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Patiromer to Enable Spironolactone Use in the Treatment of Patients with Resistant Hypertension and Chronic Kidney Disease: Rationale and Design of the AMBER Study

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Keywords
Chronic kidney disease · Hyperkalemia · Patiromer · Resistant hypertension · Spironolactone

Abstract

Background: While chronic kidney disease (CKD) is common in resistant hypertension (RHTN), prior studies evaluating mineralocorticoid receptor antagonists excluded patients with reduced kidney function due to risk of hyperkalemia. AMBER (ClinicalTrials.gov identifier NCT03071263) will evaluate if the potassium-binding polymer patiromer used concomitantly with spironolactone in patients with RHTN and CKD prevents hyperkalemia and allows more persistent spironolactone use for hypertension management. ***Methods:*** Randomized, double-blind, placebo-controlled parallel group 12-week study of patiromer and spironolactone versus placebo and spironolactone in patients with uncontrolled RHTN and CKD. RHTN is defined as unattended systolic automated office blood pressure (AOBP) of 135–160 mm Hg during screening despite taking ≥3 antihypertensives, including a diuretic, and an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (unless not tolerated or contraindicated). The CKD inclusion criterion is an estimated glomerular filtration rate (eGFR) of 25 to ≤45 mL/min/1.73 m^2. Screening serum potassium must be 4.3–5.1 mEq/L. The primary efficacy endpoint is the between-group difference (spironolactone plus patiromer versus spironolactone plus placebo) in the proportion of patients remaining on spironolactone at Week 12. ***Results:*** Baseline characteristics have been analyzed as of March 2018 for 146 (of a targeted 290) patients. Mean (SD) baseline age is 69.3 (10.9) years; 52.1% are male, 99.3% White, and 47.3% have diabetes. Mean (SD) baseline serum potassium is 4.68 (0.25) mEq/L, systolic AOBP is 144.3 (6.8) mm Hg, eGFR is 35.7 (7.7) mL/min/1.73 m^2. ***Conclusion:*** AMBER will define the ability of patiromer to facilitate the use of spironolactone, an effective antihypertensive therapy for patients with RHTN and CKD.

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Background and Study Rationale

Resistant hypertension (RHTN) is defined by blood pressure remaining above the treatment goal despite treatment with optimally tolerated doses of 3 antihypertensive agents from different drug classes, including a diuretic [1]. In addition to a diuretic, most practice guidelines recommend treatment with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and a calcium channel blocker in these patients [2–7]. Treatment-RHTN remains a significant medical problem, with prevalence estimates of up to 8% among treated hypertensive patients evaluated by 24-h ambulatory blood pressure monitoring [8], and approaching 50% in specific cohorts, such as patients with chronic kidney disease (CKD) with proteinuria [9, 10].

Despite the inhibition of the renin-angiotensin-aldosterone system with an ACEI or ARB, RHTN may result from abnormal sodium retention caused by aldosterone breakthrough, a phenomenon affecting 30–40% of patients treated with an ACEI or ARB over 1 year [11]. In non-epithelial tissues, aldosterone-induced activation of mineralocorticoid receptors in the presence of high extracellular sodium levels promotes tissue inflammation and injury, which may contribute to the progression of CKD and cardiovascular disease [12–14]. Together, these observations provide the rationale for use of aldosterone antagonists (mineralocorticoid receptor antagonists [MRAs]) such as spironolactone in patients with RHTN [15].

