Patiromer to Enable Spironolactone in Patients with Resistant Hypertension and CKD (AMBER)

Results in the Prespecified Subgroup with Diabetes

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Spironolactone is recommended in patients with resistant hypertension, including those with diabetes (1). However, spironolactone increases hyperkalemia risk, which can limit use in patients with diabetes (2).

AMBER (ClinicalTrials.gov NCT03071263) was a 12-week multicenter, randomized, double-blind, placebo-controlled, parallel-group study that evaluated the sodium-free, potassium (K^+) binder patiromer to enable more persistent spironolactone use in patients aged ≥18 years with resistant hypertension (unattended automated office systolic BP 135–160 mmHg despite ≥3 antihypertensives, including diuretic), eGFR 25–45 ml/min per 1.73 m^2, and serum K^+ 4.3–5.1 mEq/L (n=295) (3). Patients were randomized to open-label oral spironolactone 25 mg once daily with double-blind patiromer 8.4 g once daily, or placebo. Spironolactone was increased to 50 mg once daily at week 3 in patients with serum K^+ ≤5.1 mEq/L if automated office systolic BP remained ≥120 mmHg. The patiromer dose was adjusted upwards at 1-week intervals to 16.8 g once daily, then 25.2 g once daily if serum K^+ >5.1 mEq/L, or downward for serum K^+ <4.0 mEq/L. Patients received dietary counseling and were instructed not to change dietary K^+ intake during the study. Per study inclusion criteria (3), all patients received diuretics and renin-angiotensin-aldosterone system inhibitors; only one patient did not receive the latter, due to intolerance (per protocol). Investigators kept baseline antihypertensives constant, unless changes were needed for adverse events (AEs). The primary end point was the difference between treatment groups in proportion of patients remaining on spironolactone at week 12, using a Cochran-Mantel-Haenszel test. The secondary efficacy end point was the difference between treatment groups in change in automated office systolic BP from baseline to week 12, using an analysis of covariance model with baseline systolic BP as a covariate. Randomization and analyses were stratified by baseline serum K^+ (4.3 to <4.7 versus 4.7–5.1 mEq/L) and the presence/absence of diabetes. The primary and secondary end points were prespecified for subgroups. Additional end points (not prespecified for subgroups) are summarized descriptively.

In the overall AMBER population, 66% of patients treated with placebo and 86% of those treated with patiromer remained on spironolactone at week 12 (P<0.001) (3). We analyzed the prespecified subgroups with and without type 1 or 2 diabetes (diabetes$^+$, n=145; 72 randomized to placebo and 73 to patiromer, and diabetes$^-$, n=150, 76 randomized to placebo and 74 to patiromer).

Baseline demographics and disease characteristics were generally comparable between subgroups. In the diabetes$^+$ subgroup, 65% of patients receiving placebo remained on spironolactone at week 12 (Figure 1A) compared with 84% receiving patiromer (between-treatment absolute difference 18%). Figure 1B shows time to discontinuation of spironolactone. The least squares mean difference in cumulative spironolactone dose between treatments (patiromer minus placebo) was 438.7 (SEM 177.7) mg in the diabetes$^+$ subgroup (versus 317.8, SEM 175.0 in diabetes$^-$); 46% on placebo and 67% on patiromer were receiving 50 mg once daily spironolactone at week 12 in the diabetes$^+$ subgroup (versus 57% and 72%, respectively, in diabetes$^-$). In the diabetes$^+$ subgroup, serum K^+ ≥5.5 mEq/L occurred in 52 (72%) on placebo and 30 (41%) on patiromer (versus 57% and 30%, respectively, in diabetes$^-$). The least squares mean automated office systolic BP changes from baseline to week 12 were –10.7 (SEM 1.98) and –9.9 (SEM 1.98) for placebo and patiromer, respectively, in the diabetes$^+$ subgroup (P<0.001 versus baseline for both treatments; P=0.79 for difference between treatments; P=0.24 for subgroup interaction). Four placebo patients had additions to antihypertensive medications before week 12 (three diabetes$^+$; one diabetes$^-$).

AEs occurred in about 60% of patients in the diabetes$^+$ subgroup (about 50% in diabetes$^-$). In the diabetes$^+$ subgroup, AEs occurred in 44 (61%) placebo and 44 (60%) of patients on patiromer (serious AEs in three on placebo and one on patiromer; AEs leading to discontinuation in eight on placebo and five on patiromer). Diarrhea was the most common gastrointestinal AE (diabetes$^+$, seven placebo and four patiromer; diabetes$^-$, one and five, respectively). There were no clinically meaningful changes in urine albumin-creatinine ratio or

