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ABSTRACT

INTRODUCTION

Chronic Kidney Disease (CKD) is associated with significantly increased morbidity and mortality. No specific treatment of the underlying condition is available for the majority of patients, but ACE-inhibitors (ACE-I) and angiotensin II-receptor blockers (ARB) slows progression in albuminuric CKD. Adding a mineralocorticoid receptor-antagonist (MRA) like spironolactone has an additive effect. However, Renin-angiotensin-aldosterone system (RAAS)-blockade increases the risk of hyperkalaemia which is exacerbated by the presence of CKD. Thus, hyperkalaemia may prevent optimal use of RAAS-blockade in some patients.

This project hypothesizes that adding a potassium binder (patiromer) allows for improved RAAS-blockade including the use of MRA, thereby reducing albuminuria in patients with albuminuric CKD where full treatment is limited by hyperkalemia.

If successful, the study may lead to improved treatment of this subgroup of CKD patients. Furthermore, the study will examine the feasibility of potassium binders in patients with CKD.

METHODS AND ANALYSIS

An open label, randomised controlled trial including 140 patients with eGFR 25-60 mL/min/1.73m^2, a urinary albumin/creatinine ratio (UACR) > 500 mg/g (or 200mg/g if diabetes mellitus) and a current or two previous plasma-potassium >4.5mmol/L. Patients who develop hyperkaliemia >5.5 mmol/L during a run-in phase, in which RAAS-blockade is intesified with the possible addition of spironolactone, are randomised to 12-month treatment with maximal tolerated ACE-I/ARB and spironolactone with or without patiromer.

The primary endpoint is the difference in UACR measured at randomisation and 12 months compared between the two groups. Secondary endpoints include CKD progression, episodes of hyperkalaemia, blood pressure, eGFR, markers of cardiovascular disease, diet and quality of life.

ETHICS AND DISSEMINATION

This study is approved by The Central Denmark Region Committees on Health Research Ethics (REFNO 1-10-72-110-20) and is registered in the EudraCT database (REFNO 2020-001595-15). Results will be presented in peer-reviewed journals, at meetings and at international conferences.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study uses a robust randomised controlled design, investigating if patiromer, through increased RAAS-blockade, can reduce albuminuria in patients with CKD and hyperkalaemia.
- The selective run-in phase only allows randomisation of patients where RAAS-blockade is proven to be limited by hyperkalaemia.
- A one-year follow-up will examine long-term tolerability of patiromer in CKD patients, testing if such a treatment regime is feasible.
- The limited sample size and one-year follow-up that does not allow for evaluation of 'hard' endpoints such as time to renal death or decrease in eGFR

INTRODUCTION

Chronic kidney disease (CKD) is among the most common and fastest growing diseases worldwide. It is associated with substantial comorbidity and mortality[1]. No curative treatment is currently available for the majority of CKD patients, and current interventions aim to halt or slow the natural progression of the disease. Albuminuria is a well-established predictor of end stage renal disease (ESRD). The risk of progressing to ESRD is up to 75 times higher among CKD patients with significant albuminuria compared to patients without albuminuria[2]. Several studies have shown that treatment with inhibitors of the renin-angiotensin-aldosterone system (RAAS) such as angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) not only lower blood pressure (BP) but also reduce albuminuria and slow CKD progression in both diabetic and non-diabetic CKD[3,4]. RAAS-blockade, in particular the use of ACE-I or ARB, is considered first-line treatment in patients with CKD, hypertension and albuminuria. The response is dose-dependent, and higher doses further reduce albuminuria[5]. Evidence suggests that the change in albuminuria correlates with the protection provided and therefore serves as a surrogate marker of disease progression[6,7]. Other studies have shown that reducing albuminuria in CKD patients lowers the cardiovascular risk[8]. Angiotensin II stimulates vascular smooth muscle cells, monocytes, fibrosis, inflammation, oxidative stress and vascular endothelial damage[9–13], and RAAS-blockade may have anti-fibrotic and anti-inflammatory effects[14,15]. In concordance, treatment leads to regression of left ventricular hypertrophy, an independent and strong marker of cardiovascular morbidity and mortality[16,17]. Cardiovascular risk can be further assessed from arterial stiffness (pulse wave velocity (PWV) and central BP) and blood biomarkers such as endothelin-1, NT-proBNP and TnI[18–20].

Aldosterone is a regulator of blood pressure through fluid and electrolyte homeostasis primarily from its action on ENaC channels and the Na+/K+ pump in the distal nephron and collecting ducts. Evidence strongly support an additional, direct pathophysiological role for aldosterone in the development of kidney and cardiovascular disease. Mineralocorticoid receptor (MR) activation induces inflammation, oxidative stress and fibrosis[21,22] and leads to glomerulosclerosis and cardiac fibrosis [23,24], which increases the risk of kidney function decline, albuminuria and cardiovascular disease. Blood aldosterone levels increase as estimated glomerular filtration rate (eGFR) deteriorates, and CKD is considered a state of relative hyperaldosteronism [25,26]. RAAS blockade using ARB/ACE-I insufficiently lowers the aldosterone level, and plasma concentration typically rises after 6-12 months of treatment; a phenomenon known as aldosterone escape [27]. MR-antagonists (MRAs) such as spironolactone or eplerenone alone or in combination with ACE-I/ARB reduces albuminuria by 25-40%[28,29].This effect is likely independent from and not driven by a reduction in BP alone[30]. A large number of studies have suggested potential benefits of treatment with MRA in CKD with persistent albuminuria. This notion was emphasized by the recent FIDELIO-DKD trial. The trial found that the addition of the MRA finerenone to ACE-I/ARB treatment in patients with CKD, type 2 diabetes and albuminuria significantly reduced the risk of renal outcomes (time to renal death, eGFR decline over time and/or death from renal causes) and cardiovascular risk[31].

Despite inherent benefits, RAAS blockade may be hampered by fear of hyperkalaemia. Severe hyperkalaemia may cause life threatening cardiac arrhythmias[32]. CKD results in a reduced ability to excrete potassium and patients are at significant risk of hyperkalaemia, especially in the presence of other comorbidities such as diabetes, heart failure (HF) and old age[33,34]. Treatment with ACE-Is or ARBs as well as MRAs further inhibits renal potassium excretion, augmenting the risk of hyperkalaemia[35,36]. Thus, high potassium levels often limit the optimal use of RAAS blockade in many CKD patients[34]. Novel third generation nonsteroidal selective MRAs such as finerenone has a lower risk of causing hyperkalaemia compared to older generation MRAs, but the number of patients discontinuing treatment due to

hyperkalaemia is still 2.5-fold higher compared to placebo[31]. Other ongoing clinical trials evaluating the effect of ACE-I or ARB combined with MRAs in CKD exclude patients with hyperkalaemia[21]. Thus, CKD patients with hyperkalaemia may be barred from the potential benefits of complete RAAS blockade including MRA.

In recent years, novel potassium-binding agents have been introduced. These include patiromer (Veltassa), a non-absorbable sodium-free powder for oral use, which binds potassium in the gastrointestinal tract, thereby increasing fecal excretion and lowering plasma (P) potassium[34]. *In vitro* studies have shown the potassium-binding capacity of patiromer to be 1.5-2.5 times that of traditional polystyrene sulfonate based potassium-bindings agents[37]. Patiromer significantly lowers P-potassium in CKD patients with eGFR 15-60mL/min with or without RAAS blockade[38,39]. Several studies have proposed the use of patiromer to allow for increased RAAS blockade in patients with CKD, hyperkalaemia and suboptimal RAAS blockade treatment. A analysis conducted in the UK concluded that patiromer had a beneficial cost-utility profile in such patients[40]. Patiromer was well-tolerated by patients in clinical trials. A pooled analysis of 666 patients, of whom 149 received treatment for >12 months, found no serious adverse reactions related to patiromer. Although hyperkalaemia may also be addressed through dietary restrictions, these have limited effect and a profound impact on patient's lifestyle and freedom. They further limit the intake of fresh fruits and vegetables normally considered to reduce the risk of cardiovascular disease[41]. It is currently unknown whether treatment with patiromer will allow for an increased consumption of such foods with a potential benefit on health and quality of life (QoL).

Aims and Hypotheses

This trial aims to establish if the use of a potassium binding agent (patiromer) in patients with moderate or advanced CKD (eGFR 25-60 mL/min/1.73m^2) leads to a reduction in albuminuria by the concomitant intensified use of RAAS-inhibitors (losartan and/or spironolactone). In secondary analyses, it will examine the effects of this approach on markers of cardiovascular function, dietary habits (including fruit and vegetable intake) and quality-of-life as well as the potential risks; monitoring blood pressure, episodes of hyperkalaemia and renal function.

Thus, the study will address the hypotheses that treatment with patiromer and intensified RAAS-blockade in patients with eGFR 25-60mL/min, albuminuria and a tendency of high potassium levels leads to:

1. A significant reduction in albuminuria when compared to patients in maximal RAAS-blockade as allowed by their P-potassium levels without patiromer
2. A significant reduction in albuminuria during treatment
3. A reduced PWV and left ventricular mass (LVM) along with improvement in blood biomarkers of cardiovascular function
4. An increased intake of healthy foods and higher quality of life

METHODS AND ANALYSIS

The MorphCKD study is an investigator-initiated, multicenter, open label, parallel group, superiority randomised controlled trial (RCT). Randomisation is performed as a block randomisation with 1:1 allocation.

