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Patiromer to Reduce Albuminuria Through Increased Renin Angiotensin Aldosterone System Inhibition in Patients With CKD-A Feasibility Trial

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Introduction: We tested the feasibility of adding a potassium binder to enable increased renin angiotensin aldosterone system inhibition (RAASi) and reduce albuminuria in patients with chronic kidney disease (CKD). In a controlled trial design, a potassium binder was introduced exclusively in patients developing hyperkalemia after intensified RAASi, thereby mirroring clinical decision-making.

Methods: We planned to include 140 patients aged 18 to 80 years with estimated glomerular filtration rate (eGFR) 25 to 60 ml/min per 1.73 m^2, albuminuria, and a history of hyperkalemia to an open-label, randomized trial comparing treatment with or without patiromer alongside maximally tolerated RAASi. Patients were randomized only if developing a documented P-potassium >5.5 mmol/l during run-in with intensified RAASi (losartan/spironolactone). The primary end point was change in urine albumin-creatinine ratio (UACR).

Results: Screening among 800,000 individuals with available laboratory results yielded just 317 candidates meeting major selection criteria during $18^2/_3$ months, with 75 ultimately included. Among them, only 23 developed P-potassium >5.5 mmol/l, qualifying for randomization. Consequently, only 20 participants completed the study, falling short of the planned 98, precluding a significant effect on the primary outcome. Inclusion and randomization challenges stemmed from a limited pool of eligible patients for intensified RAASi at risk of hyperkalemia, along with a lower than expected incidence of hyperkalemia during run-in.

Conclusion: Despite extensive screening efforts, few eligible patients were identified, and fewer developed hyperkalemia during run-in. Hence, a trial design limited to CKD patients at high hyperkalemia risk and including a run-in phase appears unlikely to provide evidence for a potential renal benefit from additional use of potassium binders.

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RAASi using angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), is a cornerstone in slowing CKD progression. Recent studies show that mineralocorticoid receptor antagonists (MRAs) can further slow this progression.[1-3] The rationale for RAASi lies in the detrimental effects of RAAS activation on renal pathophysiology, including glomerular hypertension, inflammation, fibrosis, and oxidative stress.[4,5] Albuminuria is a marker of glomerular damage and a major risk factor for an accelerated decline in GFR. Furthermore, it is associated with an increased risk of cardiovascular events and progression to kidney failure.[6-8] Reductions in albuminuria signifies kidney protection, serving as a surrogate-marker hereof.[9]

However, RAASi increases the risk of hyperkalemia, particularly in patients with CKD.[10] CKD patients on ACEi/ARB treatment experience hyperkalemia at an incidence rate of 8 per 100 patient months, 5 times more often than those not on

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treatment.[11] Hyperkalemia increases the risk of life-threatening arrhythmias.[12] This risk may limit the use of RAASi in CKD, with 1 study showing that 1 in 4 CKD patients discontinues RAASi and that hyperkalemia is the cause in two-thirds of cases.[13] In heart failure patients, hyperkalemia limits ACEi/ARB and MRA therapy in 2% to 3% and 12% of patients, respectively.[14] Strategies to mitigate hyperkalemia have been recommended to fully utilize the potential benefits of RAASi in CKD patients.[15] This includes use of potassium binders, which reduce serum potassium by exchanging potassium for other cations in the colon, thereby increasing fecal excretion. Concomitant use of such agents may enable greater RAASi, including the combination of ACEi/ARB and MRA, in CKD patients otherwise barred from treatment by hyperkalemia.[16,17] Trials confirm the ability of potassium binders to lower plasma potassium and to allow increased MRA use,[18–20] but the potential impact on renal end points is unclear. The Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER) trial did not observe an effect of potassium binders on blood pressure despite increased use of spironolactone.[19] This may be linked to the trial design, as patients were randomized to treatment with or without a potassium binder prior to the introduction of spironolactone. This approach allows for a double-blinded design, as MRA may be titrated based on serum potassium alone. However, it also entails the possibility of allocating patients to potassium binders although they may have tolerated MRA without them. Indeed, 66% in the placebo group remained on spironolactone compared to 86% in the patiromer group.

While similar designs are employed in other studies,[20,21] the translation of this in relation to clinical practice is challenging. Clinicians are likely to reserve the use of potassium binders to patients demonstrating hyperkalemia following intensified RAASi. To address this, we explored the feasibility of an alternative design requiring a documented episode of severe hyperkalemia caused by intensified RAASi prior to randomization to the potassium binder patiromer. Using this design, we hypothesized that patiromer would allow for increased RAASi and thereby reduce albuminuria.

