serum K+ is >6 mmol/l regardless of CKD stage (See Figure 26 of Appendix 10.2.2)

Key outputs	Cardiologists	Nephrologists
	RAASi if serum K+ is >6 mmol/l (See Figure 25 of Appendix 10.2.2)	

CKD, chronic kidney disease; K+ potassium; RAASi, renin- angiotensin aldosterone system inhibitors

Nephrologists state that patients with stage 4 CKD are more vulnerable to a faster onset of high serum K+ compared to patients with stage 3 CKD, which causes concern and therefore nephrologists are likely to see this patient cohort more frequently.

At a serum K+ level of 5.5 mmol/l or above, 100% of cardiologists interviewed stated that they would stop or reduce RAASi.

Dietary control of potassium with a low potassium diet is an important first step. Although a low potassium diet can be effective, it is hard for patients to manage or comply with its requirements as it is difficult for patients to identify all sources of dietary potassium. Patiromer compliments dietary control and does not replace it.

Hyperkalaemia and comorbid conditions

The CKD cohort identified to have the greatest issue with hyperkalaemia are diabetics and HF patients, this may be due to medications or the nature of their disease

- Nephrologists are particularly concerned and aware that the main risk of hyperkalaemia is sudden death, this risk is raised for patients with CKD
- Patients miss out on triple therapy because of high serum potassium levels. The patient does not receive optimal therapy and therefore loses out on the beneficial effects of these potentially lifesaving and life enhancing treatments

Current hyperkalaemia treatment options

Physicians state that there are no current treatment options for chronic management of hyperkalaemia. This means that RAASi therapy may be stopped or reduced, that might otherwise benefit the patient. Current treatment options limit RAASi treatment opportunities.

Burden on families and their carers

The following burden on families and carers of patients with hyperkalaemia reflects an inability to successfully treat high serum K+.

- Hyperkalaemia will lead to an increased frequency of hospital attendance for adjustment in medication or repeat blood tests.

- Dietary restrictions are difficult for patients to manage, education programmes pose a burden on patients and their families. A low potassium diet has limited efficacy and poor patient compliance.

Reduction or stopping of RAASi therapy

- RAASi doses are often reduced or stopped when serum K+ is elevated, 100% of cardiologists will stop or reduce RAASi therapy if serum K+ levels are between 5.5 mmol/l and 5.9 mmol/l
- Maximal tolerable, serum K+ thresholds exist in clinical practice. All cardiologists and most nephrologists will take action at serum K+ levels between 5.5 mmol/l and 5.9 mmol/l
- There is a careful balance of risk, evaluating the danger presented for reducing dose or stopping RAASi and hyperkalaemia. Physicians are aware that RAASi evidence indicates that sub-optimal dosing or stopping treatment affects mortality risk. This weighs heavily for physicians, seeking the best outcomes for their patients.

3.3.2 Summary of physician survey results

All cardiologists interviewed stated they currently stop or reduce RAASi therapy at serum K+ levels of 5.5 mmol/l or greater, despite the patients' clinical circumstances requiring persistence with maximum dose of RAASi therapy. There is a divergence between cardiology and nephrology whereby:

- 70% of cardiologists would stop or reduce RAASi if serum K+ is between 5.1-5.4 mmol/L whereas 9% of nephrologists would only reduce RAASi at that level.
- 50% of cardiologists versus 18%-27% (depending on CKD stage) of nephrologists would stop RAASi at serum K+ between 5.5-5.9 mmol/L. 50% of cardiologists and 54% of nephrologists would reduce RAASi dosing at that level.

There is a need for a treatment to facilitate up titrating, initiating or maintaining patients on RAASi therapy where hyperkalaemia has previously prevented treatment. This need is particularly notable for poly-morbid, diabetic and HF patients.

3.3.3 Physician working group

Using previous survey opinion, the physician working group focussed on delivery of consensus outputs. These outputs followed a key question methodology, the results of which are summarised in Table 5.

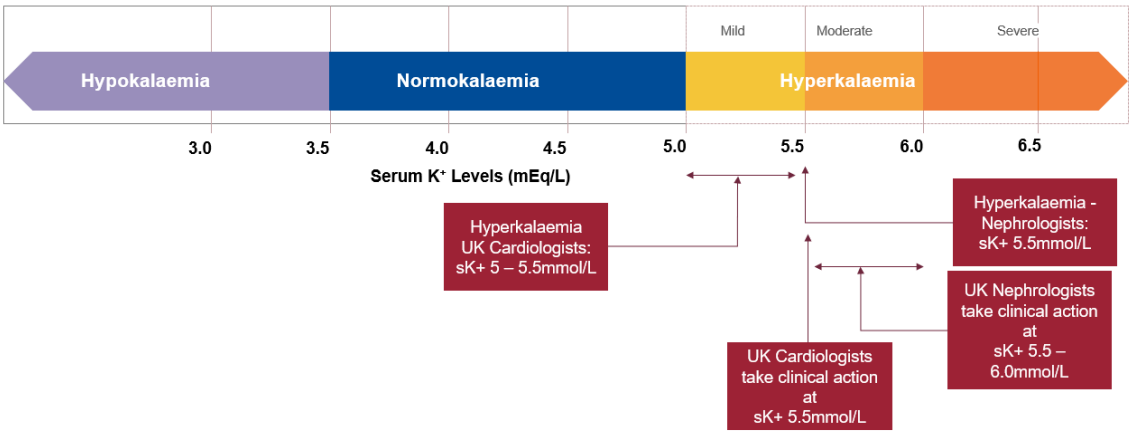
Table 5: Results of physician working group

Key question	Cardiologists	Nephrologists
At what point would you consider a patient to be hyperkalaemic?	Serum K+ 5.0-5.5 mmol/L	Serum K+ 5.5 mmol/L
When do you start to actively manage serum potassium?	All physicians are managing serum K+ levels ≥5.5mmol/L	
	• Cardiologists are monitoring K+ at a level of 5.0-5.4 mmol/L. • Active management decisions (defined as down-titrating or stopping a RAASi treatment i.e. ACEi, ARB, ARNi & spironolactone) are taken at a serum K+ level of 5.5 mmol/L.	• At a serum K+ level of 5.5 mmol/L nephrologists are not up-titrating RAASi therapies and are unlikely to initiate such drugs. • At a level of >6.0 mmol/L action is taken to down-titrate or stop RAASi therapy or "triple therapy"
How do you currently manage hyperkalaemia? How effective is this management?	Management of hyperkalaemia includes • Dietary reduction of potassium • Dose reduction of RAASi • Diuretics • Blood pressure control Physicians feel these approaches have low effect, are difficult for patients to manage and have low compliance levels.	
Does patiromer fulfil an unmet clinical need?	All participants (nephrologists and cardiologists) agreed that patiromer would fill an unmet need in allowing patients to persist with life extending RAASi treatments. Patiromer is considered important to facilitate up titrating, initiating or maintaining patients on RAASi therapy where hyperkalaemia has previously prevented treatment.	
Define the patient cohorts most suitable for patiromer?	Key patient groups defined as: • HFrEF patients with CKD 3/4 • Patiromer clear place in therapy for patients with HFrEF	Key patient groups defined as: • Proteinuric CKD with progression • CKD patients' stage 3/4, with or without heart failure Other groups to consider: • Diabetic nephropathy • CKD with uncontrolled blood pressure • Declining renal function

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor-neprilysin inhibitors; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; K+ potassium; RAASi, renin-angiotensin aldosterone system inhibitors

Figure 3 illustrates the boundaries for hyperkalaemia as defined by UK cardiologists and nephrologists and the serum K+ levels at which they would initiate clinical action.

Figure 3: Boundaries of hypokalaemia, normokalaemia and hyperkalaemia



3.4 Conclusions

UK physicians appear to have a maximal tolerable, serum K+ threshold of between 5.5-5.9 mmol/l in clinical practice. All cardiologists and most nephrologists will make changes to treatment based upon serum K+ reaching this threshold.

UK cardiologists and nephrologists report that a treatment which can reduce serum K+ has a clear place in NHS therapy for patients who have stopped or down-titrated RAASi because of hyperkalaemia or have serum K+ >5.5 mmol/L and would otherwise be unable to initiate or increase RAASi to its optimum level.

Physicians see a clear unmet clinical need for effective longer-term hyperkalaemia management such as patiromer. Physicians advise that patiromer, when made available on the NHS, will enable treatment optimisation and initiation of life-saving RAASi therapy.

When asked to identify key patient groups for whom the unmet clinical need is greatest, physicians prioritised the following:

- CKD patients' stage 3/4, with or without HFrEF
- Proteinuric CKD patients with progression
- CKD patients receiving or requiring triple therapy for HFrEF

Physicians suggested that patiromer could also have a role in the treatment of patients with diabetic nephropathy, patients CKD with uncontrolled blood pressure, and patients with declining renal function.

A small group of physicians who took part in a half day workshop provided validation that the key patient groups identified above had the greatest unmet clinical need and are therefore patients for

whom they would seek to prescribe patiromer. Inputs used in the new health economic model were also validated. For more information on the physician validation workshop see Appendix 10.2.3

3.5 Key concerns addressed

Key concerns raised by the committee
• **The patient population treated in OPAL-HK is not reflective of UK clinical practice as patients would not routinely be managed at serum K+ <6.0** The physician survey clearly shows that both nephrologists and cardiologists would actively manage serum K+ below 6.0 mmol/L by the modification or discontinuation of RAASi. Cardiologists are likely to manage patients at lower serum K+ (≥5.5) levels than nephrologists. Physicians see a clear unmet need in allowing management of hyperkalaemia while optimising RAASi and advise that patiromer, when made available on the NHS, will enable treatment optimisation and initiation of life-saving RAASi therapy.

4. Heart failure patient survey

Key messages
• Over 70% of patients were aware that their HF medications could affect K+ levels, however 76% could not recall their doctor explaining the risk of raised K+ in their blood • 35% of patients had been admitted to hospital and had their HF medications changed or stopped. • Of patients who had their HF medications stopped or reduced, 42% felt immediate effects from this HF medication modification. • 83% of patients would welcome a treatment that ensured they could stay on the optimum dosage of their HF medications

4.1 Objective

The Heart Failure Patient Opinion Poll on Hyperkalaemia was designed to gather qualitative insights into current reasons for not achieving optimal guideline recommended RAASi dosing from the perspective of people living with HF in the UK. The poll aimed to provide an insight into patients' perceptions and experience of hyperkalaemia whilst taking treatment for HF.

4.2 Methods

Vifor Pharma UK awarded an unrestricted grant to the Pumping Marvellous Foundation (PMF), UK Heart failure Charity, to conduct an online opinion poll of people living with HF to assess their awareness and recall of aspects of hyperkalaemia, and to give insight into some of the dimensions of the unmet need of its management in HF.

The PMF developed 18 questions for the online opinion poll. The questions were uploaded to the on-line polling service Survey Monkey and distributed to the PMF patient communities. The opinion poll was open for response for seven days. The list of questions can be found in the opinion poll results file embedded in Appendix 10.3.1.

4.3 Results

Results can be found at: https://de.surveymonkey.com/results/SM-KXZDGVXSV/. The raw data is embedded in Appendix 10.3.1.

During the seven days that the opinion poll was open on-line, it attracted 361 responders, of which 306 (85%) were people with HF, 49 (14%) identified themselves as carers and 6 (2%) did not disclose.

A summary of responses to the questions relating directly to the qualitative assessment of understanding and experience of hyperkalaemia (described as raised potassium levels) whilst taking treatment for HF (HF medications) is shown in Table 6.

Table 6:Summary of questions and responses assessing participant understanding and experience of hyperkalaemia whilst taking treatment for heart failure.

Question number	Question	Response (N=361)
6	Are you aware that some of your heart failure medications can affect your potassium levels?	72.6% (n=262) of participants were aware 27.4% (n=99) were not aware
7	Have you ever experienced problems with your potassium levels due to your heart failure medications?	22.7%(n=82) experienced problems 45.2% (n=163) did not experience problems 32.1% (n=116) did not know
8	Has your doctor ever explained to you the risk of having too much potassium in your blood?	24.1% (n=87) said yes 75.9% (n=274) said no
9	Did your doctor tell you that some medicines you are/were taking for your heart failure or to control your blood pressure such as ACE inhibitors, drugs ending in “pril” / ARB’s drugs ending in “artan” / MRA’s like spironolactone or eplerenone or ARNI’s namely Sacubitril Valsartan (Entresto) could contribute to increase your potassium?	33.0% (n=119) said yes 67.0% (n=242) said no
10	Did your doctor ever mention that you had raised potassium in your blood test?	17.5% (n=63) said yes 82.5% (n=298) said no
11	Have you ever been admitted to the hospital and had your heart failure medication changed or stopped?	35.2% (n=127) said yes 64.8% (n=234) said no
15[a]	Were you aware of any immediate effects of stopping or reducing the dosage of your HF meds?	31.6% (n=112) said yes 43.9% (n=156) said no 24.5% (n=87) said not applicable
17[a]	If/When your heart failure medications were reinstated, were they...?	12.2% (n=42) said same type and dosage as before they were stopped 13.4% (n=46) said same type of medication but different dosage to before they were stopped 17.4% (n=60) said different type of medication 17.7% (n=61) said never reinstated 39.4% (n=135) said not applicable
18	How beneficial would it be if there was a treatment available that ensured you stay on the optimum dosage of your heart failure medications?	59.3% (n=214) said extremely beneficial 24.1% (n=87) said very beneficial 11.4% (n=41) said somewhat beneficial

Question number	Question	Response (N=361)
		5.3% (n=19) said not at all beneficial

[a]*six participants skipped question 15 and 17 participants skipped question 17.*

ACE, angiotensin-converting enzyme; ARNi, angiotensin receptor-neprilysin inhibitors; MRA, mineralocorticoid receptor antagonist.

Key insights from the poll were:

- 23% had been advised by their doctor that they had experienced problems with raised K+ due to their heart failure medications, a further 32% responded as 'don't know' to the same question.
- Over 70% of responders were aware that their HF medications could affect K+ levels, however 76% could not recall their doctor explaining the risk of raised K+ in their blood.
- 35% of responders had been admitted to hospital and had their HF medications changed or stopped. 42% of applicable responders felt immediate effects of stopping or reducing the dosage of HF medications.
- 29% of applicable responders never had their HF medications reinstated and 29% had their medications switched.
- 83% of responders felt it would be extremely or very beneficial to have a treatment that ensured they could stay on the optimum dosage of their HF medications.

4.4 Conclusions

If this opinion poll reflects the level of understanding of hyperkalaemia in the HF patient population, then the following considerations should be made.

The potential dangers of raised serum K+ to those at risk, as recognised in NHS Improvement's Patient Safety Alert(4), should be raised with physicians with appropriate frequency to maintain vigilance and to provoke action. It is incumbent upon physicians to safeguard patients against hyperkalaemia whilst trying to manage existing conditions such as HF and its comorbidities through optimal medical management and through continuing, iterative patient education.

Potassium levels appear to feature as an item on the discussion agenda between physician and patient. However, since the only current solution available to physicians to counteract raised serum K+ levels is stopping or reducing the dosage of life preserving HF medication, this may be a more complex discussion than if a potassium binding agent was available as a potential solution.

Physicians and patients alike would welcome a medicine that could be administered to counter the raised K+ levels that often result from taking RAASi thereby allowing optimisation of therapy.

Physicians are clear, a treatment that reduced serum K+ has a place in therapy for the patients who have stopped RAASi because of hyperkalaemia or have serum K+ greater than 5.5 mmol/l where it is not possible to increase the RAASi blockade to its optimum level (See Section 3).

Physicians should be armed with more choices to manage hyperkalaemia other than dietary restrictions, down-titration or stopping guideline recommended, life-preserving HF medications:

- Previously, treatment options that manage K+ overload have been limited to therapies first developed nearly 60 years ago (53, 54).
- For nearly 60 years there have been no new treatments specifically developed and indicated for persistent elevated serum K+, available in Europe. The European Commission licencing of patiromer in hyperkalaemia offers hope to many patients to better manage elevated serum K+ and get the maximum benefit from their life preserving RAASi therapy.

Improving or maintaining quality of life for the patient should be a recognised aim of medical management

5. Generalisability of patiromer clinical trial programme to UK practice

5.1 Objectives

The committee previously commented on the generalisability of OPAL-HK (and other trials which are part of the patiromer clinical trial programme. In light of further evidence provided regarding the management of hyperkalaemia in clinical practice (please see section 3), in particular considering the cardiology perspective, Vifor Pharma believe the trial protocol does allow generalisability to UK practice. Full details of trials are provided in Appendix 10.1.3, Appendix 10.1.4 and Appendix 10.1.5.

Key findings
• When considering the cardiology and nephrology perspective, OPAL-HK is reflective of UK clinical practice for the management of hyperkalaemia given this involves RAASi modification and dietary control at serum K+ levels treated in the NHS • The placebo groups in Part B the OPAL-HK trial and the PEARL-HF trial are reflective of the standard of care in patients with CKD treated with RAASi after the initial correction of hyperkalaemia • The patiromer clinical trial programme has consistently shown the RAASi enabling benefits of patiromer

Key concerns raised by the committee
• The patient population treated in OPAL-HK is not reflective of UK clinical practice as patients would not routinely be managed at serum K+ <6.0 • The OPAL-HK trial is not reflective of UK clinical practice

5.2 OPAL-HK trial (RLY5016-301)

The placebo group in the OPAL-HK trial is generalisable to the current UK standard of care in people with CKD treated with RAASi after the initial correction of hyperkalaemia

A summary of the OPAL-HK trial study design is provided in Appendix 10.1.3. (55)

The placebo group in Part B (randomized withdrawal phase) of the OPAL-HK trial is reflective of the standard of care in patients with CKD treated with RAASi after the initial correction of hyperkalaemia in Part A. No action is taken at serum K+ 3.8–5.1 mmol/L or if there was a first instance of 5.1 to <5.5 mmol/L. For subsequent events or higher K+ readings, RAASi dose was reduced as would be the case in clinical practice, particularly from a cardiology perspective (see

section 3). Aligned with current UK clinical practice, dietary counselling (low K+ diet) was applied across both treatment arms. See Table 39 and Table 40 in Appendix 10.1.3 for full treatment algorithms.

NICE CG182: Chronic Kidney Disease in Adults: Assessment + Management (21) recommendations compliment the conduct of OPAL-HK:

- measure serum potassium concentrations and estimate the GFR before starting RAASi. Repeat these measurements between 1 and 2 weeks after starting RAASi and after each dose increase.
- do not routinely offer a RAASi to people with CKD if their pre-treatment serum potassium concentration is > 5.0 mmol/L.
- stop RAASi if the serum potassium concentration increases to 6.0 mmol/L or more and other drugs known to promote hyperkalaemia have been discontinued.
- when hyperkalaemia precludes use of RAASi, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked

5.3 PEARL-HF trial (RLY5016-202)

The placebo group in the study RLY5016-202 (PEARL-HF) is generalisable to the current standard of care in people with heart failure treated with RAASi

A summary of the PEARL-HF trial is provided in Appendix 10.1.4. (56)

The placebo group in RLY5016-202 (PEARL-HF) is reflective of the standard of care for hyperkalaemia in patients with HF treated with RAASi. This includes RAASi adjustments when hyperkalaemia occurs.

With regards to management of hyperkalaemia the ESC 2016 guidelines for the diagnosis and treatment of acute and chronic heart failure (11). recommends the following for patients with HFrEF:

- Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum K+ levels >5.0 mmol/L.

The ESC Guidelines, Web Table 7.6 Practical guidance on the use of mineralocorticoid receptor antagonists in patients with heart failure with reduced ejection fraction recommends the following:

- Check blood chemistry at 1 and 4 weeks after starting/increasing dose and at 8 and 12 weeks; 6, 9, and 12 months; 4-monthly thereafter.
    - If K+ rises above 5.5 mmol/L or creatinine rises to 221 µmol/L (2.5 mg/dL)/eGFR <30 mL/min/1.73 m2, halve dose and monitor blood chemistry closely.

- If K+ rises to >6.0 mmol/L or creatinine to >310 µmol (3.5 mg/dL) eGFR <20 mL/min/1.73 m2, stop MRA immediately and seek specialist advice.

5.4 Summary of AMBER trial

The AMBER trial is a phase 2, randomised, double-blind, placebo-controlled, parallel group study of patiromer for the enablement of spironolactone use for blood pressure control in patients with resistant hypertension and CKD. The purpose of the study was to determine if patiromer treatment in CKD subjects receiving spironolactone for the treatment of resistant hypertension (RHTN) would result in more persistent use of spironolactone through prevention of hyperkalaemia and lead to improved blood pressure control compared with treatment with spironolactone alone (placebo).(52)

The primary study outcome was treatment group difference (spironolactone plus patiromer vs. spironolactone plus placebo) in the proportion of patients remaining on spironolactone at Week 12. At 12 weeks, 98 (66.2%) placebo- and 126 (85.7%) patiromer-treated patients remained on spironolactone (between-group difference, 19.5%, 95% confidence interval [CI], 10.0, 29.0; p<0.0001). AMBER met its primary endpoint: patiromer enabled the use of spironolactone in patients with RHTN and CKD. Among patients treated with spironolactone and placebo, 2 out of 3 developed hyperkalaemia. Patiromer reduced this risk by half.

In conclusion, AMBER clearly demonstrates that patiromer enabled a significantly higher proportion of patients with RHTN and CKD to continue treatment with spironolactone with less hyperkalaemia. See Appendix 10.1.5 for further details.(52)

5.5 Key concerns addressed

Key concerns raised by the committee
• **The patient population treated in OPAL-HK is not reflective of UK clinical practice as patients would not routinely be managed at serum K+ <6.0** • **The OPAL-HK trial is not reflective of UK clinical practice** Both guidelines and clinical opinion (section 3) show that cardiologists and some nephrologists would manage patients at serum K+ below 6.0, primarily through RAASi modification and dietary control. This is consistent with the treatment algorithm in the maintenance phase of OPAL-HK. Additional trials in the patiromer clinical trial programme confirm the RAASi enabling properties of patiromer and the benefits this provides.

6. Targeted literature review

Key messages
• The overall body of evidence indicates that RAASi has a positive impact on outcomes including reducing the risk of CV events, mortality and renal progression. Studies showed that RAASi provides a significant delay in progression to end-stage renal disease (ESRD) in patients with CKD and that stopping RAASi treatment or sub-optimal RAASi dosing in patients with CKD leads to an increased risk of CV events, mortality and renal progression. • A review of the targeted literature review (TLR) findings identifies the Xie et al. network meta-analyses (NMA) as the best source of long-term efficacy data for use in the economic model. • Evidence from systematic literature reviews (SLRs) and large single studies consistently show that hypo- and hyperkalaemia are associated with increased morbidity and mortality risk. Furthermore, the use of RAASi was found to reduce mortality risk across serum K+ categories. • Studies show that increasing serum K+ levels are associated with an increasing incidence of RAASi discontinuation. Strategies that control serum K+ and avoid RAASi discontinuation could impart significant health benefits to patients with CKD. • Evidence retrieved from TLR corroborates using the Xie et al. NMA to inform the relative risks used in the economic model whereby the benefits of starting RAASi are modelled as equivalent to the benefits foregone upon discontinuing.

Key concerns raised by the committee
• Key model inputs were not sourced in a systematic manner, in particular those relating to long term outcomes, specifically • Data relating to the impact of RAASi on CV events, mortality and CKD progression were not sourced in a systematic fashion • The risk of progressing to end-stage renal disease was over-estimated. • In the original cost-effectiveness model, patients accrued quality-adjusted life years (QALYs) mainly by gaining quality of life from delayed progression to ESRD and fewer hyperkalaemia events and by extending survival from delayed progression to ESRD and death. The NICE ACD raised concerns that the relationship between serum potassium levels and mortality and other long-term outcomes was uncertain. • A single observational study was used to show an association between serum

potassium levels and death, a systematic review of the evidence was not provided.

- Although the trial results showed that continuing patiromer was associated with lower serum potassium than stopping patiromer, the benefit of this to patients in clinical practice was unclear
- It is not appropriate to use clinical-effectiveness data for people starting RAASi (Xie 2016 NMA) to model the benefits foregone upon stopping treatment with RAASi. There was considerable uncertainty associated with the benefits of continuing a RAASi.

6.1 Objectives

Targeted literature reviews (TLR) were performed to increase the robustness of inputs used in the economic model. The objective of these searches was to verify the long-term benefits of RAASi therapy and the long-term implications of hyperkalaemia in patients with CKD. All studies with a relevant patient population were synthesised to:

1. Assess the impact of RAASi therapy on CV events and CV mortality outcomes
2. Assess the impact of RAASi therapy on CKD progression
3. Assess the impact of serum potassium levels on mortality
4. Evaluate the appropriateness of applying outputs from the Xie et al. network meta-analysis (NMA) (46) to model the benefits forgone upon discontinuation of RAASi
    - i.e. are the benefits of starting RAASi therapy the same as benefits forgone if RAASi therapy is stopped for the following outcomes: Major Adverse Cardiovascular Events (MACE) events, mortality, and CKD progression.

6.2 Methods

MEDLINE (including MEDLINE® In-process) and EMBASE databases were searched to identify relevant studies. Full details of the methods applied, and results can be found in Appendix 10.4. The TLR was performed in two stages. Initially, published systematic literature reviews (SLRs) and meta-analyses (MA) identified from the database searches were reviewed for relevant and robust data that could be incorporated into the economic model. This was followed by a review of published single studies (randomised and non-randomised) to find alternative data which could be used in the absence of relevant data from SLRs or MAs.

Identified studies were used to inform economic model parameters.

6.3 Results

6.3.1 Results of review

The two database searches identified 12,223 records. Following removal of duplicates and records published prior to year 2008, 6,613 records were included for screening by title and abstract. Based on title and abstract, 5,709 records were excluded. Based on full-text review of the remaining 904 records, 89 records were included in the final extraction. An additional bibliographic search provided a further 11 articles for inclusion, giving a total of 100 records for the final analysis. Of these, 15 records were SLRs/MAs and 85 records were single studies. Publications associated with the same study were linked together resulting in 75 unique single studies. Therefore, an overall total of 90 studies were included in the review (15 SLRs/MAs and 75 single studies). Details of the number of studies included and excluded at each stage of the selection process is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram provided in Figure 27 of Appendix 10.4.2.1.

Overview of SLRs/MAs

Of the 15 SLR/MA publications identified, 13 reported on the impact of RAASi therapy on CV events and mortality, 8 reported on the impact of RAASi therapy on CKD progression, and 5 reported on the impact of serum potassium levels on mortality. No SLRs/MAs were identified that could be used to validate the Xie NMA.(46) A complete list of the studies included for each outcome is shown in Table 45 of Appendix 10.4.2.

Overview of single studies

Altogether, 75 unique single studies were identified that reported on the outcomes of interest; 37 reported on the impact of RAASi therapy on CV events and mortality, 30 reported on the impact of RAASi therapy on CKD progression, 20 reported on the impact of serum potassium levels on mortality, and 8 could be used to evaluate the appropriateness of using the Xie et al. NMA.(46) A complete list of the studies included for each outcome is shown in Table 46 of Appendix 10.4.2. A summary of the study designs of the included studies is shown in Table 47 of Appendix 10.4.2.

6.3.2 Findings for outcome one: Relative impact of RAASi therapy on cardiovascular events and mortality

The economic model applied findings from Xie et al. (46) to model the benefit of RAASi enablement in CKD patients in terms of reduced risk of both CV events and CV mortality. Since this data source was not identified in the original submission through a structured literature search, a TLR evaluating these outcomes was performed. The optimal study for use in the economic model was then determined from the studies identified in the TLR.

Of the 13 SLRs/MAs that reported on outcome one, 11 provided sufficient information to assess CV events and CV mortality in patients at different stages of CKD. A summary of the CV events and mortality outcomes extracted from the SLRs/MAs is shown in Table 48 of Appendix 10.4.3.

Overall, 37 single studies reported on outcome one. Of these, four reported on patients with CKD and heart failure.(57-60) A summary of the CV event and mortality outcomes results extracted from the single studies is shown in Table 49 of Appendix 10.4.3.

The events defining the composite outcome of MACE varied between studies; events included all-cause mortality, CV mortality, myocardial infarction, heart failure, arrhythmia, stroke, renal replacement therapy, and cardiac arrest.

Outcomes for individual CV events, including heart failure, myocardial infarction, stroke and all-cause mortality, are discussed in more detail in Appendix 10.4.3.

6.3.2.1. Cardiovascular events

For a more in-depth overview of the findings from the SLR/MAs and single studies see Appendix 10.4.3.1.

Findings from SLRs/MAs

Of the six SLRs/MAs that reported on CV events, five reported that RAASi significantly decreased the risk or odds of having a CV event when compared to placebo in patients with CKD.(46, 61-64) One SLR involving non-diabetic patients with early CKD (stage 1-3) reported a lower risk of CV events in patients treated with ACEi compared with those receiving placebo, however the difference was not statistically significant (relative risk [RR]=0.87, 95% CI: 0.66-1.14, P=0.31).(65) When compared with an active control, RAASi either non-significantly reduced the risk or odds of a CV event in patients with CKD or demonstrated no difference.(46, 61)

Findings from single studies

Of the six single studies that reported on MACE in patients with CKD, most reported that although RAASi reduced the rate or risk of MACE when compared to no-RAASi, the difference was not statistically significant (59, 66-69). Yang et al. reported that compared to no-ARB use, long-term ARB use trended towards reducing the risk of MACE (hazard ratio [HR]: 0.85, 95%CI 0.73-1.00) but short-term use increased the risk (HR: 1.24, 95%CI 1.02-1.51) (70).

Of the six single studies that reported on CV events in patients with CKD, four showed that RAASi reduced the incidence or risk of CV events compared with placebo or control.(23, 71-73) Although most studies found this reduction was not statistically significant, Kim-Mitsuyama et al. found patients with advance CKD treated with RAASi had a significantly lower risk of combined CV and renal events than non-users. (71)

Two single studies found the incidence of CV events in patients with end-stage renal disease (ESRD) on dialysis increased with the use of ACEi/ARB, suggesting that ACEI or ARB treatment in dialysis patients may not have a beneficial effect on CV outcomes. (74, 75)

6.3.2.2. Cardiovascular mortality

For a more in-depth overview of the findings from the SLR/MAs and single studies see Appendix 10.4.3.2

Findings from SLR/MAs

Of the five SLRs/MAs that reported on CV mortality in patients with CKD, one reported that RAASi significantly reduced the risk of CV mortality compared with placebo.(76)

Four of the SLRs/MAs reported that RAASi either reduced or increased CV mortality but not to a statistically significant extent; or, showed no difference in the risk or odds of CV associated mortality when compared to placebo or active control.(46, 61, 64, 77)

Findings from single studies

Of the 10 single studies that reported on CV mortality, one reported that treatment with RAASi in hypertensive patients with CKD significantly reduced the rate and risk of CV mortality versus conventional treatment.(78) Notably, two large scale observational studies found that RAASi significantly reduced the risk of CV mortality in patients with ESRD on dialysis compared with no-RAASi use or placebo.(79, 80) Seven studies found RAASi had no significant effect in patients with CKD. (23, 60, 69, 74, 81-83)

6.3.2.3. Conclusions

The SLRs/MAs mostly show that RAASi significantly reduces the risk of CV events compared to placebo and non-significantly reduces the risk compared to active control. The single studies generally showed a non-significant risk reduction in CV events with RAASi use versus placebo or active control. The overall evidence indicates that RAASi use numerically reduces CV events versus placebo or active control, with the larger SLRs/MAs demonstrating that this reduction was statistically significant versus placebo.

The SLRs/MAs and single studies mostly show a non-significant reduction or no difference in the risk of CV mortality with RAASi use versus placebo or active control.

Generally, the use of RAASi is associated with a numerical risk reduction in CV events and CV mortality, although most single studies do not show statistical significance. The SLRs/MAs which include much larger patient numbers are more likely to show a statistically significant reduction in CV event rates as well as a numerical reduction in CV mortality.

Assessment of the CV event and CV mortality outcomes verified that the NMA from Xie et al. (46) was the best available source to estimate the transition probabilities and relative risks (RRs) of CV events in the model. The NMA included patients with CKD stages 3-5 and reported the outcomes of both major CV events (MACE, defined as a composite of myocardial infarction, stroke and heart failure) and CV mortality among CKD patients treated with RAASi versus active controls.(46) Most other SLRs/MAs of RAASi therapies for patients with CKD identified in the TLR either did not report both CV event and CV mortality outcomes(62, 63, 65, 76, 77, 84-86) or assessed patients with

comorbidities e.g. diabetes. (64) Although the MA by Balamuthusamy et al. (61) reported CV event and mortality outcomes in patients with CKD, it contained fewer RCTs than the NMA by Xie et al (25 vs 119), it was an older publication with less recent evidence (publications up to 2006 vs 2014 in Xie et al.) and included patients with CKD stage 2. Single studies including observational studies were also sought for CKD stage specific data. Although some studies focused on patients with ESRD, these were either restricted to patients on dialysis (72, 74, 75, 79-82) or were for a specific ethnic group and were therefore less generalisable. (79)

The baseline probabilities of a CV event or death after a CV event were therefore derived from the NMA. (46)

6.3.3 Findings for outcome two: Relative impact of RAASi therapy on CKD progression

6.3.3.1. Findings from SLRs/MAs

Of the seven SLRs that reported on CKD progression, four assessed progression of CKD to ESRD in patients with CKD and the other three studies assessed change in GFR rate. A summary of the risk of progression to ESRD in patients with CKD identified in the SLRs is shown in Table 50 of Appendix 10.4.4. In three of the four SLRs/MAs, RAASi was shown to provide a significant reduction in progression to ESRD compared with placebo or active control in patients with CKD. (46, 84, 86) None of the SLRs provided data relating to stage specific progression of CKD from stage 3 disease to the next stage. The other SLR by Sharma et al. found no significant difference in progression to ESRD between ACEi and placebo in non-diabetic patients who had early CKD (stage 1-3) (RR: 1.00, 95%CI: 0.09-1.11, P=0.99). (65)

The other three SLRs/MAs reviewed the effect of RAASi versus placebo or active control on eGFR in patients with CKD. No significant change in GFR was reported.(64, 77, 87)

6.3.3.2. Findings from single studies

A summary of the 30 single studies that reported on CKD progression are shown in Table 51 of Appendix 10.4.4. Of these, one study by Anand et al. reported on patients with CKD and heart failure.(58) Single studies were also reviewed to assess the effect of RAASi on eGFR over time in patients with CKD. A summary of this review is provided in Appendix 10.4.4.1.

Most studies reporting on the development of ESRD in patients with CKD found that the incidence or risk of developing ESRD was either significantly lower (78, 88, 89) or numerically lower (23, 90, 91) in patients receiving RAASi than no-RAASi or conventional therapy. However, one study reported a slight but non-significant increase in ESRD in diabetic patients with CKD receiving aliskiren compared with placebo (83), while another found patients with advanced CKD who used

ACEi/ARB had a significantly higher risk of developing ESRD compared to non-users (P<0.001). (92)

Two studies reported on the effect RAASi treatment on progression to stage 5 CKD. (93, 94) ACEi and ARB treatment was shown to considerably reduced the proportion of non-diabetic patients with CKD ≤stage 4 who reached stage 5 compared with CCBs (ACEi: 11.8% vs ARB: 13.4% vs CCB: 41.7%). (94) However, among elderly non-diabetic patients with CKD, RAASi treatment did not have a significant effect on the progression to stage 5 CKD compared with other anti-hypertensive drugs (adjusted HR: 1.16, 95%CI, 0.97-1.38). (93)

Given the identified studies did not provide data regarding stage specific CKD progression, we reviewed studies to check if rate of progression varied with disease stage. Studies indicated that eGFR generally declines linearly, irrespective of stage, so allowing the use of the same progression rates identified in the literature to be applied across CKD transitions in the model (stage 3 to 4 to ESRD).

6.3.3.3. Conclusions

Most SLRs/MAs indicated that RAASi provided a significant delay in progression to ESRD compared with placebo or active control in patients with CKD, with a review of the single studies confirming this conclusion. Thus, the overall body of evidence retrieved from the TLR suggests that RAASi imparts a reno-protective effect on patients with CKD.

6.3.4 Findings for outcome three: Association between serum potassium levels and long-term mortality risk

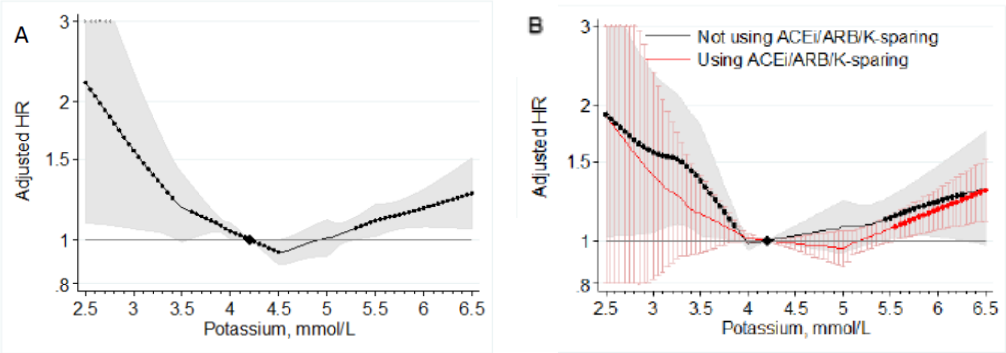
The updated economic model includes the long-term benefits of achieving normokalaemia given the known increased mortality risk associated with hypo- and hyperkalaemia. The TLR was used to identify studies which confirm the modelled benefits of controlling serum potassium.

6.3.4.1. Findings from SLRs/MAs

Of the five SLRs/MAs that reported on both serum potassium levels and mortality only two provided enough information to establish the association between serum potassium levels and mortality risk. (95, 96)

The MA by Kovesdy et al. assessed 42,170 patients with CKD over a mean follow-up of 6.9 years (96). A U-shaped association between serum potassium levels and the risk of all-cause mortality was found in patients with CKD and in subgroups of patients with CKD divided by presence or absence of treatment with ACEi/ARB/potassium sparing diuretics (Figure 4).

Figure 4: Adjusted hazard ratio of all-cause mortality associated with serum potassium concentration in CKD cohorts (A) and in subgroups divided by presence or absence of treatment with ACEi/ARB/potassium sparing diuretics in CKD cohorts (B)



Source: Kovesdy et al. 2018 (96)

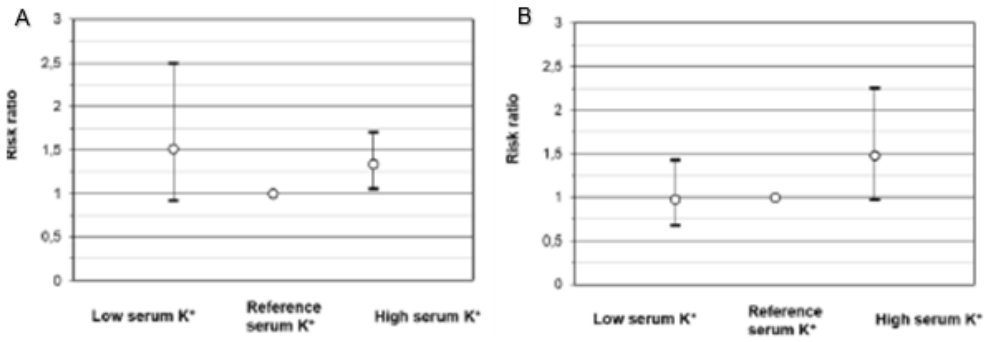
Note: black dots indicate statistical significance compared with reference serum potassium of 4.2 mmol/L. Adjusted for age, gender, race, systolic blood pressure, antihypertensive drugs, total cholesterol, diabetes, body mass index, smoking, history of coronary heart disease or stroke, history of heart failure.

The risk relationship between serum potassium and all-cause mortality found the lowest risk when levels were around 4.2-4.9 mmol/L in the CKD cohort.(96) Using ACEi/ARB/potassium sparing diuretics appeared to decrease the risk of all-cause mortality vs no-ACEi/ARB/potassium sparing diuretics use at both low (K+ <3.9 mmol/L) and high serum potassium levels (K+>4.2 mmol/L) (Figure 4B). (96)

Hoppe et al. found in patients with CKD (n=2,898), CV mortality was only increased in those with high serum potassium levels, but the risk was not statistically significant (rate ratio=1.48, 95%CI, 0.98-2.26). A U-shaped relationship was found for a composite CV outcome in patients with CKD (n=56,086), but only high serum potassium was associated with a significant increase in composite CV events (Figure 5). (95)

For patients on dialysis (n=87,774), CV mortality significantly increased for both low (rate ratio=1.11, 95%CI,1.02-1.21) and high serum potassium levels (rate ratio=1.36, 95%CI, 1.10-1.68) compared with the reference serum potassium category.(95) Cut-off values for low, reference and high serum K+ categories between the included studies varied. However, most studies generally had reference category limits similar to those proposed by the American Heart Association of 3.5–5.1 mmol/L (97). Values outside these limits defined the low and high serum categories.

Figure 5: Risk ratios of composite CV outcomes in patients with CKD (A) and CV-mortality in patients with CKD (B)



Source: Hoppe et al. 2018 (95)

A cohort of non-CKD patients, which included a general population of patients (N=332,354) and patients with high CV risk (N=843,462) was also analysed by Kovesdy et al. (96) Similar to the CKD cohort, the risk relationship between potassium and all-cause mortality in this general population/high CV cohort demonstrated lowest risk with serum potassium levels between 4 mmol/L and 4.5 mmol/L and higher risk outside of the 3.5–5.0 mmol/L range. Compared with a reference of 4.2 mmol/L, the overall adjusted HR for all-cause mortality was 1.22 (95%CI, 1.15–1.29) at serum potassium 5.5 mmol/L and 1.49 (95% CI, 1.26–1.76) at serum potassium 3.0 mmol/L. (96) Similar findings were observed in patients with heart failure whereby low and high potassium serum levels was associated with an increased risk of CV mortality. (95)

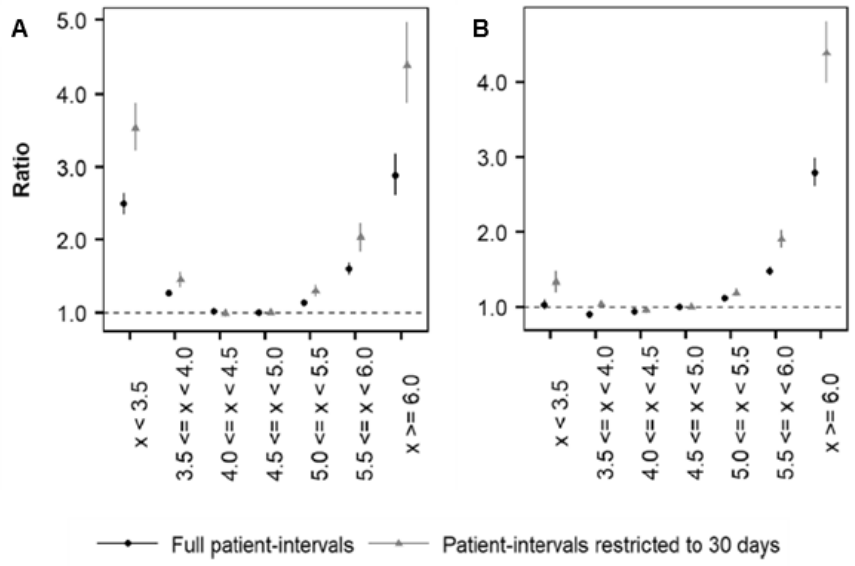
6.3.4.2. Findings from single studies

A summary of the 20 single studies that reported on serum potassium levels and mortality risks in patients with CKD is shown in Table 52, Appendix 10.4.5. Ten of these studies discussed the association between serum potassium levels and mortality.

Of these 10 studies, eight found that compared to normokalaemia, hyperkalaemia was associated with higher rate and risk of mortality in patients with CKD (98, 99) (29, 100-104).

As in the SLRs/MAs described above, Furuland et al. (102) and Luo et al. (103) observed a U-shaped association between serum potassium and mortality in patients with CKD.(102, 103) The large UK-based observational study by Furuland et al. (N=191,964) found that mortality risk was lowest among patients with serum potassium between 4.0-5.0 mmol/L and highest in patients with serum potassium ≥6.0 mmol/L (Figure 6A). The association between serum potassium and RAASi discontinuation was found to be J-shaped with higher rates of discontinuation observed at higher serum potassium levels (Figure 6B). Notably, mortality was significantly associated with RAASi usage, whereby patients prescribed RAASi had a lower predicted rate of death over the serum potassium categories compared to no-RAASi use (Figure 7). (102)

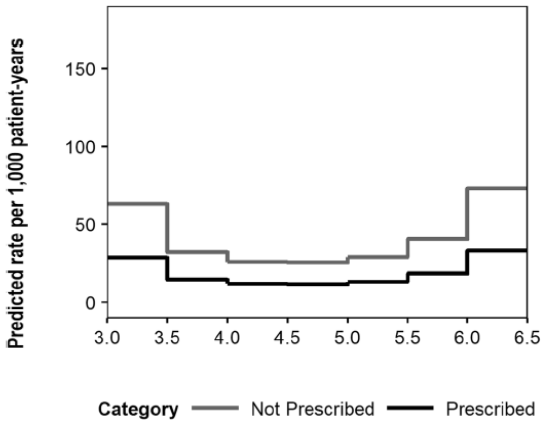
Figure 6: Adjusted incident rate ratios for (A) death and (B) RAASi discontinuation by serum potassium categories (mmol/L)



Source: Furuland et al. 2018 (102)

Note: Incident rate ratios were adjusted to account for confounding patient demographics, clinical histories and comorbidities, clinical measurements, and medication usage. Error bars represent 95% confidence intervals.

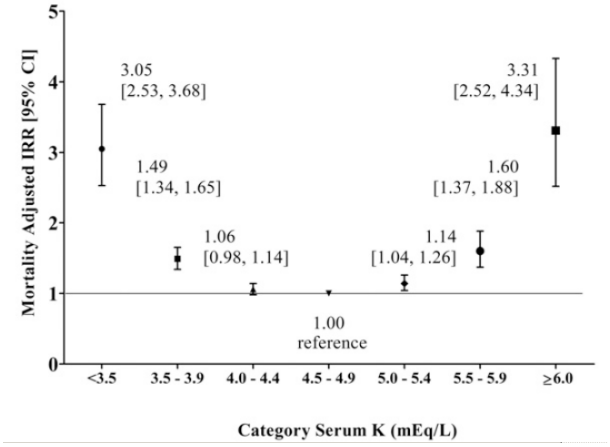
Figure 7: Predicted incidence rates of death by RAASi usage



Source: Furuland et al. 2018 (102)

The large US-based observational study on patients with CKD by Luo et al. (N=55,266) reported similar findings.(103) A U-shaped association between serum K+ and mortality was observed in patients overall and within eGFR categories (Figure 8).(103)

Figure 8: Adjusted incident rate ratios for mortality by serum potassium categories



Source: Luo et al. 2016 (103)

Note: Mortality incidence rate ratios (IRRs) were adjusted in a Poisson regression model for age, sex, race/ethnicity, diabetes, congestive heart failure, coronary artery disease, cerebral vascular accident, β-blocker use, nondihydropyridine calcium channel blocker use, loop diuretic use, and thiazide diuretic use. Estimates with 95% confidence intervals are shown for each serum K+ category.

Provenzano et al. found that although a 1 mmol/L increase in serum potassium in non-dialysis patients with CKD was associated with a 20% higher risk of ESRD (HR=1.20, 95%CI, 1.04-1.39, P=0.014), it had no effect on mortality (HR=0.94, 95%CI, 0.76-1.17, P=0.57).(105) Similarly, Garlo et al. found no significant association between serum potassium >5.0 mmol/L and mortality in patients with CKD (multivariate odd ratio [OR]: 1.07, 95%CI, 0.59-1.92, p=0.83).(106)

6.3.4.3. Conclusions

The overall body of evidence from the TLR shows that in patients with CKD, hyperkalaemia is associated with an increased risk of mortality compared with normokalaemia. Notably, in the SLRs/MAs and single studies described in detail above, morality risk generally increased at serum potassium levels >5.0 mmol/L. With hyperkalaemia treatment currently only considered at potassium serum levels ≥6.0 mmol/L, this highlights a need to control serum potassium below this current level.

Studies reporting on the association of both hypo- and hyperkalaemia observed a U-shaped association between serum potassium levels and the risk of mortality with low (generally <3.5-4.0 mmol/L) and high (generally ≥5.0 mmol/L) serum potassium positively associated with the incidence of death. However, one SLR noted no difference in risk for hypokalaemia. In general, the safest serum potassium range observed in most studies fell between 3.5 mmol/L and 5.0 mmol/L. In the OPAL-HK trial, the incidence of serum potassium levels ≤3.5 mmol/L was 3.3% (8/243 patients) during the initial treatment phase and 0.9% (1/107 patients) during the randomised withdrawal phase showing that patients were unlikely to experience levels of hypokalaemia associated with increased risk of death.

Conclusions from a large UK-based observational study (N=144,288) on the association between serum potassium and clinical outcomes in patients with CKD, further confirm these findings (conference poster presentation, therefore not identified in the TLR) (107). McEwan et al. also observed the U-shaped association between serum potassium and incidence rate ratios (IRRs) for both mortality and MACE, with low (<4.5 mmol/L) and high (≥5.5 mmol/L) potassium concentrations shown to be positively associated with increased risk of MACE and mortality during a mean follow-up of 4.9 years (107).

Although the cause of the increased mortality with hypo- and hyperkalaemia were not explored in these studies, possible suggestions included the induction of malignant arrhythmias or hypertension and their corresponding consequences such as hypotension, myocardial ischaemia, sudden cardiac death, and strokes. (96) This observation was reported in a study by Pun et al. on patients with CKD and coronary artery disease, whereby the risk of sudden cardiac arrest and death doubled when serum potassium measurements taken before the event exceeded 5.0 mmol/L. (108) Again, this highlights the importance of tight control of serum potassium.

The SLR/MAs by Kovesdy et al. and the observational study by Furuland et al. suggest that compared with no-RAASi use, using RAASi is associated with a lower risk of mortality across low to high serum potassium levels. (96, 102) This further highlights the benefits of RAASi enablement and that although this data is mostly observational in nature, the weight and consistency of the evidence suggests that the reduced risk of CV events observed in patients with CKD taking RAASi (see Section 6.3.2) outweighs the increased risk associated with hypo- and hyperkalaemia.

6.3.5 Findings for outcome four: Validation of Xie network meta-analysis

The economic model applies relative risks from the Xie NMA which evaluates the CV and mortality benefits associated with initiation of RAASi. The committee previously commented that the benefits gained from initiating RAASi may not be the same as the benefits forgone when stopping RAASi. Targeted searches were therefore performed to validate the use of the Xie NMA.

6.3.5.1. Findings from SLRs/MAs

The TLR did not identify any SLRs/MAs that contained information to confirm the appropriateness of using of the Xie NMA (46) to model the benefits foregone if RAASi are discontinued.

6.3.5.2. Findings from single studies

Overall, eight single studies were considered useful for evaluating the appropriateness of using the Xie NMA (46) in the model by providing data on the effect of discontinuing RAASi treatment in patients with CKD. These eight studies are summarised in Table 53, Appendix 10.4.6.

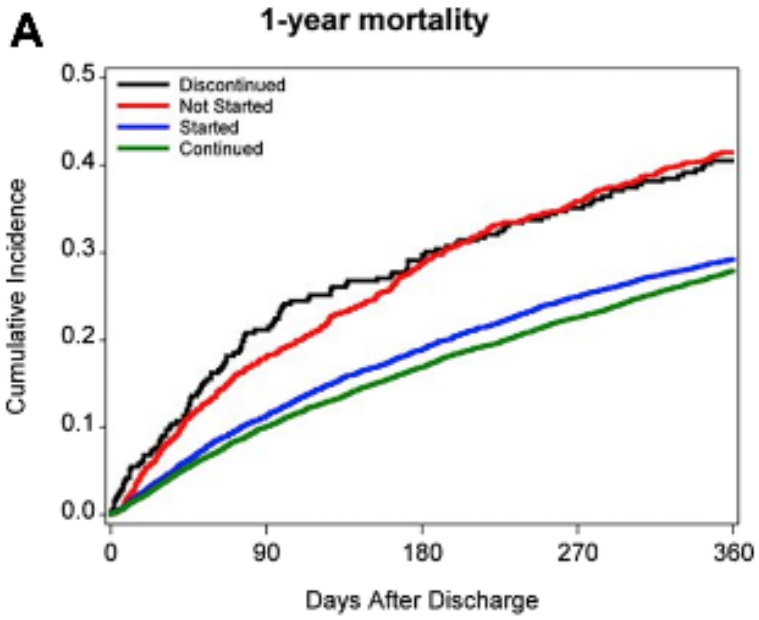
Two large observational studies found that discontinuing RAASi treatment negatively influenced morbidity and mortality outcomes in patients with CKD.(17, 98) The study by Bennett et al., which included 144,388 CKD patients, found that discontinuing RAASi increased mortality risk in CKD

patients and noted a strong association between elevated serum potassium levels and the increased incidence of RAASi discontinuation and mortality.(98) The study by Epstein et al., which included 43,288 stage 3-4 CKD patients on RAASi therapy, found that patients on sub-maximum doses or who discontinued RAASi therapy showed significantly worse adverse outcomes (CKD progression, progression to ESRD, stroke, acute myocardial infarction, coronary artery bypass and percutaneous coronary intervention) and mortality compared with patients on maximum doses. Epstein et al.'s real-world observations of prescribing patterns in the United States (US) showed that moderate-to-severe hyperkalaemia events (serum potassium ≥5.5 mmol/L) were followed by down-titration or discontinuation of RAASi therapy in nearly half of the patients on maximal doses, and discontinuation in nearly one-third of patients on submaximal doses. Thus, their study highlights the challenges associated with prescribing RAASi whereby the benefits of reduced morbidity and mortality need to be balanced with the increased risk of hyperkalaemia. (17).

A smaller observational study (N=2,354) found that in non-dialysis patients with CKD on RAASi therapy, discontinuation of RAASi after an initial rise in creatine levels did not influence the rates of emergency department visits, hospitalisations, or mortality.(106) Three studies found that discontinuation of RAASi may increase eGFR in patients with advanced CKD and possibly delay the onset of renal replacement therapy. However, CV and mortality outcomes were not discussed, and the studies were considerably smaller than the large observational studies described above (N ≤52).(109-111)

A supplementary grey search identified a study reporting the risks associated with failure to continue, initiate or switch guideline directed medical therapy (ACEI) during hospitalisation in patients with worsening heart failure with reduced ejection fraction (HFrEF).(112) While the patient population is different to the decision problem, the results show that 1-year mortality is similar in patients not starting and discontinuing medication. This indicates that patients who discontinue medication revert to the same risk as those who had not started. Similarly, mortality is well aligned in patients who started or continued medication. This provides evidence that discontinuation of RAASi will revert patients to a baseline mortality risk (Figure 9).

Figure 9: One-year mortality associated with ACEi initiation



6.3.5.3. Conclusions

The overall body of evidence retrieved from the single studies suggests that stopping treatment with RAASi in patients with CKD leads to an increased risk of CV events, mortality and renal progression. Therefore, evidence retrieved from TLR validates using the Xie et al. NMA to inform the relative risks used in the economic model.

6.4 Addressing concerns raised in NICE ACD

The following concerns raised in the NICE ACD were addressed in the TLR.

Key concerns raised by the committee
Key model inputs were not sourced in a systematic manner, in particular those relating to long term outcomes, specifically: • **Data relating to the impact of RAASi on CV events, mortality and CKD progression were not sourced in a systematic fashion** TLRs were performed to confirm the benefits of RAASi on each of these outcomes. Generally, the overall evidence indicated that RAASi impacts positively on each outcome i.e. reducing the risk of CV events, mortality and renal progression. After reviewing the findings from the TLRs, the company have chosen to continue using the Xie et al. NMA as the primary source of long-term efficacy data because: 1. Xie et al. included a large patient cohort allowing for more robust outputs compared with

single studies

2. The study follows widely accepted methods that should be adopted when performing an NMA including a systematic search of the literature and the presentation of Bayesian and Frequentist outputs
3. Results are provided for patients with CKD stage 3a and greater, so reflect a mixed population.
4. The study provides results for all long-term efficacy outcomes included in the economic model. This ensures modelled results are for a consistent population as opposed to using outputs from a disparate range of sources.
5. Results are provided for RAASi vs. active controls and placebo, individually.
6. The same study was used in the recent submission for zirconium cyclosilicate in the treatment of hyperkalaemia so allows for better comparability.

- **The risk of progressing to end-stage renal disease was over-estimated.**

A TLR was performed to identify studies that showed the effect of RAASi on progression to ESRD and studies that contained information that validates the use of the Xie et al. NMA (46) in the economic model. The overall body of evidence retrieved from the TLR suggests that RAASi provided a significant delay in progression to ESRD in patients with CKD (see Section 6.3.3) and that stopping RAASi treatment lead to an increased risk of renal progression (see Section 6.3.5).

- **In the original cost-effectiveness model, patients accrued quality-adjusted life years (QALYs) mainly by gaining quality of life from delayed progression to ESRD and fewer hyperkalaemia events and by extending survival from delayed progression to ESRD and death. The NICE ACD raised concerns that the relationship between serum potassium levels and mortality and other long-term outcomes was uncertain.**

The TLR identified SLRs/MAs and large real-world observational studies that highlighted the association between serum potassium levels and mortality. Both hypo- and hyperkalaemia was shown to be associated with an increased risk of mortality in patients with CKD. Although the cause-effect is uncertain, the large body of real-world evidence conducted in different countries including the UK, shows the presence of the relationship to be clear and the strong likelihood of the benefits of tightly controlling serum potassium (see Section 6.3.4).

- **A single observational study was used to show an association between serum potassium levels and death, a systematic review of the evidence was not provided.**

A TLR of the association between serum potassium levels and mortality was performed. Results of this review are found in Section 6.3.4. Both previous SLRs and large single studies show consistent results where hyper- and hypokalaemia are associated with increased morbidity and mortality risk. Consistent results were found across populations and geographies using large samples. Further, across serum K^+ categories, the use of RAASi was found to reduce mortality risk. The weight and consistency of results is clearly indicative of a causal relationship.

- **Although the trial results showed that continuing patiromer was associated with lower serum potassium than stopping patiromer, the benefit of this to patients in clinical practice was unclear**

Data arising from the TLR highlights the importance of sustained serum potassium management given the impact of hyperkalaemia on patient mortality and morbidity. Morality risk generally increases at serum potassium levels >5.0 mmol/L, thus highlighting the need to control serum potassium below the current treatment guideline level of ≥6.0 mmol/L. Stopping treatment with RAASi or sub-optimal RAASi dosing in patients with CKD also leads to an increased risk of CV events, mortality and renal progression. However, studies have shown that increasing serum potassium levels are associated with an increasing incidence of RAASi discontinuation. (17, 98) Strategies that control serum potassium and avoid RAASi discontinuation could impart significant health benefits to patients with CKD.

- **It is not appropriate to use clinical-effectiveness data for people starting RAASi (Xie 2016 NMA) to model the benefits foregone upon stopping treatment with RAASi. There was considerable uncertainty associated with the benefits of continuing a RAASi.**

A TLR was performed to identify studies that contained information that validates the use of the Xie et al. NMA (46) in the economic model. While the company acknowledges that it is difficult to validate this assumption, the overall body of evidence retrieved from the TLR suggests that stopping treatment with RAASi in patients with CKD leads to an increased risk of CV events, mortality and renal progression. Therefore, evidence retrieved from TLR validates using the Xie et al. NMA to inform the relative risks used in the economic model where the benefits of starting RAASi are modelled as equivalent to the benefits foregone upon discontinuing (see Section 6.3.5).

7. Clinical Practice Research Datalink (CPRD) analysis

Key messages
• The CPRD analysis captured the monthly probabilities of transitioning between serum potassium categories separately for patients with CKD3 and CKD4 • Incorporating the results of the CPRD analysis into the economic model allows the important differences between CKD3 and CKD4 to be captured in the economic model and improve generalisability to the UK setting

7.1 Objective

The aim of the Clinical Practice Research Datalink (CPRD) analysis was to:

1. Give a descriptive analysis of patients with CKD in the CPRD across a range of demographic and co-morbidity metrics.
2. Report monthly serum potassium category transitions in patients with CKD on RAASi therapy, assessed from RAASi initiation to end of study period and stratified by CKD stage.

7.2 Methods

This descriptive study used data from the CPRD to analyse patients in England with stage 3 CKD (CKD3) and stage 4 CKD (CKD4), with a RAASi prescription. The statistical analysis plan for the study can be found embedded in Appendix 10.5.1.

The study period was between 01 January 2012 and 31 December 2016. A summary of the inclusion and exclusion criteria is presented in Table 7. The study variables and definitions are described in Table 54 of Appendix 10.5.2.

Table 7: Eligibility criteria for CPRD analysis

Inclusion criteria	Exclusion criteria
• Diagnosis of CKD3 or CKD4 as identified by Read code or lab value anytime during the study period • At least one prescription for RAASi therapy during the study period after CKD diagnosis • At least one valid serum potassium laboratory value within 90 days prior to RAASi initiation • At least one valid serum potassium laboratory value after RAASi initiation • At least 12 months of baseline data at time of CKD diagnosis • Flag for 'Acceptable Quality Standards'	• Age <18 years at time of CKD diagnosis • A flag indicating non-continuous data records

CKD, chronic kidney disease; CKD3, stage 3 chronic kidney disease; CKD4, stage 4 chronic kidney disease; CPRD, Clinical Practice Research Datalink; RAASi, renin-angiotensin-aldosterone system inhibitor

Categorical variables were reported as proportion and percentages (n, %). Continuous variables were presented as means and standard deviations (SD), medians and inter-quartile ranges (IQR), and maximum and minimum value as appropriate.

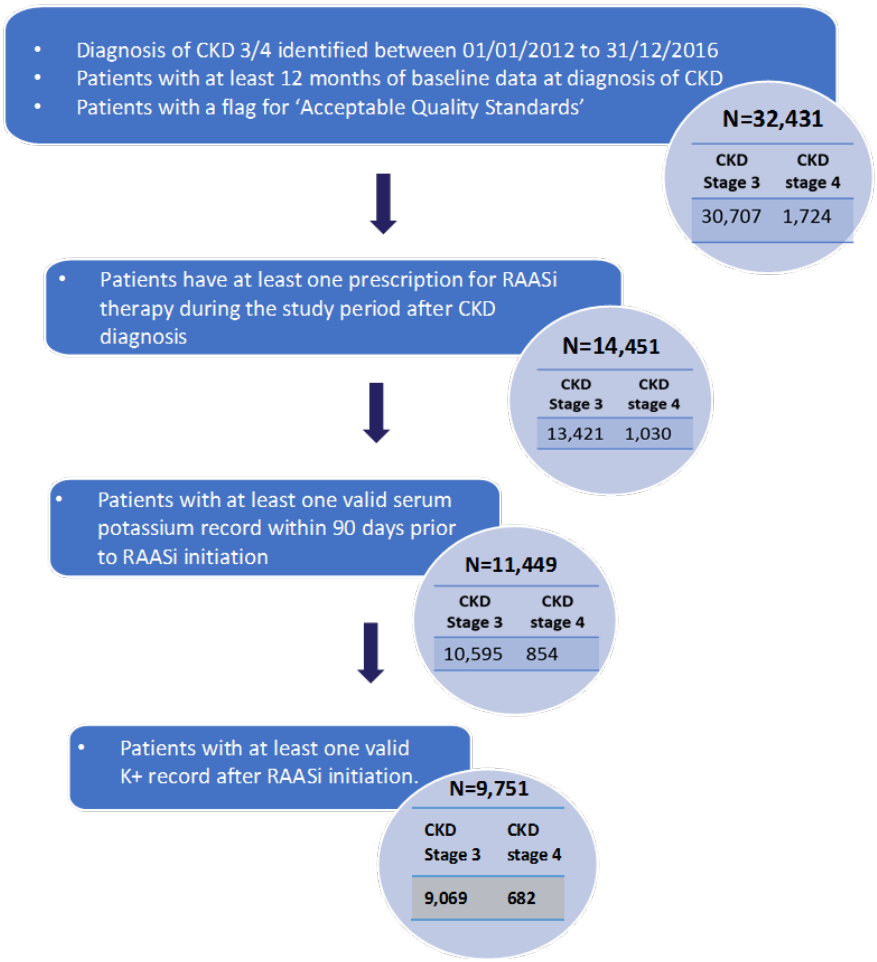
The monthly probability of transitions across potassium categories (defined as ≤5.0 mmol/L, >5.0 to ≤5.5 mmol/L, >5.5 to ≤6.0 mmol/L, and >6.0 mmol/L) were calculated in all patients and stratified by CKD stage (method provided in Appendix 10.5.3).

7.3 Results

7.3.1 Patient disposition

The patient disposition in the CPRD analysis after applying the eligibility criteria outline in Table 7 is shown in Figure 10.

Figure 10: Patient disposition in CPRD analysis



CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; K+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

7.3.2 Demographic and clinical characteristics

The demographic and clinical characteristics of patients with CKD3 and CKD4 identified in the CPRD and in patients from the OPAL-HK trial used in the economic model is provided in Table 8.

Key findings:

- Compared to the OPAL-HK trial, a lower proportion of patients identified in the CPRD were male (45% vs 56%).
- Compared to patients in the OPAL-HK trial, patients identified in the CPRD were older at index but were generally healthier, i.e. they had:
    - Fewer co-morbidities
    - Lower mean serum potassium level
    - Higher mean eGFR.

The differences seen in the CPRD patient population and the OPAL-HK patient population may be due to differences in care for these populations; the CPRD population are managed in primary care, and therefore be healthier than the OPAL-HK population (i.e. have fewer comorbidities). Patients with comorbidities are more likely to be managed by specialist cardiologists and nephrologists in the outpatient setting, thus fewer of their medical records are likely to be captured in the CPRD.

Table 8: Demographic and clinical characteristics of patients with CKD in the CPRD and in the OPAL-HK trial

Parameter	Patient population		
	Patients with CKD3 and CKD4 in CPRD (N=9751)	Patients from OPAL-HK trial used in economic model (N=[redacted])	
		Patients with HF (n=[redacted])	Patients without HF (n=[redacted])
Male sex, n (%)	4412 (45)	[redacted] ([redacted])	
Age at index, mean, years	76.0 (SD±11.1)	[redacted] (IQR: [redacted], [redacted])	
BMI at index, mean, kg/m^2	28.6 (±5.7)	NR	
Comorbidities at index, n (%)			
Diabetes mellitus	1624 (17)	[redacted]	
Heart failure	504 (5)	[redacted]	
Myocardial infarction	862 (9)	[redacted]	
Hypertension	7424 (76)	[redacted]	
Comorbidities during follow-up, n (%)			
Diabetes mellitus	2149 (22)	NR	
Heart failure	593 (6)	NR	
Myocardial infarction	275 (3)	NR	
Hypertension	3017 (31)	NR	
Serum potassium at index, mean, mmol/L	4.6 (SD±0.5)	[redacted]	[redacted]
eGFR at index, mean, ml/min/1.73 m^2	52.9 (SD±13.3)	[redacted] (IQR: [redacted], [redacted])	

BMI, body mass index; CPRD, Clinical Practice Research Datalink; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, inter-quartile range; NR, not reported; SD, standard deviation; RAASi, renin angiotensin aldosterone system inhibitor

7.3.3 Monthly serum potassium category transitions

Patient count by serum potassium category and CKD stage for each month and the corresponding probabilities of remaining or transitioning in a given serum potassium category is provided in the CPRD tables embedded in Appendix 10.5.4. Table 9 and Table 10 show the average monthly probability of transitions, over the five years from RAASi initiation, from each serum potassium category used in the economic model i.e. <5.5 mmol/L, 5.5-6.0 mmol/L, and >6.0 mmol/L for patients with CKD3 and CKD4.

Key findings:

- The average monthly probability of transitioning from serum potassium level <5.5 mmol/L to higher K^+ categories in patients with CKD was low, although the probability was higher in patients with CKD4 vs CKD3:
    - 0.31% probability of patients with CKD3 and 0.92% probability of patients with CKD4 transitioning to 5.5-6.0 mmol/L
    - 0.04% probability of patients with CKD3 and 0.10% probability of patients with CKD4 transitioning to >6.0mmol/L.
- The probability of transitioning from a higher starting K^+ category (i.e. 5.5-6.0 mmol/L or >6.0 mmol/L) to a lower K+ category was greater than the probability of transitioning from a lower starting K^+ category (i.e. <5.5 mmol/L) to a higher K^+ category This may be due to RAASi discontinuation at serum K^+ levels >5.5 mmol/L.
    - 12.15% probability of patients with CKD3 and 9.90% probability of patients with CKD4 transitioning from 5.5-6.0 mmol/L to <5.5mmol/L
    - 11.71% probability of patients with CKD3 and 7.70% probability of patients with CKD4 transitioning from >6.0 mmol/L to <5.5 mmol/L.

Table 9: Average monthly transition probabilities for patients with CKD3

Starting serum K+ category	Probability of transitioning to serum K+ category, %(SD)		
	<5.5 mmol/L	5.5-6.0 mmol/L	>6.0 mmol/L
<5.5 mmol/L	NA	0.31 (0.11)	0.04 (0.03)
5.5-6.0 mmol/L	12.15 (5.55)	NA	0.38 (0.60)
>6.0 mmol/L	11.71 (9.04)	2.37 (4.05)	NA

CKD3; stage 3 chronic kidney disease; K+ potassium; NA, not applicable; SD, standard deviation

Table 10: Average monthly transition probabilities for patients with CKD4

Starting serum K+ category	Probability of transitioning to serum K+ category, %(SD)		
	<5.5 mmol/L	5.5-6.0 mmol/L	>6.0 mmol/L
<5.5 mmol/L	NA	0.92 (0.63)	0.10 (0.18)
5.5-6.0 mmol/L	9.90 (9.45)	NA	1.03 (2.66)
>6.0 mmol/L	7.70 (14.61)	4.23 (11.12)	NA

CKD3; stage 3 chronic kidney disease; K+ potassium; NA, not applicable; SD, standard deviation

These average monthly probabilities were used to inform the economic model.

7.4 Conclusions

The NICE ACD raised the concern that important differences between CKD stages 3 and 4 were not captured by combining health states in the economic model.

In the CPRD analysis, the average monthly probabilities of transitioning between serum potassium categories were captured separately for patients with CKD3 and CKD4. These values were used to inform the economic model, allowing for differences between CKD stages and improving the generalisability of the model to UK clinical practice.

8. Economic model update

Key messages

- The base-case deterministic analysis shows that patiromer is cost-effective, supported by a high probability of being cost-effective at the NICE cost-effectiveness threshold of £30,000 per QALY, and remains cost effective under various scenario settings.
- When applying a price of £7.50 per day, in adult patients with stage 3-4 CKD on RAASi therapy with hyperkalaemia, patiromer leads to incremental costs of £3,289 and incremental QALYs of 0.17. This results in an incremental cost-effectiveness ratio (ICER) of £18,893 per QALY. This result remains stable under in number of scenarios analyses. The probability that patiromer is cost-effective compared with no patiromer is 38% and 94% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY.
- To address NICE and evidence review group (ERG) concerns, several structural modelling changes have been implemented such as incorporating Part A of OPAL-HK, including adverse events due to patiromer, and allowing for RAASi dose modification rather than RAASi discontinuation alone.
- The population included in the model has been now aligned with NICE's view and with clinical experts in Cardiology and Nephrology, in particular on the serum potassium levels which would require treatment in the UK clinical practice.
- The CPRD analysis captured the monthly transition probabilities between serum potassium categories separately for patients with CKD3 and CKD4, thus the differences between disease stages could be captured in the economic model. Incorporation of the CPRD data also improved the generalisability of the analysis to the UK setting.
- The targeted literature reviews corroborate the use of the Xie NMA for a number of key model inputs.

8.1 Aim of economic model update

The economic model assessing the cost-effectiveness of patiromer in adult patients with stage 3-4 CKD on RAASi therapy with hyperkalaemia was updated to address concerns raised in the NICE ACD and improve the robustness of the model for decision-making. A summary of the concerns raised in the NICE ACD and the updates applied to address these concerns are shown in Table 11.

Table 11: Concerns raised in the NICE ACD and corresponding model updates applied

Number	Concerns	Model update
1	OPAL-HK included patients with serum potassium levels that would not be treated in the NHS	The modelled population has been updated to be aligned with NICE's view and with the company's research with clinical experts in nephrology and cardiology, on the serum potassium levels which would determine treatment in UK clinical practice; 5.5 mmol/L for HF patients and 6.0 mmol/L for CKD patients (see section 3.1 of appraisal consultation 2 for TA ID1293) (113)
2	Observed RAASi discontinuation in OPAL-HK is protocol driven and therefore not representative of UK practice, as patients in the 5.0-6.0mmol/L range would typically undergo RAASi dose modification, not discontinuation	Health states characterising patients' serum potassium levels were added to allow for RAASi dose modifications (full dose, reduced dose and discontinued) as a function of these levels, based on nephrology and cardiology clinical expert feedback. Serum potassium transitions are populated using data from the CPRD to give context from a UK clinical setting – see section 7
3	Part A of OPAL-HK was not included in the economic model	Starting health states were included in the model to reflect Part A of OPAL-HK, where patients remain for one monthly cycle
4	Adverse events were not included in the model	Adverse events (including costs and disutilities) are now included in the updated model
5	Important differences between CKD stages 3 and 4 were not captured by combining health states in the economic model	The updated model separated CKD stage 3 and 4 into different health states, associated with different serum potassium transitions and utilities
6	Inputs for the model were not sourced systematically, therefore there was concern about potential bias	Targeted literature reviews for key model parameters were conducted and the selected source from the available choices were justified to improve the validity of the model

CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; RAASi, renin-angiotensin-aldosterone system inhibitor.

8.2 Economic analysis

The following sections describe the updates made to the cost-effectiveness analysis to address the concerns raised in the NICE ACD.

8.2.1 Population

In the original model, the patient population was defined by the inclusion criteria of the OPAL-HK study i.e. adult patients with stage 3-4 CKD on RAASi therapy with hyperkalaemia (defined as a serum potassium level of ≥5.5 mmol/L) (see Section B.3.2.1 of the original submission for further information). NICE's concern was that OPAL-HK included patients who would not routinely be treated for hyperkalaemia in UK clinical practice. The findings from the company's research with UK clinicians suggest a maximum tolerable serum potassium threshold of between 5.5mmol/l and 5.9 mmol/L. Thus, the definition of hyperkalaemia in OPAL-HK is largely consistent with UK clinical practice, however the

company's research also highlighted differences in the management of hyperkalaemia between cardiology and nephrology specialists. Nephrologists may persist with RAASi therapy until serum potassium reaches a level of 6.0 mmol/L or greater, whereas the majority of cardiologists will stop RAASi at this level. This is in line with the clinical expert advice from the committee of TA ID1293, who explained that HF patients have treatment for hyperkalaemia at serum potassium levels above 5.5 mmol/L, whereas CKD patients may have treatment at serum potassium levels above 6.0 mmol/L (113). The model was therefore updated to capture differences in treatment (in terms of RAASi therapy) between CKD patients with and without heart failure comorbidity, and the patient population was updated to reflect the findings from the company's research.

The updated model includes the following patients from OPAL-HK in the base-case analysis:

1. Patients with stage 3-4 CKD and HF comorbidity (CKD HF+) with a serum potassium of ≥5.5 mmol/L at baseline, and,
2. Patients with stage 3-4 CKD without HF comorbidity (CKD [no HF]) with a serum potassium level of >6.0 mmol/L

The updated population therefore excludes CKD (no HF) patients from OPAL-HK with a starting serum potassium level of 5.5-6.0 mmol/L.

The characteristics of this subpopulation from OPAL-HK have been shown previously in Table 8. The mean age of the population was [redacted] years and [redacted]% were male. The proportion of patients with heart failure, type II diabetes, previous myocardial infarction and hypertension were [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively. At baseline, the average serum potassium was [redacted] mmol/L with an estimated GFR of [redacted] ml/min. All patients were on at least one RAASi (the majority using ACE inhibitors, followed by ARBs and a small proportion on aldosterone antagonists) with [redacted]% on non-RAASi diuretics.

8.2.2 Comparators

As described in the original submission, there is no pharmacological comparator to patiromer and therefore standard of care (i.e. dietary modification and RAASi dose modification) is considered as the comparator.