The study will include patients from the outpatient clinics at the renal departments in Aarhus, Aalborg, Holstebro and Viborg, Denmark. The primary site, Aarhus, will also include patients from the diabetes outpatient clinic and within the hospital public admission area (see under "recruitment").

The study is divided into a run-in phase of 2-8 weeks followed by randomisation to a treatment phase involving 52 weeks of treatment with or without patiromer (see figure 1). The run-in phase will determine if maximized RAAS-blockade, including treatment with an MRA, leads to clinically significant hyperkalaemia (>5.5mmol/L) despite dietary counselling, thereby identifying the patients that may benefit from treatment with patiromer who qualify for randomisation to the treatment phase.

FIGURE1 **Flowchart of the trial design**

Participants

A total of 140 patients fulfilling the eligibility criteria below will be included.

Inclusion criteria:

1. Age 18-80
2. eGFR 25-60 mL/min/1.73m^2
3. Current P-potassium >4.5mmol/L *or* P-potassium >4.5mmol/L twice within 24 months
4. Urine albumin-creatinine ratio (UACR) >500mg/g *or* 200mg/g and diabetes

Exclusion criteria:

1. Known allergies to both ACE-I and losartan or spironolactone or patiromer
2. A history of kidney transplantation or active on the waiting list
3. ESRD (defined as the need for dialysis or kidney transplantation)
4. Any renal disease requiring or being expected to require specific immunosuppressive therapy for the duration of the trial
5. Pregnancy or inability to use contraception
6. Regular need for trimethoprim or NSAIDs
7. Current treatment with aliskiren
8. Disseminated cancer disease
9. Addison's disease
10. HF defined as ejection fraction < 40% or active treatment at a HF clinic or similar
11. Porphyria
12. Severe constipation with a regular use of laxatives or previous recurrent ileus
13. Fructose/galactose-intolerance
14. Severe liver insufficiency (Child-Pugh Score B-C)
15. Clinically significant severe renal artery stenosis
16. Investigator's evaluation that participation in the trial may cause serious harm to the patient (e.g. previous severe acute kidney injury (AKI) in relation to RAAS-blockade)
17. Initiation of an SGLT2-inhibitor within 30 days prior to inclusion

Interventions and randomisation

Dietary counselling to limit potassium intake is provided at inclusion. Patients not treated with ACE-I/ARB at inclusion will commence losartan 50mg/day for the run-in phase (step 1 below). Patients already treated

with ACE-I/ARB will continue this treatment at the current dose with the addition of an MRA (step 3 below). Based on tolerability, RAAS-blockade is increased in four steps:

1. Losartan 50mg/day
2. Losartan 100mg/day
3. Losartan 100mg/day or current ACE-I/ARB + spironolactone 25mg/day
4. Losartan 100mg/day or current ACE-I/ARB + spironolactone 50mg/day

Blood samples and home BP monitoring will be performed 1-2 weeks after each dose change and the patient is contacted by phone to record home BP and to inform about blood results. Tolerability is evaluated by P-potassium, creatinine, BP and side effects. The dose of losartan or spironolactone is reduced to the previous step and the patient proceeds to randomisation if P-potassium is >5.5mmol/L.

Patients that reach step four without significant hyperkalaemia are excluded from the study.

Patients completing the run-in phase with an episode of significant hyperkalaemia (>5.5mmol/L), a UACR > 300mg/g or 150mg/g and diabetes, a most recent P-potassium >4.0mmol/L and no other contraindications (e.g. AKI) to continued and increased RAAS-blockade are randomised to open-label treatment in one of two regimes:

1. Patiromer with stepwise dose-increase/-decrease with increased RAAS-blockade in addition to standard clinical care and dietary counselling. Patiromer will be dosed based on P-potassium and tolerability until maximal RAAS-blockade with P-potassium ≤5.5mmol/L.
2. No patiromer (control group) with standard clinical care, dietary counselling and maximal RAAS-blockade with P-potassium ≤5.5mmol/L

Permuted block randomisation with random varying block sizes of 2, 4 and 6 is used to allocate patients to the patiromer- or control group at a 1:1 ratio, stratified by albuminuria >1000mg/g (Yes/No) and diabetes (Yes/No). The Random allocation list is generated and uploaded to REDCap by an independent service provider (Clinical Trial Unit, Dept. of Clinical Medicine, Aarhus University) maintaining proper concealment of randomisation.

After randomisation, patients are followed for up to 52 weeks with blood sampling and outpatient visits every 3 months and allowing for additional visits if considered clinically required based on the assessment of the local investigator.

The dose of study drugs (RAAS-blockade) is determined by the four steps previously described, aiming at the possible highest step with a P-potassium <5.5mmol/L. Dose increases are only allowed on planned consultations (phone or outpatient clinic), but decreases may be introduced at any point depending on the results of blood test, BP or other adverse effects. In the patiromer group, patiromer is prescribed as tolerated at a daily dose of 8,4g, 16,8g or 25,2g in order to maintain P-potassium <5.5mmol/L. The dosing of patiromer is increased concomitantly with any increase in RAAS-blockade, unless P-potassium is ≤ 4.6 mmol/L. RAAS-blockade is decreased if hyperkalaemia >5.5mmol/L is recorded at the highest tolerated patiromer dose.

All study drugs are stopped at the last outpatient visit after 52 weeks. Patients entering the study on ACE-I/ARB will continue this treatment without patiromer. Blood and urine samples are collected 4 weeks later for the evaluation of eGFR, albuminuria and P-potassium after discontinuation of study drugs.

Additional medication

Any inhibitors of the RAAS-system other than those mentioned above as well as additional potassium binders are not allowed during the study period. Hypertension is treated aiming at a systolic BP between 110-130mmHg in both groups. All anti-hypertensives, except additional inhibitors of the RAAS-system, may be used as per the discretion of the treating physician. Loop and thiazide diuretics may be prescribed for hypertension and/or fluid retention. Hypomagnesemia is treated with oral magnesium supplements. Study drugs including losartan, spironolactone and patiromer can be reduced or suspended depending on blood pressure, hyperkalaemia as per protocol or any side effects deemed to outweigh the benefit of the treatment (e.g. AKI, gastrointestinal intolerance, biochemical abnormalities). SGLT2-inhibitors may not be prescribed during the trial.

Endpoints

The primary endpoint is:

- The difference in UACR from randomisation to end of treatment compared between the two groups. This is measured as an average of two morning spot UACR samples collected both at randomisation and at the last study visit

Secondary endpoints include:

- The difference in 24h urine albumine from randomisation to end of treatment compared between the two groups
- The difference in albuminuria (evaluated by morning spot UACR and 24h urine collection) at the end of treatment between the two groups
- The difference in the extent of RAAS-blockade (ACE-I/ARB and MRA) at the end of treatment between the two groups
- The difference in kidney function (eGFR and urine creatinine clearance) at the end of treatment and the changes in eGFR from randomisation to end of treatment between the two groups
- The difference in BP (ambulatory and 24h) at the end of treatment and the changes in BP from randomisation to end of treatment between the two groups
- The difference in PWV/pulse wave analysis (PWA) at the end of treatment and the changes in PWV/PWA from randomisation to end of treatment between the two groups
- The difference in LVM (ECG) at the end of treatment and the changes in LVM from randomisation to end of treatment between the two groups
- The difference in cardiac biomarkers at the end of treatment and the changes in cardiac biomarkers from randomisation to end of treatment between the two groups
- The difference in P-potassium at the end of treatment between the two groups
- The difference in the number of episodes with severe hyperkalaemia (>6.2mmol/L) from randomisation to end of treatment between the two groups
- The difference in the number of episodes with AKI (KDIGO stage 1-3) from randomisation to end of treatment between the two groups
- The difference in the questionnaire base assessment of the consumption of fruits and vegetables at the end of treatment and the changes in fruits and vegetables consumption from randomisation to end of treatment between the two groups
- The difference in QoL at the end of treatment and the changes in QoL from randomisation to end of treatment between the two groups

Sample size and power calculation

The study will include 140 patients under the assumption that 30% will not meet randomisation criteria, leaving 98 participants (49 in each group) for randomisation. This will provide 80% power to detect a clinically relevant 1.5-fold greater reduction in the amount of albuminuria in the patiromer group compared to the control group, with a risk of type 1 error of 0.05 assuming an 80% coefficient of variation in the change of UACR[42]. The study will continue as long as the number of randomised participants is expected to be no less than 55% (54 patients), which will provide power to detect a 1.75-fold greater reduction in the amount of albuminuria.

Recruitment

All patients from the renal outpatient clinics at the three centers and all patients serviced by Aarhus University Hospital (covering a population of approx. 900,000) who have provided a blood sample within the last 2 years are prescreened. The prescreening algorithm uses the LABKA II database containing the result of all blood samples analyzed within the relevant regions and identifies patients aged 18-80 with a history (within 2 years) of P-potassium > 4.5mmol/L, UACR >200mg/g and eGFR 25-60 mL/min/1.73m^2. The resulting patient records including blood samples are manually screened by a local investigator. Potentially eligible patients are contacted with the participant information by letter. In addition, patients in the nephrology outpatient clinics in Aarhus, Aalborg, Holstebro and Viborg and the diabetes outpatient clinic in Aarhus are contacted in person at their next appointment. After written informed consent they are screened for inclusion including blood samples to ensure that they meet the inclusion criteria at the time of inclusion.