METHODS

The MorphCKD trial protocol has previously been published.[22] The study (EU Clinical Trials Register 2020-001595-15) was approved by the "Central Denmark Region Committees on Health Research Ethics" (1-10-72-110-20) and the Danish Medicines Agency, adhering to the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent prior to any specific study procedures.

Design and Study Population

This open-label, randomized, multicenter clinical trial included patients aged 18 to 80 years with an eGFR between 25 to 60 ml/min per 1.73 m^2, albuminuria (UACR >200 mg/g or >500 mg/g for patients with/without diabetes, respectively), and either current hyperkalemia (P-potassium >4.5 mmol/l) or a history hereof twice within 24 months. Key exclusion criteria included renal transplant recipients, heart failure with an ejection fraction <40%, renal artery stenosis, or SGLT2i-initation within 30 days before inclusion. The study was conducted from August 20, 2020, to April 24, 2023, at Danish nephrology outpatient clinics at Aarhus University Hospital, Aalborg University Hospital and Gødstrup Hospital.

Interventions

The trial consisted of a 2- to 8-week run-in phase and a subsequent 52-week randomization phase. The run-in phase identified patients in whom significant hyperkalemia limited full RAASi. Following dietary counseling on avoidance of potassium-rich foods, RAASi was increased until participants developed significant hyperkalemia (P-potassium >5.5 mmol/l), other intolerable side effects or achieved maximum RAASi. Participants not on ACEi/ARB received losartan at 50 mg and then 100 mg, followed by addition of spironolactone at 25 mg to 50 mg. Participants already on ACEi/ARB received spironolactone at 25 mg and then 50 mg. Key metrics including eGFR, P-potassium, blood pressure and sodium were measured and assessed 2 weeks after each dose increase. In the absence of contraindications, the dose of losartan or spironolactone was increased (Supplementary Figure S1). Participants developing P-potassium >5.5 mmol/l were reduced to the preceding dose of RAASi and were randomly assigned (1:1) to a 52-week open-label treatment with or without patiromer. Those who did not were excluded. Patiromer was dosed at 8.4 mg to 25.2 mg aiming to maintain P-potassium ≤5.5 mmol/l; if unsuccessful, RAASi was reduced, mirroring control group procedures for P-potassium >5.5 mmol/l. Participants were monitored at outpatient clinics every 13 weeks. Participants on patiromer but not on full RAASi postrandomization received phone consultations and blood tests at weeks 2 and 4 to increase dose of one or both if applicable. Contraindications to RAASi increase, aside from hyperkalemia, included symptomatic

