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RESEARCH ARTICLE

Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): results in the pre-specified subgroup with heart failure

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Aims The AMBER trial demonstrated that concomitant use of patiromer enabled the more persistent use of spironolactone by reducing the risk of hyperkalaemia in patients with resistant hypertension and advanced chronic kidney disease. We report herein the pre-specified subgroup analysis in patients with heart failure (HF).

Methods and results Participants were randomly assigned (1:1) to receive either placebo or patiromer (8.4 g once daily), in addition to open-label spironolactone (starting at 25 mg once daily) and their baseline blood pressure medications. Dose titrations were permitted after 1 week for patiromer/placebo and after 3 weeks for spironolactone. The primary endpoint was the between-group difference at week 12 in the proportion of patients on spironolactone. Efficacy endpoints and safety were assessed in all randomized patients (intention to treat). A total of 295 patients were enrolled, of whom 132 (45%) had HF. In the HF subgroup, 68.1% of patients receiving placebo remained on spironolactone at week 12, compared with 84.1% of patients receiving patiromer ($P = 0.0504$). The reason for discontinuation from spironolactone use was hyperkalaemia in the majority of both groups. There was no significant interaction between the subgroups with HF and without HF ($P = 0.8085$) for the primary endpoint.

Conclusions Consistent with the overall AMBER trial results, this pre-specified subgroup analysis in patients with HF, resistant hypertension and advanced chronic kidney disease demonstrated that patiromer enabled more persistent use of spironolactone by reducing the risk of hyperkalaemia.

Keywords Heart failure • Chronic kidney disease • Hyperkalaemia • Patiromer • Resistant hypertension • Spironolactone

Introduction

Resistant hypertension is defined as blood pressure above goal despite adherence to a combination of at least three optimally dosed antihypertensive medications, one of which is a diuretic.[1,2] The prevalence of resistant hypertension is increased in patients with chronic kidney disease (CKD). Resistant hypertension worsens the cardiovascular prognosis of CKD[3] and is associated with a

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threefold increase in the risk of heart failure (HF).[4] Registry data in 1288 patients with HF showed that the percentage of resistant hypertension was 13.7%.[5]

The latest European Society of Cardiology/European Society of Hypertension guidelines, based in part on the PATHWAY-2 trial in resistant hypertension,[6] recommend that the mineralocorticoid receptor antagonist (MRA) spironolactone be the first drug added when a three-drug combination has failed to control hypertension.[2] However, this recommendation is limited to patients with an estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2 and a serum potassium <4.5 mmol/L because of the concern of hyperkalaemia in patients with more advanced CKD.[2] Among patients with HF with reduced ejection fraction (HFrEF), MRAs have been shown to reduce mortality, and as such have Level 1 evidence for use and are one of the cornerstones of therapeutics in HFrEF.[7,8] In the US, guidelines also recommend consideration of spironolactone in HF with preserved ejection fraction (HFpEF).[7,9] Despite these strong recommendations, the concern of inducing hyperkalaemia is a major barrier to the implementation of these recommendations[9,10] and more broadly for MRA use in patients with cardiorenal diseases, including those with resistant hypertension.[11,12]

The AMBER trial evaluated the use of the potassium binder patiromer to allow more persistent use of spironolactone in patients with advanced CKD and resistant hypertension.[13] Patiromer enabled more persistent use of spironolactone in the overall AMBER population by reducing the risk of hyperkalaemia.[13] We report herein the pre-specified subgroup analysis in HF patients from AMBER.

Methods

Study design and participants

The design and primary outcomes of the randomized, double-blind, placebo-controlled, parallel-group AMBER study (ClinicalTrials.gov Identifier NCT03071263) have previously been published.[13,14] The study was conducted in accordance with current standards, conforms with the principles outlined in the Declaration of Helsinki, and the study protocol was approved by the institutional review board or the independent ethics committee for each institution before study initiation. All patients provided written informed consent before participating in the study.

Briefly, eligible patients were aged ≥18 years with an eGFR of 25–45 mL/min/1.73 m^2, and had serum K^+ between 4.3 and 5.1 mmol/L. All patients had resistant hypertension, defined as unattended systolic automated office blood pressure (AOBP) of 135–160 mmHg despite taking ≥3 antihypertensives, including a diuretic, and an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (unless not tolerated or contraindicated) during screening. Reasons for exclusion included untreated secondary causes of hypertension (other than CKD), recent cardiovascular event (e.g. myocardial infarction, unstable angina, hospitalization for HF), and clinically significant ventricular arrhythmia or atrial fibrillation with heart rate >100 bpm. Based on investigator reporting of clinical history, the following information was recorded in the case report form to accurately describe this pre-specified subgroup: HF (presence/absence), type of HF (preserved ejection fraction, reduced ejection fraction, unknown), New York Heart Association (NYHA) class, and ejection fraction data (if available).

The study had a screening/run-in period (up to 4 weeks), a double-blind treatment period (12 weeks) and a follow-up visit 2 weeks after the week 12 visit or early termination. The screening period (four visits separated by 4 to 10 days) ensured that patients were on stable doses of medication, had true resistant hypertension, and met all inclusion criteria. Eligible patients were randomly assigned (1:1) via an interactive web response system at the final screening visit to receive patiromer 8.4 g once daily or matching placebo, in addition to open-label spironolactone 25 mg once daily and their baseline antihypertensive medications, starting on day 1 of randomized treatment. Visits during the double-blind treatment period were weekly (weeks 1–4) and then biweekly (weeks 6–12) at which time blood pressure, body weight, blood samples for serum chemistry assessments, and adverse events (AEs) were collected.