8.2.3 Model perspective

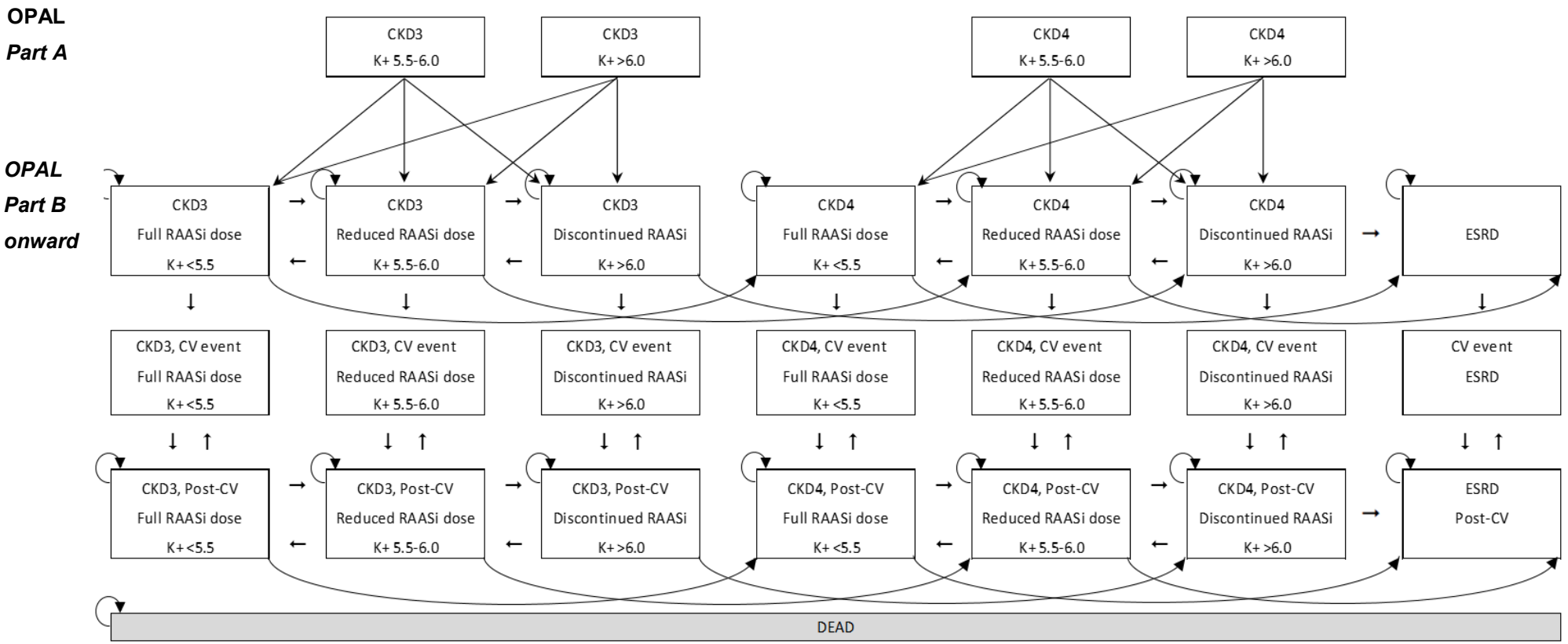
As per the original model and NICE recommendations, the NHS and Personal and Social Services (PSS) in England and Wales perspective was used for the base case analysis. Only direct healthcare costs incurred by the NHS, consisting of drug costs, adverse event costs and disease management costs were included.

8.2.4 Model structure

As per the original model, the updated model uses a Markov structure designed to reflect the OPAL-HK trial, however, the updated model now incorporates 26 health states to address the concerns raised in the NICE ACD (Table 11). The updated model structure is shown in Figure 11. Briefly, the

model includes CKD stage 3 and 4 health states which are further stratified by serum K+ category and an end-stage renal disease stage (ESRD stage). From any of these health states patients may experience a CV event or death. The model structure and main assumptions described below were validated by a working group of clinicians comprising of both cardiologists and nephrologists. The assumptions applied were used to balance the natural history of disease with appropriate simplifications to modelling approaches.

Figure 11: Markov model schematic for patiromer



Model entry and initial transitions (modelling of OPAL-HK Part A)

Patients enter the model in either CKD3 or CKD4, which are further stratified by serum potassium level categories, 5.5-6.0 mmol/L or >6.0 mmol/L. The proportions of patients in each starting health state comes from the initial distribution of relevant patients in the OPAL-HK trial (i.e. those who would be treated in UK clinical practice: CKD HF+ patients with a serum potassium of ≥5.5mmol/L, and CKD (no HF) patients with a serum potassium level of >6.0mmol/L). Given Part A of OPAL-HK does not include a placebo control, it was assumed that the initial patient distributions in the comparator arm are the same as for patiromer. Therefore, in cycle one of the model, patiromer is associated with incremental drug costs, loss of utility due to adverse events but these is no direct health benefits until patients transition to lower serum potassium levels in the subsequent cycle.

Patiromer arm

After the first one-month cycle of the model, reflecting four weeks of treatment with patiromer in Part A of OPAL-HK, all patients in the patiromer arm of the model transition according to the observed serum potassium levels at the end of Part A. Patients may transition from their starting potassium category into one of three potassium categories: <5.5 mmol/L, 5.5-6.0 mmol/L and >6.0mmol/L. Patients were assumed not to change CKD stage in the first cycle.

Standard of care arm

As there was no control arm in Part A of OPAL-HK, transition rates between the <5.5, 5.5-6.0 and >6.0 mmol/L serum potassium categories observed in the CPRD (section 7) were converted into transition probabilities to inform the initial transition probabilities for the standard of care arm.

Subsequent heath states and transitions (modelling of OPAL-HK Part B and thereafter)

Serum potassium category transitions

From the second cycle, patients can transition between all three potassium categories (<5.5 mmol/L, 5.5-6.0 mmol/L and >6.0 mmol/L), i.e. HK can develop and be resolved. In order to avoid overcomplicating the model, it is assumed that patients must transition in a stepwise manner between potassium categories (i.e. 'jumps' between <5.5 mmol/L to >6.0 mmol/L are not permitted). The transition probabilities between serum potassium categories are informed by the observed transition rates in the CPRD (section 7). Clinical advice from the working group validated that it was appropriate to simplify the model in this way.

RAASi dose associated with serum potassium categories

Based on the qualitative evidence provided earlier in this report (section 3), the model links CKD HF+ patients with a serum potassium level of <5.5 mmol/L with a full dose of RAASi, and discontinued RAASi at ≥5.5 mmol/L. CKD (no HF) patients with a serum potassium level of <5.5 mmol/L are also linked to a full RAASi dose, whereas the RAASi dose is down-titrated between 5.5-6.0 mmol/L and discontinued at serum potassium levels of >6.0 mmol/L (Table 12).

Within the model, the three serum potassium categories of <5.5 mmol/L, 5.5-6.0 mmol/L and >6.0 mmol/L are therefore assumed to directly correspond with full, reduced (a mixture of discontinued [CKD HF+] and down-titrated [CKD (no HF)] patients) and discontinued RAASi doses, respectively (Table 12). These assumptions were further validated by clinical experts in the working group.

Table 12: Assumed RAASi dose according to serum potassium category and the absence or presence of HF comorbidity

	<5.5 mmol/L	**5.5-6.0 mmol/L**	**>6.0 mmol/L**
CKD HF+	Full RAASi dose	Discontinued RAASi	Discontinued RAASi
CKD (no HF)	Full RAASi dose	Down-titrated RAASi *(assumed 50% of full dose)*	Discontinued RAASi
Combined populations (modelled population)	**Full RAASi[2]**	**Reduced RAASi[3]** *(weighted average of CKD HF+ and CKD (no HF) dose)*	**Discontinued RAASi[4]**

CKD HF+, Chronic kidney disease with heart failure comorbidity; CKD (no HF), chronic kidney disease without heart failure comorbidity; RAASi, renin-angiotensin-aldosterone system inhibitor

CKD progression

Patients can progress from CKD3 into the corresponding serum potassium level in CKD4, and from CKD4 to ESRD (it is assumed that patients cannot transition from CKD3 directly to ESRD, and that there is no risk of transitioning from higher to a lower CKD stage).

CV events and CV death

From CKD3, CKD4 or ESRD, patients can transition into a 'CV event' state, which is a tunnel health state where patients can remain for one cycle only, and either die or survive the CV event.

Post-CV event

After a CV event, surviving patients enter a 'post-CV' health state corresponding to the CKD stage and serum potassium category prior to the event. Patients can then move between serum potassium categories as before, have reoccurring CV events, and progress through CKD stages to ESRD as before.

[2] May be abbreviated to FullRAASi throughout report
[3] May be abbreviated to ReduRAASi throughout report
[4] May be abbreviated to DiscRAASi throughout report

Risks of CKD progression, CV event and CV death

The risk of CKD progression, CV events and CV death are sourced from the literature (see section 8.3.2) and varies according to RAASi status. The risk associated with a 'down-titrated dose' in CKD (no HF) patients is assumed to be 50% of a full dose. Within the model, the 'reduced RAASi' risks are calculated as a weighted average of the risks of patients on a down-titrated RAASi dose and discontinued RAASi (CKD (no HF) and CKD HF+, respectively).

Death

Death may occur from any health state (transitions not shown in Figure 11), and may be due to age-related mortality, CKD/ESRD-related mortality, CV event mortality or all-cause mortality due to raised serum potassium (which differs across serum potassium categories). See section 8.3.7 for further detail.

Treatment effect

The benefit of patiromer compared with standard of care is implemented in Part A and Part B as follows:

- Part A: Higher initial transition probabilities into lower serum potassium categories (see section 8.3.2) based on OPAL-HK Part A (patiromer) and CPRD (placebo)
    - however, the benefit only manifests as of cycle 2
- Part B: A lower risk of transitioning from a lower to a higher serum potassium level category based on the hazard ratio derived from Part B of OPAL-HK for time to sK^+ 5.5 (see section 8.3.2)
    - The hazard ratio i.e. benefit of patiromer is applied for as long as the treatment duration of patiromer only

This results in lower all-cause mortality due to raised serum potassium, slower CKD progression, and lower CV event and CV death risk. Further details for each are provided in Section 8.3.

Cycle length

As per the original model, a one-month cycle length was selected to model the progression of disease while allowing for the development (and potential resolution) of CV events.

Time horizon

As per the original model, the time horizon in the base case was 35 years to capture the lifetime of a patient with a modelled starting age of 65 (i.e. maximum age 100 years old).

Discounting

As per original model and NICE recommendations, costs and utilities were discounted at an annual rate of 3.5% in the base case analysis.

8.3 Data inputs

8.3.1 Key changes to data inputs

Key changes to efficacy, cost and utility inputs used to inform the updated model are listed in Table 13.

Table 13: Key changes to data inputs

Key input changes applied to the model	Source
Efficacy inputs	
Proportions of patients in the starting health states (equal across treatment arms) and the transition probabilities from these state (from OPAL-HK for the patiromer arm, and the CPRD for the standard of care arm)	OPAL-HK trial IPD and CPRD
Subsequent transition probabilities between different potassium level categories within CKD stage	CPRD
The relative risk of CV events and CV death in CKD3, CKD4, ESRD and the post-CV equivalents	TLR (Xie et al, 2016(46))
The probability of experiencing adverse events (AEs) due to patiromer	OPAL-HK trial (55)
All-cause mortality due to raised serum potassium	McEwan et al (107), NICE TA ID1293
Treatment duration	Based on US claims data for patiromer
Cost and utility inputs	
Cost and disutilities due to AEs	Costs: BNF (114); Disutilities: NICE TA ID1293 (115)

AE, adverse event; CKD3, stage 3 chronic kidney disease; CKD4, stage 4 chronic kidney disease; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; IPD; individual patient-level data; ESRD, end-stage renal disease; MACE, major adverse cardiovascular event; TLR, targeted literature review; NICE TA ID 1293, NICE technology appraisal identification number 1293

8.3.2 Efficacy inputs

Distribution of patients between the four starting health states

At model entry, the distribution of patients in the four starting health states in both model arms was informed by individual patient level-data (IPD) from OPAL-HK. As described in Section 8.2.4, the population was updated to align with NICE's view, and with clinical expert opinion from cardiologists and nephrologists, and included the following patients:

- CKD (no HF) >6.0 mmol/L
- CKD HF+ ≥5.5 mmol/L

Table 14 shows the distribution of patients in the starting health states according to their serum potassium levels at the start of Part A OPAL-HK. All patients in the 5.5-6.0 mmol/L categories are

CKD HF+, whereas those in the >6.0 mmol/L are both CKD HF+ and CKD (no HF) patients. There is a greater proportion of CKD 3 patients than CKD 4 patients.

Table 14: Distribution of patients in the starting health states

Starting health state	Proportion	Source
CKD3 5.5-6 mmol/L	[redacted]	OPAL-HK Part A IPD analysis
CKD3 >6 mmol/L	[redacted]	
CKD4 5.5-6 mmol/L	[redacted]	
CKD4 >6 mmol/L	[redacted]	

CKD3, stage 3 chronic kidney disease; CKD4, stage 4 chronic kidney disease; IPD, individual patient-level data

Initial transition probabilities from the four starting health states – 'patiromer' arm

The serum potassium levels at the start and end of OPAL-HK Part A in all patients (CKD HF±) with CKD 3 and CKD 4 are shown in Table 15 and Table 16 respectively, and for the subgroup of patients with heart failure (CKD HF+) in Table 17 and Table 18.

Table 15: OPAL-HK Part A IPD (CKD 3 all patients) - start and end serum potassium category

Starting potassium CKD 3	Finishing potassium (n)			
	k^+ <5.0	5.0<= k^+ <5.5	5.5<= k^+ <=6.0	Total
k^+ <5.0	[redacted]	[redacted]	[redacted]	[redacted]
5.0<= k^+ <5.5	[redacted]	[redacted]	[redacted]	[redacted]
5.5<= k^+ <=6.0	[redacted]	[redacted]	[redacted]	[redacted]
k^+ >6.0	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

CKD3, stage 3 chronic kidney disease; IPD, individual patient-level data

Table 16: OPAL-HK Part A IPD (CKD 4 all patients) - start and end serum potassium category

Starting potassium CKD 4	Finishing potassium (n)				
	k^+ <5.0	5.0<= k^+ <5.5	5.5<= k^+ <=6.0	k^+ >6.0	Total
k^+ <5.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.0<= k^+ <5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.5<= k^+ <=6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
k^+ >6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CKD4, stage 4 chronic kidney disease; IPD, individual patient-level data

Table 17: OPAL-HK Part A IPD (CKD 3 HF+ patients) - start and end serum potassium category

Starting potassium CKD 3	Finishing potassium (n)			
	k^+ <5.0	5.0<= k^+ <5.5	5.5<= k^+ <=6.0	Total
k^+ <5.0	[redacted]	[redacted]	[redacted]	[redacted]
5.0<= k^+ <5.5	[redacted]	[redacted]	[redacted]	[redacted]
5.5<= k^+ <=6.0	[redacted]	[redacted]	[redacted]	[redacted]
k^+ >6.0	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

CKD3, stage 3 chronic kidney disease; IPD, individual patient-level data

Table 18: OPAL-HK Part A IPD (CKD 4 HF+ patients) - start and end serum potassium category

Starting potassium CKD 4	Finishing potassium (n)				
	k^+ <5.0	5.0<= k^+ <5.5	5.5<= k^+ <=6.0	k^+ >6.0	Total
k^+ <5.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.0<= k^+ <5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.5<= k^+ <=6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
k^+ >6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CKD4, stage 4 chronic kidney disease; IPD, individual patient-level data

Table 19 summarises the modelled patients from the overall IPD (which are in bold in the table above) and used to calculate the transition probabilities in Table 20.

Table 19: OPAL-HK Part A IPD – modelled population

CKD stage	HF status	Starting potassium	Finishing potassium (n)			Total (n)
			<5.5	5.5-6	>6.0	
CKD 3	HF+	5.5-6.0	[redacted]	[redacted]	[redacted]	[redacted]
	HF+/-	>6.0	[redacted]	[redacted]	[redacted]	[redacted]
CKD 4	HF+	5.5-6.0	[redacted]	[redacted]	[redacted]	[redacted]
	HF+/-	>6.0	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: Transition probabilities from starting health states – 'patiromer' arm of the model

Transition	Probability	Source
CKD3 5.5-6 mmol/L to CKD3 FullRAASi (<5.5 mmol/L) CKD3 5.5-6 mmol/L to CKD3 ReduRAASi (5.5-6 mmol/L) CKD3 5.5-6 mmol/L to CKD3 DiscRAASi (>6 mmol/L)	[redacted]	OPAL-HK Part A IPD
CKD3 >6 mmol/L to CKD3 FullRAASi (<5.5 mmol/L) CKD3 >6 mmol/L to CKD3 ReduRAASi (5.5-6 mmol/L) CKD3 >6 mmol/L to CKD3 DiscRAASi (>6 mmol/L)	[redacted]	OPAL-HK Part A IPD
CKD4 5.5-6 mmol/L to CKD4 FullRAASi (<5.5 mmol/L) CKD4 5.5-6 mmol/L to CKD4 ReduRAASi (5.5-6 mmol/L) CKD4 5.5-6 mmol/L to CKD4 DiscRAASi (>6 mmol/L)	[redacted]	OPAL-HK Part A IPD
CKD4 >6 mmol/L to CKD4 FullRAASi (<5.5 mmol/L) CKD4 >6 mmol/L to CKD4 ReduRAASi (5.5-6 mmol/L) CKD4 >6 mmol/L to CKD4 DiscRAASi (>6 mmol/L)	[redacted]	OPAL-HK Part A IPD

CKD3, stage 3 chronic kidney disease; CKD4, stage 4 chronic kidney disease; IPD, individual patient-level data; FullRAASi, Full dose renin-angiotensin-aldosterone-system inhibitor; ReduRAASi, Reduced dose renin-angiotensin-aldosterone-system inhibitor; DiscRAASi, Discontinued renin-angiotensin-aldosterone-system inhibitor.

Transition probabilities from the four starting health states – standard care arm

In the absence of a control arm in Part A of OPAL-HK, transition rates between different potassium level categories observed in the CPRD (see section 7) were converted into transition probabilities to inform the comparator arm movement from cycle 1 to 2. Table 21 provides the model transition probabilities.

Table 21: Transition probabilities from starting health states – standard care arm of the model

Transition	Probability	Source
CKD3 5.5-6 mmol/L to CKD3 FullRAASi (<5.5 mmol/L)	0.9965	CPRD analysis
CKD3 5.5-6 mmol/L to CKD3 ReduRAASi (5.5-6 mmol/L)	0.0031	1-others
CKD3 5.5-6 mmol/L to CKD3 DiscRAASi (>6 mmol/L)	0.0004	CPRD analysis
CKD3 >6 mmol/L to CKD3 FullRAASi (<5.5 mmol/L)	0.1104	CPRD analysis
CKD3 >6 mmol/L to CKD3 ReduRAASi (5.5-6 mmol/L)	0.0234	CPRD analysis
CKD3 >6 mmol/L to CKD3 DiscRAASi (>6 mmol/L)	0.8662	1-others
CKD4 5.5-6 to CKD4 FullRAASi (<5.5 mmol/L)	0.0387	CPRD analysis
CKD4 5.5-6 to CKD4 ReduRAASi (5.5-6 mmol/L)	0.9511	1-others
CKD4 5.5-6 to CKD4 DiscRAASi (>6 mmol/L)	0.0102	CPRD analysis
CKD4 >6 to CKD4 FullRAASi (<5.5 mmol/L)	0.0741	CPRD analysis
CKD4 >6 to CKD4 ReduRAASi (5.5-6 mmol/L)	0.0414	CPRD analysis
CKD4 >6 to CKD4 DiscRAASi (>6 mmol/L)	0.8845	1-others

CKD3, stage 3 chronic kidney disease; CKD4, stage 4 chronic kidney disease; IPD, individual patient-level data; RAASi, Renin-angiotensin-aldosterone-system inhibitors; FullRAASi, Full dose RAASi; ReduRAASi. Reduced dose RAASi; DiscRAASi, Discontinued RAASi

Transition probabilities between serum potassium categories

Once patients enter the second cycle of the model, patients can transition between different serum potassium level categories of <5.5, 5.5-6.0 or >6.0 mmol/L in a stepwise manner (i.e. patients cannot transition from <5.5 to >6.0 mmol/L or vice versa in one cycle).

Standard of care arm

In the standard of care arm, the transition probabilities between serum potassium categories are derived from the serum potassium transition rates observed in the CPRD (section 7.3.3). As patients are not permitted to jump from <5.5 to >6.0 mmol/L or vice versa in one cycle, the following adjustments have been made to take account of all the available data:

- Transition rates for the <5.5 to >6.0 mmol/L serum potassium category transitions in the CPRD are summed with the <5.5 to 5.5-6.0 mmol/L transition rates
- Transition rates for the >6.0 to <5.5 mmol/L serum potassium category transitions in the CPRD are summed with the >6.0 to 5.5-6.0 mmol/L transition rates

Table 22 provides the monthly transition probabilities for the standard of care arm. In the absence of data, it is assumed that these transitions are the same before and after a cardiovascular event, i.e. that a cardiovascular event does not impact serum potassium levels. This was validated by clinicians in the working group to be a conservative assumption.

Table 22: Monthly transition probabilities between serum potassium categories (standard care arm, pre- and post- CV event)

Transition	Probability	Source
CKD3 FullRAASi (<5.5 mmol/L) to CKD3 ReduRAASi (5.5-6 mmol/L)	0.0035	CPRD
CKD3 ReduRAASi (5.5-6 mmol/L) to CKD3 FullRAASi (<5.5 mmol/L)	0.0640	
CKD3 ReduRAASi (5.5-6 mmol/L) to CKD3 DiscRAASi (>6 mmol/L)	0.0038	
CKD3 DiscRAASi (>6 mmol/L) to CKD3 ReduRAASi (5.5-6 mmol/L)	0.0235	
CKD4 FullRAASi (<5.5 mmol/L) to CKD4 ReduRAASi (5.5-6 mmol/L)	0.0091	CPRD
CKD4 ReduRAASi (5.5-6 mmol/L) to CKD4 FullRAASi (<5.5 mmol/L)	0.0387	
CKD4 ReduRAASi (5.5-6 mmol/L) to CKD4 DiscRAASi (>6 mmol/L)	0.0102	
CKD4 DiscRAASi (>6 mmol/L) to CKD4 ReduRAASi (5.5-6 mmol/L)	0.0414	

CKD3, stage 3 chronic kidney disease; CKD4, stage 4 chronic kidney disease; CV; cardiovascular; RAASi, Renin-angiotensin-aldosterone-system inhibitors; FullRAASi, Full dose RAASi; ReduRAASi. Reduced dose RAASi; DiscRAASi, Discontinued RAASi; CPRD (Clinical Practice Research Datalink)

'Patiromer' arm

In the patiromer arm of the model, transition probabilities between serum potassium categories are also derived from the CPRD, however, the relative efficacy of patiromer versus placebo for maintaining normokalaemia from OPAL-HK is applied to the 'upward moving' (in terms of potassium levels) transitions. This approach allows the incorporation of real-world data while also including the treatment effect from randomised data (OPAL-HK).

The 'surv' package in R was used to calculate a hazard ratio (HR) of [redacted] (likelihood ratio test on 1 degree of freedom, p=0.0005, n=[redacted], number of events=[redacted]) from the IPD to estimate the reduced risk of serum potassium rising from <5.1mmol/L to ≥5.5 mmol/L in the patiromer arm of OPAL-HK Part B compared with placebo (likelihood ratio test on 1 degree of freedom, p=0.0001082, n=[redacted], number of events=[redacted]).

The HR is applied to the lower two serum potassium categories only such that patiromer reduces the risk of moving to the higher two serum potassium categories only. This was necessary given patients cannot transition to a worse K^+ health state than serum potassium >6.0 mmol/L.

Transition probabilities after applying the HR are shown in Table 23 and are applicable for the full treatment duration on patiromer, therefore it is assumed that the treatment effect from the 8 weeks of OPAL-HK Part B can be applied beyond 8 weeks. This assumption was validated with clinical experts from the working group. After the treatment duration has ended, transition probabilities change to the standard of care arm transition probabilities (where the HR is not applied).

Table 23: Monthly transition probabilities between serum potassium categories ('patiromer' arm transitions which differ from the standard care arm, pre- and post- CV event)

Transition	Probability	Source
CKD3 FullRAASi (<5.5 mmol/L) to CKD3 ReduRAASi (5.5-6 mmol/L)	[redacted]	CPRD & OPAL-HK IPD
CKD3 ReduRAASi (5.5-6 mmol/L) to CKD3 DiscRAASi (>6 mmol/L)	[redacted]	
CKD4 FullRAASi (<5.5 mmol/L) to CKD4 ReduRAASi (5.5-6 mmol/L)	[redacted]	
CKD4 ReduRAASi (5.5-6.0 mmol/L) to CKD4 DiscRAASi (>6 mmol/L)	[redacted]	

CKD3, stage 3 chronic kidney disease; CKD4, stage 4 chronic kidney disease; RAASi, Renin-angiotensin-aldosterone-system inhibitors; FullRAASi, Full dose RAASi; ReduRAASi. Reduced dose RAASi; CPRD, Clinical Practice Research Datalink; IPD, Individual patient-level data

Patiromer treatment duration

For the base case, a 52-week treatment duration for patiromer is modelled. This reflects the longest duration of treatment (52 weeks) observed in the patiromer clinical trial programme, from AMETHYST-DN.

A number of scenarios on treatment duration have been carried out, including using US claims data to estimate average time on treatment. This is the longest available data analysing real-world drug persistence with patiromer with the longest data being collected since quarter one (Q1) 2016. The number of patients remaining on treatment at 10-day increments was recorded and used to determine the proportion of patients persisting on treatment (Figure 12).

Figure 12: All available real-world persistence data for patiromer

[redacted]

The economic model does not directly incorporate Kaplan-Meier (KM) curves to model persistence. Instead, the area under the curve (AUC) was calculated to estimate mean treatment duration using both the average across all curves ([redacted]) and longest (Q1 2016; [redacted]) available data. The impact of these assumptions are investigated in section 8.4.4. Given the model uses monthly cycles, the above is rounded to the closest month ([redacted] and [redacted] months, respectively).

Figure 13: Real-world persistence data for patiromer used in model

[redacted]

Transition probabilities for cardiovascular events, death due to cardiovascular events and CKD progression

As well as transitioning between serum potassium categories, once patients are in the second cycle of the model they may also transition to a higher CKD stage, or experience a CV event (and may die from this CV event in the third cycle). After assessing results from the TLRs, the NMA by Xie et al.(46) was deemed to be the best available source to estimate the baseline probabilities (i.e. on placebo) and RRs of CKD progression and cardiovascular events while on or off RAASi (see section 6.3.2.3 for further information), as it provides many of the model inputs for the relevant population from a single, internally consistent source. The comparison to placebo has chosen for this analysis (as opposed to active comparator), as it was the NICE committee's preference in NICE TA ID1293.

CV events

The baseline probability (i.e. while not on a RAASi but on placebo) of a CV event was derived from the NMA by Xie et al. (46), where MACE events among CKD patients were reported. In the meta-analysis, there were 1,720 MACE events among 8,537 patients, and 708 MACE events among 2,663 patients for the pooled placebo arms in the analyses being compared to angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), respectively. Event rates were calculated based on the mean follow-up time reported in the study (4 years for ACEIs versus placebo, and 3.3 years for ARBs versus placebo, respectively), and were then converted to monthly transition probabilities as per Briggs et al. (116).

$$rate = -ln\ (1 - p)/t$$
$$probability = 1 - exp\ (-rate * t)$$

Where p is the probability, and t is the time interval of interest, in months.

These two transition probabilities were then weighted by the proportions of patients on ACEIs and ARBs in the CPRD analysis submitted in the original submission (Table 27, NICE TA10273). ACEi and ARB proportions of 71:29 result in a monthly probability of 0.57% for a cardiovascular event.

CV death

The baseline probability of death after having had a cardiovascular event was also derived from Xie et al. (46) in the same manner to the probability of cardiovascular events. There were 792 cardiovascular deaths among 8,301 patients and 132 deaths among 1,604 patients in the placebo arms that were compared to ACEIs and ARBs groups, respectively (46). The weighted monthly probability of death after a cardiovascular event was estimated to be 0.21%.

CKD progression

The same approach was adopted for the estimation of baseline probability of CKD progression. According to Xie et al., there were 299 kidney failures among 3,337 patients in the placebo arm (versus ACEIs) over 4 years, and 727 kidney failures among 2,421 patients in the placebo arm (versus ARBs) over 3.3 years (46). The weighted monthly transition probability after conversion from event rate as per Briggs et al. (116) was 0.40%, and was used for the probability of transitioning from CKD stage 3 to stage 4, and stage 4 to ESRD (in the absence of CKD stage specific information).

Relative risks of CV events, CV death and CKD progression (RAASi versus placebo)

The RRs of having a cardiovascular event for RAASi versus no RAASi were transformed from the odds ratios (ORs) reported by Xie et al. (46), based on methods proposed by Zhang et al. (117).

$$RR = OR / ((1-p0) + (p0*OR))$$

Where p0 is the incidence of the outcome of interest (i.e. cardiovascular event) in the nonexposed group (i.e. placebo group).

According to the Bayesian network meta-analysis by Xie et al., the ORs of having a cardiovascular event were 0.82 and 0.76 for ACEIs and ARBs, respectively, when compared to placebos. Converting the weighted ORs (after weighting by 71:29) as per CPRD (Table 27, NICE TA10273) led to an RR of 0.80 of cardiovascular event for the RAASi group versus placebo.

Similarly, weighting the ORs of death after having a cardiovascular event (OR = 0.88 [ACEIs versus placebo], OR = 1.12 [ARBs versus placebo]) reported by Xie et al. (46) and converting to RR as per as per CPRD, the RR of death after having a cardiovascular event for RAASi group versus placebo was estimated to be 0.95.

The ORs of CKD progression were 0.61 and 0.70 for ACEIs and ARBs, respectively, when compared to placebos in the Bayesian NMA by Xie et al. (46). In the same manner to the estimation of RR of having a cardiovascular event, the RR of CKD progression for the RAASi group versus placebo was estimated to be 0.64.

Summary of baseline and relative risks (RAASi versus placebo) of CV events, CV death and CKD progression in CKD3, CKD 4 and ESRD.

Table 24 summarises the calculated monthly transition probabilities for CKD progression, CV event and CV death, and the RAASi RRs versus placebo. The 'placebo' probabilities are applied to the 'discontinued RAASi' health states in CKD 3&4. The RRs are applied to the 'placebo' probabilities to calculate the 'RAASi' transition probabilities, which are applied to the 'full RAASi' health states in CKD 3&4. The transition probabilities for the 'reduced RAASi' health states in CKD 3&4 are calculated as a weighted average of the risks of patients on a down-titrated RAASi dose (assumed 50%) and discontinued RAASi (CKD (no HF) and CKD HF+ patients, respectively), see Table 12. Clinical experts in the working group suggested that approximately 40% of patients in ESRD would be on a RAASi, therefore the risk of a CV event or CV death in ESRD is calculated as a weighted average of the RAASi and placebo transition probabilities.

Table 24: Cardiovascular events input summary

	Value	Source
Monthly transition probabilities (placebo)		
CKD/Post-CV event to CV event	0.0057	Xie et al. (46)
CV event to death	0.0021	
CKD 3 to CKD 4 and CKD 4 to ESRD	0.0040	
Relative risk (RAASi versus placebo)		
CKD to CV event	0.70	Xie et al. (46)
CV event to death	0.95	
CKD 3 to CKD 4 and CKD 4 to ESRD	0.64	

CKD, chronic kidney disease; CV, cardiovascular; RAASi, renin angiotensin aldosterone system inhibitor.

8.3.3 Clinical inputs

Clinical proportions

Dialysis proportions in ESRD

The balance in ESRD between peritoneal dialysis (PD), haemodialysis (HD) and kidney transplant were updated in accordance with the newly released UK Renal Registry Report for 2018/19.(118) The proportion of patients with PD, HD, or kidney transplant is shown in Table 25.

Table 25: ESRD dialysis proportions

Dialysis type	Proportion	Source
ESRD - peritoneal dialysis (PD)	0.205	UK Renal Registry (20th Report, Fig 1.9) (118)
ESRD - haemodialysis (HD)	0.698	
ESRD - kidney transplant	0.097	

MI and stroke proportions within 'CV event'

The proportion of patients in the CV event state who experience an MI versus a stroke is shown in Table 26, and is calculated from Kerr et al (2012) (119), as per the original submission. It is assumed that the proportions remain the same pre- and post- MI.

Table 26: CV event proportions

CV event	Proportion	Source
MI	0.350	Kerr et al (2012) (119)
Stroke	0.650	

Clinical event probabilities

Probability of hospitalisation due to a hyperkalaemic event

The baseline probabilities of hospitalisation from a hyperkalaemia event per potassium level (k+ < 5.5, 5.5-6.0, > 6.0 mmol/L) in the model were derived from Thomsen et al. (120)., where hospitalisation during six months before and after patients experiencing HK events were reported (33.8% vs 58.1% for k+ > 5.0 mmol/L, 41.6% vs 72.9% for k+ > 5.5 mmol/L, and 46.0% vs 84.0% for k + > 6.0 mmol/L, respectively) (120). Assuming the increase in the proportions hospitalised were due to HK events, it has been estimated that HK events increased the proportions of hospitalisations of 24.3%, 31.3%, and 43.4% for patients with k+ > 5.0, > 5.5, and > 6.0 mmol/L, respectively. Event rates were calculated over a six-month period, and then converted to probabilities as per Briggs et al. (116). Using the hospitalisation outcome per k + > 5.0, > 5.5, and > 6.0 mmol/L from Thomsen et al. to inform the outcome per k+ < 5.5, 5.5-6.0, and > 6.0 mmol/L in the model, the estimated monthly probabilities of hospitalisation from a HK event were 4.54%, 6.07%, and 9.05% for patients in each category, respectively (Table 27).

Table 27: Probability of hospitalisation from a HK event

Probability of hospitalisation from a HK event	Value	Source
k+ < 5.5 mmol/L	0.0454	Thomsen et al. (120)
k+ 5.5-6.0 mmol/L	0.0607	
k+ > 6.0 mmol/L	0.0905	

HK, hyperkalaemia

Probability of an in-hospital death

The probability of an in-hospital death has been updated from the 2013 Marie Curie 'Death and Dying' report (121), to a more recent statistic from the 'End of Life Care Profiles' report by Public Health England (2018) (122).

Table 28: Probability of an in-hospital death

Clinical event	Probability	Source
In-hospital death (all deaths)	0.469	Public Health England (2018) (122)

8.3.4 Adverse events

Adverse events due to patiromer were not included in the original model as each AE occurred in less than 5% of patients in Part B of the OPAL-HK. In the updated model, gastrointestinal, metabolism or nutrition AEs in both Part A and Part B were incorporated into the model when they were experienced in >3% of the population. Table 29 gives the probabilities of experiencing a gastrointestinal adverse event in Part A (applied in only the first cycle of the model) and Part B (applied in subsequent cycles for the entire treatment duration of patiromer).

Table 29: Adverse event probabilities

OPAL	Adverse event	Probability	Source
Part A	Constipation	0.113	OPAL-HK (Weir et al 2015) (55)
	Diarrhoea	0.040	
	Nausea	0.026	
	Hypomagnesemia	0.033	
Part B	Constipation	0.036	
	Diarrhoea	0.036	
	Nausea	0.036	

8.3.5 Cost inputs

The majority of sources for the cost inputs remain the same as in the original submission, however some updates have been made to the input values:

- The cost of AEs are now included in the model, with drug choice and treatment duration validated with clinical experts in the working group.
- The cost of a hyperkalaemia hospitalisation has been updated in line with the newly published NHS reference costs (2017/2018) (123)
- An error in the calculation for the cost of ESRD in the original submission was rectified, resulting in a lower overall cost of ESRD
- Where costs were adjusted for inflation, this has been updated to reflect the most recent inflation statistics
- In line with the ERG report, a prescribing cost for patiromer has been incorporated into the overall cost of patiromer. This was costed assuming 10 minutes of a hospital pharmacists time based on the 2018 PRSSU(124), and a need for quarterly hospital prescription (frequency based on clinical expert opinion from the working group).

A list of cost inputs is given in Table 30.

Table 30: Cost inputs

Drug costs	Cost	Source
Cost of patiromer (annual)	£2,770.26	NA
Cost of patiromer 8.4g (per diem)	£7.50	
Times patiromer taken (per diem)	1	
Dosage regimen for patiromer per month	30.44	
Prescribing cost for patiromer (annual)	£30.89	PRSSU (2018) (124) / Clinical expert opinion
Cost of RAASi treatment (annual) (ACEi & ARB) or active comparators	£43.18	BNF (114) / ERG validated value
Cost of concomitant medications for CKD (annual)	£600.66	Kerr et al (2012) (119), BNF (114)
Cost of post-CV event concomitant medications (annual)	£7.09	BNF (114)
Health states	**Cost**	**Source**
Cost of CKD 3 (annual)	£2,370.95	Kerr et al (2012) (119)
Cost of CKD 4 (annual)	£2,370.95	
Cost of ESRD (annual)	£26,738.17	Weighted average of ESRD costs from Kerr et al (2012) (119) and ESRD proportions from the 20th Annual UK Renal Report(118)
Cost of in-hospital death	£4,892.69	Georghiou and Bardsley (2014) (125)
Hyperkalaemia hospitalisation	£1,442.99	NHS Reference Costs (2017/2018) (123)
CV events	**Cost**	**Source**
Cost of CV event	£12,211.05	Kerr et al (2012) (119)
Cost of MI	£9,133.16	
Cost of stroke	£13,868.38	
ESRD	**Cost**	**Source**
Cost ESRD - peritoneal dialysis (PD) (annual)	£22,253.12	Kerr et al (2012) (119)
Cost ESRD - haemodialysis (HD) (annual)	£29,075.80	
Cost ESRD - post kidney transplant (annual)	£19,395.57	
AEs	**Cost**	**Source**
Constipation (annual)	£6.55	BNF (126)
Diarrhoea (annual)	£14.06	
Nausea (annual)	£1.74	
Hypomagnesemia (annual)	£96.66	

AE, adverse event; CKD, chronic kidney disease; CV, cardio-vascular; MI, myocardial infarction; TA, technology appraisal; BNF, British National Formulary, PRSSU, Personal Social Services Research Unit

It was assumed that the annual cost of CKD 3 and CKD 4 is the same, as Kerr et al (2012) (119) did not give costs split by CKD stage. In practice, CKD 4 is likely to require more healthcare resource and be costlier than CKD 3 (which was validated by clinicians in the working group). This

assumption is likely to be conservative with respect to patiromer, as in the model, patiromer (via enabling RAASi) slows progression from CKD3 to CKD4, which would result in cost savings if a difference in the cost of managing CKD 3 and 4 exists.

8.3.6 Utility inputs

Sources for the utility inputs into the updated model remain largely the same as the in original model, however the way that utilities are applied in the model has been modified. Relative utilities are no longer used, and a more straightforward multiplicative approach has been adopted. Baseline utility (which remains calculated in the same way as in the original submission) is multiplied by health state specific utility values from the literature. This approach assumes a constant proportional decrement in the utility associated with specific health states as baseline utility declines with age.

Utility penalties for one-off adverse events have been newly incorporated, taken from NICE TA ID1293(115) for comparability. To ensure that utility penalties were proportional to baseline utility, the utility penalty is weighted by the relative decline in baseline utility in each cycle. That is, if baseline utility declined by 1% from the previous cycle, the utility penalty also declines by 1% to ensure a constant proportional impact. This avoids situations where the relative impact of a fixed disutility grew as baseline utility declined with cohort age.

Other changes to utilities values since the original submission are the following:

- Rather than using utility values for ESRD based on types of dialysis or transplant, the utility value for ESRD was taken from the same source as the CKD 3 and CKD 4 utilities (Jesky et al (127)), as suggested by the ERG.
- The ERG preferred values from Pockett et al (2018) (128) have been used for the Post-CV event health states.

A list of all utility inputs in the model are shown in Table 31.

Table 31: Utility inputs

Baseline utility equation constants/coefficients	Input	Source
male	0.545	OPAL-HK (Weir et al 2015) (55)
Constant	0.968	Jones-Hughes 2016 (129)
Coefficient age	0.002	
Coefficient age2	0.000	
Coefficient sex (male)	0.023	
Health State Utilities	**Input**	**Source**
CKD3	0.800	Jesky et al (2016) (127)
CKD4	0.740	
ESRD	0.730	
CV event - MI	0.690	Pockett et al (2018) (128)
CV event - Stroke	0.496	
CV event - Combined (weighted average)	0.564	Pockett et al (2018) (128), Kerr (2012) (119)
Post CV event - MI	0.706	Pockett et al (2018) (128)
Post CV event - Stroke	0.527	
Post CV event - Combined (weighted average)	0.590	Pockett et al (2018) (128), Kerr (2012) (119)
Death	0.000	Assumption
Disutilities	**Input**	**Source**
Hyperkalaemia hospitalisation (annual)	0.000	Assumption
AE - Constipation (annual)	-0.0728	Sullivan et al (2011) (130) / TA ID1293(115)
AE - Diarrhoea (annual)	-0.01	Kristiansen et al (1999) / TA ID1293 (115)
AE - Nausea (annual)	-0.04802	Nafees et al (2008) / TA ID1293 (115)
AE - Hypomagnesemia (annual)	-0.0336	Sullivan et al (2011) (130) / TA ID1293(115)

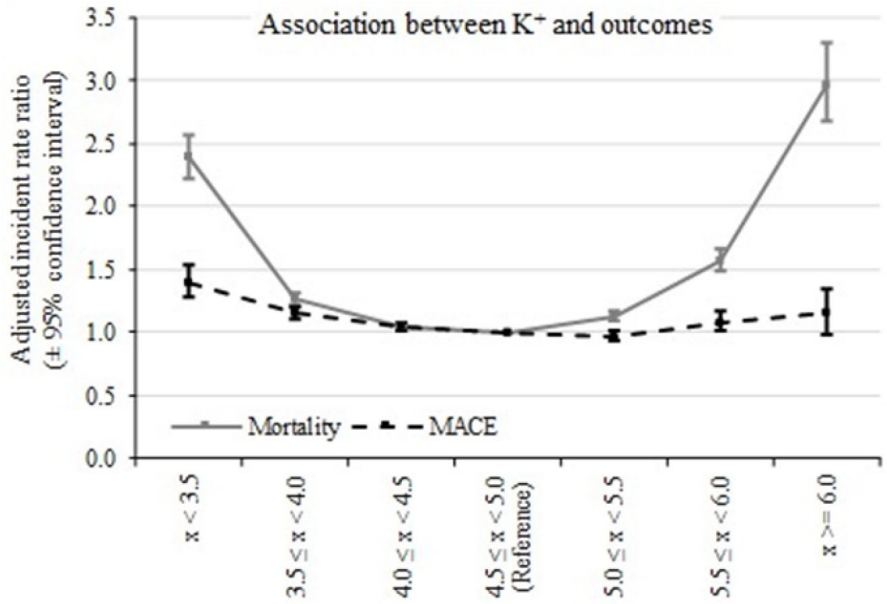
AE, adverse event; CKD, chronic kidney disease; CV, cardio-vascular; MI, myocardial infarction; TA, technology appraisal

8.3.7 Mortality inputs

Mortality due to age and CKD/ESRD is applied in the same way as the original model, using standardised mortality ratios (SMRs) for CKD stage 3 (131) and CKD stage 4 (131, 132), and ESRD (133), applied on top of age-adjusted general UK population mortality.

Due to the evidence from the TLR suggesting an association between serum potassium and mortality (section 536.3.4), a mortality risk due to raised serum potassium has also been incorporated into the updated model. For comparability with NICE TA ID1293, the source for these inputs come from McEwan et al (2017) (107), a retrospective UK observational study of patients with CKD stage 3 or higher, conducted using the CPRD. The study demonstrated the U-shaped association between serum potassium and mortality as shown in Figure 14.

Figure 14: McEwan et al (2017) observational study demonstrating association between serum potassium and all-cause mortality (107)



The above curve was digitised, and the adjusted incidence rate ratios (IRR) for mortality for serum potassium categories of 5.0≤x<5.5, 5.0≤x<6.0 and x≥6.0 mmol/L were applied to the <5.5, 5.5-6.0 and >6.0 mmol/L serum potassium categories in the model. Although this does not account for serum potassium levels of <5.0, the IRR only starts to significantly exceed that of the 5.0≤x<5.5, at serum potassium levels of <3.5 mmol/L; in OPAL-HK only 3.3% and 0.9% of patients experienced a serum potassium level of <3.5 mmol/L in Part A and Part B, respectively. The results of McEwan et al (107) are corroborated by that of et al (2019) (134), a published CPRD analysis in a heart failure population. In a scenario analysis, the impact of using a source identified from the TLR (Kovesdy et al (96)) on the association between serum potassium and mortality was carried out.

Table 32: Mortality inputs

Standardised mortality ratios (SMR)	Input	Source
SMR CKD3, less than 69 years old	3.100	Eriksen et al (2006) (131)
SMR CKD3, 70 to 79 years old	2.000	
SMR CKD3, greater than 79 years old	2.200	
HR for mortality with CKD 4 versus CKD 3	2.560	Sud et al (2016) (132)
SMR CKD4, less than 69 years old	7.936	Eriksen et al (2006) (131) & Sud et al 2016 (132)
SMR CKD4, 70 to 79 years old	5.120	
SMR CKD4, greater than 79 years old	5.632	
ESRD life tables		
Age 60-64	0.006	Steenkamp et al (2016) (133)
Age 65-69	0.009	
Age 70-74	0.012	
Age 75-79	0.017	
Age 80-84	0.021	
Age 85+	0.030	
Serum K+ mortality risk		
K+ <5.5 mmol/L	1.150	McEwan et al 2017 (107)
K+ 5.5-6 mmol/L	1.600	
K+ >6 mmol/L	2.950	

8.4 Results

8.4.1 Base-case model settings

Key model settings are shown in Table 33.

Table 33: Base case model settings

Setting	Base case	Justification
Population	CKD stage 3–4 HF+ with serum potassium >5.5mmol/L and CKD stage 3–4 (no HF) with a serum potassium >6.0mmol/L.	OPAL-HK patients who would be treated for hyperkalaemia in UK clinical practice
Intervention	Patiromer	OPAL-HK
Comparator	Placebo	OPAL-HK
Time horizon	Lifetime (35 years)	NICE reference case
Discount rate	3.5%	NICE reference case
Patiromer dose	8.4 – 16.8g	Expert clinical opinion from the working group validated that the starting dose for patiromer is 8.4g, in line with the SmPC and the World Health Organization Defined Daily Dose (WHO DDD). Experts suggested the dose would increase to 16.8g at serum potassium levels of ≥5.5 in CKD HF+ patients, and >6 in CKD (no HF) patients
Treatment duration	One year	Reflects the longest duration of treatment (52 weeks) observed in the patiromer clinical trial programme, from AMETHYST-DN.

HF+, with heart failure comorbidity

8.4.2 Base-case incremental cost-effectiveness analysis results

When applying a price of £7.50 per day, the total costs in the base-case are higher with patiromer compared with standard of care, leading to incremental costs of £3,289. Total QALYs were higher in the patiromer arm, resulting in incremental QALYs of 0.17. This results in an ICER of £18,893 per QALY. Detailed results are presented in Table 34.

Table 34: Base-case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Patiromer	£40,693	4.53367	£3,289	0.17406	£18,893
No Patiromer	£37,405	4.35961			

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

8.4.3 Sensitivity analysis

8.4.3.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to test the impact of second order uncertainty by random, simultaneous variation of the input parameters in the model. This analysis was performed by assigning probability distributions to certain variables in the model and repeatedly sampling values from these distributions so propagating uncertainty to estimate the cost effectiveness ratios. One thousand iterations were run. The results of the probabilistic sensitivity analysis are illustrated on the cost effectiveness plane and in the cost effectiveness acceptability curve. The former shows the distribution of incremental costs and benefits under uncertainty and the latter the likelihood of being cost effective at given willingness to pay thresholds.

Results

PSA results suggest that the model is robust to parameter variation, with probabilistic results remaining consistent with the deterministic results presented in the base-case section. At a price of £7.50 per day for patiromer, the probability that patiromer is cost-effective compared with no patiromer is 38% and 94% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY.

Table 35: Base-case results, probabilistic

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Patiromer	£27,852	3.86070	£3,132	0.16001	£19,577
No Patiromer	£24,719	3.70069			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 15. Base case cost-effectiveness plane

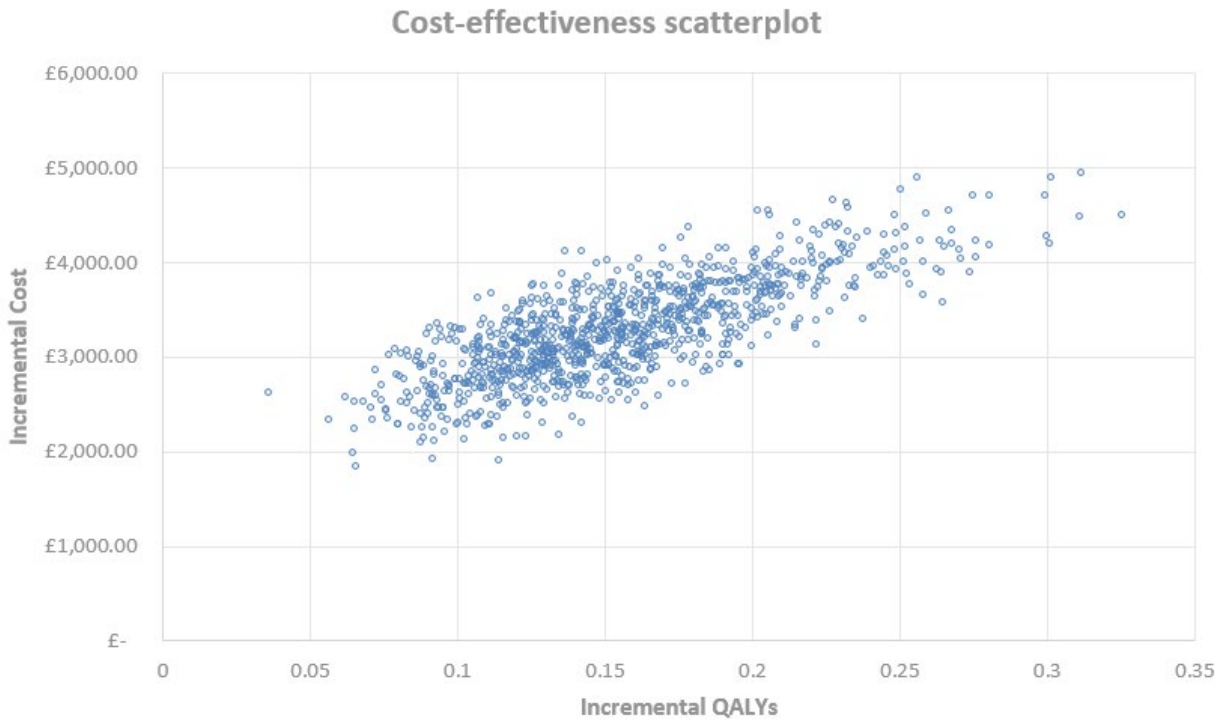
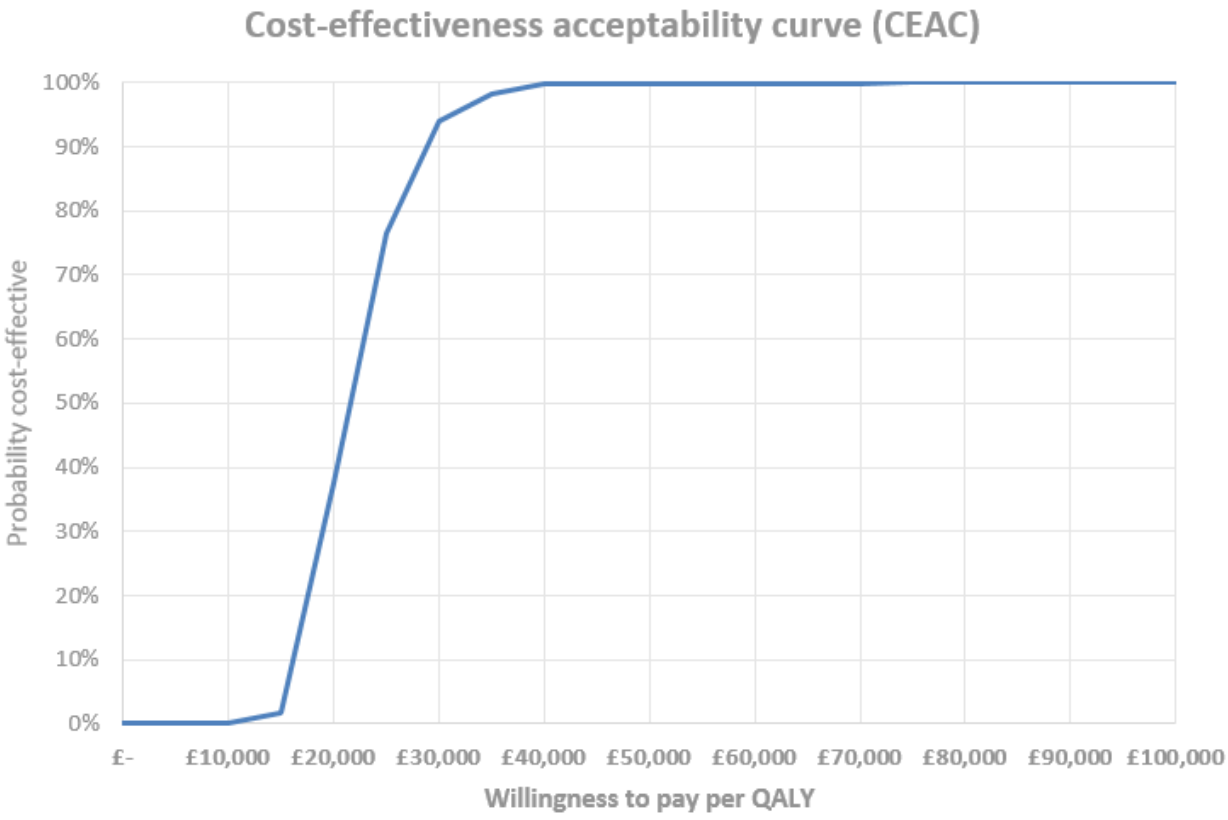


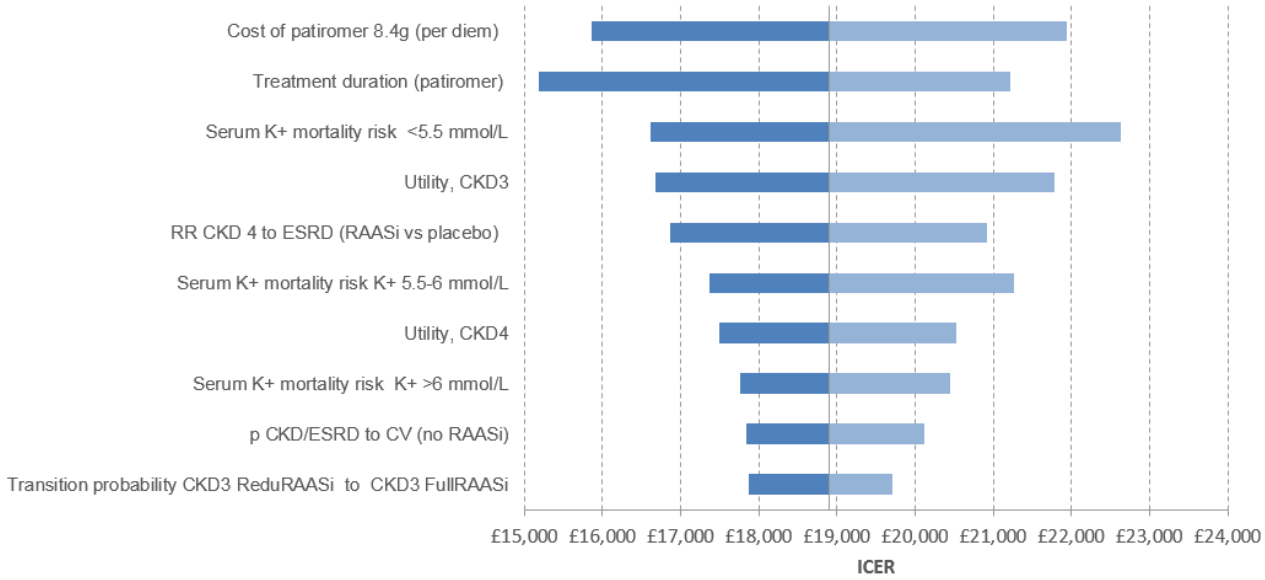
Figure 16: Base case cost-effectiveness acceptability curve (CEAC)



8.4.3.2. One-way sensitivity analysis

In order to determine the impact of single parameter variation, and identify key model drivers, one-way sensitivity analyses were performed. Base case parameters were varied by 20%. Results are presented in the tornado diagram (Figure 17) and show no individual parameter takes the ICER above £23,000 per QALY.

Figure 17: One-way sensitivity analysis



8.4.4 Scenario analyses

To assess the impact of variation in base case assumptions, a number of key scenario analyses were conducted.

Table 36: Scenario results

Concerning	Scenario	Rationale	ICER
Serum potassium mortality	Assuming no associated mortality with high serum potassium	In line with ERG base case for NICE TA ID1293, the results from McEwan et al (107) were removed from the model.	£45,748
	Kovesdy et al. (Fig S10A) (96) HRs: • 5.25mmol/L (for <5.5 potassium category): 1.12 • 5.75mmol/L (for 5.5-6 potassium category): 1.24 6.25mmol/L (for >6 potassium category): 1.36	Source from TLR on serum potassium association with mortality (section 6.3.4). Results given for population ≥65 years of age.	£33,238
Treatment duration	[redacted]	Longest available dataset from US real world usage data (from Q1 2016, see Figure 13) and most conservative real-world estimate with respect to patiromer. Patiromer has been in use in the US since early 2016, allowing a clear picture of duration of treatment to develop over three and a half years.	£12,661

	[redacted]	Average of all available datasets from US real world usage data (see Figure 12). Patiromer has been in use in the US since early 2016, allowing a clear picture of duration of treatment to develop over three and a half years.	£11,386
	84 days (i.e. three months)	This was selected on the basis of the recent ACD for STA ID1293 where NICE have proposed the recommendation of another technology for treating hyperkalaemia in adults only if the drug is stopped after 28 days of maintenance treatment, or earlier if hyperkalaemia resolves. This duration is based on the length of the clinical data driving the analysis. Vifor provide an equivalent scenario for a treatment duration of 84 days based on the length of OPAL-HK. Of the trials performed during the clinical development programme for patiromer, two phase 3 trials (OPAL-HK and AMBER) have 12-week duration, with the phase 2 trials AMETHYST-DN and PEARL-HF having 52 week and 28-day duration respectively.	£7,502
CKD health state utility	CKD3: 0.80 CKD4: 0.74 ESRD: 0.71	In line with ERG estimates of utility for NICE TA ID1293.	£18,876
Xie NMA	Active comparator baseline risks and relative risks	Preferred by the ERG (but not by the NICE committee of TA ID1293).	£18,241
	ARBs only	To understand the impact of using different drug classes.	£23,049
	ACIs only		£17,833
Hyperkalaemia hospitalisation disutility	Assume -0.1 disutility for a hyperkalaemia hospitalisation rather than no disutility	No source was identified for the disutility of a hyperkalaemia hospitalisation; however, it is likely that there would be a disutility associated with this event.	£18,821
Starting age of	70	To test other assumptions on the starting age of the model.	£20,966

cohort	75		£20,781
	80		£20,311

8.4.5 Conclusions

To address NICE's concerns on the original economic analysis, a number of model updates were made, including accounting for Part A of OPAL-HK, improving the generalisability of the results to UK clinical practice, allowing for RAASi dose modification, including adverse events due to patiromer, and refining the patient population included in the model.

The updated economic analysis was conducted to assess the cost-effectiveness of patiromer in adult patients with stage 3-4 CKD HF+ with a serum potassium level of ≥5.5 mmol/L, and, adult patients with stage 3-4 CKD (no HF) with a serum potassium level of >6mmol/L.

The results of this analysis show that patiromer is an efficient use of NHS resources in this population. This result is consistent under a range of scenarios, for example a varied treatment duration, alternative utility values, alternative assumptions on serum potassium mortality, and alternative cohort starting ages.

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10. Appendices

10.1 Appendix 1: Clinical evaluation

10.1.1 Summary of decision problem and technology being appraised

Table 37: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with hyperkalaemia	Adult patients with stage 3-4 chronic kidney disease (and other co-morbidities such as heart failure and diabetes) and hyperkalaemia treated with RAASi therapy	The safety and efficacy of patiromer were demonstrated in hyperkalaemic patients with chronic kidney disease (CKD) on stable doses of at least one renin–angiotensin–aldosterone system (RAAS) inhibitor.
Intervention	Patiromer	Patiromer (Veltassa®)	N/A
Comparator	Standard care. This includes a low-potassium diet with or without agents that reduce levels of potassium in the body.	The main comparator in the submission is discontinuation or dose modification of RAASi therapy. The final matrix lists no other companies with relevant comparators. The 'response to consultee and commentator comments on the draft remit and draft scope (pre-referral)' document also confirms that NICE have amended the comparators to "take out reference to pharmacological treatments" in defining comparators to Veltassa®	There is currently no appropriate pharmacological comparator for the long-term treatment of recurrent hyperkalaemia in adults. In consultation with the Regulatory Authorities, it was agreed that the pivotal OPAL-HK study would not include an active comparator for ethical and clinical practice reasons. A variety of measures are used to manage hyperkalaemia clinically, including discontinuation of hyperkalaemia-inducing drugs such as RAASis, diuretics, diet change, bicarbonates and potassium (K^+) binders (135-138). The cation exchange resins, sodium polystyrene sulphonate [SPS; Kayexalate®] and calcium polystyrene sulphonate [CPS; Sorbisterit®] are known to lower K+ levels in the acute setting, however, their transient effect on serum K+, limited long-term data (47), risk of serious gastrointestinal adverse events (AEs) and sodium load precautions (48) prevent their use for the management of chronic hyperkalaemia. Indeed, calcium and sodium polystyrene sulfonate are contraindicated for treating patients with a serum potassium < 5.0 mmol/L and both require frequent stop and start cycles of drug administration, further complicating chronic dosing (47). As a result of these issues, it is unlikely that either diet or SPS/CPS would be used in the key

			population of interest i.e. CKD patients managed on RAASi therapy. In addition, the Summary of Product Characteristics (SmPC) for Resonium A and Calcium Resonium state the licenced indication as for “the treatment of hyperkalaemia associated with anuria or severe oliguria. It is also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis”(48, 139). In addition, low K+ diet is included in the scope as a comparator, however, is unlikely to be used widely because its value in the management of potassium levels is limited due to the difficulties in changing dietary habits and the prevalence of K+-rich foods making long-term adherence problematic (136). A comparison with sodium bicarbonate will not be addressed in the submission as this sub-group population was not included in patiromer trials. Vifor request that this comparison is removed from the scope. The European Public Assessment Report (EPAR) for Veltassa® confirms the approach taken to determine relevant comparators in this submission. It highlights that for patients in whom the aetiology of hyperkalaemia is not reversible but rather more chronic in nature from underlying CKD and/or use of RAASi therapies, the traditional approach has relied on dietary restriction and RAASi dose reduction or discontinuation, diuretics, oral bicarbonate or cation exchange resins (SPS/CPS) (47). However, it also states the difficulties in diet modification due to the ubiquitous presence of potassium in foods and the lack of rigorous long-term safety and efficacy data for SPS/CPS. Issues with poor tolerance and life-threatening side effects including intestinal necrosis with the cation-exchange resins are also of concern. Further SPS should be administered with caution in patients who cannot tolerate even small increases in sodium load due to the effect of appreciable sodium load. These issues make long-term use of these agents difficult. The favourable effects observed with Veltassa® were considered important as currently there is an unmet need for safe and efficacious treatment of hyperkalaemia.

Outcomes	The outcome measures to be considered include: • serum potassium level • use of renin–angiotensin–aldosterone system inhibitor therapy • mortality • time to normalisation • adverse effects of treatment • health-related quality of life.	• Serum potassium levels: • Mean change in serum potassium levels from baseline to week 4. • Proportion of patients who achieved target potassium levels (3.8–<5.1 mmol/L) • Difference between patiromer and placebo in the median change in serum K+ level at the start of the phase to week 4 or the earliest visit at which the K+ level was <3.8 mmol/L or ≥5.5 mmol/L • Proportion of patients with a recurrence of hyperkalaemia (≥5.1 or ≥5.5 mmol/L) • Following exploratory endpoints are reported: 1) time to 1st recurrent hyperkalaemia; 2) proportion of patients requiring an intervention due to recurrent hyperkalaemia at any time; 3) time to RAASi dose discontinuation Use of renin-angiotensin-aldosterone system inhibitor therapy: • Proportion of patients who required RAASi dose reduction or discontinuation due to recurrent hyperkalaemia. • Exploratory endpoints included: time to RAASi dose discontinuation; and proportion of patients receiving any dose of RAASi at the end of this phase. Mortality is reported as a safety endpoint • Adverse effects are also reported. Events of interest were: • Hypokalaemia (serum K+ < 3.5 mmol/L) • Serum K+ ≥ 5.5 mmol/L • Hyperkalaemia-associated electrocardiogram (ECG) changes • Hypokalaemia-associated ECG changes • Gastrointestinal AEs • Potential allergic reactions	Time to normalisation and health-related quality of life (HRQoL) were not measured in the included trials. However, the impact HRQoL was included in the economic model by a systematic literature search of relevant utilities.

		• Changes in serum calcium, magnesium, phosphorous and fluoride
		• AEs resulting in change of dose
		• AEs resulting in addition of concomitant therapy (e.g., magnesium supplement for hypomagnesemia)
		• Worsening renal function:
		  ○ ≥ 100% increase in serum creatinine from baseline; or
		  ○ >50% decrease in eGFR from baseline
		• AE profile in subjects maintained on RAASi therapy versus those who have stopped RAASi therapy	

Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people with acidosis • people with acute hyperkalaemia • people with chronic kidney disease • people with heart failure	Pivotal OPAL-HK trial enrolled patients with chronic kidney disease with hyperkalaemia. Pre-specified sub-groups in OPAL-HK are: • Type 2 diabetes mellitus (n=67) • Heart failure • Serum potassium level (<5.8mmol/L, ≥5.8mmol/L) • Maximal dose of RAASi • Sex • Age (<65 years, ≥65 years) • Region (Non-EU Eastern Europe, EU and United States)	Patients with acidosis were not included in the patiromer trials. Given the small number of patients entering the Withdrawal phase in OPAL-HK (patiromer n=55, placebo n=52) sub-group analysis were not performed and the economic analysis is based on the whole trial population

Table 38: Technology being appraised

UK approved name and brand name	Patiromer (Veltassa®)
Mechanism of action	Patiromer is a non-absorbed, sodium-free, cation-exchange polymer that contains a calcium-sorbitol counterion. Patiromer increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction in serum potassium levels.

Marketing authorisation/CE mark status	Marketing authorisation for patiromer was received from the European Medicines Agency (EMA) on 18 July 2017. The marketing authorisation for the UK is centralised through the EMA. Patiromer was launched in the UK on 05 October 2017.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The treatment of hyperkalaemia in adults. Medicinal product subject to medical prescription. As a precautionary measure, it is preferable to avoid the use of patiromer during pregnancy. There is limited data on the use of patiromer in patients on dialysis. No special dose and administration guidelines were applied to these patients in clinical studies. Elderly population (≥65 years of age): no special dose and administration guidelines are recommended for this population. The safety and efficacy of patiromer in children aged under 18 years have not yet been established. No data are available.
Method of administration and dosage	Patiromer is available as individual sachets containing 8.4 g, 16.8 g, or 25.2 g patiromer sorbitex calcium powder for oral suspension. The 25.2 g sachet will not be commercially available in the UK. The recommended starting dose is 8.4 g patiromer once daily, with food. The daily dose may be adjusted at intervals of one week or longer, based on the serum potassium level and the desired target range. The daily dose may be increased or decreased by 8.4 g as necessary to reach the desired target range, up to a maximum dose of 25.2 g daily. If serum potassium falls below the desired range, the dose should be reduced or discontinued. If a dose is missed, the missed dose should be taken as soon as possible on the same day. The missed dose should not be taken with the next dose. Administration of patiromer should be separated by 3 hours from that of other oral medicinal products.
Additional tests or investigations	The introduction of patiromer would result in new monitoring requirements: In clinical studies, serum magnesium values <1.4 mg/dL (0.58 mmol/L) occurred in 9% of patients treated with patiromer. Mean decreases in serum magnesium were 0.17 g/dL (0.070 mol/L) or less. Serum magnesium should be monitored for at least 1 month after initiating treatment, and magnesium supplementation considered in patients who develop low serum magnesium levels. Serum potassium should be monitored when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g. RAASis or diuretics) and after the patiromer dose is titrated.
List price and average cost of a course of treatment	The list price for patiromer is £10.00 per day (£300.00 per 30-sachet pack) for both 8.4 g and 16.8 g sachets, as flat pricing is applied. The monthly treatment cost (based on 30.44 days per month) equates to £304.
Patient access scheme	The PAS price for patiromer is £7.50 per day (£225 per 30-sachet pack) for both 8.4 g and 16.8 g sachets, as flat pricing is

(PAS) (if applicable)	applied. The monthly treatment cost (based on 30.44 days per month) equates to £228.30.

10.1.2 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Further details from the 2016 ESC guidelines (11) for the diagnosis and treatment of acute and chronic heart failure:

- Why: to improve symptoms and exercise capacity, reduce the risk of HF hospitalisation and survival
- Indications: Potentially all patients with HF and a LVEF <40%
- Cautions/seek specialist advice: Significant hyperkalaemia (K≥5.0 mmol/L)
- Worsening renal function and hyperkalaemia: An increase in potassium up to ≤ 5.5 mmol/L is acceptable. If potassium rises to >5.5 mmol/L the ACEi or ARB should be stopped, and specialist advice sought
- Some rise in urea, creatinine, and potassium is to be expected after an ACEi; if an increase is small and asymptomatic, no action is necessary.
- An increase in creatinine of up to 50% above baseline, or 266 µmol/L (3 mg/dL)/eGFR <25 mL/min/1.73 m^2, whichever is the smaller, is acceptable.
- An increase in potassium to ≤5.5 mmol/L is acceptable.
- If urea, creatinine, or potassium does rise excessively, consider stopping concomitant nephrotoxic drugs (e.g. NSAIDsd) and other potassium supplements or retaining agents (triamterene, amiloride) and, if no signs of congestion, reducing the dose of diuretic.
- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ACEi (or ARB) should be halved and blood chemistry re-checked within 1–2 weeks; if there is still an unsatisfactory response, specialist advice should be sought.
- If potassium rises to >5.5 mmol/L or creatinine increases by >100% or to >310 µmol/L (3.5 mg/dL)/eGFR <20 mL/min/1.73 m^2, the ACEi (or ARB) should be stopped and specialist advice sought.
- Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued.

The ESC Guidelines (11), Web Table 7.6 Practical guidance on the use of MRAs in patients with HFrEF recommending the following:

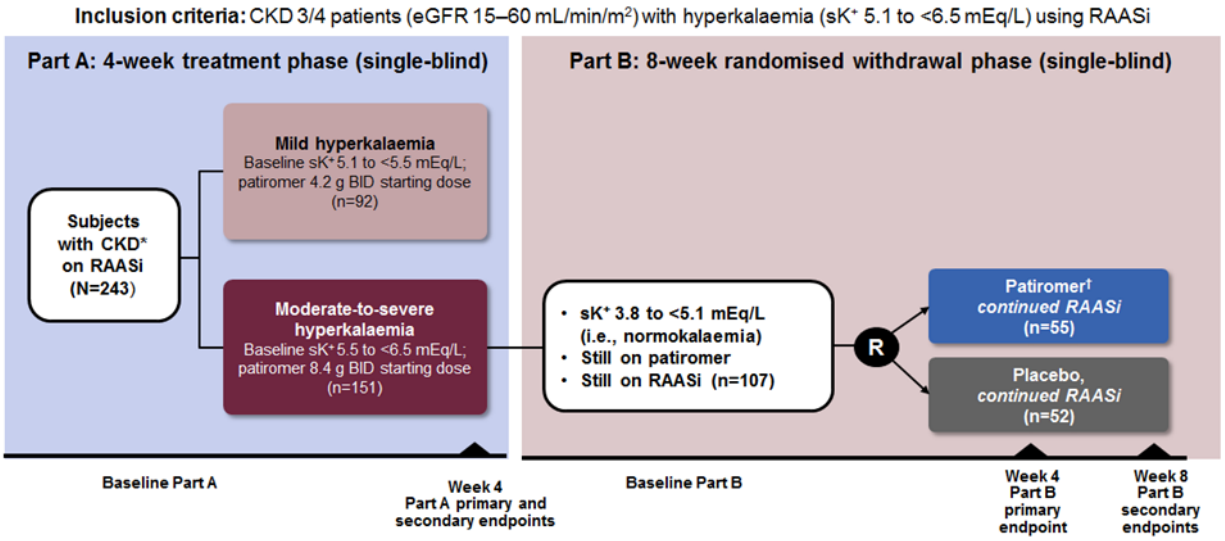
- Check renal function and electrolytes (particularly K+).
- Start with a low dose.
- Consider dose up-titration after 4–8 weeks.

- Check blood chemistry at 1 and 4 weeks after starting/increasing dose and at 8 and 12 weeks; 6, 9, and 12 months; 4-monthly thereafter.
- If K+ rises above 5.5 mmol/L or creatinine rises to 221 µmol/L (2.5 mg/dL)/eGFR <30 mL/min/1.73 m2, halve dose and monitor blood chemistry closely.
- If K+ rises to >6.0 mmol/L or creatinine to >310 µmol (3.5 mg/dL) eGFR <20 mL/min/1.73 m^2, stop MRA immediately and seek specialist advice.
- A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose up-titration.

10.1.3 OPAL-HK trial

The objective of Part B (randomized withdrawal phase) of the OPAL-HK trial was to evaluate maintenance of normokalaemia or recurrence of hyperkalaemia. An overview of the OPAL-HK study design is shown in Figure 18.

Figure 18: OPAL-HK study design



OPAL-HK Part B titration algorithms

During the Part B, prespecified treatment algorithms (Table 39 and Table 40) were developed to manage a recurrence of hyperkalaemia, either by an increase in the dose of patiromer (patiromer group) or by modification of the RAASi regimen (placebo group) at the time of the first event of hyperkalaemia. Subsequent events required discontinuation of the RAASi [Weir 2016].

Because the primary efficacy endpoint for Part B was determined during the first 4 weeks of Part B, the titration algorithm specified no change of dose or discontinuation of RLY5016 for oral suspension/placebo or RAASi during the first 4 weeks of Part B unless the serum potassium level was <3.8 mmol/L or ≥5.5 mmol/L. If a subject's serum potassium was <3.8 mmol/L, the subject

discontinued RLY5016 for oral suspension/placebo, was withdrawn early from Part B and entered a follow-up period to Part B.

To help retain subjects for the collection of 8 weeks of placebo-controlled safety data, an intervention (increase in RLY5016 for oral suspension dose or, for subjects receiving placebo, decrease in RAASi dose) was specified during the first 4 weeks of Part B if a subject's serum potassium was ≥5.5 mmol/L. After the first 4 weeks of Part B, the titration algorithm also specified an increase in RLY5016 for oral suspension dose upon the initial occurrence of a serum potassium ≥5.1 mmol/L. During Part B, the RLY5016 for oral suspension dose could be increased to a maximum of 50.4 g/day patiromer in increments of 8.4 g/day patiromer. Depending on the serum potassium level, the Part B titration algorithms also specified MSVs within 24 or 72 hours and/or early withdrawal from Part B of the study [Data on file RLY5016-301 CSR].

Table 39: Titration algorithm for first 4 weeks of the Withdrawal Phase (day 3 to week 3 visits)

Serum K^+ Threshold		Treatment Group	Intervention	Study Participation	Next Visit
< 3.8	Any event	Patiromer	Discontinue patiromer/placebo No changes to RAAS inhibitor medications	Early Withdraw	Randomized Withdrawal Phase Follow-up Visits
		Placebo:			
3.8 - < 5.1	Any event	Patiromer:	No changes	Continue	Next weekly visit
		Placebo:			
5.1 – < 5.5	1st event (5.1 – 5.4)	Patiromer:	No change to patiromer, placebo or RAAS inhibitor medication(s)	Continue	Next weekly visit
		Placebo:			
	Any subsequent event in 1st 4 weeks (5.1 – 5.4)	Patiromer:	No change to patiromer, placebo or RAAS inhibitor medication(s)	Continue	Next weekly visit
		Placebo:			
≥ 5.5 – < 6.0	1st event (≥ 5.5 - < 6.0)	Patiromer:	Increase patiromer by 8.4 g/day patiromer[a] No changes to RAAS inhibitor medications.	Continue	Next weekly visit
		Placebo:	No change to placebo. Decrease each RAAS inhibitor medication by 50% or to next available dose strength below 50%	Continue	Next weekly visit
	2nd event (≥ 5.1 - < 6.0)	Patiromer:	No change to patiromer dose. Discontinue RAAS inhibitor medication(s).	Continue	Next weekly visit
		Placebo:	No change to placebo. Discontinue RAAS inhibitor medication(s).	Continue	Next weekly visit
	3rd event (≥ 5.1 - < 6.0)	Patiromer:	Discontinue patiromer.	Early withdraw	Randomized Withdrawal Phase Follow-up Visits
		Placebo:	Discontinue placebo.	Early withdraw	Randomized Withdrawal Phase Follow-up Visits
≥ 6.0 - < 6.5[b]	1st event	Patiromer:	No change to patiromer dose. Discontinue RAAS inhibitor medication(s).	Continue	MSV within 72 hrs (At MSV, discontinue if $K^+ \geq 6.0$)
		Placebo:	No change to placebo. Discontinue RAAS inhibitor medication(s).	Continue	MSV within 72 hrs (At MSV, discontinue if $K^+ \geq 6.0$)
	2nd event (≥ 5.1)	Patiromer:	Discontinue patiromer.	Early withdraw	Randomized Wtihdrawal Follow-up Visits
		Placebo:	Discontinue placebo.	Early withdraw	Randomized Withdrawal Phase Follow-up Visits

K^+ = potassium; MSV = mandatory safety visit; RAAS = renin angiotensin aldosterone system

[a] If subject is on 50.4 g/day, decrease each RAAS inhibitor medication by 50% or to next available dose strength below 50%.

[b] Any subject with a serum $K^+ \geq 6.5$ must discontinue patiromer /placebo and all RAAS inhibitor medications and must return for a MSV within 24 hours. These subjects will be early withdrawn and will enter follow-up of the randomized Withdrawal Phase.

Note: the algorithm for the first 4 weeks of the Withdrawal Phase was developed for purposes of the trial and not as a treatment algorithm to be employed in clinical practice.