Data collection

The patient's medical history including current treatment is registered at inclusion. Patient height is measured at inclusion and weight at every visit. A physical examination including vital signs are performed at inclusion, randomisation and final visit. A urine sample for UACR is collected at inclusion, twice at randomisation and final visit for the primary outcome and at every three-month-visit during the treatment phase. If possible, a morning sample is preferred. Timed 24h urine samples are collected at randomisation and 52 weeks. P-potassium, creatinine, eGFR and sodium are measured at inclusion, weekly during the run-in phase, during titration of RAAS-blockade and every 3 months in the outpatient clinic. P-total CO_2 and ionized calcium are measured at inclusion, randomisation and every 3-month visit. P-magnesium is measured at all visits during the maintenance phase in the patiromer group. Cardiac biomarkers (Endothelin-1, NT-proBNP and TnI), ECG, blood samples evaluating biomarkers of fruit and vegetable consumption (lutein, β-cryptoxanthin, α- and β-carotene, lycopene and vitamin C[43]), PWV and PWA as a measure of arteriosclerosis, SF-36[44] questionnaire measuring QoL, MyFood24[45] food diaries and 24h ABPM are all performed at randomisation and 52 weeks. Please refer to table 1 for a timeline of data collection.

Table 1: Study timeline and visits

Timeline (weeks)	**Inclusion -8**	**-6**	**-4***	**-2***	**t_0 Randomisation /(exclusion)**	**2***	**4***	**13**	**26**	**39**	**52**	**56**
STUDY PHASE:	**Run-in phase**				**Maintenance phase**							
INTERVENTIONS:												
Increased RAAS-blockade	→											
Patiromer-treatment (intervention group) and/or RAAS-blockade titration					RAAS with patiromer → / RAAS with out patiromer →							
ASSESMENTS:												
Eligibility screen	x											
Informed consent	x											
Pregnancy test (if fertile woman)	x											
Medical record	x											
Physical examination	x				x						x	
Weight	x				x			x	x	x	x	
Dietary counselling	x											
P-Creatinine, eGFR, P-Potassium, P-Sodium	x	X	x	x	x	x	x	x	x	x	x	x
P-magnesium (patiromer group)					x	x	x	x	x	x	x	
P-total CO_2, P-ionized Calcium	x				x			x	x	x	x	x
BpTRU® or similar local ABPM	x				x			x	x	x	x	
24h ABPM					x						x	
At-home ABPM		x	x	x		x	x					
UACR	x	x	x	x	xx			x	x		xx	x
Questionnaire – Side effects	x				x			x	x	x	x	
Questionnaire – SF-36[44] (QoL)					x						x	
Questionnaire – MyFood24[45]					x						x	
Carotenoids and C-Vitamin					x						x	
24h urine collection					x						x	
PWA/PWV					x						x	
ECG					x						x	
Endothelin-1, NT-proBNP and TnI					x						x	
Pill count					x (x)			x	x	x	x	
TYPE OF VISIT:												
Phone consultation		x	x	x		x	x					
Outpatient clinic	x				x (x)			x	x	x	x	

*Only If RAAS-blockade has been increased. During the run-in phase, the patient proceeds directly to randomisation if P-potassium > 5.5mmol/L.

Questionnaires and food diaries may be filled in online prior to the visit using REDCap or the Myfood24 website. An invitation with a unique link is sent to the patient via e-mail. Alternatively, they are completed with the assistance of the investigator on the day of the visit. Vital signs are measured using BpTRU® or equivalent at every visit and with an automatic digital blood pressure monitor at home for phone consultations. Pill counts are done at every visit to assess compliance. Patients are asked if and to what extent they have taken the study drugs at all contacts. Adherence techniques such as morning routines and medication in relation to meals are discussed if required.

Blood and urine biochemical analyses are performed at local biochemical laboratories using standard automated assay. Reference intervals have been standardized on a national level and all Danish laboratory uses these for reference. The UACR at randomisation and final visit is calculated as an average of 2 measurements to minimize variability[46]. The patient is carefully instructed to provide morning urine sample. Urine collection, including 24h urine collection, is performed by the patient at home prior to the randomisation and 12-month-visit. PWV and PWA is measured using the Sphygmocor system. Applanation tonometry is applied on the carotid, femoral, and radial artery. A minimum operator index of 85 is used. Length is measured as 80% of the distance from the carotid artery to the femoral artery. Home BP is measured three times in the morning and evening for three days. An average of day 2 and 3 is reported. Twenty-four-hour ABPM is recorded with measurements every 30 minutes. ECG is recorded by an experienced nurse. Each centers' personnel will be trained and instructed in all study procedures by the study PI.

Data management

Study data, including adverse events (AE) and serious adverse events/reactions (SAE/SAR), will be collected and managed using REDCap electronic data capture tools hosted at Aarhus University[47,48]. All data are entered electronically by the local investigator at each site. Original data is stored in the patients' electronic records or in a participant file. Participant files are stored in a secure place and kept for 15 years after end of study. Data will be exported from RedCap for final analysis using a suitable statistical software package.

Statistical methods

The primary endpoint is analyzed using a t-test comparing the differences in UACR between randomisation and 12 months between the two groups. The ratio between groups with confidence intervals and the P-value will be reported. A secondary two-way repeated measures ANOVA including UACR at randomisation, 3, 6, 9 and 12 months is performed and the P-value is reported. The data is analyzed as intention-to-treat with a secondary treated-as analysis. A separate t-test will compare the difference in UACR from randomisation to the time patiromer is discontinued. Data from patients discontinuing treatment before 12 months of follow-up is included using carry-over of the last available dataset before stopping. Missing data for the primary endpoint will be replaced by the most recent observation carried over. Previous studies have shown that most of the effect of increased RAAS-blockade on albuminuria is seen early after treatment initiation with little change thereafter, suggesting that the UACR at the closest possible time-point is a fair proxy measure of the 12-month value. Imputations may be applied for secondary analyses if feasible. All variables are analyzed for normal distribution and skewed data are log-transformed when appropriate. Non-normally distributed variables on both the standard- and log-scale are analyzed using non-parametric testing. Repeated measurements are analyzed by a linear model when feasible.

Safety measures

Adverse events, defined as any medical occurrence in a trial participant without regard to the possible cause, are collected from when the consent has been signed and until final visit. Participants are asked about any new such events at each contact and will fill out a questionnaire at each outpatient clinic visit. Serious adverse events will be reported directly to the PI and sponsor. Investigators will evaluate any adverse event's possible relation to study drugs based on temporal relationship, known mechanism of action and known side effects for classification of adverse reactions.

The following individual safety-outcomes are evaluated by the investigator at each contact:

1. A decline in eGFR > 30% from inclusion, 20% from previous visit or 5 mL/min/1.73 m^2 from previous visit if eGFR < 25 mL/min/1.73 m^2 should lead to a temporary reduction or discontinuation of spironolactone and/or ACE-I/ARB (Losartan or other)
2. An increase in P-creatinine > 100% from the previous visit, the possible need for acute dialysis or other findings suggesting severe AKI leads to admittance for treatment
3. If P-potassium is >5.5mmol/L on maximal patiromer dose, RAAS-blockade is reduced by 50% or spironolactone is discontinued. P-potassium is repeated within two days or as soon as possible
4. If P-potassium is > 5.9mmol/L, ACE-I/ARB and spironolactone are temporarily discontinued. P-potassium is repeated within one day
5. If P-potassium is > 6.2mmol/L, the patient is admitted and treated in accordance with local guidelines. ACE-I/ARB and spironolactone are temporarily discontinued.
6. If P-magnesium is < 0.6mmol/L, the patient is treated with oral magnesium supplements as per discretion of the local investigator and P-magnesium is repeated within 7-10 days.
7. If P-magnesium is < 0.5mmol/L despite maximal tolerated magnesium supplement treatment, patiromer is discontinued and p-magnesium is repeated within two days

I case of events 1-5 above, RAAS-blockade may the reinitiated at the previous dosage if and when kidney function is restored and/or P-potassium < 5.4mmol/L following discontinuation or dose reduction of the RAAS inhibitor.

The study is halted if at any point a significant higher number of the following events are observed in patiromer group compared to the control group:

1. Events with hyperkalaemia > 6.2mmol/L
2. Patients with eGFR < 15 mL/min/1.73 m^2 or requiring dialysis for > 3 months
3. Deaths
4. Admissions (except events due to hyperkalaemia, covered in point 1)
5. A combined endpoint of the four above

These outcomes will be evaluated by the PI after each such event using Fischer's exact test.

Study oversight and monitoring.

The study is monitored by the GCP unit at Aarhus and Aalborg University Hospitals. It does not include an independent data monitoring committee due to the open label design, limited number of sites and continuous monitoring of significant safety outcomes as described above. Any systematic or serious risk to the participants will be immediately apparent to the PI and sponsor. The study may be audited by the Danish Medicines Agency. Safety reports are forwarded to the Danish Medicines Agency and The Central Denmark Region Committees on Health Research Ethics annually.

Patient and Public Involvement statement

Participants were involved in changes to the design of the study. They preferred less transportation and fewer hospital visits. From their feedback, some visits were replaced by phone consultations and blood sampling prior to most visits was made possible at 28 local sites across the Central Denmark Region. Once the trial has been published, participants will be informed of the results via e-mail using the REDCap distribution tool.