At each visit after the initial screening visit, unattended AOBP measurements were recorded for each patient, as described.[13] Investigators were instructed to keep baseline antihypertensive medications constant except for AE-related reasons where changes to baseline medications could be justified.

Drug treatments

Open-label oral spironolactone was started at 25 mg once daily and increased to 50 mg once daily at week 3 in patients with serum K^+ ≤5.1 mmol/L if systolic AOBP remained ≥120 mmHg. Patients initiated study drug [two similarly unmarked packets of 4.2 g of patiromer (Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA, USA) or microcrystalline cellulose placebo], taken once daily with food at least 3 h before or 3 h after other medications (including spironolactone). Study drug dosing adjustments were made at intervals of ≥1 week: upward adjustment for local laboratory serum K^+ >5.1 mmol/L, and downward adjustment for serum K^+ <4.0 mmol/L. The maximum daily dosage of patiromer/placebo was six packets (25.2 g in the patiromer group) and the minimum was no packets. The titration algorithm was designed to maximize spironolactone dose while avoiding hyperkalaemia, decreases in eGFR, and hypotension.[14] There were three protocol-specified criteria for treatment withdrawal because of high serum K^+: (i) K^+ ≥5.5 and <6.0 mmol/L, and on maximum dose of patiromer or placebo, and repeat K^+ within 1 day remained ≥5.5 mmol/L; (ii) K^+ ≥5.5 and <6.0 mmol/L, not on maximum dose but after dose was increased by two packets, and repeat K^+ within 3 days remained ≥5.5 mmol/L; and (iii) K^+ ≥6.0 mmol/L and repeat K^+ within 1 day remained ≥6.0 mmol/L. Patients who discontinued patiromer or placebo were required to discontinue spironolactone at the same time. Patients who discontinued spironolactone and patiromer or placebo for any reason remained in the study and were treated with standard medical care based on the investigator's clinical judgment.

Endpoints and statistical analysis

This pre-specified analysis evaluated AMBER primary and secondary endpoints according to HF status (as determined by patient medical history). The primary endpoint was the difference between treatment groups in the proportion of patients remaining on spironolactone at week 12. The secondary efficacy endpoint was the difference between treatment groups in the change in systolic AOBP from baseline to week

12 (or to the last available measurement before addition of any new antihypertensive medications or increase in any of the baseline antihypertensive medications). Post hoc analyses of other endpoints according to HF status included: differences in cumulative spironolactone dose, Kaplan–Meier estimated time to discontinuation of spironolactone, percent of patients receiving spironolactone 50 mg once daily, daily dose of patiromer, rate of discontinuation of spironolactone due to hyperkalaemia, Kaplan–Meier estimate of the time to serum K^+ ≥5.5 mmol/L, and serum K^+ over time. Safety was assessed by vital signs, reports of AEs, change in eGFR from baseline to week 12, and changes in laboratory parameters [including N-terminal pro B-type natriuretic peptide (NT-proBNP) levels and urine albumin/creatinine ratio]. Patiromer releases calcium as it binds potassium in the gastrointestinal tract, and it may bind other cations such as magnesium. Therefore, laboratory assessments included serum calcium (normal range 2.12–2.62 mmol/L) and magnesium (normal range 0.74–0.99 mmol/L) levels over time, and the number of patients with pre-specified serum calcium values >2.62 mmol/L and serum magnesium <0.58, <0.49, and <0.41 mmol/L. The efficacy endpoints and safety were assessed in all randomized patients; all randomized patients received at least one dose of spironolactone and at least one dose of blinded study medication (patiromer or placebo). All laboratory results are based on central laboratory data.

To evaluate the primary endpoint of between-group differences in the proportion of patients remaining on spironolactone at week 12, the Cochran–Mantel–Haenszel test was used, stratified by baseline K^+ category (4.3 to <4.7 vs. 4.7 to 5.1 mmol/L) and presence/absence of diabetes mellitus. The secondary endpoint was analysed using an analysis of covariance (ANCOVA) model, with baseline systolic AOBP as covariate, and the same categorical factors as for the primary endpoint. Time to discontinuation of spironolactone and time to hyperkalaemia (serum K^+ ≥5.5 mmol/L) were analysed using Kaplan–Meier methods, and average daily and cumulative dose of spironolactone were analysed using ANCOVA methods. Safety parameters were summarized descriptively. Statistical analyses were performed on SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and baseline characteristics

In AMBER, 295 patients were randomized to double-blind treatment with either placebo plus spironolactone (n = 148) or patiromer plus spironolactone (n = 147) in addition to their current treatment regimen of antihypertensive medications. Of these, 132 (45%) patients had a history of HF (69 randomized to placebo and 63 randomized to patiromer) and 163 (55%) patients did not have HF (79 randomized to placebo and 84 randomized to patiromer).

In the subgroup with HF, 65 (94%) patients randomized to placebo and 63 (100%) patients randomized to patiromer completed the study [76 (96%) and 81 (96%) patients without HF, respectively; online supplementary *Figure S1*]. The most common reason for study drug discontinuation was meeting a protocol-specified withdrawal criterion for high serum K^+. In the HF subgroup, study drug discontinuation due to hyperkalaemia occurred in 16 (23%) patients on placebo and 7 (11%) patients on patiromer (online supplementary *Table S1*). The last recorded dose of spironolactone in patients who discontinued study drug due to hyperkalaemia is shown in online supplementary *Table S2*.

Baseline demographics and disease characteristics were generally similar for patients with and without HF (*Table 1*). A history of hyperkalaemia was present at baseline in 11% of patients with HF and in 4% of those without HF. Patients with HF were more likely to have a history of atrial fibrillation (16%) than patients without HF (4%).