Table 40: Titration algorithm for second 4 weeks of the Withdrawal Phase (week 4 to week 7 visits)

Serum K^+ Threshold		Treatment Group	Intervention	Study Participation	Next Visit
< 3.8	Any event	Patiromer:	Discontinue patiromer/placebo No changes to RAAS inhibitor medications	Early Withdraw	Randomized Withdrawal Phase Follow-up Visits
		Placebo:			
3.8 - < 5.1	Any event	Patiromerff:	No changes	Continue	Next weekly visit
		Placebo:			
5.1 – < 6.0	1st event (5.1 - < 6.0)	Patiromer:	Increase patiromer by 8.4 g/day patiromer[a] No changes to RAAS inhibitor medications.	Continue	Next weekly visit
		Placebo:	No change to placebo. Decrease each RAAS inhibitor medication by 50% or to next available dose strength below 50%	Continue	Next weekly visit
	2nd event (5.1 - < 6.0)	Patiromer:	No change to patiromer dose. Discontinue RAAS inhibitor medication(s).	Continue	Next weekly visit
		Placebo:	No change to placebo. Discontinue RAAS inhibitor medication(s).	Continue	Next weekly visit
	3rd event (≥ 5.1 - < 6.0)	Patiromer:	Discontinue patiromer.	Early withdraw	Randomized Withdrawal Phase Follow-up Visits
		Placebo:	Discontinue placebo.	Early withdraw	Randomized Withdrawal Phase Follow-up Visits
≥ 6.0 - < 6.5[b]	Any event	Patiromer:	No change to patiromer dose. Discontinue RAAS inhibitor medication(s).	Continue	MSV, within 72 hrs (At MSV, discontinue if K^+ ≥ 6.0)
		Placebo:	No change to placebo. Discontinue RAAS inhibitor	Continue	MSV, within 72 hrs (At MSV, discontinue if K^+
			medication(s).		≥ 6.0)
	2nd event (≥ 5.1)	Patiromer:	Discontinue patiromer.	Early withdraw	Randomized Withdrawal Phase Follow-up Visits
		Placebo:	Discontinue placebo.	Early withdraw	Randomized Withdrawal Phase Follow-up Visits

K^+ = potassium; MSV = mandatory safety visit; RAAS = renin angiotensin aldosterone system

[c] If subject is on 50.4 g/d, decrease each RAAS inhibitor medication by 50% or to next available dose strength below 50%.

Any subject with a serum K^+ ≥ 6.5 must discontinue patiromer /placebo and all RAAS inhibitor medications and must return for a MSV within 24 hours. These subjects will be early withdrawn and will enter Follow-up of the randomized Withdrawal Phase.

Note: the algorithm for the second 4 weeks of the Withdrawal Phase was developed for purposes of the trial and not as a treatment algorithm to be employed in clinical practice.

10.1.4 PEARL-HF trial

The objective of the PEARL-HF trial was to determine the efficacy and safety of patiromer in subjects at risk of developing hyperkalaemia receiving standard therapy for HF and initiated with spironolactone. One hundred and five patients with HF and a history of hyperkalaemia resulting in discontinuation of a RAASi and/or beta-adrenergic blocking agent or CKD with an eGFR<60 mL/min/1.73m^2 were randomized to double-blind treatment with 25.2 g/day patiromer or placebo for 4 weeks.

Spironolactone, initiated at 25 mg/day, was increased to 50 mg/day on Day 15 if K+ was ≤5.1 mmol/L. The spironolactone dose remained at 25 mg/day if the serum K+ level was >5.1 to ≤5.5 mmol/L; and patients were discontinued from the study if their serum K+ was ≤3.5 or >5.5 mmol/L

(140). An overview of the PEARL-HF study design is shown in Figure 19. Baseline demographics and characteristics of patients in the PEARL-HF trial are shown in Table 41.

Figure 19: PEARL-HF study design

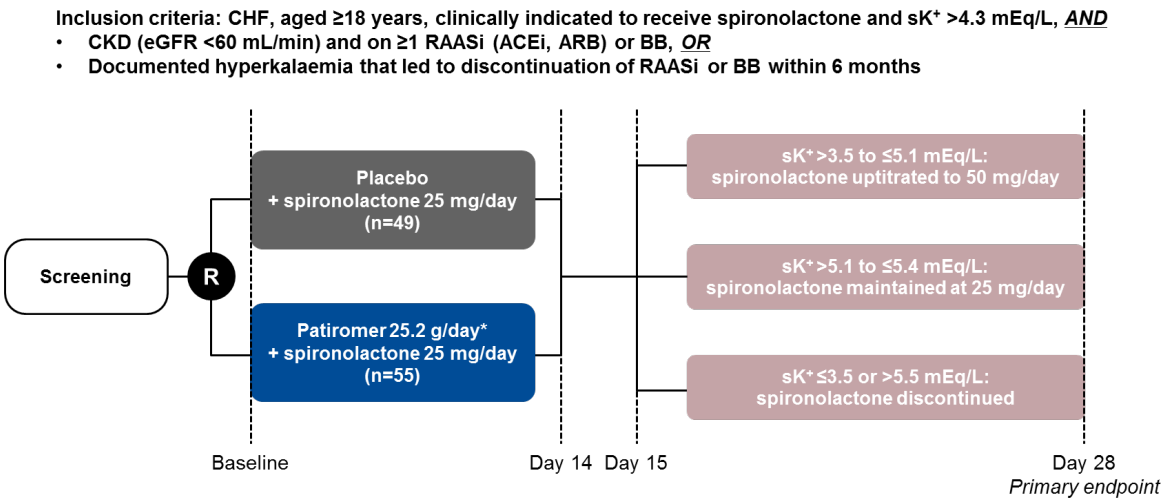


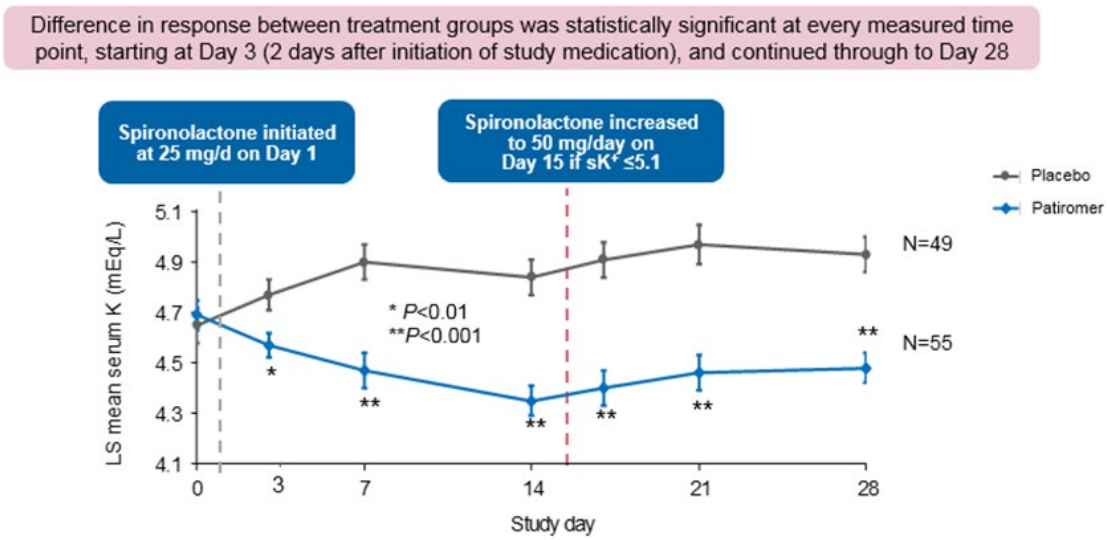
Table 41: Baseline demographics and characteristics of patients in the PEARL-HF trial

Characteristic	Patiromer (n=55)	Placebo (n=49)
Age, years, mean (SD)	68 (9)	68 (11)
Male, n (%)	29 (53)	34 (69)
Caucasian, n (%)	53 (95)	48 (98)
HF duration, years, mean (SD)	5 (5)	4 (3)
LVEF, %, mean (SD)	40 (12)	41 (12)
NYHA class II, n (%)	29 (53)	28 (57)
NYHA class III, n (%)	24 (44)	20 (41)
History of DM, n (%)	15 (27)	18 (37)
Medication at randomisation, n (%)		
ACEi	45 (82)	28 (57)
ARB	9 (16)	12 (24)
BB	45 (82)	46 (94)
ACEi, ARB or BB only	13 (24)	9 (18)
ACEi, ARB + BB	40 (73)	37 (76)
eGFR, mL/min, mean (SD)	84 (35)	78 (32)
Entry criteria, n (%)		
CKD with eGFR <60 mL/min	27 (50)	30 (63)
History of hyperkalaemia	22 (41)	15 (31)
Both of the above	5 (9)	3 (6)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation.
Pitt B, et al. *Eur Heart J*. 2011;32(7):820–8.

A summary of the results of the PEARL-HF trial is shown in Figure 20 and Figure 21. Patiromer significantly lowered serum K+ levels compared with placebo (Figure 20). Patiromer allows for spironolactone dose increase (Figure 21).

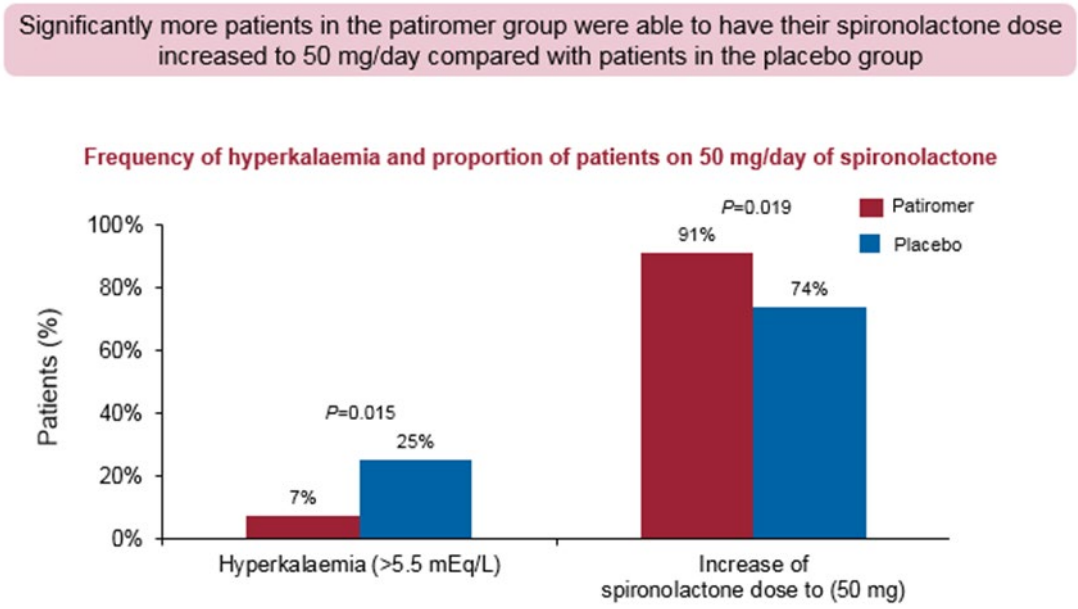
Figure 20: Serum potassium levels over time in patients receiving patiromer vs patients receiving placebo in the PEARL-HF trial



**Patients with HF with reduced ejection fraction.*

HF, heart failure; K+, potassium; MRA, mineralocorticoid receptor antagonist. Source: Pitt et al 2011 (140)

Figure 21: Frequency of hyperkalaemia and proportion of patients on 50 mg/day of spironolactone in the PEARL-HF trial



Source: Pitt et al 2011 (140)

10.1.5 AMBER trial

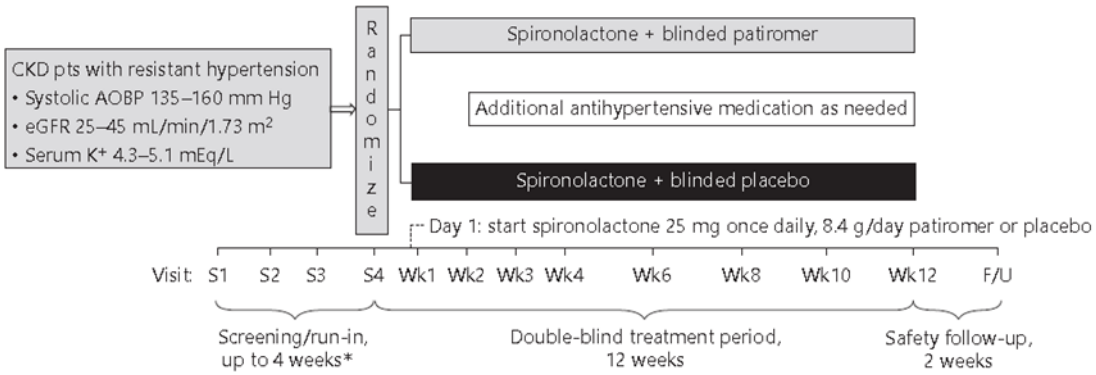
The AMBER trial is a phase 2, randomised, double-blind, placebo-controlled, parallel group study of patiromer for the enablement of spironolactone use for blood pressure control in patients with resistant hypertension and CKD.

The purpose of the study was to determine if patiromer treatment in CKD subjects receiving spironolactone for the treatment of resistant hypertension (RHTN) would result in more persistent use of spironolactone through prevention of hyperkalaemia and lead to improved blood pressure control compared with treatment with spironolactone alone (placebo) [www.clinicaltrials.gov NCT03071263]. The primary study outcome was treatment group difference (spironolactone plus patiromer vs. spironolactone plus placebo) in the proportion of patients remaining on spironolactone at Week 12. The secondary outcome was treatment group difference in systolic blood pressure change by automated office blood pressure (AOBP) measurements from baseline to Week 12 or last available AOBP prior to addition of any new or baseline medications or changes in blood pressure.

Patients aged ≥ 18 years, with CKD (eGFR=25 to ≤ 45 mL/min/1.73m2), uncontrolled high blood pressure, taking at least three medications for blood pressure (one a diuretic) and with normal blood serum potassium (between 4.3 - 5.1 mmol/L) were included in the study.

All eligible patients underwent a screening/run-in period (up to 4 weeks) to determine eligibility for study entry. In total, 295 eligible patients were randomly assigned to receive received at least one dose of spironolactone plus either placebo (n= 147) or patiromer (n=148) starting dose of 8.4g, once a day. Patients were treated for 12 weeks (Treatment Period) and followed for 2 weeks after completing the patiromer or placebo treatment. There were 8 planned clinic visits during the Treatment Period and one planned visit two weeks after the last dose of patiromer or placebo (Follow-up Period). The dose of patiromer or placebo was increased or decreased (titrated) based on patients' individual potassium response. An overview of the study design is shown in Figure 22.

Figure 22: AMBER study design



Source: Agarwal et al. 2018. (141)

Key findings from AMBER

- In advanced CKD with resistant hypertension, patiromer enables more persistent use of spironolactone
    - 86% (patiromer) vs. 66% (placebo), p<0.0001

- Among patients treated with placebo, 2 out of 3 developed hyperkalaemia
    - Patiromer reduced this risk by half.
- Patiromer use allows more spironolactone use
    - 385 mg more over 12 weeks (p=0.0021)
- Spironolactone use associates with 11–12 mmHg reduction in systolic BP from baseline to week 12
    - Change in systolic BP between groups was similar (p=0.58)
- Patiromer's safety profile was consistent with previous reports

Baseline mean systolic AOBP was 144.9 (standard deviation [SD]: 7.0) mmHg in the placebo group and 143.3 (SD: 6.5) mmHg in the patiromer group. Mean serum potassium was 4.69 (SD: 0.37) mmol/L in the placebo group and 4.74 (SD: 0.36) mmol/L in the patiromer group (142).

At 12 weeks, 98 (66.2%) placebo- and 126 (85.7%) patiromer-treated patients remained on spironolactone (between-group difference, 19.5% [95% CI, 10.0, 29.0]; p<0.0001). AMBER met its primary endpoint: patiromer enabled the use of spironolactone in patients with RHTN and CKD.

Least square mean (LSM) changes from baseline in systolic AOBP were -10.8 (95%CI: -13.2, - 8.3) in the placebo group and -11.7 (95%CI: -14.1, -9.3) in the patiromer group, both p<0.0001); LSM difference between groups was -1.0 (95%CI: -4.4, 2.4), p=0.58. Use of spironolactone was associated with a significant and clinically relevant blood pressure reduction in both patiromer and placebo groups with no statistical difference between groups.

Adverse events occurred in 53% of placebo- and 56% of patiromer-treated patients; most were mild or moderate in severity. Patiromer was well tolerated and no new safety signals were identified.

In conclusion, a significantly higher proportion of patients on patiromer (86%) compared with placebo (66%) remained on spironolactone treatment at week 12 (p<0.0001). Among the patients treated with spironolactone and placebo, 2 out of 3 developed hyperkalaemia; patiromer reduced this risk by half.

10.1.6 DIAMOND trial

Overview of NCT03888066 (143)

The purpose of this study is to determine if patiromer treatment in subjects who developed hyperkalaemia while receiving RAASi medications will result in continued use of RAASi medications in accordance with HF treatment guidelines and thereby decrease the occurrence of the combined endpoint of CV death and CV hospitalisation events compared with placebo treatment. This is a prospective, phase 3b, multi-national/multi-centre, double-blind, placebo-controlled, randomised withdrawal, parallel group study that includes screening and 12 weeks Run-in Phase (all subjects will have RAASi medications, including mineralocorticoid receptor antagonist (MRA), optimized) and a randomised withdrawal Blinded Treatment Phase. The study plans to

enrol 2,388 patients. The study started in April 2019 and has an estimated completion date of March 2022 (primary completion estimated for Dec 2021).

Detailed description

Phase 3b multi-national, multi-centre, double-blind, placebo-controlled, randomized withdrawal, parallel group study that includes screening and 12 weeks Run-in Phase (where RAASi medications, including MRA will be optimized for all subjects) and a randomized withdrawal Blinded Treatment Phase.

Subjects with heart failure with reduced ejection fraction (HFrEF) who are hyperkalaemic (serum potassium [K+] >5.0 mmol/L) while receiving treatment with RAASi medications or who are normokalaemic (serum K+ 4.0-5.0 mmol/L) but have a history of hyperkalaemia in the 12 months prior to screening with subsequent reduction or discontinuation of a RAASi medication.

Each subject's participation includes a Run-in Phase (maximum 12 weeks) followed by the Treatment Phase (anticipated to be at least 6 months per subject). The study will continue until the required number of composite endpoint events have occurred. Study duration for individual subjects will vary, depending on the rate of occurrence of composite endpoint events. Given the assumptions underlying the study design, accumulation of the requisite number of composite endpoint events is expected to occur over approximately 2.5 years. Subjects who prematurely discontinue patiromer/placebo will remain in the study for the collection of composite endpoint event data and will receive usual care.

The primary outcome is time to first occurrence of CV death or CV hospitalisation (or equivalent in outpatient clinic). This is to determine if patiromer treatment in subjects who developed hyperkalaemia while receiving RAASi medications will result in continued use of RAASi medications in accordance with HF treatment guidelines and thereby decrease the occurrence of the combined endpoint of CV death and CV hospitalisation events compared with placebo treatment.

The secondary outcomes are:

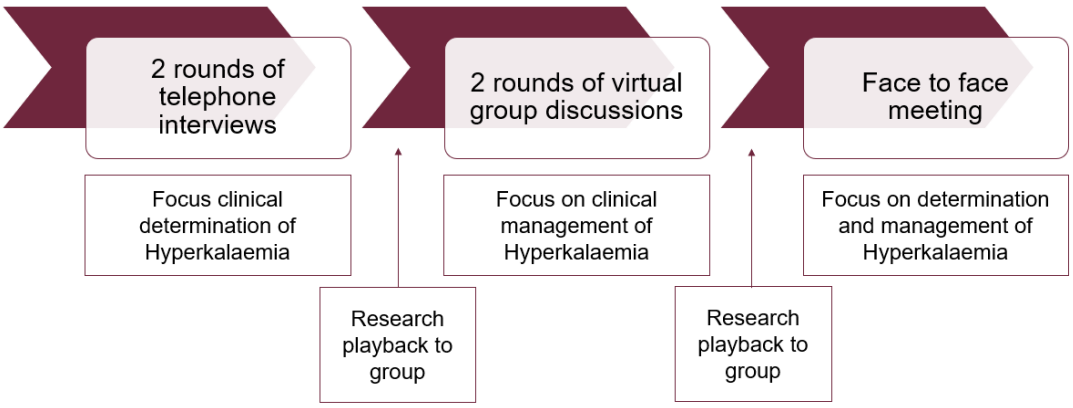
- Proportion of subjects on ≥ 50% of guideline-recommended target dose of angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or ARNi and ≥ 50% of guideline-recommended target dose of MRA at the End of Study Visit
- Total HF hospitalisations (or equivalent in outpatient clinic)
- Patient reported outcome: Kansas City Cardiomyopathy Questionnaire (KCCQ)

10.2 Appendix 2: Physician survey

10.2.1 Modified Delphi process

An overview of the modified Delphi process followed in the physician survey is shown in Figure 23.

Figure 23: Modified Delphi process



All research was conducted in-line with the British Healthcare Business Intelligence Association (BHBIA) Legal and Ethical Guidelines for Healthcare Market Research, overseen by a member of BHBIA.

A similar questionnaire was used for both nephrologists and cardiologists, with tailored questions appropriate for each therapy area. The interview explored when and how patiromer fits into the patient pathway for hyperkalaemia, considering the number of patients treated, comorbidities, current treatments, treatment objectives and the role of dietary control in hyperkalaemia. A copy of the questionnaires can be found in below in Appendix 10.2.1.1.

10.2.1.1. Nephrologist questionnaire

Nephrologist survey.docx

10.2.2 Second round physician survey results

Figure 24: Opinion on how well current treatment for hyperkalaemia allows clinicians to meet their treatment objectives

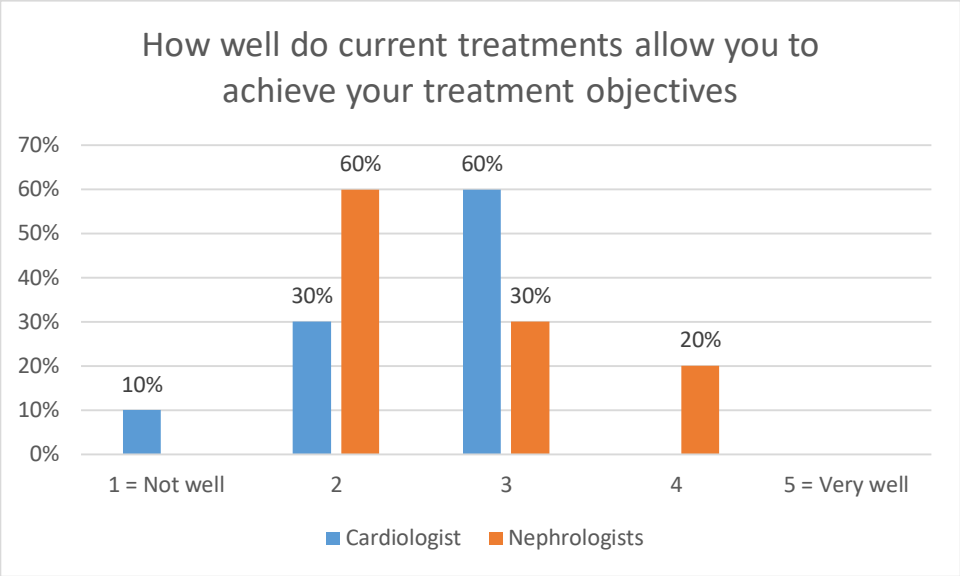


Figure 25: Cardiologist clinical actions, patients with heart failure at varying potassium levels

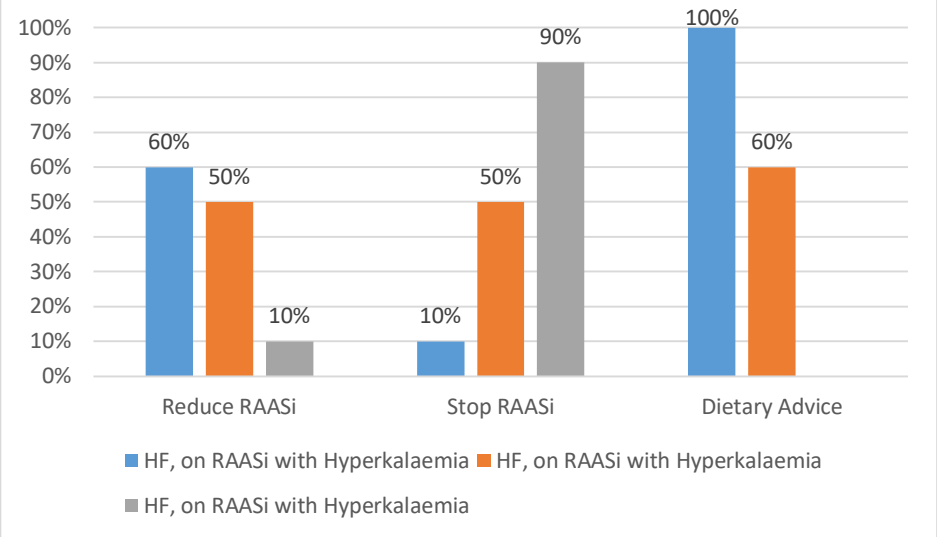
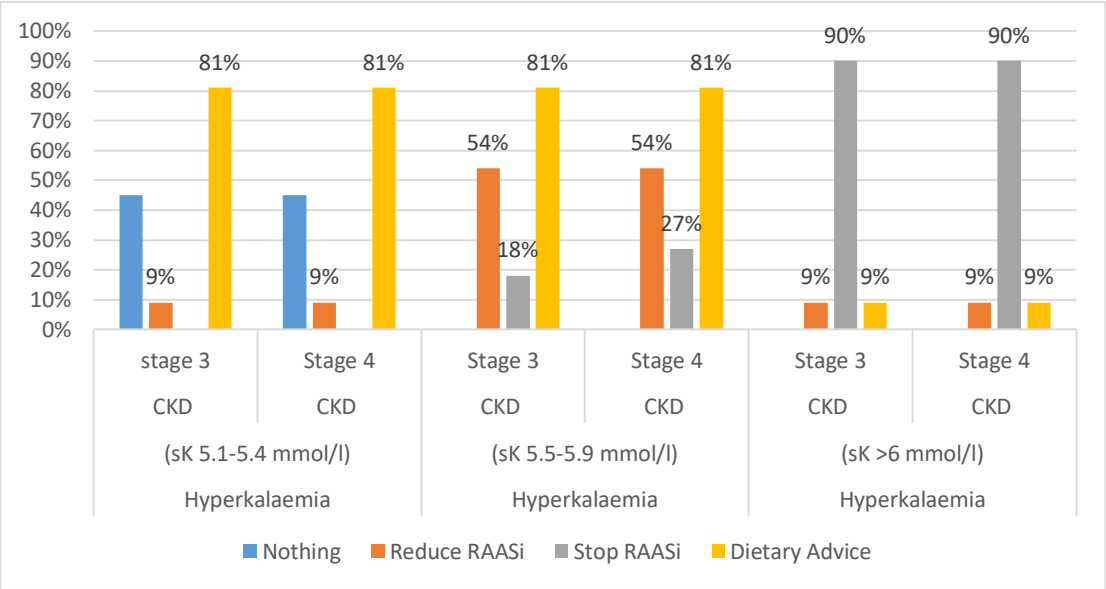


Figure 26: Nephrologist clinical actions, patients with CKD at varying potassium levels



10.2.3 Physician validation of modelling approach and inputs

Method

To seek validation on a number of topics (modelling assumptions and strategies) before making this further submission to NICE, we sought validation through a small group of clinicians in a half day workshop. All participants had previously been engaged in our working group and did receive an honorarium for their participation.

Outputs

Clinicians confirmed that the following patient groups have the greatest unmet clinical need and are therefore patients for whom they would seek to prescribe patiromer:

- Co-morbid CKD patients' stage 3/4, with or without HFrEF
- Proteinuric CKD patients with progression
- CKD patients receiving or in need of triple therapy - ACE, ARB & Spironolactone" (or ARNi) for their HFrEF

Physicians also confirmed that they envisage patiromer prescribing to be initiated in the Specialist Care setting and managed carefully.

The participants were then asked to validate a number of modelling assumption used in the new health economic model, which have been discussed in the economic analysis section.

10.3 Appendix 3: Heart failure patient survey

10.3.1 Heart failure patient opinion poll results

Your Heart Failure Meds 3 min survey.x

10.4 Appendix 4: Targeted literature review

10.4.1 Methods

Search strategy

Medline (including MEDLINE® In-process) and EMBASE database searches were conducted on 21 January 2019.

Ovid search strategies were based on the combination of thematic groups of search words based on the Population, Intervention(s), Comparators, Outcomes and Study design (PICOS) inclusion criteria outlined in Table 42. Detailed search strategies are outlined in Table 43 and Table 44. The search strategy was not limited to publication date. However, all retrieved references were screened for publication year 2008 onwards plus references of publication year 2004 to 2007 were screened for CKD stage 3 to 4 progression outcome. Two single studies from publication year 2001 known to have information on CV events, CV mortality and CKD progression in patients with CKD were included in the extraction.

Table 42: Targeted literature review eligibility criteria for PICOS

	Inclusion	Exclusion
Patient population	• Adult (≥18 years) CKD patients with or without co-morbidities	• Non-human • Children/paediatric population • Patients with disease other than CKD
Interventions	• RAASi	• Interventions other than RAASi
Comparators	• Placebo • Other than RAASi	• None
Outcomes	**Cardiovascular events and mortality** • Major adverse cardiovascular events (MACE) • Death/mortality **CKD progression** • End-stage renal disease (ESRD) • Rate of progression from CKD3 to CKD4 to CKD5/ESRD while on RAASi • Rate of progression from CKD3 to CKD4 to CKD5/ESRD while not on RAASi	• Any studies not providing specific detail on the outcomes of interest

	Serum potassium levels vs mortality • Risk of death vs chronic serum K+ level (<5.0, ≥5.0 to <5.5, ≥5.5 to <6.0, ≥6.0 mmol/L) **Xie NMA validation** • Benefits of starting RAASi vs benefits forgone if RAASi is stopped	
Study design	• Randomised Control Trials • Systematic reviews • Meta-analyses • Observational studies • Single arm trials Note: Single arm trials were included for serum potassium vs mortality and Xie validation outcomes	• Case study, editorials, letters, news and commentaries. • Non-systematic reviews
Restrictions	• English language	• Non-English language

CKD, chronic kidney disease; CKD3, stage 3 chronic kidney disease; CKD4, stage 4 chronic kidney disease; ESRD, end stage renal disease; MACE, major adverse cardiovascular event; NMA. Network meta-analysis; RAASi, renin-angiotensin-aldosterone system inhibitor

Table 43: Search strings for MEDLINE including MEDLINE In process (1946 to January 21 2019)

No.	Search string	Results
Disease search terms		
1	kidney diseases/ or kidney failure/	95,007
2	renal insufficiency, chronic/ or kidney failure, chronic/	105,642
3	((kidney failure or kidney disease or renal disease) and (chronic or end-stage or endstage)).ti,ab.	73,714
4	((chronic or progressive) adj2 (renal or kidney)).ti,ab.	76,149
5	(chronic adj (kidney or renal) adj insufficienc*).ti,ab.	4,878
6	(CKD or CKF or CRF or CRD).ti,ab.	39,335
7	("end stage kidney disease" or "end stage kidney failure" or "end stage renal dysfunction" or "end stage renal failure" or "end stage renal impairment" or "end stage renal insufficiency" or "end-stage kidney disease" or "end-stage kidney failure" or "end-stage renal disease" or esrd or "stage 5 kidney disease" or "stage 5 renal disease").ti,ab.	39,289
8	(renal insufficienc* or kidney insufficienc*).ti,ab.	21,590
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	261,392
Intervention search terms		
10	angiotensin-converting enzyme inhibitors/	31,353
11	angiotensin converting enzyme inhibit*.tw.	19,044
12	(ace adj2 inhibit*).tw.	18,735

No.	Search string	Results
13	(ACE or ACE1 or ACEI or ACE-I or ACEs).mp.	35,582
14	captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ or teprotide/	21,542
15	(alacepril or benazepril or benazeprila or benazeprilat or captopril or ceranapril or ceronapril or cilazapril or cilazaprilat or deacetylalacepril or delapril or enalapril or enalaprilat or fosinopril or fosinoprilic acid or imidapril or libenzapril or lisinopril or moexipril or perindopril or quinapril or quinaprilat or ramipril or ramiprilat or rentiapril or spirapril or temocapril or teprotide or trandolapril or zofenopril).tw.	25,638
16	(innovace* or innozide* or zestril* or carace* or zestoretic* or coversyl* or accupro* or accuretic* or tritace* or triapin* or vascace* or capoten* or capozide* or cozidocapt* or zidocapt* or gopten* or tarka* or tanatril* or perdix*).tw.	556
17	angiotensin ii type 1 receptor blockers/	8,269
18	angiotensin ii type 2 receptor blockers/	517
19	(angiotensin adj2 receptor antagonist*).tw.	2,972
20	(angiotensin 2 receptor antagonist or angiotensin receptor antagonist or angiotensin II antagonist or AT 2 receptor blocker or AT 2 receptor antagonist or ARB or ARBs).tw.	6,851
21	losartan/ or saralasin/ or valsartan/	9,809
22	(azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or olmesartan or saprisartan or saralasin or tasosartan or telmisartan or valsartan or vasvalsartan or zolasartan).tw.	18,056
23	(amias* or aprovel* or atacand* or avalide* or avapro* or benicar* or coaprovel* or codiovan* or cozaar* or diovan* or edarbi* or miardis* or micardis* or olmetec* or sevikar* or teveten*).tw.	228
24	aldosterone antagonists/	4,569
25	spironolactone/	6,493
26	(eplerenone* or spironolactone*).tw.	6,160
27	(alaton* or aldactone* or crl635 or crl635 or coflumactone* or flumactone* or inspra* or lasilactone* or osiren* or osyrol* or prilactone* or sas 1060 or sas1060 or sc 9420 or sc9420 or spiractin* or spiridon* or spiro ct or spiroctan* or spirohexal* or spirolang* or uractone* or verospiron* or xenalon*).tw.	515
28	("cgp 30 083" or cgp 30083 or cgp30083 or sc 66110 or sc66110).tw.	0
29	(aliskiren* or rasilez*).tw.	1,058
30	((angiotensin* or renin or aldosterone or ACE) adj5 (antagonist* or blocker* or inhibitor*)).tw.	47,558
31	(RAAS or RAS or RASI or RAASi or RAAS inhibit* or renin angiotensin aldosterone system inhibit*).tw.	54,554
32	(angiotensin receptor neprilysin inhibitor* or ARNi).tw.	252
33	(valsartan and sucubitril).ti,ab.	1
34	(entresto or lcz 696 or lcz696 or neparvis or "valsartan plus	220

No.	Search string	Results
	sucubitril").tw.	
35	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	153,230
Systematic reviews and meta-analysis search terms		
36	exp review literature as topic/	10,245
37	meta-analysis as topic/ or meta-analysis/	111,641
38	((meta adj analy*) or metaanalys*).tw.	135,364
39	(systematic adj2 (review* or overview*)).tw.	134,056
40	(cancerlit or cochrane or embase or medline or pubmed or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or reference list* or bibliography* or hand search* or manual search* or relevant journals).ab.	187,008
41	(search strategy or search criteria or systematic search or data extraction or selection criteria).ab.	58,875
42	review/	2,440,203
43	41 and 42	38,822
44	36 or 37 or 38 or 39 or 40 or 43	329,861
45	9 and 35 and 44	370
Randomized controlled trials search terms		
46	randomized controlled trials as topic/ or randomized controlled trial/ or random allocation/ or single blind method/ or double blind method/ or clinical trial/ or control groups/	976,265
47	exp clinical trials as topic/	320,731
48	(randomized controlled trial* or randomised controlled trial* or rct).tw.	150,256
49	(random* adj2 allocat*).tw.	30,664
50	(random allocation or randomly allocated or allocated randomly).tw.	28,511
51	(single blind* or double blind*).tw.	154,786
52	((treble or triple) adj blind*).tw.	691
53	placebos/ or placebo*.tw.	211,123
54	46 or 47 or 48 or 49 or 50 or 51 or 52 or 53	1,216,896
55	9 and 35 and 54	2,128
Observational studies search terms		
56	clinical study/ or case-control studies/ or longitudinal studies/ or retrospective studies/ or cohort studies/ or comparative study/ or cross-sectional studies/	3,068,270
57	((cohort or case control or follow up or observational or cross sectional) adj (study or studies)).tw.	498,500
58	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.	115,452
59	((longitudinal or longterm or long term) adj7 (study or studies or design	230,191

No.	Search string	Results
	or analysis or analyses or data or cohort)).ti,ab.	
60	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.	401,979
61	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.	379,947
62	56 or 57 or 58 or 59 or 60 or 61	3,657,699
63	9 and 35 and 62	2,489
64	45 or 55 or 63	4,070
Exclusion search terms		
65	letter/ or editorial/ or news/ or anecdotes as topic/ or comment/ or case report/	3,572,953
66	exp historical article/	385,739
67	(letter or comment*).ti.	131,534
68	exp animals, laboratory/	829,546
69	exp animal experimentation/	8,907
70	exp models, animal/	525,550
71	exp rodentia/	3,079,616
72	(rat or rats or mouse or mice).ti.	1,270,047
73	animal/	6,330,102
74	human/	17,487,680
75	73 not (73 and 74)	4,502,731
76	65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 75	9,204,689
77	64 not 76	3,615
Limits		
78	limit 77 to english language	3331

Table 44: Search strings for EMBASE (1974 to 21 January 2019)

No.	Search term	Results
Disease search terms		
1	kidney disease/ or kidney failure/	219,882
2	chronic kidney disease/ or chronic kidney failure/	124,093
3	((kidney failure or kidney disease or renal disease) and (chronic or end-stage or endstage)).ti,ab.	113,258
4	((chronic or progressive) adj2 (renal or kidney)).ti,ab.	111,987
5	(chronic adj (kidney or renal) adj insufficienc*).ti,ab.	5,944
6	(CKD or CKF or CRF or CRD).ti,ab.	62,691
7	exp end stage renal disease/	23,887

No.	Search term	Results
8	("end stage kidney disease" or "end stage kidney failure" or "end stage renal dysfunction" or "end stage renal failure" or "end stage renal impairment" or "end stage renal insufficiency" or "end-stage kidney disease" or "end-stage kidney failure" or "end-stage renal disease" or esrd or "stage 5 kidney disease" or "stage 5 renal disease").ti,ab.	58,075
9	(renal insufficienc* or kidney insufficienc*).ti,ab.	28,509
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	405,429
Intervention search terms		
11	*dipeptidyl carboxypeptidase inhibitor/	22,584
12	angiotensin converting enzyme inhibit*.tw.	24,374
13	(ace adj2 inhibit*).tw.	28,679
14	(ACE or ACE1 or ACEI or ACE-I or ACEs).mp.	57,864
15	alacepril/ or benazepril/ or benazeprilat/ or captopril/ or ceranapril/ or cilazapril/ or cilazaprilat/ or deacetylalacepril/ or delapril/ or enalapril maleate/ or enalapril/ or enalaprilat/ or fosinopril/ or fosinoprilat/ or imidapril/ or libenzapril/ or lisinopril/ or moexipril/ or perindopril/ or quinapril/ or quinaprilat/ or ramipril/ or ramiprilat/ or rentiapril/ or spirapril/ or temocapril/ or teprotide/ or trandolapril/ or zofenopril/	83,940
16	(alacepril or benazepril or benazeprila or benazeprilat or captopril or ceranapril or ceronapril or cilazapril or cilazaprilat or deacetylalacepril or delapril or enalapril or enalaprilat or fosinopril or fosinoprilic acid or imidapril or libenzapril or lisinopril or moexipril or perindopril or quinapril or quinaprilat or ramipril or ramiprilat or rentiapril or spirapril or temocapril or teprotide or trandolapril or zofenopril).tw.	35,112
17	(innovace* or innozide* or zestril* or carace* or zestoretic* or coversyl* or accupro* or accuretic* or tritace* or triapin* or vascace* or capoten* or capozide* or cozidocapt* or zidocapt* or gopten* or tarka* or tanatril* or perdix*).tw.	2,625
18	angiotensin receptor antagonist/	37,320
19	angiotensin ii type 1 receptor blockers/	5,270
20	angiotensin ii type 2 receptor blockers/	6,908
21	(angiotensin adj2 receptor antagonist*).tw.	4,078
22	(angiotensin 2 receptor antagonist or angiotensin receptor antagonist or angiotensin II antagonist or AT 2 receptor blocker or AT 2 receptor antagonist or ARB or ARBs).tw.	13,243
23	azilsartan/ or candesartan/ or elisartan/ or embusartan/ or eprosartan/ or forasartan/ or irbesartan/ or losartan/ or losartan potassium/ or olmesartan/ or saprisartan/ or saralasin/ or tasosartan/ or telmisartan/ or valsartan/ or zolasartan/	48,363
24	(azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or olmesartan or saprisartan or saralasin or tasosartan or telmisartan or valsartan or vasvalsartan or zolasartan).tw.	27,370
25	(amias* or aprovel* or atacand* or avalide* or avapro* or benicar* or coaprovel* or codiovan* or cozaar* or diovan* or edarbi* or miardis* or micardis* or olmetec* or sevikar* or teveten*).tw.	2,201

No.	Search term	Results
26	aldosterone antagonist/	7,171
27	spironolactone/ or eplerenone/	29,729
28	(eplerenone* or spironolactone*).tw.	9,269
29	(alaton* or aldactone* or crl635 or crl635 or coflumactone* or flumactone* or inspra* or lasilactone* or osiren* or osyrol* or prilactone* or sas 1060 or sas1060 or sc 9420 or sc9420 or spiractin* or spiridon* or spiro ct or spiroctan* or spirohexal* or spirolang* or uractone* or verospiron* or xenalon*).tw.	2,530
30	("cgp 30 083" or cgp 30083 or cgp30083 or sc 66110 or sc66110).tw.	18
31	renin inhibitor/	3,156
32	aliskiren/	3,163
33	(aliskiren* or rasilez*).tw.	1,917
34	((angiotensin* or renin or aldosterone or ACE) adj5 (antagonist* or blocker* or inhibitor*)).tw.	68,337
35	(RAAS or RAS or RASI or RAASi or RAAS inhibit* or renin angiotensin aldosterone system inhibit*).tw.	74,020
36	(angiotensin receptor neprilysin inhibitor* or ARNi).tw.	524
37	(valsartan and sucubitril).ti,ab.	1
38	(entresto or lcz 696 or lcz696 or neparvis or "valsartan plus sucubitril").tw.	774
39	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	292,545
Systematic reviews and meta-analysis search terms		
40	systematic review/	191,444
41	exp meta analysis/	156,388
42	((meta adj analy*) or metaanalys*).tw.	185,144
43	(systematic adj2 (review* or overview*)).tw.	175,947
44	(cancerlit or cochrane or embase or medline or pubmed or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or reference list* or bibliography* or hand search* or manual search* or relevant journals).ab.	241,336
45	(search strategy or search criteria or systematic search or data extraction or selection criteria).ab.	75,888
46	review.pt.	2,398,302
47	45 and 46	35,090
48	40 or 41 or 42 or 43 or 44 or 47	456,331
49	10 and 39 and 48	1,211
Randomized controlled trials search terms		
50	clinical trial/ or clinical trial topic/ or randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or prospective study/ or crossover-procedure/ or double-blind procedure/ or single-blind	1,897,928

No.	Search term	Results
	procedure/ or control group/	
51	exp randomization/	81,042
52	(randomized controlled trial* or randomised controlled trial* or rct).tw.	209,646
53	(random* adj2 allocat*).tw.	38,809
54	(random allocation or randomly allocated or allocated randomly).tw.	35,940
55	(single blind* or double blind*).tw.	214,618
56	((treble or triple) adj blind*).tw.	904
57	placebo/ or placebo*.tw.	424,580
58	50 or 51 or 52 or 53 or 54 or 55 or 56 or 57	2,239,538
59	10 and 39 and 58	8,226
Observational studies search terms		
60	clinical study/ or case control study/ or longitudinal study/ or retrospective study/ or cohort analysis/ or comparative study/ or cross-sectional study/	2,369,403
61	((cohort or case control or follow up or observational or cross sectional) adj (study or studies)).tw.	714,633
62	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.	187,347
63	((longitudinal or longterm or long term) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.	333,618
64	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.	680,095
65	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.	572,255
66	60 or 61 or 62 or 63 or 64 or 65	3,352,592
67	10 and 39 and 66	5,117
68	49 or 59 or 67	11,747
Exclusion search terms		
69	letter/ or case report/ or case study/	3,170,891
70	(letter or note or editorial).pt.	2,390,446
71	(letter or comment*).ti.	179,877
72	nonhuman/ or animal model/	5,742,749
73	exp animal experiment/	2,322,799
74	exp experimental animal/	603,605
75	exp rodent/	3,341,613
76	(rat or rats or mouse or mice).ti.	1,397,699
77	animal/	1,399,020
78	human/	19,126,355
79	77 not (77 and 78)	1,025,177

No.	Search term	Results
80	69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 79	11,927,225
81	68 not 80	9,435
Limits		
82	limit 81 to english language	8,892

Study selection

The first stage involved the review of the records title and abstract by one researcher against the pre-determined eligibility criteria for PICOS presented in Table 42. Uncertain records were discussed with a second reviewer and were included for full text review if uncertainty remained. After abstract screening, full-text articles of the included abstracts were retrieved and screened by one researcher based on the same PICOS criteria. A second reviewer screened 15% of the total studies at random against the PICOS criteria as a quality control measure. All papers included after completion of the full text review were retained for data extraction.

Data extraction

Following the full-text review, data extraction was performed by one researcher, documented in MS Excel data extraction templates, and reviewed by a second researcher. Data on study design, selection criteria, patient population and outcomes were extracted.

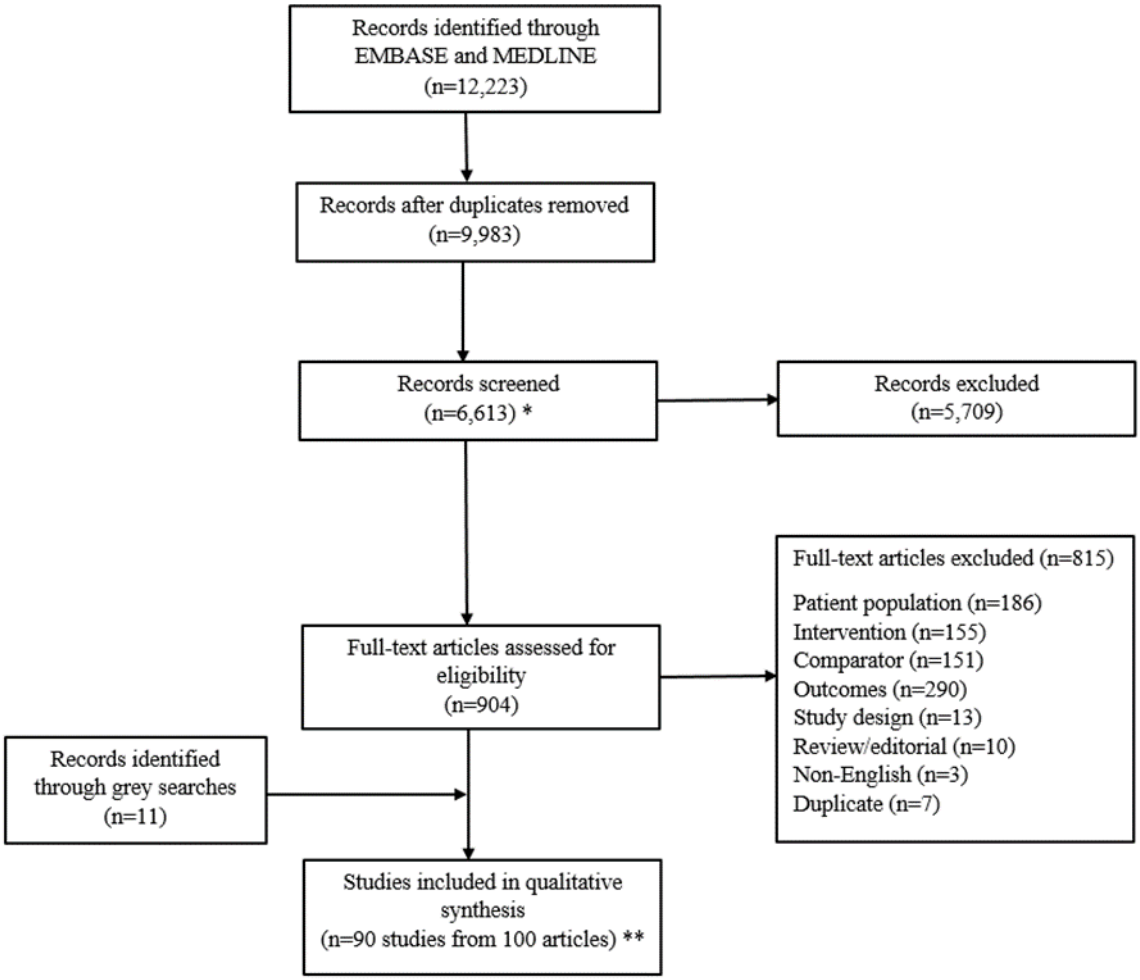
Data extraction was performed separately for each of the four outcomes of interest: 1) CV events and mortality, 2) CKD progression, 3) serum potassium levels vs mortality, and 4) Xie NMA validation. If a study reported two outcomes of interest, then the study was captured in each relevant outcome extraction template.

10.4.2 Studies included in extraction

10.4.2.1. PRISMA diagram

The number of studies included and excluded at each stage of the selection process is shown in the PRISMA diagram provided in Figure 27.

Figure 27: PRISMA flow diagram



**Abstracts of publication year 2008 onwards were included for screening purpose*

*** Systematic literature reviews/meta-analyses = 15 studies extracted; Single studies=75 unique studies extracted from 85 articles*

10.4.2.2. Complete list of included studies

Included SLR studies are shown in Table 45. Included single studies are shown in Table 46.

Table 45: Included SLR/MA studies, stratified by outcome.

Study	Outcomes			
	CV events & mortality	CKD progression	Serum potassium vs mortality	Xie NMA validation
Balamuthusamy et al 2008 (61)	X			
Xie et al. 2016 (46)	X	X		
Fink et al. 2012 (84)	X	X		
Kovesdy et al. 2018* (96)	X		X	

Study	Outcomes			
	CV events & mortality	CKD progression	Serum potassium vs mortality	Xie NMA validation
Qin et al. 2016 (85)	X			
Sharma et al. 2011 (65)	X	X		
Ninomiya et al. 2013 (63)	X			
Ng et al. 2015* (87)	X	X	X	
Nistor et al. 2018 (64)	X	X		
Lin et al. 2017 (77)	X	X		
Lu et al. 2016 (144)	X		X	
Sun et al. 2016 (76)	X			
Hoppe et al. 2018 (95)			X	
Vukadinovic et al. 2017 (145)			X	
Zhao et al. 2016 (86)	X	X		

** Note: Data on CV event and mortality outcomes in Kovesdy et al 2018 and Ng et al 2015 CKD were not sufficient to extract, chronic kidney disease; CV, cardiovascular; NMA, network meta-analysis*

Table 46: Included single studies, stratified by outcome

Study	Outcomes			
	CV events & mortality	CKD progression	Serum potassium vs mortality	Xie NMA validation
Guo et al. 2017 (66)	X			
Watanabe et al. 2011 (146)	X			
Anand et al. 2009 (58)	X	X		
Hsing et al. 2015 (78)	X	X		
Oh et al. 2017 (92)	X	X		
Vejakama et al. 2017 (89)	X	X		
Molnar et al. 2014 (22)	X			
Tseng et al. 2017 (69)	X			
Saruta et al. 2009 (73)	X			
Bowling et al. 2013 (60)	X			
Lee et al. 2018 (79)	X			
Beldhuis et al. 2019 (59)	X			
Yasuda et al. 2013 (147)	X	X		
Liao et al. 2017 (148)	X			
Matsumoto et al. 2014 (72)	X			
Agarwal et al. 2014 (74)	X			

Study	Outcomes			
	CV events & mortality	CKD progression	Serum potassium vs mortality	Xie NMA validation
Lin et al. 2016 (144)	X			
Saito et al. 2012 (149)		X		
Tokunaga et al. 2010 (150)		X		
Edwards et al. 2012 (151)		X	X	
Voskamp et al. 2017 (152)		X		
Gorriz et al. 2017 (153)			X	
Hsieh et al. 2011 (154)			X	
Jenkins et al. 2017 (155)			X	
Furuland et al. 2018 (102)			X	
Qin et al. 2017* (156)			X	
Luo et al. 2016 (103)			X	
Garlo et al. 2018 (106)			X	X
Boesby et al. 2013 (157)			X	
Bennett et al. 2017* (98)				X
Goncalves et al. 2011 (110)				X
Ahmed et al. 2010 (109)				X
Bainey et al. 2015 (158)				X
Onuigbo et al. 2008 (111)				X
Epstein et al. 2015 (17)				X
Charytan et al. 2019 (81)	X		X	
Einhorn et al. 2009 (159)			X	
Onuigbo et al. 2008 (160)				X
Bermejo et al. 2018 (161)	X	X		
Ku et al. 2018 (162)	X			
Omae et al. 2010 (94)		X		
Mimura et al. 2008 (163)	X			
Bajaj et al. 2011 (164)	X			
Ninomiya et al. 2008 (165)	X			
Ahmed et al. 2009 (57)	X			
Arora et al. 2015 (93)	X	X		
Yang et al. 2015 (70)	X			
Shen et al. 2017 (80)	X			
Sud et al. 2016 (132)		X		
Arora et al. 2017 (166)		X		

Study	Outcomes			
	CV events & mortality	CKD progression	Serum potassium vs mortality	Xie NMA validation
Hsu et al. 2014 (167)	X			
Moriyama et al. 2011 (168)		X		
Wang et al. 2012 (169)		X		
Parving et al. 2012 (83)	X	X	X	
Kim-Mitsuyama et al. 2018 (71)	X	X		
Ovbiagele et al. 2012 (67)	X			
Yoo et al. 2018 (68)	X			
Daniela et al. 2012 (170)		X	X	
Wu et al. 2015 (75)	X			
Sengul et al. 2009 (171)			X	
Dattolo et al. 2016 (172)		X		
Fogelfeld et al. 2017 (173)		X	X	
Yamashita et al. 2011 (174)		X		
Collins et al. 2017 (29)			X	
Thomsen et al. 2018 (100)			X	
Trevisan et al. 2018 (99)			X	
Orlando et al. 2007 (175)		X		
Jovanovich et al. 2015 (88)	X	X		
Gillis et al. 2017 (90)		X	X	
Zeng et al. 2015 (176)		X		
Lewis et al. 2001 (91)	X	X		
Provenzano et al. 2018 (105)		X		
Iseki et al. 2013 (82)	X			
Jun et al. 2019 (104)			X	
Cozzolino et al. 2018 (177)		X		
Brenner et al. 2001 (23)	X	X		

**Note, Quin 2017 and Bennett 2017 reported on same study but provided data for different outcomes, so both were included in the extraction. CKD, chronic kidney disease; CV, cardiovascular; NMA, network meta-analysis*

10.4.2.3. Study design of included single studies

The study designs of included single studies are summarised in Table 47.

Table 47: Study design summary of included single studies

Author & Year	Country	Study design	CKD stage	Intervention/comparator	Follow-up duration
Guo 2017 (66)	China	Observational study (prospective)	NR	ACEis/ARBs vs. No ACEis/ARBs	Median: 2.59 years
Watanabe 2011 (146)	NR	RCT	Stage 3 or 4	Telmisartan vs. Imadipril vs. Amlodipine	Median: 5.1 years
Anand 2009 (58)	USA	RCT	NR	Valsartan vs. Placebo	23 months
Hsing 2015 (78)	Taiwan	Observational study (prospective)	NR	Losartan vs. Ramipril vs. Other anti-hypertensive drugs	5.9 years
Oh 2017 (92)	Korea	Observational study (retrospective)	Stage 4 or 5	ACEis/ARBs vs. No ACEis/ARBs	28 months
Vejakama 2017 (89)	Thailand	Observational study (retrospective)	NR	RAAS blockers (3 months to 1 year) vs. RAAS blockers (>1 year) vs. No RAAS blockers	Diabetic group: 4.7 years Non-diabetic groups: 4.2 years
Molnar 2014 (22)	USA	Observational study	Stage 1-5	ACEis/ARBs vs. No ACEis/ARBs	Median cohort time was 4.7 years (IQR: 3.6 to 5.2 years)
Tseng 2017 (69)	Taiwan	Observational study	Stage 5	Spironolactone vs. No spironolactone	Median: 31 months
Saruta 2009 (73)	Japan	Sub analysis of RCT	Stage 1+2, 3, and 4	Candesartan vs. Amlodipine	3.2 years
Bowling 2013 (60)	Belgium, Canada, and USA	RCT	Undefined and stage ≥3B	Enalapril vs. Placebo	Median: 35 months
Lee 2018 (79)	Taiwan	Observational study (retrospective)	ESRD	ACEis/ARBs vs. No ACEis/ARBs	5 years from the date of first dialysis to the date of death, or December 31, 2013, whichever was earlier.

Author & Year	Country	Study design	CKD stage	Intervention/comparator	Follow-up duration
Beldhuis 2019 (59)	USA	RCT	Stage 1+2, 3A, and 3B	Spironolactone vs. Placebo	Mean: 3.3 years
Yasuda 2013 (147)	Japan	RCT	Stage 3, 4, and 5	Valsartan vs. Control	Median: 23.8 months
Liao 2017 (148)	Taiwan	Observational study (retrospective)	Stage 4 or 5	Adherent to ACEi/ARB exposure vs. Non-adherent to ACEi/ARB exposure vs. No ACEis/ARBs	December 31, 2009
Matsumoto 2014 (72)	Japan	RCT	ESRD	Spironolactone vs. Control	3 years
Agarwal 2014 (74)	USA	RCT	ESRD	Lisinopril vs. Atenolol	Lisinopril: 74.1 PYs Atenolol: 81.2 PYs
Lin 2016 (144)	China	RCT	ESRD	Spironolactone vs. Placebo	2 years
Saito 2012 (149)	Japan	Observational study (prospective)	NR	Olmesartan medoxomil (12-weeks) vs Azelnidipine (12-weeks) vs Olmesartan medoxomil (2-years)	OLM :12 weeks AZ: 12 weeks OLM: 2 years
Tokunaga 2010 (150)	NR	Observational study (retrospective)	Stage 3-4	Telmisartan vs Control	Telmisartan, median: 15.0 months Control, median: 13.1 months
Edwards 2012 (151)	UK	RCT	Stage 2 or 3	ACEi/ARB + spironolactone vs ACEi/ARB + placebo	40 weeks
Voskamp 2017 (152)	NR	Observational study (prospective)	Stage 4-5	ACEi vs ARB vs No ACEi/ARB	Followed until start of dialysis, transplantation, death or September 2012
Gorriz 2017 (153)	Spain	Observational study (prospective)	Stage 4-5	RAAS blockade vs No RAAS blockade	Mean: 47 months
Hsieh 2011 (154)	Taiwan	Observational study	Stage 3-5	ACEi/ARB vs No ACEi/ARB	1 year
Jenkins 2017 (155)	UK	Observational study (retrospective)	Stage 0-5	ACEi/ARB and MRA prescription	NR

Author & Year	Country	Study design	CKD stage	Intervention/comparator	Follow-up duration
Furuland 2018 (102)	UK	Observational study (retrospective)	Stage 3A-5	ACEs, ARBs and MRAs	4.96 years
Qin 2017 (156)	UK	Observational study (retrospective)	Stage 3A-5	Diuretics, ACEis, ARBs, MRAs, and CCBs	Mean: 4.9 years
Luo 2016 (103)	USA	Observational study (retrospective)	NR	RAAS blockers	Median: 2.76 years
Garlo 2018 (106)	USA	Observational study (prospective)	Stage 3-5	RAASIs (lisinopril, valsartan, and losartan potassium) vs Diuretics (Furosemide, hydrochlorothiazide, and combined triamterene and hydrochlorothiazide)	Follow-up extended to December 31, 2012
Boesby 2013 (157)	Denmark	RCT	Stage 3-4	Eplerenone vs Control (standard medication)	24 weeks
Bennett 2017 (98)	UK	Real-world study	Stage 3A-5	RAASi (ACEi, ARB, MRA, and renin inhibitors)	Mean: 4.9 years
Goncalves 2011 (110)	UK	Observational study	Stage 4	RAASi	24 months
Ahmed 2010 (109)	UK	Observational study	Stage 4-5	ACEi/ARB stoppage	12 months
Bainey 2015 (158)	Canada	RCT	Stage 1-3	Hold vs Continue ACEi/ARB prior to cardiac catheterization	NR
Onuigbo 2008 (111)	USA	Observational study (prospective)	NR	RAAS blockade withdrawal vs RAAS blockade	Mean: 26.4 months
Epstein 2015 (17)	USA	Observational study	Stage 3-4	RAASi vs Stop RAASi	3.4 years
Charytan 2019 (81)	USA	RCT	ESRD	Spironolactone 12.5 mg vs. Spironolactone 25 mg vs. Spironolactone 50 mg vs. Placebo	40 weeks
Einhorn 2009 (159)	NR	Observational study (retrospective)	Stage 3-5	RAAS blockers vs No RAAS blockers	NR
Onuigbo	USA	Observational study	Stage 3-5	Discontinuation of RAAS blockade	Mean: 4 years

Author & Year	Country	Study design	CKD stage	Intervention/comparator	Follow-up duration
2008 (160)		(prospective)			
Bermejo 2018 (161)	Spain	Observational study (retrospective)	Stage <3, 4/5	Inconstant RAAS blockers vs. Constant RAAS blockers vs. No RAAS blockers	At least 1-year
Ku 2018 (162)	USA	Observational study	Stage 2, 3A, 3B, 4-5	ACEis/ARBs vs. CCBs vs. β-blockers	Median: 7 years
Omae 2010 (94)	Japan	Observational study (retrospective)	Stage 2-4	ACEi vs ARB vs CCB	NR
Mimura 2008 (163)	NR	RCT	NR	ACEis/ARBs vs. No ACEis/ARBs	4 years
Bajaj 2011 (164)	Canada	Observational study (retrospective)	ESRD	ACEis/ARBs vs. CCBs vs. Statin only	ACEis/ARBs, mean: 2.4 years CCBs, mean: 2.6 years Statin only, mean: 2.1 years
Ninomiya 2008 (165)	Japan	RCT	Stage 3 and 4	Perindopril vs. Placebo	1st year: 1, 3, 6, 9, and 12 months 2nd years: 6 months
Ahmed 2009 (57)	USA	Observational study	NR	ACEis/ARBs vs. No ACEis/ARBs	4 years
Arora 2015 (93)	USA	Observational study (retrospective)	Stage 5	RAAS blockers vs. Other anti-hypertensive drugs	Median: 785 days
Yang 2015 (70)	Taiwan	Observational study (prospective)	ESRD	ARBs (short-term use) vs. ARBs (long-term use) vs. No ARBs	Until the study endpoint/5 years after enrollment.
Shen 2017 (80)	USA	Observational study	ESRD	ACEis/ARBs vs. No ACEis/ARBs	Median: 1.2 years
Sud 2016 (132)	Canada	Observational study (retrospective)	Stage 3	No intervention	Median: 2.66 years
Arora 2017 (166)	USA	Observational study	Stage 3A-4	No intervention	Followed over a 6-year period ending on March 1, 2008
Hsu 2014 (167)	Taiwan	Observational study (prospective)	Stage 5	ACEis/ARBs vs. No ACEis/ARBs	Median: 7 months
Moriyama	Japan	Observational study	Stage 3-4	ACEi vs ARB vs Control (anti-platelet agents)	ACEi, median: 6 years

Author & Year	Country	Study design	CKD stage	Intervention/comparator	Follow-up duration
2011 (168)		(retrospective)			ARB, median: 6 years Control, median: 5 years
Wang 2012 (169)	China	RCT	Stage 3	Benazepril vs TCM + Benazepril vs TCM	24 weeks
Parving 2012 (83)	North America, South America, Europe, Asian Pacific, and Africa	RCT	NR	Aliskerin vs. Placebo	Median: 32.9 months
Kim-Mitsuyama 2018 (71)	Japan	RCT	Stage 3B, 4/5	ARBs vs. No ARBs	NR
Ovbiagele 2012 (67)	NR	RCT	NR	Telmisartan vs. Placebo	2.5 years
Yoo 2018 (68)	Korea	Observational study (prospective)	ESRD	RAAS blockers vs. No RAAS blockers	NR
Daniela 2012 (170)	NR	Observational study (prospective)	Stage 3	ACEi/ARB	4 years
Wu 2015 (75)	Taiwan	Observational study	ESRD	ACEis/ARBs vs. No ACEis/ARBs	Median: 1428 days
Sengul 2009 (171)	NR	Observational study (prospective)	NR	Spironolactone	NR
Dattolo 2016 (172)	NR	Observational study (retrospective)	Stage 5	ACEi vs No ACEi	NR
Fogelfeld 2017 (173)	USA	RCT	Stage 3A-4	Multifactorial-multidisciplinary intervention combined coordinated medical care vs Control	Intervention, mean: 82.95 weeks Control, mean: 84.05 weeks
Yamashita 2011 (174)	Japan	Observational study (retrospective)	Stage 1-5	Medication (ARB, ACEi, CCB, β-blocker, statin, diuretics, anti-platelet)	5 years
Collins 2017 (29)	USA	Observational study	Stage 3-5	RAASi medications, thiazide or loop diuretics	Mean: 18 months

Author & Year	Country	Study design	CKD stage	Intervention/comparator	Follow-up duration
Thomsen 2018 (100)	Denmark	Observational study	Stage 1-5	ACEi, ARB, spironolactone, and potassium supplements	6 months
Trevisan 2018 (99)	Sweden	Observational study	Stage 1-5	Spironolactone or eplerenone	1 year
Orlando 2007 (175)	USA	Observational study (retrospective)	Stage 1-5	ACEi and anti-lipid medications	Mean: 1,296 days
Jovanovich 2015 (88)	USA	Post-hoc analysis of RCT	Advanced CKD stage and ESRD	ACEis/ARBs vs. No ACEis/ARBs	3.2 years
Gillis 2017 (90)	NR	Observational study (retrospective)	NR	MRA (spironolactone and eplerenone) vs No MRA	Median: 2,269 days
Zeng 2015 (176)	NR	Non-RCT	Stage 3-4	ACEi/ARBs and other antihypertensive drugs	9 years
Lewis 2001 (91)	NR	RCT	Stage 1-5	Irbesartan vs amlodipine vs placebo	Irbesartan, mean: 952 days Amlodipine, mean: 924 days Placebo, mean: 921 days
Provenzano 2018 (105)	Italy	Observational study (prospective)	NR	RAASi	3.6 years
Iseki 2013 (82)	Japan	RCT	ESRD	Olmesartan vs. Control	Median: 3.6 years
Jun 2019 (104)	Australia	Observational study (retrospective)	NR	RAASi	Median: 3.9 years
Cozzolino 2018 (177)	Italy	Observational study (prospective)	Stage 1-5	Cardiovascular medication, lipid-lowering medication, other medications (erythropoietin-stimulating agents (ESAs), iron-based therapy, and any form of vitamin D supplementation)	3 years
Brenner 2001 (23)	Asia, Europe, Central America, South America, and North America	RCT	Stage 1-5	Losartan vs placebo	Mean: 3.4 years

ACEis, angiotensin converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; AZ, azelnidipine; CCBs, calcium channel blockers; CKD, chronic kidney disease; ESRD, end-stage renal disease; MRA, mineralocorticoid receptor antagonists; NR, not reported; OLM, olmesartan medoxomil; RAAS blockers, renin-angiotensin-aldosterone-system blockers; RAASi, renin-angiotensin-aldosterone-system inhibitors; RCT, randomized controlled trial; TCM, traditional Chinese medicine.

10.4.3 Findings for outcome one: Cardiovascular events and mortality

A summary of the CV event and mortality outcomes in CKD patients identified in the included SLR/MAs is provided in Table 48.

A summary of the CV event and mortality outcomes in CKD patients identified in the included single studies is provided in Table 49.