Current trial status

The first participant was included in the study late August 2020 and is planned to continue until March 2022. At the time of writing (August 2021), 56 participants have been included and 14 have been randomised to the treatment phase. Enrollment was halted from December 2020 due to the lockdown following COVID-19 in Denmark but was resumed in March 2021.

ETHICS AND DISSEMINATION

The study protocol was initially approved by The Central Denmark Region Committees on Health Research Ethics (REFNO 1-10-72-110-20) on June 23rd 2020 with the latest version being approved on July 1st 2021 and by the Danish Medicines Agency on June 10th 2021. The research will be conducted in accordance with the Helsinki Declaration and Good Clinical Practice. All protocol amendments will be approved by the Ethics Committee and Danish Medicines Agency before implementation when required and all investigators will be notified directly.

A local investigator will obtain a written, informed consent from all participants prior to inclusion. The consent form follows the standards and template from the Danish National Committee on Health Research Ethics.

All principal investigators and sponsor will have access to the cleaned dataset.

Trial results, positive as well as negative, will be submitted for publication in peer reviewed, international journals and presented at conferences and meetings.

DISCUSSION

This study investigates the feasibility of daily treatment with an established potassium-binding agent in moderate and severe CKD patients with albuminuria. It will examine if treatment enables increased RAAS-blockade and leads to a greater decline in albuminuria. Previous studies have shown that patiromer allows for the use of spironolactone in CKD patients with hyperkalaemia[49]; however, it is unknown if the approach leads to an effect on albuminuria in this distinct group of patients. The study aims to fill this gap in current knowledge.

The open label study design should closely mimic the clinical decision making and the delicate task of balancing hyperkalaemia and renoprotection. This will provide information on the practicability and potential benefits of such an approach in patients with hyperkaliemia otherwise barred from full pharmaceutical blockage of the RAAS-system. Of note, the study includes a one-year follow-up to examine potential complications to long-term treatment including non-adherence, hypotension, AKI and other adverse effects. Additional strengths of the study include the extensive list of outcomes and the RCT design. Furthermore, the unique and selective run-in phase only allows randomisation of patients that are proven to potentially benefit from treatment with a potassium binder, which should be in accordance with clinical practice. In addition, since all included interventions involves established and approved drugs, the road to implementation ought to be short.

There are some potential limitations and challenges. First, the small sample size and one-year follow-up does not allow for evaluation of harder renal endpoints such as progression to end-stage renal disease or a 50% reduction in eGFR. However, albuminuria is a widely accepted surrogate marker of disease progression in albuminuric CKD. In addition, it is closely correlated to the protective effects of RAAS-blockade. Second, the study is not powered to detect minor differences in the change in albuminuria; however, it will be able to identify a 1.5 times greater reduction in UACR. Third, the one-year follow-up may challenge patient adherence to treatment. Fourth, the open-label design may introduce selection bias in physicians' use of non-investigational drugs. Standard operating procedures on concomitant treatment, including instructions for the use of diuretics, are established to mitigate such bias. The open label design does provide some potential benefits, allowing for a setup that closely resembles clinical practice and for a more practical safety algorithm to prevent potentially life-threatening hyperkalaemia. The primary outcome is based on biochemical findings and thus, we believe that it is very unlikely that this is affected by the open label design.

The power calculations are based on the number of randomised patients after the run-in phase. It is assumed that 30% of the included patient will not be eligible for randomisation; however, the accuracy of this number has not been established and thus, the number of actual randomised patients may be different. The extensive screening algorithm, which is based on results from blood samples in all 4 outpatient clinics and the entire Aarhus University public admission area, will however ensure that all eligible candidates are invited to the study. This is particularly important as the number of patients with an eGFR between 25 and 60 mL/min/1.73m^2, concomitant and significant albuminuria, and previous or current P-potassium >4.5mmol/L may be limited.

The study is partly based on the assumption that adding MRA to ACE-I/ARB treatment in this subgroup of patients is beneficial if hyperkalaemia can be controlled, supported by the recent results of the FIDELIO-DKD trial [31]; however, the underlying principle is also applicable to patients in which maximal dosing of ACE-I or ARBs is barred by hyperkalaemia. If this study establishes the feasibility of such approach, it should pave the way for larger studies with hard endpoints to corroborate the use of potassium binders in patients currently excluded from maximal RAAS-inhibition.

ROLES AND RESPONSIBILITIES

Authors' contributions: HB conceived the study and had editorial rights on the protocol. FHM was first author of the protocol, primary investigator in Aarhus and implemented the study on all sites as the coordinating investigator. CDP held an advisory role in the writing of the protocol. All authors including JHC contributed to refinement of the study protocol including the design and approved the final manuscript.

Sponsor and funder roles:

HB (sponsor) conceived the study and the design hereof. Vifor Pharma has been allowed access to and commented on the protocol before funding the study, but had no decisive influence on the design. Vifor will be informed on the progression of the study and on SAEs relating to patiromer, but will not have any influence on the execution, the data analyses, the interpretation of data, or the decision to submit results.

Lead investigators: A lead investigator (senior nephrologist) will be identified at each site. The lead investigator is responsible for identification of potential study subjects, recruitment hereof, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure. The lead investigator may appoint sub-investigators to act on his or her behalf.

FUNDING

The work is supported by Vifor Pharma who delivers patiromer free of charge and has funded the project with a research grant. The project has also received funding from Aarhus University as a Research training supplement.

Study administration, financial statement and conflicts of interest

Neither the study sponsor (HB), PI (FHM) nor any other investigators have any financial involvement with the primary funder (Vifor Pharma) or the primary study drug (patiromer). HB has previously participated in advisory boards and meetings hosted by Vifor Pharma. These have all been reported to the Danish Medicines Agency. The authors have no further conflicts of interest to declare.

REGISTRATIONS

Registration: EudraCT: 2020-001595-15

Sponsor protocol code: 270389-010520

Protocol version 15, June 26th 2021

First approval from Ethics Committee (The Central Denmark Region Committees on Health Research Ethics): June 23rd 2020

First approval from the Danish Medicines Agency: June 4th 2020

Figure 1: Flowchart of the trial design

UACR: Urine albumin/creatinine ratio, 24h ABPM: 24-hour ambulatory blood pressure monitoring, ECG: electrocardiogram, PWA: Pulse wave analysis, PWV: Pulse wave velocity, RAAS-blockade: Renin angiotensin aldosterone system blockade (losartan and/or spironolactone).

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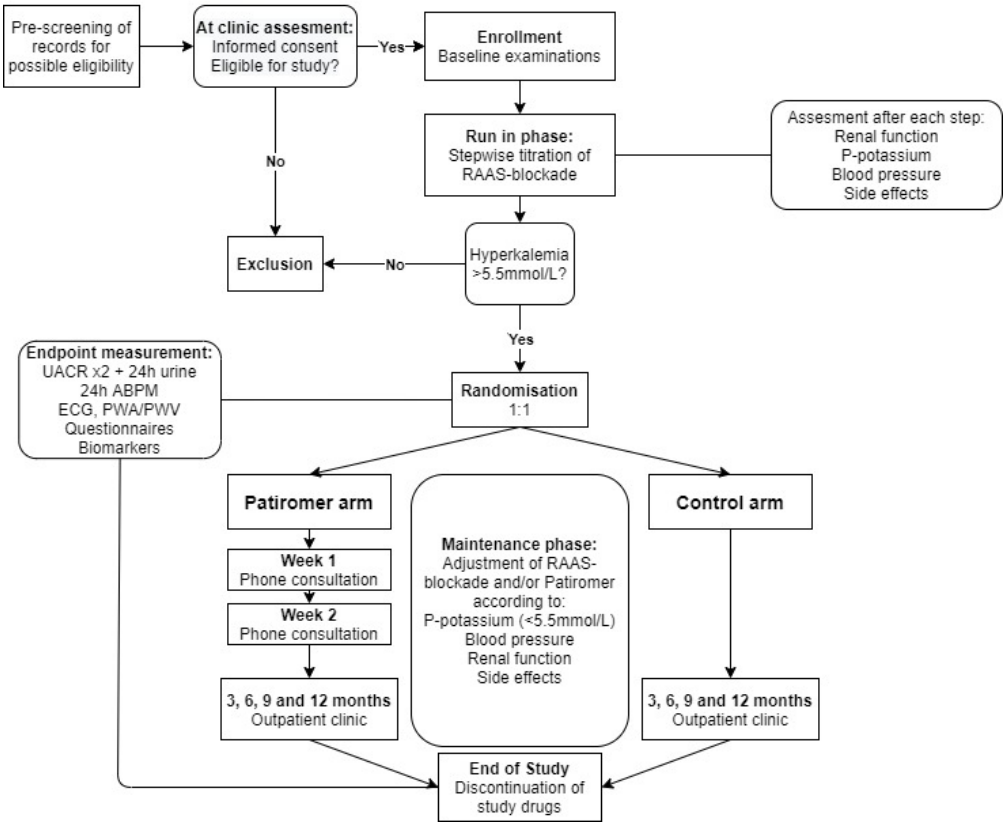

UACR: Urine albumin/creatinine ratio, 24h ABPM: 24-hour ambulatory blood pressure monitoring, ECG: electrocardiogram, PWA: Pulse wave analysis, PWV: Pulse wave velocity, RAAS-blockade: Renin angiotensin aldosterone system blockade (losartan and/or spironolactone).