Two meta-analyses of clinical and observational studies conducted from 2002 to 2013 concluded that spironolactone effectively reduces blood pressure in patients with RHTN, although the studies were often nonrandomized, and comparison between other treatment options was limited [16, 17]. Subsequent to these meta-analyses, the PATHWAY-2 study, a randomized, double-blind, crossover study, evaluated patients with RHTN rotated through 12 weeks of add-on treatment with spironolactone, bisoprolol, doxazosin, or placebo [18]. Spironolactone was found to be significantly more effective than the other drugs in reducing blood pressure, regardless of plasma renin levels, although most effective in those with the lowest renin levels. Most RHTN studies evaluating spironolactone have excluded patients with significant CKD due to the risk of hyperkalemia. In a meta-analysis, the addition of spironolactone to an ACEI or ARB doubled the risk of hyperkalemia in patients with mild to moderate CKD, which was dependent on baseline estimated glomerular filtration rate (eGFR), serum potassium (K^+) level, drug dose, and concomitant medications [19]. Similar findings were reported in an observational study, where addition of an MRA to a diuretic-renin-angiotensin-aldosterone system inhibitor regimen was most likely to cause hyperkalemia in patients with baseline eGFR ≤45 mL/min/1.73 m^2 and serum K^+ >4.5 mEq/L [20]. The development of potassium binders with improved tolerability may allow for increased persistence of MRAs in CKD patients with RHTN by reducing the risk of hyperkalemia.

Patiromer is a sodium-free, non-absorbed, K^+-binding polymer used for lowering serum K^+ in patients with hyperkalemia [21, 22]. Previously, patiromer prevented hyperkalemia in spironolactone-treated heart failure patients with eGFR <60 mL/min/1.73 m^2 and a history of hyperkalemia [23]. These findings in a heart failure population support the evaluation of patiromer as a therapy to prevent hyperkalemia when RHTN patients are treated with spironolactone, since its use in CKD is often limited by the risk of hyperkalemia [6].

Methods

This is a randomized, double-blind, placebo controlled, parallel group study of patiromer for the enablement of spironolactone use for blood pressure control in patients with RHTN and CKD (AMBER; ClinicalTrials.gov identifier NCT03071263). This multicenter, multinational study will compare patiromer versus placebo with concomitant spironolactone in patients with RHTN and CKD. AMBER is ongoing, and began enrolling patients on January 23, 2017. The study consists of a screening/run-in period of up to 4 weeks, a double-blind treatment period of 12 weeks, and a follow-up visit scheduled 2 weeks after the treatment period or early termination (Fig. 1).

Study Oversight and Eligibility

The study is being conducted in accordance with the Declaration of Helsinki and in compliance with International Conference for Harmonisation E6 Guidelines for Good Clinical Practice and all applicable local and national regulations governing the conduct of human clinical trials. Study sites must obtain the approval from the Institutional Review Board/Independent Ethics Committee before performing any study-related procedures, and all patients must provide written informed consent before participating.

Patients ≥18 years old with uncontrolled RHTN and an eGFR of 25–45 mL/min/1.73 m^2 are eligible to participate in the study. Complete lists of inclusion and exclusion criteria are given in online supplemental Tables 1, 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000492622). Prohibited medications are listed in online supplemental Table 3.

The screening/run-in period consists of 4 visits (S1, S2, S3, and S4), each separated by 4 to 10 days, and is designed to ensure that patients are on stable doses of medication, have true treatment-RHTN, can properly and reliably use a home blood pressure (HBP)