Table 48: Cardiovascular event and mortality outcomes in patients with CKD identified in SLRs/MAs

Author and year	Patient population	Intervention	Comparator	Sample size	Main outcomes		Other outcomes			
					CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality
Balamuthusamy 2008 SLR and MA (61)	CKD, stage 2 or more	ACEi/ARB	Placebo	17,357	RR=0.84 (95%CI, 0.78-0.91); P<0.0001	RR=0.94 (95%CI, 0.78-1.04); P=0.50	RR=0.74 (95%CI, 0.58-0.95); P=0.02	RR=0.95 (95%CI, 0.76-1.20); P=0.68	RR=0.78 (95%CI, 0.65-0.97); P=0.03	RR=0.94 (95%CI, 0.84-1.07); P=0.37
			Control (beta-blocker, CCBs or other antihypertensive-based therapy)	28,401	RR=1.03 (95%CI, 0.99-1.08); P=0.21	RR=0.65 (95%CI, 0.39-1.06); P=0.09	RR=1.01 (95%CI, 0.91-1.02); P=0.83	RR=1.12 (95%CI, 1-1.27); P=0.05	RR=0.97 (95%CI, 0.89-1.06); P=0.57	RR=0.62 (95%CI, 0.29-1.32); P=0.21
Xie 2016 SLR and NMA (46)	CKD, 3–5	ACEi	Placebo	21,491	OR=0.82 (95%CI, 0.71-0.92)	OR=0.88 (95%CI, 0.72-1.09)	NR	NR	NR	OR=0.87 (95%CI, 0.74-1.01)
		ARB	Placebo	4,854	OR=0.76 (95%CI, 0.62-0.89)	OR=1.12 (95%CI, 0.80-1.58)	NR	NR	NR	OR=0.99 (95%CI, 0.78-1.21)
		ACEi	Active control	10,628	OR=0.86 (95%CI, 0.70-1.03)	OR=0.77 (95%CI, 0.51-1.08)	NR	NR	NR	OR=0.72 (95%CI, 0.53-0.92)
		ARB	Active control	6,505	OR=0.94 (95%CI, 0.75-1.12)	OR=0.97 (95%CI, 0.66-1.33)	NR	NR	NR	OR=0.81 (95%CI, 0.61-1.03)
Fink 2012 SLR (84)	CKD, stage 1-3	ACEi	Placebo	NR	NR	NR	NR	RR=0.88 (95%CI, 0.61-1.27)	RR=0.89 (95%CI, 0.71-1.12)	RR=0.91 (95%CI, 0.79-1.05)
		ARB	Placebo	NR	NR	NR	NR	NR	NR	RR=1.04 (95%CI, 0.92-1.18)
Qin 2016	CKD stage,	ACEi/ARB	No-ACEi/ARB	NR	NR	NR	NR	NR	NR	HR=0.83 (95%CI,

Author and year	Patient population	Intervention	Comparator	Sample size	Main outcomes		Other outcomes			
					CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality
SLR and MA (85)	undefined									0.78-0.87); P=0.067
Sharma 2011 SLR (65)	CKD, stage 3	ACEi	Placebo	2,177	RR=0.87 (95%CI, 0.66-1.14); P=0.31	NR	NR	NR	NR	RR=1.80 (95%CI, 0.17-19.27); P=0.63
Nistor 2018 SLR and MA (64)	Diabetic patients with CKD, stage 3-5	ACEi/ARB	Placebo or alternative antihypertensive agent	9,797	RR=0.90 (95%CI, 0.81-1.00)	RR=1.03 (95%CI, 0.75-1.41)	NR	NR	NR	RR=97 (95%CI, 0.85-1.10)
Lin 2017 SLR and MA (77)	Hypertensive patients with CKD stage 3-5	ACEi	CCBs	9492	NR	RR=1.0 (95%CI, 0.93-1.08)	Incidence: 12.3% vs 13.2% RR=1.13 (95%CI, 0.87-1.47)	RR=0.96 (95%CI, 0.72-1.28)	NR	Incidence: 30.3% vs 34.1% OR=1.09 (95%CI, 0.96-1.24)
	Hypertensive patients with CKD stage 3 and 4				NR	RR=1.01 (95%CI, 0.94-1.09)	RR=0.99 (95%CI, 0.86-1.14)	RR=1.06 (995%CI, 0.86-1.31)	NR	OR=1.11 (95%CI, 0.96-1.28)
	Hypertensive patients with undefined CKD stage				NR	Incidence: 7.6% vs 5.6% RR=0.72 (95%CI, 0.48-1.08)	RR=1.58 (95%CI, 1.17-2.14)	RR=0.69 (95%CI, 0.24-1.98)	NR	OR=0.98 (95%CI, 0.72-1.34)
Sun 2016 SLR (76)	CKD and ESRD patients, undefined	Spironolactone	Placebo	737	NR	RR=0.37 (95%CI, 0.15-0.93), P=0.03 No evidence of heterogeneity	NR	NR	NR	Incidence: 4.9% vs 13.1% RR=0.387 (95%CI, 0.22-0.65), P=0.0005

Author and year	Patient population	Intervention	Comparator	Sample size	Main outcomes		Other outcomes			
					CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality
						(chi square=0.88, P=0.83, I_2=0)				No evidence of heterogeneity (chi square=3.94, P=0.27, I_2=24%)
Lu 2016 SLR and MA (62)	CKD, stage 1-5	MRA	Non-MRA	4935	MACE RR=0.65 (95%CI, 0.50-0.83), P=0.001	NR	NR	NR	NR	RR=0.78 (95%CI, 0.62-0.97), P=0.027
Ninomiya 2013 MA (63)	CKD, undefined	ACEi	Placebo	30925	MACE 14.7% vs 17.9% HR=0.81 (95%CI, 0.73-0.90)	NR	NR	NR	NR	NR
Zhao 2016 SLR and MA (86)	CKD, undefined	ACEi/ARB	CCBs	25,647	NR	NR	NR	NR	NR	OR=0.96 (95%CI, 0.89-1.03); P=0.24

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker; CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratio; MA, meta-analysis; NMA, network meta-analysis; NR, not reported; OR, odds ratio; RR, relative risk; SLR, systematic literature review

Table 49: Cardiovascular event and mortality outcomes in patients with CKD identified in single studies

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
Guo 2017 (66)	Patients with CKD	ACEi/ARB (n=1094) vs no ACEi/ARB	MACE Incidence: 11.1% vs	NR	In hospital acute HF Incidence:	In-hospital stroke Incidence:	In-hospital recurrent MI Incidence:	In-hospital mortality Incidence: 2.9%	Revascularisation Incidence: 0.3% vs 0%

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
		(n=160)	16.3%		5.1% vs 6%	0.8% vs 1.3%	0.8% vs 0%	vs 7.5%	Arrhythmia Incidence: 6.0% vs 11.9% Renal RT Incidence: 1.4% vs 3.1%
Tseng 2017 (69)	Pre-dialysis patients with CKD stage 5	Spironolactone (n=1363) vs no spironolactone (n=25850)	MACE Incidence: 3.2% vs 2.2%. Adjusted HR: 0.89 (95%CI, 0.71-1.12)	Incidence: 1.4% vs 0.7%. Adjusted HR: 0.97 (95%CI, 0.68-1.37)	Hospitalisation for HF Incidence: 4.0% vs 1.4% Adjusted HR: 1.35 (95%CI, 1.08-1.67)	NR	NR	Incidence: 24.7% vs 10.6%. Adjusted HR: 1.35 (95%CI, 1.24-1.46)	NR
Beldhuis 2019 (59)	Patients with HF with a preserved ejection fraction and CKD	Spironolactone vs placebo (total n=3445)	MACE HR: 0.82, 95%CI, 0.69-0.98), P=0.13	NR	NR	NR	NR	NR	NR
Yang 2015 (70)	Patients with ESRD on maintenance dialysis	Long-term ARB (n=515) vs short-term ARB (n=224) vs no ARB (n=1061)	MACE Long-term ARB use vs no ARB use HR: 0.85 (95%CI, 0.73-1.00). Short-term ARB use vs no ARB use HR: 1.24 (95%CI, 1.02-1.51)	NR	NR	Long-term ARB use vs no ARB use HR: 0.67 (95%CI, 0.50-0.90) Short-term ARB use vs no ARB use HR: 0.90 (95%CI, 0.63-1.29)	Long-term ARB use vs no ARB use HR: 0.58 (95%CI, 0.38-0.88) Short-term ARB use vs no ARB use HR: 0.82 (95%CI, 0.50-1.37)	NR	PTA Long-term ARB use vs no ARB use HR: 0.49 (95%CI, 0.25-0.95) Short-term ARB use vs no ARB use HR: 0.46 (95%CI0.18-1.21) PTCA Long-term ARB use vs no ARB

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
									use HR:0.94 (95%CI, 0.37-2.42) Short-term ARB use vs no ARB use HR:1.33 (95%CI, 0.44-4.01)
Ovbiagele 2012 (67)	Ischemic stroke patients with CKD	Telmisartan vs placebo (total n=20332)	MACE HR: 0.99 (95%CI, 0.85-1.16)	NR	NR	HR: 1.08 (95%CI, 0.88-1.33)	NR	NR	PAD Long-term ARB use vs no ARB use HR: 0.81 (95%CI, 0.60-1.11) Short-term ARB use vs no ARB use HR: 0.99 (95%CI, 0.67-1.47)
Yoo 2018 (68)	Patients with ESRD	RAASi (n=2320) vs no-RAASi (n=2903)	MACE Incidence: 13.9% vs 11.0%	NR	NR	NR	NR	Incidence: 19% vs 19.6%, P=0.003	NR
Saruta 2009 (73)	Hypertensive patients with CKD stage 1-4	Candesartan (n=1376) vs amlodipine (n=1344)	Incidence for stage 1-4: 7.2% vs 7.6% HR: 0.95, 95%CI, 0.72-1.25), P=0.698 Incidence for	NR	NR	Incidence: 3.1% vs 3.0%	NR	NR	NR

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
			stage 1-2: 10.5% vs 8.2% Incidence for stage 3: 6.3% vs 6.3% Incidence for stage 4: 14.1% vs 29.5%						
Matsumoto 2014 (72)	Patients with ESRD on dialysis	Spironolactone (n=157) vs control (n=152)	Incidence: 3.2% vs 7.9% HR: 0.43 (95%CI, 0.16-1.11), P=0.133	Sudden cardiac death Incidence: 2.5% vs 3.3% HR: 0.79 (95%CI, 0.21-2.9), P=0.98 CV death Incidence: 2.5% vs 4.6% HR: 0.57 (95%CI, 0.17-1.87), P=0.534	Incidence: 0.6% vs 2.0%	Incidence: 2.5% vs 7.2% HR: 0.38 (95%CI, 0.14-1.05)	Incidence: 0% vs 0.7%	Incidence 6.4% vs 19.7% HR: 0.36 (95%CI, 0.19-0.66), P=0.002 Adjusted HR: 0.34 (95%CI, 0.16-0.69), P=0.003	Angina 0% vs 2.0% Death or hospitalisation due to CCV Incidence: 5.7% vs 15.1% HR: 0.40 (95%CI, 0.20-0.81), P=0.017 Adjusted HR: 0.38 (95%CI, 0.17-0.83), P=0.016
Agarwal 2014 (74)	Patients with ESRD on dialysis	Atenolol (n=100) vs Lisinopril (n=100)	Incidence rate: 24.6/100 PY vs 58/100	Incidence rate: 2.5/100 PY vs 4/100	Incidence rate: 6.2/100 PY vs 20.2/100PY	Incidence rate: 2.5/100 PY vs 2.7/100 PY	Incidence rate: 2.5/100 PY vs	NR	Revascularisation Incidence rate: 4.9/100 PY vs

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
			PY	PY			58/100 PY		5.4/100 PY Arrhythmia Incidence rate: 2.5/100 PY vs 6.7/100PY Angina Incidence rate: 0 vs 2.7/100 PY Valve RT Incidence rate: 1.2/100 PY vs 1.3/100 PY Cardiac arrest Incidence rate: 0 vs 2.7/100 PY
Wu 2015 (75)	Patients with ESDR on dialysis	ACEi/ARB (n=50961) vs no-ACEi/ARB (n=59913)	Incidence: 18.4% vs 10.7%, P<0.001	NR	NR	<u>Ischemic stroke</u> Incidence: 5.0% vs 5.4% P=0.003 Haemorrhagic stroke Incidence: 4.7% vs 2.9% P<0.001	NR	Incidence: 30.0% vs 34.6%, P<0.001 HR: 0.90 (95%CI, 0.86-0.93)	ACS Incidence: 8.7% vs 2.4%, P<0.001
Hsing 2015 (78)	Hypertensive patients with CKD	Losartan (n=6377) vs ramipril (n=2597) vs conventional hypertensive treatment	NR	Incidence rate: 2.39/1000 PY vs 2.58/1000 PY vs 2.61/1000	NR	NR	NR	Incidence rate: 4.98/1000 PY vs 4.96/1000 PY vs 5.20/1000 PY	First hospitalisation due to CVD Incidence rate: 7.56/1000 PY vs 7.47/1000 PY vs

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
		(n=127292)		PY. Losartan vs conventional HR: 0.88 (95%CI, 0.61-0.97), P=0.03					7.68/1000 PY Losartan vs conventional HR: 0.64 (95%CI, 0.37-0.90), P=0.01 Ramipril vs conventional HR: 0.75 (95%CI, 0.65-0.97), P<0.001
Bowling 2013 (60)	Systolic HF patients with CKD (undefined)	Enalapril (n=498) vs placebo (n=538)	NR	Incidence: 36% vs 40% HR: 0.84 (95%CI, 0.69-1.02), P=0.079	Hospitalisation for HF Incidence: 27% vs 39% HR: 0.59 (95%CI, 0.48-0.73), P<0.001	NR	NR	Incidence: 42% vs 45% HR: 0.88 (95%CI, 0.73-1.06), P=0.164	Hospitalisation due to CVD Incidence: 59% vs 66% HR: 0.77 (95%CI, 0.66-0.90), P=0.001
	Systolic HF patients with CKD ≥3B stage		NR	NR	Hospitalisation for HF HR: 0.69 (95%CI, 0.46-1.02), P=0.063	NR	NR	Incidence: 44% vs 52% HR: 0.76 (95%CI, 0.54-1.08), P=0.123	Hospitalisation due to CVD HR: 0.73 (95%CI, 0.54-0.98), P=0.037
Lee 2018 (79)	Patients with ESRD on dialysis	ACEi/ARB (n=17911) vs no-ACEi/ARB (n=38894)	NR	Incidence rate: 3.36/1000 PY vs 5.56/1000 PY HR: 0.58 (95%CI, 0.55-0.62)	NR	NR	NR	Incidence rate: 9.28/1000 PY vs 18.46/1000 PY HR: 0.47 (95%CI, 0.46-0.49)	NR

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
Charytan 2019 (81)	Patients with ESRD on dialysis	Spironolactone 12.5mg (n=27) vs spironolactone 25mg (n=26) vs spironolactone 50mg (n=25) vs placebo (n=51)	NR	Incidence: 0% (12.5mg) vs 7.7% (25mg) vs 4.0% (50mg) vs 2.0% (placebo). Incidence rate: 0 (12.5mg) vs 0.11/PY (25mg) vs 0.05/PY (50mg) vs 0.03/PY (placebo)	NR	Incidence 0% (12.5mg) vs 3.8% (25mg) vs 0% (50mg)	Incidence: 0% (12.5mg) vs 11.5% (25mg) vs 4.0% (50mg)	Incidence: 0% (12.5mg) vs 7.7% (35mg) vs 4.0% (50mg) vs 3.9% (placebo) Incidence rate: 0 (12.5mg) vs 0.11/PY (25mg) vs 0.05/PY (50mg) vs 0.05/PY (placebo)	NR
Shen 2017 (80)	Patients with ESRD on dialysis	ACEi/ARB (n=2063) vs no-ACEi/ARB (n=2816)	NR	Incidence rate: 7.5/100 PY vs 10.2/100 PY HR: 0.74 (95%CI, 0.63-0.87)	NR	Ischemic stroke incidence rate: 2.6/100 PY vs 2.4/100 PY HR: 1.06 (95%CI, 0.79-1.43)	Incidence rate: 3.6/100 PY vs 4.1/100 PYs HR: 0.88 (95%CI, 0.69-1.12)	Incidence rate: 18.8/100 PY vs 22.6/100 PY HR: 0.83 (95%CI, 0.75-0.92)	NR
Parving 2012 (83)	Patients with T2DM (98.1% with CKD)	Aliskiren (n=4274) vs placebo (n=4287)	NR	Incidence: 5.8% vs 5.0% HR: 1.16 (95%CI, 0.96-1.36)	Hospitalisation for HF Incidence: 4.8% vs 5.1% HR: 0.95 (95%CI, 0.78-1.14)	Fatal or non-fatal stroke Incidence rate: 3.4% vs 2.8% HR: 1.22 (95%CI, 0.96-1.55)	Incidence: 3.4% vs 3.3% HR: 1.04 (95%CI, 0.83-1.31)	Incidence: 8.8% vs 8.4% HR: 1.06 (95%CI, 0.92-1.23)	Cardiac arrest with resuscitation Incidence: 0.4% vs 0.2% HR: 2.40 (95%CI, 1.05-5.48)
Iseki 2013	Patients with	Olmesartan	NR	Incidence:	Incidence:	Ischemic,	Incidence:	Incidence: 4.7%	Angina

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
(82)	ESRD on dialysis	(n=235) vs another non-ACEi/ARB treatment (n=234)		1.0% vs 1.2% HR: 0.80 (95%CI, 0.32-2.04), P=0.65	1.7% vs 2.4% HR: 0.73 (95%CI, 0.37-1.46), P=0.37	haemorrhagic and subarachnoid haemorrhagic stroke Incidence: 2.7% vs 1.9% HR: 1.41 (95%CI, 0.73-2.73) P=0.31	0.5% vs 0.4% HR: 1.36 (95%CI, 0.30-6.08), P=0.69	vs 4.8% HR: 0.97 (95%CI, 0.62-1.52), P=0.91	Incidence: 1.8% vs 1.9% HR: 0.92 (95%CI, 0.45-1.91), P=0.83
Brenner 2001 (23)	Patients with T2DM and nephropathy	Losartan (n=751) vs placebo (n=762) (taken in addition to conventional antihypertensive treatment)	Incidence: 32.9% vs 35.2% Risk reduction 10%, P=0.26	NR	First hospitalisation for HF Incidence: 11.9% vs 16.7% Risk reduction: 32%, P=0.005	NR	Incidence: 6.7% vs 8.9% Risk reduction 28%, P=0.08	Incidence: 21% vs 20.3% Incidence rate: 6.8/100 PY vs 6.6/100 PY	NR
Yasuda 2013 (147)	Hypertensive patients with CKD stage 3-5	Valsartan (n=149) vs control (n=144)	NR	NR	Incidence: 2.0% vs 3.5%	Incidence: 1.3% vs 1.4%	NR	Incidence: 0.7% vs 1.4%	NR
Liao 2017 (148)	Patients with ESRD (stage 4 or 5) on dialysis	No-ACEi/ARB (n=7612) vs non-adherent ACEi/ARB (n=7071) vs adherent ACEi/ARB (n=749)	NR	NR	Incidence: 3.0% vs 12.5% vs 15.6%. No-use vs non-adherent use adjusted HR: 2.69 (95%CI, 2.30-3.14). No-use vs adherent use	Ischemic stroke Incidence: 4.0% vs 8.3% vs 7.2%. No-use vs non-adherent use adjusted HR: 1.62 (95%CI, 1.40-1.88) No-use vs	Incidence: 5.1% vs 14.6% vs 17.6% No-use vs non-adherent use adjusted HR:1.75 (95%CI, 1.54-1.98)	Incidence: 37.2% vs 34.0% vs 30.8% No-use vs non-adherent use HR: 0.82 (95%CI, 0.77-0.86) No-use vs adherent use HR: 0.99 (95%CI, 0.86-	NR

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
					adjusted HR:4.64 (95%CI, 3.66-5.87)	adherent use adjusted HR: 1.76 (95% CI: 1.31–2.38) <u>Haemorrhagic stroke</u> Incidence: 2.3% vs 3.4% vs 10.4% No-use vs nonadherent use adjusted HR: 1.28 (95%CI, 1.04-1.56) No-use vs adherent use adjusted HR: 2.61 (95%CI, 1.86–3.65)	No-use vs adherent use adjusted HR: 2.69 (95%CI: 2.18-3.31)	1.13)	
Ku 2018 (162)	Patients with early CKD (stage 2-3) and advanced CKD (stage 4-5)	ACEi/ARBs vs CCBs vs β-blocker (total N=3939)	NR	NR	ACEi/ARB vs no-ACEi/ARB adjusted HR: 0.79, 95%CI, 0.64-0.97), P=0.29 CCBs vs no-CCB adjusted HR: 0.96 (95%CI, 0.79-1.16), P=0.08 β-blocker vs no-β-blocker HR: 1.62	NR	NR	ACEi/ARB vs no-ACEi/ARB HR: 0.78 (95%CI, 0.67-0.90) CCBs vs no-CCB HR:0.92 (95%CI, 0.79-1.06) β-blocker vs no-β-blocker HR: 1.22 (95%CI 1.03-1.43)	NR

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
					(95%CI, 1.29-2.04), P=0.73				
Bajaj 2011 (164)	Elderly patients with ESRD	ACEi/ARB (n=679) vs statin (n=424) vs CCB (n=847)	NR	NR	ACEi/ARB vs statin adjusted HR: 1.14 (95%CI, 0.89-1.46) CCB vs statin adjusted HR: 1.37 (95%CI, 1.04-1.82)	ACEi/ARB vs statin HR: 0.90 (95%CI, 0.56-1.47) CCB vs statin HR:0.93 (95%CI, 0.53-1.62)	ACEi/ARB vs statin HR: 0.97 (95%CI, 0.72-1.32) CCB vs statin HR: 0.95 (95%CI, 0.67-1.36)	ACEi/ARB vs statin adjusted HR: 0.87 (95%CI, 0.76-0.99), P<0.05 CCB vs statin HR: 0.95 (95%CI, 0.82-1.11)	Revascularisation ACEi/ARB vs statin HR: 0.80 (95%CI, 0.46-1.40) CCB vs statin HR: 0.92 (95%CI, 0.48-1.76)
Lewis 2001 (91)	Patients type 2 diabetic nephropathy and CKD stage 1-5	Amlodipine (n=567) vs placebo (n=569) vs irbesartan (n=579)	NR	NR	Rate of hospitalisation for HF was 23% lower in patients receiving irbesartan than placebo	NR	Rate of MI was 41% lower in patients receiving amlodipine than placebo	Incidence: 14.6% vs 16.3% vs 15.0% Irbesartan vs placebo adjusted RR:0.94 (95%CI, 0.70-1.27), P=0.69 Amlodipine vs placebo adjusted RR: 0.90 (95%CI, 0.66-1.21), P=0.47	NR
Lin 2016 (144)	Non-HF patients with ESRD on dialysis	Spironolactone (n=125) vs placebo (n=128)	NR	NR	NR	NR	NR	Incidence: 9.6% vs 19.5% HR: 0.49 (95%CI, 0.26-0.95), P=0.036	Cardiac arrest Incidence: 0% vs 0.78%, P=0.32 Death from CCV Incidence: 4.0%

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
									vs 11.7% HR: 0.33 (95%CI, 0.13-0.85), P=0.026
Watanabe 2011 (146)	Untreated hypertensive patients with CKD stage 3 or 4	Telmisartan (n=43) vs imadapril (n=44) vs amlodipine (n=43)	NR	NR	NR	NR	NR	NR	Death or hospitalisation for CVD 5.1-year cumulative event rates: 11.6% vs 34.1% vs 34.9%
Anand 2009 (58)	HF patients with CKD	Valsartan (n=1477) vs placebo (n=1439)	NR	NR	NR	NR	NR	Incidence: 24.5% vs 23.7% HR: 1.01 (95%CI, 0.85-1.20)	NR
Oh 2017 (92)	Pre-dialysis patients with CKD stage 4 or 5	ACEi/ARB (n=1237) vs no ACEi/ARB (n=839)	NR	NR	NR	NR	NR	Incidence: 12.5% vs 11.1%, P=0.075	NR
Vejakama 2017 (89)	Diabetic patients with CKD	RAAS2 (used RAAS for >12 months, n=3849) vs RAAS1 (used RAAS for 3-12 months, n=623) vs non-RAAS (never used or used for<3 months,	NR	NR	NR	NR	NR	Death prior to ESRD incidence: 14.4% vs 22.7% vs 19.6%	NR

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
		n=10560)							
	Non-diabetic patients with CKD	RAAS2 (n=1899) vs RAAS1 (n=588) vs non-RAAS (n=14587)	NR	NR	NR	NR	NR	Death prior to ESRD incidence: 15.9% vs 22.4% vs 22.3%%	NR
Molnar 2014 (22)	Non-dialysis patients with CKD stage 1-5	ACEi/ARB (n=26051) vs no-ACEi/ARB (n=115362)	NR	NR	NR	NR	NR	Incidence: 25% vs 32% Mortality rate (95%CI): 22.6 (22.0-23.2)/1000 PY vs 26.5 (25.9-27.2)/1000 PY	NR
Bermejo 2018 (161)	Diabetic patients with CKD stage 4 or 5	Inconstant RAASi (n=73) vs constant-RAASi (n=82) vs no-RAASi (n=42)	NR	NR	NR	NR	NR	Higher mortality in patients with no-RAAS vs inconsistent+ consistent RAAS, P=0.014	NR
Mimura 2008 (163)	Non-diabetic patients with CKD	ACEi (n=38) vs no-ACEi (n=37)	NR	NR	NR	NR	NR	Incidence: 2.6%vs. 10.8%, P<0.05	NR
Ahmed 2009 (57)	Elderly diastolic HF patients with CKD	ACEi/ARB (n=428) vs no-ACEi/ARB (n=709)	NR	NR	NR	NR	NR	Incidence: 57% vs 64% HR: 0.67 (95%CI, 0.53-0.85), P=0.001	NR
Arora 2015 (93)	Elderly veterans with CKD	RAASi (n=1186) vs other anti-	NR	NR	NR	NR	NR	Incidence: 12% vs 10%	NR

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
	without diabetes or proteinuria	hypertensives (n=1288)						HR: 1.08 (95%CI, 0.83-1.41)	
Hsu 2014 (167)	Pre-dialysis patients with CKD stage 5	ACEi/ARB (n=14117) vs no-ACEI/ARB (n=14380)	NR	NR	NR	NR	NR	Dialysis or death incidence rate: 90.1/100 PY vs 96.8/100 PY Unadjusted HR: 0.93 (95%CI, 0.91-0.96) Adjusted HR: 0.94 (95%CI, 0.92-0.97)	NR
Jovanovich 2015 (88)	Patients with advanced CKD and ESRD	ACEi/ARB (n=870) vs no ACEi/ARB (n=883)	NR	NR	NR	NR	NR	Incidence: 37% vs 45% Adjusted HR: 0.81 (95%CI, 0.69-0.94)	NR
Kim-Mitsuyama 2018 (71)	Hypertensive patients with CKD stage 3b, 4 or 5 Two groups: G3b and/or A3 Patients with eGFR <45 ml/min/1.73m^2 and/or urinary albumin/creatine ratio of ≥300 mg/g creatinine) Others:	G3b and/or A3 group: ARB (n=96) vs no-ARB (n=91) Other group: ARB (n=516) vs no-ARB (n=518)	CV and renal events overall. In G3b and/or A3 group Incidence: 11 (ARB) vs 22 (no-ARB) HR:0.465 (95%CI, 0.224-0.965, P=0.040)	NR	In G3b and/or A3 group Incidence: 2 (ARB) vs 4 (no-ARB) Other group: Incidence: 1 (ARB) vs 2 (no-ARB)	In G3b and/or A3 group Incidence: 1 (ARB) vs 3 (no-ARB) Other group: Incidence: 7 (ARB) vs 8 (no-ARB)	In G3b and/or A3 group Incidence: 2 (ARB) vs 0 (no-ARB) Other group: Incidence: 3 (ARB) vs 1 (no-ARB)	Sudden death In G3b and/or A3 group Incidence: 1 (ARB) vs 0 (no-ARB) Other group: Incidence: 1 (ARB) vs 2 (no-ARB)	NR

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
	Patients with eGFR ≥45 ml/min/1.73m^2 and/or urinary albumin/creatine ratio of <300 mg/g creatinine		<u>Other group:</u> 27 (ARB) vs 29 (no-ARB) HR:0.913 (95%CI, 0.538-1.551, P=0.737)						
Ninomiya 2008 (165)	Patietns with CKD 3 and 4	Perindopril (n=896) vs placebo (n=861)	NR	NR	NR	Effects of Perindopril on the risk of subtype of stroke according to baseline systolic or diastolic blood pressure levels at baseline: <u>Baseline systolic blood pressure</u> Ischemic stroke risk: HR: 0.65 (95%CI, 0.49–0.87) Haemorrhagic stroke risk: HR: 0.53 (95%CI, 0.26–1.08) <u>Baseline diastolic blood</u>	NR	NR	NR

Author & year	Patient population	Intervention vs comparator (n)	Main outcomes		Other outcomes				
			CV events	CV mortality	Heart failure	Stroke	MI	All-cause mortality	Other
						pressure Ischemic stroke risk: HR: 0.65 (95%CI, 0.49–0.87) Haemorrhagic stroke risk: HR:0.53 (95%CI, 0.26–1.08)			

ACEis, angiotensin converting enzyme inhibitors; ACS; acute coronary syndrome; ARBs, angiotensin-receptor blockers; CKD, chronic kidney disease; CCV, cerebrovascular; CV, cardiovascular; CVD, cardiovascular disease; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonists; MACE, major adverse cardiovascular event; MI, myocardial infarction; NR, not reported; PAD, peripheral artery disease; PTA, percutaneous transluminal angioplasty; PTCA, percutaneous transluminal coronary angioplasty; PY, person-years; T2DM, type 2 diabetes mellitus; RAASi, renin-angiotensin-aldosterone system inhibitor; RT, replacement therapy; RR, relative risk

10.4.3.1. Cardiovascular events

Findings from SLRs/MAs

Of the six SLRs/MAs that reported on CV events, five reported that RAASi significantly decreased the risk or odds of having a CV event when compared to placebo in patients with CKD (46, 61-64):

- ACEi and ARBs significantly reduced the odds of a CV event compared with placebo (ACEi odds ratio [OR]=0.82, 95% CI: 0.71-0.92; ARB OR=0.76, 95% CI: 0.62-0.89). (46)
- ACEi/ARB significantly decreased the risk of having a CV event when compared with placebo in patients with CKD ≥ stage 2 (relative risk [RR]=0.84, 95% CI: 0.78-0.91, P<0.0001) (61).
- ACEi significantly reduced the risk of MACE compared with placebo (hazard ratio [HR]=0.81, 95%CI, 0.73-0.90) (63).
- MRA significantly reduced the risk of a MACE compared with no-MRA treatment (RR=0.65, 95%CI, 0.50-0.83, P=0.001) (62).
- In non-dialysis diabetic patients with CKD stages 3-5, RAASi demonstrated a slight reduction in the risk of non-fatal CV events compared with placebo or alternative anti-hypertensive agent (RR=0.90, 95% CI: 0.81-1.00) (64).

One SLR involving non-diabetic patients with early CKD (stage 1-3) reported a lower risk of CV events in patients treated with ACEi compared with those receiving placebo, however the difference was not statistically significant (RR=0.87, 95% CI: 0.66-1.14, P=0.31). (65)

When compared with an active control, RAASi either non-significantly reduced the risk or odds of a CV event in patients with CKD or demonstrated no difference:

- ACEis and ARBs demonstrated a non-significant reduction in odds of having a CV event compared with active controls (ACEi OR=0.94, 95%CI: 0.75-1.12; ARBs OR=0.86, 95% CI: 0.70-1.03). (46)
- ACEi/ARBs demonstrated no difference in the risk of having a CV event compared with active controls in patients with CKD ≥ stage 2 (RR=1.03, 95% CI: 0.99-1.08, P=0.21) (61).

Findings from single studies

Of the six single studies that reported on MACE in patients with CKD, most reported that although RAASi reduced the rate or risk of MACE when compared to no-RAASi, the difference was not statistically significant (59, 66-69). Yang et al. reported that compared to no-ARB use, long-term ARB use trended towards reducing the risk of MACE (HR: 0.85, 95%CI 0.73-1.00) but short-term use increased the risk (HR: 1.24, 95%CI 1.02-1.51) (70).

Of the six single studies that reported on CV events in patients with CKD, four showed that RAASi reduced the incidence or risk of CV events compared with placebo or control (23, 71-73). Although most studies found this reduction was not statistically significant, Kim-Mitsuyama et al. found

patients with advance CKD treated with RAASi had a significantly lower risk of combined CV and renal events than non-users. (71)

- For patients with eGFR <45 ml/min per 1.73m^2 and/or urinary albumin/creatinine ratio of ≥300 mg/g creatinine, the incidence of combined CV and renal events was significantly less in those treated with ARB than no-ARB (11 vs 22, HR=0.47, 95%CI: 0.22-0.97, P=0.040). In patients with eGFR ≥45 ml/min/1.73m^2 and/or urinary albumin/creatine ratio of <300 mg/g creatinine there was no significant difference between treatment groups (27 vs 29, HR=0.91, 95%CI, 0.54-1.55, P=0.737) (71).
- Patients receiving spironolactone had a lower but non-significant incidence of CV events than those receiving control (3.2% vs 7.9% HR=0.43, 95%CI: 0.16-1.11, P=0.133) (72)
- Hypertensive patients with stage 1-4 CKD receiving the ARB therapy candesartan had a lower but non-significant incidence and risk of CV events compared to those receiving calcium channel blockers (CCBs) (7.2% vs 7.6%, HR=0.95, 95%CI, 0.72-1.25, P=0.698) (73).
- Diabetic patients with nephropathy receiving the ARB losartan had a 10% lower, but non-significant, risk of having a CV event compared to those receiving placebo (32.9% vs 35.2%, P=0.26).

Two single studies found the incidence of CV events in patients with ESRD on dialysis increased with the use of ACEi/ARB, suggesting that ACEI or ARB treatment in dialysis patients may not have a beneficial effect on CV outcomes (75, 141).

10.4.3.2. Cardiovascular mortality

Findings from SLR/MAs

Of the five SLRs/MAs that reported on CV mortality in patients with CKD, one reported that RAASi significantly reduced the risk of CV mortality compared with placebo.(76)

- Compared with placebo, spironolactone therapy significantly reduced the risk of CV mortality in patients with CKD and ESRD (RR=0.37, 95%CI: 0.15-0.93, P=0.03) (76)

Four of the SLRs/MAs reported that RAASi either reduced or increased CV mortality but not to a statistically significant extent; or, showed no difference in the risk or odds of CV associated mortality when compared to placebo or active control. (46, 61, 64, 77)

- ACEi/ARB demonstrated a non-significant reduction in risk of CV mortality in patients with CKD ≥ stage 2 when compared with placebo (RR=0.94, 95%CI: 0.78-1.04, P=0.50) or active control (RR=0.65, 95% CI: 0.39-1.06, P=0.09). (61)
- ACEis demonstrated a non-significant reduction in the odds of CV mortality compared with placebo and active control (ACEi vs. placebo, OR=0.88, 95% CI: 0.72-1.09; ACEi vs.

active control, OR=0.77, 95% CI: 0.51-1.08), whereas ARBs demonstrated mixed results for CV mortality: a non-significant increase compared with placebo but a non-significant decrease versus active control (ARB vs. placebo, OR=1.12, 95% CI: 0.80-1.58; ARB vs. active control, OR=0.97, 95% CI: 0.66-1.33). Notably, in traditional meta-analysis ACEis achieved significant odds reduction compared with placebo (OR=0.86, 95%CI: 0.76-0.96). (46)

- RAASi demonstrated no significant difference in the risk of CV mortality compared with controls (placebo/alternative anti-hypertensive agents) in non-dialysis diabetic patients with CKD stages 3-5 (RR=1.03, 95% CI: 0.75-1.41). (64)
- Compared with CCBs, ACEi demonstrated no significant difference in risk of CV mortality in hypertensive patients with CKD stage 4-5 (RR=1.00, 95%CI: 0.93-1.08), in a subgroup of hypertensive patients with mixed CKD stages 3 and 4 (RR=1.01, 95%CI: 0.94-1.09), nor in a subgroup of hypertensive patients with undefined CKD stage (RR=0.72, 95%CI: 0.48-1.08). (77)

Findings from single studies

Of the 10 single studies that reported on CV mortality, one reported that treatment with RAASi in hypertensive patients with CKD significantly reduced the rate and risk of CV mortality versus conventional treatment. (78) Notably, two large scale observational studies found that RAASi significantly reduced the risk of CV mortality in patients with ESRD on dialysis compared with no-RAASi use or placebo. (79, 80) Seven studies found RAASi had no significant effect in patients with CKD. (23, 60, 69, 74, 81-83)

10.4.3.3. Individual cardiovascular event and all-cause mortality outcomes

Heart failure

Findings from SLR/MAs

In patients with CKD, RAASi significantly decreases the rate and risk of having a heart failure event when compared to placebo.

- ACEi/ARB significantly reduced the rate and risk of heart failure events compared with placebo in patients with CKD ≥stage 2 (4% vs 5%, RR=0.74, 95%CI: 0.58-0.95, P=0.02). (61)

When compared with an active control, RAASi did not significantly reduce the risk of heart failure in patients with CKD apart from in a subgroup of hypertensive patients with undefined CKD stage.

- ACEi/ARB demonstrated no significant reduction in risk of heart failure events compared with active control therapy in patients with CKD ≥ stage 2 (RR=1.01, 95%CI: 0.91-1.02, P=0.83). (61)

- In hypertensive patients with CKD stage 3-5, the rate and risk of heart failure in patients receiving calcium channel blockers (CCBs) was similar to patients receiving ACEis (13.2% vs 12.34%, RR=1.13, 95%CI: 0.87-1.47). (77)
- In a subgroup of hypertensive patients with mixed CKD stages 3 and 4, there was no difference in the risk of heart failure between patients receiving CCBs and those receiving ACEis (RR=0.99, 95%CI: 0.86-1.14). However, in a subgroup of hypertensive patients with undefined CKD stage, patients receiving CCBs had a significantly higher risk of heart failure than patients receiving ACEIs (RR=1.58, 95%CI: 1.17-2.14).(77)

Findings from single studies

Some single studies found that the incidence of heart failure in patients with CKD treated with ACEi/ARB was slightly lower than in patients not treated with ACEi/ARB. (66, 82, 147, 162) Ku et al. found that use of ACEIs or ARBs in patients with early (stage 2-3) or advanced (stage 4-5) CKD was associated with a lower risk of heart failure (HR=0.79; 95% CI, 0.64–0.97), regardless of CKD severity. (162)

However, for patients with ESRD on dialysis the story was different. Iseki et al. found that patients with ESRD on dialysis treated with ACEi vs control did not have a significantly lower risk of heart failure (HR=0.73, 95%CI: 0.37-1.46, P=0.37. (82) Furthermore, Agarwal et al found the incidence rate of heart failure in patients with ESRD on dialysis treated with lisinopril (an ACEi) was more than those treated with atenolol (a beta-blocker) (incidence rate: 6.2/100 PY vs 20.2/100PY). (74) Liao et al. also found that compared to non-ACEi/ARB users, the risk of heart failure in patients with ESRD on dialysis was significantly higher in both nonadherent and adherent ACE/ARB users. (148)

Some studies found hospitalisations due to heart failure were lower in patients with CKD receiving ACEi/ARBs compared with placebo, including in patients with type 2 diabetes and nephropathy co-morbidities. (23, 60, 91) However, Tseng et al found that in pre-dialysis patients with stage 5 CKD, spironolactone was associated with a significantly higher risk of hospitalisation for HF compared with non-users (adjusted HR=1.35, 95%CI, 1.08-1.67). (69)

Stroke

Findings from SLR/MAs

In patients with CKD, RAASi showed no significant difference in the risk of having a stroke event when compared to placebo or active control.

- ACEi/ARB demonstrated no significant reduction in risk of stroke events when compared with placebo in patients with CKD ≥stage 2 (RR=0.95, 95%CI: 0.76-1.20, P=0.68) or active control (RR=1.12, 95%CI: 1.0-1.27, P=0.05). (61)
- ACEi demonstrated no significant reduction in risk of stroke events when compared to placebo in patients with CKD stages 1-3 (RR=0.88, 95%CI: 0.61-1.27). (84)

- ACEi demonstrated no significant reduction in risk of stroke events when compared to CCBs in hypertensive patients with CKD stage 3-5 (RR=0.96, 95%CI: 0.72-1.28), in a subgroup of hypertensive patients with mixed CKD stages 3 and 4 (RR=1.06, 95%CI, 0.86-1.31), nor in a subgroup of hypertensive patients with undefined CKD stage (RR=0.69, 95%CI: 0.24-1.98). (77)

Findings from single studies

Several single studies found that although RAASi reduced the rate or risk of stroke/cerebrovascular when compared to no-RAASi or control in patients with CKD, the difference was not significant (66, 67, 72, 147, 164).

Some studies found the risk of stroke/cerebrovascular events were increased with RAASi use compared with no-RAASi use (80, 82, 148, 178, 179):

Liao et al. found that compared to non-ACEi/ARB users, the risk of ischemic and haemorrhagic stroke in patients with ESRD on dialysis was significantly higher in both nonadherent and adherent ACE/ARB users. (148)

- Shen et al. found that the risk of ischemic stroke in ESRD patients on dialysis was higher for ACEi/ARB users than non-users, though the difference was not significant (HR=1.06, 95% CI, 0.79-1.43). (80)
- Parving et al. found the risk of stroke in patients with CKD and type 2 diabetes was higher with aliskiren treatment vs control, though the difference was not significant (HR=1.22, 95% CI, 0.96-1.55).(83)
- Iseki et al. found the risk of stroke in dialysis patients with ESRD was higher in patients treated with olmesartan (an ARB) vs control (2.7% vs 1.9%, HR=1.41, 95%CI, 0.73-2.73, P=0.31). (82)
- Wu et al. found there were significantly more haemorrhagic stroke events in patients with ESRD in the ACEi/ARB group than the control group (4.7% vs 2.9%, P<0.001). (75)

Interestingly, Wu et al. also found that there were significantly less ischemic stroke events in patients with ESRD in the ACEi/ARB group than the control group (5.0% vs 5.4%, P=0.003). (75) Furthermore, Yang et al. found that compared to no-ARB use, long-term use of ARB in patients with ESRD on dialysis significantly reduced the risk of acute stroke (HR=0.67, 95%CI, 0.50-0.90). (70)

Myocardial infarction

Findings from SLR/MAs

In patients with CKD ≥stage 2, ACEi/ARB significantly decreased the rate and risk of having myocardial infarction events when compared to placebo (4% vs 5%, RR=0.78, 95%CI: 0.65-0.97,

P=0.03) but did not significantly reduce the risk when compared with control therapy (RR=0.97, 95%CI: 0.89-1.06, P=0.57). (61)

In patients with CKD stages 1-3, ACEis and ARBs did not significantly reduce the risk of myocardial infarction when compared to placebo (ACEi RR=0.89, 95% CI: 0.71–1.12; ARB RR=1.04, 95%CI: 0.92-1.18). (84)

Findings from single studies

Five single studies found the rate and risk of myocardial infarction in patients with CKD or ESRD was lower in those who received RAASi than non-RAASi users (23, 70, 80, 82, 91). For most studies, this difference was not significant, however, Yang et al. found that compared to no-ARB use, long-term ARB use significantly reduced the risk of acute myocardial infarction in patients with ESRD on dialysis (HR=0.58, 95%CI, 0.38-0.88). (70)

Four single studies found that the rate and risk of myocardial infarction in patients with CKD or ESRD was higher in those who received RAASi than non-RAASi users (66, 74, 148, 180). However, only Liao et al. found this difference to be significant. (148)

All-cause mortality

Findings from SLR/MAs

Previously performed SLRs show a mixed picture of the impact of RAASi on all-cause mortality.

Four of the SLRs/MAs that reported on all-cause mortality found that all-cause mortality was reduced in patients receiving RAASi compared to placebo, active control, or non-RAASi users. (46, 62, 76, 85)

- ACEi achieved a significant odds reduction in all-cause mortality compared with active controls (OR=0.72, 95%CI: 0.53- 0.92). However, no significant difference was found among between ACEi vs placebo or ARB vs active control or placebo. Results of a Bayesian NMA for all-cause mortality in patients with CKD, indicated that ACEi had the highest probability of being superior (81.9%), followed ARBs (15.5%). (46)
- Spironolactone therapy significantly reduced the rate and risk of all-cause mortality compared with placebo in patients with CKD and ESRD (4.9% vs 13.1%, RR=0.38, 95%CI: 0.22-0.65, P=0.0005) (76)
- MRA significantly reduced the risk of all-cause mortality compared with non-MRA treatment in patients with CKD stages 1-5 (RR=0.78, 95%CI: 0.62-0.97, P=0.027) (62)
- ACEi/ARB reduced the risk of all-cause mortality compared with non-ACEi/ARB users in non-dialysis dependent CKD patients (HR=0.83, 95% CI: 0.78-0.87, P=0.067). (85)

However, six of the SLRs/MAs found that RAASi did not significantly reduce the risk and odds of all-cause mortality when compared to placebo or active control (61, 64, 65, 77, 84, 86).

- ACEi/ARB did not significantly reduce the risk of all-cause mortality compared with placebo in patients with CKD ≥stage 2 (RR=0.94, 95%CI: 0.84-1.07, P=0.37) or active control (RR=0.62, 95%CI: 0.29-1.32, P=0.21) (61)
- ACEi and ARB did not significantly reduce the risk of all-cause mortality compared to placebo in patients with CKD stages 1-3 (ACEi RR=0.91, 95%CI: 0.79-1.05; ARB RR=1.04, 95%CI: 0.92-1.18) However, ACEi reduced mortality compared to placebo in patients with microalbuminuria and CV disease or high-risk diabetes (RR=0.79, 95%CI: 0.66-0.96). (84)
- ACEi demonstrated no significance difference in risk of all-cause mortality compared to placebo in patients with early CKD (stage 1-3) and no diabetes mellitus (RR=1.80, 95%CI: 0.17-19.27, P=0.63) (65)
- RAASi demonstrated no significant difference in the risk of all-cause mortality compared with control (placebo/alternative anti-hypertensive agents) in non-dialysis dependent patients with CKD stages 3-5 (RR: 0.97, 95%CI: 0.85-1.10) (64)
- Compared with CCB, ACEi demonstrated no significant difference in rate and odds of all-cause mortality in hypertensive patients with CKD stage 3-5 (34.1% vs 30.3%, OR=1.09; 95%CI: 0.96-1.24), in a subgroup of hypertensive patients with mixed CKD stages 3 and 4 (OR=1.11, 95%CI, 0.96-1.28), nor in a subgroup of hypertensive patients with undefined CKD stage (OR=0.98, 95%CI, 0.72-1.34) (77)
- ACEi or ARB demonstrated no significant difference in the incidence of all-cause mortality compared with CCBs in patients with CKD (OR=0.96; 95%CI: 0.89-1.03; P=0.24) (86)

Findings from single studies

Most single studies found treatment with RAASi in patients with CKD or ESRD either significantly reduced the rate and risk of all-cause mortality vs no-RAASi use (22, 72, 75, 79, 80, 88, 144, 161-164, 167) or had no significant effect (23, 58, 60, 66, 78, 81-83, 89, 91-93, 147). However, Tseng et al. found all-cause mortality in pre-dialysis patients with CKD stage 5 was significantly higher in patients receiving spironolactone vs non-spironolactone users (24.7% vs 10.6%, adjusted HR=1.35, 95%CI, 1.24-1.46). (69) Conversely, Lin found spironolactone use in non-heart failure patients with ESRD significantly reduced the risk of all-cause mortality versus a control (HR=0.49, 95%CI, 0.26-0.95, P=0.036). (144)

10.4.4 Findings for outcome 2: CKD progression

A summary of progression to ESRD in patients with CKD identified in the single studies is provided in Table 50. A summary of disease progression in patients with CKD identified in the single studies is provided in Table 51.

Table 50: Progression to ESRD in patients with CKD identified in SLRs

Study name	Patient population	Intervention	Comparator	Sample size	ESRD progression	Change in GFR rate
Xie 2016 (46)	CKD, undefined	ACEi	Placebo	21,491	Reduce kidney failure by 39% vs placebo; OR=0.61 (95%CI, 0.47-0.79)	NR
		ARB	Placebo	4,854	Reduce kidney failure by 30% vs placebo; OR=0.70 (95%CI, 0.52-0.89)	NR
		ACEi	Active control	10,628	Reduce kidney failure by 35% vs Active control; OR=0.65 (95%CI, 0.51-0.80)	NR
		ARB	Active control	6,505	Reduce kidney failure by 25% vs Active control; OR=0.75 (95%CI, 0.54-0.97)	NR
Fink 2012 (84)	CKD, stage 1 to 3	ACEi	Placebo	NR	RR=0.65 (95%CI, 0.49-0.88)	NR
		ARB	Placebo	NR	RR=0.77 (95%CI, 0.66-0.90)	NR
Sharma 2011 (65)	CKD, stage 3	ACEi	Placebo	2177	RR=1.00 (95%CI, 0.09-1.11); P=0.99	NR
Zhao 2016 (86)	CKD, undefined	CCB	ACE inhibitor/ARB	25,647	OR=1.25 (95%CI, 1.05-1.48); P=0.01	NR
Ng 2015 (87)	CKD, Stage 1-5	Spironolactone/eplerenone with or without ACEi and/or ARB	Placebo	1217	NR	Intervention: No significant change in the GFR: 0.03 (95%CI; -0.08–0.14) ml/min per 1.73 m^2
Nistor 2018 (64)	Diabetic patients with CKD, stage 3-5	ACEi/ARB	Placebo or alternative antihypertensive	2,074	NR	No difference in the effect estimates between the groups,

			agent			Relative effect=-0.09 (95%CI, -2.75–2.57)
Lin 2017 (77)	Hypertensive patients with CKD stage 3-5	ACEi	CCBs	4,904	NR	No significant differences in the GFRs between the CCB and ACEI Groups: RR=1.14 (95%CI, 0.95-1.37).
	Hypertensive patients with CKD stage 3 and 4	ACEi	CCBs	3702	NR	No significant differences in the GFRs between the CCB and ACEI Groups: RR=1.03 (95%CI, 0.62-1.72)
	Undefined CKD	ACEi	CCBs	1202	NR	No significant differences in the GFRs between the CCB and ACEI Groups: RR=1.19 (95%CI, 0.95-1.49)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker; CI, confidence intervals; CKD, chronic kidney disease; ESRD, end-stage renal disease; OR, odds ratio; RR, relative risk

Table 51: CKD progression identified in single studies

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
Fogelfeld 2017 (173)	Low-income adults with T2DM and CKD stage 3-4	Multifactorial-multidisciplinary intervention combined coordinated medical care including ACEi and ARB (Intervention n=60) vs usual care (ACEi/ARB) (control n=60)	Intervention: % of patients at baseline and at study end with: Stage 2: 0% and 3.3% Stage 3: 31.7% and 23.3% Stage 4: 30.0% and 41.7% Control: % of patients at baseline and at study end with: Stage 2: 0% and 5.0% Stage 3: 31.7% and 13.3%	eGFR (ml/min per 1.73 m^2): Intervention: 37.95±10.74 at baseline and 30.98±15.49 at study end, P=0.001 Control: 37.18±13.00 at baseline and 28.95±15.06 at study end, P=0.001 Intervention vs control: Annual GFR decline ≥10 ml/min/1.73 m^2: RR=0.938,	Incidence: 33% during 82.95 weeks mean follow-up vs 57% during 84.05 weeks mean follow-up

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
			Stage 4: 35.0% and 25.0%	P=0.946 Annual GFR change >15 ml/min/1.73 m^2: RR=0.875, P=0.559	
Orlando 2007 (175)	Patients with CKD	ACEi (52% or patients and anti-lipid medications (39% of patients) (N=1217)	48% progressed from stage 1 to 2 and 21% died. 31% progressed from stage 2 to 3 and 31% died. 17% of patients progressed from stage 3 to 4 and 49% died. Median days spent in stage 3 to 4 was 1,158. 24% of patients progressed from stage 4 to 5 and 52% died. Median days spent in stage 4 to 5 was 794.	NR	23% of patients progressed from stage 5 to ESRD and 27% died. Median days spent by in stage 5 to ESRD was 709.
Brenner 2001 (23)	Patients with T2DM and nephropathy	Losartan (n=751) vs placebo (n=762) (taken in addition to conventional antihypertensive treatment)	losartan reduced the rate of decline in renal function by 18% over mean 3.4 years follow-up (assessed by the reciprocal of the serum creatinine concentration, median slope: -0.056 dl/mg/year in vs -0.069 dl/mg/year; P=0.01).	Median rate of eGFR decline (ml/min per 1.73 m^2/year) during mean 3.4 years follow-up: 4.4 vs 5.2, P=0.01 Losartan was associated with a 15.2% reduction in eGFR decline vs placebo.	Incidence: 19% vs 25.5% Incidence rate: 6.8/100 PY vs 9.1/100 PYs Risk of ESRD was reduced by 28% with losartan during 3.4 years mean follow-up.
Saito 2012 (149)	Patients with hypertension and CKD in Japan	Olmesartan medoxomil for 12 weeks (OLM, n=1317) vs Azelnidipine for 12 weeks (AZ, n=952) vs Olmesartan medoxomil for 2	NR	Change from baseline (ml/min per 1.73 m^2): 0.81 after 12 weeks (OLM) vs 2.42 after 12 weeks (AZ) vs 1.53 after 2 years (OLM). Change in eGFR with AZ was significantly larger than with OLM after 12 weeks (eGFR difference in least square means =1.23,	NR

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
		years (OLM, n=109)		P=0.0069).	
Anand 2009 (58)	HF (moderate to severe) patients with CKD	Valsartan (n=1477) vs placebo (n=1439)	NR	Mean decrease in eGFR from baseline (ml/min per 1.73 m^2): -6.2 vs -3.0 during 24 months of follow-up.	NR
Tokunaga 2010 (150)	Patients with advanced CKD (stage 3-4)	Telmisartan (n=36) vs conventional anti-hypertensive therapy (n=36)	NR	Rate of decline in eGFR from baseline over 12 months (ml/min per 1.73 m^2/month: -0.35 vs -1.00. Telmisartan was associated with a 49.6% reduction in the rate of decline vs control	NR
Edwards 2012 (151)	Non-diabetic patients with early stage CKD (stage 2 or 3)	ACEi/ARB + spironolactone (intervention n=56) vs ACEi/ARB + placebo (control n=56)	NR	Mean eGFR (ml/min per 1.73 m^2): Intervention: 49 at baseline and 46 at week 40, P<0.01 Control: 53 at baseline and 52 at week 40, P=0.48	NR
Voskamp 2017 (152)	Incident pre-dialysis patients with CKD stage 4-5	ACEi (n=161) vs ARB (n=140) vs combined ACEi/ARB (n=71) vs non-ACEi/ARB use (n=122)	NR	Mean annual rate of decline in eGFR (ml/min per 1.73 m^2/year): All patients: -1.41 (95%CI: -1.83 to -1.00) ACEi use was associated with an extra decline of -0.76 (95%CI: -2.05 to 0.53). ARB use was associated with an extra decline of -0.65 (95%CI: -1.89 to 0.58) Combined ACEi/ARB use was associated with an extra decline of -0.65 (95%CI: -2.18 to 0.79)	NR
Yasuda	Japanese	Conventional	NR	Mean annual rate of decline in	NR

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
2013 (147)	hypertensive patients with advanced pre-dialysis CKD (Stage 3-5)	therapy + valsartan (n=149) vs conventional therapy (n=149)		eGFR (ml/min per 1.73 m^2/year) during median 23.8 months follow-up: 3.66 vs 5.20, difference not significant.	
Bermejo 2018 (161)	Diabetic patients with CKD stage 4 or 5	Inconstant RAASi (n=73) vs constant-RAASi (n=82) vs no-RAASi (n=42)	NR	Mean change in eGFR (ml/min per 1.73 m^2) after 1 year follow-up: -1.96±9.3 vs -0.15±10.66 vs -2.43±7.88 (using CKD-EPI formula) and -2.4±7.7 vs -0.5±8.4 vs -3.61±6.52 (using MDRD formula). Mean change in eGFR (ml/min per 1.73 m2) after 3 years follow-up: -6.3±12.55 vs -2.32±11.35 vs -7.52±11.00 (using CKD-EPI formula) and -6.9±12.4 vs -3.3±10.6 vs -8.12±10.20 (using MDRD formula)	NR
Moriyama 2011 (168)	Patients with advanced immunoglobin A nephropathy and impaired renal function (CKD stage 3 and 4)	ACEi (n=20) vs ARB (n=23) vs anti-platelet agents (n=23)	NR	Mean eGLF (ml/min) at biopsy and 1 year after biopsy: ACEi group: 47.7 and 47.7 (eGFR maintained) vs ARB group: 48.8 and 43.3 (eGFR not maintained) vs Anti-platelet group: 48.2 and 45.3 (eGFR not maintained). Median rate of eGFR decline: 1.33% vs 12.86% vs 6.85% 50% decrease of eGFR from baseline (per 10ml/min): HR: 0.45 (95%CI, 0.19-1.01, P=0.0537)	NR

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
Wang 2012 (169)	Chinese patients with primary glomerulonephritis in CKD stage 3	Benazepril (n=189) vs Benazepril + TCM (n=191) vs TCM only (n=192)	NR	Change in eGFR from baseline to 24 weeks follow-up (ml/min): Benazepril: 44.5 to 43.0, P>0.05 Benazepril+TCM: 44.68 to 48.31, P<0.05 TCM only: 45.26 to 48.46, P<0.05	Composite end-point of a 50% increase of the serum creatinine, ESRD, or death during 24 weeks of follow-up: Benazepril: 11 patients Benazepril+TCM: 4 patients TCM only: 45 patients
Dattolo 2016 (172)	Patients with CKD stage 5	ACEi (n=188) vs no-ACEi (n=154)	NR	Mean annual rate of eGFR reduction (ml/min per 1.73 m^2): 0.96 vs 3.12, P<0.04.	NR
Yamashita 2011 (174)	Patients with CKD stage 1-5	Patient treated with medication N=1115 (ARB 35.8%, ACEi 19.1%, CCB 32%, β-blocker 9.1%, statin 18.7%, diuretics 13.4%, anti-platelet 35.7%)	NR	Mean annual eGFR decline was -1.01 ml/min per 1.73 m^2. Mean annual eGFR decline by CKD stage (ml/min per 1.73 m^2): Stage 1: -2.33 Stage 2: -1.10 Stage 3: -0.75 Stage 4: -1.32 Stage 5: -0.31	NR
Gillis 2017 (90)	Patients with CKD	MRA (n=402) vs no-MRA (n=NR) (Total N=7766)	NR	Annual reduction in eGFR from baseline during median 2269 days follow-up (ml/min per 1.73 m^2/year): 3.0 vs 2.3, P<0.001. Annual change in eGFR was greatest with eplerenone group and lowest with no-MRA (3.3 vs 2.9, P=0.001) Annual change in eGFR was greatest with high-dose MRA vs low-dose MRA or no-MRA (4.5 vs	Incidence during median 2269 days follow-up: 11.4% vs 14.9%, P=0.06

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
				2.9 vs 2.3, P=0.001)	
Lewis 2001 (91)	Patients type 2 diabetic nephropathy and CKD stage 1-5	Amlodipine (n=567) vs placebo (n=569) vs irbesartan (n=579)	NR	Rate of change in eGFR decline (ml/min per 1.73 m^2): -3.76 vs -3.52 vs -2.34. Irbesartan significantly slowed the rate of change in eGFR decline from 6 to 21 months (P=0.0048) versus amlodipine and 24 to 48 months (P<0.0001) vs placebo.	Incidence: 18.3% vs 17.8% vs 14.2% during mean follow-up of 924 days vs 952 days vs 921 days. Unadjusted RR was 23% lower in irbesartan group than either amlodipine group or placebo group (P=0.07)
Cozzolino 2018 (177)	Patients with CKD stage 1-5	Patient treated with medication N=868 (CV medication 94.6%, lipid-lowering medication 52.6%, ESAs 16.6%, iron-based therapy 17.9%, vitamin D supplements 35.0%)	NR	Mean eGFR (ml/min per 1.73 m^2): Baseline: 50.73 6 months: 49.11 12 months: 47.69 18 months: 47.36 24 months:47.21 30 months:46.23 36 months:45.86	NR
Sud 2016 (132)	Patients with CKD stage 3	No intervention (N=1607)	21% patients progressed from CKD stage 3 to 4, during median follow-up of 2.66 years. Of these, 17% were stage 3A and 83% were stage 3B at baseline. Mean eGFR in patients who progressed vs those who did not progress (ml/min per 1.73 $m^{2)}$: 24 vs 46	NR	3% of patients developed ESRD during median follow- up of 2.66 years.
Daniela 2012 (170)	Patients with CKD stage 3 Elderly (>70 yrs) n=162	ACEis and/or ARBs	Incidence of stage 3 to 4 progression over 4 years of follow-up: 14.8% in elderly vs 23% in younger adults.	NR	Progression to ESRD was significantly slower in elderly than in younger adults (p<0.001) during 4 years follow-up

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
	Younger adults (<70 yrs) n=165				
Oh 2017 (92)	Pre-dialysis patients with CKD stage 4 or 5	ACEi/ARB (n=1237) vs no ACEi/ARB (n=839)	NR	NR	ACEi/ARB users had a significantly higher risk of developing ESRD compared to non-users (P<0.001) during 28 months of follow-up.
Omae 2010 (94)	Patients with non-diabetic CKD stage ≤4	ACEi (n=85) vs ARB (n=127) vs CCB (n=36)	Proportion of patients reaching stage 5: 11.8% vs 13.4% vs 41.7%	NR	NR
Arora 2015 (93)	Elderly veterans with CKD without diabetes or proteinuria	RAASi (n=1186) vs other anti-hypertensives (n=1288)	Proportion of patients reaching stage 5 during median follow-up of 785 days: 4.3% vs 3.4% Effect of RAASi on progression (combined stage 5 CKD and doubling of serum creatinine): Adjusted HR: 1.16 (95%CI: 0.97-1.38)	NR	NR
Arora 2017 (166)	Elderly patients with CKD stage 3 or 4	No intervention N=4562 Stage 3A (n=2917), stage 3B (n=1436), stage 4 (n=209)	<u>Progression rate during 6-year follow-up:</u> Patients with stage 3A: >1% rate: 49.4% of patients 1-4% rate: 48.3% of patients >4% rate: 2.3% Patients with stage 3B: >1% rate: 61.8% of patients 1-4% rate: 37.7% of patients >4% rate: 0.5% of patients Patients with stage 4:	NR	NR

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
			>1% rate: 69.4% of patients 1-4% rate: 30.6% of patients >4% rate: no patients		
Jovanovich 2015 (88)	Patients with advanced CKD and ESRD	ACEi/ARB (n=870) vs no-ACEi/ARB (n=883)	NR	NR	Incidence of chronic dialysis initiation was lower in ACEI/ARB group vs no-ACEI/ARB group: Propensity-adjusted HR for dialysis initiation among ACEI/ARB group = 0.81 (95%CI: 0.69-0.95)
Hsing 2015 (78)	Hypertensive patients with CKD	Losartan (n=6377) vs ramipril (n=2597) vs conventional hypertensive treatment (n=127292)	NR	NR	Incidence during 4.9 years follow-up: 5.25% vs 5.12% vs 5.42%. Incidence rate/1000 PYs: 9.01 vs 9.03 vs 9.18. Risk of reaching ESRD: Losartan vs conventional: HR=0.908 (95%CI, 0.802-0.975, P=0.01) Ramipril vs conventional: HR=0.902 (95%CI, 0.811-0.964, P=0.02).
Vejakama 2017 (89)	Diabetic patients with CKD	RAAS2 (used RAAS for >12 months, n=3849) vs RAAS1 (used RAAS for 3-12 months, n=623) vs non-RAAS (never used or used for<3 months, n=10560)	NR	NR	Risk of having ESRD during 4.7 years follow-up: 12.9% vs 19% vs 20.0% The risk difference was significant between RAAS2 and no-RAASi
	Non-diabetic patients with CKD	RAAS2 (n=1899) vs RAAS1 (n=588) vs non-RAAS	NR	NR	Risk of having ESRD during 4.2 years follow-up: 11.4% vs 16.1% vs 18.1%. The risk difference was significant

Author & year	Patient population	Intervention vs comparator	Outcomes		
			CKD progression	Change in eGFR	Development of ESRD
		(n=14587)			between RAAS2 and no-RAASi
Parving 2012 (83)	Patients with T2DM (98.1% with CKD)	Aliskiren (n=4274) vs placebo (n=4287)	NR	NR	Onset of ESRD or renal death during median follow-up of 32.9 months: Aliskiren: 2.8% of patients. HR=1.08 (95%CI, 0.84-1.40) Placebo: 2.6% Onset of ESRD or renal death at second interim analysis: Aliskiren: 1.7% of patients. HR=1.22 (95%CI, 0.87-1.72) Placebo: 1.4%
Kim-Mitsuyama 2018 (71)	Hypertensive patients with CKD stage 3b,4 or 5	ARB (n=612) vs no-ARB (n=610)	NR	NR	ARB group: ESRD developed in one patient with stage 3B and no patients with CKD stage 4/5. No-ARB group: no patients developed ESRD
Zeng 2015 (176)	Hypertension patients with CKD stage 3-4 and macroproteinuria	Treated for 1 year with ACEi/ARB and other hypertensives (n=122)	NR	NR	16 (13.1%) patients progressed to renal dialysis: 4 stage 3 patients and 12 stage 4 patients during 9 years of follow-up
Provenzano 2018 (105)	Non-dialysis patients with CKD	RAASi (single arm study n=2443)	NR	NR	567 (23.2%) patients reached ESRD during 3.6-year follow-up, Incidence rate (95%CI): 6.4 (5.8-6.9)/100 PYs New onset hyperkalaemia sHR: 1.34, (95%CI, 1.05-1.72) and persistent hyperkalaemia sHR: 1.27, (95%CI 1.02-1.58) predicted higher ESRD risk versus absent

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CKD-EPI; chronic kidney disease epidemiology collaboration; ESAs, erythropoietin-stimulating agents; HF, heart failure; HR, hazard ratio; MDRD, modification of diet in renal disease; MRA, mineralocorticoid receptor antagonist; NR, not reported; PY, patient-years; RAASi, renin-angiotensin aldosterone system inhibitors; TCM, traditional Chinese medicine

10.4.4.1. Change in eGFR

Single studies were reviewed to assess the effect of RAASi on eGFR in patients with CKD.

While many studies indicated that RAASi use on patients with CKD had a beneficial effect on eGFR over time, others found that it may increase the rate of eGFR decline.

Notably, two studies found that treatment with RAASi could increase or maintain mean eGFR for up to two years in patients with CKD (149, 168). Furthermore, six studies found RAASi reduced the rate of decline in eGFR in patients with CKD compared with conventional therapy, no-RAASi or placebo, although the relative reduction was not always significant (23, 91, 147, 150, 161, 172).

Conversely, five studies found that RAASi caused a greater decline in mean eGFR over time in patients with CKD when compared to placebo, non-RAASi users or traditional Chinese medicine, (58, 90, 151, 152, 181).

In conclusion, the single study review of eGFR provided a mixed outcome with many studies reporting a beneficial effect of RAASi on eGFR with others reporting a detrimental effect compared with conventional therapy or no-RAASi.

10.4.5 Findings for outcome 3: Association between serum potassium level and mortality

A summary of the 15 single studies that reported on the association between serum potassium level and mortality in patients with CKD is provided in Table 52.

Table 52: Association between serum potassium level and mortality reported in single studies

Author & year	Patient population	Treatment	Hyperkalaemia	Hyperkalaemia and mortality
Bennett 2017 (98)	Patients with HF or CKD (stage 3-5)	ACEi, ARB, MRA and/or renin inhibitors (observational study N=144388)	NR	In the CKD cohort, predicted mortality rates increased with increasing serum K+: • 0.100 (K+ 4.5-5.0 mmol/L) to 0.308 (K+ ≥6.0 mmol/L) for males • 0.069 (K+ 4.5-5.0 mmol/L) to 0.213 (K+ ≥6.0 mmol/L) for females. Compared to the reference category (K+ 4.5-5.0 mmol/L), predicted mortality rates increased by the following factor with increasing serum K+: • 1.13 (K+ 5.0-5.5 mmol/L) • 1.60 (K+ >5.5 mmol/L) • 3.07 (K+ >6.0 mmol/L) Expected five-year mortality rates in CKD patients prescribed RAASi were: • 0.114 for K+ 4.5 mmol/L • 0.116 for K+ 5.5 mmol/L • 0.142 for K+ 6.5 mmol/L
Provenzano 2018 (105)	Non-dialysis patients with CKD	RAASi (single arm study N=2443)	New onset and persistent HK (serum K+ ≥5.0 mmol/L) were reported in 15% and 22% of CKD patients, respectively	A 1 mmol/L serum K+ increase at visit 2 was associated with 20% higher risk of ESRD: HR=1.20 (95%CI, 1.04-1.39, P=0.014) with no effect on mortality: HR=0.94 (95%CI, 0.76-1.17, P=0.57). The crude incidence of ESRD progressively increased from absent to persistent HK while the association with mortality was less evident.
Trevisan 2018 (99)	Patients with CKD, all stages	Spironolactone or eplerenone (observational study N=13726)	18.5% of CKD patients experienced at least one detected hyperkalaemia (K+ >5.0 mmol/L). Mild HK (5.0–5.5 mmol/L) observed in 14.9% of patients. Moderate (5.5–6.0 mmol/L)/severe HK	Development of HK was associated with a significantly higher risk of mortality: HR=4.3 (95%CI, 3.8-4.7)

			(>6.0 mmol/L) observed in 7.1% of patients	
Thomsen 2018 (100)	Patients with CKD stage 1-5	ACEi prescribed in 23% of patients, ARB in 14%, spironolactone in 8% and potassium supplements in 17% (cohort study N=157766)	During median follow-up of 2.9 years, 28% of CKD patients experienced a first HK event (elevated K+ >5.0 mmol/L), corresponding to an overall incidence rate of 70/1000 PY. HK incidence increased with CKD severity with highest rates observed in patients with CKD stages 3B-5 (events/1000 PY): Stage 3B = 119 Stage 4 = 239 Stage 5 = 333 Proportion of patients who experienced HK within the first year following CKD diagnosis: Stage 3A = 9% Stage 3B = 18% Stage 4 = 31%	The 6-month mortality following HK was 26% compared with 6% in CKD patients without HK.
Collins 2017 (29)	Patients with and without HF, CKD (stage 3-5) and/or diabetes mellitus.	RAASi prescribed in 30% of patients, thiazide in 19% and loop diuretics in 6% (observational study N=911698)	NR	All-cause mortality rates per index serum K+ between 2.5 and 8.0 mmol/L were consistently greater with CKD 16.6% vs controls 1.2%. All-cause mortality increased continuously with serum K+ values above or below the 4.0–5.0 mmol/L range in CKD patients and control group. In the CKD cohort, predicted mortality rates increased with increasing serum K+ from 28.6% (K+ 5.5 to <6.0 mmol/L) to 79.5% (K+ 6.5-8.0 mmol/L).
Einhorn 2009 (159)	Patients with and without CKD (stage 3-5)	RAASi vs no-RAASi (observational study N=70873)	The adjusted rate of HK (≥5.5 mmol/L) was higher in patients with CKD than in those without CKD (events/100 PM): • Patients treated with RAASi: 7.67 vs 2.30, P<0.001 • Patients with no-RAAS treatment:	As the stage of CKD becomes more severe, the odds of death with a moderate (K+, ≥5.5 and <6.0 mmol/L and severe (potassium, ≥6.0 mmol/L) HK event decreased. Adjusted OR vs normokalaemia and no CKD: No CKD: OR=10.32 (moderate HK), OR=31.64 (severe HK). Stage 3: OR=5.35 (moderate HK), OR=19.52 (severe HK)

			8.22 vs 1.77, P<0.001	Stage 4: OR=5.73 (moderate HK), OR=11.56 (severe HK) Stage 5: OR=2.31 (moderate HK), OR=8.02 (severe HK) all P<0.001 and no CKD. The mortality rate increased as K+ concentration increased from <5.5 to ≥6.0: • OR from 1.07 to 19.52 in stage 3 CKD patients • OR from and 1.04 to 11.56 in stage 4 CKD patients • OR from 1.27 to 8.02 in stage 5 CKD patients
Parving 2012 (83)	Patients with T2DM (98.1% with CKD)	Aliskiren (n=4274) vs placebo (n=4287)	NR	The association between serum K+ and mortality was not reported. However, in subgroup analysis of patients with ≥5.0 mmol/L, a higher mortality rate was reported in patients treated with Aliskiren vs placebo: 10.7% vs 8.1%, HR=1.36, (95%CI, 0.95-1.95; P=0.09).
Gorriz 2017 (153)	Non-dialysis patients with CKD stage 4-5	RAASi (n=727) vs no-RAASi (n=268)	The prevalence of HK (K+ >5.5 mmol/L) during follow-up of 3 years was 15% in patients receiving RAASi vs 9.3% in patients with no-RAASi (P<0.001)	NR
Hsieh 2011 (154)	Patients with late stage CKD (stage 3-5)	ACEis/ARBs (n=443) vs no-ACEis/ARBs (n=88)	During follow-up of 12 months, patients with stage 4 and 5 CKD had significantly higher serum K+ levels (p<0.05). compared with patients with stage 3 CKD (stage 3: 4.36 mmol/L, stage 4: 4.50 mmol/L, stage 5: 4.69 mmol/L). A rise of 0.117 mmol/L of serum K+ per 10 eGFR (ml/min) decrease was reported. Serum K+ levels did not differ between patients with or without ACEIs/ARBs	NR
Jenkins 2017 (155)	HF patients with CKD	ACEi/ARB and MRA prescriptions (observational study N=851)	No significant difference in the mean serum K+ between the ACE/ARB users and non-users. In patients with eGFR <60 ml/min/1.73 m^2, those prescribed ACE/ARB had a mean serum K+ of 4.44 mmol/L vs 4.37 mmol/L in those with no ACE/ARB	NR

			(P=0.353). In patients with eGFR >60 ml/min/1.73 m^2, those prescribed ACE/ARB had a mean serum K+ of 4.19 mmol/L compared with 4.38 mmol/L in those with no ACE/ARB (P=0.05).	
Edwards 2012 (151)	Non-diabetic patients with early stage CKD (stage 2 or 3)	ACEi/ARB + spironolactone (intervention n=56) vs ACEi/ARB + placebo (control n=56)	<1% of serious HK events (K+ 6.0 mmol/L) after 40 weeks of treatment. Mean serum K+ increased by 0.22 mmol/L (95%CI, 0.14-0.30, P<0.01) over the first 4 weeks of treatment with spironolactone. After randomization mean serum K+ concentrations were persistently higher (P<0.05) with spironolactone than with placebo. A serum K+ level of 5.5–5.9 mmol/L occurred on ≥1 occasion over follow-up in nine patients on spironolactone and two patients on placebo and was predicted by baseline K+ ≥5.0 mmol/L and eGFR ≤45 ml/min/1.73 m^2	NR
Charytan 2019 (81)	Patients with ESRD on dialysis	Spironolactone 12.5mg (n=27) vs spironolactone 25mg (n=26) vs spironolactone 50mg (n=25) vs placebo (n=51)	Similar frequency of HK between spironolactone and placebo (0.49 vs 0.50 events/PY) but a significant linear trend was observed primarily due to the increased event rate at the 50 mg dose (0.89 events/PY).	NR
Sengul 2009 (171)	Patients with CKD and proteinuria	Spironolactone (N=33)	18.2% of CKD patients experience HK after 8 weeks of spironolactone therapy. A mean increase of 0.55 mmol/L was detected in serum K+ level (P<0.001).	NR
Gillis 2017 (90)	Patients with CKD	MRA (n=402) vs no-MRA (n=NR) (Total N=7766)	No significant difference in the proportion of patients experiencing a HK event (6.5 mmol/L) between the MRA group and no-	NR

			MRA group: 16.9% vs 15.5%; P=0.60	
Fogelfeld 2017 (173)	Low-income adults with T2DM and CKD stage 3-4	Multifactorial-multidisciplinary intervention combined coordinated medical care including ACEi and ARB (Intervention n=60) vs usual care (ACEi/ARB) (control n=60)	Higher incidence of HK (K+ >5.5 mmol/L) in intervention vs. control: 46.7% vs. 23.3%, P=0.012 but no difference for HK rates for recorded K+ tests: 5.2% vs. 5.7%. No significant difference in HK (K+ >6 mmol/L) incidence between intervention and control: 13.3% vs 8.3% and rates for recorded potassium tests: 0.8% vs. 1.3%.	NR
Furuland 2018 (102)	Patients with CKD (stage 3a-5, pre-dialysis)	ACEi, ARB and MRA (observational study N=191964)	NR	CKD patients were stratified by serum K+ level at baseline. Model output for risk equations reported the co-efficient estimates for different serum K+ level by using incidence of death as an exploratory variable. Co-efficient estimates were: • 0.9137 for serum K+ <3.5 mmol/L • 0.2385 for serum K+ 3.5 to <4.0 mmol/L • 0.0184 for serum K+ 4.0 to <4.5 mmol/L • 0.1304 for serum K+ 5.0 to <5.5 mmol/L • 0.4689 for serum K+ 5.5 to <6.0 mmol/L • 1.0578 for serum K+ for ≥6.0 mmol/L was and A U-shaped association between serum K+ and mortality was shown. Mortality risk was lowest among patients with serum K+ between 4.0–5.0 mmol/L. Patients prescribed RAASi had a lower predicted rate of death over the all the serum K+ categories compared to no-RAASi.
Luo 2016 (103)	Patients with CKD	RAASi	NR	Mortality rates were reported by serum K+ exposure groups within eGFR strata (<30, 30–39, 40–49, and 50–59 ml/min/1.73 m2. Within eGFR strata, there were significant U-shaped associations between serum K+ and mortality: eGFR <30 ml/min/1.73 m^2 Adjusted mortality rate was higher for K+ levels ≥6.0 mmol/L (IRR: 3.08, 95%CI, 2.17-4.37) than K+ levels 5.0-5.4 mmol/L (IRR: 1.01, 95%CI, 0.83-1.22) and K+ levels 5.5-5.9 mmol/L

				(IRR: 1.11, 95%CI, 0.84-1.47). eGFR 30-39 ml/min per 1.73 m^2 Adjusted mortality rate was higher for K+ levels ≥6.0 mmol/L (IRR: 2.74, 95%CI, 1.13-6.74) than K+ levels 5.0-5.4 mmol/L (IRR: 0.73, 95%CI, 0.47-1.11) and K+ levels 5.5-5.9 mmol/L [IRR: 0.98, 95%CI, 0.52-1.88). For eGFR 40-49 ml/min per 1.73 m^2 Adjusted mortality rate for K+ levels 5.0-5.4 mmol/L (IRR: 1.18, 95%CI, 0.99-1.42), K+ levels 5.5-5.9 mmol/L (IRR: 1.68, 95%CI, 1.23-2.30), and K+ levels ≥6.0 mmol/L (IRR: 1.72, 95%CI, 0.76-3.86). eGFR 50-59 ml/min per 1.73 m^2 Adjusted mortality rate was higher for K+ levels ≥6.0 mmol/L (IRR: 3.90, 95%CI, 1.23-12.32) than K+ levels 5.0-5.4 mmol/L (IRR: 1.02, 95%CI, 0.74-1.42) and K+ levels 5.5-5.9 mmol/L (IRR: 0.99, 95%CI, 0.49-2.01). Pooled across eGFR strata Pooled mortality adjusted IRRs were statistically significant for all serum K+ categories versus the reference K+ level of 4.5-4.9 mmol/L
Boesby 2013 (157)	Patients with CKD stage 3-4	Eplerenone (N=26) vs standard medication (control) (N=25)	The mean values of plasma K+ for the control visits did not differ significantly between the groups. In total three measurements of plasma K+ were above 5.5 mmol/L in the eplerenone group, maximum value 5.7 mmol/L, while in the control group two measurements of plasma K+ were above 5.5 mmol/L, maximum value 5.6 mmol/L. During treatment mean plasma K+ was 4.6 mmol/L (4.4, 4.7) in the eplerenone group and 4.4 mmol/L (4.3, 4.6) in the control group. The difference between changes in the groups was -0.2 mM (-0.5, 0.0), p=0.2.	NR

Garlo 2018 (106)	Patients with CKD stage 3-5 (stage 3 n=4198, stage 4 n=382, stage 5 n=81]	RAASi (lisinopril, valsartan, and losartan potassium) (N=2354) vs diuretics (furosemide, hydrochlorothiazide, and combined triamterene and hydrochlorothiazide) (N=2307)	Incidence of hyperkalaemia within one year after treatment: <u>In RAASi group</u> • >5.0 mmol/L occurred in 251 patients (10.7%) • >5.0 to 5.5 mmol/L occurred in 210 patients (8.9%) • >5.5 to 6.0 mmol/L occurred in 33 patients (1.4%) • >6.0 mmol/L occurred in 8 patients (0.3%) <u>In Diuretic group</u> • >5.0 mmol/L occurred in 162 patients (7.0%) • >5.0 to 5.5 mmol/L occurred in 113 patients (4.9%) • >5.5 to 6.0 mmol/L occurred in 38 (1.6%) >6.0 mmol/L occurred in 11 (0.5%)	Association between >5.0 mmol/L and mortality within 1 year after RAASi or diuretic prescription: • Univariate OR: 1.07 (95%CI, 0.68-1.66), p=0.78 • Multivariate OR: 1.07 (95% CI, 0.59-1.92), p=0.83
Jun 2019 (104)	Patients with CKD	RAASI prescription (N=20,184)	9.9% of patients experienced hyperkalaemia (>6.0 mmol/L). Incidence of hyperkalaemia: 3.1 (95%CI: 2.9–3.2)/100 PY	During the study period, mortality was higher among patients who experienced incident hyperkalaemia (356/1,992; 17.9%) compared with those who did not (2,051/18,192; 11.3%).

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; IRR, incidence rate ratio; K+ potassium; MRA, mineralocorticoid receptor antagonist; NR, not reported; OR, odds ratio; PM, patient-months; PY, patient-years; RAASi, renin-angiotensin aldosterone system inhibitors; T2DM, type 2 diabetes mellitus

10.4.6 Findings for outcome 4: Validation of Xie NMA

A summary of the eight studies that were considered useful for Xie et al's NMA validation outcomes are shown in Table 53.

Table 53: Xie NMA validation outcomes reported in single studies

Author & year	Patient population	Treatment	NMA validation
Bennett 2017 (98)	Patients with HF or CKD (stage 3-5)	ACEi, ARB, MRA and/or renin inhibitors (observational study N=144388 CKD patients)	RAASi discontinuation rates increased with increase in K+ levels: 0.326 for K+ 4.5 mmol/L, 0.419 for K+ 5.5 mmol/L, and 0.576 for K+ 6.5 mmol/L. Discontinuing RAASi was associated with increased mortality risk: 0.263 for K+ 4.5 mmol/L, 0.269 for K+ 5.5 mmol/L, and 0.329 for K+ 6.5 mmol/L.
Goncalves 2011 (110)	Hypertensive patients with progressive CKD (stage 4)	Patients on RAASi who then stopped RAASi (observational study N=43)	9 (21%) patients died who were not on RAASi.
Ahmed 2010 (109)	Patients with advanced CKD (stages 4 and 5)	Patients on ACEi/ARB who then stopped ACEi/ARB (Observational study N=52)	After 12 months of discontinuation of ACEi/ARB: eGFR increased significantly (P=0.0001) from 16.38 ± 1 ml/min/1.73 m^2 to 26.6 ± 2.2 ml/min/1.73 m2. 61.5% of patients had >25% increase in eGFR. 36.5% had a > 50% increase in eGFR. 25% of patients changed from CKD stage 5 to 4 19% of patients changed from CKD stages from stage 4 to 3.
Garlo 2018 (106)	Non-dialysis patients with CKD (stage3-5) newly prescribed a RAASi or diuretic	Patients with RAASi prescription (n=2354)	Association with mortality within one year of new RAASi prescription: OR if RAASi therapy discontinued: 0.91 (95%CI, 0.54-1.52, P=0.72) as per univariate analysis 0.56 (95%CI, 0.16-1.92, P=0.36) as per multivariate analysis
Bainey 2015 (158)	Patients with moderate renal insufficiency (creatinine ≥150 µmol/L within 3 months and/or documented creatinine ≥132 µmol/L within 1 week before cardiac catheterisation)	Continued ACEi/ARB prior to cardiac catheterisation (n=102) vs hold ACEi/ARB prior to cardiac catheterisation (n=106)	At 72 hours post-follow-up, patients who continued ACEi/ARB therapy prior to cardiac catheterisation reported: • No risk of MI and CHF events • Risk of ischemic stroke event vs hold ACEi/ARB: HR =0.32 (95%CI, 0.01-7.79) • Risk of re-hospitalisation for CV causes vs hold ACEi/ARB: HR=0.14 (95%CI, 0.01-2.63) • Mortality risk vs hold ACEi/ARB: HR=0.32 (95%CI, 0.01-7.79). Patients who held ACEi/ARB therapy (n=106) reported no risk of MI, CHF, ischemic stroke, re-hospitalisation for CV cause, and mortality risk. The clinical composite of death, myocardial infarction, ischemic stroke, congestive heart failure, rehospitalisation for cardiovascular cause, or need for dialysis pre-procedure occurred in 3.9% who continued ACEI/ARB vs 0% who held ACEI/ARB: HR=0.11 (95%CI, 0.01-2.96, P=0.06).
Onuigbo 2008 (111)	Patients with CKD	Withdrawal of RAASi therapy	After withdrawal of RAASi therapy, eGFR increased during the mean follow-up of 34.8 months: mean change from 27.8

		(lisinopril was most commonly used) (n=19)	ml/min/1.73 m^2 to 36.7 ml/min/1.73 m^2, (P=0.014). Despite withdrawal of RAASi therapy, 5 (19%) patients progressed to ESRD of which 4 (80%) patients died 5.5 months after starting haemodialysis.
Epstein 2015 (17)	Patients with CKD stages 3-4 and/or heart failure or diabetes mellitus	RAASi (total population N=205108, CKD population receiving RAASi N=43288)	During 3.4 years of follow-up, 54.4% of patients who discontinued RAASi experienced an adverse outcome or died compared with 47.4% of patients on submaximal doses (defined as any RAASi dose lower than the labelled dose) and 42.6% of patients on maximum doses (defined as the labelled dose) (all comparisons P<0.05). 22.4% of patients who discontinued RAASi died vs 20.3% on submaximal dose and 9.8% on maximum dose.
Onuigbo 2008 (160)	A cohort of patients with CKD who exhibited ≥25% increase in baseline serum creatinine	Patients were using an ACEi, an ARB or both then RAASi was discontinued (n=100)	After a mean 4 years of follow-up, 18 (18%) developed ESRD, of whom 8 died. The final eGFR in 70 patients was 38 mL/min per 1.73 m^2 after 43 months. Of those 70 patients, 50% improved by ≥1 CKD stage after 45 months, 40% remained in the same CKD stage after 40 months (including 23% who remained at stage 4), 10% showed progression of CKD stage after 43 months.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; CHF, chronic heart failure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; K+ potassium; OR, odds ratio; MI, myocardial infarction; RAASi, renin-angiotensin aldosterone system inhibitor

10.5 Appendix 5: CPRD

10.5.1 CPRD study statistical analysis plan

CPRD SAP.docx

10.5.2 CPRD study variables and definitions

Table 54: CPRD study variables and definitions

Variable	Definition
Demographic and clinical characteristics at RAASi initiation	
Age	Reported as continuous and in the following categories (years): 18-30, 31-40, 41-50, 51-60, 61-70, and 70+.
Sex	Male, Female
BMI	Underweight, normal weight, overweight and obese
eGFR	Continuous (ml/min)
Serum potassium	Continuous (mmol/L)
Comorbidities	Arrhythmia, coronary artery disease, cerebrovascular disease, diabetes mellitus, heart failure, hypertension, myocardial infarction, and peripheral vascular disease. Based on Read codes recorded in the CPRD at any point during the study period.