259x218mm (72 x 72 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-17
Protocol version	#3	Date and version identifier	17
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	5

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6, 11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Can Patiromer allow for intensified Renin Angiotensin Aldosterone System Blockade with Losartan and Spironolactone leading to decreased albuminuria in patients with Chronic Kidney Disease, albuminuria and hyperkalaemia? An open-label randomised controlled trial - MorphCKD

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TITLE: Can Patiromer allow for intensified Renin Angiotensin Aldosterone System blockade with Losartan and Spironolactone leading to decreased albuminuria in patients with Chronic Kidney Disease, albuminuria and hyperkalaemia? An open-label randomised controlled trial - MorphCKD

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ABSTRACT

INTRODUCTION

Chronic Kidney Disease (CKD) is associated with significantly increased morbidity and mortality. No specific treatment of the underlying condition is available for the majority of patients, but ACE-inhibitors (ACE-I) and angiotensin II-receptor blockers (ARB) slows progression in albuminuric CKD. Adding a mineralocorticoid receptor-antagonist (MRA) like spironolactone has an additive effect. However, Renin-angiotensin-aldosterone system (RAAS)-blockade increases the risk of hyperkalaemia which is exacerbated by the presence of CKD. Thus, hyperkalaemia may prevent optimal use of RAAS-blockade in some patients.

This project hypothesizes that adding a potassium binder (patiromer) allows for improved RAAS-blockade including the use of MRA, thereby reducing albuminuria in patients with albuminuric CKD where full treatment is limited by hyperkalemia.

If successful, the study may lead to improved treatment of this subgroup of CKD patients. Furthermore, the study will examine the feasibility of potassium binders in patients with CKD.

METHODS AND ANALYSIS

An open label, randomised controlled trial including 140 patients with eGFR 25-60 mL/min/1.73m^2, a urinary albumin/creatinine ratio (UACR) > 500 mg/g (or 200mg/g if diabetes mellitus) and a current or two previous plasma-potassium >4.5mmol/L. Patients who develop hyperkaliemia >5.5 mmol/L during a run-in phase, in which RAAS-blockade is intesified with the possible addition of spironolactone, are randomised to 12-month treatment with maximal tolerated ACE-I/ARB and spironolactone with or without patiromer.

The primary endpoint is the difference in UACR measured at randomisation and 12 months compared between the two groups. Secondary endpoints include CKD progression, episodes of hyperkalaemia, blood pressure, eGFR, markers of cardiovascular disease, diet and quality of life.

ETHICS AND DISSEMINATION

This study is approved by The Central Denmark Region Committees on Health Research Ethics (REFNO 1-10-72-110-20) and is registered in the EudraCT database (REFNO 2020-001595-15). Results will be presented in peer-reviewed journals, at meetings and at international conferences.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study uses a robust randomised controlled design, investigating if patiromer, through increased RAAS-blockade, can reduce albuminuria in patients with CKD and hyperkalaemia.
- The selective run-in phase only allows randomisation of patients where RAAS-blockade is proven to be limited by hyperkalaemia.
- A one-year follow-up will examine long-term tolerability of patiromer in CKD patients, testing if such a treatment regime is feasible.
- The limited sample size and one-year follow-up that does not allow for evaluation of 'hard' endpoints such as time to renal death or decrease in eGFR

INTRODUCTION

Chronic kidney disease (CKD) is associated with substantial comorbidity and mortality[1]. No curative treatment is currently available for the majority of patients, and current interventions aim to halt or slow the natural progression of the disease. Albuminuria is a well-established predictor of end stage renal disease (ESRD). The risk of progressing to ESRD is up to 75 times higher among CKD patients with significant albuminuria compared to patients without albuminuria[2]. Treatment with inhibitors of the renin-angiotensin-aldosterone system (RAAS) such as angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) reduce albuminuria in a dose-dependent manner[3]. Furthermore, treatment slows CKD progression in both diabetic and non-diabetic CKD[4,5]. RAAS-blockade, in particular the use of ACE-I or ARB, is considered first-line treatment in patients with CKD and albuminuria. Evidence suggests that the change in albuminuria correlates with the protection provided and therefore serves as a surrogate marker of disease progression[6,7]. Other studies have shown that reducing albuminuria in CKD patients lowers the cardiovascular risk[8–10]. Cardiovascular risk can be assessed from left ventricular hypertrophy, arterial stiffness (pulse wave velocity (PWV) and central BP) and blood biomarkers such as endothelin-1, NT-proBNP and TnI[11–15].

Aldosterone is a regulator of blood pressure through fluid and electrolyte homeostasis. Evidence strongly support an additional, direct pathophysiological role for aldosterone in the development of kidney and cardiovascular disease. Mineralocorticoid receptor (MR) activation induces inflammation, oxidative stress and fibrosis[16,17] and leads to glomerulosclerosis and cardiac fibrosis [18,19]. This increases the risk of kidney function decline, albuminuria and cardiovascular disease. Blood aldosterone levels increase as estimated glomerular filtration rate (eGFR) deteriorates, and CKD is considered a state of relative hyperaldosteronism [20,21]. RAAS blockade using ARB/ACE-I insufficiently lowers the aldosterone level, and plasma concentration typically rises after 6-12 months of treatment; a phenomenon known as aldosterone escape [22]. MR-antagonists (MRAs) such as spironolactone or eplerenone alone or in combination with ACE-I/ARB reduces albuminuria by 25-40%[23,24]. A large number of studies have suggested renoprotective benefits of treatment with MRA in CKD with persistent albuminuria. This notion was emphasized by the recent FIDELIO-DKD trial. The trial found that the addition of the MRA finerenone to ACE-I/ARB treatment in patients with CKD, type 2 diabetes and albuminuria significantly reduced the risk of renal outcomes and cardiovascular risk[25].

Despite inherent benefits, RAAS blockade may be hampered by fear of hyperkalaemia. Severe hyperkalaemia may cause life threatening cardiac arrhythmias[26]. CKD results in a reduced ability to excrete potassium and patients are at significant risk of hyperkalaemia[27,28]. Treatment with ACE-Is or ARBs as well as MRAs further inhibits renal potassium excretion, augmenting the risk of hyperkalaemia[29,30]. Thus, high potassium levels often limit the optimal use of RAAS blockade in many CKD patients[28]. Novel third generation nonsteroidal selective MRAs such as finerenone has a lower risk of causing hyperkalaemia compared to older generation MRAs, but the number of patients discontinuing treatment due to hyperkalaemia is still 2.5-fold higher compared to placebo[25]. Other ongoing clinical trials evaluating the effect of ACE-I or ARB combined with MRAs in CKD exclude patients with hyperkalaemia[16]. Thus, CKD patients with hyperkalaemia may be barred from the potential benefits of complete RAAS blockade including MRA.

In recent years, novel potassium-binding agents have been introduced. These include patiromer (Veltassa), a non-absorbable sodium-free powder for oral use, which binds potassium in the gastrointestinal tract, thereby increasing fecal excretion and lowering plasma (P) potassium[28]. Patiromer significantly lowers P-potassium in patients with CKD[31,32]. Several studies have proposed the use of patiromer to allow for

increased RAAS blockade in patients with hyperkalaemia, CKD and suboptimal RAAS blockade treatment.[33]. Hyperkalaemia may be addressed through dietary restrictions, but these have limited effect,a profound impact on patient's lifestyle and freedom and limit the intake of healthy fresh fruits and vegetables[34].

Aims and Hypotheses

This trial aims to establish if the use of a potassium binding agent (patiromer) in patients with moderate or advanced CKD (eGFR 25-60 mL/min/1.73m^2) leads to a reduction in albuminuria by the concomitant intensified use of RAAS-inhibitors (losartan and/or spironolactone). In secondary analyses, it will examine the effects of this approach on markers of cardiovascular function, dietary habits (including fruit and vegetable intake) and quality-of-life as well as the potential risks; monitoring blood pressure, episodes of hyperkalaemia and renal function.

Thus, the study will address the hypotheses that treatment with patiromer and intensified RAAS-blockade in patients with eGFR 25-60mL/min, albuminuria and a tendency of high potassium levels leads to:

1. A significant reduction in albuminuria when compared to patients in maximal RAAS-blockade as allowed by their P-potassium levels without patiromer
2. A significant reduction in albuminuria during treatment
3. A reduced PWV and left ventricular mass (LVM) along with improvement in blood biomarkers of cardiovascular function
4. An increased intake of healthy foods and higher quality of life

METHODS AND ANALYSIS

The MorphCKD study is an investigator-initiated, multicenter, open label, parallel group, superiority randomised controlled trial (RCT). Randomisation is performed as a block randomisation with 1:1 allocation.

The study will include patients from the outpatient clinics at the renal departments in Aarhus, Aalborg, Holstebro and Viborg, Denmark. The primary site, Aarhus, will also include patients from the diabetes outpatient clinic and within the hospital public admission area (see under "recruitment").

The study is divided into a run-in phase of 2-8 weeks followed by randomisation to a treatment phase involving 52 weeks of treatment with or without patiromer (see figure 1). The run-in phase will determine if maximized RAAS-blockade, including treatment with an MRA, leads to clinically significant hyperkalaemia (>5.5mmol/L) despite dietary counselling, thereby identifying the patients that may benefit from treatment with patiromer who qualify for randomisation to the treatment phase.

FIGURE1 **Flowchart of the trial design**

Participants

A total of 140 patients fulfilling the eligibility criteria below will be included.