In the subgroup with HF, the proportions of patients classified by the investigator as having HFpEF at baseline were 46% and 35% in the placebo and patiromer groups, respectively (online supplementary *Table S3*). The majority of HF patients in the placebo and patiromer groups had NYHA class II HF (80% and 65%, respectively), while 4% and 18%, respectively, had NYHA class III HF. Left ventricular ejection fraction (LVEF) data were available for 51 (74%) and 44 (70%) patients in the placebo and patiromer groups, respectively (online supplementary *Table S3*). Among those with data, mean (standard deviation) LVEF reported by investigators was 50% (8%) in the placebo group and 48% (11%) in the patiromer group. In patients with HF, median (Q1, Q3) NT-proBNP levels were 730 (302, 1972) ng/L and 1062 (333, 2375) ng/L in the placebo and patiromer groups, respectively (online supplementary *Table S3*). At baseline, 93% and 89% of HF patients randomized to placebo and patiromer, respectively, displayed a NT-proBNP concentration >125 ng/L.

Efficacy endpoints

There was no significant interaction between the subgroups with HF and without HF (P = 0.8085) for the primary endpoint. In the HF subgroup, 68.1% of patients receiving placebo remained on spironolactone at week 12 (*Figure 1*), compared with 84.1% of patients receiving patiromer [between-group absolute difference 16.0%, 95% confidence interval (CI) 1.8–30.2; P = 0.0504]. Among patients without HF, 64.6% of patients in the placebo group remained on spironolactone at week 12, compared with 86.9% of patients in the patiromer group (between-group absolute difference 22.4%, 95% CI 9.6–35.1; P = 0.0006). The Kaplan–Meier estimates of the time to early discontinuation of spironolactone are shown in *Figure 2*.

The cumulative dose of spironolactone over 12 weeks by treatment group is shown in online supplementary *Table S4*. The least square (LS) mean [standard error (SE)] difference between treatment groups (patiromer group minus placebo group) in cumulative spironolactone dose was 387.5 (196.4) mg in patients with HF and 398.4 (160.1) mg in patients without HF. In the HF group, 59% in the placebo group and 76% in the patiromer group were receiving the 50 mg once daily dose of spironolactone at week 12 (44% and 64% in the subgroup without HF, respectively). Median (Q1, Q3) daily doses of patiromer were 8.5 (8.4, 16.0) g/day and 11.9 (8.4, 16.0) g/day in patients with and without HF, respectively.

In patients with HF, serum K^+ ≥5.5 mmol/L occurred in 42 (61%) patients receiving placebo and in 28 (44%) patients receiving patiromer. In patients without HF, serum K^+ ≥5.5 mmol/L occurred

Table 1 Baseline characteristics in AMBER patients with and without heart failure

Characteristic	Patients with HF			Patients without HF		
	Spironolactone + placebo (*n* = 69)	Spironolactone + patiromer (*n* = 63)	Subgroup total (*n* = 132)	Spironolactone + placebo (*n* = 79)	Spironolactone + patiromer (*n* = 84)	Subgroup total (*n* = 163)
Age, years, mean (SD)	69.4 (9.9)	70.9 (10.4)	70.1 (10.1)	67.7 (12.1)	65.4 (13.1)	66.5 (12.6)
≥65 years, *n* (%)	53 (77)	46 (73)	99 (75)	51 (65)	52 (62)	103 (63)
White race, *n* (%)	68 (99)	63 (100)	131 (99)	77 (98)	82 (98)	159 (98)
Male, *n* (%)	36 (52)	32 (51)	68 (52)	41 (52)	44 (52)	85 (52)
Systolic AOBP, mmHg, mean (SD)	145.1 (6.8)	143.2 (6.4)	144.2 (6.6)	144.8 (7.3)	143.3 (6.6)	144.0 (7.0)
Serum K^+, mmol/L, mean (SD)	4.70 (0.42)	4.73 (0.42)	4.71 (0.42)	4.69 (0.33)	4.75 (0.31)	4.72 (0.32)
History of hyperkalaemia, *n* (%)	7 (10)	8 (13)	15 (11)	5 (6)	2 (2)	7 (4)
Diabetes mellitus, *n* (%)	33 (48)	24 (38)	57 (43)	39 (49)	49 (58)	88 (54)
eGFR, mL/min/1.73 m^2, mean (SD)	37.3 (8.3)	34.6 (6.1)	36.0 (7.5)	35.0 (6.7)	35.9 (8.0)	35.5 (7.4)
eGFR <30 mL/min/1.73 m^2, *n* (%)	15 (22)	14 (22)	29 (22)	19 (24)	18 (21)	37 (23)
Urine albumin/creatinine ratio, mg/g, mean (SD)	356.2 (714.8)	430.5 (990.2)	391.6 (854.8)	426.5 (740.0)	433.5 (681.4)	430.1 (708.2)
Atrial fibrillation, *n* (%)	12 (17)	9 (14)	21 (16)	5 (6)	2 (2)	7 (4)
NT-proBNP, ng/L, median (Q1, Q3)	730 (302, 1972)[a]	1062 (333, 2375)	787 (320, 2352)	243 (104.0, 608)	290.5 (107, 618.5)	268 (105, 618)
Patients with atrial fibrillation	2667 (1155, 3633)[a]	1945 (631, 2652)	2148.5 (895.5, 3509)	1594 (671, 2220)	1376 (619, 2133)	1594 (619, 2220)
Patients without atrial fibrillation	603 (262, 1500)	896 (329, 2367)	670 (275, 1990)	230 (90, 484)	286 (107, 566)	259 (97, 532)
No. of antihypertensive meds, mean (SD)	3.6 (0.7)	3.8 (1.0)	3.7 (0.8)	3.6 (0.8)	3.7 (0.8)	3.6 (0.8)
No. (%) of patients on:						
RAASi	69 (100)	63 (100)	132 (100)	78 (99)	84 (100)	162 (99)
Diuretics	69 (100)	63 (100)	132 (100)	79 (100)	84 (100)	163 (100)
Calcium channel blockers	53 (77)	51 (81)	104 (79)	53 (67)	56 (67)	109 (67)
Beta-blockers	50 (73)	54 (86)	104 (79)	47 (60)	47 (56)	94 (58)
Other	10 (15)	9 (14)	19 (14)	21 (27)	31 (37)	52 (32)