Variable	Definition
Co-medication prescriptions	Betablockers, digoxin, lithium, metformin, NSAIDs, SGLT2 inhibitors, sulphonylureas
RAASi variables	
RAASi index dose	Dose of the initial RAASi prescription received after CKD3 or CKD4 diagnoses during the study period.
RAASi initiation	Date of RAASi index dose.
Serum potassium variables	
Serum potassium category	Serum potassium values were categorised as follows: • ≤5.0 • >5.0 to ≤5.5 • >5.5 to ≤6.0 • >6.0 These were grouped into two summary categories: • <5.5 • ≥5.5
Index serum potassium value	Closest serum potassium value recorded within 90-days prior to RAASi initiation.

BMI, body mass index; CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drugs; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2, sodium/glucose cotransporter 2

10.5.3 Transition probability calculation

Patients' medical records were reviewed for serum potassium levels on a rolling 30-day cycle from RAASi initiation date to the end of record. The most recent serum potassium measurement recorded within the 90 days prior to RAASi initiation was deemed the baseline serum potassium value. The number of patients within each serum potassium category was reported each month starting from RAASi initiation date. If a serum potassium value was missing in a given month, the previous recorded serum potassium value was imputed and used until such time that a new value was recorded.

The number of patients transitioning or remaining in each serum potassium category was stratified by CKD stage (CKD3 or CKD4). In the event of CKD progression (i.e. from CKD3 to CKD4), the patients' serum potassium category was counted in CKD4 until the end of record or further stage change.

The probability of transitioning or remaining in a given serum potassium category was calculated as

$$\text{Probability transition/remain} = \frac{\text{No. of patients in a serum potassium category in month m+1}}{\text{Total no. of patients in source serum potassium category in month m}}$$

follows:

10.5.4 CPRD data tables

CPRD outputs.xlsx

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Patiromer for treating hyperkalaemia [ID877]

Company evidence submission 2: revised base case following ERG report

October 2019

File name	Version	Contains confidential information	Date
ID877_CS2_revised_company_base case_v2.docx	2.0	Yes	18.10.2019

Contents

Abbreviations

Abbreviation	Definition
AEs	Adverse events
AUC	Area under the curve
CEAC	Cost-effectiveness acceptability curve
CS2	Company submission 2
ERG	Evidence Review Group
HK	Hyperkalaemia
HR	Hazard ratio
ICER	Incremental cost effectiveness ratio
KM	Kaplan Meier
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
PAS	Patient access scheme
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RWPDC	Real-world patiromer discontinuation curve
SMRs	Standardised mortality ratios
US	United States

1. Revised Base Case

Following Company Submission 2 (CS2) for patiromer, Vifor Pharma have implemented three key changes to the modelling of patiromer for the treatment of adults with hyperkalaemia. Changes suggested by the Evidence Review Group (ERG) following CS2 have also been implemented, resulting in a revised company base case analysis. The details of the changes and the updated cost effectiveness results are presented below.

1.1 Change 1: incorporation of a treatment discontinuation curve based on real-world data

1.1.1 Reason for change

In CS2, the company presented scenario analyses on the average duration of treatment with patiromer informed by real-world US claims data, which provided drug prescription and dispensing data from 2016 through to 2019. An 'area under the curve' (AUC) method was utilised, therefore applying the mean observed treatment duration to all patients in the economic model (CS2 Section 8.4.4). Subsequently, the ERG requested the data underlying the Kaplan-Meier (KM) curve on real-world patiromer persistence at the clarification stage, as well as the patiromer discontinuation curve from AMETHYST. After up-to-date real-world persistence data and the associated KM curve was provided to the ERG, the company decided to directly incorporate this data into the model by way of a treatment discontinuation curve (as an alternative to using the AUC method, as this offers a more accurate way to model time on treatment than using an average).

1.1.2 Rationale for approach

A consultation on NICE's Statement of Intent, which set out the ways in which NICE already use real-world data and how they would like to extend this in the future, was open from June to September this year.

Randomised controlled trials (RCTs) are generally considered to provide the highest standard of evidence on treatment efficacy. These studies have strict inclusion and exclusion criteria within controlled and experimental conditions. However, due to their highly controlled nature, it is possible that results from RCTs may not be generalisable to the more varied and diverse patient groups seen in real-world clinical practice. This seems particularly true for compliance and persistence of treatments. When available, real-world data may supplement RCT results to provide insights on the real-world usage of treatment as well as physician and patient behaviours. [Bell et al., 2016; Webster & Smith, 2019]

The company believe real-world data on utilisation of patiromer is a more appropriate data source to inform patiromer discontinuation than AMETHYST. These are the longest cohorts of patients treated with patiromer since its adoption in 2016 analysing real-world drug persistence with patiromer. The

real-world data is likely to provide a more accurate estimation of real-world usage of patiromer given it observes usage in the clinical setting and data is available for a longer duration than the 52 weeks available in AMETHYST.

1.1.3 Parametric extrapolation

Approximately three years of real-world persistence data exists for patiromer, therefore there was a need to extrapolate this to the modelled lifetime horizon (i.e. 35 years). Table 1 shows the AIC and BIC statistics for five parametric curves; exponential, Weibull, loglogistic, gompertz and lognormal. The log-normal parametric curve was selected and incorporated into the model on the basis of being the best statistical fit over the observed period.

Table 1. Parametric fit statistics to the US real world data

Parametric	AIC	BIC
Exponential	532,955.38	532,964.18
Weibull	531,295.28	531,312.88
Loglogistic	522,728.03	522,745.63
Gompertz	526,885.81	526,903.41
Lognormal	***522,206.80***	***522,224.40***

Figure 1 shows the probability of remaining on patiromer over time based on the KM analysis of the real-world data and the associated lognormal parametric curve. The parametric function can be seen to provide a close fit to the data over the entire duration. There is initially a sharp drop in usage (suggesting use in the 'acute' setting) followed by a slower decline. At one, two and three years after initiating patiromer, [redacted], [redacted] and [redacted] of patients remain on treatment, respectively.

Figure 1. US real-world patiromer persistence and lognormal fit

1.1.4 Incorporation into model

Using the proportion of patients on patiromer in each cycle, both the cost and efficacy of patiromer in each cycle was altered according to the lognormal curve, by taking weighed averages of the following:

- Cost of patiromer:
  - (proportion *on* patiromer * cost of patiromer) + (proportion *off* patiromer * £0)
- Hazard ratio for patiromer:
  - (proportion *on* patiromer * hazard ratio) + (proportion *off* patiromer * 1)
- Cost of adverse events (AEs) due to patiromer:
  - (proportion *on* patiromer * cost of AE in the cycle) + (proportion *off* patiromer * £0)
- Disutility of adverse events due to patiromer:
  - (proportion *on* patiromer * disutility due to AE in the cycle) + (proportion *off* patiromer * 0)

1.2 Change 2: Limiting the eligible population to patients with a serum potassium level of >6.0 mmol/L

NICE technology appraisal guidance TA599 was published following the CS2 for patiromer, on the 4th September 2019. The guidance states that sodium zirconium cyclosilicate is recommended as an option for treating hyperkalaemia in adults if used in outpatient care for people with persistent hyperkalaemia and chronic kidney disease stage 3b to 5 or heart failure, *if they have a confirmed*

serum potassium level of at least 6.0 mmol/L. Given this restriction, and to align with this recent guidance, the company have also limited the eligible population to patients with a serum potassium level of >6.0mmol/L. The revised base case population is based on serum potassium at Part A baseline of OPAL-HK. It should be noted that patient numbers for this analysis are reduced (n=[redacted]) and therefore results are also provided for the originally submitted population for reference and comparison.

1.3 Change 3: Reduced daily price of patiromer

The company has reviewed and revised the daily cost of patiromer with the patient access scheme (PAS) from £7.50/day to £5.75/day. We believe this revised price ensures the cost effectiveness of patiromer for the revised patient population.

1.4 Clarification for the ERG on the CS2 population

Page 68 of the ERG report highlights that the number of patients who were recruited into Part A of OPAL-HK was 243, however the total number of patients analysed for Part A serum potassium transitions was [redacted], and the final number of patients included in the CS2 model was [redacted]. The company would like to clarify the reason for these differences.

The OPAL-HK trial included patients with CKD stages 2 and 5, who were not eligible to enter the model. This accounts for [redacted] patients (*243*–[redacted]=[redacted] patients). The analysis also required that patients have a serum potassium reading at both the start and the end of Part A. [redacted] patients did not have a reading at the end of Part A ([redacted]-[redacted]=[redacted] resulting in [redacted] patients for analysis. Restricting the population to only include patients with a serum potassium level of ≥5.5 mmol/L (with heart failure co-morbidity) or serum potassium of >6.0mmol/L (without heart failure comorbidity) i.e. the 'CS2 target population' gives the final [redacted] patients included in the CS2 base case. An excel file containing IPD has been provided so that the ERG can verify the above.

The [redacted] patients who did not have a serum potassium reading at the end of Part A were withdrawn from the trial due to one or more of the following reasons: adverse events, withdrawal of consent, serum potassium outside of the permitted range, CKD progression/dialysis, non-compliance or protocol variations. The company acknowledge that it is possible that patients without a serum potassium reading at the end of Part A may be more likely to be those who do less well on patiromer, therefore excluding these patients may bias the model in favour of patiromer. The company have provided sensitivity analyses in section 3.4 where the proportion of patients who do not respond to patiromer is varied. The company would like to highlight that in the revised population (only patients with a serum potassium level of >6mmol/L, n=[redacted]) only [redacted] patient was missing a serum potassium recording at the end of Part A and was not included in the analysis.

2. ERG suggested changes

2.1 Effects of individual ERG changes to revised company model

The ERG report recommended several changes to the modelling. The effect of each of the ERG revisions to the original company base case, and the effect of combining these revisions are provided in Table 2 (as per Table 25 in the ERG report). The company have reproduced these results for the revised company model containing the real-world patiromer discontinuation curve (RWPDC), at a daily patiromer price of £5.75, for both the full CS2 target population and the revised population of patients. All corrections have been implemented into the revised company model with the following exceptions:

- Revision 7 (REV7, AMETHYST discontinuation curve) is not included, given the use of the RWPDC.
- Revision 9 (REV9) is included but altered due to factual inaccuracy. The ERG state that:

*"As far as the ERG can see the electronic model costs the OPAL-HK Part-A patiromer use on the basis of 4 weeks cost. But the numbers needed to treat [NNT] to be enrolled in OPAL-HK Part-B were 243/107=2.27. In the opinion of the ERG this argues for costing patiromer use during OPAL-HK Part-A as 2.27*4=9.08 weeks' patiromer treatment costs"*.

The company would like to highlight that while Part A included 243 patients, only [redacted] patients had a serum potassium level of ≥5.5 at baseline to be considered potentially eligible for Part B in the first instance (see supplementary Excel file). Of these [redacted] patients, 107 met all eligibility criteria (including a serum potassium reading in the target range of 3.8 to <5.1 mmol/L) and were randomised, therefore the NNT calculation should be [redacted]*/107=*[redacted].

Table 2. Individual ERG revisions to original company base case (Table 25 in the ERG report) and to the revised company model

Analysis	ERG revision	ICER		
		ERG	Revised company model (with RWPDC)	
		£7.50/day	£5.75/day	
		CS2 population	CS2 population	>6.0 mmol/L population
..	Company base case (CS2)	£18,893	£9,738	£8,770
REV1	No direct K^+ SMRs	£45,748	£8,718	£4,126
REV2	ERG Kovesdy direct K^+ SMRs	£36,761	£9,281	£6,002
REV3	Age weighting QoL values correction	£15,426	£7,969	£7,184
REV4	Cycle weighting event costs correction	£18,553	£8,821	£8,108
REV5	CPRD probability averaging	£20,907	£10,671	£9,336
REV6	Pockett QoL values not multiplicative	£19,262	£9,926	£8,815
REV7	AMETHYST-DN patiromer dosing, max 5 years	£41,318	NA	NA
REV8	Midpoint RAASi dosing	£21,052	£11,332	£9,366
REV9	OPAL-HK Part A patiromer dosing NNT (2.27)	£20,578	£11,044	£9,611
Corrected REV9	OPAL-HK Part A patiromer dosing NNT (1.32)	-	£10,067	£8,982
REV1 & 3-9	**ERG revised base case (A):** No direct K^+ SMRs	**£681k**	**-**	**-**
REV1 & 3-6, 8, Corrected REV9	**Company revised base case (A):** No direct K^+ SMRs, No REV 7 (RWPDC instead), corrected REV9 (alternative NNT calculation)	**-**	**£26,379***	**£4,510***
REV2 & 3-9	**ERG revised base case (B):** ERG Kovesdy direct K^+ SMRs	**£232k**	**-**	**-**
REV2 & 3-6, 8, Corrected REV9	**Company revised base case (B):** ERG Kovesdy direct K^+ SMRs, No REV 7 (RWPDC instead), corrected REV9 (alternative NNT calculation)	**-**	**£18,166****	**£7,010****

CS2, Company submission 2; ERG, Evidence Review Group; QoL; quality of life; RAASi, renin-angiotensin-aldosterone inhibitor; NNT, number needed to treat; REV, revision; RWPDC, real-world patiromer discontinuation curve; SMR, Standardised mortality ratio.

**Breakdowns of these results are presented in the results section 3.1.*

***Breakdowns of these results are presented in the results section 3.2*

The ERG presented two base cases, A and B. ERG base case A includes REV1 (no direct serum potassium SMRs) in combination with all other revisions 3-9. ERG base case B includes REV2 (ERG derived Kovesdy et al direct serum potassium SMRs) in combination with all other revisions 3-9.

When considering the same CS2 population, the ERG and company base cases A and B result in markedly different ICERs. This is a result of the change in:

1. The daily price for patiromer
2. The altered NNT calculation due to factual inaccuracy (corrected REV9)
3. The data source used to model patiromer discontinuation, and the method by which the discontinuation curve is applied within the model:
    - The ERG uses a discontinuation curve informed by AMETHYST impacting costs only, with a cap of 5 years of treatment (for internal modelling validity)
    - The company uses a discontinuation curve informed by US real-world patiromer persistence data, and link this to both cost and efficacy of patiromer over the full 35-year time horizon
        - The company believe this is a more accurate representation of patiromer usage in the real world, and a more appropriate modelling approach given the link to both costs and efficacy over the full time horizon

2.2 Revised company base case incorporating ERG changes

Given the decision by the NICE committee for TA599 to exclude a direct link between serum potassium and mortality (i.e. REV1), the revised company model is now aligned to the ERG base case A, with the exception of the aforementioned three key changes:

- US real-world data to model patiromer discontinuation (as opposed to the ERG-preferred source, AMETHYST), with an alternative application of the curve with regards to costs and efficacy
- Revised patient population to include only patients with a serum potassium level of >6.0mmol/L
- Daily price of patiromer of £5.75

This revised base case will be referred to as 'company base case A', and includes ERG revisions 1 (no serum potassium SMRs), 3-6, 8 and a corrected version of revision 9. Results are also presented for the 'company base case B', which is aligned to ERG base case B and includes ERG revisions 2 (ERG-derived Kovesdy et al serum potassium SMRs), 4-6, 8 and a corrected version of revision 9, with the aforementioned three key changes.

3. Results

Deterministic results have been provided for both the company base case A and B, for both the full CS2 target population and the company preferred revised population, which includes only those patients with a starting serum potassium level of >6.0mmol/L.

3.1 Company revised analysis (A) and sensitivity analyses: no direct potassium SMRs

The company revised base case A, which does not apply direct K^+ SMRs results (i.e. no direct link between elevated serum potassium and mortality), provides the results shown in Table 3 below (corresponding to Table 26 of ERG report).

Table 3. Company revised base case: No direct K+ SMRs

	CS2 target population			>6.0mmol/L population		
	QALYs	**Costs**	**ICER**	**QALYs**	**Costs**	**ICER**
Patiromer	6.096	£53,407		6.181	£53,265	
Placebo	6.079	£52,954		6.154	£53,147	
Net	0.017	£453	£26,379	0.026	£118	**£4,510**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

The ERG and corresponding company univariate sensitivity analyses for the population submitted in CS2 are shown in Table 4. The results for the company's revised base case (>6.0mmol/L) are presented in the final column in **bold** text.

Table 4. ERG and company scenario analyses: No direct K+ SMRs (Table 27 of ERG report)

Analysis	ERG revision	ICER		
		ERG model	Revised company model with RWPDC	
		£7.50/day	£5.75/day	
		CS2 population	CS2 population	>6mmol/L population
..	ERG revised base case (A)	£681k	£26,379	**£4,510**
SA01a	McEwan et al direct K^+ SMRs	NA	NA	**NA**
SA01b	Company Kovesdy et al direct K^+ SMRs	NA	NA	**NA**
SA02a	Patiromer HR worsening K^+ halved	£674k	£26,283	**£4,464**
SA02b	Patiromer HR worsening K^+ doubled	£695k	£26,571	**£4,602**
SA02c	Patiromer HR worsening K^+ unity	£789k	£27,719	**£5,150**
SA03	RAASi RR events unity	NA	NA	**NA**
SA04	RAASi active comparator	£2.1mn	£47,631	**£13,700**
SA05a	Mid RAASi 25% of Full RAASi	£402k	£15,066	**£505**
SA05b	Mid RAASi 75% of Full RAASi	£2.0mn	£48,513	**£10,606**
SA06	AMETHYST-DN patiromer dosing, max 2 years	£240k	NA	**NA**
SA07a	Patiromer dosing, all patients 5 years	£3.1mn	NA	**NA**
SA07b	Patiromer dosing, all patients 2 years	£391k	NA	**NA**
SA07c	Patiromer dosing, all patients 1 years	£139k	NA	**NA**
Sa07d	Patiromer dosing, all patients 7 months	£70,542	NA	**NA**
SA08a	CKD3 and CKD4 costs halved	£675k	£23,658	**£1,930**
SA08b	CKD3 and CKD4 costs doubled	£692k	£31,820	**£9,668**
SA09	AE events require 2 GP visits	£683k	£26,617	**£4,666**
SA10	No HK hospitalisations	£712k	£42,164	**£20,736**
SA11	Monthly prescription costs	£698k	£28,304	**£5,773**
SA12a	5 year time horizon	Dominated	£176,449	**£48,496**
SA12b	10 year time horizon	£6.1mn	£49,069	**£9,106**

AE, adverse event; CKD, chronic kidney disease; CS2, Company submission 2; ERG, Evidence Review Group; HK, hyperkalaemia; HR, Hazard ratio; QoL; quality of life; RAASi, renin-angiotensin-aldosterone inhibitor; REV, revision; RWPDC, real-world patiromer discontinuation curve; SMR, Standardised mortality ratio

For transparency, the company have provided all results to the scenarios presented by the ERG, however, the company would like to contest the following scenarios in Table 5.

Table 5. Objections to ERG scenarios

Scenario	Description	Objection
SA04	RAASi active comparator	The NICE committee for TA599 preferred a placebo comparator
SA02c	Patiromer HR worsening K+ unity	It is clinically implausible that patiromer has no effect on serum potassium given the evidence from the OPAL-HK trial
SA10	No HK hospitalisations	This is an unrealistic scenario given that, on assessment of a patient presenting with hyperkalaemia, if there are changes in their ECG or acute increases in serum K+ patients are highly likely to be hospitalised to avoid a life-threatening emergency [NHS/PSA/RE/2018/006; Kovesdy et al., 2014].

ECG, electrocardiogram; HK, hyperkalaemia; HR, Hazard ratio; RAASi, renin-angiotensin-aldosterone inhibitor; REV, revision; RWPDC, real-world patiromer discontinuation curve; SMR, Standardised mortality ratio;

3.2 Company revised analysis (B): Kovesdy et al potassium SMRs

The company revised base case (B) which applies the ERG derived Kovesdy et al direct K^+ SMRs results in the outputs shown in Table 6 (corresponding to Table 27 of ERG report).

Table 6. Company revised base case: ERG derived Kovesdy et al direct K+ SMRs

	CS2 target population			>6.0mmol/L population		
	QALYs	Costs	ICER	QALYs	Costs	ICER
Patiromer	5.929	£51,781		6.013	£51,660	
Placebo	5.896	£51,170		5.963	£51,306	
Net	0.034	£611	£18,166	0.050	£353	£7,010

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

The ERG scenarios for base case B have not been reproduced given the company expect the NICE committee to express a preference for base case A.

3.3 Probabilistic model results

A breakdown of the probabilistic results can be found in Table 7. Please note the PSA has been updated since version 1.0 of this report to exclude serum potassium SMRs from the PSA (rather than varying them around unity, given the assumption of no direct relationship between serum potassium and mortality).

Table 7. Probabilistic base-case results

	CS2 target population			>6.0mmol/L population		
	QALYs	**Costs**	**ICER**	**QALYs**	**Costs**	**ICER**
Patiromer	6.173	£52,590		6.221	£52,145	
Placebo	6.161	£52,040		6.196	£51,971	
Net	0.012	£550	£45,509	0.026	£174	**£6,774**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

The cost-effectiveness plane for the revised company base case A, at a daily price of £5.75, for the revised >6.0mmol/L population is shown in Figure 2. At a price of £5.75 per day for patiromer, the probability that patiromer is cost-effective compared with no patiromer is 85% and 95% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY (Figure 3).

Figure 2. Base case cost-effectiveness plane

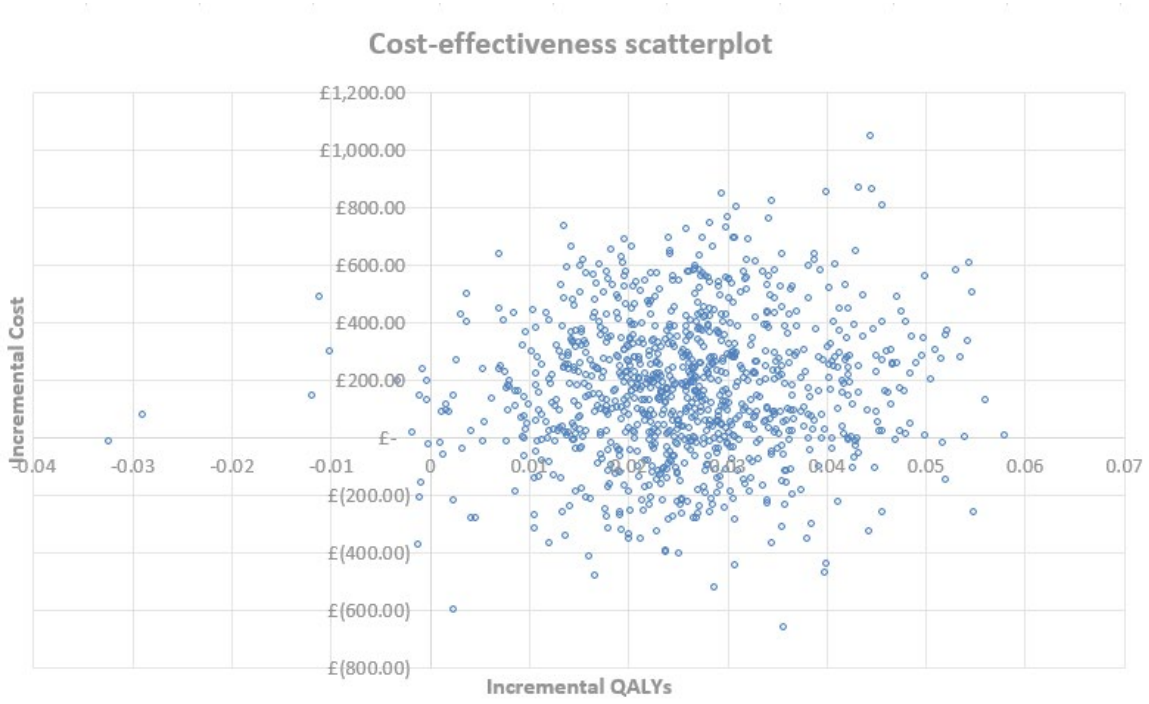
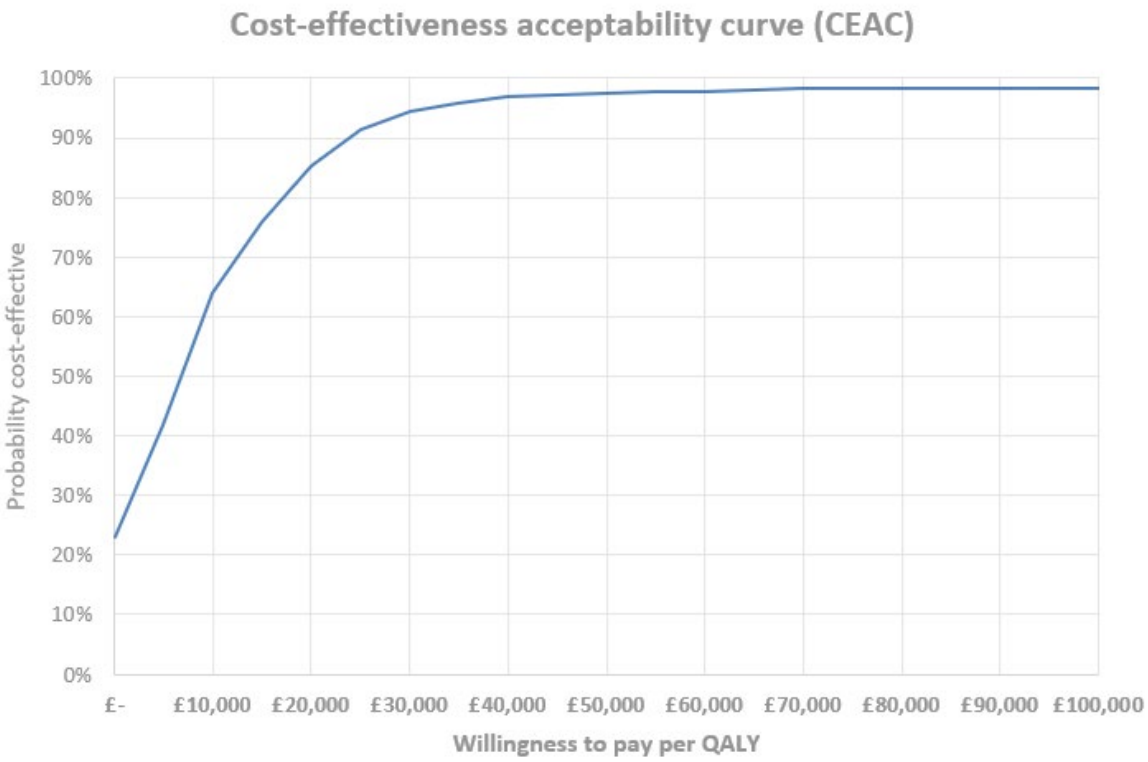


Figure 3. Base case cost-effectiveness acceptability curve (CEAC)



3.4 Further sensitivity analysis: effect of patiromer on reducing serum K^+ levels in OPAL-HK Part A

Given there is some uncertainty in the comparison between the CPRD and OPAL-HK datasets, scenario analyses have been performed on the revised company preferred base case. Scenarios varied the efficacy of patiromer in the first model cycle, reflecting Part A OPAL-HK. It was assumed that patiromer had no effect in an increasing proportion of patients i.e. patients remain in the same serum potassium category from the start to end of the first model cycle.

Table 8. OPAL-HK Part A scenarios

Percentage of patients assumed to remain in the same serum potassium category from the first to second cycle in the patiromer arm of the model	**Base Case A** **>6.0mmol/L population only** **£5.75**	**Base Case B** **>6.0mmol/L population only** **£5.75**
Base case (0%)	£4,510	£7,010
10%	£10,810	£10,271
20%	£19,410	£14,668
30%	£31,847	£20,923
40%	£51,428	£30,524
50%	£86,790	£47,141

In patients with moderate-to-severe hyperkalaemia (5.5-6.5mmol/L) in OPAL-HK Part A, the mean change in serum potassium from baseline to week 4 was −1.23±0.04mmol/L (95% CI, −1.31 to −1.16), and the estimated proportion of patients with a serum potassium level in the target range (3.8 to <5.1mmol/L) at week 4 was 77% [95% CI, 70 to 83]. Therefore, the scenarios presented above are likely to be highly conservative given that to remain in the >6.0mmol/L category after 4 weeks (i.e. no response) patients must have a less than 0.5mmol/L reduction in their serum potassium level.

The average reduction in only patients with sK^+ >6.0mmol/L was [redacted] (see supplementary IPD) which is an even greater reduction than the moderate-severe OPAL-HK population as a whole.

In addition, as mentioned in section 1.4, only [redacted] out of [redacted] patients ([redacted]) was missing a serum potassium reading at the end of Part A and can be assumed not to respond to patiromer. The other [redacted] patients all had a sK^+ reading of <5.5mmol/L by week 4.

4. Discussion

The company base case has been revised since CS2 to strengthen the modelling of patiromer discontinuation (using real-world evidence and an improved modelling approach), incorporate the updated drug price and to reflect the decisions made during TA599. Specifically, the removal of a direct link between elevated serum potassium and mortality (K+ SMRs) and the potassium thresholds at which patients are expected to be treated. The updated analysis shows that patiromer is cost effective at a price of £5.75/day under a range of scenarios and has a high probability of being cost-effective at the accepted NICE willingness-to-pay thresholds of £20 and 30k per QALY.

There are some limitations to this analysis. The ERG commented that the company were not clear on the derivation of the hazard ratio applied in the model to estimate the efficacy benefit associated with patiromer. The company would like to clarify that the hazard ratio for Part B of OPAL-HK was derived for the CS2 target population (i.e. patients who were eligible for Part B of OPAL-HK and had CKD without heart failure and a serum potassium of >6.0mmol/L, or patients with CKD and heart failure, and a serum potassium level of ≥5.5mmol/L). However, due to time constraints, the company was not able to re-estimate the hazard ratio for the revised population (>6.0mmol/L, all patients). The company has instead provided results of scenarios where the hazard ratio is varied (see Table 4). A further limitation of this analysis is that restricting the eligible population to those with a serum potassium of >6.0mmol/L at baseline (to align with NICE guidance for TA599) results in low patient numbers for analysis (n=[redacted]).

5. References

Bell et al., The use of real world data for the estimation of treatment effects in NICE decision making (June 2016, updated December 2016) http://nicedsu.org.uk/methods-development/real-world-data/

Webster J, Smith BD. The Case for Real-world Evidence in the Future of Clinical Research on Chronic Myeloid Leukemia. Clin Ther. 2019

NHS Improvement. Patient Safety Alert: Resources to support safe and timely management of hyperkalaemia 2018 [updated 9 August 2018. Available from: https://improvement.nhs.uk/news-alerts/safe-and-timely-management-of-hyperkalaemia/.

Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. Nature reviews Nephrology. 2014;10(11):653-62.

Nephrologist Questionnaire

1. On average, how many patients with CKD do you treat each week?
   5 patients or less
   6—10 patients
   11—20 patients
   21—30 patients
   31—40 patients
   41—50 patients
   51—75 patients
   76—100 patients
   More than 100 patients

2. When considering the impact of Hyperkalemia on patients with CKD and comorbid conditions.

   a. Which major comorbidies associated with CKD/HK come to mind first?
   Interviewer note, potential examples maybe: chronic heart failure, type 2 diabetes, poly-medicated patients

   b. How would you describe the burden of Hyperkalemia on these patients' and carers lives?
   Interviewer note, it may be worthwhile prompting: lab tests, diet, medical visits?

Interviewer notes: Probing questions re: RAASi
We are looking for clinical aspiration of care, prioritise question e and f below if needed.

   c. What are your objectives in treating patients with CKD/HK? For example, RAASi management / HK treatment or avoidance / ESRD or MACE avoidance

   d. How do you currently manage such a patient in your clinical practice?

   e. How well do current treatments allow you achieve your treatment objectives? Please rate:

      1 = Not well
      2
      3
      4
      5 = Very well

   f. How would your treatment objectives change if new Potassium binding agents were available for you to prescribe?

   g. What would you like to see change in your management of Hyperkalemia?

Interviewer note: We want to facilitate in the discussion, the clinician's thinking as to where the unmet need is, considering late stage CKD, patients with CHF as a comorbid condition and for proteinuric diabetic patients.
Discussion aim is to seek to validate previous answers above, by asking the probing question below:

3. Please could you describe patient case(s) or practical example(s) where, you would take clinical action after considering:
    a. Elevated sK level (please define "elevated" and if possible, potassium level)?

    b. What immediate action would you take?

    c. What action would you take medium to long term?

    d. How would you manage RAASi medication in patients with elevated sK level?

4. In a recent publication (Kalsi.N, et al., 2018) 58% of Cardiologists stated they reference the European Society for Cardiology Heart Failure Guidelines (European Society of Cardiology, 2016) and 29% reference the NICE CG182 CKD (NICE Clinical guideline [CG182], 2015).

    a. Is this reflective of your clinical practice?

    b. If No – why? Please discuss and describe?

Interviewer note: This section may appear repetitive, but the questions do relate to different cohorts of patients. Please ask the interviewee to concentrate on patients they have seen recently (the last 4 - 8 weeks)

5. Approximately, how many patients with CKD stage 3 or 4 have you seen in the last 4 weeks (or 8 weeks)?
    How many patients with CKD stage 3?

    How many patients with CKD stage 4?

6. Approximately, how many patients with CKD stage 3 - 4 have you seen in the last 4 weeks (or 8 weeks) are **Treated with RAASi**?

    How many patients with CKD stage 3 treated with RAASi?

    How many patients with CKD stage 4 treated with RAASi?

7. Approximately how many patients with CKD stage 3-4 on RAASi **with Hyperkalaemia** have you seen in the last 4 weeks (or 8 weeks)?

    How many patients with CKD stage 3 on RAASi and Hyperkalaemia?

    How many patients with CKD stage 4 on RAASi and Hyperkalaemia?

8. On those patients with CKD stage 3-4 **on RAASi with Hyperkalaemia** that you have you seen in the last 4 weeks….

    How many have Heart Failure?

    How many have Diabetes?

9. How would you define chronic vs. short term HK treatment?

10. How would you define:

    a. RAASi enabling treatment
    b. RAASi maintenance treatment
    c. RAASi optimisation treatment

11. How frequently are RAASi doses reduced in patients?
    a. For what reason?
    b. What alternatives are used?

12. What impact does RAASi reduction have on these patients?

13. How frequently are your patients hospitalised due to HK?

14. Approximately how many patients with CKD stage 3-4 on RAASi and with Hyperkalaemia have serum K

    5.1-5.4?

    How many 5.5-5.9?

    How many >6?

15. What role does dietary control play in managing Hyperkalaemia in your clinical practice?

16. How effective do you think is a low potassium diet (0-10)?

17. How manageable for patients is a low potassium diet (0-10)?

18. How compliant are patients to a low potassium diet (0-10)?

19. When you see patients with CKD stage 3 on RAASi and with Hyperkalaemia (sK 5.1-5.4) what do you do?

    Nothing

    Reduce RAASi

Stop RAASi

Dietary Advice

Other please specify

20. When you see patients with CKD stage 4 on RAASi and with Hyperkalaemia (sK 5.1-5.4) what do you do?

    Nothing

    Reduce RAASi

    Stop RAASi

    Dietary Advice

    Other please specify

21. When you see patients with CKD stage 3 on RAASi and with Hyperkalaemia (sK 5.5-5.9) what do you do?

    Nothing

    Reduce RAASi

    Stop RAASi

    Dietary Advice

    Other please specify

22. When you see patients with CKD stage 4 on RAASi and with Hyperkalaemia (sK 5.5-5.9) what do you do?

    Nothing

    Reduce RAASi

    Stop RAASi

    Dietary Advice

    Other please specify

23. When you see patients with CKD stage 3 on RAASi and with Hyperkalaemia (sK >6) what do you do?

Nothing

Reduce RAASi

Stop RAASi

Dietary Advice

Other please specify

24. When you see patients with CKD stage 4 on RAASi and with Hyperkalaemia (sK >6) what do you do?

    Nothing

    Reduce RAASi

    Stop RAASi

    Dietary Advice

    Other please specify

Cardiologist Questionnaire

1. On average, how many patients with HF do you treat each week?

    5 patients or less
    6—10 patients
    11—20 patients
    21—30 patients
    31—40 patients
    41—50 patients
    51—75 patients
    76—100 patients
    More than 100 patients

2. When considering the impact of Hyperkalaemia on patients with HF and comorbid conditions.

    a. Which major comorbidities associated with HF/HK come to mind first?

    Interviewer note, potential examples maybe: chronic kidney disease, type 2 diabetes, poly-medicated patients

    b. How would you describe the burden of Hyperkalaemia on these patients' and carers' lives?

Interviewer note, it may be worthwhile prompting: lab tests, diet, medical visits? What are patients and carers worried about- how do they manage hyperkalaemia- how concerning is it compared to the other conditions the patient is living with?

Interviewer notes: Probing questions re: RAASi
We are looking for clinical aspiration of care, prioritise question e and f below if needed.

c. What are your objectives in treating patients with HF/HK patients?

Interviewer note: For example, RAASi optimisation / HK treatment or avoidance / ESRD or MACE avoidance/ improve patient symptoms such oedema, shortness of breath / reduce cardiovascular morbidity mortality and complications

d. How do you currently manage such a patient in your clinical practice?

e. How well do current treatments allow you to achieve your treatment objectives? Please rate:

1 = Not well
2
3
4
5 = Very well

f. How would your treatment objectives change if new Potassium binding agents were available for you to prescribe?

g. What would you like to change in your management of Hyperkalaemia?

Interviewer note: We want to facilitate in the discussion, the clinician's thinking as to where the unmet need is, considering late stage CKD, patients with CHF as a comorbid condition and for proteinuric diabetic patients
Discussion aim is to seek to validate previous answers above, by asking the probing question below:

3. Please could you describe patient case(s) or practical example(s) where you would take clinical action after considering:
   a. Elevated sK level. Please define what you mean by "elevated"

   b. What immediate action would you take?

   c. What action would you take medium to long term?

   d. How would you manage RAASi medication in patients with elevated sK level?

4. In a recent publication (Kalsi.N, et al., 2018) 58% of Cardiologists stated they reference the European Society for Cardiology Heart Failure Guidelines (European Society of Cardiology, 2016) and 29% reference the NICE CG182 CKD (NICE Clinical guideline [CG182], 2015).

a. Is this reflective of your clinical practice?

b. If No – why? Please discuss and describe?

Interviewer note: This section may appear repetitive, but the questions do relate to different cohorts of patients . Please ask the interviewee to concentrate on patients they have seen recently (the last 4-8 weeks)

5. Approximately, how many patients with HF have you seen in the last 4 weeks (or 8 weeks)?

6. Approximately, how many patients with HF have you seen in the last 4 weeks (or 8 weeks) are **Treated with RAASi**?

7. Approximately how many patients with HF on RAASi **and Hyperkalaemia** have you seen in the last 4 weeks?

8. On those patients with HF **on RAASi with Hyperkalaemia** that you have you seen in the last 4 weeks….

   How many have CKD stage 3?

   How many have CKD stage 4?

   How many have Diabetes?

9. How would you define chronic vs. short term HK treatment?

10. How would you define:

    a. RAASi enabling treatment
    b. RAASi maintenance treatment
    c. RAASi optimisation treatment

11. How frequently are RAASi doses reduced in patients?
    a. For what reason?
    b. What alternatives are used?

12. What impact does RAASi reduction have on these patients?

13. How frequently are patients taken off RAASi treatment?

    a. For what reason?

b. What alternatives are used?

14. What impact does RAASi withdrawal have on these patients?
15. How frequently are your patients hospitalised primarily due to HK?
16. Approximately how many patients with HF on RAASi and Hyperkalaemia have serum K

    5.1-5.4?

    How many 5.5-5.9?

    How many >6?
17. What role does dietary control play in managing Hyperkalaemia in your clinical practice?
18. How effective do you think is a low potassium diet (0-10)?
19. How manageable for patients is a low potassium diet (0-10)?
20. How compliant are patients to a low potassium diet (0-10)?
21. When you see patients with HF on RAASi with Hyperkalaemia (sK 5.1-5.4) what do you do?

    Nothing

    Reduce RAASi

    Stop RAASi

    Dietary Advice

    Other please specify
22. When you see patients with HF on RAASi and Hyperkalaemia (sK 5.5-5.9) what do you do?

    Nothing

    Reduce RAASi

    Stop RAASi

    Dietary Advice

    Other please specify
23. When you see patients with HF on RAASi and Hyperkalaemia (sK >6) what do you do?

Nothing

Reduce RAASi

Stop RAASi

Dietary Advice

Other please specify

Clinician Questionnaire References

European Society of Cardiology, 2016. ESC Clinical Practice Guidelines.

Kalsi.N, Birkhoelzer.S, Kalra.P & Kalra.P, 2018. Impact of hyperkalaemia in managing cardiorenal patients – a healthcare professional perspective. *The British Journal of Cardiology,* p. 25:97–101.

NICE Clinical guideline [CG182], 2015. Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. *National Institute for Health and Care Excellence,* p. January.

ERG – Clarification questions – Part I – Health Economics

Q1 Please clarify if the definition of the revised target groups of (A) patients who were K+ > 6.0 at baseline and (B) patients with heart failure at baseline who were K+ > 5.5 at baseline defined baseline as the OPAL-HK Part A baseline or the OPAL-HK Part B baseline and on which basis the OPAL-HK data is analysed.

The 'baseline' serum potassium levels of the revised target groups refer to the Part A baseline serum potassium levels. As such, the first monthly cycle in the model reflects Part A of OPAL-HK, which was 4 weeks.

The model includes the following patients from OPAL-HK:

1. Patients with stage 3-4 CKD and HF comorbidity (CKD HF+) with a serum potassium of ≥5.5 mmol/L at Part A baseline (n=[redacted]), and,
2. Patients with stage 3-4 CKD without HF comorbidity (CKD [no HF]) with a serum potassium level of >6.0 mmol/L at Part A baseline (n=[redacted])

Q2 Please provide the OPAL-HK part B baseline characteristics in the same format as Table 4 of the 03/09/2018 ERG report, ignoring the CPRD column, split by arm separately for:

A. Patients with heart failure at baseline who were K+ ≥ 6.0 at baseline
B. Patients with heart failure at baseline who were 6.0 > K+ ≥ 5.5 at baseline
C. Patients without heart failure at baseline who were K+ ≥ 6.0 at baseline
D. Patients without heart failure at baseline who were 6.0 > K+ ≥ 5.5 at baseline

Please see Table 1 with the summary of the Part A baseline characteristics for the Part B subjects of OPAL-HK. The baseline characteristics were collected at the Part A baseline.

Table 1. Baseline patient characteristics in OPAL-HK Part B

	301 Part B Placebo Subjects (N=52)				301 Part B Patiromer Subjects (N=55)			
	Subjects with Heart Failure $5.5 \leq K^+ < 6.0$ (n=[redacted])	Subjects with Heart Failure $K^+ \geq 6.0$ (n=[redacted])	Subjects without Heart Failure $5.5 \leq K^+ < 6.0$ (n=[redacted])	Subjects without Heart Failure $K^+ \geq 6.0$ (n=[redacted])	Subjects with Heart Failure $5.5 \leq K^+ < 6.0$ (n=[redacted])	Subjects with Heart Failure $K^+ \geq 6.0$ (n=[redacted])	Subjects without Heart Failure $5.5 \leq K^+ < 6.0$ (n=[redacted])	Subjects without Heart Failure $K^+ \geq 6.0$ (n=[redacted])
Male, % (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAASi (ACE), % (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAASi (ARB), % (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAASi (MRA), % (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serum K^+, mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of Myocardial Infarction, % (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of Hypertension, % (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes Mellitus, % (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart Failure, % (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Q7 Does the PSA sample the patient numbers in the *Calcs* worksheet cells B8:F86? If it does, where does this sampling occur? If it does not, given that small patient numbers are likely to result in significant uncertainty why does it not?

The patients in the *Calcs* worksheet cells B58:F86 are the patients included in the analysis; these are patients with stage 3-4 CKD and HF comorbidity (CKD HF+) with a serum potassium of ≥5.5 mmol/L at Part A baseline, and patients with stage 3-4 CKD without HF comorbidity (CKD [no HF]) with a serum potassium level of >6.0 mmol/L at Part A baseline.

The Part A 'start', and Part A 'end' serum potassium levels of these patients are used to calculate transition probabilities from the health states in the first cycle to the health states in the second cycle, for the patiromer arm of the model. This represents Part A of the OPAL-HK trial.

These transition probabilities feed through to the *SA Inputs* worksheet, cells C24:G30 (for CKD 3 patients) and C69:G74 (for CKD 4 patients) and are shown below in Table 2. These transition probabilities were not sampled by the PSA, as ten out of twelve of the calculated probabilities take a value of one or zero, based on OPAL-HK Part A patient movements.

Table 2. Transition probabilities of first to second model cycle - 'Patiromer' arm

Transition (First model cycle to second model cycle)	Transition probability
CKD3 5.5-6.0 mmol/L to CKD3 Full RAASi (<5.5 mmol/L)	1.0000
CKD3 5.5-6.0 mmol/L to CKD3 Reduced RAASi (5.5-6.0 mmol/L)	0.0000
CKD3 5.5-6.0 mmol/L to CKD3 Discontinued RAASi (>6.0 mmol/L)	0.0000
CKD3 >6.0 mmol/L to CKD3 Full RAASi (<5.5 mmol/L)	1.0000
CKD3 >6.0 mmol/L to CKD3 Reduced RAASi (5.5-6.0 mmol/L)	0.0000
CKD3 >6.0 mmol/L to CKD3 Discontinued RAASi (>6.0 mmol/L)	0.0000
CKD4 5.5-6.0 mmol/L to CKD4 Full RAASi (<5.5 mmol/L)	0.9167
CKD4 5.5-6.0 mmol/L to CKD4 Reduced RAASi (5.5-6.0 mmol/L)	0.0000
CKD4 5.5-6.0 mmol/L to CKD4 Discontinued RAASi (>6.0 mmol/L)	0.0833
CKD4 >6.0 mmol/L to CKD4 Full RAASi (<5.5 mmol/L)	1.0000
CKD4 >6.0 mmol/L to CKD4 Reduced RAASi (5.5-6.0 mmol/L)	0.0000
CKD4 >6.0 mmol/L to CKD4 Discontinued RAASi (>6.0 mmol/L)	0.0000

The intention was to vary the corresponding transitions in the 'no patiromer' arm of the model (where the transition probabilities are informed by the CPRD analysis). Varying these transition probabilities in the PSA would result in variation in the difference between the 'patiromer' and 'no patiromer' arms of the model, in terms of the proportion of patients moving to each potassium category in the second model cycle. Upon investigation, it was found that some but not all of the 'no patiromer' transitions were sampled in the PSA. This has now been corrected (using the standard errors from the CPRD analysis, see model sheet *Calcs* cells H162:H172) and results in a very similar probabilistic result to the base case analysis – see Figure 1 for the base case cost-effectiveness acceptability curve (CEAC) and Figure 2 for the CEAC from the corrected model. It can be seen that the probability of patiromer being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY reduces from approximately 38% and 94% to 28% and 93%, respectively.

Figure 1. Base case cost-effectiveness acceptability curve (CEAC)

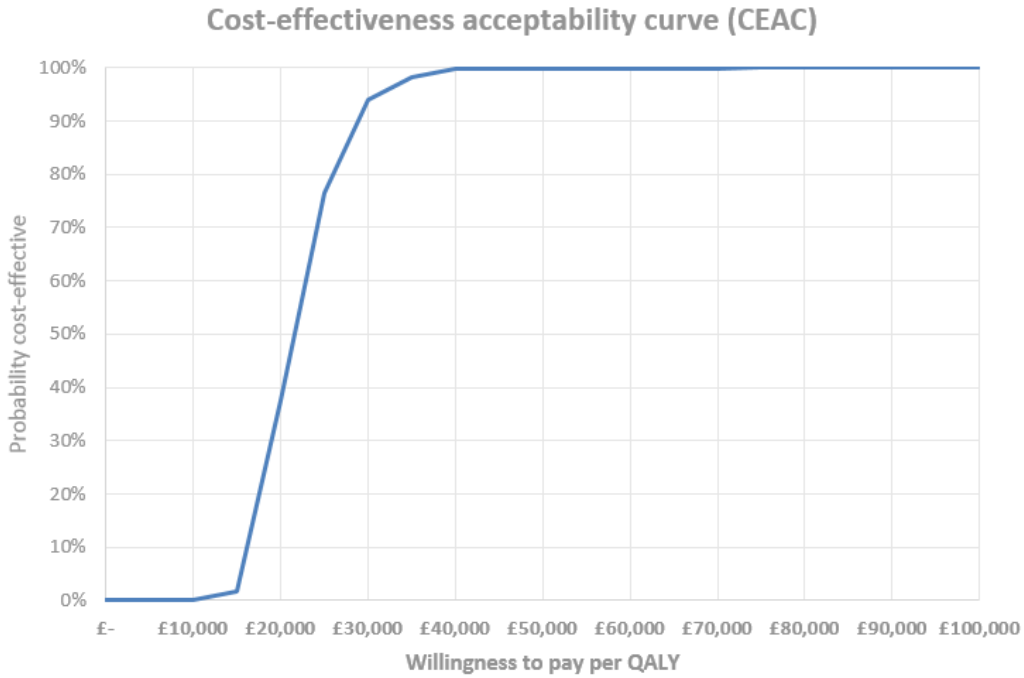
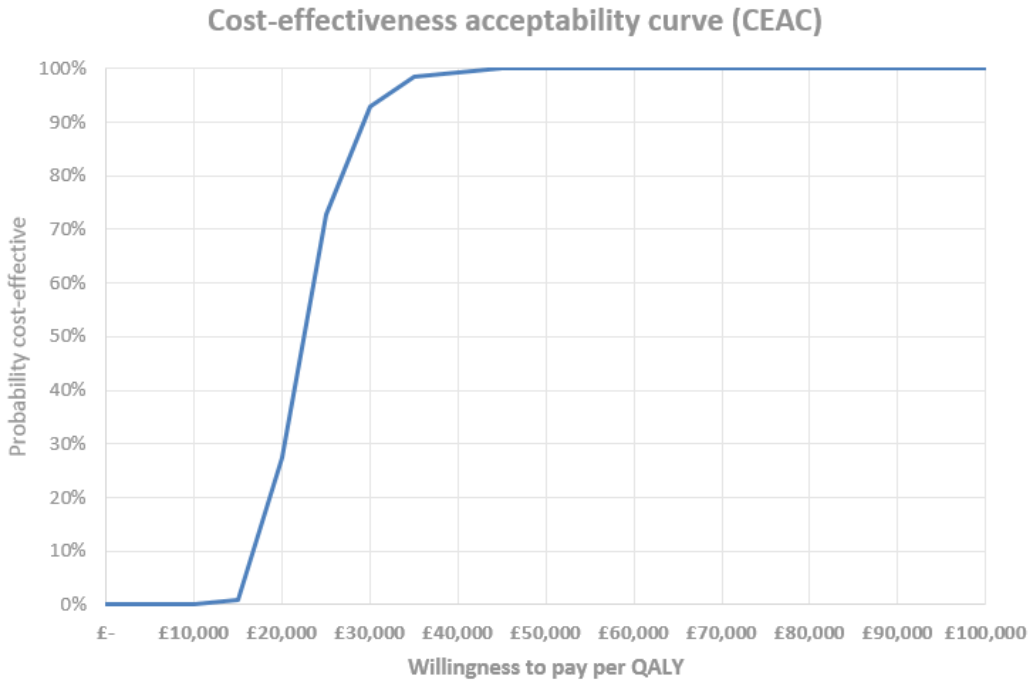


Figure 2. Corrected cost-effectiveness acceptability curve (CEAC)



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patiromer for treating hyperkalaemia in adults

ID877

Company response to ERG Clarification Questions for Evidence Submission 2

Part I:
Cost-effectiveness

Contents

Abbreviations

Abbreviation	Definition
CKD	Chronic kidney disease
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CSR	Clinical study report
ERG	Evidence review group
FDA	U.S. Food and Drug Administration
HF	Heart failure
HK	Hyperkalaemia
IPD	Individual patient data
K+	Serum potassium
MSV	Mandatory safety visit
PSA	Probabilistic sensitivity analysis
RAASi	Renin-angiotensin-aldosterone-system inhibitors
SPA	Special Protocol Assessment

Q1: Target patient group clarification

Please clarify if the definition of the revised target groups of (A) patients who were K+ > 6.0 at baseline and (B) patients with heart failure at baseline who were K+ > 5.5 at baseline defined baseline as the OPAL-HK Part A baseline or the OPAL-HK Part B baseline and on which basis the OPAL-HK data is analysed.

[Response previously provided]

Q2: Baseline characteristics

Please provide the OPAL-HK part B baseline characteristics in the same format as Table 4 of the 03/09/2018 ERG report, ignoring the CPRD column, split by arm separately for:

A. Patients with heart failure at baseline who were K+ ≥ 6.0 at baseline
B. Patients with heart failure at baseline who were 6.0 > K+ ≥ 5.5 at baseline
C. Patients without heart failure at baseline who were K+ ≥ 6.0 at baseline
D. Patients without heart failure at baseline who were 6.0 > K+ ≥ 5.5 at baseline

[Response previously provided]

Q3: RAASi status transitions analysis

Please provide the equivalent of the *R output: All patients* and *R Output: CKD+HF* that overlies cells G6:K53 of the *Calcs* worksheet but split by transitions between RAASi status: Full RAASi, Reduced RAASi, Discontinued RAASi, separately for OPAL-HK Part A and for OPAL-HK Part B.

OPAL-HK Part A RAASi modifications

The nature of the available individual patient data (IPD) for OPAL-HK Part A does not allow for the generation of outputs in the format requested by the ERG, as explained below.

Vifor are able provide a summary of RAASi transitions for all patients in Part A, using the Clinical Study Report (CSR). Patient numbers by RAASi status for the sub-group of patients with heart failure (HF) and a baseline serum potassium >5.5mmol/L could not be analysed although comparative efficacy results for patients with and without HF are provided.

Part A of OPAL-HK consists of chronic kidney disease (CKD) patients with hyperkalaemia (HK) who were receiving a stable dose of at least one RAASi for at least 28 days prior to screening. HK patients on RAASi are treated with patiromer and the RAASi doses are adjusted as per the titration algorithm (see appendix). The study was designed and conducted under a Special Protocol Assessment (SPA) with the FDA, with separate analyses specified for each study phase. To facilitate interpretation of the primary end-point in the Withdrawal Phase, and as a requirement of the SPA, the dose of investigational product had to be kept stable (i.e., not titrated), and the doses of RAAS inhibitor medications could not be changed.

The only reference to RAASi in the Part A titration algorithm (Appendix 1: Titration algorithm: Part A) is RAASi discontinuation for safety reasons:

The Part A titration algorithm specified discontinuation of the RAASi dose:

1. if the serum potassium level was ≥ 6.5 mEq/L or
2. *if the serum potassium level was ≥ 5.1 mEq/L and the subject was receiving the maximum dose of RLY5016 for Oral Suspension (50.4 g/day patiromer)*

Depending on the serum potassium level, the titration algorithm specified mandatory safety visits (MSVs) within 24 or 72 hours (OPAL-HK CSR).

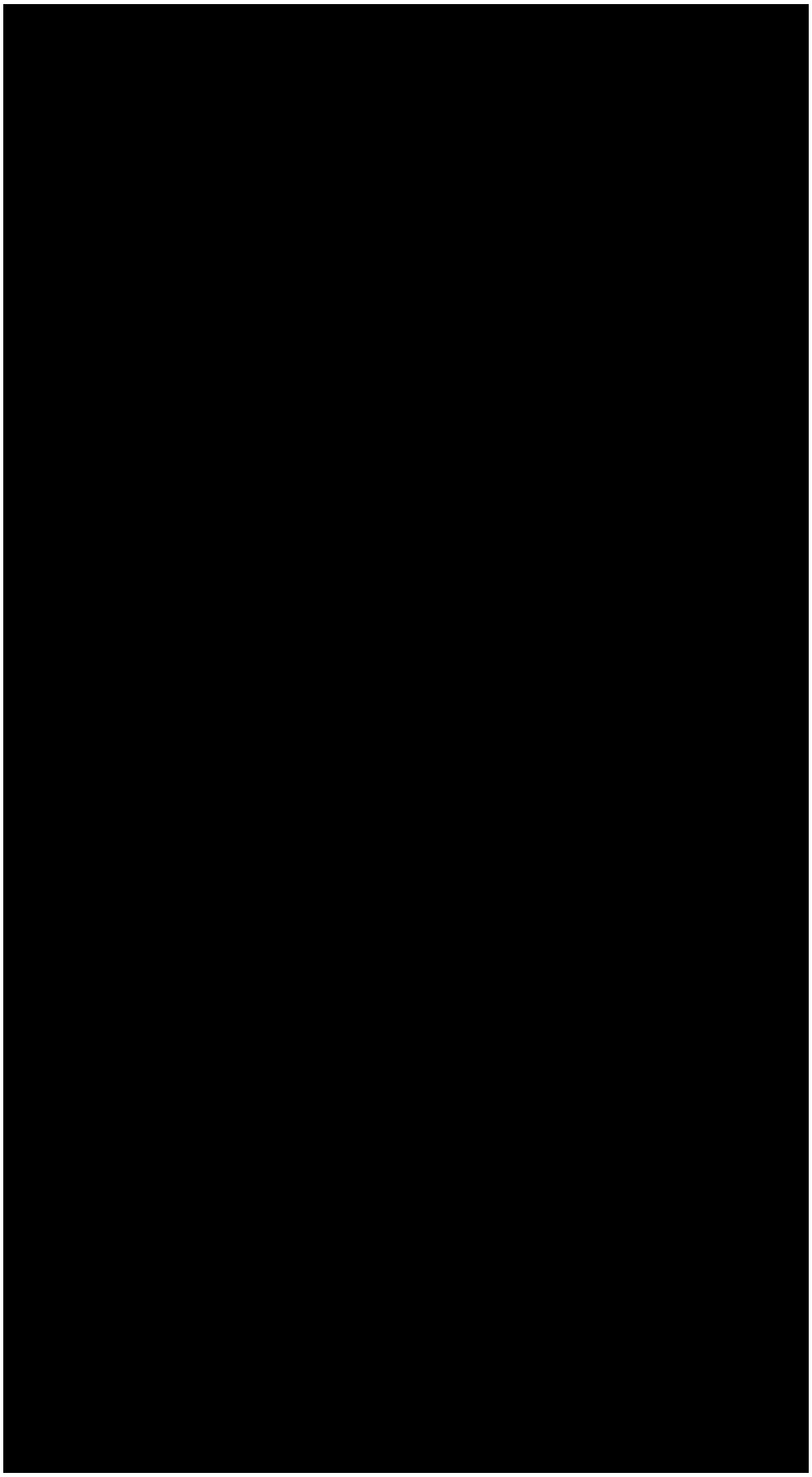
As a result, there were very few modifications to RAASi dose in Part A of OPAL-HK. In Part A, the following modifications occurred out of 237 patients:

- [redacted] patients ([redacted]%) **discontinued RAASi** for any reason
- [redacted] patients ([redacted]%) had a **RAASi dose reduction**:
  - [redacted] of these patients ([redacted]% of all patients) reduced due to potassium levels, as per the titration guidelines
  - [redacted] of these patients ([redacted]% of all patients) reduced due to reasons other than serum potassium levels
- [redacted] patient ([redacted]%) had a **RAASi dose increase**

Only patients with a serum K+ ≥ 5.5mmol/L at Part A baseline were eligible to enter the economic model (see 'Dose Group 2' of Table 1). Therefore, of the patients eligible to enter the model, an even smaller number of patients experienced a RAASi dose modification in Part A:

- [redacted] patients ([redacted]% of all Part A patients) **discontinued RAASi** for any reason
- [redacted] patients ([redacted]% of all Part A patients) had a **RAASi dose reduction**
- [redacted] patient ([redacted]% of all Part A patients) had a **RAASi dose increase**

Table 1. RAASi exposure: OPAL-HK Part A



OPAL-HK Part B RAASi modifications

The following assumptions were made in order to perform analyses of Part B as requested by the ERG:

- If a patient discontinued RAASi at any visit before Part B Week 8 (end of OPAL-HK Part B), they were also assumed to be discontinued at Week 8.
- Only patients with a Part B Baseline and Part B Week 8 RAASi status recording were included in this analysis (including patients who were assumed to be discontinued at Week 8)

R output: All patients (by CKD stage) in placebo arm

R output: CKD+HF patients (by CKD stage) in placebo arm

R output: All patients (by CKD stage) in patiromer arm

R output: CKD+HF patients (by CKD stage) in patiromer arm

Q4: Serum potassium category transition analysis

Please provide the equivalent of the *R output: All patients* and *R Output: CKD+HF* that overlies cells G6:K53 of the *Calcs* worksheet separately by OPAL-HK arm for:

- OPAL-HK Part A, from Part A baseline to Part A week 4 (1 * 4 tables).
- OPAL-HK Part B, from Part B baseline to Part B week 4 (2 * 4 tables).
- OPAL-HK Part B, from Part B baseline to Part B week 8 (2 * 4 tables).

OPAL-HK Part A Baseline to Week 4 serum potassium (central laboratory) transitions (equivalent to model)

Note that both responder and non-responder patients are included

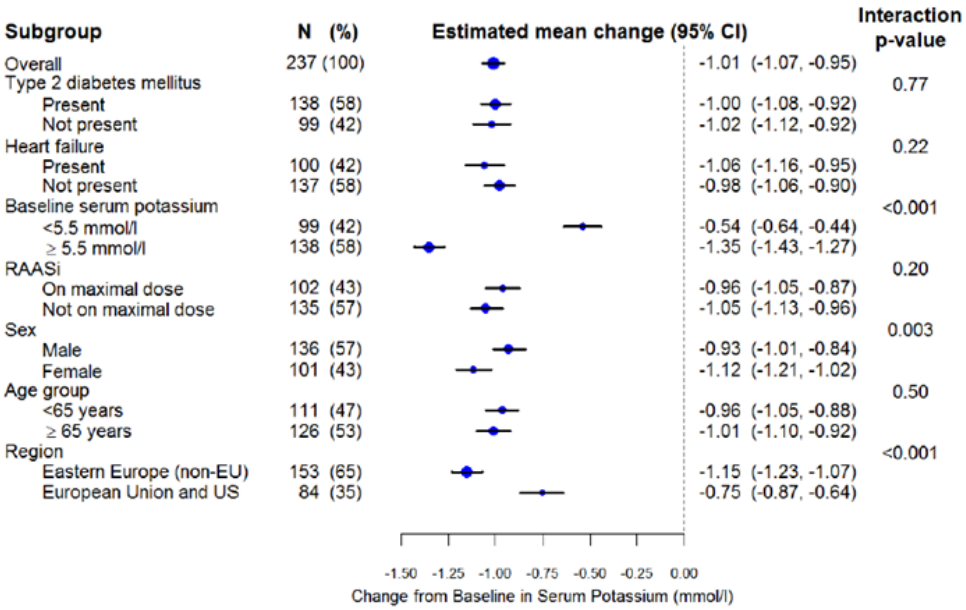
R output: All patients

R Output: CKD+HF

A summary of mean change in serum potassium from Part A Baseline to Part A Week 4 is provided in Figure 1 below. The presence of heart failure does not have a statistically significant impact on mean change in serum potassium. Similarly, the presence of heart failure did not result in a statistically significant difference in mean change in serum potassium when stratified by baseline serum potassium (and patiromer dose [Table 2]). Finally, the proportion of patients with or without heart failure achieving a serum potassium within the target range of 3.8 to 5.1mEq/L at the end of Part A did not differ within dose groups (Table 3). The results confirm that the presence of heart failure does not impact the efficacy of patiromer.

Figure 1. Change in serum potassium from Part A Baseline to Part A Week 4 by subgroup

Figure 8 **Forest Plot of the Part A Primary Efficacy Endpoint by Subgroups: Change in Serum Potassium from Part A Baseline to Part A Week 4 (Part A ITT Population[a])**



[redacted]

Across all patients, the magnitude of the mean change in serum potassium in Part A was greater in the subgroup with baseline serum potassium ≥5.5 [mean change of [redacted] mEq/L; 95% CI of ([redacted], [redacted])] who received 16.8 g/day patiromer as compared to the subgroup with baseline serum potassium <5.5 mEq/L [mean change of [redacted] mEq/L; 95% CI of ([redacted], [redacted])] who received 8.4 g/day patiromer, indicating that the mean change in potassium with patiromer is dependent on the dose and baseline serum potassium and efficacy is similar between groups.

Table 2. Change in serum potassium from Part A Baseline to Part A Week 4 by subgroup and baseline serum potassium

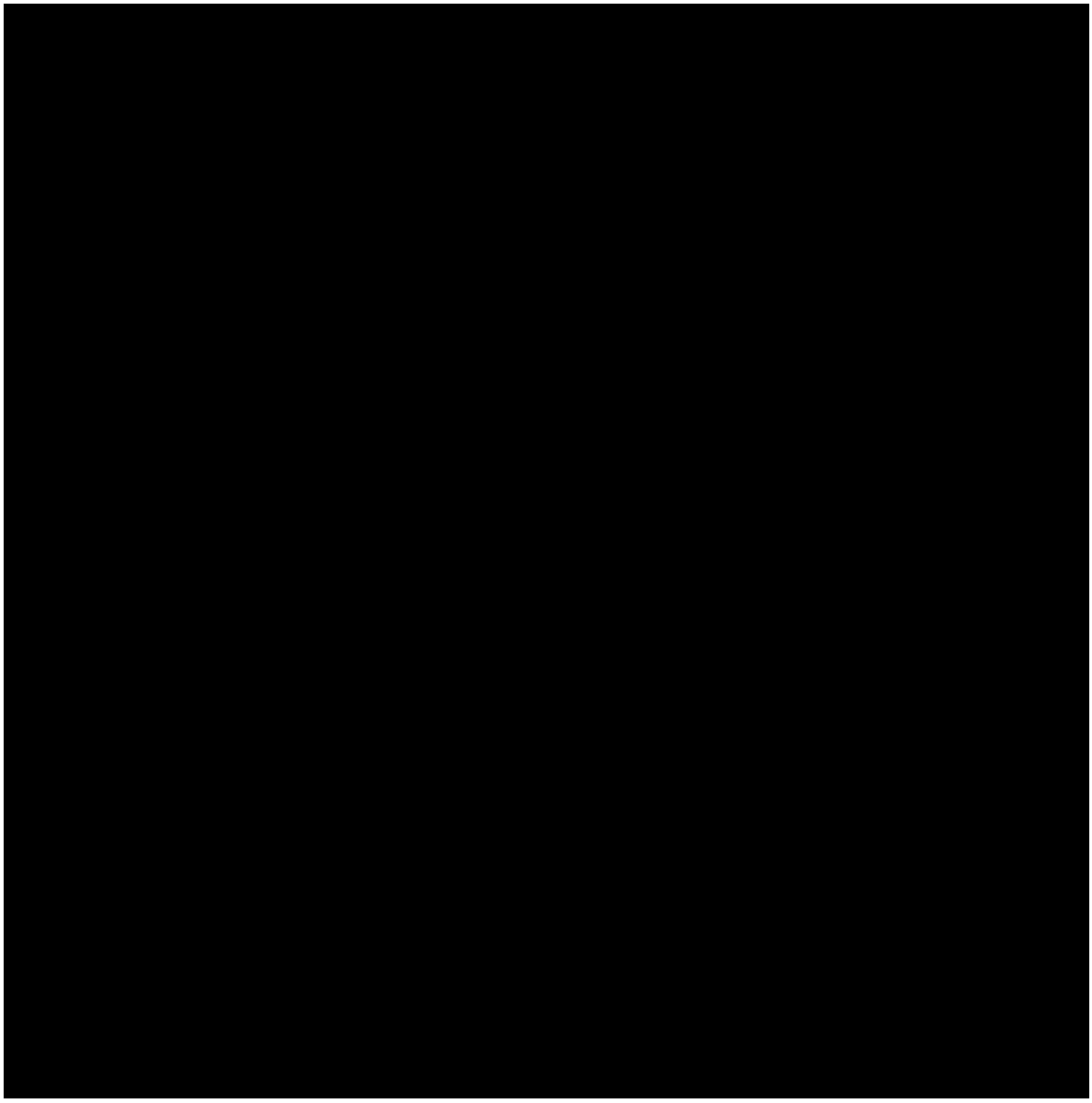


Table 3. Proportion of patients achieving target serum potassium range at week 4 Part A

OPAL-HK Part B

Due to the data available in the IPD, this analysis was not feasible for Part B, however, further information regarding change in serum potassium level in Part B is provided below.

Change from Part B Baseline to Part B Week 4

The primary efficacy endpoint for Part B was the change from Part B Baseline (central laboratory) serum potassium to the serum potassium (central laboratory) at either:

- the Part B Week 4 visit, if the subject's serum potassium based on the local laboratory remained ≥ 3.8 mEq/L and < 5.5 mEq/L up to the Part B Week 4 visit

or

- the earliest Part B visit at which the subject's local laboratory serum potassium was< 3.8 mEq/L or ≥ 5.5 mEq/L

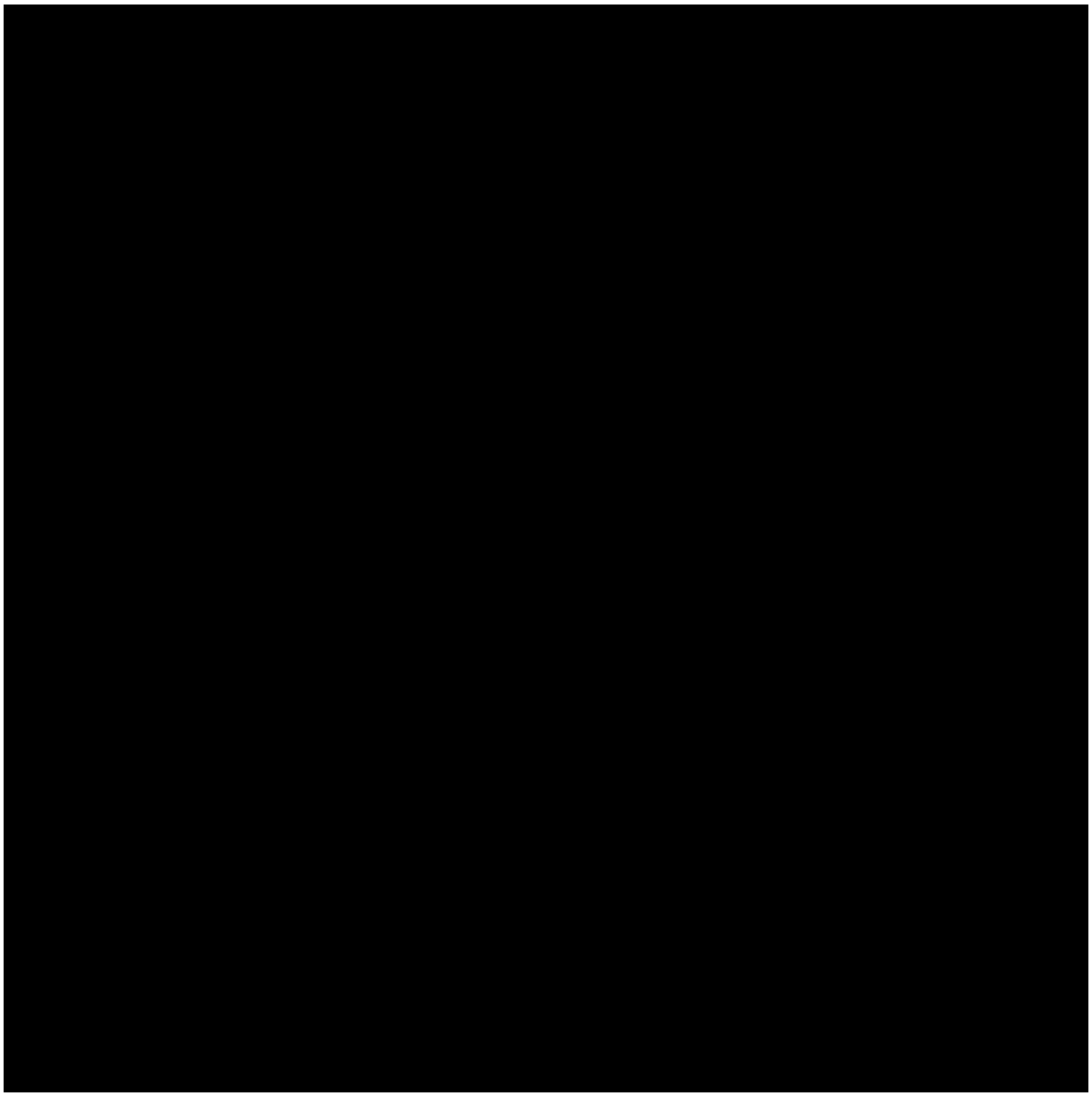
Table 4 shows the estimated median change from Part B Baseline in serum potassium in the placebo and patiromer groups, respectively; as well as the estimated difference in median change from Part B Baseline between the two groups. Patients in the patiromer arm experienced a mean change of 0.00mEq/L, statistically significantly lower than placebo where the change was +0.72mEq/L.

Table 4. Change in serum potassium from Part B Baseline to Part B Week 4

While a statistically significant difference was observed across treatment arms, there was no difference when results were stratified by the presence or absence of heart failure across all patients (Figure 2) or within treatment arms (Table 5).

Figure 2. Primary efficacy outcome by subgroup

Table 5. Primary efficacy outcome by subgroup and treatment arm



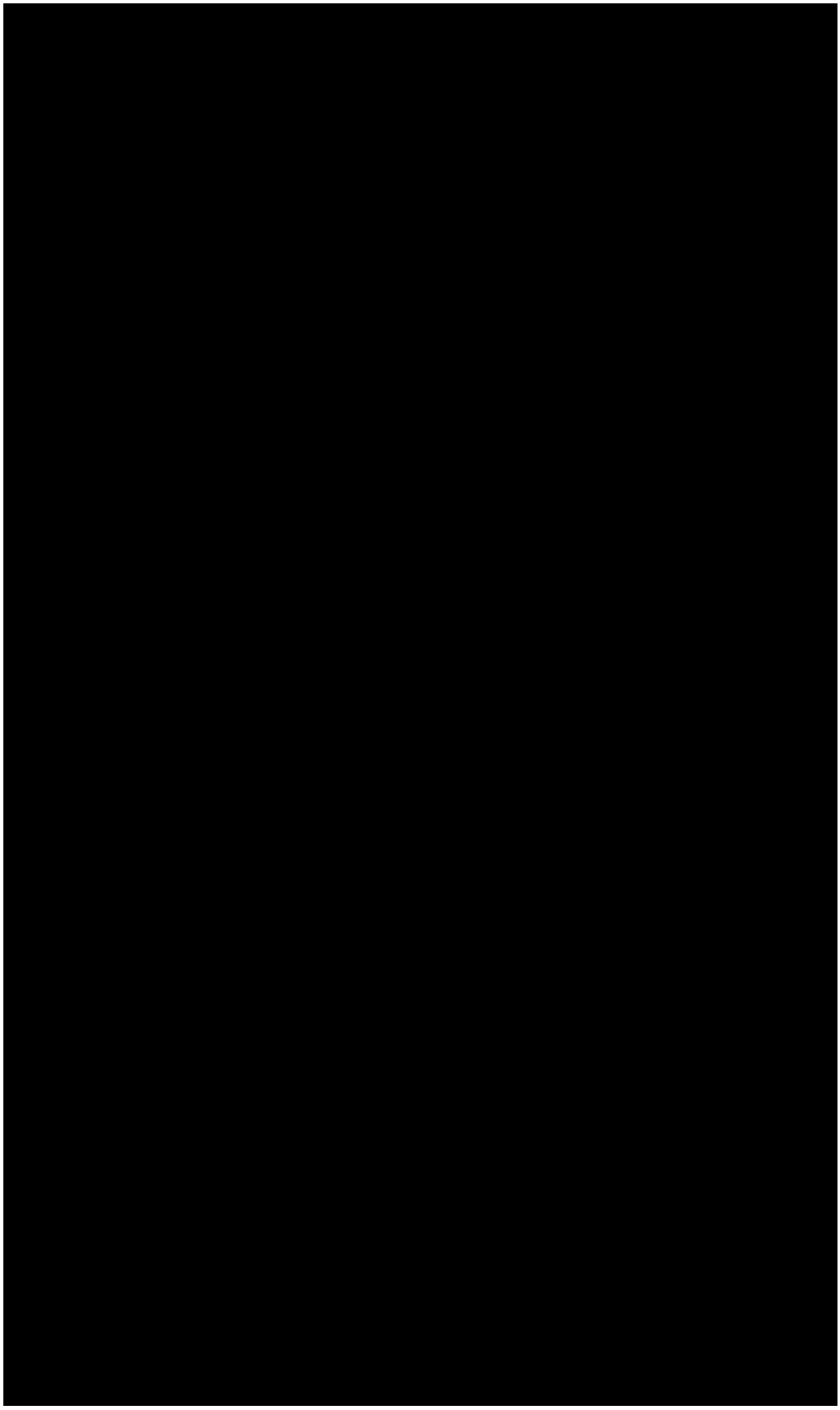
Change from Part B Baseline to Part B Week 8

Change in potassium level from Part B Baseline to Part B Week 8 was not assessed as primary or secondary endpoint for Part B. However, the proportions of subjects with a central laboratory serum potassium ≥ 5.5 mEq/L and ≥ 5.1 mEq/L, respectively, at any time (post-Part B Baseline) through the Part B Week 8 visit were assessed as secondary endpoints for Part B (Table 6). Results show a statistically significant difference in the proportion of patients having a hyperkalaemic event across treatment arms as defined by a cut-off of 5.1 and 5.5mEq/L.