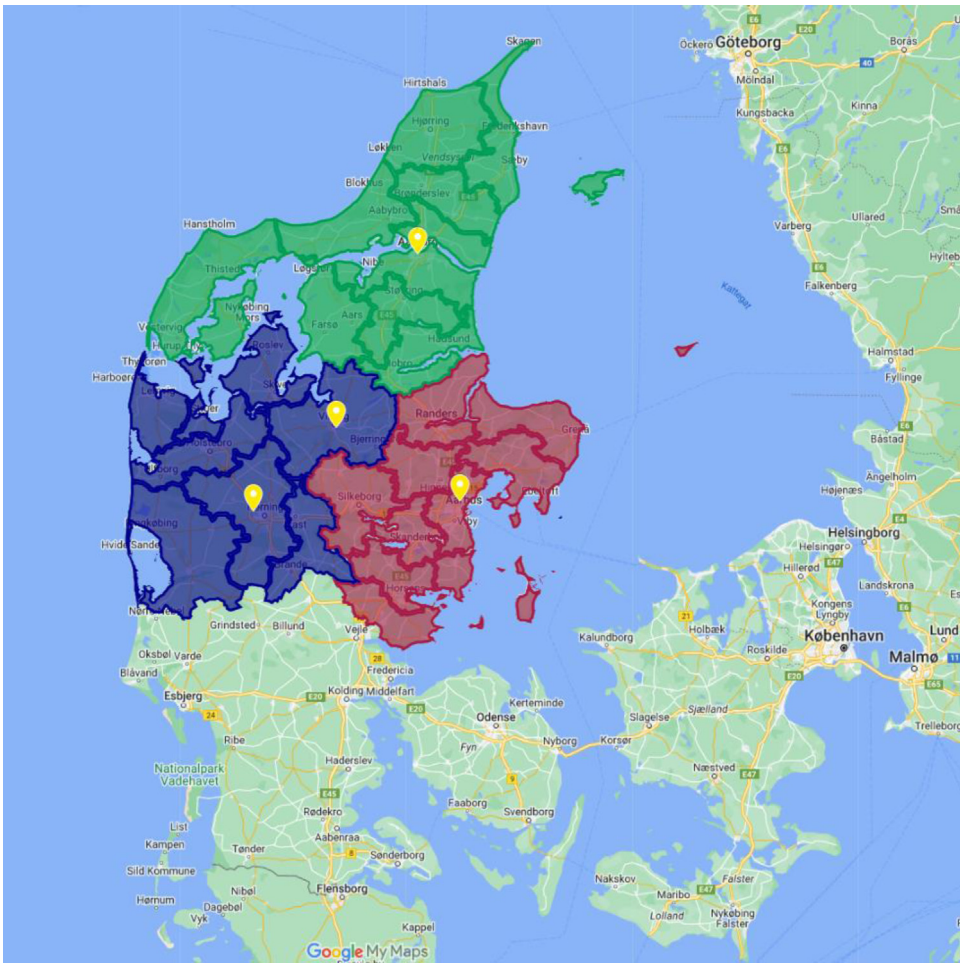

Figure 1. Study inclusion area. Map of Denmark with the Central Denmark Region (red and blue) and North Denmark Region (green). In the red area serviced by Aarhus University Hospital (approx. 800,000 people), all eligible patients as assessed from all blood- and urine samples from August 20, 2020, to March 9, 2022, were invited to the study independent of the clinical setting. In the areas serviced by Aalborg University Hospital (green) and Gødstrup and Viborg Hospitals (blue) (approximately 1,200,000 people), only eligible patients from the nephrology outpatient clinics were invited. The yellow pins are the locations of the *4* hospitals. Map created using Google My Maps.

hypotension, a >30% sustained eGFR decline from the start of RAASi titration, or P-sodium <130 mmol/l.

Outcomes

The primary end point was difference in the change in UACR, measured as an average of the 2 morning spot urines, from randomization to 52 weeks, between the 2 groups. Secondary end points included difference in UACR measured by 24-hour urine albumin excretion, difference in the incidence of acute kidney injury (AKI) or episodes with P-potassium >6.2 mmol/l during treatment, difference in UACR and maximal RAASi between the groups at 52 weeks, and differences in quality of life based on the short form 36 health survey (SF–36).[23]

Recruitment

Patients were recruited from all nephrology clinics in the North and Central Denmark Regions (serving a population of approximately 2,000,000). Since there is no private nephrology in Denmark, all clinics were hospital based. We further included patients from the entire population living within Aarhus University Hospital's service area (approx. 800,000 residents) (Figure 1) based on centrally recorded laboratory data from central database containing the results of all blood and urine analyses performed at hospitals, clinics, and general practitioners. Thus, inclusion from this population was independent of any current contact to hospital clinics or general practitioners. Prescreening utilized laboratory data retrieved from the central database via an algorithm designed to identify potential candidates aged 18 to 80. Individuals were considered potential candidates if, at any time within the preceding 24 months, they had an episode of eGFR between 20 to 65 ml/min per 1.73 m^2, an UACR >100 mg/g or >300 mg/g for diabetic/nondiabetic patients, respectively, and an episode of P-potassium >4.5 mmol/l, although not necessarily concurrently. The prescreening criteria were intentionally broader than the final

inclusion criteria, aiming to capture all potential participants, including individuals who could potentially meet eligibility requirements at a later stage. The algorithm was validated against approximately 300 randomly selected medical records from Aarhus University Hospital's nephrology clinic showing that all eligible candidates were successfully identified by the algorithm. Prescreening was performed at 4- to 12-month intervals to identify both prevalent and incident cases. Records from patients fulfilling age eGFR, UACR and P-potassium criteria within 24 months from prescreening were manually reviewed for eligibility. Eligibility of those not currently attending hospital clinics were based on age, diagnoses, and lab results. Eligible individuals at nephrology clinics and the Diabetes Clinic at Aarhus University Hospital were invited at planned visits to the clinics, while others were invited by letter. Consenting patients were screened after informed consent.

Sample Size and Statistical Methods

Calculations showed that 98 participants (49 in each group) were required for randomization to provide 80% power do detect a clinically relevant 1.5-fold greater reduction in albuminuria in the patiromer group compared with the control group with an alpha of 0.05 assuming a coefficient of variation of 80%. Under the assumption that 70% of participant would develop a P-potassium $\geq$5.5 mmol/l in the run-in phase, we aimed to include 140 participants. The primary end point was analyzed using unpaired *t*-test and secondarily with a multivariate 2-way repeated measures analysis of variance including UACR measurements from 3, 6 and 9 months. Secondary end points were analyzed using paired/unpaired *t*-test and Fisher's exact test depending on the variable of interest. Statistical analyses were performed using the STATA version 17.0 software package (StataCorp LP, College Station, TX). A two-sided *P*-value <0.05 was considered statistically significant.