AOBP, automated office blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide; RAASi, renin–angiotensin–aldosterone system inhibitor; SD, standard deviation.

[a]One patient with HF and atrial fibrillation did not have NT-proBNP assessment.

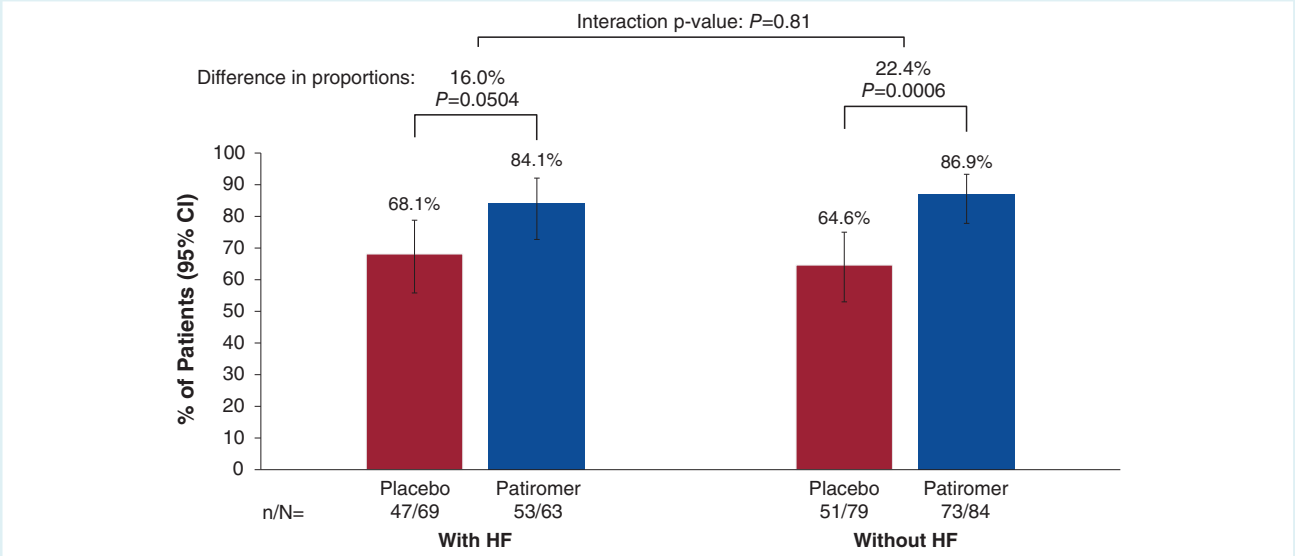

Figure 1 Percent of AMBER patients with and without heart failure (HF) who remained on spironolactone at week 12. CI, confidence interval.