Table 6. Proportion of patients with serum K+ ≥ 5.5 mEq/L and ≥ 5.1 mEq/L at any time through the Part B Week 8

Table 7 shows the proportion of subjects with serum potassium values within specified ranges
(<3.8 mEq/L, ≥ 3.8 to < 5.1 mEq/L, ≥ 5.1 to < 5.5 mEq/L, and ≥ 5.5 mEq/L) at each Part B visit through Part B Week 8. All patients were in the serum potassium (local laboratory) range of (≥ 3.8 mEq/L and < 5.1 mEq/L) at Part B Baseline (per trial protocol). From Part B Week 1 through Week 8, there were more patients in the higher serum potassium ranges (≥ 5.1 to < 5.5 mEq/L and ≥ 5.5 mEq/L) in the placebo arm when compared with the patiromer arm. There were also more patients in the patiromer arm remaining in the serum potassium range of ≥ 3.8 to < 5.1 mEq/L from Week 1 through Week 8. Results confirm efficacy of patiromer in maintaining normokalaemia.

Table 7. Proportion of subjects with serum potassium values in range by week (Part B)



Subgroup considerations

Consistent with results from Part A and baseline to Week 4 of Part B, no difference was observed within treatment arms in the proportion of patients with a serum potassium value of ≥5.5 (defined as HK) through to Week 8 of Part B when stratifying on the presence or absence of heart failure (Table 8).

Table 8. Secondary efficacy outcome by subgroup

Q5: Hazard ratio clarification and serum potassium category transition analysis

What is the standard error of the hazard ratio of [redacted]? Within the PSA has the hazard ratio been sampled and if so where does this sampling occur within the model? The relationship between the hazard ratio of [redacted] and the data overlying the *Calcs* worksheet is unclear.

To the extent that it differs from the data requested under Q4 above please provide the patient numbers separately by OPAL-HK Part B arm of those transitioning between Part B baseline and Part B week 8 between the 3 K+ categories in the same format as the *R*

output: All patients and *R Output: CKD+HF* that overlies cells G6:K53 of the *Calcs* worksheet separately for the three patient groups of:

A. all patients
B. patients who were K+ > 6.0 at baseline
C. patients with heart failure at baseline who were K+ > 5.5 at baseline

Hazard ratio

The standard error of the hazard ratio is [redacted], entered in *SA Inputs* sheet cell N13 and N14. The PSA samples this in *SA Inputs* sheet cell L13 and L14.

The data overlying the *Calcs* sheet is for Part A (single arm) serum potassium transitions. However, the hazard ratio estimates the risk reduction of serum potassium rising from <5.1mmol/L to ≥5.5 mmol/L based on OPAL-HK Part B for the modelled population:

1. Patients with stage 3-4 CKD and HF comorbidity (CKD HF+) with a serum potassium of ≥5.5 mmol/L at Part A Baseline, and,
2. Patients with stage 3-4 CKD without HF comorbidity (CKD [no HF]) with a serum potassium level of >6.0 mmol/L at Part A Baseline

Transitions between Part B Baseline and Part B Week 8

Due to the same reason as for Q4, this analysis was not feasible. Please see the response to Q4 for the available information.

- *All patients:*
  Proportion of patients with serum potassium values in range at each week of Part B is shown in Table 7 within Q4.
- *Subgroup considerations*
  Part B secondary efficacy outcome by subgroup (i.e. presence of heart failure) is shown in Table 8 within Q4

Q6: CPRD analysis clarification

For the CPRD data within the *CPRD outputs.xlsx* spreadsheet, please clarify if Month 0 corresponds to the 1st RAASi prescription subsequent to CKD3/4 diagnosis. Is this data restricted to those remaining on full RAASi, or may some patients contributing data subsequent to Month 0 have reduced or discontinued RAASi (or recommenced or up titrated RAASi)? To what extent is this data specific to the revised target group of (A) patients who were K+ > 6.0 at baseline. To what extent is this data specific to the revised target group of (B) patients with heart failure at baseline who were K+ > 5.5 at baseline?

The output tables in *CPRD outputs.xlsx* show the transition of patients with CKD stage 3 and 4 between four serum potassium categories: ≤5.0, >5.0 to ≤5.5, >5.5 to ≤6.0 and >6.0mmol/L.

The objective of the analysis was to report monthly serum potassium transitions in CKD patients who start on RAASi therapy. To be included in the analysis, patients were required to have at least one record of a prescription for a RAASi during the study period after their diagnosis of CKD. Patients were followed through their medical records, beginning from the date of RAASi prescription initiation and followed to the end of records, hence month zero corresponds to the first prescription for a RAASi post diagnosis of CKD.

The data is not restricted to patients who remained on full RAASi for the duration of the study. Therefore, patients who up titrated, down titrated or discontinued RAASi continued to contribute to the analysis. This is because the intention of the analysis was to observe changes in serum potassium in a cohort of patients initiating RAASi.

The CPRD data was not further stratified to include only CKD patients with serum potassium >6.0mmol/L or those with heart failure and serum potassium >5.5mmol/L. This was in order to maintain generalisability to the UK patient population.

Q7: PSA clarification

Does the PSA sample the patient numbers in the *Calcs* worksheet cells B8:F86? If it does, where does this sampling occur? If it does not, given that small patient numbers are likely to result in significant uncertainty why does it not?

[Response previously provided]

Q8: RAASi 'survival' analysis

For (1) OPAL-HK Part A taking the Part A baseline as T=0 and (2) separately for each arm of OPAL-HK Part B through to Part B week 8 taking the Part B baseline as T=0, for the three patient groups of:

A. all patients
B. patients who were K+ > 6.0 at baseline
C. patients with heart failure at baseline who were K+ > 5.5 at baseline

please provide the following Kaplan-Meier data among those on full RAASi at baseline.

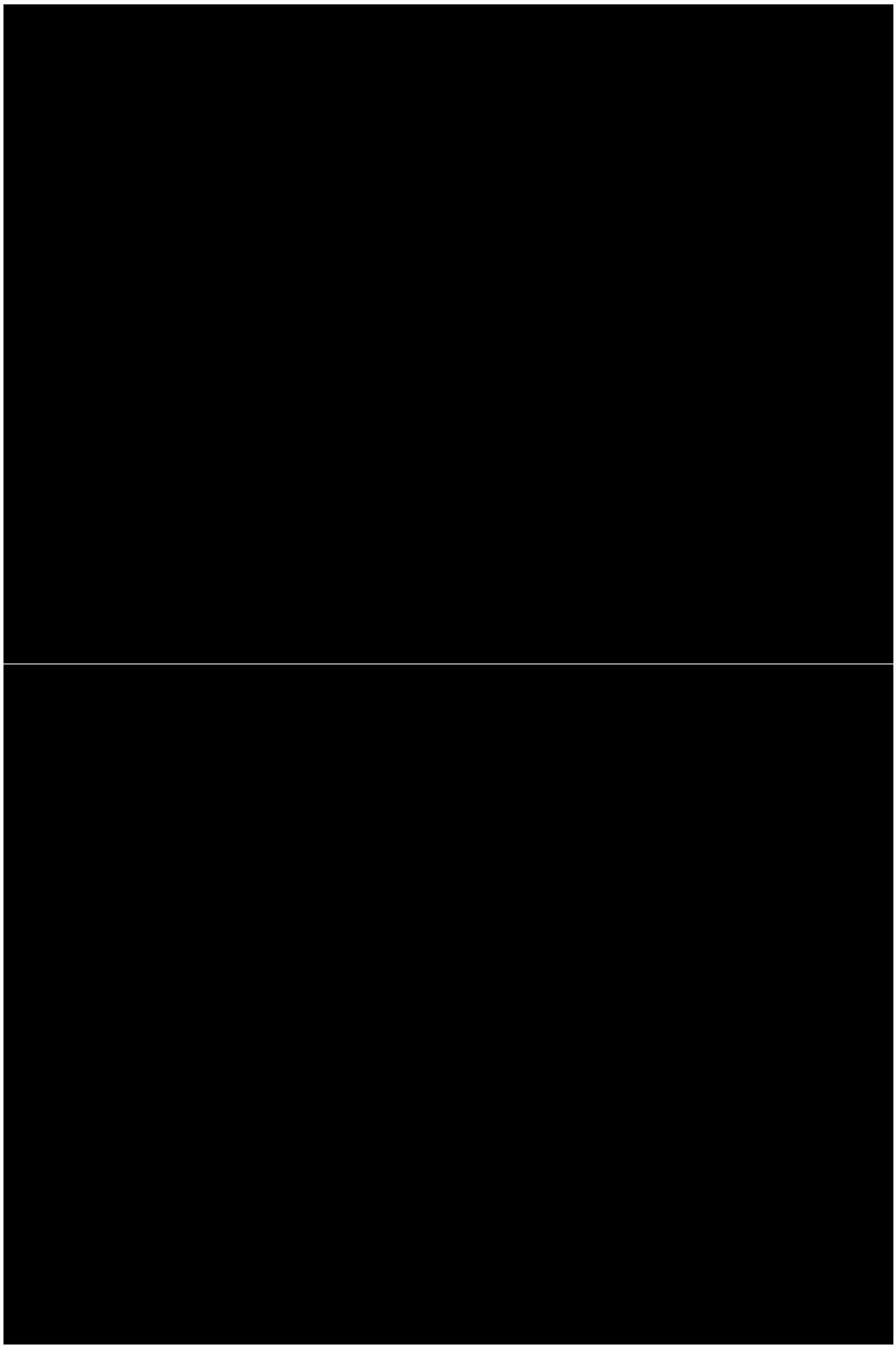
		Events		
Time	N at risk	Reduce RAASi	Stop RAASi	Censored
T=0 T=? Etc.	N=? N=? Etc.	 N=? Etc.	 N=? Etc.	 N=? Etc.

The IPD only contains information on RAASi reductions and increases by weekly visit, rather than by day. Therefore, the data is not sufficiently granular to produce the 'Reduce RAASi' column for this analysis. However further information regarding RAASi reduction is provided below. Stratified data by baseline serum potassium or the HF subgroup was not available although no difference in the control of serum potassium was observed in the absence or presence of HF. Similarly, results indicate patiromer has a greater potassium lowering activity at higher serum potassium levels (see above).

Part A

As described in Q3, a very small proportion of patients experienced a RAASi modification in Part A of OPAL-HK ([redacted]/237). Information on RAASi modification in Part A over time is available in Table 9.

Table 9. Part A RAASi modifications over time



Part B

During Part B, patiromer (and RAASi) dose modification or discontinuation was performed according to protocol-specified titration algorithms (Appendix 2: Titration algorithm: Part B) based on serum potassium (local laboratory) levels assessed starting at the Part B Day 3 visit and continuing through weekly visits (Part B Week 1, 2, 3, 4, 5, 6 and 7) to the end of the 8 weeks of the patiromer withdrawal phase.

Because the primary efficacy endpoint for Part B was determined during the first 4 weeks of Part B, the titration algorithm specified no change of dose or discontinuation of patiromer/placebo or RAASi during the first 4 weeks of Part B unless the serum potassium level was <3.8 mEq/L or ≥5.5 mEq/L. If a subject's serum potassium was <3.8 mEq/L, the subject discontinued patiromer/placebo, was withdrawn early from Part B and entered a follow-up period to Part B. To help retain subjects for the collection of 8 weeks of placebo-controlled safety data, an intervention (increase in patiromer dose or, for subjects receiving placebo, decrease in RAASi dose) was specified during the first 4 weeks of Part B if a subject's serum potassium was ≥5.5 mEq/L.

After the first 4 weeks of Part B, the titration algorithm also specified an increase in patiromer dose upon the initial occurrence of a serum potassium ≥5.1 mEq/L. During Part B, the patiromer dose could be increased to a maximum of 50.4 g/day patiromer in increments of 8.4 g/day patiromer.

Depending on the serum potassium level, the Part B titration algorithms also specified MSVs within 24 or 72 hours and/or early withdrawal from Part B of the study.

During Part B, more placebo subjects required dose modification (dose reduction, dose discontinuation or both) of their RAASi therapies as a result of recurrent hyperkalaemia (66%) than patiromer subjects (6%). For most subjects in the placebo group, RAASi dose reduction was insufficient to control recurrent hyperkalaemia, resulting in discontinuation of RAASi medication. By the end of Part B, more patiromer subjects (94%) than placebo subjects (44%) were still receiving RAASi medication.

In Part B, [redacted]% of patiromer subjects compared with [redacted]% of placebo subjects did not require a protocol-specified intervention for recurrent hyperkalaemia during Part B and completed Part B (Table 10). There were [redacted] patients who experienced RAASi reduction in the patiromer arm when compared to [redacted] patients in the placebo arm who experienced RAASi reduction from Week 1 through Week 8. A summary of interventions by treatment arm is provided in Table 10.

Table 10. Part B RAASi modifications in Part B

Information on RAASi modification in Part B over time is provided in Table 11. In the patiromer arm, [redacted] patients discontinued RAASi (at Week 3, Week 5, and Week 7). In the placebo arm, [redacted] patients discontinued RAASi from Day 3 through Week 8.

Table 11. Part B RAASi modifications over time

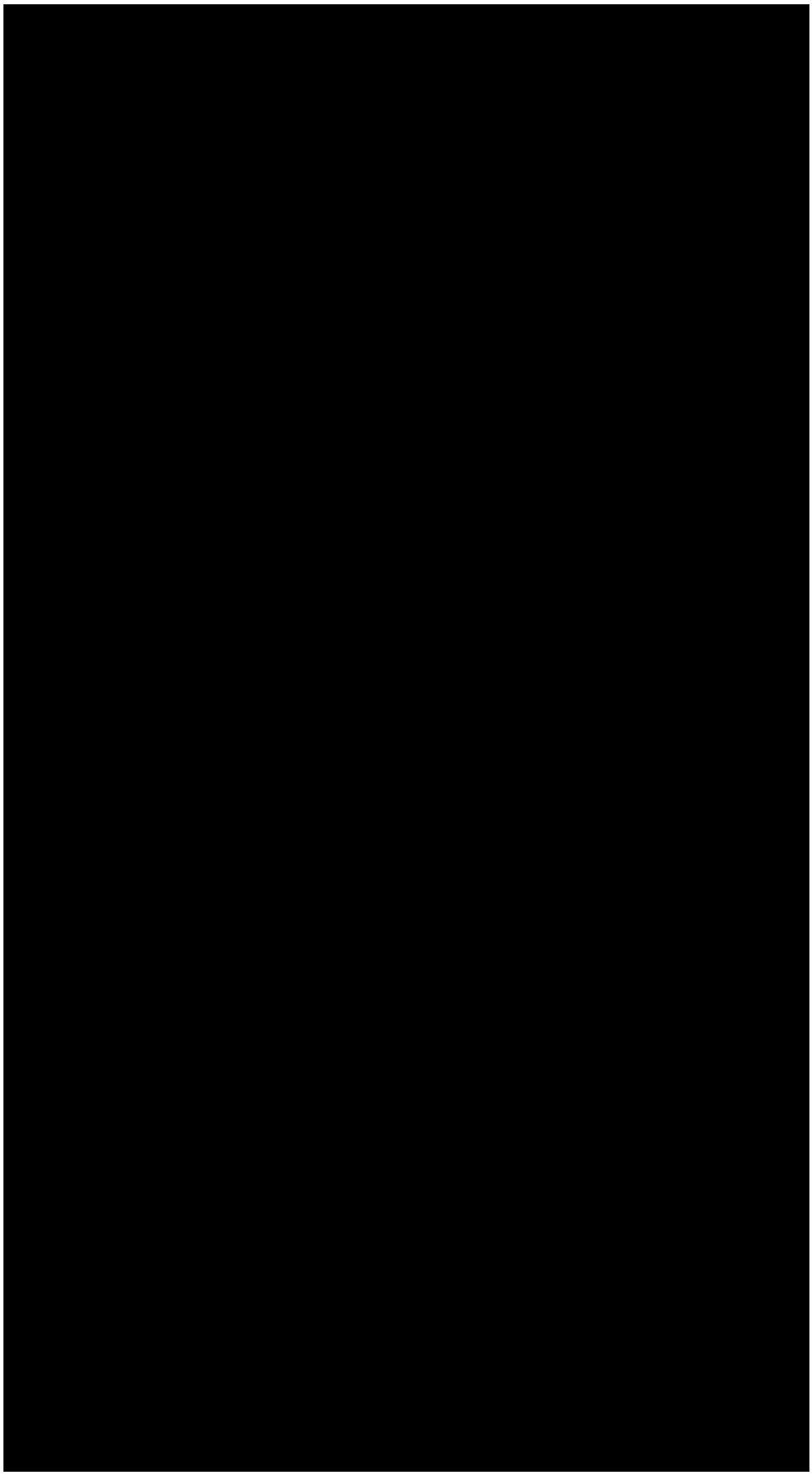
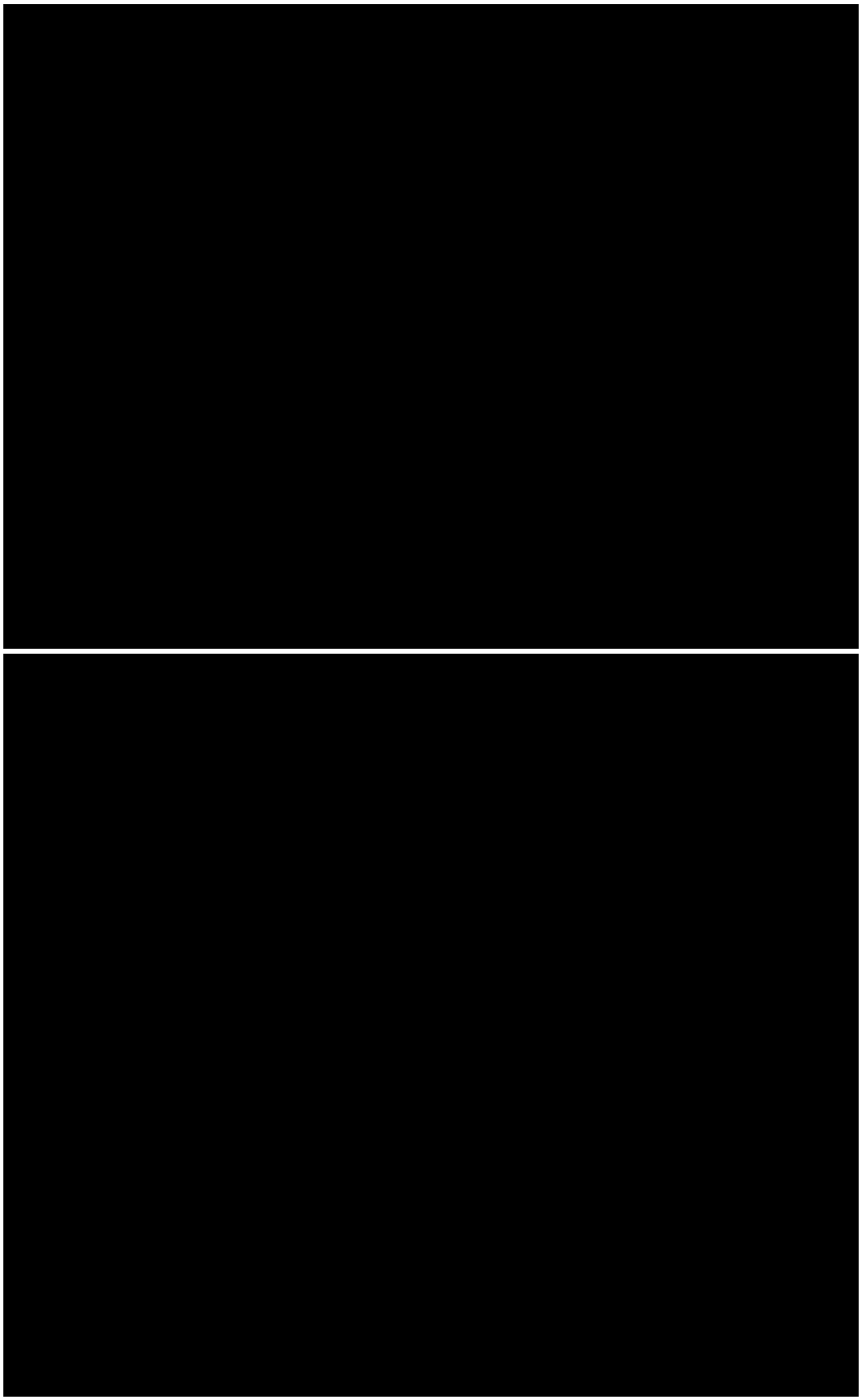


Table 12 and Finally, Table 13 provides data as available relating to the proportion of patients remaining on RAASi over time. As clarified earlier, data was only available on a weekly basis.

Table 13 provide further information regarding RAASi modification and RAASi discontinuation over time in Part B.

Table 12. OPAL-HK Part B RAASi modification



Finally, Table 13 provides data as available relating to the proportion of patients remaining on RAASi over time. As clarified earlier, data was only available on a weekly basis.

Table 13. Estimated proportion remaining on RAASi in Part B

Q9: RAASi 'survival' analysis

Separately for each arm of OPAL-HK Part B through to Part B week 8 taking the time of 1st RAASi reduction as T=0, for the three patient groups of:

A. all patients
B. patients who were K+ > 6.0 at baseline
C. patients with heart failure at baseline who were K+ > 5.5 at baseline

please provide the following Kaplan-Meier data among those on reduced RAASi at T=0.

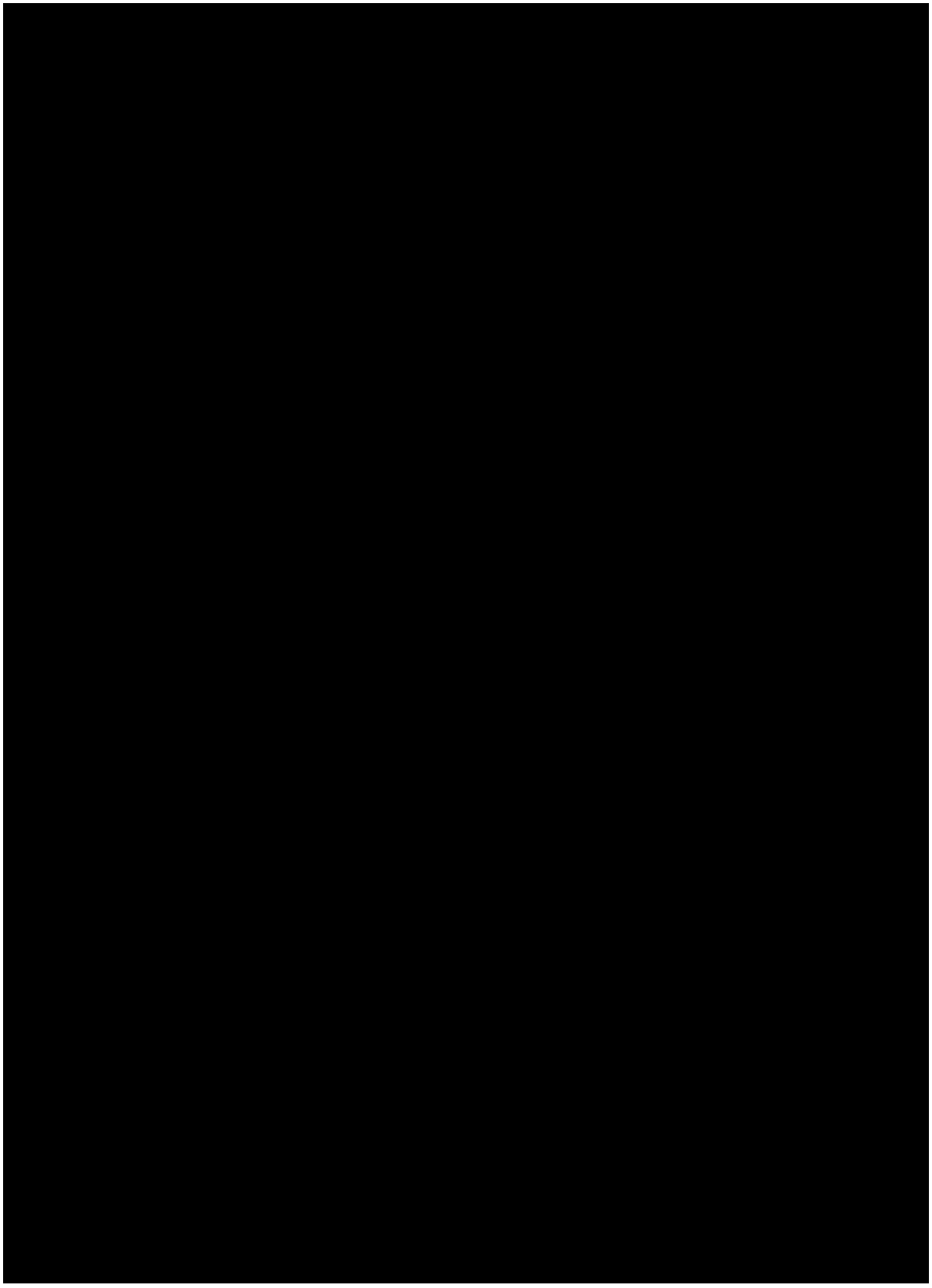
		Events		
Time	N at risk	Increase RAASi	Stop RAASi	Censored
T=0 T=? Etc.	N=? N=? Etc.	 N=? Etc.	 N=? Etc.	 N=? Etc.

As highlighted in response to Q8, RAASi reduction by day was not available in the IPD.

In Part B only three patients in the patiromer arm stopped RAASi and no patients had a RAASi reduction (shown in Table 12 for Q8). Due to the very limited number of patients, this analysis would have limited value given no patients would be analysed in the patiromer arm

Figure 3 provides supporting information regarding RAASi discontinuation after RAASi reduction in Part B.

Figure 3. RAASi Modifications over Time (Part B ITT Population) CSR tables and figures full, page 752



Q10: Patiromer treatment duration analyses

Please present the US claims Kaplan Meier data that underlies Figure 12, ignoring end of trial, and the equivalent data for AMETHYST-DN in the following format.

		Events		
Time	N at risk	Stop patiromer	End of Trial	Censored
T=0 T=? Etc.	N=? N=? Etc.	 N=? Etc.	 N=? Etc.	 N=? Etc.

See supporting Excel file *Q10_patiromer_discontinuation_v1.0.xlsx* for tables.

Appendices

Appendix 1: Titration algorithm: Part A

Table 14. Titration algorithm for the 4-week initial treatment phase (Part A)

	Serum K^+ (mmol/L)				
	<3.8	**3.8–<5.1**	**5.1–<5.5**	**5.5–<6.5**	**≥6.5**
Patiromer dose	• Decrease by 8.4 g/day or more or to 0 g/day • (If already on 0 g/day, early withdraw)	• No change	• Increase by 8.4 g/day*†	• Increase by 8.4 g/day*	• Increase to 50.4 g/day • (If already on 50.4 g/day, early withdraw)
RAASi dose	• No change • (If already on patiromer 0 g/day, early withdraw)	• No change	• No change	• No change	• Discontinue
Study participation	• Continue • (If already on patiromer 0 g/day, early withdraw)	• Continue	• Continue	• Continue	• Continue • (If already on 50.4 g/day, early withdraw)
Next visit	• Next weekly visit • (Follow-up visit if early withdrawn)	• Next weekly visit	• Next weekly visit	• Next weekly visit	• MSV, within 24 hours • (Follow-up visit if early withdrawn)
2 consecutive values					
Patiromer dose	• Decrease to 0 g/day • (If already on 0 g/day, early withdraw)	–	–	• Increase by 8.4 g/day or • Increase to 50.4 g/day *	• Discontinue
RAASi dose	• No change • (If already on patiromer 0 g/day, early withdraw)	–	–	• No change	• Discontinue
Study participation	• Continue • (If already on patiromer 0 g/day, early withdraw)	–	–	• Continue	• Early withdraw
Next visit	• MSV within 72 hours	–	–	• MSV within 72 hours	• Part A • Follow-up visits
3 consecutive values					
Patiromer	• Discontinue	–	–	• Discontinu	–

	Serum K^+ (mmol/L)				
	<3.8	**3.8–<5.1**	**5.1–<5.5**	**5.5–<6.5**	**≥6.5**
dose				e	
RAASi dose	• Early withdraw	–	–	• Discontinue	–
Study participation	• Early withdraw	–	–	• Early withdraw	–
Next visit	• Part A • Follow-up visits	–	–	• Part A • Follow-up visits	–

*No titration required if the serum K^+ decreased from the previous visit was ≥0.4 mmol/L.

†If subject is on 50.4 g/day, discontinue RAASi. Return for next specified visit in the table. Two consecutive values on 50.4 g/day, early withdraw.

Any subject on 50.4 g/day, who discontinued RAASi and whose serum K^+ was still ≥5.1 mmol/L was to be early withdrawn. Any subject who had a serum K^+ of <3.8 mmol/L and was on 0 g/day of patiromer was to be early withdrawn.

Abbreviations: K^+, potassium; MSV, mandatory safety visit; RAASi, renin–angiotensin–aldosterone system inhibitor.

Appendix 2: Titration algorithm: Part B

Table 15: Titration algorithm for the first 4 weeks of the withdrawal phase

Serum K^+ threshold (mmol/L)		Treatment group	Intervention	Study participation	Next visit
<3.8	Any event	Patiromer: Placebo:	• Discontinue patiromer/placebo • No change to RAASi medication(s)	Early withdraw	• Part B • Follow-up visits
3.8–<5.1	Any event	Patiromer: Placebo:	• No change	Continue	• Next weekly visit
5.1–<5.5	1st event (5.1–5.4)	Patiromer: Placebo:	• No change to patiromer placebo or RAASi medication(s)	Continue	• Next weekly visit
	Any subsequent event in 1st 4 weeks (5.1–5.4)	Patiromer: Placebo:	• No change to patiromer, placebo or RAASi medication(s)	Continue	• Next weekly visit
5.5–<6.0	1st event (5.5–<6.0)	Patiromer:	• Increase patiromer by 8.4 g/day* • No change to RAASi medication(s)	Continue	• Next weekly visit
		Placebo:	• No change to placebo • Decrease each RAASi medication by 50% or to next available dose strength below 50%	Continue	• Next weekly visit
	2nd event (5.1–<6.0)	Patiromer:	• No change to patiromer dose • Discontinue RAASi medication(s)	Continue	• Next weekly visit
		Placebo:	• No change to placebo • Discontinue RAASi medication(s)	Continue	• Next weekly visit
	3rd event (5.1–<6.0)	Patiromer:	• Discontinue patiromer	Early withdraw	• Part B • Follow-up visits
		Placebo:	• Discontinue placebo	Early withdraw	• Part B • Follow-up visits
6.0–<6.5†	1st event	Patiromer:	• No change to patiromer dose • Discontinue RAASi medication(s)	Continue	• MSV within 72 hours • (At MSV, discontinue if K^+ ≥6.0)
		Placebo:	• No change to placebo • Discontinue RAASi medication(s)	Continue	• MSV within 72 hours • (At MSV, discontinue if K^+ ≥6.0)

Serum K^+ threshold (mmol/L)		Treatment group	Intervention	Study participation	Next visit
	2nd event (≥5.1)	Patiromer:	• Discontinue patiromer	Early withdraw	• Part B • Follow-up visits
		Placebo:	• Discontinue placebo	Early withdraw	• Part B • Follow-up visits

*If subject is on 50.4 g/day, decrease each RAASi by 50% or to next available dose strength below 50%.

†Any subject with a serum K^+ ≥6.5 mmol/L must discontinue patiromer/placebo and all RAASi medications and must return for an MSV within 24 hours. These subjects will be early withdrawn and will enter the Part B follow-up phase.

Abbreviations: K^+, potassium; MSV, mandatory safety visit; RAASi, renin–angiotensin–aldosterone system inhibitor.

Table 16: Titration algorithm for the second 4 weeks of the withdrawal phase

Serum K^+ threshold (mmol/L)		Treatment group	Intervention	Study participation	Next visit
<3.8	Any event	Patiromer:	• Discontinue patiromer/placebo • No change to RAASi medication(s)	Early withdraw	• Part B • Follow-up visits
		Placebo:			
3.8–<5.1	Any event	Patiromer:	• No change	Continue	• Next weekly visit
		Placebo:			
5.1–<6.0	1st event (5.1–<6.0)	Patiromer:	• Increase patiromer by 8.4 g/day* • No change to RAASi medication(s)	Continue	• Next weekly visit
		Placebo:	• No change to placebo • Decrease each RAASi medication by 50% or to next available dose strength below 50%	Continue	• Next weekly visit
	2nd event (5.1–<6.0)	Patiromer:	• No change to patiromer dose • Discontinue RAASi medication(s)	Continue	• Next weekly visit
		Placebo:	• No change to placebo • Discontinue RAASi medication(s)	Continue	• Next weekly visit
	3rd event (5.1–<6.0)	Patiromer:	• Discontinue patiromer	Early withdraw	• Part B • Follow-up visits
		Placebo:	• Discontinue placebo	Early withdraw	• Part B • Follow-up visits
6.0–<6.5[†]	Any event	Patiromer:	• No change to patiromer dose • Discontinue RAASi medication(s)	Continue	• MSV, within 72 hours • (At MSV, discontinue if K^+ ≥6.0)
		Placebo:	• No change to placebo • Discontinue RAASi medication(s)	Continue	• MSV, within 72 hours • (At MSV, discontinue if K^+ ≥6.0)
	2nd event (≥5.1)	Patiromer:	• Discontinue patiromer	Early withdraw	• Part B • Follow-up visits
		Placebo:	• Discontinue placebo	Early withdraw	• Part B • Follow-up visits

*If subject is on 50.4 g/d, decrease each RAASi medication by 50% or to next available dose strength below 50%.

[†]Any subject with a serum K^+ ≥6.5 mmol/L must discontinue patiromer/placebo and all RAASi medications and must return for an MSV within 24 hours. These subjects will be early withdrawn and will enter the Part B follow-up phase.

Abbreviations: K^+, potassium; MSV, mandatory safety visit; RAASi, renin–angiotensin–aldosterone system inhibitor.

ERG – Clarification questions – Part II – Clinical effectiveness

Q1. Please define suboptimal dosing of RAASi?

The phrase “suboptimal dosing of RAASi” is used interchangeably with “lower than recommended” or “submaximum” RAASi dosing.

In a US study [Epstein et al., 2015] RAASi dose levels were examined in a US patient population and the impact of hyperkalaemia on RAASi dose and the association between dose levels and clinical outcomes was investigated. The study concludes that patients on submaximum doses or who discontinued RAAS inhibitors had worse outcomes than patients on maximum doses.

In the study, RAAS inhibitor prescriptions were classified by dose level using the following dose categories: “supramaximum,” defined as any RAAS inhibitor dose above the labelled dose; “maximum,” defined as the labelled dose; “submaximum,” defined as any RAAS inhibitor dose lower than the labelled dose; or “discontinued,” defined as the absence of RAAS inhibitor prescriptions for a period of more than 390 days subsequent to prior prescription. (The 390-day period allows 360 days (longest common prescription length in the database) plus 30 additional days for patients to see or contact their healthcare provider for a refill).

The 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure [Ponikowski et al., 2016] summarises available evidence at the time of writing to provide practical, evidence-based guidelines for the diagnosis and treatment of Heart Failure (HF).

Table 7.2 below, extracted from the ESC Guidelines [Ponikowski et al., 2016], shows evidence-based doses of disease modifying drugs from key randomised trials in patients with HF with a reduced ejection fraction (HFrEF). In relevance to Q1 from the ERG, please see the ESC recommended starting and target doses for ACEi, ARBs, MRAs and ARNI which are RAAS modifying medications.

Table 7.2 Evidence-based doses of disease-modifying drugs in key randomized trials in heart failure with reduced ejection fraction (or after myocardial infarction)

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
Lisinopril[a]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 *o.d.*	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 *o.d.*
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
I_f-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

The ERC starting and targeted recommended doses are evidence based as shown in Web Table 7.1 of the supplements to the ESC 2016 Guidelines [Ponikowski et al., 2016]. The ESC 2016 Guidelines [Ponikowski et al., 2016] state clearly "…the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition.."

Q2. Please provide details on the physicians involved in the Delphi process for example:

- **how were they recruited/selected, including how conflicts of interest were considered**
- **how experienced the are**
- **how many patients did they report seeing on a regular basis with hyperkalaemia (chronic or acute)**
- **how many use patiromer already**
- **what are their sociodemographic details such as their geographical region, type of centre, private or NHS practice?**

The research followed the following phases:

- 1st round telephone interviews – 10 (No honoraria paid)
- 2nd round interviews – 21 (No honoraria paid)
- Working group – 9 (honoraria paid)

1st Round telephone interviews	
Recruitment	Email contact, web search highlighting Cardiologists with a speciality in Heart Failure and Nephrologists
Selection	Availability for short interview
Conflict of interests	Exclusion upon declaration of conflicts of interest (e.g. NICE advisor)
Experience levels	Minimum inclusion of consultant grade (4 x Cardiologists, 6 x Nephrologists)
Sociodemographic details	All NHS practitioners, covering London, South West, West Midlands, East Midlands, North West and Scotland – broad spectrum of district general and

	teaching hospitals
Experience of patiromer	Unknown
Patient numbers	Unknown

2nd Round telephone interviews	
Recruitment	Email contact, web search highlighting Cardiologists with a speciality in Heart Failure and Nephrologists. Previous participation
Selection	Availability for interview, geographical and clinical speciality balance
Conflict of interests	Exclusion upon declaration of conflicts of interest (e.g. NICE advisor)
Experience levels	Minimum inclusion of consultant grade (10 x Cardiologists, 11 x Nephrologists)
Sociodemographic details	All NHS practitioners, covering London, South West, South East West Midlands, East Midlands, North West and Scotland – broad spectrum of district general and teaching hospitals
Experience of patiromer	Unknown
Patient numbers	Nephrologists reported an average of 15% of their caseload suffering Hyperkalaemia. Cardiologists reported an average of 17% of their Heart Failure caseload suffering Hyperkalaemia

Working group participation	
Recruitment	Previous participation
Selection	Availability for meetings

Conflict of interests	Exclusion upon declaration of conflicts of interest (e.g. NICE advisor)
Experience levels	Minimum inclusion of consultant grade (3 x Cardiologists, 6 x Nephrologists)
Sociodemographic details	All NHS practitioners, covering London, South East, East Midlands, North West and Scotland –teaching hospitals
Experience of patiromer	Unknown
Patient numbers	Not explored

Q3. Please provide details of the interviewer(s) used in the Delphi process, e.g were they independent, what experience do they have with Delphi?

All research was conducted by an independent agency, in line with British Healthcare Business Intelligence Association (BHBIA) Legal and Ethical Guidelines for Healthcare Market Research, overseen by a member of the BHBIA.

The interviewers utilised in the Modified Delphi process are all experienced interviewers (7-20 years' experience in market research type projects) who have delivered such market research in the UK and other European markets for incorporation into Health Technology Assessment submissions. This has previously included submissions to NICE, SMC and the NCPE in Ireland.

Q4. Please discuss the limitations of the Delphi process

We utilised a modified Delphi method to derive consensus on the following points:

- At what point would you consider a patient to be hyperkaliaemic?

- When do you start to actively manage serum potassium?
- How do you currently manage hyperkalaemia?
- Does Patiromer fill any unmet need?
- Define the patient cohorts most suitable for Patiromer?

One limitation of using the modified Delphi method is the loss of subject anonymity when the participants attended web and physical meetings. While anonymity can reduce the impact of individuals and reduce manipulation or coercion, a face-to-face meeting allows experts to exchange relevant information, such the clarification or reasoning for differences in subject matter opinion. The final meeting seeks clarification in order to reach consensus.

Another limitation would be the willingness to participate in this research. There were a limited number of clinicians who were able to participate fully, which may have introduced a bias, although any effect appears to have been small given the consistency of outputs displayed between phases of the research.

Q5. The old and new submissions make use of the NMA by Xie et al., to calculate relative risks for various events. The submission also states that the Xie et al., NMA was used in TA599, sodium zirconium cyclosilicate. Please tabulate all values derived from Xie in the 2 Vifor submissions and the submission for TA599.

Table 1 lists the relative risks (RRs) and odds ratios (ORs) from Xie et al. that were used in the two Vifor submissions and the submission for TA599 (as provided in the committee papers). The different estimates in the second vs. the first Vifor submission were due to 1) correction of an error in the calculations of the RRs in the original submission, and 2) a weighted average per ACEi and ARB proportions (71:29) being considered in the second submission

Compared with the first Vifor submission, some estimates (i.e. RR of CKD to HK, RR of CKD to death [non-CV]) were not used in the second Vifor submission due to the updated model structure. In TA599, the only specified estimate derived from Xie et al. for the model was the OR of all-cause mortality (others were not explicitly stated to have been used in the model).

The RR of CKD to CV event was stated as 0.70 in the second Vifor submission. This was a typographical error in the report such that the value should be 0.80, which was used in the submission model.

Table 1: Values derived from Xie in the submissions

RR (event with RAASi vs placebo)	Vifor submissions		Submission for TA599
	1st submission	2nd submission	
CKD to CKD progression	0.64	0.64	Model input value not specified in committee papers
CKD to CV event (MI/stroke)	0.82	0.80	Model input value not specified in committee papers
CKD to HK	2.06	-	Model input value not specified in committee papers
CKD to death (non-CV)	0.87	-	OR (all-cause mortality; RAASi vs. No RAASi): 0.870
CV event (MI/stroke) to death	0.88	0.95	

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HK, hyperkalaemia; MI, myocardial infarction; OR, odds ratio; RAASi; Renin-angiotensin-aldosterone system inhibitors; RR, relative risk.

Q6. The Committee were concerned that the benefit of starting RAASi may not be equivalent quantitatively to the benefit forgone when stopping (or decreasing) RAASI. Submission section 6.3.5.2 states the evidence shows that discontinuation of RAASi will revert patients to a baseline mortality risk and refers to Figure 9. Please Tabulate the differences in population and pharmacological intervention between patients entering the submission economic model and those depicted in Figure 9 (from Bhagat et al., JACC Heart failure. 2019;7(1):1-12)

Table 2 summarises the included populations and the pharmacological interventions used in patients entering the economic model and those depicted in Figure 9 of the submission (see Figure 1 below). The study cited in Figure 9 was a review study [Bhagat et al., 2019] with the original study performed by Gilstrap et al. [Gilstrap et al., 2017]. The two populations are, as stated in the submission, different. However, Gilstrap et al. does demonstrate that continuation and initiation of ACEi/ARB are associated with a better 1-year mortality outcome, while patients who discontinue ACEi/ARB revert to a similar mortality risk as those who had not started treatment. While the study populations do differ, the impact of changes in risk as a function of RAASi use were confirmed.

It should be noted that no input data in the submission model was derived from the study by Gilstrap et al, rather this study helps in confirming the appropriateness of using Xie et al in the economic model.

Table 2: Population and treatment in the submission model vs the ones from Bhagat et al.

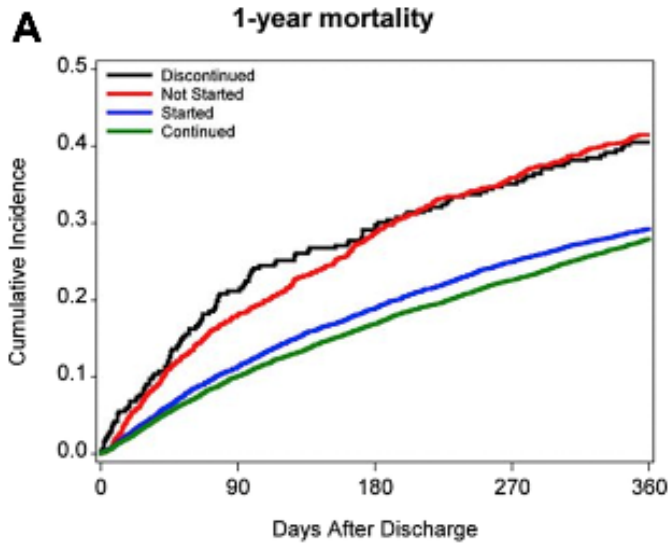
	Used in model in submission (OPAL-HK)	**Reported in Gilstrap et al.***
Population	- Patients with stage 3-4 CKD and HF with sK+ ≥ 5.5 mmol/L at baseline, and, - Patients with stage 3-4 CKD without HF with sK+ > 6.0 mmol/L at baseline	Patients with Heart Failure with Reduced Ejection Fraction (HFrEF) hospitalised for Acute Decompensated Heart Failure (ADHF)
Pharmacological intervention	- *"Full RAASi":* patients on a stable RAASi dose In the submission, all patients enter the model at *Full RAASi* status. - *"Reduced RAASi":* patients on down-titrated RAASi (assumed 50% of full dose) - *"Discontinued RAASi":* patients discontinued RAASi	- *"Continued":* patients on ACEi/ARB at admission and discharge - *"Discontinued":* patients on ACEi/ARB at admission but not at discharge - *"Not started":* patients on ACEi/ARB at admission or discharge - *"Started":* patients not on

	RAASi medications include ACEi, ARB, direct renin inhibitors, MRA and ARNi	ACEi/ARB at admission but who were discharged on ACEi/ARB

*Source: Gilstrap et al., J Am Heart Assoc. 2017 Feb 11;6(2).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ADHF, acute decompensated heart failure; ARB, angiotensin II receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitors; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; sK+, serum potassium.

Figure 1: One-year mortality by ACEi/ARB treatment groups (source: Gilstrap et al.)



Q7. Please clarify the likely proportion of patients depicted in Figure 9 that were receiving beta-blocker therapy in addition to ACEi therapy.

The percentage of the patients with Heart Failure with Left Ventricular Systolic Dysfunction hospitalised for Acute Decompensated Heart Failure **discharged on beta-blocker, are:**

- Total: 93.59%
- Continued ACEi/ARB: 94.96%
- Started ACEi/ARB: 94.79%

- Discontinued ACEi/ARB: 75.95%
- Not started ACEi/ARB: 82.38%

The authors note that patients discontinued or not started on ACEi/ARB had lower rates of beta-blocker prescription at discharge.

The study cited in Figure 9 was a review study [Bhagat et al., 2019] with the original study performed by Gilstrap et al. [Gilstrap et al., 2017]. The data is not used in the model as stated in the response to q6 above.

Q8. The submission appears to base persistence of patiromer treatment on data from AMETHYST, but scenarios were undertaken using data shown in Figure 13, page 84. Furthermore, the previous submission used CPRD data to model RAASi continuation

a) **Please clarify how persistence was estimated in the new and previous submissions using these sources, and provide reasons for any change in methodology from the first submission**

b) **Please clarify if stopping patiromer was a patient reported outcome in AMETHYST, and whether this was also the case for data shown in Figure 13**

In the previous submission, patiromer persistence was built into the model via a treatment discontinuation curve based on semi-parametric extrapolation of individual patient level data (IPD) from AMETHYST. The best fitting curve was selected on the basis of best statistical fit (AIC and BIC).

In the updated model, a treatment discontinuation curve was not built into the model. Instead, a base case treatment duration of one year was chosen as this reflects the longest duration of treatment (52 weeks) observed in the patiromer clinical trial programme, from AMETHYST. This approach was taken in the second submission in order to be aligned with TA599 where, at the committee meeting, it was “understood the company chose 52 weeks because it had no data beyond 52 weeks” (TA599 ACD, p19). This was accepted in TA599.

In order to consider the totality of evidence, scenarios were provided based on real-world usage of patiromer in the US. The data suggests a shorter mean treatment duration of approximately [redacted], as detailed in the evidence submission, resulting in improved cost-effectiveness of

patiromer. Details including the length of follow-up and the data cut used are provided in the submission document.

Estimates of mean treatment duration were calculated using area under the curve methods for both AMETHYST and real-world US data.

The use of CPRD to model RAASi discontinuation was removed from the model based on previous feedback from both the ERG and committee as it was considered to not be representative of real-world discontinuation. Vifor therefore took an alternative approach whereby RAASi usage (full dose, reduced dose or discontinued) is a function of serum potassium. This was aligned to both clinical guidelines as well as the UK clinician survey undertaken by Vifor. Further information is provided in the submission document. Stopping patiromer was not a patient reported outcome in AMETHYST or the US claims data.

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Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD, Smith EE, Heidenreich P, Hernandez AF, Yancy CW, Bhatt DL. **Initiation, Continuation, or Withdrawal of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Outcomes in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction**. J Am Heart Assoc. 2017 Feb 11;6(2).

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Patiromer for treating hyperkalaemia [ID877] – Evidence submission 2 (response to first Appraisal consultation)

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Contributions of authors: Lena Al-Khudairy, Emma Mead and Jill Colquitt co-ordinated, reviewed and critiqued the clinical effectiveness evidence. Ewen Cummins conducted, reviewed and critiqued the cost-effectiveness evidence. Martin Connock supported the critique of clinical and cost effectiveness evidence. Rachel Court conducted the critique of the company searches and conducted ERG searches. Paul Sutcliffe provided coordination.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

Contents

List of tables

List of figures

ACE	Angiotensin-converting enzyme
AE	Adverse event
ARB	Angiotensin II receptor blocker
CEAC	Cost-effectiveness acceptability curve
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
CRIB	Chronic Renal Impairment in Birmingham
CS1	Previous company submission
CS2	Current company submission
CV	Cardiovascular
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
ERG	Evidence Review Group
ESC	European Society of Cardiology
ESRD	End stage renal disease
EQ-5D	EuroQol Five Dimensions
GP	General practitioner
HR	Hazard ratio
HK	Hyperkalaemia
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intention to treat
K^+	Potassium
KM	Kaplan-Meier
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
OR	Odds ratio
PATR	Patiromer
PAS	Patient access scheme
PBO	Placebo
Phase A	The (uncontrolled) treatment phase of the OPAL-HK trial
Phase B	The (randomised) withdrawal phase of the OPAL-HK trial
PLAC	Placebo
prob	Probability
prog	Progression

PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
QoL	Quality of life
RAAS	Renin–angiotensin–aldosterone system
RAASi	RAAS inhibitor/inhibition
RCT	Randomised controlled trial
RD	RAASi discontinuation
refs	References
SD	Standard deviation
s.e.	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SMR	Standardised mortality ratio
STA	Single technology assessment
TP	Transition probability
T2DM	Type 2 diabetes mellitus
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
US	United States

1 Summary

1.1 Critique of the decision problem in the company's submission

In its first submission (CS1) the company target population restricted the scope to patients with CKD stage 3 or 4 with hyperkalaemia (K+ > 5.0 mmol/L). In the second submission (CS2) the decision problem refers to the same population, however, in the economic evaluation the company further narrows the target population to (1) patients with K+ > 5.5 mmol/L and heart failure and (2) patients with K+ > 6.0 mmol/L without heart failure. OPAL-HK data for this group is limited to [redacted] patients.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submitted additional clinical evidence to address the committee's concerns around the clinical effectiveness of patiromer, the ACD 3.1 *do not usually treat serum potassium levels <6.0 mmol/l* and regarding the *generalisability of patiromer clinical trials to UK practice*. The submission also aims to address concerns on the impact of RAASi on long-term outcomes, progression to end-stage renal disease and the effects of stopping RAASi in the CS1 economic model through targeted literature reviews. The submission does not provide additional evidence for ACD 3.12: *The submission does not provide evidence that supports patiromer treatment extends life.* The submission also included evidence that was not related to the NICE committee's concerns which the ERG has not critiqued.

The clinical effectiveness evidence in CS2 included:

1. Two surveys: a published survey and a physician opinion and consensus survey funded by the company

The published survey included 112 healthcare practitioners who were involved in the care of patients with cardiorenal conditions. Participants were from the UK (81%) and Europe, and other countries not stated (19%).

For cardiology, the average potassium level necessitating action was 5.7 mmol/L among all grades (n=62) and consultants only (n=18).

For nephrology, the average potassium level necessitating action was 5.8 mmol/L among all grades (n=27) and 5.7 mmol/L among consultants only (n=15).

The company survey included interviews and web-based or face to face discussions. Consultant level cardiologists and nephrologists were included, the numbers differed at different rounds but ranged between nine and 21.

- A maximum tolerable serum potassium threshold in clinical practice is between 5.5-5.9 mmol/l. All cardiologists and most nephrologists will alter treatment when serum potassium reaches this threshold (the ERG note that for the nephrologists this would be to not up-titrate RAASi therapies; consensus to down-titrate or stop RAASi therapy was only at >6.0 mmol/L).

- Based on the second round of extended telephone interviews with 21 physicians:

    - 70% (7/10) of cardiologists would stop (1/7) or reduce (6/7) RAASi if serum potassium is between 5.1-5.4 mmol/L.

    - 9% (1/11) of nephrologists would reduce RAASi dosing if serum potassium is between 5.1-5.4 mmol/L and none would stop RAASi.

    - 50% (5/10) of cardiologists would stop RAASi and 50% would reduce RAASi at serum potassium between 5.5-5.9 mmol/L.

    - 18%-27% (2-3/11, depending on CKD stage) of nephrologists would stop RAASi and 50% (6/11) would reduce RAASi at serum potassium between 5.5-5.9 mmol/L. 18-27% wouldn't stop or reduce RAASi at serum potassium between 5.5-5.9 mmol/L.

2. A description of four trials in the company's patiromer programme:
    a. OPAL-HK (CS1):

No new evidence was provided. Phase A was mainly used in the economic model and Clinical Practice Research Datalink (CPRD) data (patient's characteristics) was used as a comparator. The worsening from phase B was used in the economics model after comparing phase A to CPRD data.

    b. PEARL-HF and AMBER:

ERG considers these not relevant to the scope as participants did not have hyperkalaemia at baseline. PEAR-HF and AMBER are not used in the company's economic model.

    c. DIAMOND trial (ongoing trial): an ongoing multicentre randomised withdrawal study conducted in the US (completion date March 2022).

The study aims to assess the efficacy of patiromer in participants with heart failure with either serum potassium > 5.0 mmol/l while receiving treatment with RAASi or serum potassium 4.0 to 5.0 mmol/l with a history of hyperkalemia (not defined) in the past 12 months causing reduction or discontinuation of a RAASi. Following a 12 weeks run-in period to optimize RAASi, participants are

randomised to patiromer with possible adjustments based on serum potassium levels or placebo for at least 6 months.

Outcomes were measured at 6 months to 2.5 years follow-up. The primary outcome is time to cardiovascular death or cardiovascular hospitalization. Secondary outcomes include Proportion of participants on ≥ 50% of guideline-recommended target dose of RAASi; heart failure hospitalization and Kansas City Cardiomyopathy Questionnaire.

3. Targeted literature reviews

Targeted literature reviews were undertaken to identify evidence to support four assumptions made in the original economic model and to respond to some of the issues raised in the NICE ACD. The submission does not provide additional evidence for ACD 3.12: *The submission does not provide evidence that supports patiromer treatment extends life.* The literature covered the following:

ACD 3.15: Impact of RAASi therapy of CKD progression

The ERG has focused on the systematic reviews *(n = 7)* identified. These reviews reported CKD progression in those receiving RAASi compared with no-RAASI or conventional therapy; four reported progression to end-stage renal disease. Although RAASi provided delay in progression in most reviews, none of these provided data relating to progression from stage 3 disease to the next stage.

ACD 3.13: The model's outputs were not useful for decision-making because the results were driven by the assumed surrogate relationship between serum potassium levels and mortality and other long-term outcomes

Five systematic reviews and/or meta-analyses were included. There is some evidence that there is an association between low and high serum potassium levels and all-cause mortality based on two meta-analyses of large datasets. The evidence of an association between serum potassium and CVD mortality is less clear. Three reviews did not provide useful data.

ACD 3.14: It is not appropriate to use clinical-effectiveness data for people starting RAAS inhibitors to model people stopping treatment with RAAS inhibitors

Eight primary studies were included. There is some evidence to suggest that there may be disbenefits in terms of adverse outcomes and mortality when discontinuing RAASi treatments in CKD, however this is not unequivocal and the company has not provided an interpretation of the evidence. The question of whether the benefits of starting RAASi therapy are the same as benefits forgone if RAASi therapy is stopped has not been addressed and this remains unclear.

CS2 also included five systematic reviews / meta-analyses reporting on cardiovascular mortality in those with CKD and concludes that the evidence mostly showed a non-significant reduction or no difference in the risk of cardiovascular mortality with RAASi compared to placebo or active control but that generally the use of RAASi is associated with a numerical risk reduction in cardiovascular mortality.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

In the published survey, just 65% were doctors (37.5% consultants, 23% training grades and 4.5% GPs), with 27% nurses, 3.6% clinical pharmacists and 4.5% 'other' practitioners. The ERG clinical expert confirmed that in the UK only doctors would treat hyperkalaemia. The ERG considers this limits the generalisability of the findings of the survey despite most respondents being from the UK.

There is an unknown risk of bias in the company consensus survey, and it is unclear how representative the population is of UK clinical practice. The ERG considers that other methods may be more informative in answering the question on current practice (e.g. a large survey of cardiologists and nephrologists experienced in treating relevant populations) due to the small number of participants involved in a Delphi approach.

In terms of superiority of patiromer to current clinical practice: OPAL-HK and AMBER did not add additional evidence on whether patiromer is more clinically effective than current standard care in the NHS.

In terms of the generalisability of the placebo arm current standard care for hyperkalemia: PEARL-HF is not relevant to the scope, as participants did not have hyperkalaemia at baseline.

Limited methodological details are reported for the ongoing DIAMOND trial. The trial partly addresses the NICE scope subgroup 'adults with hyperkalaemia and with heart failure'. The population of the trial includes people with serum potassium >5.0 mmol/l or with normal serum possession levels (with a history of hyperkalaemia causing reduction or discontinuation of RAASi). The relevance of the first group to UK practice is unclear, since the company's own evidence suggested UK cardiologists would not alter treatment until a threshold of 5.5 mmol/l. The relevance of the second group, those with normal serum potassium, to the NICE scope is unclear as the purpose and outcome of the 12-week run-in is ambiguous. Participants in the trial are required to have 'kidney

function not more than mild or moderately impaired', therefore the trial does not meet the population with CKD stage 3 to 4 defined in the company's decision problem.

The submission does not provide additional evidence that supports patiromer treatment extending life (ACD 3.12).

There is some evidence that there is an association between low and high serum potassium levels and all-cause mortality based on meta-analysis of large datasets. However, the evidence of an association between serum potassium and CVD mortality is less clear.

For the clinical evidence for the transition probabilities between serum potassium categories the company uses a hazard ratio (HR) of [redacted] as a treatment effect to modify transitions modelled between different potassium levels. The HR value is different to what was presented in CS1, and may be inappropriate for UK patients. The ERG was not very clear on the derivation of the HR.

1.4 Summary of cost-effectiveness evidence submitted by the company

The company develops a de-novo economic model which is entirely different from the de-novo economic model of its first submission. It has a monthly cycle and a 35 year time horizon. It models patients starting in CKD3 or CKD4 and able to experience cardiovascular events and CKD progressions. The health states are further split into potassium categories of:

- Low K^+: $5.5 > K^+$
- Mid K^+: $6.0 > K^+ \geq 5.5$
- High K^+: $K^+ \geq 6.0$

The RAASi dosing assumed for the above three potassium categories is Fully Optimised, [redacted] of Fully Optimised and 0% respectively.

The baseline distribution is estimated from the [redacted] patients in OPAL-HK of the revised target population, possibly limited to those with both baseline and end of OPAL-HK Part-A data.

- In the comparator arm the 1st cycle transitions are estimated from a company analysis of CPRD patients, possibly largely of those initiating RAASi at baseline.
- In the patiromer arm the 1st cycle transitions are estimated from OPAL-HK Part-A.

The model structure changes between the 1st cycle and the 2nd cycle, and patients are limited to only improve by a single health state each cycle.

- In the comparator arm the CPRD cycle transitions probabilities are revised to reflect the revised model structure.
- In the patiromer arm a [redacted] hazard ratio for the probability of worsening potassium estimated from OPAL-HK Part-B data is applied to the revised CPRD cycle transitions probabilities.
- In the patiromer arm, patiromer use is assumed to be limited to 1 year from which point the same revised CPRD transition probabilities of the comparator arm are applied.

The RAASi dosing determines the risks of cardiovascular events and CKD progressions, as sourced from the meta-analysis of Xie et al for the low potassium (Full RAASi) and the high potassium (Off RAASi). The risks for the mid potassium health state are a [redacted] weighted average of these, so are little different from those of the high potassium (Off RAASi) health state.

In the model the main clinical effect of patiromer is not due to hyperkalaemia limiting RAASi use, so resulting in more cardiovascular events and CKD progressions. It is through the direct effects of hyperkalaemia upon all-cause mortality.

The company undertakes a systematic literature review of the association between potassium and all-cause mortality, the results of which are summarised in sections 6.3.4.1 and 6.3.4.2 of the company submission. The conference abstract of McEwan et al, which is outside the company systematic literature review, is referenced in the company conclusions of section 6.3.4.3. It is also the company source for its economic modelling.

The association between potassium and all-cause mortality is assumed to apply independently of cardiovascular events and CKD progressions. It is assumed to apply multiplicatively to CKD standardised mortality multipliers, resulting in combined standardised mortality multipliers for e.g. CKD4 of up to 24 being applied.

Adverse events and hyperkalaemia hospitalisations are included, but these are not model drivers.

Quality of life values for the CKD health states are sourced from Jesky et al. Quality of life values for cardio-vascular events are source from Pockett et al and are assumed to apply multiplicatively to the CKD health state quality of life values. Multiplicative age weighting of quality of life values is also applied.

Patiromer costs inclusive of the patiromer patient access scheme are applied for 1 year of treatment, with annual prescribing costs of £31 also being included.

Annual CKD3 and CKD4 costs of £2,631 and CKD5 costs of £26,738 are derived from Kerr et al. Kerr et al also supplies cost estimates of £7,734 for MI and £12,200 for stroke which when combined and uprated for inflation yield a cardiovascular event cost of £12,211. Annual concomitant medication costs of £601 are also applied.

The company base deterministic estimates are a net gain of 0.174 QALYs, net costs of £3,289 and an ICER of £18,893 per QALY. The probabilistic estimates are broadly in line with this, with a central ICER of £19,577 per QALY.

The company conducts a range of univariate sensitivity analyses, none of which result in the ICER exceeding £30k per QALY. Of the univariate sensitivity analyses that are conducted the ICER is most sensitive to:

- The cost of patiromer
- The duration of treatment, a longer duration worsening the ICER
- The serum potassium mortality risks
- The quality of life values for CKD3 and CKD4
- The relative risk for progression from CKD4 to CKD5 for RAASi versus placebo
- The probabilities of CV events
- The transition probability for CKD3 from Mid K^+/Mid RAASi to Low K^+/Full RAASi

The company also conducts a number of scenario analyses and finds that:

- Not applying the serum potassium SMRs worsened the ICER to £45,748 per QALY
- Applying the serum potassium SMRs of Kovesdy et al worsened the ICER to £33,328 per QALY.
- Restricting the patiromer treatment duration to [redacted] and 3 months improved the ICER to £12,661 per QALY, £11,386 per QALY and £7,502 per QALY, respectively.
- Applying the ID1293 sodium zirconium cyclosilicate ERG preferred quality of life estimates for CKD stages had minimal effect and resulted in an ICER of £18,876 per QALY.
- Applying the RAASi versus active comparator estimates and baseline risks of Xie et al had minimal effect and resulted in an ICER of £18,241 per QALY.
- Rather than pooling the ARB estimates and the ACI estimates of Xie et al, applying them individually resulted in ICERs of £23,049 per QALY and £17,833 per QALY, respectively.
- Baseline ages of 70, 75 and 80 years worsened the ICER to £20,966 per QALY, £20,781 per QALY and £20,311 per QALY, respectively.

1.5 Summary of the ERG's critique of the cost-effectiveness evidence submitted

The ERG thinks that the CS2 is incomplete in its presentation of the OPAL-HK data that underlies the clinical effectiveness estimates for the 1st model cycle as taken from Part-A and the clinical effectiveness estimates for all subsequent cycles as taken from Part-B. This data is not presented in the clinical effectiveness section of the CS2 and there is minimal presentation of it in the economic section. There is also no consideration of alternative analyses which could have been undertaken, and no consideration of the effects and handling of lost to follow-up and missing data. This may introduce bias to the company analyses.

The ERG thinks that the comparison of OPAL-HK patients with those of the company CPRD analysis may not be valid. The patient characteristics appear very different and many if not all of the CPRD patients may have been initiating RAASi at baseline. At a minimum, the lack of a control arm in OPAL-HK very much increases the uncertainty around the inferred net clinical effectiveness estimates with this rolling through to the uncertainty around the modelled net effects.

The company model contains three quite major errors. Correcting them improves the ICER for patiromer.

There are three main further sources of possible bias in the company submission:

- The assumption that elevated serum potassium has a direct causal effect upon mortality risks through a route other than increased risks of cardiovascular events and progression to end stage renal disease.
- The assumption that the association between elevated serum potassium and mortality risks can be multiplied with CKD standardised mortality multipliers.
- The assumption that treatment with patiromer will be limited to one year, based upon the duration of AMETHYST-DN. This is entirely at odds with the CS1 which relied upon extrapolations of the AMETHYST-DN dosing data.

Other concerns and sources of bias include:

- The company model structure not permitting the patient transitions that were observed in the CPRD data, limiting patients to at best improving to the neighbouring health state each model cycle.
- The company model assumes all patients have no history of cardiovascular events when the OPAL-HK data is that at baseline a substantial minority of patients had had an MI.

It can also be noted that the company has redefined the target population to one that is very much narrower than the "*Adults with hyperkalaemia*" of the final scope, with the OPAL-HK data within the model for the company revised target population being limited to [redacted] patients.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company has tried to address some of the concerns expressed in the previous ERG report and ACD.

1.6.2 Weaknesses and areas of uncertainty

A number of concerns raised by the NICE committee have not been sufficiently addressed. The level of potassium leading to alteration of treatment is unclear; there is no further evidence provided to support patiromer extending life; and it remains unclear what the risk of progressing to end-stage renal disease is. There is some evidence to suggest that there may be disbenefits in terms of adverse outcomes and mortality when discontinuing RAASi treatments in CKD, however this is not unequivocal. The question of whether the benefits of starting RAASi therapy are the same as benefits forgone if RAASi therapy is stopped has not been addressed and this remains unclear.

An overarching question is whether the company has presented the clinical effectiveness data for the revised target group in sufficient detail. Is there enough supporting data on the changes in potassium and the assumed changes in RAASi, and also on lost to follow up and the handling of missing data? There is no detail in the clinical effectiveness section.

The key data for the patiromer arm of the model comes from OPAL-HK Part-A, a single arm study. The key data for the comparator arm comes from a company analysis of CPRD data.

- There might be placebo and other trial effects in OPAL-HK Part-A which would not be present in the CPRD data. Does this invalidate the comparison?
- The baseline patient characteristics of patients in OPAL-HK Part-A are hugely different from those of CPRD patients. Does this invalidate the comparison?
- Patients recruited to OPAL-HK Part-A were on RAASi at baseline. It appears that the patients of the CPRD data might have been initiating RAASi at baseline so might have rather different probabilities of hyperkalaemia and worsening of hyperkalaemia. Does this invalidate the comparison?

The ERG thinks that the other key economic issues are:

- Is there a distinction between transient hyperkalaemia and chronic hyperkalaemia, and if so how might this affect any direct mortality multipliers for hyperkalaemia in the current setting?

- Is it reasonable to apply direct mortality multipliers for hyperkalaemia within a model which separately models its effects upon RAASi use, CV events and CKD progressions? If so, what is the most reasonable source for these estimates?

- Is it reasonable to combine direct hyperkalemia mortality multipliers of up to 2.95 with CKD mortality multipliers of up to 7.94 to arrive at combined mortality multipliers of up to 23.41, or does this double count the effects of the CKD mortality multipliers?

- Is an assumption of a maximum of 1 year of patiromer treatment based upon the duration of the AMETHYST-DN trial more reasonable than the previous company analysis and extrapolation of AMETHYST-DN data? If the previous company analysis and extrapolation of AMETHYST-DN data is more reasonable should a maximum treatment duration still be applied, and if so how long should it be and why?

Other issues which could be described as secondary are:

- What RAASi does reduction is appropriate for the Mid K^+ / Mid RAASi health state and what effect will this dose reduction have upon the probabilities of events? The ERG thinks that the company assumed reduction of [redacted] is excessive, not supported by ESC guidelines and prefers a simple 50% reduction as a half-way house.

- Would those coming off RAASi have another active treatment initiated for their heart condition?

- Should the number needed to treat to get to OPAL-HK Part-B condition the first cycle patiromer drug cost?

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG revised analyses are tabulated in section 5.4. In brief the ERG presents two sets of analyses.

- The first assumes that there are no direct causal effects from potassium upon all-cause mortality. To the degree that any such effects apply these work through the effect of potassium on RAASi use, and thereby upon the probabilities of CV events and CKD progression.

- The second assumes that there are direct causal effects from potassium upon all-cause mortality, based upon the estimates of Kovesdy et al. The base case of this modelling also includes the effect of potassium on RAASi use, and thereby upon the probabilities of CV events and CKD progression, so there will be some degree of double counting.

Within these analyses the ERG has made three reasonably major corrections to the company model, the combined effect of which is to improve the company base case ICER.

The other main change made by the ERG is to apply the company AMETHYST-DN treatment discontinuation curve for patiromer, but with a maximum treatment duration of 5 years due to the potassium distributions converging between the arms from this point.

The modelling that does not apply direct potassium mortality multipliers results in an ICER of £681k per QALY. This worsens somewhat to £2.1mn if those discontinuing RAASi receive another active treatment for their heart condition. Shorter patiromer treatment duration improves the ICER, but even the company's most optimistic estimate of [redacted] taken from US claims data results in an ICER well above conventional willingness to pay thresholds.

The modelling that applies the direct potassium mortality multipliers source from Kovesdy et al results in an ICER of £232k per QALY. If these mortality multipliers are sourced from McEwan et al the ICER improves to £47,480 per QALY, while applying the company values of Kovesdy et al improves the ICER to £166k. The ICER worsens somewhat to £303k per QALY if those discontinuing RAASi receive another active treatment for their heart condition. Removing the double counting of effects in a scenario analysis which does not apply the RAASi relative risks of events worsens the ICER to £970k. Shorter patiromer treatment duration improves the ICER, but even the company's most optimistic estimate of [redacted] taken from US claims data results in an ICER that is notably above conventional willingness to pay thresholds.

All results show very little sensitivity to the hazard ratio of worsening potassium that the company estimates from OPAL-HK Part-B. This underlines that the main treatment effect occurs in the 1st model cycle, when the OPAL-HK Part-A data in the patiromer arm is set against the company CPRD analysis which is assumed to apply in the comparator arm.

Results are also insensitive to the ERG scenarios around CKD3 and CKD4 annual costs and adverse event costs. It is likely that the CKD3 and CKD4 annual costs would come more to the fore if the modelling were more aligned with the company base case assumptions.

Shorter time horizons of 5 years and 10 years significantly worsen the ICERs.

A possible source of bias may be the handling of patients who are lost to follow-up and of OPAL-HK Part-A missing data. It is possible that the company analysis only considers patients with both baseline and week 4 data. These patients may tend to have done better than those without week 4 data. Further information and scenario analyses on this may be warranted.

An unquantifiable bias in the modelling arises from the company assumption that after the 1st model cycle patients can only improve by a single health state. This is the intended company model structure, as shown in Figure 11 of its submission. It requires revision of transition probabilities that the company derives from the CPRD, with some being set to zero and others the summation of two transition probabilities. Within the ERG cross check rebuild of the company model applying the same CPRD probabilities in the 2nd and subsequent cycles as in the 1st cycle worsens the ICER by around 20%.

The company model assumes that in the revised target group no patients have had a prior CV event. In OPAL-HK around [redacted] of patients had had a previous MI. Not taking this into account biases the ICER in favour of patiromer.

2 Decision problem

The decision problem presented in the company's revised submission (CS2, appendix 10.1, page 113) is stated by the company to be similar to the previous submission. Table 1 describes the decision problem along the ERG comments.

Table 1. Decision problem

	NICE Scope	Previous CS	Current CS	ERG comments
Population (s)	Adults with hyperkalaemia	Adult patients with stage 3-4 chronic kidney disease (and other co-morbidities such as heart failure and diabetes) and hyperkalaemia treated with RAASi therapy	As previous	In its first submission the company target population restricted the NICE scope to patients with CKD stage 3 or 4 with hyperkalemia (K+> 5.0 mmol/L). In the second submission the company further narrows the target population to CKD stage 3 or 4 patients with (1) K+ >5.5 mmol/L and heart failure and (2) K+ >6.0 mmol/L without heart failure.
Intervention	Patiromer	Patiromer (Veltassa)	As previous	In line with the scope.
Comparators	Standard care. This includes a low-potassium diet with or without agents that reduce levels of potassium in the body	The main comparator in the submission is discontinuation or dose modification of RAAS inhibitor therapy. The final matrix lists no other companies with relevant comparators. The 'response to consultee and commentator comments on the draft remit and draft scope (pre-referral)' document also confirms that NICE have amended the comparators to "take out reference to pharmacological treatments" in defining comparators to Veltassa®	As previous	In accordance with guidelines, standard care preceding use of patiromer might include introducing support for a low-potassium diet and optimised hypertension management (as various drugs are potassium sparing or depleting). Recent evidence highlights the benefits of dietary modification on renal parameters in patients with CKD.[1, 2] The modelling does not appear to have an explicit comparator. Instead the company appears to analyse retrospective CPRD data of patients possibly initiating RAASi to provide the alternative.
Outcomes	• serum potassium level • use of renin–angiotensin–aldosterone system inhibitor therapy • mortality	Serum potassium levels: • Mean change in serum potassium levels from baseline to week 4. • Proportion of patients who achieved target potassium levels (3.8–<5.1 mmol/L)	As previous	In line with the scope. However, trial-based evidence is currently lacking for the longer-term consequences of hyperkalaemia and RAASi discontinuation, lifetime cardiovascular and stroke events, survival and health related quality of life, direct mortality of

	• time to normalisation • adverse effects of treatment • health-related quality of life.	• Difference between patiromer and placebo in the median change in serum K+ level at the start of the phase to week 4 or the earliest visit at which the K+ level was <3.8 mmol/L or ≥5.5 mmol/L • Proportion of patients with a recurrence of hyperkalaemia (≥5.1 or ≥5.5 mmol/L) • Following exploratory endpoints are reported: 1) time to 1st recurrent hyperkalaemia; 2) proportion of patients requiring an intervention due to recurrent hyperkalaemia at any time; 3) time to RAAS inhibitor dose discontinuation Use of renin-angiotensin-aldosterone system inhibitor therapy: • Proportion of patients who required RAAS inhibitor dose reduction or discontinuation due to recurrent hyperkalaemia. • Exploratory endpoints included: time to RAASi dose discontinuation; and proportion of patients receiving any dose of RAASi at the end of this phase. Mortality is reported as a safety endpoint Adverse effects are also reported. Events of interest were: • Hypokalaemia (serum K+ < 3.5 mmol/L) • Serum K+ ≥ 5.5 mmol/L • Hyperkalaemia-associated ECG changes • Hypokalaemia-associated ECG changes • Gastrointestinal AEs • Potential allergic reactions • Changes in serum calcium, magnesium, phosphorous and fluoride • AEs resulting in change of dose • AEs resulting in addition of concomitant therapy (e.g., magnesium supplement for hypomagnesemia) • Worsening renal function: o ≥ 100% increase in serum creatinine from		hyperkalaemia and CKD progression.

		baseline; or o >50% decrease in eGFR from baseline • AE profile in subjects maintained on RAASi therapy versus those who have stopped RAASi therapy		

3 Clinical effectiveness

3.1 Previous submission (CS1)

The ERG has summarised the previous submission of clinical effectiveness for context.

The clinical effectiveness evidence in the CS comes from a single randomized controlled trial (RCT), the OPAL-HK trial of Patiromer in people with hyperkalaemia, stage 3-4 CKD and receiving a RAAS inhibitor therapy (NCT01810939). The trial was a phase III, two-phase, single-blind, multi-national study sponsored by Relypsa (a Vifor Pharma Group Company) that included 10 countries from Europe, Eastern Europe and the US. The OPAL-HK trial provides evidence that Patiromer reduces serum potassium (K) and RAASi discontinuation in patients with CKD.[3] A total of 243 patients entered the two phase trial:

- A single arm treatment phase (A) for 4 weeks: initial oral intake of 4.2g of Patiromer (twice daily) for 92 patients with mild hyperkalemia (serum K^+ 5.1-<5.5 mmol/l) or 8.4g initially of Patiromer (twice daily) for 151 patients with moderate to severe hyperkalemia (K^+ 5.5-<6.5 mmol/l). In the CS2, phase A was mainly used in the economic model and CPRD data (patient's characteristics) was used as a comparator.