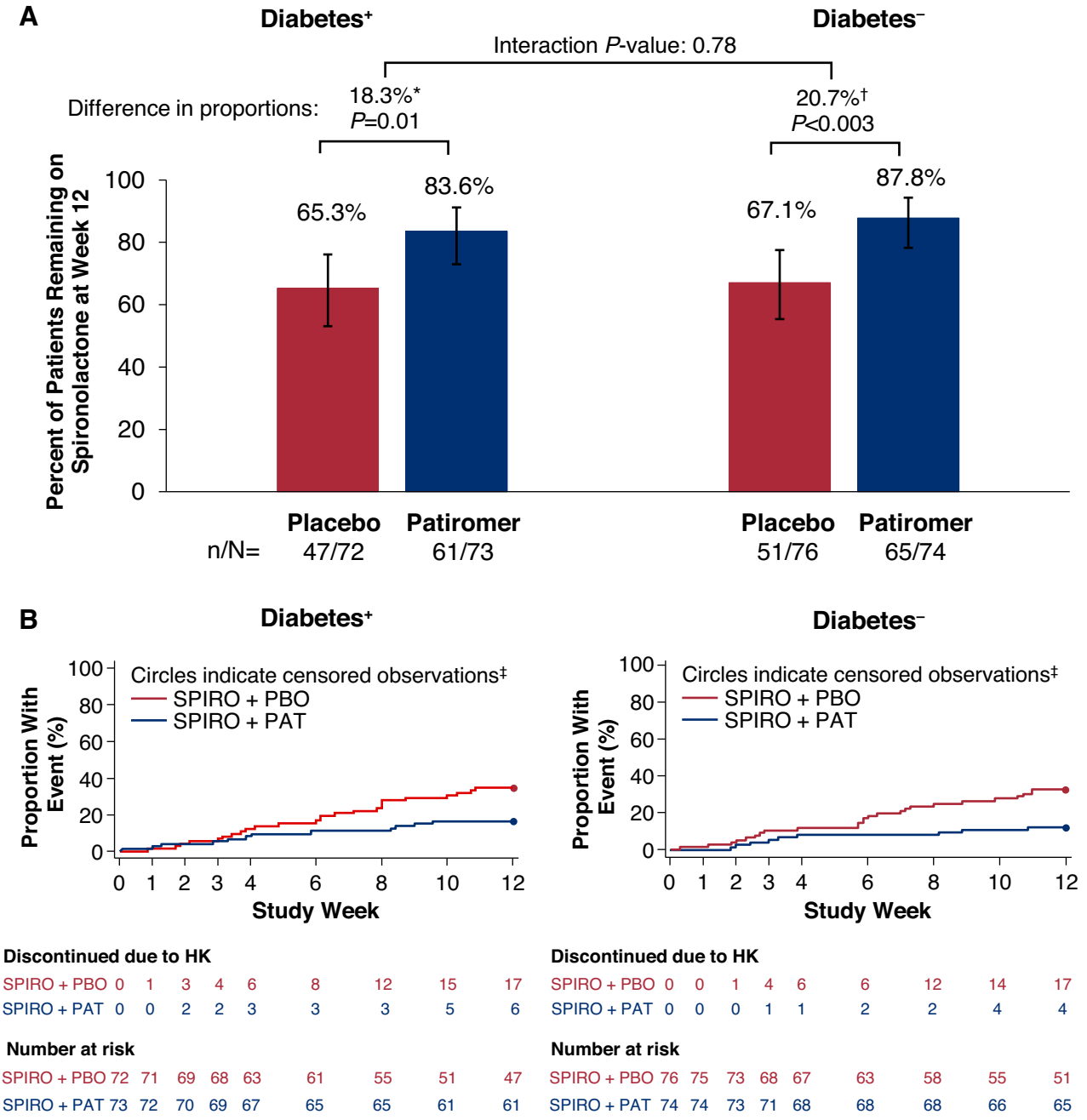

Figure 1. | Patiromer enabled more persistent use of spironolactone regardless of diabetes status. (A) Percentage of patients who remained on spironolactone at week 12 by diabetes subgroup. (B) Time to discontinuation of spironolactone in patients who are with and without type 1 or 2 diabetes (diabetes$^+$ and diabetes$^-$). *95% confidence interval, 4.4 to 32.2. †95% confidence interval, 7.8 to 33.7. ‡Patients who completed 12 weeks of study treatment and had not had any event are censored at week 12. HK, hyperkalemia; PAT, patiromer; PBO, placebo; SPIRO, spironolactone.

eGFR; 1–2 patients per treatment group discontinued because of prespecified decreases in eGFR (>50% decrease or ≥30% decrease for ≥4 weeks). In the diabetes$^+$ subgroup, no patient had serum K^+ <3.5 mEq/L; in the diabetes$^-$ subgroup, one had serum K^+ between 3.0 and 3.5 mEq/L. Serum magnesium <1.4 mg/dl was observed rarely (three in the diabetes$^+$ subgroup; one on placebo, two on patiromer; and one in the diabetes$^-$ subgroup, on patiromer). No serum magnesium <1.2 mg/dl was observed.