Inclusion criteria:

1. Age 18-80

2. eGFR 25-60 mL/min/1.73m^2
3. Current P-potassium >4.5mmol/L *or* P-potassium >4.5mmol/L twice within 24 months
4. Urine albumin-creatinine ratio (UACR) >500mg/g *or* 200mg/g and diabetes

A lower UACR threshold for patients with diabetes is based on international guidelines suggesting a more aggressive approach when treating albuminuria in this group of patients[35], in which the renoprotective effects of treating lower levels of albuminuria is well documented[36].

Exclusion criteria:

1. Known allergies to both ACE-I and losartan or spironolactone or patiromer
2. A history of kidney transplantation or active on the waiting list
3. ESRD (defined as the need for dialysis or kidney transplantation)
4. Any renal disease requiring or being expected to require specific immunosuppressive therapy for the duration of the trial
5. Pregnancy or inability to use contraception
6. Regular need for trimethoprim or NSAIDs
7. Current treatment with aliskiren
8. Disseminated cancer disease
9. Addison's disease
10. HF defined as ejection fraction < 40% or active treatment at a HF clinic or similar
11. Porphyria
12. Severe constipation with a regular use of laxatives or previous recurrent ileus
13. Fructose/galactose-intolerance
14. Severe liver insufficiency (Child-Pugh Score B-C)
15. Clinically significant severe renal artery stenosis
16. Investigator's evaluation that participation in the trial may cause serious harm to the patient (e.g. previous severe acute kidney injury (AKI) in relation to RAAS-blockade)
17. Initiation of an SGLT2-inhibitor within 30 days prior to inclusion

Interventions and randomisation

Dietary counselling to limit potassium intake is provided at inclusion. Patients not treated with ACE-I/ARB at inclusion will commence losartan 50mg/day for the run-in phase (step 1 below). Patients already treated with ACE-I/ARB will continue this treatment at the current dose with the addition of an MRA (starting at step 3 below). Based on tolerability, RAAS-blockade is increased in four steps:

1. Losartan 50mg/day
2. Losartan 100mg/day
3. Losartan 100mg/day or current ACE-I/ARB + spironolactone 25mg/day
4. Losartan 100mg/day or current ACE-I/ARB + spironolactone 50mg/day

Blood samples and home BP monitoring will be performed 1-2 weeks after each dose change and the patient is contacted by phone to record home BP and to inform about blood results. Tolerability is evaluated by P-potassium, creatinine, BP and side effects. The dose of losartan or spironolactone is reduced to the previous step and the patient proceeds to randomisation if P-potassium is >5.5mmol/L.

Patients that reach step four without significant hyperkalaemia are excluded from the study.

Patients completing the run-in phase with an episode of significant hyperkalaemia (>5.5mmol/L), a UACR > 300mg/g or 150mg/g and diabetes, a most recent P-potassium >4.0mmol/L and no other contraindications (e.g. AKI) to continued and increased RAAS-blockade are randomised to open-label treatment in one of two regimes:

1. Patiromer with stepwise dose-increase/-decrease with increased RAAS-blockade in addition to standard clinical care and dietary counselling. Patiromer will be dosed based on P-potassium and tolerability until maximal RAAS-blockade with P-potassium ≤5.5mmol/L.
2. No patiromer (control group) with standard clinical care, dietary counselling and maximal RAAS-blockade with P-potassium ≤5.5mmol/L

The lower threshold for albuminuria at randomisation compared to baseline is used to allow for some reduction of albuminuria resulting from the increase in RAAS-blockade during the run-in phase. Permuted block randomisation with random varying block sizes of 2, 4 and 6 is used to allocate patients to the patiromer- or control group at a 1:1 ratio, stratified by albuminuria >1000mg/g (Yes/No) and diabetes (Yes/No). These stratifications have been included to minimize imbalances in patients with diabetes or severe albuminuria as such may have a different pathophysiology and thereby response to treatment compared to non-diabetics and patients with moderate albuminuria. The Random allocation list is generated and uploaded to REDCap by an independent service provider (Clinical Trial Unit, Dept. of Clinical Medicine, Aarhus University) maintaining proper allocation concealment of randomisation.

After randomisation, patients are followed for up to 52 weeks with blood sampling and outpatient visits every 3 months and allowing for additional visits if considered clinically required based on the assessment of the local investigator.

The dose of study drugs (RAAS-blockade) is determined by the four steps previously described, aiming at the possible highest step with a P-potassium <5.5mmol/L. Dose increases are only allowed on planned consultations (phone or outpatient clinic), but decreases may be introduced at any point depending on the results of blood test, BP or other adverse effects. In the patiromer group, patiromer is prescribed as tolerated at a daily dose of 8,4g, 16,8g or 25,2g in order to maintain P-potassium <5.5mmol/L. The dosing of patiromer is increased concomitantly with any increase in RAAS-blockade, unless P-potassium is ≤ 4.6 mmol/L. RAAS-blockade is decreased if hyperkalaemia >5.5mmol/L is recorded at the highest tolerated patiromer dose.

All study drugs are stopped at the last outpatient visit after 52 weeks. Patients entering the study on ACE-I/ARB will continue this treatment without patiromer. Blood and urine samples are collected 4 weeks later for the evaluation of eGFR, albuminuria and P-potassium after discontinuation of study drugs.

Additional medication

Any inhibitors of the RAAS-system other than those mentioned above as well as additional potassium binders are not allowed during the study period. Hypertension is treated aiming at a systolic BP between 110-130mmHg in both groups. All anti-hypertensives, except additional inhibitors of the RAAS-system, may be used as per the discretion of the treating physician. Loop and thiazide diuretics may be prescribed for hypertension and/or fluid retention. Hypomagnesemia is treated with oral magnesium supplements. Study drugs including losartan, spironolactone and patiromer can be reduced or suspended depending on blood pressure, hyperkalaemia as per protocol or any side effects deemed to outweigh the benefit of the treatment (e.g. AKI, gastrointestinal intolerance, biochemical abnormalities). SGLT2-inhibitors may not be prescribed during the trial.

Endpoints

The primary endpoint is:

- The difference in UACR from randomisation to end of treatment compared between the two groups. This is measured as an average of two morning spot UACR samples collected both at randomisation and at the last study visit

Secondary endpoints include:

- The difference in 24h urine albumin from randomisation to end of treatment compared between the two groups
- The difference in albuminuria (evaluated by morning spot UACR and 24h urine collection) at the end of treatment between the two groups
- The difference in the extent of RAAS-blockade (ACE-I/ARB and MRA) at the end of treatment between the two groups
- The difference in kidney function (eGFR and urine creatinine clearance) at the end of treatment and the changes in eGFR from randomisation to end of treatment between the two groups
- The difference in BP (ambulatory and 24h) at the end of treatment and the changes in BP from randomisation to end of treatment between the two groups
- The difference in PWV/pulse wave analysis (PWA) at the end of treatment and the changes in PWV/PWA from randomisation to end of treatment between the two groups
- The difference in LVM (ECG) at the end of treatment and the changes in LVM from randomisation to end of treatment between the two groups
- The difference in cardiac biomarkers at the end of treatment and the changes in cardiac biomarkers from randomisation to end of treatment between the two groups
- The difference in P-potassium at the end of treatment between the two groups
- The difference in the number of episodes with severe hyperkalaemia (>6.2mmol/L) from randomisation to end of treatment between the two groups
- The difference in the number of episodes with AKI (KDIGO stage 1-3) from randomisation to end of treatment between the two groups
- The difference in the questionnaire base assessment of the consumption of fruits and vegetables at the end of treatment and the changes in fruits and vegetables consumption from randomisation to end of treatment between the two groups
- The difference in QoL at the end of treatment and the changes in QoL from randomisation to end of treatment between the two groups

Sample size and power calculation

The study will include 140 patients under the assumption that 30% will not meet randomisation criteria, leaving 98 participants (49 in each group) for randomisation. This will provide 80% power to detect a clinically relevant 1.5-fold greater reduction in the amount of albuminuria in the patiromer group compared to the control group, with a risk of type 1 error of 0.05 assuming an 80% coefficient of variation in the change of UACR[37]. The study will continue as long as the number of randomised participants is expected to be no less than 55% (54 patients), which will provide power to detect a 1.75-fold greater reduction in the amount of albuminuria.

Recruitment

All patients from the renal outpatient clinics at the three centers and all patients serviced by Aarhus University Hospital (covering a population of approx. 900,000) who have provided a blood sample within the last 2 years are prescreened. The prescreening algorithm uses the LABKA II database containing the result of all blood samples analyzed within the relevant regions and identifies patients aged 18-80 with a history (within 2 years) of P-potassium > 4.5mmol/L, UACR >200mg/g and eGFR 25-60 mL/min/1.73m^2. The resulting patient records including blood samples are manually screened by a local investigator. Potentially eligible patients are contacted with the participant information by letter. In addition, patients in the nephrology outpatient clinics in Aarhus, Aalborg, Holstebro and Viborg and the diabetes outpatient clinic in Aarhus are contacted in person at their next appointment. After written informed consent they are screened for inclusion including blood samples to ensure that they meet the inclusion criteria at the time of inclusion.