- A randomized 8-week placebo controlled withdrawal phase (B): patients who completed phase A remaining on RAAS inhibition, with a baseline serum $K^+ \geq 5.5$ mmol/l in phase A, and responding to Patiromer (K^+ 3.8 to <5.1 mmol per liter)) were randomly assigned either to intervention (same dose they were receiving at the end of phase A) or to placebo. In the CS2, the worsening from phase B was used in the economics model after comparing phase A to CPRD data.

Pre-specified primary outcome (ITT population):

- Phase A: serum potassium levels (mean± SE) from baseline to week 4 was −1.01 ± 0.03 mmol/l (95% confidence interval [CI]: −1.07 to −0.95; p<0.001).

- Phase B: serum potassium levels (median change) from the start of phase B to week 8 was 0.00 mmol/l (95% CI: −0.30 to 0.30) in the Patiromer group and 0.72 mmol/l (95% CI: 0.22 to 1.22) in the placbo group. The between-group difference of 0.72 mmol/l was statistically significant ($p < 0.001$).

Secondary outcomes (ITT population), Phase B:

- The proportion of patients at 8 weeks having serum K^+ ≥5.5 mmol/l was 60% (95% CI: 47% to 74%) in the placebo group and 15% (95% CI: 6% to 24% in the Patiromer group ($p < 0.001$ for the between group difference). The proportion of patients with serum K^+ ≥5.1 mmol/l was 91% (95% CI: 83% to 99%) in the placebo group and 43% (95% CI: 30% to 56%) in the Patiromer group ($p < 0.001$ for the between group difference).

- Time to first occurrence of hyperkalaemia for serum K^+ ≥ 5.5 mmol/l and ≥ 5.1 mmol/l over the eight weeks. At 8 weeks, HK recurrence (≥5.5 mmol/l) occurred in 60% of the placebo patients and 15% of Patiromer patients. .

- Continuation of RAAS inhibitor therapy was higher in the Patiromer group (94%) compared to the placebo group (44%) at the end of phase B ($p < 0.001$).

- RAASi discontinuation occurred in 56% of placebo and 6% of Patiromer patients.

Some of the ERGs concerns included:

- There was no formal test of a potassium reducing diet before recruitment, as recommended in guidelines and the ERG's clinical experts.
- The specified OPAL-HK population was limited to patients with stage 3-4 CKD (and other co-morbidities) on RAASi therapy with hyperkalaemia: the benefit in the broader hyperkalaemia population is not addressed.
- OPAL-HK was conducted in the US, EU and Eastern Europe (not the UK) with the majority of patients from Eastern Europe (65%). It is unclear if these populations, or the care they receive, are representative of the UK. The withdrawal phase included 100% white patients.
- During the withdrawal phase the titration algorithm for RAAS inhibitor therapy was more aggressive in the placebo than the Patiromer arm and was different in the first 4 weeks in comparison to the second 4 weeks (CS2, page 122-123). The difference in the management protocol may contributed to the difference in RAASi discontinuation rates.
- Patients responding in the treatment phase and included in the withdrawal phase had initial serum K^+ 5.5 to <6.5 mmol/l and achieved the target range 3.8 to <5.1 mmol/l while receiving Patiromer and RAASi over 4 weeks. Thus no randomised evidence is offered for the patients included in the treatment phase with mild hyperkalaemia at baseline (5.1 to <5.5 mmol/l) or non-responders. These two groups constitute 56% of recruitment.

The CS1 also draws upon the AMETHYST-DN trial.[4] This was a one-year uncontrolled, dose-ranging study of patiromer including 306 patients with diabetic kidney disease and hyperkalaemia who were receiving RAAS inhibitors. AMETHYST-DN was not judged by the company relevant to inform

effectiveness, but is used to provide longer-term safety data and model Patiromer discontinuation in the company model.

The company provided CPRD (English GP database) analysis of CKD patients to provide their model with representative estimates of RAASi discontinuation. This analysis shows that CKD patients in primary care are different to the OPAL-HK trial population. CPRD patients were more likely to be female ([redacted] vs 42%), on average [redacted] younger ([redacted] vs 65.0), less severe CKD (eGFR [redacted] vs 39.0), considerably less likely to have diabetes ([redacted] vs 63%), hypertension ([redacted] vs 96%), heart failure ([redacted] vs 42%) or previous myocardial infarction ([redacted] vs 27%). Thus, the trial population are not representative of the UK population.

3.2 Current submission

The current submission (CS2) aimed to address the committee's concerns around the clinical effectiveness of patiromer, ACD 3.1. *do not usually treat serum potassium levels <6.0 mmol/l and the generalisability of patiromer clinical trials to UK practice*. The submission also aimed to address concerns on the impact of RAASi on long-term outcomes, progression to end-stage renal disease and the effects of stopping RAASi used in the economic model. The submission also included evidence that was not related to the NICE committee's concerns which the ERG has not critiqued.

The clinical effectiveness evidence in the revised submission of relevance to the NICE committee concerns included:

1. Two surveys: a) published survey b) a physician opinion and consensus survey
2. OPAL-HK trial (previous submission, summarised in 3.1 above)
3. PEARL-HF trial
4. AMBER trial
5. DIMAOND trial (ongoing trial)
6. Targeted literature reviews

3.2.1 The surveys

i) The company aimed to reveal the variation in serum potassium levels that triggers hyperkalaemia treatment initiation in clinical practice in the UK. They cite a survey by Kalsi 2018,[5] which found that the serum potassium level reported as requiring treatment ranged from 4.8 to 6.6 mmol/l [mean 5.7 mmol/L] across all respondents. The company noted that higher values of hyperkalaemia prompting treatment were more likely to be given by nephrologists, and that the reasons given for consideration of intervention at a lower level included concerns regarding cardiac stability (31.5%) and deterioration in renal function (15.7%). Limited details of the survey are provided by the company.

The survey included 112 healthcare practitioners from The British Journal of Cardiology and the Cardiorenal Forum databases who were involved in the care of patients with cardiorenal conditions. Participants were from the UK (81%) and Europe and other countries not stated (19%). The ERG notes that just 65% were doctors (37.5% consultants, 23% training grades and 4.5% GPs), with 27% nurses, 3.6% clinical pharmacists and 4.5% 'other' practitioners. However, the ERG clinical expert confirmed that in the UK only doctors would treat hyperkalemia. The ERG considers this limits the generalisability of the findings of the survey despite most respondents being from the UK.

The ERG notes that the reported range of values at which treatment is considered to be required (4.8 to 6.6 mmol/L) includes normal values, and there is no indication of the number of responses at each value so it is unclear where the majority of responses lay.

The publication also reported the average potassium level necessitating action separately for cardiologists and nephrologists. For cardiology, among all grades (n=62) and consultants only (n=18), this was 5.7 mmol/L with a mode of response range of 5.5 (SD 0.4) and 6.0 (SD 0.3), respectively. For nephrology, the average potassium level necessitating action was 5.8 mmol/L among all grades (n=27) and 5.7 mmol/L among consultants only (n=15), with a mode of response range of 6.0 (SD 0.4) and 6.0 (SD 0.3), respectively. It is unclear how questions were posed to the respondents or how the averages were derived.

The numbers of consultant nephrologists and cardiologists included in the survey was relatively small, and it is unclear how representative the population is of UK clinical practice. The survey was funded by Vifor Pharma UK and two of the four authors reported conflicts of interest related to Vifor.

ii) The company undertook a modified Delphi exercise to address five questions:

- At what point would a patient be considered hyperkalaemic?
- When would they start to actively manage serum potassium?
- How do they currently manage hyperkalaemia?
- Does patiromer address an unmet need?
- What patient cohorts are most suitable for patiromer?

The ERG has focused on the aspects of the Delphi aimed to understand the maximal tolerable threshold of hyperkalaemia and the management approach used once this threshold of hyperkalaemia is reached (questions 1-3), which the company used to respond to the point made in the ACD 3.1 (*Do*

not usually treat serum potassium levels <6.0 mmol/l). The ERG notes that whilst a Delphi exercise may be helpful in answering the some of the other questions, the aim of a Delphi exercise is to reach a consensus, for example for guiding future practice. The ERG considers that other methods may be more informative in answering the question on current practice (e.g. a large survey of cardiologists and nephrologists experienced in treating relevant populations) due to the small number of participants involved in a Delphi.

The company stated that the modification of the Delphi was through the reduction of interview rounds and a face-to-face meeting. The main body of the CS2 reports that three rounds were used, two telephone rounds and one web based or face to face round. The appendix to the submission states there were two telephone interview rounds which focused on the clinical determination of hyperkalaemia, two rounds of web based discussion which focused on the clinical management of hyperkalaemia and a final round via face to face discussion focused on both clinical determination and management of hyperkalaemia. The appendix does not report any further details of these additional rounds and it is not clear which description is correct.

In the first set of telephone interviews 10 physicians (6 nephrologists and 4 cardiologists) were interviewed; in the second round of telephone interviews there were 21 physicians (11 nephrologists and 10 cardiologists) and in the final round there were nine physicians (the numbers of nephrologists and cardiologists varied). Questions were similar but tailored to the different consultant specialisms. The questions used by the interviewer to the nephrologists were presented in Appendix 10.2.1.1. The ERG notes that the questions were open ended which is appropriate for a Delphi exercise. The company also states that bias was managed through anonymisation and blinding of responses at the telephone stage.

Limited details of the methods of the modified Delphi technique were reported. The rationale for the modification was based on the timeframe required for the survey to be completed. The results presented report the current approach to practice for these individual clinicians and as noted by the company there are some differences between nephrologists and cardiologists over the threshold to define hyperkalaemia requiring treatment and the nature of treatment changes. In addition, there was not 100% consensus within the two clinical specialisms (see below).

There may be risk of bias in the methods undertaken. The experience and independence of the interviewer / facilitator was not reported in the CS but was provided in response to clarification Q3 where the company confirmed that the interviewers all had between 7-10 years' experience in 'such market research' and that they were from an independent agency. In response to clarification Q2 the

company confirmed that physicians were recruited via email or web searching and were selected if they had availability for involvement. Those with conflicts of interest, such as NICE advisor, were excluded ('conflicts of interest' was not defined further). The number of nephrologists and cardiologists involved was reasonable for a Delphi but small for an understanding of UK practice (acknowledged as a limitation in clarification response Q4). All physicians were consultant grade (clarification response Q2) but overall it is unclear how many patients they saw regularly with hyperkalaemia as this was generally not explored. The clinician's experience of using patiromer was also not explored. Although all clinicians were NHS practitioners and came from a broad spectrum of district general and teaching hospitals across regions of England and Scotland (clarification response Q2), it is unclear whether the patients the cardiologists see are similar to those covered in the company decision problem (hyperkalaemia and stage 3 or 4 chronic kidney disease and receiving RAASi). Finally, there was no discussion of any piloting or external validation, although limitations of the Delphi approach were acknowledged (clarification response Q2). Limited details of the results were reported and the ERG are unable to verify statements made from the first and third stages.

The ERG considers there to be an unknown risk of bias and could not be certain of the representativeness of the findings. The company's key conclusions were:

- A maximum tolerable serum potassium threshold in clinical practice is between 5.5-5.9 mmol/l. All cardiologists and most nephrologists will alter treatment when serum potassium reaches this threshold (the ERG note that for the nephrologists this would be to not up-titrate RAASi therapies; consensus to down-titrate or stop RAASi therapy was only at >6.0 mmol/L).
- Based on the second round of extended telephone interviews with 21 physicians:
    - 70% (7 of 10) of cardiologists would stop (1) or reduce (6) RAASi if serum potassium is between 5.1-5.4 mmol/L
    - 9% (1 of 11) of nephrologists would reduce RAASi dosing if serum potassium is between 5.1-5.4 mmol/L and none would stop RAASi
    - 50% (5 of 10) of cardiologists would stop RAASi and 50% would reduce RAASi at serum potassium between 5.5-5.9 mmol/L.
    - 18%-27% (2-3 of 11, depending on CKD stage) of nephrologists would stop RAASi and 50% (6 of 11) would reduce RAASi at serum potassium between 5.5-5.9 mmol/L. 18-27% wouldn't stop or reduce RAASi at serum potassium between 5.5-5.9 mmol/L.

ERG summary

Two pieces of survey evidence were presented in the submission to respond to NICE ACD statement 3.1 that in clinical practice serum potassium levels <6.0 mmol/l would not normally be treated. In a 2018 published survey the average potassium level necessitating action was 5.7 mmol/L for cardiologists and 5.8 mmol/L for nephrologists. In a Delphi survey undertaken by the company, the acceptable serum potassium level that nephrologists and cardiologists reported was between 5.5 – 5.9 mmol/L. At this level, cardiologists would adjust treatment through down-titrating or stopping RAASi therapy, while nephrologists would not take this action but would not increase existing RAASi or initiate RAASi. Nephrologists would down-titrate or stop RAASi therapy at >6.0 mmol/L.
Both surveys have methodological concerns and it is unclear how representative the results are to UK NHS clinical practice.

The ERG clinical experts were asked if they would usually treat serum potassium levels below 6 mmol/l and for their view on treatment options to aid interpretation of the economic model (4.1.2). Treatments would only usually be given when serum potassium is below 6 mmol/L in an acute event or when the patient is on digoxin or has a history of ischaemic heart disease. Treatment with RAASi would rarely be commenced with a serum potassium of 6 mmol/l. In people with CKD stage 3 /4 with heart failure and without hyperkalaemia typical RAASi doses were 10 mg ramipril, 100 mg losartan or 150 -300 mg aliskiren. If serum potassium rose to >6.0 mmol/l treatment would usually be halved if on maximum dose or would be stopped in currently on a lower dose. If serum potassium rose to between 5.5 and 6.0 mmol/l treatment would usually continue if on half the maximum dose with instigation of dietary advice. In people with CKD stage 3 /4 without heart failure and without hyperkalaemia typical RAASi doses were usually 5 mg Ramipril, 50 mg losartan and 150 mg aliskiren. Treatment alterations if serum potassium rose to >6.0 mmol/l and if serum potassium rose to between 5.5 and 6.0 mmol/l mimicked those for people with heart failure.

3.2.2 Patiromer clinical trial programme

The company states that they believe the trial protocol does allow generalisability to UK clinical practice and describes four trials in their patiromer trial programme.

OPAL-HK[3] (original submission, see section 3.1 above): the company states that the placebo group in Part B (randomized withdrawal phase) of OPAL-HK is generalisable to the current UK standard of care in people with CKD treated with RAASi after the initial correction of hyperkalaemia in Part A. No new evidence is provided. The ERG notes that this does not address the committee's concerns in ACD 3.7 (*the key trial does not show whether patiromer is more clinically effective than current standard care in the NHS*). In comparison to the previous submission, the company provides further

details on the titration algorithm (at first 4 weeks and at second 4 weeks) in tables 39 and 40 on page 122 but did not provide any additional evidence for the trial.

PEARL-HF[6] (NCT00868439): the company states the placebo arm is generalisable to the current standard of care for hyperkalaemia in patients with heart failure treated with RAASi. PEARL-HF was a 4-week RCT published in 2011 that evaluated the effects of patiromer on potassium levels in people with chronic heart failure and either CKD or a history of hyperkalaemia or both. Eligibility criteria required serum potassium to be between 4.3 to 5.1 mmol/L, which is mostly within the normal range (3.5 to 5.0 mmol/L), and the mean baseline level was 4.7 mmol/L. The study was not included in the original CS. The ERG considers it is not relevant to the scope as participants did not have hyperkalaemia at baseline. PEAR-HF is not used in the company's economic model.

AMBER[7] (NCT03071263): was a 4-week RCT that aimed to evaluate patiromer for prevention of hyperkalemia and enablement of spironolactone use for hypertension management in people with uncontrolled resistant hypertension and CKD (eGFR 25 to ≤ 45 mL/min/1.73m^2). Screening serum potassium levels were required to be 4.3 to 5.1 mmol/L and the mean baseline level was 4.7 mmol/L. The study completed in November 2018 but has not yet been published (key findings presented in CS2 page 126). The ERG considers the trial is not relevant to the scope as participants did not have hyperkalaemia at baseline; the trial examines the effectiveness of patiromer in enabling persistent spironolactone use by maintaining normal potassium levels and minimising the risk of hyperkalaemia (therefore prevention of hyperkalaemia). This evidence does not address the committee's concern that the key trial does not show whether patiromer is more clinically effective than current standard care in the NHS (ACD 3.7). The company does not use AMBER in their economic model.

DIAMOND[8] (NCT03888066): is an ongoing multicentre randomised withdrawal study conducted in the US (status: recruiting, estimated completion date March 2022). It is not discussed in CS2 within the clinical trials programme section, but is described in CS Appendix 10.1.6. The study aims to assess the efficacy of patiromer in participants with heart failure with either serum potassium > 5.0 mmol/l while receiving treatment with RAASi or serum potassium 4.0 to 5.0 mmol/l with a history of hyperkalemia (not defined) in the past 12 months causing reduction or discontinuation of a RAASi. Following a 12 weeks run-in period to optimize RAASi, participants are randomised to:

1) Patiromer with possible adjustments based on serum potassium levels for at least 6 months
2) Placebo for at least 6 months

The primary outcome (6 months to 2.5 years follow-up) is time to cardiovascular death or cardiovascular hospitalization.

Secondary outcomes (6 months to 2.5 years follow-up) include:

a) Proportion of participants on ≥ 50% of guideline-recommended target dose of RAASi
b) Heart failure hospitalization
c) Kansas City Cardiomyopathy Questionnaire (end of study)

Limited methodological details are provided by the company or the clinical trial record, and the withdrawal study design is not described. The trial partly addresses the NICE scoped subgroup 'adults with hyperkalaemia and with heart failure'. The population of the trial includes people with serum potassium >5.0 mmol/l or with normal serum possession levels (with a history of hyperkalaemia causing reduction or discontinuation of RAASi). The relevance of the first group to UK practice is unclear, since the company's own evidence suggested UK cardiologists would not alter treatment until a threshold of 5.5 mmol/l. The relevance of the second group, those with normal serum potassium, to the NICE scope is unclear as the purpose and outcome of the 12-week run-in is ambiguous. Participants in the trial are required to have 'kidney function not more than mild or moderately impaired', therefore the trial does not meet the population with CKD stage 3 to 4 defined in the company's decision problem.

A summary of the clinical trials is presented in Table 2 (appendix 1)

3.2.3 Targeted literature review

Targeted literature reviews were undertaken to identify evidence to support four assumptions made in the original economic model and to respond to some of the issues raised in the NICE ACD. The submission does not provide additional evidence for ACD 3.12: *The submission does not provide evidence that supports patiromer treatment extends life.* Literature relating to the following issues was presented:

1. ACD 3.15: *The company overestimated the risk of progressing to end-stage renal disease*, see ERG Critique of CS 6.3.3

2. ACD 3.13: *The model's outputs were not useful for decision-making because the results were driven by the assumed surrogate relationship between serum potassium levels and mortality and other long-term outcome*s, see ERG Critique of CS 6.3.4

3. ACD 3.14: *It is not appropriate to use clinical-effectiveness data for people starting RAAS inhibitors to model people stopping treatment with RAAS inhibitors* , see ERG Critique of CS 6.3.5. In addition, the company presented literature assessing the impact of RAASi therapy on cardiovascular events and mortality, see ERG Critique of CS 6.3.2.

Broad searches of MEDLINE (including MEDLINE® In-process) and EMBASE were undertaken on 21st January 2019. Searches combined a variety of terms for CKD, RAASi and study design (systematic reviews, RCTs and observational studies) using appropriate syntax. Eligibility criteria were pre-defined (reported in submission appendix 10.4.1 Table 42) and were applied to searches via a two-stage approach. Although no date limit was applied to the searches, only records published in or after 2008 were assessed. One reviewer assessed studies at both stages. At the title and abstract stage a second reviewer discussed any uncertain records; at the full text stage a second reviewer screened a randomly selected 15% of studies. One reviewer undertook data extraction and this was checked by a second reviewer. There was no risk of bias assessment of the studies. A PRISMA diagram was provided and summary tables of included primary studies (but not of all included reviews) were presented along with narrative summaries. A list of excluded studies was not provided.

Overall the approach to the systematic review was reasonable, however the company did not discuss the quality of the evidence or provide an interpretation of the results in light of this.

Critique of CS 6.3.3: impact of RAASi therapy of CKD progression

The NICE ACD stated that the *company overestimated the risk of progressing to end-stage renal disease for people with stage 3 and 4 CKD from data that included people with end-stage renal disease (ACD 3.15)***.** In the targeted literature review seven systematic reviews and 30 primary studies were identified and the ERG has focused on the systematic reviews only. These reviews reported CKD progression in those receiving RAASi compared with no-RAASI or conventional therapy; four reported progression to end-stage renal disease and three reported progression in terms of changes in glomerular filtration rate and therefore do not address the question. Although RAASi provided delay in progression in most reviews, none of these provided data relating to progression from stage 3 disease to the next stage. Similarly, the primary studies identified did not provide this information. The submission does not provide further discussion of how these reviews and studies support the estimations of the risk of progression to end-stage renal disease used in the model.

ERG summary

The literature search has not addressed the concern raised in ACD 3.15 that the company overestimated the risk of progressing to end-stage renal disease.

Critique of CS 6.3.4 - Association between serum potassium levels and long-term mortality risk

The targeted literature review was used to identify studies of relevance to the updated model assumption (also critiqued in 4.2.2.1) that controlling serum potassium has a mortality benefit (*NICE ACD 3.13 The model's outputs were not useful for decision-making because the results were driven by the assumed surrogate relationship between serum potassium levels and mortality and other long-term outcomes*). Five systematic reviews and 20 studies were identified, but not all were relevant to the question. The ERG has concentrated on the systematic reviews, but has also cross-checked that data presented in the company Appendix summary tables (Tables 48-52) from the primary studies reflect what is reported in the submission.

The submission states that only two of the five systematic reviews provided enough information to establish the association between serum potassium levels and mortality risk. The first of these (Kovesdy 2018 [9]) was a meta-analysis of individual patient data from the CKD Prognosis Consortium (an international cohort study), the other was a systematic review and meta-analysis of published observational study data (Hoppe 2018 [10]).

Kovesdy 2018 assessed all-cause mortality[9] in 42,170 patients with CKD. The study found a U-shaped association between serum potassium levels and the risk of all-cause mortality (i.e both hypokalaemia and hyperkalaemia were associated with increased risk of mortality). The lowest risk of all-cause mortality was for potassium around 4.2-4.9 mmol/L.

In the second review, cardiovascular mortality was assessed (Hoppe 2018 [10]). The study found in the 2,898 people with CKD that cardiovascular mortality was only increased in those with high serum potassium levels (although not statistically significant). The submission notes that a U-shaped relationship was found for a composite CV outcome in a bigger sample but the ERG notes this outcome was defined differently across the included studies and in one of the two included studies did not include mortality.

The three other systematic reviews were stated in the submission to report serum potassium levels and mortality but not the association between them (Ng 2015[11] Lu 2016[12]; Vukadinovic 2017[13]). We agree there are no useful data for this particular question in these systematic reviews of all which are treatment reviews.

The CS does not discuss the methodological attributes of these SRs or tabulate the key details. Although not formally assessed, the ERG has considered the quality of the two meta-analyses with relevant data. Both of these appear to be of good quality.

The submission also states that of 20 primary studies only 10 discussed the association between serum potassium and mortality. All 20 studies are summarised in CS2 Appendix Table 52. The CS2 states that of the 10 studies, eight found higher rates with hyperkalaemia. These have been checked in the

CS Appendix Table 52 and the ERG concurs. Two of these are reported in detail in the main body of the submission (Furuland 2018[14]; Luo 2016[15]) as these found U-shaped relationships between potassium levels and mortality. One of these studies (Luo 2016[15]) was included in the Hoppe 2018 meta-analysis of two studies, therefore there is double-reporting of results in the CS.

The two other studies that reported no association between serum potassium mortality were also reported in the main body of the submission.

The submission also reports that compared with no-RAASi use, using RAASi is associated with a lower risk of mortality across low to high serum potassium levels (Kovesdy 2018[9]; Furuland 2018[14]).

In the conclusions of CS2 Section 6.3.4.3 data from McEwan et al 2017[16] are presented. The company states this publication was not picked up as part of the targeted literature review as it was a conference abstract. These data are used in CS2 economic model (see Section 4.2.2 for ERG discussion). It is unclear whether this abstract is linked to the Furuland 2018 (#257} publication discussed above. Although the numbers are different (Furuland 191,964; McEwen 144,388) the inclusion criteria, including the years sampled from the CPRD, are the same.

The CS does not compare methodological aspects or risk of bias of the primary studies.

ERG summary

There is some evidence that there is an association between low and high serum potassium levels and all-cause mortality based on meta-analysis of large datasets. The evidence of an association between serum potassium and CVD mortality is less clear. The ERG notes that in TA599,[17] the committee concluded that observational data did not guarantee an independent association between high serum potassium levels and death and there was insufficient evidence to prove definitively that lowering serum potassium levels in the outpatient setting leads to improved outcomes. The Kovesdy 2018 meta-analysis was discussed in the CS for TA599.

Critique of CS 6.3.5: are the benefits of starting RAASi therapy the same as benefits forgone if RAASi therapy is stopped?

The company's economic model applies relative risks from the Xie NMA,[18] which evaluates the CV and mortality benefits associated with starting RAASi treatment. In response to NICE ACD 3.14 (*It is not appropriate to use clinical-effectiveness data for people starting RAAS inhibitors to model people stopping treatment with RAAS inhibitors*), the company conducted a targeted literature review to evaluate the appropriateness of applying outputs from the Xie NMA to model the benefits forgone

upon discontinuation of RAASi on Major Adverse Cardiovascular Events (MACE), mortality and CKD progression.

The company identified eight studies they considered relevant,[19-26] two of which are not discussed in the text (CS refs 158 and 160).[23, 26] They also reported an additional study in a different population (heart failure)[27] that was not tabulated in CS Appendix 10.4.6.

The company states two large observational studies found that discontinuing RAASi treatment negatively influenced morbidity and mortality outcomes in patients with CKD. The first study[19] (Bennett 2017 CS ref 98) observed that in both CKD and heart failure, mortality rates were higher in those who discontinued RAASi than in those who were prescribed RAASI. The study was published as an abstract only with limited details and no statistical analysis, and three of the authors were from AstraZeneca Pharmaceuticals (manufacturers of sodium zirconium cyclosilicate for hyperkalaemia, NICE TA599). The second study[25] (Epstein 2015 CS ref 17), funded by Relypsa (a Vifor company), found that more CKD stage 3-4 patients who discontinued RAASi died or had an adverse outcome (CKD progression, progression to ESRD, stroke, acute myocardial infarction, coronary artery bypass, percutaneous coronary intervention) than those on maximal or submaximal RAASi doses ($P<0.05$); and all-cause mortality only was also higher in this group (p value not reported).

However, a third large observational study[22] (non-commercial funding, CS ref 106) found no association with mortality within one year of a new RAASi prescription and discontinuation. In addition, four small observational studies[20, 21, 24, 26] (CS refs 109-111, 160-not cited in CS text) found improvement in kidney function or kidney stage after stopping RASSi. The final study[23] (CS ref 158, not cited in CS text) assessed the effect of holding ACEI/ARB therapy prior to coronary angiography on the incidence of acute kidney injury at 72 hrs in moderate renal insufficiency (CKD stage ≥4 excluded), therefore is of limited relevance.

The CS does not compare methodological aspects or risk of bias of the studies.

ERG summary

There is some evidence to suggest that there may be disbenefits in terms of adverse outcomes and mortality when discontinuing RAASi treatments in CKD, however this is not unequivocal and the company has not provided an interpretation of the evidence. The question of whether the benefits of starting RAASi therapy are the same as benefits forgone if RAASi therapy is stopped has not been addressed and this remains unclear. The ERG notes that in TA599, the committee concluded that starting RAAS inhibitors prolongs life for many people, so stopping them for people who benefit from them would likely shorten life.[17] The Epstein 2015 study was discussed in the CS for TA599.

Critique of CS 6.3.2: impact of RAASi therapy on cardiovascular events and mortality

The benefits of RAASi therapy on cardiovascular events and mortality was modelled with results from Xie et al[18] in the original CS economic evaluation. The targeted literature review identified 13 systematic reviews or meta-analyses, 11 of which had sufficient information and were tabulated in CS Table 48, and 37 single studies of which four reported on people with CKD and heart failure. The ERG has been unable to independently check the status of these reviews and studies and has concentrated on those summarised in Sections 6.3.2.2 of the submission (impact on mortality). The ERG has also concentrated on the systematic reviews only.

Five systematic reviews / meta-analyses [18, 28-31] were identified that reported on cardiovascular mortality in those with CKD, including Xie 2016[18] (CS ref 46). Only one of these reported that RAASi significantly reduced the risk of cardiovascular mortality compared with placebo (Sun 2016, ref 76).[31] This study considered spironolactone versus placebo in a population with CKD and end-stage renal disease. Xie 2016 and three other reviews did not find significant effects or showed no difference in cardiovascular mortality.

The submission concludes that the evidence mostly showed a non-significant reduction or no difference in the risk of cardiovascular mortality with RAASi compared to placebo or active control but that generally the use of RAASi is associated with a numerical risk reduction in cardiovascular mortality.

ERG summary

The ERG reiterates that only one systematic review found a significant effect on cardiovascular mortality and does not consider that the evidence provides further verification of the results of the NMA from Xie et al. As noted by the submission, the populations included in these reviews differed from those included in Xie et al.

3.3 Transition probabilities between serum potassium categories (use of HR [redacted])

CS2 page 76 states: *A lower risk of transitioning from a lower to a higher serum potassium level category was based on the hazard ratio derived from Part B of OPAL-HK for time to serum potassium 5.5mmol/L (see section 8.3.2).* In Section 8.3.2 page 82: *The 'surv' package in R was used to calculate a hazard ratio (HR) of [redacted] (likelihood ratio test on 1 degree of freedom, p=0.0005, n=[redacted], number of events=[redacted]) from the IPD to estimate the reduced risk of serum potassium rising from <5.1mmol/L to ≥5.5 mmol/L in the patiromer arm of OPAL-HK Part B compared with placebo (likelihood ratio test on 1 degree of freedom, p=0.0001082, n=[redacted], number of events=[redacted]).*

Thus a HR of [redacted] applies for "*the reduced risk of serum potassium rising from <5.1mmol/L to ≥5.5 mmol/L in the patiromer arm of OPAL-HK Part B compared with placebo*". In the CS1, Kaplan Meier plots for this outcome were provided in Figure 1 and Figure 2 (Fig 6A and in Section 3.3.3 Figure 18); these are reproduced below.

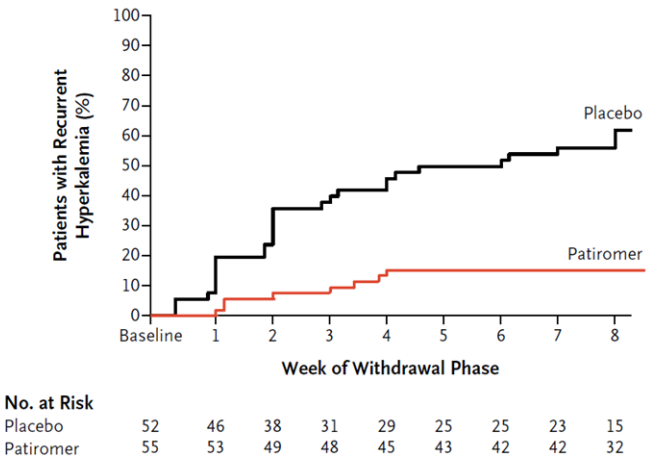

Figure 1. figure 6A CS1

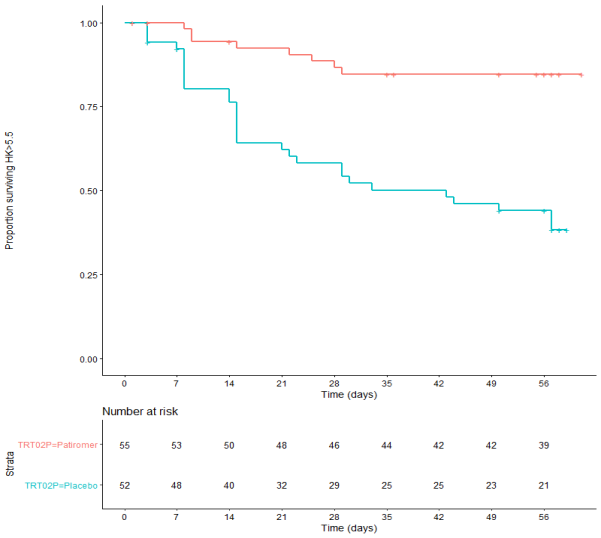

Figure 2. figure 18 CS1

For these plots 107 patients were enrolled in OPAL part B and at the end of phase A their serum potassium was in the range 3.1 to < 5.1mmol/L (also they were on patiromer and RAASi); thus all patients (N=107) were at potassium <5.1 mmol/L at start of phase B.

In the CS2 section 8.3.2 statement/description of the generation of the HR appears to be incomplete and unclear. The source of data is not unequivocally stated, it is unclear if the HR was unadjusted or adjusted for covariates; if adjusted then the covariates will be pertinent to the OPAL-HK phase B population and probably inappropriate for the CPRD population that differed materially in many characteristics. The quoted HR has no confidence intervals but in clarification (Q5 for CS2) the SE (0.168) was provided by the company. The method of HR estimation used is described in CS2 as using "R package *surv*"; this is insufficiently informative to be useful since various procedures may be used to derive the HR. The statement quotes of two likelihood test results which is confusing; there is an implication that the number of patients and events for both the patiromer and placebo arms in the test appears to be quoted as [redacted] and [redacted] (yielding [redacted] total events).

In CS1 Section 3.3.3 a HR of 0.187 rather than [redacted] is supplied. IPD were supplied during clarification of CS1 (B6.1 and B6.2 for CS1). The number of patients by arm in OPAL-HK part B

was placebo *n*=52 and patiromer *n*=55 and total observed events was 38 (8 patiromer, 30 placebo). Using IPD supplied during clarification of CS1 the ERG obtained a Cox unadjusted HR of 0.192 [95% CI 0.088 to 0.419].

The reasons for the discrepancies between HR 0.187, CS2 page 82 HR [redacted], and Cox HR (0.192) are unclear but may relate use of covariates in the HR estimation for CS2.

ERG comments on the use of HR from OPAL-HK to adjust transition probabilities derived from analyses of the CPRD:

Use of the CPRD for transition probabilities estimations between serum potassium categories addresses committee concerns that the algorithm employed for this in CS1 was unlikely to represent clinical practice within the UK NHS. However, applying the HR from OPAL-HK B to modify transition probabilities from CPRD somewhat offsets this potential advantage because of the material differences in characteristics (tabulated in CS2 section 7.3.2). Thus the HR derived from analysis of a very different population to that of the CPRD is being applied to CPRD data. The OPAL-HK B population was exclusively non-UK. In the trial there were 70 centres in ten countries comprising Croatia, Czech Republic, Denmark, Georgia, Hungary, Italy, Serbia, Slovakia, Ukraine, USA. Since OPAL-HK B comprised only 107 participants it is possible several centres and countries may not have contributed any patients to part B. Of 107 patients [redacted] were classified at the time of the trial as from non- EU/US centres. IPD data supplied during clarification of CS1 revealed considerable difference between patients from different trial regions in reaching serum potassium ≥5.5 mmol/L; this was associated with region for both patiromer and placebo arms. Patients from non-EU US regions exhibited less frequent events in both arms than patients from EU US. ERG analyses of IPD supplied in clarification are summarised the Table 2 and Figure 3 below. The HR for a population likely more similar to the UK (EU/US) yielded a HR of [redacted]. There were few patients and all 95% confidence intervals are wide.

Table 2. Summary of ERG analyses of IPD supplied in clarification

Patients	**Patiromer; N | *events***	**Placebo; N | *events***	**HR patiromer vs placebo [95% CI]**
ALL	55 | *8*	52 | *30*	0.192 [0.088 – 0.419]
EU US	[redacted]	[redacted]	[redacted]
Non EU US (East Europe)	[redacted]	[redacted]	[redacted]

[redacted]

Figure 3. Summary of ERG analyses of IPD supplied in clarification

The use of a treatment effect assumes that a single measure potentially derived from 70 centres that completely excluded UK patients may be valid for UK patients; the ERG considers this a large assumption and that a HR appropriate for the UK is likely larger than that used in the submission. Additionally, any HR derived from OPAL-HK B has a substantial chance of being inappropriate unless the treatment effect of patiromer is constant across many populations; no evidence was submitted to support such an assertion.

In CS1 the manufacturer selected a lognormal parametric model to describe time to hyperkalaemia >5.5 mmol/L in the patiromer arm and a parametric loglogistic model for the no-patiromer arm (Figure 4). The former appears to have been employed in the CS2 economic model.

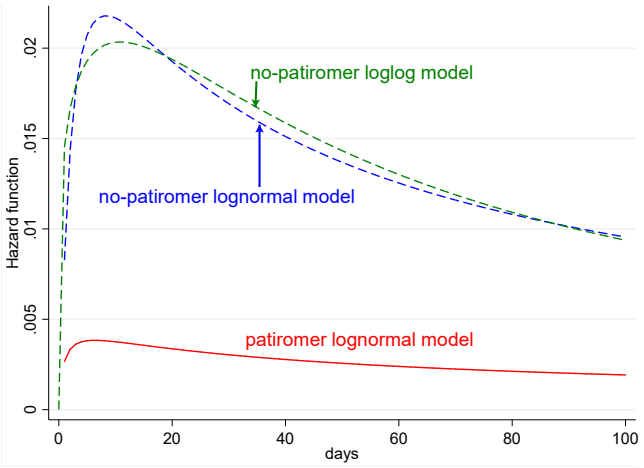

Figure 4. Hazard function of parametric models

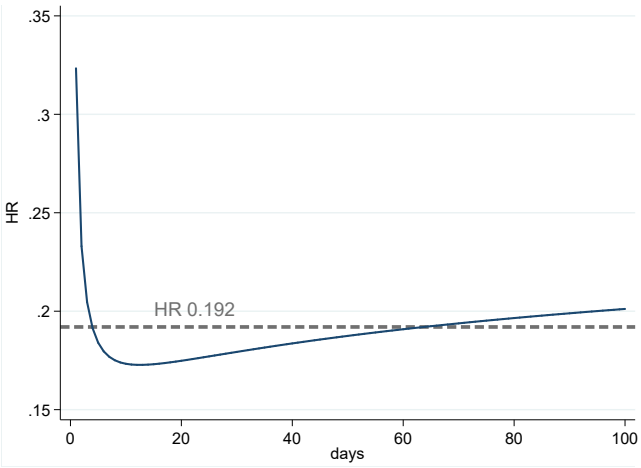

Figure 5. HR of lognormal models

The HR generated by these parametric models vary through time, for lognormal models the HR lies between about 0.18 and 0.2 for most of the duration and a HR 0.192 represents an approximate average (Figure 5); the modelled HR is substantially larger than the submission value of [redacted].

For completeness and because the use of a single HR ([redacted]) in CS2 to modify CPRD transition probabilities between various serum potassium levels, the ERG additionally analysed time to move from "controlled potassium" to levels above 5.1 mmol/L as depicted in Figure 6B of CS1, using IPD supplied during clarification (Figure 6). The resulting HR of 0.267 [95% CI: 0.159 - 0.450] denotes a different and more moderate treatment effect size than for Figure 6B.

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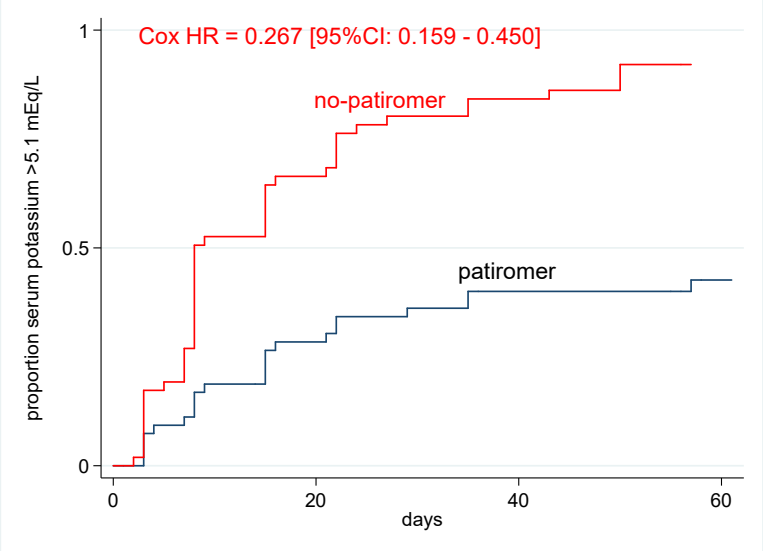

Figure 6. Time to move from "controlled potassium" to levels above 5.1 mmol/L

4 COST EFFECTIVENESS

4.1 Summary of company's submitted economic evaluation

4.1.1 NICE reference case checklist

Attribute	**Reference case and TA Methods guidance**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice. The scope specifies "*Standard care. This includes a low-*	The modelling does not really have an explicit comparator. Instead the company appears to analyse retrospective CPRD data of patients initiating RAASi to

	potassium diet with or without agents that reduce levels of potassium in the body".	provide the alternative.
Patient group	As per NICE scope. "*Adults with hyperkalaemia*".	The company has restricted the patient group to CKD patients with either (1) $K^+ > 5.5$ coupled and heart failure or (2) $K^+ > 6.0$ with or without heart failure.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost per QALY.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	For the 1st month of the model: • The comparator arm is modelled using a new company analysis of CPRD data of what appears to be patients initiating RAASi to estimate K^+ transitions. • The patiromer arm is modelled using OPAL-HK Part-A data. For the subsequent months: • The comparator arm is modelled using the new company analysis of CPRD data, but with an additional assumption that patients cannot improve by more than one health state per cycle. • Those remaining on patiromer are modelled by applying a hazard ratio of K^+ worsening estimated from OPAL-HK Part-B to the revised CPRD

		transition probabilities. The key assumption is that: • $K^+ < 5.5$ is the same as full RAASi • $5.5 < K^+ < 6.0$ is the same as [redacted] RAASi dosing • $6.0 < K^+$ is the same as no RAASi The other key model clinical inputs are: • K^+ direct mortality multipliers • CKD mortality multipliers • RAASi relative risks for CV events, deaths and CKD progressions
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	The main quality of life values are taken from Jesky et al [32] and Pockett et al [33]. Both use the EQ-5D-3L valued using the UK social tariff.
Benefit valuation	Time-trade off or standard gamble	The time trade off exercise that underlies the UK social tariff.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.

Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		Yes.

4.1.2 Model structure

The company develops a new markov model with a monthly cycle, the model diagram being presented as Figure 11 on page 73 of the June 2019 CS2 and reproduced below (Figure 7).

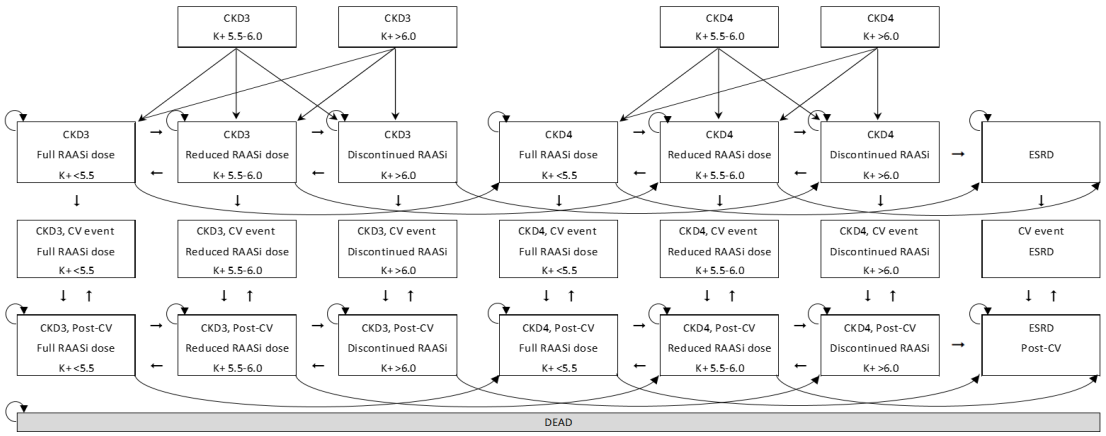

Figure 7. Company model structure

In brief, patients start the model with CKD3 or CKD4 and are assumed to have no history of a cardiovascular event. There are three K^+ levels of $5.5 > K^+$, $6.0 > K^+ \geq 5.5$ and $K^+ \geq 6.0$ with the patient distribution between these being taken from the OPAL-HK Part-A baseline distribution among the revised target group.

Patients are differentiated by their potassium status and are further differentiated by:

- CKD stage: CKD3, CKD4 and CKD5, and
- Cardiovascular (CV) event status: no prior event hence No CV, Event CV, which is a tunnel health state lasting only 1 model cycle, and Post CV event.

With it being possible to both progress through CKD health states and experience CV events.

The company assumes the following serum potassium levels (Figure 8) are synonymous with the following RAASi usage for those without heart failure.

Serum Potassium	
K^+ (mmol/L)	ERG shorthand

RAASi usage	
RAASi dose	ERG shorthand

$5.5 > K^+$	Low K^+	⟷	Fully optimised	Full RAASi
$6.0 > K^+ \geq 5.5$	Mid K^+	⟷	Halved	Mid RAASi
$K^+ \geq 6.0$	High K^+	⟷	Discontinued	Off RAASi

Figure 8. Serum potassium to RAASi use relationship: Heart Failure Free Patients [redacted]

For those with heart failure the following is assumed (Figure 9):

Serum Potassium			RAASi usage	
K^+ (mmol/L)	ERG shorthand		RAASi dose	ERG shorthand
$5.5 > K^+$	Low K^+	⟷	Fully optimised	Full RAASi
$6.0 > K^+ \geq 5.5$	Mid K^+	⟷	Discontinued	Mid RAASi
$K^+ \geq 6.0$	High K^+	⟷	Discontinued	Off RAASi

Figure 9. Serum potassium to RAASi use relationship: Heart Failure Patients [redacted]

The baseline distribution of patients in OPAL-HK Part-A is split roughly equally between Mid K^+ / Mid RAASi and High K^+ / Off RAASi. In this regard, it can be noted that at OPAL-HK Part A baseline all were on RAASi, so the clinical data may not be particularly aligned with the modelling assumption in this regard.

The large majority, [redacted]% of patients in the revised target group, have heart failure. As a consequence for the Mid K^+ / Mid RAASi the RAASi dose is assumed to be [redacted]% * 50% of the fully optimised dose and [redacted]% * 0% of the fully optimised dose, hence a weighted average of only [redacted]% of the fully optimised dose.

RAASi use determines the probabilities of MI, stroke, CV deaths and CKD progression with the values for these being derived from the meta-analysis of Xie et al.[18] The probabilities of the MI, stroke, CV deaths and CKD progression that are related to RAASi dose are assumed to be proportionate to the RAASi dose. As a consequence, for the Mid K^+ / Mid RAASi the probabilities of these events are very little different from those of the High K^+ / Off RAASi group.

The ERG shorthand for this group may consequently be slightly misleading. It should be borne in mind throughout that in the company submission Mid K^+ / Mid RAASi is not midway between Low K^+ / Full RAASi and High K^+ / Off RAASi. The Mid K^+ / Mid RAASi is so little difference from

High K^+ / Off RAASi in terms of RAASi use and the associated risks as to be practically indistinguishable from it.

The model structure of the 1st cycle differs from that of the subsequent cycles. During the 1st cycle the patient group is assumed to remain No CV and it is assumed that there is no CKD progression. Patients only change their K^+/RAASi status.

- For the comparator arm this is based upon an analysis of CPRD data of monthly transitions between the three potassium levels among CKD3 and CKD4 patients initiating RAASi, yielding estimates of CKD level specific transition probabilities.

- For the patiromer arm this is based upon OPAL-HK Part A transitions between the three K^+ levels.

There is no connection between the clinical effectiveness estimates for the comparator arm and those of the patiromer arm for the 1st cycle due to OPAL-HK Part-A being single arm.

For subsequent cycles of the model patients still change their K^+/RAASi status, but the model structure restricts patients to change by at most one level per cycle.

- For the comparator arm the CPRD monthly transitions between potassium levels are applied, but:
    - The probability of worsening from Low K^+/Full RAASi to High K^+/Off RAASi is set to 0%, with the probability of worsening from Low K^+/Full RAASi to Mid K^+/Mid RAASi being increased by the required amount.
    - The probability of improving from High K^+/Off RAASi to Low K^+/Full RAASi is set to 0%, with the probability of improving from High K^+/Off RAASi to Mid K^+/Mid RAASi being increased by the required amount.
    - The main effect of this is to slow the rate at which patients in the comparator arm improve to Low K^+/Full RAASi.
- For the patiromer arm:
    - When patiromer is still being used a relative risk of worsening K^+/RAASi of [redacted] is estimated from OPAL-HK Part B data. This is applied to the placebo arm CPRD probabilities of worsening K^+/RAASi.

- When patiromer use has ceased the transition probabilities of the comparator arm are applied.

For the pooled target group of those with heart failure and those without heart failure common probabilities of CV Events and CV Event Deaths for those on RAASi and those not on RAASi are estimated from Xie et al.[18] These are assumed to apply to Low K^+/Full RAASi and to High K^+/Off RAASi respectively. As previously outlined, estimates for Mid K^+/Mid RAASi are based upon a weighted average of [redacted]% of the risks of the Low K^+/Full RAASi and [redacted]% of the risks of the High K^+/Off RAASi These probabilities are assumed to apply equally across CKD3 and CKD4 status, and across No CV and Post CV status.

The Xie et al [18] data and a similar approach is used to estimate the probabilities of CKD progression, with the K^+/RAASi specific probability of progression for CKD3 to CKD4 being assumed equal to that of CKD4 to CKD5.

In addition to the CV event mortality, all-cause mortality is applied to those not experiencing a CV event.

- Age specific CKD3 standardised mortality ratios (SMRs) and CKD4 SMRs are taken from Eriksen et al [34] while CKD5 age specific mortality estimates are drawn from Steenkamp et al.[35]

- Serum potassium related SMRs of 1.15. 1.60 and 2.65 for patients in Low K^+, Mid K^+ and High K^+ respectively are taken from McEwan et al.[16]

These SMRs are combined multiplicatively; e.g. a 65 year old CKD3 patients with Low K^+ has a combined SMR of 3.1*1.15=3.56 while a CKD3 patient with High K^+ has a combined SMR of 3.1*2.95=9.14. These combined SMRs are applied to England and Wales life table data to estimate all-cause mortality risks by CKD and potassium health status.

4.1.3 Population

The company models a pooled population of:

- Patients with heart failure at baseline who were $K^+ \geq 5.5$ at baseline

- Patients without heart failure at baseline who were $K^+ \geq 6.0$ at baseline

The distribution of patients with and without heart failure at OPAL-HK Part A baseline is in Table 3, with those in italics falling outside the revised target population and those in bold being the target population. Those with and without HF are assumed to have the same probabilities of CV events and CKD progression, so are pooled for modelling purposes.

Table 3. OPAL-HK Part A Baseline patient distribution

Serum Potassium	K^+<5.0	5.0≤K^+<5.5	5.5≤K^+<6.0	6.0≤K^+	Total
With HF					
CKD3 CKD4	[redacted]				
Without HF					
CKD3 CKD4	[redacted]				
Target population					
CKD3 CKD4	.. ..	.. ..	[redacted]		

For future reference it can also be noted that within the target population (n=[redacted]), a majority of [redacted] ([redacted]) had heart failure at baseline.

It can also be noted that the above data relates to a subset of [redacted] patients of the 243 patients recruited to OPAL-HK Part-A, with only [redacted] patients among the [redacted] patients of the above data being within the revised target group.

4.1.4 Interventions and comparators

Patiromer is compared to data from a company analysis of CPRD data. As a consequence, it is unclear quite what the comparator is though it could be described as usual care.

4.1.5 Perspective, time horizon and discounting

The perspective and discounting is as per the NICE reference case. The time horizon is 35 years, which is effectively a lifetime horizon.

4.1.6 Treatment effectiveness and extrapolation

4.1.6.1 1st cycle patiromer arm

The clinical effectiveness of patiromer for the 1st cycle is derived from the OPAL-HK Part-A transitions among the [redacted] patients of the revised patient group, though note that these patients may not fully reflect number of patients in the revised patient group who were recruited to OPAL-HK Part-A.

[redacted] of these [redacted] patients transitioned to low hyperkalaemia between OPAL-HK baseline and 4 weeks.

[redacted] The resulting patient transitions and transition probabilities are in Table 4.

Table 4. 1st cycle transition probabilities: Patiromer

	CKD3			CKD4		
From \ To	Low K+	Mid K+	High K+	Low K+	Mid K+	High K+
HF patient transitions						
Mid K+ High K+	[redacted]					
HF Free (NoHF) patient transitions						
Mid High	[redacted]					
Pooled patient transitions						
Mid High	[redacted]					
Pooled patient transition probabilities						
Mid High	[redacted]					

4.1.6.2 1st cycle comparator arm

For the 1st cycle of the model for the placebo arm an analysis of CPRD data yields the following monthly transition probabilities between potassium states (Table 5).

Table 5. CPRD transition probability matrices (TPMs): 1st cycle

	CKD3			CKD4		
From \ To	Low K+	Mid K+	High K+	Low K+	Mid K+	High K+
Low K+	99.65%	0.31%	0.04%	98.98%	0.92%	0.10%

Mid K+	12.15%	87.48%	0.38%	9.90%	89.07%	1.03%
High K+	11.71%	2.37%	85.92%	7.70%	4.23%	88.07%

4.1.6.3 End of 1st cycle patient distribution

Applying the CPRD transition probabilities in the usual care arm and the OPAL-HK transition probabilities in the patiromer arm results in the following patient distributions at the end of the 1st cycle.

Table 6. End of 1st cycle patient distribution by arm

	CKD3			CKD4		
	Low K+	Mid K+	High K+	Low K+	Mid K+	High K+
	Full RAASi	Mid RAASi	Off RAASi	Full RAASi	Mid RAASi	Off RAASi
Baseline						
End of 1st cycle						
Usual care						
Patiromer						

By the end of the 1st cycle (Table 6) the patient distribution in the usual care arm is little changed from baseline. In contrast, by the end of the 1st cycle patiromer has effectively cured virtually all patients.

Adverse Events

Rates of adverse events for patients receiving patiromer (Table 7) are taken from OPAL-HK Part-A for the 1st cycle and from OPAL-HK Part-B for subsequent cycles, as reported in Weir et al.[3] Adverse event rates are zero for those not receiving patiromer.

Table 7. Adverse event rates for those on patiromer

OPAL-HK	Part-A	Part-B
Constipation	0.113	0.036
Diarrhoea	0.040	0.036
Nausea	0.026	0.036
Hypomagnesia	0.033	..

4.1.6.4 Clinical effect extrapolation subsequent cycles

For subsequent cycles in the comparator arm the company revises the CPRD TPMs to not permit worsening from Low K^+/Full RAASi to High K^+/Off RAASi of improving from High K^+/Off RAASi to Low K^+/Full RAASi, with these probabilities being added to that of the neighbouring transition

(Table 8). This particularly affects the probabilities of improving as shown below. Given the end of 1st cycle patient distributions, this in turn particularly affects the comparator arm but has little effect on the patiromer arm.

Table 8. CPRD transition probability matrices (TPMs): Subsequent cycles

	CKD3			CKD4		
From/To	Low K+	Mid K+	High K+	Low K+	Mid K+	High K+
Low K+	99.65%	0.35%	..	98.98%	1.02%	..
Mid K+	12.15%	87.48%	0.38%	9.90%	89.07%	1.03%
High K+	..	14.08%	85.92%	..	11.93%	88.07%

For those on patiromer a relative risk of worsening potassium of [redacted] is estimated from OPAL-HK Part B data is applied to the CPRD probabilities of worsening.

There is relatively little information on the derivation of this hazard ratio within the company submission. It notes that it is derived from OPAL-HK Part-B data using data for all patients, and is not restricted to the patients of the revised target group. It is estimated as the hazard ratio of worsening from $K^+<5.0$ to $K^+>5.5$, and is statistically significant ($p<0.001$). This hazard ratio is assumed to apply to the revised target groups' probabilities of worsening from:

- $K^+ < 5.0$ to $5.0 \leq K^+ < 5.5$
- $K^+ < 5.0$ to $5.5 \leq K^+ < 6.0$
- $K^+ < 5.0$ to $6.0 \leq K^+$

The CPRD probabilities of improving are retained, with the probability of remaining in with the same potassium being the residual. This results in the following (Table 9) transition probability matrices for patiromer for subsequent cycles:

Table 9. Patiromer transition probability matrices (TPMs): Subsequent cycles

	CKD3			CKD4		
From/To	Low K+	Mid K+	High K+	Low K+	Mid K+	High K+
Low K+	99.96%	0.04%	..	99.87%	0.13%	..
Mid K+	12.15%	87.81%	0.05%	9.90%	89.96%	0.13%
High K+	..	14.08%	85.92%	..	11.93%	88.07%

Patients in the patiromer arm are assumed to receive patiromer for 12 months, resulting in the above TPMs being applied 11 times. They are then assumed to cease patiromer treatment, with the CPRD usual care TPMs being applied thereafter.

CV Events and Deaths and CKD progression

Xie et al,[18] in a meta-analysis of ACE inhibitor (ACEi) and angiotensin-receptor blocker (ARB) against placebo among CKD patients, report the number of CV events, CV deaths and CKD progressions for placebo and the odds ratios for ACEi and ARB. The company estimates the monthly probabilities for placebo, combining them using the OPAL-HK 71:29 ratio of ACEi:ARB to derive monthly probabilities for High K^+/Off RAASi. The odds ratios for ACEi and ARB are similarly combined 71:29, and the result applied to the placebo monthly probabilities to derive the corresponding monthly probabilities for Low K^+/Full RAASi.

For the Mid K^+/Mid RAASi the company first takes the average of the High K^+/Off RAASi and Low K^+/Full RAASi monthly probabilities. This average is then combined [redacted] with High K^+/Off RAASi monthly probabilities, the [redacted] being the ratio of NoHF:HF in the OPAL-HK target population. The underlying assumptions are that

- NoHF patients moving into Mid K^+/Mid RAASi reduce RAASi and have probabilities of events that are the average of those on Full RAASi and Off RAASi.
- HF patients moving into Mid K^+/Mid RAASi reduce RAASi to such an extent that they have probabilities of events that are equal to those who are Off RAASi.

This results in monthly probabilities for the Mid K^+/Mid RAASi that are little different from those of the High K^+/Off RAASi as shown below, where n is the number of events, N the number of patients and mths the months of follow-up (Table 10).

Table 10. CV Events and Deaths, and CKD progressions

	Placebo arms					ACEi/ARB arms			Mid K^+
	High K+/OFF RAASi					Low K^+/Full RAASi			Mid RAASi.
	n	N	Mths	Prob.	Pooled	OR	Pooled	Prob.	Prob.
CV.Events									
vs ACEi	1,720	8,357	48.0	0.48%	0.57%	0.82	0.80	0.45%	0.55%
vs ARB	708	2,663	39.6	0.78%		0.76			
CV.Deaths									

vs ACEi vs ARB	792 132	8,301 1,604	48.0 39.6	0.21% 0.22%	0.21%	0.88 1.12	0.95	0.20%	0.21%
CKD progressions									
vs ACEi vs ARB	299 727	3,337 2,421	48.0 39.6	0.20% 0.90%	0.40%	0.61 0.70	0.64	0.25%	0.38%

The above monthly probabilities are assumed to apply equally to CKD3 and CKD4 patients. For CKD5 patients expert opinion suggests that 60% will be Off RAASi and 40% will be Full RAASi. Weighting the Off RAASi and Full RAASi estimates accordingly results in a CKG5 monthly probabilities of a CV event of 0.52% and of a CV death of 0.21%.

Serum potassium mortality risk

Mortality multipliers associated with potassium levels are drawn from McEwan et al [16] conference abstract (Table 11) , with the company also sourcing alternative estimates from the full paper of Kovesdy et al (2018).[9]

Table 11. Serum potassium mortality multipliers

		McEwan et al	Kovesdy et al
Low K+/Full RAASi	$K^+ < 5.5$	1.15	1.12
Mid K+/Mid RAASi	$5.5 \leq K^+ < 6.0$	1.60	1.24
High K^+/Off RAASi	$6.0 \leq K^+$	2.95	1.36

CKD mortality

The treatment of CKD mortality is as per the original company model.

CKD stage 3 patients have age banded SMRs of 3.1, 2.0 and 2.2 for those aged under 70, 70 to 79 and 80 plus respectively, taken from the Norwegian study of Eriksen et al.[34] A mortality multiplier CKD stage 4 patients of 2.56 taken from Sud et al[36] is applied to these SMRs, resulting in pooled age banded SMRs of 5.2, 3.4 and 3.7 for those aged under 70, 70 to 79 and 80 plus respectively.

ESRD patients have age banded annual mortality risks taken from Steenkamp et al,[35] in bands of 5 years from age 65 of 114 per 1,000, 143 per 1,000, 200 per 1,000, 258 per 1,000 rising to 371 per 1,000 for those aged 85 plus.

It can be noted that due to the CKD mortality risks calculated using SMRs increasing with the general population all-cause mortality risks as patients age, the increased mortality risk from ESRD relative to

CKD declines with age. By age 85 the mortality risks in the model for CKD and ESRD are the same. This may suggest that the application of the CKD SMRs for those who are very old may exaggerate the effects of CKD due to the SMRs that are applied to general population all-cause mortality risks being too high.

4.1.7 Health related quality of life

Main health states: Quality of life values (Table 12)

Baseline quality of life values for CKD3, CKD4 and CKD5 of 0.800, 0.740 and 0.730 are taken from Jesky et al.[32] Quality of life values for MI and stroke of 0.690 and 0.496 are taken from Pockett et al[33] and combined with the ratio of MI:Stroke for CV events of 35:65 from Kerr et al[37] to result in a CV event disutility multiplier of 0.35*0.690+0.65*0.496 = 56%. Similarly, quality of life values for post MI and post stroke of 0.706 and 0.527 are also taken from Pockett et al[33] and similarly combined to yield a post CV event disutility multiplier of 0.35*0.706+0.65*0.527 = 59%. This result in the following health state quality of life values.

Table 12. Main health state quality of life values

		CV free	CV Event	Post CV
	Base QoL\Multiplier	100%	56%	59%
CKD3	0.800	0.800	0.451	0.472
CKD4	0.740	0.740	0.417	0.436
CKD5	0.730	0.730	0.412	0.430

Quality of life age weighting: Main health states

The above quality of life values are applied in the 1st cycle. Thereafter they are weighted by the quality of life function taken from Jones-Hughes et al.[38] For instance, for the baseline age with 46% female the age related quality of life from Jones-Hughes et al is 0.821. Ten years later it is 0.789. The main health state quality of life values are weighted by these amounts.

Quality of life: adverse events

Quality of life decrements of -0.034 for hypomagnesia, -0.073 for constipation, -0.010 for diarrhoea and -0.048 for nausea are taken from the literature and applied to those on patiromer.

The hypomagnesia adverse event only applies in the 1st cycle of the model, with all patients on patiromer incurring it and the other adverse events.

4.1.8 Resources and costs

4.1.8.1 Patiromer direct drug and administration costs

Patiromer is available as a 30-day pack costing £300, providing an annual cost of £3,652 per patient. A simple PAS discount of [redacted] applies, which reduces the pack cost to [redacted], or an annual cost of [redacted] per patient.

In addition to the direct drug costs an additional £31 annual prescribing cost is included, based upon 4 prescriptions per year each requiring 10 minutes of hospital pharmacist time. The assumption of 4 prescriptions per year is based upon expert opinion. Given the cost of patiromer this may not be realistic if it implies that patients will typically receive a 3 month supply with each prescription which could increase wastage. Rather than explore increased wastage, the ERG explores monthly prescribing finding it to have little effect upon results.

4.1.8.2 CKD costs

Annual CKD3 and CKD4 costs are apparently based upon Kerr et al (2012).[37]

- Primary care is quarterly, alternating between a GP visit and a nurse visit. This yields an annual cost of £91.
- Outpatient costs are rather peculiarly estimated as the average cost per nephrology outpatient visit of £155, with this being halved due to an assumption of only half of these appointments applying to CKD3 and CKD4. This is equivalent to assuming an annual average of 0.5 outpatient visits among CKD3 and CKD4 patients. This yields an annual cost of £78.
- Inpatient costs are based upon an assumption of an average of 1 inpatient stay per year with a length of stay of 9.2 days at £225 per day to yield an annual cost of £2,228.

These sum to an annual cost of £2,631.

Annual CKD5 cost estimates adopt the same method as the previous company submission, with the updated proportions for those on peritoneal dialysis, those on haemodialysis and those receiving transplant, with an average survival post-transplant of 3.5 years. This yields an average annual cost for CKD5 of £26,738.

Annual concomitant medication costs are based upon the proportion of CKD patient receiving vitamin D as Calcitriol, EPO/EAS as Aranesp or Eprex and phosphate binders as Forerenol or Velphoro. At BNF list prices the annual average cost is £601.

4.1.8.3 CV Event costs

Costs of MI and stroke of £7,734 and £12,200 are taken from Kerr et al,[37] combined 35:65 and uprated for inflation to yield a cost per event of £12,211.

After experiencing a CV event, patients have an additional £17 cost for clopidogrel added to their health state cost.

4.1.8.4 Hyperkalaemia hospitalisation costs

These are costed using NHS reference cost for Fluid or electrolyte disorders without intervention, with an average cost of £1,443.

4.1.8.5 Adverse event costs

Adverse events costs are minor and only relate to the direct drug costs of their treatment. This seems likely to underestimate their cost as additional GP or OP visits will be required. The ERG will explore assuming each adverse event incurs an additional 2 GP visits.

4.1.9 Cost effectiveness results

4.1.9.1 Company base case cost effectiveness results

The company deterministic base case estimates the following disaggregate discounted event costs, with the total also including the costs of adverse events and in hospital deaths the net costs of which are minor.

Table 13. Company deterministic base case disaggregate costs

	PATR	RAASi	Meds.	CKD	ESRD	Total
Patiromer	[redacted]				£14,000	[redacted]
Placebo					£14,305	
Net					-£305	£3,289

Higher costs in the patiromer arm are in part the result of increased overall survival. The main net costs of interest are the direct drug costs of patiromer and the cost saving offsets from reduced ESRD (Table 13).

The company deterministic base case estimates the following (Table 14) aggregate undiscounted life years and discounted life years, QALYs, costs and resulting ICER:

Table 14. Company deterministic base case

		Discounted			
	LYs	LYs	QALYs	Costs	ICER
Patiromer Placebo	[redacted]				
Net	0.353	0.273	0.174	£3,289	£18,893

The company probabilistic modelling (**Figure 10)** results in reasonably similar net gains of 0.160 QALYs at a net cost of £3,132 resulting in a central estimate of £19,577 per QALY .

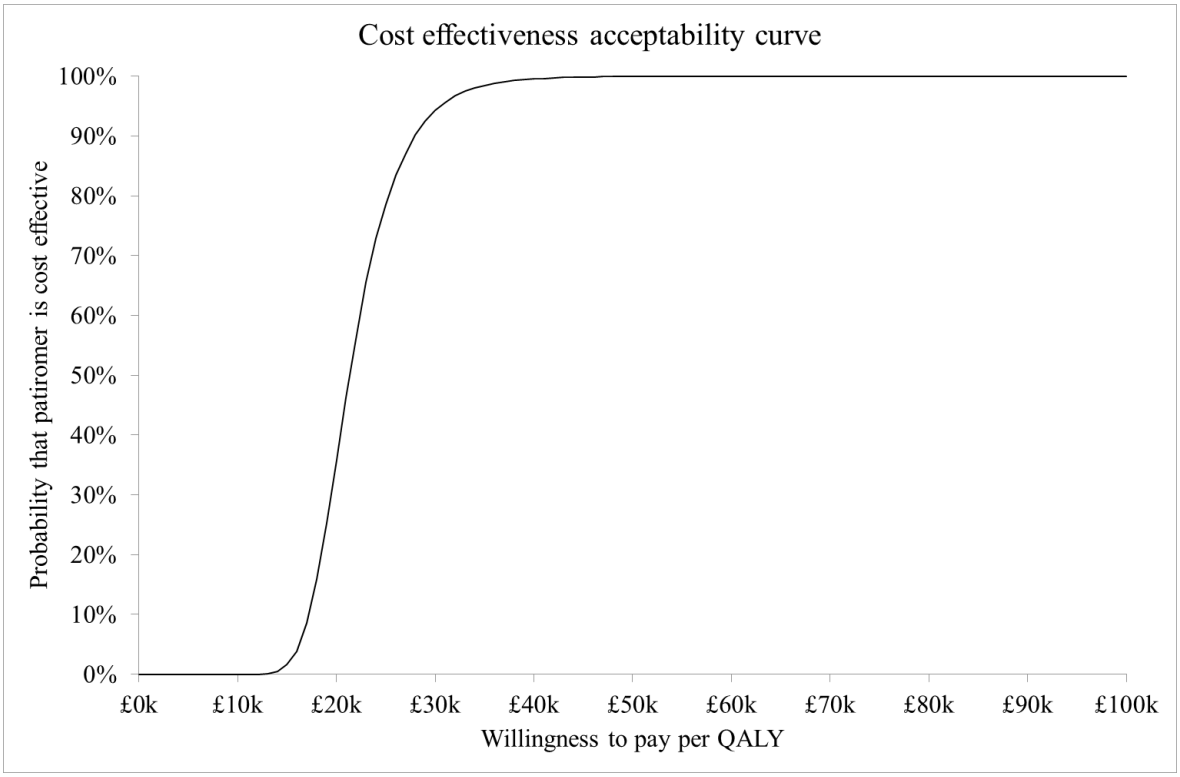

Figure 10. Company base case cost effectiveness acceptability curve

4.1.10 Sensitivity analyses

The company conducts a range of univariate sensitivity analyses, none of which result in the ICER exceeding £30k per QALY. Of the univariate sensitivity analyses that are conducted the ICER is most sensitive to:

- The cost of patiromer
- The duration of treatment, a longer duration worsening the ICER
- The serum potassium mortality risks

- The quality of life values for CKD3 and CKD4
- The relative risk for progression from CKD4 to CKD5 for RAASi versus placebo
- The probabilities of CV events
- The transition probability for CKD3 from Mid K^+/Mid RAASi to Low K^+/Full RAASi

The company also conducts a number of scenario analyses and finds that:

- Not applying the serum potassium SMRs worsened the ICER to £45,748 per QALY
- Applying the serum potassium SMRs of Kovesdy et al[9] worsened the ICER to £33,328 per QALY.
- Restricting the patiromer treatment duration to [redacted] and 3 months improved the ICER to £12,661 per QALY, £11,386 per QALY and £7,502 per QALY respectively.
- Applying the ID1293 sodium zirconium cyclosilicate ERG preferred quality of life estimates for CKD stages had minimal effect and resulted in an ICER of £18,876 per QALY.
- Applying the RAASi versus active comparator estimates and baseline risks of Xie et al had minimal effect and resulted in an ICER of £18,241 per QALY.
- Rather than pooling the ARB estimates and the ACI estimates of Xie et al, applying them individually resulted in ICERs of £23,049 per QALY and £17,833 per QALY respectively.
- Baseline ages of 70, 75 and 80 years worsened the ICER to £20,966 per QALY, £20,781 per QALY and £20,311 per QALY respectively.

4.1.11 Model validation and face validity check

No model validation data is presented.

4.1.11.1Minimum additional data required

In the opinion of the ERG the submission is incomplete. The economics models a revised target group. The clinical section of the submission does not present or consider the results of OPAL-HK Part-A for the revised target group or the results of either arms of OPAL-HK Part-B for the revised target group.

At a minimum the company should present the results of both arms of OPAL-HK Part-B for the revised target group, for both potassium and RAASi dose reductions and cessation, recognising that a treatment effect for treatment with RAASi would be at least in part be protocol driven. There also needs to be more consideration of the handling of lost to follow-up and of missing data within the company analyses and whether any biases may result.

The company should also present more detail on the numbers of patients and events that underlie it hazard ratio estimate of [redacted], at both week 4 and week 8 of OPAL-HK Part-B, alongside the parallel numbers of patients and events for the other transitions that are possible:

- $K^+ < 5.0$ to $5.0 \leq K^+ < 5.5$
- $K^+ < 5.0$ to $6.0 \leq K^+$

And while numbers of patients and events would be small for the revised target group these should also be presented for completeness.

4.1.11.2Movement through the main health states over time

The clinical effectiveness estimates result in the following proportions of patients remaining alive and in the three K^+/RAASi health states over time (Figure 11).

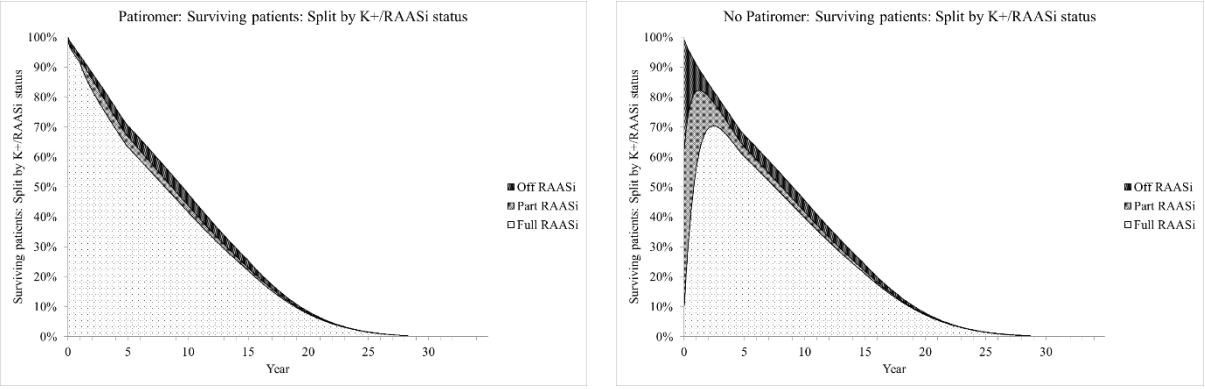

Figure 11. Proportions of patients in K+/RAASi health states over time

Virtually all patients in the patiromer arm are modelled as being in Low K^+/Full RAASi from the 1st model cycle. In time, a small proportion of around 4% of patients fall into Mid K^+/Part RAASi and a similarly small proportion of around 4% of patients fall into High K^+/Off RAASi. This is due to the [redacted] hazard ratio conditioned CRPD transition probability matrix only applying for the 1st year

when patients are on patiromer, and the unconditioned CRPD transition probability matrix applying thereafter.

The large majority of patients in the comparator arm are modelled as being in either High K^+/Off RAASi or the Mid K^+/Part RAASi at the start of the 1st model cycle (Figure 12), and only 10% of patients are in Low K^+/Full RAASi. The CPRD transition probability matrices suggest that by around year 3 the majority of patients regain in Low K^+/Full RAASi. It takes until around year 5 for the proportions of patients in Mid K^+/Part RAASi High K^+/Off RAASi to fully converge with those in the patiromer arm. But the large differences in the proportion of patients in the High K^+/Off RAASi declines rapidly as graphed below.

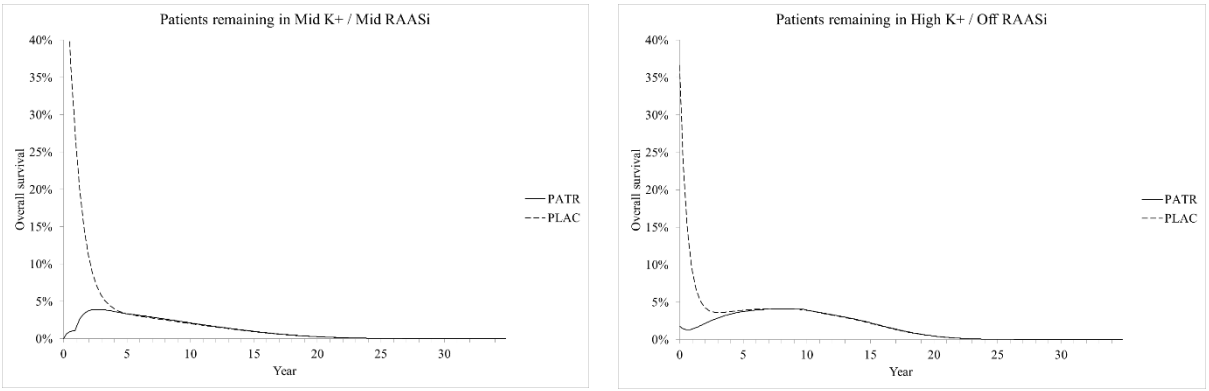

Figure 12. Proportion of patients remaining in Mid K+/Mid RAASi and High K+/Off RAASi

Note in passing that given the convergence at year 5 this can be used to argue that there is patient benefit from continued use of patiromer to year 5. As a consequence, for reasons of internal modelling consistency the maximum treatment duration with patiromer should probably be 5 years. The ERG will apply this maximum when using the AMETHYST-DN treatment discontinuation curves.

The above flow through to differences between the distributions of patients' CKD health states and CV health states, but the differences are not visually dramatic. The modelled survival curves are presented alongside one another (Figure 13) and show the patiromer is anticipated to result in a small gain in survival over the time horizon, with the net gain as an absolute percentage, Net Abs., and the net gain as a proportion of those surviving, Net Prop., also being presented.