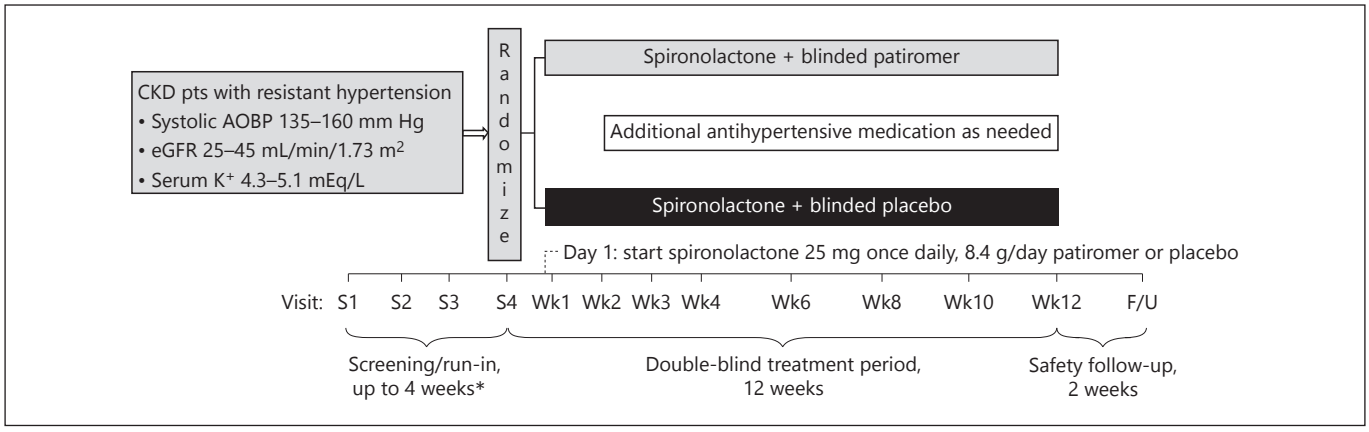

Fig. 1. AMBER study design. AOBP, automated office blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBP, home blood pressure. * To ensure eligibility criteria, stable medication, and competent use of HBP monitor.

monitor, and meet all inclusion criteria. At each visit after the initial screening visit, 2 types of office blood pressure measurements will be made on the patient: Automated office blood pressure (AOBP) and self-measured blood pressure (SMBP).

Automated Office Blood Pressure

AOBP will be performed by an oscillometric blood pressure monitoring device (Intellisense® HEM-907; Omron Healthcare Inc., Kyoto, Japan). AOBP will be measured in triplicate. The device is programmed to allow a 5-min rest period before initiating the sequence of triplicate measurements, with a 1-min interval between each measurement. The site staff leaves the room for these automated measurements.

Self-Measured Blood Pressure

At the first visit, patients are provided with an HBP monitor (Tel-O-Graph®, I.E.M. GmbH, Stolberg, Germany). Patients are trained in its use, and are instructed to measure HBP in triplicate twice daily after 5 min of seated rest at the same times each day (e.g., 8:00 am and 8:00 pm). For each scheduled office visit, patients are instructed to bring their HBP monitor with them. Immediately following the measurement of AOBP, patients will then take SMBP in triplicate before site staff returns to the room. If a patient does not bring their HBP device, then only AOBP will be taken during that visit (SMBP data will be recorded as missing).

Treatment Assignment

Patients meeting all eligibility criteria at the final screening visit will be stratified by the local K^+ measurement (4.3 to <4.7 vs. 4.7 to 5.1 mEq/L) and history of diabetes (yes versus no), then randomized (1:1) to receive patiromer or placebo in addition to open-label spironolactone. The blinded study drug will be provided in packets as a powder for oral suspension, with each packet containing patiromer (4.2 g) or microcrystalline cellulose placebo. The treatment assignment will be determined via an interactive web response system, with study personnel blinded to the results. All randomized patients will be instructed when to take spironolactone, patiromer or placebo, and their antihypertensive medications, starting on Day 1 of the randomized treatment period. Visits during the treatment period are weekly (Weeks 1–4) and then biweekly (Weeks 6–12).

Spironolactone

Open-label spironolactone will be started at 25 mg once daily and increased to 50 mg once daily at Week 3 in patients with systolic AOBP ≥120 mm Hg and K^+ ≤5.1 mEq/L (as shown in the spironolactone dosing algorithm in Fig. 2). Patients with systolic AOBP ≥120 mm Hg and serum K^+ >5.1 mEq/L at Week 3 will continue on the 25-mg spironolactone dose until the first subsequent visit at which serum K^+ is ≤5.1 mEq/L (and systolic AOBP remains ≥120 mm Hg), at which time the spironolactone dose will be raised to 50 mg. Patients with systolic AOBP <120 mm Hg at Week 3 will continue on the 25-mg dose. At any visit, if a patient experiences hypotensive symptoms, with systolic AOBP <120 mm Hg, or if systolic AOBP is <100 mm Hg, the spironolactone dose may be reduced to 25 mg every other day or discontinued at the investigator's discretion. If spironolactone is discontinued, double-blind study drug (patiromer or placebo) will be discontinued at the same time. Patients who discontinue spironolactone and patiromer/placebo for any reason will remain in the study and be treated with standard medical care based on the investigator's clinical judgment. Dietary counseling will also be provided at each visit in accordance with the standard practices of the investigator.