Changes to the Protocol After Study Initiation

To increase inclusion rates, the protocol was adjusted during the inclusion period: (i) the UACR inclusion criterion was reduced from 500 mg/g to 200 mg/g for diabetic patients; (ii) upper eGFR and age limits were increased from 45 to 60 ml/min per 1.73 m^2 and 75 to 80 years, respectively; (iii) patients from Gødstrup and Viborg nephrology clinics were included in the study; and (iv) all individuals within Aarhus University Hospital's service area were prescreened as described. Additionally, patients initiating SGLT2i treatment within 30 days prior to enrolment were considered ineligible, and participants starting SGLT2i during the study were excluded.

RESULTS

Screening for Inclusion

Between August 20, 2020, and March 9, 2022, more than 10,000 patients attended scheduled nephrology clinic visits. Prescreening using the algorithm was performed 11 times at different sites during the study period. No eligible patients were manually identified from the outpatient clinics without concurrent detection by the prescreening algorithm. Investigators manually reviewed the resulting 3109 patient records recognized by the prescreening algorithm, identifying 317 eligible cases. The majority of ineligible patients did not fulfill all of the eGFR, P-potassium and/or UACR inclusion criteria at the time of their record review, despite meeting each criterion at some point within the preceding 24 months. Noneligible patients included patients with resolved AKI, progression of eGFR below 25 ml/min per 1.73 m^2, or patients with only single episodes of albuminuria or P-potassium $>$4.5 mmol/l. Other reasons included current MRA use, inability to provide informed consent, autosomal dominant polycystic kidney disease, vasculitis, or active malignancy. Of the 317 invited patients, 118 were not followed at study clinics and were invited by letter. Among these 118 patients, 30 (25%) consented to participate, with 21 being included. Twenty (17%) declined to participate, while 68 (58%) did not respond. In comparison, among the 199 patients invited in person at the study clinics, 71 (36%) consented to participate, 85 (43%) declined, and 43 (22%) did not respond (Figure 2). The reasons for declining participation were systematically recorded in the outpatient clinic at the primary site in Aarhus University Hospital only ($n = 30$). The most common cause ($n = 20$; 67%) was that participation was impractical, either due to patient-related factors such as the time required to travel from home to the hospital, lack of convenient transportation form and comorbidities, or study-related factors such as the length and/or number of visits and examinations. Seven (23%) did not provide a reason for declining to participate.

Of the 96 consenting patients screened, 75 entered the run-in phase (Figure 3). Inclusion was stopped after $18^2/_3$ months as prevalent cases were exhausted leaving inclusion to depend on few incident cases, strongly suggesting that the target could not be reached.

Participants

During the run-in-phase, most participants ($n = 44$) tolerated maximal RAASi without significant hyperkalemia or contraindications (Figure 3). Seven were

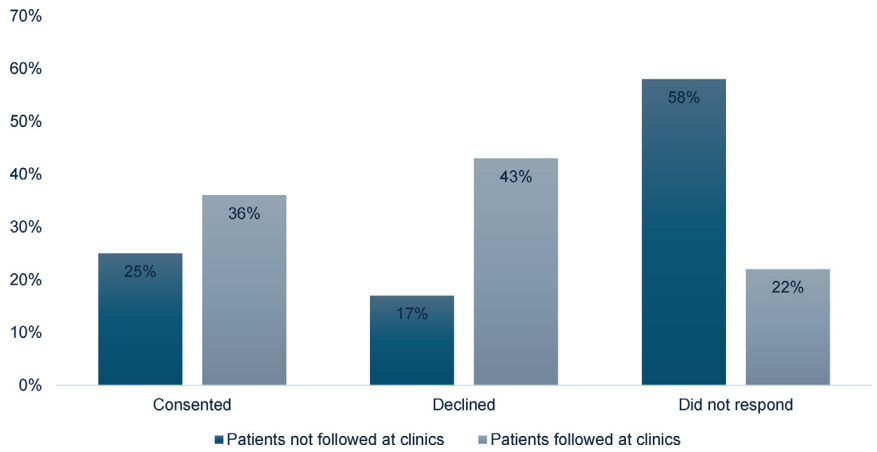

Figure 2. Response to study invitation. Responses from patients in the outpatient clinics (light blue) who were invited in-person and from patients not followed at the clinics (dark blue) who were invited via letter. The numbers are percentages of the total number of invited patients in that group.

excluded due to hypotension, sustained eGFR-decline, or withdrawal. Twenty-three developed significant hyperkalemia and were eligible for randomization. Two were excluded due to withdrawal or hyponatremia, leaving 21 participants for randomization to open-label treatment with patiromer ($n = 10$) or without ($n = 11$). One participant in the control group developed AKI progressing to kidney failure and discontinued the study shortly after the 6-month visit. Due to intolerable side effects, only 5 participants in the patiromer group received patiromer after 3 months (see section: other safety outcomes and adverse events).