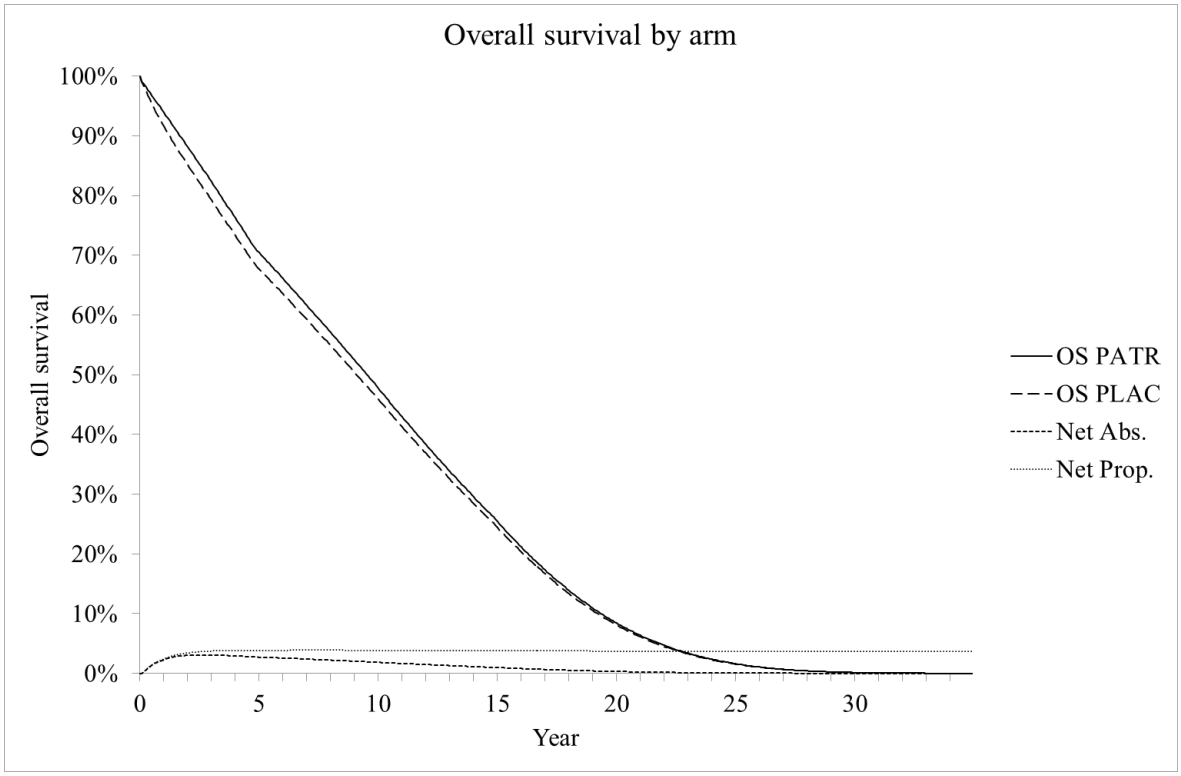

Figure 13. Overall survival by arm

The 1st year of treatment with patiromer results in immediate absolute survival gains. By the end of the 1st year there is a 2.3% survival gain. This absolute gain peaks at 3.1% at 2 years then declines due to overall survival in both arms falling. But the proportionate gain among those remaining alive is retained. This suggests that the main absolute survival gains are realised in the 1st year of the model with some limited additional gains in the 2nd year of the model and that thereafter the mortality rate is similar in both arms.

The above tallies with the company scenario analysis which find that the serum potassium SMRs are the key driver of results, coupled with the proportion of patients modelled as being High K^+/Off RAASi falling rapidly in the comparator arm by the end of the 2nd year. This is due to High K^+/Off RAASi having a serum potassium SMR of 2.95 compared to those in Low K^+/Full RAASi having a serum potassium SMR of 1.15, with the CKD SMRs then multiplying the effect of the serum potassium SMRs.

There will also be some mortality effect from the Mid K^+/Mid RAASi curves showing some separation between year 3 to 5, but the effect of this upon overall survival appears to be muted due to Mid K^+/Mid RAASi having a serum potassium SMR of 1.60 which is more aligned with the Low K^+/Full RAASi serum potassium SMR of 1.15.

It is not particularly the effects of RAASi, CV events and progression through the CKD stages that drive the anticipated gains in overall survival. It seems to be the immediate survival gains from having fewer patients in High K^+/Off RAASi for a period of around 2 years and them having a serum potassium SMR of 2.95. The CKD3 and CKD4 SMR of 3.10 and 7.94 of the first two years of the model multiply this up to yield combined SMRs of 9.15 and 23.41.

4.1.11.3Model validation and the DIAMOND trial

If the modelling is correct and the absolute gains in overall survival mainly occur in the 1st year with smaller additional gains in the 2nd year, this suggests that patiromer trials with a longer term follow up than OPAL-HK should, if sufficiently powered, be able to demonstrate an overall survival benefit after 1 year with this slightly increasing after 2 years.

The DIAMOND trial may provide supportive data in due course, but recruitment only began in April 2019 and the primary completion date is not until December 2021. It is a double blind RCT recruiting 2,388 patients[i] "*to determine if patiromer treatment of subjects who developed hyperkalemia while receiving RAASi medications will result in continued use of RAASi medications in accordance with heart failure (HF) treatment guidelines and thereby decrease the occurrence of the combined endpoint of cardiovascular (CV) death and CV hospitalization events compared with placebo treatment*". The primary outcome is time to 1st occurrence of CV death or CV hospitalisation with a time frame of 6 months to 2.5 years. It should also be noted that inclusion criteria include "*Kidney function not more than mild or moderately impaired*" which would exclude CKD4 patients at enrolment. So DIAMOND may not address the patient group for the position currently sought by the company, but it may address much of the position specified in the original scope of this assessment. It is also possible that DIAMOND will also have more patients in the revised target group than the [redacted] patients of OPAL-HK.

4.2 ERG cross check and critique

4.2.1 ERG rebuild of company base case results

The ERG has attempted to rebuild the deterministic model of the company base case, with the following results in Table 15

Table 15. ERG rebuild of company deterministic base case

[i] https://www.clinicaltrials.gov/ct2/show/NCT03888066

	QALYs	Costs	ICER	QALYs	Costs	ICER
Patiromer Placebo	[redacted]			[redacted]		
Net	0.174	£3,289	£18,893	0.178	£3,301	£18,523

The ERG rebuild estimates similar absolute costs and absolute QALYs, though all estimates are slightly larger than those of the company model. But the net quantities are extremely similar, and the ICER is near identical at £18,523 per QALY.

4.2.1.1 Modelling error: Age weighting of main health state utilities

The company weights the main quality of life values by the age relate quality of life norms; e.g. 0.821 for the 1st cycle and 0.789 by year 10. The ERG thinks that this weighting should be by how much the age related norms decline over time relative to the baseline; i.e. 100% for baseline and 96% by year 10.

There is an argument if the main quality of life values of the CKD health states are drawn from a younger cohort than that modelled, there should be some age adjustment to these values to align them with the cohort modelled. The patients of Jesky et al[32] had a mean age of 64 compared to the model baseline age of 65 years so this does not appear to apply.

Applying the ERG preferred quality of life weighting improves the company base case ICER from £18,893 per QALY to £15,426 per QALY.

4.2.1.2 Modelling error: Cost of hospitalisations and CV events

The model cycle length is 1 month. To calculate the cost associated with remaining in CKD3 for 1 model cycle the annual CKD3 cost of £2,631 is conditioned by the cycle length of 0.083 to yield a cost of £219.

It appears that this approach is carried over to the costs of HK hospitalisations and CV events. The costs per event of £1,443 and £12,211 are conditioned by the cycle length of 0.083, resulting in event costs of £120 and £1,018.

Not conditioning these costs by the cycle length improves the company base case ICER from £18,893 per QALY to £17,966 per QALY.

4.2.1.3 Modelling error: Probability of CKD3 Low K^+/Full RAASi CV event

Among CKD3 Low K+/Full RAASi patients for the probability of experiencing a CV event the model applies a 0.0033 monthly probability, which is the probability of worsening from CKD3 to CKD4, and not the correct 0.0045 monthly probability.

Correcting this has a reasonable effect upon the company base case ICER, worsening it from £18,893 per QALY to £20,907 per QALY.

4.2.1.4 Modelling errors: Combined effect

Correcting the three modelling errors identified above improves the company base case ICER from £18,893 per QALY to £16,810 per QALY.

4.2.2 Correspondence between written submission and cited sources

4.2.2.1 Association between K+ and all-cause mortality

The company literature review of its second submission in section 6.3.4.1 (page 53) notes that:

> "*Of the five SLRs/MAs that reported on both serum potassium levels and mortality only two provided enough information to establish the association between serum potassium levels and mortality risk*": Kovesdy et al[9] and Hoppe et al.[10]

It goes on to note that the meta-analysis of Kovesdy et al[9] assessed 42,170 patients with CKD over a mean follow-up of 6.9 years. The relationships between serum potassium and the adjusted hazard ratio are presented as figure 4 of the second company submission. But the company does not present the accompanying figures in Kovesdy et al that show an increased risk of CV mortality and ESRD among those with serum potassium outside the reference 4.2 mmol/L.

Section 6.3.4.2 notes that 10 single studies were identified, stating that 8 found a positive association between serum potassium and mortality in patients with CKD. The section focusses upon a subset of 5 single studies: Furuland et al,[14] Luo et al,[15], Provenzano et al,[39] Garlo et al.[22]

The McEwan et al[16] AstraZeneca[ii] sponsored conference abstract is not included in the company SLR of sections 6.3.4.1 and 6.3.4.2, though oddly there is passing reference to it in the conclusions of section 6.3.4.3. For it not to appear in the company SLR but to be the source that the company relies upon in its economic modelling seems odd.

[ii] Manufacturer of sodium zirconium cyclosilicate

There is very little detail of the analyses performed by McEwan et al[16] in the conference abstract, though as with Kodesdy et al [9] an association between increased potassium, increased MACE events and increased mortality is graphed.

The ERG thinks that given the company SLR and the above the natural source for the estimates of the association between potassium and mortality is meta-analysis of Kovesdy et al.[9] But the estimates are an association and do not imply a direct causality. It is also unclear to what extent the estimates reflect chronic hyperkalaemia and if so the relevance of this to the current setting. Also, in the light of the modelling of higher potassium increasing the risks of CV events and CKD progressions, applying these estimates within the company model will double count any effects of elevated potassium on all-cause mortality.

4.2.2.2 All-cause mortality from Kovesdy et al [9]

The hazard ratios for all-cause mortality associated with serum potassium sourced from Kovesdy et al[9] is sourced from supplementary Figure 10A for the age 65+ subgroup. Perhaps due to the logarithmic vertical axis the company estimates differ quite markedly from the ERG estimates (Table 16).

Table 16. Serum potassium and all-cause mortality: Age 65+: Kovesdy et al

K^+	Company	ERG
$K^+ = 5.25$	1.12	1.07
$K^+ = 5.75$	1.24	1.14
$K^+ = 6.25$	1.36	1.22

The ERG finds it difficult to see how the company values can be correct. In Figure 10A the value for K+ = 6.25 lies at or slightly below the midpoint between hazard ratios of 1.0 and 1.5. In the light of the vertical axis being on the log scale, the midpoint between hazard ratios of 1.0 and 1.5 must be less than 1.25.

If the ERG values are applied this worsens the company scenario analysis ICER from £33,238 per QALY to £36,761 per QALY.

4.2.2.3 Costs sourced from Kerr et al [37]

While there is some read across between some elements of the direct CKD3 and CKD4 costs, Kerr et al[37] aim to estimate the total annual cost and do not provide a total annual cost per CKD3 and CKD4 patient. They conclude that:

"The overall annual cost of CKD is estimated at £1.44 to £1.45 billion. This is equivalent to ≈£795 for every person recorded with a diagnosis of CKD in the QOF. Direct costs account for ≈85% and dialysis alone for 35% of the total expenditure."

Uprating the £795 annual cost for inflation yields an annual average cost of £938, with this encompassing CKD5 patients. Based upon Kerr et al, the £2,631 estimate of the company appears to be too high. The ERG will explore halving and doubling the company estimate.

The costs of MI and stroke correspond with the reference.

4.2.3 Correspondence between written submission and electronic model

The written submission provides a reasonable account of much of the electronic model.

Some aspects, such as Mid K^+ / Mid RAASi having virtually the same RAASi dosing and risks as High K^+ / Off RAASi could have been brought out more clearly.

The submission could also have been more forthright about the change in the model structure between the 1st cycle and all subsequent cycles and how this relates to the underlying CPRD data.

4.2.4 ERG commentary on model structure, assumptions and data inputs

4.2.4.1 Presentation of revised target group clinical effectiveness data

Unusually, the company does not present the OPAL-HK Part-A data for the revised target group in the clinical effectiveness section.

The company also does not present or particularly comment upon the OPAL-HK Part-B data for the revised target group in either the clinical effectiveness section or the economic section in terms of either potassium or RAASi or the assumed links between these. The randomised data and net effects during OPAL-HK Part-B is not presented in the submission.

OPAL-HK Part-B is only used to derive the poorly documented [redacted] hazard ratio of worsening hyperkalaemia for patiromer versus the comparator arm that is used to extrapolate patiromer use beyond the 1st cycle of the model.

4.2.4.2 OPAL-HK patients included in the analyses

The economic model is based upon an R analysis of OPAL-HK Part-A data (Table 17). It can be noted that the total number of patients reported this only [redacted], which is less than the 243 patients who were recruited to OPAL-HK.

Table 17. Patient flow through OPAL-HK

	Low		Mod/Sev		All	
	N	%	N	%	N	%
Enrolled Part A	92		151		243	
Completed Part A	85	92%	134	89%	219	90%
Eligible for Part B	16	17%	94	62%	110	45%
Randomised Part B	15	16%	92	61%	107	44%

The reason for this discrepancy may be that the R analysis of OPAL-HK Part-A data is of those with transition data from baseline to end of OPAL-HK Part-A. But this cannot entirely explain the discrepancy.

Patient withdrawals during part A were linked to adverse events (n=10), withdrawal of consent (n=5), high K+ (n=3), low K+ (n=1), CKD progression or dialysis (n=2) and not compliant or protocol variations (n=3). It seems probable that those without Part-A baseline and week 4 data will tend to have been patients who did less well on patiromer.

The data discrepancy between the 243 patients recruited to OPAL-HK Part-A, the 219 patients completing OPAL-HK Part-A and the [redacted] patients who had their OPAL-HK Part-A data analysed to provide the transition probabilities may have been mainly due to it being restricted to those with baseline to 4 week transition data. This may bias the analysis in favour of patiromer.

The CONSORT diagram for OPAL-HK Part-B in figure 4 of the original submission outlines that 52 were randomised to placebo and 55 to patiromer, with 30 (58%) and 45 (82%) remaining by arm at Part-B week 8. It is unclear how the company has analysed this data to derive the [redacted] hazard ratio for worsening of hyperkalaemia and what has been assumed for missing data within this analysis.

The proportion of patients who were eligible for and randomised to OPAL-HK Part-B is quite low, less than 50% of those recruited to Part-A. By definition, the subset of those randomised during OPAL-HK Part-B had responded reasonably well during OPAL-HK Part-A. It may be reasonable to apply the company estimated [redacted] hazard ratio for patiromer relative to withdrawal of patiromer and

treatment with placebo for the OPAL-HK Part-B patients. But it is far from obvious that that it is reasonable to apply it to the OPAL-HK Part-A patients, the majority of whom were not eligible to enter OPAL-HK Part-B.

4.2.4.3 Revised CRPD data analysis

The revised CPRD data analysis is key to the revised submission so warrants a reasonably full consideration.

It appears that the CPRD data is not restricted to the revised patient group of those with mild to moderate hyperkalaemia with heart failure and those with severe hyperkalaemia with and without heart failure.

Based upon the electronic model, the CPRD data is analysed based upon "*monthly serum potassium category transitions in CKD patients initiating from RAASi index date*". In other words the baseline of the analysis is around when patients initiate RAASi. The patient transitions between potassium health states are then analysed, though in this context the CPRD database notes that [redacted]% of potassium records were missing. There is no analysis presented of patient transitions between RAASi health states by K^+ health states.

The 2016 European Society of Cardiology guidelines note that initiation of RAASi can increase potassium. Heart failure patients with severe hyperkalaemia, $K^+ \geq 6.0$, may require short term cessation of potassium retaining agents and RAASi, but this should be minimised and RAASi should be carefully reintroduced as soon as possible while monitoring potassium.

The CPRD data for CKD3 and CKD4 patients has [redacted] patients and [redacted] patients respectively with a $K^+ \geq 6.0$ at baseline when initiating RAASi. As a consequence, it may be questionable quite how many of these patients correspond to the revised patient group.

This also seems to be logically inconsistent with the underlying modelling assumptions. The underlying modelling assumption is that those with $K^+ \geq 6.0$ are off RAASi. But the baseline CPRD data for patients with $K^+ \geq 6.0$ seems to relate to those initiating RAASi. In essence the company assumes that those with a high potassium are off RAASi, but to estimate the transition probabilities for these patients uses CPRD data from patients with $K^+ \geq 6.0$ who are initiating RAASi.

It also seems likely that since RAASi can increase potassium, those with a high potassium when initiating RAASi are likely to remain with a high potassium. But this is not really the data that is required. The data that is required would seem to relate to, or at a minimum include, those on established RAASi who progress to some level of hyperkalaemia.

Separately for CKD3 and CKD4 there are four sets of CPRD transitions data (Table 18): those initiating RAASi with $K^+<5.0$, those initiating RAASi with $5.0\leq K^+<5.5$, those initiating RAASi with $5.5\leq K^+<6.0$, those initiating RAASi with $K^+\geq 6.0$. For current modelling purposes the first two groups are combined into those initiating RAASi with $K^+<5.5$. The patient numbers in each group at initiation of RAASi is as below.

For reasons that are not clear to the ERG the company restricts the data set to patients with at least 12 months of baseline data at the time of CKD diagnosis.

Table 18. CPRD patient numbers initiating RAASi

Baseline K^+	$K^+<5.5$	$5.5\leq K^+<6.0$	$K^+\geq 6.0$
CKD3	[redacted]		
CKD4			

The bulk of the CPRD data relates to those with $K^+<5.5$ at initiation of RAASi. There are reasonable patient numbers at baseline for CKD3 patients with $K^+\geq 6.0$ at initiation of RAASi, but the number of CKD4 patients with $K^+\geq 6.0$ at initiation of RAASi is very small. The transitions from $K^+\geq 6.0$ to better K^+ health states are key to the cost effectiveness estimates.

For reasons of space the ERG only presents the CPRD patient transitions for the group initiating RAASi with $K^+\geq 6.0$ at initiation of RAASi. Note that the general tailing off in patient numbers is in part due to patients improving from $K^+\geq 6.0$ but is mainly due to censoring in the overall CPRD data set and the total number of patients with data falling as the months progress (Table 19).

Table 19. CPRD monthly patient transitions among those with K+≥6.0

	CKD3			CKD4		
Month	$K^+<5.5$	$5.5\leq K^+<6.0$	$6.0\leq K^+$	$K^+<5.5$	$5.5\leq K^+<6.0$	$6.0\leq K^+$
0						
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						
32						
33						
34						
35						
36						

There is some patient churn, with patients both entering and leaving $K^+ \geq 6.0$. But it is possible that the patients tending to churn into and out of $K^+ \geq 6.0$ tend to be the same patients. It is possible that those initiating RAASi while having a $K^+ \geq 6.0$ tend to remain with a $K^+ \geq 6.0$. It is not possible to determine whether this is or is not the case. But the key point is that, if the ERG has interpreted the CPRD data set correctly, for whatever reason these patients are initiating RAASi with $K^+ \geq 6.0$. These patients may be hard to treat or unusual in some other way, but it is not obvious to the ERG that their data is relevant to the revised target group and particularly not to the [redacted]% of the revised target group with heart failure.

There is also a modelling error in that the simple averaging across the 49 months also includes months in which there are no patients, for which the probabilities of improving and of worsening are assumed to be zero. This is incorrect.

The ERG thinks that the simple average is also incorrect: e.g. the [redacted] CKD4 patients at baseline combined have the same weight as the [redacted] CKD4 patients at month 40. There may be no definitively correct means of averaging these transitions (Table 20), but to the ERG an average weighted by the number of patients with data for each month seems the most appropriate. The differences in transition probabilities estimating using the company unweighted average and the ERG weighted average are presented below (Table 21), the probabilities of remaining in the same health state being a residual so that the transition probabilities sum to 100%.

Table 20. Company simple averaging of CPRD transition probabilities

	CKD3			CKD4		
From\To	K^+<5.5	5.5≤ K^+<6.0	6.0≤K^+	K^+<5.5	5.5≤ K^+<6.0	6.0≤K^+
K^+<5.5	99.7%	0.3%	0.0%	99.0%	0.9%	0.1%
5.5≤ K^+<6.0	12.1%	87.5%	0.4%	9.9%	89.1%	1.0%
6.0≤K^+	11.7%	2.4%	85.9%	7.7%	4.2%	88.1%

Table 21. ERG weighted averaging of CPRD transition probabilities

	CKD3			CKD4		
From\To	K^+<5.5	5.5≤ K^+<6.0	6.0≤K^+	K^+<5.5	5.5≤ K^+<6.0	6.0≤K^+
K^+<5.5	99.6%	0.3%	0.0%	98.7%	1.1%	0.1%
5.5≤ K^+<6.0	12.8%	86.8%	0.4%	12.7%	86.2%	1.1%
6.0≤K^+	13.1%	2.8%	84.2%	10.8%	5.1%	84.1%

The weighted averaging results in higher monthly probabilities of improving, particularly for CKD4 patients and those with K^+≥6.0, as would be expected. Applying the ERG weighted averages worsens the company base case ICER from £18,893 per QALY to £21,433 per QALY.

4.2.4.4 CPRD data: company assumption that patients can only improve by 1 health state

For the 2nd cycle of the model onwards the company model assumes that patients can only improve to neighbouring health states (Table 22). It sets the CPRD probabilities of worsening and improving by more than one health state to 0%. The CPRD probabilities for these transitions are simply added to the neighbouring probabilities of worsening / improving by one health state.

Table 22. Company CPRD transition probabilities: 2nd cycle onwards

	CKD3			CKD4		
From\To	K^+<5.5	5.5≤ K^+<6.0	6.0≤K^+	K^+<5.5	5.5≤ K^+<6.0	6.0≤K^+
K^+<5.5	99.7%	0.4%	..	99.0%	1.0%	..
5.5≤ K^+<6.0	12.1%	87.5%	0.4%	9.9%	89.1%	1.0%
6.0≤K^+	..	14.1%	85.9%	..	11.9%	88.1%

The main effect of this is to prevent patients in the placebo arm improving from High K^+ / Off RAASi to Low K^+ / Full RAASi in a single cycle and forcing them to transition through the Mid K^+ / Mid RAASi health state, which as noted elsewhere is little better than the High K^+ / Off RAASi health state.

This is not an error. It is the model structure chosen by the company, and is as per the model diagram of Figure 11 of the company submission. But the CPRD data shows patients making this transition. The ERG can think of no reasonable justification for this model structure.

The company model has been built with this change in structure between the 1st cycle and all subsequent cycles. The ERG cannot revise the company model so that the model structure of the 1st cycle is applied to all subsequent cycles.

Using the ERG cross check model rebuild suggests that not making the assumption that patients can only improve to neighbouring health states worsens the ICER from £18,523 per QALY to £21,811 per QALY, or by around 20%. Similarly, if the ERG weighted averaging of the CPRD transitions is applied the ERG model rebuild suggests an ICER of £20,958 per QALY. Not making the assumption that patients can only change to neighbouring health states worsens this to £24,943 per QALY, or by around 20%.

4.2.4.5 CPRD data analyses undertaken but not presented

It can be noted that the table of contents for the Excel file of the company CPRD data analysis contains the following (Table 23):

Table 23.Company CPRD analyses undertaken

1	Monthly serum potassium category transitions and probability in CKD stage 3 and 4 patients initiating RAASi (from RAASi initiation date)
2	Monthly serum potassium category transitions and probability in CKD stage 3 patients initiating RAASi (from RAASi initiation date)
3	Monthly serum potassium category transitions and probability in CKD stage 4 patients initiating RAASi (from RAASi initiation date)
4	Mean RAASi dose (in terms of standardized doses) by CKD stage and serum potassium category
5	CKD stage progressions in patients initiating on optimal RAASi dose and remaining on optimal until end (Table 5a)
6	CKD stage progression in patients who discontinued RAASi and remained discontinued until end of record (Table 5b)
7	CKD progression in patients with no record of RAASi treatment at any point during the study period (Table 06)
8	Demographics across four sub cohorts
9	Matched Summary
10	Demographics for matched cohorts Table 05a and Table 06 (Optimal RAASi vs No RAASi)

1 1	Standard differences in matched cohorts of interest (Table5a & 6)
i) 1 2	CKD progression in table 05a and Table 06 matched 1:1 caliper excluding incident comorbidties Demographics for matched cohorts Table 05a and Table 5b (Optimal RAASi vs Discontinued RAASi)
i) 1 3	CKD progression in table 05a and Table 05b matched 1:1 caliper excluding incident comorbidties Demographics for matched cohorts Table 05a and Table 5b (Optimal RAASi vs Discontinued RAASi)
i) 1 4	CKD progression in table 05a and Table 05b matched 1:1 caliper excluding incident comorbidities Demographics for matched cohorts Table 05a and Table 5e (Optimal RAASi vs Suboptimal RAASi)
i) 1 5	CKD progression in table 05a and Table 05e matched 1:1 caliper excluding incident comorbidties CKD progression in table 05a and Table 05e : Sub cohort with Cardiovascular conditions

Only the 1st three analyses are included in the Excel file and only the 1st three contribute to the revised company submission. But other elements could help support the company base case assumptions, such as the mean RAASi dose by CKD stage and serum potassium category. The assumptions around this are central to the company modelling and CPRD data supporting these assumptions could reduce the uncertainty around these elements. Elements 5 and 6 could be used to support the data inputs derived from Xie et al,[18] though this might require more thought and information as to the relevance of the CPRD patients' data to the position sought.

4.2.4.6 Association between potassium and RAASi use

In CS1 the company presented (Figure 14) an analysis CPRD data of hyperkalaemia and RAASi discontinuations. In the opinion of the ERG this data suggests that fewer patients who experience a hyperkalaemia event may cease RAASi than implied by the company modelling assumptions.

Figure 14. CRPD RAASi cessation after hyperkalaemia: CS1

The FAD of the assessment of sodium zirconium cyclosilicate for treating hyperkalaemia [TA599][17] noted that in the cost effectiveness modelling of the association between RAASi use and events:

> *"The company modelled an association between use of RAAS inhibitors and the risks of mortality, hospitalisation and major adverse cardiovascular events… based on odds ratios from … Xie et al. The committee recalled and accepted evidence from the clinical and patient experts that maintaining RAAS inhibitor therapy is likely to be beneficial for certain patients … The committee did not see robust evidence of the effect of sodium zirconium cyclosilicate on RAAS inhibitor use. However, it was aware that clinicians are encouraged to stop RAAS inhibitor treatment in people with serum potassium levels of 6.0 mmol/litre and above."*

The FAD of the assessment of sodium zirconium cyclosilicate for treating hyperkalaemia [TA599] further noted that:

> *"The committee and the clinical experts at the committee meetings agreed that RAAS inhibitors would be used in the NHS for many people with serum potassium levels 5.0 mmol/litre and above, and would be stopped when serum potassium levels are 6.0 mmol/litre and above. At levels of serum potassium below 6.0 mmol/litre, clinicians would likely recommend reducing, rather than stopping, the RAAS inhibitor. This is because the perceived benefits of being on treatment outweigh the risks of having a serum potassium level between 5.0 mmol/litre and 6.0 mmol/litre. The committee noted that some people stop RAAS inhibitors for reasons other than hyperkalaemia."*

The perfect mappings between:

- Low K+ / Full RAASi, Mid K+ / Mid RAASi and High K+ / Off RAASi among those without heart failure, and
- Low K+ / Full RAASi, Mid K+ / Off RAASi and High K+ / Off RAASi among those with heart failure.

may not be entirely warranted, with the equivalence of Mid K+ and Off RAASi among those with heart failure being particularly open to question. The company has not presented evidence on K^+ and RAASi use in the revised patient population of OPAL-HK.

4.2.4.7 Association between potassium and all-cause mortality

The FAD of the assessment of sodium zirconium cyclosilicate for treating hyperkalaemia [TA599][17] noted that in the cost effectiveness modelling of the association between serum potassium and events:

> *"In its base case, the company modelled an association between serum potassium levels and the risks of mortality, hospitalisation and major adverse cardiovascular events using observational studies. The committee recalled that the observational studies supporting this assumption did not establish that lowering serum potassium improved outcomes. Also, it was aware that the underlying causes of hyperkalaemia may have led to poor outcomes rather than the hyperkalaemia itself. Importantly, it had not been presented with evidence that lowering serum potassium in chronic hyperkalaemia prolongs life. The committee concluded that it was not appropriate to assume that lowering serum potassium prolongs life in people with chronic hyperkalaemia, based only on observational studies relating a surrogate end point to adverse outcomes … The committee concluded that it was appropriate to use the scenario analysis removing the association between serum potassium and adverse outcomes in its decision making."*

The ERG also thinks it may be significant that the DIAMOND trial (n=2,388) primary outcome measure[iii] is:

> "*Time to first occurrence of CV death or CV hospitalization (or equivalent in outpatient clinic) [Time Frame: 6 months to 2.5 years]. To determine if patiromer treatment of subjects who developed hyperkalemia while receiving RAASi medications will result in continued use of RAASi medications in accordance with heart failure (HF) treatment guidelines and thereby decrease the occurrence of the combined endpoint of cardiovascular (CV) death and CV hospitalization events compared with placebo treatment*."

If the avoidance of hyperkalaemia led to an immediate direct reduction in deaths among heart failure patients within 2 years via a route other than CV events and CKD progression, as in the current company model, this might need to be taken into account in the design of the DIAMOND trial. It might also tend to argue for these direct hyperkalaemia deaths being either a part of the combined primary endpoint, or at a minimum a secondary outcome measure or a part of a combined secondary outcome measure.

4.2.4.8 Baseline proportion of patients who have had a prior CV event

The company model assumes that all are CV event free at baseline. This is invalid. Table 8 of the CS2 indicates that [redacted] of the revised OPAL-HK target group have had a prior MI at baseline. The

[iii] https://www.clinicaltrials.gov/ct2/show/NCT03888066

assumption that none have had a prior CV event biases the analysis in favour of patiromer. The ERG has not had time to quantify the size of this bias.

4.2.4.9 Relevant RAASi comparator

The original ERG report noted that those discontinuing RAASi would not remain untreated and that it was more appropriate to apply the relative risks of Xie et al[18] for the active comparator rather than those of placebo. The relative risks for the active comparator worsen the company base case ICER from £18,893 per QALY to £20,246 per QALY.

4.2.4.10Quality of life effects of CV events and Post CV

The quality of life multipliers for CV Events and post CV events are derived from Pockett et al.[33] This is a study of the quality of life effects among patients within 1 month of discharge from three UK hospitals after MI, stroke or unstable angina, and is sponsored by Roche. 1,176 post-MI patients, 898 unstable angina patients but only 29 stroke patients were enrolled in the study, with a mean age of 68 and 24% being diabetic. Quality of life was assessed through the EQ-5D-3L with an overall response rate of 62% at baseline, the response rate actually rising over the 6, 12 18 and 24-month follow-up period to 68%. The values for stroke and MI are reported in Table 24.

Table 24. Pockett et al Quality of life values

	MI			**Stroke**		
	n	QoL	(s.e.)	n	QoL	(s.e.)
Baseline	702	0.690	(0.011)	20	0.496	(0.081)
6 months	733	0.702	(0.014)	13	0.525	(0.118)
12 months	817	0.708	(0.011)	21	0.498	(0.082)
18 months	844	0.692	(0.012)	17	0.448	(0.103)
24 months	888	0.706	(0.011)	16	0.527	(0.101)

The company selects the baseline values for CV events and the 24 month values for post CV, combining them 35:65 to arrive at mean values of 0.564 for a CV event and 0.590 for post CV. This is reasonable. But the company then uses these as multipliers to condition the quality of life values of CKD3 and CKD4 patients. This is not reasonable.

In the light of a quarter of the patients being diabetics and having a similar mean age as the model baseline the ERG thinks it is more reasonable to apply these as quality of life values.

Perhaps surprisingly, applying these as quality of life values rather than as multipliers only worsens the company base case from £18,893 per QALY to £19,262 Per QALY.

4.2.4.11Patiromer treatment cessation

The company base case assumes all patients remain on patiromer for 1 year at which point all patients discontinue patiromer. The reason for this given by the company is that this reflects the longest treatment duration within the clinical trial programme, that of AMETHYST-DN.

The company also cites US claims data to yield average treatment durations of around [redacted] and [redacted]. The ERG is uncomfortable with the application of US claims data as this may not reflect probable use in the UK.

The CS1 also relied upon AMETHYST-DN, with the company fitting parameterised curves to the AMETHYST-DN patiromer discontinuation data. This extended to around 1 year by which point around 30% of patients had discontinued treatment. But the AMETHYST-DN Kaplan-Meier discontinuation curve was quite flat at this point as in Figure 15. It bears little relation to the company assumed base case patiromer discontinuation curve of the current submission.

Figure 15. OPAL-HK KM and AMETHYST-DN KM and parameterised discontinuation curves

Of the parameterised curves the log-normal has the best visual fit and the best information criteria, and the company applied this in its original base case.

The parameterised curves fitted to the AMETHYST-DN patiromer discontinuation data were extrapolated into the longer term as in Figure 16.

Figure 16. AMETHYST-DN parameterised discontinuation curves: Long term

The ERG thinks that in the light of the CS1 and the AMETHYST-DN data, the revised company base case that assumes all remain on patiromer for 1 year at which point all cease patiromer lacks credibility and is difficult to justify given previous company arguments.

The US claims data is interesting but of questionable relevance to the UK.

The company has not provided any account if why it has switched from the AMETHYST-DN curves of its original submission. The ACD to the original submission did not express an opinion on this. Consequently, the ERG will apply the company's AMETHYST-DN log-normal TTD curve[iv]. But in the light of the model estimating that patient benefits in terms of potassium status have largely converged between the arms after 5 years, a maximum treatment duration of 5 years will be applied.

[iv] This is implemented by the ERG in the company model by recording the estimated costs and QALYs for patiromer treatment durations of 1 month, 2 months, 3 months etc and weighting these by the proportions estimated to remain on patiromer treatment for 1 month, 2 months, 3 months etc using the AMETHYST-DN log-normal curve.

4.2.4.12 OPAL-HK Part-A, patient drop-outs, missing data and patiromer costing

The OPAL-HK is an unusual trial. It could be crudely characterised as having a Part-A which was designed to find patients whose hyperkalaemia improved over a period of 4 weeks. The improvement in hyperkalaemia is attributed to a response to patiromer. A little less than half of those enrolled both completed Part-A and were in some sense deemed to respond to patiromer. These patiromer responders were enrolled in Part-B, half being randomised to having their patiromer withdrawn. To the extent that these were responders to patiromer, it is perhaps unsurprising that they did relatively badly compared to those who remained on patiromer.

There submission does not consider the effects of lost to follow up and missing data within its analysis of OPAL-HK Part-A. There are concerns that the base case company analysis may be unduly favourable to patiromer if, in effect, it is assumed that those lost to follow up or with missing data at the end of OPAL-HK Part-A had the same experience as those not lost to follow up and with data at the end of OPAL-HK Part-A.

This raises a costing issue which is most simply seen through numbers needed to treat. As far as the ERG can see the electronic model costs the OPAL-HK Part-A patiromer use on the basis of 4 weeks cost. But the numbers needed to treat to be enrolled in OPAL-HK Part-B were 243/107=2.27. In the opinion of the ERG this argues for costing patiromer use during OPAL-HK Part-A as 2.27*4=9.08 weeks' patiromer treatment costs.

4.2.4.13Prescription costs

It is assumed that hospital prescription costs will only be incurred every 3 months. This could argue for 3 months drug costs being applied at the start of each quarter. But if hospital prescription costs are incurred every month this only worsens the company base case ICER from £18,983 per QALY to £19,236 per QALY.

4.3 Exploratory and sensitivity analyses undertaken by the ERG

In the light of the FAD to TA599, the company position and the ERG review of the McEwan et al abstract[16] and Kovesdy et al,[9] the ERG presents two sets of analyses.

- REV1: This does not apply the direct mortality multipliers associated with serum potassium levels, but retains its modelled effects upon RAASi use, cardiovascular events and CKD progression.

- REV2: This applies the direct mortality multipliers associated with serum potassium levels sourced from Kovesdy et al[9] by the ERG, in addition to the modelled effects of serum potassium upon RAASi use, cardiovascular events and CKD progression.

The first set of analyses may appear pointless, because the company base case estimated an ICER of £45,748 per QALY for this. But correcting the company model for the age weighting of quality of life values and correcting event cost multiplication by the cycle length improves this ICER to £27,559 per QALY.

The ERG further revises the company model along the following lines:

- REV3: Correcting the age weighting of quality of life values.
- REV4: Correcting the event cost multiplication by the cycle length.
- REV5: Correcting the CPRD averaging to remove "0%" probabilities for periods of no data, and applying observation weighted averages.
- REV6: Revising the Pockett et al CV event and post CV event QoL values from being multiplicative to being absolute values, but still subject to age weighting.
- REV7: Applying the company AMETHYST-DN time to discontinuation curve, but with a maximum treatment duration of 5 years which roughly corresponds to the convergence of serum potassium distributions between the arms.
- REV8: Assuming RAASi dosing for the Mid K^+ / Mid RAASi of 50% and that by implication the risks of events are midway between Low K^+ / Full RAASi and High K^+ / Off RAASi.
- REV9: Applying 1st cycle patiromer costs that reflect patiromer use during OPAL-HK Part-A in terms of the number needed to treat to progress to OPAL-HK Part B.

The ERG conducts the following sensitivity analyses:

- SA01: Applying the serum potassium direct mortality multipliers of the McEwen et al[16] abstract and the company mortality multipliers sourced from Kovesdy et al[9]
- SA02: Arbitrarily doubling and halving the company estimate of the hazard ratio of worsening hyperkalaemia for patiromer compared to usual care from [redacted] to [redacted] and [redacted], and also setting it to unity.

- SA03: Set the RAASi relative risks to unity to avoid double counting deaths directly attributed to hyperkalaemia.
- SA04: Assume an active comparator for RAASi relative risks rather than placebo.
- SA05: Assuming RAASi dosing for the Mid K^+ / Mid RAASi of 25% and 75% that of Low K^+ / Full RAASi.
- SA06: Retaining the company AMETHYST-DN treatment discontinuation curve but with a maximum treatment duration of 2 years.
- SA07: All patiromer patients remain on treatment for 5 years, 2 years, 1 year, and [redacted]
- SA08: Annual CKD3 and CKD4 costs halved and doubled.
- SA09: AE events require 2 GP visits
- SA10: Assuming no hospitalisations from hyperkalaemia.
- SA11: Monthly prescription costs.
- SA12: Time horizons of 5 and 10 years.

4.3.1 Effects of individual ERG changes to company base case

The effects of each of the ERG revisions to the company base case are in Table 25.

Table 25. Individual ERG revisions to company base case

Analysis	ERG revision	ICER
..	Company base case	£18,893
REV1	No direct K^+ SMRs	£45,748
REV2	ERG Kovesdy direct K^+ SMRs	£36,761
REV3	Age weighting QoL values correction	£15,426
REV4	Cycle weighting event costs correction	£18,553
REV5	CPRD probability averaging	£20,907
REV6	Pockett QoL values not multiplicative	£19,262
REV7	AMETHYST-DN patiromer dosing, max 5 years	[redacted]
REV8	Midpoint RAASi dosing	£21,052
REV9	OPAL-HK Part A patiromer dosing NNT	£20,578

REV1 & 3-9	ERG revised base case (A): No direct K^+ SMRs	£681k
REV2 & 3-9	ERG revised base case (B): ERG Kovesdy direct K^+ SMRs	£232k

The ERG revisions with the largest individual effects are assuming no direct potassium mortality multipliers, and dosing being as per the CS1 AMETHYST-DN curve but with a maximum of 5 years. The ERG model corrections typically improve the ICER, while the other changes worsen it by around 10% or so.

Collectively the ERG revisions seriously worsens the ICER: to £681k per QALY if there are no direct potassium mortality multipliers, and to £232k if the direct potassium mortality multipliers of Kovesdy et al[9] apply.

4.3.2 ERG revised analysis (A) and sensitivity analyses: no direct potassium SMRs

The ERG revised base case which does not apply direct K^+ SMRs results in the following model outputs (Table 26):

Table 26. ERG revised base case: No direct K+ SMRs

	QALYs	Costs	ICER
Patiromer Placebo	[redacted]		
Net	0.009	£6,346	£680,769

The ERG univariate sensitivity analyses are in Table 27:

Table 27. ERG scenario analyses: No direct K+ SMRs

Analysis	ERG revision	ICER
..	ERG revised base case (A)	£681k
SA01a	McEwan et al direct K^+ SMRs	n.a.
SA01b	Company Kovesdy et al direct K^+ SMRs	n.a.
SA02a	Patiromer HR worsening K^+ halved	£674k
SA02b	Patiromer HR worsening K^+ doubled	£695k
SA02c	Patiromer HR worsening K^+ unity	£789k
SA03	RAASi RR events unity	n.a.
SA04	RAASi active comparator	£2.1mn

SA05a	Mid RAASi 25% of Full RAASi	£402k
SA05b	Mid RAASi 75% of Full RAASi	£2.0mn
SA06	AMETHYST-DN patiromer dosing, max 2 years	[redacted]
SA07a	Patiromer dosing, all patients 5 years	
SA07b	Patiromer dosing, all patients 2 years	
SA07c	Patiromer dosing, all patients 1 years	
Sa07d	Patiromer dosing, all patients [redacted]	
SA08a	CKD3 and CKD4 costs halved	£675k
SA08b	CKD3 and CKD4 costs doubled	£692k
SA09	AE events require 2 GP visits	£683k
SA10	No HK hospitalisations	£712k
SA11	Monthly prescription costs	£698k
SA12a	5 year time horizon	Dominated
SA12b	10 year time horizon	£6.1mn

Unfortunately, due to the ERG implementation of the company AMETHYST-DN patiromer TTD curve within the model, the ERG has had insufficient time to run the probabilistic model.

4.3.3 ERG revised analysis (B) and sensitivity analyses: Kovesdy et al potassium SMRs

The ERG revised base case which apply the ERG Kovesdy et al [9] direct K^+ SMRs results in the following model outputs Table 28:

Table 28. ERG revised base case: ERG derived Kovesdy et al direct K+ SMRs

	QALYs	Costs	ICER
Patiromer Placebo	[redacted]		
Net	0.028	£6,479	£232,343

The ERG univariate sensitivity analyses are in Table 29:

Table 29. ERG scenario analyses: ERG derived Kovesdy et al direct K+ SMRs

Analysis	ERG revision	ICER
..	ERG revised base case (B)	£232k
SA01a	McEwan et al direct K^+ SMRs	£47,480
SA01b	Company Kovesdy et al direct K^+ SMRs	£166k

SA02a	Patiromer HR worsening K^+ halved	£230k
SA02b	Patiromer HR worsening K^+ doubled	£237k
SA02c	Patiromer HR worsening K^+ unity	£268k
SA03	RAASi RR events unity	£970k
SA04	RAASi active comparator	£303k
SA05a	Mid RAASi 25% of Full RAASi	£188k
SA05b	Mid RAASi 75% of Full RAASi	£301k
SA06	AMETHYST-DN patiromer dosing, max 2 years	[redacted]
SA07a	Patiromer dosing, all patients 5 years	
SA07b	Patiromer dosing, all patients 2 years	
SA07c	Patiromer dosing, all patients 1 years	
Sa07d	Patiromer dosing, all patients [redacted]	
SA08a	CKD3 and CKD4 costs halved	£229k
SA08b	CKD3 and CKD4 costs doubled	£238k
SA09	AE events require 2 GP visits	£233k
SA10	No HK hospitalisations	£242k
SA11	Monthly prescription costs	£237k
SA12a	5 year time horizon	£2.3mn
SA12b	10 year time horizon	£405k

Unfortunately, due to the ERG implementation of the company AMETHYST-DN patiromer TTD curve within the model, the ERG has had insufficient time to run the probabilistic model.

4.4 Conclusions of the cost effectiveness section

The ERG thinks that the CS1 is incomplete in its presentation of the OPAL-HK data that underlies the clinical effectiveness estimates for the 1st model cycle as taken from Part-A and the clinical effectiveness estimates for all subsequent cycles as taken from Part-B. This is not presented in the clinical effectiveness section of the CS1 and there is minimal presentation of it in the economic section. There is also no consideration of alternative analyses which could have been undertaken, and no consideration of the effects and handling of lost to follow up and missing data. This may introduce bias to the company analyses.

The ERG thinks that the comparison of OPAL-HK patients with those of the company CPRD analysis may not be valid. The patient characteristics appear very different and many if not all of the CPRD patients may have been initiating RAASi at baseline. At a minimum, the lack of a control arm in

OPAL-HK very much increases the uncertainty around the inferred net clinical effectiveness estimates with this rolling through to the uncertainty around the modelled net effects.

The company model contains three quite major errors. Correcting them improves the ICER for patiromer.

There are three main further sources of possible bias in the company submission:

- The assumption that elevated serum potassium has a direct causal effect upon mortality risks through a route other than increased risks of cardiovascular events and progression to end stage renal disease.
- The assumption that the association between elevated serum potassium and mortality risks can be multiplied with CKD standardised mortality multipliers.
- The assumption that treatment with patiromer will be limited to one year. This is entirely at odds with the previous company submission.

Other concerns and sources of bias include:

- The company model structure not permitting the patient transitions that were observed in the CPRD data, limiting patients to at best improving to the neighbouring health state each model cycle. ERG model validation work suggests that this may bias the ICER by 20% in favour of patiromer. The degree of bias cannot be stated definitively and the ERG cannot correct the company model for this.
- The company model assumes all patients have no history of cardiovascular events when the OPAL-HK data is that at baseline a substantial minority of patients had had an MI. This will bias the ICER in favour of patiromer. The ERG has not had time to quantify this.

It can also be noted that the company has redefined the target population to one that is very much narrower than the "*Adults with hyperkalaemia*" of the final scope, with the OPAL-HK data within the model for the company revised target population being limited to [redacted] patients.

5 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG revised analyses are tabulated in section 5.4 above. In brief the ERG presents two sets of analyses.

- The first assumes that there are no direct causal effects from potassium upon all-cause mortality. To the degree that any such effects apply these work through the effect of potassium on RAASi use, and thereby upon the probabilities of CV events and CKD progression.

- The second assumes that there are direct causal effects from potassium upon all-cause mortality, based upon the estimates of Kovesdy et al[9]. The base case of this modelling also includes the effect of potassium on RAASi use, and thereby upon the probabilities of CV events and CKD progression, so there will be some degree of double counting.

Within these analyses the ERG has made three reasonably major corrections to the company model, the combined effect of which is to improve the company base case ICER.

The other main change made by the ERG is to apply the company AMETHYST-DN treatment discontinuation curve for patiromer, but with a maximum treatment duration of 5 years due to the potassium distributions converging between the arms from this point.

The modelling that does not apply direct potassium mortality multipliers results in an ICER of £681k per QALY. This worsens somewhat to £2.1mn if those discontinuing RAASi receive another active treatment for their heart condition. Shorter patiromer treatment duration improves the ICER, but even the company's most optimistic estimate of [redacted] taken from US claims data results in an ICER well above conventional willingness to pay thresholds.

The modelling that applies the direct potassium mortality multipliers source from Kovesdy et al[9]results in an ICER of £232k per QALY. If these mortality multipliers are sourced from McEwan et al[16] the ICER improves to £47,480 per QALY, while applying the company values of Kovesdy et al[9] improves the ICER to £166k. The ICER worsens somewhat to £303k per QALY if those discontinuing RAASi receive another active treatment for their heart condition. Removing the double counting of effects in a scenario analysis which does not apply the RAASi relative risks of events worsens the ICER to £970k. Shorter patiromer treatment duration improves the ICER, but even the company's most optimistic estimate of [redacted] taken from US claims data results in an ICER that is notably above conventional willingness to pay thresholds.

All results show very little sensitivity to the hazard ratio of worsening potassium that the company estimates from OPAL-HK Part-B. This underlines that the main treatment effect occurs in the 1st model cycle, when the OPAL-HK Part-A data in the patiromer arm is set against the company CPRD analysis which is assumed to apply in the comparator arm.

Results are also insensitive to the ERG scenarios around CKD3 and CKD4 annual costs and adverse event costs. It is likely that the CKD3 and CKD4 annual costs would come more to the fore if the modelling were more aligned with the company base case assumptions.

Shorter time horizons of 5 years and 10 years significantly worsen the ICERs.

A possible source of bias may be the handling of patients who are lost to follow-up and of OPAL-HK Part-A missing data. It is possible that the company analysis only considers patients with both baseline and week 4 data. These patients may tend to have done better than those without week 4 data. Further information and scenario analyses on this may be warranted.

An unquantifiable bias in the modelling arises from the company assumption that after the 1st model cycle patients can only improve by a single health state. This is the intended company model structure, as shown in Figure 11 of its submission. It requires revision of transition probabilities that the company derives from the CPRD, with some being set to zero and others the summation of two transition probabilities. Within the ERG cross check rebuild of the company model applying the same CPRD probabilities in the 2nd and subsequent cycles as in the 1st cycle worsens the ICER by around 20%.

The company model assumes that in the revised target group no patients have had a prior CV event. In OPAL-HK around [redacted] of patients had had a previous MI. Not taking this into account biases the ICER in favour of patiromer.

6 END OF LIFE

End of life does not apply

7 OVERALL CONCLUSION

A number of concerns raised by the NICE committee have not been sufficiently addressed. The level of potassium leading to alteration of treatment is unclear; there is no further evidence provided to support patiromer extending life; and it remains unclear what the risk of progressing to end-stage renal disease is. There is some evidence to suggest that there may be disbenefits in terms of adverse outcomes and mortality when discontinuing RAASi treatments in CKD, however this is not unequivocal. The question of whether the benefits of starting RAASi therapy are the same as benefits forgone if RAASi therapy is stopped has not been addressed and this remains unclear.
An overarching question is whether the company has presented the clinical effectiveness data for the revised target group in sufficient detail. Is there enough supporting data on the changes in potassium and the assumed changes in RAASi, and also on lost to follow up and the handling of missing data? There is no detail in the clinical effectiveness section.

The key data for the patiromer arm of the model comes from OPAL-HK Part-A, a single arm study. The key data for the comparator arm comes from a company analysis of CPRD data.

- There might be placebo and other trial effects in OPAL-HK Part-A which would not be present in the CPRD data. Does this invalidate the comparison?
- The baseline patient characteristics of patients in OPAL-HK Part-A are hugely different from those of CPRD patients. Does this invalidate the comparison?
- Patients recruited to OPAL-HK Part-A were on RAASi at baseline. It appears that the patients of the CPRD data might have been initiating RAASi at baseline so might have rather different probabilities of hyperkalaemia and worsening of hyperkalaemia. Does this invalidate the comparison?

The ERG thinks that the other key economic issues are:

- Is an assumption of a maximum of 1 year of patiromer treatment based upon the duration of the AMETHYST-DN trial more reasonable than the previous company analysis and extrapolation of AMETHYST-DN data? If the previous company analysis and extrapolation of AMETHYST-DN data is more reasonable should a maximum treatment duration still be applied, and if so how long should it be and why?

- Is there a distinction between transient hyperkalaemia and chronic hyperkalaemia, and if so how might this affect any direct mortality multipliers for hyperkalaemia in the current setting?

- Is it reasonable to apply direct mortality multipliers for hyperkalaemia within a model which separately models its effects upon RAASi use, CV events and CKD progressions? If so, what is the most reasonable source for these estimates?

- Is it reasonable to combine direct hyperkalemia mortality multipliers of up to 2.95 with CKD mortality multipliers of up to 7.94 to arrive at combined mortality multipliers of up to 23.41, or does this double count the effects of the CKD mortality multipliers?

Other issues which could be described as secondary are:

- What RAASi does reduction is appropriate for the Mid K^+ / Mid RAASi health state and what effect will this dose reduction have upon the probabilities of events? The ERG thinks that the company assumed reduction of [redacted] is excessive, not supported by ESC guidelines and prefers a simple 50% reduction as a half-way house.

- Would those coming off RAASi have another active treatment initiated for their heart condition?

- Should the number needed to treat to get to OPAL-HK Part-B condition the first cycle patiromer drug cost?

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9 APPENDIX 1

Table 30. Overall summary of clinical trials presented in the CS2

Study	Design	Duration	Population	Potassium levels (mmol/L)	Intervention	Comparator	Primary outcomes
OPAL-HK	Single arm	Phase A: 4 weeks	CKD and hyperkalemia	5.1-<6.5	Patiromer	Placebo	-Change in serum K^+
	Randomised	Phase B: 6 weeks		Baseline: 5.5-<6.5 Post phase A: 3.8-<5.1			-Change in serum K^+
PEARL-HF	Randomised	4 weeks	History of heart failure, indication to initiate spironolactone therapy, and either (1) CKD or (2) history of hyperkalemia in the past 6 months lead to aldosterone antagonists/ angiotensin converting enzyme inhibitors/ angiotensin receptor blockers.	4.3–5.1	Patiromer	Placebo	Change in serum K^+
AMBER		4 weeks run-in	CKD with resistant hypertension and normal potassium levels	4.5-5.1	Spironolactone + patiromer	Spironolactone + placebo	
	Randomised	12 weeks +2 weeks safety follow-up					Proportion of participants remaining on

							spironolactone at Week 12
DIAMOND	Randomised	6 months - 2.5 years of follow up	Heart failure, mild-moderate CKD, high potassium or history of hyperkalemia in the past 12 months	>5.0	Patiromer	Placebo	Cardiovascular death or hospitalization

ERG addendum: Revised patiromer PAS and other company changes

1. Company revised analyses

The company has submitted additional analyses which:

1. Applies a second restriction to the patient group, to those with a baseline $K^+ > 6.0$ mmol/L.
2. Apply new treatment discontinuation curves estimated from US insurance claims data.
3. Increase the patiromer PAS from [redacted] to [redacted].

The ERG has not reviewed these in detail and has not cross checked the correctness of the company modelling, but provides comments below.

In the opinion of the ERG all of the critique of the main ERG report remains valid. The comments below should be read in conjunction with the main ERG report.

1.1 Further restricting the patient group to those with a baseline K+ > 6.0 mmol/L

This has two effects.

1. It changes the OPAL-HK patients selected for analysis.
2. It places increased reliance upon the CPRD data among patients with a $K^+ > 6.0$ mmol/L

1.1.1 Restriction to OPAL-HK patients with a baseline $K^+ > 6.0$ mmol/L

The second company restriction to the target patient group revises the patient numbers as follows, with the [redacted] CKD3 and [redacted] CKD4 patients with mid K^+ and heart failure now being excluded.

Table 01: OPAL-HK Part A Baseline patient distribution

	Low K^+		Mid K^+	High K^+	
Serum Potassium	$K^+<5.0$	$5.0\leq K^+<5.5$	$5.5\leq K^+<6.0$	$6.0\leq K^+$	Total
With HF					
CKD3	[redacted]				
CKD4					
Without HF					
CKD3	[redacted]				
CKD4					
Revised target population					
CKD3	..	..	..	[redacted]	
CKD4	..	..	..		

The further restriction of the patient group results in there only being data for [redacted] OPAL-HK patients. As per the main ERG report, it is unclear how missing data has been handled within the company analysis.

The company has clarified that the hazard ratio applied in the model was estimated from the previous target group and not from OPAL-HK data as a whole. The company has not revised its hazard ratio estimate to reflect its revised target group, apparently due to time constraints.

The further restriction of the patient also slightly changes the balance between CKD3:CKD4 from [redacted] to [redacted]. Within the model the CKD3 age banded SMRs have a hazard ratio of 2.56 applied to them to derive the corresponding CKD4 age banded SMRs. If it is questionable to combine these CKD SMRs with K^+ related SMRs, the effect of this will be that bit greater in the revised target group.

In terms of how this affects the transition probabilities applied within the patiromer arm during the first cycle of the model, the original transitions and transition probabilities are reproduced below.

Table 02: 1st cycle transition probabilities: Patiromer: Previously revised target population

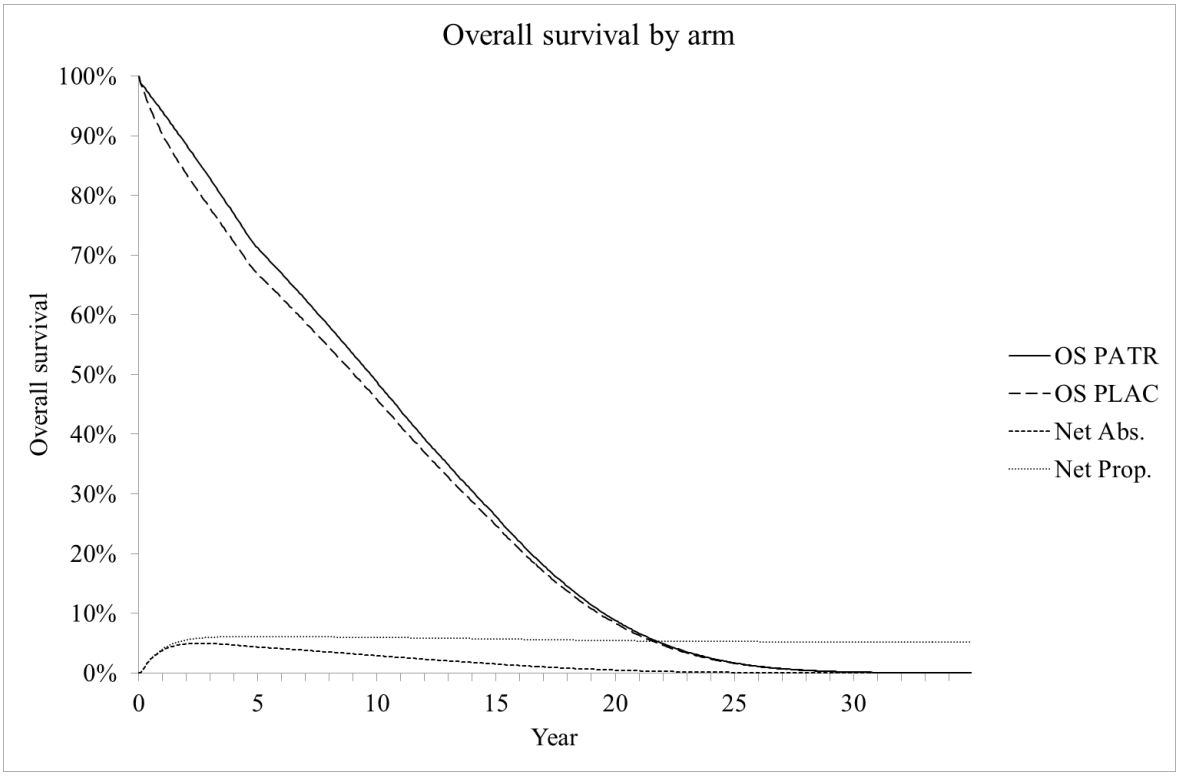
	CKD3			CKD4		
From \ To	Low K^+	Mid K^+	High K^+	Low K^+	Mid K^+	High K^+
HF patient transitions						
Mid K^+	[redacted]					
High K^+						
HF Free (NoHF) patient transitions						
Mid K^+	[redacted]					
High K^+						
Pooled patient transitions						
Mid K^+	[redacted]					
High K^+						
Pooled patient transition probabilities						
Mid K^+	[redacted]					
High K^+						

[redacted]

[redacted] Making this change to the original company model results in the net absolute survival

gain at 2 years increasing from around 3% to around 5% as graphed below, with the net proportionate survival gain going on to rise to around 6%. In other words the estimated number needed to treat to save one life within 2 years falls from around 33 to around 20.

Figure 01: Overall survival: Revised target group and original company assumptions



The above estimates are based upon the original company assumptions. If the company K^+ SMRs taken from Kovesdy are applied the absolute survival gains at 2 years of 0.7% estimated for the first revised target group increase to 0.9% with the second revision to the target group. These correspond to NNTs to save one life within 2 years of roughly 160 and 110.

1.1.2 CPRD patients with a $K^+ > 6.0$ mmol/L

The company CPRD data had the following numbers of patients with $K^+ > 6.0$ mmol/L at baseline:

- CKD3: [redacted]
- CKD4: [redacted]

The further restriction of the patient group to those with $K^+ > 6.0$ mmol/L at baseline severely restricts the CPRD patient numbers. It also slightly increases the proportion of patients with CKD4 at baseline, for whom the CPRD patient group at baseline is only [redacted].

1.1.3 Restricted patient group with a $K^+ > 6.0$ mmol/L: OPAL-HK vs CPRD

The main ERG report noted that the patient characteristics of the OPAL-HK patients were very different from those of the CPRD patients. The company has not supplied the corresponding table that

compares the patient characteristics of the [redacted] OPAL HK patients with the [redacted][1] CPRD patients of the revised target group, as well as the CPRD patient group as a whole. It would be reasonable to have supplied this, along with a further analysis of this data split by CKD status.

1.1.4 Restricted patient group with a $K^+ > 6.0$ mmol/L: Company model structure

As noted in the ERG report the company model structure does not permit the observed CPRD transition probability between High K^+ and Low K^+ from the second model cycle. High K^+ patients are restricted to improving to at best Mid K^+ each cycle. In the first revised target group the baseline balance between Mid K^+ ([redacted]) and High K^+ ([redacted]) was [redacted]. Within the ERG cross check model rebuild when, instead of the company model structure, the observed CPRD transition probabilities between High K^+ and Low K^+ were applied the ICER worsened by around 20%.

The second revised target group restricts the patient group to be 100% High K^+ ([redacted]). As a consequence, if the observed CPRD transition probability between High K^+ and Low K^+ are applied it seems very likely that the ICER for the second revised target group will worsen by more than the corresponding worsening of the ICER for the first revised target group.

1.2 Applying US insurance claims data patiromer discontinuation curves

The ERG remains unclear why the company proposes rejecting the AMETHYST-DN data when it argued strongly for in its first submission. US insurance claims data resource is typically not viewed as being representative of UK NHS resource use.

The ERG has not reviewed the discontinuation curves the company estimates from US insurance claims data. But in the opinion of the ERG, the ERG sensitivity analysis SA07d reasonably conforms to the previous company analyses that applied the average treatment duration of [redacted] as estimated from the US insurance claims data.

1.3 Revised patiromer PAS

Patiromer is available as a 30-day pack costing £300, providing an annual cost of £3,652 per patient. The old PAS of a discount of [redacted], which reduced the annual cost to [redacted] per patient, has been increased to the new PAS discount of [redacted], which reduces the annual cost to [redacted] per patient.

The ERG has updated its analyses to reflect the effect of the revised patiromer PAS.

1.3.1 Effects of individual ERG changes to company base case

The effects of each of the ERG revisions to the company base case are as below, with the results for the old patiromer PAS and the revised patiromer PAS being presented alongside one another.

[1] The calculation of the transition probabilities also include subsequent transitions into and out of $K^+ > 6.0$ mmol/L so are not formally restricted to the patients with baseline $K^+ > 6.0$ mmol/L, but the patient numbers involved each month decline over time.

Table 03: Individual ERG revisions to company base case

Analysis	ERG revision	Old PAS	New PAS
..	Company base case (June 2019)	£18,893	£15,346
REV1	No direct K^+ SMRs	£45,748	£31,317
REV2	ERG Kovesdy direct K^+ SMRs	£36,761	£26,073
REV3	Age weighting QoL values correction	£15,426	£12,530
REV4	Cycle weighting event costs correction	£18,553	£15,006
REV5	CPRD probability averaging	£20,907	£17,260
REV6	Pockett QoL values not multiplicative	£19,262	£15,646
REV7	AMETHYST-DN patiromer dosing, max 5 years	[redacted]	[redacted]
REV8	Midpoint RAASi dosing	£21,052	£17,313
REV9	OPAL-HK Part A patiromer dosing NNT	£20,578	£16,642
REV1 & 3-9	ERG revised base case (A): No direct K^+ SMRs	£681k	£504k
REV2 & 3-9	ERG revised base case (B): ERG Kovesdy direct K^+ SMRs	£232k	£174k

1.3.2 ERG revised analysis (A) and sensitivity analyses: no direct K^+ SMRs

The ERG revised base case which does not apply direct K^+ SMRs results in the following model outputs.

Table 04: ERG revised base case: No direct K^+ SMRs

		Old PAS		New PAS	
	QALYs	Costs	ICER	Costs	ICER
Patiromer Placebo	[redacted]	[redacted]		[redacted]	
Net	0.009	£6,346	£680,769	£4,703	£504,492

The ERG univariate sensitivity analyses are as below.

Table 05: ERG scenario analyses: No direct K^+ SMRs

Analysis	ERG revision	Old PAS	New PAS
..	ERG revised base case (A)	£681k	£504k
SA01a	McEwan et al direct K^+ SMRs	n.a.	n.a.
SA01b	Company Kovesdy et al direct K^+ SMRs	n.a.	n.a.

SA02a	Patiromer HR worsening K^+ halved	£674k	£499k
SA02b	Patiromer HR worsening K^+ doubled	£695k	£515k
SA02c	Patiromer HR worsening K^+ unity	£789k	£588k
SA03	RAASi RR events unity	n.a.	n.a.
SA04	RAASi active comparator	£2.1mn	£1.6mn
SA05a	Mid RAASi 25% of Full RAASi	£402k	£296k
SA05b	Mid RAASi 75% of Full RAASi	£2.0mn	£1.5mn
SA06	AMETHYST-DN patiromer dosing, max 2 years	[redacted]	
SA07a	Patiromer dosing, all patients 5 years		
SA07b	Patiromer dosing, all patients 2 years		
SA07c	Patiromer dosing, all patients 1 years		
Sa07d	Patiromer dosing, all patients [redacted]		
SA08a	CKD3 and CKD4 costs halved	£675k	£499k
SA08b	CKD3 and CKD4 costs doubled	£692k	£515k
SA09	AE events require 2 GP visits	£683k	£506k
SA10	No HK hospitalisations	£712k	£536k
SA11	Monthly prescription costs	£698k	£521k
SA12a	5 year time horizon	Dominated	Dominated
SA12b	10 year time horizon	£6.1mn	£4.5mn

1.3.3 ERG revised analysis (B) and sensitivity analyses: Kovesdy et al K^+ SMRs

The ERG revised base case which apply the ERG Kovesdy et al direct K^+ SMRs results in the following model outputs.

Table 06: ERG revised base case: ERG derived Kovesdy et al direct K^+ SMRs

		Old PAS		New PAS	
	QALYs	Costs	ICER	Costs	ICER
Patiromer Placebo	[redacted]				
Net	0.028	£6,479	£232,343	£4,848	£173,846

The ERG univariate sensitivity analyses are as below.

Table 07: ERG scenario analyses: ERG derived Kovesdy et al direct K^+ SMRs

Analysis	ERG revision	Old PAS	New PAS
..	ERG revised base case (B)	£232k	£174k
SA01a	McEwan et al direct K^+ SMRs	£47,480	£37,486
SA01b	Company Kovesdy et al direct K^+ SMRs	£166k	£125k
SA02a	Patiromer HR worsening K^+ halved	£230k	£172k
SA02b	Patiromer HR worsening K^+ doubled	£237k	£177k
SA02c	Patiromer HR worsening K^+ unity	£268k	£201k
SA03	RAASi RR events unity	£970k	£743k
SA04	RAASi active comparator	£303k	£228k
SA05a	Mid RAASi 25% of Full RAASi	£188k	£139k
SA05b	Mid RAASi 75% of Full RAASi	£301k	£227k
SA06	AMETHYST-DN patiromer dosing, max 2 years	[redacted]	
SA07a	Patiromer dosing, all patients 5 years		
SA07b	Patiromer dosing, all patients 2 years		
SA07c	Patiromer dosing, all patients 1 years		
Sa07d	Patiromer dosing, all patients [redacted]		
SA08a	CKD3 and CKD4 costs halved	£229k	£171k
SA08b	CKD3 and CKD4 costs doubled	£238k	£180k
SA09	AE events require 2 GP visits	£233k	£174k
SA10	No HK hospitalisations	£242k	£184k
SA11	Monthly prescription costs	£237k	£180k
SA12a	5 year time horizon	£2.3mn	£1.7mn
SA12b	10 year time horizon	£405k	£303k

ERG addendum: Revised patiromer PAS and other company changes

1. Patiromer discontinuation data

The first company submission argued that 1 year AMETHYST-DN was the most appropriate source of discontinuation data, with the company extrapolating using a fitted log-normal curve.

During the first assessment the ERG also fitted an exponential curve to the 2 month OPAL-HK Part B patiromer discontinuation data. The ACD does not comment upon this, but the short duration of the OPAL-HK data makes extrapolation using it quite uncertain.

The current company submission argues that 3 years' US insurance claims data is the most appropriate source of discontinuation data, with the company extrapolating using a fitted log-normal curve.

Figure 01: Patiromer Kaplan Meier discontinuation curves and parameterised curves

The US insurance claims data is driven to a significant degree by [redacted] of patients only receiving [redacted] of patiromer. The service setting, patient characteristics and reasons for discontinuation; e.g. adverse event, lack of efficacy, etc., are not presented for the US insurance claims data. The patient characteristics are unknown.

The extrapolated curves are as below.

Figure 02: Patiromer parameterised curves extrapolation

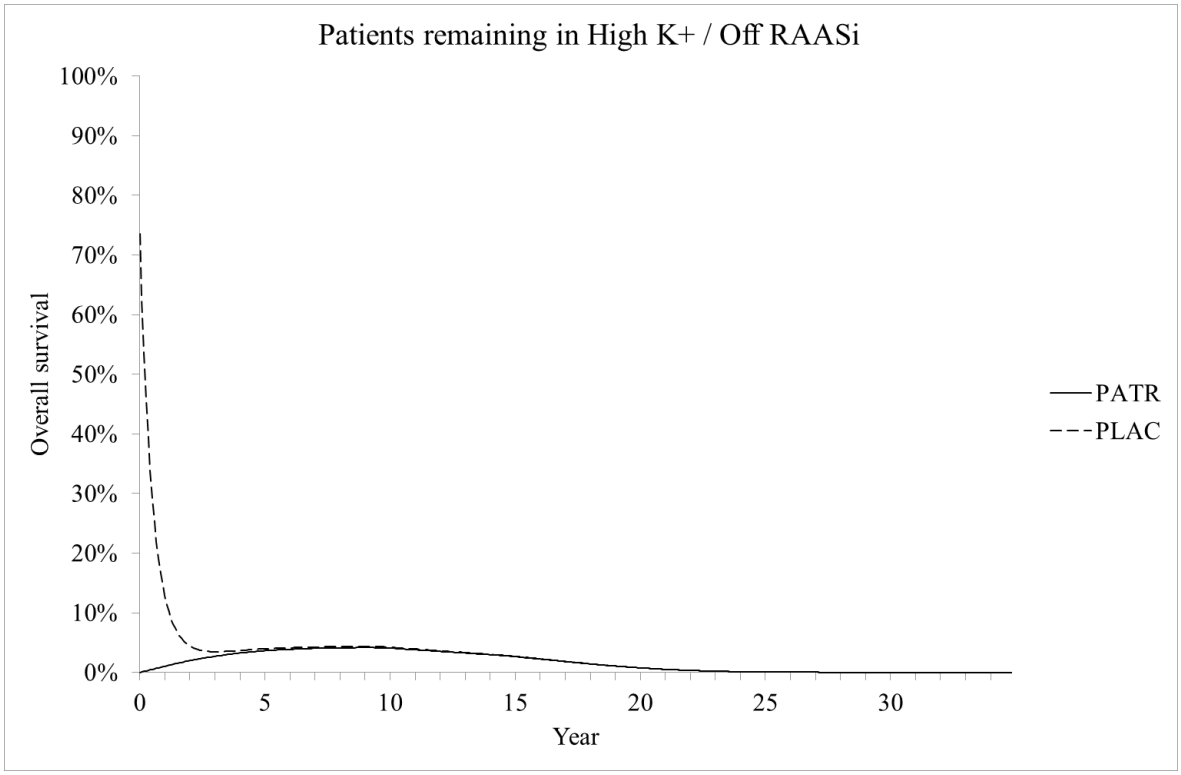
The proportions modelled as remaining on treatment at 1 month, 1 year and 3 years are as below.

Table 01: Patiromer parameterised curves proportions remaining on treatment

	1 month	1 year	3 years
AMETHYST-DN LogN	[redacted]	[redacted]	[redacted]
OPAL-HK Exponential	[redacted]	[redacted]	[redacted]
US insurance claims LogN	[redacted]	[redacted]	[redacted]

It should be noted that within the current company model, if patiromer patients are assumed to receive patiromer for the mean US claims duration of [redacted] the recurrence of severe hyperkalaemia and K^+>6.0mmol/L in the patiromer arm remains relatively low throughout. This also applies in the comparator arm from year 3-5.

Figure 03: Modelled hyperkalaemia recurrence in patiromer arm



All the above data is subject to the criticism that the patient data presented in the Kaplan Meier curves does not correspond with the company revised target population: patients with a baseline K^+>6.0mmol/L. Patients with a baseline K^+>6.0mmol/L and a good response may tend to remain on patiromer for longer than patients with less severe hyperkalaemia. As a consequence, all the above curves may overestimate patiromer discontinuations compared to the data that would result from analysing patients with a baseline K^+>6.0mmol/L.

2. Patiromer use during OPAL-HK Part-A among those eligible for OPAL-HK Part-B

The company accepts the ERG criticism about the OPAL-HK Part A NNT to be enrolled in OPAL-HK Part B. The ERG noted that OPAL-HK Part included 243 patients but only 107 met all eligibility criteria for Part-B, and so calculated a NNT to get into Part B of 243/107=2.27. The company has clarified that OPAL-HK included 102 patients with a Part-A baseline K^+<5.5mmol/L and that these patients were not eligible for Part B. As a consequence the NNT to enter into OPAL-HK Part B is only 141/107=1.32.

Quite what should be assumed for the 141-107=34 patients with an OPAL-HK Part A baseline K^+>5.5mmol/L who were not subsequently eligible for OPAL-HK Part-B remains a moot point. The implicit assumption may be that their experience would be the same as the average assumed for the comparator arm. If this group is in some sense harder to treat or came off RAASi so were not eligible for OPAL-HK Part B this may not be valid.

3. Missing data

The company has clarified that the revised patient group with K^+>6.0mmol/L at baseline is actually [redacted] patients, with [redacted] missing a serum potassium reading at the end of Part A. Patients with missing data have been excluded from the analysis; i.e. censoring has been treated as non-informative and these patients have implicitly been assumed to have the same experience as observed patients. The ERG will conduct a scenario analysis which assumes informative censoring, and that these patients did not improve during OPAL-HK Part A.

4. ERG sensitivity analyses

The main ERG report presents sensitivity analyses for the first revision to the target group (CS2) and the original company PAS. The ERG subsequently updated these analyses to reflect the revised upadacitinib PAS.

This document extends these to the second revision to the target group to be those with K^+>6.0 at baseline, CS3. It also revises the ERG base case to apply the 1.32 NNT patiromer costing.

The company originally applied the mean [redacted] US claims data treatment duration. It has since revised the electronic model to apply the fitted curve. The ERG does not understand the company implementation of this and has not cross checked its implementation. In the light or this, the ERG expands the scenario analyses using the ERG method to include application of the company US claims log-normal patiromer TTD curve and the ERG OPAL-HK exponential patiromer TTD curve.

Given the additional information on missing OPAL-HK Part A data for the second revised CS3 target group, the ERG expands the scenario analyses to include assumptions that this missing data reflects non-response with SA13a assuming this in CKD3 and SA13b assuming this in CKD4.

The company accepts that it is not appropriate to apply the K^+ SMRs, so the ERG only updates its revised base case (A).

Table 02: Revised ERG base case (A) and additional scenario analyses: CS Target population

		Patiromer TTD curve		
Analysis	ERG revision	AMETHYST	US Claims	OPAL-HK
..	ERG revised base case (A)	£232k	£4,405	£26,353
SA01a	McEwan et al direct K^+ SMRs	n.a.	n.a.	n.a.
SA01b	Company Kovesdy et al direct K^+ SMRs	n.a.	n.a.	n.a.
SA02a	Patiromer HR worsening K^+ halved	£230k	£4,353	£26,239
SA02b	Patiromer HR worsening K^+ doubled	£235k	£4,512	£26,584
SA02c	Patiromer HR worsening K^+ unity	£253k	£5,149	£27,975

SA03	RAASi RR events unity	n.a.	n.a.	n.a.
SA04	RAASi active comparator	£466k	£13,575	£47,624
SA05a	Mid RAASi 25% of Full RAASi	£167k	£389	£18,122
SA05b	Mid RAASi 75% of Full RAASi	£358k	£10,553	£39,292
SA06	AMETHYST patiromer dosing, max 2 years	[redacted]		
SA08a	CKD3 and CKD4 costs halved	£228k	£1,821	£23,635
SA08b	CKD3 and CKD4 costs doubled	£240k	£9,574	£31,791
SA09	AE events require 2 GP visits	£233k	£4,562	£26,589
SA10	No HK hospitalisations	£256k	£20,651	£43,395
SA11	Monthly prescription costs	£240k	£5,669	£28,313
SA12a	5 year time horizon	Dominated	£48,319	£185k
SA12b	10 year time horizon	£662k	£8,941	£49,407
SA13a	Missing data is CKD3 and no improvement	£253k	£6,473	£29,783
SA13b	Missing data is CKD4 and no improvement	£247k	£6,631	£29,617
		All on patiromer until specified cut-off		
SA07a	Patiromer dosing, all patients 5 years	[redacted]		
SA07b	Patiromer dosing, all patients 2 years			
SA07c	Patiromer dosing, all patients 1 years			
Sa07d	Patiromer dosing, all patients [redacted]			