Patiromer

Patients will initiate study medication with 2 packets daily taken with food at least 3 h before or 3 h after other medications, including spironolactone. Dosing adjustments will be made at intervals of ≥1 week in 2-packet/day increments upward for local serum K^+ >5.1 mEq/L and downward for serum K^+ <4.0 mEq/L (as shown in the patiromer/placebo dosing algorithm in Fig. 3). The maximum daily dosage is 6 packets; the minimum is 0 packets. Patients who develop serum K^+ ≥5.5 mEq/L that cannot be managed with blinded patiromer/placebo dosage escalation will discontinue spironolactone and patiromer/placebo treatments. These patients will remain in the study and will be followed per protocol, with hyperkalemia treated using standard of care.

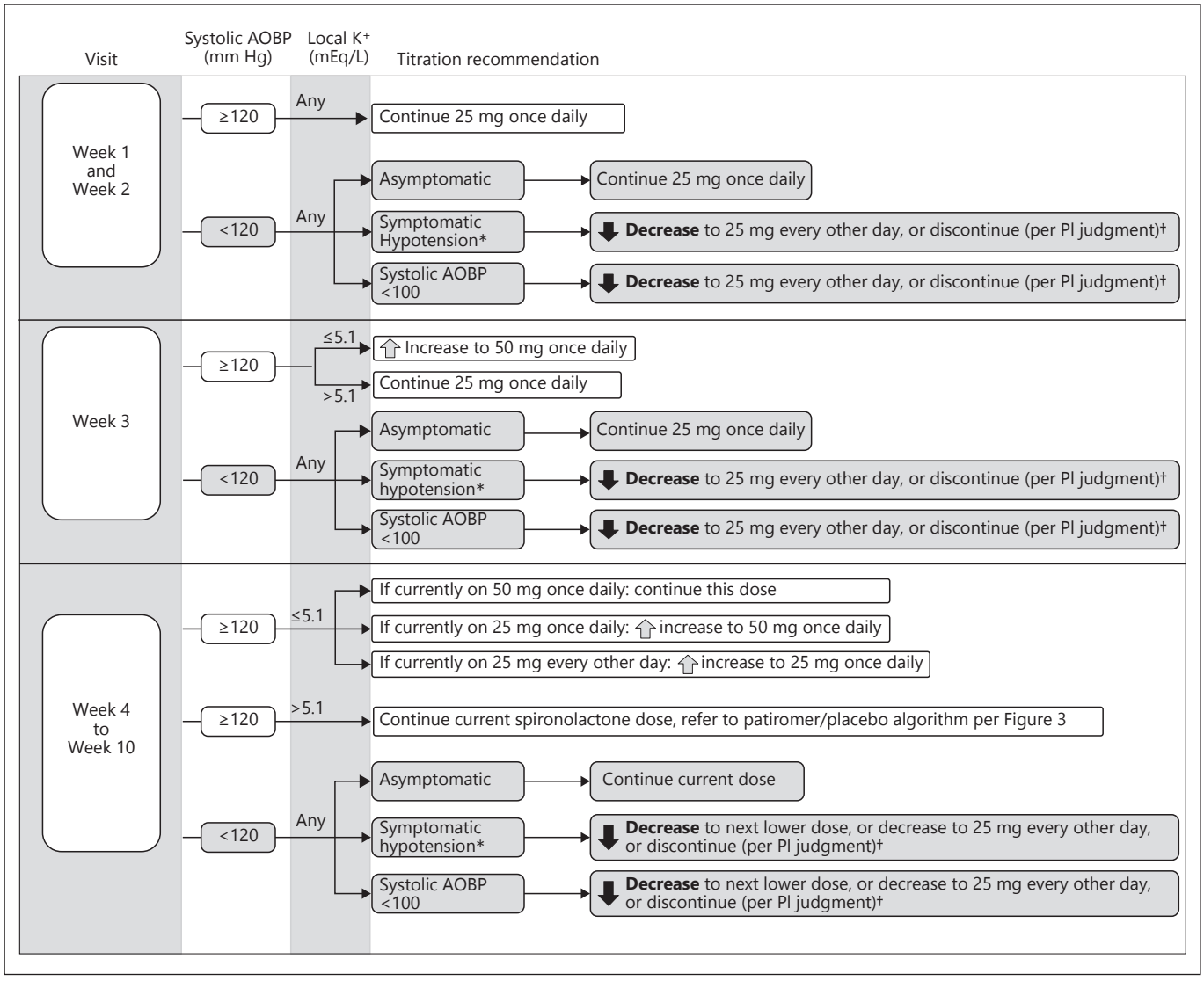

Fig. 2. Spironolactone dosing algorithm. AOBP, automated office blood pressure; K^+, potassium; PI, principal investigator. * Investigator determined. † If spironolactone is discontinued, patiromer/placebo must be discontinued at the same time.

Study Endpoints

The primary endpoint is the difference in the proportion of patients remaining on spironolactone at Week 12 between treatment groups (spironolactone plus patiromer versus spironolactone plus placebo). A key secondary endpoint is the difference in systolic AOBP from baseline to Week 12 (or to the last available AOBP before addition of any new antihypertensive medications or change in any of the baseline antihypertensive medications) between treatment groups. Other endpoints include the following: within-group changes in systolic AOBP from baseline to Week 12, changes in K^+ levels over time measured by a central laboratory and by local laboratories, proportion of patients with serum K^+ ≥5.5 mEq/L, average daily dose and cumulative dose of spironolactone, time to discontinuation of spironolactone, and changes in albuminuria (urine albumin to creatinine ratio) from baseline to Week 12. HBP data will be examined via exploratory analysis. In addition, the EuroQol Group 5-domain 5-level (EQ-5D-5L) questionnaire, a generic patient-reported instrument for measuring incremental changes in health, will be collected at baseline and Week 12 (or early termination) [24]. The questionnaire is composed of 5 questions representing 5 health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Sample Size Determination

AMBER plans to enroll approximately 290 patients at 60 sites in the United States, South Africa, the United Kingdom, France, Germany, Croatia, Hungary, Georgia, and Ukraine. The planned sample size ensures that at least 280 patients will be available for the