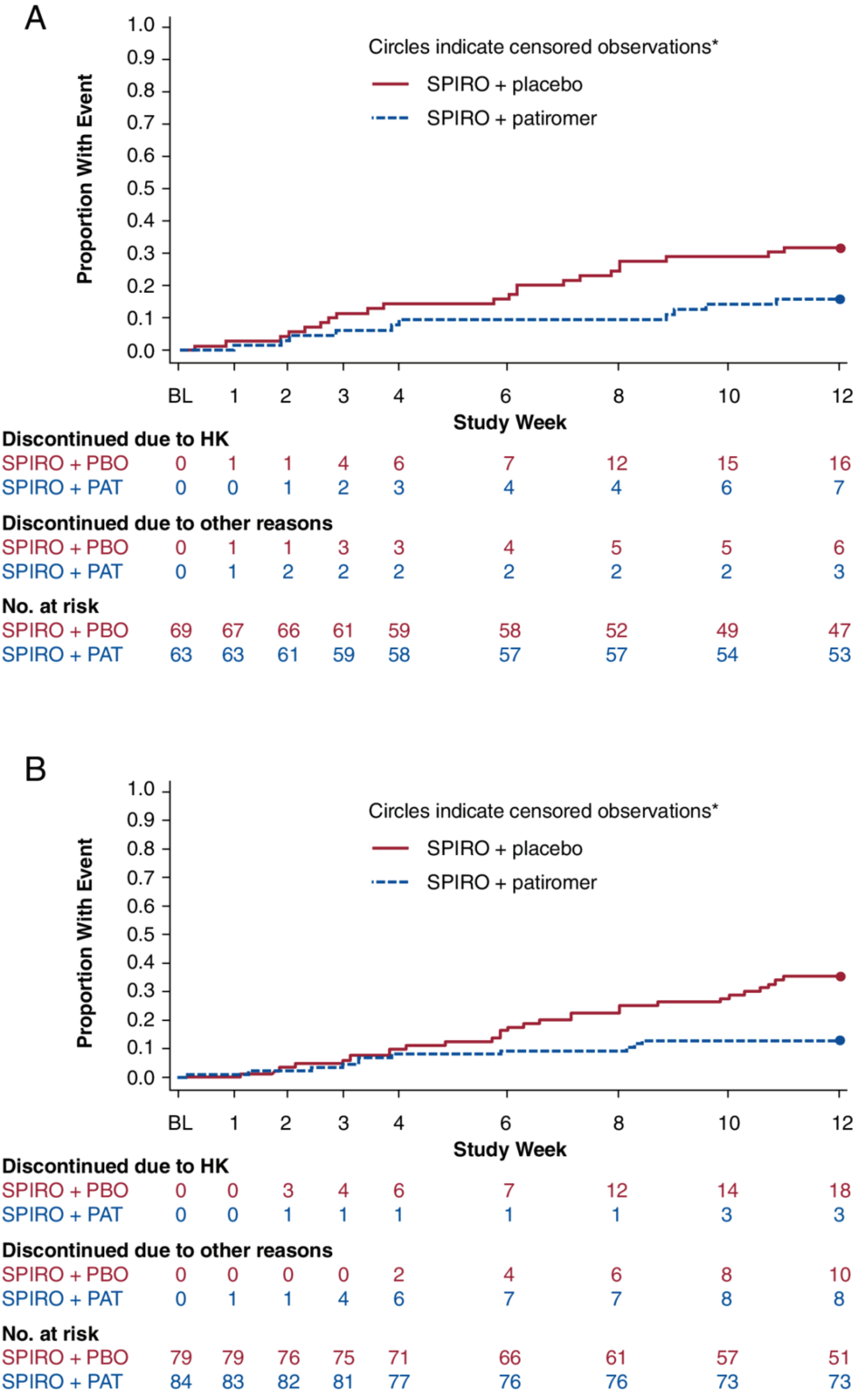

Figure 2 Time to discontinuation of spironolactone in AMBER patients (*A*) with heart failure and (*B*) without heart failure. *Patients who completed 12 weeks of study treatment and had not had any event are censored at week 12. BL, baseline; HK, hyperkalaemia; PAT, patiromer; PBO, placebo; SPIRO, spironolactone.

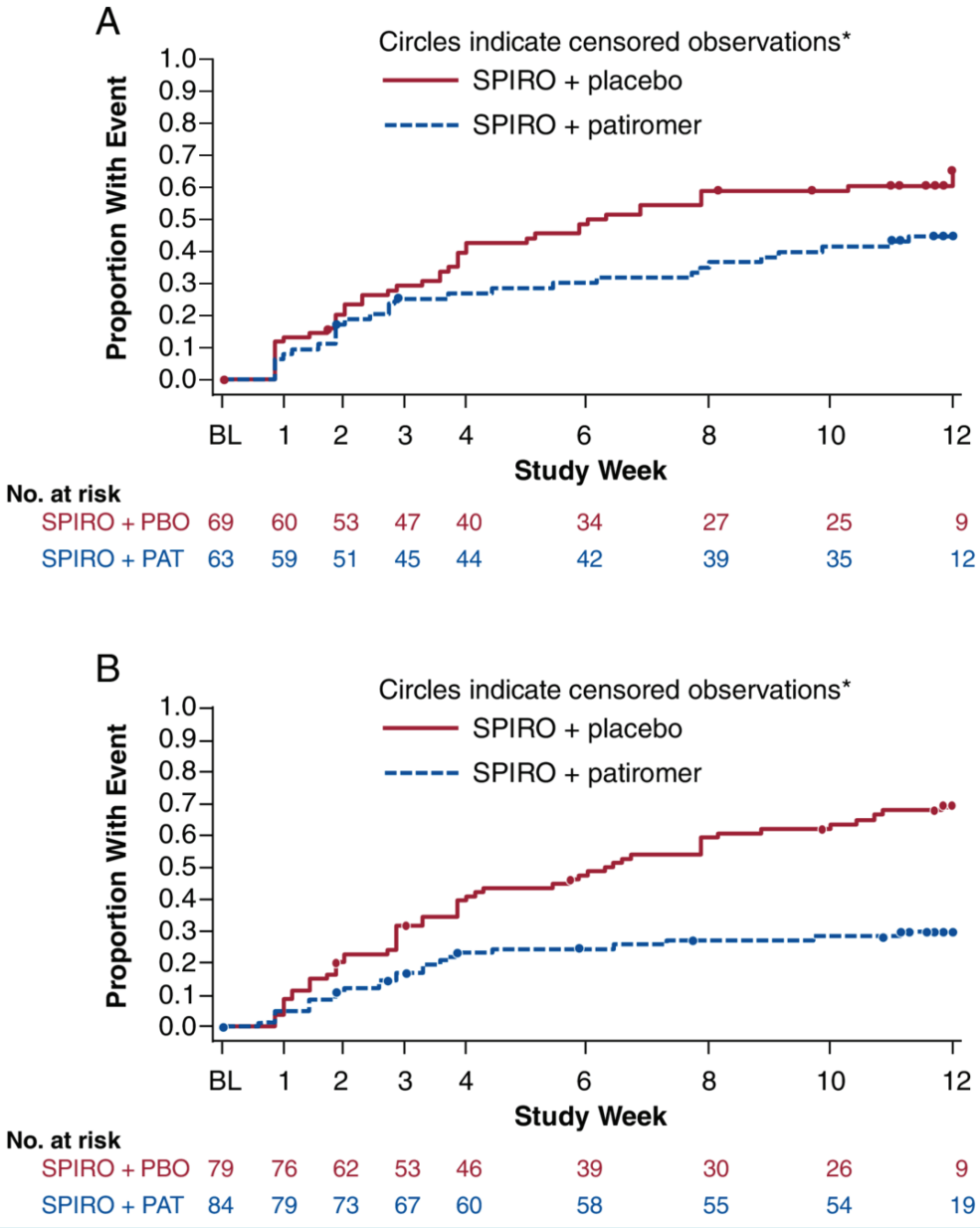

Figure 3 Time to first central serum potassium value ≥5.5 mmol/L during treatment in patients (*A*) with heart failure and (*B*) without heart failure. *Patients who completed 12 weeks of study treatment and had not had any event are censored at week 12. BL, baseline; PAT, patiromer; PBO, placebo; SPIRO, spironolactone.