Characteristics of the 20 participants at the time of randomization were similar, although the control group had higher BP and more albuminuria (Table 1).

Hyperkalemia and AKI

During run-in, 46 participants developed a P-potassium >5.0 mmol/l. Four required per protocol hospitalization due to a P-potassium >6.2 mmol/l; All were asymptomatic and discharged within 24 hours. Four participants experienced eGFR-declines >30% during titration requiring temporary reductions in RAASi. Following randomization, 2 participants from the patiromer group were hospitalized: 1 due to an inaccurate measurement indicating elevated potassium and the other due to ventricular arrhythmia associated with a potassium level of 5.9 mmol/l. Neither were on study medications at the time of the incidents. Event rates were too low for comparative statistics between groups. One participant in the control group developed of AKI with kidney failure and was excluded from the study.

Other Safety Outcomes and Adverse Events

No other serious adverse events occurred during run-in. Following randomization, 8 and 26 adverse events were observed in the control and patiromer groups, respectively (Table 2). In the latter, 9 experienced suspected patiromer-related gastrointestinal side effects. Diarrhea ($n = 4$) was most common, followed by constipation ($n = 2$) and abdominal pain ($n = 2$). Five discontinued patiromer before the 3 months. Reintroduction led to the reappearance of side effects in 4 participants. There were no serious adverse reactions to study drugs.

Effects on Albuminuria

Twenty participants completed the study. The 2 groups revealed similar reductions in UACR of around 27% (Supplementary Table S1, Supplementary Figure S2) that were not significantly different (Ratio 1.01; 95% confidence interval: 0.37–2.78; $P = 0.99$). Similar findings were observed using multivariate 2-way repeated measures analysis of variance or 24 hour urine albumin excretion.

DISCUSSION

The trial did not meet the targeted inclusion and only a small number of the included patients were eligible for randomization. Thus, no conclusions as to potential benefit of patiromer in combination with maximal tolerable RAASi with respect to a reduction in albuminuria in patients with CKD can be made.

Feasibility, Inclusion, and Randomization Criteria

Our efforts led to the inclusion of approximately half of the planned number of participants, with less than half of these being successfully randomized. This represents about 20% of the intended number. This was despite extensive efforts to identify eligible candidates using validated, regular prescreening of laboratory results among the large population described above. Thus, we