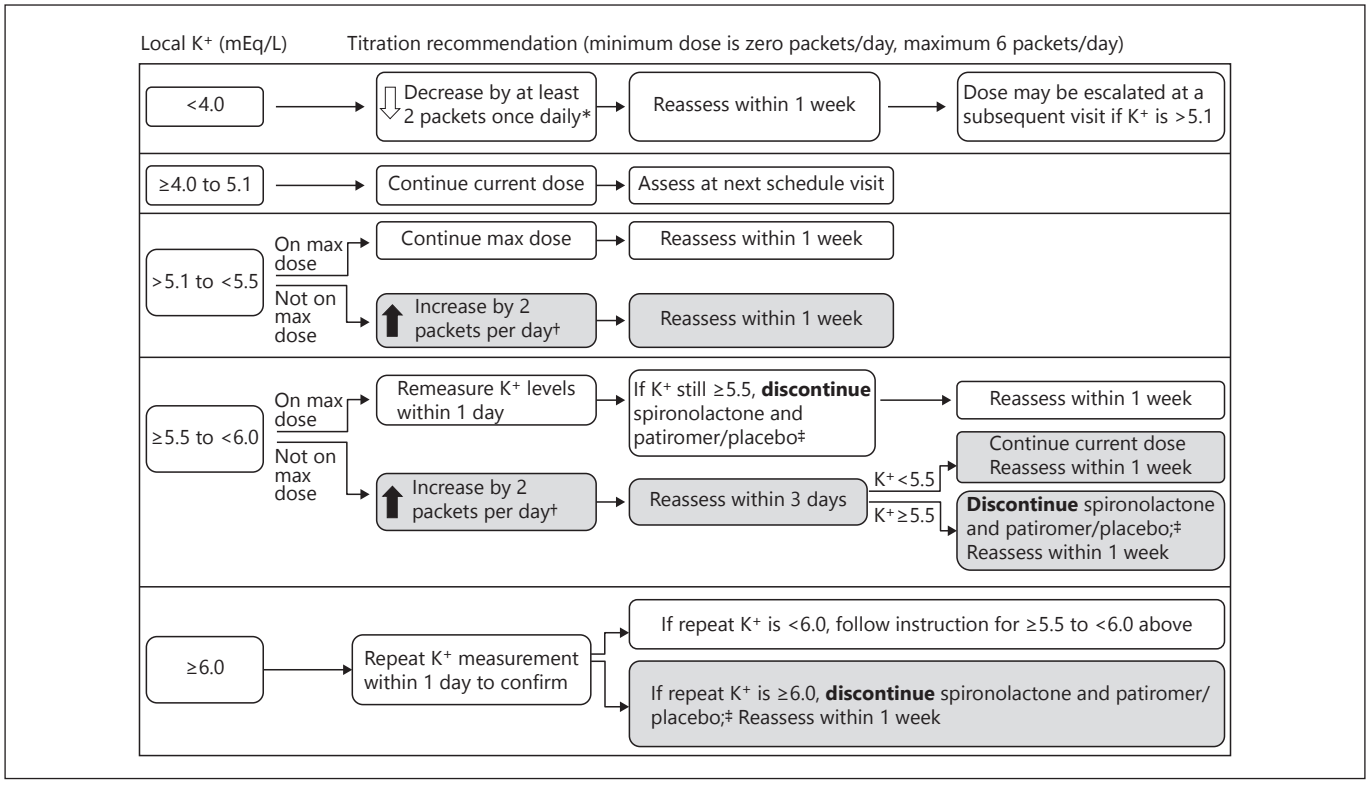

Fig. 3. Patiromer dosing algorithm. K^+, potassium. * Each packet contains patiromer (4.2 g) or microcrystalline cellulose placebo. † All dose increases should be made no less than 1 week apart. ‡ After discontinuation, hyperkalemia may be treated at any time using standard of care per Investigator judgment.

primary endpoint analysis, allowing for the possibility that up to 10 randomized patients will not take any study medication. A cohort of 280 patients provides 90% power to detect a difference between treatment groups of ≥20% in the proportion of patients remaining on spironolactone at Week 12 at an $\alpha = 0.05$. Assuming a dropout rate of 15%, the sample size also provides approximately 80% power to detect a 4 mm Hg difference between treatment groups in change in systolic AOBP from Baseline to Week 12 (or to the last available AOBP before addition of any new antihypertensive medications or change in any of the baseline antihypertensive medications).

Monitoring Changes in Renal Function

Acute reductions in GFR have been reported with the initiation of spironolactone, similar to those observed when starting an ACEI or ARB, and have been attributed to transient changes in glomerular hemodynamics [6, 25]. Similar to renin-angiotensin blocker agents, these changes typically do not impact long-term renal function [26–28]. Therefore, subjects will be monitored for changes in renal function, especially during periods of medication changes or adjustments. Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations for the detection and management of early decreases in GFR when initiating ACEIs or ARBs will be considered in this study for spironolactone when reductions in renal function occur [29].