Data collection

The patient's medical history including current treatment is registered at inclusion. Patient height is measured at inclusion and weight at every visit. A physical examination including vital signs are performed at inclusion, randomisation and final visit. A urine sample for UACR is collected at inclusion, twice at randomisation and final visit for the primary outcome and at every three-month-visit during the treatment phase. If possible, a morning sample is preferred. Timed 24h urine samples are collected at randomisation and 52 weeks. P-potassium, creatinine, eGFR and sodium are measured at inclusion, weekly during the run-in phase, during titration of RAAS-blockade and every 3 months in the outpatient clinic. P-total CO_2 and ionized calcium are measured at inclusion, randomisation and every 3-month visit. P-magnesium is measured at all visits during the maintenance phase in the patiromer group. Cardiac biomarkers (Endothelin-1, NT-proBNP and TnI), ECG, blood samples evaluating biomarkers of fruit and vegetable consumption (lutein, β-cryptoxanthin, α- and β-carotene, lycopene and vitamin C[38]), PWV and PWA as a measure of arteriosclerosis, SF-36[39] questionnaire measuring QoL, MyFood24[40] food diaries and 24h ABPM are all performed at randomisation and 52 weeks. Please refer to table 1 for a timeline of data collection.

Table 1: Study timeline and visits

Timeline (weeks)	**Inclusion -8**	**-6**	**-4***	**-2***	**t_0 Randomisation /(exclusion)**	**2***	**4***	**13**	**26**	**39**	**52**	**56**
STUDY PHASE:	**Run-in phase**				**Maintenance phase**							
INTERVENTIONS:												
Increased RAAS-blockade	→	→	→									
Patiromer-treatment (intervention group) and/or RAAS-blockade titration					RAAS with patiromer → / RAAS with out patiromer →							
ASSESMENTS:												
Eligibility screen	x											
Informed consent	x											
Pregnancy test (if fertile woman)	x											
Medical record	x											
Physical examination	x				x						x	
Weight	x				x			x	x	X	x	
Dietary counselling	x											
P-Creatinine, eGFR, P-Potassium, P-Sodium	x	X	x	x	x	x	x	x	x	X	x	x
P-magnesium (patiromer group)					x	x	x	x	x	X	x	
P-total CO_2, P-ionized Calcium	x				x			x	x	X	x	x
BpTRU® or similar local ABPM	x				x			x	x	X	x	
24h ABPM					x						x	
At-home ABPM		x	x	x		x	x					
UACR	x	x	x	x	xx			x	x		xx	x
Questionnaire – Side effects	x				x			x	x	X	x	
Questionnaire – SF-36[39] (QoL)					x						x	
Questionnaire – MyFood24[40]					x						x	
Carotenoids and C-Vitamin					x						x	
24h urine collection					x						x	
PWA/PWV					x						x	
ECG					x						x	
Endothelin-1, NT-proBNP and TnI					x						x	
Pill count					x (x)			x	x	X	x	
TYPE OF VISIT:												
Phone consultation		x	x	x		x	x					
Outpatient clinic	x				x (x)			x	x	X	x	

*Only If RAAS-blockade has been increased. During the run-in phase, the patient proceeds directly to randomisation if P-potassium > 5.5mmol/L.

Questionnaires and food diaries may be filled in online prior to the visit using REDCap or the Myfood24 website. An invitation with a unique link is sent to the patient via e-mail. Alternatively, they are completed with the assistance of the investigator on the day of the visit. Vital signs are measured using BpTRU® or equivalent at every visit and with an automatic digital blood pressure monitor at home for phone consultations. Pill counts are done at every visit to assess compliance. Patients are asked if and to what

extent they have taken the study drugs at all contacts. Adherence techniques such as morning routines and medication in relation to meals are discussed if required.

Blood and urine biochemical analyses are performed at local biochemical laboratories using standard automated assay. Reference intervals have been standardized on a national level and all Danish laboratory uses these for reference. The UACR at randomisation and final visit is calculated as an average of 2 measurements over two days at each timepoint to minimize variability[41]. The patient is carefully instructed to provide morning urine samples. Urine collection, including 24h urine collection, is performed by the patient at home prior to the randomisation and 12-month-visit. PWV and PWA are measured using the Sphygmocor system. Applanation tonometry is applied on the carotid, femoral, and radial artery. A minimum operator index of 85 is used. Length is measured as 80% of the distance from the carotid artery to the femoral artery. Home BP is measured three times in the morning and evening for three days. An average of day 2 and 3 is reported. Twenty-four-hour ABPM is recorded with measurements every 30 minutes. ECG is recorded by an experienced nurse. Each centers' personnel will be trained and instructed in all study procedures by the study PI.

Data management

Study data, including adverse events (AE) and serious adverse events/reactions (SAE/SAR), will be collected and managed using REDCap electronic data capture tools hosted at Aarhus University[42,43]. All data are entered electronically by the local investigator at each site. Original data is stored in the patients' electronic records or in a participant file. Participant files are stored in a secure place and kept for 15 years after end of study. Data will be exported from RedCap for final analysis using a suitable statistical software package.

Statistical methods

The primary endpoint is analyzed using a t-test comparing the differences in UACR between randomisation and 12 months between the two groups. The ratio between groups with confidence intervals and the P-value will be reported. A secondary two-way repeated measures ANOVA including UACR at randomisation, 3, 6, 9 and 12 months is performed and the P-value is reported. The data is analyzed as intention-to-treat with a secondary treated-as analysis. A separate t-test will compare the difference in UACR from randomisation to the time patiromer is discontinued. Data from patients discontinuing treatment before 12 months of follow-up is included using carry-over of the last available dataset before stopping. Missing data for the primary endpoint will be replaced by the most recent observation carried over. Previous studies have shown that most of the effect of increased RAAS-blockade on albuminuria is seen early after treatment initiation with little change thereafter, suggesting that the UACR at the closest possible time-point is a fair proxy measure of the 12-month value. Imputations may be applied for secondary analyses if feasible. All variables are analyzed for normal distribution and skewed data are log-transformed when appropriate. Non-normally distributed variables on both the standard- and log-scale are analyzed using non-parametric testing. Repeated measurements are analyzed by a linear model when feasible.

Safety measures

Adverse events, defined as any medical occurrence in a trial participant without regard to the possible cause, are collected from when the consent has been signed and until final visit. Participants are asked about any new such events at each contact and will fill out a questionnaire at each outpatient clinic visit. Serious adverse events will be reported directly to the PI and sponsor. Investigators will evaluate any adverse event's possible relation to study drugs based on temporal relationship, known mechanism of action and known side effects for classification of adverse reactions.

The following individual safety-outcomes are evaluated by the investigator at each contact:

1. A decline in eGFR > 30% from inclusion, 20% from previous visit or 5 mL/min/1.73 m^2 from previous visit if eGFR < 25 mL/min/1.73 m^2 should lead to a temporary reduction or discontinuation of spironolactone and/or ACE-I/ARB (Losartan or other)
2. An increase in P-creatinine > 100% from the previous visit, the possible need for acute dialysis or other findings suggesting severe AKI leads to admittance for treatment
3. If P-potassium is >5.5mmol/L on maximal patiromer dose, RAAS-blockade is reduced by 50% or spironolactone is discontinued. P-potassium is repeated within two days or as soon as possible
4. If P-potassium is > 5.9mmol/L, ACE-I/ARB and spironolactone are temporarily discontinued. P-potassium is repeated within one day
5. If P-potassium is > 6.2mmol/L, the patient is admitted and treated in accordance with local guidelines. ACE-I/ARB and spironolactone are temporarily discontinued.
6. If P-magnesium is < 0.6mmol/L, the patient is treated with oral magnesium supplements as per discretion of the local investigator and P-magnesium is repeated within 7-10 days.
7. If P-magnesium is < 0.5mmol/L despite maximal tolerated magnesium supplement treatment, patiromer is discontinued and p-magnesium is repeated within two days

In case of events 1-5 above, RAAS-blockade may the reinitiated at the previous dosage if and when kidney function is restored and/or P-potassium < 5.4mmol/L following discontinuation or dose reduction of the RAAS inhibitor.

The study is halted if at any point a significant higher number of the following events are observed in patiromer group compared to the control group:

1. Events with hyperkalaemia > 6.2mmol/L
2. Patients with eGFR < 15 mL/min/1.73 m^2 or requiring dialysis for > 3 months
3. Deaths
4. Admissions (except events due to hyperkalaemia, covered in point 1)
5. A combined endpoint of the four above

These outcomes will be evaluated by the PI after each such event using Fischer's exact test.

Study oversight and monitoring.

The study is monitored by the GCP unit at Aarhus and Aalborg University Hospitals. It does not include an independent data monitoring committee due to the open label design, limited number of sites and continuous monitoring of significant safety outcomes as described above. Any systematic or serious risk to the participants will be immediately apparent to the PI and sponsor. The study may be audited by the Danish Medicines Agency. Safety reports are forwarded to the Danish Medicines Agency and The Central Denmark Region Committees on Health Research Ethics annually.

Patient and Public Involvement statement

Participants were involved in changes to the design of the study. They preferred less transportation and fewer hospital visits. From their feedback, some visits were replaced by phone consultations and blood sampling prior to most visits was made possible at 28 local sites across the Central Denmark Region. Once

the trial has been published, participants will be informed of the results via e-mail using the REDCap distribution tool.

Current trial status

The first participant was included in the study late August 2020 and is planned to continue until March 2022. At the time of writing (August 2021), 56 participants have been included and 14 have been randomised to the treatment phase. Enrollment was halted from December 2020 due to the lockdown following COVID-19 in Denmark but was resumed in March 2021.