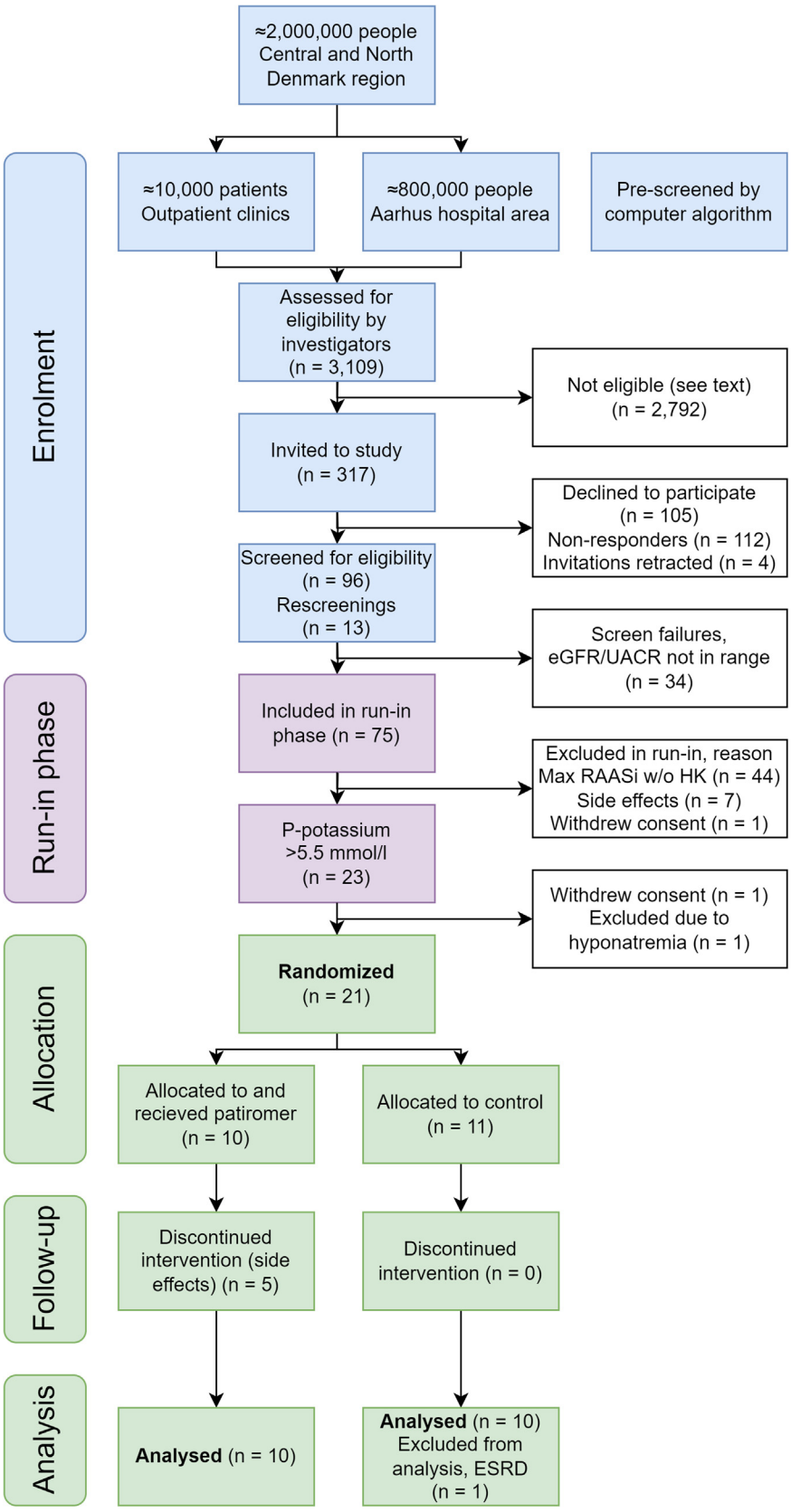

Figure 3. Flow diagram of the study. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RAASi, renin angiotensin aldosterone system inhibition; UACR, urine albumin-creatinine ratio.

Table 1. Patient characteristics at the time of randomization

Characteristics	Patiromer $n = 10$		Control $n = 10$	
Age (yr), mean (SD)	65.4	(12.5)	64.5	(6.0)
Male gender[a], *n* (%)	8	(80)	10	(100)
White race, *n* (%)	10	(100)	10	(100)
Systolic blood pressure (mm Hg), mean (SD)	122	(13.6)	131	(17.6)
Diastolic blood pressure (mm Hg), mean (SD)	75	(14.1)	80	(12.6)
BMI (kg/m^2), mean (SD)	29.2	(4.8)	27.1	(8.1)
Plasma creatinine (mmol/l), mean (SD)	181	(57)	185	(37)
eGFR (ml/min per 1.73 m^2), mean (SD)	34	(8.2)	33	(8.9)
UACR (mg/g), median (IQR)	486	(231)	657	(310)
P-Potassium (mmol/l), mean (SD)	5.0	(.4)	4.9	(.4)
Cause of CKD, *n* (%)				
Diabetes	3	(30)	4	(40)
Reflux nephropathy	1	(10)	1	(10)
Hypertension	1	(10)	4	(40)
Unknown	3	(30)	1	(10)
Other	2	(20)	0	
Comorbidities, *n* (%)				
Hypertension	10	(100)	9	(90)
Diabetes	4	(40)	4	(40)
Insulin-dependent	2	(20)	3	(30)
Gout	7	(70)	5	(50)
Atrial fibrillation/flutter	2	(20)	0	
Stroke	2	(20)	1	(10)
Heart failure	0		0	
Charlson comorbidity index,[46] mean (SD)	5.4	(2.1)	5.2	(1.3)
Started run-in on losartan, *n* (%)	1	(10)	2	(20)
Started run-in on spironolactone, *n* (%)	9	(90)	8	(80)
Antihypertensives, *n* (%)				
ARB (losartan)	5	(50)	6	(60)
ACEi[b]	4	(40)	3	(30)
Ramipril	4	(40)	2	(20)
Enalapril	0		1	(10)
Loop diuretic	3	(30)	4	(40)
Thiazide	4	(40)	0	
Ca-antagonist	5	(50)	6	(60)
Beta-blocker	4	(40)	2	(20)
Other antihypertensives	0		1	(10)

ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BMI, body mass index; CKD, Chronic kidney disease; Loop diuretic, Na^+-K^+-$2Cl^-$ cotransporter inhibitors; P-Potassium, Plasma potassium; SD, Standard deviation; UACR, urine albumin-creatinine ratio.
[a]Gender refers to the biological sex assigned at birth (male or female).
[b]Two patients, one in each group, temporarily withheld ACEi treatment prior to randomization due to severe of hyperkalemia. It was resumed at randomization.