Extrapolating from the KDOQI guidelines for ACEI/ARBs, in this study, we define an early decline in eGFR as a >15% reduction from baseline within 4 weeks of starting spironolactone; no change in spironolactone dose is needed for decreases in eGFR ≤30%. However, for decreases in eGFR of 30–50%, the spironolactone dose should be decreased and eGFR monitored weekly; spironolactone should be discontinued if eGFR does not return to within 30% of baseline within 4 weeks. For eGFR decreases >50%, spironolactone should be discontinued and eGFR monitored weekly until it returns to within 15% of baseline.

Assessments

AOBP will be measured at all visits. These measurements will be performed before other scheduled assessments except for the S4 and Week 12 visits, when EQ-5D-5L will be administered first. A 24-h urine collection will be performed prior to the baseline visit, and the first 3 morning urine samples will be collected at baseline and periodically throughout the study for central laboratory assessment of albuminuria (urine albumin-to-creatinine ratio). Serum K^+ will be assessed locally and by a central laboratory at all study visits. The central laboratory will analyze all other laboratory tests, including serum and urine chemistry, creatinine, and hematology. N-terminal pro b-type natriuretic peptide levels will also be measured as a biomarker of cardiac stress. Spironolactone levels in blood will be measured by mass spectrometry. Adverse events will be monitored at all visits, and physical examinations and 12-lead electrocardiograms will be performed at the S1 and Week 12 visits.