in 53 (67%) patients receiving placebo and in 24 (29%) patients receiving patiromer. The Kaplan–Meier estimates of the time to first serum K^+ ≥5.5 mmol/L are shown in *Figure 3*. Mean serum K^+ over time through week 12 according to HF status is shown in online supplementary *Figure S2*.

In patients with HF, the LS mean (SE) AOBP reductions from baseline to week 12 (*Figure 4*) were 9.0 (1.6) mmHg in the placebo group and 7.8 (1.7) mmHg in the patiromer group ($P < 0.0001$ vs. baseline for both treatment groups; $P = 0.60$ for difference between treatment groups). In patients without HF, the LS mean (SE) AOBP reductions were 12.1 (1.8) mmHg in the placebo group and 14.4 (1.7) mmHg in the patiromer group ($P < 0.0001$ vs. baseline for both treatment groups; $P = 0.36$ for difference between treatment groups). There was no significant interaction between the subgroups with HF and without HF ($P = 0.2973$) for AOBP change from baseline. Additions to antihypertensive medications before week 12 occurred in four placebo patients (one with HF, three without HF) and no patiromer patients. No additions in antihypertensive medications were reported to be due to new oedematous states.

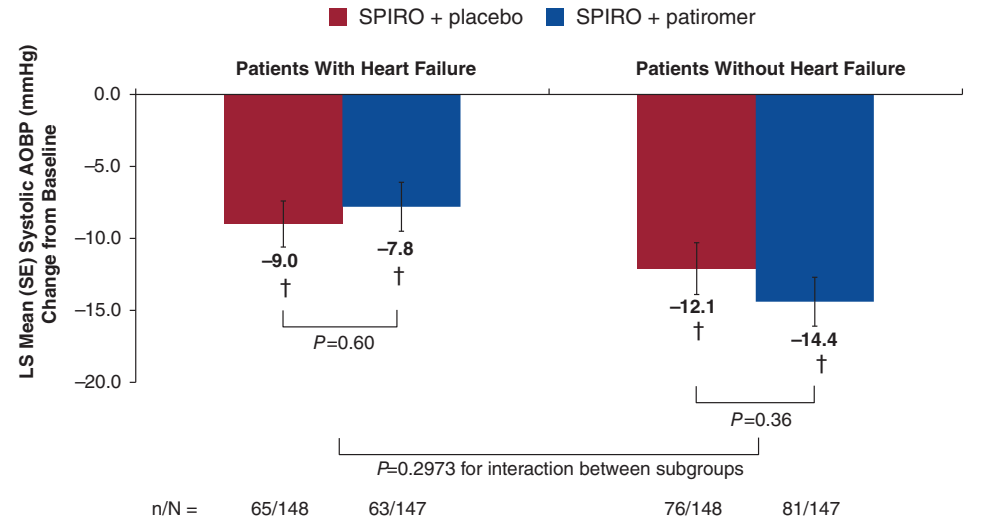

Figure 4 AMBER secondary endpoint: least square (LS) mean systolic automated office blood pressure (AOBP) change from baseline to week 12 by heart failure status. Change from baseline to week 12, or the last available systolic AOBP on or prior to the first date of addition of any new antihypertensive medications or increases to any baseline antihypertensive medications. $^{\dagger}P < 0.0001$. SE, standard error; SPIRO, spironolactone.

Safety

Overall, AEs (*Table 2*) occurred in 48% and 46% of HF patients randomized to placebo and patiromer, respectively (58% and 63% in patients without HF). AEs were generally mild to moderate in severity. The most frequently occurring AE class was gastrointestinal disorders, occurring in 17% and 11% of HF patients randomized to placebo and patiromer, respectively (15% and 20% in patients without HF). Diarrhoea was the most common AE in this class, reported in 6% and 3% of HF patients in the placebo and patiromer groups, respectively.

The most common individual AE was renal impairment in patients with HF (none serious) and hyperkalaemia or increased blood potassium in patients without HF (none serious; *Table 2*). The number of patients with a serum K^+ measurement <3.8 mmol/L and <3.5 mmol/L through week 12 is reported according to HF status in online supplementary *Table S5*. One HF patient receiving patiromer had a post-baseline serum K^+ measurement <3.5 mmol/L through week 12; none of the patients without HF had serum K^+ <3.5 mmol/L. In addition, no patients in either subgroup had serum K^+ <3.0 mmol/L.

In the HF subgroup, one serious AE occurred in each of three patients receiving placebo [hypersensitivity, renal colic, and aortic rupture (the serious AE leading to death)]. In the subgroup without HF, one serious AE occurred in each of two patients; one receiving placebo (renal failure), and one receiving patiromer (humerus fracture).