Table 2. Adverse events

Event type	Run-in	Control	Patiromer
Any event	31	8	26
Adverse events	27	5	22
Diarrhea			6
Rash			1
Constipation			3
Gout		1	1
Kidney biopsy		1	
Erysipelas		1	
Angina pectoris		1	
Pruritis		1	
eGFR decline >25%	4		2
P-potassium >5.5 mmol/l	23		1
Acidosis			2
Gynecomastia			1
Abdominal pain			2
Nausea			1
Hypomagnesemia			1
Feeling unwell			1
Serious adverse events	4	3	4
Hyperkalemia >6.2 mmol/l	4		
Appendectomy			1
Admitted due to erroneous potassium measurement			1
Ventricular tachycardia			1
New onset cancer			1
Acute kidney injury		1	
Fractured hip		1	
Psychiatric admission		1	

eGFR, estimated glomerular filtration rate.
Note that episodes of hyperkalemia with P-potassium < 5.5 mmol/l are not reported, as this was in accordance with the protocol.

are confident that we invited the vast majority of eligible candidates. The unexpectedly low number of eligible patients is surprising given the reported incidence of hyperkaliemia as a limiting factor of RAASi.[11,13] In our experience, hyperkalemia, albuminuria or eGFR in the range of 25 to 60 ml/min per 1.73 m^2 are each common occurrences; however, as demonstrated here, their coexistence is infrequent. Our lack of success identifying CKD patients who may benefit from increased RAASi while constrained by hyperkalemia are reflected in a similar study stopped early due to low inclusion (P. Rossing, personal communication; September 6, 2023).[24] There are several issues that should be considered addressing the lack of feasibility relation to inclusion and randomization. Expanding inclusion and/or randomization criteria might have increased target population diversity and thus feasibility. However, it would also risk including patients in whom hyperkalemia is not a relevant concern or who might not benefit from intensified RAASi. Notably, our eGFR and albuminuria criteria align with those from guidelines and trials demonstrating clinical benefit of RAASi and other CKD interventions[3,25–28] with respect to the progression of CKD. Furthermore, the STOP ACEi trial[29] suggested no harm, but also no renal benefit of continuing RAS-inhibition in patients with eGFR less than 30 ml/min per 1.73 m^2. Thus, we believe that there is currently little evidence supporting renal benefit from increasing RAAS-inhibition in patients with very low eGFR. However, RAASi may also reduce cardiovascular risk, even in patients with low eGFR.[29–31] Inclusion of improved blood pressure control as well as cardiovascular end points or surrogate markers hereof may increase the relevant target population to patients with an eGFR <25 ml/min per 1.73 m^2 as well as patients without albuminuria. This may have significantly increased the number of eligible patients as most patients with hyperkalemia have GFR levels below 30 ml/

min per 1.73 m^2.[32] Similarly, potassium binders may be applied to minimize the need for restricting potassium rich foods that may exclude patients from an otherwise healthy diet[33] with potential cardiovascular benefits. This aim was not explored in this study.

A P-potassium >5.5 mmol/l was required for randomization to patiromer, as such levels are associated with increased mortality, indicating the need for potassium-lowering interventions.[34–36] Lowering this threshold would increase participant randomization, advancing study feasibility. Indeed, a cut-off of P-potassium >5.0 mmol/l would double the number of eligible participants from 23 to 46 (data not shown). No consensus exists on the potassium level necessitating potassium binder treatment during RAASi. Kidney Disease Improving Global Outcomes guidelines advise dietary or medication adjustments, including potassium binders, to mitigate hyperkalemia if serum potassium exceeds 5.5 mmol/l with nonsteroidal MRA usage, while the European Society of Cardiology guidelines recommend potassium binder initiation if serum potassium is >5.0 mmol/l.[37,38] Although no serious hyperkalemia-related adverse events were observed postrandomization, 4 participants required short admissions for hyperkalemia treatment during run-in, suggesting that a threshold under 5.5 mmol/l might be appropriate to minimize such events.