Statistical Plan

The primary endpoint will be compared between treatment groups using the Cochran-Mantel-Haenszel test, stratified by baseline K^+ category (4.3 to <4.7 vs. 4.7 to 5.1 mEq/L) and presence/absence of diabetes mellitus. The secondary endpoint will be analyzed using an analysis of covariance (ANCOVA) model, with baseline systolic AOBP as a covariate and baseline serum K^+ and presence/absence of diabetes mellitus as categorical factors. The primary and secondary endpoints will also be evaluated in several pre-specified subgroups of interest, including gender, age group (<65 vs. ≥65 years), and diabetes (yes vs. no). Change in systolic AOBP at Week 12 will be analyzed with an ANCOVA model for patients with non-missing systolic AOBP at both baseline and Week 12, and additionally using a repeated measures mixed model that includes all patients with at least one post-baseline measurement of systolic AOBP. These models will also include baseline systolic AOBP as a covariate and presence/absence of diabetes mellitus and baseline serum K^+ as categorical factors. Time to discontinuation of spironolactone will be analyzed using Kaplan-Meier methods, and average daily and cumulative dose of spironolactone will be analyzed using ANCOVA methods. Change in albuminuria, serum K^+ levels, EQ-5D-5L questionnaire results, and safety parameters will be summarized descriptively.

Characteristics of Randomized Patients

Baseline characteristics, analyzed as of March 2018 for 146 randomized patients (of a targeted 290 patients) who had completed through Week 12, are shown in Table 1. Overall, the mean (SD) baseline age is 69.3 (10.9) years, with 52.1% male, and 99.3% of White race. Roughly half of the patient population (47.3%) has diabetes mellitus, with a mean time since the diagnosis of 13.4 years; 50.7% have a history of heart failure. The mean (SD) baseline values are as follows: for eGFR, 35.7 (7.7) mL/min/1.73 m^2, for serum K^+, 4.68 (0.25) mEq/L, for systolic AOBP, 144.3 (6.8) mm Hg, and for diastolic AOBP, 79.7 (12.1) mm Hg.

Table 1. Baseline characteristics of randomized patients*

Characteristic	Randomized (n = 146)
Age, years, mean (SD)	69.3 (10.9)
≥65 at informed consent, *n* (%)	104 (71.2)
Male, *n* (%)	76 (52.1)
White race, *n* (%)	145 (99.3)
Ethnicity, *n* (%)	
Hispanic or Latino	12 (8.2)
Non-Hispanic and non-Latino	133 (91.1)
Not reported	1 (0.7)
Diabetes mellitus, *n* (%)	69 (47.3)
Time since diagnosis, years, mean (SD)	13.4 (8.3)
Serum potassium (local), mEq/L, mean (SD)	4.68 (0.25)
eGFR, mL/min/1.73 m^2, mean (SD)	35.7 (7.7)
Automated office blood pressure, mm Hg, mean (SD)	
Systolic	144.3 (6.8)
Diastolic	79.7 (12.1)
Antihypertensive medications, *n* (%)	
Beta blockers	89 (61.0)
Calcium channel blockers	105 (71.9)
Non-RAASi diuretics	132 (90.4)
RAASi	145 (99.3)
Other	34 (23.3)
History of hyperkalemia associated with the use of ACEi, ARB, or MRA, *n* (%)	2 (1.4)
Cardiac disorders, *n* (%)	88 (60.3)
Atrial fibrillation	14 (9.6)
Atrial flutter	1 (0.7)
History of stroke or cerebrovascular accident, *n* (%)	18 (12.3)
History of myocardial infarction, *n* (%)	31 (21.2)
History of heart failure, *n* (%)	74 (50.7)
Ejection fraction, mean (SD)	47.5 (9.6)
Preserved ejection fraction, *n* (%)	24 (16.4)
Reduced ejection fraction, *n* (%)	36 (24.7)
Unknown	14 (9.6)
NYHA class, *n* (%)	
I	11 (7.5)
II	55 (37.7)
III	8 (5.5)

* Analyzed as of March 2018 for 146 randomized patients (of a targeted 290 patients) who had completed through Week 12.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation.