In the HF subgroup, rates of AEs indicative of worsening kidney function were consistent with those in the overall AMBER population. These included AEs of renal failure (0.8% in HF and 1.7% in the overall population), renal impairment (6.8% in HF and 7.8% overall), CKD (0% in HF and 0.7% overall), and nephropathy (0% in HF and 0.3% overall). AEs indicative of worsening kidney function led to spironolactone withdrawal or dose reduction in 8% of HF patients (five patients in the placebo group and six patients in the patiromer group). In patients without HF, AEs indicative of worsening kidney function led to spironolactone withdrawal or dose reduction in 6% of patients (four patients in the placebo group and six patients in the patiromer group). Mean changes in eGFR and urine albumin/creatinine ratio are shown in online supplementary *Table S6*. In HF patients, post-baseline declines in eGFR of more than 30% occurred in 16% and 24% of patients in the placebo and patiromer groups, respectively; one HF patient on placebo had an eGFR decline of more than 50%. As in the overall population, among the HF patients with baseline eGFR <30 mL/min/1.73 m^2, none had declines in eGFR of more than 50% and none went on dialysis during the study.

Mean serum magnesium and calcium levels in patients with and without HF remained within the normal range in both treatment groups during the study (online supplementary *Table S7*). Three patients with HF (one placebo, two patiromer) and one without HF (placebo) had serum magnesium <0.58 mmol/L and none had a value <0.49 mmol/L. In two of these patients, serum magnesium was below the lower limit of normal (0.74 mmol/L) at baseline. None of these patients had cardiac arrhythmias temporally associated with low magnesium levels, neuromuscular abnormalities, or serum K^+ below the lower limit of normal (3.5 mmol/L). Four patients with HF (two in each treatment group) and five patients without HF (three placebo, two patiromer) had serum calcium >2.62 mmol/L between baseline and week 12. All four patients with HF and one placebo patient without HF had serum calcium >2.62 mmol/L at baseline. The number of patients with baseline or any post-baseline serum magnesium or calcium measurements above or below pre-specified thresholds are reported

Table 2 Adverse event summary in patients with and without heart failure

	With HF			Without HF		
	Spironolactone + placebo (*n* = 69)	Spironolactone + patiromer (*n* = 63)	Subgroup total (*n* = 132)	Spironolactone + placebo (*n* = 79)	Spironolactone + patiromer (*n* = 84)	Subgroup total (*n* = 163)
Adverse events	33 (48)	29 (46)	62 (47)	46 (58)	53 (63)	99 (61)
Most common class of adverse events						
Gastrointestinal disorders	12 (17)	7 (11)	19 (14)	12 (15)	17 (20)	29 (18)
Severe adverse events	1 (1)	2 (3)	3 (2)	2 (3)	0	2 (1)
Serious adverse events	3 (4)	0	3 (2)	1 (1)	1 (1)	2 (1)
Adverse event leading to study treatment discontinuation	6 (9)	3 (5)	9 (7)	15 (19)	7 (8)	22 (14)
Adverse event leading to death	1 (1)	0	1 (1)	0	0	0
Most common individual adverse events						
Hyperkalaemia or blood potassium increased	3 (4)	3 (5)	6 (5)	11 (14)	6 (7)	17 (10)
Renal impairment	3 (4)	6 (10)	9 (7)	7 (9)	7 (8)	14 (9)
Headache	5 (7)	2 (3)	7 (5)	6 (8)	7 (8)	13 (8)
Diarrhoea	4 (6)	2 (3)	6 (5)	4 (5)	7 (8)	11 (7)
Hypotension	0	4 (6)	4 (3)	6 (8)	5 (6)	11 (7)

Data are *n* (%) of patients with at least one event; each patient is counted only once for each adverse event. Serum magnesium 0.5–0.6 mmol/L occurred in one placebo patient and two patiromer patients in the HF subgroup.
HF, heart failure.

according to HF status in online supplementary *Table S5* and online supplementary *Appendix S1*. In patients with and without HF, median (Q1, Q3) NT-proBNP levels at baseline and at week 12 are shown in online supplementary *Figure S3B and S3C*; results are also shown by presence or absence of atrial fibrillation at baseline. Median (Q1, Q3) NT-proBNP levels in the HF subgroup were numerically higher than those in the non-HF subgroup at baseline and at week 12. In the HF subgroup, NT-proBNP concentrations were numerically higher at baseline in the patiromer group. In patients with and without HF, NT-proBNP levels numerically decreased in both treatment groups at week 12 (online supplementary *Figure S3A*).

Discussion

In this pre-specified analysis of patients with HF from the AMBER trial, who comprised 45% of the randomized patients, once daily oral administration of patiromer significantly increased the proportion of patients who remained on spironolactone over 12 weeks of treatment. Furthermore, patiromer use was associated with a reduced risk for hyperkalaemia during spironolactone therapy. In terms of the safety over 12 weeks, rates of AEs indicative of worsening kidney function (e.g. renal failure, renal impairment, and nephropathy) in the HF subgroup and the number of patients exceeding pre-specified cut-points for low serum magnesium and high serum calcium in both subgroups were consistent with those in the overall AMBER study population, while the AMBER study also provided evidence of the tolerability of patiromer relative to placebo.[14]

As AMBER was a phase II, relatively short-term (12 weeks) trial, it cannot provide insights related to long-term cardiovascular and renal outcomes. In this population of patients with HF (balanced between those reported as HFrEF and HFpEF), AMBER nevertheless provides relevant information on the short-term safety (particularly cardiac and renal safety) and maintenance of MRA therapy over 12 weeks in an advanced CKD population, who are prone to experience hyperkalaemia, worsening renal function, and poor clinical outcomes. Hence, these data provide evidence that patiromer enables the use of spironolactone in this high-risk group.