Consistent with results in the overall AMBER population (3), patiromer enabled use of spironolactone independently of diabetes status. Hyperkalemia was more common in those with diabetes. Automated office BP decreased significantly from baseline in the placebo and patiromer groups in each subgroup, with no difference between treatments. Patiromer's safety profile in patients with diabetes from the AMBER study is consistent with previous reports (4,5). Whether patiromer enabling spironolactone may ultimately

lead to improved cardiovascular outcomes is being tested in the ongoing DIAMOND trial (NCT03888066) in patients with heart failure.

Disclosures

B. Williams reports consultancy agreements with Vascular Dynamics Inc. and Vifor Pharma, Inc.; reports receiving research funding from Vascular Dynamics Inc.; reports receiving honoraria from Boehringer Ingelheim, Daiichi Sankyo, Novartis, Pfizer, and Servier, and consulting for Vifor Pharma, Inc.; reports serving as a University College London Hospitals (National Health Service) Executive Board member, member of the Executive committee of the European Society of Cardiology Council on Hypertension, member of Council of the International Society of Hypertension, and member of Council of the European Society of Hypertension. M.R. Mayo reports consultancy agreements from Vifor Pharma, Inc., and reports receiving research funding from Vifor Pharma, Inc. At the time this study was conducted and analyzed, M.R. Mayo was an employee of Vifor Pharma, Inc. P. Rossignol reports consulting for Bayer, G3P, Idorsia, and KBP; reports receiving honoraria from Ablative Solutions, AstraZeneca, Bayer, Boehringer-Ingelheim, Corvidia, CVRx, Fresenius, Grunenthal, Novartis, Novo Nordisk, Sanofi, Sequana Medical, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, and Vifor Pharma, Inc.; reports receiving personal fees from Ablative Solutions, Bayer, Boehringer Ingelheim, Corvidia, CVRx, Grunenthal, Idorsia, KBP, NovoNordisk, Sanofi, Sequana Medical, Servier, Stealth Peptides, Vifor Pharma, Inc.; reports receiving grants and personal fees from AstraZeneca, Bayer, Fresenius, Novartis, and Vifor Fresenius Medical Care Renal Pharma and nonfinancial support from Fresenius; reports having an ownership interest in G3P and is cofounder of CardioRenal; and reports receiving research funding from Vifor Fresenius Medical Care Renal Pharma and Vifor Pharma, Inc. P. Rossignol also reports serving as European Society of Hypertension: "Hypertension and the Kidney" Working Group (WG) board member since 2016; American Society of Nephrology Kidney Health Initiative workgroup board member: Understanding and Overcoming the Challenges to Involving Patients with Kidney Disease in Cardiovascular Trials; WG board member Heart Faiure Association (HFA), cardio renal and translational 2016–2020; WG board member Eurecam European Renal Association-European Dialysis and Transplant Association 2021–2023; and WG on biomarkers board member HFA, 2020–2022. R. Agarwal reports employment by Indiana University Heath Physicians, and Veterans Affairs Medical Center, Indiana University; reports consultancy agreements with Abbvie, Akebia, Amgen, AstraZeneca, Bayer, Birdrock Bio, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Ironwood Pharmaceuticals, Johnson & Johnson, Merck, Novartis, Opko, Otsuka, Reata, Sandoz, Sanofi, Takeda, Vifor Pharma, Inc., and ZS Pharma; reports receiving honoraria from Abbvie, Akebia, Amgen, AstraZeneca, Bayer, Birdrock Bio, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Diamedica, Eli Lilly, GlaxoSmithKline, Ironwood Pharmaceuticals, Johnson & Johnson, Merck, Novartis, Opko, Otsuka, Reata, Sandoz, Sanofi, Takeda, Vifor Pharma, Inc., and ZS Pharma; reports receiving research grants from the US Veterans Administration and the National Institutes of Health; reports having served as associate editor of the *American Journal of Nephrology, Nephrology Dialysis Transplantation*; has served as an author on UpToDate; and serving as a scientific advisor or member of Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, *Hypertension*, Ironwood Pharmaceuticals, *Journal of the American Society of Hypertension*, Johnson & Johnson, Kidney Disease Improving Global Outcomes, *Nephrology Dialysis Transplantation*, Reata, Relypsa, Sanofi, and *Seminars in Dialysis*. S. Arthur and A. Conrad report employment by and stock in Vifor Pharma, Inc. W.B. White reports serving as a safety consultant (Data Safety Monitoring Board, Steering Committee, Cardiovascular endpoints committee) for Aegerion, AstraZeneca, Bristol-Myers Squibb, Millenium-Takeda, and UCB; serving as a Section Editor for UpToDate (Wolters Kluwer); and serving as fellow (volunteer) on the American Heart Association Council on Hypertension, board member (volunteer) of Juvenile Diabetes Research Foundation, and Faculty (volunteer) of Validated Device Listing Project of American Medical Association.

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