Discussion

Spironolactone has been shown to reduce blood pressure in the general RHTN population [16, 17], and in RHTN patients with heart failure with preserved ejection fraction [30]. It has been found to be a more effective BP-lowering agent compared with other medication classes, as demonstrated in PATHWAY-2 [18]. Despite having a high prevalence of RHTN, patients with clinically significant CKD are typically excluded from treatment trials, as these patients have higher risk and often develop clinically significant hyperkalemia when exposed to renin-angiotensin blocking agents and MRAs. Hence, the CKD population with RHTN remains understudied and underserved.

The AMBER study design was based on the hypothesis that concomitant use of spironolactone and patiromer in CKD patients with RHTN will better manage the risk of hyperkalemia, and thereby allow more persistent use of spironolactone – which ultimately would lead to improved blood pressure control. A unique aspect of the AMBER trial is that it will measure AOBP while the patient is unat-

tended in the clinical setting, thereby minimizing potential "white coat hypertension". This methodology was used in most patients in the SPRINT trial and the values were correlated with ambulatory blood pressure during that study [31]. The values from this methodology will lead to a more precise diagnosis of RHTN. At the time the study was begun, the gold standard for defining hypertension was the awake ambulatory blood pressure. AOBP readings have been shown to be equivalent, and so a cut point of 135 mm Hg was used as had been used for ambulatory BP [4, 32, 33]. Although the upper limit of automated office systolic blood pressure of 160 mm Hg excludes patients with more severe RHTN, it was selected because higher systolic AOBP would likely compel investigators to add additional antihypertensive medications during the treatment period if blood pressure remained uncontrolled, which could confound interpretation of study results.

Eligibility also requires an eGFR of 25–45 mL/min/1.73 m^2 (mean of 2 screening values). Risk of hyperkalemia during spironolactone therapy is substantially increased with eGFR <45 mL/min/1.73 m^2 [20]. Furthermore, spironolactone is contraindicated for patients with acute renal insufficiency or significant impairment of renal excretory function [34]. To minimize patient risk, laboratory assessment will be performed regularly through the trial, including serum creatinine, eGFR, and potassium measurements. An initial decrease in renal function is expected following the addition of spironolactone to a background regimen of 3 antihypertensive agents that include a diuretic and renin-angiotensin blocking agent. Investigators are recommended to follow KDOQI guidelines for the detection and management of early decreases in eGFR. According to KDOQI recommendations, significant declines from baseline in eGFR >30% may require dose adjustment or discontinuation of spironolactone [29].

An important consideration for the trial design was the use of 24-h ambulatory blood pressure monitoring. While we recognize the value of this technique, we reasoned that given frequent titrations of the drug and downstream blood pressure measurements, we may have missing data if we required frequent 24-h ambulatory blood pressure monitoring. Given that the pattern of missing data may not be random, it may introduce bias in the study design. In view of the important relationships observed between AOBP and CV outcomes, we chose this as the primary endpoint in this trial.

If the primary endpoint is positive in the AMBER study, it would indicate that patiromer effectively enabled persistent spironolactone use in CKD patients by maintaining serum K^+ in a normal range and minimizing the risk of hyperkalemia. If the secondary endpoint assessing reductions in blood pressure is also positive, it would indicate that the ability of patiromer to permit chronic spironolactone use translates into better blood pressure control, extending previous findings from PATHWAY-2 and other studies to the CKD population with RHTN [18, 30, 35–37]. Finally, because albuminuria is a marker of cardiovascular and renal outcomes [38–40], positive reductions in albuminuria favoring the spironolactone and patiromer arm may set the stage for a renal outcomes study with these agents.

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Author Contributions

The authors made substantial contributions to the conception or design of the work (R.A., P.R., D.G., M.R.M., S.A., W.B.W., and B.W.), or to the acquisition, analysis, or interpretation of data for the work (all); participated in drafting and revising the manuscript (all); approved the final version to be published (all); and agreed to be accountable for all aspects of the work (all).

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