In this pre-specified subgroup analysis of patients with and without HF, patient numbers were too small to perform a post hoc exploratory analysis comparing the HFrEF vs. HFpEF patterns in patients receiving patiromer vs. placebo. However, the finding that patiromer safely enabled spironolactone use whilst preventing the occurrence of hyperkalaemia in this mixed HFrEF/HFpEF population is highly clinically relevant. Indeed, along with concerns regarding potential hypotension and worsening renal function, hyperkalaemia is a major reason for not using, or underdosing, renin–angiotensin–aldosterone system inhibitors (RAASi) including MRAs in HFrEF.[15,16] Not using or underdosing of RAASi is associated with worse clinical outcomes in HFrEF.[17] In a recent observational study including all Stockholm citizens initiating MRA therapy,[17] development of hyperkalaemia within a year was associated with a fourfold significantly higher risk in overall mortality, and the results were consistent in the subpopulation of patients

with HF. Following the occurrence of hyperkalaemia, 47% discontinued MRA and only 10% reduced the prescribed dose. Importantly, when MRA was discontinued, most patients (76%) were not reintroduced to therapy during the subsequent year.[18]

The present data, stemming from a trial aimed at demonstrating the MRA-enabling effect of the potassium binder patiromer in high cardiovascular risk patients, corroborate and extend the results obtained in another HFrEF population.[19] In that trial (PEARL-HF), patiromer enabled spironolactone use and prevented hyperkalaemia in patients with predominantly HFrEF with an eGFR <60 mL/min/1.73 m^2 or a history of hyperkalaemia that provoked discontinuation of drugs blocking the renin–angiotensin–aldosterone system.[19] Whether this enabling effect may ultimately lead to improved cardiovascular outcomes is currently being tested in the ongoing DIAMOND trial (ClinicalTrials.gov Identifier NCT03888066).

Several clinical outcome trials have been performed in patients with HFpEF, yet none have met their primary endpoint.[9] The TOPCAT trial comparing spironolactone with placebo did not meet its primary endpoint, with an 11% non-significant reduction in cardiovascular death or HF hospitalization. The 18% nominally significant risk reduction of the primary outcome in the Americas has encouraged societies in the US to believe that, if properly implemented, spironolactone may improve outcomes in patients with HFpEF.[9] In HFpEF patients with resistant hypertension from the Americas enrolled in TOPCAT, a post hoc analysis showed that spironolactone enabled better blood pressure control.[20] The magnitude of the blood pressure-lowering effect [−5.53 (1.95) mmHg vs. placebo] after 4 months in TOPCAT[20] was actually close to that observed after 3 months (−8 to −9 mmHg) in both treatment groups of HF patients receiving open-label spironolactone in AMBER, despite the fact that the two study populations were notably different (i.e. kidney function being more impaired in AMBER: mean of 36 mL/min/1.73 m^2 in AMBER vs. 61–64 mL/min/1.73 m^2 in TOPCAT). Moreover, the blood pressure reductions in the HF subgroup in AMBER were generally consistent with those observed in the overall study population (−11 to −12 mmHg). If the guidelines for the treatment of HFpEF include spironolactone, the results of the AMBER subgroup analysis presented here would become even more broadly applicable.

As already acknowledged,[13] our study has some limitations. Although we actively recruited patients from sites in South Africa and the US, the patients enrolled in the study were predominantly white, and our results might not extend to other racial or ethnic populations. In addition, 12 weeks might not have been long enough to assess differences between treatments in AOBP arising from the more persistent use of spironolactone. Of note, the influence of blood pressure changes on outcomes in HF is uncertain and may even differ between HFrEF and HFpEF. Moreover, we were evaluating the persistence of spironolactone use in the HF subgroup for reasons beyond blood pressure control, i.e. the previously proven benefits of spironolactone on clinical outcomes in HF. Furthermore, the morbidity and mortality benefits of MRAs in HF may be mediated by several proposed actions, including antifibrotic mechanisms that slow HF progression, prevent or reverse cardiac remodelling, or reduce arrhythmogenesis.[21]

Finally, while patients were classified as 'HF patients' based on their medical records, they displayed numerically much higher NT-proBNP concentrations at blinded baseline central laboratory assessment, substantiating the classification. Median NT-proBNP levels in patients with HF also remained numerically higher at week 12. Of note, there was a numerical imbalance at baseline regarding NT-proBNP, with the patients assigned to patiromer displaying higher levels, concordant with a higher prevalence of NYHA class III. In both treatment groups, a numerical decrease was observed over the 12 weeks; however, because the follow-up was relatively short and the AMBER study was not powered to detect changes in NT-proBNP, the effects of study treatment on NT-proBNP cannot be determined.

In conclusion, consistent with the overall AMBER trial, this pre-specified subgroup analysis showed that in a mixed (HFrEF and HFpEF) HF patient population with resistant hypertension and advanced CKD, concomitant use of patiromer enabled more persistent use of spironolactone by reducing the risk of hyperkalaemia.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Serum calcium and magnesium levels during the study.

Table S1. Reasons for early discontinuation of study treatment.

Table S2. Last recorded spironolactone dose in patients who discontinued because of hyperkalaemia.

Table S3. Heart failure characteristics.

Table S4. Cumulative spironolactone dose over 12 weeks.

Table S5. Pre-specified laboratory values of interest.

Table S6. Estimated glomerular filtration rate and urine albumin/creatinine ratio change from baseline at week 12.

Table S7. Serum calcium and magnesium level results over time and change from baseline.

Figure S1. Patient disposition by heart failure subgroups.

Figure S2. Mean (SE) central laboratory serum potassium during active treatment in patients (*A*) with heart failure, and (*B*) without heart failure.

Figure S3. N-terminal pro B-type natriuretic peptide levels at baseline and week 12 in (*A*) the overall population, (*B*) patients with atrial fibrillation, and (*C*) patients without atrial fibrillation.

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