ETHICS AND DISSEMINATION

The study protocol was initially approved by The Central Denmark Region Committees on Health Research Ethics (REFNO 1-10-72-110-20) on June 23rd 2020 with the latest version being approved on July 1st 2021 and by the Danish Medicines Agency on June 10th 2021. The research will be conducted in accordance with the Helsinki Declaration and Good Clinical Practice. All protocol amendments will be approved by the Ethics Committee and Danish Medicines Agency before implementation when required and all investigators will be notified directly.

A local investigator will obtain a written, informed consent from all participants prior to inclusion. The consent form follows the standards and template from the Danish National Committee on Health Research Ethics.

All principal investigators and sponsor will have access to the cleaned dataset.

Trial results, positive as well as negative, will be submitted for publication in peer reviewed, international journals and presented at conferences and meetings.

DISCUSSION

This study investigates the feasibility of daily treatment with an established potassium-binding agent in moderate and severe CKD patients with albuminuria. It will examine if treatment enables increased RAAS-blockade and leads to a greater decline in albuminuria. Previous studies have shown that patiromer allows for the use of spironolactone in CKD patients with hyperkalaemia[44]; however, it is unknown if the approach leads to an effect on albuminuria in this distinct group of patients. The study aims to fill this gap in current knowledge.

The open label study design should closely mimic the clinical decision making and the delicate task of balancing hyperkalaemia and renoprotection. This will provide information on the practicability and potential benefits of such an approach in patients with hyperkaliemia otherwise barred from full pharmaceutical blockage of the RAAS-system. Of note, the study includes a one-year follow-up to examine potential complications to long-term treatment including non-adherence, hypotension, AKI and other adverse effects. Additional strengths of the study include the extensive list of outcomes and the RCT design. Furthermore, the unique and selective run-in phase only allows randomisation of patients that are proven to potentially benefit from treatment with a potassium binder, which should be in accordance with clinical practice. In addition, since all included interventions involves established and approved drugs, the road to implementation ought to be short.

There are some potential limitations and challenges. First, the small sample size and one-year follow-up does not allow for evaluation of harder renal endpoints such as progression to end-stage renal disease or a 50% reduction in eGFR. However, albuminuria is a widely accepted surrogate marker of disease progression in albuminuric CKD. In addition, it is closely correlated to the protective effects of RAAS-blockade. Second, the study is not powered to detect minor differences in the change in albuminuria; however, it will be able to identify a 1.5 times greater reduction in UACR. Third, the one-year follow-up may challenge patient adherence to treatment. Fourth, patients already treated with ACE-I or ARB may be on a sub-maximal dose of these medications when Spironolactone is added as per protocol to their current treatment. This was considered necessary to avoid the complexity of either having to manage a large number of different ACE-Is or ARBs as potential study drugs or requiring an initial switch to e.g. Losartan, which may increase the duration of the run-in phase significantly and thus, the risk of early participant drop out. Fifth, the open-label design may introduce selection bias in physicians' use of non-investigational drugs. Standard operating procedures on concomitant treatment, including instructions for the use of diuretics, are established to mitigate such bias. The open label design does provide some potential benefits, allowing for a setup that closely resembles clinical practice and for a more practical safety algorithm to prevent potentially life-threatening hyperkalaemia. The primary outcome is based on biochemical findings. It is very unlikely that this is affected by the open label design.

The power calculations are based on the number of randomised patients after the run-in phase. It is assumed that 30% of the included patient will not be eligible for randomisation; however, the accuracy of this number has not been established and thus, the number of actual randomised patients may be different. The extensive screening algorithm, which is based on results from blood samples in all 4 outpatient clinics and the entire Aarhus University public admission area, will however ensure that all eligible candidates are invited to the study. This is particularly important as the number of patients with an eGFR between 25 and 60 mL/min/1.73m^2, concomitant and significant albuminuria, and previous or current P-potassium >4.5mmol/L may be limited.

The study is partly based on the assumption that adding MRA to ACE-I/ARB treatment in this subgroup of patients is beneficial if hyperkalaemia can be controlled, supported by the recent results of the FIDELIO-DKD trial [25]; however, the underlying principle is also applicable to patients in which maximal dosing of ACE-I or ARBs is barred by hyperkalaemia. If this study establishes the feasibility of such approach, it should pave the way for larger studies with hard endpoints to corroborate the use of potassium binders in patients currently excluded from maximal RAAS-inhibition.

ROLES AND RESPONSIBILITIES

Contributorship statement: HB conceived the study and had editorial rights on the protocol. FHM was first author of the protocol, primary investigator in Aarhus and implemented the study on all sites as the coordinating investigator. CDP held an advisory role in the writing of the protocol. JHC was the primary investigator in Aalborg. All authors contributed to refinement of the study protocol including the design and approved the final manuscript.

Sponsor and funder roles:

HB (sponsor) conceived the study and the design hereof. Vifor Pharma has been allowed access to and commented on the protocol before funding the study, but had no decisive influence on the design. Vifor

will be informed on the progression of the study and on SAEs relating to patiromer, but will not have any influence on the execution, the data analyses, the interpretation of data, or the decision to submit results.

Lead investigators: A lead investigator (senior nephrologist) will be identified at each site. The lead investigator is responsible for identification of potential study subjects, recruitment hereof, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure. The lead investigator may appoint sub-investigators to act on his or her behalf.

FUNDING

This work is supported by Aarhus University Graduate School and by Vifor Pharma. The latter includes free of charge patiromer.

Study administration, financial statement and conflicts of interest

Neither the study sponsor (HB), PI (FHM) nor any other investigators have any financial involvement with the primary funder (Vifor Pharma) or the primary study drug (patiromer). HB has previously participated in advisory boards and meetings hosted by Vifor Pharma. These have all been reported to the Danish Medicines Agency. The authors have no further conflicts of interest to declare.

REGISTRATIONS

Registration: EudraCT: 2020-001595-15

Sponsor protocol code: 270389-010520

Protocol version 15, June 26th 2021

First approval from Ethics Committee (The Central Denmark Region Committees on Health Research Ethics): June 23rd 2020

First approval from the Danish Medicines Agency: June 4th 2020

Figure 1: Flowchart of the trial design

UACR: Urine albumin/creatinine ratio, 24h ABPM: 24-hour ambulatory blood pressure monitoring, ECG: electrocardiogram, PWA: Pulse wave analysis, PWV: Pulse wave velocity, RAAS-blockade: Renin angiotensin aldosterone system blockade (losartan and/or spironolactone).

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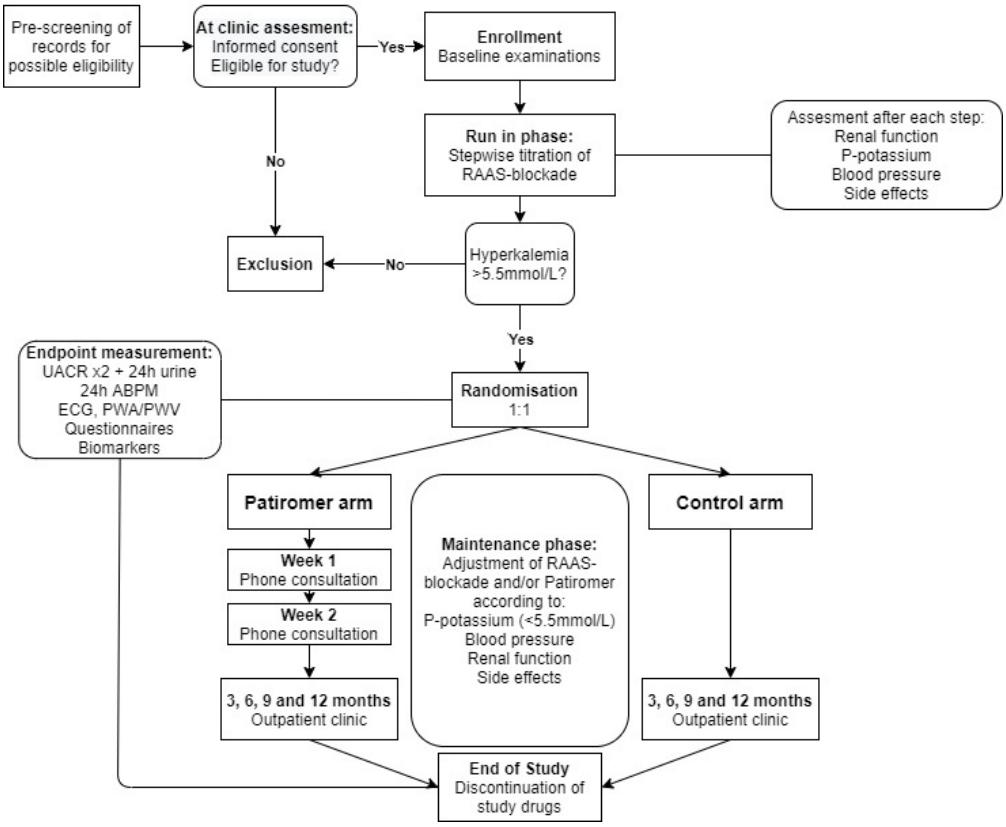

UACR: Urine albumin/creatinine ratio, 24h ABPM: 24-hour ambulatory blood pressure monitoring, ECG: electrocardiogram, PWA: Pulse wave analysis, PWV: Pulse wave velocity, RAAS-blockade: Renin angiotensin aldosterone system blockade (losartan and/or spironolactone).

259x218mm (72 x 72 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-17
Protocol version	#3	Date and version identifier	17
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	5

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6, 11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A