The study required that participants developed hyperkalemia within 2 weeks of increased RAASi to be randomized. However, hyperkalemia may take longer to develop, and P-potassium levels fluctuate. Hence, it is likely that a longer run-in period would yield a higher number of randomized participants, consistent with data from the AMBER trial showing an increase in number of participants with hyperkalemia in the control group over time.[19] This must be weighed against increasing study complexity and burden on participants with a long run-in, which may also hamper patient recruitment.[39] In addition to the short follow-up, the inclusion of dietary counseling may have affected the incidence of hyperkalemia during run-in, particularly as many of many of the included patients had no previous recorded evidence of dietary counseling. Thus, dietary counseling may likely have attenuated the immediate impact of RAASi on potassium levels in patients with high potassium intake. In the present study, only participants with a current episode of hyperkalemia following an increase in RAASi were randomized to a potassium binder. This was aimed to mimic clinical practice, in which potassium binders are most likely to be prescribed in response to a documented, hyperkalemic event after intensified RAASi treatment, rather than preemptively before increasing RAAS. Other study designs have assigned participants to a potassium binder prior to significant hyperkalemia, thus possibly increasing feasibility,[19] but with the risk of including a large proportion of participants on potassium binders that do not require these to maintain safe potassium levels. This may make it difficult to identify an appropriate target population and complicate evaluation of both clinical benefit and safety outcomes when translating such studies to clinical practice. Conversely, adopting a design closely mirroring clinical practice, as presented here, does not appear feasible given the low number of eligible patients.

Limitations

Of the 317 patients invited to participate, 96 (30%) accepted the invitation. This acceptance rate falls below the approximately 50% reported in other studies.[40–42] This may in part be due to the fact, that more than a third of the patients were invited by letter only, a format known to have a lower recruitment success.[43] This is supported by the larger number of nonresponders and a lower recruitment rate among those invited via letter (Figure 2).

In addition to the unsuccessful inclusion of the required number of patients, half of the participants randomized to patiromer discontinued treatment within 3 months due to suspected gastrointestinal side effects. Furthermore, 4 of the 5 that remained on treatment reported gastrointestinal side effects. While these are known side effects from patiromer, they are reported in much lower rates (around 10%) in other long-term open-label trials and real-world data.[44,45] We have no explanation for this disparity, but we can only speculate on possible effects of more advanced CKD, frailty, comorbidities, or systematic information to participants on these possible side effects prior to initiation.

Also, the open-label use of patiromer may bias both participants and investigators, affecting the distinction between adverse events and reactions or their ability to make unbiased decisions regarding the use of study drugs and other antihypertensives. Strict protocols governed therapy adjustment, but bias can never be ruled out completely. Our primary end point was albuminuria. Although an established marker of CKD progression,[9] it is not a hard renal end point, and as previously discussed, the study did not address other potential benefits from the use of potassium binders and increased RAASi, e.g., improved blood pressure control, reduced cardiovascular risk and/or a more liberal oral potassium intake.

In conclusion, this trial explored the feasibility of a study design aimed to mimic clinical practice, in which a documented episode of hyperkalemia caused by intensified RAASi was required prior to the introduction of the potassium binder patiromer. Despite

screening of a large group of patients, including patients not under nephrology care, the study failed to demonstrate any effect on albuminuria. Our findings emphasize the importance of defining the circumstances that warrants initiation of potassium binder treatment in clinical practice and to include these in trial designs aimed to demonstrate the potential benefit from additional us of potassium binders.

DISCLOSURE

FHMa has received consultancy fees, honoraria, and/or meeting attendance support from AstraZeneca and CSL Vifor. CDP obtained honoraria, consultancy fees, funding, and travel expenses from AstraZeneca Astellas, CSL Vifor, and Boehringer Ingelheim. SFN and BM have no conflict of interests to declare. LN received speaker honoraria from Vifor Pharma. FHMo has received speaker honoraria from Baxter, Boehringer Ingelheim and AstraZeneca. HB has received a research grant from GlaxoSmithKline and Vifor Pharma (institutionally paid), consulting fees/honoraria from CSL Vifor, AstraZeneca, Boehringer Ingelheim, GSK, Galapagos, Alexion, MSD, and Novo Nordisk, plus meeting support from Novartis and AstraZeneca.

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DATA AVAILABILITY STATEMENT

Data are available upon reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

HB, FHMa, and CDP conceptualized and designed the study. FHMa, SFN, LN, BM, and FHMo acquired the data. FHMa wrote the initial draft, with HB performing primary revisions. All authors revised the manuscript for important intellectual content and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. RAASi titration algorithm for the run-in phase of the study.

Figure S2. Changes in albuminuria from randomization to 12 months.

Table S1. Changes in clinical parameters from randomization to 12 months.

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